

Chiral Hypervalent Iodine Mediated Enantioselective Oxidative Dearomatization of Naphthols

by

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Abstract

This dissertation investigates and describes the hypervalent iodine mediated dearomatization of naphthols, thereby yielding diversity of spiro-heterocyclic compounds in both racemic and chiral form.

The first part of this thesis discloses the synthesis of racemic spiropyrrolidines and spiro lactams via oxidative amidation of corresponding naphtholic sulfonamides, employing DIB as the oxidant. Enantioselective variant of the same have been demonstrated by using *in situ* generated chiral hypervalent iodine to provide chiral spiropyrrolidines. A noteworthy side reaction discovered in the course of these studies is the asymmetric oxidative addition of *meta*-chlorobenzoic acid to the naphtholic sulfonamides. The resulting acyloxyated adducts were formed with a greater degree of asymmetric induction compared to spiropyrrolidines in the same reaction mixture. Based on the results obtained from optimization study and substrate scope, plausible mechanistic insights of both cyclization and acyloxylation reactions have been provided.

The second part of this thesis unravels the spiroetherification of naphtholic alcohols, thereby yielding spiroethers both in racemic and chiral form. Chiral hypervalent iodine reagents generated *in situ* provided a range of spiroethers with excellent *ee*'s and high yields. These chiral oxidants have been evaluated for kinetic resolution of naphtholic primary alcohols bearing stereogenic center at β -position in the side chain.

Lay summary

Hypervalent iodine reagents are used as environmentally friendly, mild and selective oxidants for various synthetic conversions. This thesis describes their utility to provide easy access to useful building blocks which forms the core of natural products with important biological significance.

Preface

This thesis is written by N. Jain. Prof. M. A. Ciufolini provided the overall project design, helpful suggestions during the course of research and thoroughly edited this thesis. All the experiments and data analyses in Chapters 3, 4 and 5 were carried out by N. Jain, except for the Coupled Preferential Crystallization of compound **4.2a** mentioned in Section 4.3.9, which were performed by Prof. J. Hein (Department of Chemistry, UBC) and Dr. C. Rougeot. Prof. J. Hein thoroughly edited Section 4.3.9 of this thesis. Dr. S. Xu performed the analysis of COSY and NOESY data of compounds mentioned in section 5.2.6.

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List of Abbreviations

Ac	acetyl
anh.	anhydrous
aq.	aqueous
Ar	generic aryl group
Bn	benzyl
Boc	<i>t</i> -butyloxycarbonyl
br	broad
brsm	based on recovered starting material
Bu	butyl
<i>ca.</i>	circa
calcd	calculated
Ch.	chapter
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl
dec.	decomposition
DIAD	diisopropyl azodicarboxylate
diast	diastereomer
DIB	diacetyliodobenzene
DIBAL	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane

DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
d.r.	diastereomeric ratio
e	elementary charge
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>ee</i>	enantiomeric excess
Et	ethyl
eq.	equation
equiv	equivalent(s)
g	gram(s)
h	hour(s)
hfc	heptafluoropropylhydroxymethylene-(+)-camphorate
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HOBt	hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
<i>i</i>	iso (as an alkyl group)
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	milli or multiplet
M	molarity

MCBA	<i>meta</i> -chlorobenzoic acid
MCPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MHz	mega hertz
min	minute(s)
mol	mole(s)
m.p.	melting point
Ms	methanesulfonyl
MTBE	methyl- <i>tert</i> -butyl ether
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -BuLi	<i>n</i> -butyllithium
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	generic nucleophile
Ph	phenyl
PIFA	phenyliodine bis(trifluoroacetate)
ppm	part per million
Pr	propyl
pyr	pyridine
RSM	recovered starting material
RT	room temperature
satd.	saturated
SFC	supercritical fluid chromatography

<i>t</i>	tertiary (as an alkyl group)
t_R	retention time
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
4-Tol	<i>para</i> -methylphenyl
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet
μ	micro
$^{\circ}\text{C}$	degree Celsius
Δ	heat
μ	micro

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Dedication

“Every accomplishment starts with the decision to try.”

-Steve Jobs

Chapter 1: Introduction

1.1 Hypervalency

The Lewis octet rule states that atoms of main group elements tend to combine in such a way that the number of electrons formally assignable to the valence shell of each atom is closest to a noble gas configuration; i.e., it is equal to eight.^[1] However, third-row and heavier elements in groups 15-18 form bonded states in which more than eight electrons are present within their valence shell.^[2] According to a definition introduced by J. I. Musher in 1969,^{[2],[3]} compounds of this sort are described as incorporating hypervalent or polyvalent atoms, because they establish more bonds than anticipated on the basis of the octet rule.

Iodine being the least electronegative and most polarizable of all the common halogens, forms a range of hypervalent compounds, in which it exists in the trivalent, pentavalent, and heptavalent state (oxidation states of +3, +5 and +7, respectively), instead of the anticipated monovalent one. Soon after the discovery of iodine by Bernard Courtois in 1813,^[4] Joseph-Louis Gay-Lussac described iodine trichloride (oxidation state of iodine = +3) and potassium iodate (oxidation state of iodine = +5).^[5]

Of special relevance to the present discussion are hypervalent organoiodine compounds; namely, those in which the iodine atom is bound to at least one carbon ligand.^[6] Familiar examples are the common laboratory reagents, diacetoxyiodobenzene (DIB, **1.1**), iodoxybenzoic acid (IBX, **1.2**), and the Dess-Martin reagent (DMP, **1.3**; Figure 1.1).

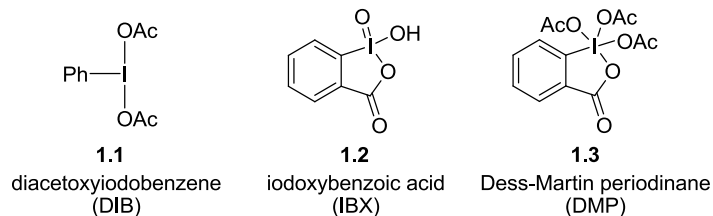


Figure 1.1 Structures of DIB, IBX and DMP

1.2 History of hypervalent organoiodine compounds

The German chemist, Conrad Willgerodt was the first to prepare a hypervalent organoiodine compound. He obtained (dichloroiodo)benzene (PhICl₂) in 1886 by passing excess chlorine gas through a cooled solution of iodobenzene in chloroform.^[7] This was followed by discovery of several other hypervalent iodine compounds like iodosobenzene (1892) and DIB (1892), which will be discussed in further detail in section 1.5.

Several new polyvalent iodine compounds have been developed since the early 1980's, many of which have found very useful synthetic applications.^[8] Efforts in the area continue unabated to this day. Indeed, remarkable advances in the chemistry of hypervalent iodine compounds have been recorded since the beginning of 21st century, on account of their valuable oxidizing properties, environmentally benign nature, and easy commercial availability.^[9]

The generation of hypervalent iodine species *in situ*, by reaction of a substoichiometric amount of an organoiodine compound with oxidants such as MCPBA, peracetic acid, or oxone[®], and their subsequent use in various transformations, has further expanded the application of hypervalent iodine for synthesis of a wide variety of products.^{[9c], [9f]}

1.3 Nomenclature of hypervalent iodine compounds

The Martin-Arduengo N-X-L designation^[10] (N = number of electrons formally assignable to the valence shell of atom X, L = number of ligands) can be used to classify hypervalent species. Furthermore, hypervalent iodine compounds are currently described as iodanes. According to the Martin-Arduengo convention, (dichloriodo)benzene **1.4** is then a *10-I-3* iodane; the Dess-Martin periodinane **1.3**, a *12-I-5* iodane, and IF₇ **1.5**, a *14-I-7* iodane (Figure 1.2).

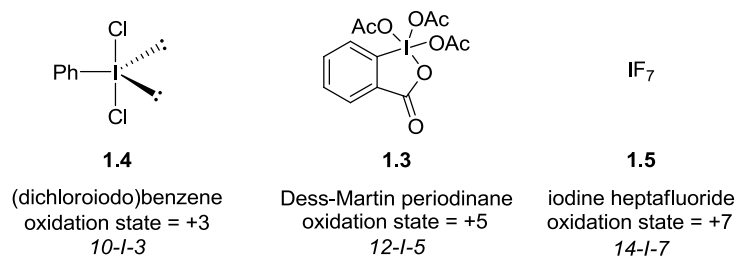


Figure 1.2 Examples of hypervalent iodine compounds

A more commonly employed nomenclature is the IUPAC lambda notation.^[11] An electrostatically neutral compound incorporating an element in a non-standard valence state is designated as being a λ^n species, where n is the number of primary bonds at the iodine atom. For example, PhICl₂ is referred to as a λ^3 -iodane and the Dess-Martin reagent as a λ^5 -iodane. In a λ^3 -iodane, the I atom itself has seven valence electrons and three more electrons are contributed from three ligands, creating a decet structure. Similarly, λ^5 -iodanes have a dodecet structure.

1.4 Structure and bonding in hypervalent iodine

On the basis of molecular orbital considerations, G. C. Pimentel and R. E. Rundle proposed in 1951 that hypervalency is best understood in terms of 3-center, 4-electron (3c-4e) bonding.^[12] To illustrate, a λ^3 -iodane like ArIL₂ **1.6** (L = ligand) has pseudotrigonal bipyramidal geometry. The aryl group forms an ordinary two-electron covalent σ bond with the iodine, and together

with two lone pairs, it resides in the equatorial plane of the molecule. Ligands L occupy apical position, and the L-I-L bond is linear, resulting in a T shape (Figure 1.3). The iodine contributes 2 electrons from one of its doubly occupied 5p orbitals; the ligands, one electron each. This result in formation of three molecular orbitals occupied by 4 electrons shared between three centers. The lowest-energy orbital is bonding; the high-energy one is antibonding, and the one of intermediate energy is nonbonding. The four electrons occupy the bonding and the nonbonding orbital; the latter corresponding to the HOMO.

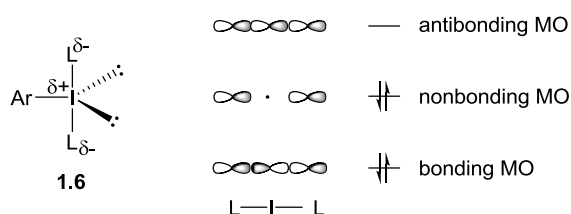


Figure 1.3 Pseudotrigonal bipyramidal structure of ArIL_2 and $3c-4e^-$ orbital diagram

The non-bonding orbital (HOMO) has a node at the central iodine atom and the electron density is concentrated towards the ligands. This result in the development of partial positive charge at the iodine centre, which therefore is electrophilic, while the negative charge is concentrated on the apical heteroatomic ligands. Hence, a hypervalent iodine compound of the type ArIL_2 is best stabilized when the more electronegative atoms at the apical position.^[13]

Hypervalent iodine species like ArIL_4 **1.7** (L = heteroatom) have a roughly octahedral geometry (Figure 1.4). The five groups bound to the iodine atom are arranged in a square pyramidal structure, in which the aryl substituent occupies the apical position and it established a normal covalent bond to the I atom. The ligands occupy basal positions. There are thus two orthogonal $3c-4e^-$ bonds in the basal plane. The remaining lone pair is *trans* to the Ar residue.^[13]

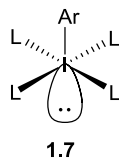


Figure 1.4 Square pyramidal structure of ArIL_4

1.5 General reactivity pattern of hypervalent iodine

The strongly electrophilic character of hypervalent iodine centers, along with the excellent leaving group ability of an aryliodo group, enables a variety of unique reactions. Their chemical properties somewhat resembles to that of heavy metals like Hg(II), Ti (II), Pb (IV). However, hypervalent iodine species are considerably less toxic, enabling the replacement of heavy metals with more environmentally benign reagents.

Examples of some common λ^3 -iodanes appear in Figure 1.5. These are generally used for oxidative dearomatization of electron rich aromatics, oxidation of sulfides, functionalization of alkenes, arylation reactions, and α -functionalization of ketones. These applications are discussed in detail in section 1.7.

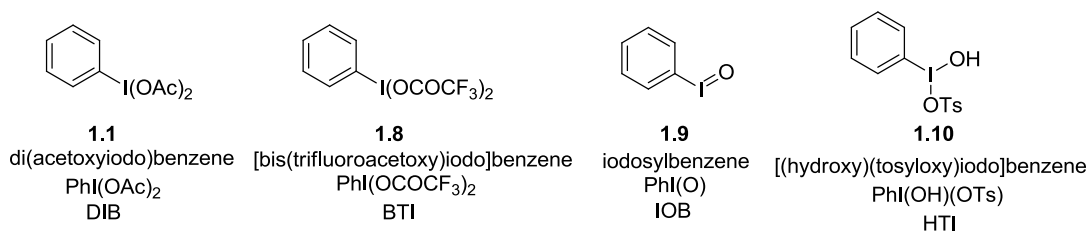


Figure 1.5 Examples of λ^3 -iodanes

Organo- λ^5 -iodanes, especially IBX and DMP (Figure 1.6), have found application as efficient reagents for the oxidation of alcohols to carbonyl compounds. Recently, Wirth and coworkers

have developed a fluorinated analog of IBX, which they called FIBX **1.11**. Due to its increased solubility in organic solvents, it is being used widely for oxidative synthetic transformations.

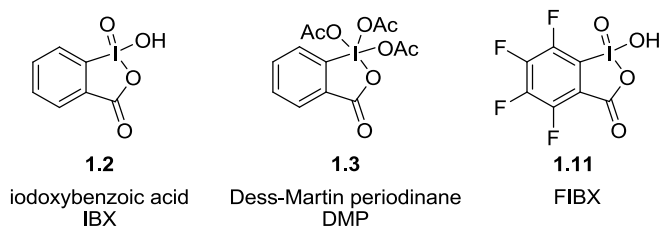


Figure 1.6 Some commonly used organo- λ^5 -iodanes

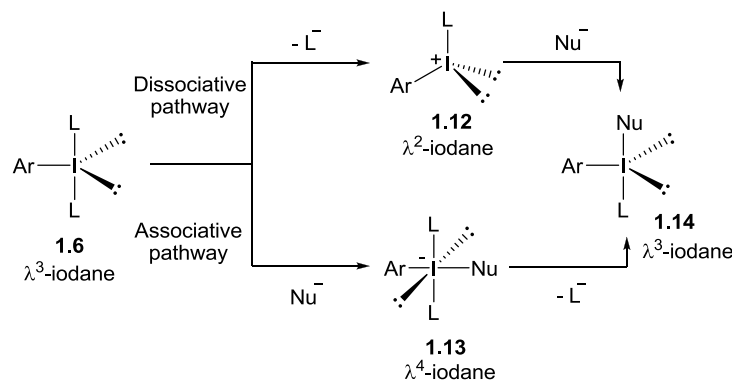
There is no report of an organo- λ^7 -iodane in the literature so far, but inorganic iodine (VII) agents are known, e.g, IF_7 and periodic acids such as H_5IO_6 and HIO_4 . The inorganic periodic acids and metal periodates are used for the oxidative cleavage of glycols, oxidation of sulfides, and other applications. The focus of this thesis is on synthetic transformations mediated by organo- λ^3 -iodanes. Hence, iodine at the oxidation states of +5 and +7 is not discussed further.

1.5.1 Ligand exchange and reductive elimination

Reactions mediated by iodine(III) reagents generally involve nucleophilic ligand exchange followed by reductive elimination of an iodine(I) species. The latter step may take place with ligand coupling. In this respect, the chemistry of hypervalent iodine compounds reflects that of transition metals.

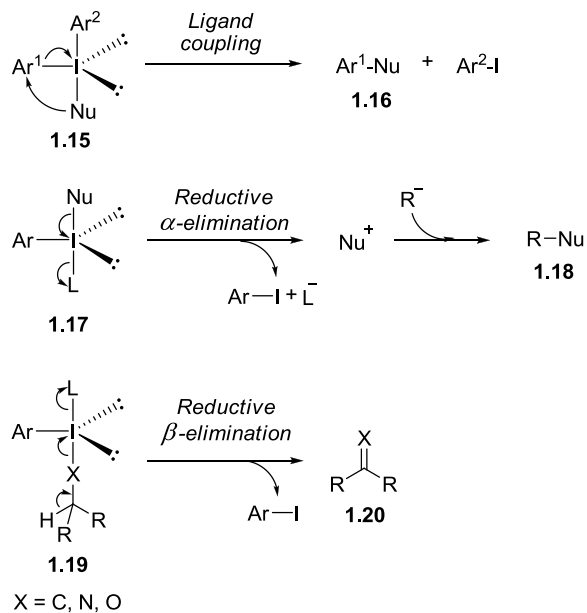
Two mechanistic pathways, associative and dissociative, have been proposed for ligand exchange in λ^3 -iodanes.^{[14],[16]} The dissociative pathway starts with departure of a ligand from **1.6** to form dicoordinated λ^2 -iodane **1.12**, which is trapped by a suitable nucleophile, Nu^- , to provide **1.14** (Scheme 1.1). The associative pathway starts with the addition of the nucleophile to the

iodane **1.6**, leading to the formation of square planar λ^4 -iodane **1.13**. This is followed by dissociation of one of the original ligands from **1.13** to form **1.14**.



Scheme 1.1 Pathways for the ligand exchange reactions of λ^3 -iodanes with nucleophiles Nu^-

Ligand exchange is customarily followed by an energetically favourable reductive elimination of Ar-I. This is due to excellent leaving ability of an Ar-I group (about a million times better than that of triflate ion, OTf^-).^[15] The reductive elimination of Ar-I can occur with or without concomitant ligand coupling. An especially significant mode of ligand coupling leads to the arylation of the incoming nucleophile, an outcome that requires an equatorial and apical placement of Ar^1 and Nu (**1.15** \rightarrow **1.16**; Scheme 1.2).^[16] Reductive elimination without ligand coupling involves fragmentation of the hypervalent iodine complex by either an α - or a β -elimination mechanism. The α -elimination pathway (**1.17** \rightarrow **1.18**; Scheme 1.2) results in the liberation of an electrophilic, possibly cationic, form of one of the ligands. Of special interest is the release of Nu as Nu^+ : an event that achieves reactivity umpolung^[17] of Nu^- to Nu^+ and that can result in the formation of products of nucleophilic capture, fragmentation, or rearrangement.^[18] The β -elimination mechanism typically results in formation of π bonds (**1.19** \rightarrow **1.20**; Scheme 1.2).



Scheme 1.2 Types of reductive elimination of λ^3 -iodanes

1.6 Introduction to chiral hypervalent iodine complexes

The widespread use of hypervalent iodine in organic synthesis has enabled the replacement of use of transition metal complexes with more environmentally benign reagents. In this context, increasing demand for the enantiopure compounds has led to remarkable advances in the field of chiral hypervalent iodine reagents, especially λ^3 -iodanes of the type ArIL_2 .^[19]

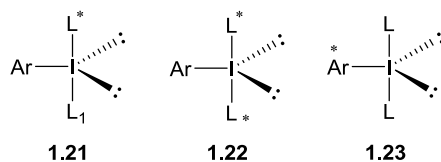
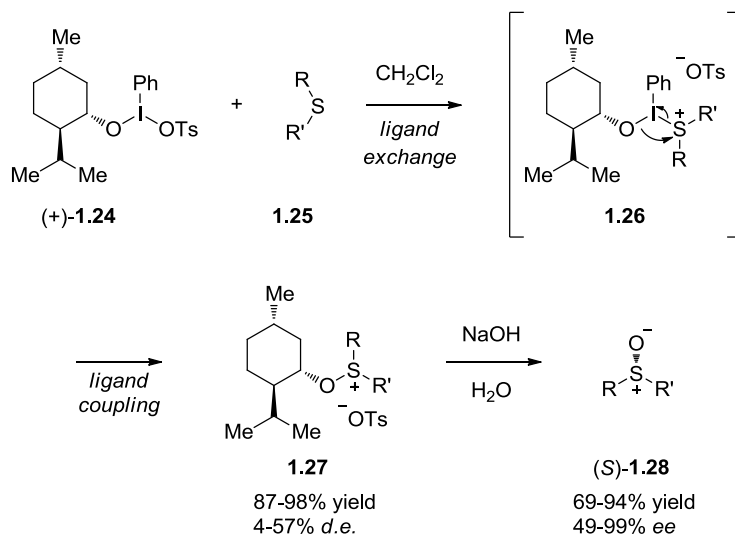


Figure 1.7 Chiral hypervalent iodine reagents of ArIL_2 type

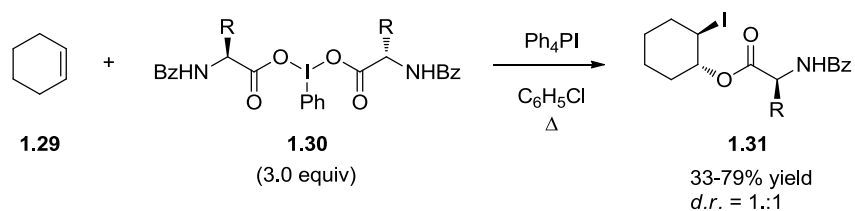
Hypervalent iodine reagents bearing chiral ligands (cf. **1.21**) are used in stoichiometric amounts for oxidation of sulfides **1.25** to sulfoxides **1.27** (Scheme 1.3). Hypervalent iodine derived from (+)-menthol **1.24** reacted with sulfides generating mixture of diastereomers **1.27**

which upon separation by crystallization followed by basic hydrolysis, afforded **1.28** with excellent optical purity.^[20] Other types of hypervalent iodine (cf. **1.22**) used for same transformation (**1.25** \rightarrow **1.28**) is discussed in detail in Section 1.7.



Scheme 1.3 Oxidation of sulphides to sulfoxides using chiral **1.24**

Hypervalent iodine reagent **1.30** (cf. **1.22**) was used by Zhdankin and co-workers for iodocarboxylation reaction of cyclohexene **1.29** (Scheme 1.4). This process yielded racemic ester **1.30** as a mixture of 1:1 diastereomers in moderate to good yields.^[21]



Scheme 1.4 Iodocarboxylation of cyclohexene using **1.30**

More interesting are species like **1.23**, wherein the chiral moiety is present as a substituent of aryl group. A noteworthy feature of these compounds is that they can be used in catalytic

amount, wherein a substoichiometric or catalytic quantity of the chiral aryl iodide **1.32** is converted to the hypervalent state *in situ* with oxidants such as MCPBA, peracetic acid, DMDO, Oxone[®], and the like. The resulting **1.23** oxidizes the substrate into the product, in the process becoming reduced back to aryl iodide **1.32**. The generated **1.32** is reoxidized to **1.23**, and the cycle goes on (Figure 1.8).^[22]

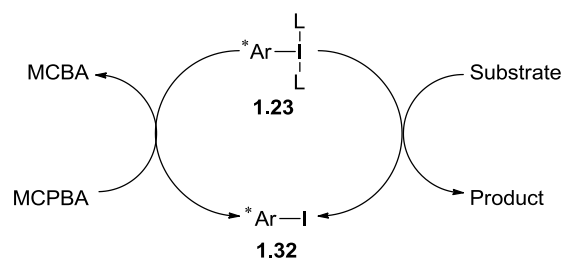


Figure 1.8 Catalytic cycle for generation of hypervalent iodine

The use of chiral hypervalent iodine complexes for asymmetric transformations has emerged as an active area of research, and several comprehensive reviews of the field have appeared in recent times.^{[9d-f],[23]} Important enantioselective reactions promoted by these reagents are highlighted below.

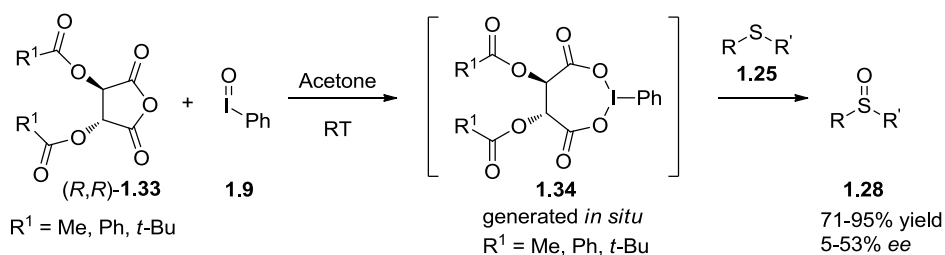
1.7 Applications of chiral hypervalent iodine

Chiral hypervalent iodine reagents are known to perform a number of enantioselective transformations like oxidation of sulfides to sulfoxides, arylation of enolates, α -functionalization of ketones, functionalization of alkenes, and oxidative dearomatization reactions. These are discussed in detail below.

1.7.1 Oxidation of sulfides to sulfoxides

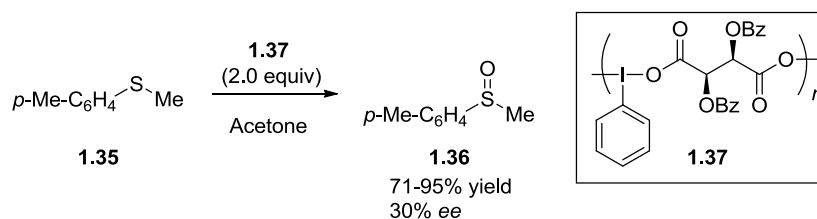
The first chiral hypervalent iodine complex, diphenyliodonium tartrate, was described by Pribram^[24] in 1907. In 1986, Imamoto *et al.* reported the enantioselective oxidation of sulfides

1.25 to sulfoxides **1.28** with a related reagent presumed to possess a seven membered cyclic structure **1.34**. This material was prepared by reaction of iodosobenzene **1.9** with tartaric anhydrides **1.33** (Scheme 1.5).^[25] Scalemic sulfoxides (5-53% *ee*) **1.28** were obtained in moderate to excellent yield.



Scheme 1.5 Oxidation of sulfides to sulfoxides using *in situ* generated **1.34**

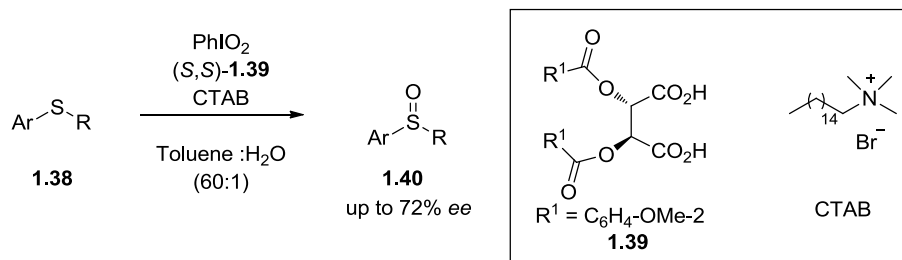
Subsequently, Koser *et al.* obtained hypervalent iodine complex **1.34** by treating diacetoxyiodobenzene (DIB) with dibenzoyl-L-tartaric acid.^[26] An exhaustive NMR study revealed the compound to exist in polymeric form **1.37** (Scheme 1.6). The enantioselective oxidation of sulfides **1.35** to sulfoxides **1.36** with the new reagent **1.37** proceeded in yields and selectivities similar to those observed by Imamoto, suggesting that the reagent employed by the latter was also polymeric in nature.



Scheme 1.6 Asymmetric oxidation of sulfides to sulfoxides using **1.37**

In 1999, Kita *et al.* described an asymmetric oxidation of sulfides **1.38** to sulfoxides **1.40** with iodoxybenzene (0.5 equiv) in the presence of 10 mol% of (*S,S*)-2-methoxydibenzoyl tartaric

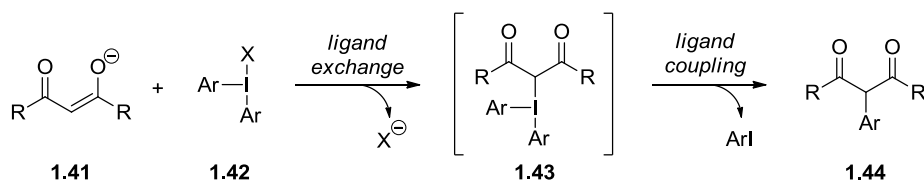
acid **1.39** and 0.5 equiv of cetyltrimethylammonium bromide (CTAB) as a phase transfer agent (Scheme 1.7). Sulfoxides of up to 72% *ee* were thus obtained.^[27]



Scheme 1.7 Catalytic asymmetric oxidation of sulfides to sulfoxides

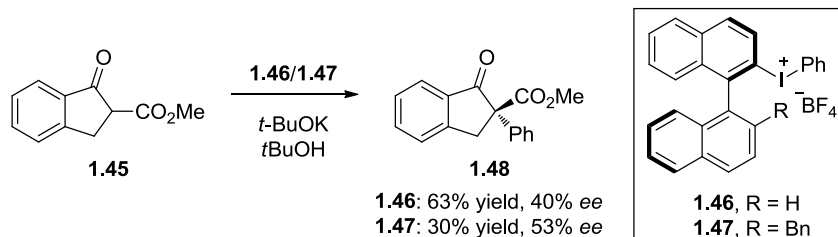
1.7.2 α -arylation of ketones

Diaryliodonium species of type **1.42** are known to arylate carbonyl enolates **1.41**, presumably by the mechanism outlined in Scheme 1.8.^[28] To illustrate, compounds containing active methylene group or corresponding carbanions **1.41** undergoes ligand exchange with **1.42** followed by ligand coupling to yield **1.44**.



Scheme 1.8 General mechanism for aryl transfer to carbonyl enolates

Asymmetric variants of this useful transformation have been pioneered by Ochiai and coworkers, who in 1999 described the phenylation of compound **1.45** with chiral, BINAP-based diaryliodonium salts **1.46-1.47**.^[29] Product **1.48** was obtained in moderate yield and *ee* (Scheme 1.9).



Scheme 1.9 Phenylation of cyclic β -ketoesters

Curiously, very little additional work has been published in this area. For instance, chiral diaryliodonium salts like **1.49-1.52**^{[30],[31]} do not appear to have been tested in this reaction (Figure 1.9).

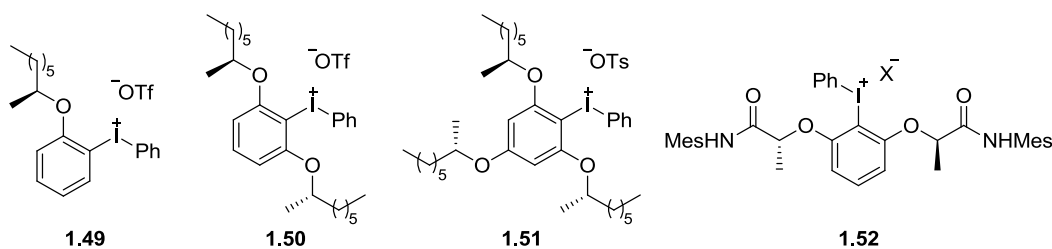
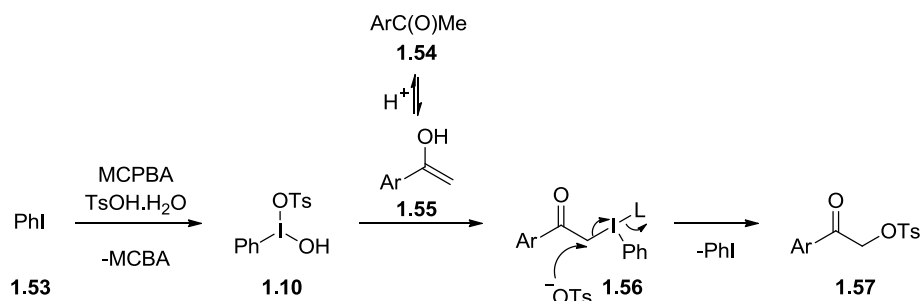


Figure 1.9 Some chiral diaryliodonium salts

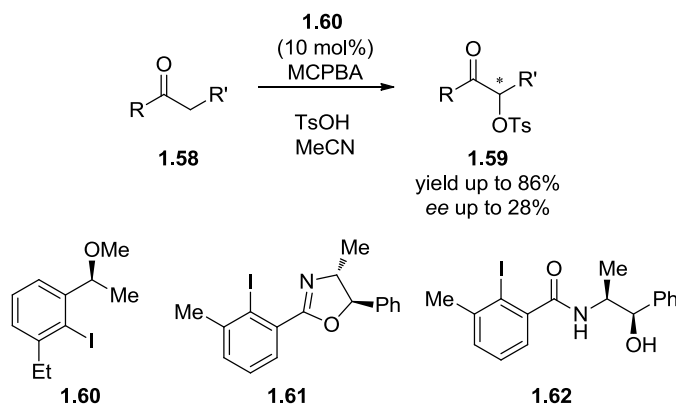
1.7.3 α -functionalization of ketones

The α -oxygenation of carbonyl compounds provides valuable intermediates for the synthesis of complex molecules. This transformation can be achieved by reaction of the enol derivative **1.55** of a carbonyl compound **1.54** with iodine(III) species such as hydroxy(tosyloxy)iodobenzene (Koser reagent, **1.10**)^[32] and related oxidants,^[33] which can be generated *in situ* by MCPBA oxidation of iodobenzene **1.53** (Scheme 1.10).^{[22],[34b]} Mechanistically, the reaction of **1.55** with *in situ* generated **1.10** is believed to produce **1.56** which is subsequently attacked by tosylate in S_N2 fashion to produce α -tosylated ketone **1.57**.^{[34b],[35]}



Scheme 1.10 General mechanism for α -tosyloxylation of ketone using Koser reagent **1.10**

On the basis of the foregoing, Wirth developed the first enantioselective variant of α -tosyloxylation of ketones through *in situ* MCPBA oxidation of chiral iodide **1.60** (Scheme 1.11).^[34] Products **1.59** were obtained in good yield but poor *ee*. Enantioselectivities remained modest when oxazoline **1.61**^[35] or amide **1.62**^[36] were employed in lieu of **1.60**.

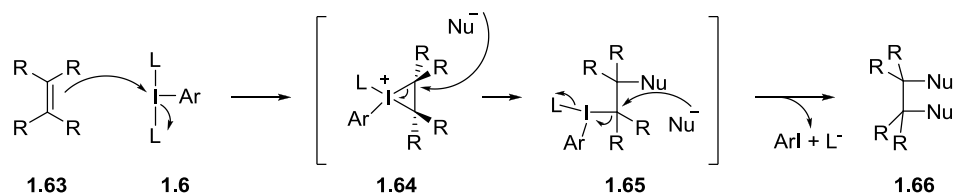


Scheme 1.11 Asymmetric tosyloxylation of ketones

1.7.4 Functionalization of alkenes

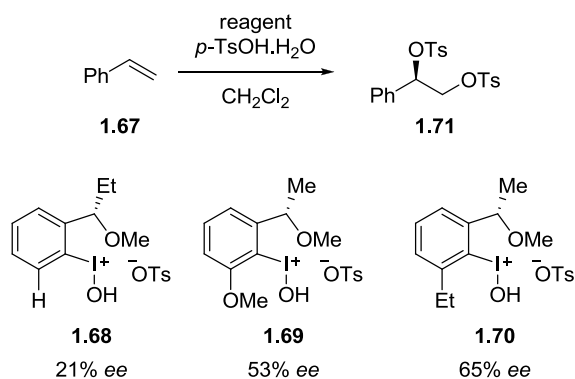
Many iodine (III) complexes undergo electrophilic addition to alkenes according to the general mechanism outlined in Scheme 1.12.^{[19],[38]} Hypervalent iodine (III) **1.6** adds to the olefinic bond **1.63** to provide the presumed intermediate **1.64**. Subsequent S_N2 displacement of **1.64** by desired nucleophile affords **1.65** which undergoes another nucleophilic displacement to

afford product **1.66**. Unlike α -arylation and oxidation of ketones, this transformation has been studied extensively, in that it provides access to a diversity of useful compounds such as diols, diamines, lactones and various rearranged products.



Scheme 1.12 General mechanism of difunctionalization of alkenes using hypervalent iodine

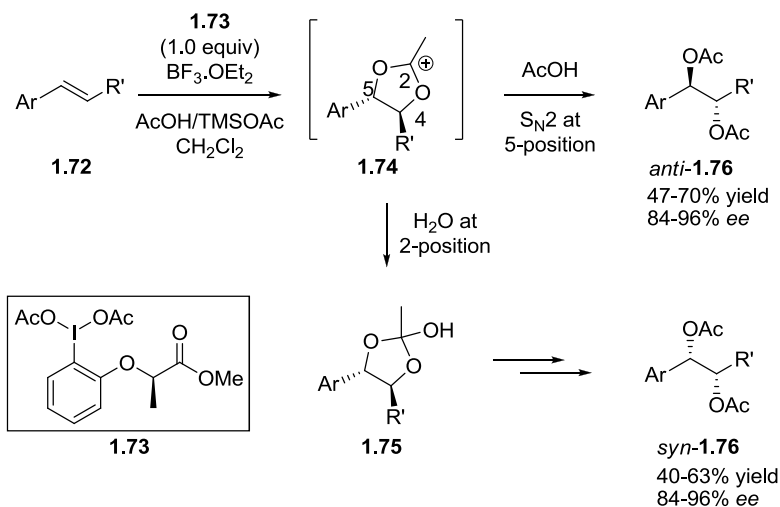
Pioneering efforts by Wirth *et al.* on the enantioselective tosyloxylation of styrene **1.67** relied upon chiral Koser-type reagents **1.68-1.70** (Scheme 1.13). The extent of enantioinduction improved from 21% to 65% *ee* by changing functionality in hypervalent iodine from H (**1.68**)^[37] to OMe (**1.69**)^[38] to Et (**1.70**).^[39]



Scheme 1.13 Tosyloxylation of styrene promoted by **1.68**, **1.69** and **1.70**

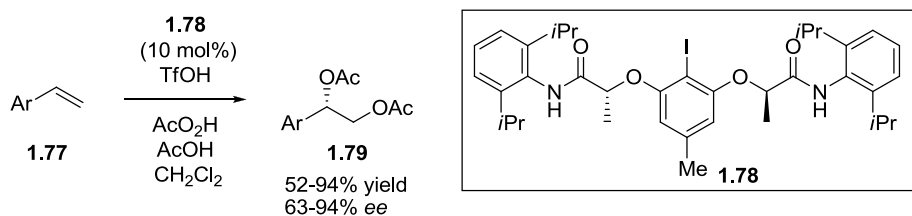
Fujita *et al.* reported an interesting variant of the above transformation that involves the reaction of alkenes **1.72** with chiral hypervalent iodine agent **1.73**, acetic acid and trimethylsilyl acetate. This results in a Prévost-Woodward reaction: depending on whether the presumed 1,3-

dioxolan-2-yl cation intermediate **1.74** is generated in the presence of H₂O or in an anhydrous medium, either the *syn*- or the *anti*- diacetoxylation product is obtained (Scheme 1.14).^[40]



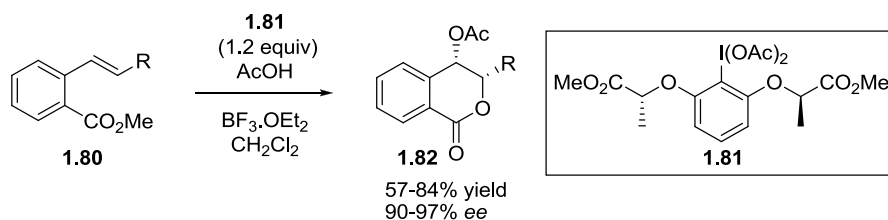
Scheme 1.14 *Syn*- and *anti*-acetyloxylation of alkenes promoted by hypervalent iodine **1.73**

A very recent report on the diacetyloxylation of alkenes by Muñiz et al., describes the reaction of alkenes **1.77** with lactic acid derived C₂ symmetric iodoarene **1.78** (10 mol%) and peracetic acid (2 equiv) to provide **1.79** in moderate to high enantioselectivity (63-94%) and yield (52-94%) (Scheme 1.15).^[41]



Scheme 1.15 Acetyloxylation of alkenes **1.77**

An intramolecular variant of the above reactions is the Fujita oxylactonization of *ortho*-alkenyl benzoate **1.80** mediated by iodine(III) species **1.81** (Scheme 1.16).^[42] The result is the formation of 4-oxyisochroman-1-ones **1.82** with two *cis* substituents.



Scheme 1.16 Oxylactonization of *ortho*-alkenyl benzoate

The same group subsequently disclosed a catalytic version of the process that relies on the treatment of the alkene with 10 mol% of chiral iodoarene version of **1.81**, MCPBA (1.5 equiv) and trifluoroacetic acid, leading to trifluoroacetoxy lactones in high yield (up to 80%) and excellent enantioselectivity (up to 96%).^[43] This methodology forms the centerpiece of the synthesis of 4-hydroxymellein **1.83** and monocerin **1.84** (Figure 1.10).^[44]

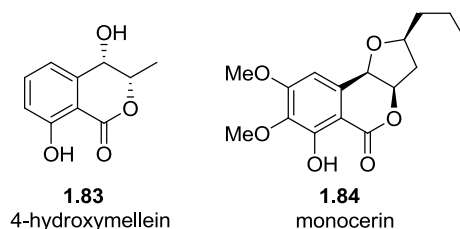
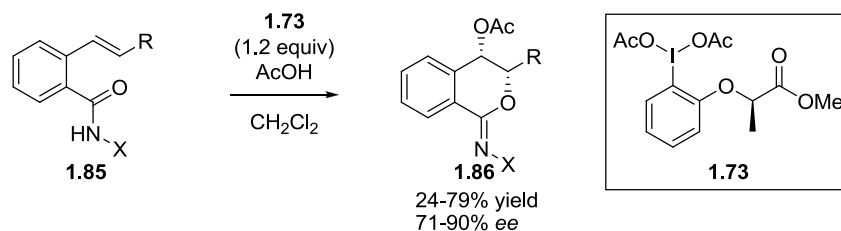


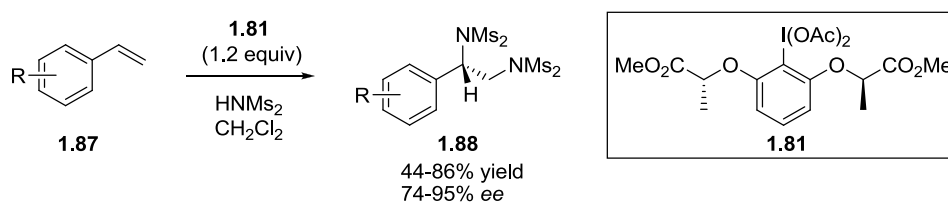
Figure 1.10 Structures of 4-hydroxymellein and monocerin

Recently, Fujita et al. reported similar reaction including oxidation of *ortho*-alkenylbenzamide **1.85** using chiral hypervalent iodine **1.73** to provide isochroman-1-imine products **1.86** with moderate yields (24-79%) and high enantioselectivity (71-90%; Scheme 1.17).^[45]



Scheme 1.17 Oxidation of *ortho*-alkenylbenzamide **1.85**

Muñiz and coworkers demonstrated that hypervalent iodine reagent **1.81** can be used to effect the enantioselective diamination of alkenes **1.87** with mesylimide, providing compounds **1.88** in high yield and enantioselectivity (Scheme 1.18).^[46]



Scheme 1.18 Intermolecular diamination of alkenes mediated by hypervalent iodine **1.81**

The BINAP-based reagent **1.89** was not as efficient in this reaction, and it yielded product **1.88** only with 32% ee (Figure 1.11).^[47]

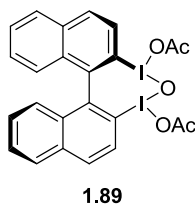
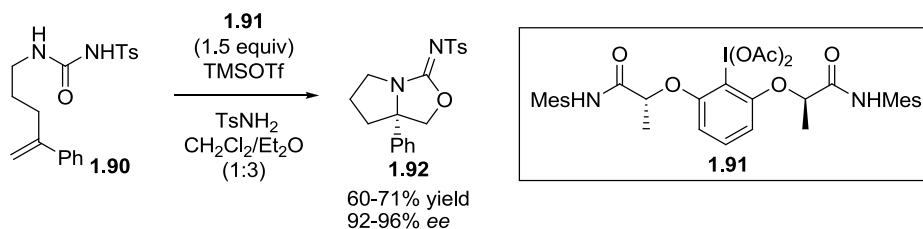


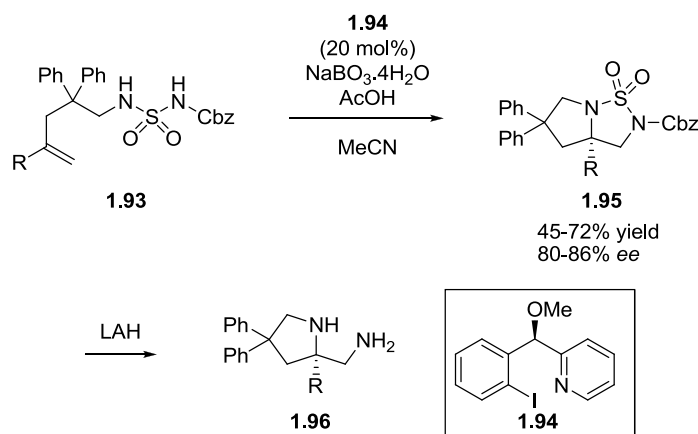
Figure 1.11 Structure of hypervalent iodine **1.89**

Wirth and coworkers achieved an asymmetric oxyamination of alkenes in the form of the cyclization of *N*-sulfonyl urea **1.90** with reagent **1.91** (Scheme 1.19).^[48]



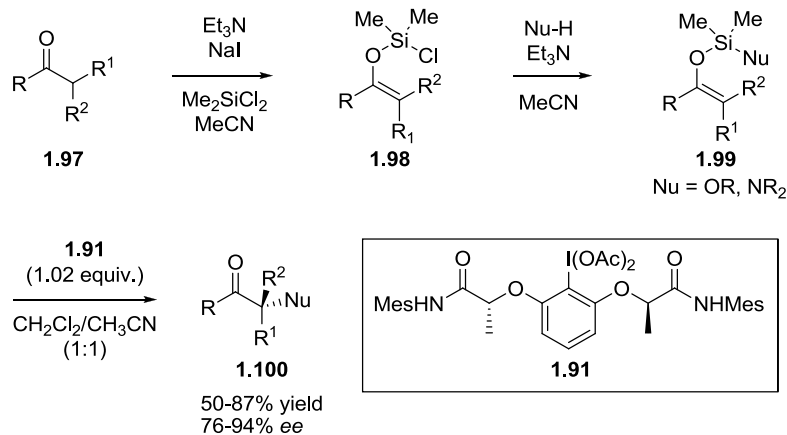
Scheme 1.19 Stereoselective oxyamination of alkenes

More recently, these researchers devised an analogous vicinal diamination technique that affords good yields (45-72%) and selectivities (80-86% *ee*; Scheme 1.20).^[49]



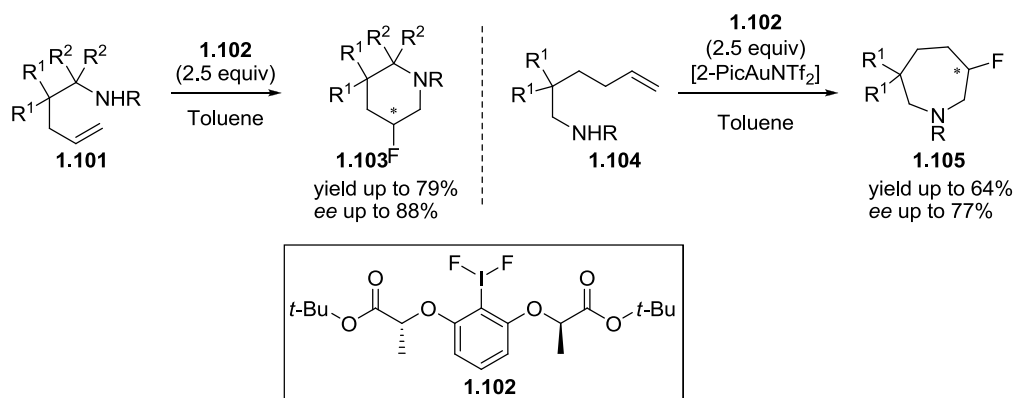
Scheme 1.20 Vicinal diamination of alkenes **1.93**

The same authors elaborated a novel strategy for asymmetric α -heterofunctionalization of ketones. The process involves the condensation of an amine or an alcohol with the chlorosilyl enol ether derivative **1.98** of a ketone **1.97**, followed by reaction of the resulting **1.99** (Nu = O-R or NH-R) with reagent **1.91** (Scheme 1.21).^[50] Products **1.100** are thus obtained in high yields and enantioselectivities.



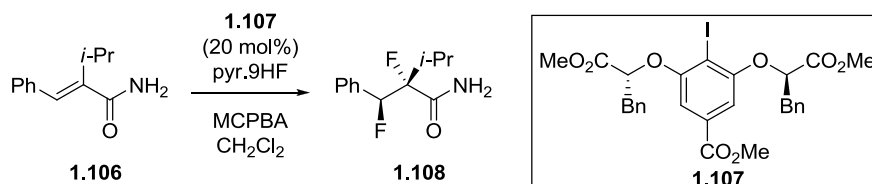
Scheme 1.21 Reaction of silyl enol ethers with tethered nitrogen and oxygen

Nevado et al. developed an intramolecular aminofluorination of alkenes **1.101** promoted by chiral difluoroiodane **1.102** (Scheme 1.22).^[51] The reaction proceeds regioselectively to furnish exclusively products of 6-*endo* cyclization, **1.103**. Moreover, this methodology provided an access to 3-fluorinated azepanes **1.105**. Addition of catalytic amount of [2-PicAuNTf₂] was necessary to facilitate the activation of double bond; otherwise no conversion of **1.104** was observed even after prolonged reaction times (Scheme 1.22).



Scheme 1.22 Aminofluorination of alkenes mediated by chiral difluoroiodonium complex **1.102**

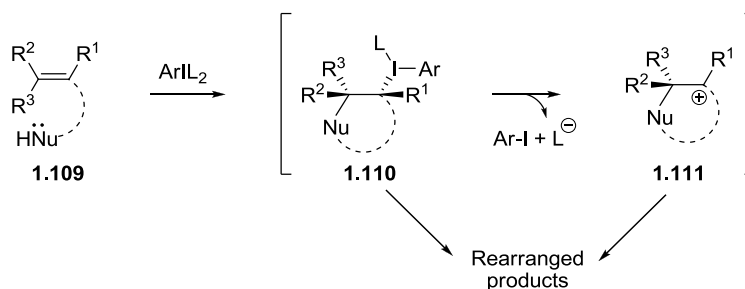
Jacobsen and coworkers have devised an enantioselective alkene difluorination mediated by chiral iodide **1.107** (Scheme 1.23).^[52] The reaction employs a nucleophilic fluoride source (pyr.9HF) with a sub-stoichiometric amount of **1.107** and MCPBA as the oxidant. Vicinal difluoride **1.108** was formed with moderate yield and excellent enantioselectivity.



Scheme 1.23 Vicinal difluorination of alkene **1.106**

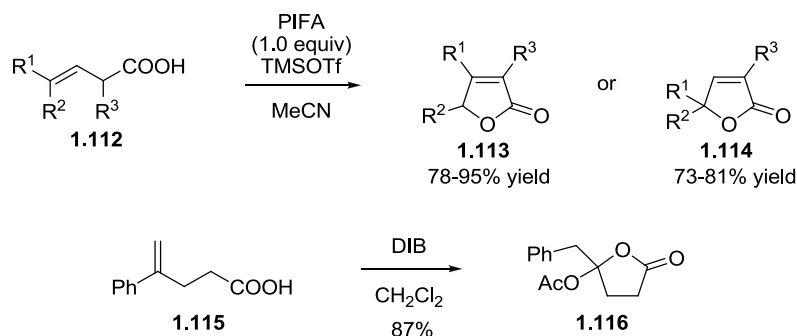
1.7.5 Rearrangement

The ability of hypervalent iodine to behave as an electrophile and then a good leaving group enables the generation of carbocationic intermediates **1.111** (Scheme 1.24). Either **1.110** or **1.111** can then give rise to rearranged products.



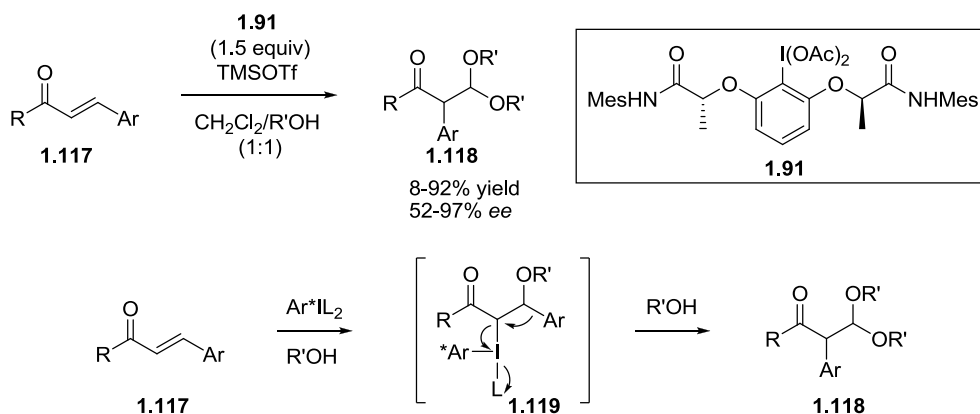
Scheme 1.24 Formation of rearranged products mediated by hypervalent iodine

Noteworthy examples of rearrangement have been described by Wirth et al. For instance, the action of PIFA upon **1.112** produces **1.113** or **1.114** (Scheme 1.25),^[53] while reaction of DIB with **1.115** leads to lactones **1.116** (Scheme 1.26).^[54]



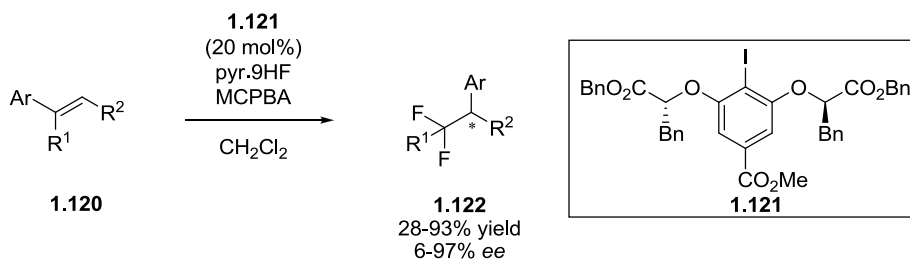
Scheme 1.25 Oxidative rearrangement of alkene **1.112** and **1.115**

Hypervalent iodine reagent **1.91** in conjunction with TMSOTf was found to convert enones **1.117** into enantioenriched ketoacetals **1.118**^[55] arguably by the mechanism delineated in Scheme 1.26.



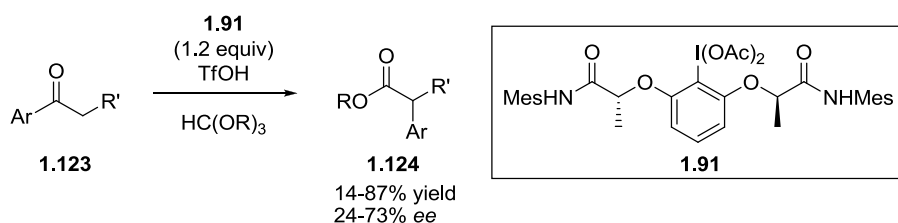
Scheme 1.26 Mechanism of rearrangement mediated by hypervalent iodine yielding ketoacetals

Jacobsen and coworkers devised a variant of the above reaction that converts enones **1.120** into difluorides **1.122** (Scheme 1.27).^[56]



Scheme 1.27 Oxidative rearrangement of **1.120** to generate difluorinated product **1.122**

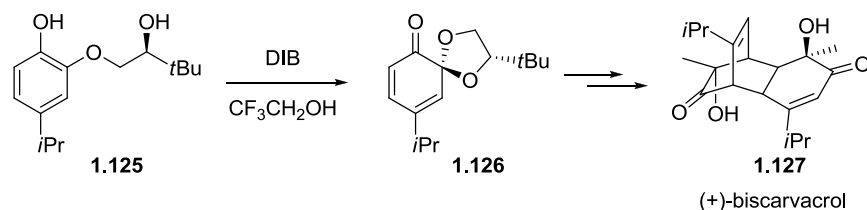
In a like vein, the reaction of aryl ketones **1.123** with **1.91** in the presence of triflic acid and triethyl orthoformate leads to enantioenriched esters **1.124** (Scheme 1.28).^[57]



Scheme 1.28 Rearrangement of **1.123** to **1.124** mediated by hypervalent iodine **1.91**

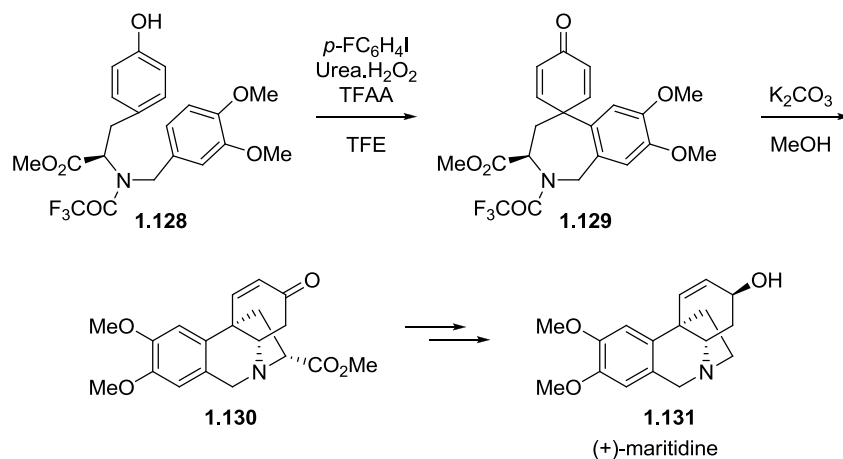
1.7.6 Dearomatization reactions

Hypervalent iodine reagents efficiently promote a range of oxidative dearomatization reactions that have found use in the total synthesis of various natural products.^[58] Many such reactions are intramolecular. For instance, Quideau employed a DIB-mediated oxidative cyclization of compound **1.125** to ketal **1.126** as a key step of the synthesis of (+)-biscarvacrol, **1.127** (Scheme 1.29).^[59]



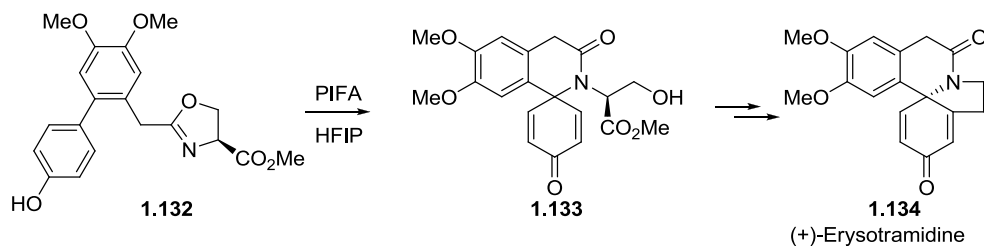
Scheme 1.29 Total synthesis of (+)-biscarvacrol employing spiroketalization of **1.125**

While the above reaction created a new C-O bond, an oxidative C-C bond formation was key to a synthesis of (+)-maritidine, **1.131**, by Kita and coworkers. Thus, exposure of phenol **1.128** to 10 mol% of 4-fluoro-iodobenzene and urea*H₂O₂ as the oxidant produced dienone **1.129**, which was then elaborated to the target **1.131** (Scheme 1.30).^[60]



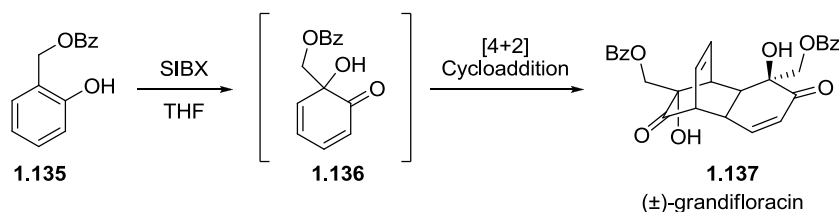
Scheme 1.30 Formal synthesis of (+)-maritidine employing oxidative dearomatization with concomitant C-C bond formation

The oxidative dearomatization of a phenol with concomitant C-N bond formation has been employed extensively by Ciufolini and collaborators in the total synthesis of several natural products.^[61] A recent development in this area is the synthesis of (+)-Erysotramidine through an oxidative cyclization of phenolic oxazoline **1.132** with PIFA (Scheme 1.31).^[62]



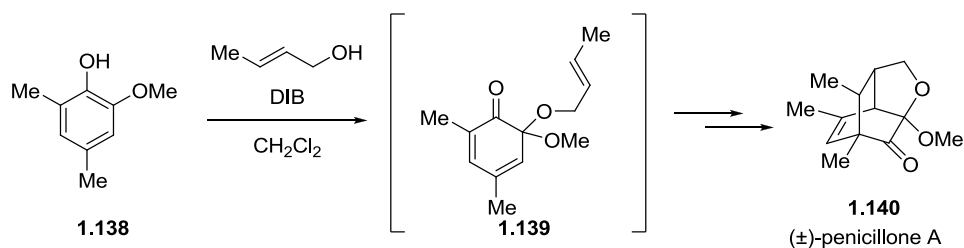
Scheme 1.31 Total synthesis of (+)-Erysotramidine employing oxidative cyclization of phenolic oxazolines

Noteworthy among bimolecular oxidative dearomatization processes are the conversion of phenolic substrates into *ortho*- and *para*-quinols,^[63] or *para*-amidodienones,^[64] all of which are useful educts in natural products synthesis. For instance, the Quideau synthesis of (±)-grandifloracin, **1.137**, starts with the formation of *ortho*-quinol **1.136** by reaction of **1.135** with SIBX (Scheme 1.33).^{[63e],[63f]} SIBX is a nonexplosive formulation of IBX composed of a mixture of benzoic acid (22%), isophthalic acid (29%) and IBX itself (49%).^[65] Compound **1.136** undergoes spontaneous Diels Alder dimerization *in situ* to generate the natural product.



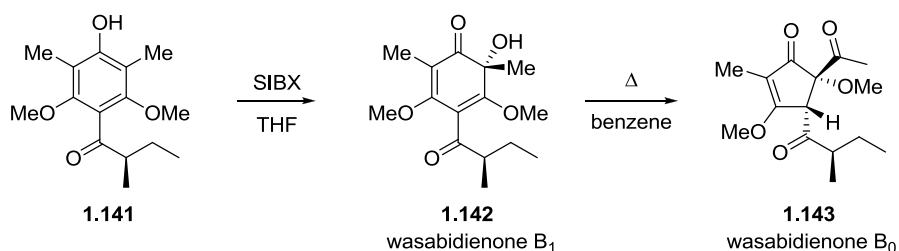
Scheme 1.32 Total synthesis of (±)-grandifloracin mediated by SIBX

A synthesis of (±)-penicillone A **1.140** by Liao co-workers relies instead on an intramolecular Diels-Alder reaction of an *ortho*-quinol ether. Thus, the action of DIB upon phenol **1.138** in the presence of crotyl alcohol produced species **1.139**, which spontaneously cyclized *in situ* to the desired **1.140** (Scheme 1.33).^[66]



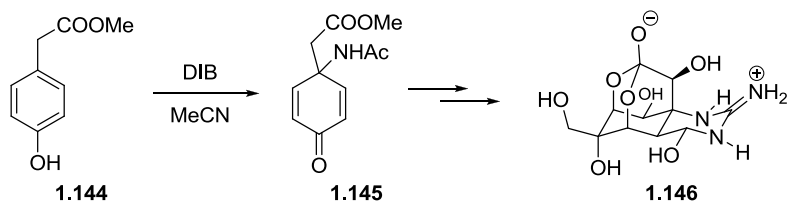
Scheme 1.33 Total synthesis of (±)-penicillone A employing IMDA reaction of *ortho*-quinols

Quideau and co-workers synthesized wasabidienone B₁, **1.142**, via a hydroxylyative dearomatization of phenol **1.141** with SIBX (Scheme 1.35). Wasabidienone B₀, **1.143**, emerged upon heating **1.142** in refluxing benzene.^[63a]



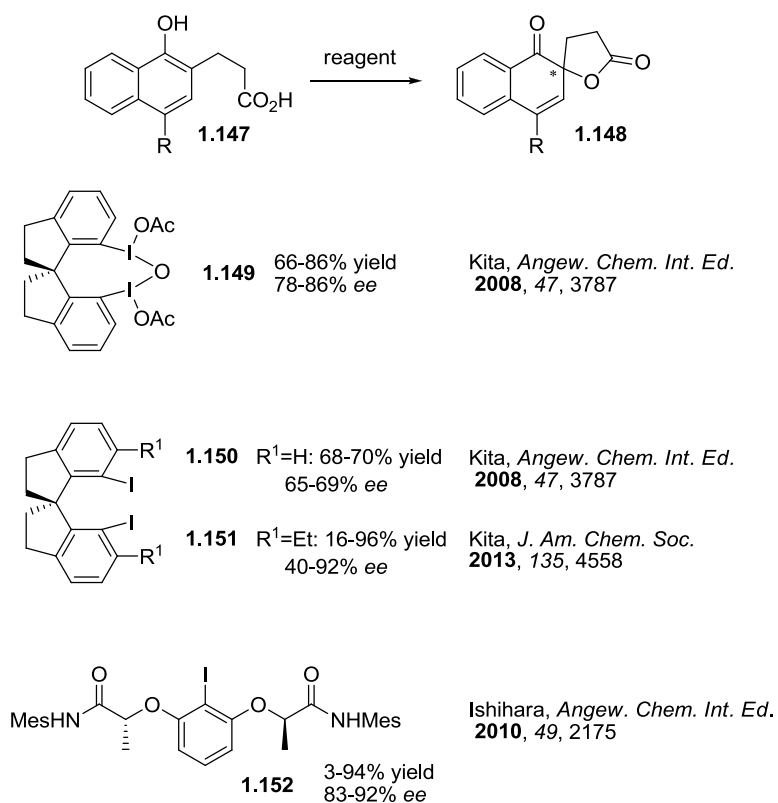
Scheme 1.34 Total synthesis of wasabidienone B₁ and B₀ employing dearomatization of phenol

Our group recently described a formal total synthesis of (±)-tetrodotoxin, **1.146**, from *para*-amidodienone **1.145** (Scheme 1.35),^[67] which is easily prepared by oxidation of phenol **1.144** with DIB in MeCN.^[68]



Scheme 1.35 Formal total synthesis of (±)-tetrodotoxin employing bimolecular oxidative dearomatization approach

Asymmetric variants of the above reactions began to appear in the literature in the late 2000's. In 2008, Kita et al. disclosed the enantioselective *ortho*-spirocyclization of 1-naphtholic acids **1.147** to lactones **1.148** with chiral iodane **1.149** (Scheme 1.36).^[69] The same reaction could be carried out using only 15 mol% of aryl iodide **1.150** and 1.3 equiv of MCPBA as the oxidant to provide product **1.148** in moderate yield and enantioselectivity. In 2010, Ishihara et al. described a more efficient catalyst in the form of C₂ symmetric iodide **1.152**. The spirocyclization of substrates **1.147** could thus be achieved in higher yields and *ee*'s in the presence of only 10 mol% of **1.152** (Scheme 1.36).^[70] Recently, Kita and coworkers evaluated new spirobiindane iodides **1.151** for asymmetric *ortho*-lactonization of **1.147** and they found that enantioselectivity of **1.148** was improved by presence of *ortho* substituents in **1.150**. Indeed, **1.151** having ethyl substitution at *ortho* position (ethyl) proved to be superior than its unsubstituted analog in terms of yield and *ee* of **1.148**.^[71]



Scheme 1.36 Enantioselective dearomatization of naphthols to form *ortho*-substituted γ -lactones

Other chiral iodides such as **1.153**^[72] and **1.154**^[73] were also evaluated for *ortho*-spirocyclization of **1.147**. Low to moderate yields (32-65%) and *ee*'s (18-67%) of the product were obtained which meant that these chiral aryl iodides were no better than **1.151** or even **1.149** (Figure 1.12).

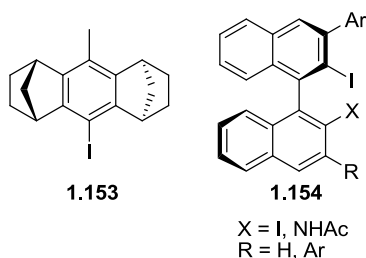
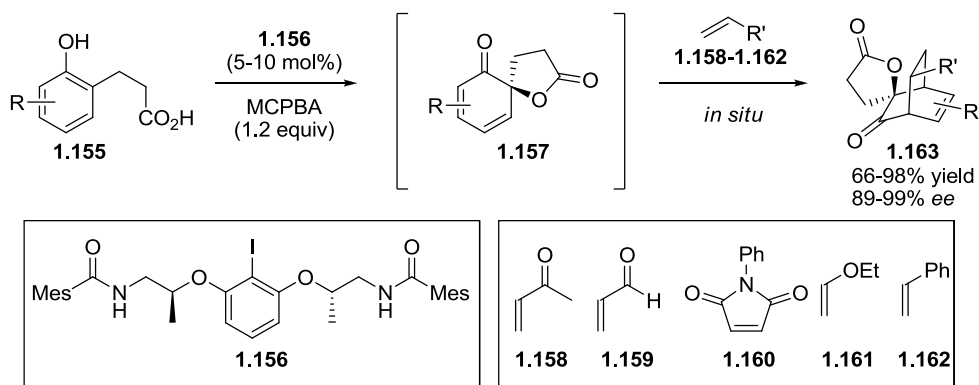


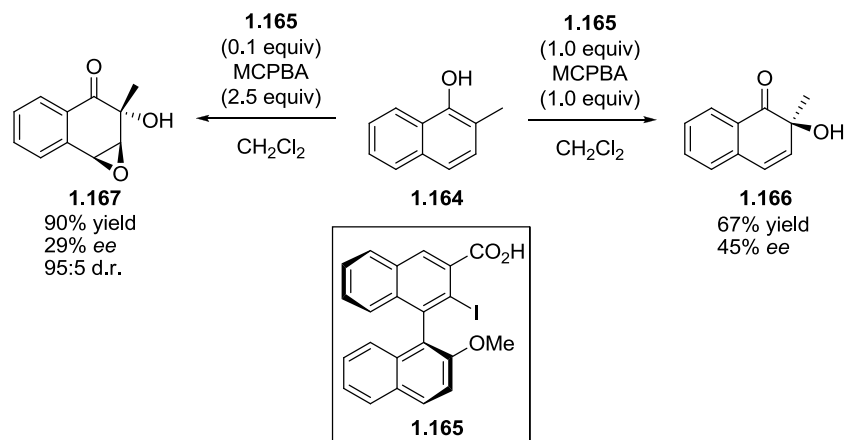
Figure 1.12 Structures of iodoarene **1.153** and **1.154**

However, in 2013 Ishihara discovered that iodide **1.156** performs even more efficiently than the structurally related **1.152**.^[74] This catalyst appears to be especially competent for the enantioselective *ortho*-lactonization of phenols **1.155** to reactive cyclohexadienones **1.157**. The products **1.157** can be intercepted *in situ* with appropriate dienophiles **1.158-1.162**, leading to tricyclic products **1.163** (Scheme 1.37).



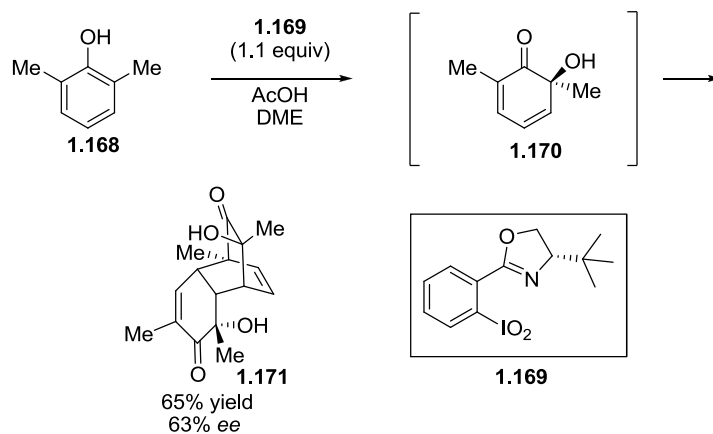
Scheme 1.37 Enantioselective oxidative dearomatization of phenols and subsequent Diels-Alder reaction with dienophiles

The enantioselective oxidative dearomatization in the bimolecular mode was disclosed in 2009 by Quideau and co-workers. They demonstrated the asymmetric hydroxylative dearomatization of 2-methyl-1-naphthol **1.164** with a reagent generated *in situ* by MCPBA oxidation of aryl iodide **1.165** (Scheme 1.38).^[75] *Ortho*-quinols **1.166** was formed with moderate yields and *ee*. Addition of 2.5 equivalents of MCPBA resulted in the further oxidation of **1.166** to generate **1.167** with low *ee* (Scheme 1.38).



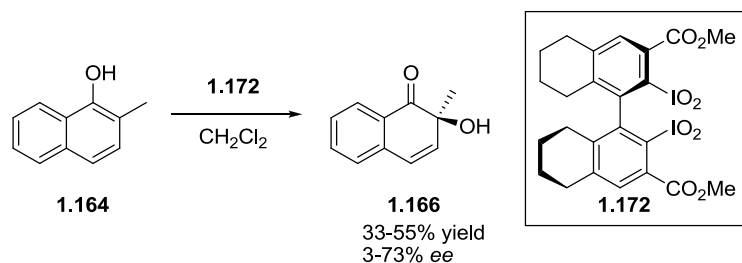
Scheme 1.38 Enantioselective hydroxylation of naphthols

Iodoxy compounds (λ^5 -iodanes) have also been employed in this type of transformation. Birman et al. described an early example in 2009, in the guise of the hydroxylation dearomatization of phenols with chiral iodane **1.169** (Scheme 1.39).^[76] No external dienophile was used to intercept the primary products **1.170**, which therefore dimerized to **1.171**.



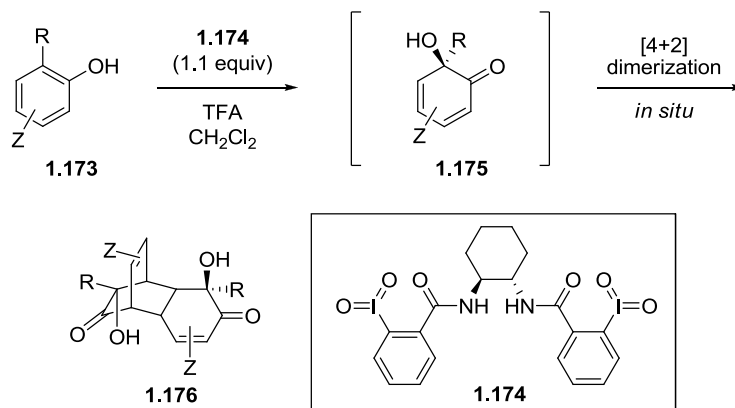
Scheme 1.39 Hydroxylation dearomatization of 2,6-dimethylphenol

More recently, Quideau recorded moderate yields (33-55%) and variable *ee*'s (3-73%) in hydroxylation dearomatizations promoted by λ^5 -iodane **1.172** (Scheme 1.40).^[77]



Scheme 1.40 Enantioselective hydroxylative dearomatization of naphthols

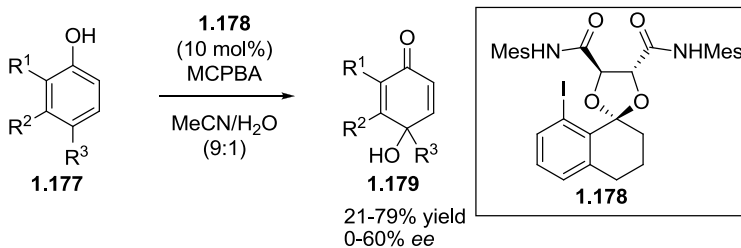
Whereas products **1.166** derived from 1-naphthols were stable, *ortho*-quinols **1.175** obtained from 2-alkyl phenols **1.173** again underwent Diels-Alder dimerization to compounds **1.176** (Scheme 1.41). This propensity was nicely harnessed in a noteworthy synthesis of bis(sesquiterpene) (–)-bacchopetiolone.^[78] Thus, hydroxylative dearomatization of phenol **1.173** mediated by λ^5 -iodane **1.174** triggered a highly stereoselective dimerization to tricyclic adduct **1.176**, which was elaborated to the target compound as outlined in Scheme 1.41.



Scheme 1.41 Hydroxylative phenol dearomatization/[4+2] dimerization cascade

The enantioselective *para*-oxidative dearomatization of phenolic substrates constitutes a more difficult goal, for which a good solution is still lacking. An important first step in this direction is apparent in the work of Harned et al., who devised a weakly enantioselective

oxidation of phenols **1.177** to *para*-quinols **1.179** with the hypervalent form of iodide **1.178** (Scheme 1.42).^[79]



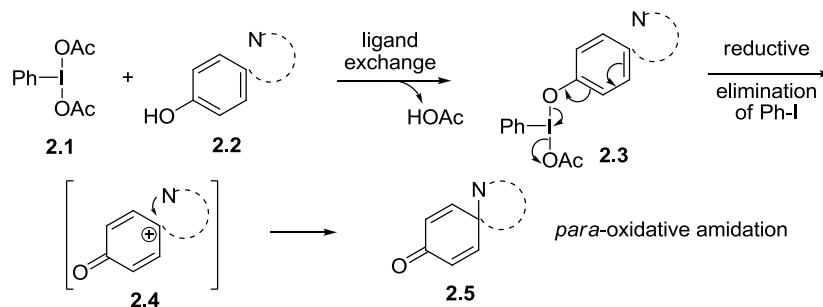
Scheme 1.42 Asymmetric synthesis of *para*-quinols mediated by **1.178**

It is apparent from the foregoing that as of early 2017 no examples of enantioselective dearomatization of phenols with concomitant C–N bond formation were known. Likewise, no instances of enantioselective oxidative cyclization of phenolic substrates other than carboxylic acids had been described. The research summarized in the present dissertation aimed to devise techniques that would enable the conduct of such transformations.

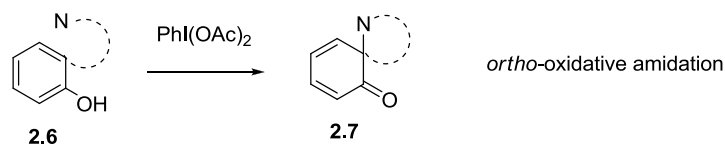
Chapter 2: Background

2.1 Genesis of the research project

The C-N bond is very important in the field of synthetic organic and medicinal chemistry, because nitrogen atoms are present in a variety of important intermediates and pharmaceutical drugs. The formation of C-N bond usually involves nucleophilic substitution or reductive amination reactions. Our group has developed a new technique for C-N bond formation that is described as the "oxidative amidation" of phenols.^[80] As implied by this terminology, the reaction involves the oxidative dearomatization of phenols. Thus, the reaction of **2.2** or **2.6** with (diacetoxyiodo)benzene **2.1** (or related λ^3 -iodanes) results in formation of dienones **2.5** or **2.7** (Scheme 2.1, 2.2). The "N" group in **2.2-2.7** represents a suitable nitrogen nucleophile, while the dotted line signifies that "N" may be tethered to the phenol (intramolecular reaction) or be independent (bimolecular reaction). In all these cases, the nitrogen atom emerges as a part of amide functionality, hence the terminology "oxidative amidation." Depending on whether "N" connects to the phenolic *para*- (Scheme 2.1) or *ortho*-position (Scheme 2.2), the reaction is further qualified as a *para*- or an *ortho*-oxidative amidation.^{[81],[82]}



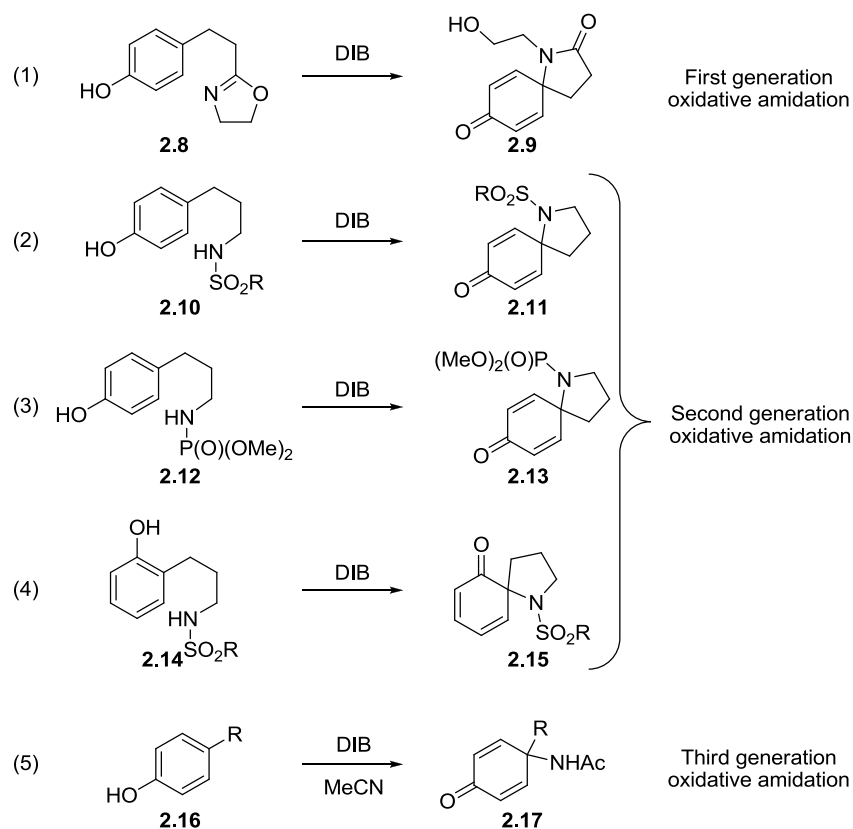
Scheme 2.1 Presumed mechanism of *para*-oxidative amidation of phenols



Scheme 2.2 *ortho*-oxidative amidation of phenols

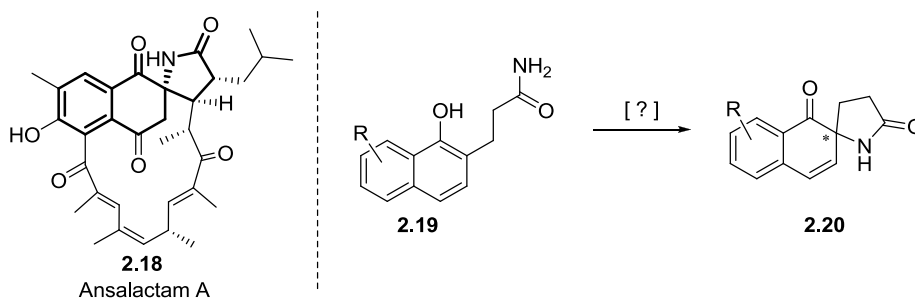
Mechanistically, the process is believed to start with ligand exchange at the hypervalent iodine atom, leading to complex **2.3**. A subsequent reductive fragmentation of the latter produces an electrophilic derivative of the starting phenol, perhaps cation **2.4**, which is intercepted by "N" to furnish dienones **2.5** (Scheme 2.1).^[83] The technique therefore achieves reversal of polarity (umpolung)^[17] of the normally nucleophilic phenol, causing it to express electrophilic character. Dienones **2.5** have been used as key intermediates in a number of synthetic efforts.^{[62],[67],[84]}

Three modes – or generations – of oxidative amidation had been devised at the onset of the present research. The cyclization of oxazolines **2.8** to lactams **2.9** (Scheme 2.3, eq. 1) was the first reaction of this type ever recorded,^[85] and it constitutes what we describe as the "first generation" process. Such a transformation was employed as the key step of the total synthesis of (-)-FR901483^[84a-b] and Erythrina alkaloids.^[62] The "second generation" reaction entailed the oxidative cyclization of sulfonamides (**2.10** and **2.14**) and phosphoramides **2.12**, and it was devised to effect the equivalent of the cyclization of a primary amine (Scheme 2.3, eq. 2, 3 and 4).^{[86],[87]} The method was applied to the total synthesis of cylindricine^[84c] and it is currently being explored in connection with an ongoing synthesis of himandrine.^[84d] In response to certain limitations of oxazoline and sulfonamide technology, a bimolecular, "third generation" oxidative amidation was developed, which relies on the reaction of phenols **2.16** with acetonitrile (Scheme 2.3, eq. 5).^{[88],[68]} This methodology is key to a formal synthesis of (±)-tetrodotoxin.^[67]



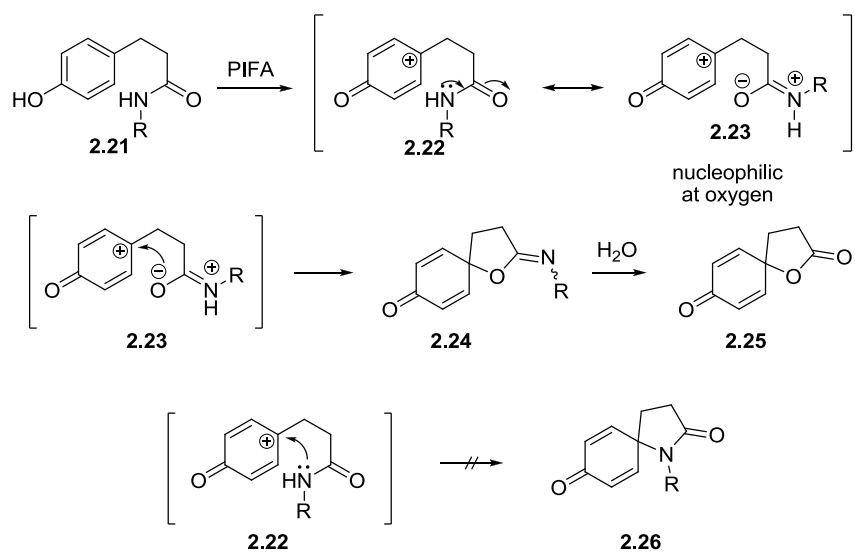
Scheme 2.3 Oxidative amidation of phenolic sulfonamides and related substrates

The recent discovery of ansalactam A^[89] (**2.18**, Scheme 2.4) ignited our interest in pursuing an enantioselective variant of oxidative amidation that would produce the spirocyclic core of the natural product by cyclization of α -naphthol substrates **2.19** (cf. **2.19** \rightarrow **2.20**). No such process was known at the onset of the research described in this dissertation.



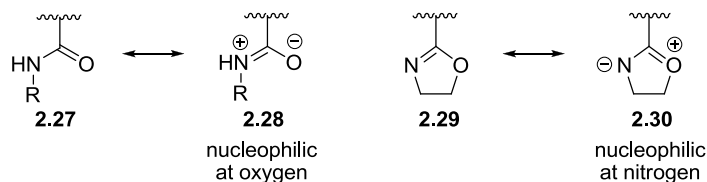
Scheme 2.4 Possible enantioselective oxidative amidation of α -naphthols

Some comments are in order at this juncture. First, the conversion of amide **2.19** into spiro lactam **2.20** was known not to be feasible. Already in 1987, Kita *et al.* had observed that the oxidative cyclization of phenolic amides **2.21** with PIFA or DIB yielded lactones **2.25** instead of lactams **2.26** (Scheme 2.5).^[90]



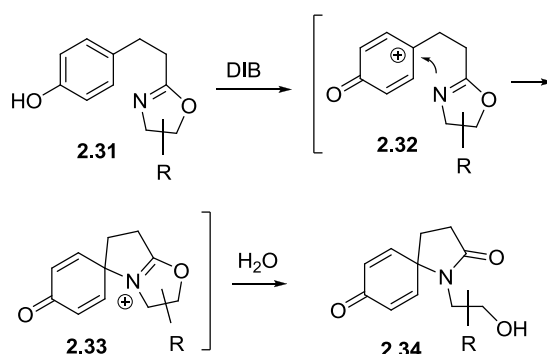
Scheme 2.5 Oxidative dearomatization of amides **2.21**

The effort that led to the development of the first-generation oxidative amidation started with the surmise that the undesired mode of cyclization of **2.21** was due to mesomeric redistribution of electron density from the amide nitrogen to the oxygen (**2.22** ↔ **2.23**), causing the oxygen atom to capture electrophilic species **2.23**. The resulting iminolactone **2.24** would then undergo hydrolysis to lactone **2.25**.



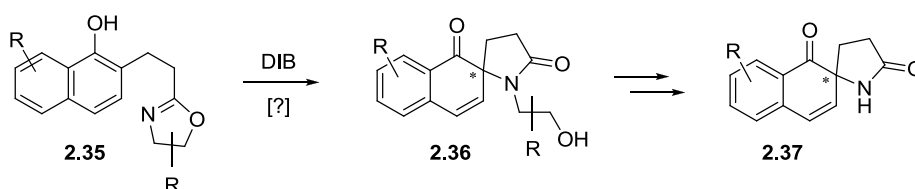
Scheme 2.6 Resonance interactions showing the nucleophilicity of oxygen and nitrogen

The same resonance interactions that promote nucleophilicity at oxygen in amides (**2.27** ↔ **2.28**) were expected to give rise to nucleophilic reactivity at nitrogen in imino analogues of amides; e.g., in oxazolines (**2.29** ↔ **2.30**, Scheme 2.6). Indeed, oxidative activation of phenolic oxazolines **2.31** provided the desired spirolactams **2.34** (Scheme 2.7).



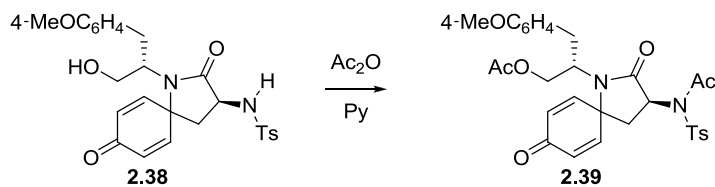
Scheme 2.7 Oxidative cyclization of phenolic oxazoline **2.31**

In light of the above, spirolactams **2.36** could possibly be prepared by enantioselective cyclization of oxazolines **2.35**, followed by release of the *N*-substituent (Scheme 2.8).



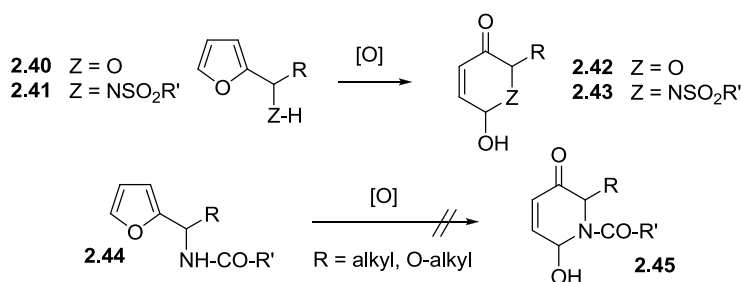
Scheme 2.8 Possible formation of spirolactams **2.37** via oxazoline technology

A more direct approach was envisioned based on the fact that, in many respects, the nucleophilic reactivity of sulfonamides parallels that of alcohols.^{[81],[91]} For instance the sulfonamide unit in **2.38**, an intermediate in the synthesis of FR-901483,^[84a-b] undergoes *N*-acetylation at a rate comparable to that of the primary alcohol moiety (Scheme 2.9).



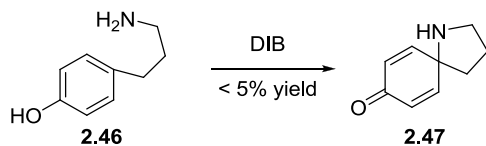
Scheme 2.9 Similar nucleophilic reactivity of alcohols and sulfonamides – I

Moreover, both furyl alcohols **2.40** and furyl sulfonamides **2.41** undergo efficient Achmatowicz reaction to provide dihydro- β -pyranones **2.42** and dihydro- β -pyridones **2.43**, respectively,^[92] whereas furyl amides or carbamates **2.44** are poor substrates for this transformation (Scheme 2.10).



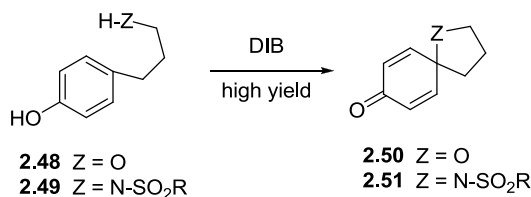
Scheme 2.10 Similar nucleophilic reactivity of alcohols and sulfonamides – II

The foregoing logic served as the guiding principle for the development of second-generation oxidative amidation technology. Various synthetic projects in our group required a method to achieve the oxidative cyclization of phenolic primary amines **2.46** (Scheme 2.11). Such a reaction proved to be extremely problematic,^[93] even though analogous transformations of secondary amines are reasonably efficient.^[94]



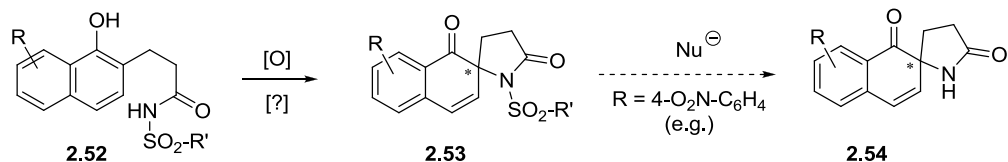
Scheme 2.11 Oxidative cyclization of phenolic primary amine **2.46**

The fact that phenolic alcohols **2.48** cyclize smoothly to **2.50** upon exposure to DIB induced us to explore the same reaction of sulfonamides, a process that indeed proved to be clean and high-yielding (Scheme 2.12).^[87]



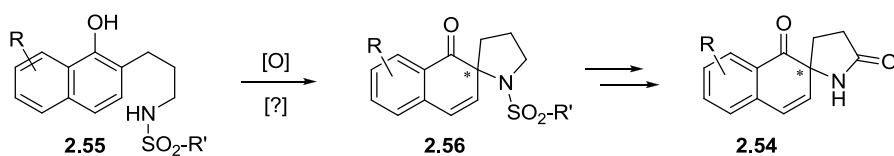
Scheme 2.12 Oxidative dearomatization of phenolic alcohols and sulfonamides

Accordingly, it was hypothesized that a phenolic/naphtholic *N*-sulfonyl carboxamide such as **2.52** (Scheme 2.13) might be a good substrate for oxidative cyclization, because its chemical behavior could be similar to that of the corresponding carboxylic acid, which would be an excellent substrate for oxidative cyclization (see above). Furthermore, a Fukuyama-type nitrosulfonyl group^[95] in product **2.53** could be excised under mild nucleophilic conditions, enabling the facile release of the free lactam **2.54** and achieving the equivalent of an oxidative cyclization of a primary carboxamide. Again, no examples of oxidative cyclization of phenolic *N*-acylsulfonamides were known at the beginning of the present investigation, let alone in an enantioselective manner.



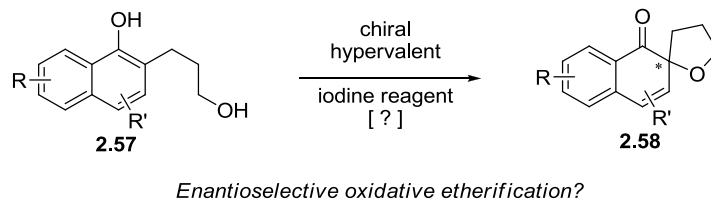
Scheme 2.13 Hypothetical oxidative cyclization of acyl sulfonamide **2.52** and release of the sulfonyl group

Yet another option for the assembly of spiroactams **2.54** was an asymmetric cyclization of naphtholic sulfonamides **2.55** to products **2.56**, followed by oxidative conversion of the latter into the desired **2.54** (Scheme 2.14). The oxidative cyclization of naphtholic sulfonamides such as **2.55**, either in the racemic or the asymmetric series, was also undocumented.



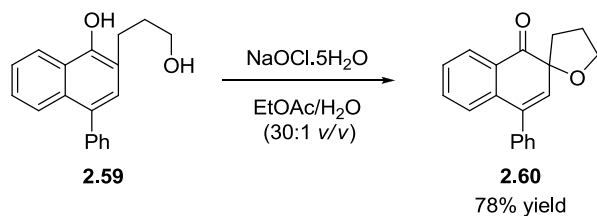
Scheme 2.14 Hypothetical oxidative cyclization of sulfonamide **2.55** and oxidative conversion to **2.54**

Two key objectives of this study thus were to ascertain the feasibility of the reactions depicted in Schemes 2.13 and 2.14 above, and to devise an enantioselective variant thereof. This also provided an incentive to explore the oxidative spiroetherification of naphtholic alcohols **2.57** (Scheme 2.15). Such a transformation was poorly documented at the beginning of this effort, and certainly was unknown in the enantioselective regime. Furthermore, it had never been carried out with hypervalent iodine oxidants.



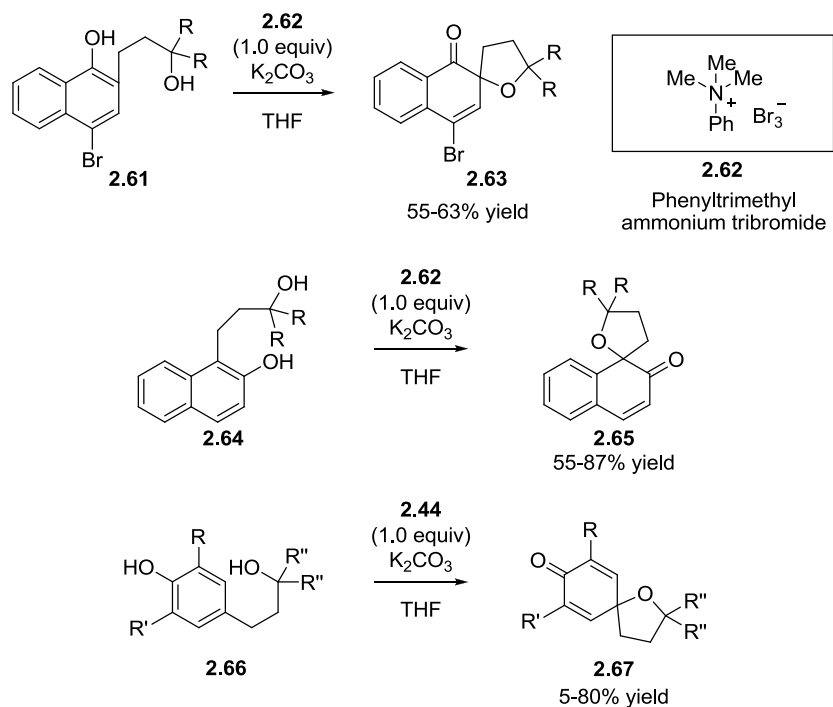
Scheme 2.15 Possible enantioselective oxidative cycloetherification of naphtholic alcohols

To illustrate, Ishihara et al. achieved the spiroetherification of α -naphthols **2.59** in high yield using bleach as the oxidant (Scheme 2.16),^[96] whereas Sarkar et al. investigated the use of



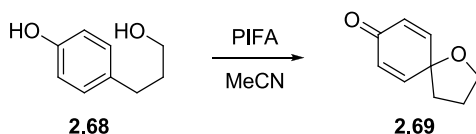
Scheme 2.16 Spiroetherification mediated by bleach

phenyltrimethylammonium tribromide **2.62** as a reagent for the analogous reaction of α -naphthols **2.61**, β -naphthols **2.64**, and phenols **2.66**. Racemic spiro-oxacycles **2.63**, **2.65** and **2.67** were thus obtained in moderate to high yields (Scheme 2.17).^[97]



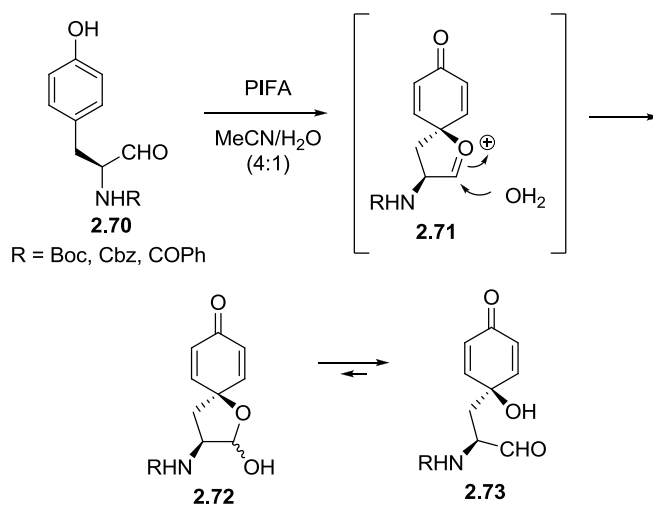
Scheme 2.17 Oxidative spiroetherification mediated by phenyltrimethylammonium tribromide

This stands in contrast to the oxidative cyclization of phenolic alcohols, which is well documented in the literature and that can be readily accomplished with hypervalent iodine reagents. For instance, the spiroetherification of phenolic alcohols **2.68** (Scheme 2.18) may be performed either with PIFA^[90a] or with DIB.^[98]



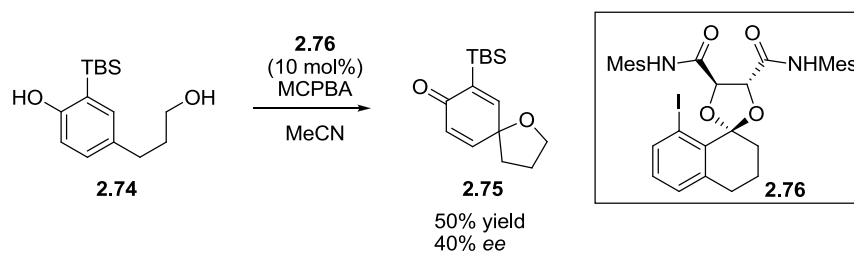
Scheme 2.18 Spiroetherification of **2.68** mediated by PIFA

Related transformations include the oxidative cyclization of phenolic aldehydes **2.70** to hemiacetals **2.72** (Scheme 2.19),^[99] a reaction that served as a key step in the total synthesis of the antibiotic, aranorosin.



Scheme 2.19 Synthesis of hemiacetals **2.72** mediated by PIFA

So far, there has been only one report of enantioselective spiroetherification using chiral hypervalent iodine reagents. Thus, Harned and coworkers prepared spiroether **2.75** in low yield and *ee* by reaction of phenolic alcohol **2.74** with a catalytic amount of chiral iodide **2.76** in the presence of MCPBA (Scheme 2.20).^[79]

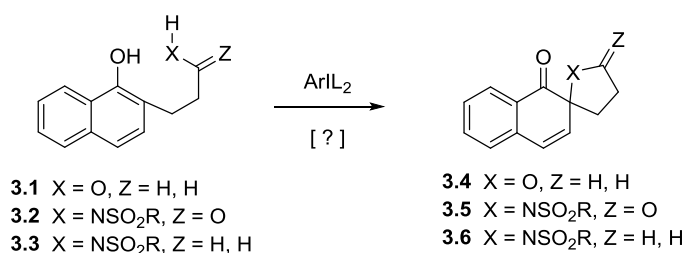


Scheme 2.20 Enantioselective spiroetherification mediated by hypervalent form of **2.76**

Chapter 3. Preparation of the substrates employed in the present study

3.1 Initial objectives and preparation of the substrates

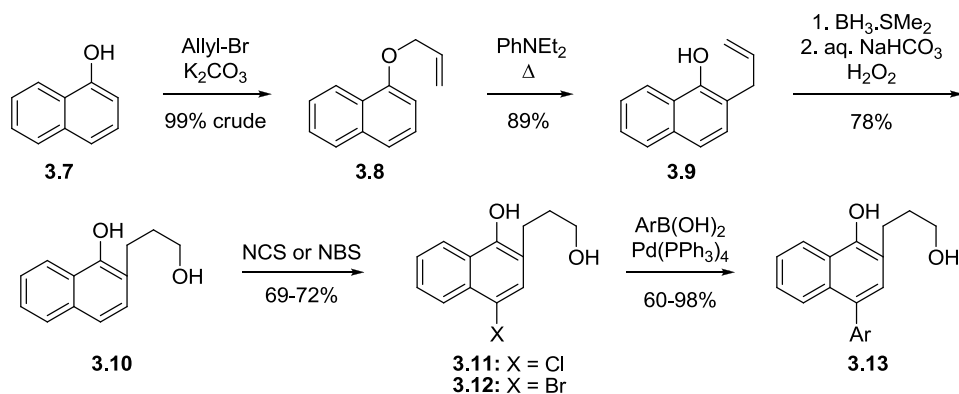
As indicated in chapter 2 (Scheme 2.13-2.15), an initial phase of this research focused on ascertaining whether the oxidative cyclization of alcohols **3.1**, *N*-acylsulfonamides **3.2**, and sulfonamides **3.3** were at all feasible (Scheme 3.1). This required the preparation a number of appropriate substrates.



Scheme 3.1 Possible oxidative amidation and spiroetherification

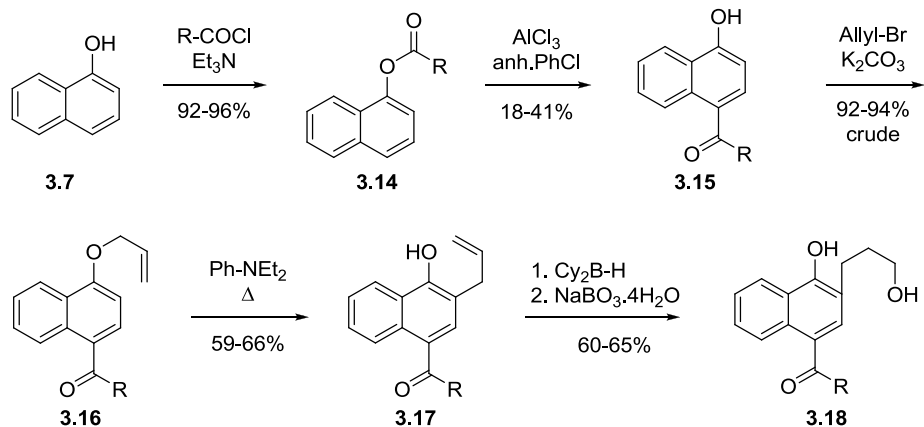
3.2 Synthesis of substrates: naphtholic alcohols

A number of compounds of general structure **3.13** were prepared from inexpensive 1-naphthol, **3.7**, which upon *O*-allylation and Claisen rearrangement afforded **3.9** (Scheme 3.2). Hydroboration-oxidation of **3.9** returned naphtholic alcohol **3.10**. The latter underwent a highly selective halogenation at the phenolic *para*-position upon exposure to an appropriate *N*-halo succinimide. Compound **3.12**, was further elaborated to various 4-aryl derivatives **3.13** via Suzuki coupling.^[100]



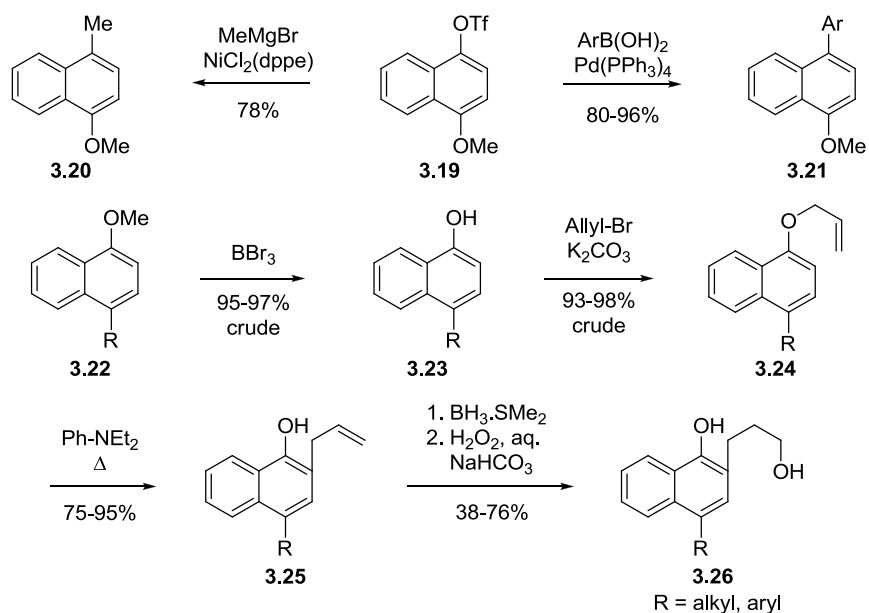
Scheme 3.2 Synthesis of 4-halide/aryl substituted naphtholic alcohols

The synthesis of naphtholic alcohols bearing a 4-carbonyl substituent proceeded via Fries rearrangement of esters **3.14** in the presence of AlCl_3 (Scheme 3.3).^[101] The emerging phenols **3.15** were advanced to compounds **3.18** substantially by the method outlined earlier in Scheme 3.2, except that dicyclohexylborane was employed in lieu of BH_3 in the hydroboration/oxidation sequence. This is due to the reduction of ketone in **3.17** by using BH_3 along with hydroboration-oxidation of terminal alkene. Hydroboration-oxidation of **3.17** with 9-BBN resulted in formation of complex mixtures of products, but *in situ* generated dicyclohexylborane reacted only with the terminal alkene, leading to the desired **3.18** in moderate yield after a subsequent oxidation with sodium perborate.^[102]



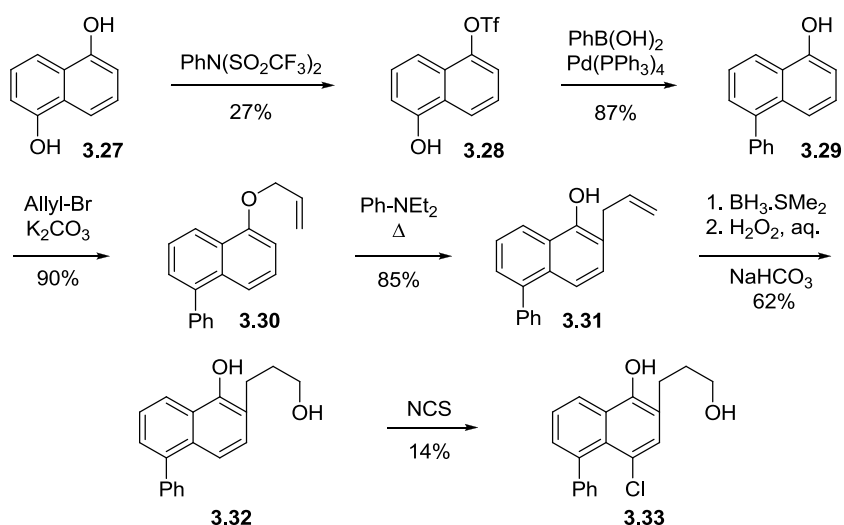
Scheme 3.3 Synthesis of 4-carbonyl substituted naphtholic alcohols

Inexpensive 4-methoxy-1-naphthol was the starting material of choice for the preparation of alcohols **3.26**. Conversion to triflate **3.19** followed by Kumada^[103] or Suzuki^[100] coupling provided **3.20** and **3.21** respectively (Scheme 3.4). These substances were advanced to **3.26** as seen earlier in Scheme 3.2.



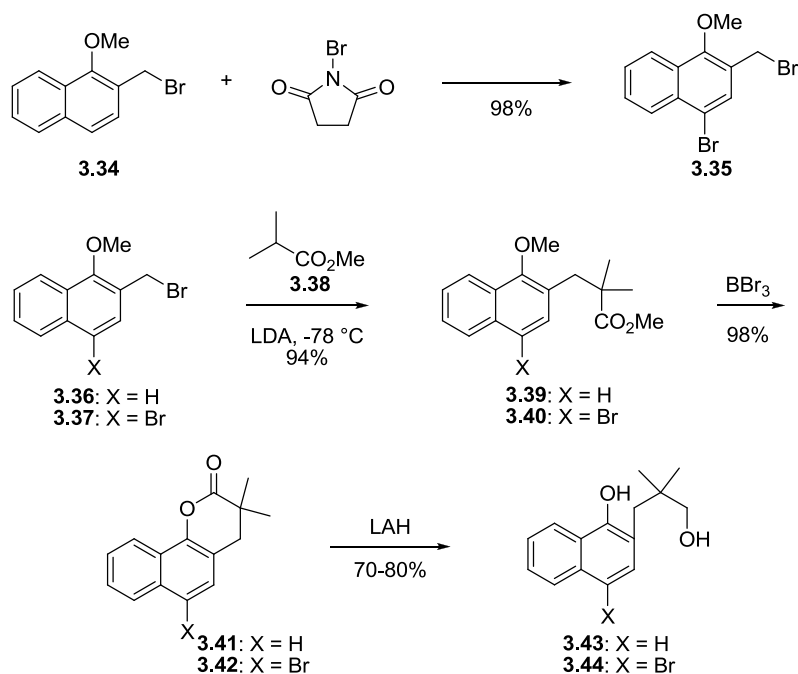
Scheme 3.4 Synthesis of 4-alkyl/aryl substituted naphtholic alcohols

The 5-substituted naphtholic alcohols **3.33** were best made from very economical 1,5-dihydroxynaphthalene **3.27**, which upon reaction with *N*-phenyl triflimide, provided mono-triflate **3.28** (Scheme 3.5).^[104] Suzuki coupling afforded **3.29**, which, once again, was elaborated to **3.32** – **3.33** as described above.



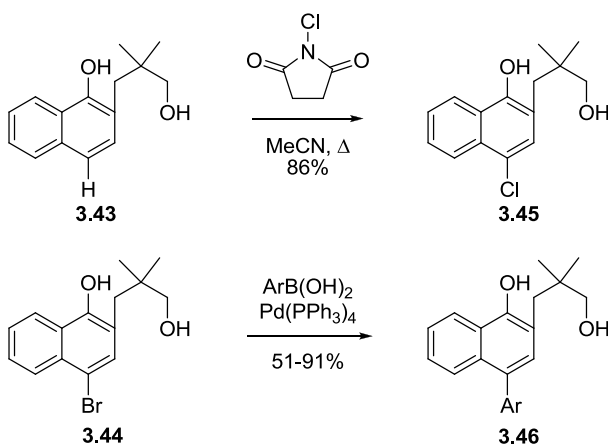
Scheme 3.5 Synthesis of 5-substituted naphtholic alcohols

In the course of our efforts, it became desirable to explore how the so-called *gem*-dialkyl effect^[105] influenced the rate of cyclization of naphtholic alcohols. Accordingly, substrates exhibiting a *gem*-dimethyl group at the 2' position of the side chain were synthesized as delineated in Scheme (Scheme 3.6). In accord with a literature procedure,^[106] commercial 1-hydroxy-2-naphthoic acid was advanced to compounds **3.34** and **3.35**, either of which reacted with the lithium enolate of methyl isobutyrate **3.38** to provide **3.39** and **3.40** respectively. The action of BBr_3 upon these resulted in demethylation of the phenol and lactonization. A final LAH reduction produced **3.43** and **3.44**. The latter underwent Suzuki coupling with appropriate



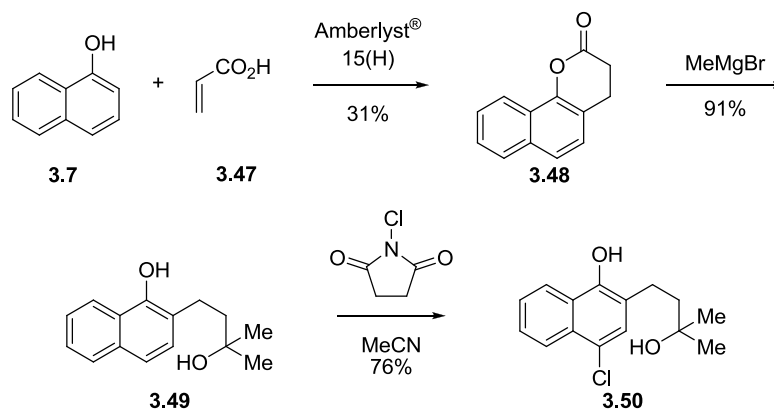
Scheme 3.6 Synthesis of naphtholic alcohols with *gem*-dimethyl group in side chain

boronic acids to furnish 4-aryl substituted alcohols **3.46** (Scheme 3.7). Substrate **3.45** was prepared by chlorination of **3.43** with NCS in acetonitrile. It is worthy of note that **3.43** failed to undergo chlorination at RT, but when the reaction mixture was refluxed for 2h, the desired **3.45** was obtained in 86% yield.



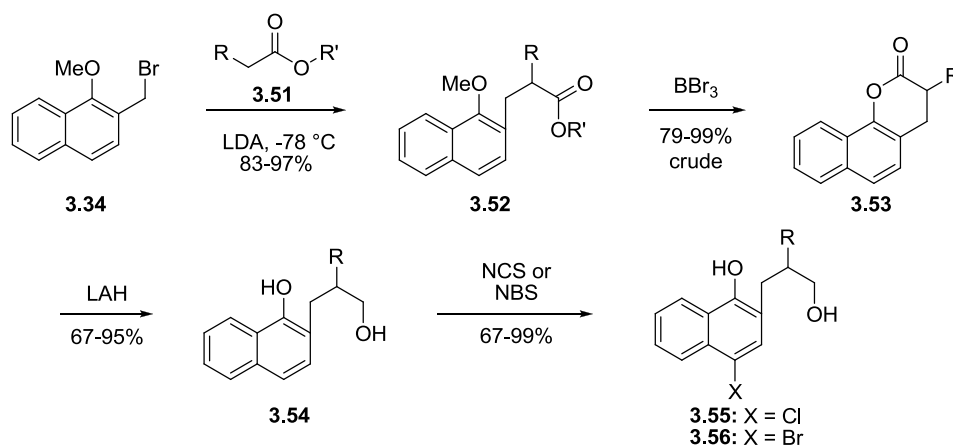
Scheme 3.7 Synthesis of 4-halo/aryl naphtholic alcohols with *gem*-dimethyl group at 2' position

Related substrates displaying a *gem*-dimethyl group at the OH-bearing side-chain carbon atom were assembled starting with reaction of 1-naphthol **3.7** with acrylic acid **3.47** in the presence of the strongly acidic resin, Amberlyst[®] 15(H) (Scheme 3.8). The resulting lactone **3.48** reacted with MeMgBr to provide **3.49**, which was converted into **3.50** as described above.



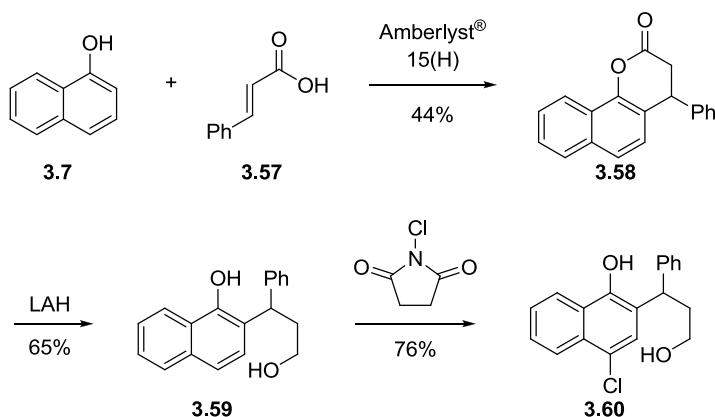
Scheme 3.8 Synthesis of naphtholic alcohol **3.50**

Substrates incorporating a single substituent on the side chain also became of interest. The preparation of these compounds retraced the sequences outlined earlier in Schemes 3.6-3.7. Thus, 2'-monosubstituted compounds were obtained as shown in Scheme 3.9.



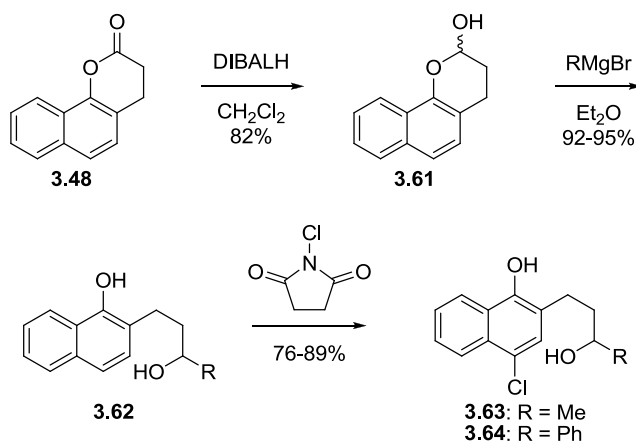
Scheme 3.9 Synthesis of substrates with stereogenic centre at 2' position in side chain

Substrates carrying a single substituent at the benzylic position were accessed starting with Amberlyst[®] 15(H)-catalyzed reaction of conjugated carboxylic acids **3.57** with 1-naphthol **3.7** (Scheme 3.10).



Scheme 3.10 Synthesis of substrates with stereogenic centre at benzylic position

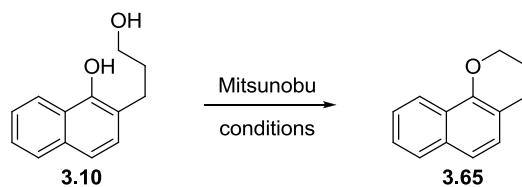
Finally, secondary alcohol substrates emerged upon DIBAL reduction of lactone **3.48** to afford lactal **3.61** followed by Grignard reaction (Scheme 3.11).



Scheme 3.11 Synthesis of naphtholic secondary alcohol substrates **3.63-3.64**

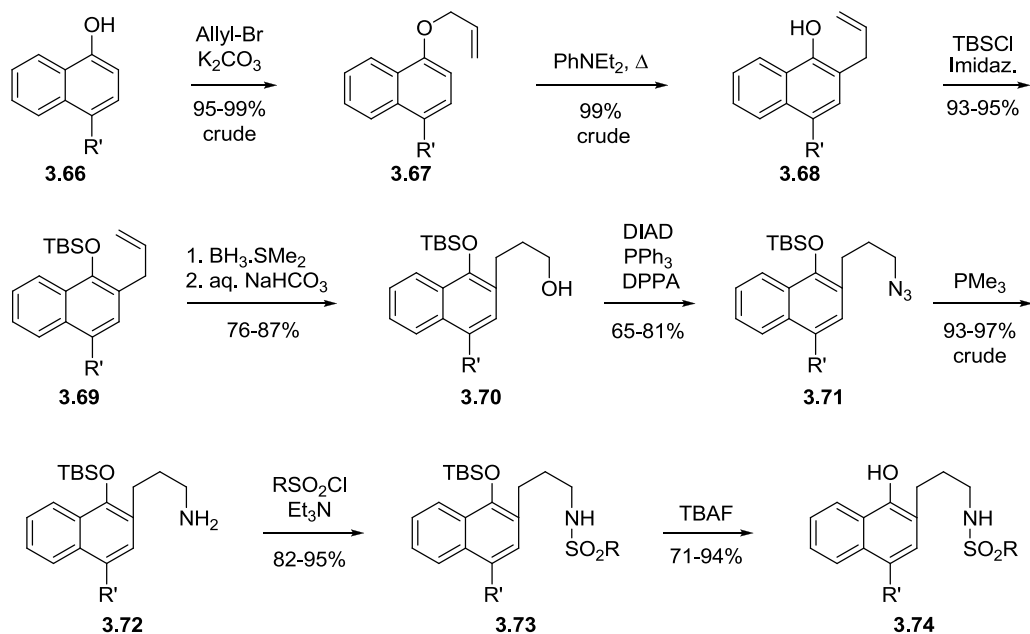
3.3 Synthesis of substrates: naphtholic sulfonamides

The synthesis of sulfonamides **3.3** retraced that of the corresponding alcohols, but with one modification. The introduction of the nitrogenous functionality proved to be best achieved via a Mitsunobu reaction, which, however, would have failed if carried out with an unprotected naphthol. Indeed, a substrate such as **3.10** would probably cyclize to undesired pyran **3.65** under Mitsunobu conditions (Scheme 3.12). This mandated protection of the phenolic OH group immediately after the aromatic Claisen rearrangement shown in Schemes 3.2-3.5 above.



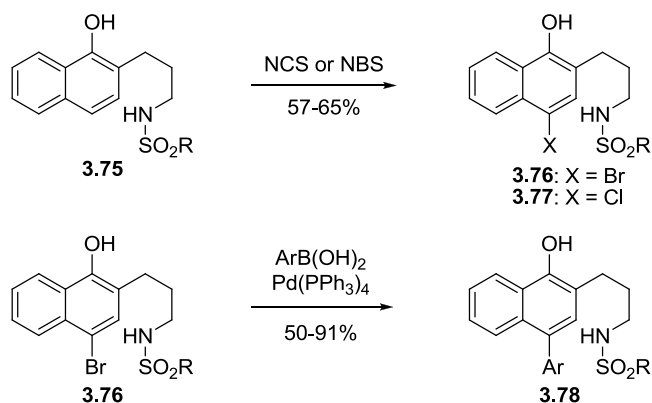
Scheme 3.12 Possible synthesis of pyran **3.65** under Mitsunobu conditions

Protection of naphthols **3.68** as the TBS ethers **3.69** set the stage for hydroboration-oxidation to alcohols **3.70** and Mitsunobu reaction of the latter with DPPA to yield azides **3.71**. Staudinger reaction, sulfonylation of the resulting amines **3.72**, and release of the TBS group with TBAF generated desired sulfonamides **3.74** (Scheme 3.13).



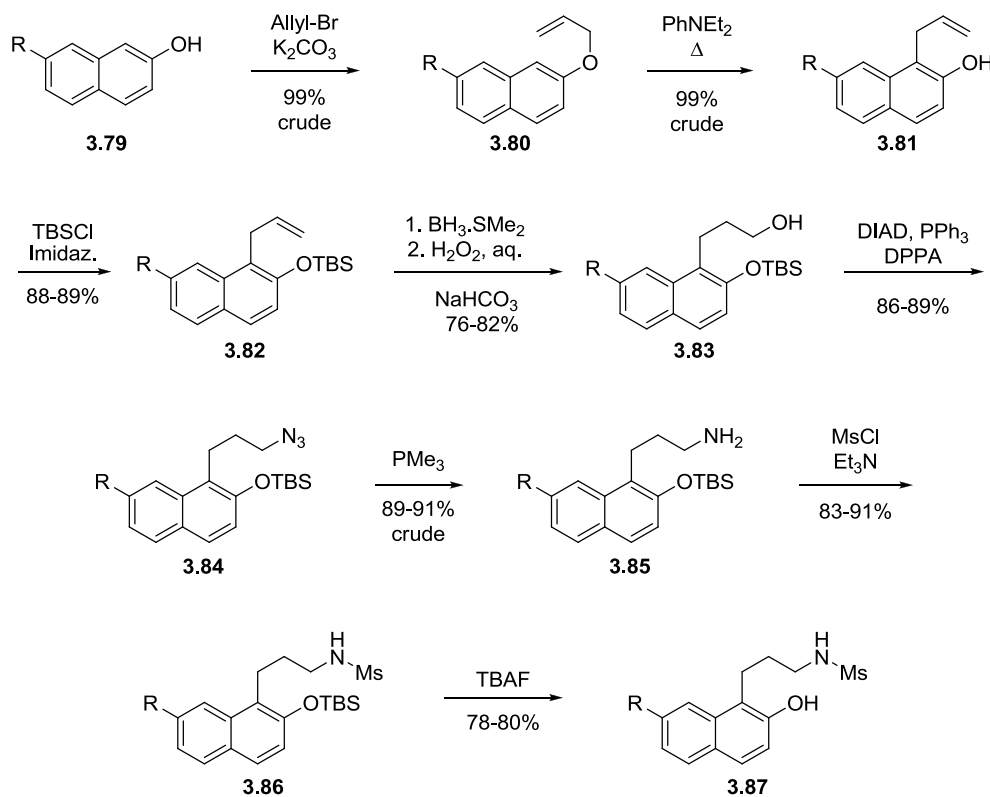
Scheme 3.13 Synthesis of naphtholic sulfonamide **3.74**

Compounds **3.74** were elaborated to more complex sulfonamides **3.76-3.78** by halogenation followed by Suzuki coupling of **3.76** with appropriate boronic acids (Scheme 3.14), just as shown earlier for alcohols **3.11-3.13**.



Scheme 3.14 Synthesis of 4-halo/aryl substituted naphtholic sulfonamides

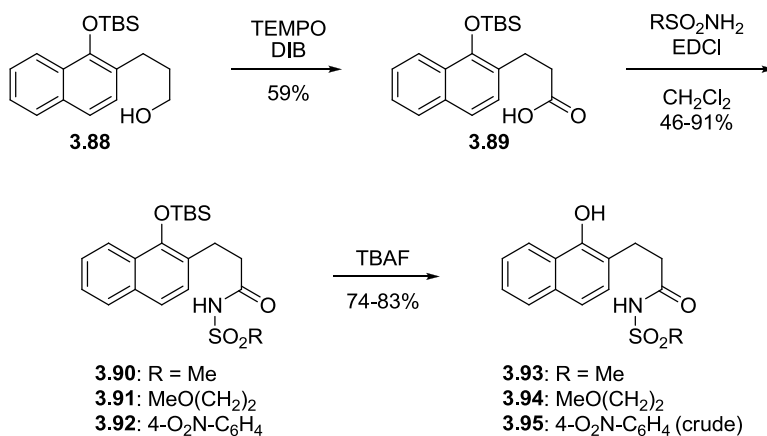
In the case of sulfonamides, we deemed it desirable also to explore the oxidative cyclization of 2-naphtholic substrates. These compounds were prepared from appropriate 2-naphthols **3.79** by the same method outlined above for 1-naphtholic sulfonamides (Scheme 3.15).



Scheme 3.15 Synthesis of 2-naphtholic sulfonamides **3.87**

3.4 Synthesis of substrates: naphtholic *N*-acyl-sulfonamides

Alcohol **3.88** obtained as described earlier in Scheme 3.13 was oxidized to carboxylic acid **3.89** using TEMPO and DIB. Subsequent EDCI mediated coupling of **3.89** with appropriate sulfonamides afforded products **3.90-3.92** in moderate (46%) to excellent (91%) yield (Scheme 3.16).



Scheme 3.16 Synthesis of *N*-acyl sulfonamide substrates

Deprotection of the naphthol using TBAF provided **3.93-3.95**. This step was problematic in the case of compound **3.92**, because of the tendency of the product to cyclize to lactone **3.48** or form carboxylic acid **3.96** (Figure 3.1) as a consequence of the pronounced nucleofugal character of 4-nitrobenzenesulfonamide. For instance, desilylation with 1.1 equivalents of TBAF yielded mostly **3.48** and **3.96** and a very small amount of desired **3.95**.

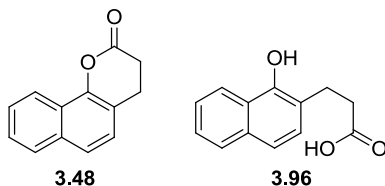


Figure 3.1 Structure of lactone **3.48** and carboxylic acid **3.96**

Moreover, **3.95** decomposed to a mixture of **3.48** and **3.96** upon standing. Desilylation with HF•pyridine produced a very complex reaction mixture. Successful deprotection was finally achieved in the presence of 2.2 equivalents of TBAF, whereupon the expected product was obtained in the form of *bis*-tetrabutylammonium salt **3.97** (Figure 3.2).

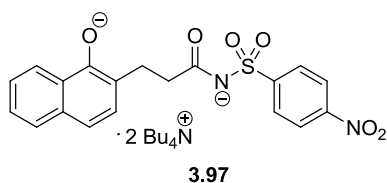


Figure 3.2 *bis*-tetrabutylammonium salt of **3.97**

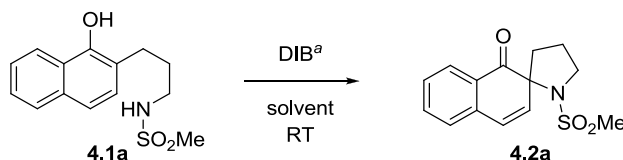
Attempts to restore the neutral form of the compound by treatment with a mildly acidic solution (0.5 M HCl or satd. aq. NH₄Cl) resulted in rapid degradation and precipitation of 4-nitrobenzenesulfonamide. The material was therefore employed as such in subsequent steps.

Crude **3.93-3.94** were amenable to purification by column chromatography. Such an operation was carried out rapidly, in order to minimize the formation of **3.48** or **3.96**. Moreover, the purified products had limited shelf life. They could be stored at -20 °C under argon for some days, but decomposition into **3.48** and **3.96** was already apparent (¹H NMR) after around 10 days. In contrast, the *bis*-tetrabutylammonium salt **3.97** was too sensitive. It did not withstand chromatography either on silica or neutral alumina, and attempted recrystallization induced extensive degradation. Hence, it was directly subjected to oxidative cyclization in crude form.

Chapter 4: Oxidative amidation in naphthalene series

4.1 Oxidative cyclization of naphtholic sulfonamides in the racemic series

Non-nucleophilic protic solvents like trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), and especially trifluoroacetic acid (TFA) are ideal for the oxidative cyclization of phenolic sulfonamides.^[87] Therefore, the same reaction of test substrate **4.1a** was initially attempted in the same solvents. Spiropyrrolidine **4.2a** was obtained in low yield when the reaction was carried out TFE or HFIP (Table 4.1, entry 1 and 2), but operation in TFA resulted in a satisfactory 65% yield (entry 3). Acetic acid was an especially poor solvent (entry 4). Halogenated solvents like neat CH_2Cl_2 and CHCl_3 were also unsatisfactory, even though addition of some TFA^[87] was beneficial (entries 5-8). In accord with previous observations,^[87] TFA was the best solvent for this reaction.

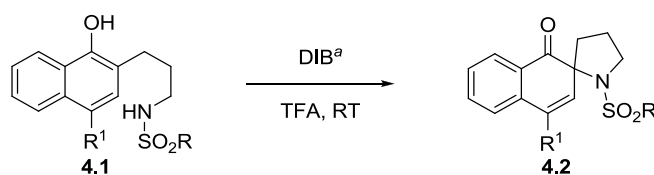


Entry	Solvent	Yield (%) ^b
1	$\text{CF}_3\text{CH}_2\text{OH}$	20
2	$(\text{CF}_3)_2\text{CHOH}$	28
3	CF_3COOH	65
4	CH_3COOH	4
5	CH_2Cl_2	14
6	CHCl_3	12
7	$\text{CH}_2\text{Cl}_2 + \text{TFA}$ (1.1 equiv)	30
8	$\text{CHCl}_3 + \text{TFA}$ (1.1 equiv)	18

^aDIB (1.1 equiv), Solvent (0.3 M), 10-15 mins. ^bIsolated yields after column chromatography.

Table 4.1 Optimization of solvent for oxidative cyclization of **4.1a**

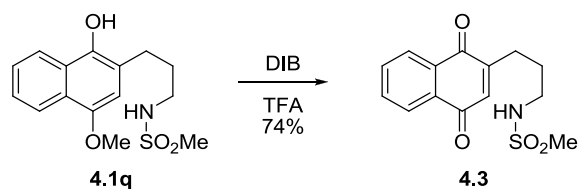
Based on the optimized conditions obtained as a result of solvent screening, the oxidative cyclization of other naphtholic sulfonamides was carried out in TFA, wherein conversion into spiropyrrolidines was achieved in moderate (45%) to excellent (96%) yield (Table 4.2). These reactions were best carried out by adding a TFA solution of sulfonamide to a TFA solution of DIB. A variety of substituents [Br, Cl, Ph, 4-F-C₆H₄, 4-CF₃-C₆H₄, Ph, 3,5-(CF₃)₂C₆H₃] were tolerated at the naphtholic 4-position, with the exception of a methoxy group (entry 17). In the latter case, none of the spirocyclic sulfonamide was obtained. Instead, the starting **4.1q** was oxidized to naphthoquinone **4.3** in 74% yield (Scheme 4.1).



Entry	R ¹	R	Product	Yield ^b
1	H	4-Me-C ₆ H ₄	4.2b	74
2	Br	4-Me-C ₆ H ₄	4.2c	73
3	H	4-O ₂ N-C ₆ H ₄	4.2d	75
4	Br	4-O ₂ N-C ₆ H ₄	4.2e	70
5	H	4-MeO-C ₆ H ₄	4.2f	80
6	H	PhCH ₂	4.2g	96
7	Br	PhCH ₂	4.2h	87
8	H	CF ₃ CH ₂	4.2i	45
9	Br	CF ₃ CH ₂	4.2j	93
10	H	Me	4.2a	65
11	Br	Me	4.2k	83
12	Cl	Me	4.2l	85
13	Ph	Me	4.2m	55
14	4-F-C ₆ H ₄	Me	4.2n	85
15	4-CF ₃ -C ₆ H ₄	Me	4.2o	85
16	3,5-(CF ₃) ₂ C ₆ H ₃	Me	4.2p	60
17	OMe	Me	-	--

^aDIB (1.1 equiv), TFA (0.3 M), 10-15 mins. ^bIsolated yields after column chromatography.

Table 4.2 Substrate scope-Oxidative cyclization of 1-naphtholic sulfonamides



Scheme 4.1 Formation of naphthaquinone **4.3**

The oxidative cyclization of 2-naphtholic sulfonamides afforded the expected spiropyrrolidines **4.5a-4.5b** in lower yield compared to 1-naphtholic analogs (Scheme 4.2).



Scheme 4.2 Oxidative cyclization of 2-naphtholic sulfonamides

4.2 Oxidative cyclization of naphtholic *N*-acylsulfonamides in the racemic series

As indicated earlier (Ch. 2, Scheme 2.13), the undocumented oxidative cyclization of *N*-acylsulfonamides **2.52** constitutes a direct avenue to spirolactams of the type found in ansalactam A. Furthermore, the successful execution of this transformation would circumvent the problems affecting the cyclization of carboxamides and thus establish a new mode ("fourth generation") of oxidative amidation. It was therefore pleasing to observe that reaction of **4.13** with DIB under the conditions developed earlier for the cyclization of sulfonamides indeed produced some of the desired spirolactams **4.9** (Table 4.3). However, it also became clear that the conditions for the reaction of sulfonamides were not immediately transposable to the *N*-acylsulfonamide series. This is due to returns of only small amounts of the desired products, accompanied by significant quantities of lactone **4.6** and acid **4.7** (Figure 4.1).

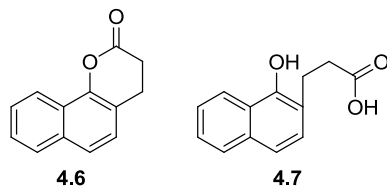
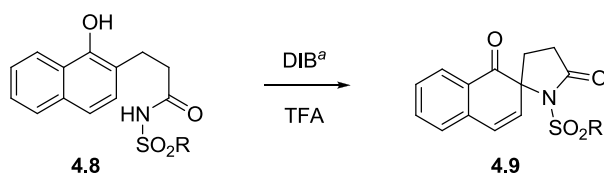


Figure 4.1 Structure of lactone **4.11** and carboxylic acid **4.12**

It was determined that formation of byproducts **4.6** and **4.7** occurred simply upon dissolution of the substrates in TFA. It was thus essential to minimize contact time of **4.8** with TFA, which, in the absence of DIB, was promoting the acid-catalyzed conversion of the substrates into unwanted materials. Addition of TFA to a mixture of *N*-acyl sulfonamide and DIB, in the hope that oxidative cyclization would take place immediately upon dissolution of the reactants, led only to intractable mixtures. A better option was to minimize exposure of the substrates to TFA by operating as quickly as possible: rapid (seconds) dissolution of the acylsulfonamides in TFA and prompt addition the resulting solution to one of DIB resulted in formation of the desired spiro lactams **4.9** in moderate yield (Table 4.3).



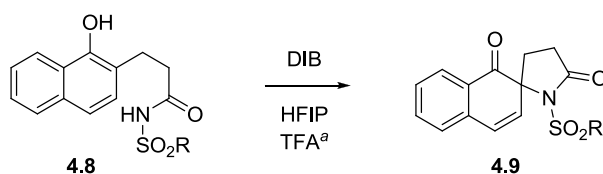
Entry	Product	Yield ^b
1	4.9a (R = Me)	36
2	4.9b (R = MeO(CH ₂) ₂)	40
3 ^c	4.9c (R = 4-O ₂ NC ₆ H ₄)	20

^aDIB (1.1 equiv), TFA (0.3 M), RT, 10-15 mins. ^bIsolated yields after column chromatography. ^cYield obtained from *bis*-tetrabutylammonium salt **3.97**.

Table 4.3 Synthesis of spirocyclic γ -lactams

An even better remedy was to dissolve the substrates in a solvent that was less acidic than TFA, so as to minimize decomposition, and then add the resulting solution to one of DIB. The

use of HFIP was revisited in that connection. While HFIP solutions of the acylsulfonamides were fairly stable, addition of such solutions to one of DIB also in HFIP produced no spiro lactams. We thus concluded that an acidic medium was necessary for the success of the reaction. Accordingly, an HFIP solution of *N*-acylsulfonamide **4.8** was added to a TFA solution of DIB, whereupon spiro lactams **4.9** were obtained in improved – if still moderate – yield. Additional experiments revealed that best results were obtained when the ratio of HFIP to TFA was 8:1 v/v. The yields of spiro lactams thus obtained are reported in Table 4.4.



Entry	Product	Yield ^b
1	4.9a (R = Me)	42
2	4.9b (R = MeO(CH ₂) ₂)	47
3 ^c	4.9c (R = 4-O ₂ NC ₆ H ₄)	29

^aDIB (1.1 equiv), HFIP:TFA (8:1 v/v, 0.05M), RT, 10-15 mins. ^bIsolated yields after column chromatography. ^cYield obtained from *bis*-tetrabutylammonium salt **3.97**.

Table 4.4 Synthesis of spirocyclic γ -lactams using modified conditions

Single crystals of product **4.9a** were obtained upon recrystallization via slow evaporation of its solution in toluene, which enabled a structural confirmation by X-ray diffractometry (Figure 4.2).

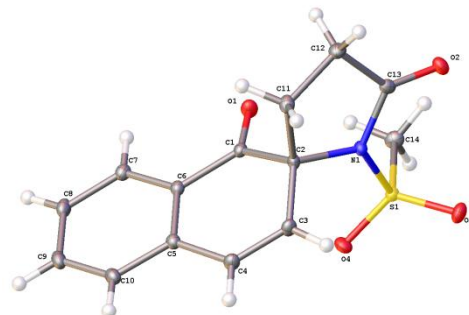
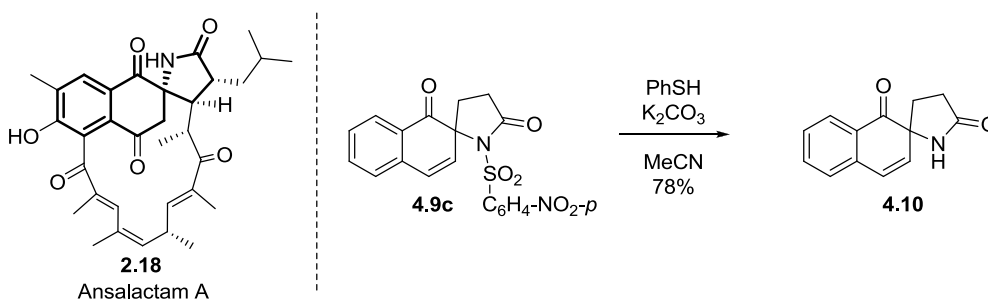


Figure 4.2 X-ray structure of spiro lactam **4.9a**

As anticipated, the nitrosulfonyl group in compound **4.9c** was easily released upon reaction with thiophenoxide ion, generated *in situ* by deprotonation of thiophenol with K_2CO_3 (Scheme 4.3). The resulting *N*-unsubstituted spirocyclic γ -lactam **4.10** was formed in 78% yield. Compound **4.10** possess structural similarity with the core of ansalactam A **2.18** (Scheme 4.3).

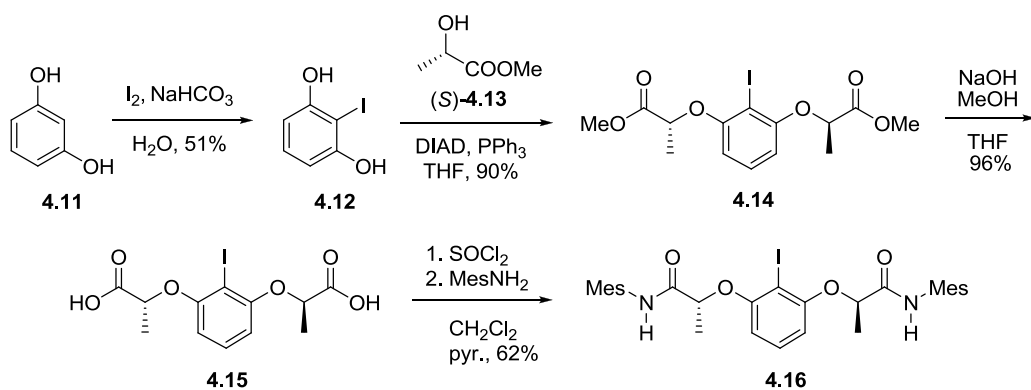


Scheme 4.3 *N*-Deblocking of nitrosulfonamide **4.9c**

4.3 Enantioselective oxidative cyclization of naphtholic sulfonamides

Having confirmed that the oxidative cyclization of naphtholic sulfonamides with hypervalent iodine reagents is indeed feasible, our attention refocused on the development of an enantioselective variant of the reaction. To the best of our knowledge, no such process had been recorded before in the literature.

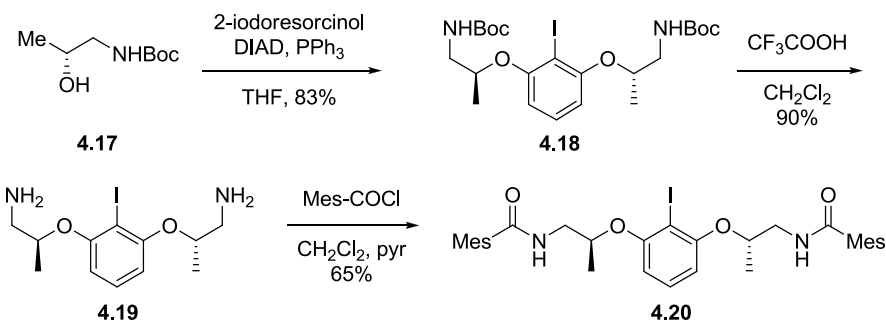
Initial experiments aiming to achieve the transformation of interest centered on the use of various Ishihara type, C_2 -symmetric, chiral aryl iodides in the presence of MCPBA.^[70] The reason for using C_2 -symmetric chiral iodoarenes is that these had already been shown to be effective catalysts for the oxidative cyclization of carboxylic acids (Scheme 1.37) and are readily prepared. The synthesis of C_2 -symmetric chiral aryl iodides began with iodination of resorcinol,^[107] **4.11**, followed by Mitsunobu reaction of 2-iodo resorcinol **4.11**^[70] with (-)-(*S*)-methyl lactate, **4.13** (Scheme 4.4). Diester **4.14** was hydrolyzed under basic conditions to provide diacid **4.15**, which was elaborated to **4.16** *via* the acid chloride.



Scheme 4.4 Synthesis of Ishihara's C_2 symmetric chiral aryl iodides

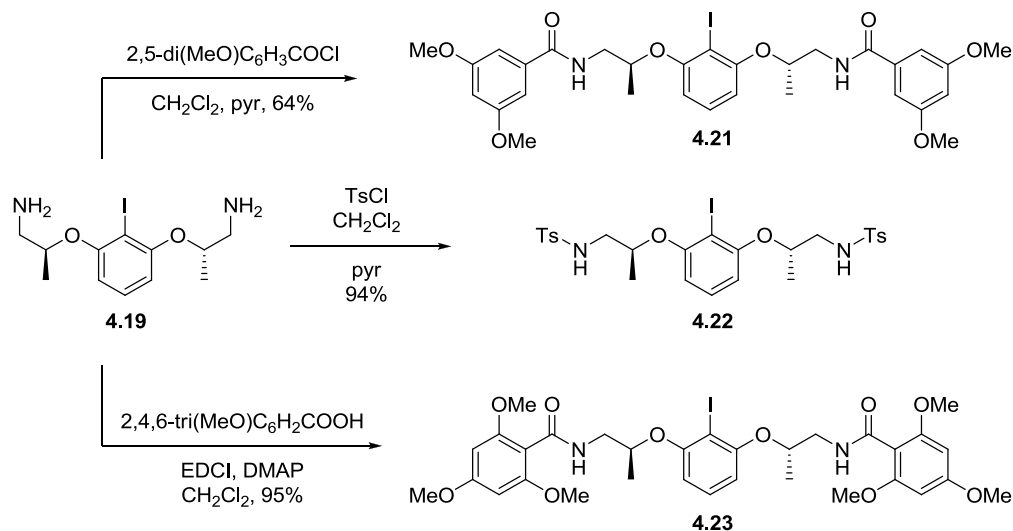
Similarly, chiral iodoarenes **4.20**^[74] were made starting with Mitsunobu reaction of 2-iodoresorcinol with *N*-Boc-(*R*)-1-amino-2-propanol, **4.17** (Scheme 4.5). Amine **4.19** produced

upon release of the Boc units from **4.18** was then advanced to iodoarenes **4.20** (Scheme 4.5) and **4.21-4.22** (Scheme 4.6) by reaction with appropriate acid chlorides.



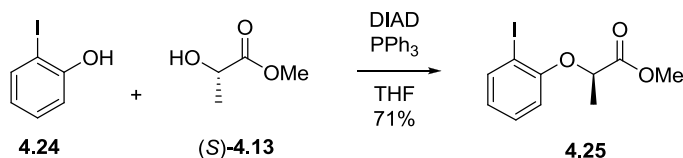
Scheme 4.5 Synthesis of chiral aryl iodide **4.20**

The *N,N*-diacylation of **4.19** with 2,4,6-trimethoxybenzoyl chloride proceeded poorly (<5% yield). The problem was attributable to the inefficient conversion of 2,4,6-trimethoxybenzoic acid to the chloride upon reaction with SOCl_2 or oxalyl chloride. Either method led to the formation of an uncharacterized complex mixture. Fortunately, EDCI mediated coupling of **4.19** with 2,4,6-trimethoxybenzoic acid provided **4.23** in 95% yield.



Scheme 4.6 Synthesis of chiral aryl iodides **4.21-4.23**

Chiral iodide **4.31** was synthesized via Mitsunobu reaction of lactate (*S*)-**4.19** with 2-iodophenol **4.30** as outlined in Scheme 4.7.^[70]

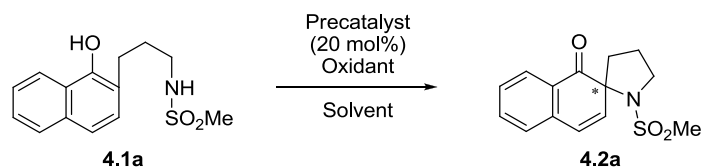


Scheme 4.7 Synthesis of chiral iodide **4.25**

4.3.1 Screening of conditions

At the onset of this project, only iodoarenes **4.14-4.16** and **4.25** were known. Hence, these were used to explore the enantioselective cyclization of test substrate **4.1a**. Treatment of the latter with MCPBA in the presence of 20-40 mol% of a chiral iodoarene, in TFA or in mixtures of TFA and HFIP (the best solvents for oxidative cyclization, Table 4.1-4.4), afforded a product that was racemic. Thus, the solvents that performed the best in the racemic series were entirely unsuitable for the enantioselective reaction.

It will be recalled that the enantioselective cyclization of carboxylic acids had been carried out in CH₂Cl₂ (Scheme 1.37).^[69-71] The same reaction of **4.1a** was thus attempted in CH₂Cl₂, in the presence of 20 mol% of chiral iodide and MCPBA as the oxidant. Reactions run at 0 °C with the C₁-symmetric iodide **4.25** afforded product **4.2a** in poor yields and *ee* (Table 4.5, entry 1). The C₂ symmetric iodides **4.14** and **4.16** provided better *ee* but comparable yields (entries 2 and 3). In all cases, however, reaction rates were considerably slower in CH₂Cl₂ than in protic solvents. Upon lowering the temperature from 0 to -10 °C to -20 °C, *ee*'s improved slightly, but at the cost of rate and yield (entries 4-5).



Entry	Precatalyst	Reaction conditions	Yield ^a (%)	ee ^b (%)
1	4.25	MCPBA (1.3 equiv.), 0 °C, CH ₂ Cl ₂ , 2.3 h	23	<5
2	4.14	MCPBA (1.3 equiv.), 0 °C, CH ₂ Cl ₂ , 2.5 h	12	19
3	4.16	MCPBA (1.3 equiv.), 0 °C, CH ₂ Cl ₂ , 1.5 h	20	11
4	4.16	MCPBA (1.3 equiv.), -10 °C, CH ₂ Cl ₂ , 7.5 h	12	16
5	4.16	MCPBA (1.3 equiv.), -20 °C, CH ₂ Cl ₂ , 13.5 h	13	20
6	4.14^c	MCPBA (1.3 equiv.), -20 °C, CH ₂ Cl ₂ , 26 h	15	37
7	4.14^c	MCPBA (1.3 equiv.), -20 °C, CHCl ₃ , 24 h	10	31
8	4.14^c	MCPBA (1.3 equiv.), -20 °C, (CH ₂ Cl) ₂ , 36 h	14	26
9	4.14^c	MCPBA (1.3 equiv.), -20 °C, CH ₂ Cl ₂ : hexane (2:1), 18 h	12	30
10	4.14^c	MCPBA (1.3 equiv.), MeOH (2.0 equiv.), -20 °C, CH ₂ Cl ₂ , 12 h	15	31
11	4.16	MCPBA (1.3 equiv.), 0 °C, acetone	- ^d	-
12	4.16	Oxone [®] (3.0 equiv.), RT, CH ₂ Cl ₂ , 46 h	- ^e	-
13	4.14	Oxone [®] (3.0 equiv.), RT, MeOH:HFIP:H ₂ O (10:10:1), 5.5 h	- ^d	-
14	4.14	Oxone [®] (3.0 equiv.), RT, CH ₃ CN	- ^d	-
15	4.14	Oxone [®] (3.0 equiv.), RT, MeOH	- ^d	-
16	4.14	Oxone [®] (3.0 equiv.), RT, HFIP, 11 h	35	0

^aIsolated yields after column chromatography. ^bEnantiomeric excess of the product were determined using Eu(hfc)₃ (Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate) as a shift reagent. ^c40 mol% of the precatalyst was used. ^dThe starting compound was consumed generating a complex reaction mixture. ^eThe starting material remained unreacted.

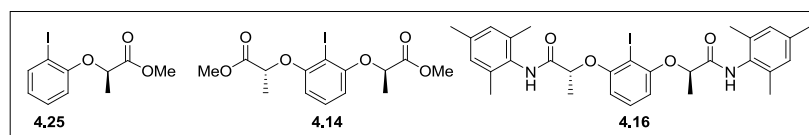


Table 4.5 Optimization of reaction conditions

Increasing the catalyst load to 40 mol% had a favorable influence on rate and *ee* but no effect on yield (entry 6). Solvents other than CH₂Cl₂, e.g., chloroform (entry 7) or 1,2-dichloroethane (entry 8) were less satisfactory. Attempts to modulate the polarity of the reaction

medium by admixture of CH₂Cl₂ with nonpolar hexanes (entry 9) or polar methanol (entry 10) failed to improve yields or *ee*'s. In the latter respect, Ishihara et al. had shown that addition of some MeOH to the reaction mixture improved the yield and the *ee* of products of oxidative *ortho*-lactonization.^[74] Polar solvents such as acetone (entry 11) were especially poor, promoting the formation of complex product mixtures containing none of the desired **4.2a**. The choice of this solvent was motivated by the expectation that its reaction with MCPBA would produce dimethyldioxirane (DMDO): it seemed interesting to explore alternative oxidants for the desired transformation. In that connection, Oxone[®] was also examined as the terminal oxidant. No reaction occurred when CH₂Cl₂ was used as the solvent (entry 12), presumably because of the insolubility of the oxidant in that medium. Attempts to solubilize Oxone[®] in CH₂Cl₂ by the use of one full equivalent of a phase-transfer agent such as tetrabutylammonium tetrafluoroborate (Bu₄N⁺BF₄⁻) were unproductive, resulting only in the formation of complex reaction mixtures. The same outcome was obtained in polar solvents like H₂O, MeOH and MeCN (entries 13-15). The use of Oxone[®] in HFIP produced **4.2a** in 35% yield, but the product was racemic (entry 16).

From the above results we concluded that CH₂Cl₂ is the best reaction solvent, just as in the case of the oxidative cyclization of phenolic acids. Polar solvents, and especially polar, protic ones such as HFIP or TFA, are entirely unsuitable, in that either no desired **4.2a** is formed in these media, or the product is obtained as the racemate. This observation has significant mechanistic implications, as outlined in Section 4.3.4 below.

At this point, a comment is in order about the technique that was employed to evaluate the extent of asymmetric induction in the above reactions. It was determined that a rapid way to do so entailed a ¹H NMR shift study that relied upon europium tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorate (Eu(hfc)₃) as a chiral shift reagent. Thus, progressive

addition of small portions (tip of a spatulaful) of $\text{Eu}(\text{hfc})_3$ to a CDCl_3 solution of $(\pm)\text{-4.2a}$ resulted in greater splitting of the resonances of the methyl group of methanesulfonamide in the two enantiomers (Figure 4.3). As seen in Figure 4.4, nearly baseline resolution of the methyl signals of $(+)\text{-4.2a}$ was achieved. Integration of these resonances provided the enantiomeric ratio, and consequently the *ee*, of an enantioenriched product.

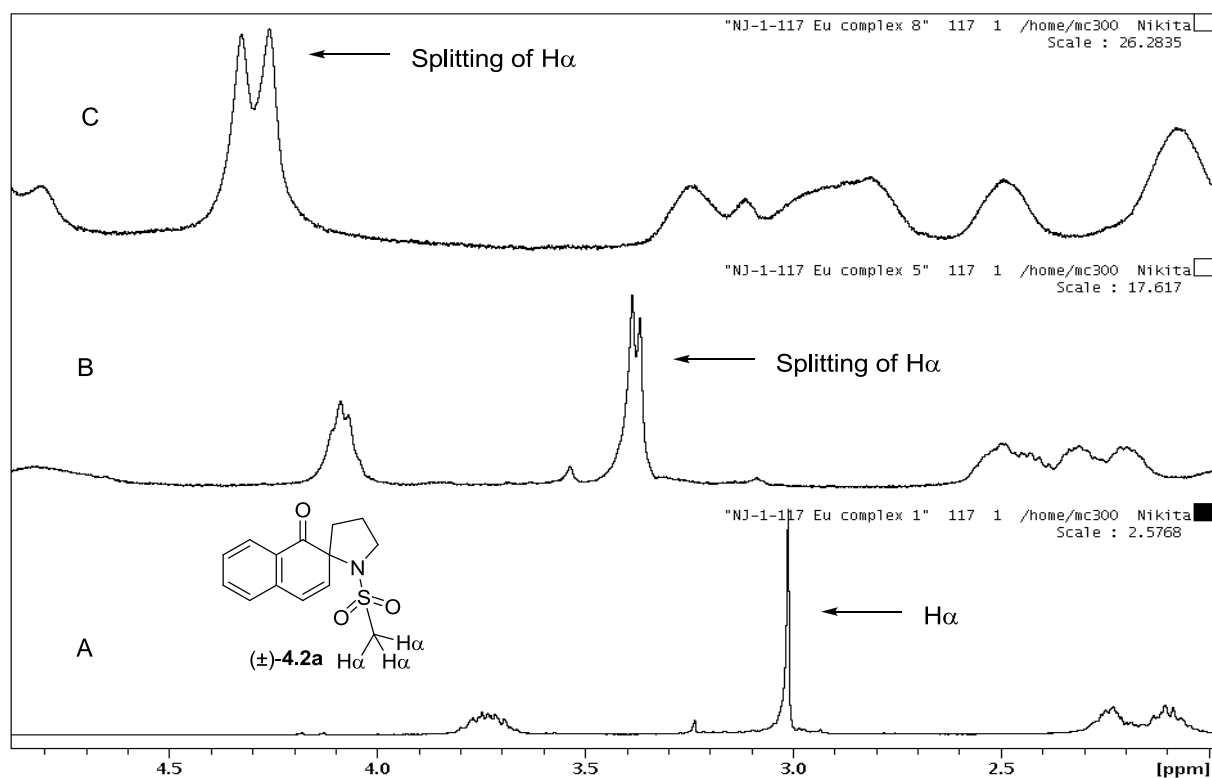


Figure 4.3 Splitting of mesyl peak of $(\pm)\text{-4.2a}$ in presence of $\text{Eu}(\text{hfc})_3$

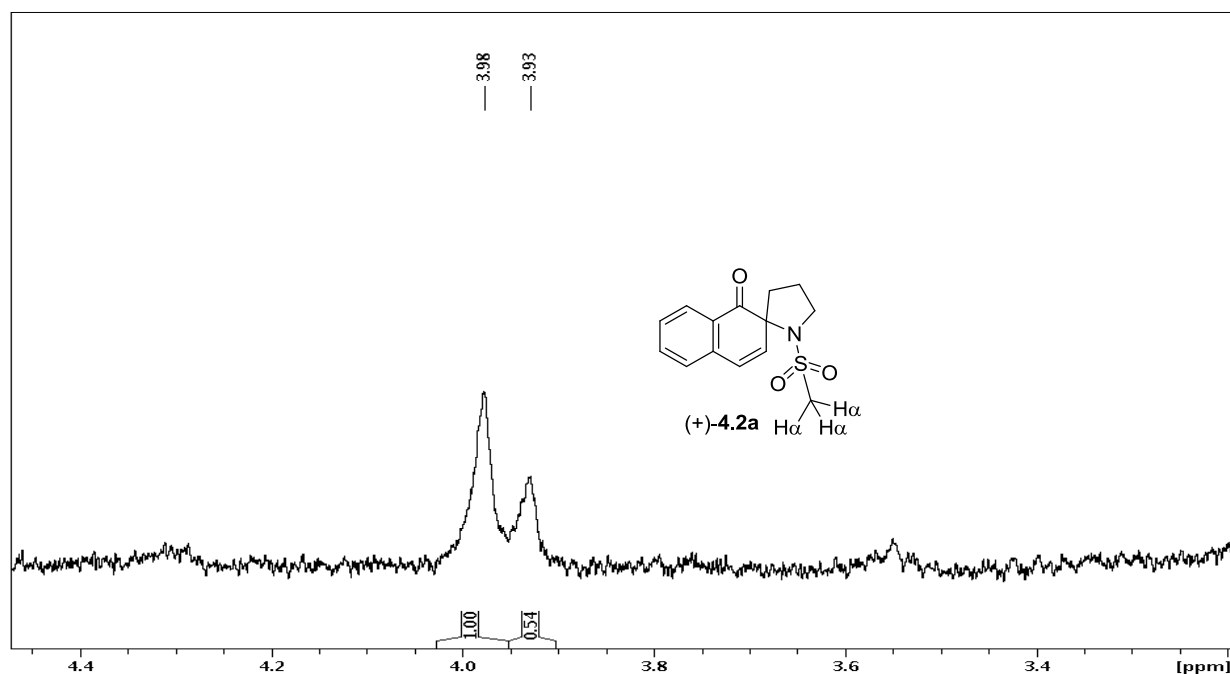


Figure 4.4 Splitting of mesyl peak of (+)-**4.2a** (30% *ee*) in presence of $\text{Eu}(\text{hfc})_3$

More accurate measurements of asymmetric induction were carried out using chiral Supercritical Fluid Chromatography (SFC), but only for those reactions that produced significant *ee*'s. The sample was prepared by dissolving ~3 mg of the compound in ~1.3 mL of methanol followed by its filtration so that the insoluble solid particles, if any, can be removed. The prepared sample was then run through chiral columns under high pressure (~120 bar) by using *i*PrOH with 0.1% of diethylamine as polar solvent and liquid CO_2 as the non-polar form. The retention time (t_R) of eluting enantiomers were recorded and compared to the enantiomeric peaks of racemic compound. Difference between the area of the peaks of enantiomers provided the *ee* of the product. Figure 4.5-4.6 shows that excellent separation of the enantiomers of the product could be achieved by using SFC.

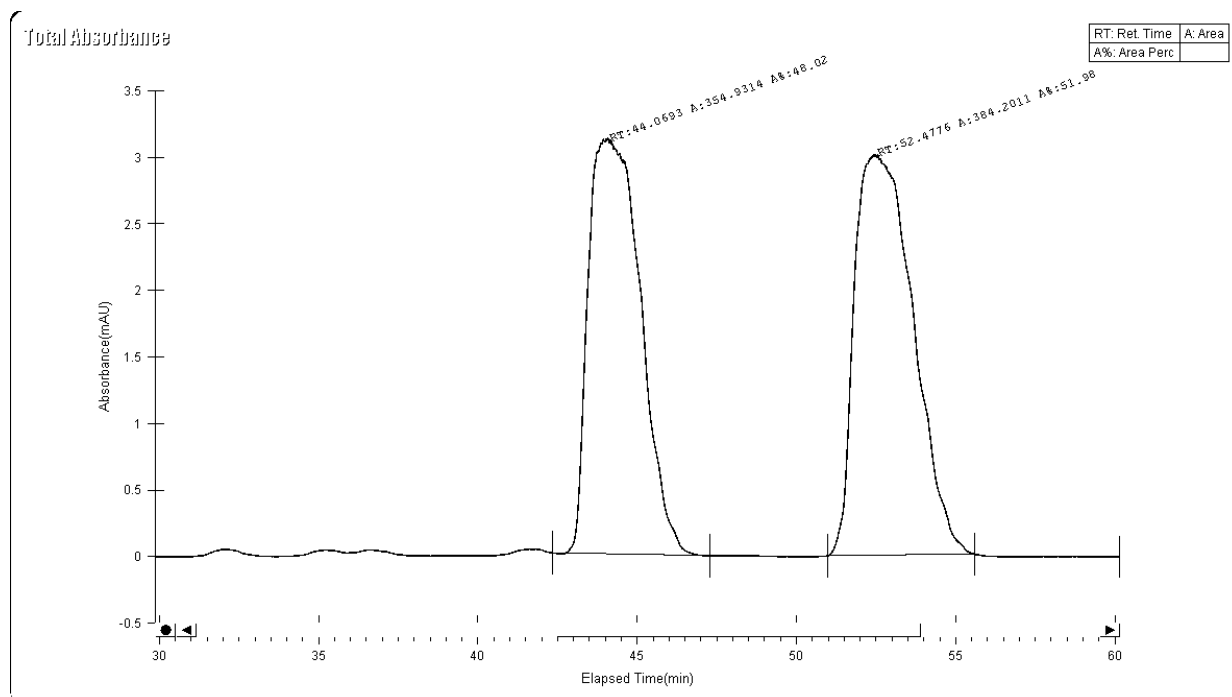


Figure 4.5 SFC chromatogram of (±)-**4.2a** (229 nm)

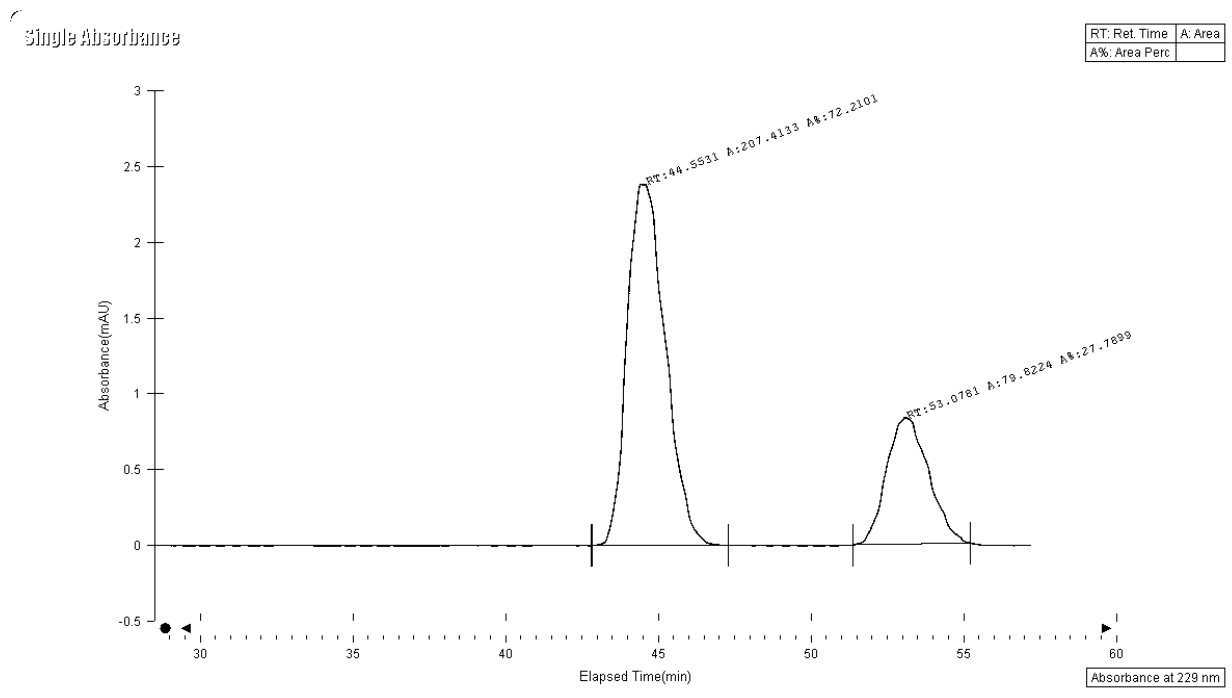
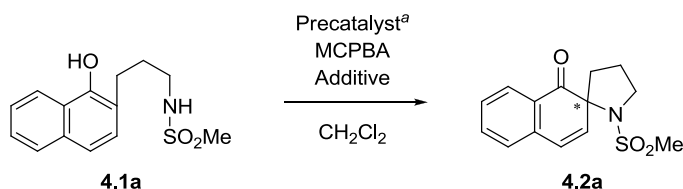


Figure 4.6 SFC chromatogram of (-)-**4.2a** (229 nm, 44% *ee*)

4.3.2 Effect of additives

The next phase of the research examined the use of additives in order to accelerate reaction rates and improve yields and *ee*'s (Table 4.6). Reportedly, additives such as AcOH^[71] and MeOH^[74] enhance the yield and *ee* of *ortho*-lactonization reactions of naphtholic acids. However, we had already determined that AcOH (Table 4.1, entry 4) or MeOH (Table 4.5, entry 10) were best avoided in our case. Conduct of the reaction in CH₂Cl₂ containing TFA (the best solvent for the generation of **4.2a** in racemic form) resulted in a low yield of racemic product (entry 1).



Entry	Additive (1.1 equiv)	Precatalyst	Yield ^b (%)	<i>ee</i> ^c (%)
1	TFA	4.14	29	0
		4.16	19	0
2	BF ₃ ·OEt ₂	4.14	27	0
		4.16	21	0
3	TBDMSOTf	4.14	20	0
		4.16	25	0
4	Yb(OTf) ₃	4.14	24	0
5	TMSOTf	4.14	17	0
6	Sc(OTf) ₃	4.14	25	0
7	TfOH	4.14	15	0

^aprecatalyst (20 mol%), MCPBA (1.3 equiv), additive (1.1 equiv), 0 °C, CH₂Cl₂ (0.02M). ^bIsolated yields after column chromatography. ^cEnantiomeric excess of the product were determined using Eu(hfc)₃ (Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as a shift reagent.

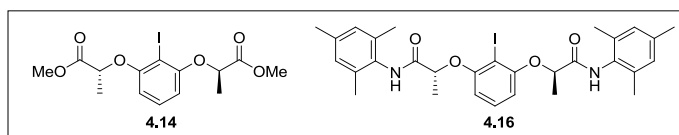
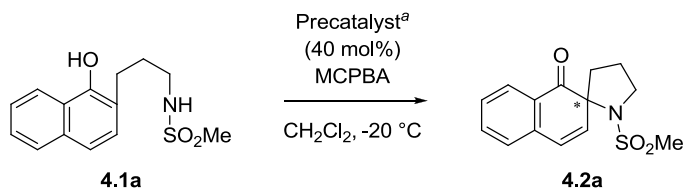


Table 4.6 Effect of addition of additives

Use of $\text{BF}_3 \cdot \text{OEt}_2$ promoted formation of polymeric products from which only ~20% of racemic **4.2a** was isolated (entry 2). No enhancement in yield and no enantioinduction was observed when triflic acid or other triflates like TBDMSOTf, $\text{Yb}(\text{OTf})_3$, TMSOTf, $\text{Sc}(\text{OTf})_3$ were used as additives (entries 3-7). These results indicate that Bronsted or Lewis acids promotes the formation of racemic **4.2a**. Mechanistic ramifications of these results are discussed in Section 4.3.4

4.3.3 Precatalyst screening

At this juncture, a screen of alternative chiral iodides was launched. Table 4.7 summarizes the results obtained with C_1 -symmetric iodoarene **4.25**, and with various structural analogues of Ishihara iodide **4.16**. All experiments were run in CH_2Cl_2 at $-20\text{ }^\circ\text{C}$ with 40 mol%



Entry	Precatalyst	Time (h)	Yield ^b (%)	ee ^c (%)
1	4.25	18	15	17
2	4.14	15.5	26	37
3	4.15	10.5	15	12
4	4.16	12	15	20
5	4.26	-	- ^d	-

^aPrecatalyst (40 mol%), MCPBA (1.3 equiv), $-20\text{ }^\circ\text{C}$, CH_2Cl_2 (0.02M). ^bIsolated yields after column chromatography. ^cEnantiomeric excess of the product were determined using $\text{Eu}(\text{hfc})_3$ (Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as a shift reagent. ^dThe starting compound was consumed generating a complex reaction mixture.

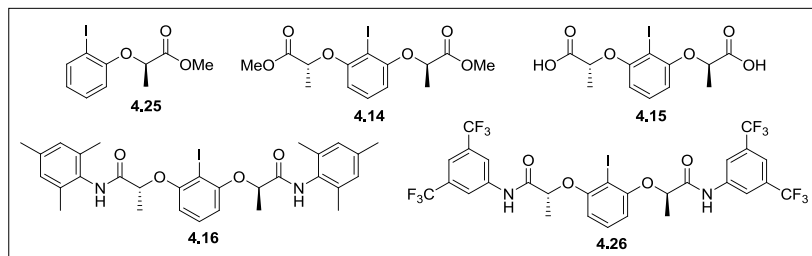
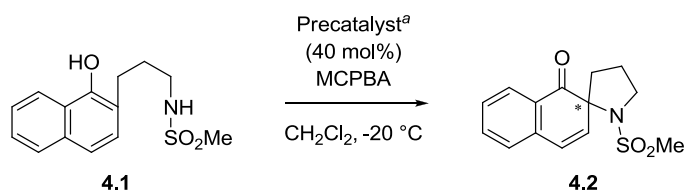


Table 4.7 Precatalyst screening - I

of precatalyst and MCPBA as the oxidant. The C_1 symmetric iodide **4.25** was ineffective (entry 1). The C_2 diester **4.14** fared better (entry 2), while the corresponding diacid **4.15** proved inferior (entry 3). Ishihara iodide **4.16** was less efficacious than diester **4.14**. Chiral iodide **4.26**, wherein electron-withdrawing CF_3 groups were present on the aryl moiety in lieu of methyl, promoted the formation of complex mixtures of products containing no desired **4.2a** (entry 5).



Entry	Precatalyst	Time (h)	Yield ^b (%)	ee ^c (%)
1	4.20 ^d	14.5	20	46 ^f
2	4.18	13	11	<5
3	4.21	12	15	6
4	4.23 ^d	13.5	15	15
5	4.22 ^d	12	15	18

^aPrecatalyst (40 mol%), MCPBA (1.3 equiv), -20 °C, CH_2Cl_2 (0.02M). ^bIsolated yields after column chromatography. ^cEnantiomeric excess of the product were determined using $Eu(hfc)_3$ (Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate) as a shift reagent. ^d20 mol% of the precatalyst was used. ^eEnantiomeric excess of the product were determined using chiral SFC.

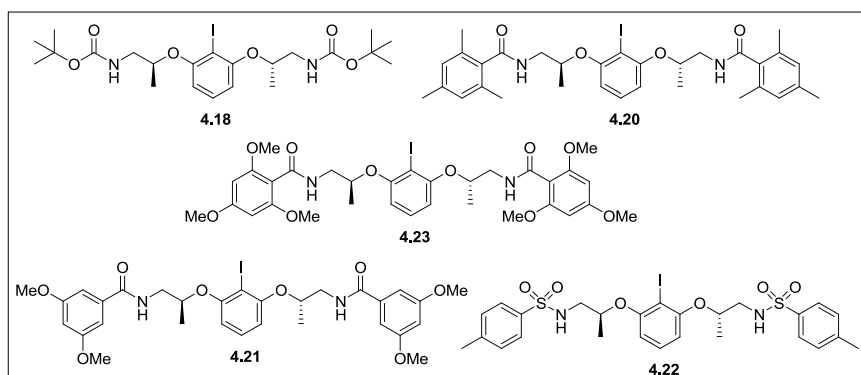
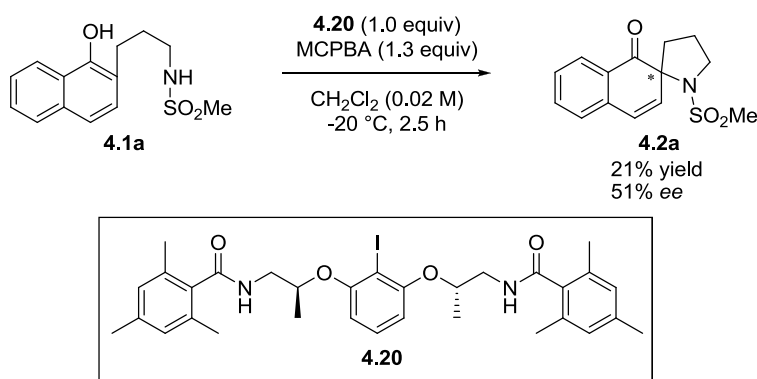


Table 4.8 Precatalyst screening - II

During optimization of the oxidative amidation of **4.2a**, Ishihara and coworkers described a “second generation” catalyst, iodide **4.20** (figure below Table 4.8) that was particularly effective for the oxidative cyclization of carboxylic acids.^[74] This induced us to test **4.20** and its

structural congeners for the analogous reaction of **4.1a**. Among all iodides tested, **4.20** indeed afforded by far the best degree of asymmetric induction in the cyclization of **4.1** (46%, Table 4.8, entry 1). The yield of **4.2a**, however, was only 20%.

The use of a stoichiometric amount of iodide **4.20** in the oxidative cyclization of **4.1a** resulted only in a marginal increase in asymmetric induction (*ee* 46% \rightarrow 51%) which can be attributed to the instrumental errors, but chemical yields remained unaffected (Scheme 4.8). Thus, the use of sub-stoichiometric amount of chiral iodide was preferable.



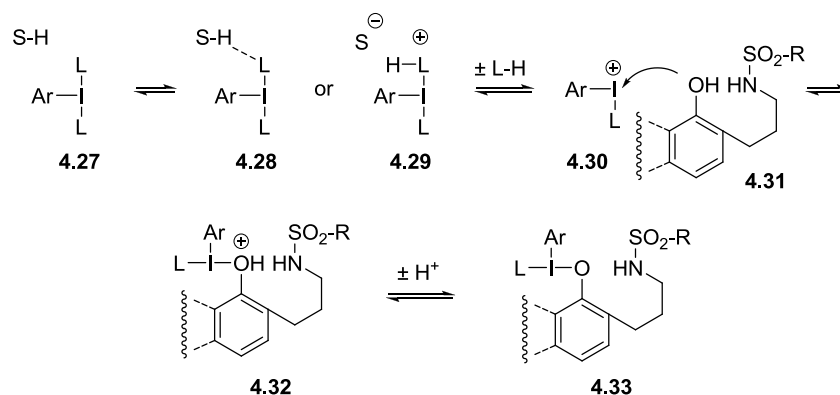
Scheme 4.8 Oxidative amidation of **4.1a** employing stoichiometric amount of iodide **4.20**

4.3.4 Mechanistic aspects

The above results lead to the following conclusions. First, polar, non-nucleophilic, protic, Bronsted acidic solvents, such as HFIP ($\text{pK}_a = 9.3$)^[108] and – especially – TFA ($\text{pK}_a = 0.3$)^[108] are optimal for the conduct of the oxidative cyclization of sulfonamides in the racemic series, but they are entirely inadequate for the asymmetric reaction, in that they promote the formation of racemic products. Second, the reaction of interest is best carried out in moderately polar CH_2Cl_2 , just as in the case of the analogous cyclization of carboxylic acids. However, the use of this solvent results in slow reaction rates and yields of only about 20%, both in the racemic or the

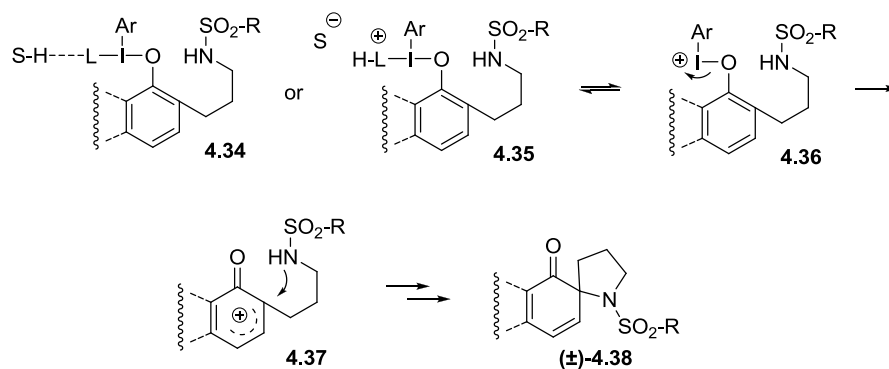
asymmetric series. Third, the asymmetric reaction affords the best *ee*'s in the presence of 20-40 mol % of chiral catalyst, instead of the customary 10 mol %. Fourth, Bronsted or Lewis acidic additives also induce the formation of racemic products.

These observations lead to the following mechanistic picture. The phenolic OH must first ligate the hypervalent iodine species, whether DIB, PIFA, or the oxidized form of a chiral iodide, via a ligand exchange event. This step is more likely to occur by a dissociative mechanism than an associative one. Indeed, the observation that the reaction is faster in protic, Bronsted acidic solvents may reflect the fact that one of the original ligands, L, on the iodine atom departs either upon establishing a strong H-bond with the solvent (S-H in Scheme 4.9) or upon full protonation (structures **4.28** and **4.29**). The resulting iodonium ion **4.30** then combines with the substrate, **4.31**, to produce complex **4.33**.



Scheme 4.9 Initial steps of the oxidative cyclization of sulfonamides

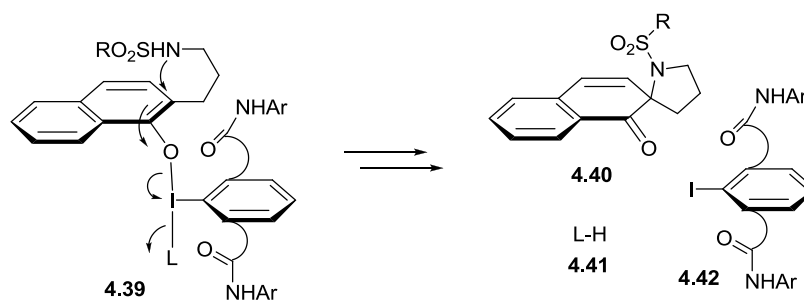
By the same logic, it seems plausible that in polar, protic solvents, complex **4.34** or **4.35** will rapidly equilibrate with iodonium ion **4.36**, which then fragments quickly to produce cation **4.37**. The latter then cyclizes to give racemic **4.38** (Scheme 4.10).



Scheme 4.10 Presumed mechanism of cyclization of complex **4.33** in polar, protic media

Clearly, an enantioselective variant of the above process is possible only within the asymmetric environment of the chiral catalyst. The chiral iodoarene must then remain associated with the substrate for the reaction to occur with asymmetric induction: any factor that promotes dissociation of **4.36** to cation **4.37** will result in formation of racemic product. This may be the reason why polar solvents – especially protic ones – as well as Bronsted and Lewis acids have an adverse effect on asymmetric induction: electrostatic effects (polar solvents), H-bonding or protonation (protic solvents, Bronsted acids) interactions, as well as coordination of ligand L with a Lewis acid, would all favor equilibration of **4.34** or **4.35** with **4.36**, and consequent rapid fragmentation of the latter to **4.37**.

Less polar, aprotic solvents such as CH_2Cl_2 retard the rate of fragmentation of complex **4.39**. The chirality of **4.42** can now direct the nucleophilic sulfonamide to one diastereotopic face of the naphthalene segment, resulting in formation of an enantioenriched product (Scheme 4.11). On the other hand, the naphthalene ring in complex **4.39** is surely less electrophilic than than cation **4.37** (Scheme 4.10 above), accounting for a significantly slower overall reaction rate.



Scheme 4.11 Presumed mechanism of formation of enantioenriched products

4.3.5 Asymmetric oxidative cyclization of naphtholic sulfonamides: a new catalyst design

In 2013, Ishihara and collaborators obtained an X-ray crystal structure of the hypervalent form of iodide **4.20**.^[74] It thus transpired that – at least in the solid state – such a species exists as a helical structure held together by hydrogen bonds between the amide N–H's and the oxygen ligands on the iodine(III) atom (Figure 4.7). The authors further posited that such a helical arrangement is crucial for catalysts performance.

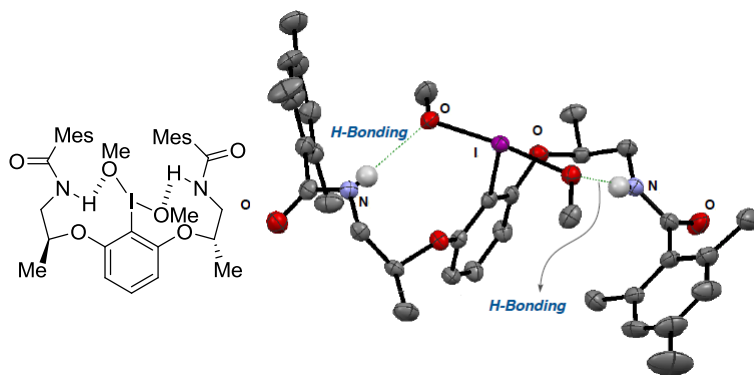


Figure 4.7 Ishihara's X-ray structure of hypervalent form of **4.20**

On such a basis, we hypothesized that relocating the stereocenters closer to the NH group might enforce the hydrogen-bonded conformation of the I(III) variant of the catalyst through a Thorpe-Ingold-like effect,^[105] especially if one were to increase the steric demand of the R

group. The stereocenters would thus become closer to the iodine atom, enhancing the chiral nature of the environment around it and possibly providing a more efficient catalyst (Figure 4.8).

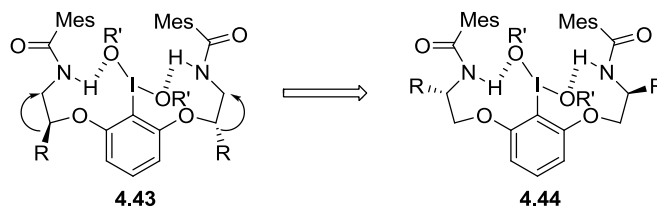
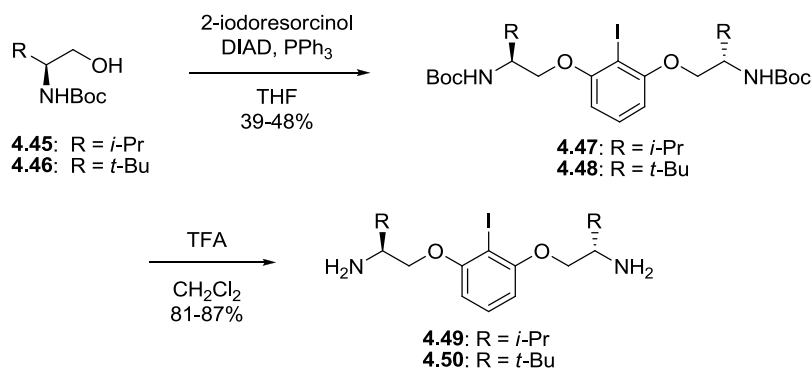


Figure 4.8 Working hypothesis for a new catalyst design

As evident from results of precatalyst screening (Table 4.8), a mesityl amide was important for optimal catalyst performance. In addition, the presence of secondary amide was mandatory for H-bonding to occur. It was thus concluded that the new catalyst architecture should be embodied in the form of iodides **4.51** and **4.52**.

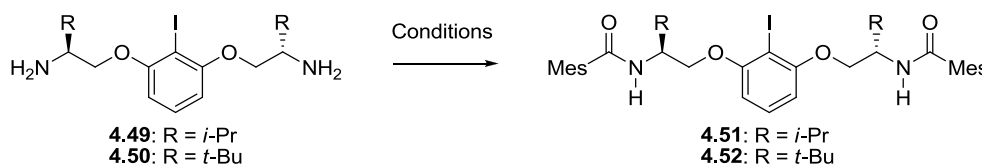
The synthesis of the new iodoarenes started with Mitsunobu reaction of 2-iodoresorcinol with Boc-protected valinol (**4.45**) or *tert*-leucinol (**4.46**), followed by deprotection of the resulting **4.47-4.48** (Scheme 4.12).



Scheme 4.12 Synthesis of amine **4.49-4.50**

The subsequent acylation of free amines **4.49-4.50** proved to be less than straightforward. To illustrate, reaction of **4.49** with MesCOCl generated **4.51** in poor yield, possibly because of

the bulky nature of amine (Table 4.9, entry 1). The same reaction of the even bulkier **4.50** afforded no desired product whatsoever (^1H NMR). An EDCI mediated coupling of the amines with 2,4,6-trimethylbenzoic acid in CH_2Cl_2 fared better, but yields were low (entry 2). A significant improvement in the yield of **4.51** (18% \rightarrow 52%) and **4.52** (13% \rightarrow 47%) was achieved by operating at reflux (entry 3). However, yields dropped drastically (**4.51**: 52% \rightarrow 5%; **4.52**: 47% \rightarrow 6%) when the reaction was scaled up from 0.1 to 1.0 mmol (entry 4). This problem was circumvented by changing the solvent from CH_2Cl_2 to $\text{DMF}^{[109]}$ and employing $\text{HOBT}^{[109],[110]}$ as a catalyst. Compounds **4.51** and **4.52** were thus isolated in much higher yields even when the reaction was performed on 3.5 mmol scale (entry 5).



Entry	Conditions	Yield ^a (%)	
		4.51	4.52
1	MesCOCl (3.0 equiv), Pyridine (excess), CH_2Cl_2 , 0 \square C to RT	14	- ^b
2 ^c	MesCO ₂ H (2.5 equiv), EDCI (2.5 equiv), DMAP (2.5 equiv), CH_2Cl_2 , RT	18	13
3 ^c	MesCO ₂ H (2.5 equiv), EDCI (2.5 equiv), DMAP (2.5 equiv), CH_2Cl_2 , Δ	52	47
4 ^d	MesCO ₂ H (2.5 equiv), EDCI (2.5 equiv), DMAP (2.5 equiv), CH_2Cl_2 , Δ	5	6
5 ^e	MesCO ₂ H (2.5 equiv), EDCI (2.5 equiv), HOBT (2.5 equiv), DMF, RT	53	57

^aIsolated yields after column chromatography. ^bComplex reaction mixture was obtained with no desired compound seen in crude NMR. ^cReactions were done on 0.1 mmol scale. ^dReactions were done on 1.0 mmol scale. ^eReactions were done on 3.5 mmol scale.

Table 4.9 Optimization of conditions for the acylation of amines **4.51-4.52**

The structure of iodide **4.52** was confirmed via X-ray analysis of crystals grown via slow evaporation of an ethanolic solution (Figure 4.9).

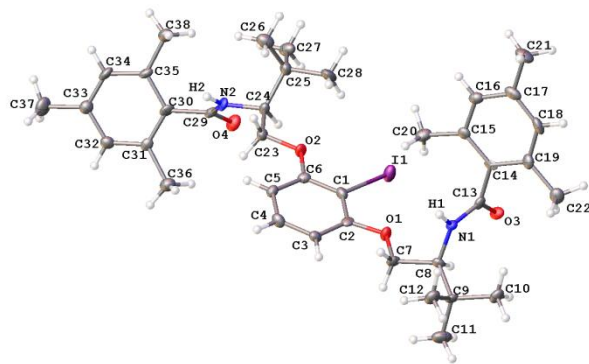
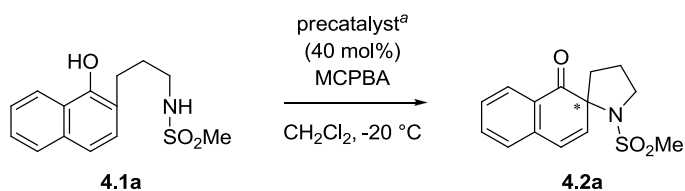


Figure 4.9 X-ray structure of iodide **4.52**

Compounds **4.51** and **4.52** were then evaluated for the enantioselective oxidative dearomatization of **4.1a**. Catalyst **4.51** proved no better than Ishihara's iodide **4.20** (Table 4.10, entry 1); however, the bulkier **4.52** provided significantly higher *ee* (66%), although yields remained around 20% (entry 2). Lowering the catalyst load from 40 mol% to 20 mol% had no effect on selectivity and yield (entry 3). However, a catalyst load lower than 20 mol% resulted in longer reaction times and formation of several side products (TLC), thereby diminishing the yield of desired **4.2a**.



Entry	Precatalyst	Time (h)	Yield ^b (%)	<i>ee</i> ^c (%)
1	4.51	12	17	35
2	4.52	13.5	21	66
3	4.52 ^d	15.5	20	67

^aPrecatalyst (40 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02M). ^bIsolated yields after column chromatography. ^cEnantiomeric excess of the product were determined using chiral SFC. ^d20 mol% of the precatalyst was used.

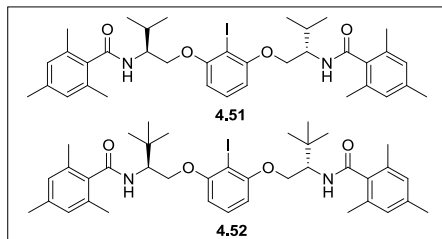


Table 4.10 Precatalyst screening with iodides **4.51** and **4.52**

It is worthy of note that Ishihara iodide **4.20** and the new catalysts afforded an opposite sense of asymmetric induction: spiropyrrolidine **4.2a** obtained by the use of **4.20** was levorotatory; that prepared in the presence of **4.51-4.52** exhibited positive rotation. Either racemic or enantioenriched **4.2a** was nicely crystalline. This induced us to determine the absolute configuration of either enantiomer by X-ray diffractometry.

A single recrystallization of material of 67% *ee* (Table 4.10, entry 3) from toluene-hexane afforded product of 96% *ee*. A single crystal of this compound was grown via the vapor diffusion technique, again using toluene/hexane as solvent pair. An X-ray diffractometric study revealed that the compound was of (*R*)-configuration (Figure 4.10).

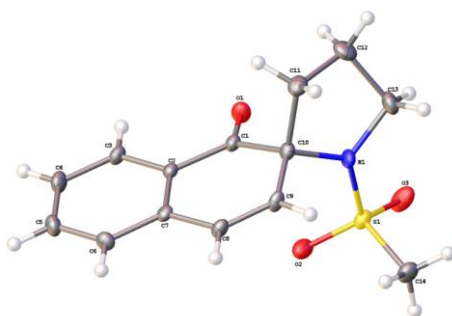


Figure 4.10 X-ray structure of (+)-(*R*)-**4.2a**

In a like manner, a single crystallization of material obtained using Ishihara's iodide **4.20** increased the *ee* from 46% to 88%. A single crystal grown as detailed above enabled a structural study by X-ray analysis, which confirmed that the compound was (-)-(*S*)-**4.2a** (Figure 4.11).

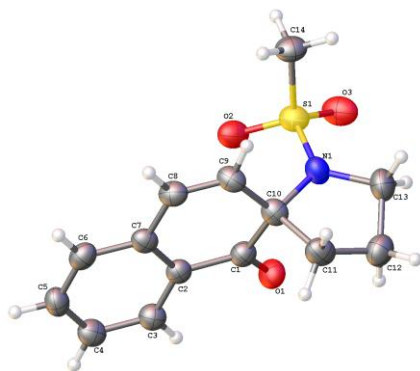


Figure 4.11 X-ray structure of (-)-(*S*)-**4.2a**

4.3.6 Oxidative cyclization of para-substituted 1-naphtholic sulfonamides

Our apparent inability to achieve yields of **4.2a** above 20% induced us to determine the nature of at least some of the side products formed in the course of the reaction, with the hope that pertinent information may assist us to devise a way to contain their formation. The major side product was identified as compound **4.53** (27% yield), which had obviously arisen through a bimolecular oxidative addition of MCBA to **4.1a**. The fact that **4.45** was enantioenriched to an *ee* of 80% was noteworthy, in that virtually all known asymmetric dearomatization reactions promoted by chiral hypervalent iodine reagents are intramolecular. An exception is the Quideau-Birman *ortho*-hydroxylative dearomatization of phenols.^[75-77] Yet, there seems to be no literature precedent for asymmetric bimolecular oxidative acyloxylation of phenolic or naphtholic substrates. Once again, an opposite sense of asymmetric induction was observed for catalyst **4.52** (generation of (+)-**4.53**) relative to Ishihara iodide **4.20** (formation of (-)-**4.53**). However, the absolute configuration of **4.53** remains to be determined. Further aspects of this novel oxidative

acyloxylation reaction, along with details of how the enantiomeric excess of **4.53** was determined, are discussed in Section 4.3.10.

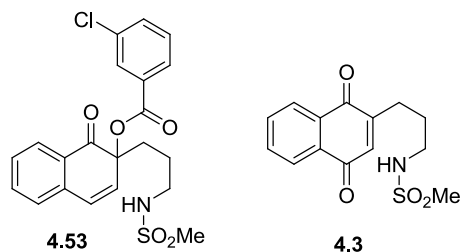
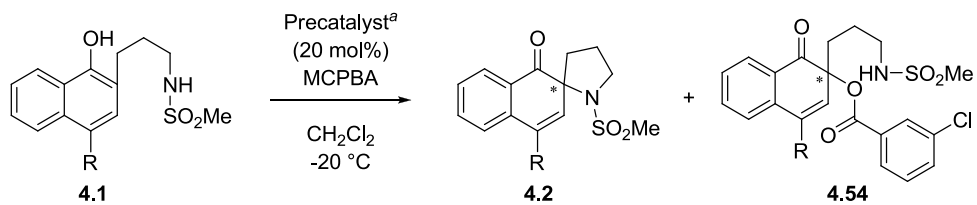


Figure 4.12 Side products formed during oxidative amidation of **4.1a**

The second more significant by product was *para*-naphthoquinone **4.3** (Figure 4.12, 20-35%). The undesired formation of this material could arguably be contained / suppressed by the use of appropriately *para*-substituted substrates. Interestingly, most reported examples of oxidative cyclization of naphtholic acids employed substrates carrying a 4-substituent; often, a chlorine atom.^{[69-72],[74]} In retrospect, this may be attributable to an effort to suppress naphthoquinone formation, even though the reason was not expressly mentioned. Regardless, the next phase of this research focused on the oxidative cyclization of 4-substituted naphtholic sulfonamides.

Table 4.11 shows the results of a comparative study of the performance of catalyst **4.20** and **4.52** in oxidative cyclization of sulfonamides **4.1**. In all cases, the acyloxyated adduct **4.54** was formed along with cyclized product **4.2**. Entries 1 and 2 serve as a reminder that precatalyst **4.52** provided superior *ee* (67%) compared to Ishihara's iodide **4.20** (46%). Doubling the loading of **4.52** had no effect on the *ee* of both cyclic product and MCBA adduct (entry 3). Hence, all other experiments were carried out using 20 mol% of chiral iodide.

As expected, the 4-substituent suppressed formation of quinone **4.3**. Yields of cyclized products were generally higher relative to **4.2**, but the *ee*'s were lower. The behavior of the 4-bromo substrate is representative: the yield of cyclized product nearly doubled, but the *ee* dropped from 67% to 17% (entries 4 and 5). However, the acyloxylated product **4.54**, R = Br was still obtained in significantly enantioenriched form. Asymmetric induction was consistently better for acyloxylated adducts **4.54** than for the cyclic products **4.2**. Yet, just as in the case of the cyclic products, 4-substitution was not beneficial to asymmetric induction. A 4-Br substituent caused a greater extent of *ee* erosion relative to a 4-Cl group (entries 4-7). Overall, precatalyst **4.52** provided a generally better extent of asymmetric induction relative to Ishihara iodide **4.20**, except in the case of 4-chloro naphtholic sulfonamides **4.1**, R = Cl (entries 6 and 7). Aryl substitution at the *para* position afforded spiro-sulfonamides with inferior *ee*'s (entries 8-15). While corresponding acyloxylated products were still present in reaction mixtures arising from these substrates, their isolation proved to be quite problematic. Therefore, no yield and *ee* data are reported for these materials (entries 8-15) because of our inability to produce pure samples.



Entry	Precatalyst	R	Time (h)	Selectivity		Yield ^b (%)		<i>ee</i> ^c (%)	
				4.2	4.54	4.2	4.54	4.2	4.54
1	4.20	H	14.5	(-)-(<i>S</i>)	(-) ^e	20	27	46	64
2	4.52	H	15.5	(+)-(<i>R</i>)	(+) ^e	20	25	67	80
3	4.52 ^d	H	13.5	(+)-(<i>R</i>)	(+) ^e	21	28	66	80
4	4.20	Br	12	(-) ^e	(-) ^e	45	28	17	50
5	4.52	Br	13	(+) ^e	(+) ^e	35	21	17	62
6	4.20	Cl	19	(-) ^e	(-) ^e	16	17	37	59
7	4.52	Cl	26	(+) ^e	(+) ^e	20	19	30	72
8	4.20	Ph	15.5	(-) ^e	-	30	-	18	-
9	4.52	Ph	21	(+) ^e	-	31	-	24	-
10	4.20	4-F-C ₆ H ₄	15	(-) ^e	-	25	-	24	-
11	4.52	4-F-C ₆ H ₄	26	(+) ^e	-	27	-	29	-
12	4.20	4-CF ₃ -C ₆ H ₄	15.5	(-) ^e	-	22	-	20	-
13	4.52	4-CF ₃ -C ₆ H ₄	25.5	(+) ^e	-	23	-	28	-
14	4.20	4-(3,5-di-CF ₃ -C ₆ H ₃)	14.5	(-) ^e	-	15	-	14	-
15	4.52	4-(3,5-di-CF ₃ -C ₆ H ₃)	26	(+) ^e	-	18	-	39	-

^aPrecatalyst (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02M). ^bIsolated yields after column chromatography. ^cDetermined by chiral SFC. ^d40 mol% of precatalyst was used. ^eAbsolute configuration was not determined.

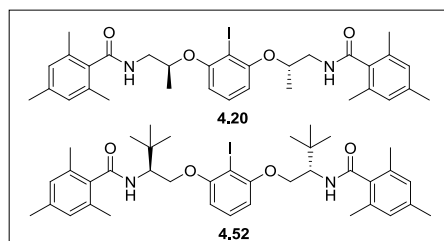
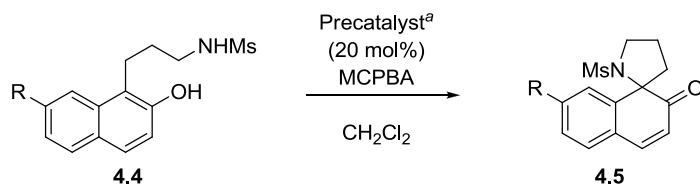


Table 4.11 Oxidative cyclization and acyloxylation of 4-substituted naphtholic methane sulfonamides

4.3.7 Enantioselective oxidative amidation of 2-naphtholic sulfonamides

The above results encouraged us briefly to examine the enantioselective cyclization of 2-naphtholic sulfonamide. Only two substrates of structure **4.4**, wherein R = H or OMe, were examined (Table 4.12), because it was immediately apparent that the reaction was less efficient in the 2-naphtholic series. For instance, the oxidative cyclization of **4.4a**, in the presence of catalyst **4.52** and under the same conditions developed for reaction of 1-naphtholic substrates afforded a complex mixture containing only 15% of desired **4.5a**. This material was formed in only 16% *ee* (entry 1). Iodide **4.20** provided better results in this case (22% yield of **4.5a**, 36% *ee*; entry 2). A single recrystallization from EtOAc / hexanes increased the *ee* of the product to 47% (entry 2).



Entry	Precatalyst	Product	Time (h)	Yield ^b (%)	<i>ee</i> ^c (%)
1	4.52	4.5a (R = H)	14	15	16
2	4.20	4.5a (R = H)	14.5	22	36(47) ^e
3	4.14 ^d	4.5a (R = H)	12	26	24
4	4.20 ^d	4.5b (R = OMe)	12	22	30
5	4.14 ^d	4.5b (R = OMe)	36	21	47(96) ^{e,f}

^aPrecatalyst (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02M). ^bIsolated yields after column chromatography. ^cDetermined by chiral SFC. ^d40 mol% precatalyst was used. ^e*ee* after single crystallization. ^f*ee* was determined by chiral HPLC.

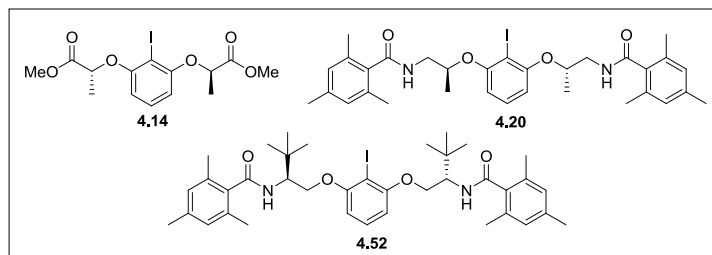


Table 4.12 Oxidative cyclization of 2-naphtholic sulfonamides

Surprisingly, iodide **4.14** performed rather well in this case, except that reaction rates were especially slow at 20 mol% catalyst load. A faster rate was achieved through the use of 40 mol% of catalyst, but with no significant effect on yield and *ee* (entry 3). Because **4.14** performed better than **4.52** in terms of both *ee* and yield, the cyclization of **4.4b** was carried out only with catalysts **4.14** and **4.20**. Yields remained around 20%, but iodide **4.14** afforded the highest product *ee* (47%; entry 5). Formation of MCBA adduct could not be confirmed via ¹H NMR of crude due to its complex nature. Moreover, mass spectrometry of crude sample and attempts to purify the reaction mixture did not give any indication of MCBA adduct formation.

The enantiomeric excess of **4.5b** increased from 47% to 96% upon a single recrystallization from methanol (slow evaporation of a solution), enabling a determination of the absolute configuration by X-ray diffractometry. The compound, which was dextrorotatory, was found to be of (*R*)-configuration (Figure 4.13).

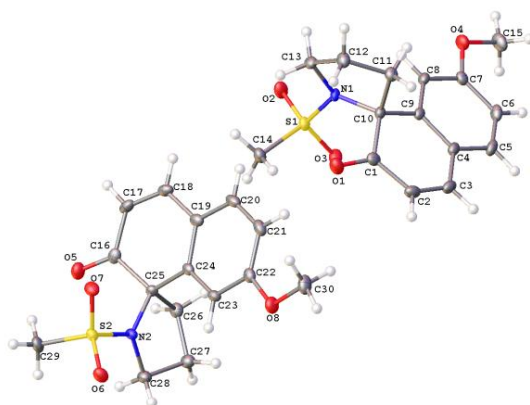
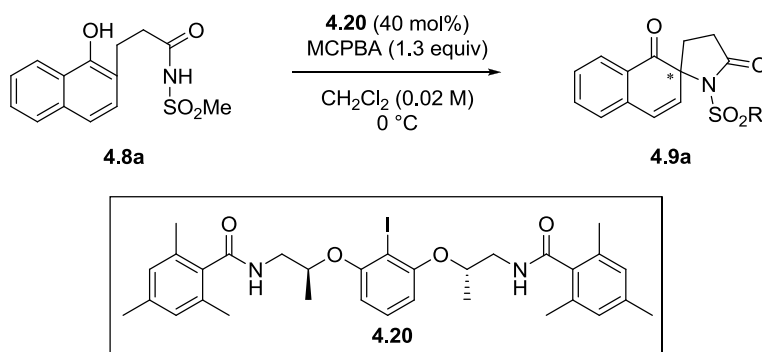


Figure 4.13 X-ray structure of (+)-(R)-**4.5b**

4.3.8 Attempted enantioselective cyclization of acyl sulfonamides

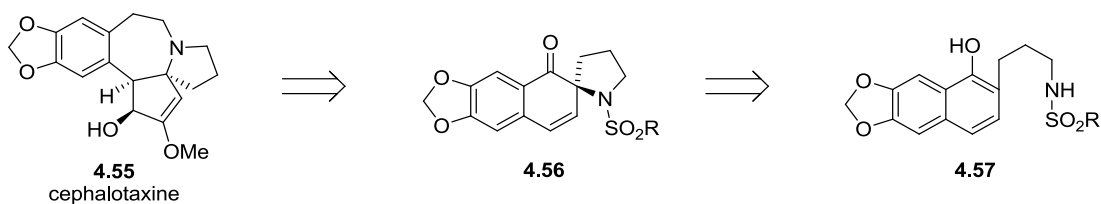
Conditions optimized for enantioselective oxidative amidation of naphtholic sulfonamides were applied to naphtholic acyl sulfonamide **4.8a** (Scheme 4.13). The resulting spiro lactam **4.9a** could serve as the core of Ansalactam A. Unfortunately, complex product mixtures were obtained when **4.8a** was subjected to enantioselective cyclization using iodide **4.20**. Comparison of the ^1H NMR spectra of such crude mixtures with that of authentic (\pm)-**4.9a** suggested that none of it had formed. Therefore, no attempts were made to purify the crude mixture, to optimize the reaction, or to examine the cyclization of other related substrates.



Scheme 4.13 Enantioselective oxidative amidation of acyl sulfonamide **4.8a**

4.3.9 Enantioenriched 4.2a by flow resolution of the racemate

It will be recalled from Section 4.3 that the preparation of spiro pyrrolidine **4.2a** is especially problematic because of concomitant formation of naphthoquinone **4.3** and MCBA adduct **4.53**. Yet, **4.2a** itself and congeners bearing substituents on the benzene ring, but not at the ketone 4-position **4.56**, appear to be valuable building blocks in alkaloid synthesis (Scheme 4.14). For instance, cephalotaxine **4.55** (*Cephalotaxus* alkaloid) may be prepared from spiro pyrrolidine **4.56** which can be produced via oxidative dearomatization of corresponding naphtholic sulfonamide **4.57** (Scheme 4.14). Moreover, chiral spiro pyrrolidine would provide chiral cephalotaxine.



Scheme 4.14 Possible synthesis of cephalotaxine

This provided an incentive to explore the preparation of enantiopure **4.2a**, on scale, by methods other than solely asymmetric synthesis. An interesting solution emerged thanks to a collaborative effort with our colleague, Prof. Jason Hein.

Prof. Hein and Dr. Rougeot from Hein group found that racemic **4.2a**, crystallizes as a conglomerate. In a conglomerate, homochiral interactions, i.e., the energy of association of between molecules of identical chirality (R-R or S-S), is stronger than that of heterochiral (R-S) interactions.^[111] Thus, for a conglomerate forming compound, the racemic mixture is composed of a mechanical mixture of two discrete homochiral crystals, each crystal comprising only one of the two enantiomers. This contrasts with the case of a true racemic crystal, which constitutes a heterochiral crystal phase, containing both enantiomers in the repeating unit cell of the crystal (Figure 4.14).

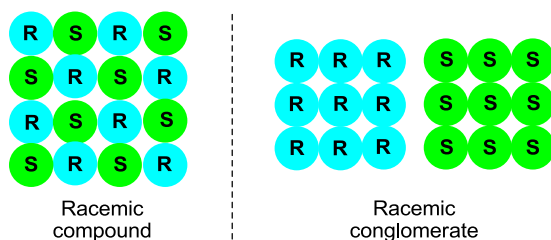


Figure 4.14 Crystal packing of a racemic solid: conglomerate (right) vs. racemic (left)

The physical properties of a conglomerate are such that the solubility of homochiral crystals is lower than that of heterochiral ones.^[112] This enables efficient enantiomeric enrichment by recrystallization: the enantiomer present in excess tends to crystallize, leaving racemic material in the mother liquor. This is indeed what was observed with scalemic mixture of **4.2a** (46% *ee*).

The experiment for resolution of (\pm)-**4.2a** via Coupled Preferential Crystallization (CPC) was performed by Prof. Hein using the following procedure. A satd. solution of (\pm)-**4.2a** was prepared by suspending 80 mg of (\pm)-**4.2a** in toluene (~ 1.5 mL) and stirred overnight at 20 °C. The clear filtrate (satd. solution) obtained after filtering the suspended solution (~1.3 mL) was added to vial A of the EasyMax (T= 20 °C) (Figure 4.15). Vial A was then charged with 20 mg of (\pm)-**4.2a** (solid) and Vial B was charged with super satd. solution of (-)-**4.2a** (~30 mg, 0.5 mL, 46% *ee*). Both vials were stirred at 250 RPM for 30 minutes, keeping the internal temperature constant at 20 °C. Vials A and B were then connected to two separate Ismatec REGLO-CPF *Digital* pumps using Teflon® PFA tubing (1/16 OD) fitted on the uptake with a fritted PTFE-filter (0.5 μ m porosity). The filtered solution phase was circulated between the two flasks at 1.0 mL/min. After 30 minutes of stirring, temperature of the vial B was slowly decreased to 18 °C. During the crystallization process, the racemic liquid phase was circulated on the average of 1.0 mL/min for 24 hours. Solid phases from vial A and vial B were filtered to produce (-)-(*S*)-**4.2a** and (+)-(*R*)-**4.2a** in high optical purity (>98% *ee* by HPLC). This experiment was done only once and needs to be repeated on large scale in order to reproduce the resolution of **4.2a** via CPC technique.

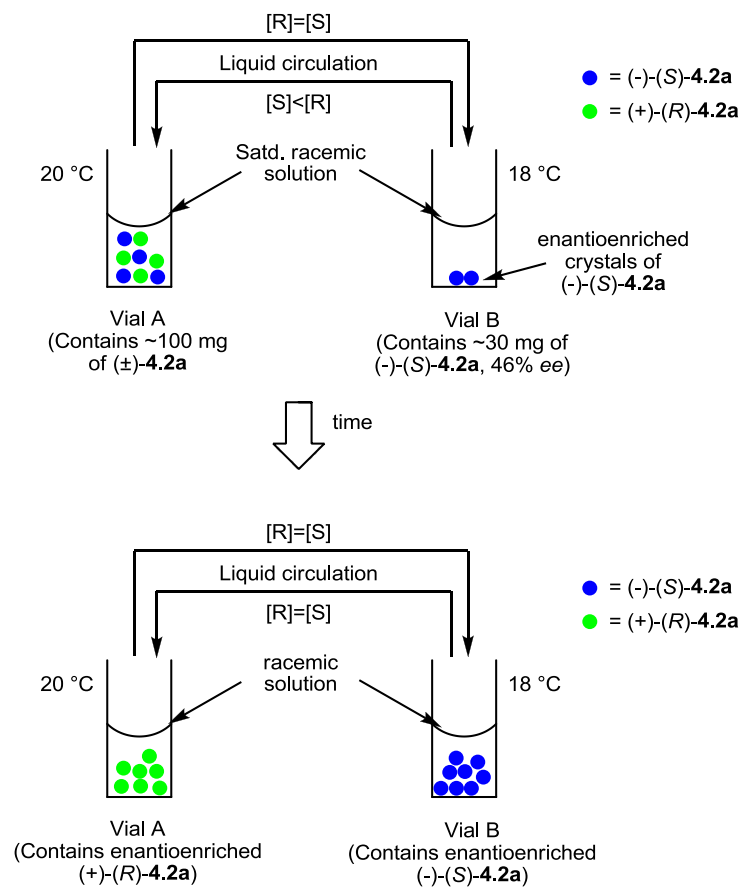
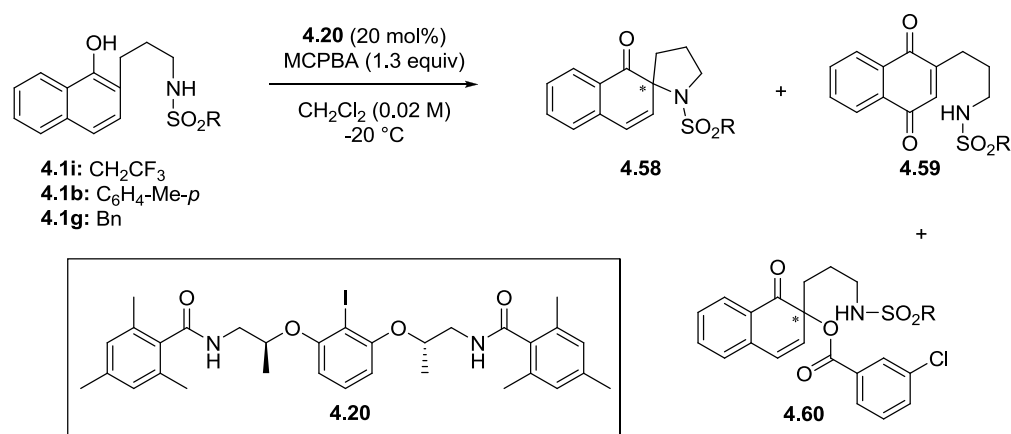


Figure 4.15 Schematic of a two-vial CPC experiment for resolution of (\pm) -4.2a to result both enantiomers, (R) and (S) , in high optical purity

4.3.10 Aspects of the enantioselective acyloxylation reaction

The novelty of the bimolecular acyloxylation reaction leading to enantioenriched products **4.54** kindled our interest in exploring this reaction further. Recall that the transformation was discovered during a study of the oxidative cyclization of methanesulfonamide **4.1a** (Section 4.3.6). This led to the hypothesis that replacement of the methanesulfonyl group with a bulkier one might disfavor spiropyrrolidine formation and encourage that of the acyloxylated product. Accordingly, sulfonamides **4.1i**, **4.1b** and **4.1g** were subjected to the action of MCPBA in the presence of Ishihara catalyst **4.20** (Scheme 4.15). This resulted largely in formation of naphthoquinone **4.59** (NMR). Insignificant amount of **4.58** were apparent from the ^1H NMR spectra of crude reaction mixture, and no signals attributable to MCBA adduct **4.60** were detectable.



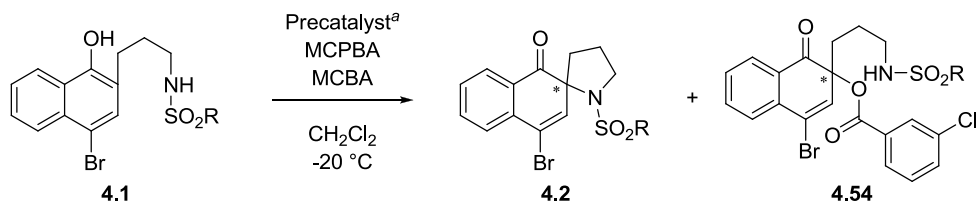
Scheme 4.15 Oxidative cyclization and acyloxylation of 4-unsubstituted naphtholic sulfonamides

No attempts were made to isolate either **4.58** or **4.59**. Instead, the same reaction was studied with a series of 4-bromo naphtholic sulfonamides, which had already been proven to resist naphthoquinone formation. Preliminary investigations revealed that the formation of acyloxylated products could be favored by running the reaction in the presence of added MCBA.

This resulted in higher yields, but *ee*'s were largely unaffected. However, *ee*'s were generally lower in the 4-bromo series relative to the unsubstituted case (80% *ee*; entries 2 and 3, Table 4.11). In any event, all but one (entry 1) of the experiments summarized in Table 4.13 were run in the presence of 2 equivalents of MCBA.

As evident from the Table, each sulfonamide afforded a mixture of enantioenriched spiropyrrolidine **4.2** and acyloxylated product **4.54**. Substrates incorporating a bulky sulfonamide such a benzyl, tolyl, or nitrophenyl one, reacted to form a greater proportion of **4.54** at the expenses of spiropyrrolidine **4.2**. The *ee*'s of spirocyclic compounds remained low in most cases (entries 2, 3 and 8-11). Unexpectedly, the trifluoroethyl sulfonamide reacted with a significant degree of asymmetric induction both as far as the cyclic product (44% *ee*) and the MCPBA adduct (74% *ee*) are concerned (entry 6). That product **4.54** was formed in higher *ee* relative to **4.2** is not unique to the trifluoroethyl sulfonamide: all substrates yet tested behaved in the same manner. Mechanistic implications of this observation are discussed in Section 4.3.11.

The same reaction provided only trace of cyclic product when iodide **4.52** was used. Hence, the *ee* of the same is not reported (entry 7). Overall, the performance of iodide **4.20** was better than **4.52** in terms of chemoselectivity in favor of **4.54**. As far as asymmetric induction goes, no clear trends are apparent: some substrates afforded higher *ee*'s with **4.20** (entries 6-7), others with **4.52** (10-11), other still produced comparable results with either catalyst.



Entry	Precatalyst	R	Time (h)	Selectivity		Yield ^b		ee ^c (%)	
				4.60	4.61	4.60	4.61	4.60	4.61
1	4.52^d	Me	13	(+)	(+)	35	21	17 ^e	62 ^e
2	4.20	Me	11	(-)	(-)	22	33	22	62
3	4.52	Me	12	(+)	(+)	31	28	24	58
4	4.20	Bn	11	(-)	(-)	28	41	- ^f	54
5	4.52	Bn	12.5	(+)	(+)	24	29	- ^f	60
6	4.20	CH ₂ CF ₃	10.5	(-)	(-)	16	37	44	74
7	4.52	CH ₂ CF ₃	11	-	(+)	- ^g	28	-	60
8	4.20	4-Tol	11	(+)	(-)	25	31	23	62
9	4.52	4-Tol	12.5	(-)	(+)	22	30	26	65
10	4.20	4-NO ₂ -C ₆ H ₄	10.5	(-)	(-)	18	37	37 ^h	55 ^h
11	4.52	4-NO ₂ -C ₆ H ₄	18	(+)	(+)	13	24	11 ^h	68 ^h

^aPrecatalyst (20 mol%), MCPBA (1.3 equiv), MCBA (2.0 equiv) -20 °C, CH₂Cl₂ (0.02M). ^bYields after column chromatography. ^cDetermined by chiral HPLC. ^dNo extra MCBA was added. ^eDetermined by chiral SFC. ^fThe ee could not be determined because the enantiomers were inseparable by chiral HPLC. ^gTrace amount of product was obtained. ^hee were determined by synthesizing corresponding diastereomer using (1S)-(+)-camphorsulfonyl chloride.

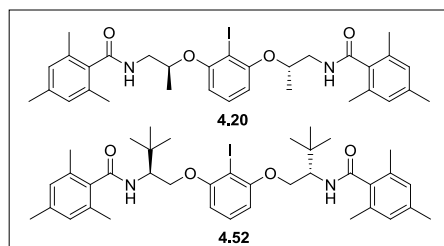
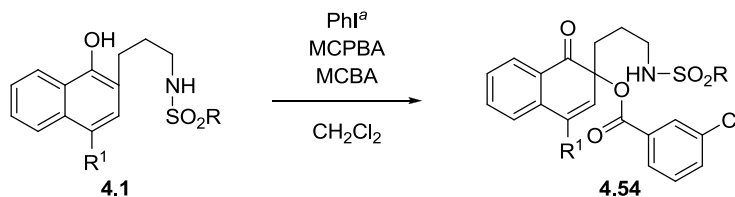


Table 4.13 Oxidative cyclization and acyloxylation of 4-bromo substrates with added MCBA

Enantiomeric excesses were mostly determined by comparison / integration of the chiral HPLC traces of racemic and enantioenriched products. In all but three cases, separation of enantiomeric products was achieved. The synthesis of racemic spiropyrrolidines **4.2** has already been discussed (Table 4.2). Racemic MCBA adducts were prepared in a similar manner. Thus, reaction of sulfonamides **4.1** with a stoichiometric amount of iodobenzene (in place of 20 mol% of chiral iodide), MCBA and MCPBA afforded racemic products **4.54** in low to moderate yields

(Table 4.14). Once again, methanesulfonamides generated the desired products in lower yield (entries 1, 2 and 3) relative to more sterically demanding sulfonamides (entries 4-7).

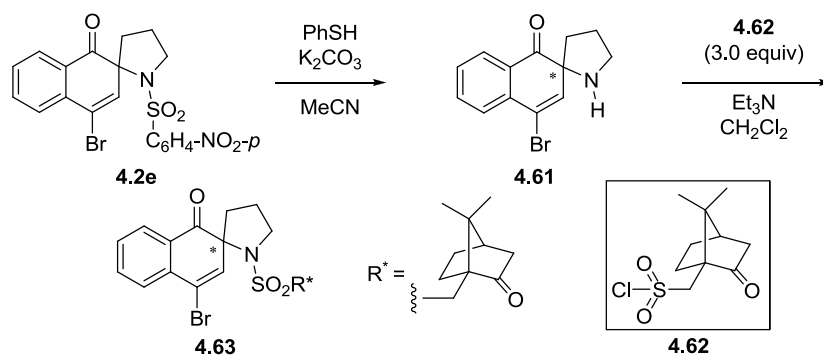


Entry	R ¹	R	Product	Yield ^b
1	H	Me	4.54a	22
2	Br	Me	4.54b	24
3	Cl	Me	4.54c	17
4	Br	Bn	4.54d	43
5	Br	CF ₃ CH ₂	4.54e	42
6	Br	C ₆ H ₄ -Me- <i>p</i>	4.54f	36
7	Br	C ₆ H ₄ -NO ₂ - <i>p</i>	4.54g	39

^aPhI (1.1 equiv), MCPBA (1.3 equiv), MCBA (2.0 equiv), CH₂Cl₂ (0.02 M), RT. ^bIsolated yields after column chromatography.

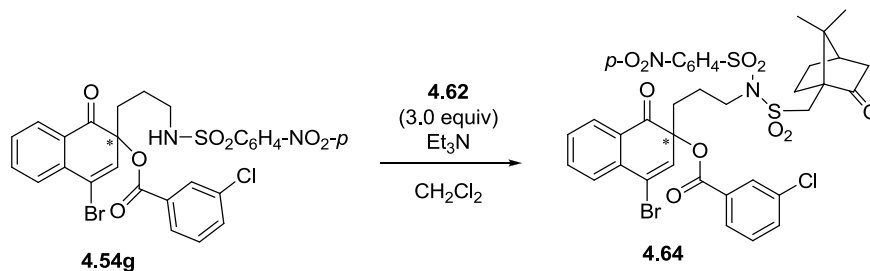
Table 4.14 Acyloxylation of 1-naphtholic sulfonamides

The enantiomers of cyclic compounds **4.2h**, R = Bn or **4.2e**, R = 4-NO₂-C₆H₄, and acyloxylation adduct **4.54g**, R = 4-NO₂-C₆H₄ (Table 4.13) were inseparable by chiral HPLC. The enantiomeric ratio of these products was then determined as follows. The 4-nitrosulfonamido group in spirocycle **4.2e** was removed by reaction with sodium thiophenoxide.^[95] Subsequent reaction of free amine **4.61** with (1*S*)-(+)-camphorsulfonyl chloride **4.62** generated **4.63** as a mixture of diastereomers (Scheme 4.16). The diastereomeric ratio of camphorsulfonamides **4.63** was determined by integration of the ¹H NMR spectrum of the crude reaction mixture, enabling a calculation of the *ee* of **4.63** and consequently of **4.2e**.



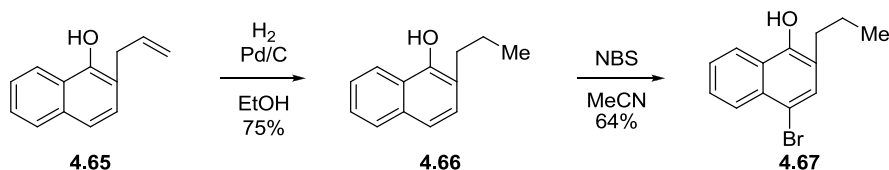
Scheme 4.16 Determination of *ee* of **4.2e**

Similarly, acyloxylated product **4.54g** was derivatized to a mixture of diastereomers of (1*S*)-(+)-camphorsulfonylimides **4.64**, and the *ee* of **4.64**, and consequently of **4.54g**, was calculated by integration of ^1H NMR spectra (Scheme 4.17).



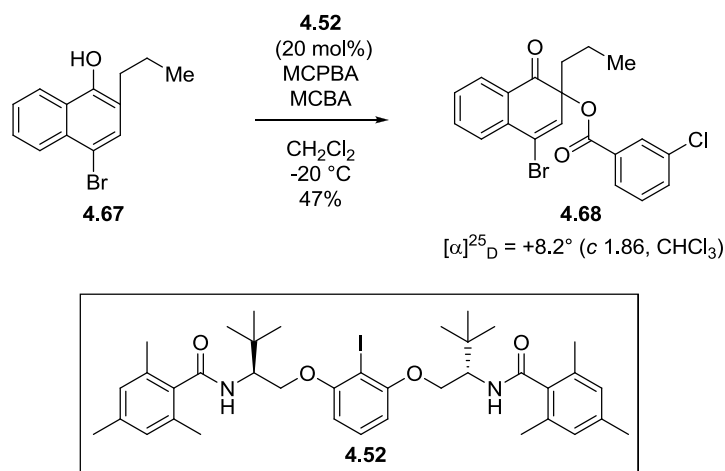
Scheme 4.17 Determination of *ee* of **4.54g** via derivatization

We conclude this section by pointing out that the sulfonamido group is not required for the acyloxylation reaction, as apparent from results obtained with control substrate **4.67**, prepared by hydrogenation of **4.65** followed by *para*-bromination (Scheme 4.18).



Scheme 4.18 Synthesis of 2-propyl naphtholic substrate **4.67**

When **4.67** was subjected to the reaction condition developed earlier (Table 4.13) for acyloxylation, the MCBA adduct **4.68** was obtained in 47% yield (Scheme 4.19). The specific optical rotation of the product was low $\{[\alpha]_{\text{D}}^{25} = +8.2^{\circ} (c\ 1.86, \text{CHCl}_3)\}$. It remains unclear whether this corresponds to a low *ee*, since the enantiomeric enrichment of **4.68** could not be determined because of technical difficulties. For instance, the compound seemingly decomposed during chiral HPLC analysis, as suggested by the appearance of several peaks in the chromatogram. Moreover, the chiral shift reagent $\text{Eu}(\text{hfc})_3$ failed to produce desired splitting pattern of **4.68** for *ee* determination via ^1H NMR.

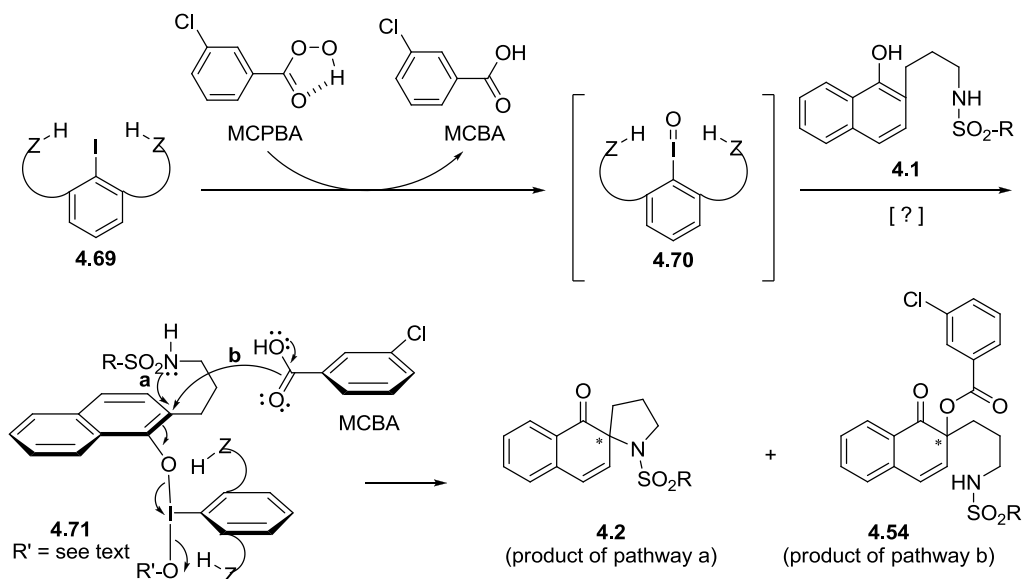


Scheme 4.19 Acyloxylation of control substrate **4.67**

4.3.11 Mechanistic aspects for acyloxylation reaction

A naïve mechanism for the acyloxylation reaction may be envisioned as outlined in Scheme 4.20. Oxidation of chiral iodoarene **4.69** to the iodoso state (**4.70**) by MCPBA necessarily generates MCBA. Combination of substrate **4.1** with **4.70** produces **4.71**, wherein R' may be H, or 3-chlorobenzoyl, or even a second phenoxy ligand derived from the substrate. Nucleophilic fragmentation of **4.71** by an intramolecular pathway orchestrated by the

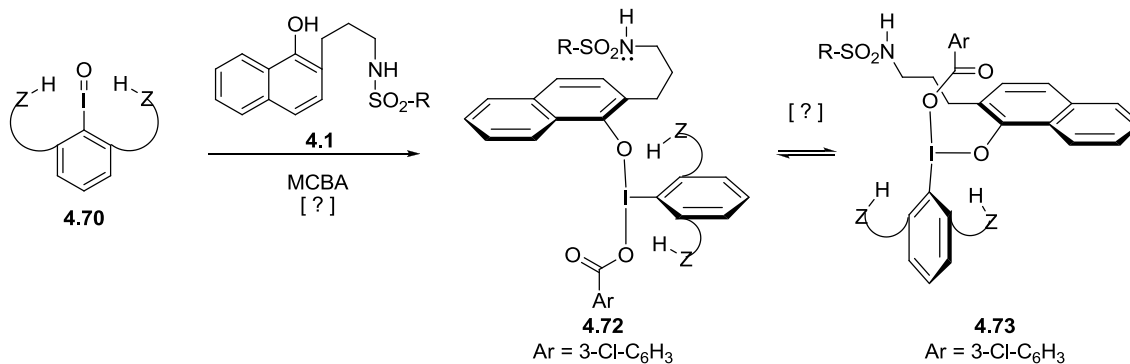
sulfonamide (pathway *a*) produces spiropyrrolidine **4.2**. Alternatively, a bimolecular reaction of complex **4.71** with MCBA leads to adduct **4.54** (pathway *b*).



Scheme 4.20 Possible mechanism for the formation of the acyloxylated product

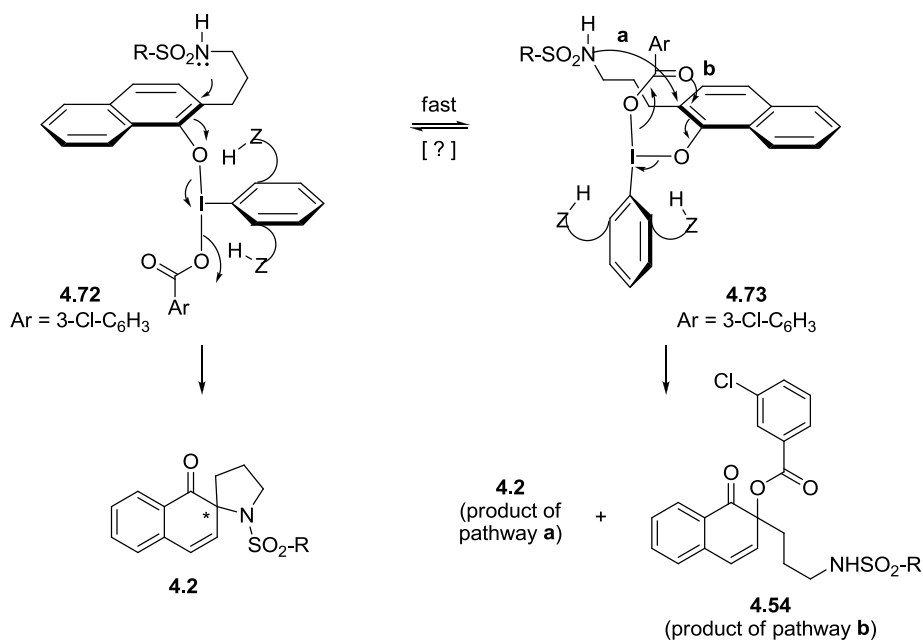
Plausible as it might be, such a mechanistic picture suffers from two major shortcomings. First, in many cases, the reaction produces a greater proportion of MCBA adduct relative to spiropyrrolidine, implying that the rate of the bimolecular pathway *b* is faster than that of the intramolecular one, *a*. Second, the *ee* of acyloxylated products is generally higher than that of spiropyrrolidines, implying that the bimolecular reaction occurs with a greater degree of diastereofacial selectivity relative to the intramolecular one. Either phenomenon seems improbable. That both operate simultaneously is even less likely.

An alternative interpretation is as follows. The iodoso form of the chiral catalyst could combine with one molecule of substrate and one of MCBA to afford **4.72** (Scheme 4.21). It is well established that λ^3 iodanes undergo fast pseudorotation.^{[113],[114]} Complex **4.72** could thus exist in rapid equilibrium with stereoisomer **4.73**.



Scheme 4.21 Possible equilibrium between **4.72** and **4.73**

While **4.72** appears to be liable only to nucleophilic fragmentation leading to a spiropyrrolidine, complex **4.73** can fragment by two competing intramolecular pathways: one leading to a spiropyrrolidine (**a**), the other, to the acyloxylated product (**b**; Scheme 4.22). Although it seems that aryl group bearing chiral motif **4.72** is more stable in equatorial position for the ground state, major product **4.54** is formed via reductive elimination of less stable isomer **4.73**. This is presumably due to *trans* to *cis* (**4.72** \rightarrow **4.73**) isomerisation, wherein the eliminating ligands are *cis* to each other and the transition state leading to MCBA **4.54** adduct from **4.73** is more stable compared to **4.72**. Overall, the process appeared to be controlled by transition state and not ground state.



Scheme 4.22 Possible mechanism for the formation of acyloxylated adduct

The above hypothesis is consistent with additional aspects of the asymmetric cyclization of naphtholic carboxylic acids, sulfonamides (this chapter), and alcohols (chapter 5). Details will be discussed at the end of Chapter 5.

4.4 Summary and conclusion

We have demonstrated the DIB-mediated oxidative cyclization of 1-naphtholic sulfonamides in the racemic series: a reaction that could be useful for the assembly of the core structure of the natural product, ansalactam A. An enantioselective version of the methodology that relies on the use of chiral iodoarene catalysts in the presence of MCPBA as the stoichiometric oxidant has been devised. The reaction can be extended to 2-naphtholic sulfonamides, which, however, seem to react less efficiently.

New chiral iodides were designed and evaluated in an effort to maximize yields and *ee*'s of the products. Yet, the simultaneous attainment of high yields and high enantioselectivities

remains elusive, because solvents that afford high yields (TFA, etc.) promote the formation of racemic products, while solvents that promote asymmetric induction afford low yields.

The enantioselective reaction is highly sensitive to presence of Bronsted or Lewis acids, which completely suppress asymmetric induction. This is likely to be due to premature dissociation of the reactive complex formed upon combination of the substrate with the hypervalent form of the catalyst. This releases a cationic form of the substrate, which then cyclizes in an achiral environment, leading to racemic spiropyrrolidines.

A noteworthy side reaction discovered in the course of these studies is the asymmetric oxidative addition of *meta*-chlorobenzoic acid to the substrates. The resulting acyloxylation products were formed along with aza-spirocyclic compounds. The acyloxylation reaction often occurred with a greater degree of asymmetric induction compared to spirocyclization. Furthermore, it was found to be more tolerant of substitutions in the naphthalene ring relative to the cyclization process. Addition of extra MCBA (2.0 equiv) led to slight improvement in the yield of acyloxylation adduct without affecting the enantioselectivity.

The problem of poor to moderate *ee*'s for at least one aza-spirocyclic compound (**4.2a**) was circumvented upon the discovery that the racemic material crystallizes as a conglomerate. This enabled the development of a resolution method based on continuous preferential crystallization (CPC) in collaboration with Prof. J. Hein, of this Department. It is noted that CPC provides access to both enantiomers of a compound in excellent optical purity and nearly complete mass recovery. Thus, a sample of **4.2a**, of 96% *ee* was secured after a single recrystallization of material prepared by enantioselective cyclization. This small sample (some mg) served as a seed crystal for the CPC resolution of a much larger quantity (several grams) of

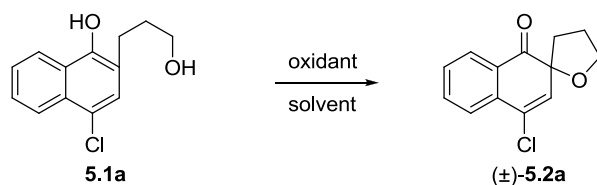
racemic substance, which is readily prepared as described at the beginning of this chapter. Optimization of CPC technology is still in progress in the laboratory of Prof. Hein.

Chapter 5: Oxidative cyclization of naphtholic alcohols with iodine(III) reagents

5.1 Oxidative cyclization of naphtholic alcohols in the racemic series

Similarities between the reactivity of sulfonamides and alcohols (Scheme 2.9-2.10) induced us to study the enantioselective oxidative cyclization of 1-naphtholic alcohols. As explained in Chapter 2 (Scheme 2.16-2.17), the reaction was known only in the racemic series at the beginning of this research. Moreover, it had never been accomplished with hypervalent iodine oxidants (Scheme 2.15). Therefore, our initial objective was to ascertain whether it could be carried out with such reagents.

Alcohol **5.1a** was selected as a test substrate to prevent quinone formation. Its oxidative cyclization was attempted with DIB or Ph-I / MCPBA in TFE, neat CH₂Cl₂, and CH₂Cl₂ containing TFA. Based on the experience accumulated during work with sulfonamides, we predicted that TFE was likely to be a better solvent for the racemic series, but that the asymmetric reaction would have to be carried out in CH₂Cl₂ to minimize dissociation of the reactive complex formed upon combination of the substrate with the hypervalent iodine species. Indeed, racemic **5.2a** was obtained in moderate yield in all cases, but higher yields were observed when TFE was used as the solvent (Table 5.1). Notice that the conditions of entry 3 are identical to those employed for the asymmetric oxidative cyclization of sulfonamides, except for the nature of the aryl iodide. Notice also that the yield of spiroether **5.2a** (40%) was double that of the corresponding spiro-methanesulfonamide (ca. 20%; Ch. 4, Table 4.1).

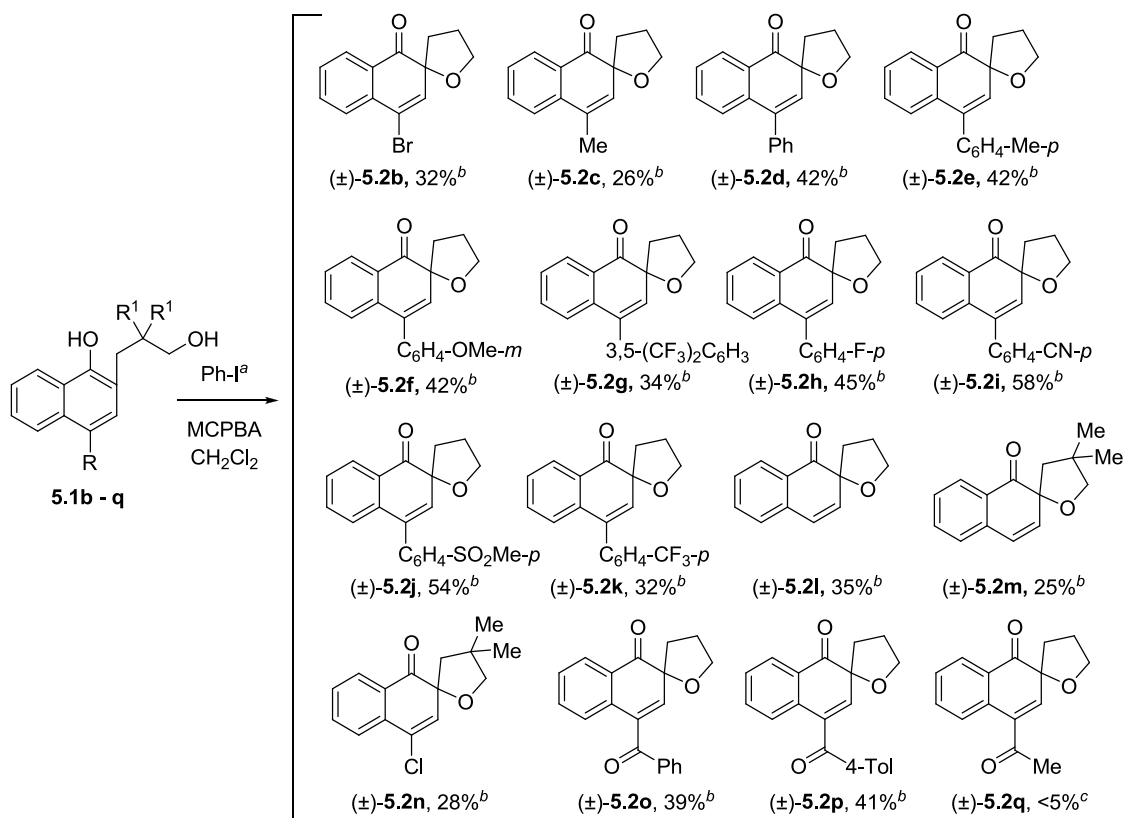


Entry	Conditions	Yield ^a
1	DIB (1.1 equiv), TFE (0.02 M), RT	51
2	DIB (1.1 equiv), TFA (2.0 equiv), CH ₂ Cl ₂ (0.02 M), RT	30
3	PhI (1.0 equiv), MCPBA (1.3 equiv), CH ₂ Cl ₂ (0.02 M), RT	40

^aIsolated yields after column chromatography.

Table 5.1 Oxidative cyclization of **5.1a** in various solvents

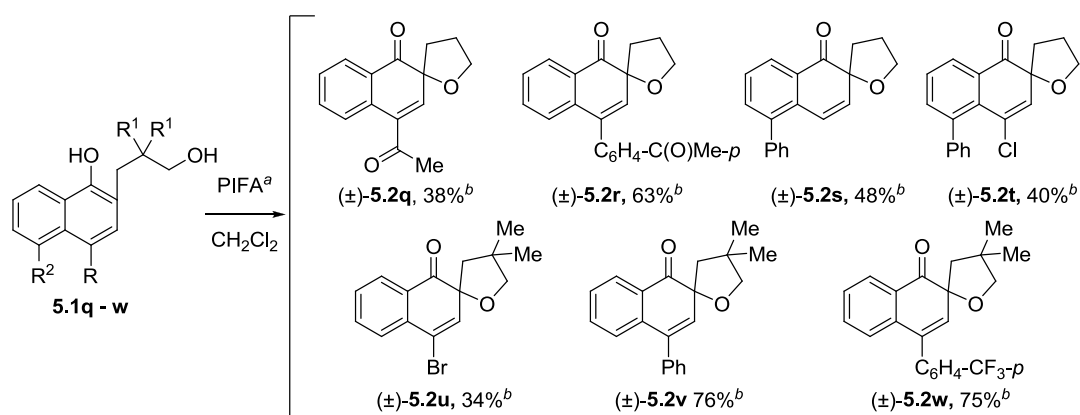
A number of racemic spiroethers were thus prepared by cyclization of 1-naphtholic alcohols in CH₂Cl₂, under conditions analogous to those that would be later employed for the asymmetric reaction. Pertinent results are summarized in Scheme 5.2. The yields of desired products were often around 40-50%, but poorer results were observed with a number of substrates. The reaction of **5.1q** (R = C(O)Me), was quite inefficient, affording a complex mixture of products containing less than 5% of **5.2q** as seen in crude ¹H NMR. No desired spiroether **5.2q** was isolated when this complex mixture was subjected to purification via column chromatography of the complex mixture. Oxidative cyclization with stoichiometric DIB in CH₂Cl₂ was equally poor (< 10% yield according to ¹H NMR of crude), probably because of the low solubility of the reagent in CH₂Cl₂.



^aPhI (1.0 equiv), MCPBA (1.3 equiv), CH₂Cl₂ (0.02 M), RT. ^bIsolated yields after column chromatography. ^cApproximate yield according to ¹H NMR of crude reaction mixture.

Scheme 5.1 Oxidative cyclization of 1-naphtholic alcohols with Ph-I / MCPBA in CH₂Cl₂

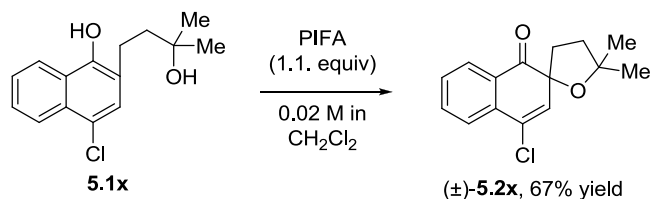
Much better results were obtained with stoichiometric PIFA in CH₂Cl₂, which gave the desired (±)-5.2q in 38% yield. This is shown in Scheme 5.2, which also tabulates further examples of the PIFA-mediated reaction.



^a PIFA (1.1 equiv), CH₂Cl₂ (0.02 M), RT. ^b Isolated yields after column chromatography.

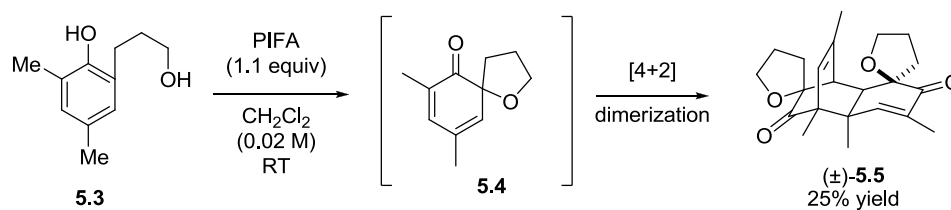
Scheme 5.2 Oxidative cyclization of 1-naphtholic alcohols with PIFA in CH₂Cl₂

The oxidative cyclization of tertiary alcohol substrate **5.1x** in the presence of PIFA was also efficient (67% yield, Scheme 5.3).



Scheme 5.3 Oxidative cyclization of substrate **5.1x**

As discussed earlier (Scheme 1.40 and 1.42), dienones arising upon *ortho*-oxidative dearomatization of phenolic substrates are quite prone to undergo Diels-Alder dimerization. Indeed, an attempt to obtain compound **5.4** by reaction of **5.3** with PIFA gave only dimer **5.5** (25% yield, Scheme 5.4), the structure of which was subsequently ascertained by X-ray diffractometry (Figure 5.9).



Scheme 5.4 Formation of cycloadduct (±)-5.5

It is noted that product (±)-5.5 was obtained in a highly diastereoselective manner through Diels-Alder dimerization of two dienones of identical configuration. This reflects the tendency of a spiroether of, *e.g.*, (*R*) configuration to react with another (*R*)-molecule (homodimerization), instead of an (*S*)-one (heterodimerization). Considering that the product results through an *endo*-[4+2]-cycloaddition proceeding with topology 5.7 (Figure 5.1), the homodimerization pathway appears to be favored on steric grounds. In fact, transition state model 5.7 suffers from a nonbonding interaction between the oxygen atoms of the tetrahydrofuran ring. In contrast, a more severe nonbonding interaction subsists between an O atom and a more sterically demanding CH₂ group in *endo*-[4+2]-heterodimerization transition state model 5.6.

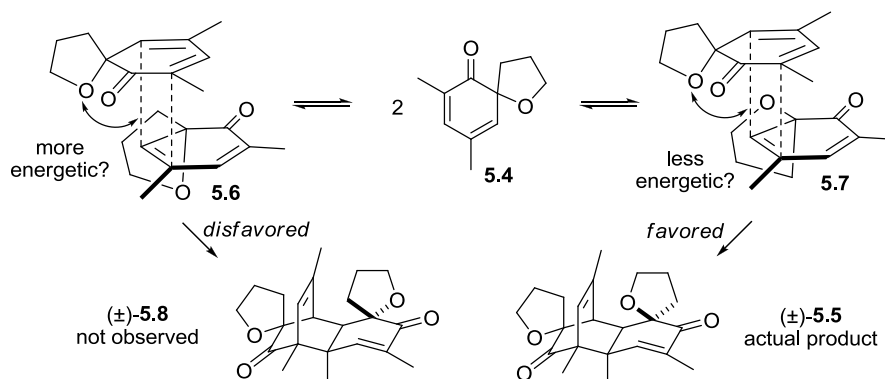
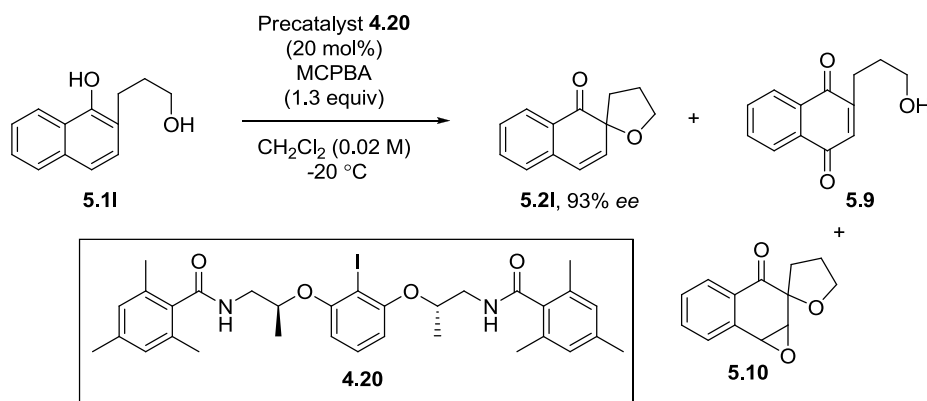


Figure 5.1 Transition state model for heterodimerization of dienone (±)-5.4

These results demonstrated that the oxidative cycloetherification of naphtholic alcohols may indeed be carried out by the use of iodine(III) reagents, albeit in generally moderate yields. This laid the foundation for the development of an asymmetric variant of the process.

5.2 Asymmetric oxidative cyclization of naphtholic alcohols: catalyst screening

Preliminary experiments directed toward ascertaining the feasibility of an asymmetric variant of the reaction centered on the use of Ishihara iodide **4.20** under the conditions developed earlier for sulfonamides.^[70] Accordingly, test substrate **5.11** was treated with 20 mol% of chiral iodoarene **4.20** and 1.3 equivalents of MCPBA in CH₂Cl₂ solution at -20 °C (Scheme 5.5). The desired spiroether **5.21** did form, but it was accompanied by several side products, the major one, not unexpectedly, being naphthoquinone **5.9**, the yield of which approached 30%. Subsequent experiments were therefore carried out with the 4-chloro analog of **5.11** (*vide infra*).

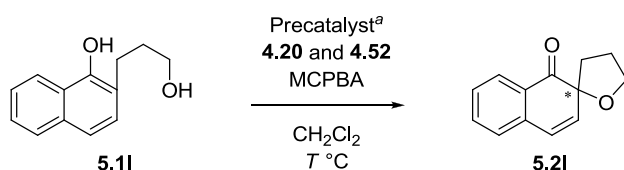


Scheme 5.5 Side reactions when unsubstituted naphthol substrate **5.11** was used

A second byproduct was epoxide **5.10**, which was isolated as a single diastereomer by column chromatography. However, the quantities of **5.10** produced during the reaction were so small (ca. 5% yield) that the possible presence of a diastereomer in crude product mixtures could

neither be ascertained nor excluded (^1H NMR). Furthermore, NOE correlations were not helpful in determining the product's relative configuration, which remains undefined.

A comparison of the relative effectiveness of iodides **4.20** and **4.52** in the oxidative cyclization of **5.11** under various conditions revealed that **4.52** retained efficacy, as far as *ee*'s are concerned, even at RT and 5 mol% catalyst loading (Table 5.2, entry 6). However, yields dropped significantly under the latter conditions, and much **5.11** was lost to formation of naphthaquinone **5.9** and epoxide **5.10**.



Entry	Precatalyst (mol%)	T ($^{\circ}\text{C}$)	Time (h) 4.52 (4.20)	<i>ee</i> ^b 4.52 (4.20) (%)	Yield ^c 4.52 (4.20) (%)
1	20	-20	21 (12)	93 (93)	67 (61)
2	20	RT	3.5 (2.5)	93 (86)	45 (43)
3	10	-20	20.5 (16)	96 (90)	50 (46)
4	10	0	9.0 (5.5)	93 (89)	46 (42)
5	10	RT	6.5 (4.5)	92 (86)	41 (30)
6	5	RT	8.5 (7.0)	89 (82)	35 (23)

^aPrecatalyst, MCPBA (1.3 equiv), T $^{\circ}\text{C}$, CH_2Cl_2 (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields.

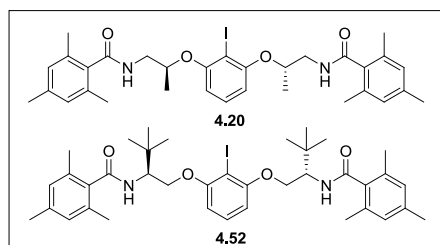
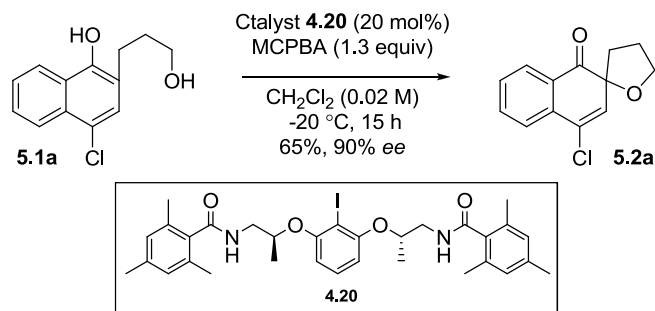


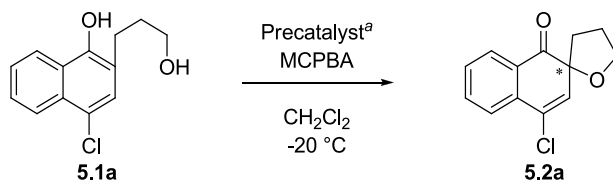
Table 5.2 Relative efficiency of precatalyst **4.52** and **4.20** in the cyclization of **5.11**

In contrast to the case of **5.11**, the oxidative cyclization of alcohol **5.1a** in the presence of iodide **4.20** proceeded quite well and afforded **5.2a** in 65% yield and 90% *ee* (Scheme 5.6).



Scheme 5.6 Oxidative cyclization of **5.1a** in the presence of iodide **4.20**

Other Ishihara-type iodides produced results that nicely reflect trends observed earlier with naphtholic sulfonamides, except that chemical yields and *ee*'s were generally higher in the alcohol series (Table 5.3). As before, none of the alternative catalysts was better than **4.20** (entry 1). Diester **4.14** and diacid **4.15** afforded spiroether **5.2a** in low yield and optical purity (entries 2 and 3). *N*-Mesitylamide **4.16** performed reasonably well (entry 4), but amides **4.21** and **4.23** were less efficient (entries 5 and 6), and tosylamide **4.22** was significantly poorer (entry 7).



Entry	Catalyst	Time (h)	<i>ee</i> (%) ^b	Yield (%) ^c
1	4.20	15	90	65
2	4.14	42	13	27
3	4.15	18	29	51
4	4.16	32	65	62
5	4.23	33	74	60
6	4.21	36	64	52
7	4.22	37	27	46

^aPrecatalyst (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields.

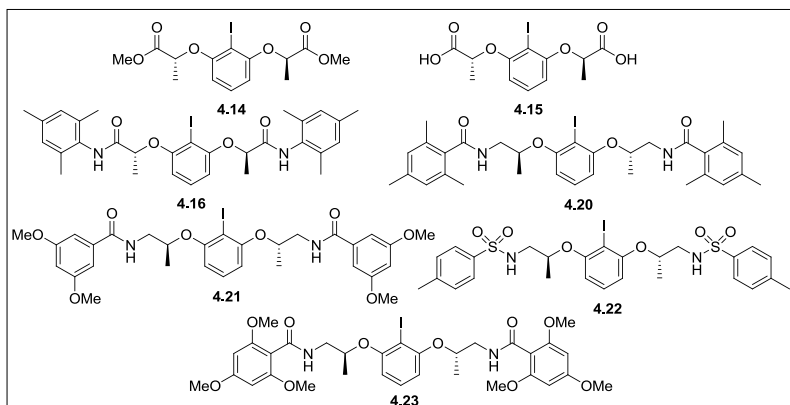
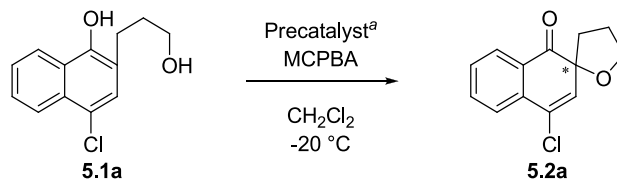


Table 5.3 Catalyst screening

As far as asymmetric induction is concerned, the new iodides **4.51** and **4.52**, proved to be as efficient as **4.20** (Table 5.4). However, it was pleasing to discover that catalyst **4.52** afforded distinctively better yields than **4.20** (entry 2). This provided an incentive to launch a screen of reaction conditions aiming to improve efficiency even further.



Entry	Precatalyst	Time (h)	<i>ee</i> ^b (%)	Yield ^c (%)
1	4.51	12.5	90	66
2	4.52	25	93	79

^aPrecatalyst (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02M). ^bDetermined by chiral SFC. ^cIsolated yields.

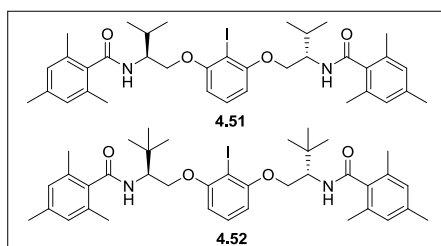
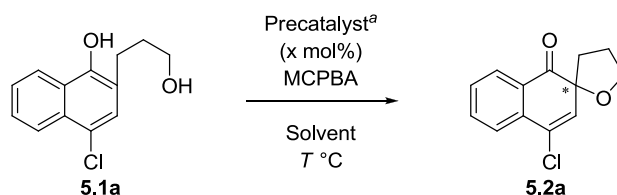


Table 5.4 Performance of newly designed iodoarenes in the spiroetherification reaction

5.2.1 Screening of alternative reaction conditions

A rapid screen of alternative conditions served only to confirm that the protocol devised earlier for sulfonamides were optimal in the case of alcohols as well. Thus, varying solvent, catalyst loading, temperature and concentration led to generally less satisfactory results (Table 5.5). Both *ee* and yield of **5.2a** remained unchanged when catalyst loading was increased from 20 to 30 mol% (Table 5.5, entry 1), but a reduction in the amount of **4.52** translated into longer reaction times and a significant drop in yields and asymmetric induction (entries 5, 7 and 8).



Entry	Precatalyst (x mol%)	Conditions	<i>ee</i> ^b (%)	Yield ^c (%)
1	4.52 (30)	MCPBA, CH ₂ Cl ₂ , -20 °C, 12.5 h	92	78
2	4.52 (20)	MCPBA, CHCl ₃ , -20 °C, 26 h	93	61
3	4.52 (20)	MCPBA, CH ₃ NO ₂ , -20 °C, 29 h	58	46
4	4.52 (20)	MCPBA, CH ₂ Cl ₂ , MeOH (10.0 equiv.), -20 °C, 42 h	77	45
5	4.52 (15)	MCPBA, CH ₂ Cl ₂ , -20 °C, 38 h	92	58
6	4.52 (15)	MCPBA, CH ₂ Cl ₂ (0.04 M), -20 °C, 33 h	90	51
7	4.52 (10)	MCPBA, CH ₂ Cl ₂ , -20 °C, 4.4 d	86	46
8	4.52 (5)	MCPBA, CH ₂ Cl ₂ , -20 °C, 8.5 d	82	47
9	4.52 (20)	MCPBA, CH ₂ Cl ₂ , 0 °C, 8.5 h	85	63
10	4.52 (20)	MCPBA, CH ₂ Cl ₂ , 25 °C, 5.5 h	86	75
11	4.20 (20)	MCPBA, CH ₂ Cl ₂ , 25 °C, 4 h	85	64

^aPrecatalyst (x mol%), MCPBA (1.3 equiv), -20 °C, Solvent (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields.

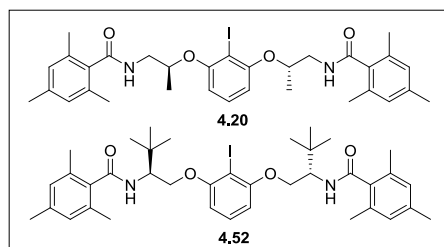
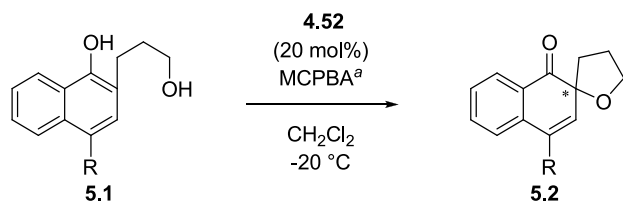


Table 5.5 Alternative reaction conditions

Less polar solvent like CHCl_3 had an adverse effect on yield, but not on *ee* (entry 2), whereas polar solvent like nitromethane or polar additives such as MeOH negatively affected both (entries 3 and 4). Lower yields were obtained when the concentration of substrate was doubled from 0.02 M to 0.04 M (entry 6). Catalysts **4.52** performed surprisingly well even at RT, better so than **4.20** in terms of yield of **5.2a** (entries 10 and 11). However, best results were obtained by operating at $-20\text{ }^\circ\text{C}$. At even lower temperatures ($-50\text{ }^\circ\text{C}$), the reaction became exceedingly slow and generated a multitude of new side products. No efforts were made to purify the resulting crude reaction mixtures.

5.2.2 Substrate Scope

The scope of the reaction with respect to the substrate was probed by examining the spiroetherification of various 4-substituted naphtholic alcohols under the previously optimized conditions. Pertinent results are summarized in Table 5.6. Substituents less electronegative than chlorine at the phenolic *para*-position of **5.1** afforded products of lower *ee* (entries 1, 2 and 3). In contrast, electron-withdrawing carbonyl groups at C-4 promoted high enantioselectivity (entries 4-7). Iodide **4.52** performed better than **4.20** with carbonyl-substituted alcohol **5.1p** (entries 4 and 5). However, the reaction of the 4-acetyl substrate **5.1q** was extremely slow and it generated a complex mixture of products, from which the desired **5.2q** was isolated in poor yield (entry 6). The efficiency of the cyclization of substrates bearing a C-4 phenyl group was sensitive to the nature of substituents present on the same. Thus, the expected spiroethers emerged in good yield and high to excellent *ee* when the phenyl group bore electron-withdrawing substituents (entries 8, 13-17), but lower *ee*'s were obtained when phenyl group carried electron donating ones (entries 10, 11 and 12). Alcohol **5.1g** cyclized equally efficiently in the presence of either **4.52** or **4.20** (entries 8 and 9).



Entry	Product	Time (h)	<i>ee</i> ^b (%)	Yield ^c (%)
1	5.2a (R = Cl)	25	93 ^d	79
2	5.2b (R = Br)	27	84	73
3	5.2c (R = Me)	20	76	29
4	5.2p (R = C(O)(4-Tol))	55	92	41 ^e
5 ^f	5.2p (R = C(O)(4-Tol))	18	83	36 ^g
6	5.2q (R = C(O)Me)	134	92	15
7	5.2o (R = C(O)Ph)	46	92	42 ^h
8	5.2g (R = 3,5-(CF ₃) ₂ C ₆ H ₃)	35	93	47
9 ^f	5.2g (R = 3,5-(CF ₃) ₂ C ₆ H ₃)	15	91	46
10	5.2d (R = 4-Ph)	18	80	63 ⁱ
11	5.2e (R = 4-Tol)	38	75 (98) ^j	52
12	5.2f (R = 3-MeO-C ₆ H ₄)	41	69	73
13	5.2r (R = 4-MeC(O)-C ₆ H ₄)	21	88	75
14	5.2h (R = 4-F-C ₆ H ₄)	14	83 (90) ^j	64
15	5.2i (R = 4-NC-C ₆ H ₄)	38	92	71
16	5.2j (R = 4-MeSO ₂ -C ₆ H ₄)	13	90	78
17	5.2k (R = 4-CF ₃ -C ₆ H ₄)	39	90 ^d (98) ^j	55

^aPrecatalyst **4.52** (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields. ^dAbsolute configuration was found to be *R*. ^e50% yield based on RSM (Recovered Starting Material). ^fReaction was performed using 20 mol% of **4.20** as precatalyst. ^g41% yield based on RSM. ^h47% yield based on RSM. ⁱ69% yield based on RSM. ^j*ee* of material remaining in the mother liquor after single recrystallization.

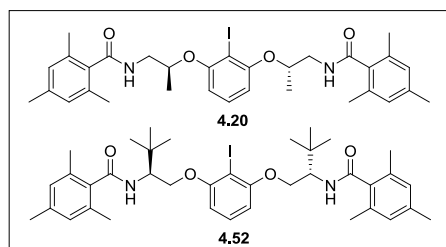
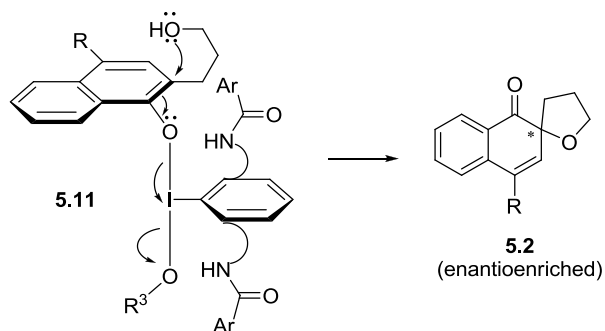


Table 5.6 Substrate scope: 4-substituted naphtholic alcohols

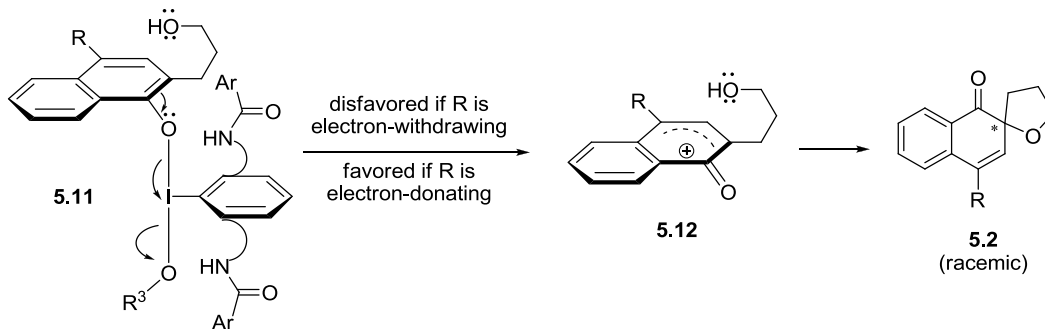
The foregoing observations are in accord with the principle that the substrate must remain firmly anchored to the chiral catalyst for the reaction to proceed with a high degree of

asymmetric induction (Ch. 4, Section 4.3.4). To illustrate, nucleophilic fragmentation of complex **5.11** by the mechanism shown in Scheme 5.7 is likely to produce **5.2** with a good degree of asymmetric induction.



Scheme 5.7 Enantiocontrol during nucleophilic fragmentation of complex **5.11**

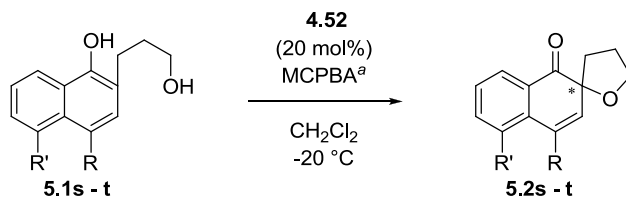
But if **5.11** were to fragment prematurely and liberate cation **5.12**, the latter would cyclize to form a racemic spiroether (Scheme 5.8). Clearly, electron-withdrawing substituents R will disfavor fragmentation of **5.11** to **5.12**, because they destabilize cationic species. This would promote good enantioselectivity. The opposite is true if electron-donating R groups were present.



Scheme 5.8 Loss of enantiocontrol upon dissociation of complex **5.11**

Yields and *ee*'s for the asymmetric cycloetherification of two 5-substituted naphtholic alcohols of structure **5.1s-t** mediated by catalyst **4.52**, were very similar to those observed for the

5-unsubstituted case, suggesting that substitution at the 5-position has only a minor influence on the outcome of the reaction (Table 5.7).



Entry	Product	Time (h)	<i>ee</i> ^b (%)	Yield ^c (%)
1	5.2s (R = H, R' = Ph)	20	92	43
2	5.2t (R = Cl, R' = Ph)	17	88	63

^aPrecatalyst **4.52** (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields.

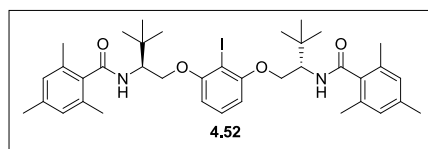
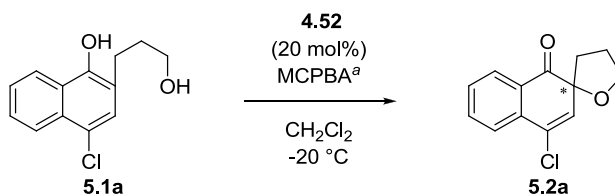


Table 5.7 Oxidative cyclization of 5-substituted naphtholic alcohols

5.2.3 Recycling of the catalyst

Iodide **4.52** was easily retrieved from reaction mixtures by column chromatography (>90% recovery) and it could be recycled several times with no effect on product yield or *ee*. Results of the experiment carried out with **4.52** recycled three times appear in Table 5.8.



Cycle	Time (h)	<i>ee</i> (%) ^b	Yield (%) ^c	Recovered 4.52 (%) ^c
1 ^d	25	93	79	96
2	29	93	74	90
3	27	92	77	95
4	27	92	78	93

^aPrecatalyst **4.52** (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields after column chromatography. ^dFresh precatalyst.

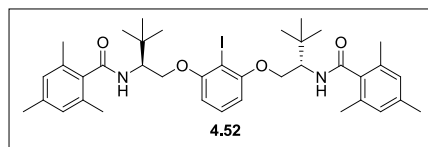


Table 5.8 Cyclization of alcohol **5.1a** with recycled precatalyst **4.52**

5.2.4 Determination of absolute configuration of spiroethers

Several enantioenriched spiroethers obtained during this study were oils; e.g., **5.2a**, precluding a determination of absolute configuration by X-ray diffractometry. Among those that were solid, spiroethers **5.2h**, R = 4-F-C₆H₄ and **5.2e**, R = 4-Tol, crystallized in a centrosymmetric space group and their absolute configuration could not be determined. Moreover, the absence of heavy atoms caused these crystals to diffract poorly. Thus an X-ray analysis of crystals of **5.2h**, R = 4-F-C₆H₄, and **5.2e**, R = 4-Tol, grown in toluene/hexane by the vapor diffusion technique could only ascertain the constitution (Figures 5.2 and 5.3).

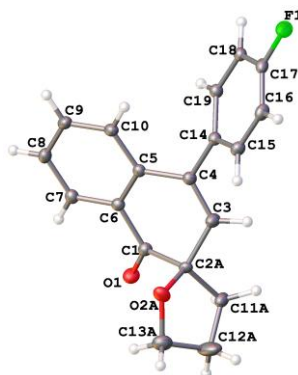


Figure 5.2 X-ray structure of **5.2h**, R = 4-(4-F-C₆H₄)

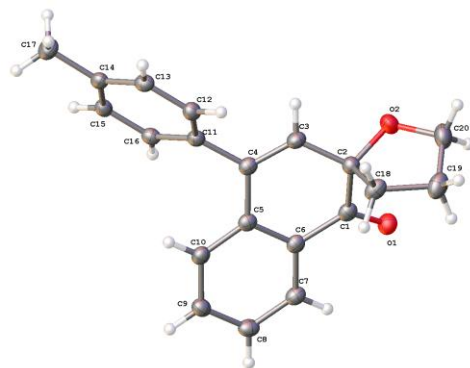
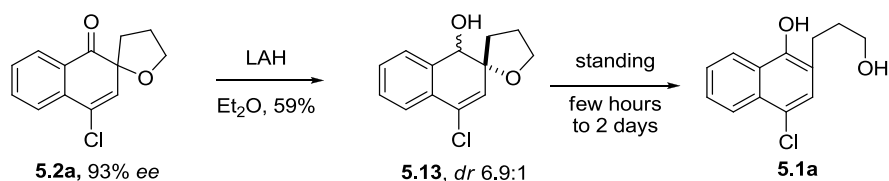


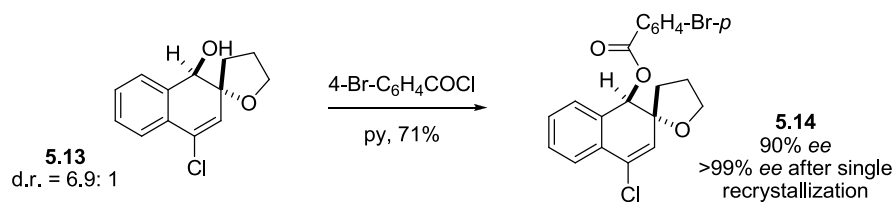
Figure 5.3 X-ray structure of **5.2e**, R = 4-Tol

A derivatization scheme was thus devised to obtain crystalline derivatives suitable for X-ray analysis. Reduction of the ketone (LAH) **5.2a** of 93% *ee* provided a 6.9:1 mixture of diastereomeric alcohols (Scheme 5.9). These were prone to eliminative aromatization back to **5.1a**. Some naphthol was already apparent in the ^1H NMR spectra of material that had been standing at RT for a few hours, and conversion back to **5.1a** was complete in two days. Accordingly, subsequent operations had to be performed rapidly.



Scheme 5.9 Conversion of **5.13** back to **5.1a**

The diastereomeric alcohols were readily separated by column chromatography and the major isomer **5.13** was immediately converted into the *p*-bromobenzoate ester **5.14**, which seemed to be considerably more stable than the alcohol (Scheme 5.10). A single recrystallization by slow evaporation of a solution in CH_2Cl_2 and hexanes at RT afforded material of greater than 99% *ee*. X-ray diffractometry revealed the absolute configuration of spirocenter to be (*R*) (Figure 5.4).



Scheme 5.10 Derivatization of spiroether **5.13**

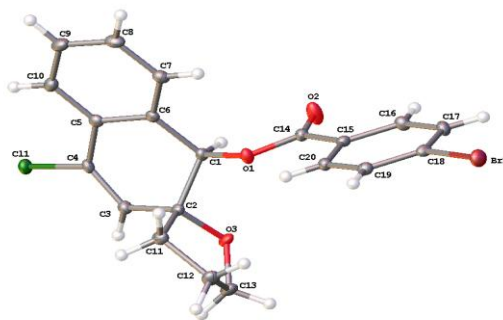
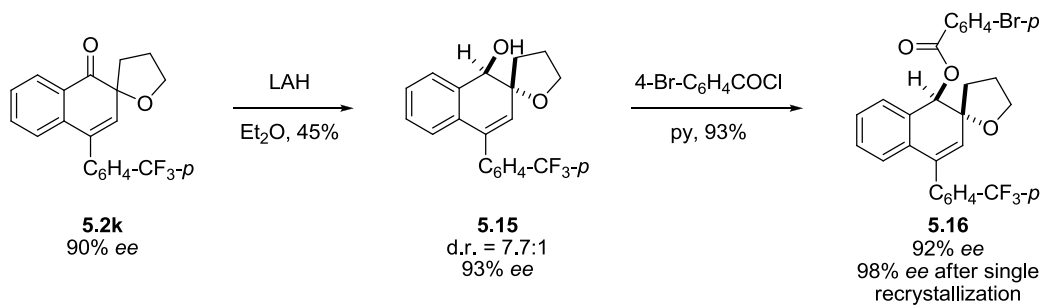


Figure 5.4 X-ray structure of (-)-(R, R)-**5.14**

Similarly, *p*-bromobenzoate ester of **5.2k** was synthesized as outlined in Scheme 5.11. It should be noted that **5.15** did not undergo any conversion back into corresponding starting material like **5.13**.



Scheme 5.11 Derivatization of spiroether **5.2k**

A single recrystallization by slow evaporation of a solution in CH_2Cl_2 and methanol at RT afforded material of 98% *ee*. X-ray analysis revealed the absolute configuration of spirocenter to be (*R*) as well (Figure 5.5).

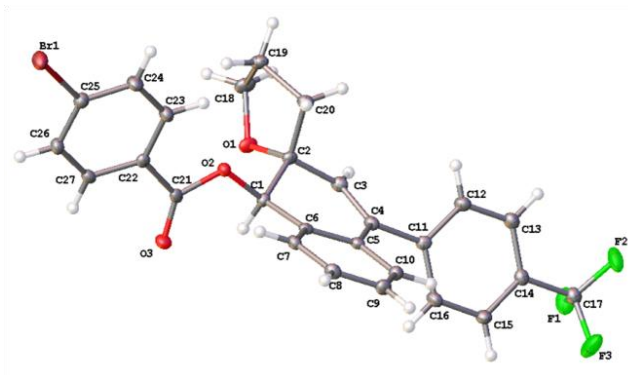
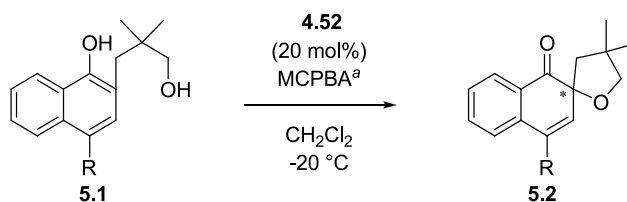


Figure 5.5 X-ray structure of (-)-(*R, R*)-**5.16**

5.2.5 Attempts to accelerate the reaction rate

The above cycloetherification reactions occurred at a rather slow rate, in some cases requiring upward of 12 hours to complete. This drawback induced us to explore the oxidative cyclization of alcohols incorporating *gem*-dimethyl substitution on the aliphatic chain, in the hope that the *gem*-dialkyl effect^[105] would promote a rate acceleration.



Entry	Product	Time (h)	<i>ee</i> ^b (%)	Yield ^c (%)
1	5.2m (R = H)	70	98	61
2	5.2n (R = Cl)	60	76	66
3 ^d	5.2u (R = Br)	36	74	77
4 ^d	5.2v (R = Ph)	36	90	50
5 ^d	5.2w (R = 4-CF ₃ -C ₆ H ₄)	36	87	64

^aPrecatalyst **4.52** (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields after column chromatography. ^d1.8 equivalents of MCPBA was used.

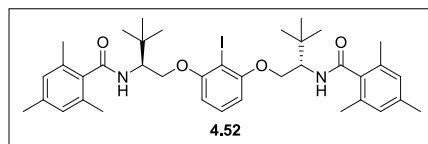
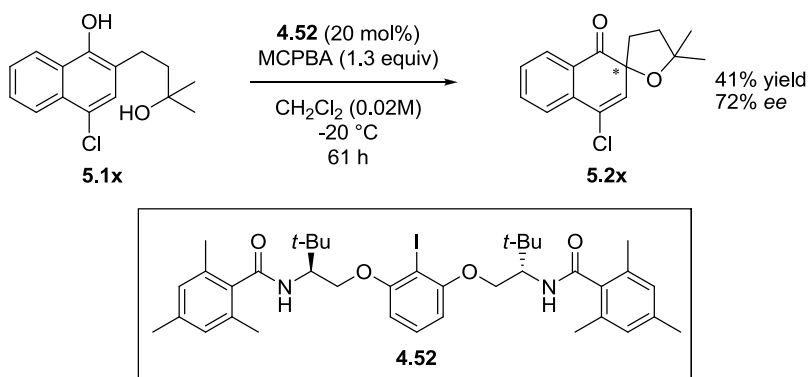


Table 5.9 Effect of *gem*-dimethyl substituents on the rate of cycloetherification

Contrary to the above expectation, the rate of cyclization of substrates with *gem*-dimethyl substitution in the side chain was much slower than that of unsubstituted congeners (Table 5.9). Interestingly, *para*-unsubstituted naphthol **5.1m** afforded essentially enantiomerically pure product **5.2m** (entry 1). Substitution at 4- position resulted in lowering of *ee* of spiroethers regardless of the nature of substituents (entries 2-5). Abnormally slow reaction rates were also observed with **5.1x** (Scheme 5.12).



Scheme 5.12 Cycloetherification of **5.1x** mediated by **4.52**

5.2.6 Kinetic resolution of primary naphtholic alcohols

The above results suggest that unfavorable steric interactions with the *gem*-dimethyl arrangement within the substrate-catalyst complex must override the Thorpe-Ingold effect. This raised an interesting question: could one harness such interactions and use a chiral catalyst to influence the stereochemical outcome of the oxidative cyclization of substrates bearing a single substituent on the side chain? Such compounds would be chiral, raising the possibility that a chiral catalyst might promote faster cyclization of one of the two enantiomers. This would allow the kinetic resolution of the substrates. Such a process would be especially interesting in the case of compounds **5.17** (Figure 5.6) displaying the R group at the 2' carbon. The materials in question are primary alcohols incorporating a stereogenic center at β position. The kinetic resolution of primary alcohols of this type is challenging.^[115] Furthermore, would a chiral catalyst modulate the innate degree of diastereoselectivity attending the cyclization of **5.17**?

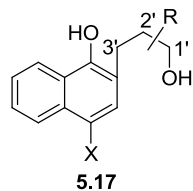
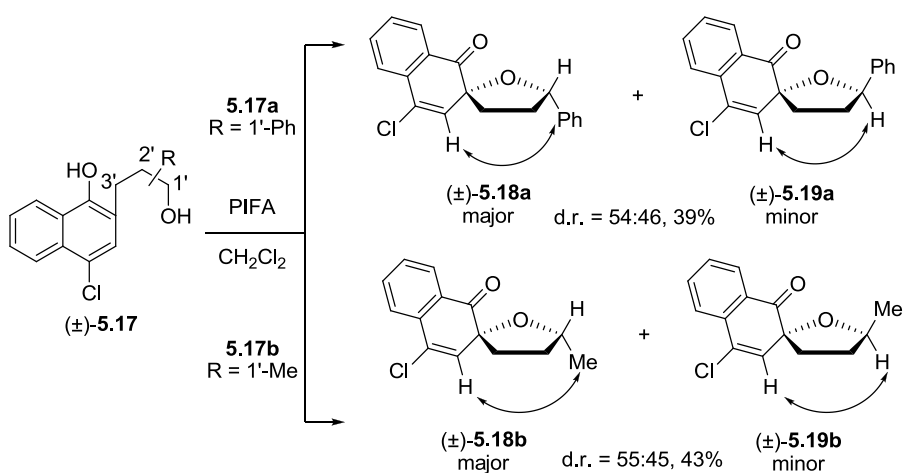


Figure 5.6 1-Naphtholic alcohol bearing a single substituent at the 1', 2', or 3' position

The foregoing issues were addressed by examining the behavior of alcohols **5.17** in the non-enantioselective reaction and in its asymmetric variant. Thus, oxidation of compounds **5.17** with PIFA in CH_2Cl_2 consistently furnished the expected racemic spiroethers in about 40% yield. Compounds bearing a C-1' group cyclized with poor diastereoselectivity (d.r. = 55:45), regardless of the steric demand of the substituent (Scheme 5.13). Chiral SFC readily separated the four stereoisomers of the product (two enantiomers of each diastereomer), enabling a precise

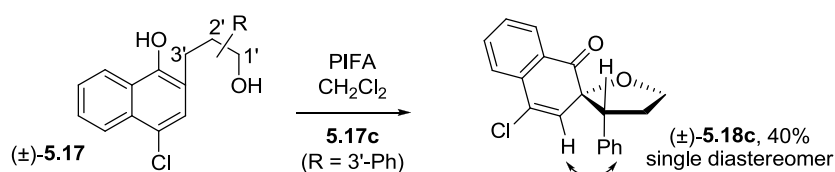


Scheme 5.13 Diastereoselectivity in the cyclization of 1'-substituted alcohols **5.17**

determination of diastereomeric ratios, and later, of *ee*'s. However, the diastereomers were inseparable by preparative column chromatography. Fortunately their ^1H NMR signals were well resolved, enabling the assignment of relative configurations based on the NOESY-2D spectra of the purified product mixture. In either case, the major diastereomer was the one which the C-1'

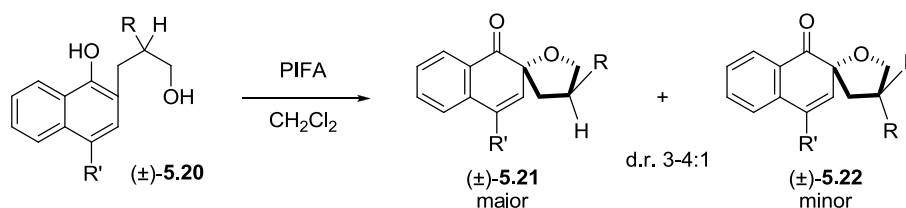
group was *cis* to the olefinic segment within the newly formed tetrahydrofuran ring. This conclusion is based upon the diagnostic NOE enhancements indicated in Scheme 5.13.

The product **5.18c** of oxidative cyclization of alcohol (\pm)-**5.17c** emerged as single diastereomer. Its NOESY-2D spectrum displayed the strong dipolar coupling shown in Scheme 5.14, indicating that the phenyl group was again *cis* to the olefinic substituent.

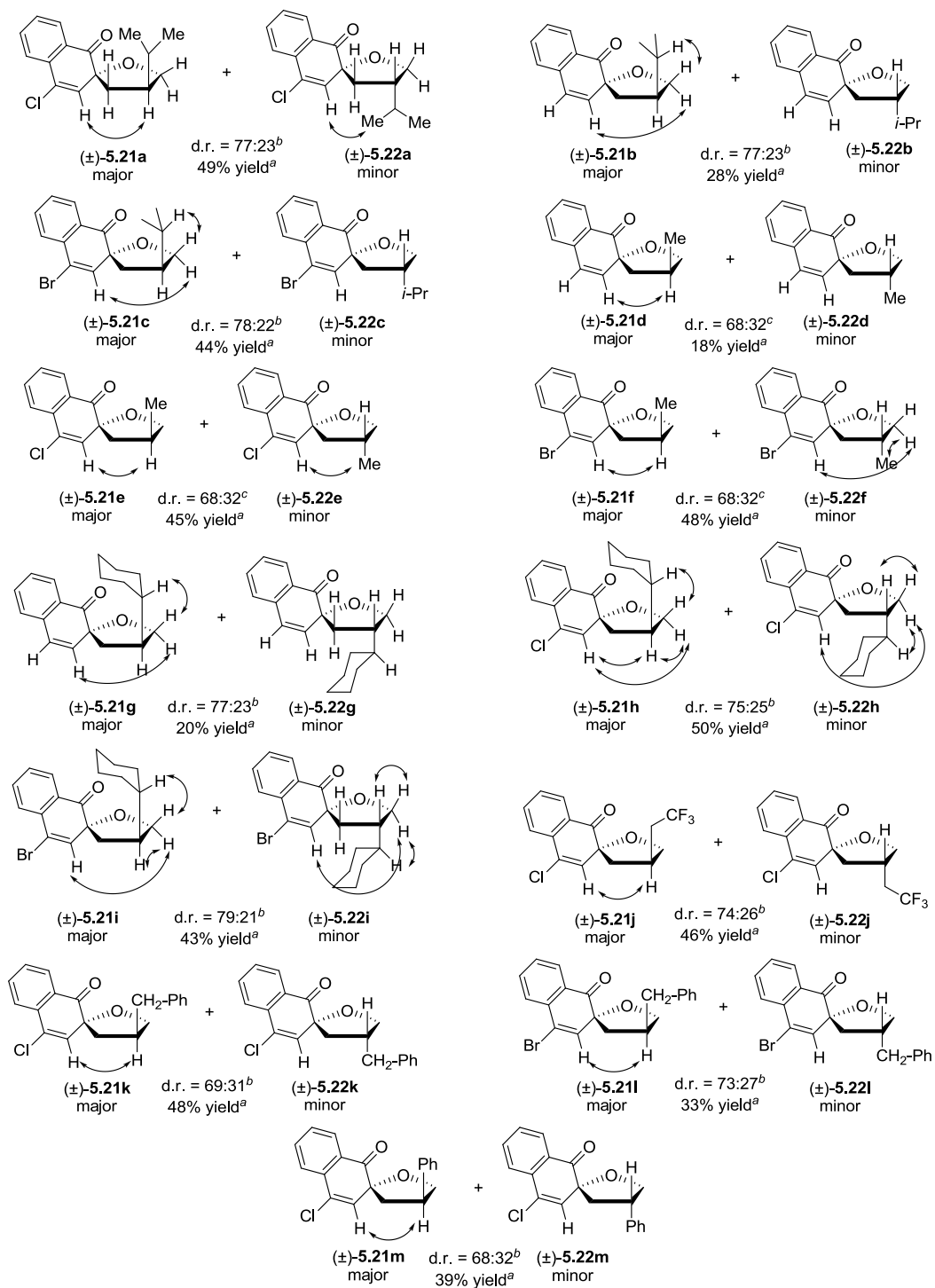


Scheme 5.14 Cyclization of 3'-Ph alcohol (\pm)-**5.17**

In contrast to the previous cases, substituent R was *trans* to the olefinic segment in the major product formed during the cyclization of 2'-substituted alcohols **5.20** (Scheme 5.15). Diastereoselectivity was consistently around 3-4:1, regardless of the nature of the 2'-group. Chemical yields were often better in this series, except when *para*-phenolic substituent R' was H. As seen earlier, this was because of competing naphthoquinone formation. No attempts were made to isolate the quinone or determine its yield, since this material was of no interest to us. A tabulation of 13 racemic products of structure **5.21-5.22** thus obtained is provided in Figure 5.7.



Scheme 5.15 Cyclization of 2'-substituted alcohols (\pm)-**5.20**

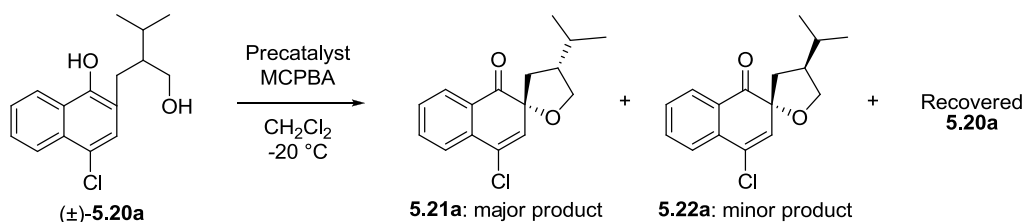


^aIsolated yields after column chromatography. ^bDetermined by chiral SFC. ^cDetermined from ¹H NMR of crude reaction mixture.

Figure 5.7 Spiroethers derived from substrates bearing a C-2' substituent

5.2.6.1 Enantioselective cyclization: catalyst screening

The enantioselective variant of spiroetherification reaction and the possible kinetic resolution of the substrate were initially explored using test alcohol **5.20a** (Table 5.10). Compound (\pm)-**5.20** was subjected to oxidative cyclization in the presence of various chiral catalysts. All reactions were run to ~50% conversion to evaluate the enantiomeric enrichment of both products and starting material. To that end, only 0.6 equivalents of MCPBA were used in each experiment.



Entry	Pre catalyst	Time (h)	% Conversion ^b	d.r. ^c (5.21a : 5.22a)	Yield ^d (%)		<i>ee</i> (%) ^c		<i>ee</i> (%) 5.20a ^c	Abs. conf. of 5.20a ^e	<i>S</i> ^f
					Product	Rec. 5.20a	5.21a	5.22a			
1	4.20	6	54	77:23	50	30	89	97	54	(<i>R</i>)	4.5
2	4.52	20	52	80:20	49	30	90	97	57	(<i>S</i>)	5.6
3	4.51	13.3	56	83:17	52	35	94	98	79	(<i>S</i>)	10.0

^aPrecatalyst (20 mol%), MCPBA (0.6 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bConversion determined by ¹H NMR using 3,5-dimethoxybenzaldehyde as the internal standard, c=(1-yield of starting material)*100%. ^cDetermined by chiral SFC. ^dIsolated yields. ^eAbsolute configuration of recovered starting material was determined via X-ray analysis of its derivative (See section 5.2.6.3). ^fSelectivity factor, $S = \ln[(1-c)(1-ee_{SM})] / \ln[(1-c)(1+ee_{SM})]$; $ee_{SM} = ee$ of recovered starting material, c=conversion.

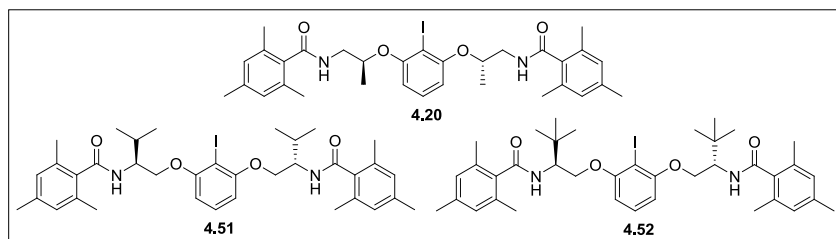
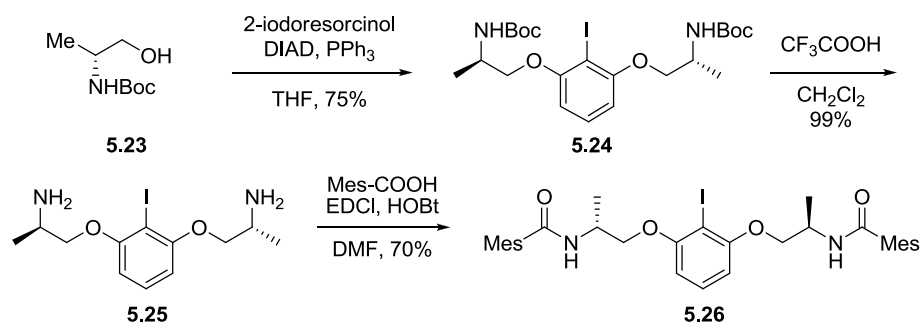


Table 5.10 Catalyst screening

In all cases, the chiral catalyst had no effect on the diastereoselectivity of the reaction, which remained identical to that observed in the racemic series. The diastereomeric products were inseparable by column chromatography, and the relative configurations were assigned based on NOESY-2D study of the mixture after purification, as described earlier.

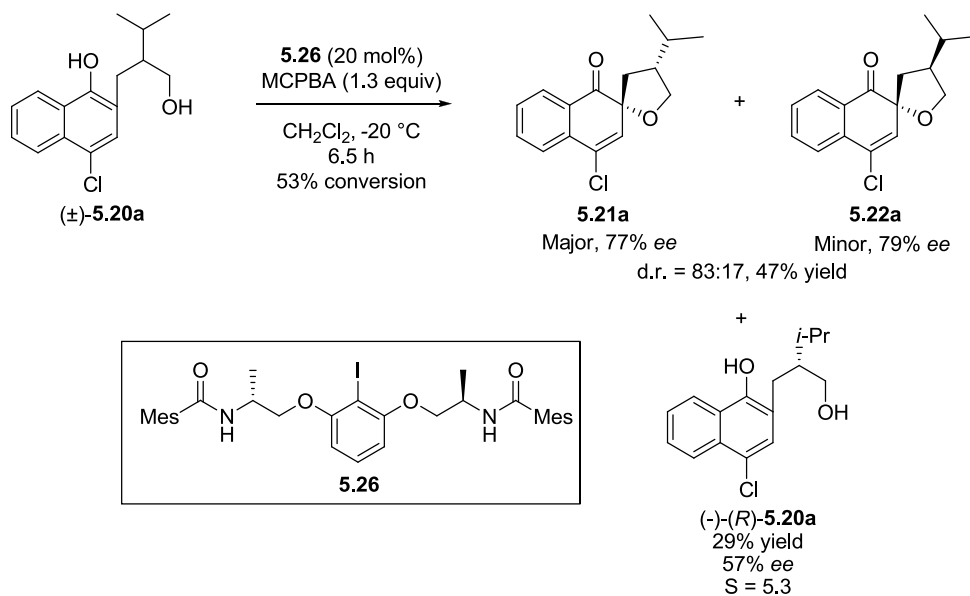
Regarding the enantioselectivity of spiroethers obtained, all iodides (**4.20**, **4.51** and **4.52**) provided spiroethers **5.21a** and **5.22a** with similar *ee*'s, except that, **4.51** and **4.52** promoted an opposite sense of asymmetric induction relative to **4.20** (Table 5.10, entries 1-3). This is consistent with previous observations (Table 5.3 and 5.4). With regard to kinetic resolution, **4.20** and **4.52** afforded unreacted alcohol of a moderate 54-57% *ee* (Table 5.10, entries 1 and 2). Much better results were obtained with catalyst **4.51**, which returned recovered **5.20** of 79% *ee* and selectivity factor of 10 (entry 3). Reactions run with iodide **4.51** also proceeded at a faster rate relative to **4.52** (13.5 h vs. 20 h).

The observation that a decrease in the steric demand of the alkyl group in the new chiral iodides (*t*-Bu → *i*-Pr) resulted in better catalytic performance induced us to evaluate their methyl analog, **5.26** (Scheme 5.16). Retracing established pathways, the compound was prepared by Mitsunobu reaction of Boc-protected (*R*)-2-amino-1-propanol **5.23** with 2-iodoresorcinol, followed by *N*-deprotection and EDCI mediated coupling of amine **5.25** with mesitoic acid.



Scheme 5.16 Synthesis of chiral iodoarene **5.26**

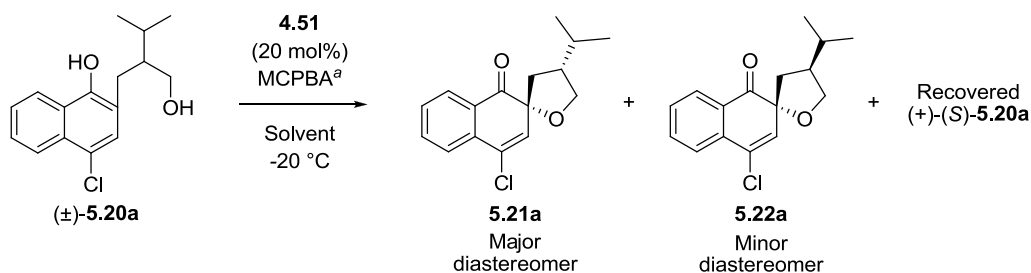
Unfortunately, iodide **5.26** provided inferior degrees of asymmetric induction compared to other catalysts, in terms of both *ee*'s of cyclic products and of recovered starting material (S = 5.3; Scheme 5.17). Overall, **4.51** was the best catalyst for this type of transformation.



Scheme 5.17 Evaluation of iodide **5.26** for cycloetherification of test substrate (\pm)-**5.20a**

5.2.6.2 Alternative reaction conditions

In accord with previous observations, any change in solvent, temperature and concentration translated into less satisfactory outcomes (Table 5.11). Reactions run in CHCl_3 returned spiroethers of excellent *ee*, but the enantiomeric enrichment of recovered **5.20** was lower than in CH_2Cl_2 (entries 1 and 2). Polar solvents were deleterious (e.g., entry 5). An abnormally slow reaction ensued in a mixture of CH_2Cl_2 and MTBE, with an estimated 5% conversion attained after 6 h (entry 6).



Entry	Solvent	Time (h)	% Conv. ^b	d.r. ^c (5.21 : 5.22)	Yield ^d (%)		<i>ee</i> of product ^c		<i>ee</i> (%) ^c 5.20a	S ^e
					Product	Rec. 5.20a	5.21	5.22		
1	CHCl_3	16.5	51	82:18	50	35	94	98	62	7.3
2	CH_2Cl_2	13.3	56	83:17	52	35	94	98	79	10.0
3	Toluene	14.3	53	88:12	34	38	90	71	45	3.5
4	$\text{MeNO}_2:\text{CH}_2\text{Cl}_2$ (3:1 v/v)	18.5	50	82:18	44	30	80	79	48	4.5
5	$\text{CF}_3\text{CH}_2\text{OH}$	13.5	59	75:25	48	32	<5	<5	<5	-
6	MTBE: CH_2Cl_2 (4:3 v/v)	6	<5	-	-	-	-	-	-	-
7 ^f	CH_2Cl_2	7.3	58	84:16	53	36	89	92	80	8.9
8 ^g	CH_2Cl_2	9.7	60	80:20	52	35	90	97	78	7.2

^a**4.51** (20 mol%), MCPBA (0.6 equiv), $-20\text{ }^\circ\text{C}$, Solvent (0.02 M). ^bConversion determined by ^1H NMR using 3,5-dimethoxybenzaldehyde as the internal standard, $c=(1-\text{yield of starting material})\times 100\%$. ^cDetermined by chiral SFC. ^dIsolated yields. ^eSelectivity factor, $S=\ln[(1-c)(1-ee_{SM})]/\ln[(1-c)(1+ee_{SM})]$; $ee_{SM}=ee$ of recovered starting material, c =conversion. ^fReaction was performed at $0\text{ }^\circ\text{C}$. ^gConcentration of reaction mixture was 0.05 M with respect to starting material.

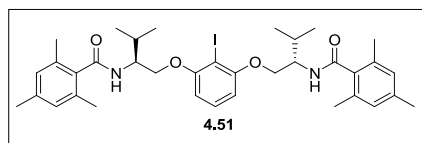


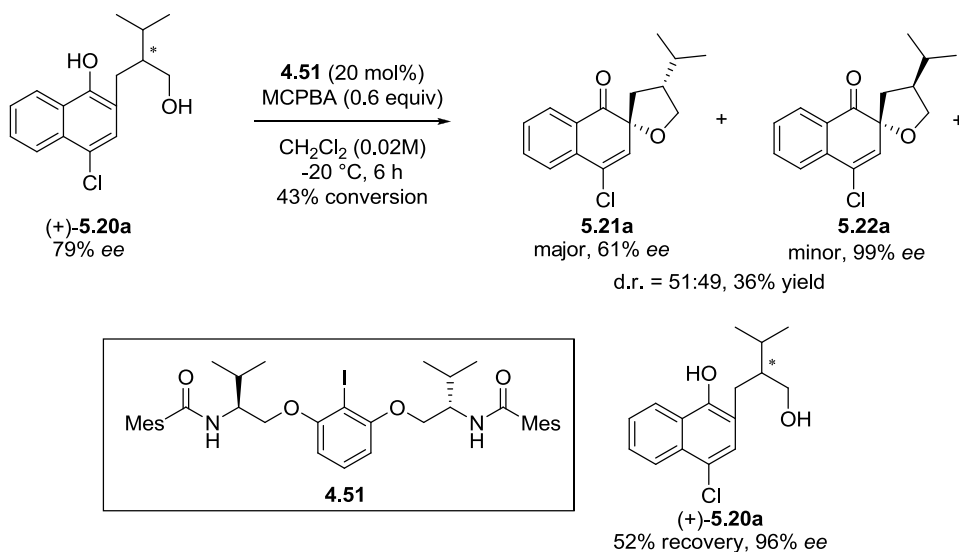
Table 5.11 Further optimization study

Higher temperature (-25 °C → 0 °C) and concentrations (0.02 M → 0.05 M) resulted in slightly lower *ee* of the spiroethers without affecting the *ee* of recovered **5.20** (entries 7 and 8). Overall, the best conditions for effective cycloetherification and kinetic resolution were the same as those developed earlier for other enantioselective reactions (entry 2).

5.2.6.3 Determination of the absolute configuration of **5.21a**, **5.22a** and recovered **5.20a**

The oily mixture of products **5.21a** and **5.22a** was inseparable by column chromatography. Their absolute configuration, as well as that of recovered **5.20a**, was thus determined by a method similar to that described earlier for spiroethers **5.2a** and **5.2k** (Section 5.2.4).

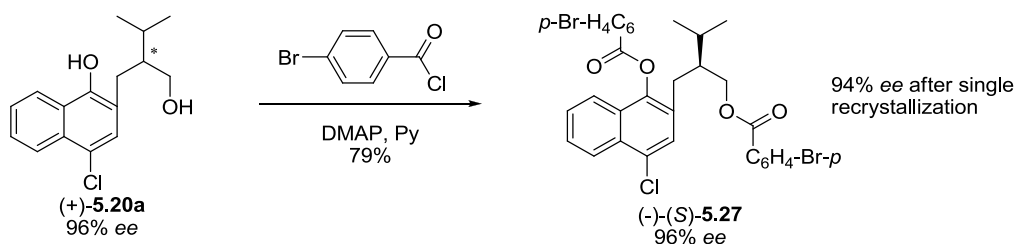
Recovered (+)-**5.20a** of 79% *ee* was subjected to a second round of oxidative cyclization mediated by iodide **4.51** (Scheme 5.18). The reaction was stopped at 43% conversion, whereupon residual (+)-**5.20a** was found to be 96% *ee*.



Scheme 5.18 Cycloetherification of (+)-**5.20a** mediated by **4.51**

This highly enantioenriched material was converted into the crystalline bis-*p*-bromobenzoate ester (-)-**5.27** (Scheme 5.19), which was found to be of (*S*)-configuration by X-

ray analysis (Figure 5.8). This means that (*S*)-(+)-**5.20a** is the slow reacting alcohol enantiomer when (\pm)-**5.20a** is subjected to spiroetherification using iodide **4.51**, and (*R*)-(-)-**5.20a** is the fast reacting one (Table 5.10). Consequently, the absolute configuration of the carbon atom bearing the *i*-Pr group in major diastereomer **5.21a** (94% *ee*, Table 5.10) must be (*R*).



Scheme 5.19 Derivatization of (+)-**5.20a** as ester (-)-**5.27**

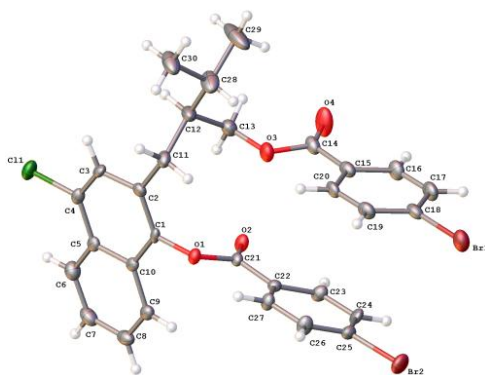
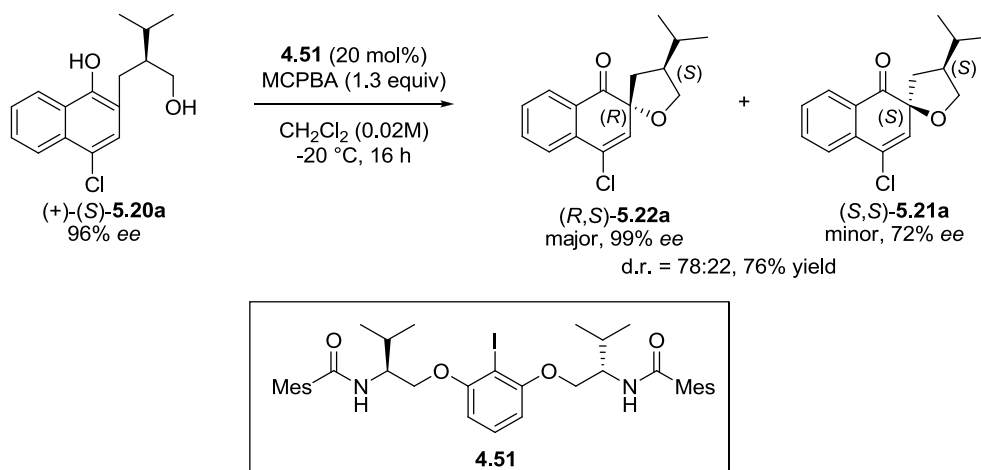


Figure 5.8 X-ray structure of (-)-(*S*)-**5.27**

Because in **5.21a** the *i*-Pr group and the olefinic residue are *trans* within the tetrahydrofuran ring (NOESY-2D spectroscopy, Figure 5.7), the spirocenter must be of (*R*)-configuration. Therefore, the major diastereomer is (*R,R*)-(+)-**5.21a**.

Another portion of (*S*)-(+)-**5.20a** of 96% *ee* was subjected to cyclization in the presence of iodide **4.51**, thereby yielding **5.22a** as major diastereomer (Scheme 5.20). This product was identical to the major enantiomer of the minor diastereomer produced in the previous experiments. So, the absolute configuration of the carbon atom bearing the *i*-Pr group in **5.22a** is

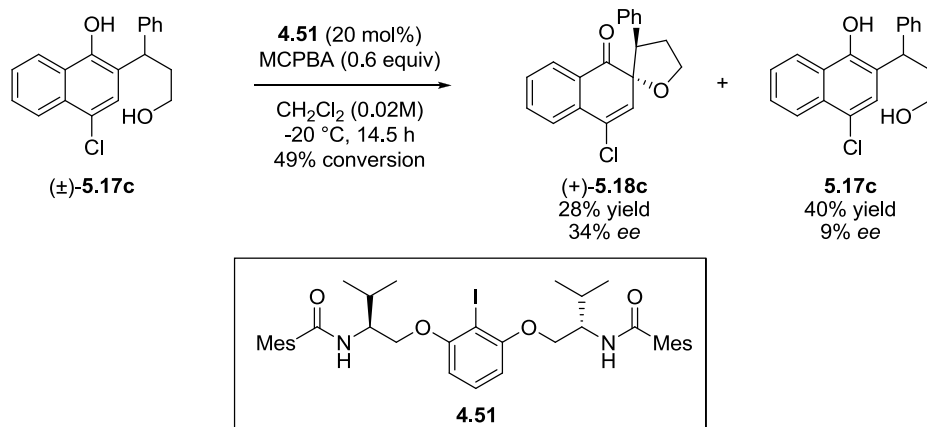
(*S*), and from the NOE correlations, the absolute configuration of the spirocenter must be (*R*). So, the overall absolute configuration of **5.22a** is (*R,S*). This is consistent with the sense of enantioinduction that was obtained with simpler naphtholic alcoholic substrates.



Scheme 5.20 Cycloetherification of enantioenriched (+)-**5.20a**

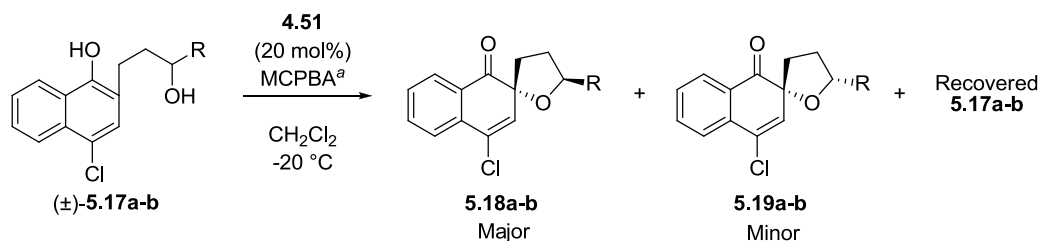
5.2.6.4 Substrate scope

The cyclization of 3'-substituted (\pm)-**5.17c** provided (+)-**5.18c** as a single diastereomer, but in poor yield and low *ee*. Recovered starting material was of only 9% *ee* (Scheme 5.21). Clearly, neither enantioinduction nor kinetic resolution operated properly in the cyclization of this type of alcohol, which nonetheless occurred with complete diastereoselectivity.



Scheme 5.21 Cycloetherification of (±)-**5.17c** mediated by **4.51**

In contrast to the above, the cyclization of 1'-substituted alcohols (±)-**5.17a-b** was highly enantioselective, but poorly diastereoselective (Table 5.12). Also, recovered starting material was of low *ee*, indicating that the kinetic resolution of these substrates is problematic, at least with catalysts of the type **4.51**.



Entry	R	Time (h)	% Conv. ^b	d.r. ^c (5.18 : 5.19)	Yield ^d (%)		<i>ee</i> of product ^c		<i>ee</i> (%) ^c 5.17
					Product	Recovered 5.17	5.18	5.19	
1	Me	14.5	49	59:41	33	36	90	90	8
2	Ph	9.3	60	65:35	27	36	97	75	<5

^a**4.51** (20 mol%), MCPBA (0.6 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bConversion determined by ¹H NMR using 3,5-dimethoxybenzaldehyde as the internal standard, c=(1-yield of starting material)*100%. ^cDetermined by chiral SFC. ^dIsolated yields after column chromatography.

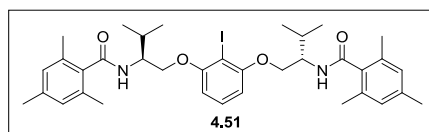
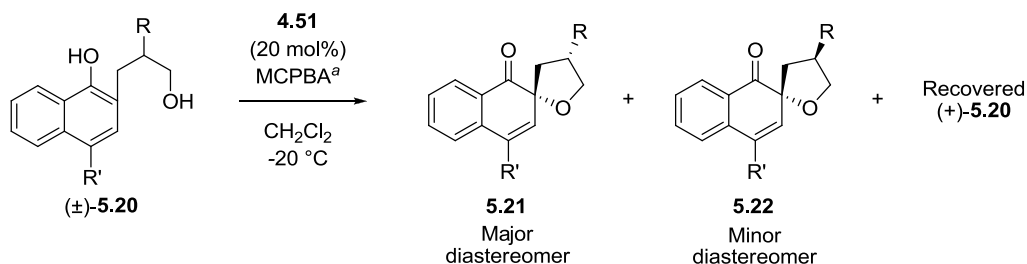


Table 5.12 Evaluation of iodide **4.51** in the cycloetherification of (±)-**5.17a-b**

The observation that only naphtholic alcohols with a stereogenic center at the 2' position undergo efficient kinetic resolution provided an incentive to examine the cyclization of substrates **5.20** incorporating diverse R and R' groups. Pertinent results are summarized in Table 5.13. Spiroethers obtained from 4-H and 4-Cl naphtholic alcohols were of generally excellent *ee* (Table 5.13, entries 1-10), except for the minor diastereomer **5.22** with R = CH₂CF₃ (entry 7) or Ph (entry 10) and R' = Cl. The 4-bromo substrates yielded spiroethers of slightly lower *ee* (entries 11-14). Most substrates cyclized with moderate diastereoselectivity; however, a high diastereomeric ratio (~10:1) was observed when R = CH₂CF₃, R' = Cl (entry 7). With respect to kinetic resolution, the highest enantiomeric enrichments of recovered (+)-**5.20** were attained in the 4-Cl series (*ee* > 70%), especially when R = CH₂CF₃ (S = 19). The recovered (+)-**5.20** was obtained with lower *ee* (just under 50% in all cases) when R = Me.



Entry	Product	% Conv. ^b	d.r. ^c (5.21 : 5.22)	% Yield of product ^d	% ee of product ^c		Recovered 5.20 % Yield ^d (% ee) ^c	S ^e
					5.21	5.22		
1	R = Me, R' = H	55	86:14 ^f	50	- ^g	- ^g	40 (48)	3.6
2	R = <i>i</i> -Pr, R' = H	60	82:18	48	96	- ^g	35 (62)	4.3
3	R = CH ₂ CF ₃ , R' = H	48	83:17 ^h	40 ⁱ	- ^g	- ^g	44 (57)	7.4
4	R = Cy, R' = H	57	81:19	45	94	- ^g	33 (41)	2.7
5	R = Me, R' = Cl	44	79:21 ^f	42	- ^g	- ^g	40 (47)	6.2
6	R = <i>i</i> -Pr, R' = Cl	56	83:17	52	94	98	35 (79)	10.0
7	R = CH ₂ CF ₃ , R' = Cl	47	91:9	45	94	79	37 (71)	19.0
8	R = Bn, R' = Cl	50	87:13	47	94	91	40 (72)	13.0
9	R = Cy, R' = Cl	58	80:20	53	92	95	38 (76)	7.6
10	R = Ph, R' = Cl	42	86:14	37	93	59	40 (51)	9.5
11	R = Me, R' = Br	59	81:19 ^f	45	- ^g	- ^g	35 (49)	3.2
12	R = <i>i</i> -Pr, R' = Br	57	86:14	51	73	87	35 (67)	5.9
13	R = Bn, R' = Br	52	88:12	45	86	82	42 (71)	10.0
14	R = Cy, R' = Br	60	83:17	53	72	86	28 (65)	4.7

^a**4.51** (20 mol%), MCPBA (0.6 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bConversion determined by ¹H NMR using 3,5-dimethoxybenzaldehyde as the internal standard, c=(1-yield of starting material)*100%. ^cDetermined by chiral SFC. ^dIsolated yields after column chromatography. ^eSelectivity factor, S=ln[(1-c)(1-ee_{SM})]/ln[(1-c)(1+ee_{SM})]; ee_{SM}=ee of recovered starting material, c=conversion. ^fDetermined by ¹H NMR after column chromatography. ^gThe ee could not be determined because the enantiomers were inseparable by chiral SFC. ^hDetermined by ¹H NMR of crude reaction mixture. ⁱCombined yield of individual diastereomers isolated (36% major + 4% minor).

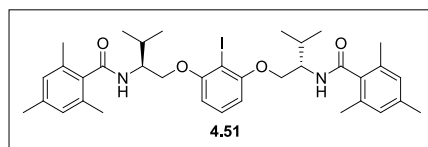
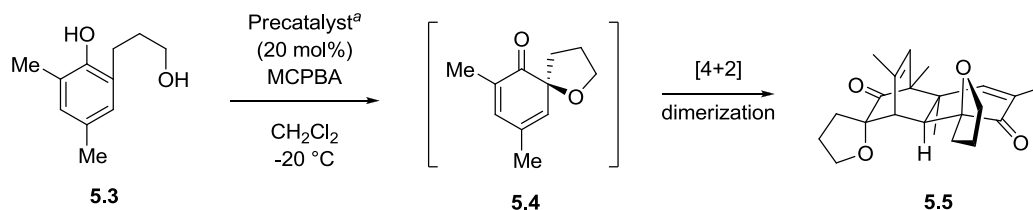


Table 5.13 Oxidative cyclization of substrates with a 2'-stereogenic center

5.2.7 Enantioselective oxidative cyclization of phenolic alcohol

The relative efficacy of catalysts **4.20** and **4.52** was evaluated also in the cycloetherification of phenolic alcohol **5.3**. Recall that the primary product of the reaction, **5.4** undergoes a highly diastereoselective [4+2]-homodimerization *in situ* to give cycloadduct **5.5** (Scheme 5.4).

Iodide **4.20** proved to be much better than **4.52** in the present case, providing (-)-**5.5** in 57% yield and 94% *ee* (Table 5.14). A single recrystallization of the product by slow evaporation of a solution in ethanol at RT afforded material of >99% *ee*. X-ray analysis of crystals revealed that the spirocenters (-)-**5.5** are of (*S*) configuration (Figure 5.9).



Entry	Precatalyst	Product	Time (h)	<i>ee</i> ^b (%)	Yield ^c (%)
1	4.20	(-)- 5.5	15	94 (>99) ^d	57
2	4.52	(+)- 5.5	18	90	13

^aPrecatalyst (20 mol%), MCPBA (1.3 equiv), -20 °C, CH₂Cl₂ (0.02 M). ^bDetermined by chiral SFC. ^cIsolated yields after column chromatography. ^d*ee* after single recrystallization.

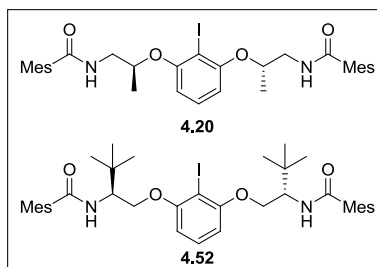


Table 5.14 Formation of enantioenriched dimer **5.5**

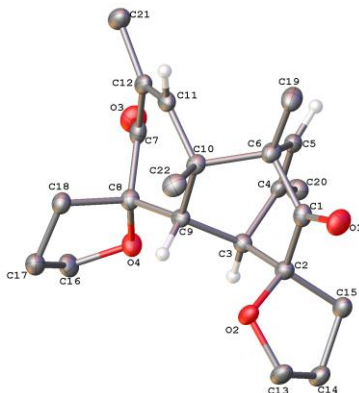


Figure 5.9 X-ray structure of (*S,S*)-(-)-**5.5**

5.3 Summary and Conclusion

The enantioselective oxidative cyclization of naphtholic alcohols mediated by hypervalent iodine reagents is generally more efficient than the analogous reaction of sulfonamides, in terms of both asymmetric induction and chemical yields. The transformation is best carried out under the same conditions employed for cyclization of sulfonamides (20 mol% of chiral catalyst, stoichiometric amount of MCPBA, CH₂Cl₂, -20 °C).

Electron-withdrawing groups at the naphthol 4-position promoted high levels of asymmetric induction. The opposite was true for electron donating substituents. This is attributable to a greater ease of fragmentation of the complex resulting through the union of the substrate with the hypervalent form of the catalyst. Such an event releases a cationic form of the substrate that cyclizes in an achiral environment, leading to a racemic product.

Enantioselective cycloetherification reactions are generally slow. Attempts to harness the Thorpe-Ingold *gem*-dimethyl effect to increase their rate were unfruitful, resulting instead in further deceleration. This observation suggested that a kinetic resolution of racemic substrates mediated by chiral aryl iodides may be possible. This was found to be the case for naphtholic

alcohols bearing a single substituent at the side chain 2' position. The best catalyst for such a process was iodide **4.51**, which afforded good to excellent levels of asymmetric induction, but that had no influence on the innate diastereoselectivity of the transformation.

A single case of oxidative cyclization of a phenolic alcohol was studied, because the spiroether thus obtained underwent fast Diels-Alder homodimerization *in situ*.

Finally, the absolute configuration of a number of spiroethers or their derivatives, as well as of kinetically resolved substrates, was determined by X-ray diffractometry.

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Appendices

A. Experimental protocols

Unless otherwise stated, ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded from CDCl_3 solutions, at RT. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, J , are in hertz (Hz). Multiplicities are reported as “s” (singlet), “d” (doublet), “t” (triplet), “q” (quartet), “p” (pentet), “dd” (doublet of doublets), “ddd” (doublet of doublet of doublets), “m” (multiplet), “td” (triplet of doublets) and further qualified as “br” (broad), “app” (apparent). Infrared (IR) spectra (cm^{-1}) were recorded from films (Perkin Elmer[®] Universal ATR Sampling Accessories). Low and high-resolution mass spectra (m/z) were obtained in the electron impact (EI) or electrospray (ESI) mode, as specified, in methanol solution. Melting points (uncorrected) were measured on a Mel-Temp apparatus. Optical rotations were measured at the sodium D line (589 nm) with a Perkin Elmer[®] 241 polarimeter.

All reagents and solvents were commercial products and used without further purification except THF (freshly distilled from Na/benzophenone under argon), CH_2Cl_2 (freshly distilled from CaH_2 under argon) and diisopropylamine (distilled from CaH_2 under Ar then stored over KOH). Commercial $n\text{-BuLi}$ was titrated against *N*-benzylbenzamide in THF at $-40\text{ }^\circ\text{C}$ until persistence of a light blue color. Commercial MCPBA of a stated purity of 77% was used as oxidant. The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} pre-coated plates. Spots were visualized with a UV lamp, KMnO_4 stain or vanillin stain. Flash chromatography was performed on Silicycle[®] 230 – 400 mesh silica gel. All reactions were performed under dry argon in flame or oven dried flasks equipped with Teflon[™] stirring bars. All flasks were fitted with rubber septa for the introduction of substrates, reagents and solvents

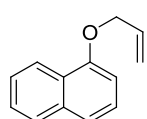
via syringe. Solvents, pure liquid reagents or reagents in solution, and solids were added in one portion, unless otherwise stated.

Enantiomeric excesses were determined using a Thar SFC method station (Model 840) equipped with chiral columns OD-H (0.46 cm × 25 cm 5 μm), AD-H (0.46 cm × 25 cm 5 μm), AS-H (0.46 cm × 25 cm 5 μm), OJ-H (0.46 cm × 25 cm 5 μm) and Lux 3u Cellulose 2 (50 × 4.60 mm). The standard operating pressure was 120 bar and the temperature of the chiral column was 33-34 °C. Enantiomeric excesses of some of the compounds were determined using a high performance liquid chromatography (HPLC), which was performed on an Agilent 1100 HPLC, equipped with a variable wavelength UV-Vis detector and Chiralcel OD-H chiral column (0.46 cm x 25 cm 5 μm), Chiralcel AD-H chiral column (0.46 cm x 25 cm 5 μm), Chiralcel OJ-RH (0.46 cm × 15 cm 5 μm).

B. Preparation of substrates employed in the present study experimental section

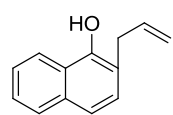
B.1 Preparation and characterization of intermediates towards naphtholic alcohol 3.10

B.1.1 Preparation of 1-(allyloxy)naphthalene (3.8)



[known compound]^[1] Allyl bromide (6.5 mL, 76.3 mmol, 1.1 equiv) was added dropwise over 10 minutes to a solution of 1-naphthol (10.0 g, 69.4 mmol, 1.0 equiv) in acetone (70.0 mL) containing suspended K_2CO_3 (10.6 g, 76.3 mmol, 1.1 equiv). The mixture was stirred at RT for 15 min, then it was heated to reflux for 7 h, after which time TLC showed that the reaction was complete. The mixture was cooled to RT and the solvent was evaporated. The residue was quenched with H_2O (80 mL) and extracted with Et_2O (3×15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated. The residue was dried under high vacuum to provide 12.5 g of **3.8** (98% crude yield) as light brown oil and used for the next step without purification. **IR**: 1271. **¹H**: 8.40-8.37 (m, 1H), 7.88-7.82 (m, 1H), 7.57-7.38 (m, 4H), 6.85 (d, 1H, $J = 6.0$), 6.29-6.16 (m, 1H), 5.58 (dd, 1H, $J = 18.0, 3.0$), 5.39 (dd, 1H, $J = 12.0, 3.0$), 4.76 (d, 2H, $J = 3.0$). **¹³C**: 154.4, 134.7, 133.5, 127.6, 126.5, 125.9 (2C), 125.3, 122.2, 120.5, 117.5, 105.2, 69.0.

B.1.2 Preparation of 2-allylnaphthalen-1-ol (3.9)

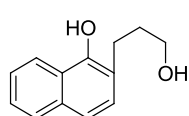


[known compound]^[1] A solution of crude **3.8** (12.0 g, 65.1 mmol, 1.0 equiv) in *N,N*-diethylaniline (120.0 mL) was refluxed overnight. The reaction mixture was cooled to RT and was diluted with $EtOAc$ (90 mL) and washed with 3M HCl (4×30 mL). The

[1] Reich, S. H.; Melnick, M.; Pino, M. J.; Fuhry, M. A. M.; Trippe, A. J.; Appelt, K; Davies II, J. F.; Wu, B.-W; Musik, L. *J. Med. Chem.* **1996**, *39*, 2781.

organic phase was washed with brine (30 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 1:9 EtOAc/hexanes) to provide 9.5 g (79% yield) of **3.9** as yellow oil. **IR**: 3659-3055 (broad). ¹**H**: 8.22-8.19 (m, 1H), 7.83-7.80 (m, 1H), 7.51-7.48 (m, 2H), 7.44 (d, 1H, *J* = 6.0), 7.25 (d, 1H, *J* = 9.0), 6.17-6.04 (m, 1H), 5.60 (br s, 1H), 5.31-5.25 (m, 2H), 3.61 (d, 2H, *J* = 9.0). ¹³**C**: 149.7, 136.3, 133.9, 128.6, 127.6, 125.9, 125.4, 125.0, 121.5, 120.5, 118.1, 117.0, 35.8.

B.1.3 Preparation of 2-(3-Hydroxypropyl)naphthalen-1-ol (**3.10**)

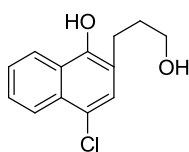


[known compound]^[2] Commercial BH₃•SMe₂ (~10 M solution, 1.1 mL, 10.8 mmol, 2.0 equiv) was added to a cold (0 °C) solution of **3.9**, (1.0 g, 5.4 mmol, 1.0 equiv) in THF (10 mL) and the mixture was stirred at 0 °C for 3 h. Aqueous 30% H₂O₂ (2 mL) was added followed by addition of NaHCO₃ (2 mL) to the cold solution and the mixture was stirred at RT overnight. The reaction was quenched with aq. satd. NH₄Cl (10 mL) and extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (10mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 3:7 EtOAc/hexanes) to provide 854 mg (78% yield) of **3.10**, light yellow solid, m.p.: 81-83 °C (lit.^[3] 84-86 °C). **IR**: 3699-3097 (broad). ¹**H**: 8.29-8.26 (m, 1H), 7.79-7.76 (m, 1H), 7.50-7.44 (m, 2H), 7.40 (d, 1H, *J* = 9.0), 7.22 (d, 1H, *J* = 9.0), 3.67 (t, 2H, *J* = 6.0), 2.97 (app t, 2H, *J* = 7.5), 1.96 (p, 2H, *J* = 6.0). ¹³**C**: 150.2, 133.6, 128.6, 127.3, 125.6, 125.3, 125.1, 122.1, 120.1, 119.7, 60.3, 31.4, 25.1. **HRMS**: calcd for C₁₃H₁₄O₂Na [M+Na]⁺: 225.0891; found: 225.0886.

[2] De Benneville, P. L.; Connor, R. *J. Am. Chem. Soc.* **1940**, *62*, 3067.

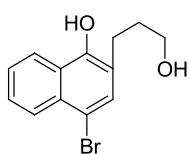
[3] Huffman, J. W.; Wu, M. J.; Lu, J. *J. Org. Chem.* **1998**, *63*, 4510.

B.2 Preparation of 4-Chloro-2-(3-hydroxypropyl)-naphthalen-1-ol (3.11)



Solid NCS (218 mg, 1.7 mmol, 1.1 equiv) was added in several portions over a period of 30 min to a solution of **3.10** (300 mg, 1.5 mmol, 1.0 equiv) in MeCN (1.5 mL) at RT. The mixture was stirred for 3h at RT, after which time TLC showed that the reaction was complete. The solution was diluted with H₂O (5 mL) and extracted with Et₂O (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 1:3 EtOAc/hexanes) to provide 251 mg (72% yield) of **3.11** as light yellow solid, m.p.: 97-99 °C. **IR**: 3675-3045 (broad). **¹H**: 8.31 (d, 1H, *J* = 6.0), 8.16 (d, 1H, *J* = 9.0), 7.98 (br s, 1H), 7.59-7.50 (m, 2H), 7.31 (s, 1H), 3.68 (t, 2H, *J* = 6.0), 2.94 (app t, 2H, *J* = 6.0), 2.01-1.93 (m, 3H). **¹³C**: 149.7, 130.4, 128.3, 126.6, 126.5, 125.8, 124.0, 122.8, 122.7, 120.1, 60.1, 31.1, 24.9. **HRMS**: calcd for C₁₃H₁₂O₂Cl [M-H]⁻: 235.0526; found: 235.0526.

B.3 Preparation of 4-Bromo-2-(3-hydroxypropyl)naphthalene-1-ol (3.12)



[Known compound]^[4] Solid NBS (288 mg, 1.7 mmol, 1.1 equiv) was added in several portions over a period of 30 min to a solution of **3.10** (300 mg, 1.5 mmol, 1.0 equiv) in MeCN (1.5 mL) at RT. The mixture was stirred for 3h at RT, after which time TLC showed that the reaction was complete. The solution was diluted with H₂O (5 mL) and extracted with Et₂O (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 1:3 EtOAc/hexanes) to provide 266 mg (69% yield) of **3.12** as tan solid, m.p. 99-101 °C (lit. m.p.^[4] not reported). **IR**: 3692-3009 (broad). **¹H**: 8.30 (d, 1H, *J* = 6.0), 8.12 (d, 1H, *J* = 9.0), 7.59-7.49 (m, 3H), 3.67 (t, 2H, *J* = 6.0), 2.93 (app t, 2H, *J* =

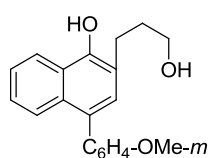
[4] Sarkar, D.; Ghosh, M. K.; Rout, N. *Org. Biomol. Chem.* **2016**, *14*, 7883.

6.0), 1.96 (p, 2H, $J = 6.0$). ^{13}C : 150.3, 132.0, 131.6, 126.9, 126.7, 126.6, 125.8, 122.7, 120.8, 112.8, 60.1, 31.2, 24.8. **HRMS**: calcd for $\text{C}_{13}\text{H}_{12}\text{O}_2^{79}\text{Br}$ [M-H] $^-$: 279.0021; found: 279.0014.

B.4 General procedure for Suzuki coupling of **3.12** with aryl boronic acids

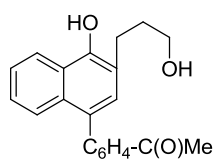
A solution of **3.12** (300 mg, 1.1 mmol, 1.0 equiv), $\text{Pd}(\text{PPh}_3)_4$ (64 mg, 55 μmol , 0.05 equiv), appropriate boronic acid (1.3 mmol, 1.2 equiv), and Cs_2CO_3 (424 mg, 1.3 mmol, 1.2 equiv) in 1,4-dioxane (6.0 mL) and water (1.2 mL) was stirred at 80 °C for 6 h, after which time TLC showed that the reaction was complete. The cooled mixture was diluted with Et_2O (6.0 mL) and filtered through a Celite[®] pad, which was washed with more Et_2O (3 \times 10 mL). The combined filtrate was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography to provide corresponding products.

B.4.1 Characterization of 2-(3-Hydroxypropyl)-4-(3-methoxyphenyl)naphthalen-1-ol (**3.13**, Ar = $\text{C}_6\text{H}_4\text{-OMe-}m$)



The procedure described above, but employing 3-methoxyphenylboronic acid, afforded 312 mg (95% yield) of **3.13**, Ar = $\text{C}_6\text{H}_4\text{-OMe-}m$ from 300 mg of **3.12** (eluent: 1:9 to 1:3 EtOAc/hexanes), colorless oil. **IR**: 3636-3122 (broad). ^1H : 8.38 (d, 1H, $J = 9.0$), 8.01 (br s, 1H), 7.91 (d, 1H, $J = 9.0$), 7.52-7.38 (m, 3H), 7.21 (s, 1H), 7.11-7.06 (m, 2H), 6.98 (d, 1H, $J = 9.0$), 3.88 (s, 3H), 3.71 (t, 2H, $J = 4.5$), 3.00 (app t, 2H, $J = 6.0$), 2.40 (br s, 1H), 1.98 (p, 2H, $J = 6.0$). ^{13}C : 159.5, 149.9, 142.4, 132.5, 131.5, 129.6, 129.2, 125.7, 125.6, 125.5, 125.1, 122.8, 122.4, 119.4, 115.8, 112.4, 60.4, 55.4, 31.5, 25.2. **HRMS**: calcd for $\text{C}_{20}\text{H}_{21}\text{O}_3$ [M+H] $^+$: 309.1491; found: 309.1499.

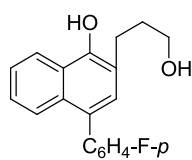
B.4.2 Characterization of 1-(4-(4-Hydroxy-3-(3-hydroxypropyl)naphthalen-1-yl)phenyl)ethanone (**3.13**, Ar = C₆H₄-C(O)Me)



The procedure described above, but employing 4-acetylphenylboronic acid, afforded 216 mg (73% yield) of **3.13**, Ar = C₆H₄-C(O)Me from 260 mg of **3.12** (eluent: 1:4 to 3:7 EtOAc/hexanes), light yellow solid, m.p. 147-149 °C.

IR: 3643-2995 (broad), 1669. **¹H**: 8.39 (d, 1H, *J* = 8.3), 8.10 (br s, 1H), 8.07 (d, 2H, *J* = 8.2), 7.81 (d, 1H, *J* = 8.3), 7.60 (d, 2H, *J* = 8.2), 7.51 (app t, 1H, *J* = 7.3), 7.42 (app t, 1H, *J* = 7.2), 7.19 (s, 1H), 3.73 (t, 2H, *J* = 5.0), 3.01 (t, 2H, *J* = 6.4), 2.69 (s, 3H), 2.24 (br s, 1H), 2.00 (p, 2H, *J* = 6.0). **¹³C**: 198.2, 150.8, 146.3, 135.6, 131.4, 131.3, 130.6, 130.1, 128.5, 126.2, 125.7, 125.4, 125.2, 122.8, 119.5, 60.4, 31.5, 26.9, 25.2. **HRMS**: calcd for C₂₁H₂₀O₃Na [M+Na]⁺: 343.1310; found: 343.1313.

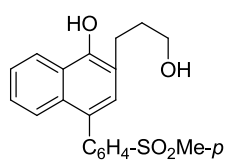
B.4.3 Characterization of 4-(4-Fluorophenyl)-2-(3-hydroxypropyl)naphthalen-1-ol (**3.13**, Ar = C₆H₄-F-*p*)



The procedure described above, but employing 4-fluorophenylboronic acid, provided 190 mg (60% yield) of **3.13**, Ar = C₆H₄-F-*p* from 300 mg of **3.12** (eluent: 3:17 to 3:7 EtOAc/hexanes), yellow solid, m.p. 127-129 °C. **IR**: 3597-

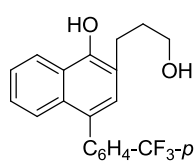
3045 (broad). **¹H**: 8.37 (d, 1H, *J* = 9.0), 7.92 (br s, 1H), 7.78 (d, 1H, *J* = 6.0), 7.52-7.39 (m, 4H), 7.19-7.13 (m, 3H), 3.72 (t, 2H, *J* = 6.0), 3.00 (app t, 2H, *J* = 6.0), 2.06-1.95 (m, 3H). **¹³C**: 162.0 (d, *J* = 246.1), 150.0, 136.8 (d, *J* = 3.0), 131.7 (d, *J* = 8.3), 131.6, 131.5, 129.8, 125.8, 125.5, 125.3, 125.1, 122.5, 119.2, 115.1 (d, *J* = 21.1), 60.3, 31.4, 25.1. **EI**: calcd for C₁₉H₁₇O₂F: 296.1213; found: 296.1208.

B.4.4 Characterization of 2-(3-Hydroxypropyl)-4-(4-(methylsulfonyl)phenyl)naphthalen-1-ol (**3.13**, Ar = C₆H₄-SO₂Me-*p*)



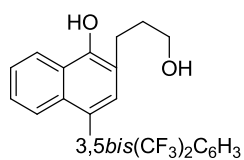
The procedure described above, but employing 4-(methylsulfonyl)-phenylboronic acid, returned 216 mg (85% yield) of **3.13**, Ar = C₆H₄-SO₂Me-*p* from 200 mg of **3.12** (eluent: 1:4 to 9:11 EtOAc/hexanes), light yellow solid, m.p.: 94-96 °C. **IR**: 3694-3134 (broad). **¹H**: 8.40 (d, 1H, *J* = 9.0), 8.27 (br s, 1H), 8.04 (d, 2H, *J* = 9.0), 7.75 (d, 1H, *J* = 6.0), 7.68 (d, 2H, *J* = 9.0), 7.53-7.40 (m, 2H), 7.17 (s, 1H), 3.72 (t, 2H, *J* = 4.5), 3.16 (s, 3H), 3.00 (t, 2H, *J* = 6.0), 2.51 (br s, 1H), 1.98 (p, 2H, *J* = 6.0). **¹³C**: 151.0, 147.0, 138.6, 131.1, 131.0, 130.2, 127.3, 126.3, 125.6, 125.4, 124.7, 122.8, 119.5, 60.2, 44.7, 31.4, 25.2. **HRMS**: calcd for C₂₀H₂₀O₄SNa [M+Na]⁺: 379.0980; found: 379.0977.

B.4.5 Characterization of 2-(3-Hydroxypropyl)-4-(4-(trifluoromethyl)phenyl)naphthalen-1-ol (**3.13**, Ar = C₆H₄-CF₃-*p*)



The procedure described above, but employing 4-(trifluoromethyl)-phenylboronic acid, gave 241 mg (98% yield) of **3.13**, Ar = C₆H₄-CF₃-*p* from 200 mg of **3.12** (eluent: 1:9 to 1:4 EtOAc/hexanes), white solid, m.p. 145-147 °C. **IR**: 3548-3017 (broad). **¹H**: 8.39 (d, 1H, *J* = 9.0), 8.04 (br s, 1H), 7.79-7.72 (m, 3H), 7.61 (d, 2H, *J* = 9.0), 7.54-7.40 (m, 2H), 7.17 (s, 1H), 3.73 (t, 2H, *J* = 6.0), 3.01 (app t, 2H, *J* = 6.0), 2.08 (br s, 1H), 2.00 (p, 2H, *J* = 6.0). **¹³C**: 150.6, 144.7, 131.2, 131.0, 130.5, 129.9, 129.0 (q, *J* = 32.5), 126.1, 125.5, 125.3, 125.2 (q, *J* = 3.8), 125.0, 124.4 (q, *J* = 271.8), 122.7, 119.3, 60.3, 31.4, 25.1. **HRMS**: calcd for C₂₀H₁₆F₃O₂ [M-H]⁻: 345.1102; found: 345.1094.

B.4.6 Characterization of 4-(3,5-Bis(trifluoromethyl)phenyl)-2-(3-hydroxypropyl)naphthalen-1-ol (**3.13**, Ar = 3,5bis(CF₃)₂C₆H₃)



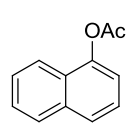
The procedure described above, but employing 3,5-bis(trifluoromethyl)-phenylboronic acid, produced 257 mg (87% yield) of **3.13**, Ar = 3,5bis(CF₃)₂C₆H₃ from 200 mg of **3.12** (eluent: 1:9 to 1:4 EtOAc/hexanes), yellow solid, m.p. 124-126 °C. IR: 3689-3097 (broad). ¹H: 8.41 (d, 1H, *J* = 6.0), 8.22 (br s, 1H), 7.95-7.92 (m, 3H), 7.66 (d, 1H, *J* = 6.0), 7.56-7.44 (m, 2H), 7.18 (s, 1H), 3.74 (t, 2H, *J* = 6.0), 3.02 (app t, 2H, *J* = 7.5), 2.19 (br s, 1H), 2.01 (p, 2H, *J* = 6.0). ¹³C: 151.2, 143.1, 131.6 (q, *J* = 33.2), 131.0, 130.4, 130.3 (app d, *J* = 3.0), 129.2, 126.6, 125.6, 125.5, 124.3, 123.5 (q, *J* = 272.6), 122.9, 120.8-120.5 (m), 119.4, 60.3, 31.3, 25.1. HRMS: calcd for C₂₁H₁₆O₂F₆: 414.1055; found: 414.1051.

B.5 Preparation and characterization of intermediates towards naphtholic alcohol **3.18**

B.5.1 General procedure for *O*-acylation of α -naphthols

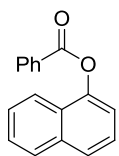
Neat acid chloride (4.5 mmol, 1.3 equiv) was added dropwise to the solution of 1-naphthol (500 mg, 3.47 mmol, 1.0 equiv), DMAP (208 mg, 1.74 mmol, 0.5 equiv) and Et₃N (0.5 mL, 3.8 mmol, 1.1 equiv) in CH₂Cl₂ (10.0 mL) at 0 °C. The mixture was warmed to RT and then stirred overnight, after which time TLC showed that the reaction was complete. The reaction was quenched with 1M HCl (10 mL) and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were washed successively with H₂O (10 mL), satd. NaHCO₃ solution (2×5 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to provide corresponding products.

B.5.1.1 Characterization of Naphthalen-1-yl acetate (3.14, R = Me)



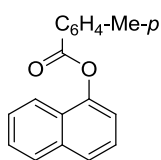
[Known compound]^[5] 4.8 g (93% yield) from 4.0 g of 1-naphthol, light brown solid, m.p.: 40-42 °C (lit.^[5] m.p. not reported), eluent: 1:19 to 1:9 EtOAc/hexanes. **IR:** 1756. **¹H:** 7.91-7.88 (m, 2H), 7.76 (d, 1H, *J* = 8.3), 7.56-7.50 (m, 2H), 7.47 (d, 1H, *J* = 8.), 7.27 (d, 1H, *J* = 7.4), 2.48 (s, 3H). **¹³C:** 169.6, 146.7, 134.8, 128.2, 126.9, 126.6, 126.2, 125.5, 121.3, 118.2, 21.2.

B.5.1.2 Characterization of Naphthalen-1-yl benzoate (3.14, R = Ph)



0.80 g (96% yield) from 0.50 g of 1-naphthol, colorless oil, eluent: 1:19 to 1:9 EtOAc/hexanes. **IR:** 1733. **¹H:** 8.43 (d, 2H, *J* = 7.8), 8.05-8.02 (m, 1H), 7.98-7.95 (m, 1H), 7.85 (d, 1H, *J* = 8.2), 7.76-7.71 (m, 1H), 7.64-7.53 (m, 5H), 7.46 (d, 1H, *J* = 7.4). **¹³C:** 165.3, 146.9, 134.8, 133.9, 130.4, 129.5, 128.8, 128.2, 127.1, 126.6 (2C), 126.2, 125.6, 121.3, 118.3.

B.5.2 Preparation of Naphthalen-1-yl 4-methylbenzoate (3.14, R = *p*-tolyl)



To a solution of 1-naphthol (2.5 g, 17.3 mmol, 1.0 equiv) in CH₂Cl₂ (30 mL) was added EDCI (4.0 g, 20.8 mmol, 1.2 equiv), DMAP (1.06 g, 8.7 mmol, 0.5 equiv) and *p*-toluic acid (2.8 g, 20.8 mmol, 1.2 equiv) at 0 °C with good stirring. The reaction mixture was warmed to RT and stirred for overnight, after which time TLC showed that the reaction was complete. The reaction was quenched with 1M HCl (15 mL) and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were washed successively with H₂O (20 mL), satd. NaHCO₃ solution (3×10 mL), brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 3:17:0.1 to 5:15:0.1 EtOAc/hexanes/Et₃N) to

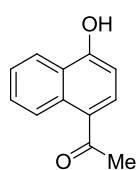
[5] Barbero, M.; Cadamuro, S.; Dughera, S.; Venturello, P. *Synthesis* **2008**, 3625.

provide 4.16 g (92% yield) of **3.14**, R = *p*-tolyl, as white solid, m.p. 111-113 °C. **IR**: 1733. **¹H**: 8.27 (d, 2H, *J* = 9.0), 7.99-7.91 (m, 2H), 7.81 (d, 1H, *J* = 6.0), 7.57-7.49 (m, 3H), 7.42-7.38 (m, 3H), 2.51 (s, 3H). **¹³C**: 165.3, 147.0, 144.7, 134.7, 130.4, 129.5, 128.1, 127.1, 126.7, 126.5, 126.0, 125.5, 121.4, 118.3, 21.8.

B.5.3 General procedure for Fries rearrangement of **3.14**

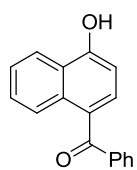
A mixture of **3.14** (12.2 mmol, 1.0 equiv) and anhydrous AlCl₃ (1.8 g, 13.5 mmol, 1.1 equiv) in chlorobenzene (42 mL) was stirred at 100 °C for 2 h. The reaction mixture was cooled to 0 °C, quenched with 1M HCl (30 mL) and extracted with EtOAc (4×15 mL). The combined extracts were washed with H₂O (25 mL), brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to provide **3.15**.

B.5.3.1 Characterization of 1-(4-Hydroxynaphthalen-1-yl)ethanone (**3.15**, R = Me)



[Known compound]^[6] 0.91 g (18% yield) from 5.0 g of **3.14**, R = Me, off white solid, dec. 197 °C (lit.^[6] m.p. not reported), eluent: 3:17 to 2:3 EtOAc/hexanes. **IR**: 3374-2553 (broad), 1638. **¹H**: 9.04 (d, 1H, *J* = 8.7), 8.28 (d, 1H, *J* = 8.2), 7.97 (d, 1H, *J* = 8.0), 7.68-7.53 (m, 2H), 6.84 (d, 1H, *J* = 8.0), 6.13 (br s, 1H). **¹³C**: 200.3, 155.9, 132.6, 131.8, 129.1, 127.9, 126.6, 126.0, 124.7, 122.0, 107.0, 29.5.

B.5.3.2 Characterization of (4-Hydroxynaphthalen-1-yl)(phenyl)methanone (**3.15**, R = Ph)



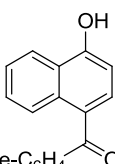
[Known compound]^[7] 0.37 g (35% yield) from 1.1 g of **3.14**, R = Ph, yellow solid, m.p.: 162-164 °C (lit.^[7] m.p. 166-167 °C), eluent: 3:17 to 3:7 EtOAc/hexanes. **IR**: 3625-2925 (broad), 1630. **¹H**: 8.40-8.37 (m, 1H), 8.31-8.28 (m, 1H), 7.85 (d, 2H, *J* =

[6] Allen, A.; Marquand, P. L.; Burton, R.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7849.

[7] Huffman, J. W.; Wu, M. J.; Lu, J. *J. Org. Chem.* **1998**, *63*, 4510.

7.3), 7.62-7.44 (m, 6H), 6.79 (d, 1H, $J = 7.9$). ^{13}C : 198.3, 155.5, 139.4, 133.2, 132.9, 131.7, 130.6, 128.5, 128.3, 128.2, 126.0, 125.9, 124.8, 122.3, 107.0.

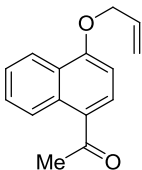
B.5.3.3 Characterization of (4-Hydroxynaphthalen-1-yl)(*p*-tolyl)methanone (**3.15**, R = *p*-tolyl)

 1.33 g (41% yield) from 3.21 g of **3.14**, R = *p*-tolyl, yellow solid, dec. 184 °C, eluent: 1:4 to 7:13 EtOAc/hexanes. **IR**: 3618-2746 (broad), 1678. ^1H (acetone- d_6): 9.8 (br s, 1H), 8.38-8.31 (m, 2H), 7.70 (d, 2H, $J = 6.0$), 7.59-7.51 (m, 3H), 7.34 (d, 2H, $J = 9.0$), 6.98 (d, 1H, $J = 6.0$), 2.43 (s, 3H). ^{13}C (acetone- d_6): 196.8, 157.2, 143.9, 138.0, 134.0, 132.2, 131.0, 129.8, 128.5, 128.3, 126.6, 126.1, 126.0, 123.3, 107.3, 21.5.

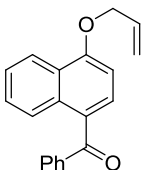
B.5.4 Preparation of compounds 3.16

These substances were prepared by the same procedure described above for the synthesis of compound **3.8** and used in the subsequent step without purification.

B.5.4.1 Characterization of (4-(Allyloxy)naphthalen-1-yl)(phenyl)methanone (**3.16**, R = Me)

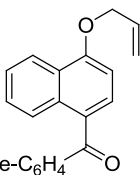
 688 mg (93% crude yield) from 606 mg of **3.15**, R = Me, yellow solid, m.p.: 56-58 °C. **IR**: 1663, 1230. ^1H : 9.05 (d, 1H, $J = 9.0$), 8.38 (d, 1H, $J = 9.0$), 7.96 (d, 1H, $J = 6.0$), 7.64 (t, 1H, $J = 7.5$), 7.53 (t, 1H, $J = 7.5$), 6.73 (d, 1H, $J = 9.0$), 6.23-6.10 (m, 1H), 5.54 (d, 1H, $J = 15.0$), 5.38 (d, 1H, $J = 12.0$), 4.75 (d, 2H, $J = 3.0$), 2.70 (s, 3H). ^{13}C : 200.0, 158.1, 132.5, 132.1, 131.9, 128.8, 127.3, 126.3, 125.9, 125.8, 122.2, 118.0, 103.1, 69.1, 29.3.

B.5.4.2 Characterization of (4-(Allyloxy)naphthalen-1-yl)(phenyl)methanone (**3.16**, R = Ph)

 288 mg (94% crude yield) from 265 mg of **3.15**, R = Ph, colorless oil. **IR**: 1646, 1241. ^1H : 8.43-8.36 (m, 2H), 7.85 (d, 2H, $J = 6.0$), 7.62-7.44 (m, 6H), 6.81 (d, 1H, $J = 9.0$), 6.27-6.14 (m, 1H), 5.57 (dd, 1H, $J = 15.0, 3.0$), 5.40 (dd, 1H, $J = 9.0, 3.0$),

4.81 (d, 2H, $J = 3.0$). ^{13}C : 197.4, 157.2, 139.4, 132.7, 132.6, 132.5, 131.3, 130.3, 128.3, 128.2, 128.1, 125.9 (2C), 125.7, 122.4, 118.0, 103.1, 69.1.

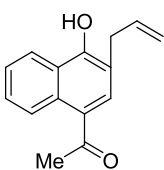
B.5.4.3 Characterization of (4-(Allyloxy)naphthalen-1-yl)(*p*-tolyl)methanone (**3.16**, R = *p*-tolyl)

 659 mg (92% crude yield) from 624 mg of **3.15**, R = *p*-tolyl, light yellow oil.
IR: 1646, 1245. ^1H : 8.43-8.40 (m, 1H), 8.32-8.29 (m, 1H), 7.76 (d, 2H, $J = 6.0$), 7.58-7.53 (m, 3H), 7.27 (d, 2H, $J = 9.0$), 6.81 (d, 1H, $J = 9.0$), 6.27-6.14 (m, 1H), 5.56 (d, 1H, $J = 18.0$), 5.40 (d, 1H, $J = 9.0$), 4.80 (d, 2H, $J = 6.0$), 2.44 (s, 3H). ^{13}C : 197.1, 156.9, 143.4, 136.7, 132.7 (2C), 130.6, 130.5, 129.0, 128.7, 127.9, 125.9, 125.8 (2C), 122.3, 117.9, 103.1, 69.1, 21.7.

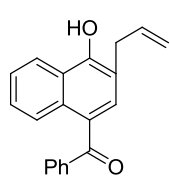
B.5.5 Preparation of compounds 3.17

These substances were prepared by the same procedure detailed above for the synthesis of compound **3.9**.

B.5.5.1 Characterization of (3-Allyl-4-hydroxynaphthalen-1-yl)(phenyl)methanone (**3.17**, R = Me)

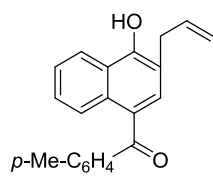
 392 mg (59% yield) from 668 mg of **3.16**, R = Me, yellow solid, m.p. 182-184 °C; eluent: 1:4 to 2:3 EtOAc/hexanes. **IR**: 3534-2837 (broad), 1639. ^1H (acetone d_6): 9.03 (d, 1H, $J = 9.0$), 8.35 (d, 1H, $J = 6.0$), 8.08 (s, 1H), 7.60-7.50 (m, 2H), 6.15-6.02 (m, 1H), 5.15-5.06 (m, 2H), 3.68 (d, 2H, $J = 6.0$), 2.66 (s, 3H). ^{13}C (acetone d_6): 198.9, 153.8, 136.4, 134.5, 131.3, 127.5, 126.7, 126.3, 125.5, 125.4, 121.8, 118.1, 115.3, 33.7, 28.5.

B.5.5.2 Characterization of (3-Allyl-4-hydroxynaphthalen-1-yl)(phenyl)methanone (**3.17**, R = Ph)



366 mg (66% yield) from 556 mg of **3.16**, R = Ph, brown oil; eluent: 1:4 to 3:7 EtOAc/hexanes. **IR**: 3629-3122 (broad), 1641. **¹H**: 8.32-8.29 (m, 2H), 7.87 (d, 2H, *J* = 9.0), 7.63-7.44 (m, 7H), 6.12-5.99 (m, 1H), 5.29-5.23 (m, 2H), 3.57 (d, 2H, *J* = 6.0). **¹³C**: 197.6, 153.1, 139.3, 135.6, 133.2, 132.7, 132.0, 130.4, 128.3 (2C), 127.4, 125.9, 125.7, 125.1, 121.9, 117.5, 116.4, 35.4.

B.5.5.3 Characterization of (3-Allyl-4-hydroxynaphthalen-1-yl)(*p*-tolyl)methanone (**3.17**, R = 4-Tol)



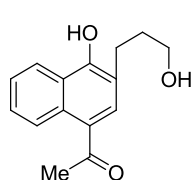
431 mg (65% yield) from 659 mg of **3.16**, R = 4-Tol, yellow solid, m.p.: 113-115 °C; eluent: 1:4 to 3:7 EtOAc/hexanes; **IR**: 3639-3136 (broad), 1635. **¹H**: 8.27-8.20 (m, 2H), 7.76 (d, 2H, *J* = 6.0), 7.54-7.47 (m, 2H), 7.41 (s, 1H), 7.27 (d, 2H, *J* = 9.0), 6.13-6.00 (m, 2H), 5.31-5.25 (m, 2H), 3.56 (d, 2H, *J* = 6.0), 2.45 (s, 3H). **¹³C**: 197.2, 152.8, 143.6, 136.5, 135.6, 132.5, 131.9, 130.6, 129.1, 128.9, 127.3, 125.8 (2C), 125.0, 121.7, 117.6, 116.1, 35.6, 21.7.

B.5.6 General procedure for the hydroboration oxidation of **3.17** for the synthesis of 4-acyl naphtholic alcohols **3.18**

Neat cyclohexene (279 mg, 344 μ L, 3.4 mmol, 2.0 equiv) was added dropwise over 10 min to a cold (0 °C) solution of $\text{BH}_3 \cdot \text{SMe}_2$ (commercial 10 M solution, 170 μ L, 1.7 mmol, 1.0 equiv) in 1.5 mL THF and maintained under Ar atmosphere. The mixture was stirred for 1h at 0 °C, then a solution of **3.17** (1.7 mmol, 1 equiv) in THF (4.5 mL) was added dropwise. The mixture was warmed to RT and stirred for 2h. Solid $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (1.1 g, 6.8 mmol,

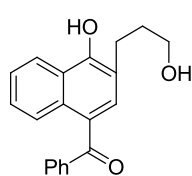
4.0 equiv) was then added to the mixture at RT and then H₂O (3.0 mL) was added dropwise. The mixture was stirred for 2h at RT. The reaction mixture was extracted with EtOAc (4×10 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography on silica gel to provide 4-acyl naphtholic alcohols.

B.5.6.1 Characterization of 1-(4-Hydroxy-3-(3-hydroxypropyl)naphthalen-1-yl)ethanone (3.18, R = Me)



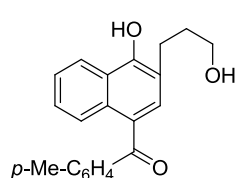
246 mg (60% yield) from 382 mg of **3.17**, R = Me yellow solid, m.p. 143-145 °C, eluent: 1:4 to 7:13 EtOAc/hexanes. **IR**: 3615-3020 (broad), 1632. **¹H** (acetone-*d*₆): 9.02 (d, 1H, *J* = 9.0), 8.35 (d, 1H, *J* = 9.0), 8.12 (s, 1H), 7.52 (app p, 2H, *J* = 8.0), 3.64 (t, 2H, *J* = 6.0), 3.00 (app t, 2H, *J* = 6.0), 2.67 (s, 3H), 1.97 (p, 2H, *J* = 6.0). **¹³C** (acetone-*d*₆): 199.8, 155.9, 136.1, 132.2, 128.3, 127.3, 127.0, 126.6, 126.1, 123.1, 120.3, 60.4, 32.7, 29.4, 26.3. **HRMS**: calcd for C₁₅H₁₆O₃Na [M+Na]⁺: 267.0997; found: 267.0992.

B.5.6.2 Characterization of (4-Hydroxy-3-(3-hydroxypropyl)naphthalen-1-yl)(phenyl)methanone (3.18, R = Ph)



243 mg (65% yield) from 354 mg of **3.17**, R = Ph, yellow oil, eluent: 1:3 to 2:3 EtOAc/hexanes. **IR**: 3658-3113 (broad), 1637. **¹H**: 8.61 (br s, 1H), 8.40-8.36 (m, 1H), 8.31-8.26 (m, 1H), 7.86-7.83 (m, 2H), 7.62-7.43 (m, 6H), 3.66 (t, 2H, *J* = 4.5), 2.92 (app t, 2H, *J* = 6.0), 2.43 (br s, 1H), 1.90 (p, 2H, *J* = 6.0). **¹³C**: 197.7, 154.2, 139.5, 133.9, 132.5, 131.9, 130.3, 128.3, 127.9, 127.3, 125.7, 125.6, 125.5, 122.7, 118.1, 60.1, 31.2, 25.0. **HRMS**: calcd for C₂₀H₁₈O₃Na [M+Na]⁺: 329.1154; found: 329.1161.

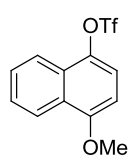
B.5.6.3 Characterization of (4-Hydroxy-3-(3-hydroxypropyl)naphthalen-1-yl)(p-tolyl)methanone (3.18, R = 4-Tol)



263 mg (62% yield) from 400 g of **3.17**, R = 4-Tol, yellow solid, m.p. 107-109 °C, eluent: 1:3 to 2:3 EtOAc/hexanes. **IR**: 3650-3087 (broad), 1633. **¹H**: 8.73 (br s, 1H), 8.38-8.35 (m, 1H), 8.24-8.21 (m, 1H), 7.75 (d, 2H, *J* = 6.0), 7.50-7.47 (m, 2H), 7.41 (s, 1H), 7.26 (d, 2H, *J* = 6.0), 3.60 (t, 2H, *J* = 4.5), 3.01 (br s, 1H), 2.88 (t, 2H, *J* = 6.0), 2.44 (s, 3H), 1.85 (p, 2H, *J* = 6.0). **¹³C**: 197.8, 154.0, 143.6, 136.7, 133.5, 131.8, 130.6, 129.1, 128.2, 127.1, 125.6 (2C), 125.5, 122.7, 118.3, 60.0, 31.2, 25.1, 21.7. **HRMS**: calcd for C₂₁H₂₀O₃Na [M+Na]⁺: 343.1310; found: 343.1306.

B.6 Preparation and characterization of intermediates towards naphtholic alcohol 3.26, R = Me

B.6.1 Preparation of 4-Methoxynaphthalen-1-yl trifluoromethanesulfonate (3.19)

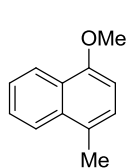


This compound has been mentioned in the literature,^[8] but seemingly neither experimental procedures for its preparation nor physical data have been reported. Trifluoromethanesulfonic anhydride (~1.0 M in CH₂Cl₂, 6.9 mL, 6.9 mmol, 1.2 equiv) was carefully added dropwise to a cold (0 °C) solution of *N,N*-diisopropyl-ethylamine (1.2 mL, 6.9 mmol, 1.2 equiv), 1-naphthol (1.0 g, 5.7 mmol, 1.0 equiv) and DMAP (0.84 g, 6.9 mmol, 1.2 equiv) in CH₂Cl₂ (13.0 mL). The mixture was warmed to RT and then stirred at RT for 3h, after which time TLC showed that the reaction was complete. The mixture was cooled to 0 °C, quenched with H₂O (10.0 mL), and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was

[8] Peterson, G. A.; Kunng, F.-A.; McCallum, J. S.; Wulffe, W. D. *Tetrahedron Lett.* **1987**, 28, 1381.

purified by flash column chromatography (eluent: 1:19 EtOAc/hexanes) to provide 1.7 g (95% yield) of **3.19** as white solid; m.p. 49-50 °C (lit. m.p. not reported). **IR**: 1209, 1088. **¹H**: 8.32 (d, 1H, *J* = 8.3), 8.02 (d, 1H, *J* = 8.3), 7.70-7.56 (m, 2H), 7.38 (d, 1H, *J* = 8.5), 6.75 (d, 1H, *J* = 8.6), 4.03 (s, 3H). **¹³C**: 155.4, 139.3, 128.4, 127.3, 126.7, 126.5, 122.7, 120.7, 118.9 (q, *J* = 641.0, 320.6), 118.1, 102.4, 56.0. **¹⁹F**: -73.67.

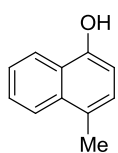
B.6.2 Preparation of 1-Methoxy-4-methylnaphthalene (**3.20**)



This compound is known,^[9] but it was prepared by the following alternative method. Commercial MeMgBr (~3.0 M in Et₂O, 1.6 mL, 4.9 mmol, 3.0 equiv) was added to a cold (0 °C) solution of triflate **3.19** (0.5 g, 1.6 mmol, 1.0 equiv) and NiCl₂(dppe) (42 mg, 0.08 mmol, 0.05 equiv) in Et₂O (5.0 mL) and the mixture was warmed to RT and then stirred at 50 °C for 4h, after which time TLC showed that the reaction was complete. The mixture was cooled to RT and diluted with Et₂O (7.0 mL). The solution was then filtered through celite and the celite pad was washed with Et₂O (3×15 mL). The filtrate was dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 2:23 EtOAc/hexanes) to provide 218 mg (78% yield) of **3.20** as a colorless oil. **IR**: 1245, 1223, 1214, 1026. **¹H**: 8.32 (d, 1H, *J* = 9.0), 7.95 (d, 1H, *J* = 9.0), 7.58-7.48 (m, 2H), 7.23 (d, 1H, *J* = 9.0), 6.74 (d, 1H, *J* = 9.0), 4.00 (s, 3H), 2.63 (s, 3H). **¹³C**: 154.1, 133.3, 126.2, 126.1 (2C), 125.7, 124.9, 124.0, 122.4, 103.4, 55.5, 18.8.

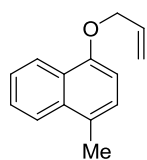
[9] Xing, L.; Wang, X.; Cheng, C.; Zhu, R.; Liu, B.; Hu, Y. *Tetrahedron* **2007**, *63*, 9382.

B.6.3 Preparation of 4-Methylnaphthalen-1-ol (**3.23**, R = Me)



[Known compound]^[10] Commercial BBr₃ (~1.0 M solution in CH₂Cl₂, 1.2 mL, 1.2 mmol, 1.1 equiv) was added to a cold (0 °C) solution of **3.20** (180 mg, 1.1 mmol, 1.0 equiv) in CH₂Cl₂ (6.0 mL) and the mixture was warmed to RT and stirred for 5 h after which time TLC showed that the reaction was complete. The mixture was cooled to 0 °C and quenched with H₂O (8.0 mL) and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 1:19 EtOAc/hexanes) to provide 157 mg (95% yield) of **3.23**, R = Me as tan solid, m.p. 80-82 °C (lit.^[10] m.p. 83-84 °C), eluent: 1:19 to 1:9 EtOAc/hexanes. **IR**: 3659-3113 (broad). **¹H**: 8.25 (dd, 1H, *J* = 7.5, 1.7), 7.97 (dd, 1H, *J* = 7.5, 1.4), 7.61-7.50 (m, 2H), 7.15 (d, 1H, *J* = 7.5), 6.75 (d, 1H, *J* = 7.6), 2.64 (s, 3H). **¹³C**: 150.0, 133.6, 126.7, 126.3, 126.2, 125.0, 124.7, 124.3, 122.2, 108.3, 20.0.

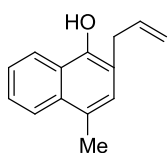
B.6.4 Characterization of 1-(Allyloxy)-4-methylnaphthalene (**3.24**, R = Me)



The procedure described above for **3.8** gave 194 mg (93% crude yield) of **3.24**, R = Me from 167 mg of **3.23**, R = Me as light yellow oil. **IR**: 1274. **¹H**: 8.36 (d, 1H, *J* = 6.0), 7.94 (d, 1H, *J* = 9.0), 7.58-7.46 (m, 2H), 7.20 (d, 1H, *J* = 9.0), 6.73 (d, 1H, *J* = 6.0), 6.25-6.12 (m, 1H), 5.53 (dd, 1H, *J* = 18.0, 3.0), 5.34 (dd, 1H, *J* = 12.0, 3.0), 4.71 (d, 2H, *J* = 6.0), 2.62 (s, 3H). **¹³C**: 152.9, 133.5, 133.4, 126.3, 126.2, 126.0, 125.9, 124.9, 124.0, 122.5, 117.3, 104.8, 69.0, 18.9.

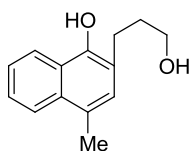
[10] Ballantine, M.; Menard, M. L.; Tam, W. *J. Org. Chem.* **2009**, *74*, 7570.

B.6.5 Characterization of (2-Allyl-4-methylnaphthalen-1-ol (3.25, R = Me)



The procedure described above for **3.9** delivered 181 mg (95% yield) of **3.25**, R = Me from 190 mg of **3.24**, R = Me as light brown oil, eluent: 1:9 to 1:4 EtOAc/hexanes. **IR**: 3653-3129 (broad). **¹H**: 8.25-8.21 (m, 1H), 7.97-7.91 (m, 1H), 7.55-7.49 (m, 2H), 7.08 (s, 1H), 6.17-6.04 (m, 1H), 5.31-5.24 (m, 2H), 3.57 (d, 2H, *J* = 6.0), 2.63 (s, 3H). **¹³C**: 148.0, 136.3, 132.5, 128.9, 126.4, 125.6, 125.1, 125.0, 124.1, 121.9, 117.3, 116.9, 35.8, 18.7.

B.6.6 Characterization of 2-(3-Hydroxypropyl)-4-methylnaphthalen-1-ol (3.26, R = Me)



Hydroboration-oxidation of **3.25**, R = Me (564 mg, 2.8 mmol) by the procedure described above for compound **3.10** afforded 143 mg (23% yield) of **3.26**, R = Me as colorless oil, eluent: 1:9 to 1:5 EtOAc/hexanes. **IR**: 3660-3034 (broad). **¹H**: 8.32-8.29 (m, 1H), 7.92-7.89 (m, 1H), 7.68 (br s, 1H), 7.51-7.48 (m, 2H), 7.05 (s, 1H), 3.65 (t, 2H, *J* = 6.0), 2.93 (app t, 2H, *J* = 8.0), 2.61 (s, 3H), 2.30 (br s, 1H), 1.94 (p, 2H, *J* = 6.0). **¹³C**: 148.5, 132.4, 129.1, 126.1, 125.6, 125.4, 124.8, 123.9, 122.6, 119.4, 60.3, 31.5, 25.0, 18.7. **HRMS**: calcd for C₁₄H₁₅O₂ [M-H]⁻: 215.1072; found: 215.1073.

B.7 Preparation and characterization of intermediates towards naphtholic alcohols 3.26

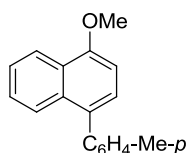
B.7.1 General procedure for Suzuki coupling of triflate 3.19 with aryl boronic acids

A literature procedure^[11] for the preparation of these compounds was modified as follows. A solution of **3.19** (500 mg, 1.6 mmol, 1.0 equiv), Pd(PPh₃)₄ (94 mg, 82 μmol, 0.05 equiv), an appropriate boronic acid (1.9 mmol, 1.2 equiv), and Cs₂CO₃ (620 mg, 1.9 mmol, 1.2 equiv) in 1,4-dioxane (6.0 mL) and H₂O (1.5 mL) was stirred at 80 °C for 6 h, after which time

[11] Zhao, Y. L.; Li, Y.; Gao, L. X.; Han, F. S. *Chem. Eur. J.* **2010**, *16*, 4991.

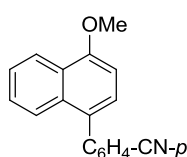
TLC showed that the reaction was complete. The cooled mixture was diluted with Et₂O (6.0 mL) and filtered through a Celite[®] pad, which then was washed with more Et₂O (3×10 mL). The combined filtrates were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography to afford corresponding products. Compound **3.21**, Ar = Ph is known.^[12]

B.7.1.1 Characterization of 1-Methoxy-4-(p-tolyl)naphthalene (**3.21**, Ar = 4-Tol)



[Known compound]^[11] 389 mg (96% yield) from 500 mg of **3.19** and 267 mg of *p*-tolylboronic acid, white solid, m.p. 112-114 °C (lit.^[11] m.p. 114-116 °C), eluent: 1:19 to 1:9 EtOAc/hexanes. **IR**: 1236, 1082. **¹H**: 8.38 (d, 1H, *J* = 8.5), 7.92 (d, 1H, *J* = 8.3), 7.55-7.45 (m, 2H), 7.43-7.29 (m, 5H), 6.90 (d, 1H, *J* = 7.9), 4.07 (s, 3H), 2.49 (s, 3H). **¹³C**: 154.9, 138.1, 136.6, 132.8, 132.7, 130.3, 129.1, 126.9, 126.6, 126.0, 125.8, 125.2, 122.3, 103.6, 55.7, 21.4.

B.7.1.2 Characterization of 4-(4-Methoxynaphthalen-1-yl)benzonitrile (**3.21**, Ar = 4-cyanophenyl)



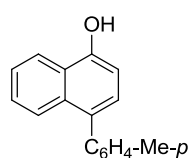
The above procedure, but using 4-cyanophenylboronic acid, gave 340 mg (80% yield) of **3.21**, Ar = 4-cyanophenyl, from 500 mg of **3.19**, white solid, m.p. 138-140 °C, eluent: 3:17 EtOAc/hexanes. **IR**: 2227, 1238. **¹H**: 8.39 (d, 1H, *J* = 9.0), 7.78-7.76 (m, 3H), 7.60 (d, 2H, *J* = 9.0), 7.56-7.46 (m, 2H), 7.33 (d, 1H, *J* = 6.0), 6.90 (d, 1H, *J* = 6.0), 4.07 (s, 3H). **¹³C**: 155.8, 145.9, 132.1, 131.8, 130.9, 130.6, 127.3, 127.1, 125.7, 125.5, 124.9, 122.5, 119.1, 110.6, 103.4, 55.7.

[12] Basarić, N.; Došlić, N.; Ivković, J.; Wang, Y.-H.; Veljković, J.; Mlinarić-Majerski, K.; Wan, P. *J. Org. Chem.* **2013**, *78*, 1811.

B.7.2 General procedure for the demethylation of compounds 3.21

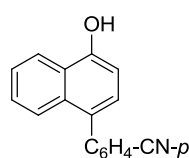
These substances were prepared by the same procedure described above for the synthesis of compound **3.23**, R = Me and used in the subsequent step without purification. Compound **3.23**, R = Ph is known.^[12]

B.7.2.1 Characterization of 4-*p*-Tolynaphthalen-1-ol (**3.23**, R = 4-Tol)



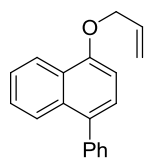
371 mg (97% crude yield) from 400 mg of **3.21**, R = *p*-tolyl as tan solid, m.p. 115-117 °C. **IR**: 3481-3119 (broad). **¹H**: 8.28 (d, 1H, *J* = 9.0), 7.93 (d, 1H, *J* = 9.0), 7.56-7.44 (m, 2H), 7.39 (d, 2H, *J* = 6.0), 7.32-7.26 (m, 3H), 6.88 (d, 1H, *J* = 9.0), 5.25 (s, 1H), 2.47 (s, 3H). **¹³C**: 150.7, 137.8, 136.6, 133.3, 132.8, 130.1, 129.5, 129.0, 126.8 (2C), 126.5, 126.1, 125.2, 124.4, 121.8, 108.2, 21.2.

B.7.2.2 Characterization of 4-(4-Hydroxynaphthalen-1-yl)benzotrile (**3.23**, Ar = 4-NC-C₆H₄)



305 mg (95% crude yield) of product from 340 mg of **3.21**, R = 4-NC-C₆H₄ as white solid, m.p.: 205-206 °C. **IR**: 3636-2988 (broad), 2228. **¹H** (acetone-*d*₆): 8.40-8.37 (m, 1H), 7.93 (d, 2H, *J* = 9.0), 7.83-7.80 (m, 1H), 7.71 (d, 2H, *J* = 9.0), 7.58-7.51 (m, 2H), 7.34 (d, 1H, *J* = 6.0), 7.06 (d, 1H, *J* = 9.0). **¹³C** (acetone-*d*₆): 153.6, 146.0, 132.2, 132.1, 131.0, 129.6, 127.8, 126.9, 125.1, 124.9, 124.7, 122.6, 118.6, 110.4, 107.7.

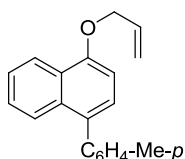
B.7.3 Characterization of 1-(Allyloxy)-4-phenylnaphthalene (**3.24**, R = Ph)



The procedure described above for **3.8** provided 1.17 g (99% crude yield) of **3.24**, R = Ph from 0.9 g of **3.23**, R = Ph as light brown oil. **IR**: 1234, 1074. **¹H**: 8.42 (d, 1H, *J* = 8.8), 7.88 (d, 1H, *J* = 8.3), 7.53-7.39 (m, 7H), 7.33 (d, 1H, *J* = 7.9), 6.89 (d, 1H, *J* = 7.9), 6.29-6.16 (m, 1H), 5.57 (dd, 1H, *J* = 17.3, 1.4), 5.38 (dd, 1H, *J* = 10.5, 1.2), 4.79 (dt,

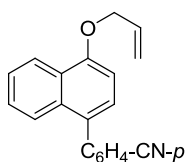
2H, $J = 5.1, 1.4$). ^{13}C : 153.8, 140.8, 133.3, 132.8, 132.5, 130.3, 128.2, 126.9, 126.8, 126.5, 125.8, 125.7, 125.1, 122.3, 117.5, 104.7, 69.0. **HRMS**: calcd for $\text{C}_{19}\text{H}_{15}\text{O}$ $[\text{M}-\text{H}]^-$: 259.1123; found: 259.1121.

B.7.4 Characterization of 1-(Allyloxy)-4-p-tolynaphthalene (**3.24**, Ar = 4-Tol)



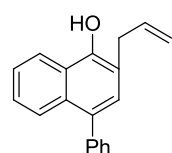
The procedure described above for **3.8** provided 420 mg (98% crude yield) of product as light yellow oil from 365 mg of **3.23**, R = 4-Tol. **IR**: 1235. ^1H : 8.41 (d, 1H, $J = 9.0$), 7.89 (d, 1H, $J = 9.0$), 7.52-7.23 (m, 7H), 6.88 (d, 1H, $J = 6.0$), 6.28-6.16 (m, 1H), 5.57 (d, 1H, $J = 15.0$), 5.38 (d, 1H, $J = 9.0$), 4.78 (d, 2H, $J = 3.0$), 2.46 (s, 3H). ^{13}C : 153.7, 137.9, 136.5, 133.4, 132.8, 132.6, 130.1, 129.4, 128.9, 126.8, 126.7, 126.4, 125.8, 125.1, 122.3, 117.4, 104.7, 69.0, 21.2.

B.7.5 Characterization of 4-(4-(Allyloxy)naphthalen-1-yl)benzonitrile (**3.24**, Ar = 4-NC-C₆H₄)



The procedure described above for **3.8** provided 341 mg (96% crude yield) of **3.24**, R = 4-NC-C₆H₄ from 305 mg of **3.23**, R = 4-NC-C₆H₄ as white solid, m.p. 96-98 °C. **IR**: 2226. ^1H : 8.45 (d, 1H, $J = 6.0$), 7.79-7.75 (m, 3H), 7.59 (d, 2H, $J = 6.0$), 7.55-7.47 (m, 2H), 7.31 (d, 1H, $J = 9.0$), 6.90 (d, 1H, $J = 9.0$), 6.28-6.16 (m, 1H), 5.58 (dd, 1H, $J = 15.0, 3.0$), 5.40 (dd, 1H, $J = 9.0, 3.0$), 4.79 (d, 2H, $J = 6.0$). ^{13}C : 154.7, 145.8, 133.0, 132.1, 131.9, 130.9, 130.7, 127.3, 127.1, 125.9, 125.5, 124.9, 122.7, 119.1, 117.7, 110.6, 104.6, 69.1.

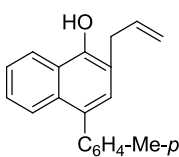
B.7.6 Characterization of 2-Allyl-4-phenylnaphthalen-1-ol (**3.25**, R = Ph)



The procedure described above for **3.9** provided 1.16 g (99% crude yield) of **3.25**, R = Ph from 1.17 g of **3.24**, R = Ph as brown oil. **IR**: 3651-3105 (broad). ^1H : 8.27

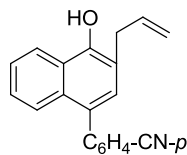
(d, 1H, $J = 8.3$), 7.87 (d, 1H, $J = 8.4$), 7.53-7.40 (m, 7H), 7.20 (s, 1H), 6.19-6.06 (m, 1H), 5.35-5.26 (m, 2H), 3.63 (app d, 2H, $J = 6.2$). ^{13}C : 149.2, 140.7, 136.1, 132.9, 131.7, 130.2, 129.5, 128.2, 126.9, 125.9, 125.8, 125.2, 125.0, 121.6, 117.3, 117.2, 35.9. **HRMS**: calcd for $\text{C}_{19}\text{H}_{15}\text{O}$ $[\text{M}-\text{H}]^-$: 259.1123; found: 259.1122.

B.7.7 Characterization of 2-allyl-4-*p*-tolynaphthalen-1-ol (**3.25**, Ar = 4-Tol)



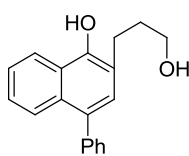
The procedure described above for **3.9** furnished 353 mg (85% yield) of product from 414 mg of **3.24**, R = *p*-tolyl as light yellow oil, eluent: 1:4 EtOAc/hexanes. **IR**: 3668-3312 (broad). ^1H : 8.27 (d, 1H, $J = 9.0$), 7.90 (d, 1H, $J = 9.0$), 7.53-7.38 (m, 4H), 7.31 (d, 2H, $J = 9.0$), 7.19 (s, 1H), 6.19-6.06 (m, 1H), 5.59 (br s, 1H), 5.36-5.26 (m, 2H), 3.62 (d, 2H, $J = 6.0$), 2.47 (s, 3H). ^{13}C : 149.1, 137.7, 136.6, 136.1, 132.9, 131.8, 130.1, 129.4, 129.0, 126.8, 125.9, 125.8, 125.2, 125.0, 121.6, 117.3, 117.2, 35.9, 21.2.

B.7.8 Characterization of 4-(3-Allyl-4-hydroxynaphthalen-1-yl)benzotrile (**3.25**, Ar = 4-NC-C₆H₄)



The procedure described above for **3.9** furnished 249 mg (75% yield) of product from 332 mg of **3.24**, R = 4-NC-C₆H₄ as light yellow oil, eluent: 1:4 to 7:13 EtOAc/hexanes. **IR**: 3657-3147 (broad), 2228. ^1H : 8.32 (d, 1H, $J = 9.0$), 7.78-7.75 (m, 3H), 7.60 (d, 2H, $J = 6.0$), 7.56-7.43 (m, 2H), 7.19 (s, 1H), 6.19-6.06 (m, 1H), 5.84 (br s, 1H), 5.35-5.28 (m, 2H), 3.64 (d, 2H, $J = 6.0$). ^{13}C : 150.2, 145.7, 135.8, 132.1, 131.1, 131.0, 130.8, 129.8, 126.6, 125.6, 125.1, 125.0, 122.1, 119.1, 117.5 (2C), 110.6, 35.7.

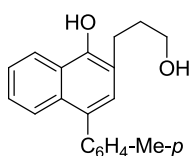
B.7.9 Characterization of 2-(3-Hydroxypropyl)-4-phenylnaphthalen-1-ol (3.26, R = Ph)



The hydroboration-oxidation procedure described above for compound **3.10** afforded 291 mg (74% yield) of product from 370 mg of **3.25**, R = Ph as white solid, m.p.: 127-129 °C (dec.), eluent: 1:4 to 2:3 EtOAc/hexanes. **IR**: 3681-3108

(broad). **¹H**: 8.37 (d, 1H, *J* = 6.0), 7.91 (br s, 1H), 7.87 (d, 1H, *J* = 9.0), 7.52-7.39 (m, 7H), 7.19 (s, 1H), 3.72 (t, 2H, *J* = 6.0), 3.00 (app t, 2H, *J* = 8.0), 2.11 (br s, 1H), 1.99 (p, 2H, *J* = 6.0). **¹³C**: 149.8, 140.9, 132.6, 131.5, 130.3, 129.7, 128.2, 126.8, 125.7, 125.6, 125.5, 125.0, 122.4, 119.3, 60.4, 31.4, 25.1. **HRMS**: calcd for C₁₉H₁₇O₂ [M-H]⁻: 277.1229; found: 277.1221.

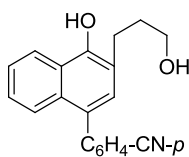
B.7.10 Characterization of 2-(3-Hydroxypropyl)-4-*p*-tolynaphthalen-1-ol (3.26, R = 4-Tol)



The hydroboration-oxidation procedure described above for compound **3.10** afforded 278 mg (76% yield) of product from 343 mg of **3.25**, R = 4-Tol as yellow solid, m.p.: 106-108 °C, eluent: 3:17 to 3:7 EtOAc/hexanes. **IR**: 3632-

3143 (broad). **¹H**: 8.36 (d, 1H, *J* = 9.0), 7.87 (d, 1H, *J* = 9.0), 7.83 (br s, 1H), 7.49 (app t, 1H, *J* = 7.5), 7.42-7.37 (m, 3H), 7.29 (d, 2H, *J* = 9.0), 7.16 (s, 1H), 3.72 (t, 2H, *J* = 6.0), 3.00 (app t, 2H, *J* = 7.5), 2.46 (s, 3H), 1.99 (p, 2H, *J* = 6.0). **¹³C**: 149.7, 138.0, 136.4, 132.6, 131.6, 130.1, 129.6, 128.9, 125.7, 125.6, 125.5, 125.0, 122.4, 119.2, 60.4, 31.4, 25.1, 21.2. **HRMS**: calcd for C₂₀H₁₉O₂ [M-H]⁻: 291.1385; found: 291.1387.

B.7.11 Characterization of 4-(4-Hydroxy-3-(3-hydroxypropyl)naphthalen-1-yl)benzonitrile (3.26, R = 4-NC-C₆H₄)



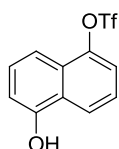
The hydroboration-oxidation procedure described above for compound **3.10** afforded 190 mg (38% yield) of product from 472 mg of **3.25**, R = 4-cyanophenyl (eluent: 1:3 to 7:13 EtOAc/hexanes), yellow solid, m.p. 149-151

°C. **IR**: 3674-3002 (broad), 2229. **¹H**: 8.39 (d, 1H, *J* = 6.0), 8.10 (br s, 1H), 7.78-7.73 (m, 3H),

7.61 (d, 2H, $J = 9.0$), 7.54-7.41 (m, 2H), 7.16 (s, 1H), 3.73 (t, 2H, $J = 4.5$), 3.01 (t, 2H, $J = 6.0$), 2.04-1.96 (m, 3H). ^{13}C : 151.0, 146.0, 132.1, 130.9, 130.4, 130.1, 126.3, 125.6, 125.4, 124.7, 122.9, 119.3, 119.1, 110.4, 60.2, 31.3, 25.1. **EI**: calcd for $\text{C}_{20}\text{H}_{17}\text{O}_2\text{N}$: 303.1259; found: 303.1262.

B.8 Preparation and characterization of intermediates towards 5-substituted naphtholic alcohols 3.32-3.33

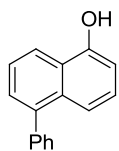
B.8.1 Preparation of 5-hydroxynaphthalen-1-yl trifluoromethanesulfonate (3.28)



A literature procedure^[13] for the preparation of these compounds was modified as follows. A solution of 1,5-dihydroxynaphthalene (4.0 g, 25.0 mmol, 1.0 equiv), *N*-phenyltrifluoromethanesulfonimide (8.9 g, 25.0 mol, 1.0 equiv), DMAP (367 mg, 3.0 mmol, 0.12 equiv) and 2,6-lutidine (2.9 mL, 25.0 mmol, 1.0 equiv) in $\text{CH}_2\text{Cl}_2/\text{DMF}$ (19:5 v/v; 95 mL) was refluxed overnight, after which time TLC showed that the reaction was complete. The cooled mixture was evaporated under reduced pressure and then the residue was dissolved in EtOAc (60 mL). The organic layer was sequentially washed with aq. 5% HCl (30 mL), H_2O (30 mL) and brine (15 mL). The combined filtrates were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography to provide 1.97 g (27% yield) of **3.28** as brown solid, m.p.: 62-64 °C (lit. m.p not reported), eluent: 1:3 to 1:1 EtOAc/hexane. **IR**: 3627-3434 (broad). ^1H ($\text{DMSO}-d_6$): 10.7 (s, 1H), 8.27 (d, 1H, $J = 9.0$), 7.63 (d, 1H, $J = 9.0$), 7.58-7.52 (m, 2H), 7.39 (d, 1H, $J = 9.0$), 7.05 (d, 1H, $J = 6.0$). ^{13}C : 153.8, 145.0, 129.2, 126.9, 126.2, 124.2, 123.3, 118.6, 110.0, 109.7.

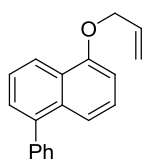
[13] Giubellino, A.; Shi, Z.-D.; Miller J., Lisa M.; Worthy, K. M.; Bindu, L. K.; Athauda, G.; Peruzzi, B.; Fisher, R. J.; Appella, E.; Burke, T. R. *J. Med. Chem.* **2008**, *51*, 7459.

B.8.2 Preparation of 5-phenylnaphthalen-1-ol (3.29)



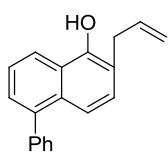
[Known compound]^[12] See general procedure for Suzuki coupling of triflates with arylboronic acids, 0.77 g (87% yield) from 1.17 g of **3.28**, light brown solid, m.p.: 81-83 °C (lit. m.p not reported), eluent: 1:9 to 1:3 EtOAc/hexane. **IR**: 3636-3119 (broad). **¹H**: 8.33 (d, 1H, *J* = 9.0), 7.63-7.50 (m, 8H), 7.30 (app t, 1H, *J* = 7.5), 6.86 (d, 1H, *J* = 9.0), 5.64 (br s, 1H). **¹³C**: 151.6, 141.1, 140.2, 133.1, 130.2, 128.3, 127.7, 127.3, 125.9, 124.9 (2C), 121.2, 119.1, 108.7.

B.8.3 Characterization of 1-(allyloxy)-5-phenylnaphthalene (3.30)



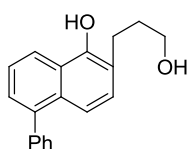
The procedure described above for **3.8** provided 0.77 g (90% crude yield) of product from 0.73 g of **3.29** as yellow oil. **IR**: 1234. **¹H**: 8.40 (d, 1H, *J* = 9.0), 7.57-7.45 (m, 8H), 7.33 (app t, 1H, *J* = 7.5), 6.86 (d, 1H, *J* = 6.0), 6.28-6.16 (m, 1H), 5.57 (d, 1H, *J* = 18.0), 5.38 (d, 1H, *J* = 9.0), 4.77 (d, 2H, *J* = 6.0). **¹³C**: 154.6, 141.3, 140.0, 133.5, 132.9, 130.2, 128.3, 127.7, 127.3, 125.9, 124.8, 121.8, 118.7, 117.6, 114.9, 105.1, 69.2.

B.8.4 Characterization of 2-allyl-5-phenylnaphthalen-1-ol (3.31)



The procedure described above for **3.9** provided 0.64 g (85% yield) of product from 0.75 g of **3.30** as yellow oil, eluent: 1:19 EtOAc/hexane. **IR**: 3655-3212 (broad). **¹H**: 8.25 (d, 1H, *J* = 9.0), 7.56-7.40 (m, 8H), 7.18 (d, 1H, *J* = 9.0), 6.17-6.04 (m, 1H), 5.60 (s, 1H), 5.33-5.26 (m, 2H), 3.60 (d, 2H, *J* = 6.0). **¹³C**: 150.0, 141.1, 140.1, 136.2, 132.1, 130.2, 128.5, 128.3, 127.3, 127.1, 125.4, 125.0, 121.1, 118.8, 117.7, 117.3, 35.9.

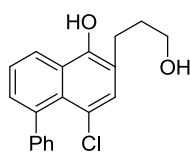
B.8.5 Characterization of 2-(3-hydroxypropyl)-5-phenylnaphthalen-1-ol (3.32)



The hydroboration-oxidation procedure described above for compound **3.10** afforded 0.40 g (62% yield) of product from 0.60 g of **3.31** as light yellow oil,

eluent: 1:9 to 1:3 EtOAc/hexanes. **IR**: 3632-3119 (broad). **¹H**: 8.37 (d, 1H, *J* = 9.0), 8.00 (br s, 1H), 7.57-7.40 (m, 8H), 7.18 (d, 1H, *J* = 9.0), 3.68 (t, 2H, *J* = 6.0), 2.98 (app t, 2H, *J* = 7.5), 2.51 (br s, 1H), 1.96 (p, 2H, *J* = 6.0). **¹³C**: 150.3, 141.3, 139.9, 131.9, 130.2, 128.7, 128.3, 127.2, 126.8, 125.8, 124.8, 121.8, 120.0, 118.5, 60.4, 31.5, 25.2. **HRMS**: calcd for C₁₉H₁₉O₂ [M+H]⁺: 279.1385; found: 279.1389.

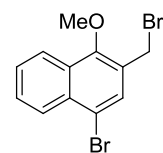
B.8.6 Characterization of 4-chloro-2-(3-hydroxypropyl)-5-phenylnaphthalen-1-ol (3.33)



The procedure described above for **3.11** provided 0.064 g (14% yield) of product from 0.40 g of **3.32** as yellow oil, eluent: 1:9 to 3:7 EtOAc/hexane. **IR**: 3653-3108 (broad). **¹H**: 8.43 (d, 1H, *J* = 9.0), 7.50 (d, 1H, *J* = 9.0), 7.37-7.33 (m, 6H), 7.27 (s, 1H), 3.69 (t, 2H, *J* = 6.0), 2.93 (app t, 2H, *J* = 6.0), 1.96 (p, 2H, *J* = 6.0). **¹³C**: 150.0, 143.7, 139.1, 131.5, 130.9, 129.8, 128.2, 127.9, 127.3, 126.7, 124.7, 122.9, 122.2, 120.4, 60.3, 31.2, 24.9. **HRMS**: calcd for C₁₉H₁₆O₂Cl [M-H]⁻: 311.0839; found: 311.0835.

B.9 Preparation and characterization of intermediates towards naphtholic alcohols with *gem*-dimethyl substitution in side chain 3.43-3.46

B.9.1 Preparation of 4-Bromo-2-(bromomethyl)-1-methoxynaphthalene (3.35)

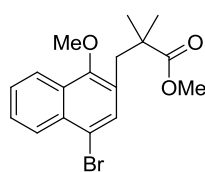


Solid NBS (4.1 g, 22.9 mmol, 1.1 equiv) was added in several portions at RT over a period of 25 min to a solution of 2-bromomethyl-1-methoxynaphthalene, **3.34**,^[14] (5.2 g, 20.8 mmol, 1.0 equiv) in MeCN (78 mL). The mixture was stirred at RT for 3h, after which time TLC showed that the reaction was complete. The solution was diluted with H₂O (20 mL) and extracted with Et₂O (3×15 mL). The combined extracts were washed with brine (20 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified

[14] Kongkathip, N.; Kongkathip, B.; Siripong, P.; Sangma, C.; Luangkamin, S.; Niyomdecha, M.; Pattanapa, S.; Piyaviriyagul, S.; Kongsaree, P. *Bioorg. Med. Chem.* **2003**, *11*, 3179.

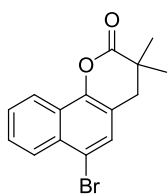
by flash column chromatography (eluent: 1:9 EtOAc/hexanes) to provide 6.7 g (98% yield) of **3.35** as off white solid, m.p.: 97-99 °C. **IR**: 1204, 990. **¹H**: 8.22-8.19 (m, 1H), 8.14-8.11 (m, 1H), 7.79 (s, 1H), 7.66-7.57 (m, 2H), 4.71 (s, 2H), 4.07 (s, 3H). **¹³C**: 154.2, 133.3, 131.5, 129.2, 128.3, 127.8, 127.4, 127.3, 123.1, 118.2, 62.8, 27.3.

B.9.2 Preparation of Methyl 3-(4-bromo-1-methoxynaphthalen-2-yl)-2,2-dimethylpropanoate (**3.40**)



n-BuLi (~1.5 M solution in hexanes, 9.4 mL, 14.0 mmol, 1.0 equiv) was added dropwise over 5 minutes to the flame dried round bottom flask containing solution of diisopropylamine (2.1 mL, 15.0 mmol, 1.07 equiv) in THF (63 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 minutes. Neat ester **3.38** (1.6 mL, 14.0 mmol, 1.0 equiv) was then added dropwise over 15 minutes at -78 °C and stirred for another 1 hour. Solution of **3.35** (5.5 g, 16.8 mmol, 1.2 equiv) in THF (28 mL) was then added dropwise over 20 minutes at -78 °C. The reaction mixture was then warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The reaction mixture was cooled to 0 °C and then quenched with H₂O (25 mL) and extracted with Et₂O (3×15 mL). The combined extracts were washed with brine (20 mL), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 3:97 EtOAc/hexanes) to provide 4.53 g (94% yield) of **3.40** as colorless oil. **IR**: 1729. **¹H**: 8.19-8.16 (m, 1H), 8.10-8.07 (m, 1H), 7.60-7.55 (m, 2H), 7.53 (s, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 3.04 (s, 2H), 1.22 (s, 6H). **¹³C**: 178.1, 154.6, 133.0, 132.5, 129.3, 127.7, 127.6, 127.2, 126.8, 122.9, 117.2, 62.1, 52.0, 44.1, 39.9, 25.2.

B.9.3 Preparation of 6-Bromo-3,3-dimethyl-3,4-dihydro-2H-benzo[*h*]chromen-2-one (3.42)



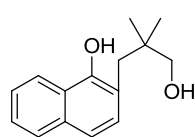
Commercial BBr_3 (~1.0 M solution in CH_2Cl_2 , 20.1 mL, 20.1 mmol, 1.1 equiv) was added dropwise over 5 minutes to the solution of **3.40** (5.6 g, 18.3 mmol, 1.0 equiv) in CH_2Cl_2 (46 mL) at 0 °C. The reaction mixture was then warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The reaction mixture was cooled to 0 °C and then quenched with H_2O (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dried under high vacuum and used for further steps without purification. 4.72 g (98% crude yield); white solid, m.p.: 84-86 °C; **IR**: 1770. **^1H** : 8.26 (d, 1H, $J = 7.9$), 8.19 (d, 1H, $J = 8.0$), 7.66-7.60 (m, 2H), 7.57 (s, 1H), 2.98 (s, 2H), 1.35 (s, 6H). **^{13}C** : 173.1, 146.0, 131.8, 129.5, 127.9, 127.4, 127.2, 124.5, 121.7, 117.4, 38.5, 37.2, 24.9.

B.9.4 General procedure for reduction of lactone for the synthesis of naphtholic alcohols 3.43-3.44

A solution of crude **3.41** or **3.42** (6.87 mmol, 1.0 equiv) in dry THF (17 mL) was added over 15 minutes to a cold (0 °C) solution of lithium aluminium hydride (0.65 g, 17.2 mmol, 2.5 equiv) in dry THF (9 mL). The mixture was then warmed to RT and stirred for 2 h, after which time TLC showed that the reaction was complete. The mixture was cooled to 0 °C, diluted with Et_2O (20 mL) and sequentially treated with H_2O (0.7 mL; added slowly and dropwise, **CAUTION**: vigorous reaction, evolution of flammable H_2), 15% aq. NaOH (0.7 mL) and more H_2O (2.1 mL). The mixture was warmed to RT and stirred for another 15 minutes, then it was filtered through a Celite[®] pad, which was washed with more Et_2O (4×10 mL). The combined

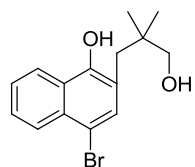
filtrates were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography to provide corresponding products.

B.9.4.1 Characterization of 2-(3-Hydroxy-2,2-dimethylpropyl)naphthalen-1-ol (3.43)



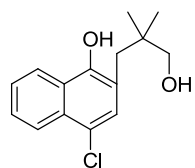
[Known compound]^[14] 560 mg (80% yield) from 690 mg of crude **3.41**^[14], white solid, m.p.: 118-120 °C (lit. m.p.,^[14] 123-124 °C), eluent: 1:3 EtOAc/hexane. **IR**: 3642-3000 (broad). **¹H**: 8.53-8.50 (m, 1H), 8.33-8.30 (m, 1H), 7.77-7.76 (m, 1H), 7.48-7.45 (m, 2H), 7.35 (d, 1H, *J* = 8.3), 7.17 (d, 1H, *J* = 8.3), 3.26 (d, 2H, *J* = 4.1), 2.78 (s, 2H), 2.42-2.36 (m, 1H), 1.05 (s, 6H). **¹³C**: 151.1, 133.8, 130.9, 127.3, 125.8, 125.6, 125.0, 122.6, 119.1, 117.6, 69.4, 38.5, 36.8, 25.3.

B.9.4.2 Characterization of 4-Bromo-2-(3-hydroxy-2,2-dimethylpropyl)naphthalen-1-ol (3.44)



3.91 g (70% yield) from 5.51 g of crude **3.42**, off-white solid, m.p.: 98-100 °C, eluent: 1:9 to 3:17 EtOAc/hexane. **IR**: 3641-3022 (broad). **¹H**: 8.33 (d, 1H, *J* = 7.9), 8.11 (d, 1H, *J* = 7.9), 7.59-7.48 (m, 2H), 7.46 (s, 1H), 3.28 (s, 2H), 2.74 (s, 2H), 1.06 (s, 6H). **¹³C**: 151.2, 133.9, 131.8, 127.2, 126.9, 126.7, 125.8, 123.2, 118.7, 111.9, 69.4, 38.3, 36.8, 25.3. **HRMS**: calcd for C₁₅H₁₇O₂⁷⁹BrNa [M+Na]⁺: 331.0310; found: 331.0311.

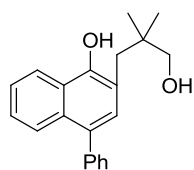
B.9.5 Preparation of 4-Chloro-2-(3-hydroxy-2,2-dimethylpropyl)naphthalen-1-ol (3.45)



Solid NCS (191 mg, 1.4 mmol, 1.1 equiv) was added in several portions over a period of 30 mins to a solution of **3.43** (300 mg, 1.3 mmol, 1.0 equiv) in MeCN (1.5 mL) at RT. The mixture was refluxed for 5h, after which time TLC showed that the reaction was complete. The solution was cooled to RT and then diluted with H₂O (5 mL) and extracted with Et₂O (3×10 mL). The combined extracts were washed with brine (10 mL),

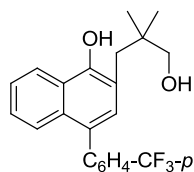
dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: 1:3 EtOAc/hexanes) to provide 296 mg (86% yield) of **3.45**, yellow solid, m.p. 98-100 °C. **IR**: 3636-3041 (broad). ¹**H**: 8.62 (br s, 1H), 8.34 (d, 1H, *J* = 9.0), 8.16 (d, 1H, *J* = 9.0), 7.59-7.50 (m, 2H), 7.26 (s, 1H), 3.27 (s, 2H), 2.74 (s, 2H), 2.34 (br s, 1H), 1.06 (s, 6H). ¹³**C**: 150.4, 130.5, 130.2, 126.7, 126.6, 125.6, 123.9, 123.1, 121.7, 117.9, 69.2, 38.3, 36.6, 25.1. **HRMS**: calcd for C₁₅H₁₆O₂Cl [M-H]⁻: 263.0839; found: 263.0834.

B.9.6 Characterization of 2-(3-Hydroxy-2,2-dimethylpropyl)-4-phenylnaphthalen-1-ol (3.46, Ar = Ph)



The procedure described in title B.4, but employing phenylboronic acid, afforded 450 mg (91% yield) of **3.46**, Ar = Ph from 500 mg of **3.44** (eluent: 1:9 to 3:17 EtOAc/hexanes), off white solid, m.p.: 110-112 °C. **IR**: 3680-3001 (broad). ¹**H**: 8.42 (d, 1H, *J* = 8.3), 7.87 (d, 1H, *J* = 8.3), 7.52-7.40 (m, 7H), 7.15 (s, 1H), 3.32 (s, 2H), 2.83 (s, 2H), 1.07 (s, 6H). ¹³**C**: 150.7, 141.1, 132.0, 131.7, 131.6, 130.4, 128.3, 126.9, 125.9, 125.7, 125.6, 125.0, 122.9, 117.2, 69.4, 38.6, 36.8, 25.4. **HRMS**: calcd for C₂₁H₂₁O₂ [M-H]⁻: 305.1542; found: 305.1541.

B.9.7 Characterization of 2-(3-Hydroxy-2,2-dimethylpropyl)-4-(4-(trifluoromethyl)phenyl)naphthalen-1-ol (3.46, Ar = C₆H₄-CF₃-*p*)

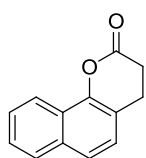


The procedure described in title B.4, but employing 4-(trifluoromethyl)-phenylboronic acid, delivered 310 mg (51% yield) of **3.46**, Ar = C₆H₄-CF₃-*p* from 500 mg of **3.44** (eluent: 1:9 to 3:17 EtOAc/hexanes), light yellow solid, m.p.: 165-167 °C. **IR**: 3671-3031 (broad). ¹**H**: 8.42 (d, 1H, *J* = 8.2), 7.79-7.72 (m, 3H), 7.60 (d, 2H, *J* = 8.0), 7.53-7.41 (m, 2H), 7.12 (s, 1H), 3.33 (s, 2H), 2.82 (s, 2H), 1.07 (s, 6H). ¹³**C**: 151.5, 144.9, 132.2, 131.4, 130.7, 130.0, 129.0 (q, *J* = 32.4), 126.3, 125.8, 125.3 (q, *J* = 3.7), 125.2,

125.0, 124.5 (q, $J = 272.1$), 123.2, 117.2, 69.4, 38.5, 36.8, 25.3. **HRMS**: calcd for $C_{22}H_{20}O_2F_3$ [M-H]⁻: 373.1415; found: 373.1414.

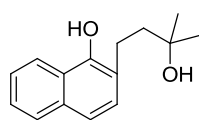
B.10 Preparation and characterization of intermediates towards naphtholic alcohols 3.49-3.50

B.10.1 Preparation of 3,4-dihydro-2H-benzo[h]chromen-2-one (3.48)



A literature procedure^[15] for the preparation of these compounds was as follows. Amberlyst[®] 15(H) (400 mg) was added to a solution of 1-naphthol (4 g, 27.8 mmol, 1.0 equiv) and acrylic acid (3.8 mL, 55.6 mmol, 2.0 equiv) in toluene (56 mL). The mixture was heated to reflux for 12 hours, after which time TLC showed that the reaction was complete. The reaction mixture was then filtered and evaporated. The residue was purified by flash column chromatography (eluent: 1:19 to 3:17 EtOAc/hexane) to provide 1.73 g (31% yield) of **3-W** as yellow oil. **IR**: 1760. **¹H**: 8.24 (d, 1H, $J = 6.0$), 7.83 (d, 1H, $J = 6.0$), 7.60 (d, 1H, $J = 6.0$), 7.57-7.49 (m, 2H), 7.27 (d, 1H, $J = 9.0$), 3.14 (app t, 2H, $J = 7.5$), 2.89 (app t, 2H, $J = 7.5$). **¹³C**: 168.6, 147.0, 133.5, 127.7, 126.7, 126.6, 125.4, 124.1, 123.8, 121.0, 117.3, 29.3, 24.0.

B.10.2 Preparation of 2-(3-hydroxy-3-methylbutyl)naphthalen-1-ol (3.49)

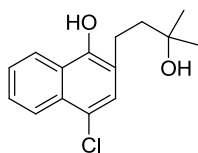


This compound is known and was prepared by the literature procedure.^[4] Commercial MeMgBr (~3.0 M in Et₂O, 9.5 mL, 28.5 mmol, 5.0 equiv) was added dropwise to a cold (0 °C) solution of **3.48** (1.13 g, 5.7 mmol, 1.0 equiv) in dry THF (10.0 mL). The mixture was warmed to RT and then stirred for 1h, after which time TLC showed that the reaction was complete. The mixture was cooled to 0 °C and quenched with aq. satd. NH₄Cl (15.0 mL) and extracted with Et₂O (3×10 mL). The combined extracts were washed with brine

[15] Rudolph, A.; Bos, P. H.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5834.

(10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 1:9 to 3:17 EtOAc/hexane) on silica gel to provide 1.20 g (91% yield) of **3.49** as white solid, m.p.: 91-93 °C (lit. m.p not reported). **IR**: 3634-3085 (broad). **¹H**: 8.29-8.26 (m, 1H), 7.79-7.76 (m, 1H), 7.49-7.41 (m, 2H), 7.38 (d, 1H, *J* = 6.0), 7.23 (d, 1H, *J* = 6.0), 5.05 (br s, 1H), 2.90 (t, 2H, *J* = 7.5), 1.89 (t, 2H, *J* = 6.0), 1.32 (s, 6H). **¹³C**: 149.2, 133.6, 128.6, 127.5, 125.6, 125.5, 125.1, 122.4, 122.1, 119.8, 72.3, 43.1, 29.8, 24.9. **HRMS**: calcd for C₁₅H₁₈O₂Na [M+Na]⁺: 253.1204; found: 253.1201.

B.10.3 Characterization of 4-chloro-2-(3-hydroxy-3-methylbutyl)naphthalen-1-ol (**3.50**)



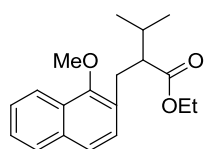
The procedure described above for **3.11** produced 0.35 g (76% yield) of product from 0.40 g of **3.49** as pale yellow oil, eluent: 1:9 to 3:17 EtOAc/hexane. **IR**: 3624-3099 (broad). **¹H**: 8.29 (d, 1H, *J* = 9.0), 8.15 (d, 1H, *J* = 9.0), 7.57-7.48 (m, 2H), 7.32 (s, 1H), 2.86 (t, 2H, *J* = 7.5), 1.88 (t, 2H, *J* = 6.0), 1.32 (s, 6H). **¹³C**: 148.7, 130.4, 128.4, 126.7, 126.6, 125.8, 124.1, 122.9, 122.7, 122.3, 72.4, 42.8, 29.9, 24.7. **HRMS**: calcd for C₁₅H₁₆O₂Cl [M-H]⁻: 263.0839; found: 263.0841.

B.11 Preparation and characterization of intermediates towards naphtholic alcohols **3.54-3.56** with stereogenic center at 2' position

B.11.1 Preparation of compounds **3.52**

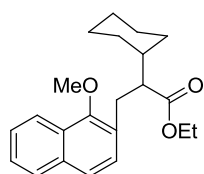
These substances were prepared by the same procedure detailed above for the synthesis of compound **3.40**.

B.11.1.1 Characterization of ethyl 2-((1-methoxynaphthalen-2-yl)methyl)-3-methylbutanoate (3.52; R = *i*-Pr, R' = Et)



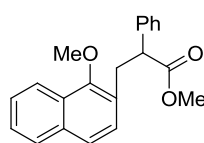
1.71 g (95% yield) from 0.9 mL of ethyl isovalerate (eluent: 1:19 to 1:9 EtOAc/hexane), colorless oil. **IR**: 1726. **¹H**: 8.09 (d, 1H, *J* = 8.2), 7.81 (d, 1H, *J* = 7.6), 7.55-7.42 (m, 3H), 7.30 (d, 1H, *J* = 8.5), 4.08-3.91 (m, 5H), 3.15 (dd, 1H, *J* = 15.0, 4.8), 3.00 (dd, 1H, *J* = 15.0, 10.2), 2.69-2.62 (m, 1H), 2.07-1.96 (m, 1H), 1.11-1.03 (m, 9H). **¹³C**: 175.1, 153.9, 134.0, 128.5, 128.4, 128.0 (2C), 125.8, 125.5, 123.8, 122.0, 61.9, 59.9, 53.3, 30.9, 30.2, 20.4, 20.2, 14.1.

B.11.1.2 Characterization of ethyl 2-cyclohexyl-3-(1-methoxynaphthalen-2-yl)propanoate (3.52; R = Cy, R' = Et)



1.81 g (96% yield) from 1.0 mL of ethyl cyclohexaneacetate (eluent: 1:19 EtOAc/hexane), colorless oil. **IR**: 1726. **¹H**: 8.09 (d, 1H, *J* = 8.2), 7.82 (d, 1H, *J* = 7.7), 7.56-7.42 (m, 3H), 7.30 (d, 1H, *J* = 8.5), 4.08-3.94 (m, 5H), 3.19 (dd, 1H, *J* = 13.5, 4.5), 2.98 (dd, 1H, *J* = 13.4, 10.6), 2.73-2.62 (m, 1H), 1.99-1.95 (m, 1H), 1.79-1.68 (m, 5H), 1.33-1.10 (m, 5H), 1.03 (t, 3H, *J* = 7.1). **¹³C**: 175.4, 154.0, 134.1, 128.6 (2C), 128.1 (2C), 125.9, 125.6, 123.9, 122.1, 62.0, 60.0, 52.8, 40.7, 30.9 (2C), 30.2, 26.5 (2C), 26.4, 14.2.

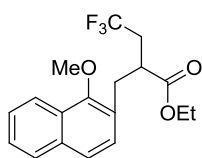
B.11.1.3 Characterization of methyl 3-(1-methoxynaphthalen-2-yl)-2-phenylpropanoate (3.52; R = Ph, R' = Me)



0.924 g (83% yield) from 0.5 mL of methyl phenylacetate (eluent: 1:49 to 1:19 EtOAc/hexane), colorless oil. **IR**: 1732. **¹H**: 8.10 (d, 1H, *J* = 8.2), 7.82 (d, 1H, *J* = 7.6), 7.54-7.44 (m, 3H), 7.40-7.29 (m, 5H), 7.21 (d, 1H, *J* = 8.4), 4.12 (app

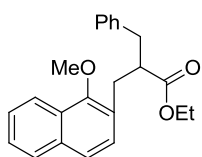
t, 1H, $J = 7.7$), 3.94 (s, 3H), 3.64-3.56 (m, 4H), 3.28 (dd, 1H, $J = 13.7, 6.9$). ^{13}C : 174.2, 154.2, 139.1, 134.2, 128.8, 128.6, 128.1 (2C), 127.5 (2C), 125.9, 125.7, 123.9, 122.2, 62.0, 52.2, 52.1, 34.6.

B.11.1.4 Characterization of ethyl 4,4,4-trifluoro-2-((1-methoxynaphthalen-2-yl)methyl)butanoate (3.52; $\text{R} = \text{CH}_2\text{CF}_3$, $\text{R}' = \text{Et}$)



1.73 g (93% yield) from 0.8 mL of ethyl 4,4,4-trifluorobutyrate, colorless oil, eluent: 1:19 EtOAc/hexane. **IR**: 1730. ^1H : 8.10 (d, 1H, $J = 8.0$), 7.85 (d, 1H, $J = 7.4$), 7.60 (d, 1H, $J = 8.4$), 7.57-7.47 (m, 2H), 7.27 (d, 1H, $J = 8.4$), 4.16-4.05 (m, 2H), 3.95 (s, 3H), 3.21-3.10 (m, 3H), 2.79-2.61 (m, 1H), 2.33-2.16 (m, 1H), 1.13 (t, 3H, $J = 7.1$). ^{13}C : 173.8, 154.5, 134.5, 128.2, 128.1 (2C), 126.4 (q, $J = 277.1$), 126.3, 126.1, 125.9, 124.5, 122.3, 62.2, 61.2, 40.6 (q, $J = 2.2$), 35.4 (q, $J = 29.0$), 33.0, 14.1.

B.11.1.5 Characterization of ethyl 2-benzyl-3-(1-methoxynaphthalen-2-yl)propanoate (3.52; $\text{R} = \text{Bn}$, $\text{R}' = \text{Et}$)

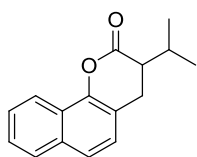


2.13 g (97% yield) from 1.1 mL of ethyl 3-phenylpropionate, colorless oil, eluent: 1:19 to 1:9 EtOAc/hexane. **IR**: 1727. ^1H : 8.08 (d, 1H, $J = 6.0$), 7.83 (d, 1H, $J = 9.0$), 7.56 (d, 1H, $J = 6.0$), 7.53-7.43 (m, 2H), 7.32-7.18 (m, 6H), 3.96 (q, 2H, $J = 15.0, 9.0$), 3.84 (s, 3H), 3.19-3.03 (m, 4H), 2.87-2.80 (m, 1H), 0.98 (t, 3H, $J = 7.5$). ^{13}C : 175.3, 154.2, 139.4, 134.2, 129.1, 128.5 (2C), 128.1 (2C), 127.7, 126.5, 126.0, 125.7, 124.0, 122.2, 61.9, 60.4, 48.5, 38.7, 32.7, 14.1.

B.11.2 Preparation of compounds 3.53

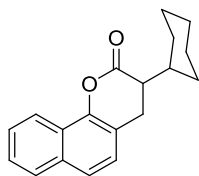
These substances were prepared by the same procedure described above for the synthesis of compound 3.42 and used in the subsequent step without purification.

B.11.2.1 Characterization of 3-isopropyl-3,4-dihydro-2H-benzo[*h*]chromen-2-one (3.53, R = *i*-Pr)



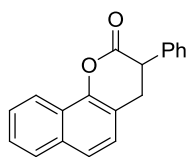
1.45 g (95% crude yield) from 1.91 g of **3.52** (R = *i*-Pr, R' = Et), light yellow oil. **IR**: 1763. **¹H**: 8.24 (d, 1H, *J* = 8.3), 7.83 (d, 1H, *J* = 8.0), 7.59 (d, 1H, *J* = 8.3), 7.57-7.48 (m, 2H), 7.27 (d, 1H, *J* = 8.2), 3.14-2.99 (m, 2H), 2.65 (app q, 1H, *J* = 14.0, 8.0), 2.35-2.24 (m, 1H), 1.10 (d, 3H, *J* = 6.9), 1.06 (d, 3H, *J* = 6.8). **¹³C**: 170.2, 146.3, 133.4, 127.6, 126.5, 126.3, 125.6, 123.8, 123.4, 121.0, 117.2, 45.4, 27.1, 25.6, 20.7, 18.8.

B.11.2.2 Characterization of 3-cyclohexyl-3,4-dihydro-2H-benzo[*h*]chromen-2-one (3.53, R = Cy)



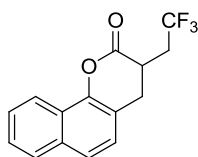
2.08 g (97% crude yield) from 2.61 g of **3.52** (R = Cy, R' = Et), light yellow oil. **IR**: 1731. **¹H**: 8.24 (d, 1H, *J* = 9.0), 7.83 (d, 1H, *J* = 8.0), 7.59 (d, 1H, *J* = 8.3), 7.57-7.48 (m, 2H), 7.26 (d, 1H, *J* = 8.3), 3.16-3.01 (m, 2H), 2.67 (app q, 1H, *J* = 6.4), 1.89-1.66 (m, 6H), 1.31-1.07 (m, 5H). **¹³C**: 170.3, 146.4, 133.5, 127.7, 126.6, 126.4, 125.7, 123.9, 123.5, 121.2, 117.3, 45.0, 36.8, 31.4, 29.3, 26.4, 26.3, 26.2.

B.11.2.3 Characterization of 3-phenyl-3,4-dihydro-2H-benzo[*h*]chromen-2-one (3.53, R = Ph)



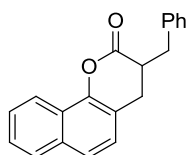
0.62 g (79% crude yield) from 0.91 g of **3.52** (R = Ph, R' = Me), off white solid. **IR**: 1762. **¹H**: 8.31 (d, 1H, *J* = 8.3), 7.86 (d, 1H, *J* = 8.0), 7.63 (d, 1H, *J* = 8.0), 7.61-7.52 (m, 2H), 7.43-7.26 (m, 6H), 4.07 (dd, 1H, *J* = 10.8, 6.8), 3.47 (dd, 1H, *J* = 15.9, 11.2), 3.32 (dd, 1H, *J* = 16.1, 6.5). **¹³C**: 169.2, 146.6, 136.7, 133.6, 128.9, 128.2, 127.9, 127.7, 126.7, 126.6, 125.3, 124.2, 123.6, 121.1, 117.3, 45.6, 31.9.

B.11.2.4 Characterization of 3-(2,2,2-trifluoroethyl)-3,4-dihydro-2H-benzo[h]chromen-2-one (3.53, R = CH₂CF₃)



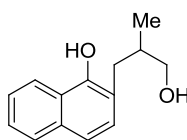
1.74 g (99% crude yield) from 2.13 g of **3.52** (R = CH₂CF₃, R' = Et), light yellow oil. **IR**: 1766. **¹H**: 8.22 (d, 1H, *J* = 7.4), 7.85 (d, 1H, *J* = 7.7), 7.64 (d, 1H, *J* = 8.3), 7.60-7.52 (m, 2H), 7.28 (d, 1H, *J* = 9.2), 3.39-3.06 (m, 4H), 2.51-2.32 (m, 1H). **¹³C**: 168.8, 146.4, 133.8, 127.8, 127.0, 126.9, 126.5 (q, *J* = 276.8), 125.3, 124.6, 123.6, 121.0, 116.5, 34.6 (q, *J* = 2.7), 34.1 (q, *J* = 29.6), 29.7.

B.11.2.5 Characterization of 3-benzyl-3,4-dihydro-2H-benzo[h]chromen-2-one (3.53, R = Bn)



1.59 g (95% crude yield) from 2.03 g of **3.52** (R = Bn, R' = Et), light yellow oil. **IR**: 1765. **¹H**: 8.26 (d, 1H, *J* = 6.0), 7.83 (d, 1H, *J* = 6.0), 7.59-7.50 (m, 3H), 7.38-7.28 (m, 3H), 7.25-7.16 (m, 3H), 3.48 (dd, 1H, *J* = 12.0, 4.5), 3.17-2.77 (m, 4H). **¹³C**: 170.6, 146.6, 138.2, 133.6, 129.3, 128.8, 127.7, 127.0, 126.7, 126.6, 125.6, 124.1, 123.6, 121.1, 117.0, 41.0, 35.8, 28.6.

B.11.3 Preparation of 2-(3-hydroxy-2-methylpropyl)naphthalen-1-ol (3.54, R = Me)

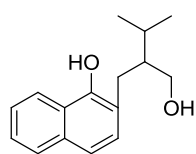


[Known compound]^[14] Hydroboration-oxidation of 2-(2-methylallyl)naphthalen-1-ol^[14] (7.2 g, 36.3 mmol) by the procedure described above for compound **3.10** afforded 7.0 g (89% yield) of **3.54**, R = Me, white solid, m.p.: 85-87 °C (lit. m.p.,^[14] 89-90 °C), eluent: 1:9 to 3:7 EtOAc/hexane. **IR**: 3645-3096 (broad). **¹H**: 8.31-8.28 (m, 1H), 8.08 (br s, 1H), 7.79-7.76 (m, 1H), 7.50-7.42 (m, 2H), 7.37 (d, 1H, *J* = 6.0), 7.20 (d, 1H, *J* = 9.0), 3.63-3.59 (m, 1H), 3.41-3.34 (m, 1H), 2.95-2.81 (m, 2H), 2.23-2.05 (m, 2H), 1.08 (d, 3H, *J* = 9.0). **¹³C**: 150.5, 133.8, 129.8, 127.4, 125.7, 125.5, 125.1, 122.4, 119.6, 118.5, 65.6, 36.0, 32.7, 17.2.

B.11.4 Preparation of compounds 3.54

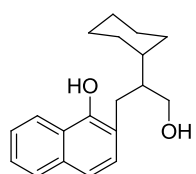
These substances were prepared by the same procedure described above for the synthesis of compound 3.43-3.44.

B.11.4.1 Characterization of (\pm)-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol (3.54, R = *i*-Pr)



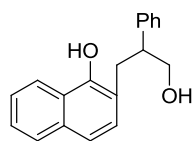
1.13 g (67% yield) from 1.65 g of crude **3.53**, R = *i*-Pr, off white solid, m.p.: 81-83 °C, eluent: 1:9 to 1:4 EtOAc/hexane. **IR**: 3650-3021 (broad). **¹H**: 8.28 (d, 1H, *J* = 7.7), 8.21 (s, 1H), 7.76 (d, 1H, *J* = 6.9), 7.49-7.41 (m, 2H), 7.36 (d, 1H, *J* = 8.3), 7.21 (d, 1H, *J* = 8.3), 3.74-3.61 (m, 2H), 2.99 (dd, 1H, *J* = 14.1, 8.5), 2.82 (dd, 1H, *J* = 14.2, 4.4), 1.99 (br s, 1H), 1.90-1.79 (m, 1H), 1.65-1.52 (m, 1H), 1.12 (d, 3H, *J* = 6.6), 1.02 (d, 3H, *J* = 6.7). **¹³C**: 150.4, 133.5, 129.1, 127.2, 125.5 (2C), 125.0, 122.3, 119.9, 119.6, 62.8, 48.0, 29.7, 29.1, 21.1, 20.6. **HRMS**: calcd for C₁₆H₁₉O₂ [M-H]⁻: 243.1385; found: 243.1385.

B.11.4.2 Characterization of (\pm)-2-(2-(cyclohexyl)-3-hydroxypropyl)naphthalen-1-ol (3.54, R = Cy)



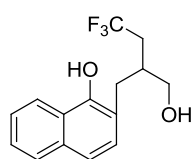
1.49 g (71% yield) from 2.08 g of **3.53**, R = Cy, off white solid, m.p.: 106-108 °C, eluent: 3:17 to 1:4 EtOAc/hexane. **IR**: 3648-3004 (broad). **¹H**: 8.41 (s, 1H), 8.31 (d, 1H, *J* = 8.7), 7.79 (d, 1H, *J* = 8.6), 7.50-7.43 (m, 2H), 7.39 (d, 1H, *J* = 8.3), 7.21 (d, 1H, *J* = 8.3), 3.68-3.57 (m, 2H), 2.98 (dd, 1H, *J* = 15.0, 8.4), 2.82 (dd, 1H, *J* = 14.2, 4.5), 2.45 (br s, 1H), 1.97-1.71 (m, 5H), 1.61-1.44 (m, 2H), 1.39-0.99 (m, 5H). **¹³C**: 150.4, 133.6, 129.2, 127.4, 125.6 (2C), 125.1, 122.3, 120.4, 119.8, 62.6, 47.1, 39.7, 31.5, 30.8, 29.2, 26.7 (3C). **HRMS**: calcd for C₁₉H₂₄O₂Na [M+Na]⁺: 307.1674; found: 307.1669.

B.11.4.3 Characterization of (±)-2-(3-hydroxy-2-phenylpropyl)naphthalen-1-ol (3.54, R = Ph)



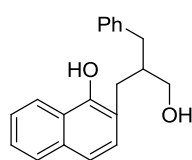
0.59 g (95% yield) from 0.61 g of **3.53**, R = Ph, colourless oil, eluent: 1:4 EtOAc/hexane. **IR**: 3669-3098 (broad). **¹H**: 8.33-8.30 (m, 1H), 7.84 (br s, 1H), 7.80-7.77 (m, 1H), 7.52-7.45 (m, 2H), 7.40-7.29 (m, 6H), 7.07 (d, 1H, *J* = 8.4), 3.81 (app br s, 2H), 3.45 (dd, 1H, *J* = 13.4, 8.7), 3.18-3.03 (m, 2H), 2.32 (br s, 1H). **¹³C**: 150.4, 142.7, 133.8, 129.3, 128.9, 127.9, 127.5, 127.1, 125.8, 125.6, 125.3, 122.3, 120.1, 118.9, 64.8, 47.8, 31.9. **HRMS**: calcd for C₁₉H₁₇O₂ [M-H]⁻: 277.1229; found: 277.1234.

B.11.4.4 Characterization of (±)-2-(4,4,4-trifluoro-2-(hydroxymethyl)butyl)naphthalen-1-ol (3.54, R = CH₂CF₃)



1.38 g (78% yield) from 1.75 g of **3.53**, R = CH₂CF₃, light yellow oil, eluent: 1:9 to 3:17 EtOAc/hexane. **IR**: 3710-3104 (broad). **¹H**: 8.27-8.24 (m, 1H), 7.80-7.77 (m, 1H), 7.52-7.45 (m, 2H), 7.41 (d, 1H, *J* = 8.4), 7.20 (d, 1H, *J* = 8.4), 3.65-3.55 (m, 2H), 3.05-2.91 (m, 2H), 2.39-2.25 (m, 3H). **¹³C**: 150.7, 133.9, 129.1, 127.6, 127.1 (q, *J* = 277.1), 126.1, 125.5 (2C), 122.2, 120.4, 117.4, 62.2, 35.6 (q, *J* = 28.1), 35.5 (q, *J* = 2.0), 30.9. **HRMS**: calcd for C₁₅H₁₄O₂F₃ [M-H]⁻: 283.0946; found: 283.0942.

B.11.4.5 Characterization of (±)-2-(2-benzyl-3-hydroxypropyl)naphthalen-1-ol (3.54, R = Bn)



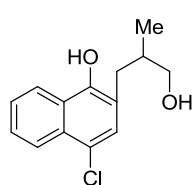
1.46 g (81% yield) from 1.79 g of **3.53**, R = Bn, yellow oil, eluent: 1:5 to 1:4 EtOAc/hexane. **IR**: 3680-3103 (broad). **¹H**: 8.31-8.28 (m, 1H), 8.14 (br s, 1H), 7.79-7.76 (m, 1H), 7.50-7.43 (m, 2H), 7.39-7.32 (m, 3H), 7.28-7.22 (m, 3H),

7.14 (d, 1H, $J = 8.3$), 3.55-3.44 (m, 2H), 3.03-2.71 (m, 4H), 2.28-2.15 (m, 1H). ^{13}C : 150.6, 140.2, 133.8, 129.4, 129.2, 128.7, 127.4, 126.4, 125.8, 125.6, 125.2, 122.4, 119.9, 118.8, 62.8, 43.1, 38.4, 31.1. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{O}_2$ [$\text{M}-\text{H}$]: 291.1385; found: 291.1393.

B.11.5 Preparation of compounds 3.55

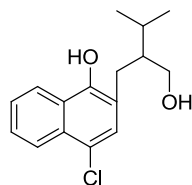
These substances were prepared by the same procedure detailed above for the synthesis of compound 3.11.

B.11.5.1 Characterization of (\pm)-4-chloro-2-(3-hydroxy-2-methylpropyl)naphthalen-1-ol (3.55, R = Me)



1.10 g (87% yield) from 1.10 g of **3.54**, R = Me, off white solid, m.p.: 74-76 °C; eluent: 1:9 to 1:4 EtOAc/hexane. **IR**: 3643-3017 (broad). ^1H : 8.32 (d, 1H, $J = 7.7$), 8.20 (br s, 1H), 8.15 (d, 1H, $J = 7.9$), 7.59-7.50 (m, 2H), 7.30 (s, 1H), 3.63 (dd, 1H, $J = 10.3, 3.5$), 3.39 (dd, 1H, $J = 9.9, 6.8$), 2.92-2.78 (m, 2H), 2.18-2.00 (m, 2H), 1.09 (d, 3H, $J = 6.9$). ^{13}C : 149.8, 130.5, 129.3, 126.8, 126.7, 125.8, 124.1, 122.9, 122.4, 119.1, 65.4, 35.8, 32.5, 17.2. **HRMS**: calcd for $\text{C}_{14}\text{H}_{14}\text{ClO}_2$ [$\text{M}-\text{H}$]: 249.0682; found: 249.0682.

B.11.5.2 Characterization of (\pm)-4-chloro-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol (3.55, R = *i*-Pr)



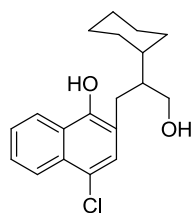
0.45 g (99% yield) from 0.40 g of **3.54**, R = *i*-Pr, off white solid, m.p.: 95-97 °C; eluent: 3:17 EtOAc/hexane. **IR**: 3654-3035 (broad). ^1H : 8.32 (d, 1H, $J = 9.0$), 8.15 (d, 1H, $J = 9.0$), 7.58-7.49 (m, 2H), 7.30 (s, 1H), 3.73 (dd, 1H, $J = 9.0, 4.5$), 3.65 (dd, 1H, $J = 9.0, 3.0$), 2.98 (dd, 1H, $J = 15.0, 9.0$), 2.78 (dd, 1H, $J = 15.0, 3.0$), 1.90-1.78 (m, 1H), 1.64-1.54 (m, 1H), 1.11 (d, 3H, $J = 6.0$), 1.02 (d, 3H, $J = 6.0$). ^{13}C : 149.9,

130.5, 128.9, 126.8, 126.7, 125.8, 124.1, 123.0, 122.4, 120.6, 62.9, 48.0, 29.9, 29.1, 21.2, 20.7.

HRMS: calcd for C₁₆H₁₈ClO₂ [M-H]⁻: 277.0995; found: 277.0994.

B.11.5.3 Characterization of (±)-4-chloro-2-(2-cyclohexyl-3-hydroxypropyl)naphthalen-1-ol

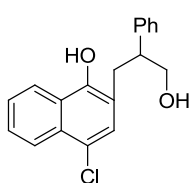
(3.55, R = Cy)



0.46 g (90% yield) from 0.46 g of **3.54**, R = Cy, off white solid, m.p.: 105-107 °C; eluent: 1:9 EtOAc/hexane. **IR:** 3662-3004 (broad). **¹H:** 8.46 (br s, 1H), 8.31 (d, 1H, *J* = 7.8), 8.15 (d, 1H, *J* = 7.9), 7.58-7.49 (m, 2H), 7.29 (s, 1H), 3.73-3.68 (m, 1H), 3.60-3.57 (m, 1H), 2.95 (dd, 1H, *J* = 14.1, 8.7), 2.76 (dd, 1H, *J* = 14.2, 4.1), 2.22 (br s, 1H), 1.94-1.69 (m, 5H), 1.59-1.46 (m, 2H), 1.34-0.99 (m, 5H). **¹³C:** 149.8, 130.4, 128.8, 126.8, 126.7, 125.8, 124.1, 122.9, 122.4, 120.8, 62.5, 47.0, 39.8, 31.5, 30.8, 29.1, 26.7 (2C), 26.6. **HRMS:** calcd for C₁₉H₂₂ClO₂ [M-H]⁻: 317.1308; found: 317.1315.

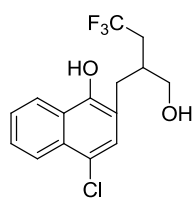
B.11.5.4 Characterization of (±)-4-chloro-2-(3-hydroxy-2-phenylpropyl)naphthalen-1-ol

(3.55, R = Ph)



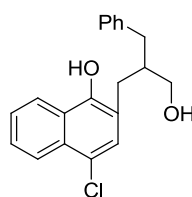
0.18 g (67% yield) from 0.24 g of **3.54**, R = Ph, colourless oil; eluent: 3:17 EtOAc/hexane. **IR:** 3650-3098 (broad). **¹H:** 8.34 (d, 1H, *J* = 7.7), 8.18 (d, 1H, *J* = 8.0), 8.03 (br s, 1H), 7.62-7.52 (m, 2H), 7.41-7.28 (m, 5H), 7.18 (s, 1H), 3.80 (app d, 2H, *J* = 4.4), 3.42 (dd, 1H, *J* = 13.8, 9.3), 3.16-3.08 (m, 1H), 3.00 (dd, 1H, *J* = 13.8, 4.7), 2.35 (br s, 1H). **¹³C:** 149.7, 142.4, 130.6, 128.9 (2C), 127.8, 127.3, 126.9, 126.7, 126.0, 124.2, 122.9, 122.8, 119.4, 64.8, 47.6, 31.7. **HRMS:** calcd for C₁₉H₁₇ClO₂Na [M+Na]⁺: 335.0815; found: 335.0818.

B.11.5.5 Characterization of (\pm)-4-chloro-2-(4,4,4-trifluoro-2-(hydroxymethyl)butyl)naphthalen-1-ol (3.55, R = CH₂CF₃)



0.37 g (96% yield) from 0.43 g of **3.54**, R = CH₂CF₃, light yellow solid, m.p.: 69-71 °C; eluent: 1:9 to 1:4 EtOAc/hexane; **IR**: 3687-3032 (broad). **¹H**: 8.30 (d, 1H, *J* = 8.3), 8.17 (d, 1H, *J* = 8.3), 7.62-7.52 (m, 2H), 7.30 (s, 1H), 3.65-3.64 (m, 2H), 3.03-2.87 (m, 2H), 2.41-2.29 (m, 3H). **¹³C**: 150.2, 130.8, 128.6, 127.2, 127.0 (q, *J* = 277.0), 126.7, 126.2, 124.3, 123.1, 122.9, 117.7, 62.2, 35.7 (q, *J* = 28.2), 35.3 (q, *J* = 2.0), 30.8. **HRMS**: calcd for C₁₅H₁₃ClO₂F₃ [M-H]⁻: 317.0556; found: 317.0561.

B.11.5.6 Characterization of (\pm)-2-(2-benzyl-3-hydroxypropyl)-4-chloronaphthalen-1-ol (3.55, R = Bn)



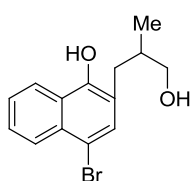
0.39 g (86% yield) from 0.40 g of **3.54**, R = Bn, off white solid, m.p.: 106-108 °C; eluent: 1:4 EtOAc/hexane; **IR**: 3666-3099 (broad). **¹H**: 8.32 (d, 1H, *J* = 7.7), 8.16 (d, 1H, *J* = 7.8), 7.60-7.50 (m, 2H), 7.37-7.20 (m, 6H), 3.56-3.45 (m, 2H), 2.99-2.71 (m, 4H), 2.27-2.14 (m, 1H). **¹³C**: 149.9, 139.9, 130.6, 129.1, 128.9, 128.8, 126.8, 126.7, 126.6, 125.9, 124.1, 123.0, 122.5, 119.3, 62.9, 43.0, 38.5, 30.9. **HRMS**: calcd for C₂₀H₁₈ClO₂ [M-H]⁻: 325.0995; found: 325.0988.

B.11.6 Preparation of compounds 3.56

These substances were prepared by the same procedure detailed above for the synthesis of compound **3.12**.

B.11.6.1 Characterization of 4-bromo-2-(3-hydroxy-2-methylpropyl)naphthalen-1-ol (3.56,

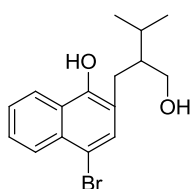
R = Me)



0.54 g (79% yield) from 0.50 g of **3.54**, R = Me, light brown solid, m.p.: 75-77 °C; eluent: 3:17 EtOAc/hexane; **IR**: 3638-3022 (broad). **¹H**: 8.31 (d, 1H, *J* = 7.7), 8.11 (d, 1H, *J* = 7.9), 7.58-7.50 (m, 3H), 3.48 (dd, 1H, *J* = 10.3, 3.8), 3.39 (dd, 1H, *J* = 10.3, 6.7), 2.92-2.78 (m, 2H), 2.15-2.06 (m, 1H), 1.09 (d, 3H, *J* = 6.9). **¹³C**: 150.7, 133.0, 131.8, 127.1, 126.9, 126.7, 125.9, 123.0, 119.6, 112.4, 65.5, 35.8, 32.4, 17.2. **HRMS**: calcd for C₁₄H₁₄⁷⁹BrO₂ [M-H]⁻: 293.0177; found: 293.0182.

B.11.6.2 Characterization of 4-bromo-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol

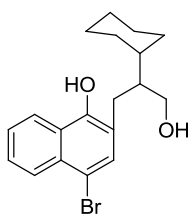
(3.56, R = *i*-Pr)



0.29 g (76% yield) from 0.29 g of **3.54**, R = *i*-Pr, off white solid, m.p.: 96-98 °C, colour changes to black; eluent: 1:9 to 1:4 EtOAc/hexane; **IR**: 3655-3018 (broad). **¹H**: 8.31 (d, 1H, *J* = 7.7), 8.10 (d, 1H, *J* = 7.8), 7.58-7.48 (m, 3H), 3.73 (dd, 1H, *J* = 10.4, 5.5), 3.64 (dd, 1H, *J* = 10.3, 3.7), 2.97 (dd, 1H, *J* = 14.3, 8.6), 2.77 (dd, 1H, *J* = 14.3, 4.5), 1.90-1.79 (m, 1H), 1.64-1.54 (m, 1H), 1.11 (d, 3H, *J* = 6.7), 1.02 (d, 3H, *J* = 6.8). **¹³C**: 150.6, 132.5, 131.7, 127.0 (2C), 126.7, 125.8, 123.0, 121.3, 112.5, 62.8, 48.0, 29.9, 29.1, 21.2, 20.7. **HRMS**: calcd for C₁₆H₁₈⁷⁹BrO₂ [M-H]⁻: 321.0490; found: 321.0499.

B.11.6.3 Characterization of 4-bromo-2-(2-cyclohexyl-3-hydroxypropyl)naphthalen-1-ol

(3.56, R = Cy)

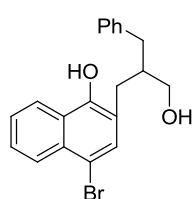


0.34 g (83% yield) from 0.32 g of **3.54**, R = Cy, off white solid, m.p.: 87-90 °C, colour changes to brown; eluent: 1:9 EtOAc/hexane; **IR**: 3648-3008 (broad). **¹H**: 8.31 (d, 1H, *J* = 7.7), 8.10 (d, 1H, *J* = 7.8), 7.57-7.49 (m, 3H), 3.75 (dd, 1H, *J* =

10.4, 5.1), 3.61 (dd, 1H, $J = 10.4, 3.5$), 2.96 (dd, 1H, $J = 14.2, 8.8$), 2.77 (dd, 1H, $J = 14.1, 4.3$), 1.96-1.70 (m, 5H), 1.61-1.45 (m, 2H), 1.39-0.99 (m, 5H). ^{13}C : 150.6, 132.5, 131.7, 127.0 (2C), 126.7, 125.8, 123.0, 121.4, 112.5, 62.5, 47.0, 39.9, 31.6, 30.8, 29.0, 26.7 (2C), 26.6. **HRMS**: calcd for $\text{C}_{19}\text{H}_{22}^{79}\text{BrO}_2$ [M-H] $^-$: 361.0803; found: 361.0805.

B.11.6.4 Characterization of 2-(2-benzyl-3-hydroxypropyl)-4-bromonaphthalen-1-ol (3.56,

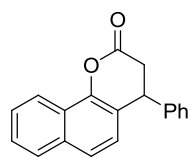
R = Bn)



0.11 g (29% yield) from 0.30 g of **3.54**, R = Bn, light brown solid, m.p.: 111-113 °C, colour changes to black; eluent: 1:9 to 1:4 EtOAc/hexane; **IR**: 3662-3099 (broad). ^1H : 8.31 (d, 1H, $J = 8.3$), 8.10 (d, 1H, $J = 7.8$), 7.58-7.49 (m, 2H), 7.39-7.32 (m, 3H), 7.28-7.22 (m, 3H), 3.58-3.48 (m, 2H), 2.99-2.73 (m, 4H), 2.28-2.15 (m, 1H). ^{13}C : 150.7, 139.9, 132.6, 131.8, 129.2, 128.8, 127.1, 126.9, 126.7, 126.6, 125.9, 123.0, 119.9, 112.6, 62.9, 43.0, 38.5, 30.9. **HRMS**: calcd for $\text{C}_{20}\text{H}_{18}^{79}\text{BrO}_2$ [M-H] $^-$: 369.0490; found: 369.0498.

B.12 Preparation and characterization of intermediates towards 3.59-3.60

B.12.1 Preparation of 4-phenyl-3,4-dihydro-2H-benzo[h]chromen-2-one (3.58)

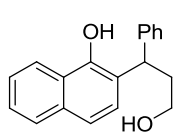


[Known compound]^[16] The procedure described above for **3.48** afforded 1.68 g (44% yield) of **3.58** from 2.0 g of 1-naphthol and 4.1 g of *trans*-cinnamic acid, light yellow solid, m.p.: 107-109 °C (lit.^[16] m.p.: 111-113 °C); eluent: 1:9 to 1:3 EtOAc/hexane; **IR**: 1764. ^1H : 8.34 (d, 1H, $J = 9.0$), 7.85 (d, 1H, $J = 6.0$), 7.62-7.54 (m, 3H), 7.38-7.30 (m, 3H), 7.20-7.18 (m, 2H), 7.12 (d, 1H, $J = 9.0$), 4.49 (t, 1H, $J = 7.5$), 3.23 (dd, 1H, J

[16] Zadsirjan, V.; Heravi, M. M.; Tajbakhsh, M.; Oskooie, H. A.; Shiri, M.; Hosseinejad, T. Res. Chem. Intermed. **2016**, *42*, 6407.

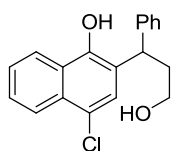
= 15.0, 6.0), 3.13 (dd, 1H, $J = 15.0, 6.0$). ^{13}C : 167.6, 146.9, 140.8, 133.8, 129.3, 127.8, 127.7 (2C), 127.0, 126.9, 125.5, 124.4, 123.9, 121.5, 120.0, 41.2, 37.4.

B.12.2 Characterization of (\pm)-2-(3-hydroxy-1-phenylpropyl)naphthalen-1-ol (3.59)



[Known compound]^[17] The procedure described above for **3.43-3.44** afforded 0.80 g (65% yield) of **3.59** from 1.20 g of **3.58**, white solid, m.p.: 86-88 °C, eluent: 3:17 to 1:3 EtOAc/hexane. **IR**: 3638-3106 (broad). ^1H : 8.29 (d, 1H, $J = 7.8$), 7.73 (d, 1H, $J = 8.0$), 7.51-7.43 (m, 3H), 7.34-7.31 (m, 5H), 6.99 (d, 1H, $J = 8.6$), 4.84 (dd, 1H, $J = 11.4, 4.7$), 3.95-3.87 (m, 1H), 3.54-3.47 (m, 1H), 2.59-2.47 (m, 1H), 2.26-2.15 (m, 1H), 2.08 (br s, 1H). ^{13}C : 149.6, 144.0, 133.4, 128.6, 128.4, 127.5, 126.6, 126.4, 126.0, 125.7, 125.4, 123.8, 122.4, 120.8, 60.6, 38.4, 36.7. **HRMS**: calcd for $\text{C}_{19}\text{H}_{18}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 301.1204; found: 301.1211.

B.12.3 Characterization of (\pm)-4-chloro-2-(3-hydroxy-1-phenylpropyl)naphthalen-1-ol (3.60)

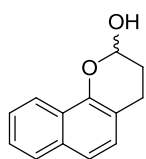


The procedure described for **3.11** afforded 0.298 g (76% yield) of (\pm)-**3.60** from 0.35 g of (\pm)-**3.59** as yellow solid, m.p.: 139-141 °C, colour changes to brown; eluent: 3:17 to 3:7 EtOAc/hexane; **IR**: 3631-3103 (broad). ^1H : 8.36-8.33 (m, 1H), 8.14-8.10 (m, 1H), 7.69 (br s, 1H), 7.60-7.52 (m, 2H), 7.38-7.24 (m, 5H), 7.04 (s, 1H), 4.82 (dd, 1H, $J = 11.6, 4.5$), 3.99-3.92 (m, 1H), 3.50 (td, 1H, $J = 10.9, 3.1$), 2.59-2.47 (m, 1H), 2.24-2.14 (m, 1H), 2.01 (br s, 1H). ^{13}C : 149.0, 143.2, 130.4, 128.8, 128.4, 127.1, 126.9, 126.3, 126.2, 124.4, 124.2, 123.7, 123.1, 60.5, 38.3, 35.5. **HRMS**: calcd for $\text{C}_{19}\text{H}_{16}\text{ClO}_2$ $[\text{M}-\text{H}]^-$: 311.0839; found: 311.0833.

[17] Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6881.

B.13 Preparation and characterization of intermediates towards 3.63-3.64

B.13.1 Preparation of 3,4-dihydro-2*H*-benzo[*h*]chromen-2-ol (3.61)

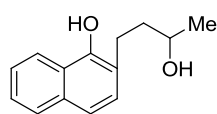


This compound is known and was prepared by the literature procedure.^[15] DIBALH (~1.0 M solution in hexane, 9.8 mL, 9.8 mmol, 1.12 equiv) was added by syringe pump over 30 minutes to a solution of **3.48** (1.73 g, 8.7 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) at -78 °C. The mixture was stirred for 2 h at -78 °C and then poured into satd. aqueous solution of Rochelle's salt (45mL). The mixture was then stirred for 2 h at RT and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 1:9 to 1:4 Et₂O/pentane) on silica gel to provide 1.41 g (82% yield) of **3.61** as white solid, m.p.: 62-64 °C (lit. m.p. not reported). **IR**: 3645-3117 (broad). **¹H**: 8.18-8.15 (m, 1H), 7.78-7.75 (m, 1H), 7.49-7.43 (m, 2H), 7.39 (d, 1H, *J* = 8.4), 7.18 (d, 1H, *J* = 8.3), 5.83 (s, 1H), 3.16-3.04 (m, 2H), 2.85 (app dt, 1H, *J* = 16.5, 5.4), 2.22-2.06 (m, 2H). **¹³C**: 146.8, 133.4, 127.6, 127.5, 125.8, 125.5, 125.3, 121.4, 120.4, 115.8, 92.5, 27.2, 20.8.

B.13.2 General procedure for reaction of Grignard reagent with 3.61

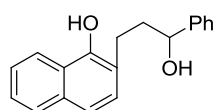
Commercial Grignard (~3.0 M in Et₂O, 1.3 mL, 4.0 mmol, 4.0 equiv) was added dropwise to a cold (0 °C) solution of **3.61** (0.2 g, 1.0 mmol, 1.0 equiv) in dry Et₂O (2.0 mL). The mixture was warmed to RT and then stirred for 1h, after which time TLC showed that the reaction was complete. The mixture was cooled to 0 °C and quenched with aq. satd. NH₄Cl (5.0 mL) and extracted with Et₂O (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography on silica gel to provide **3.62**.

B.13.2.1 Characterization of (±)-2-(3-hydroxybutyl)naphthalen-1-ol (**3.62**, R = Me)



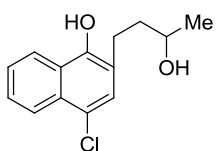
0.40 g (92% yield) from 0.4 g of **3.61** and 2.7 mL of MeMgBr, light yellow oil, eluent: 1:9 to 1:4 EtOAc/hexane. **IR**: 3650-3094 (broad). **¹H**: 8.29-8.26 (m, 1H), 8.06 (br s, 1H), 7.78-7.75 (m, 1H), 7.49-7.41 (m, 2H), 7.38 (d, 1H, *J* = 8.9), 7.21 (d, 1H, *J* = 8.3), 3.82-3.71 (m, 1H), 3.18-3.08 (m, 1H), 2.77 (dt, 1H, *J* = 14.3, 4.4), 1.86-1.80 (m, 2H), 1.24 (d, 3H, *J* = 6.1). **¹³C**: 150.3, 133.7, 128.7, 127.4, 125.7, 125.5, 125.2, 122.3, 120.3, 120.1, 66.7, 38.8, 26.0, 24.2. **HRMS**: calcd for C₁₄H₁₅O₂ [M-H]⁻: 215.1072; found: 215.1069.

B.13.2.2 Characterization of (±)-2-(3-hydroxy-3-phenylpropyl)naphthalen-1-ol (**3.62**, R = Ph)



0.53 g (95% yield) from 0.4 g of **3.61** and 2.7 mL of PhMgBr, light yellow solid, m.p.: 94-96 °C, eluent: 1:9 to 1:3 EtOAc/hexane. **IR**: 3655-3103 (broad). **¹H**: 8.32-8.29 (m, 1H), 7.92 (br s, 1H), 7.81-7.78 (m, 1H), 7.51-7.46 (m, 2H), 7.42 (d, 1H, *J* = 8.4), 7.36-7.23 (m, 6H), 4.62 (dd, 1H, *J* = 11.0, 3.0), 3.30-3.20 (m, 1H), 2.87(dt, 1H, *J* = 14.3, 4.5), 2.41 (br s, 1H), 2.27-2.15 (m, 1H), 2.07-1.95 (m, 1H). **¹³C**: 150.2, 143.8, 133.8, 128.8, 128.7, 128.2, 127.5, 125.9, 125.8, 125.4, 125.3, 122.3, 120.2, 120.1, 72.9, 39.1, 26.2. **HRMS**: calcd for C₁₉H₁₈O₂Na [M+Na]⁺: 301.1204; found: 301.1204.

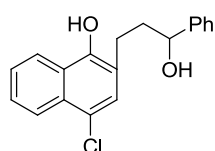
B.13.3 Characterization of (±)-4-chloro-2-(3-hydroxybutyl)naphthalen-1-ol (**3.63**)



The procedure described for **3.11** afforded 0.37 g (76% yield) of product from 0.42 g of **3.62**, R = Me as white solid, m.p.: 64-66 °C, colour changes to brown; eluent: 1:9 EtOAc/hexane; **IR**: 3648-3011 (broad). **¹H**: 8.32-8.29 (m, 1H), 8.16-8.13 (m, 1H), 7.59-7.49 (m, 2H), 7.31 (s, 1H), 3.81-3.70 (m, 1H), 3.16-3.06 (m, 1H), 2.72 (dt, 1H, *J* = 14.4, 4.3), 1.86-1.80 (m, 2H), 1.75 (d, 3H, *J* = 6.1). **¹³C**: 149.7, 130.5, 128.5,

126.8, 126.7, 125.9, 124.1, 122.9, 122.7, 120.8, 66.7, 38.5, 25.9, 24.2. **HRMS**: calcd for $C_{14}H_{14}ClO_2$ $[M-H]^-$: 249.0682; found: 249.0675.

B.13.4 Characterization of (\pm)-4-chloro-2-(3-hydroxy-3-phenylpropyl)naphthalen-1-ol (3.64)



The procedure described for **3.11** afforded 0.33 g (89% yield) of product from 0.33 g of **3.62**, R = Ph as light yellow solid, m.p.: 108-110 °C, eluent: 1:9 to 1:4 EtOAc/hexane. **IR**: 3634-2994 (broad). **¹H**: 8.33 (d, 1H, $J = 8.0$), 8.19 (d, 1H, $J = 8.0$), 8.11 (br s, 1H), 7.61-7.52 (m, 2H), 7.34-7.30 (m, 6H), 4.62 (dd, 1H, $J = 9.8, 2.5$), 3.27-3.17 (m, 1H), 2.83 (dt, 1H, $J = 14.4, 3.9$), 2.44 (br s, 1H), 2.23-2.14 (m, 1H), 2.04-1.96 (m, 1H). **¹³C**: 149.7, 143.5, 130.6, 128.9, 128.5, 128.4, 126.9, 126.6, 126.0, 125.9, 124.2, 122.9, 120.5, 72.9, 38.9, 26.1. **HRMS**: calcd for $C_{19}H_{16}ClO_2$ $[M-H]^-$: 311.0839; found: 311.0837.

B.14 Preparation and characterization of various intermediates towards amine 3.72

B.14.1 General procedure for protection of 3.68 as TBS ether

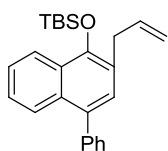
A solution of **3.68** (35 mmol, 1.0 equiv), imidazole (46 mmol, 1.3 equiv) and TBSCl (42 mmol, 1.2 equiv) in CH_2Cl_2 (55 mL) was stirred at RT overnight, after which time TLC showed that the reaction was complete. The mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography to provide **3.69**.

Compound **3.69** with R = H is known.^[18]

[18] Schuenemann, K.; Furkert, D. P.; Connelly, S.; Fraser, J. D.; Sperry, J.; Brimble, M. A. *Eur. J. Org. Chem.* **2014**, 122-128.

B.14.1.1 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-2-allyl-4-phenylnaphthalene

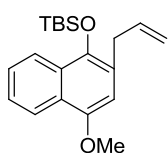
(**3.69**, R' = Ph)



1.37 g (95% yield) from 1.65 g of **3.68**, R' = Ph, colorless oil, eluent: 1:19 EtOAc/hexane. **IR**: 1252, 1099. **¹H**: 8.15 (d, 1H, *J* = 8.2), 7.84 (d, 1H, *J* = 7.9), 7.49-7.34 (m, 7H), 7.25 (s, 1H), 6.05-5.91 (m, 1H), 5.17-5.07 (m, 2H), 3.59 (dt, 2H, *J* = 6.6, 1.2), 1.16 (s, 9H), 0.23 (s, 6H). **¹³C**: 147.6, 140.9, 137.0, 133.8, 131.6, 130.2, 129.3, 128.3, 128.2, 126.9, 125.8, 125.4, 124.6, 124.3, 123.3, 116.2, 34.5, 26.1, 18.7, -3.1. **HRMS**: calcd for C₂₅H₃₀OSiNa [M+Na]⁺: 397.1968; found: 397.1964.

B.14.1.2 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-2-allyl-4-methoxynaphthalene

(**3.69**, R' = OMe)

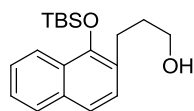


1.42 g (93% yield) from 1.55 g of **3.68**, R' = OMe, colorless oil, eluent: 1:19 EtOAc/hexane. **IR**: 1258, 1096. **¹H**: 8.18 (dd, 1H, *J* = 7.8, 1.1), 8.02 (dd, 1H, *J* = 7.1, 1.9), 7.48-7.40 (m, 2H), 6.62 (s, 1H), 6.03-5.90 (m, 1H), 5.19-5.11 (m, 2H), 3.96 (s, 3H), 3.55 (app d, 2H, *J* = 6.5), 1.13 (s, 9H), 0.16 (s, 6H). **¹³C**: 149.9, 141.5, 137.2, 128.8, 125.4, 125.3, 124.7, 124.0, 122.9, 121.7, 116.1, 105.8, 55.6, 34.8, 26.1, 18.7, -3.3.

B.14.2 General procedure for hydroboration-oxidation of terminal alkenes **3.69**

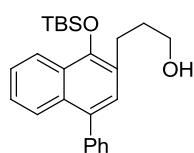
These substances were prepared by the same procedure detailed above for the synthesis of compound **3.10**.

B.14.2.1 Characterization of 1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl-propan-1-ol (3.70, R' = H)



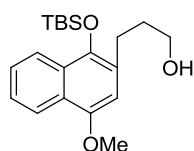
This compound has been described only in a patent.^[19] 4.03 g (76% yield) from 5.00 g of **3.69**, R' = H, white solid, m.p.: 78-80 °C; eluent: 3:7 EtOAc/hexane; **IR**: 3636-3133 (broad). **¹H**: 8.08-8.05 (m, 1H), 7.79-7.76 (m, 1H), 7.48 (d, 1H, *J* = 8.3), 7.44-7.38 (m, 2H), 7.30 (d, 1H, *J* = 8.4), 3.58 (t, 2H, *J* = 6.3), 2.89 (t, 2H, *J* = 7.2), 1.90 (p, 2H, *J* = 6.9), 1.13 (s, 9H), 0.19 (s, 6H). **¹³C**: 148.2, 133.7, 128.2, 128.1, 127.6, 126.7, 125.2, 124.8, 123.0, 121.9, 62.0, 33.1, 26.5, 26.1, 18.7, -3.2.

B.14.2.2 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-(4-phenylnaphthalen-2-yl)-propan-1-ol (3.70, R' = Ph)



1.47 g (76% yield) from 1.85 g of **3.69**, R' = Ph, white solid, m.p.: 57-59 °C; eluent: 1:3 EtOAc/hexane. **IR**: 3546-3168 (broad), 1252, 965. **¹H**: 8.16 (d, 1H, *J* = 7.8), 7.86 (d, 1H, *J* = 8.2), 7.52-7.35 (m, 7H), 7.27 (s, 1H), 3.63 (t, 2H, *J* = 6.4), 2.93 (app t, 2H, *J* = 7.2), 1.94 (p, 2H, *J* = 6.9), 1.17 (s, 9H), 0.24 (s, 6H). **¹³C**: 147.7, 140.8, 134.2, 131.5, 130.2, 129.4, 128.2 (2C, shoulder), 126.9, 126.2, 125.9, 125.3, 124.7, 123.3, 62.1, 33.2, 26.5, 26.2, 18.7, -3.1. **HRMS**: calcd for C₂₅H₃₂O₂SiNa [M+Na]⁺: 415.2069; found: 415.2077.

B.14.2.3 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-(4-methoxynaphthalen-2-yl)-propan-1-ol (3.70, R' = OMe)



1.41 g (87% yield) from 1.63 g of **3.69**, R' = OMe, colorless oil, eluent: 3:7 EtOAc/hexane; **IR**: 3693-3126 (broad). **¹H**: 8.19-8.16 (m, 1H), 8.02-7.99 (m,

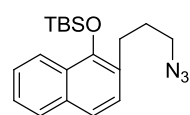
[19] Batt, D. G. *Eur. Pat. Appl.* **1986**, EP 201071 A2 19861112.

1H), 7.49-7.39 (m, 2H), 6.61 (s, 1H), 3.97 (s, 3H), 3.56 (t, 2H, $J = 6.2$), 2.88 (t, 2H, $J = 7.2$), 1.90 (p, 2H, $J = 6.8$), 1.12 (s, 9H), 0.16 (s, 6H). ^{13}C : 150.3, 141.5, 128.6, 125.9, 125.5, 125.2, 124.6, 122.8, 121.7, 105.8, 61.9, 55.6, 33.1, 26.8, 26.1, 18.6, -3.3.

B.14.3 General procedure for azidation of primary alcohols

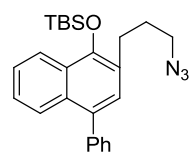
Neat DPPA (10.4 mL, 48.3 mmol, 2.1 equiv) was added dropwise to a cold (0 °C) solution of **3.70** (23 mmol, 1.0 equiv) and PPh_3 (48.3 mmol, 2.1 equiv) in THF (65 mL). Neat diisopropyl azodicarboxylate (9.5 mL, 48.3 mmol, 2.1 equiv) was then added dropwise to the cold solution over 10 min and with good stirring. The mixture was warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The solution was evaporated and the residue was purified by flash column chromatography to provide **3.71**.

B.14.3.1 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-2-(3-azido-1-propyl)-naphthalene (**3.71**, $\text{R}' = \text{H}$)



2.1 g (78% yield) from 2.5 g of **3.70**, $\text{R}' = \text{H}$, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 2092. ^1H : 8.08-8.05 (m, 1H), 7.79-7.76 (m, 1H), 7.49-7.41 (m, 3H), 7.28 (d, 2H, $J = 7.1$), 3.27 (t, 2H, $J = 6.9$), 2.87 (t, 2H, $J = 7.8$), 1.93 (p, 2H, $J = 7.2$), 1.13 (s, 9H), 0.19 (s, 6H). ^{13}C : 148.4, 133.7, 128.1(2C), 127.6, 125.9, 125.3, 124.9, 123.0, 121.7, 51.0, 29.4, 27.7, 26.1, 18.7, -3.2.

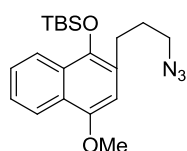
B.14.3.2 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-2-(3-azido-1-propyl)-4-phenylnaphthalene (**3.71**, $\text{R}' = \text{Ph}$)



0.81 g (65% yield) from 1.17 g of **3.70**, $\text{R}' = \text{Ph}$, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 2094. ^1H : 8.15 (d, 1H, $J = 8.1$), 7.86 (d, 1H, $J = 8.4$), 7.50-7.36 (m, 7H), 7.24 (s, 1H), 3.31 (t, 2H, $J = 6.9$), 2.91 (app t, 2H, $J = 7.3$), 1.97

(p, 2H, $J = 7.2$), 1.17 (s, 9H), 0.24 (s, 6H). ^{13}C : 147.9, 140.7, 134.1, 131.6, 130.2, 129.2, 128.3, 128.2, 127.0, 125.9, 125.4 (2C), 124.8, 123.3, 51.1, 29.5, 27.7, 26.1, 18.7, -3.1.

B.14.3.3 Characterization of 1-(*tert*-Butyldimethylsilyloxy)-2-(3-azido-1-propyl)-4-methoxynaphthalene (**3.71**, $\text{R}' = \text{OMe}$)

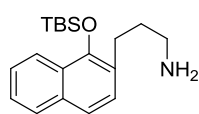


0.85 g (81% yield) from 1.05 g of **3.70**, $\text{R}' = \text{OMe}$, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 2094. ^1H : 8.19-8.16 (m, 1H), 8.02-7.99 (m, 1H), 7.49-7.40 (m, 2H), 6.59 (s, 1H), 3.98 (s, 3H), 3.28 (t, 2H, $J = 6.9$), 2.85 (app t, 2H, $J = 7.3$), 1.93 (p, 2H, $J = 7.2$), 1.12 (s, 9H), 0.16 (s, 6H). ^{13}C : 150.1, 141.8, 128.7, 125.5, 125.3, 125.1, 124.7, 122.8, 121.7, 105.8, 55.6, 51.0, 29.4, 28.1, 26.1, 18.6, -3.3. **HRMS**: calcd for $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2\text{SiNa}$ [$\text{M}+\text{Na}$] $^+$: 394.1927; found: 394.1919.

B.14.4 General procedure for synthesis of amines from azides

Commercial 1M Me_3P in THF (4.6 mL, 4.6 mmol, 2.0 equiv) was added slowly at RT to solution of **3.71** (23 mmol, 1.0 equiv) in THF (50 mL). H_2O (25 mL) was added to the reaction mixture and the solution was stirred at RT for 7 h, after which time TLC showed that the reaction was complete. The mixture was quenched with aq. satd. NH_4Cl (20 mL) and extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated and the residue was dried under high vacuum and used for the next step without purification.

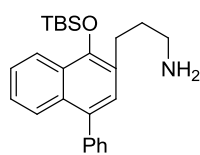
B.14.4.1 Characterization of 3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-2-yl)propan-1-amine (**3.72**, $\text{R}' = \text{H}$)



2.7 g (96% crude yield) from 3.0 g of **3.71**, $\text{R}' = \text{H}$, brown oil; **IR**: 3109-2752 (broad). ^1H : 8.06-8.05 (m, 1H), 7.76-7.72 (m, 1H), 7.44-7.37 (m, 3H), 7.29 (d,

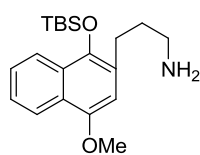
1H, $J = 8.5$), 3.71 (br s, 2H), 2.86-2.76 (m, 4H), 1.93 (p, 2H, $J = 7.4$), 1.11 (s, 9H), 0.16 (s, 6H). ^{13}C : 148.2, 133.7, 128.1, 128.0, 127.6, 125.7, 125.3, 124.8, 123.0, 121.9, 40.3, 30.6, 27.4, 26.1, 18.7, -3.2. **HRMS**: calcd for $\text{C}_{19}\text{H}_{30}\text{NOSi}$ $[\text{M}+\text{H}]^+$: 316.2097; found: 316.2094.

B.14.4.2 Characterization of 3-(1-(*tert*-butyldimethylsilyloxy)-4-phenylnaphthalen-2-yl)propan-1-amine (3.72, R' = Ph)



898 mg (97% crude yield) from 986 mg of **3.71**, R' = Ph, yellow solid; **IR**: 3403-2647 (broad). ^1H : 8.11 (d, 1H, $J = 7.7$), 7.82 (d, 1H, $J = 8.1$), 7.48-7.33 (m, 7H), 7.21 (s, 1H), 5.42 (br s, 2H), 2.87-2.83 (m, 4H), 2.00 (p, 2H, $J = 7.6$), 1.12 (s, 9H), 0.19 (s, 6H). ^{13}C : 147.8, 140.4, 134.3, 131.7, 130.2, 128.8, 128.2 (2C), 126.9, 125.9, 125.5, 124.7, 124.6, 123.3, 39.7, 28.0, 27.1, 26.1, 18.6, -3.1. **HRMS**: calcd for $\text{C}_{25}\text{H}_{34}\text{NOSi}$ $[\text{M}+\text{H}]^+$: 392.2410; found: 392.2411.

B.14.4.3 Characterization of 3-(1-(*tert*-butyldimethylsilyloxy)-4-methoxynaphthalen-2-yl)propan-1-amine (3.72, R' = OMe)



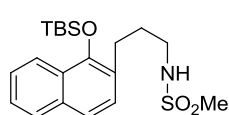
738 mg (93% crude yield) from 853 mg of **3.71**, R' = OMe, colorless oil; **IR**: 2752-3172 (broad). ^1H : 8.35 (br s, 2H), 8.15 (dd, 1H, $J = 7.2, 1.9$), 7.96 (dd, 1H, $J = 7.3, 1.7$), 7.48-7.39 (m, 2H), 6.65 (s, 1H), 3.93 (s, 3H), 2.86-2.78 (m, 4H), 2.11 (p, 2H, $J = 7.2$), 1.07 (s, 9H), 0.11 (s, 6H). ^{13}C : 150.3, 141.8, 128.6, 125.6, 125.4, 124.8, 123.9, 122.8, 121.8, 105.4, 55.8, 39.1, 28.1, 27.4, 26.1, 18.6, -3.3. **HRMS**: calcd for $\text{C}_{20}\text{H}_{32}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 346.2202; found: 346.2199.

B.15 General procedure for coupling reaction between amine and sulfonyl chloride

An appropriate sulfonyl chloride (25.2 mmol, 1.2 equiv) was added to a cold (0 °C) solution of **3.72** (21 mmol, 1.0 equiv) and Et_3N (3.8 mL, 27.3 mmol, 1.3 equiv) in CH_2Cl_2 (45

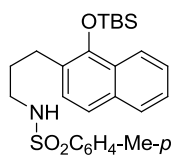
mL). The resulting mixture was warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The mixture was quenched with aq. satd. NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography to provide **3.73**.

B.15.1 Characterization of *N*-(3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-2-yl)propyl)methanesulfonamide (3.73; R = Me, R' = H)



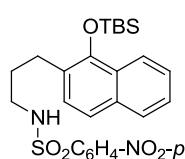
1.18 g (86% yield) from 1.10 g of **3.72**, R' = H, yellow solid, m.p.: 92-94 °C; eluent: 1:3 EtOAc/hexane; **IR**: 3150-3440 (broad). **¹H**: 8.07-8.04 (m, 1H), 7.79-7.76 (m, 1H), 7.50-7.42 (m, 3H), 7.28-7.25 (m, 1H), 4.44 (t, 1H, $J = 5.9$), 3.03 (q, 2H, $J = 13.4, 6.8$), 2.88 (t, 2H, $J = 7.3$), 2.83 (s, 3H), 1.93 (p, 2H, $J = 7.0$), 1.13 (s, 9H), 0.19 (s, 6H). **¹³C**: 148.3, 133.7, 128.1, 127.8, 127.6, 125.7, 125.5, 125.0, 122.9, 122.2, 42.4, 40.1, 30.4, 27.0, 26.1, 18.7, -3.2. **HRMS**: calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_3\text{SSiNa}$ [$\text{M}+\text{Na}$]⁺: 416.1692; found: 416.1686.

B.15.2 Characterization of *N*-(3-(1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl)propyl)-4-methylbenzenesulfonamide (3.73; R = 4-Tol, R' = H)



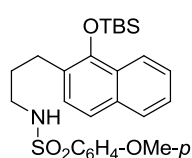
397 mg (89% yield) from 300 mg of **3.72**, R' = H, colorless oil, eluent: 1:3 EtOAc/hexane; **IR**: 3441-3126 (broad). **¹H**: 8.06-8.02 (m, 1H), 7.77-7.74 (m, 1H), 7.60 (d, 2H, $J = 8.3$), 7.49-7.40 (m, 3H), 7.17-7.11 (m, 3H), 4.58 (t, 1H, $J = 6.1$), 2.82-2.75 (m, 4H), 2.34 (s, 3H), 1.82 (p, 2H, $J = 7.0$), 1.12 (s, 9H), 0.16 (s, 6H). **¹³C**: 148.1, 143.1, 136.6, 133.7, 129.5, 128.0, 127.8, 127.6, 126.9, 125.7, 125.4, 125.0, 123.0, 122.1, 42.2, 29.8, 26.8, 26.1, 21.4, 18.7, -3.2. **HRMS**: calcd for $\text{C}_{26}\text{H}_{35}\text{NO}_3\text{SSiNa}$ [$\text{M}+\text{Na}$]⁺: 492.2005; found: 492.2002.

B.15.3 Characterization of *N*-(3-(1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl)propyl)-4-nitrobenzenesulfonamide (3.73; R = C₆H₄-NO₂-*p*, R' = H)



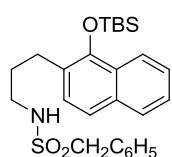
433 mg (91% yield) from 300 mg of **3.72**, R' = H, colorless oil, eluent: 1:2 EtOAc/hexane; **IR**: 3420-3168 (broad), 1530, 1347. **¹H**: 8.02-7.99 (m, 3H), 7.76-7.72 (m, 3H), 7.53-7.40 (m, 2H), 7.43 (d, 1H, *J* = 8.4), 7.13 (d, 1H, *J* = 8.4), 4.94 (t, 1H, *J* = 6.2), 2.84 (t, 2H, *J* = 6.9), 2.74 (q, 2H, *J* = 12.9, 6.5), 1.88 (p, 2H, *J* = 6.7), 1.13 (s, 9H), 0.17 (s, 6H). **¹³C**: 149.6, 147.8, 145.3, 133.7, 127.9, 127.8, 127.7, 127.5, 125.8, 125.3, 125.2, 124.1, 122.8, 122.6, 42.0, 29.3, 26.2, 26.1, 18.7, -3.3. **HRMS**: calcd for C₂₅H₃₂N₂O₅SSiNa [M+Na]⁺: 523.1699; found: 523.1700.

B.15.4 Characterization of *N*-(3-(1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl)propyl)-4-methoxybenzenesulfonamide (3.73; R = C₆H₄-OMe-*p*, R' = H)



585 mg (90% yield) from 300 mg of **3.72**, R' = H, colorless oil, eluent: 1:3 EtOAc/hexane; **IR**: 3462-3168 (broad), 1259, 1093. **¹H**: 8.05 (dd, 1H, *J* = 8.6, 1.8), 7.76 (dd, 1H, *J* = 6.9, 2.1), 7.63 (d, 2H, *J* = 8.9), 7.49-7.40 (m, 3H), 7.16 (d, 1H, *J* = 8.4), 6.76 (d, 2H, *J* = 8.9), 4.59 (t, 1H, *J* = 6.2), 3.79 (s, 3H), 2.83-2.71 (m, 4H), 1.83 (p, 2H, *J* = 7.0), 1.12 (s, 9H), 0.16 (s, 6H). **¹³C**: 162.6, 148.1, 133.7, 131.2, 129.0, 128.0, 127.8, 127.6, 125.7, 125.4, 125.0, 123.0, 122.1, 114.0, 55.5, 42.1, 29.7, 26.8, 26.1, 18.7, -3.2. **HRMS**: calcd for C₂₆H₃₅NO₄SSiNa [M+Na]⁺: 508.1954; found: 508.1956.

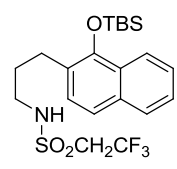
B.15.5 Characterization of *N*-(3-(1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl)propyl)-1-phenylmethanesulfonamide (3.73; R = Bn, R' = H)



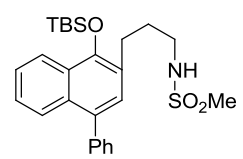
424 mg (95% yield) from 300 mg of **3.72**, R' = H, colorless oil, eluent: 1:3 EtOAc/hexane; **IR**: 3126-3441 (broad). **¹H**: 8.06-8.03 (m, 1H), 7.80-7.77 (m, 1H),

7.53-7.38 (m, 3H), 7.34-7.19 (m, 6H), 4.27-4.23 (m, 1H), 4.16 (s, 2H), 2.86 (q, 2H, $J = 13.4$, 6.7), 2.80 (t, 2H, $J = 7.4$), 1.81 (p, 2H, $J = 7.1$), 1.09 (s, 9H), 0.15 (s, 6H). ^{13}C : 148.2, 133.7, 130.5, 129.3, 128.7, 128.6, 128.1, 127.9, 127.6, 125.7, 125.4, 125.0, 123.0, 122.1, 58.7, 42.8, 30.8, 27.0, 26.1, 18.7, -3.2. **HRMS**: calcd for $\text{C}_{26}\text{H}_{35}\text{NO}_3\text{SSiNa}$ $[\text{M}+\text{Na}]^+$: 492.2005; found: 492.1994.

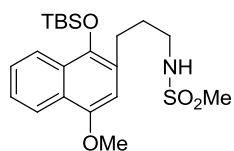
B.15.6 Characterization of *N*-(3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-2-yl)propyl)-2,2,2-trifluoroethanesulfonamide (3.73; R = CH_2CF_3 , R' = H)

 373 mg (85% yield) from 300 mg of **3.72**, R' = H, yellow oil; eluent: 1:3 EtOAc/hexane; **IR**: 3462-3189 (broad), 1253, 1162. ^1H : 8.07-8.03 (m, 1H), 7.79-7.76 (m, 1H), 7.50-7.40 (m, 3H), 7.24 (d, 1H, $J = 8.3$), 4.81 (br s, 1H), 3.66 (q, 2H, $J = 9$), 3.04 (q, 2H, $J = 6.6$), 2.89 (t, 2H, $J = 7.2$), 1.93 (p, 2H, $J = 7.0$), 1.12 (s, 9H), 0.18 (s, 6H). ^{13}C : 148.3, 133.8, 128.0, 127.7, 127.6, 125.6, 125.3, 125.1, 123.0, 122.3, 121.5 (q, $J = 276.3$), 54.0 (q, $J = 31.0$), 42.5, 30.5, 26.8, 26.1, 18.7, -3.3. **HRMS**: calcd for $\text{C}_{21}\text{H}_{31}\text{F}_3\text{NO}_3\text{SSi}$ $[\text{M}+\text{H}]^+$: 462.1746; found: 462.1750.

B.15.7 Characterization of *N*-(3-(1-(*tert*-Butyldimethylsilyloxy)-4-phenylnaphthalen-2-yl)propyl)methanesulfonamide (3.73; R = Me, R' = Ph)

 963 mg (82% yield) from 980 mg of **3.72**, R' = Ph, colorless oil, eluent: 1:3 EtOAc/hexane; **IR**: 3462-3126 (broad), 1244, 1102. ^1H : 8.14 (d, 1H, $J = 8.3$), 7.85 (d, 1H, $J = 8.4$), 7.50-7.36 (m, 7H), 7.22 (s, 1H), 4.44 (t, 1H, $J = 5.7$), 3.08 (q, 2H, $J = 13.2$, 6.7), 2.91 (t, 2H, $J = 7.3$), 1.96 (p, 2H, $J = 7.1$), 1.17 (s, 9H), 0.23 (s, 6H). ^{13}C : 147.8, 140.6, 134.5, 131.7, 130.2, 128.9, 128.3, 128.2, 127.1, 125.9, 125.6, 125.2, 124.9, 123.2, 42.5, 40.1, 30.4, 27.1, 26.1, 18.7, -3.1.

B.15.8 Characterization of *N*-(3-(1-(*tert*-butyldimethylsilyloxy)-4-methoxynaphthalen-2-yl)propyl)-methanesulfonamide (**3.73**; R = Me, R' = OMe)

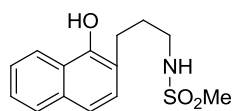


883 mg (90% yield) from 800 mg of **3.72**, R' = OMe, yellow oil, eluent: 1:3 EtOAc/hexane; **IR**: 3462-3126 (broad). **¹H**: 8.18 (dd, 1H, *J* = 7.1, 1.9), 7.99 (dd, 1H, *J* = 7.1, 1.7), 7.50-7.40 (m, 2H), 6.57 (s, 1H), 4.50 (t, 1H, *J* = 6.0), 3.98 (s, 3H), 3.00 (q, 2H, *J* = 13.1, 6.6), 2.87 (t, 2H, *J* = 7.1), 2.80 (s, 3H), 1.94 (p, 2H, *J* = 6.9), 1.12 (s, 9H), 0.15 (s, 6H). **¹³C**: 150.5, 141.6, 128.6, 125.7, 125.4, 124.9 (2C), 122.7, 121.9, 105.3, 55.6, 42.2, 39.9, 30.3, 27.2, 26.1, 18.6, -3.3. **HRMS**: calcd for C₂₁H₃₃NO₄SSiNa [M+Na]⁺: 446.1797; found: 446.1806.

B.16 General procedure for deprotection of TBS ether using TBAF

A 1M solution of TBAF in THF (19.8 mL, 19.8 mmol, 1.1 equiv) was slowly added to a cold (0 °C) solution of **3.73** (18 mmol, 1.0 equiv) in THF (55 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, after which time TLC showed that the reaction was complete. The mixture was quenched with aq. satd. NH₄Cl (20 mL) and extracted with EtOAc (3×15 ml). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to provide **3.74**.

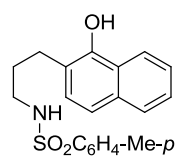
B.16.1 Characterization of *N*-(3-(1-hydroxynaphthalen-2-yl)propyl)methanesulfonamide (**3.74**; R = Me, R' = H)



0.78 g (85% yield) from 1.29 g of **3.73** (R = Me, R' = H), light yellow solid, m.p.: 78-80 °C, eluent: 2:3 EtOAc/hexane; **IR**: 3672-3399 (broad), 3399-3672 (broad). **¹H**: 8.08 (d, 1H, *J* = 8.1), 7.79 (d, 1H, *J* = 8.1), 7.51-7.41 (m, 3H), 7.22 (d, 1H, *J* = 8.4), 6.04 (br s, 1H), 5.01 (br s, 1H), 3.14 (t, 2H, *J* = 5.8), 2.96 (s, 3H), 2.90 (t, 2H, *J* = 7.1), 1.97

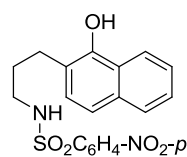
(p, 2H, $J = 6.8$). ^{13}C : 148.4, 133.4, 128.1, 127.8, 125.7, 125.6, 124.7, 120.9, 120.7, 120.6, 42.2, 40.0, 30.3, 26.2. **HRMS**: calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S}$ $[\text{M}+\text{Na}]^+$: 302.0827; found: 302.0826.

B.16.2 Characterization of *N*-(3-(1-Hydroxynaphthalen-2-yl)propyl)-4-methylbenzenesulfonamide (3.74; R = 4-Tol, R' = H)



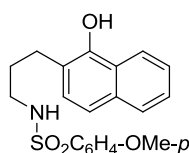
230 mg (87% yield) from 350 mg of **3.73** (R = 4-Tol, R' = H), yellow oil, eluent: 2:3 EtOAc/hexane; **IR**: 3689-3399 (broad), 3399-3126 (broad). ^1H : 8.05 (d, 1H, $J = 7.7$), 7.78-7.72 (m, 3H), 7.51-7.41 (m, 2H), 7.38 (d, 1H, $J = 8.4$), 7.15 (d, 1H, $J = 8.4$), 5.79 (br s, 1H), 4.93 (br s, 1H), 2.94 (app q, 2H, $J = 11.5, 5.8$), 2.84 (t, 2H, $J = 7.3$), 2.39 (s, 3H), 1.87 (p, 2H, $J = 6.8$). ^{13}C : 148.4, 143.6, 136.4, 133.4, 129.7, 128.0, 127.8, 127.1, 125.6, 125.5, 124.6, 120.7(2C), 120.5, 42.2, 29.7, 26.2, 21.5. **HRMS**: calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 356.1320; found: 356.1324.

B.16.3 Characterization of *N*-(3-(1-Hydroxynaphthalen-2-yl)propyl)-4-nitrobenzenesulfonamide (3.74; R = $\text{C}_6\text{H}_4\text{-NO}_2\text{-p}$, R' = H)



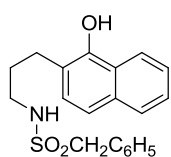
236 mg (94% yield) from 325 mg of **3.73** (R = $\text{C}_6\text{H}_4\text{-NO}_2\text{-p}$, R' = H), green solid, m.p.: 133-135 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3464, 3232, 1540, 1347. ^1H : 8.25 (d, 2H, $J = 8.6$), 7.98-7.93 (m, 3H), 7.80 (d, 1H, $J = 8.6$), 7.55-7.45 (m, 2H), 7.41 (d, 1H, $J = 8.6$), 7.16 (d, 1H, $J = 8.5$), 5.03 (br s, 1H), 3.00 (app t, 2H, $J = 6.2$), 2.87 (t, 2H, $J = 7.1$), 1.91 (p, 2H, $J = 6.8$). ^{13}C : 149.9, 147.9, 145.6, 133.4, 128.2, 128.0, 127.9, 125.8, 124.4 (2C), 124.3, 121.2, 120.7, 120.0, 42.2, 29.6, 26.0. **HRMS**: calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_5\text{S}$ $[\text{M}-\text{H}]^-$: 385.0858; found: 385.0847.

B.16.4 Characterization of *N*-(3-(1-Hydroxynaphthalen-2-yl)propyl)-4-methoxybenzenesulfonamide (3.74; R = C₆H₄-OMe-*p*, R' = H)



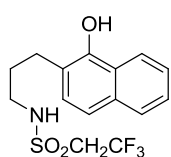
241 mg (92% yield) from 343 mg of **3.73** (R = C₆H₄-OMe-*p*, R' = H), yellow solid, m.p.: 145-147 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3672-3420 (broad), 3420-3189 (broad), 1261, 1094. **¹H**: 8.08 (d, 1H, *J* = 8.3), 7.83-7.56 (m, 3H), 7.51-7.40 (m, 2H), 7.38 (d, 1H, *J* = 8.4), 7.16 (d, 1H, *J* = 8.4), 6.92 (d, 2H, *J* = 9.0), 5.86 (br s, 1H), 4.95 (br s, 1H), 3.83 (s, 3H), 2.95-2.91 (m, 2H), 2.85 (t, 2H, *J* = 7.3), 1.88 (p, 2H, *J* = 6.8). **¹³C**: 162.9, 148.4, 133.4, 130.8, 129.3, 128.1, 127.8, 125.6, 125.5, 124.6, 120.7 (2C), 120.5, 114.3, 55.6, 42.1, 29.7, 26.2. **HRMS**: calcd for C₂₀H₂₁NO₄SNa [M+Na]⁺: 394.1089; found: 394.1097.

B.16.5 Characterization of *N*-(3-(1-Hydroxynaphthalen-2-yl)propyl)-1-phenylmethanesulfonamide (3.74; R = Bn, R' = H)



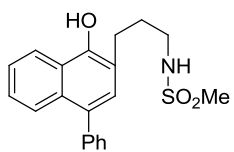
186 mg (91% yield) from 270 mg of **3.73** (R = Bn, R' = H), yellow solid, m.p.: 122-124 °C; eluting solvent: 2:3 hexane/EtOAc; **IR**: 3668-3420 (broad), 3420-3189 (broad). **¹H**: 8.03 (d, 1H, *J* = 8.0), 7.79 (d, 1H, *J* = 8.2), 7.53-7.45 (m, 2H), 7.41 (d, 1H, *J* = 8.4), 7.35-7.31 (m, 5H), 7.18 (d, 1H, *J* = 8.4), 4.57 (br s, 1H), 4.25 (s, 2H), 2.98 (q, 2H, *J* = 12.1, 6.1), 2.82 (t, 2H, *J* = 7.1), 1.86 (p, 2H, *J* = 6.8). **¹³C**: 148.3, 133.4, 130.6, 129.2, 128.9, 128.8, 128.1, 127.9, 125.6, 125.5, 124.6, 120.9, 120.7, 120.5, 58.7, 42.6, 30.7, 26.1. **HRMS**: calcd for C₂₀H₂₁NO₃SNa [M+Na]⁺: 378.1140; found: 378.1144.

B.16.6 Characterization of 2,2,2-trifluoro-*N*-(3-(1-hydroxynaphthalen-2-yl)propyl)ethanesulfonamide (3.74; R = CH₂CF₃, R' = H)



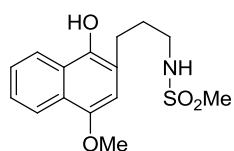
163 mg (78% yield) from 278 mg of **3.73** (R = CH₂CF₃, R' = H), light yellow solid, m.p.: 100-102 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3567, 3249, 1245, 1167. **¹H**: 7.98 (d, 1H, *J* = 8.1), 7.82 (d, 1H, *J* = 7.6), 7.55-7.44 (m, 3H), 7.24 (d, 1H, *J* = 8.4), 5.47 (br s, 1H), 5.13 (br s, 1H), 3.79 (q, 2H, *J* = 9.0), 3.19 (q, 2H, *J* = 6.3), 2.93 (t, 2H, *J* = 7.1), 1.99 (p, 2H, *J* = 6.8). **¹³C**: 148.2, 133.6, 128.2 (2C), 125.9 (2C), 124.5, 121.7 (q, *J* = 277.8), 121.4, 120.9, 120.1, 54.4 (q, *J* = 31.7), 42.6, 30.6, 26.2. **HRMS**: calcd for C₁₅H₁₆F₃NO₃SNa [M+Na]⁺: 370.0701; found: 370.0705.

B.16.7 Characterization of *N*-(3-(1-hydroxy-4-phenylnaphthalen-2-yl)propyl)methanesulfonamide (3.74; R = Me, R' = Ph)



0.81 g (71% yield) from 1.50 g of **3.73** (R = Me, R' = Ph), white solid, dec. 165 °C, eluent: 2:3 EtOAc/hexane; **IR**: 3477, 3283. **¹H** (acetone-*d*₆): 8.34 (d, 1H, *J* = 8.3), 8.19 (br s, 1H), 7.81 (d, 1H, *J* = 8.6), 7.53-7.38 (m, 7H), 7.28 (s, 1H), 6.01 (br s, 1H), 3.25-3.19 (m, 2H), 2.99 (app t, 2H, *J* = 7.7), 2.90 (s, 3H), 2.09-1.98 (m, 2H). **¹³C**: 149.0, 140.9, 132.2, 131.3, 130.1, 129.7, 128.2, 126.8, 125.7, 125.4 (2C), 124.8, 122.0, 121.3, 42.8, 38.8, 30.6, 27.0. **HRMS**: calcd for C₂₀H₂₁NO₃SNa [M+Na]⁺: 378.1140; found: 378.1141.

B.16.8 Characterization of *N*-(3-(1-hydroxy-4-methoxynaphthalen-2-yl)propyl)methanesulfonamide (3.74; R = Me, R' = OMe)



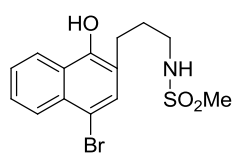
522 mg (83% yield) from 862 mg of **3.73** (R = Me, R' = OMe), yellow solid, m.p.: 112-114 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3626-3378 (broad), 3378-

3126 (broad). ^1H : 8.21 (d, 1H, $J = 8.2$), 8.00 (d, 1H, $J = 8.2$), 7.55-7.44 (m, 2H), 6.56 (s, 1H), 5.29 (s, 1H), 4.86 (br s, 1H), 3.96 (s, 3H), 3.13 (q, 2H, $J = 12.6, 6.3$), 2.98-2.89 (m, 5H), 1.99 (p, 2H, $J = 6.7$). ^{13}C : 150.1, 141.7, 126.3, 125.9, 125.1, 125.0, 122.2, 120.9, 120.5, 105.7, 55.8, 42.0, 40.0, 30.3, 26.5. **HRMS**: calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 332.0932; found: 332.0926.

B.17 General procedure for *para*-bromination of naphtholic sulfonamides

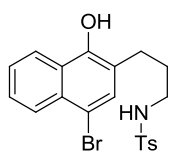
These substances were prepared by the same procedure detailed above for the synthesis of compound **3.12**.

B.17.1 Characterization of *N*-(3-(4-bromo-1-hydroxynaphthalen-2-yl)propyl)methanesulfonamide (**3.76**, **R = Me**)



0.22 g (57% yield) from 0.3 g of **3.74** (**R = Me**, **R' = H**), white solid, m.p.: 101-103 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3463, 3287, 1075. ^1H : 8.15-8.11 (m, 2H), 7.59-7.50 (m, 3H), 6.14 (br s, 1H), 4.85 (t, 1H, $J = 1.1$), 3.17 (q, 2H, $J = 12.5, 6.2$), 2.99 (s, 3H), 2.88 (t, 2H, $J = 7.3$), 1.97 (p, 2H, $J = 6.8$). ^{13}C : 148.5, 131.5, 131.4, 127.1 (2C), 126.3, 126.2, 121.7, 121.5, 113.7, 42.1, 40.1, 30.3, 25.9. **HRMS**: calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_3\text{S}^{79}\text{BrNa}$ $[\text{M}+\text{Na}]^+$: 379.9932; found: 379.9924.

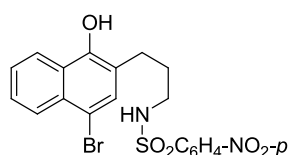
B.17.2 Characterization of *N*-(3-(4-bromo-1-hydroxynaphthalen-2-yl)propyl)-4-methylbenzenesulfonamide (**3.76**, **R = 4-Tol**)



0.14 g (39% yield) from 0.3 g of **3.74** (**R = 4-Tol**, **R' = H**), yellow solid, dec. 110 °C, eluent: 1:5 EtOAc/hexane; **IR**: 3657-3129 (broad). ^1H : 8.13 (t, 2H, $J = 7.3$), 7.75 (t, 2H, $J = 8.1$), 7.59-7.50 (m, 2H), 7.45 (s, 1H), 7.29-7.26 (m, 2H), 6.14 (s,

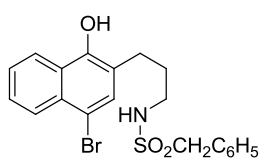
1H), 5.03 (br s, 1H), 2.95 (q, 2H, $J = 12.2, 6.0$), 2.83 (t, 2H, $J = 7.4$), 2.40 (s, 3H), 1.87 (p, 2H, $J = 6.7$). ^{13}C : 148.5, 143.8, 136.0, 131.4 (2C), 129.8, 127.2, 127.0 (2C), 126.2, 121.7, 121.6, 113.5, 42.1, 29.6, 25.9, 21.5. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_3\text{S}^{79}\text{Br}$ $[\text{M}-\text{H}]^-$: 432.0269; found: 432.0258.

B.17.3 Characterization of *N*-(3-(4-bromo-1-hydroxynaphthalen-2-yl)propyl)-4-nitrobenzenesulfonamide (**3.76**, $\text{R} = \text{C}_6\text{H}_4\text{-NO}_2\text{-}p$)



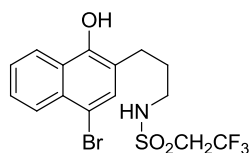
0.11 g (88% yield) from 0.98 g of **3.74** ($\text{R} = \text{C}_6\text{H}_4\text{-NO}_2\text{-}p$, $\text{R}' = \text{H}$), yellow solid, dec. 98 °C, eluent: 1:3 EtOAc/hexane; **IR**: 3604-3393 (broad), 3287-3161 (broad). ^1H (acetone- d_6): 8.40 (d, 2H, $J = 8.6$), 8.27 (d, 1H, $J = 8.1$), 8.10 (d, 2H, $J = 8.6$), 8.06 (d, 1H, $J = 8.3$), 7.61-7.52 (m, 3H), 3.10 (t, 2H, $J = 7.0$), 2.87 (t, 2H, $J = 7.5$), 1.88 (p, 2H, $J = 7.4$). ^{13}C (acetone- d_6): 150.0, 149.5, 146.6, 131.9, 131.2, 128.3, 126.9, 126.8, 126.4, 125.9, 124.4, 122.9, 122.3, 111.8, 42.7, 29.9, 26.6. **HRMS**: calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_5\text{S}^{79}\text{Br}$ $[\text{M}-\text{H}]^-$: 462.9963; found: 462.9950.

B.17.4 Characterization of *N*-(3-(4-bromo-1-hydroxynaphthalen-2-yl)propyl)-1-phenylmethanesulfonamide (**3.76**, $\text{R} = \text{Me}$)



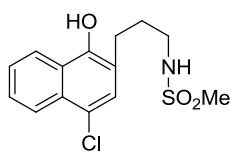
0.13 g (86% yield) from 0.12 g of **3.74** ($\text{R} = \text{Bn}$, $\text{R}' = \text{H}$), yellow solid, dec. 129 °C, eluent: 1:4 EtOAc/hexane; **IR**: 3653-3157 (broad). ^1H : 8.13 (app t, 2H, $J = 7.5$), 7.60-7.50 (m, 2H), 7.48 (s, 1H), 7.39-7.29 (m, 5H), 6.04 (s, 1H), 4.71 (t, 1H, $J = 6.0$), 4.26 (s, 2H), 2.97 (q, 2H, $J = 12.4, 6.2$), 2.78 (t, 2H, $J = 7.2$), 1.83 (p, 2H, $J = 6.8$). ^{13}C : 148.4, 131.4, 130.6, 129.0, 128.9, 127.1, 127.0, 126.2 (2C), 121.7, 121.6, 113.6, 58.7, 42.6, 30.6, 25.8. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_3\text{S}^{79}\text{Br}$ $[\text{M}-\text{H}]^-$: 432.0269; found: 432.0269.

B.17.5 Characterization of N-(3-(4-bromo-1-hydroxynaphthalen-2-yl)propyl)-2,2,2-trifluoroethanesulfonamide (3.76, R = Me)



0.05 g (86% yield) from 0.05 g of **3.74** (R = CH₂CF₃, R' = H), yellow solid, m.p.: 122-124 °C, eluent: 1:5 EtOAc/hexane; **IR**: 3629-3143 (broad). **¹H** (acetone-*d*₆): 8.45 (br s, 1H), 8.32 (d, 1H, *J* = 8.2), 8.10 (d, 1H, *J* = 8.0), 7.69 (s, 1H), 7.64-7.54 (m, 2H), 6.80 (br s, 1H), 4.23 (q, 2H, *J* = 9.7), 3.36-3.26 (m, 2H), 2.99-2.94 (m, 2H), 2.03-1.96 (m, 2H). **¹³C** (acetone-*d*₆): 149.6, 132.0, 131.3, 126.9 (2C), 126.4, 125.8, 123.1, 122.6 (q, *J* = 276.3), 122.3, 111.8, 53.0 (q, *J* = 31.0), 42.8, 30.5, 26.7. **HRMS**: calcd for C₁₅H₁₄NO₃F₃S⁷⁹Br [M-H]⁻: 423.9830; found: 423.9824.

B.18 Preparation of N-(3-(4-chloro-1-hydroxynaphthalen-2-yl)propyl)methanesulfonamide (3.77, R = Me)



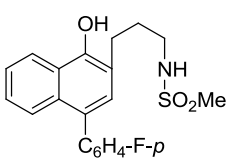
The procedure described above for **3.11** produced 365 mg (65% yield) of **3.77**, R = Me from 500 mg of **3.74** (R = CH₂CF₃, R' = H) as off yellow solid, m.p.: 114-117 °C (color changes to brown), eluent: 1:3 to 2:3 EtOAc/hexanes; **IR**: 3615-3393 (broad), 3382-3136 (broad). **¹H** (acetone *d*₆): 8.32 (d, 1H, *J* = 6.0), 8.12 (d, 1H, *J* = 6.0), 7.63-7.54 (m, 2H), 7.49 (s, 1H), 6.03 (br s, 1H), 3.77 (s, 1H), 3.20 (q, 2H, *J* = 12.0, 6.0), 2.97-2.86 (m, 2H), 1.96 (p, 2H, *J* = 6.0). **¹³C**: 148.7, 129.9, 128.3, 126.5 (2C), 125.7, 123.6, 122.4, 122.2, 121.6, 42.5, 38.7, 30.3, 26.6. **HRMS**: calcd for C₁₄H₁₆NO₃SClNa [M+Na]⁺: 336.0437; found: 336.0439.

B.19 General procedure for Suzuki coupling of 3.76 and aryl boronic acid

A solution of **3.76**, R = Me (500 mg, 1.4 mmol, 1.0 equiv), Pd(PPh₃)₄ (81 mg, 50 μmol, 0.05 equiv), boronic acid (1.7 mmol, 1.2 equiv), and Cs₂CO₃ (547 mg, 1.7 mmol, 1.2 equiv) in 1,4-dioxane (4.0 mL) and water (1.0 mL) was stirred at 80 °C for 6 h, after which time TLC

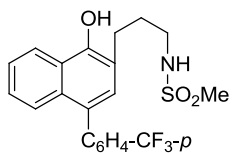
showed that the reaction was complete. The cooled mixture was diluted with EtOAc (10.0 mL) and filtered through a Celite[®] pad, which was washed with more EtOAc (3×10 mL). The combined filtrate was dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography to provide **3.78**.

B.19.1 Characterization of *N*-(3-(4-(4-fluorophenyl)-1-hydroxynaphthalen-2-yl)propyl)methanesulfonamide (3.78**, Ar = C₆H₄-F-*p*)**



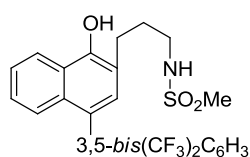
420 mg (80% yield) from 500 mg of **3.76**, R = Me, off white solid, dec. 160 °C (color changes to brown), eluent: 1:4 to 2:3 EtOAc/hexanes; **IR**: 3636-3129 (broad). **¹H**: 8.34 (d, 1H, *J* = 9.0), 7.76 (d, 1H, *J* = 9.0), 7.51-7.39 (m, 4H), 7.27-7.22 (m, 3H), 6.03 (br s, 1H), 3.19 (t, 2H, *J* = 6.0), 2.99-2.94 (m, 2H), 2.91 (s, 3H), 1.98 (p, 2H, *J* = 9.0). **¹³C**: 162.8 (d, *J* = 243.9), 150.0, 138.0 (d, *J* = 3.8), 132.7 (d, *J* = 8.3), 132.1, 131.8, 130.7, 126.6, 126.4, 126.0, 125.8, 122.9, 122.2, 117.7, 115.8 (d, *J* = 21.9), 43.6, 39.7, 31.4, 27.8. **HRMS**: calcd for C₂₀H₁₉NO₃FS [M-H]⁻: 372.1070; found: 372.1078.

B.19.2 Characterization of *N*-(3-(1-hydroxy-4-(4-(trifluoromethyl)phenyl)naphthalen-2-yl)propyl)methanesulfonamide (3.78**, Ar = C₆H₄-CF₃-*p*)**



298 mg (50% yield) from 500 mg of **3.76**, R = Me, off white solid, m.p.: 129-132 °C, eluent: 1:4 to 3:7 EtOAc/hexanes; **IR**: 3599-3388 (broad), 3360-3184 (broad). **¹H**: 8.20 (d, 1H, *J* = 6.0), 7.79 (d, 1H, *J* = 9.0), 7.73 (d, 2H, *J* = 6.0), 7.59-7.41 (m, 4H), 7.18 (s, 1H), 6.17 (s, 1H), 4.92 (t, 1H, *J* = 6.0), 3.21 (q, 2H, *J* = 12.0, 6.0), 3.00 (s, 3H), 2.95 (t, 2H, *J* = 7.5), 2.01 (p, 2H, *J* = 6.0). **¹³C**: 148.8, 144.5, 132.0, 131.2, 130.6, 129.5, 129.3 (q, *J* = 32.5), 126.4, 125.9, 125.7, 125.4 (q, *J* = 3.8), 125.1, 124.5 (q, *J* = 271.8), 121.4, 120.3, 42.4, 40.3, 30.5, 26.4. **HRMS**: calcd for C₂₁H₁₉NO₃F₃S [M-H]⁻: 422.1038; found: 422.1044.

B.19.3 Characterization of *N*-(3-(4-(3,5-bis(trifluoromethyl)phenyl)-1-hydroxynaphthalen-2-yl)propyl)methanesulfonamide (**3.78**, Ar = 3,5-bis(CF₃)₂C₆H₃)



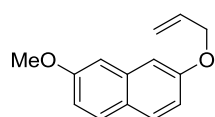
625 mg (91% yield) from 500 mg of **3.76**, R = Me, off white solid, m.p.: 153-155 °C, eluent: 1:3 to 1:2 EtOAc/hexanes. **IR**: 3550-3377 (broad), 3307-3148 (broad). **¹H**: 8.24 (d, 1H, *J* = 9.0), 7.92 (app s, 3H), 7.67 (d, 1H, *J* = 9.0), 7.57-7.45 (m, 2H), 7.20 (s, 1H), 6.35 (s, 1H), 4.96 (t, 1H, *J* = 6.0), 3.23 (q, 2H, *J* = 6.0), 3.03 (s, 3H), 2.97 (t, 1H, *J* = 7.5), 2.03 (p, 2H, *J* = 6.0). **¹³C**: 149.5, 142.9, 131.8 (q, *J* = 33.2), 131.0, 130.4 (app d, *J* = 3.0), 130.1, 129.9, 126.9, 126.1, 125.2, 124.9, 123.6 (q, *J* = 273.3), 121.8, 121.1-120.9 (m), 120.3, 42.4, 40.2, 30.6, 26.3. **HRMS**: calcd for C₂₂H₁₈NO₃F₆S [M-H]⁻: 490.0912; found: 490.0918.

B.20 Preparation and characterization of various intermediates towards 2-naphtholic sulfonamides **3.87**

B.20.1 General procedure for *O*-allylation of 2-naphthols

These substances were prepared by the same procedure described above for the synthesis of compound **3.8** and used in the subsequent step without purification. Compound **3.80**, R = H is known.^[15]

B.20.1.1 Characterization of 2-(Allyloxy)-7-methoxynaphthalene (**3.80**, R = OMe)

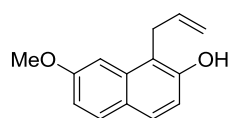


3.65 g (99% crude yield) from 3.00 g of **3.79**, R = OMe, yellow oil; **IR**: 1210, 1031. **¹H**: 7.67 (app dd, 2H, *J* = 8.7, 2.2), 7.13-6.99 (m, 4H), 6.20-6.08 (m, 1H), 5.48 (dd, 1H, *J* = 17.3, 1.5), 5.34 (dd, 1H, *J* = 10.5, 1.3), 4.67-4.65 (m, 2H), 3.92 (s, 3H). **¹³C**: 158.2, 157.1, 135.8, 133.2, 129.2, 129.1, 124.3, 117.8, 116.3, 116.1, 106.5, 105.2, 68.8, 55.3.

B.20.2 General procedure for Claisen rearrangement of 3.80

These substances were prepared by the same procedure described above for the synthesis of compound 3.9 and used in the subsequent step without purification. Compound 3.81, R = H is known.^[15]

B.20.2.1 Characterization of 1-allyl-7-methoxynaphthalen-2-ol (3.81, R = OMe)

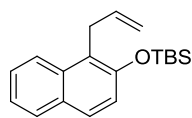


3.61 g (99% crude yield) from 3.65 g of 3.80, R = OMe, light brown oil; **IR**: 3626-3126 (broad). **¹H**: 7.68 (d, 1H, *J* = 8.9), 7.60 (d, 1H, *J* = 8.7), 7.19 (d, 1H, *J* = 2.3), 7.02 (dd, 1H, *J* = 8.9, 2.4), 6.96 (d, 1H, *J* = 8.7), 6.14-6.01 (m, 1H), 5.14-5.07 (m, 2H), 3.93 (s, 3H), 3.81-3.78 (m, 2H). **¹³C**: 158.3, 151.7, 135.7, 134.6, 130.1, 128.0, 124.8, 115.9, 115.8, 115.4, 115.3, 102.3, 55.2, 29.5. **HRMS**: calcd for C₁₄H₁₃O₂ [M-H]⁻: 213.0916; found: 213.0914.

B.20.3 General procedure for protection of 2-naphthols 3.81 as TBS ether

These substances were prepared by the same method detailed above in title B.14.1.

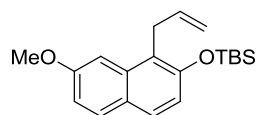
B.20.3.1 Characterization of 1-Allyl-2-(*tert*-butyldimethylsilyloxy)naphthalene (3.82, R = H)



4.04 g (89% yield) from 4.54 g of 3.81, R = H, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 1244, 987. **¹H**: 7.93 (d, 1H, *J* = 8.4), 7.79 (d, 1H, *J* = 8.0), 7.65 (d, 1H, *J* = 8.9), 7.47 (ddd, 1H, *J* = 8.4, 6.8, 1.4), 7.35 (ddd, 1H, *J* = 8.0, 6.9, 1.1), 7.12 (d, 1H, *J* = 8.9), 6.10-5.97 (m, 1H), 5.05-4.94 (m, 2H), 3.86 (app dt, 2H, *J* = 5.7, 1.7), 1.08 (s, 9H), 0.29 (s, 6H). **¹³C**: 150.7, 136.7, 133.6, 129.5, 128.3, 127.6, 126.0, 123.8, 123.3, 122.6, 120.4, 115.1, 29.6, 25.9, 18.3, -3.9.

B.20.3.2 Characterization of 1-Allyl-2-(*tert*-butyldimethylsilyloxy)-7-methoxynaphthalene

(**3.82**, R = OMe)



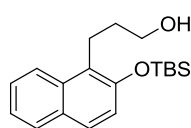
5.67 g (88% yield) from 4.16 g of **3.81**, R = OMe, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 1237, 889. **¹H**: 7.67 (d, 1H, *J* = 8.9), 7.56 (d, 1H, *J* = 8.8), 7.20 (d, 1H, *J* = 2.4), 7.01 (dd, 1H, *J* = 8.9, 2.5), 6.96 (d, 1H, *J* = 8.8), 6.06-5.93 (m, 1H), 5.06-4.98 (m, 2H), 3.91 (s, 3H), 3.81 (app dt, 2H, *J* = 5.8, 1.7), 1.06 (s, 9H), 0.27 (s, 6H). **¹³C**: 157.9, 151.3, 136.5, 134.9, 129.8, 127.3, 124.9, 121.5, 117.9, 115.6, 115.1, 102.8, 55.2, 30.0, 25.9, 18.3, -3.9. **HRMS**: calcd for C₂₀H₂₉O₂Si [M+H]⁺: 329.1937; found: 329.1934.

B.20.4 General procedure for hydroboration-oxidation of terminal alkenes

These substances were prepared by the same procedure detailed above for the synthesis of compound **3.10**.

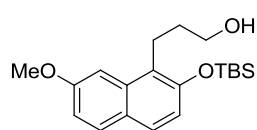
B.20.4.1 Characterization of 3-(2-(*tert*-Butyldimethylsilyloxy)naphthalen-1-yl)propan-1-ol

(**3.83**, R = H)



3.91 g (82% yield) from 4.77 g of **3.82**, R = H, colorless oil, eluent: 3:7 EtOAc/hexane; **IR**: 3668-3084 (broad), 1244. **¹H**: 7.98 (d, 1H, *J* = 8.5), 7.79 (d, 1H, *J* = 8.0), 7.63 (d, 1H, *J* = 8.9), 7.49 (t, 1H, *J* = 7.8), 7.36 (t, 1H, *J* = 7.0), 7.10 (d, 1H, *J* = 8.9), 3.60 (q, 2H, *J* = 11.5, 5.7), 3.20 (t, 2H, *J* = 7.2), 1.98-1.92 (m, 3H), 1.07 (s, 9H), 0.29 (s, 6H). **¹³C**: 150.5, 133.3, 129.8, 128.5, 127.3, 126.2, 124.5, 123.4 (2C), 120.5, 62.1, 32.4, 25.9, 21.4, 18.4, -3.9. **HRMS**: calcd for C₁₉H₂₈O₂SiNa [M+Na]⁺: 339.1756; found: 339.1750.

B.20.4.2 Characterization of 3-(2-(*tert*-butyldimethylsilyloxy)-7-methoxynaphthalen-1-yl)propan-1-ol (**3.83**, R = OMe)

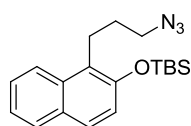


3.61 g (76% yield) from 4.50 g of **3.82**, R = OMe, colorless oil, eluent: 1:3 EtOAc/hexane; **IR**: 3626-3126 (broad), 1230. **¹H**: 7.68 (d, 1H, *J* = 8.9), 7.55 (d, 1H, *J* = 8.8), 7.27 (s, 1H), 7.03 (dd, 1H, *J* = 8.9, 2.5), 6.95 (d, 1H, *J* = 8.8), 3.94 (s, 3H), 3.60 (t, 2H, *J* = 6.1), 3.16 (t, 2H, *J* = 7.2), 1.95 (p, 2H, *J* = 6.7), 1.06 (s, 9H), 0.28 (s, 6H). **¹³C**: 158.1, 151.2, 134.5, 130.0, 127.1, 125.1, 123.4, 117.9, 115.6, 102.5, 62.0, 55.3, 31.8, 25.9, 21.5, 18.4, -3.9. **HRMS**: calcd for C₂₀H₃₁O₃Si [M+H]⁺: 347.2042; found: 347.2044.

B.20.5 General procedure for azidation of 2-naphtholic primary alcohol

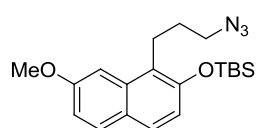
These substances were prepared by the same method detailed above in title B.14.3.

B.20.5.1 Characterization of 1-(3-azidopropyl)-2-(*tert*-butyldimethylsilyloxy)naphthalene (**3.84**, R = H)



1.79 g (89% yield) from 1.87 g of **3.83**, R = H, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 2095. **¹H**: 7.94 (d, 1H, *J* = 8.6), 7.79 (d, 1H, *J* = 8.1), 7.64 (d, 1H, *J* = 8.9), 7.50 (app td, 1H, *J* = 6.9, 1.3), 7.35 (app td, 1H, *J* = 7.0, 1.0), 7.10 (d, 1H, *J* = 8.9), 3.38 (t, 2H, *J* = 6.9), 3.18-3.13 (m, 2H), 1.94 (p, 2H, *J* = 7.3), 1.08 (s, 9H), 0.29 (s, 6H). **¹³C**: 150.7, 133.2, 129.5, 128.5, 127.5, 126.3, 124.1, 123.3, 123.0, 120.3, 51.5, 29.1, 25.8, 22.7, 18.3, -3.9.

B.20.5.2 Characterization of 1-(3-azidopropyl)-2-(*tert*-butyldimethylsilyloxy)-7-methoxynaphthalene (**3.84**, R = OMe)



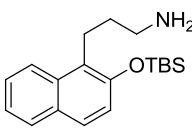
2.82 g (86% yield) from 3.05 g of **3.83**, R = OMe, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 2096. **¹H**: 7.68 (d, 1H, *J* = 8.9), 7.55 (d, 1H, *J* =

8.8), 7.23 (d, 1H, $J = 2.3$), 7.02 (dd, 1H, $J = 8.9, 2.4$), 6.94 (d, 1H, $J = 8.8$), 3.95 (s, 3H), 3.38 (t, 2H, $J = 6.7$), 3.10 (t, 2H, $J = 7.8$), 1.94 (p, 2H, $J = 7.2$), 1.06 (s, 9H), 0.28 (s, 6H). ^{13}C : 158.2, 151.3, 134.6, 130.1, 127.2, 124.8, 123.0, 117.7, 115.6, 102.0, 55.3, 51.4, 28.6, 25.8, 22.8, 18.3, -3.9. **HRMS**: calcd for $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 394.1927; found: 394.1931.

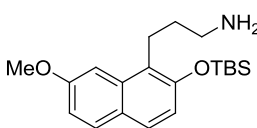
B.20.6 General procedure for synthesis of amine from azide

These substances were prepared by the same method detailed above in title B.14.4.

B.20.6.1 Characterization of 3-(2-(*tert*-Butyldimethylsilyloxy)naphthalen-1-yl)propan-1-amine (3.85, R = H)

 1.09 g (91% crude yield) from 1.30 g of **3.84**, R = H, light brown oil; **IR**: 3378, 3294. ^1H : 7.95 (d, 1H, $J = 8.5$), 7.78 (d, 1H, $J = 8.1$), 7.61 (d, 1H, $J = 8.8$), 7.47 (td, 1H, $J = 7.8, 1.3$), 7.32-7.27 (m, 1H), 7.08 (d, 1H, $J = 8.9$), 3.10 (t, 2H, $J = 7.6$), 2.80 (t, 2H, $J = 7.0$), 1.80 (p, 2H, $J = 7.4$), 1.07 (s, 9H), 0.28 (s, 6H). ^{13}C : 150.4, 133.3, 129.5, 128.5, 127.1, 126.0, 125.2, 123.3, 123.2, 120.4, 42.4, 34.1, 25.9, 22.9, 18.3, -3.9.

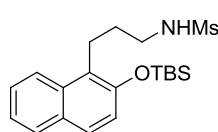
B.20.6.2 Characterization of 3-(2-(*tert*-Butyldimethylsilyloxy)-7-methoxynaphthalen-1-yl)propan-1-amine (3.85, R = OMe)

 1.24 g (89% crude yield) from 1.50 g of **3.84**, R = OMe, light brown oil; **IR**: 3368, 3302. ^1H : 7.65 (d, 1H, $J = 8.9$), 7.52 (d, 1H, $J = 8.8$), 7.15 (d, 1H, $J = 2.3$), 6.99 (dd, 1H, $J = 8.9, 2.3$), 6.91 (d, 1H, $J = 8.8$), 5.47 (br s, 2H), 3.89 (s, 3H), 3.07 (t, 2H, $J = 7.4$), 2.90 (t, 2H, $J = 7.7$), 1.99 (p, 2H, $J = 7.5$), 1.02 (s, 9H), 0.26 (s, 6H). ^{13}C : 158.2, 151.2, 134.4, 130.0, 127.3, 124.9, 122.6, 117.7, 115.6, 102.3, 55.4, 40.6, 29.6, 25.9, 22.6, 18.3, -3.8.

B.20.7 General procedure for coupling of amine with methanesulfonyl chloride

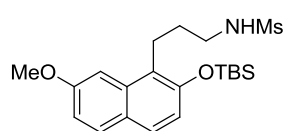
These substances were prepared by the same method detailed above in title B.15.

B.20.7.1 Characterization of *N*-(3-(2-(*tert*-Butyldimethylsilyloxy)naphthalen-1-yl)propyl)methanesulfonamide (3.86, R = H)



1.48 g (91% yield) from 1.30 g of **3.85**, R = H, colorless oil; eluent: 1:3 EtOAc/hexane; **IR**: 3420-3168 (weak, broad). **¹H**: 7.91 (d, 1H, *J* = 8.5), 7.80 (d, 1H, *J* = 8.1), 7.64 (d, 1H, *J* = 8.9), 7.50 (app td, 1H, *J* = 7.6, 1.3), 7.37 (app td, 1H, *J* = 7.0, 0.9), 7.10 (d, 1H, *J* = 8.9), 4.62 (t, 1H, *J* = 5.8), 3.18 (t, 2H, *J* = 7.2), 3.10 (q, 2H, *J* = 13.2, 6.6), 2.84 (s, 3H), 1.98 (p, 2H, *J* = 7.1), 1.07 (s, 9H), 0.29 (s, 6H). **¹³C**: 150.6, 133.0, 129.7, 128.7, 127.7, 126.4, 123.6 (2C), 123.1, 120.5, 42.7, 40.2, 29.7, 25.9, 22.2, 18.4, -3.9. **HRMS**: calcd for C₂₀H₃₁NO₃SSiNa [M+Na]⁺: 416.1692; found: 416.1692.

B.20.7.2 Characterization of *N*-(3-(2-(*tert*-butyldimethylsilyloxy)-7-methoxynaphthalen-1-yl)propyl)methanesulfonamide (3.86, R = OMe)



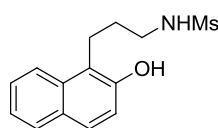
2.41 g (83% yield) from 2.37 g of **3.85**, R = OMe, colorless oil; eluent: 1:3 EtOAc/hexane; **IR**: 3100-3400 (weak, broad). **¹H**: 7.69 (d, 1H, *J* = 8.9), 7.56 (d, 1H, *J* = 8.8), 7.18 (d, 1H, *J* = 2.3), 7.04 (dd, 1H, *J* = 8.9, 2.4), 6.95 (d, 1H, *J* = 8.8), 4.65 (br s, 1H), 3.95 (s, 3H), 3.16-3.07 (m, 4H), 2.83 (s, 3H), 1.98 (p, 2H, *J* = 6.9), 1.06 (s, 9H), 0.29 (s, 6H). **¹³C**: 158.2, 151.2, 134.3, 130.2, 127.5, 125.1, 122.5, 118.0, 115.7, 102.3, 55.4, 42.7, 40.1, 29.2, 25.9, 22.3, 18.4, -3.9.

B.20.8 General procedure for deprotection of TBS ether using TBAF

These substances were prepared by the same method detailed above in title B.16.

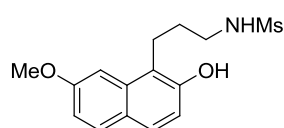
B.20.8.1 Characterization of *N*-(3-(2-Hydroxynaphthalen-1-yl)propyl)methanesulfonamide

(**3.87**, **R = H**)



451 mg (78% yield) from 815 mg of **3.86**, **R = H**, white solid, m.p.: 89-91 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3680-3100 (broad), 3256. **¹H**: 7.89 (d, 1H, *J* = 8.5), 7.79 (d, 1H, *J* = 8.0), 7.65 (d, 1H, *J* = 8.8), 7.50 (t, 1H, *J* = 8.0), 7.35 (t, 1H, *J* = 7.8), 7.10 (d, 1H, *J* = 8.8), 6.26 (br s, 1H), 5.43 (t, 1H, *J* = 6.2), 3.22 (t, 2H, *J* = 6.7), 3.10 (q, 2H, *J* = 6.4), 2.96 (s, 3H), 2.03 (p, 2H, *J* = 6.5). **¹³C**: 150.7, 133.1, 129.5, 128.8, 128.2, 126.6, 123.3, 122.7, 118.1, 117.5, 41.9, 40.2, 29.1, 20.9. **HRMS**: calcd for C₁₄H₁₇NO₃SNa [M+Na]⁺: 302.0827; found: 302.0820.

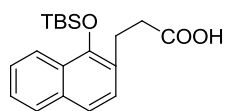
B.20.8.2 Characterization of *N*-(3-(2-Hydroxy-7-methoxynaphthalen-1-yl)propyl)methanesulfonamide (**3.87**, **R = OMe**)



404 mg (80% yield) from 691 mg of **3.86**, **R = OMe**, white solid, m.p.: 141-143 °C; eluent: 2:3 EtOAc/hexane; **IR**: 3252, 3315. **¹H**: 7.69 (d, 1H, *J* = 8.9), 7.57 (d, 1H, *J* = 8.7), 7.17 (d, 1H, *J* = 2.3), 7.03 (dd, 1H, *J* = 8.9, 2.4), 6.91 (d, 1H, *J* = 8.7), 5.64 (br s, 1H), 5.15 (br s, 1H), 3.95 (s, 3H), 3.19-3.08 (m, 4H), 2.94 (s, 3H), 2.03 (p, 2H, *J* = 6.5). **¹³C**: 158.5, 151.1, 134.4, 130.3, 128.0, 124.9, 117.2, 115.3, 114.9, 102.0, 55.3, 42.0, 40.3, 28.7, 21.0. **HRMS**: calcd for C₁₅H₁₉NO₄S [M+Na]⁺: 332.0932; found: 332.0937.

B.21 Preparation and characterization of various intermediates towards naphtholic acyl sulfonamides 3.93-3.95

B.21.1 Preparation of 3-(1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl)propanoic acid (3.89)



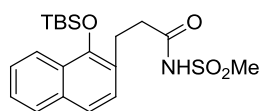
To a solution of **3.70**, R' = H (0.32 g, 1.0 mmol, 1.0 equiv) and DIB (0.71 g, 2.2 mmol, 2.2 equiv) in CH₃CN (2.5 mL) at RT was added TEMPO (31 mg, 0.2 mmol, 0.2 equiv) followed by H₂O (2.5 mL). The resulting mixture was stirred overnight at RT, after which time TLC showed that the reaction was complete. The mixture was acidified by the addition of 1M HCl and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to provide 194 mg (59% yield) of **3.89** as yellow solid, m.p.: 121-123 °C; eluent: 1:5 EtOAc/hexane; **IR**: 3350-2750 (broad), 1708. **¹H**: 8.10-8.07 (m, 1H), 7.80-7.77 (m, 1H), 7.49-7.43 (m, 3H), 7.31 (d, 1H, *J* = 8.4), 3.14 (t, 2H, *J* = 7.7), 2.71 (t, 2H, *J* = 8.2), 1.14 (s, 9H), 0.22 (s, 6H). **¹³C**: 179.3, 148.5, 133.9, 128.1, 127.9, 127.6, 125.4, 125.2, 124.9, 123.0, 121.8, 34.4, 26.1, 26.0, 18.7, -3.1. **HRMS**: calcd for C₁₉H₂₆O₃SiNa [M+Na]⁺: 353.1549; found: 353.1549.

B.21.2 General procedure for coupling of carboxylic acid 3.89 and sulfonamide

To a solution of **3.89** (500 mg, 1.5 mmol, 1.0 equiv) in CH₂Cl₂ (8 mL) was added EDCI (2.0 mmol, 1.3 equiv), DMAP (4.1 mmol, 2.7 equiv) and appropriate sulfonamide (1.8 mmol, 1.2 equiv) at 0 °C with good stirring. The reaction mixture was warmed to RT and stirred for overnight, after which time TLC showed that the reaction was complete. The reaction was quenched with 1M HCl and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were

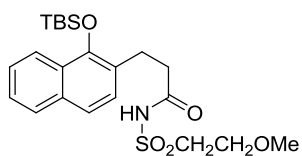
washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography on silica gel to provide corresponding products.

B.21.2.1 Characterization of 3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-2-yl)-*N*-(methylsulfonyl)propanamide (3.90)



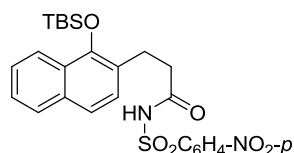
561 mg (91% yield) from 500 mg of **3.89**, yellow solid, m.p.: 99-101 °C; eluent: 1:3 EtOAc/hexane; **IR**: 3300-3150 (weak, broad), 1715. **¹H**: 8.07-8.04 (m, 1H), 7.94 (br s, 1H), 7.79-7.76 (m, 1H), 7.50-7.43 (m, 3H), 7.25 (d, 1H, *J* = 7.2), 3.14 (t, 2H, *J* = 7.4), 3.06 (s, 3H), 2.67 (t, 2H, *J* = 7.4), 1.12 (s, 9H), 0.20 (s, 6H). **¹³C**: 170.9, 148.4, 134.0, 128.0, 127.8, 127.7, 125.8, 125.3, 124.5, 122.8, 122.4, 41.2, 37.1, 26.0, 25.8, 18.7, -3.2. **HRMS**: calcd for C₂₀H₂₉NO₄SSi [M+Na]⁺: 430.1484; found: 430.1492.

B.21.2.2 Characterization of 3-(1-(*tert*-butyldimethylsilyloxy)naphthalen-2-yl)-*N*-(2-methoxyethylsulfonyl)propanamide (3.91)



207 mg (46% yield) from 330 mg of **3.89**, colorless oil, eluent: 3:4 EtOAc/hexane; **IR**: 3378-3083 (broad), 1716. **¹H**: 8.07-8.04 (m, 1H), 7.78-7.75 (m, 1H), 7.49-7.42 (m, 3H), 7.26 (d, 1H, *J* = 8.4), 3.59-3.52 (m, 4H), 3.15-3.10 (m, 5H), 2.66 (t, 1H, *J* = 7.6), 1.12 (s, 9H), 0.20 (s, 6H). **¹³C**: 170.9, 148.4, 134.0, 128.0, 127.8, 127.7, 125.7, 125.2, 124.7, 122.9, 122.3, 65.8, 58.8, 52.3, 37.1, 26.1, 25.4, 18.7, -3.2.

B.21.2.3 Characterization of 3-(1-(*tert*-Butyldimethylsilyloxy)naphthalen-2-yl)-*N*-(4-nitrophenylsulfonyl)propanamide (3.92)



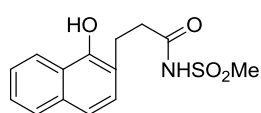
184 mg (55% yield) from 215 mg of **3.89**, yellow oil, eluent: 1:4 EtOAc/hexane; **IR**: 3250-3100 (weak, broad), 1732, 1539, 1349. **¹H**:

8.05-8.02 (m, 1H), 7.95 (d, 2H, $J = 9.0$), 7.80 (d, 2H, $J = 9.0$), 7.76-7.73 (m, 1H), 7.53-7.46 (m, 2H), 7.32 (d, 1H, $J = 8.4$), 7.07 (d, 1H, $J = 8.4$), 3.03 (t, 2H, $J = 7.0$), 2.68 (t, 2H, $J = 7.1$), 1.11 (s, 9H), 0.17 (s, 6H). ^{13}C : 169.7, 150.4, 148.0, 143.6, 134.0, 129.4, 127.9, 127.8, 127.4, 126.1, 125.5, 124.1, 123.6, 122.8, 122.6, 37.0, 26.0, 25.3, 18.7, -3.3. **HRMS**: calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_6\text{SSiNa}$ $[\text{M}+\text{Na}]^+$: 537.1498; found: 537.1498.

B.21.3 General procedure for deprotection of TBS ether of naphtholic acyl sulfonamides using TBAF

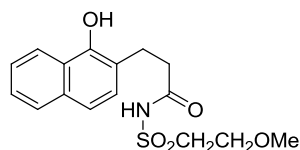
These substances were prepared by the same method detailed above in title B.16.

B.21.3.1 Characterization of 3-(1-Hydroxynaphthalen-2-yl)-*N*-(methylsulfonyl)propanamide (3.93)



135 mg (74% yield) from 254 mg of **3.90**, colorless oil; eluent: 3:7 EtOAc/hexane; **IR**: 3550-2950 (broad), 1694. ^1H : 8.25-8.22 (m, 1H), 7.77-7.74 (m, 1H), 7.49-7.42 (m, 2H), 7.39 (d, 1H, $J = 8.4$), 7.15 (d, 1H, $J = 8.4$), 3.19 (s, 3H), 3.09-3.05 (m, 2H), 2.81-2.77 (m, 2H). ^{13}C : 174.3, 149.4, 133.7, 128.0, 127.4, 126.0, 125.7, 125.4, 122.1, 120.6, 119.7, 41.5, 37.4, 23.9. **HRMS**: calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 316.0618; found: 316.0616.

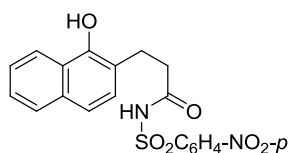
B.21.3.2 Characterization of 3-(1-hydroxynaphthalen-2-yl)-*N*-(2-methoxyethylsulfonyl)propanamide (3.94)



97 mg (76% yield) from 170 mg of **3.91**, colorless oil; eluent: 2:3 EtOAc/hexane; **IR**: 3693-3420 (broad), 3693-3420 (broad), 1696. ^1H : 8.26-8.23 (m, 1H), 7.75-7.72 (m, 1H), 7.48-7.41 (m, 2H), 7.37 (d, 1H, $J = 8.4$), 7.14 (d, 1H, $J = 8.4$), 3.62-3.53 (m, 4H), 3.07-3.03 (m, 2H), 2.97 (s, 3H), 2.80-2.76 (m,

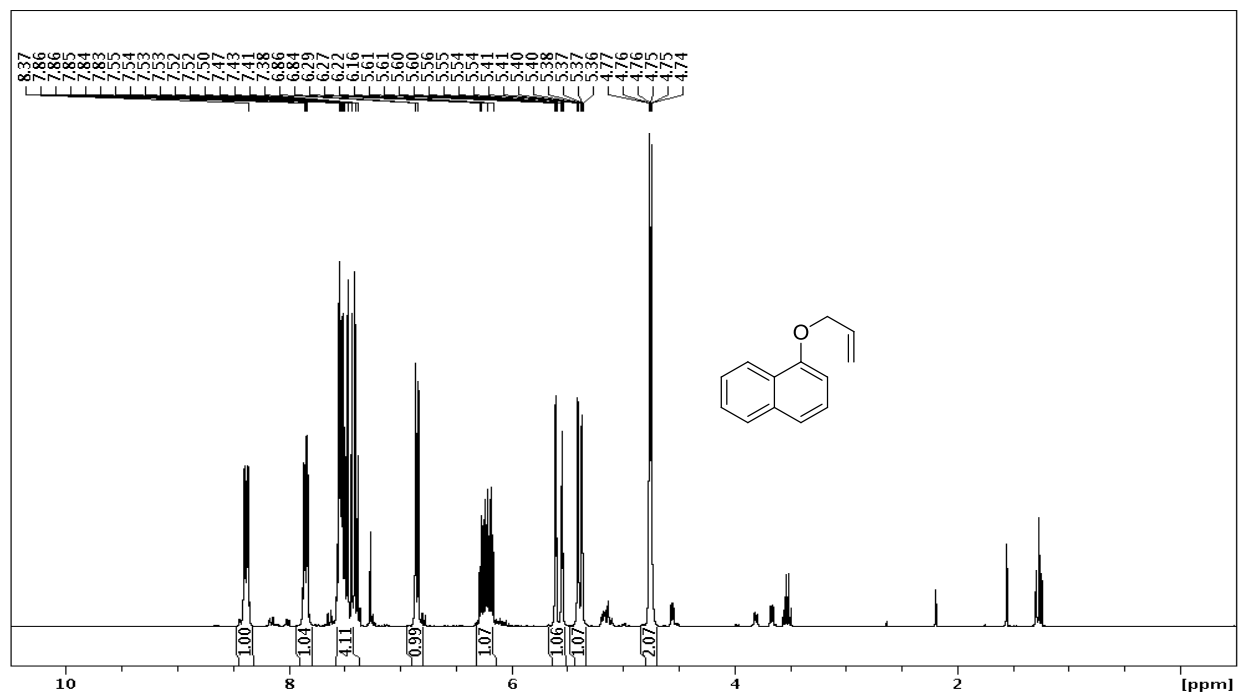
2H). ^{13}C : 174.4, 149.4, 133.7, 128.0, 127.3, 126.0, 125.8, 125.4, 122.2, 120.6, 119.8, 65.7, 58.6, 52.4, 37.5, 23.8. **HRMS**: calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 336.0906; found: 336.0911.

B.21.3.3 Preparation of Crude 3-(1-hydroxynaphthalen-2-yl)-N-(4-nitrophenylsulfonyl)propanamide (**3.95**), *bis*-tetrabutylammonium salt

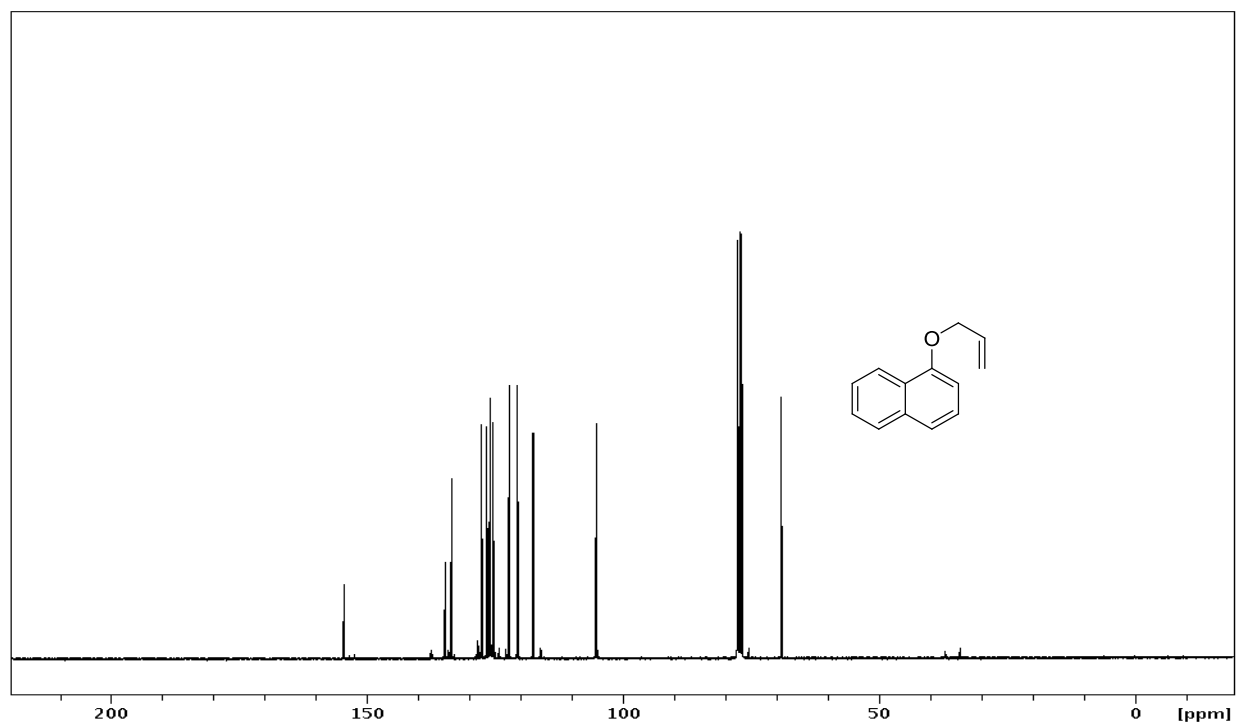


The procedure detailed in title B.16 above was modified by employing 2.2 equivalents of TBAF (use of 1.1 equiv of TBAF resulted in formation of lactone **3.48**; see (Figure 3.1, pp. 54). The crude product thus obtained was the *bis*-tetrabutylammonium salt of **3.95**. The integrated ^1H NMR spectra of the material clearly suggested the presence of two Bu_4N^+ ions for each molecule of "**3.95**" (Figure 3.2, pp. 55). No resonances for phenolic and the sulfonamide protons were apparent. Furthermore, the IR spectrum of the substance showed no OH or NH absorptions. Attempts to obtain actual **3.95**, either by chromatography or by partitioning of the crude between dilute aqueous acid and organic solvents, returned only lactone **3.48** (Figure 3.1, pp. 54). Therefore, the crude *bis*- Bu_4N^+ salt was used directly in the subsequent oxidative cyclization step. 233 mg (83% crude yield) from 165 mg of **3.92**, yellow oil; ^1H : 8.26-8.22 (m, 1H), 8.09 (app s, 4H), 7.71-7.67 (m, 1H), 7.40-7.34 (m, 2H), 7.26 (d, 1H, $J = 8.5$), 7.15 (d, 1H, $J = 8.3$), 2.93-2.89 (m, 2H), 2.73-2.69 (m, 2H). ^{13}C : 180.3, 150.5, 148.7, 133.4, 129.2, 128.5, 127.8, 127.2, 126.3, 125.3, 124.5, 123.1, 122.7 (2C), 119.0, 40.2, 25.9. **HRMS**: calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_6\text{S}$ $[\text{M}-\text{H}]^-$: 399.0651; found: 399.0652.

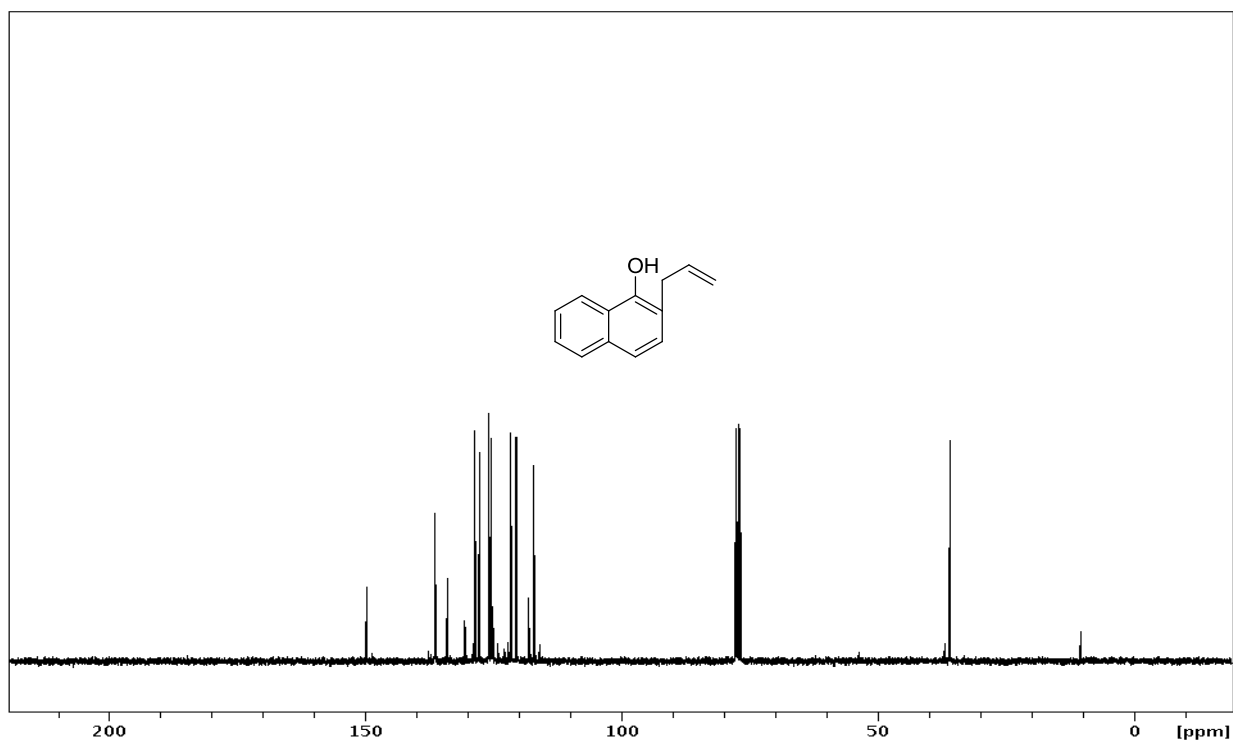
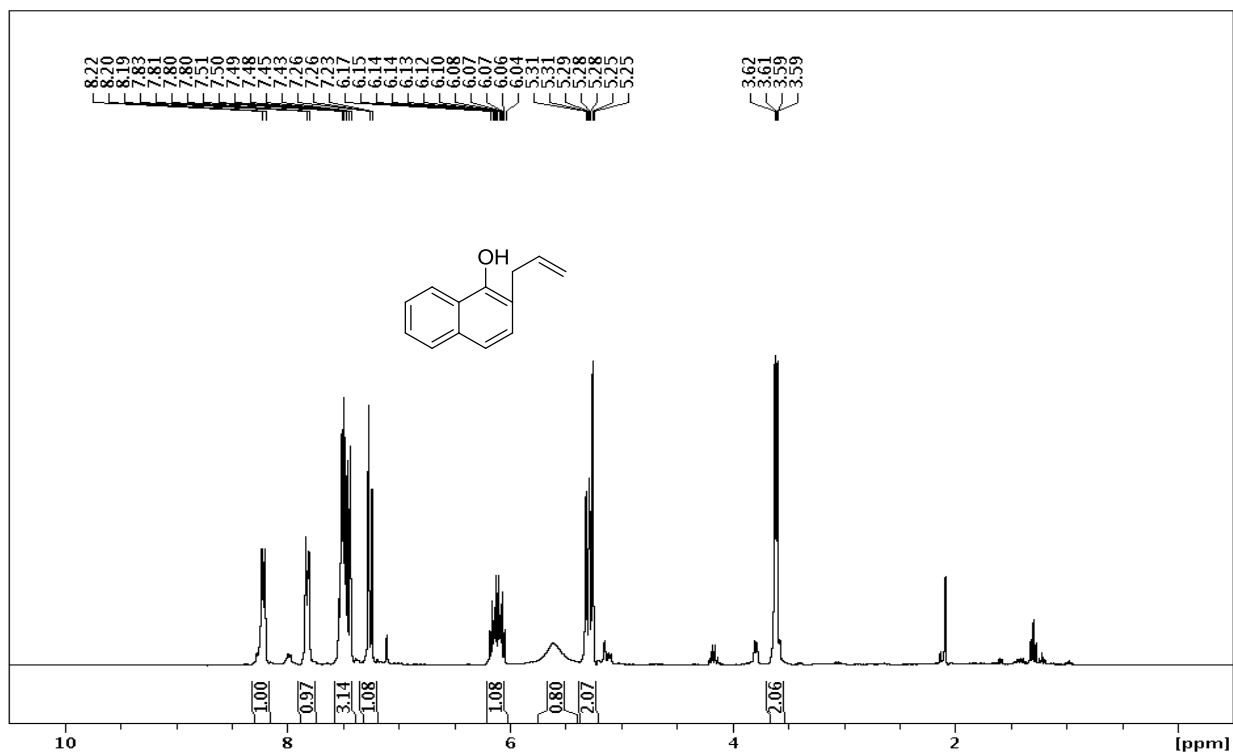
B.22 ^1H and ^{13}C spectra from chapter 3

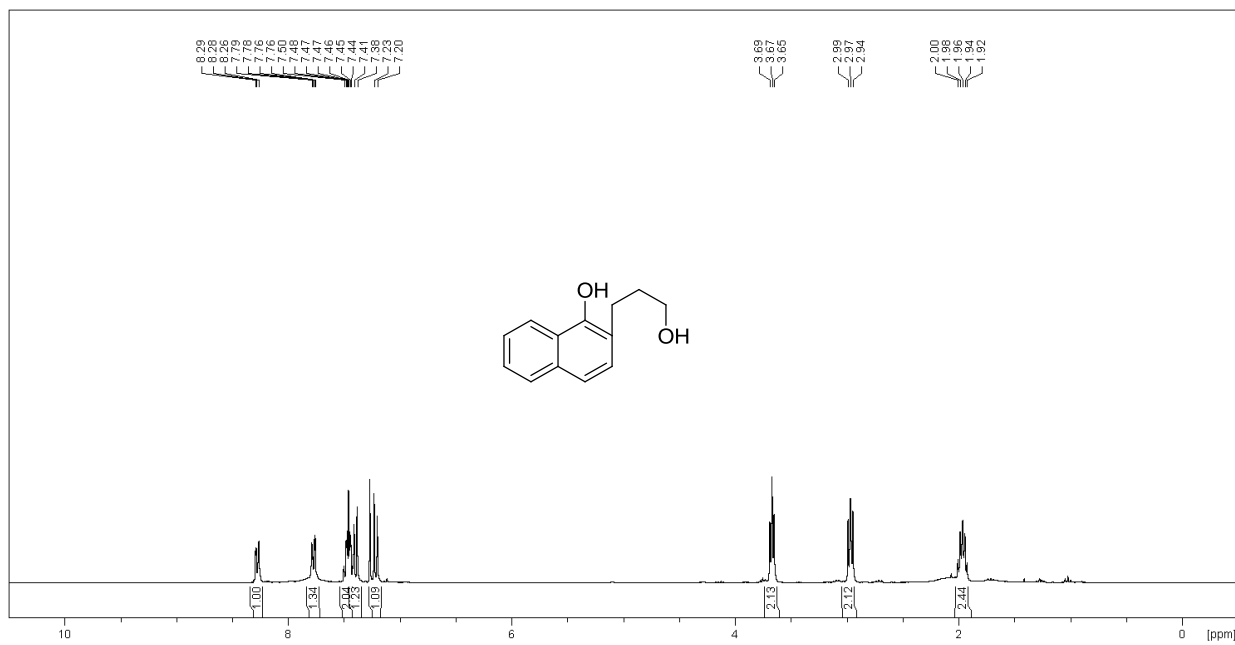


^1H NMR spectrum of crude 3.8 (300 MHz, CDCl_3)

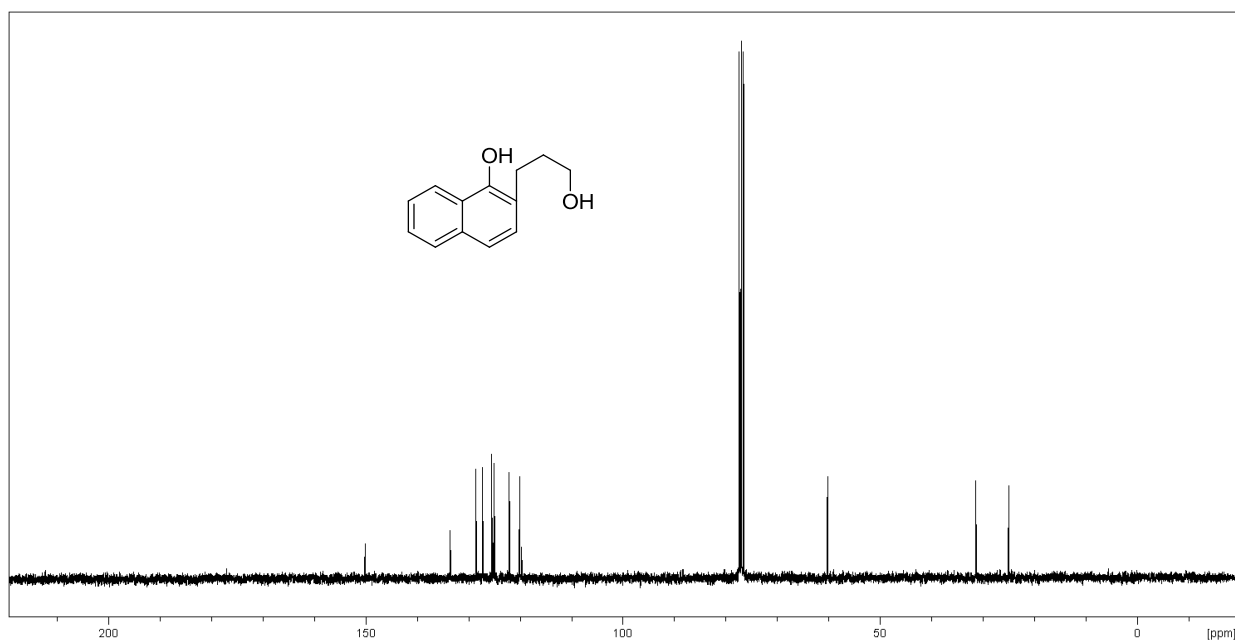


^{13}C NMR spectrum of crude 3.8 (75 MHz, CDCl_3)

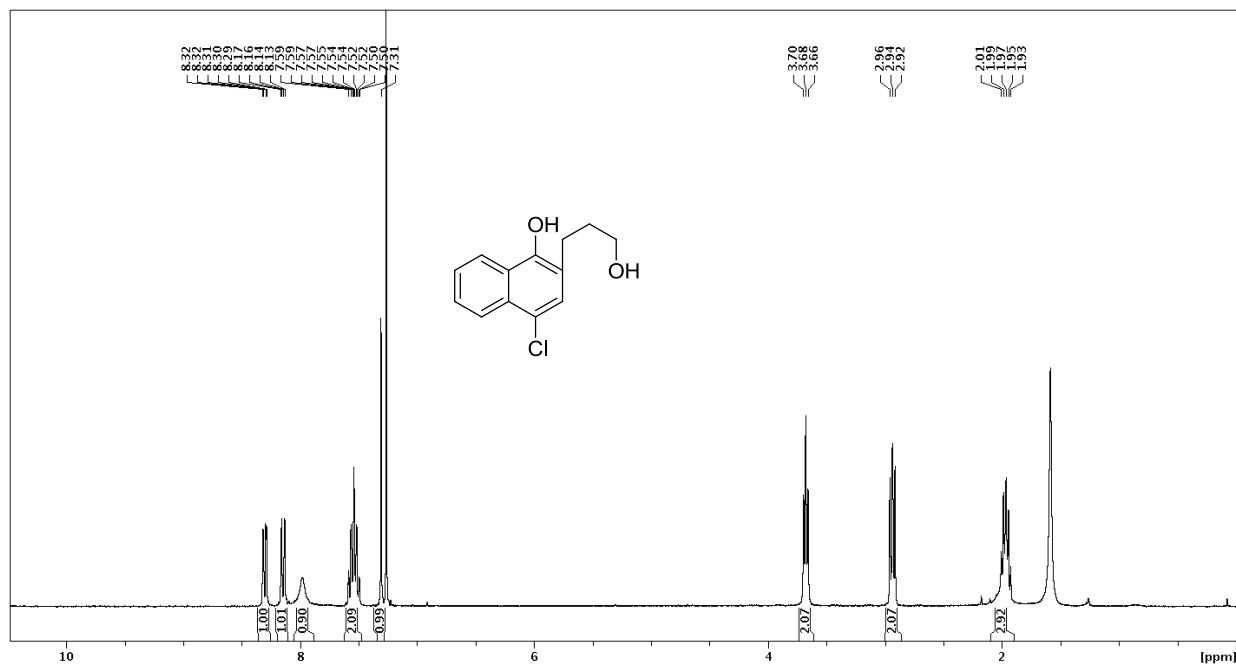




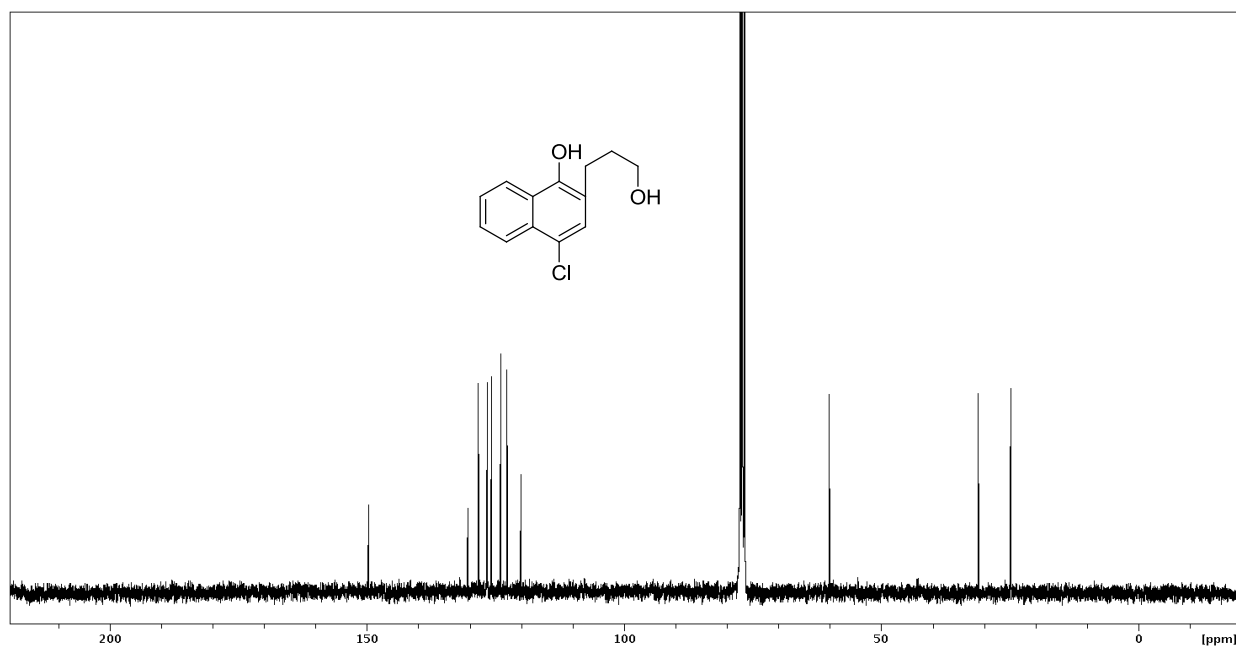
¹H NMR spectrum of 3.10 (300 MHz, CDCl₃)



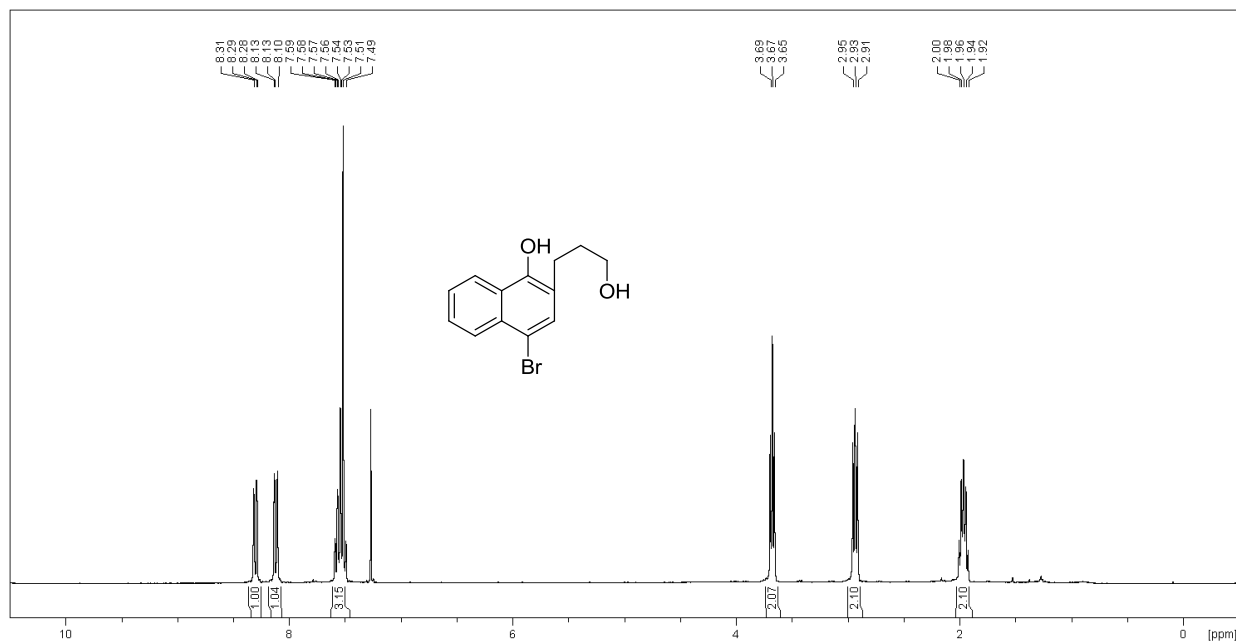
¹³C NMR spectrum of 3.10 (75 MHz, CDCl₃)



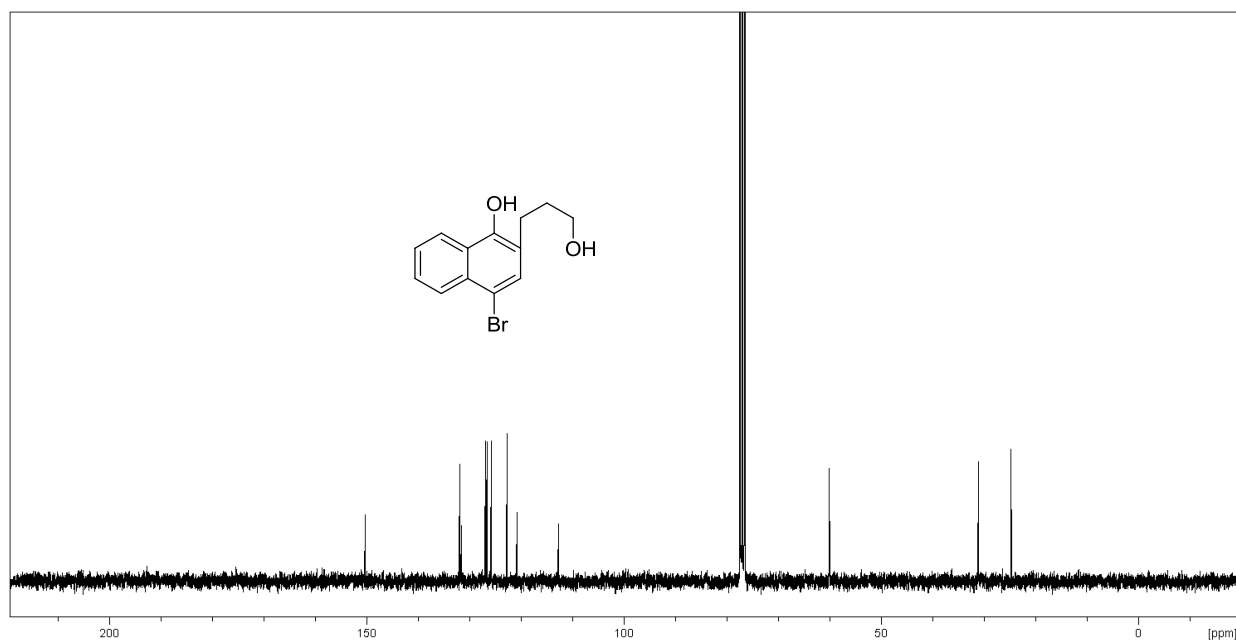
^1H NMR spectrum of 3.11 (300 MHz, CDCl_3)



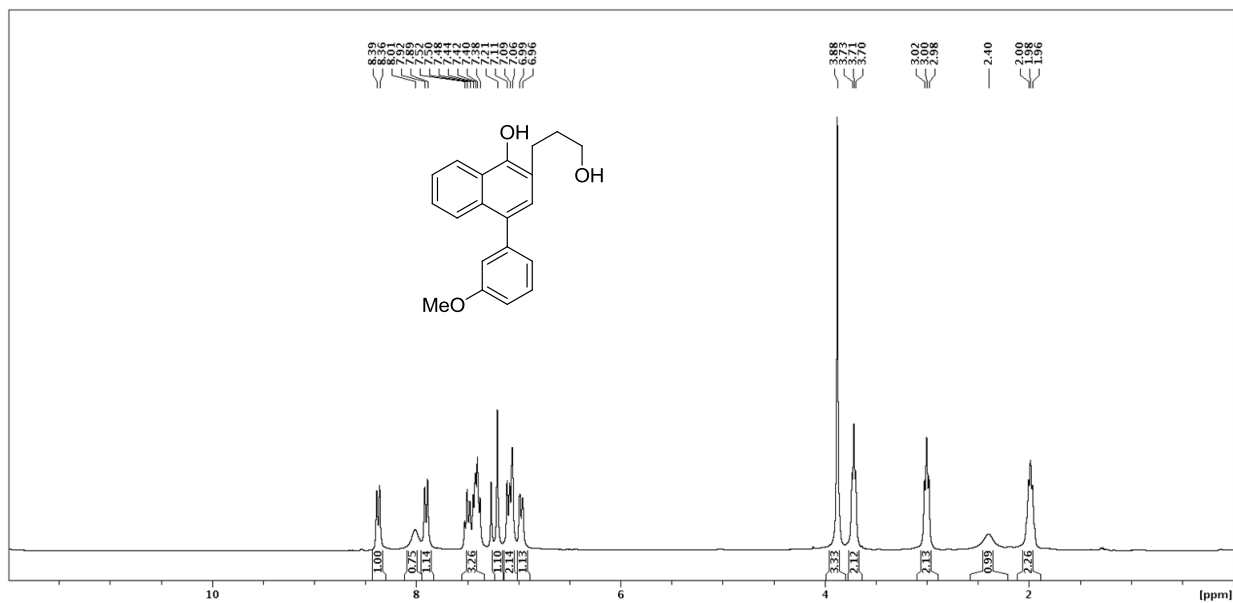
^{13}C NMR spectrum of 3.11 (75 MHz, CDCl_3)



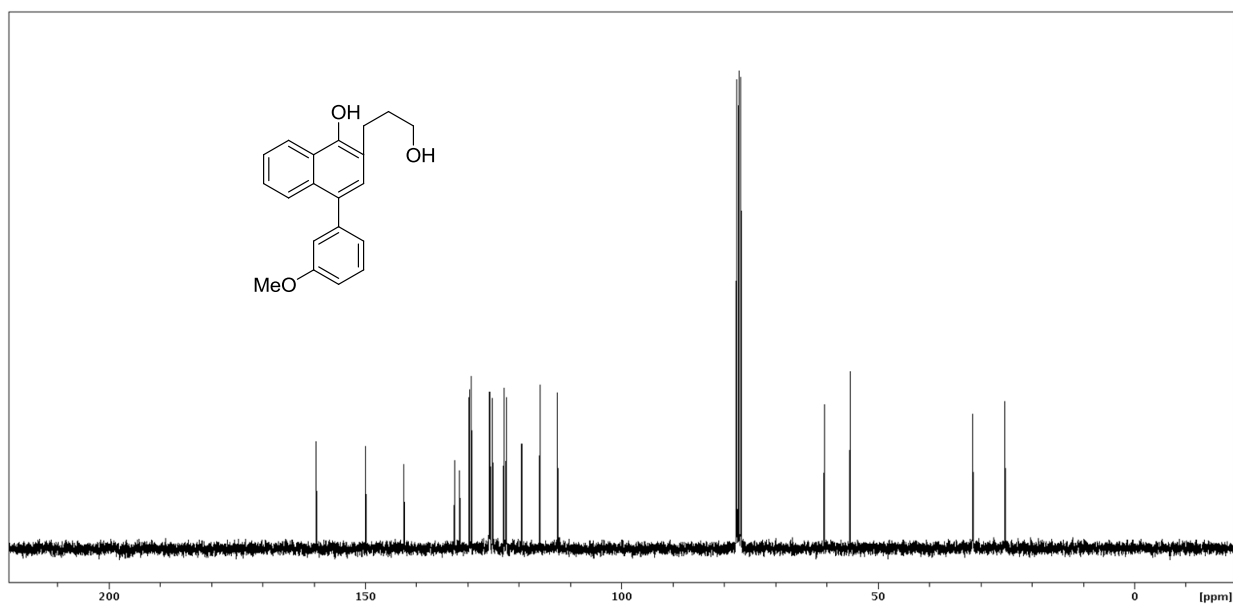
^1H NMR spectrum of 3.12 (300 MHz, CDCl_3)



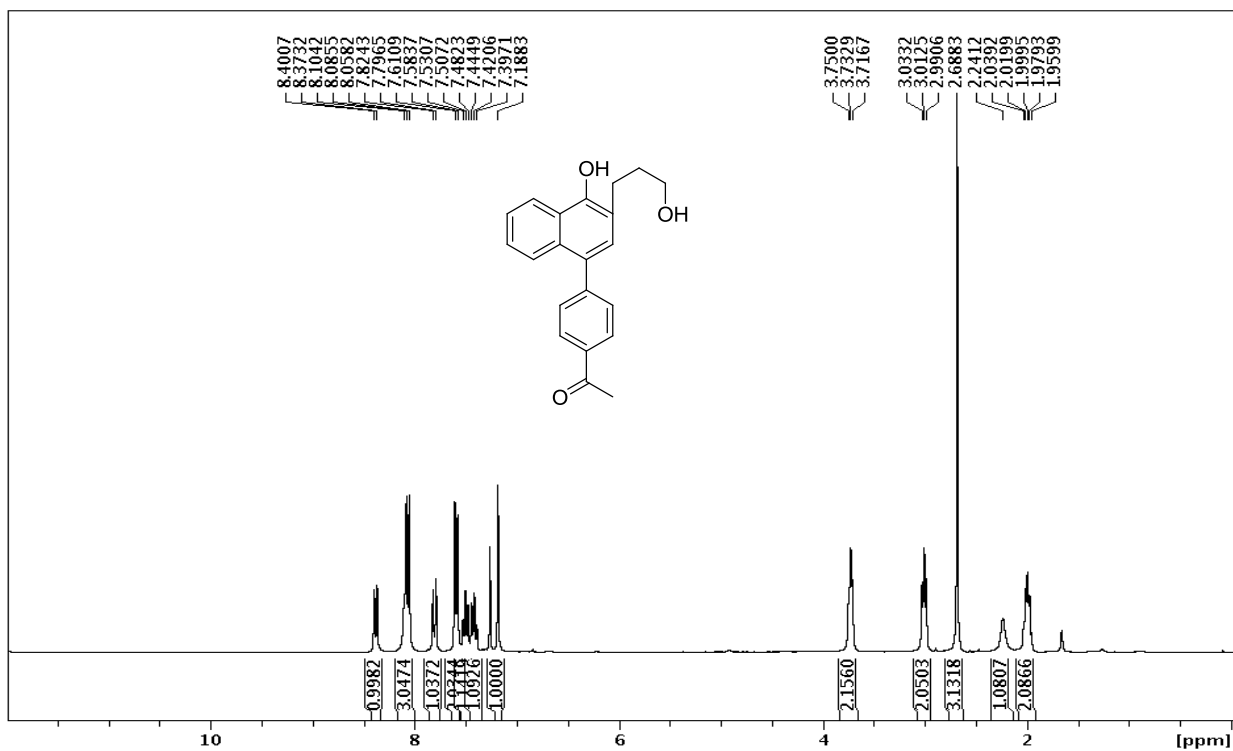
^{13}C NMR spectrum of 3.12 (75 MHz, CDCl_3)



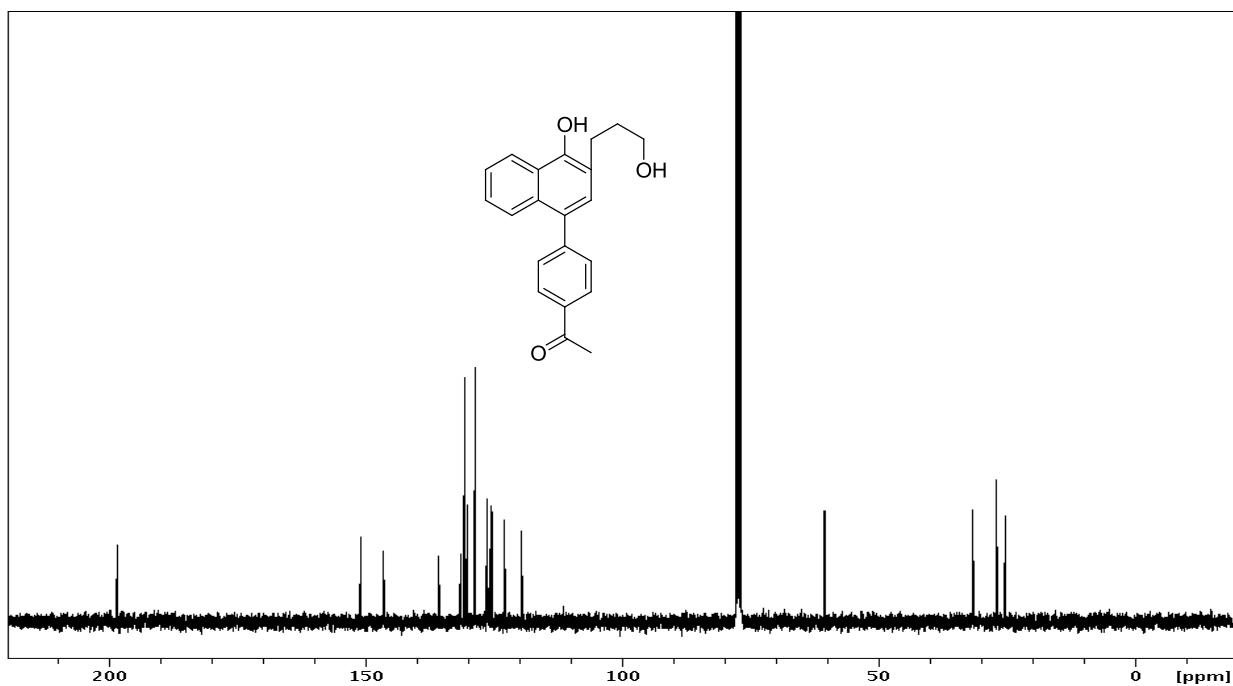
¹H NMR spectrum of 3.13, Ar = C₆H₄-OMe-*m* (300 MHz, CDCl₃)



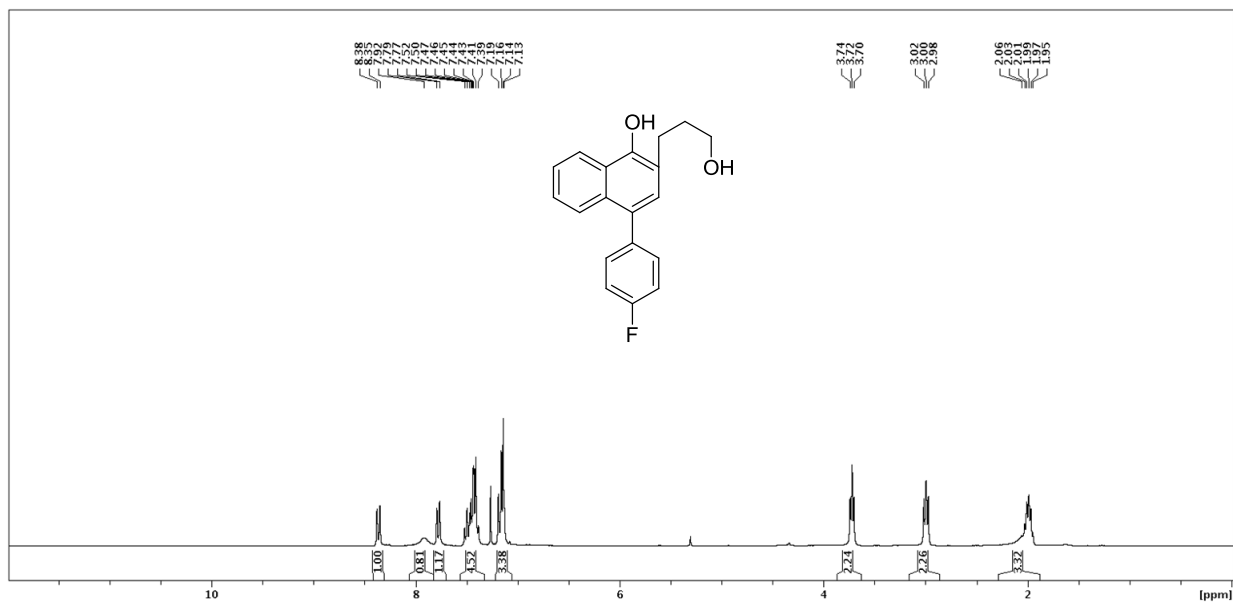
¹³C NMR spectrum of 3.13, Ar = C₆H₄-OMe-*m* (75 MHz, CDCl₃)



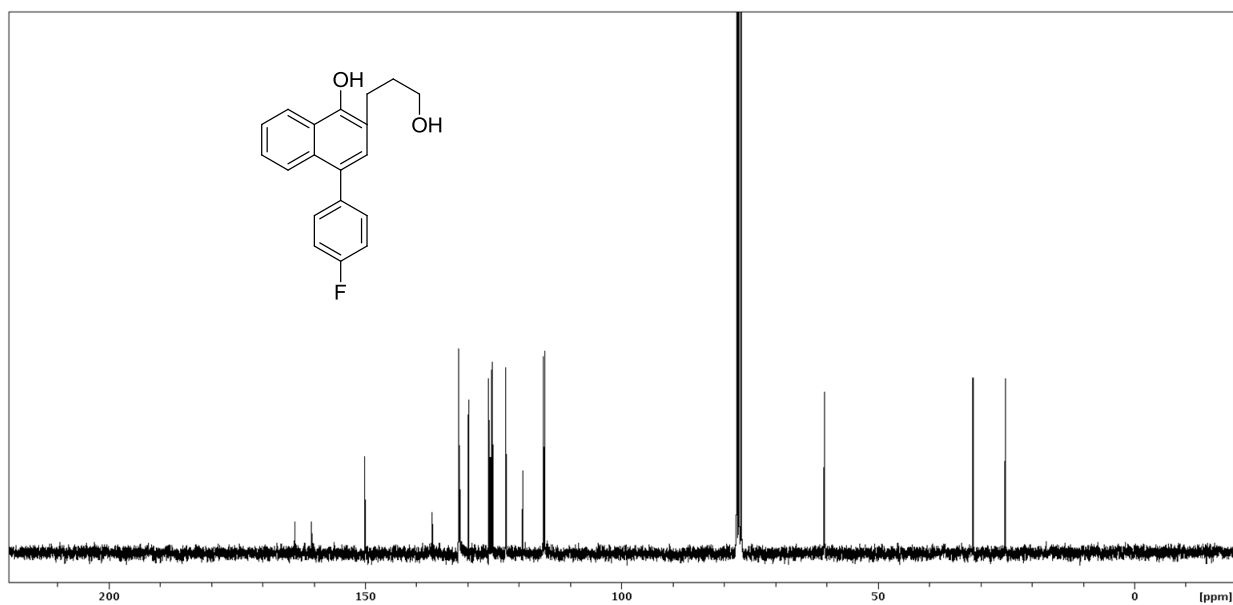
¹H NMR spectrum of 3.13, Ar = C₆H₄-C(O)Me (300 MHz, CDCl₃)



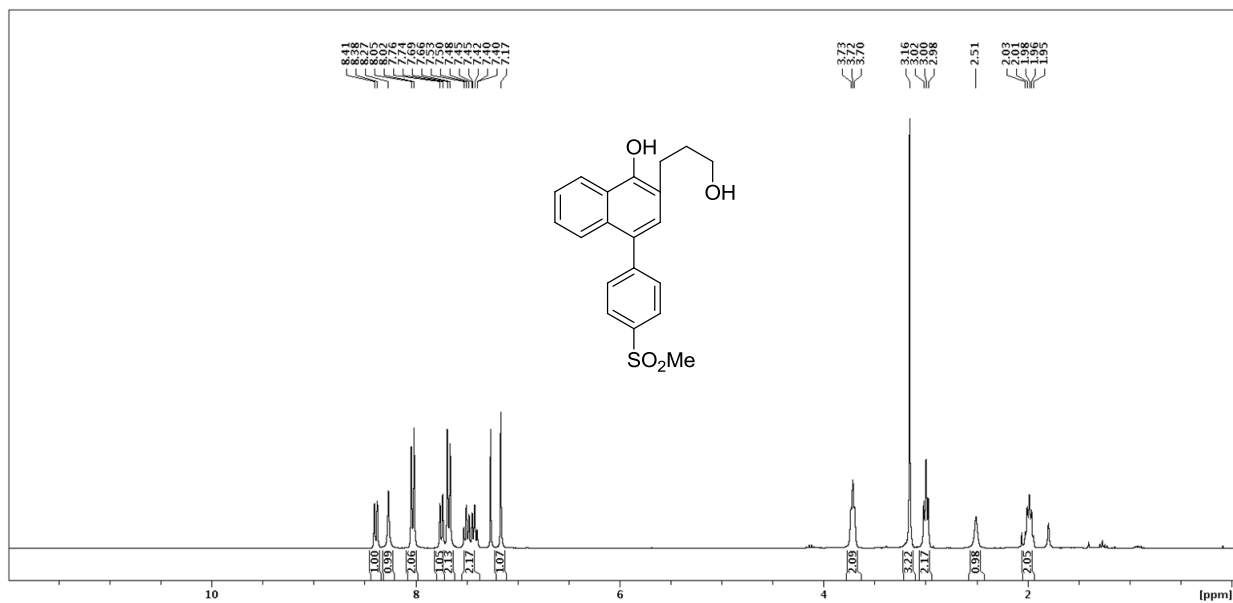
¹³C NMR spectrum of 3.13, Ar = C₆H₄-C(O)Me (75 MHz, CDCl₃)



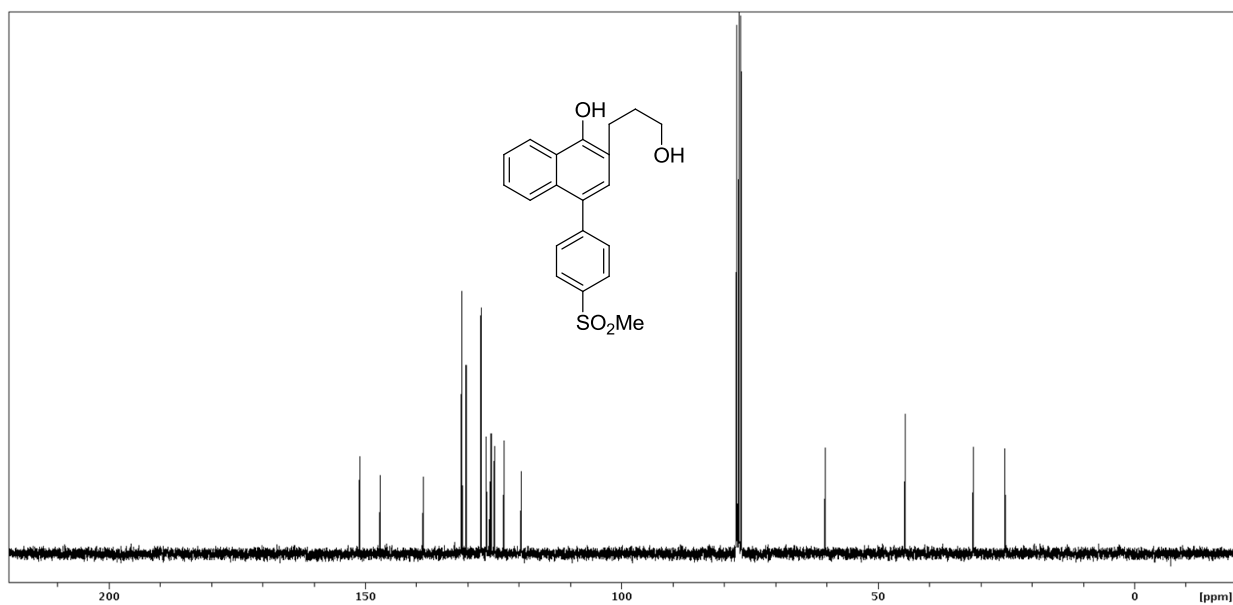
¹H NMR spectrum of 3.13, Ar = C₆H₄-F-*p* (300 MHz, CDCl₃)



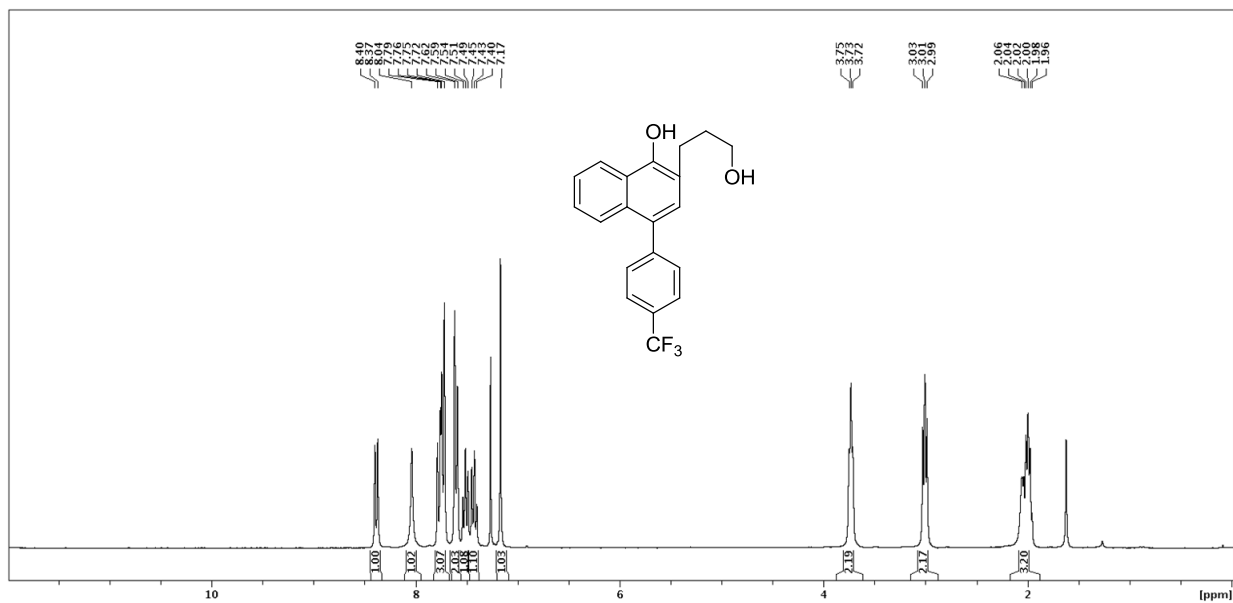
¹³C NMR spectrum of 3.13, Ar = C₆H₄-F-*p* (75 MHz, CDCl₃)



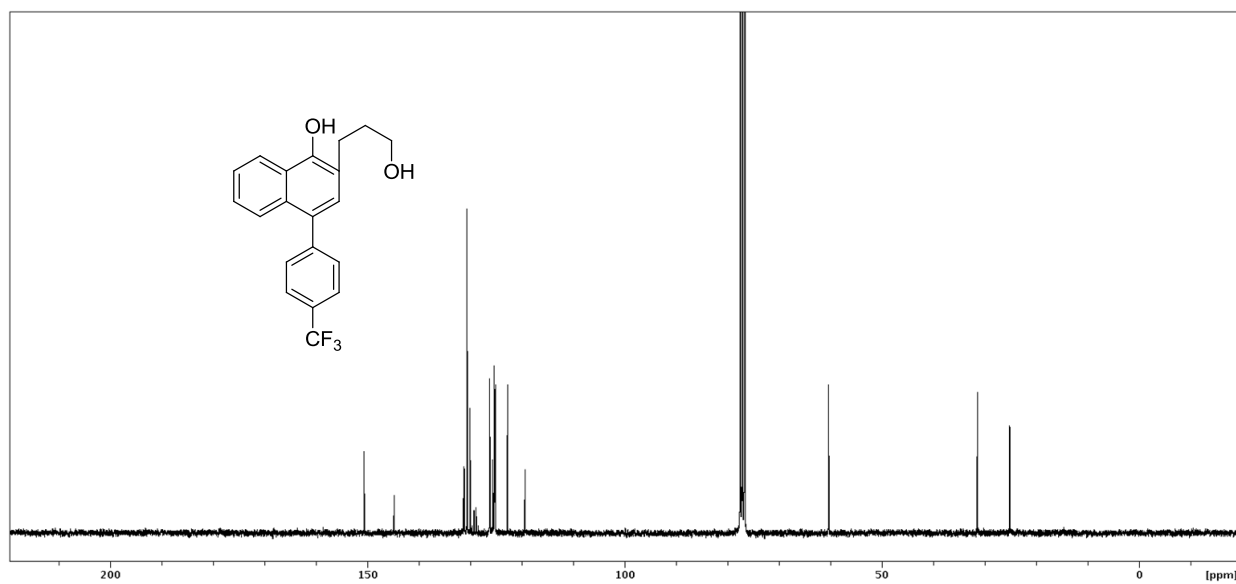
¹H NMR spectrum of 3.13, Ar = C₆H₄-SO₂Me-*p* (300 MHz, CDCl₃)



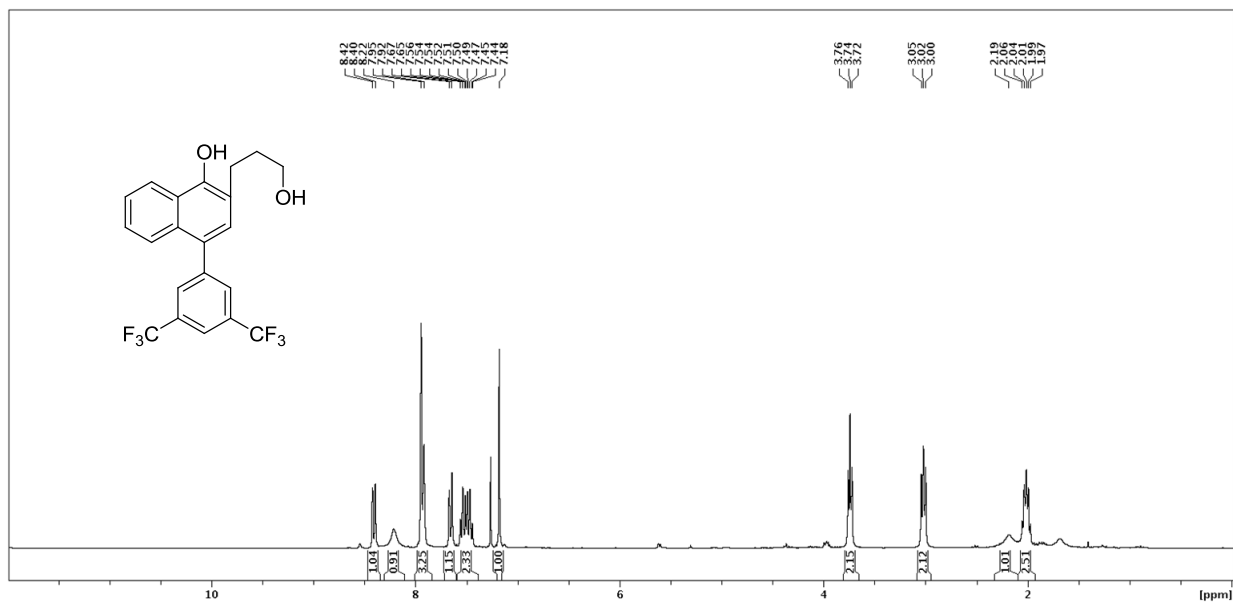
¹³C NMR spectrum of 3.13, Ar = C₆H₄-SO₂Me-*p* (75 MHz, CDCl₃)



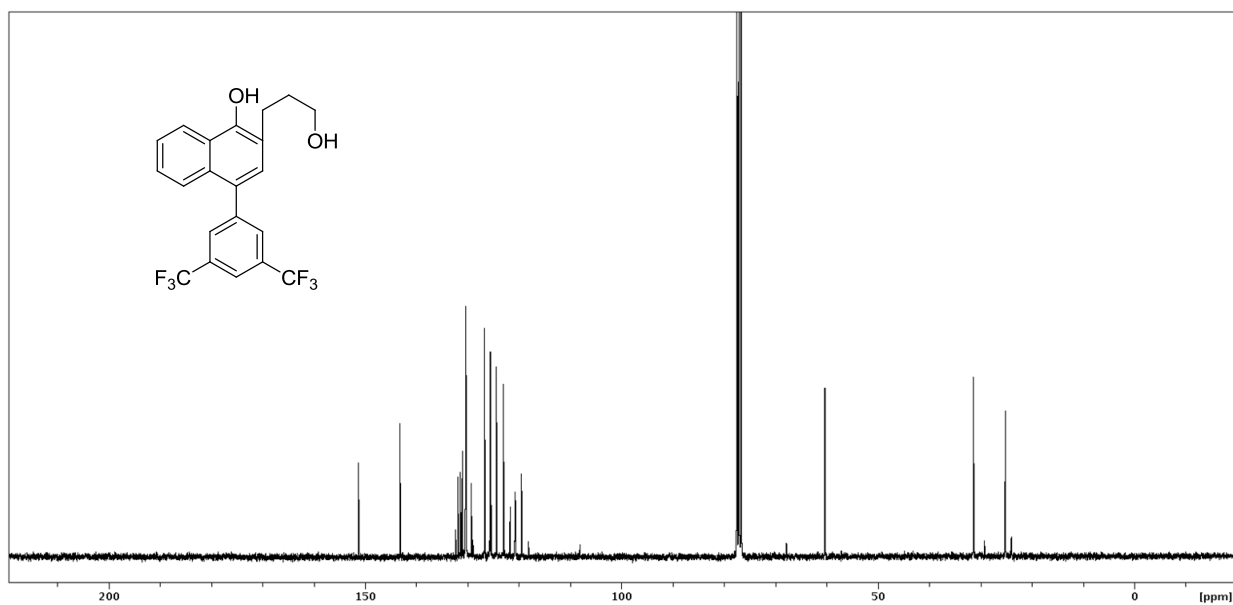
¹H NMR spectrum of 3.13, Ar = C₆H₄-CF₃-*p* (300 MHz, CDCl₃)



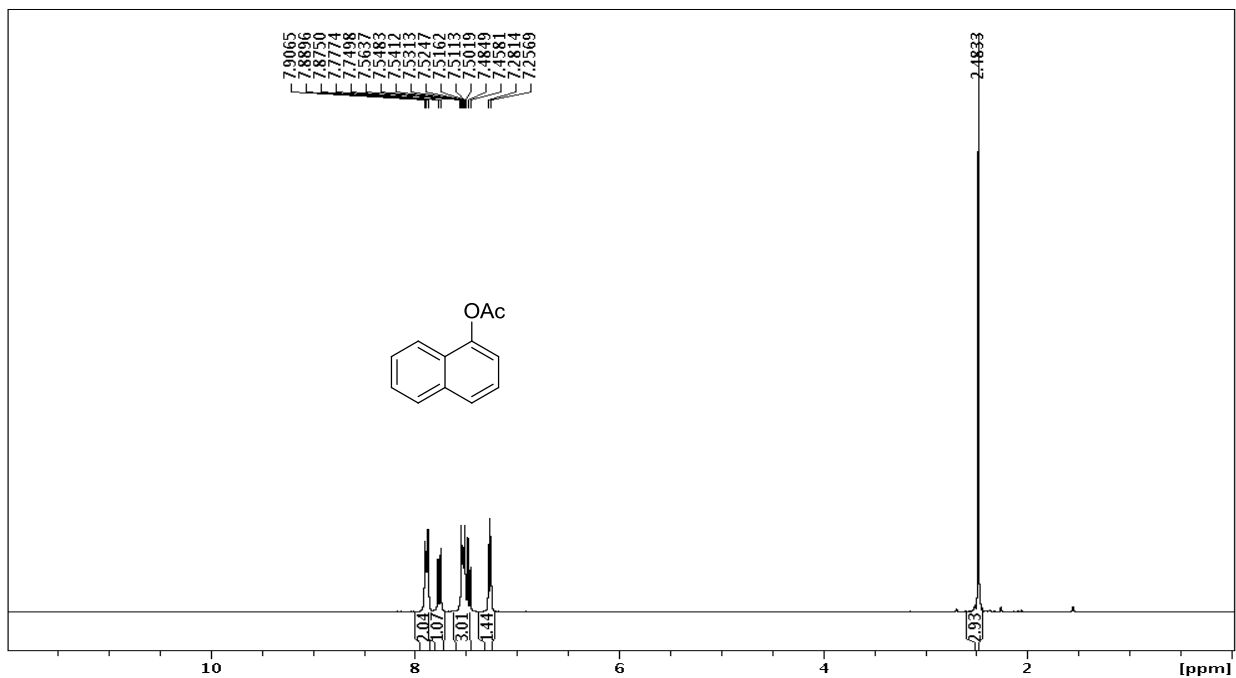
¹³C NMR spectrum of 3.13, Ar = C₆H₄-CF₃-*p* (75 MHz, CDCl₃)



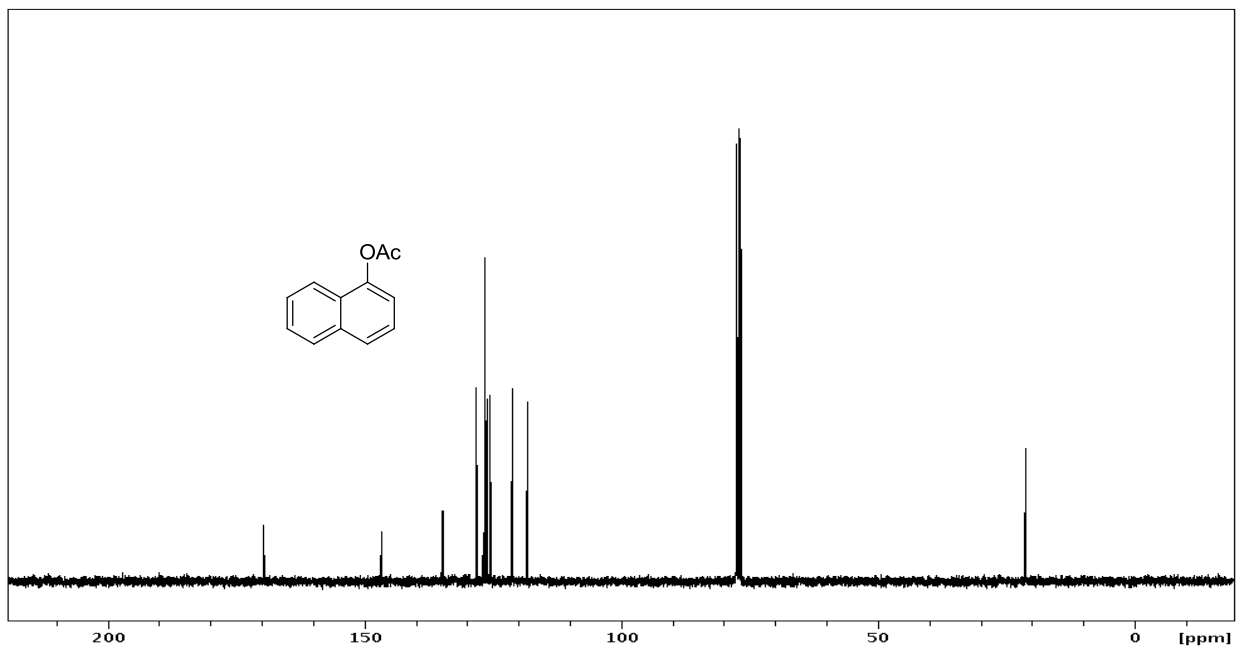
¹H NMR spectrum of 3.13, Ar = 3,5bis(CF₃)₂C₆H₃ (300 MHz, CDCl₃)



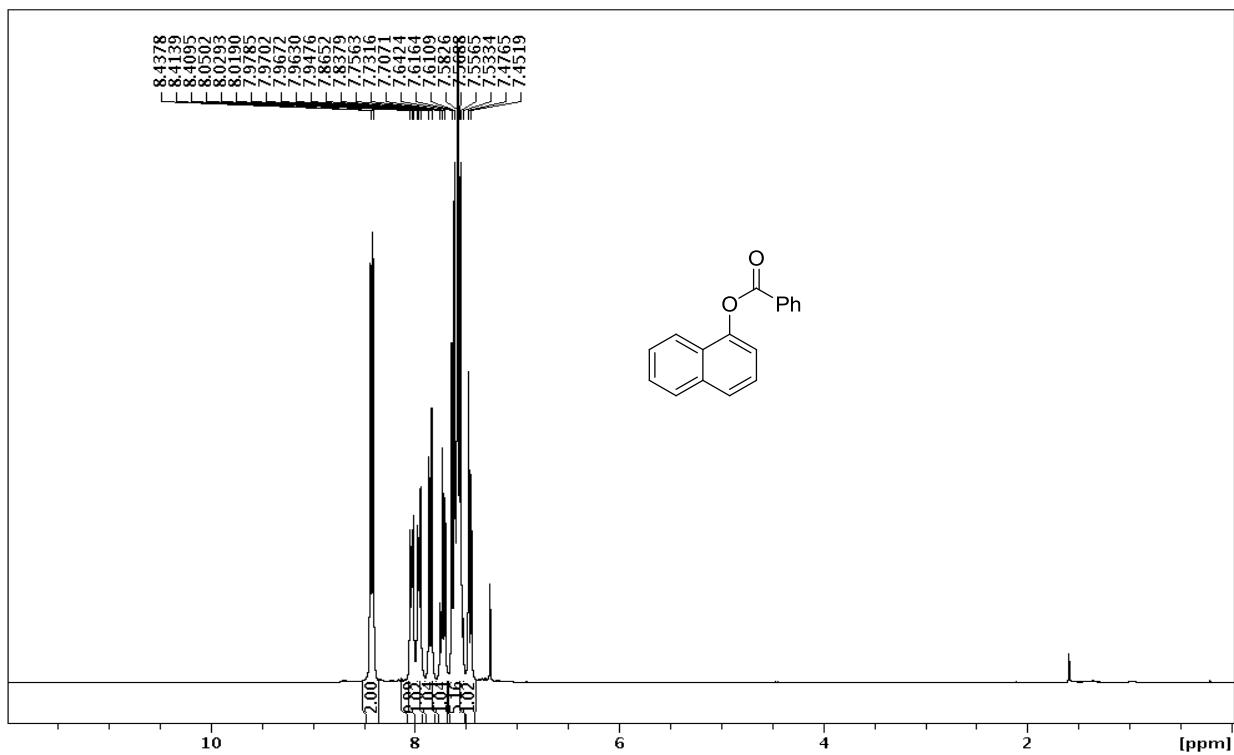
¹³C NMR spectrum of Ar = 3,5bis(CF₃)₂C₆H₃ (75 MHz, CDCl₃)



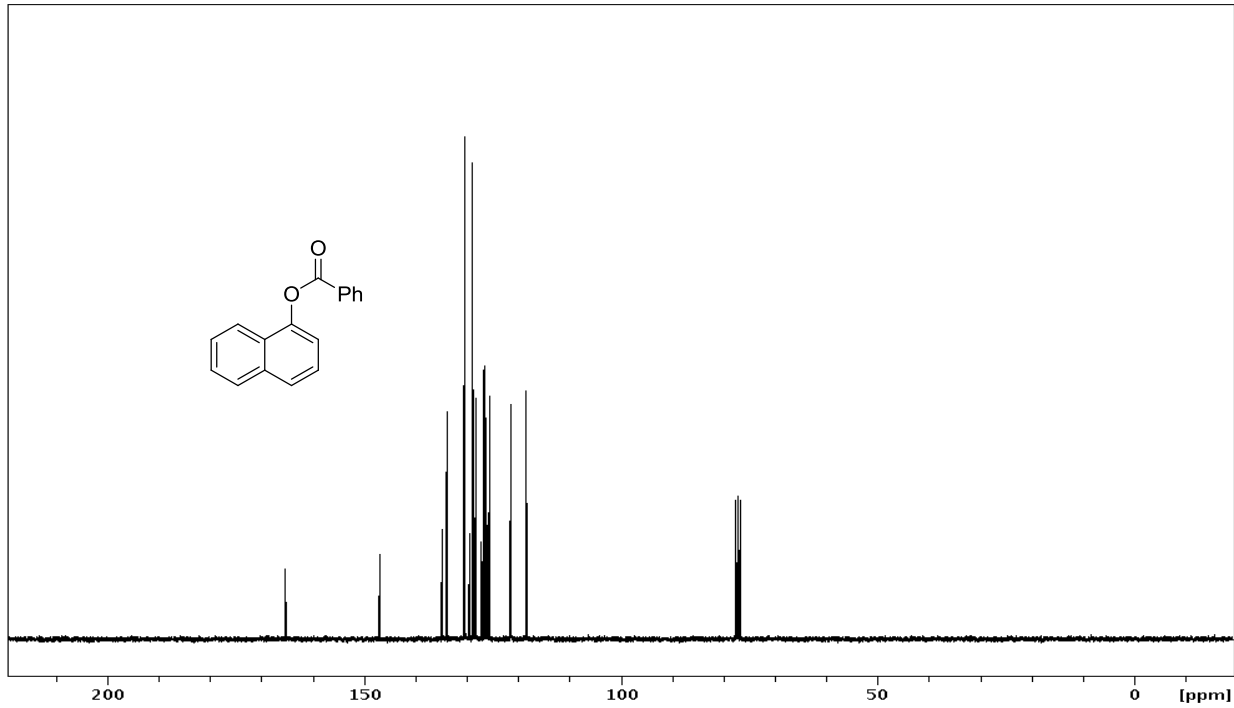
¹H NMR spectrum of 3.14, R = Me (300 MHz, CDCl₃)



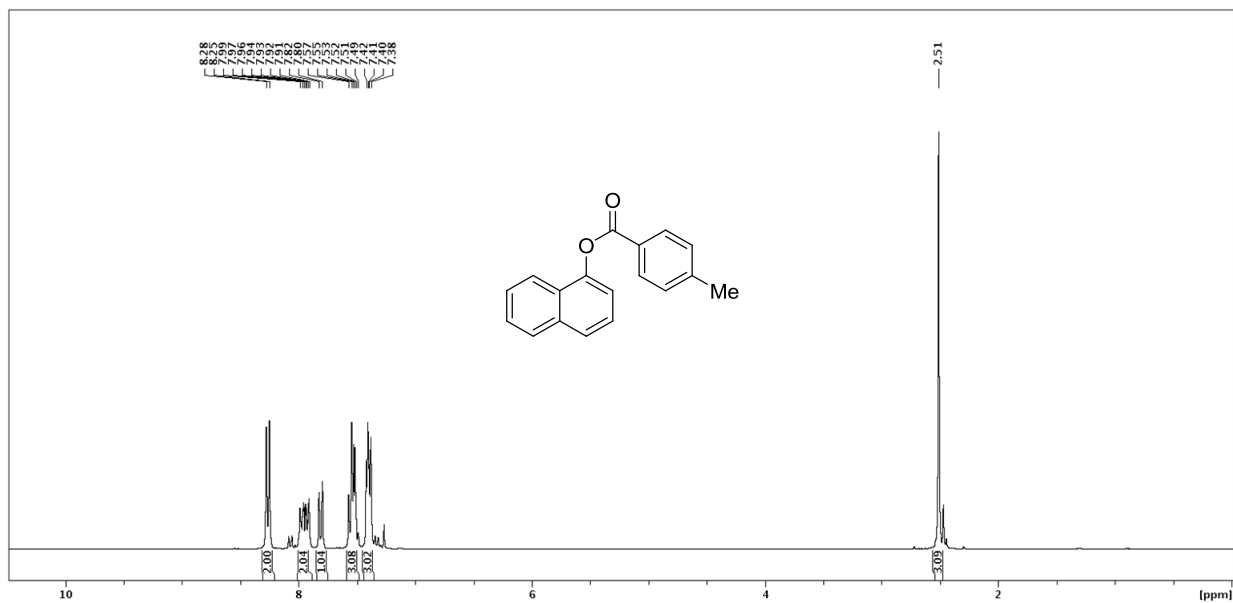
¹³C NMR spectrum of 3.14, R = Me (75 MHz, CDCl₃)



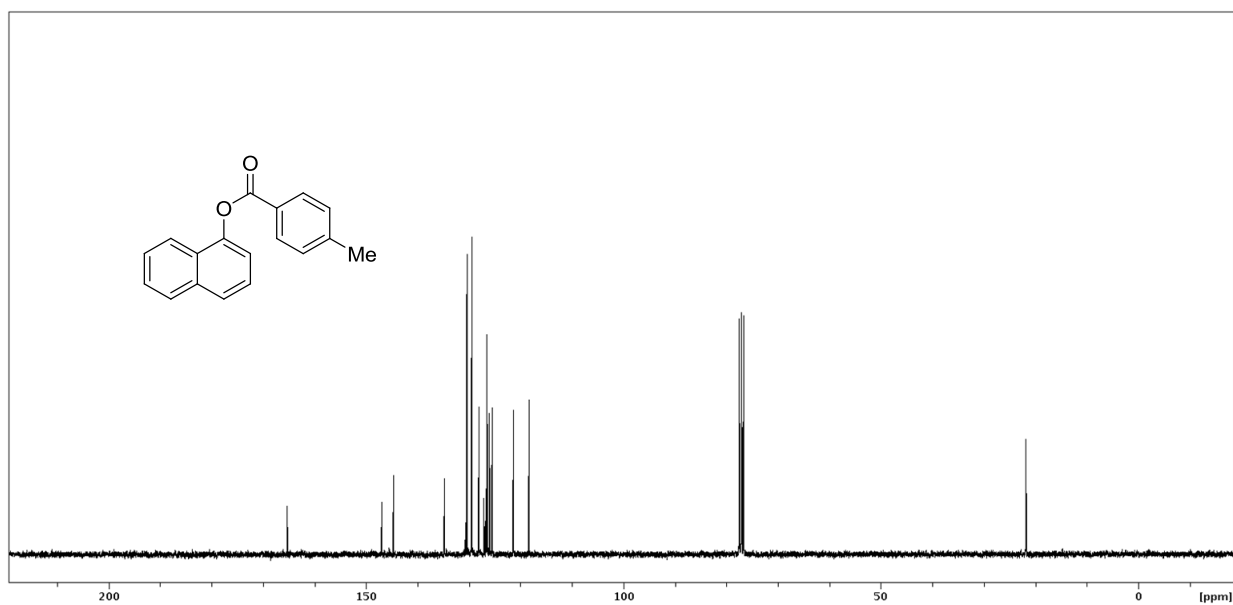
¹H NMR spectrum of 3.14, R = Ph (300 MHz, CDCl₃)



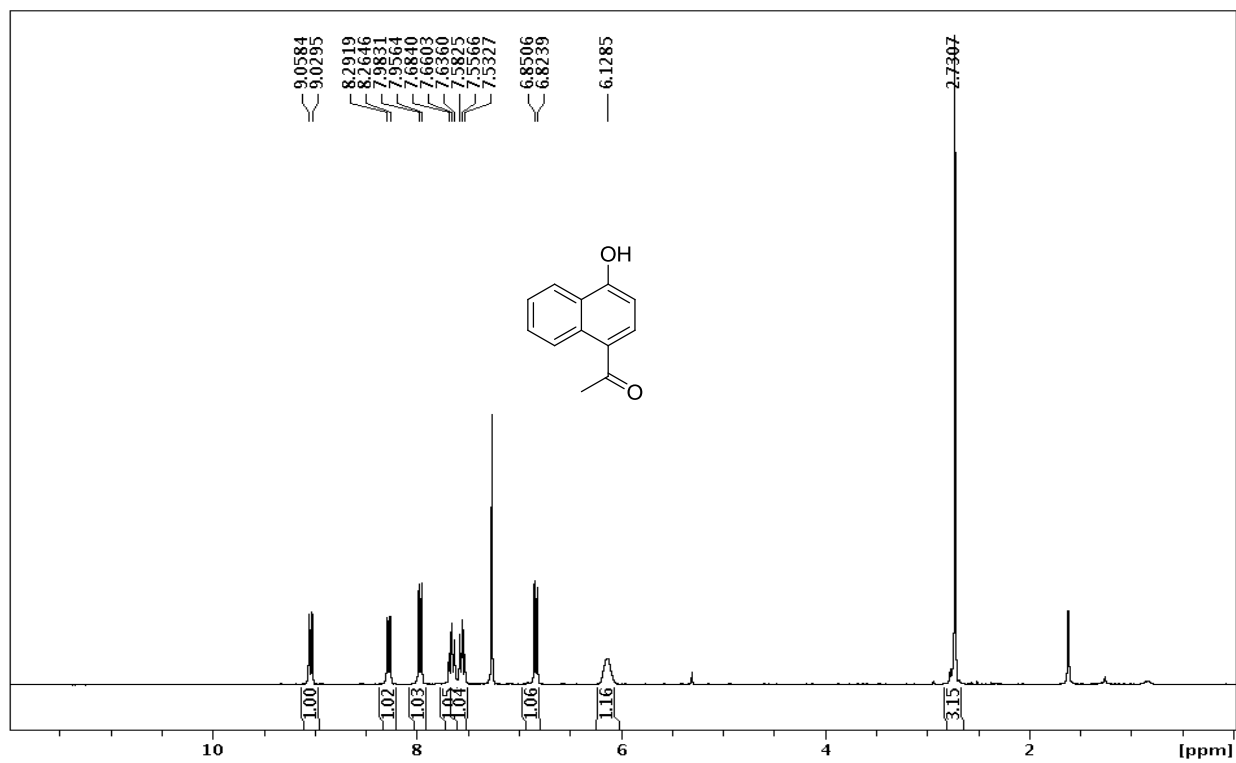
¹³C NMR spectrum of 3.14, R = Me (75 MHz, CDCl₃)



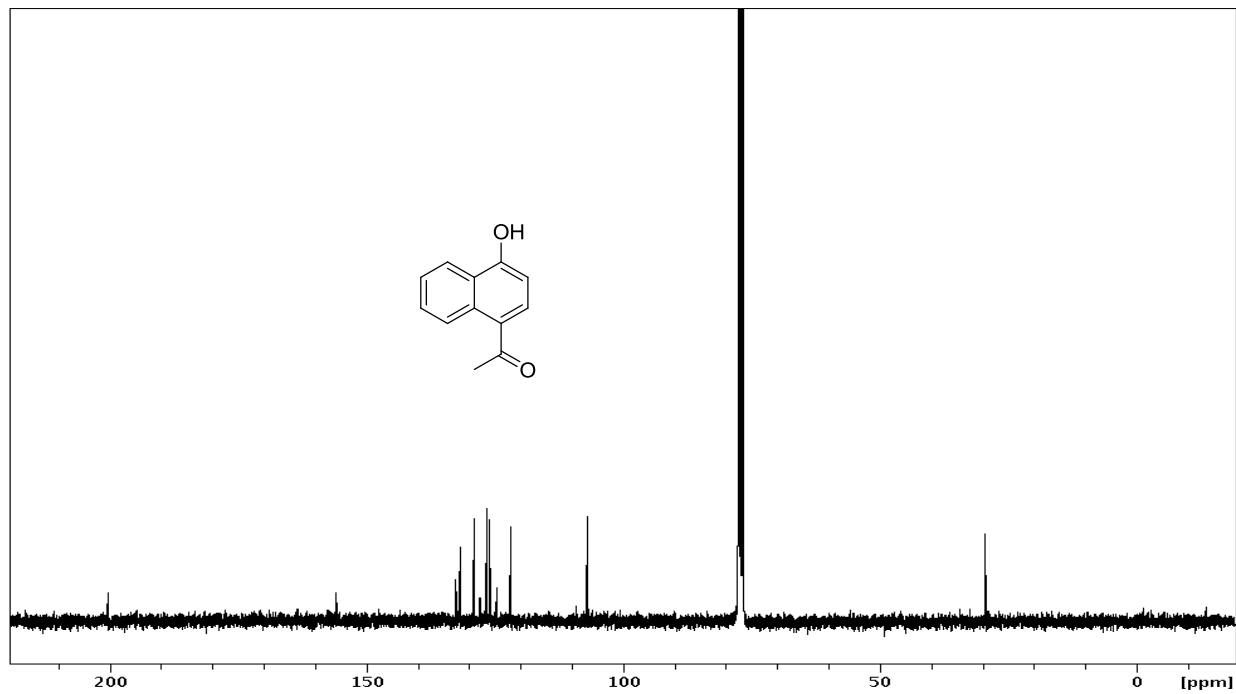
¹H NMR spectrum of 3.14, R = 4-Tol (300 MHz, CDCl₃)



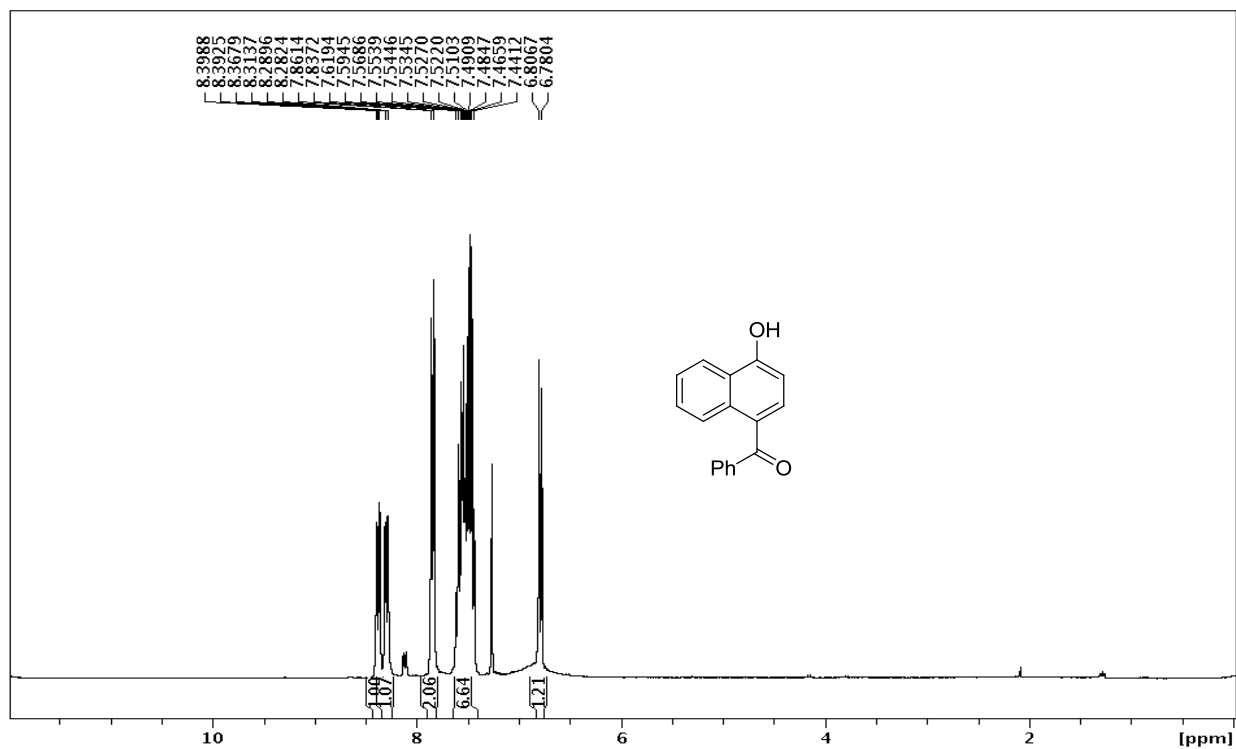
¹³C NMR spectrum of 3.14, R = 4-Tol (75 MHz, CDCl₃)



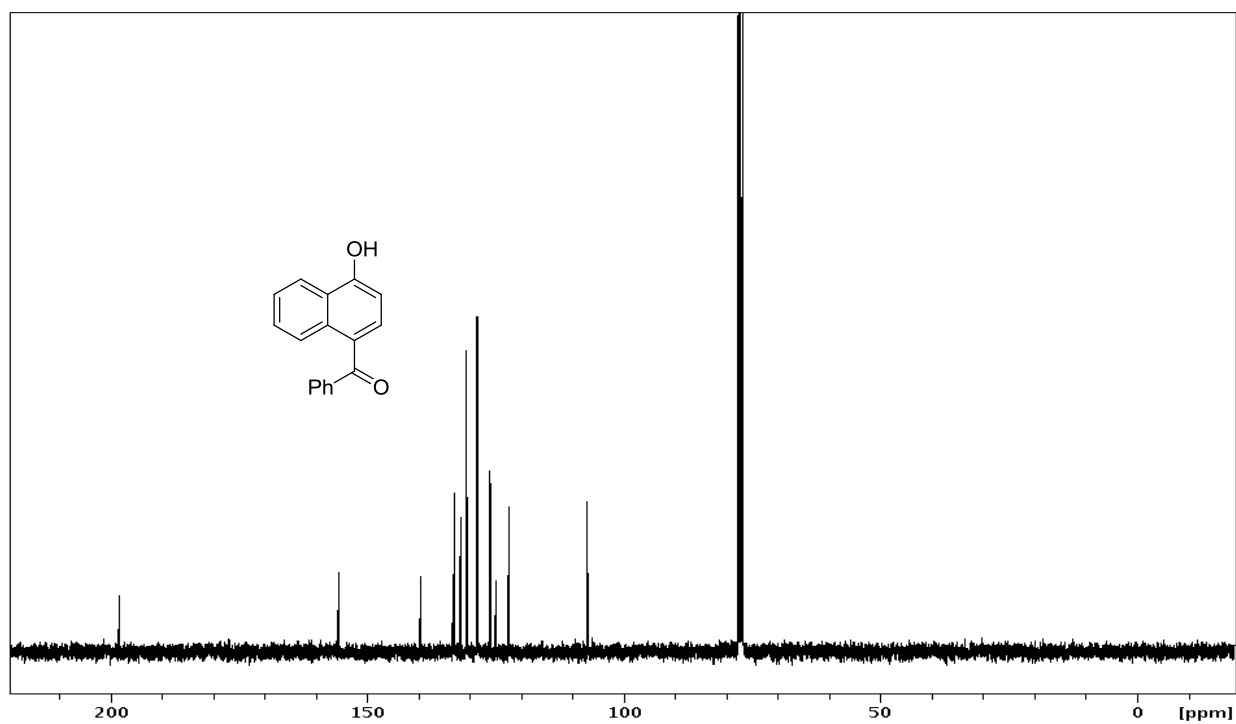
¹H NMR spectrum of 3.15, R = Me (300 MHz, CDCl₃)



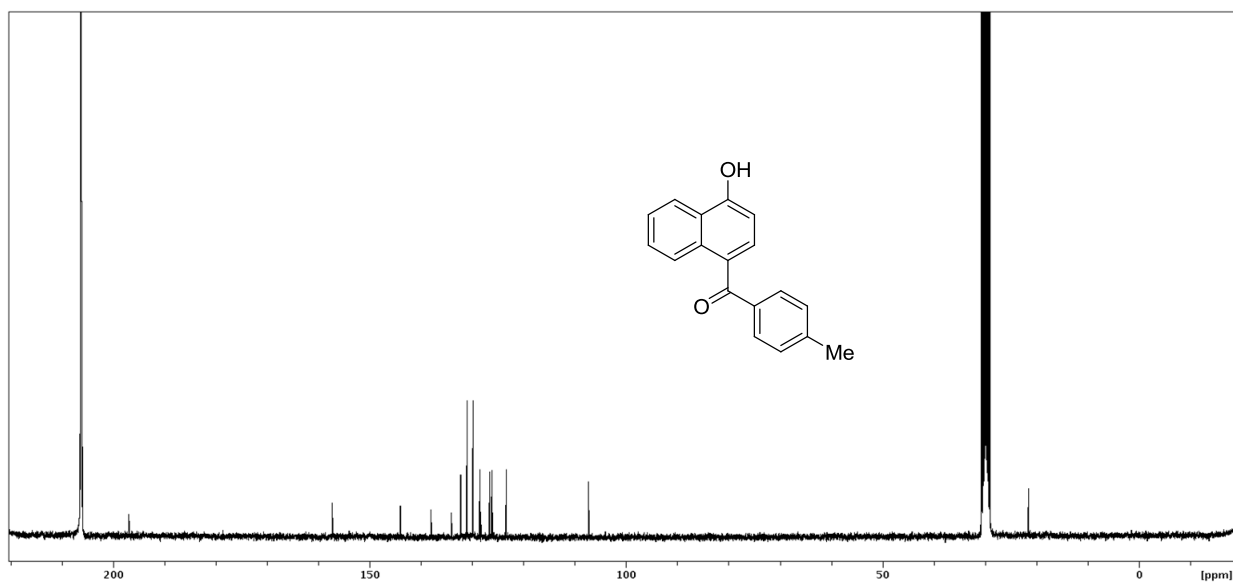
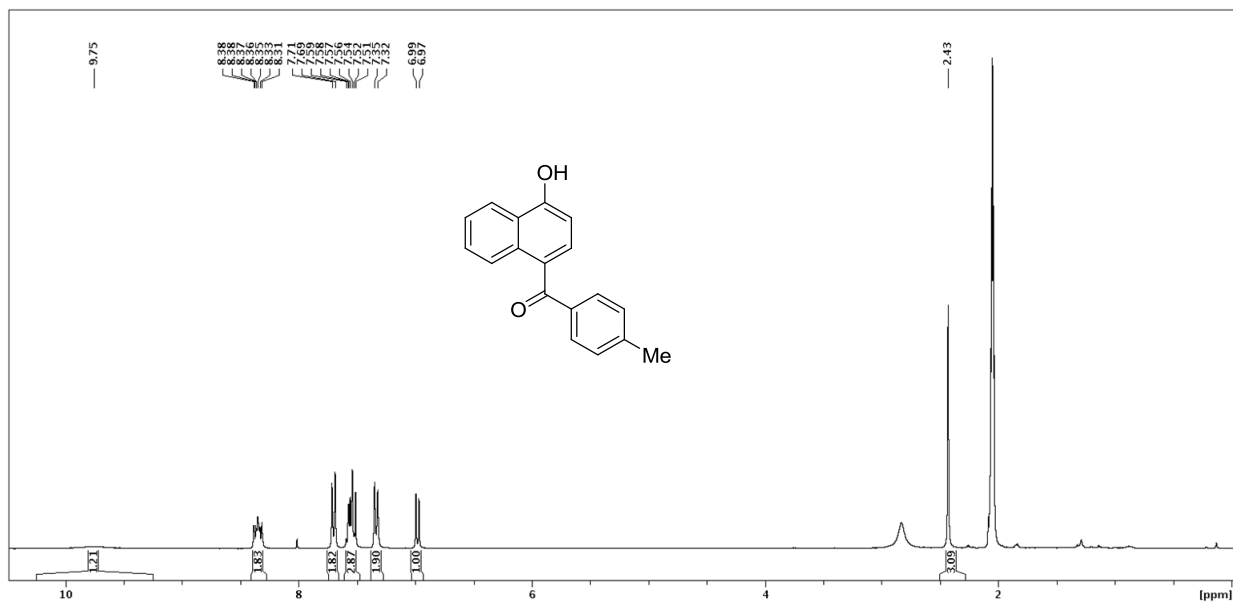
¹³C NMR spectrum of 3.15, R = Me (75 MHz, CDCl₃)

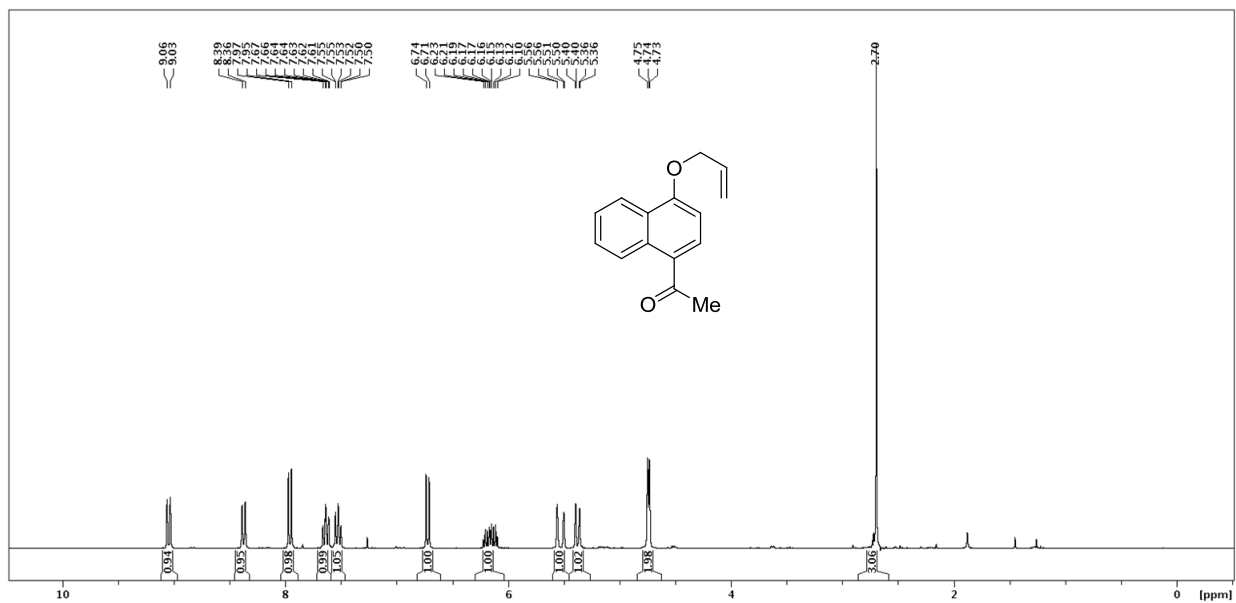


¹H NMR spectrum of 3.15, R = Ph (300 MHz, CDCl₃)

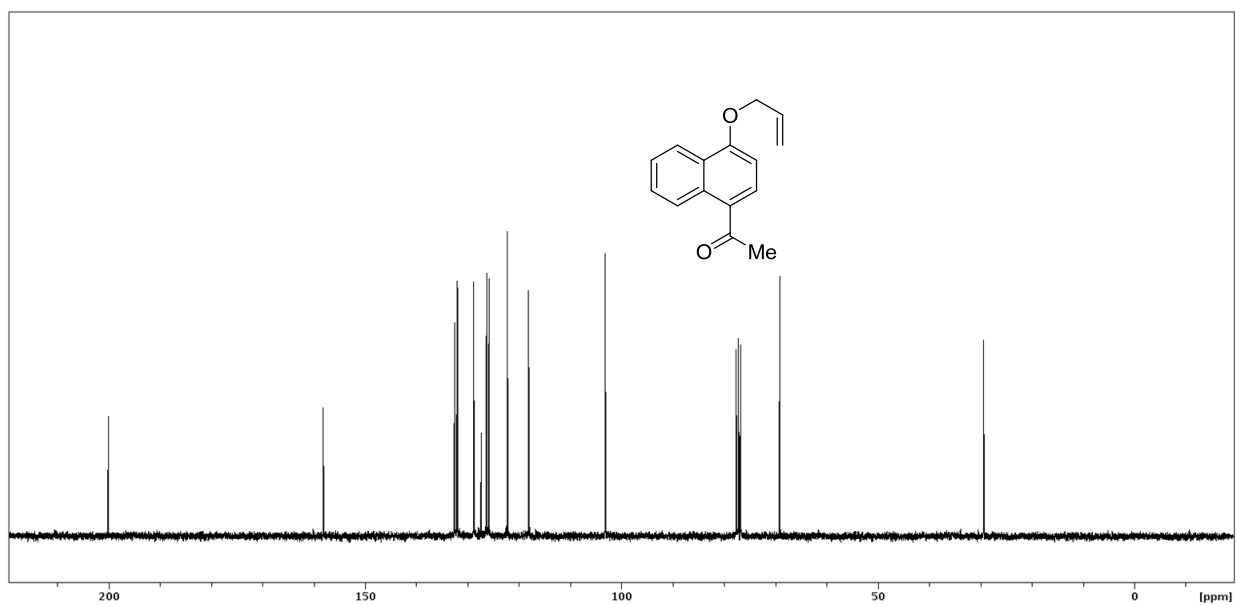


¹³C NMR spectrum of 3.15, R = Ph (75 MHz, CDCl₃)

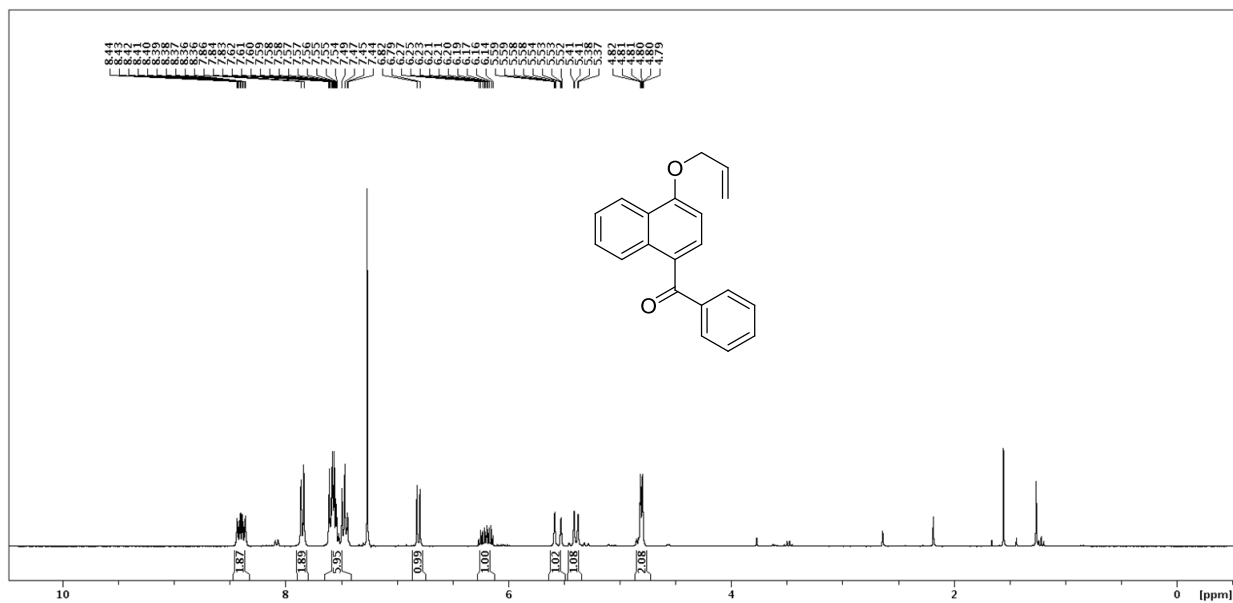




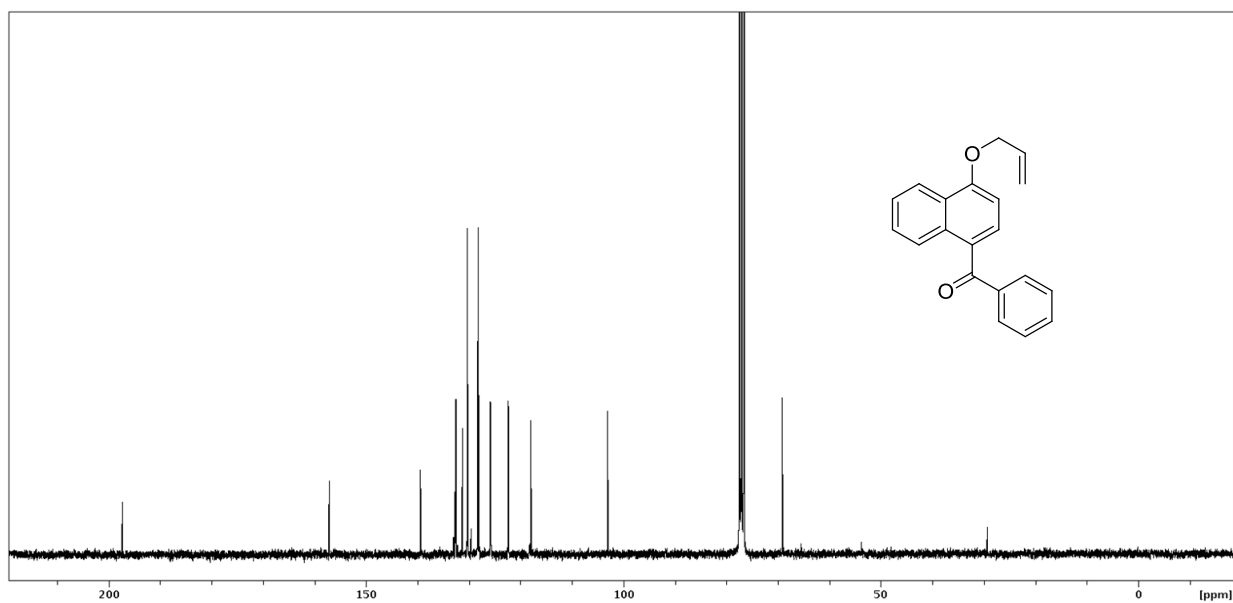
¹H NMR spectrum of 3.16, R = Me (300 MHz, CDCl₃)



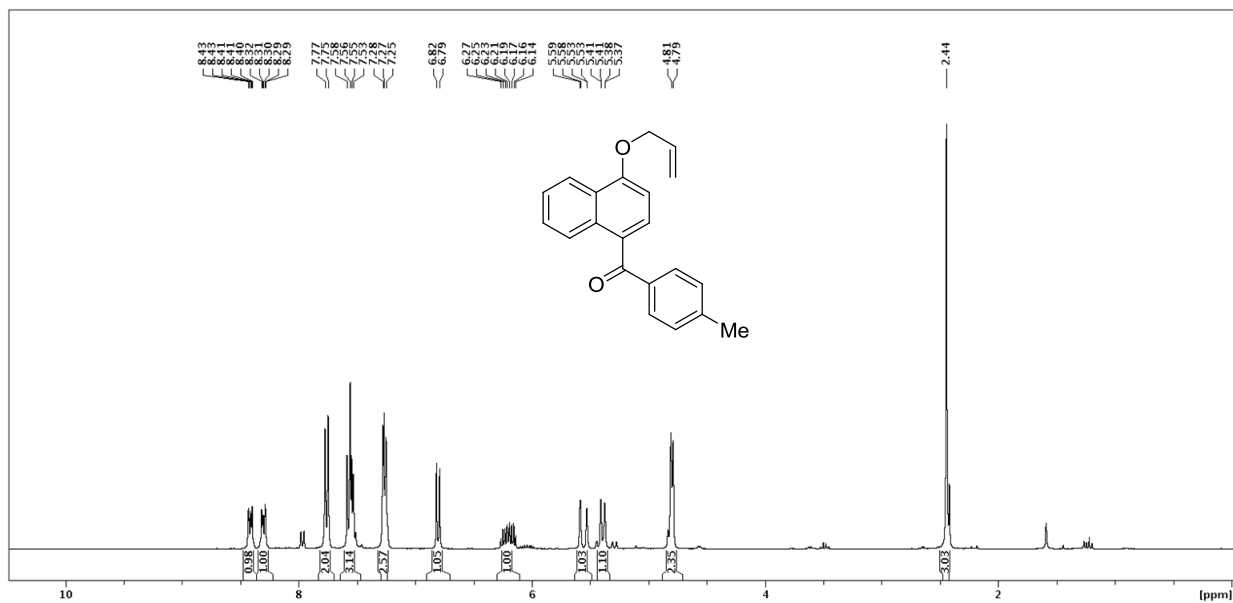
¹³C NMR spectrum of 3.16, R = Me (75 MHz, CDCl₃)



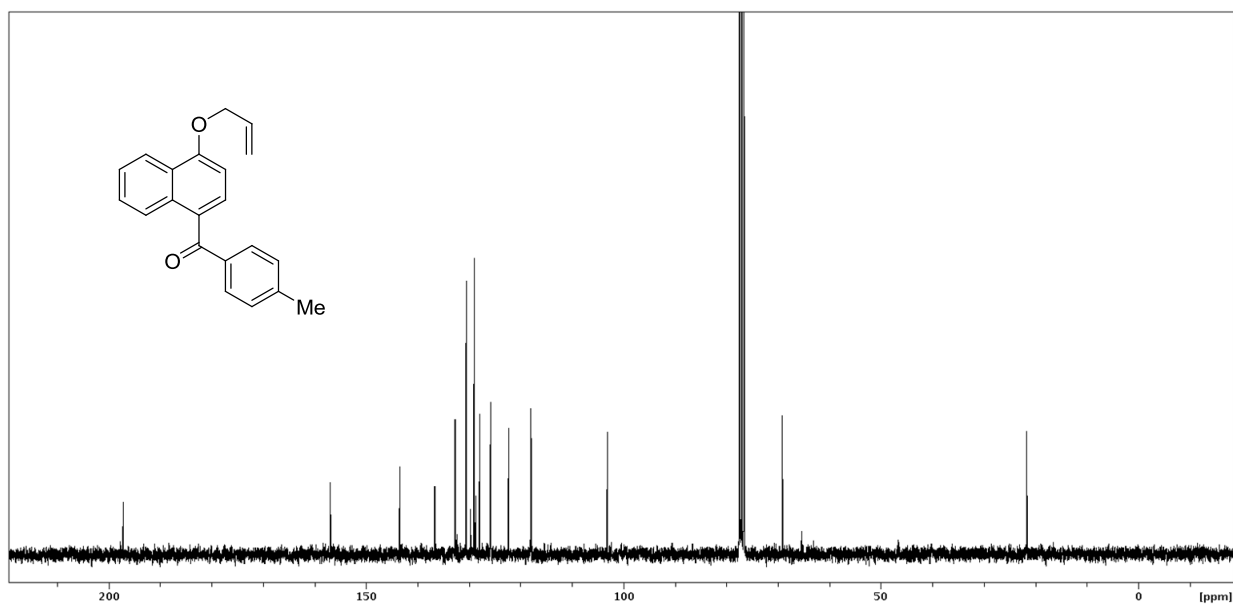
¹H NMR spectrum of 3.16, R = Ph (300 MHz, CDCl₃)



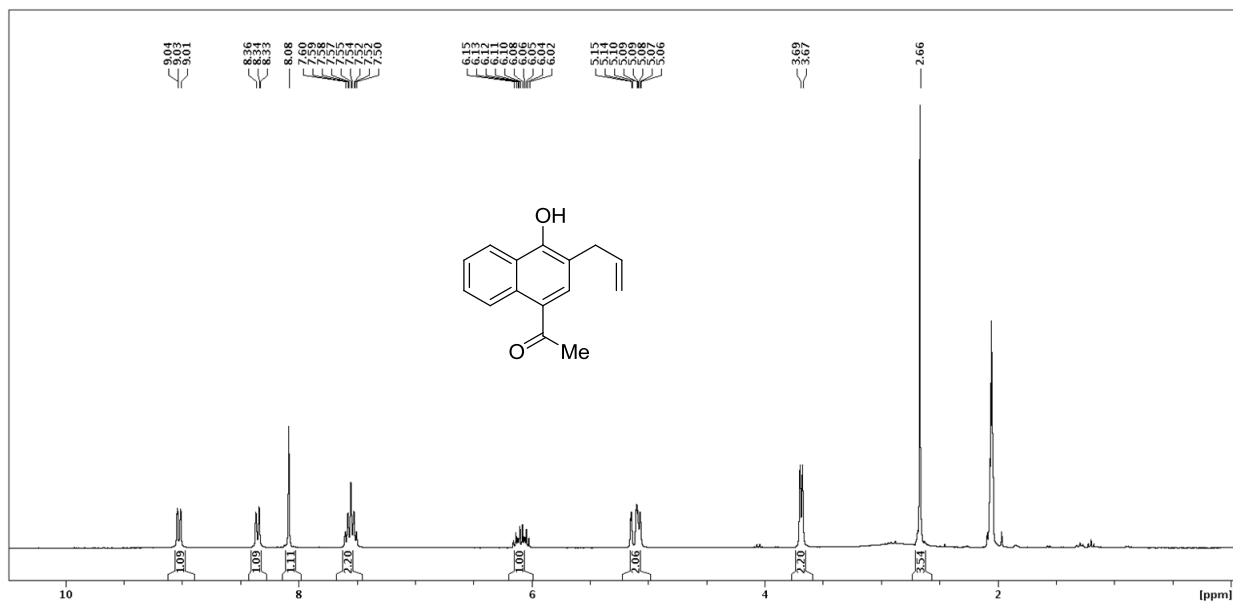
¹³C NMR spectrum of 3.16, R = Ph (75 MHz, CDCl₃)



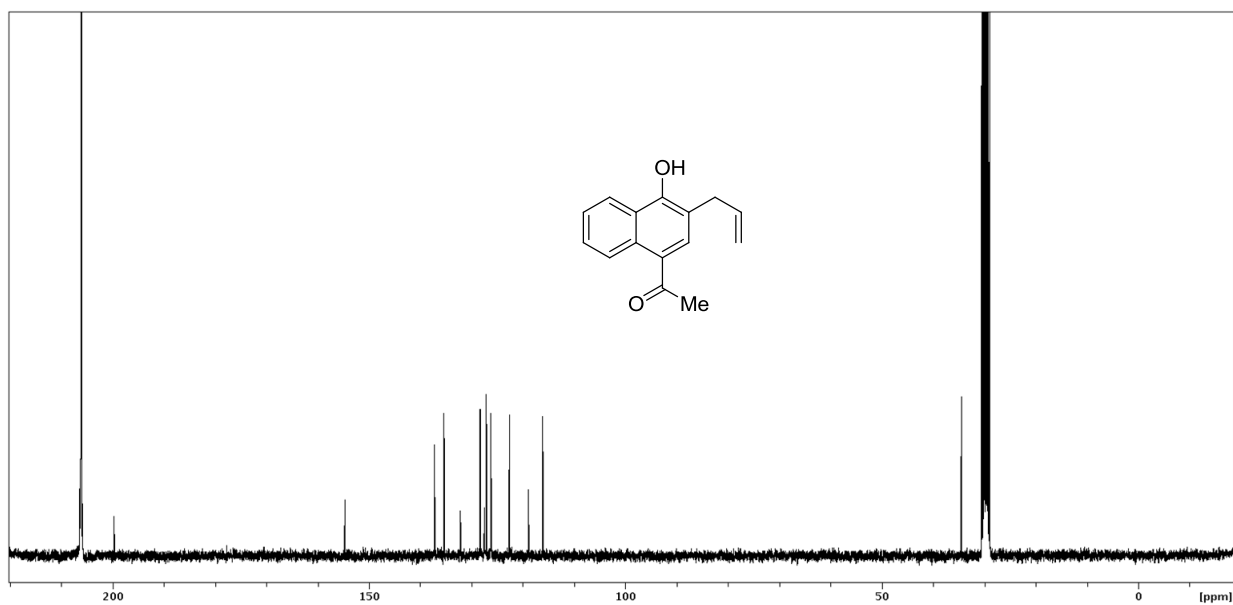
¹H NMR spectrum of 3.16, R = 4-Tol (300 MHz, CDCl₃)



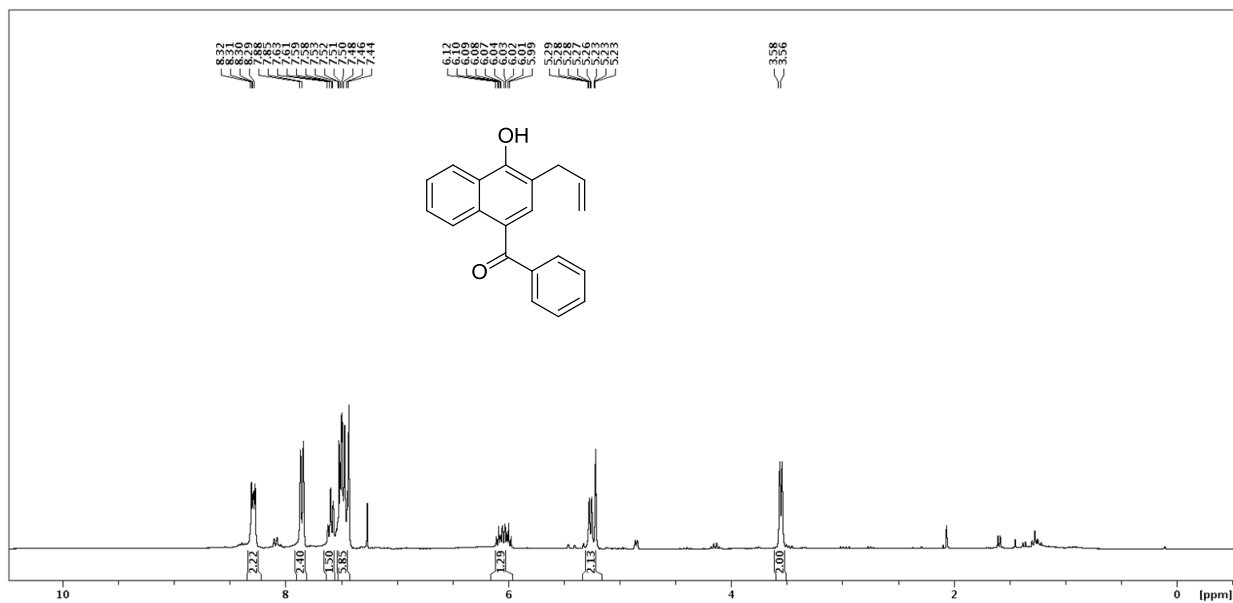
¹³C NMR spectrum of 3.16, R = 4-Tol (75 MHz, CDCl₃)



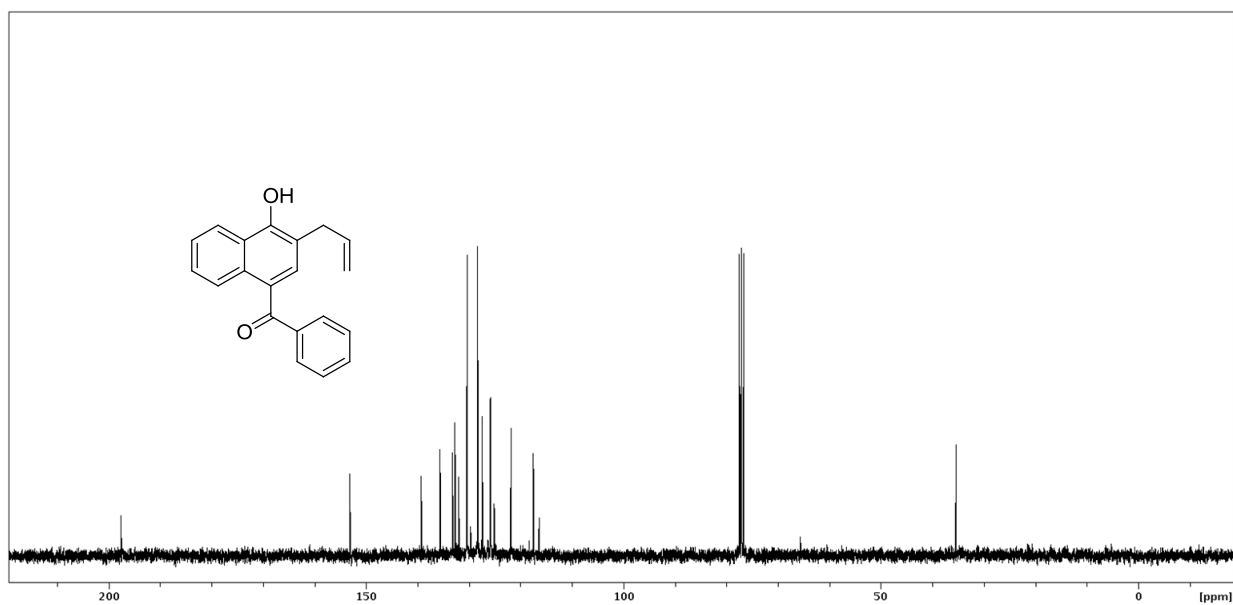
¹H NMR spectrum of 3.17, R = Me (300 MHz, acetone-*d*₆)



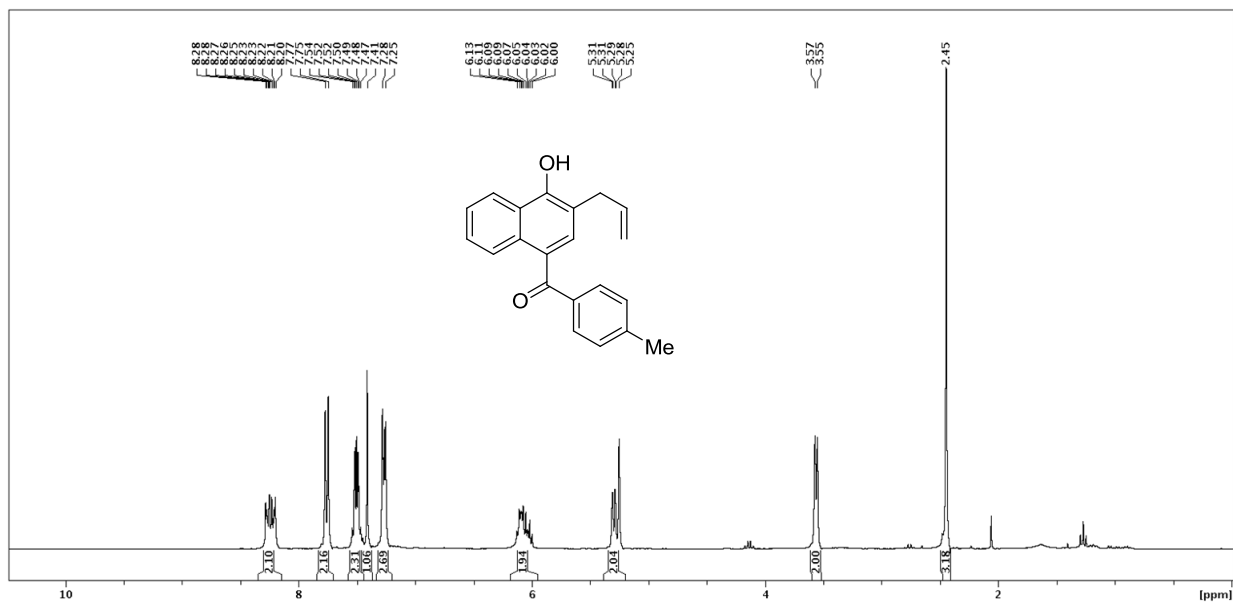
¹³C NMR spectrum of 3.17, R = Me (75 MHz, acetone-*d*₆)



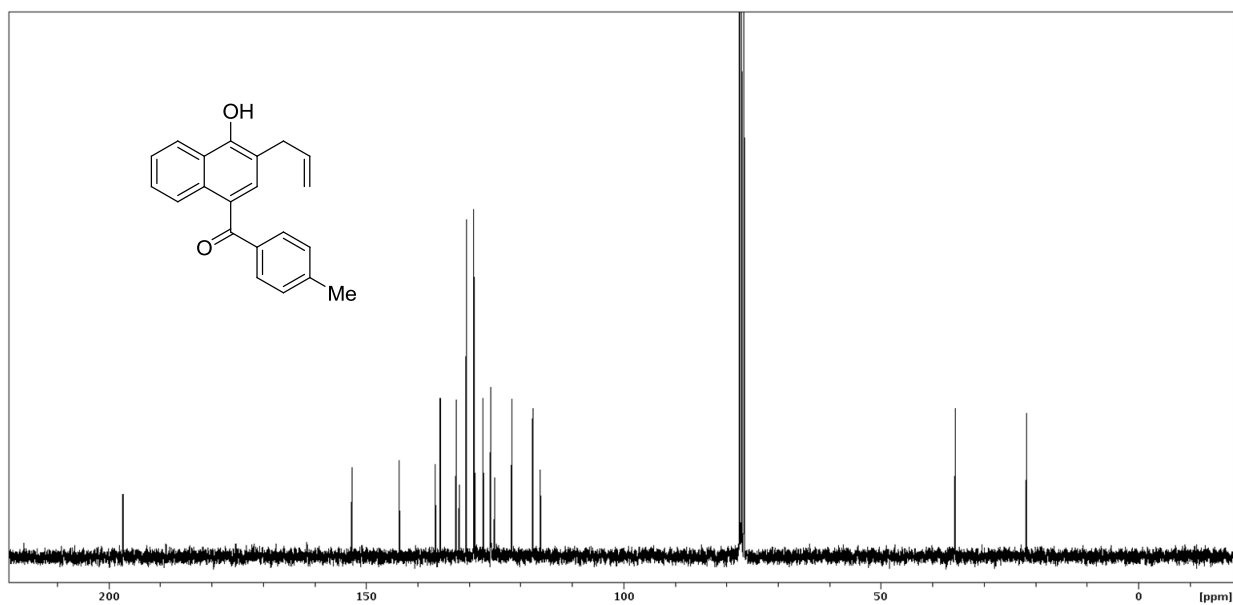
^1H NMR spectrum of 3.17, R = Ph (300 MHz, CDCl_3)



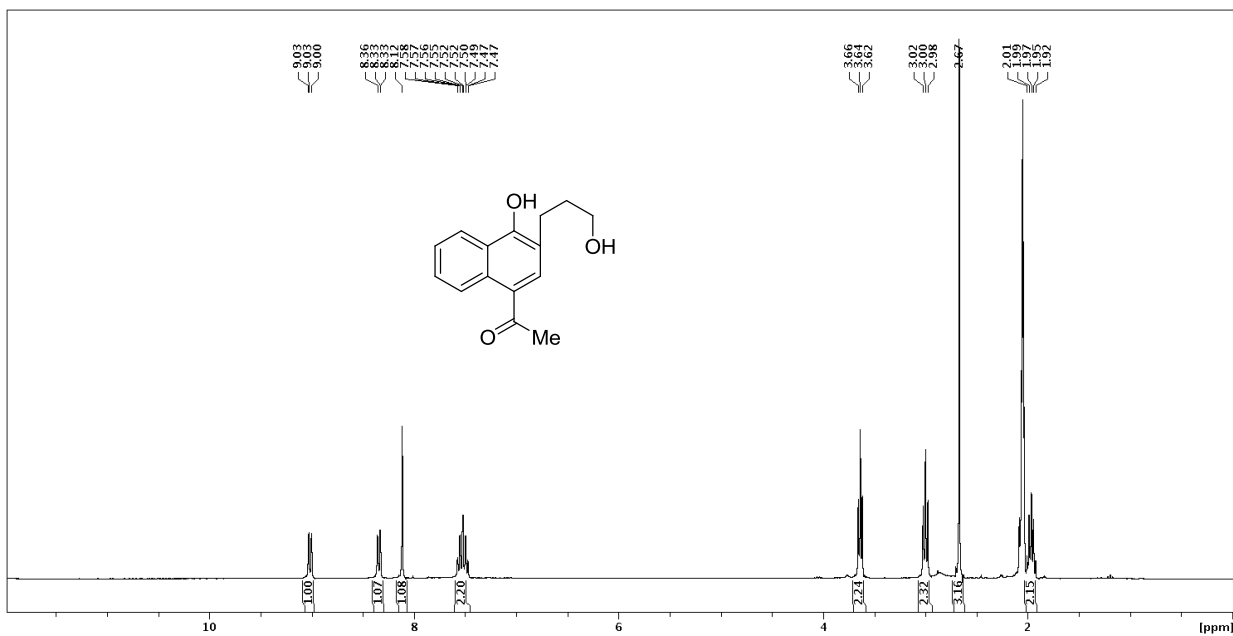
^{13}C NMR spectrum of 3.17, R = Ph (75 MHz, CDCl_3)



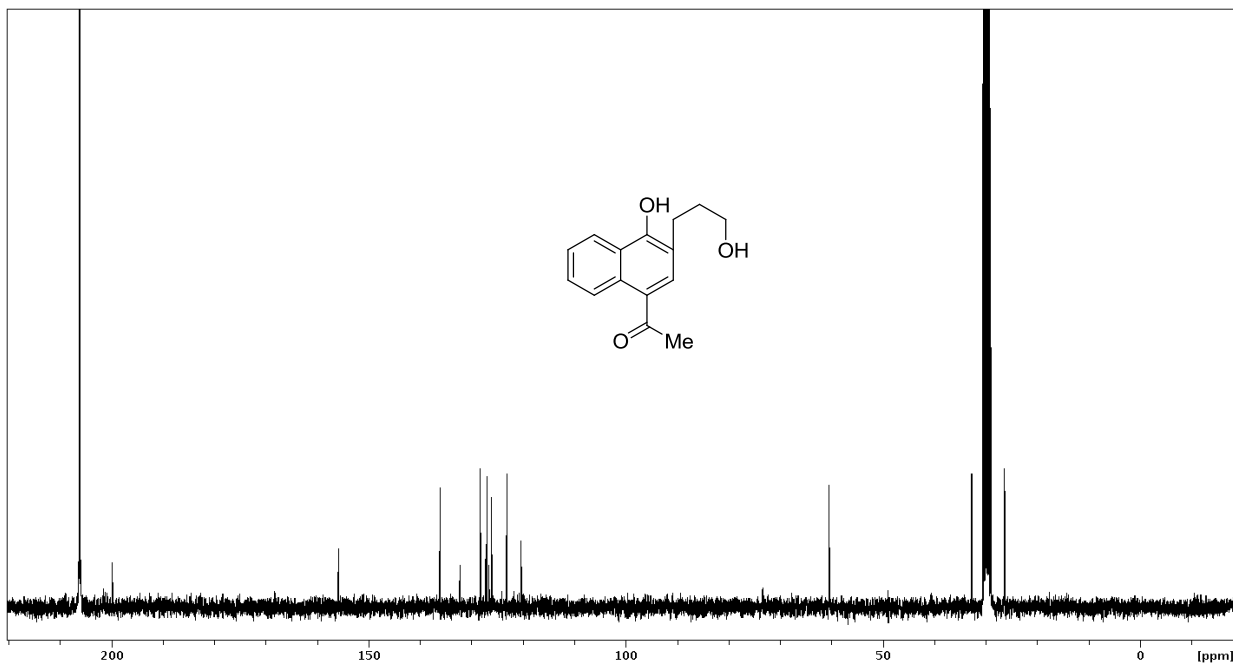
¹H NMR spectrum of 3.17, R = 4-Tol (300 MHz, CDCl₃)



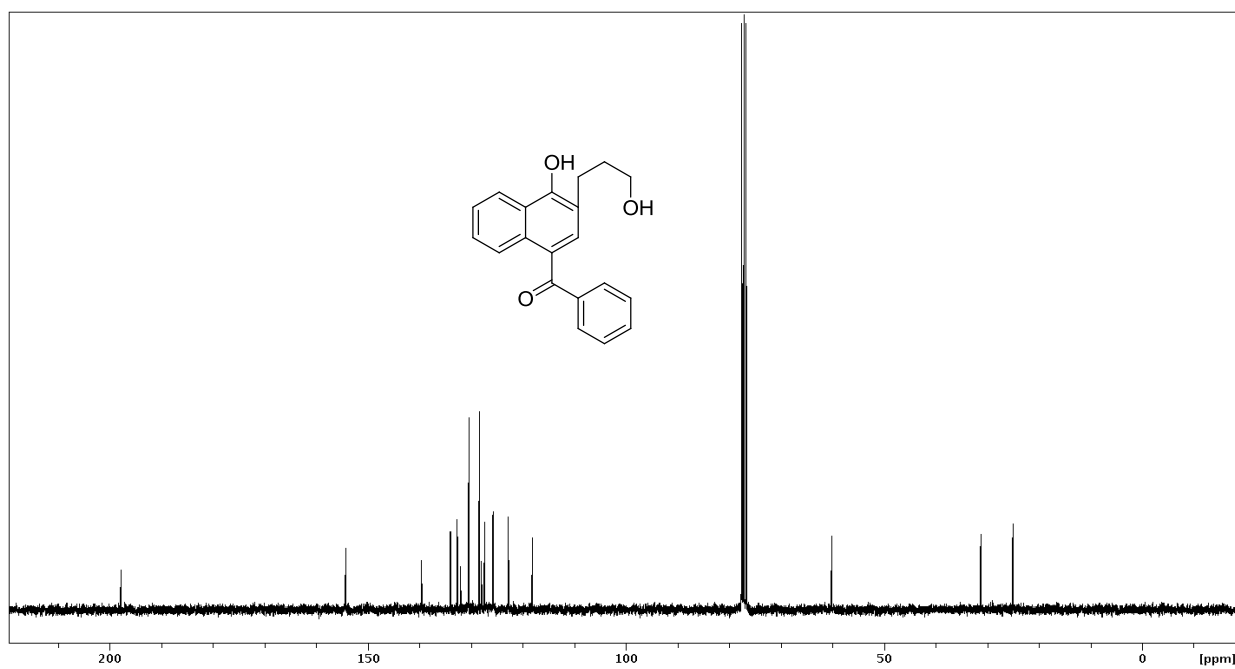
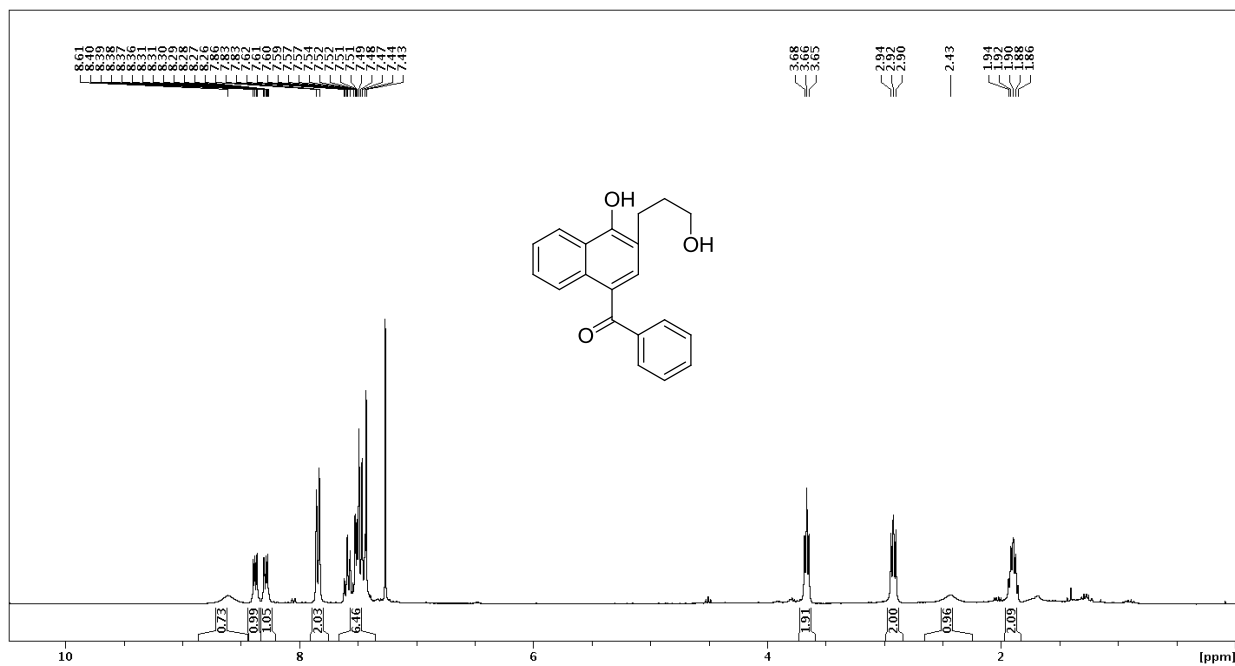
¹³C NMR spectrum of 3.17, R = 4-Tol (75 MHz, CDCl₃)

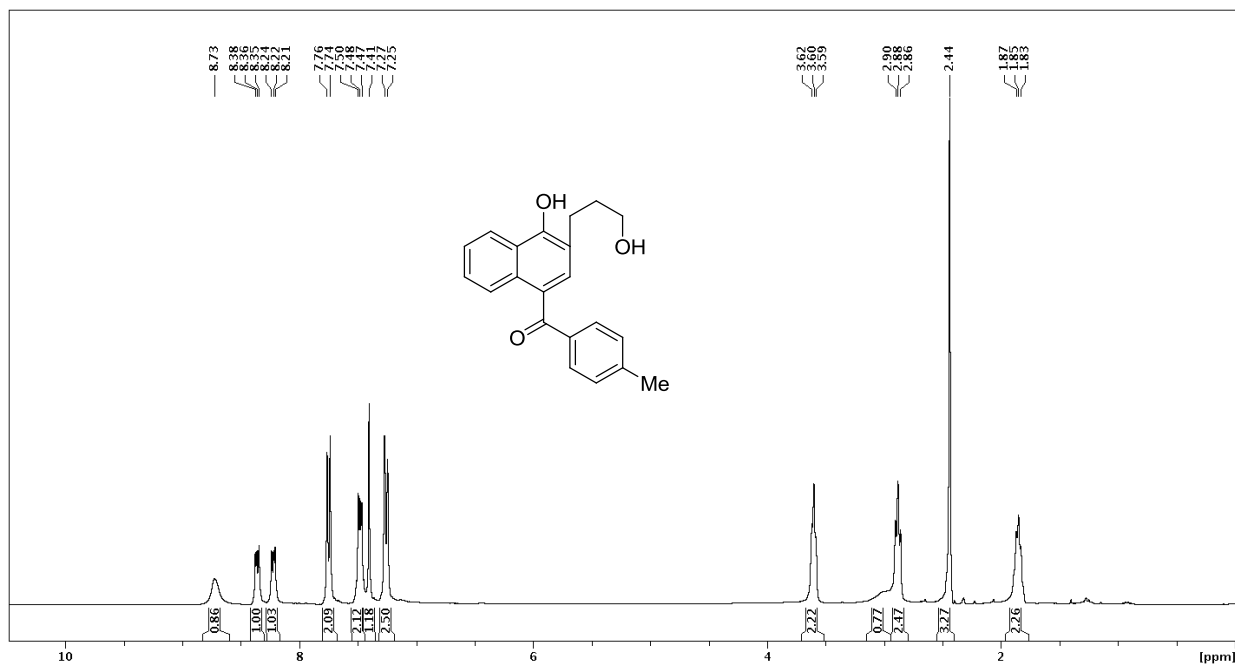


¹H NMR spectrum of 3.18, R = Me (300 MHz, acetone-*d*₆)

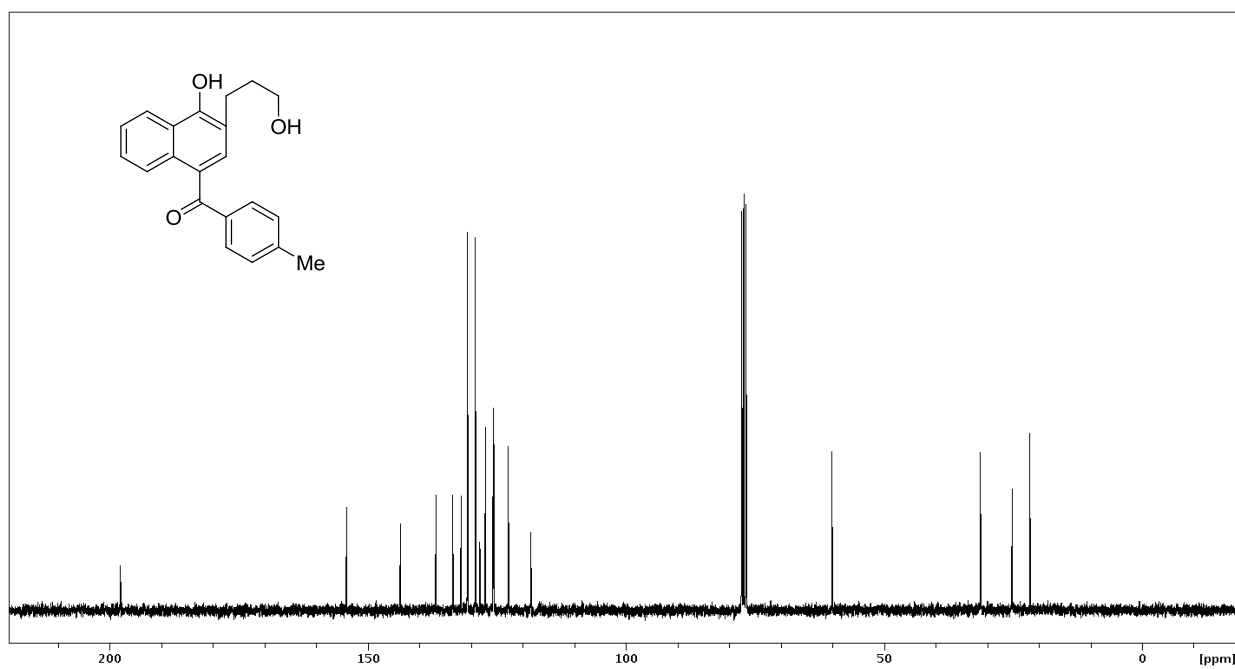


¹³C NMR spectrum of 3.18, R = Me (75 MHz, acetone-*d*₆)

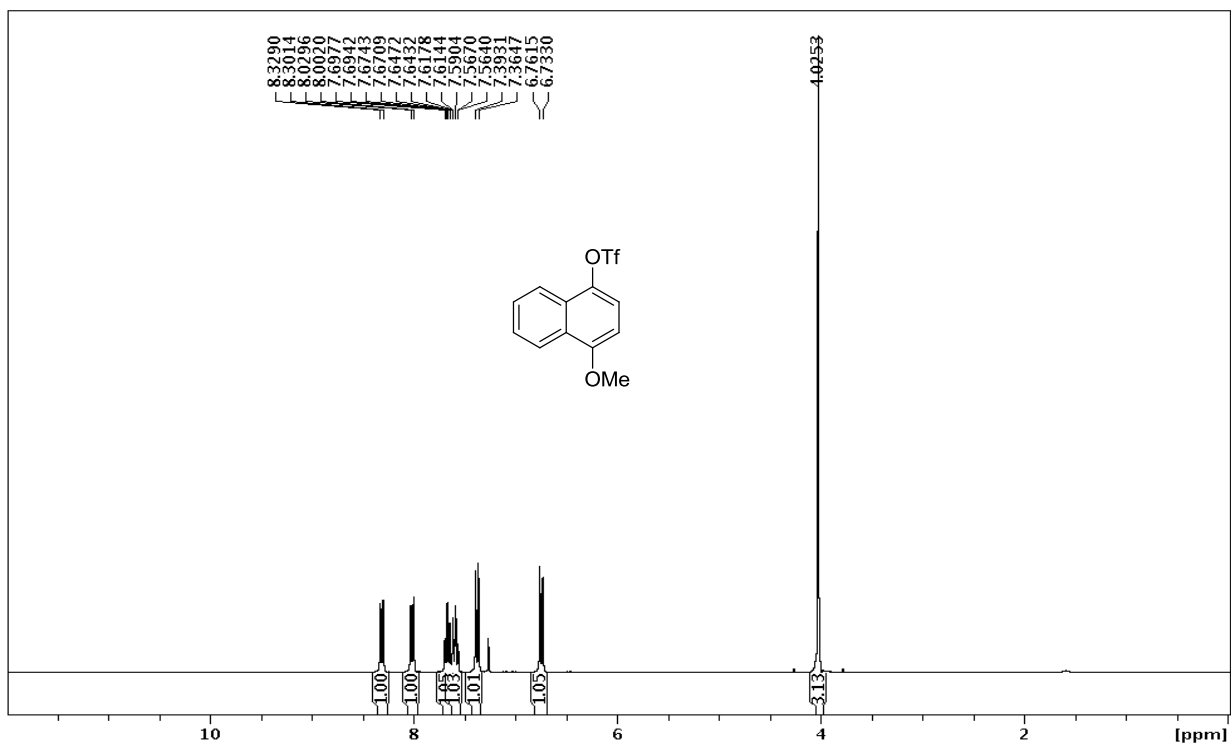




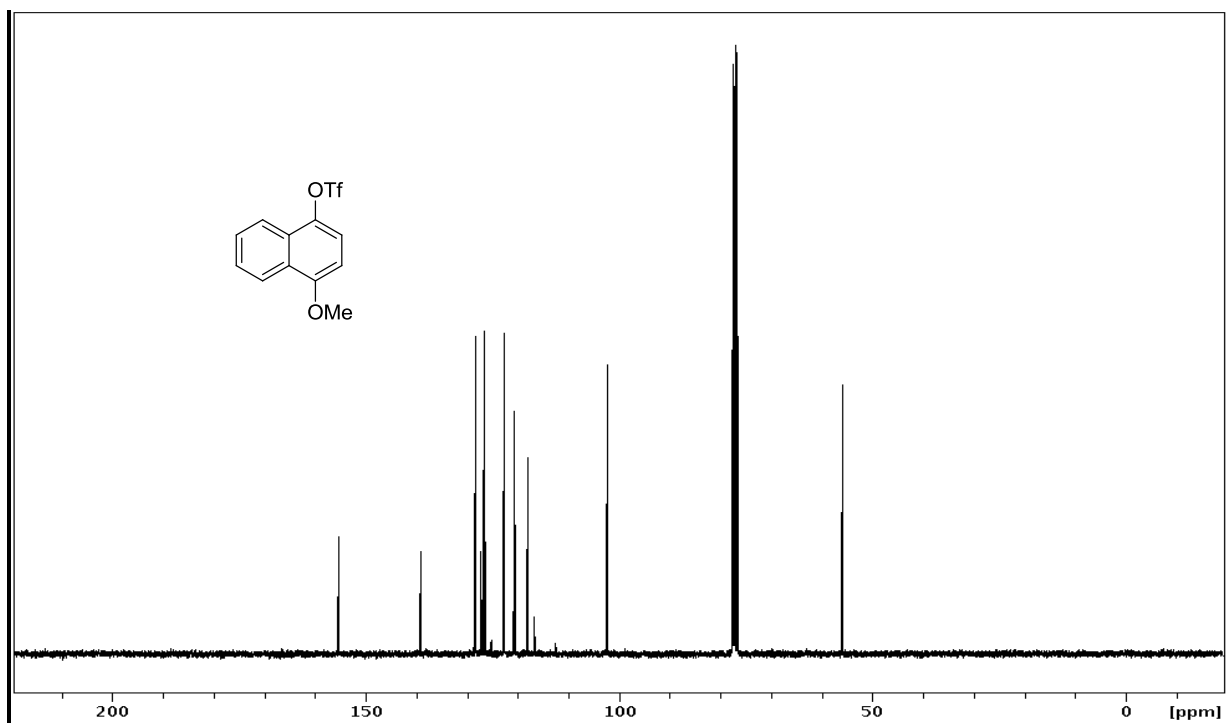
¹H NMR spectrum of 3.18, R = 4-Tol (300 MHz, CDCl₃)



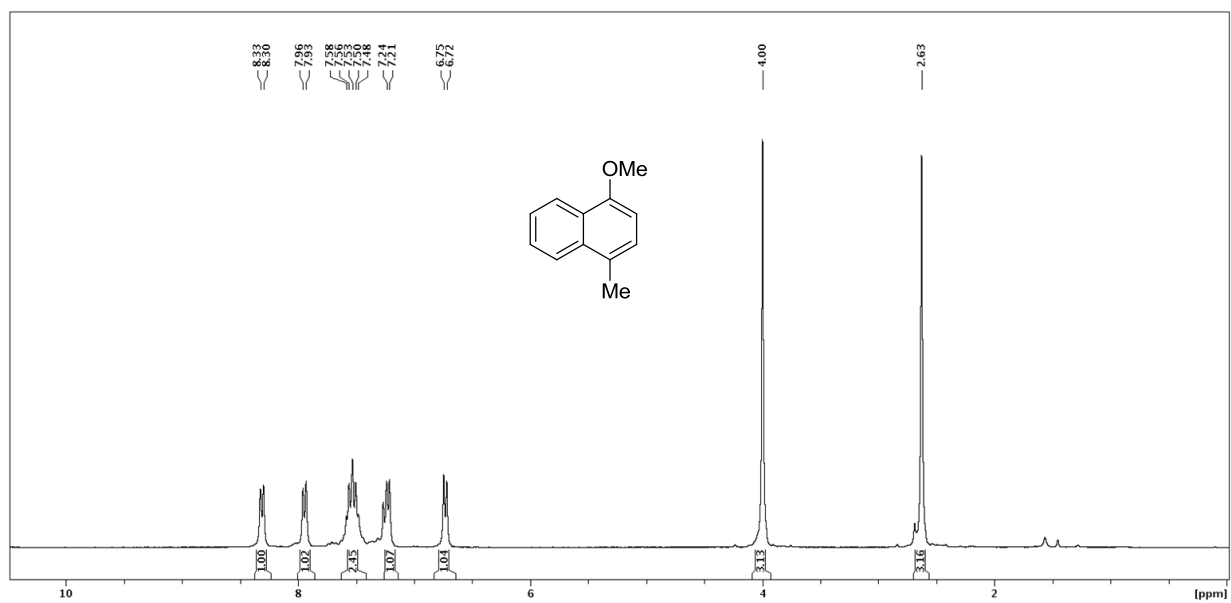
¹³C NMR spectrum of 3.18, R = 4-Tol (75 MHz, CDCl₃)



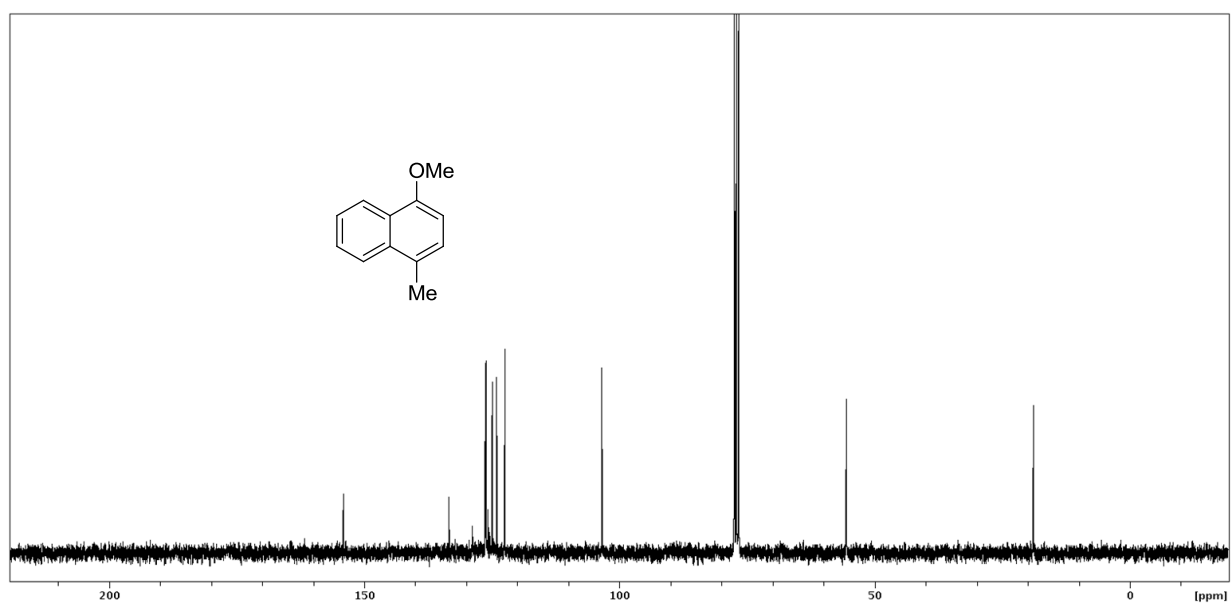
¹H NMR spectrum of 3.19 (300 MHz, CDCl₃)



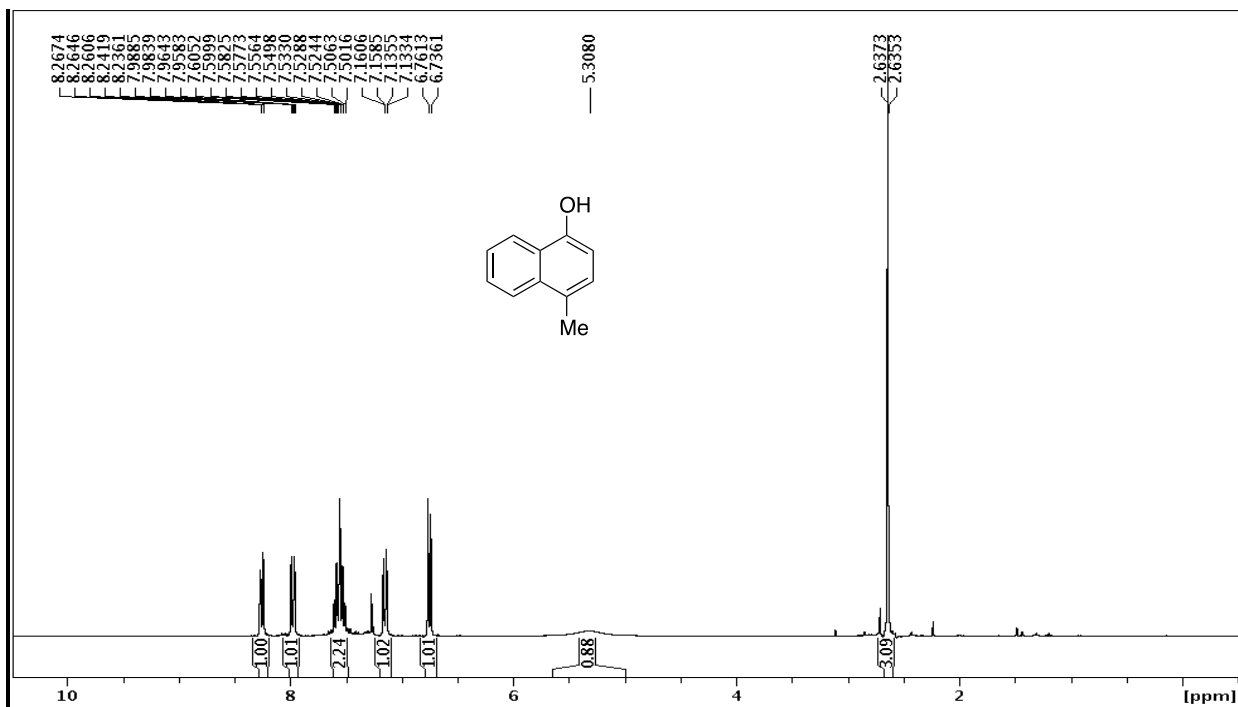
¹³C NMR spectrum of 3.19 (75 MHz, CDCl₃)



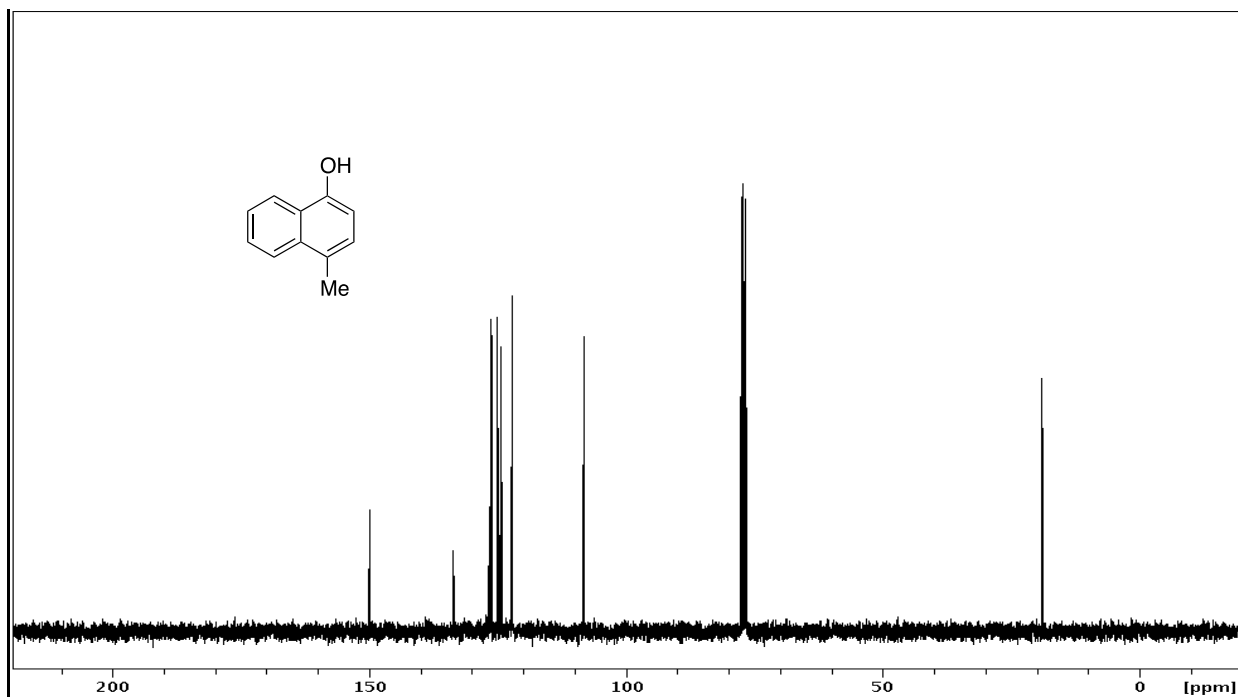
¹H NMR spectrum of 3.20 (300 MHz, CDCl₃)



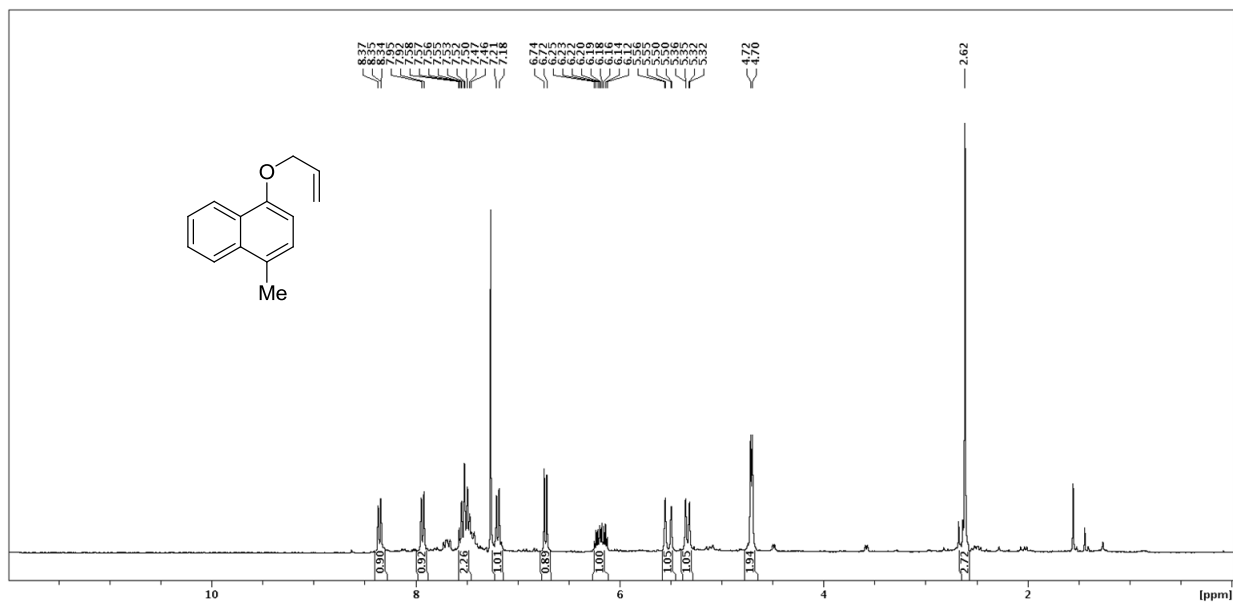
¹³C NMR spectrum of 3.20 (75 MHz, CDCl₃)



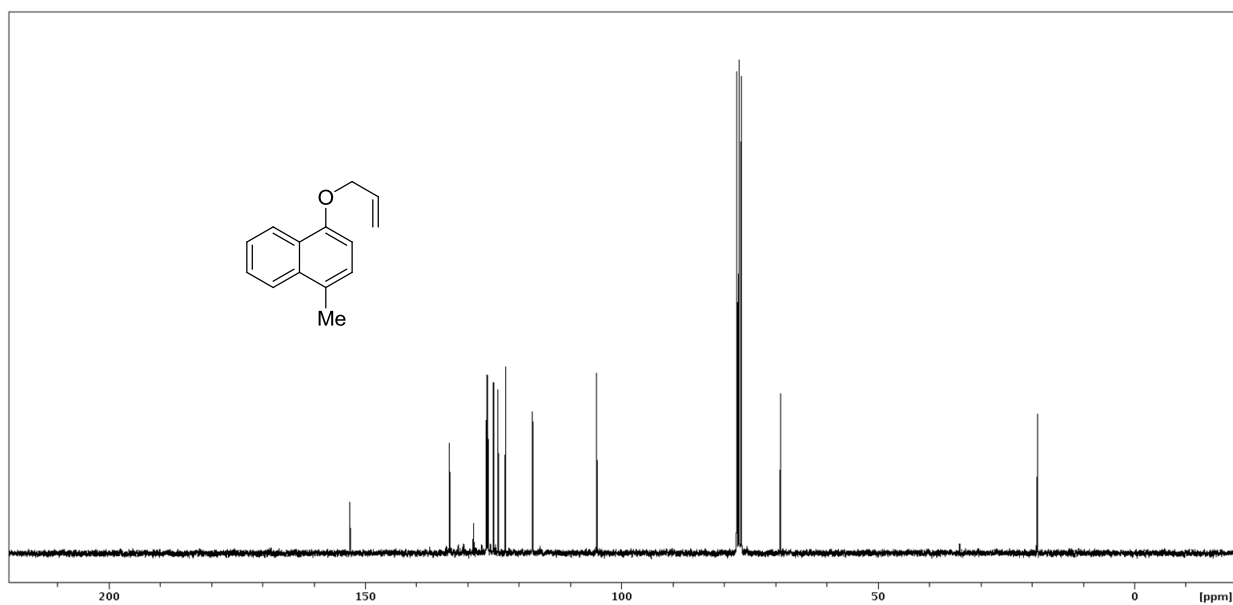
¹H NMR spectrum of 3.23, R = Me (300 MHz, CDCl₃)



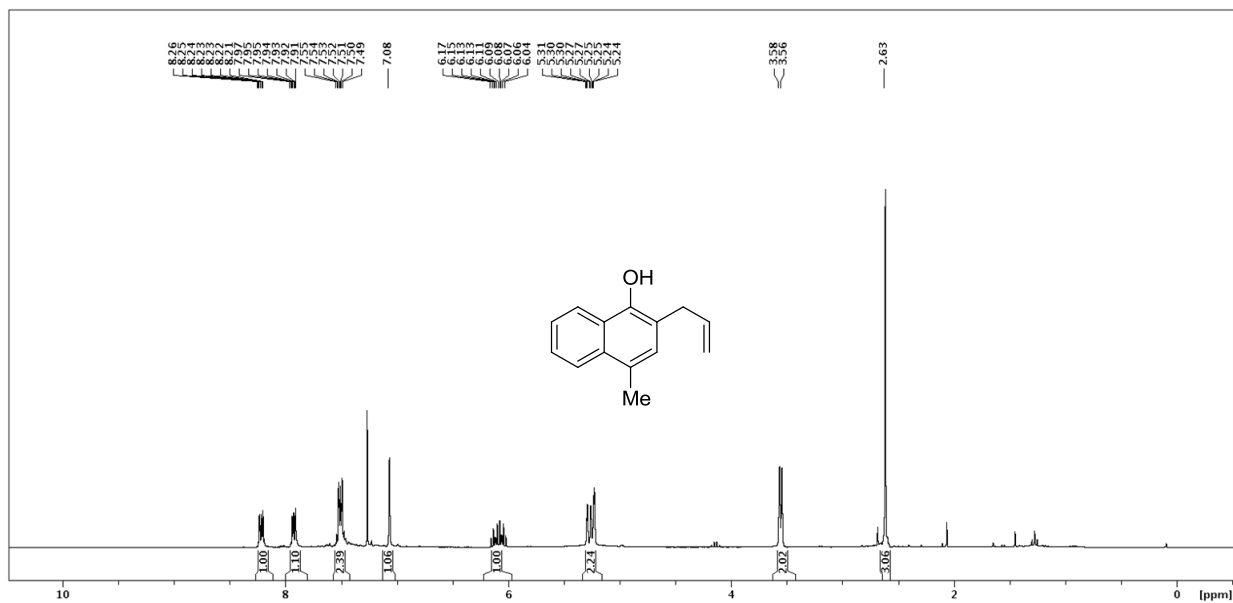
¹³C NMR spectrum of 3.23, R = Me (75 MHz, CDCl₃)



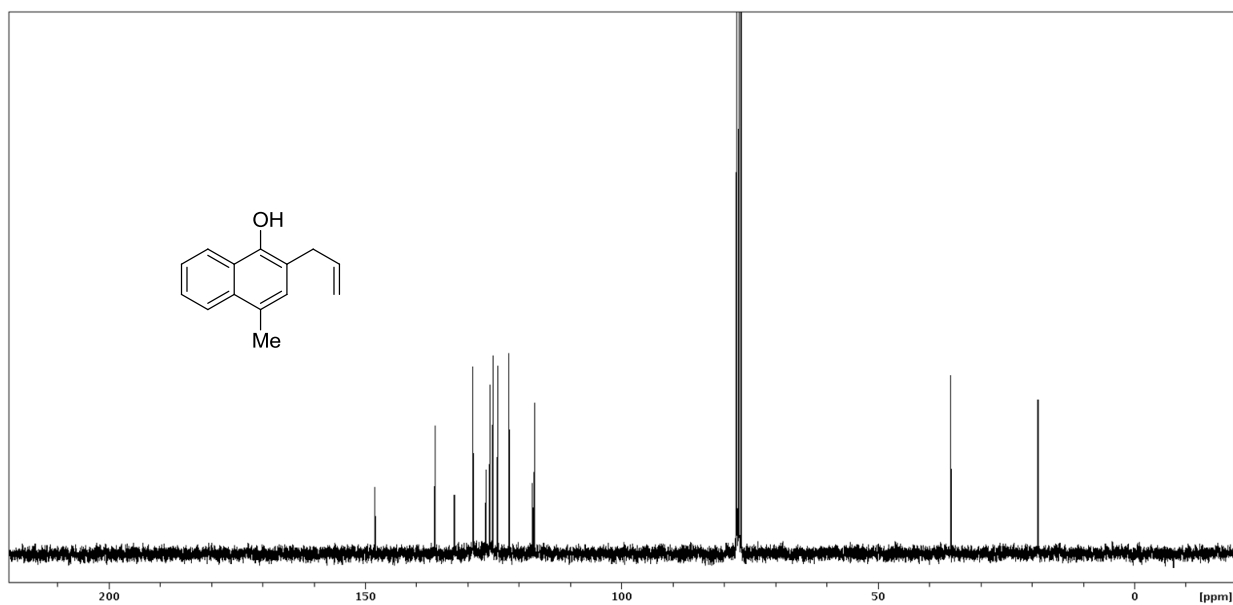
¹H NMR spectrum of crude 3.24, R = Me (300 MHz, CDCl₃)



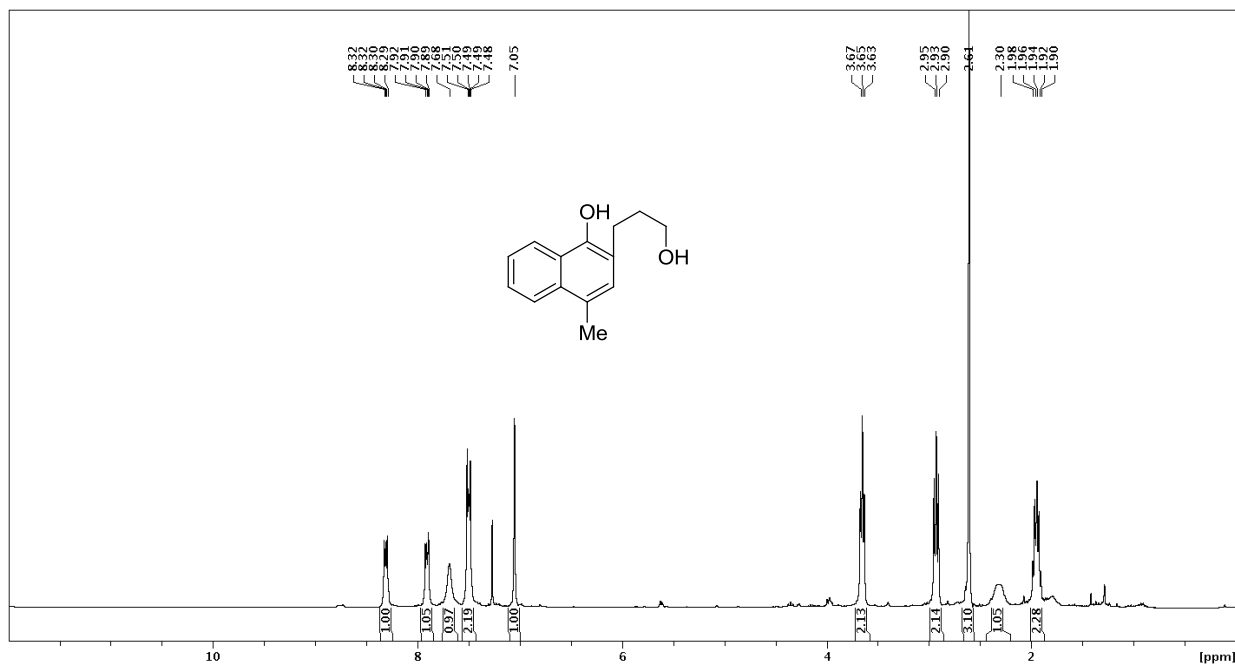
¹³C NMR spectrum of crude 3.24, R = Me (75 MHz, CDCl₃)



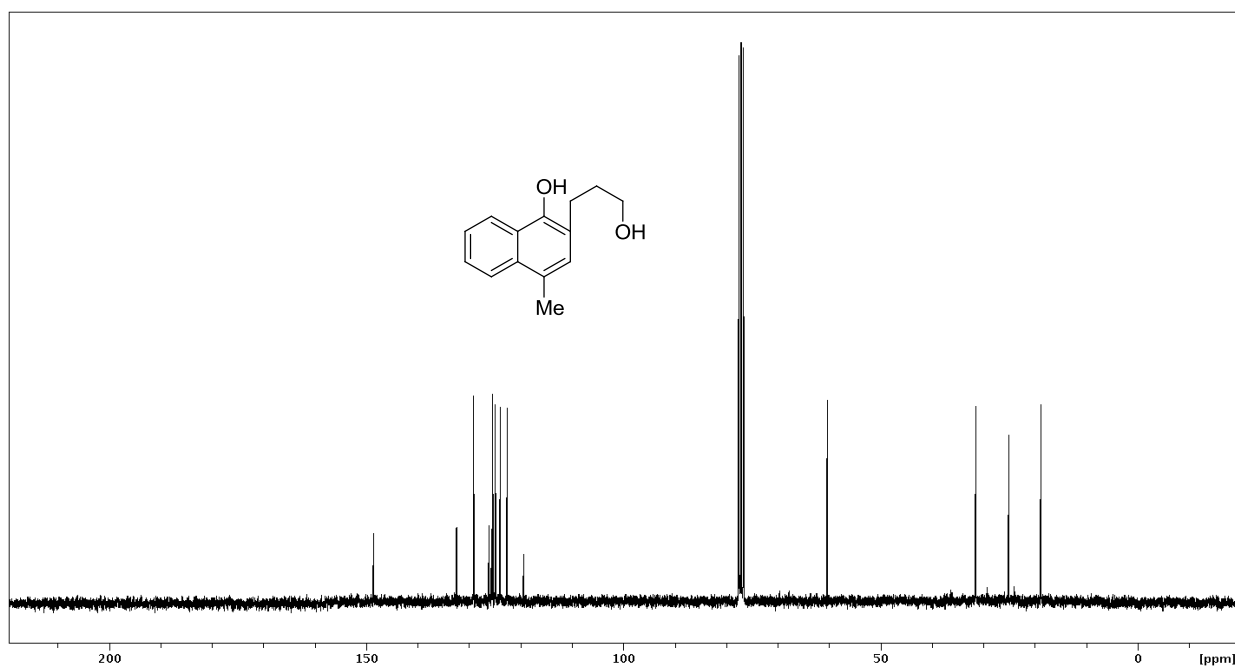
¹H NMR spectrum of 3.25, R = Me (300 MHz, CDCl₃)



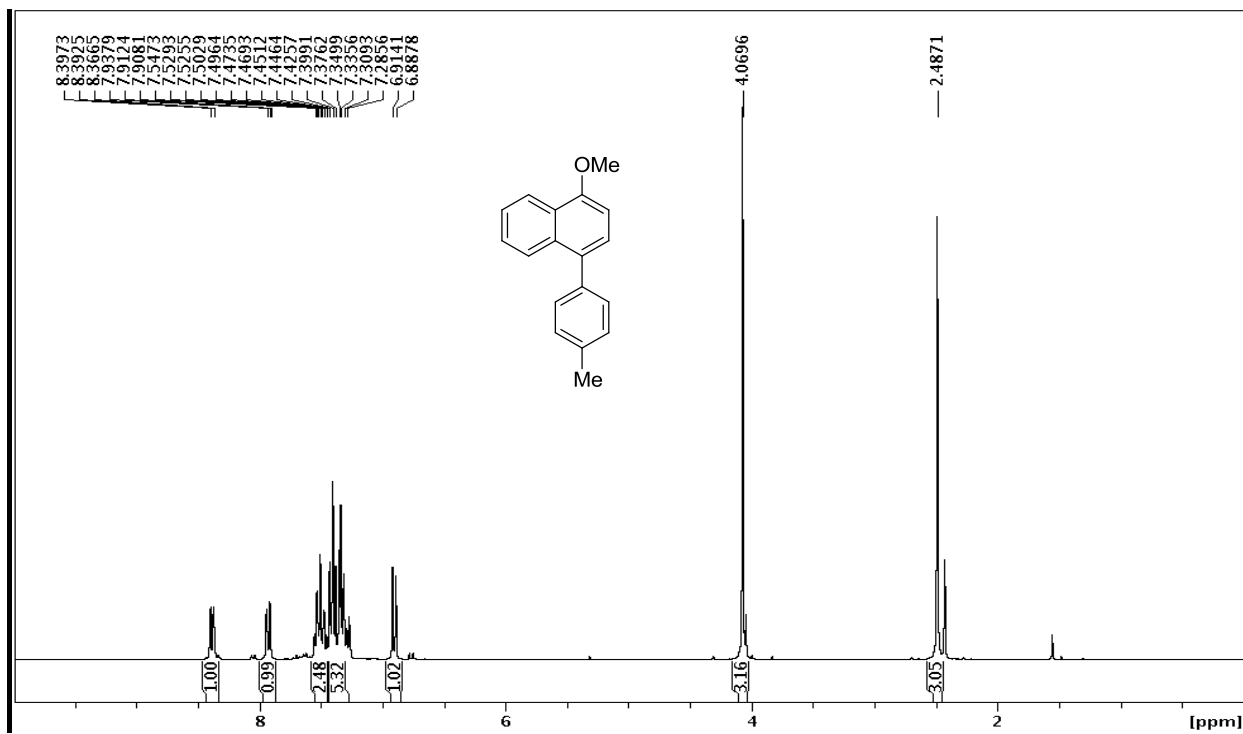
¹³C NMR spectrum of 3.25, R = Me (75 MHz, CDCl₃)



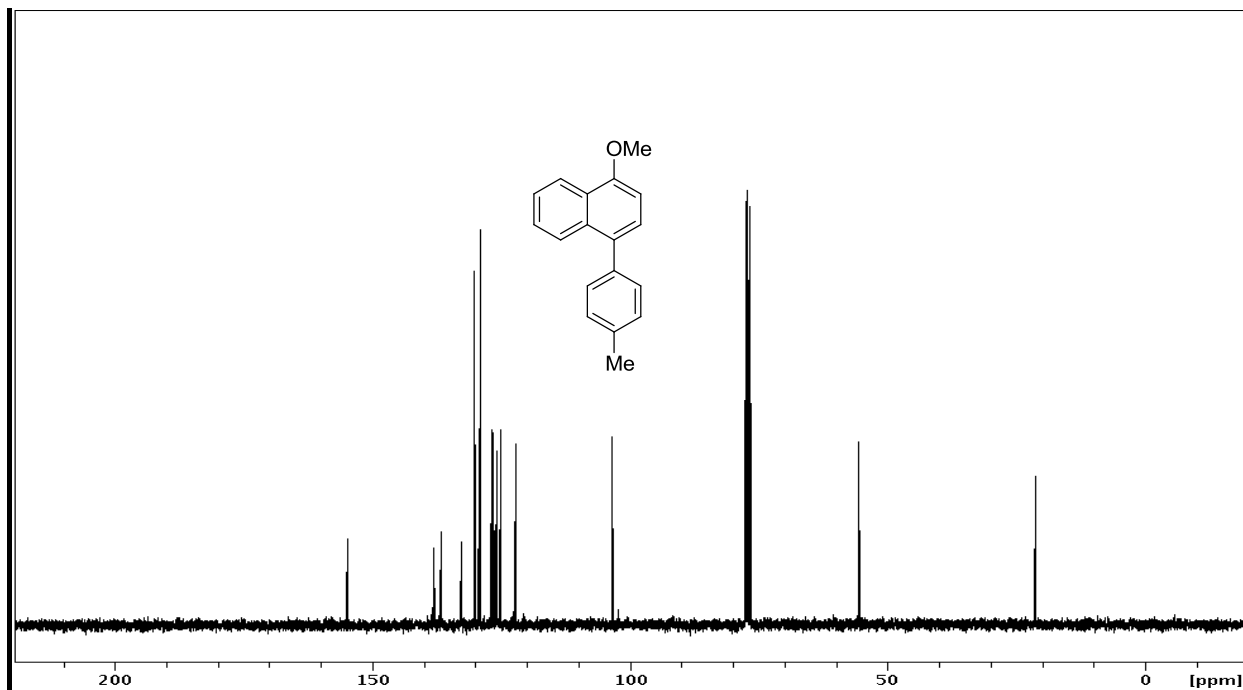
¹H NMR spectrum of 3.26, R = Me (300 MHz, CDCl₃)



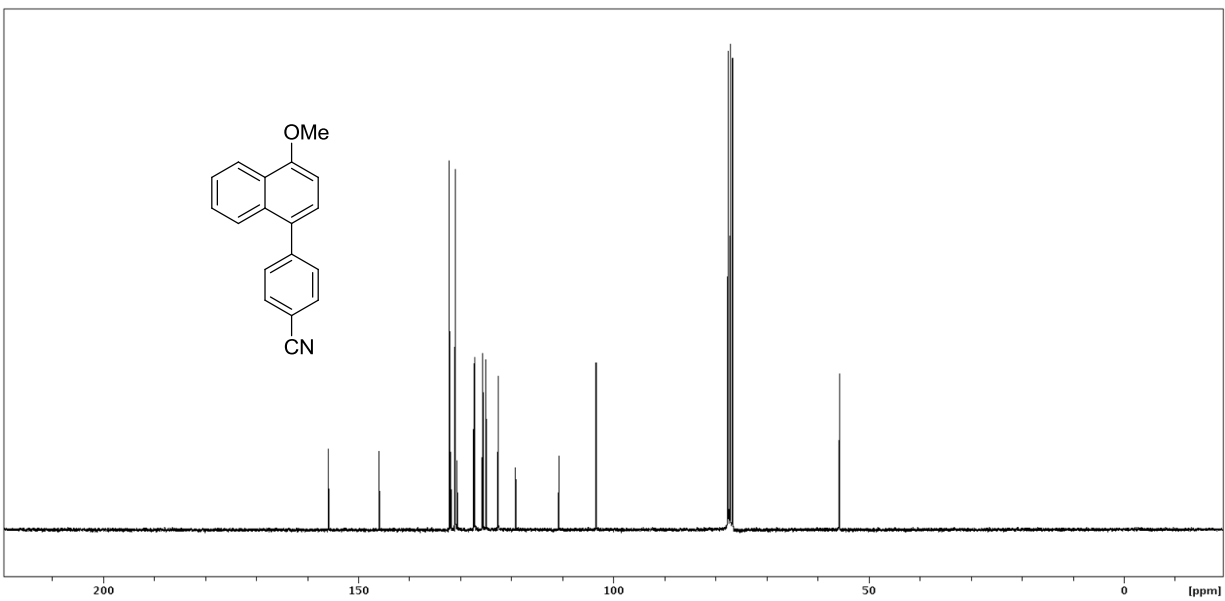
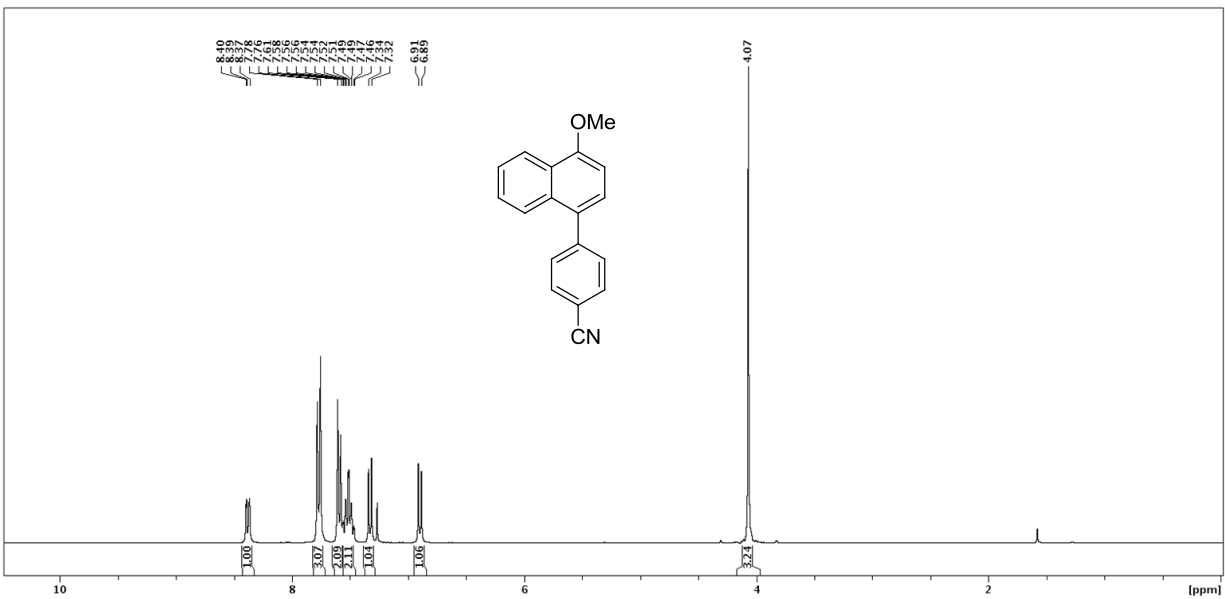
¹³C NMR spectrum of 3.26, R = Me (75 MHz, CDCl₃)

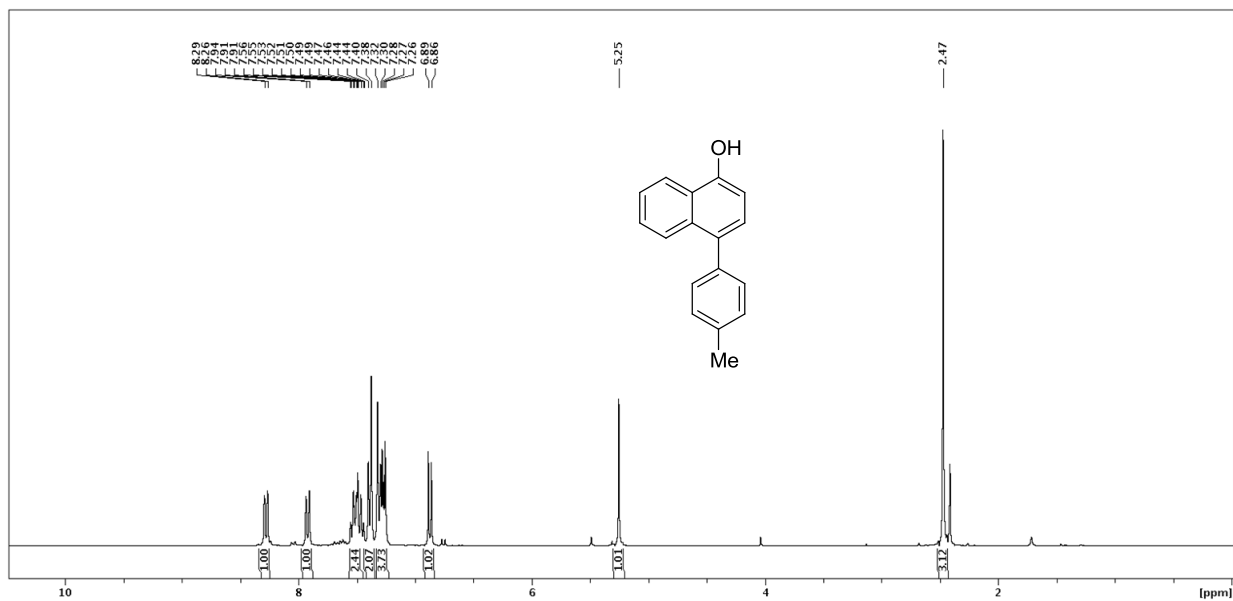


¹H NMR spectrum of 3.21, Ar = 4-Tol (300 MHz, CDCl₃)

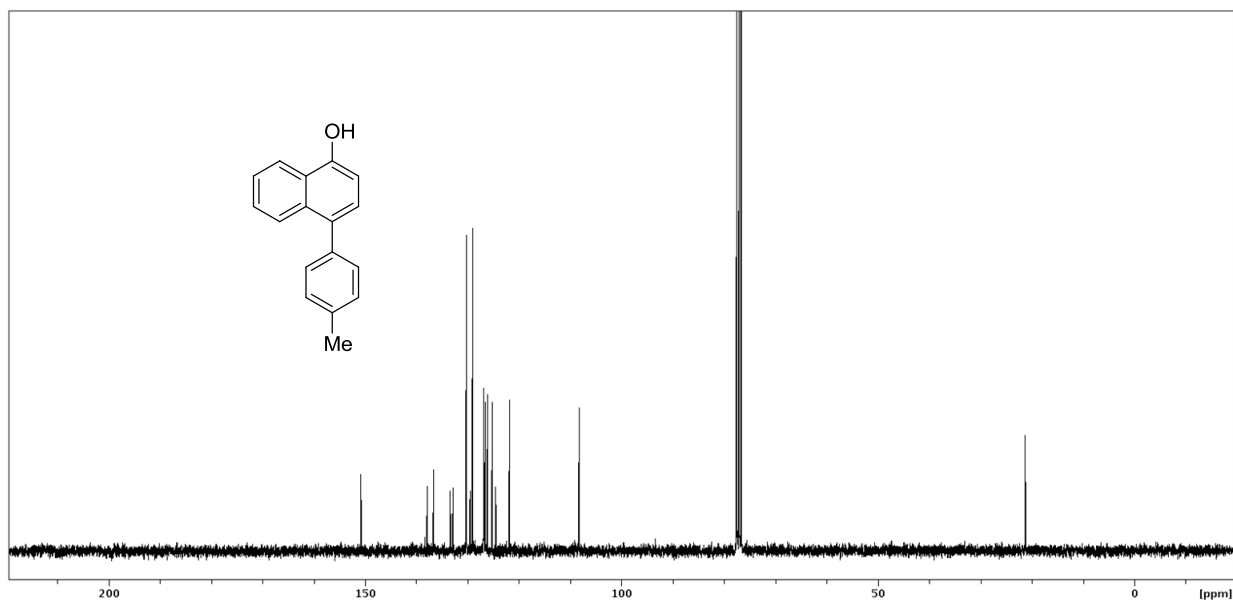


¹³C NMR spectrum of 3.21, Ar = 4-Tol (75 MHz, CDCl₃)

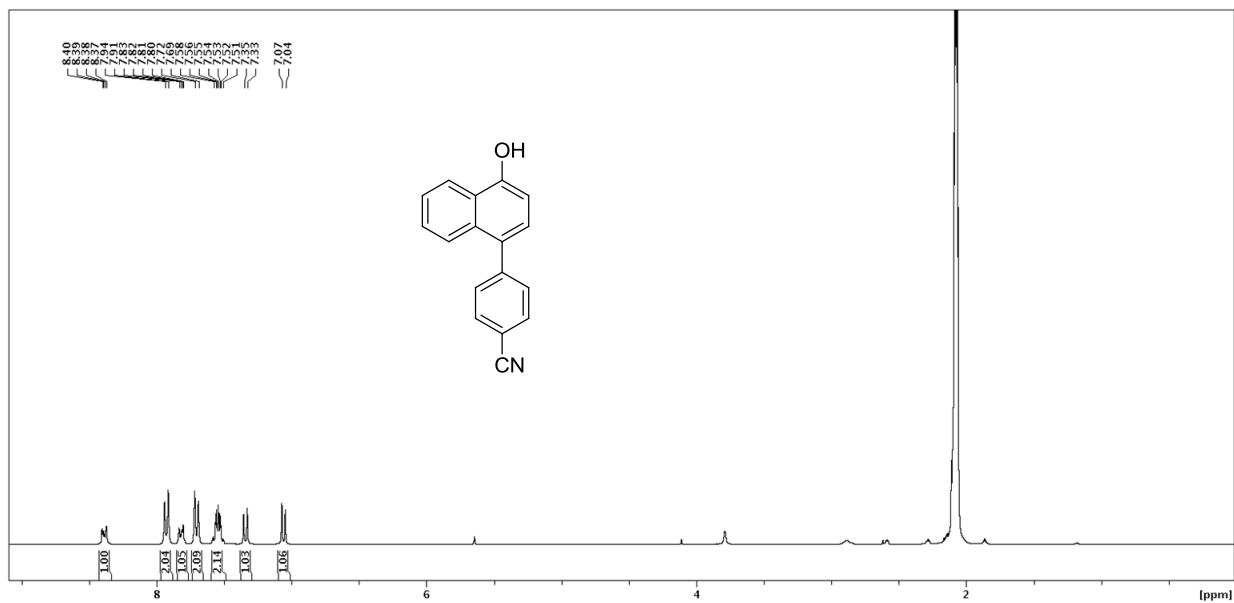




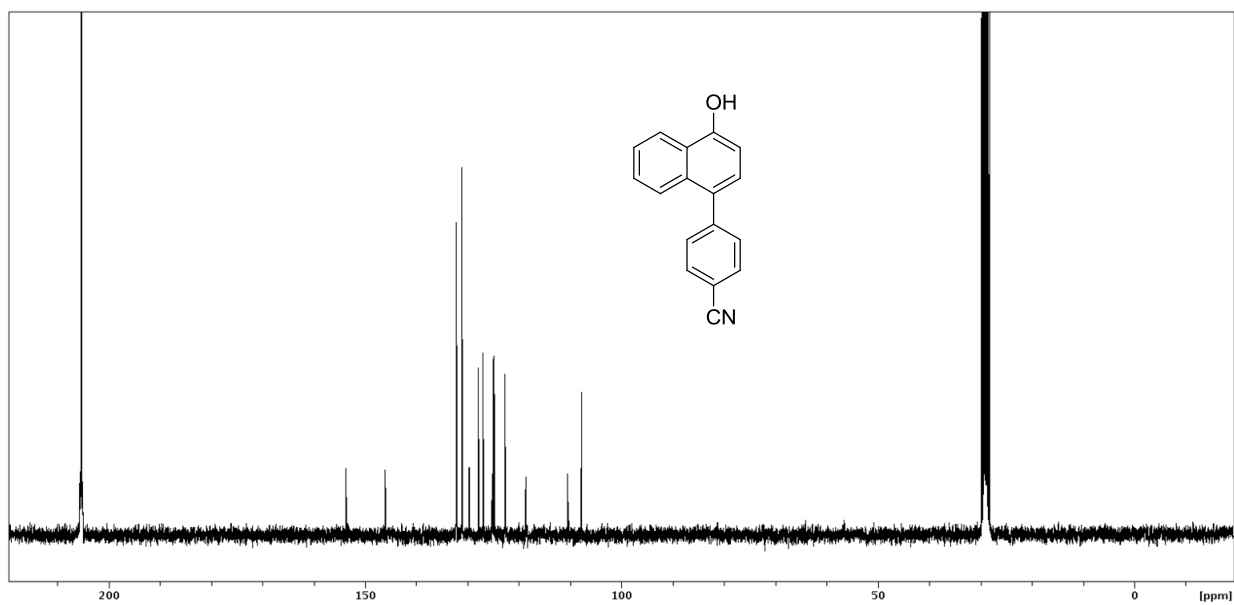
¹H NMR spectrum of 3.23, R = 4-Tol (300 MHz, CDCl₃)



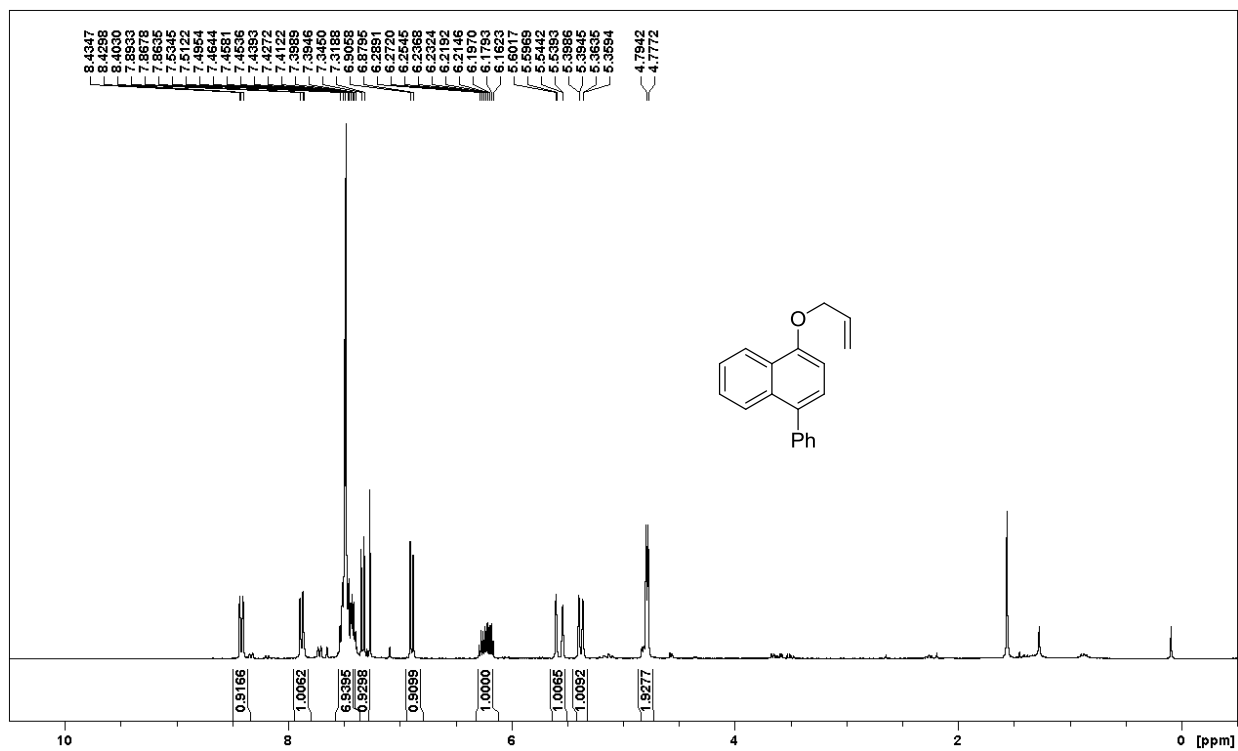
¹³C NMR spectrum of 3.23, R = 4-Tol (75 MHz, CDCl₃)



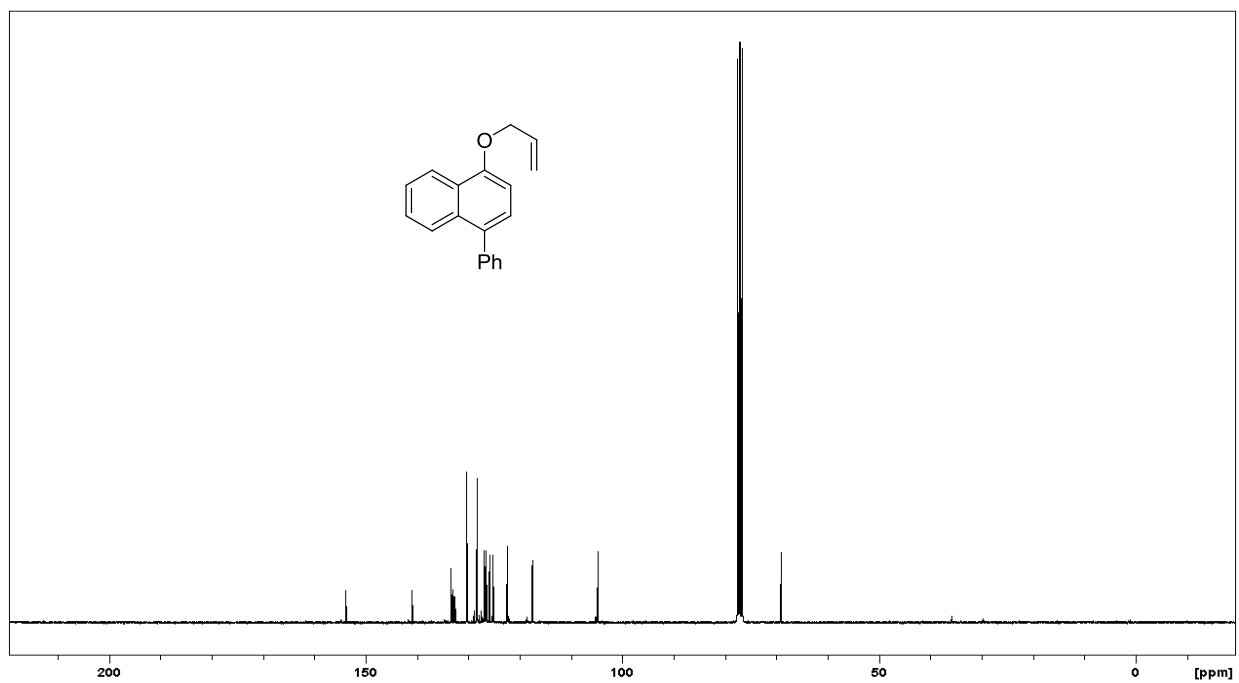
^1H NMR spectrum of 3.23, R = 4-NC-C $_6$ H $_4$ (300 MHz, acetone- d_6)



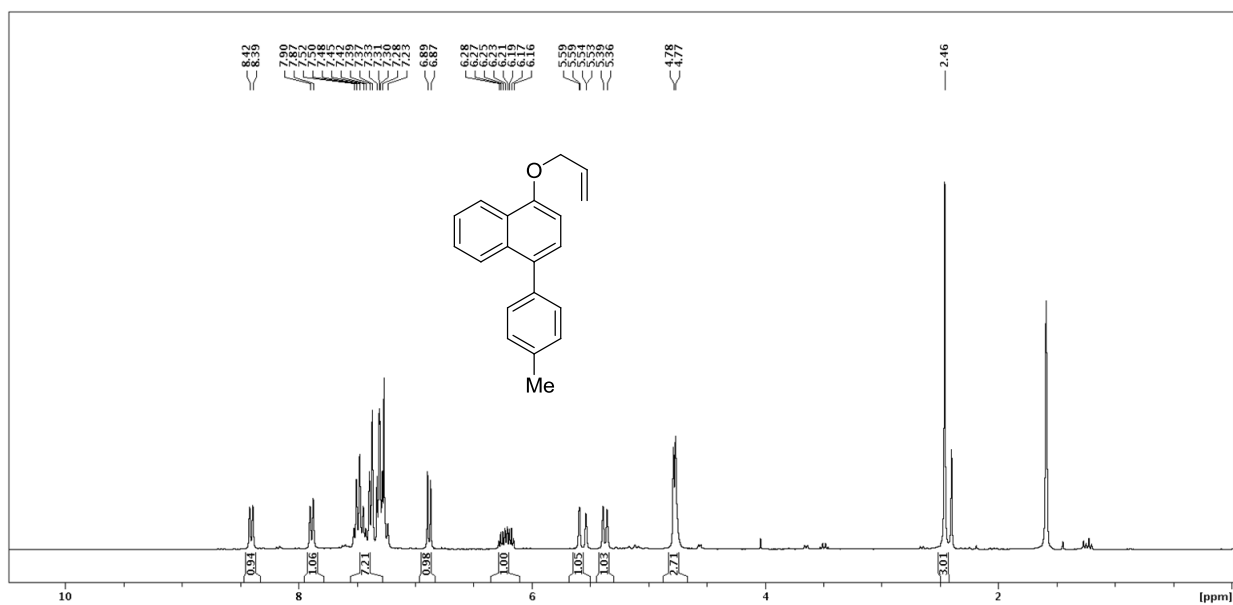
^{13}C NMR spectrum of 3.23, R = 4-NC-C $_6$ H $_4$ (75 MHz, acetone- d_6)



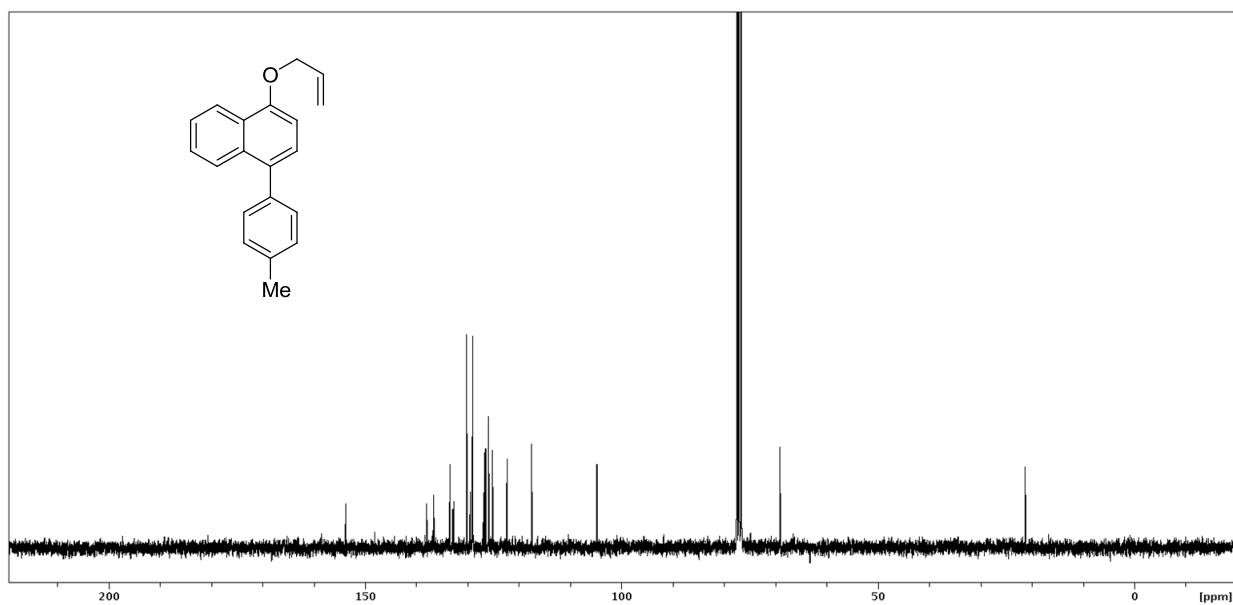
¹H NMR spectrum of crude 3.24, R = Ph (300 MHz, CDCl₃)



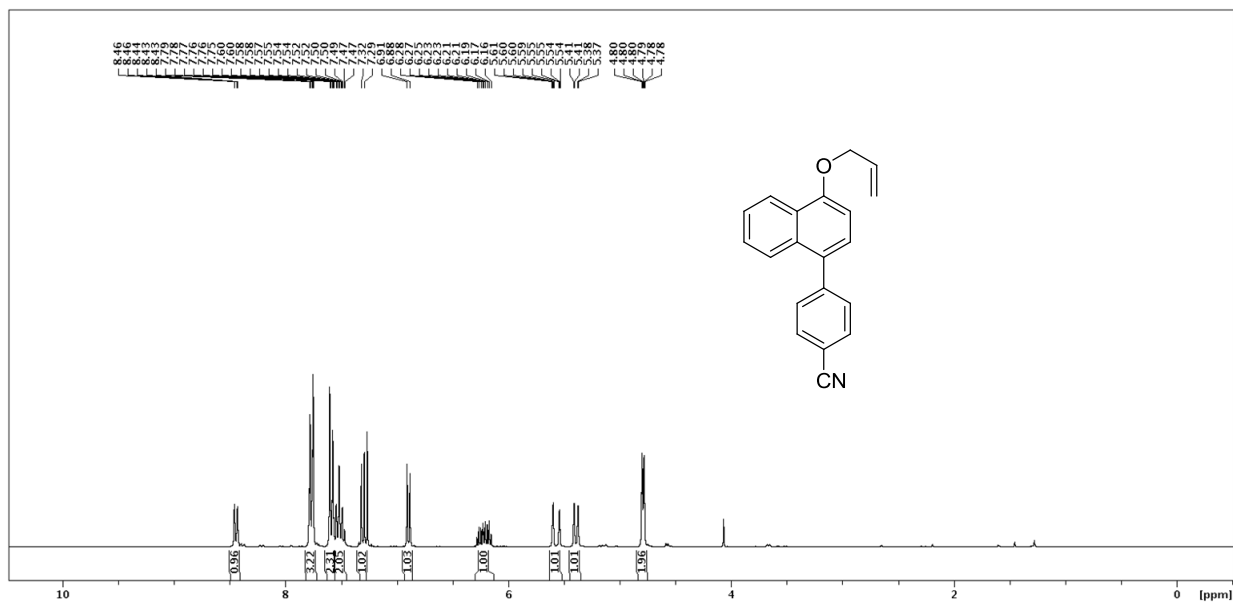
¹³C NMR spectrum of crude 3.24, R = Ph (75 MHz, CDCl₃)



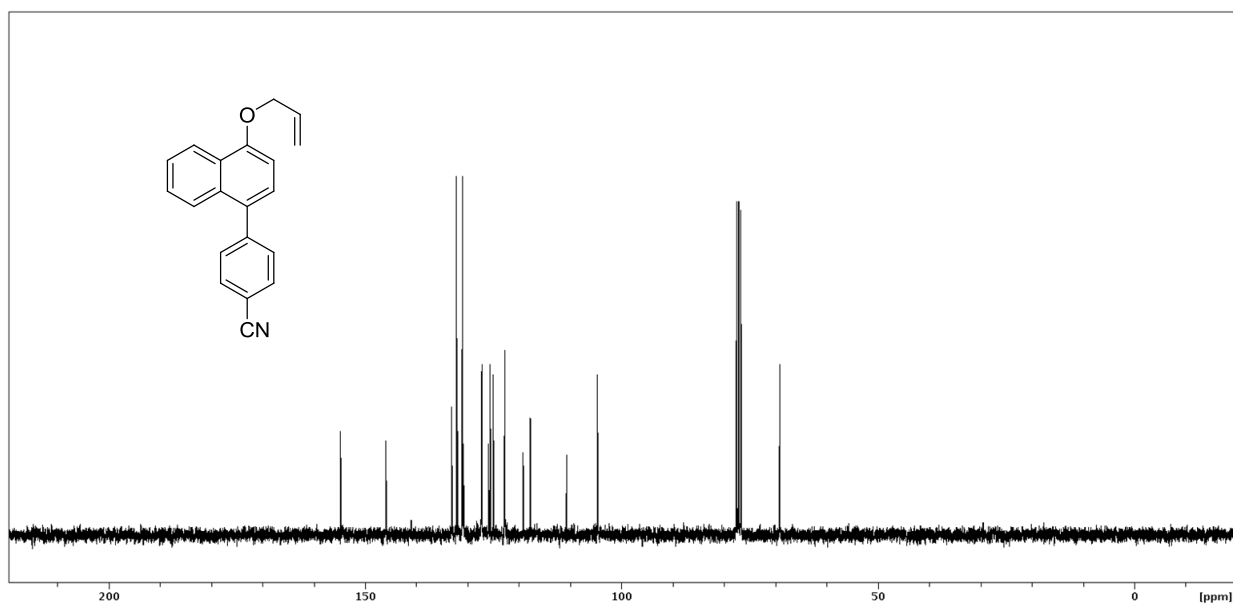
¹H NMR spectrum of crude 3.24, R = 4-Tol (300 MHz, CDCl₃)



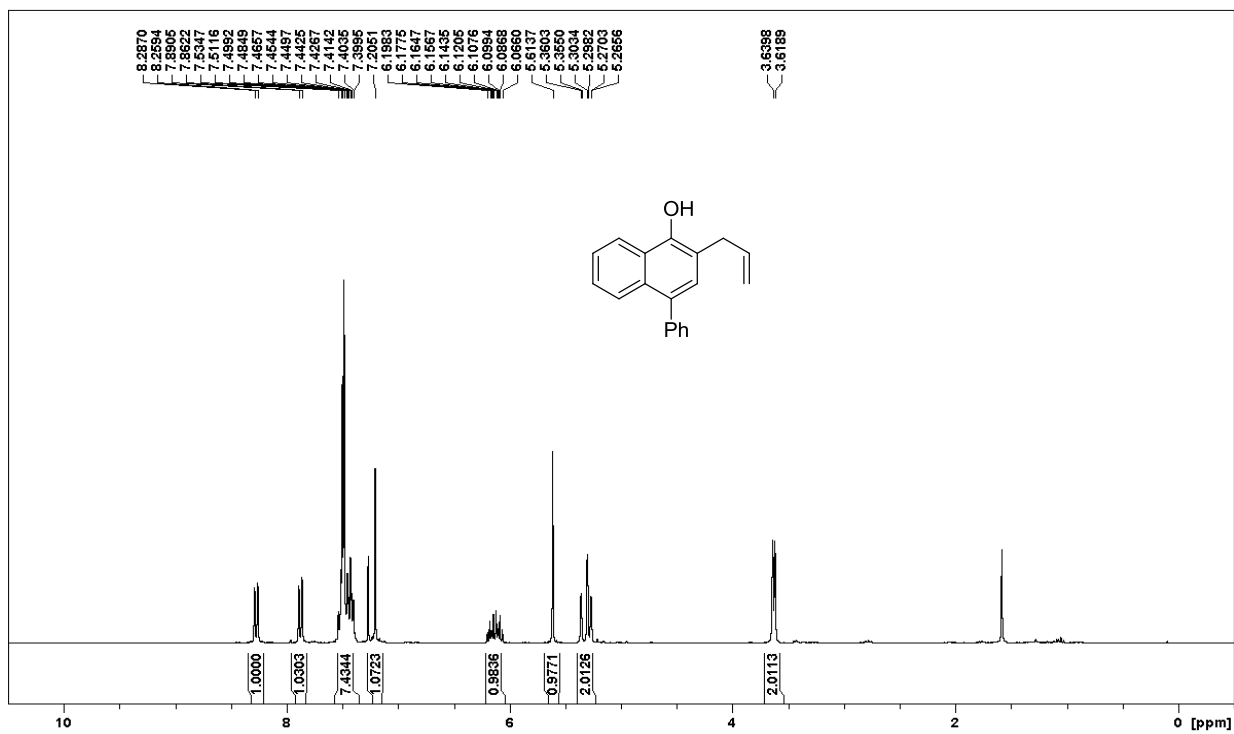
¹³C NMR spectrum of crude 3.24, R = 4-Tol (75 MHz, CDCl₃)



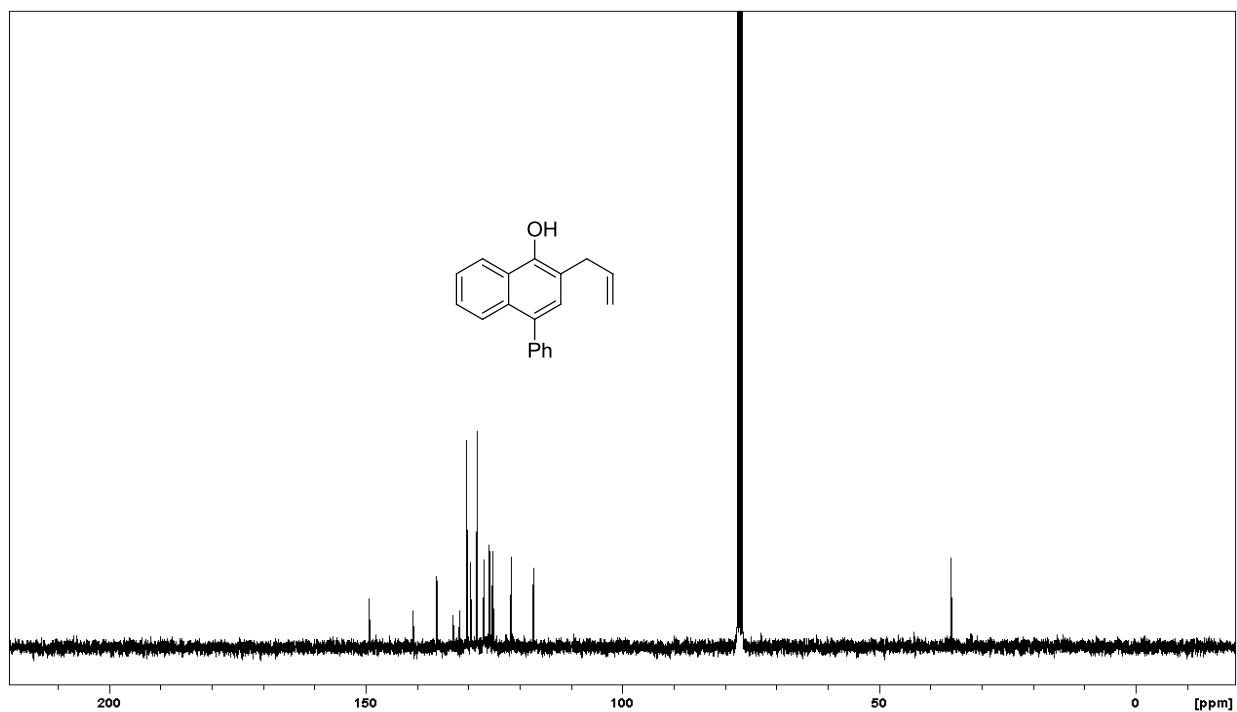
¹H NMR spectrum of crude 3.24, R = 4-NC-C₆H₄ (300 MHz, CDCl₃)



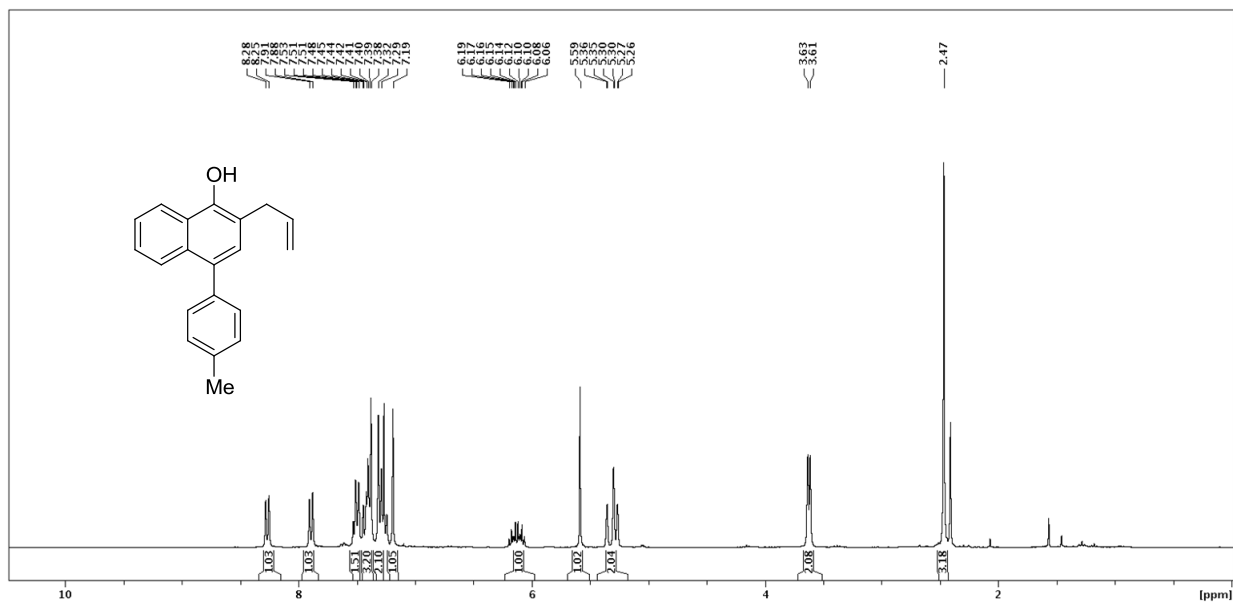
¹³C NMR spectrum of crude 3.24, R = 4-NC-C₆H₄ (75 MHz, CDCl₃)



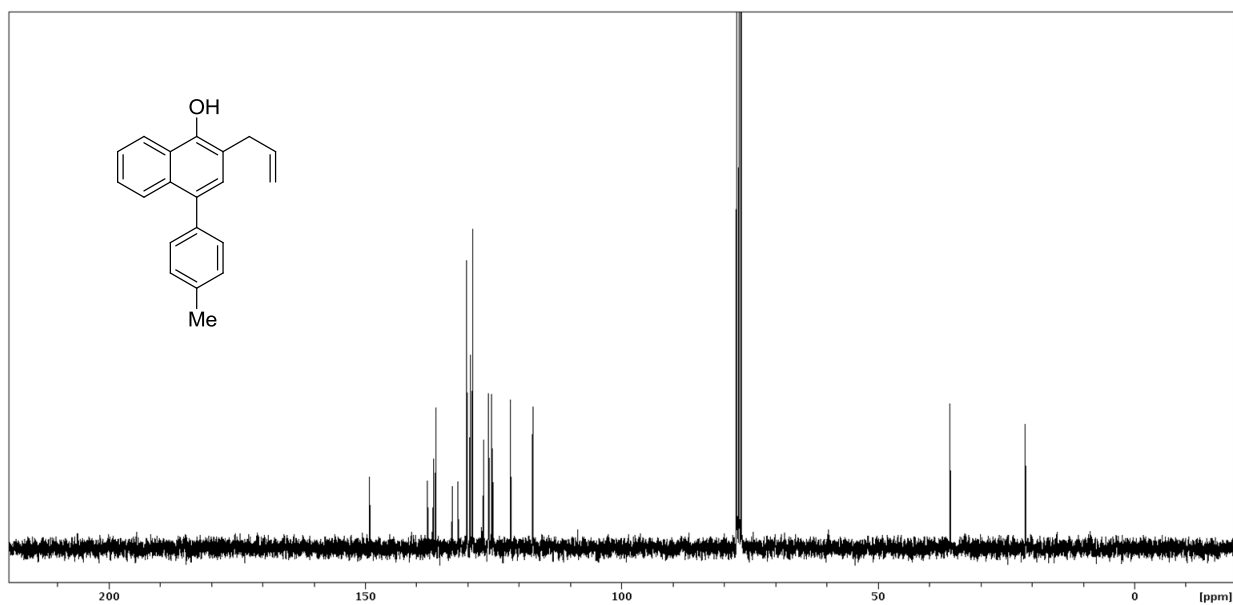
¹H NMR spectrum of 3.25, R = Ph (300 MHz, CDCl₃)



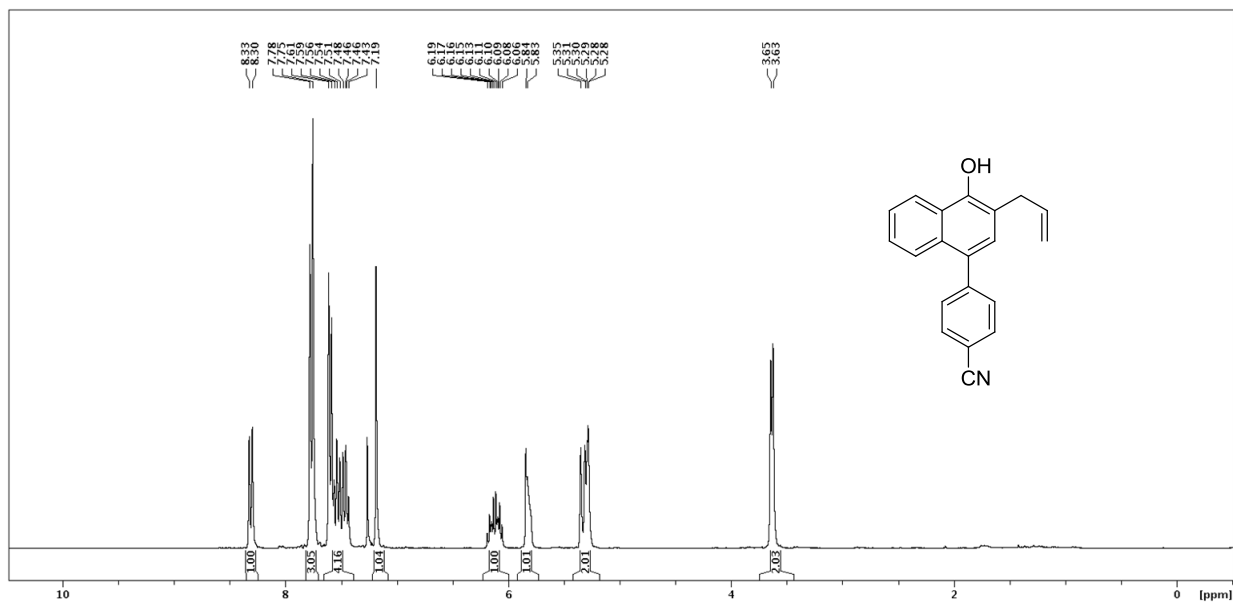
¹³C NMR spectrum of 3.25, R = Ph (75 MHz, CDCl₃)



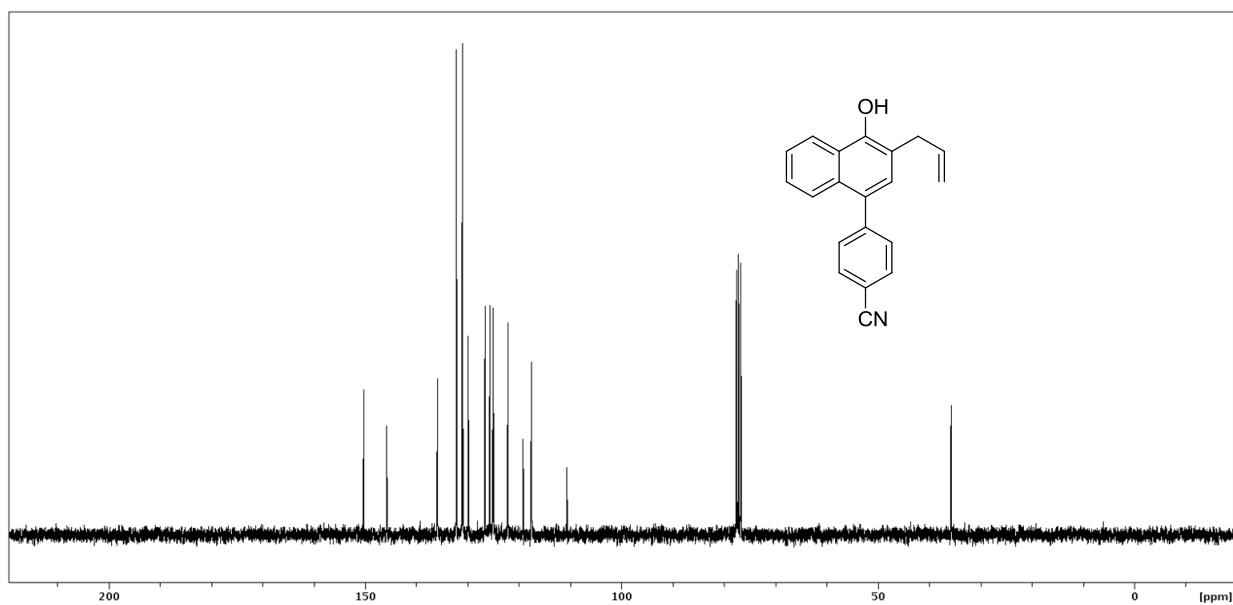
¹H NMR spectrum of 3.25, R = 4-Tol (300 MHz, CDCl₃)



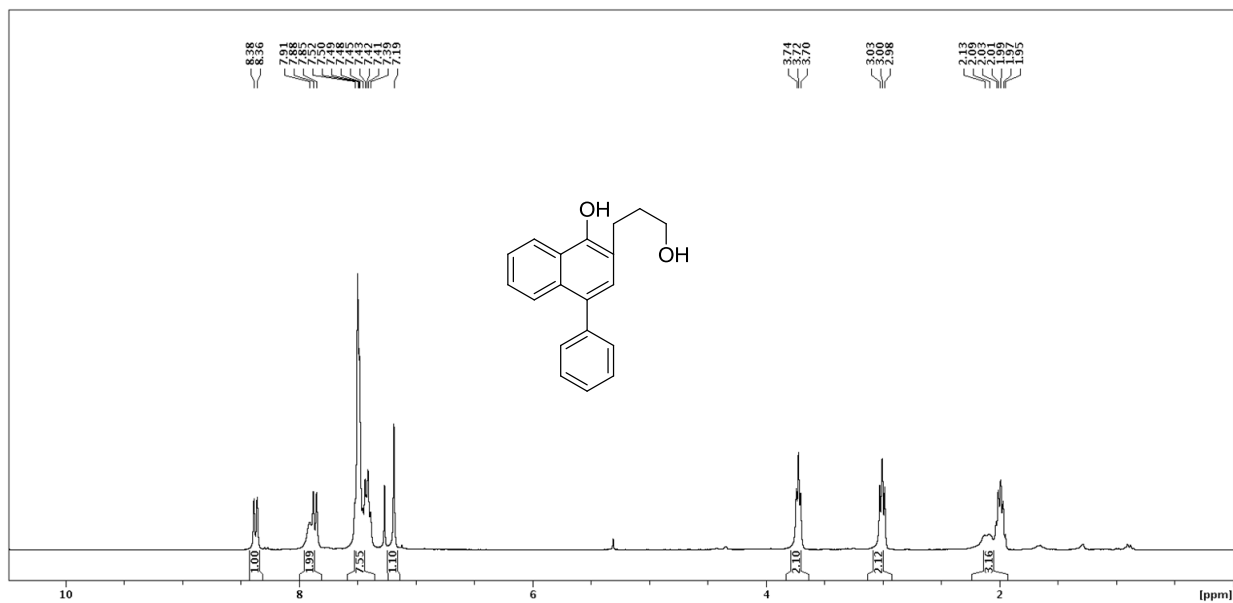
¹³C NMR spectrum of 3.25, R = 4-Tol (75 MHz, CDCl₃)



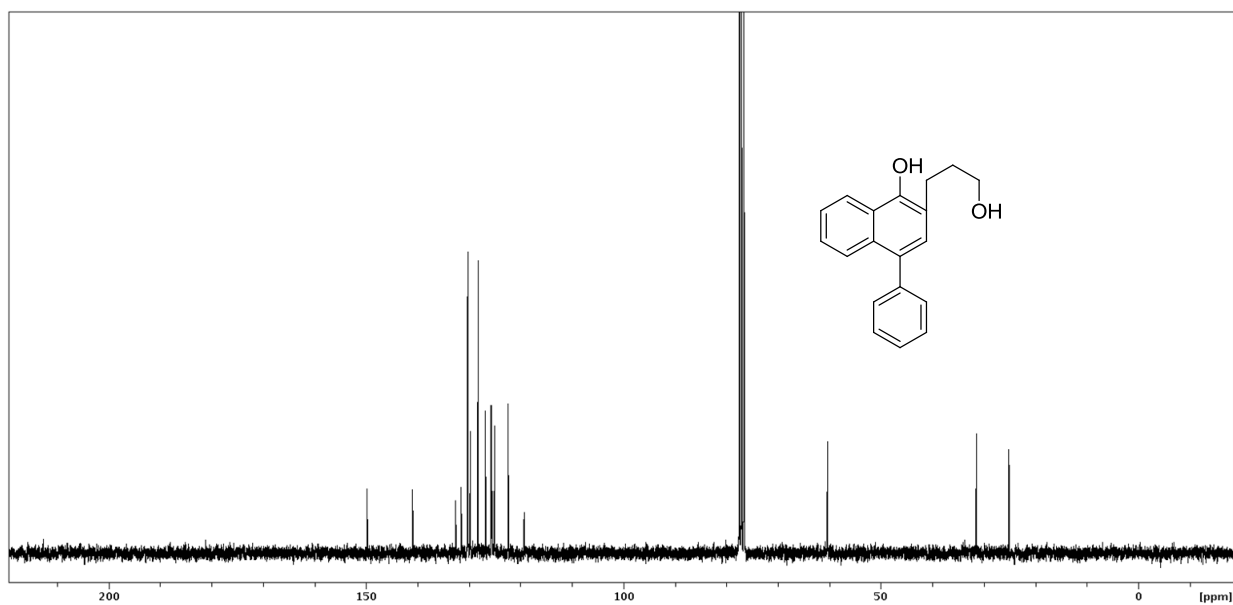
^1H NMR spectrum of 3.25, R = 4-NC-C₆H₄ (300 MHz, CDCl₃)



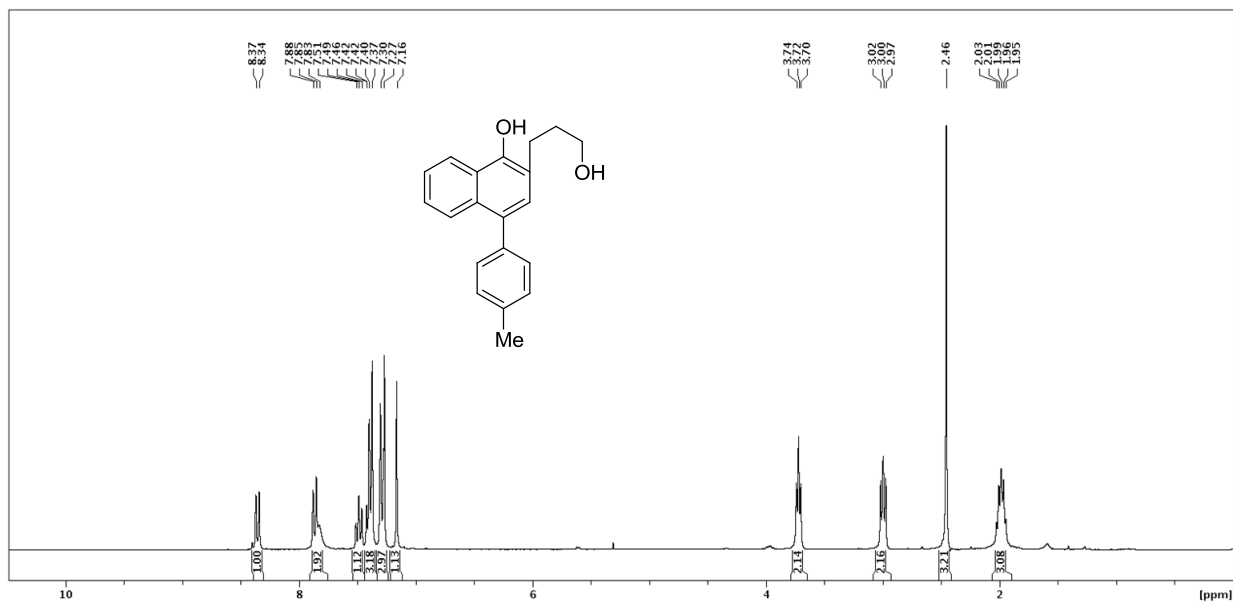
^{13}C NMR spectrum of 3.25, R = 4-NC-C₆H₄ (75 MHz, CDCl₃)



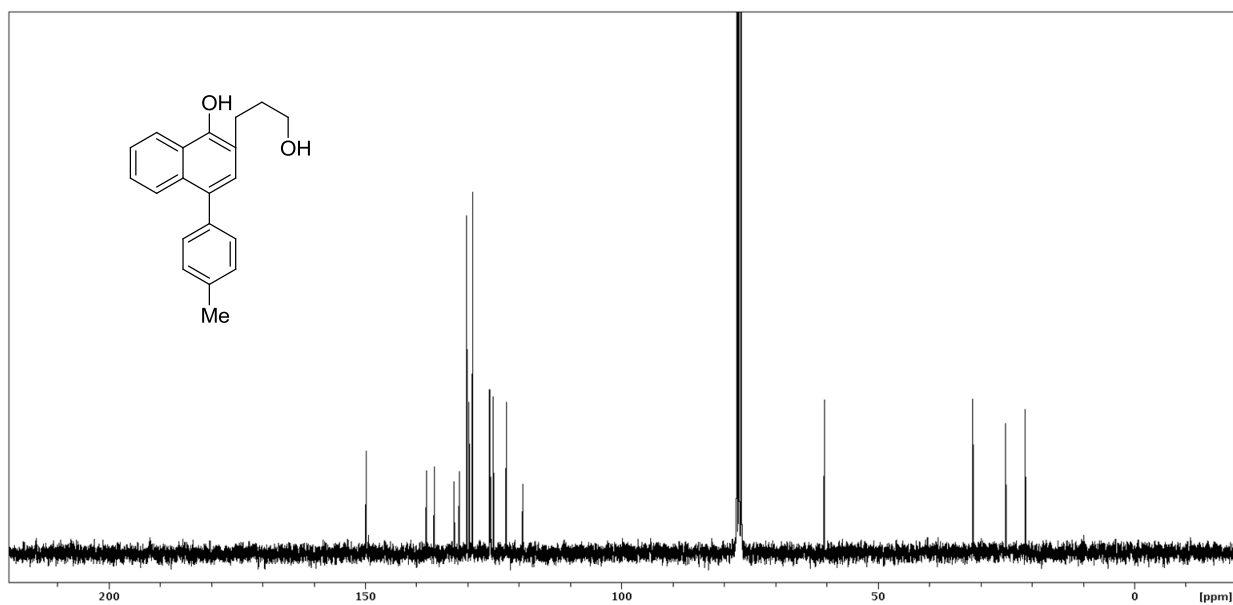
¹H NMR spectrum of 3.26, R = Ph (300 MHz, CDCl₃)



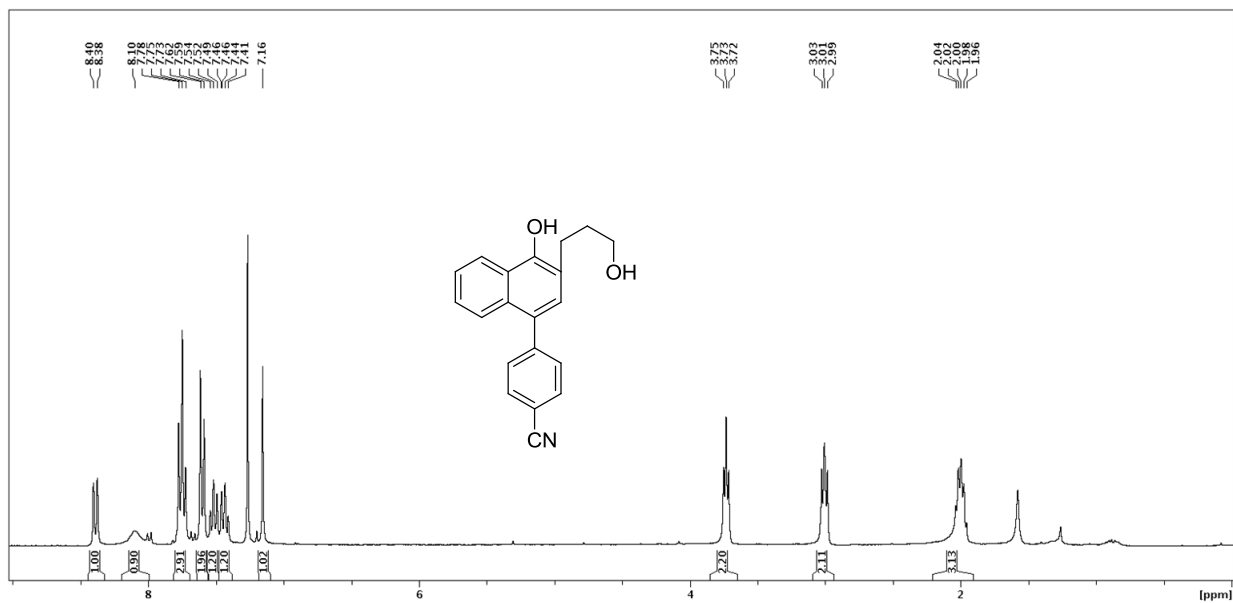
¹³C NMR spectrum of 3.26, R = Ph (75 MHz, CDCl₃)



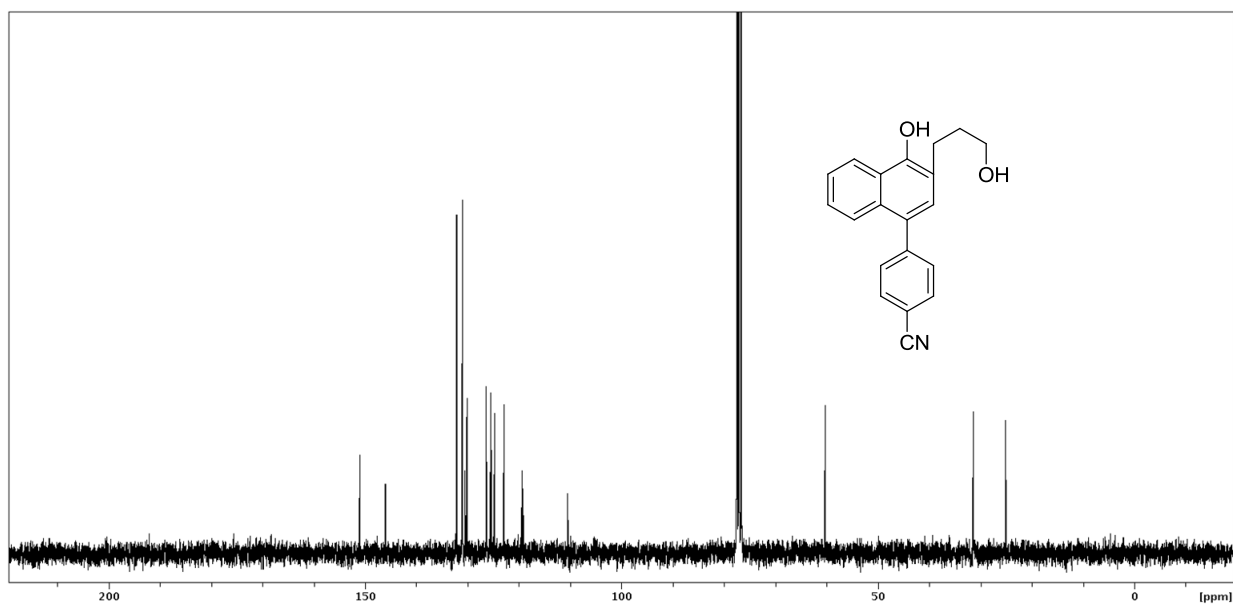
¹H NMR spectrum of 3.26, R = 4-Tol (300 MHz, CDCl₃)



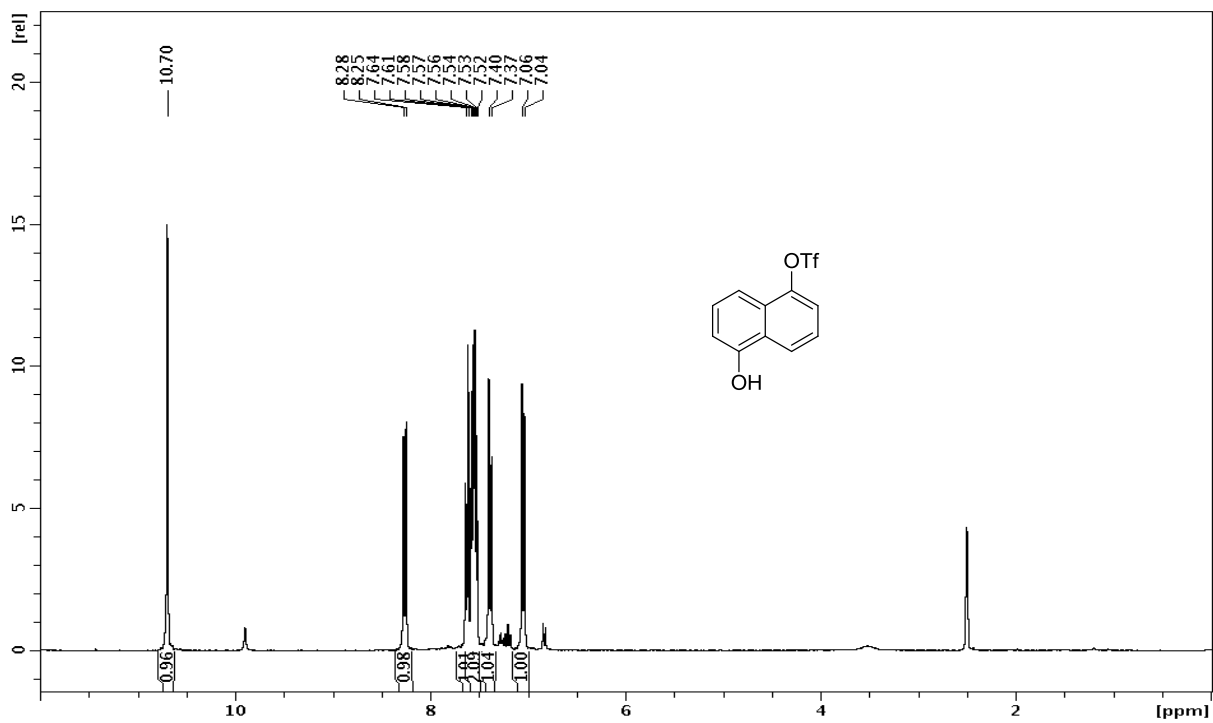
¹³C NMR spectrum of 3.26, R = 4-Tol (75 MHz, CDCl₃)



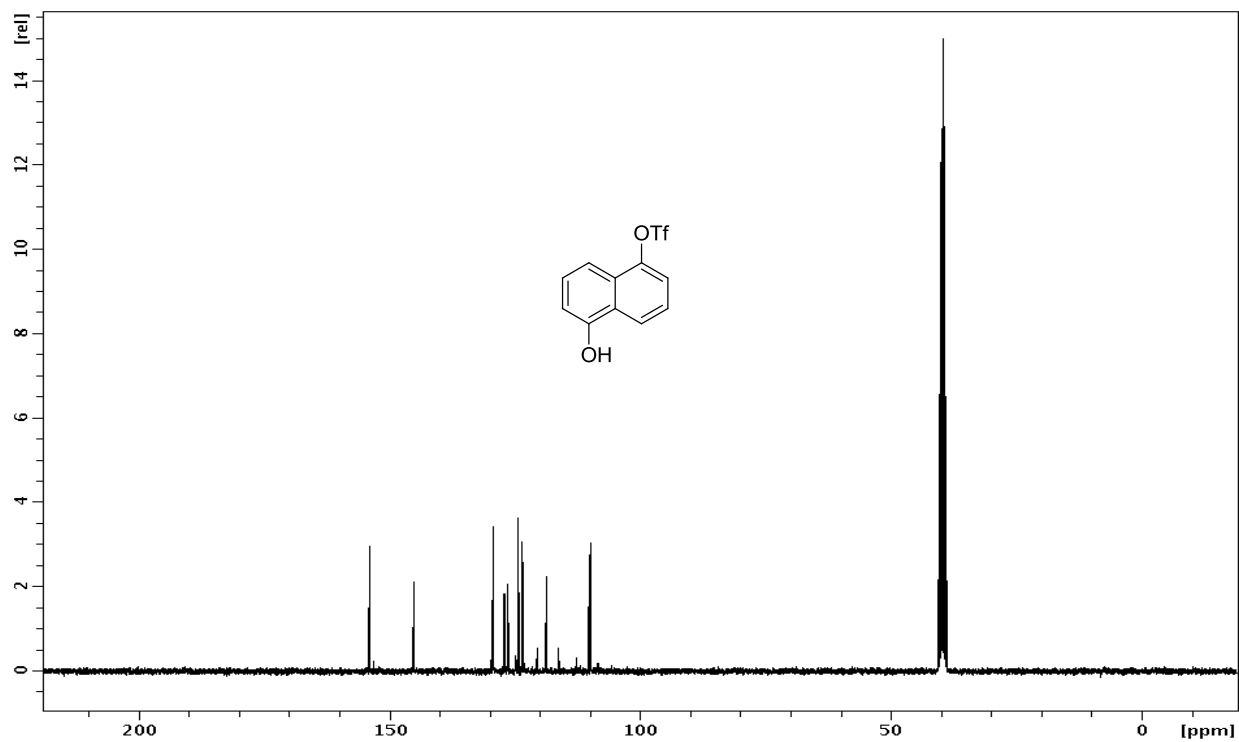
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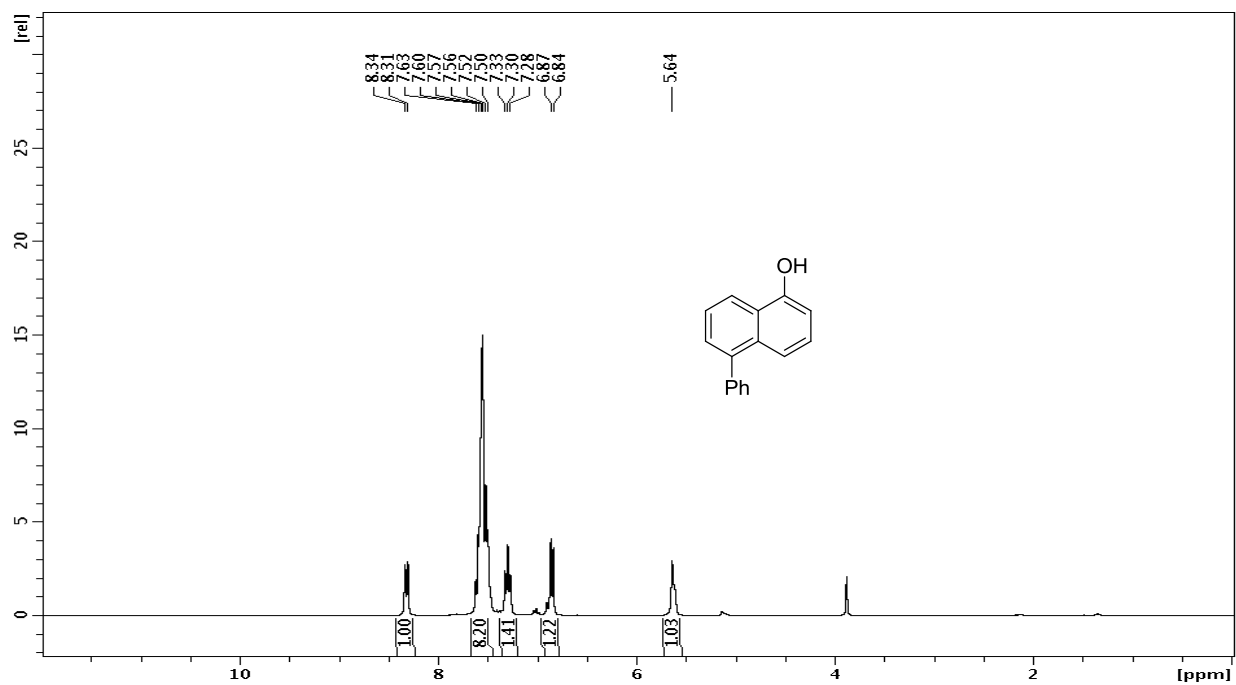
¹³C NMR spectrum of 3.26, R = 4-NC-C₆H₄ (75 MHz, CDCl₃)



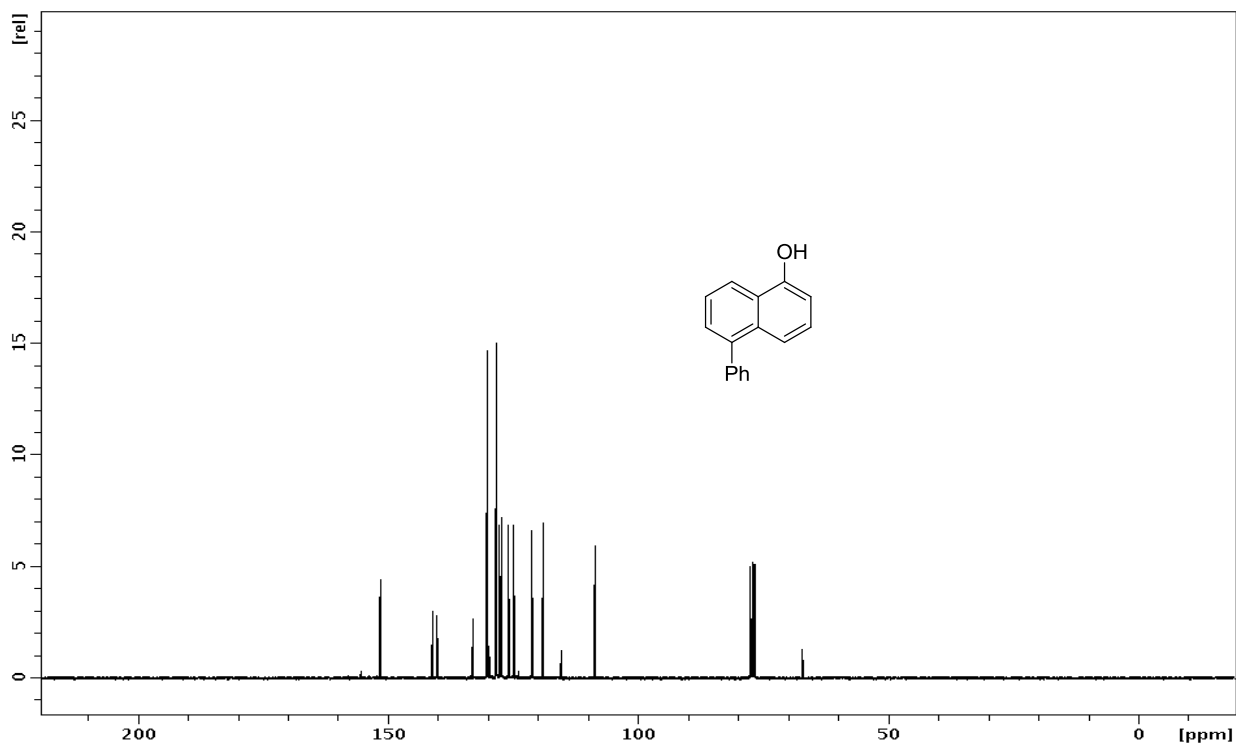
^1H NMR spectrum of 3.28 (300 MHz, $\text{DMSO-}d_6$)



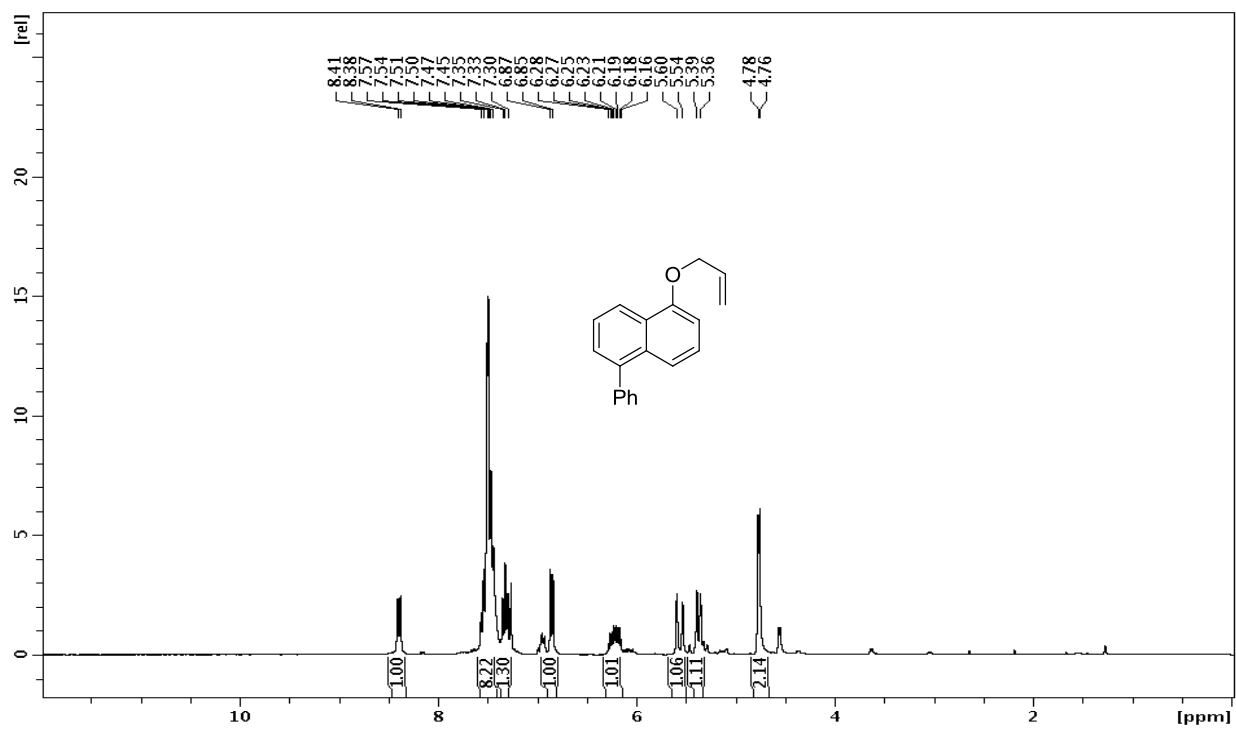
^{13}C NMR spectrum of compound 3.28 (75 MHz, $\text{DMSO-}d_6$)



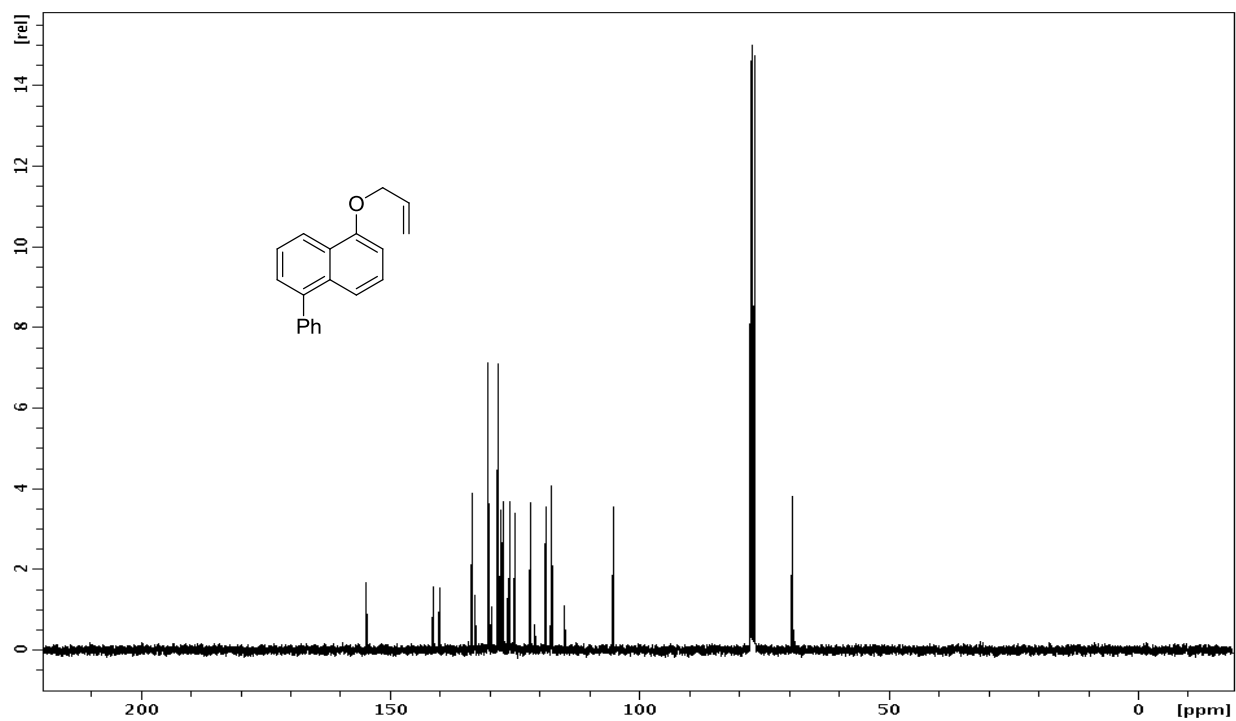
^1H NMR spectrum of 3.29 (300 MHz, CDCl_3)



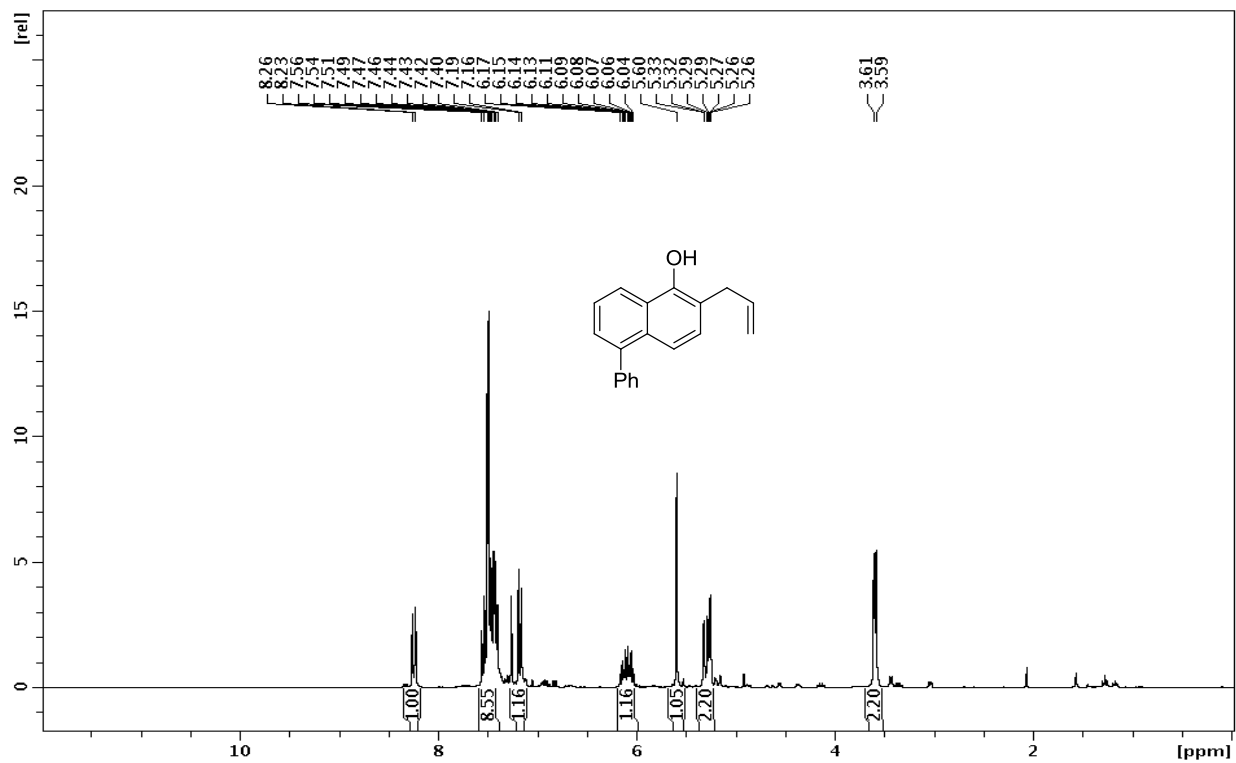
^{13}C NMR spectrum of compound 3.29 (75 MHz, CDCl_3)



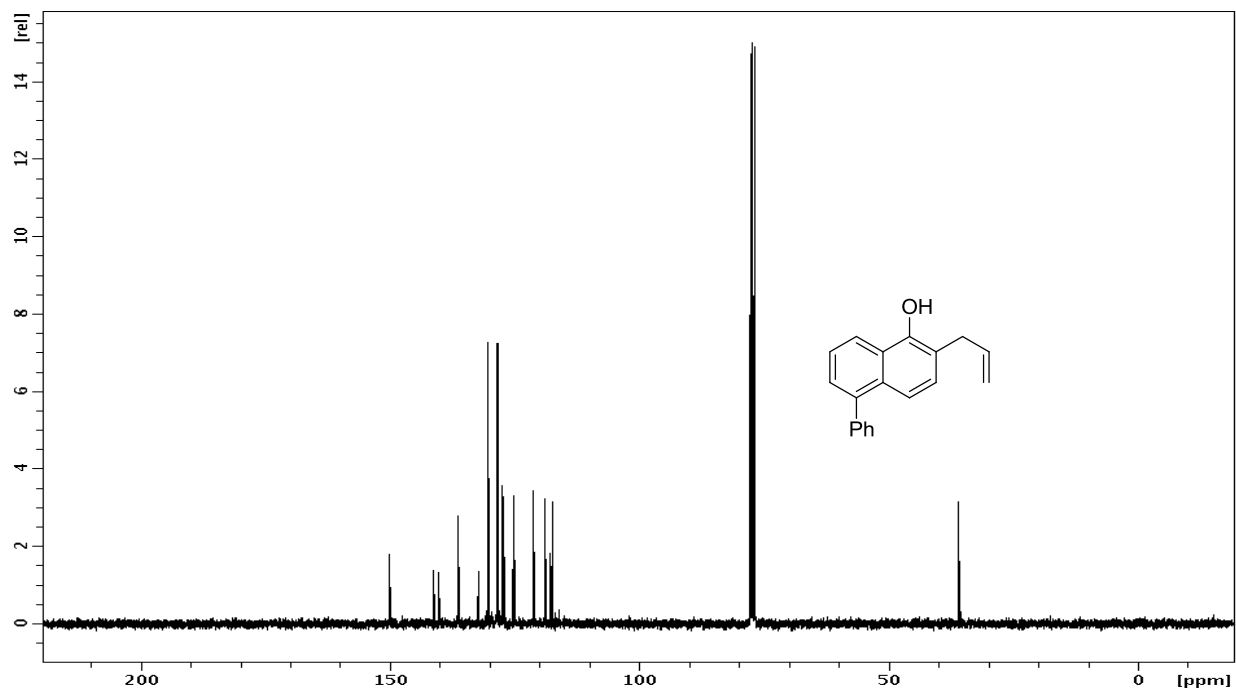
¹H NMR spectrum of crude 3.30 (300 MHz, CDCl₃)



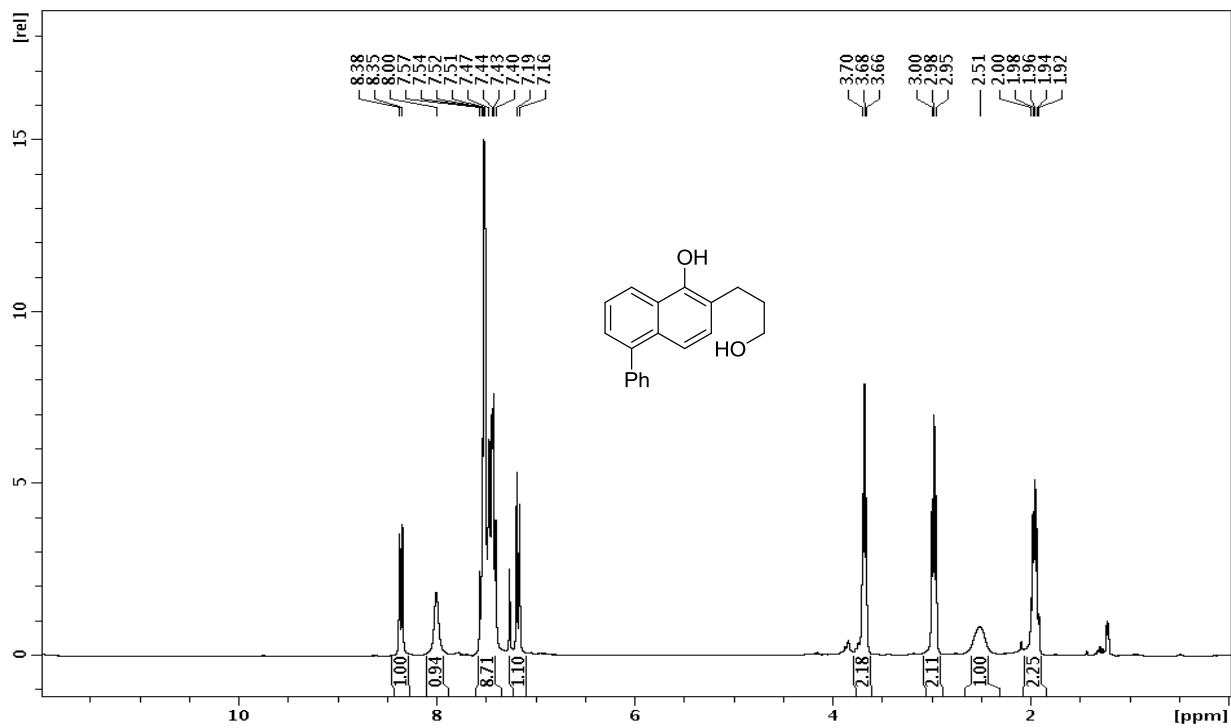
¹³C NMR spectrum of crude 3.30 (75 MHz, CDCl₃)



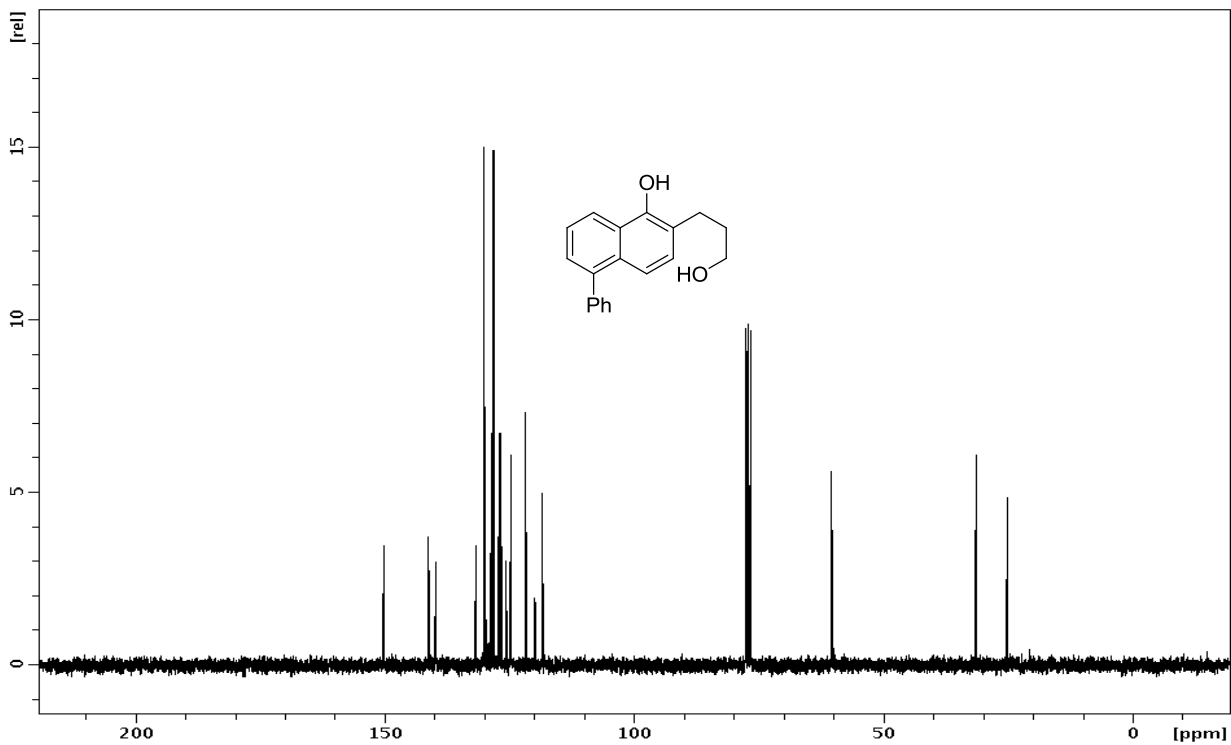
^1H NMR spectrum of 3.31 (300 MHz, CDCl_3)



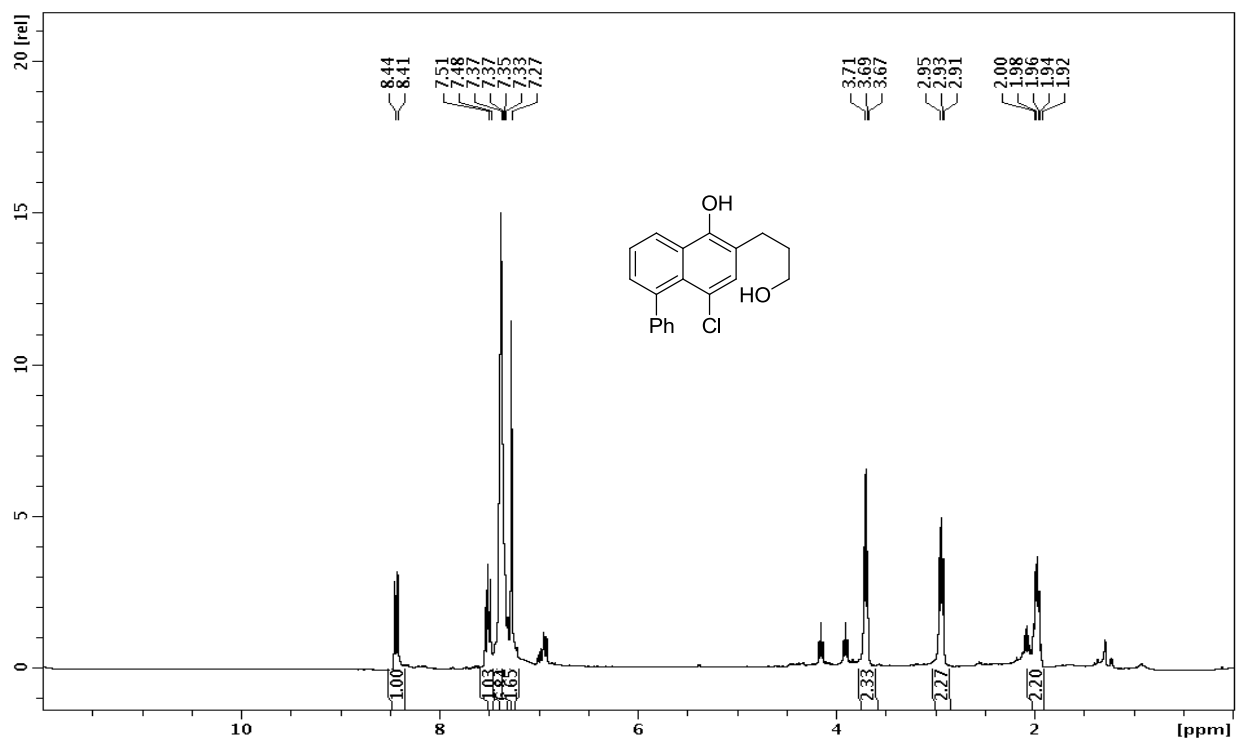
^{13}C NMR spectrum of 3.31 (75 MHz, CDCl_3)



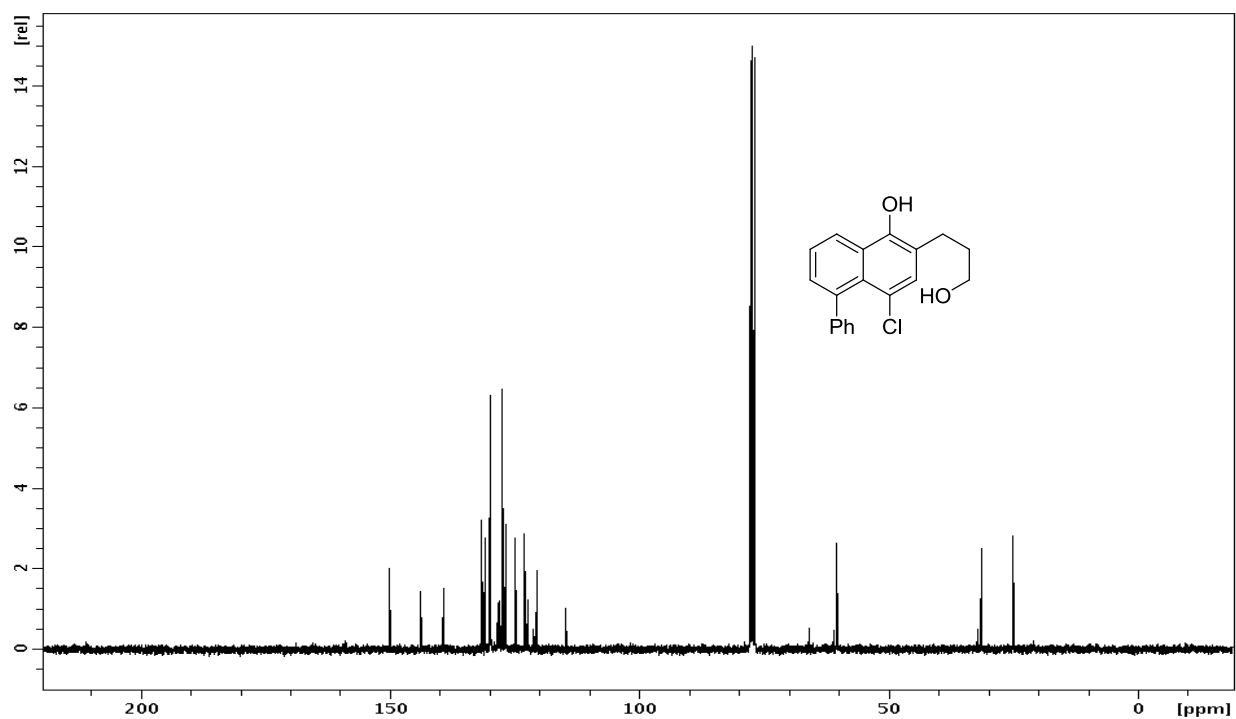
¹H NMR spectrum of 3.32 (300 MHz, CDCl₃)



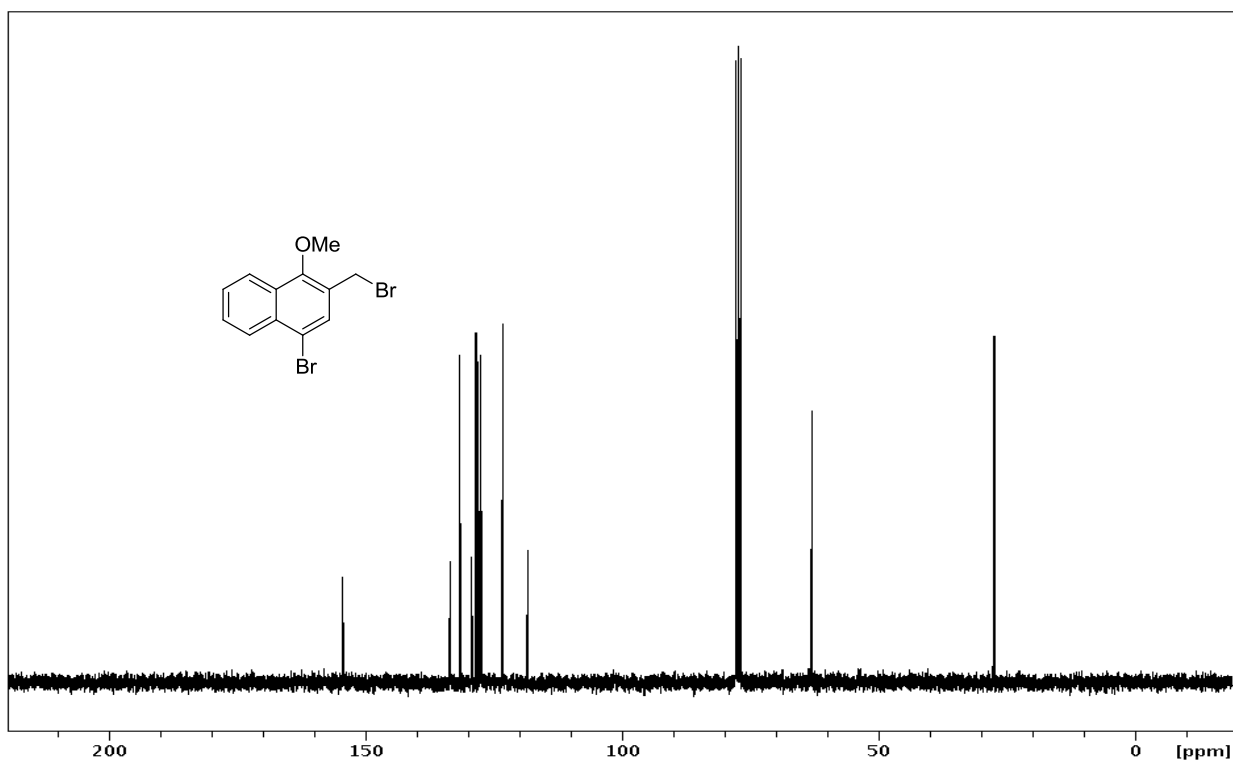
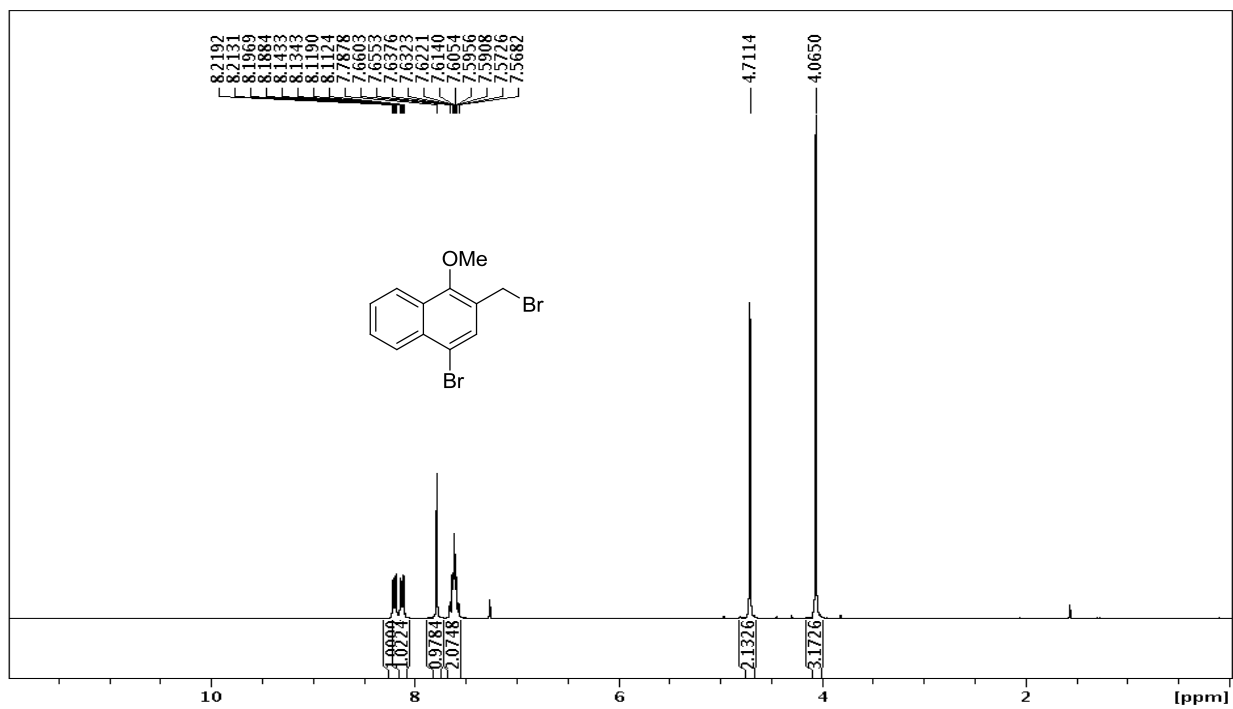
¹³C NMR spectrum of 3.32 (75 MHz, CDCl₃)

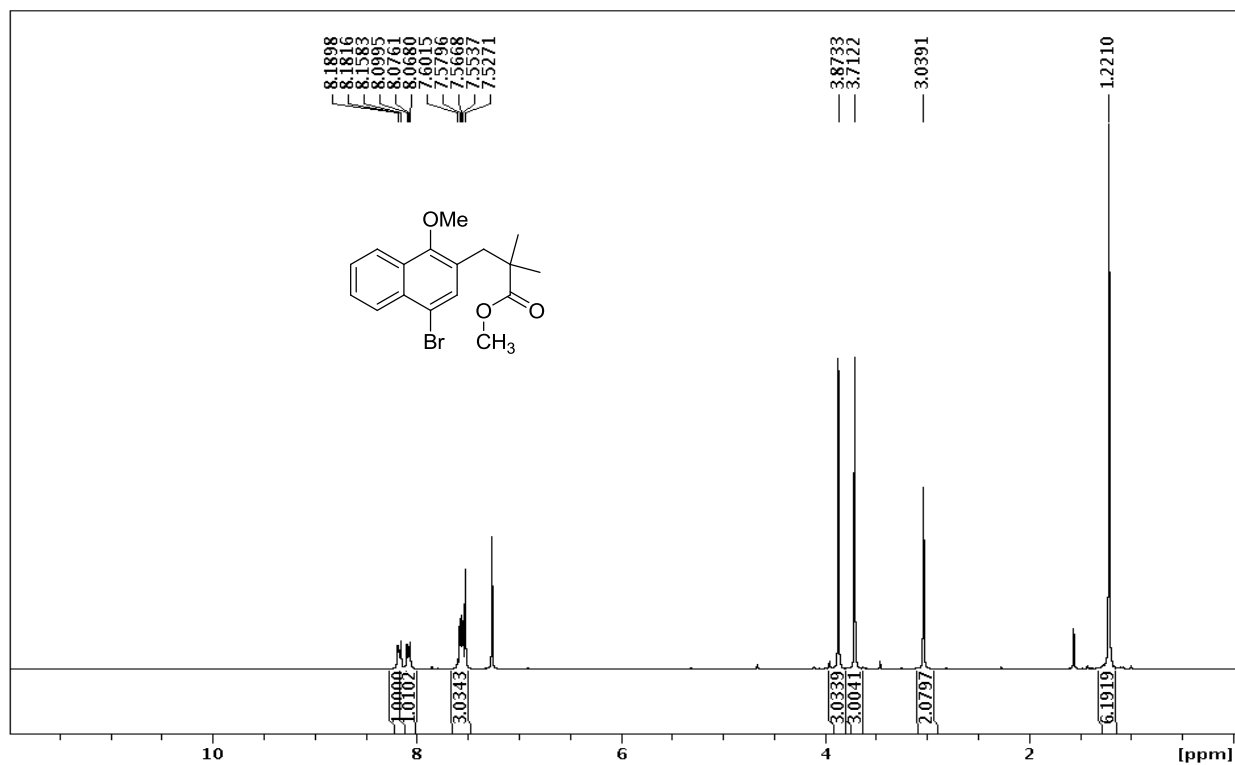


^1H NMR spectrum of 3.33 (300 MHz, CDCl_3)

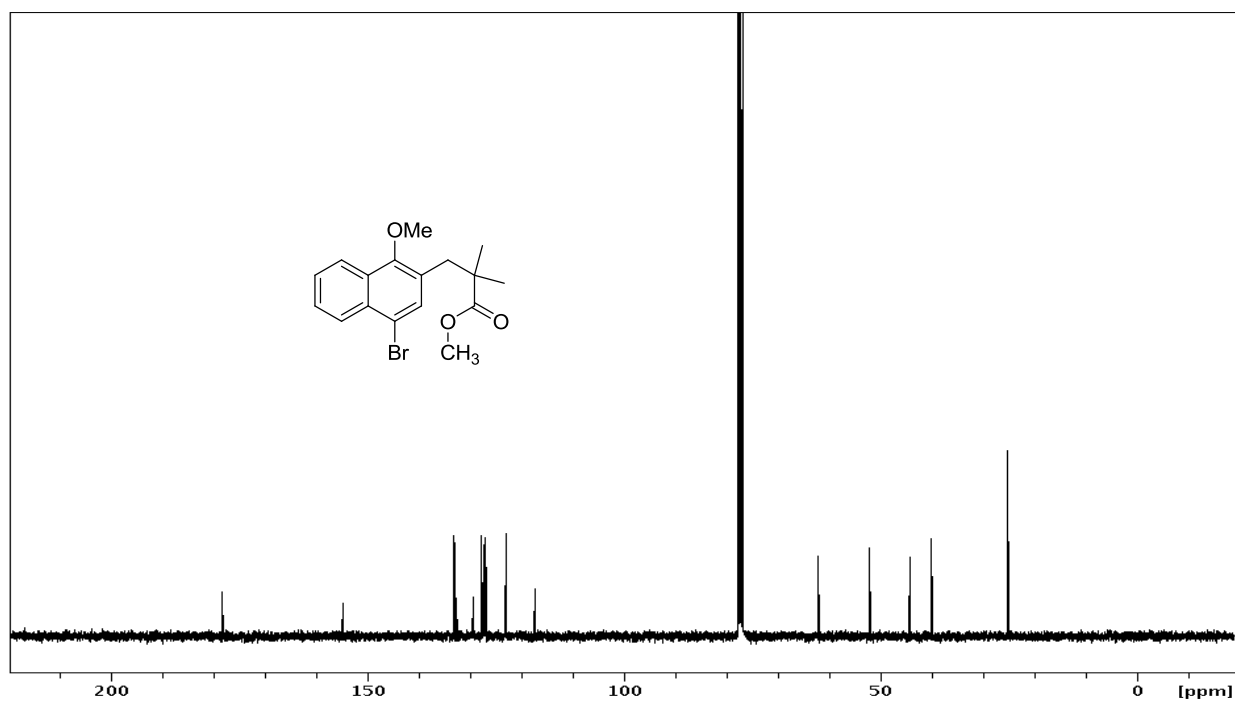


^{13}C NMR spectrum of 3.33 (75 MHz, CDCl_3)

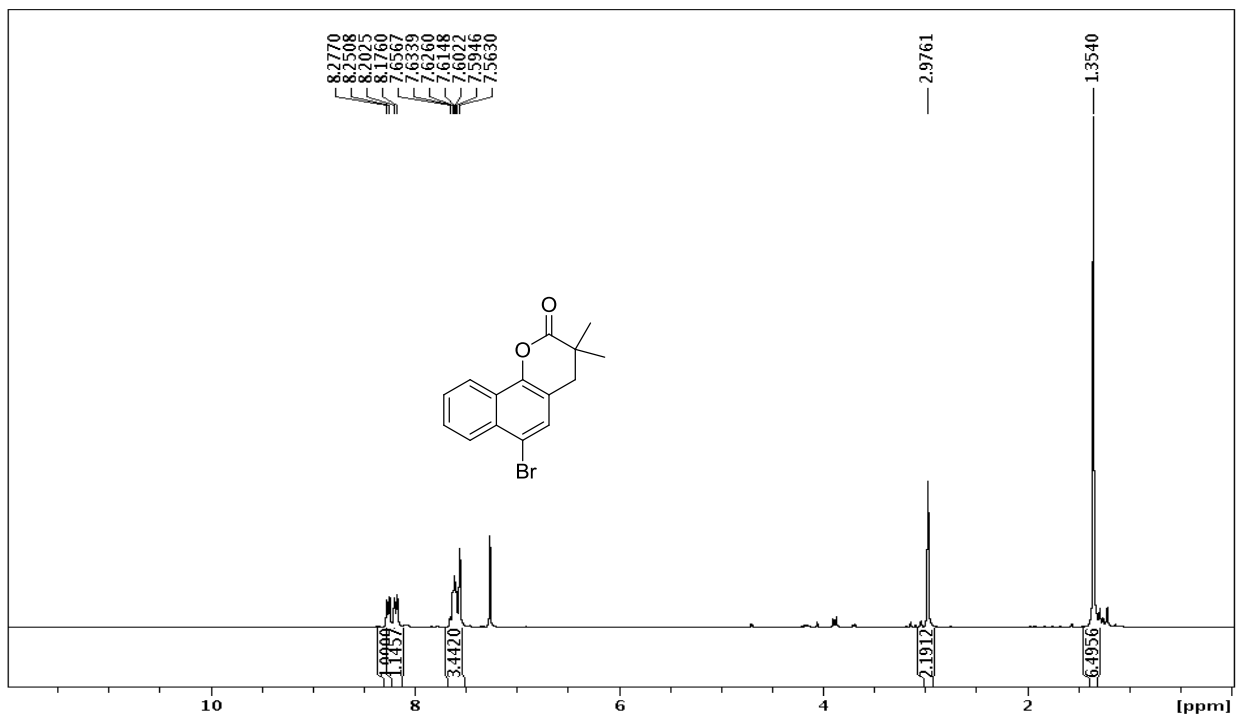




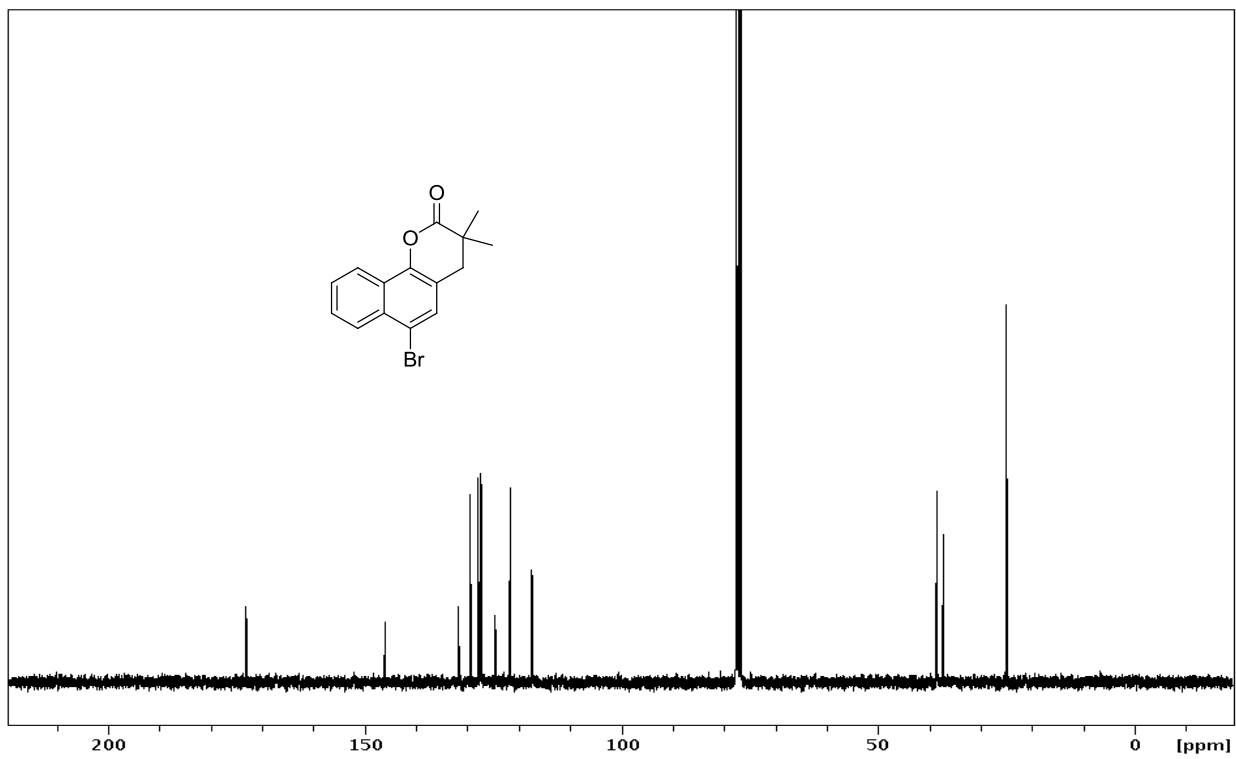
¹H NMR spectrum of 3.40 (300 MHz, CDCl₃)



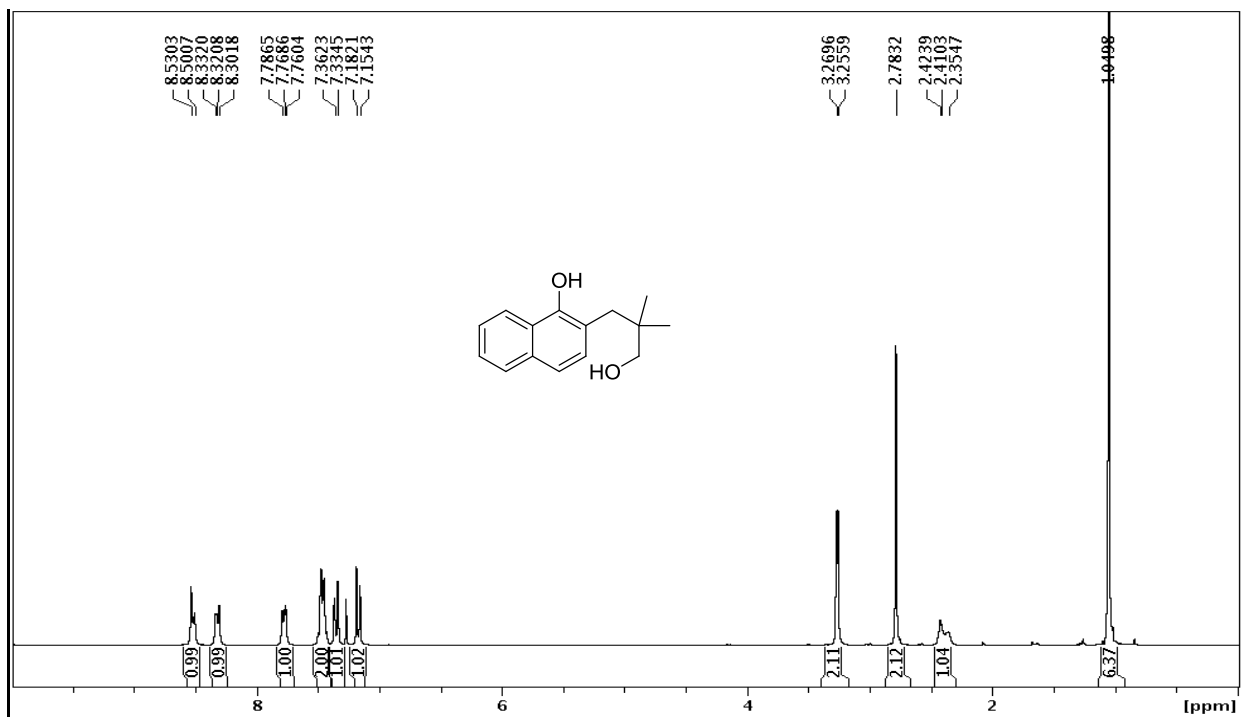
¹³C NMR spectrum of 3.40 (75 MHz, CDCl₃)



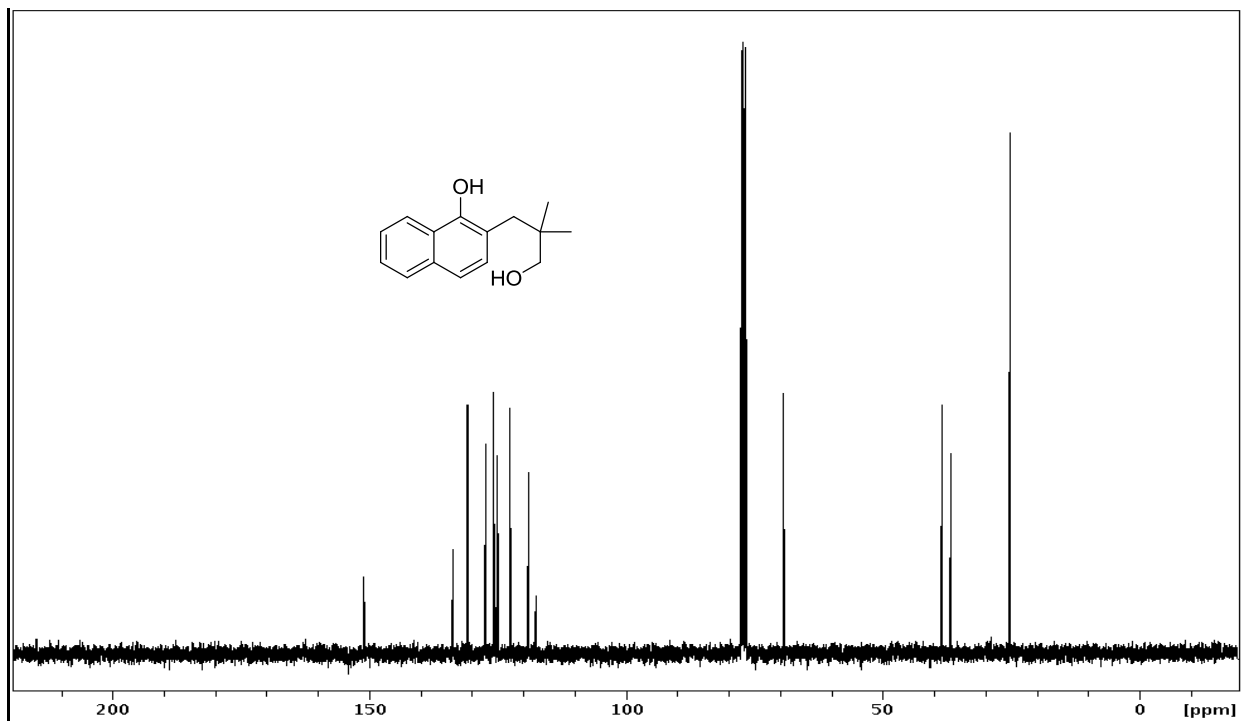
¹H NMR spectrum of crude 3.42 (300 MHz, CDCl₃)



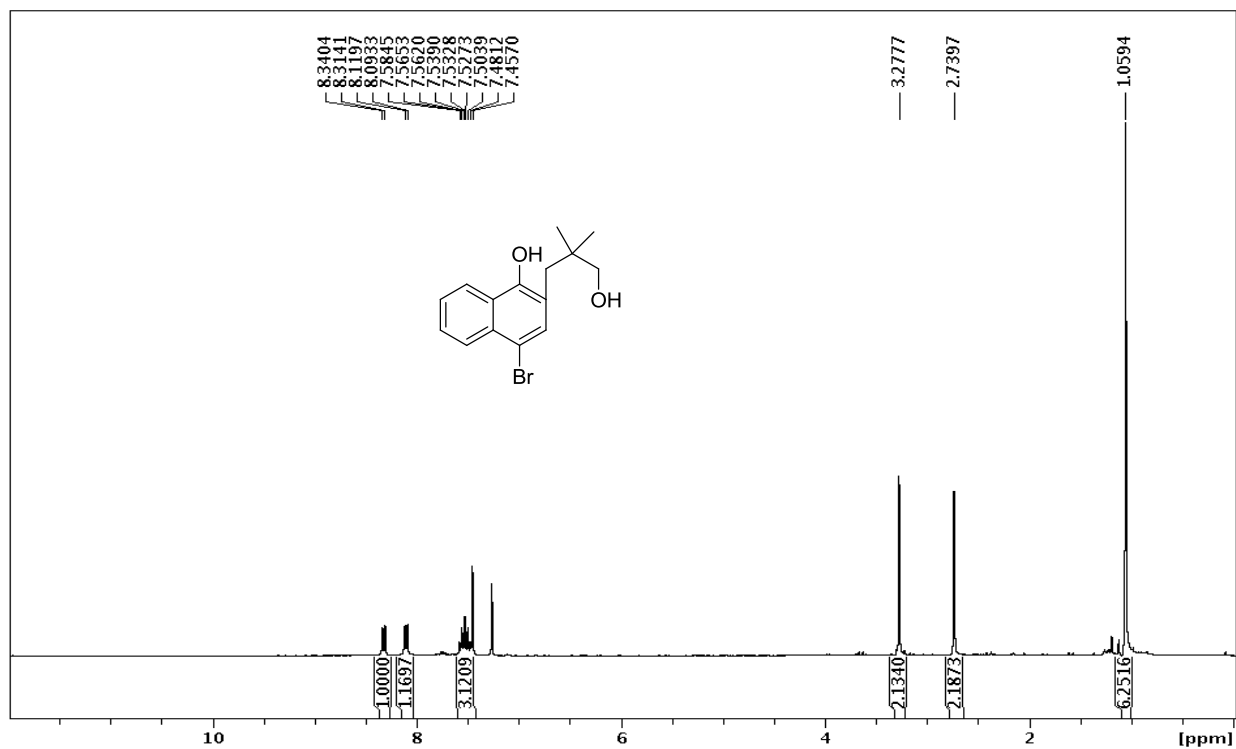
¹³C NMR spectrum of crude 3.42 (75 MHz, CDCl₃)



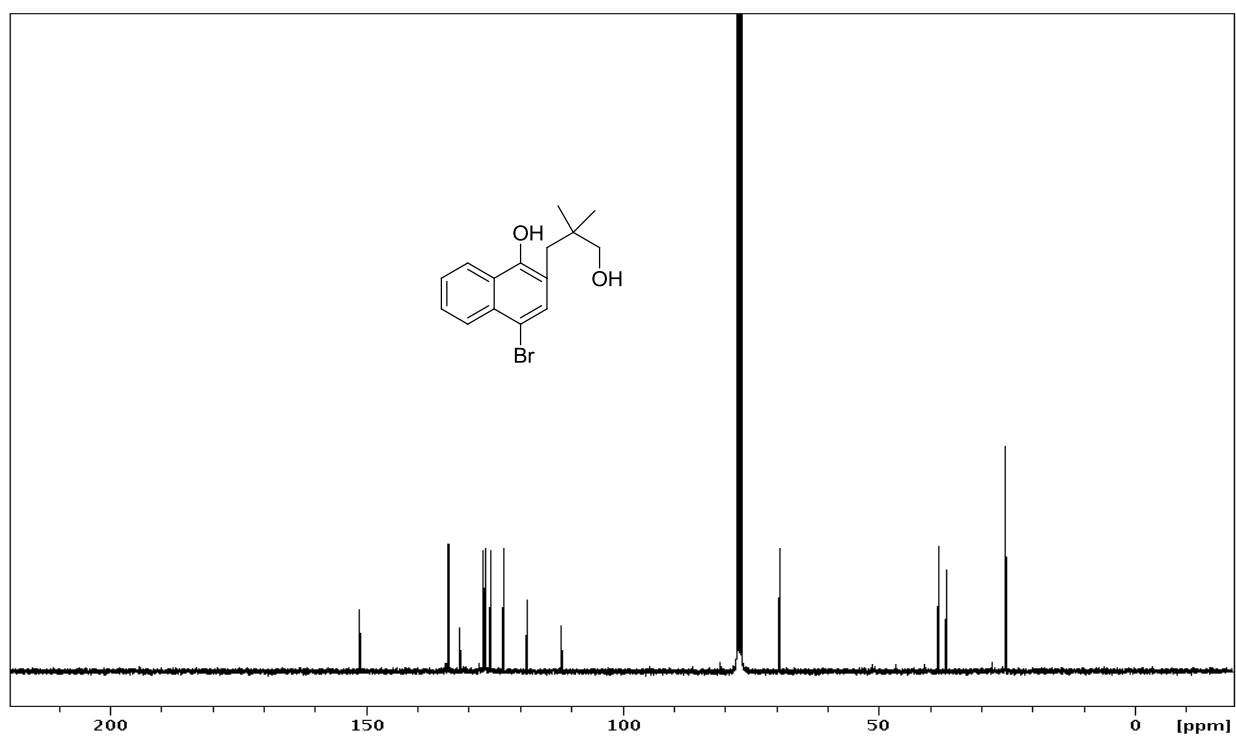
¹H NMR spectrum of 3.43 (300 MHz, CDCl₃)



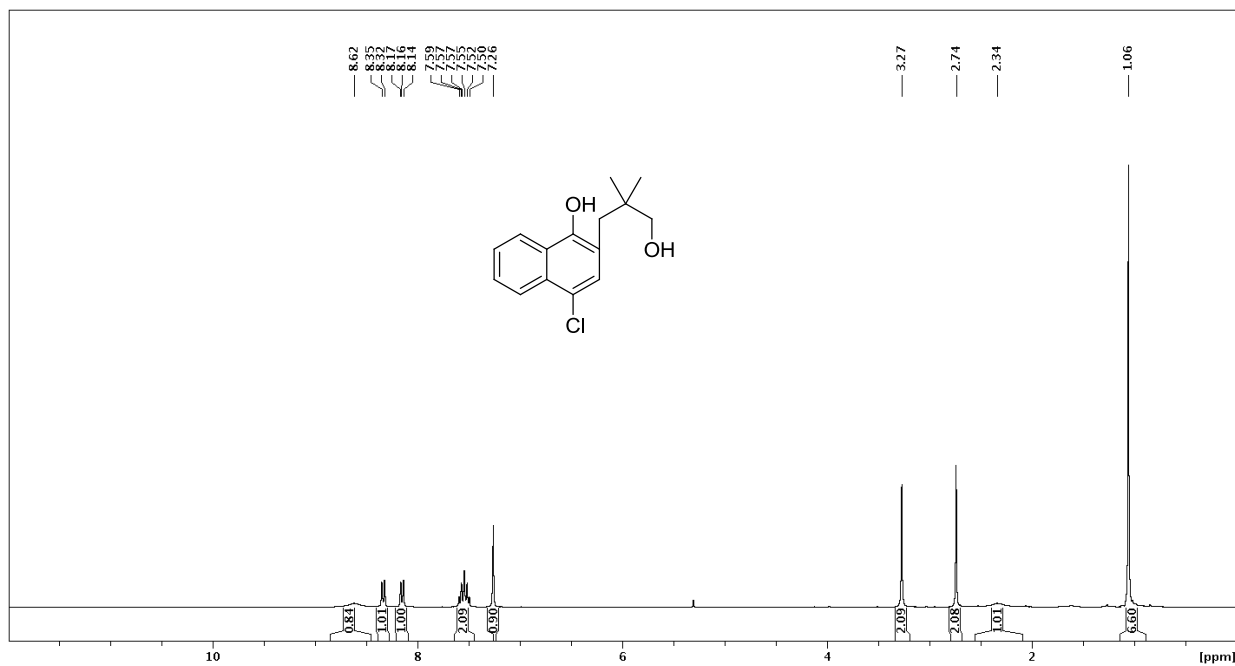
¹³C NMR spectrum of 3.43 (75 MHz, CDCl₃)



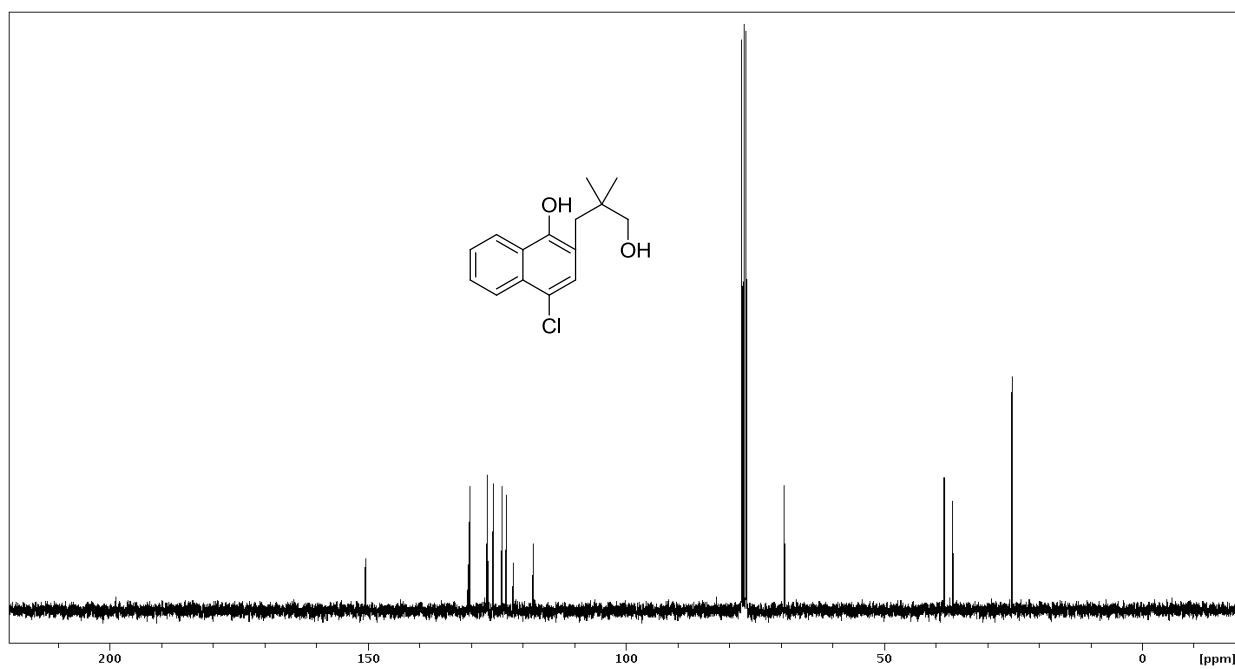
¹H NMR spectrum of 3.44 (300 MHz, CDCl₃)



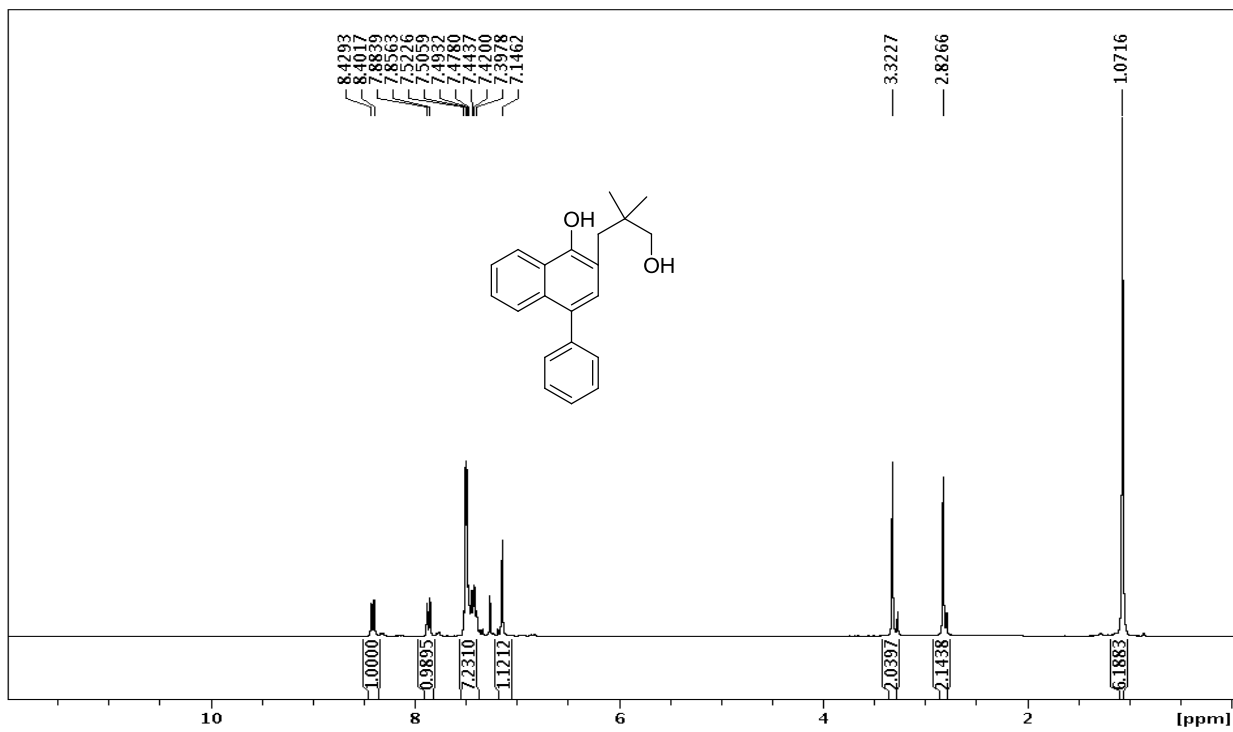
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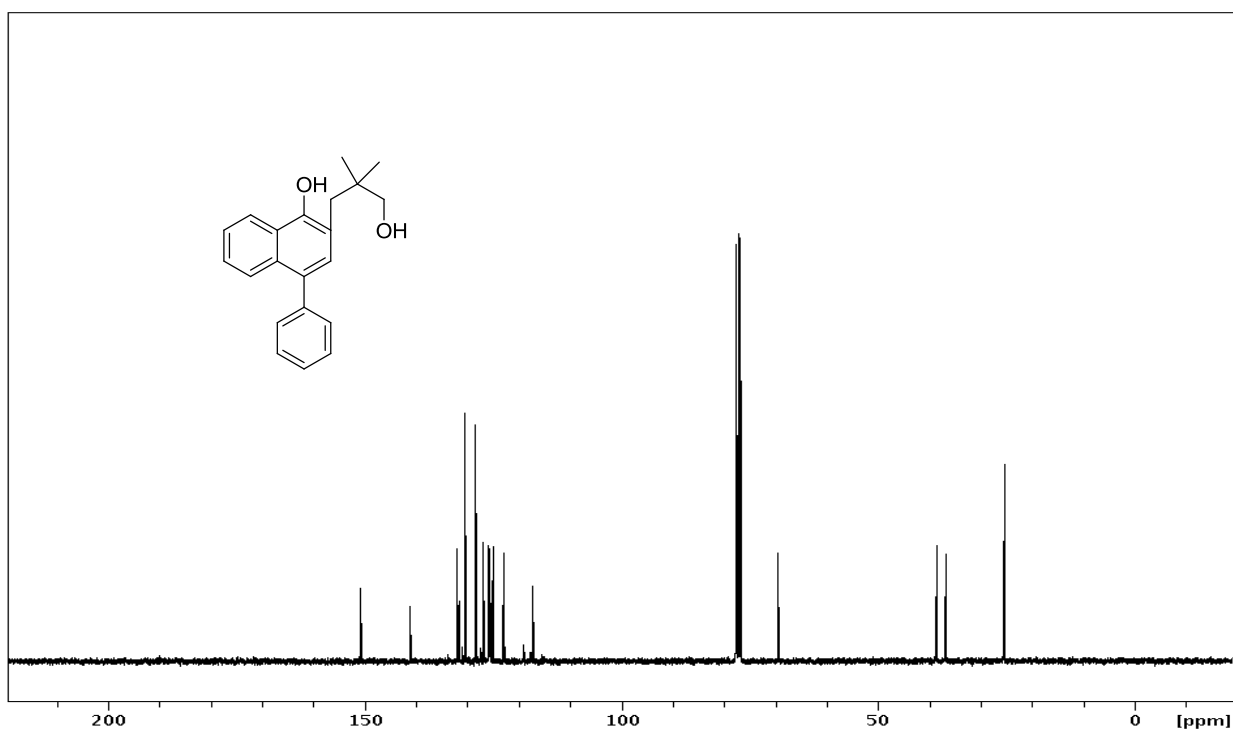
¹H NMR spectrum of 3.45 (300 MHz, CDCl₃)



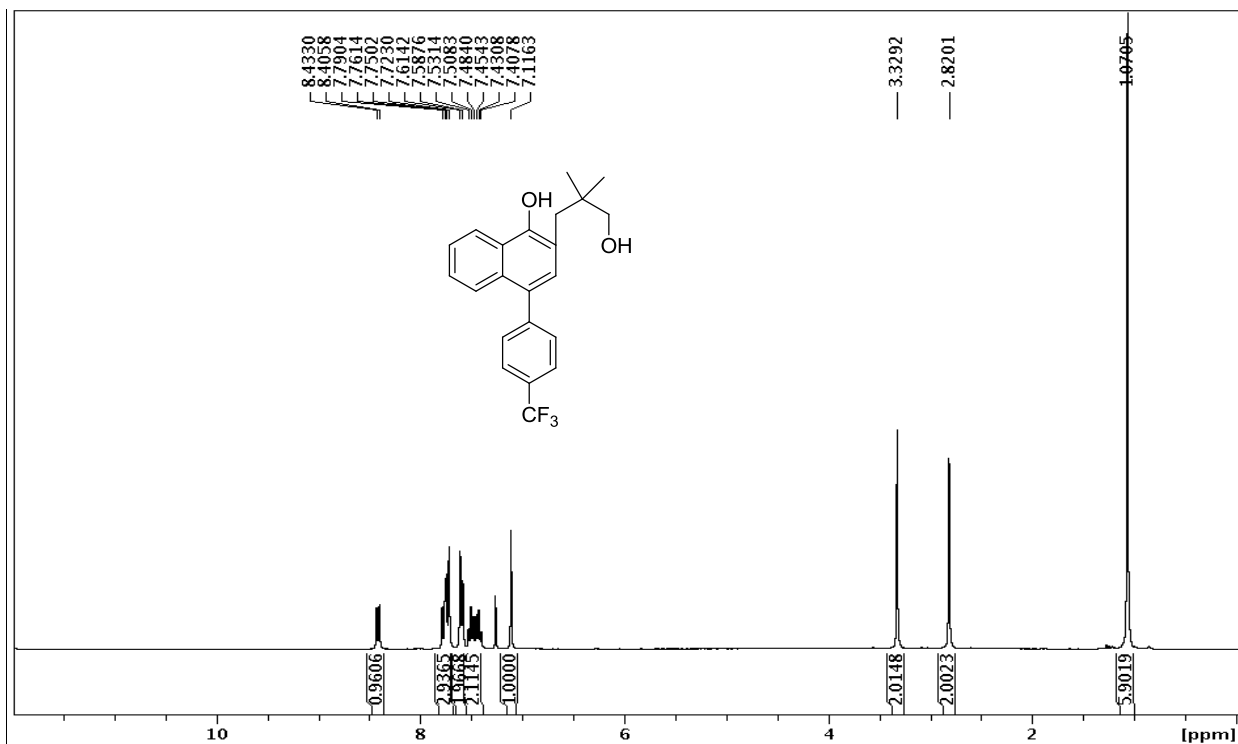
¹³C NMR spectrum of 3.45 (75 MHz, CDCl₃)



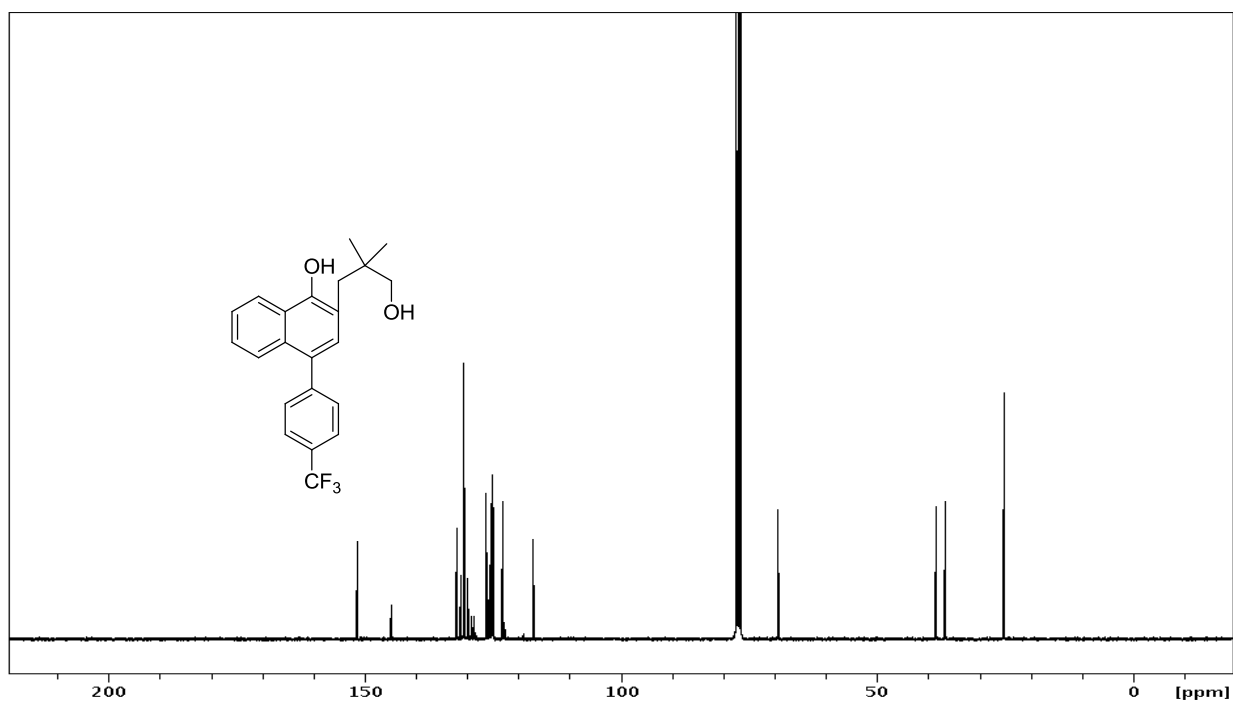
¹H NMR spectrum of 3.46, Ar = Ph (300 MHz, CDCl₃)



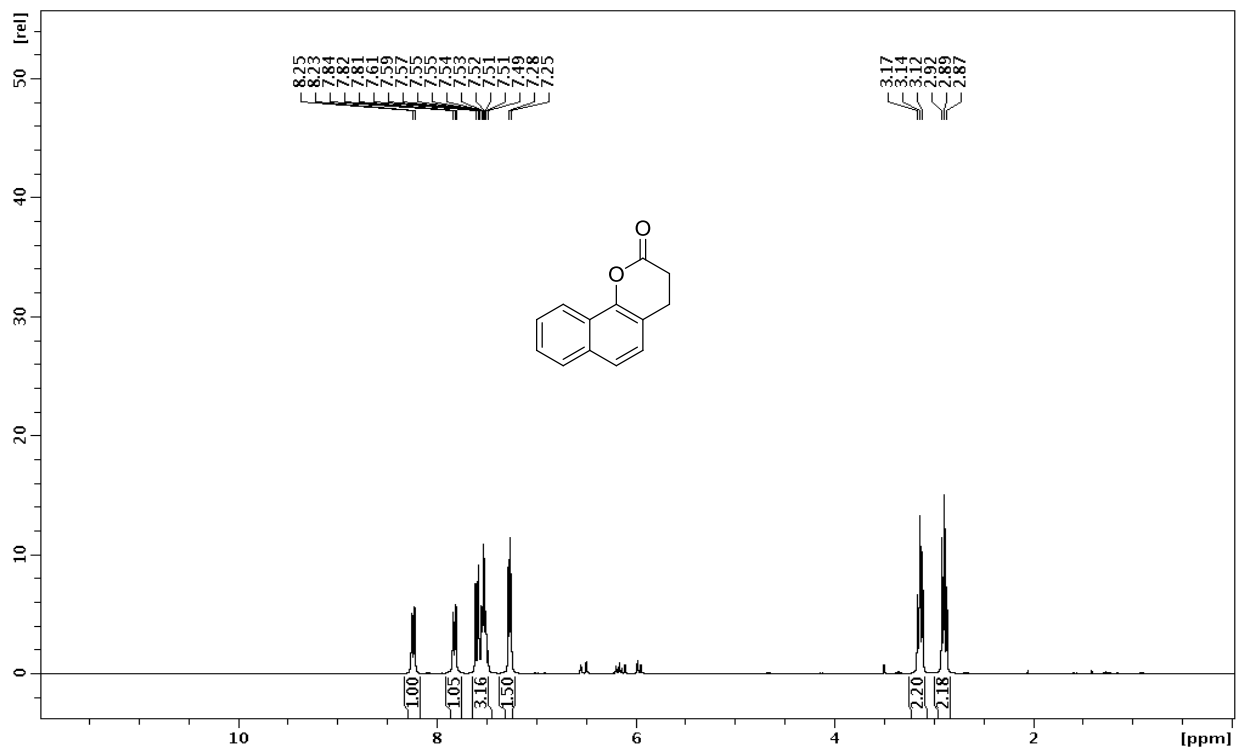
¹³C NMR spectrum of 3.46, Ar = Ph (75 MHz, CDCl₃)



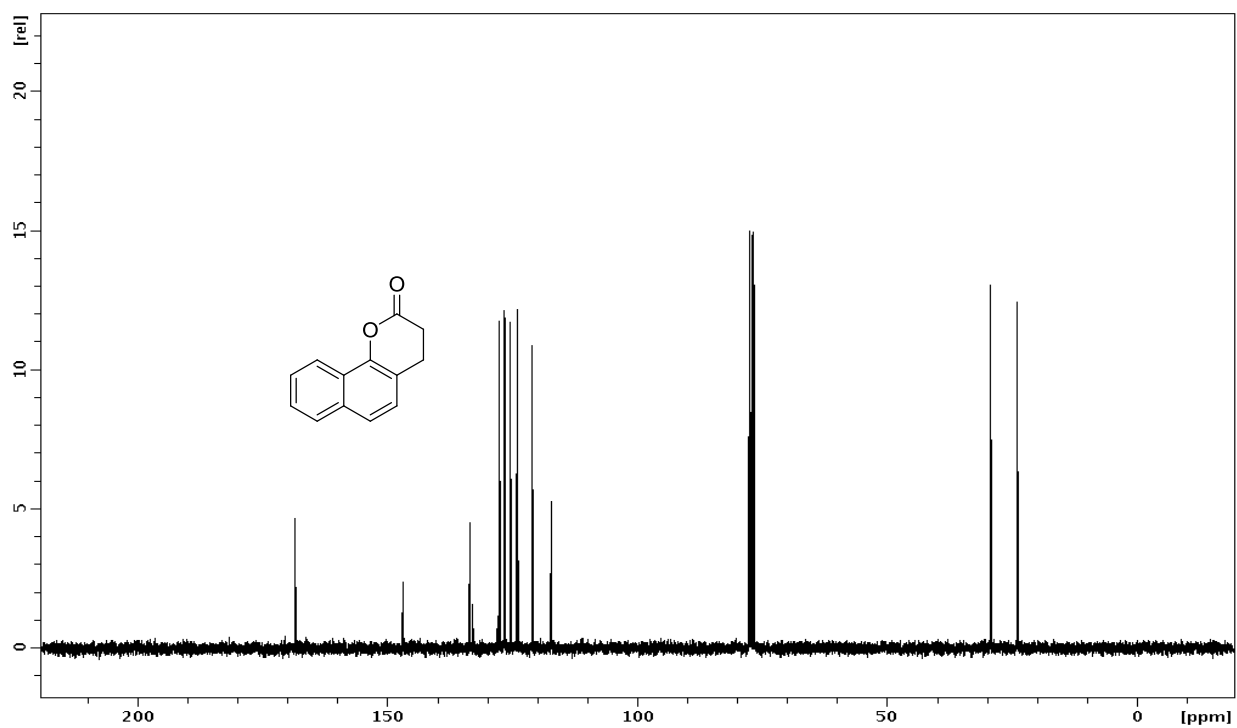
¹H NMR spectrum of 3.46, Ar = C₆H₄-CF₃-p (300 MHz, CDCl₃)



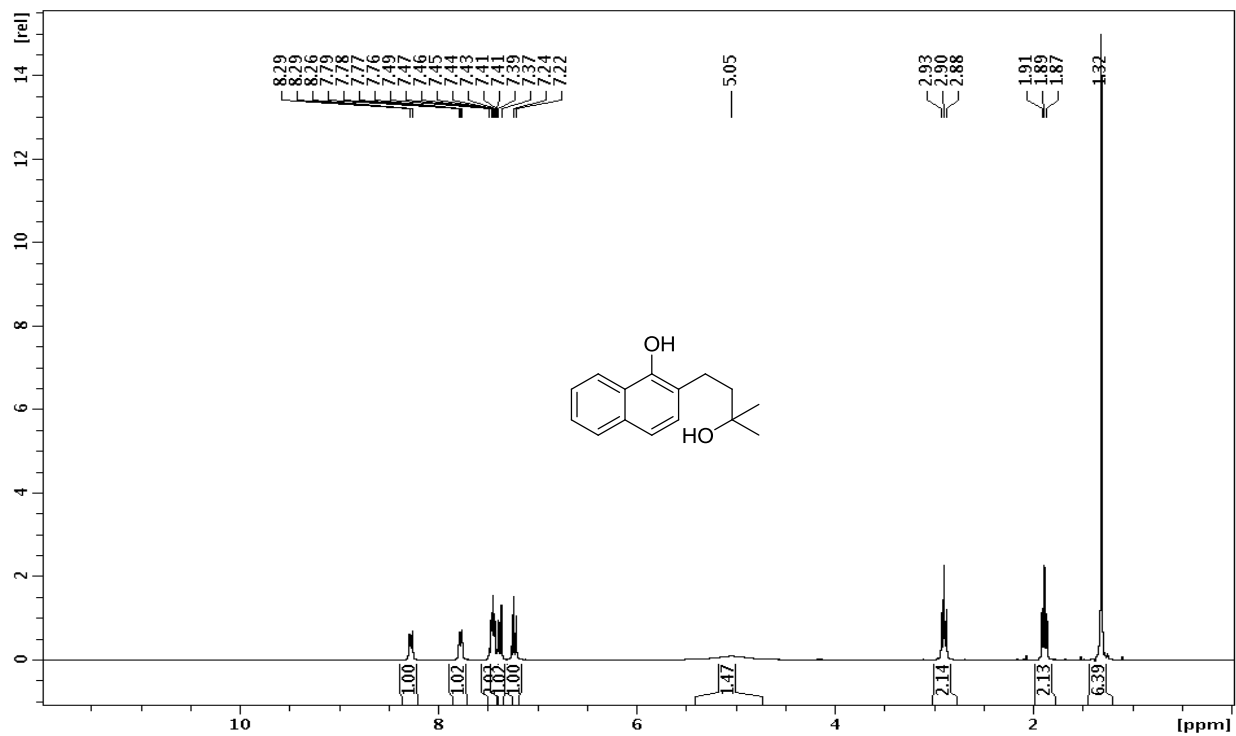
¹³C NMR spectrum of 3.46, Ar = C₆H₄-CF₃-p (75 MHz, CDCl₃)



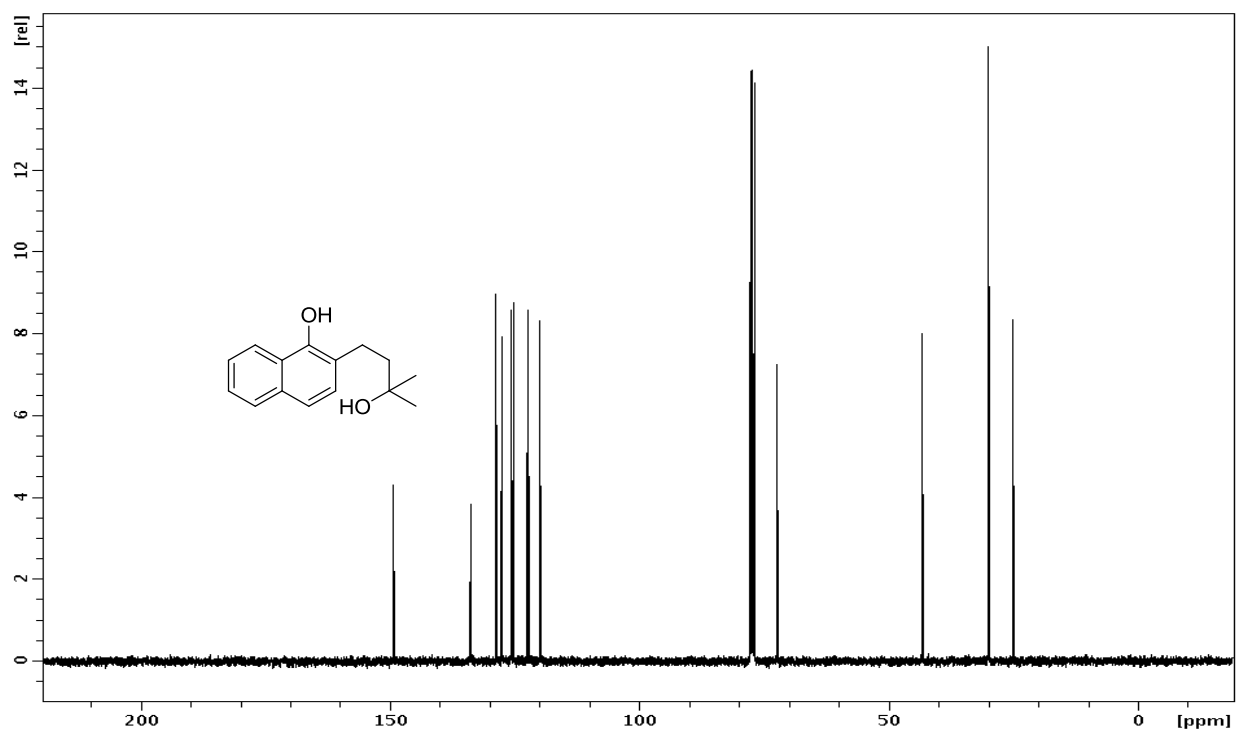
¹H NMR spectrum of 3.48 (300 MHz, CDCl₃)



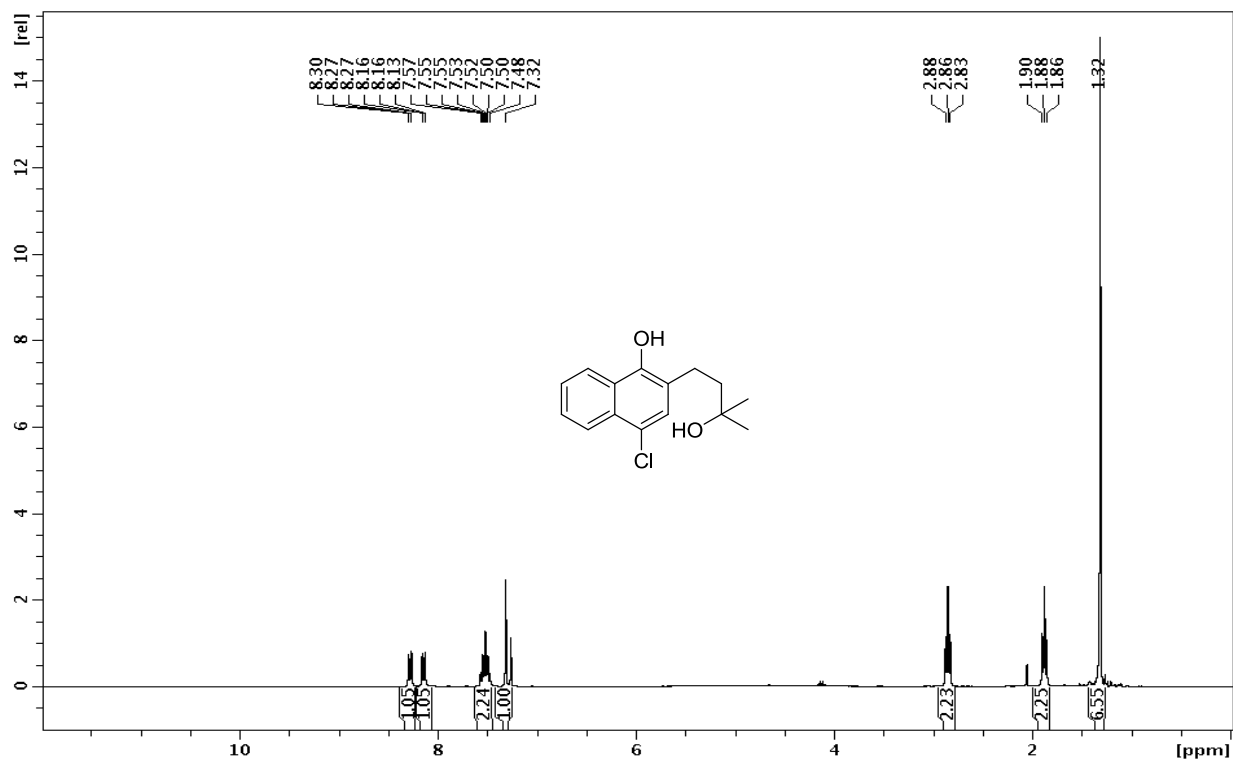
¹³C NMR spectrum of 3.48 (75 MHz, CDCl₃)



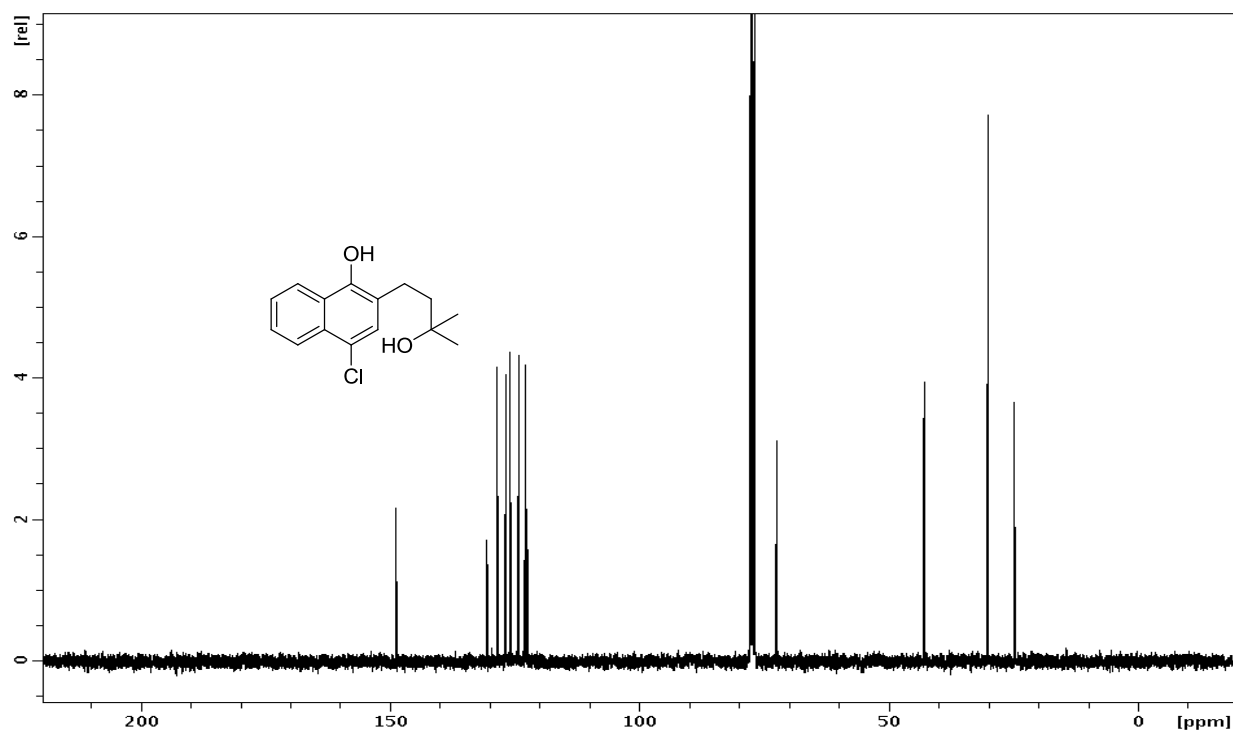
¹H NMR spectrum of 3.49 (300 MHz, CDCl₃)



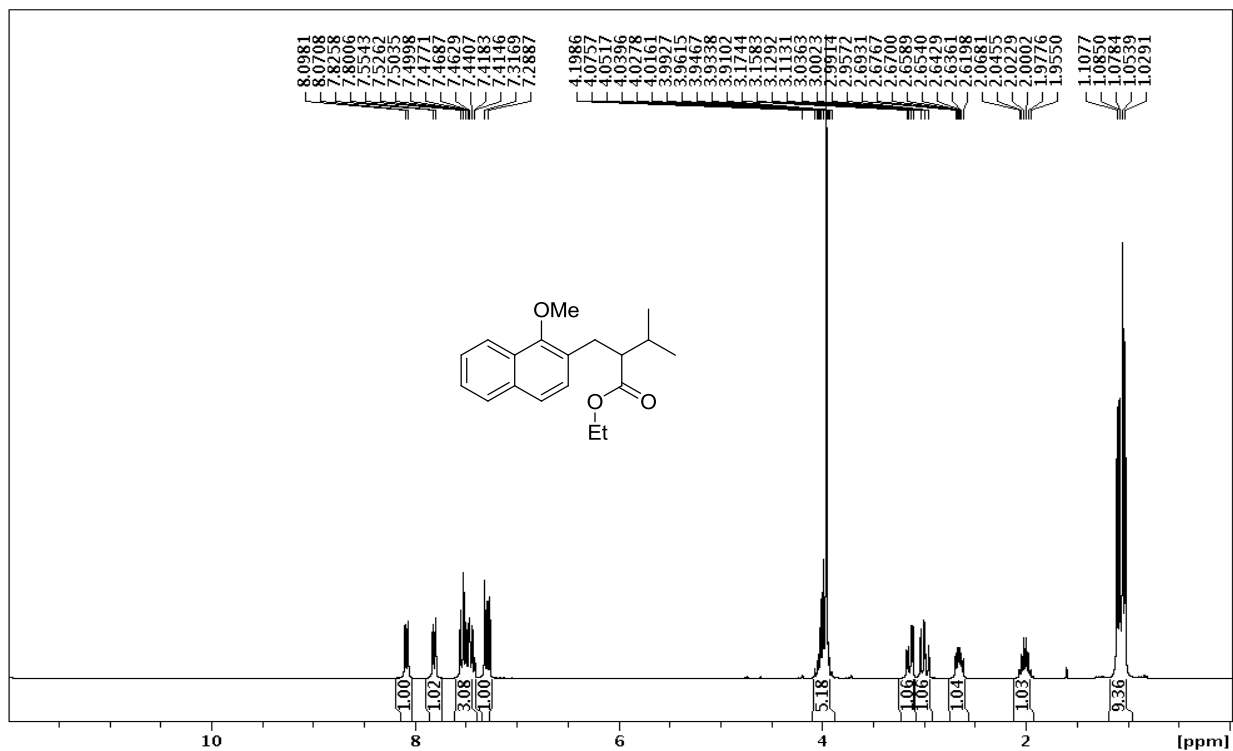
¹³C NMR spectrum of 3.49 (75 MHz, CDCl₃)



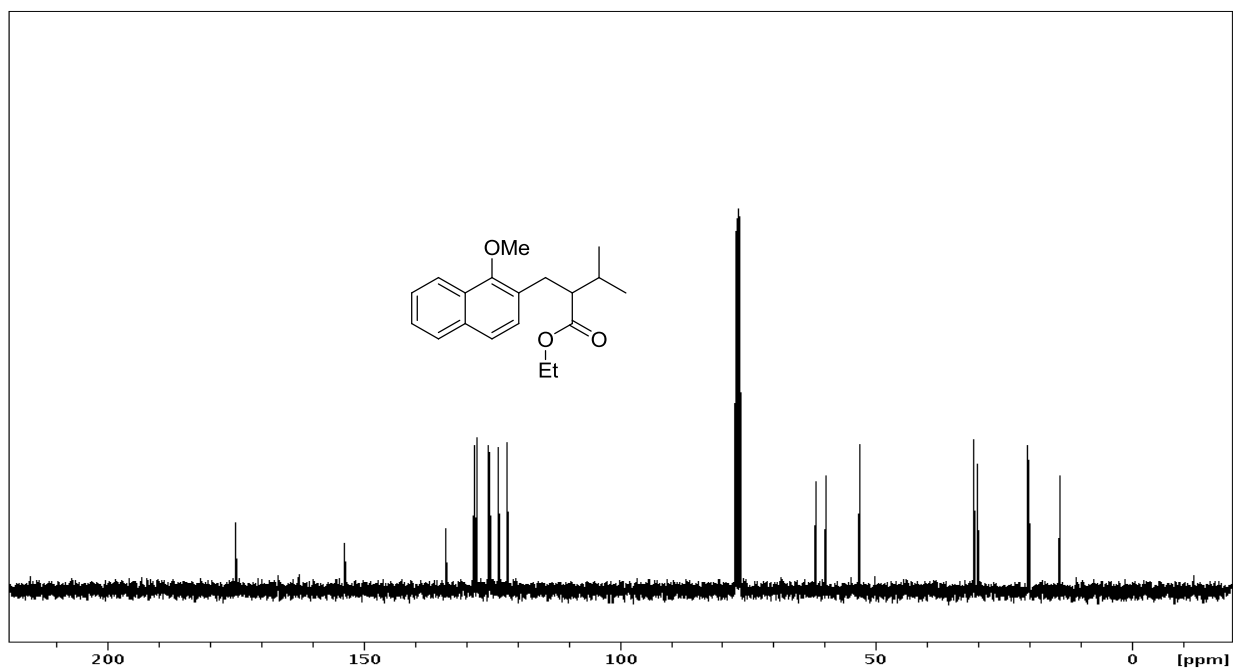
¹H NMR spectrum of 3.50 (300 MHz, CDCl₃)



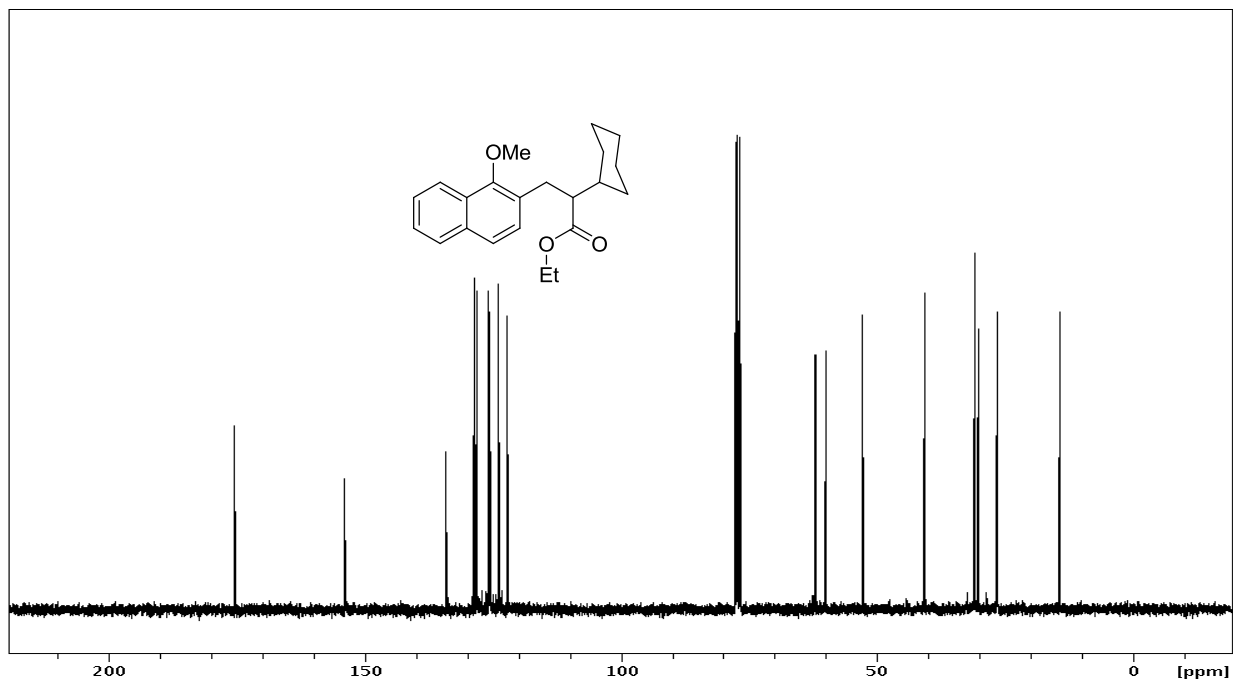
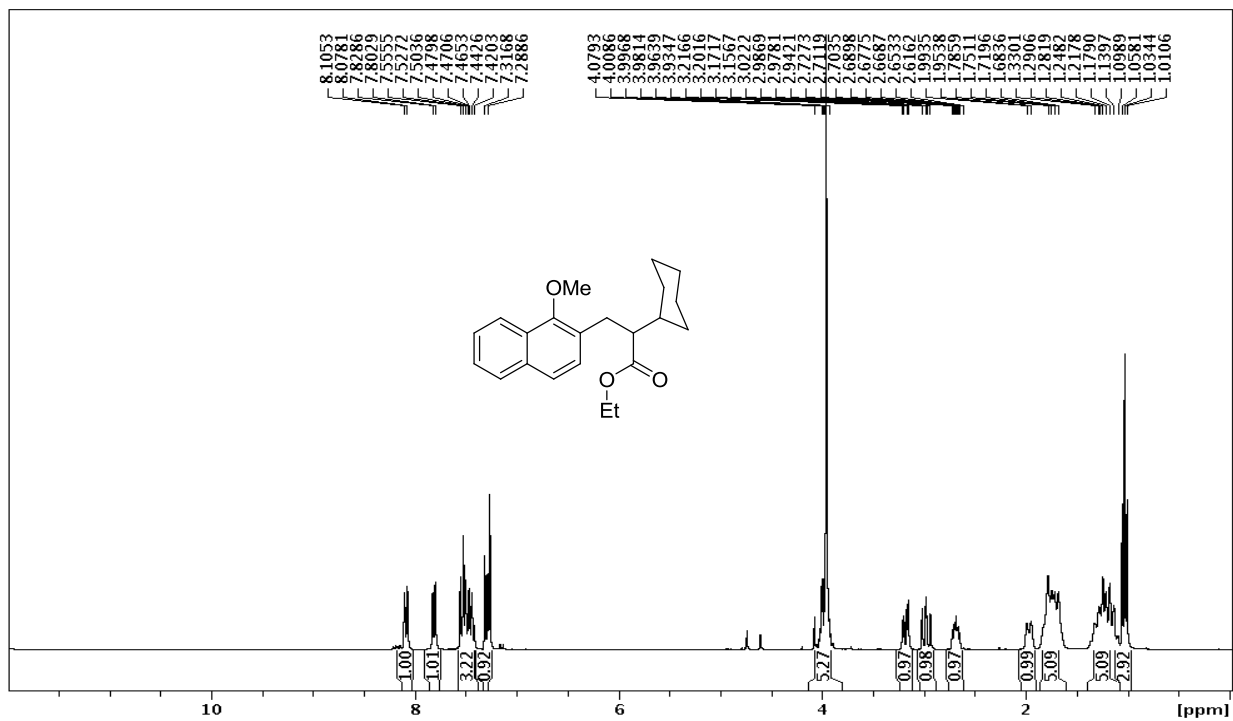
¹³C NMR spectrum of 3.50 (75 MHz, CDCl₃)

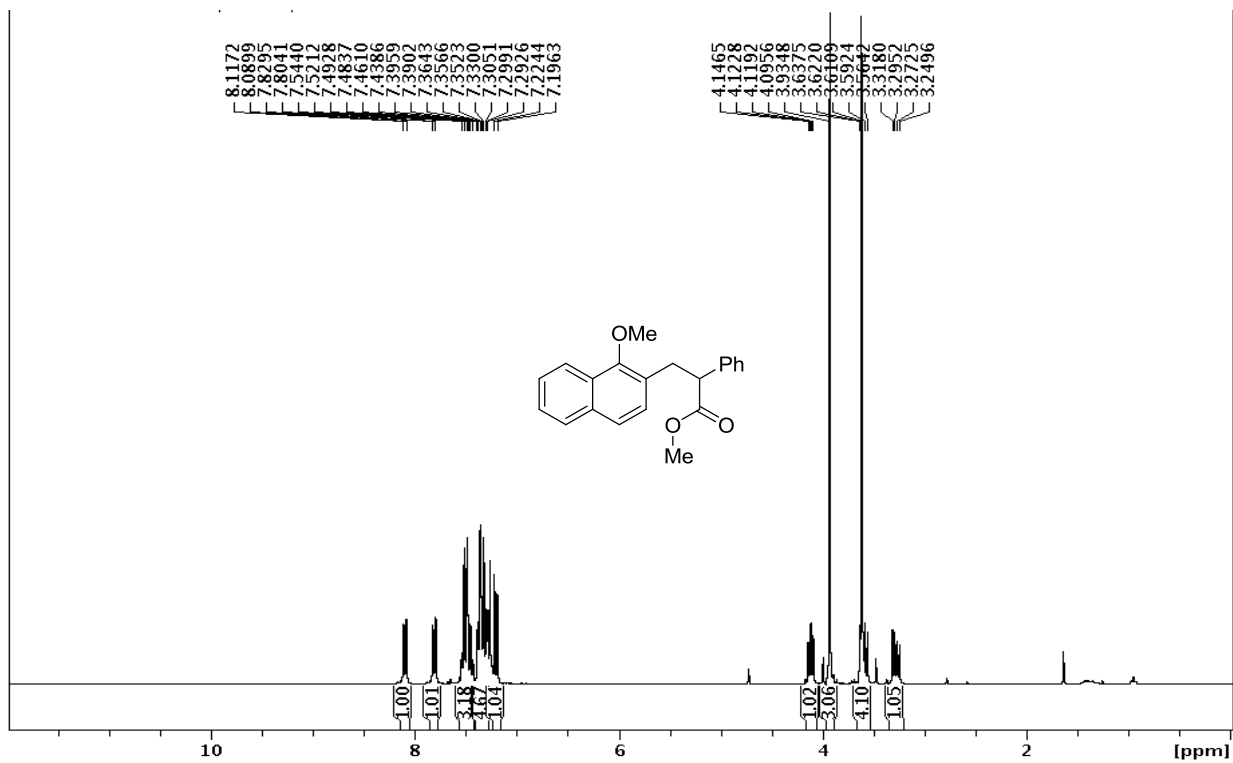


^1H NMR spectrum of 3.52, R = *i*-Pr, R' = Et (300 MHz, CDCl_3)

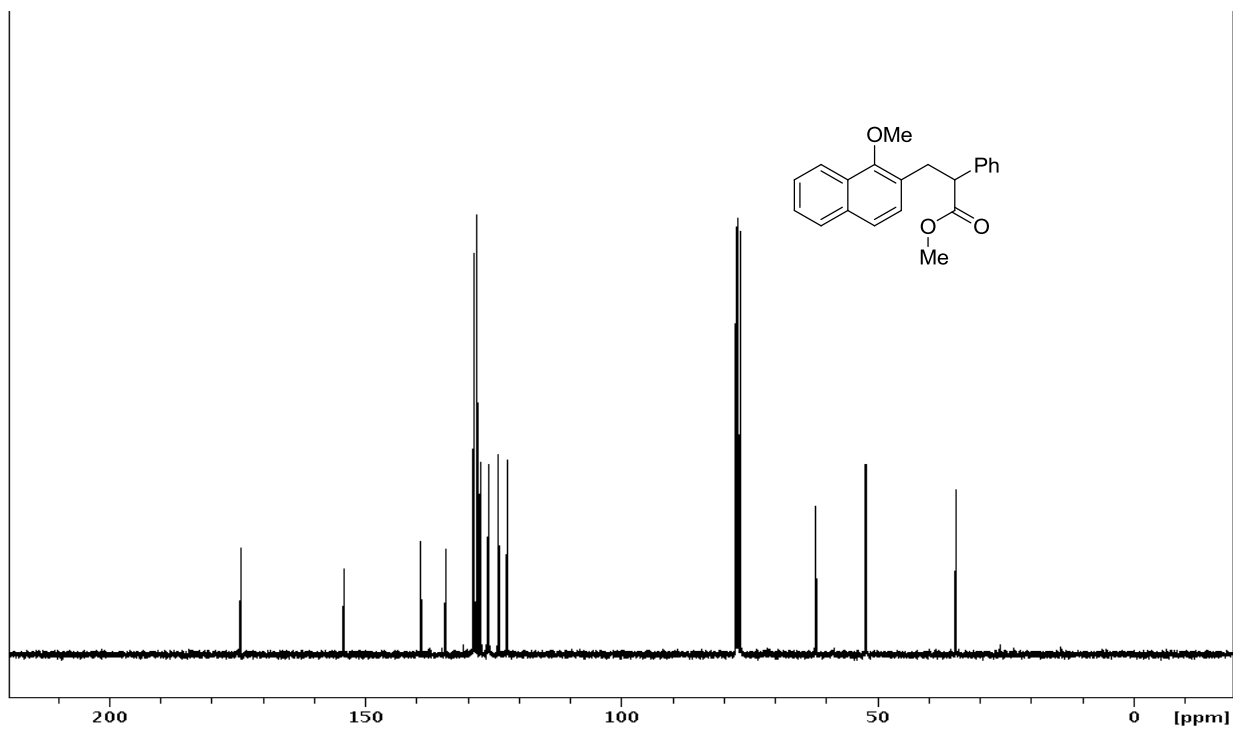


^{13}C NMR spectrum of 3.52, R = *i*-Pr, R' = Et (75 MHz, CDCl_3)

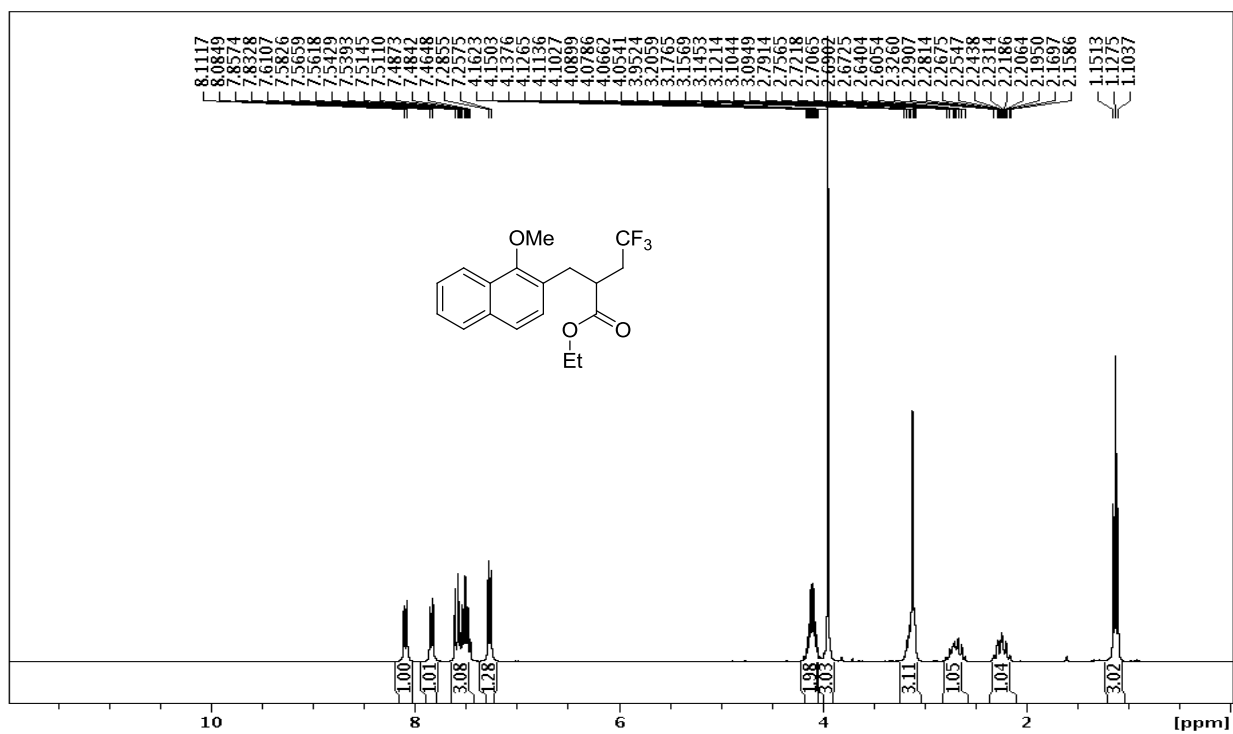




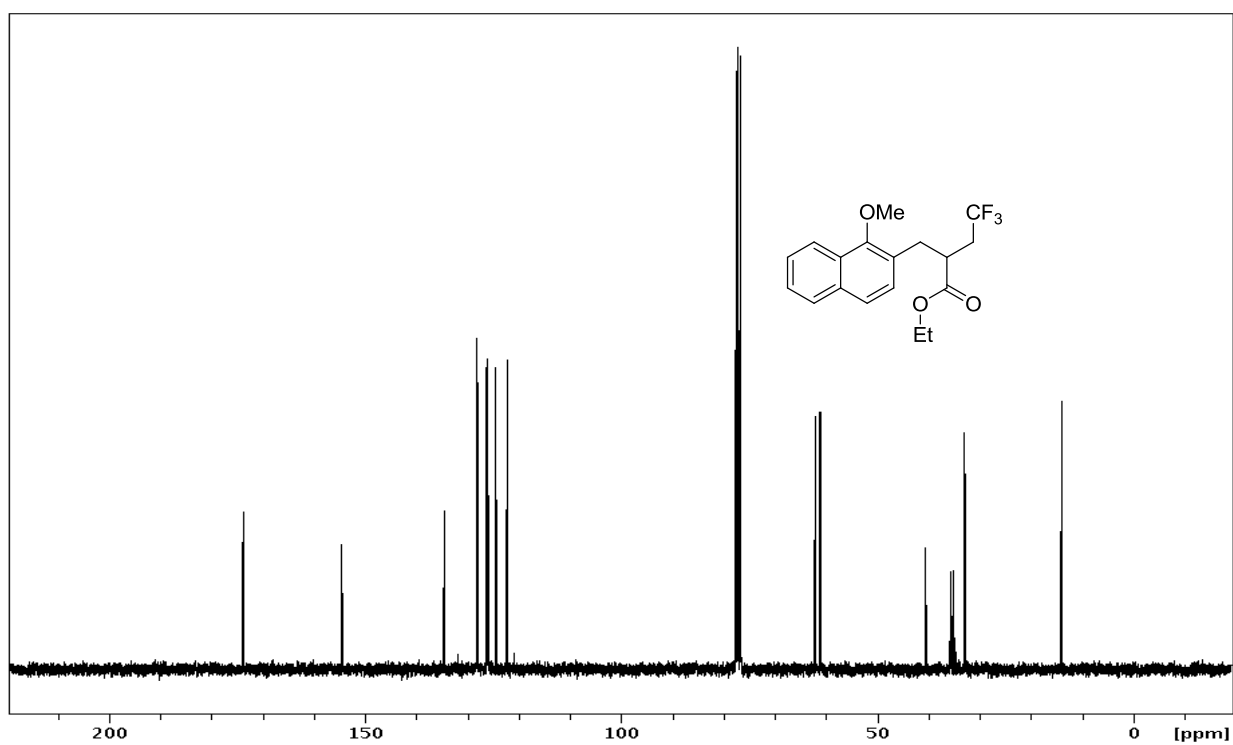
¹H NMR spectrum of 3.52, R = Ph, R' = Me (300 MHz, CDCl₃)



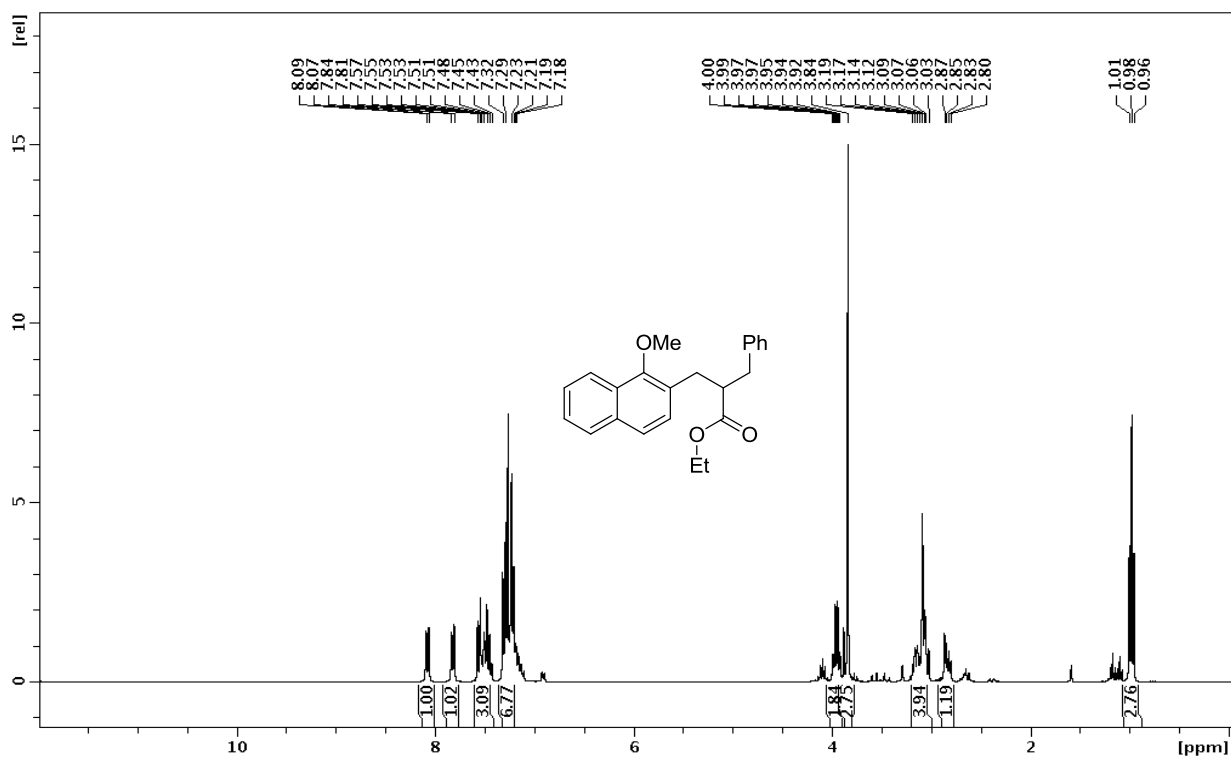
¹³C NMR spectrum of 3.52, R = Ph, R' = Me (75 MHz, CDCl₃)



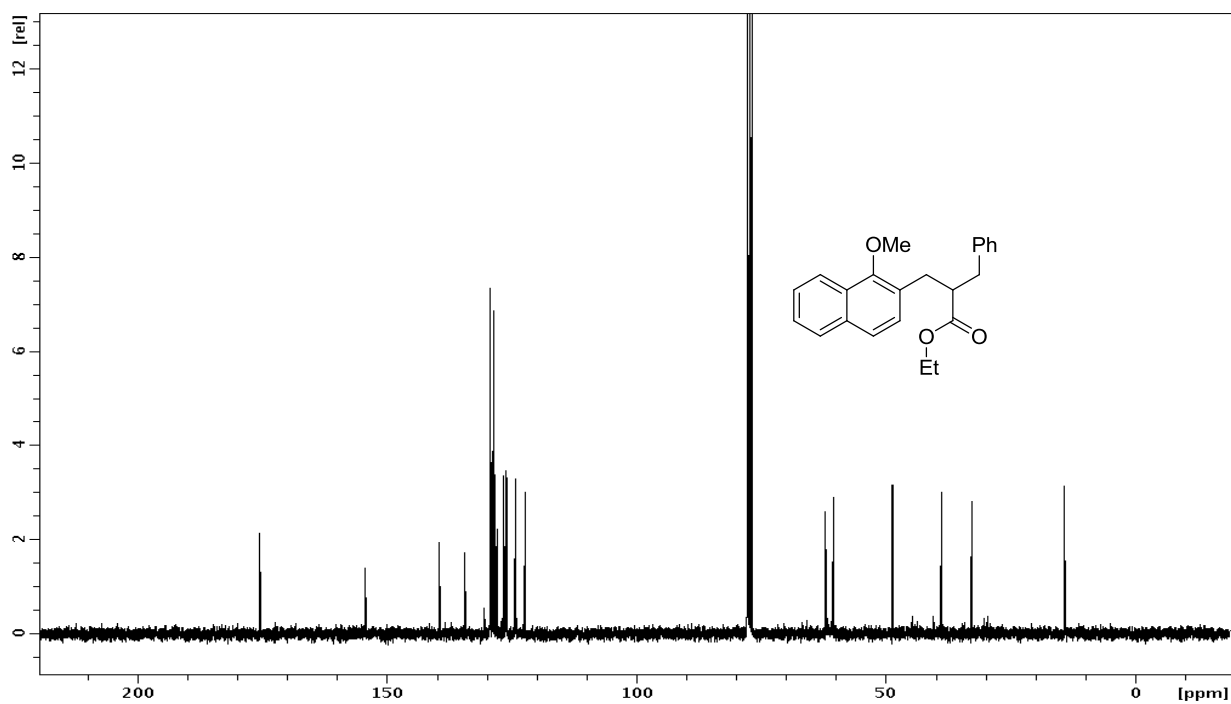
¹H NMR spectrum of 3.52, R = CH₂CF₃, R' = Et (300 MHz, CDCl₃)



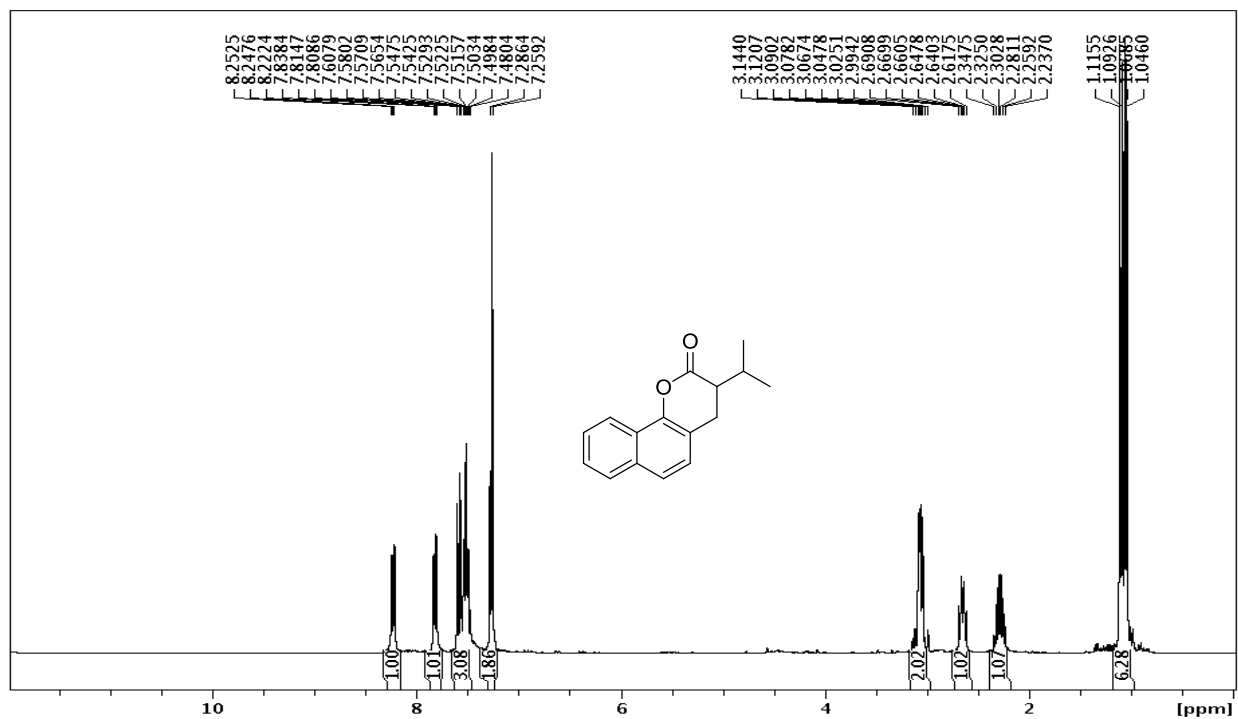
¹³C NMR spectrum of 3.52, R = CH₂CF₃, R' = Et (75 MHz, CDCl₃)



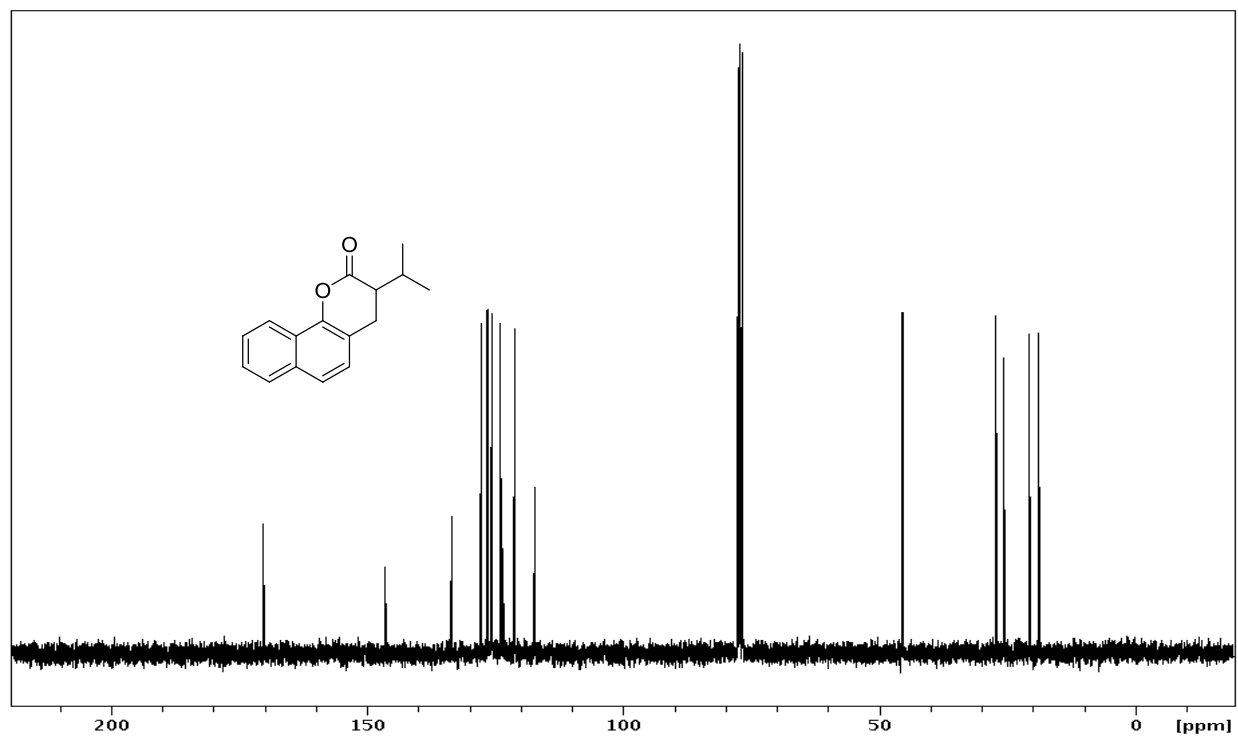
¹H NMR spectrum of 3.52, R = Bn, R' = Et (300 MHz, CDCl₃)



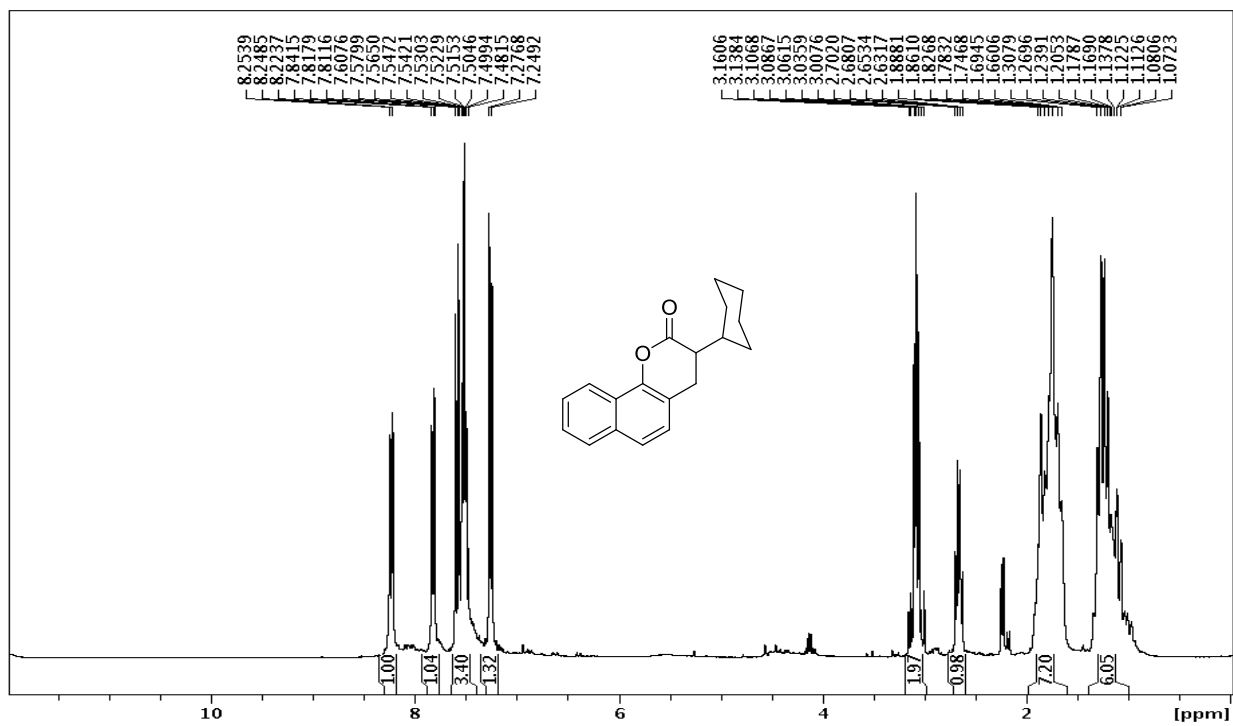
¹³C NMR spectrum of 3.52, R = Bn, R' = Et (75 MHz, CDCl₃)



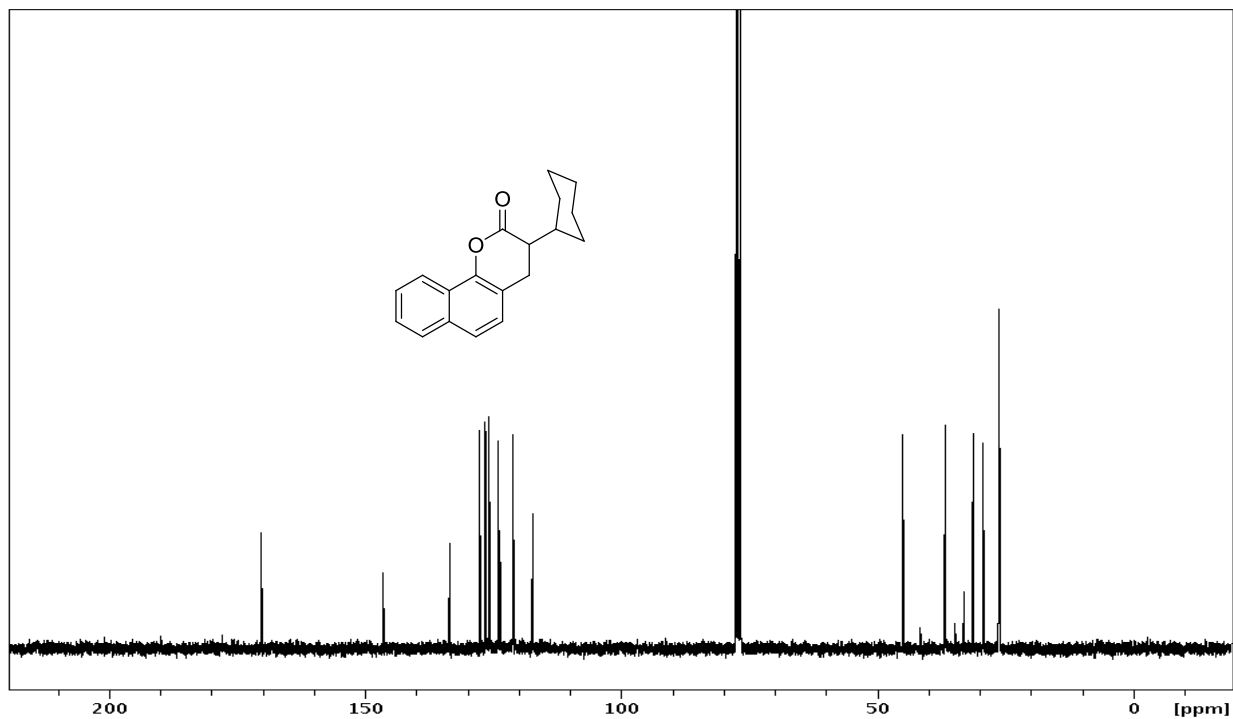
^1H NMR spectrum of 3.53, R = *i*-Pr (300 MHz, CDCl_3)



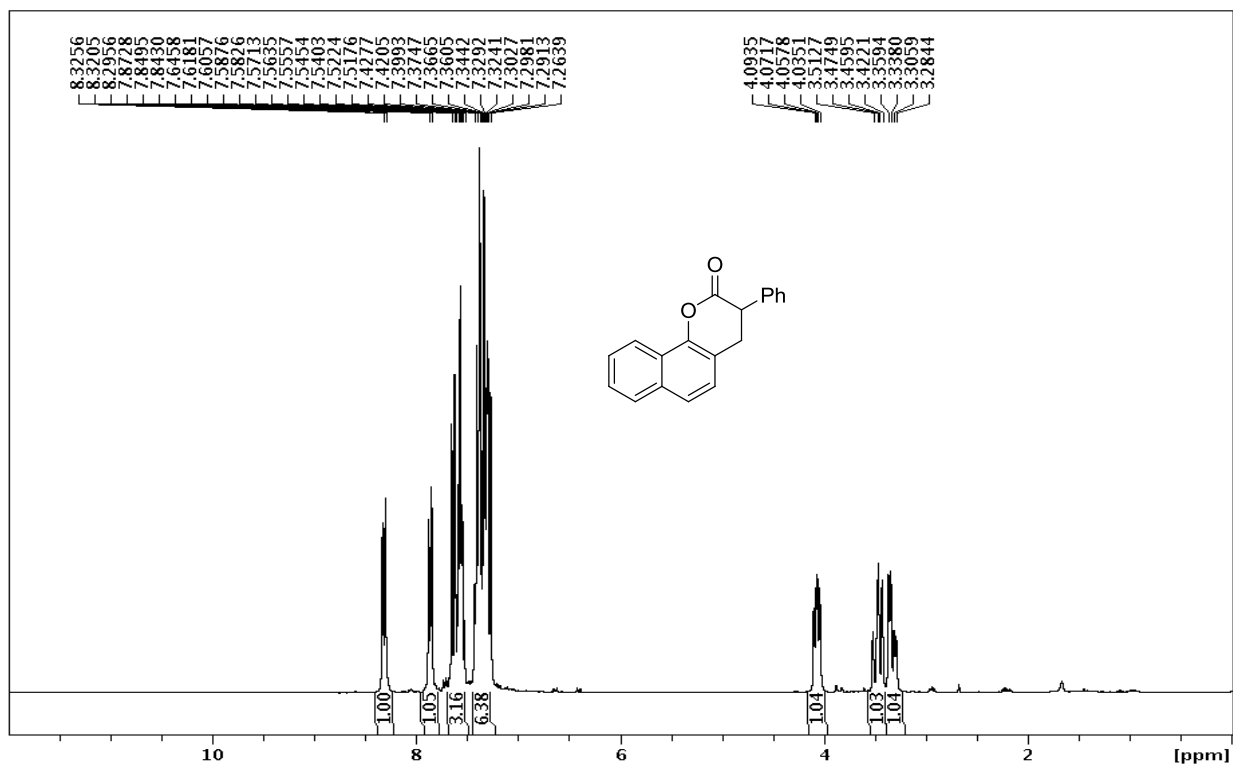
^{13}C NMR spectrum of 3.53, R = *i*-Pr (75 MHz, CDCl_3)



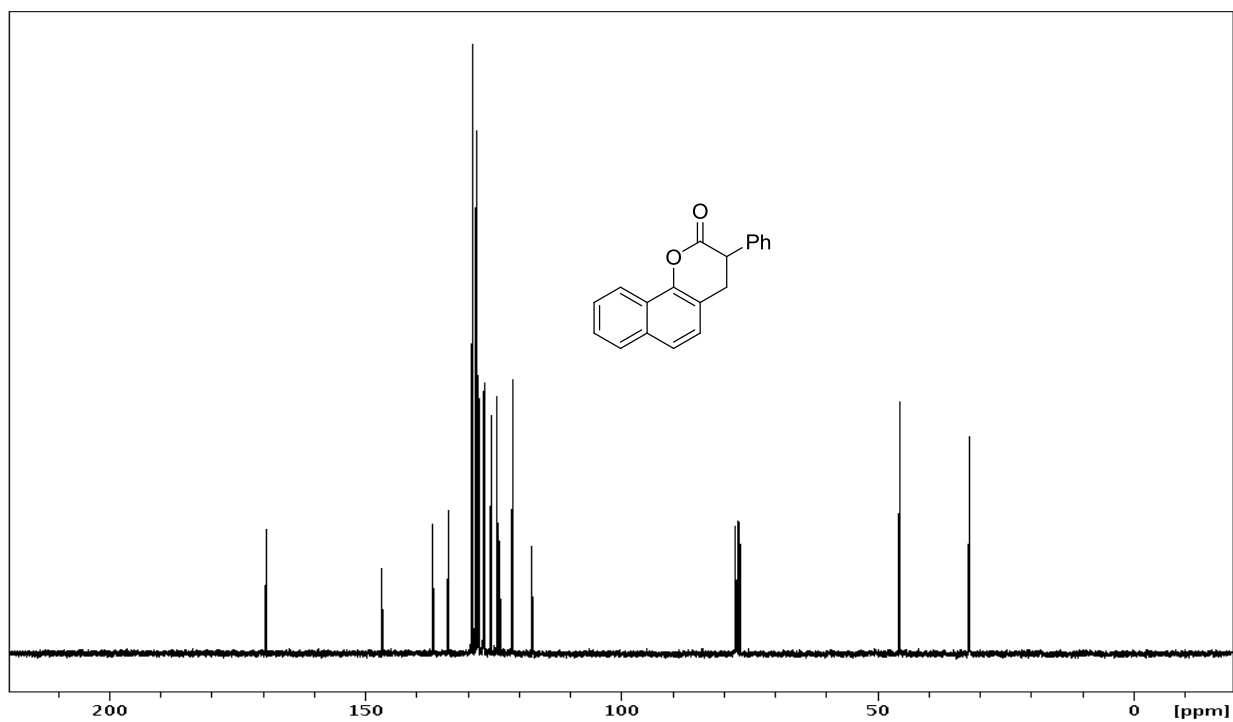
¹H NMR spectrum of crude 3.53, R = Cy (300 MHz, CDCl₃)



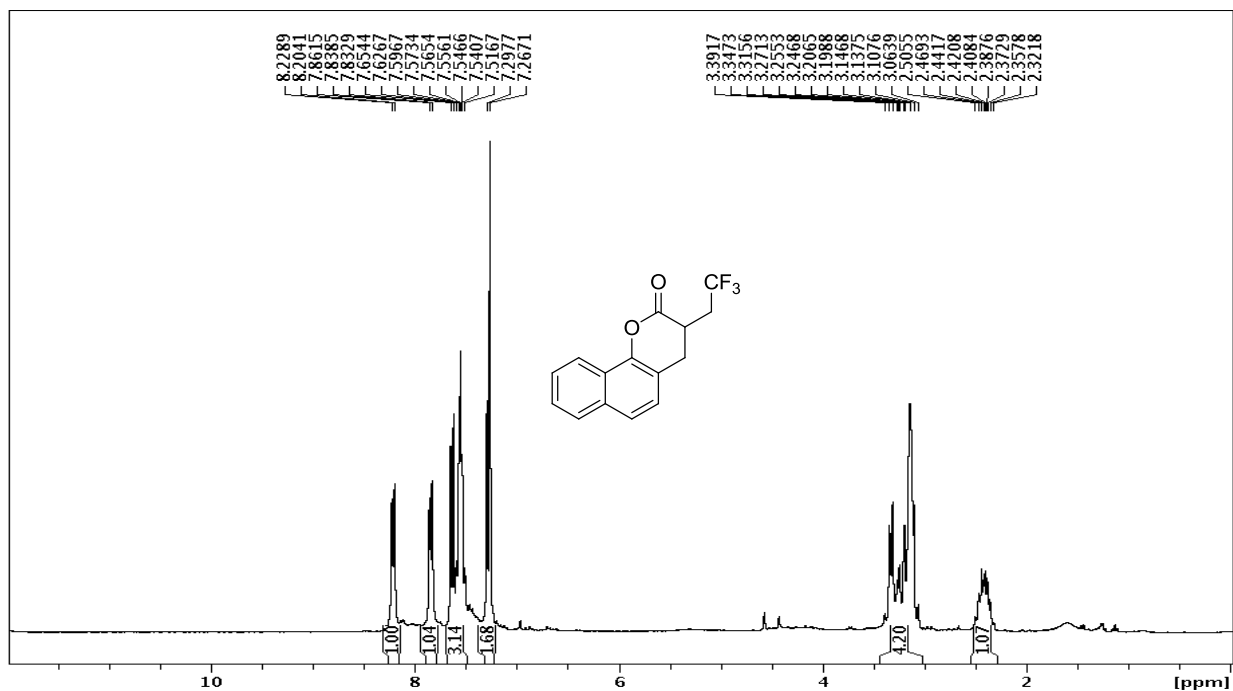
¹³C NMR spectrum of crude 3.53, R = Cy (75 MHz, CDCl₃)



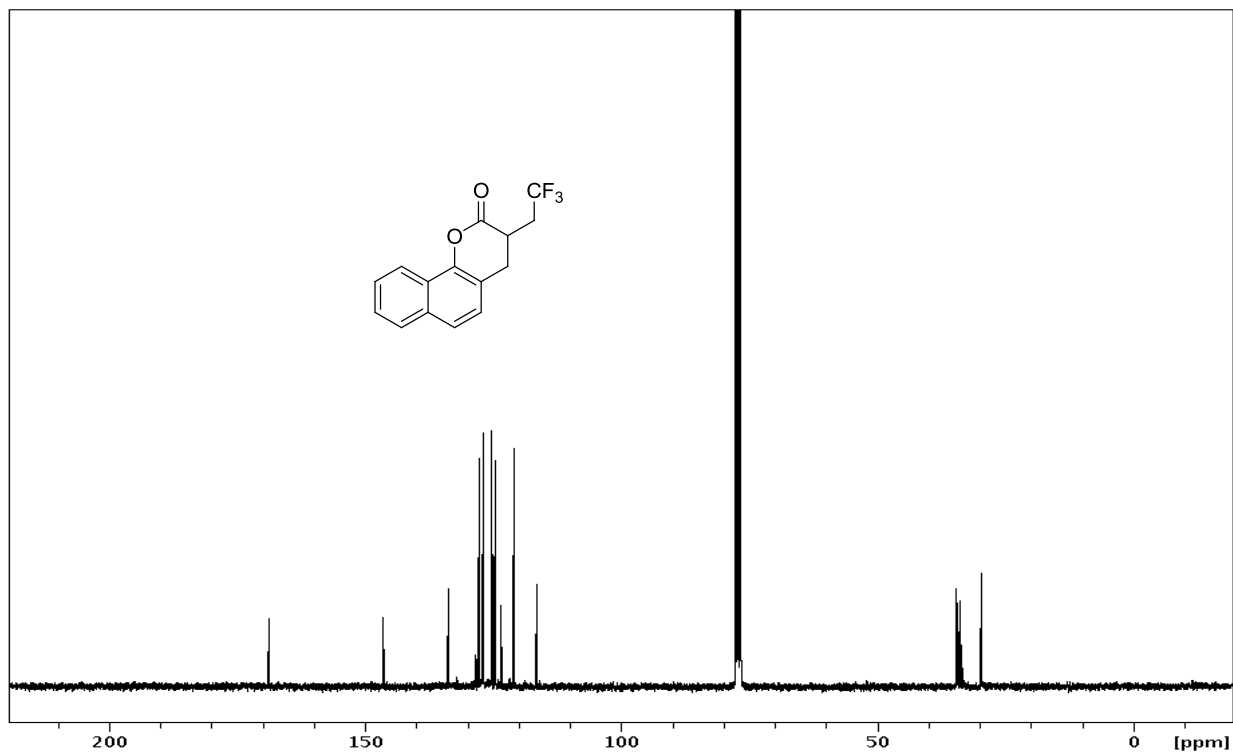
¹H NMR spectrum of crude 3.53, R = Ph (300 MHz, CDCl₃)



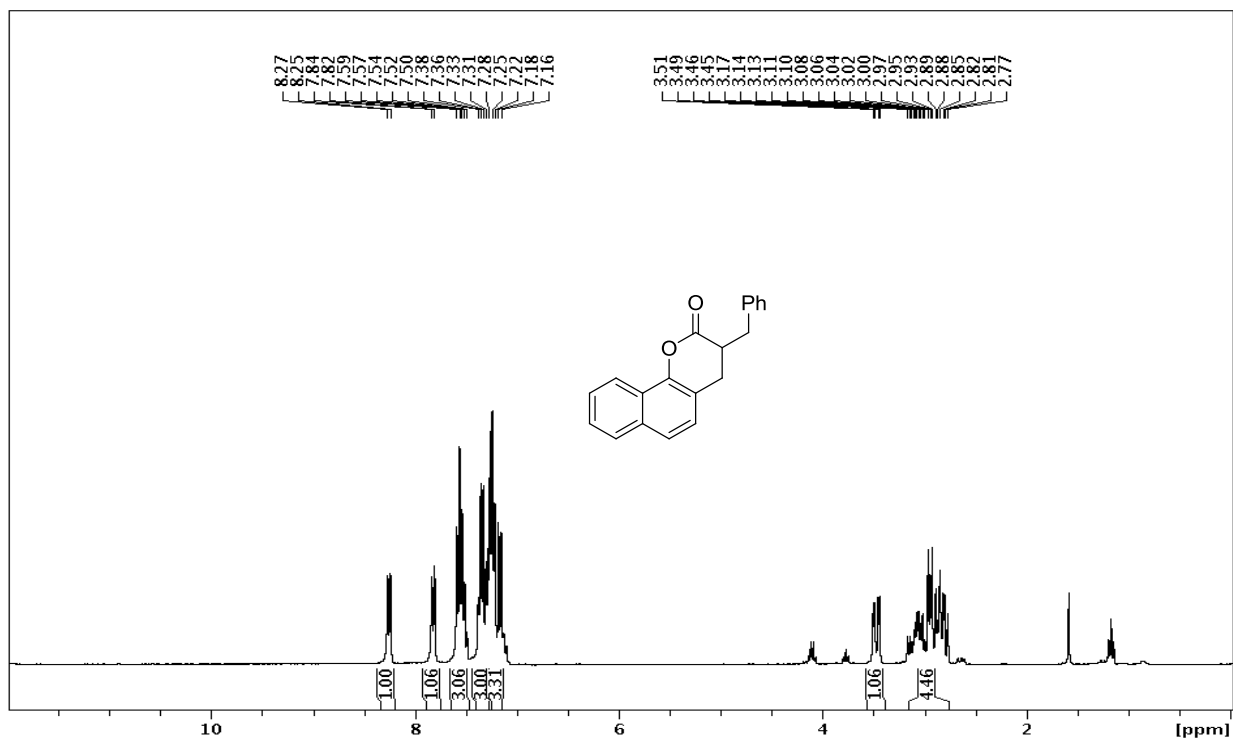
¹³C NMR spectrum of crude 3.53, R = Ph (75 MHz, CDCl₃)



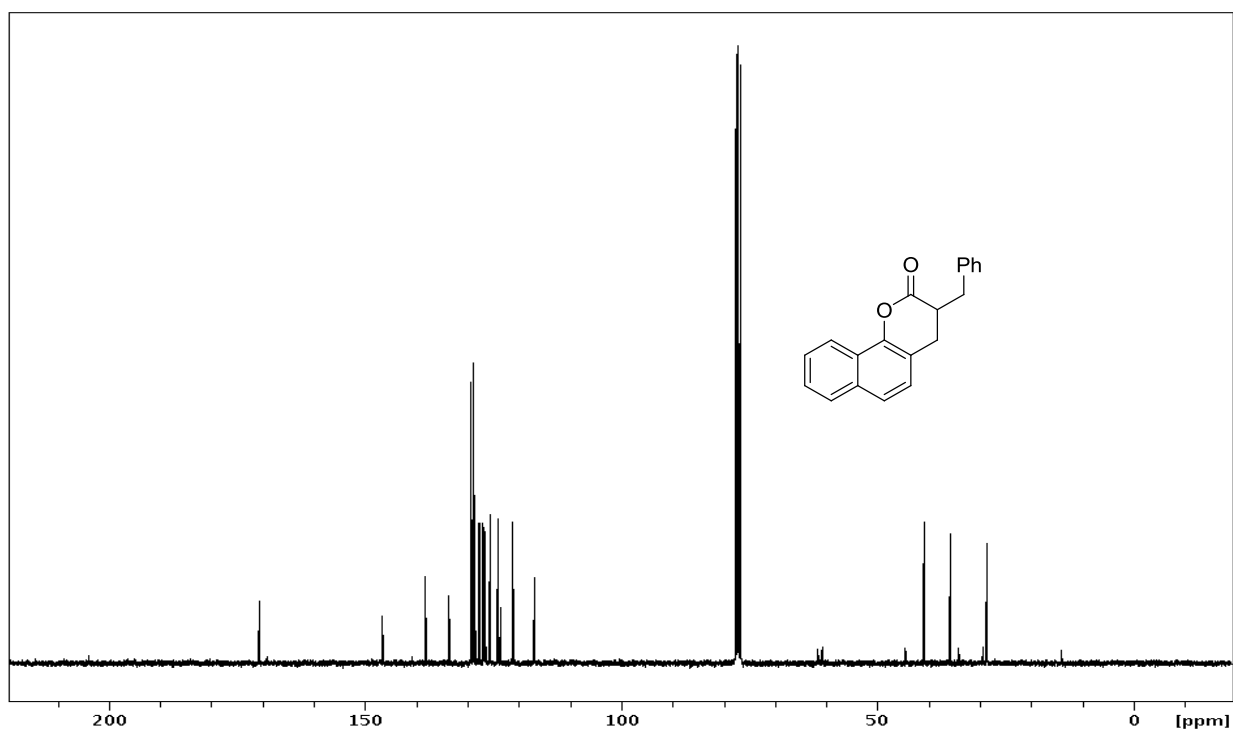
¹H NMR spectrum of crude 3.53, R = CH₂CF₃ (300 MHz, CDCl₃)



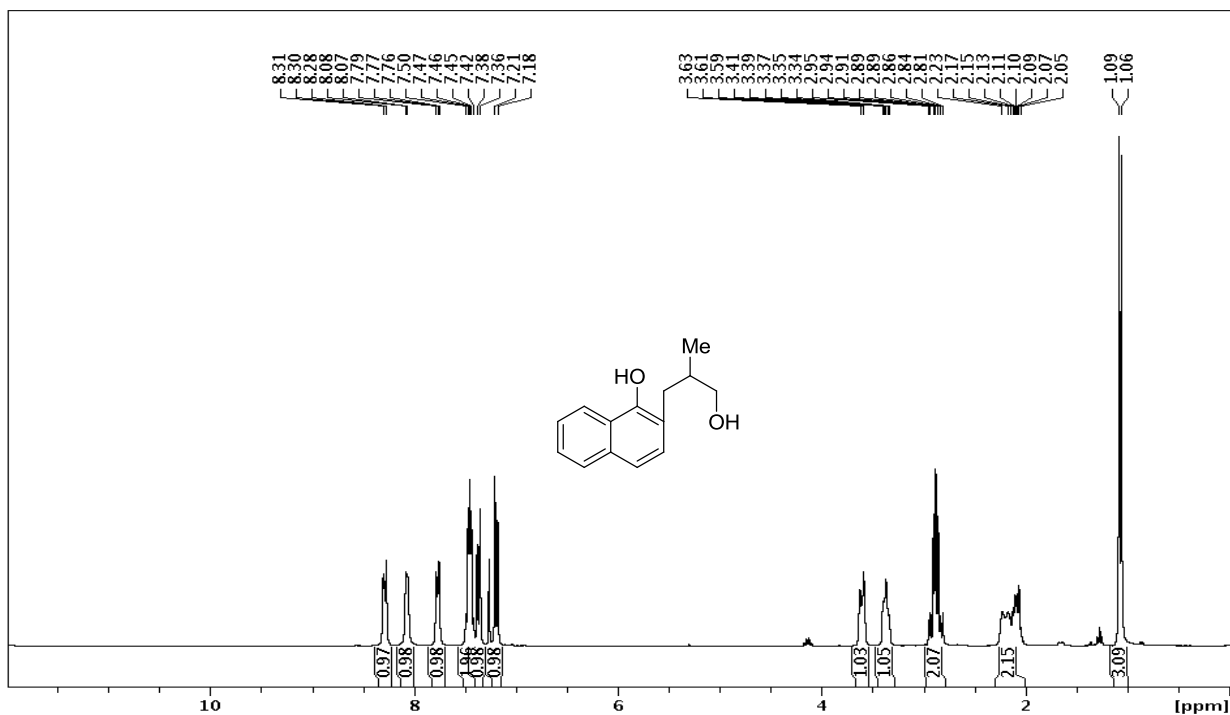
¹³C NMR spectrum of crude 3.53, R = CH₂CF₃ (75 MHz, CDCl₃)



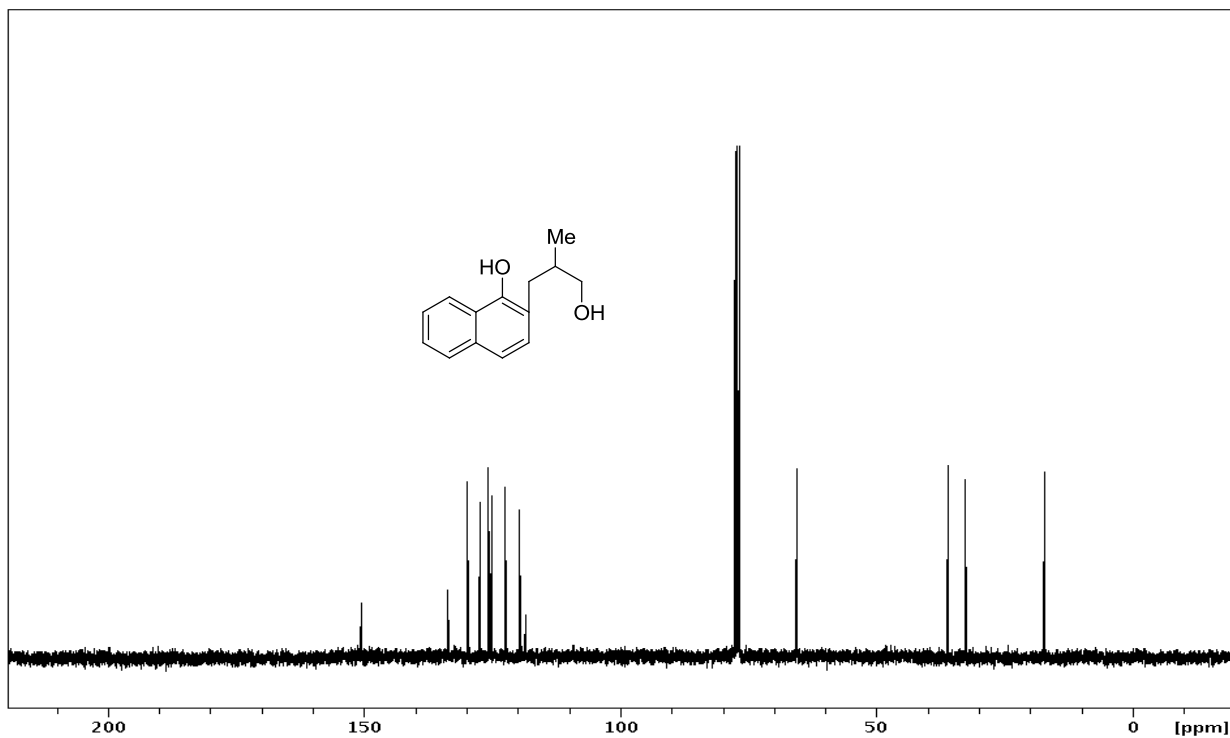
¹H NMR spectrum of crude 3.53, R = Bn (300 MHz, CDCl₃)



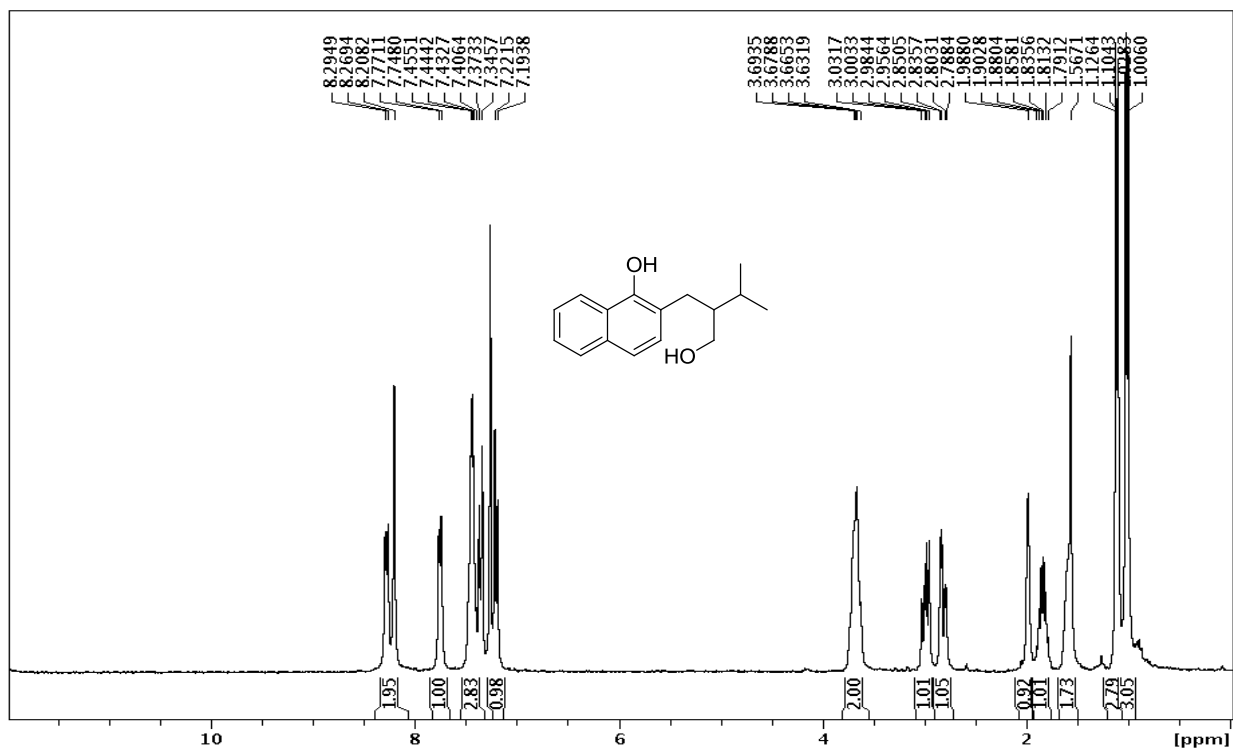
¹³C NMR spectrum of crude 3.53 (75 MHz, CDCl₃)



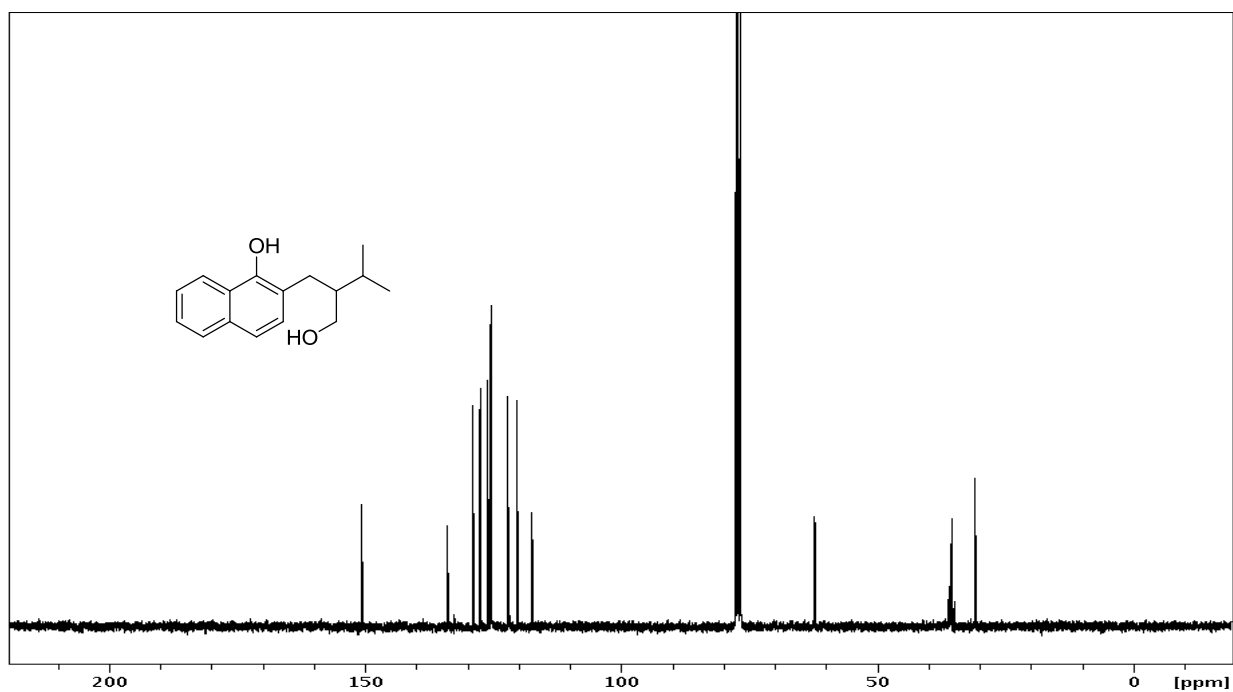
^1H NMR spectrum of 3.54, R = Me (300 MHz, CDCl_3)



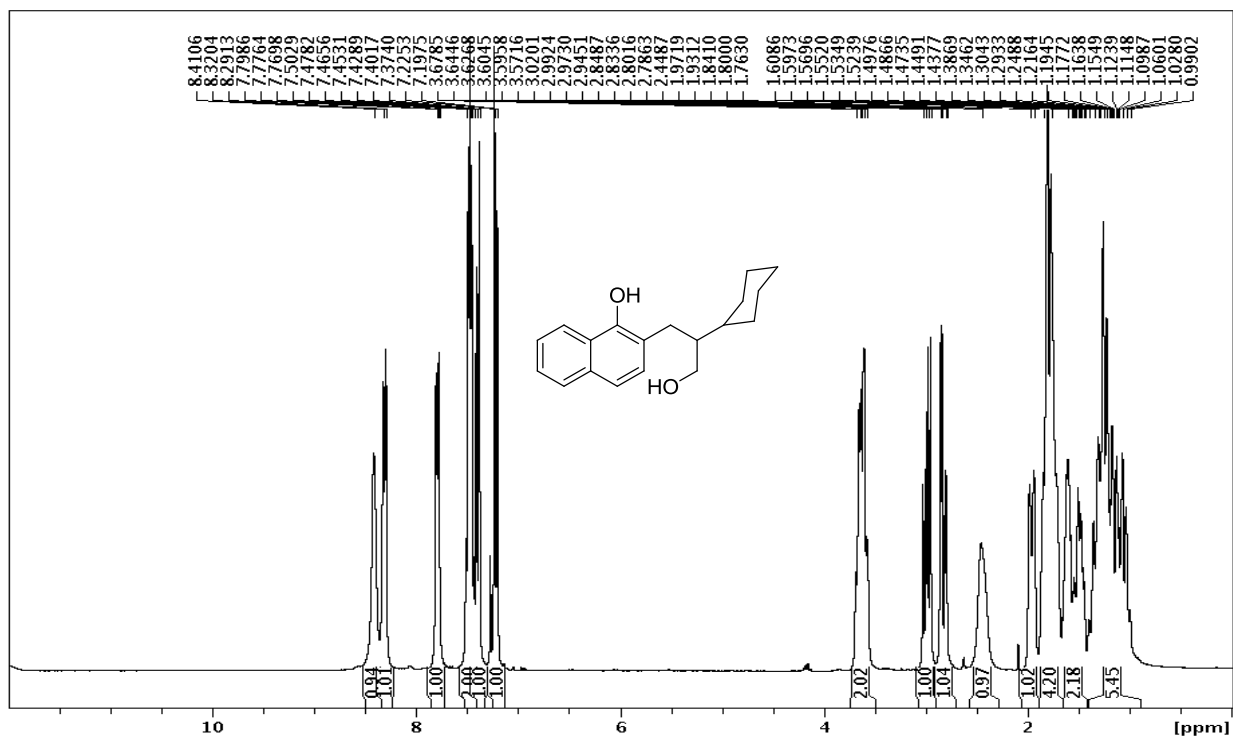
^{13}C NMR spectrum of 3.54, R = Me (75 MHz, CDCl_3)



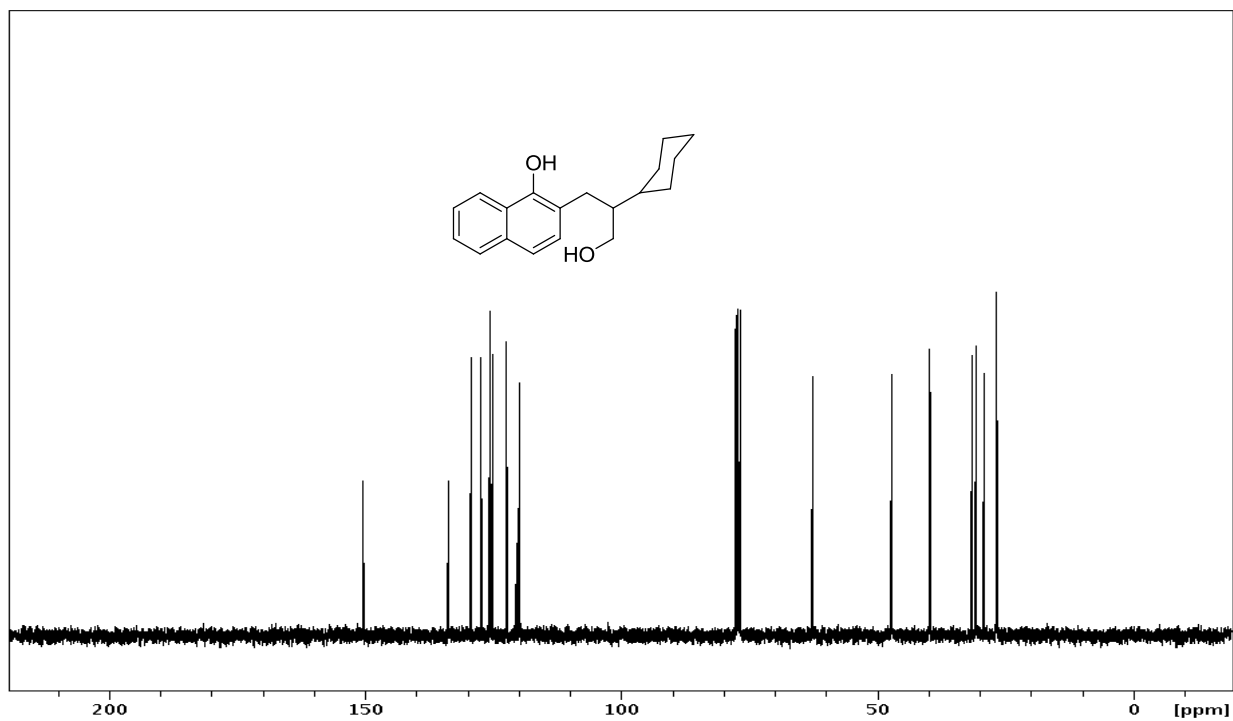
¹H NMR spectrum of 3.54, R = *i*-Pr (300 MHz, CDCl₃)



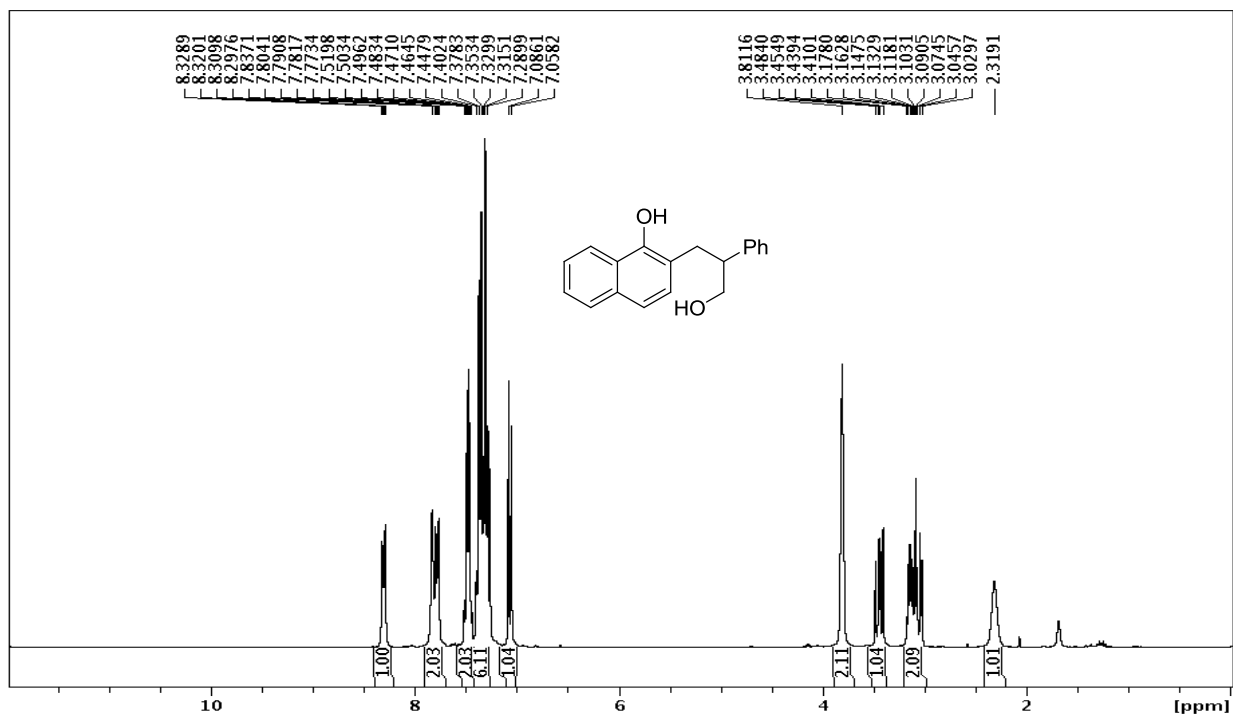
¹³C NMR spectrum of 3.54, R = *i*-Pr (75 MHz, CDCl₃)



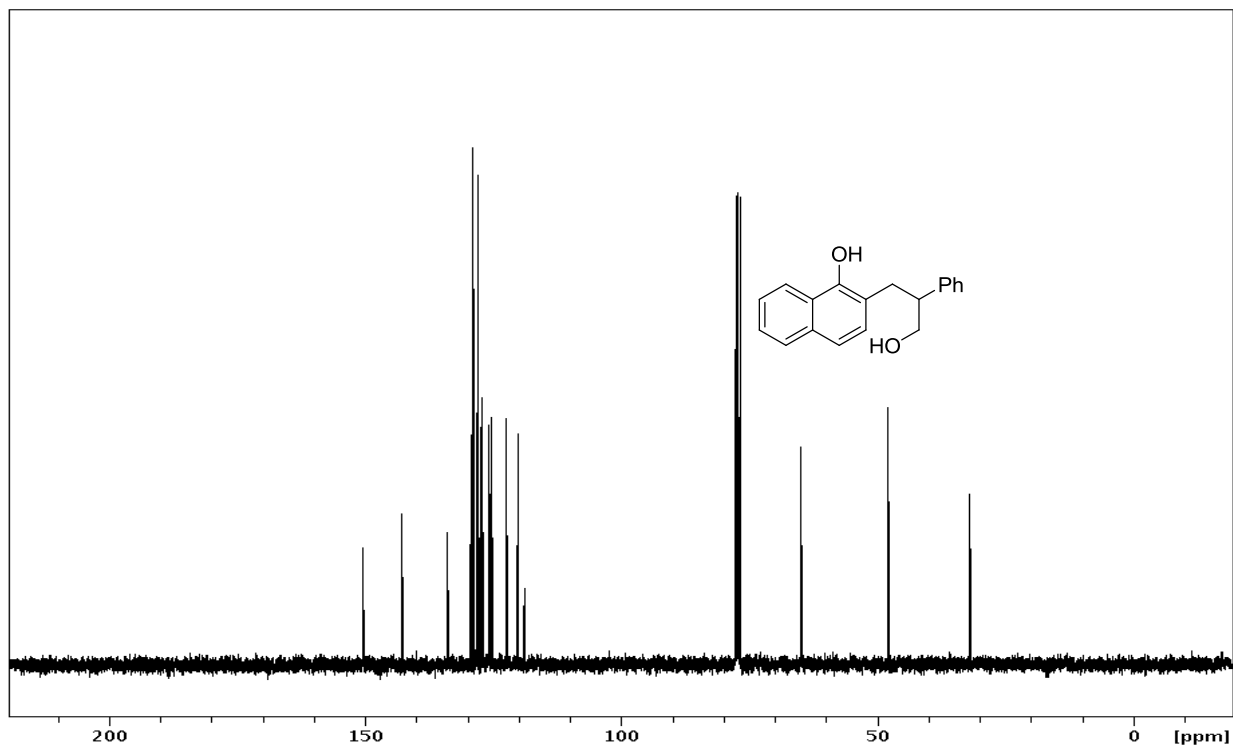
¹H NMR spectrum of 3.54, R = Cy (300 MHz, CDCl₃)



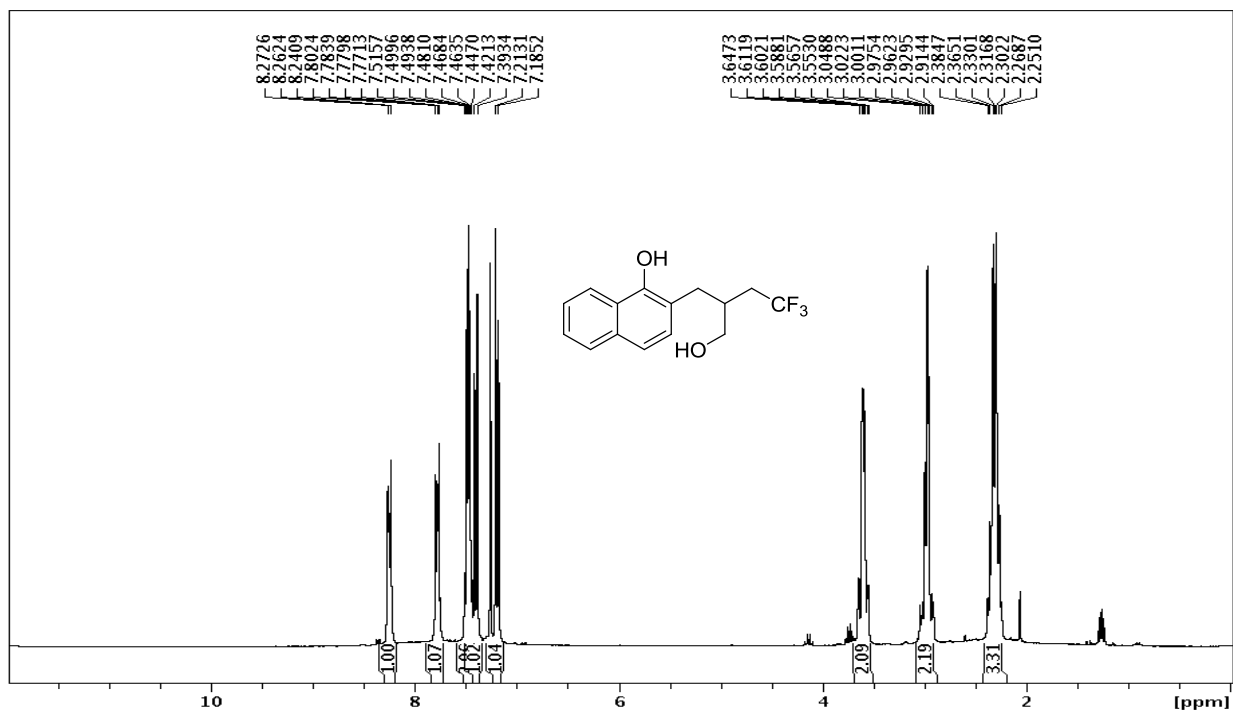
¹³C NMR spectrum of 3.54, R = Cy (75 MHz, CDCl₃)



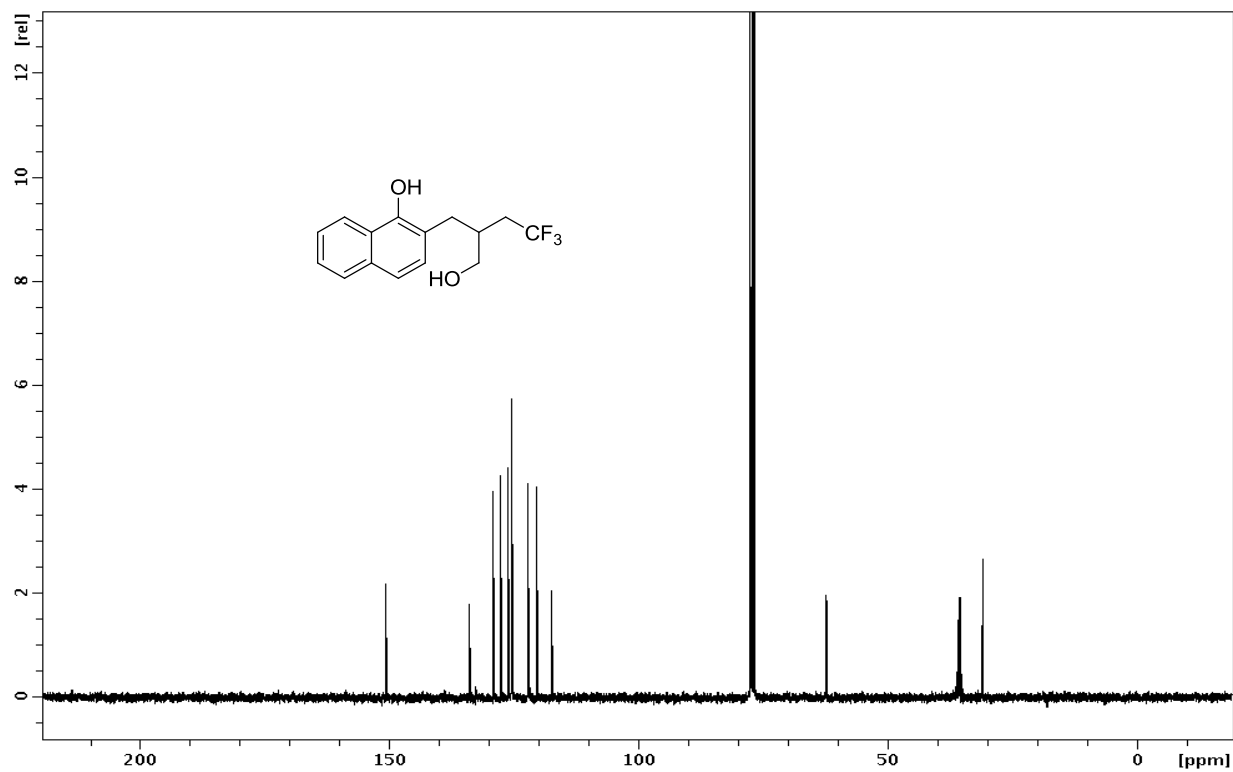
¹H NMR spectrum of 3.54, R = Ph (300 MHz, CDCl₃)



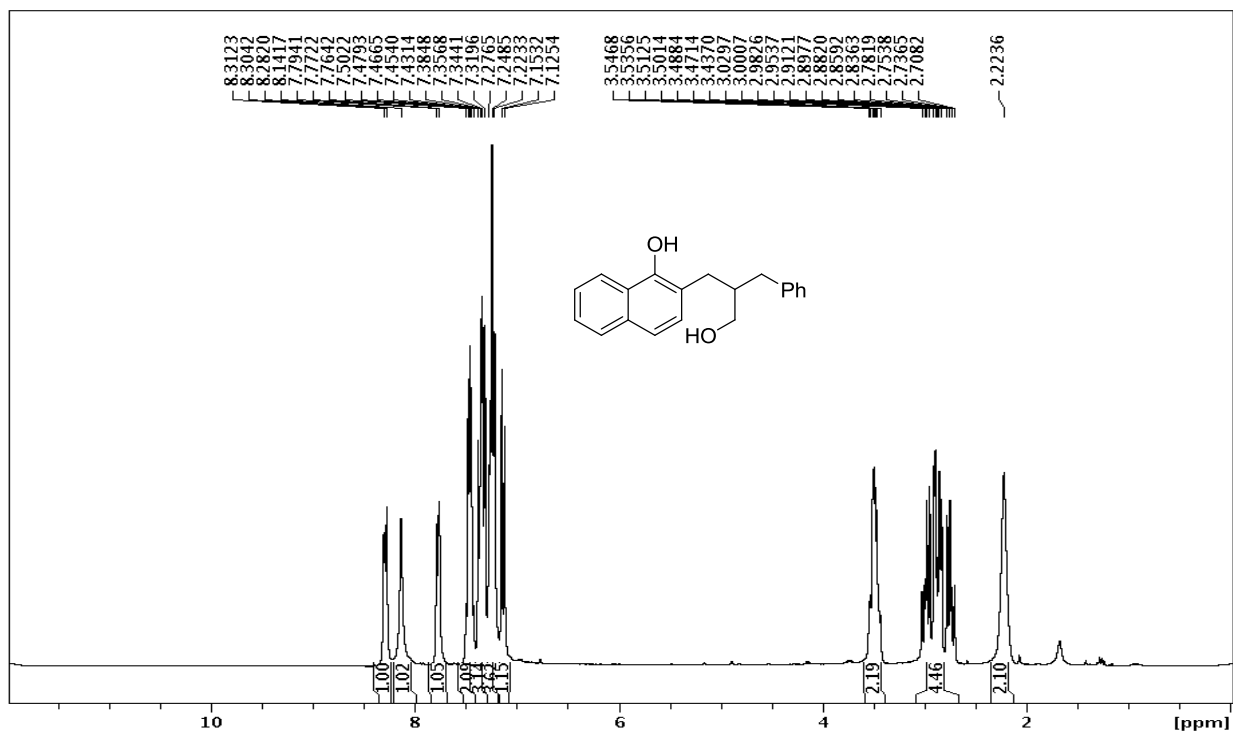
¹³C NMR spectrum of 3.54, R = Ph (75 MHz, CDCl₃)



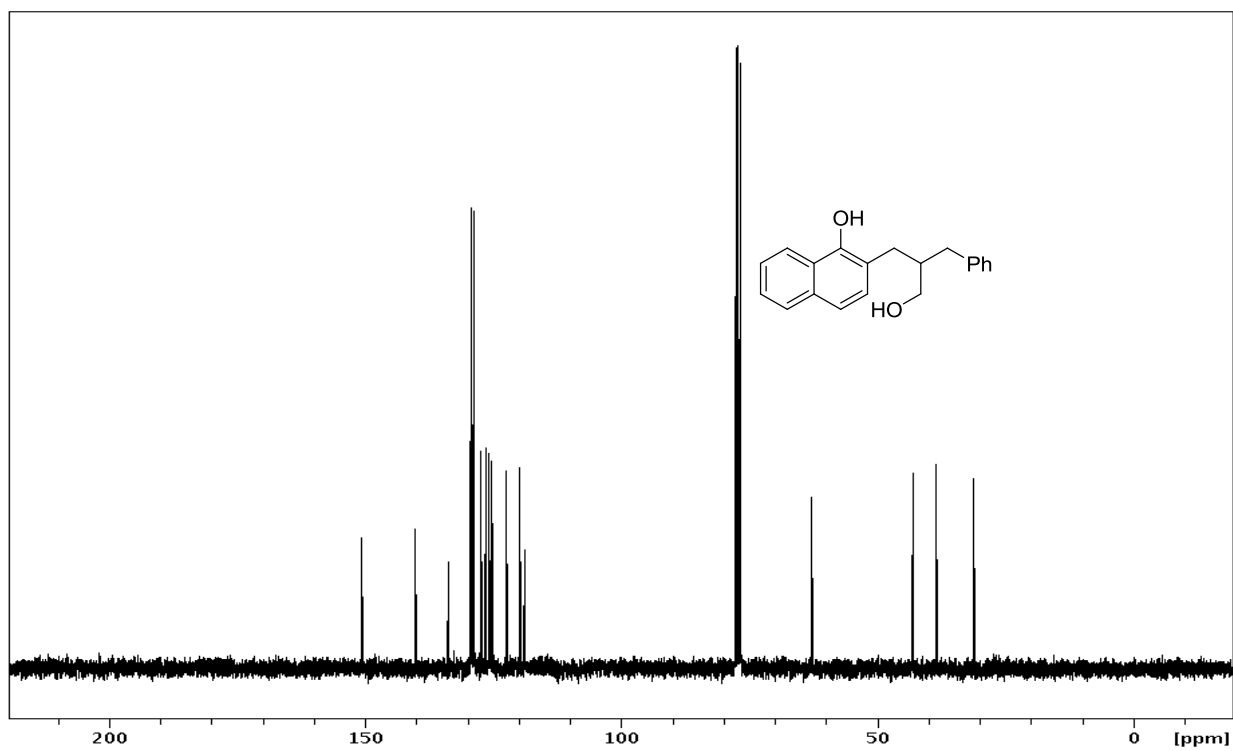
¹H NMR spectrum of 3.54, R = CH₂CF₃ (300 MHz, CDCl₃)



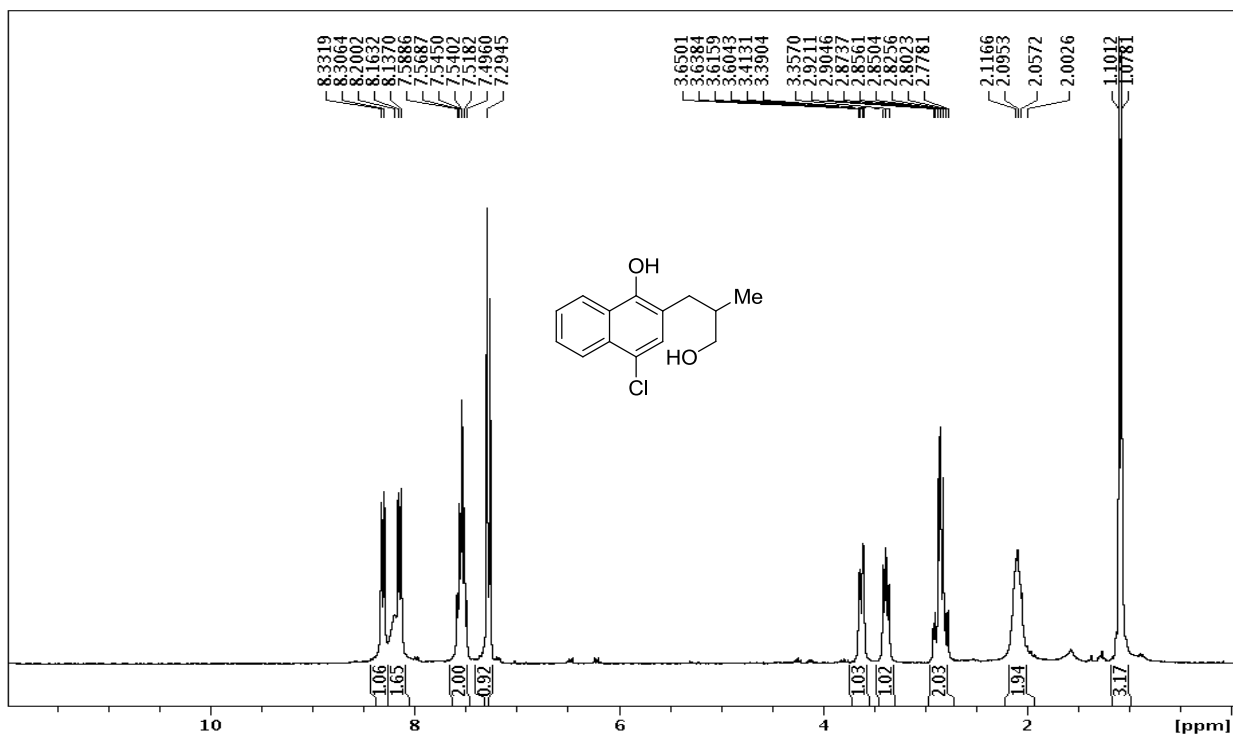
¹³C NMR spectrum of 3.54, R = CH₂CF₃ (75 MHz, CDCl₃)



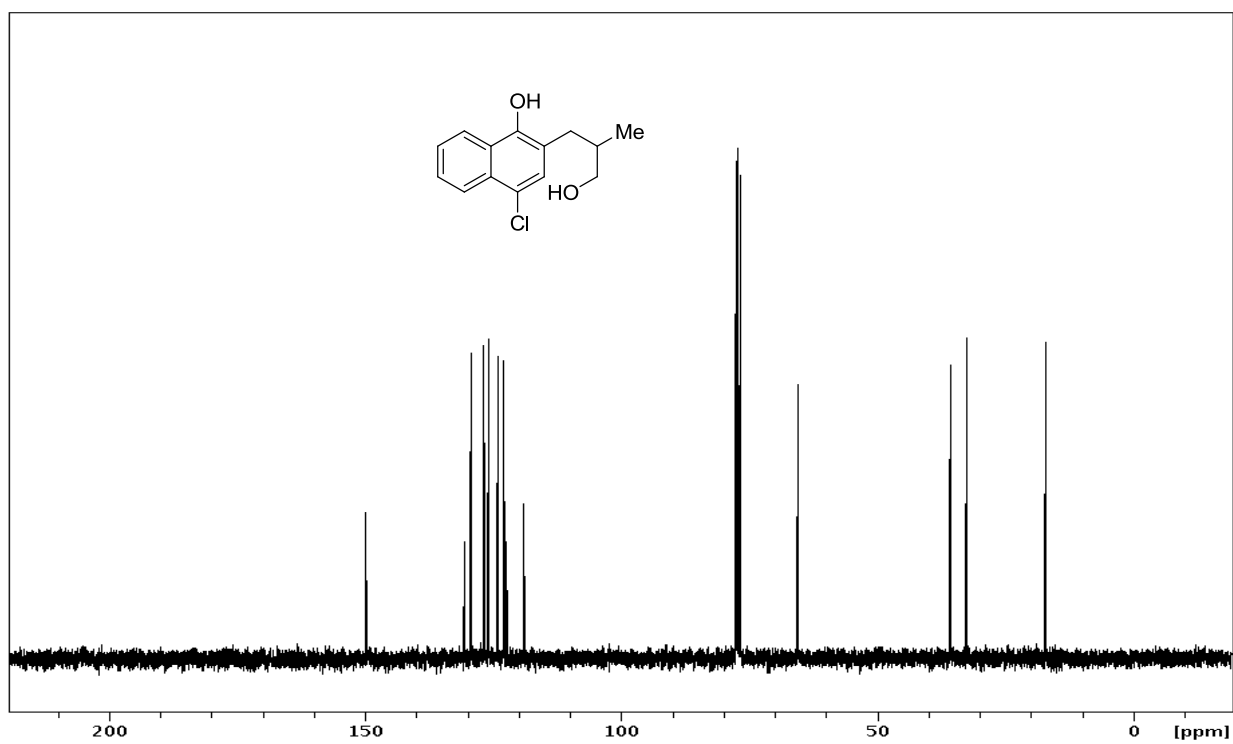
¹H NMR spectrum of 3.54, R = Bn (300 MHz, CDCl₃)



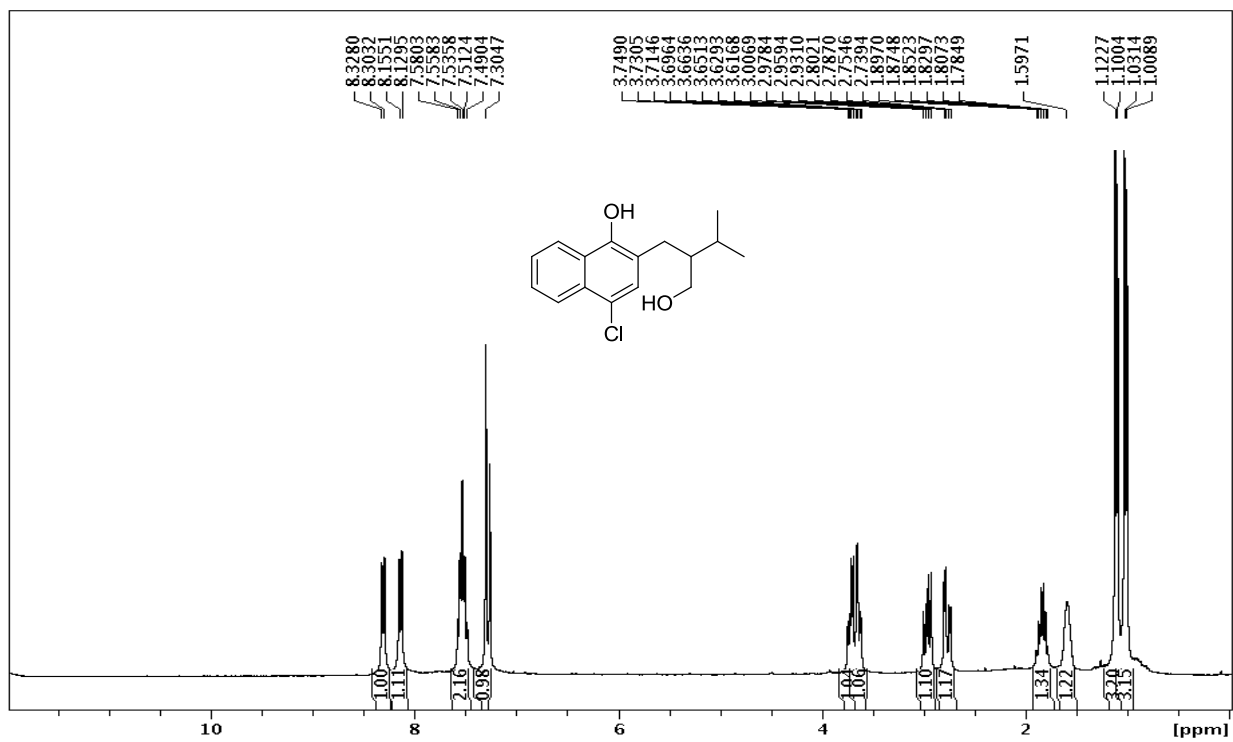
¹³C NMR spectrum of 3.54, R = Bn (75 MHz, CDCl₃)



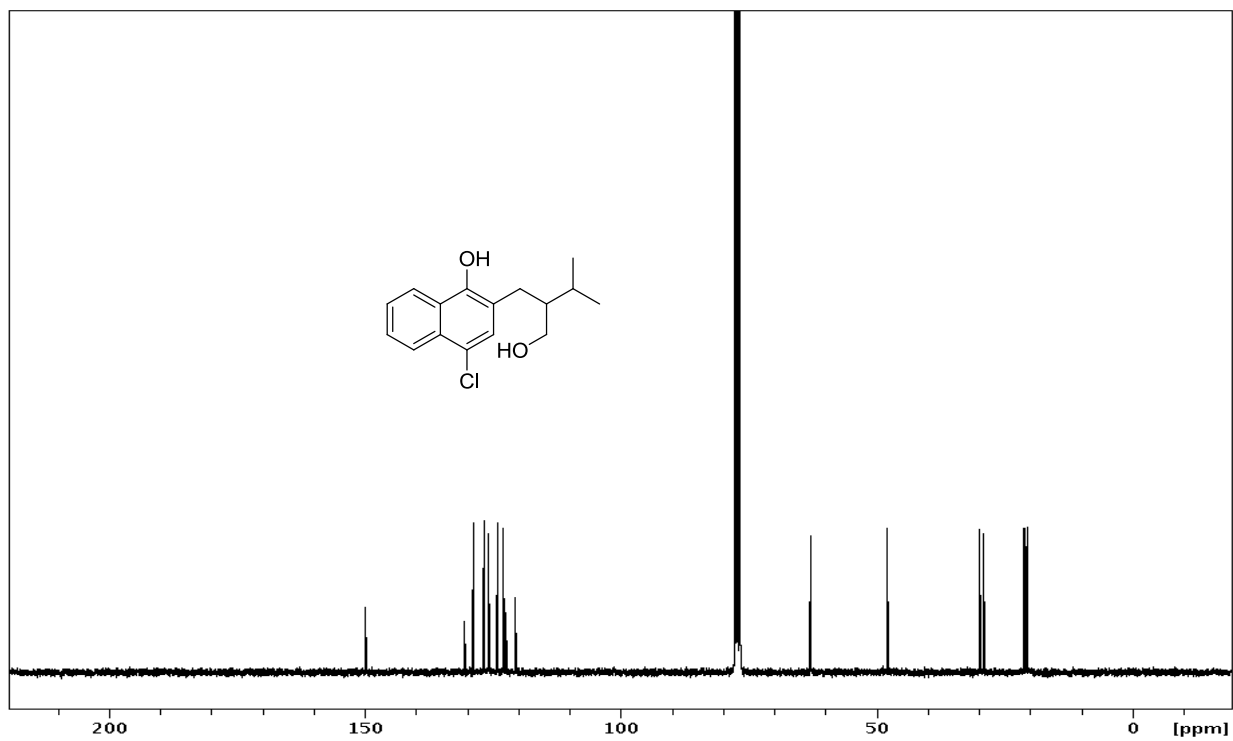
^1H NMR spectrum of 3.55, R = Me (300 MHz, CDCl_3)



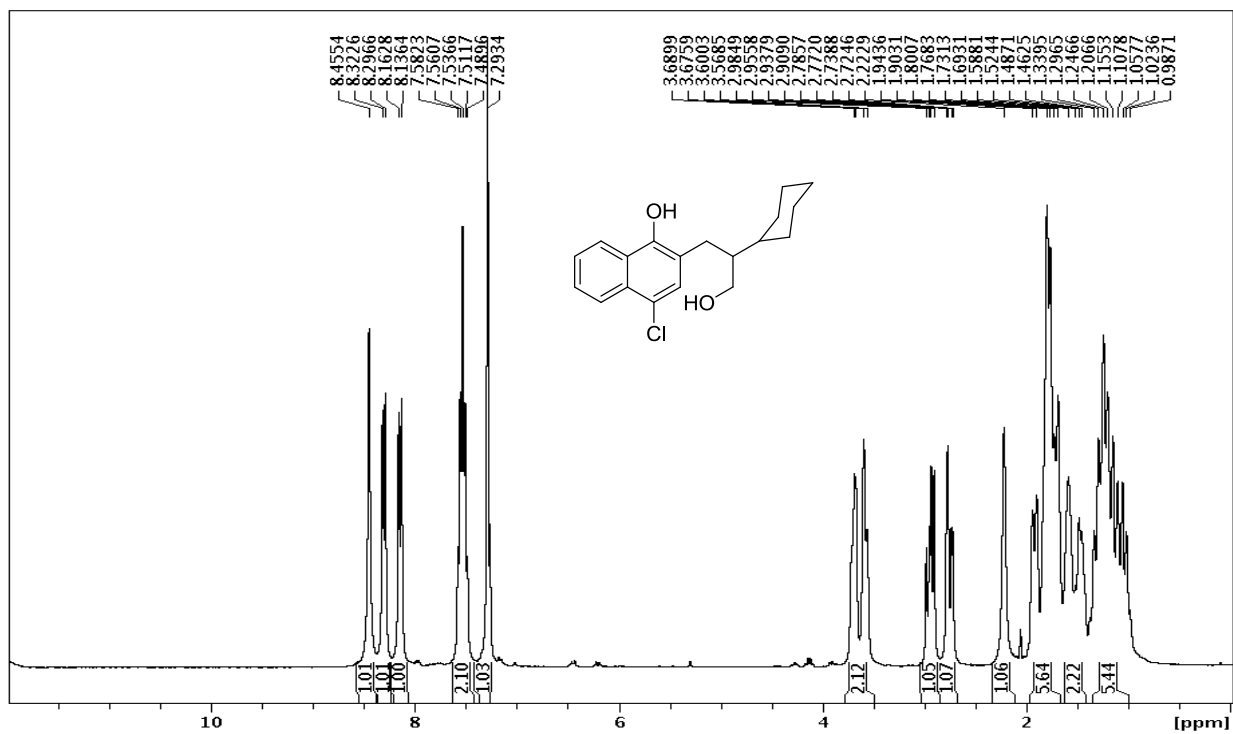
^{13}C NMR spectrum of 3.55, R = Me (75 MHz, CDCl_3)



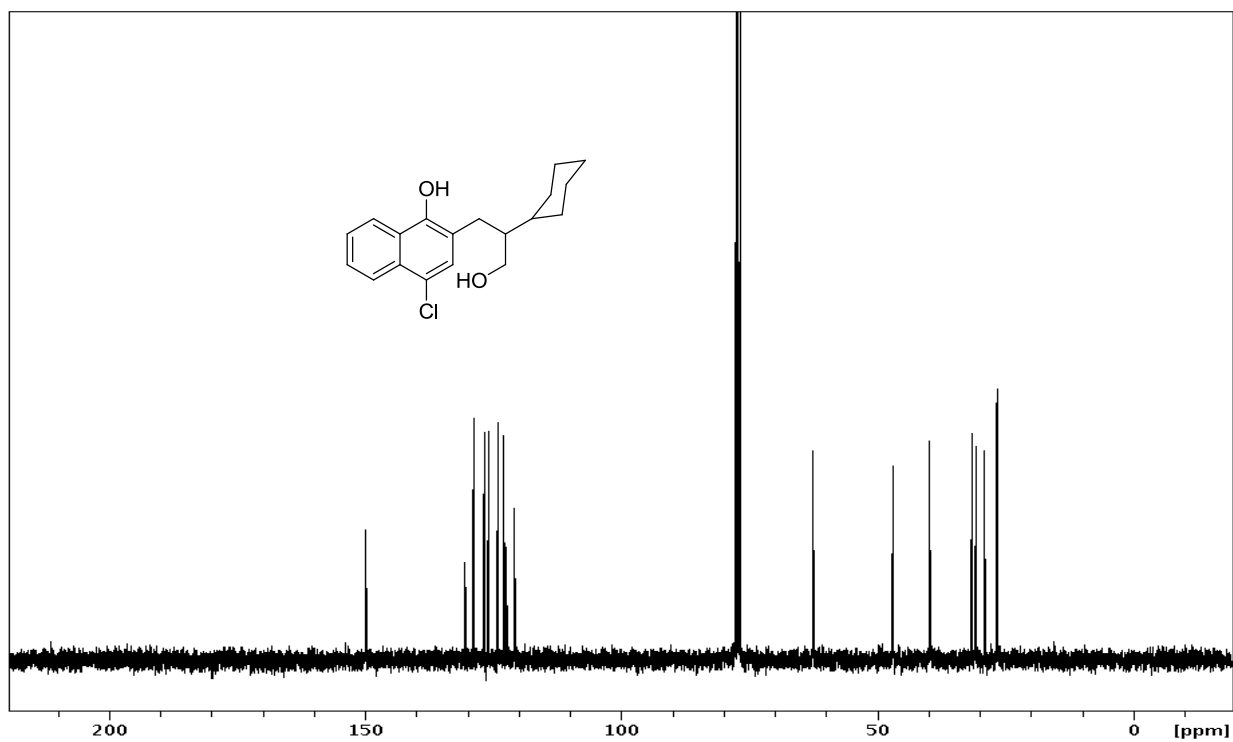
¹H NMR spectrum of 3.55, R = *i*-Pr (300 MHz, CDCl₃)



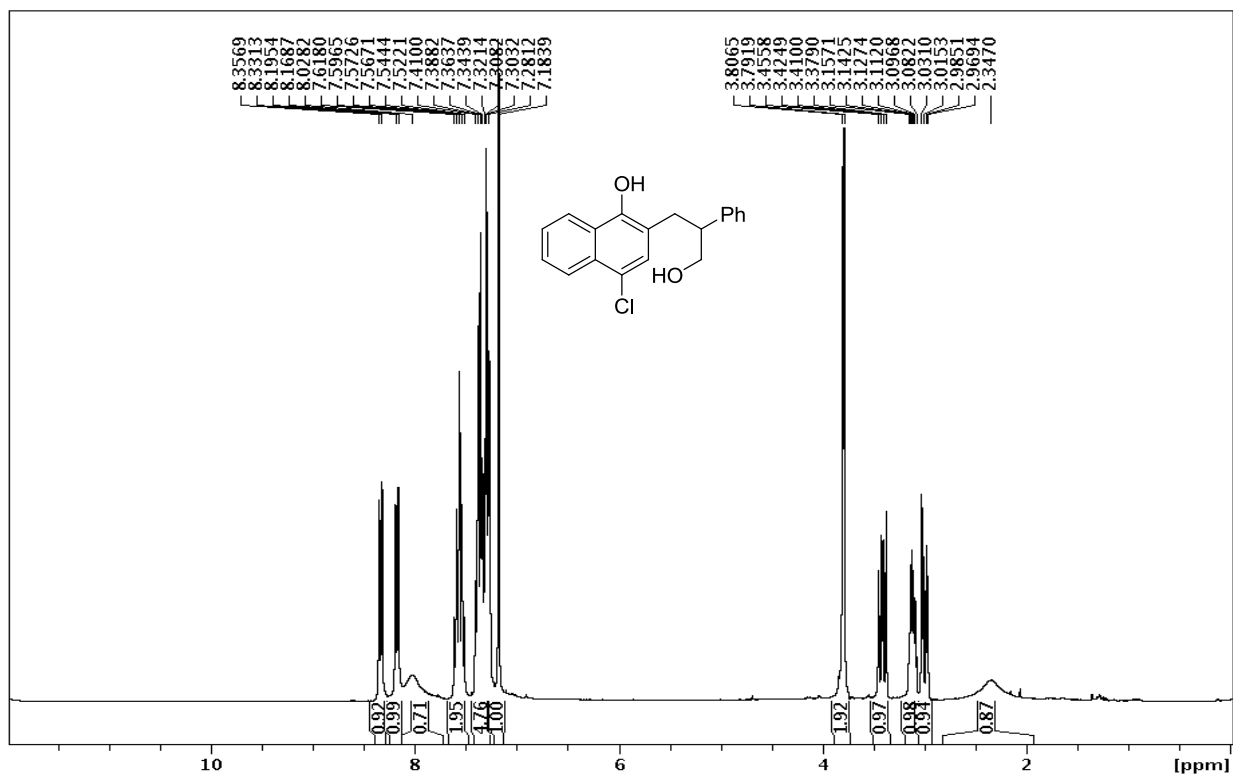
¹³C NMR spectrum of 3.55, R = *i*-Pr (75 MHz, CDCl₃)



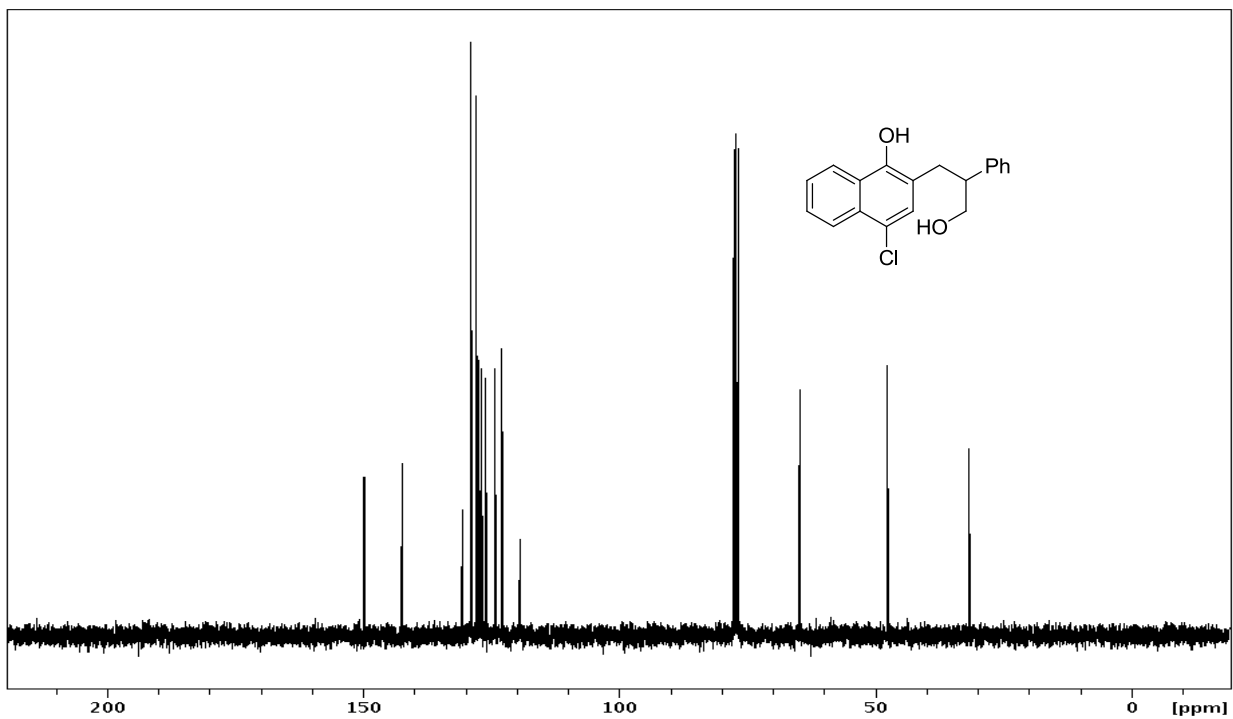
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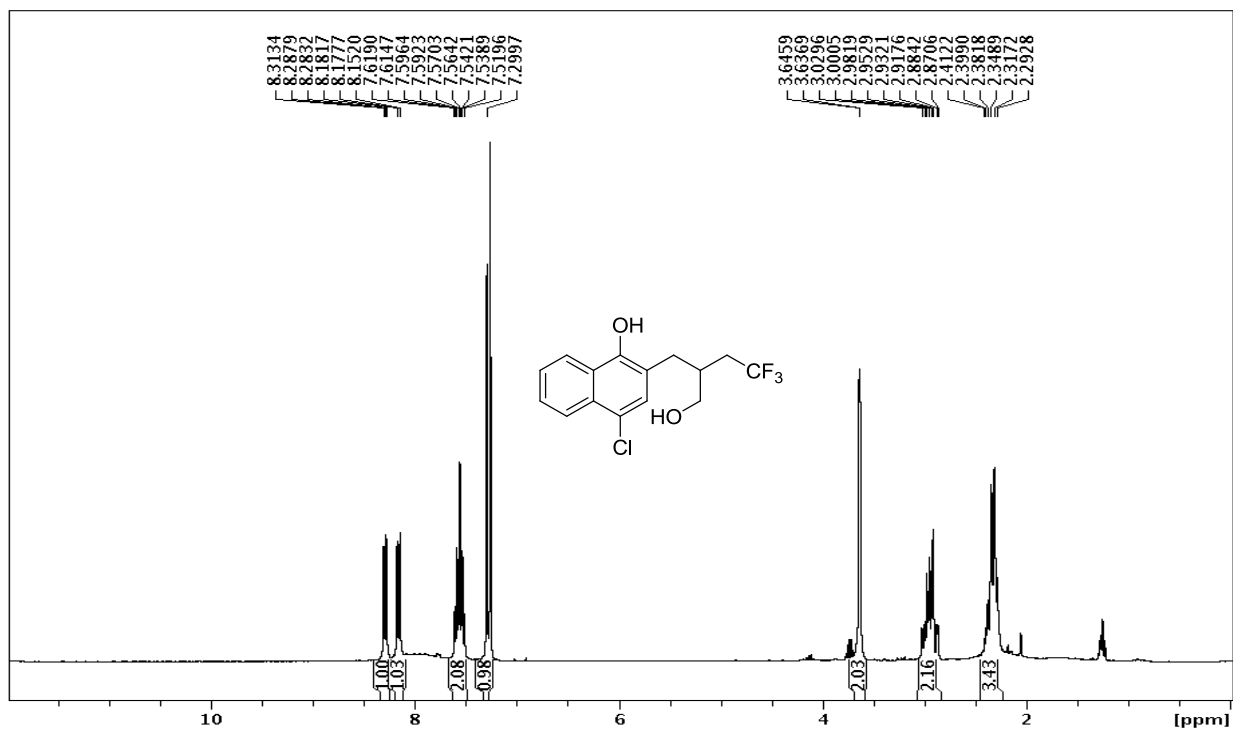
¹³C NMR spectrum of 3.55, R = Cy (75 MHz, CDCl₃)



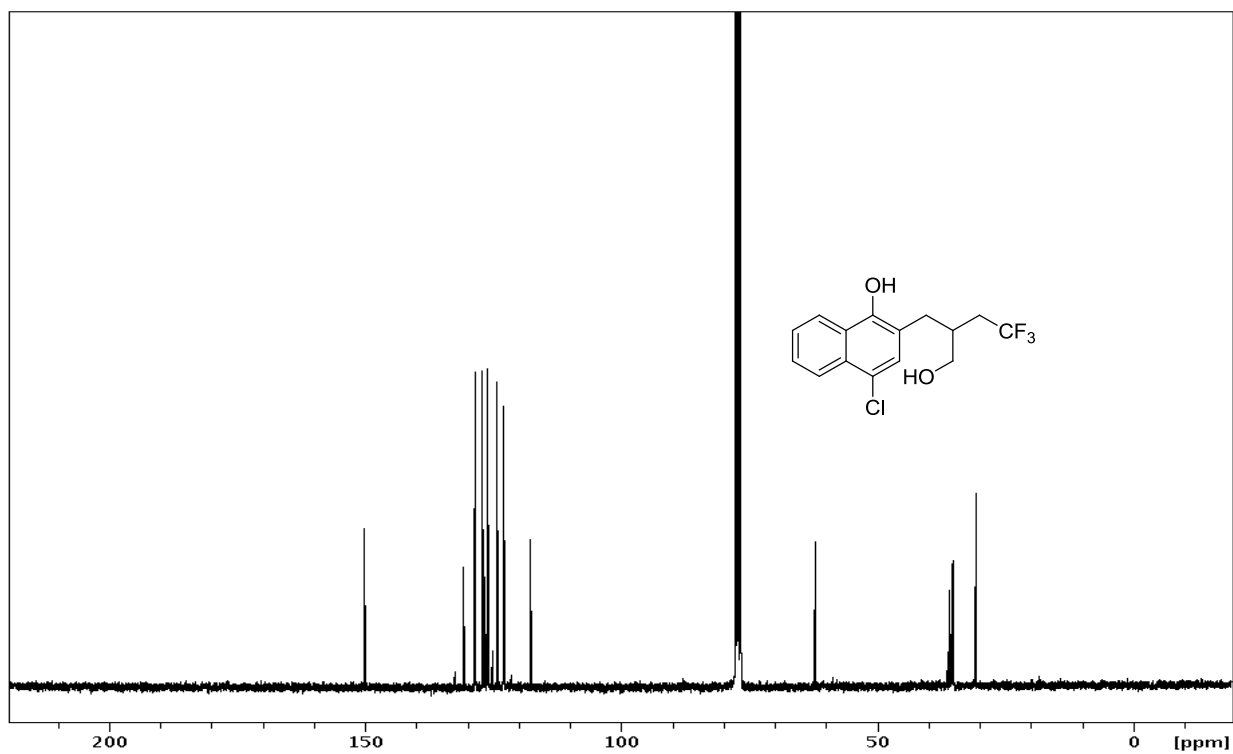
¹H NMR spectrum of 3.55, R = Ph (300 MHz, CDCl₃)



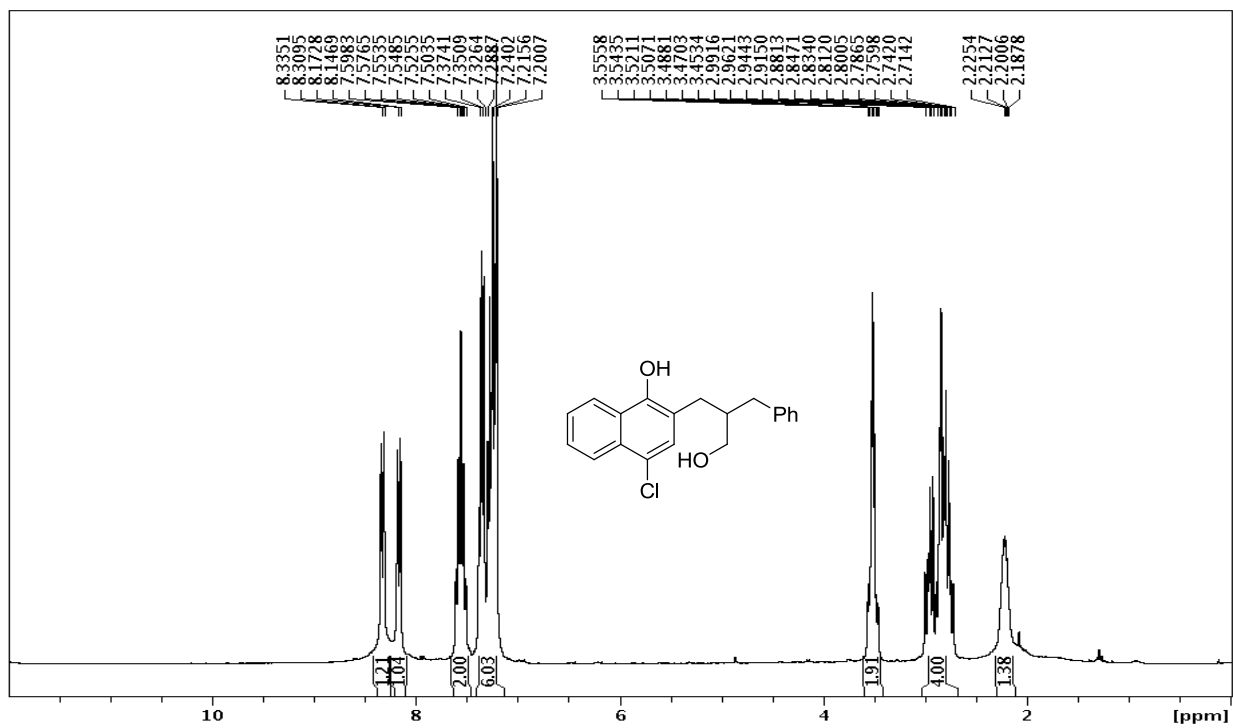
¹³C NMR spectrum of 3.55, R = Ph (75 MHz, CDCl₃)



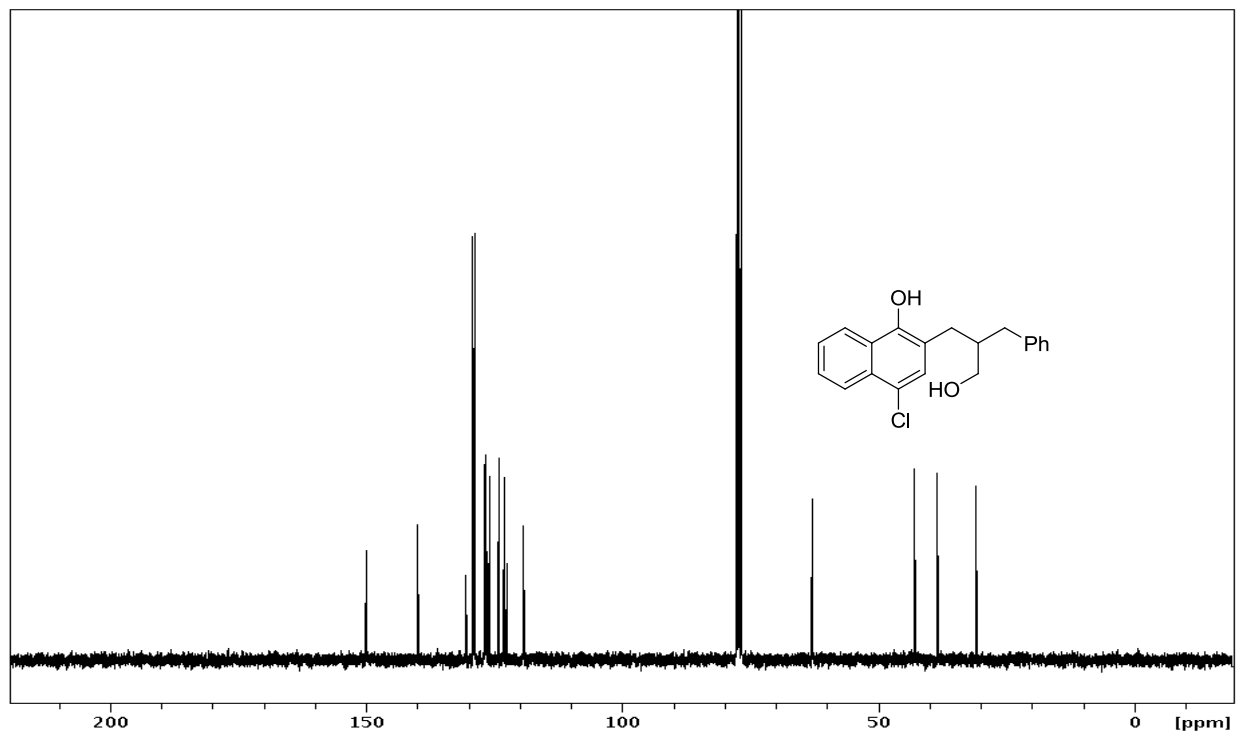
¹H NMR spectrum of 3.55, R = CH₂CF₃ (300 MHz, CDCl₃)



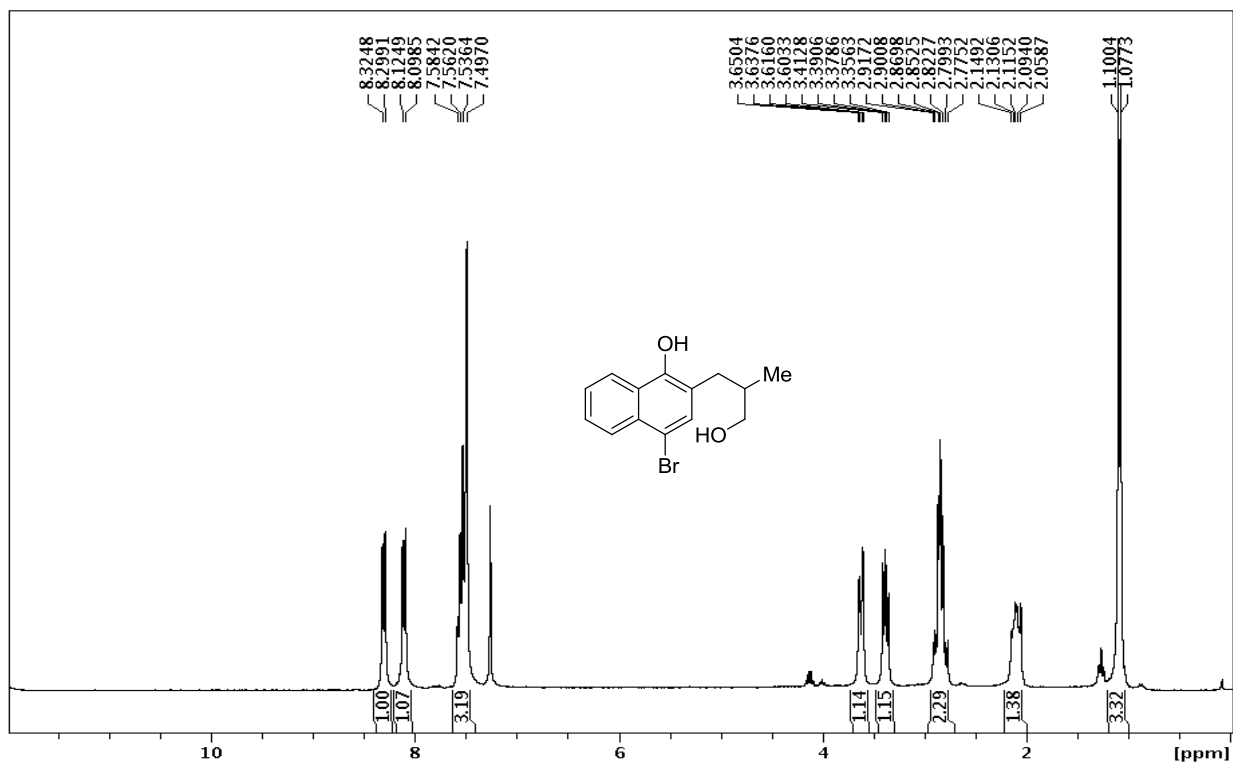
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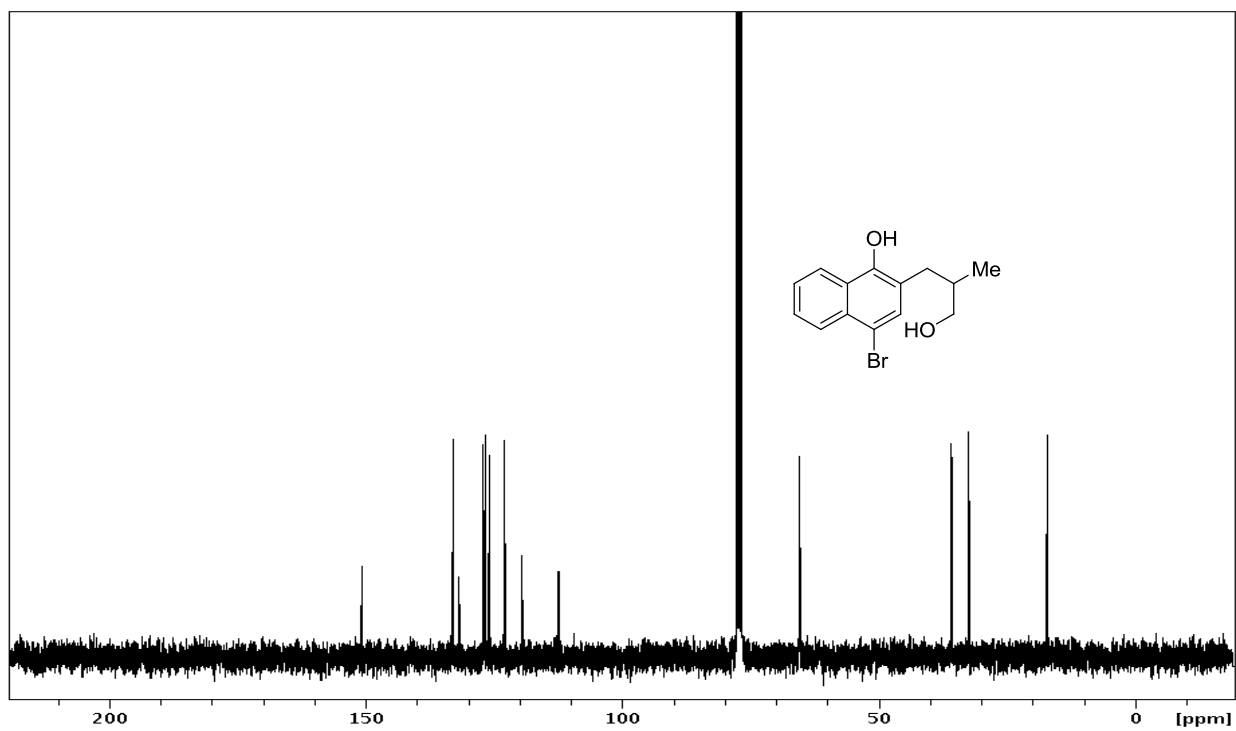
¹H NMR spectrum of 3.55, R = Bn (300 MHz, CDCl₃)



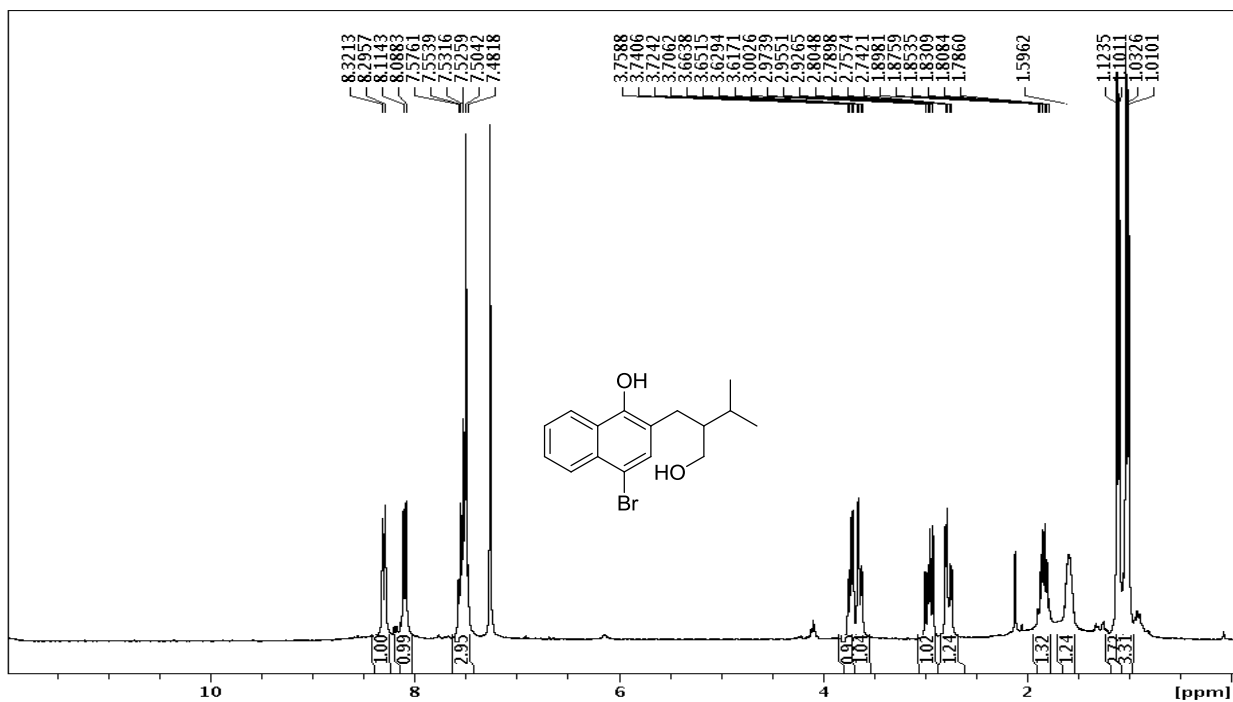
¹³C NMR spectrum of 3.55, R = Bn (75 MHz, CDCl₃)



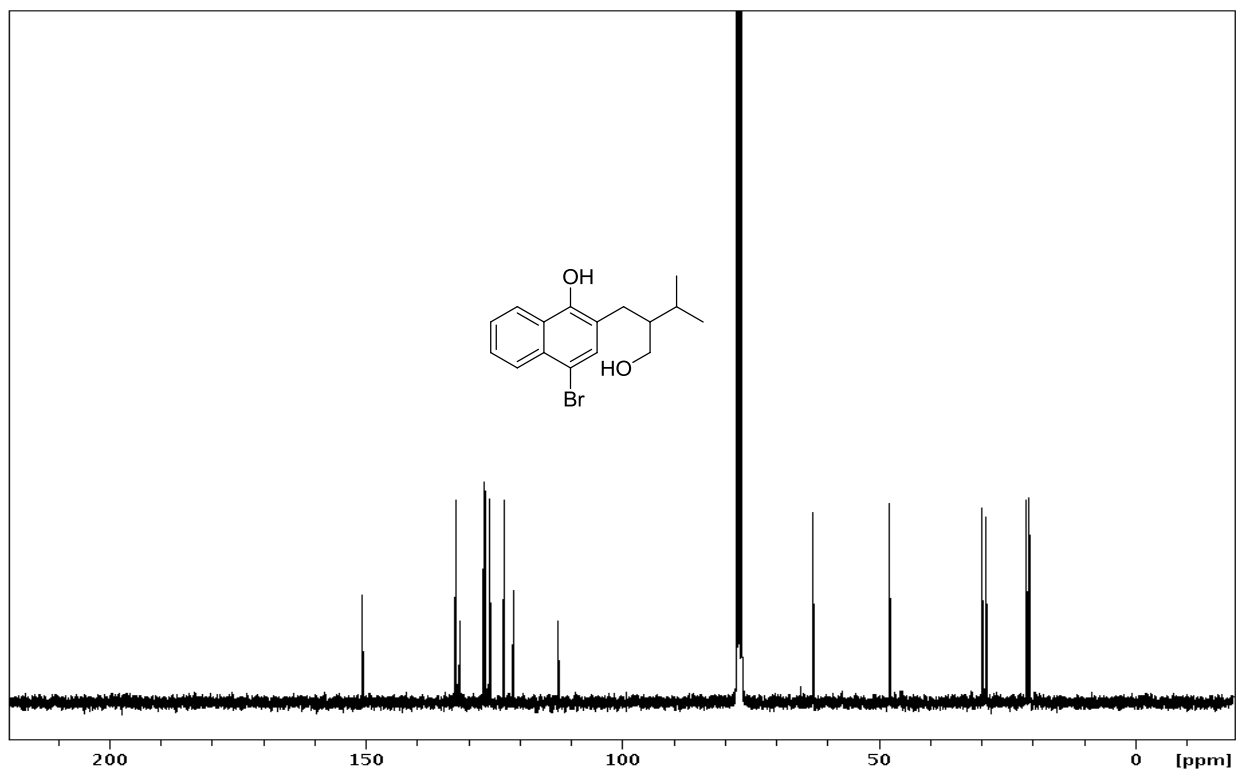
¹H NMR spectrum of 3.56, R = Me (300 MHz, CDCl₃)



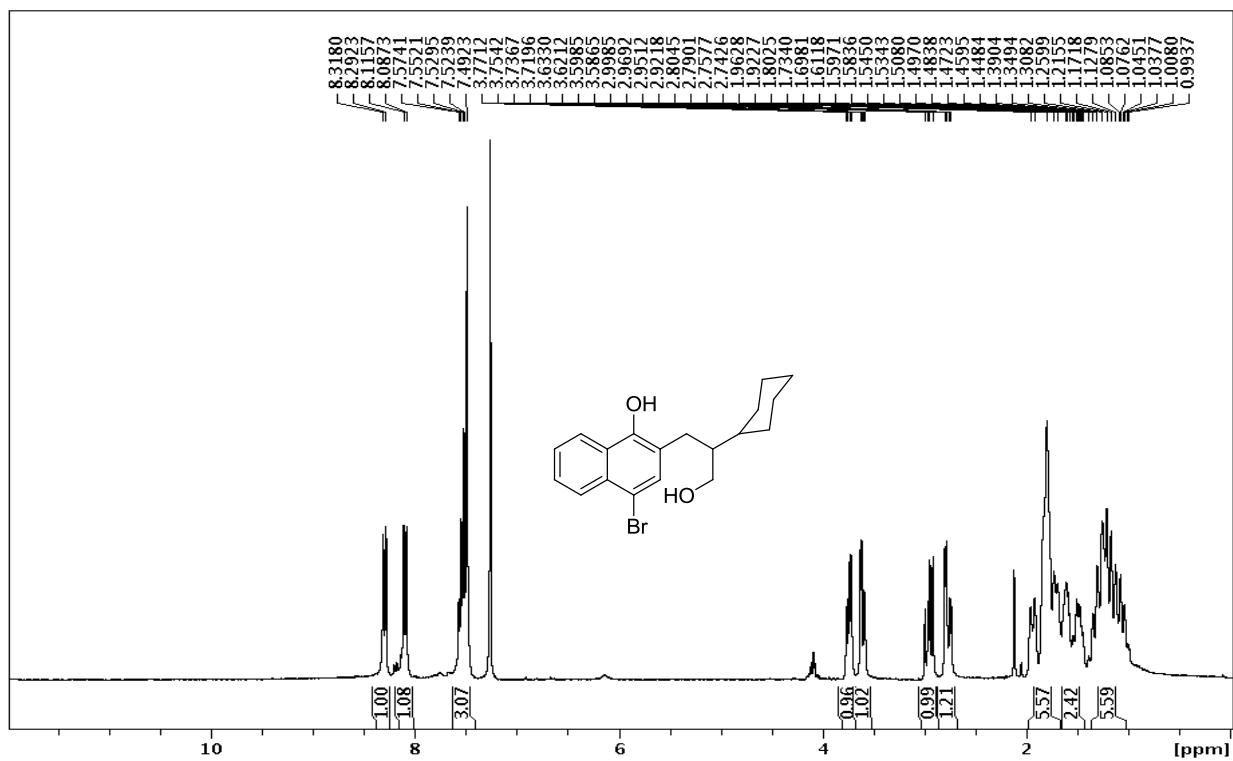
¹³C NMR spectrum of 3.56, R = Me (75 MHz, CDCl₃)



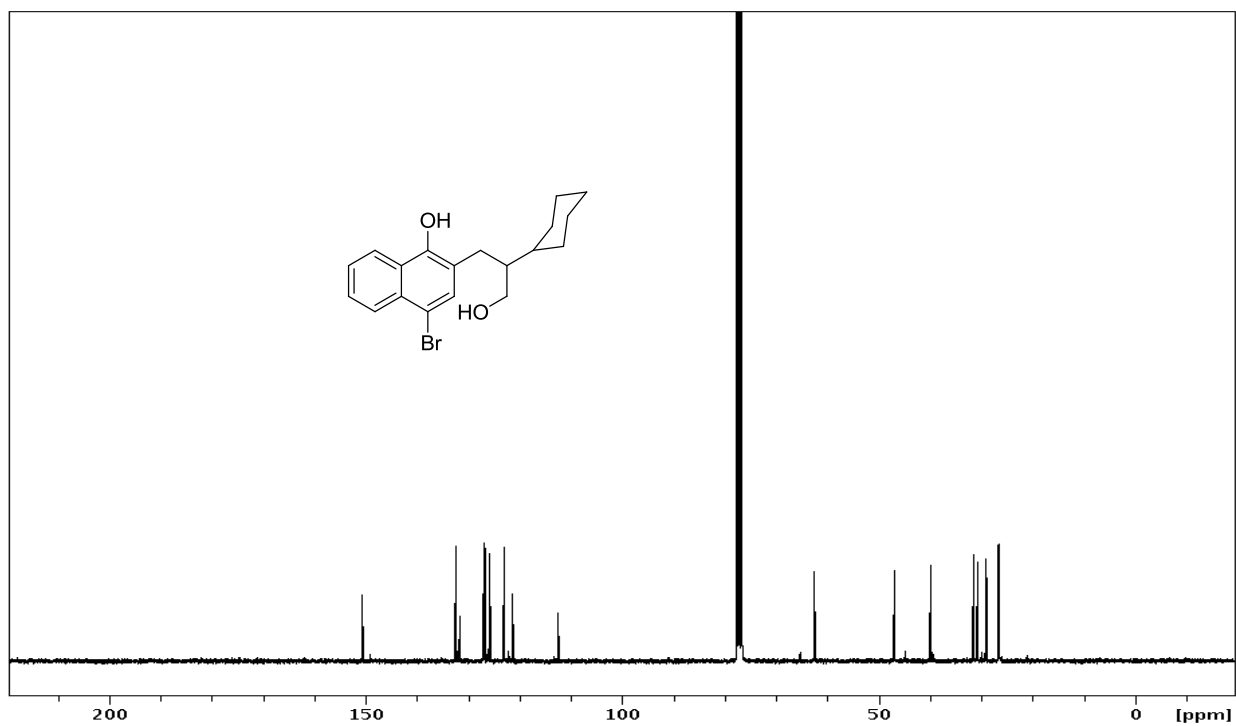
^1H NMR spectrum of 3.56, R = *i*-Pr (300 MHz, CDCl_3)



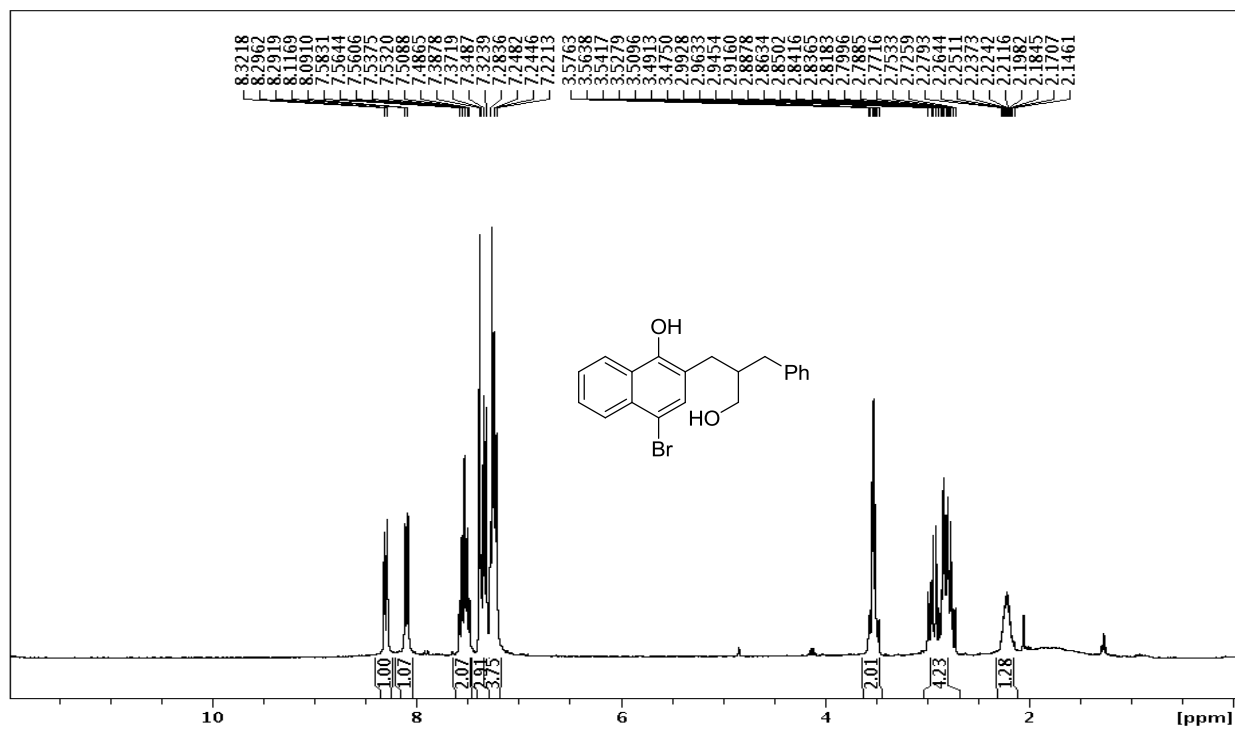
^{13}C NMR spectrum of 3.56, R = *i*-Pr (75 MHz, CDCl_3)



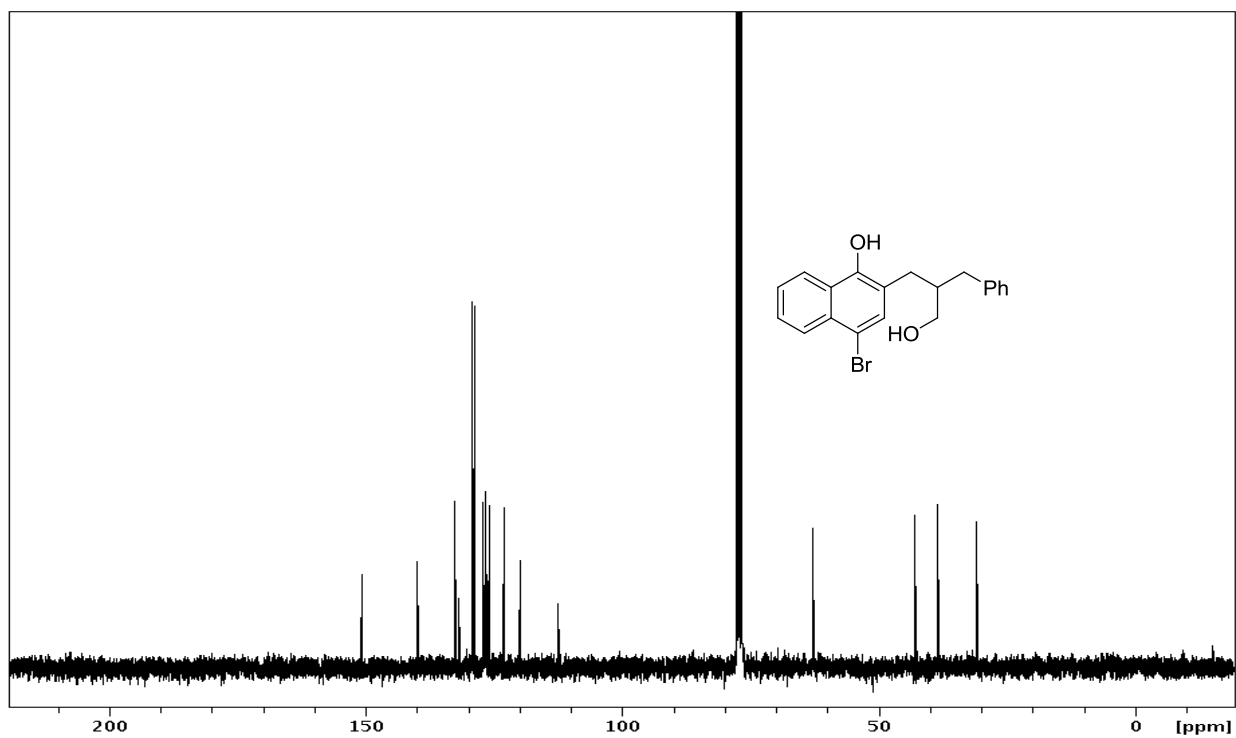
¹H NMR spectrum of 3.56, R = Cy (300 MHz, CDCl₃)



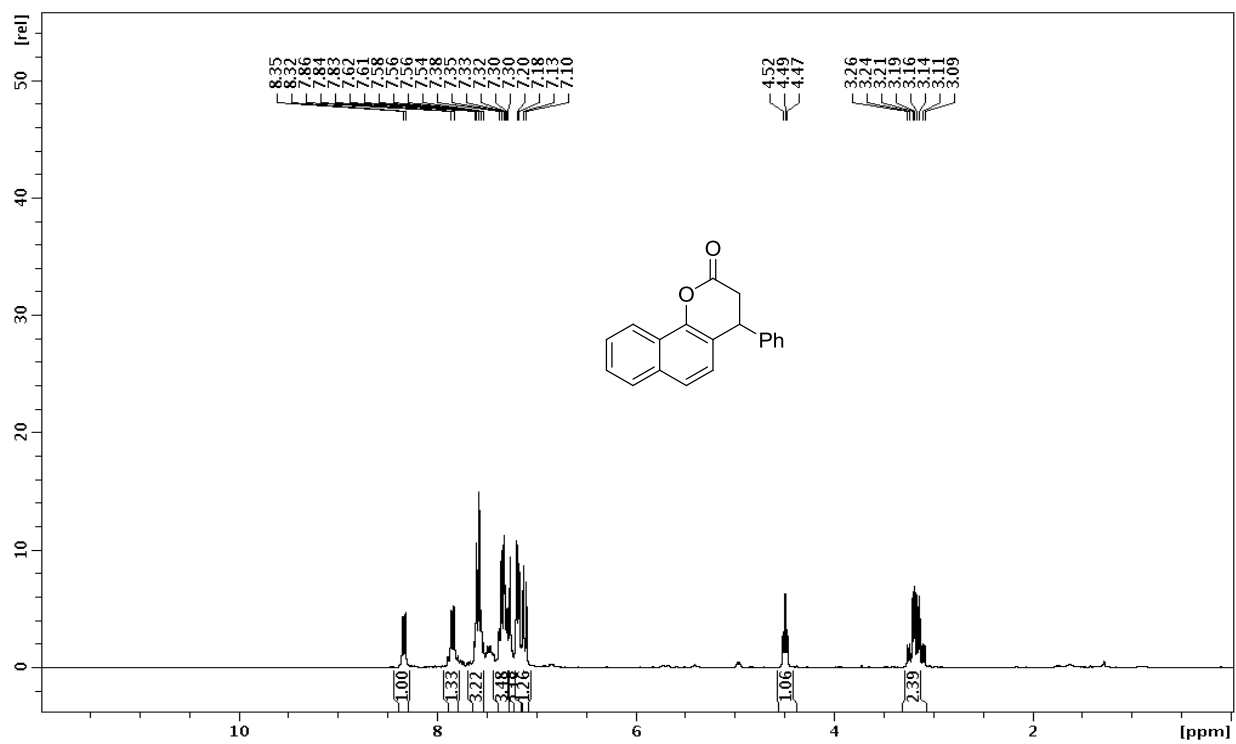
¹³C NMR spectrum of 3.56, R = Cy (75 MHz, CDCl₃)



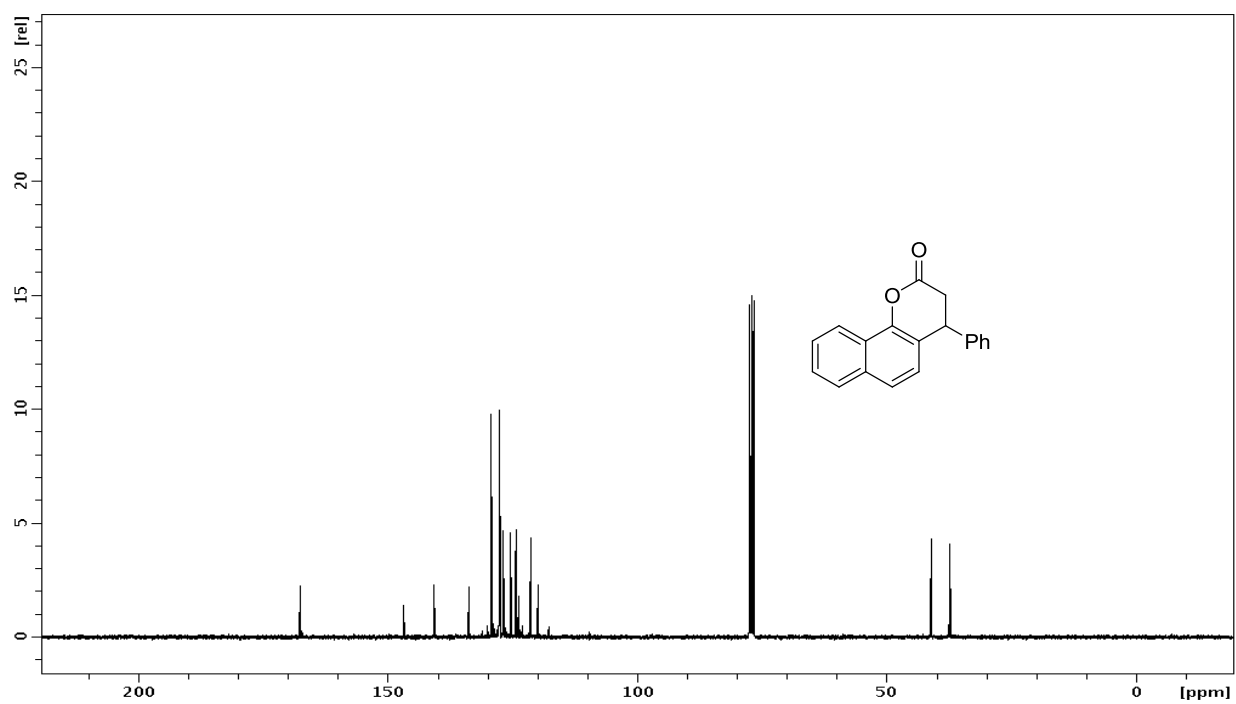
¹H NMR spectrum of 3.56, R = Bn (300 MHz, CDCl₃)



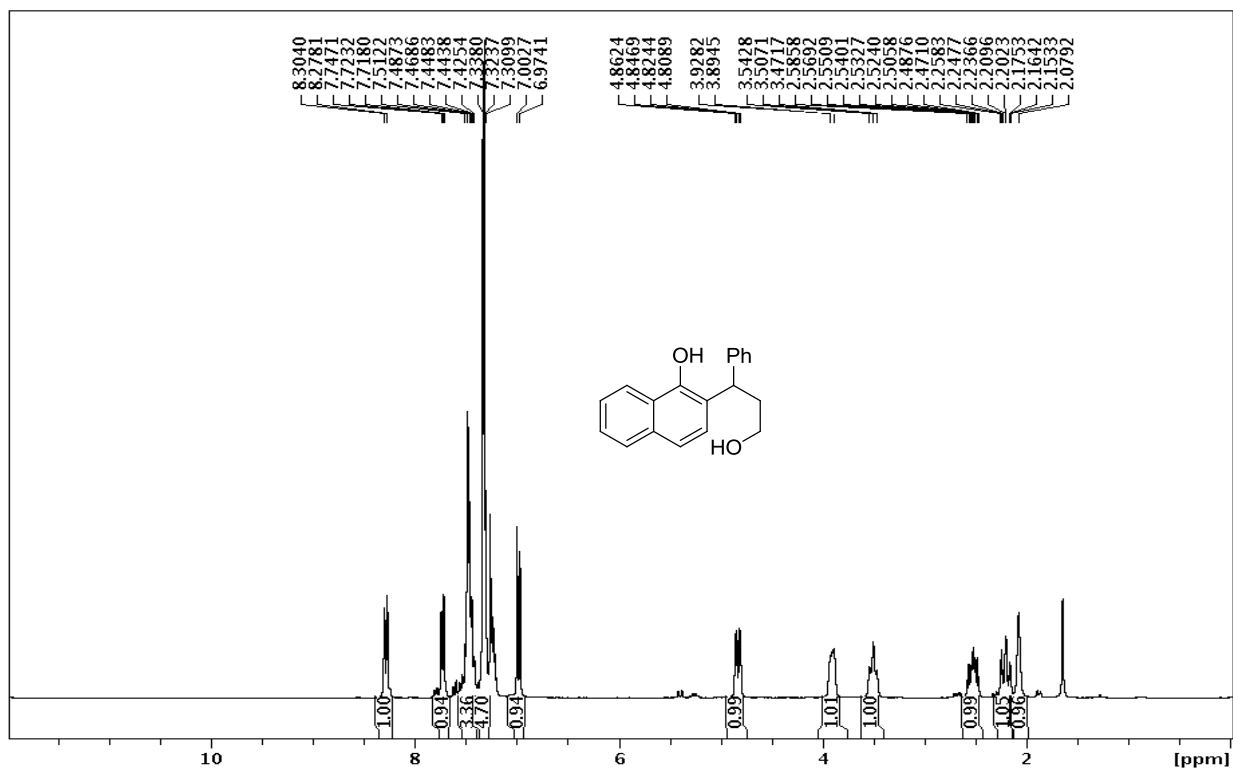
¹³C NMR spectrum of 3.56, R = Bn (75 MHz, CDCl₃)



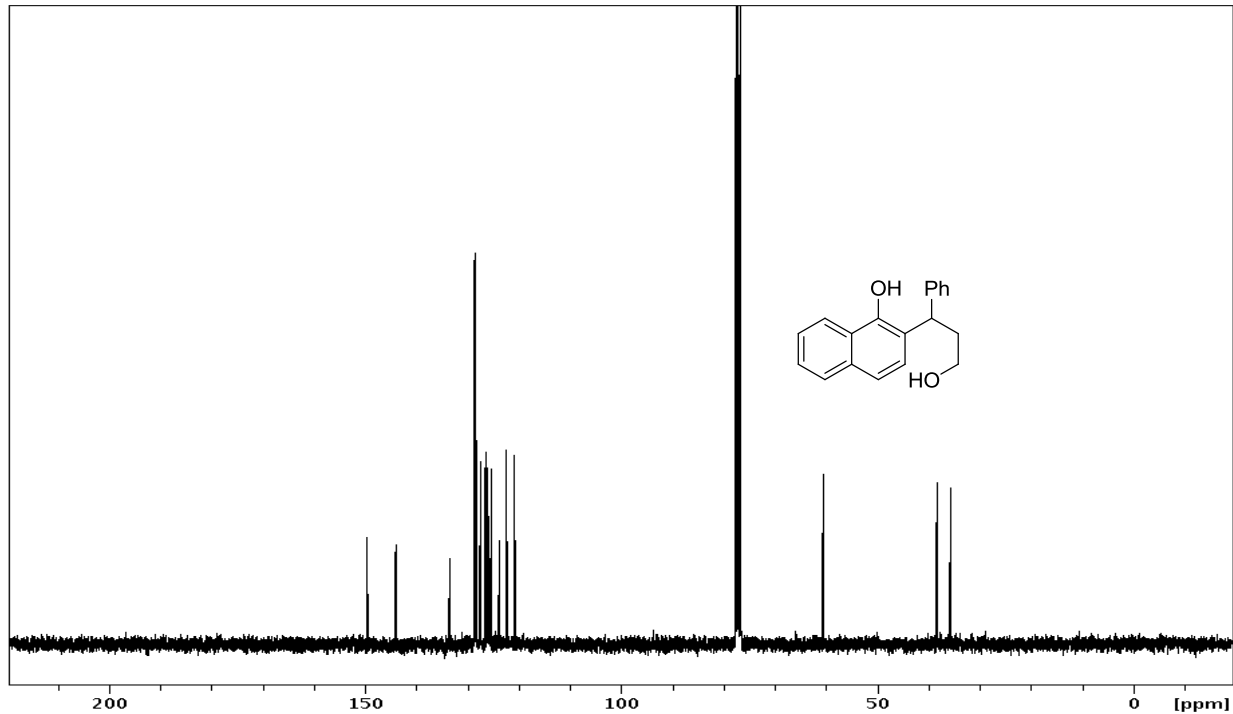
¹H NMR spectrum of 3.58 (300 MHz, CDCl₃)



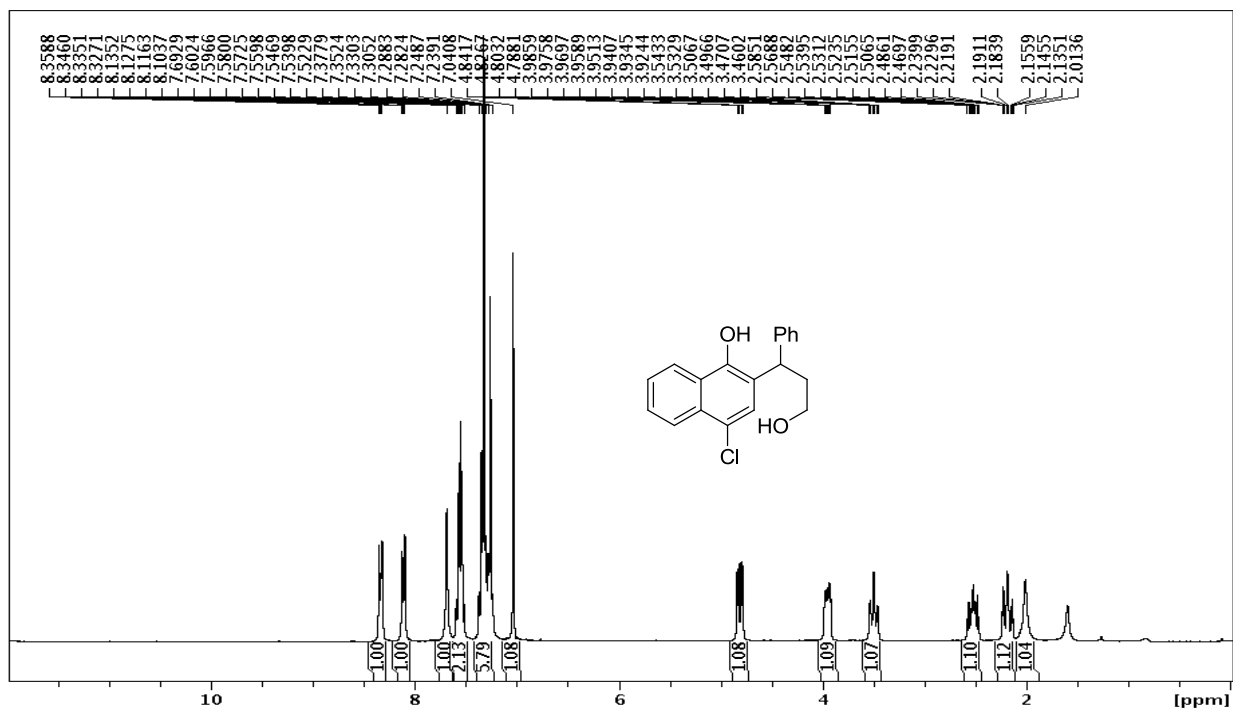
¹³C NMR spectrum of 3.58 (75 MHz, CDCl₃)



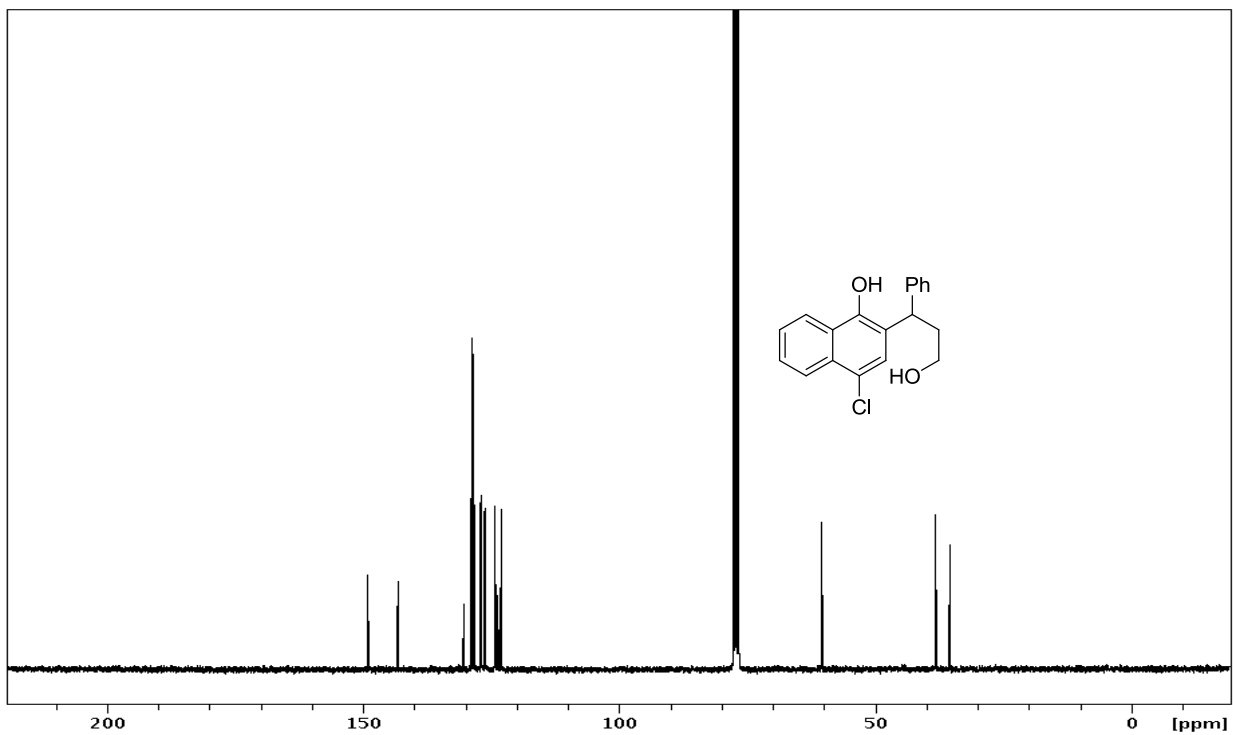
¹H NMR spectrum of 3.59 (300 MHz, CDCl₃)



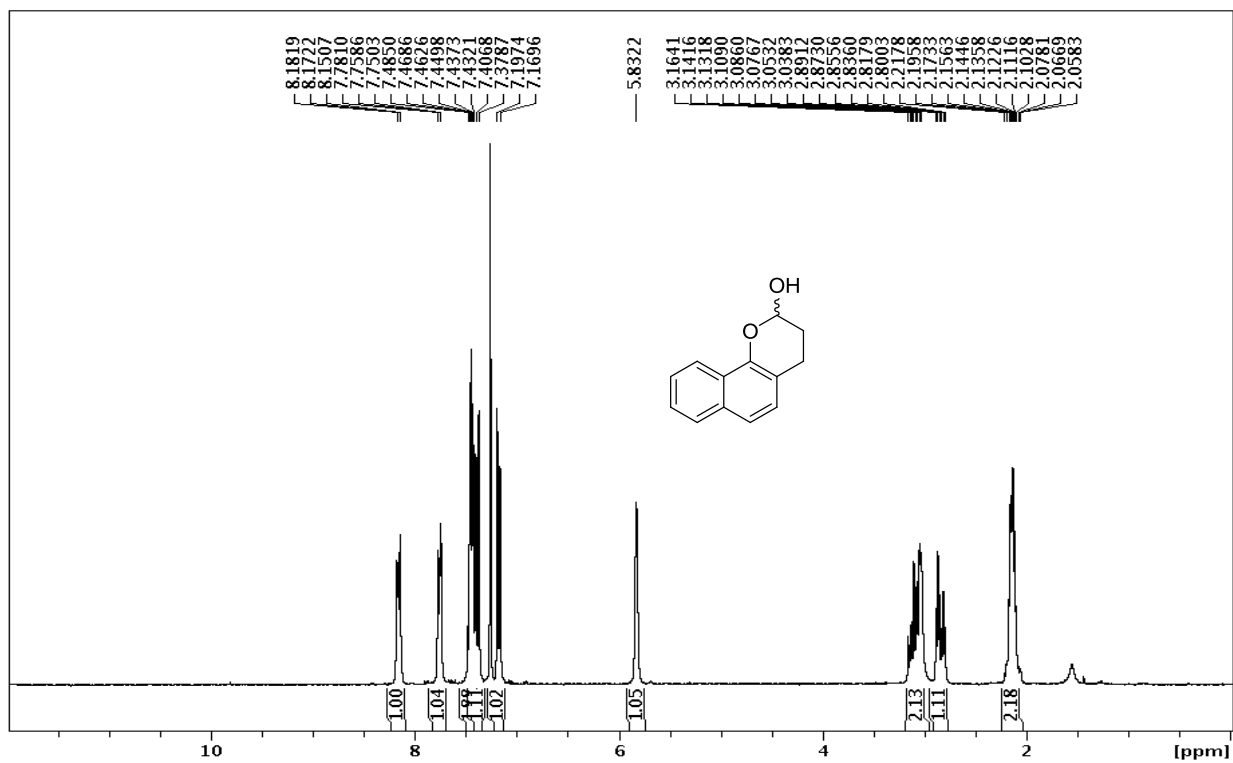
¹³C NMR spectrum of 3.59 (75 MHz, CDCl₃)



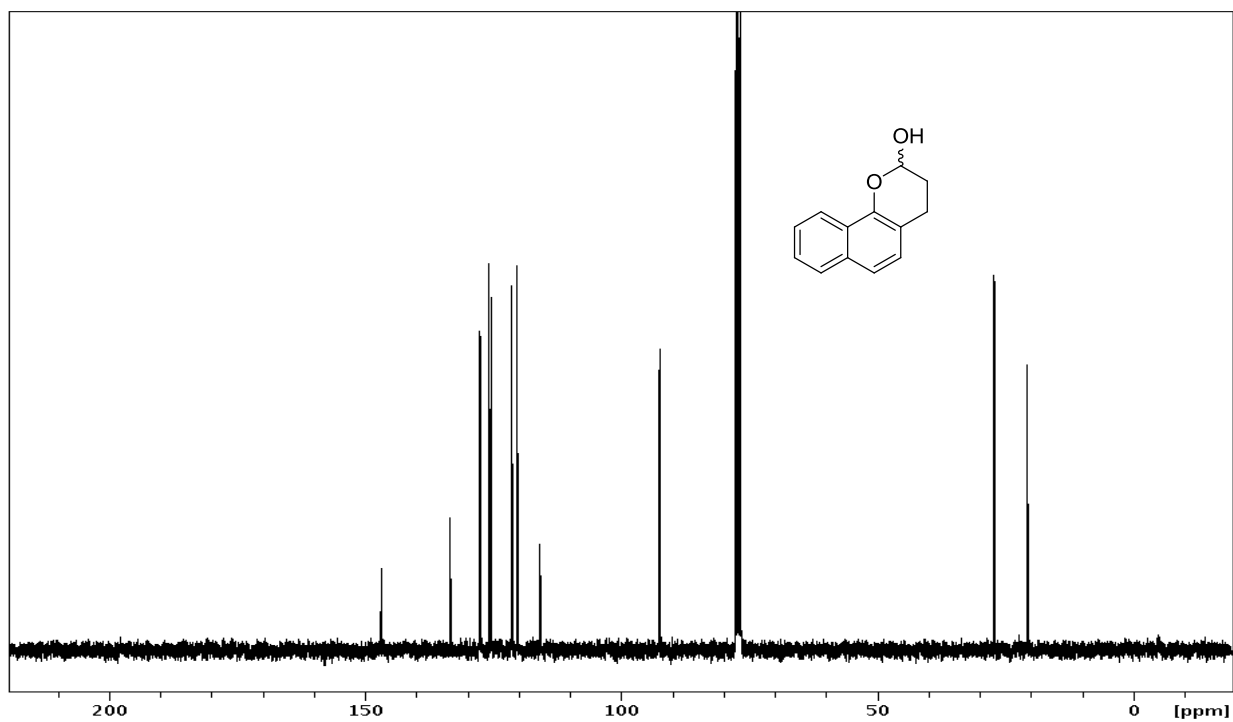
¹H NMR spectrum of 3.60 (300 MHz, CDCl₃)



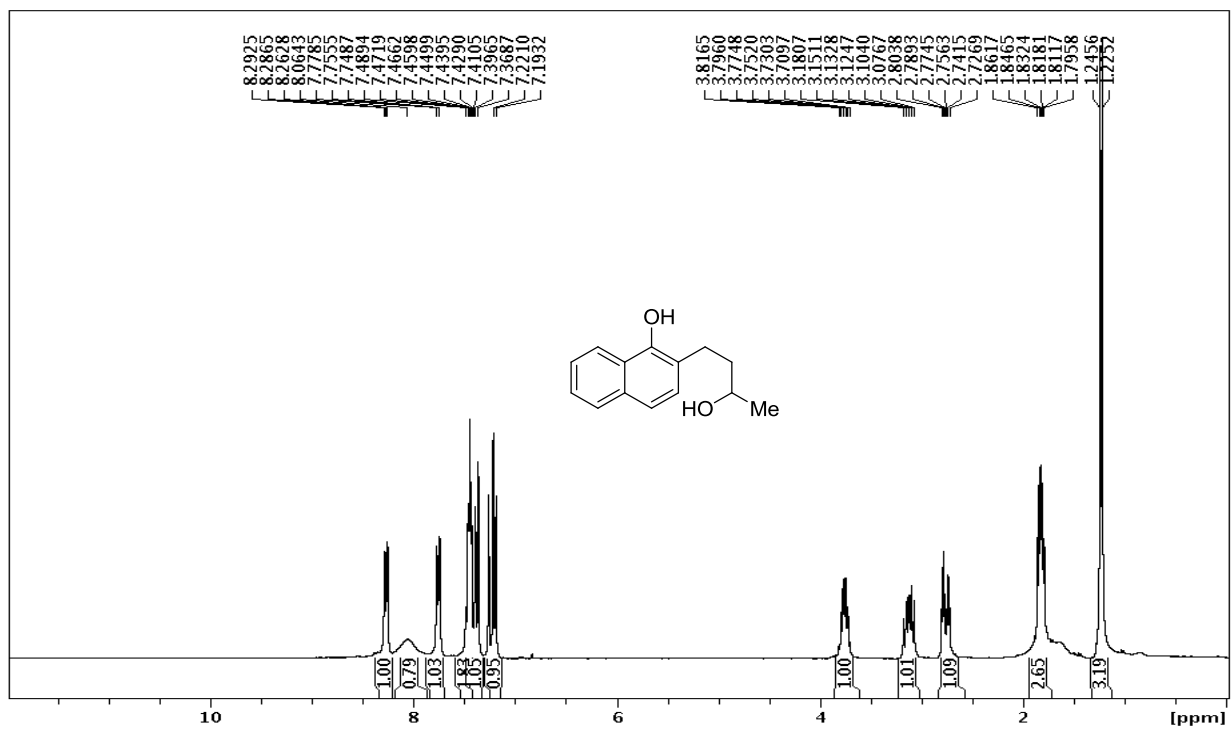
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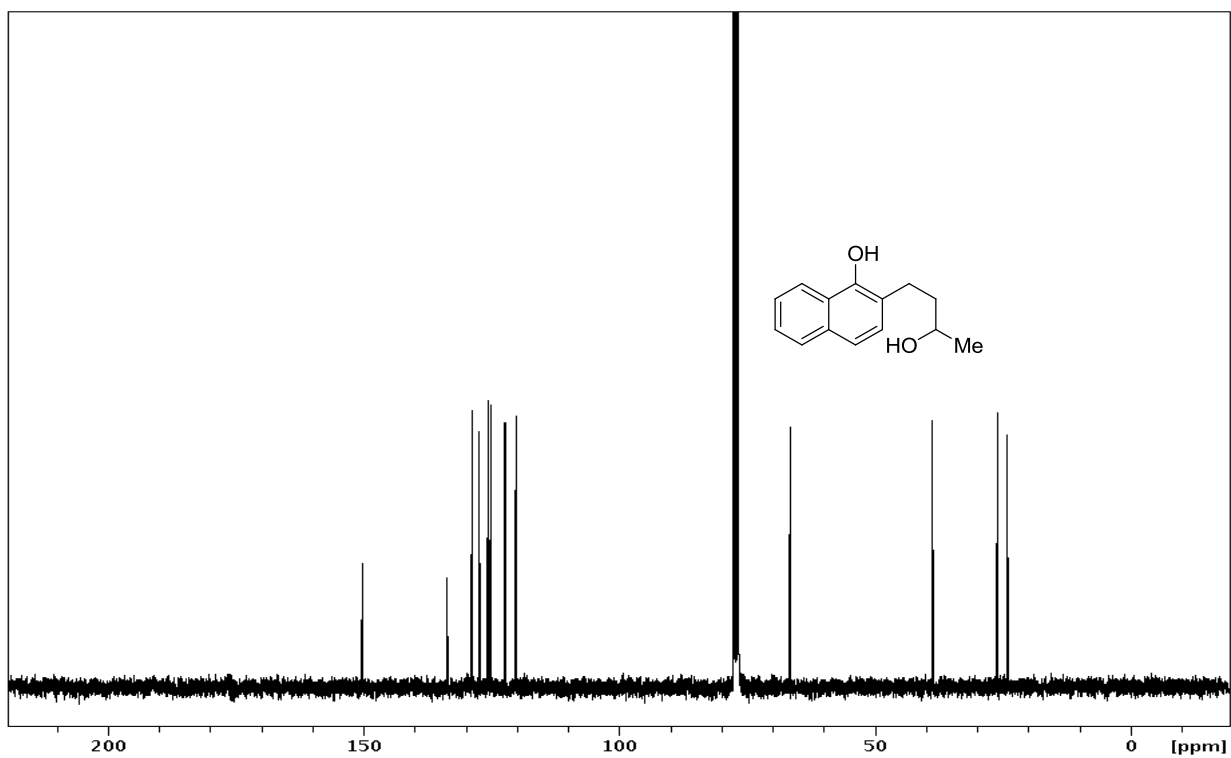
¹H NMR spectrum of 3.61 (300 MHz, CDCl₃)



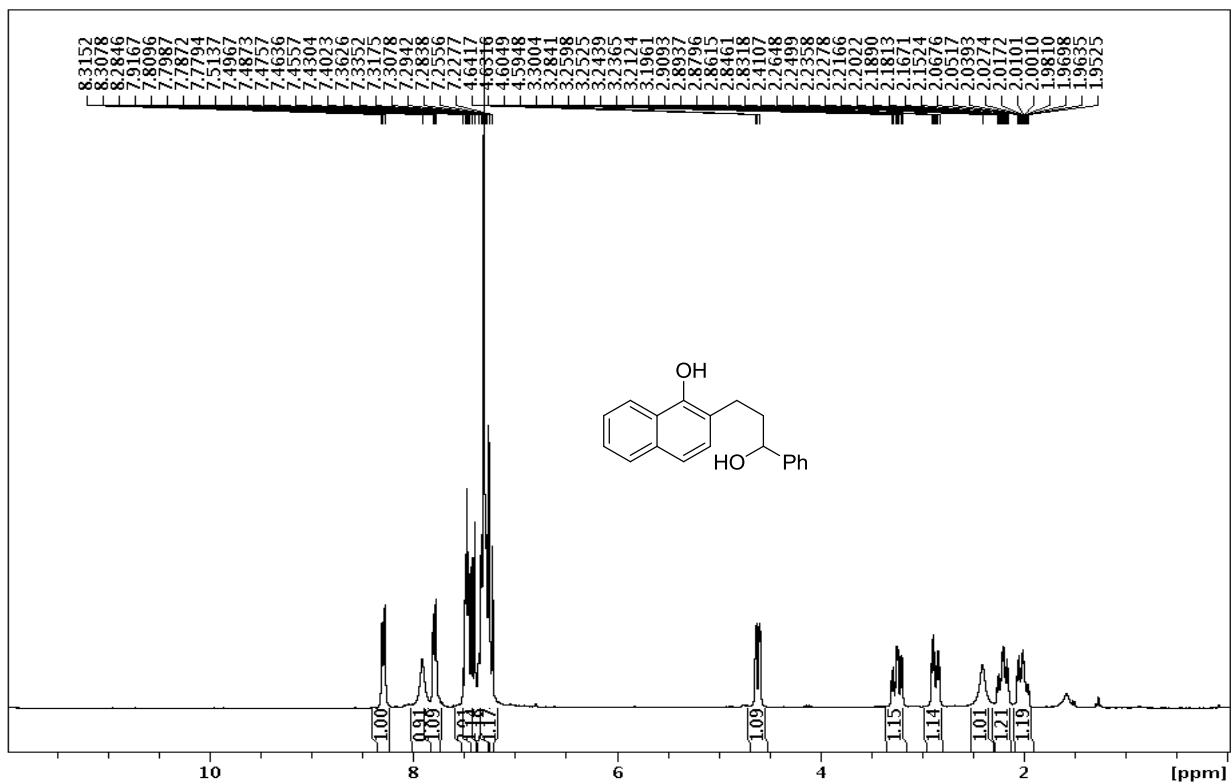
¹³C NMR spectrum of 3.61 (75 MHz, CDCl₃)



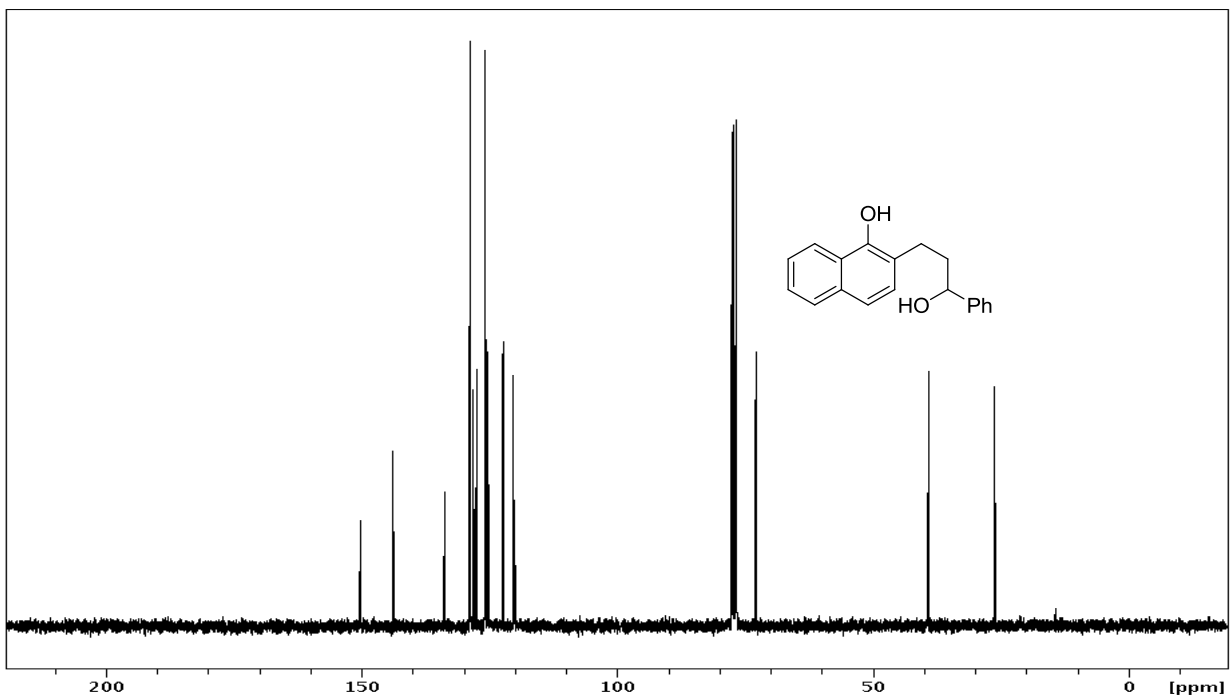
¹H NMR spectrum of 3.62, R = Me (300 MHz, CDCl₃)



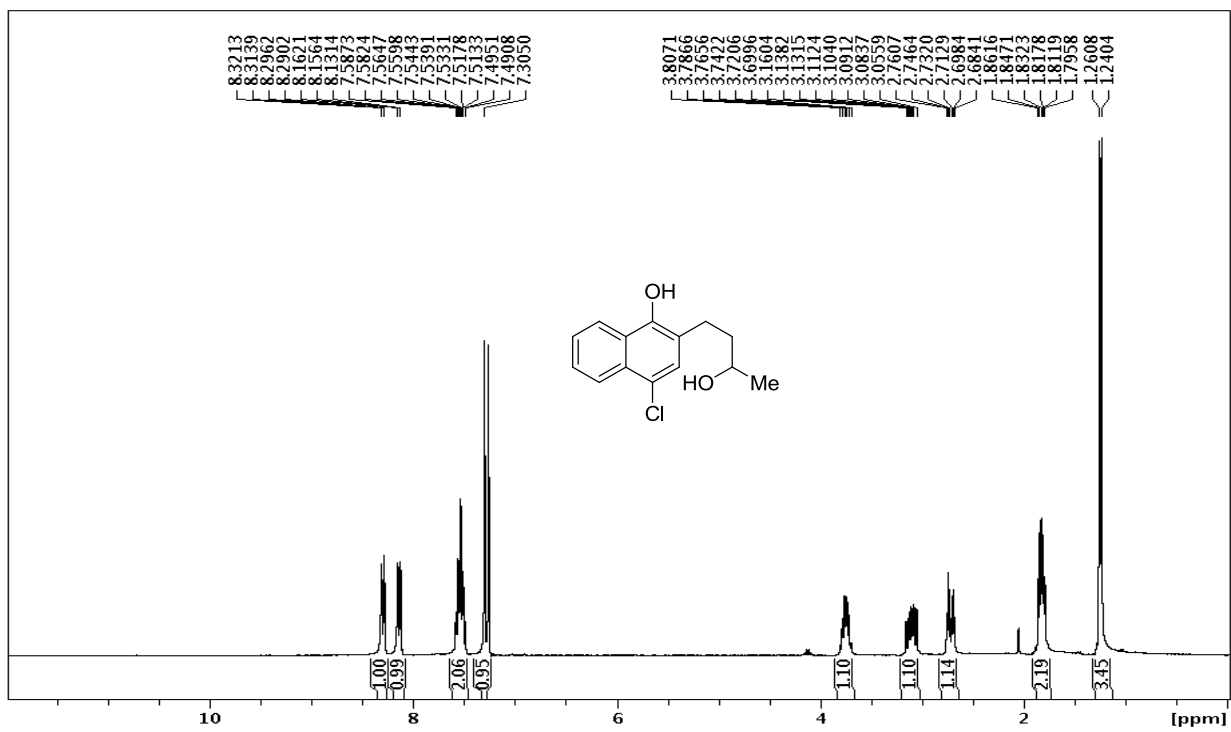
¹³C NMR spectrum of 3.62, R = Me (75 MHz, CDCl₃)



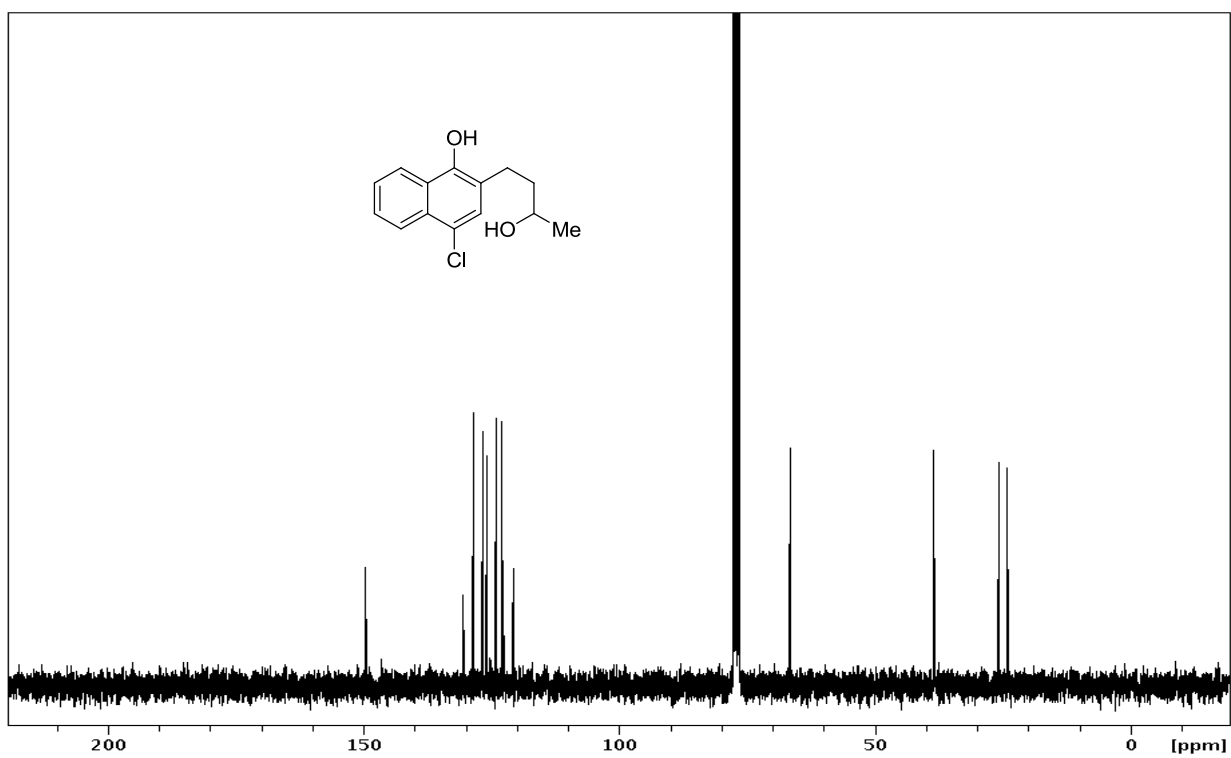
¹H NMR spectrum of 3.62, R = Ph (300 MHz, CDCl₃)



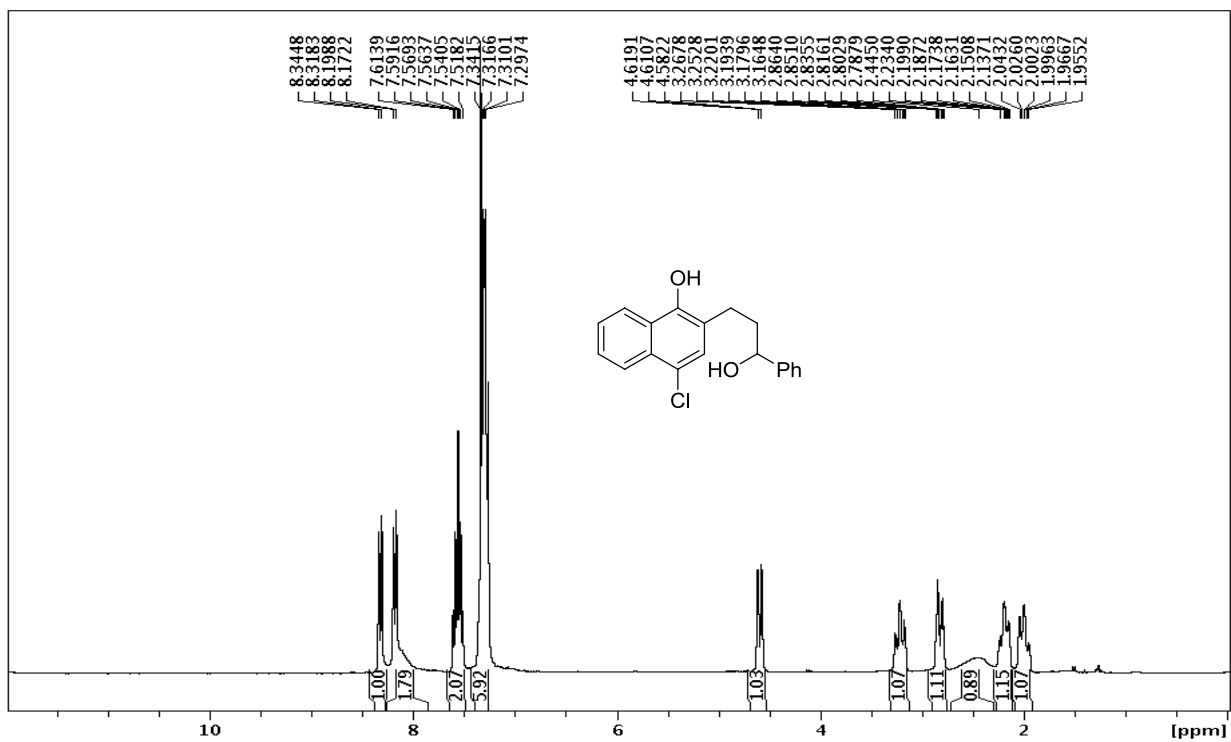
¹³C NMR spectrum of 3.62, R = Ph (75 MHz, CDCl₃)



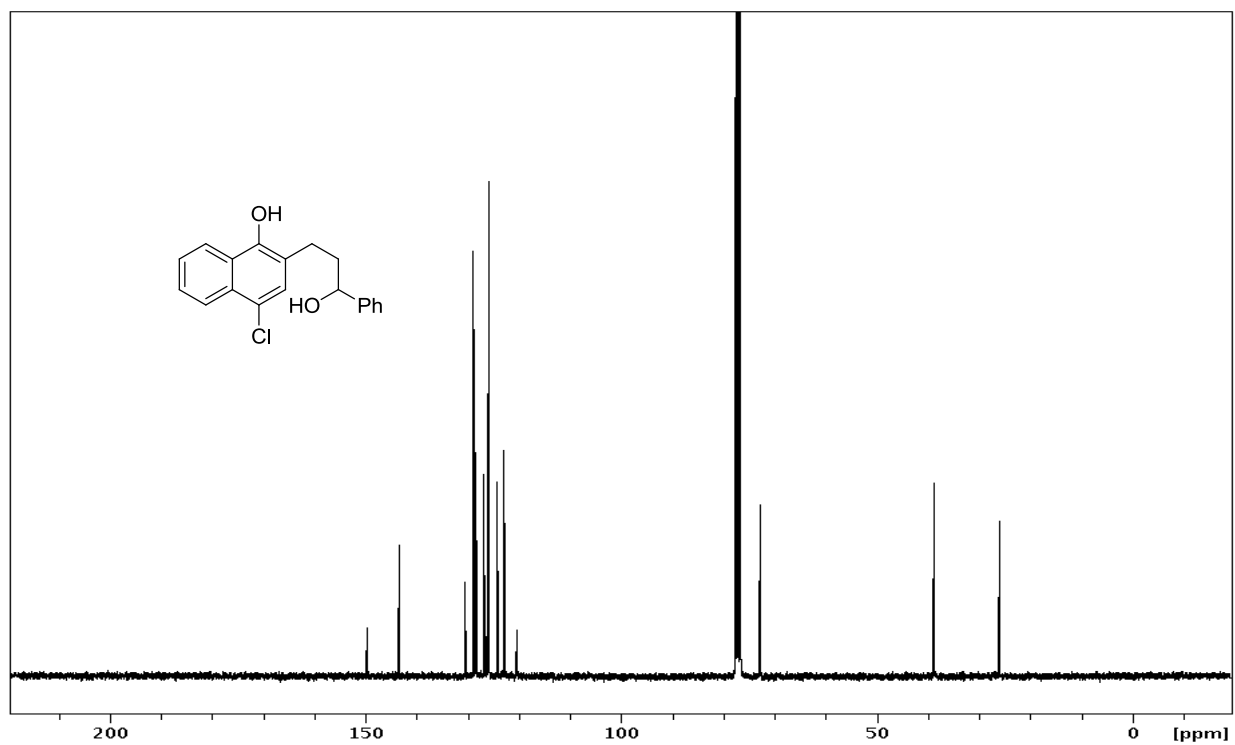
¹H NMR spectrum of 3.63 (300 MHz, CDCl₃)



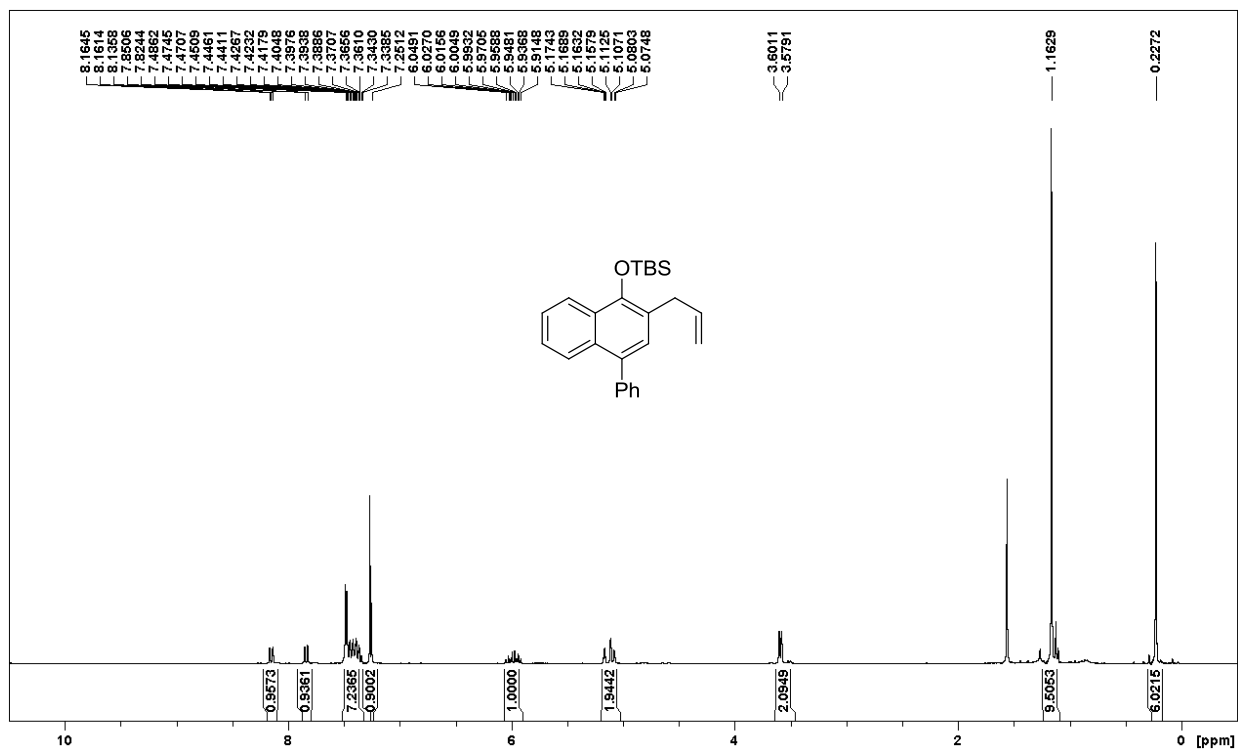
¹³C NMR spectrum of 3.63 (75 MHz, CDCl₃)



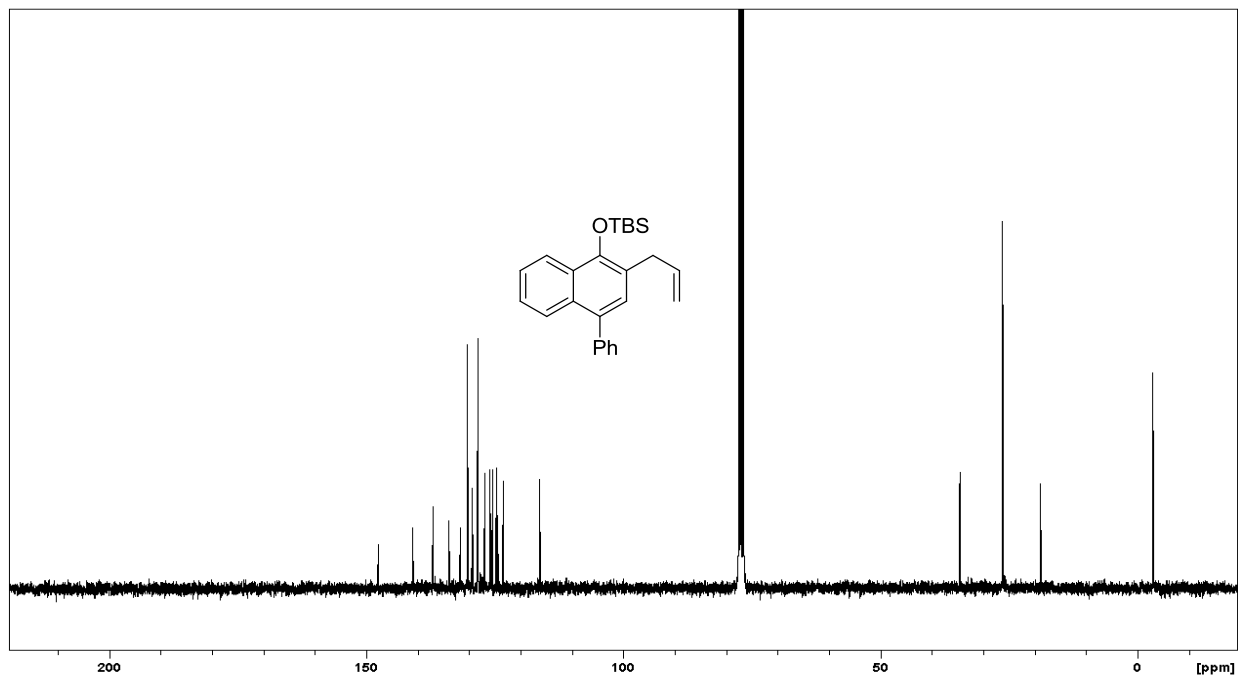
¹H NMR spectrum of 3.64 (300 MHz, CDCl₃)



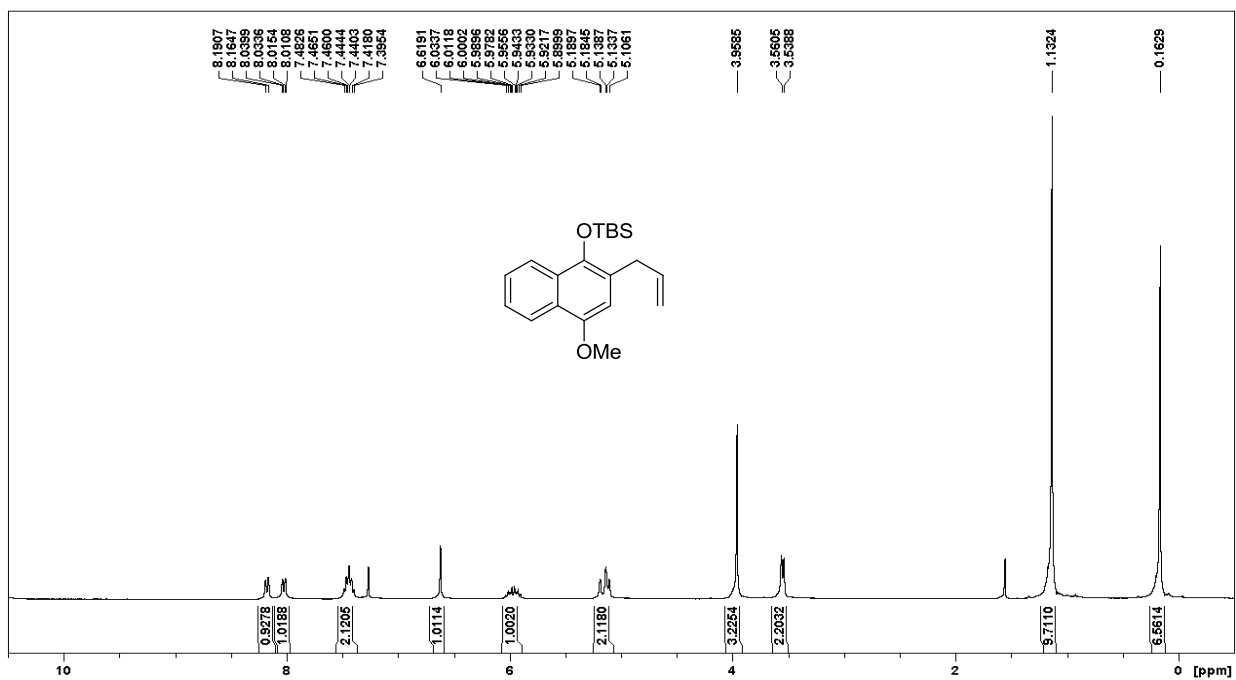
¹³C NMR spectrum of compound 3.64 (75 MHz, CDCl₃)



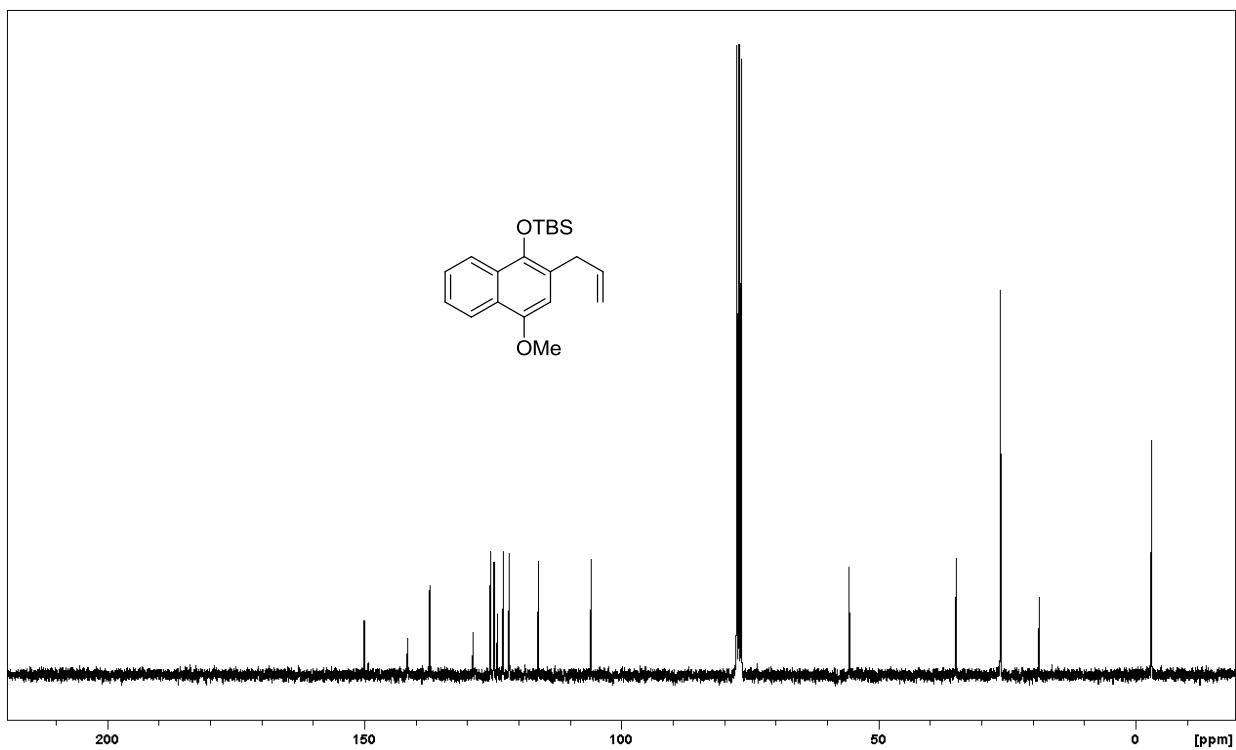
¹H NMR spectrum of 3.69, R' = H (300 MHz, CDCl₃)



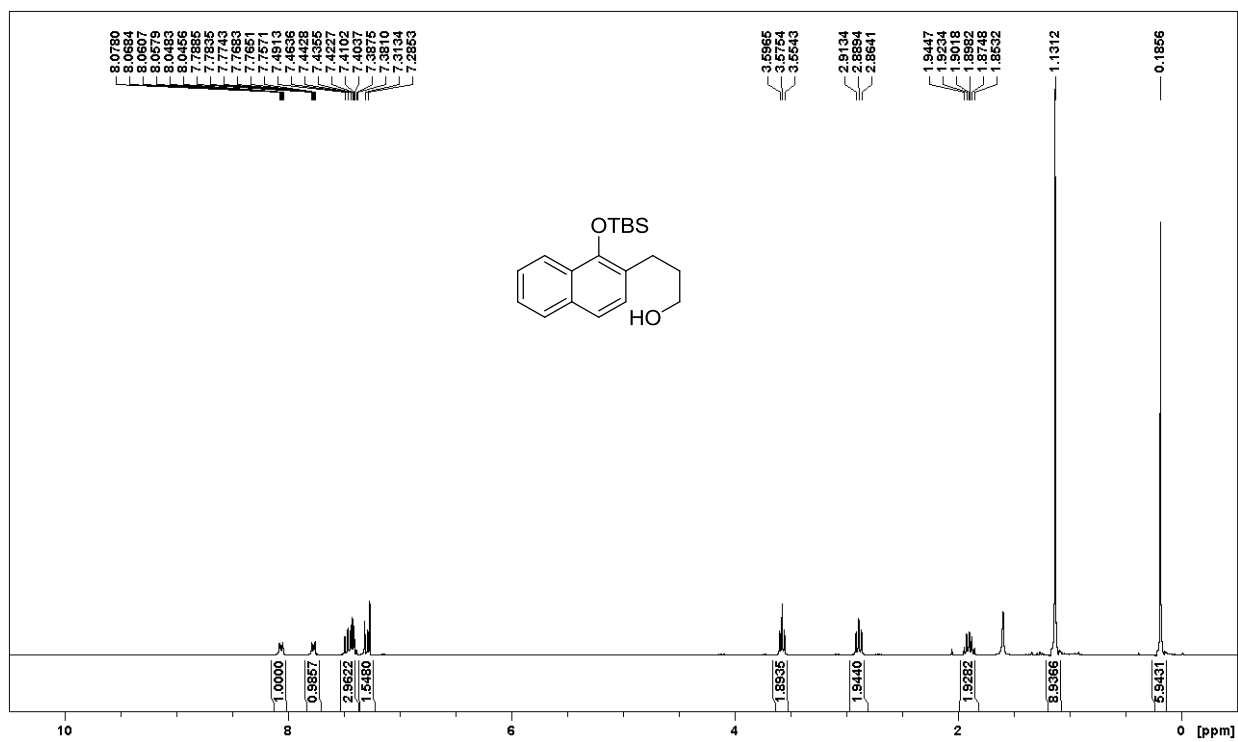
¹³C NMR spectrum of 3.69, R' = H (75 MHz, CDCl₃)



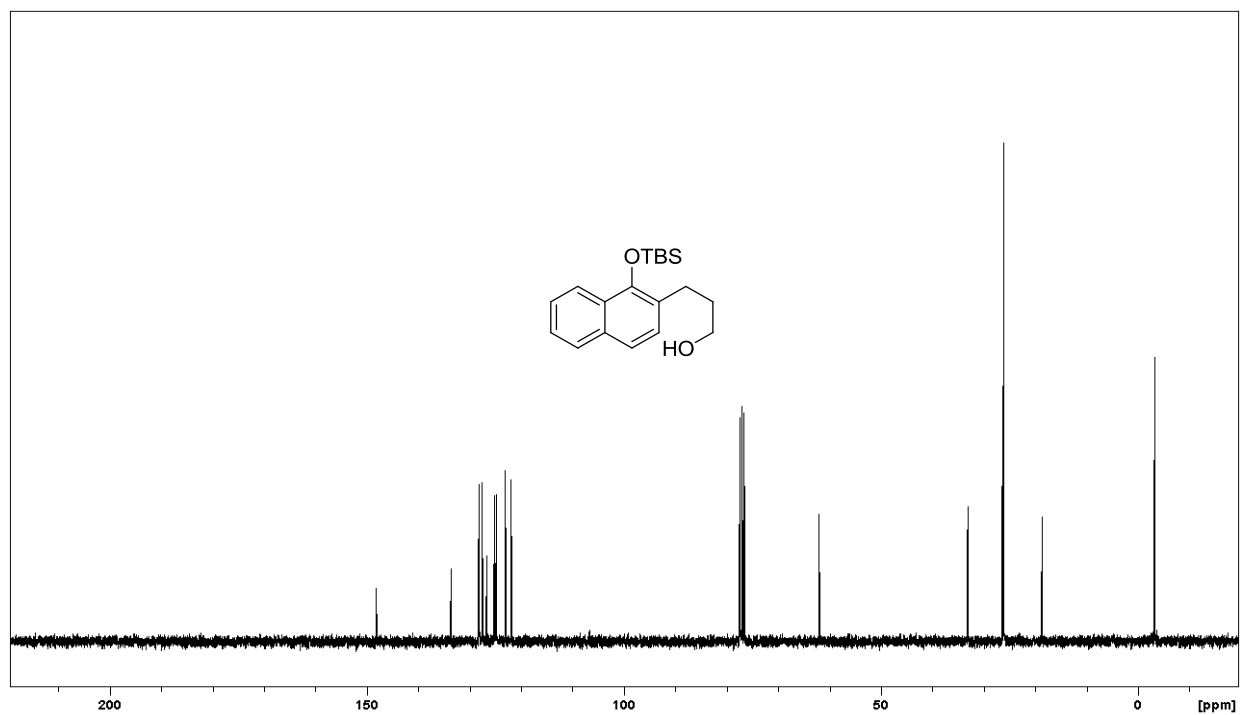
¹H NMR spectrum of 3.69, R' = OMe (300 MHz, CDCl₃)



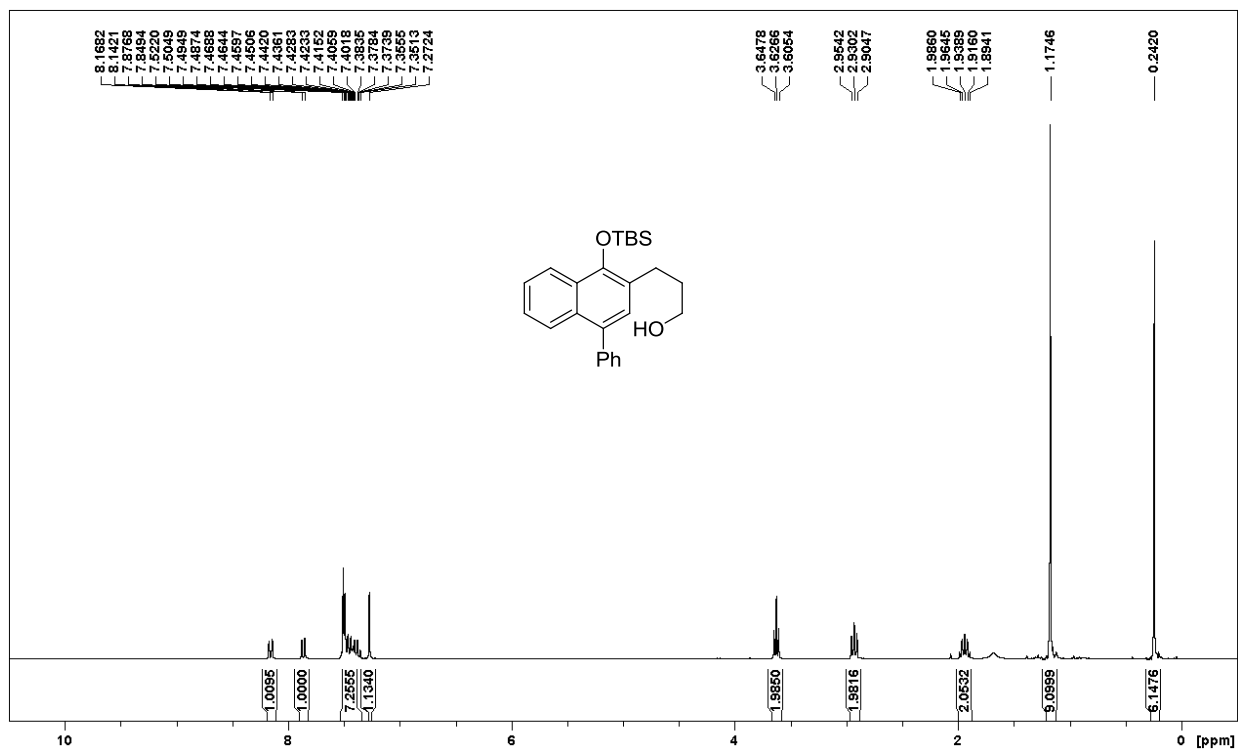
¹³C NMR spectrum of 3.69, R' = OMe (75 MHz, CDCl₃)



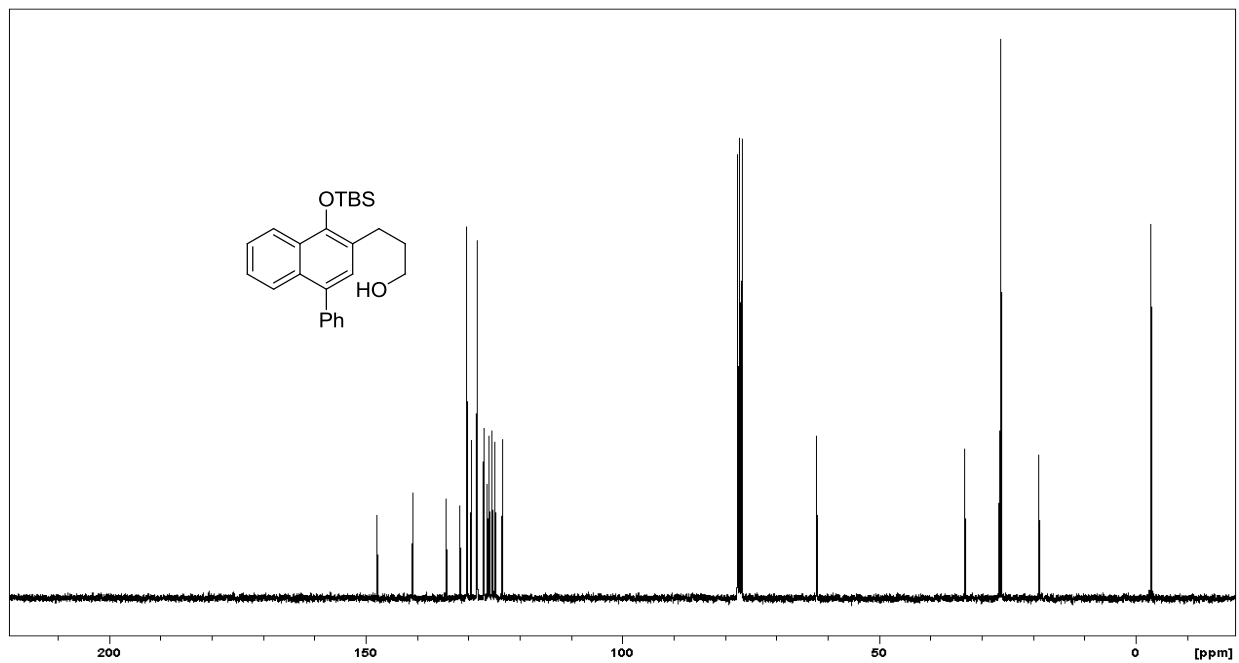
¹H NMR spectrum of 3.70, R' = H (300 MHz, CDCl₃)



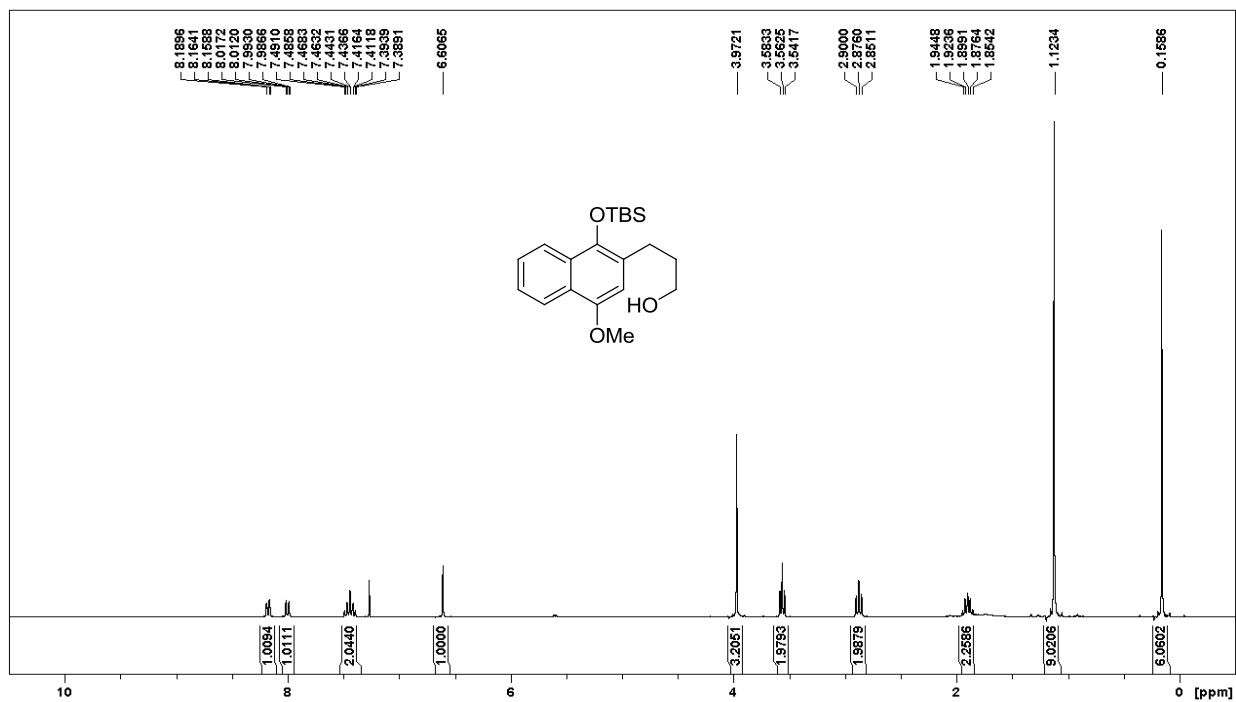
¹³C NMR spectrum of 3.70, R' = H (75 MHz, CDCl₃)



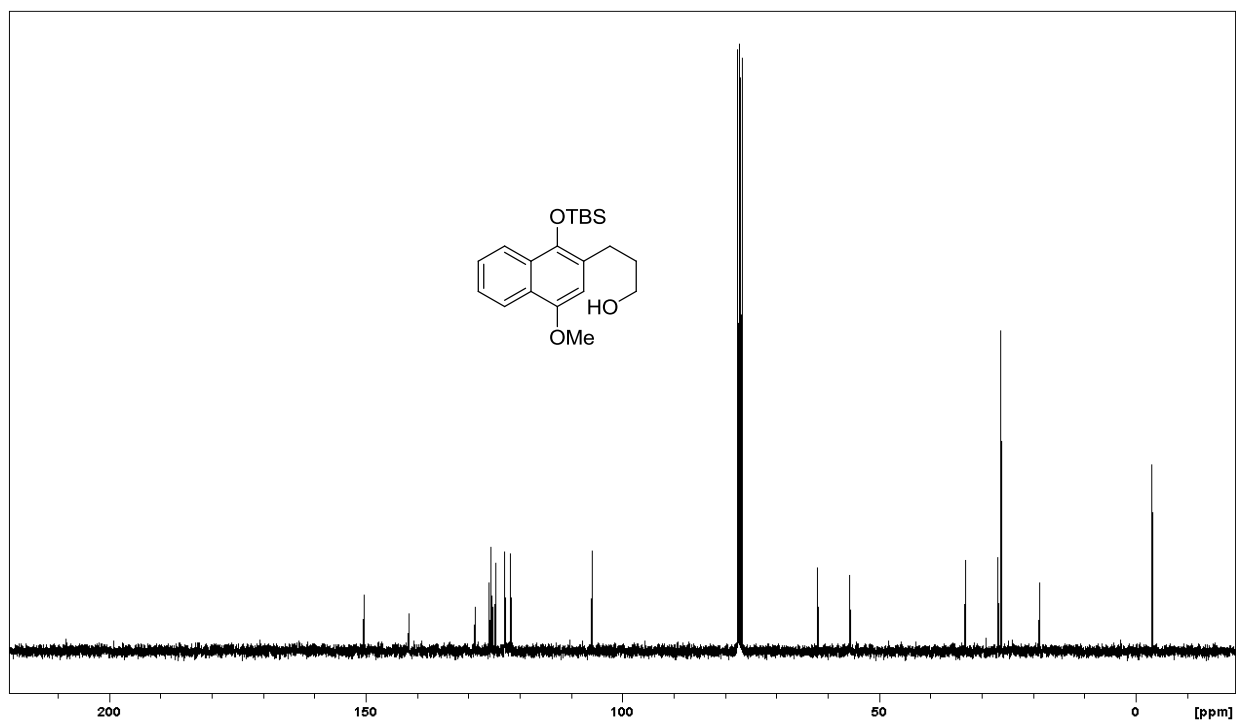
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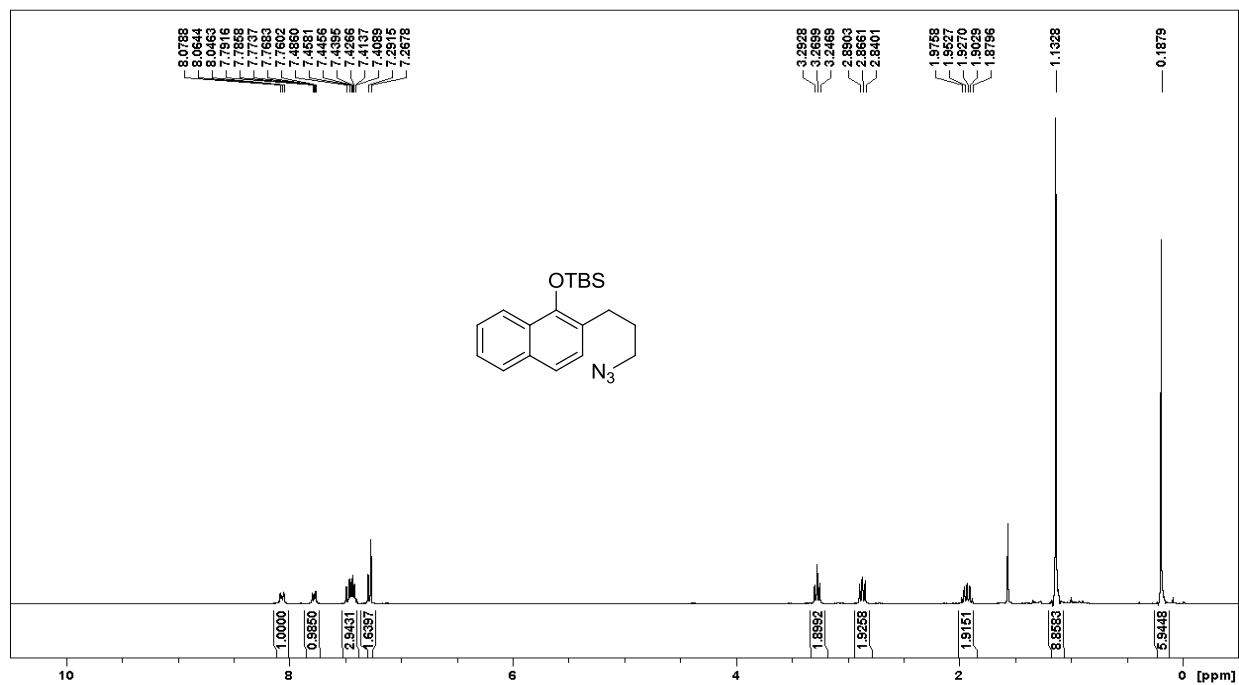
¹³C NMR spectrum of 3.70, R' = Ph (75 MHz, CDCl₃)



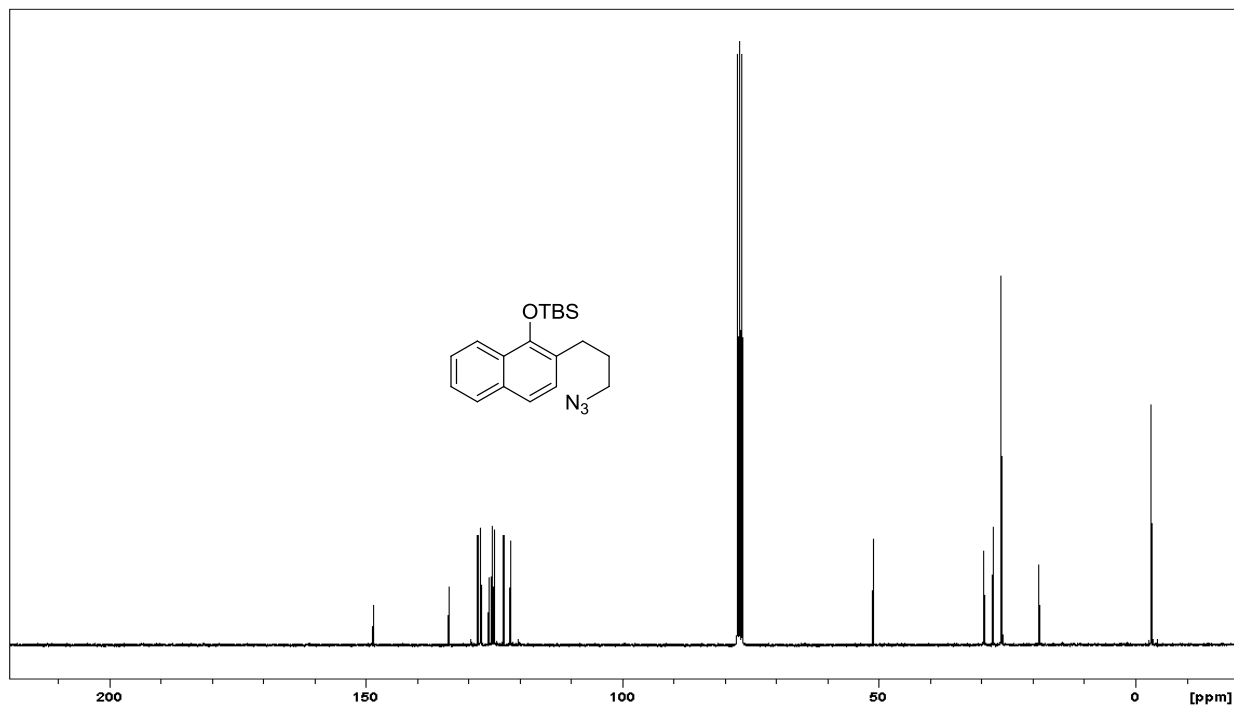
¹H NMR spectrum of 3.70, R' = OMe (300 MHz, CDCl₃)



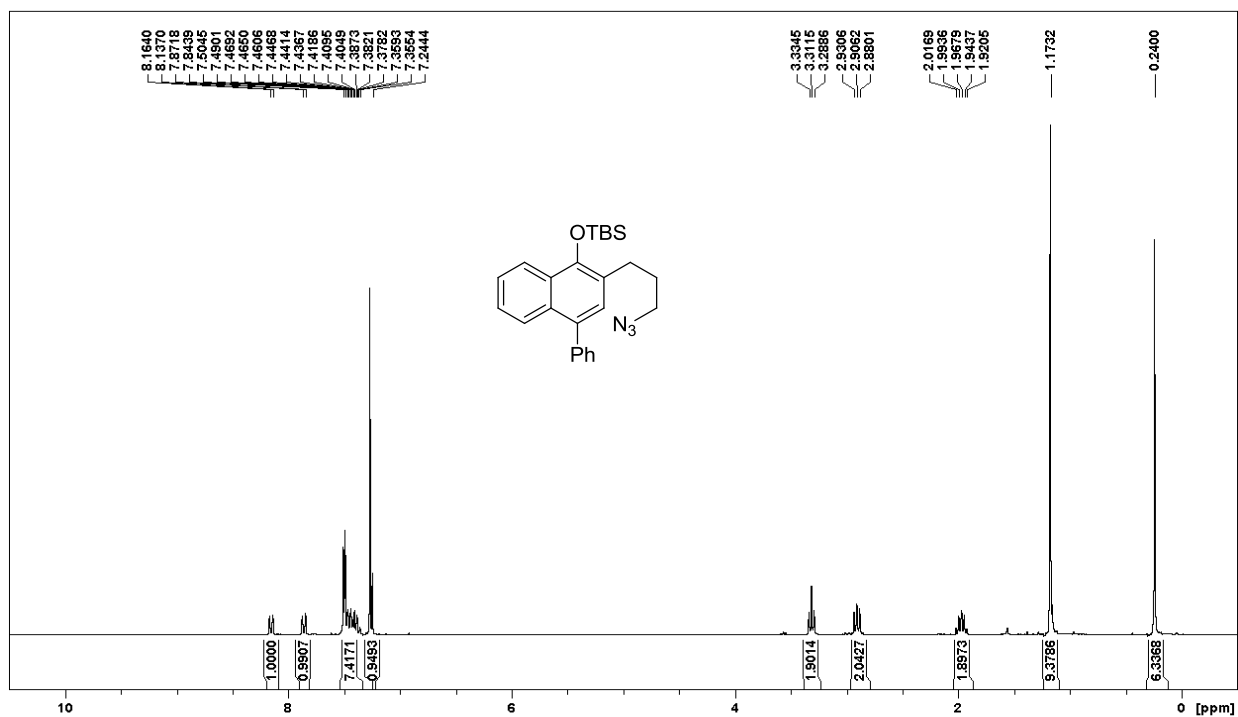
¹³C NMR spectrum of 3.70, R' = OMe (75 MHz, CDCl₃)



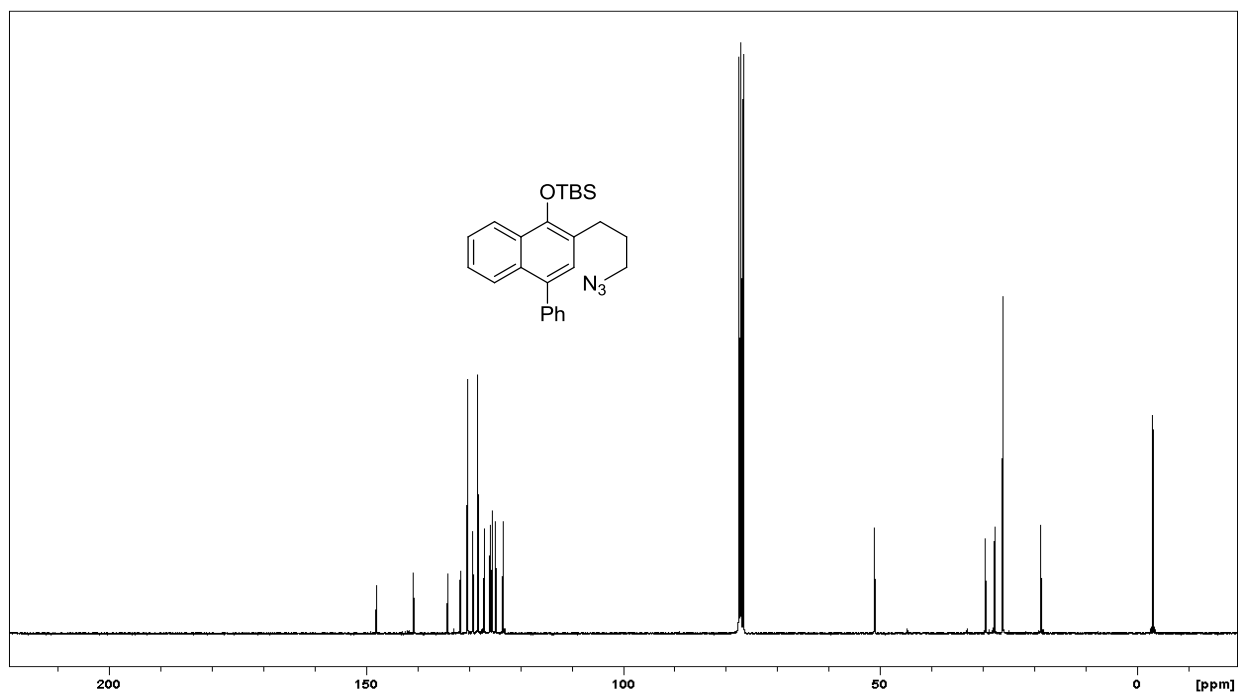
¹H NMR spectrum of 3.71, R' = H (300 MHz, CDCl₃)



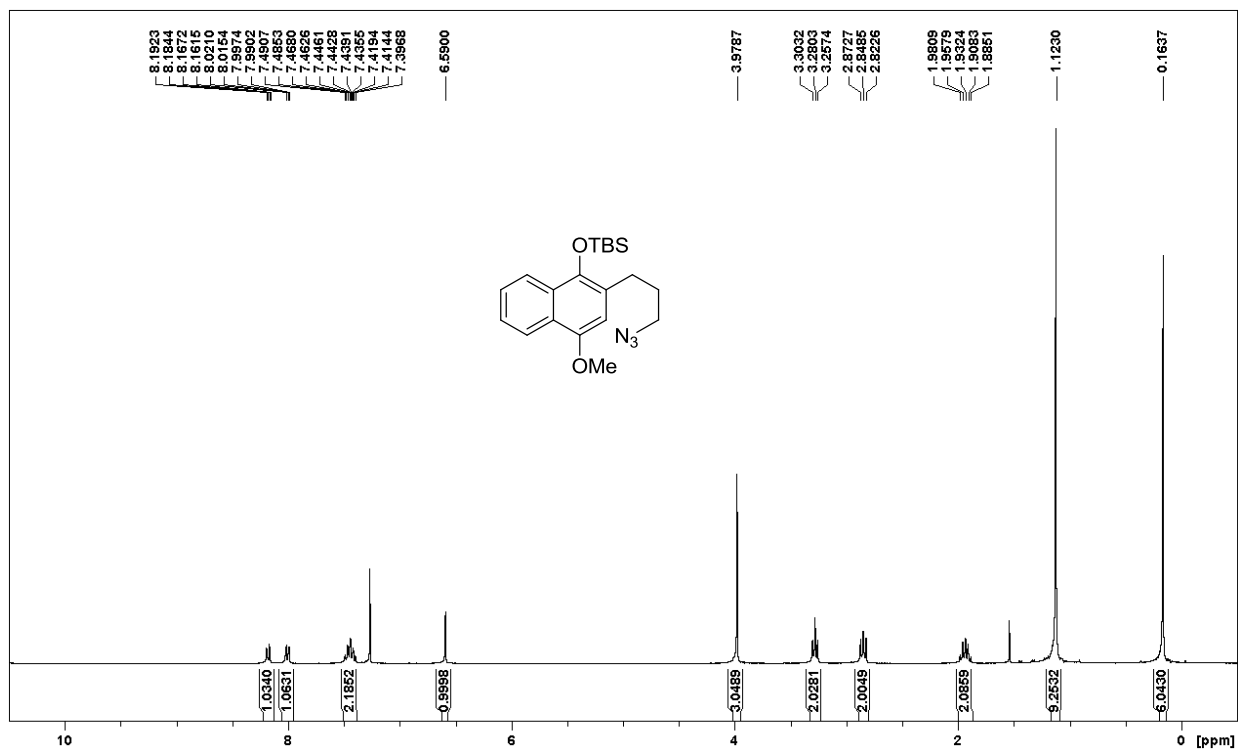
¹³C NMR spectrum of 3.71, R' = H (75 MHz, CDCl₃)



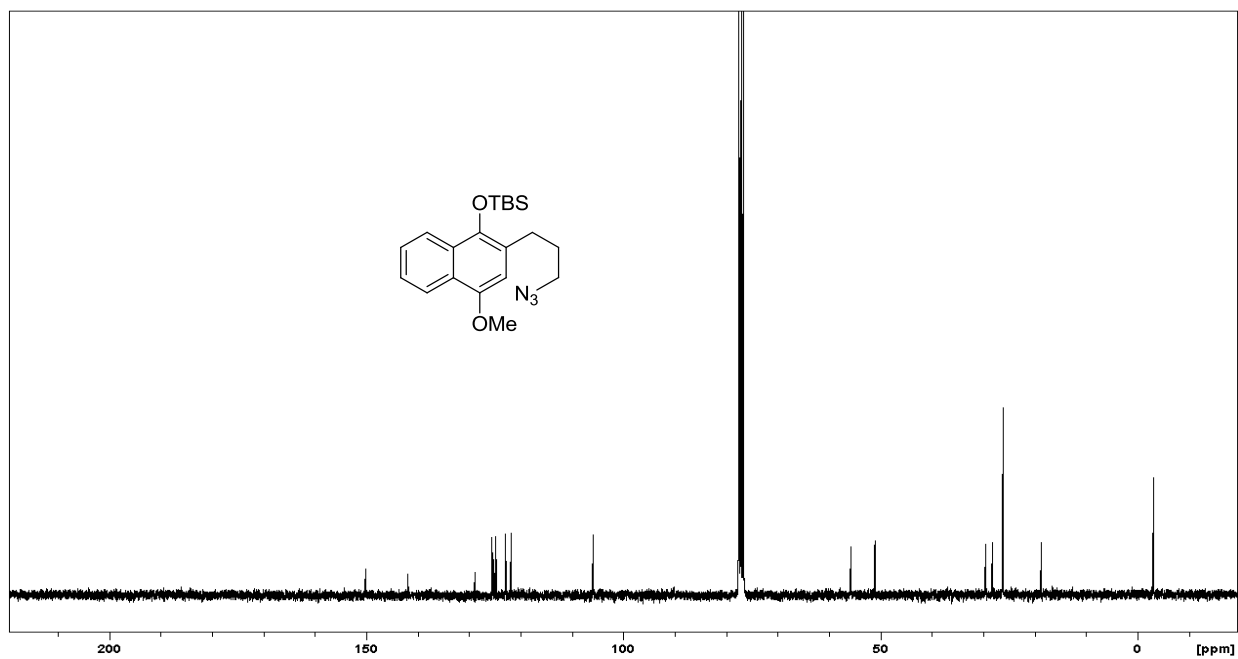
¹H NMR spectrum of 3.71, R' = Ph (300 MHz, CDCl₃)



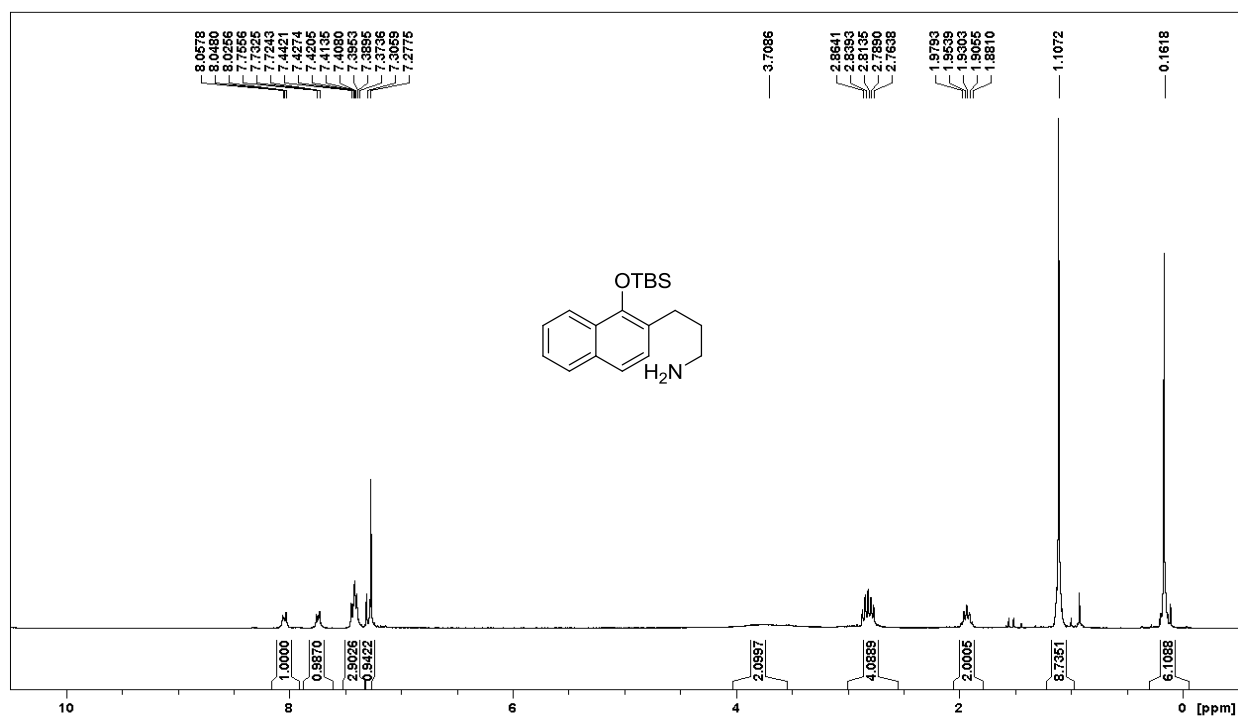
¹³C NMR spectrum of 3.71, R' = Ph (75 MHz, CDCl₃)



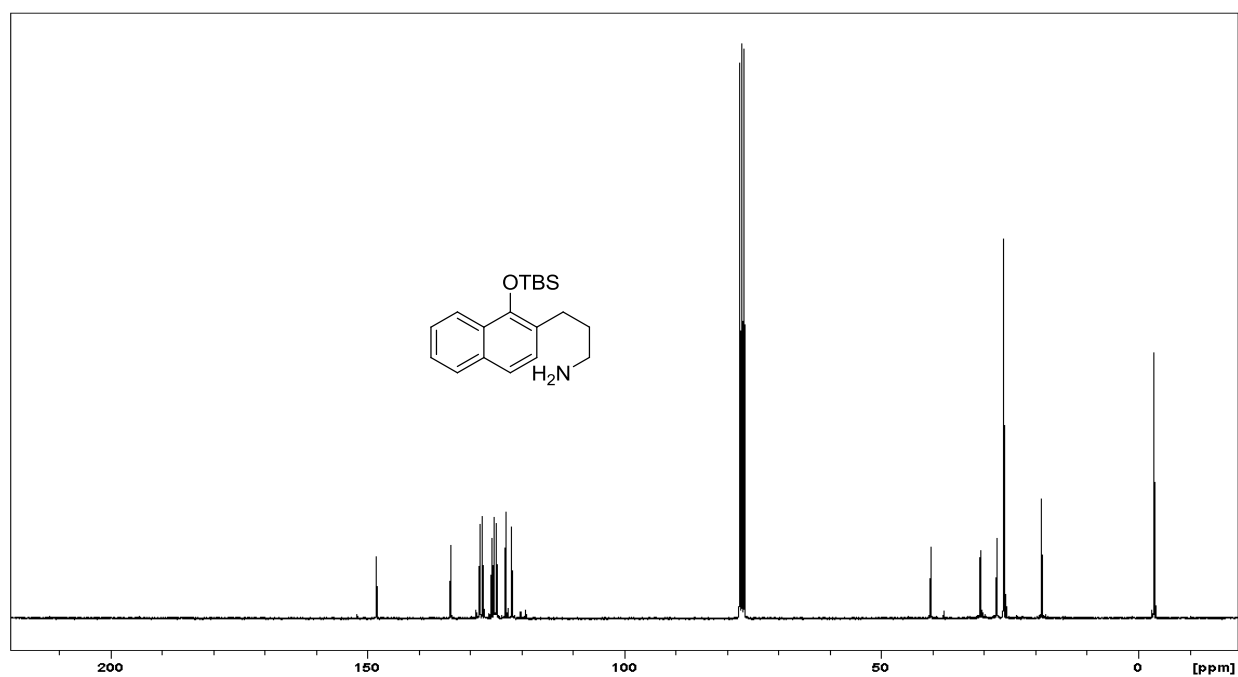
¹H NMR spectrum of 3.71, R' = OMe (300 MHz, CDCl₃)



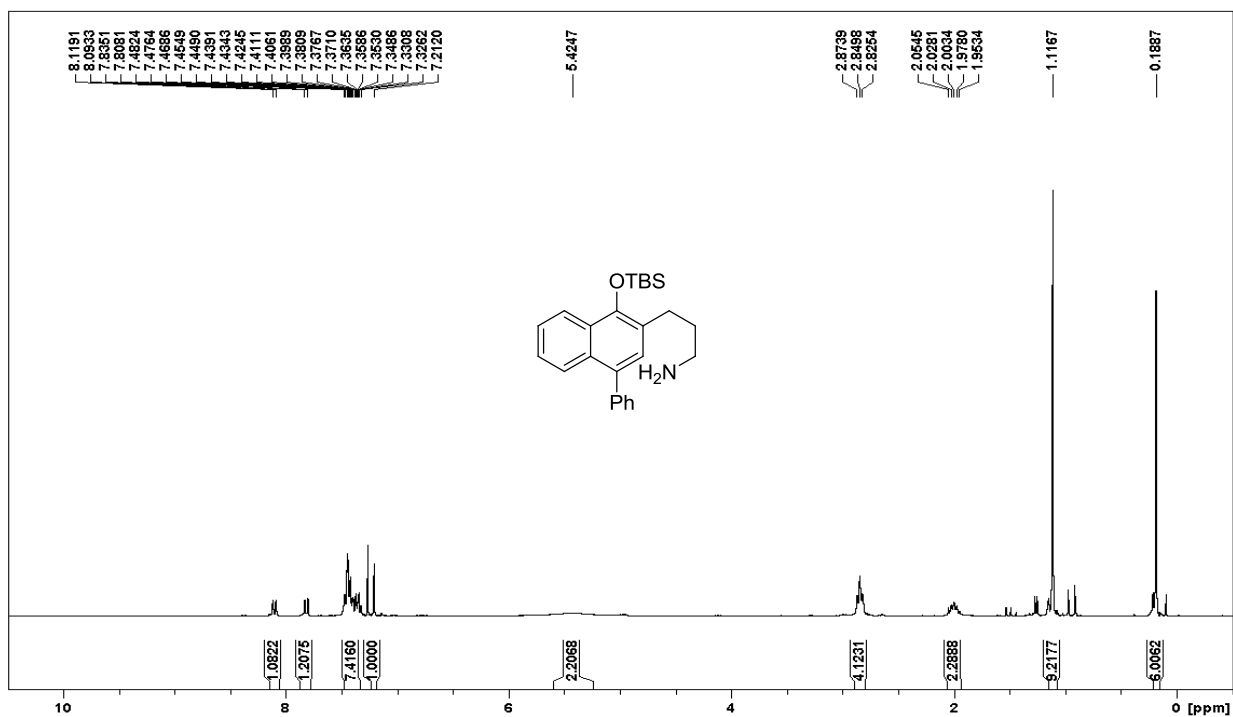
¹³C NMR spectrum of 3.71, R' = OMe (75 MHz, CDCl₃)



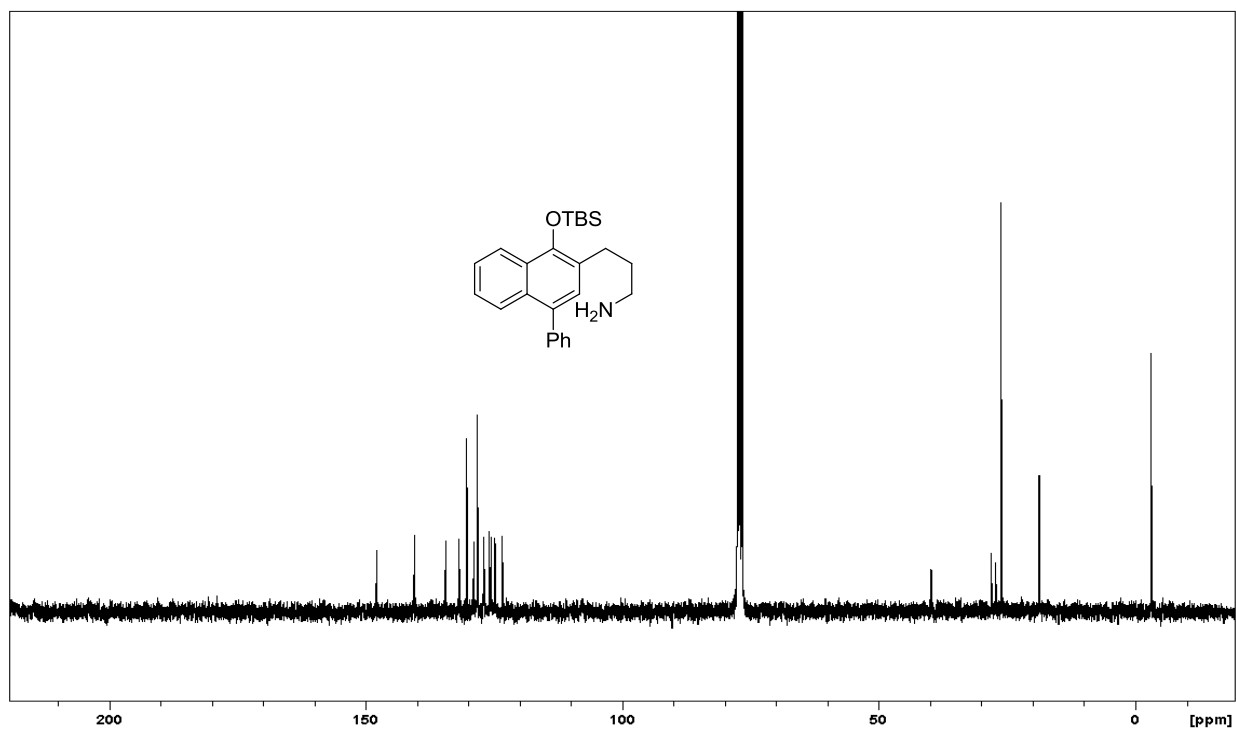
¹H NMR spectrum of crude 3.72, R' = H (300 MHz, CDCl₃)



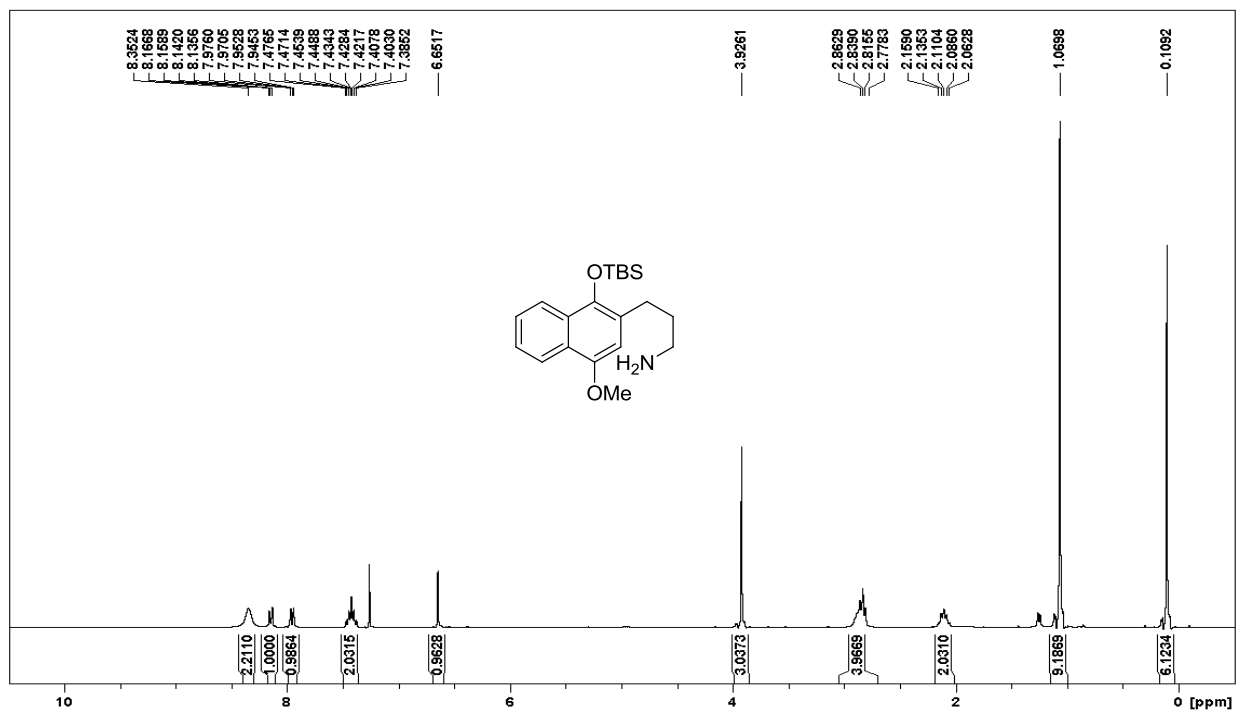
¹³C NMR spectrum of crude 3.72, R' = H (75 MHz, CDCl₃)



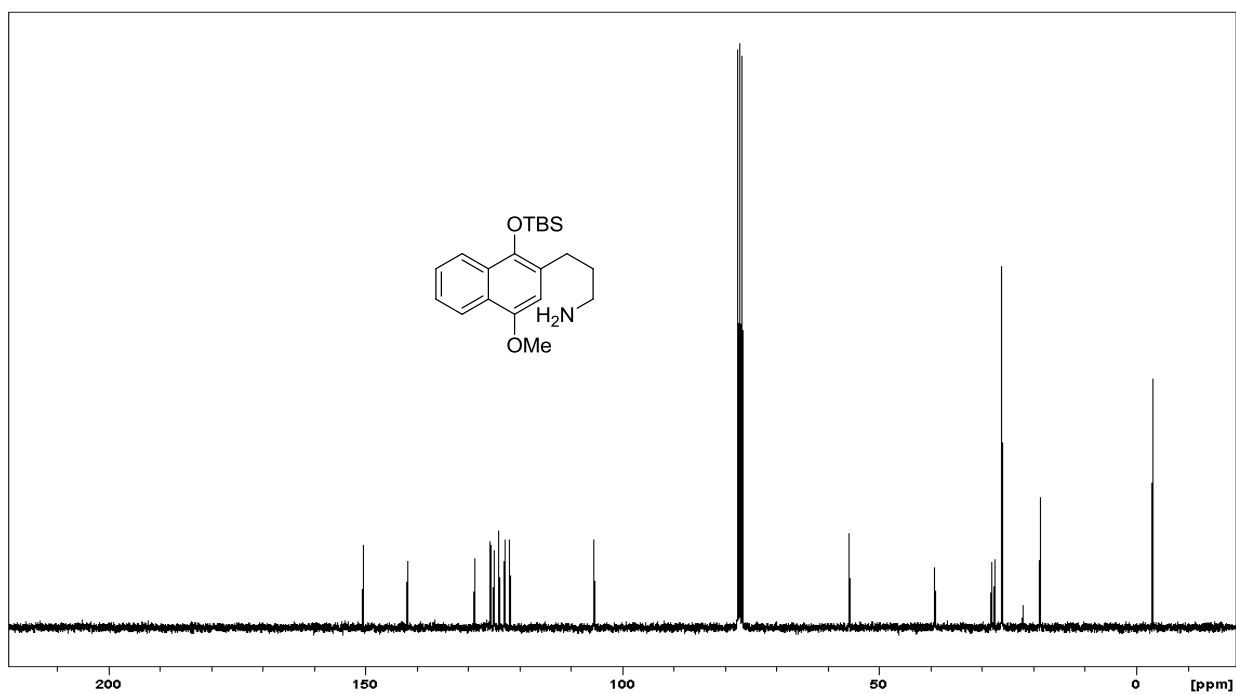
¹H NMR spectrum of crude 3.72, R' = Ph (300 MHz, CDCl₃)



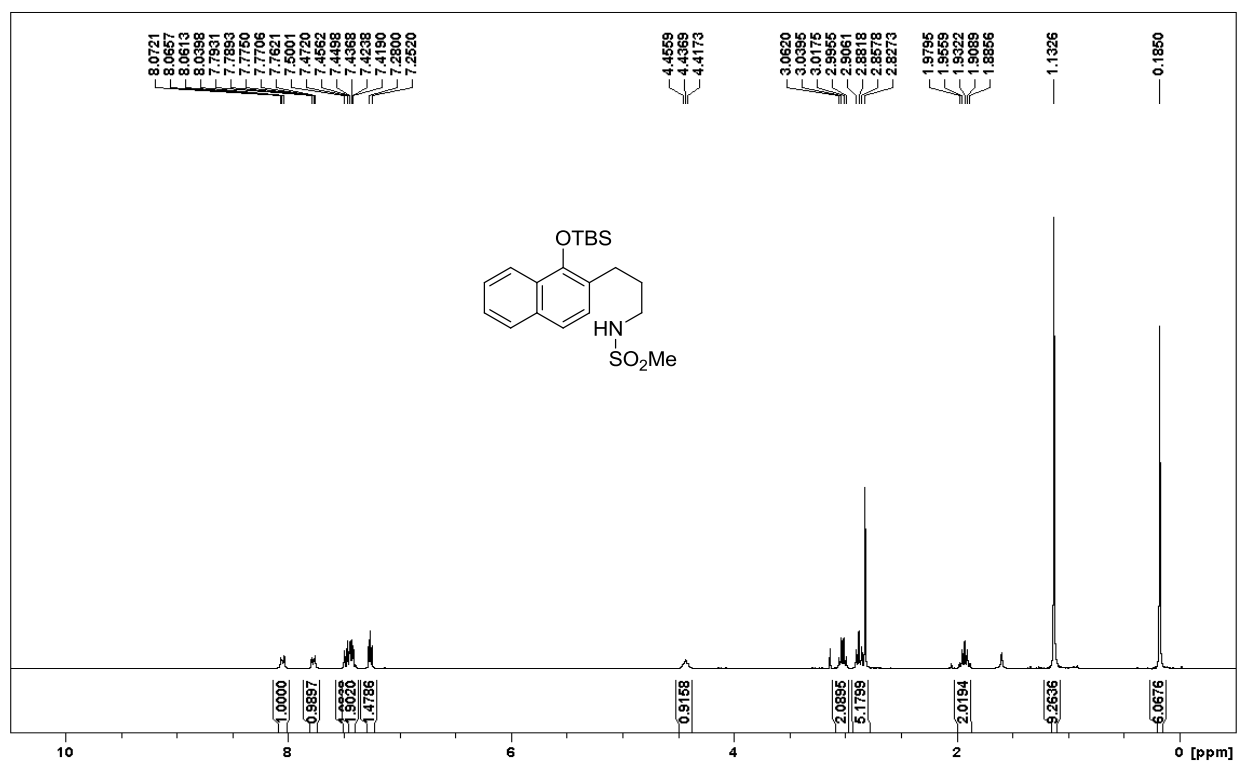
¹³C NMR spectrum of crude 3.72, R' = Ph (75 MHz, CDCl₃)



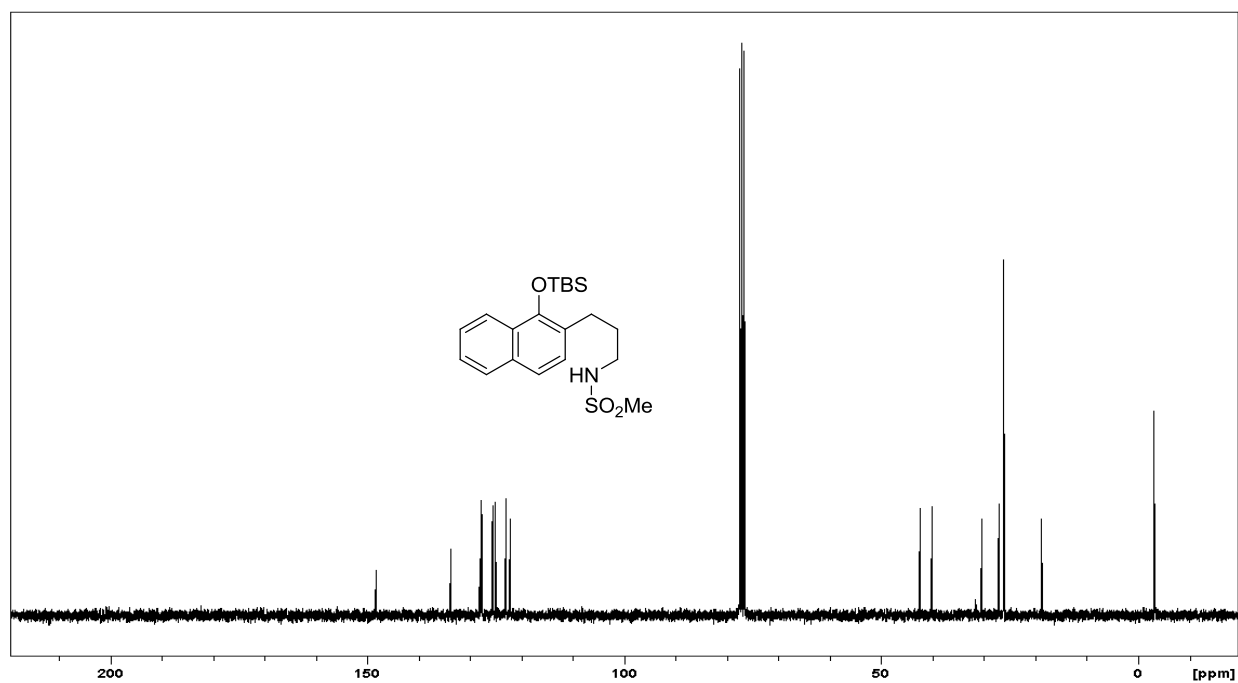
¹H NMR spectrum of crude 3.72, R' = OMe (300 MHz, CDCl₃)



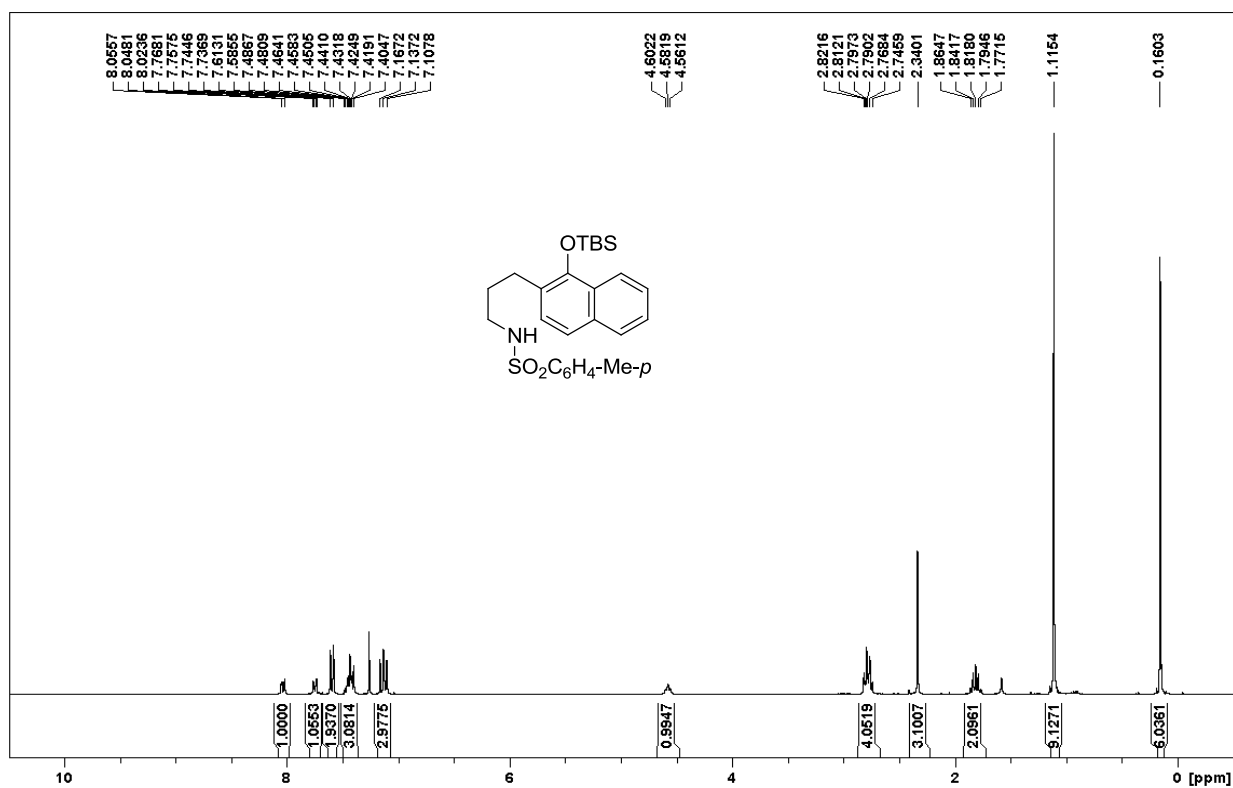
¹³C NMR spectrum of crude 3.72, R' = OMe (75 MHz, CDCl₃)



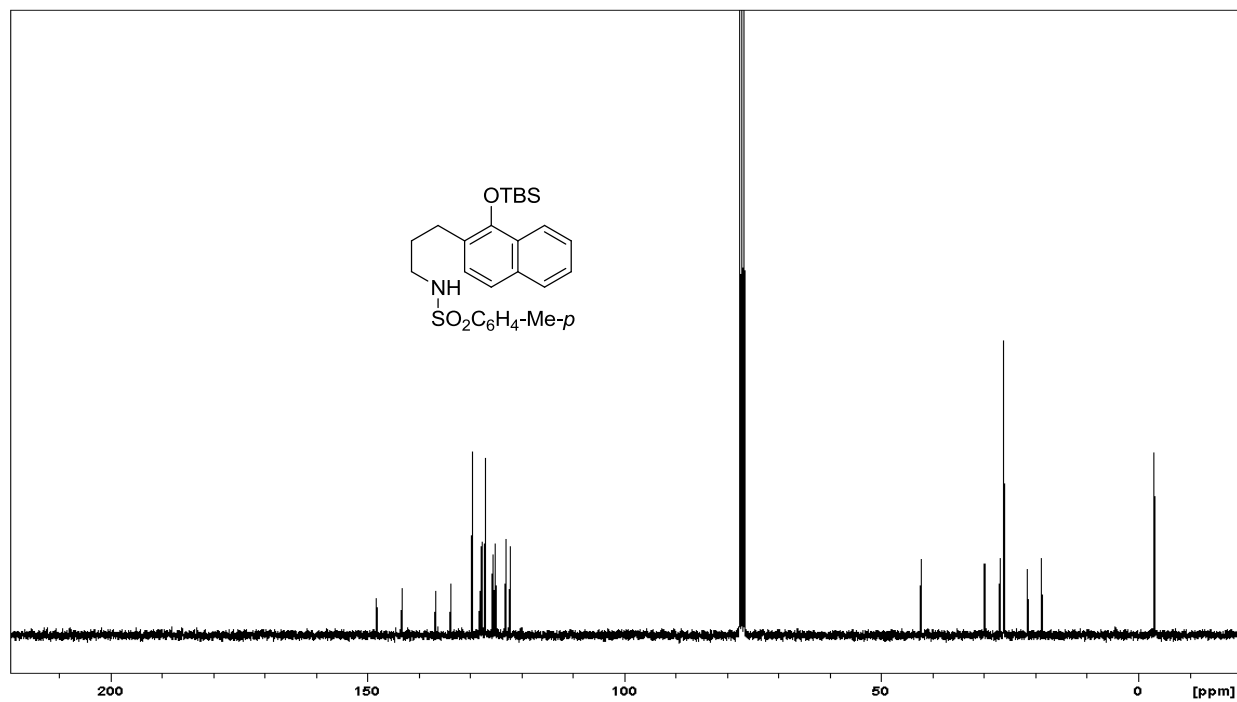
¹H NMR spectrum of 3.73, R = Me, R' = H (300 MHz, CDCl₃)



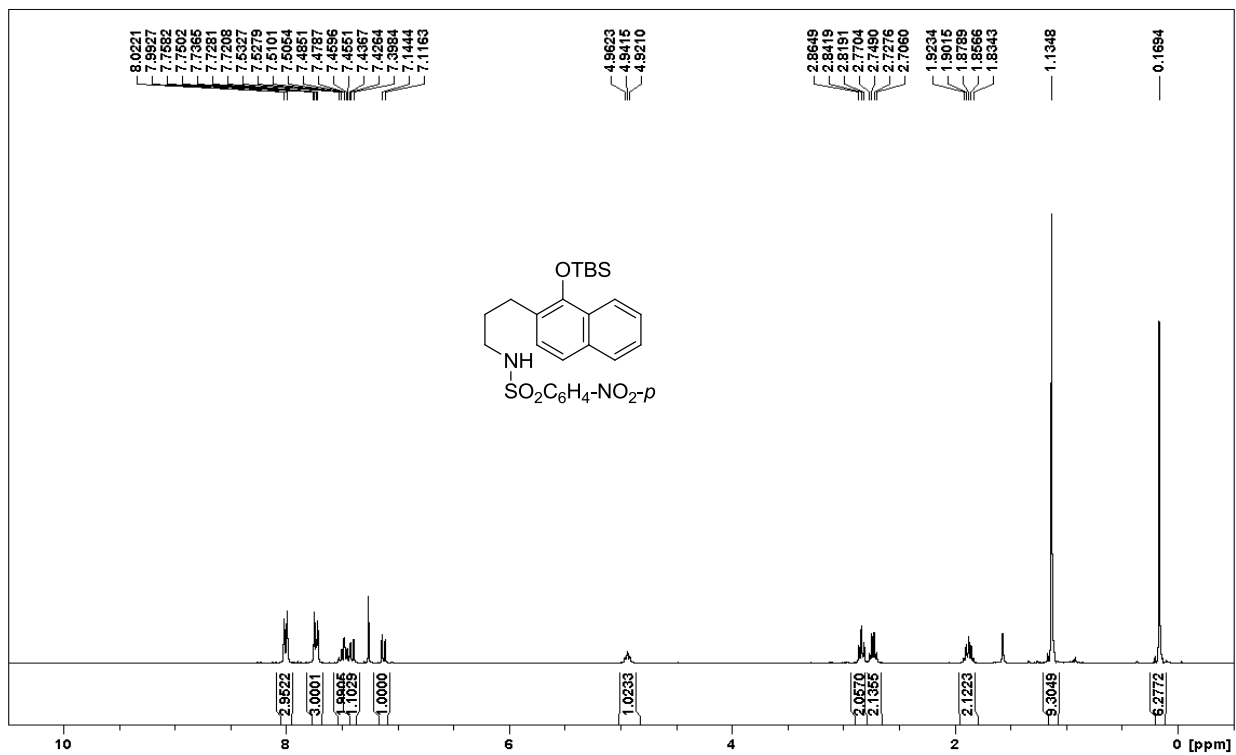
¹³C NMR spectrum of 3.73, R = Me, R' = H (75 MHz, CDCl₃)



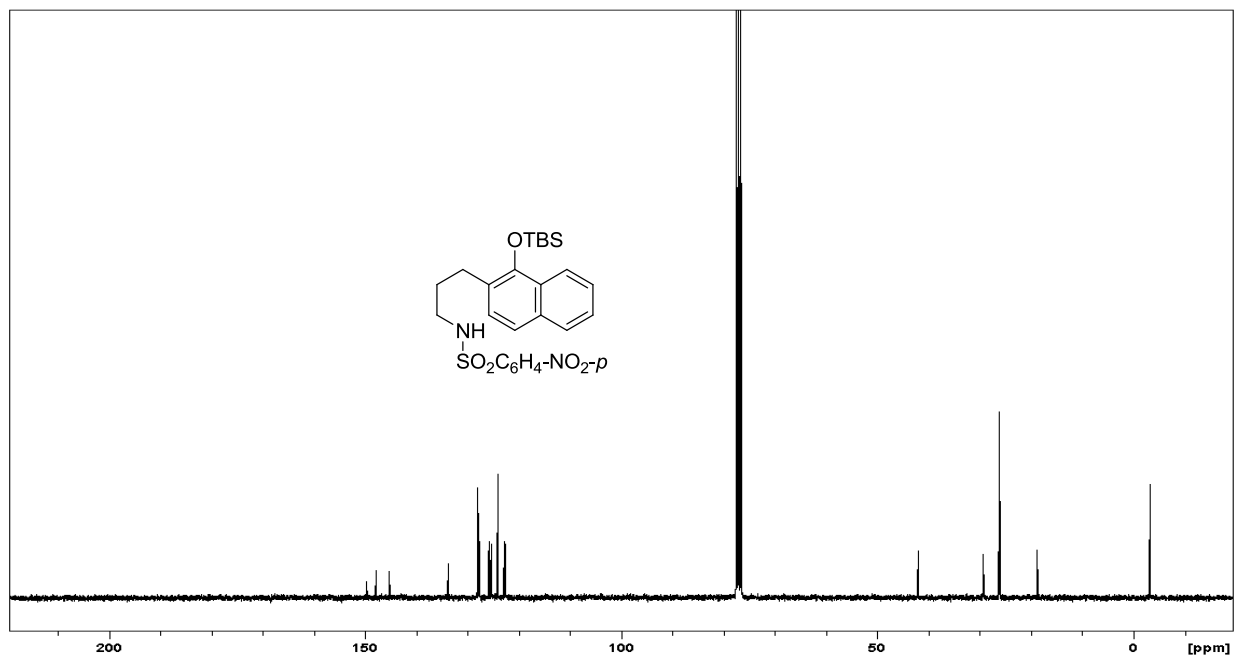
^1H NMR spectrum of 3.73, R = 4-Tol, R' = H (300 MHz, CDCl_3)



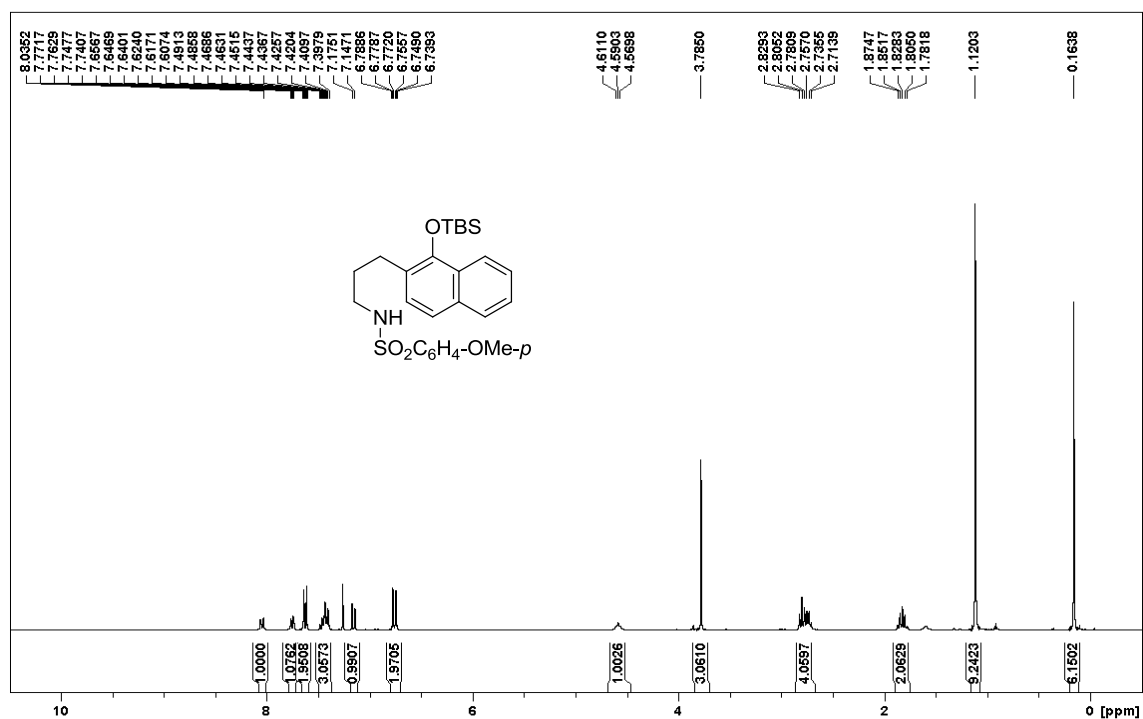
^{13}C NMR spectrum of 3.73, R = 4-Tol, R' = H (75 MHz, CDCl_3)



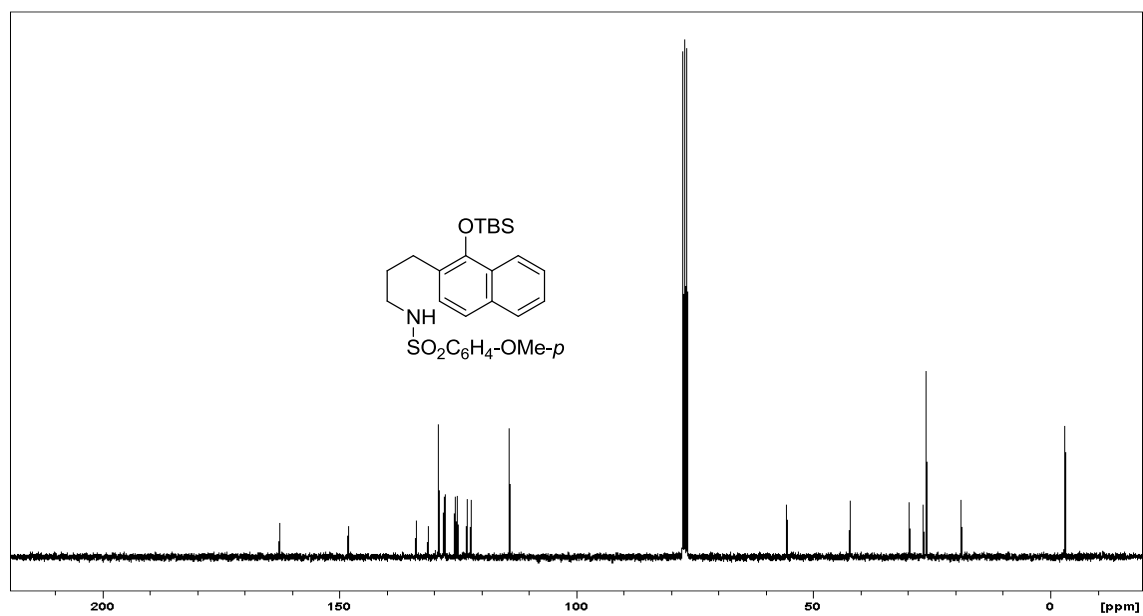
^1H NMR spectrum of 3.73, $\text{R} = \text{C}_6\text{H}_4\text{-NO}_2\text{-}p$, $\text{R}' = \text{H}$ (300 MHz, CDCl_3)



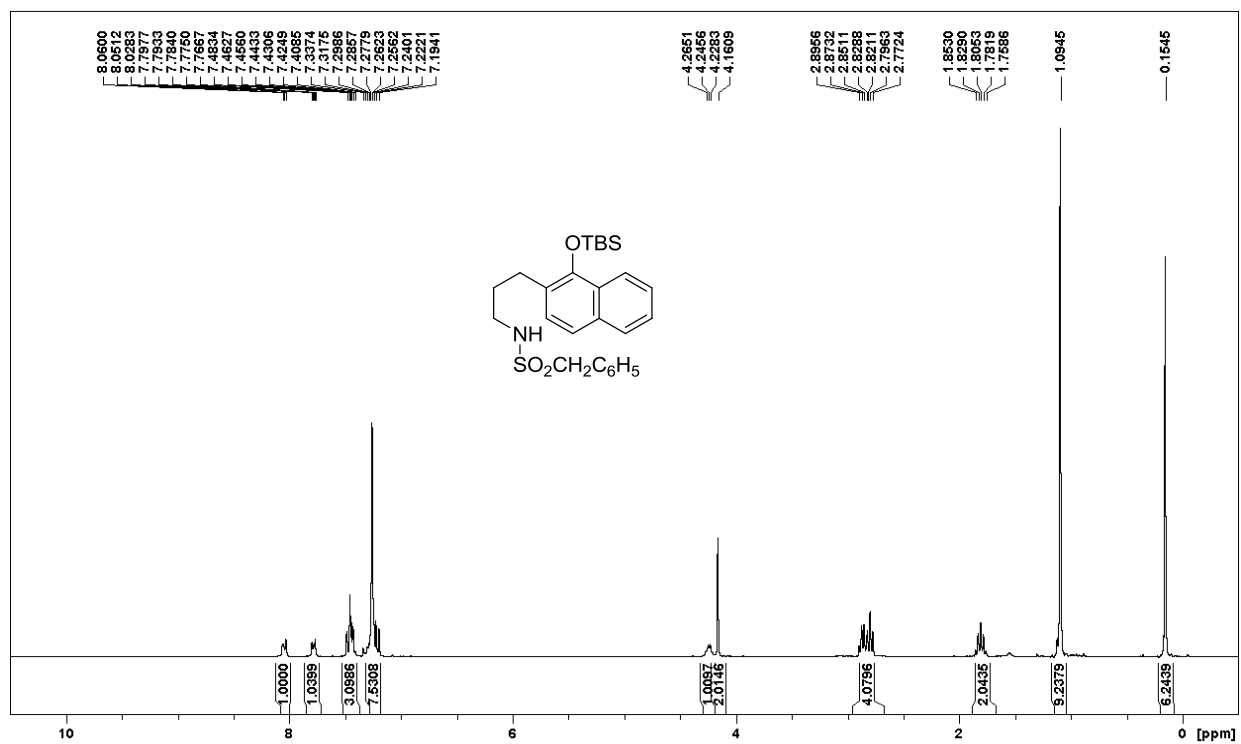
^{13}C NMR spectrum of 3.73, $\text{R} = \text{C}_6\text{H}_4\text{-NO}_2\text{-}p$, $\text{R}' = \text{H}$ (75 MHz, CDCl_3)



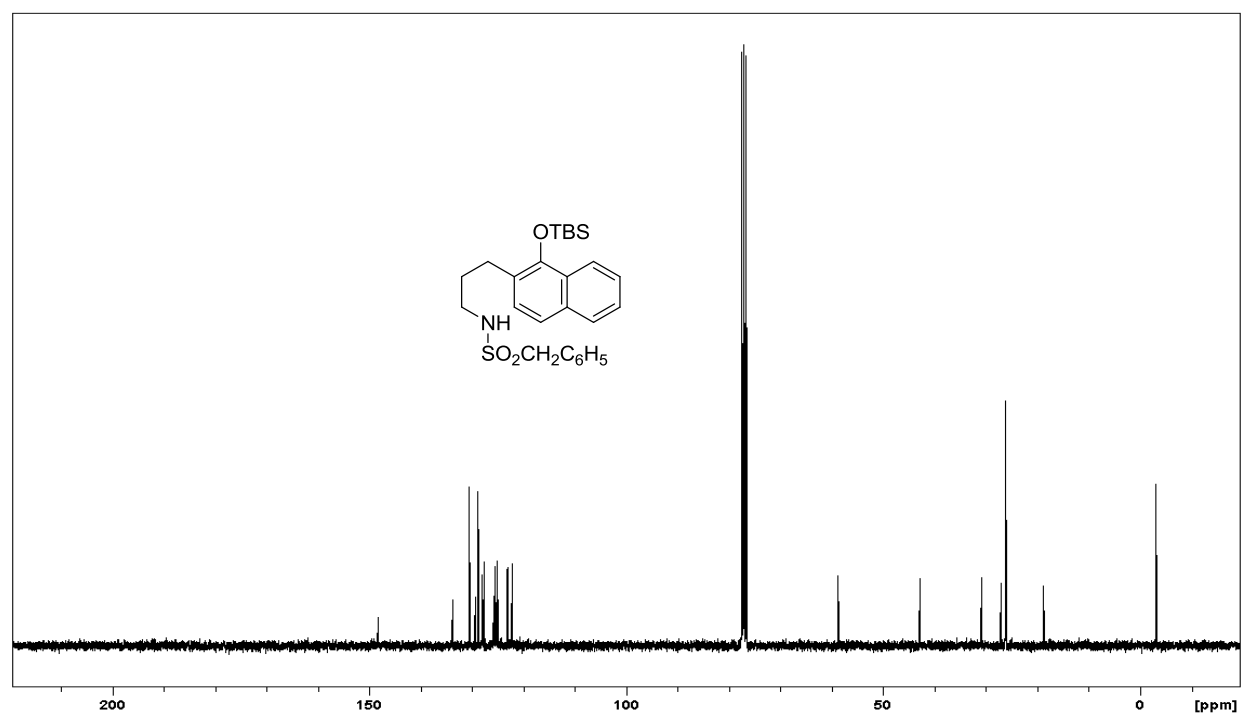
¹H NMR spectrum of 3.73, R = C₆H₄-OMe-*p*, R' = H (300 MHz, CDCl₃)



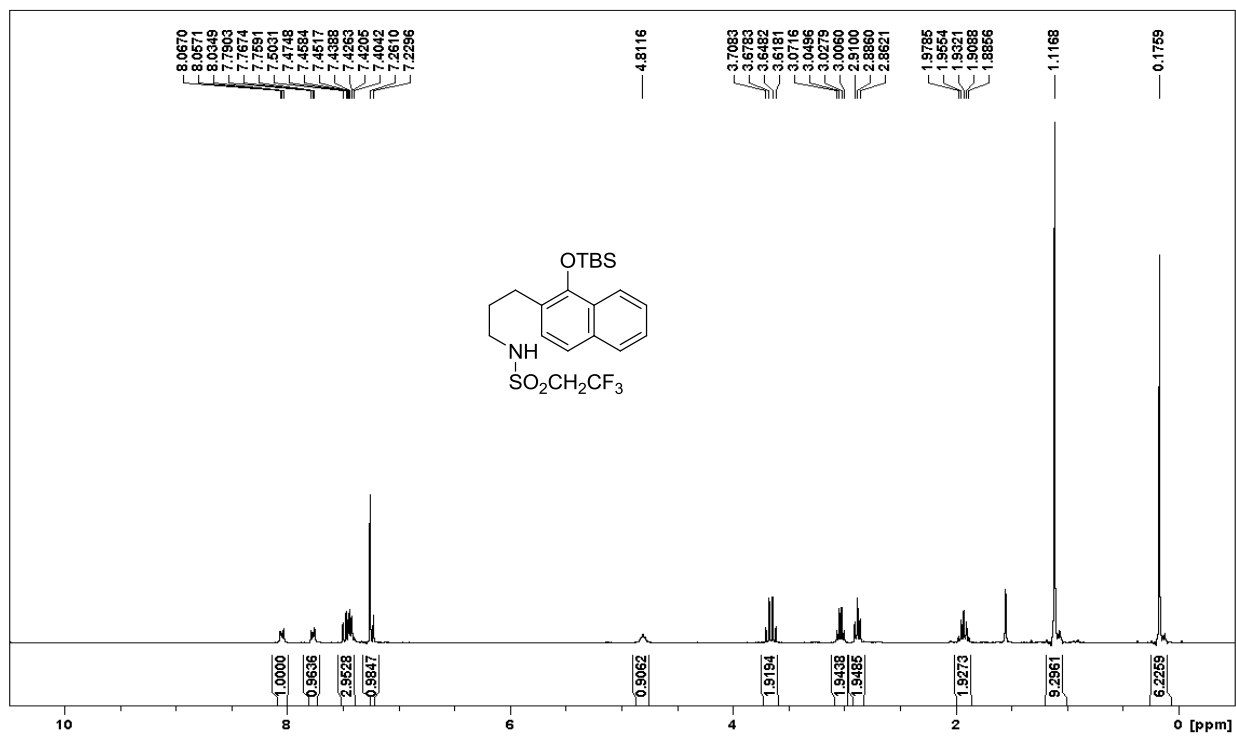
¹³C NMR spectrum of R = C₆H₄-OMe-*p*, R' = H (75 MHz, CDCl₃)



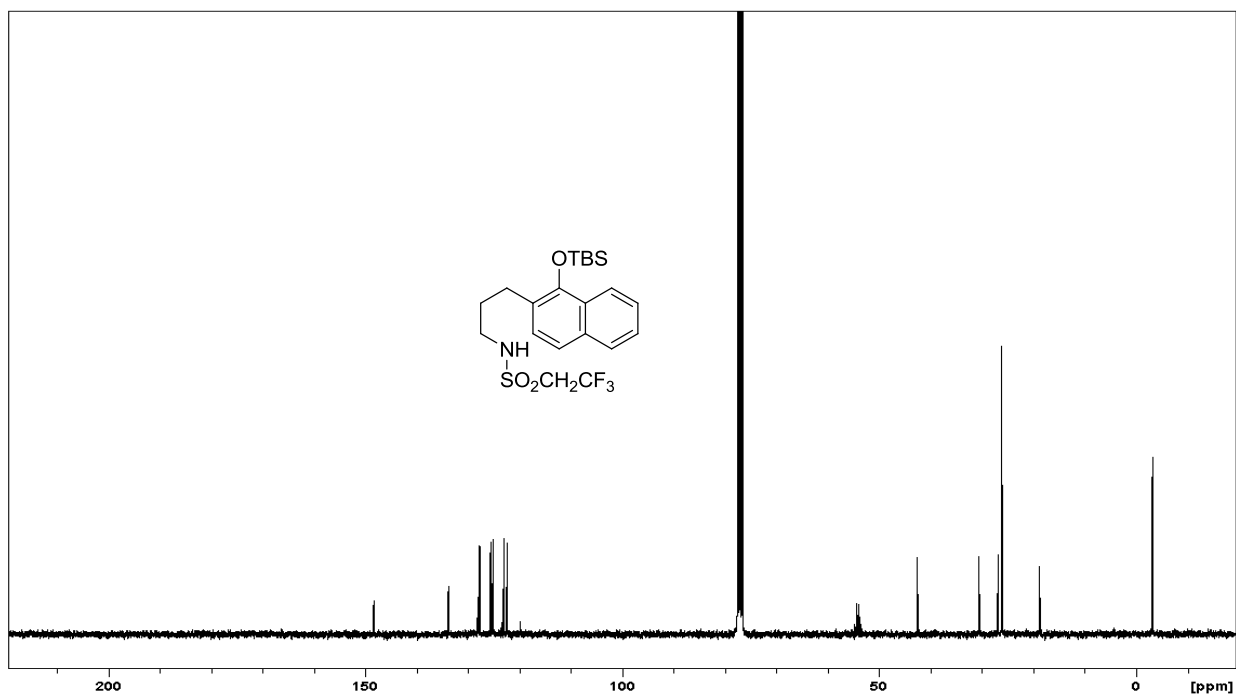
¹H NMR spectrum of 3.73, R = Bn, R' = H (300 MHz, CDCl₃)



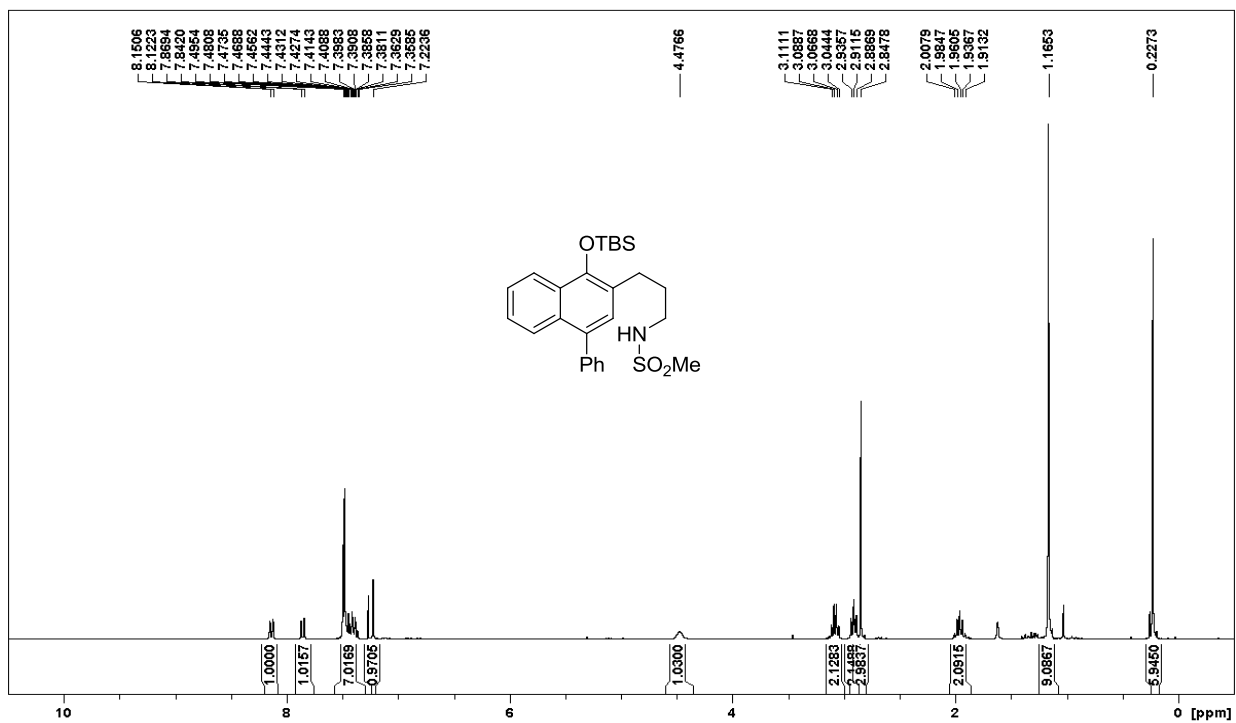
¹³C NMR spectrum of 3.73, R = Bn, R' = H (75 MHz, CDCl₃)



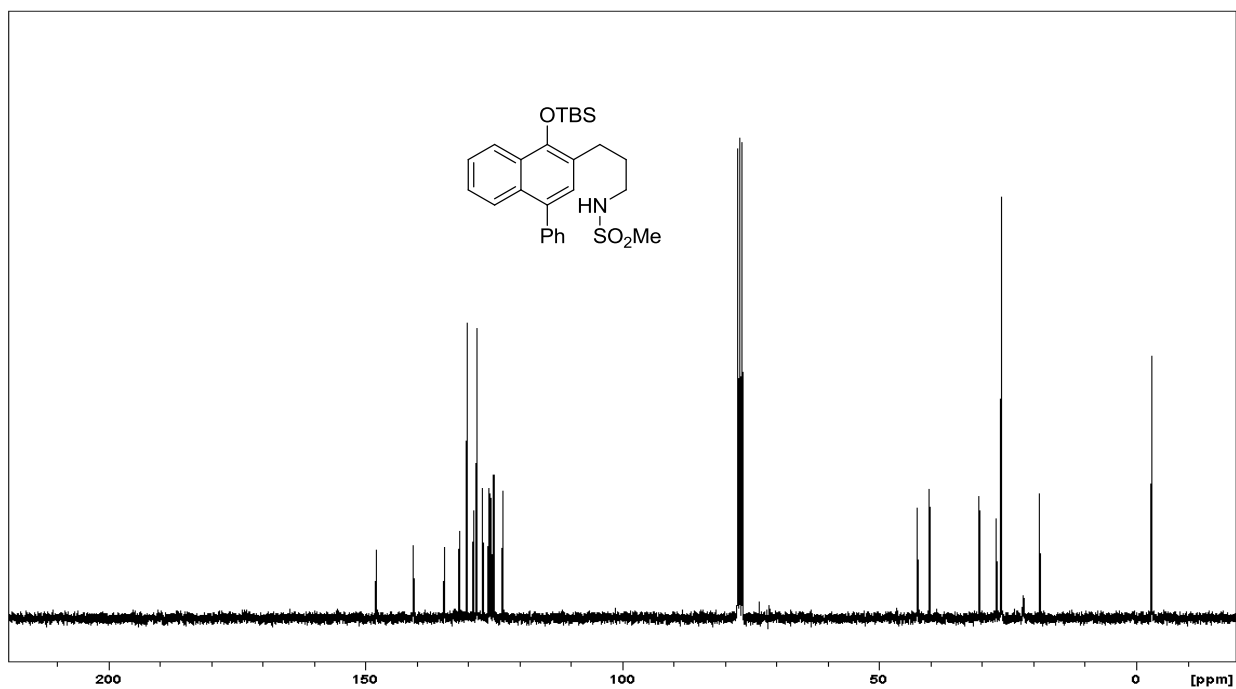
^1H NMR spectrum of 3.73, R = CH_2CF_3 , R' = H (300 MHz, CDCl_3)



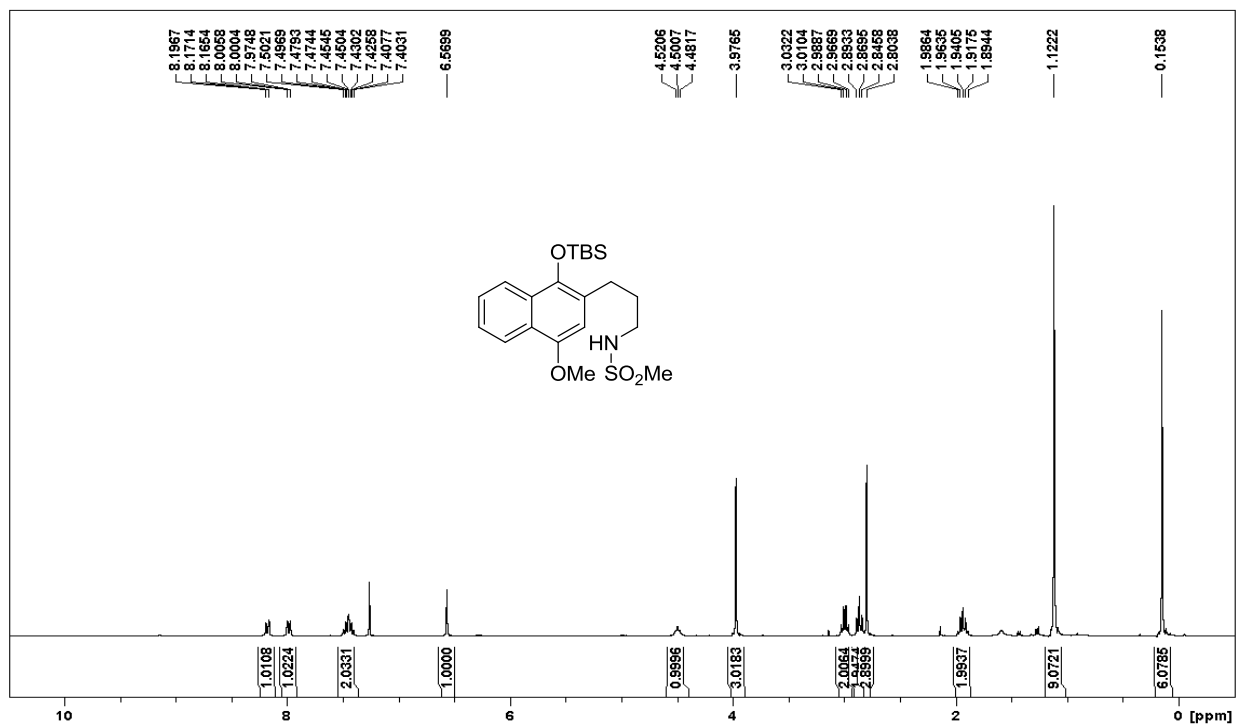
^{13}C NMR spectrum of 3.73, R = CH_2CF_3 , R' = H (75 MHz, CDCl_3)



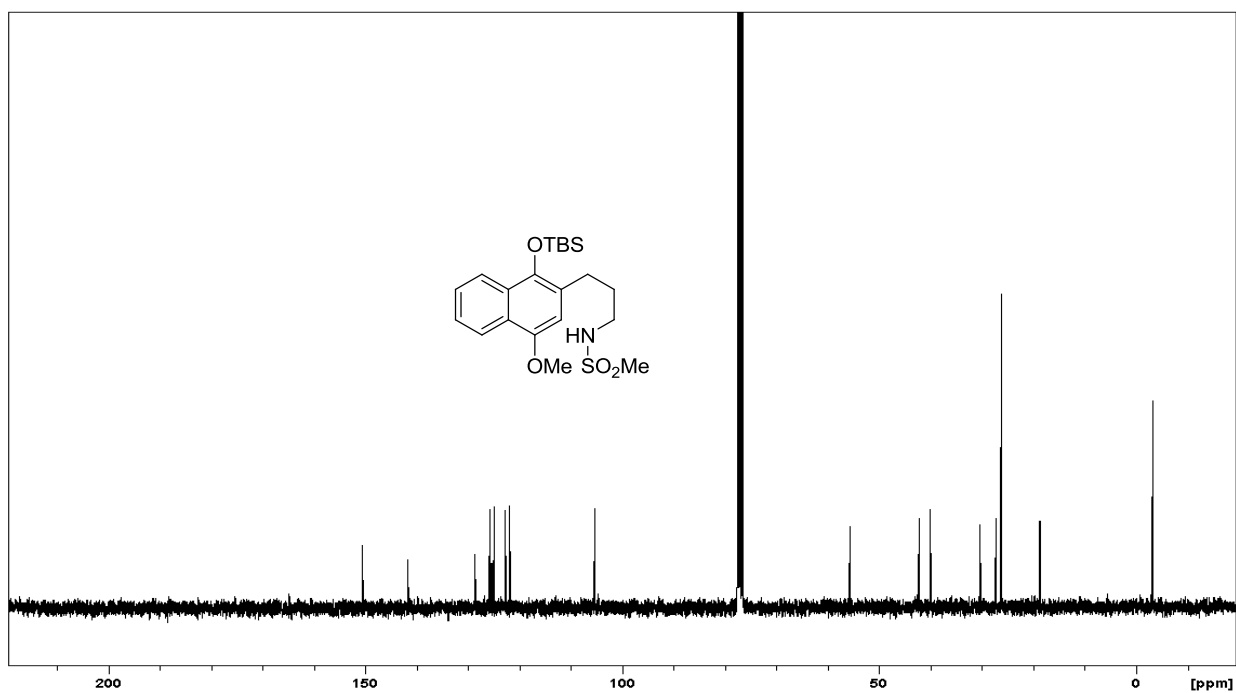
¹H NMR spectrum of 3.73, R = Me, R' = Ph (300 MHz, CDCl₃)



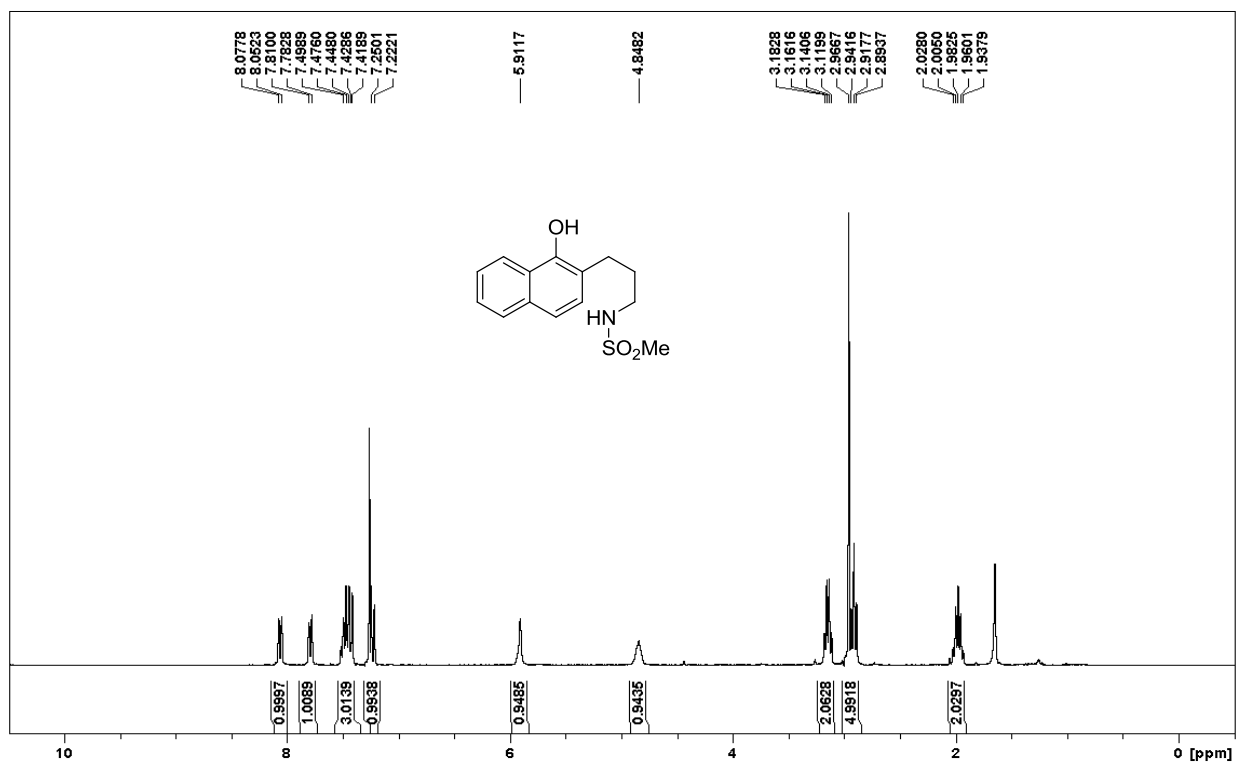
¹³C NMR spectrum of 3.73, R = Me, R' = Ph (75 MHz, CDCl₃)



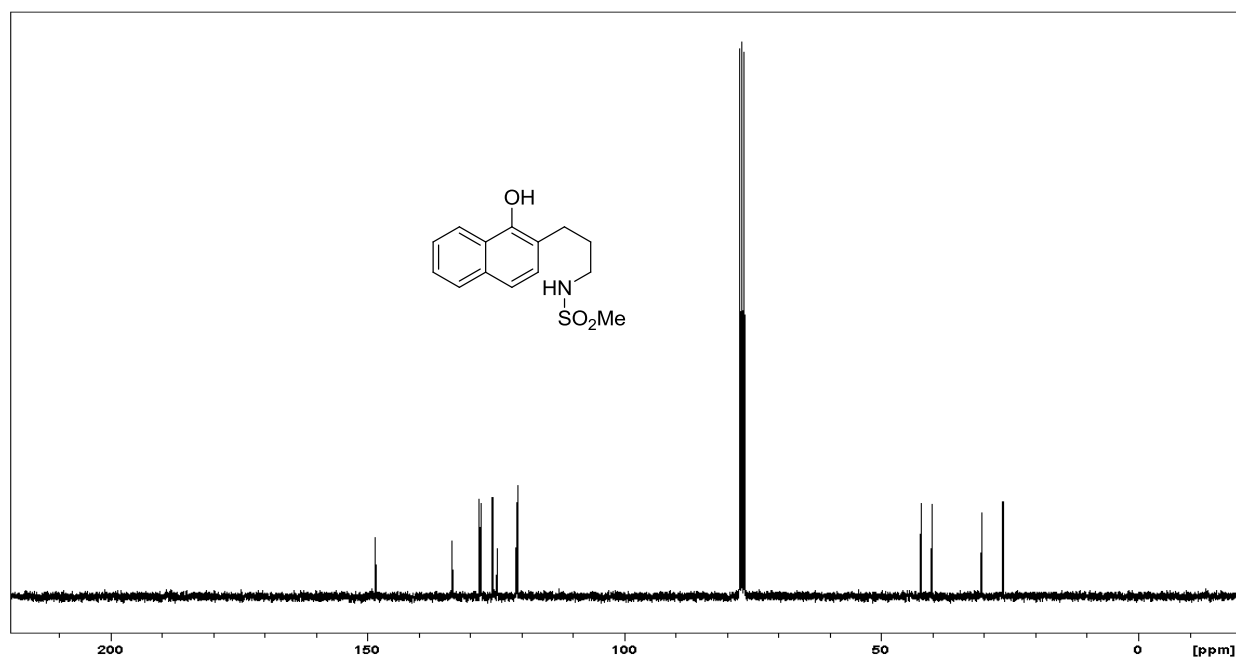
^1H NMR spectrum of 3.73, R = Me, R' = OMe (300 MHz, CDCl_3)



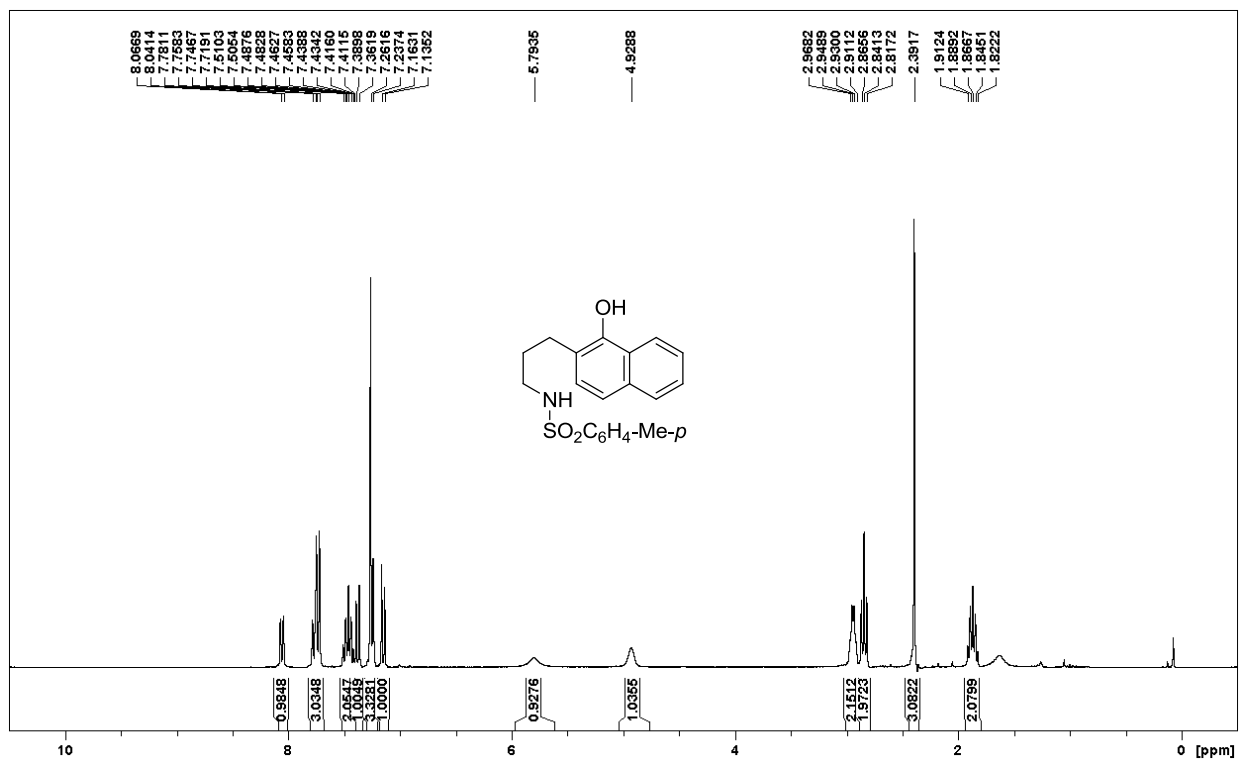
^{13}C NMR spectrum of 3.73, R = Me, R' = OMe (75 MHz, CDCl_3)



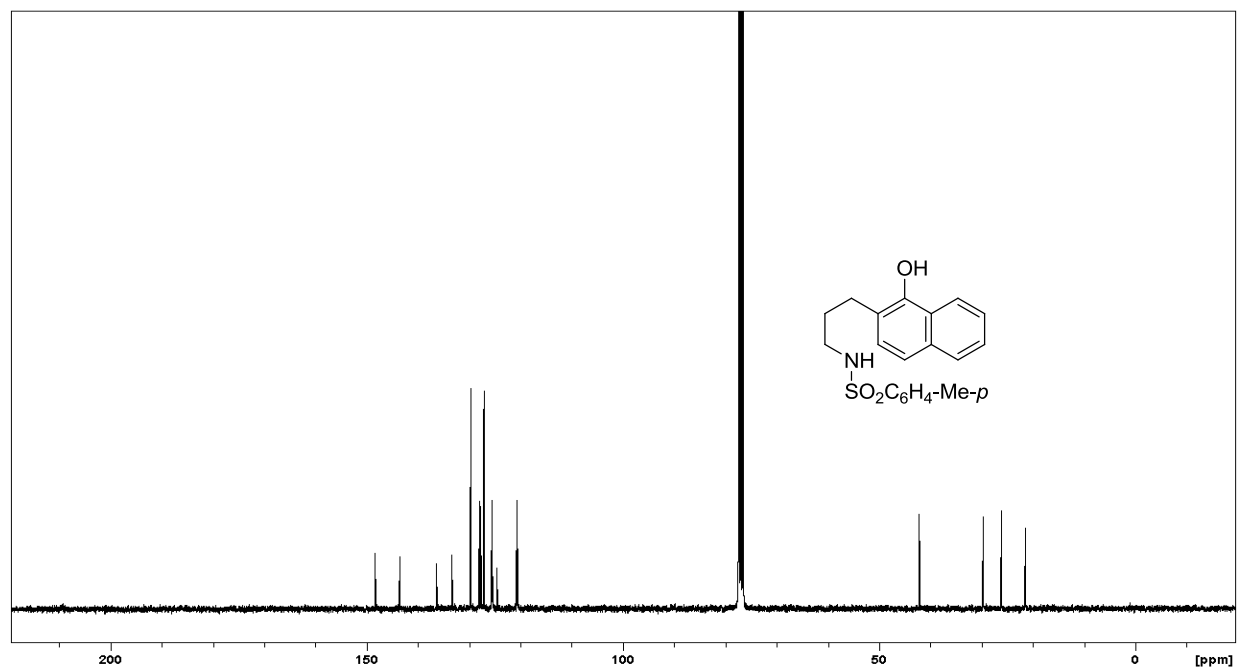
^1H NMR spectrum of 3.74, R = Me, R' = H (300 MHz, CDCl_3)



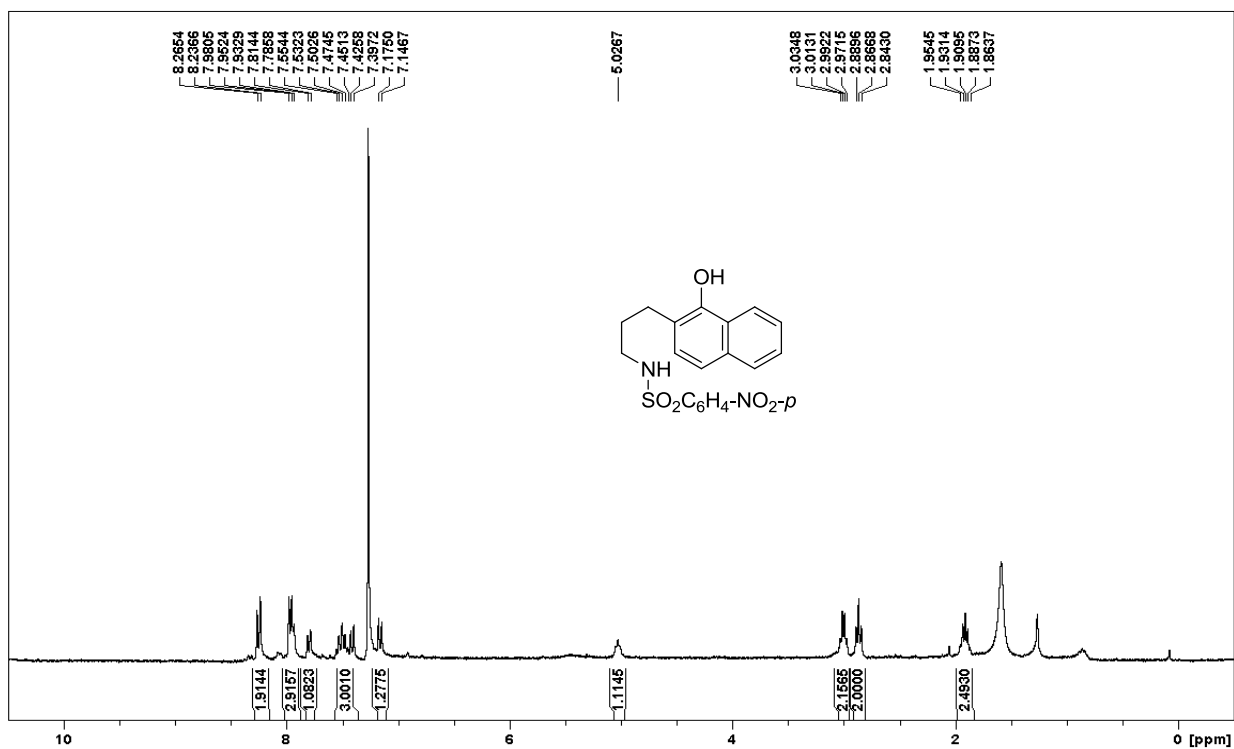
^{13}C NMR spectrum of 3.74, R = Me, R' = H (75 MHz, CDCl_3)



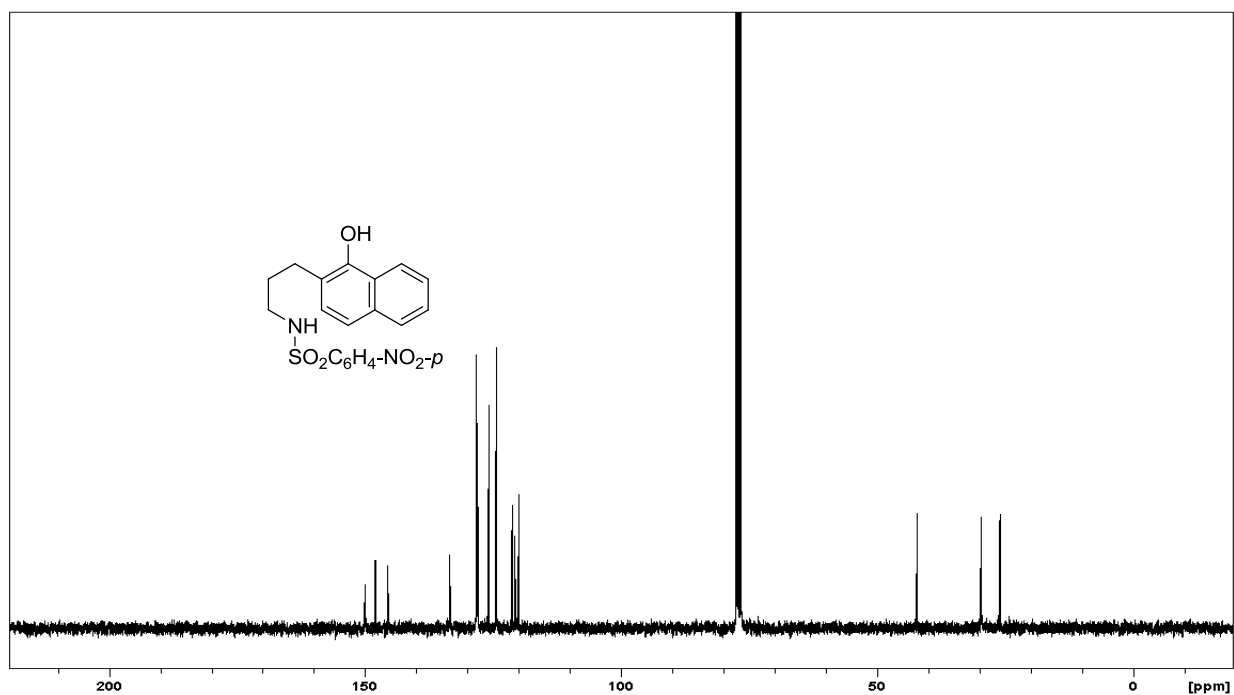
^1H NMR spectrum of 3.74, R = 4-Tol, R' = H (300 MHz, CDCl_3)



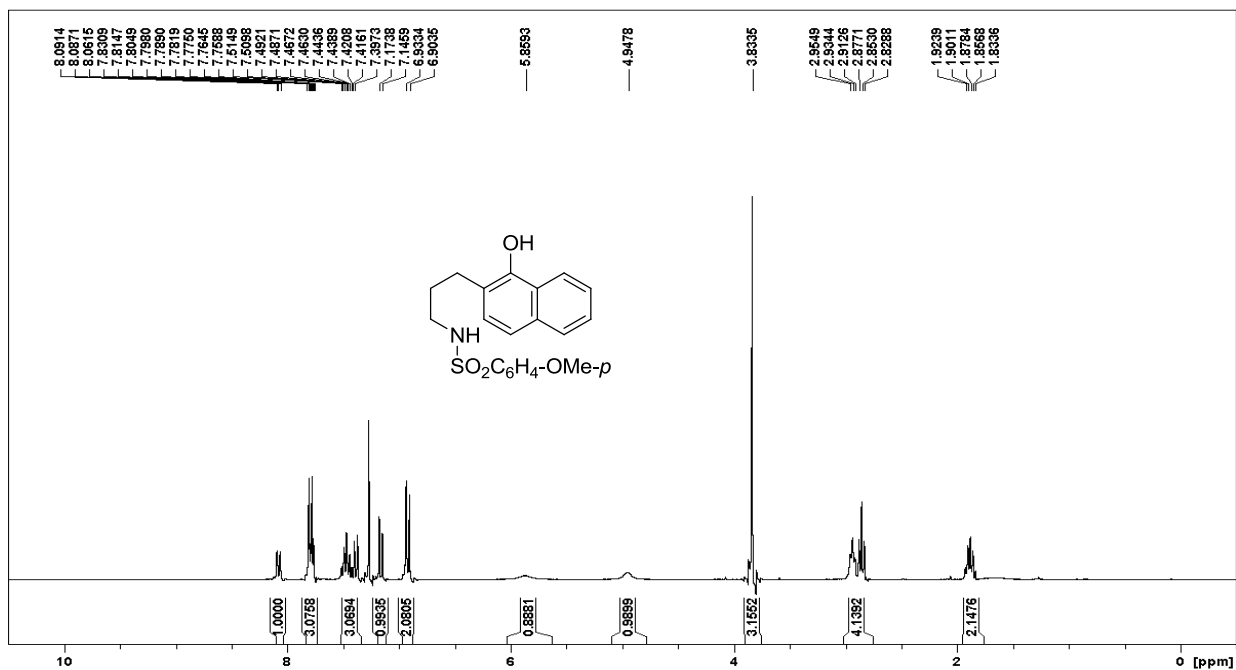
^{13}C NMR spectrum of 3.74, R = 4-Tol, R' = H (75 MHz, CDCl_3)



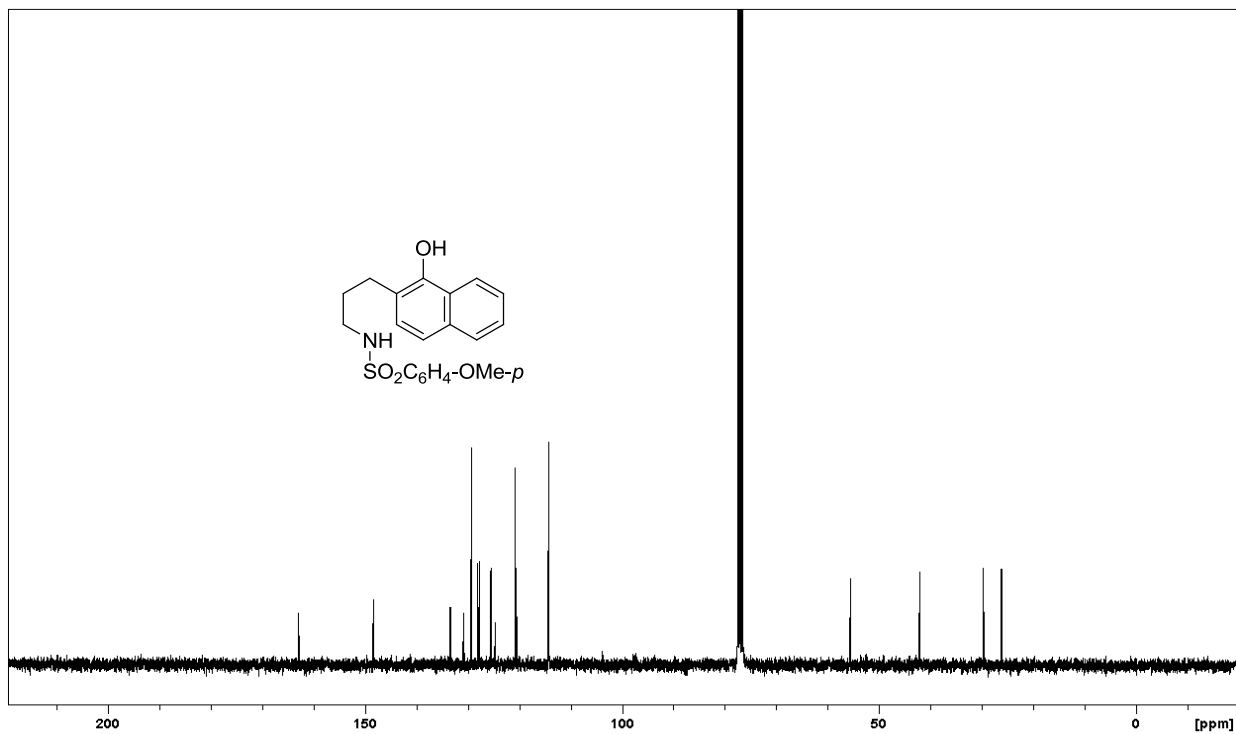
¹H NMR spectrum of 3.74, R = C₆H₄-NO₂-p, R' = H (300 MHz, CDCl₃)



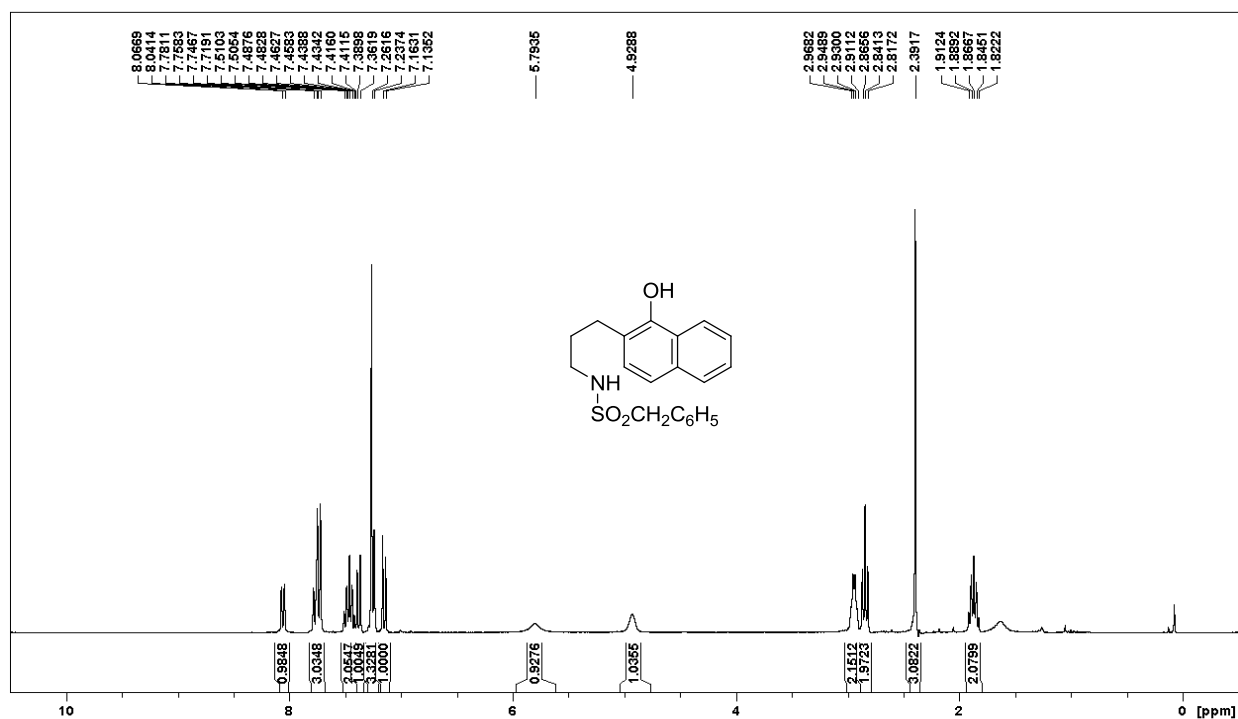
¹³C NMR spectrum of 3.74, R = C₆H₄-NO₂-p, R' = H (75 MHz, CDCl₃)



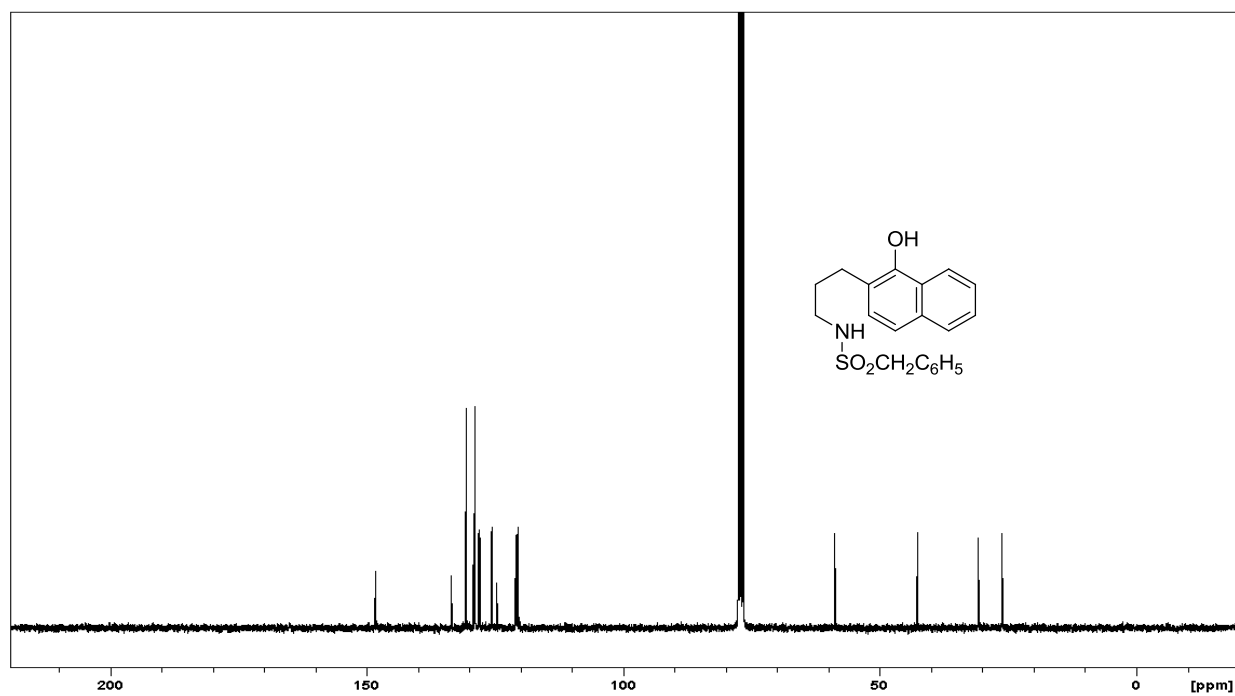
¹H NMR spectrum of R = C₆H₄-OMe-*p*, R' = H (300 MHz, CDCl₃)



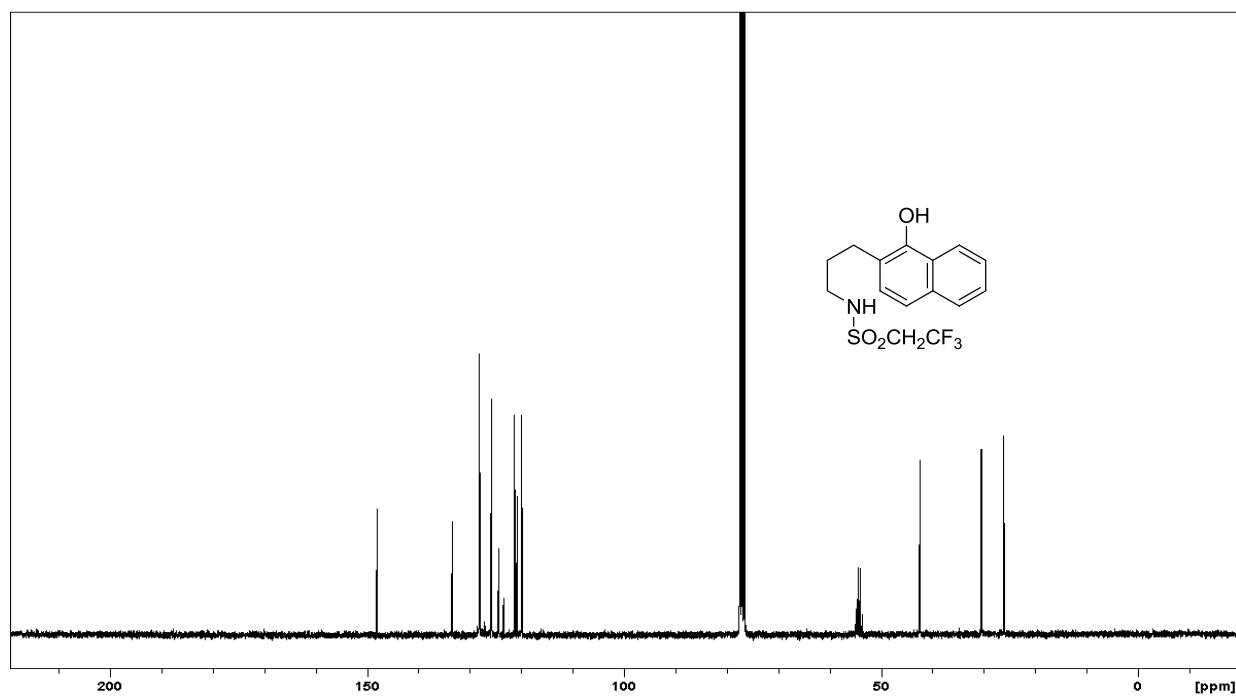
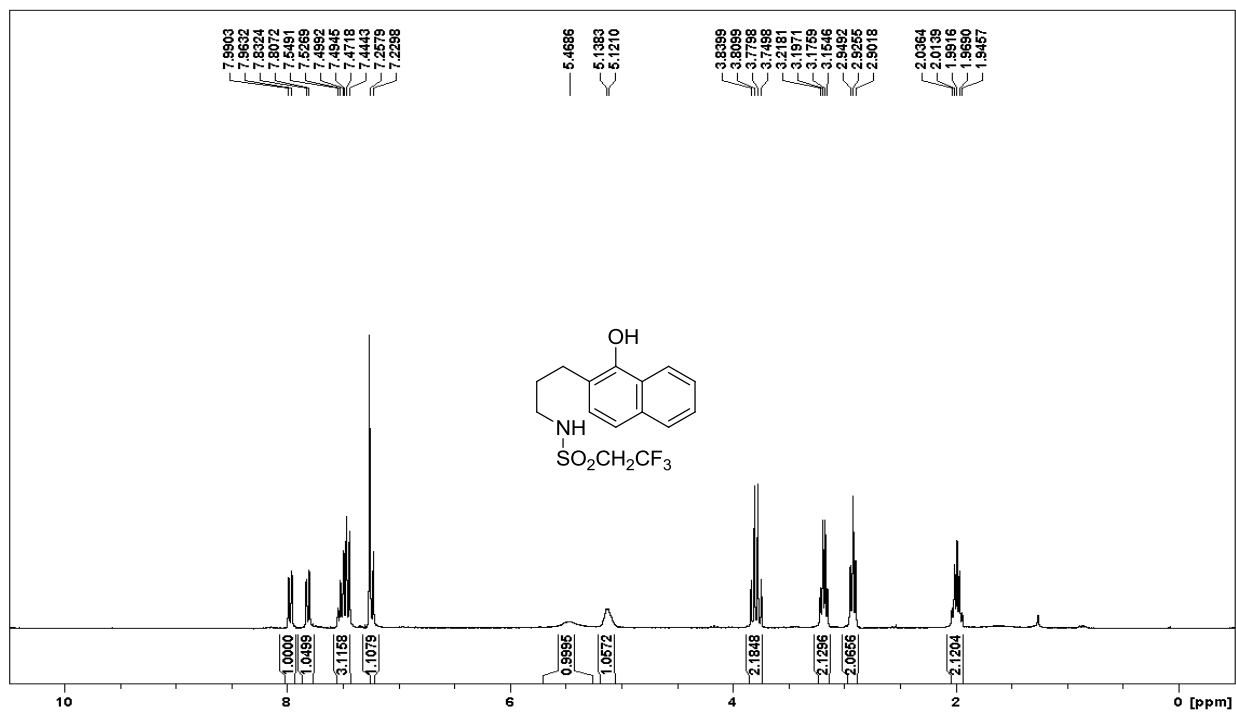
¹³C NMR spectrum of R = C₆H₄-OMe-*p*, R' = H (75 MHz, CDCl₃)

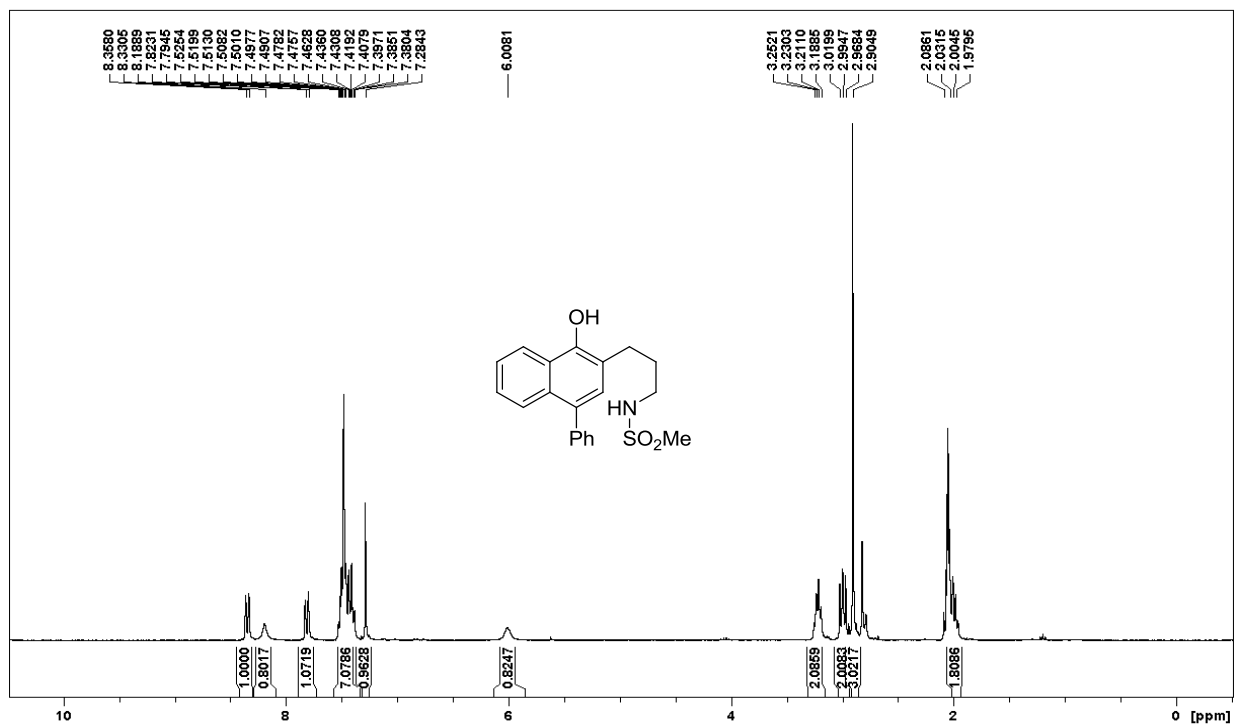


¹H NMR spectrum of R = Bn, R' = H (300 MHz, CDCl₃)

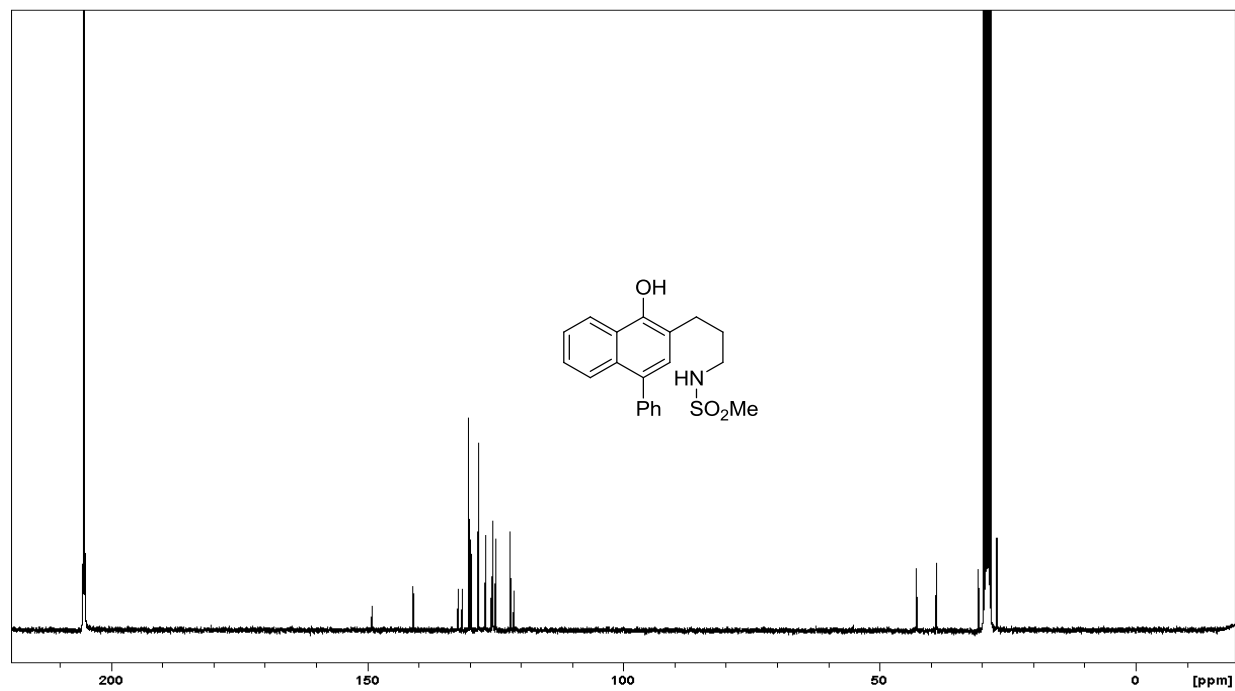


¹³C NMR spectrum of R = Bn, R' = H (75 MHz, CDCl₃)

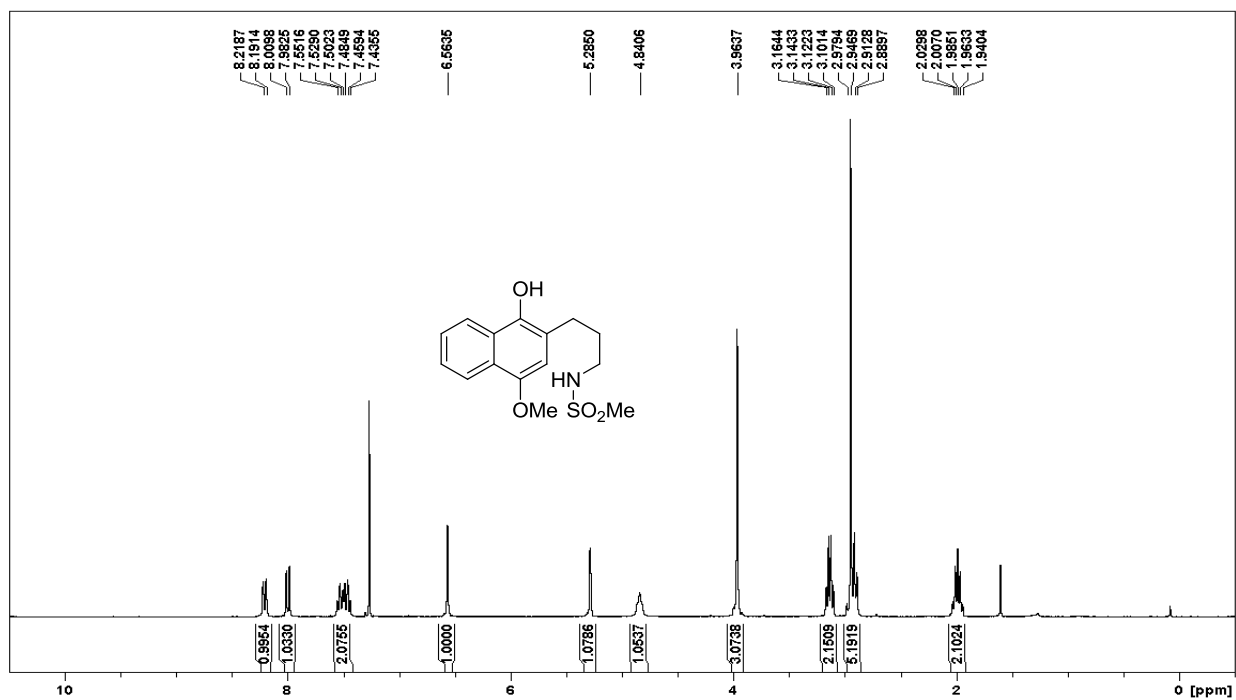




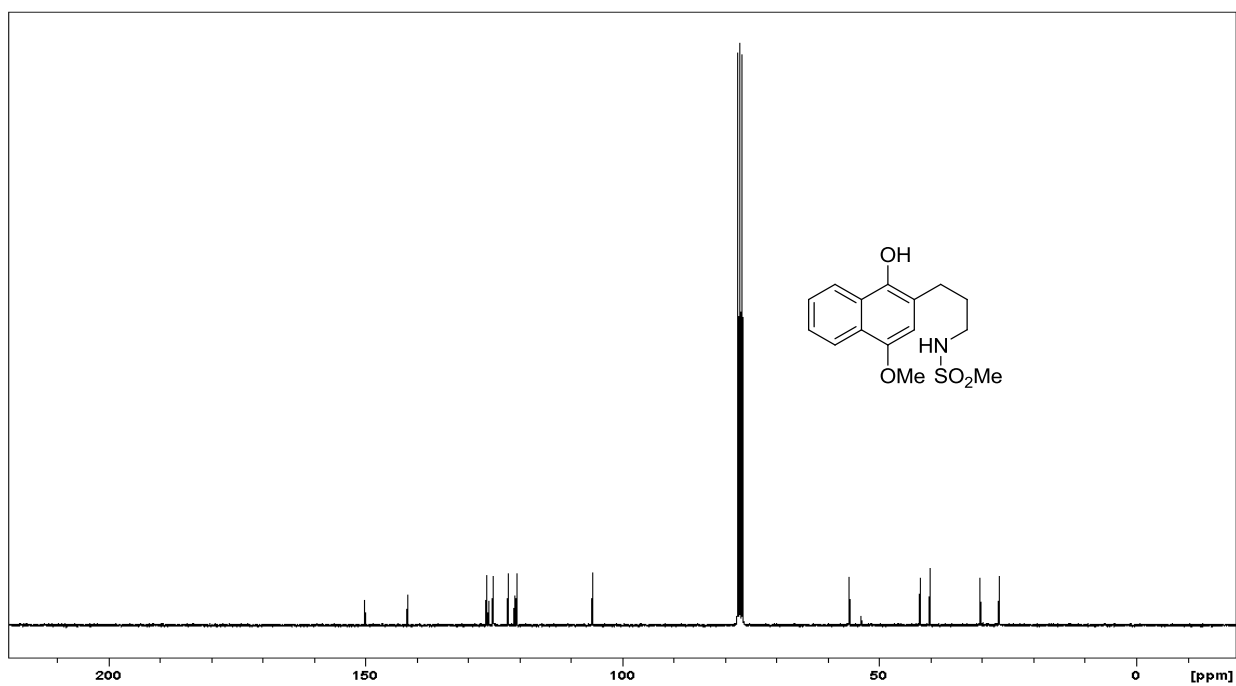
¹H NMR spectrum of R = Me, R' = Ph (300 MHz, acetone-*d*₆)



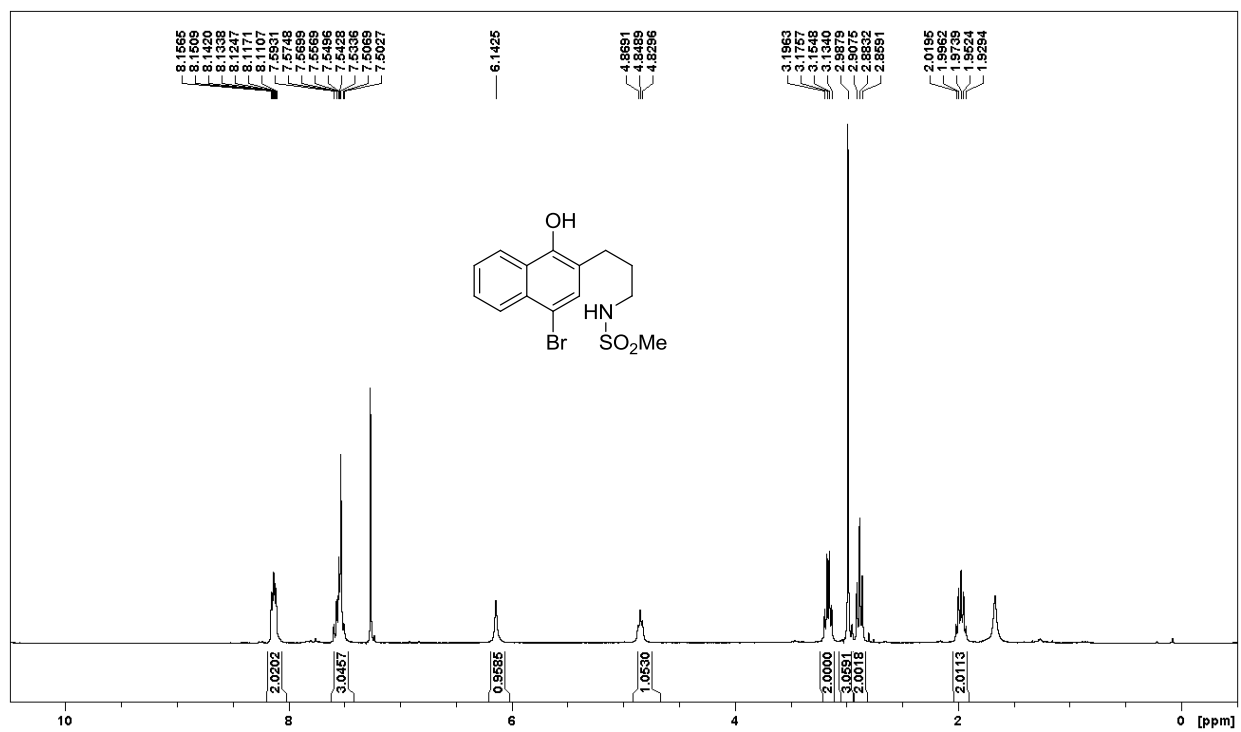
¹³C NMR spectrum of R = Me, R' = Ph (75 MHz, acetone-*d*₆)



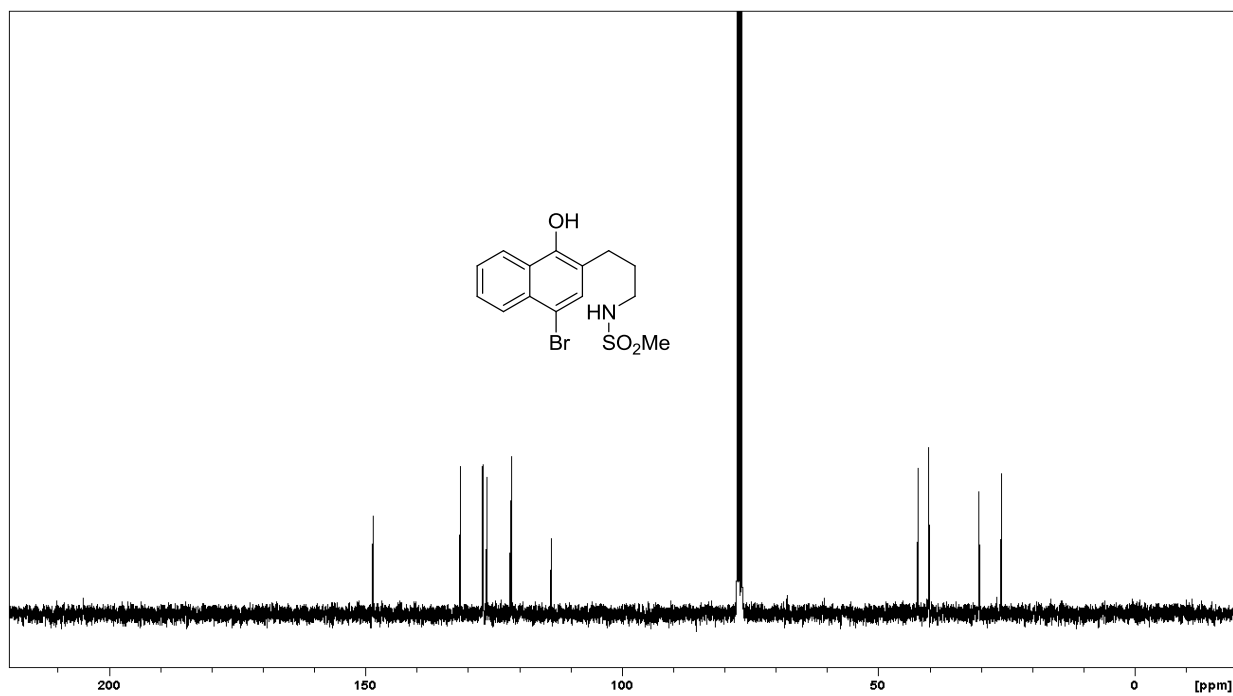
^1H NMR spectrum of R = Me, R' = OMe (300 MHz, CDCl_3)



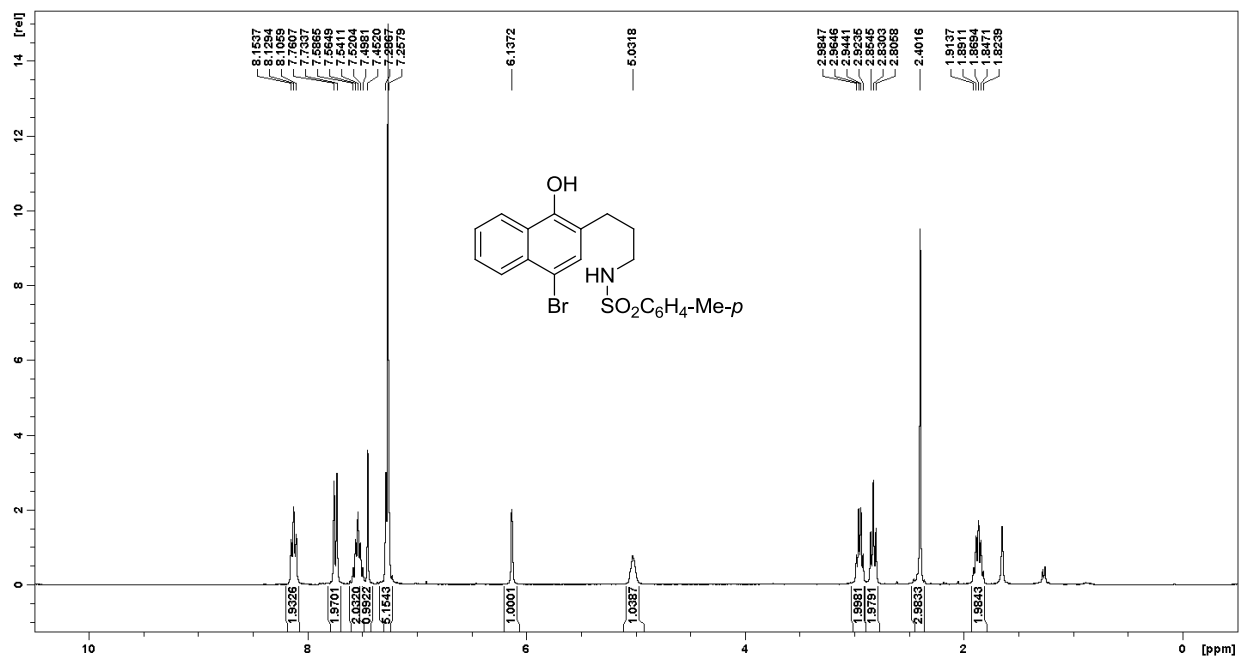
^{13}C NMR spectrum of R = Me, R' = OMe (75 MHz, CDCl_3)



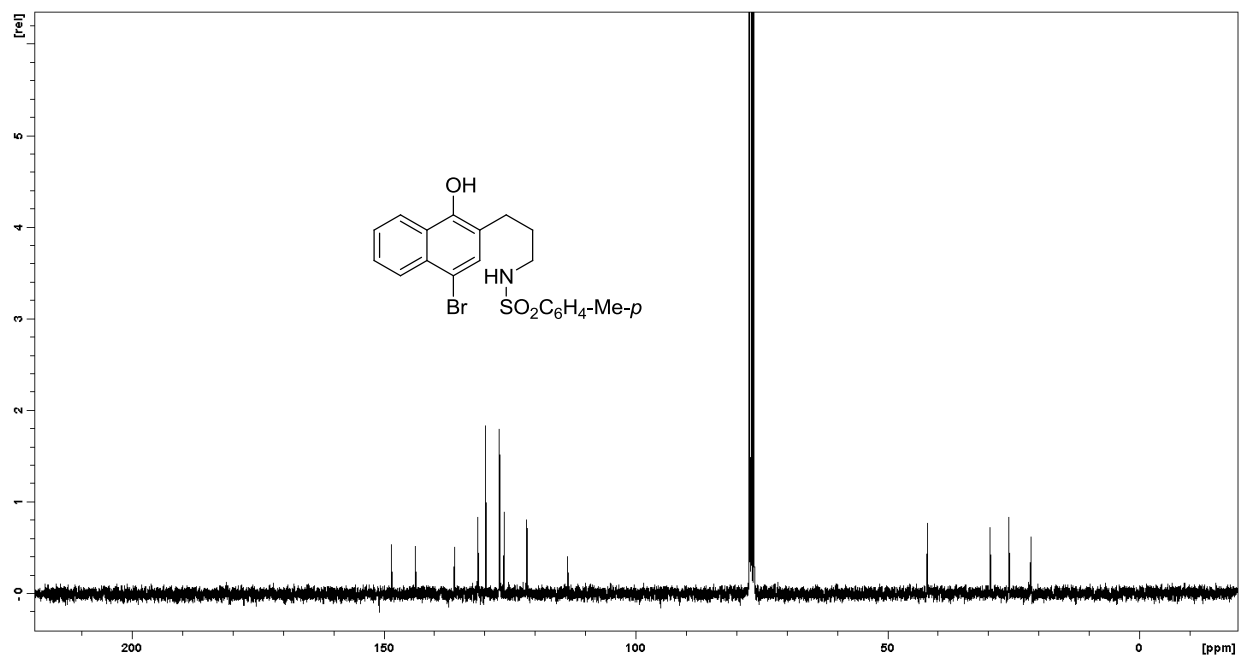
¹H NMR spectrum of 3.76, R = Me (300 MHz, CDCl₃)



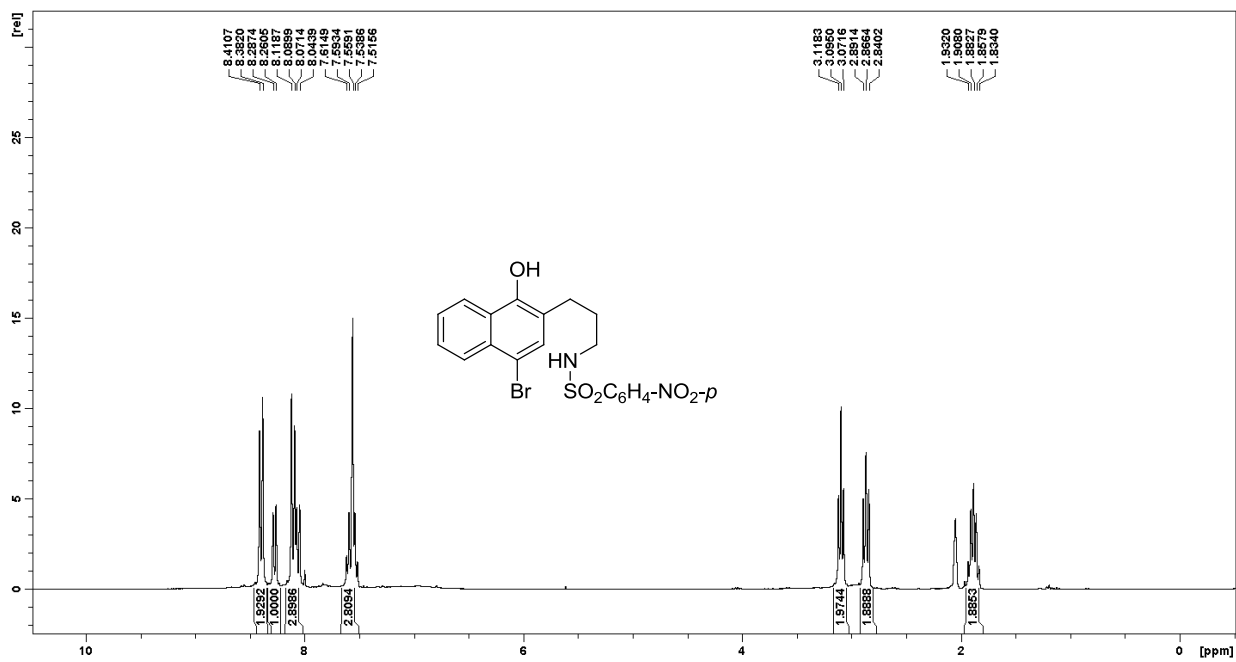
¹³C NMR spectrum of 3.76, R = Me (75 MHz, CDCl₃)



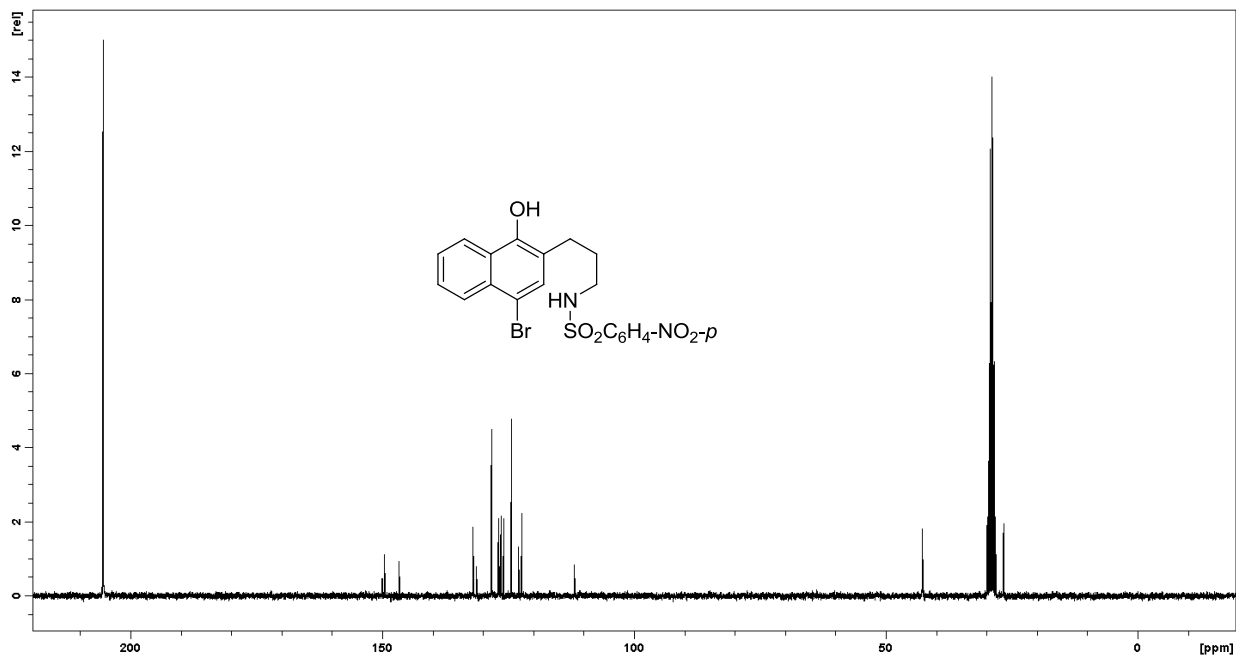
¹H NMR spectrum of 3.76, R = 4-Tol (300 MHz, CDCl₃)



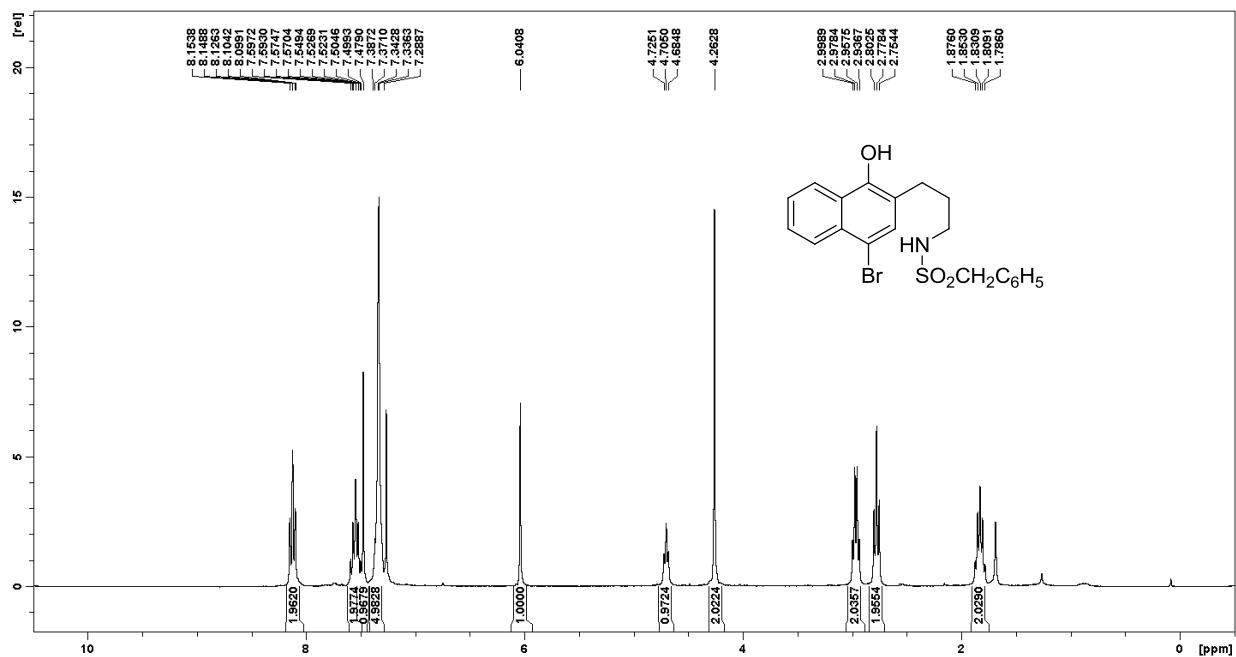
¹³C NMR spectrum of 3.76, R = 4-Tol (75 MHz, CDCl₃)



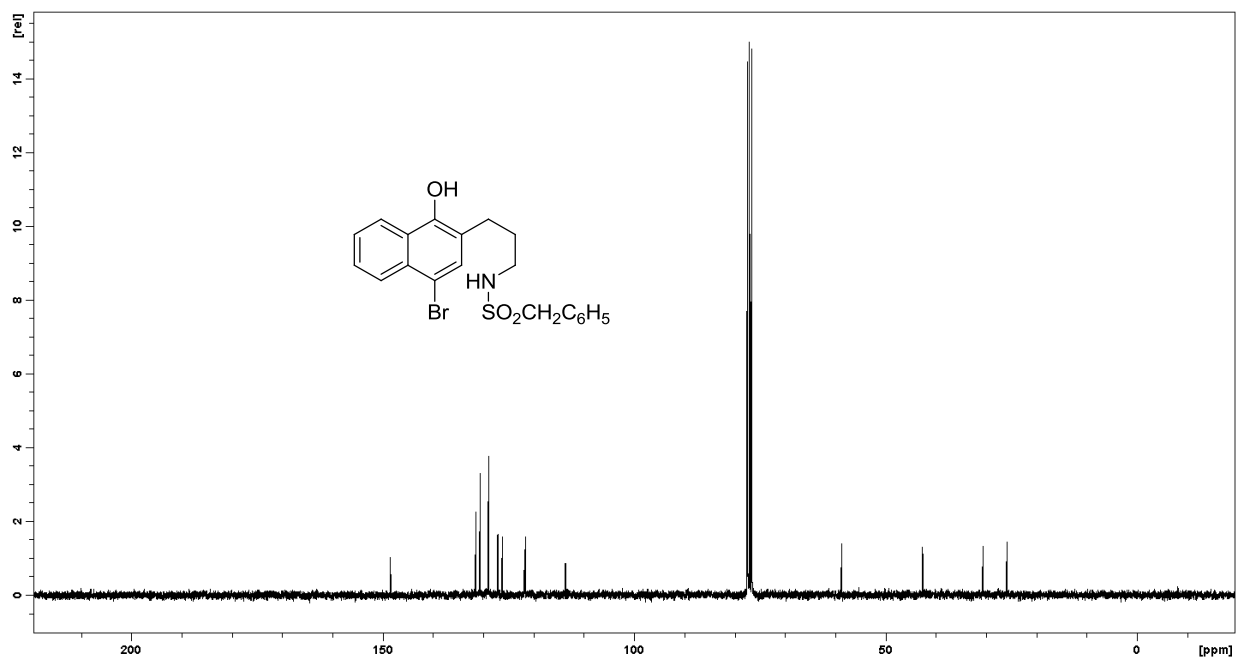
¹H NMR spectrum of 3.76, R = C₆H₄-NO₂-p (300 MHz, acetone-d₆)



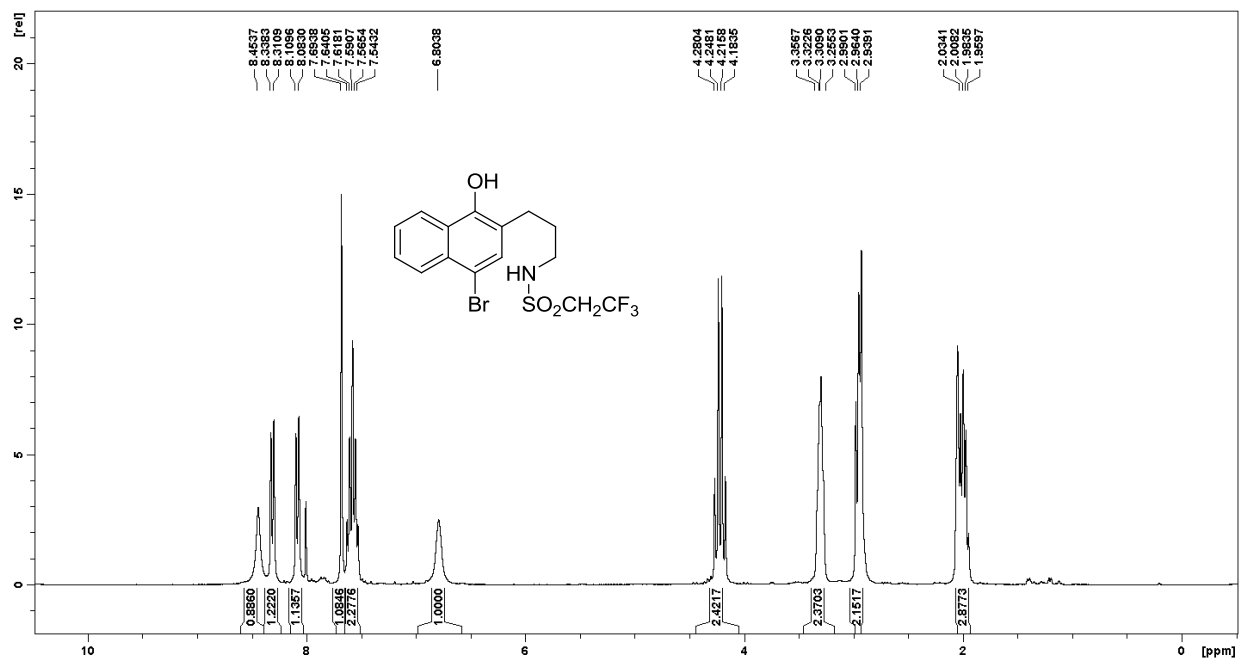
¹³C NMR spectrum of 3.76, R = C₆H₄-NO₂-p (75 MHz, acetone-d₆)



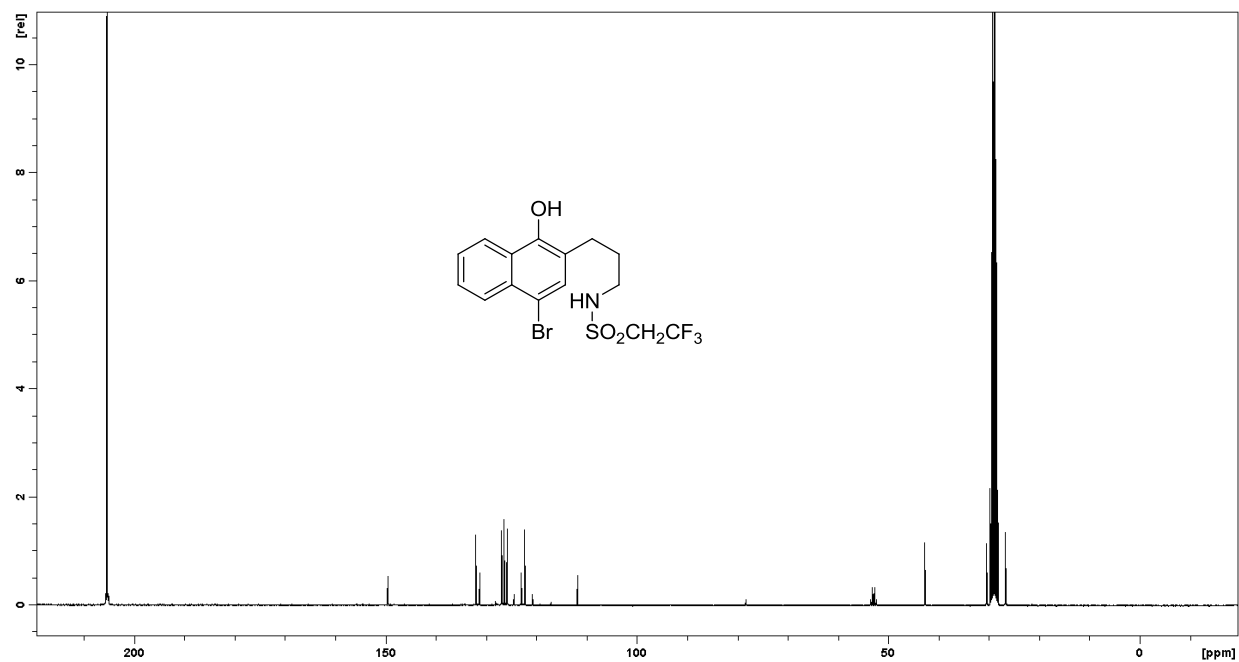
¹H NMR spectrum of 3.76, R = Bn (300 MHz, CDCl₃)



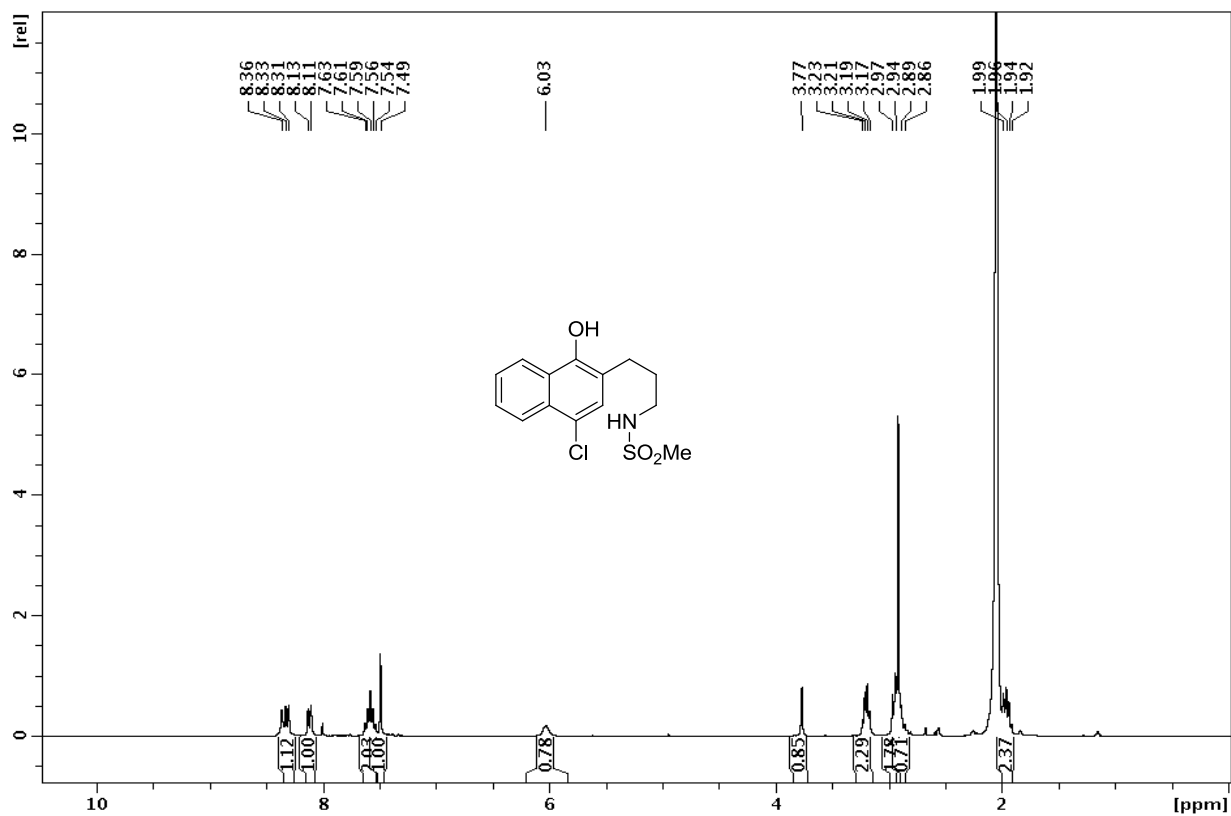
¹³C NMR spectrum of 3.76, R = Bn (75 MHz, CDCl₃)



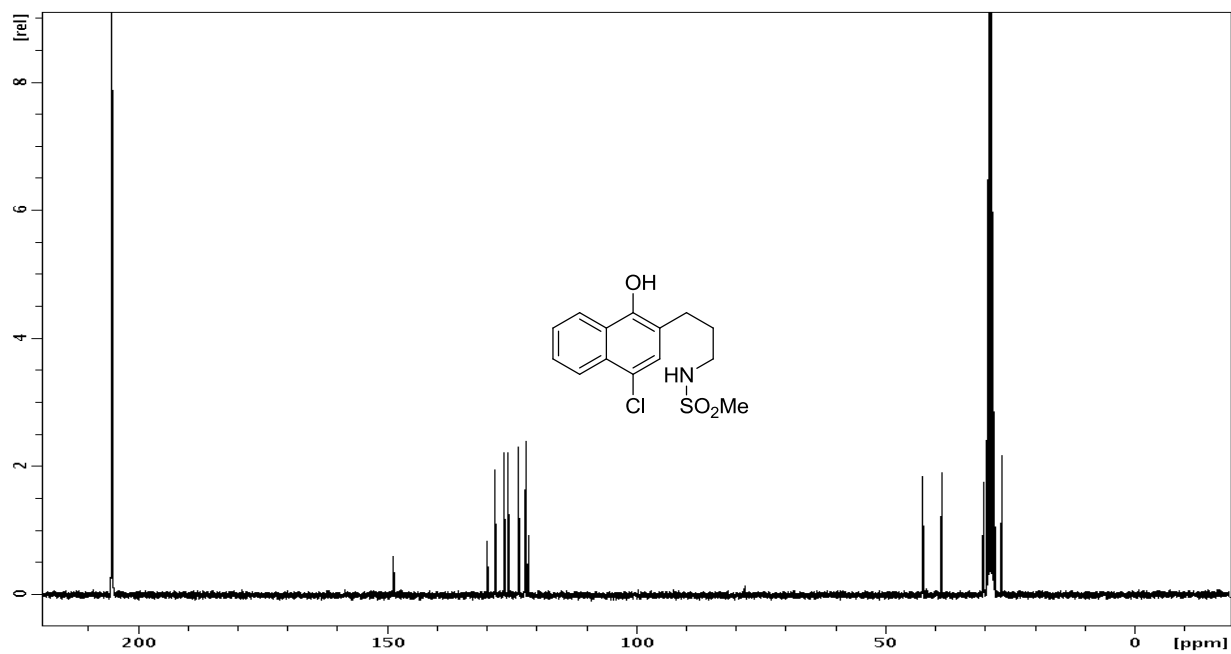
¹H NMR spectrum of 3.76, R = CH₂CF₃ (300 MHz, acetone-*d*₆)



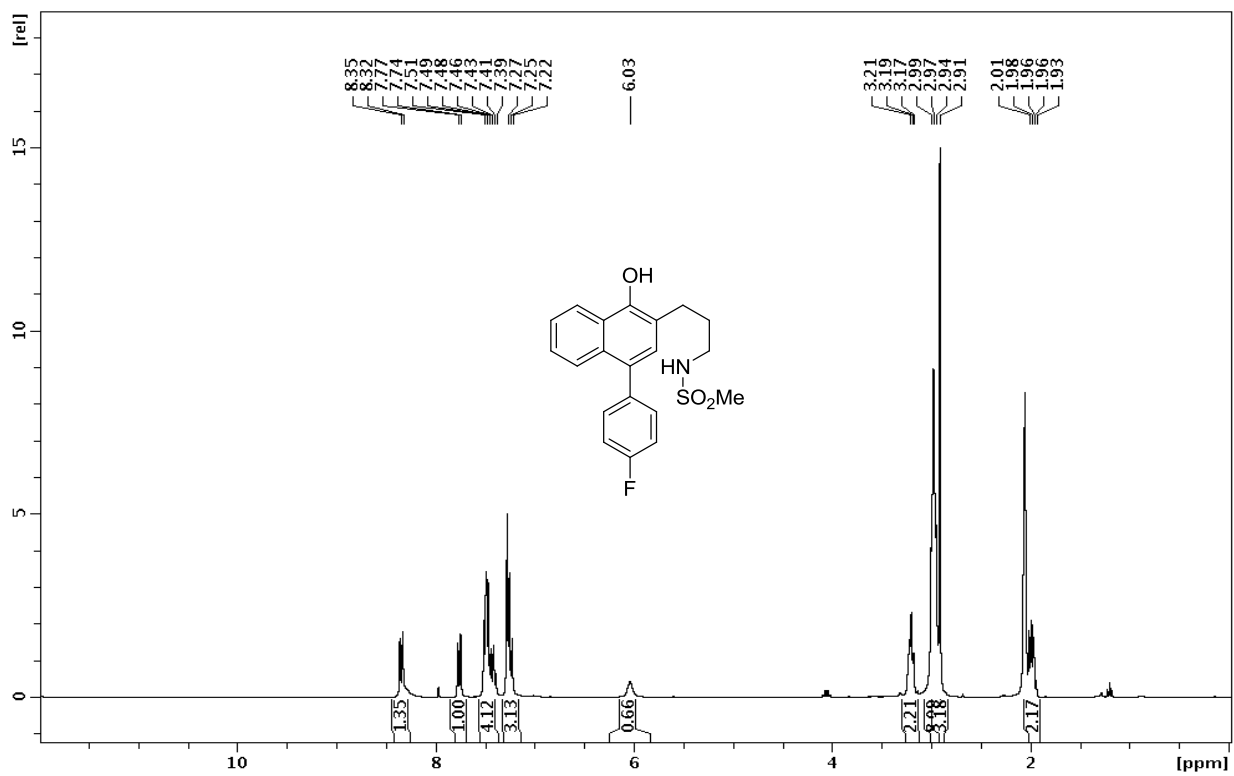
¹³C NMR spectrum of 3.76, R = CH₂CF₃ (75 MHz, acetone-*d*₆)



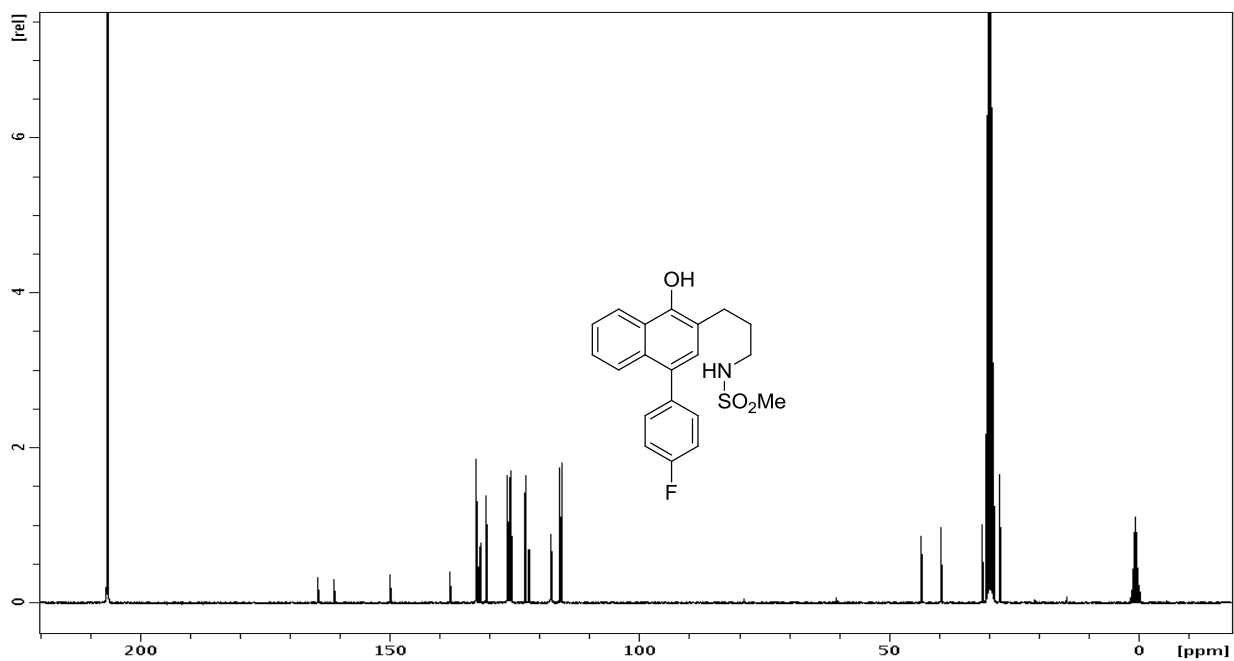
¹H NMR spectrum of 3.77, R = Me (300 MHz, acetone-*d*₆)



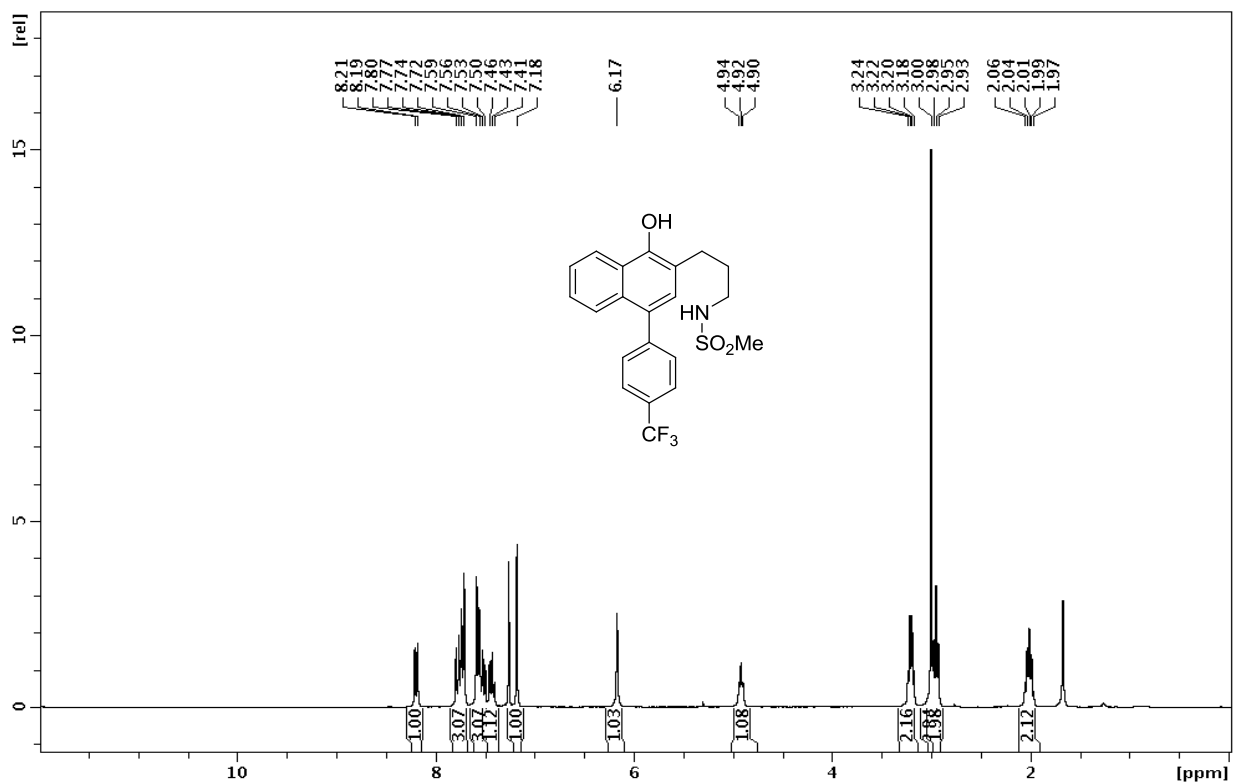
¹³C NMR spectrum of 3.77, R = Me (75 MHz, acetone-*d*₆)



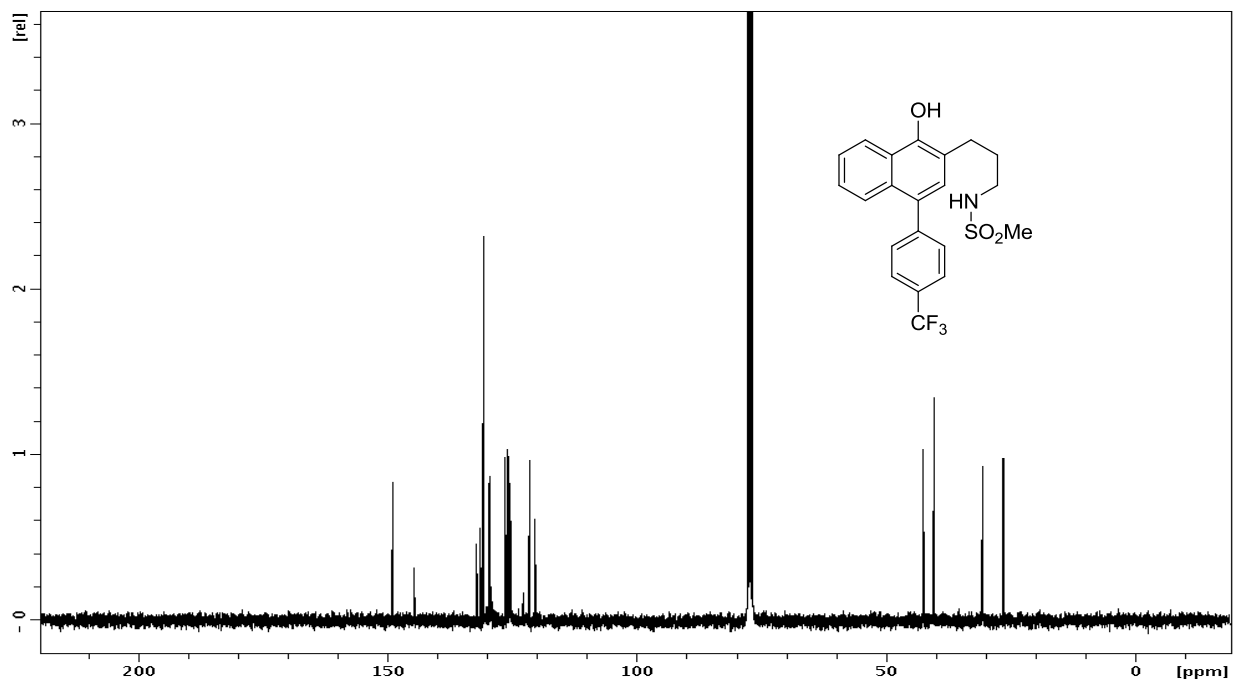
^1H NMR spectrum of 3.78, Ar = C₆H₄-F-*p* (300 MHz, acetone-*d*₆)



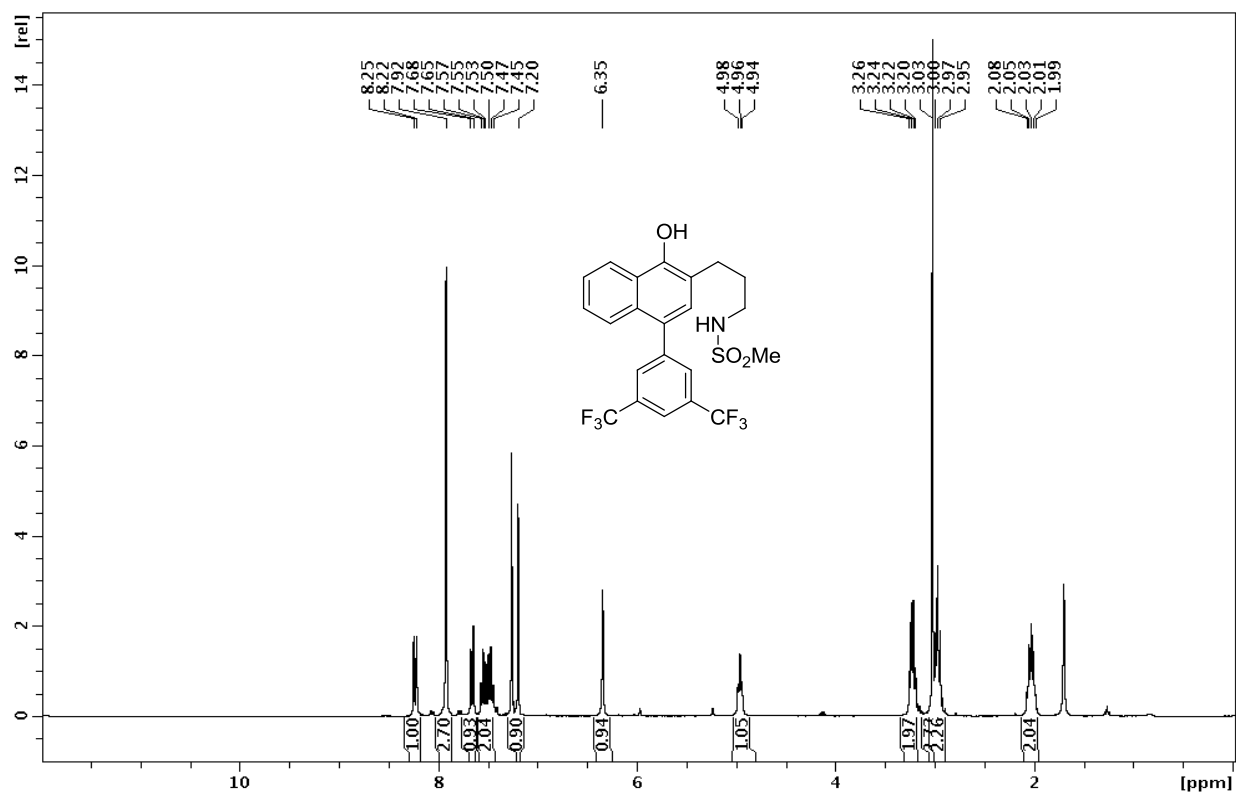
^{13}C NMR spectrum of 3.78, Ar = C₆H₄-F-*p* (75 MHz, acetone-*d*₆)



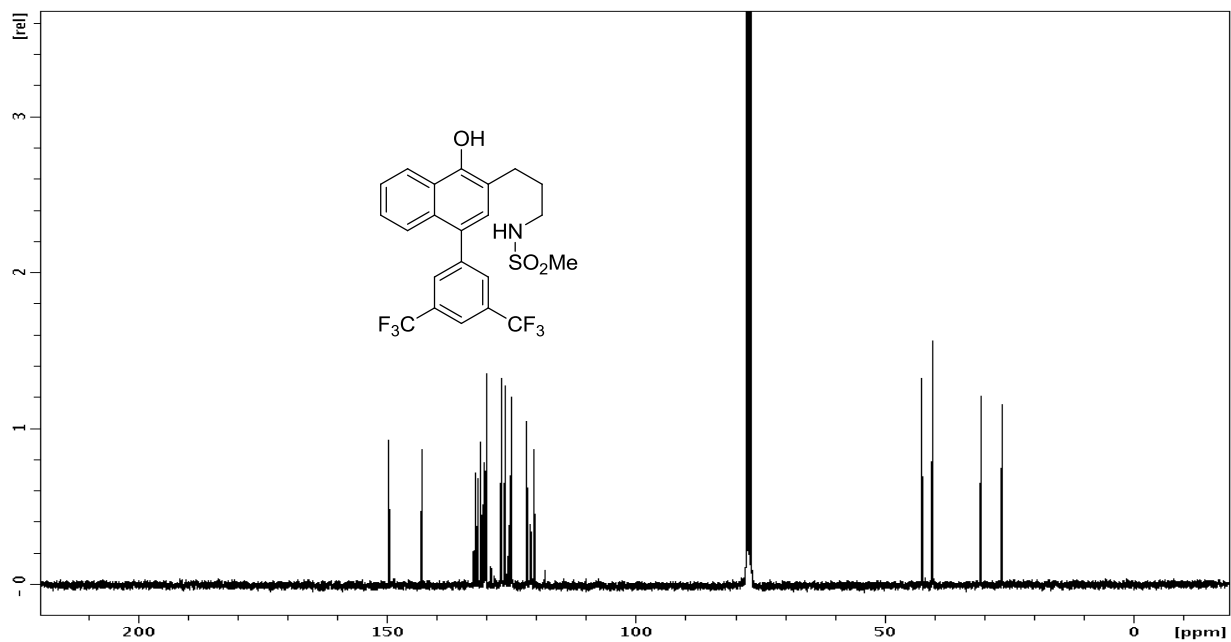
¹H NMR spectrum of 3.78, Ar = C₆H₄-CF₃-*p* (300 MHz, CDCl₃)



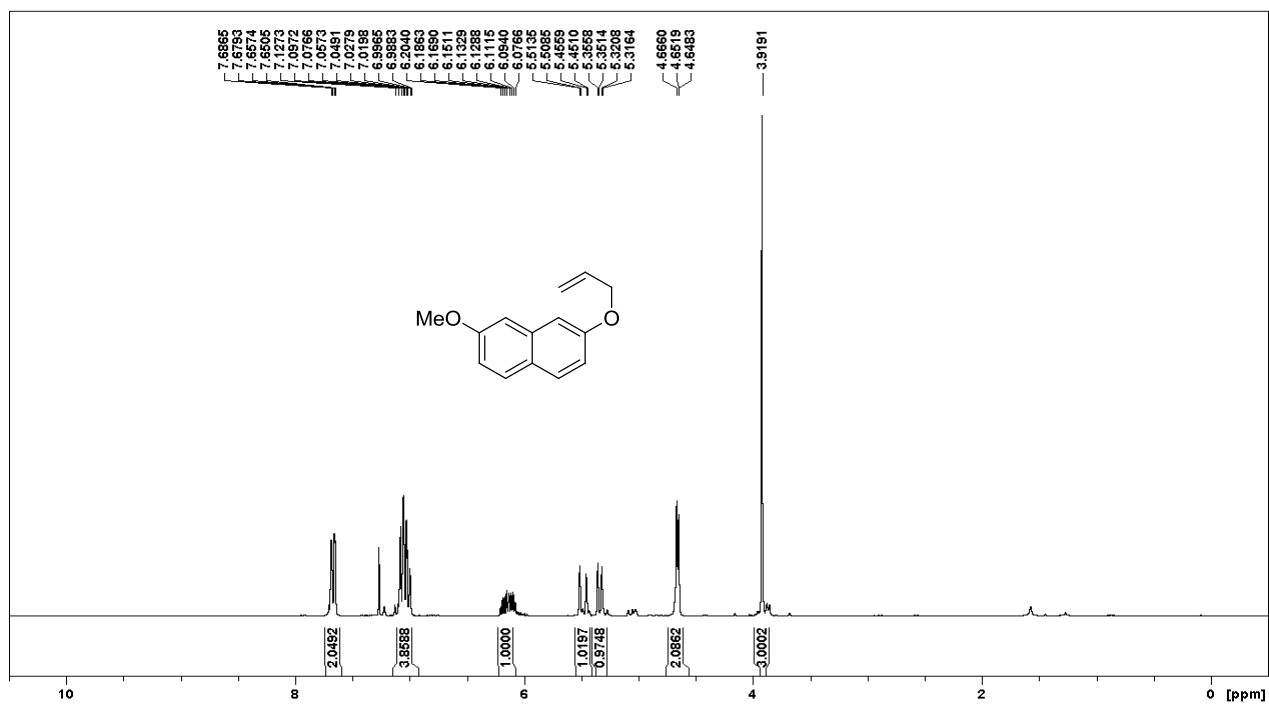
¹³C NMR spectrum of 3.78, Ar = C₆H₄-CF₃-*p* (75 MHz, CDCl₃)



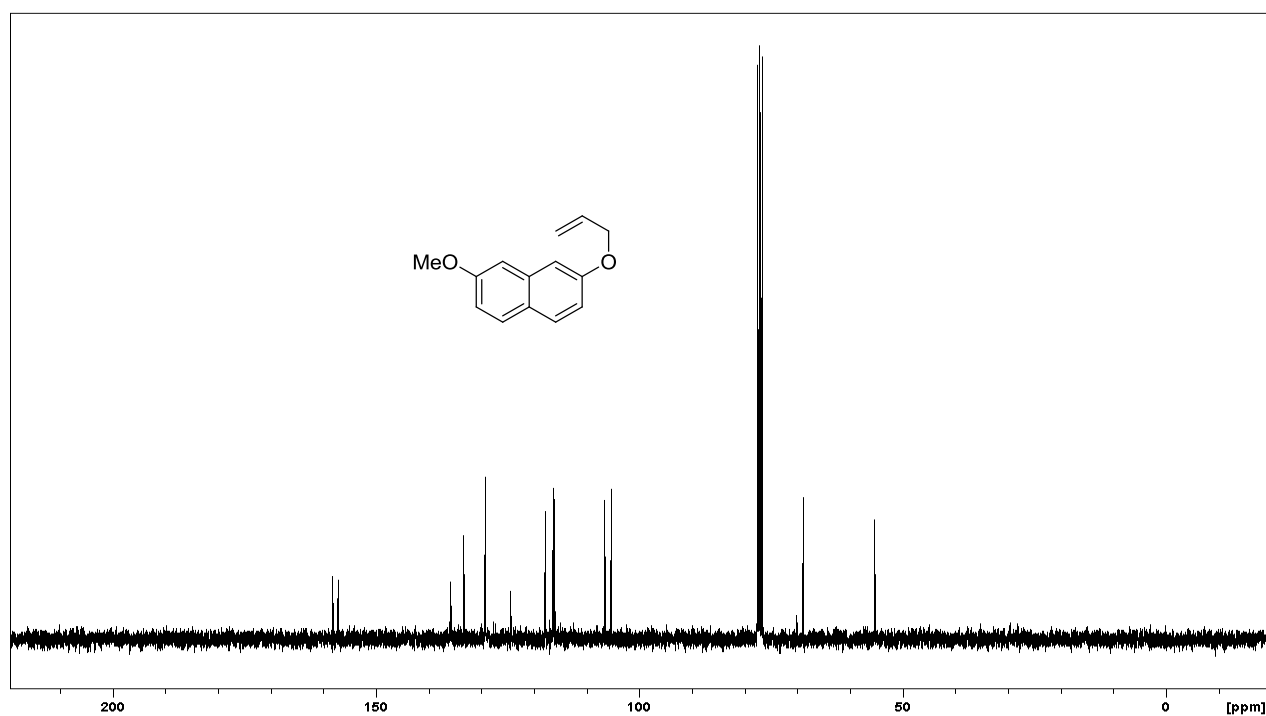
^1H NMR spectrum of 3.78, Ar = 3,5-bis(CF_3) $_2\text{C}_6\text{H}_3$ (300 MHz, CDCl_3)



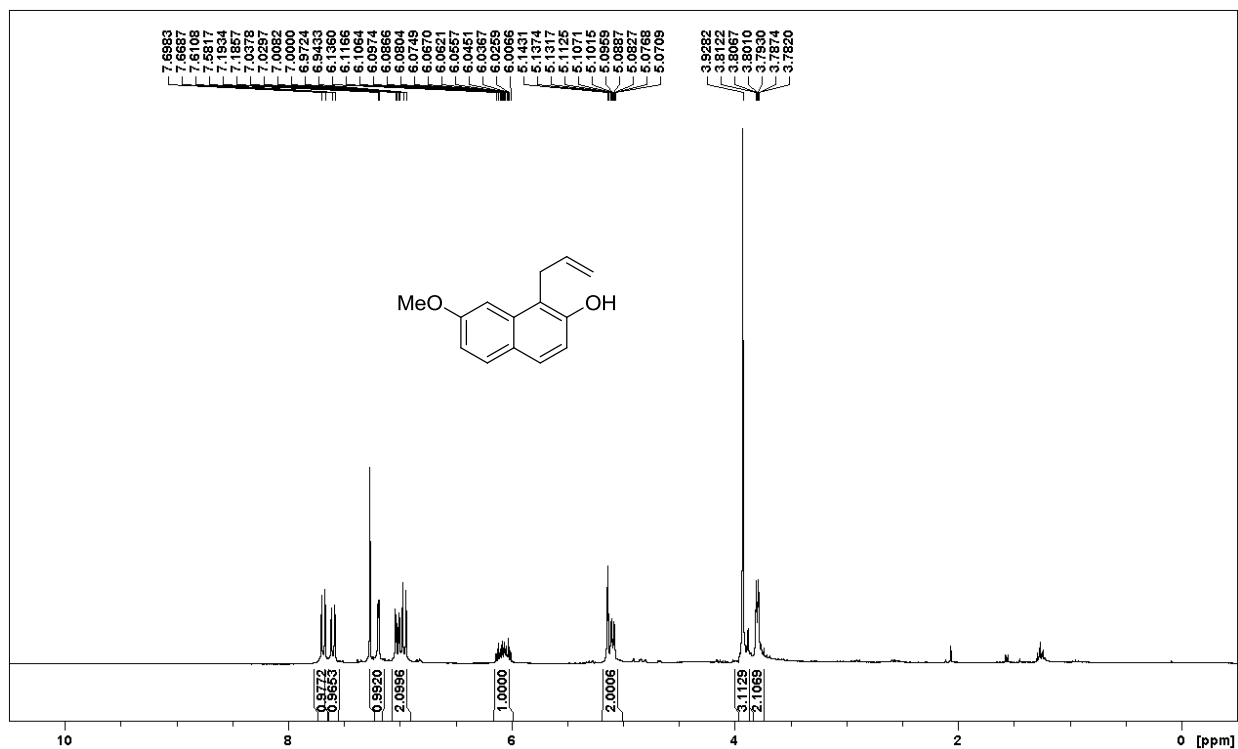
^{13}C NMR spectrum of 3.78, Ar = 3,5-bis(CF_3) $_2\text{C}_6\text{H}_3$ (75 MHz, CDCl_3)



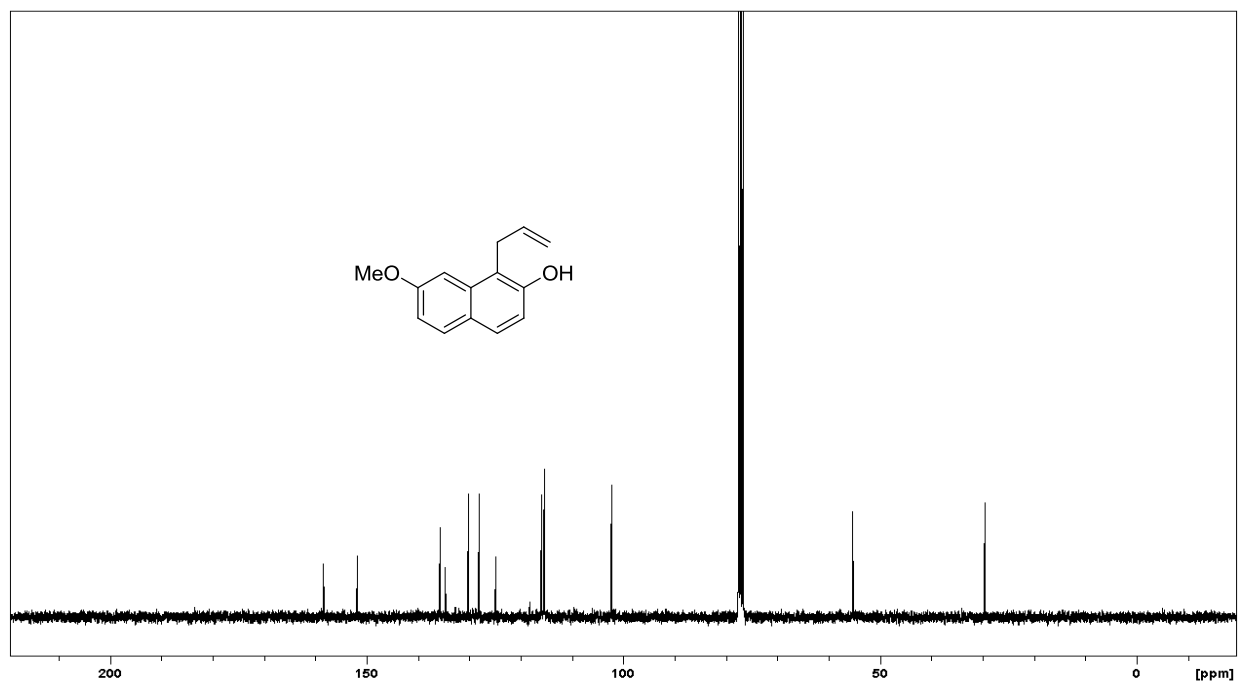
¹H NMR spectrum of crude 3.80, R = OMe (300 MHz, CDCl₃)



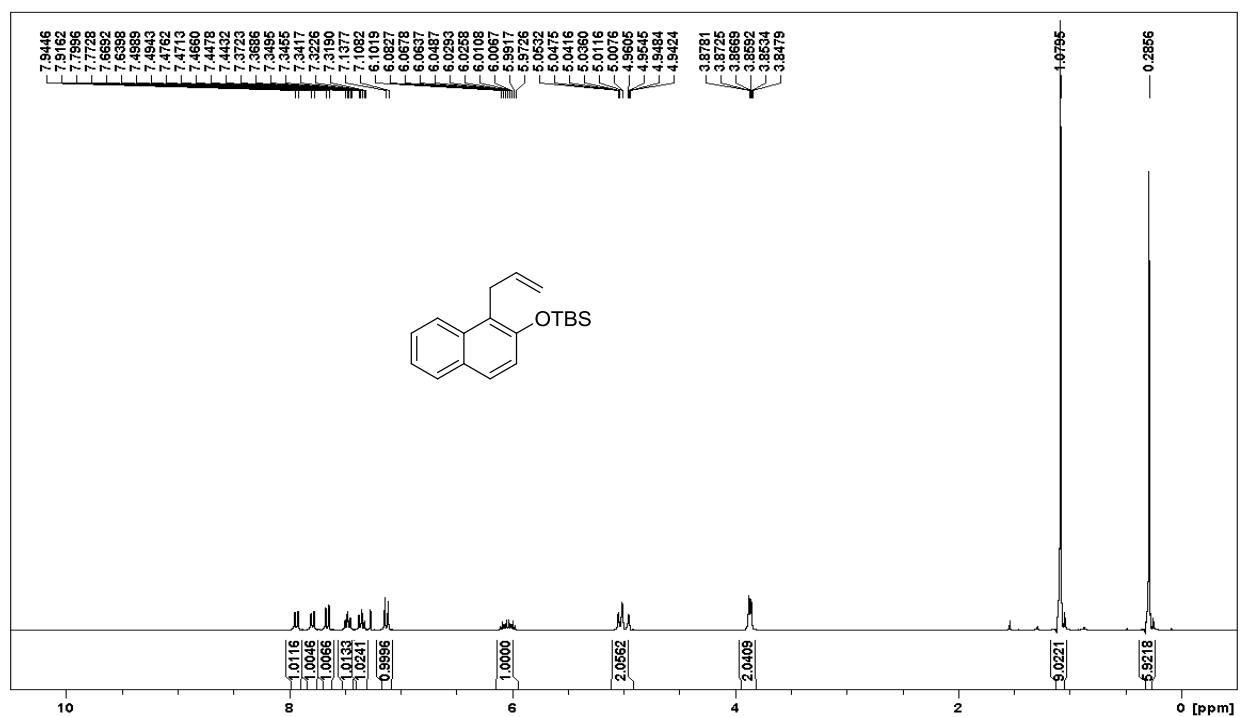
¹³C NMR spectrum of crude 3.80, R = OMe (75 MHz, CDCl₃)



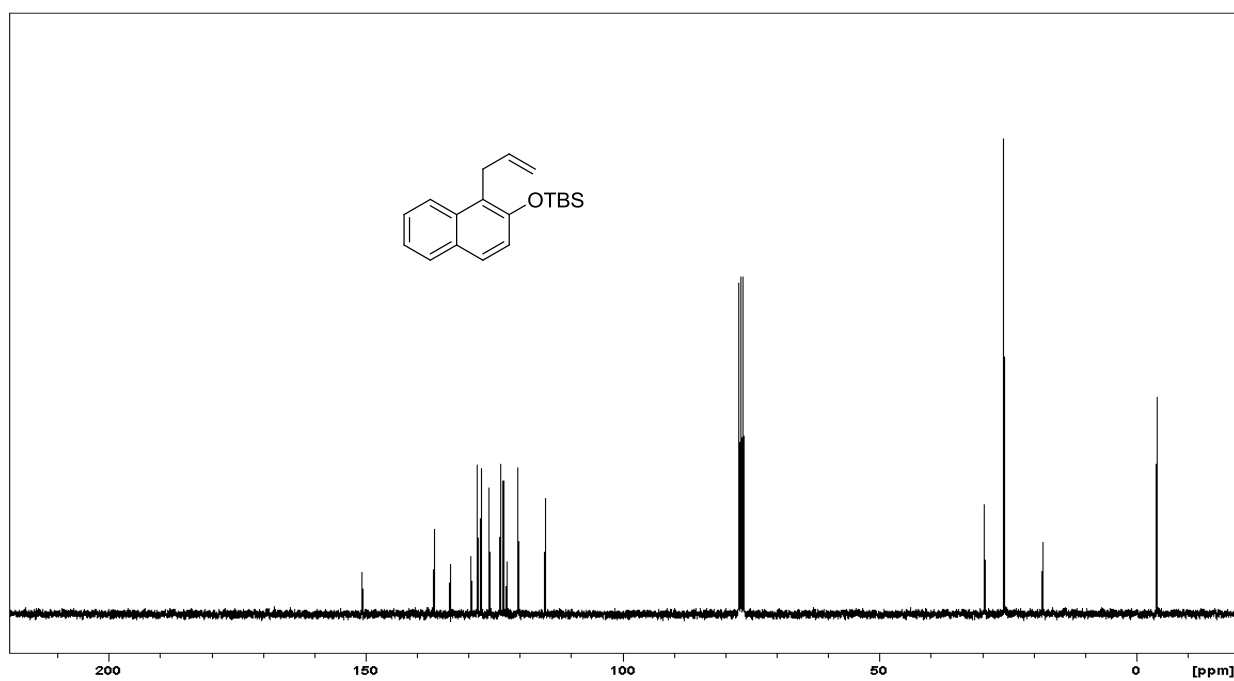
¹H NMR spectrum of crude 3.81, R = OMe (300 MHz, CDCl₃)



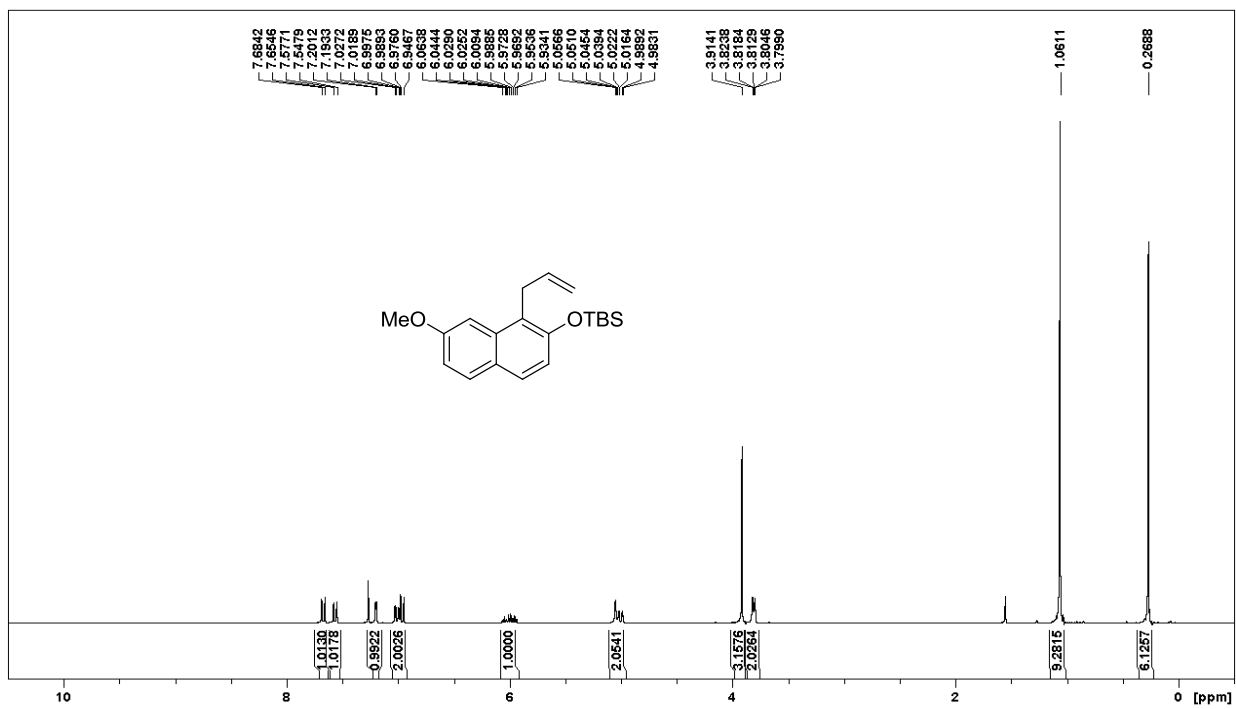
¹³C NMR spectrum of crude 3.81, R = OMe (75 MHz, CDCl₃)



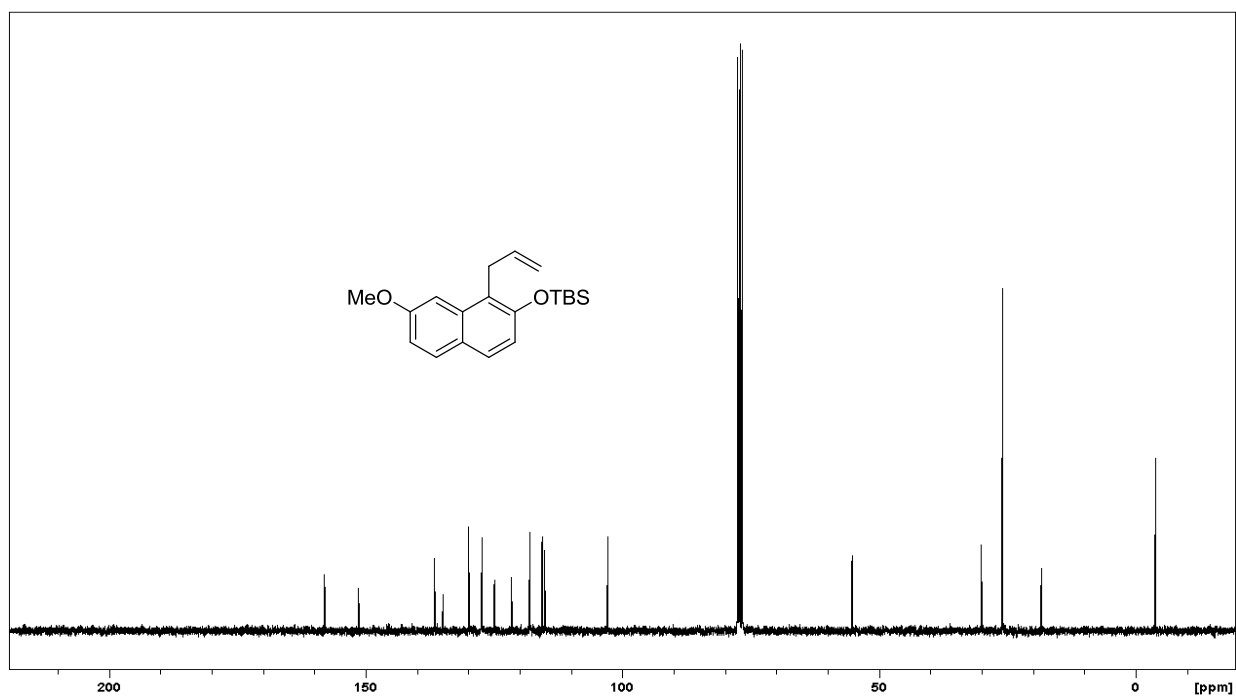
¹H NMR spectrum of 3.82, R = H (300 MHz, CDCl₃)



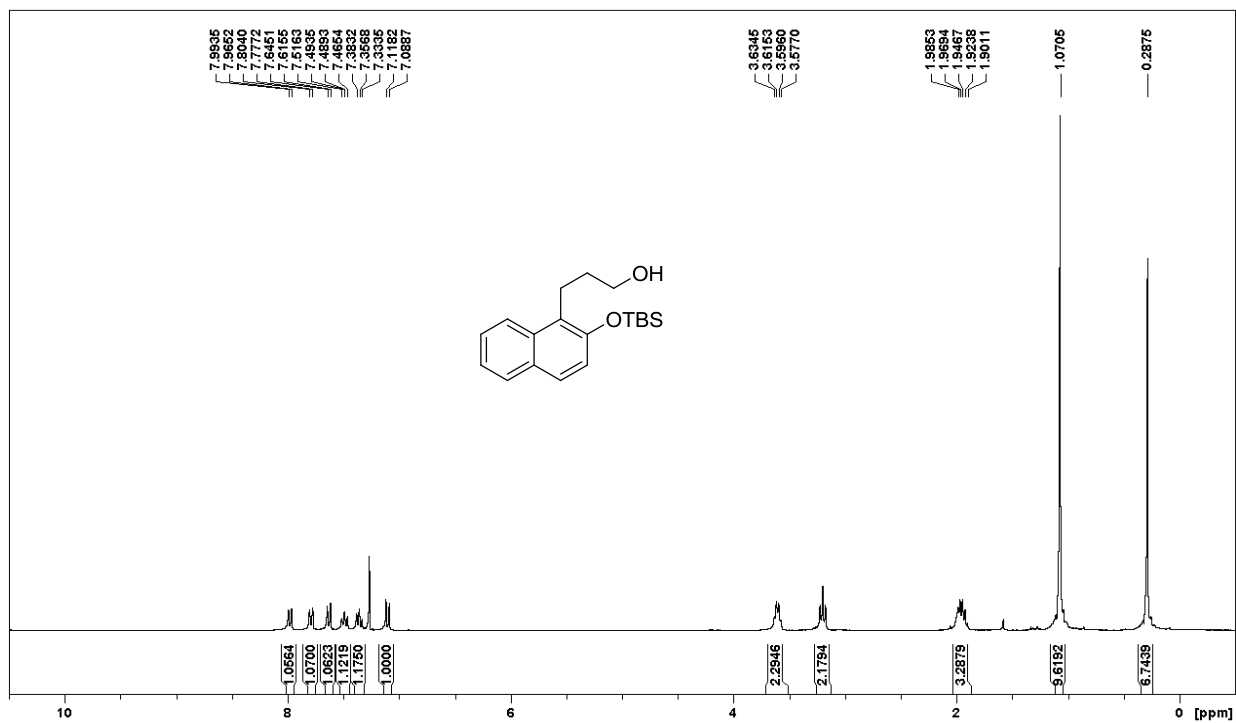
¹³C NMR spectrum of 3.82, R = H (75 MHz, CDCl₃)



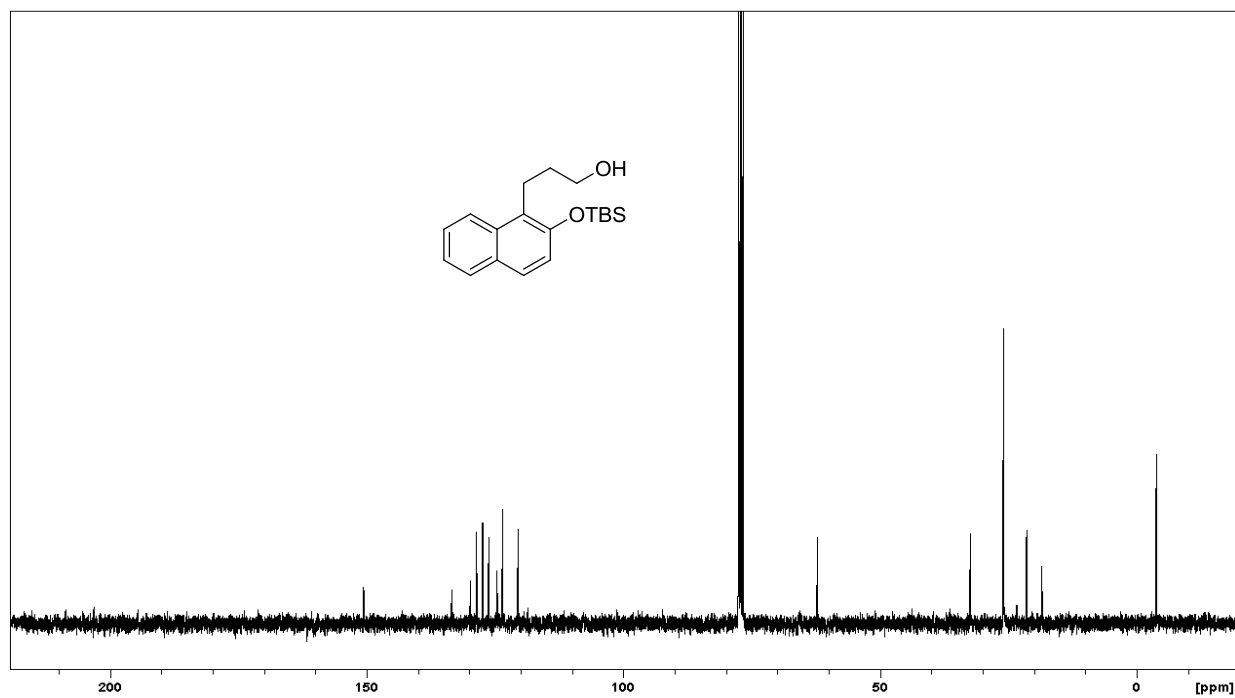
^1H NMR spectrum of 3.82, R = OMe (300 MHz, CDCl_3)



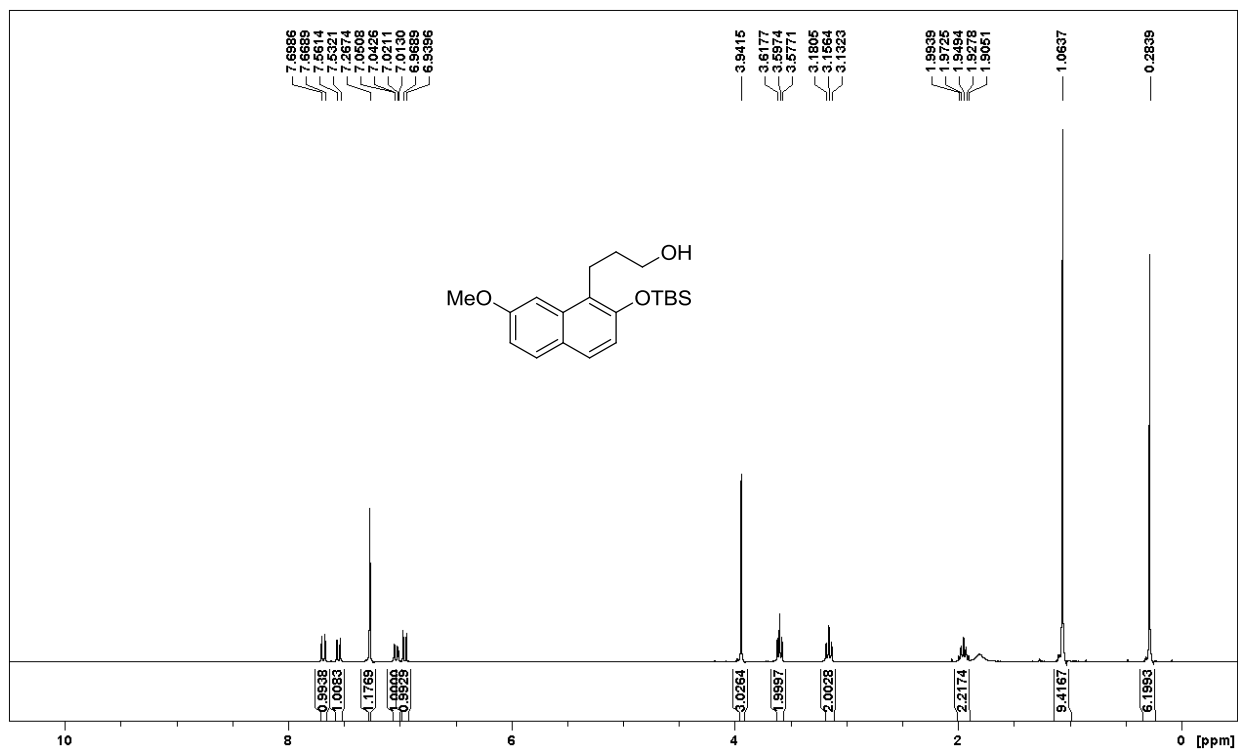
^{13}C NMR spectrum of 3.82, R = OMe (75 MHz, CDCl_3)



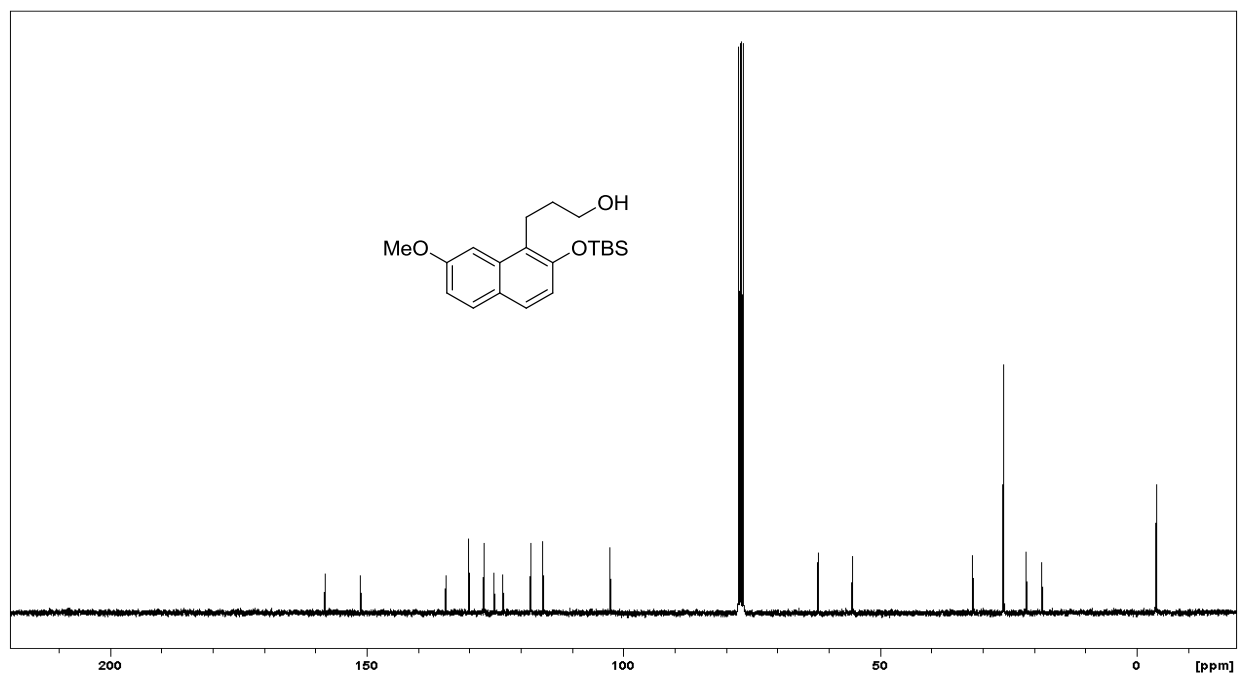
¹H NMR spectrum of 3.83, R = H (300 MHz, CDCl₃)



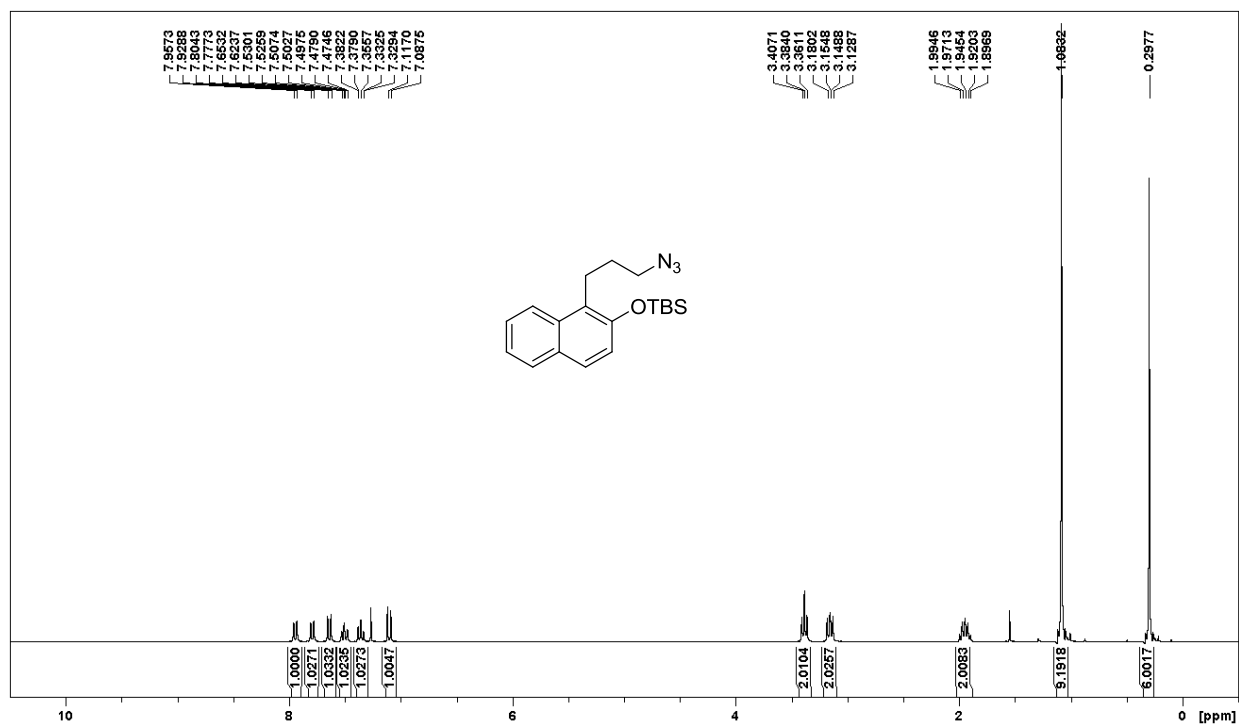
¹³C NMR spectrum of 3.83, R = H (75 MHz, CDCl₃)



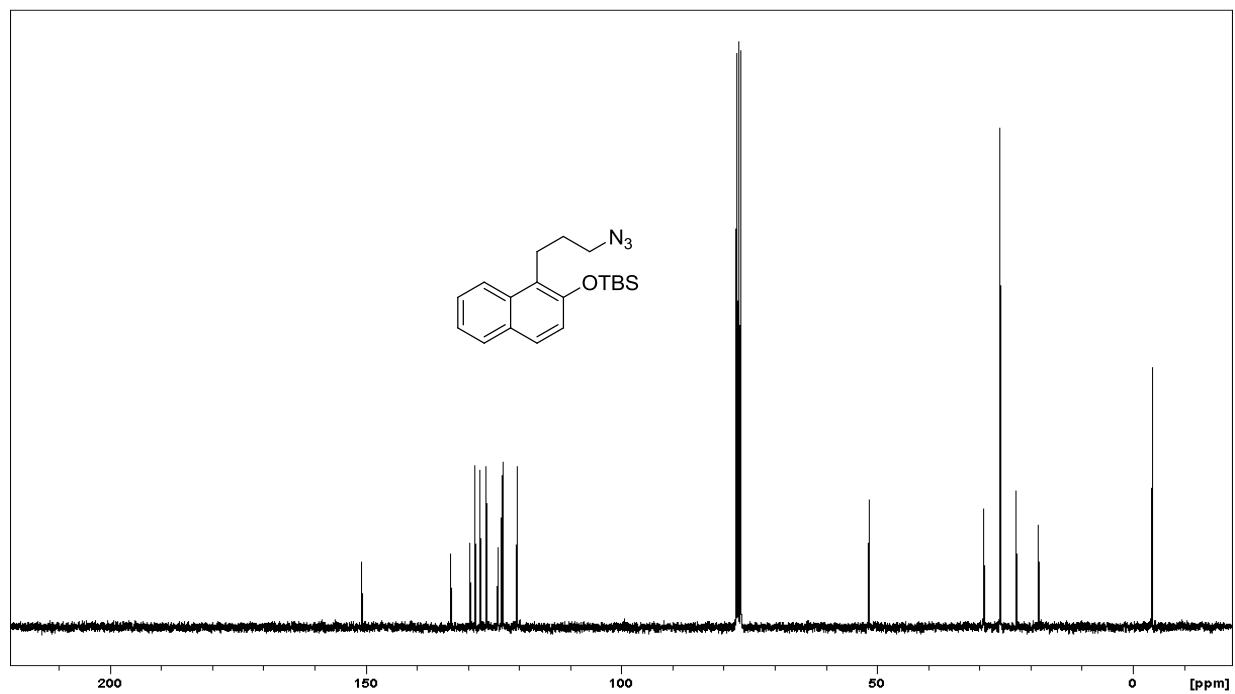
¹H NMR spectrum of 3.83, R = OMe (300 MHz, CDCl₃)



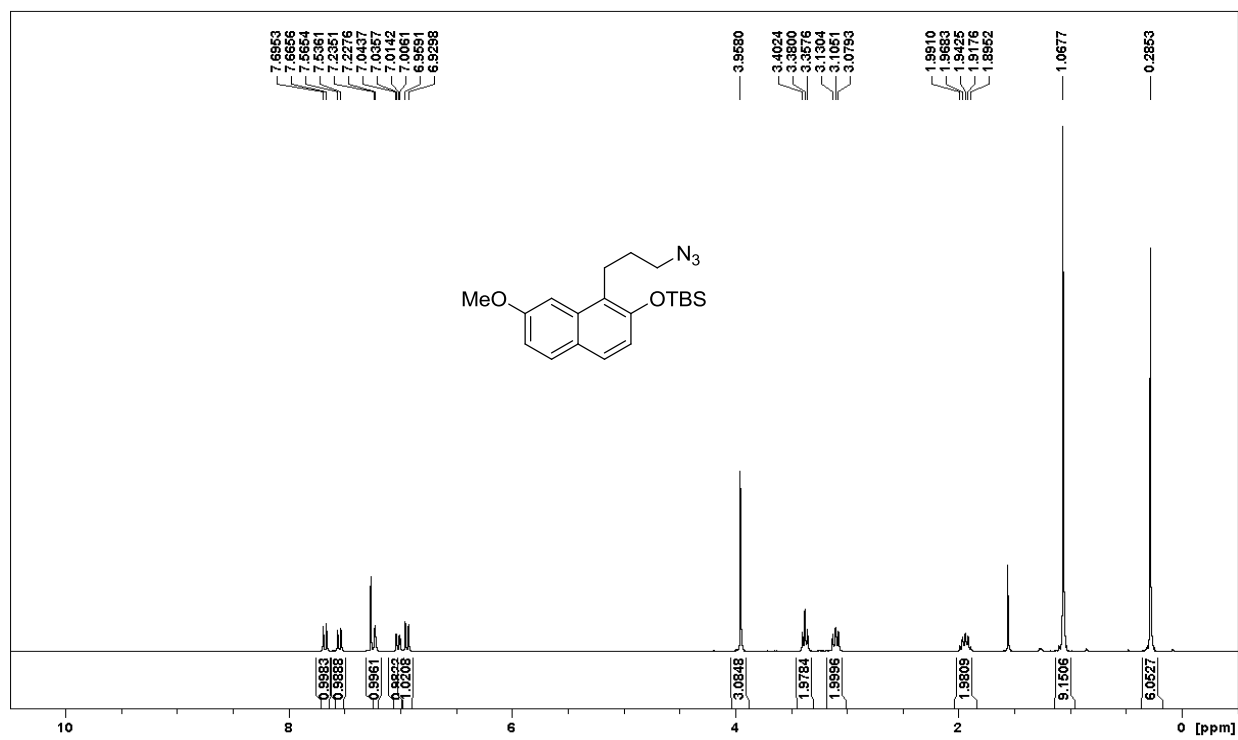
¹³C NMR spectrum of 3.83, R = OMe (75 MHz, CDCl₃)



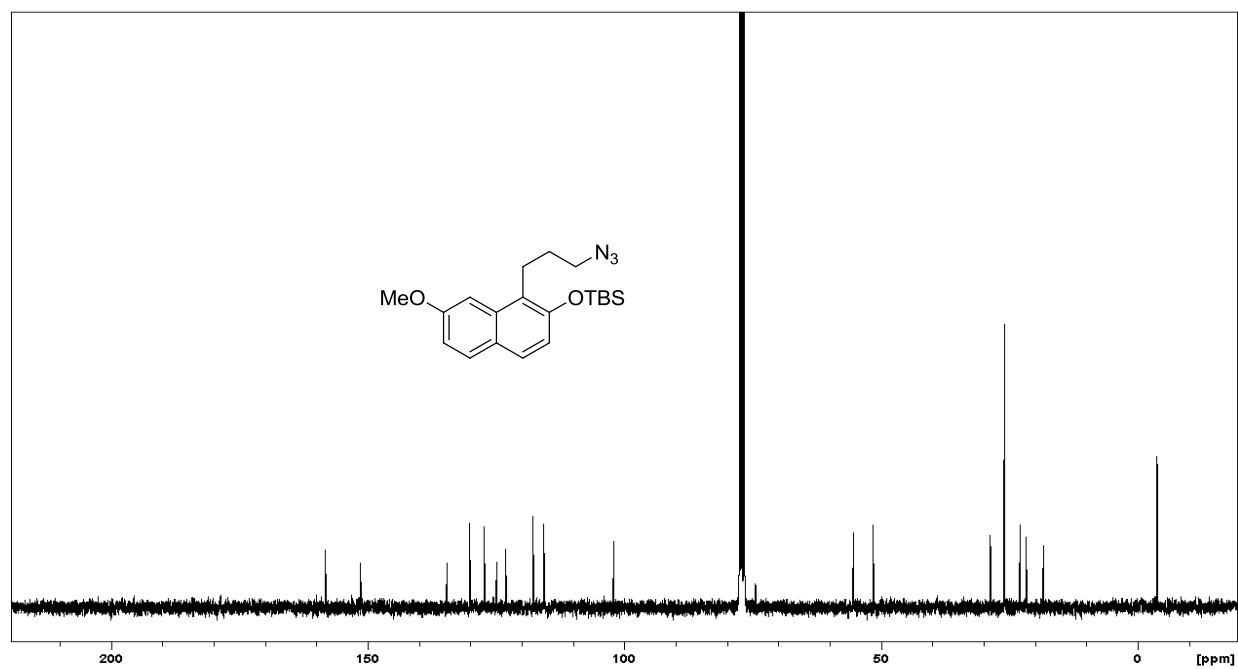
¹H NMR spectrum of 3.84, R = H (300 MHz, CDCl₃)



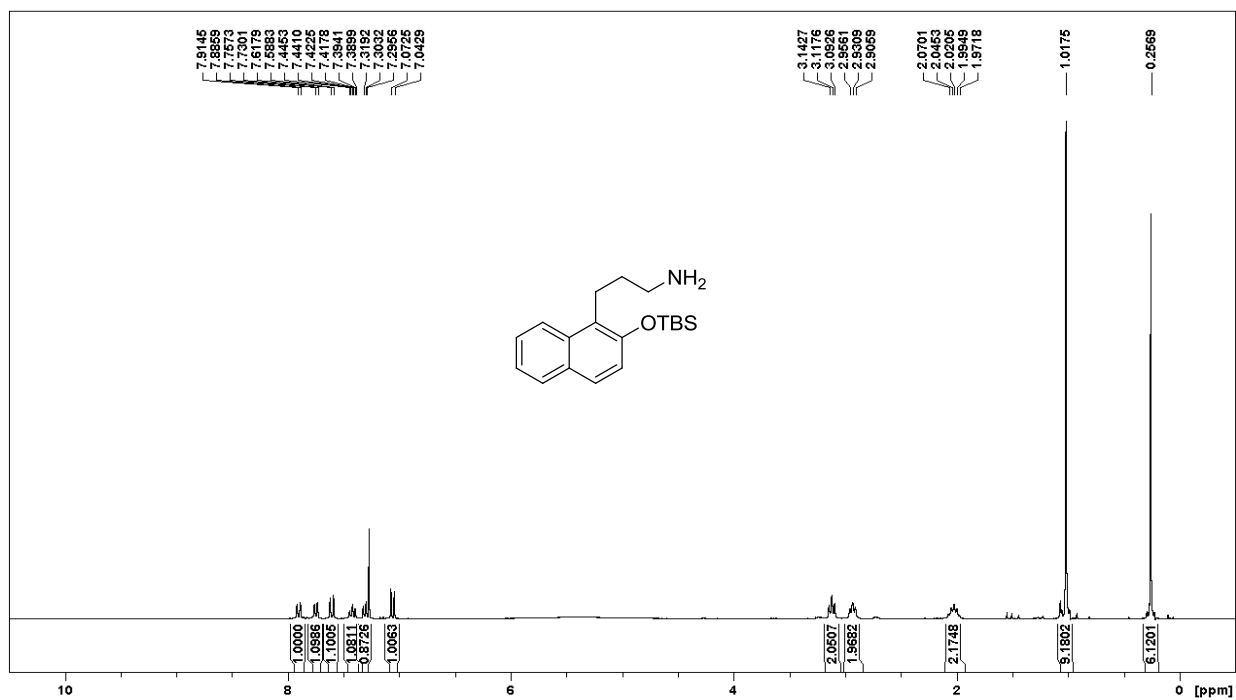
¹³C NMR spectrum of 3.84, R = H (75 MHz, CDCl₃)



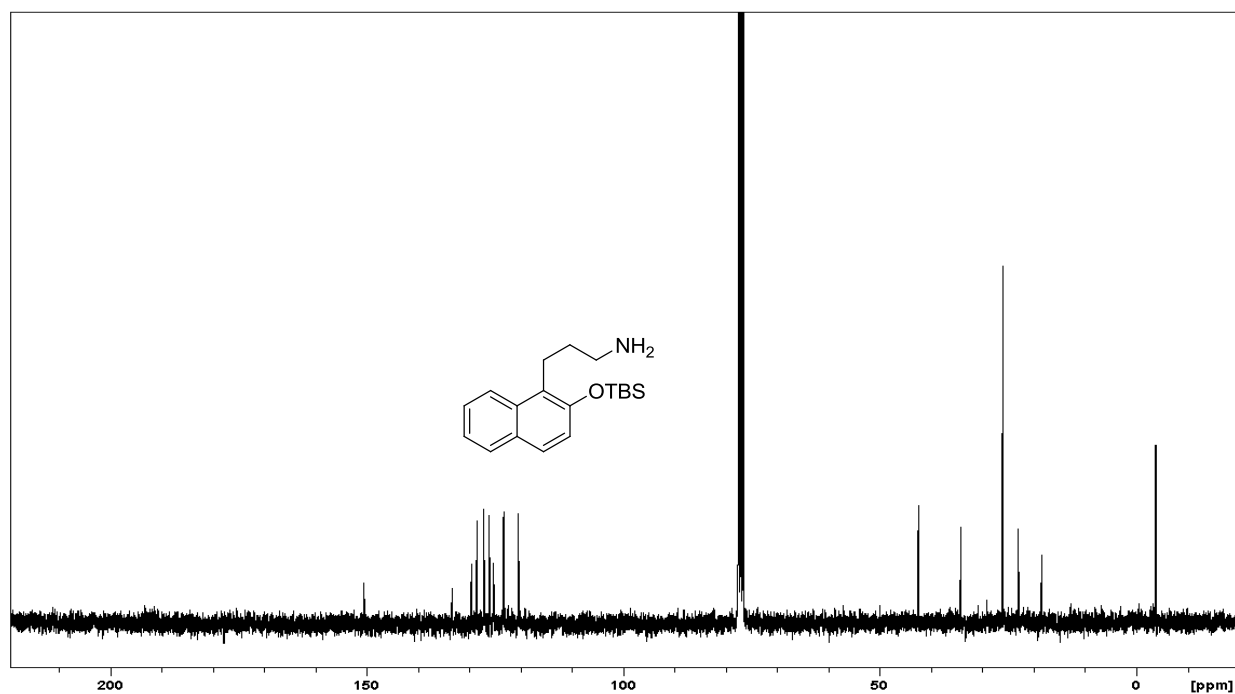
¹H NMR spectrum of 3.84, R = OMe (300 MHz, CDCl₃)



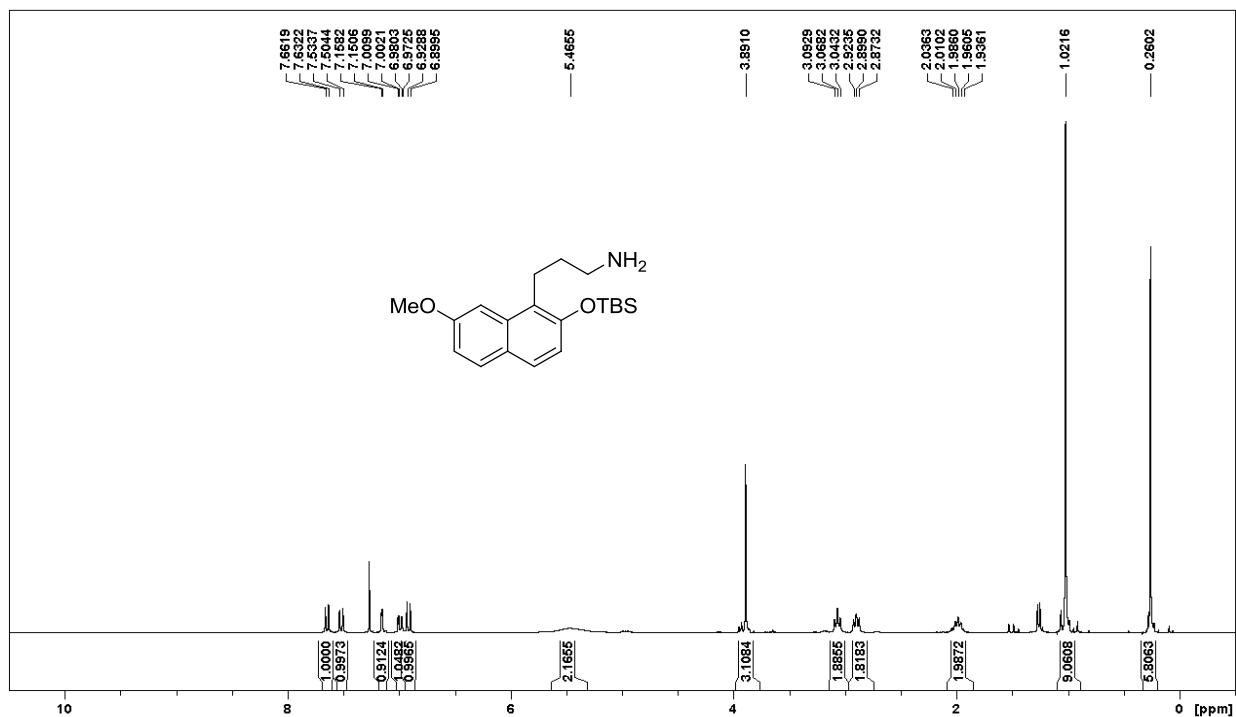
¹³C NMR spectrum of 3.84, R = OMe (75 MHz, CDCl₃)



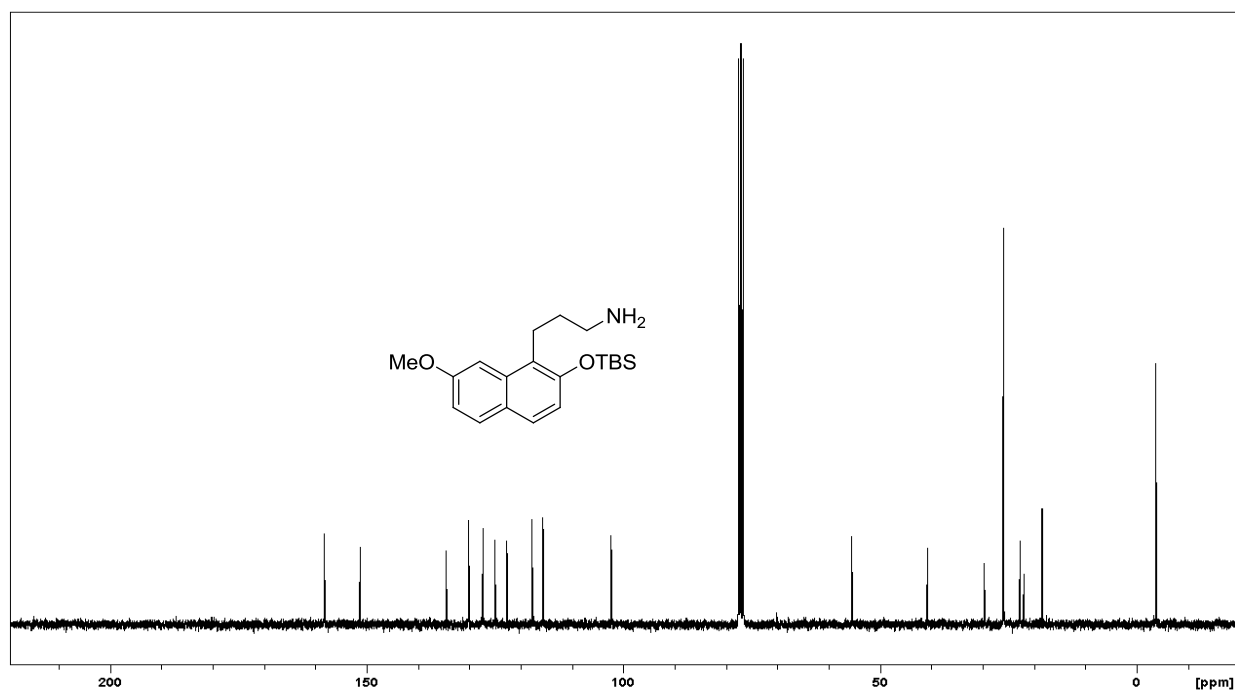
¹H NMR spectrum of crude 3.85, R = H (300 MHz, CDCl₃)



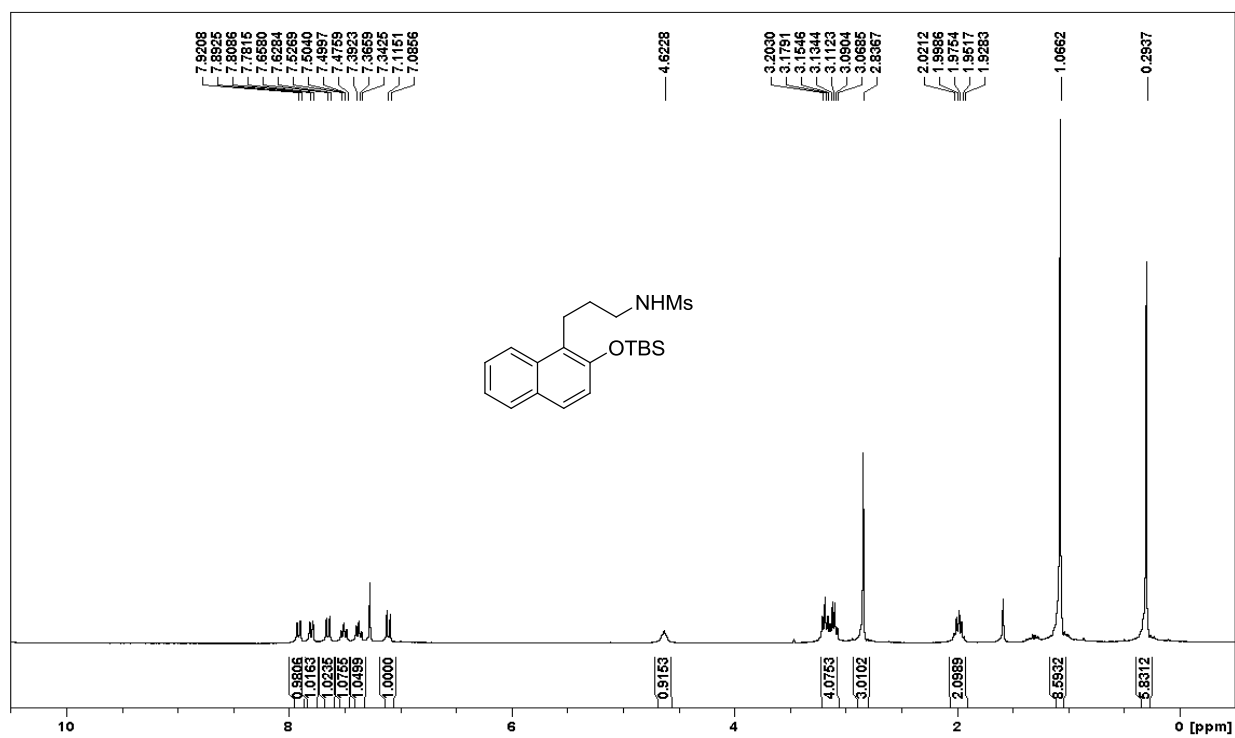
¹³C NMR spectrum of crude 3.85, R = H (75 MHz, CDCl₃)



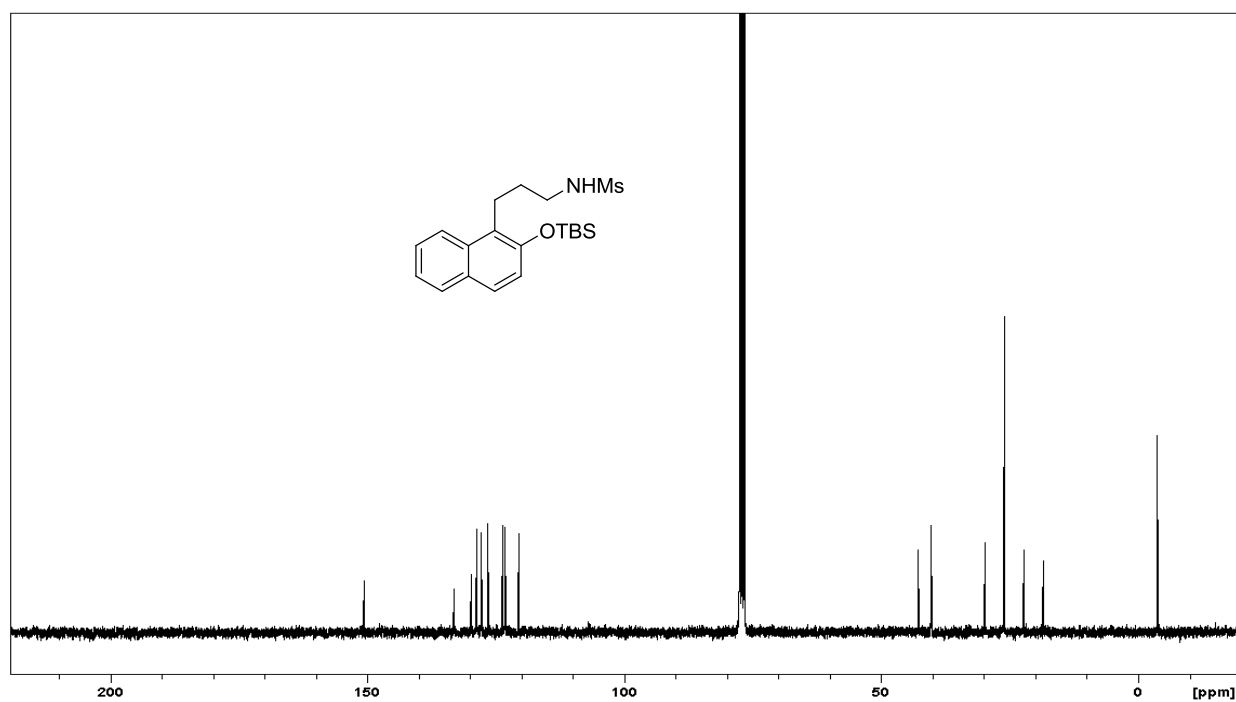
^1H NMR spectrum of crude 3.85, R = OMe (300 MHz, CDCl_3)



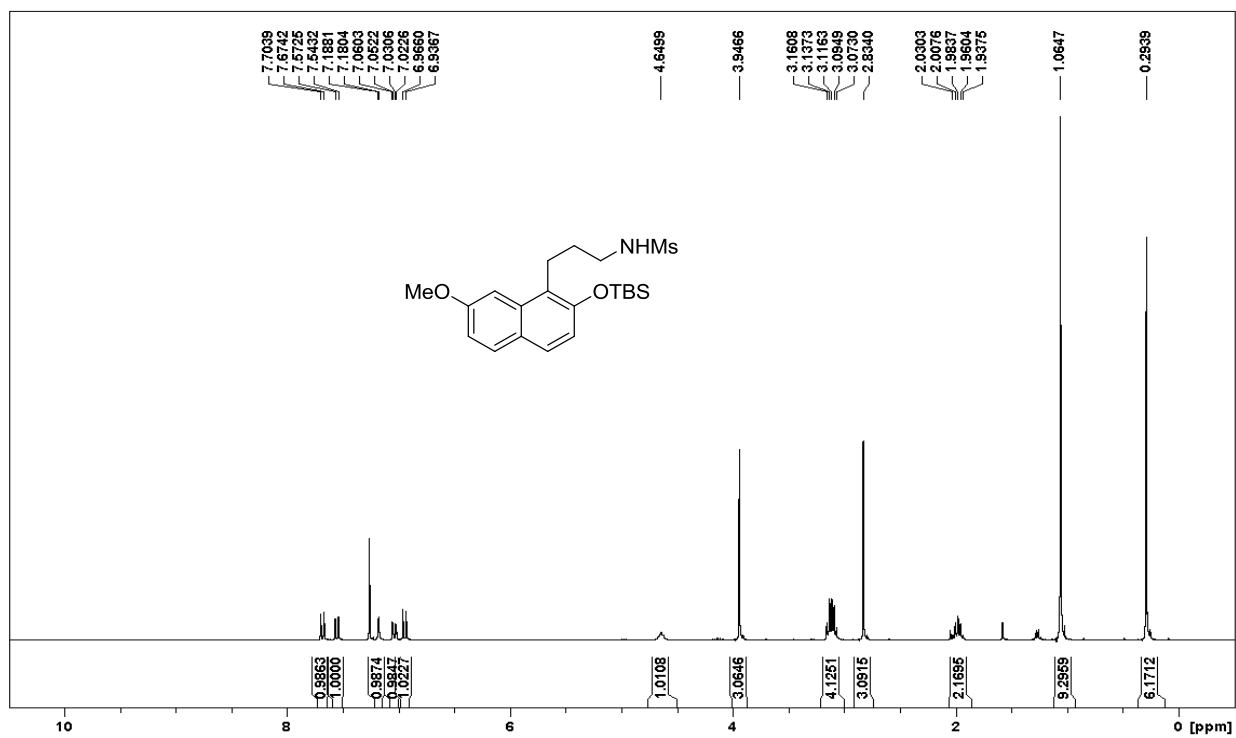
^{13}C NMR spectrum of crude 3.85, R = OMe (75 MHz, CDCl_3)



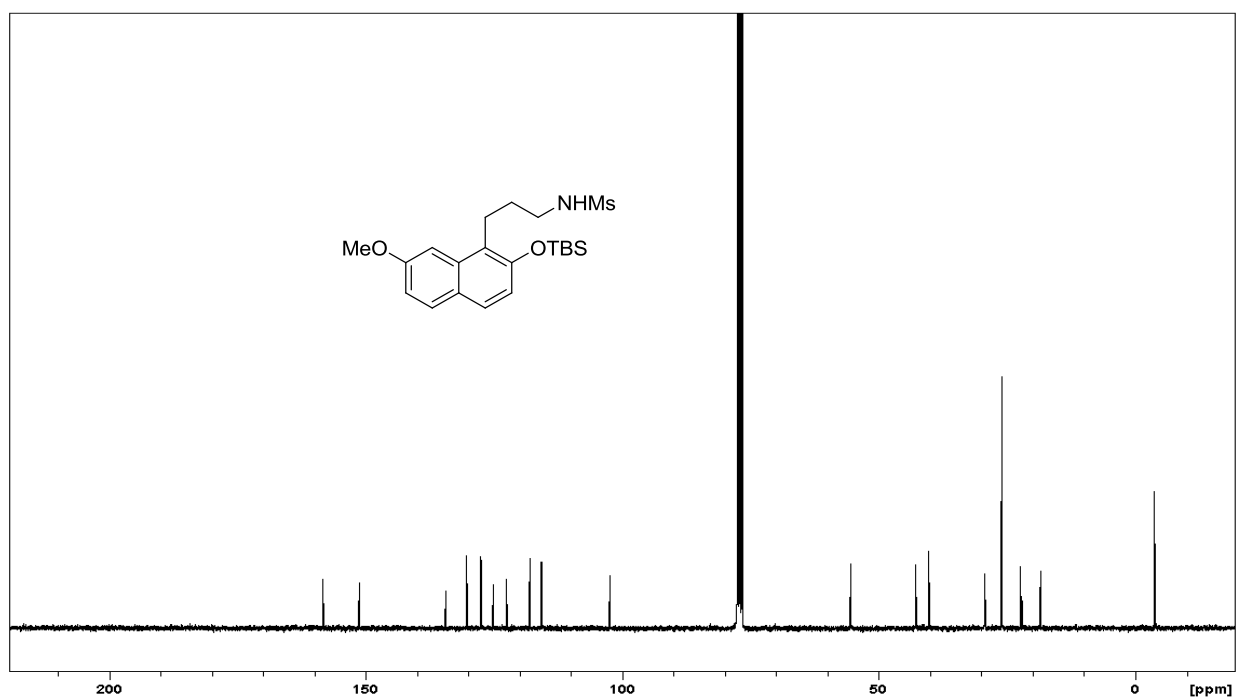
¹H NMR spectrum of 3.86, R = H (300 MHz, CDCl₃)



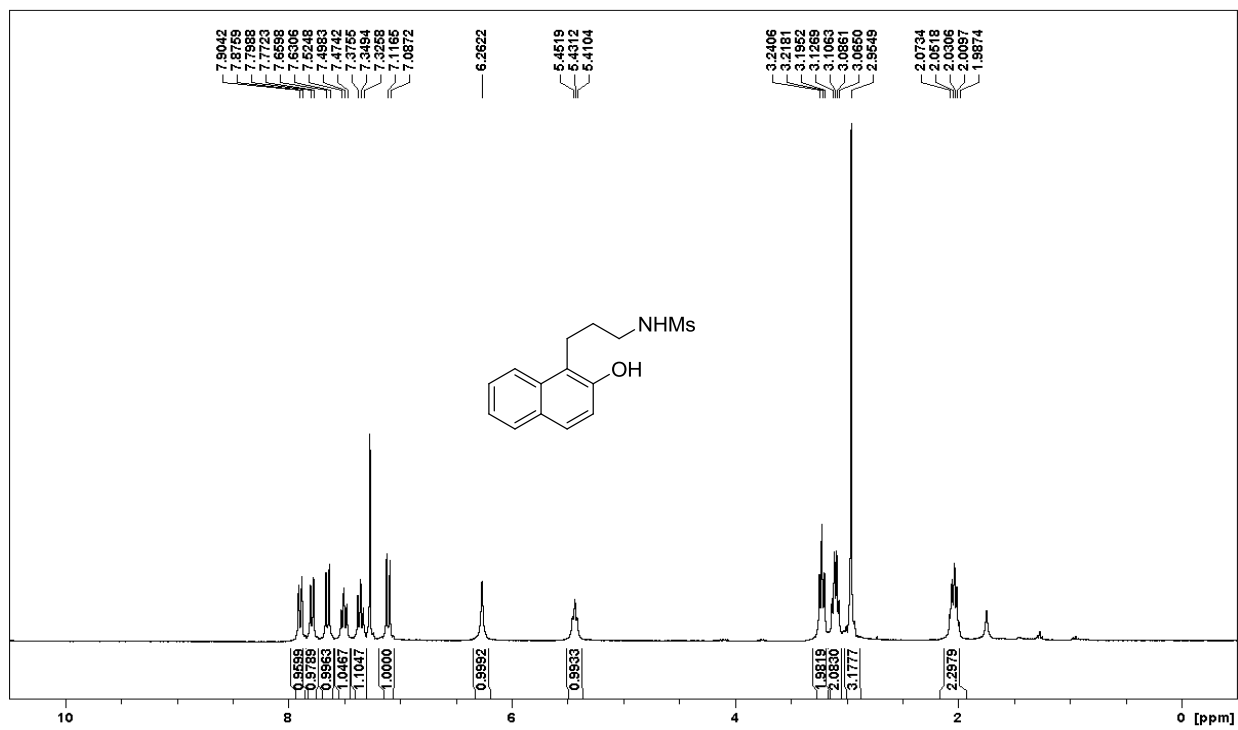
¹³C NMR spectrum of 3.86, R = OMe (75 MHz, CDCl₃)



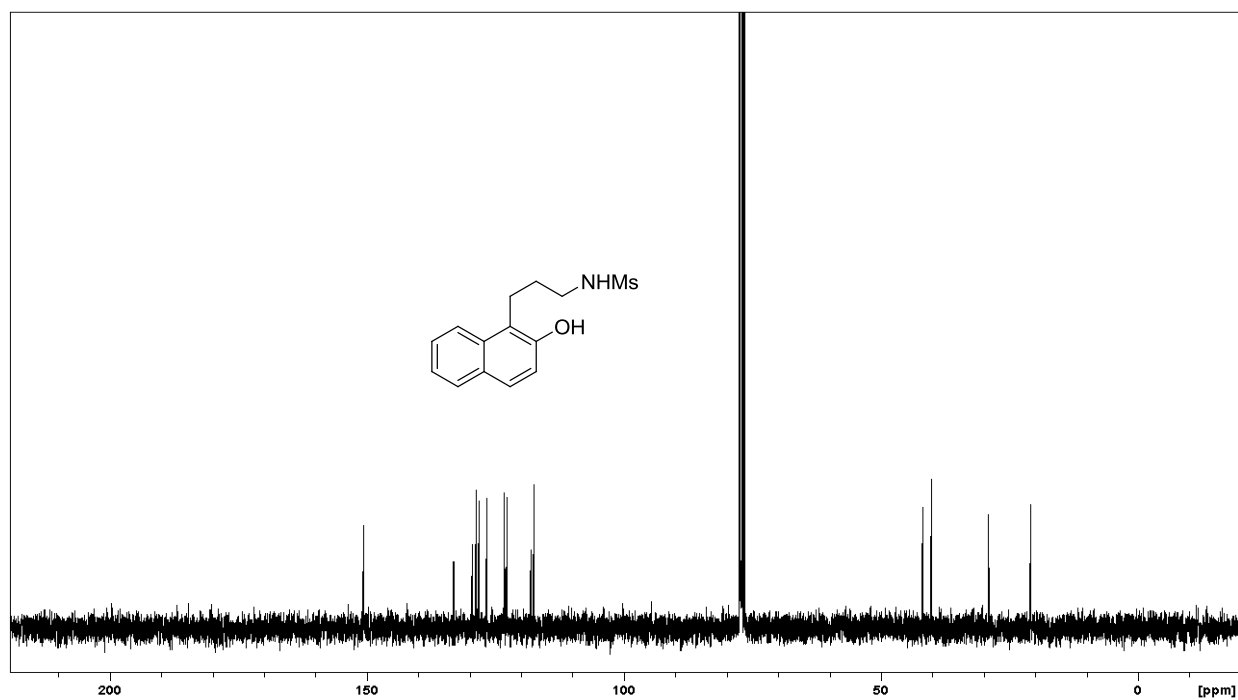
¹H NMR spectrum of 3.86, R = OMe (300 MHz, CDCl₃)



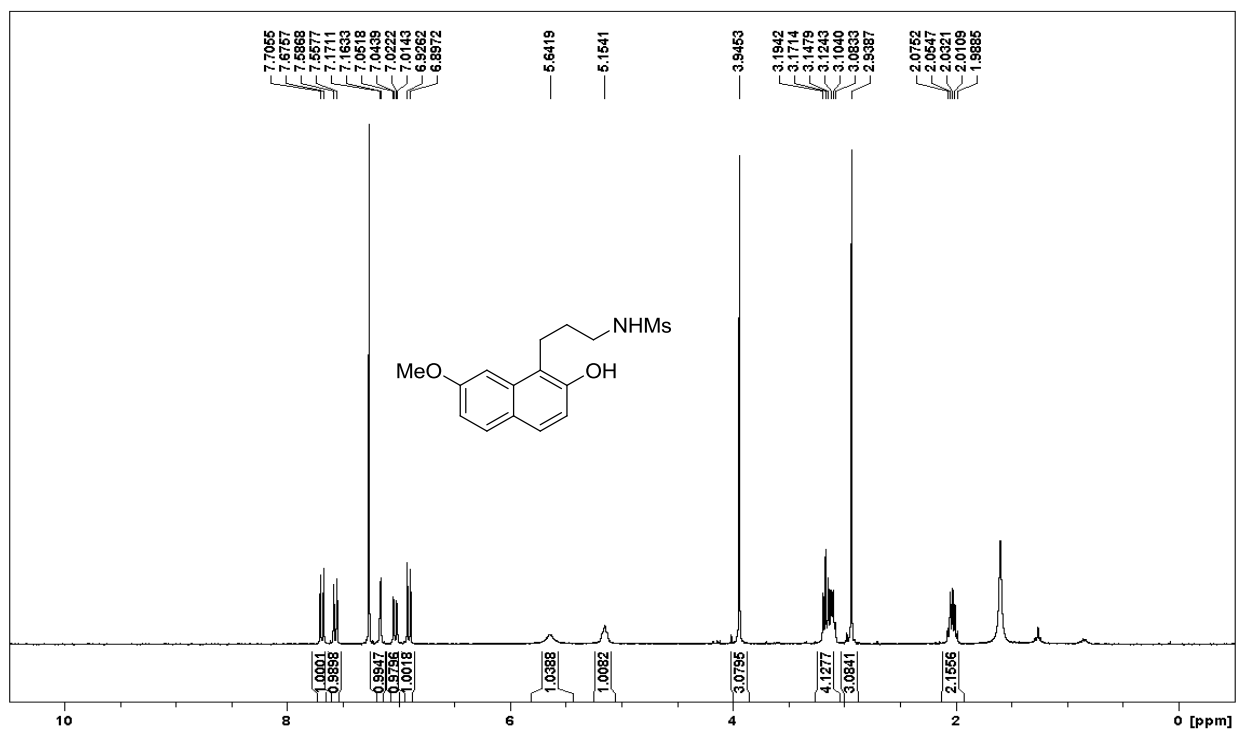
¹³C NMR spectrum of 3.86, R = OMe (75 MHz, CDCl₃)



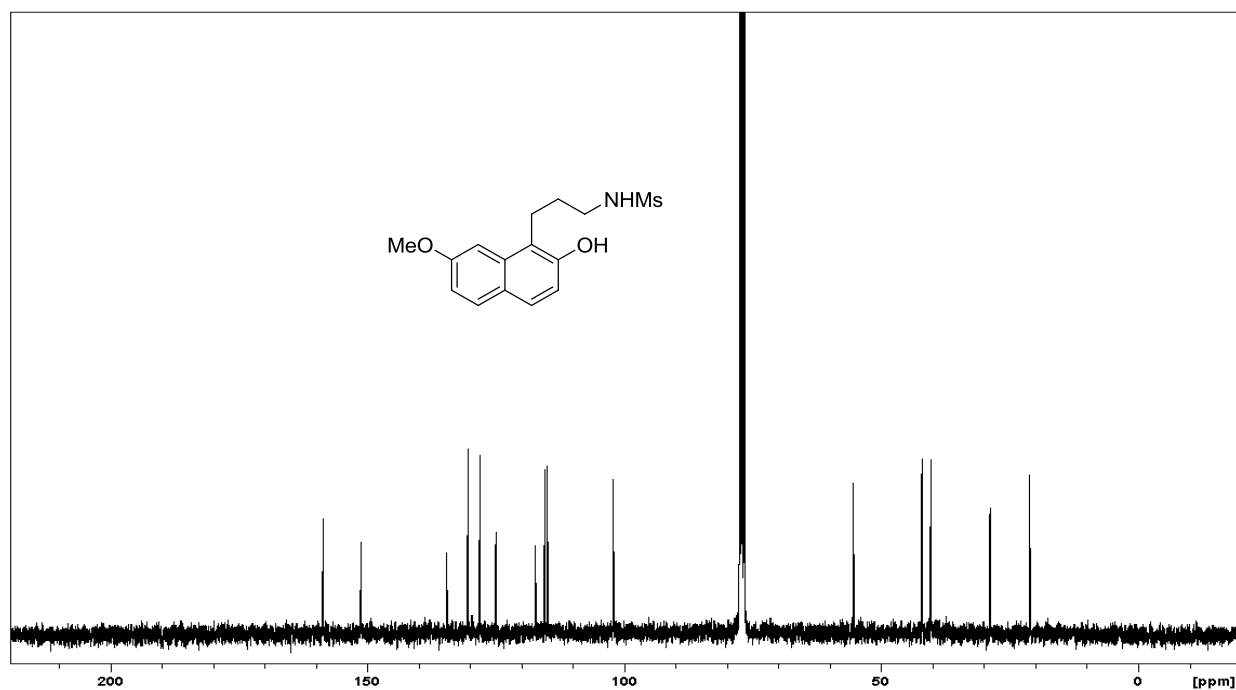
¹H NMR spectrum of 3.87, R = H (300 MHz, CDCl₃)



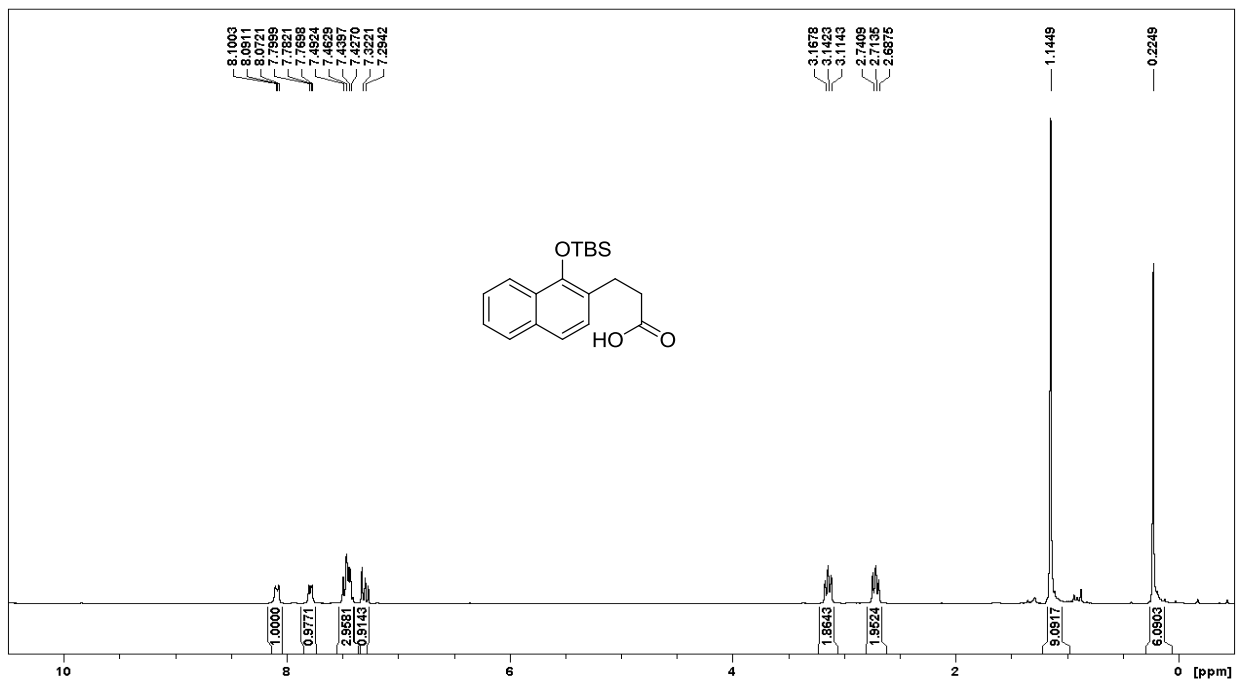
¹³C NMR spectrum of 3.87, R = H (75 MHz, CDCl₃)



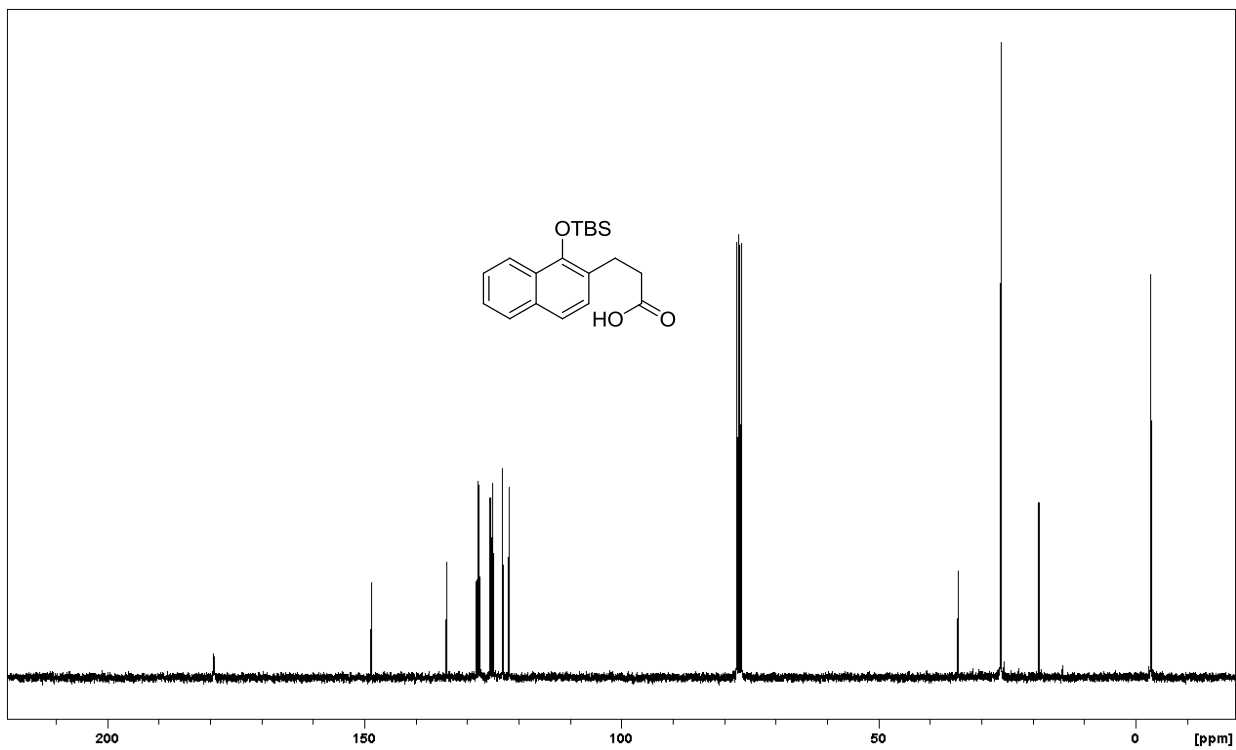
¹H NMR spectrum of 3.87, R = OMe (300 MHz, CDCl₃)



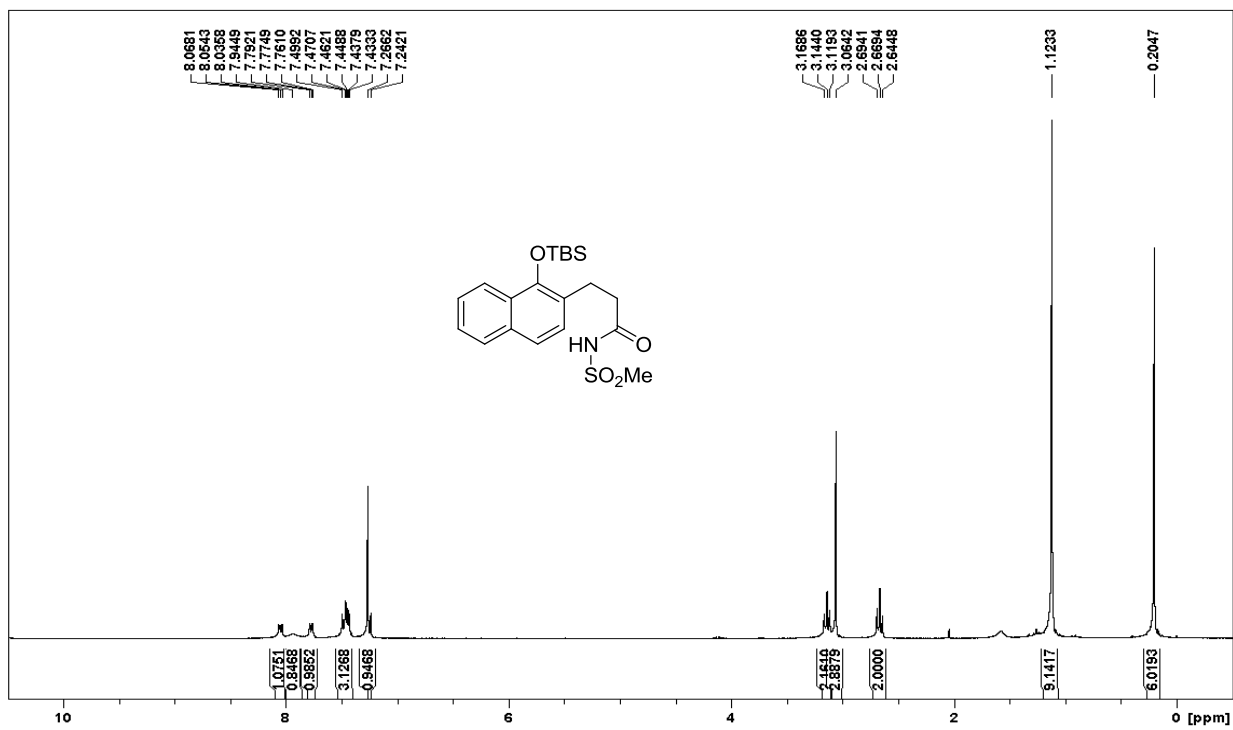
¹³C NMR spectrum of 3.87, R = OMe (75 MHz, CDCl₃)



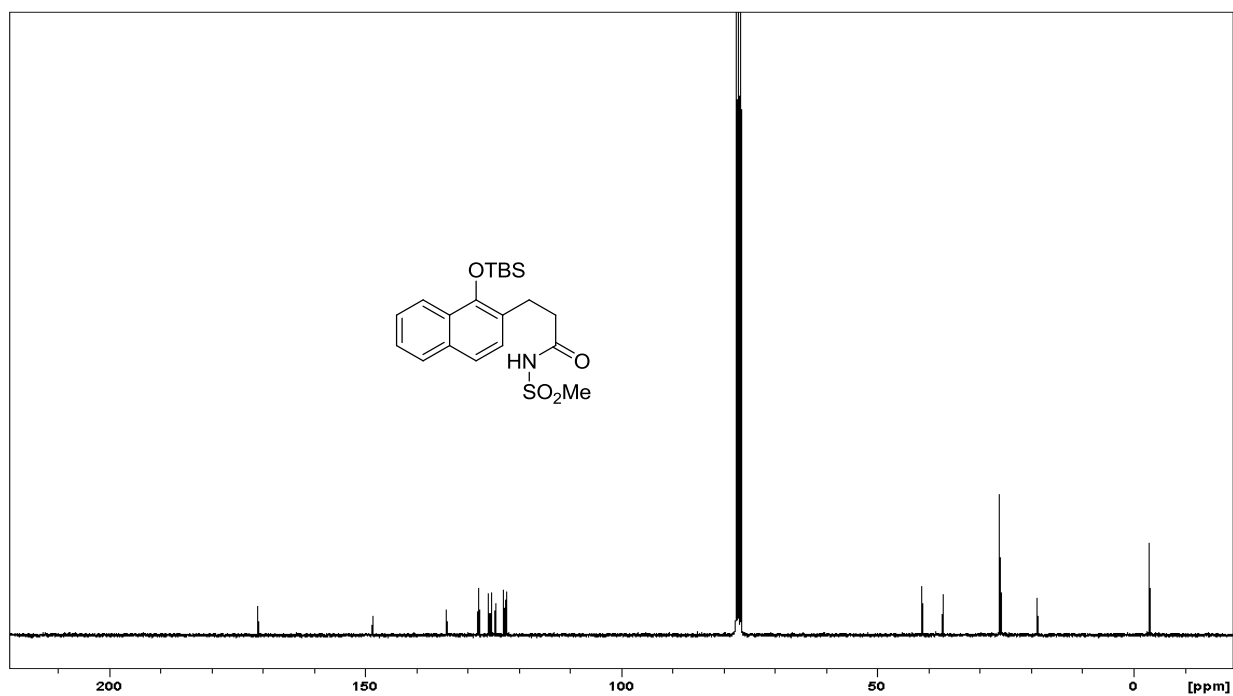
¹H NMR spectrum of 3.89 (300 MHz, CDCl₃)



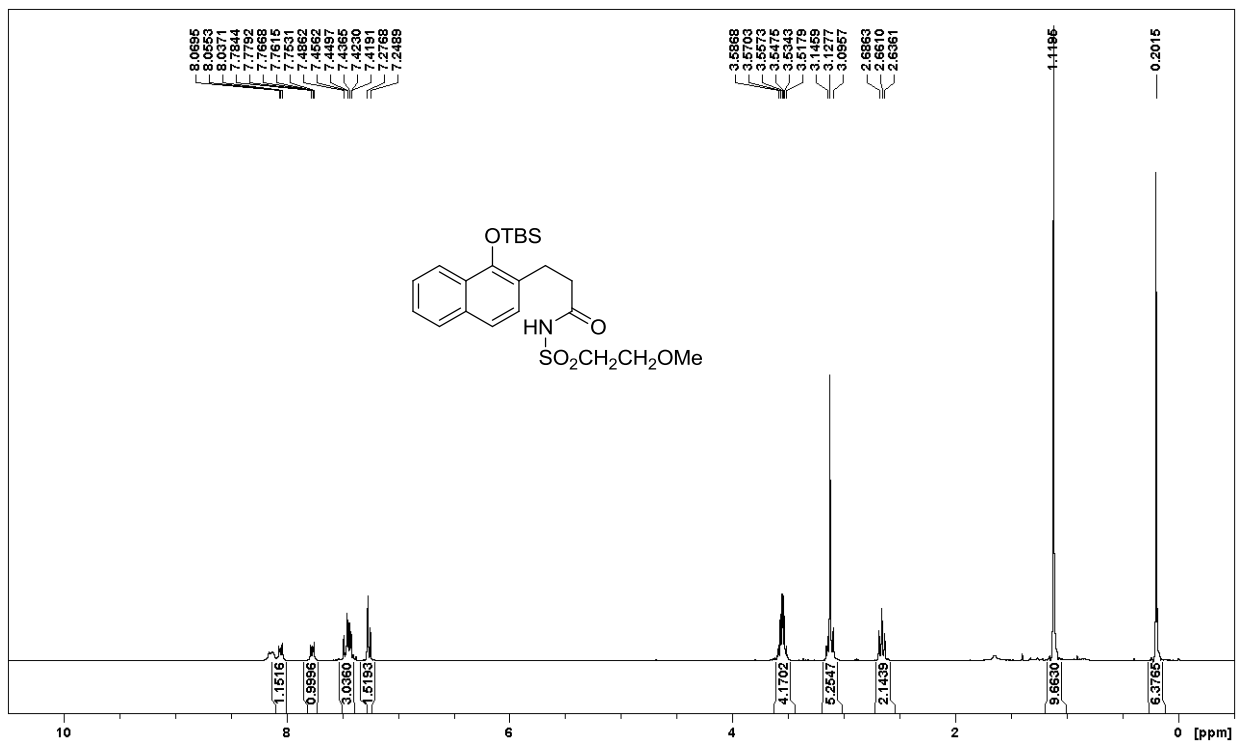
¹³C NMR spectrum of 3.89 (75 MHz, CDCl₃)



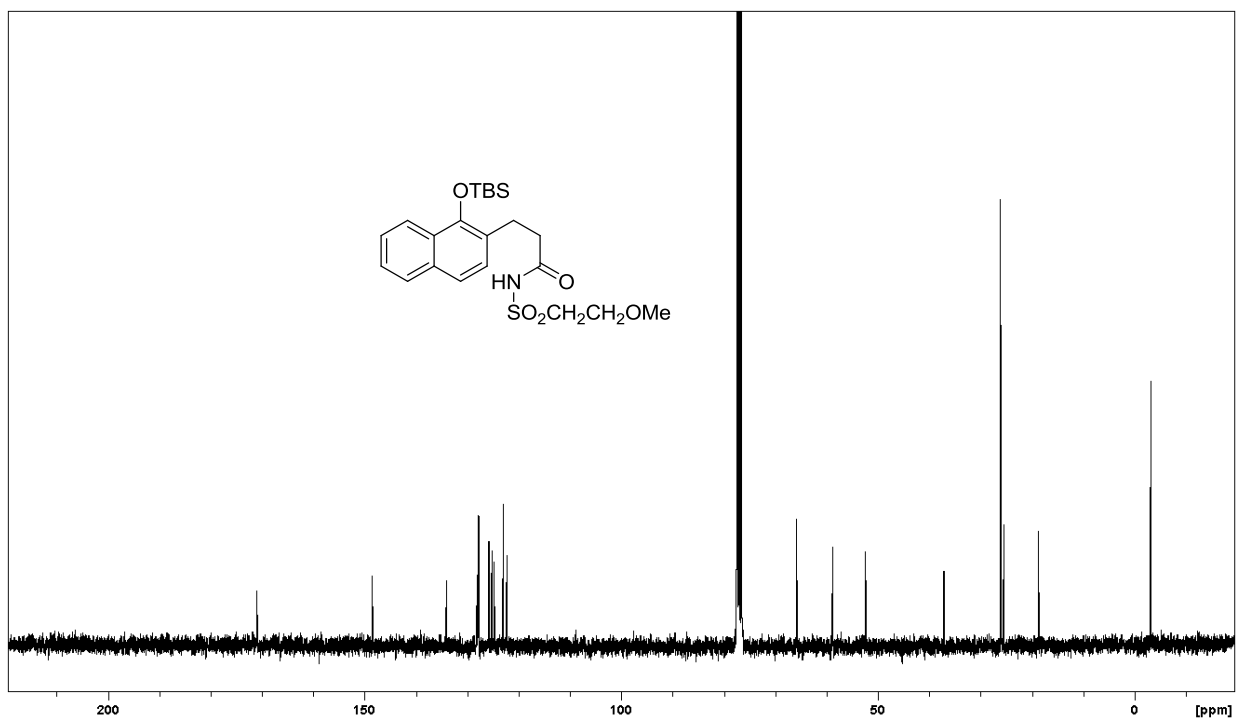
¹H NMR spectrum of 3.90 (300 MHz, CDCl₃)



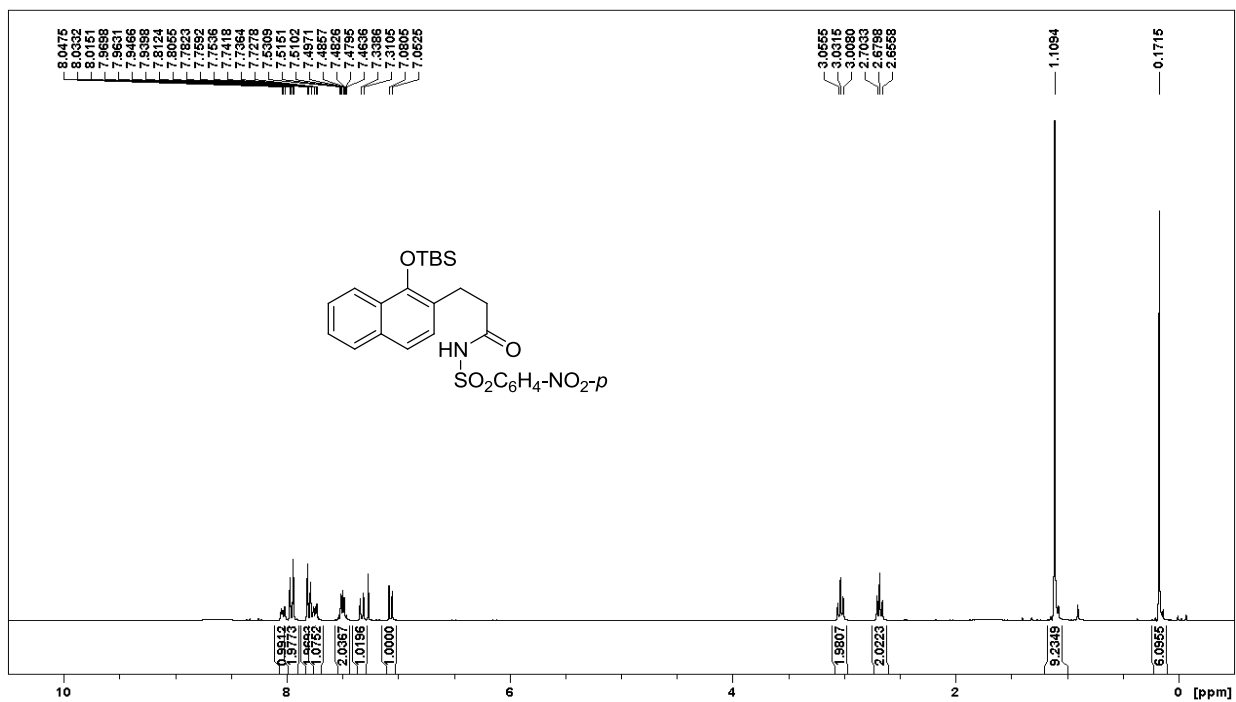
¹³C NMR spectrum of 3.90 (75 MHz, CDCl₃)



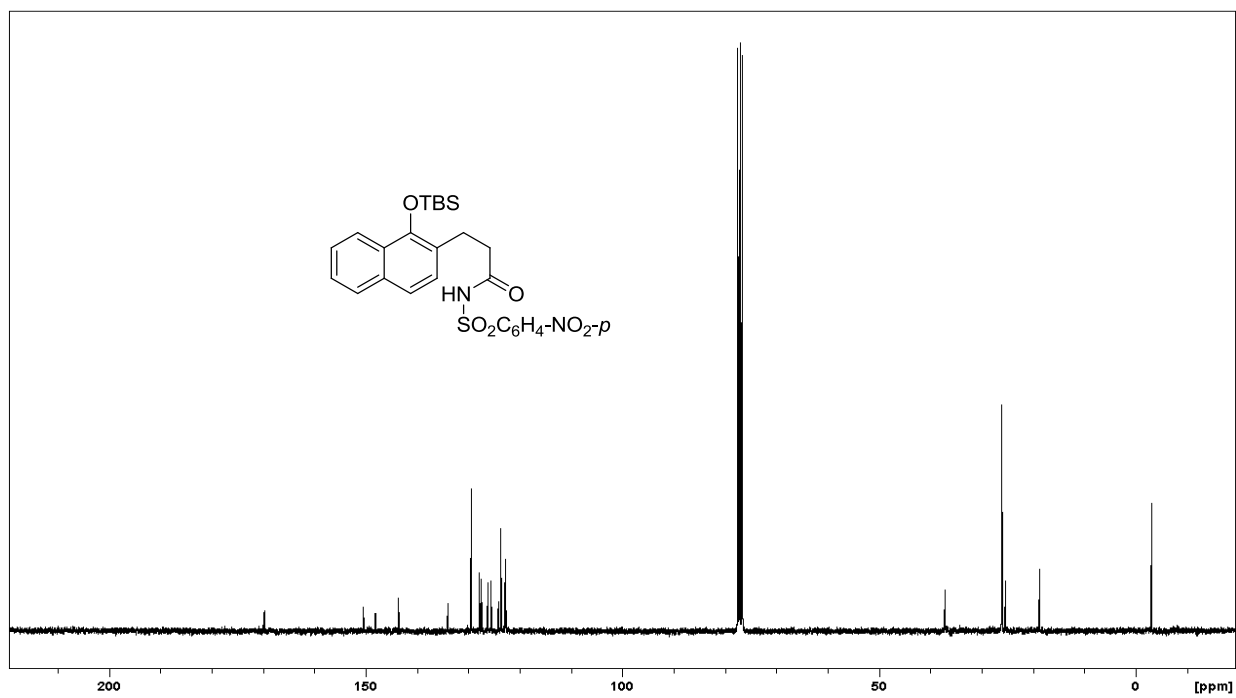
¹H NMR spectrum 3.91 (300 MHz, CDCl₃)



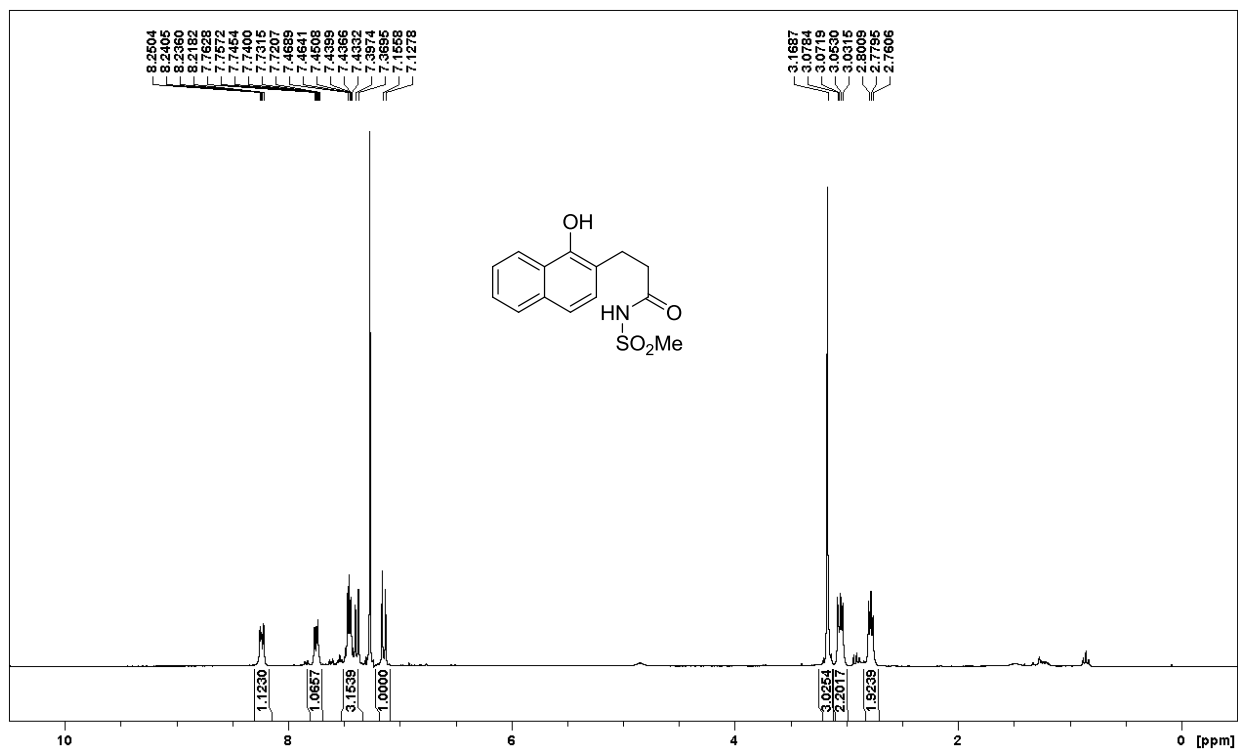
¹³C NMR spectrum of 3.91 (75 MHz, CDCl₃)



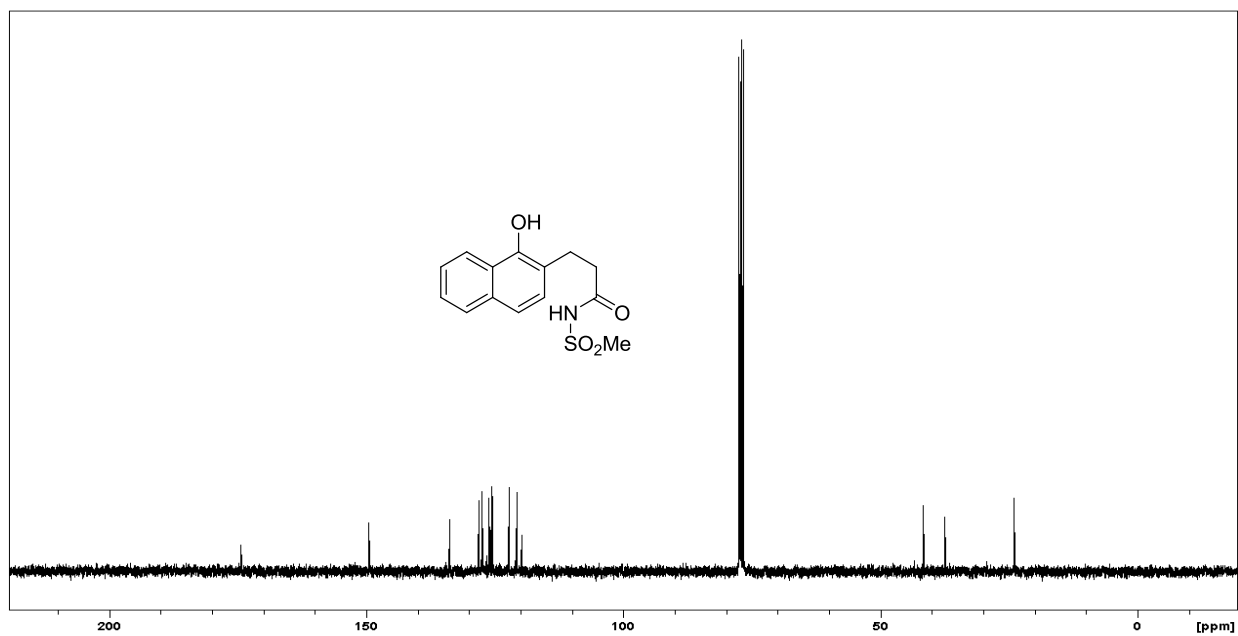
¹H NMR spectrum of 3.92 (300 MHz, CDCl₃)



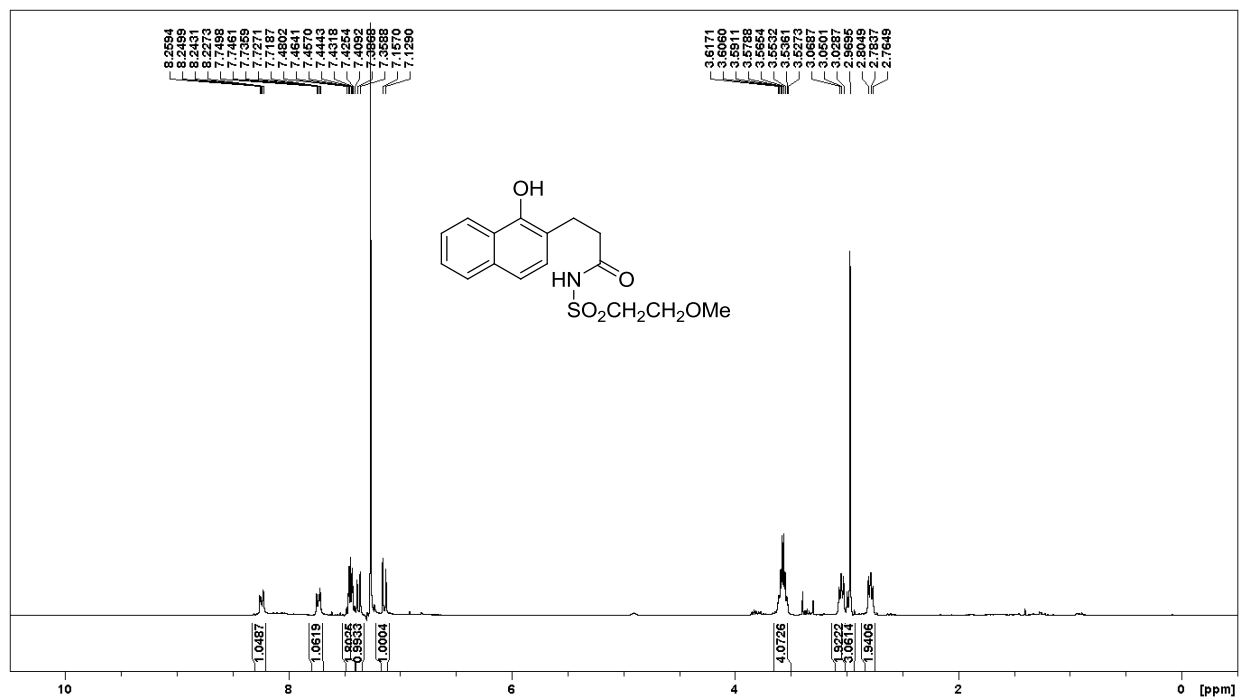
¹³C NMR spectrum of 3.92 (75 MHz, CDCl₃)



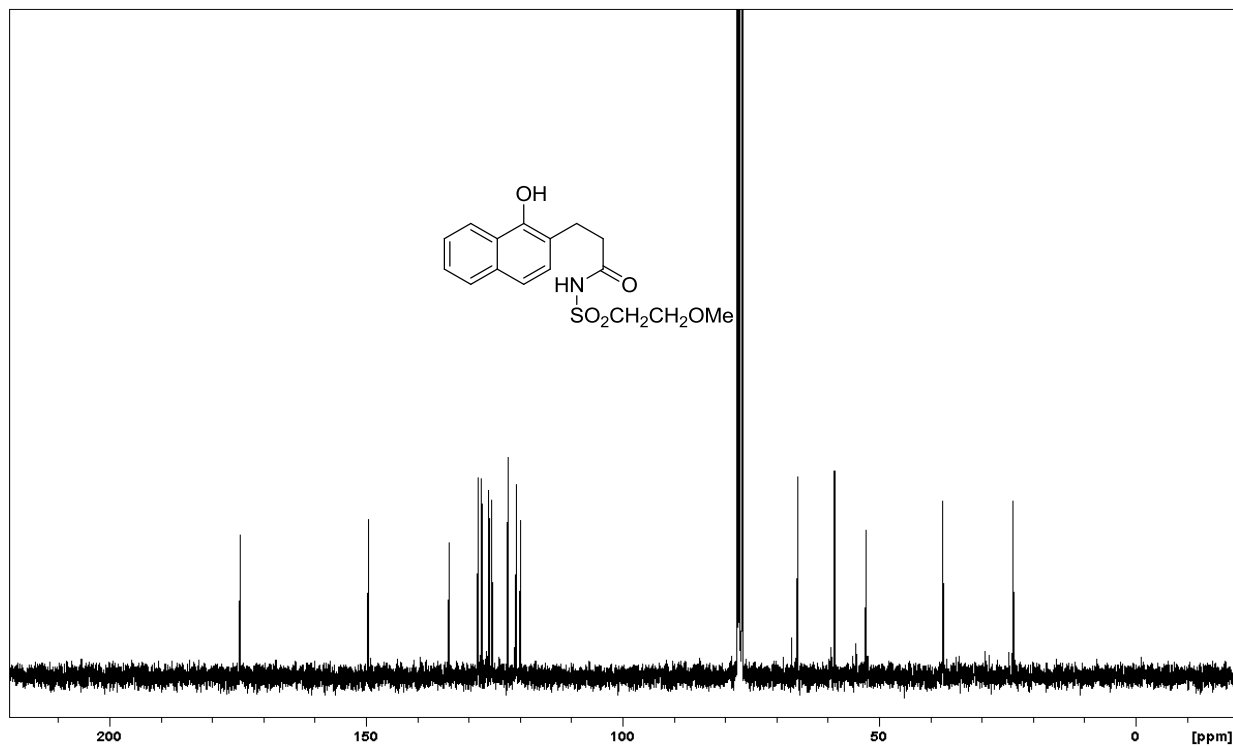
¹H NMR spectrum of 3.93 (300 MHz, CDCl₃)



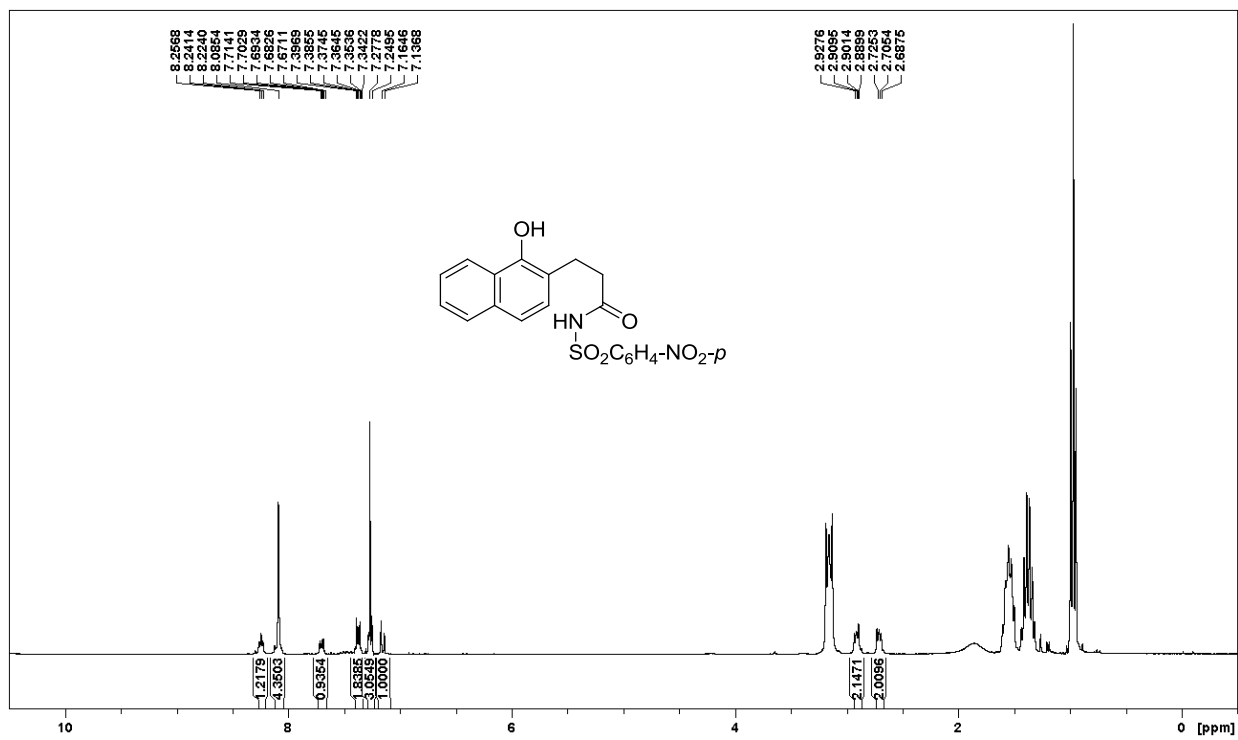
¹³C NMR spectrum of 3.93 (75 MHz, CDCl₃)



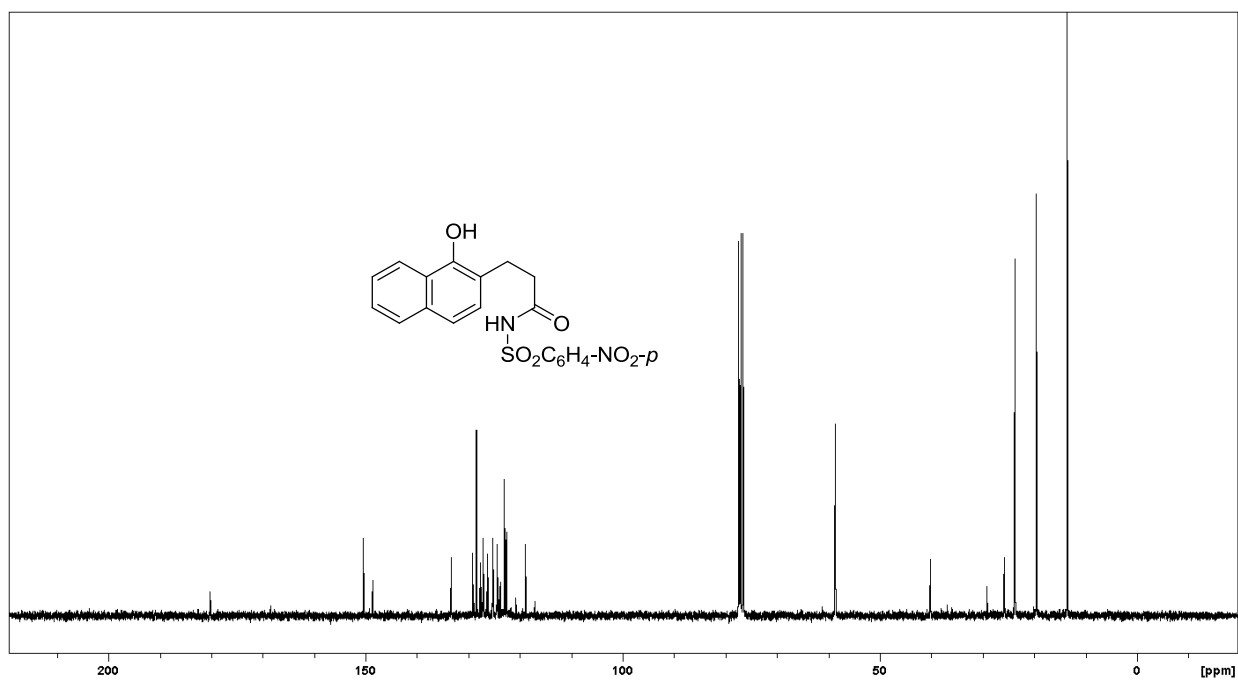
¹H NMR spectrum of 3.94 (300 MHz, CDCl₃)



¹³C NMR spectrum of 3.94 (75 MHz, CDCl₃)

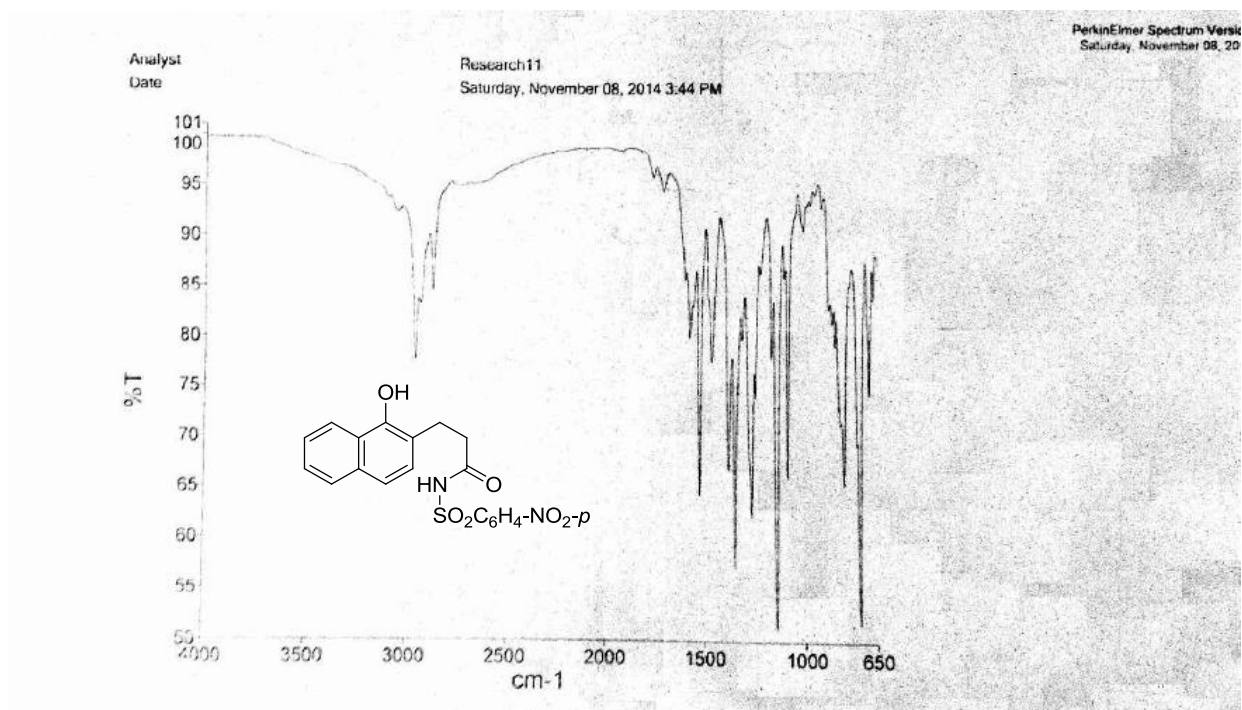


¹H NMR spectrum of crude 3.95 (300 MHz, CDCl₃)



¹³C NMR spectrum of crude 3.95 (75 MHz, CDCl₃)

B.23 IR spectrum of compound crude 3.95



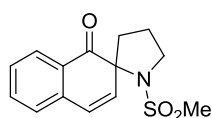
C. Oxidative amidation in naphthalene Series section

C.1 Synthesis and characterization of spiropyrrolidines

C.1.1 Representative protocol for *ortho*-oxidative cyclization of sulfonamides

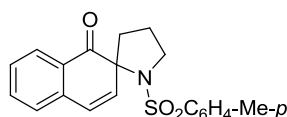
A solution of sulfonamide **4.1** (0.4 mmol, 1.0 equiv) in TFA (0.7 mL) was slowly added at room temperature over a period of 2 minutes to a solution containing DIB (0.44 mmol, 1.1 equiv) in TFA (0.5 mL) so that the final concentration is 0.3 M. Upon completion of the reaction (TLC, 7-17 min), the mixture was evaporated to dryness. Chromatography of the residue afforded the azaspirocyclic compound.

C.1.1.1 Characterization of (\pm)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidine]-1,5'-dione (**4.2a**)



13 mg (65% yield) from 20 mg of **4.1a**, white solid, m.p.: 112-114 °C; eluent: 2:3 EtOAc/hexane; **IR**: 1682. **¹H**: 8.01 (d, 1H, *J* = 7.7), 7.58 (td, 1H, *J* = 7.5, 1.3), 7.36 (td, 1H, *J* = 7.6, 1.0), 7.23 (d, 1H, *J* = 7.6), 6.53 (d, 1H, *J* = 9.8), 6.35 (d, 1H, *J* = 9.8), 3.80-3.66 (m, 2H), 3.01 (m, 3H), 2.31-2.02 (m, 4H). **¹³C**: 199.4, 137.8, 137.7, 135.1, 128.5, 128.0, 127.6, 127.4, 123.7, 72.1, 49.3, 39.6, 39.5, 22.8. **HRMS**: calcd for C₁₄H₁₅NO₃SNa [M+Na]⁺: 300.0670; found: 300.0672.

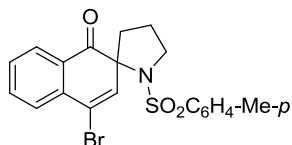
C.1.1.2 Characterization of (\pm)-1'-Tosyl-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (**4.2b**)



15 mg (74% yield) from 20 mg of **4.1b**, yellow solid, m.p.: 115-117 °C; eluent: 1:3 EtOAc/hexane; **IR**: 1686. **¹H**: 8.03 (d, 1H, *J* = 7.2), 7.72 (d, 2H, *J* = 8.3), 7.58 (td, 1H, *J* = 7.5, 1.4), 7.36 (td, 1H, *J* = 7.6, 1.1), 7.29-7.24 (m, 3H), 6.59 (d, 1H, *J* = 9.9), 6.27 (d, 1H, *J* = 9.8), 3.64-3.60 (m, 2H), 2.42 (s, 3H), 2.26-2.03 (m, 2H), 2.02-1.95 (m, 2H). **¹³C**: 198.4, 143.2, 137.4, 137.1, 136.6, 134.8, 129.3, 128.7, 128.0, 127.7, 127.6, 127.5,

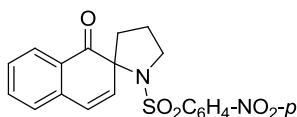
124.5, 70.9, 48.9, 39.5, 23.0, 21.6. **HRMS**: calcd for C₂₀H₁₉NO₃SNa [M+Na]⁺: 376.0983; found: 376.0983.

C.1.1.3 Characterization of (±)-4-bromo-1'-tosyl-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2c)



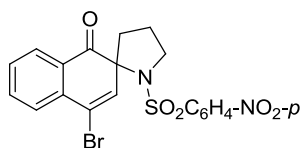
11 mg (73% yield) from 15 mg of **4.1c**, yellow solid, m.p. 63-65 °C, eluent: 1:4 EtOAc/hexane; **IR**: 1693. **¹H**: 8.10 (dd, 1H, *J* = 7.7, 1.1), 7.77-7.67 (m, 4H), 7.47 (td, 1H, *J* = 7.5, 1.3), 7.31 (d, 2H, *J* = 8.1), 6.52 (s, 1H), 3.77-3.70 (m, 1H), 3.60-3.52 (m, 1H), 2.44 (s, 3H), 2.29-2.16 (m, 2H), 2.09-1.99 (m, 2H). **¹³C**: 196.7, 143.4, 137.2, 137.1, 135.4, 135.0, 129.5, 129.3, 128.8, 128.4, 127.8, 127.6, 119.2, 71.9, 48.8, 39.5, 23.3, 21.6. **HRMS**: calcd for C₂₀H₁₈NO₃S⁷⁹BrNa [M+Na]⁺: 454.0088; found: 454.0070.

C.1.1.4 Characterization of (±)-1'-(4-Nitrophenylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2d)



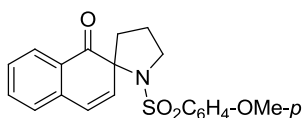
15 mg (75% yield) from 20 mg of **4.1d**, green solid, dec. 134 °C; eluent: 2:3 EtOAc/hexane; **IR**: 1685. **¹H**: 8.34 (d, 2H, *J* = 8.9), 7.99 (m, 3H), 7.62 (td, 1H, *J* = 7.5, 1.3), 7.39 (td, 1H, *J* = 7.6, 1.1), 7.28 (d, 1H, *J* = 6.7), 6.62 (d, 1H, *J* = 9.8), 6.28 (d, 1H, *J* = 9.8), 3.77-3.61 (m, 2H), 2.24-1.99 (m, 4H). **¹³C**: 198.0, 149.9, 145.4, 137.3, 136.1, 135.2, 129.0, 128.5, 128.4, 127.8, 127.5, 124.8, 123.9, 71.8, 49.4, 39.6, 22.9. **HRMS**: calcd for C₁₉H₁₆N₂O₅S [M+Na]⁺: 407.0678; found: 407.0685.

C.1.1.5 Characterization of (\pm)-4-bromo-1'-(4-nitrophenylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2e)



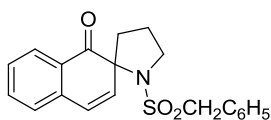
10.5 mg (70% yield) from 15 mg of **4.1e**, yellow solid, dec. 110 °C, eluent: 2:3 EtOAc/hexane; **IR**: 1691. **¹H**: 8.37 (d, 2H, $J = 8.8$), 8.07 (d, 1H, $J = 7.7$), 7.99 (d, 2H, $J = 8.8$), 7.79-7.71 (m, 2H), 7.50 (t, 1H, $J = 7.4$), 6.53 (s, 1H), 3.77-3.63 (m, 2H), 2.33-2.18 (m, 2H), 2.15-2.01 (m, 2H). **¹³C**: 196.3, 150.0, 145.5, 136.6, 135.4, 135.3, 129.6, 128.8, 128.6 (2C), 127.8, 124.1, 119.6, 72.6, 49.3, 39.5, 23.3. **HRMS**: calcd for C₁₉H₁₅N₂O₅S⁷⁹Br [M]⁺: 461.9885; found: 461.9887.

C.1.1.6 Characterization of (\pm)-1'-(4-Methoxyphenylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2f)



16 mg (80% yield) from 20 mg of **4.1f**, colorless oil, eluent: 2:3 EtOAc/hexane; **IR**: 1690, 1149. **¹H**: 8.03 (d, 1H, $J = 7.7$), 7.78 (d, 2H, $J = 8.9$), 7.58 (td, 1H, $J = 7.5, 1.3$), 7.36 (td, 1H, $J = 7.6, 0.9$), 7.25 (d, 1H, $J = 7.5$), 6.94 (d, 2H, $J = 8.9$), 6.59 (d, 1H, $J = 9.9$), 6.30 (d, 1H, $J = 9.8$), 3.86 (s, 3H), 3.62-3.58 (m, 2H), 2.24-1.95 (m, 4H). **¹³C**: 198.6, 162.8, 137.4, 136.7, 134.8, 131.7, 129.9, 128.7, 128.0, 127.6, 127.4, 124.5, 113.8, 70.9, 55.5, 48.8, 39.5, 23.0. **HRMS**: calcd for C₂₀H₂₀NO₄S [M+H]⁺: 370.1113; found: 370.1115.

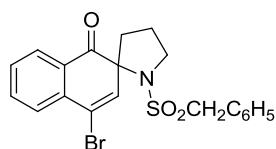
C.1.1.7 Characterization of (\pm)-1'-(Benzylsulfonyl)-4-bromo-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2g)



19 mg (96% yield) from 20 mg of **4.1g**, colorless oil, eluent: 2:3 EtOAc/hexane; **IR**: 1685. **¹H**: 8.06 (d, 1H, $J = 7.7$), 7.59-7.54 (m, 3H), 7.38-7.36 (m, 4H), 7.20 (d, 1H, $J = 7.6$), 6.45 (d, 1H, $J = 9.8$), 6.03 (d, 1H, $J = 9.8$), 4.44 (d, 1H, $J = 13.6$), 4.28 (d, 1H, $J = 13.5$), 3.40 (t, 2H, $J = 6.8$), 2.23-1.85 (m, 4H). **¹³C**: 199.3, 137.5 (2C),

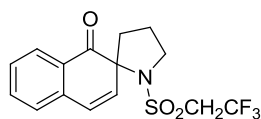
134.9, 131.1, 129.6, 128.6 (2C, shoulder), 128.5, 128.0, 127.6, 127.5, 124.0, 72.1, 59.8, 50.0, 39.8, 23.1. **HRMS**: calcd for C₂₀H₁₉NO₃SNa [M+Na]⁺: 376.0983; found: 376.0986.

C.1.1.8 Characterization of (±)-1'-(benzylsulfonyl)-4-bromo-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2h)



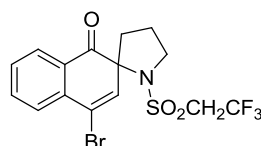
13 mg (87% yield) from 15 mg of **4.1h**, yellow solid, dec. 113 °C, eluent: 1:4 EtOAc/hexane; **IR**: 1693. **¹H**: 8.09 (d, 1H, *J* = 7.6), 7.72-7.62 (m, 2H), 7.56-7.37 (m, 6H), 6.17 (s, 1H), 4.42 (d, 1H, *J* = 13.7), 4.29 (d, 1H, *J* = 13.7), 3.53-3.36 (m, 2H), 2.23-2.00 (m, 4H). **¹³C**: 197.4, 138.2, 135.6, 135.1, 131.0, 129.3, 129.2, 128.7, 128.6, 128.3, 127.8, 118.1, 73.4, 59.8, 49.8, 39.4, 23.2. **HRMS**: calcd for C₂₀H₁₈NO₃S⁷⁹BrNa [M+Na]⁺: 454.0088; found: 454.0074.

C.1.1.9 Characterization of (±)-1'-(2,2,2-Trifluoroethylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2i)



9 mg (45% yield) from 20 mg of **4.1i**, light yellow solid, m.p.: 121-123 °C; eluent: 2:3 EtOAc/hexane; **IR**: 1685. **¹H**: 8.02 (dd, 1H, *J* = 7.4, 0.7), 7.61 (td, 1H, *J* = 7.6, 1.4), 7.39 (td, 1H, *J* = 7.7, 1.1), 7.24 (d, 1H, *J* = 7.6), 6.56 (d, 1H, *J* = 9.8), 6.34 (d, 1H, *J* = 9.8), 4.11-3.75 (m, 4H), 2.31-2.03 (m, 4H). **¹³C**: 199.1, 137.5, 136.6, 135.4, 128.4, 128.3, 127.7, 127.6, 124.5, 121.9(q), 72.8, 55.1(q), 49.8, 40.2, 23.0. **HRMS**: calcd for C₁₅H₁₄F₃NO₃SNa [M+Na]⁺: 368.0544; found: 368.0540.

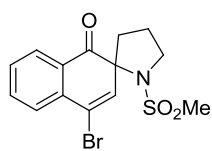
C.1.1.10 Characterization of (±)-4-bromo-1'-(2,2,2-trifluoroethylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2j)



13.8 mg (93% yield) from 15 mg of **4.1j**, yellow solid, m.p. 51-53 °C, eluent: 1:4 EtOAc/hexane; **IR**: 1690. **¹H**: 8.05 (d, 1H, *J* = 7.6), 7.75-7.69

(m, 2H), 7.48 (app t, 1H, $J = 6.8$), 6.77 (s, 1H), 4.12-3.71 (m, 4H), 2.31-2.13 (m, 4H). ^{13}C : 197.3, 137.4, 135.6, 129.5, 128.5, 128.4, 127.8, 121.8 (q), 118.6, 74.1, 55.2 (q), 49.7, 40.2, 23.3. **HRMS**: calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_3\text{F}_3\text{S}^{79}\text{BrNa}$ $[\text{M}+\text{Na}]^+$: 445.9649; found: 445.9655.

C.1.1.11 Characterization of (\pm)-4-Bromo-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2k)

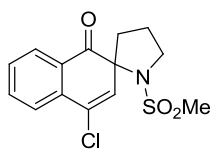


21 mg (83% yield) from 25 mg of **4.1k**, yellow oil; eluent: 3:7 EtOAc/hexane;

IR: 1690. ^1H : 8.05 (d, 1H, $J = 7.6$), 7.74-7.66 (m, 2H), 7.45 (t, 1H, $J = 7.1$), 6.78 (s, 1H), 3.79-3.65 (m, 2H), 3.02 (s, 3H), 2.28-2.07 (m, 4H). ^{13}C : 197.6,

138.5, 135.8, 135.3, 129.2, 128.5, 128.4, 127.6, 117.9, 73.4, 49.2, 39.7(2C), 23.1. **HRMS**: calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3\text{S}^{79}\text{BrNa}$ $[\text{M}+\text{Na}]^+$: 377.9775; found: 377.9783.

C.1.1.12 Characterization of (\pm)-4-chloro-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2l)

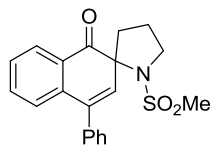


17 mg (85% yield) from 20 mg of **4.1l**, colorless oil, eluent: 1:3 to 2:3

EtOAc/hexanes; **IR**: 1692. ^1H : 8.07 (d, 1H, $J = 6.0$), 7.76-7.67 (m, 2H), 7.47 (app t, 1H, $J = 7.5$), 6.52 (s, 1H), 3.78-3.65 (m, 2H), 3.01 (s, 3H), 2.29-1.99

(m, 4H). ^{13}C : 197.7, 135.4, 135.3, 134.4, 129.3, 128.6, 127.9, 127.5, 125.8, 72.6, 49.3, 40.1, 39.8, 23.3. **HRMS**: calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3\text{SClNa}$ $[\text{M}+\text{Na}]^+$: 334.0281; found: 334.0276.

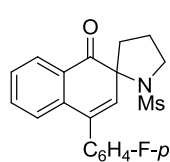
C.1.1.13 Characterization of (\pm)-1'-(Methylsulfonyl)-4-phenyl-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2m)



11 mg (55% yield) from 20 g of **4.1m**, white solid, m.p.: 145-147 °C (color changes to brown); eluent: 3:7 EtOAc/hexane; **IR**: 1688. ^1H : 8.10 (dd, 1H, $J = 7.7, 1.2$), 7.52 (td, 1H, $J = 7.7, 1.5$), 7.44-7.36 (m, 6H), 7.16 (d, 1H, $J = 7.8$),

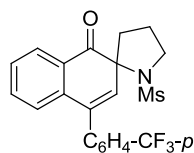
6.27 (s, 1H), 3.78-3.71 (m, 2H), 3.04 (s, 3H), 2.39-2.06 (m, 4H). ^{13}C : 199.3, 138.4, 138.1, 136.5, 135.3, 134.8, 129.1, 128.7, 128.4, 127.9, 127.8 (2C), 126.8, 72.1, 49.3, 39.9, 39.6, 23.0. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 376.0983; found: 376.0990.

C.1.1.14 Characterization of (\pm)-4-(4-fluorophenyl)-1'-(methylsulfonyl)-1H-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2n)



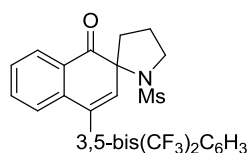
16.9 mg (85% yield) from 20 mg of **4.1n**, off white solid, turns brown at 125 °C and then melts at 148-149 °C, eluent: 1:4 EtOAc/hexanes; **IR**: 1687. ^1H : 8.10 (d, 1H, $J = 6.0$), 7.55-7.50 (m, 1H), 7.41-7.32 (m, 3H), 7.15-7.09 (m, 3H), 6.26 (s, 1H), 3.80-3.67 (m, 2H), 3.03 (s, 3H), 2.34-2.05 (m, 4H). ^{13}C : 199.4, 162.6 (d, $J = 246.9$), 138.1, 137.0, 135.0, 134.5 (d, $J = 3.8$), 134.4, 131.0 (d, $J = 8.3$), 128.7, 128.2, 128.1, 126.7, 115.6 (d, $J = 21.1$), 72.3, 49.4, 40.0, 39.7, 23.1. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_3\text{FS}$ $[\text{M}+\text{H}]^+$: 372.1070; found: 372.1078.

C.1.1.15 Characterization of (\pm)-1'-(methylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2o)



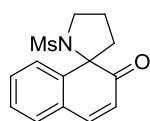
17 mg (85% yield) from 20 mg of **4.1o**, off white solid, m.p.: 160-161 °C (color changes to brown), eluent: 1:4 EtOAc/hexanes; **IR**: 1690. ^1H : 8.12 (d, 1H, $J = 9.0$), 7.70 (d, 2H, $J = 6.0$), 7.56-7.49 (m, 3H), 7.43-7.38 (m, 1H), 7.07 (d, 1H, $J = 6.0$), 6.31 (s, 1H), 3.81-3.67 (m, 2H), 3.04 (s, 3H), 2.36-2.06 (m, 4H). ^{13}C : 199.1, 142.3, 137.6, 137.5, 135.1, 134.3, 130.3 (q, $J = 33.2$), 129.7, 128.7, 128.5, 128.2, 126.6, 125.6 (q, $J = 3.8$), 120.6 (q, $J = 272.6$), 72.3, 49.4, 39.9, 39.7, 23.2. **HRMS**: calcd for $\text{C}_{21}\text{H}_{18}\text{NO}_3\text{F}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 444.0857; found: 444.0859.

C.1.1.16 Characterization of (\pm)-4-(3,5-bis(trifluoromethyl)phenyl)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2p)



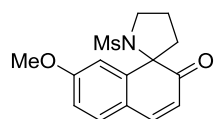
12 mg (60% yield) from 20 mg of **4.1p**, off white solid, m.p.: 76-78 °C, eluent: 1:4 EtOAc/hexanes; **IR**: 1715. **¹H**: 8.14 (d, 1H, *J* = 6.0), 7.93 (s, 1H), 7.83 (s, 2H), 7.61-7.42 (m, 2H), 6.96 (d, 1H, *J* = 6.0), 6.38 (s, 1H), 3.83-3.68 (m, 2H), 3.05 (s, 3H), 2.41-2.09 (m, 4H). **¹³C**: 198.7, 140.7, 138.9, 136.9, 135.3, 133.0, 132.2 (q, *J* = 34.0), 129.5 (app d, *J* = 3.0), 128.9, 128.7, 128.5, 126.1, 123.3 (q, *J* = 273.3), 122.2-122.0 (m), 72.5, 49.4, 39.8 (2C), 23.2. **HRMS**: calcd for C₂₂H₁₇NO₃F₆SNa [M+Na]⁺: 512.0731; found: 512.0745.

C.1.1.17 Characterization of (\pm)-1'-(Methylsulfonyl)-2*H*-spiro[naphthalene-1,2'-pyrrolidin]-2-one (4.5a)



16 mg (67% yield) from 25 g of **4.4a**, white solid, m.p.: 116-118 °C; eluent: 2:3 EtOAc/hexane; **IR**: 1672. **¹H**: 7.62 (d, 1H, *J* = 7.8), 7.47-7.42 (m, 2H), 7.32-7.31 (m, 2H), 6.17 (d, 1H, *J* = 9.9), 3.99-3.92 (m, 1H), 3.80-2.72 (m, 1H), 3.10 (s, 3H), 2.43-2.34 (m, 1H), 2.22-2.13 (m, 2H), 2.07-1.98 (m, 1H). **¹³C**: 200.5, 146.5, 146.0, 130.6, 129.8, 128.5, 127.7, 125.8, 123.7, 75.8, 49.9, 44.2, 40.0, 22.8. **HRMS**: calcd for C₁₄H₁₅NO₃SNa [M+Na]⁺: 300.0670; found: 300.0665.

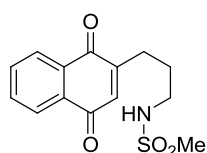
C.1.1.18 Characterization of (\pm)-7-Methoxy-1'-(methylsulfonyl)-2*H*-spiro[naphthalene-1,2'-pyrrolidin]-2-one (4.5b)



12 mg (58% yield) from 20 mg of **4.4b**, white solid, m.p.: 144-146 °C; eluent: 2:3 EtOAc/hexane; **IR**: 1669. **¹H**: 7.40 (d, 1H, *J* = 9.8), 7.25 (d, 1H, *J* = 7.6), 7.16 (d, 1H, *J* = 2.5), 6.81 (dd, 1H, *J* = 8.4, 2.5), 6.04 (d, 1H, *J* = 9.8), 3.98-3.91 (m, 1H), 3.86 (s, 3H), 3.78-3.71 (m, 1H), 3.11 (s, 3H), 2.42-2.34 (m, 1H), 2.21-2.12 (m, 2H), 2.06-1.98 (m, 1H).

^{13}C : 200.4, 161.8, 149.0, 145.9, 131.5, 121.8, 121.0, 112.5, 112.3, 76.0, 55.5, 49.9, 44.3, 39.9, 22.7. **HRMS**: calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 330.0776; found: 330.0782.

C.2 Characterization of *N*-(3-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)propyl)methanesulfonamide (4.3)



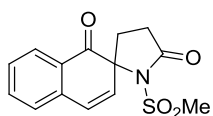
4.2-7.0 mg (20-35% yield) from 20 mg of **4.1q**, yellow solid, m.p. 120-122 °C, eluent: 2:3 EtOAc/hexane; **IR**: 3378-3126 (broad), 1659. ^1H : 8.11-8.06 (m, 2H), 7.78-7.72 (m, 2H), 6.85 (s, 1H), 4.57 (br s, 1H), 3.23 (q, 2H, $J = 12.0$, 6.0), 2.99 (s, 3H), 2.67 (app t, 2H, $J = 7.5$), 1.90 (p, 2H, $J = 6.0$). ^{13}C : 185.3, 184.8, 150.3, 135.6, 133.9, 133.8, 132.1, 126.7, 126.2, 42.5, 40.6, 29.2, 26.6. **HRMS**: calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 316.0619; found: 316.0625.

C.3 Synthesis and characterization of spiroactams

C.3.1 Representative protocol for the *ortho*-oxidative cyclization of *N*-acyl sulfonamides

A solution of sulfonamide **4.8** (0.1 mmol, 1.0 equiv) in HFIP (2.0 mL) was added to a solution containing DIB (0.11 mmol, 1.1 equiv) in TFA (0.23 mL) at RT so that the final concentration was 0.05 M. Upon completion of the reaction (TLC, 5-12 min), the reaction mixture was evaporated to dryness. Chromatography of the residue afforded the azaspirocyclic compound.

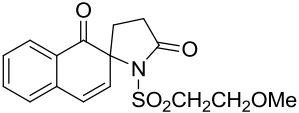
C.3.1.1 Characterization of (\pm)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidine]-1,5'-dione (4.9a)



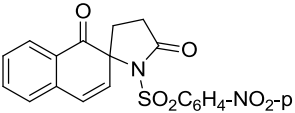
8 mg (42% yield) from 19 mg of **4.8a**, white solid, m.p.: 169-171 °C; eluent: 3:7 EtOAc/hexane; **IR**: 1737, 1686. ^1H : 8.05 (d, 1H, $J = 7.7$), 7.64 (t, 1H, $J = 7.5$), 7.42 (t, 1H, $J = 7.6$), 7.30-7.27 (m, 1H), 6.61 (d, 1H, $J = 9.8$), 6.43 (d, 1H, $J = 9.8$), 3.38 (s,

3H), 2.84-2.58 (m, 2H), 2.33 (ddd, 1H, $J = 13.4, 9.4, 3.9$), 2.20-2.09 (m, 1H). ^{13}C : 197.1, 174.7, 137.5, 135.8, 135.3, 128.6, 128.1, 127.9, 127.4, 124.7, 71.4, 41.6, 29.8, 28.9. **HRMS**: calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 314.0463; found: 314.0468.

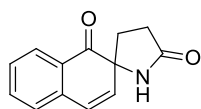
C.3.1.2 Characterization of (\pm)-1'-(2-methoxyethylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidine]-1,5'-dione (**4.9b**)

 9 mg (47% yield) from 20 mg of **4.8b**, colorless oil, eluent: 2:3 EtOAc/hexane; **IR**: 1737, 1687. ^1H : 8.05 (d, 1H, $J = 7.6$), 7.63 (t, 1H, $J = 7.4$), 7.41 (t, 1H, $J = 7.6$), 7.29-7.26 (m, 1H), 6.61 (d, 1H, $J = 9.8$), 6.43 (d, 1H, $J = 9.8$), 4.09-4.01 (m, 1H), 3.88 (td, 2H, $J = 5.9, 1.2$), 3.71-3.62 (m, 1H), 3.36 (s, 3H), 2.85-2.73 (m, 1H), 2.67-2.57 (m, 1H), 2.32 (ddd, 1H, $J = 13.4, 9.3, 4.2$), 2.19-2.08 (m, 1H). ^{13}C : 196.9, 174.7, 137.4, 135.7, 135.0, 128.6, 128.0, 127.9, 127.5, 124.9, 70.9, 65.1, 58.9, 54.3, 30.1, 29.1. **HRMS**: calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 358.0725; found: 358.0729.

C.3.1.3 Characterization of (\pm)-1'-(4-nitrophenylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidine]-1,5'-dione (**4.9c**)

 6 mg (29% yield) from 20 mg of **4.8c**, 29% yield, yellow solid, dec. 104 °C; eluent: 1:4 EtOAc/hexane; **IR**: 1747, 1679. ^1H : 8.39 (d, 2H, $J = 9.1$), 8.25 (d, 2H, $J = 9.1$), 8.12 (d, 1H, $J = 7.7$), 7.69 (td, 1H, $J = 7.6, 1.4$), 7.48 (td, 1H, $J = 7.7, 1.0$), 7.35 (d, 1H, $J = 7.6$), 6.73 (d, 1H, $J = 9.8$), 6.48 (d, 1H, $J = 9.8$), 2.73-2.50 (m, 2H), 2.32 (ddd, 1H, $J = 13.5, 8.9, 4.8$), 2.20-2.10 (m, 1H). ^{13}C : 196.3, 173.2, 150.9, 143.1, 137.2, 135.9, 134.3, 131.2, 128.9, 128.2, 128.0, 127.7, 125.8, 123.6, 71.1, 30.5, 29.0. **HRMS**: calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$: 421.0470; found: 421.0463.

C.3.2 Preparation of 1*H*-spiro[naphthalene-2,2'-pyrrolidine]-1,5'-dione (**4.10**)



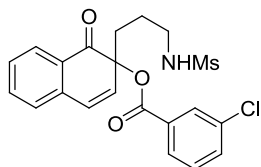
A solution of sulfonamide **4.9c** (20 mg, 0.05 mmol, 1.0 equiv) in CH₃CN (1.0 mL) was added at RT to a solution of PhSH (15 μL, 150 μmol, 3.0 equiv) in CH₃CN (0.4 mL) containing suspended K₂CO₃ (28 mg, 0.2 mmol, 4.0 equiv). Next, DMSO (0.1 mL) was added to the reaction mixture and stirring was continued at room temperature for 2 h, after which time TLC showed that the reaction was complete. The reaction was quenched with H₂O (5 mL) and extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: 3:4 EtOAc/hexane) to provide 8 mg (78% yield) of **4.10** as a white solid, m.p.: 131-133 °C. **IR**: 3430-3100 (broad), 1698. **¹H**: 8.03 (d, 1H, *J* = 7.6), 7.62 (td, 1H, *J* = 7.6, 1.3), 7.41 (td, 1H, *J* = 7.7, 0.7), 7.30-7.29 (m, 1H), 6.62 (d, 1H, *J* = 9.8), 6.18 (d, 1H, *J* = 9.8), 5.57 (br s, 1H), 2.71-2.59 (m, 1H), 2.46-2.31 (m, 2H), 2.17-2.05 (m, 1H). **¹³C**: 199.4, 178.8, 137.1, 135.3 (2C), 128.7, 127.9, 127.7 (2C), 127.0, 65.0, 32.2, 28.2. **HRMS**: calcd for C₁₃H₁₁NO₂ [M+Na]⁺: 236.0687; found: 236.0687.

C.4 Synthesis and characterization of acyloxylated adducts

C.4.1 Representative protocol for acyloxylation of naphtholic sulfonamides

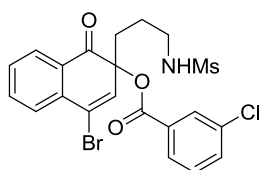
A solution of MCPBA (0.09 mmol, 1.5 equiv) in CH₂Cl₂ (2.5 mL) was added at RT to solution of a substrate **4.1** (0.06 mmol, 1.0 equiv), MCBA (0.12 mmol, 2.0 equiv) and iodobenzene (0.06 mmol, 1.0 equiv) in CH₂Cl₂ (1.5 mL). The mixture was stirred at RT, whereupon TLC indicated complete reaction. The mixture was quenched with aq. sat. NaHCO₃ (3.0 mL) and aq. sat. Na₂S₂O₃ (1.5 mL) solutions and extracted with CH₂Cl₂ (3×5 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to afford product (±)-**4.54**.

C.4.1.1 Characterization of (±)-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54a)



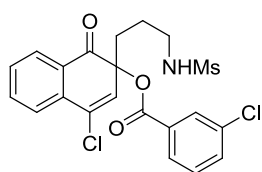
17 mg (22% yield) from 50 mg of **4.1a**, yellow oil, eluent: 2:3 Et₂O/pentane; **IR**: 3390-3156 (broad), 1721, 1690. **¹H**: 8.09 (d, 1H, *J* = 7.8), 8.00 (s, 1H), 7.91 (d, 1H, *J* = 7.7), 7.64 (t, 1H, *J* = 7.5), 7.56 (d, 1H, *J* = 8.1), 7.45-7.37 (m, 2H), 7.32 (d, 1H, *J* = 7.7), 6.78 (d, 1H, *J* = 10.0), 6.13 (d, 1H, *J* = 9.9), 4.33 (t, 1H, *J* = 5.9), 3.15 (app q, 2H, *J* = 6.7), 2.93 (s, 3H), 2.20-2.10 (m, 1H), 2.06-1.96 (m, 1H), 1.91-1.75 (m, 1H), 1.68-1.57 (m, 1H). **¹³C**: 195.7, 164.0, 136.8, 135.0, 134.6, 133.5, 132.6, 130.9, 129.9, 129.8, 129.4, 128.8, 128.2, 128.1, 127.7, 127.3, 80.6, 43.1, 40.4, 35.0, 23.5. **HRMS**: calcd for C₂₁H₁₉NO₅SCl [M-H]⁻: 432.0672; found: 432.0670.

C.4.1.2 Characterization of (±)-4-bromo-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54b)



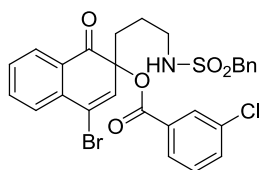
7.0 mg (24% yield) from 20 mg of **4.1k**, white solid, m.p.: 56-58 °C, eluent: 2:3 EtOAc/hexane; **IR**: 3421-3161 (broad), 1725, 1695. **¹H**: 8.12 (d, 1H, *J* = 7.7), 8.00 (s, 1H), 7.91 (d, 1H, *J* = 8.0), 7.84-7.73 (m, 2H), 7.59-7.50 (m, 2H), 7.41 (t, 1H, *J* = 7.9), 6.59 (s, 1H), 4.24 (t, 1H, *J* = 5.7), 3.18 (app q, 2H, *J* = 6.6), 2.95 (s, 3H), 2.23-2.13 (m, 1H), 2.09-2.00 (m, 1H), 1.87-1.75 (m, 1H), 1.71-1.59 (m, 1H). **¹³C**: 193.8, 163.9, 135.2, 135.1, 134.7, 134.0, 133.7, 130.5, 129.9 (3C), 129.5, 129.0, 128.1, 127.5, 121.7, 81.5, 42.9, 40.5, 34.8, 23.5. **HRMS**: calcd for C₂₁H₁₈NO₅SCl⁷⁹Br [M-H]⁻: 509.9778; found: 509.9784.

C.4.1.3 Characterization of (±)-4-chloro-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54c)



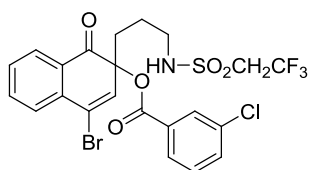
12.7 mg (17% yield) from 50 mg of **4.11**, colorless oil, eluent: 1:3 EtOAc/hexanes; **IR**: 3426-3159 (broad), 1723, 1696. **¹H**: 8.15 (d, 1H, *J* = 9.0), 7.99 (s, 1H), 7.90 (d, 1H, *J* = 6.0), 7.85 (d, 1H, *J* = 6.0), 7.76 (app t, 1H, *J* = 7.5), 7.58-7.52 (m, 2H), 7.40 (app t, 1H, *J* = 9.0), 6.33 (s, 1H), 4.34 (br s, 1H), 3.17 (app q, 2H, *J* = 7.0), 2.94 (s, 3H), 2.18-2.00 (m, 2H), 1.89-1.75 (m, 1H), 1.70-1.60 (m, 1H). **¹³C**: 194.0, 164.1, 135.3, 134.8, 134.6, 133.8, 131.4, 130.7, 130.1, 130.0 (2C), 129.8, 129.6, 128.3, 127.8, 126.4, 80.9, 43.1, 40.6, 35.2, 23.6. **HRMS**: calcd for C₂₁H₁₈NO₅SCl₂ [M-H]⁻: 466.0283; found: 466.0280.

C.4.1.4 Characterization of (±)-4-bromo-1-oxo-2-(3-(phenylmethylsulfonamido)propyl)-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54d)



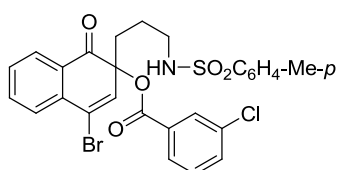
9.3 mg (43% yield) from 16 mg of **4.1h**, light yellow solid, m.p.: 86-88 °C, eluent: 1:5 EtOAc/hexane; **IR**: 3400-3207 (broad). **¹H**: 8.11 (d, 1H, *J* = 7.6), 7.98 (s, 1H), 7.89 (d, 1H, *J* = 7.7), 7.90-7.72 (m, 2H), 7.58-7.49 (m, 2H), 7.42-7.34 (m, 6H), 6.54 (s, 1H), 4.24 (s, 2H), 4.11 (t, 1H, *J* = 6.0), 2.97 (app q, 2H, *J* = 6.5), 2.12-2.01 (m, 1H), 1.99-1.89 (m, 1H), 1.74-1.57 (m, 1H), 1.55-1.43 (m, 1H). **¹³C**: 193.8, 163.9, 135.2, 135.1, 134.6, 134.1, 133.7, 130.5, 129.9 (2C), 129.8, 129.5, 129.2, 128.9, 128.1, 127.5, 121.7, 81.5, 59.0, 43.4, 34.8, 23.7. **HRMS**: calcd for C₂₇H₂₂NO₅SCl⁷⁹Br [M-H]⁻: 586.0091; found: 586.0071.

C.4.1.5 Characterization of (±)-4-bromo-1-oxo-2-(3-(2,2,2-trifluoroethylsulfonamido)propyl)-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54e)



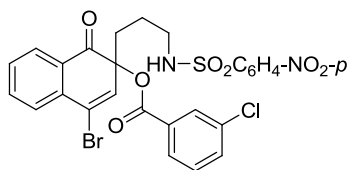
11.5 mg (42% yield) from 20 mg of **4.1j**, light yellow solid, m.p.: 48-50 °C, eluent: 3:17 EtOAc/hexane; **IR**: 3446-3182 (broad). **¹H**: 8.12 (d, 1H, *J* = 7.7), 7.99 (s, 1H), 7.90 (d, 1H, *J* = 7.8), 7.84-7.73 (m, 2H), 7.59-7.50 (m, 2H), 7.40 (t, *J* = 8.0, 1H), 6.58 (s, 1H), 4.66 (t, 1H, *J* = 6.1), 3.79 (q, 2H, *J* = 9.0), 3.22 (app q, 2H, *J* = 6.8), 2.22-2.12 (m, 1H), 2.08-1.98 (m, 1H), 1.89-1.77 (m, 1H), 1.73-1.60 (m, 1H). **¹³C**: 193.8, 163.9, 135.3, 135.0, 134.7, 133.9, 133.7, 130.4, 129.9 (3C), 129.4, 129.0, 128.1, 127.6, 121.8, 121.5 (q, *J* = 277.5), 81.4, 54.4 (q, *J* = 31.5), 43.3, 34.6, 23.6. **HRMS**: calcd for C₂₂H₁₇BrNO₅F₃SCl⁷⁹Br [M-H]⁻: 577.9651; found: 577.9659.

C.4.1.6 Characterization of (±)-4-bromo-2-(3-(4-methylphenylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54f)



9.7 mg (36% yield) from 20 mg of **4.1c**, light yellow solid, m.p.: 73-75 °C; eluent: 1:4 EtOAc/hexane; **IR**: 3411-3178 (broad), 1723, 1695. **¹H**: 8.08 (d, 1H, *J* = 7.6), 7.97 (t, 1H, *J* = 1.6), 7.88 (d, 1H, *J* = 7.8), 7.81-7.70 (m, 4H), 7.57 (d, 1H, *J* = 7.5), 7.51 (t, 1H, *J* = 7.4), 7.39 (t, 1H, *J* = 7.9), 7.29 (d, 2H, *J* = 8.2), 6.52 (s, 1H), 4.41 (t, 1H, *J* = 5.9), 2.97 (app q, 2H, *J* = 6.6), 2.42 (s, 3H), 2.13-2.03 (m, 1H), 2.01-1.91 (m, 1H), 1.74-1.62 (m, 1H), 1.59-1.47 (m, 1H). **¹³C**: 193.8, 163.9, 143.6, 136.7, 135.2, 135.0, 134.6, 134.0, 133.7, 130.5, 129.9 (2C), 129.8, 129.4, 128.9, 128.1, 127.5, 127.0, 121.6, 81.6, 42.9, 34.9, 23.0, 21.6. **HRMS**: calcd for C₂₇H₂₃NO₅SCl⁷⁹BrNa [M+Na]⁺: 610.0067; found: 610.0095.

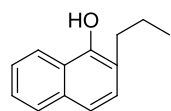
C.4.1.7 Characterization of (\pm)-4-bromo-2-(3-(4-nitrophenylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54g)



10.4 mg (39% yield) from 20 mg of **4.1e**, yellow solid, m.p.: 72-74 °C; eluent: 1:3 EtOAc/hexane; **IR**: 3421-3199 (broad), 1725, 1700. **¹H**: 8.33 (d, 2H, $J = 8.9$), 8.06 (d, 1H, $J = 7.3$), 8.00 (d, 2H, $J = 8.9$), 7.95 (t, 1H, $J = 1.8$), 7.87 (d, 1H, $J = 7.8$), 7.81-7.71 (m, 2H), 7.57 (d, 1H, $J = 8.0$), 7.51 (td, 1H, $J = 7.4, 1.4$), 7.39 (t, 1H, $J = 7.9$), 6.52 (s, 1H), 4.74 (t, 1H, $J = 6.1$), 3.07 (app q, 2H, $J = 6.8$), 2.14-2.04 (m, 1H), 2.00-1.90 (m, 1H), 1.78-1.64 (m, 1H), 1.60-1.45 (m, 1H). **¹³C**: 193.7, 163.8, 150.1, 145.8, 135.3, 134.9, 134.7, 133.8, 133.7, 130.4, 129.9, 129.3, 128.9, 128.2, 128.1, 127.5, 124.5, 121.8, 81.3, 43.1, 34.8, 23.1. **HRMS**: calcd for C₂₆H₂₀N₂O₇SCl⁷⁹BrNa [M+Na]⁺: 640.9761; found: 640.9745.

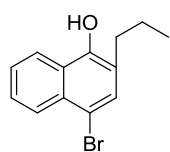
C.5 Preparation and characterization of intermediates towards acyloxylated adduct 4.68

C.5.1 Preparation of 2-propylnaphthalen-1-ol (4.66)



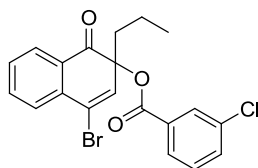
A solution of commercial 10 wt % palladium on carbon (0.74 g, 0.05 equiv) and substrate **4.65** (2.72 g, 14.7 mmol) in EtOH (35.0 mL) was stirred under inert atmosphere at RT. Hydrogen gas was bubbled into the solution overnight. Upon the completion of the reaction, the mixture was filtered through 2-inch Celite using EtOH. The filtrate was evaporated and was purified by flash column chromatography (eluent: 1:49 to 1:19 EtOAc/hexanes) on silica gel to provide 2.06 g (75% yield) of **4.66** as brown oil. **IR**: 3641-3152 (broad). **¹H**: 8.14 (d, 1H, $J = 9.0$), 7.80 (d, 1H, $J = 9.0$), 7.51-7.44 (m, 2H), 7.42 (d, 1H, $J = 9.0$), 7.26 (d, 1H, $J = 6.0$), 5.17 (s, 1H), 2.75 (t, 2H, $J = 7.5$), 1.80-1.68 (m, 2H), 1.03 (t, 3H, $J = 7.5$). **¹³C**: 148.3, 133.4, 128.3, 127.7, 126.9, 125.5, 125.3, 124.6, 121.1, 120.3, 32.0, 23.3, 14.1.

C.5.2 Preparation of 4-bromo-2-propylnaphthalen-1-ol (4.67)



The procedure described above for **3.12** afforded 1.36 g (64% yield) of **4.67** from 1.5 g of **4.66** as light yellow solid, m.p.: 73-75 °C (color changes to black), eluent: 1:19 EtOAc/hexanes. **IR**: 3525-3120 (broad). **¹H**: 8.17 (d, 2H, *J* = 6.0), 7.60-7.51 (m, 3H), 5.20 (br s, 1H), 2.69 (t, 2H, *J* = 7.5), 1.78-1.66 (m, 2H), 1.03 (t, 3H, *J* = 7.5). **¹³C**: 148.2, 131.6, 131.4, 127.1, 127.0, 126.1, 125.8, 122.3, 121.7, 113.3, 31.8, 23.2, 14.1. **HRMS**: calcd for C₁₃H₁₂OBr [M-H]⁻: 263.0072; found: 263.0071.

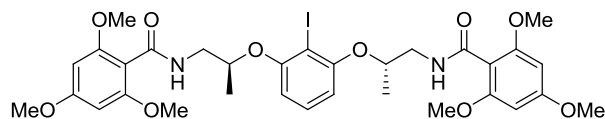
C.5.3 Characterization of (±)-4-bromo-1-oxo-2-propyl-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.68)



The procedure described above for **4.54** afforded 33 mg (42% yield) of **4.68** from 50 mg of **4.67** as light yellow oil, eluent: 1:19 EtOAc/hexanes. **IR**: 3606-3314 (broad), 1724, 1697. **¹H**: 8.13 (d, 1H, *J* = 9.0), 8.02 (s, 1H), 7.92 (d, 1H, *J* = 9.0), 7.82-7.70 (m, 2H), 7.57 (d, 1H, *J* = 9.0), 7.50 (t, 1H, *J* = 7.5), 7.39 (t, 1H, *J* = 7.5), 6.61 (s, 1H), 2.11-1.91 (m, 2H), 1.67-1.49 (m, 1H), 1.41-1.26 (m, 1H), 0.95 (t, 3H, *J* = 7.5). **¹³C**: 194.5, 164.2, 135.4, 135.1, 134.9, 134.7, 133.7, 131.0, 130.1, 129.9, 129.8, 128.9, 128.3, 127.6, 121.2, 82.6, 40.5, 16.4, 14.4. **HRMS**: calcd for C₂₀H₁₆O₃Cl⁷⁹BrNa [M+Na]⁺: 440.9869; found: 440.9871.

C.6 Preparation of chiral iodoarene precatalysts

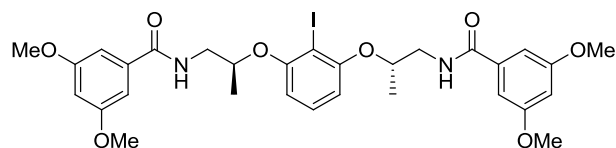
C.6.1 Preparation of *N,N'*-(2*S*,2'*S*)-2,2'-(2-Iodo-1,3-phenylene)*bis*-(oxy)*bis*(propane-2,1-diyl)*bis*(2,4,6-trimethoxybenzamide) (4.23)



A solution of (2*S*,2'*S*)-2,2'-((2-iodo-1,3-phenylene)*bis*(oxy))*bis*(propan-1-amine)

4.19^[20] (50 mg, 0.14 mmol, 1.0 equiv), DMAP (43 mg, 0.35 mmol, 2.5 equiv), 2,4,6-trimethoxybenzoic acid (74 mg, 0.35 mmol, 2.4 equiv), and EDCI (67 mg, 0.35 mmol, 2.4 equiv) in CH₂Cl₂ (5.0 mL) was stirred overnight at RT, whereupon TLC showed that the reaction was complete. The reaction was quenched with 1M HCl (10.0 mL) and extracted with CH₂Cl₂ (5×10 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 1:49 MeOH/CH₂Cl₂) to provide 100 mg (95% yield) of **4.23** as white solid, dec. 182 °C; [α]_D²³ = +67.4° (c 2.0, CHCl₃). IR: 3468-3286 (broad), 1652. ¹H: 7.21 (t, 1H, *J* = 8.3), 6.56 (d, 2H, *J* = 8.3), 6.41 (t, 2H, *J* = 5.9), 6.05 (s, 4H), 4.66-4.61 (m, 2H), 3.88 (ddd, 2H, *J* = 13.8, 7.2, 3.4), 3.79 (s, 6H), 3.63 (s, 12H), 3.56-3.47 (m, 2H), 1.39 (d, 6H, *J* = 6.1). ¹³C: 166.0 (2C), 162.1 (2C), 158.5 (4C), 158.0 (2C), 129.9 (1C), 108.5 (2C), 106.8 (2C), 90.4 (4C), 81.7 (1C), 75.4 (2C), 55.7 (4C), 55.4 (2C), 44.4 (2C), 17.4 (2C). HRMS: calcd for C₃₂H₃₉IN₂O₁₀Na [M+Na]⁺: 761.1547; found: 761.1569.

C.6.2 Preparation of *N,N'*-(2*S*,2'*S*)-2,2'-((2-Iodo-1,3-phenylene)bis-(oxy))bis(propane-2,1-diyl)bis(3,5-dimethoxybenzamide) (**4.21**)

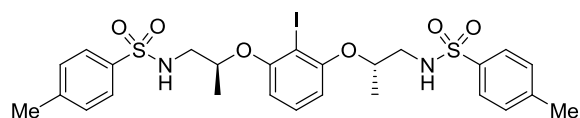


3,5-Dimethoxybenzoyl chloride (114 mg, 0.57 mmol, 1.5 equiv) was added to a cold (0 °C) solution of (2*S*,2'*S*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(propan-1-amine) **4.19**^[20] (65 mg, 0.19 mmol, 1.0 equiv) and pyridine (0.15 mL, 1.9 mmol, 10.0 equiv) in CH₂Cl₂ (2.5 mL). The reaction was warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The reaction was quenched with 1M HCl and extracted with CH₂Cl₂ (3×10 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash

[20] Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 9215.

column chromatography (eluent: 1:49 MeOH/CH₂Cl₂) to provide 81 mg (64% yield) of **4.21** as white solid, m.p. 133-135 °C, $[\alpha]_D^{23} = +78.5^\circ$ (*c* 0.84, CHCl₃). **IR**: 3495-3175 (broad), 1645. **¹H**: 7.22 (t, 1H, *J* = 8.3), 6.93 (d, 4H, *J* = 2.3), 6.78 (t, 2H, *J* = 5.3), 6.57 (t, 2H, *J* = 2.3), 6.54 (d, 2H, *J* = 8.3), 4.70-4.61 (m, 2H), 3.90 (ddd, 2H, *J* = 13.9, 6.3, 3.3), 3.80 (s, 12H), 3.67-3.56 (m, 2H), 1.41 (d, 6H, *J* = 6.2). **¹³C**: 167.3 (2C), 160.9 (4C), 157.7 (2C), 136.4 (2C), 130.2 (1C), 107.3 (2C), 104.8 (4C), 103.9 (2C), 81.9 (1C), 75.1 (2C), 55.6 (4C), 44.6 (2C), 17.4 (2C). **HRMS**: calcd for C₃₀H₃₅IN₂O₈Na [M+Na]⁺: 701.1336; found: 701.1335.

C.6.3 Preparation of *N,N'*-(2*S*,2'*S*)-2,2'-(2-Iodo-1,3-phenylene)bis-(oxy)bis(propane-2,1-diyl)bis(4-methylbenzene-sulfonamide) (**4.22**)

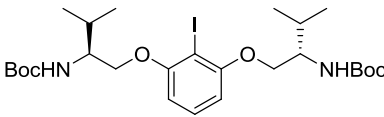


Tosyl chloride (97 mg, 0.51 mmol, 3.0 equiv) was added to a cold (0 °C) solution of (2*S*,2'*S*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(propan-1-amine) **4.19**^[20] (60 mg, 0.17 mmol, 1.0 equiv) and pyridine (0.14 mL, 1.7 mmol, 10 equiv) in CH₂Cl₂ (2.5 mL). The reaction was warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The reaction was quenched with 1M HCl (10.0 mL) and extracted with CH₂Cl₂ (3×10 mL). The combined extracts were washed with brine (15 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography (eluent: 2:1 hexanes/EtOAc) to provide 106 mg (94% yield) of **4.22** as white solid, m.p. 42-44 °C; $[\alpha]_D^{23} = +132.0^\circ$ (*c* 0.55, CHCl₃). **IR**: 3396-3208 (broad), 1157, 1085. **¹H**: 7.73 (d, 4H, *J* = 8.2), 7.25 (d, 4H, *J* = 8.3), 7.11 (t, 1H, *J* = 8.2), 6.34 (d, 2H, *J* = 8.3), 5.11 (t, 2H, *J* = 6.0), 4.46-4.40 (m, 2H), 3.33-3.25 (m, 2H), 3.17-3.08 (m, 2H), 2.40 (s, 6H), 1.31 (d, 6H, *J* = 6.1). **¹³C**: 157.2 (2C), 143.5 (2C), 136.9 (2C), 129.8 (1C), 129.7 (4C), 127.0 (4C), 107.2 (2C), 82.0 (1C), 74.6 (2C), 48.1 (2C), 21.5 (2C), 17.3 (2C). **HRMS**: calcd for C₂₆H₃₁N₂O₆S₂INa [M+Na]⁺: 681.0566; found: 681.0567.

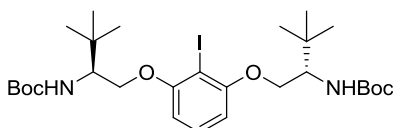
C.6.4 General procedure for Mitsunobu reaction of amino alcohol with 2-iodo resorcinol

Neat diisopropyl azodicarboxylate (0.18 mL, 0.93 mmol, 2.4 equiv) was added dropwise to a cold (0 °C) solution of 2-iodoresorcinol (87 mg, 0.37 mmol, 1.0 equiv), *N*-BOC-valinol **4.45** or *N*-BOC-*tert*-leucinol **4.46** (202 mg, 0.93 mmol, 2.4 equiv) and PPh₃ (244 mg, 0.93 mmol, 2.4 equiv) in THF (2.0 mL). The mixture was then warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The solution was evaporated and the residue was purified by flash column chromatography to provide the desired product.

C.6.4.1 Characterization of *tert*-Butyl (2*S*,2'*S*)-1,1'-(2-iodo-1,3-phenylene)*bis*(oxy)*bis*(3-methylbutane-2,1-diyl)dicarbamate (**4.47**)

 115 mg (48% yield) from 93 mg of 2-iodoresorcinol, colorless oil; $[\alpha]_{\text{D}}^{23} = -102.7^\circ$ (*c* 5.1, CHCl₃); eluent: 1:3 EtOAc/hexanes. **IR**: 3468-3286 (broad), 1699. **¹H**: 7.22 (t, 1H, *J* = 8.3), 6.46 (d, 2H, *J* = 8.3), 5.00 (d, 2H, *J* = 9.6), 4.15 (dd, 2H, *J* = 9.2, 2.4), 3.99 (dd, 2H, *J* = 9.2, 3.5), 3.70-3.64 (m, 2H), 2.21-2.10 (m, 2H), 1.44 (s, 18H), 1.03 (d, 6H, *J* = 6.8), 0.99 (d, 6H, *J* = 6.7). **¹³C**: 158.5 (2C), 155.8 (2C), 130.0 (1C), 105.2 (2C), 79.3 (2C), 78.8 (1C), 69.5 (2C), 55.4 (2C), 29.8 (2C), 28.4 (6C), 19.7 (2C), 19.2 (2C). **HRMS**: calcd for C₂₆H₄₃N₂O₆INa [M+Na]⁺: 629.2064; found: 629.2058.

C.6.4.2 Characterization of *tert*-Butyl (2*S*,2'*S*)-1,1'-(2-iodo-1,3-phenylene)*bis*(oxy)*bis*(3,3-dimethylbutane-2,1-diyl)dicarbamate (**4.48**)

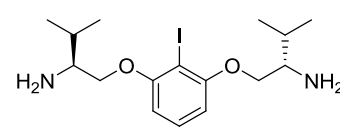
 91 mg (39% yield) from 87 mg of 2-iodoresorcinol, colorless oil; $[\alpha]_{\text{D}}^{23} = -70.5^\circ$ (*c* 3.75, CHCl₃); eluent: 1:3 EtOAc/hexanes. **IR**: 3474-3240 (broad), 1699. **¹H**: 7.23 (t, 1H, *J* = 8.2), 6.46 (d, 2H, *J* = 8.3), 5.18 (d, 2H, *J* = 10.1), 4.19 (dd, 2H, *J* = 9.5, 3.0), 4.02 (dd, 2H, *J* = 9.6, 4.1), 3.80-3.76 (m, 2H), 1.45 (s, 18H), 1.06 (s, 18H). **¹³C**: 158.7 (2C), 155.9 (2C), 129.9 (1C), 105.2 (2C), 79.2 (2C), 78.7 (1C), 68.8

(2C), 57.2 (2C), 34.6 (2C), 28.4 (6C), 27.4 (6C). **HRMS**: calcd for C₂₈H₄₇N₂O₆INa [M+Na]⁺: 657.2377; found: 657.2374.

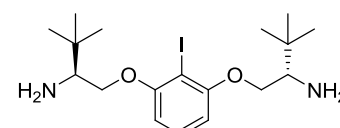
C.6.5 General procedure for Boc deprotection of 4.47 and 4.48

Trifluoroacetic acid (61 μ L, 0.8 mmol, 5 equiv) was slowly added to a solution of **4.47** or **4.48** (0.16 mmol) in CH₂Cl₂ (0.3 mL) and the mixture was stirred overnight at RT, whereupon TLC showed that the reaction was complete. The mixture was cooled to 0 °C, quenched with 2M NaOH (1.0 mL) and extracted with CH₂Cl₂ (5 \times 5 ml). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated to provide the *N*-deblocked product. The residue was dried under high vacuum and used in the subsequent step without purification.

C.6.5.1 Characterization of (2*S*,2'*S*)-1,1'-(2-Iodo-1,3-phenylene)*bis*(oxy)*bis*(3-methylbutan-2-amine) (4.49)

 51 mg (81% yield) from 95 mg of **4.47**, yellow oil; $[\alpha]_D^{23} = +37.4^\circ$ (*c* 2.05, CHCl₃). **IR**: 3520-3208 (broad). **¹H**: 7.21 (t, 1H, *J* = 8.1), 6.47 (d, 2H, *J* = 8.2), 4.07 (dd, 2H, *J* = 8.8, 3.4), 3.84 (app t, 2H, *J* = 8.2), 3.03-2.97 (m, 2H), 1.91-1.79 (m, 2H), 1.61 (br s, 4H), 1.02 (d, 6H, *J* = 4.0), 0.99 (d, 6H, *J* = 4.1). **¹³C**: 158.8 (2C), 129.8 (1C), 105.3 (2C), 79.1 (1C), 72.9 (2C), 56.1 (2C), 30.9 (2C), 19.5 (2C), 18.4 (2C). **HRMS**: calcd for C₁₆H₂₈IN₂O₂ [M+H]⁺: 407.1195; found: 407.1197.

C.6.5.2 Characterization of (2*S*,2'*S*)-1,1'-(2-Iodo-1,3-phenylene)*bis*(oxy)*bis*(3,3-dimethylbutan-2-amine) (4.50)

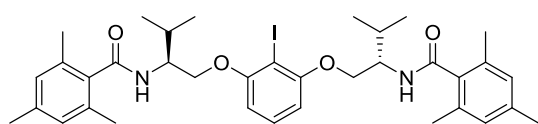
 48 mg (87% yield) from 80 mg of **4.48**, yellow oil; $[\alpha]_D^{23} = +40.5^\circ$ (*c* 2.30, CHCl₃). **IR**: 3468-3234 (broad). **¹H**: 7.21 (t, 1H, *J* = 8.2), 6.47 (d, 2H, *J* = 8.3), 4.20 (dd, 2H, *J* = 8.8, 3.0), 3.77 (t, 2H, *J* = 8.9), 3.01 (dd, 2H, *J* = 9.0, 2.9),

1.62 (br s, 4H), 1.01 (s, 18H). ^{13}C : 158.7 (2C), 129.8 (1C), 105.5 (2C), 79.2 (1C), 71.4 (2C), 59.1 (2C), 33.1 (2C), 26.7 (6C). **HRMS**: calcd for $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_2\text{I}$ $[\text{M}+\text{H}]^+$: 435.1509; found: 435.1500.

C.6.6 General procedure for the coupling of amine and 2,4,6-trimethylbenzoic acid

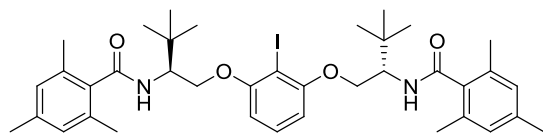
A solution of **4.49** or **4.50** (1.1 mmol, 1.0 equiv) in DMF (3.0 mL) was added dropwise at RT over 10 min to a solution of EDCI (435 mg, 2.8 mmol, 2.5 equiv), HOBt (430 mg, 2.8 mmol, 2.5 equiv) and 2,4,6-trimethylbenzoic acid (460 mg, 2.8 mmol, 2.5 equiv) in dry DMF (1.2 mL) that had previously been stirred for 15 min. The mixture was stirred overnight at RT, whereupon TLC showed that the reaction was complete. The mixture was diluted with CH_2Cl_2 (20.0 mL) and the organic layer was sequentially washed with 0.1 M HCl (2×15 mL), H_2O (10.0 mL), satd. aq. NaHCO_3 (15 mL), and brine (10.0 mL), then dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography to provide **4.51** and **4.52**.

C.6.6.1 Characterization of *N,N'*-(2*S*,2'*S*)-1,1'-(2-Iodo-1,3-phenylene)*bis*(oxy)*bis*(3-methylbutane-2,1-diyl)*bis*(2,4,6-trimethylbenzamide) (**4.51**)



406 mg (53% yield) from 447 mg of **4.49**; white solid, m.p. 79-81 °C, $[\alpha]_{\text{D}}^{23} = -169.6^\circ$ (c 0.80, CHCl_3) eluent: 7:3 hexanes/EtOAc; **IR**: 3338-3156 (broad), 1636. ^1H : 7.27 (t, 1H, $J = 8.2$), 6.83 (s, 4H), 6.52 (d, 2H, $J = 8.3$), 6.10 (d, 2H, $J = 8.9$), 4.29-4.16 (m, 6H), 2.33-2.25 (m, 20 H), 1.12 (d, 6H, $J = 6.8$), 1.07 (d, 6H, $J = 6.7$). ^{13}C : 170.5 (2C), 158.3 (2C), 138.5 (2C), 134.8 (2C), 134.2 (4C), 130.2 (1C), 128.2 (4C), 105.3 (2C), 78.6 (1C), 69.0 (2C), 54.5 (2C), 29.2 (2C), 21.1 (2C), 19.8 (4C), 19.2 (4C). **HRMS**: calcd for $\text{C}_{36}\text{H}_{48}\text{N}_2\text{O}_4\text{I}$ $[\text{M}+\text{H}]^+$: 699.2659; found: 699.2657.

C.6.6.2 Characterization of *N,N'*-(2*S*,2'*S*)-1,1'-(2-Iodo-1,3-phenylene)*bis*(oxy)*bis*-(3,3-dimethylbutane-2,1-diyl)*bis*(2,4,6-trimethylbenzamide) (4.52)

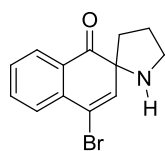


143 mg (57% yield) from 150 mg of **4.50**; white solid, m.p. 109-111 °C, $[\alpha]_D^{23} = -134.0^\circ$ (*c* 2.10, CHCl₃) eluent: 3:1 hexanes/EtOAc; **IR**: 3442-3156

(broad), 1638. **¹H**: 7.27 (t, 1H, *J* = 6.5), 6.82 (s, 4H), 6.52 (d, 2H, *J* = 8.3), 6.30 (d, 2H, *J* = 9.9), 4.40-4.34 (m, 4H), 4.12 (dd, 2H, *J* = 9.8, 4.3), 2.27 (s, 6H), 2.24 (s, 12H), 1.15 (s, 18H). **¹³C**: 170.4 (2C), 158.5 (2C), 138.4 (2C), 135.0 (2C), 134.2 (4C), 130.2 (1C), 128.3 (4C), 105.2 (2C), 78.2 (1C), 68.5 (2C), 55.7 (2C), 34.1 (2C), 27.8 (6C), 21.1 (2C), 19.4 (4C). **HRMS**: calcd for C₃₈H₅₂N₂O₄I [M+H]⁺: 727.2972; found: 727.2972.

C.7 Synthesis of (1*S*)-(+)-10-Camphorsulfonyl based derivatives of spiropyrrolidine and acyloxylated adducts

C.7.1 Preparation of 4-bromo-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.61)

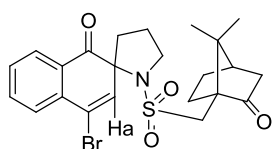


A solution of sulfonamide **4.2e** (9.0 mg, 0.02 mmol, 1.0 equiv) in CH₃CN (0.8 mL) was added at RT to a solution of PhSH (6 μL, 0.06 mmol, 3.0 equiv.) in CH₃CN (0.2 mL) containing suspended K₂CO₃ (11 mg, 0.08 mmol, 4.0 equiv).

Next, DMSO (0.1 mL) was added to the reaction mixture and stirring was continued at RT for 3 h, after which time TLC showed that the reaction was complete. The reaction was quenched with H₂O (5 mL) and extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography on silica gel (eluting solvent: 2:3 EtOAc/hexane) to provide 4.1 mg (75% yield) of **4.61** as a brown oil. **IR**: 3467-3210 (broad), 1684. **¹H**: 7.98 (d, 1H, *J* = 9.0), 7.69-7.67 (m, 2H), 7.46-7.41 (m, 1H), 6.73 (s, 1H), 3.43-3.36 (m, 1H), 3.18-3.10 (m, 1H), 2.18-2.07 (m, 2H),

1.98-1.87 (m, 3H). ^{13}C : 201.0, 140.0, 136.1, 134.9, 129.0 (2C), 127.9, 127.3, 117.6, 72.4, 48.1, 38.4, 25.4. **HRMS**: calcd for $\text{C}_{13}\text{H}_{13}^{79}\text{BrNO}$ $[\text{M}+\text{H}]^+$: 278.0181; found: 278.0186.

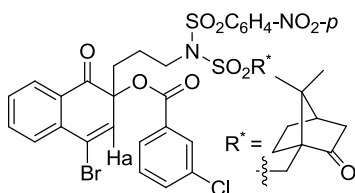
C.7.2 Preparation of 4.63



(1*S*)-(+)-10-Camphorsulfonyl chloride (15 mg, 0.06 mmol, 3.0 equiv) was added to a cold (0 °C) solution of **4.61** (6 mg, 0.02 mmol, 1.0 equiv) and Et_3N (14 μL , 0.1 mmol, 5.0 equiv) in CH_2Cl_2 (0.4 mL). The resulting

mixture was warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The mixture was quenched with aq. satd. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 \times 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and evaporated. The residue was dried under high vacuum and analyzed for calculation for diastereomeric excess. The diastereomeric excess was obtained by integrating the peak for H_a .

C.7.3 Preparation of 4.64



(1*S*)-(+)-10-Camphorsulfonyl chloride (0.05 mmol, 3.0 equiv) was added to a solution of **4.54g** (0.015 mmol, 1.0 equiv) and Et_3N (10 μL , 0.08 mmol, 5.0 equiv) in CH_2Cl_2 (0.4 mL) at 0 °C. The

resulting mixture was warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The mixture was quenched with aq. satd. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 \times 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and evaporated. The residue was dried under high vacuum and analyzed for the calculation of diastereomeric excess. The diastereomeric excess was obtained by integrating the peak for H_a .

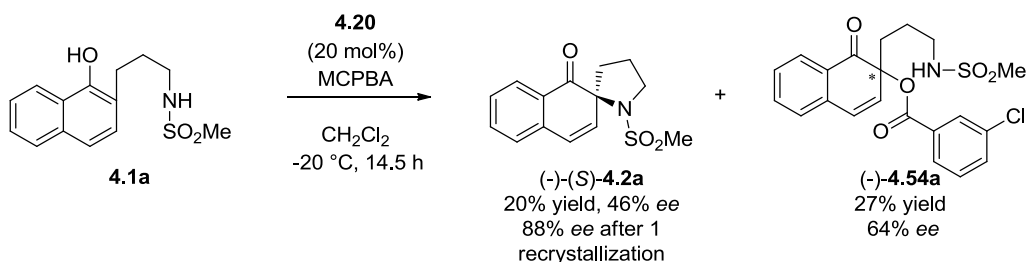
C.8 General procedure for the synthesis of chiral spiropyrrolidines and acyloxyated adducts

A solution of MCPBA (105 mg, 0.47 mmol, 1.3 equiv) in CH₂Cl₂ (8.0 mL) was added at –20 °C to solution of a substrate **4.1** (0.36 mmol, 1.0 equiv) and a chiral iodide precatalyst (0.072 mmol, 0.2 equiv) in CH₂Cl₂ (12.0 mL). The mixture was stirred overnight at –20 °C, whereupon TLC indicated complete reaction. The mixture was quenched with aq. sat. NaHCO₃ (10.0 mL) and aq. sat. Na₂S₂O₃ (5.0 mL) solutions and extracted with CH₂Cl₂ (4×15 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to afford products **4.2** and **4.54**.

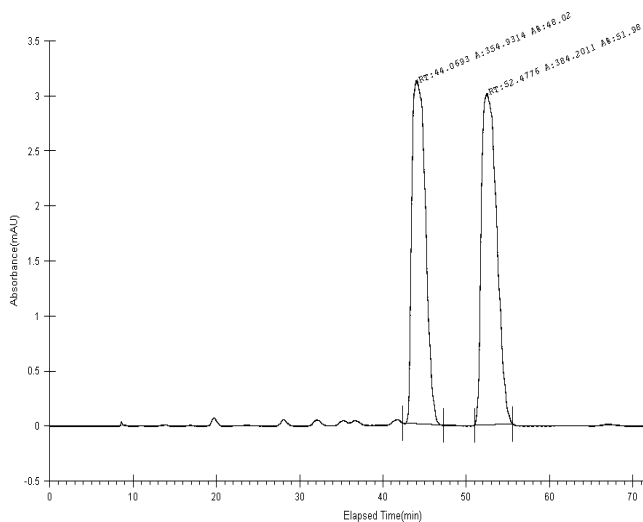
C.9 Data and chromatograms of chiral compounds

C.9.1 (-)-(S)-1'-(methylsulfonyl)-1H-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2a)

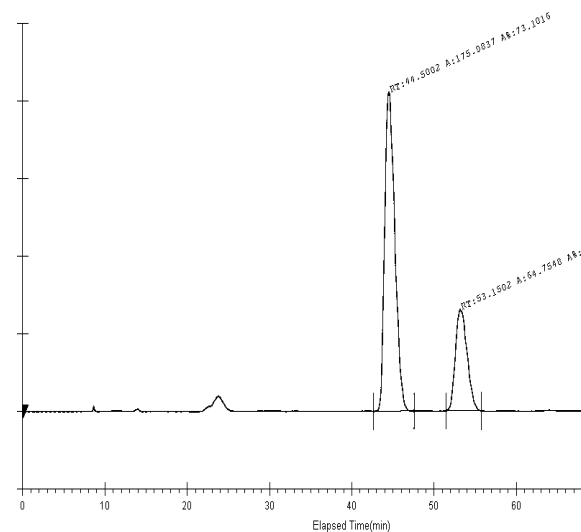
20.1 mg (20% yield) from 100 mg of **4.1a** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = -24.2^\circ$ (*c* 0.58, CHCl₃). SFC analysis indicates a 46% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 44.50 min (major), *t_R* (2) = 53.15 (minor).



chromatogram of (\pm)-4.2a (240 nm)

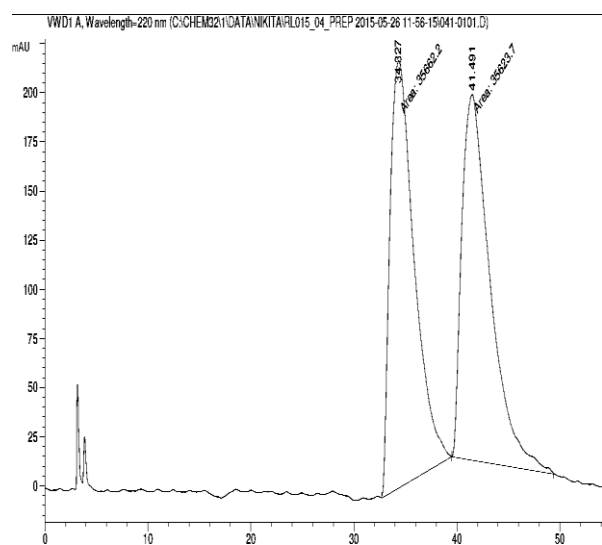


chromatogram of (-)-4.2a, (240 nm, 46% *ee*)

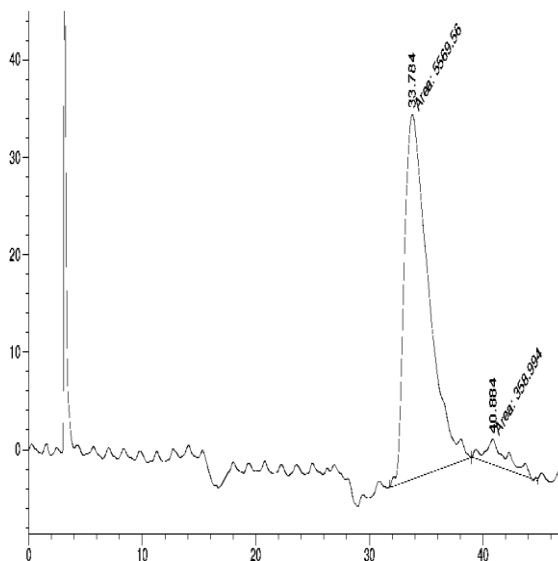


One recrystallization (toluene/hexane; vapor diffusion technique, RT) afforded material of 88% *ee*, the optical purity of which was determined by chiral HPLC: Column (OD-H) 5:95 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 33.78 min (major), t_R (2) = 40.88 (minor).

chromatogram of (\pm)-4.2a (220 nm)



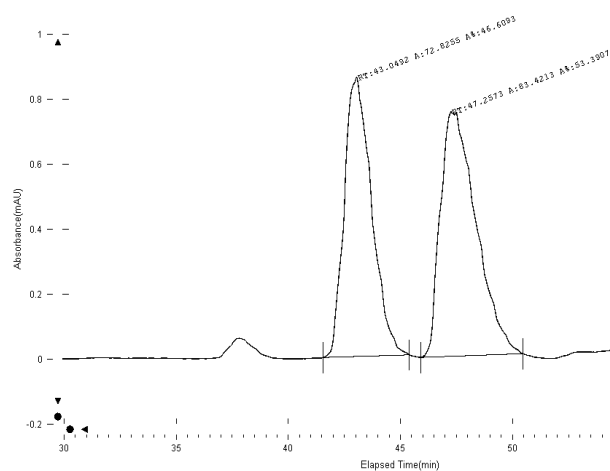
chromatogram of (-)-4.2a, (220 nm, 88% *ee*)



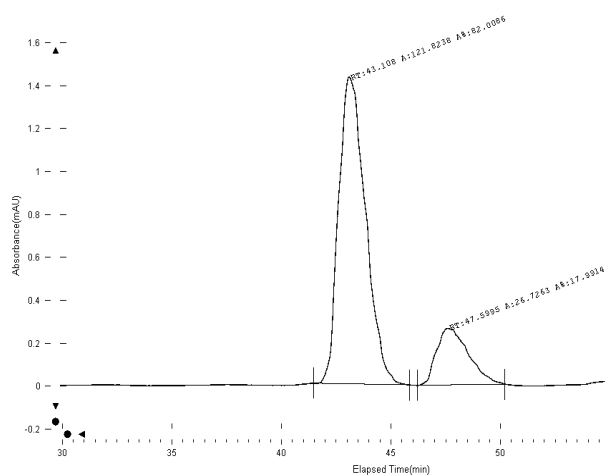
**(-)-2-(3-(methylsulfonamido)-propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate
(4.54a)**

41.7 mg (27% yield) from 100 mg of **4.1a** as yellow oil, eluent: 2:3 Et₂O/pentane; $[\alpha]_D^{25} = -13.4^\circ$
(c 0.17, CHCl₃). SFC analysis indicates a 64% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂:
diethylamine), flow rate = 1.0 mL/min; t_R (1) = 43.11 min (major), t_R (2) = 47.60 (minor).

chromatogram of (±)-4.54a (240 nm)

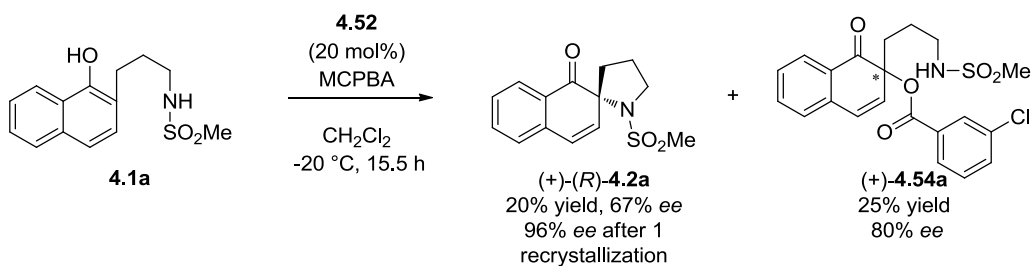


chromatogram of (-)-4.54a, (240 nm, 64% ee)

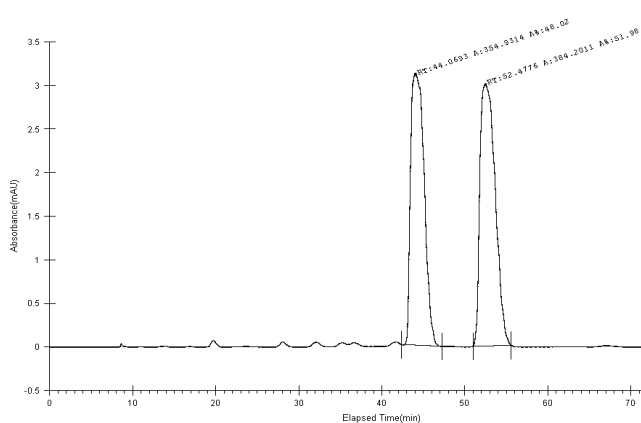


C.9.2 (+)-(R)-1'-(methylsulfonyl)-1H-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2a)

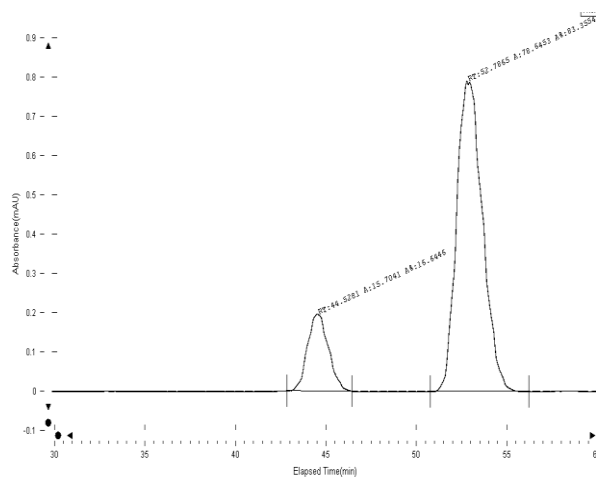
19.9 mg (20% yield) from 100 mg of **4.1a** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = +36.5^\circ$ (c 0.59, CHCl_3). SFC analysis indicates a 67% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 44.53 min (minor), t_R (2) = 52.79 (major).



chromatogram of (\pm)-**4.2a** (240 nm)

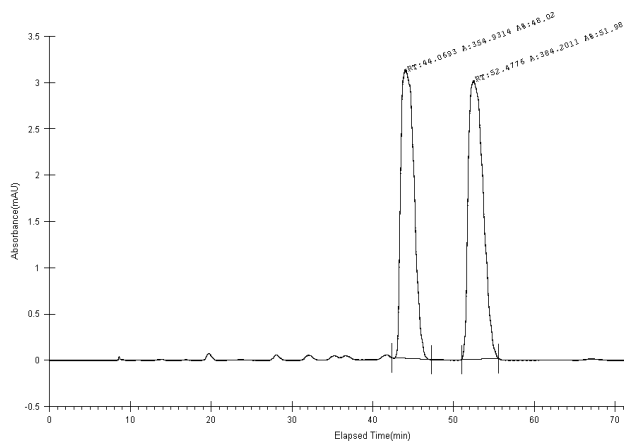


chromatogram of (+)-**4.2a**, (240 nm, 67% *ee*)

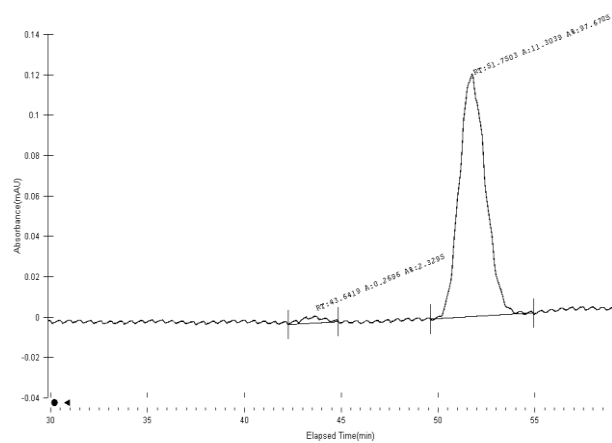


Material of 96% *ee* was obtained after a single recrystallization from toluene/hexane (vapor diffusion technique) at RT.

chromatogram of (\pm)-4.2a (240 nm)



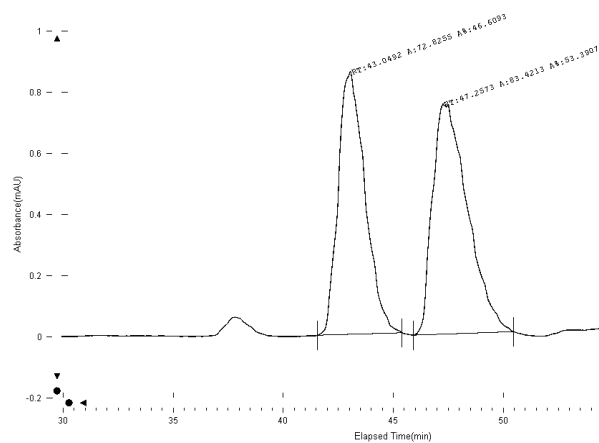
chromatogram of (+)-4.2a, (229 nm, 96% *ee*)



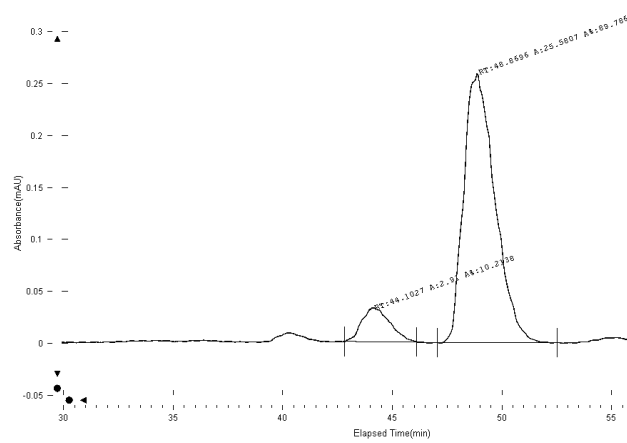
**(+)-2-(3-(methylsulfonamido)-propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate
(4.54a)**

38.4 mg (25% yield) from 100 mg of **4.1a** as yellow oil, eluent: 2:3 Et₂O/pentane; $[\alpha]_D^{23} = +16.8^\circ$ (c 0.06, CHCl₃). SFC analysis indicates a 80% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 44.10 min (minor), t_R (2) = 48.87 (major).

chromatogram of (±)-4.54a (240 nm)

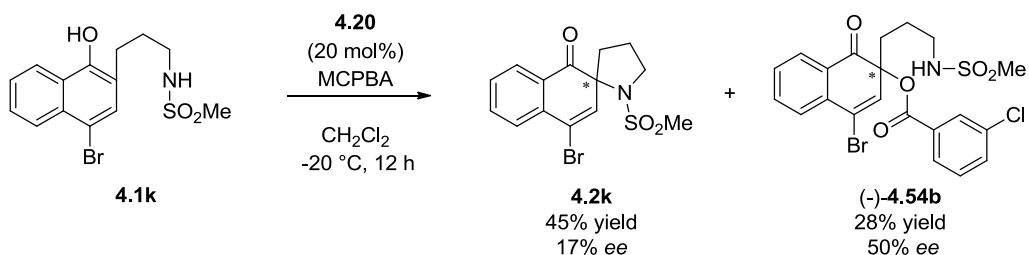


chromatogram of (+)-4.54a, (240 nm, 80% ee)

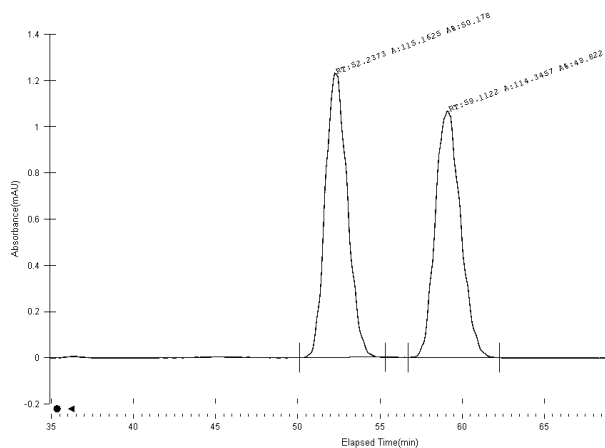


C.9.3 (-)-4-Bromo-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2k)

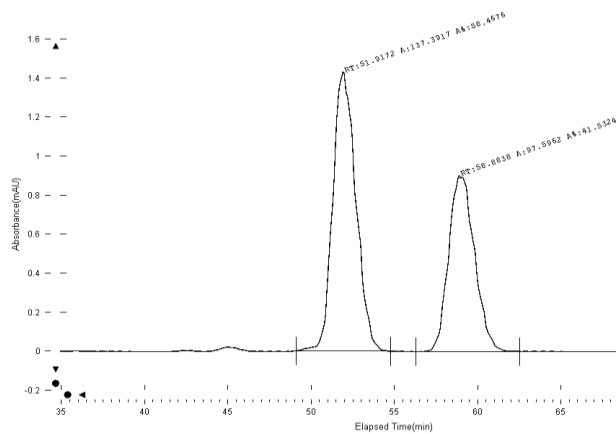
44.5 mg (45% yield) from 100 mg of **4.1k** as yellow oil, eluent: 3:7 EtOAc/hexane; $[\alpha]_{\text{D}}^{23} = -7.1^{\circ}$ (*c* 1.00, CHCl₃). SFC analysis indicates a 17% *ee*: Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_{R} (1) = 51.92 min (major), t_{R} (2) = 58.88 (minor).



chromatogram of (\pm)-4.2k (229 nm)



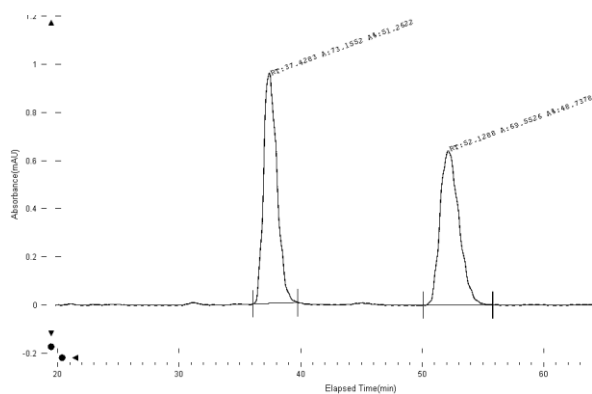
chromatogram of (-)-4.2k, (229 nm, 17% *ee*)



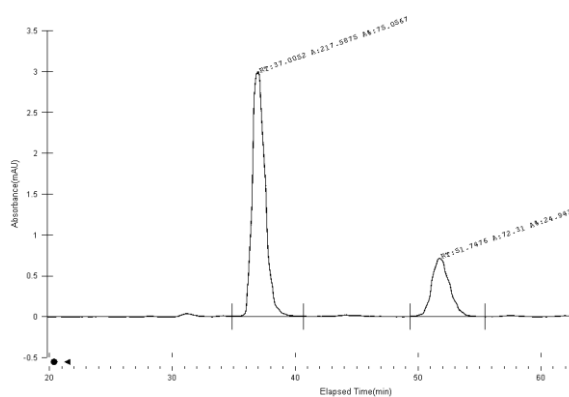
(-)-4-bromo-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54b)

39.8 mg (28% yield) from 100 mg of **4.1k** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = -7.2^\circ$ (*c* 0.89, CHCl_3). SFC analysis indicates a 50% *ee*. Column (AD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 37.01 min (major), t_R (2) = 51.75 (minor).

chromatogram of (\pm)-4.54b (229 nm)

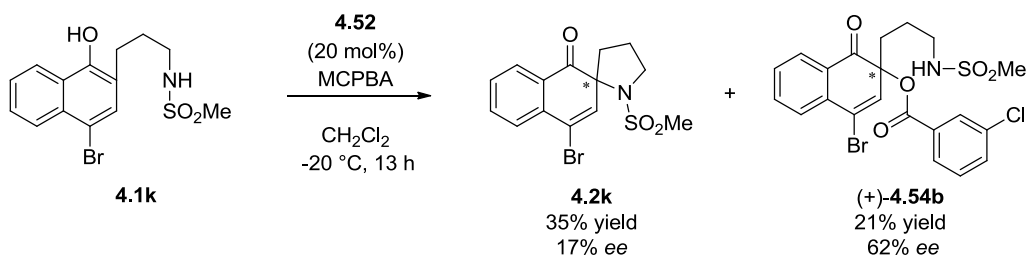


chromatogram of (-)-4.54b, (229 nm, 50% ee)

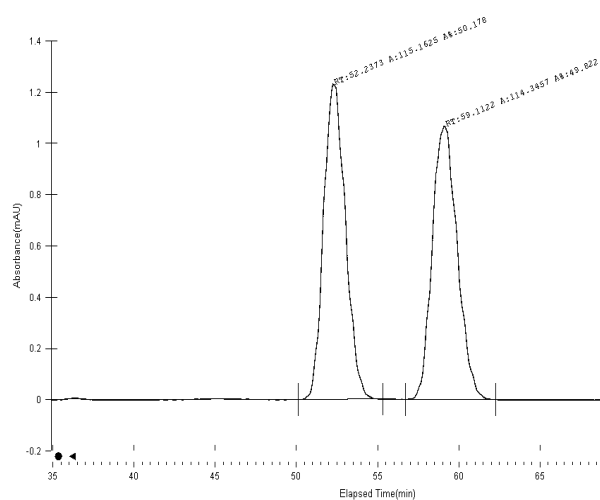


C.9.4 (+)-4-Bromo-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2k)

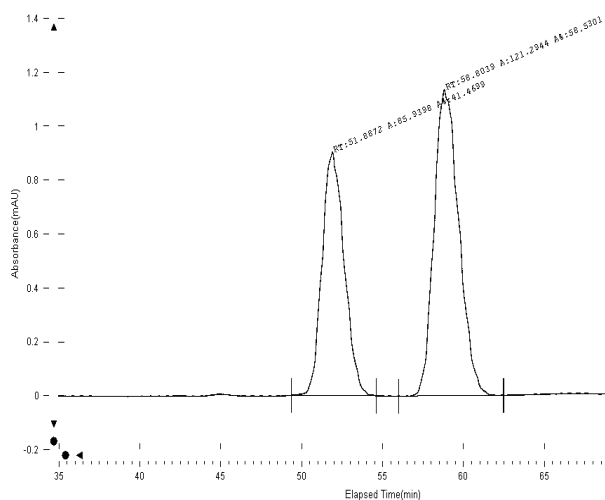
34.7 mg (35% yield) from 100 mg of **4.1k** as yellow oil, eluent: 3:7 EtOAc/hexane; $[\alpha]_D^{23} = +7.4^\circ$ (*c* 0.55, CHCl₃). SFC analysis indicates a 17% *ee*: Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 51.89 min (minor), *t_R* (2) = 58.80 (major).



chromatogram of (\pm)-4.2k (229 nm)



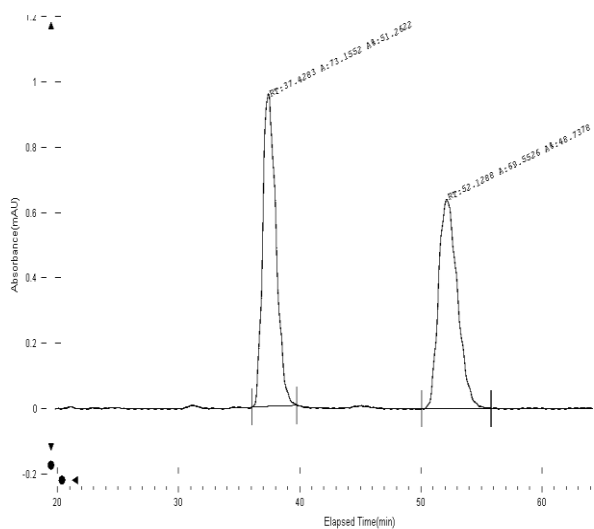
chromatogram of (+)-4.2k, (229 nm, 17% *ee*)



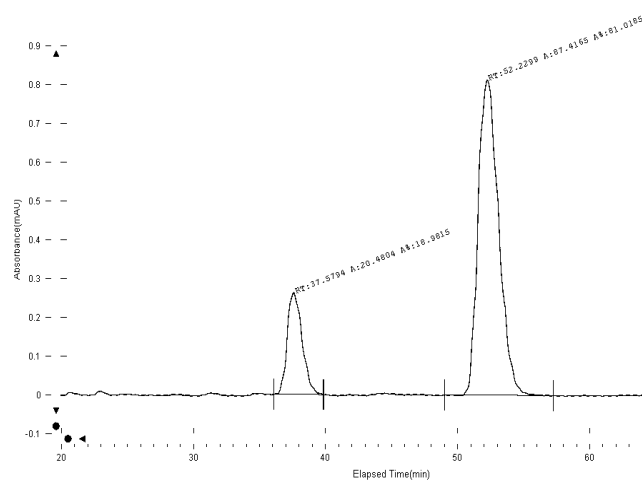
(+)-4-bromo-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54b)

29.8 mg (21% yield) from 100 mg of **4.1k** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = +9.01^\circ$ (c 0.36, CHCl_3). SFC analysis indicates a 62% *ee*. SFC: Column (AD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 37.58 min (minor), t_R (2) = 52.23 (major).

chromatogram of (\pm)-4.54b (229 nm)

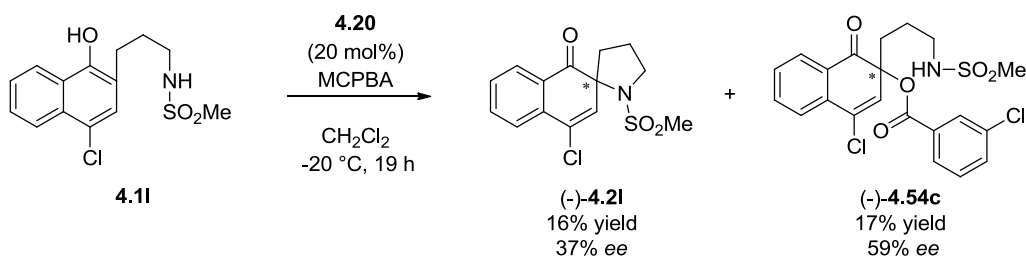


chromatogram of (+)-4.54b, (229 nm, 62% ee)

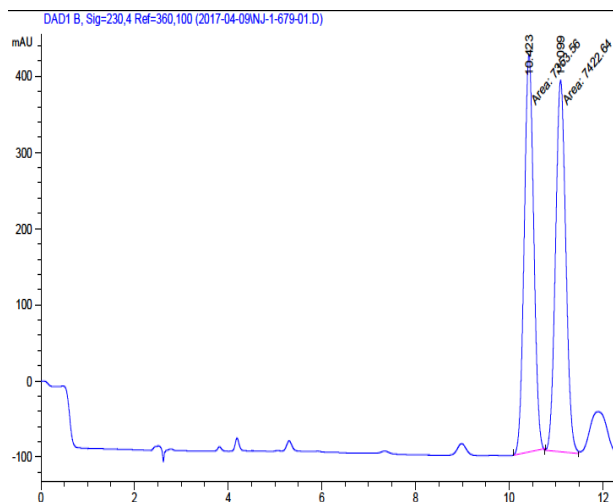


C.9.5 (-)-4-chloro-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2l)

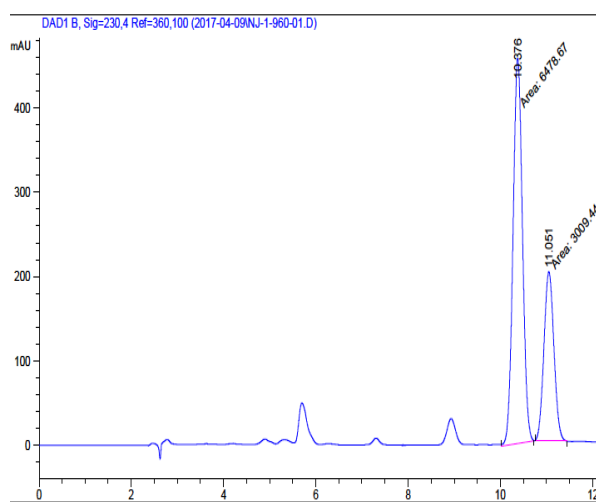
16 mg (16% yield) from 100 mg of **4.1l** as light yellow oil, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = -7.4^\circ$ (*c* 0.22, CHCl₃). HPLC analysis indicates a 37% *ee*. Column (OJ-RH) 60:40 (0.1% AcOH in H₂O: MeCN), flow rate = 0.7 mL/min; *t*_R (1) = 10.38 min (major), *t*_R (2) = 11.05 (minor).



chromatogram of (\pm)-4.2l (230 nm)



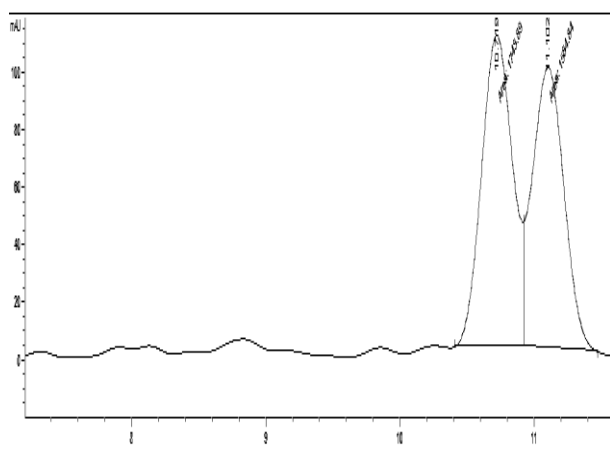
chromatogram of (-)-4.2l, (230 nm, 37% *ee*)



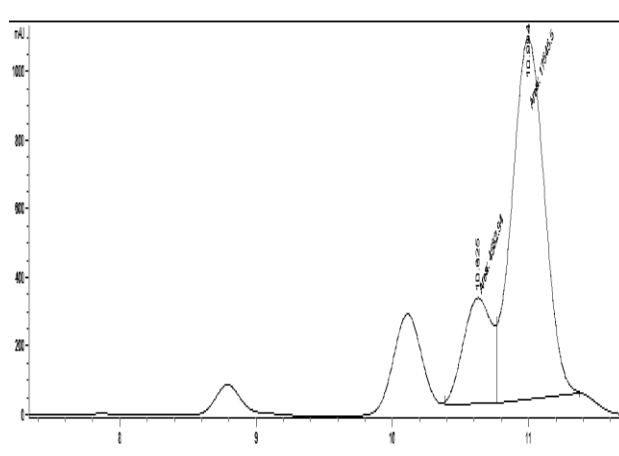
(-)-4-chloro-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54c)

25.1 mg (17% yield) from 100 mg of **4.11** as colorless oil, eluent: 1:3 EtOAc/hexane; $[\alpha]_D^{25} = -7.22^\circ$ (*c* 0.28, CHCl_3). HPLC analysis indicates a 59% *ee*. Column (OJ-RH) 50:50 (0.1% AcOH in H_2O : MeCN), flow rate = 0.7 mL/min; t_R (1) = 10.63 min (minor), t_R (2) = 10.99 (major).

chromatogram of (\pm)-4.54c (230 nm)

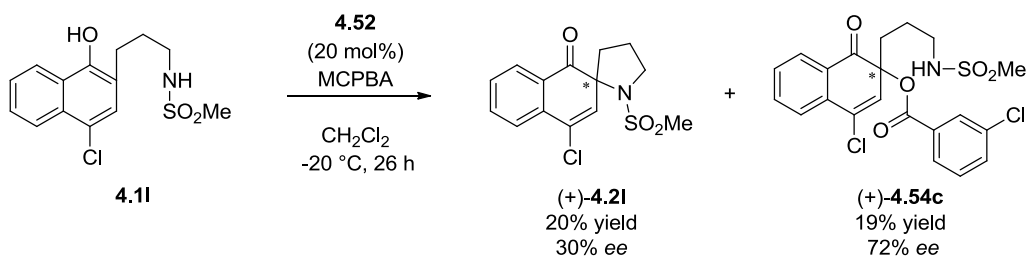


chromatogram of (-)-4.54c, (230 nm, 59% ee)

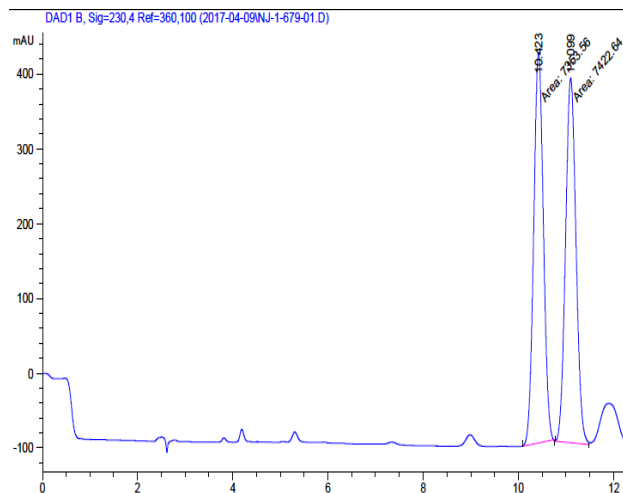


C.9.6 (+)-4-chloro-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2l)

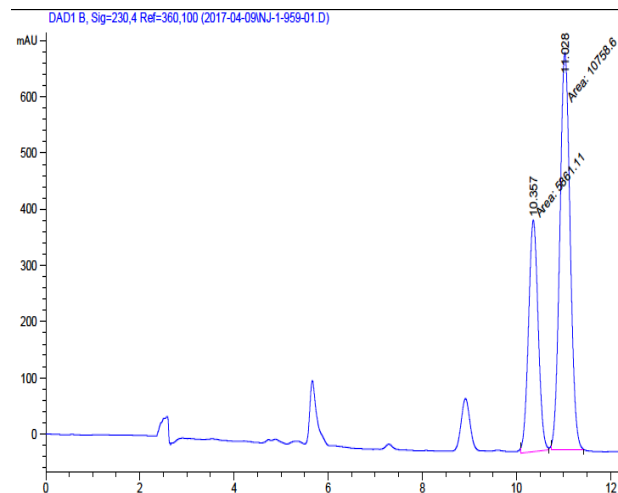
20.2 mg (20% yield) from 100 mg of **4.1l** as light yellow oil, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = +15.7^\circ$ (*c* 0.27, CHCl₃). HPLC analysis indicates a 30% *ee*. Column (OJ-RH) 60:40 (0.1% AcOH in H₂O: MeCN),, flow rate = 0.7 mL/min; *t_R* (1) = 10.36 min (minor), *t_R* (2) = 11.03 (major).



chromatogram of (\pm)-4.2l (230 nm)



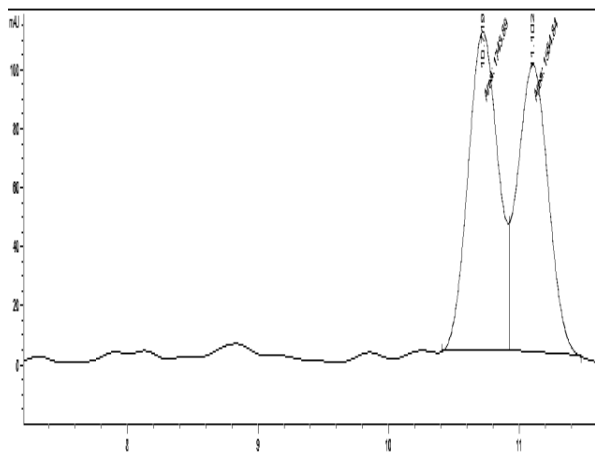
chromatogram of (+)-4.2l, (230 nm, 93% *ee*)



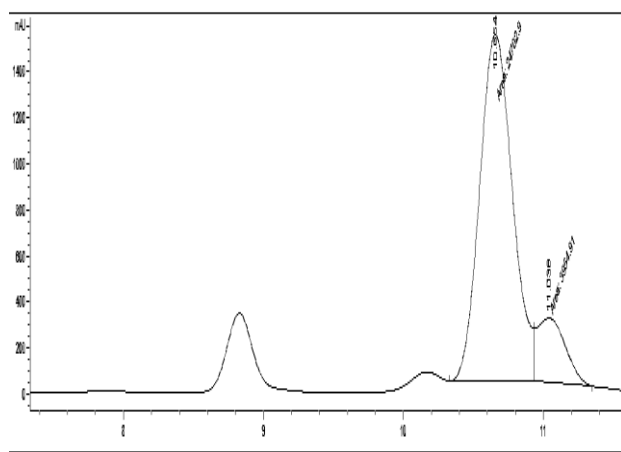
(+)-4-chloro-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54c)

28.5 mg (19% yield) from 100 mg of **4.11** as colorless oil, eluent: 1:3 EtOAc/hexane; $[\alpha]_D^{25} = +10.4^\circ$ (c 0.36, CHCl_3). HPLC analysis indicates a 72% *ee*. Column (OJ-RH) 50:50 (0.1% AcOH in H_2O : MeCN), flow rate = 0.7 mL/min; t_R (1) = 10.66 min (major), t_R (2) = 11.04 (minor).

chromatogram of (\pm)-4.54c (230 nm)

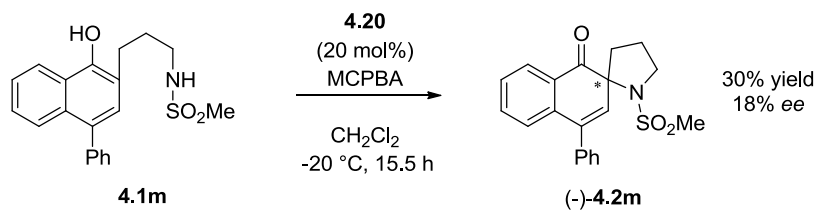


chromatogram of (+)-4.54c, (230 nm, 72% ee)

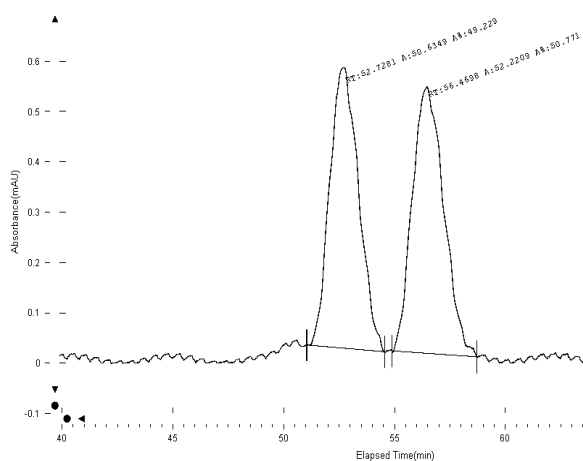


C.9.7 (-)-1'-(methylsulfonyl)-4-phenyl-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2m)

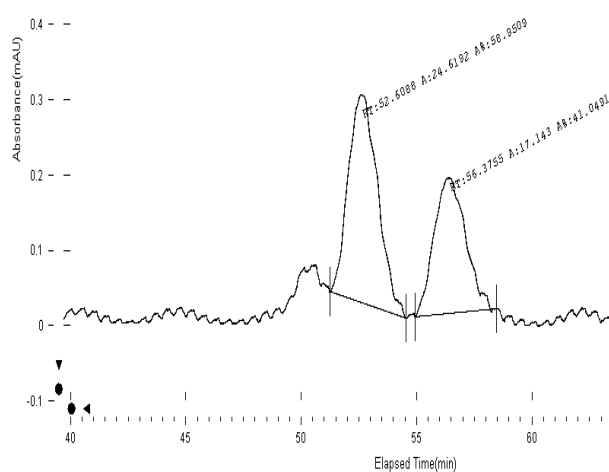
29.6 mg (30% yield) from 100 mg of **4.1m** as white solid, eluent: 3:7 EtOAc/hexane; $[\alpha]_D^{24} = -14.8^\circ$ (*c* 0.27, CHCl₃). SFC analysis indicates a 18% *ee*. SFC: Column (OD-H) 5: 95: 0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 52.61 min (major), *t_R* (2) = 56.38 (minor).



chromatogram of (\pm)-4.2m (229 nm)

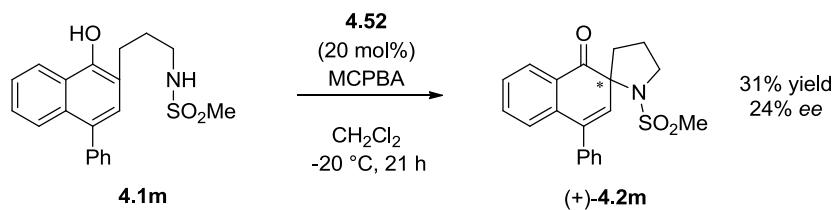


chromatogram of (-)-4.2m, (229 nm, 18% *ee*)

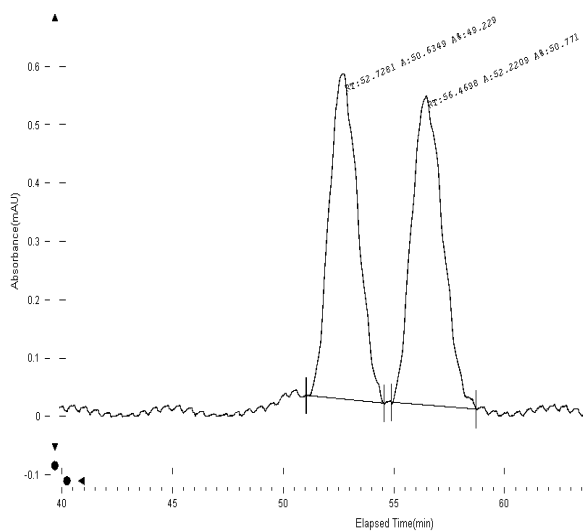


C.9.8 (+)-1'-(methylsulfonyl)-4-phenyl-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2m)

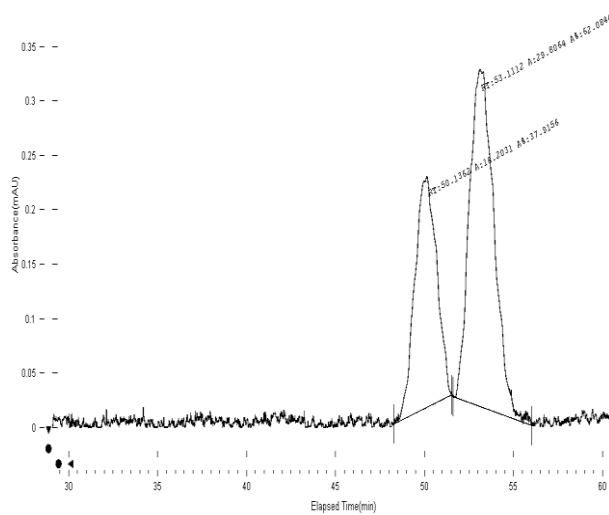
30.6 mg (31% yield) from 100 mg of **4.1m** as white solid, eluent: 3:7 EtOAc/hexane; $[\alpha]_D^{25} = +25.1^\circ$ (*c* 0.14, CHCl₃). SFC analysis indicates a 24% *ee*. SFC: Column (OD-H) 5: 95: 0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 50.14 min (minor), *t_R* (2) = 53.11 (major).



chromatogram of (\pm)-4.2m (229 nm)

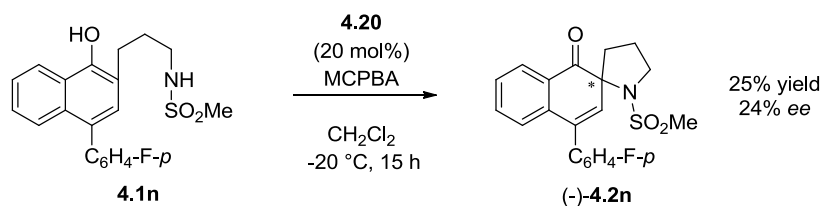


chromatogram of (+)-4.2m, (229 nm, 24% *ee*)

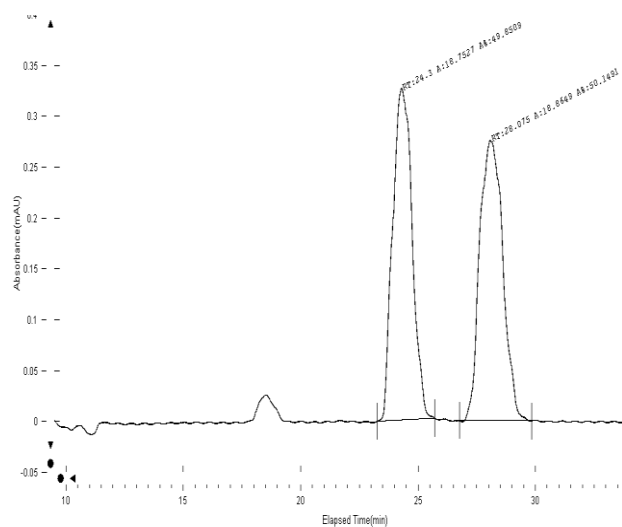


C.9.9 (-)-4-(4-fluorophenyl)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2n)

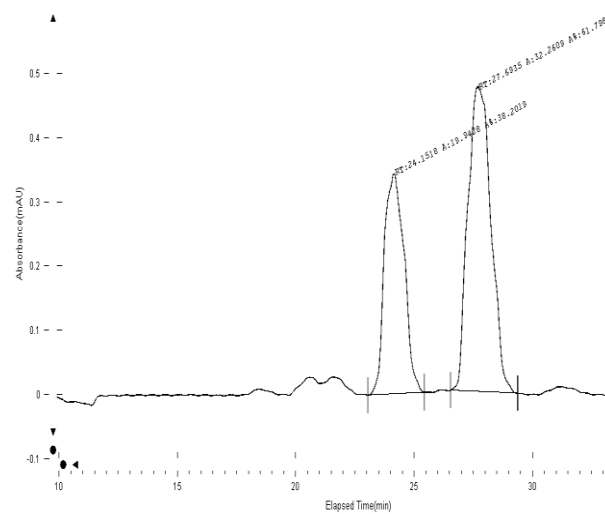
24.7 mg (25% yield) from 100 mg of **4.1n** as off white solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = -6.6^\circ$ (c 0.25, CHCl_3). SFC analysis indicates a 24% *ee*. Column (AD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 24.15 min (minor), t_R (2) = 27.69 (major).



chromatogram of (\pm)-4.2n (240 nm)

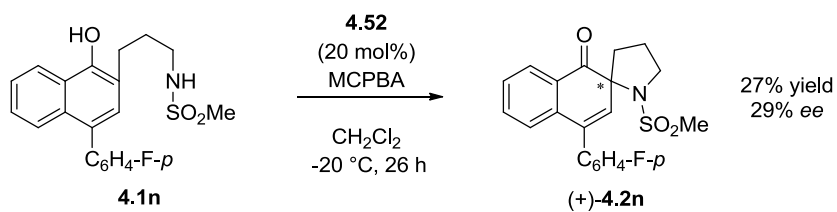


chromatogram of (-)-4.2n, (240 nm, 24% *ee*)

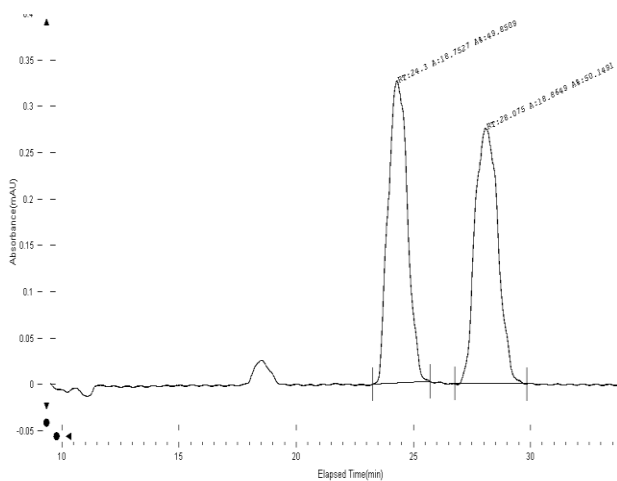


C.9.10 (+)-4-(4-fluorophenyl)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2n)

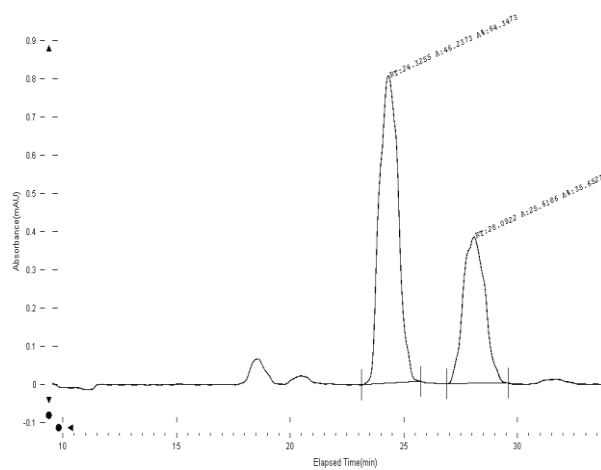
26.5 mg (27% yield) from 100 mg of **4.1n** as off white solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = +10.9^\circ$ (c 0.39, CHCl_3). SFC analysis indicates a 29% *ee*. Column (AD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), t_R (1) = 24.33 min (major), t_R (2) = 28.09 (minor).



chromatogram of (\pm)-4.2n (240 nm)

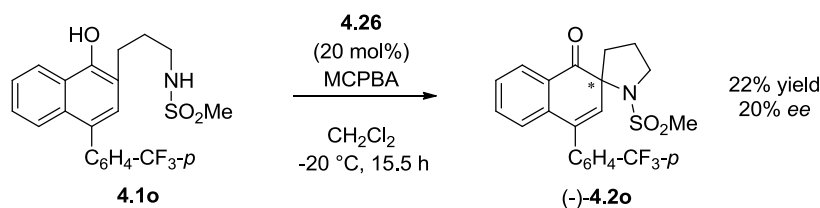


chromatogram of (+)-4.2n, (240 nm, 29% *ee*)

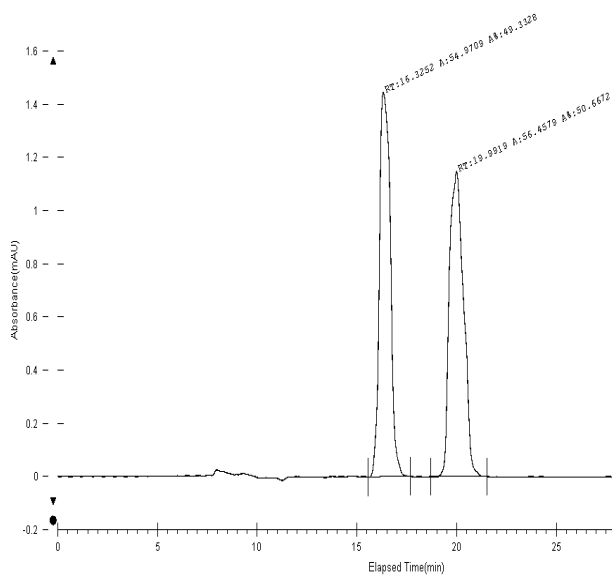


C.9.11 (-)-1'-(methylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2o)

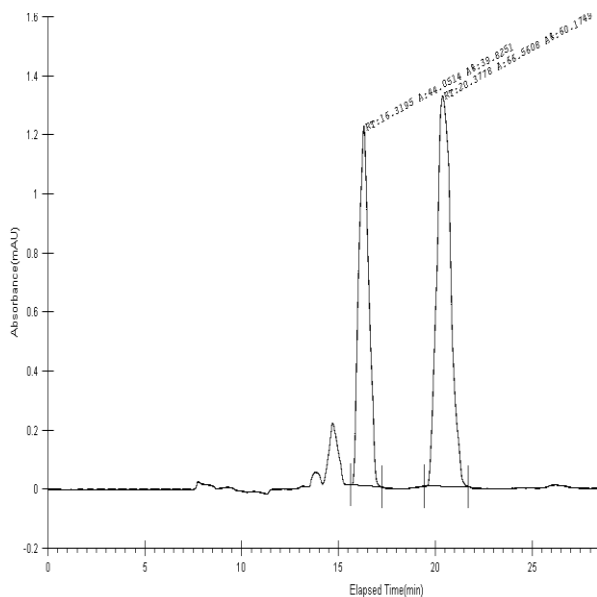
22 mg (22% yield) from 100 mg of **4.1o** as off white solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{26} = -9.5^\circ$ (*c* 0.20, CHCl₃). SFC analysis indicates a 20% *ee*. Column (AD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), t_R (1) = 16.32 min (minor), t_R (2) = 20.38 (major).



chromatogram of (\pm)-4.2o (240 nm)

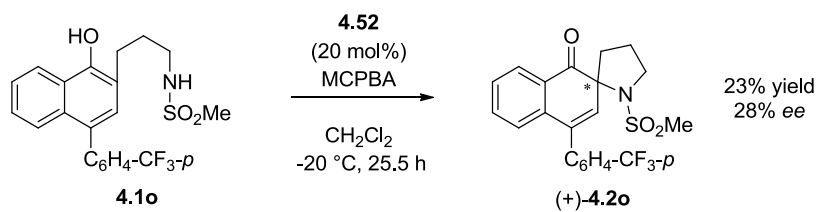


chromatogram of (-)-4.2o, (240 nm, 20% ee)

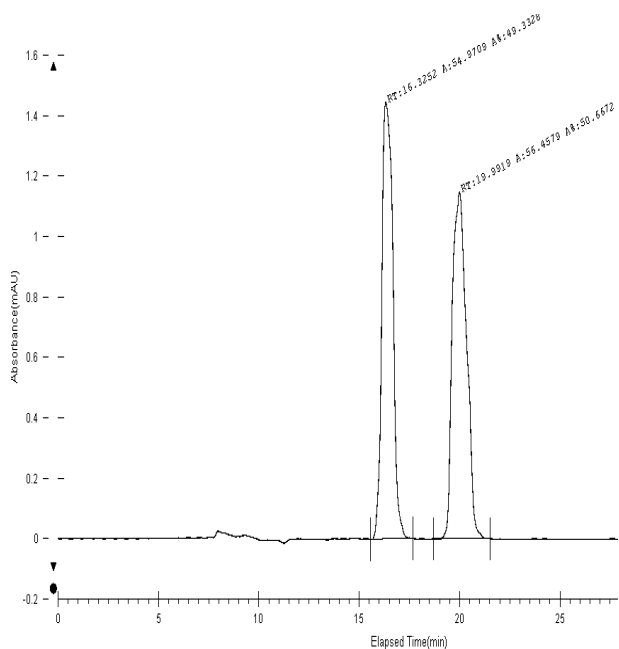


C.9.12 (+)-1'-(methylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2o)

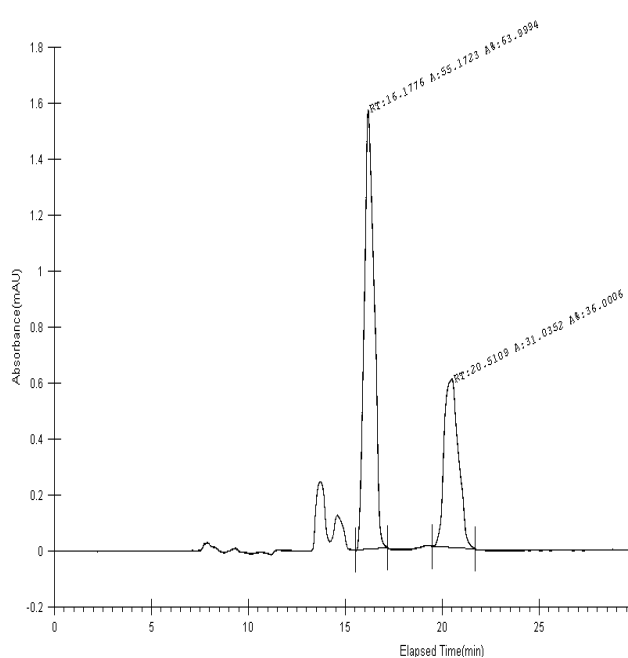
23 mg (23% yield) from 100 mg of **4.1o** as off white solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = +15.5^\circ$ (*c* 0.33, CHCl₃). SFC analysis indicates a 28% *ee*. Column (AD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), *t_R* (1) = 16.18 min (major), *t_R* (2) = 20.51 (minor).



chromatogram of (±)-4.2o (240 nm)

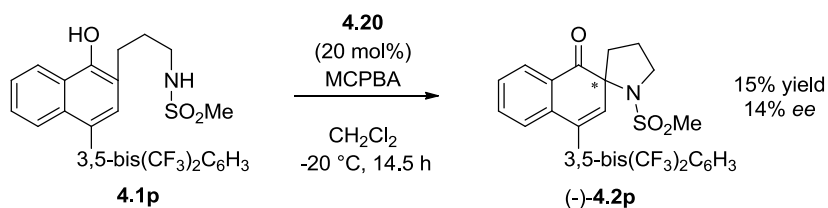


chromatogram of (+)-4.2o, (240 nm, 28% ee)

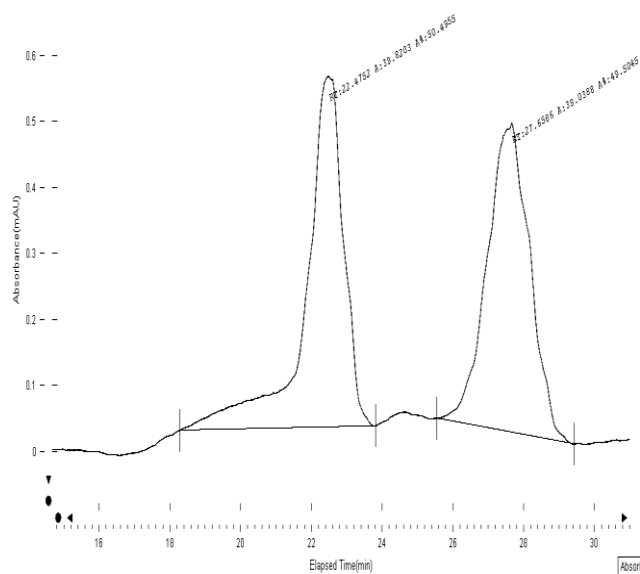


C.9.13 (-)-4-(3,5-bis(trifluoromethyl)phenyl)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2p)

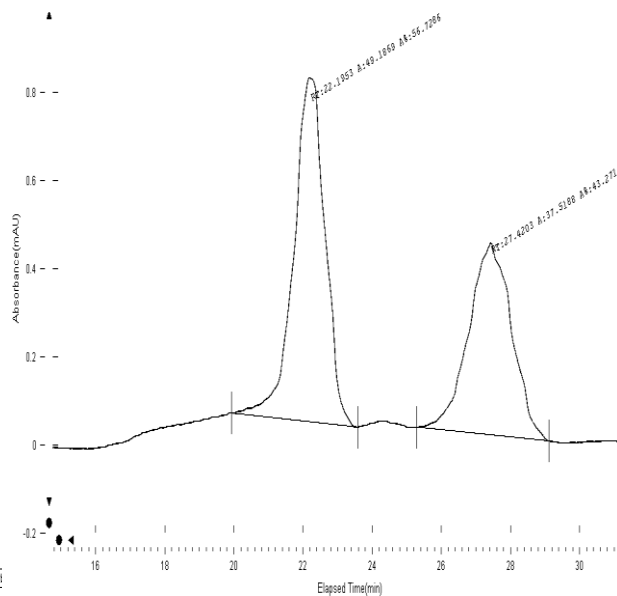
15.1 mg (15% yield) from 100 mg of **4.1p** as off white solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{24} = -5.4^\circ$ (*c* 0.10, CHCl₃). SFC analysis indicates a 14% *ee*. Column (AD-H) 1:99:0.1 (*i*PrOH: liq CO₂: diethylamine), t_R (1) = 22.20 min (major), t_R (2) = 27.42 (minor).



chromatogram of (\pm)-4.2p (240 nm)

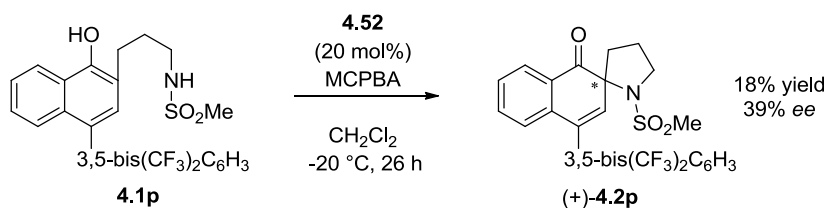


chromatogram of (-)-4.2p, (240 nm, 14% ee)

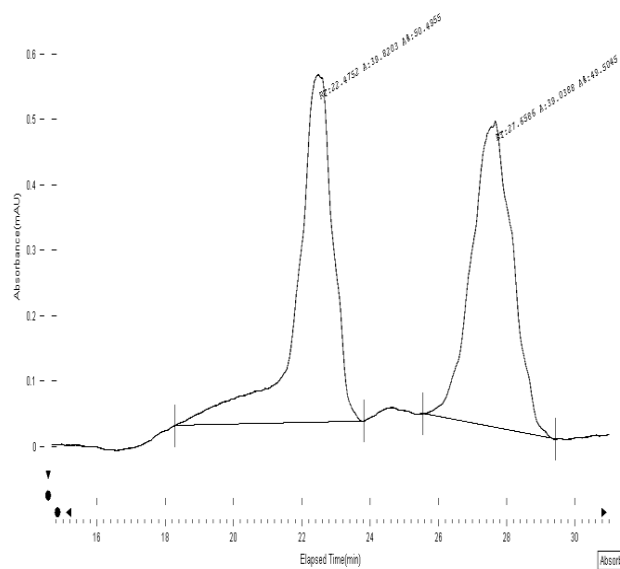


C.9.14 (+)-4-(3,5-bis(trifluoromethyl)phenyl)-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2p)

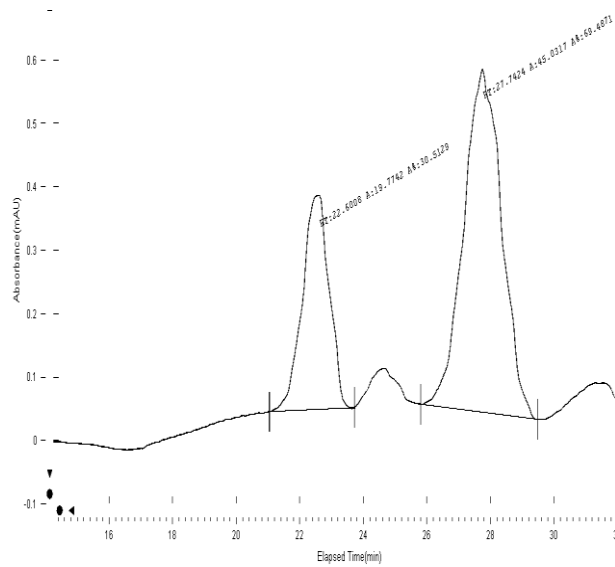
17.7 mg (18% yield) from 100 mg of **4.1p** as off white solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{24} = +11.2^\circ$ (*c* 0.32, CHCl₃). SFC analysis indicates a 39% *ee*. Column (AD-H) 1:99:0.1 (*i*PrOH: liq CO₂: diethylamine), t_R (1) = 22.60 min (minor), t_R (2) = 27.74 (minor).



chromatogram of (\pm)-4.2p (240 nm)

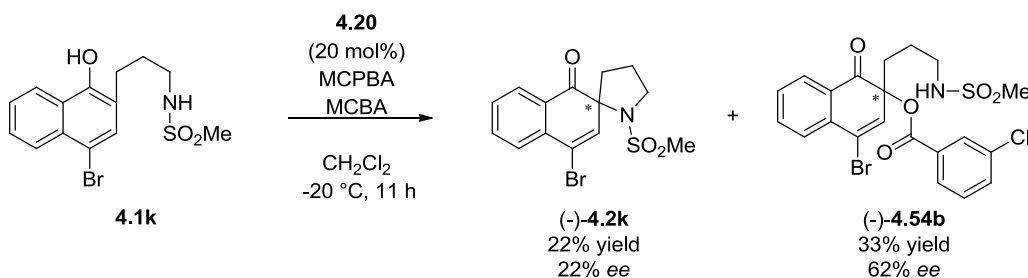


chromatogram of (+)-4.2p, (240 nm, 39% *ee*)

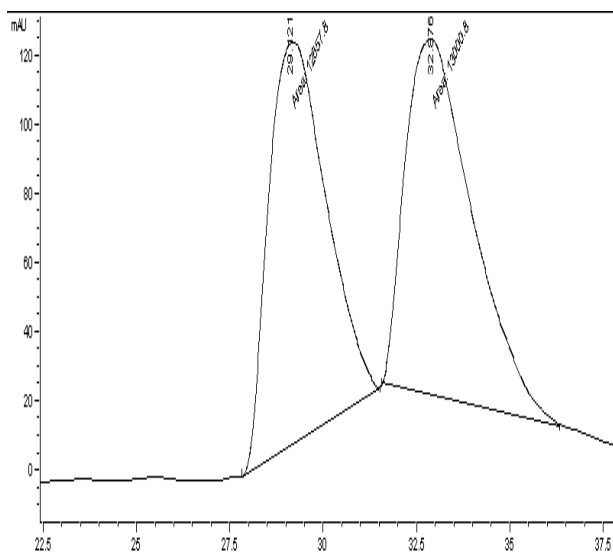


C.9.15 (-)-4-Bromo-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2k)

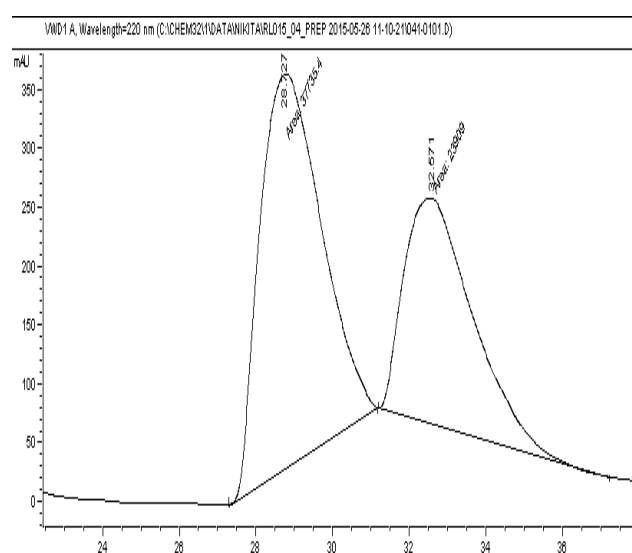
22.3 mg (22% yield) from 100 mg of **4.1k** as yellow oil, eluent: 3:7 EtOAc/hexane; $[\alpha]_D^{23} = -4.3^\circ$ (*c* 0.21, CHCl₃); HPLC analysis indicates a 22% *ee*: Column (OD-H) 5:95 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 28.73 min (major), t_R (2) = 32.57 (minor).



chromatogram of (±)-**4.2k** (220 nm)



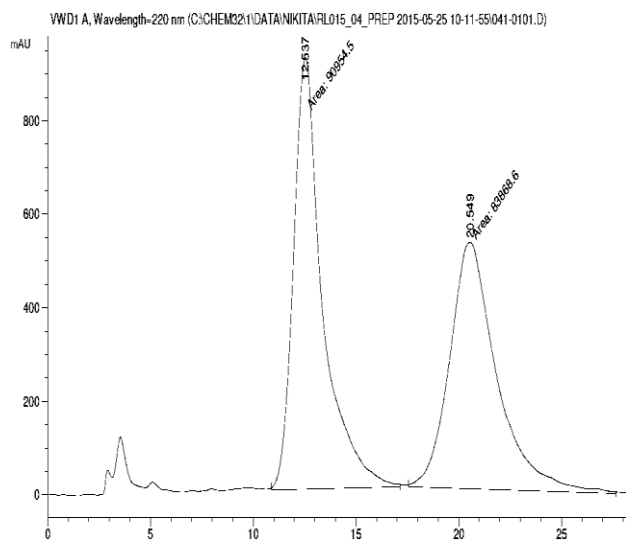
chromatogram of (+)-**4.2k**, (220 nm, 22% *ee*)



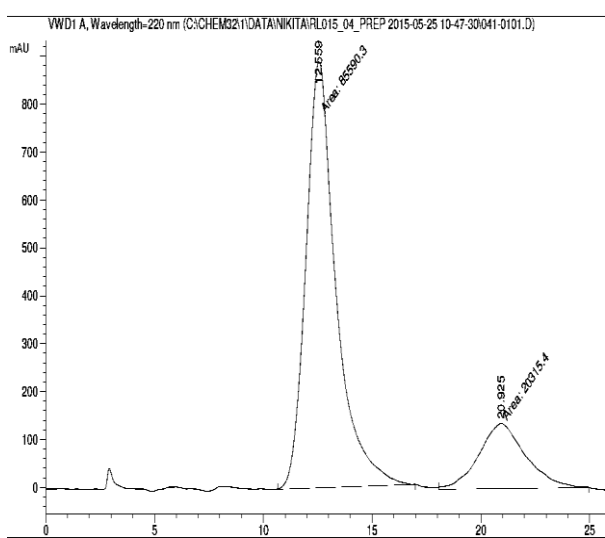
(-)-4-bromo-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54b)

47.4 mg (33% yield) from 100 mg of **4.1k** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{24} = -9.8^\circ$ (*c* 0.24, CHCl₃). HPLC analysis indicates a 62% *ee*. Column (AD-H) 10:90 (*i*PrOH:hexane), flow rate = 1.0 mL/min; t_R (1) = 12.56 min (major), t_R (2) = 20.93 (minor).

chromatogram of (±)-4.54b (220 nm)

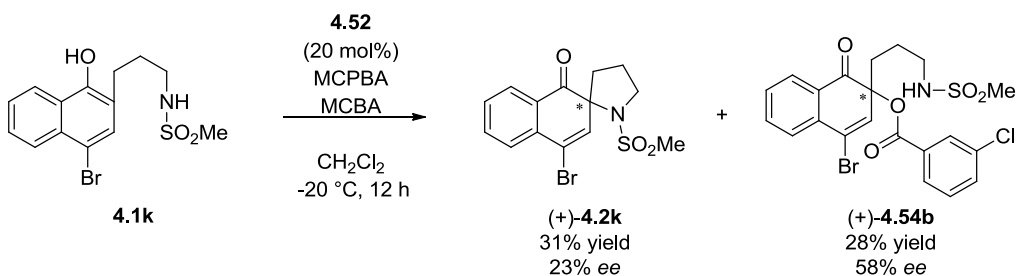


chromatogram of (-)-4.54b, (220 nm, 62% ee)

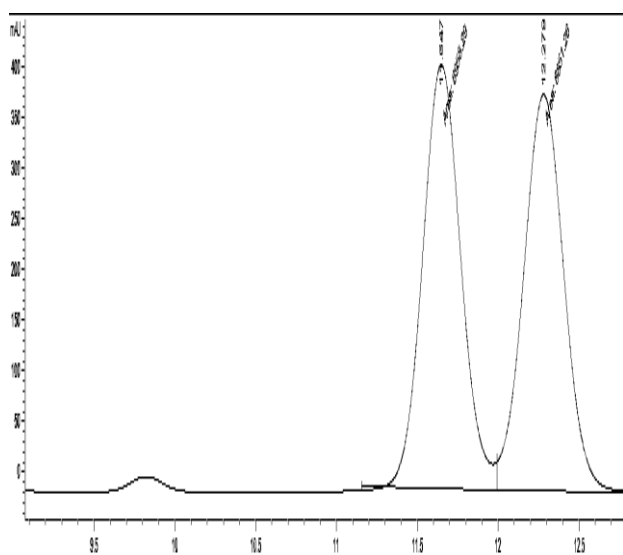


C.9.16 (+)-4-Bromo-1'-(methylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2k)

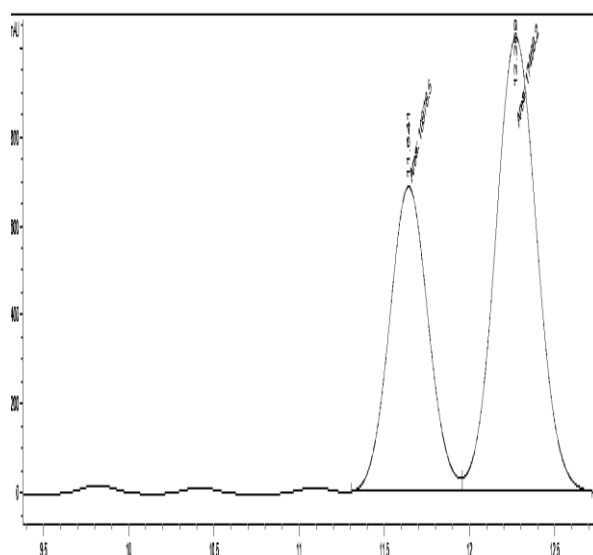
30.5 mg (31% yield) from 100 mg of **4.1k** as yellow oil, eluent: 3:7 EtOAc/hexane; $[\alpha]_D^{23} = +6.6^\circ$ (*c* 0.59, CHCl₃); HPLC analysis indicates a 23% *ee*: Column (OJ-RH) 60:40 (0.1% AcOH in H₂O: MeCN), flow rate = 0.7 mL/min; *t_R* (1) = 11.64 min (minor), *t_R* (2) = 12.27 (major).



chromatogram of (±)-4.2k (230 nm)



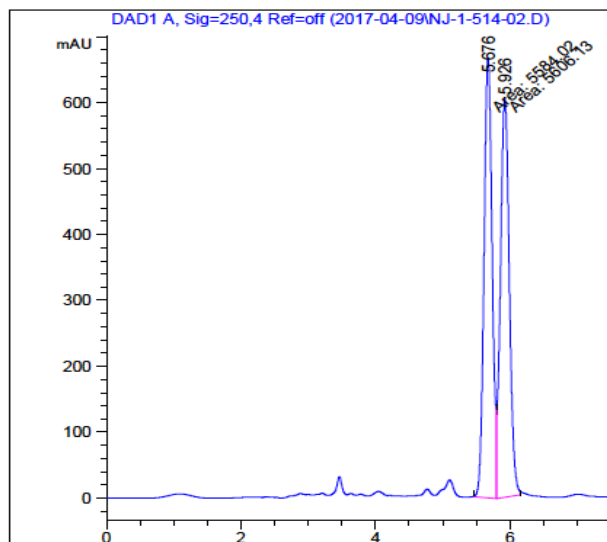
chromatogram of (+)-4.2k, (230 nm, 23% *ee*)



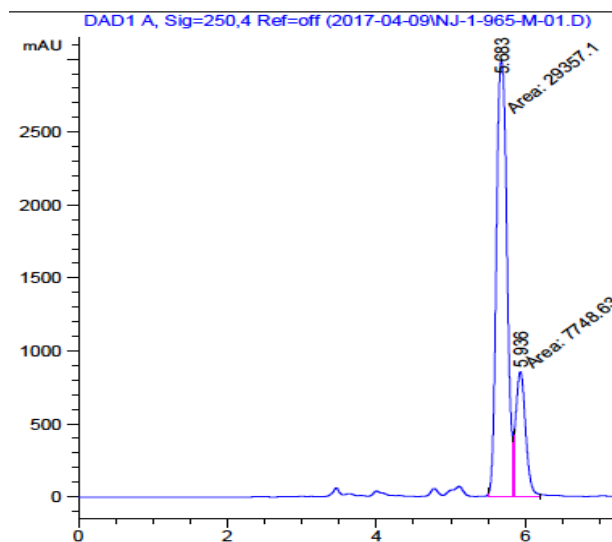
(+)-4-bromo-2-(3-(methylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54b)

39.6 mg (28% yield) from 100 mg of **4.1k** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = +9.6^\circ$ (*c* 0.38, CHCl₃). HPLC analysis indicates a 58% *ee*. Column (OJ-RH) 40:60 (0.1% AcOH in H₂O: MeCN), flow rate = 0.7 mL/min; t_R (1) = 5.68 min (major), t_R (2) = 5.94 (minor).

chromatogram of (±)-4.54b (250 nm)



chromatogram of (+)-4.54b, (250 nm, 58% ee)

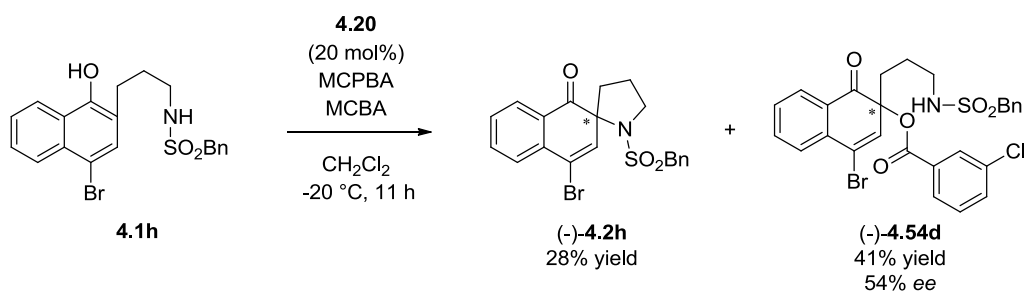


C.9.17 (-)-4-Bromo-1'-(benzylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2h)

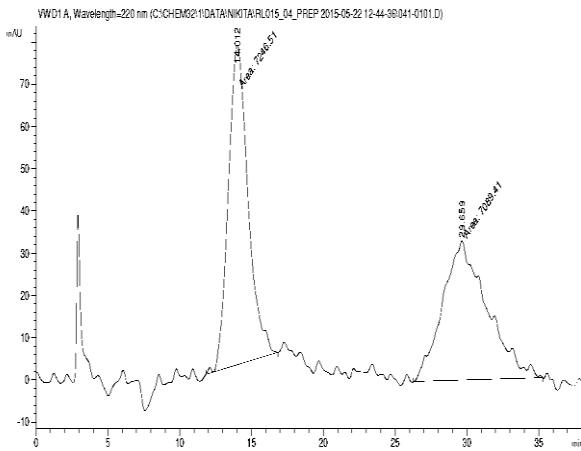
28.1 mg (28% yield) from 100 mg of **4.1h** as yellow solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = -5.7^\circ$ (*c* 0.18, CHCl₃). The *ee* could not be determined because enantiomers failed to separate regardless of chiral column used.

(-)-4-bromo-1-oxo-2-(3-(phenylmethylsulfonylamido)propyl)-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54d)

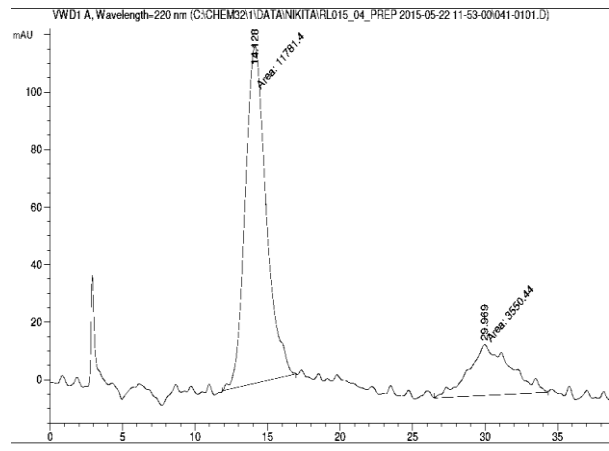
56.1 mg (41% yield) from 100 mg of **4.1h** as light yellow solid, eluent: 1:5 EtOAc/hexane; $[\alpha]_D^{25} = -23.0^\circ$ (*c* 0.37, CHCl₃). HPLC analysis indicates a 54% *ee*. HPLC: Column (AD-H) 20:80 (*i*PrOH: hexane), flow rate = 1.0 mL/min; *t_R* (1) = 14.13 min (major), *t_R* (2) = 29.97 (minor).



chromatogram of (\pm)-4.54d (220 nm)



chromatogram of (-)-4.54d, (220 nm, 54% ee)

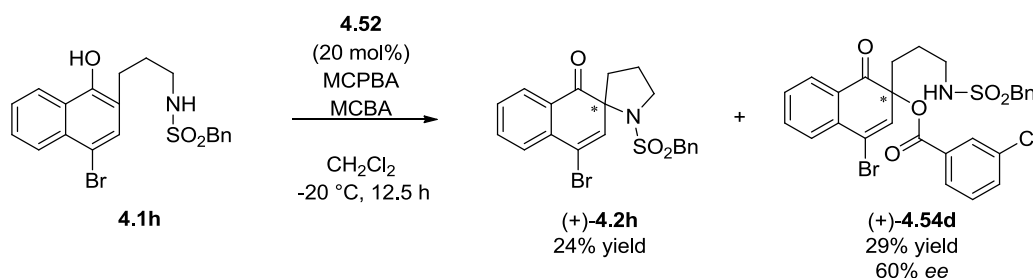


C.9.18 (+)-4-Bromo-1'-(benzylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2h)

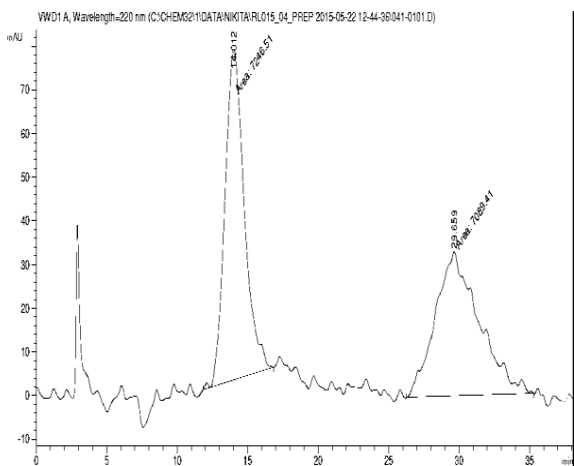
24.1 mg (24% yield) from 100 mg of **4.1h** as yellow solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{23} = +7.5^\circ$ (c 0.24, CHCl_3). The *ee* could not be determined because enantiomers of the compound failed to separate regardless of chiral column used.

(+)-4-bromo-1-oxo-2-(3-(phenylmethylsulfonylamido)propyl)-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54d)

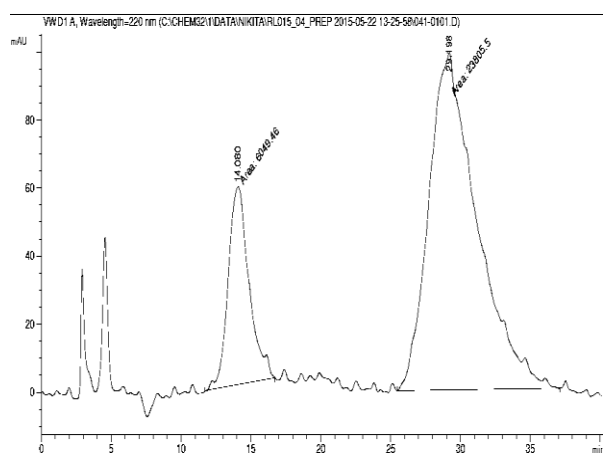
38.9 mg (29% yield) from 100 mg of **4.1h** as light yellow solid, eluent: 1:5 EtOAc/hexane; $[\alpha]_D^{23} = +29.1^\circ$ (c 0.12, CHCl_3). HPLC analysis indicates a 60% *ee*. HPLC: Column (AD-H) 20:80 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 14.08 min (minor), t_R (2) = 29.20 min (major).



chromatogram of (±)-4.54d (220 nm)

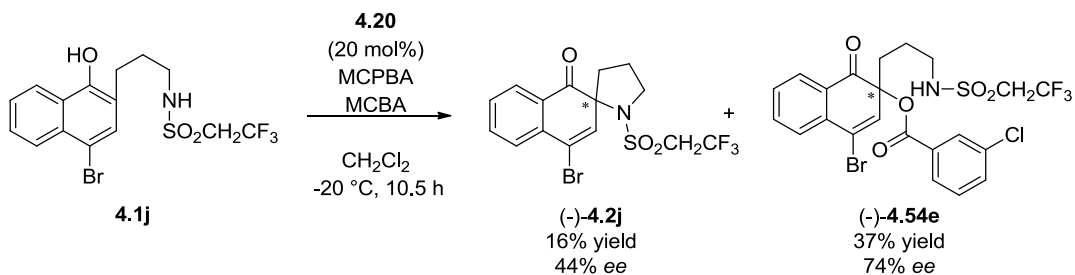


chromatogram of (+)-4.54d, (220 nm, 60% ee)

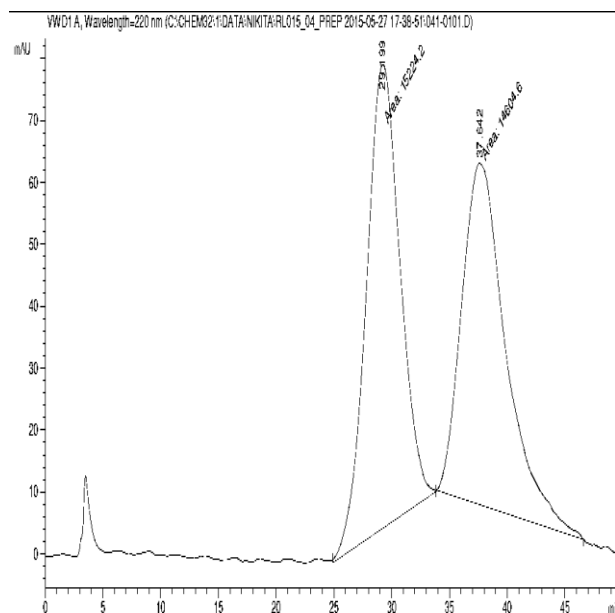


C.9.19 (-)-4-bromo-1'-(2,2,2-trifluoroethylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2j)

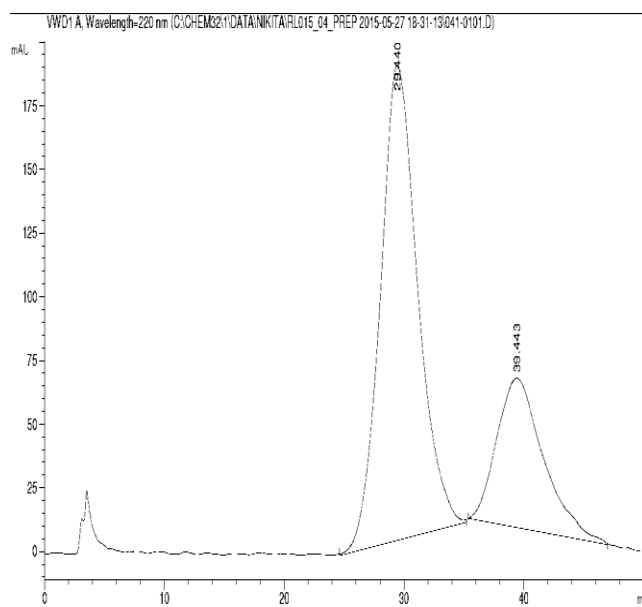
15.6 mg (16% yield) from 100 mg of **4.1j** as yellow solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{23} = -13.1^\circ$ (*c* 0.13, CHCl₃); HPLC analysis indicates a 44% *ee*: Column (AD-H) 2.5:97.5 (*i*PrOH:hexane), flow rate = 1.0 mL/min; t_R (1) = 29.44 min (major), t_R (2) = 39.44 min (minor).



chromatogram of (±)-4.2j (220 nm)



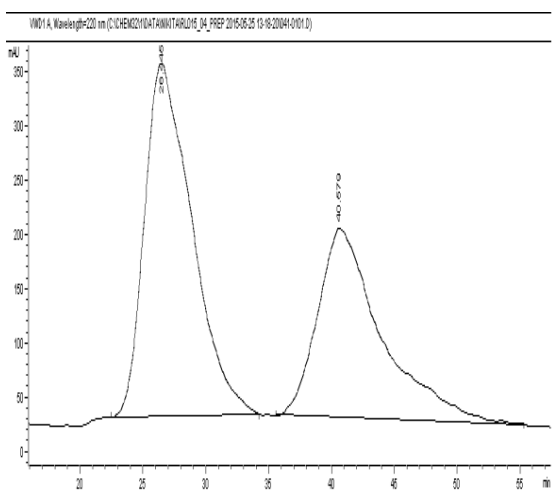
chromatogram of (-)-4.2j, (220 nm, 44% ee)



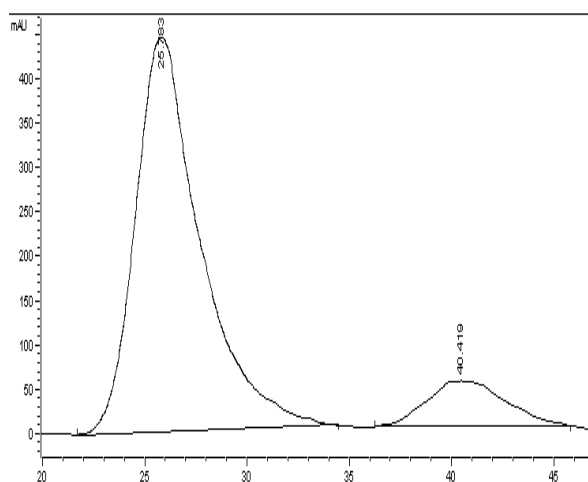
(-)-4-bromo-1-oxo-2-(3-(2,2,2-trifluoroethylsulfonamido)propyl)-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54e)

49.8 mg (37% yield) from 100 mg of **4.1j** as light yellow solid, eluent: 3:17 EtOAc/hexane; $[\alpha]_D^{23} = -12.7^\circ$ (*c* 0.44, CHCl₃). HPLC analysis indicates a 74% *ee*. HPLC: Column (AD-H) 10:90 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 25.78 min (major), t_R (2) = 40.42 (minor).

chromatogram of (±)-4.54e (220 nm)

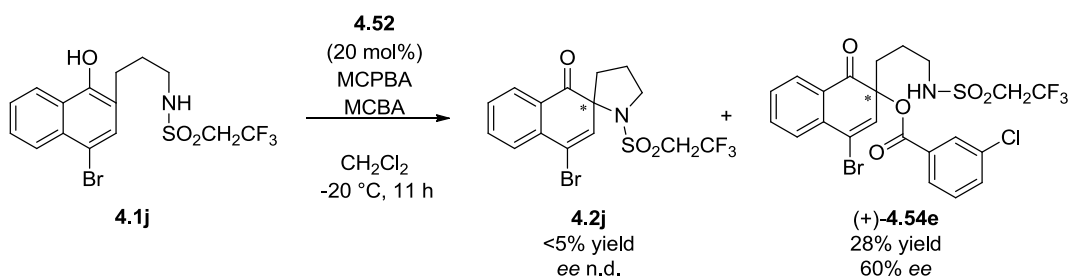


chromatogram of (-)-4.54e, (220 nm, 74% ee)

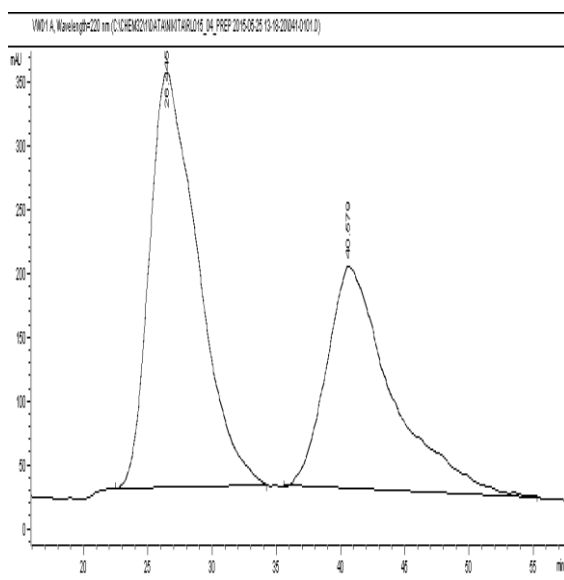


C.9.20 **(+)-4-bromo-1-oxo-2-(3-(2,2,2-trifluoroethylsulfonamido)propyl)-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54e)**

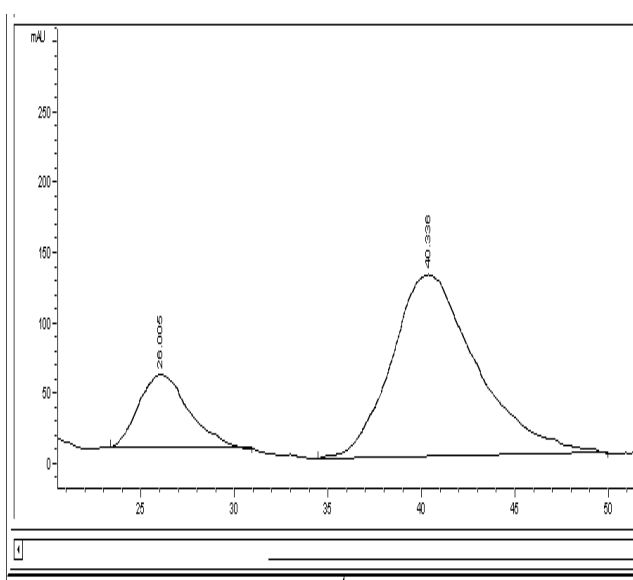
37.9 mg (28% yield) from 100 mg of **4.1j** as light yellow solid, eluent: 3:17 EtOAc/hexane; $[\alpha]_D^{25} = +9.8^\circ$ (*c* 0.15, CHCl₃). HPLC analysis indicates a 60% *ee*. HPLC: Column (AD-H) 10:90 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 26.01 min (minor), t_R (2) = 40.34 min (major).



chromatogram of (±)-4.54e (220 nm)

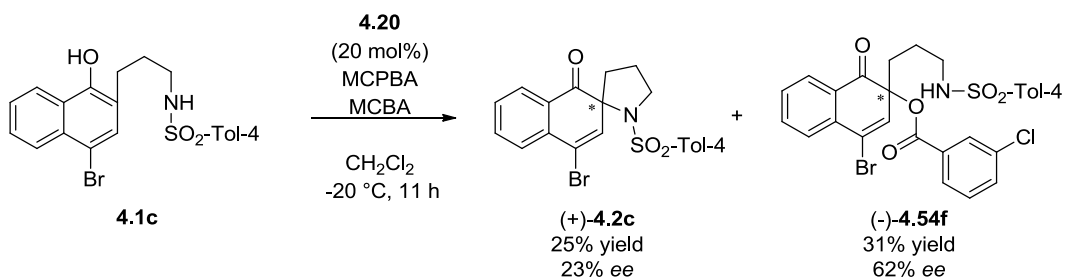


chromatogram of (+)-4.54e, (220 nm, 60% ee)

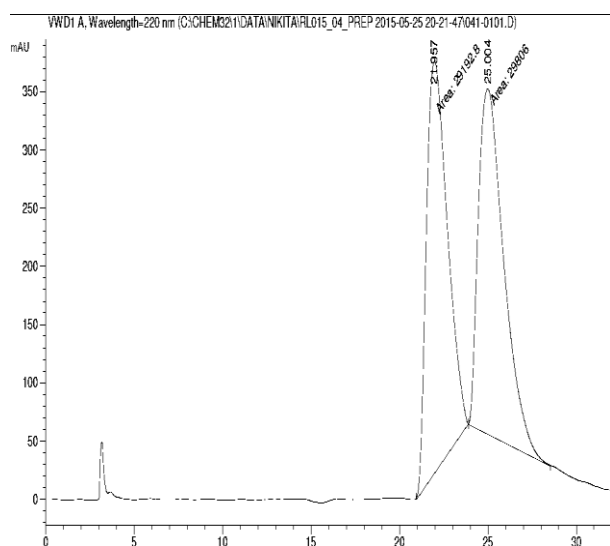


C.9.21 (+)-4-Bromo-1'-(4-tolylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2c)

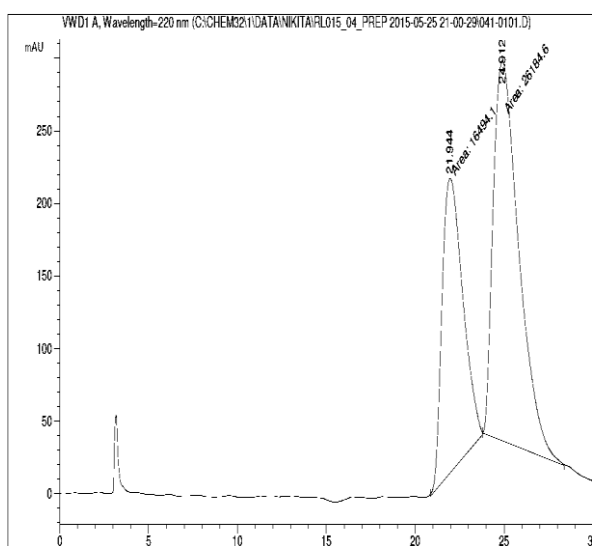
25.2 mg (25% yield) from 100 mg of **4.1c** as yellow solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{26} = +7.21^\circ$ (*c* 0.21, CHCl₃); SFC analysis indicates a 23% *ee*: Column (OD-H) 5:95 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 21.94 min (minor), t_R (2) = 24.91 (major).



chromatogram of (±)-4.2c (220 nm)



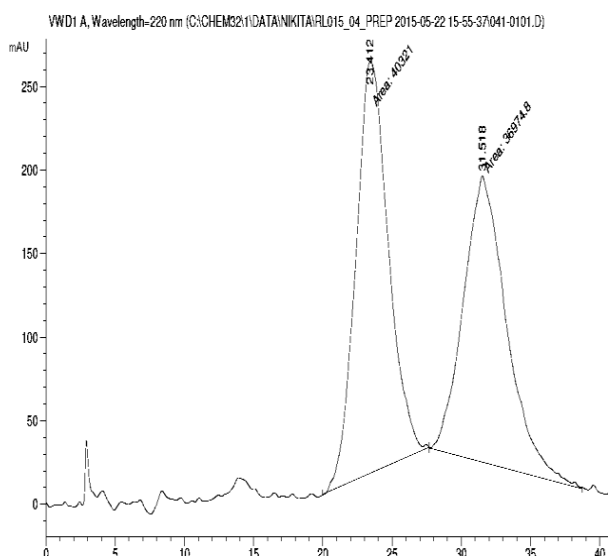
chromatogram of (+)-4.2c, (220 nm, 23% *ee*)



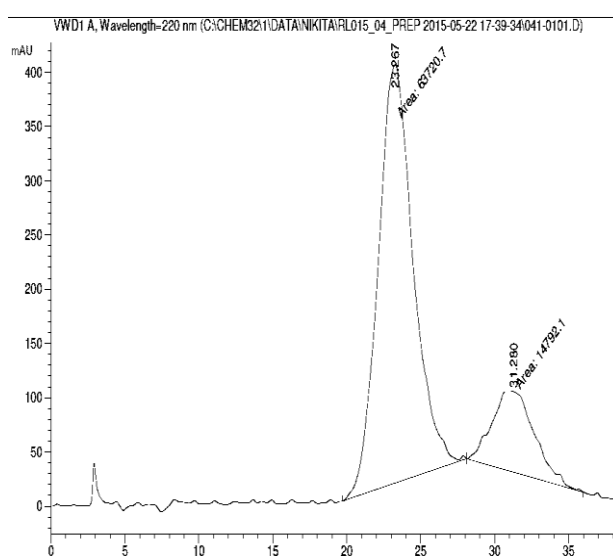
(-)-4-bromo-2-(3-(4-methylphenylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54f)

41.4 mg (31% yield) from 20 mg of **4.1c** as light yellow solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{26} = -16.9^\circ$ (*c* 0.32, CHCl₃). HPLC analysis indicates a 62% *ee*. HPLC: Column (AD-H) 20:80 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 23.27 min (major), t_R (2) = 31.28 (minor).

chromatogram of (±)-4.54f (220 nm)

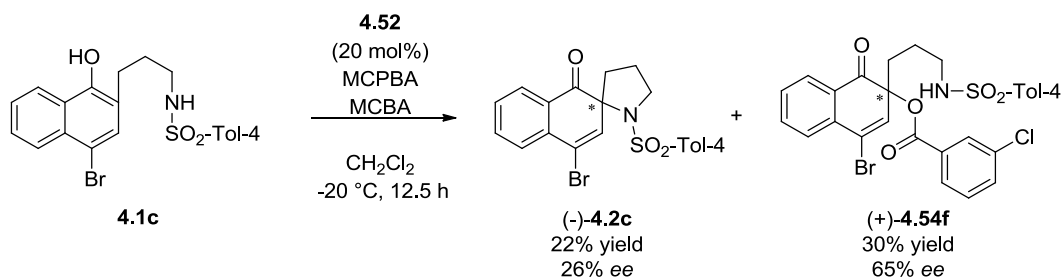


chromatogram of (-)-4.54f, (220 nm, 62% *ee*)

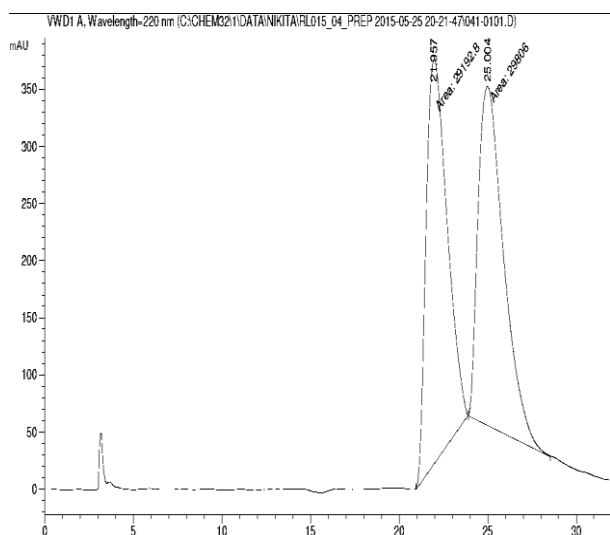


C.9.22 (-)-4-Bromo-1'-(4-tolylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one (4.2c)

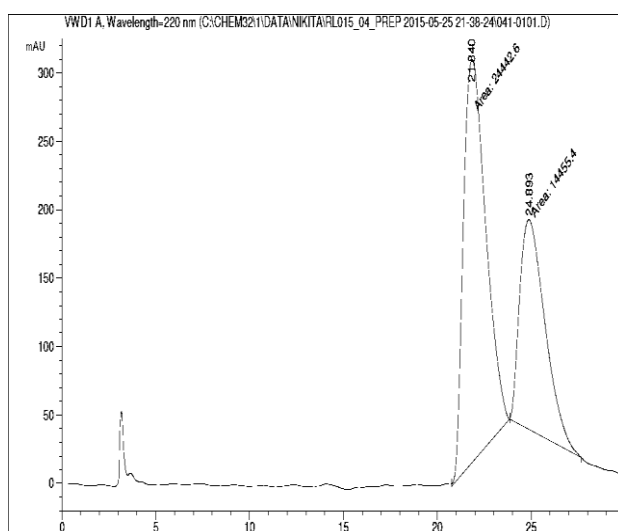
21.8 mg (22% yield) from 100 mg of **4.1c** as yellow solid, eluent: 1:4 EtOAc/hexane, $[\alpha]_D^{23} = -7.5^\circ$ (c 0.17, CHCl_3); SFC analysis indicates a 26% *ee*: Column (OD-H) 5:95 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 21.84 min (major), t_R (2) = 24.89 (minor).



chromatogram of (\pm)-4.2c (220 nm)



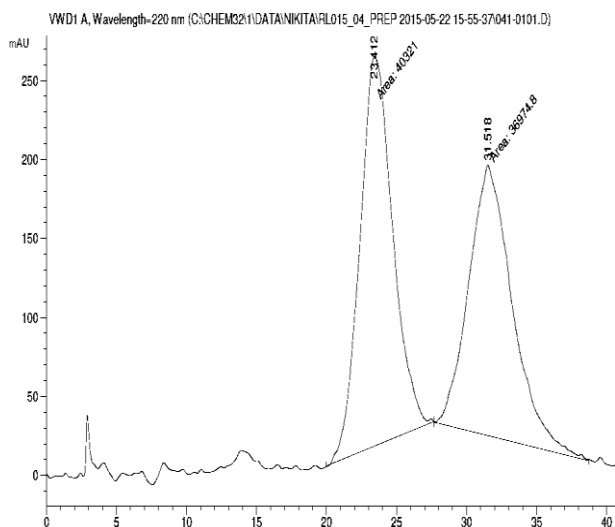
chromatogram of (-)-4.2c, (220 nm, 26% *ee*)



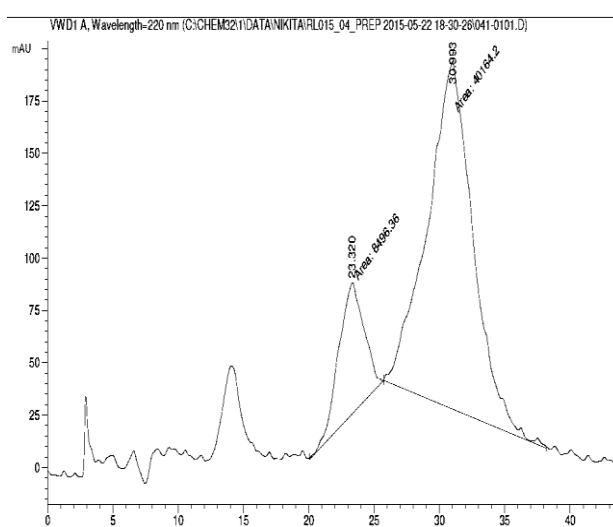
**(+)-4-bromo-2-(3-(4-methylphenylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl
3-chlorobenzoate (4.54f)**

40.2 mg (30% yield) from 100 mg of **4.1c** as light yellow solid, eluent: 1:4 EtOAc/hexane; $[\alpha]_D^{25} = +15.0$ (*c* 0.2, CHCl₃). HPLC analysis indicates a 65% *ee*. HPLC: Column (AD-H) 20:80 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 23.32 min (minor), t_R (2) = 30.99 (major).

chromatogram of (±)-4.54f (220 nm)

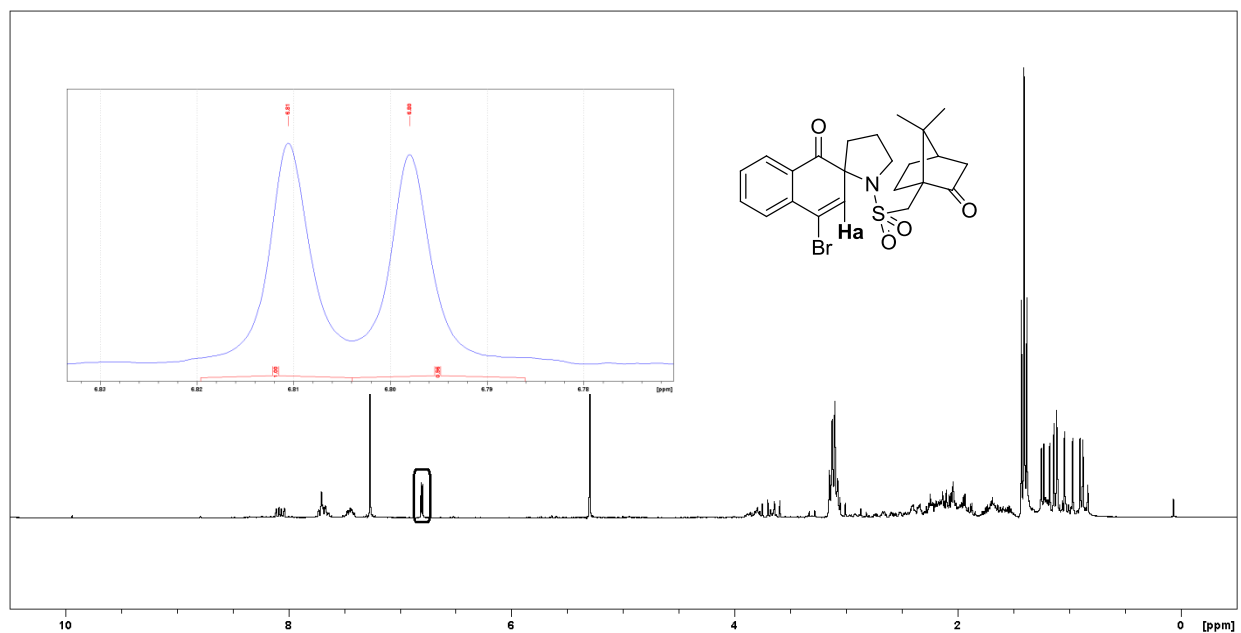
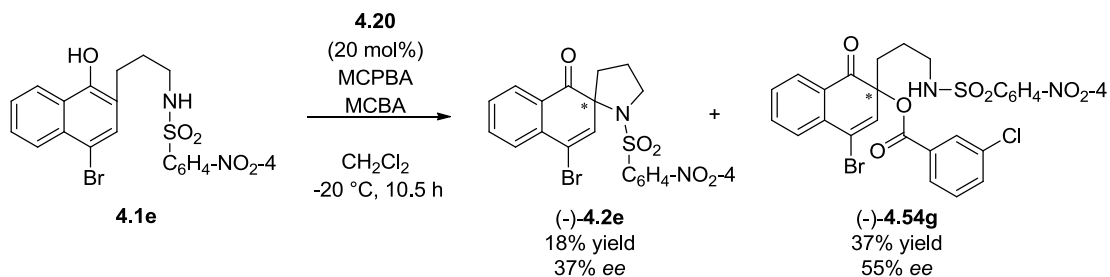


chromatogram of (+)-4.54f, (220 nm, 65% ee)

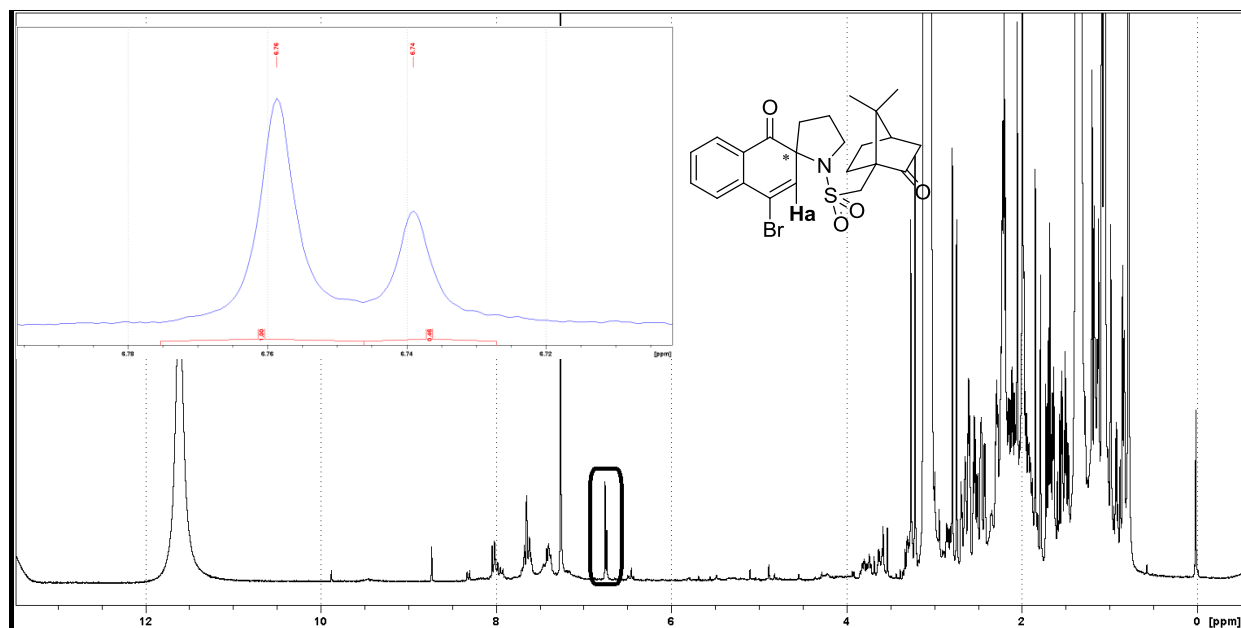


C.9.23 (-)-4-Bromo-1'-(4-nitrophenylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one
(4.2e)

17.4 mg (18% yield) from 100 mg of **4.1e** as yellow solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{24} = -9.2^\circ$ (*c* 0.16, CHCl₃). The *ee* of this compound was determined by forming (1*S*)-(+)-10-Camphorsulfonyl derivative of **4.61**. Diastereomeric excess obtained in this case was 37%.



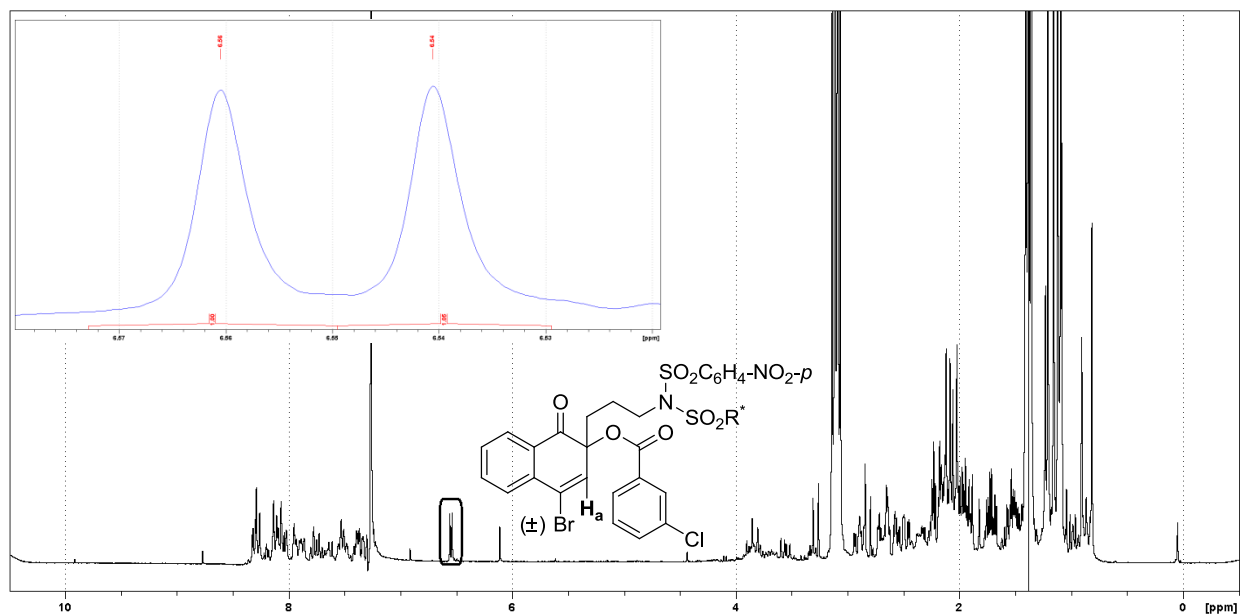
¹H NMR spectrum of crude (±)-**4.63** (300 MHz, CDCl₃)



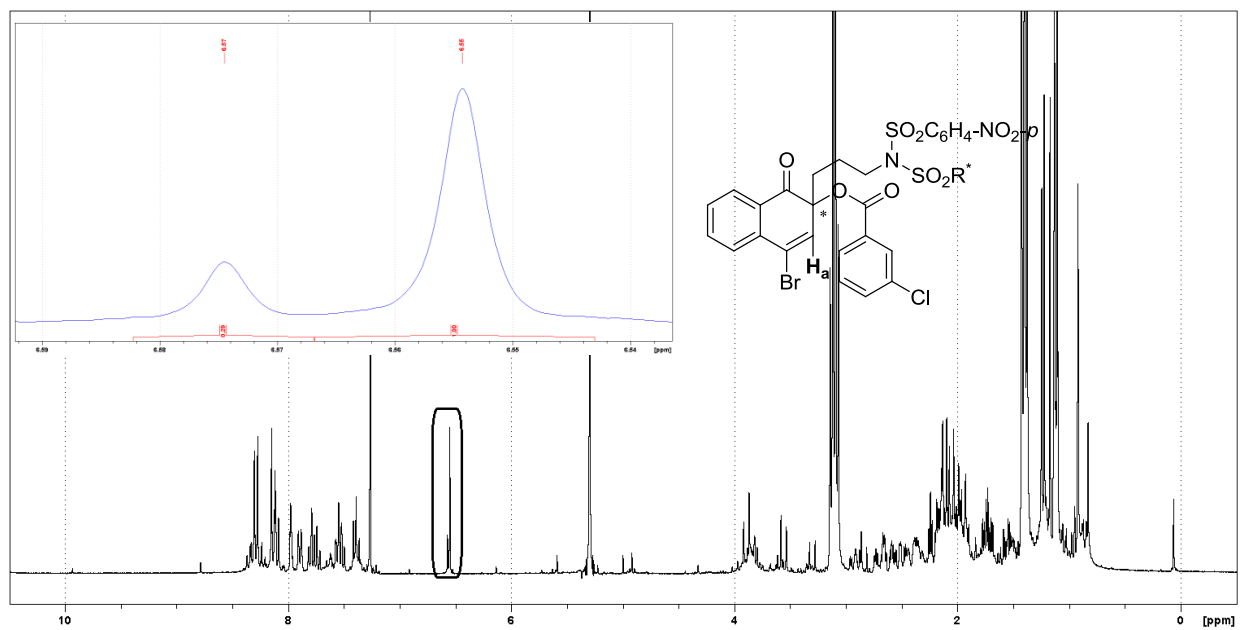
^1H NMR spectrum of chiral crude (\pm)-**4.63** (37% *de*; 300 MHz, CDCl_3)

(-)-**4-bromo-2-(3-(4-nitrophenylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54g)**

49.2 mg (37% yield) from 100 mg of **4.1e** as yellow solid, eluent: 1:3 EtOAc/hexane; $[\alpha]_{\text{D}}^{23} = -22.3^\circ$ (*c* 0.43, CHCl_3). The *ee* of this compound was determined by forming (1*S*)-(+)-10-Camphorsulfonyl derivative of (-)-**4.54g**. Diastereomeric excess obtained in this case was 55%.



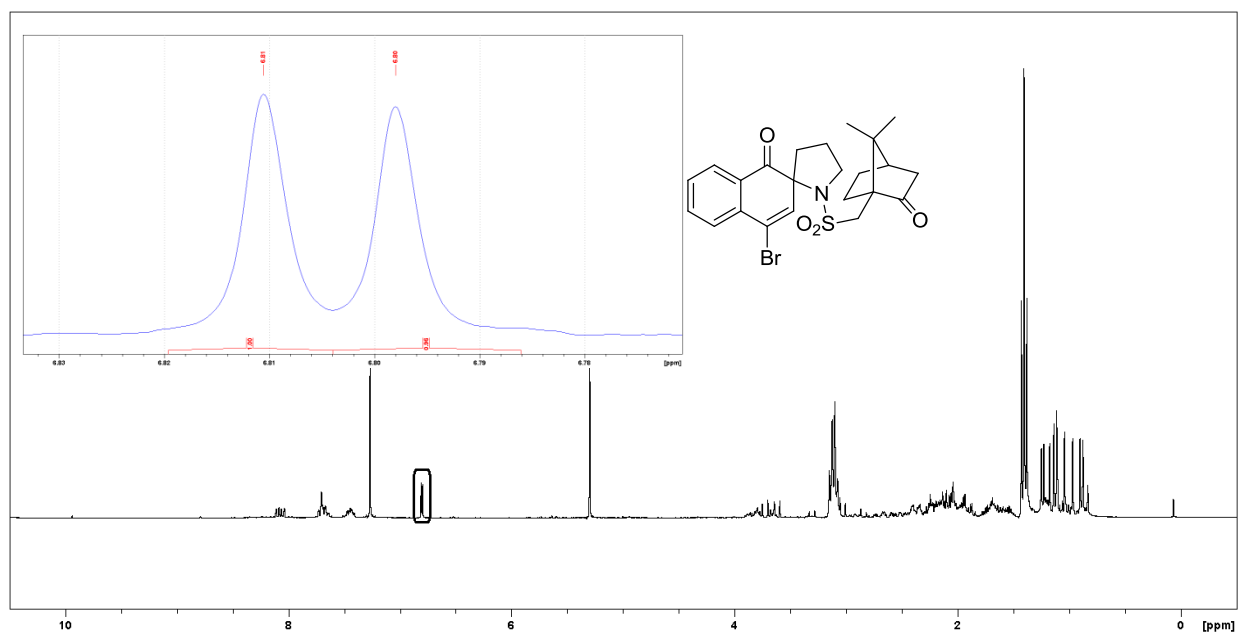
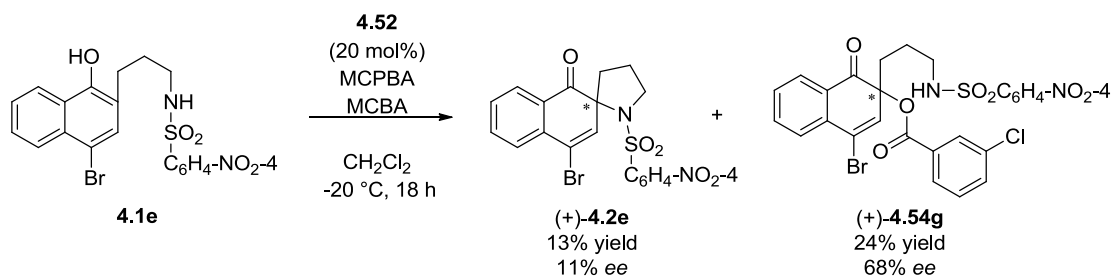
^1H NMR spectrum of crude (\pm)-4.64 (300 MHz, CDCl_3)



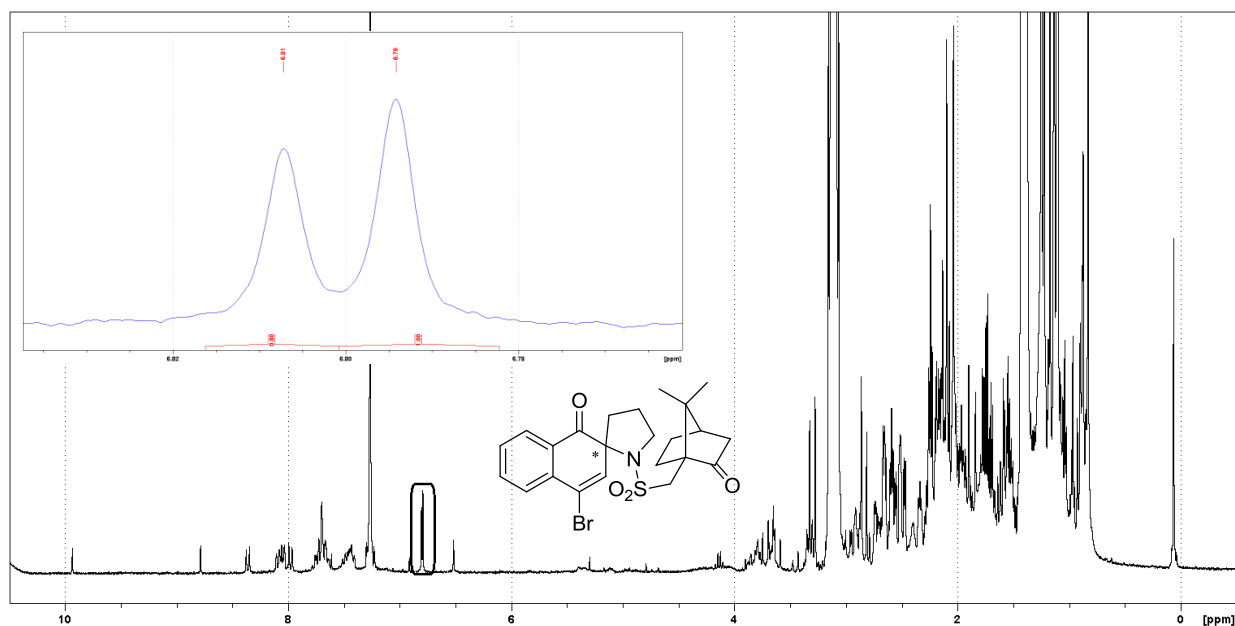
^1H NMR spectrum of chiral crude 4.64 (55% *de*; 300 MHz, CDCl_3)

C.9.24 (+)-4-Bromo-1'-(4-nitrophenylsulfonyl)-1*H*-spiro[naphthalene-2,2'-pyrrolidin]-1-one
(4.2e)

13 mg (13% yield) from 100 mg of **4.1e** as yellow solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = +3.8^\circ$ (*c* 0.13, CHCl₃). The *ee* of this compound was determined by forming (1*S*)-(+)-10-Camphorsulfonyl derivative of **4.61**. Diastereomeric excess obtained in this case was 11%.



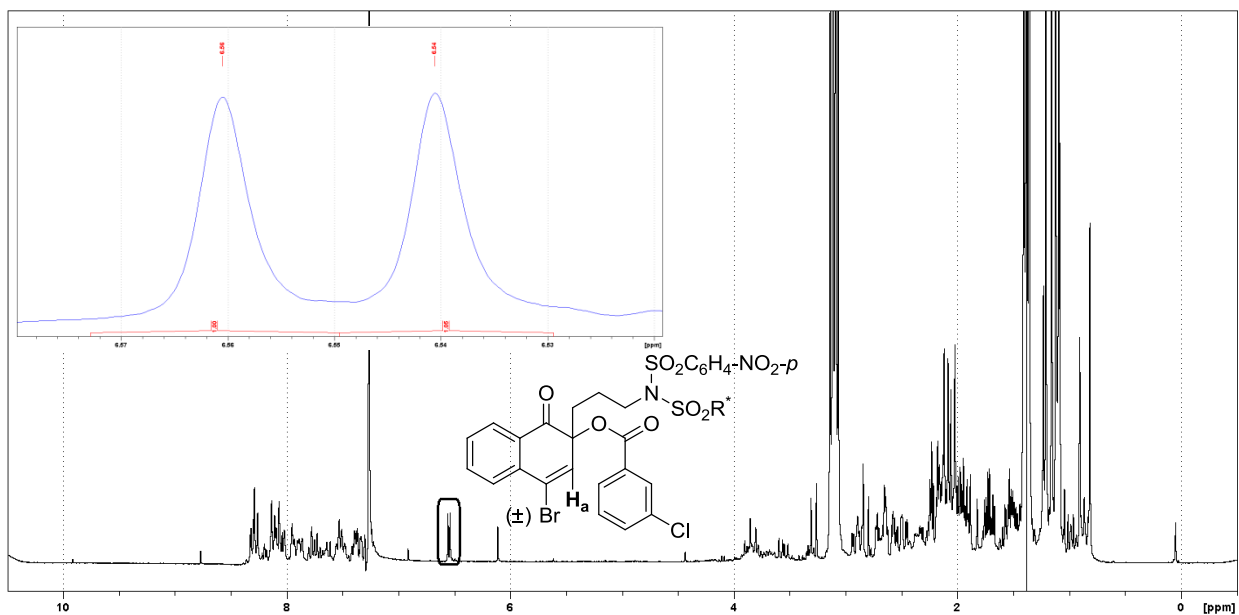
¹H NMR spectrum of crude (±)-4.63 (300 MHz, CDCl₃)



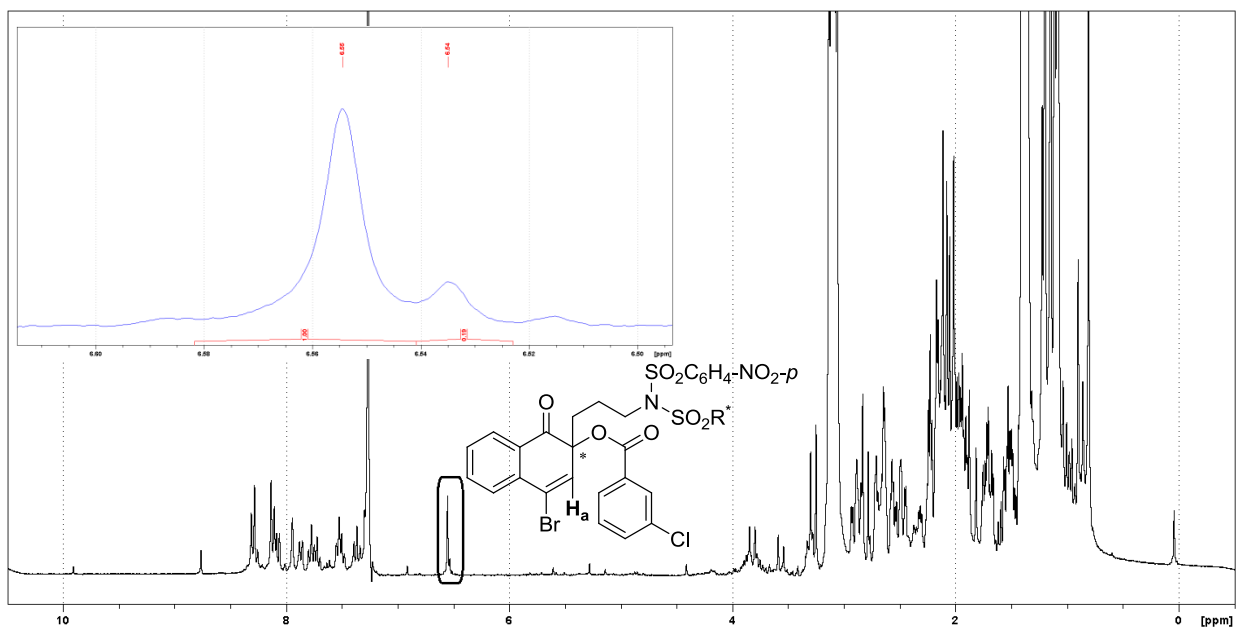
^1H NMR spectrum of chiral crude (\pm)-4.63 (11% *de*; 300 MHz, CDCl_3)

(+)-4-bromo-2-(3-(4-nitrophenylsulfonamido)propyl)-1-oxo-1,2-dihydronaphthalen-2-yl 3-chlorobenzoate (4.54g)

31.4 mg (24% yield) from 100 mg of **4.1e** as yellow solid, eluent: 1:3 EtOAc/hexane; $[\alpha]_{\text{D}}^{23} = +25.6^\circ$ (*c* 0.50, CHCl_3). The *ee* of this compound was determined by forming (1*S*)-(+)-10-Camphorsulfonyl derivative of (+)-**4.54g**. Diastereomeric excess obtained in this case was 66%.



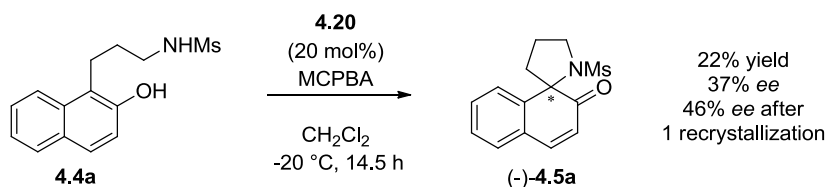
^1H NMR spectrum of crude (\pm) -4.64 (300 MHz, CDCl_3)



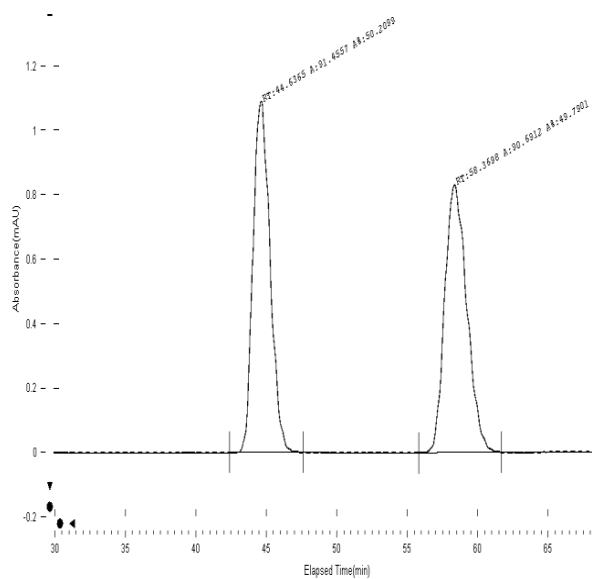
^1H NMR spectrum of chiral crude 4.64 (68% *de*; 300 MHz, CDCl_3)

C.9.25 (-)-1'-(methylsulfonyl)-2*H*-spiro[naphthalene-1,2'-pyrrolidin]-2-one (4.5a)

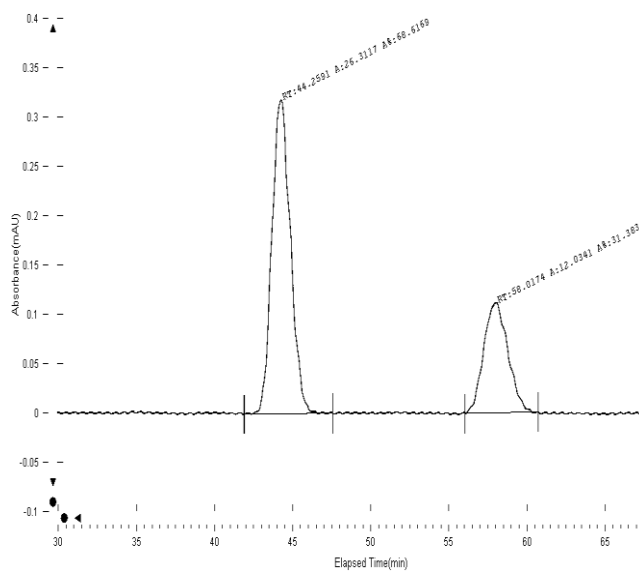
4.4 mg (22% yield) from 20 mg of **4.4a** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = -31.0^\circ$ (*c* 0.65, CHCl₃). SFC analysis indicates a 37% *ee*: Column (AD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 44.26 min (major), *t_R* (2) = 58.02 (minor).



chromatogram of (\pm)-4.5a (229 nm)

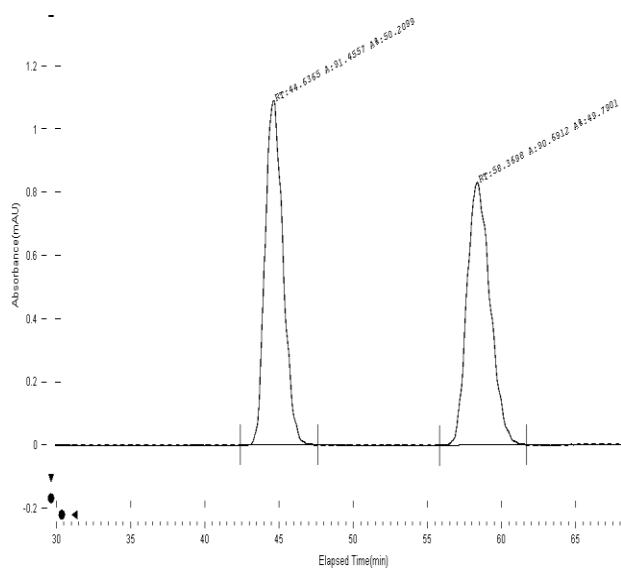


chromatogram of (-)-4.5a, (229 nm, 37% *ee*)

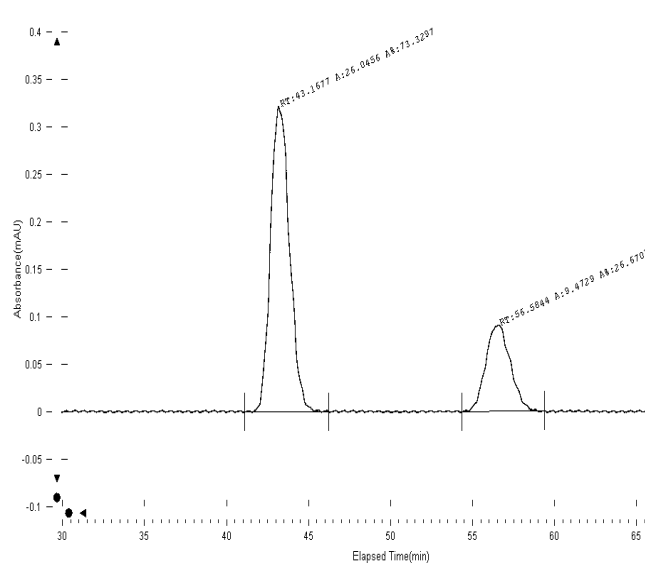


One recrystallization (EtOAc / hexane; slow evaporation, room temp.) afforded material of 46% *ee*, the optical purity of which was determined by SFC: Column (AD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 43.17 min (major), t_R (2) = 56.58 (minor).

chromatogram of (\pm)-4.5a (229 nm)

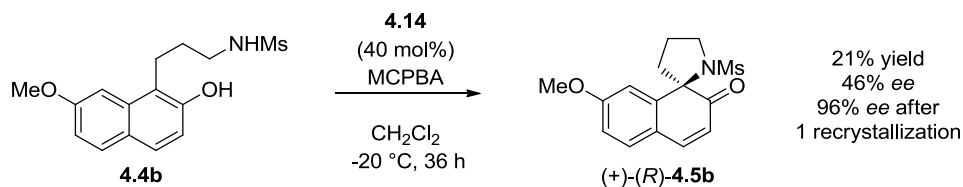


chromatogram of (-)-4.5a, (229 nm, 46% *ee*)

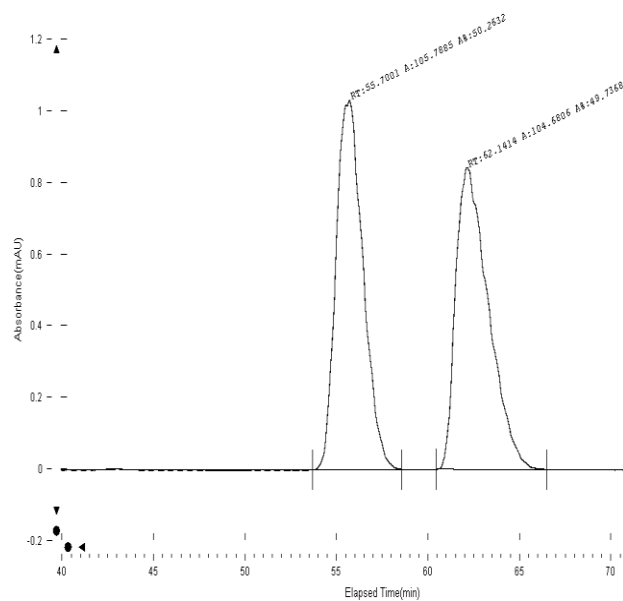


C.9.26 (+)-(R)-7-methoxy-1'-(methylsulfonyl)-2H-spiro[naphthalene-1,2'-pyrrolidin]-2-one (4.5b)

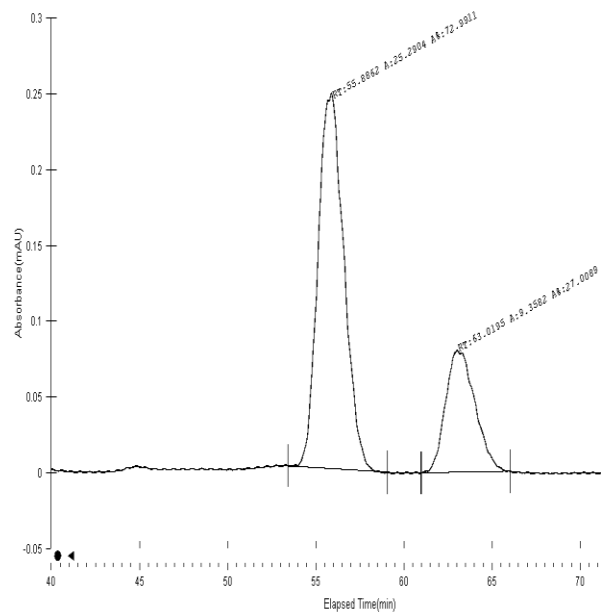
4.2 mg (21% yield) from 20 mg of **4.4b** as white solid, eluent: 2:3 EtOAc/hexane; $[\alpha]_D^{23} = +72.2^\circ$ (*c* 0.67, CHCl₃). SFC analysis indicates a 46% *ee*: Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 55.89 min (major), t_R (2) = 63.02 (minor).



chromatogram of (\pm)-**4.5b** (240 nm)

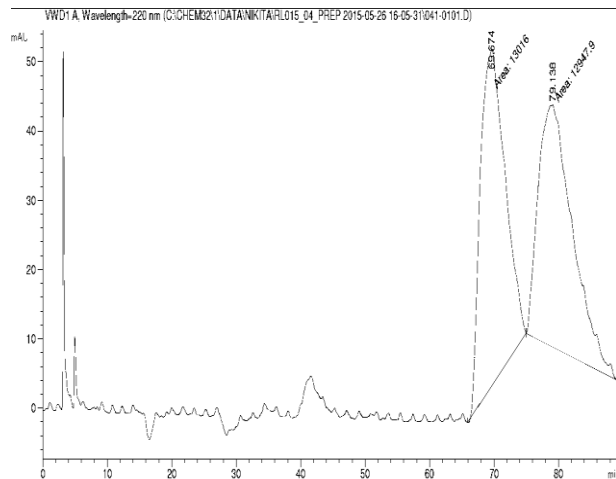


chromatogram of (+)-**4.5b**, (240 nm, 46% *ee*)

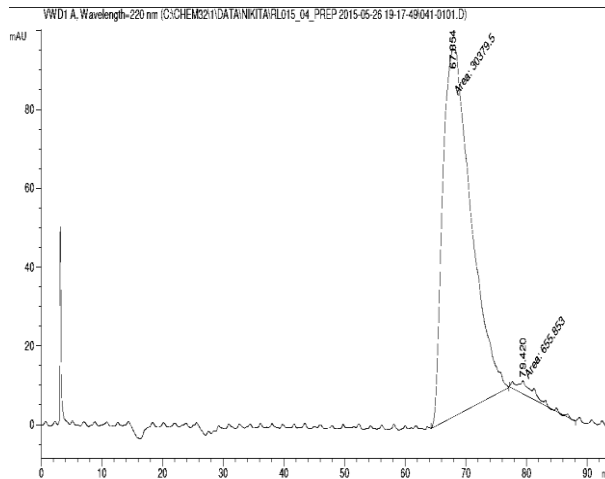


One recrystallization (Methanol; slow evaporation, RT) afforded material of 96% *ee*, the optical purity of which was determined by chiral HPLC: Column (OD-H) 5:95 (*i*PrOH: hexane), flow rate = 1.0 mL/min; t_R (1) = 67.85 min (major), t_R (2) = 79.42 min (minor).

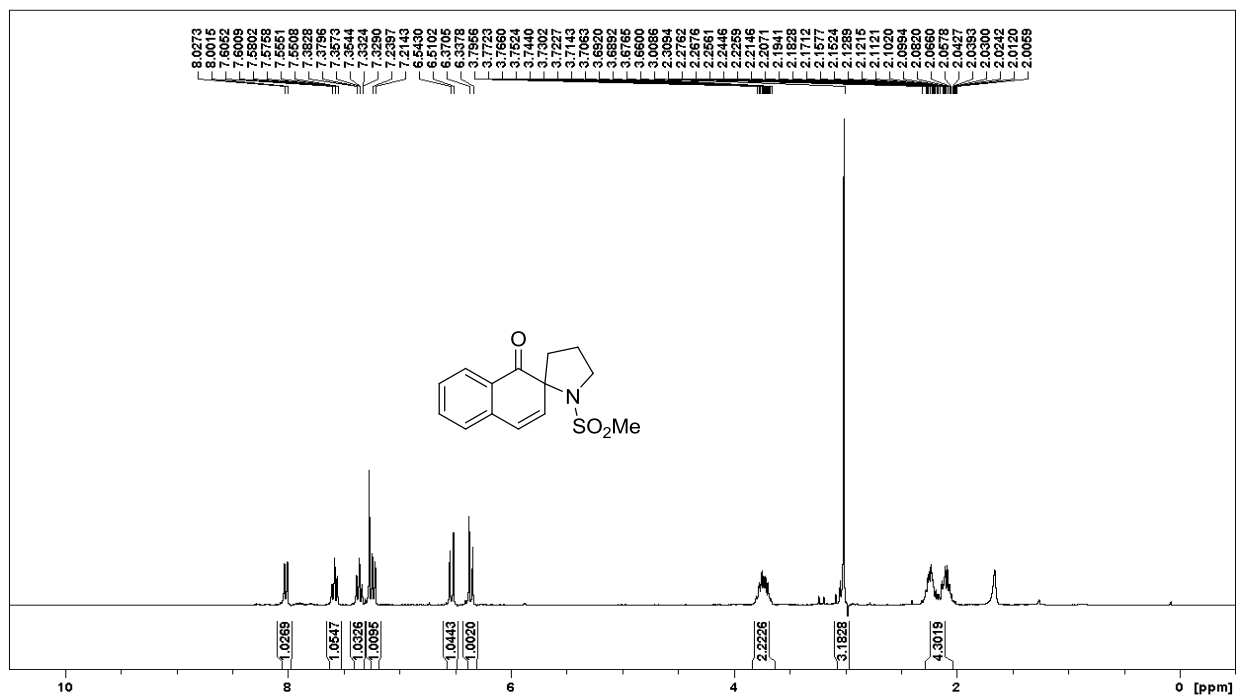
chromatogram of (\pm)-4.5b (220 nm)



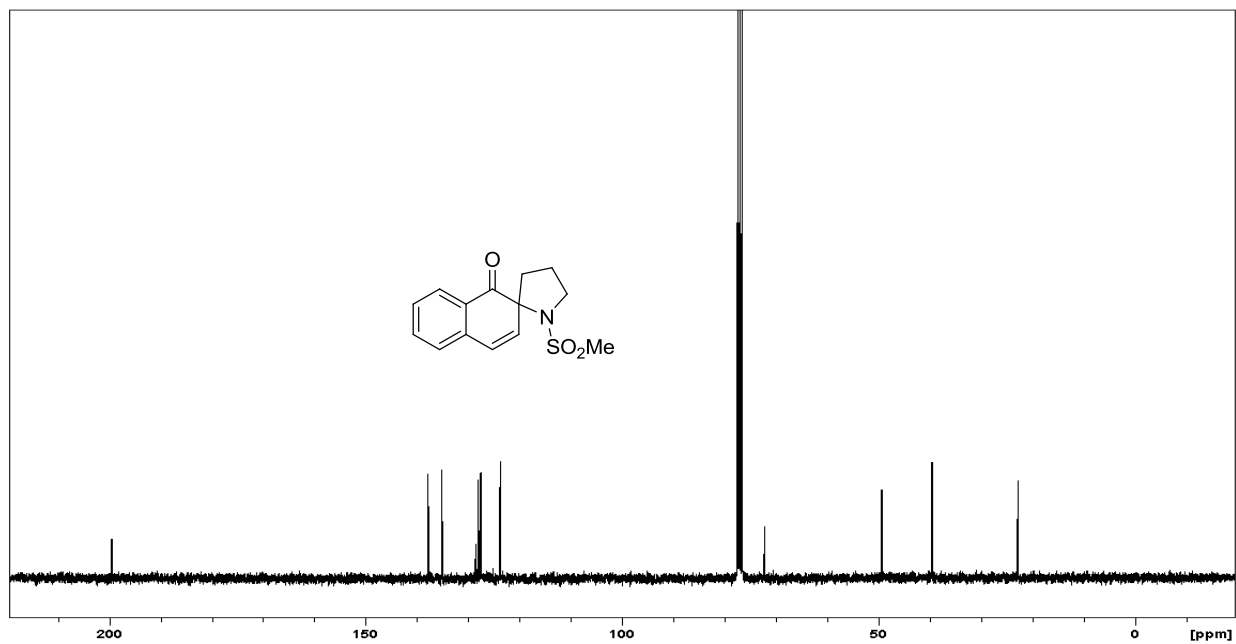
chromatogram of (+)-4.5b, (220 nm, 96% *ee*)



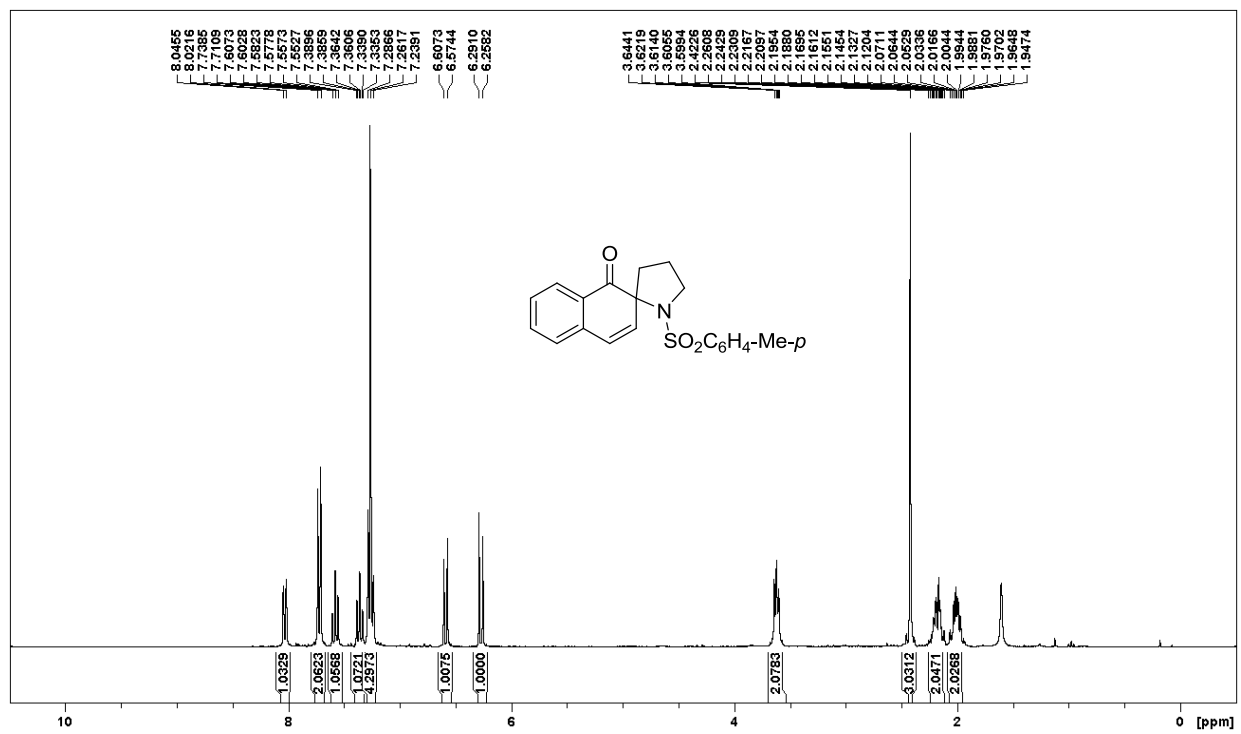
C.10 ^1H and ^{13}C spectra from chapter 4



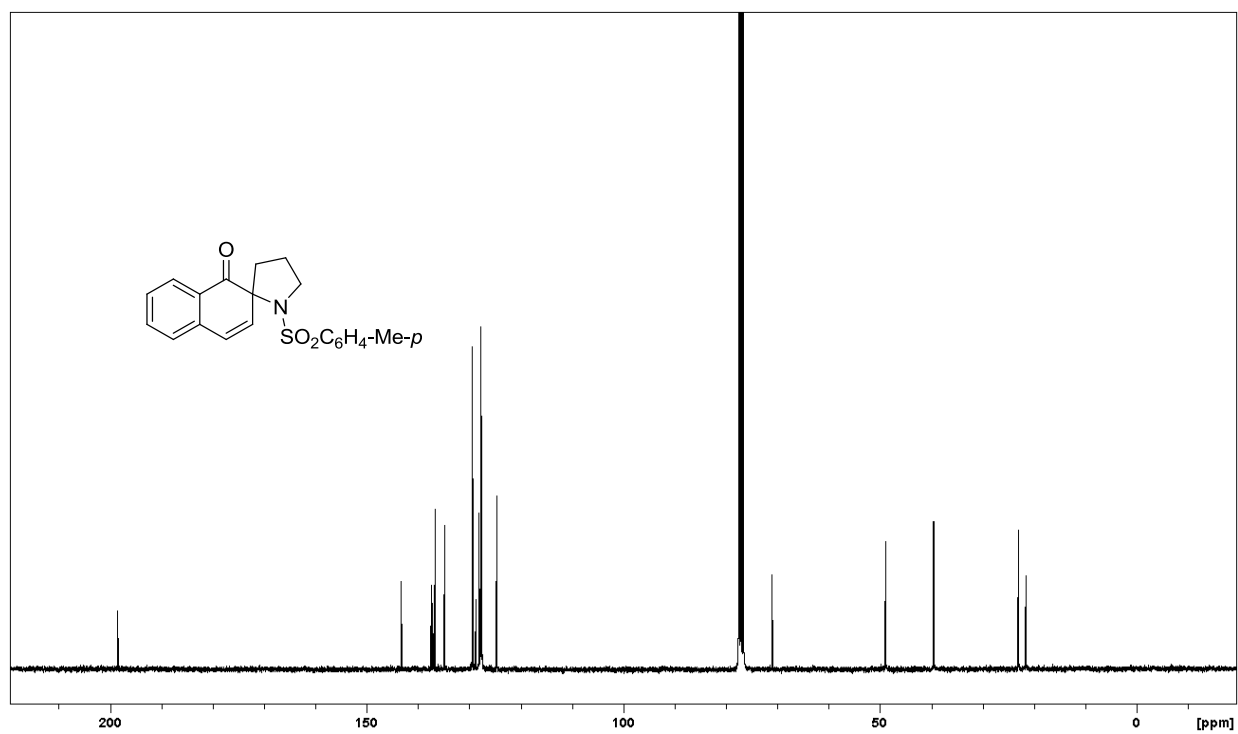
^1H NMR spectrum of 4.2a (300 MHz, CDCl_3)



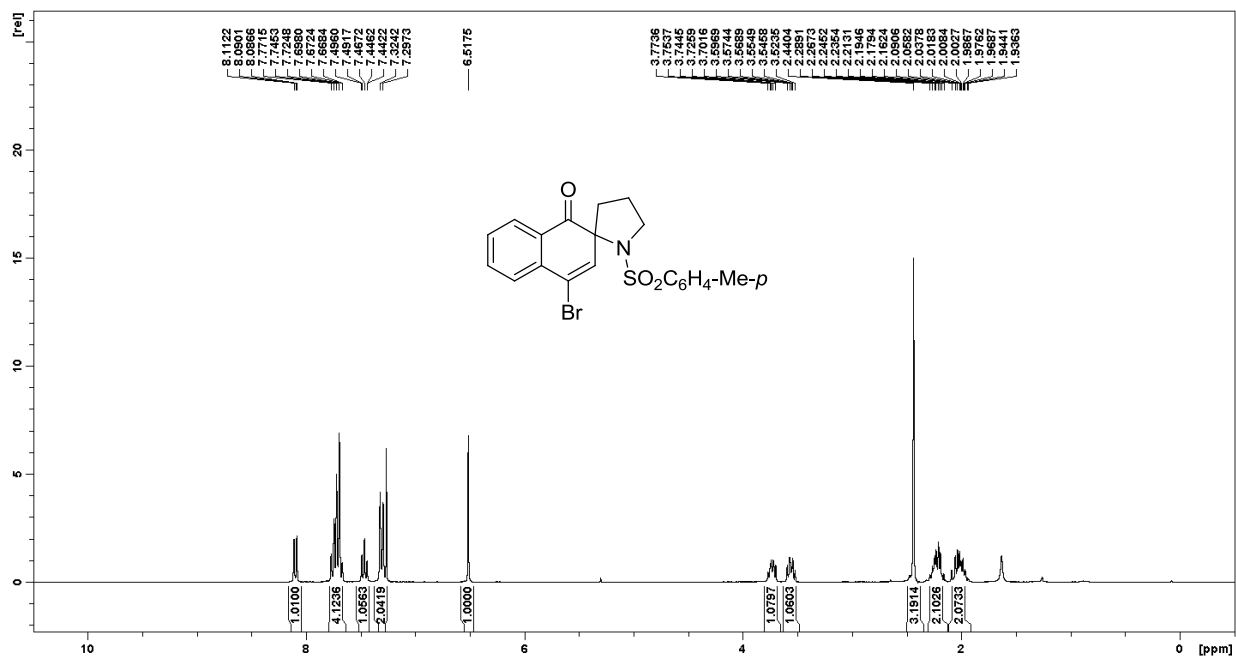
^{13}C NMR spectrum of 4.2a (75 MHz, CDCl_3)



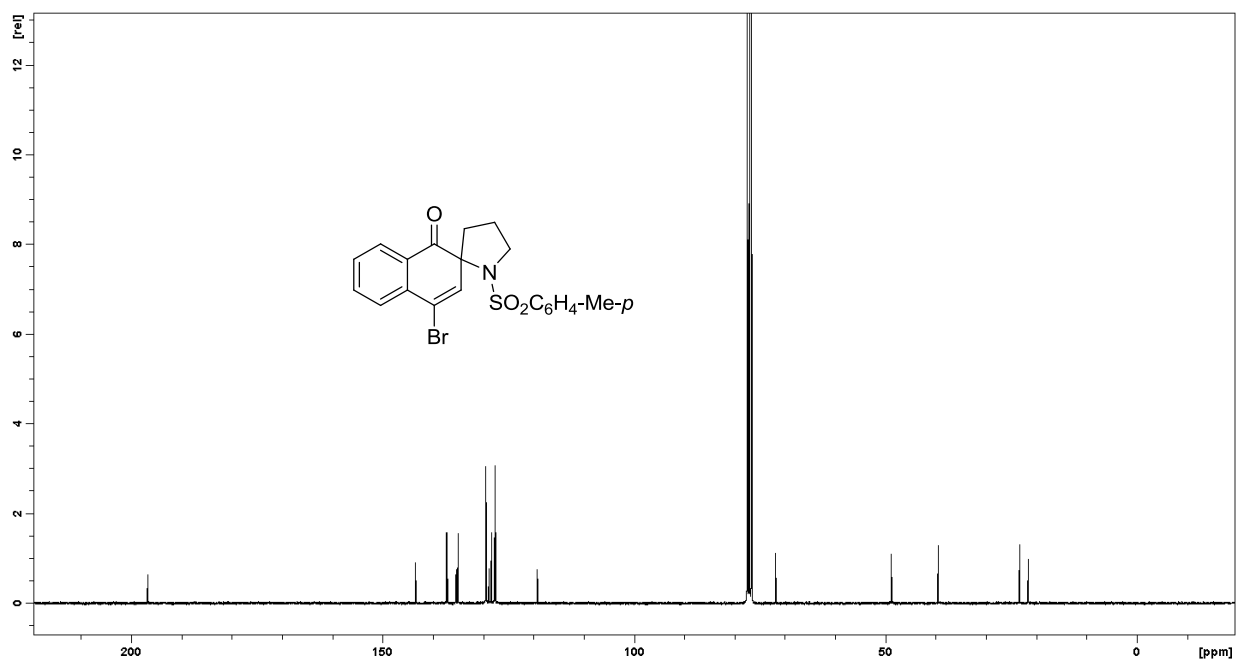
¹H NMR spectrum of 4.2b (300 MHz, CDCl₃)



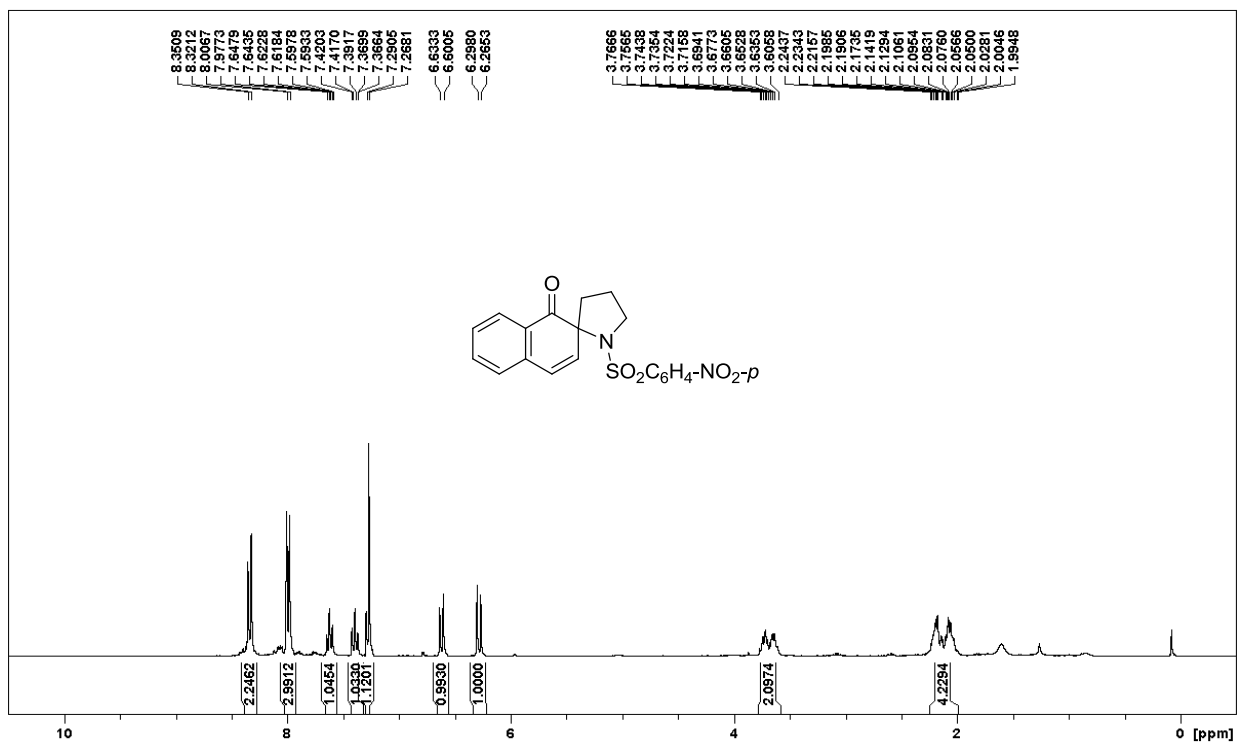
¹³C NMR spectrum of 4.2b (75 MHz, CDCl₃)



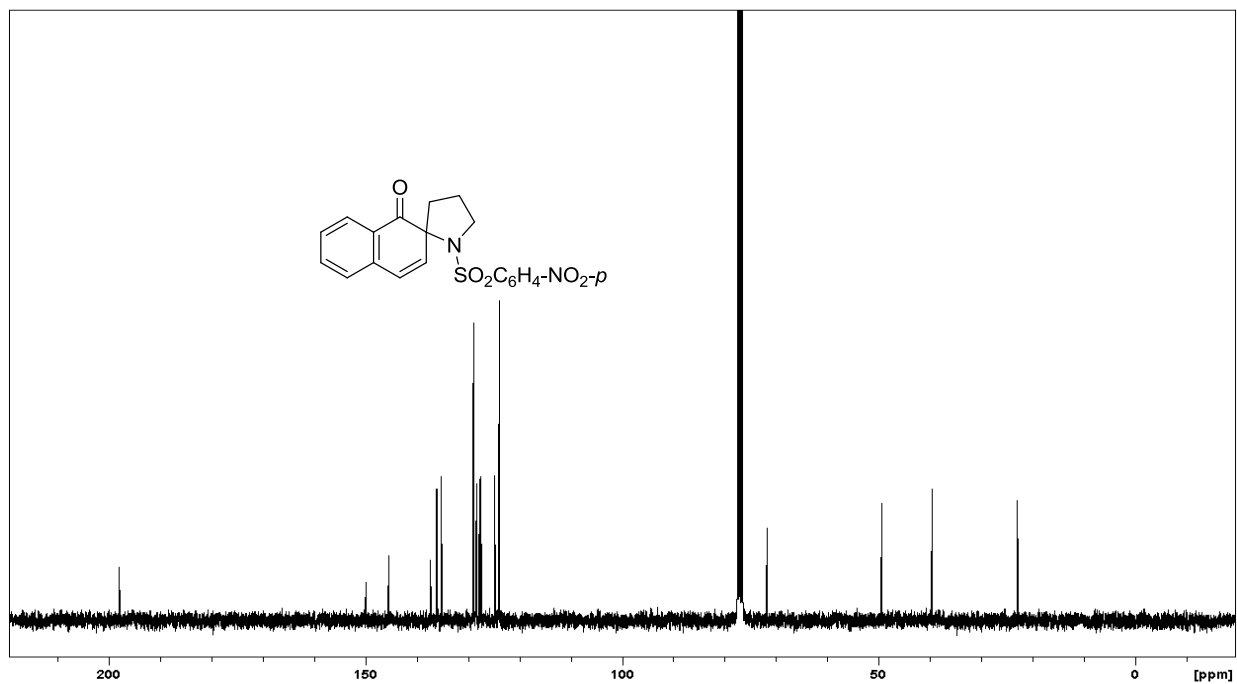
¹H NMR spectrum of 4.2c (300 MHz, CDCl₃)



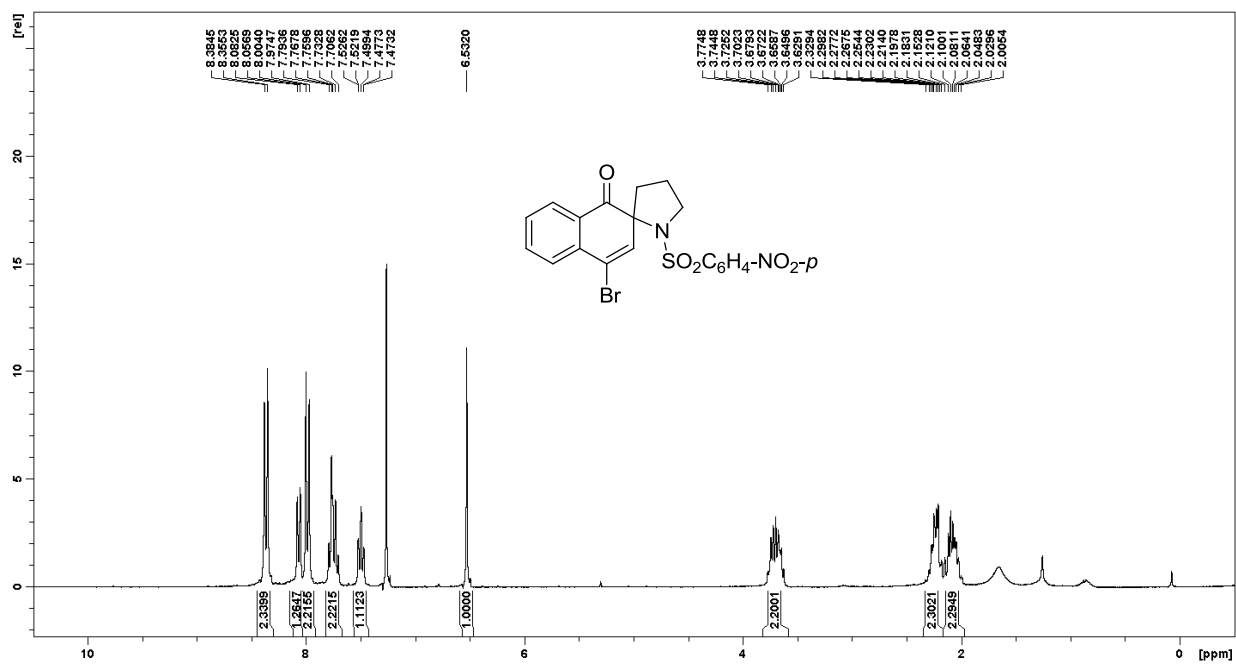
¹³C NMR spectrum of 4.2c (75 MHz, CDCl₃)



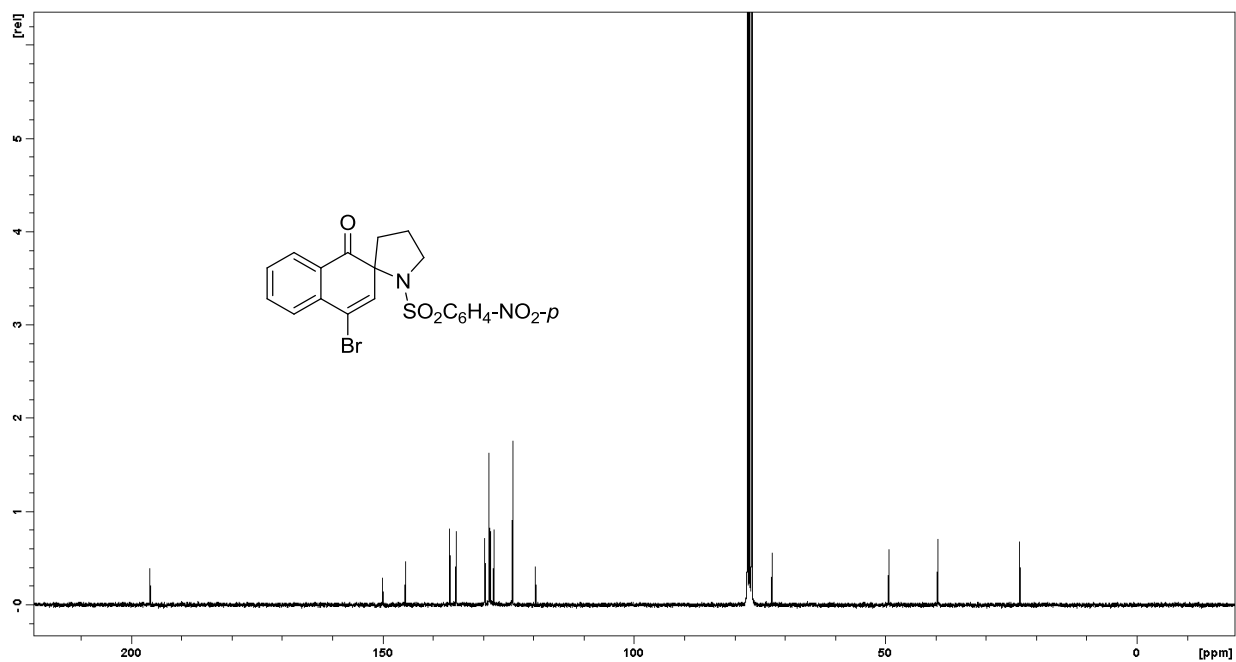
¹H NMR spectrum of 4.2d (300 MHz, CDCl₃)



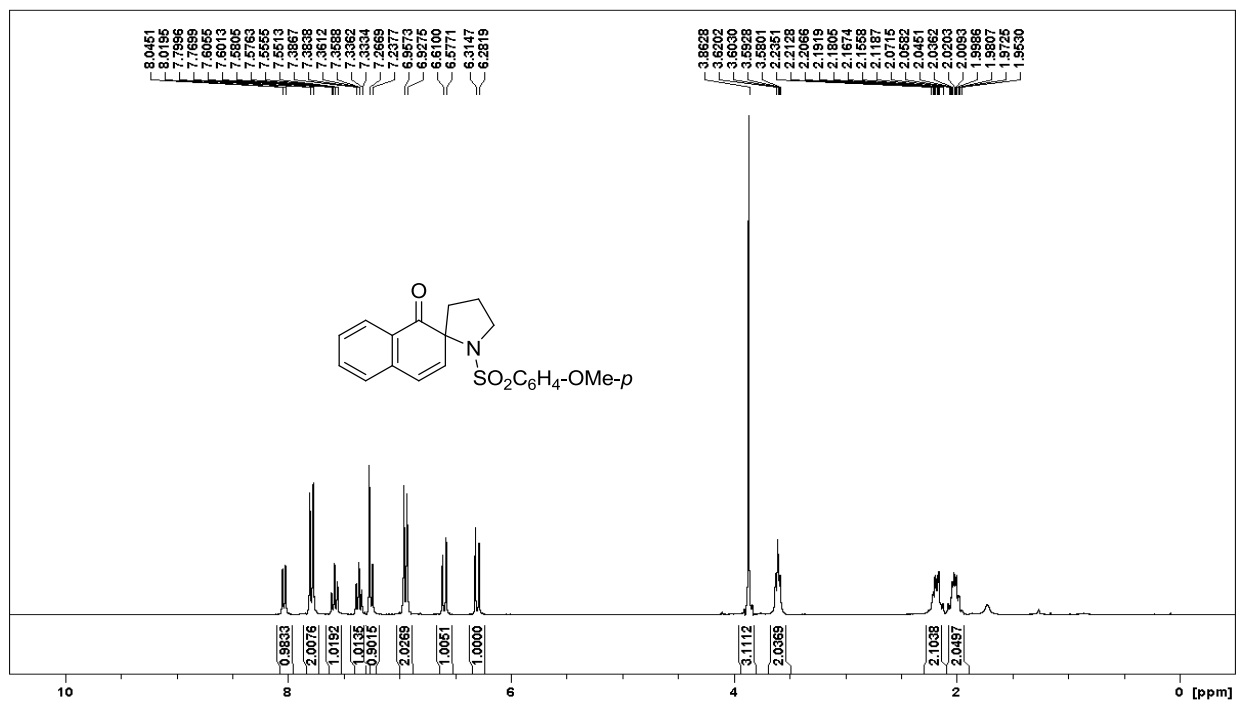
¹³C NMR spectrum of 4.2d (75 MHz, CDCl₃)



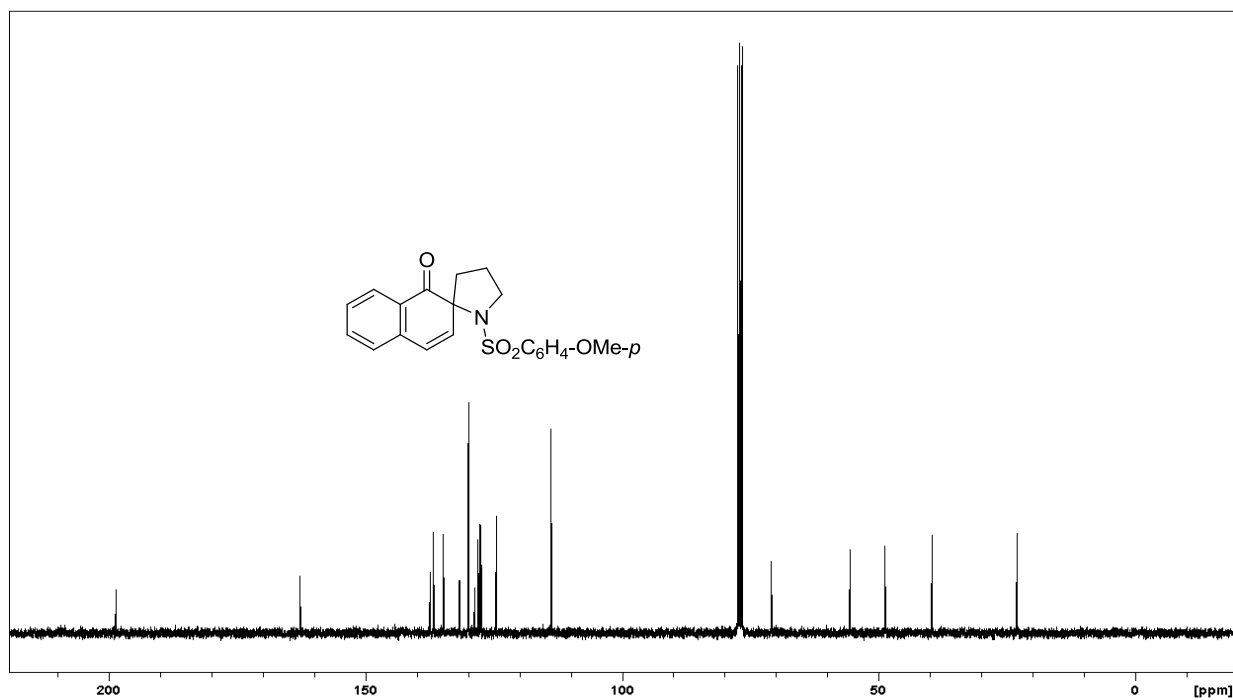
¹H NMR spectrum of 4.2e (300 MHz, CDCl₃)



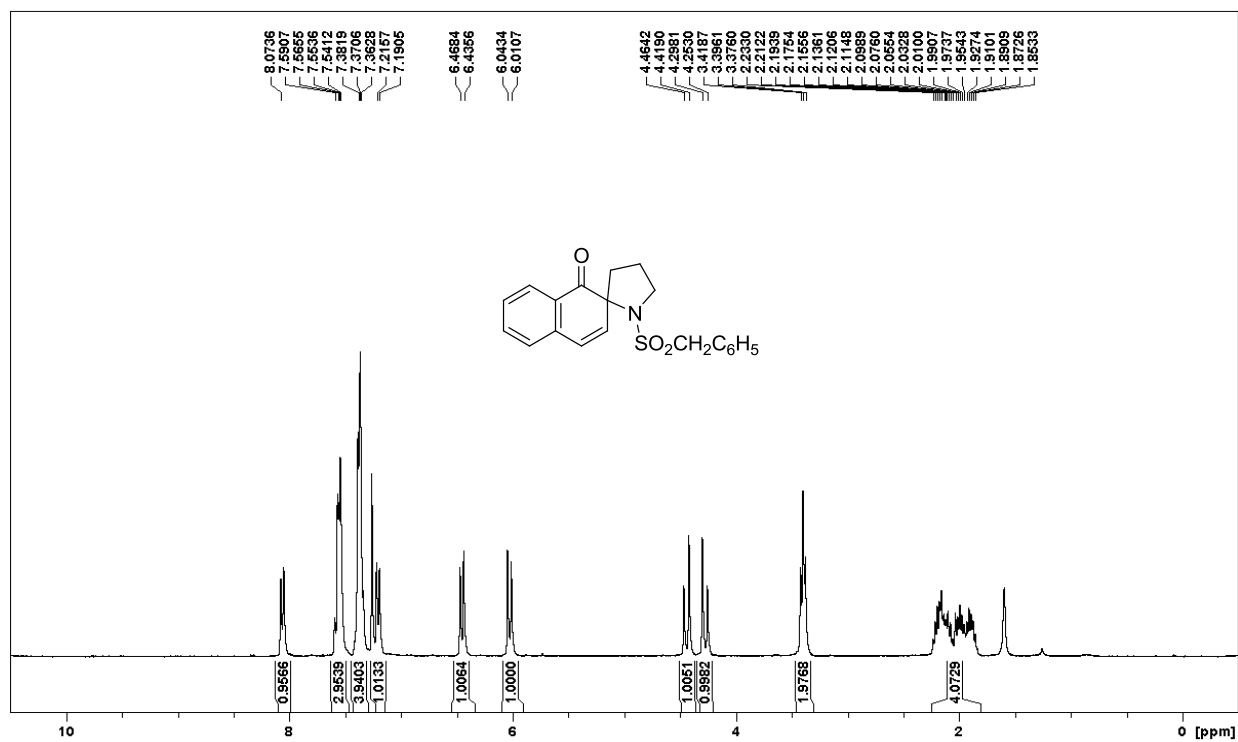
¹³C NMR spectrum of 4.2e (75 MHz, CDCl₃)



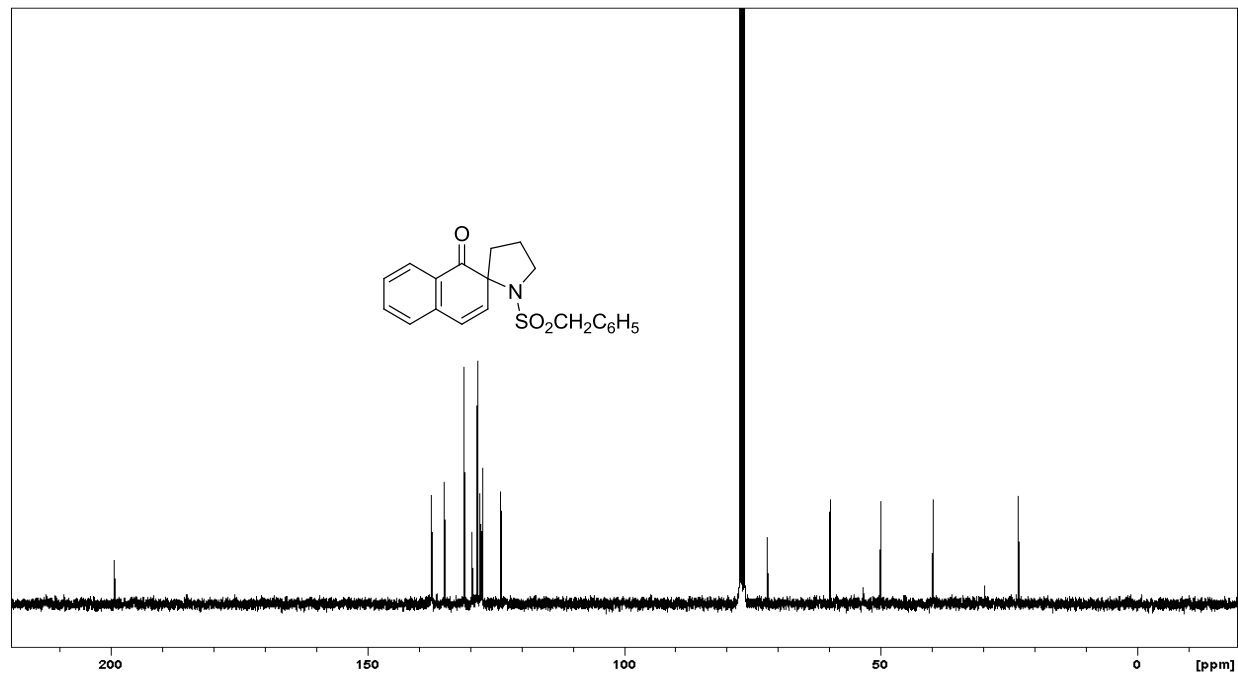
¹H NMR spectrum of 4.2f (300 MHz, CDCl₃)



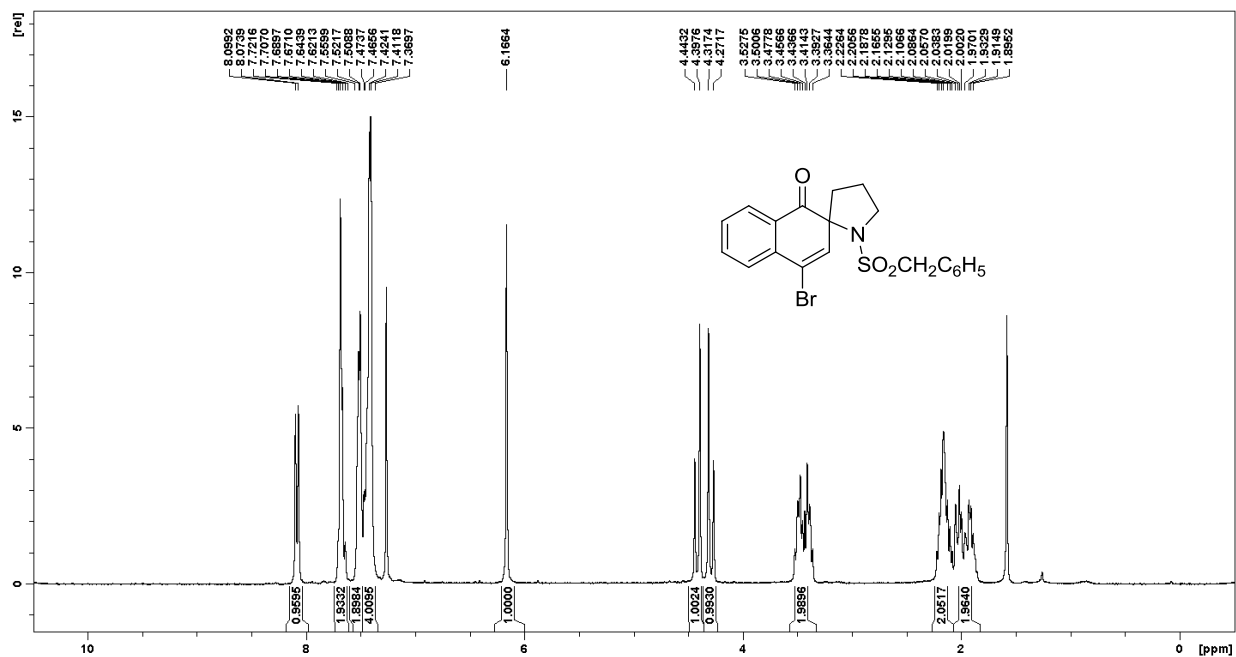
¹³C NMR spectrum of 4.2f (75 MHz, CDCl₃)



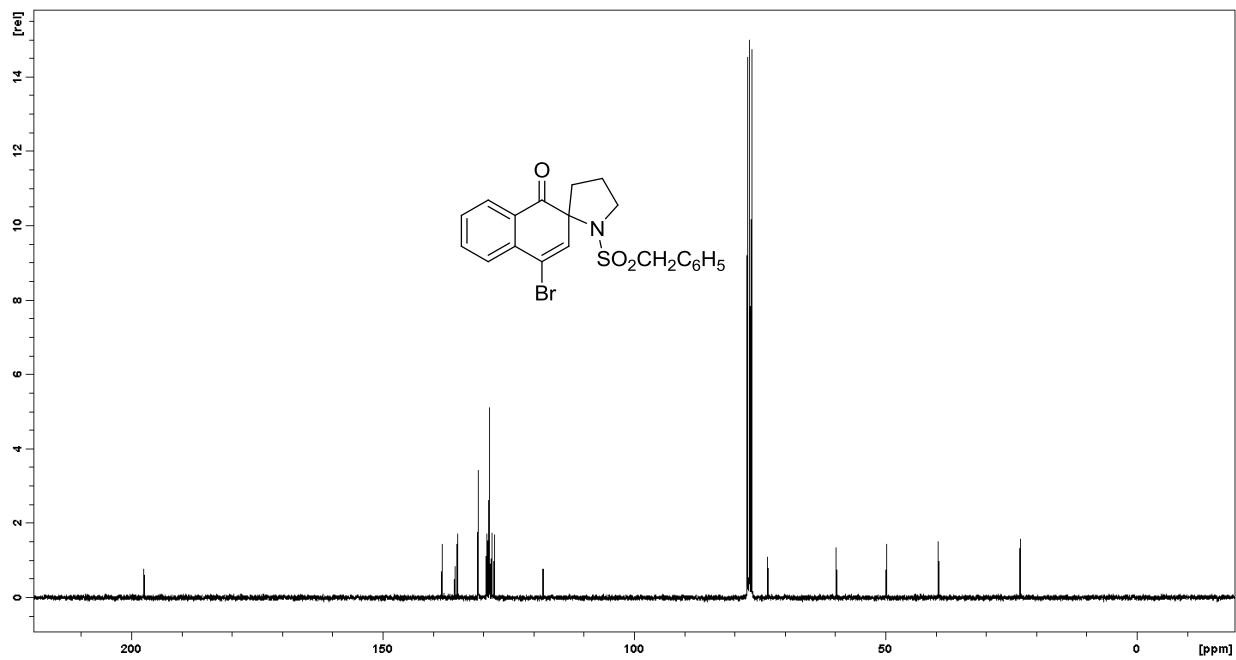
¹H NMR spectrum of 4.2g (300 MHz, CDCl₃)



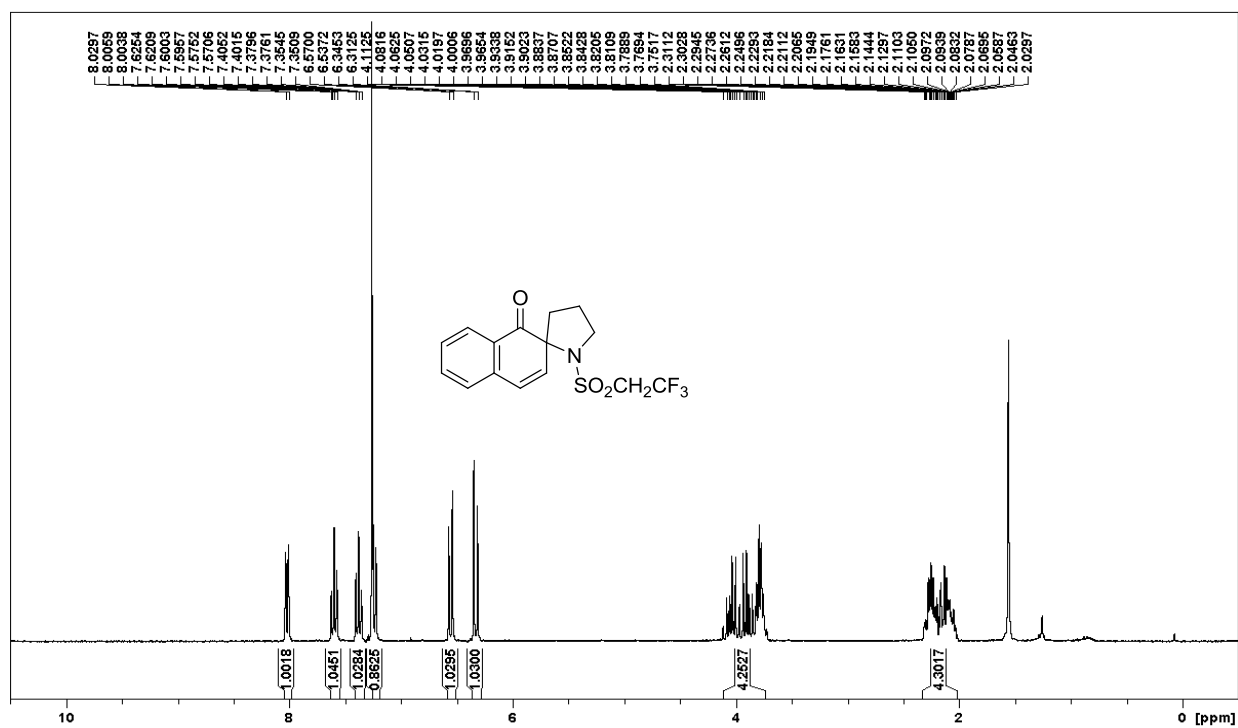
¹³C NMR spectrum of 4.2g (75 MHz, CDCl₃)



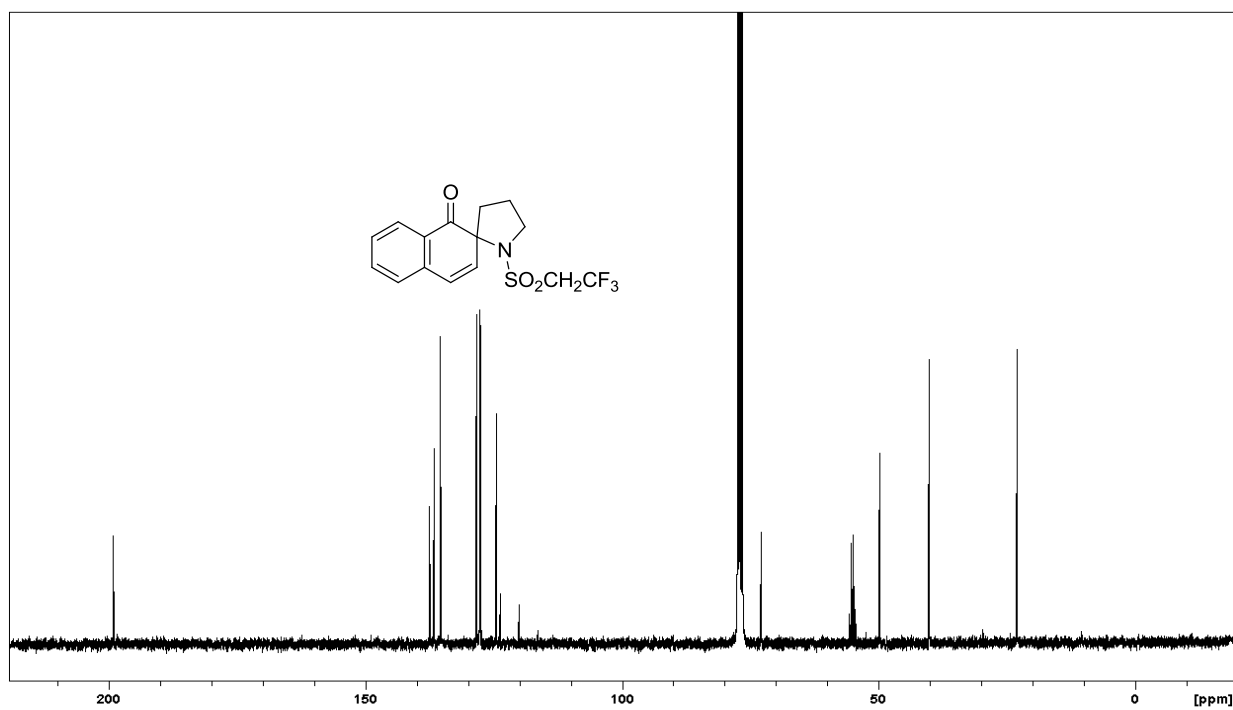
¹H NMR spectrum of 4.2h (300 MHz, CDCl₃)



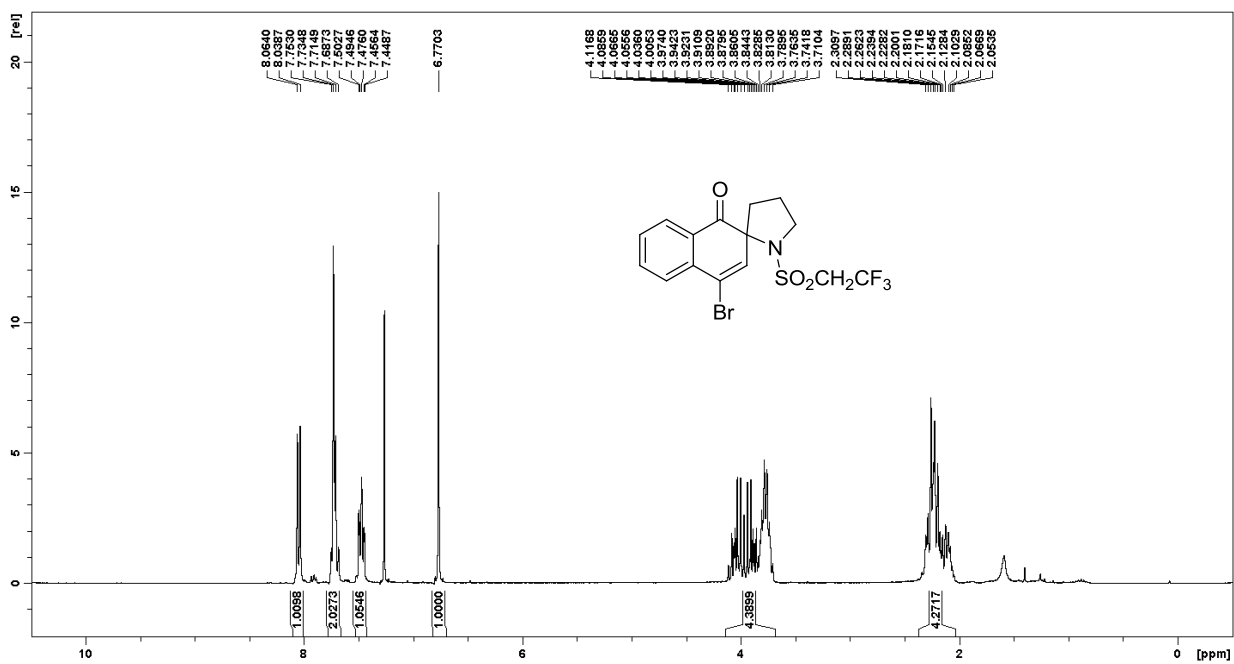
¹³C NMR spectrum of 4.2h (75 MHz, CDCl₃)



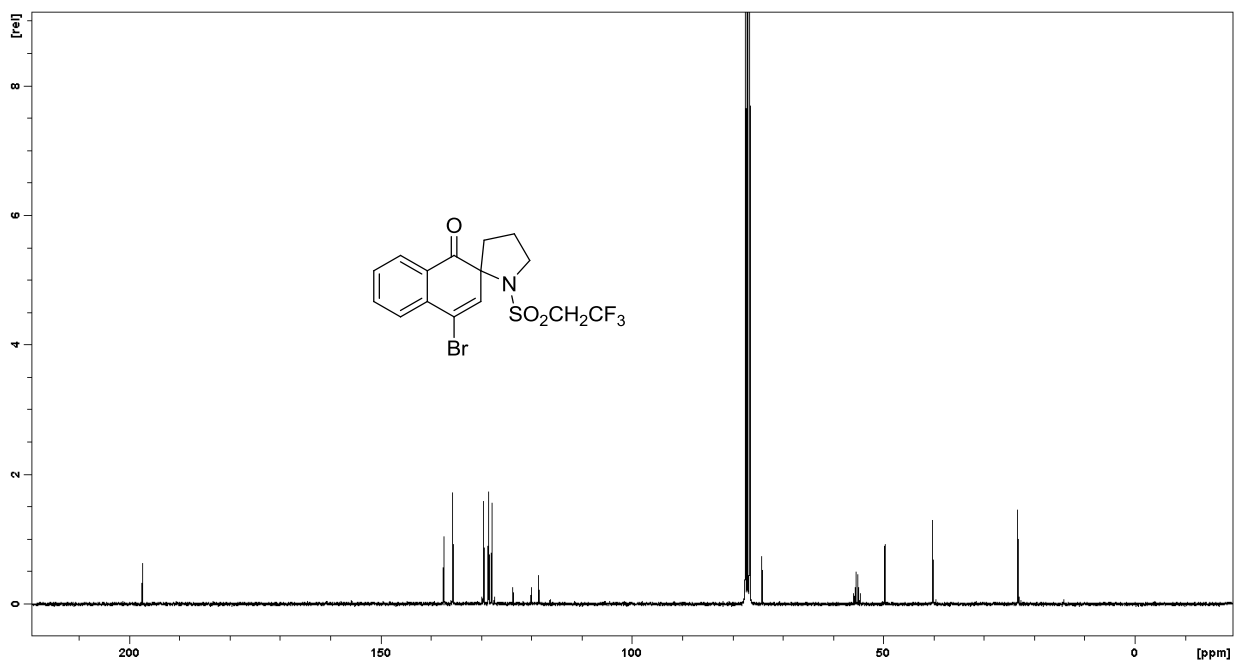
¹H NMR spectrum of 4.2i (300 MHz, CDCl₃)



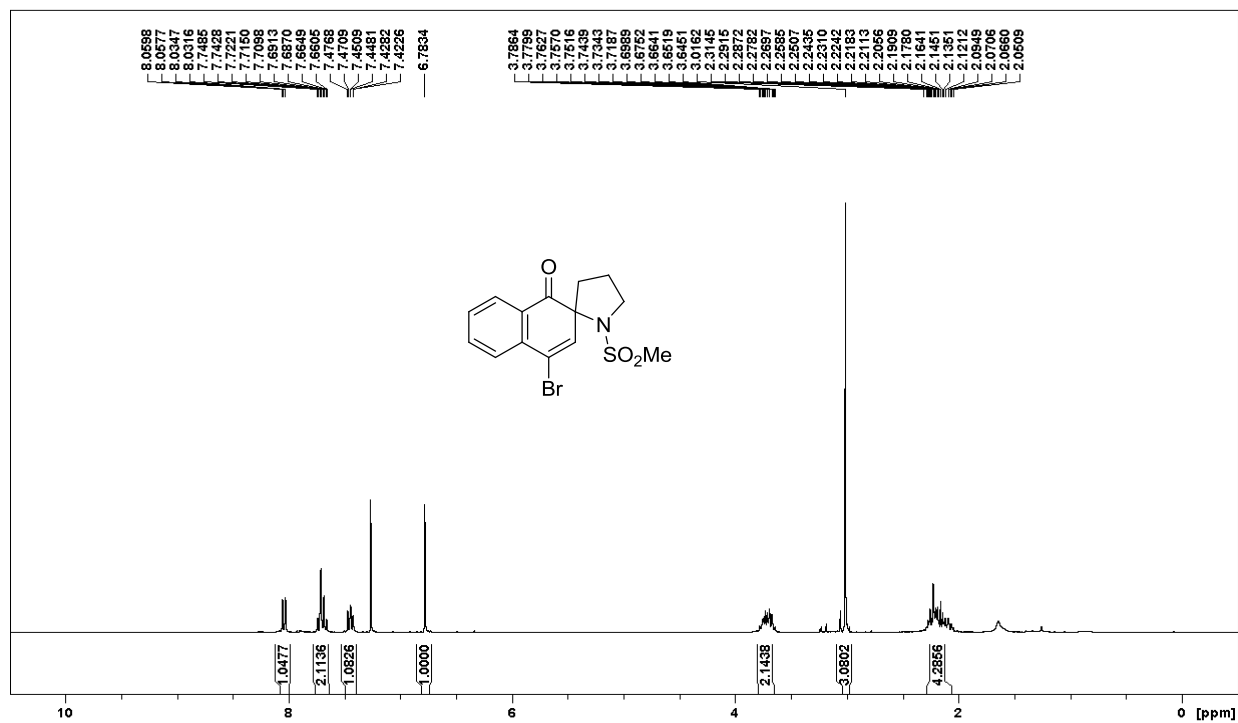
¹³C NMR spectrum of 4.2i (75 MHz, CDCl₃)



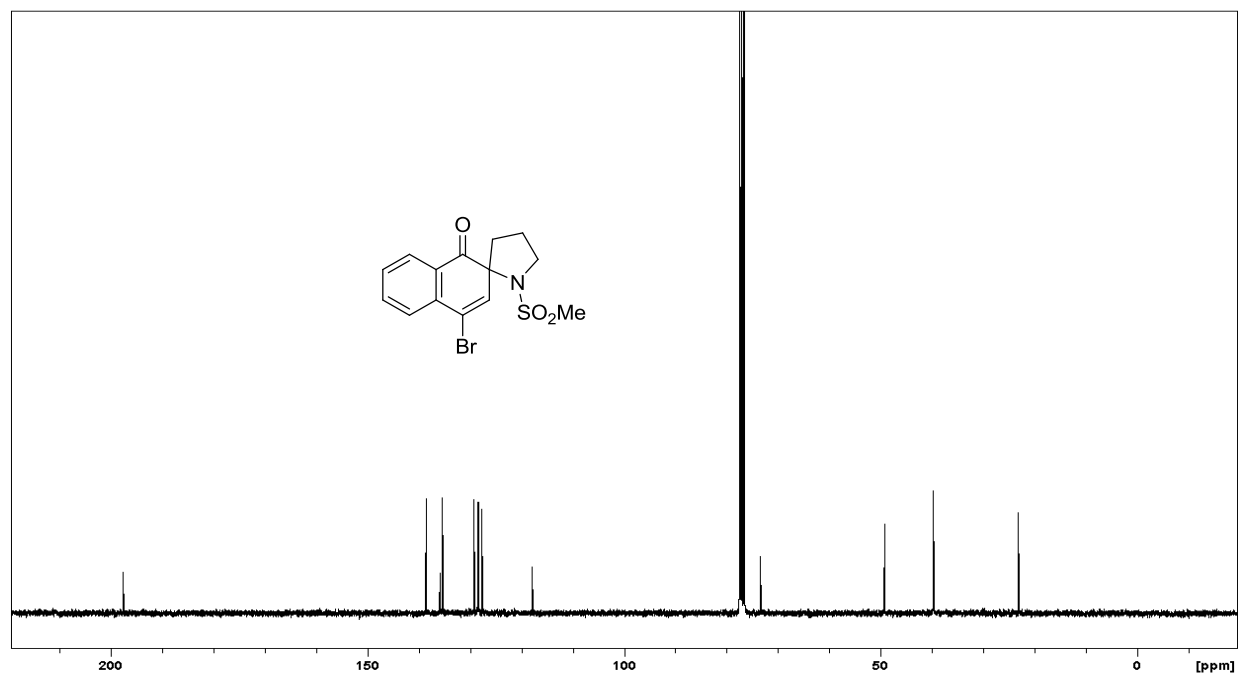
¹H NMR spectrum of 4.2j (300 MHz, CDCl₃)



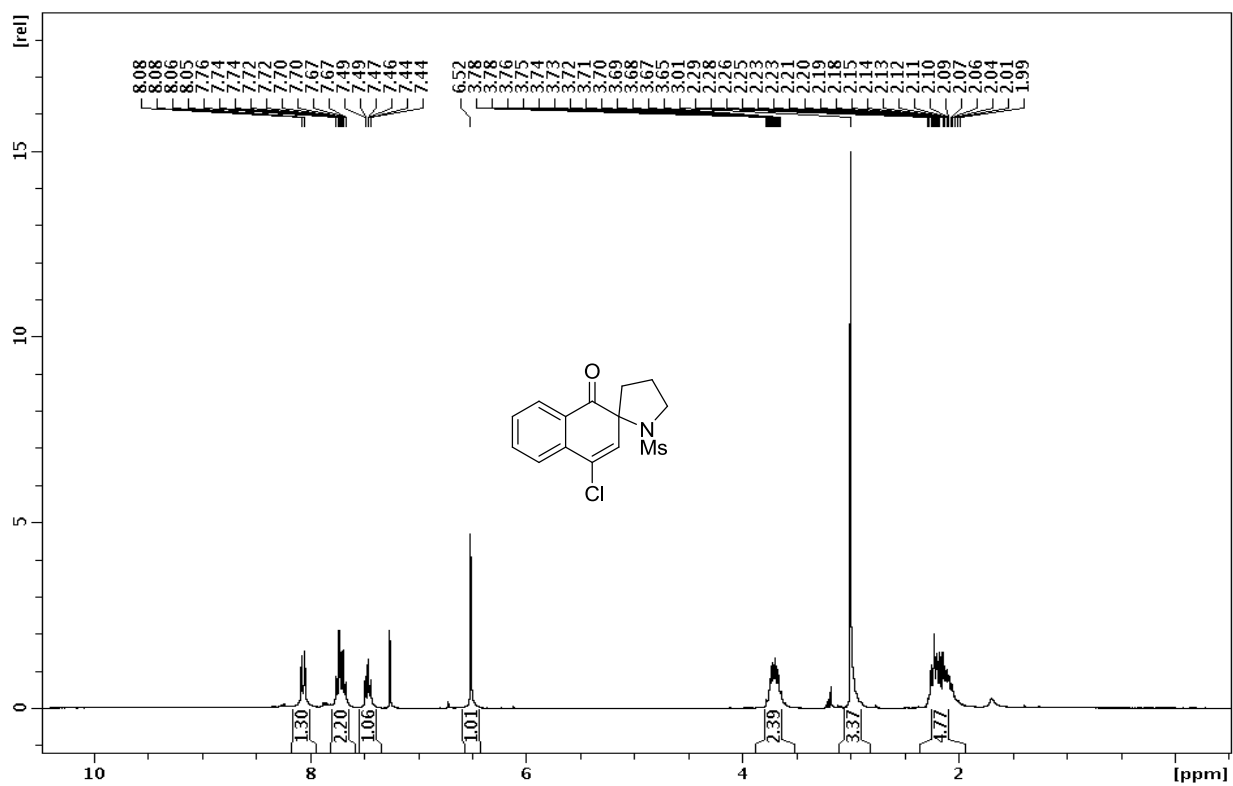
¹³C NMR spectrum of 4.2j (75 MHz, CDCl₃)



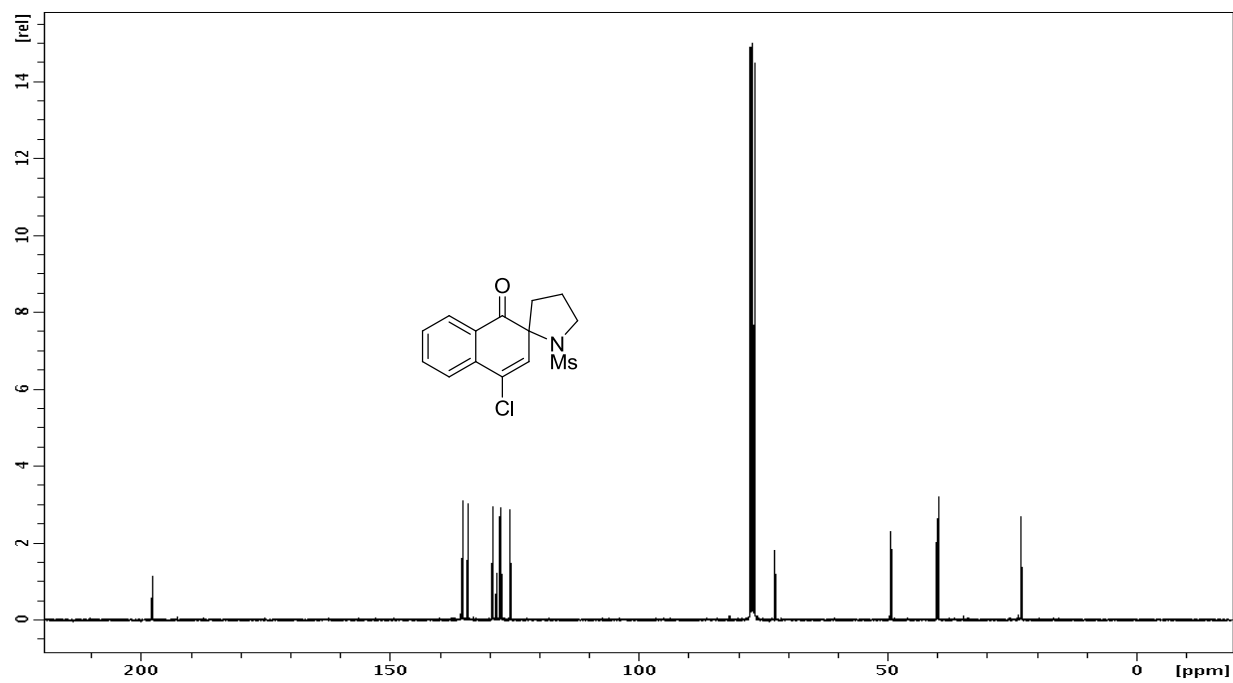
¹H NMR spectrum of 4.2k (300 MHz, CDCl₃)



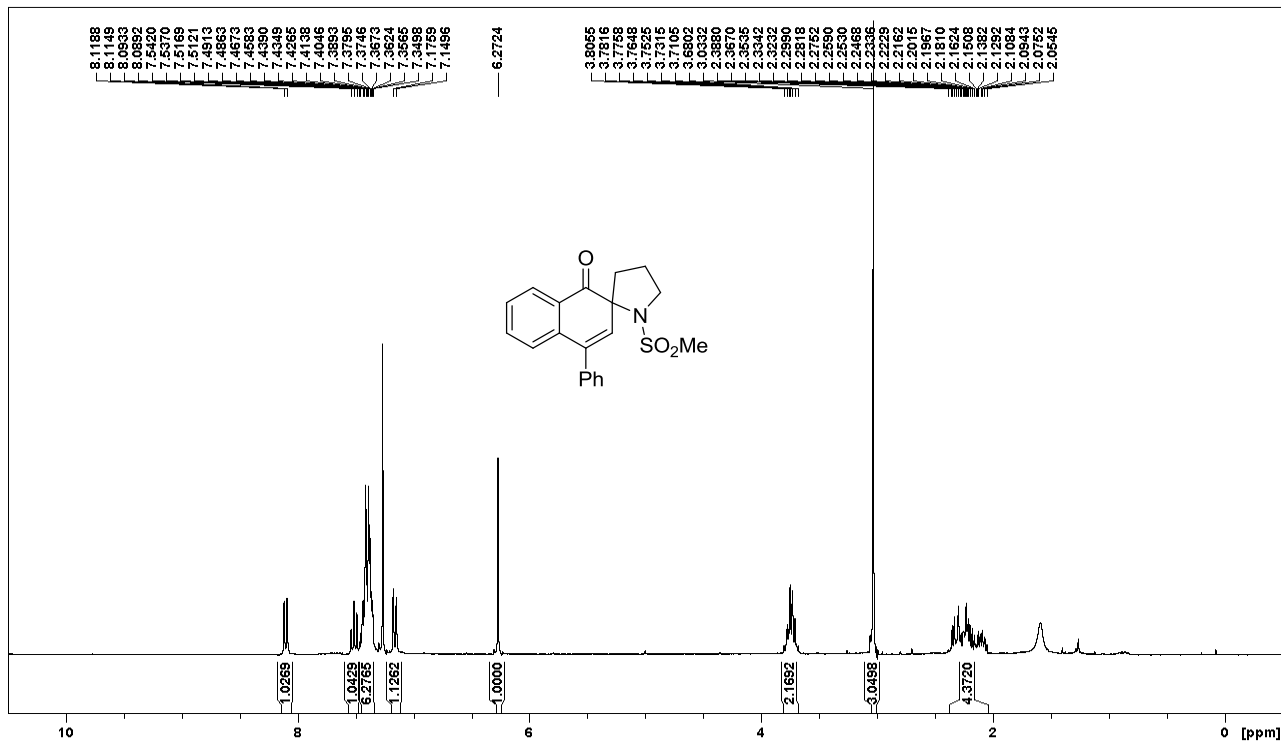
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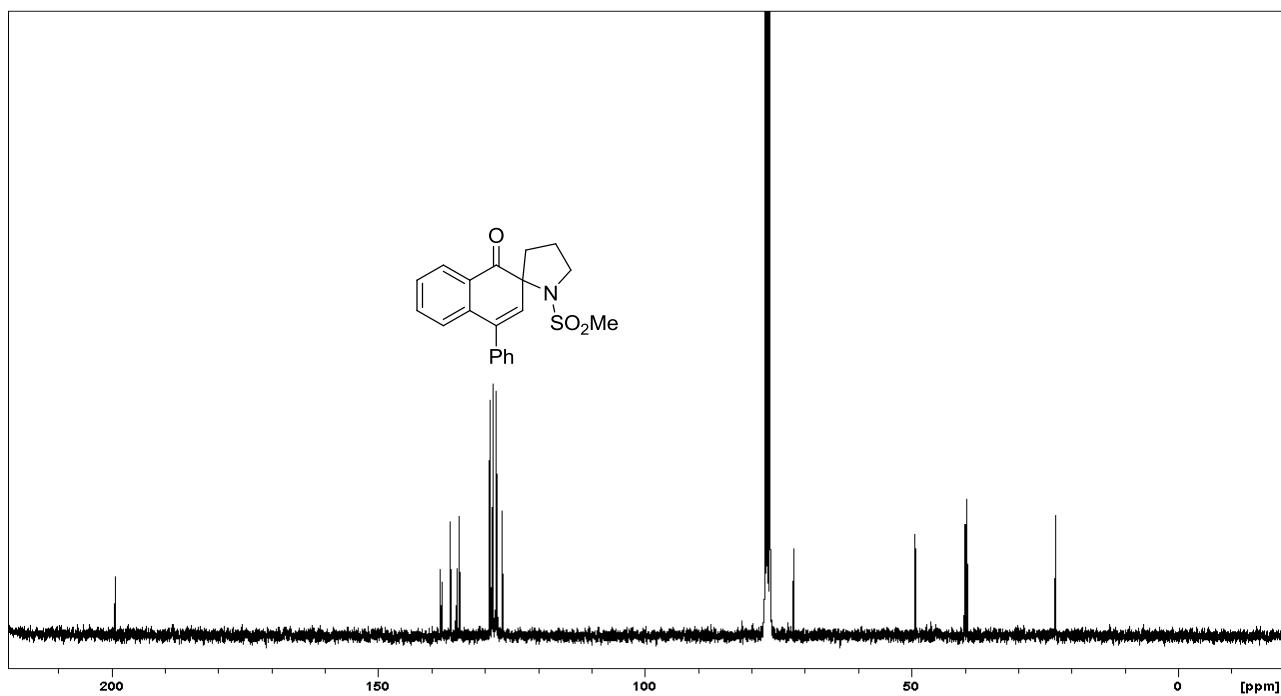
¹H NMR spectrum of 4.21 (300 MHz, CDCl₃)



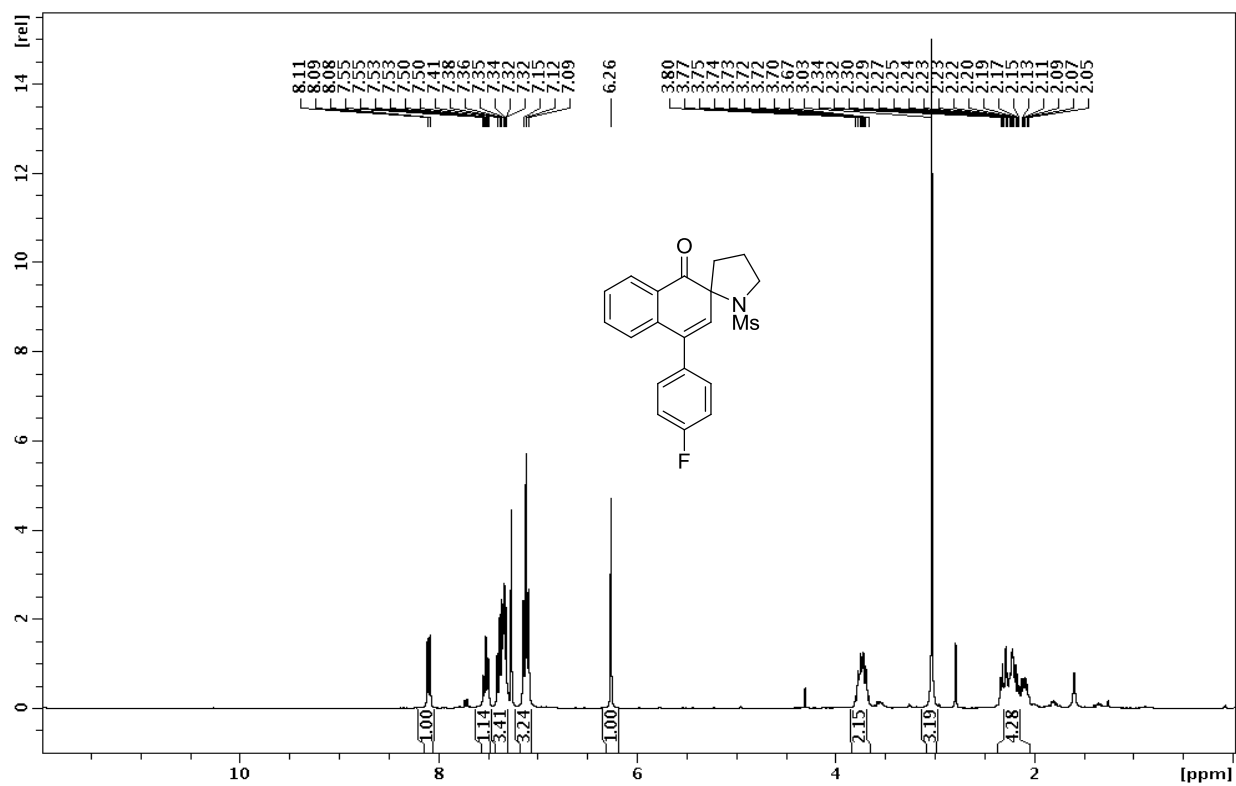
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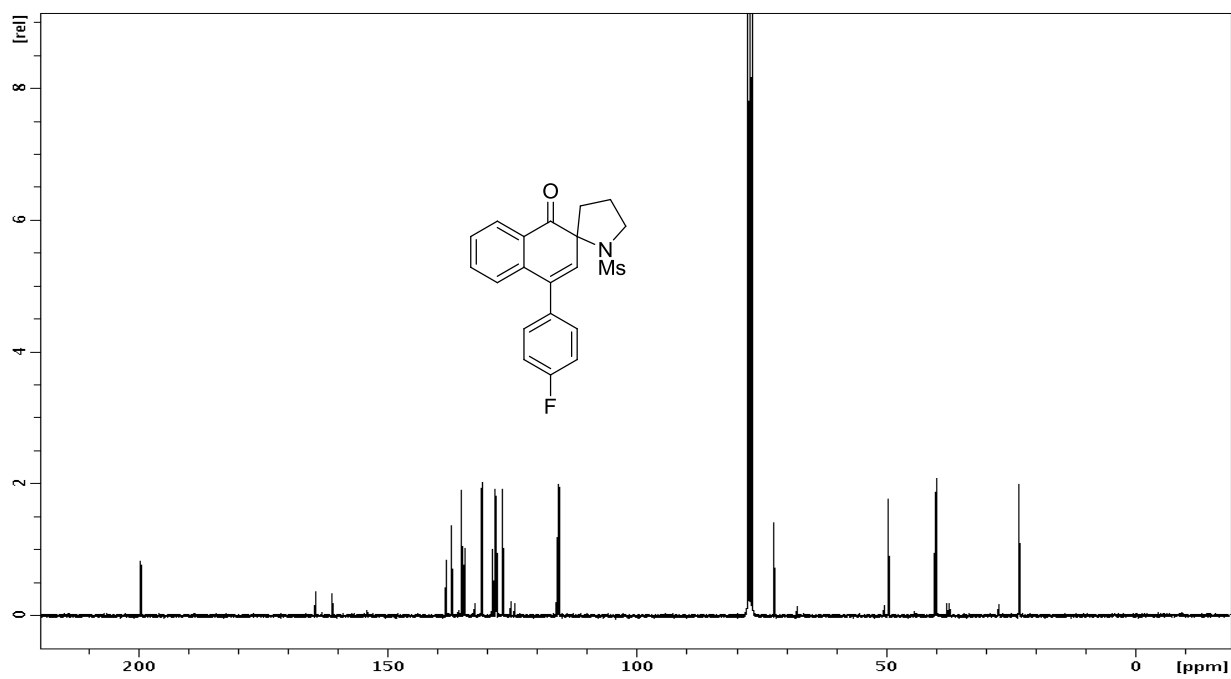
¹H NMR spectrum of 4.2m (300 MHz, CDCl₃)



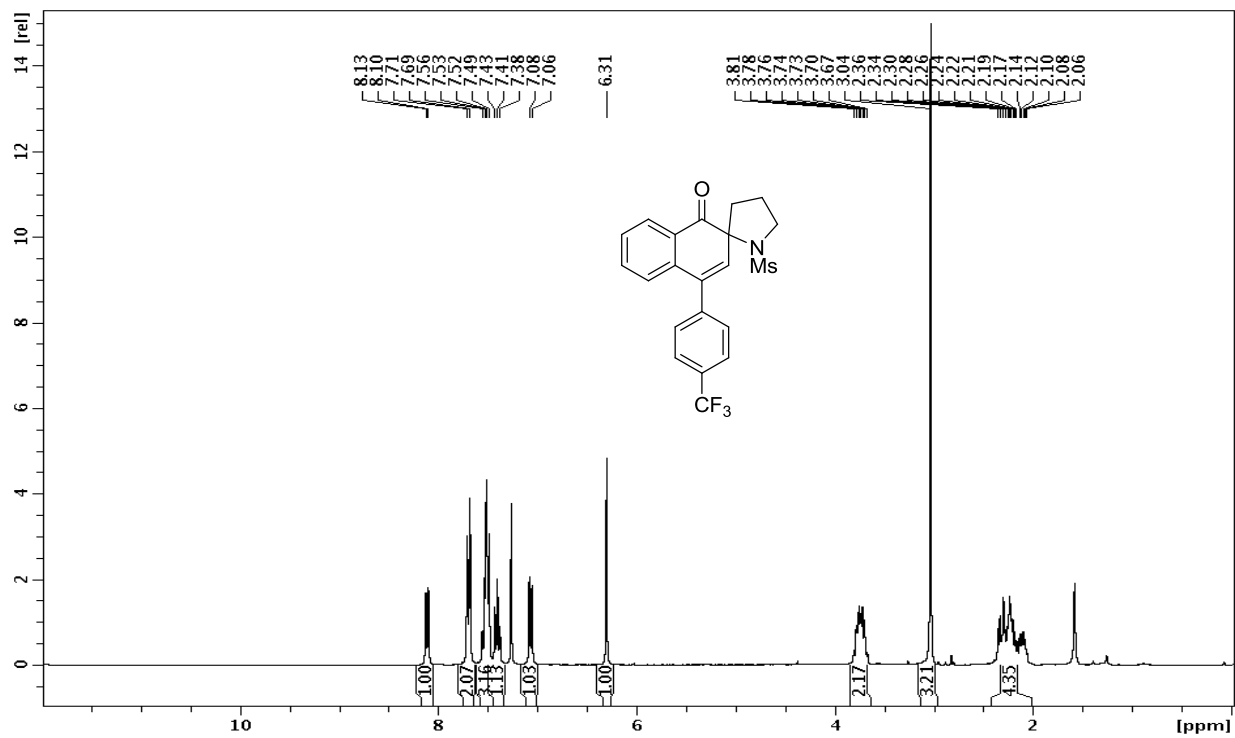
¹³C NMR spectrum of 4.2m (75 MHz, CDCl₃)



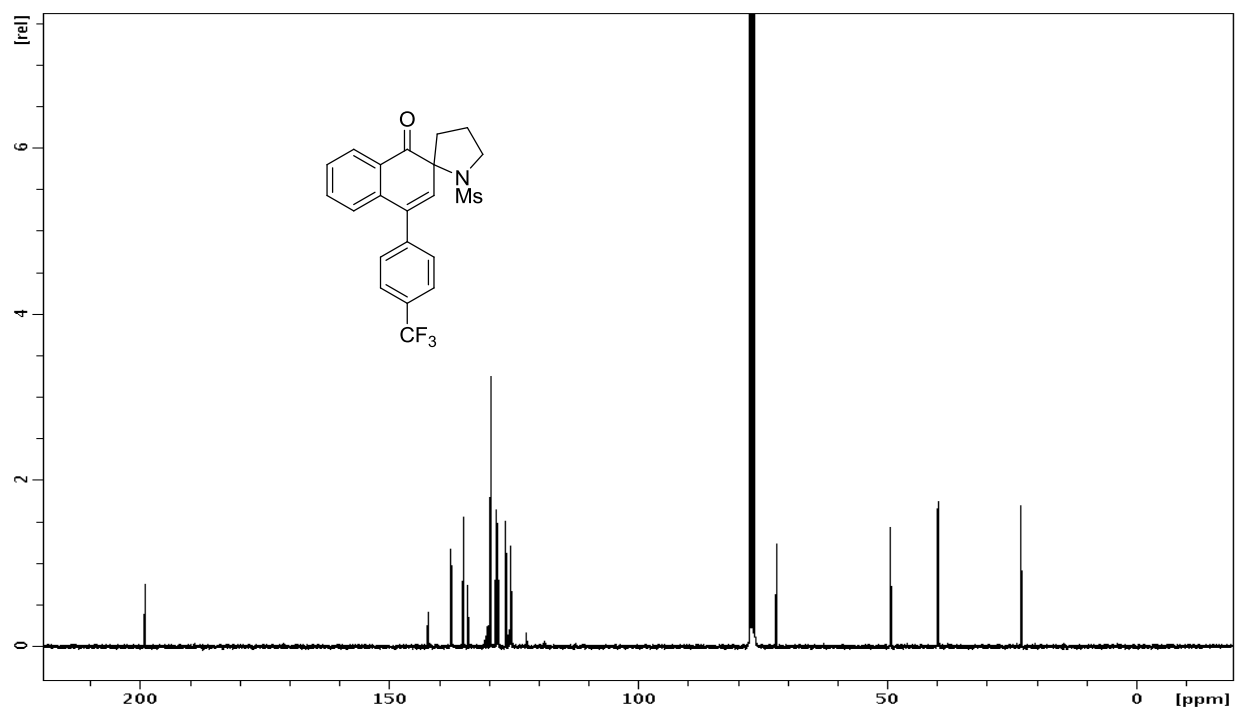
^1H NMR spectrum of 4.2n (300 MHz, CDCl_3)



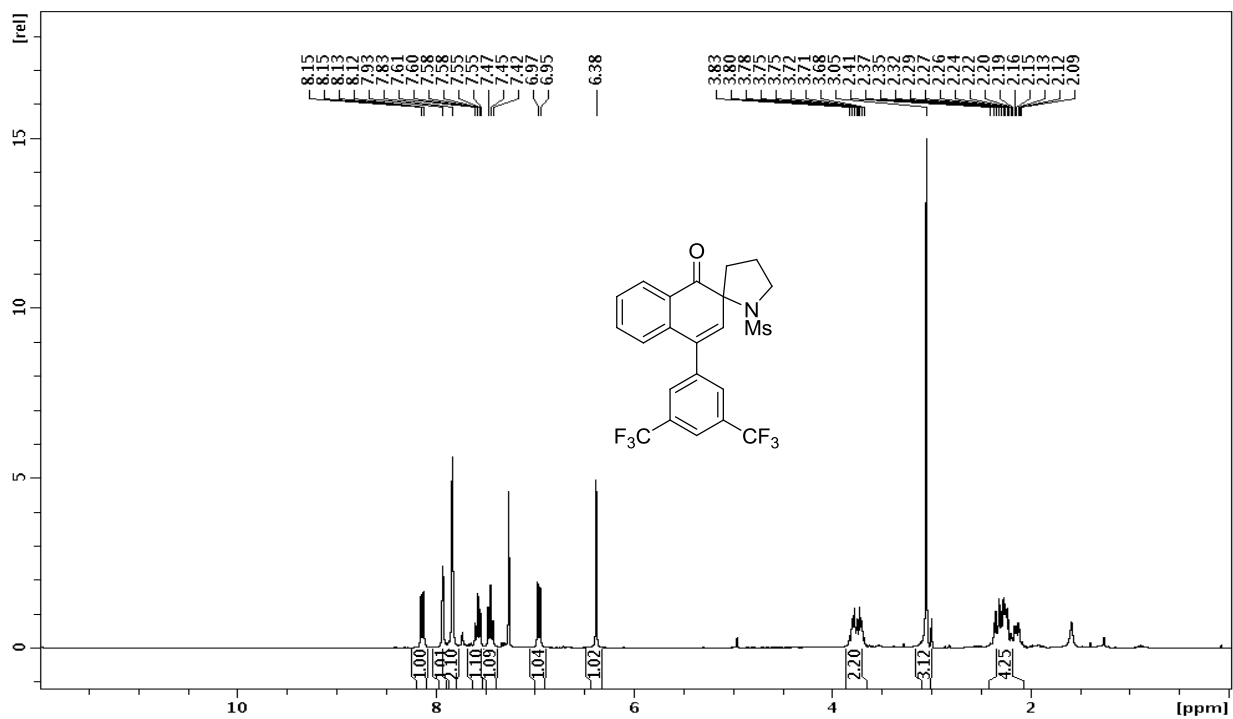
^{13}C NMR spectrum of 4.2n (75 MHz, CDCl_3)



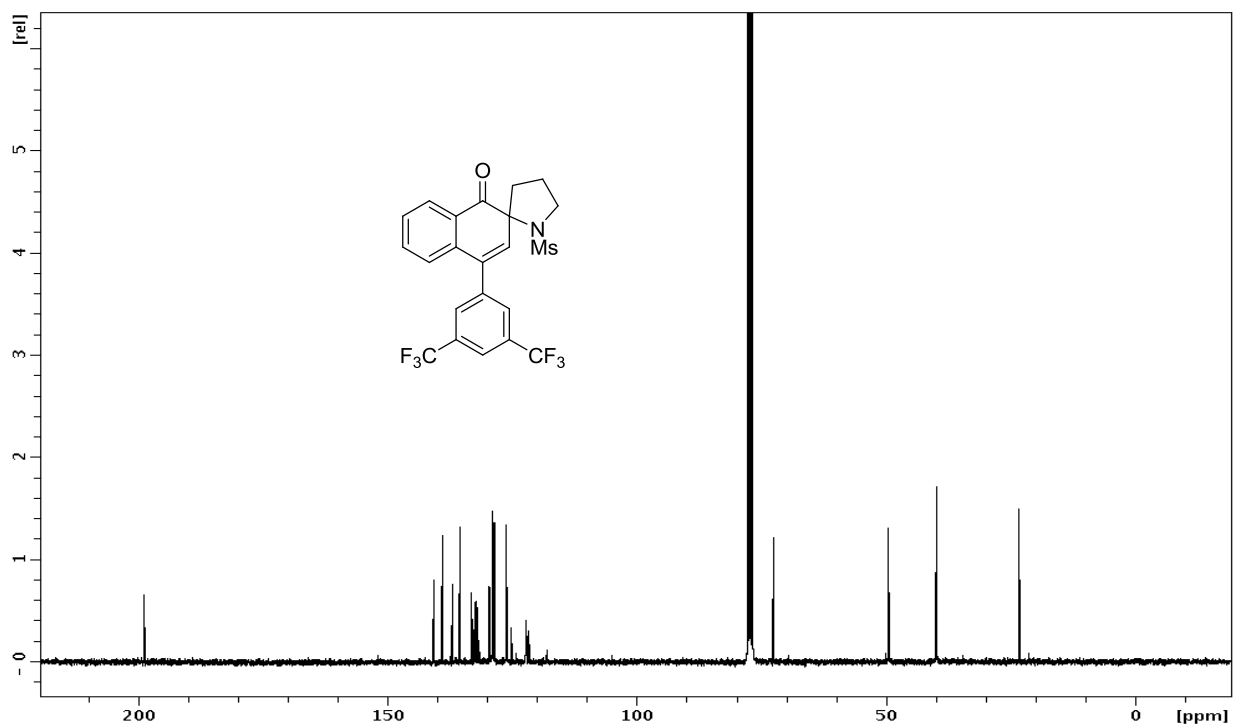
¹H NMR spectrum of 4.2o (300 MHz, CDCl₃)



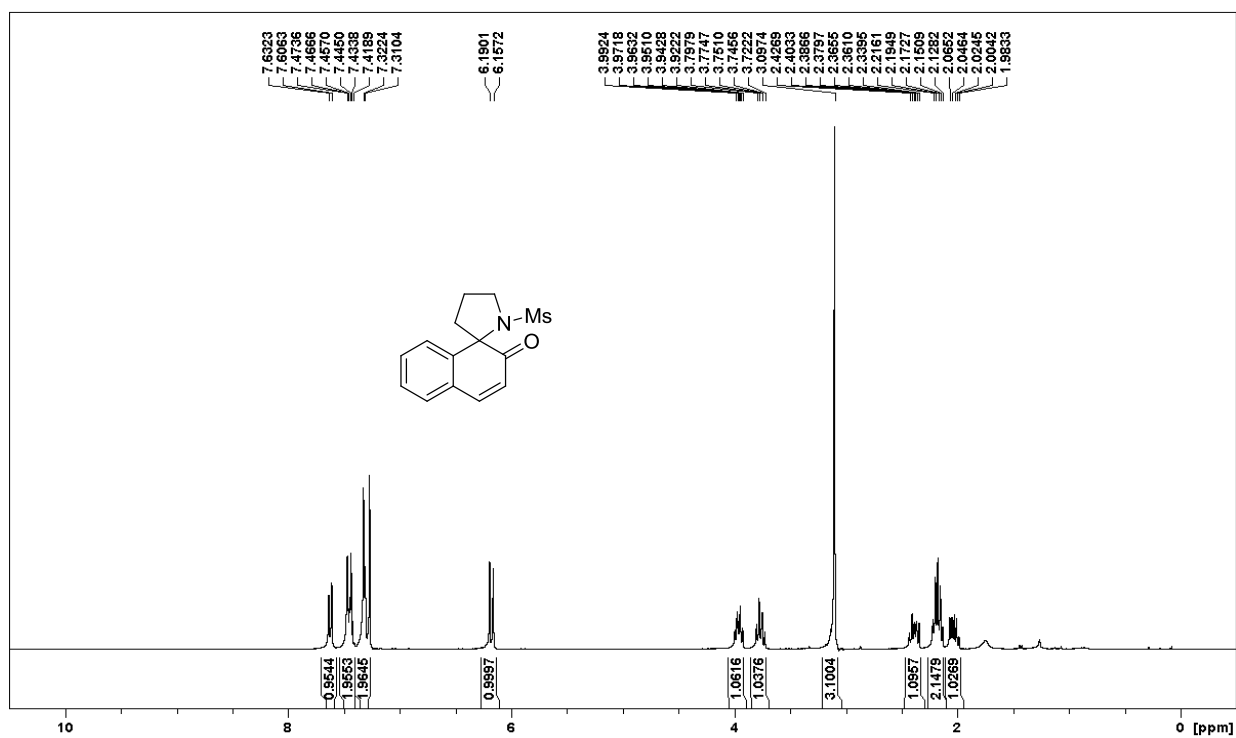
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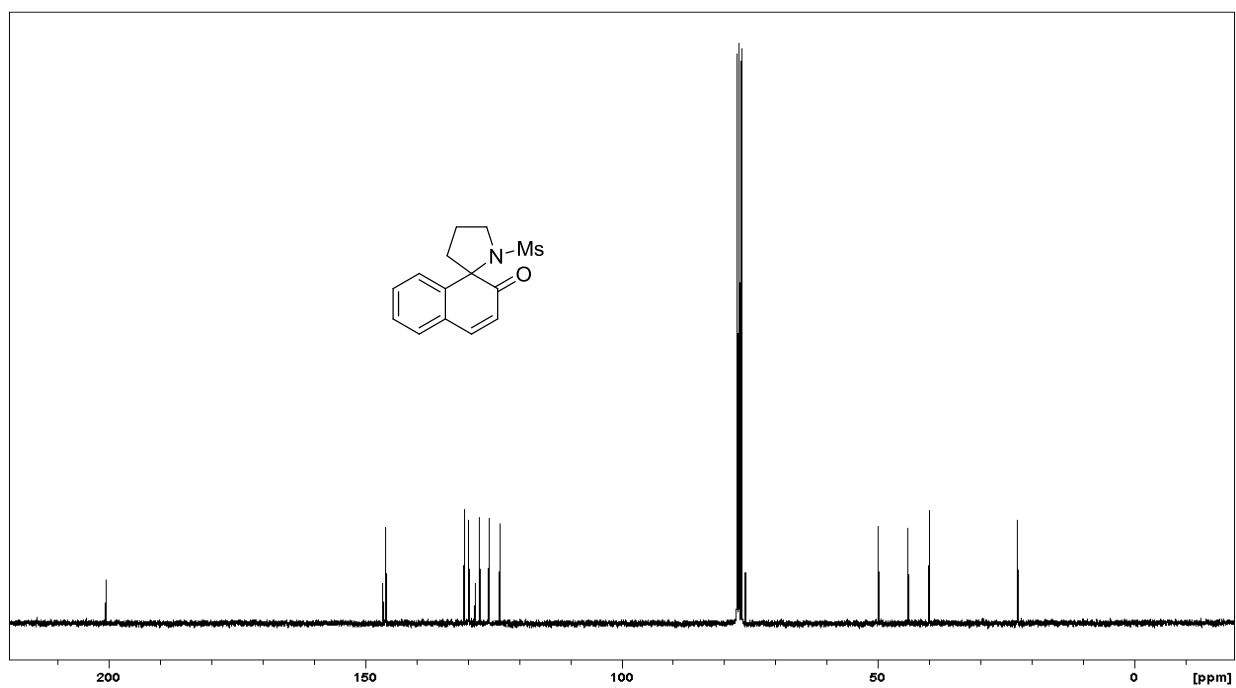
¹H NMR spectrum of 4.2p (300 MHz, CDCl₃)



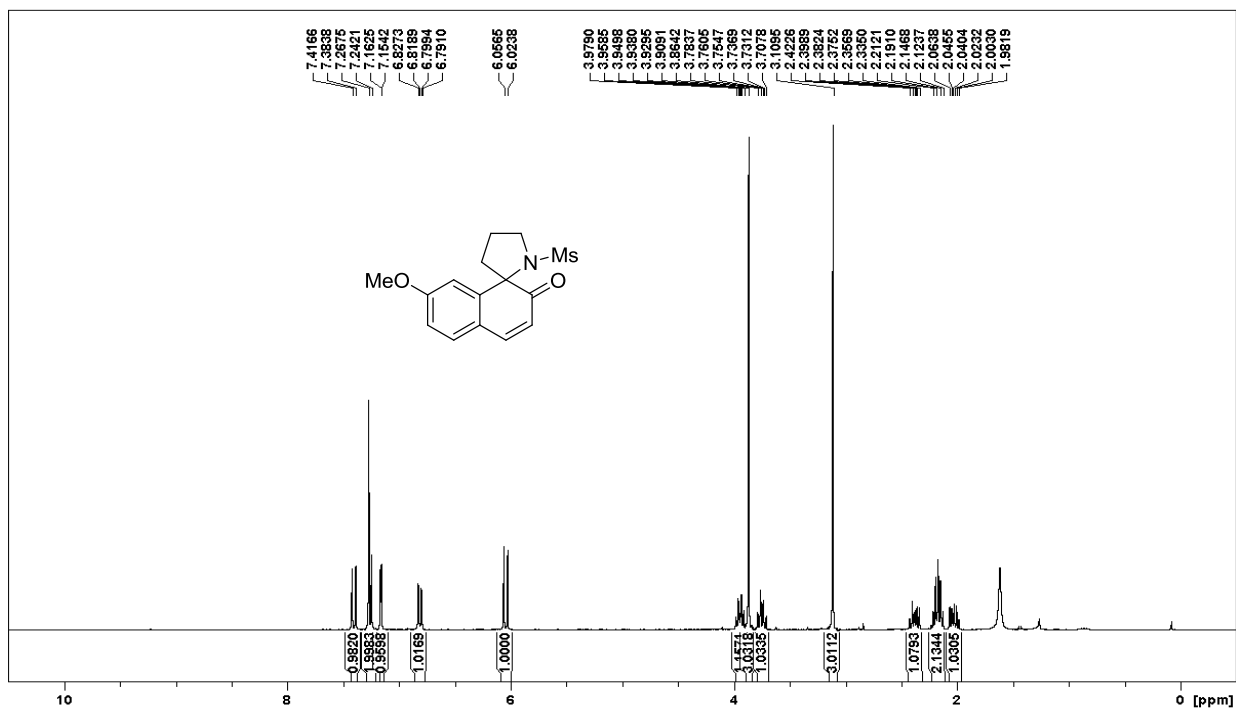
¹³C NMR spectrum of 4.2p (75 MHz, CDCl₃)



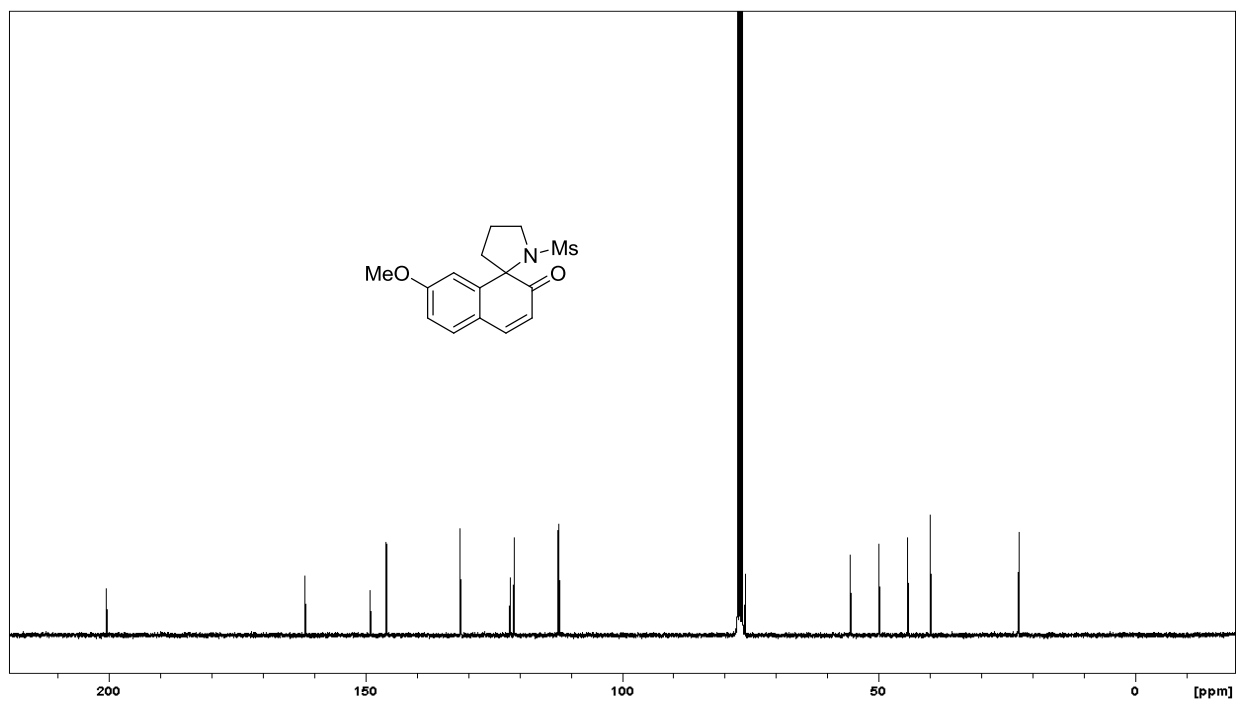
¹H NMR spectrum of 4.5a (300 MHz, CDCl₃)



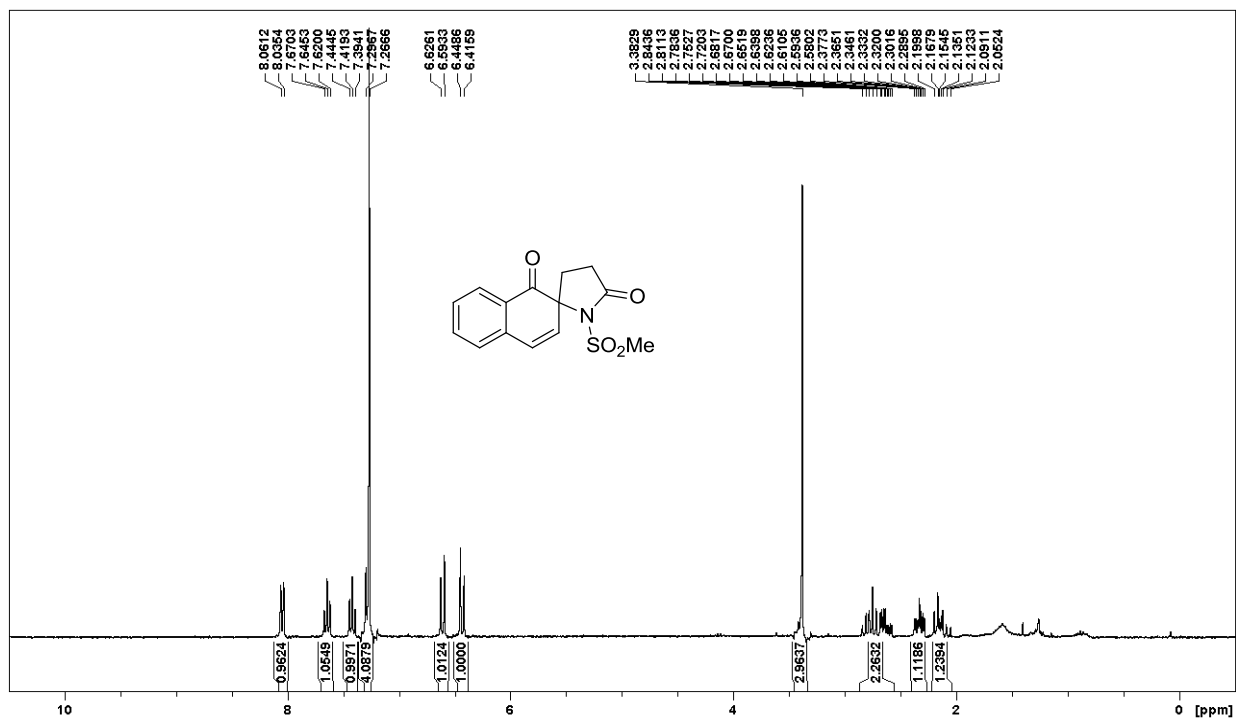
¹³C NMR spectrum of 4.5a (75 MHz, CDCl₃)



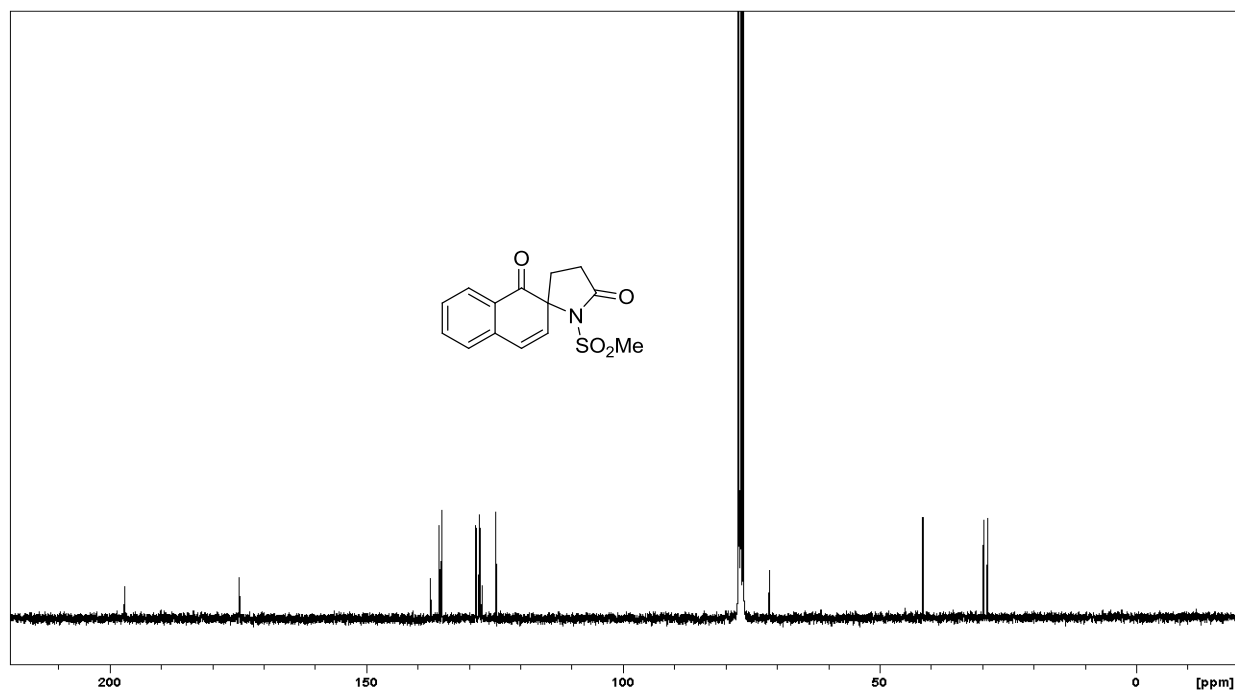
^1H NMR spectrum of 4.5b (300 MHz, CDCl_3)



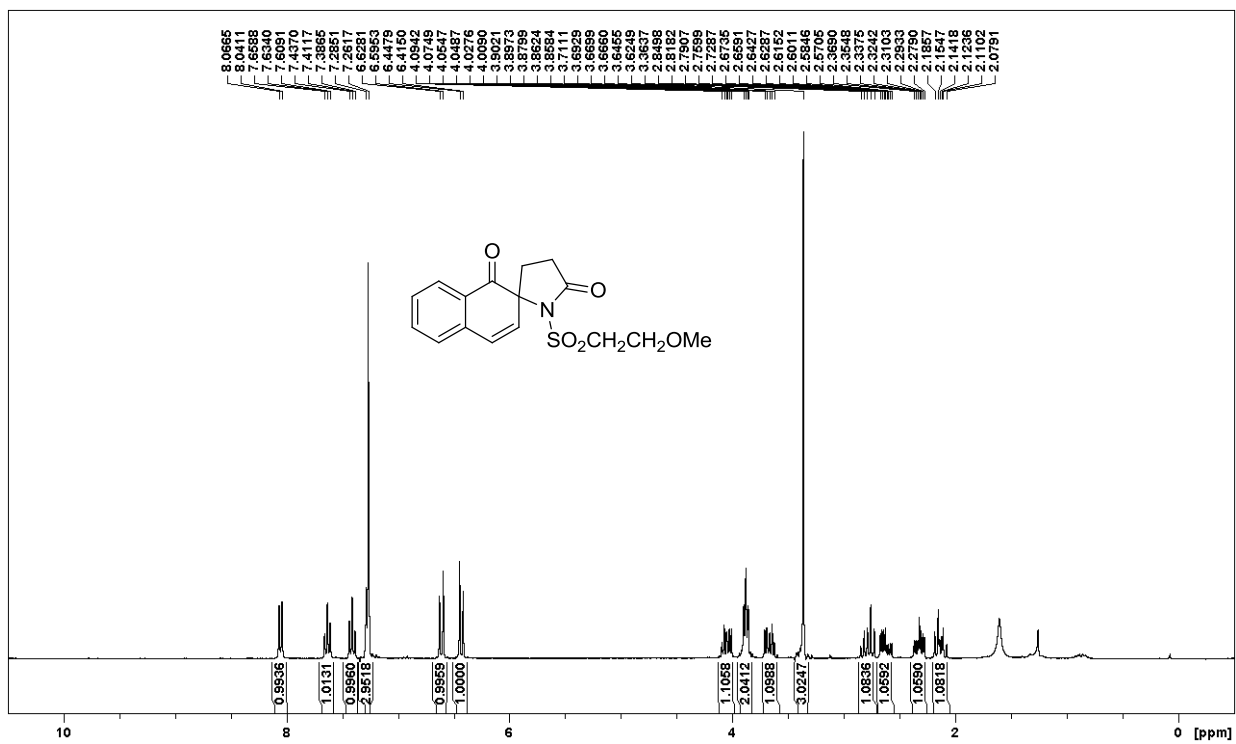
^{13}C NMR spectrum of 4.5b (75 MHz, CDCl_3)



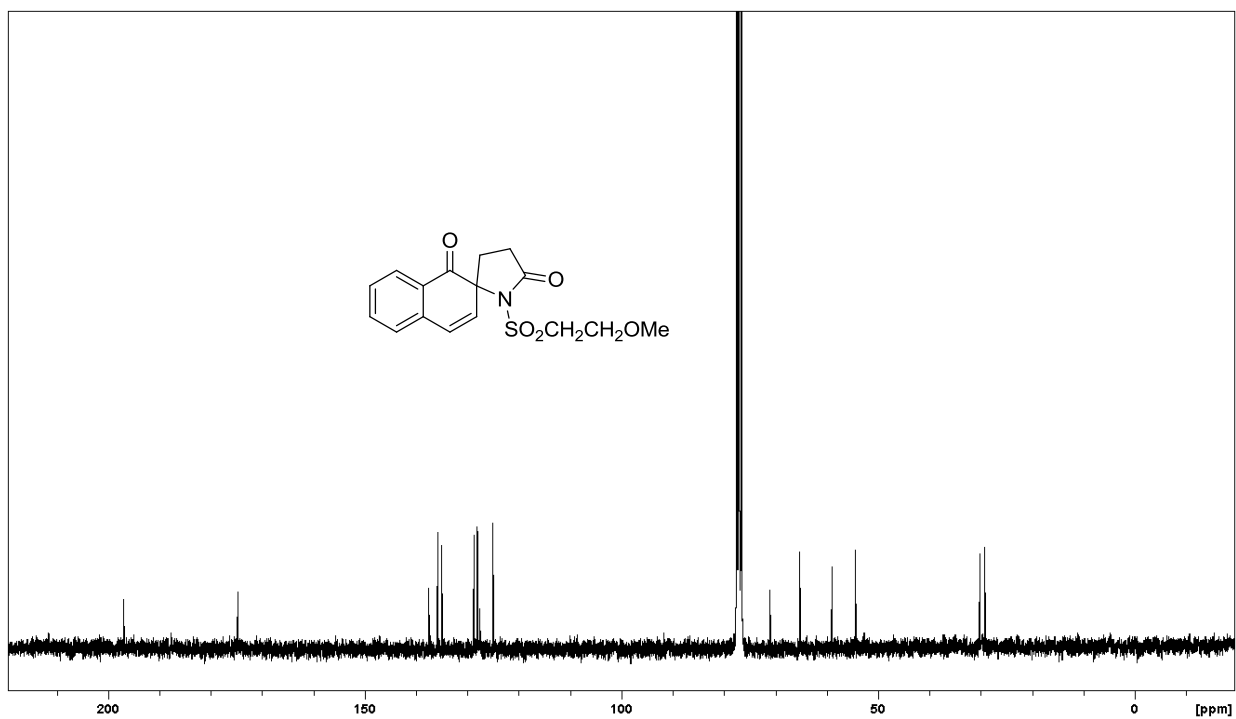
¹H NMR spectrum of 4.9a (300 MHz, CDCl₃)



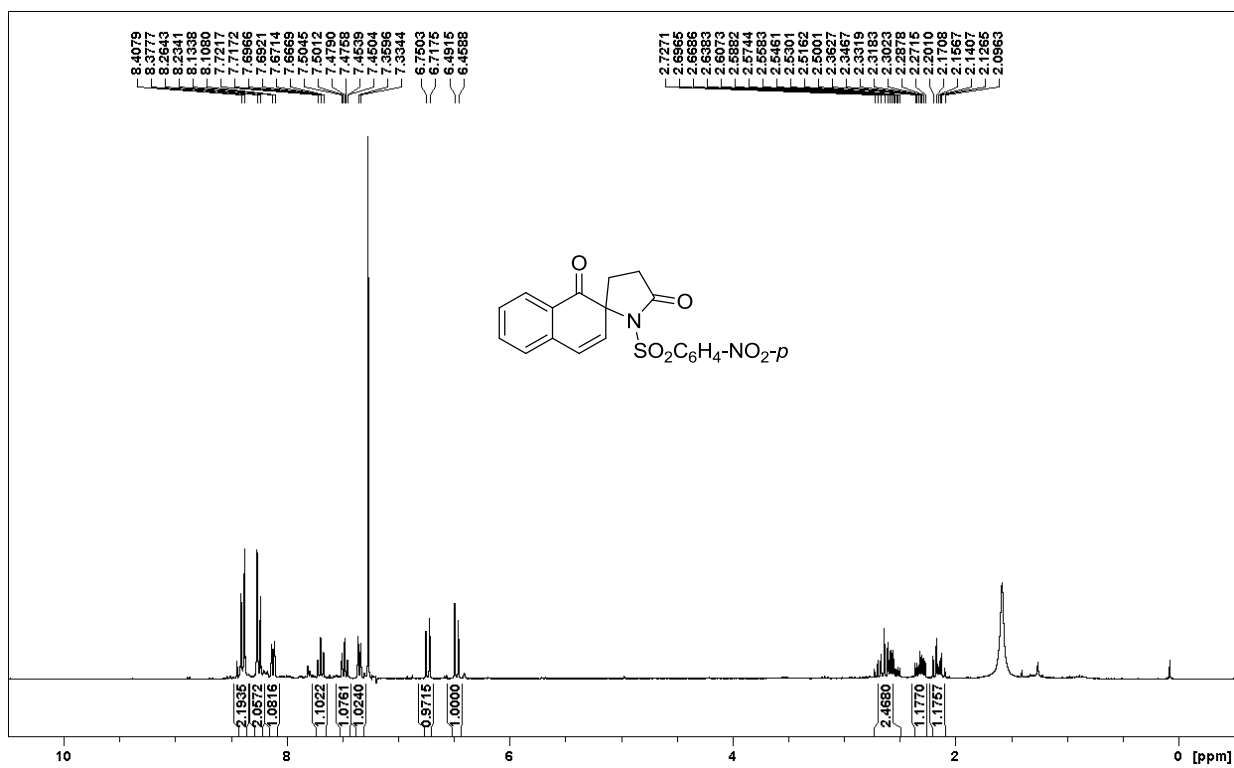
¹³C NMR spectrum of 4.9a (75 MHz, CDCl₃)



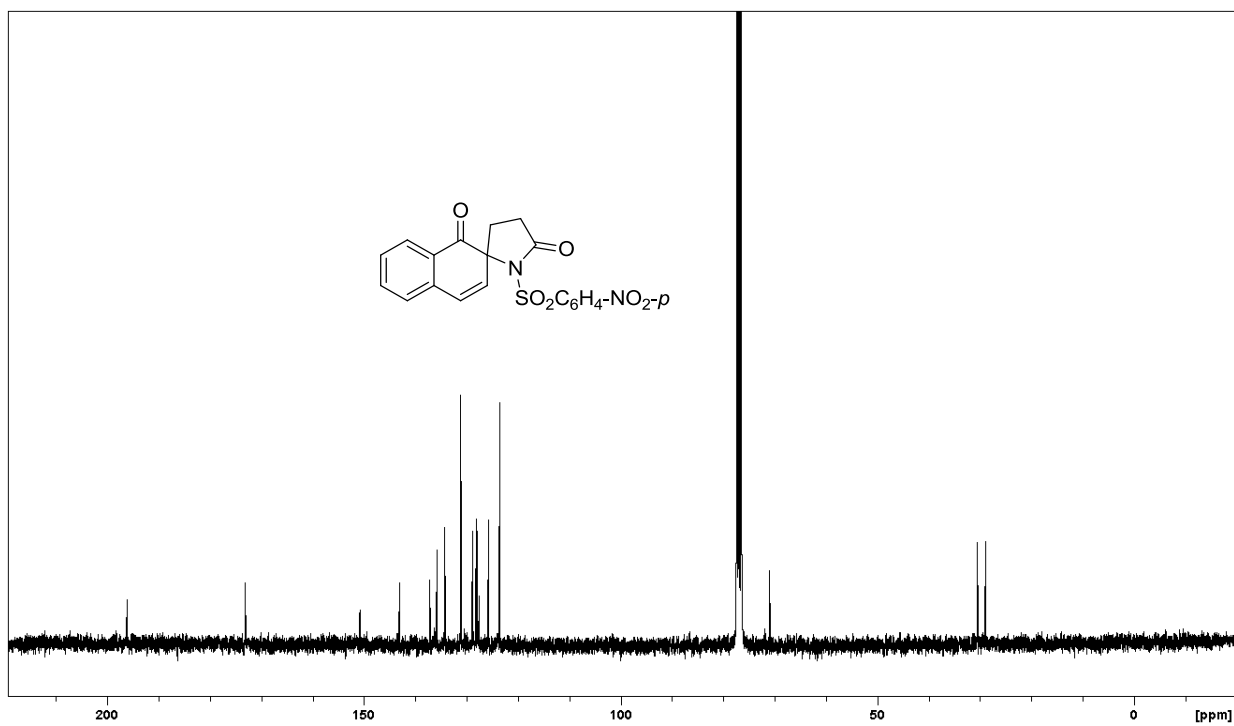
¹H NMR spectrum of 4.9b (300 MHz, CDCl₃)



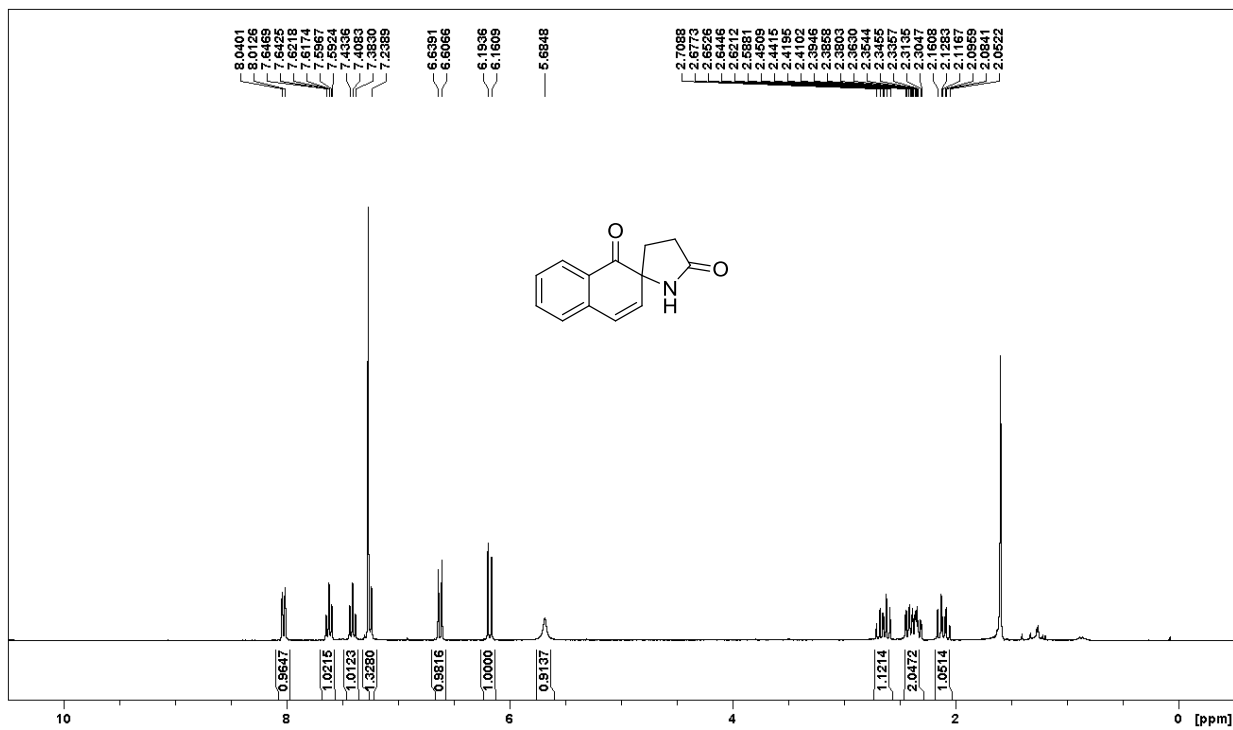
¹³C NMR spectrum of 4.9b (75 MHz, CDCl₃)



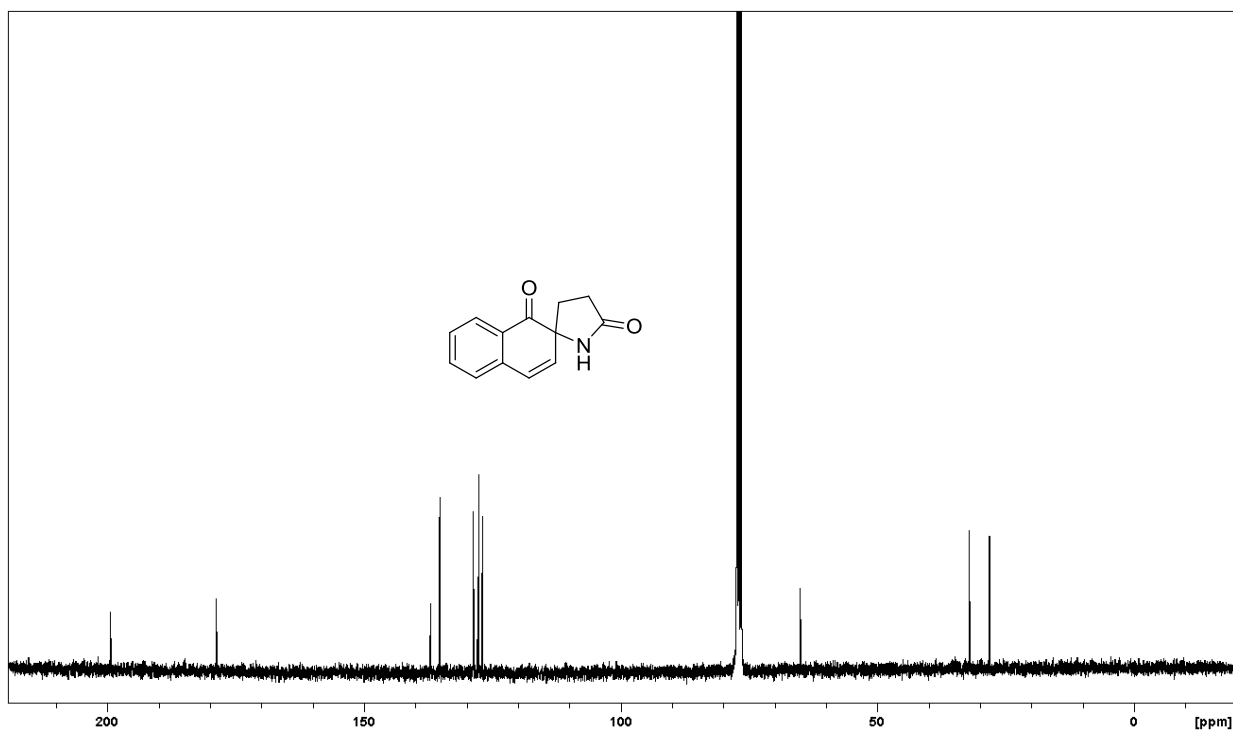
¹H NMR spectrum of 4.9c (300 MHz, CDCl₃)



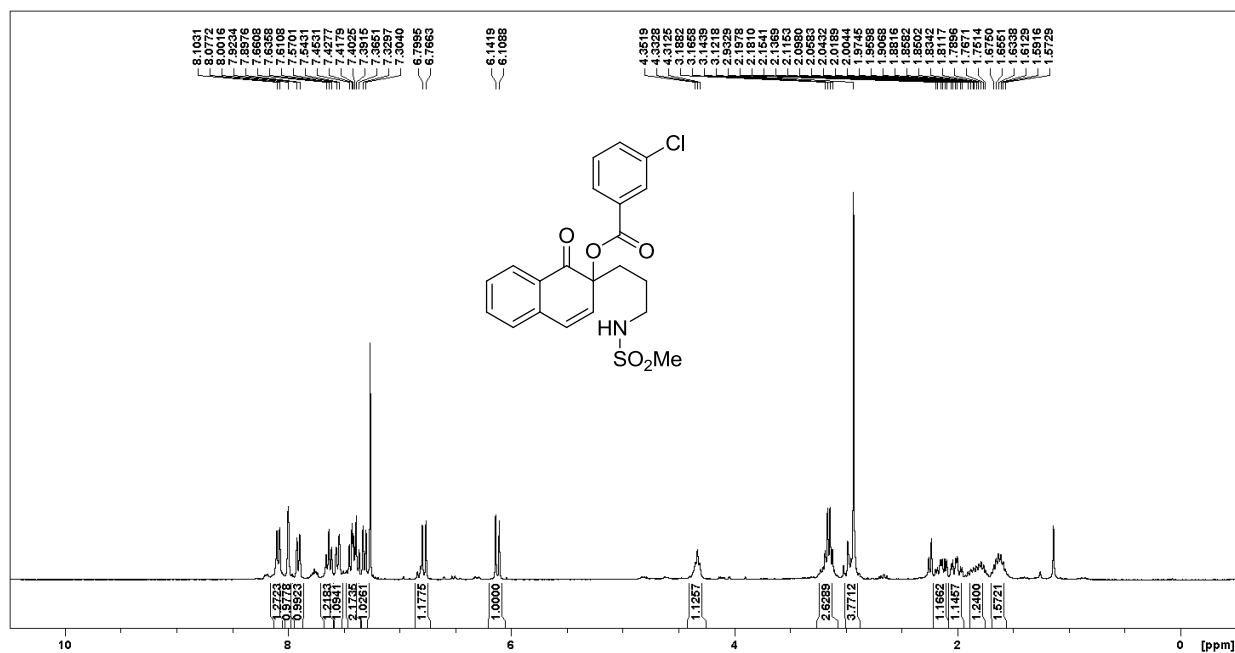
¹³C NMR spectrum of 4.9c (75 MHz, CDCl₃)



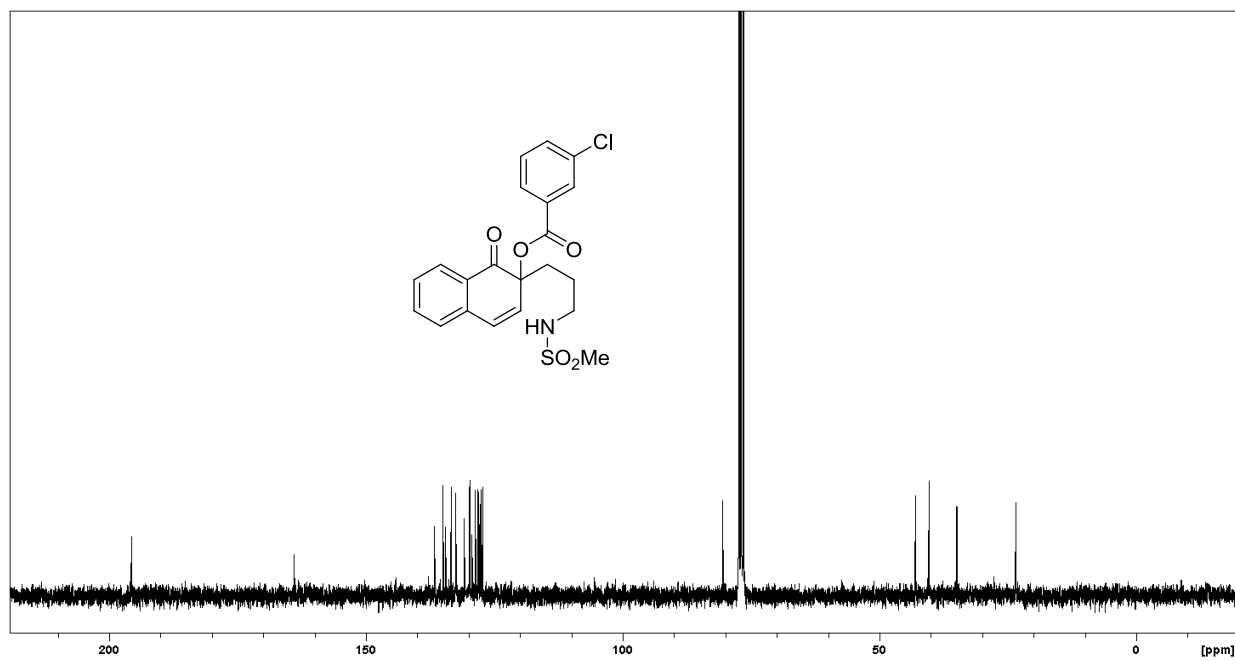
¹H NMR spectrum of 4.10 (300 MHz, CDCl₃)



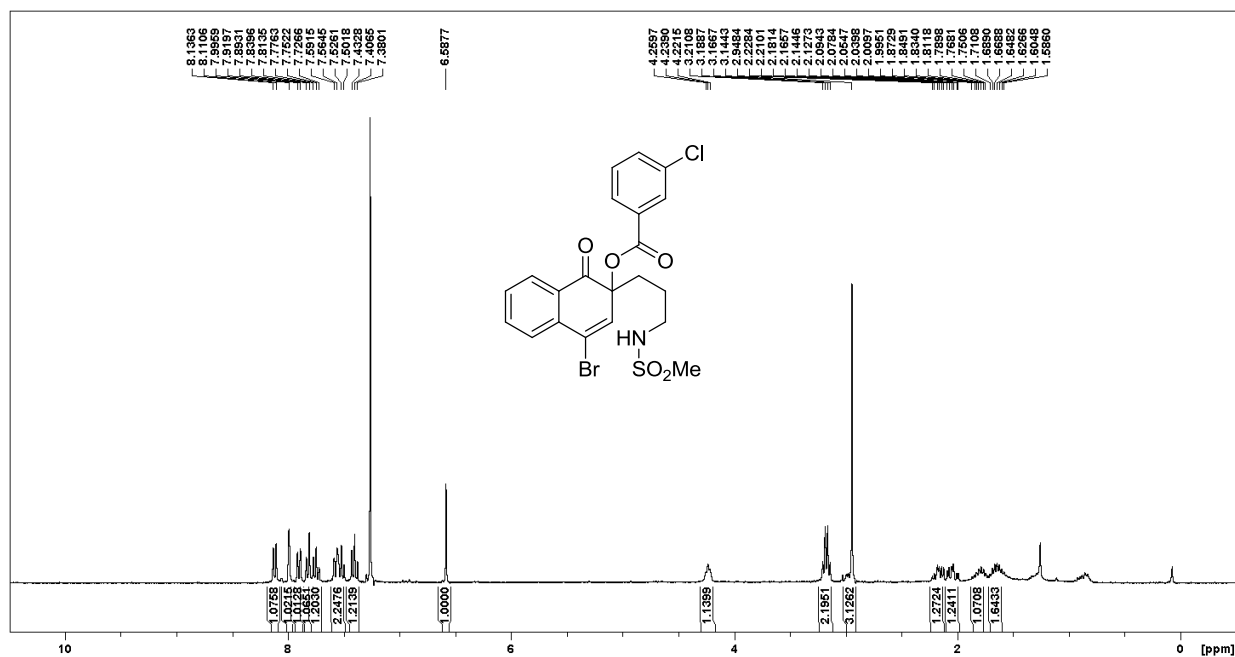
¹³C NMR spectrum of 4.10 (75 MHz, CDCl₃)



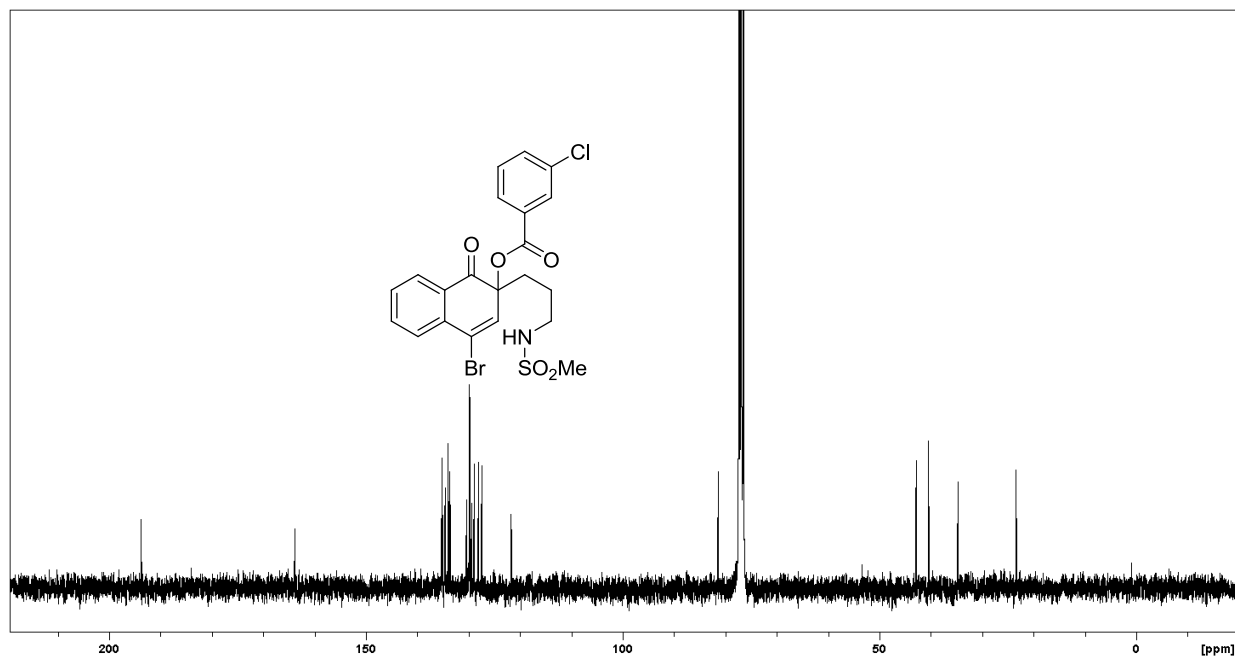
¹H NMR spectrum of 4.54a (300 MHz, CDCl₃)



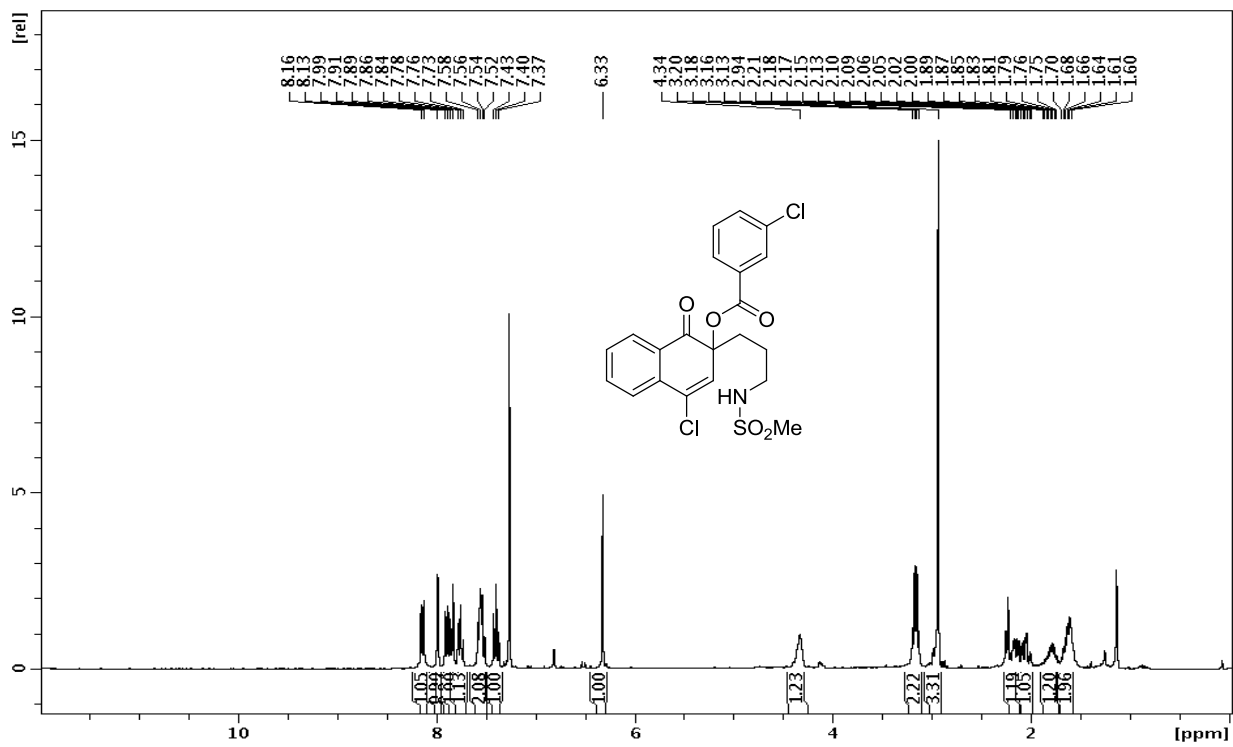
¹³C NMR spectrum of 4.54a (75 MHz, CDCl₃)



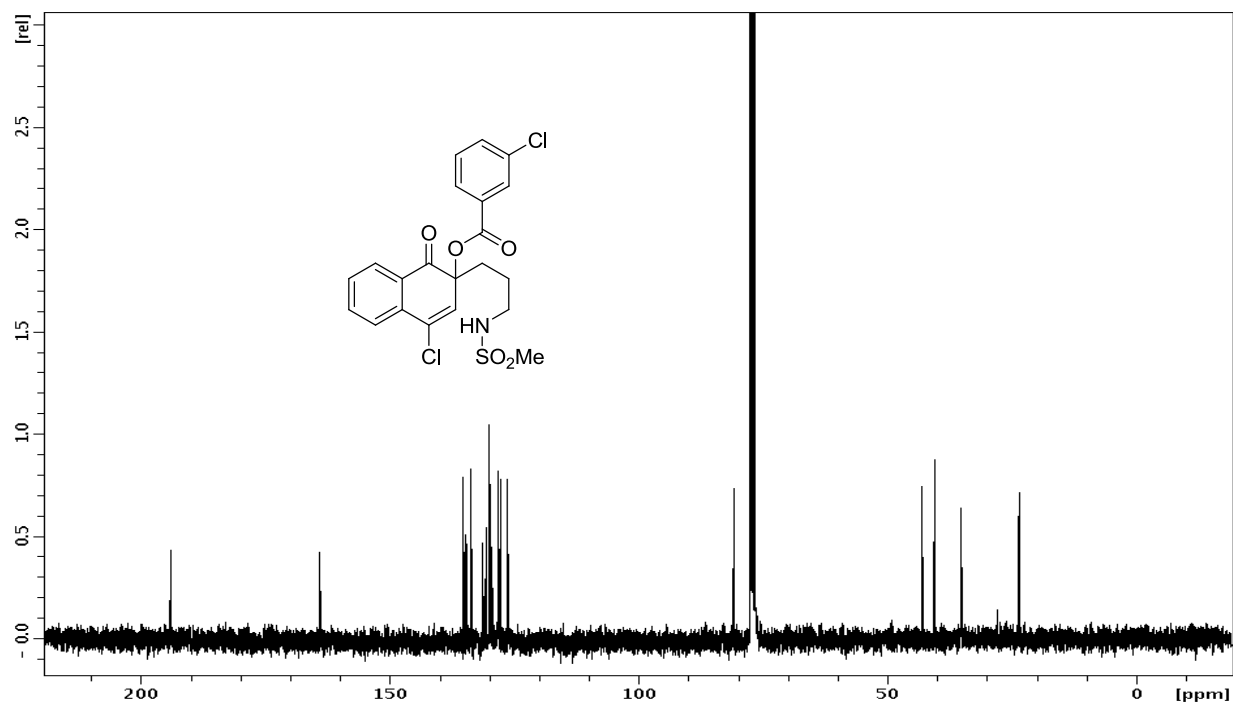
¹H NMR spectrum of 4.54b (300 MHz, CDCl₃)



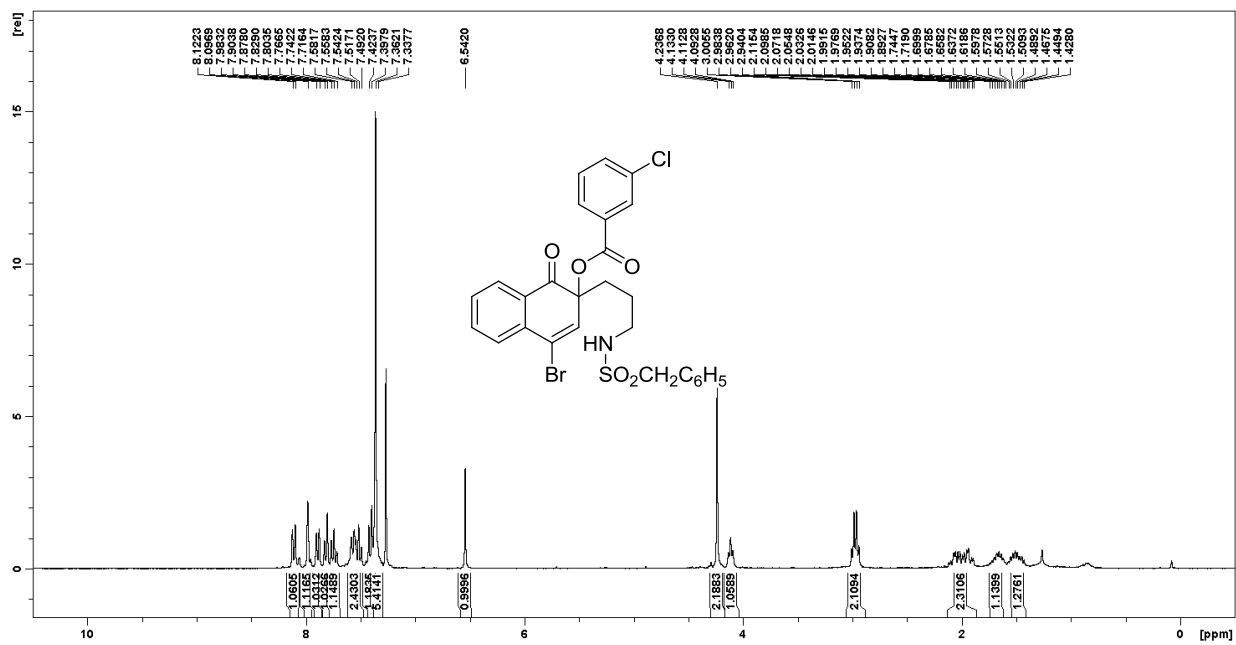
¹³C NMR spectrum of 4.54b (75 MHz, CDCl₃)



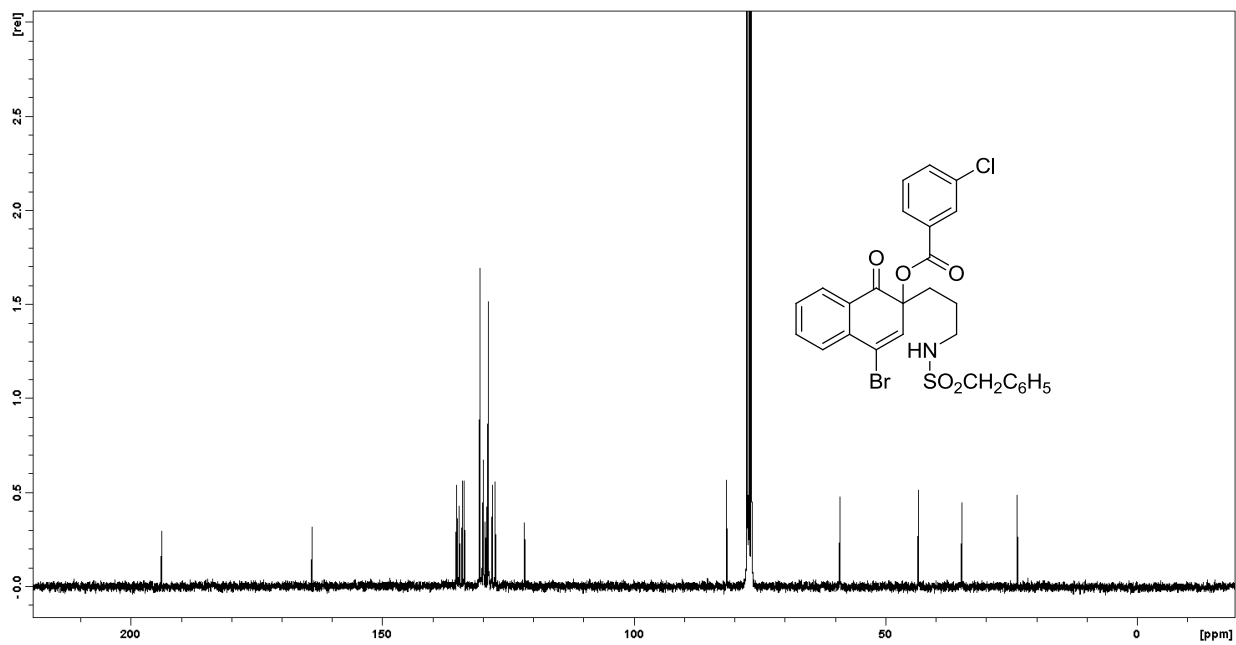
¹H NMR spectrum of 4.54c (300 MHz, CDCl₃)



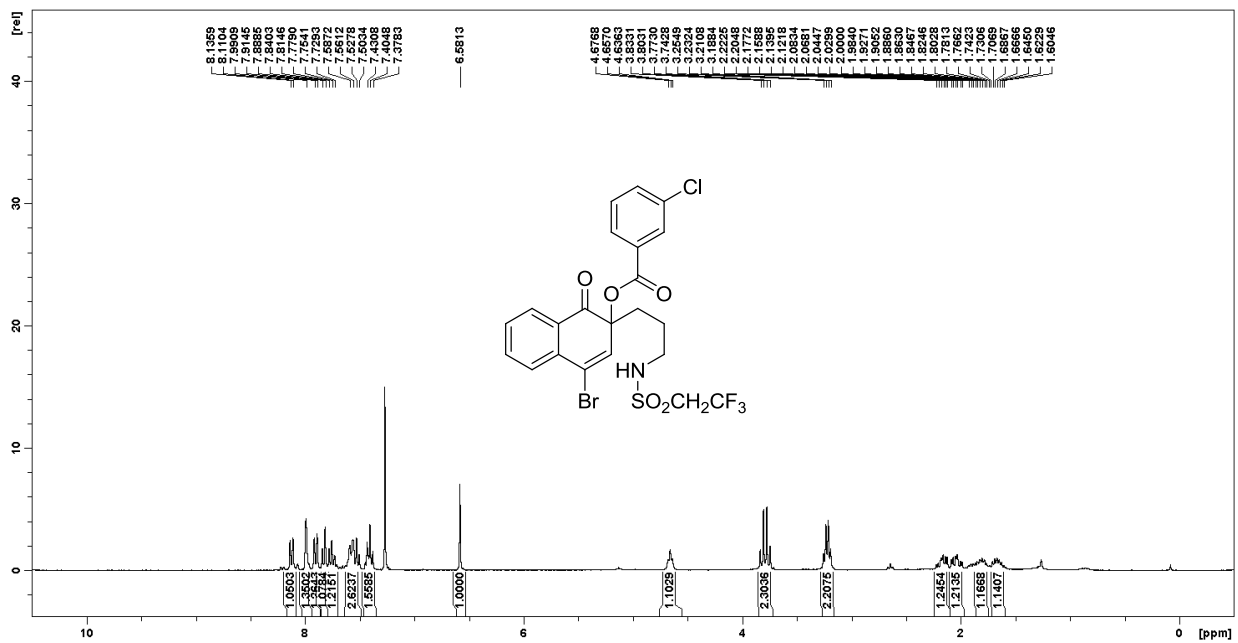
¹³C NMR spectrum of 4.54c (75 MHz, CDCl₃)



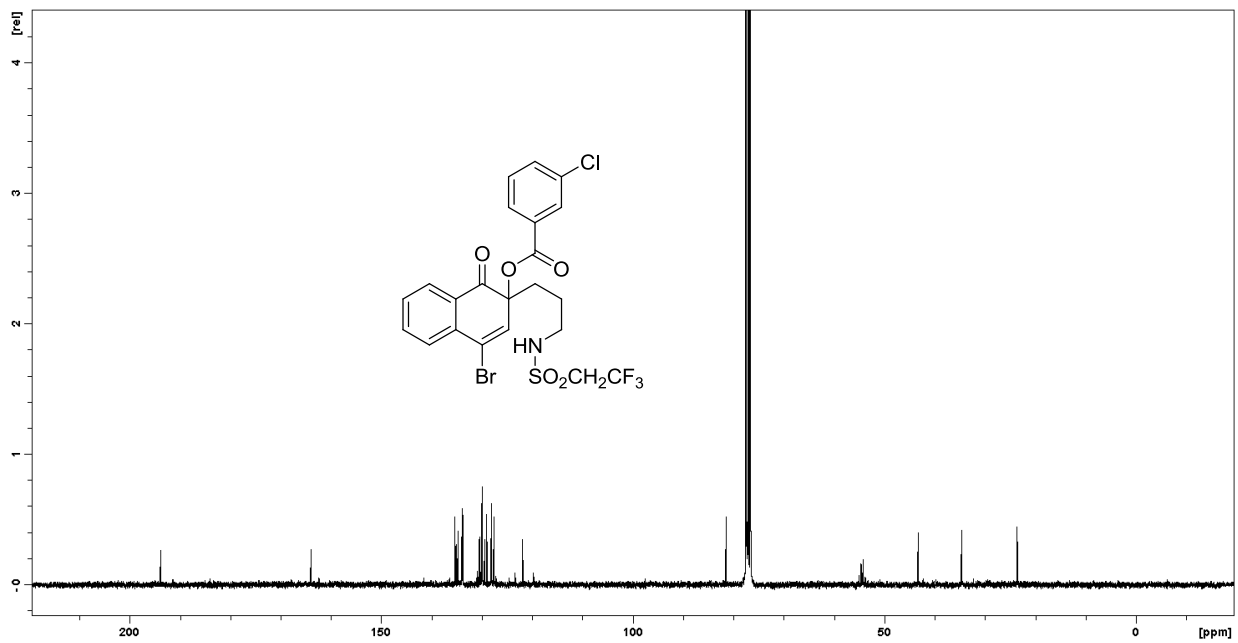
¹H NMR spectrum of 4.54d (300 MHz, CDCl₃)



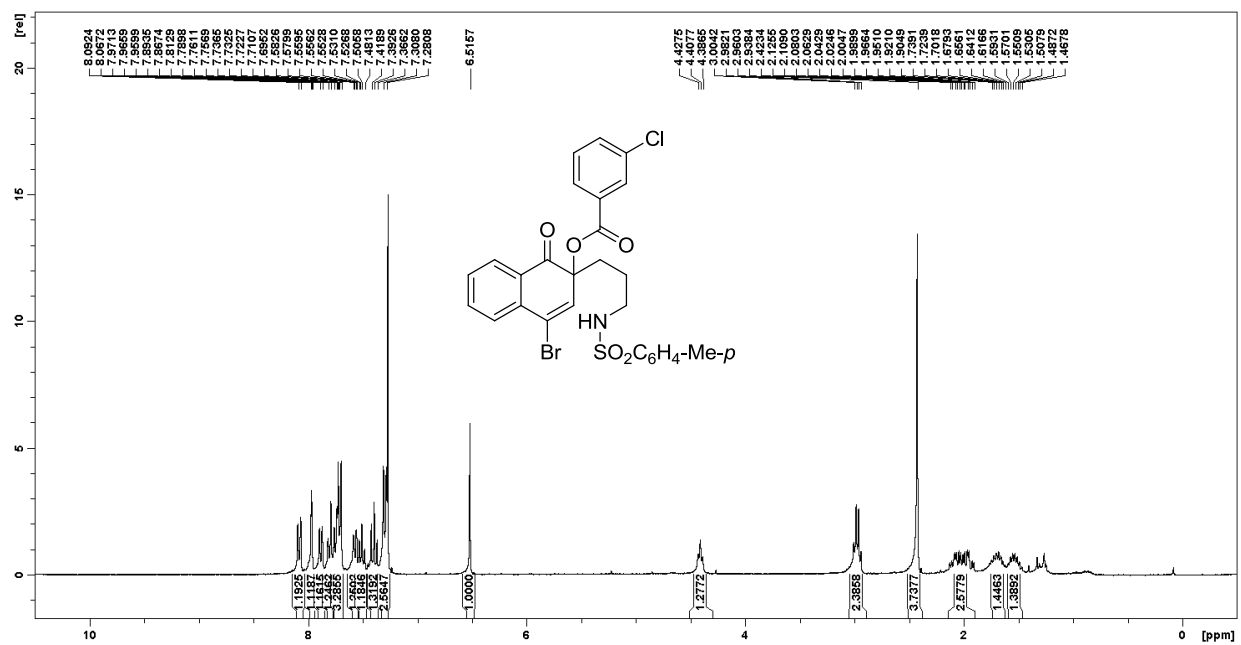
¹³C NMR spectrum of 4.54d (75 MHz, CDCl₃)



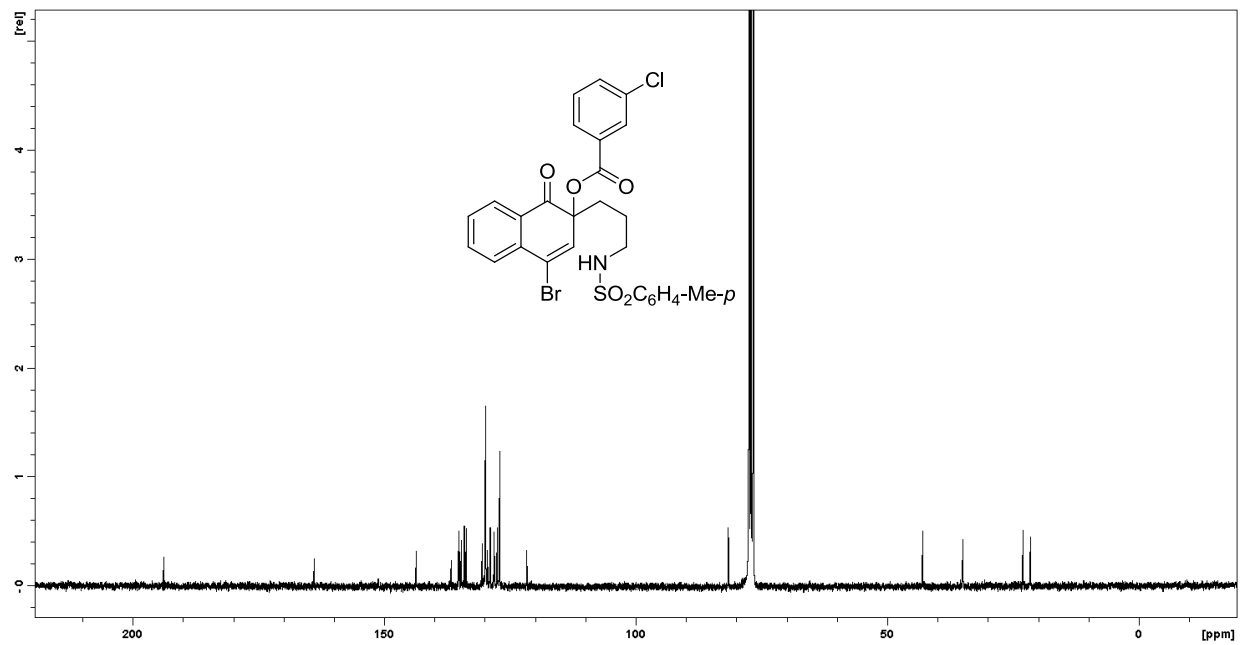
¹H NMR spectrum of 4.54e (300 MHz, CDCl₃)



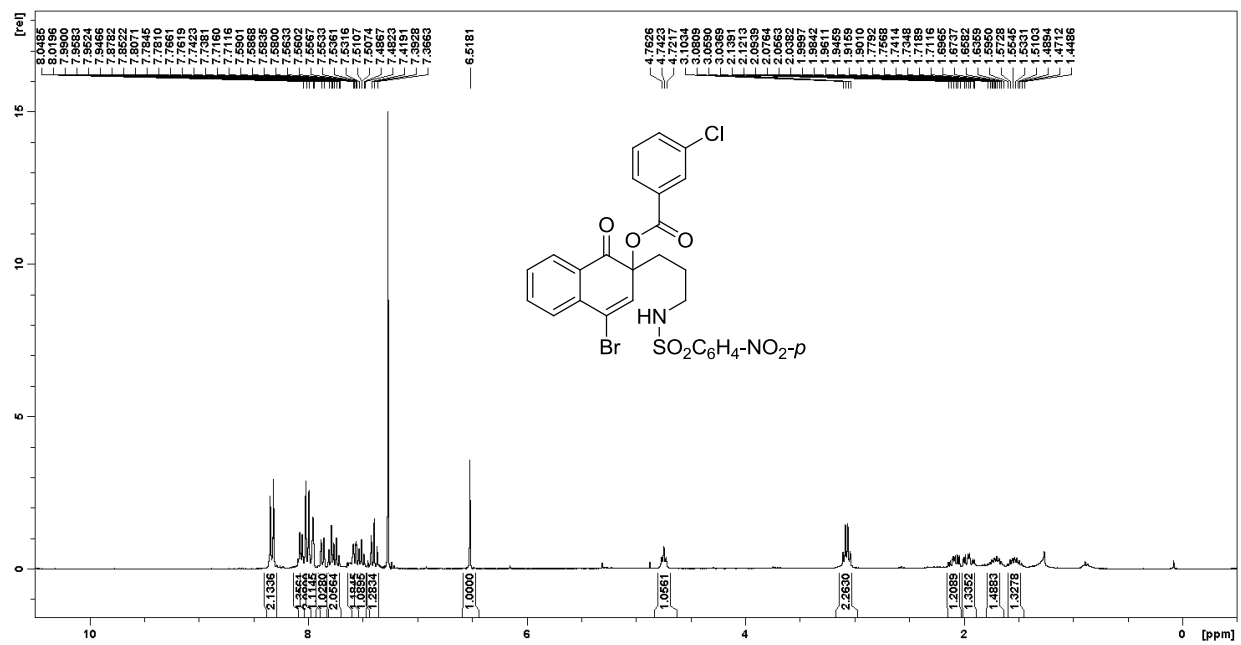
¹³C NMR spectrum of 4.54e (75 MHz, CDCl₃)



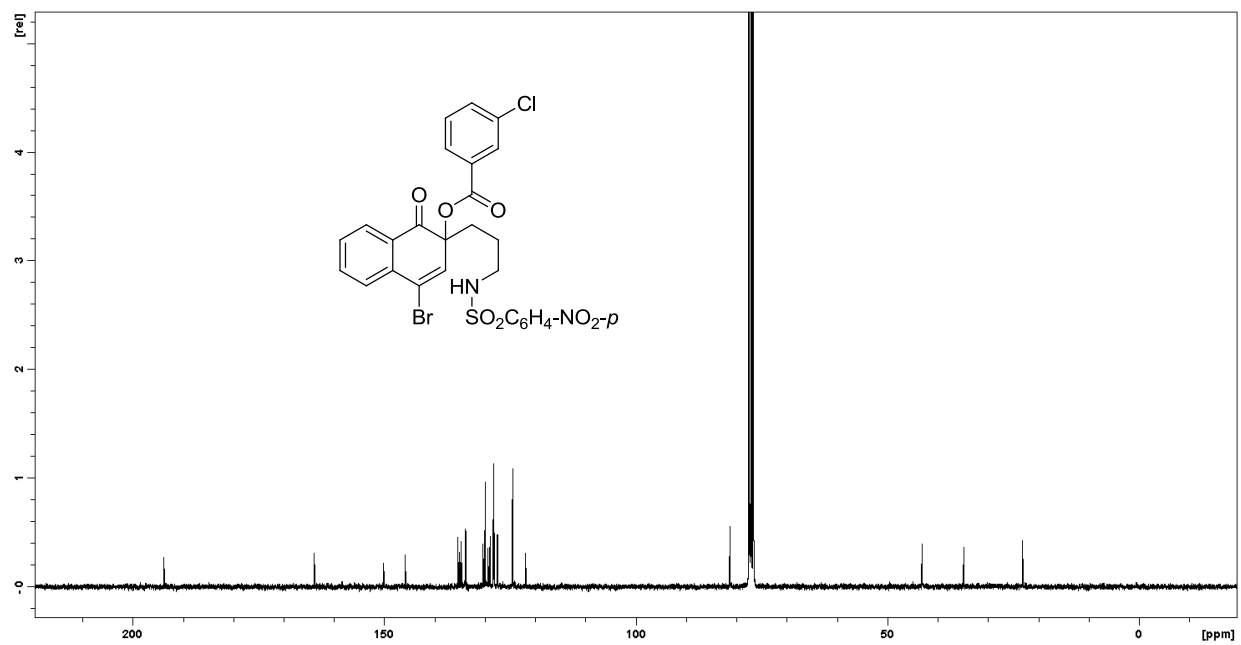
^1H NMR spectrum of 4.54f (300 MHz, CDCl_3)



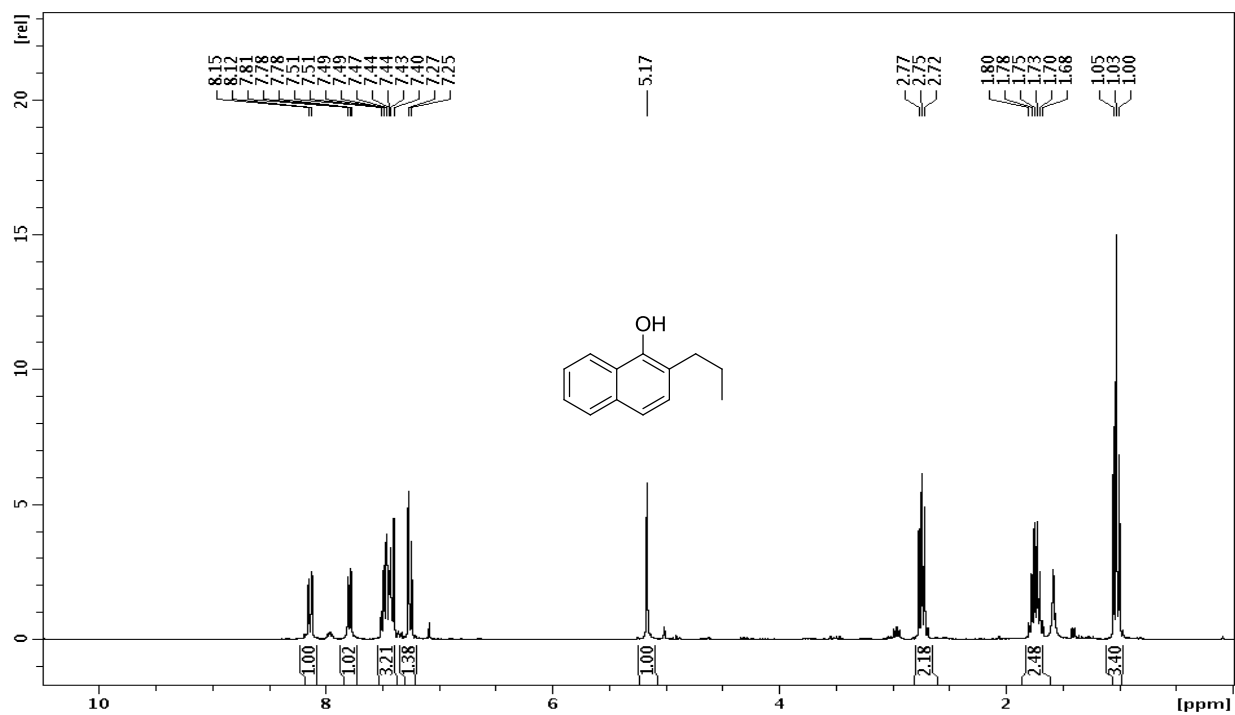
^{13}C NMR spectrum of 4.54f (75 MHz, CDCl_3)



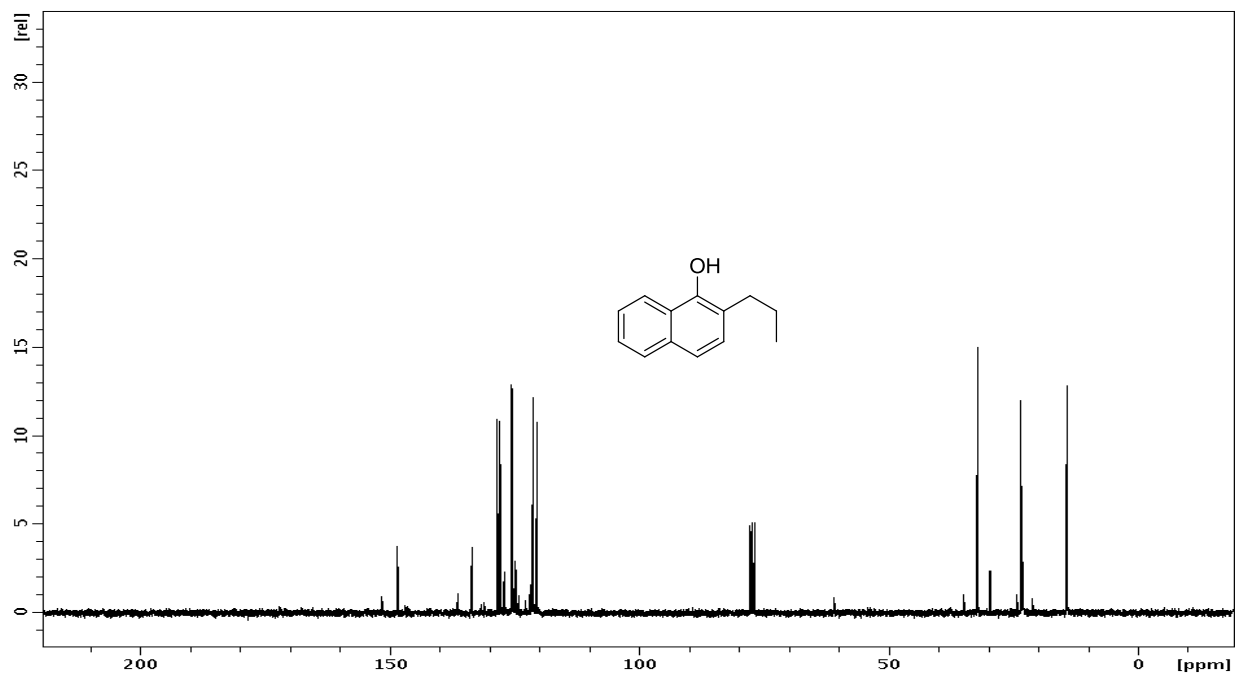
¹H NMR spectrum of 4.54g (300 MHz, CDCl₃)



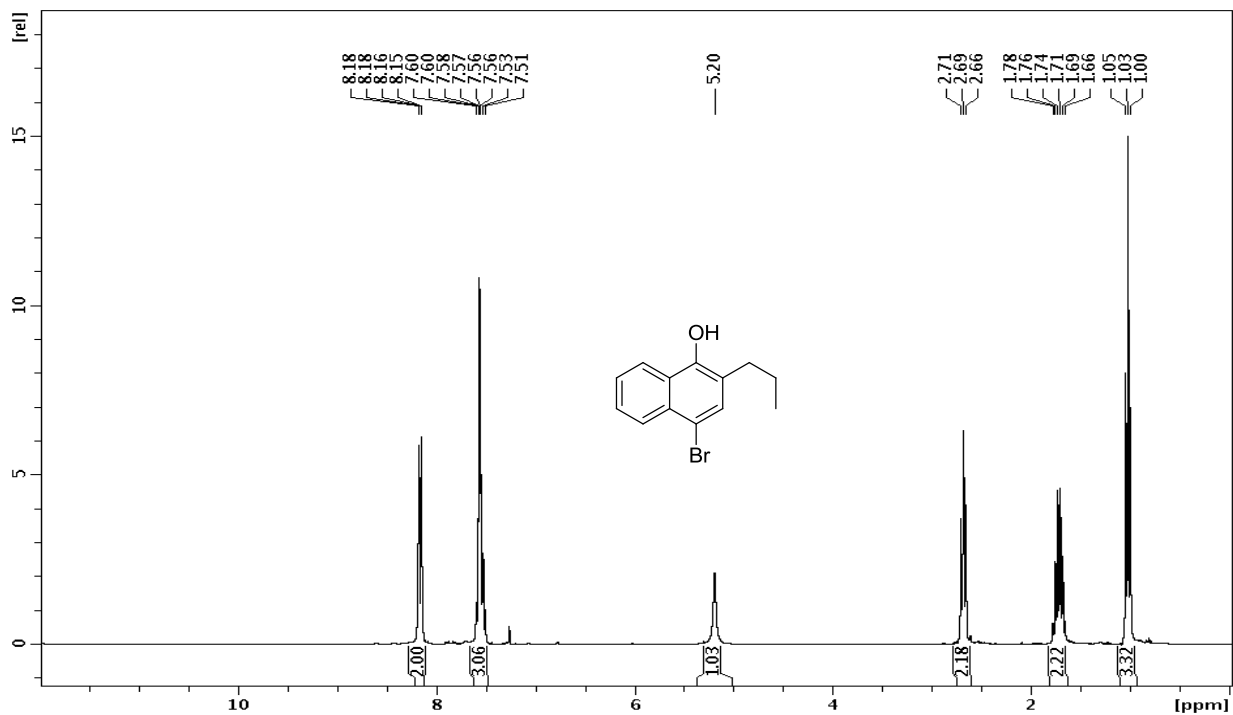
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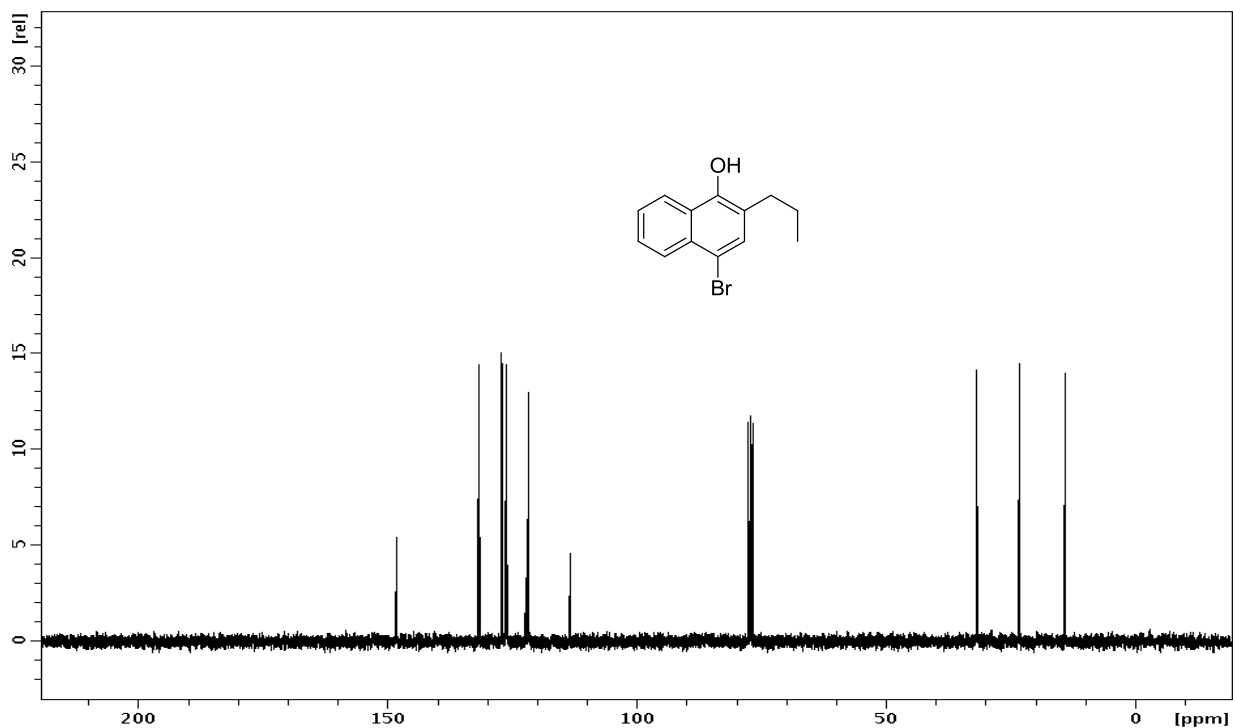
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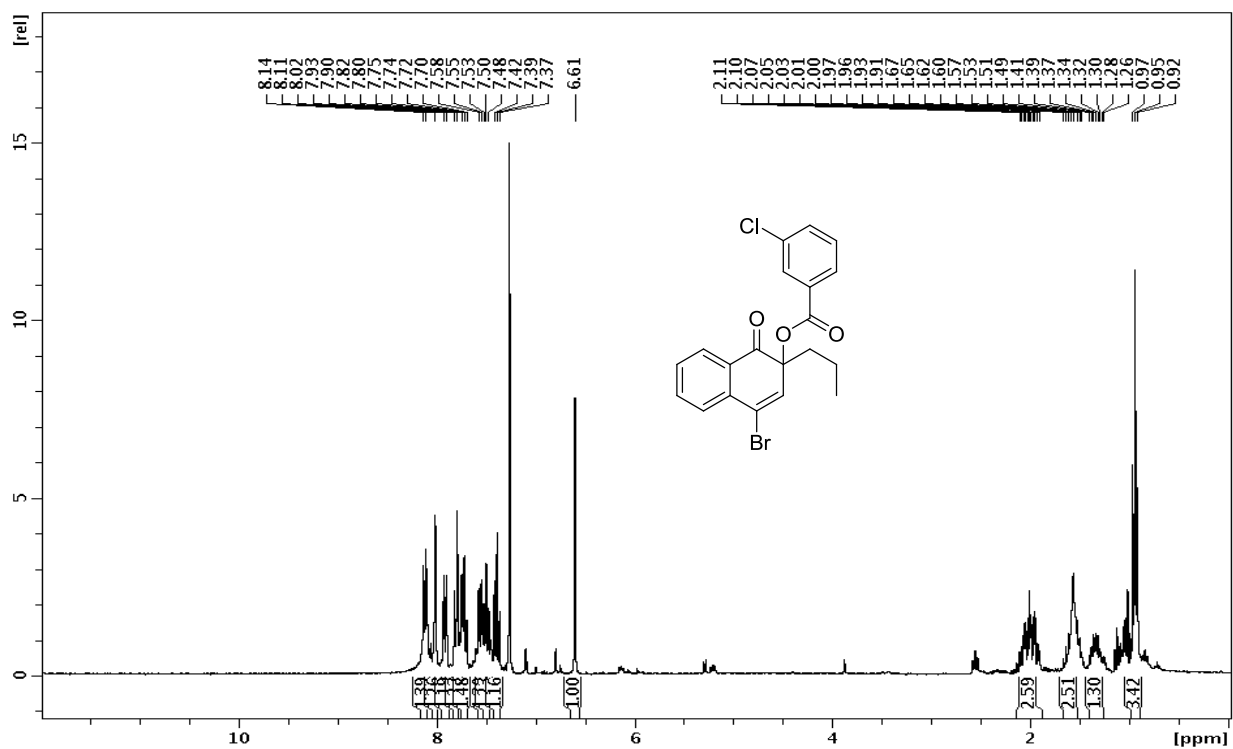
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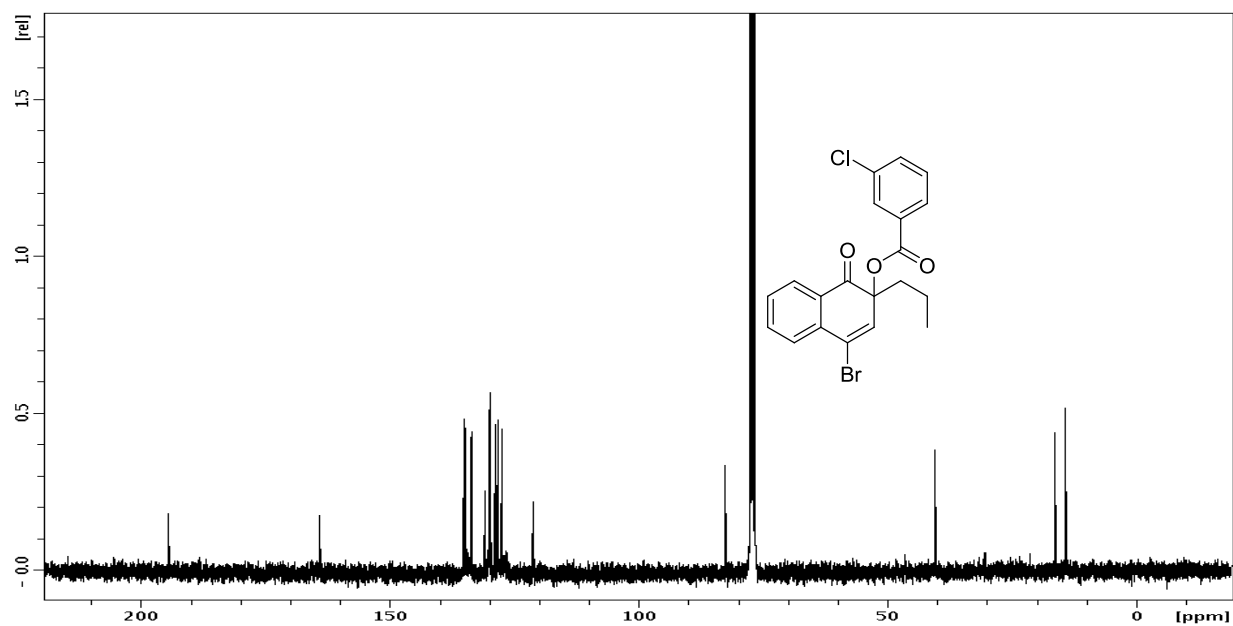
¹H NMR spectrum of 4.67 (300 MHz, CDCl₃)



¹³C NMR spectrum of 4.67 (75 MHz, CDCl₃)



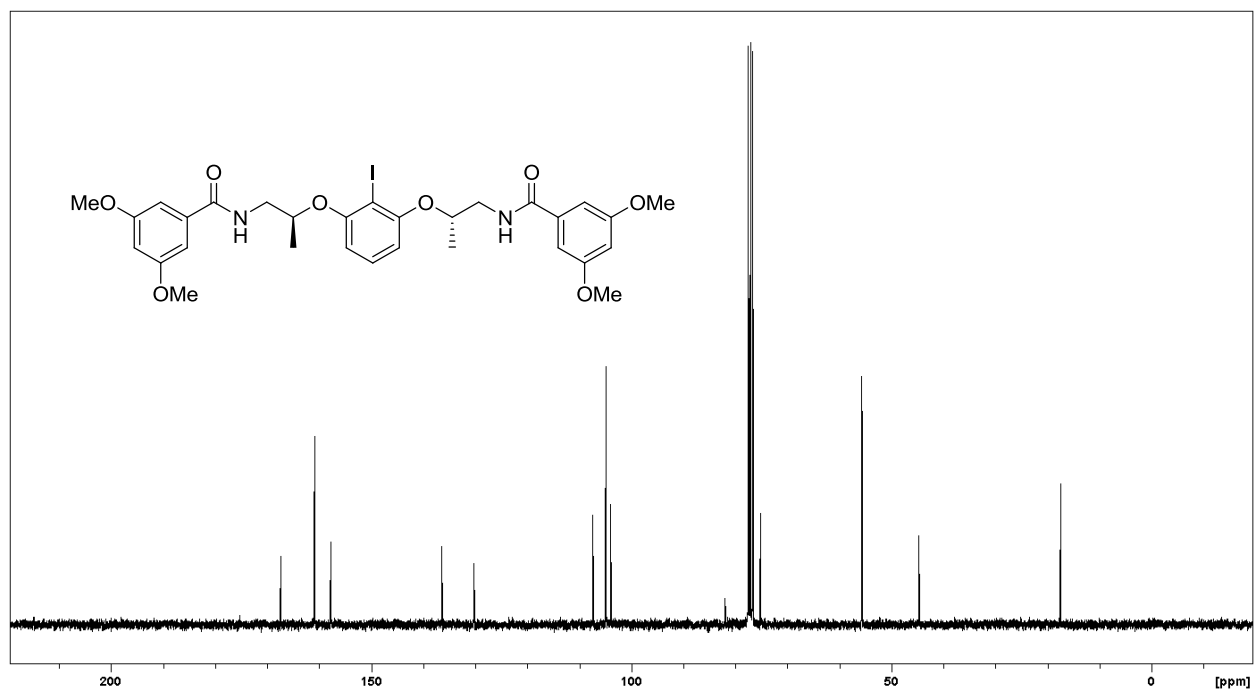
¹H NMR spectrum of 4.68 (300 MHz, CDCl₃)



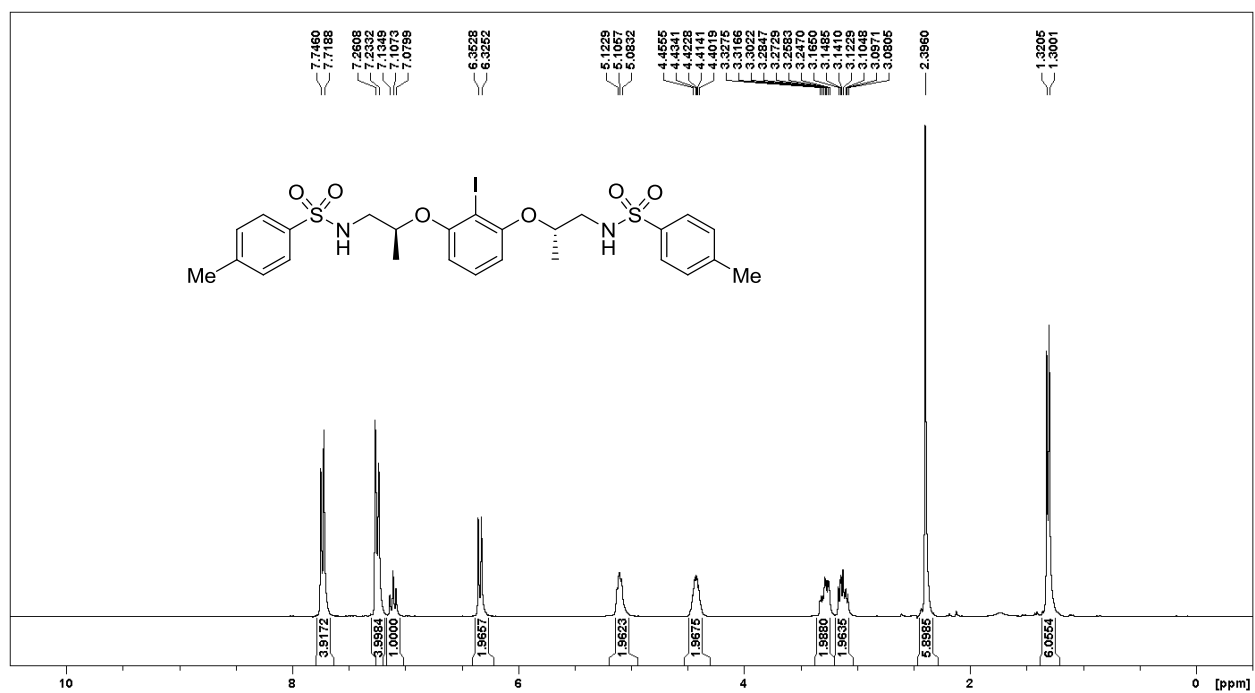
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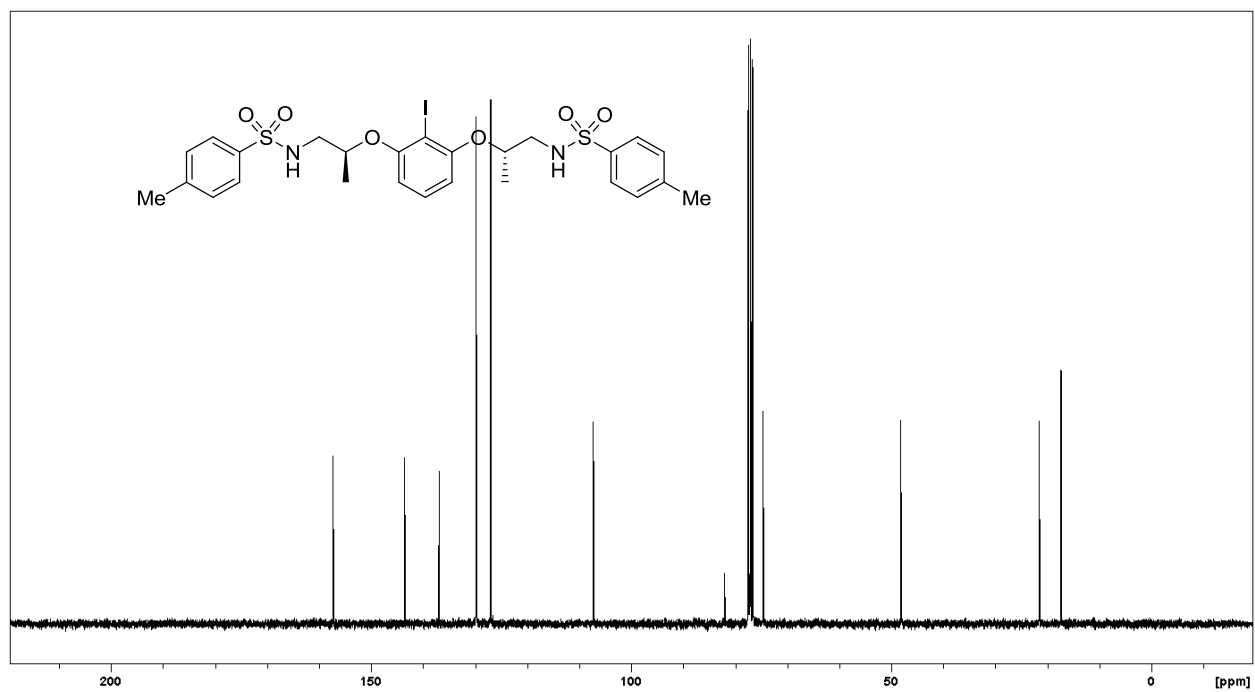
¹H NMR spectrum of 4.21 (300 MHz, CDCl₃)



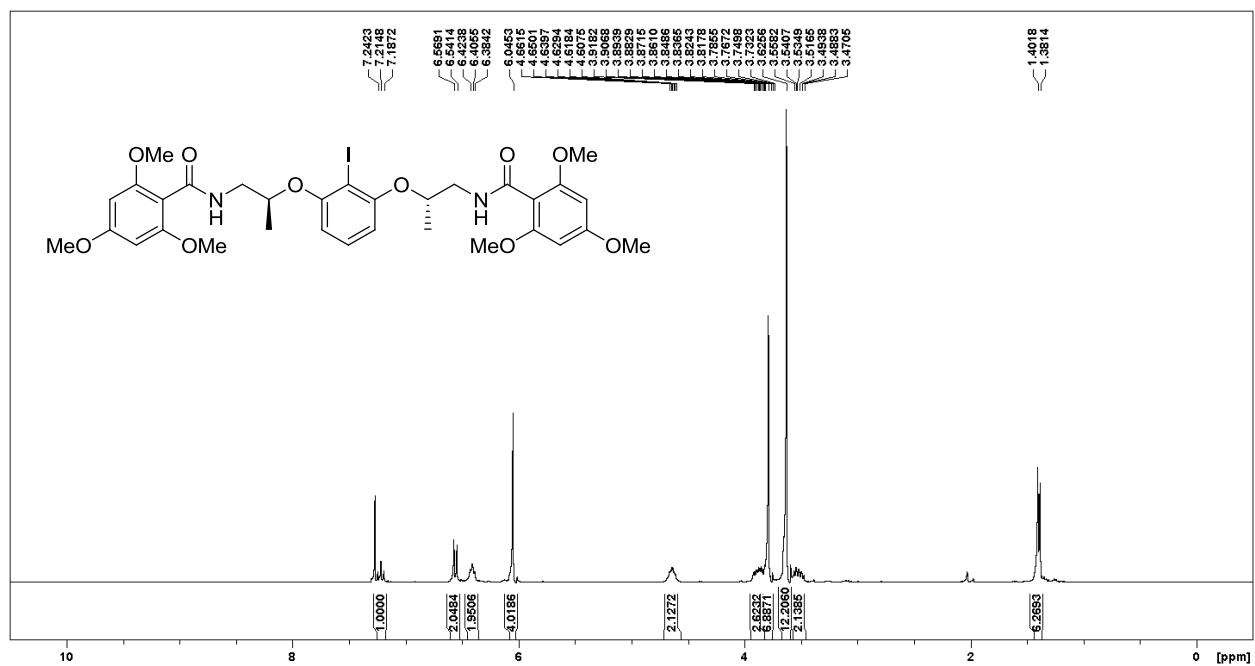
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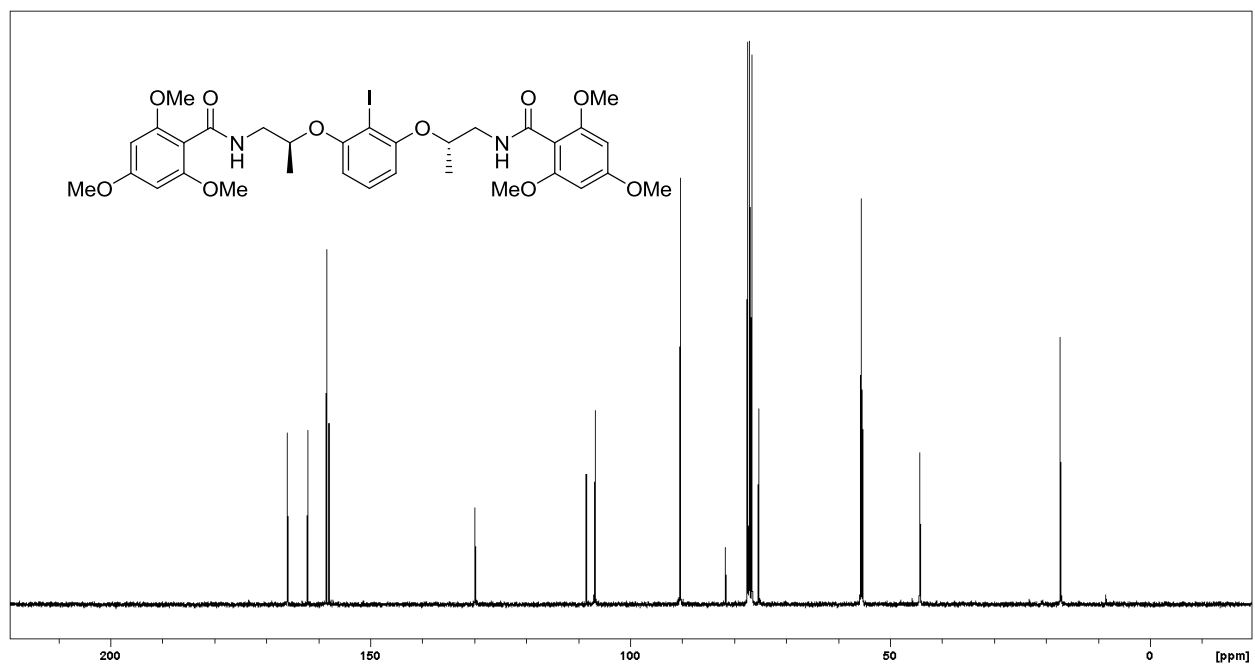
¹H NMR spectrum of 4.22 (300 MHz, CDCl₃)



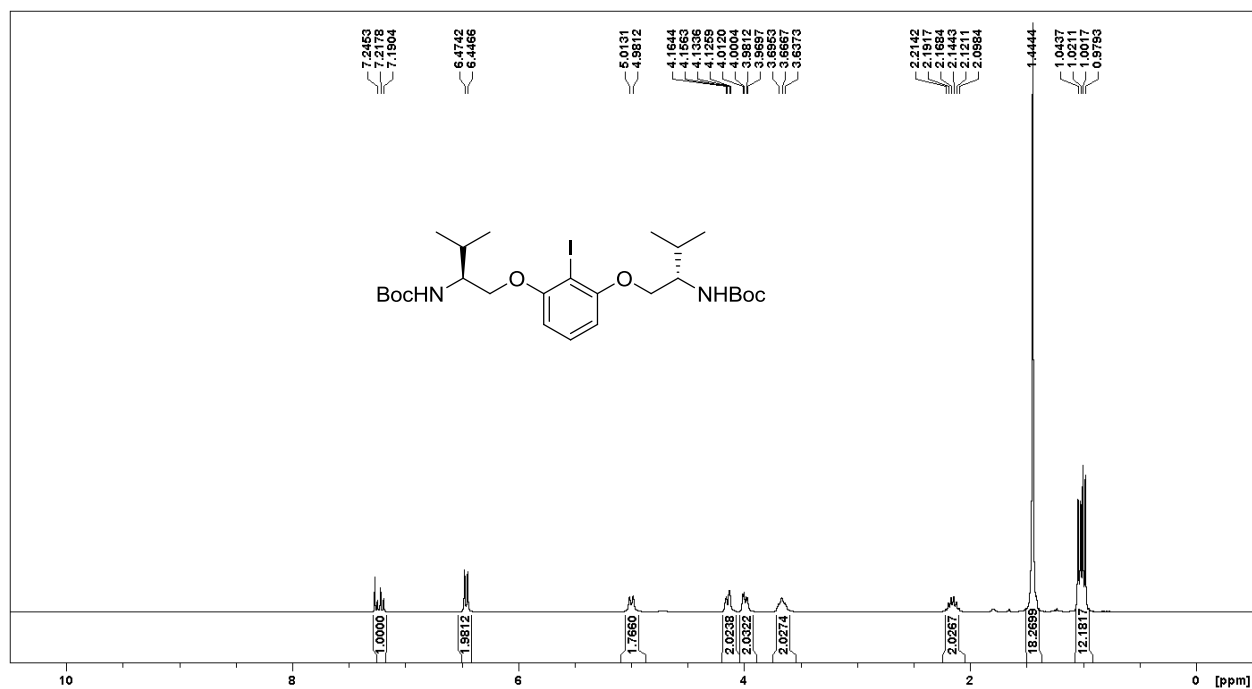
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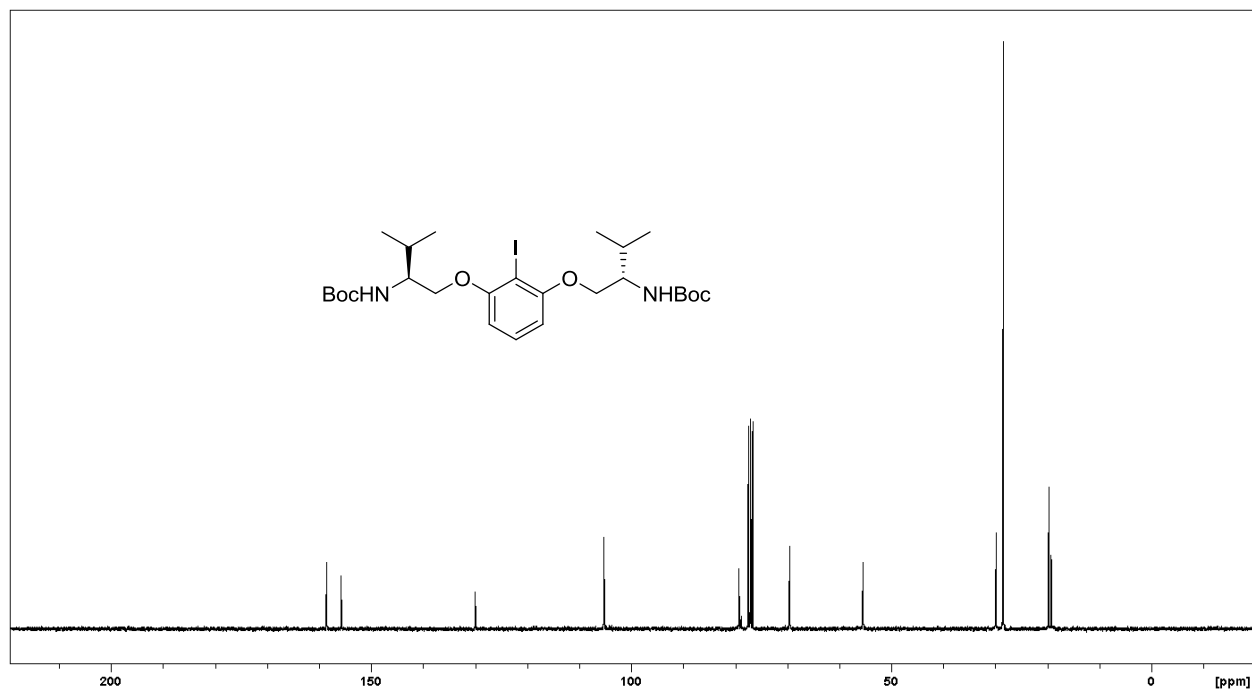
¹H NMR spectrum of 4.23 (300 MHz, CDCl₃)



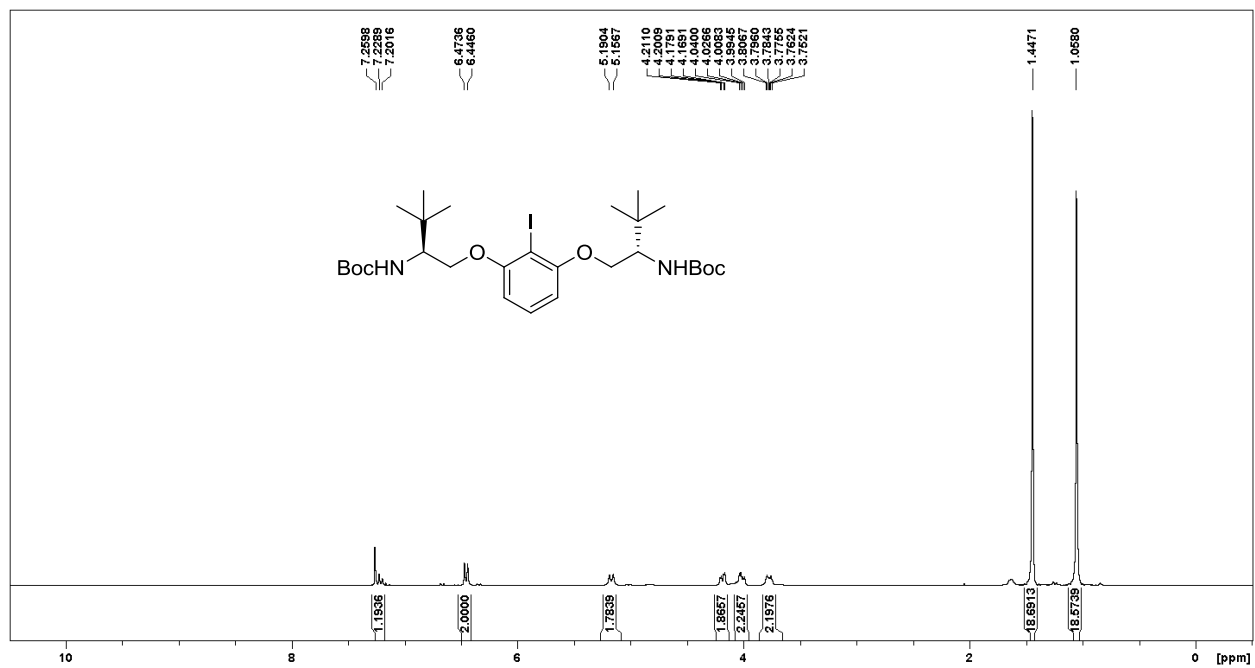
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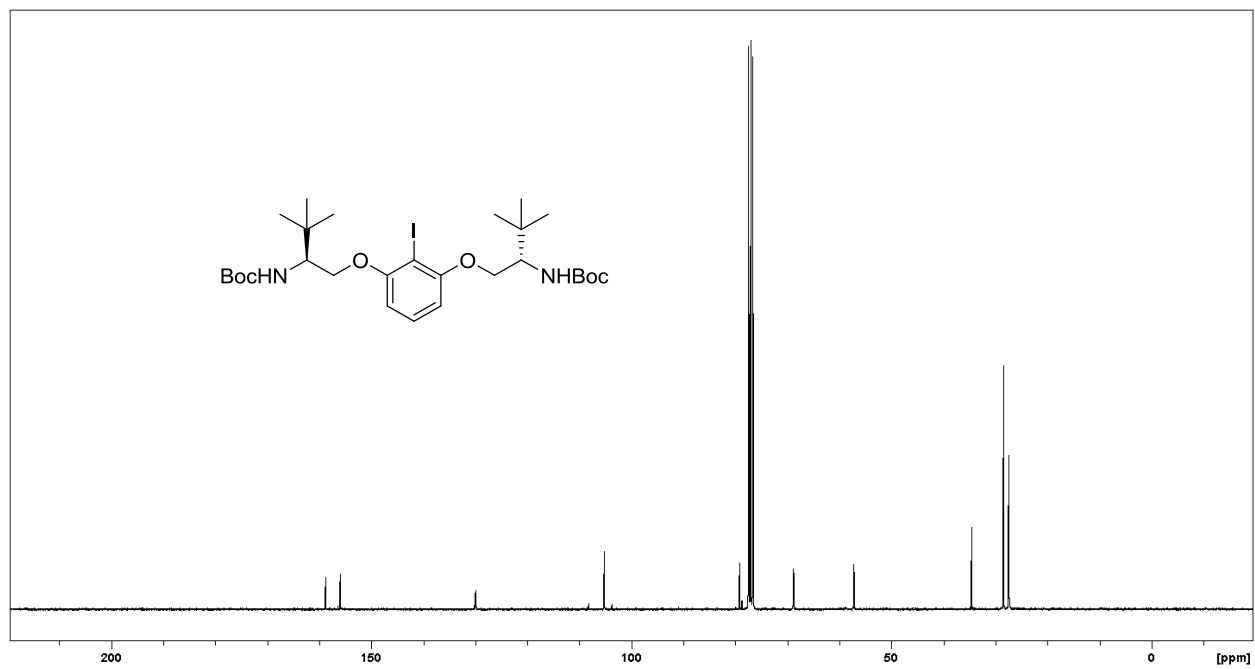
¹H NMR spectrum of 4.47 (300 MHz, CDCl₃)



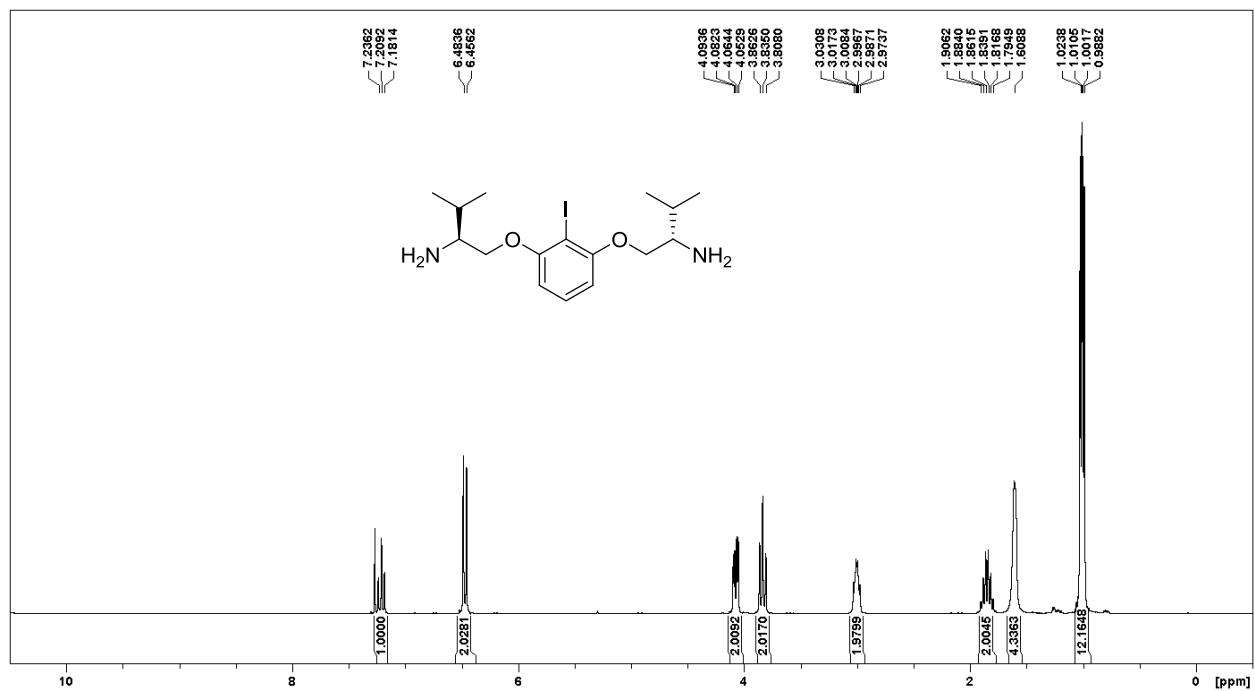
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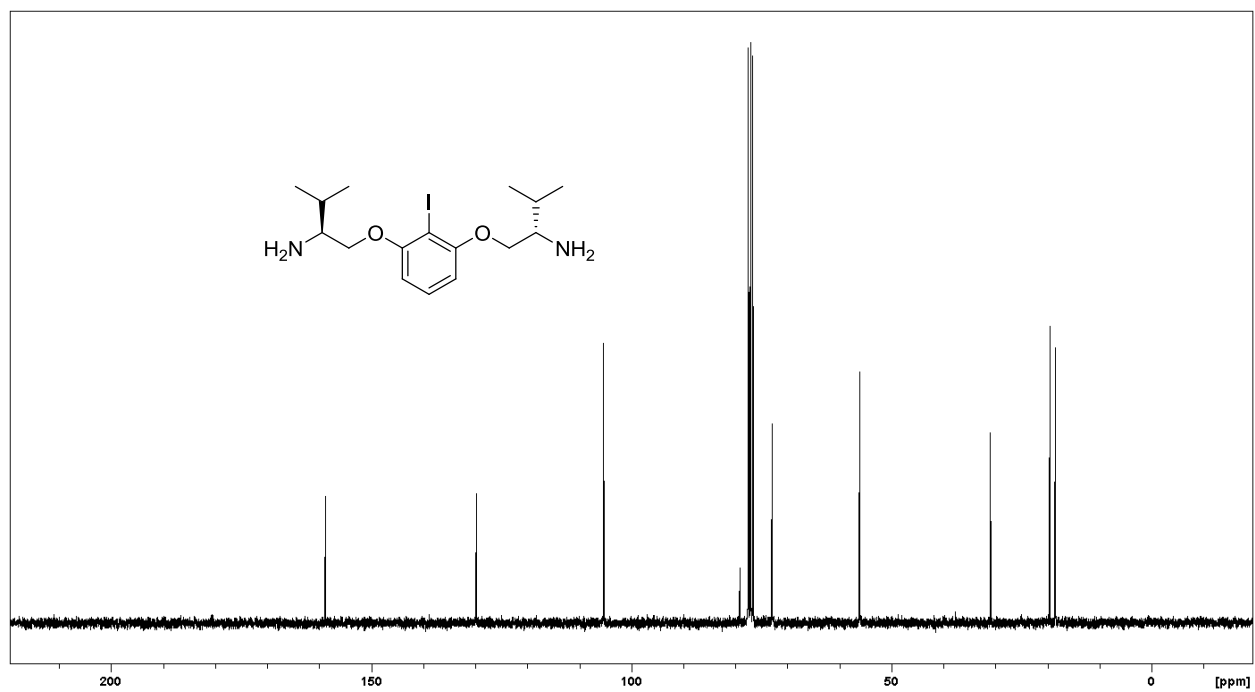
¹H NMR spectrum of 4.48 (300 MHz, CDCl₃)



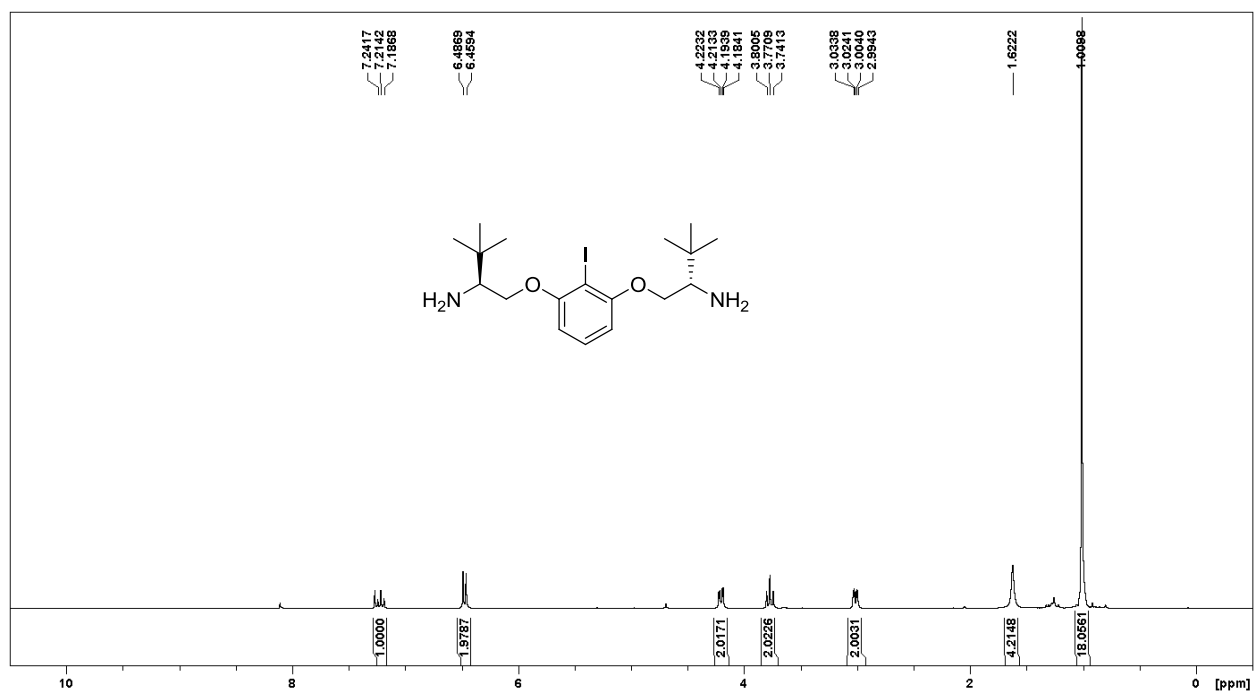
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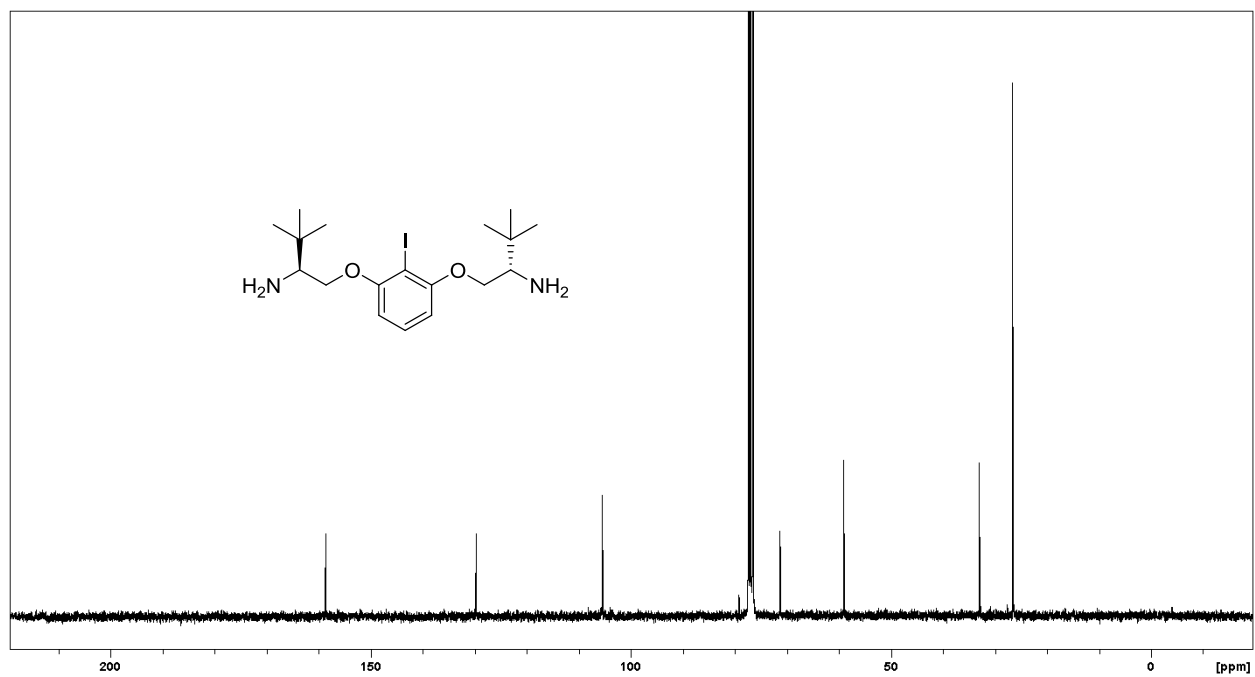
¹H NMR spectrum of 4.49 (300 MHz, CDCl₃)



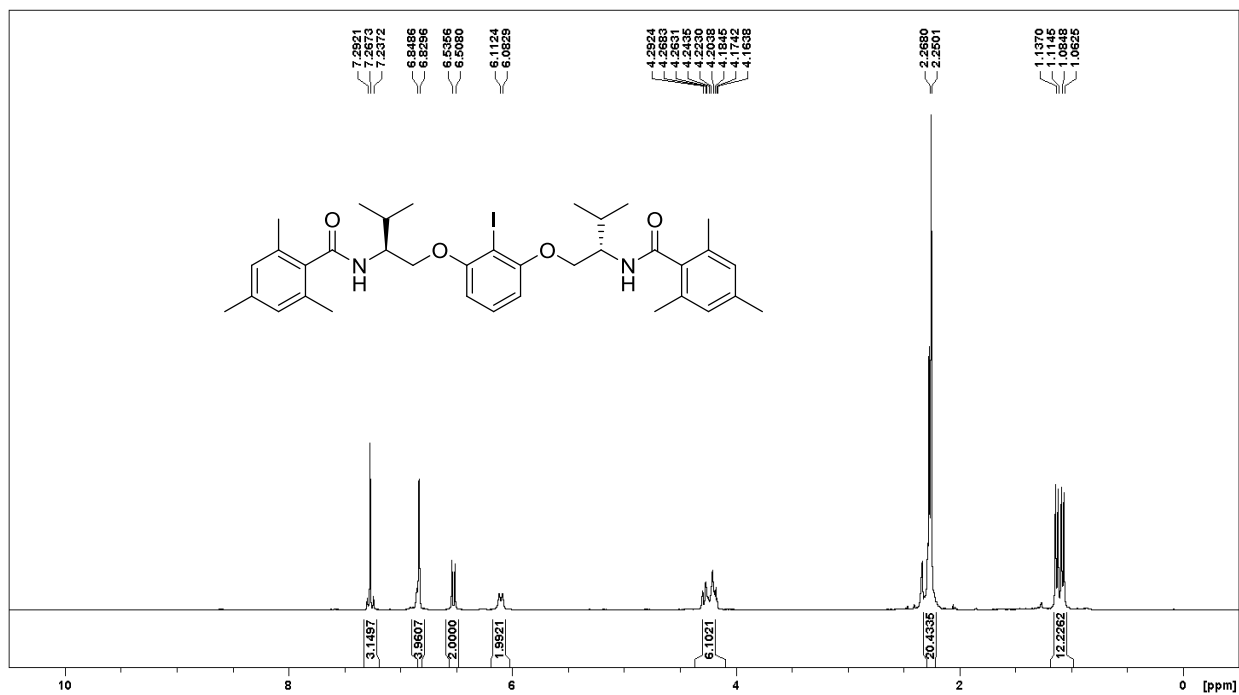
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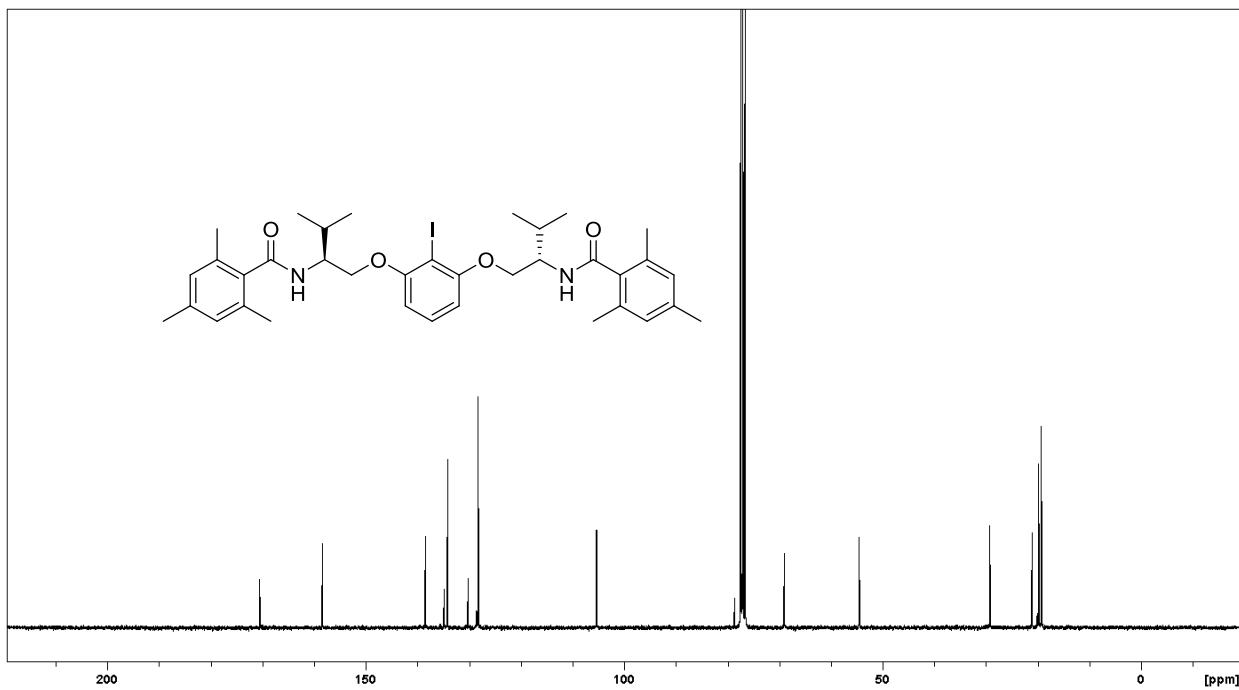
¹H NMR spectrum of 4.50 (300 MHz, CDCl₃)



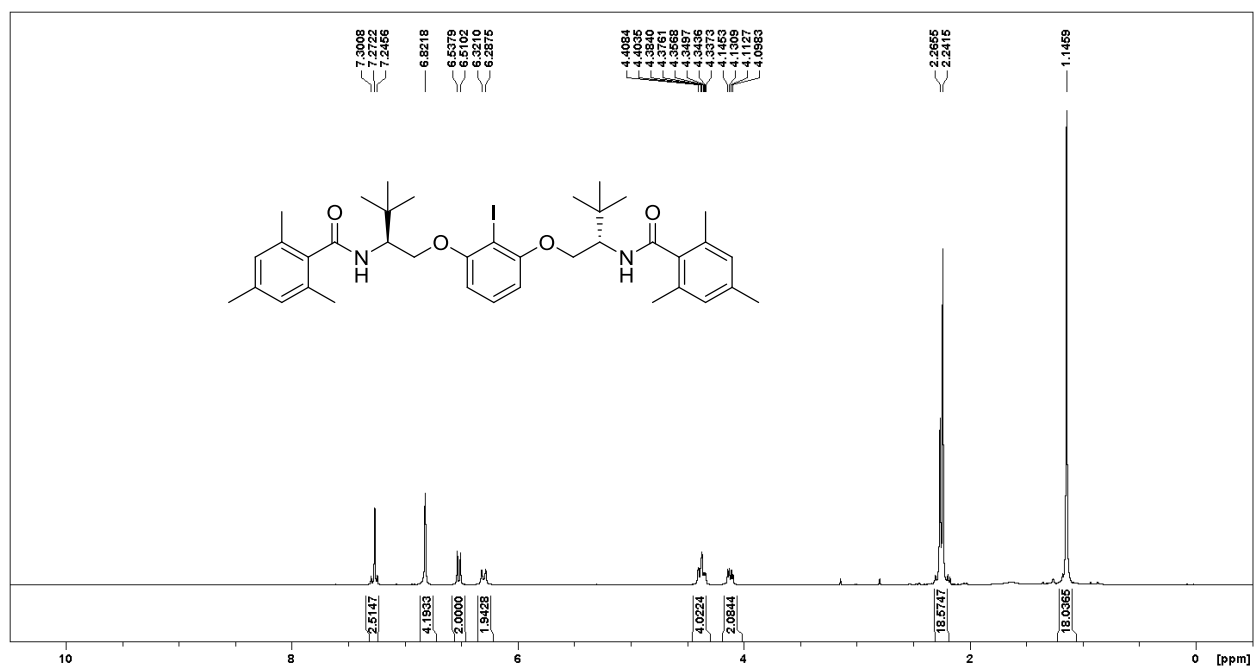
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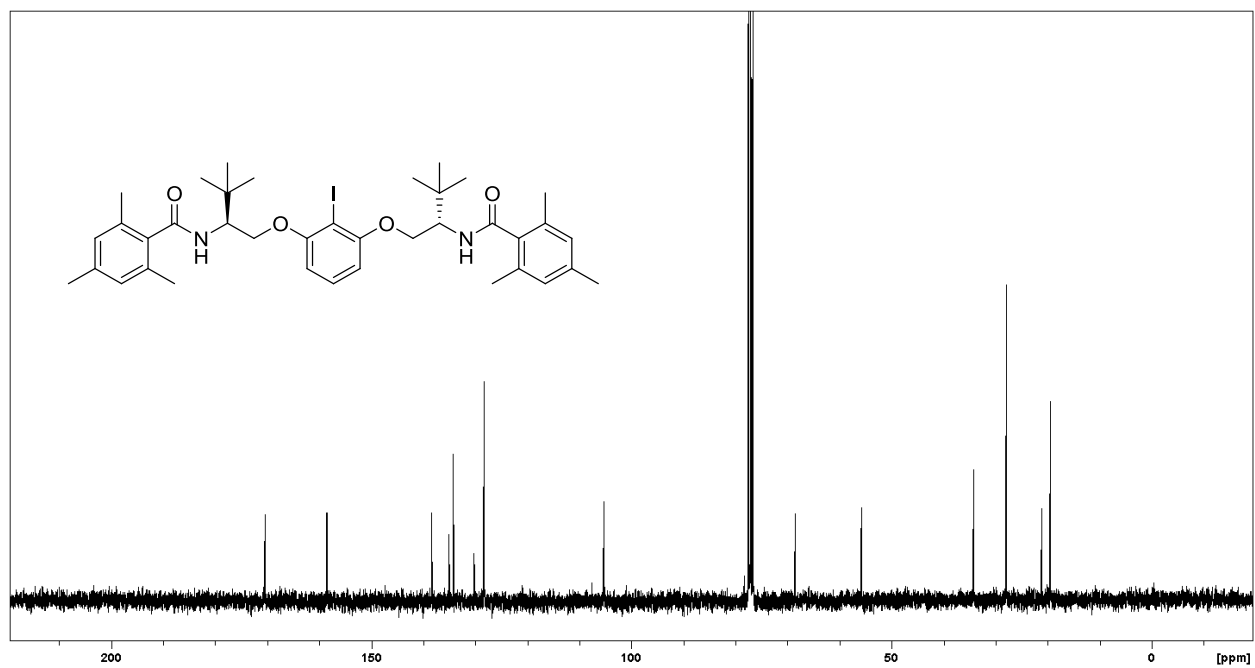
¹H NMR spectrum of 4.51 (300 MHz, CDCl₃)



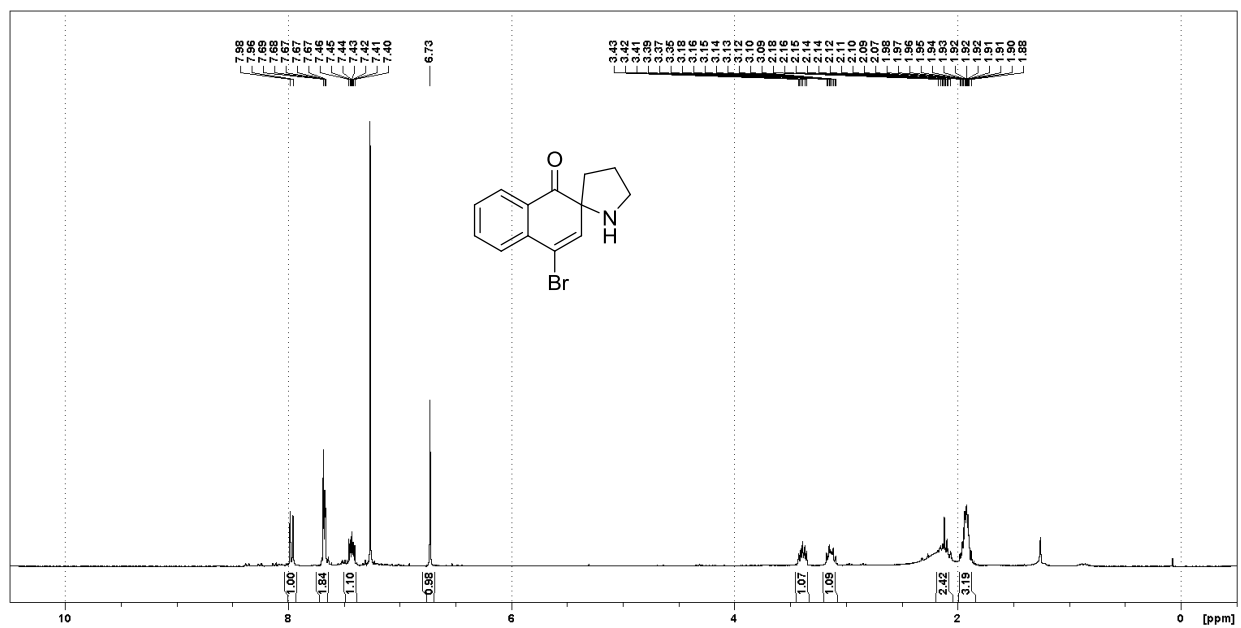
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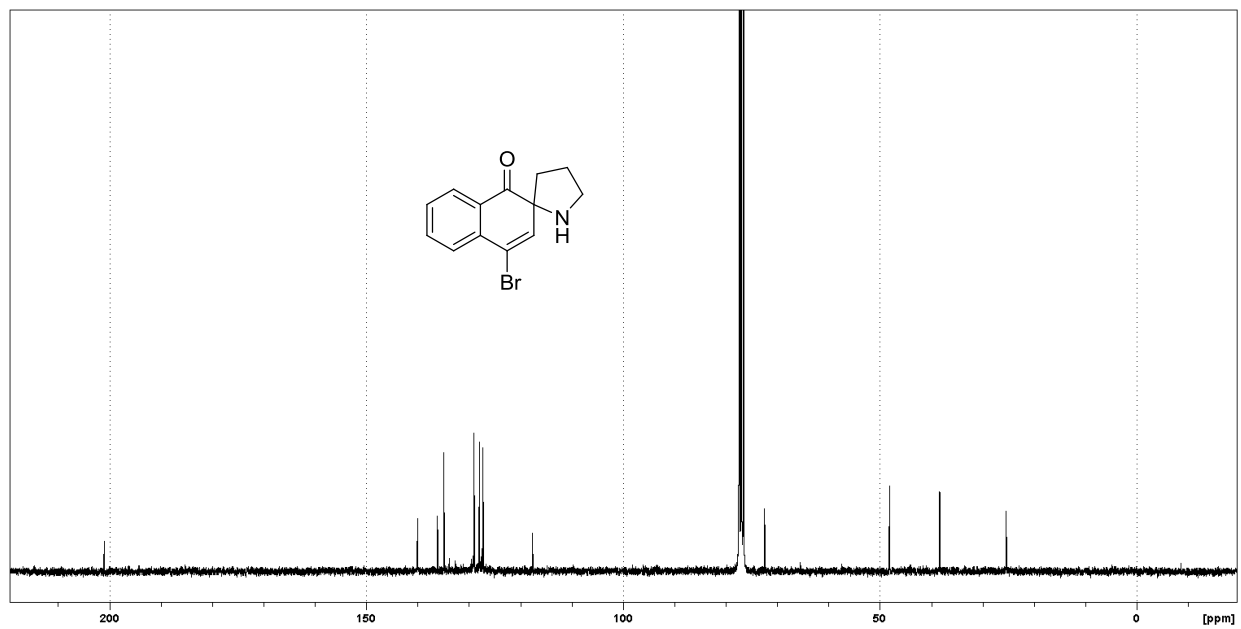
¹H NMR spectrum of 4.52 (300 MHz, CDCl₃)



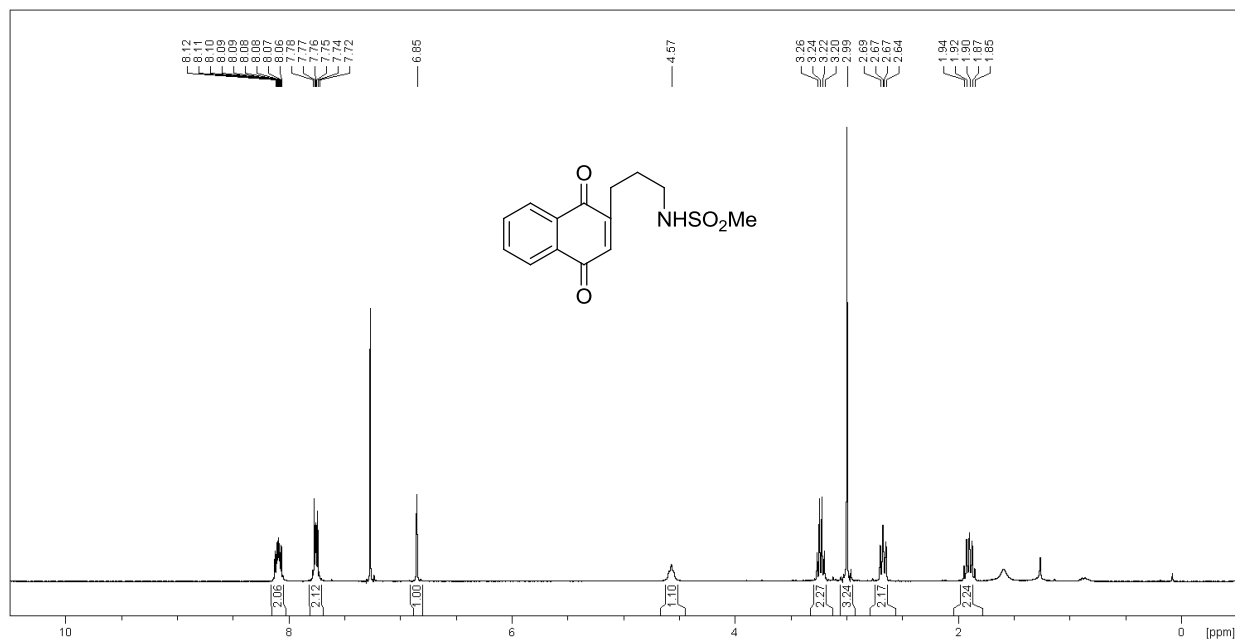
¹³C NMR spectrum of 4.52 (75 MHz, CDCl₃)



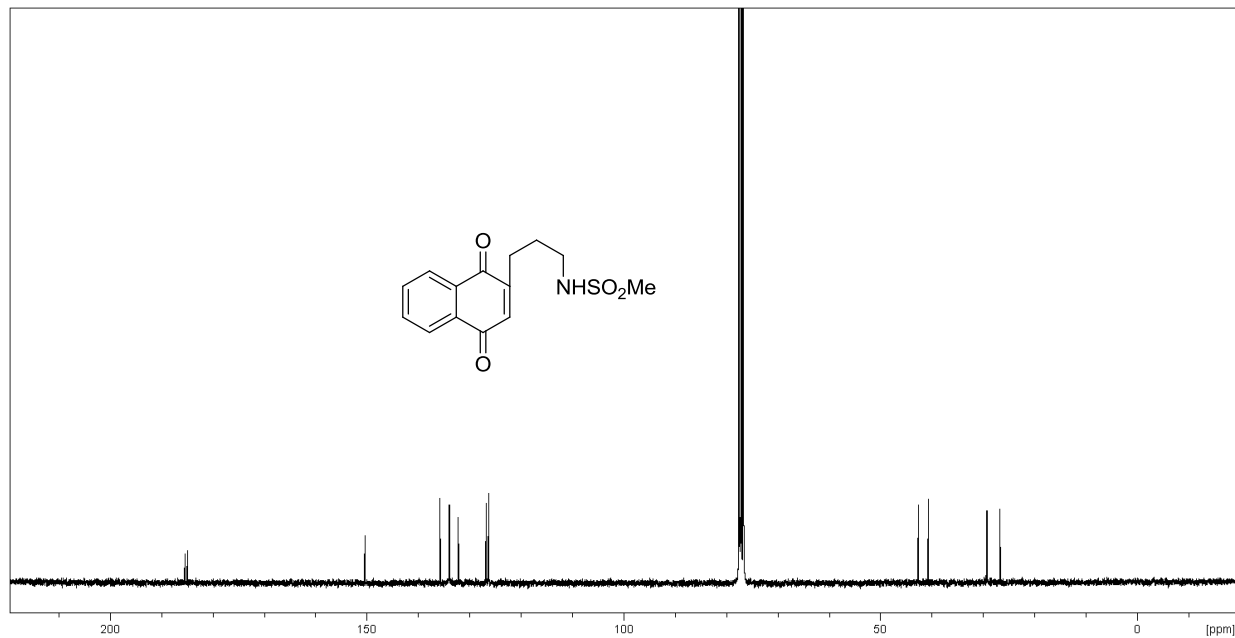
¹H NMR spectrum of 4.61 (300 MHz, CDCl₃)



¹³C NMR spectrum of 4.61 (75 MHz, CDCl₃)



¹H NMR spectrum of 4.3 (300 MHz, CDCl₃)



¹³C NMR spectrum of 4.3 (75 MHz, CDCl₃)

D. Asymmetric oxidative cycloetherification experimental section

D.1 Representative protocols for cycloetherification of naphtholic alcohols at *ortho*-position

A solution of MCPBA (123 mg, 550 μmol , 1.3 equiv) in CH_2Cl_2 (10.0 mL) was added to solution of alcohol **5.1** (0.42 mmol, 1.0 equiv) and iodobenzene (0.42 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) at RT. The mixture was stirred for 4 to 6 hours at RT, whereupon TLC indicated complete reaction. The mixture was quenched with aq. sat. NaHCO_3 (10.0 mL) and aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5.0 mL) and extracted with CH_2Cl_2 (4 \times 15 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography with an appropriate eluent to afford spiroethers. Spiroethers **5.2b - 5.2p** were prepared by this method.

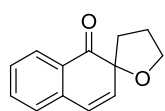
D.2 Representative protocols for cycloetherification of naphtholic alcohols at *ortho*-position using PIFA

A solution of **5.1** (100 mg, 0.36 mmol, 1.0 equiv) in CH_2Cl_2 (12.0 mL) was slowly added at RT over a period of 2 minutes to a solution containing PIFA (170 mg, 0.4 mmol, 1.1 equiv) in CH_2Cl_2 (8.0 mL) so that the final concentration is 0.02 M. The reaction was stirred for 1 to 2 hours, after which time TLC showed that the reaction was complete. The mixture was evaporated to dryness. The residue was purified by flash column chromatography to afford spiroethers. Spiroethers **5.2q - 5.2w** were prepared by this method.

D.3 Characterization of various spiroethers

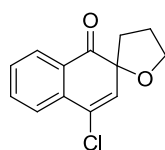
D.3.1 Characterization of (\pm)-4,5-Dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one

(5.2l)



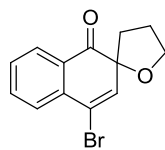
35 mg (35% yield) from 100 mg of **5.1l**, colorless oil, eluent: 1:19 EtOAc/hexanes; **IR**: 1686. **¹H**: 7.97 (d, 1H, *J* = 9.0), 7.55 (td, 1H, *J* = 7.5, 3.0), 7.33 (t, 1H, *J* = 7.5), 7.19 (d, 1H, *J* = 9.0), 6.51 (d, 1H, *J* = 12.0), 6.17 (d, 1H, *J* = 12.0), 4.36-4.29 (m, 1H), 4.19-4.12 (m, 1H), 2.32-2.17 (m, 2H), 2.11-1.97 (m, 2H). **¹³C**: 201.7, 137.4, 136.5, 134.6, 128.9, 128.0, 127.2 (2C), 125.7, 84.1, 70.6, 36.5, 25.2. **HRMS**: calcd for C₁₃H₁₂O₂Na [M+Na]⁺: 223.0735; found: 223.0736.

D.3.2 Characterization of (\pm)-4'-Chloro-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2a)



40 mg (40% yield) from 100 mg of **5.1a**, colorless oil, eluent: 1:19 EtOAc/hexanes; **IR**: 1690. **¹H**: 8.03 (d, 1H, *J* = 9.0), 7.74-7.66 (m, 2H), 7.49-7.43 (m, 1H), 6.37 (s, 1H), 4.33-4.26 (m, 1H), 4.20-4.13 (m, 1H), 2.33-2.21 (m, 2H), 2.14-1.98 (m, 2H). **¹³C**: 199.5, 135.0, 134.8, 133.3, 129.3, 129.1, 128.8, 127.5, 125.5, 84.6, 70.6, 36.6, 25.4. **HRMS**: calcd for C₁₃H₁₀O₂Cl [M+H]⁺: 233.0369; found: 233.0364.

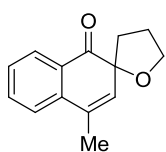
D.3.3 Characterization of (\pm)-4'-Bromo-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2b)



32 mg (32% yield) from 100 mg of **5.1b**, colorless oil, eluent: 1:19 EtOAc/hexanes; **IR**: 1692. **¹H**: 7.99 (d, 1H, *J* = 9.0), 7.70-7.63 (m, 2H), 7.46-7.40 (m, 1H), 6.63 (s, 1H), 4.32-4.25 (m, 1H), 4.19-4.12 (m, 1H), 2.31-2.18 (m, 2H),

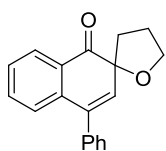
2.15-1.93 (m, 2H). ^{13}C : 199.5, 137.7, 135.6, 134.8, 129.2, 128.9, 128.1, 127.3, 119.7, 85.4, 70.6, 36.4, 25.3. **HRMS**: calcd for $\text{C}_{13}\text{H}_{11}\text{O}_2^{79}\text{BrNa} [\text{M}+\text{Na}]^+$: 300.9840; found: 300.9844.

D.3.4 Characterization of (\pm)-4'-Methyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2c)



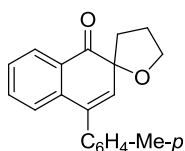
26 mg (26% yield) 100 mg of **5.1c**, colorless oil, eluent: 1:19 EtOAc/hexanes; **IR**: 1688. ^1H : 7.99 (d, 1H, $J = 6.0$), 7.61 (app t, 1H, $J = 8.0$), 7.39-7.32 (m, 2H), 5.99 (s, 1H), 4.32-4.25 (m, 1H), 4.18-4.11 (m, 1H), 2.27-2.18 (m, 2H), 2.14 (s, 3H), 2.10-1.98 (m, 1H), 1.94-1.82 (m, 1H). ^{13}C : 201.9, 138.4, 134.5, 133.1, 130.5, 128.9, 127.8, 127.3, 124.2, 83.9, 70.3, 36.3, 25.4, 19.2. **HRMS**: calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2 [\text{M}+\text{H}]^+$: 215.1072; found: 215.1077.

D.3.5 Characterization of (\pm)-4'-Phenyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2d)



41.5 mg (42% yield) of (\pm)-**7g** from 100 mg of **6g**, white solid, m.p. 91-93 °C, eluent: 3:47 EtOAc/hexanes; **IR**: 1689. ^1H : 8.05 (dd, 1H, $J = 9.0, 3.0$), 7.51-7.34 (m, 7H), 7.10 (d, 1H, $J = 6.0$), 6.12 (s, 1H), 4.37-4.30 (m, 1H), 4.20-4.13 (m, 1H), 2.38-2.22 (m, 2H), 2.17-1.97 (m, 2H). ^{13}C : 201.6, 138.6, 137.8, 137.5, 135.1, 134.3, 129.2, 128.9, 128.5, 128.1, 127.9, 127.5, 126.7, 84.4, 70.5, 36.6, 25.4. **EI**: calcd for $\text{C}_{19}\text{H}_{16}\text{O}_2$: 276.1150; found: 276.1152.

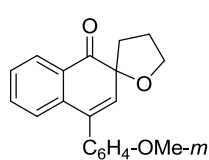
D.3.6 Characterization of (\pm)-4'-*p*-Tolyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2e)



41.8 mg (42% yield) from 100 mg of **5.1e**, white solid, m.p. 135-137 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1688. ^1H : 8.04 (d, 1H, $J = 9.0$), 7.48 (app t, 1H, $J =$

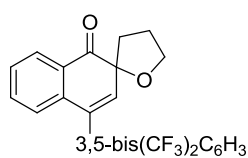
7.5), 7.35 (app t, 1H, $J = 6.0$), 7.24 (br s, 4H), 7.13 (d, 1H, $J = 9.0$), 6.09 (s, 1H), 4.36-4.29 (m, 1H), 4.20-4.13 (m, 1H), 2.42 (s, 3H), 2.37-2.16 (m, 2H), 2.13-1.96 (m, 2H). ^{13}C : 201.7, 137.9, 137.6, 137.4, 135.7, 134.8, 134.3, 129.2, 129.1, 128.8, 128.0, 127.5, 126.7, 84.4, 70.5, 36.6, 25.4, 21.3. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$: 291.1385; found: 291.1393.

D.3.7 Characterization of (\pm)-4'-(3-Methoxyphenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2f)



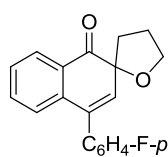
41.6 mg (42% yield) from 100 mg of **5.1f**, colorless oil, eluent: 2:23 EtOAc/hexanes; **IR**: 1702. ^1H : 8.04 (d, 1H, $J = 9.0$), 7.51-7.46 (m, 1H), 7.38-7.32 (m, 2H), 7.13 (d, 1H, $J = 6.0$), 6.95-6.89 (m, 3H), 6.12 (s, 1H), 4.36-4.29 (m, 1H), 4.20-4.13 (m, 1H), 3.84 (s, 3H), 2.37-2.21 (m, 2H), 2.11-1.96 (m, 2H). ^{13}C : 201.5, 159.6, 140.0, 137.7, 137.4, 134.9, 134.3, 129.5, 129.2, 128.1, 127.5, 126.7, 121.3, 114.5, 113.4, 84.3, 70.5, 55.3, 36.6, 25.4. **HRMS**: calcd for $\text{C}_{20}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 307.1334; found: 307.1336.

D.3.8 Characterization of (\pm)-4'-(3,5-Bis(trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2g)



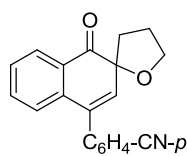
33.9 mg (34% yield) from 100 mg of **5.1g**, colorless oil, eluent: 1:19 EtOAc/hexanes. **IR**: 1695. ^1H : 8.09 (d, 1H, $J = 6.0$), 7.93 (s, 1H), 7.83 (s, 2H), 7.55 (app t, 1H, $J = 7.5$), 7.44 (app t, 1H, $J = 7.5$), 6.92 (d, 1H, $J = 9.0$), 6.20 (s, 1H), 4.39-4.32 (m, 1H), 4.22-4.15 (m, 1H), 2.42-2.24 (m, 2H), 2.15-2.00 (m, 2H). ^{13}C : 200.6, 140.7, 137.3, 136.3, 135.3, 134.7, 132.1 (q, $J = 33.2$), 129.2 (br s), 129.1, 128.9, 128.1, 125.8, 123.2 (q, $J = 273.3$), 122.0-121.8 (m), 84.2, 70.7, 36.6, 25.3. **HRMS**: calcd for $\text{C}_{21}\text{H}_{14}\text{O}_2\text{F}_6$: 412.0898; found: 412.0901.

D.3.9 Characterization of (±)-4'-(4-Fluorophenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2h)



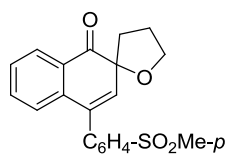
44.8 mg (45% yield) from 100 mg of **5.1h**, white solid, m.p.: 96-98 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1690. **¹H**: 8.04 (d, 1H, *J* = 6.0), 7.53-7.47 (m, 1H), 7.39-7.30 (m, 3H), 7.15-7.04 (m, 3H), 6.10 (s, 1H), 4.36-4.29 (m, 1H), 4.20-4.13 (m, 1H), 2.38-2.19 (m, 2H), 2.11-2.04 (m, 2H). **¹³C**: 201.4, 162.5 (d, *J* = 246.9), 137.6, 136.6, 135.4, 134.5 (d, *J* = 3.8), 134.4, 130.6 (d, *J* = 8.3), 129.2, 128.2, 127.6, 126.5, 115.4 (d, *J* = 21.9), 84.4, 70.5, 36.6, 25.3. **HRMS**: calcd for C₁₉H₁₅O₂F: 294.1056; found: 294.1055.

D.3.10 Characterization of (±)-4-(1'-Oxo-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalene]-4'-yl)benzo-nitrile (5.2i)



57.6 mg (58% yield) from 100 mg of **5.1i**, light yellow oil, eluent: 2:23 EtOAc/hexanes; **IR**: 2229, 1691. **¹H**: 8.06 (d, 1H, *J* = 6.0), 7.74 (d, 2H, *J* = 6.0), 7.54-7.47 (m, 3H), 7.43-7.38 (m, 1H), 6.98 (d, 1H, *J* = 9.0), 6.15 (s, 1H), 4.37-4.30 (m, 1H), 4.21-4.14 (m, 1H), 2.39-2.21 (m, 2H), 2.12-1.97 (m, 2H). **¹³C**: 200.9, 143.4, 136.6, 136.4, 136.3, 134.5, 132.4, 129.9, 129.7, 129.6, 129.2, 128.7, 127.9, 126.1, 118.6, 111.9, 84.3, 70.7, 36.6, 25.3. **HRMS**: calcd for C₂₀H₁₅O₂N: 301.1103; found: 301.1101.

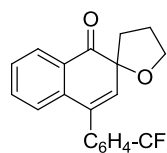
D.3.11 Characterization of (±)-4'-(4-(Methylsulfonyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2j)



53.6 mg (54% yield) from 100 mg of **5.1j**, white solid, m.p. 74-76 °C, eluent: 1:4 to 2:3 EtOAc/hexanes; **IR**: 1691. **¹H**: 8.07-8.01 (m, 3H), 7.58 (d, 2H, *J* = 9.0), 7.54-7.38 (m, 2H), 6.99 (d, 1H, *J* = 9.0), 6.16 (s, 1H), 4.37-4.30 (m,

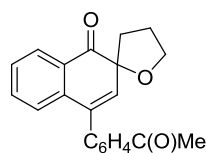
1H), 4.21-4.14 (m, 1H), 3.13 (s, 3H), 2.40-2.22 (m, 2H), 2.19-2.04 (m, 2H). ¹³C: 200.9, 144.4, 140.1, 136.6 (2C), 136.2, 134.5, 129.9, 129.2, 128.7, 127.9, 127.7, 126.2, 84.3, 70.7, 44.5, 36.6, 25.3. **HRMS**: calcd for C₂₀H₁₉O₄S [M+H]⁺: 355.1004; found: 355.0996.

D.3.12 Characterization of (±)-4'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2k)



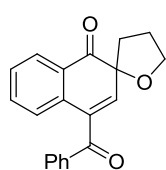
31.5 mg (32% yield) from 100 mg of **5.1k**, white solid, m.p. 155-157 °C, eluent: 1:19 EtOAc/hexanes. **IR**: 1691. ¹H: 8.06 (d, 1H, *J* = 6.0), 7.71 (d, 2H, *J* = 9.0), 7.53-7.37 (m, 4H), 7.02 (d, 1H, *J* = 9.0), 6.14 (s, 1H), 4.35-4.31 (m, 1H), 4.21-4.14 (m, 1H), 2.37-2.22 (m, 2H), 2.13-2.02 (m, 2H). ¹³C: 201.1, 142.3, 137.0, 136.5, 136.0, 134.4, 130.2 (*q*, *J* = 34.0), 129.3, 129.2, 128.5, 127.7, 126.3, 125.5 (*q*, *J* = 3.8), 124.1 (*q*, *J* = 271.8), 84.3, 70.6, 36.6, 25.3. **EI**: calcd for C₂₀H₁₆O₂F₃: 345.1100; found: 345.1101.

D.3.13 Characterization of (±)-4'-(4-Acetylphenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2r)



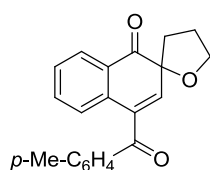
62.7 mg (63% yield) from 100 mg of **5.1r**, off white solid, m.p. 134-136 °C, eluent: 1:9 EtOAc/hexanes; **IR**: 1683. ¹H: 8.06-8.01 (m, 3H), 7.52-7.45 (m, 3H), 7.38 (app t, 1H, *J* = 7.3), 7.04 (d, 1H, *J* = 7.7), 6.15 (s, 1H), 4.37-4.30 (m, 1H), 4.21-4.14 (m, 1H), 2.66 (s, 3H), 2.40-2.21 (m, 2H), 2.19-1.98 (m, 2H). ¹³C: 201.3, 197.8, 143.5, 137.2, 136.9, 136.7, 135.9, 134.5, 129.3, 128.7, 128.5, 127.8, 126.5, 84.5, 70.7, 36.7, 26.8, 25.4. **HRMS**: calcd for C₂₁H₁₈O₃Na [M+Na]⁺: 341.1154; found: 341.1154.

D.3.14 Characterization of (\pm)-4'-Benzoyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2o)



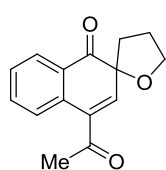
38.7 mg (39% yield) from 100 mg of **5.1o**, yellow oil, eluent: 1:19 to 1:9 EtOAc/hexanes; **IR**: 1694, 1665. **¹H**: 8.07 (d, 1H, *J* = 6.0), 7.97-7.94 (m, 2H), 7.65-7.39 (m, 6H), 6.43 (s, 1H), 4.40-4.33 (m, 1H), 4.19-4.12 (m, 1H), 2.39-2.19 (m, 2H), 2.11-1.99 (m, 2H). **¹³C**: 200.4, 195.3, 140.0, 136.7, 135.3, 134.7, 134.6, 133.8, 130.1, 129.0, 128.9, 128.7, 127.8, 126.4, 84.2, 71.0, 36.7, 25.1. **HRMS**: calcd for C₂₀H₁₆O₃Na [M+Na]⁺: 327.0997; found: 327.0997.

D.3.15 Characterization of (\pm)-4'-(4-Methylbenzoyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2p)



41 mg (41% yield) from 100 mg of **5.1p**, yellow oil, eluent: 1:19 to 1:9 EtOAc/hexanes; **IR**: 1692, 1661. **¹H**: 8.06 (d, 1H, *J* = 6.0), 7.87 (d, 2H, *J* = 9.0), 7.54 (t, 1H, *J* = 7.5), 7.43-7.37 (m, 2H), 7.28 (d, 2H, *J* = 6.0), 6.39 (s, 1H), 4.40-4.33 (m, 1H), 4.18-4.11 (m, 1H), 2.43 (s, 3H), 2.39-2.16 (m, 2H), 2.13-1.99 (m, 2H). **¹³C**: 200.5, 195.0, 144.9, 139.3, 135.5, 134.7 (2C), 134.1, 130.3, 129.4, 129.0, 128.8, 127.8, 126.4, 84.1, 71.0, 36.7, 25.1, 21.8. **HRMS**: calcd for C₂₁H₁₈O₃Na [M+Na]⁺: 341.1154; found: 341.1159.

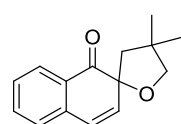
D.3.16 Characterization of (\pm)-4'-Acetyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2q)



38 mg (38% yield) from 100 mg of **5.1q**, colorless oil, eluent: 1:9 to 3:17 EtOAc/hexanes; **IR**: 1684. **¹H**: 8.00-7.96 (m, 2H), 7.61 (app t, 1H, *J* = 8.0), 7.40 (app t, 1H, *J* = 8.0), 6.89 (s, 1H), 4.41-4.35 (m, 1H), 4.24-4.17 (m, 1H), 2.52 (s, 3H), 2.34-2.13 (m, 2H), 2.09-1.94 (m, 2H). **¹³C**: 200.2, 199.2, 143.0, 135.4, 134.6, 133.5, 129.1,

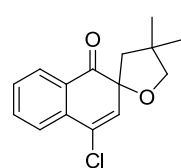
128.8, 127.6, 127.1, 84.6, 71.1, 36.6, 28.7, 25.0. **HRMS**: calcd for C₁₅H₁₄O₃Na [M+Na]⁺: 265.0841; found: 265.0848.

D.3.17 Characterization of (±)-4,4-Dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2m)



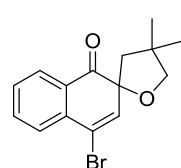
24.5 mg (25% yield) from 100 mg of **5.1m**, colorless oil, eluent: 1:19 EtOAc/hexanes; **IR**: 1687. ¹H: 7.96 (d, 1H, *J* = 9.0), 7.54 (app t, 1H, *J* = 7.5), 7.33 (app t, 1H, *J* = 7.5), 7.18 (d, 1H, *J* = 9.0), 6.47 (d, 1H, *J* = 9.0), 6.31 (d, 1H, *J* = 12.0), 4.04 (d, 1H, *J* = 9.0), 3.81 (d, 1H, *J* = 9.0), 2.24 (d, 1H, *J* = 12.0), 1.78 (d, 1H, *J* = 12.0), 1.23 (s, 3H), 1.19 (s, 3H). ¹³C: 201.9, 137.4, 137.2, 134.6, 129.0, 128.1, 127.3, 127.2, 125.2, 84.3, 81.9, 51.2, 41.1, 27.9, 25.4. **HRMS**: calcd for C₁₅H₁₇O₂ [M+H]⁺: 229.1229; found: 229.1230.

D.3.18 Characterization of (±)-4'-Chloro-4,4-dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2n)



27.5 mg (28% yield) from 100 mg of **5.1n**, colorless oil, eluent: 3:97 EtOAc/hexanes; **IR**: 1694. ¹H: 8.00 (d, 1H, *J* = 9.0), 7.71-7.63 (m, 2H), 7.47-7.42 (m, 1H), 6.48 (s, 1H), 3.98 (d, 1H, *J* = 9.0), 3.79 (d, 1H, *J* = 6.0), 2.26 (d, 1H, *J* = 12.0), 1.83 (d, 1H, *J* = 12.0), 1.24 (s, 3H), 1.20 (s, 3H). ¹³C: 199.4, 134.9, 134.7, 133.8, 129.3, 129.0, 128.9, 127.5, 125.4, 84.7, 81.8, 50.8, 41.2, 27.8, 25.3. **HRMS**: calcd for C₁₅H₁₅O₂ClNa [M+Na]⁺: 285.0658; found: 285.0659.

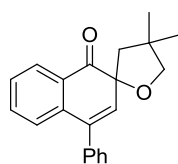
D.3.19 Characterization of (±)-4'-Bromo-4,4-dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2u)



33.4 mg (34% yield) from 100 mg of **5.1u**, light yellow oil, eluent: 1:19 EtOAc/hexanes; **IR**: 1693. ¹H: 7.96 (d, 1H, *J* = 7.6), 7.66-7.62 (m, 2H), 7.43

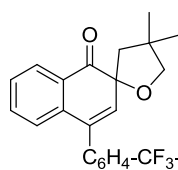
(ddd, 1H, $J = 7.8, 5.0, 3.4$), 6.75 (s, 1H), 3.97 (d, 1H, $J = 8.3$), 3.79 (d, 1H, $J = 8.3$), 2.24 (d, 1H, $J = 13.0$), 1.84 (d, 1H, $J = 13.0$), 1.23 (s, 3H), 1.19 (s, 3H). ^{13}C : 199.6, 138.4, 135.7, 134.9, 129.5, 129.2, 128.2, 127.6, 119.8, 85.9, 82.0, 50.8, 41.2, 27.9, 25.5. **HRMS**: calcd for $\text{C}_{15}\text{H}_{15}\text{O}_2^{79}\text{BrNa}$ $[\text{M}+\text{Na}]^+$: 329.0153; found: 329.0144.

D.3.20 Characterization of (\pm)-4,4-Dimethyl-4'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2v)



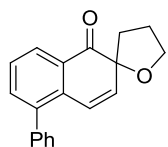
75.2 mg (76% yield) from 100 mg of **5.1v**, white solid, m.p.: 113-115 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1692. ^1H : 8.02 (d, 1H, $J = 7.2$), 7.50-7.33 (m, 7H), 7.08 (d, 1H, $J = 7.7$), 6.25 (s, 1H), 4.02 (d, 1H, $J = 8.3$), 3.82 (d, 1H, $J = 8.2$), 2.33 (d, 1H, $J = 12.8$), 1.88 (d, 1H, $J = 12.8$), 1.24 (s, 3H), 1.21 (s, 3H). ^{13}C : 201.7, 138.7, 137.9, 137.1, 135.8, 134.3, 129.6, 129.0, 128.6, 128.2, 128.0, 127.7, 126.8, 84.8, 82.0, 51.5, 41.2, 28.0, 25.6. **HRMS**: calcd for $\text{C}_{21}\text{H}_{20}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 327.1361; found: 327.1369.

D.3.21 Characterization of (\pm)-4,4-Dimethyl-4'-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2w)



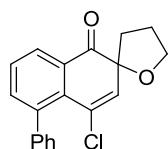
74.8 mg (75% yield) from 100 mg of **5.1w**, white solid, m.p.: 123-125 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1694. ^1H : 8.04 (d, 1H, $J = 6.7$), 7.70 (d, 2H, $J = 8.1$), 7.52-7.47 (m, 3H), 7.41-7.36 (m, 1H), 7.00 (d, 1H, $J = 7.7$), 6.27 (s, 1H), 4.02 (d, 1H, $J = 8.3$), 3.83 (d, 1H, $J = 8.3$), 2.33 (d, 1H, $J = 12.8$), 1.88 (d, 1H, $J = 12.8$), 1.24 (s, 3H), 1.21 (s, 3H). ^{13}C : 201.2, 142.5, 137.1, 136.8, 136.2, 134.5, 130.3 (q, $J = 32.7$), 129.5, 129.4, 128.6, 127.9, 126.4, 125.7 (q, $J = 3.7$), 124.2 (q, $J = 272.1$), 84.7, 82.1, 51.5, 41.3, 28.0, 25.5. **HRMS**: calcd for $\text{C}_{22}\text{H}_{19}\text{F}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 395.1235; found: 395.1231.

D.3.22 Characterization of (\pm)-5'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2s)



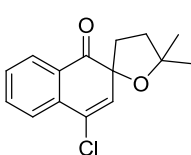
24.1 mg (48% yield) from 50 mg of **5.1s**, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 1689. **¹H**: 8.01 (d, 1H, $J = 9.0$), 7.53-7.33 (m, 7H), 6.57 (d, 1H, $J = 9.0$), 6.12 (d, 1H, $J = 9.0$), 4.36-4.30 (m, 1H), 4.19-4.12 (m, 1H), 2.35-2.18 (m, 2H), 2.13-1.88 (m, 2H). **¹³C**: 202.2, 140.4, 139.4, 136.2 (2C), 134.5, 129.8, 129.5, 128.5, 127.8, 127.7, 126.7, 123.6, 84.1, 70.7, 36.6, 25.4. **HRMS**: calcd for C₁₉H₁₆O₂Na [M+Na]⁺: 299.1048; found: 299.1049.

D.3.23 Characterization of (\pm)-4'-chloro-5'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2t)



8 mg (40% yield) from 20 mg of **5.1t**, light yellow oil; eluent: 1:19 EtOAc/hexane; **IR**: 1702. **¹H**: 7.98 (d, 1H, $J = 9.0$), 7.55 (d, 1H, $J = 9.0$), 7.47-7.32 (m, 6H), 6.39 (s, 1H), 4.28-4.21 (m, 1H), 4.18-4.11 (m, 1H), 2.40-2.29 (m, 1H), 2.19-2.02 (m, 3H). **¹³C**: 199.7, 141.3, 140.8, 138.3, 135.4, 132.7, 130.0, 128.8, 128.5, 127.7, 126.9, 86.0, 70.5, 36.7, 25.5. **HRMS**: calcd for C₁₉H₁₅O₂ClNa [M+Na]⁺: 333.0658; found: 333.0656.

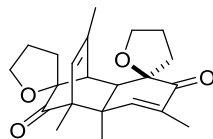
D.3.24 Characterization of (\pm)-4'-chloro-5,5-dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2x)



20 mg (67% yield) from 30 mg of **5.1x**, colorless oil, eluent: 1:19 EtOAc/hexane; **IR**: 1697. **¹H**: 8.01 (d, 1H, $J = 9.0$), 7.70-7.63 (m, 2H), 7.46-7.41 (m, 1H), 6.36 (s, 1H), 2.35-2.25 (m, 1H), 2.19-2.09 (m, 2H), 1.94-1.82 (m,

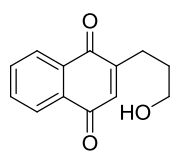
1H), 1.52 (s, 3H), 1.37 (s, 3H). ^{13}C : 199.2, 135.1, 134.8, 129.3, 129.1, 128.6, 127.7, 125.5, 85.7, 85.2, 37.2, 36.8, 29.3, 28.2. **HRMS**: calcd for $\text{C}_{15}\text{H}_{15}\text{O}_2\text{ClNa}$ $[\text{M}+\text{Na}]^+$: 285.0658; found: 285.0653.

D.4 Preparation of cycloadduct (\pm)-5.5



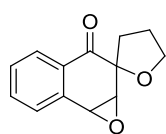
A solution of **5.3** (50 mg, 0.28 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) was slowly added at RT over a period of 2 minutes to a solution containing PIFA (131 mg, 0.31 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) so that the final concentration is 0.03 M. The reaction was stirred for 3.5 hours at RT, after which time TLC showed that the reaction was complete. The mixture was evaporated to dryness. The residue was purified by flash column chromatography (eluent: 3:17 to 1:3 EtOAc/hexane) to afford 12.3 mg (25% yield) of **5.5** as white solid, m.p.: 186-188 °C. **IR**: 1724, 1694. ^1H : 5.94 (s, 1H), 5.04 (app t, 1H, $J = 3.0$), 4.09-3.92 (m, 4H), 2.93 (app t, 1H, $J = 3.0$), 2.55 (d, 1H, $J = 3.0$), 2.16-2.04 (m, 1H), 1.99-1.83 (m, 6H), 1.80 (d, 3H, $J = 3.0$), 1.78 (d, 3H, $J = 3.0$), 1.68-1.59 (m, 1H), 1.26 (s, 3H), 1.15 (s, 3H). ^{13}C : 213.1, 199.8, 145.1, 143.4, 135.5, 128.1, 85.7, 82.1, 69.6, 68.5, 58.2, 49.8, 48.5, 45.5, 39.8, 34.7, 26.1, 24.9, 23.8, 21.6, 16.6, 12.5. **HRMS**: calcd for $\text{C}_{22}\text{H}_{28}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 379.1885; found: 379.1891.

D.5 Characterization of 2-(3-Hydroxypropyl)naphthalene-1,4-dione (**5.9**)



21 mg (20 % yield) from 100 mg of **5.11**, yellow oil, eluent: 1:4 to 3:7 EtOAc/hexanes; **IR**: 3676-3145 (broad), 1661. ^1H : 8.11-8.05 (m, 2H), 7.75-7.71 (m, 2H), 6.84 (s, 1H), 3.72 (t, 2H, $J = 6.0$), 2.69 (app t, 2H, $J = 7.5$), 1.86 (p, 2H, $J = 6.0$). ^{13}C : 185.5, 185.1, 151.4, 135.3, 133.8, 133.7, 132.2, 132.1, 126.7, 126.1, 61.7, 31.2, 26.0.

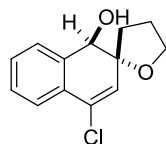
D.6 Characterization of 4,5-Dihydro-1a'H,3H-spiro[furan-2,2'-naphtho[1,2-b]oxiren]-3'(7b'H)-one (5.10)



3-5.4 mg (3-5% yield) from 100 mg of **5.11**, colorless oil, eluent: 1:9 to 1:4 EtOAc/hexanes; **IR**: 1699. **¹H**: 7.92 (d, 1H, *J* = 7.6), 7.59-7.58 (m, 2H), 7.52-7.42 (m, 1H), 4.43-4.33 (m, 1H), 4.24-4.17 (m, 1H), 4.09 (d, 1H, *J* = 4.1), 3.78 (d, 1H, *J* = 4.1), 2.10-1.93 (m, 3H), 1.90-1.83 (m, 1H). **¹³C**: 197.1, 138.3, 133.6, 132.1, 129.7, 129.6, 128.5, 85.9, 71.1, 57.7, 53.0, 33.7, 25.3. **HRMS**: calcd for C₁₃H₁₂O₃Na [M+Na]⁺: 239.0684; found: 239.0684.

D.7 Synthesis of *p*-bromobenzoate esters of spiroether 5.2a and 5.2k

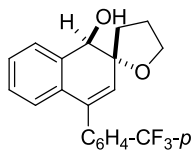
D.7.1 Preparation of (±)-4'-Chloro-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-ol (5.13)



A solution of (±)-**5.2a** (110 mg, 0.5 mmol, 1.0 equiv) in dry Et₂O (4.0 mL) was added over 10 minutes to a cold (0 °C) solution of lithium aluminium hydride (21 mg, 0.55 mmol, 1.1 equiv) in Et₂O (2.0 mL) and the mixture was stirred at 0 °C for 2 h after which time TLC showed that the reaction was complete. The reaction mixture was diluted with Et₂O (6.0 mL) and then H₂O (20 μL) was added dropwise at 0 °C. 15% aq. NaOH (20 μL) was then added followed by the addition of H₂O (60 μL). The reaction mixture was warmed to RT and stirred for 15 minutes and then filtered through a pad of Celite,[®] which was washed with more Et₂O (3×5 mL). The filtrate was dried (Na₂SO₄) and evaporated under reduced pressure to provide the crude product (d.r. = 6.9:1; ¹H NMR). The residue was purified by flash column chromatography (eluent: 1:9 EtOAc/hexanes) to provide 65 mg (59% yield) of diastereomerically pure (±)-**5.13** as white solid. This compound reverts to **5.1a** upon standing or upon dissolution in MeOH. Furthermore, its m.p. of 96-98 °C is identical to that of alcohol

5.1a, indicating that complete conversion to **5.1a** must have occurred upon heating. **IR**: 3651-3073 (broad). ^1H : 7.61-7.53 (m, 2H), 7.37-7.30 (m, 2H), 6.19 (s, 1H), 5.06 (d, 1H, $J = 3.5$), 4.04-3.89 (m, 2H), 2.93 (d, 1H, $J = 3.7$), 2.36 (app dt, 1H, $J = 12.8, 7.6$), 1.99-1.90 (m, 2H), 1.60 (app dt, 1H, $J = 12.8, 7.1$). ^{13}C : 136.6, 132.2, 130.6, 129.2, 129.1, 127.8, 124.9, 124.5, 87.5, 73.4, 68.9, 29.7, 26.7. **HRMS**: calcd for $\text{C}_{13}\text{H}_{12}\text{ClO}_2$ [M-H]: 235.0526; found: 235.0524.

D.7.2 Preparation of (\pm)-4'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-ol (**5.15**)



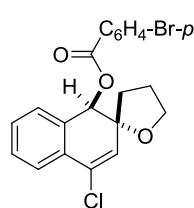
A solution of (\pm)-**5.2k** (64 mg, 0.2 mmol, 1.0 equiv) in dry THF (1.0 mL) was added over 10 minutes to a cold (0 °C) solution of lithium aluminium hydride (8.5 mg, 0.22 mmol, 1.1 equiv) in Et_2O (1.5 mL) and the mixture was stirred at 0 °C for 2 h after which time TLC showed that the reaction was complete. The reaction mixture was diluted with Et_2O (3.0 mL) and then H_2O (10 μL) was added dropwise at 0 °C. 15% aq. NaOH (10 μL) was then added followed by the addition of H_2O (30 μL). The reaction mixture was warmed to RT and stirred for 15 minutes and then filtered through a Celite[®] pad, which was washed with more EtOAc (3 \times 5 mL). The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to provide the crude product (dr = 7.7:1; ^1H NMR). The residue was purified by flash column chromatography (eluent: 1:9 EtOAc/hexanes) to provide 30 mg (47% yield) of diastereomerically pure (\pm)-**5.15** as white solid. This material was significantly more stable than **5.13** upon storage at RT, but its m.p. of 140-142 °C is very similar to that of alcohol **5.1k**, again indicating that reversal to **5.1k** may have occurred upon heating. **IR**: 3668-3171 (broad). ^1H : 7.68-7.63 (m, 3H), 7.47 (d, 2H, $J = 8.0$), 7.32 (app t, 1H, $J = 7.5$), 7.19 (app t, 1H, $J = 7.5$), 6.92 (d, 1H, $J = 7.5$), 6.08 (s, 1H), 5.20 (s, 1H), 4.09-3.94 (m, 2H), 2.56 (br s, 1H), 2.40 (app dt,

1H, $J = 12.8, 7.5$), 2.03-1.94 (m, 2H), 1.63 (app dt, 1H, $J = 12.8, 7.2$). ^{13}C : 143.1, 137.5, 137.1, 135.2, 132.7, 129.9 (q, $J = 32.5$), 129.1, 128.3, 127.4, 125.7, 125.4 (q, $J = 3.7$), 125.0, 124.3 (q, $J = 272.1$), 87.2, 73.9, 68.9, 29.6, 27.0. **HRMS**: calcd for $\text{C}_{20}\text{H}_{16}\text{O}_2\text{F}_3$ $[\text{M}-\text{H}]^-$: 345.1102; found: 345.1109.

D.7.3 General procedure for synthesis of *p*-bromobenzoate ester **5.14** and **5.16**

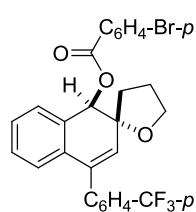
A solution of **5.13** or **5.15** (0.1 mmol, 1.0 equiv), DMAP (0.03 mmol, 0.3 equiv), 4-bromobenzoyl chloride (0.3 mmol, 3.0 equiv) in pyridine (0.2 mL) was stirred at 70 °C overnight after which time TLC showed that the reaction was complete. The mixture was acidified by the addition of 1M HCl and extracted with CH_2Cl_2 (3×5 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography to provide corresponding products.

D.7.3.1 Characterization of (±)-4'-Chloro-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalene]-1'-yl 4-bromobenzoate (**5.14**)



25 mg (71% yield) from 20 mg of (±)-**5.13**, white solid, m.p. 121-123 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1721. ^1H : 7.93 (d, 2H, $J = 8.5$), 7.70-7.59 (m, 3H), 7.40-7.29 (m, 3H), 6.36 (s, 1H), 6.18 (s, 1H), 3.97-3.84 (m, 2H), 2.35 (app dt, 1H, $J = 12.3, 7.2$), 2.06-1.97 (m, 2H), 1.94-1.85 (m, 1H). ^{13}C : 165.1, 133.0, 132.1, 131.5, 131.4, 131.1, 130.5, 129.2, 129.1, 128.8, 128.7, 127.3, 125.2, 83.9, 74.8, 68.9, 32.6, 26.2. **HRMS**: calcd for $\text{C}_{20}\text{H}_{16}\text{O}_3\text{Cl}^{79}\text{BrNa}$ $[\text{M}+\text{Na}]^+$: 440.9869; found: 440.9867.

D.7.3.2 Characterization of (±)-4'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalene]-1'-yl 4-bromobenzoate (**5.16**)

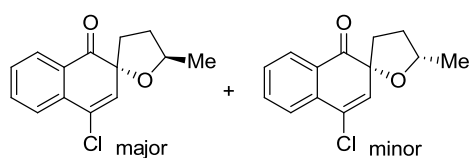


28 mg (93% yield) from 20 mg of (\pm)-**5.15**, white solid, m.p.: 181-182 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1725. **¹H**: 7.98 (d, 2H, $J = 8.4$), 7.69 (d, 2H, $J = 8.0$), 7.63 (d, 2H, $J = 8.4$), 7.53 (d, 2H, $J = 8.0$), 7.38-7.36 (m, 1H), 7.28-7.21 (m, 1H), 7.01-6.98 (m, 1H), 6.52 (s, 1H), 6.06 (s, 1H), 4.01-3.88 (m, 2H), 2.46 (app dt, 1H, $J = 12.6, 7.0$), 2.09-2.00 (m, 2H), 1.95-1.86 (m, 1H). **¹³C**: 165.3, 142.9, 138.4, 133.8, 133.6, 133.2, 132.5, 132.1, 131.4, 130.1 (q, $J = 32.5$), 129.2, 129.0, 128.6, 128.3, 126.9, 126.3, 125.5 (q, $J = 3.8$), 124.3 (q, $J = 272.1$), 83.6, 75.6, 68.9, 32.2, 26.5. **HRMS**: calcd for C₂₇H₂₀O₃F₃⁷⁹BrNa [M+Na]⁺: 551.0446; found: 551.0447.

D.8 General procedure for the synthesis of spiroethers (\pm)-**5.18**, (\pm)-**5.19**, (\pm)-**5.21** and (\pm)-**5.22**

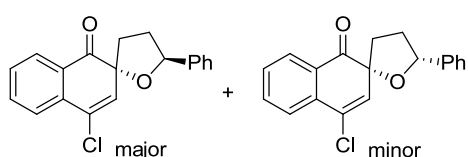
These substances were prepared by the same procedure described above for the synthesis of spiroethers (\pm)-**5.2q-5.2x**.

D.8.1 Characterization of (\pm)-4'-chloro-5-methyl-4,5-dihydro-1'*H*,3'*H*-spiro[furan-2,2'-naphthalen]-1'-one (ca. 55:45 mixture of **5.18b/5.19b**)



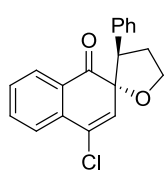
21.5 mg (43% yield) as a mixture of diastereomers (d.r. = 55:45) from 50 mg of (\pm)-**5.17b**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1693. **¹H**: 8.02 (app d, 1H, $J = 7.7$), 7.72-7.64 (m, 2H), 7.44 (app t, 1H, $J = 7.2$), 6.38-6.36 (m, 1H), 4.64-4.54 (m, 0.55H), 4.48-4.37 (m, 0.45H), 2.37-2.20 (m, 1.55H), 2.13-1.85 (m, 2H), 1.78-1.63 (m, 0.45H), 1.46 (d, 1.45H, $J = 6.6$), 1.34 (d, 1.55H, $J = 6.1$). **¹³C**: 199.8, 199.2, 135.1 (2C), 134.9, 134.8, 134.2 (2C), 129.4, 129.3, 129.1, 129.0 (2C), 128.7, 127.7, 127.6, 125.6, 125.5, 85.3, 84.6, 78.6, 78.4, 37.3, 37.0, 33.1, 32.3, 21.5, 20.7. **HRMS**: calcd for C₁₄H₁₃ClO₂Na [M+Na]⁺: 271.0502; found: 271.0500.

D.8.2 Characterization of (\pm)-4'-chloro-5-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 55:45 mixture of 5.18a/5.19a)



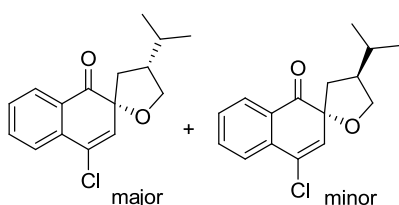
19.6 mg (39% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.17a**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1694. **^1H** : 8.07-8.05 (m, 1H), 7.75-7.66 (m, 3H), 7.50-7.29 (m, 5H), 6.52 (s, 0.55H), 6.48 (s, 0.45H), 5.51 (t, 0.55H, $J = 7.5$), 5.22 (t, 0.45H, $J = 7.5$), 2.68-2.58 (m, 0.55H), 2.49-2.31 (m, 1.9H), 2.20-1.98 (m, 1.55H). **^{13}C** : 199.5, 199.0, 142.0, 141.0, 135.1 (2C), 135.0, 134.0, 133.3, 129.7, 129.5, 129.4, 129.1, 129.0, 128.9, 128.6 (2C), 128.1, 127.8, 127.7 (2C), 126.9, 126.0, 125.7, 125.6, 85.0, 84.9, 83.9, 83.7, 37.4, 36.8, 34.3, 34.2. **HRMS**: calcd for $\text{C}_{19}\text{H}_{15}\text{ClO}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 333.0658; found: 333.0656.

D.8.3 Characterization of (\pm)-4'-chloro-3-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.18c)



20.1 mg (40% yield) as a single diastereomer from 50 mg of (\pm)-**5.17c**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1693. **^1H** : 8.03 (d, 1H, $J = 7.6$), 7.61-7.56 (m, 1H), 7.49-7.40 (m, 2H), 7.19-7.17 (m, 3H), 6.99-6.96 (m, 2H), 6.01 (s, 1H), 4.46-4.42 (m, 2H), 3.79 (app t, 1H, $J = 8.6$), 2.60-2.41 (m, 2H). **^{13}C** : 200.0, 137.4, 135.1, 134.9, 131.1, 129.6, 129.5, 129.3, 128.3, 128.2, 127.5, 127.3, 125.4, 87.9, 70.0, 55.1, 32.0. **HRMS**: calcd for $\text{C}_{19}\text{H}_{15}\text{ClO}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 333.0658; found: 333.0654.

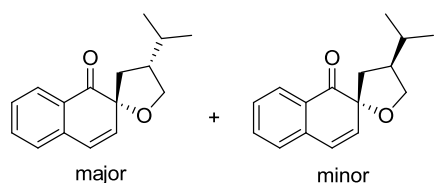
D.8.4 Characterization of (\pm)-4'-chloro-4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 3:1 mixture of 5.21a/5.22a)



24.5 mg (49% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20a**, colorless oil; eluent: 1:19 EtOAc/hexane; **IR**:

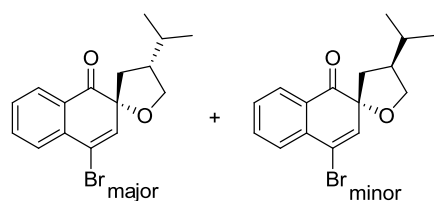
1693. ^1H : 8.04-7.99 (m, 1H), 7.72-7.64 (m, 2H), 7.48-7.43 (m, 1H), 6.42 (s, 0.75H), 6.37 (s, 0.25H), 4.42 (app t, 0.25H, $J = 7.5$), 4.26 (app t, 0.75H, $J = 7.5$), 3.86 (app t, 0.75H, $J = 9.0$), 3.76 (app t, 0.25H, $J = 7.5$), 2.43-1.99 (m, 3H), 1.70-1.49 (m, 1H), 0.95-0.88 (m, 6H). ^{13}C : 199.6, 135.1 (2C), 135.0, 134.9, 133.8, 133.7, 129.4, 129.3, 129.2, 129.0, 128.9 (2C), 127.7, 125.6, 125.5, 86.3, 84.6, 48.4, 45.3, 43.4, 40.9, 32.1, 31.5, 22.1, 22.0, 21.9, 21.7. **HRMS**: calcd for $\text{C}_{16}\text{H}_{16}\text{ClO}_2$ $[\text{M}-\text{H}]^-$: 275.0844; found: 275.0816.

D.8.5 Characterization of (\pm)-4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 3:1 mixture of 5.21b/5.22b)



8.4 mg (28% yield) as a mixture of diastereomers from 30 mg of (\pm)-**5.20b**, colourless oil, eluent: 1:19 to 1:9 EtOAc/hexane; **IR**: 1711. ^1H : 8.00-7.95 (m, 1H), 7.57-7.52 (m, 1H), 7.36-7.31 (m, 1H), 7.20-7.17 (m, 1H), 6.50-6.46 (m, 1H), 6.23 (d, 0.75H, $J = 9.9$), 6.18 (d, 0.25H, $J = 9.9$), 4.48 (app t, 0.25H, $J = 7.8$), 4.27 (app t, 0.75H, $J = 7.6$), 3.90 (dd, 0.75H, $J = 9.8$, 8.5), 3.78 (app t, 0.25H, $J = 8.5$), 2.44-1.97 (m, 3H), 1.68-1.46 (m, 1H), 0.94-0.88 (m, 6H). ^{13}C : 201.8, 137.5 (2C), 137.1, 137.0, 134.8, 134.7, 129.2, 129.1, 128.2, 128.1, 127.4 (3C), 127.3, 125.6, 125.2, 86.0, 83.9, 75.0, 74.9, 48.5, 45.2, 43.7, 40.8, 32.2, 31.6, 22.1, 22.0 (2C), 21.7. **HRMS**: calcd for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 265.1204; found: 265.1213.

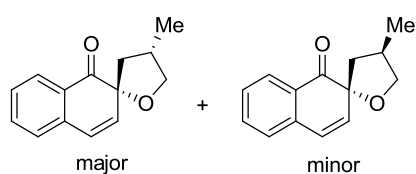
D.8.6 Characterization of (\pm)-4'-bromo-4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 4:1 mixture of 5.21c/5.22c)



22 mg (44% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20c**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1692. ^1H : 8.02-7.97 (m, 1H), 7.70-7.63 (m, 2H), 7.46-7.41 (m, 1H), 6.68 (s, 0.8H), 6.64 (s, 0.2H), 4.42 (app t, 0.2H, $J = 7.8$), 4.26 (app t, 0.8H, $J = 7.6$),

3.86 (app t, 0.8H, $J = 9.5$), 3.76 (app t, 0.2H, $J = 8.5$), 2.39-1.97 (m, 3H), 1.70-1.60 (m, 1H), 0.95-0.88 (m, 6H). ^{13}C : 199.6, 138.3, 138.2, 135.8, 135.7, 135.0 (2C), 129.5, 129.3 (2C), 128.3, 128.2, 127.6, 119.8, 87.2, 85.5, 75.1, 74.9, 48.4, 45.3, 43.3, 40.6, 32.9, 31.6, 22.0, 21.9 (2C), 21.7. **HRMS**: calcd for $\text{C}_{16}\text{H}_{17}^{79}\text{BrO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 343.0310; found: 343.0315.

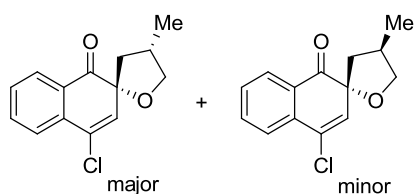
D.8.7 Characterization of (\pm)-4-methyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (ca. 7:3 mixture of 5.21d/5.22d)



5.5 g (18% yield) as a mixture of diastereomers from 30 mg of (\pm)-**5.20d**, colourless oil, eluent: 1:19 to 1:9 EtOAc/hexane;

IR: 1685. ^1H : 8.00-7.95 (m, 1H), 7.55 (app td, 1H, $J = 7.5$, 1.2), 7.34 (app t, 1H, $J = 7.2$), 7.19 (app d, 1H, $J = 7.6$), 6.50-6.46 (m, 1H), 6.24-6.18 (m, 1H), 4.41 (app t, 0.30H, $J = 7.6$), 4.24 (app t, 0.7H, $J = 7.6$), 3.79 (dd, 0.7H, $J = 10.1$, 8.2), 3.65 (app t, 0.3H, $J = 8.1$), 2.84-2.68 (m, 0.3H), 2.63-2.45 (m, 0.7H), 2.35 (dd, 0.3H, $J = 12.8$, 7.0), 2.13 (dd, 0.7H, $J = 12.4$, 7.6), 1.97 (dd, 0.7H, $J = 12.3$, 10.4), 1.60-1.52 (m, 0.3H), 1.13-1.07 (m, 3H). ^{13}C : 201.8, 137.5 (2C), 137.2, 136.9, 134.8, 134.7, 129.2, 129.1, 128.2, 128.1, 127.4 (2C), 127.3, 125.6, 125.2, 85.4, 83.9, 77.0, 46.4, 44.1, 35.3, 32.6, 16.9, 15.7. **HRMS**: calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$: 215.1072; found: 215.1067.

D.8.8 Characterization of (\pm)-4'-chloro-4-methyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (ca. 7:3 mixture of 5.21e/5.22e)

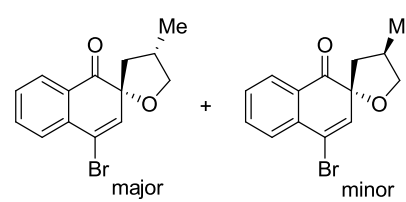


8.9 mg (45% yield) as a mixture of diastereomers from 20 mg of (\pm)-**5.20e**, colourless oil; eluent: 1:19 EtOAc/hexane; **IR**:

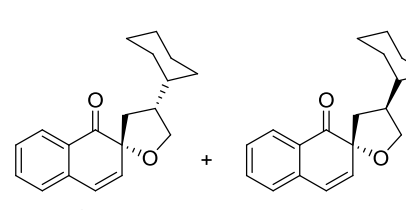
1692. ^1H : 8.04-7.99 (m, 1H), 7.72-7.64 (m, 2H), 7.48-7.43 (m, 1H), 6.40 (s, 0.7H), 6.39 (s, 0.3H), 4.38 (app t, 0.3H, $J = 7.6$), 4.23 (app t, 0.7H, $J = 7.6$), 3.74 (app t, 0.7H, $J = 9.9$), 3.65 (app t, 0.3H, $J = 8.1$), 2.80-2.61 (m, 0.3H), 2.59-2.45 (m, 0.7H), 2.37

(dd, 0.3H, $J = 12.9, 7.0$), 2.19 (dd, 0.7H, $J = 12.5, 7.5$), 1.99 (dd, 0.7H, $J = 11.5, 10.7$), 1.66-1.61 (m, 0.3H), 1.13 (d, 2.3H, $J = 6.5$), 1.09 (d, 0.7H, $J = 6.7$). ^{13}C : 199.5, 135.1 (2C), 135.0, 134.9, 133.9, 133.6, 129.4, 129.3, 129.2, 129.1, 128.9, 127.7, 125.6, 125.5, 85.8, 84.5, 77.1, 77.0, 46.0, 44.1, 35.2, 32.8, 16.8, 15.6. **HRMS**: calcd for $\text{C}_{14}\text{H}_{13}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 271.0502; found: 271.0509.

D.8.9 Characterization of (\pm)-4'-bromo-4-methyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 7:3 mixture of 5.21f/5.22f)

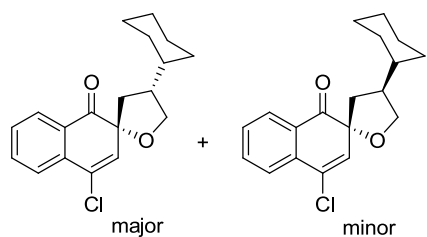

 24.2 mg (48% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20f**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1691. ^1H : 8.02-7.96 (m, 1H), 7.70-7.63 (m, 2H), 7.46-7.41 (m, 1H), 6.67-6.66 (m, 1H), 4.38 (app t, 0.3H, $J = 7.6$), 4.24 (app t, 0.7H, $J = 7.6$), 3.75 (dd, 0.7H, $J = 9.9, 8.4$), 3.64 (app t, 0.3H, $J = 8.1$), 2.78-2.66 (m, 0.3H), 2.61-2.45 (m, 0.7H), 2.37 (dd, 0.3H, $J = 12.9, 7.0$), 2.20 (dd, 0.7H, $J = 12.5, 7.5$), 1.97 (dd, 0.7H, $J = 12.3, 10.6$), 1.66-1.62 (m, 0.3H), 1.13-1.07 (m, 3H). ^{13}C : 199.6, 138.4, 138.1, 135.8, 135.7, 135.0 (2C), 129.5, 129.4, 129.3, 129.0, 128.3, 128.2, 127.6, 119.8, 119.5, 86.7, 85.4, 77.0, 46.0, 43.9, 35.2, 32.7, 16.7, 15.6. **HRMS**: calcd for $\text{C}_{14}\text{H}_{13}^{79}\text{BrO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 314.9997; found: 314.9993.

D.8.10 Characterization of (\pm)-4-cyclohexyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 3:1 mixture of 5.21g/5.22g)


 10.1 mg (20% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20g**, colourless oil, eluent: 1:19 to 1:9 EtOAc/hexane; **IR**: 1711. ^1H : 8.00-7.95 (m, 1H), 7.57-7.52 (m, 1H), 7.36-7.31 (m, 1H), 7.18 (app d, 1H, $J = 7.5$), 6.50-6.45 (m, 1H), 6.22 (d, 0.75H, $J = 9.9$), 6.17 (d, 0.25H, $J = 9.9$), 4.45 (app t, 0.25H, $J = 7.8$), 4.27

(app t, 0.75H, $J = 7.6$), 3.90 (dd, 0.75H, $J = 10.2, 8.2$), 3.78 (app t, 0.25H, $J = 8.8$), 2.47-2.38 (m, 0.25H), 2.31-1.97 (m, 2.75H), 1.75-1.59 (m, 5H), 1.38-1.13 (m, 4H), 1.08-0.89 (m, 2H). ^{13}C : 201.9, 137.5 (2C), 137.2, 137.0, 134.8, 134.7, 129.2, 129.1, 128.2, 128.1, 127.4 (3C), 127.3, 125.5, 125.2, 85.8, 83.7, 74.9, 74.8, 47.1, 43.8, 43.3, 41.9, 41.3, 40.5, 32.7, 32.6, 32.4, 32.1, 26.5, 26.4, 26.2 (2C). **HRMS**: calcd for $\text{C}_{19}\text{H}_{22}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 305.1517; found: 305.1520.

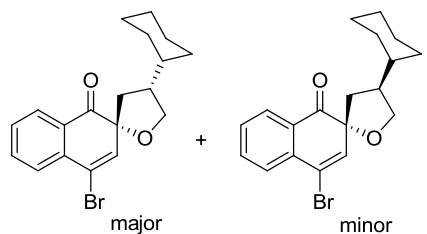
D.8.11 Characterization of (\pm)-4'-chloro-4-cyclohexyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 3:1 mixture of 5.21h/5.22h)



15.1 mg (50% yield) as a mixture of diastereomers from 30 mg of (\pm)-**5.20h**, Colourless oil; eluting solvent: 1:19 EtOAc/hexane; **IR**: 1692. ^1H : 8.04-7.99 (m, 1H), 7.72-7.64 (m, 2H), 7.48-7.42 (m, 1H), 6.40 (s, 0.75H), 6.36 (s, 0.25H),

4.42 (app t, 0.25H, $J = 7.8$), 4.27 (app t, 0.75H, $J = 7.5$), 3.86 (app t, 0.75H, $J = 8.3$), 3.77 (app t, 0.25H, $J = 8.5$), 2.46-1.99 (m, 3H), 1.75-1.61 (m, 5H), 1.37-1.13 (m, 4H), 1.68-0.92 (m, 2H). ^{13}C : 199.7, 199.6, 135.1 (2C), 135.0, 134.9, 133.9, 133.7, 129.4, 129.3, 129.2, 129.0 (2C), 128.8, 127.7, 125.6, 125.5, 86.2, 84.4, 74.9, 74.8, 47.0, 44.0, 43.0, 41.8, 41.2, 40.6, 32.7, 32.6, 32.4, 32.1, 26.4, 26.2 (2C). **HRMS**: calcd for $\text{C}_{19}\text{H}_{21}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 339.1128; found: 339.1128.

D.8.12 Characterization of (\pm)-4'-bromo-4-cyclohexyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 4:1 mixture of 5.21i/5.22i)

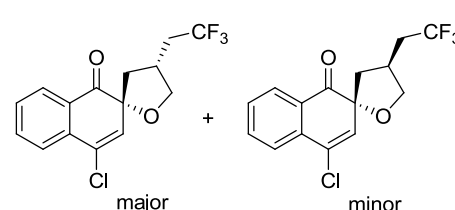


21.4 mg (43% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20i**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1692. ^1H : 8.01-7.96 (m, 1H), 7.70-7.63 (m, 2H), 7.46-7.40 (m, 1H), 6.67 (s, 0.8H), 6.63 (s, 0.2H), 4.42 (app t, 0.2H, $J =$

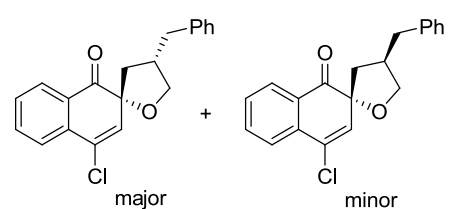
7.7), 4.27 (app t, 0.8H, $J = 7.7$), 3.86 (app t, 0.8H, $J = 9.5$), 3.77 (app t, 0.2H, $J = 8.7$), 2.44-1.97

(m, 3H), 1.74-1.59 (m, 5H), 1.37-1.13 (m, 4H), 1.08-0.92 (m, 2H). ^{13}C : 199.7, 138.4, 138.2, 135.8, 135.7, 135.0, 134.9, 129.4, 129.3 (2C), 129.0, 128.3, 128.2, 127.6, 119.7, 119.3, 87.1, 85.3, 74.9, 74.8, 47.0, 43.9, 43.0, 41.8, 41.2, 40.3, 32.7, 32.5, 32.3, 32.1, 26.4, 26.2. **HRMS**: calcd for $\text{C}_{19}\text{H}_{22}^{79}\text{BrO}_2$ $[\text{M}+\text{H}]^+$: 361.0803; found: 361.0800.

D.8.13 Characterization of (\pm)-4'-chloro-4-(2,2,2-trifluoroethyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 3:1 mixture of 5.21j/5.22j)

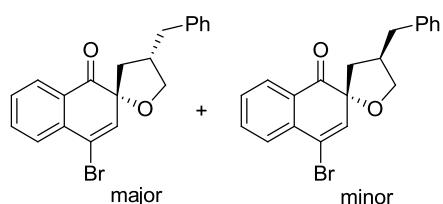
 23.1 mg (46% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20j**, light yellow oil; eluent: 1:19 EtOAc/hexane; **IR**: 1692. ^1H : 8.03 (app d, 1H, $J = 7.6$), 7.74-7.67 (m, 2H), 7.50-7.45 (m, 1H), 6.36 (s, 0.75H), 6.33 (s, 0.25H), 4.49 (app t, 0.25H, $J = 8.0$), 4.31 (app t, 0.75H, $J = 7.8$), 3.88 (app t, 0.75H, $J = 9.1$), 3.77 (app t, 0.25H, $J = 8.4$), 3.07-2.96 (m, 0.25H), 2.84-2.67 (m, 0.75H), 2.50-2.22 (m, 3H), 2.15 (dd, 0.75H, $J = 12.8, 9.6$), 1.73 (dd, 0.25H, $J = 12.9, 10.6$). ^{13}C : 198.9, 198.6, 135.3, 135.2, 134.9, 132.6, 132.2, 130.4, 130.1, 129.7, 129.6, 128.8, 127.8, 126.5 (q, $J = 277.0$), 125.8, 125.7, 85.0, 83.2, 74.5, 74.3, 42.8, 41.7, 35.9 (q, $J = 28.9$), 34.3 (q, $J = 3.1$). **HRMS**: calcd for $\text{C}_{15}\text{H}_{12}\text{ClF}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 339.0376; found: 339.0374.

D.8.14 Characterization of (\pm)-4-benzyl-4'-chloro-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 7:3 mixture of 5.21k/5.22k)

 23.8 mg (48% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20k**, light yellow oil, eluent: 1:19 to 1:9 EtOAc/hexane; **IR**: 1691. ^1H : 8.05 (d, 0.7H, $J = 9.0$), 7.97 (d, 0.3H, $J = 6.0$), 7.71-7.64 (m, 2H), 7.49-7.43 (m, 1H), 7.32-7.16 (m, 5H), 6.40 (s, 0.3H), 6.37 (s, 0.7H), 4.38 (app t, 0.3H, $J = 9.0$), 4.22 (app t, 0.7H, $J = 6.0$), 3.94 (app t, 0.7H, $J = 9.0$), 3.83

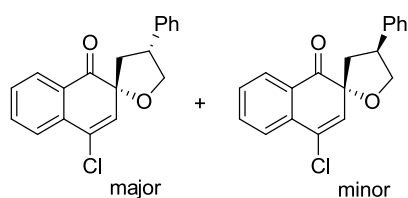
(app t, 0.3H, $J = 7.5$), 3.00-2.66 (m, 3H), 2.29 (dd, 0.3H, $J = 12.0, 6.0$), 2.12 (app d, 1.4H, $J = 6.0$), 1.75 (dd, 0.3H, $J = 15.0, 10.5$). ^{13}C : 199.4, 140.3, 140.0, 135.1, 135.0, 134.9, 133.6, 133.3, 129.5, 129.4, 129.2 (2C), 129.1, 128.7 (3C), 128.6, 127.7, 126.5, 125.6 (2C), 85.6, 84.3, 75.5, 75.3, 44.0, 42.6, 42.0, 40.0, 38.8, 38.0. **HRMS**: calcd for $\text{C}_{20}\text{H}_{17}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 347.0815; found: 347.0818.

D.8.15 Characterization of (\pm)-4-benzyl-4'-bromo-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 3:1 mixture of 5.21l/5.22l)



16.7 mg (33% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20l**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1691. ^1H : 8.02 (d, 0.75H, $J = 7.7$), 7.95 (d, 0.25H, $J = 7.7$), 7.67-7.66 (m, 2H), 7.47-7.41 (m, 1H), 7.31-7.16 (m, 5H), 6.66-6.64 (m, 1H), 4.38 (app t, 0.25H, $J = 7.7$), 4.22 (dd, 0.75H, $J = 8.1, 6.4$), 3.94 (app t, 0.75H, $J = 8.6$), 3.82 (app t, 0.25H, $J = 8.1$), 2.99-2.63 (m, 3H), 2.29 (dd, 0.25H, $J = 13.0, 7.0$), 2.13-2.10 (m, 1.75H), 3.50 (dd, 0.25H, $J = 13.1, 9.8$). ^{13}C : 199.4, 140.2, 140.0, 138.1, 137.8, 135.7, 135.1, 135.0, 129.5, 129.4, 129.2, 128.7 (2C), 128.6, 128.3, 128.2, 127.6, 126.5, 120.0, 86.6, 85.3, 75.6, 75.3, 43.9, 42.6, 41.8, 39.9, 38.8, 38.0. **HRMS**: calcd for $\text{C}_{20}\text{H}_{17}^{79}\text{BrO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 391.0310; found: 391.0301.

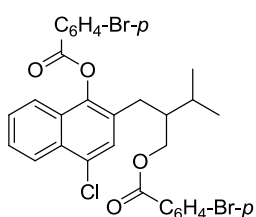
D.8.16 Characterization of (\pm)-4'-chloro-4-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (ca. 7:3 mixture of 5.21m/5.22m)



19.7 mg (39% yield) as a mixture of diastereomers from 50 mg of (\pm)-**5.20m**, light yellow oil, eluent: 1:19 EtOAc/hexane; **IR**: 1690. ^1H : 8.09-8.04 (m, 1H), 7.76-7.67 (m, 2H), 7.51-7.46 (m, 1H), 7.37-7.32 (m, 4H), 7.29-7.24 (m, 1H), 6.51 (s, 0.7H), 6.47 (s, 0.3H), 4.66 (app t, 0.3H, $J = 8.0$), 4.45 (app t, 0.7H, $J = 7.9$), 4.22 (dd, 0.7H, $J = 10.8, 8.5$), 4.10 (app t, 0.3H, $J = 8.6$), 3.98-

3.86 (m, 0.3H), 3.71-3.59 (m, 0.7H), 2.66-2.43 (m, 1.7H), 2.16 (dd, 0.3H, $J = 12.9, 10.6$). ^{13}C : 199.2, 139.9, 138.7, 135.1 (2C), 135.0, 133.2, 132.9, 129.9, 129.6, 129.5, 129.0, 128.9, 127.8 (2C), 127.5, 127.4, 127.2, 125.8, 125.7, 85.8, 83.9, 76.4, 76.3, 46.1, 45.6, 43.6, 43.5. **HRMS**: calcd for $\text{C}_{19}\text{H}_{15}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 333.0658; found: 333.0659.

D.9 Preparation of (\pm)-2-((1-(4-bromobenzoyloxy)-4-chloronaphthalen-2-yl)methyl)-3-methylbutyl 4-bromobenzoate (5.27)

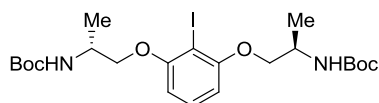


See general procedure for synthesis of *p*-bromobenzoate ester, 77 mg (84% yield) from 40 mg of (\pm)-**5.1a**, white solid, m.p.: 99-101 °C, eluent: 1:19 EtOAc/hexanes; **IR**: 1738, 1718. ^1H : 8.22 (d, 1H, $J = 6.0$), 8.10 (app d, 2H, $J = 6.0$), 7.61-7.50 (m, 8H), 7.35 (br s, 2H), 4.30 (app d, 2H, $J = 3.0$), 2.85-

2.74 (m, 2H), 2.12 (br s, 1H), 1.89-1.87 (m, 1H), 1.01 (d, 6H, $J = 6.0$). ^{13}C : 165.8, 164.3, 143.6, 132.4, 131.9, 131.6, 130.9, 130.5, 130.3, 130.0, 129.7, 128.9, 128.2, 128.1, 127.8, 127.4, 127.1, 125.0, 121.5, 66.0, 30.4, 29.2, 20.1, 19.5. **HRMS**: calcd for $\text{C}_{30}\text{H}_{25}\text{O}_4\text{Cl}^{79}\text{Br}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 664.9706; found: 664.9703.

D.10 Preparation of chiral iodoarene precatalyst 5.26

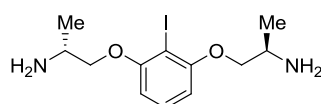
D.10.1 Preparation of *tert*-butyl (2*R*,2'*R*)-1,1'-(2-iodo-1,3-phenylene)*bis*(oxy)*bis*(propane-2,1-diyl)dicarbamate (5.24)



Neat diisopropyl azodicarboxylate (2.7 mL, 13.68 mmol, 2.5 equiv) was added dropwise to a cold (0 °C) solution of 2-iodoresorcinol (1.3 g, 5.47 mmol, 1.0 equiv), (*R*)-*N*-BOC-alaninol (2.4 g, 13.68 mmol, 2.5 equiv) and PPh_3 (3.6 g, 13.68 mmol, 2.5 equiv) in THF (30.0 mL). The mixture was then warmed to RT and stirred overnight, after which time TLC showed that the reaction was complete. The solution

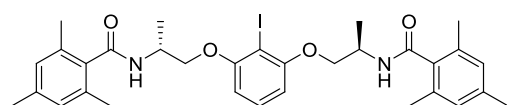
was evaporated and the residue was purified by flash column chromatography to provide 2.26 g (75% yield) of **5.24** as white solid, m.p.: 116-118 °C; eluent: 1:9 to 7:13 EtOAc/hexane, $[\alpha]_D^{24} = +90.8^\circ$ (*c* 2.96, CHCl₃). **IR**: 3442, 3238, 1693. **¹H**: 7.20 (t, 1H, *J* = 8.2), 6.45 (d, 2H, *J* = 8.3), 4.96 (br s, 2H), 4.07 (app brs, 2H), 3.99-3.98 (m, 4H), 1.44 (s, 18H), 1.37 (d, 6H, *J* = 6.7). **¹³C**: 158.5 (2C), 155.3 (2C), 130.1, 105.5 (2C), 79.5 (2C), 79.0, 72.4 (2C), 45.9 (2C), 28.5 (6C), 18.3 (2C). **HRMS**: calcd for C₂₂H₃₆N₂O₆I [M+H]⁺: 551.1618; found: 551.1614.

D.10.2 Preparation of (2*R*,2'*R*)-1,1'-(2-iodo-1,3-phenylene)bis(oxy)dipropylamine (5.25)



Trifluoroacetic acid (1.3 mL, 16.9 mmol, 5.0 equiv) was slowly added to a solution of **5.24** (1.9 g, 3.38 mmol, 1.0 equiv) in CH₂Cl₂ (5.0 mL) and the mixture was stirred overnight at RT, whereupon TLC showed that the reaction was complete. The mixture was cooled to 0 °C, quenched with 2M NaOH (15 mL) and extracted with CH₂Cl₂ (5×15 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was dried under high vacuum to provide 1.17 g (99% crude yield) of the *N*-deblocked product as pale yellow solid (m.p.: 61-64 °C) and used in the subsequent step without purification. $[\alpha]_D^{24} = -40.3^\circ$ (*c* 1.11, CHCl₃); **IR**: 3664-3034. **¹H**: 7.21 (t, 1H, *J* = 8.3), 6.46 (d, 2H, *J* = 8.3), 3.96 (dd, 2H, *J* = 8.7, 3.9), 3.71 (app t, 2H, *J* = 7.9), 3.46-3.36 (m, 2H), 1.57 (br s, 4H), 1.21 (d, 6H, *J* = 6.5). **¹³C**: 158.8 (2C), 129.9, 105.5 (2C), 79.2, 76.0 (2C), 46.5 (2C), 19.9 (2C). **HRMS**: calcd for C₁₂H₂₀N₂O₂I [M+H]⁺: 351.0570; found: 351.0572.

D.10.3 Preparation of *N,N'*-(2*R*,2'*R*)-1,1'-(2-iodo-1,3-phenylene)bis(oxy)bis(propyl)bis(2,4,6-trimethylbenzamide) (5.26)



A solution of **5.24** (1.17 g, 3.34 mmol, 1.0 equiv) in DMF (8.0 mL) was added dropwise at RT over 10 min to a solution of EDCI (1.60 g, 8.34 mmol, 2.5 equiv), HOBT (1.28 g, 8.34 mmol, 2.5 equiv) and

2,4,6-trimethylbenzoic acid (1.37 g, 8.34 mmol, 2.5 equiv) in dry DMF (7 mL) that had previously been stirred for 15 min. The mixture was stirred overnight at RT, whereupon TLC showed that the reaction was complete. The mixture was diluted with CH₂Cl₂ (35.0 mL) and the organic layer was sequentially washed with 0.1 M HCl (3×20 mL), H₂O (25.0 mL), satd. aqueous NaHCO₃ (35 mL), and brine (15 mL), then dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to provide 1.50 g (70% yield) of **5.26** as white solid, m.p.: 181-183 °C, eluent: 1:4 to 1:1 EtOAc/hexane, $[\alpha]_D^{24} = +95.3^\circ$ (*c* 1.44, CHCl₃). **IR**: 3449-3129 (broad), 1635. **¹H**: 7.26 (t, 1H, *J* = 8.2), 6.83 (s, 4H), 6.51 (d, 2H, *J* = 8.3), 6.10 (d, 2H, *J* = 8.3), 4.70-4.56 (m, 2H), 4.21 (dd, 2H, *J* = 9.1, 3.5), 4.08 (dd, 2H, *J* = 9.0, 2.6), 2.27 (s, 18H), 1.50 (d, 6H, *J* = 6.8). **¹³C**: 170.1 (2C), 158.4 (2C), 138.6 (2C), 134.8 (2C), 134.3 (4C), 130.3, 128.4 (4C), 105.6 (2C), 78.8, 72.0 (2C), 45.0 (2C), 21.2 (2C), 19.3 (4C), 17.9 (2C). **HRMS**: calcd for C₃₂H₃₉N₂O₄INa [M+Na]⁺: 665.1852; found: 665.1852.

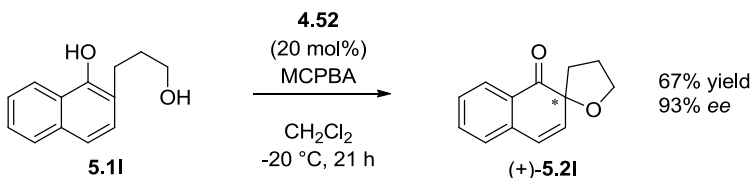
D.11. General procedure for enantioselective oxidative spiroetherification of naphtholic alcohols

A solution of MCPBA (123 mg, 550 μmol, 1.3 equiv) in CH₂Cl₂ (10.0 mL) was added over 5 min (syringe) to a cold (−20 °C) solution of a naphtholic alcohol (420 μmol, 1.0 equiv) and a chiral iodide precatalyst (8.4 μmol, 0.2 equiv) in CH₂Cl₂ (10.0 mL). The mixture was stirred at −20 °C for several hours, and when TLC indicated complete reaction it was quenched with aq. sat. NaHCO₃ (10.0 mL) and aq. sat. Na₂S₂O₃ (5.0 mL) solutions and extracted with CH₂Cl₂ (3×15 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography to afford the spiroether product. The diastereomeric ratio and enantiomeric excess of the purified product were then determined by supercritical fluid chromatography (SFC) under the conditions specified below.

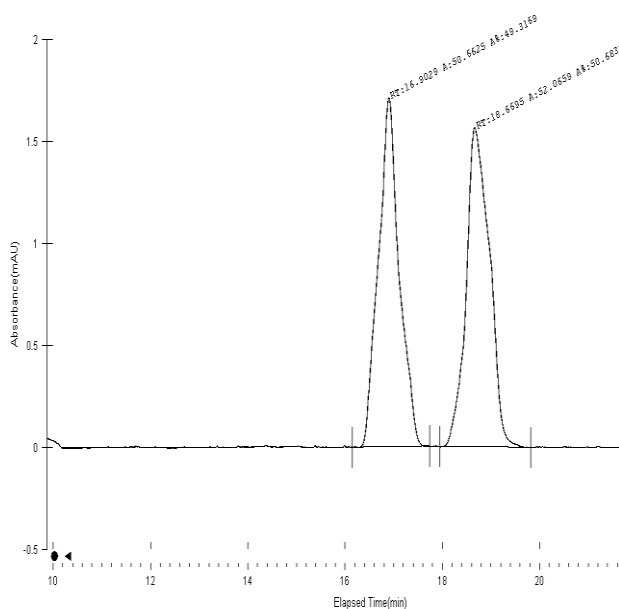
D.12 Data and SFC chromatograms of chiral compounds

D.12.1 (+)-4,5-Dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (**5.2l**)

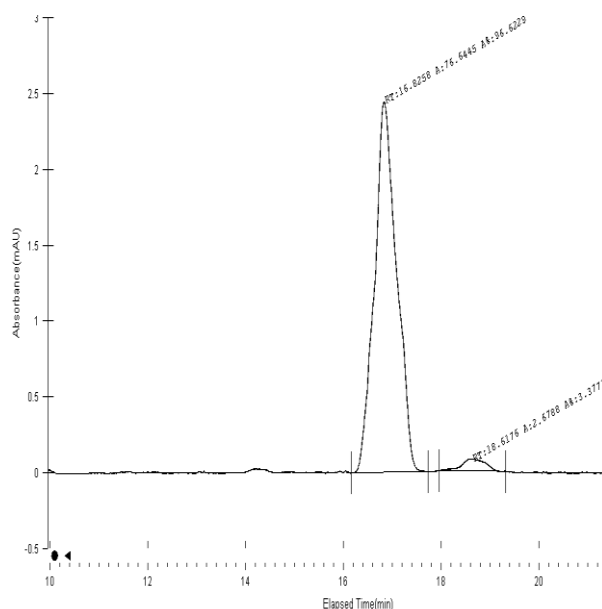
65.9 mg (67% yield) from 100 mg of **5.1l**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{24} = +185.5^\circ$ (*c* 0.17, CHCl₃). SFC analysis indicates a 93% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 16.83 min (major), t_R (2) = 18.62 min (minor).



chromatogram of (\pm)-**5.2l** (240 nm)

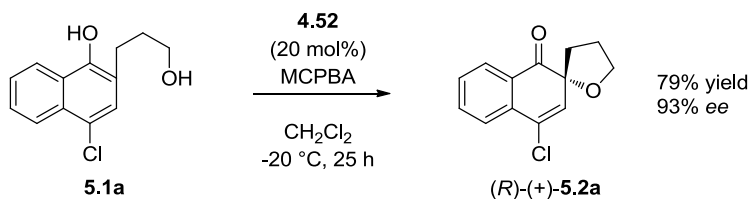


chromatogram of (+)-**5.2l**, (240 nm, 93% *ee*)

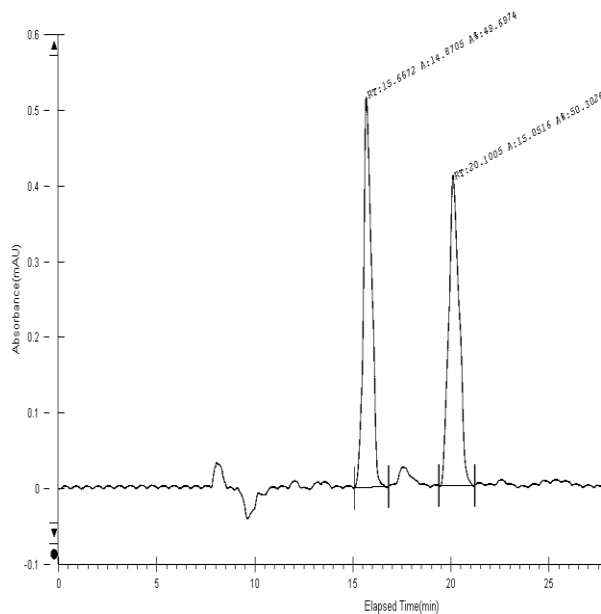


D.12.2 (+)-4'-Chloro-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2a)

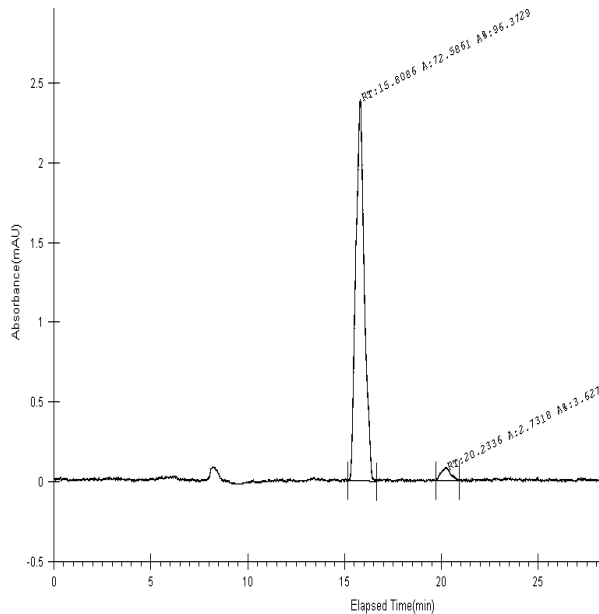
78 mg (79% yield) from 100 mg of **5.1a**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{22} = +112.2^\circ$ (c 0.65, CHCl_3). SFC analysis indicates a 93% *ee*. Column (OD-H) 10:90:0.1 *i*PrOH: CO_2 : diethylamine, flow rate = 1.0 mL/min; t_R (1) = 15.81 min (major), t_R (2) = 20.23 min (minor). Compound (+)-**5.2a** was subsequently shown to be of (*R*)-configuration (see p. 546).



chromatogram of (\pm)-**5.2a** (230 nm)

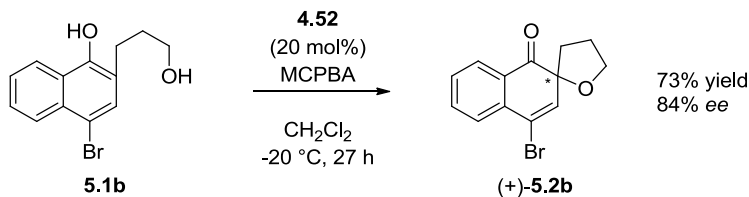


chromatogram of (+)-**5.2a**, (230 nm, 93% *ee*)

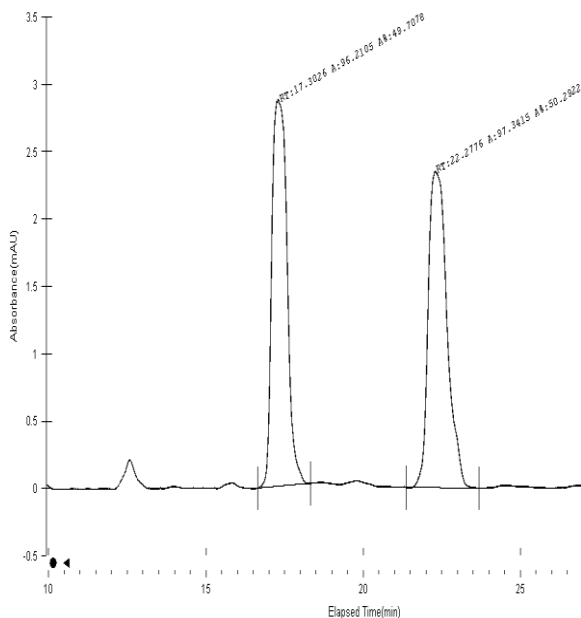


D.12.3 (+)-4'-Bromo-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2b)

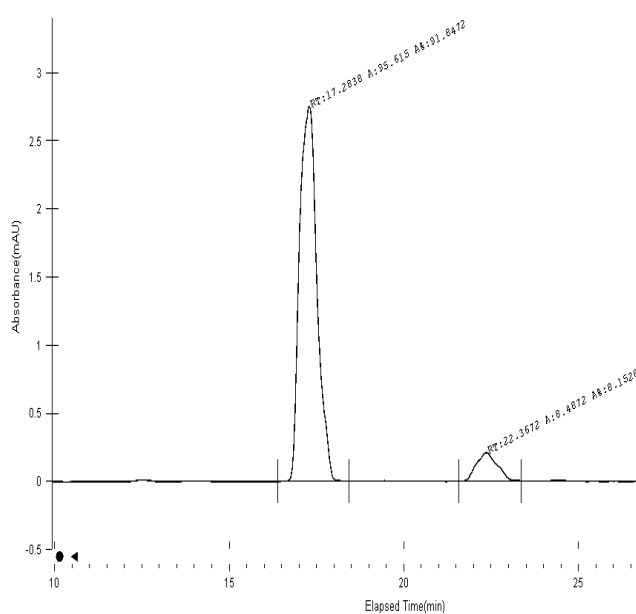
72.1 mg (73% yield) from 100 mg of **5.1b**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{24} = +113.6^\circ$ (*c* 0.13, CHCl₃). SFC analysis indicates a 84% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 17.28 min (major), t_R (2) = 22.37 min (minor).



chromatogram of (\pm)-5.2b (240 nm)

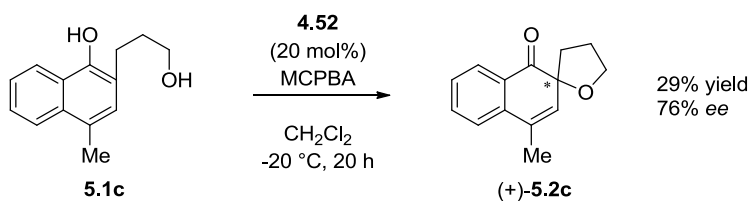


chromatogram of (+)-5.2b, (240 nm, 84% *ee*)

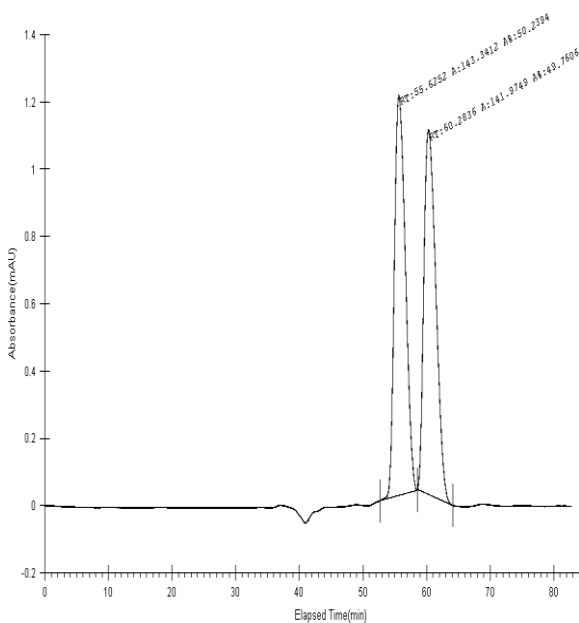


D.12.4 (+)-4'-Methyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2c)

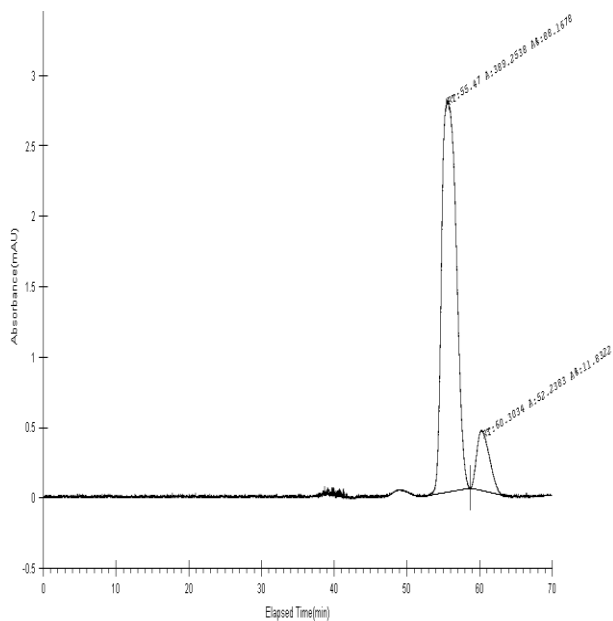
29 mg (29% yield) from 100 mg of **5.1c**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{23} = +133.3^\circ$ (c 0.22, CHCl_3). SFC analysis indicates a 76% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 55.47 min (major), t_R (2) = 60.30 min (minor).



chromatogram of (\pm)-5.2c (229 nm)

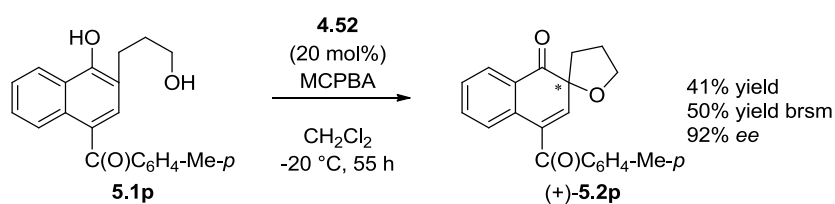


chromatogram of (+)-5.2c, (229 nm, 76% *ee*)

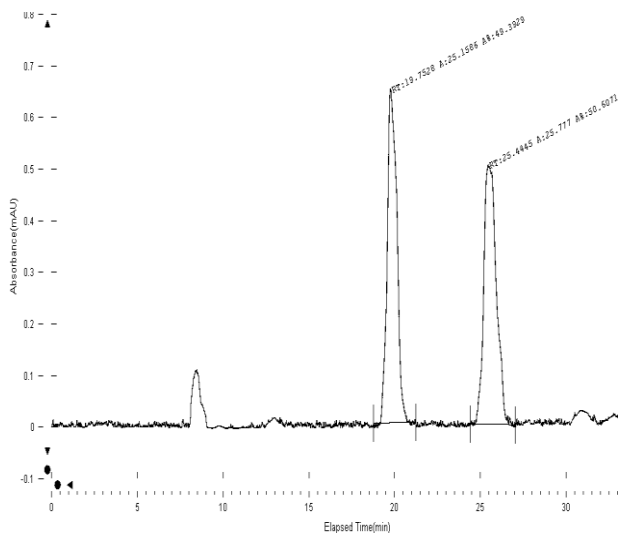


D.12.5 (+)-4'-(4-Methylbenzoyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2p)

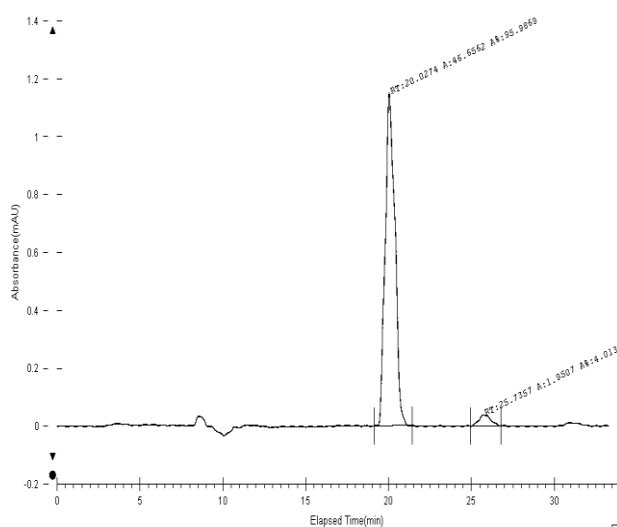
41 mg (50% yield) from 82 mg of **5.1p**, yellow oil, eluent: 1:19 to 1:9 EtOAc/hexanes, $[\alpha]_D^{23} = +3.3^\circ$ (*c* 0.31, CHCl₃). SFC analysis indicates a 92% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 20.03 min (major), *t_R* (2) = 25.74 min (minor).



chromatogram of (±)-5.2p (229 nm)

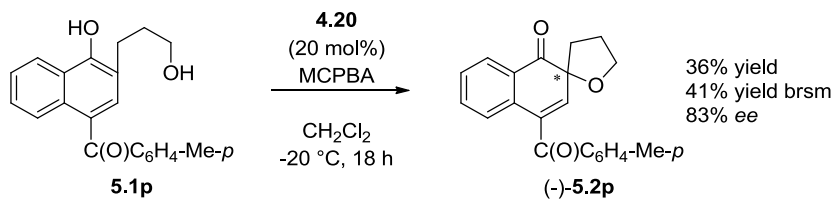


chromatogram of (+)-5.2p, (229 nm, 92% *ee*)

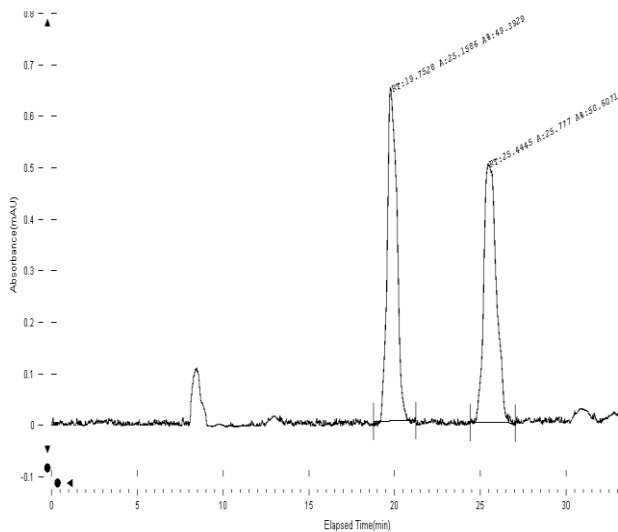


D.12.6 (-)-4'-(4-Methylbenzoyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2p)

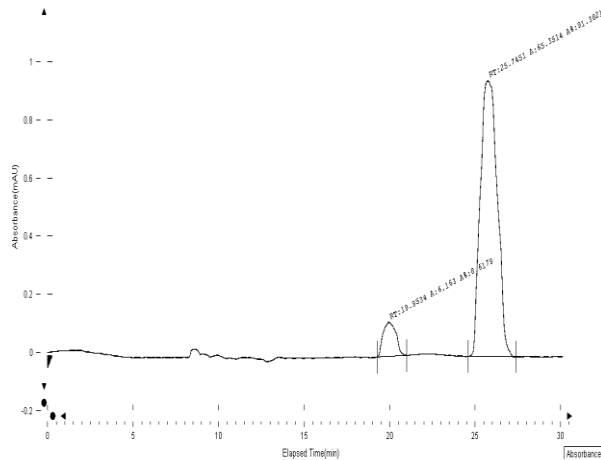
35.6 mg (41% yield) from 86.2 mg of **5.1p**, yellow oil, eluent: 1:19 to 1:9 EtOAc/hexanes, $[\alpha]_D^{24} = -2.1^\circ$ (*c* 0.50, CHCl₃). SFC analysis indicates a 83% *ee*. Column (OD-H) 10:90:0.1 (iPrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 19.95 min (minor), t_R (2) = 25.75 min (minor).



chromatogram of (\pm)-5.2p (229 nm)



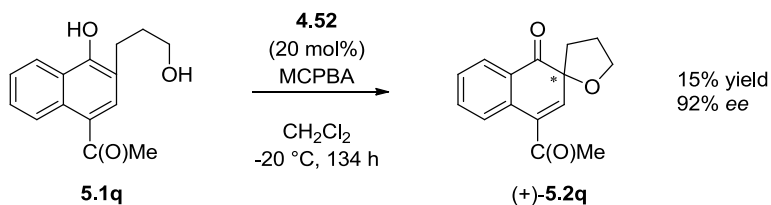
chromatogram of (-)-5.2p, (229 nm, 83% *ee*)



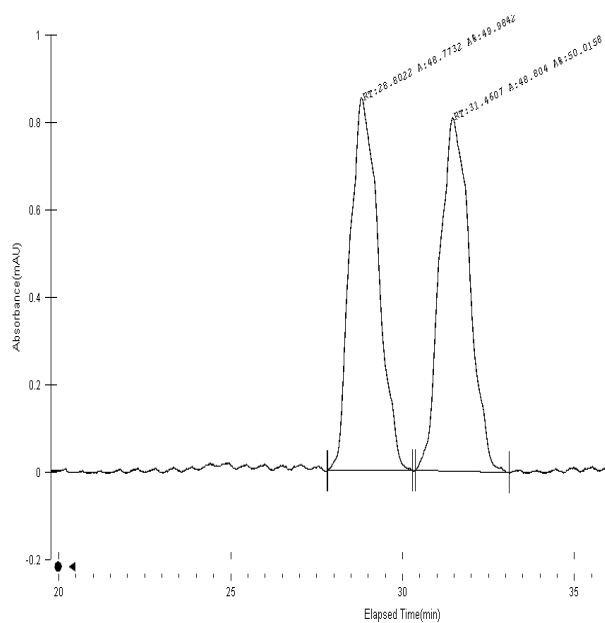
D.12.7 (+)-4'-Acetyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2q)

15 mg (15% yield) from 100 mg of **5.1q**, colorless oil, eluent: 1:19 to 3:17 EtOAc/hexanes,

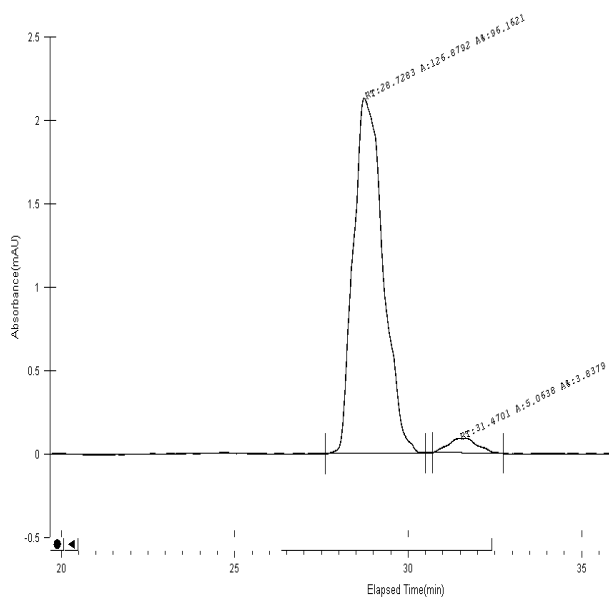
$[\alpha]_D^{23} = +156.7^\circ$ (*c* 0.1, CHCl₃). SFC analysis indicates a 92% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 28.73 min (major), *t*_R (2) = 31.47 min (minor).



chromatogram of (±)-5.2q (230 nm)

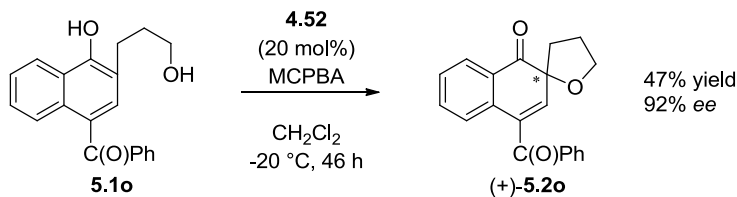


chromatogram of (+)-5.2q, (230 nm, 92% *ee*)

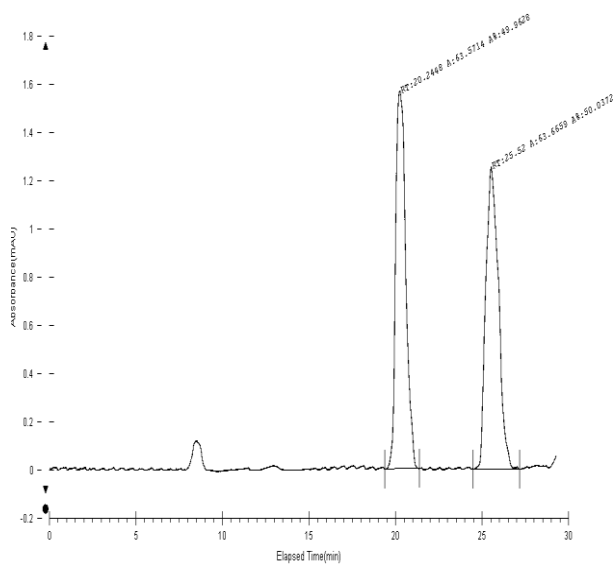


D.12.8 (+)-4'-Benzoyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2o)

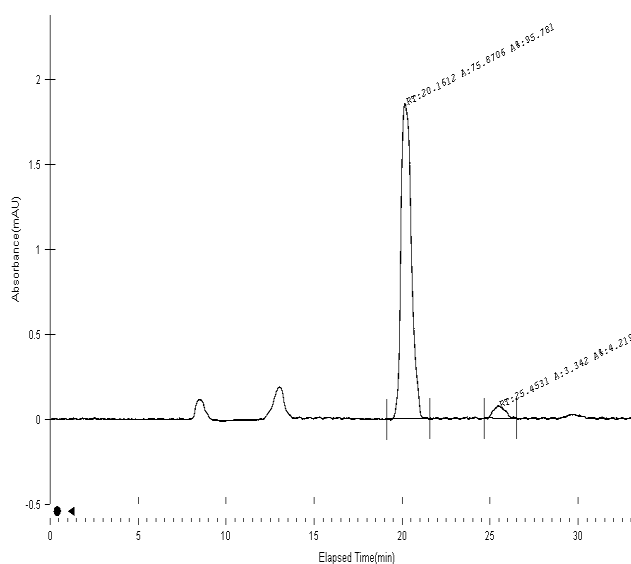
41 mg (47% yield) from 89 mg of **5.1o**, yellow oil, eluent: 1:19 to 1:9 EtOAc/hexanes, $[\alpha]_D^{22} = +13.1^\circ$ (*c* 0.36, CHCl₃). SFC analysis indicates a 92% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 20.16 min (major), *t_R* (2) = 25.45 min (minor).



chromatogram of (\pm)-5.2o (230 nm)

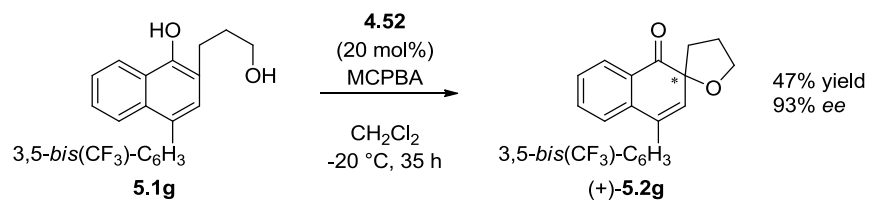


chromatogram of (+)-5.2o, (230 nm, 92% *ee*)

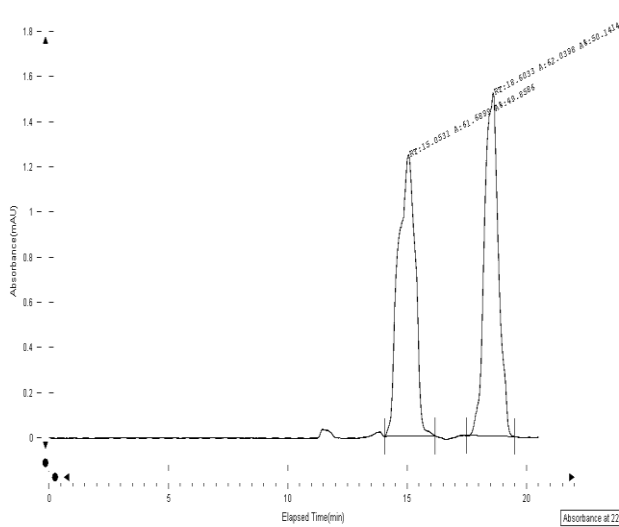


D.12.9 (+)-4'-(3,5-Bis(trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (**5.2g**)

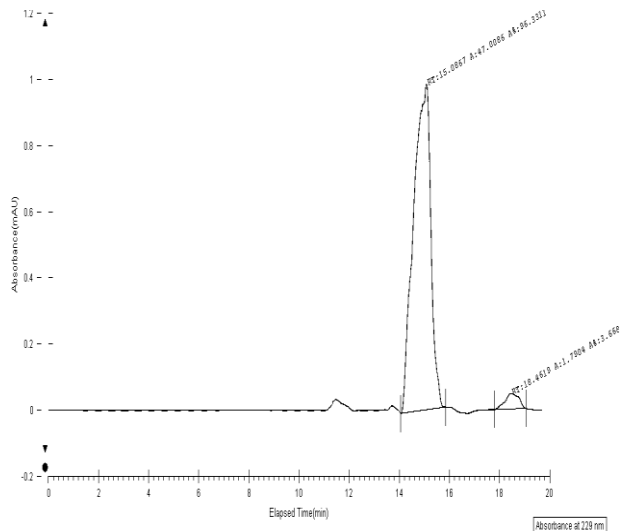
47 mg (47% yield) from 100 mg of **5.1g**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{22} = +98.5^\circ$ (*c* 0.4, CHCl_3). SFC analysis indicates a 93% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 15.09 min (major), t_R (2) = 18.46 min (minor).



chromatogram of (\pm)-**5.2g** (229 nm)

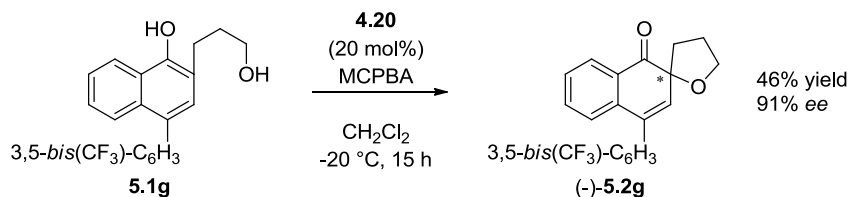


chromatogram of (+)-**5.2g**, (229 nm, 93% *ee*)

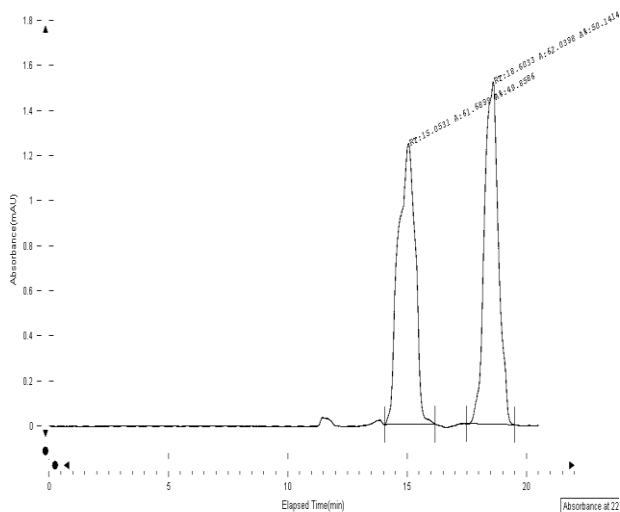


D.12.10 (-)-4'-(3,5-Bis(trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (**5.2g**)

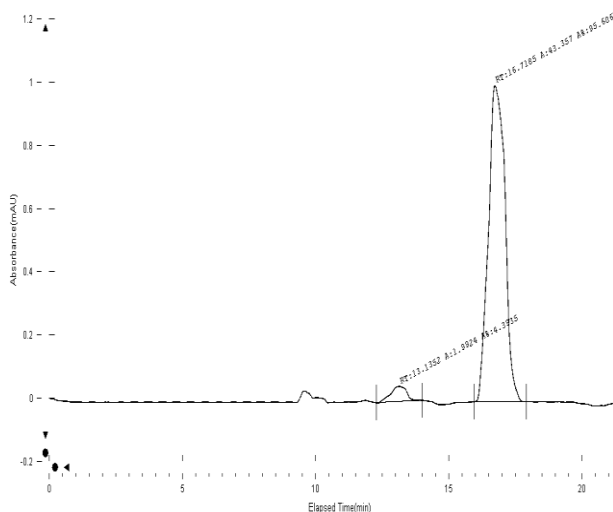
45.8 mg (46% yield) from 100 mg of **5.1g**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{24} = -89.7^\circ$ (*c* 0.70, CHCl₃). SFC analysis indicates a 91% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 13.14 min (minor), *t*_R (2) = 16.72 min (major).



chromatogram of (±)-**5.2g** (229 nm)

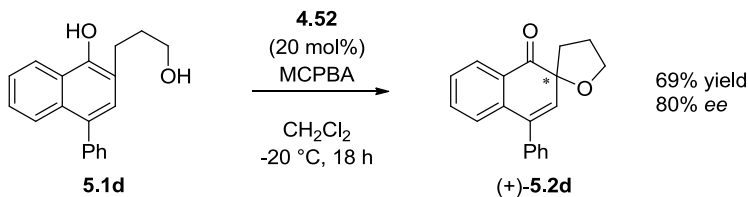


chromatogram of (-)-**5.2g**, (240 nm, 91% *ee*)

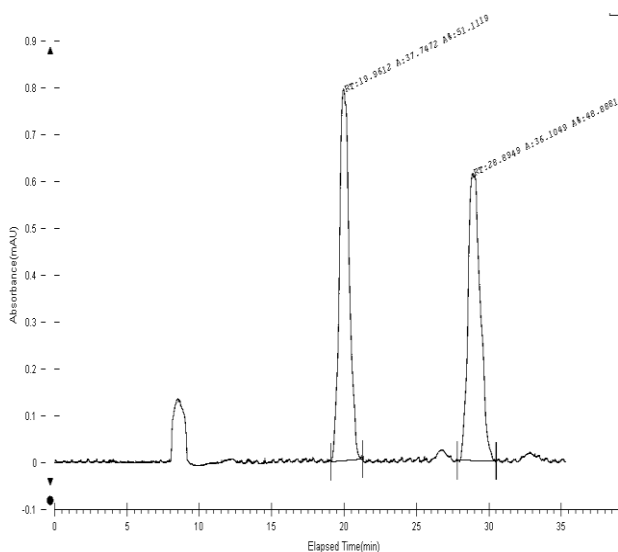


D.12.11 (+)-4'-Phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2d)

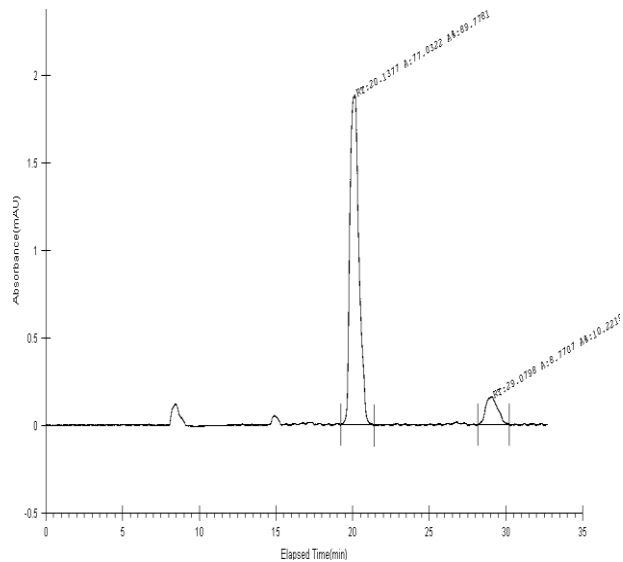
62.1 mg (69% yield) from 91 mg of **5.1d**, white solid, m.p.: 91-93 °C, eluent: 3:47 EtOAc/hexanes, $[\alpha]_D^{24} = +101.3^\circ$ (*c* 0.57, CHCl₃). SFC analysis indicates an 80% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 20.14 min (major), t_R (2) = 29.08 min (minor).



chromatogram of (\pm)-5.2d (230 nm)

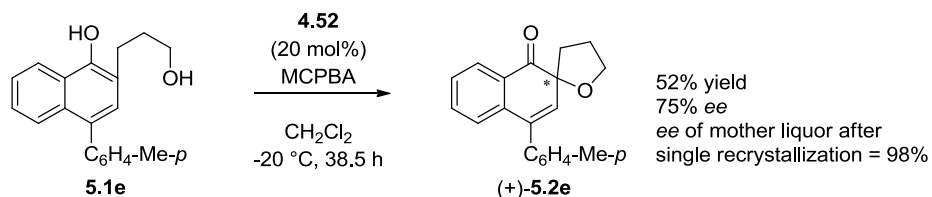


chromatogram of (+)-5.2d, (230 nm, 80% *ee*)

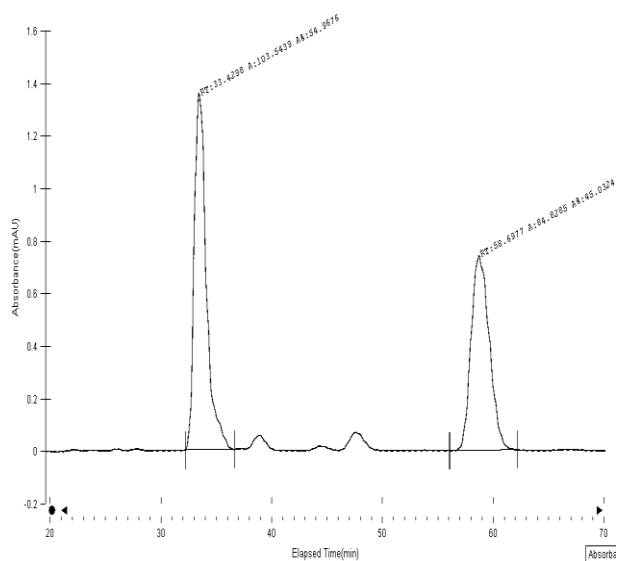


D.12.12 (+)-4'-*p*-Tolyl-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (5.2e)

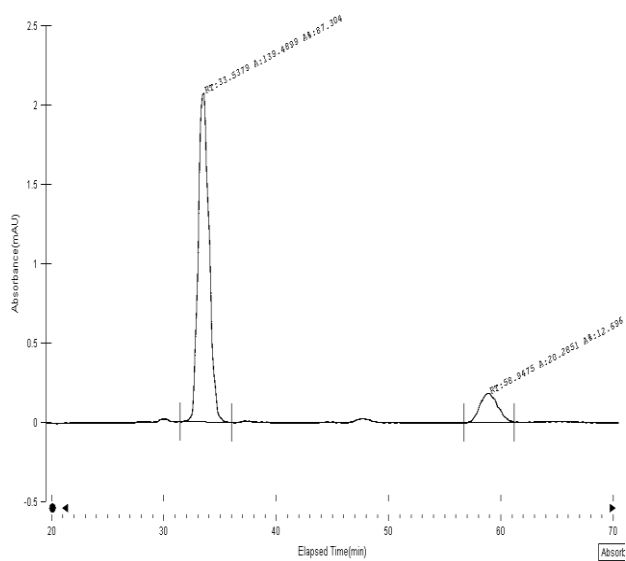
51.2 mg (52% yield) from 100 mg of **5.1e**, white solid, m.p.: 135-137 °C, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{23} = +96.6^\circ$ (c 0.47, CHCl₃). SFC analysis indicates a 75% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 33.54 min (major), t_R (2) = 58.95 min (minor).



chromatogram of (\pm)-5.2e (229 nm)

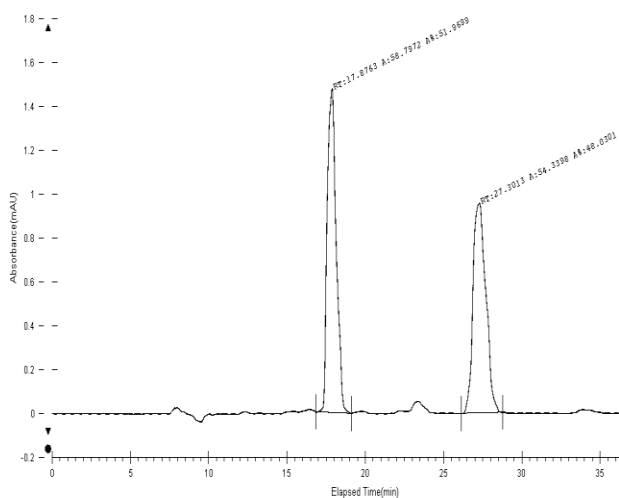


chromatogram of (+)-5.2e, (229 nm, 75% *ee*)

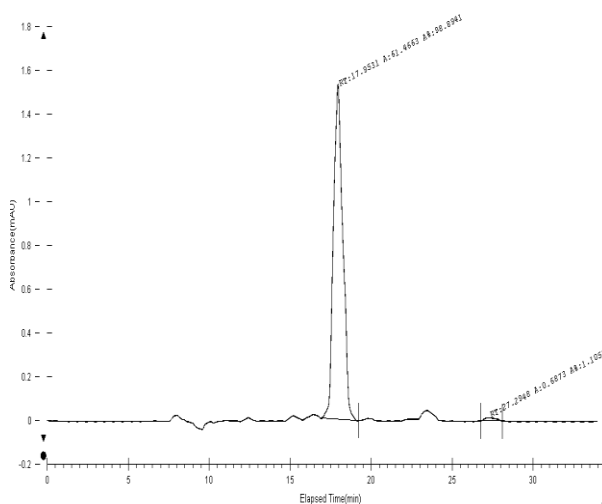


A single recrystallization from toluene/hexanes (vapor diffusion technique, RT) of (+)-**5.2e** thus obtained induced selective crystallization of the racemate, leaving a mother liquor strongly enriched in the (+)-enantiomer. The *ee* of the latter was found to be equal to 98% upon chiral SFC analysis. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 17.95 min (major), *t_R* (2) = 27.30 min (minor).

chromatogram of (±)-5.2e** (230 nm)**

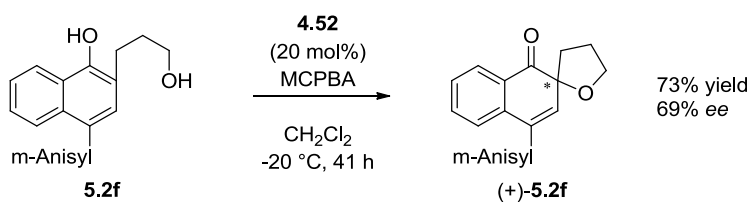


chromatogram of (+)-5.2e**, (230 nm, 98% *ee*)**

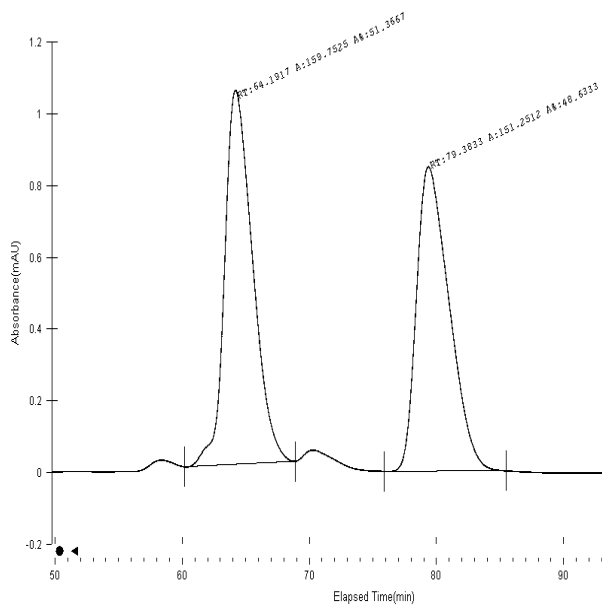


D.12.13 (+)-4'-(3-Methoxyphenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2f)

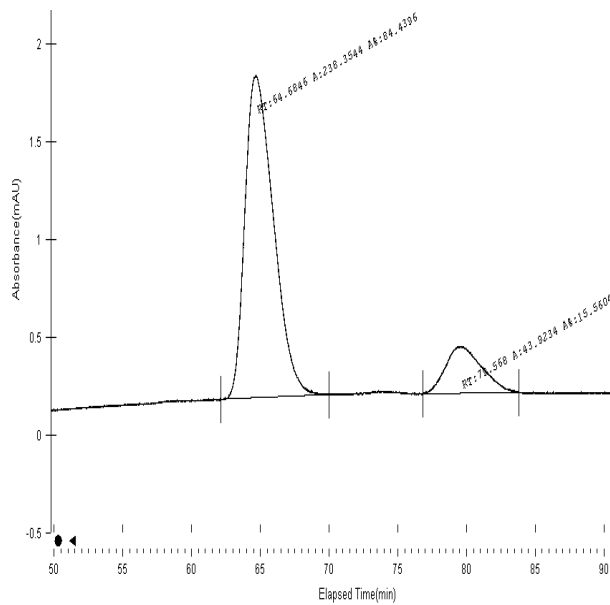
72 mg (73% yield) from 100 mg of **5.1f**, colorless oil, eluent: 2:23 EtOAc/hexanes, $[\alpha]_D^{23} = +87.3^\circ$ (*c* 0.65, CHCl₃). SFC analysis indicates a 69% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 64.69 min (major), *t*_R (2) = 79.57 min (minor).



chromatogram of (\pm)-5.2f (229 nm)

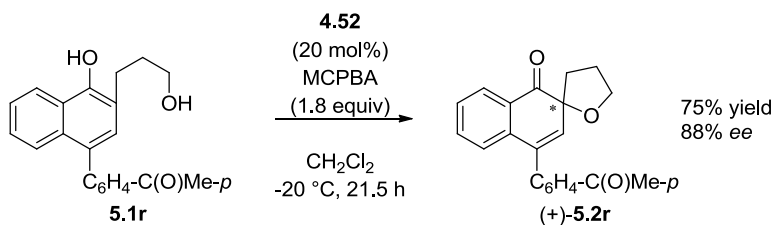


chromatogram of (+)-5.2f, (229 nm, 69% ee)

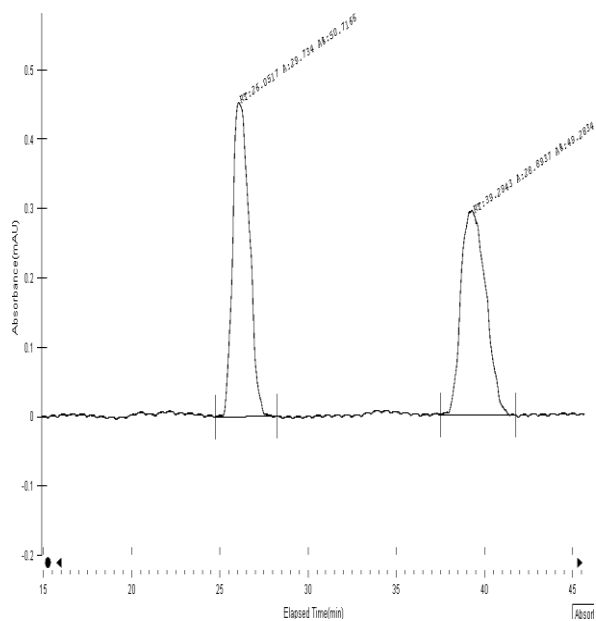


D.12.14 (+)-4'-(4-Acetylphenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2r)

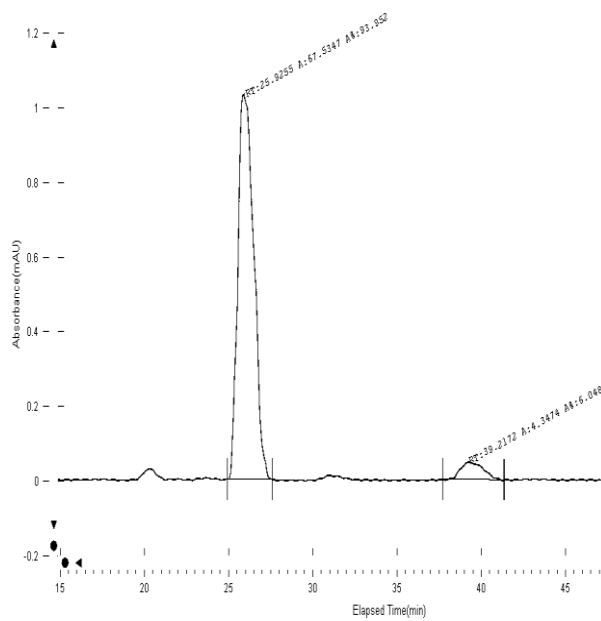
74 mg (75% yield) from 100 mg of **5.1r**, off white solid, eluent: 1:9 EtOAc/hexanes, $[\alpha]_D^{19} = +89.0^\circ$ (c 0.69, CHCl_3). SFC analysis indicates an 88% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 25.93 min (major), t_R (2) = 39.22 min (minor).



chromatogram of (±)-5.2r (229 nm)

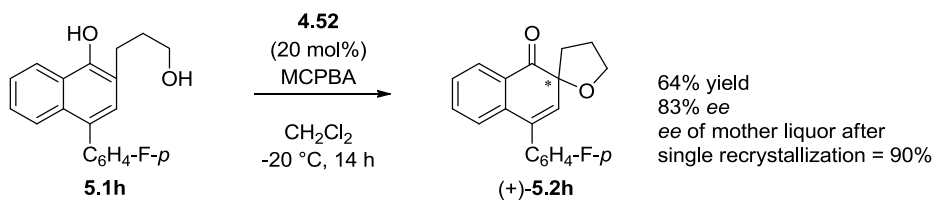


chromatogram of (+)-5.2r, (229 nm, 88% ee)

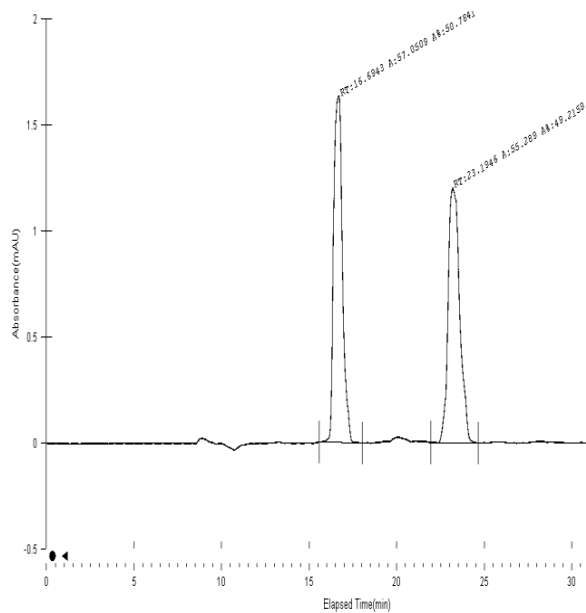


D.12.15 (+)-4'-(4-Fluorophenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2h)

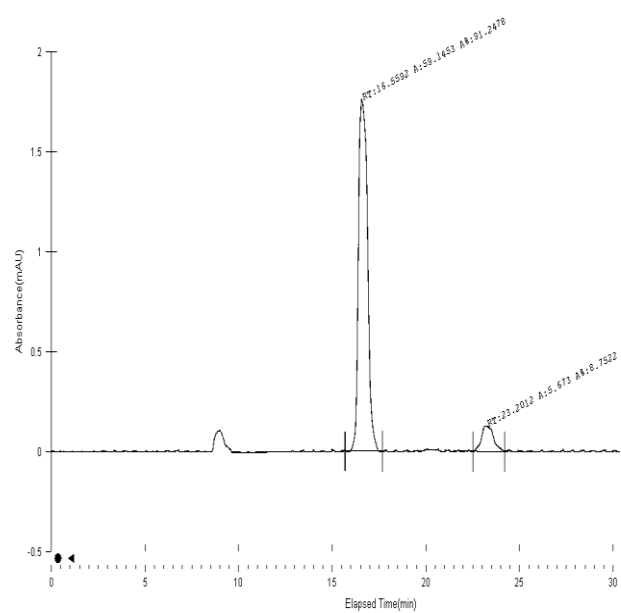
63 mg (64% yield) from 100 mg of **5.1h**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{22} = +122.9^\circ$ (*c* 0.51, CHCl₃). SFC analysis indicates an 83% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 16.56 min (major), *t*_R (2) = 23.20 min (minor).



chromatogram of (±)-5.2h (230 nm)

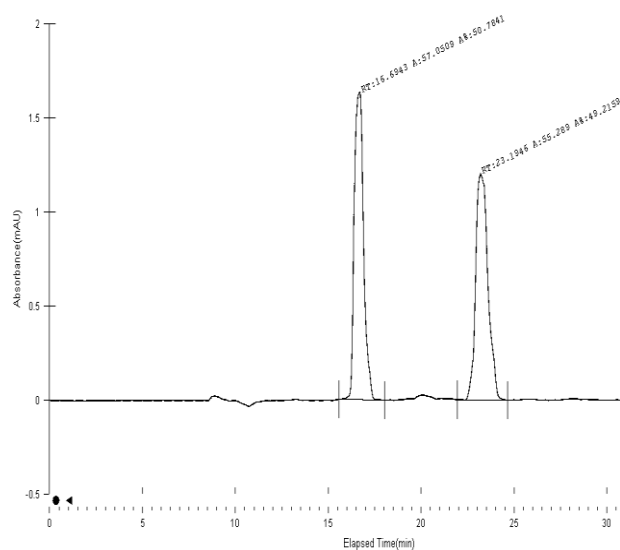


chromatogram of (+)-5.2h, (230 nm, 83% ee)

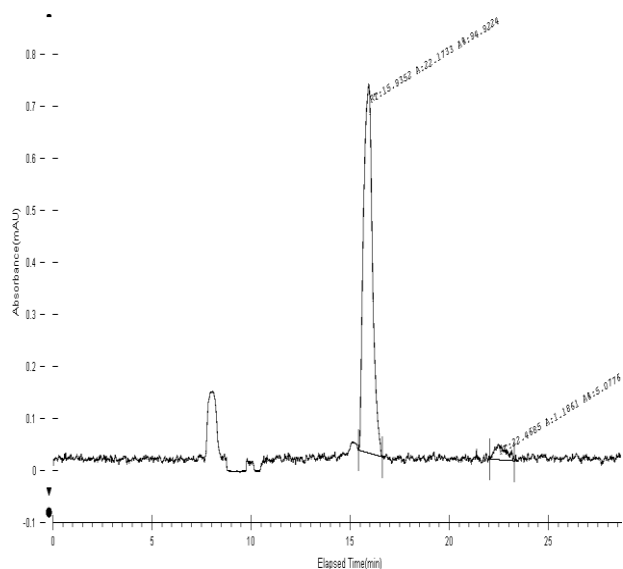


A single recrystallization from toluene/hexanes (vapor diffusion technique, RT) of (+)-**5.2h** thus obtained induced selective crystallization of the racemate, leaving a mother liquor strongly enriched in the (+)-enantiomer. The *ee* of the latter was found to be equal to 90% upon chiral SFC analysis. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 15.94 min (major), t_R (2) = 22.47 min (minor).

chromatogram of (\pm)-**5.2h** (229 nm)

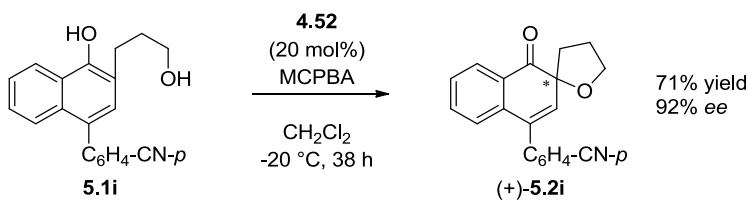


chromatogram of (+)-**5.2h**, (229 nm, 90% *ee*)

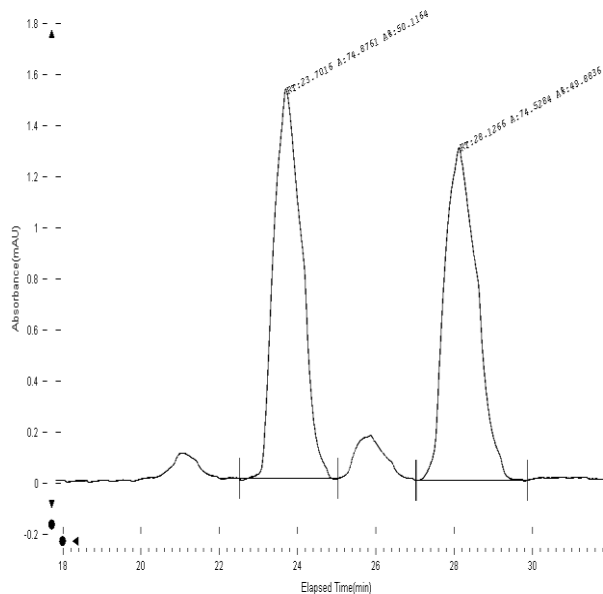


D.12.16 (+)-4-(1'-Oxo-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalene]-4'-yl)benzonitrile (5.2i)

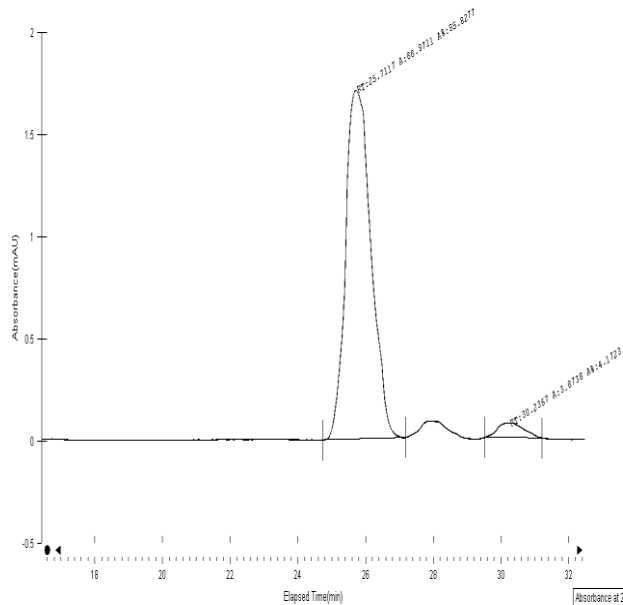
70 mg (71% yield) from 100 mg of **5.1i**, light yellow oil, eluent: 2:23 EtOAc/hexanes, $[\alpha]_D^{23} = +98.4^\circ$ (*c* 0.65, CHCl₃). SFC analysis indicates a 92% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 25.71 min (major), *t*_R (2) = 30.24 min (minor).



chromatogram of (±)-5.2i (230 nm)

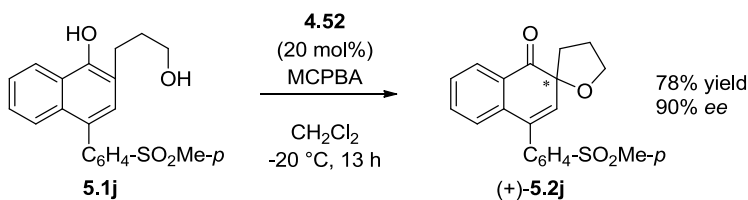


chromatogram of (+)-5.2i, (230 nm, 92% ee)

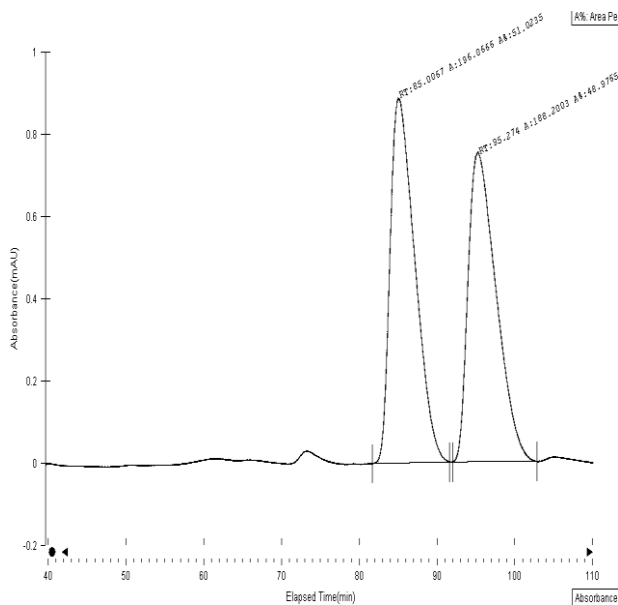


D.12.17 **(+)-4'-(4-(Methylsulfonyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2j)**

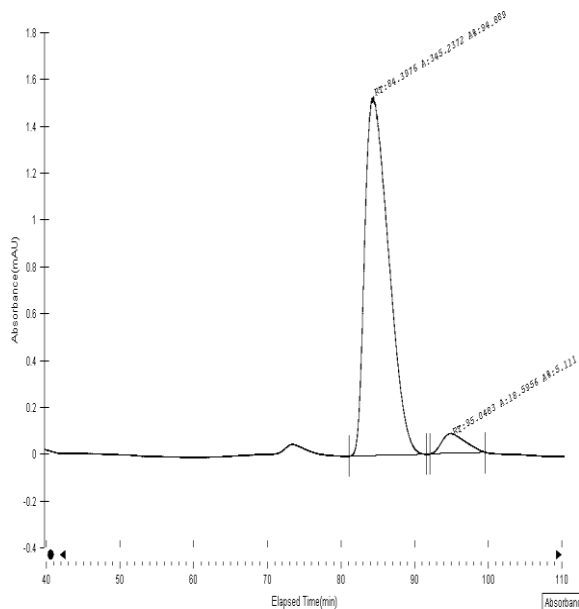
77 mg (78% yield) from 100 mg of **5.1j**, white solid, eluent: 1:4 to 2:3 EtOAc/hexanes, $[\alpha]_D^{22} = +74.7^\circ$ (*c* 0.77, CHCl₃). SFC analysis indicates a 90% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 84.40 min (major), *t*_R (2) = 95.05 min (minor).



chromatogram of (±)-5.2j (229 nm)

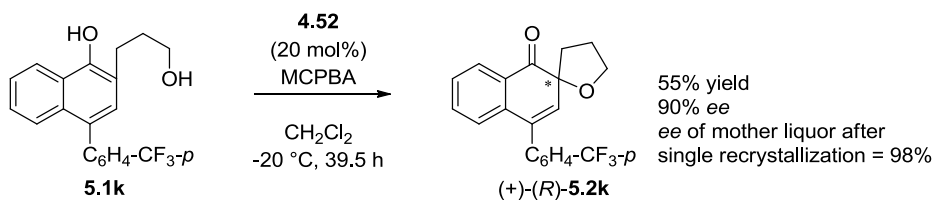


chromatogram of (+)-5.2j, (229 nm, 90% ee)

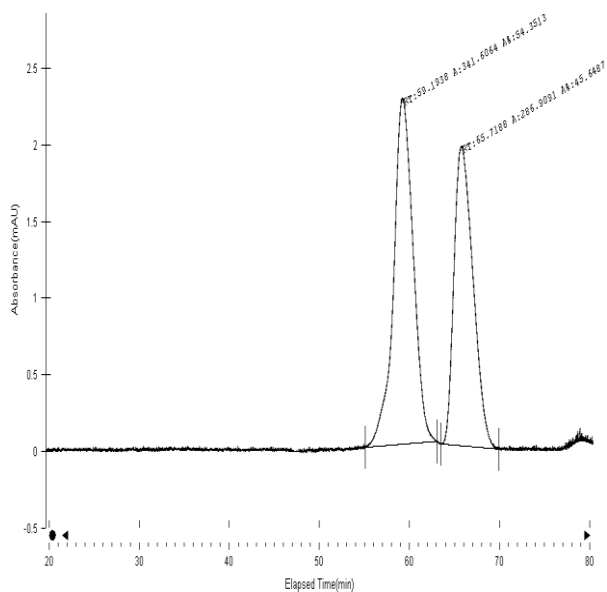


D.12.18 (+)-(*R*)-4'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one (**5.2k**)

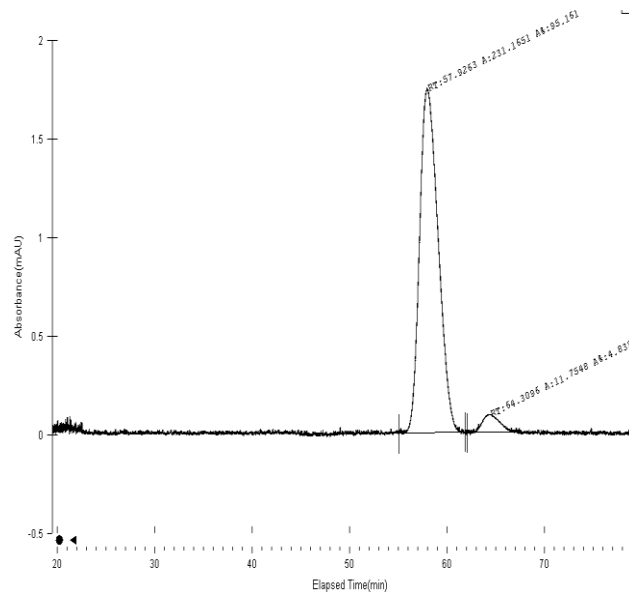
54 mg (55% yield) from 100 mg of **5.1k**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{23} = +111.7^\circ$ (*c* 0.50, CHCl₃). SFC analysis indicates a 90% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 57.96 min (major), *t*_R (2) = 64.31 min (minor). Compound (+)-**5.2k** was subsequently shown to be of (*R*)-configuration (see p. 548).



chromatogram of (±)-5.2k (230 nm)

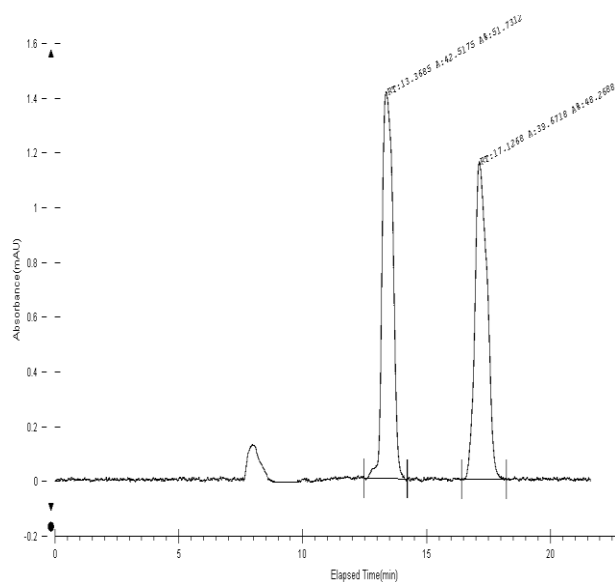


chromatogram of (+)-5.2k, (230 nm, 90% *ee*)

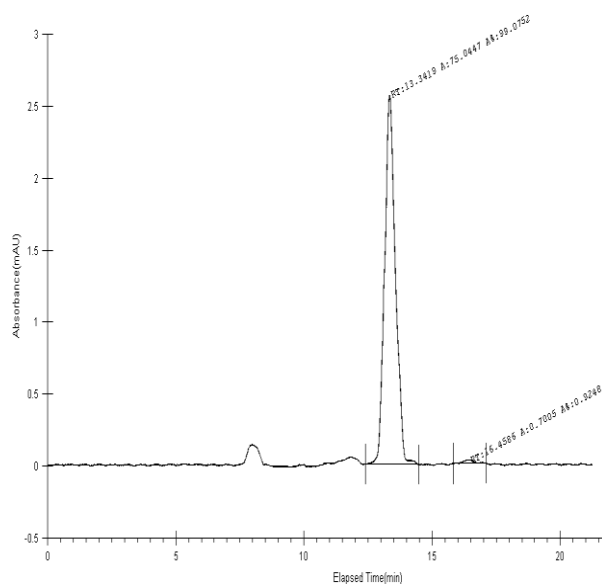


A single recrystallization from toluene/hexanes (vapor diffusion technique, RT) of (+)-**5.2k** thus obtained induced selective crystallization of the racemate, leaving a mother liquor strongly enriched in the (+)-enantiomer. The *ee* of the latter was found to be equal to 98% upon chiral SFC analysis. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 13.34 min (major), t_R (2) = 16.46 min (minor).

chromatogram of (\pm)-**5.2k** (230 nm)

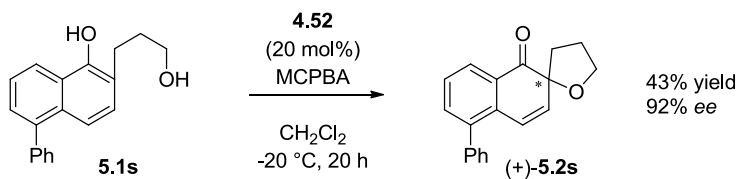


chromatogram of (+)-**5.2k**, (230 nm, 98% *ee*)

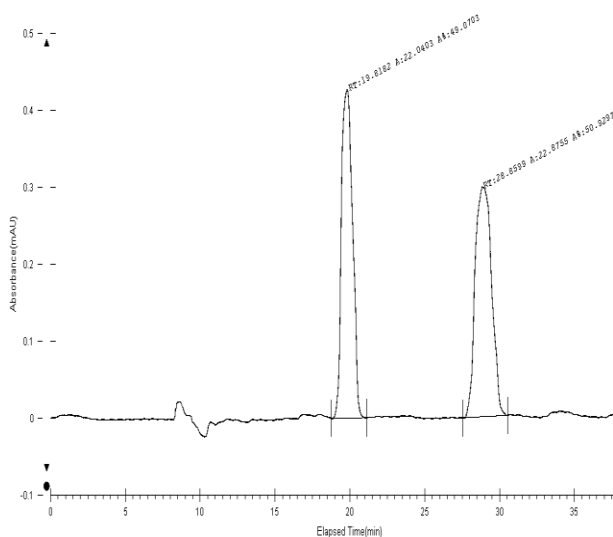


D.12.19 (+)-5'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2s)

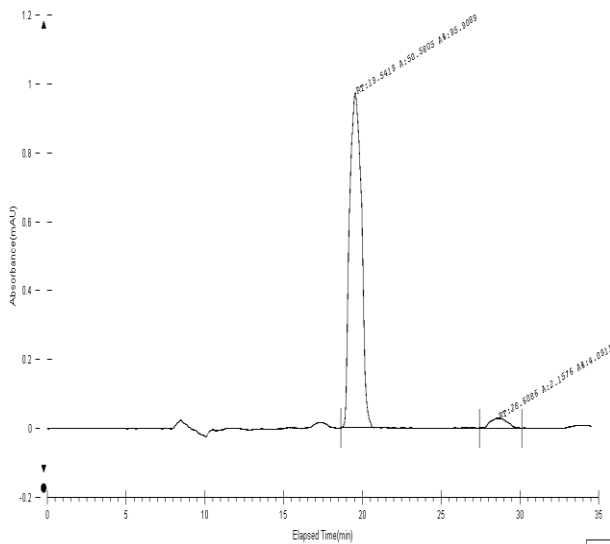
43.1 mg (43% yield) from 100 mg of **5.1s**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{25} = +143.7^\circ$ (*c* 0.45, CHCl₃). SFC analysis indicates a 92% *ee*. Column (OD-H) 10:90:0.1 (iPrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 19.54 min (major), *t_R* (2) = 28.61 min (minor).



chromatogram of (\pm)-5.2s (240 nm)

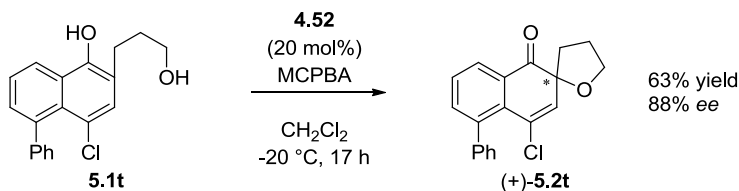


chromatogram of (+)-5.2s, (240 nm, 92% *ee*)

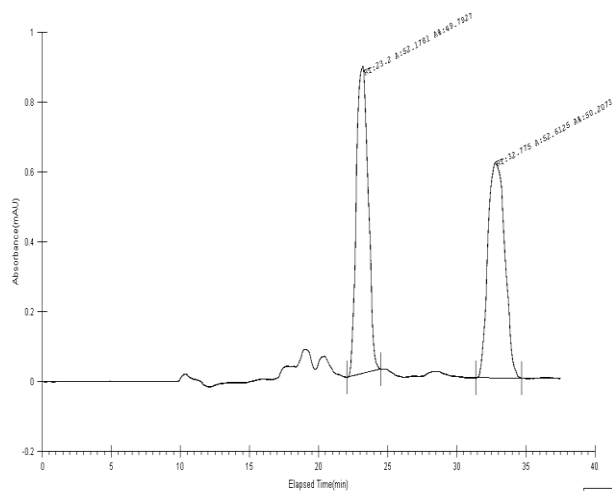


D.12.20 (+)-4'-chloro-5'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2t)

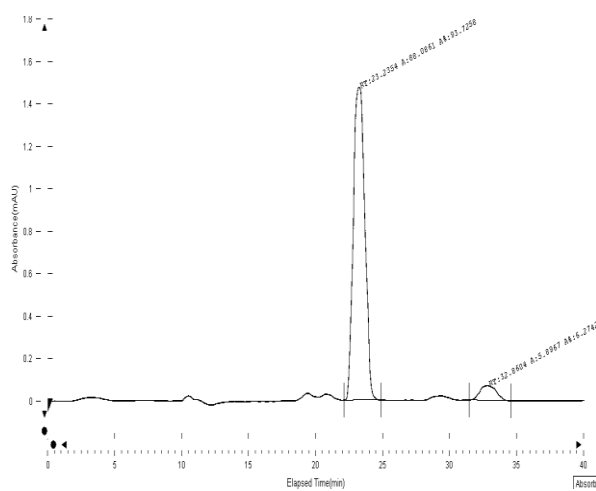
62.8 mg (63% yield) from 100 mg of **5.1t**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{24} = +69.9^\circ$ (*c* 0.49, CHCl₃). SFC analysis indicates a 88% *ee*. Column (OD-H) 10:90:0.1 (iPrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 23.24 min (major), *t*_R (2) = 32.86 min (minor).



chromatogram of (±)-5.2t (240 nm)

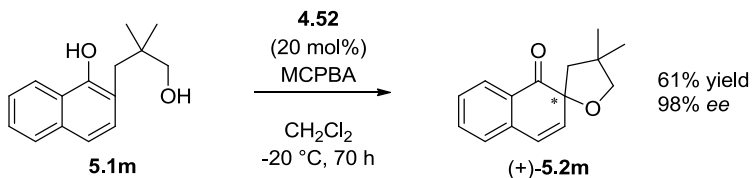


chromatogram of (+)-5.2t, (240 nm, 88% ee)

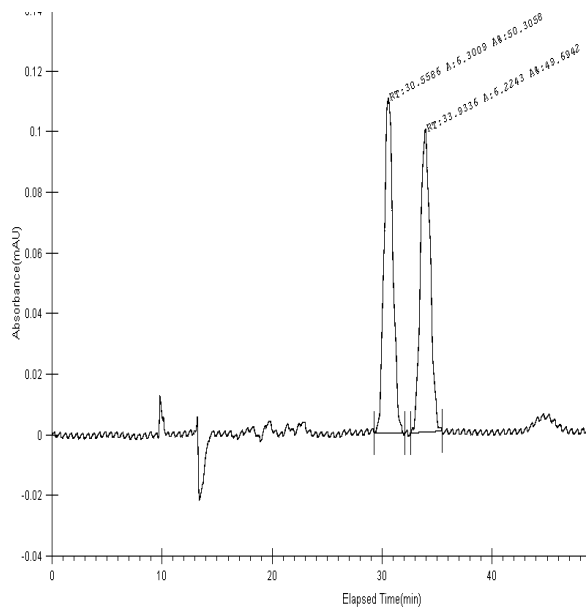


D.12.21 (+)-4,4-Dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2m)

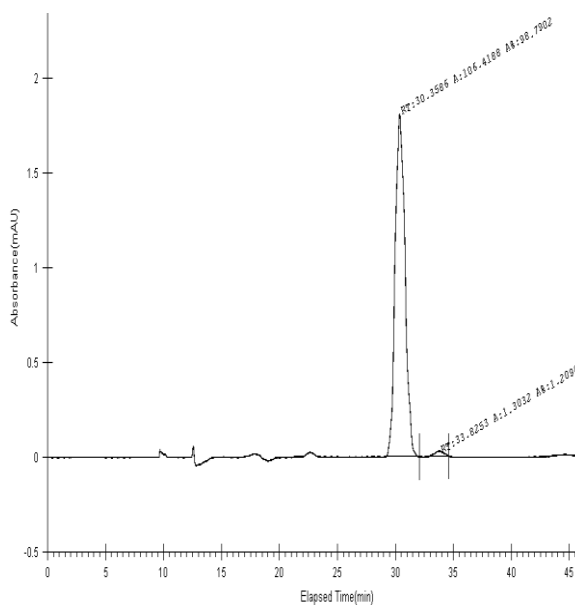
60.1 mg (61% yield) from 100 mg of **5.1m**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{23} = +216.9^\circ$ (*c* 0.57, CHCl_3). SFC analysis indicates a 98% *ee*. Column (OD-H) 3:97:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 30.36 min (major), t_R (2) = 33.83 min (minor).



chromatogram of (\pm)-5.2m (229 nm)

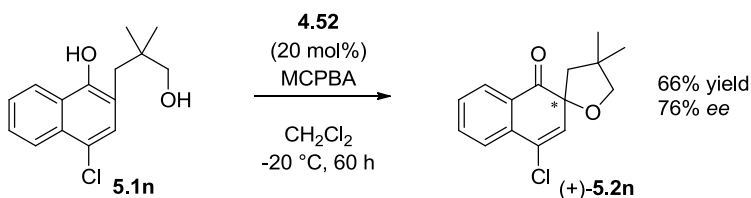


chromatogram of (+)-5.2m (229 nm, 98% *ee*)

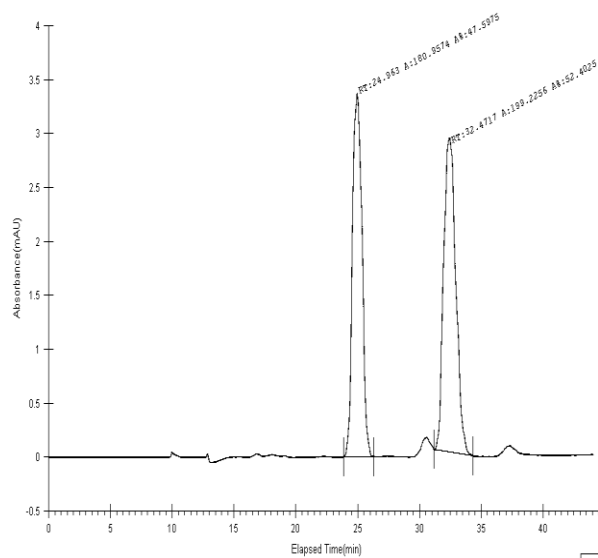


D.12.22 (+)-4'-chloro-4,4-dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2n)

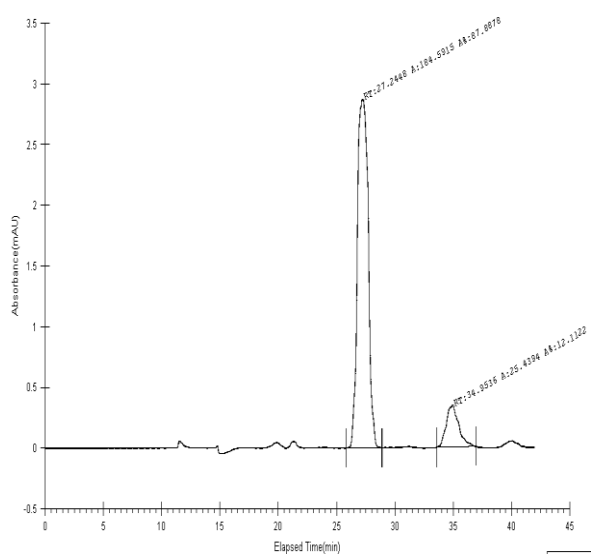
65.3 mg (66% yield) from 100 mg of **5.1n**, colorless oil, eluent: 3:97 EtOAc/hexanes, $[\alpha]_D^{23} = +88.3^\circ$ (*c* 0.43, CHCl₃). SFC analysis indicates a 76% *ee*. Column (OD-H) 3:97:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t_R* (1) = 27.25 min (major), *t_R* (2) = 34.95 min (minor).



chromatogram of (±)-5.2n (229 nm)

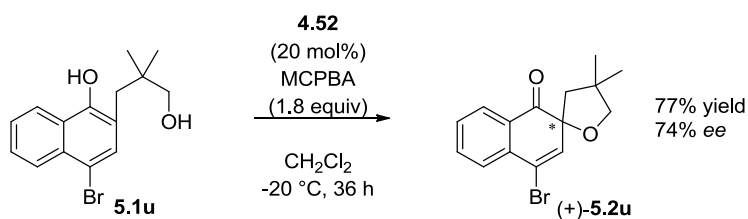


chromatogram of (+)-5.2n, (229 nm, 76% ee)

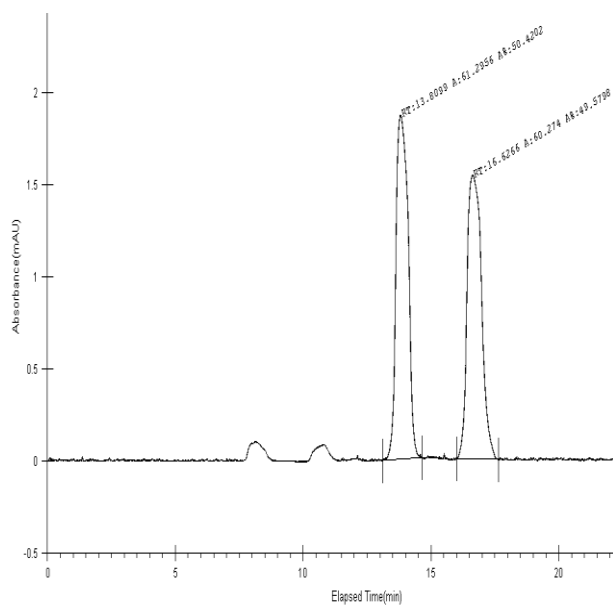


D.12.23 (+)-4'-Bromo-4,4-dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2u)

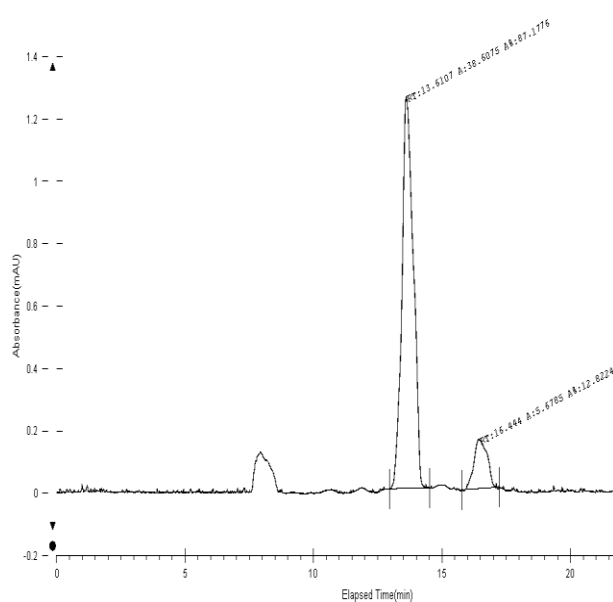
76 mg (77% yield) from 100 mg of **5.1u**, light yellow oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{23} = +101.4^\circ$ (c 0.59, CHCl_3). SFC analysis indicates a 74% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 13.61 min (major), t_R (2) = 16.44 min (minor).



chromatogram of (\pm)-5.2u (229 nm)

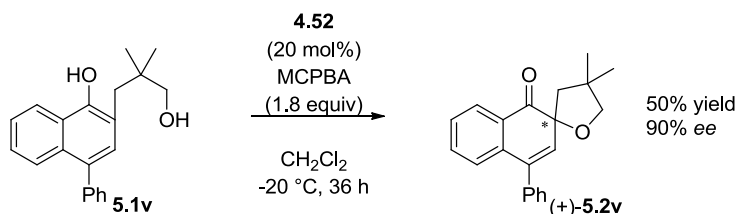


chromatogram of (+)-5.2u (229 nm, 74% *ee*)

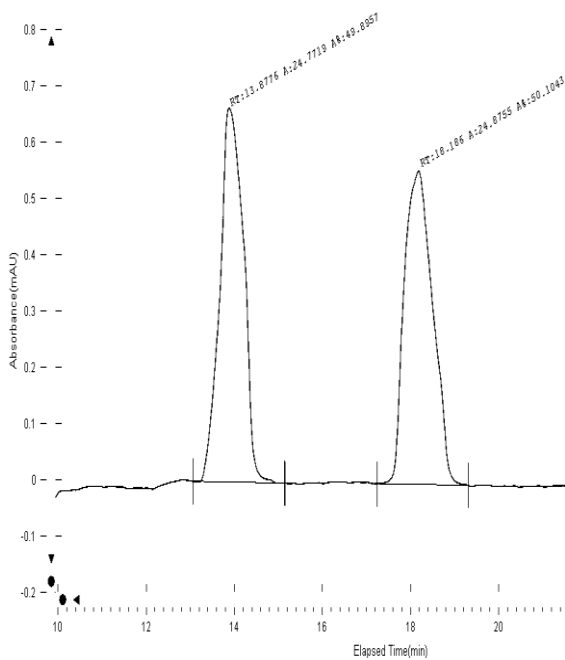


D.12.24 (+)-4,4-Dimethyl-4'-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2v)

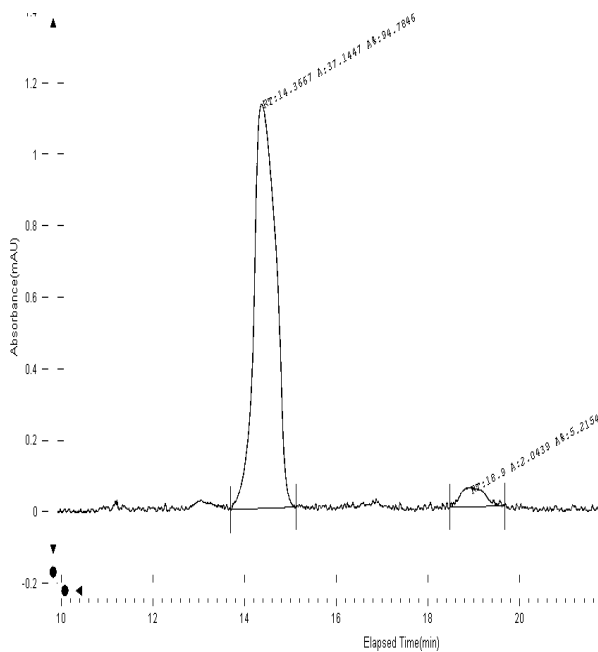
49.2 mg (50% yield) from 100 mg of **5.1v**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{21} = +157.6^\circ$ (c 0.47, CHCl_3). SFC analysis indicates a 90% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 14.37 min (major), t_R (2) = 18.90 min (minor).



chromatogram of (±)-5.2v (229 nm)

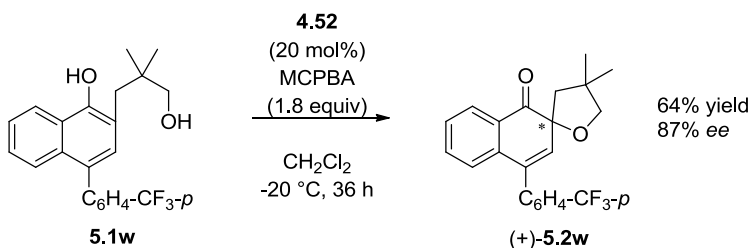


chromatogram of (+)-5.2v, (229 nm, 90% ee)

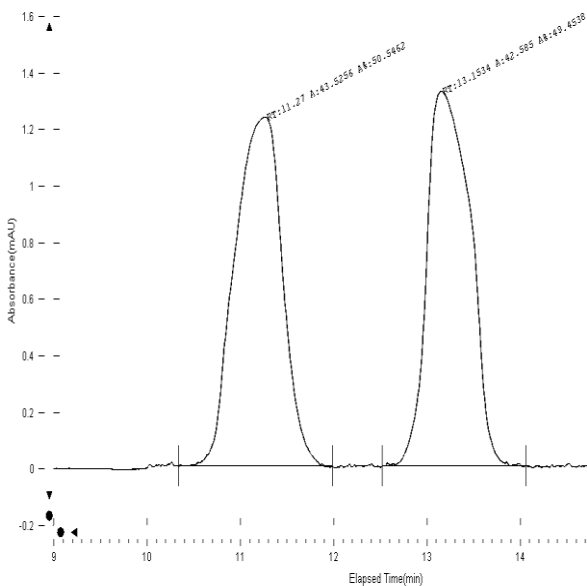


D.12.25 (+)-4,4-Dimethyl-4'-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2w)

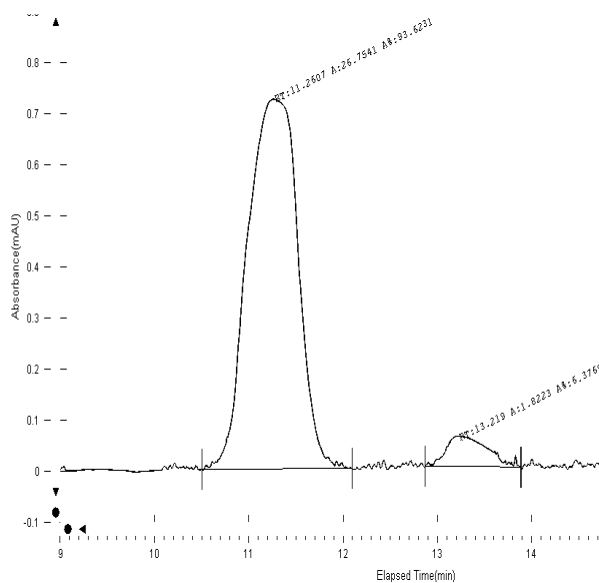
64 mg (64% yield) from 100 mg of **5.1w**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{22} = +126.6^\circ$ (*c* 0.67, CHCl₃). SFC analysis indicates a 87% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 11.26 min (major), t_R (2) = 13.22 min (minor).



chromatogram of (±)-5.2w (229 nm)

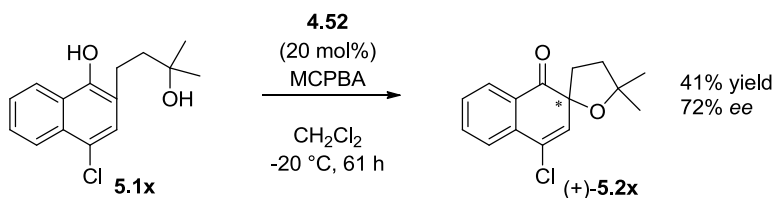


chromatogram of (+)-5.2w (229 nm, 87% ee)

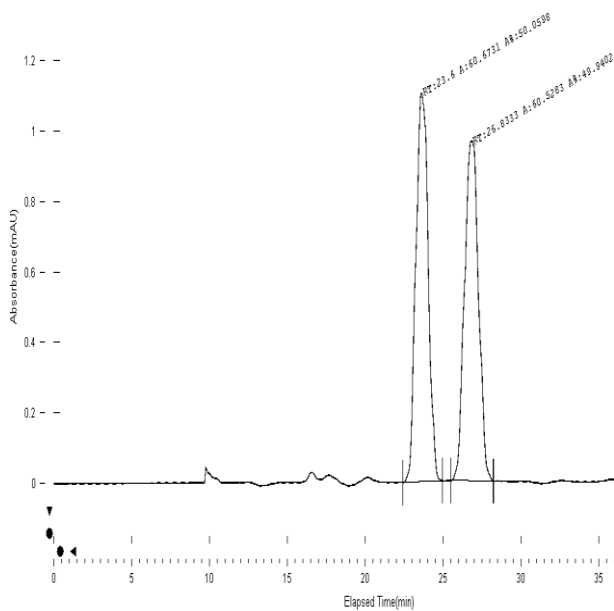


D.12.26 (+)-4'-chloro-5,5-dimethyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (5.2x)

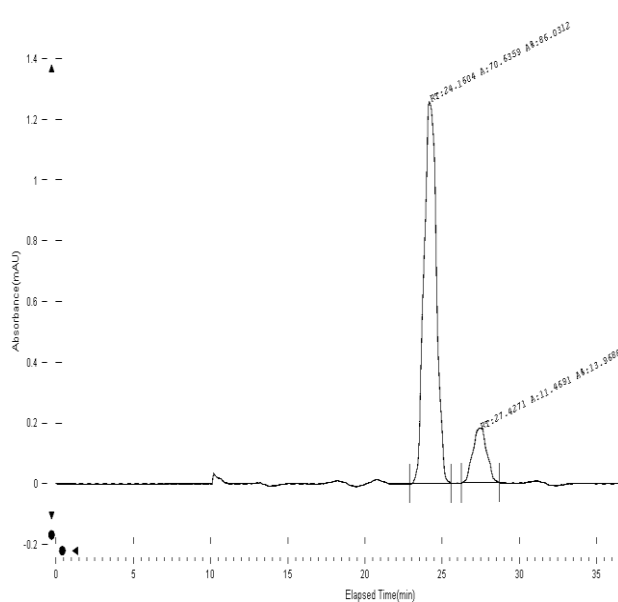
40.6 mg (41% yield) from 100 mg of **5.1x**, colorless oil, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{24} = +46.4^\circ$ (*c* 0.37, CHCl₃). SFC analysis indicates a 72% *ee*. Column (OD-H) 3:97:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 24.16 min (major), t_R (2) = 27.43 min (minor).



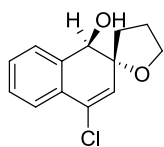
chromatogram of (±)-5.2x (240 nm)



chromatogram of (+)-5.2x (240 nm, 72% ee)



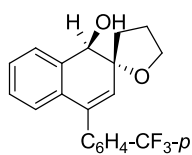
D.12.27 (+)-(1*R*,2*R*)-4'-Chloro-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-ol (5.13)



71 mg (59% yield) from 120 mg of (+)-**5.2a** (93% *ee*), white solid, eluent: 1:9 EtOAc/hexanes, $[\alpha]_{\text{D}}^{25} = +12.5^{\circ}$ (*c* 0.51, CHCl₃). The *ee* of **5.13** could not be determined using chiral SFC as just like the racemate, this compound reverts to **6a**

upon standing or upon dissolution in MeOH.

D.12.28 (+)-(1*R*,2*R*)-4'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-ol (5.15)



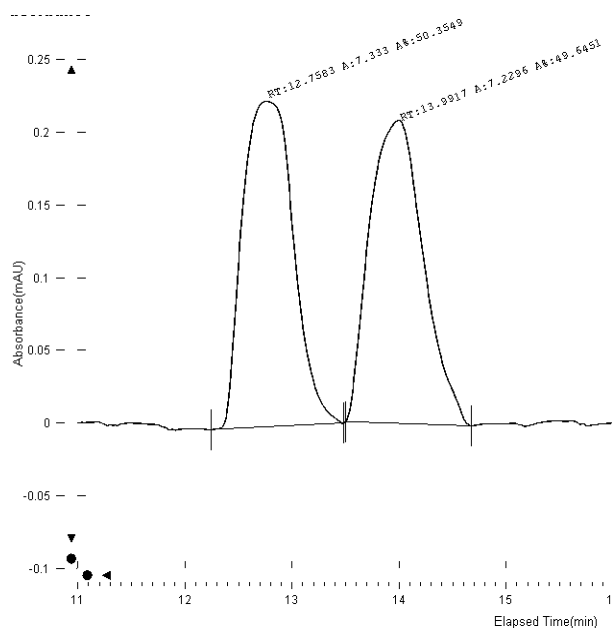
31 mg (45% yield) from 68 mg of (+)-**5.2k** (90% *ee*), white solid, eluent: 1:9

EtOAc/hexane, $[\alpha]_D^{27} = +92.4^\circ$ (*c* 1.0, CHCl₃). SFC analysis indicates a 93% *ee*.

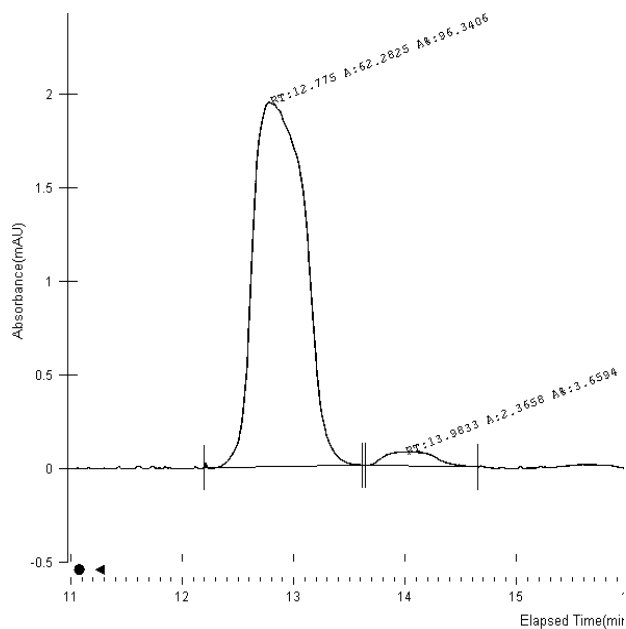
Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0

mL/min; t_R (1) = 12.78 min (major), t_R (2) = 13.98 min (minor).

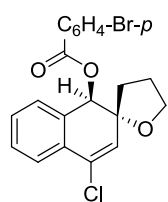
chromatogram of (±)-5.15 (229 nm)



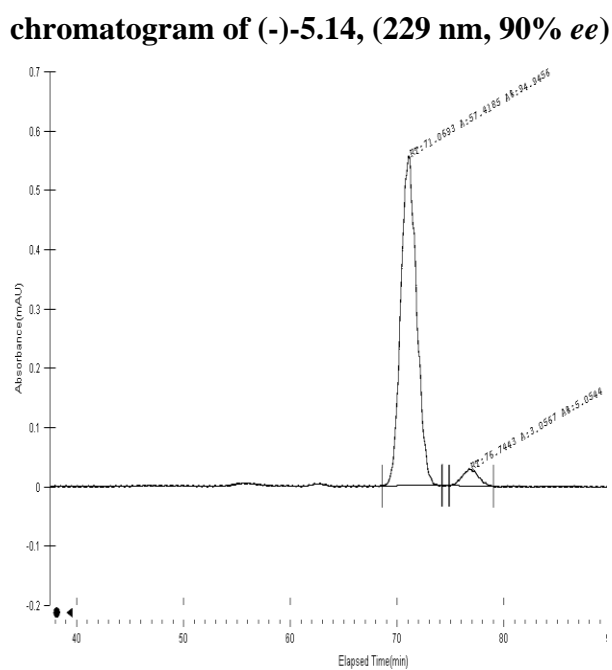
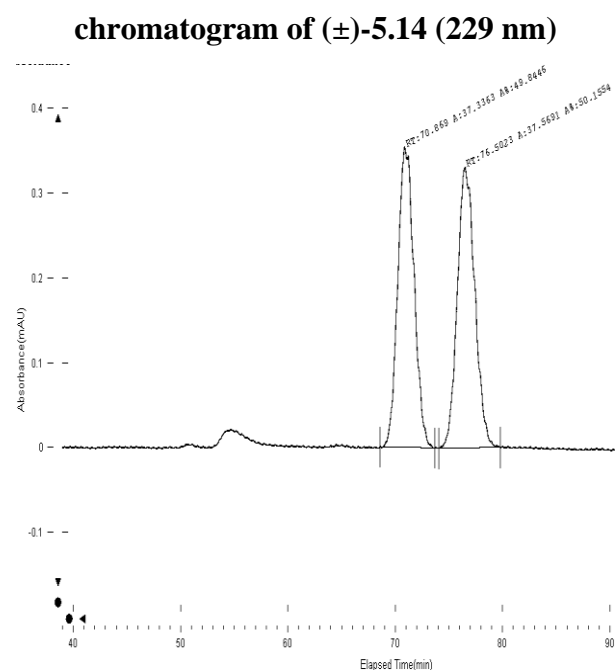
chromatogram of (+)-5.15 (229 nm, 93% ee)



D.12.29 (-)-(1*R*,2*R*)-4'-Chloro-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalene]-1'-yl 4-bromobenzoate (5.14)

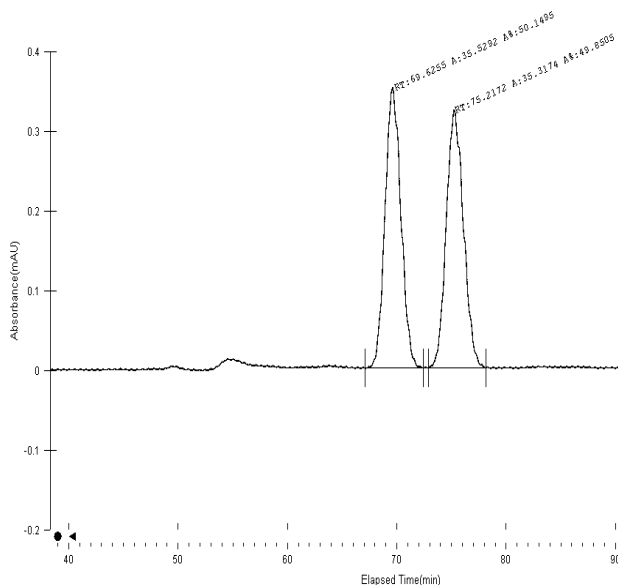


29 mg (71% yield) from 23 mg of (+)-**5.13**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{27} = -114.5^\circ$ (c 1.23, CHCl_3). SFC analysis indicates a 90% *ee*. Column (OJ-H) 2:98:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 71.07 min (major), t_R (2) = 76.74 min (minor). X-ray structural analysis determined that the product is of (*R,R*)-configuration.

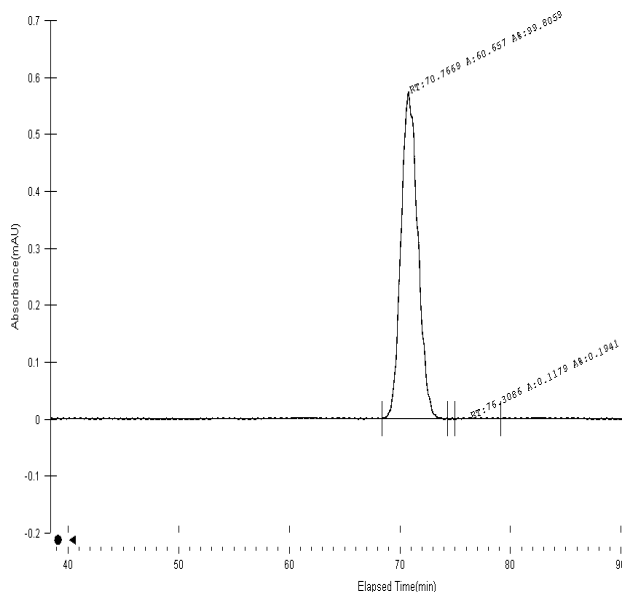


A single recrystallization by slow evaporation of a solution in CH_2Cl_2 and hexanes at RT afforded material of greater than 99% *ee*. A single crystal of this substance was suitable for X-ray structural analysis. Column (OJ-H) 2:98:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_{R} (1) = 70.77 min (minor), t_{R} (2) = 76.31 min (major).

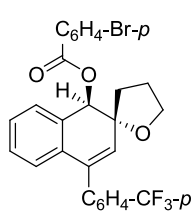
chromatogram of (\pm)-5.14 (229 nm)



chromatogram of (-)-5.14 (229 nm, >99% *ee*)

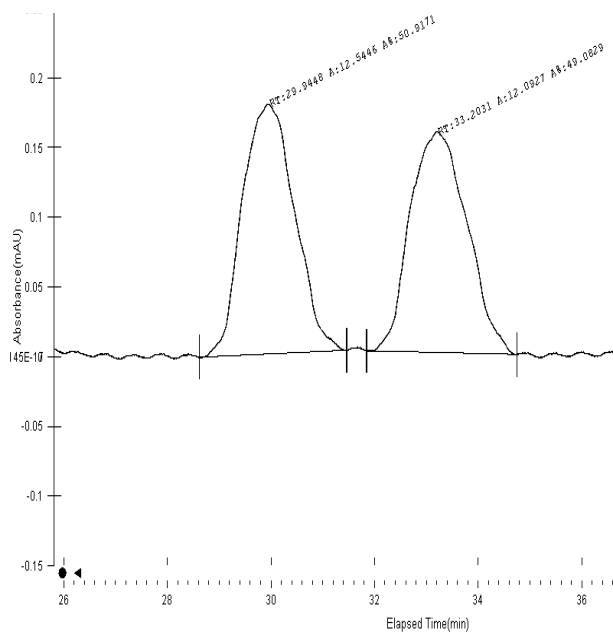


D.12.30 (-)-(1*R*,2*R*)-4'-(4-(Trifluoromethyl)phenyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalene]-1'-yl 4-bromobenzoate (**5.16**)

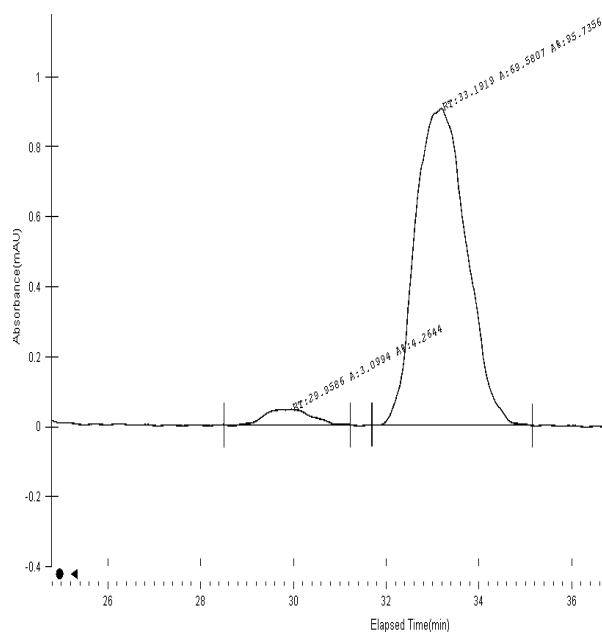


35 mg (93% yield) from 25 mg of (+)-**5.15**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_{\text{D}}^{27} = -53.7^\circ$ (c 1.3, CHCl_3). SFC analysis indicates a 92% *ee*. Column (OD-H) 6:94:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_{R} (1) = 29.96 min (minor), t_{R} (2) = 33.19 min (major).

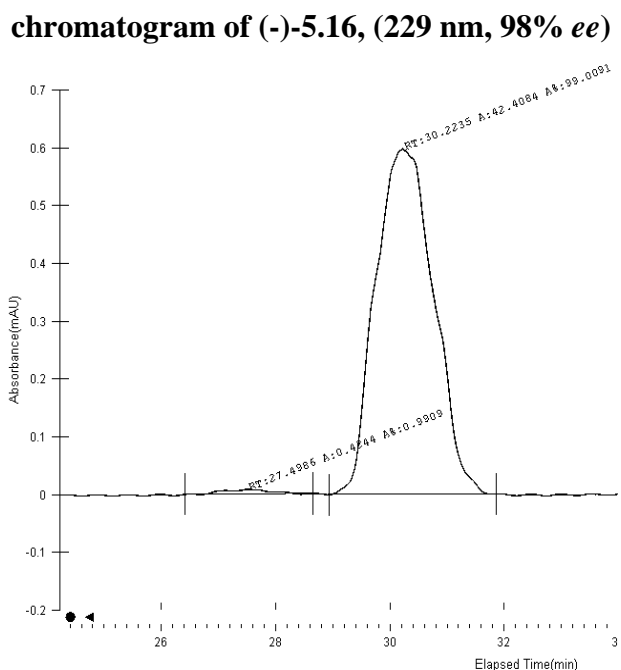
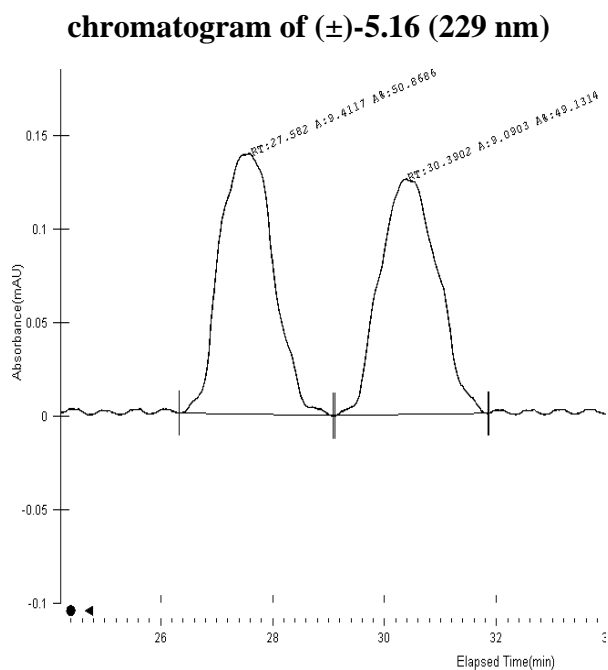
chromatogram of (\pm)-**5.16** (229 nm)



chromatogram of (-)-**5.16** (229 nm, 92% *ee*)

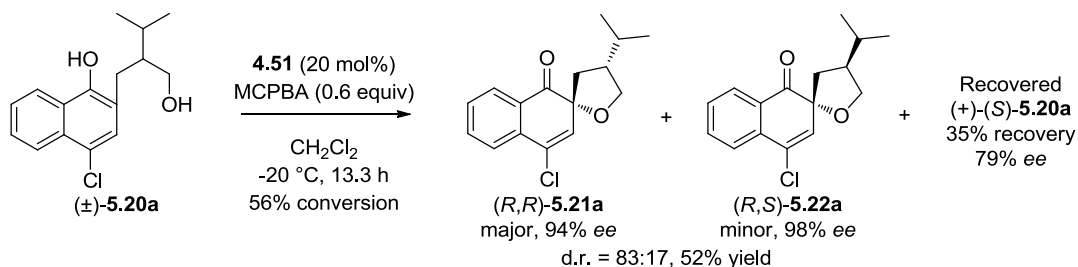


A single recrystallization by slow evaporation of a solution in CH_2Cl_2 and methanol at RT afforded material of 98% *ee*. A single crystal of this substance was suitable for X-ray structural analysis. Column (OD-H) 6:94:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 27.50 min (minor), t_R (2) = 30.22 min (major).

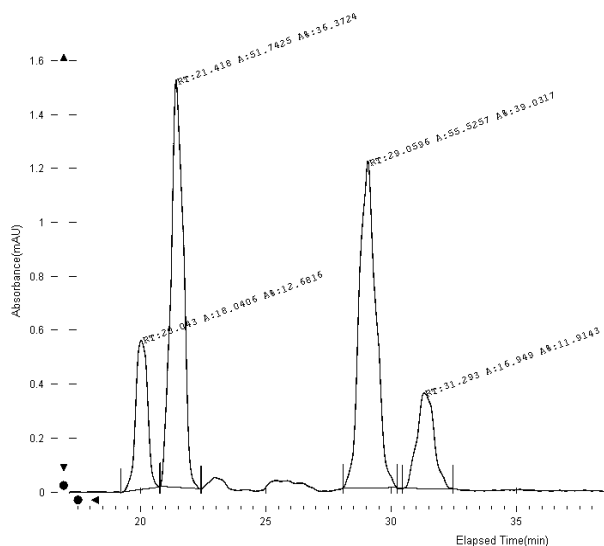


D.12.31 **4'-chloro-4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one**
(83:17 mixture of 5.21a/5.22a)

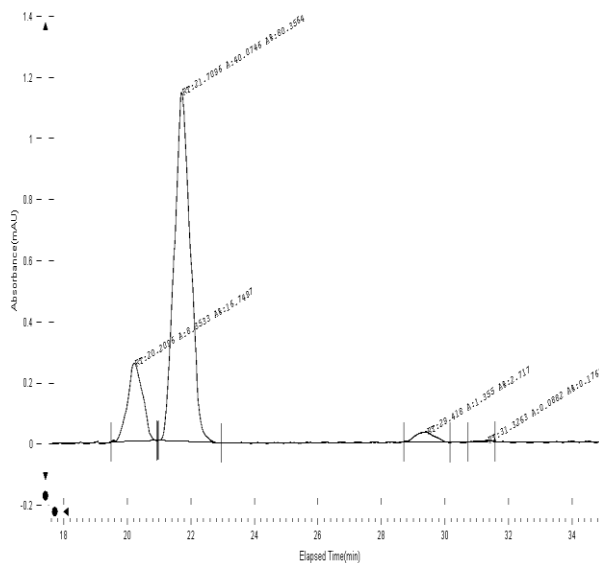
51.2 mg (52% yield) from 100 mg of (\pm)-**5.20a**, colorless oil, eluent: 1:19 EtOAc/hexanes. The d.r. was found to be 83:17 using SFC. SFC analysis indicates a 94% *ee* for **5.21a** and 98% *ee* for **5.22a**. Column (OJ-H) 2:98:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{minor diast}}$ (1) = 20.21 min (major), $t_{\text{major diast}}$ (2) = 21.71 min (major), $t_{\text{major diast}}$ (3) = 29.42 min (minor), $t_{\text{minor diast}}$ (4) = 31.33 min (minor). Compounds **5.21a** and **5.22a** was subsequently shown to be of (*R,R*) and (*R,S*) configuration respectively (see p. 584).



chromatogram of (\pm)-5.21-5.22a (229 nm)



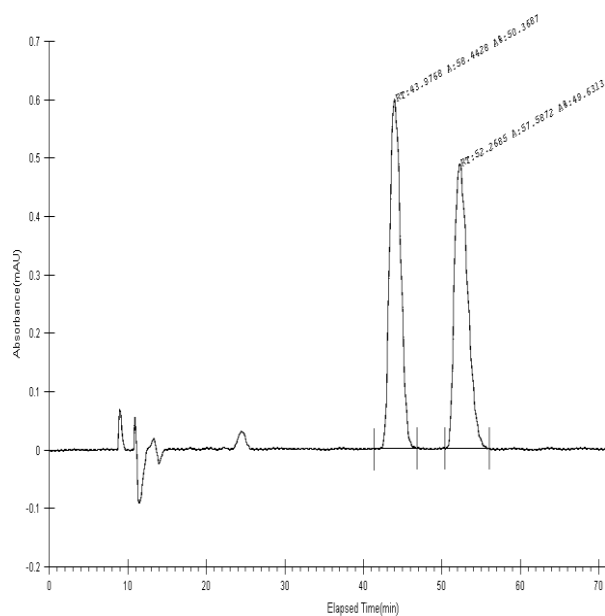
chromatogram of 5.21-5.22a (229 nm)



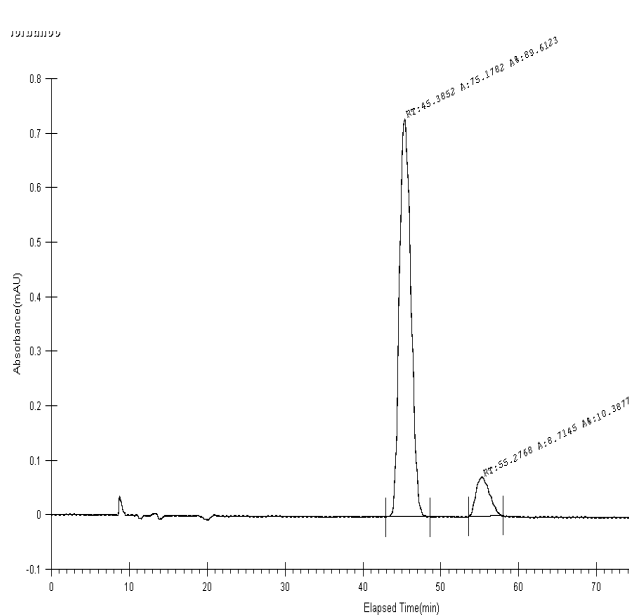
Recovered (+)-(S)-4-chloro-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol (5.20a)

35.1 mg (35% recovery) from 100 mg of (\pm)-**5.20a**, off white solid, eluent: 3:17 EtOAc/hexanes, $[\alpha]_D^{23} = +35.9^\circ$ (c 0.35, CHCl_3). SFC analysis indicates a 79% *ee*. Column (OD-H) 5:95:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 45.39 min (major), t_R (2) = 55.28 (minor). Compound (+)-**5.20a** recovered was subsequently shown to be of (*S*)-configuration (see p. 584).

chromatogram of (\pm)-5.20a (229 nm)

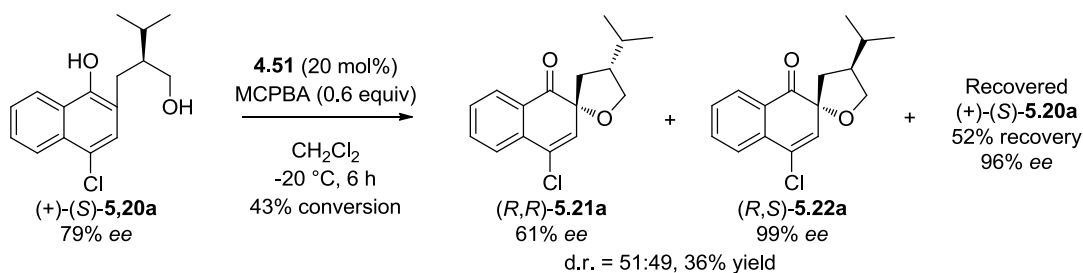


chromatogram of (+)-5.20a (240 nm, 79% ee)

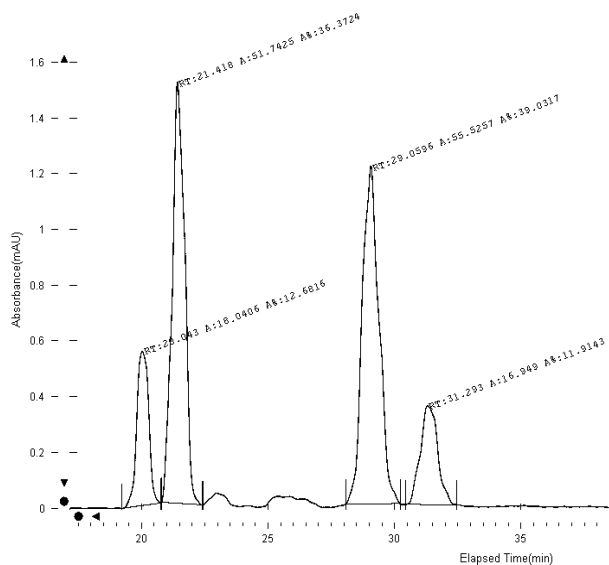


D.12.32 **4'-chloro-4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one**
(51:49 mixture of 5.21a/5.22a)

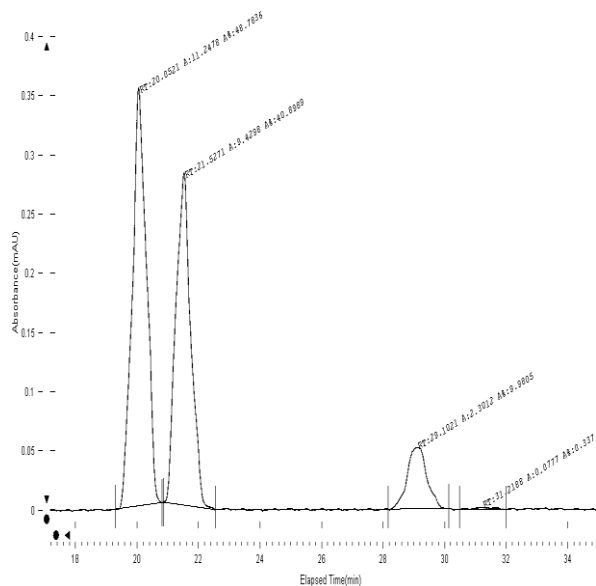
29.6 mg (36% yield) from 82 mg of (+)-**5.20a**, colorless oil, eluent: 1:19 EtOAc/hexanes. The d.r. was found to be 51:49 using SFC. SFC analysis indicates a 61% *ee* for **5.21a** and 99% *ee* for **5.22a**. Column (OJ-H) 2:98:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_{minor diast} (1) = 20.05 min (major), *t*_{major diast} (2) = 21.53 min (major), *t*_{major diast} (3) = 29.10 min (minor), *t*_{minor diast} (4) = 31.22 min (minor).



chromatogram of (±)-5.21-5.22a (229 nm)



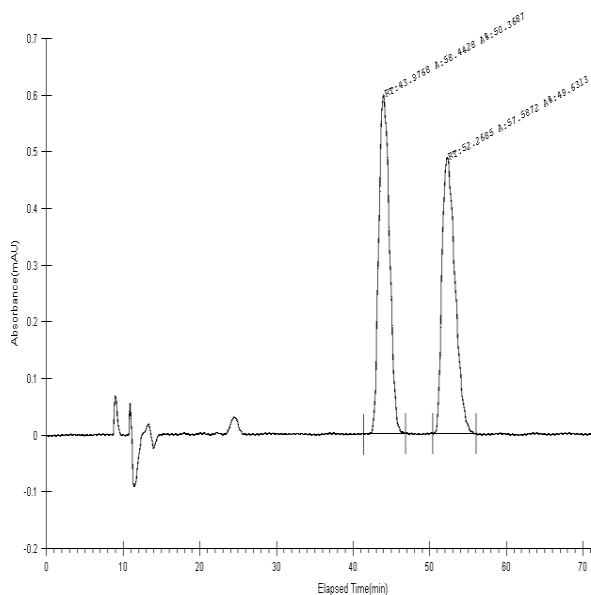
chromatogram of 5.21-5.22a (229 nm)



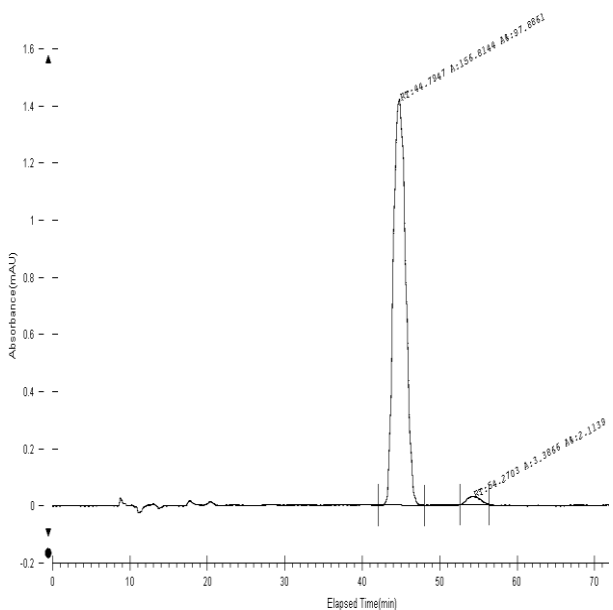
Recovered (+)-(*S*)-4-chloro-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol (5.20a)

42.2 mg (52% recovery) from 82 mg of (+)-**5.20a**, off white solid, eluent: 3:17 EtOAc/hexanes, $[\alpha]_D^{24} = +39.5^\circ$ (c 1.86, CHCl_3). SFC analysis indicates a 96% *ee*. Column (OD-H) 5:95:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 44.79 min (major), t_R (2) = 54.27 (minor).

chromatogram of (\pm)-5.20a (229 nm)

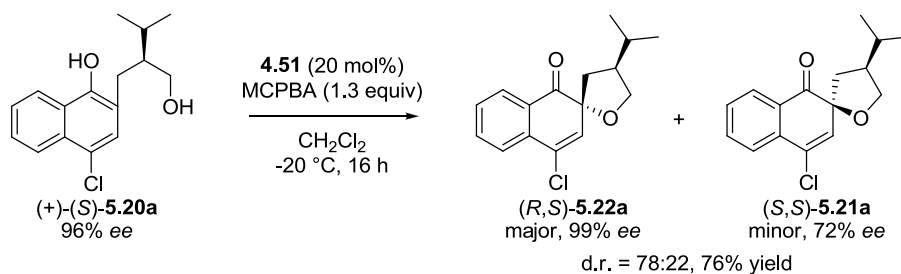


chromatogram of (+)-5.20a, (240 nm, 96% ee)

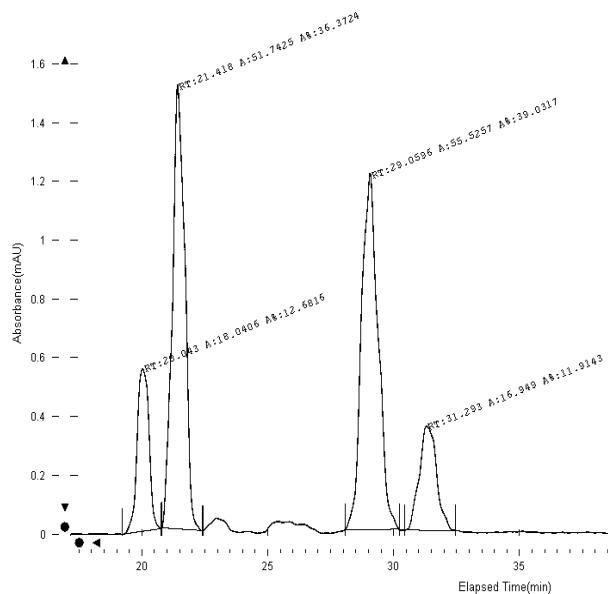


D.12.33 **4'-chloro-4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one**
(78:22 mixture of 5.22a/5.21a)

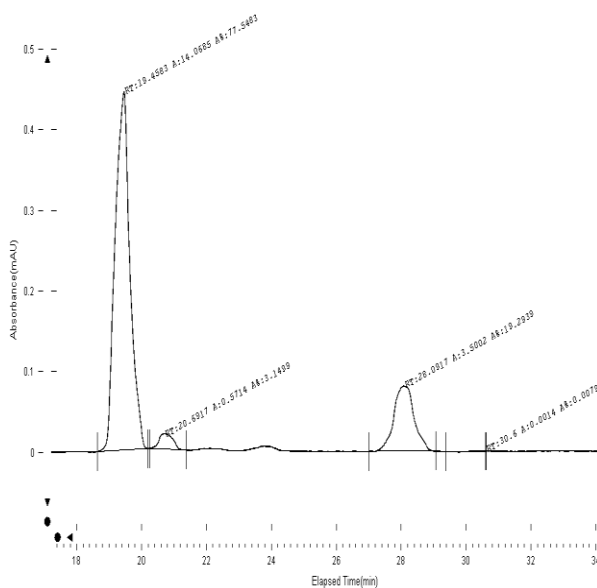
24 mg (76% yield) from 32 mg of (+)-(*S*)-**5.20a**, colorless oil, eluent: 1:19 EtOAc/hexanes. The d.r. was found to be 78:22 using SFC. SFC analysis indicates a 99% *ee* for **5.21a** and 72% *ee* for **5.22a**. Column (OJ-H) 2:98:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_{minor diast} (1) = 19.46 min (major), *t*_{major diast} (2) = 20.69 min (minor), *t*_{major diast} (3) = 28.09 min (major), *t*_{minor diast} (4) = 30.60 min (minor).



chromatogram of (±)-5.21-5.22a (229 nm)

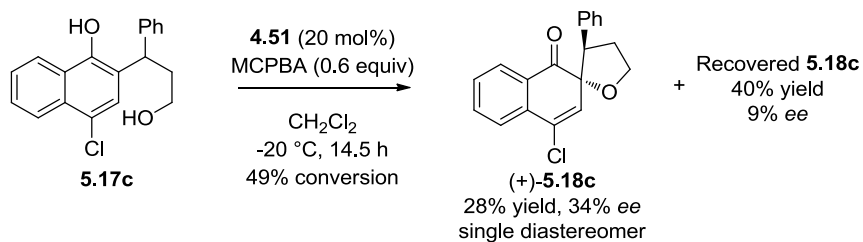


chromatogram of 5.21-5.22a (229 nm)

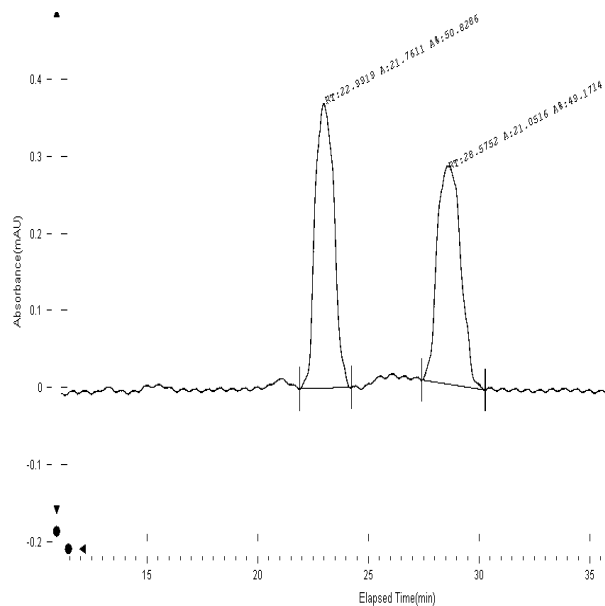


D.12.34 **(+)-4'-chloro-3-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one**
(5.18c)

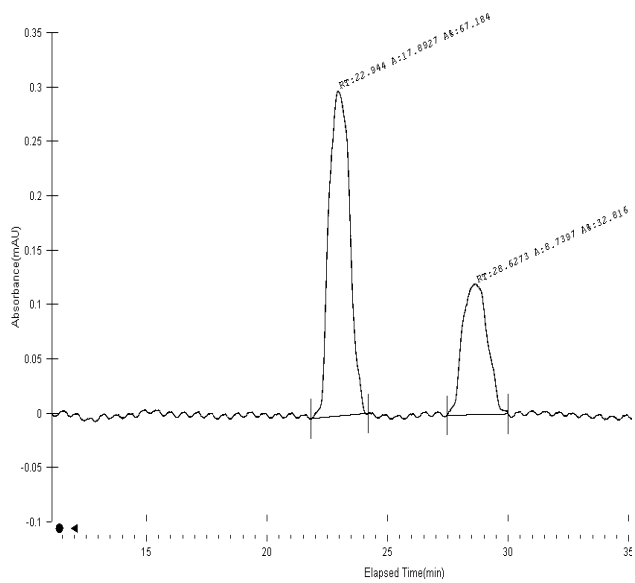
27.3 mg (28% yield) from 100 mg of (\pm)-**5.17c**, light yellow oil, eluent: 1:19 EtOAc/hexane, $[\alpha]_D^{25} = +77.6^\circ$ (c 0.28, CHCl_3). SFC analysis indicates a 34% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t (1) = 22.94 min (major), t (2) = 28.63 min (minor).



chromatogram of (\pm)-5.18c (229 nm)



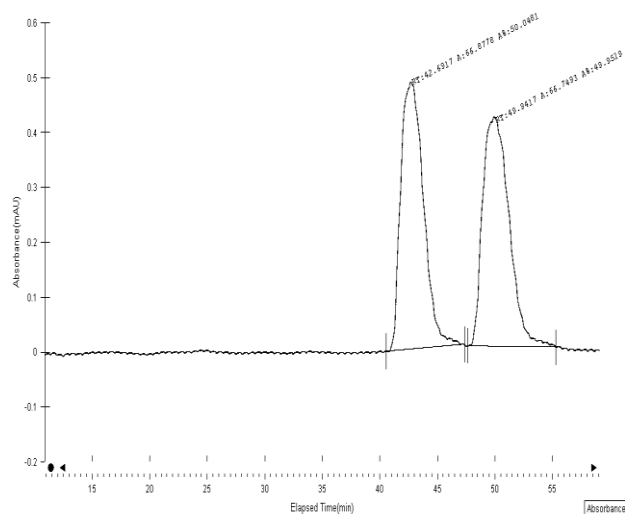
chromatogram of (+)-5.18c (229 nm, 34% ee)



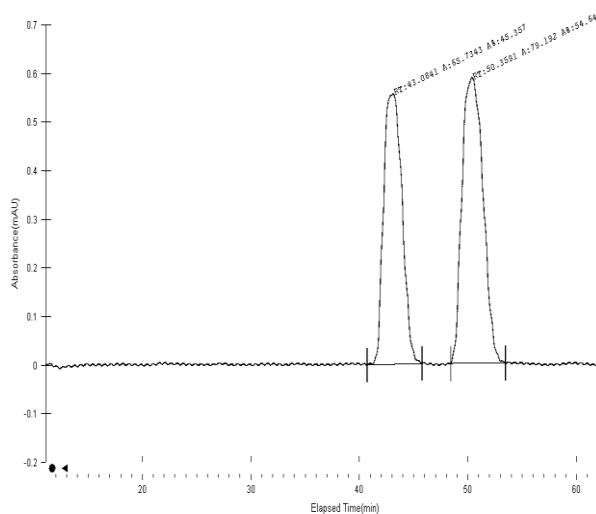
Recovered 4-chloro-2-(3-hydroxy-1-phenylpropyl)naphthalen-1-ol (5.17c)

39.5 mg (40% recovery) from 100 mg of (\pm)-5.17c, yellow solid, eluent: 3:17 to 3:7 EtOAc/hexanes. SFC analysis indicates a 9% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 43.08 min (minor), t_R (2) = 50.36 (major).

chromatogram of (\pm)-5.17c (229 nm)

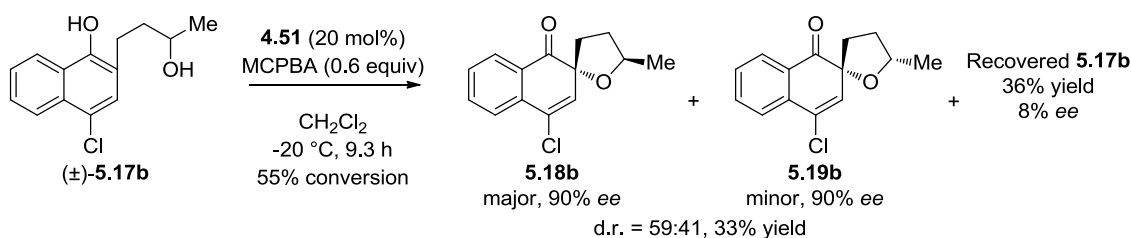


chromatogram of 5.17c (229 nm, 9% *ee*)

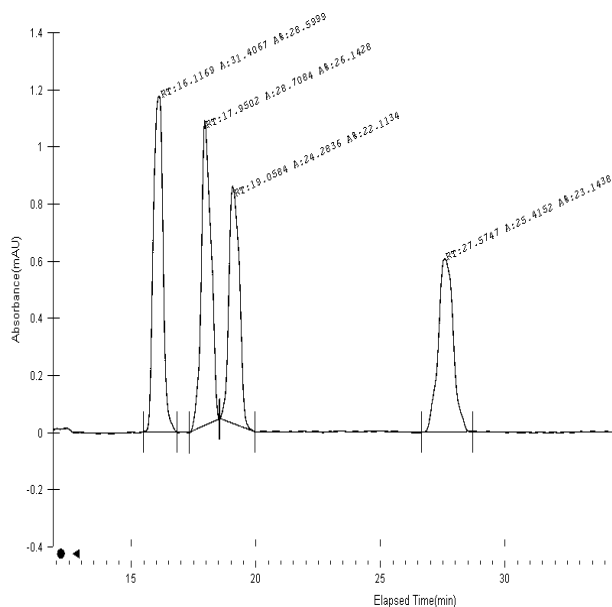


D.12.35 4'-chloro-5-methyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (59:41 mixture of 5.18b/5.19b)

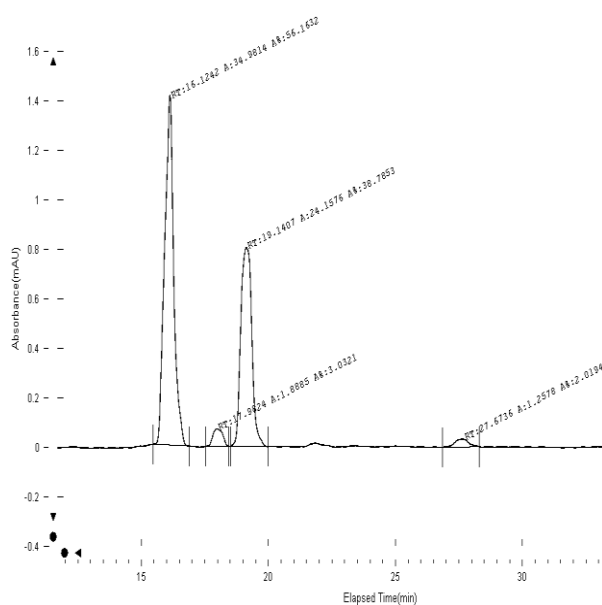
32.6 mg (33% yield) from 100 mg of (\pm)-**5.17b**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 59:41 using SFC. SFC analysis indicates a 90% *ee* for **5.18b** and 90% *ee* for **5.19b**. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{major diast (1)}}$ = 16.12 min (major), $t_{\text{major diast (2)}}$ = 17.98 min (minor), $t_{\text{minor diast (3)}}$ = 19.14 min (major), $t_{\text{minor diast (4)}}$ = 27.67 min (minor)



chromatogram of (\pm)-5.18-5.19b (229 nm)



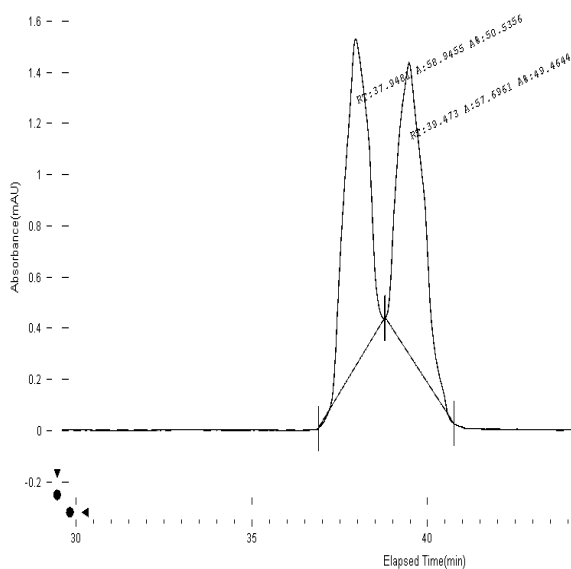
chromatogram of 5.18-5.19b (229 nm)



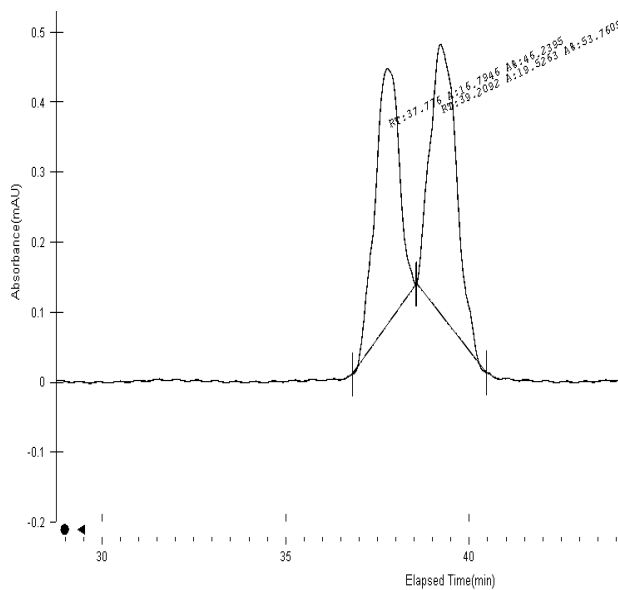
Recovered 4-chloro-2-(3-hydroxybutyl)naphthalen-1-ol (5.17b)

35.7 mg (36% recovery) from 100 mg of (\pm)-**5.17b**, white solid, eluent: 1:9 EtOAc/hexanes. SFC analysis indicates a 8% *ee*. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 37.78 min (minor), t_R (2) = 39.21 (major).

chromatogram of (\pm)-**5.17b** (229 nm)

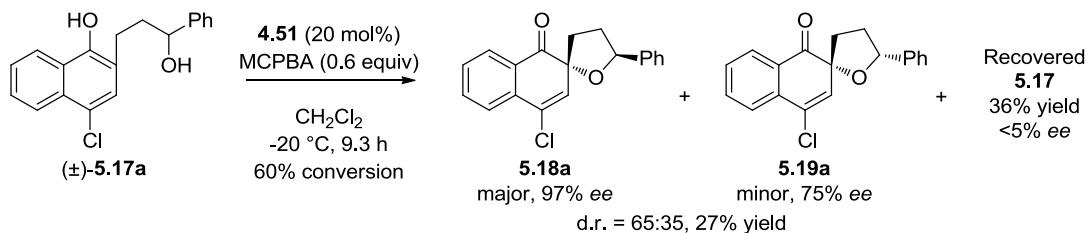


chromatogram of **5.17b**, (229 nm, 8% *ee*)

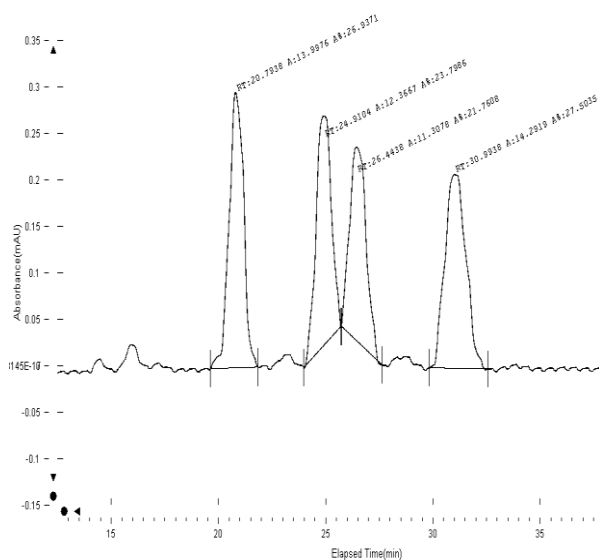


D.12.36 4'-chloro-5-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (65:35 mixture of 5.18a/5.19a)

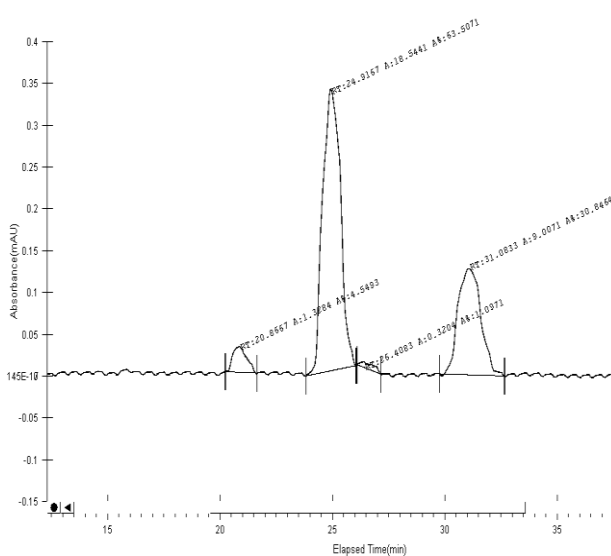
26.9 mg (27% yield) from 100 mg of (\pm)-**5.17a**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 65:35 using SFC. SFC analysis indicates a 97% *ee* for **5.18a** and 75% *ee* for **5.19a**. Column (AD-H) 10:90:0.1 *i*PrOH: liq CO₂: diethylamine, flow rate = 1.0 mL/min; $t_{\text{minor diast}}$ (1) = 20.87 min (minor), $t_{\text{major diast}}$ (2) = 24.92 min (major), $t_{\text{major diast}}$ (3) = 26.41 min (minor), $t_{\text{minor diast}}$ (4) = 31.08 min (major).



chromatogram of (\pm)-5.18-5.19a (229 nm)



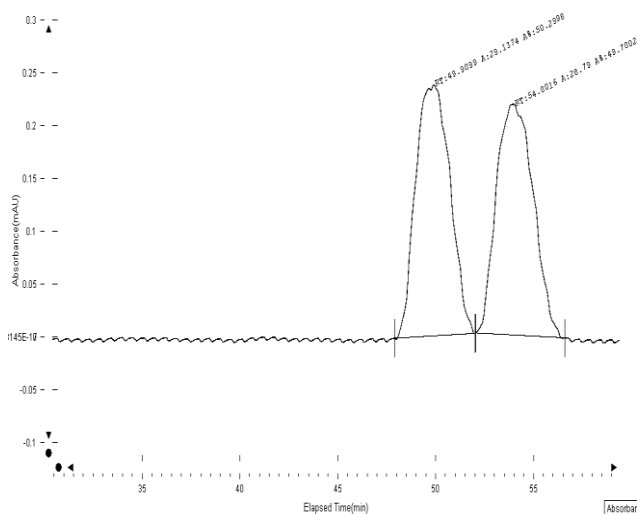
chromatogram of 5.18-5.19a (229 nm)



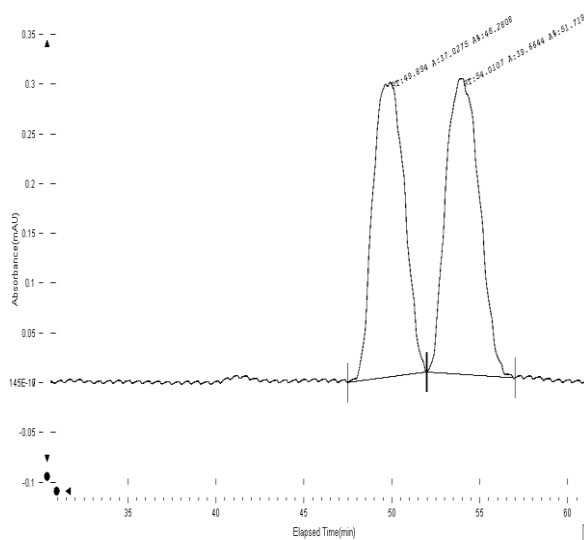
Recovered 4-chloro-2-(3-hydroxy-3-phenylpropyl)naphthalen-1-ol (5.17a)

35.5 mg (36% recovery) from 100 mg of (\pm)-5.17a, light yellow solid, eluent: 1:9 to 1:4 EtOAc/hexanes. SFC analysis indicates a 3% *ee*. Column (OD-H) 8:92:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 49.89 min (minor), t_R (2) = 54.01 (major).

chromatogram of (\pm)-5.17a (229 nm)



chromatogram of 5.17a, (229 nm, 3% *ee*)

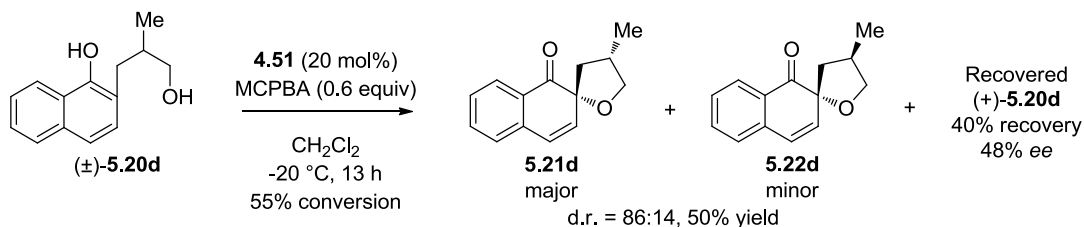


D.12.37 4-methyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (86:14 mixture of 5.21d/5.22d)

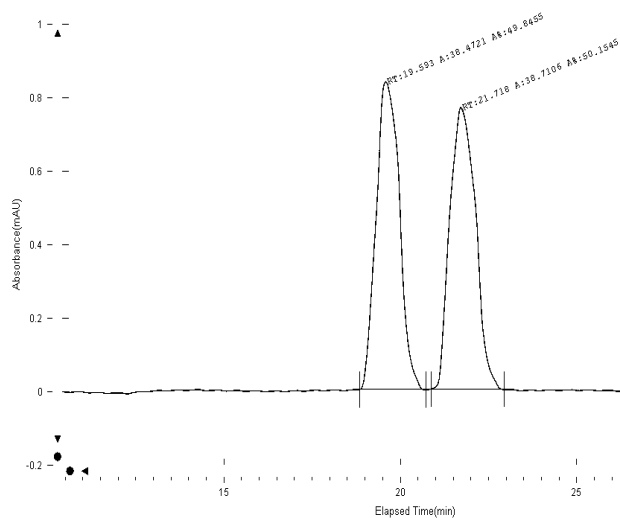
49.2 mg (50% yield) from 100 mg of (\pm)-**5.20d**, colourless oil. The d.r. was found to be 86:14 using ^1H NMR. The peaks of enantiomers could not be separated using the available columns.

Recovered (+)-2-(3-hydroxy-2-methylpropyl)naphthalen-1-ol (5.20d)

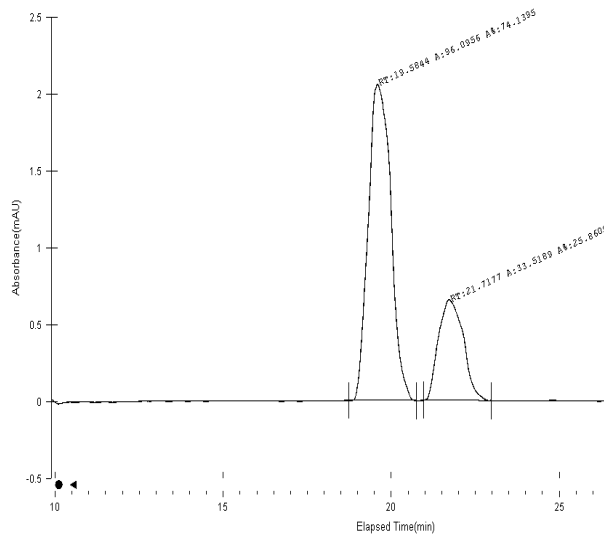
39.8 mg (40% recovery) from 100 mg of (\pm)-**5.20d**, white solid, eluent: 1:9 to 3:7 EtOAc/hexanes, $[\alpha]_D^{25} = +1.3^\circ$ (c 0.40, CHCl_3). SFC analysis indicates a 48% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 19.58 min (major), t_R (2) = 21.72 (minor).



chromatogram of (\pm)-5.21-5.22d (229nm)

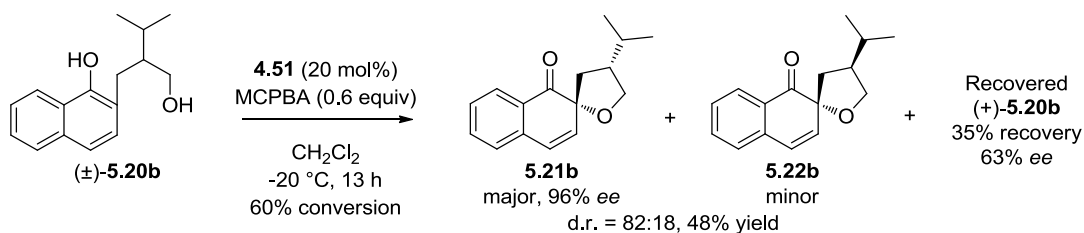


chromatogram of 5.21-5.22d, (229 nm)

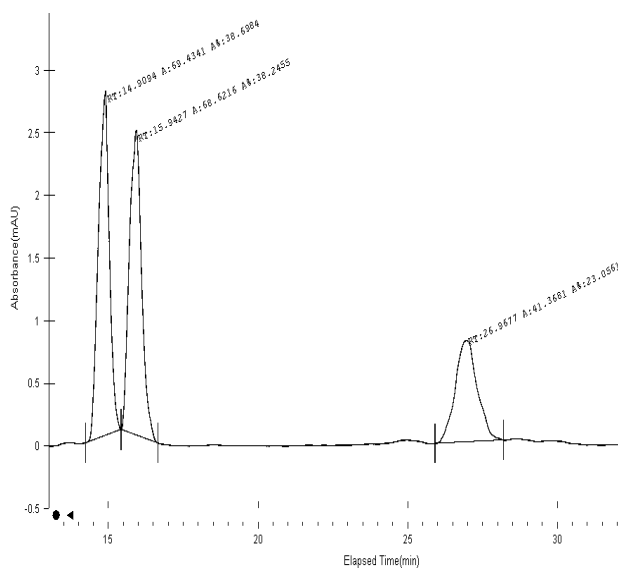


D.12.38 4-isopropyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (82:18 mixture of 5.21b/5.22b)

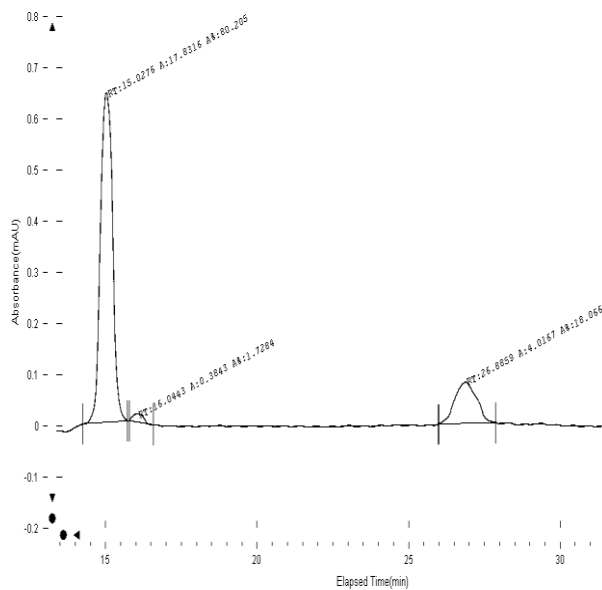
47.4 mg (48% yield) from 100 mg of (\pm)-**5.20b**, colorless oil, eluent: 1:19 to 1:9 EtOAc/hexane. The d.r. was found to be 82:18 using SFC. SFC analysis indicates a 96% *ee* for **5.21b** and the peak for **5.22b** could not be separated using any of the columns available. Column (AS-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{major diast}}$ (1) = 15.03 min (major), $t_{\text{major diast}}$ (2) = 16.04 min (minor), $t_{\text{minor diast}}$ (3) = 26.89 min.



chromatogram of (\pm)-5.21-5.22b (229 nm)



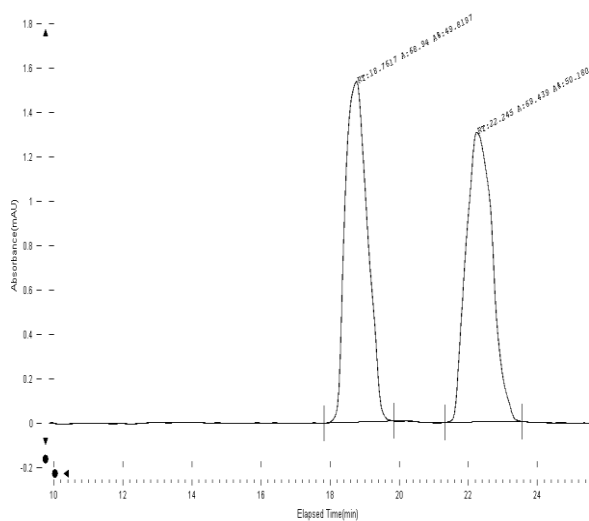
chromatogram of 5.21-5.22b (229 nm)



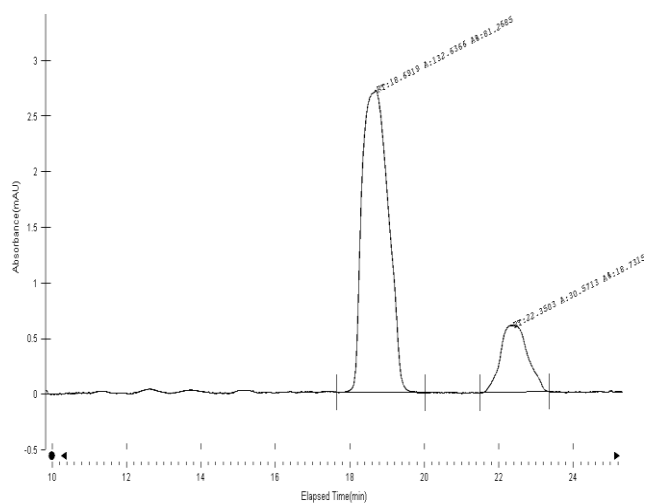
Recovered (+)-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol (5.20b)

34.6 mg (35% recovery) from 100 mg of (±)-5.20b, off white solid, eluent: 1:9 to 1:4 EtOAc/hexanes, $[\alpha]_D^{26} = +34.3^\circ$ (*c* 0.36, CHCl₃). SFC analysis indicates a 62% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 18.69 min (major), *t*_R (2) = 22.35 (minor).

chromatogram of (±)-5.20b (229 nm)



chromatogram of (+)-5.20b, (229 nm, 62% *ee*)

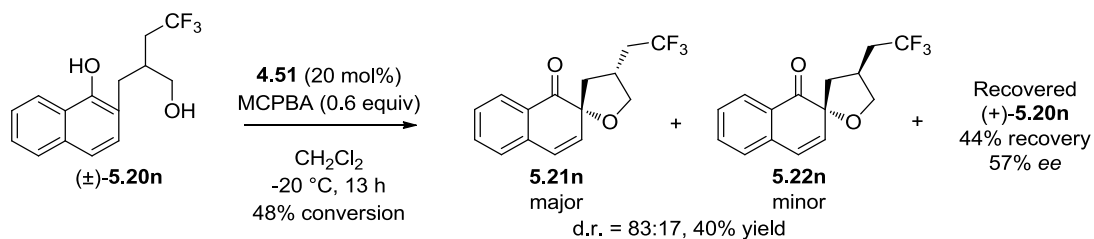


D.12.39 4-(2,2,2-trifluoroethyl)-4,5-dihydro-1'*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one
(83:17 mixture of 5.21n/5.22n)

The d.r. was found to be 83:17 according to ¹H NMR of crude reaction mixture and were separable via column chromatography (eluent: 1:19 to 1:9 EtOAc/hexane).

(+)-**5.21n**: 36.1 mg (36% yield) from 100 mg of (±)-**5.20n**, white solid, $[\alpha]_D^{25} = +132.7^\circ$ (*c* 0.93, CHCl₃), white solid, m.p.: 39-41 °C; **IR**: 1685. **¹H**: 7.98 (d, 1H, *J* = 7.7), 7.57 (app t, 1H, *J* = 7.5), 7.36 (app t, 1H, *J* = 7.5), 7.20 (d, 1H, *J* = 7.6), 6.54 (d, 1H, *J* = 9.8), 6.17 (d, 1H, *J* = 9.9), 4.32 (app t, 1H, *J* = 7.8), 3.93 (app t, 1H, *J* = 9.0), 2.83-2.41 (m, 1H), 2.37-2.07 (m, 4H). **¹³C**: 200.9, 137.3, 135.5, 135.2, 128.8, 128.5, 127.6, 127.5, 126.4, 126.6 (q, *J* = 276.8), 82.6, 74.4, 43.1, 36.0 (q, *J* = 28.7), 34.4 (q, *J* = 2.6). **HRMS**: calcd for C₁₅H₁₃O₂F₃Na [M+Na]⁺: 305.0765; found: 305.0765. The peaks of enantiomers could not be separated by using any of the available columns.

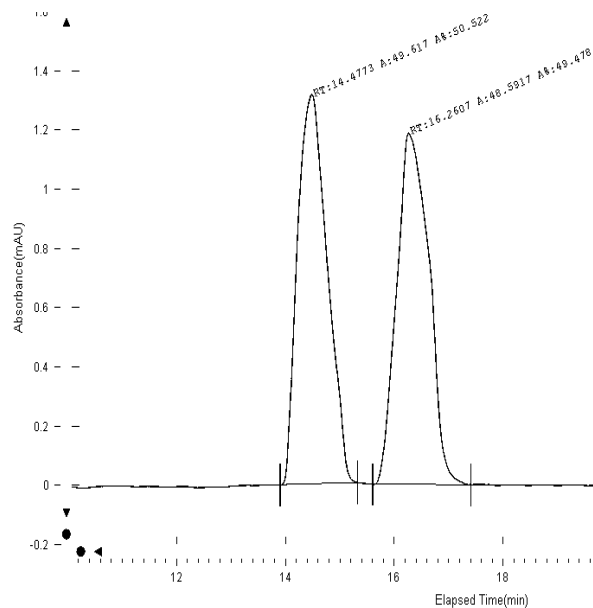
(+)-**5.22n**: 4.0 mg (4% yield) from 100 mg of (±)-**5.20n**, colorless oil, $[\alpha]_D^{25} = +190.1^\circ$ (*c* 0.31, CHCl₃); **IR**: 1688. **¹H**: 7.97 (d, 1H, *J* = 7.7), 7.56 (app t, 1H, *J* = 7.5), 7.35 (app t, 1H, *J* = 7.4), 7.19 (d, 1H, *J* = 7.5), 6.54 (d, 1H, *J* = 9.8), 6.14 (d, 1H, *J* = 9.8), 4.53 (app t, 1H, *J* = 8.0), 3.78 (app t, 1H, *J* = 8.4), 3.10-2.97 (m, 1H), 2.44 (dd, 1H, *J* = 13.0, 7.1), 2.33-2.11 (m, 2H), 1.68 (dd, 1H, *J* = 12.8, 10.6). **¹³C**: 201.1, 137.3, 135.8, 135.1, 128.7, 128.4, 127.5, 126.7, 126.5 (q, *J* = 277.1), 84.6, 74.6, 41.7, 36.6 (q, *J* = 29.0), 32.1 (q, *J* = 2.3). The peaks of enantiomers could not be separated by using any of the available columns.



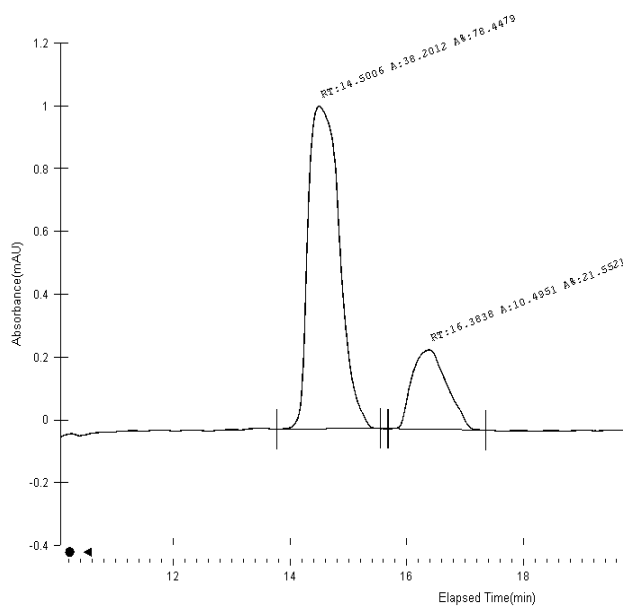
Recovered (+)-2-(4,4,4-trifluoro-2-(hydroxymethyl)butyl)naphthalen-1-ol (5.20n)

43.7 mg (44% recovery) from 100 mg of (\pm)-5.20n, light yellow oil, eluent: 1:9 to 3:17 EtOAc/hexanes. $[\alpha]_D^{20} = +4.6^\circ$ (c 0.42, CHCl_3). SFC analysis indicates a 57% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 14.50 min (major), t_R (2) = 16.38 (minor).

chromatogram of (\pm)-5.20n (229 nm)

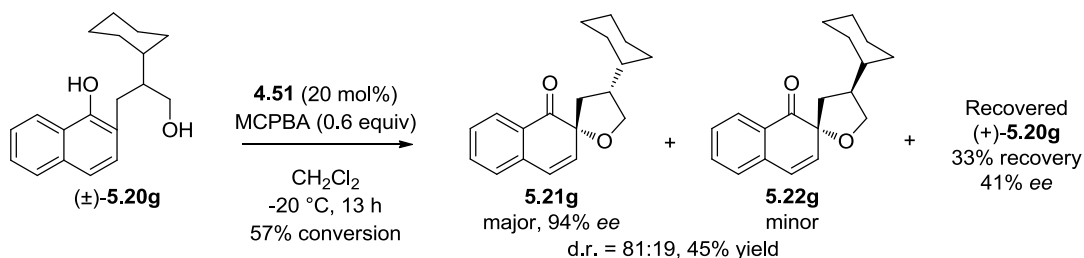


chromatogram of (+)-5.20n, (229 nm, 57% ee)

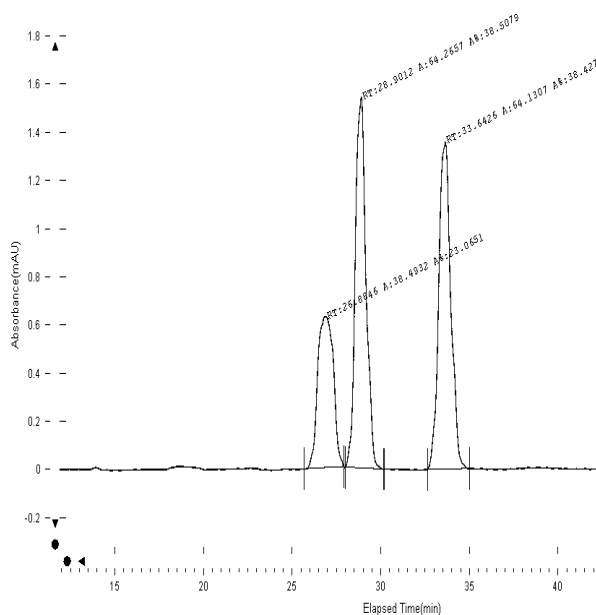


D.12.40 4-cyclohexyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (81:19 mixture of 5.21g/5.22g)

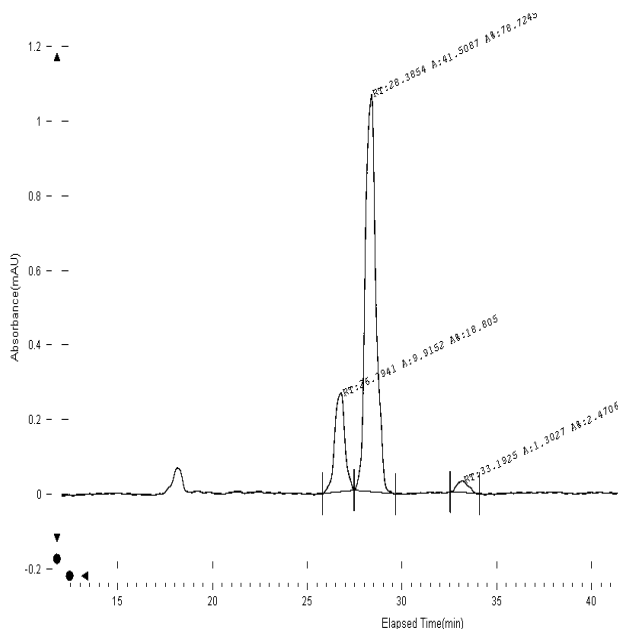
44.3 mg (45% yield) from 100 mg of (\pm)-**5.20g**, colorless oil, eluent: 1:19 to 1:9 EtOAc/hexane. The d.r. was found to be 81:19 using SFC. SFC analysis indicates a 94% *ee* for **5.21g** and the peak for **5.22g** could not be separated using any of the columns available. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{minor diast}}$ (1) = 26.79 min, $t_{\text{major diast}}$ (2) = 28.39 min (major), $t_{\text{major diast}}$ (3) = 33.19 min (minor).



chromatogram of (\pm)-5.21-5.22g (229 nm)



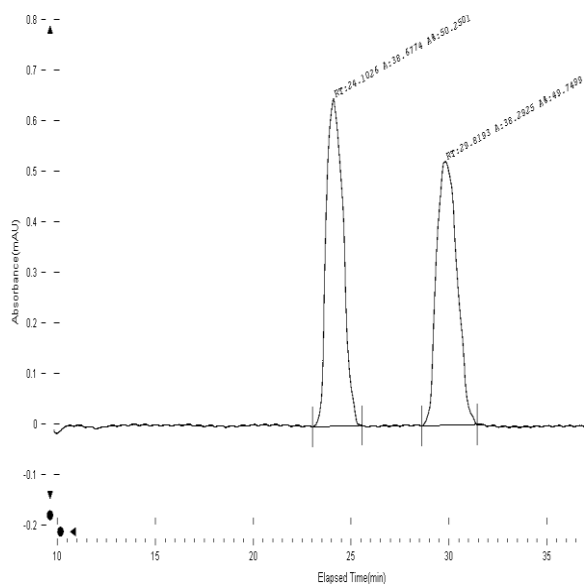
chromatogram of 5.21-5.22g (229 nm)



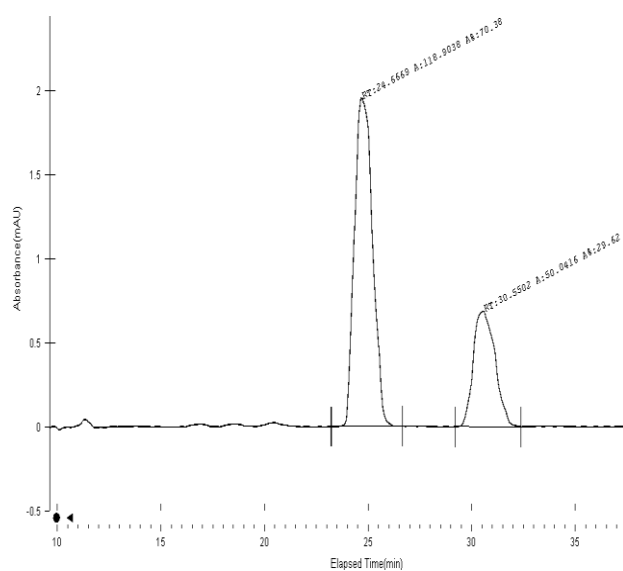
Recovered (+)-2-(2-cyclohexyl-3-hydroxypropyl)naphthalen-1-ol (5.20g)

32.6 mg (33% recovery) from 100 mg of (\pm)-**5.20g**, off white solid, eluent: 3:17 to 1:4 EtOAc/hexanes, $[\alpha]_D^{26} = +40.8^\circ$ (c 0.14, CHCl_3). SFC analysis indicates a 41% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 24.67 min (major), t_R (2) = 30.55 (minor).

chromatogram of (\pm)-5.20g (229 nm)



chromatogram of (+)-5.20g, (229 nm, 41% ee)

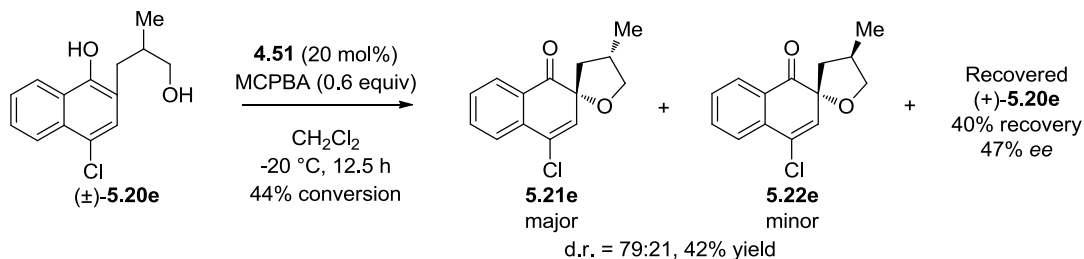


D.12.41 4-methyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (79:21 mixture of 5.21e/5.22e)

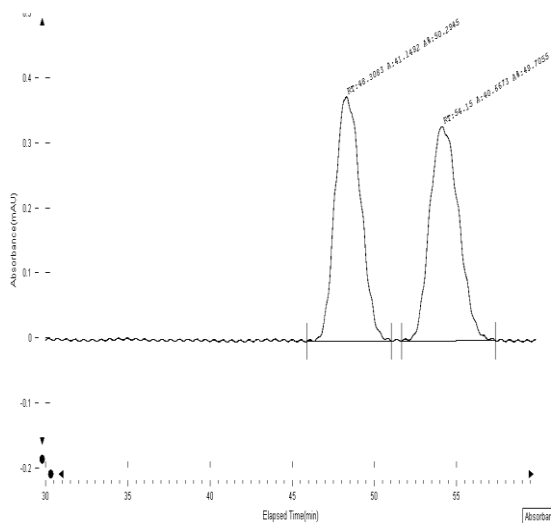
41.3 mg (42% yield) from 100 mg of (\pm)-**5.20e**, colorless oil, eluent: 1:19 EtOAc/hexane. The peaks of enantiomers could not be separated using any of the available columns. The d.r. was found to be 79:21 using ^1H NMR.

Recovered (+)-4-chloro-2-(3-hydroxy-2-methylpropyl)naphthalen-1-ol (5.20e)

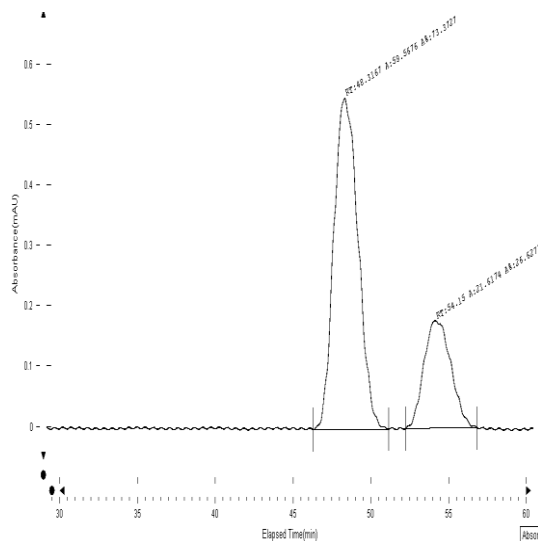
39.5 mg (40% recovery) from 100 mg of (\pm)-**5.20e**, off white solid, eluent: 1:9 to 1:4 EtOAc/hexanes, $[\alpha]_D^{23} = +1.7^\circ$ (c 0.40, CHCl_3); SFC analysis indicates a 47% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 48.32 min (major), t_R (2) = 54.15 (minor).



chromatogram of (\pm)-5.20e (229 nm)

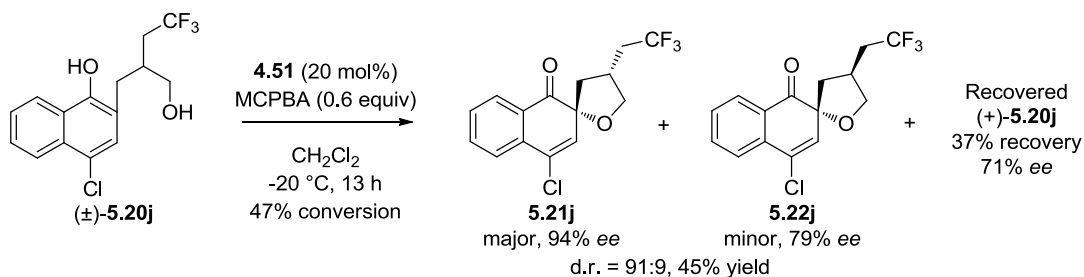


chromatogram of (+)-5.20e (229 nm, 47% ee)

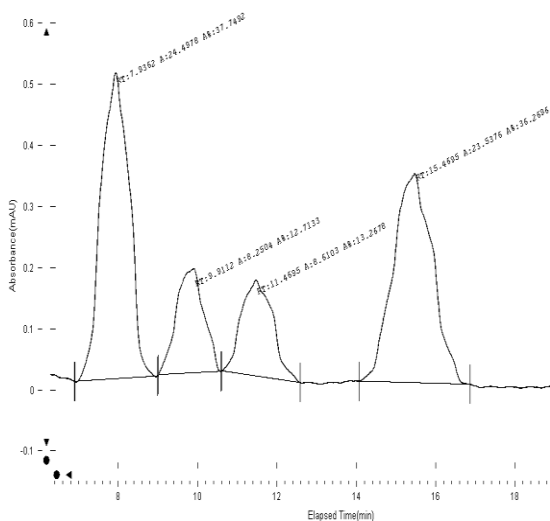


D.12.42 4'-chloro-4-(2,2,2-trifluoroethyl)-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (91:9 mixture of 5.21j/5.22j)

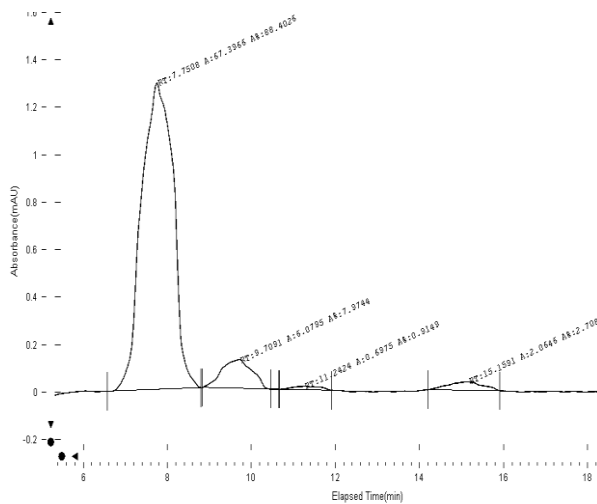
44.3 mg (45% yield) from 100 mg of (\pm)-**5.20j**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 91:9 using SFC. SFC analysis indicates a 94% *ee* for **5.21j** and 79% *ee* for **5.22j**. Column (Lux 3u cellulose) 1:99:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{major diast}}$ (1) = 7.75 min (major), $t_{\text{minor diast}}$ (2) = 9.71 min (major), $t_{\text{minor diast}}$ (3) = 11.24 min (minor), $t_{\text{major diast}}$ (4) = 15.16 min (minor).



chromatogram of (\pm)-5.21-5.22j (229 nm)



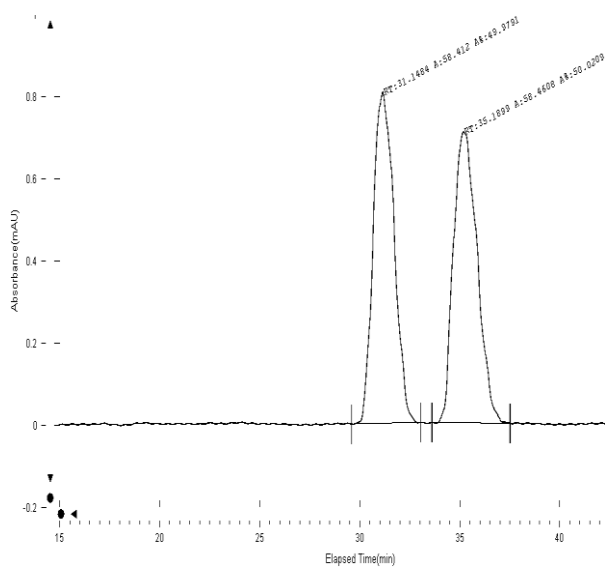
chromatogram of 5.21-5.22j (229 nm)



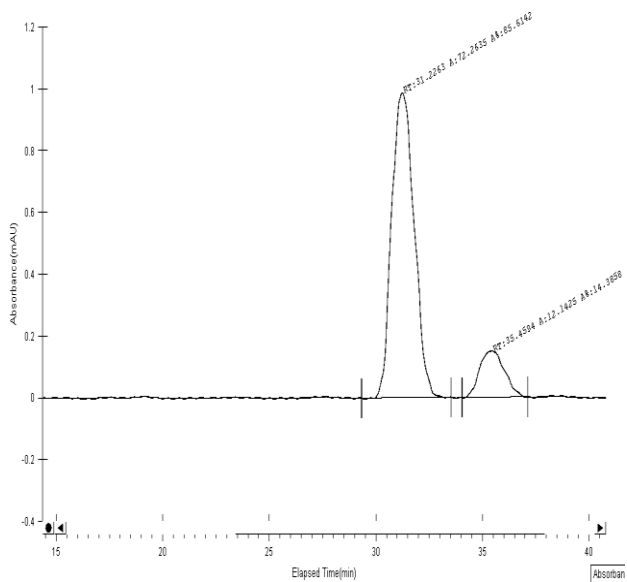
Recovered (+)-4-chloro-2-(4,4,4-trifluoro-2-(hydroxymethyl)butyl)naphthalen-1-ol (5.20j)

36.7 mg (37% recovery) from 100 mg of (\pm)-5.20j, pale yellow solid, eluent: 1:9 to 1:4 EtOAc/hexanes, $[\alpha]_D^{24} = +5.8^\circ$ (c 0.37, CHCl_3). SFC analysis indicates a 71% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 31.23 min (major), t_R (2) = 35.46 min (minor).

chromatogram of (\pm)-5.20j (229 nm)

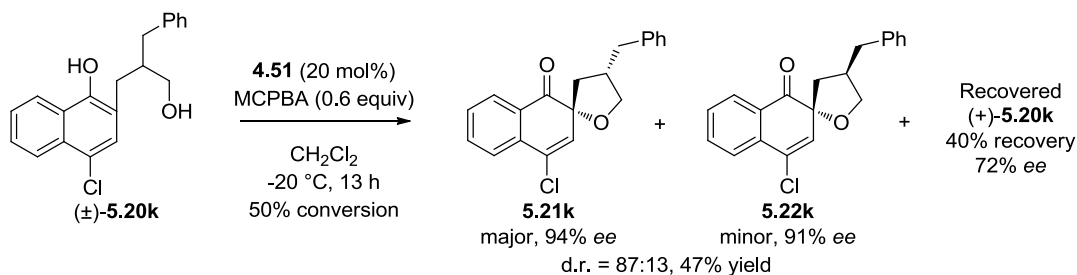


chromatogram of (+)-5.20j, (229 nm, 71% ee)

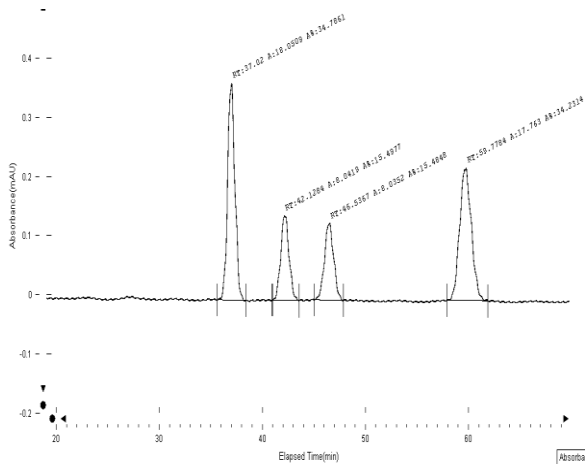


D.12.43 4-benzyl-4'-chloro-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (87:13 mixture of 5.21k/5.22k)

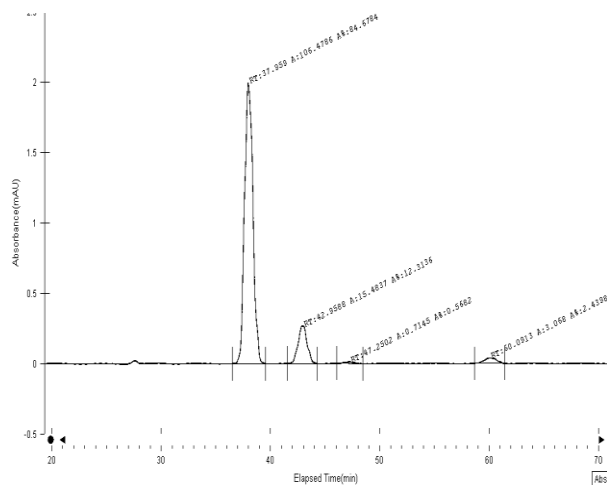
46.5 mg (47% yield) from 100 mg of (\pm)-**5.20k**, light yellow oil, eluent: 1:19 to 1:9 EtOAc/hexane. The d.r. was found to be 87:13 using SFC. SFC analysis indicates a 94% *ee* for **5.21k** and 91% *ee* for **5.22k**. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{major diast}}$ (1) = 37.96 min (major), $t_{\text{minor diast}}$ (2) = 42.96 min (major), $t_{\text{minor diast}}$ (3) = 47.25 min (minor), $t_{\text{major diast}}$ (4) = 60.09 min (minor).



chromatogram of (\pm)-5.21-5.22k (229 nm)



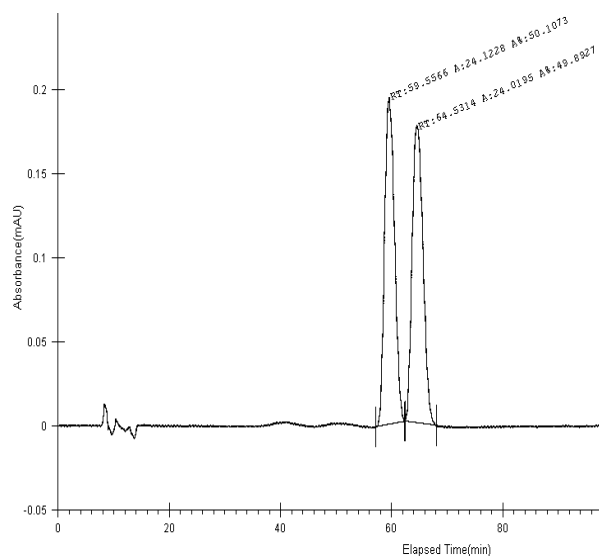
chromatogram of 5.21-5.22k (229 nm)



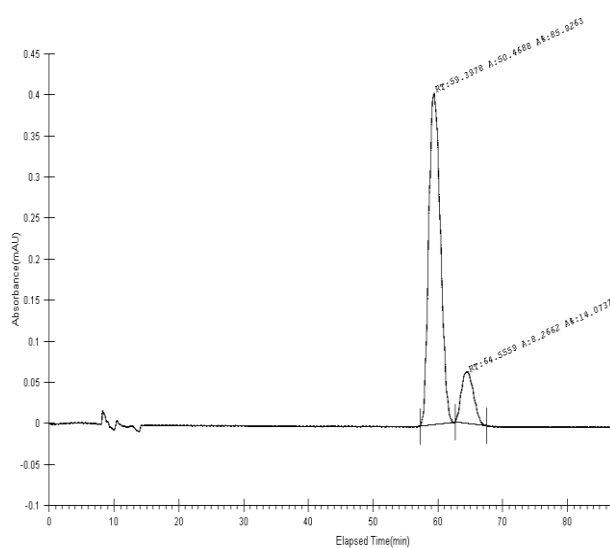
Recovered (+)-2-(2-benzyl-3-hydroxypropyl)-4-chloronaphthalen-1-ol (5.20k)

39.6 mg (40% recovery) from 100 mg of (\pm)-5.20k, off white solid, eluent: 1:4 EtOAc/hexanes, $[\alpha]_D^{22} = +22.4^\circ$ (c 0.37, CHCl_3). SFC analysis indicates a 72% *ee*. Column (AD-H) 7:93:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 59.40 min (major), t_R (2) = 64.56 (minor).

chromatogram of (\pm)-5.20k (229 nm)

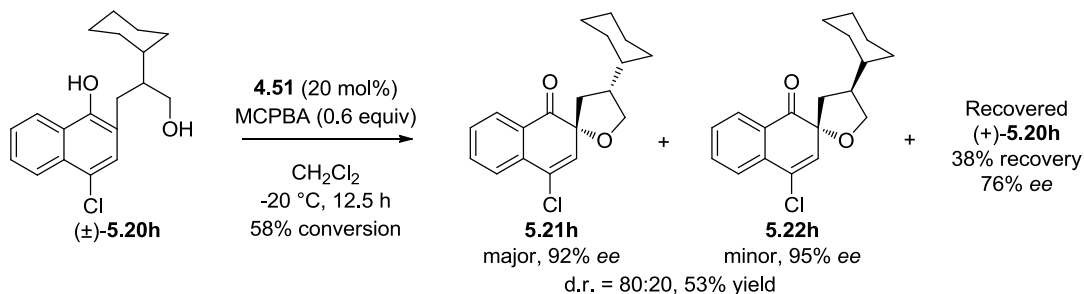


chromatogram of (+)-5.20k (229 nm, 72% *ee*)

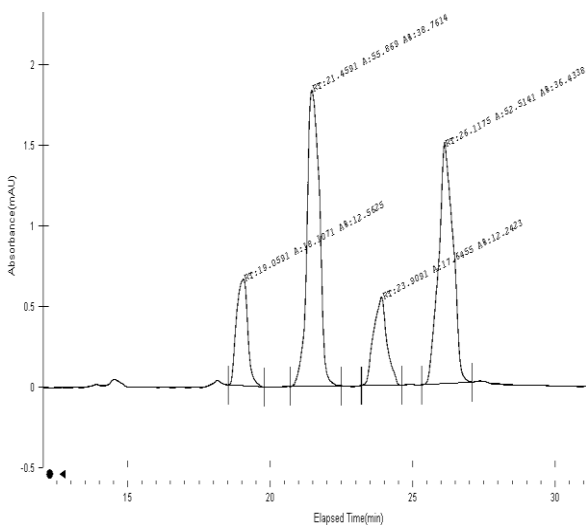


D.12.44 4'-chloro-4-cyclohexyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one
(80:20 mixture of 5.21h/5.22h)

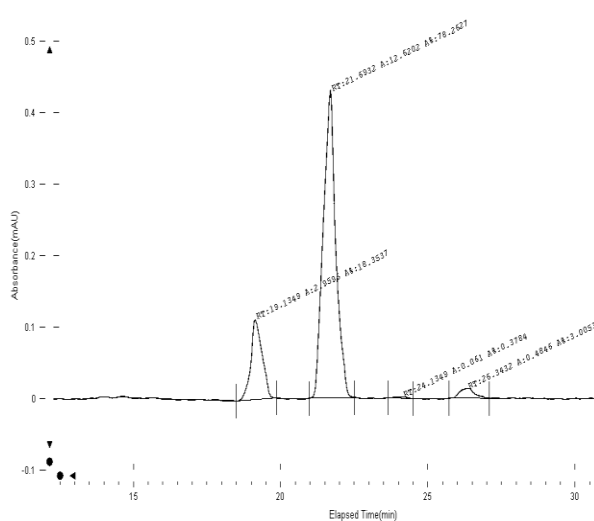
52.3 mg (53% yield) from 100 mg of (±)-**5.20h**, colorless oil, eluent: 1:19 EtOAc/hexanes. The d.r. was found to be 80:20 using SFC. SFC analysis indicates a 92% *ee* for **5.21h** and 95% *ee* for **5.22h**. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_{minor diast} (1) = 19.14 min (major), *t*_{major diast} (2) = 21.59 min (major), *t*_{minor diast} (3) = 24.14 min (minor), *t*_{major diast} (4) = 26.34 min (minor).



chromatogram of (±)-5.21-5.22h (229 nm)



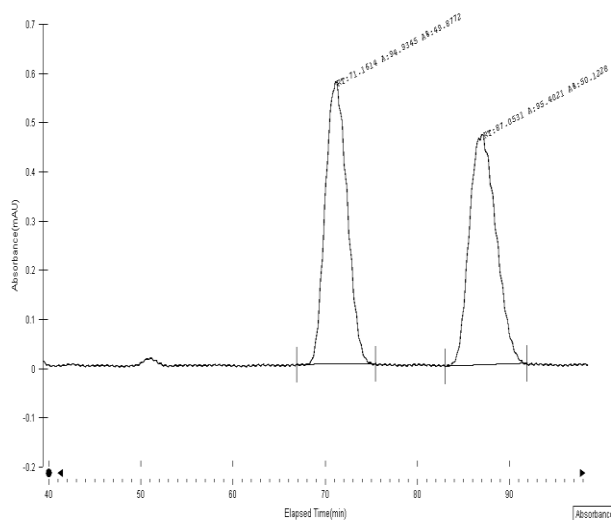
chromatogram of 5.21-5.22h (229 nm)



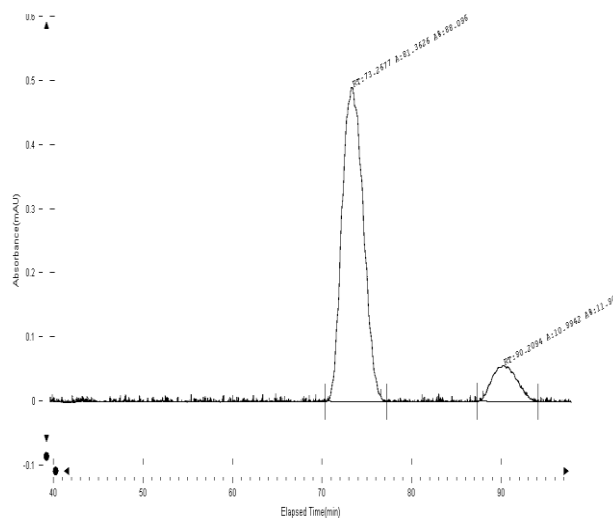
Recovered (+)-4-chloro-2-(2-cyclohexyl-3-hydroxypropyl)naphthalen-1-ol (5.20h)

38.2 mg (38% recovery) from 100 mg of (\pm)-5.20h, off white solid, eluent: 1:9 EtOAc/hexanes, $[\alpha]_D^{23} = +43.4^\circ$ (c 0.34, CHCl_3); SFC analysis indicates a 76% *ee*. Column (OD-H) 5:95:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 73.27 min (major), t_R (2) = 90.21 (minor).

chromatogram of (\pm)-5.20h (229 nm)

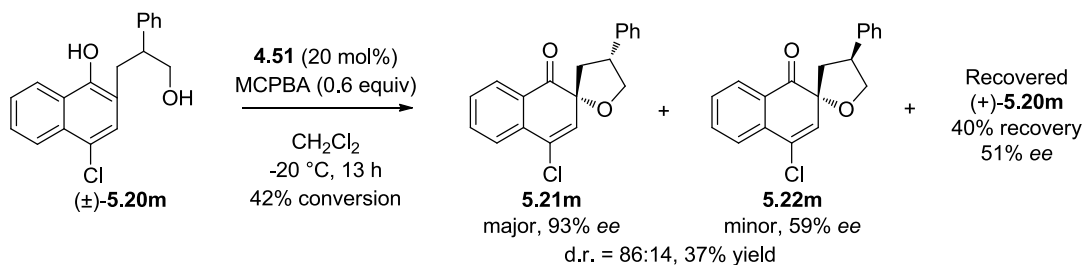


chromatogram of (+)-5.20h (229 nm, 76% ee)

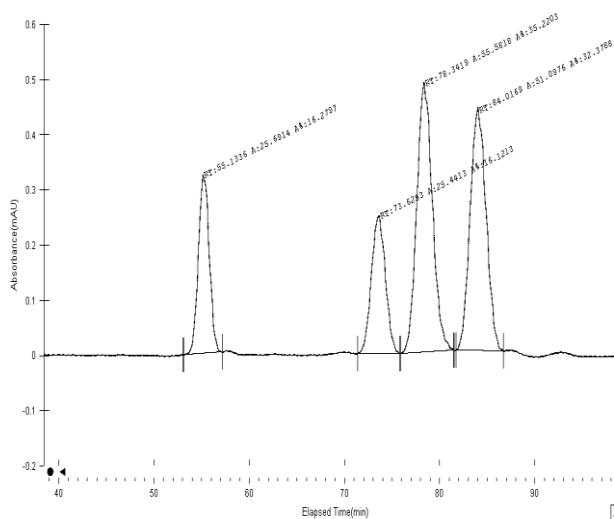


D.12.45 4'-chloro-4-phenyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (86:14 mixture of 5.21m/5.22m)

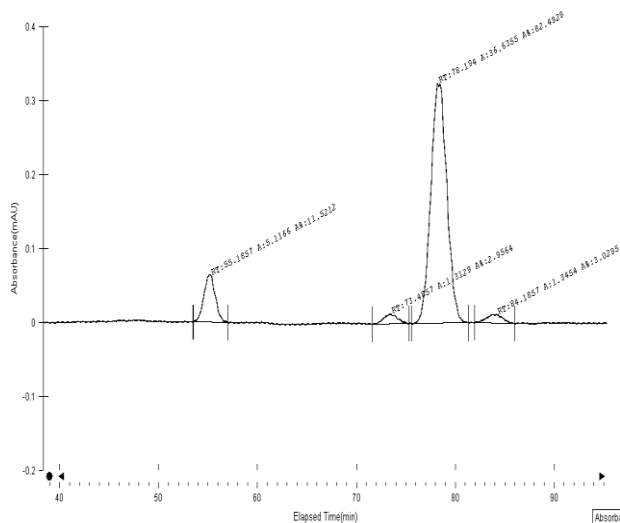
36.4 mg (37% yield) from 100 mg of (\pm)-**5.20m**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 86:14 using SFC. SFC analysis indicates a 93% *ee* for **5.21m** and 59% *ee* for **5.22m**. Column (OJ-H) 3:97:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{minor diast (1)}}$ = 55.19 min (major), $t_{\text{minor diast (2)}}$ = 73.49 min (minor), $t_{\text{major diast (3)}}$ = 78.19 min (major), $t_{\text{major diast (4)}}$ = 84.19 min (minor).



chromatogram of (\pm)-5.21-5.22m (229 nm)



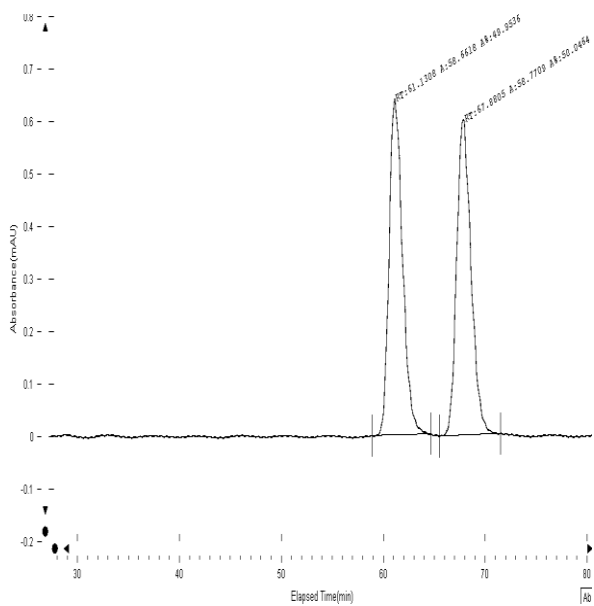
chromatogram of 5.21-5.22m (229 nm)



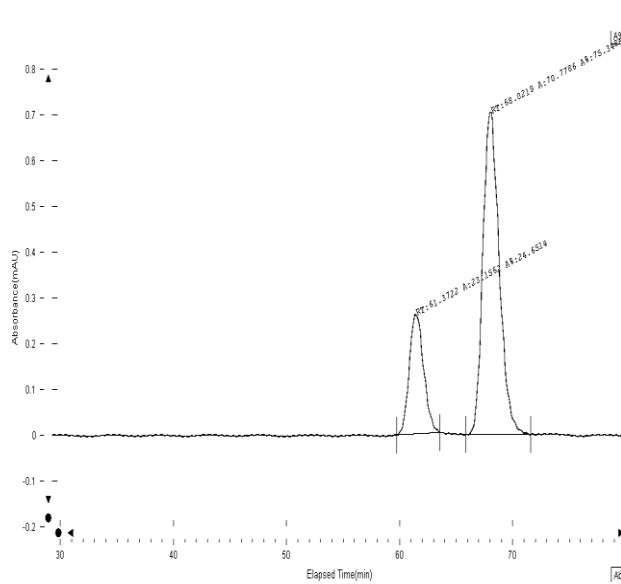
Recovered (+)-4-chloro-2-(3-hydroxy-2-phenylpropyl)naphthalen-1-ol (5.20m)

39.8 mg (40% recovery) from 100 mg of (\pm)-5.20m, colorless oil, eluent: 3:17 EtOAc/hexanes, $[\alpha]_D^{24} = +5.2^\circ$ (c 0.40, CHCl_3). SFC analysis indicates a 51% *ee*. Column (AS-H) 5:95:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 61.37 min (minor), t_R (2) = 68.02 (minor).

chromatogram of (\pm)-5.20m (229 nm)



chromatogram of (+)-5.20m (229 nm, 51% ee)

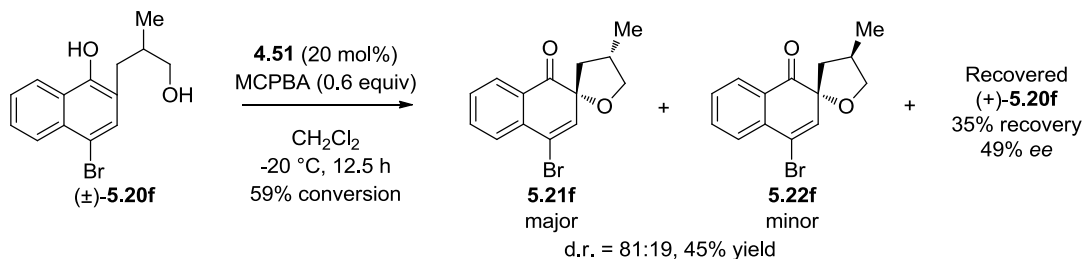


D.12.46 4'-bromo-4-methyl-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (81:19 mixture of 5.21f/5.22f)

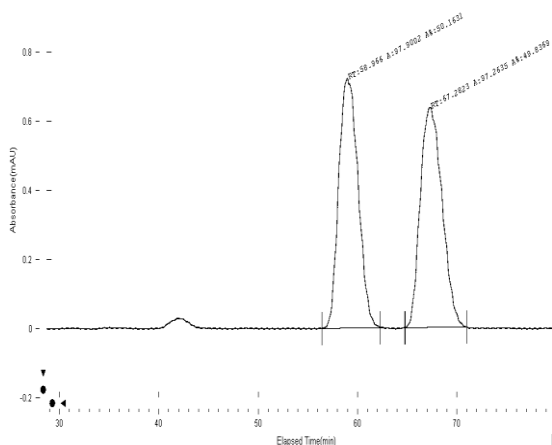
44.4 mg (45% yield) from 100 mg of (\pm)-**5.20f**, light yellow oil, eluent: 1:19 EtOAc/hexane. The peaks could not be separated using any of the available columns. The d.r. was found to be 81:19 using ^1H NMR after column chromatography.

Recovered (+)-4-bromo-2-(3-hydroxy-2-methylpropyl)naphthalen-1-ol (5.20f)

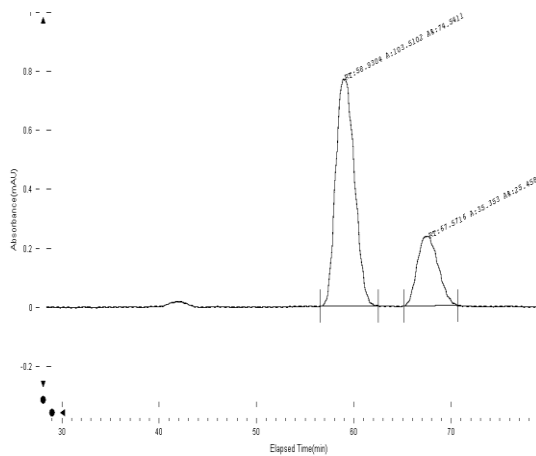
35.2 mg (35% recovery) from 100 mg of (\pm)-**5.20f**, light brown solid, eluent: 3:17 EtOAc/hexanes, $[\alpha]_D^{26} = +2.3^\circ$ (c 0.35, CHCl_3). SFC analysis indicates a 49% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 58.93 min (major), t_R (2) = 67.57 min (minor).



chromatogram of (\pm)-5.20f (229 nm)

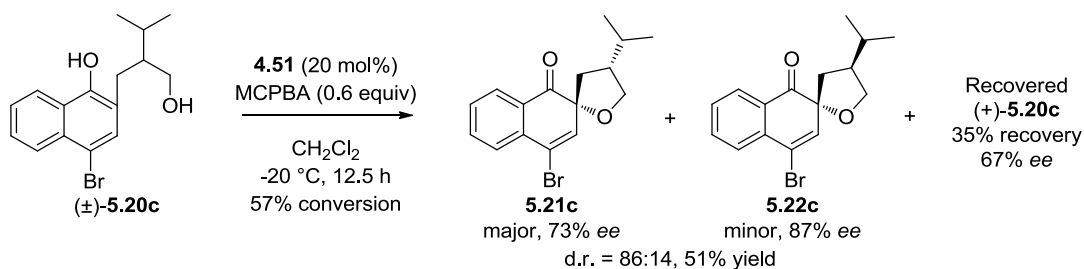


chromatogram of (+)-5.20f (229 nm, 49% ee)

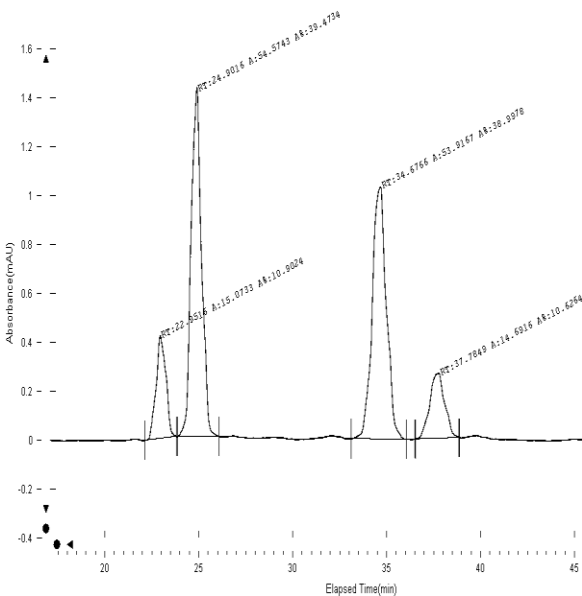


D.12.47 **4'-bromo-4-isopropyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one**
(86:14 mixture of 5.21c/5.22c)

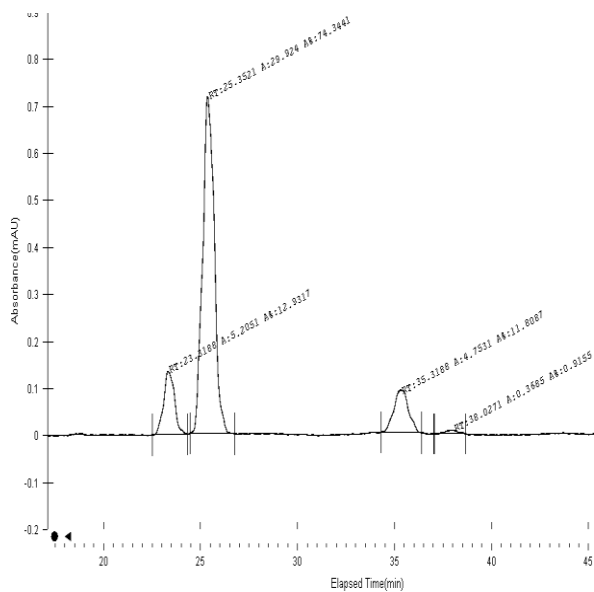
50.3 mg (51% yield) from 100 mg of (±)-**5.20c**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 86:14 using SFC. SFC analysis indicates a 73% *ee* for **5.21c** and 87% *ee* for **5.22c**. Column (OJ-H) 2:98:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_{minor diast} (1) = 23.32 min (major), *t*_{major diast} (2) = 25.35 min (major), *t*_{major diast} (3) = 35.32 min (minor), *t*_{minor diast} (4) = 38.03 min (minor).



chromatogram of (±)-5.21-5.22c (229 nm)



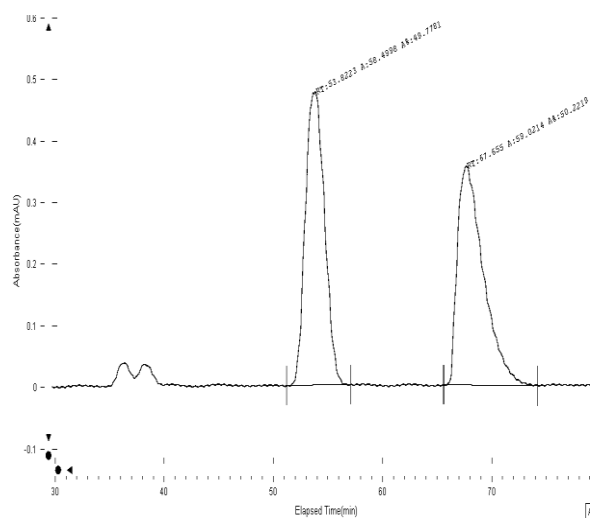
chromatogram of 5.21-5.22c (229 nm)



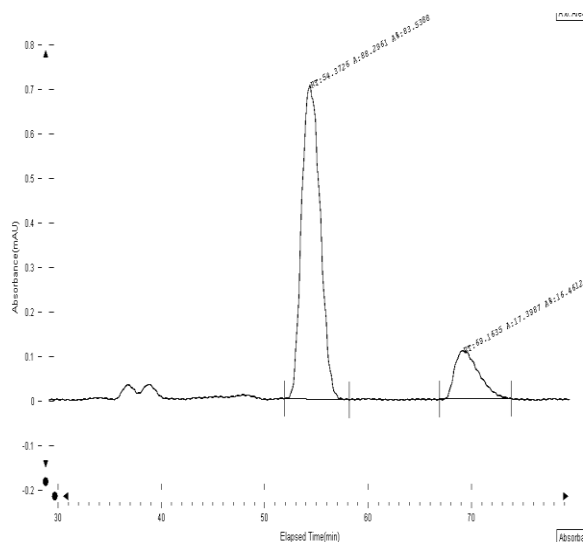
Recovered (+)-4-bromo-2-(2-(hydroxymethyl)-3-methylbutyl)naphthalen-1-ol (5.20c)

35.2 mg (35% recovery) from 100 mg of (\pm)-5.20c, off white solid, eluent: 1:9 to 1:4 EtOAc/hexanes, $[\alpha]_D^{26} = +20.6^\circ$ (c 0.35, CHCl_3). SFC analysis indicates a 67% *ee*. Column (OD-H) 5:95:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 54.37 min (major), t_R (2) = 69.16 min (minor).

chromatogram of (\pm)-5.20c (229 nm)

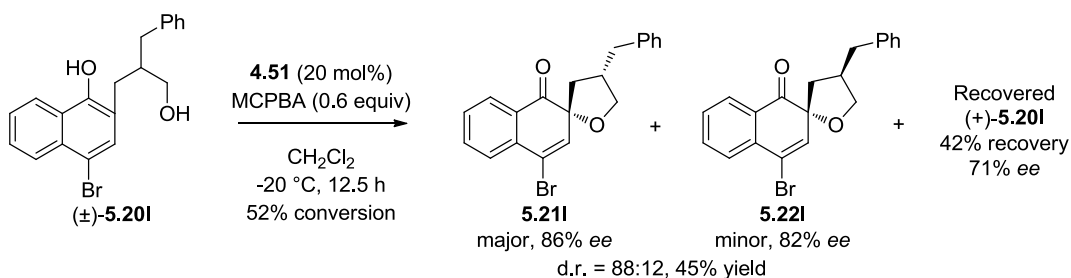


chromatogram of (+)-5.20c (229 nm, 67% *ee*)

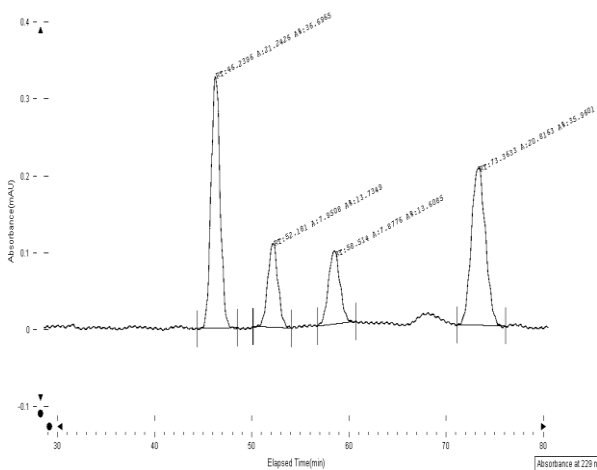


D.12.48 4-benzyl-4'-bromo-4,5-dihydro-1'H,3H-spiro[furan-2,2'-naphthalen]-1'-one (88:12 mixture of 5.211/5.221)

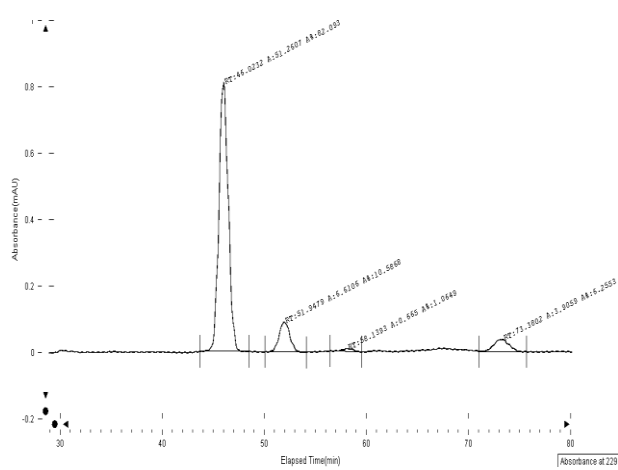
44.3 mg (45% yield) from 100 mg of (\pm)-**5.201**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 88:12 using SFC. SFC analysis indicates a 86% *ee* for **5.211** and 82% *ee* for **5.221**. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; $t_{\text{major diast}}$ (1) = 46.02 min (major), $t_{\text{minor diast}}$ (2) = 51.95 min (major), $t_{\text{minor diast}}$ (3) = 58.14 min (minor), $t_{\text{major diast}}$ (4) = 73.38 min (minor).



chromatogram of (\pm)-5.21-5.221 (229 nm)



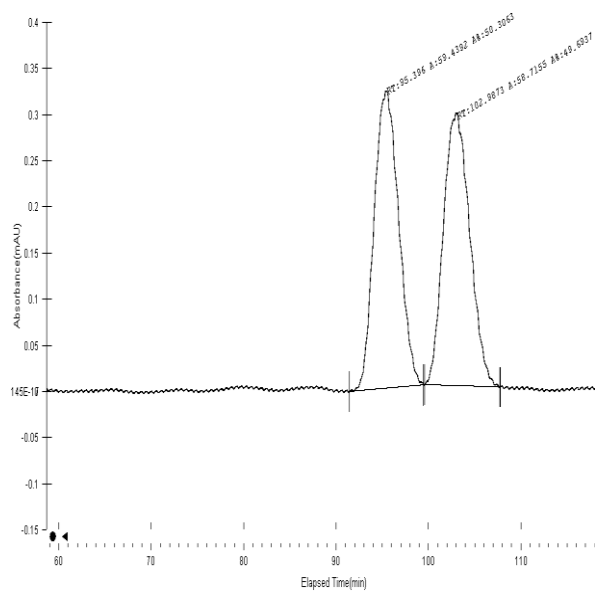
chromatogram of 5.21-5.221 (229 nm)



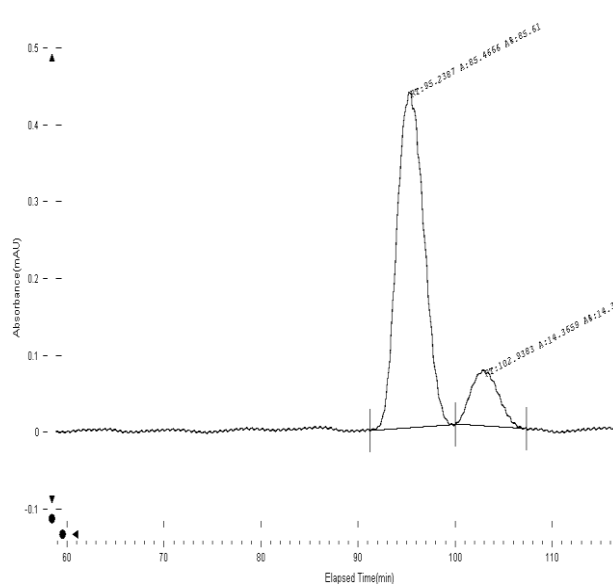
Recovered (+)-2-(2-benzyl-3-hydroxypropyl)-4-bromonaphthalen-1-ol (5.20l)

41.7 mg (42% recovery) from 100 mg of (\pm)-5.20l, light brown solid, eluent: 1:9 to 1:4 EtOAc/hexanes, $[\alpha]_D^{25} = +13.5^\circ$ (c 0.42, CHCl_3). SFC analysis indicates a 71% *ee*. Column (AD-H) 6:94:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 95.24 min (major), t_R (2) = 102.94 (minor).

chromatogram of (\pm)-5.20l (229 nm)

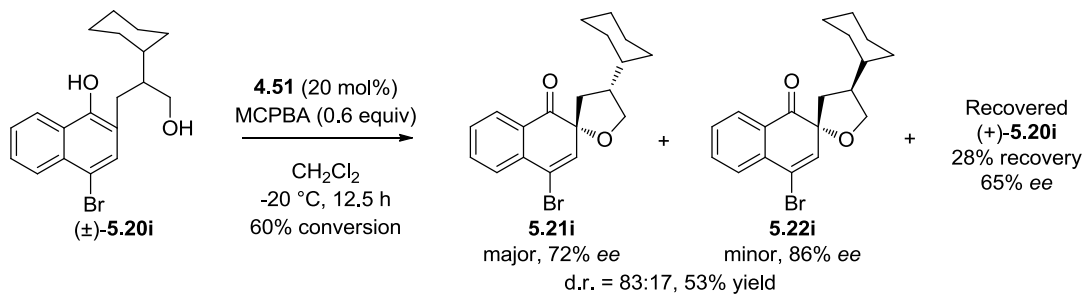


chromatogram of (+)-5.20l (229 nm, 71% *ee*)

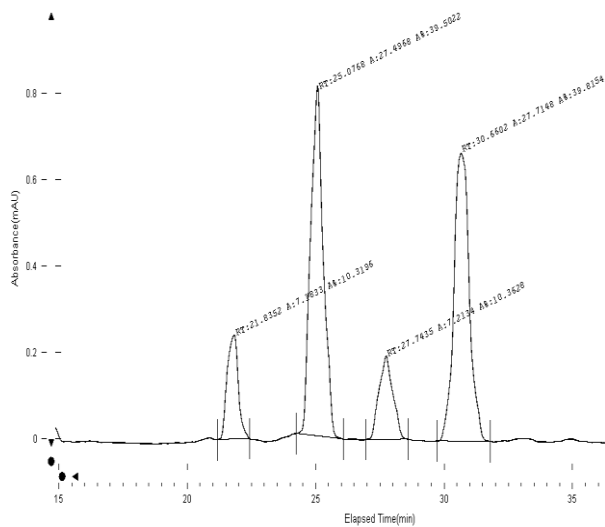


D.12.49 4'-bromo-4-cyclohexyl-4,5-dihydro-1*H*,3*H*-spiro[furan-2,2'-naphthalen]-1'-one
(83:17 mixture of 5.21i/5.22i)

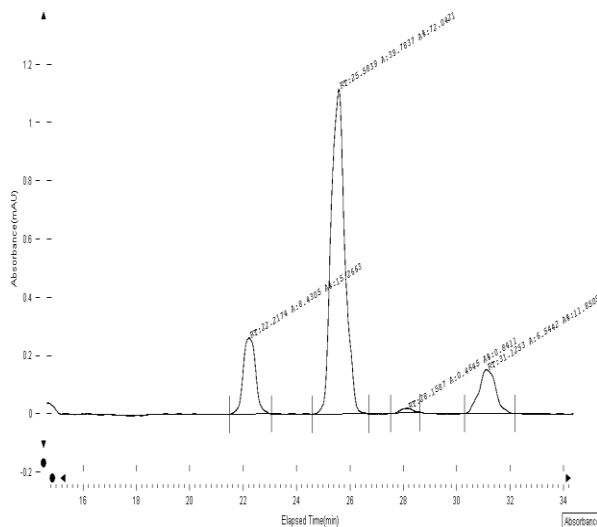
52.6 mg (53% yield) from 100 mg of (±)-**5.20i**, light yellow oil, eluent: 1:19 EtOAc/hexane. The d.r. was found to be 83:17 using SFC. SFC analysis indicates a 72% *ee* for **5.21i** and 86% *ee* for **5.22i**. Column (OJ-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_{minor diast} (1) = 22.22 min (major), *t*_{major diast} (2) = 25.58 min (major), *t*_{minor diast} (3) = 28.16 min (minor), *t*_{major diast} (4) = 31.13 min (minor).



chromatogram of (±)-5.21-5.22i (229 nm)



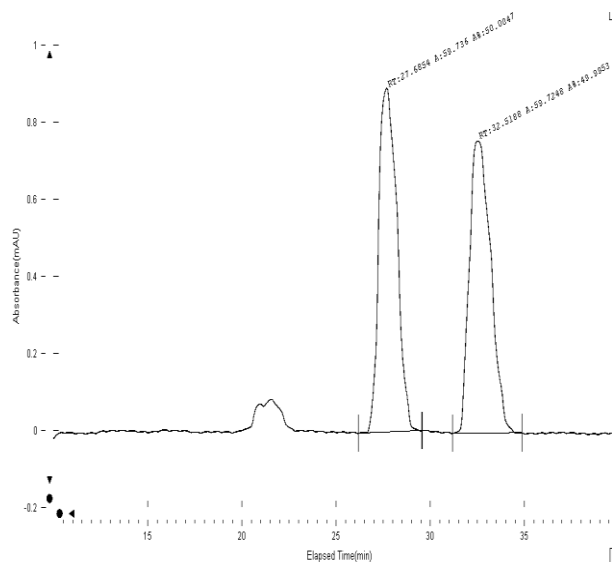
chromatogram of 5.21-5.22i (229 nm)



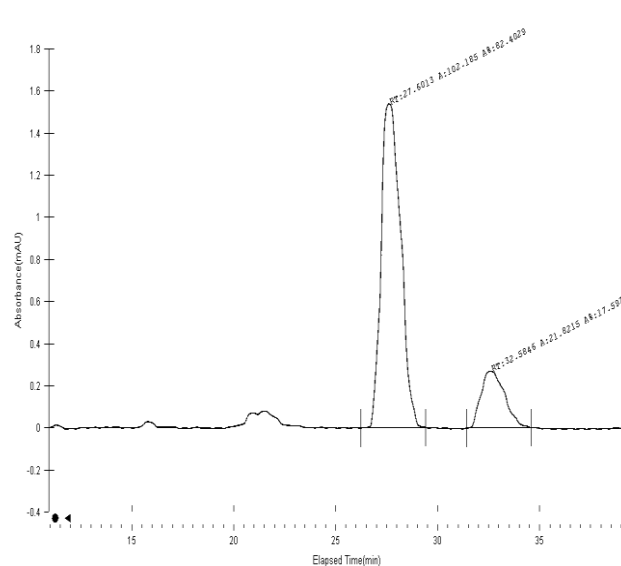
Recovered (+)-4-bromo-2-(2-cyclohexyl-3-hydroxypropyl)naphthalen-1-ol (5.20i)

27.7 mg (28% recovery) from 100 mg of (\pm)-**5.20i**, off white solid, eluent: 1:9 EtOAc/hexanes, $[\alpha]_D^{26} = +37.5^\circ$ (c 0.28, CHCl_3). SFC analysis indicates a 65% *ee*. Column (OD-H) 10:90:0.1 (iPrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 27.60 min (major), t_R (2) = 32.59 (minor).

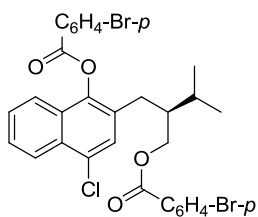
chromatogram of (\pm)-5.20i (229 nm)



chromatogram of (+)-5.20i (229 nm, 65% ee)



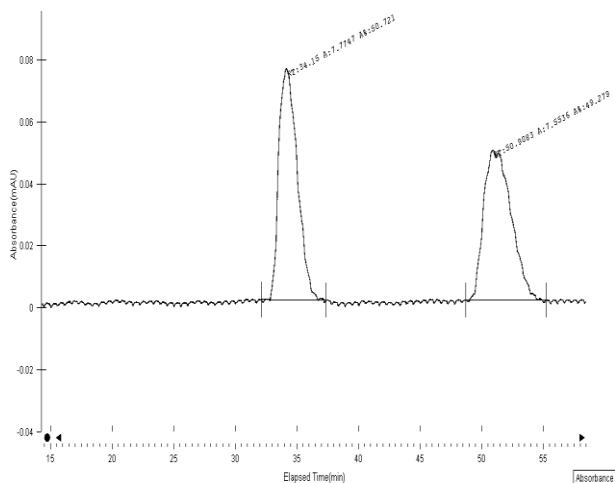
D.12.50 (-)-(S)-2-((1-(4-bromobenzoyloxy)-4-chloronaphthalen-2-yl)methyl)-3-methylbutyl 4-bromobenzoate (5.27)



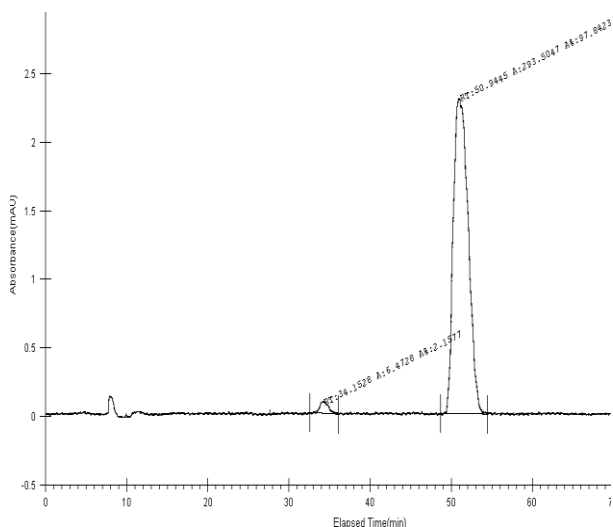
36.4 mg (79% yield) from 20 mg of (+)-**5.20a**, white solid, eluent: 1:19 EtOAc/hexanes, $[\alpha]_D^{23} = -37.5^\circ$ (c 1.82, CHCl_3). SFC analysis indicates a 96% *ee*. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 34.15 min (minor), t_R (2) = 50.95 min (major).

X-ray structural analysis determined that the product is of (*S*) configuration.

chromatogram of (\pm)-5.27** (240 nm)**

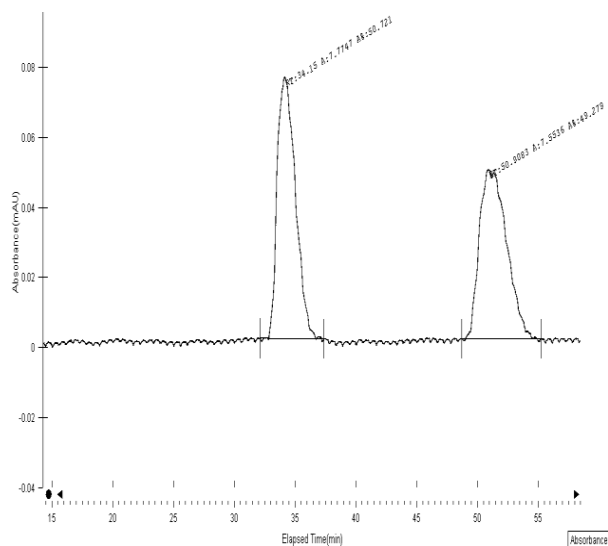


chromatogram of (-)-5.27** (240 nm, 96% ee)**

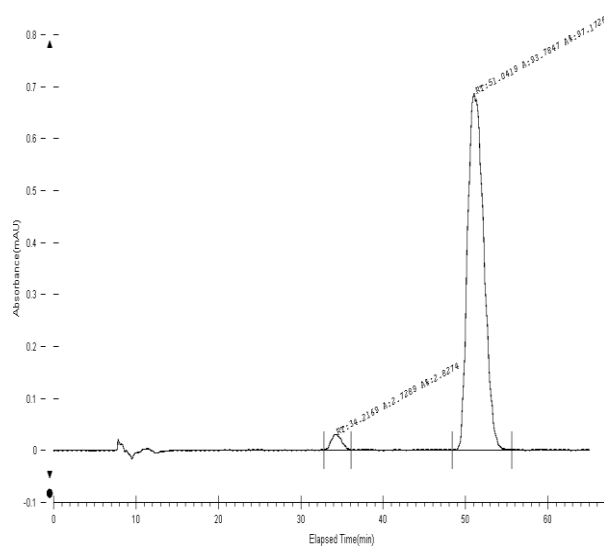


A single recrystallization by slow evaporation of a solution in CH_2Cl_2 and methanol at RT afforded material of 94% *ee*. A single crystal of this substance was suitable for X-ray structural analysis. Column (OD-H) 10:90:0.1 (*i*PrOH: liq CO_2 : diethylamine), flow rate = 1.0 mL/min; t_R (1) = 34.22 min (minor), t_R (2) = 51.04 min (major).

chromatogram of (\pm)-5.27 (240 nm)

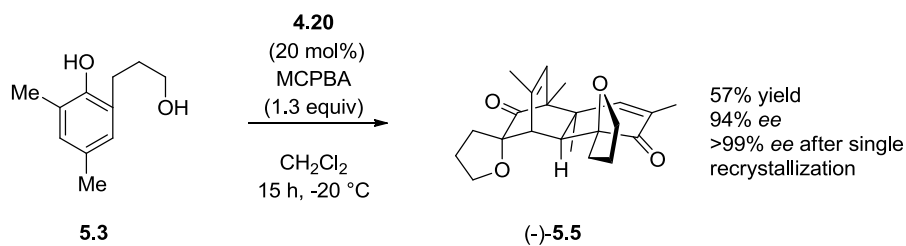


chromatogram of (-)-5.27 (240 nm, 94% *ee*)

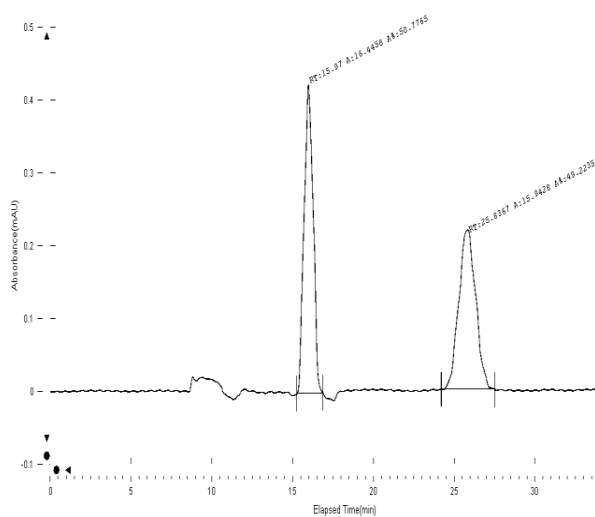


D.12.51 Data for chiral (-)-cycloadduct (5.5)

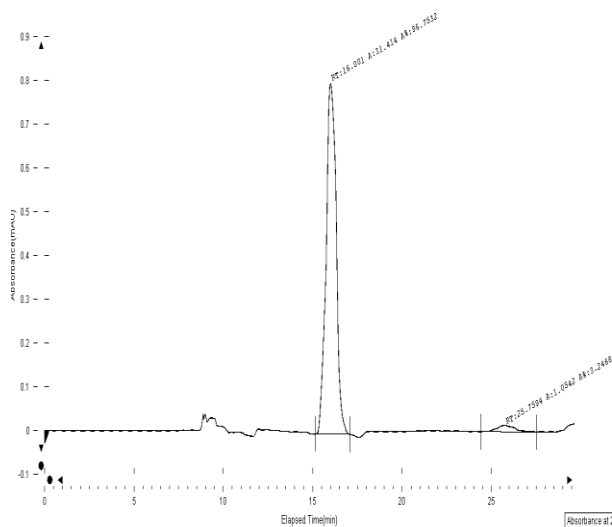
56.1 mg (57% yield) from 100 mg of **5.3**, white solid, eluent: 3:17 to 1:4 EtOAc/hexanes, $[\alpha]_D^{24} = -42.1^\circ$ (*c* 0.53, CHCl₃). SFC analysis indicates a 94% *ee*. Column (AD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 16.00 min (major), t_R (2) = 25.76 min (minor).



chromatogram of (±)-5.5 (240 nm)

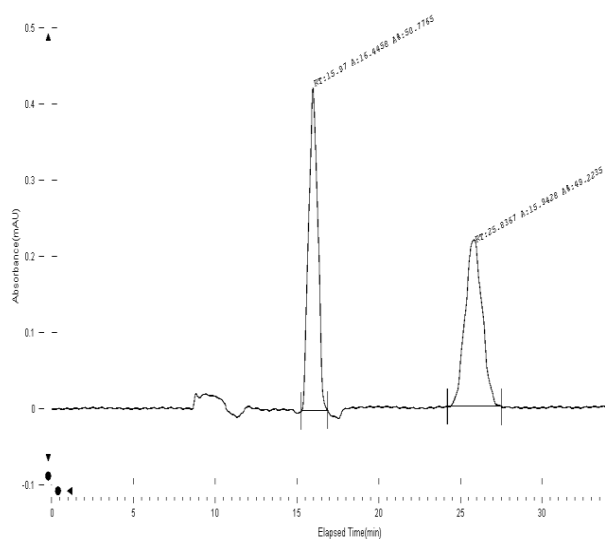


chromatogram of (-)-5.5 (240 nm, 94% *ee*)

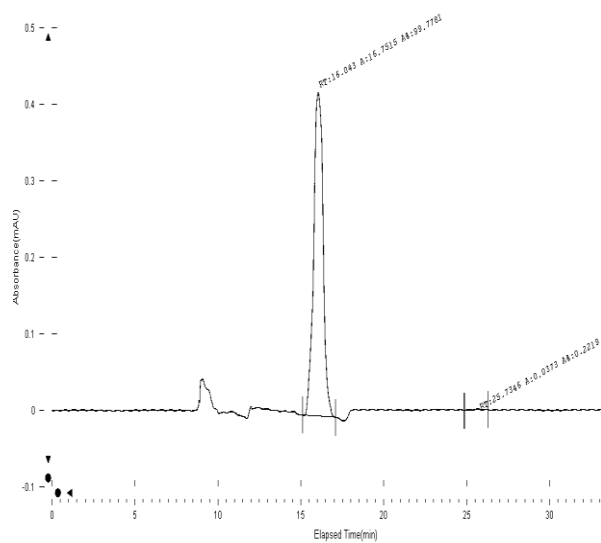


A single recrystallization by slow evaporation of a solution in ethanol at RT afforded material of greater than 99% *ee*. A single crystal of this substance was suitable for X-ray structural analysis. Column (AD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; t_R (1) = 16.04 min (major), t_R (2) = 25.74 min (minor).

chromatogram of (\pm)-5.5 (240 nm)

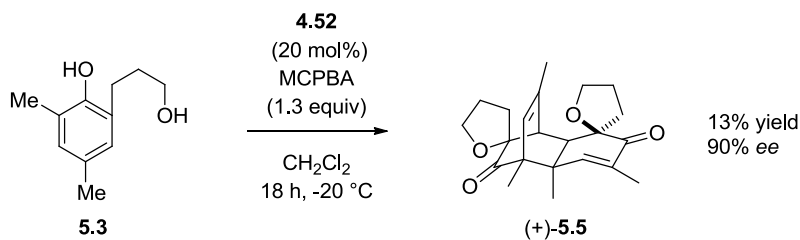


chromatogram of recrystallized (-)-5.5 (240 nm, >99% *ee*)

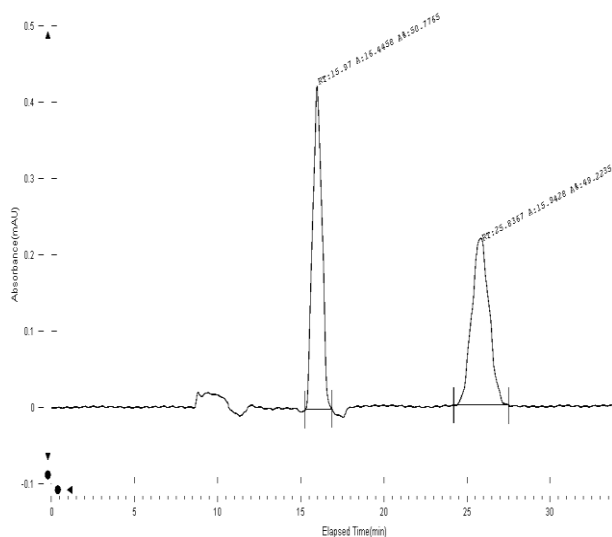


D.12.52 Data for chiral (+)-cycloadduct (5.5)

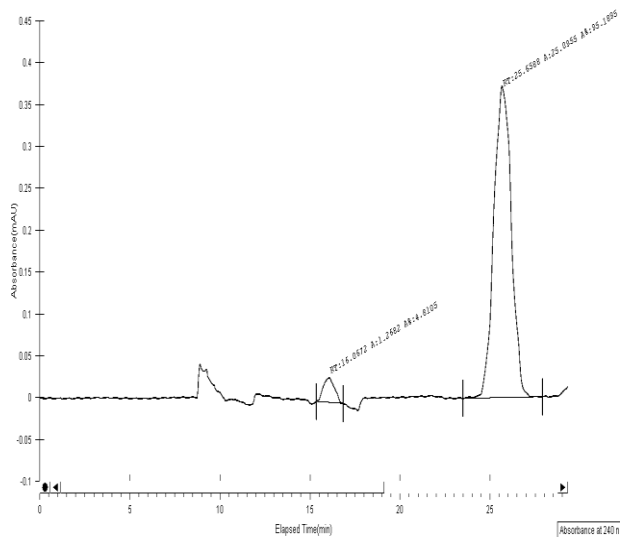
12.9 mg (13% yield) from 100 mg of **5.3**, white solid, eluent: 3:17 to 1:4 EtOAc/hexanes. SFC analysis indicates a 90% *ee*. Column (AD-H) 5:95:0.1 (*i*PrOH: liq CO₂: diethylamine), flow rate = 1.0 mL/min; *t*_R (1) = 16.07 min (minor), *t*_R (2) = 25.66 min (major).



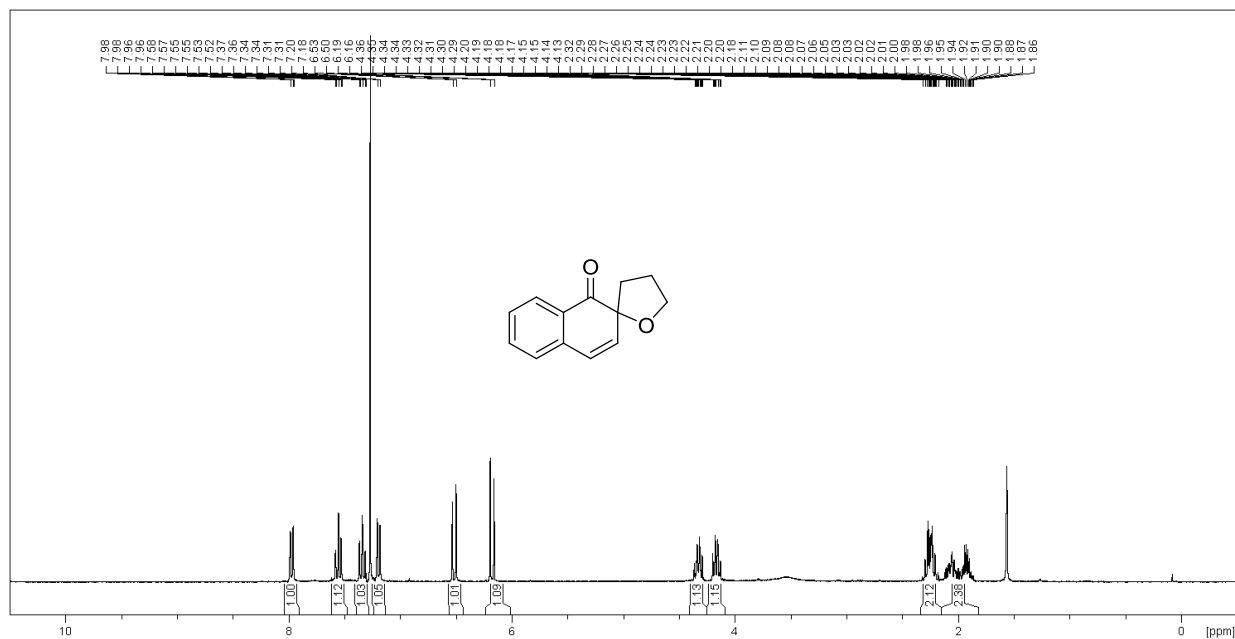
chromatogram of (±)-5.5 (240 nm)



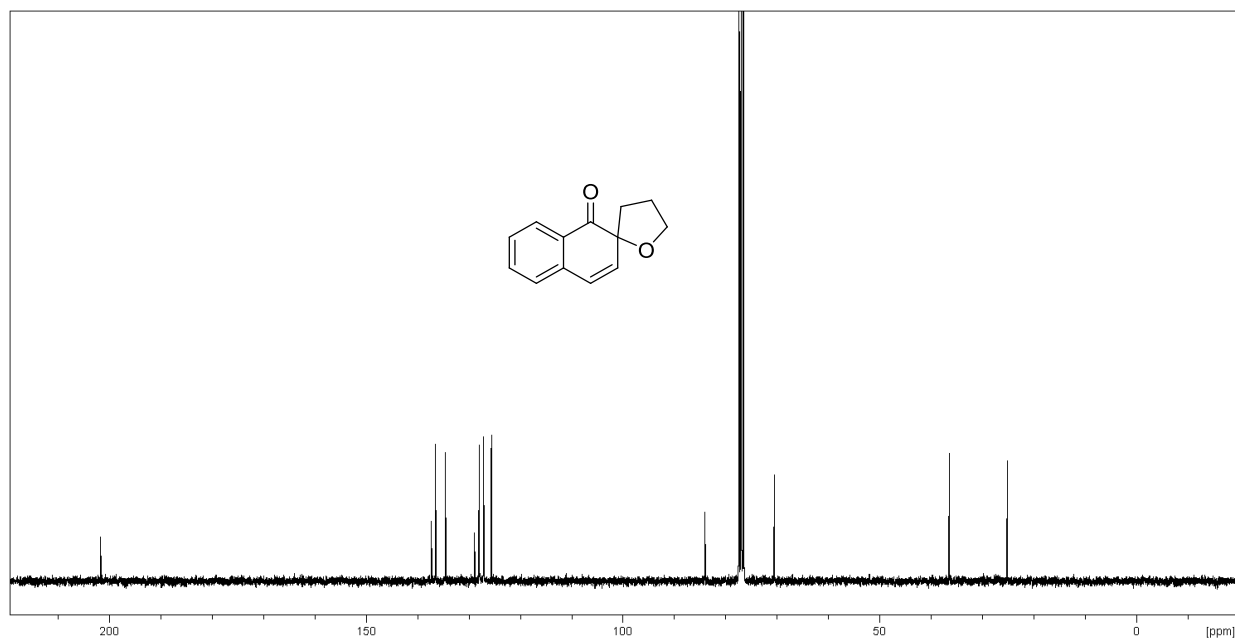
chromatogram of (+)-5.5 (240 nm, 90% *ee*)



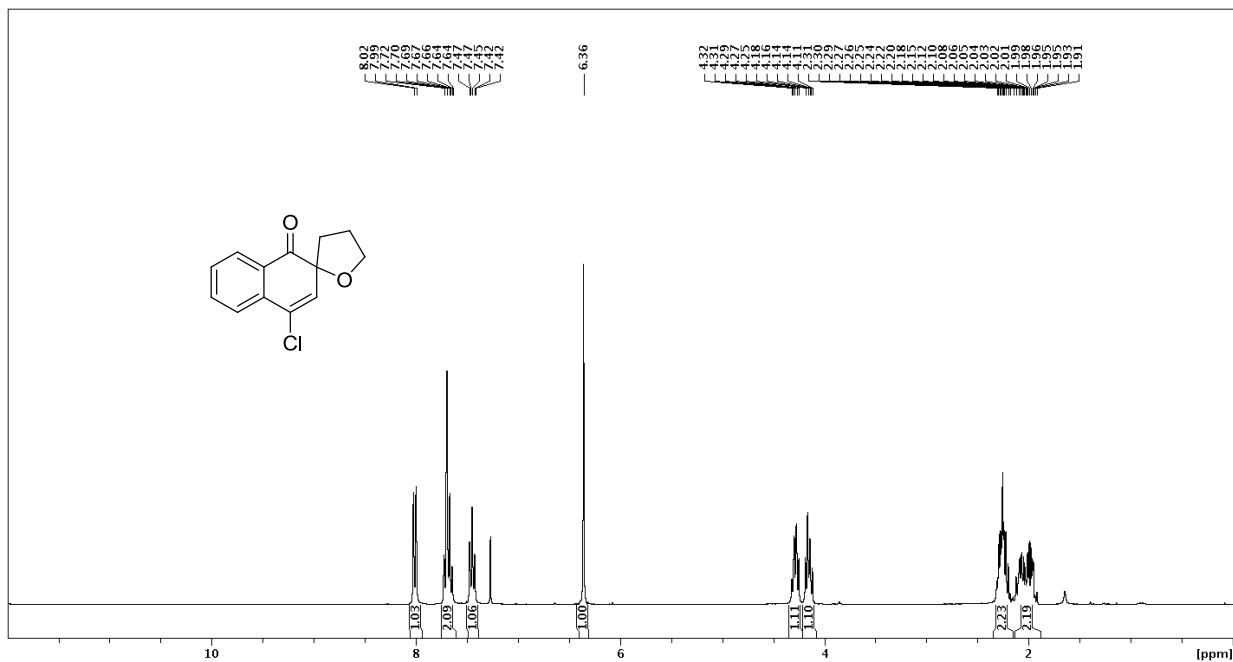
D.13 ^1H and ^{13}C spectra from chapter 5



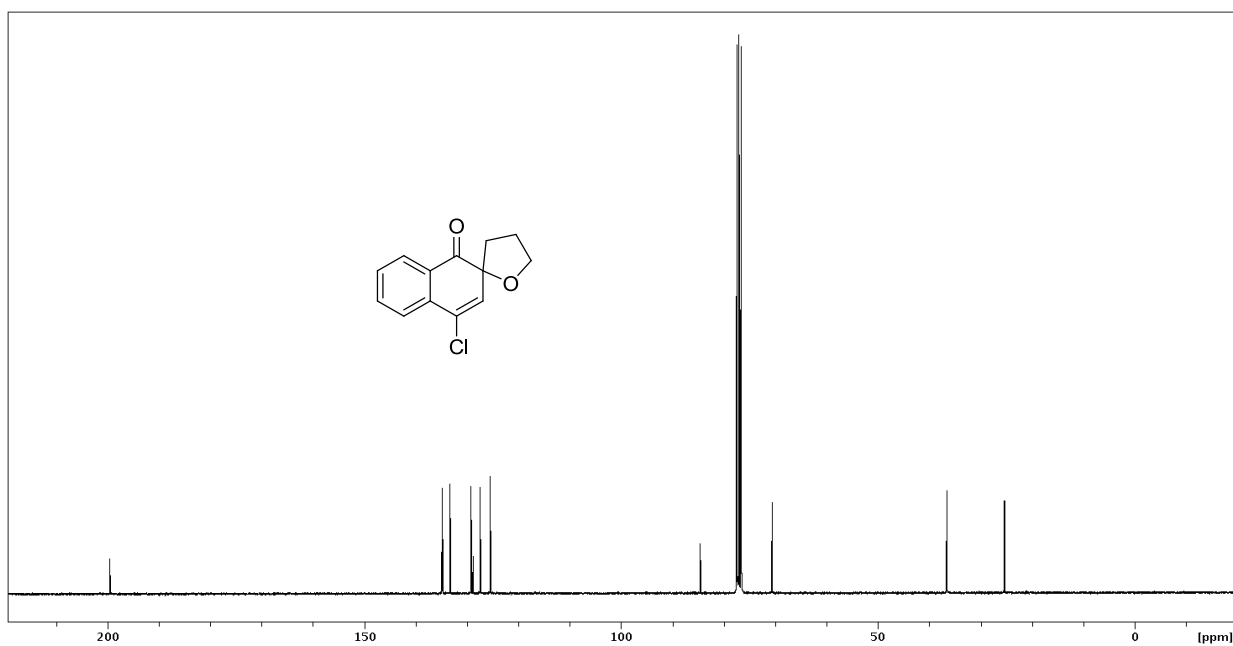
^1H NMR spectrum of 5.21 (300 MHz, CDCl_3)



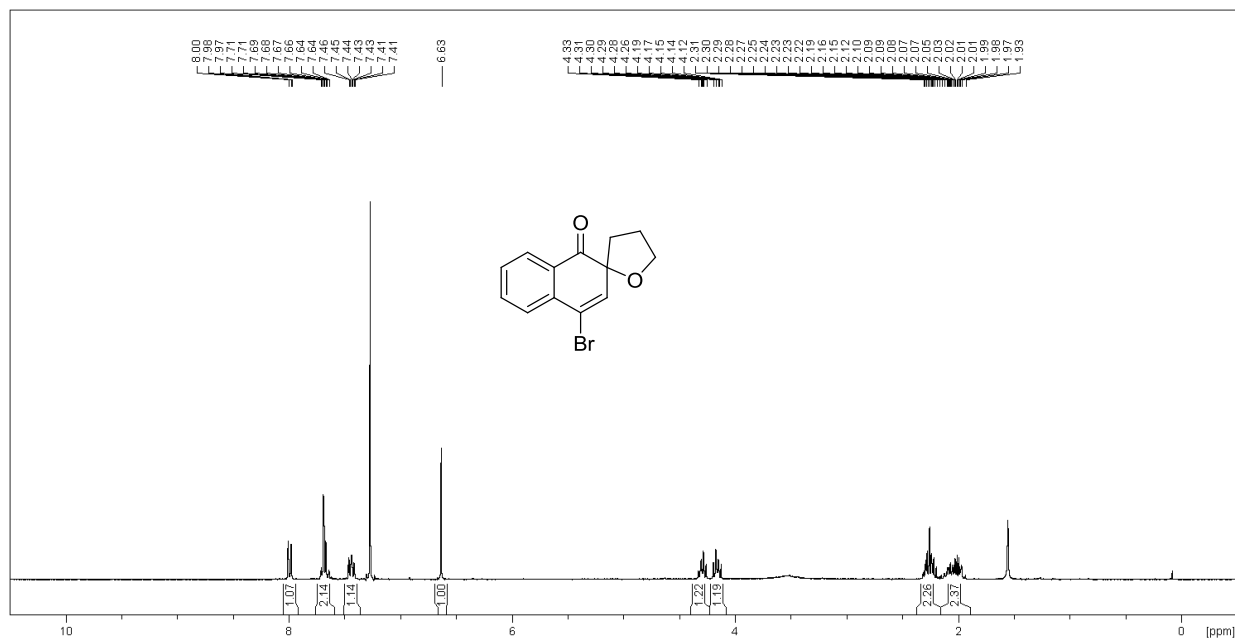
^{13}C NMR spectrum of 5.21 (75 MHz, CDCl_3)



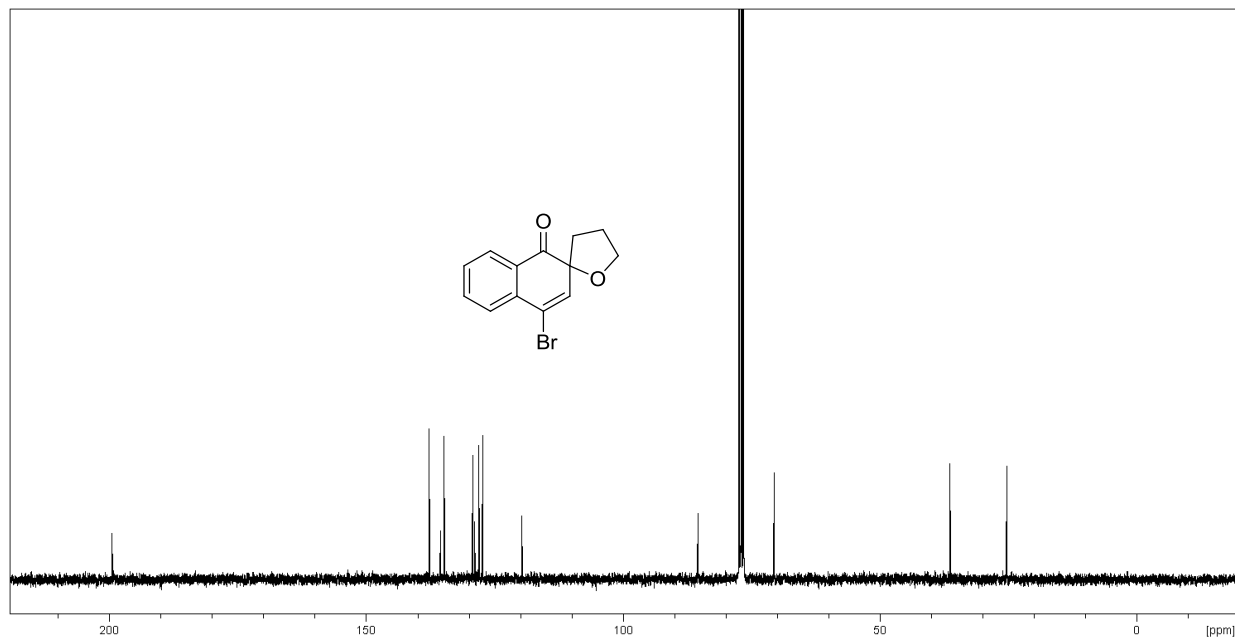
¹H NMR spectrum of 5.2a (300 MHz, CDCl₃)



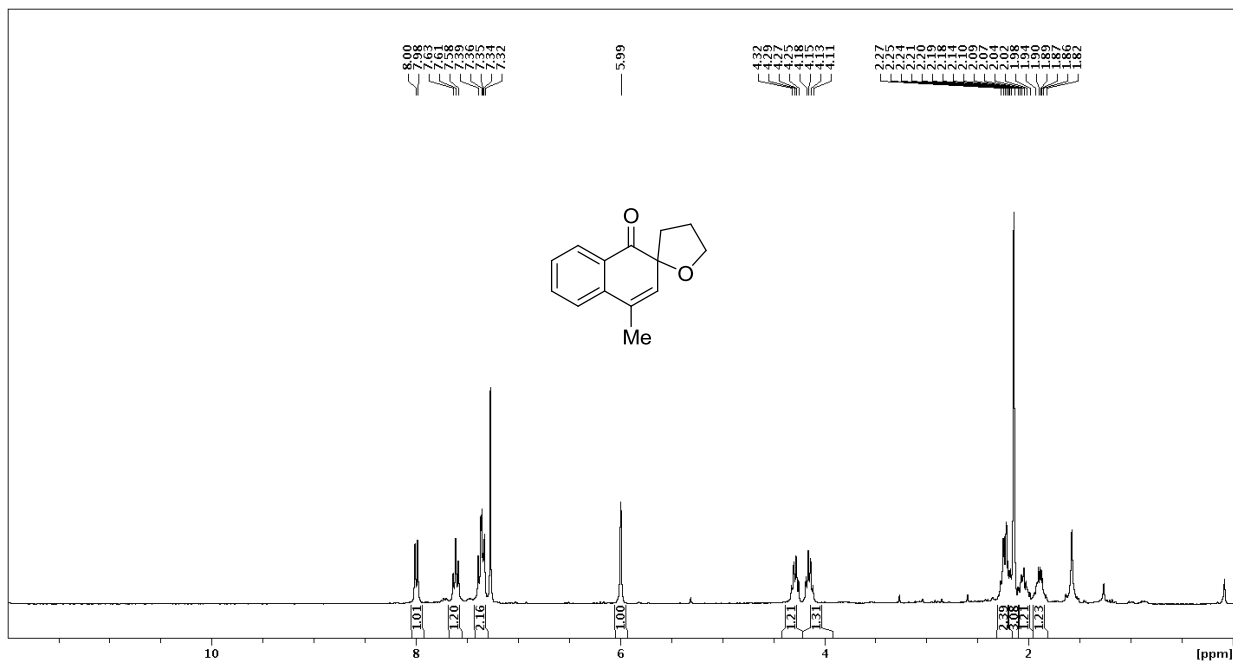
¹³C NMR spectrum of 5.2a (75 MHz, CDCl₃)



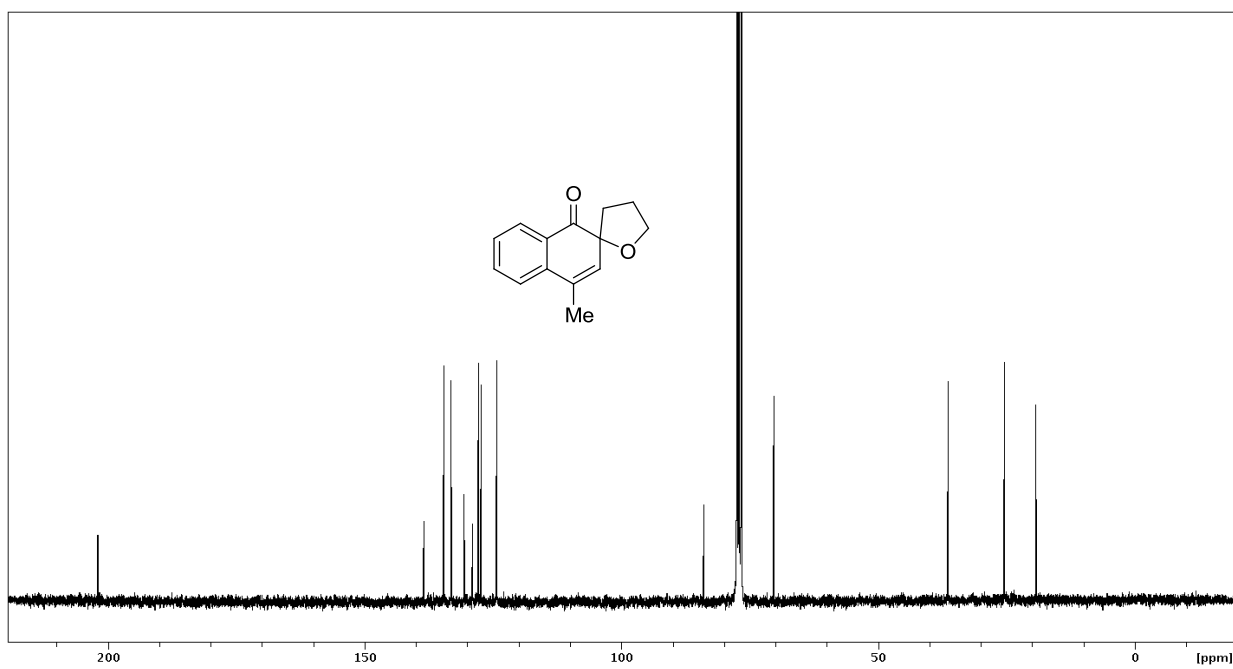
¹H NMR spectrum of 5.2b (300 MHz, CDCl₃)



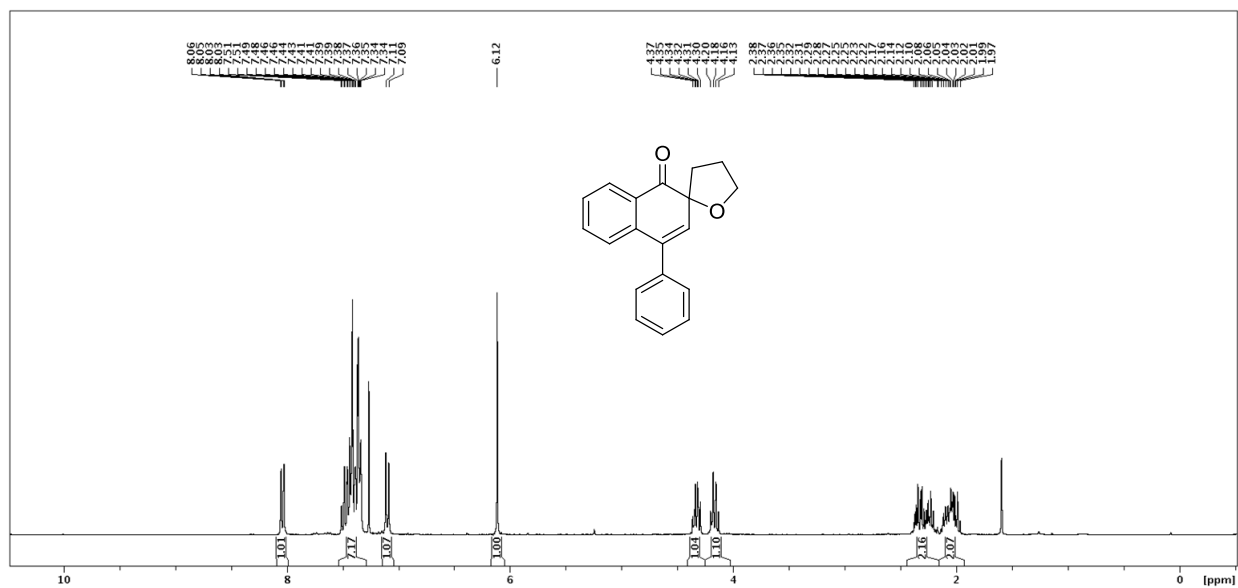
¹³C NMR spectrum of 5.2b (75 MHz, CDCl₃)



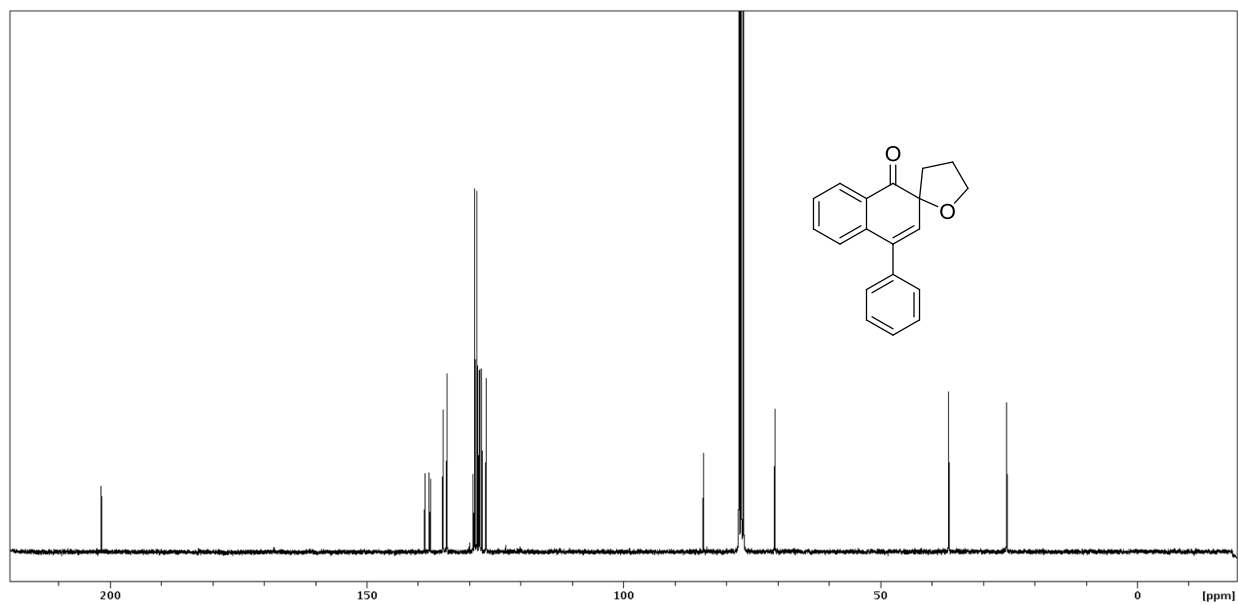
¹H NMR spectrum of 5.2c (300 MHz, CDCl₃)



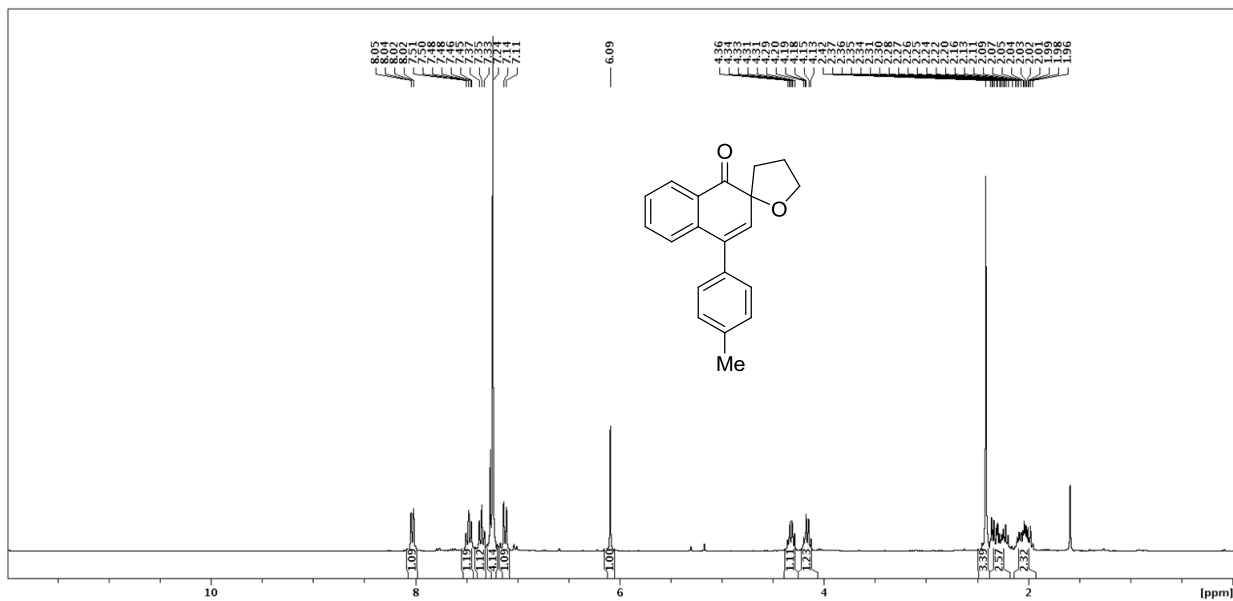
¹³C NMR spectrum of 5.2c (75 MHz, CDCl₃)



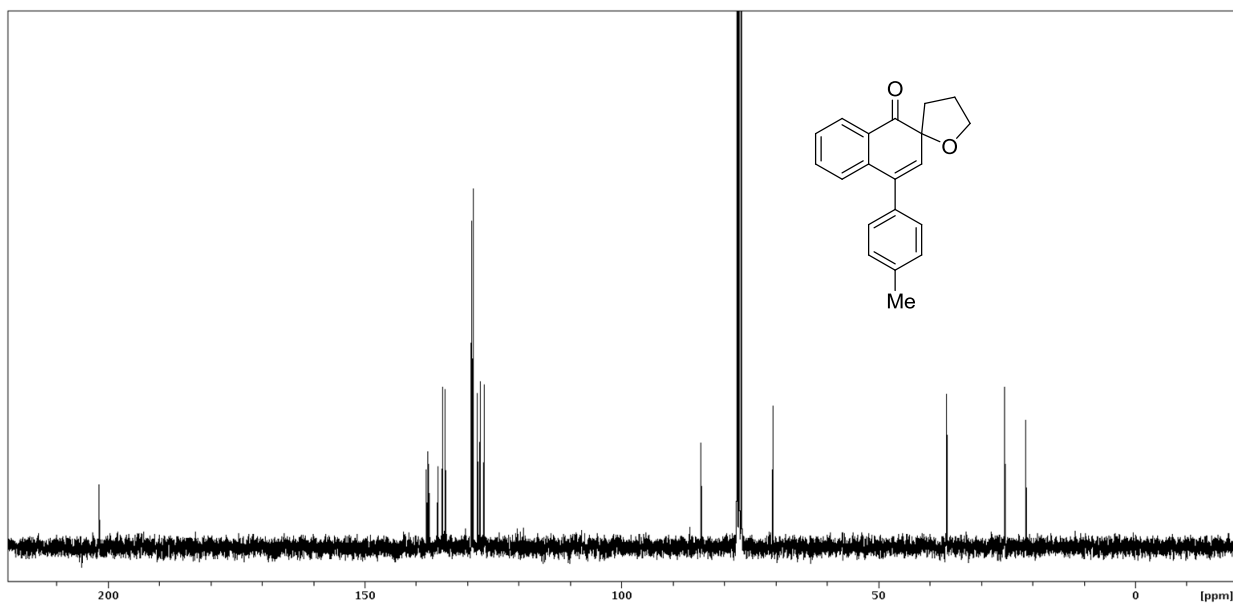
¹H NMR spectrum of 5.2d (300 MHz, CDCl₃)



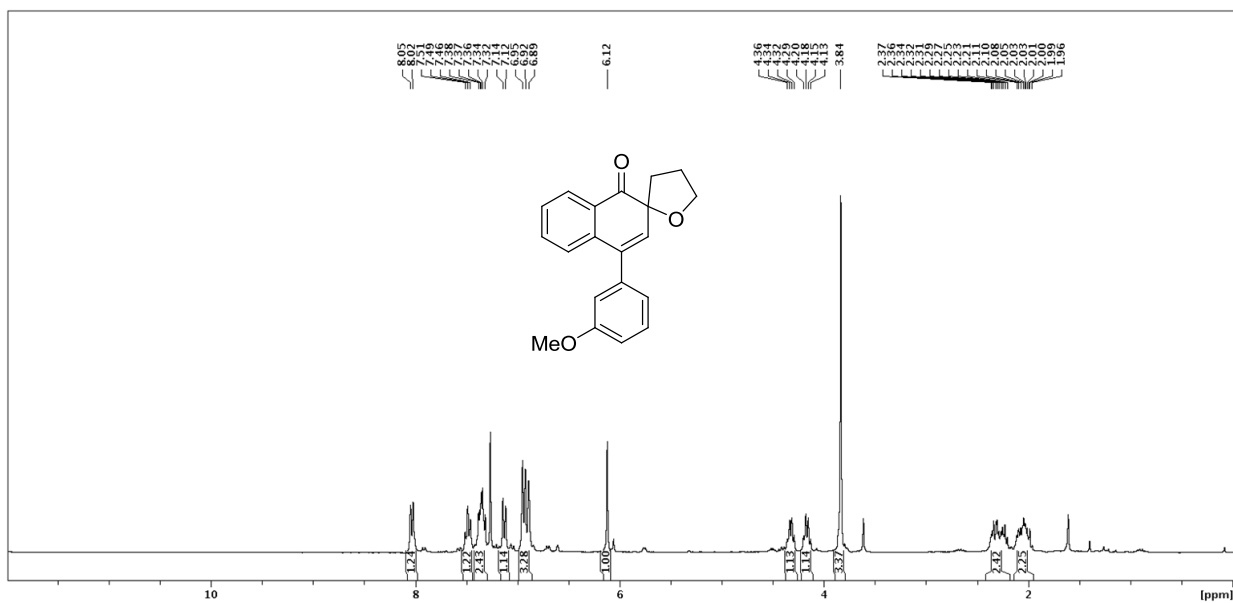
¹³C NMR spectrum of 5.2d (75 MHz, CDCl₃)



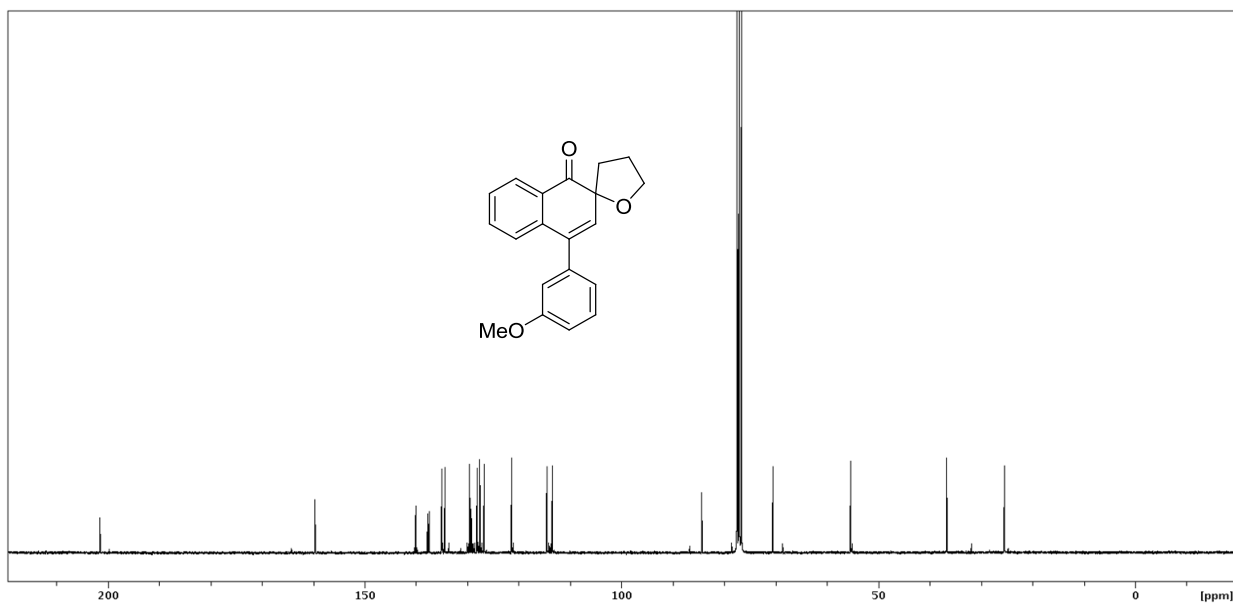
^1H NMR spectrum of 5.2e (300 MHz, CDCl_3)



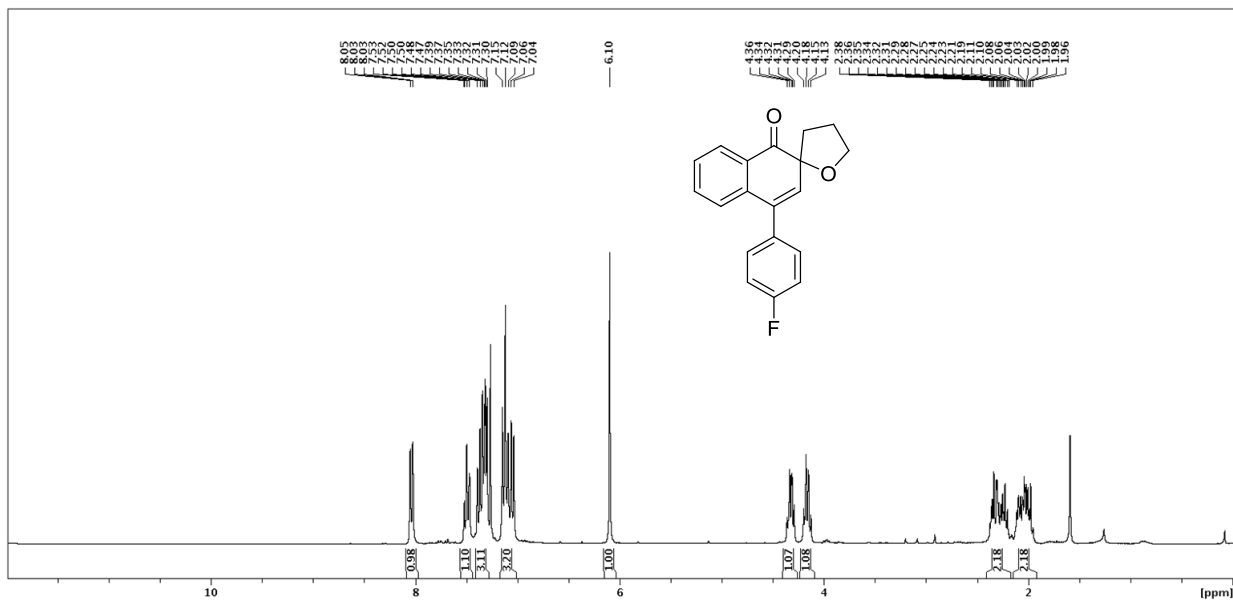
^{13}C NMR spectrum of 5.2e (75 MHz, CDCl_3)



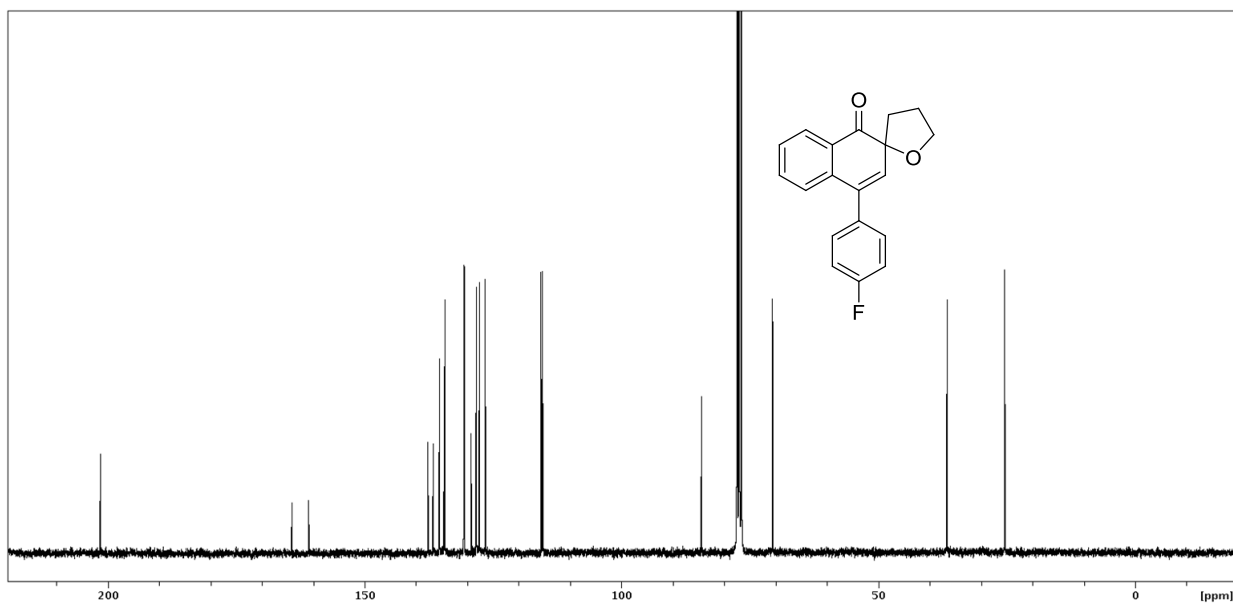
¹H NMR spectrum of 5.2f (300 MHz, CDCl₃)



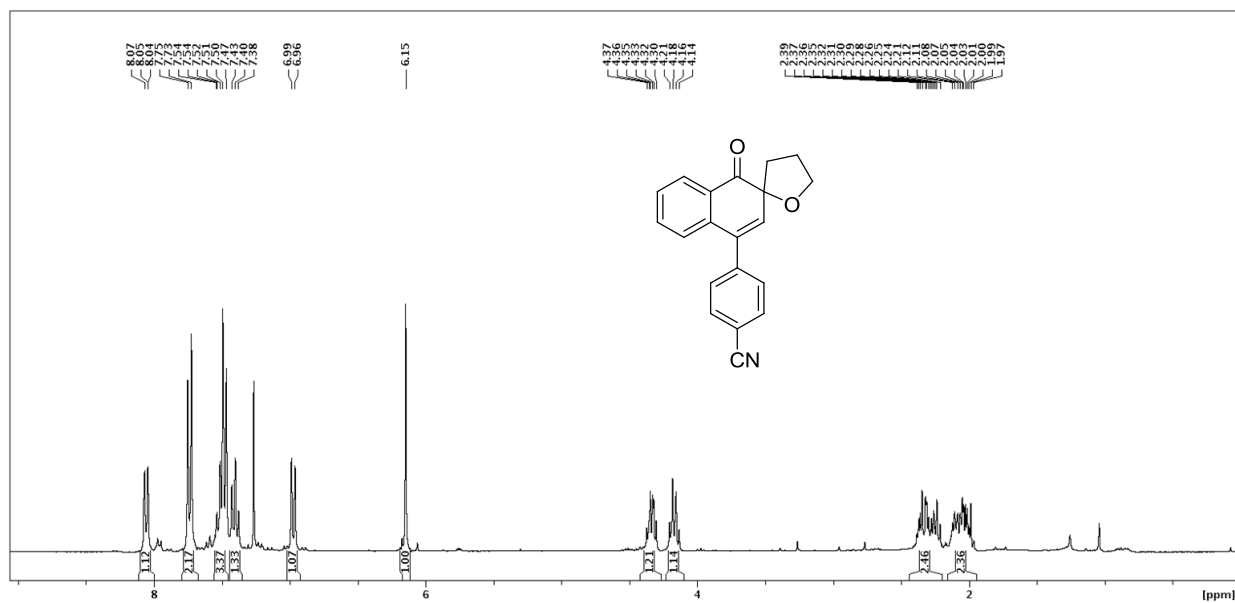
¹³C NMR spectrum of 5.2f (75 MHz, CDCl₃)



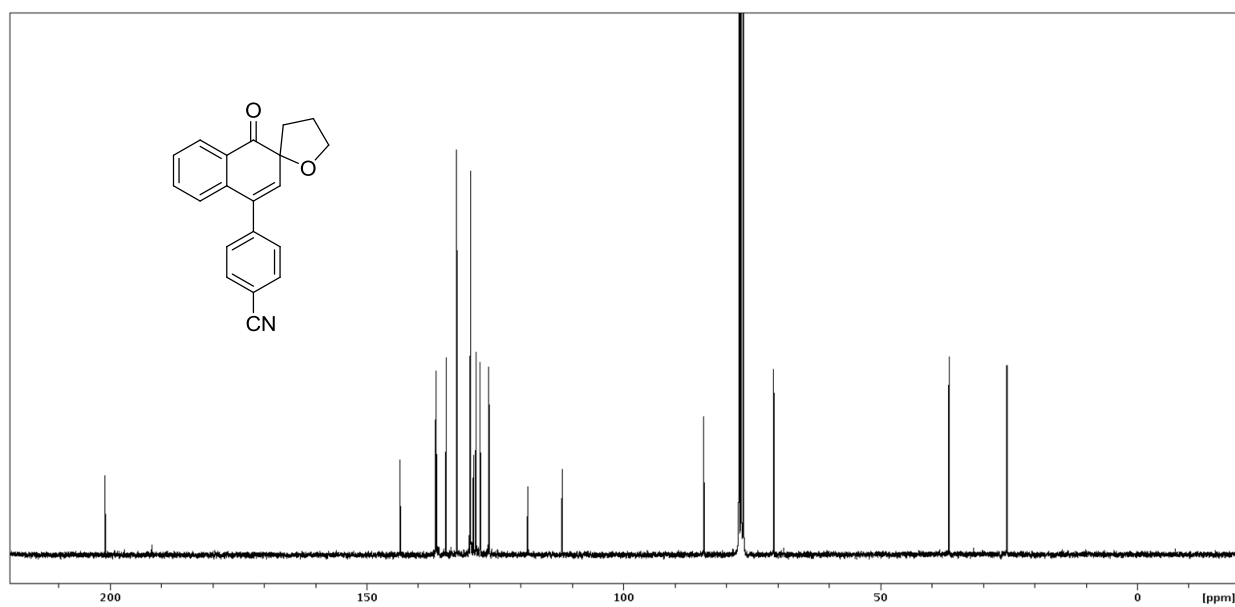
¹H NMR spectrum of 5.2h (300 MHz, CDCl₃)



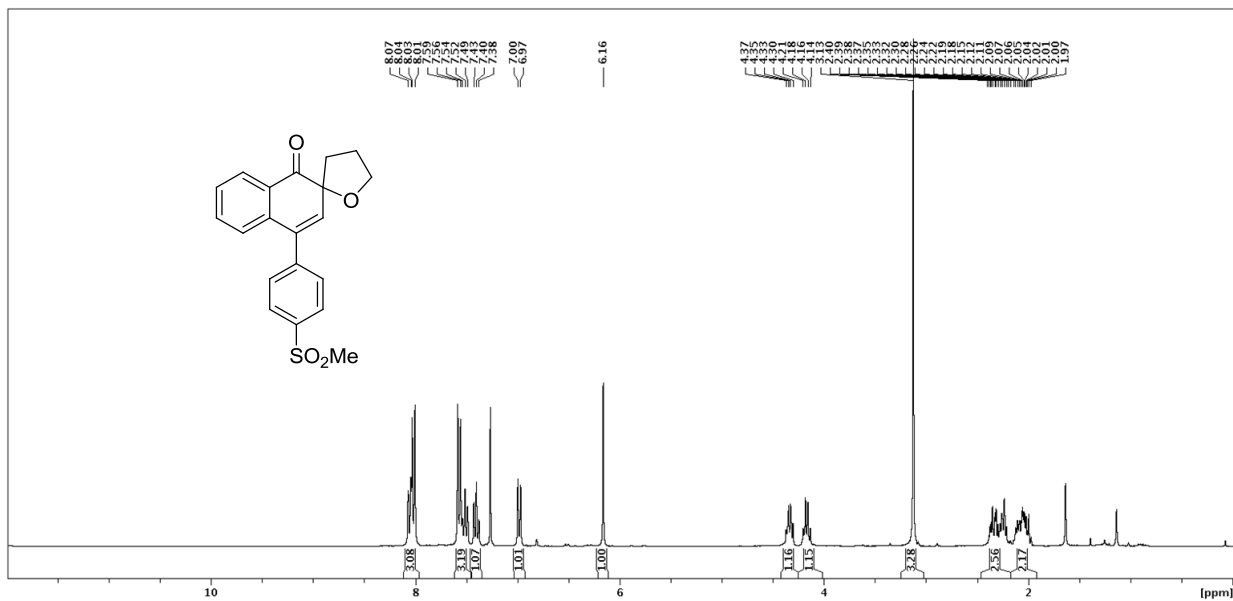
¹³C NMR spectrum of 5.2h (75 MHz, CDCl₃)



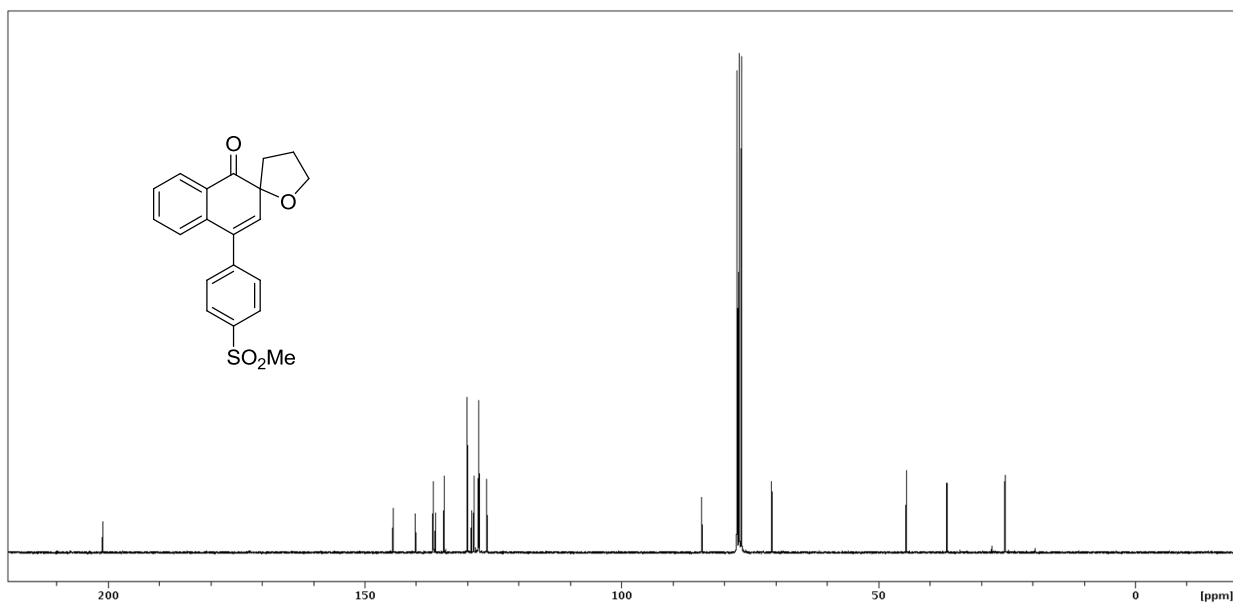
¹H NMR spectrum of 5.2i (300 MHz, CDCl₃)



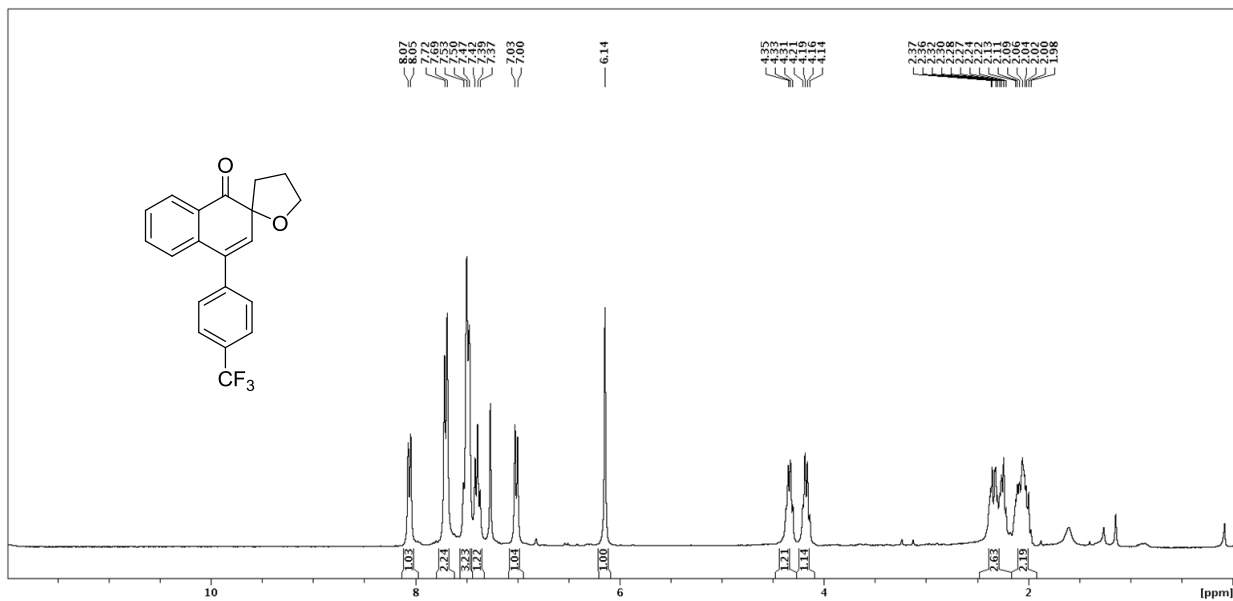
¹³C NMR spectrum of 5.2i (75 MHz, CDCl₃)



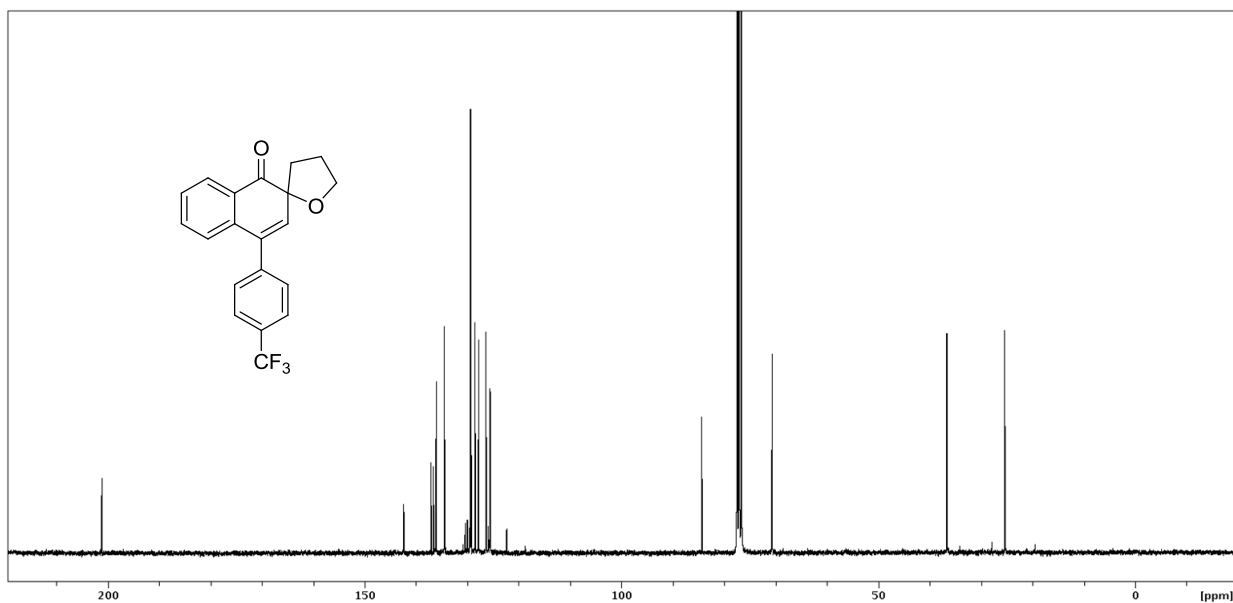
¹H NMR spectrum of 5.2j (300 MHz, CDCl₃)



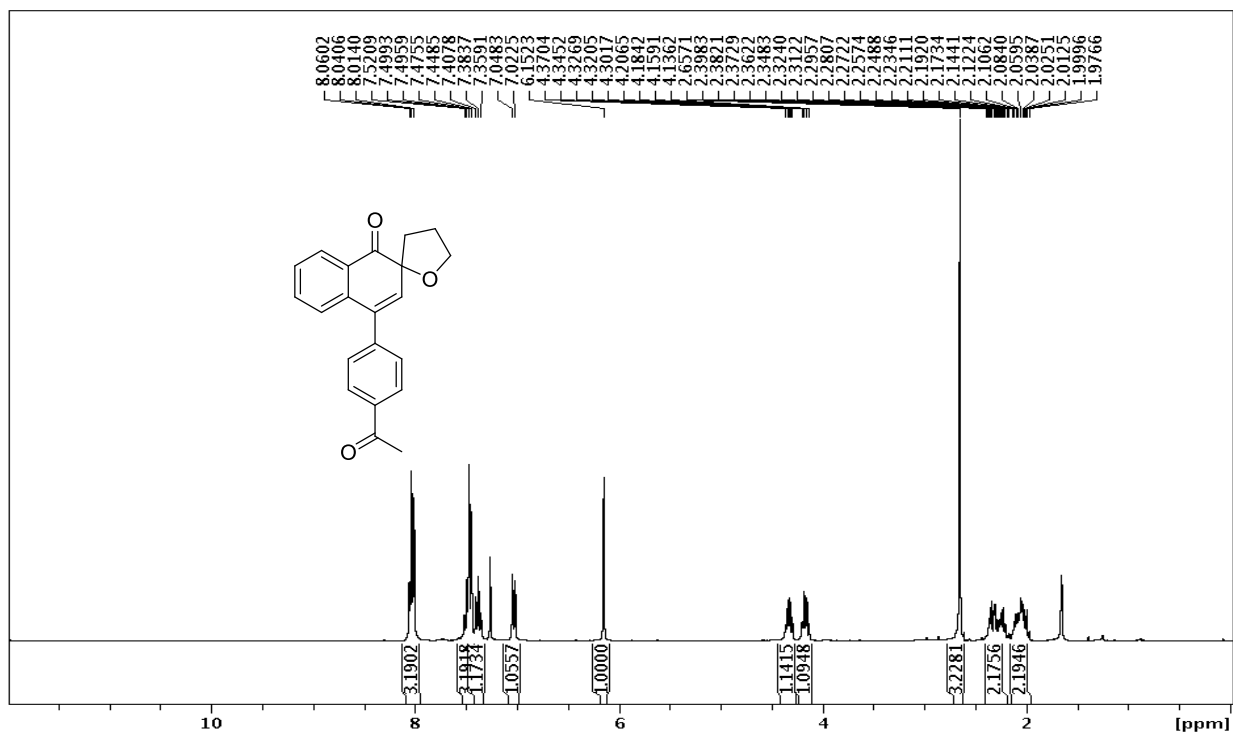
¹³C NMR spectrum of 5.2j (75 MHz, CDCl₃)



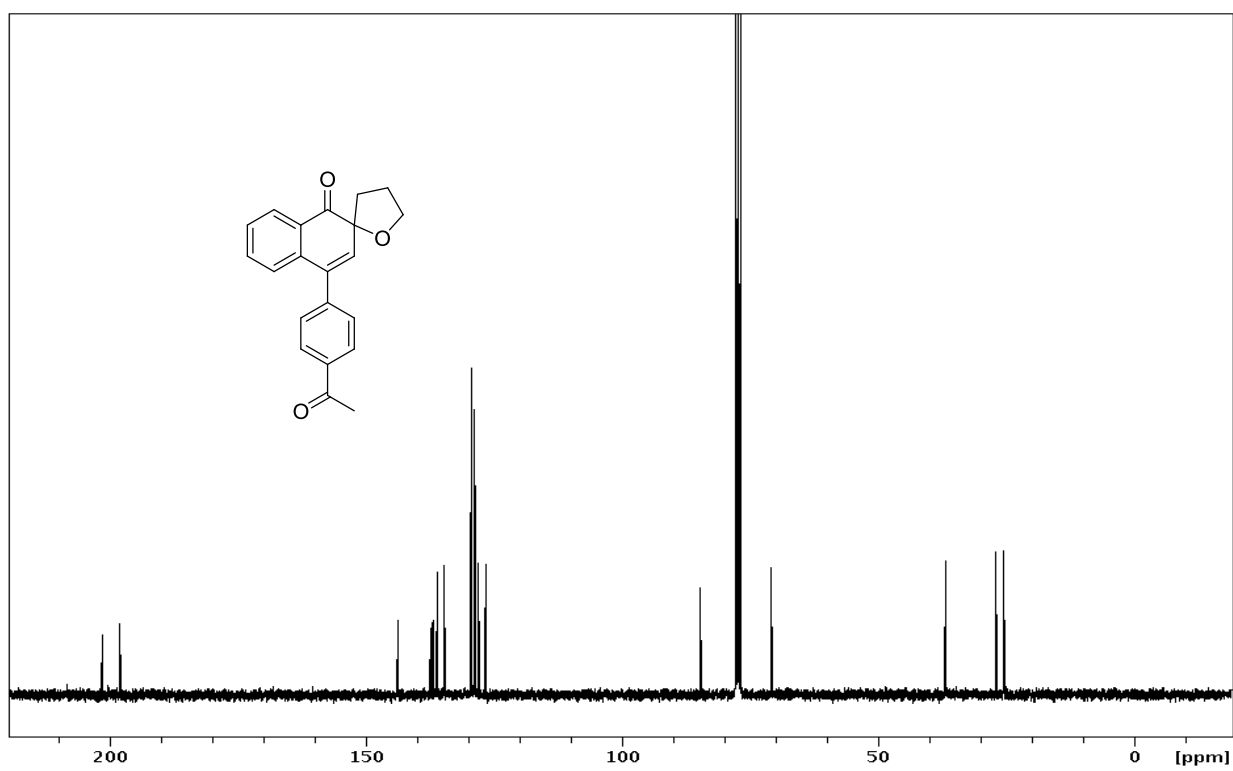
¹H NMR spectrum of 5.2k (300 MHz, CDCl₃)



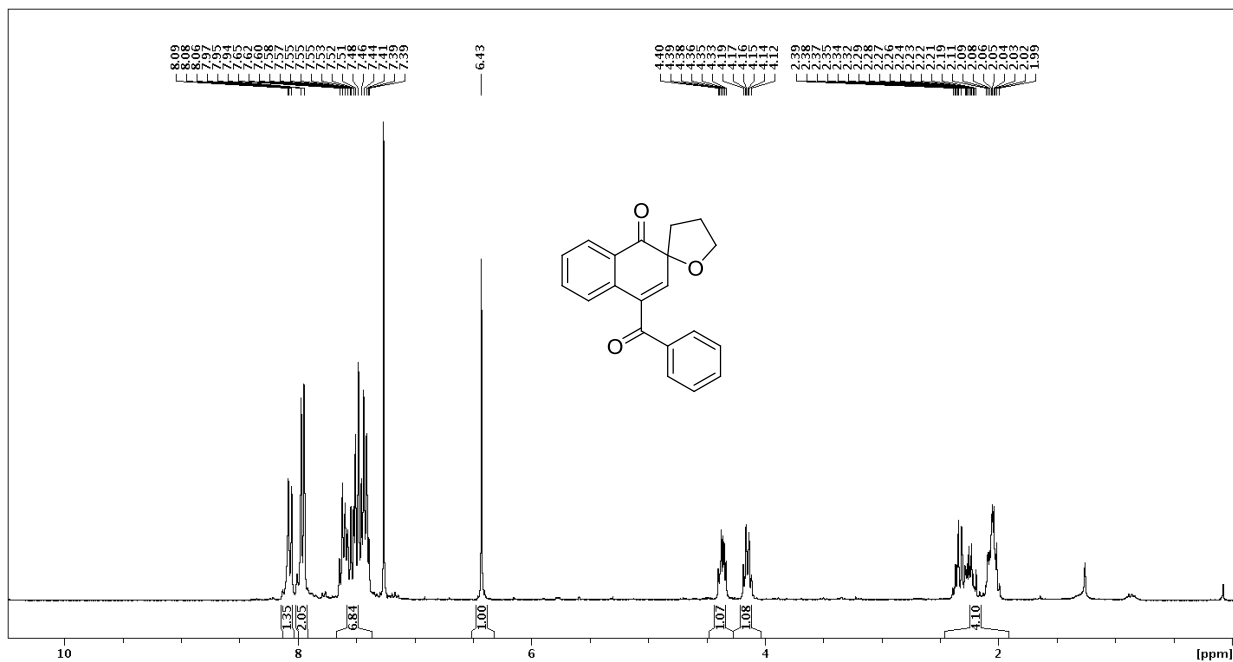
¹³C NMR spectrum of 5.2k (75 MHz, CDCl₃)



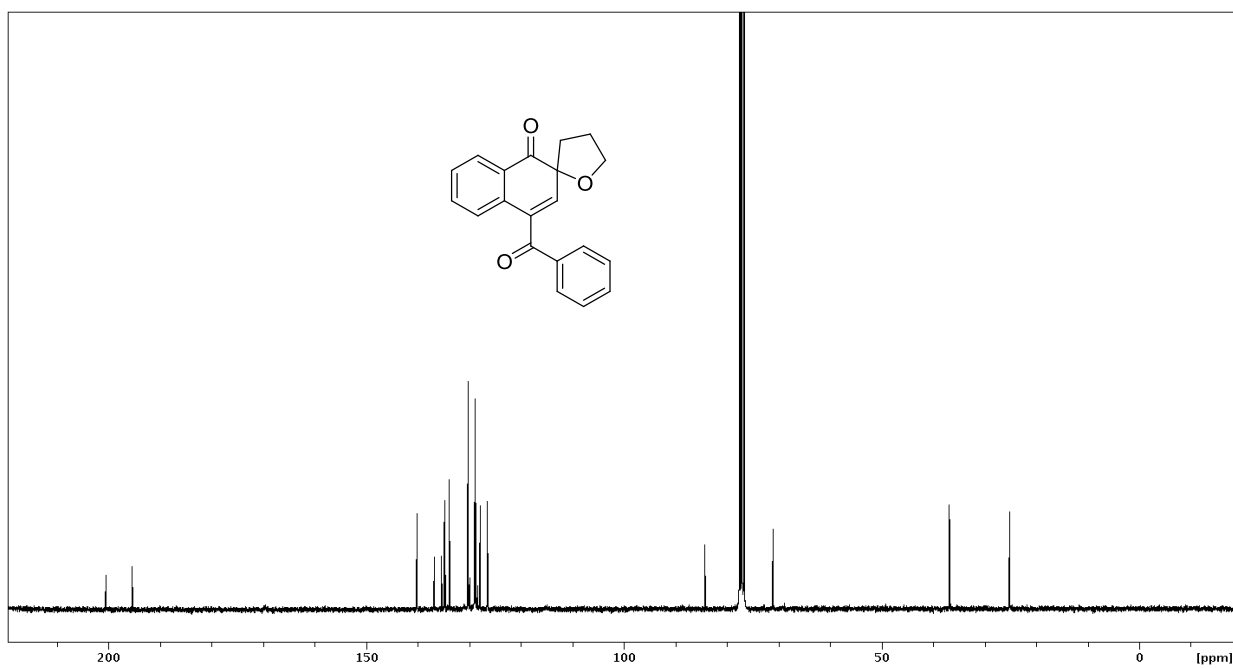
¹H NMR spectrum of 5.2r (300 MHz, CDCl₃)



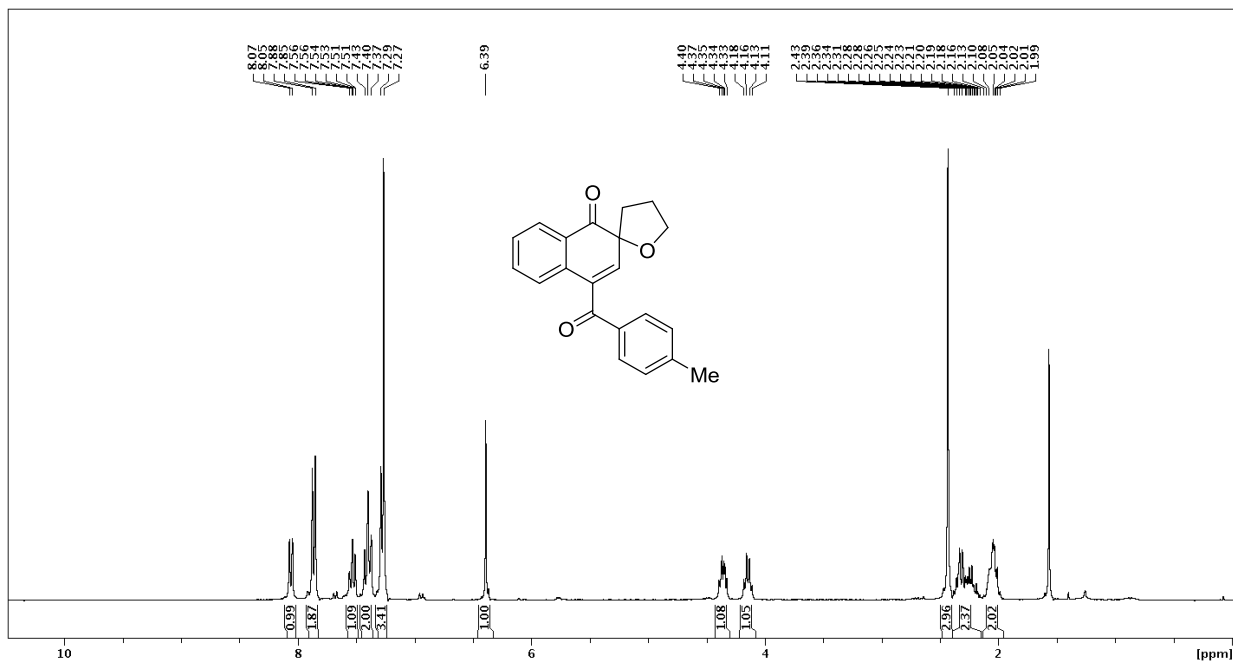
¹³C NMR spectrum of 5.2r (75 MHz, CDCl₃)



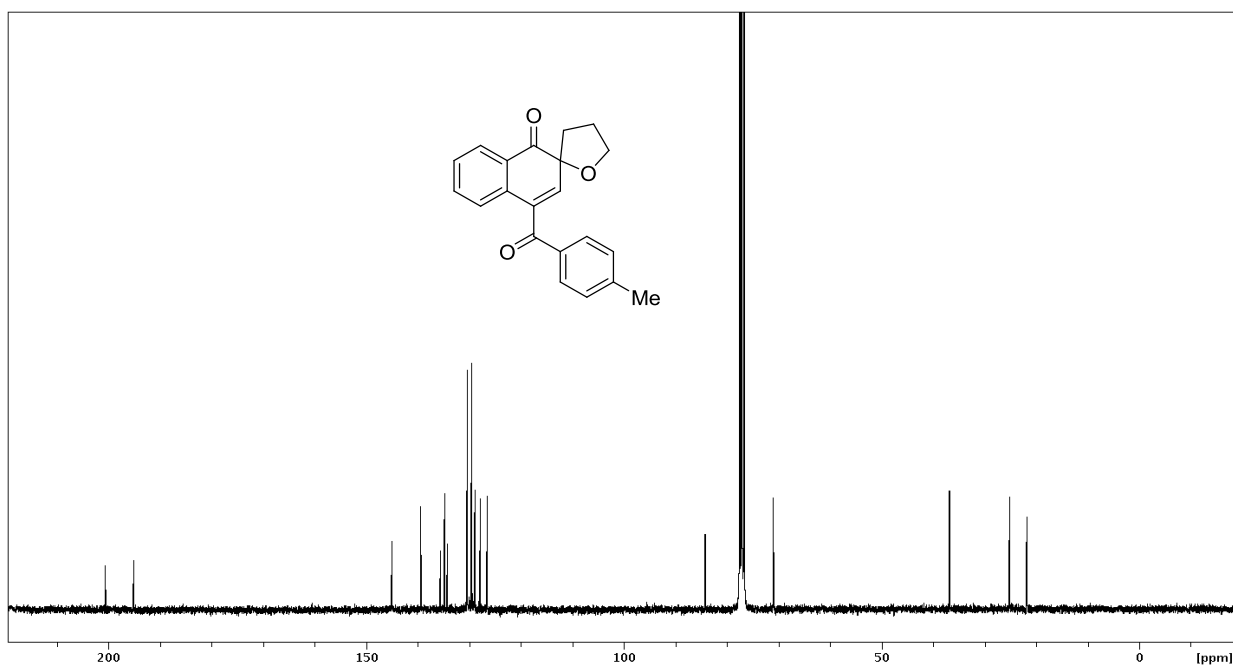
¹H NMR spectrum of 5.2o (300 MHz, CDCl₃)



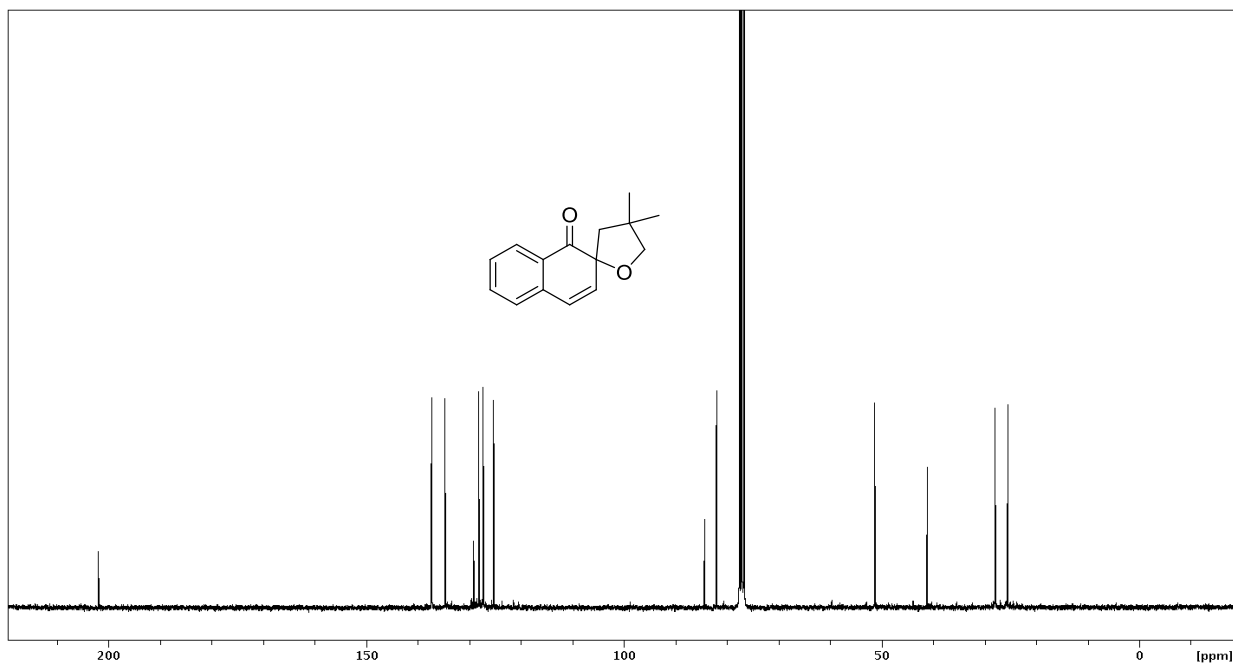
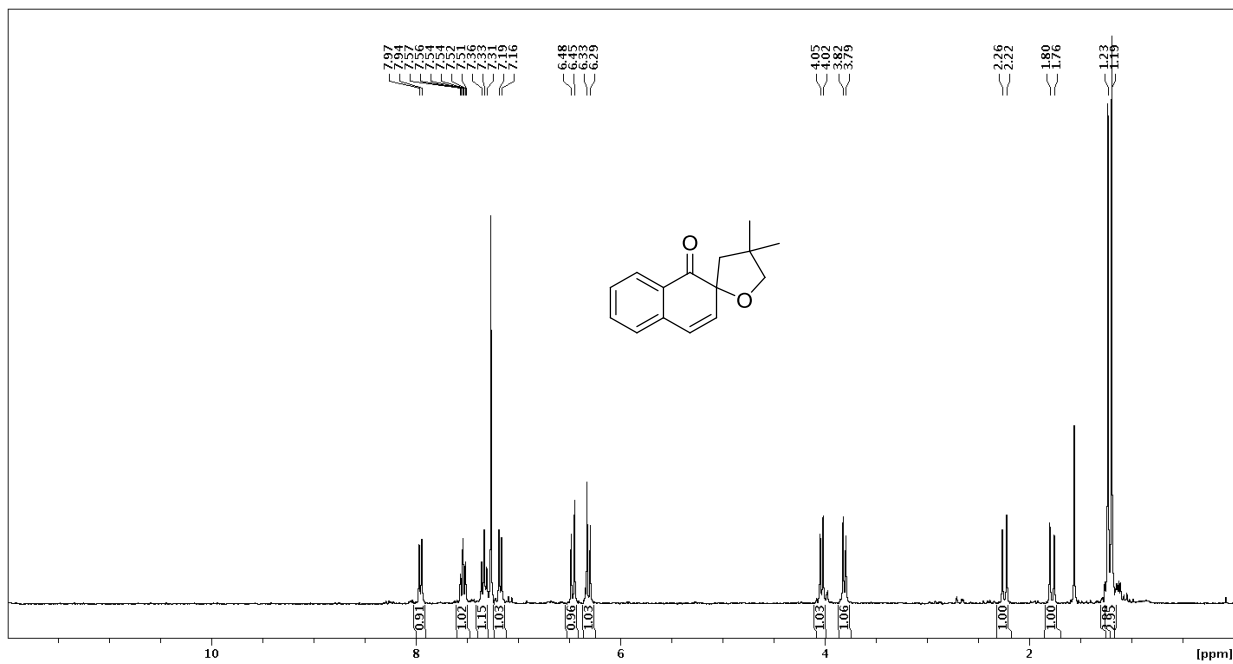
¹³C NMR spectrum of 5.2o (75 MHz, CDCl₃)

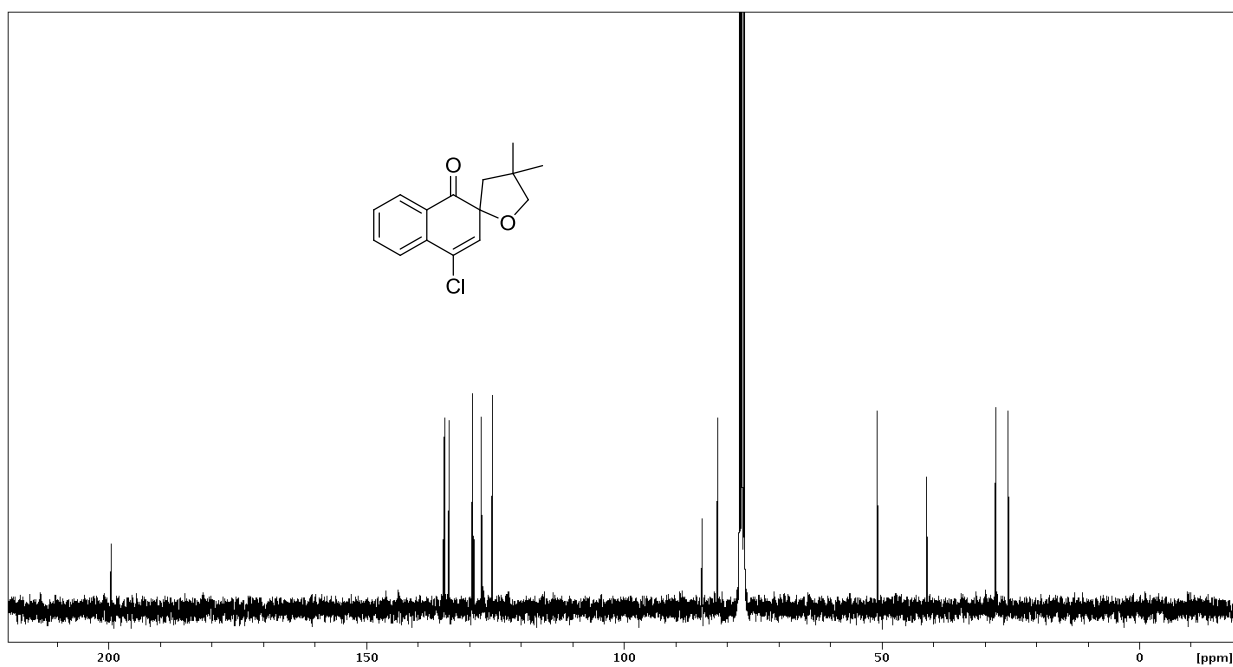
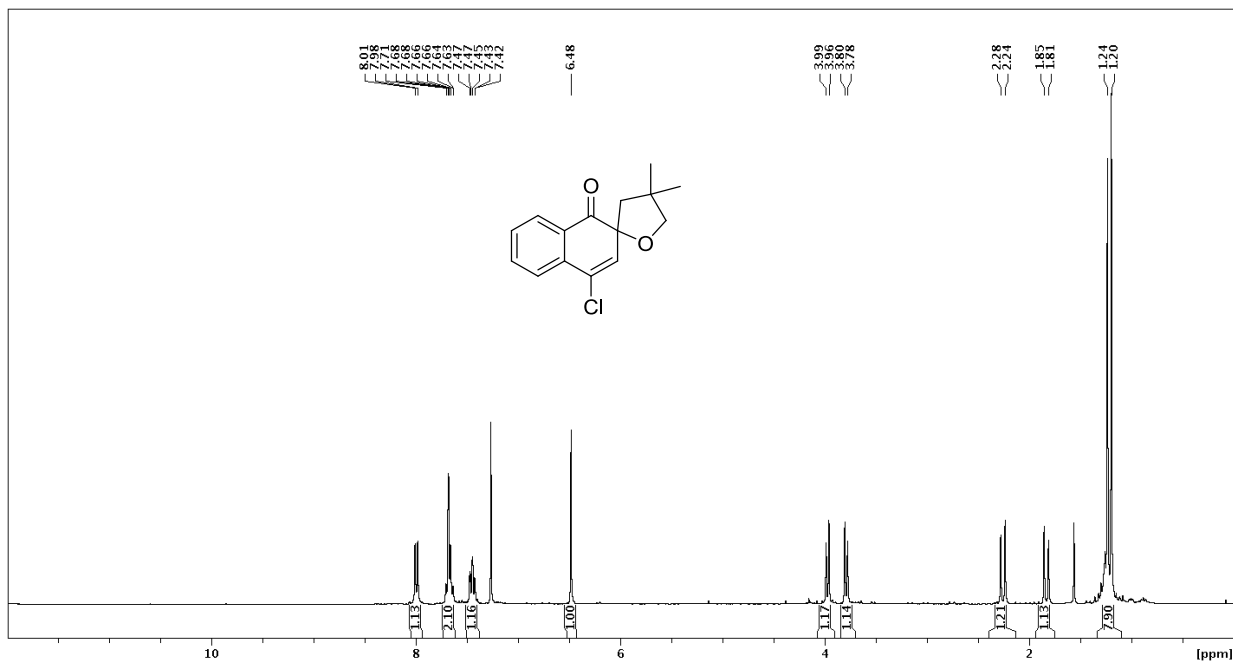


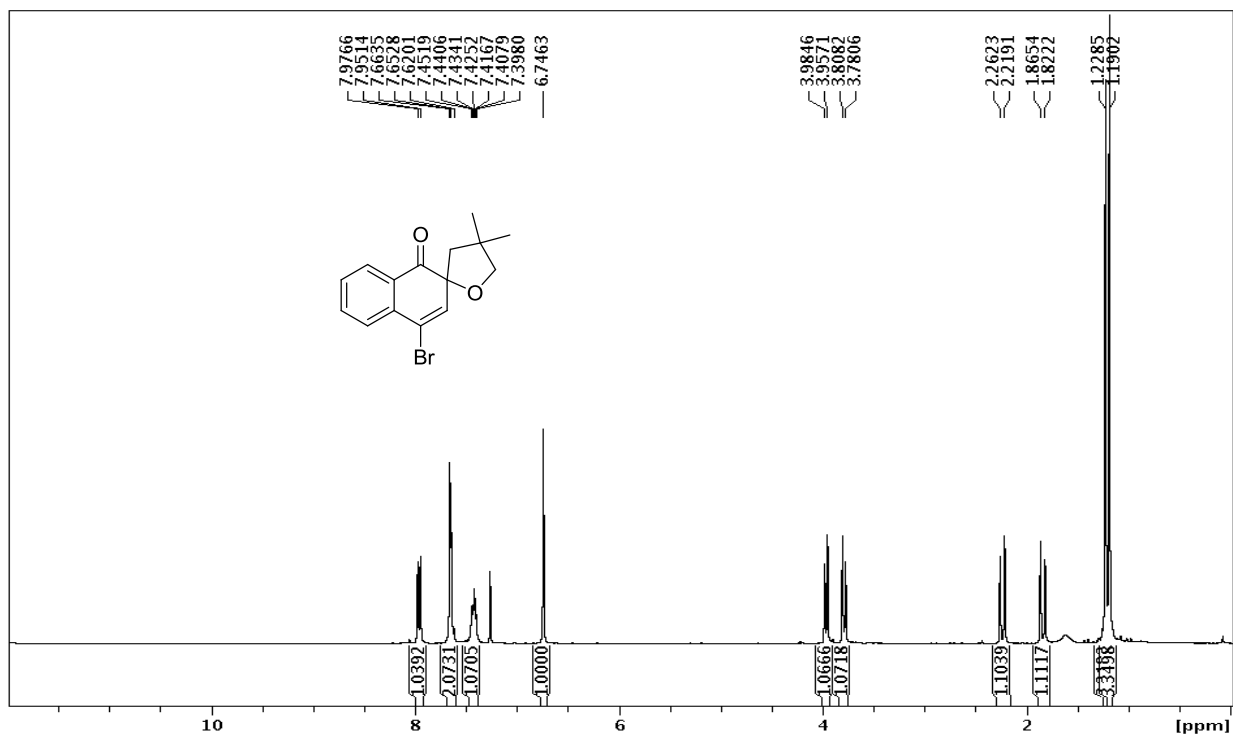
¹H NMR spectrum of 5.2p (300 MHz, CDCl₃)



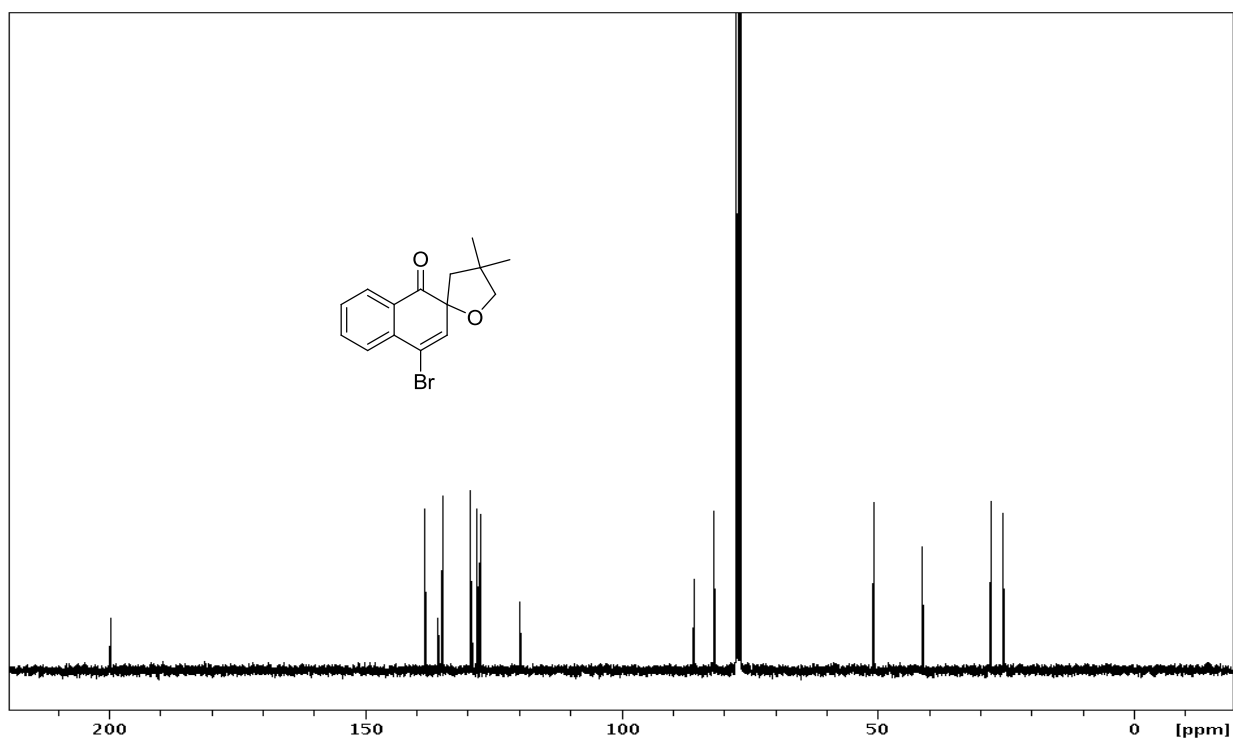
¹³C NMR spectrum of 5.2p (75 MHz, CDCl₃)



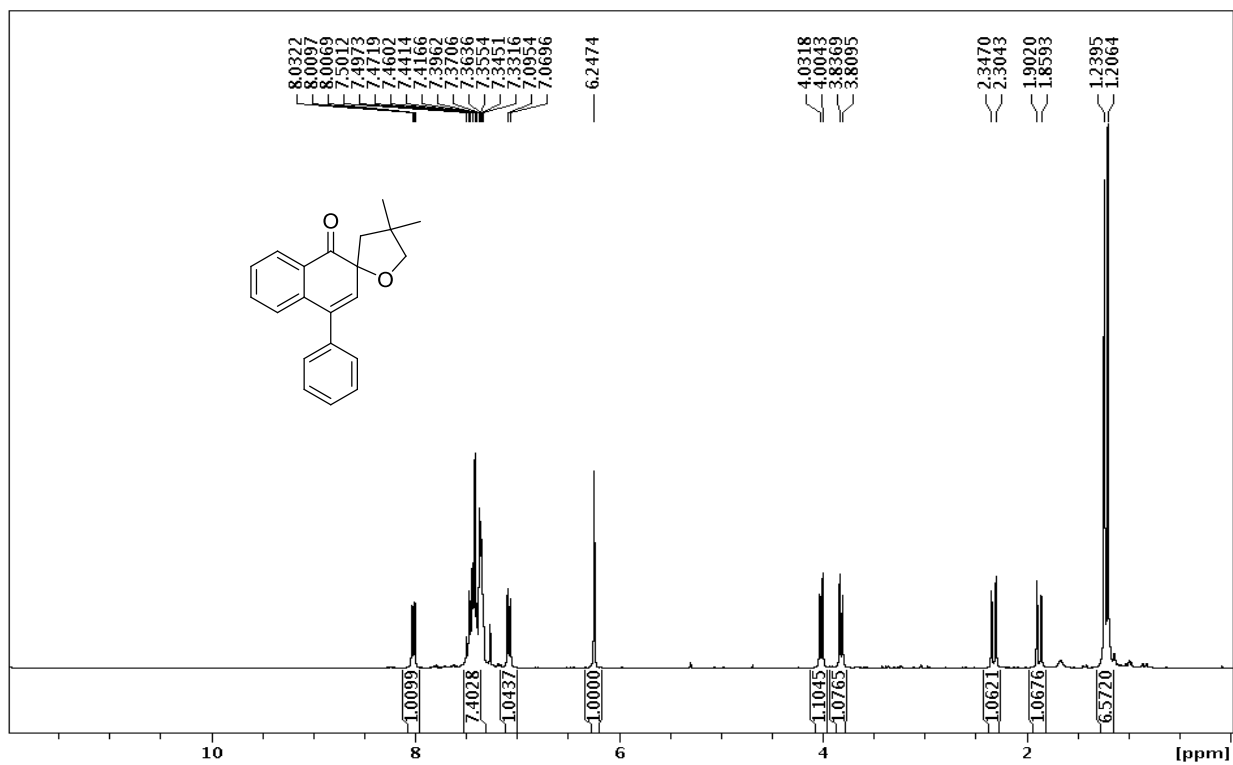




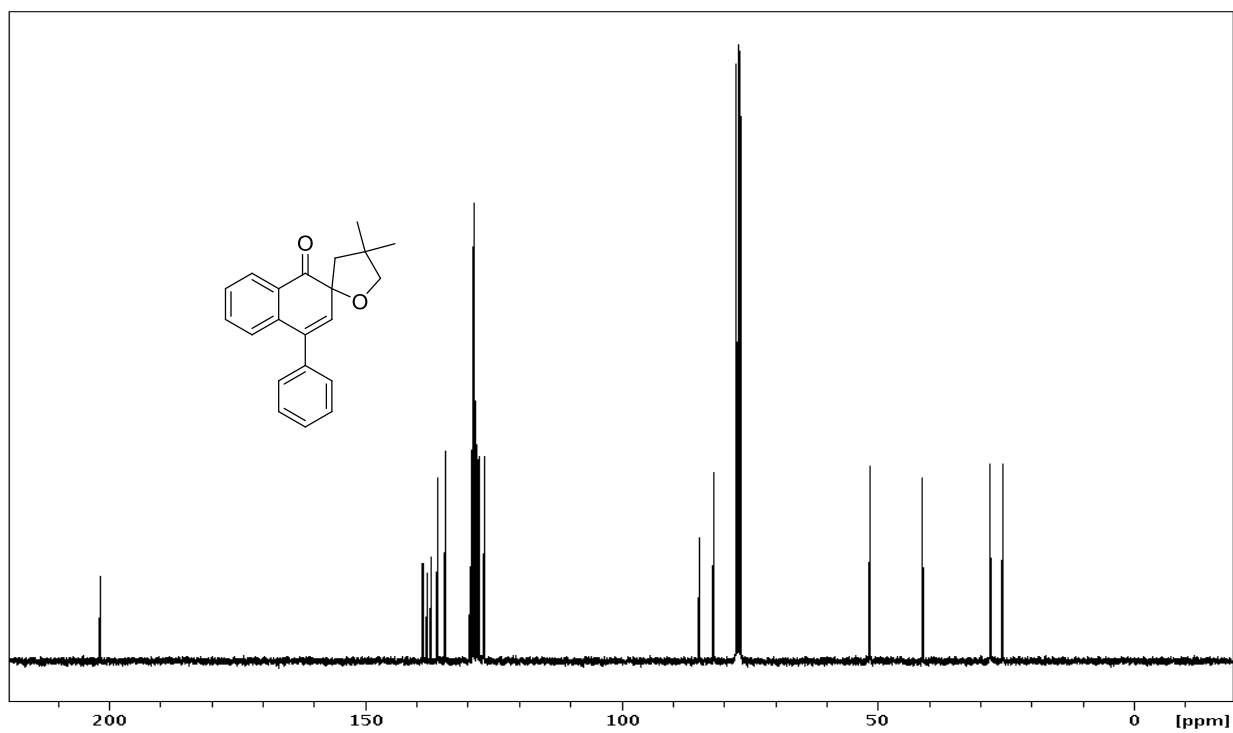
¹H NMR spectrum of 5.2u (300 MHz, CDCl₃)



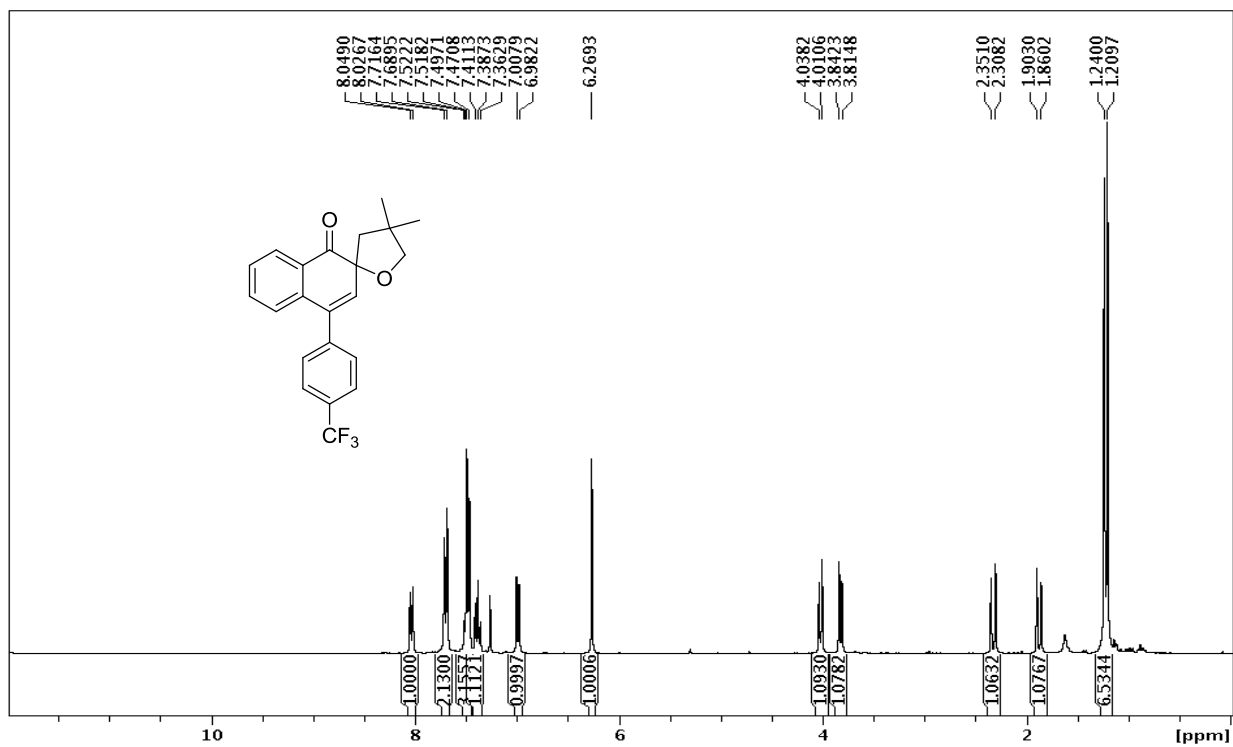
¹³C NMR spectrum of 5.2u (75 MHz, CDCl₃)



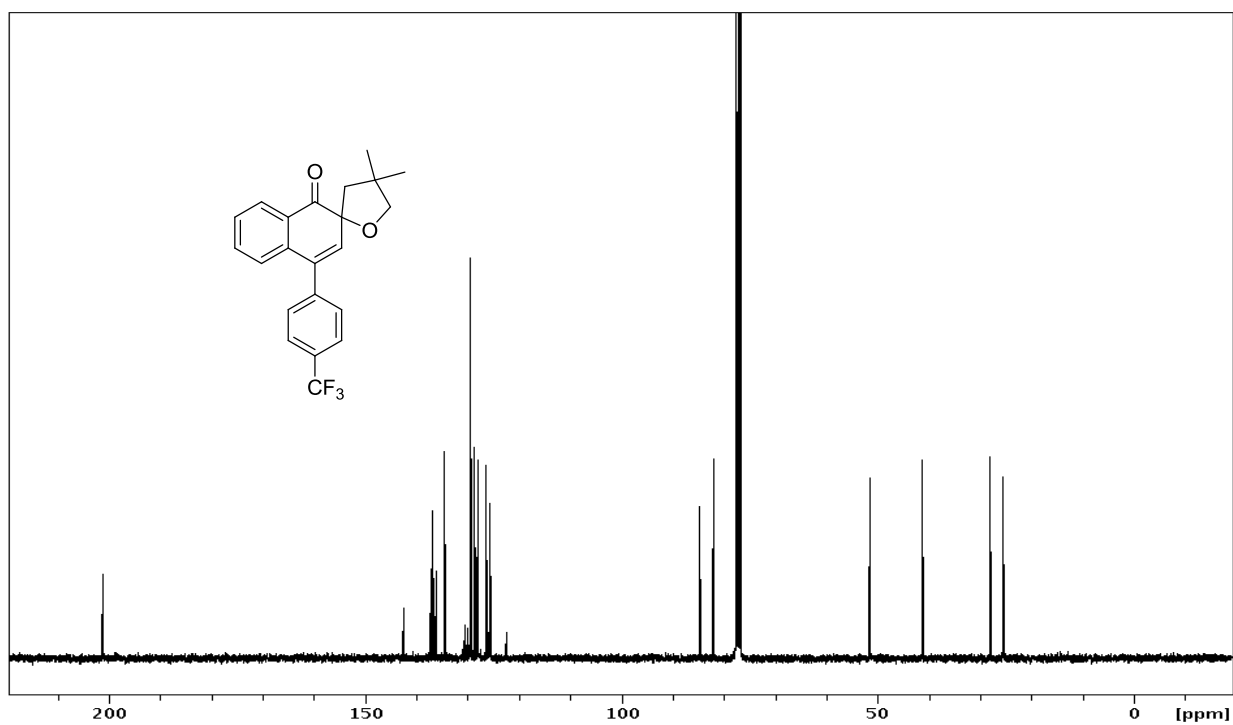
¹H NMR spectrum of 5.2v (300 MHz, CDCl₃)



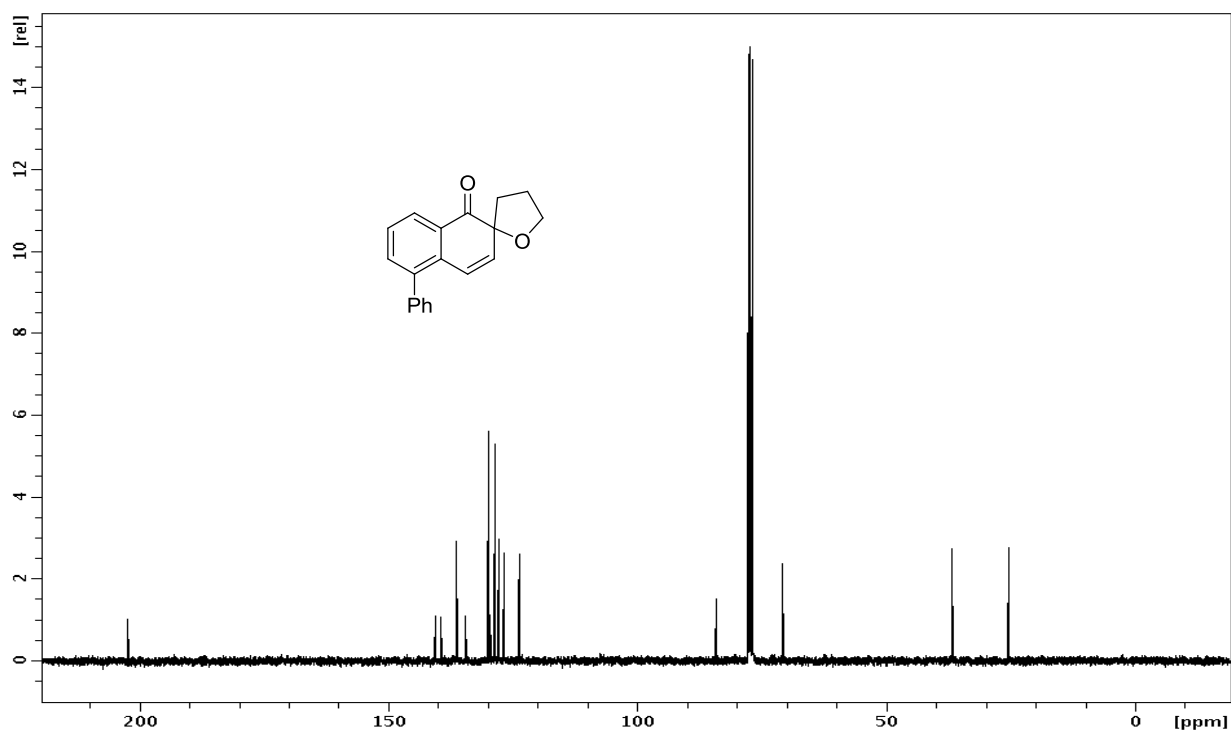
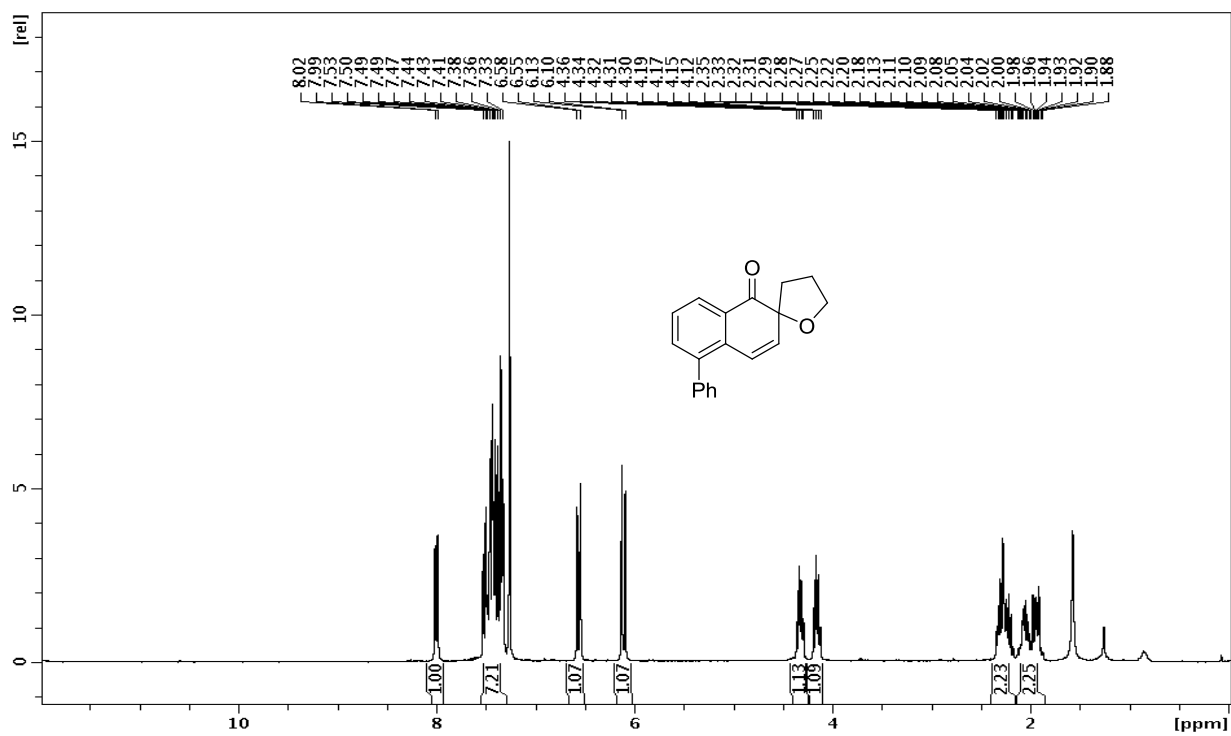
¹³C NMR spectrum of 5.2v (75 MHz, CDCl₃)

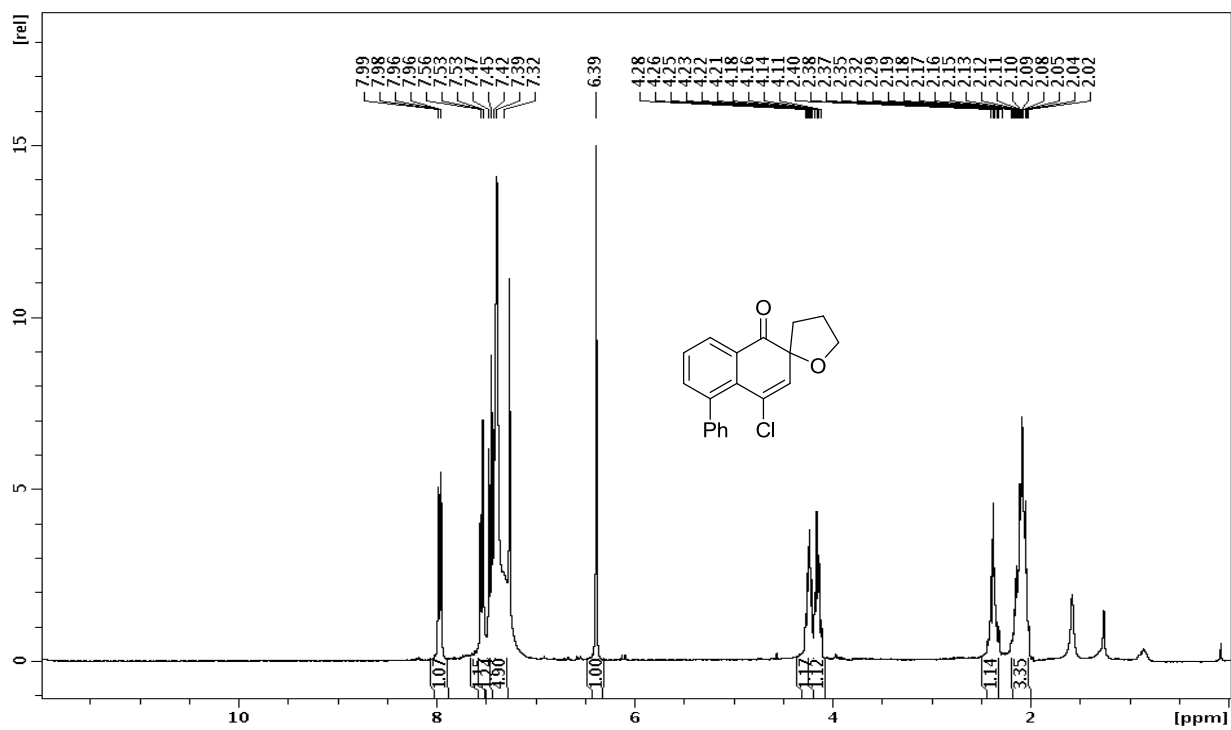


¹H NMR spectrum of 5.2w (300 MHz, CDCl₃)

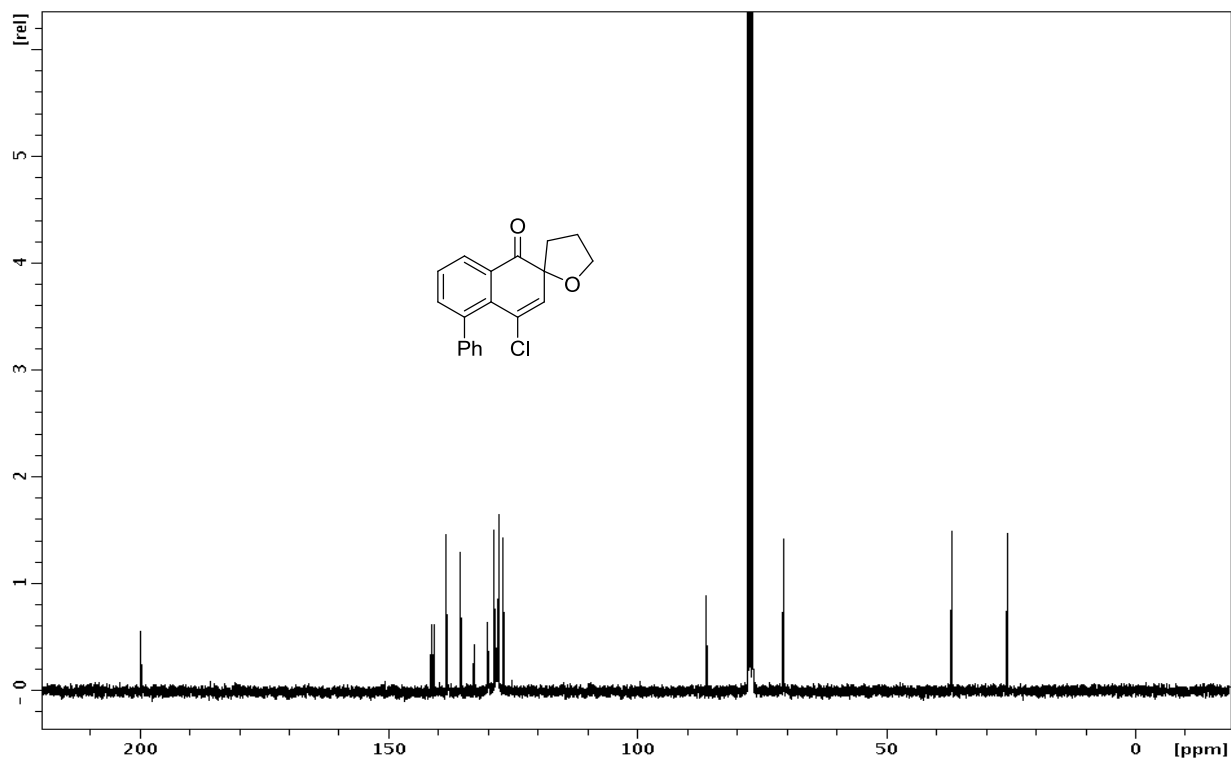


¹³C NMR spectrum of 5.2w (75 MHz, CDCl₃)

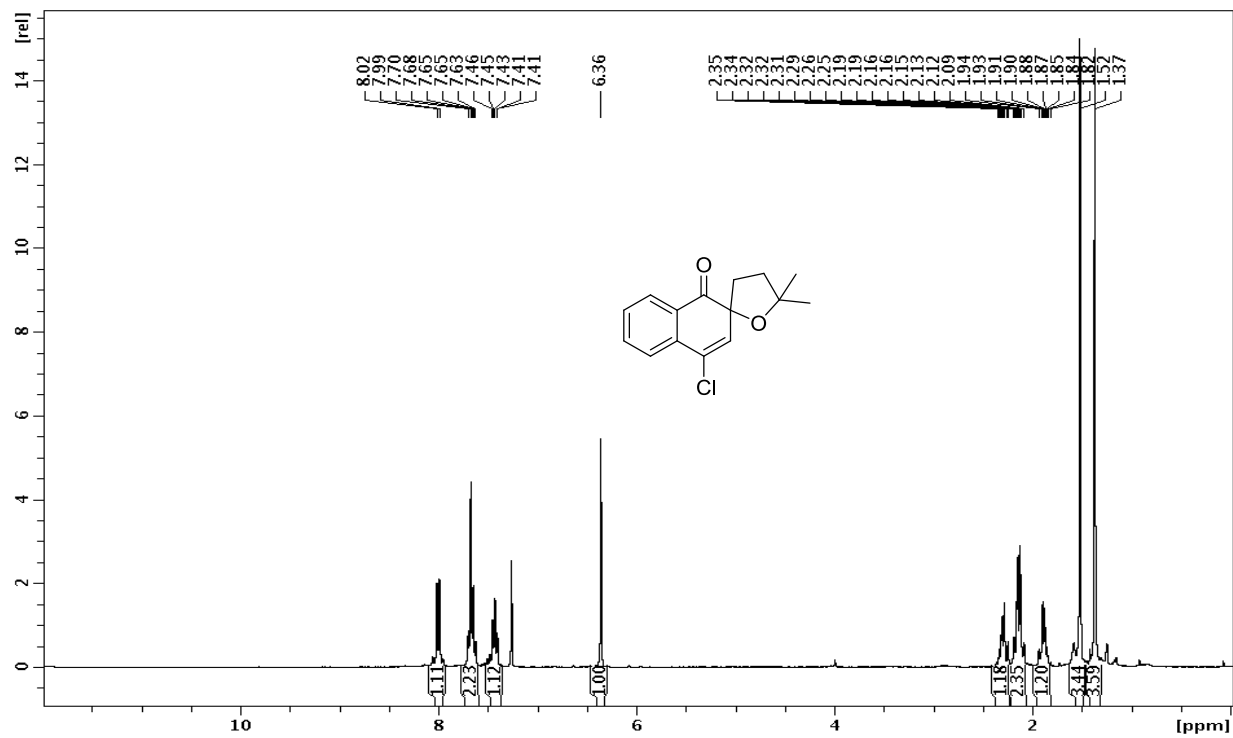




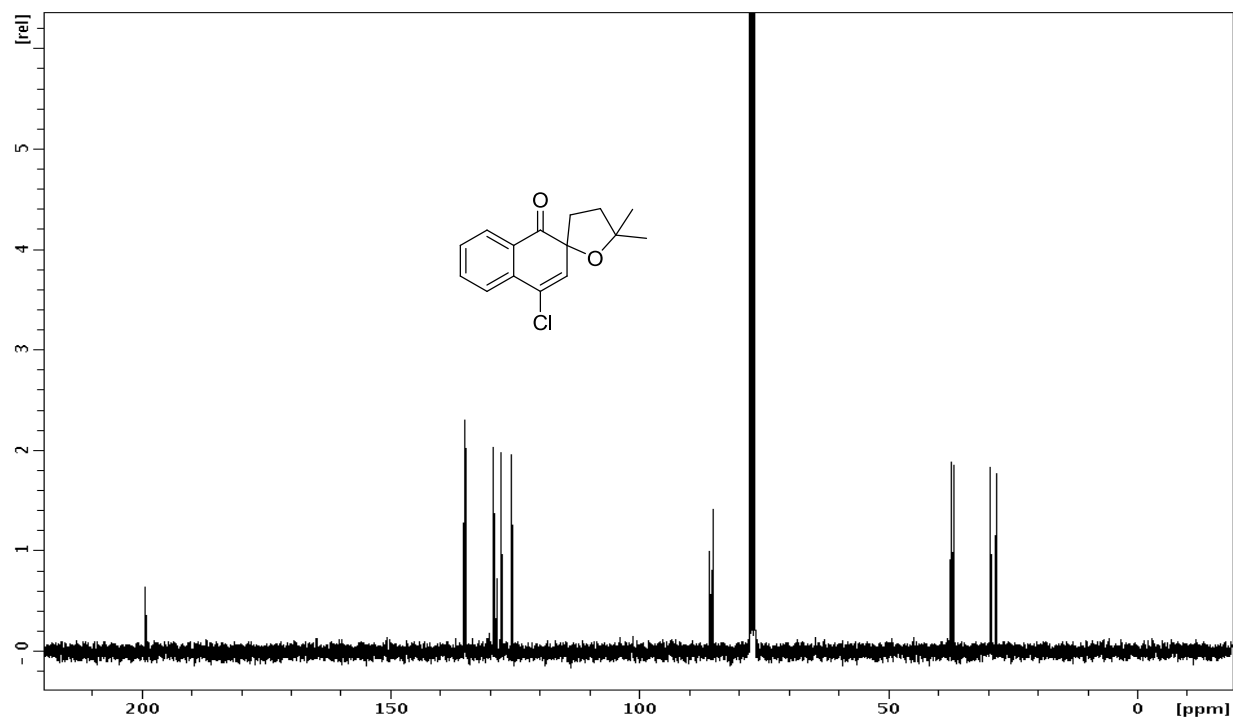
¹H NMR spectrum of 5.2t (300 MHz, CDCl₃)



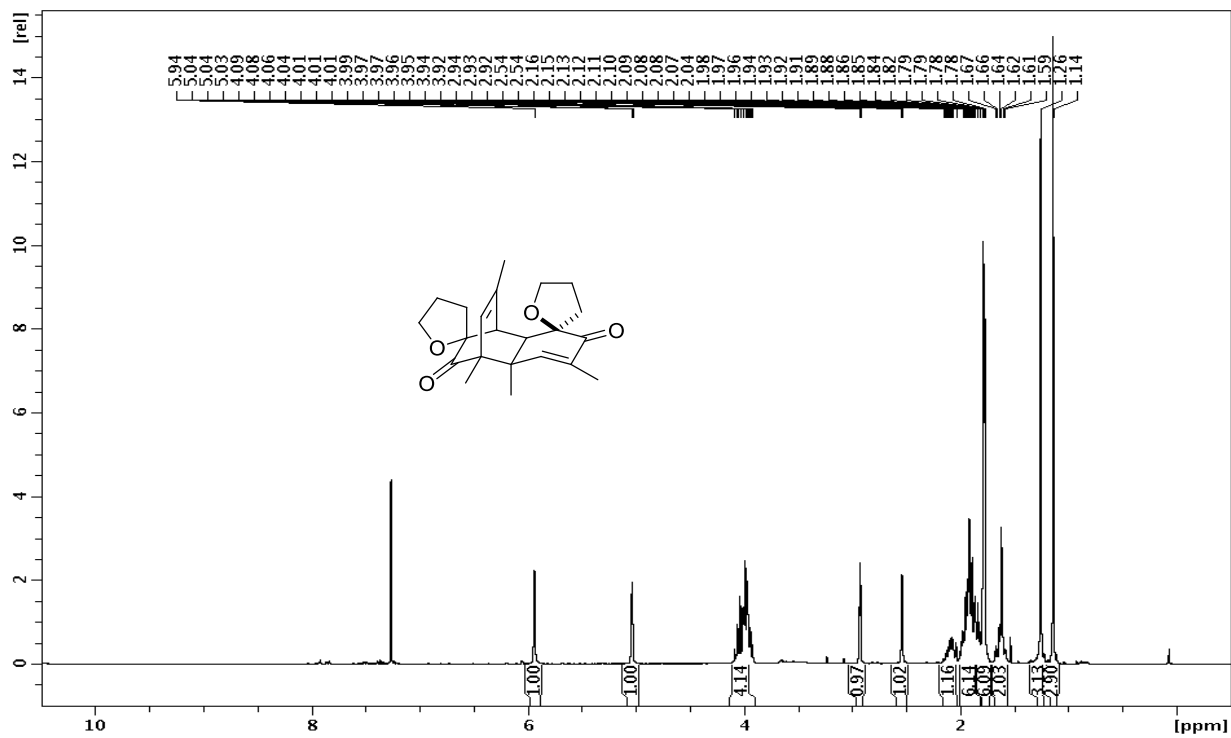
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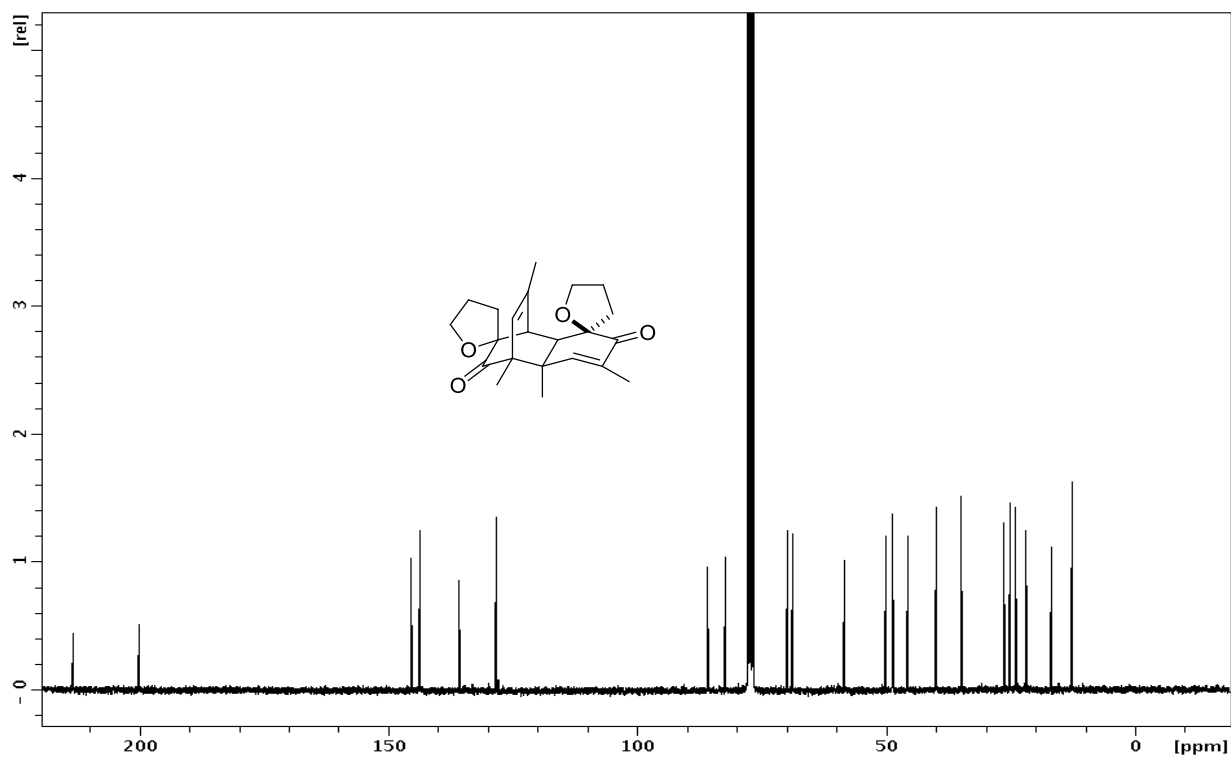
¹H NMR spectrum of 5.2x (300 MHz, CDCl₃)



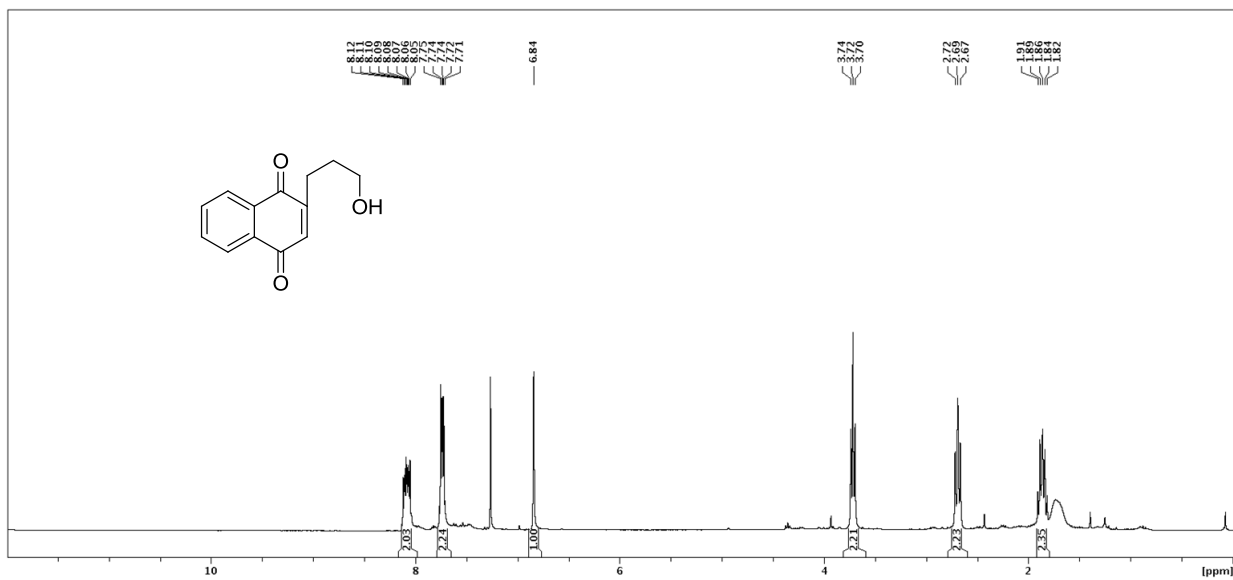
¹³C NMR spectrum of 5.2x (75 MHz, CDCl₃)



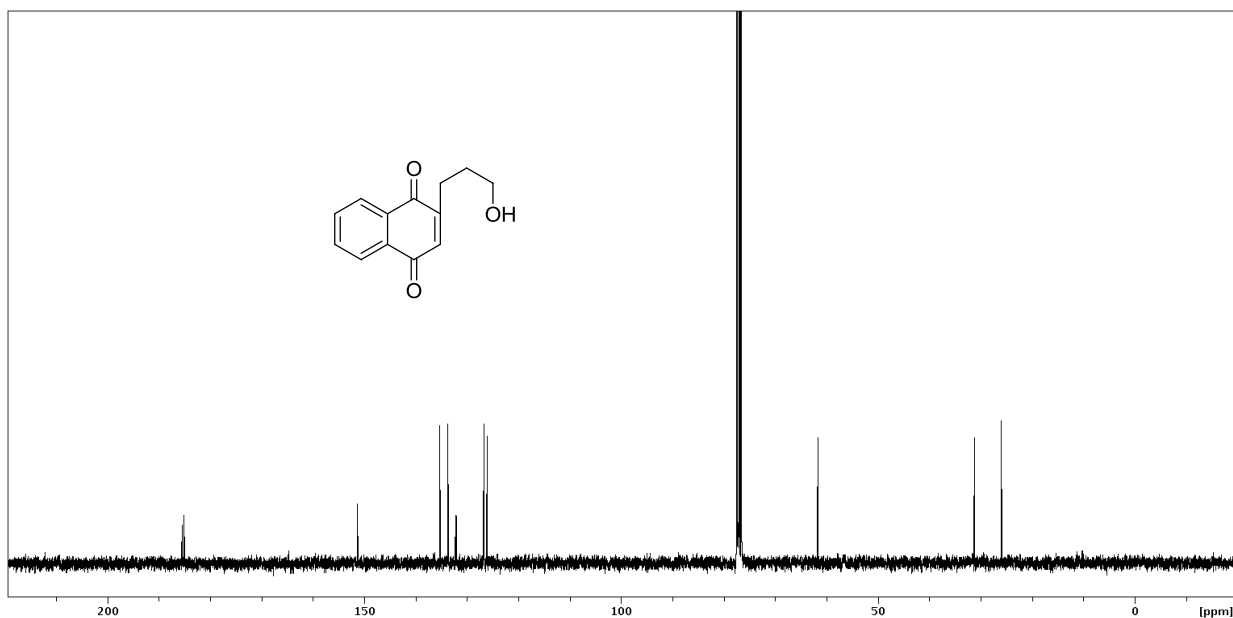
¹H NMR spectrum of 5.5 (300 MHz, CDCl₃)



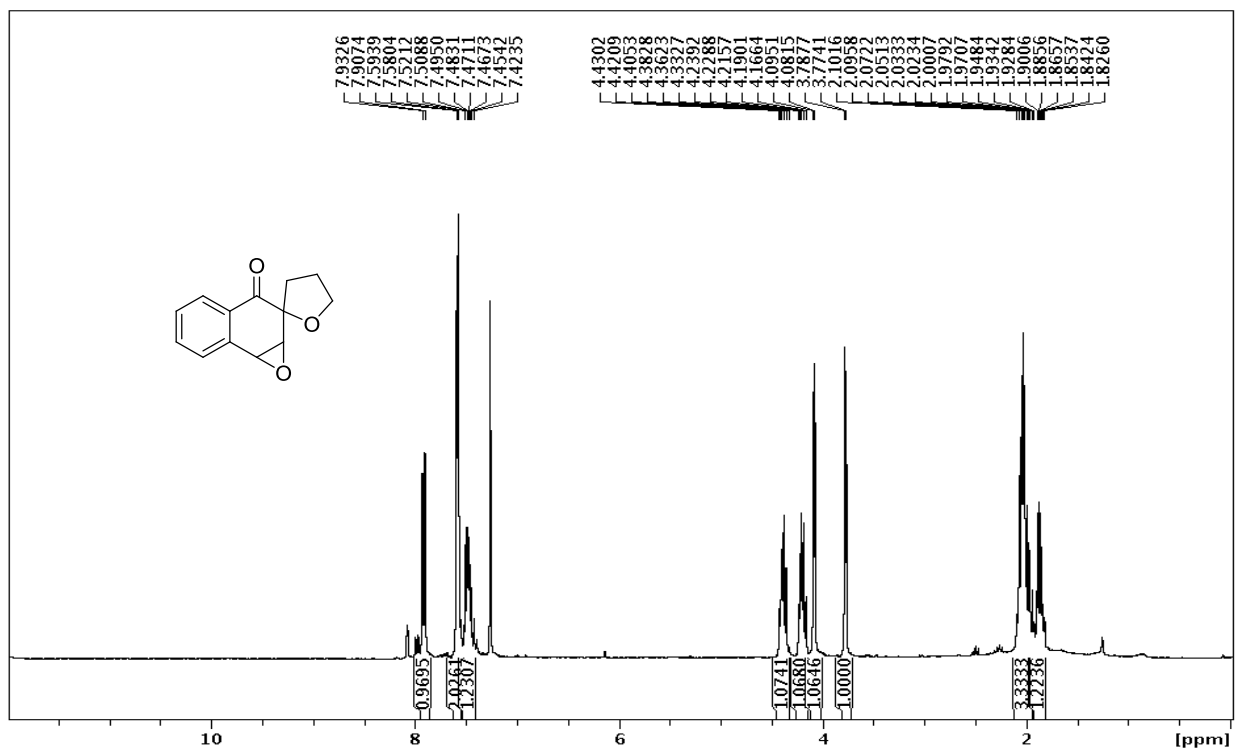
¹³C NMR spectrum of 5.5 (75 MHz, CDCl₃)



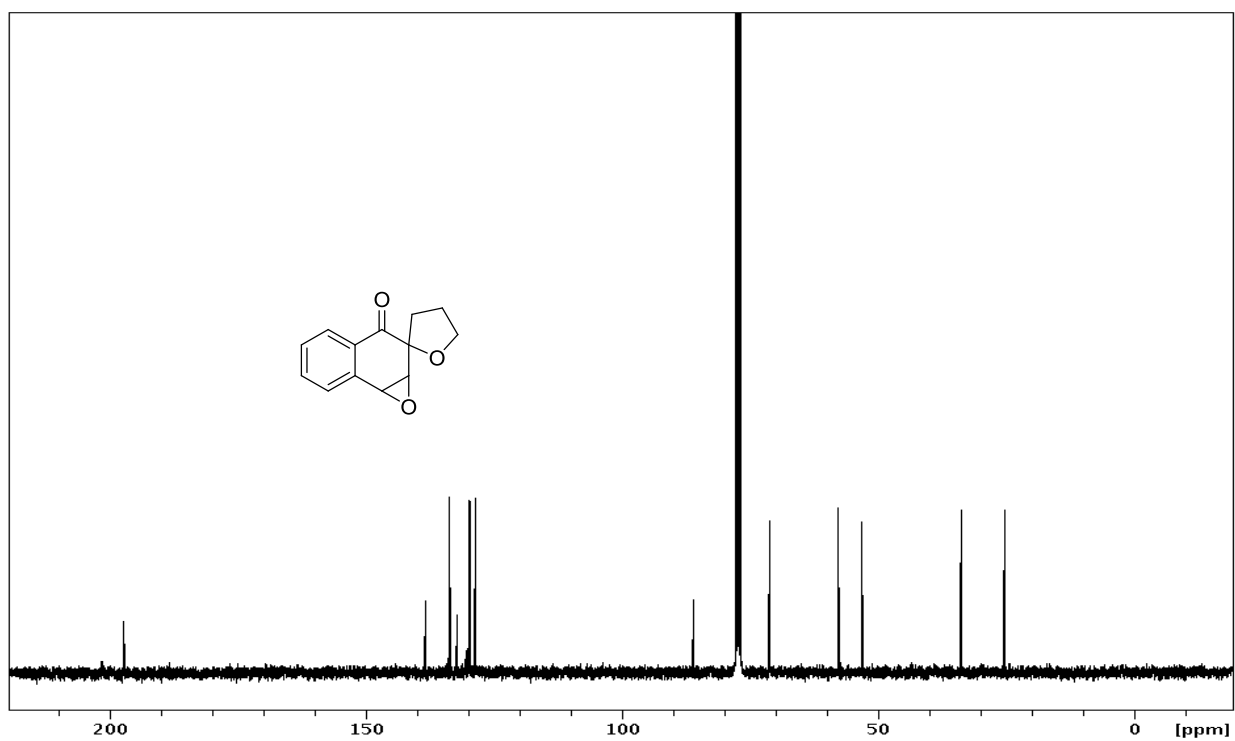
¹H NMR spectrum of 5.9 (300 MHz, CDCl₃)



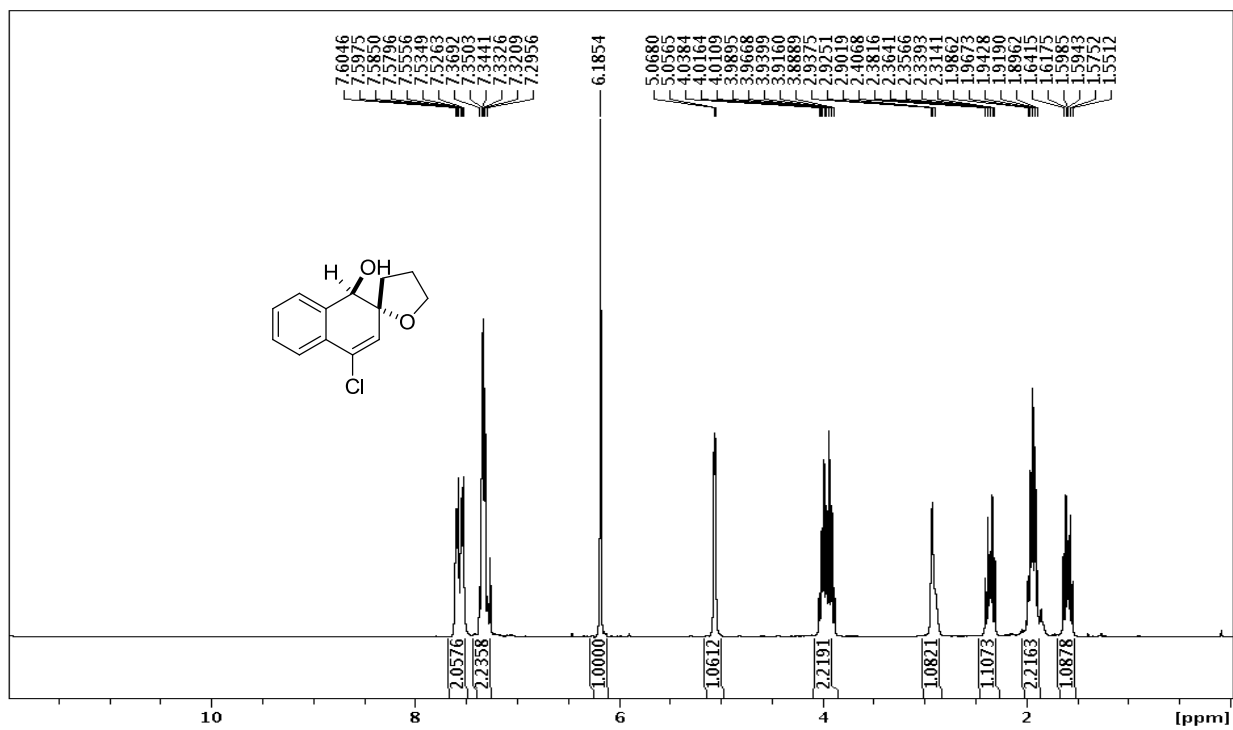
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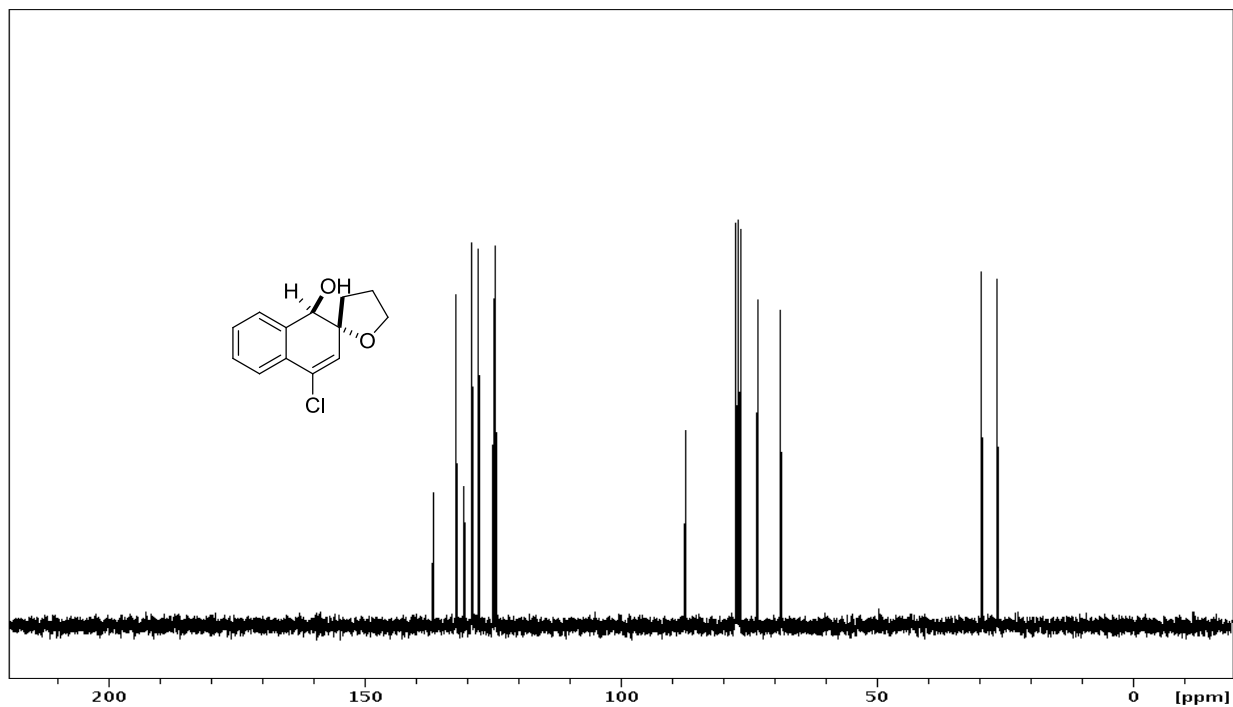
¹H NMR spectrum of 5.10 (300 MHz, CDCl₃)



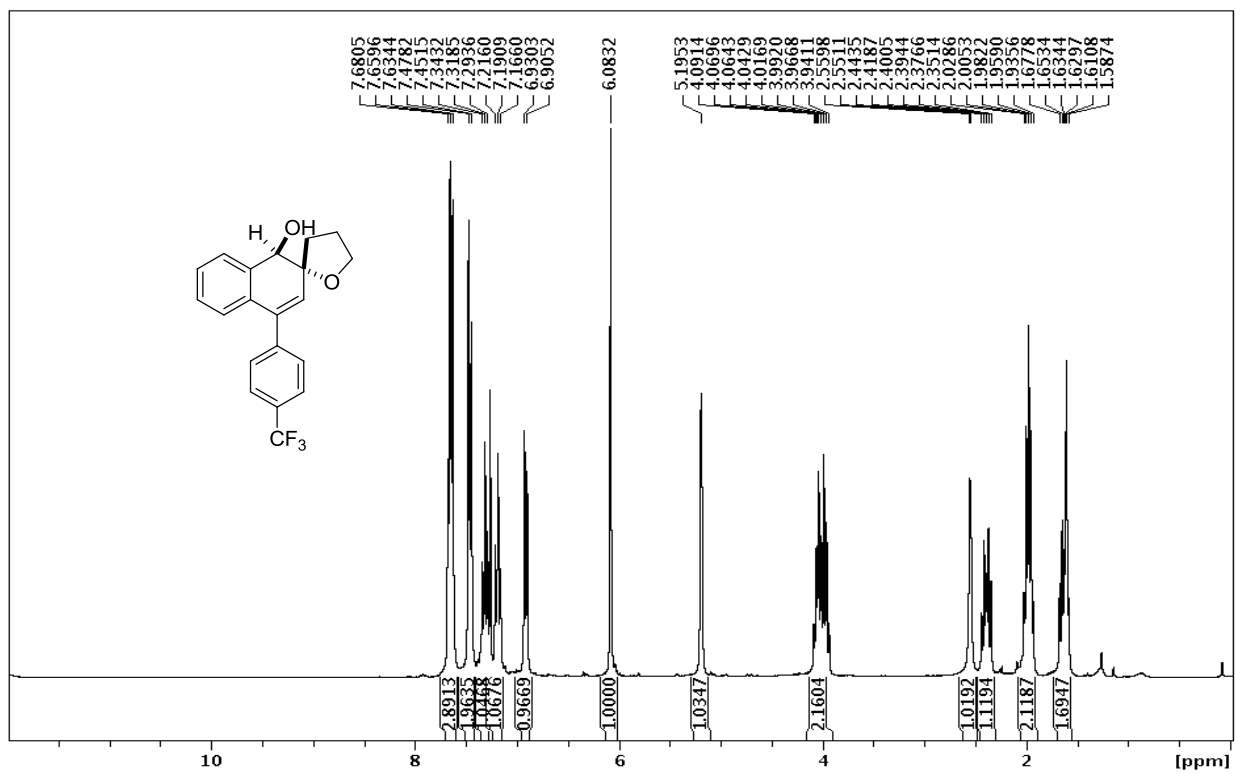
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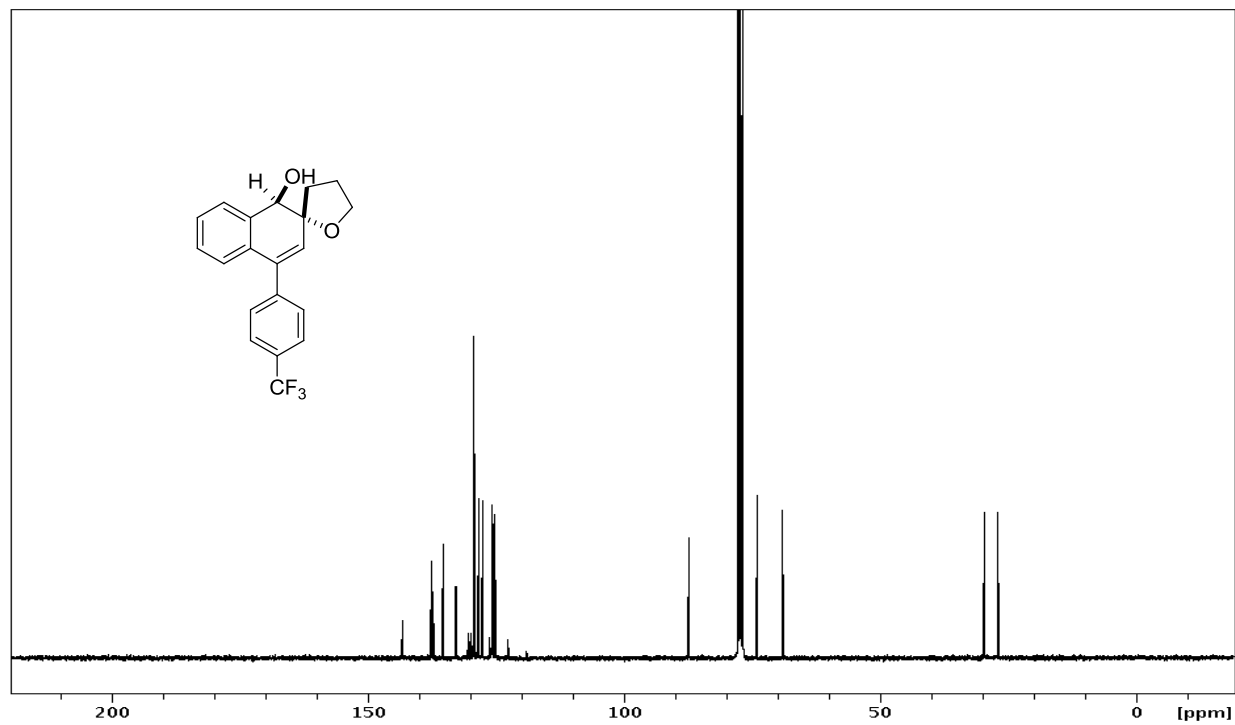
¹H NMR spectrum of 5.13 (300 MHz, CDCl₃)



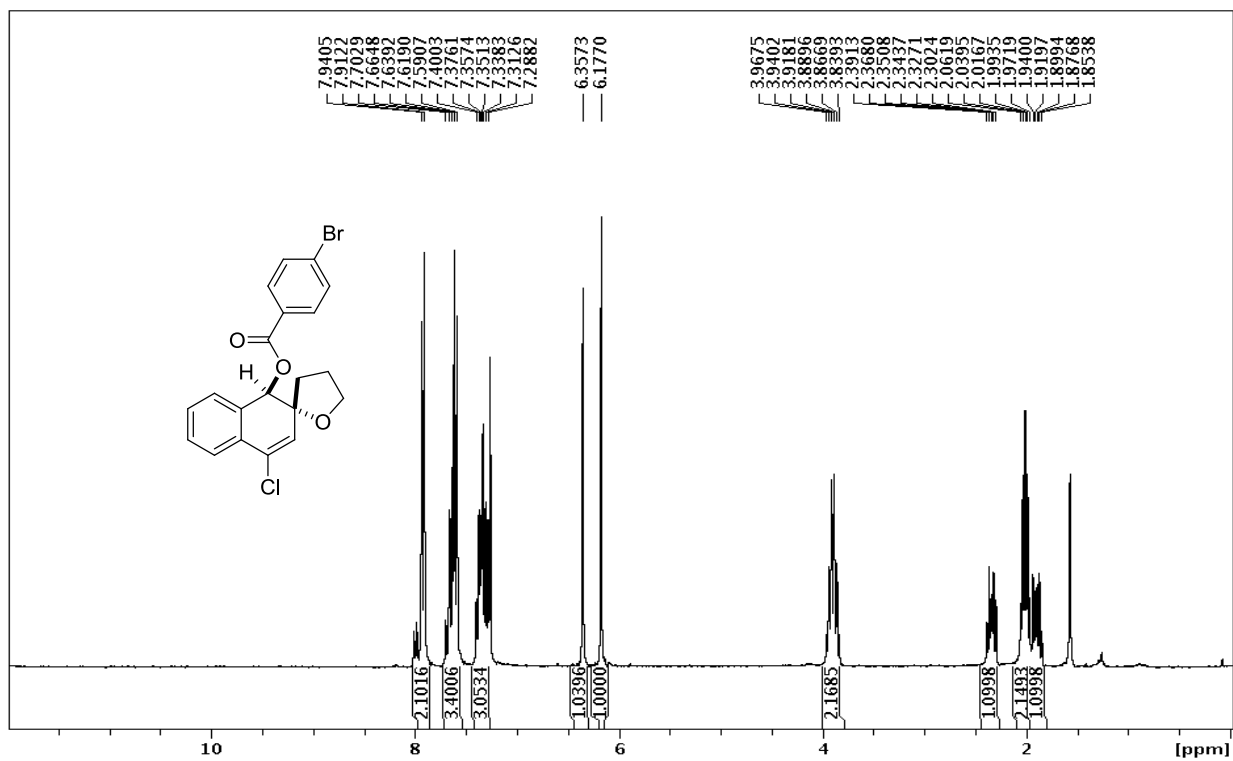
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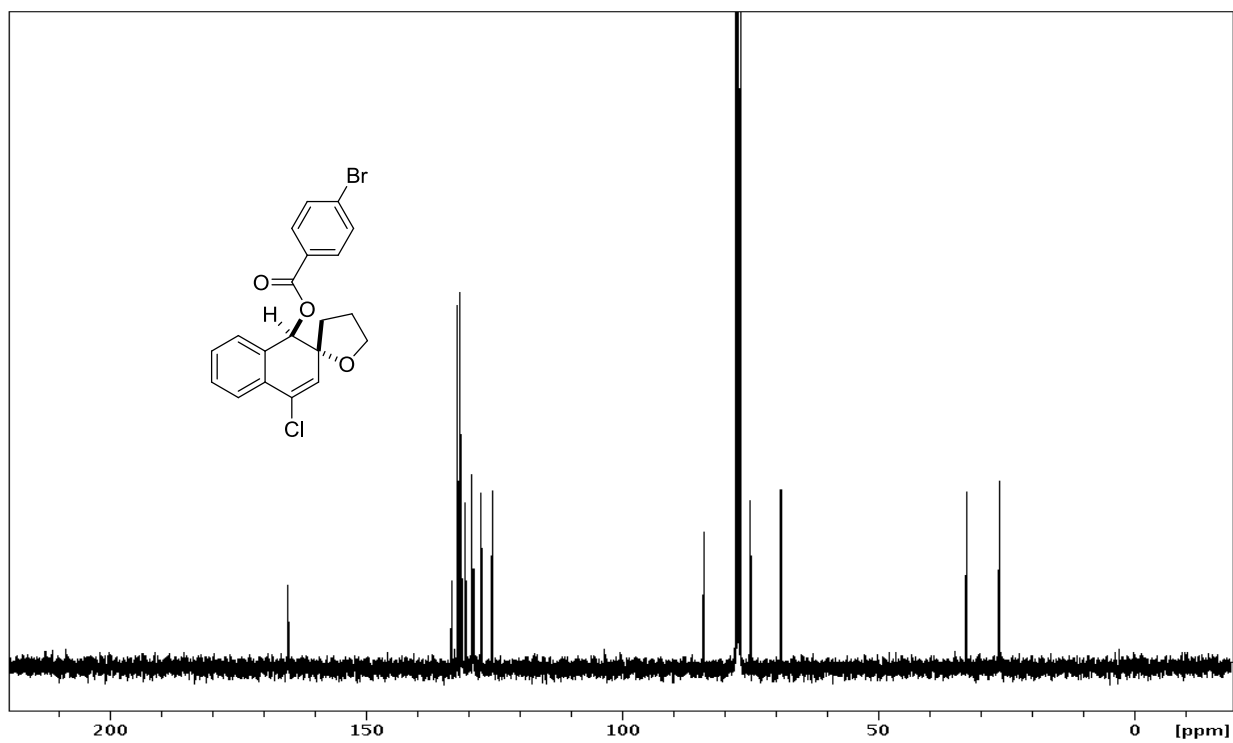
¹H NMR spectrum of 5.15 (300 MHz, CDCl₃)



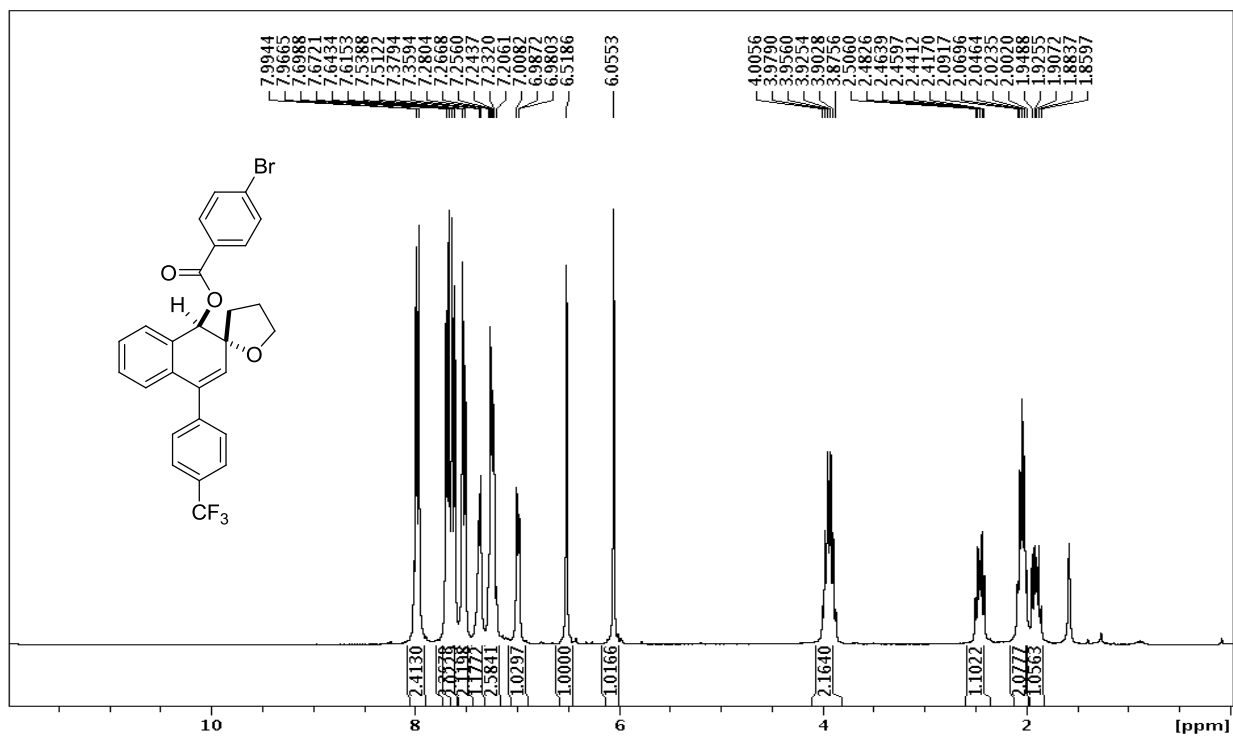
¹³C NMR spectrum of 5.15 (75 MHz, CDCl₃)



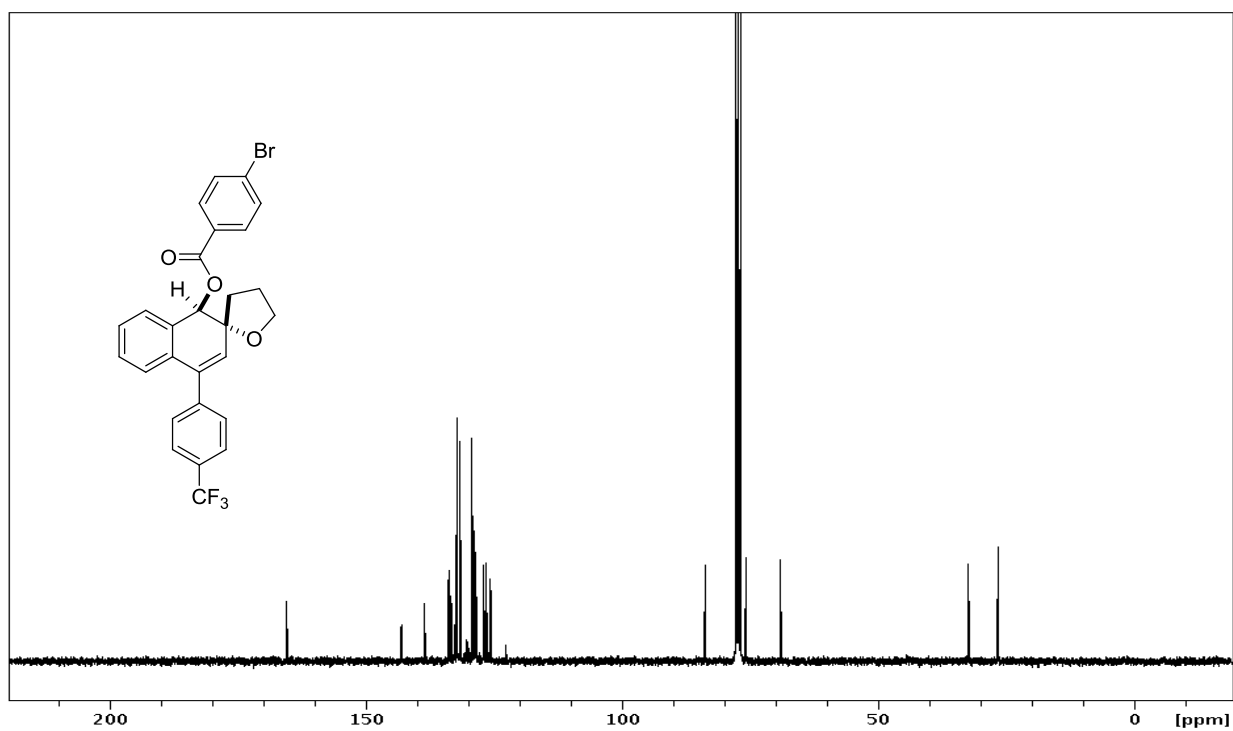
¹H NMR spectrum of 5.14 (300 MHz, CDCl₃)



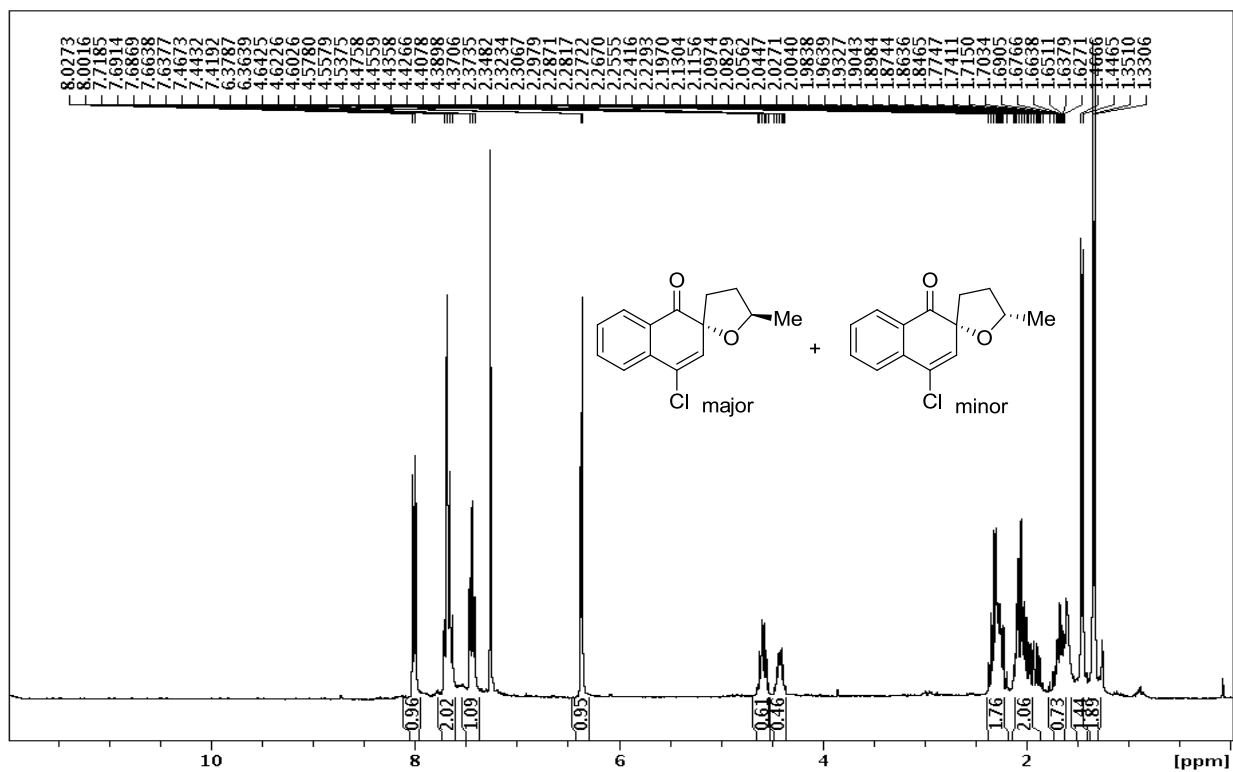
¹³C NMR spectrum of 5.14 (75 MHz, CDCl₃)



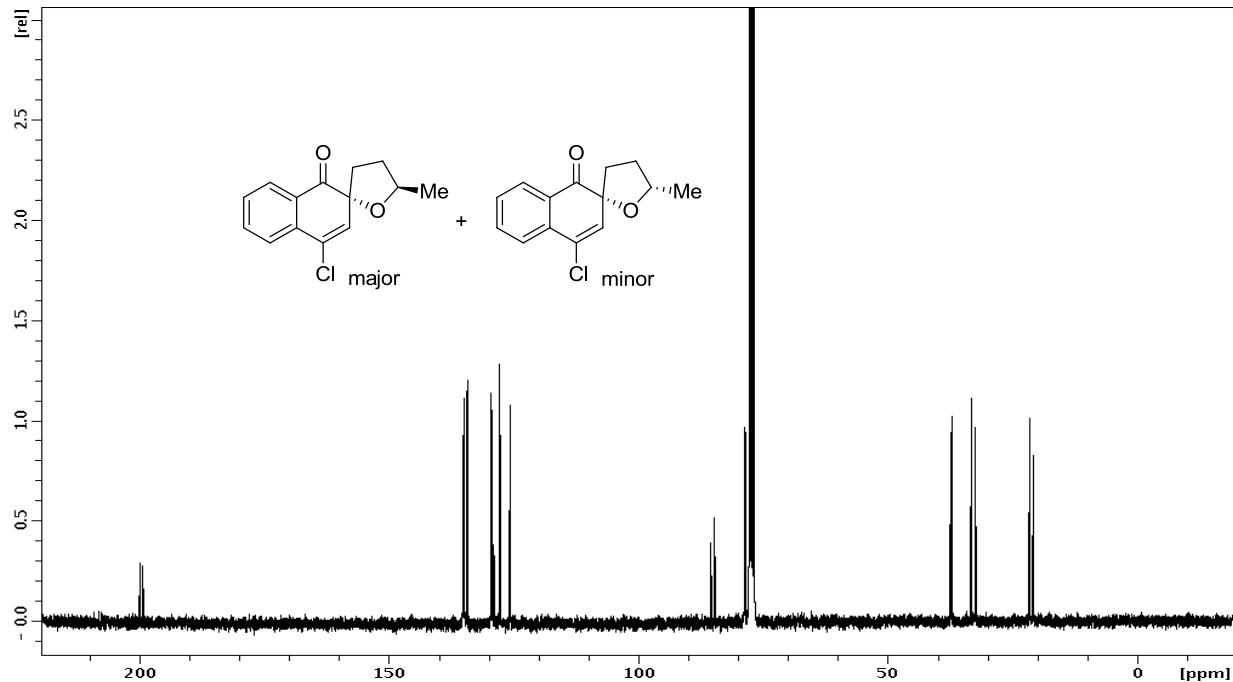
¹H NMR spectrum of 5.16 (300 MHz, CDCl₃)



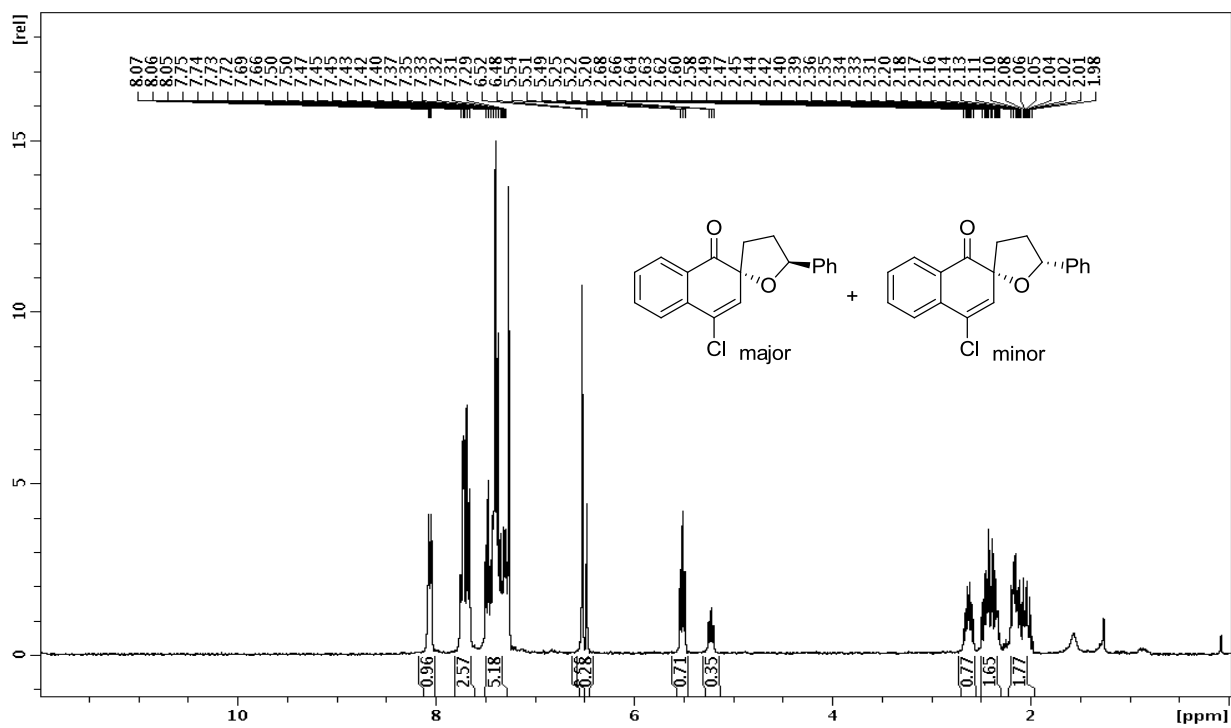
¹³C NMR spectrum of 5.16 (75 MHz, CDCl₃)



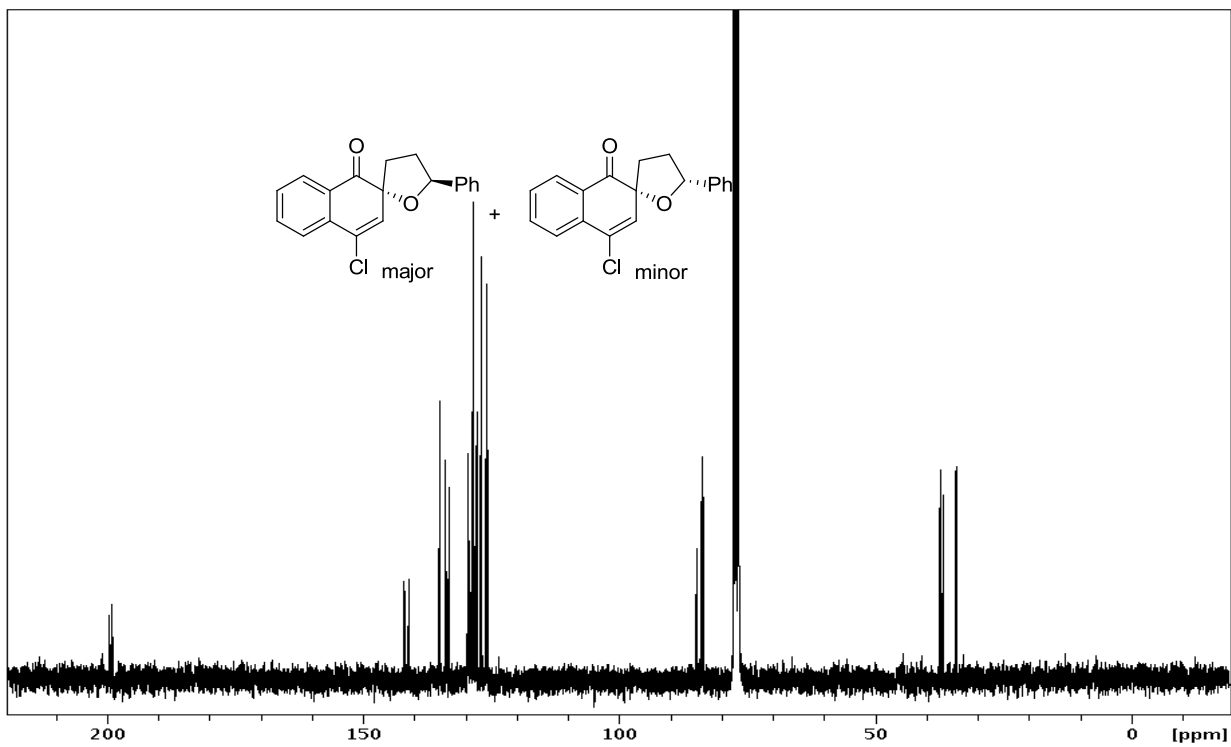
¹H NMR spectrum of *ca.* 55:45 mixture of 5.18b/5.19b (300 MHz, CDCl₃)



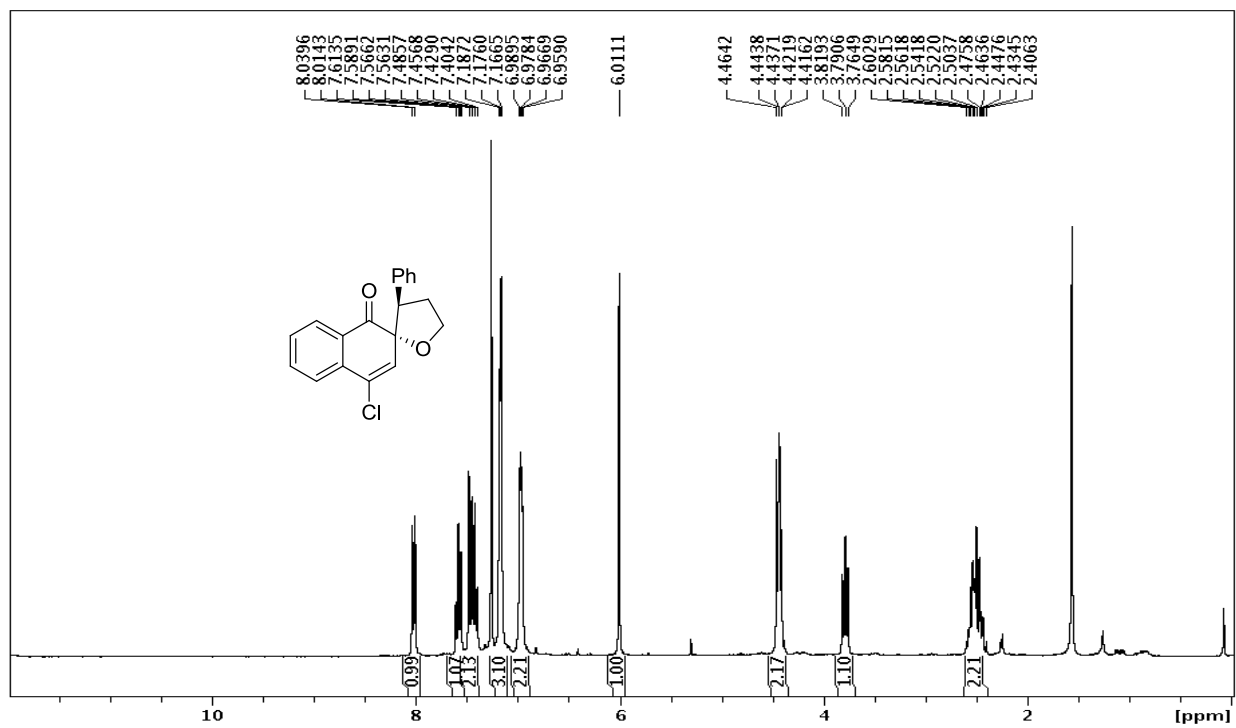
¹³C NMR spectrum of *ca.* 55:45 mixture of 5.18b/5.19b (75 MHz, CDCl₃)



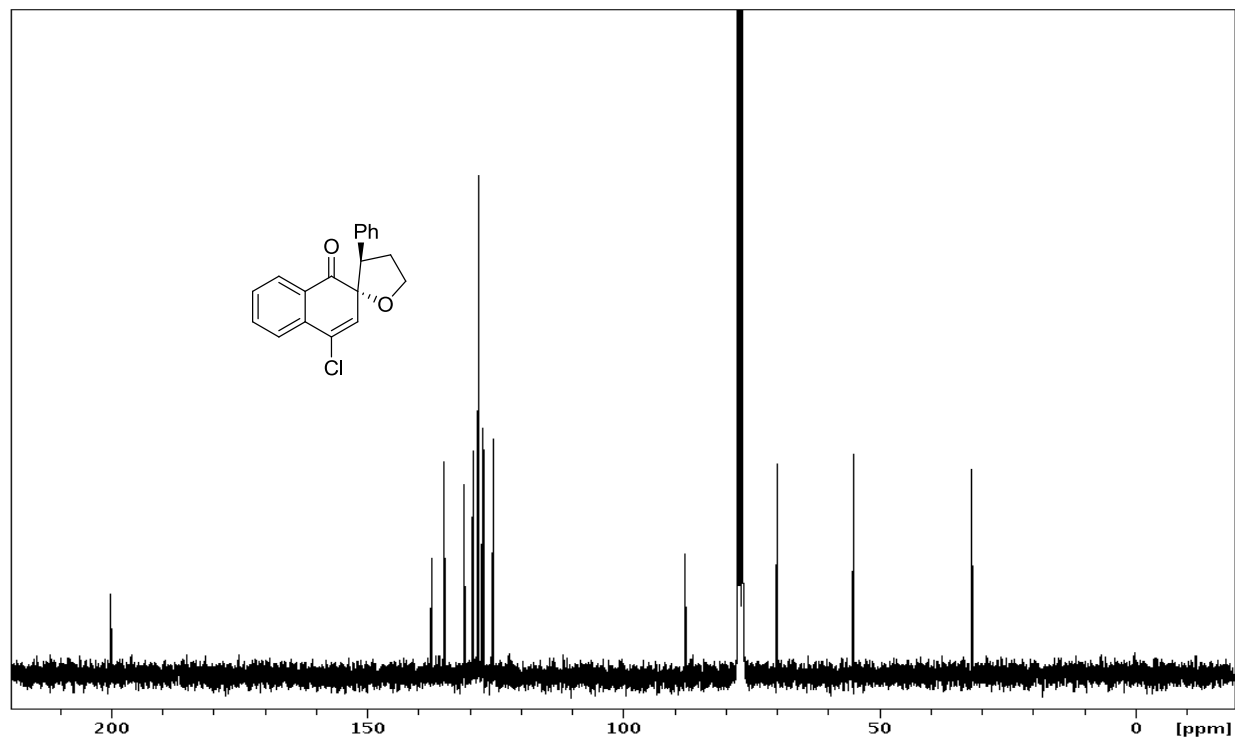
¹H NMR spectrum of *ca.* 13:7 mixture of 5.18a/5.19a (300 MHz, CDCl₃)



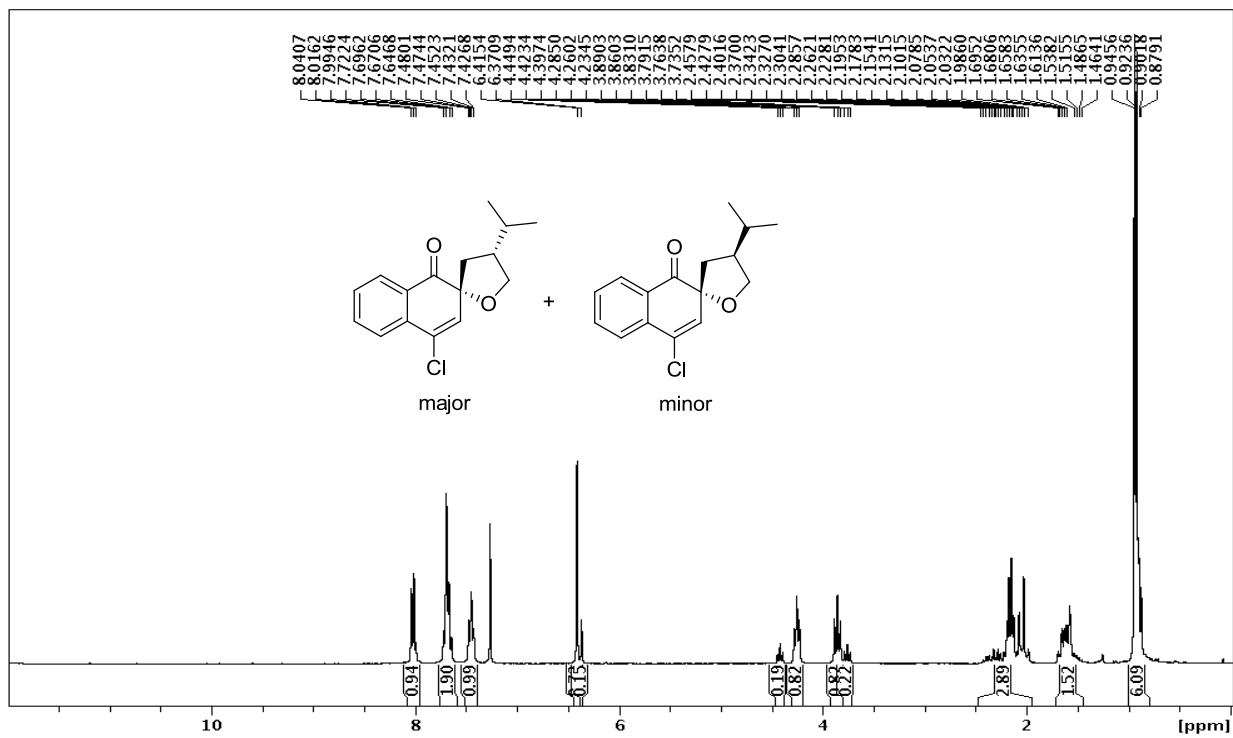
¹³C NMR spectrum of *ca.* 13:7 mixture of 5.18a/5.19a (75 MHz, CDCl₃)



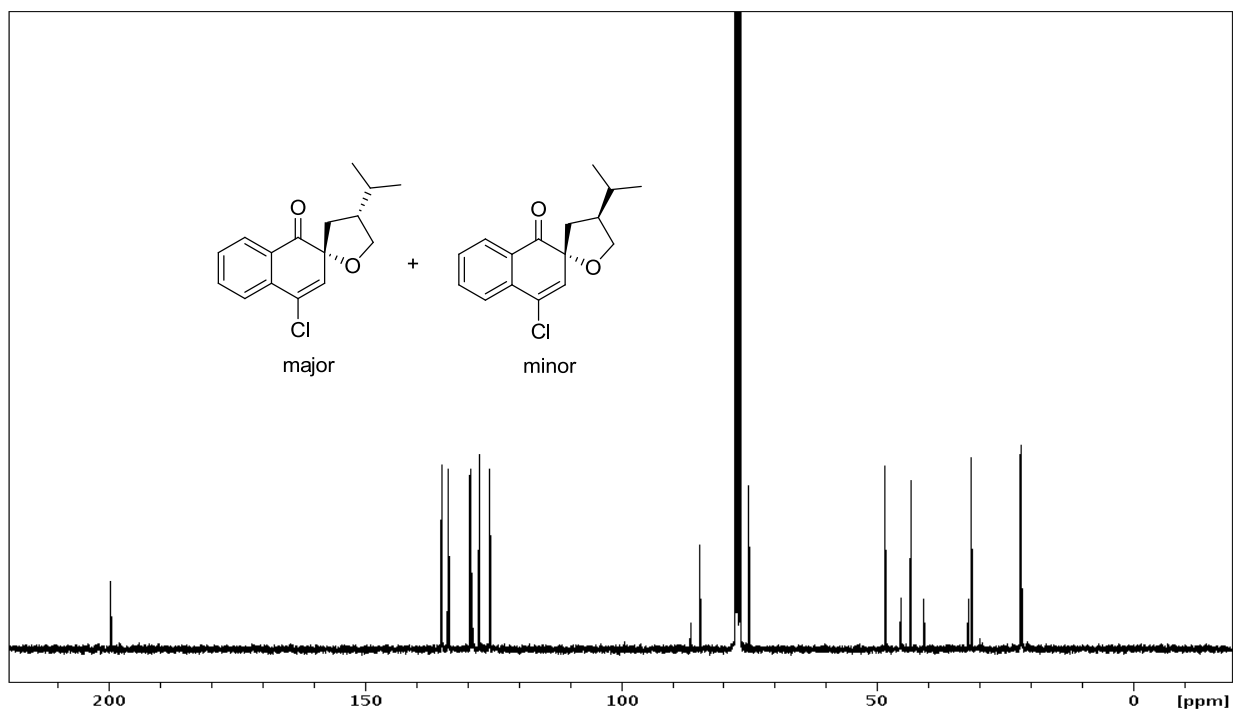
¹H NMR spectrum of 5.18c (300 MHz, CDCl₃)



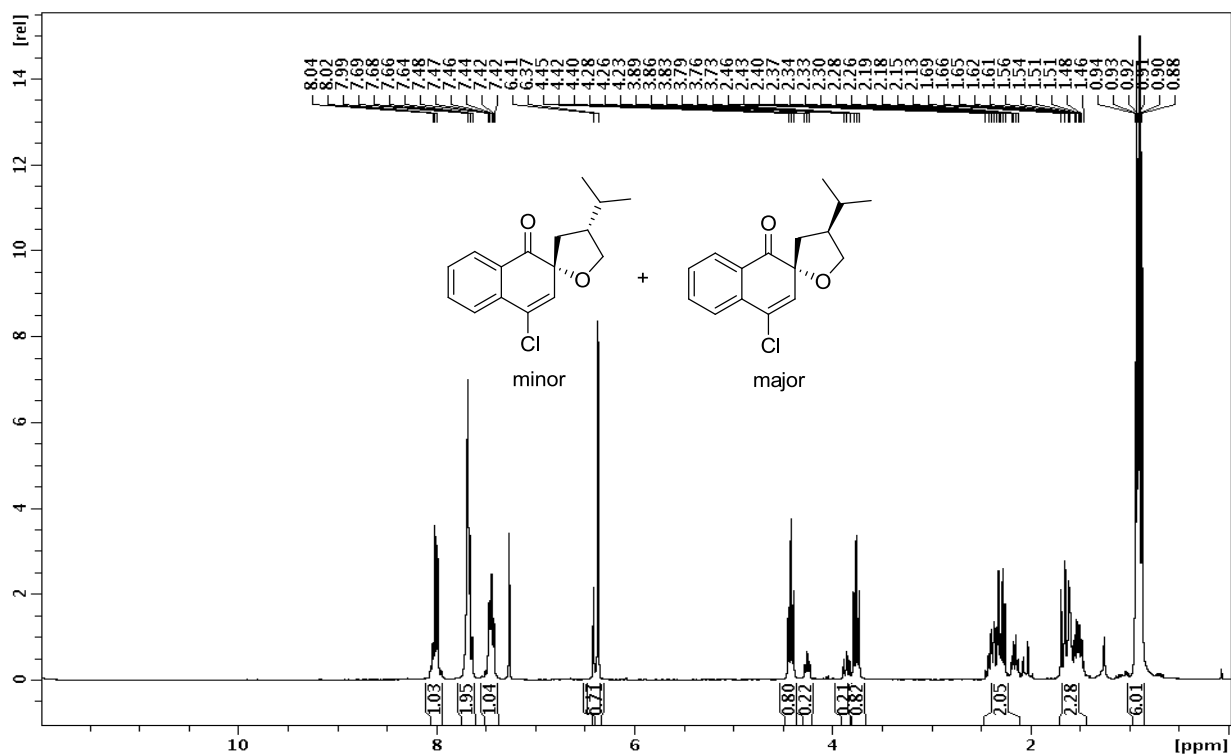
¹³C NMR spectrum of 5.18c (75 MHz, CDCl₃)



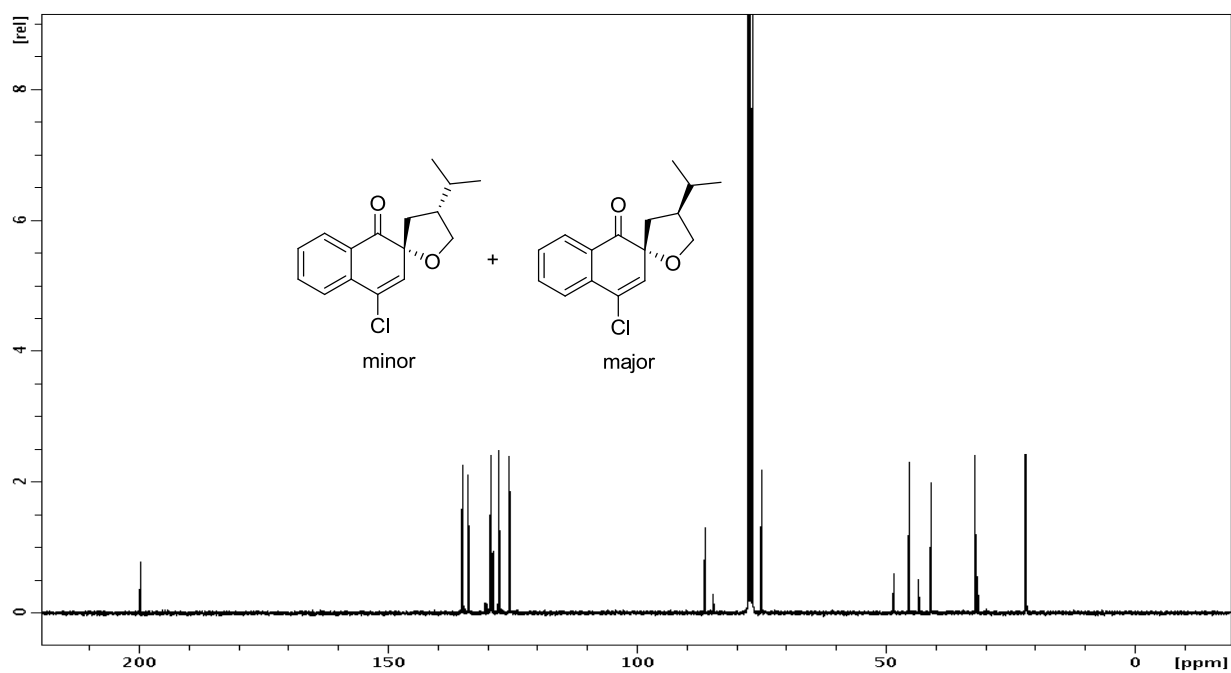
¹H NMR spectrum of *ca.* 4:1 mixture of 5.21a/5.22a (300 MHz, CDCl₃)



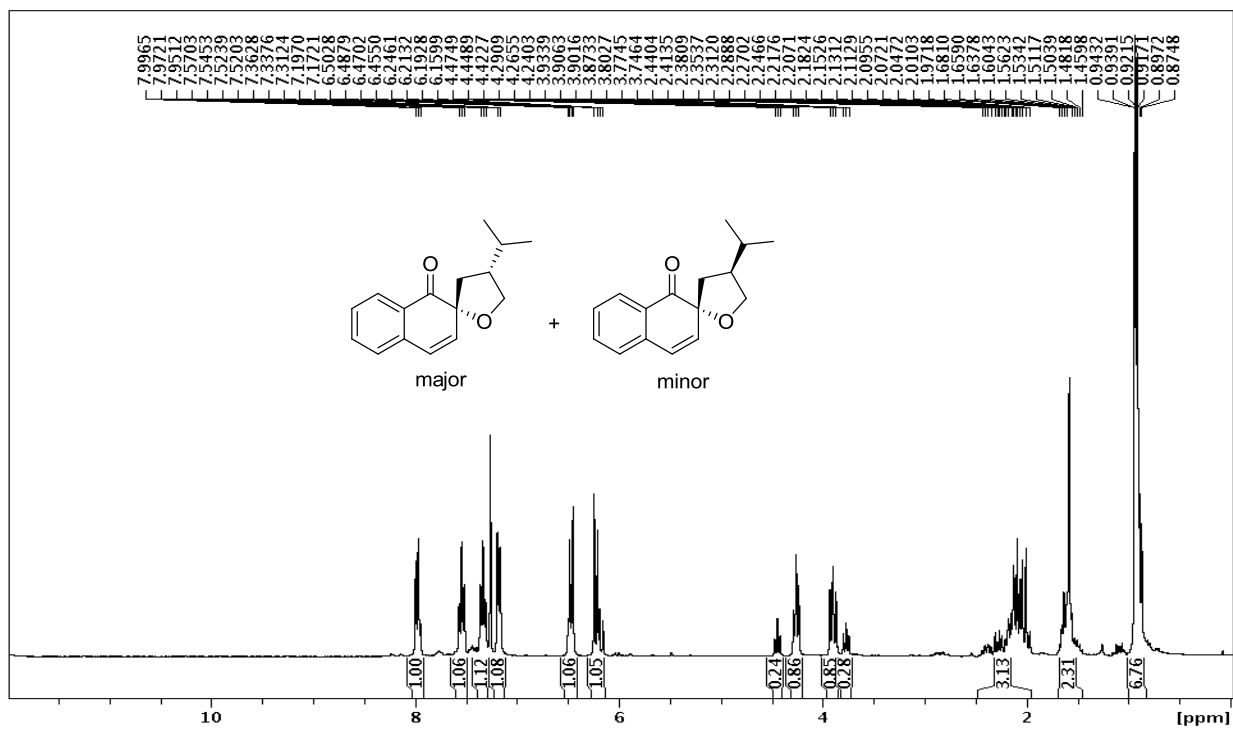
¹³C NMR spectrum of *ca.* 4:1 mixture of 5.21a/5.22a (75 MHz, CDCl₃)



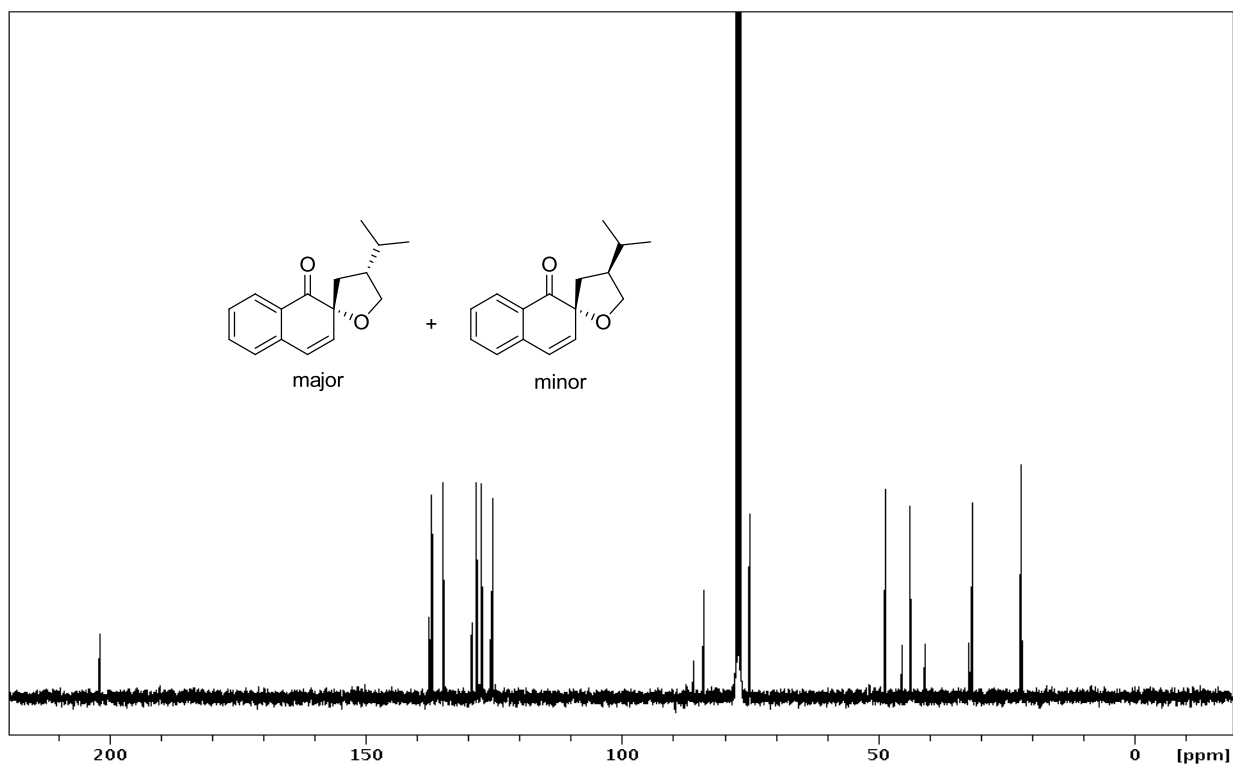
¹H NMR spectrum of *ca.* 1:4 mixture of 5.21a/5.22a (300 MHz, CDCl₃)



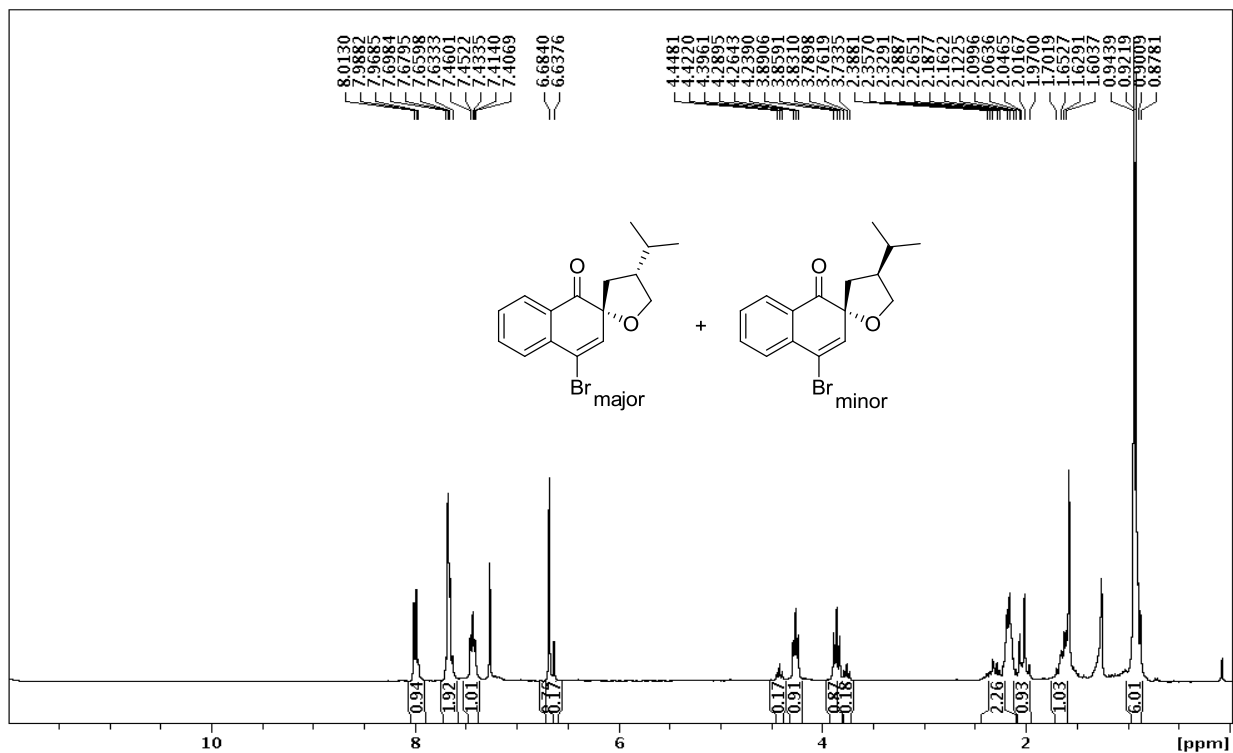
¹³C NMR spectrum of *ca.* 1:4 mixture of 5.21a/5.22a (75 MHz, CDCl₃)



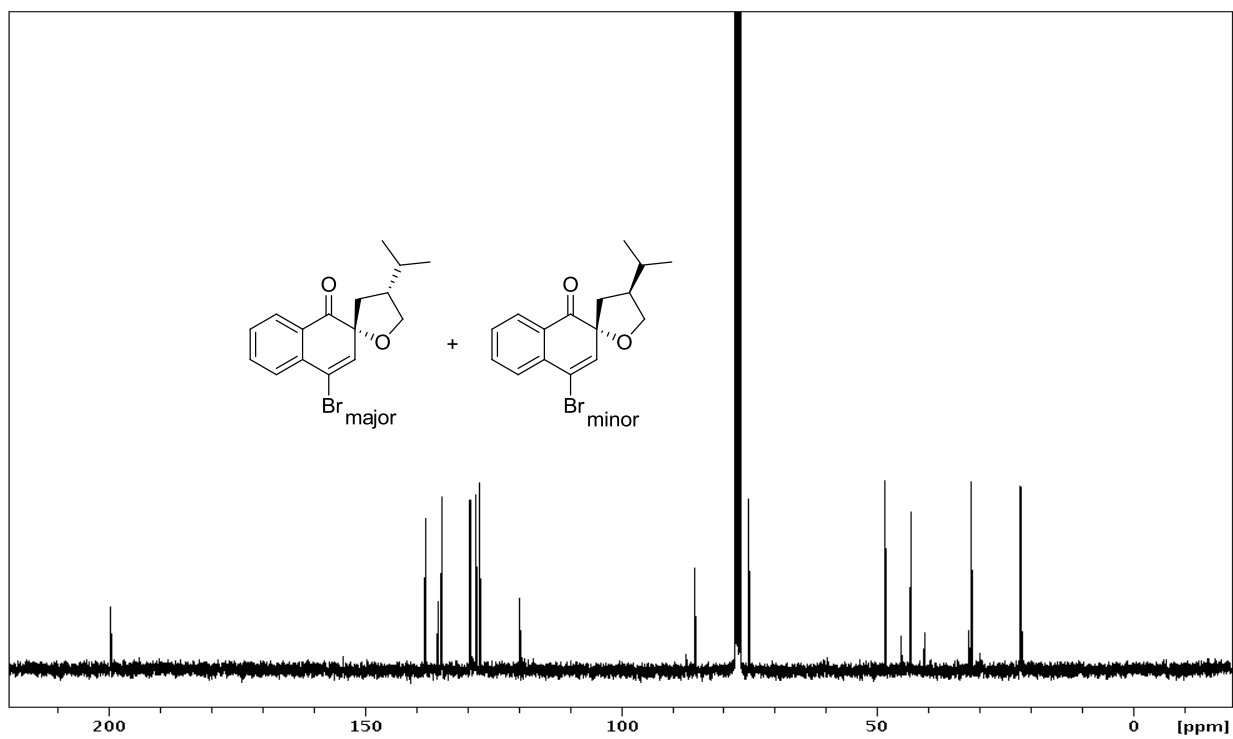
^1H NMR spectrum of *ca.* 3:1 mixture of 5.21b/5.22b (300 MHz, CDCl_3)



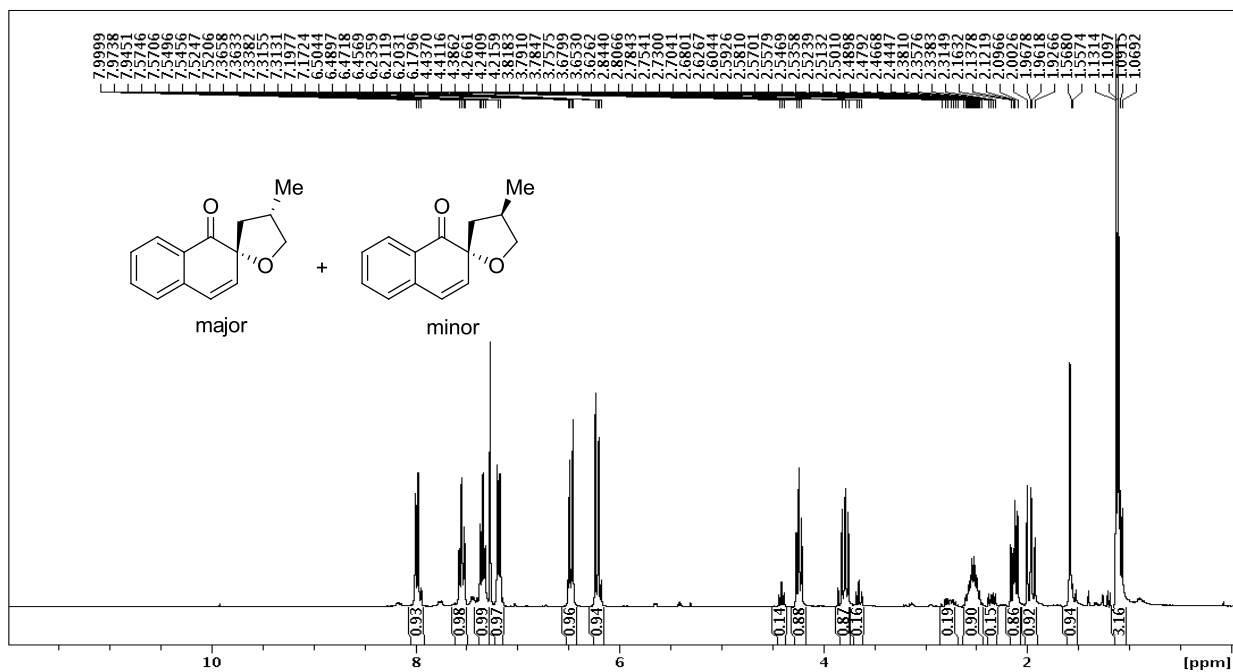
^{13}C NMR spectrum of *ca.* 3:1 mixture of 5.21b/5.22b (75 MHz, CDCl_3)



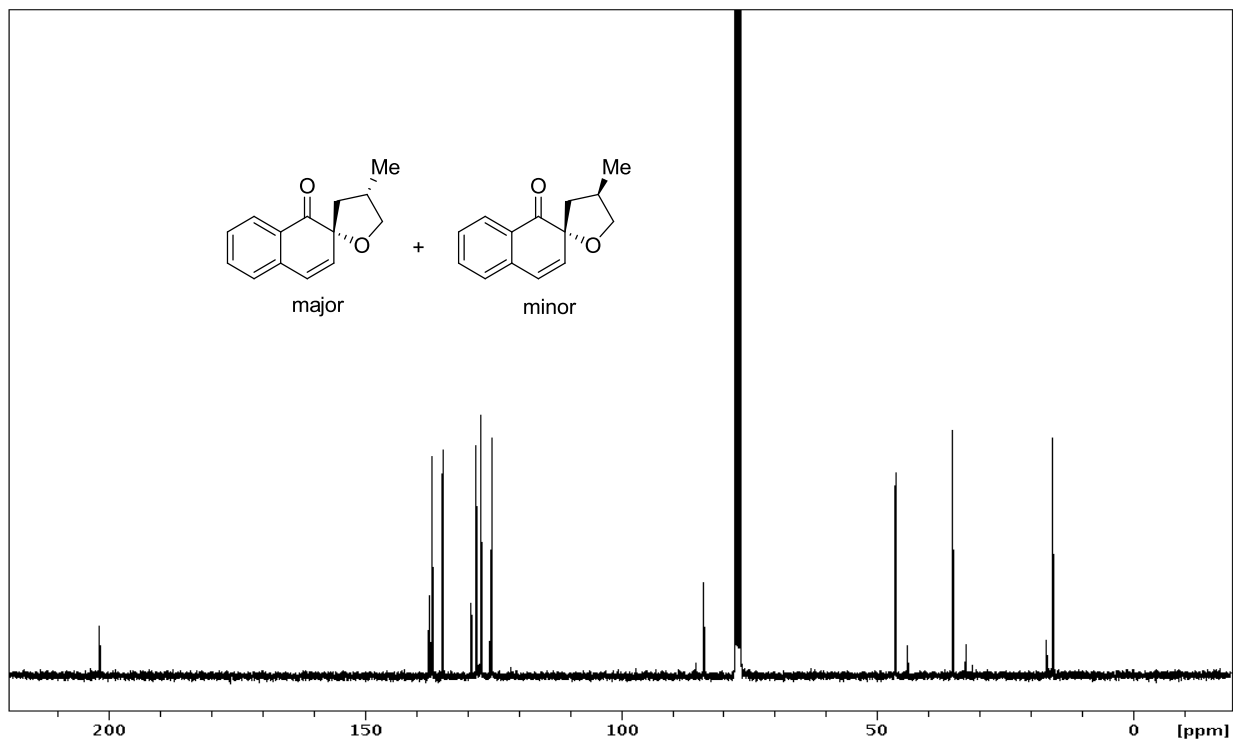
^1H NMR spectrum of *ca.* 4:1 mixture of 5.21c/5.22c (300 MHz, CDCl_3)



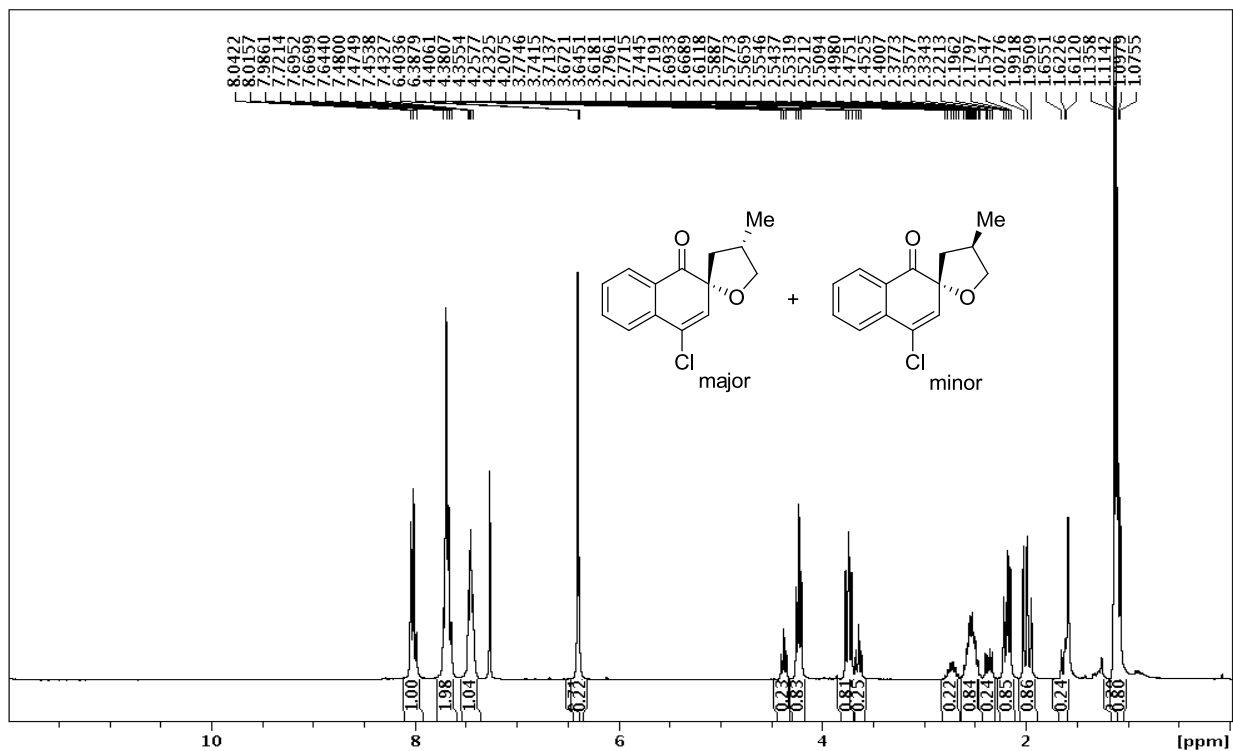
^{13}C NMR spectrum of *ca.* 4:1 mixture of 5.21c/5.22c (75 MHz, CDCl_3)



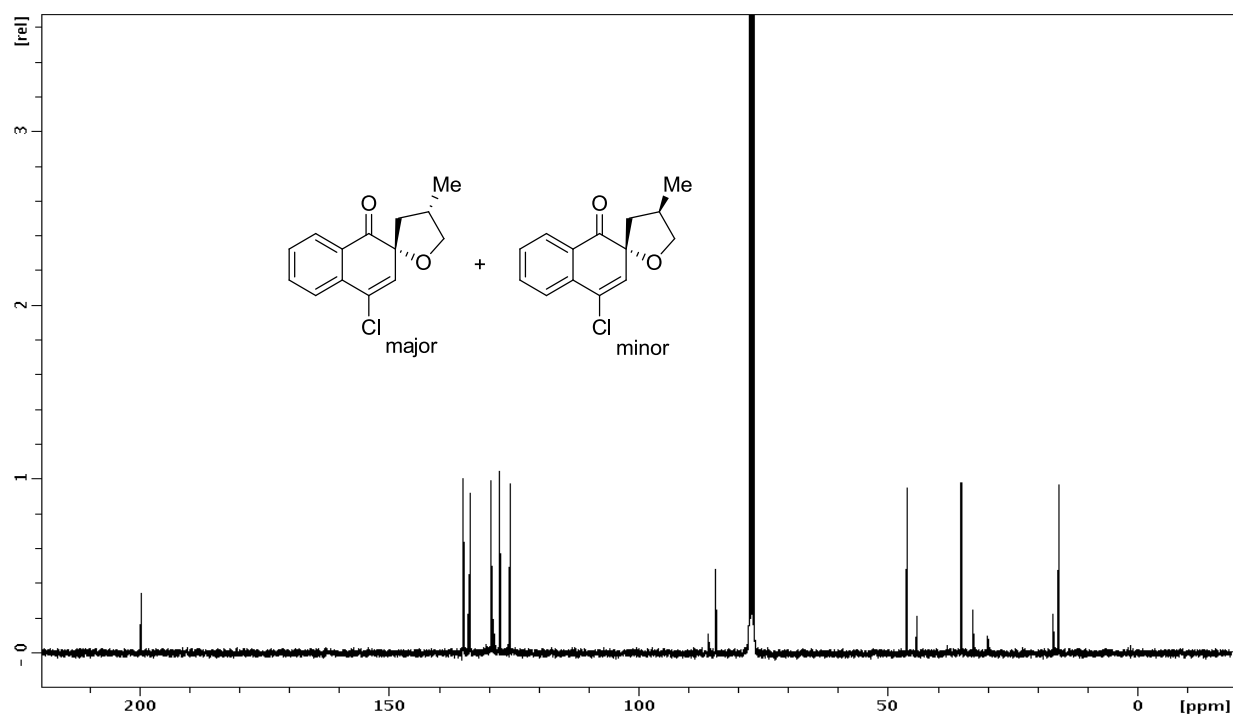
¹H NMR spectrum of *ca.* 17:3 mixture of 5.21d/5.22d (300 MHz, CDCl₃)



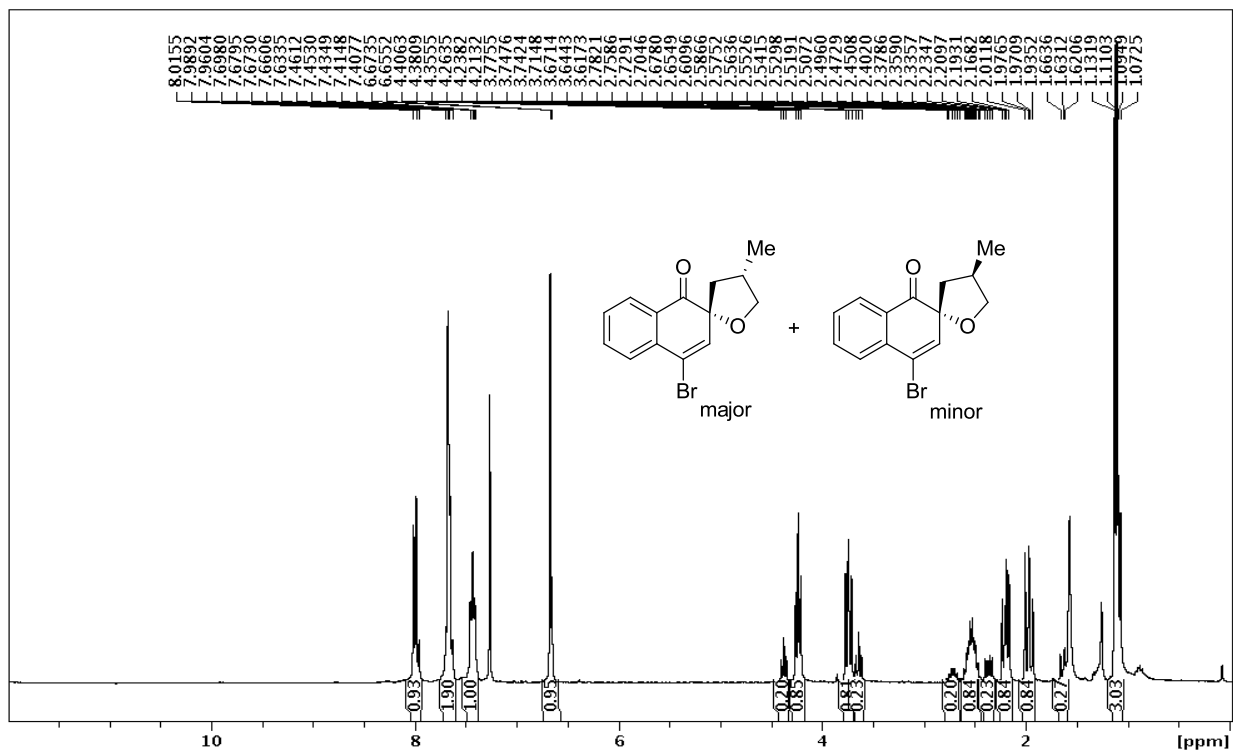
¹³C NMR spectrum of *ca.* 17:3 mixture of 5.18d/5.19d (75 MHz, CDCl₃)



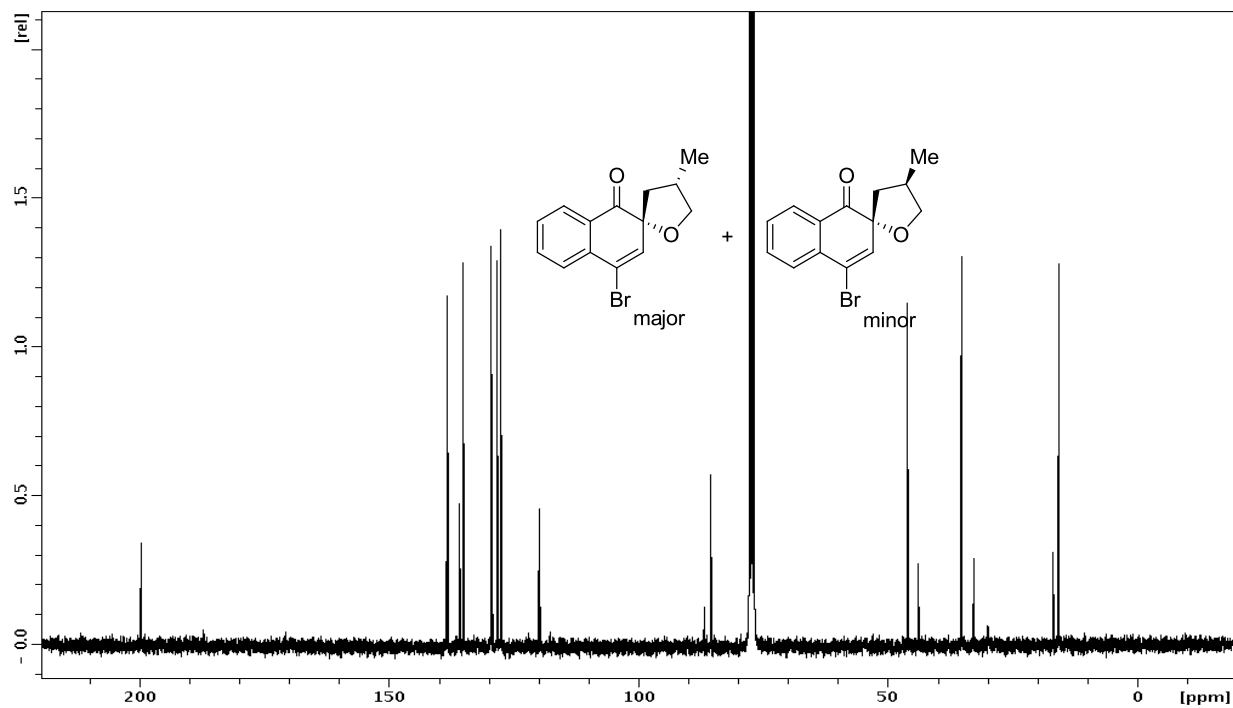
^1H NMR spectrum of *ca.* 7:3 mixture of 5.21e/5.22e (300 MHz, CDCl_3)



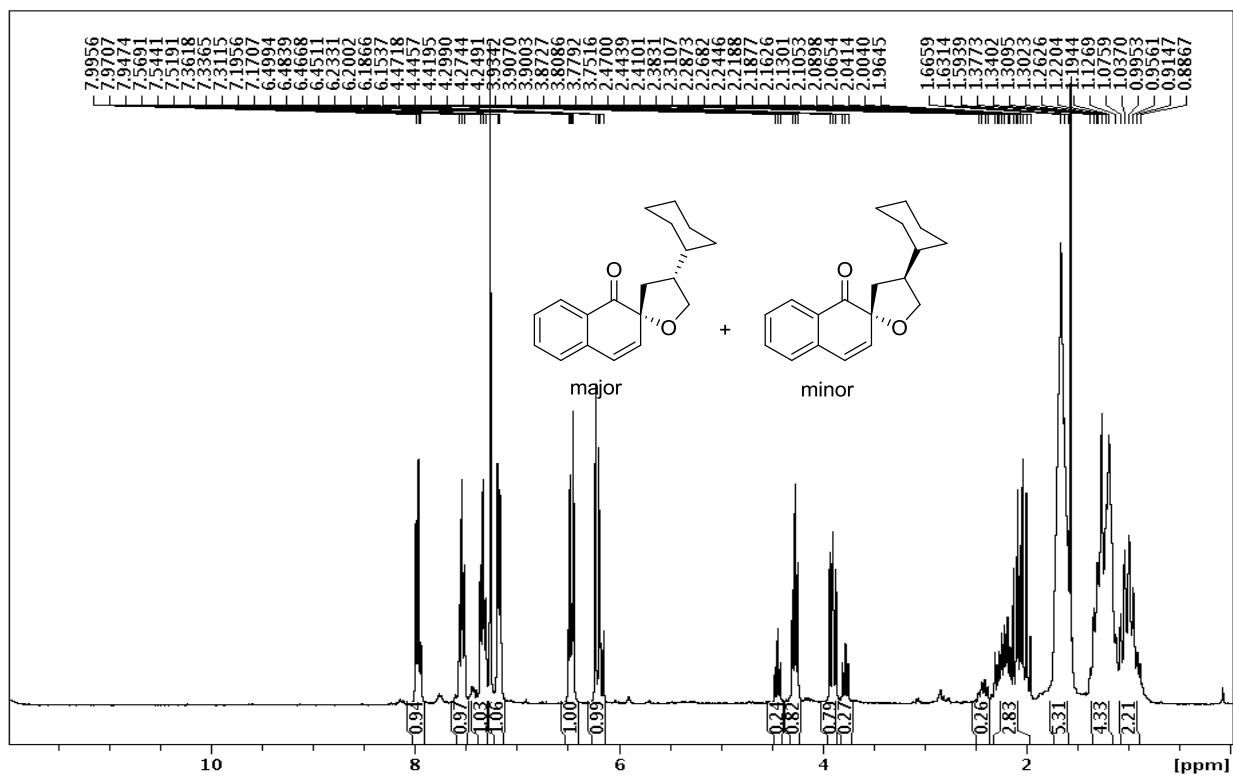
^{13}C NMR spectrum of *ca.* 7:3 mixture of 5.21e/5.22e (75 MHz, CDCl_3)



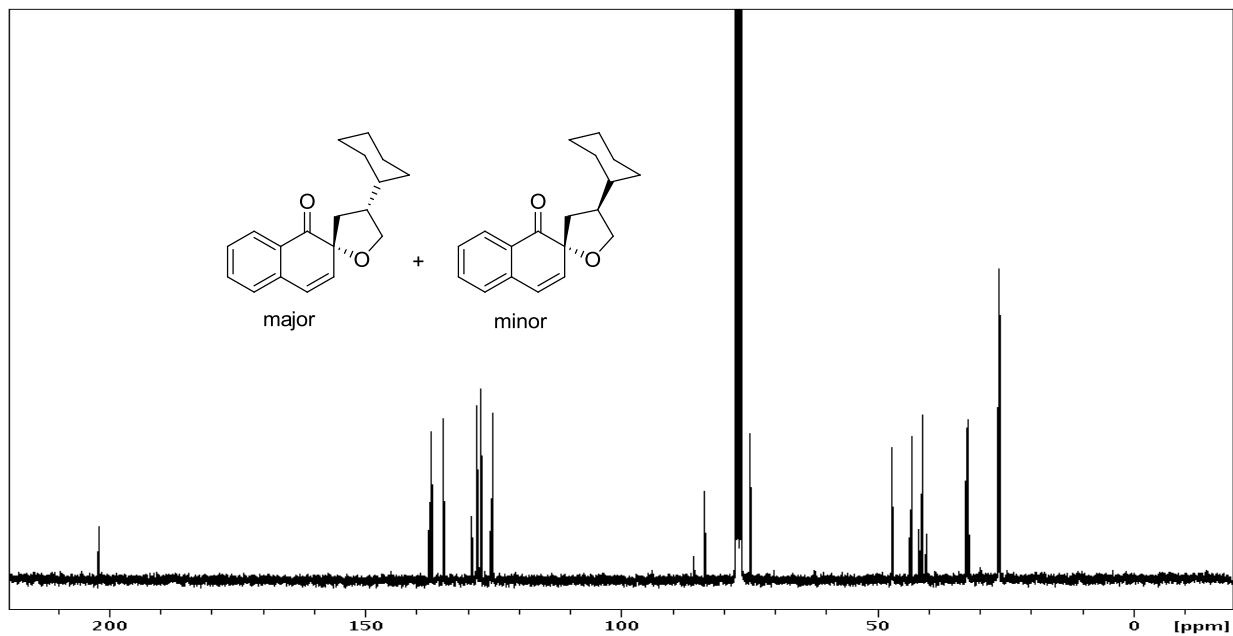
¹H NMR spectrum of *ca.* 4:1 mixture of 5.21f/5.22f (300 MHz, CDCl₃)



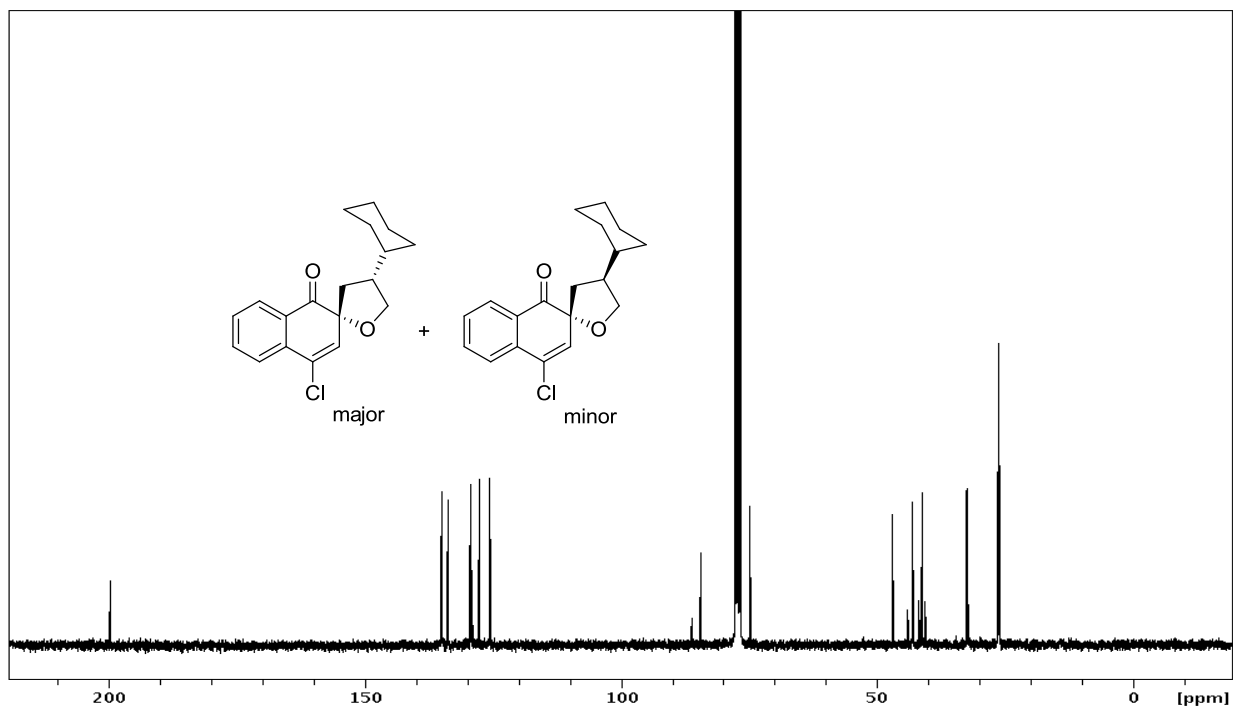
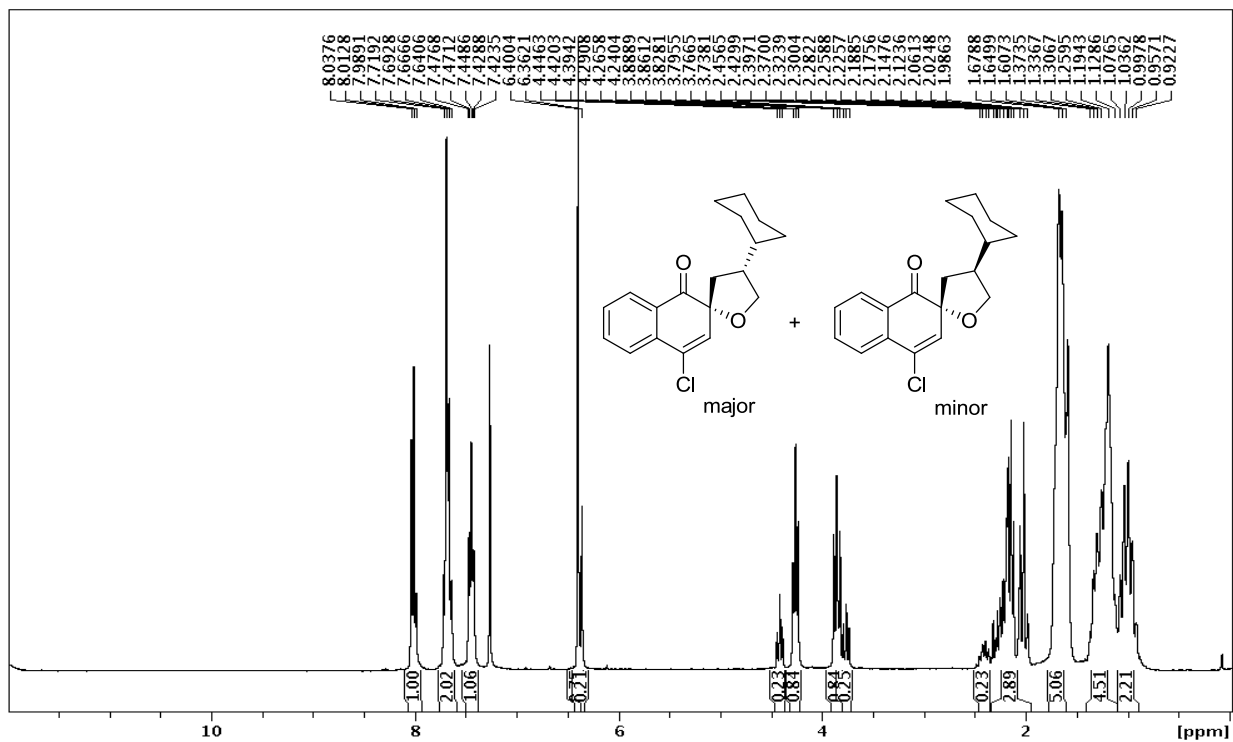
¹³C NMR spectrum of *ca.* 4:1 mixture of 5.21f/5.22f (75 MHz, CDCl₃)

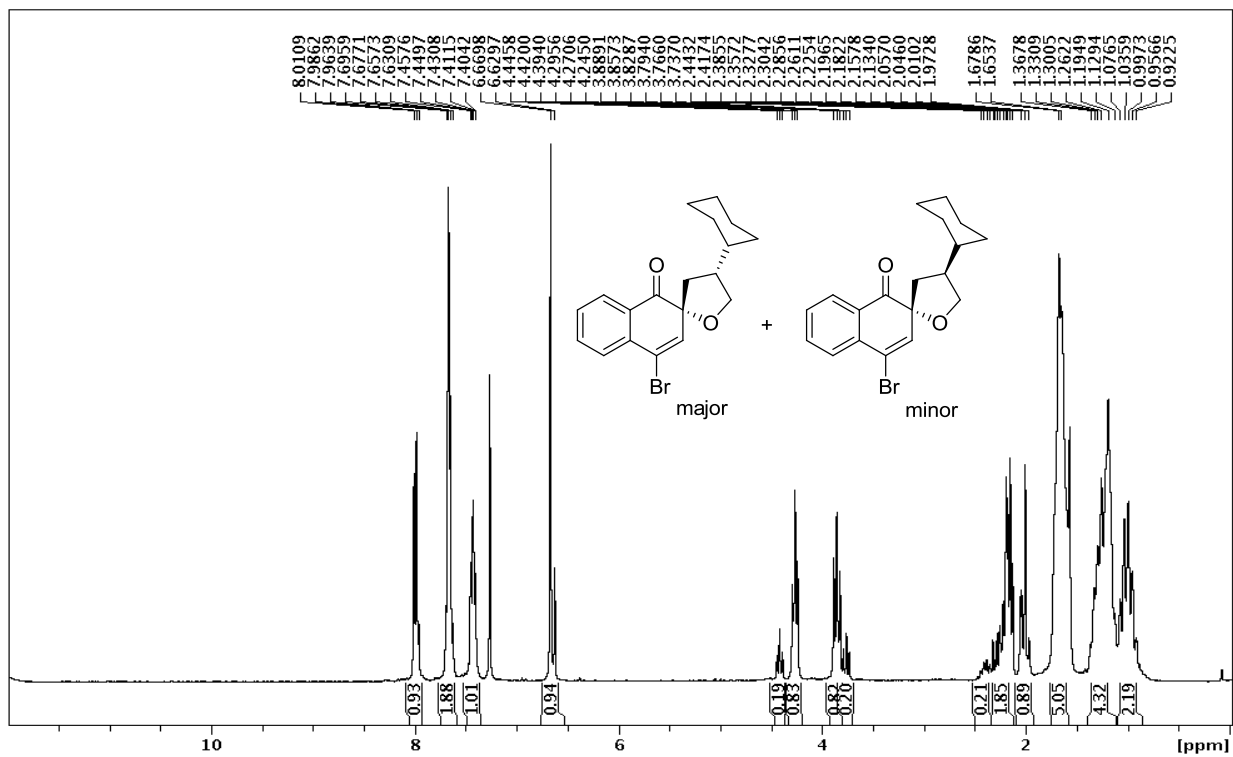


^1H NMR spectrum of *ca.* 3:1 mixture of 5.21g/5.22g (300 MHz, CDCl_3)

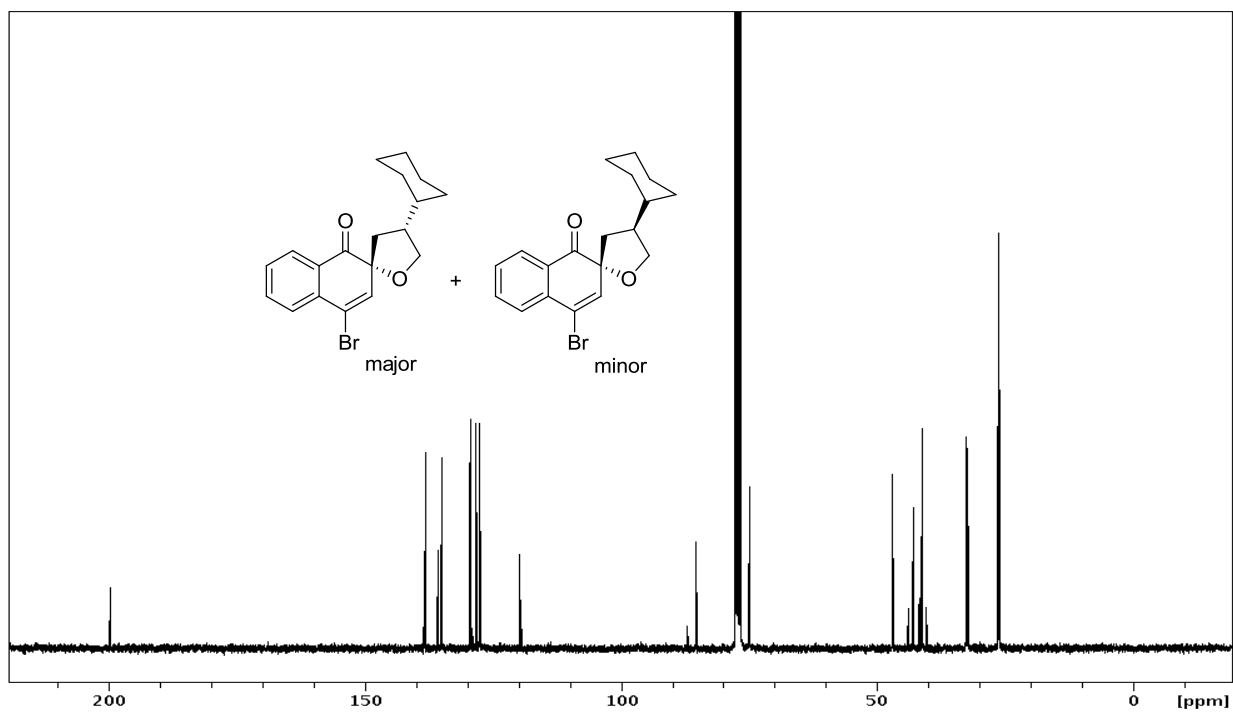


^{13}C NMR spectrum of *ca.* 3:1 mixture of 5.21g/5.22g (75 MHz, CDCl_3)

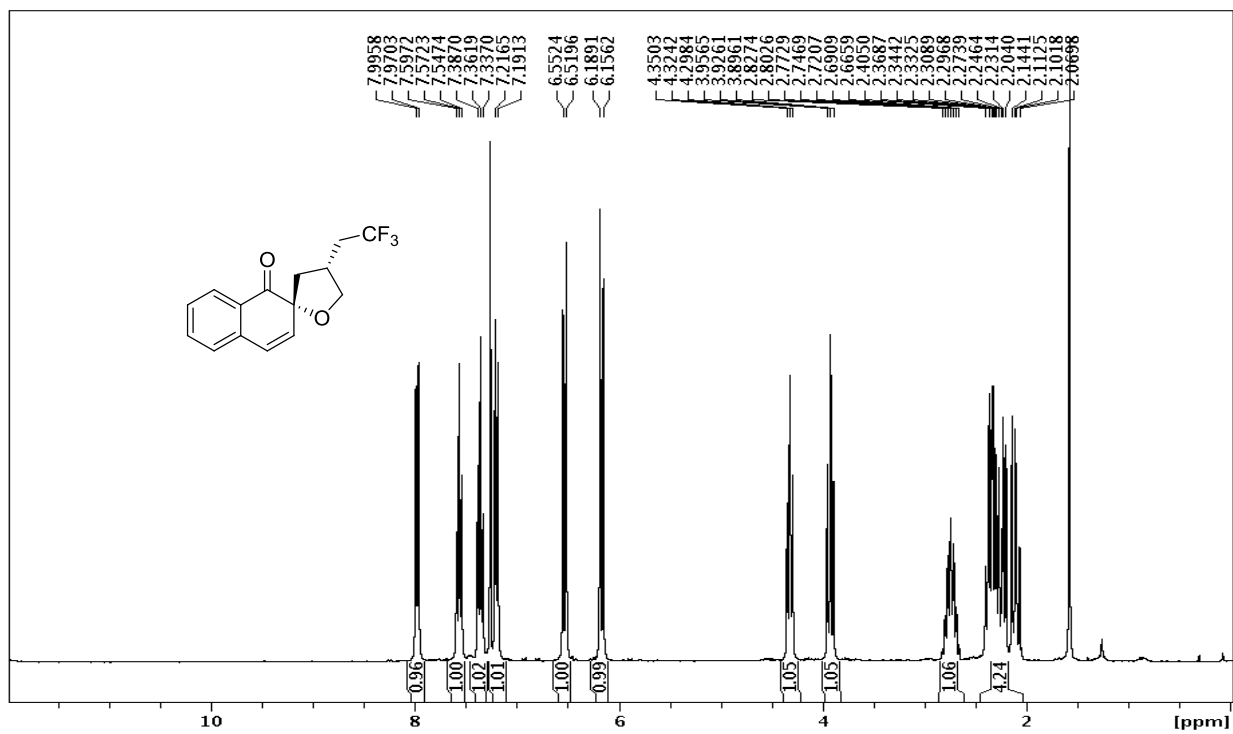




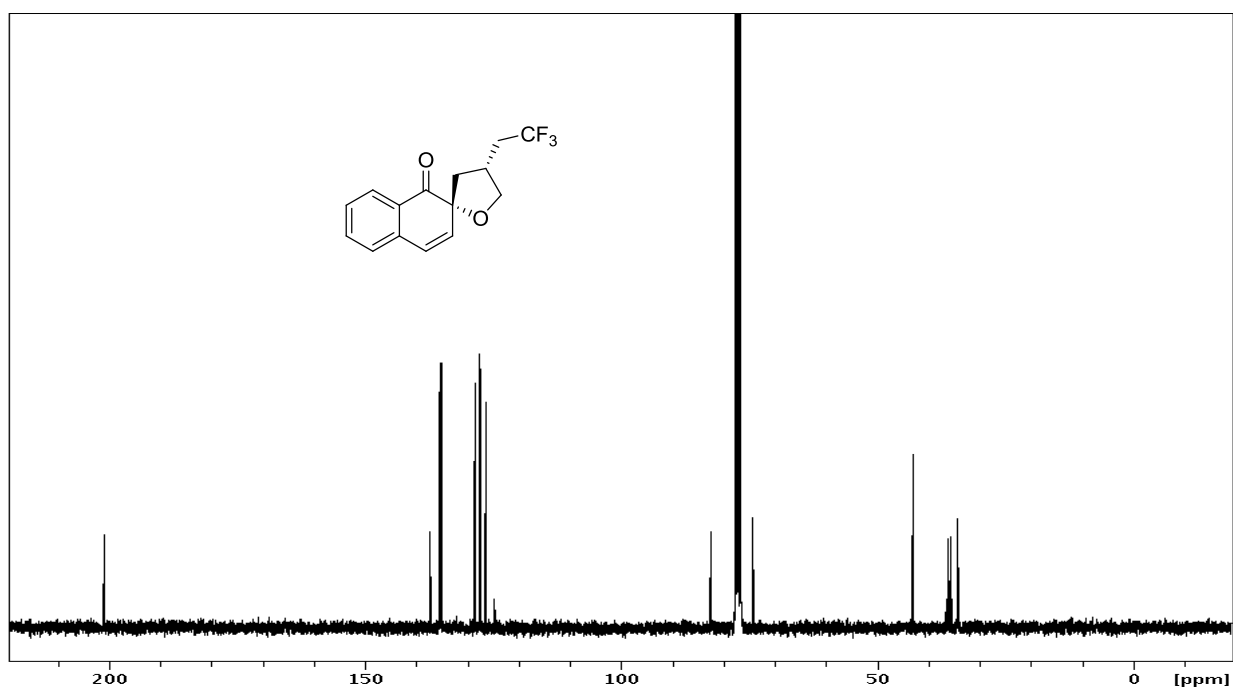
^1H NMR spectrum of *ca.* 4:1 mixture of 5.21i/5.22i (300 MHz, CDCl_3)



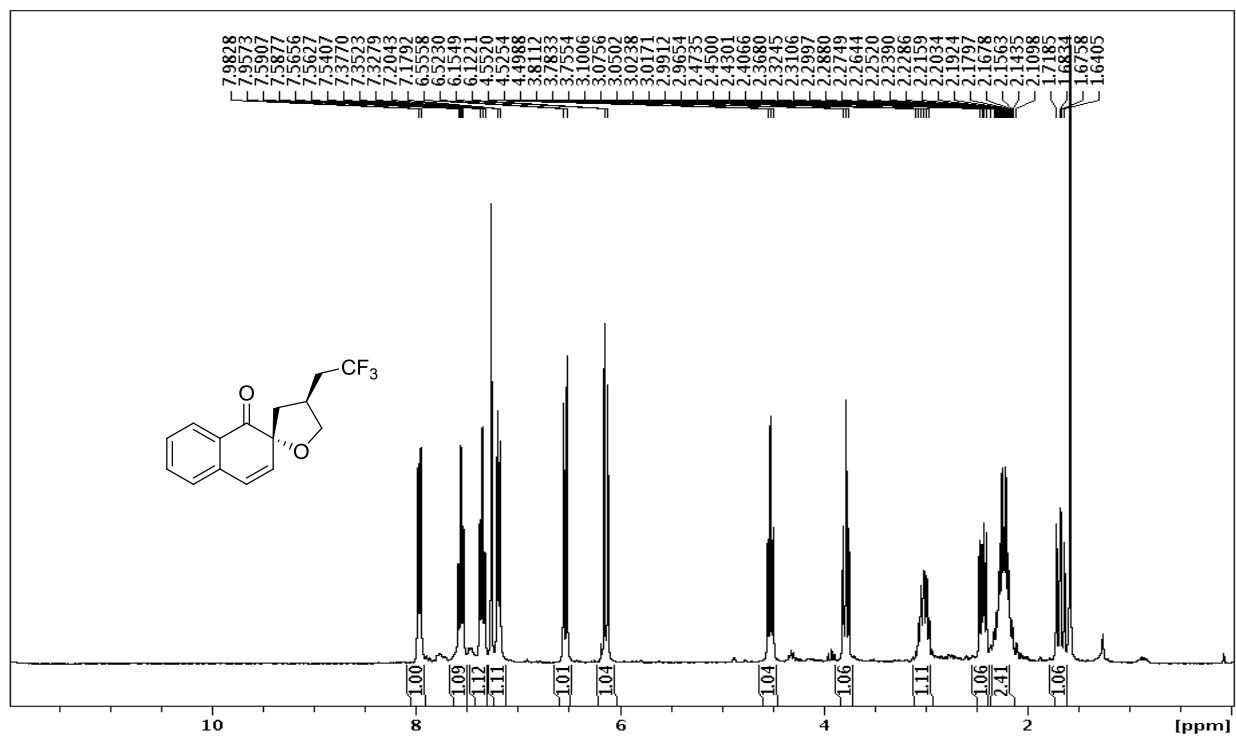
^{13}C NMR spectrum of *ca.* 4:1 mixture of 5.21i/5.22i (75 MHz, CDCl_3)



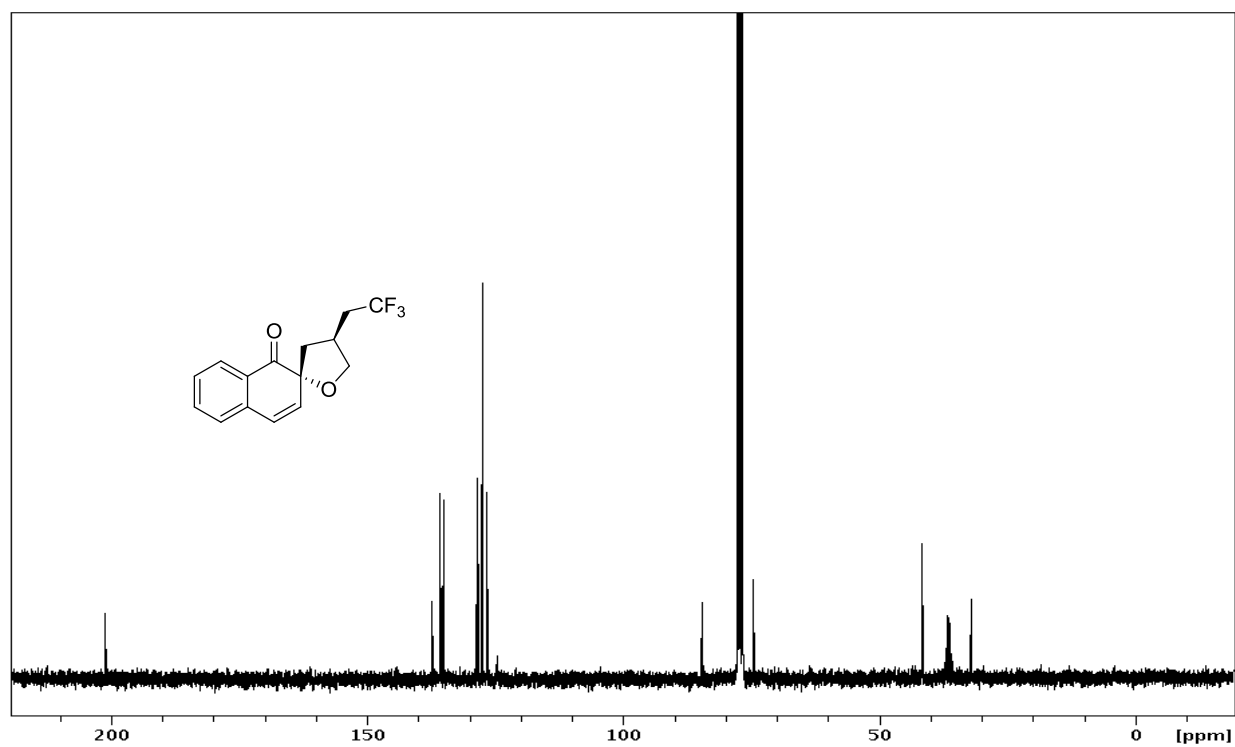
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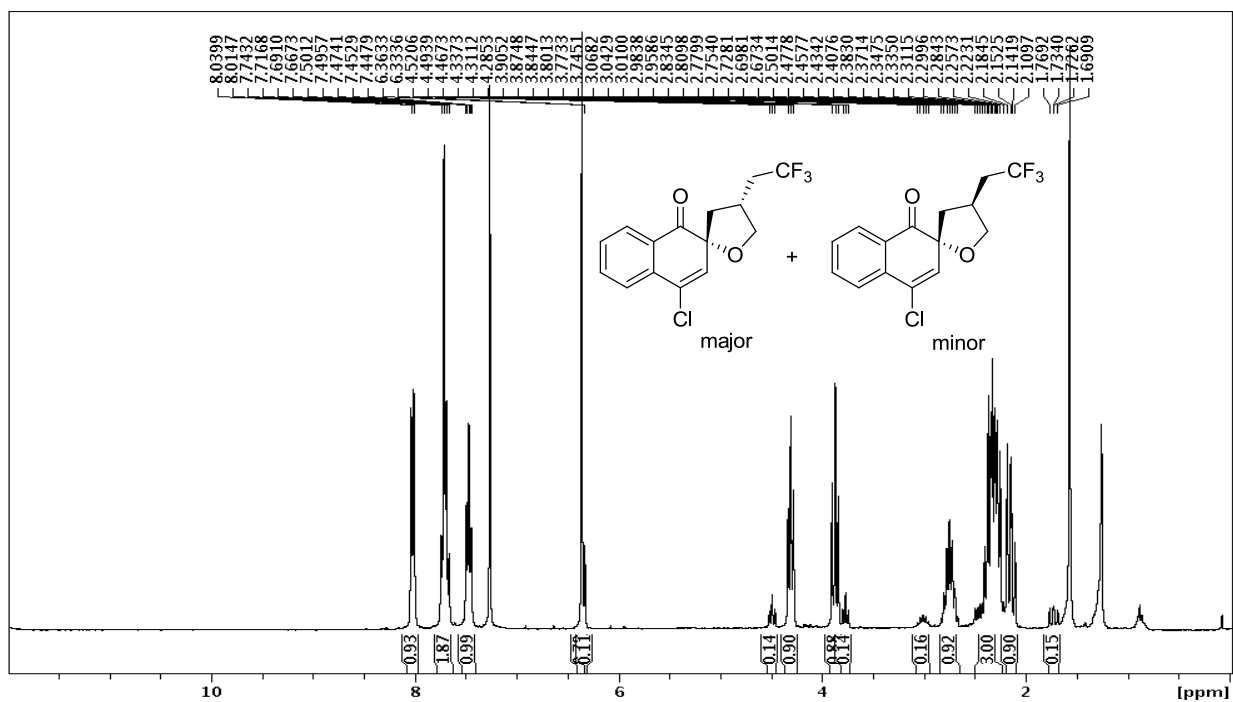
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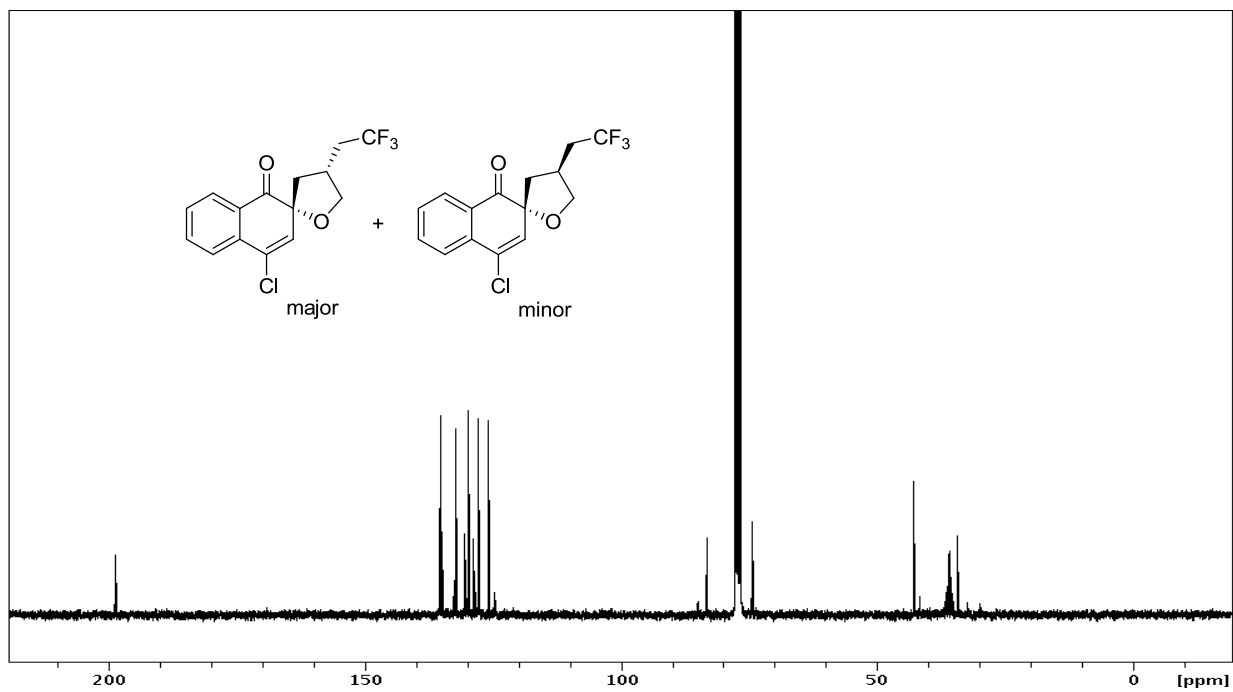
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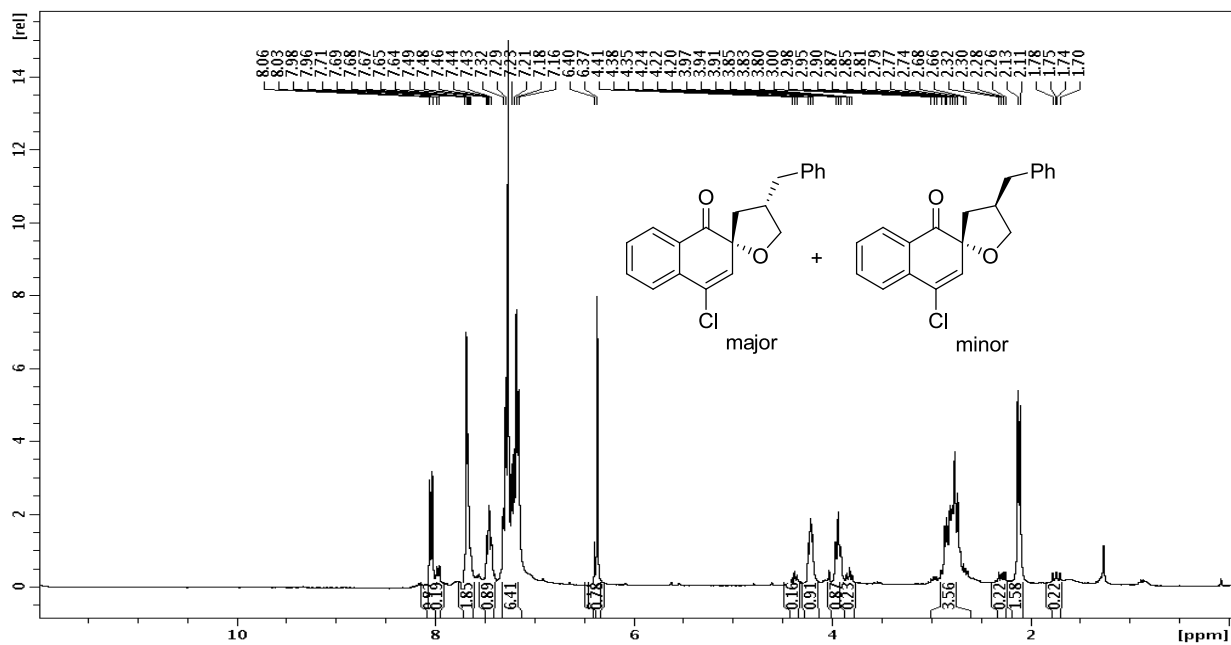
¹³C NMR spectrum of 5.22n (75 MHz, CDCl₃)



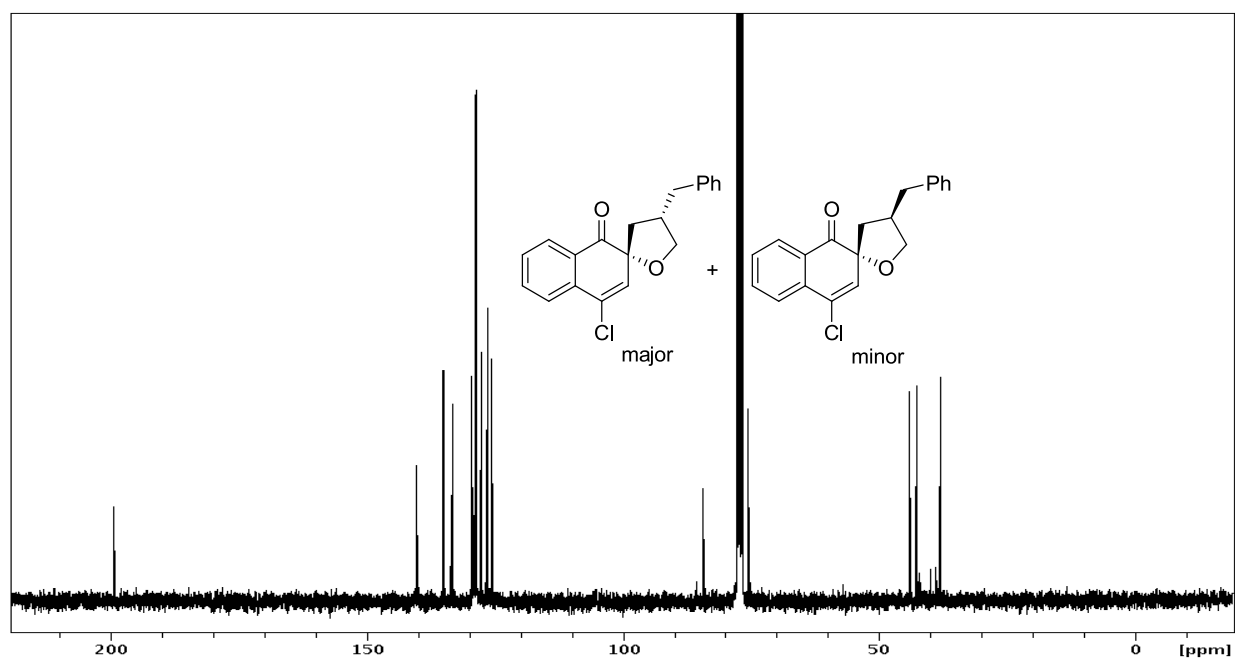
^1H NMR spectrum of *ca.* 9:1 mixture of 5.21j/5.22j (300 MHz, CDCl_3)



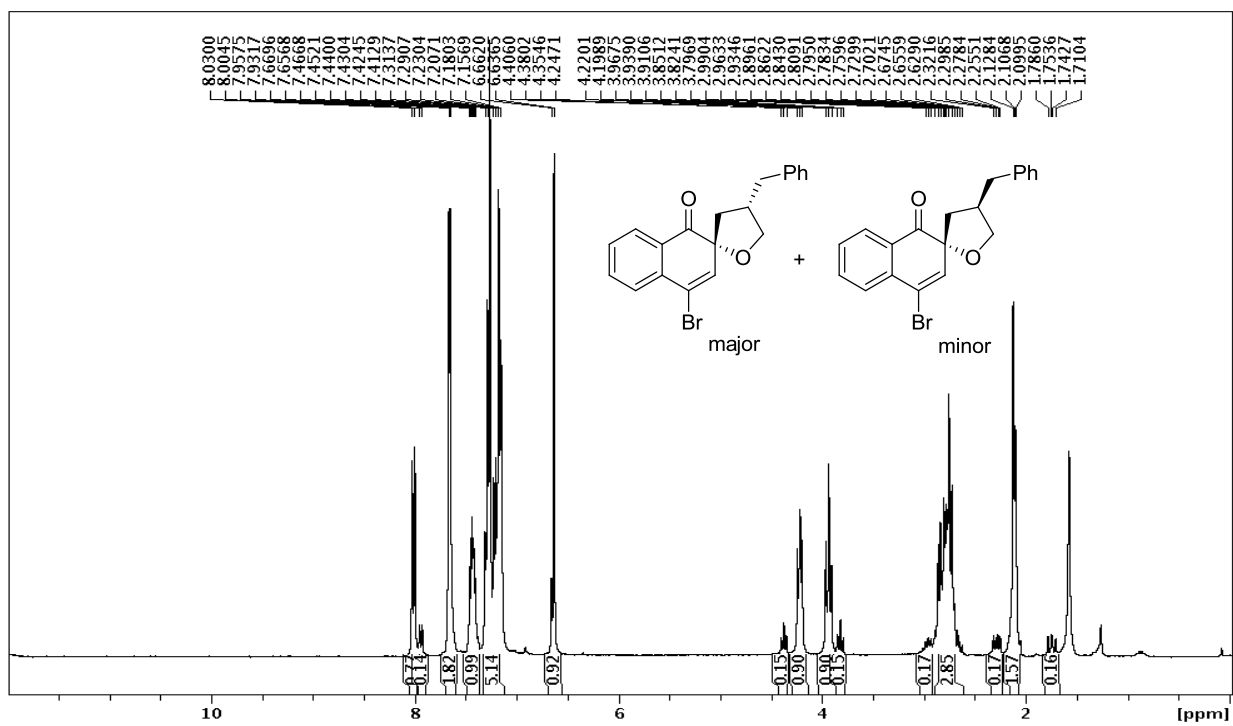
^{13}C NMR spectrum of *ca.* 9:1 mixture of 5.21j/5.22j (75 MHz, CDCl_3)



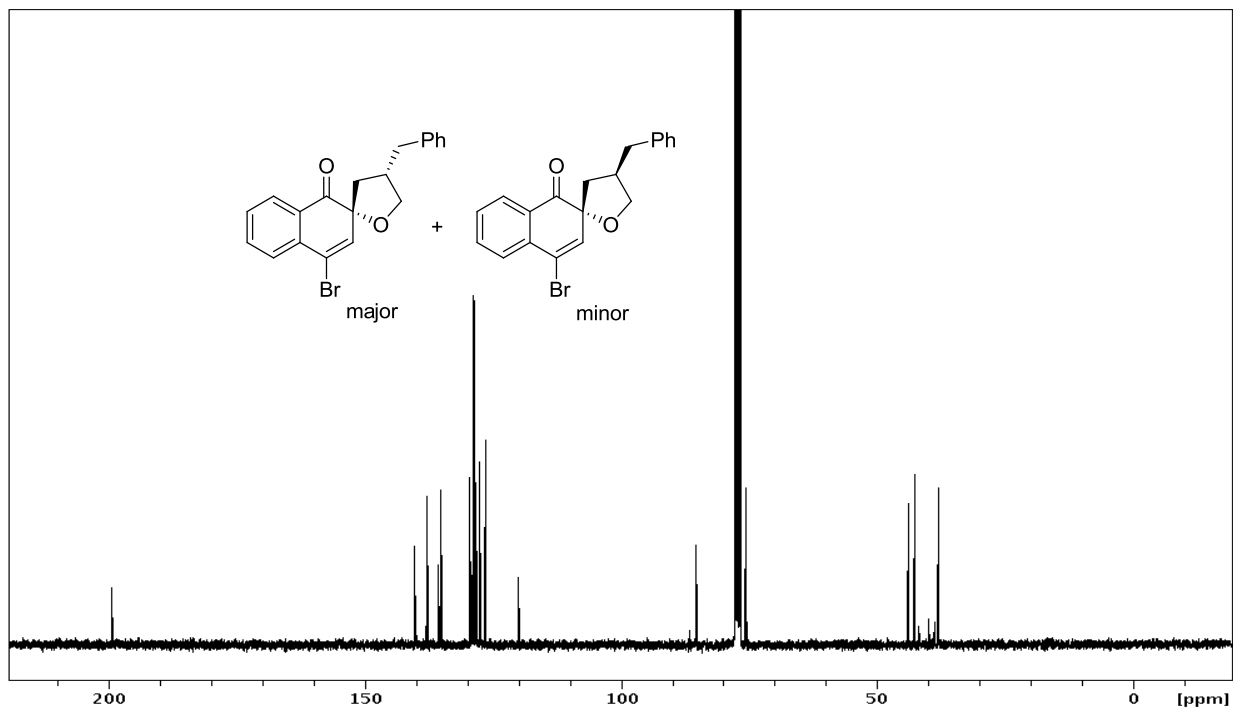
¹H NMR spectrum of *ca.* 17:3 mixture of 5.21k/5.22k (300 MHz, CDCl₃)



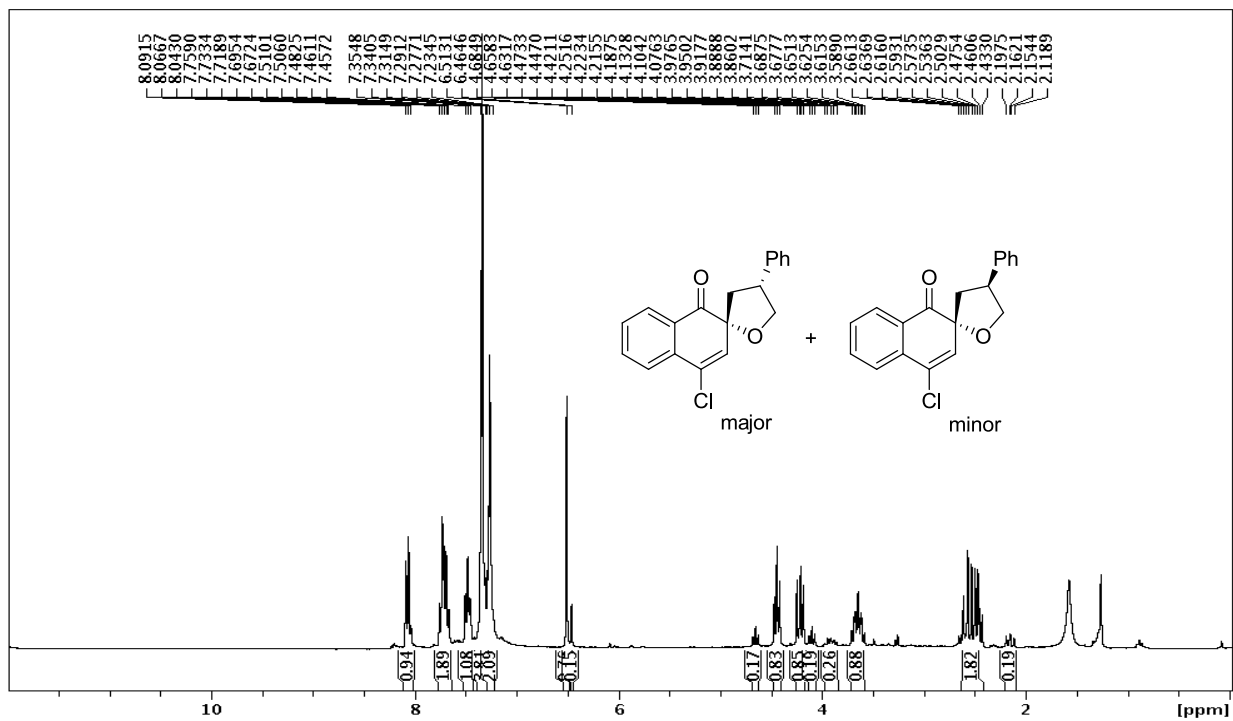
¹³C NMR spectrum of *ca.* 17:3 mixture of 5.21k/5.22k (75 MHz, CDCl₃)



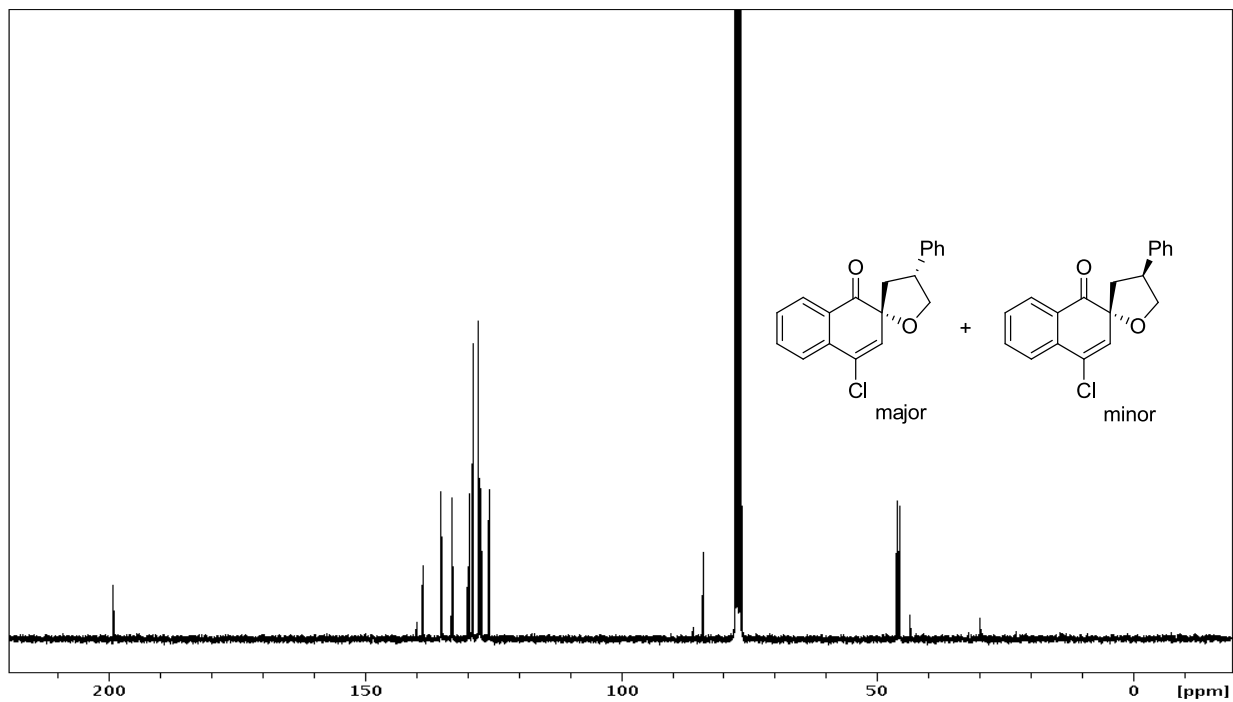
¹H NMR spectrum of *ca.* 9:1 mixture of 5.211/5.221 (300 MHz, CDCl₃)



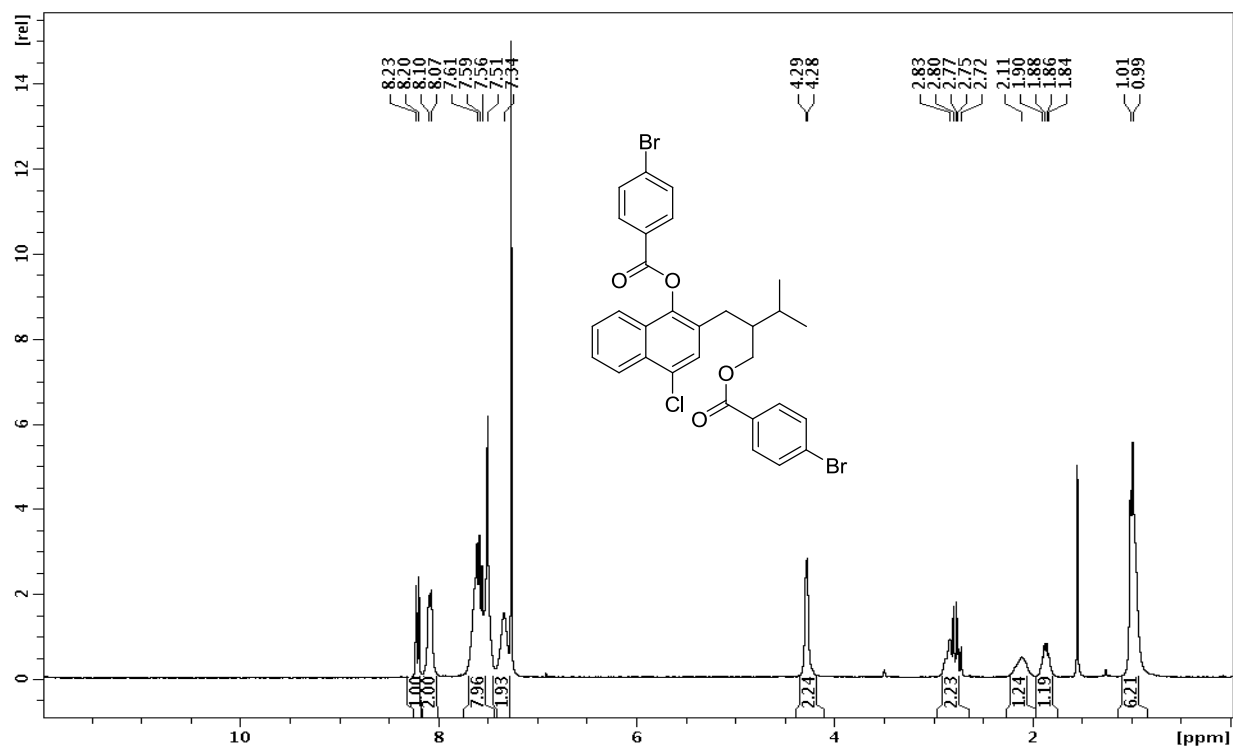
¹³C NMR spectrum of *ca.* 9:1 mixture of 5.211/5.221 (75 MHz, CDCl₃)



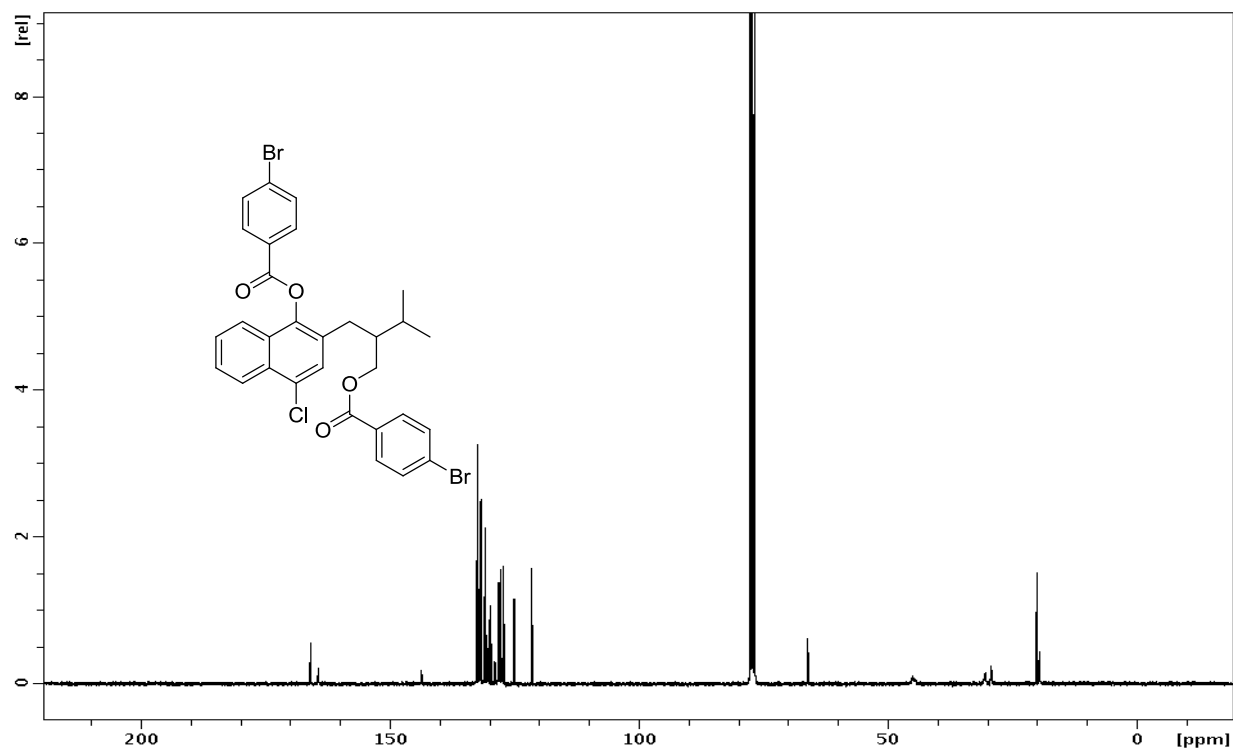
¹H NMR spectrum of *ca.* 17:3 mixture of 5.21m/5.22m (300 MHz, CDCl₃)



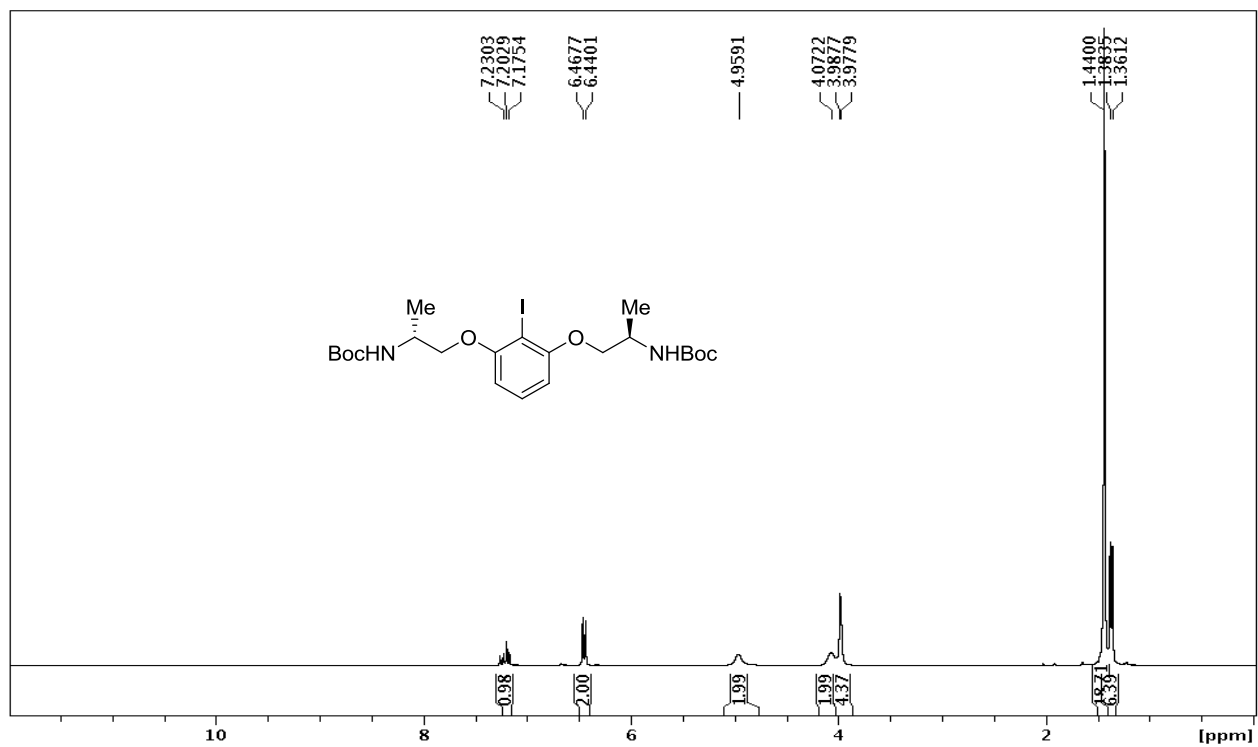
¹³C NMR spectrum of *ca.* 17:3 mixture of 5.21m/5.22m (75 MHz, CDCl₃)



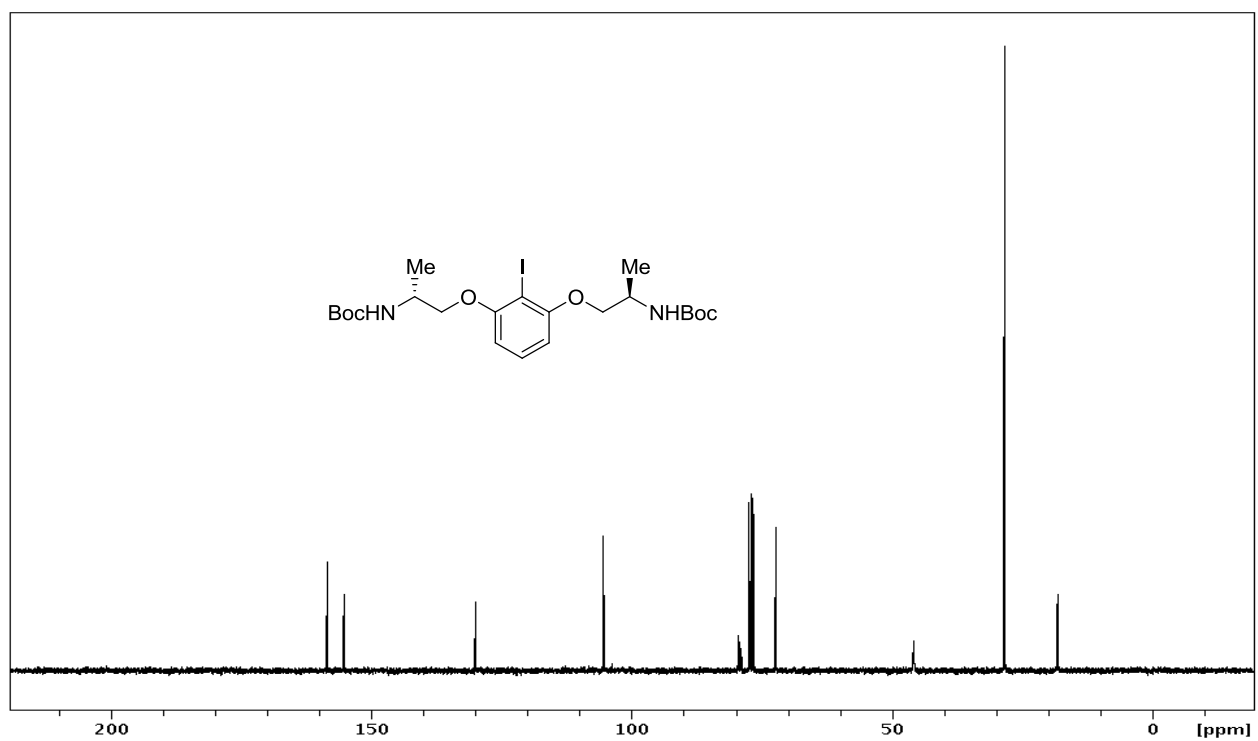
¹H NMR spectrum of 5.27 (300 MHz, CDCl₃)



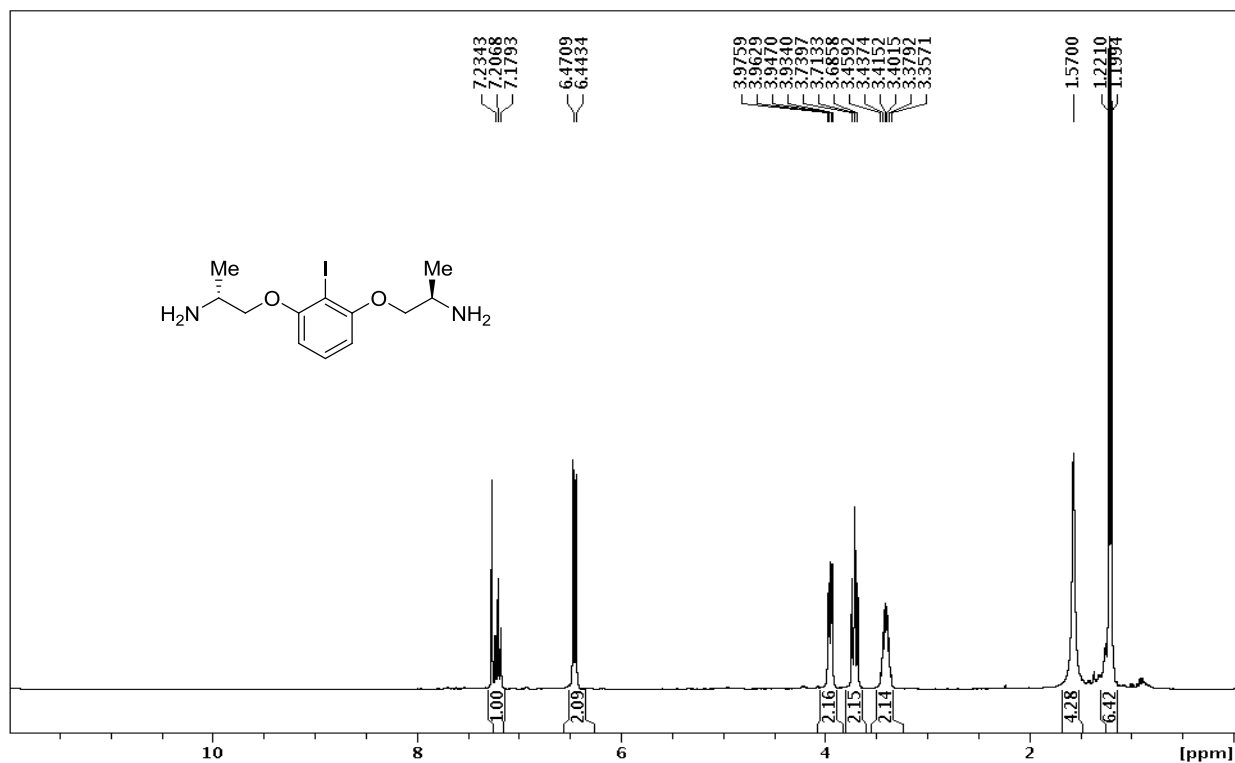
¹³C NMR spectrum of 5.27 (75 MHz, CDCl₃)



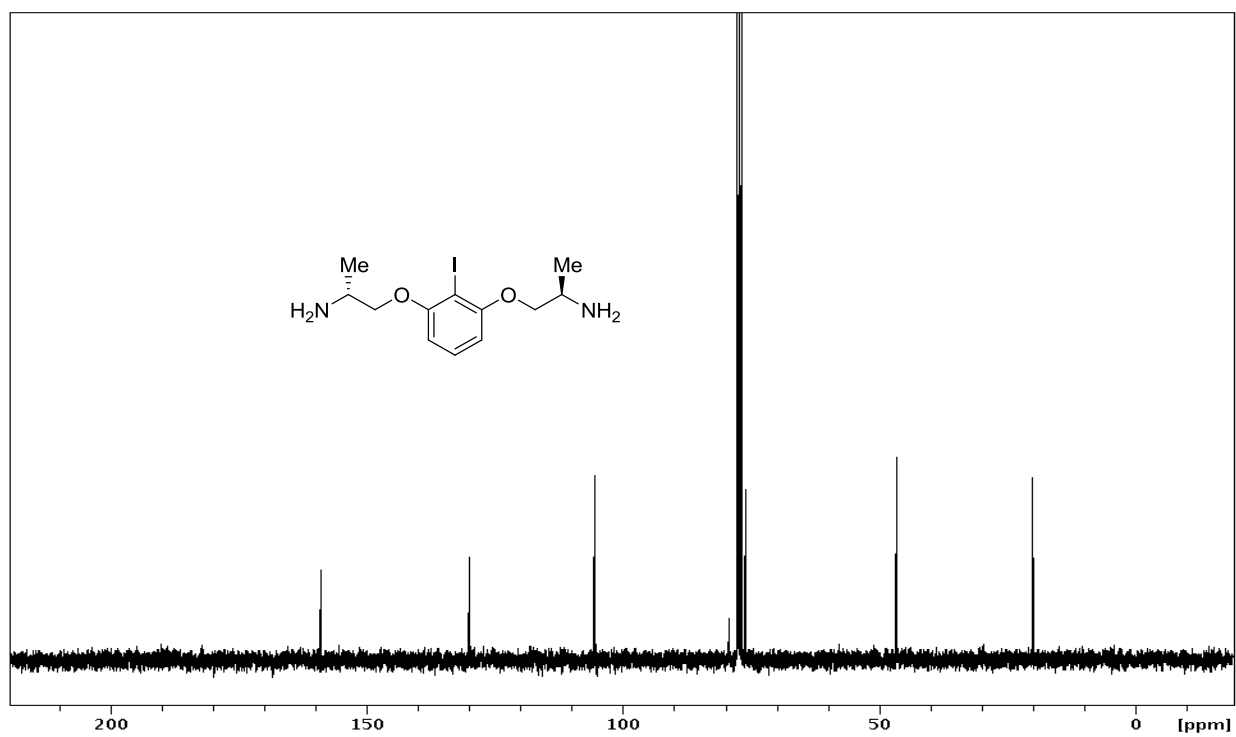
¹H NMR spectrum of 5.24 (300 MHz, CDCl₃)



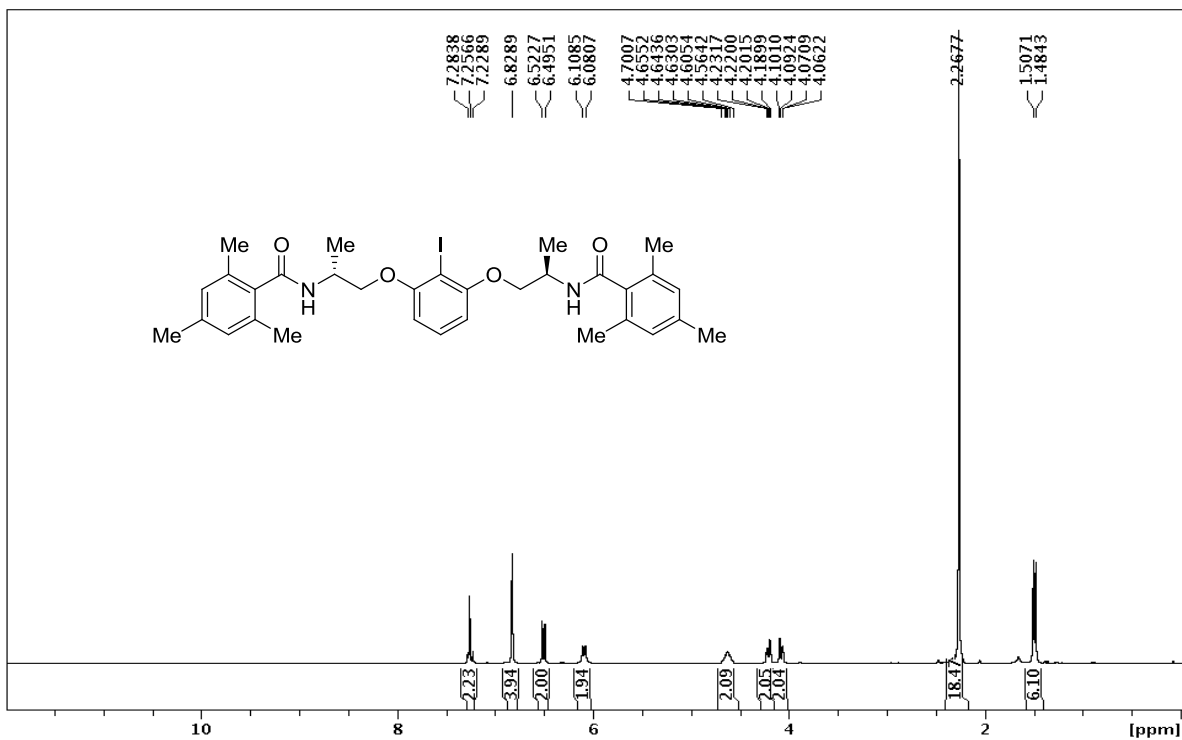
¹³C NMR spectrum of 5.24 (75 MHz, CDCl₃)



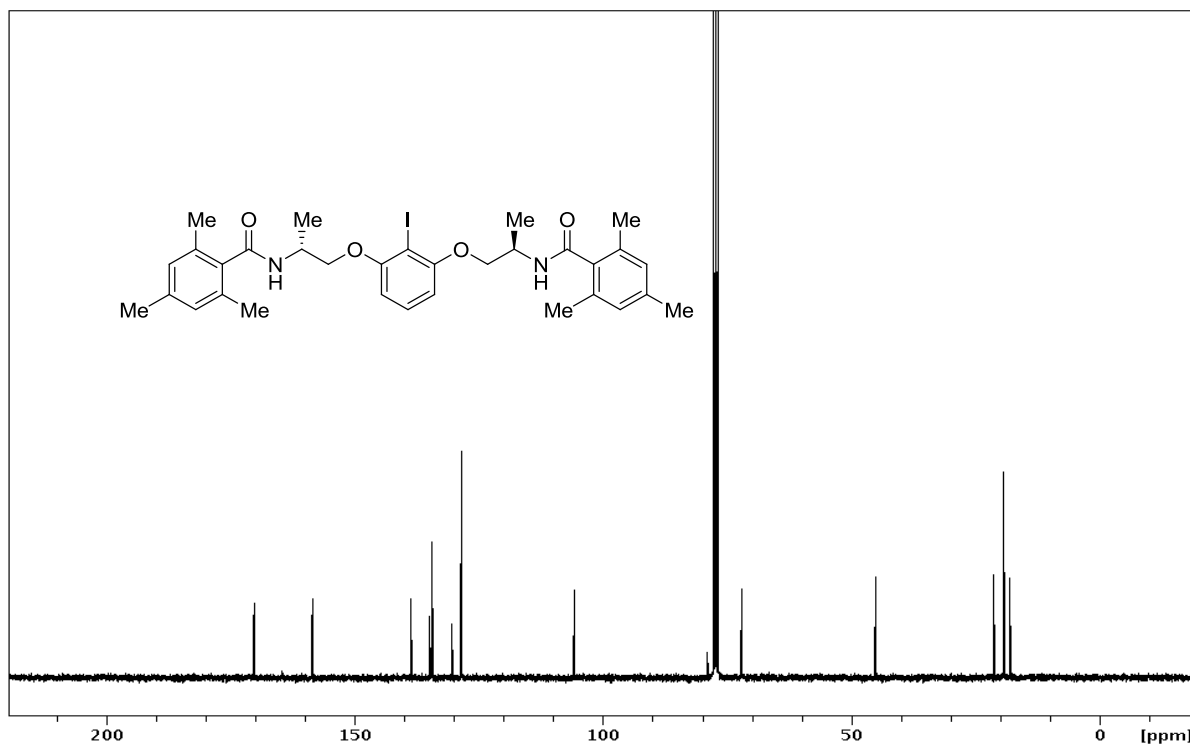
¹H NMR spectrum of 5.25 (300 MHz, CDCl₃)



¹³C NMR spectrum of 5.25 (75 MHz, CDCl₃)

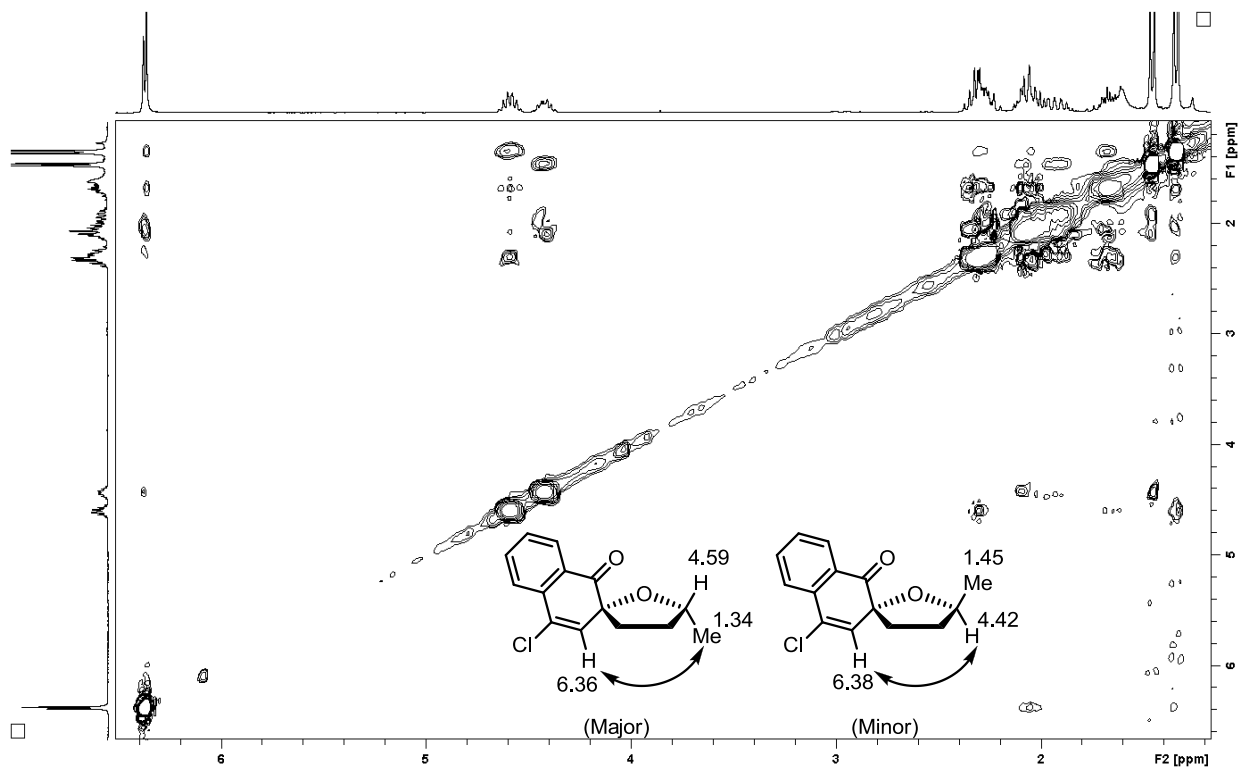
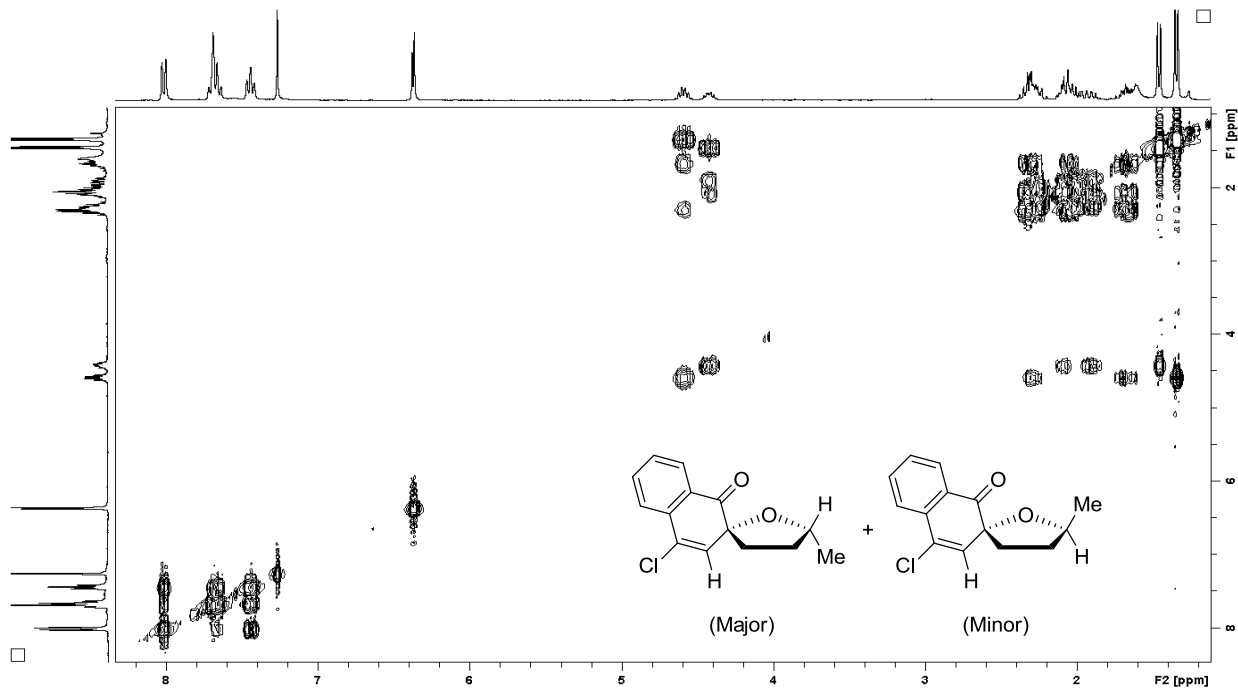


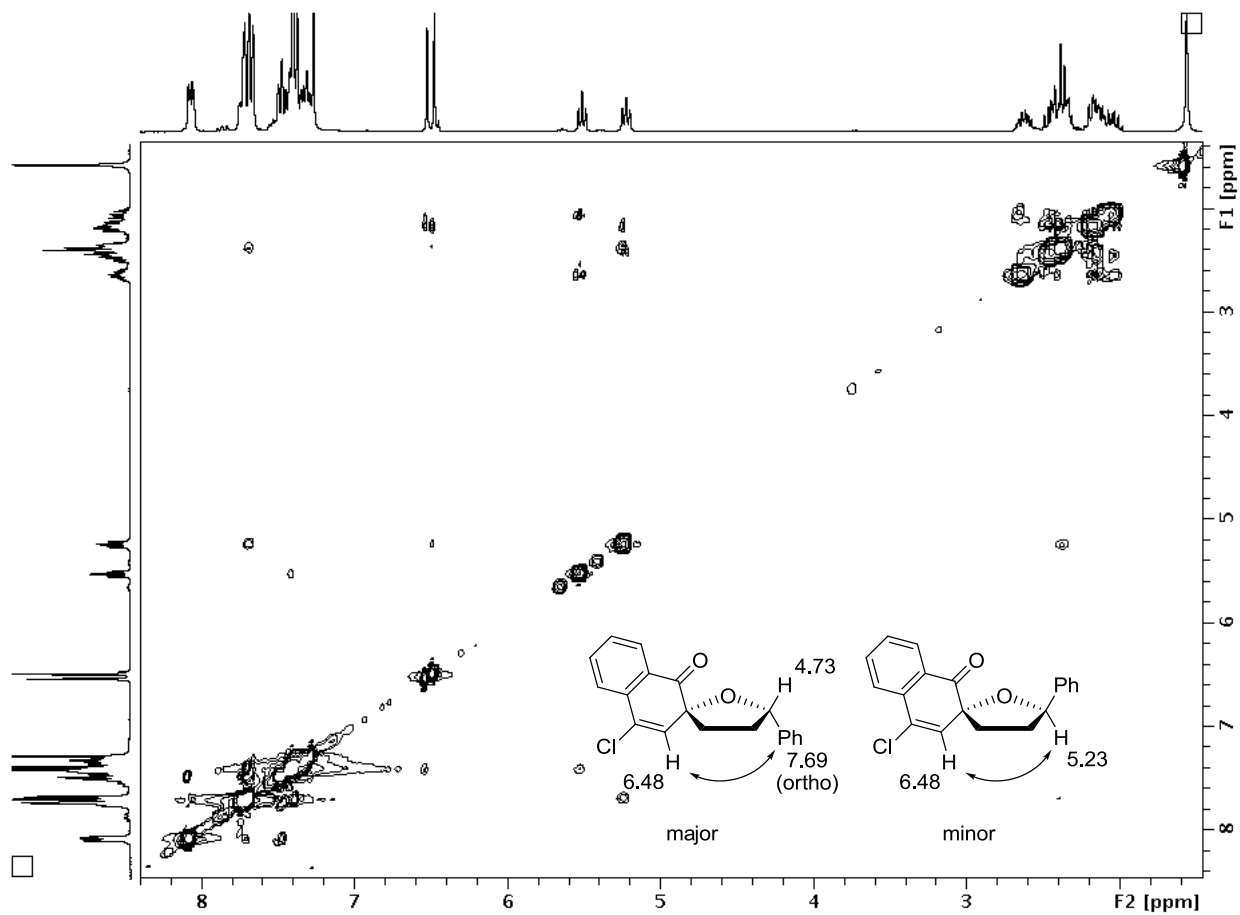
¹H NMR spectrum of 5.26 (300 MHz, CDCl₃)



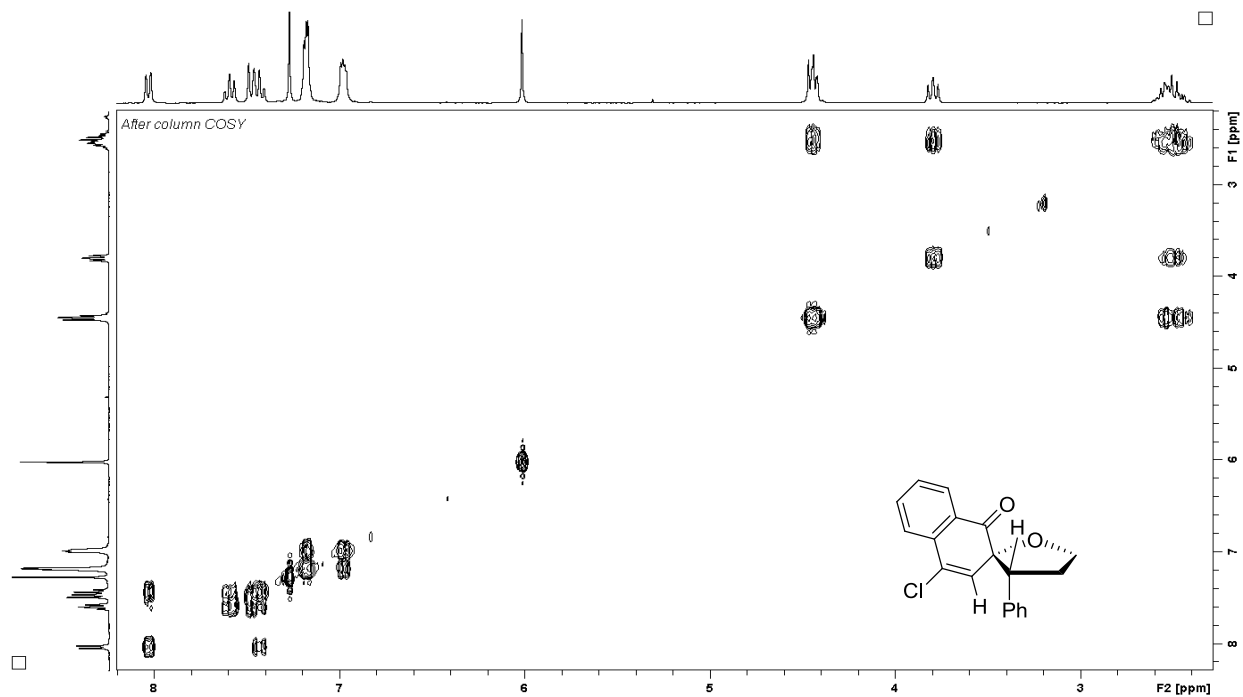
¹³C NMR spectrum of 5.26 (75 MHz, CDCl₃)

D.14 COSY and NOESY spectra of spiroethers

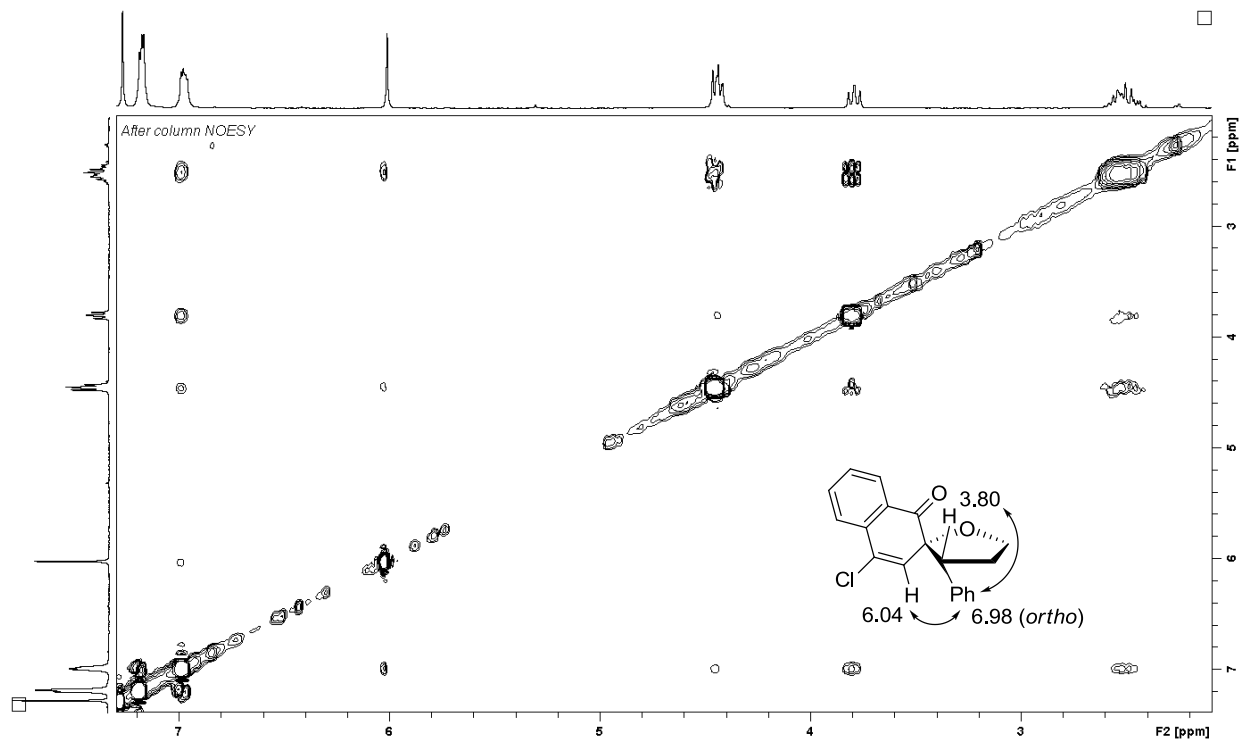




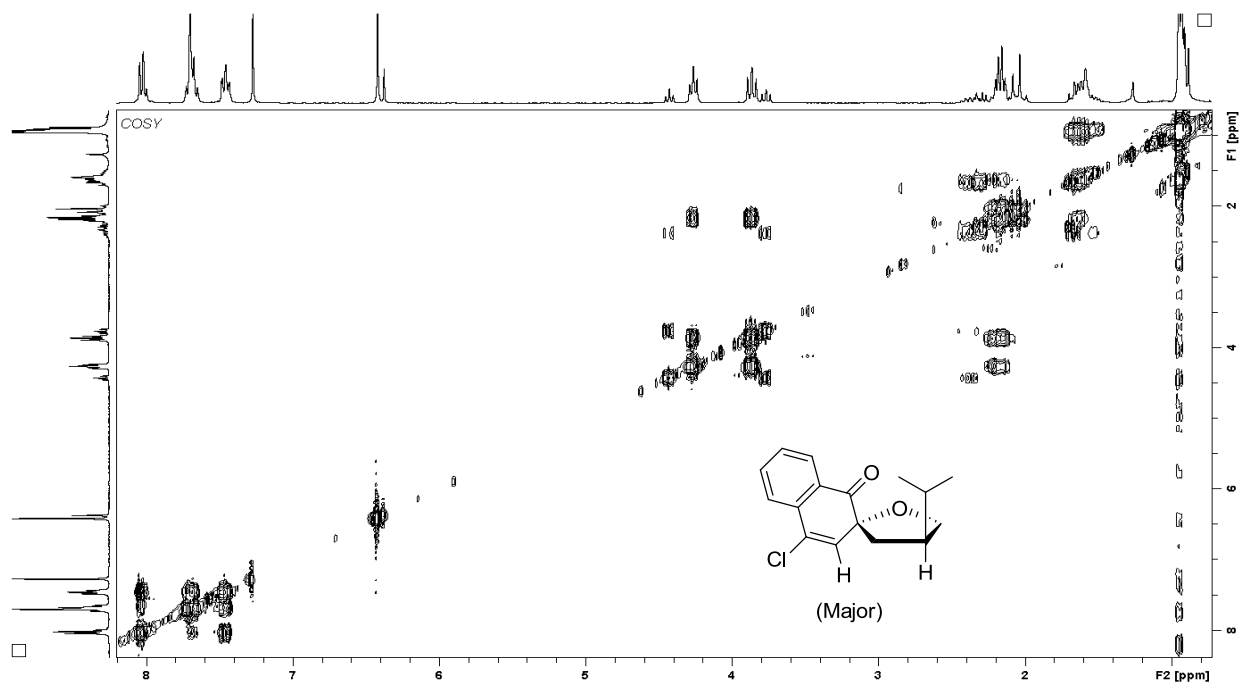
Expansion of NOESY spectrum of *ca.* 13:7 mixture of 5.18a/5.19a (CDCl₃)



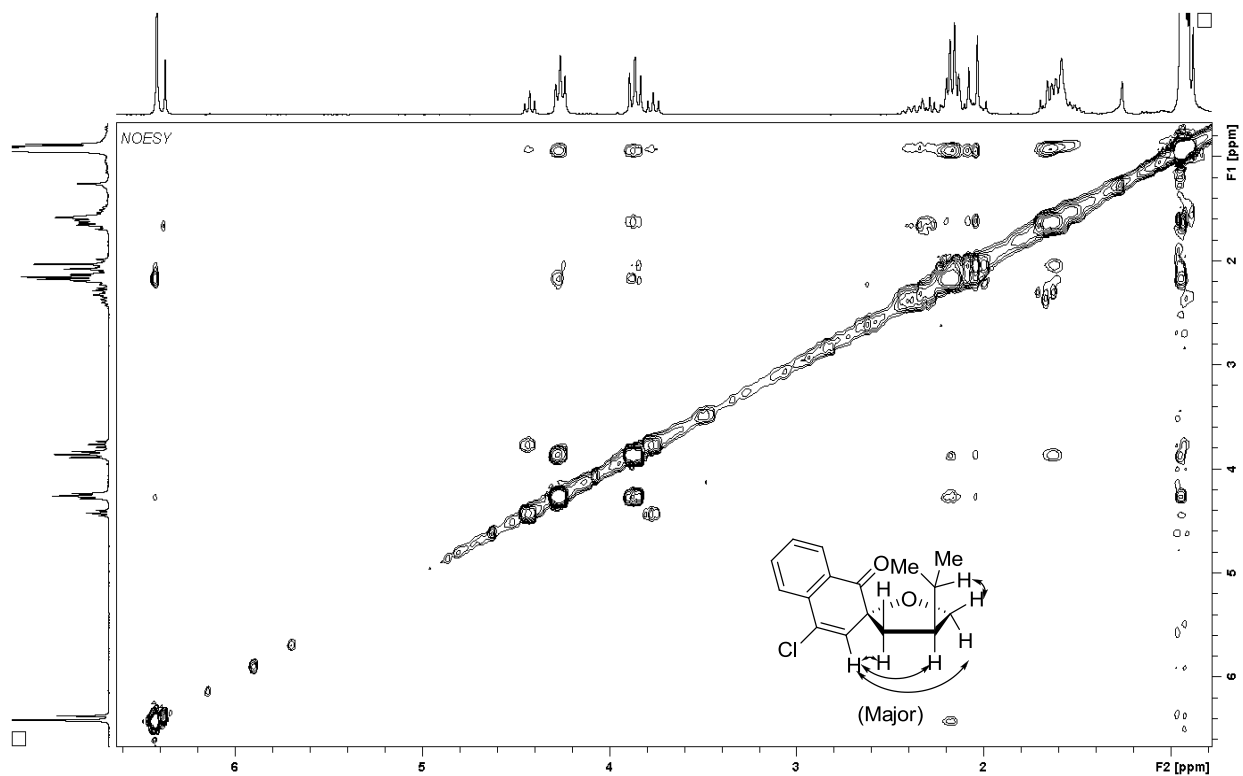
Expansion of COSY spectrum of 5.18c (CDCl₃)



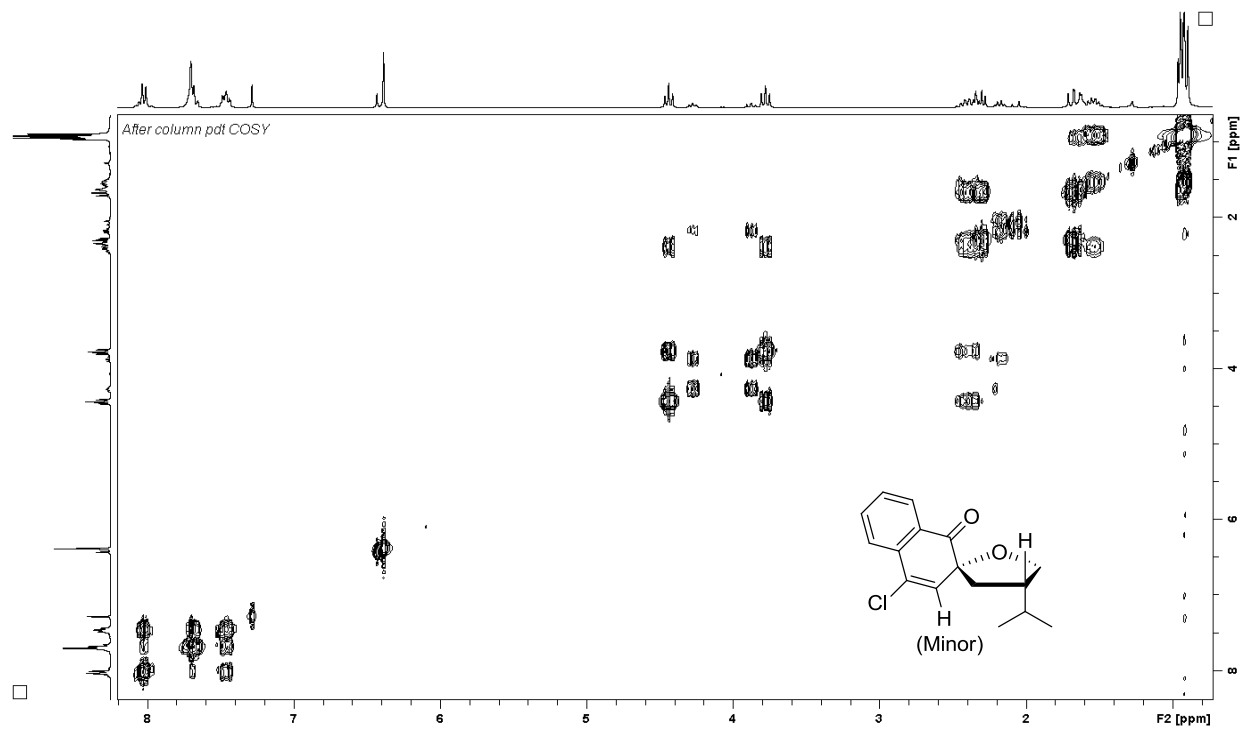
Expansion of NOESY spectrum of 5.18c (CDCl₃)



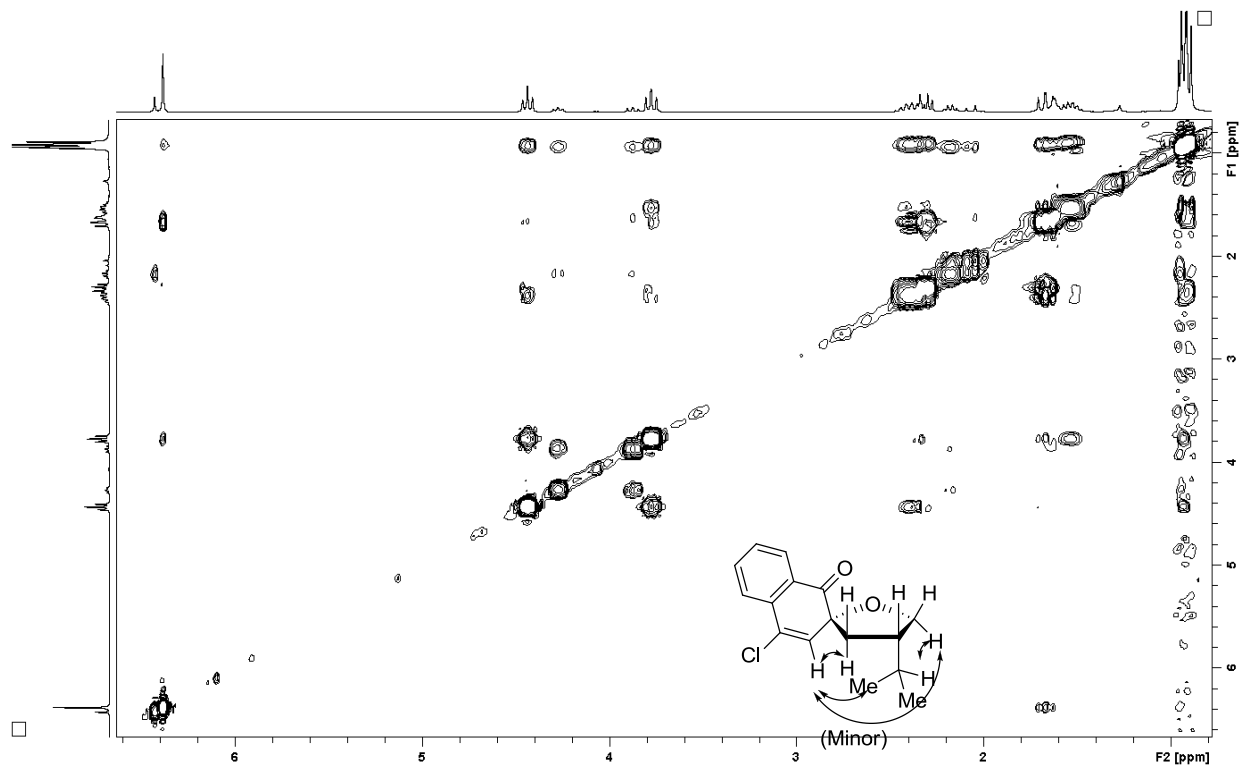
Expansion of COSY spectrum of *ca.* 4:1 mixture of 5.21a/5.22a (CDCl₃)



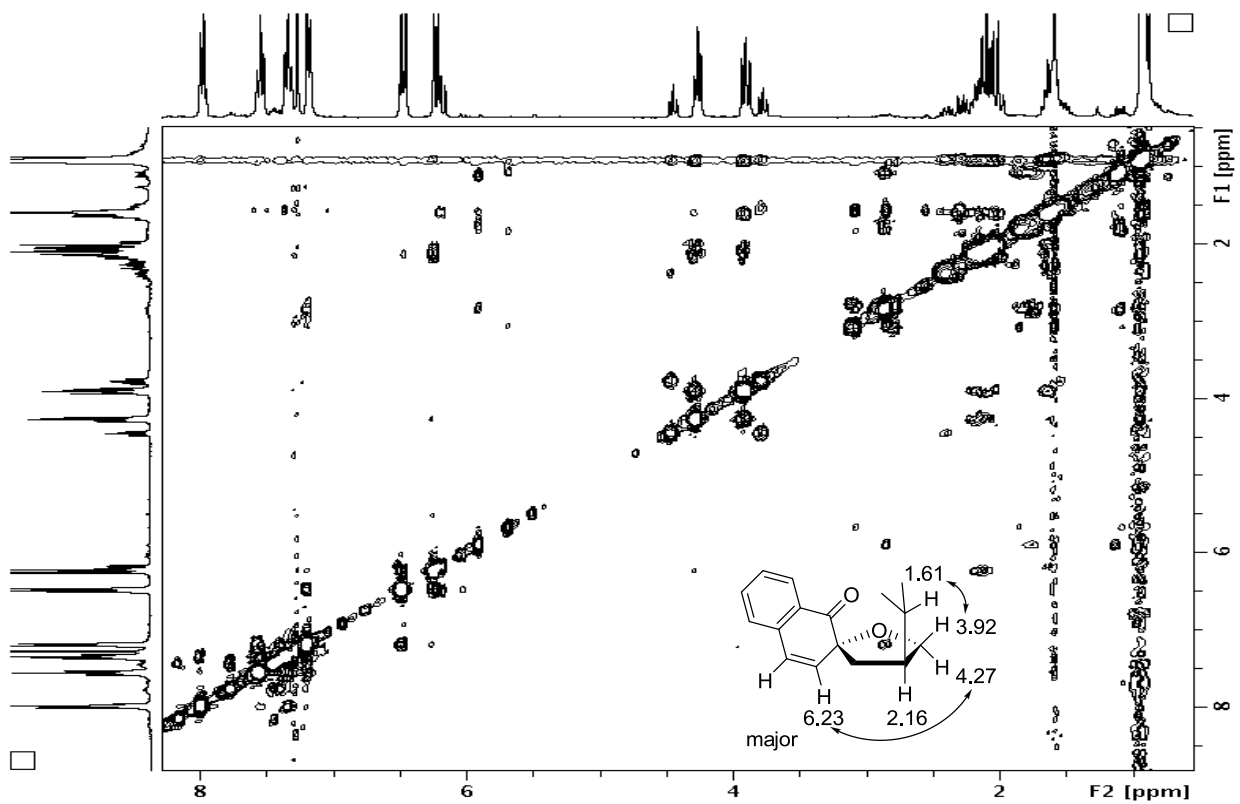
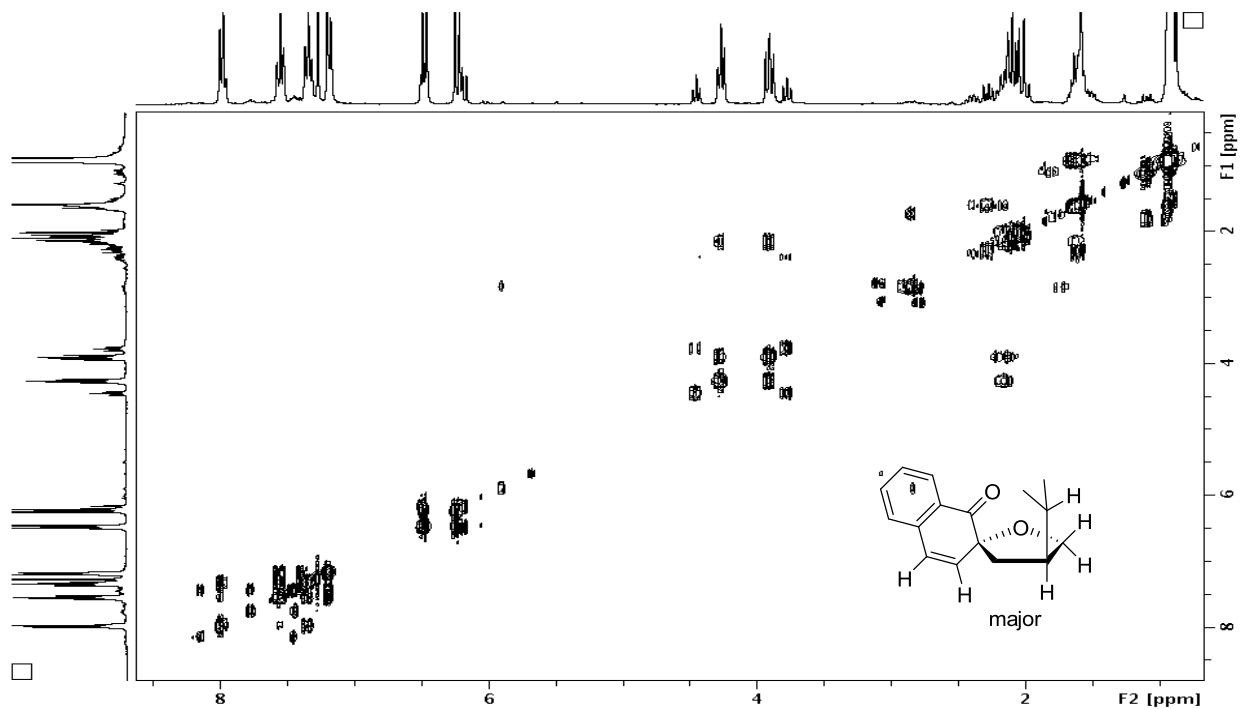
Expansion of NOESY spectrum of *ca.* 4:1 mixture of 5.21a/5.22a (CDCl₃)

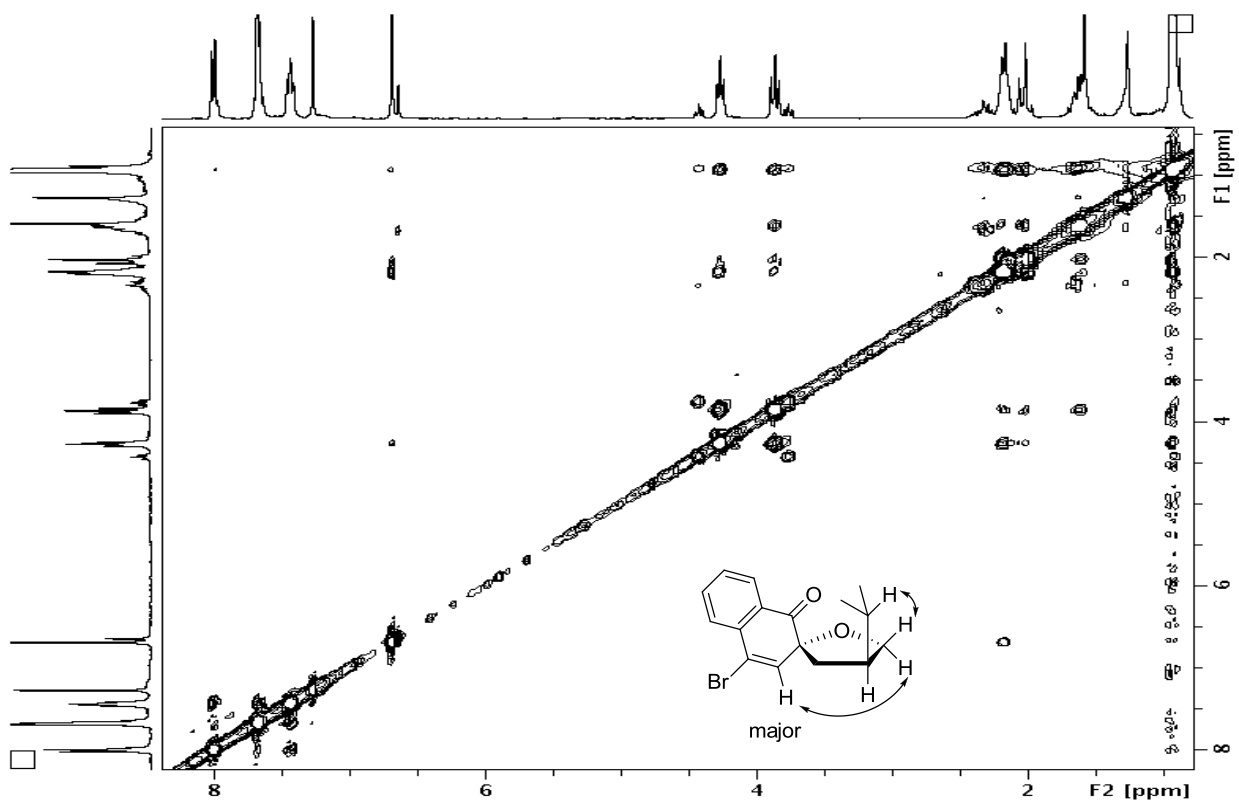
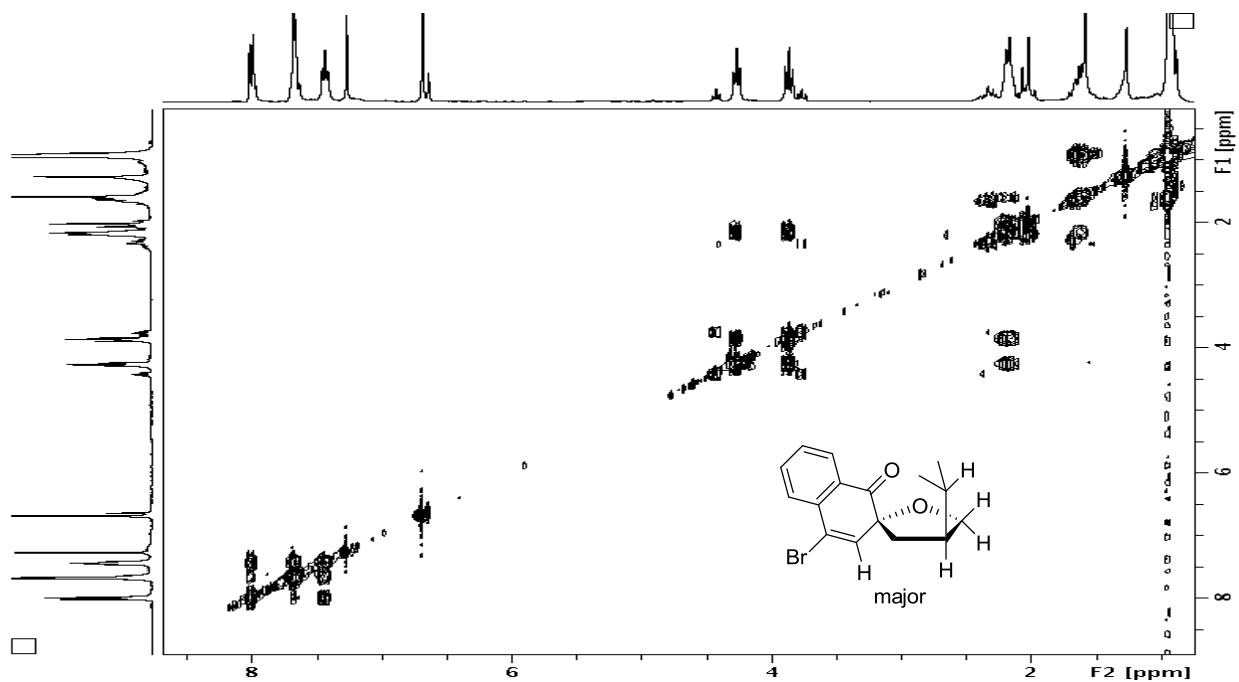


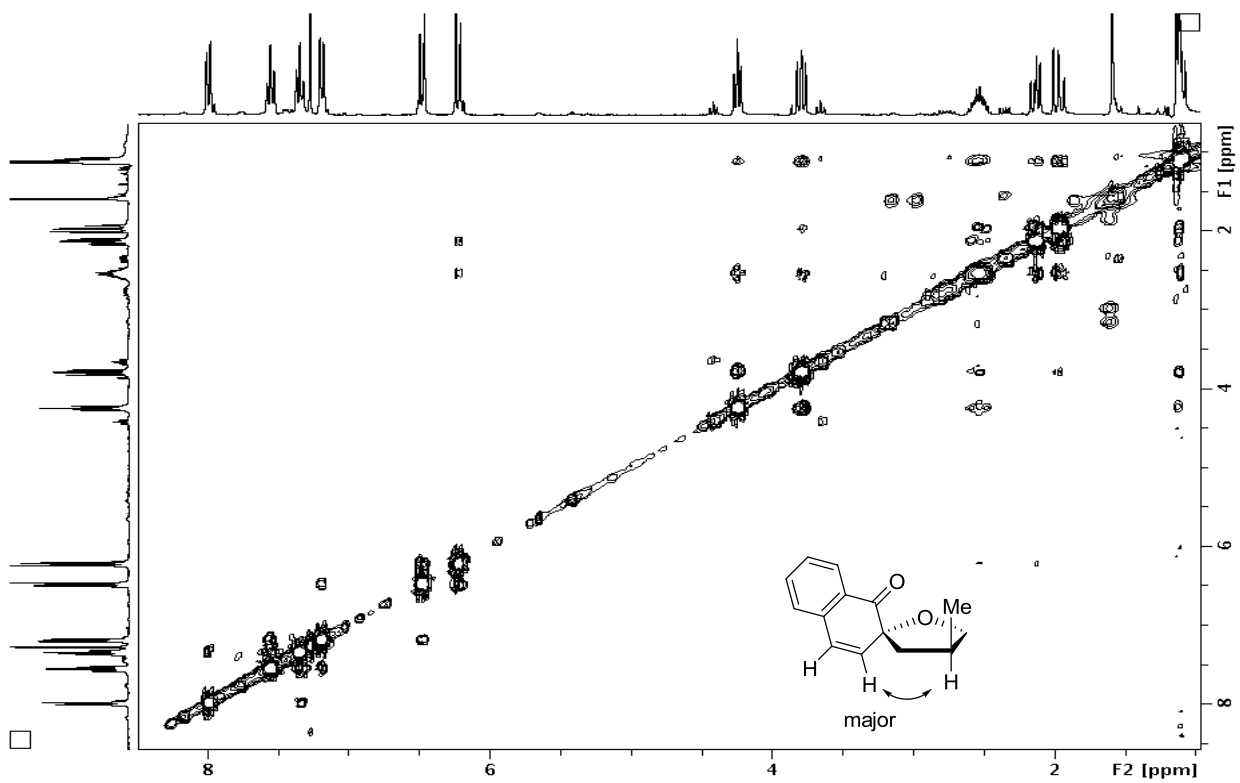
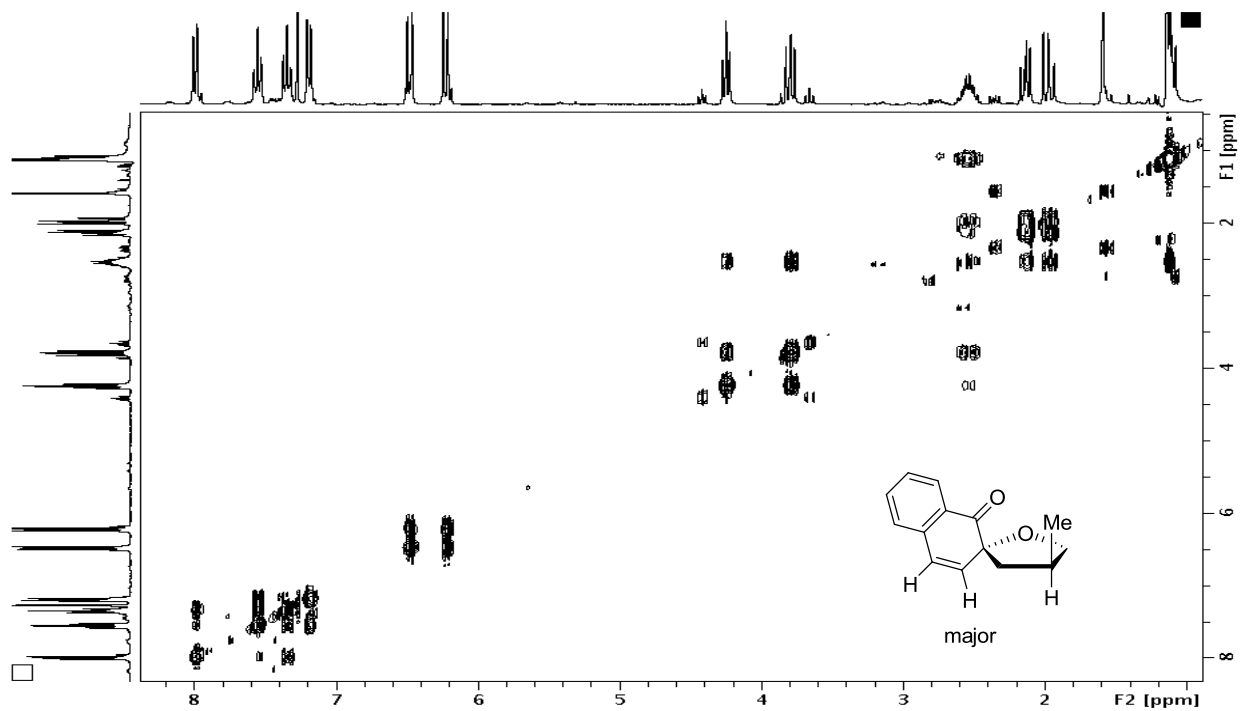
Expansion of COSY spectrum of *ca.* 1:4 mixture of 5.21a/5.22a (CDCl₃)

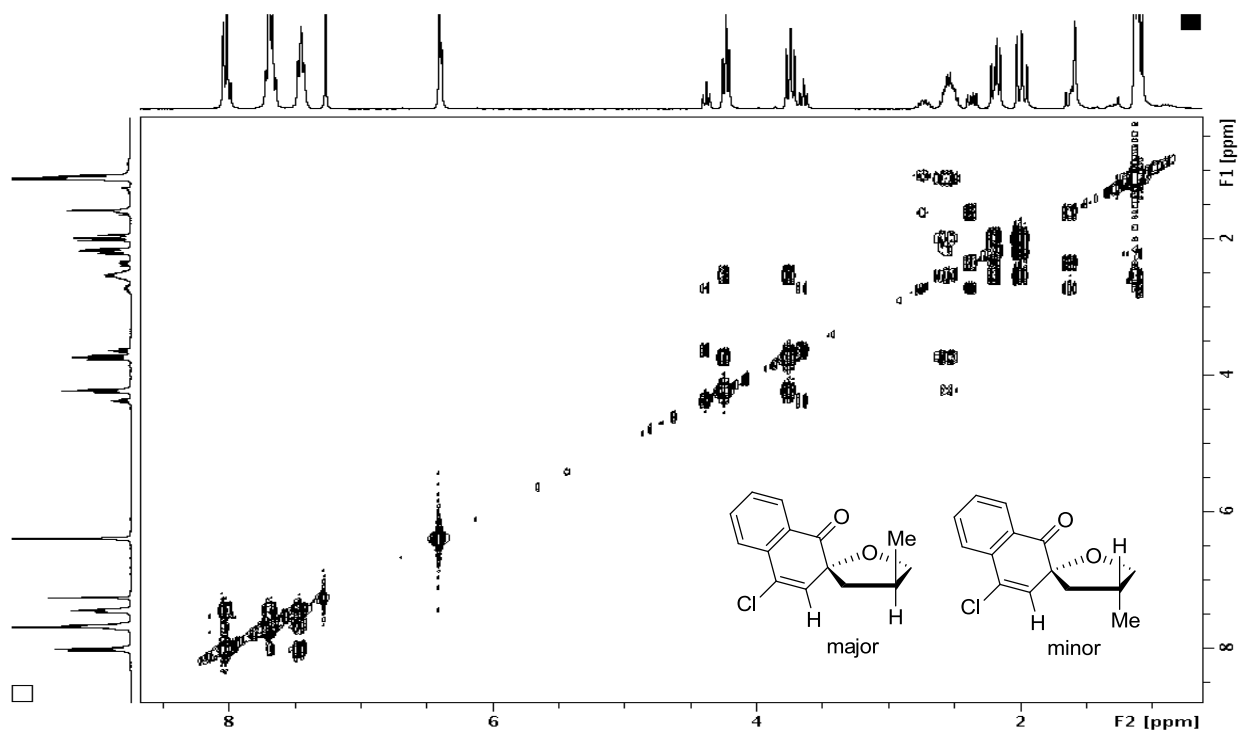


Expansion of NOESY spectrum of *ca.* 1:4 mixture of 5.21a/5.22a (CDCl₃)

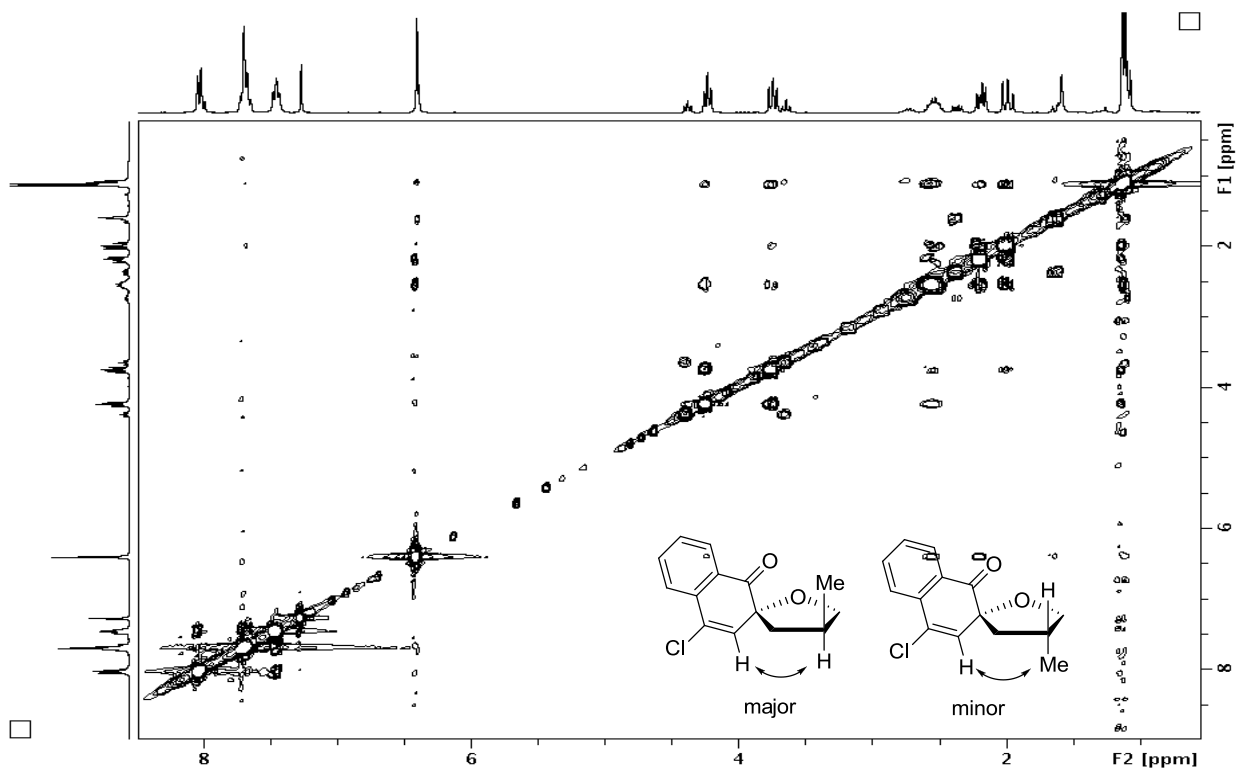




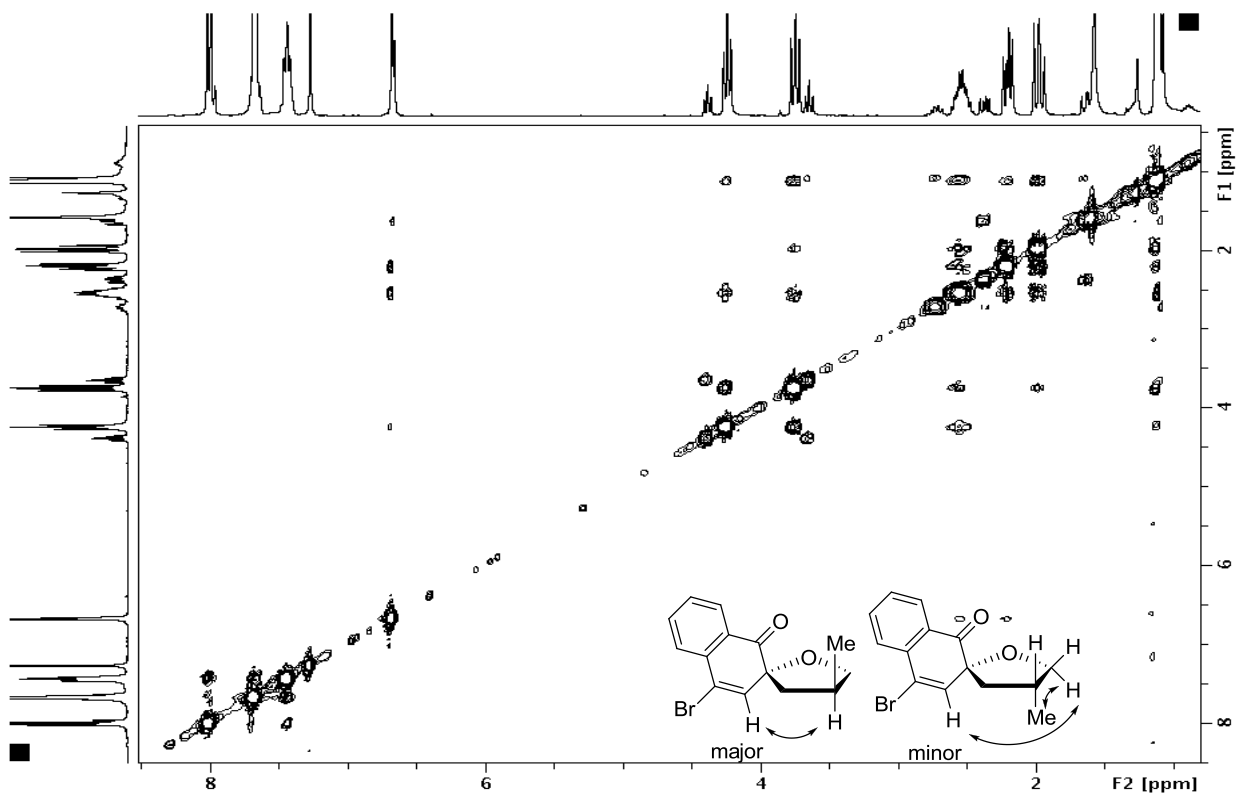
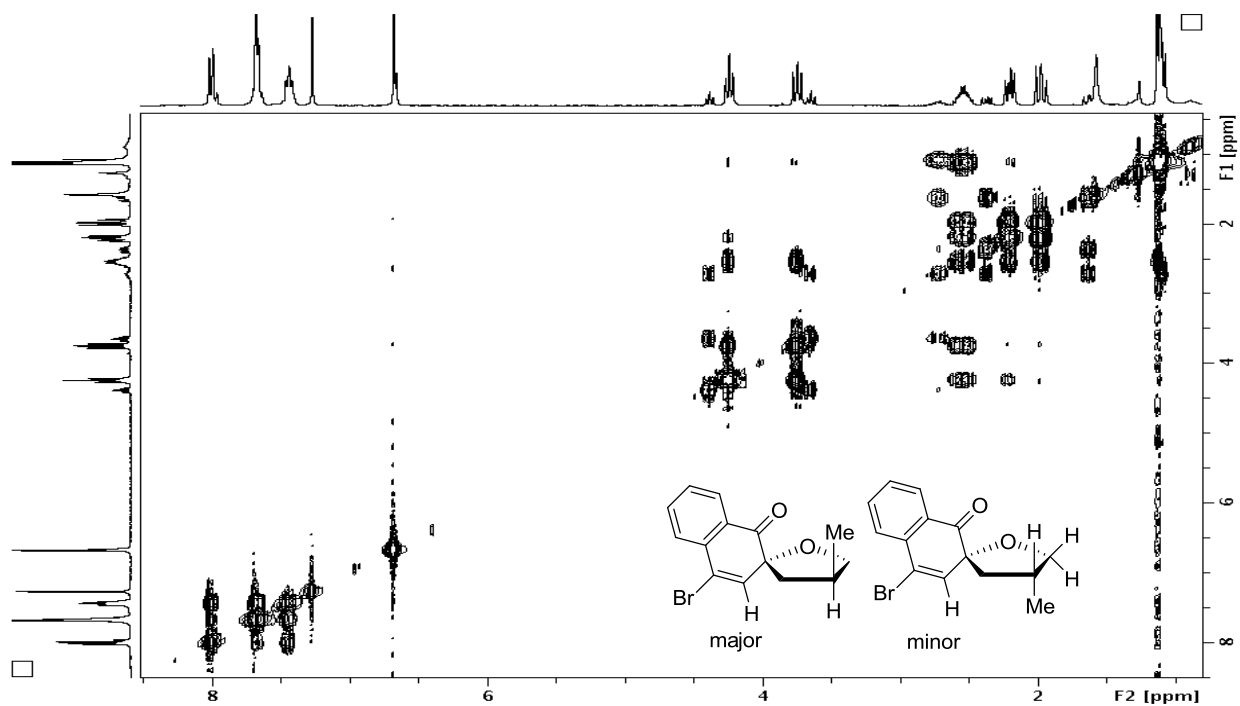


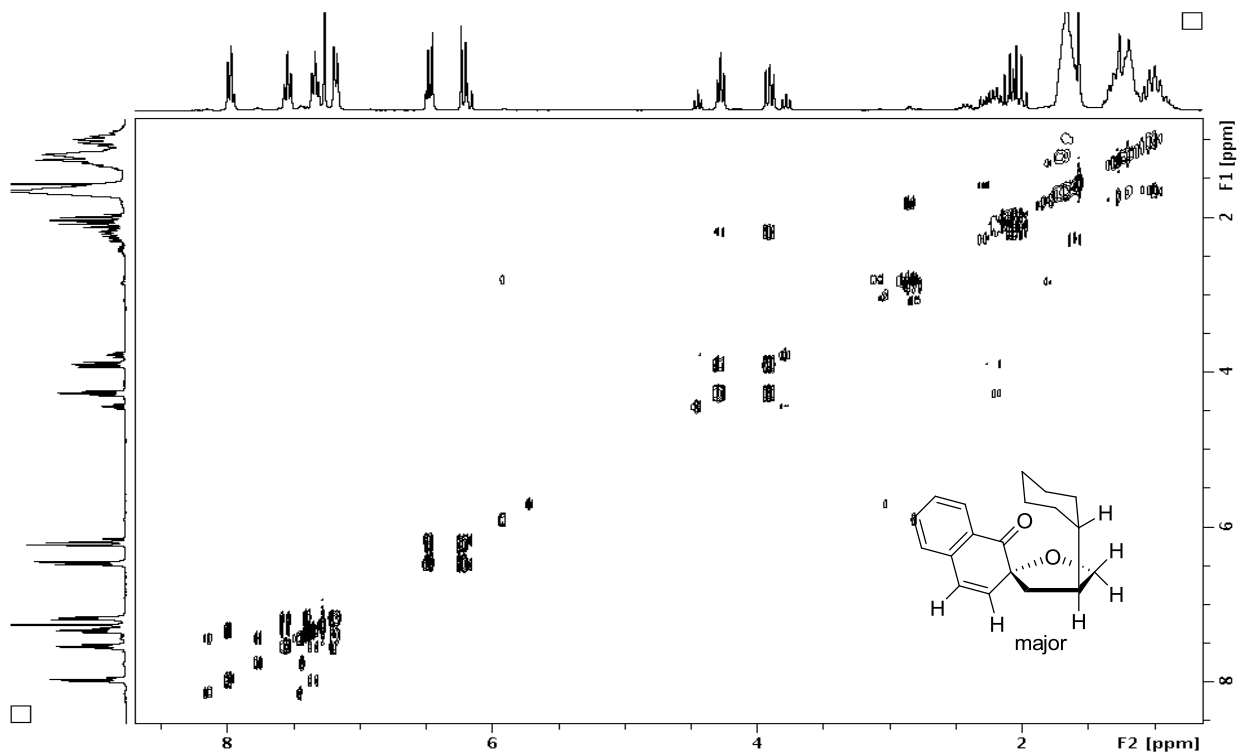


Expansion of COSY spectrum of *ca.* 7:3 mixture of 5.21e/5.22e (CDCl₃)

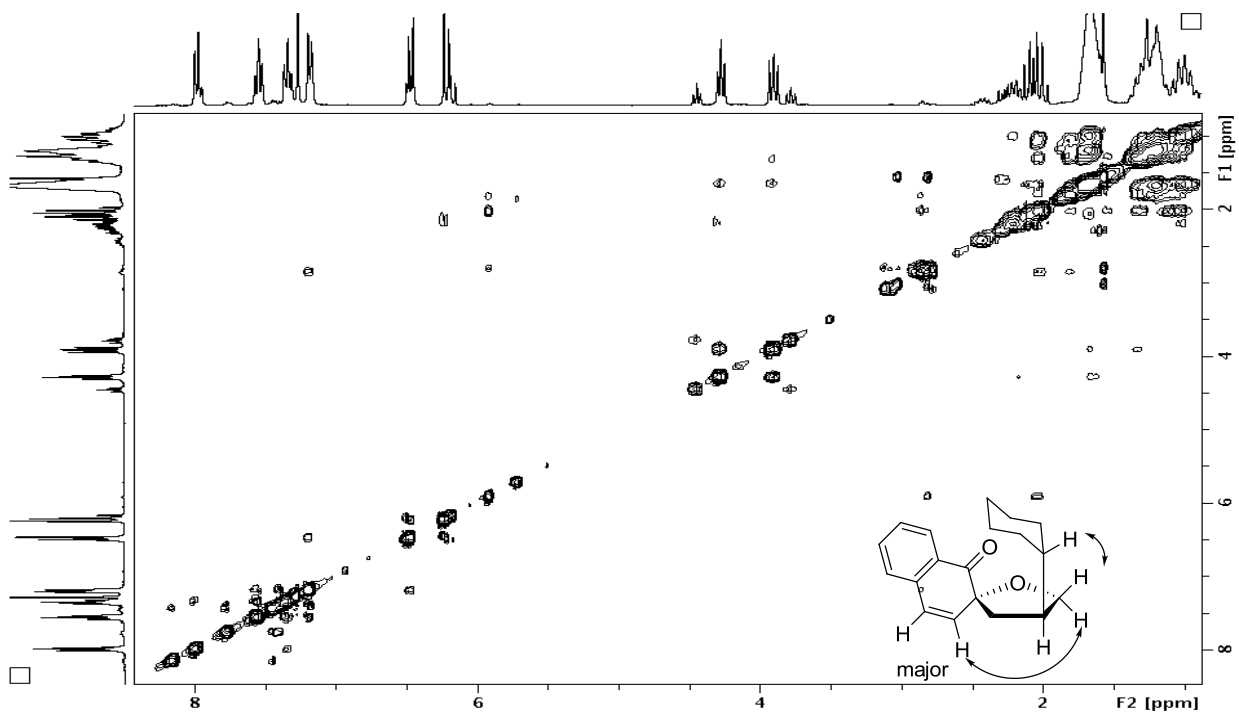


Expansion of NOESY spectrum of *ca.* 7:3 mixture of 5.21e/5.22e (CDCl₃)

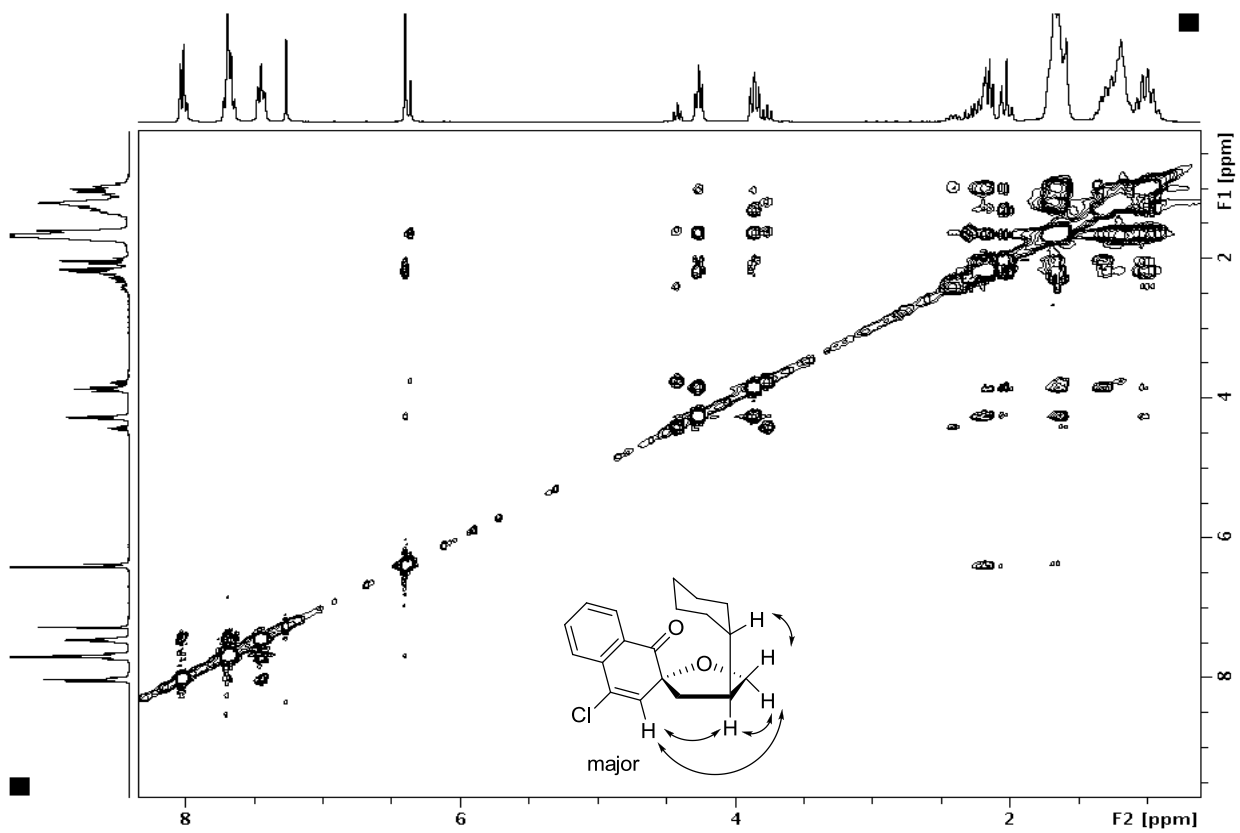
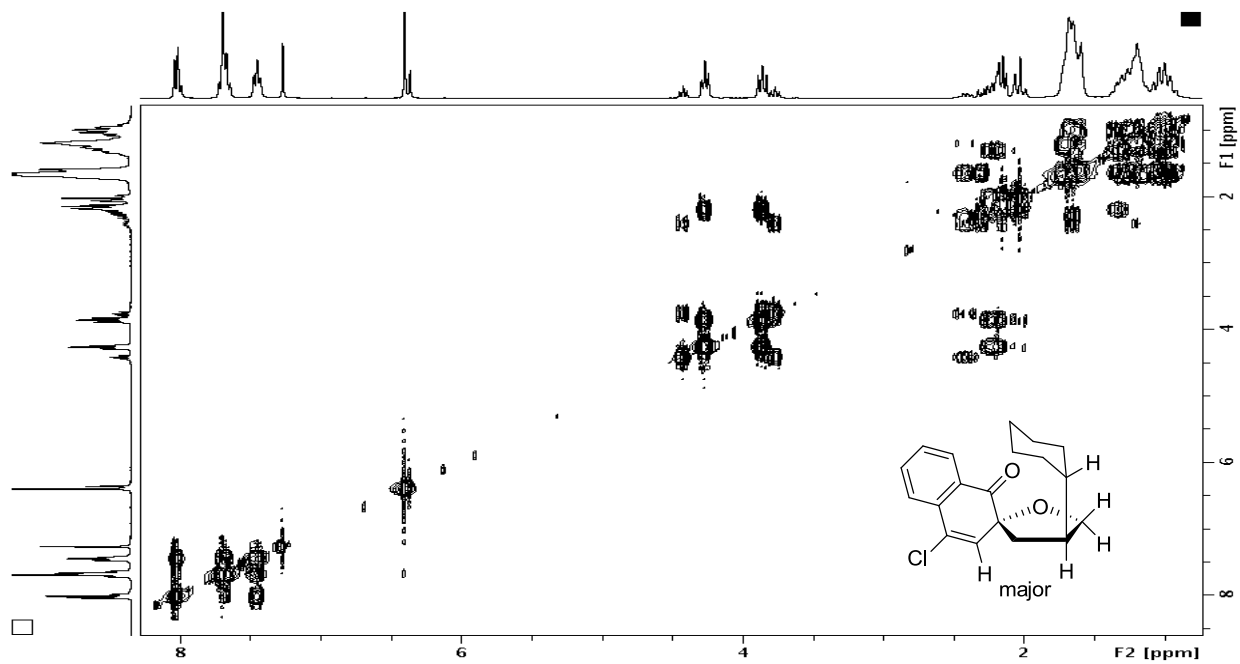


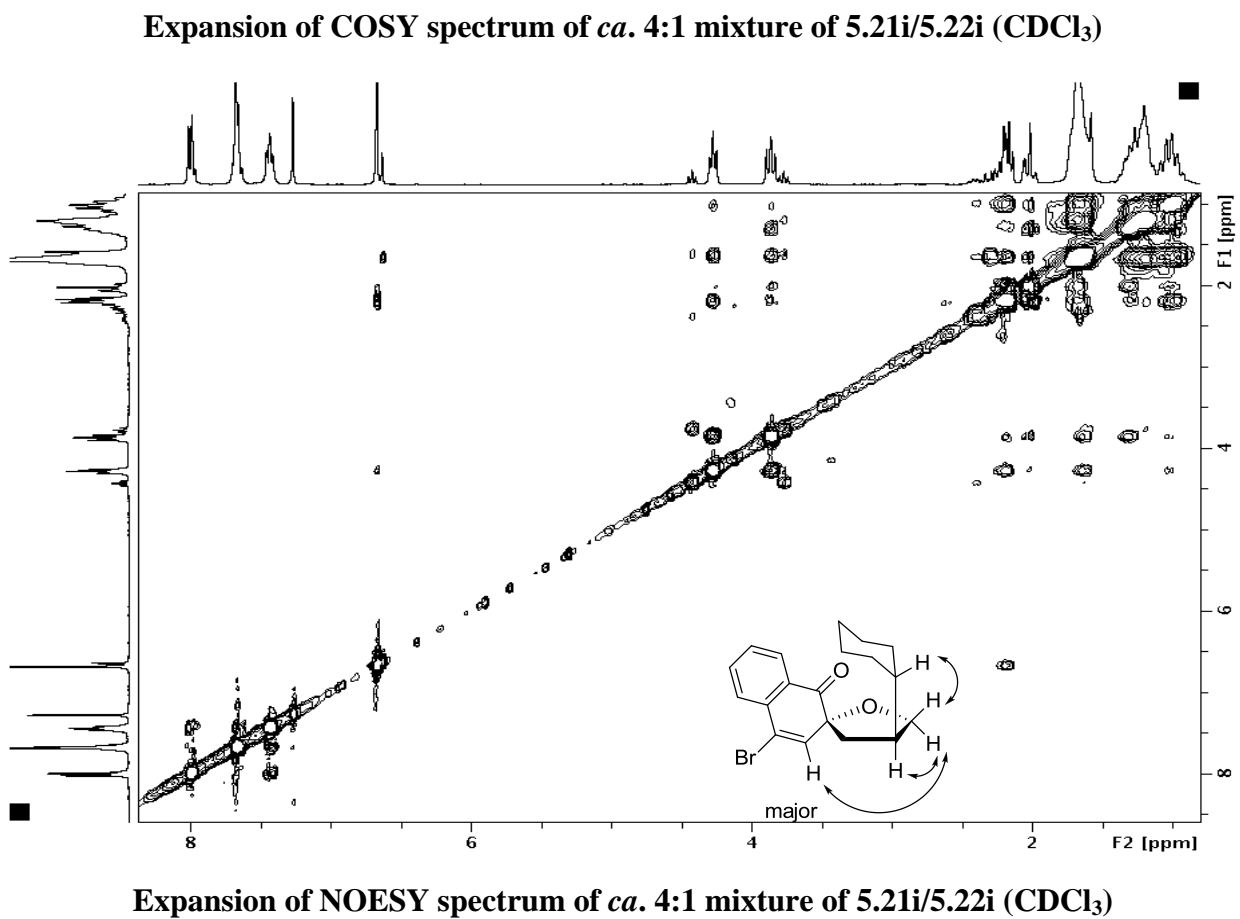
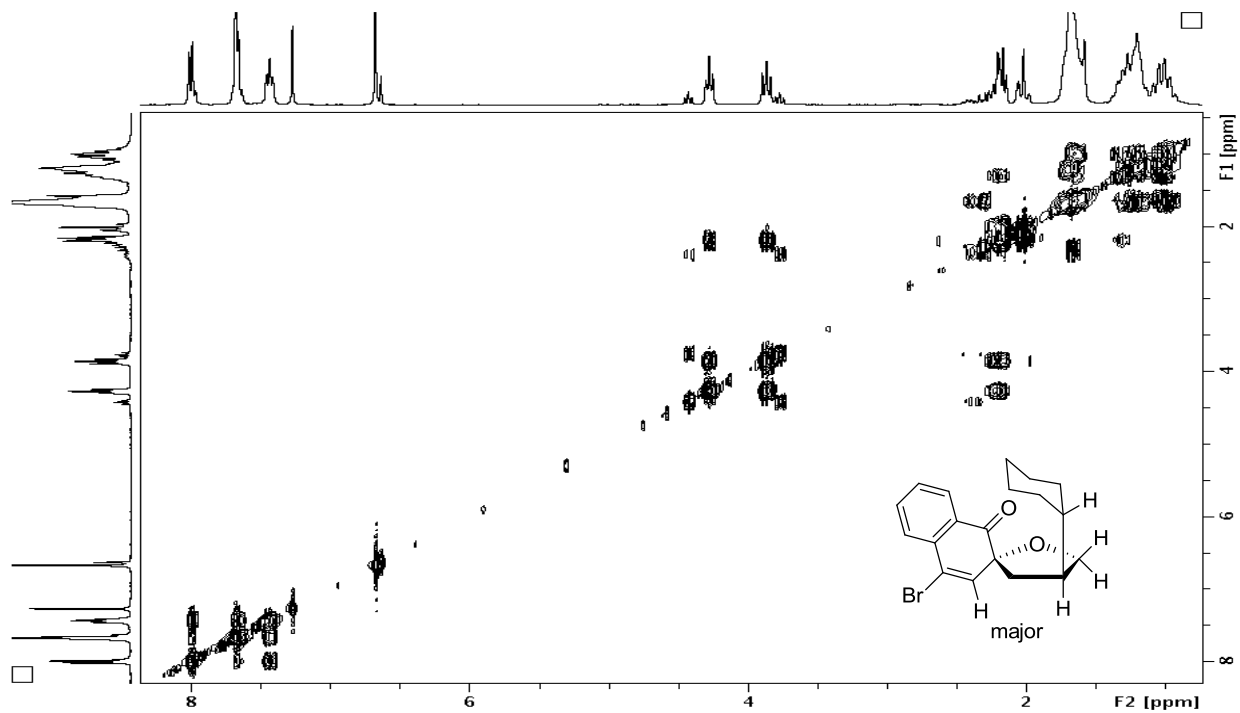


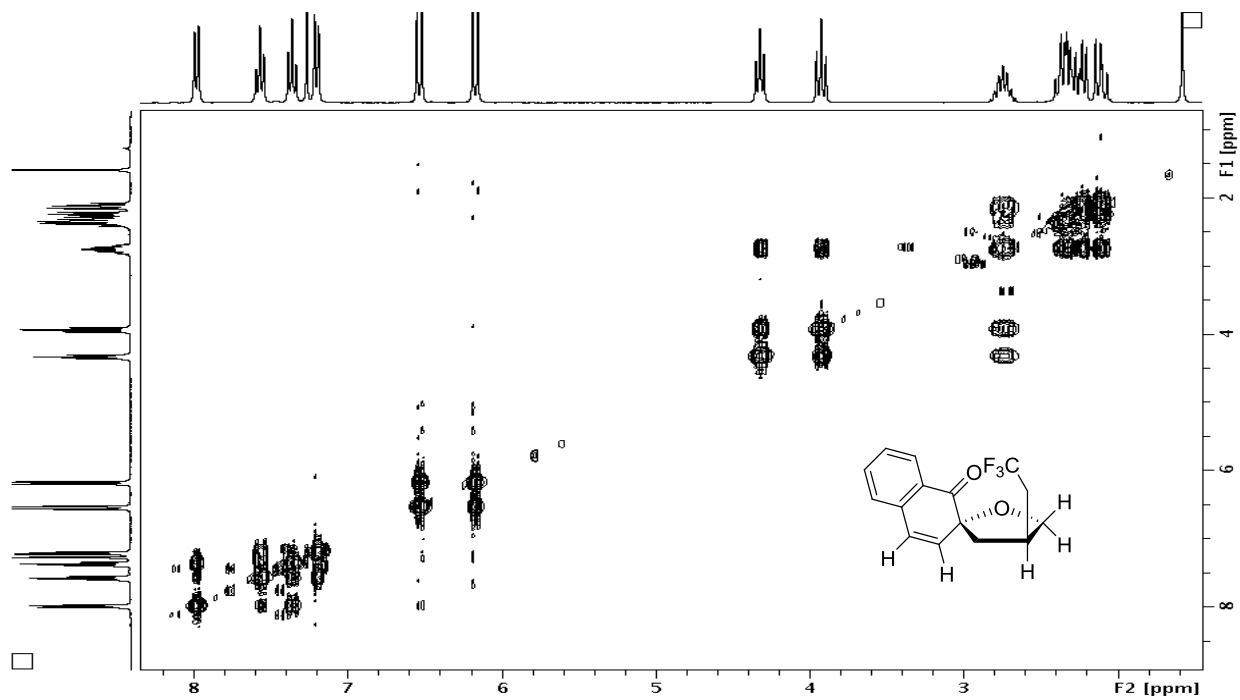
Expansion of COSY spectrum of *ca.* 3:1 mixture of 5.21g/5.22g (CDCl₃)



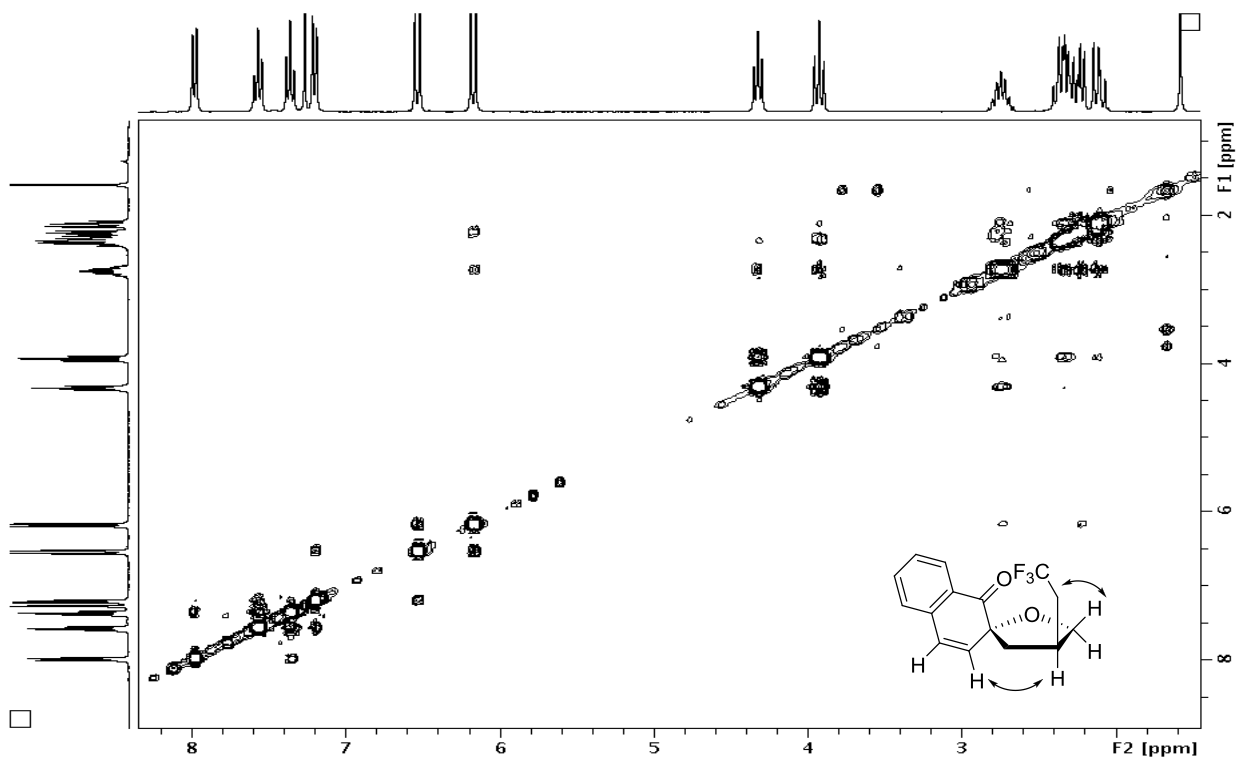
Expansion of NOESY spectrum of *ca.* 3:1 mixture of 5.21g/5.22g (CDCl₃)



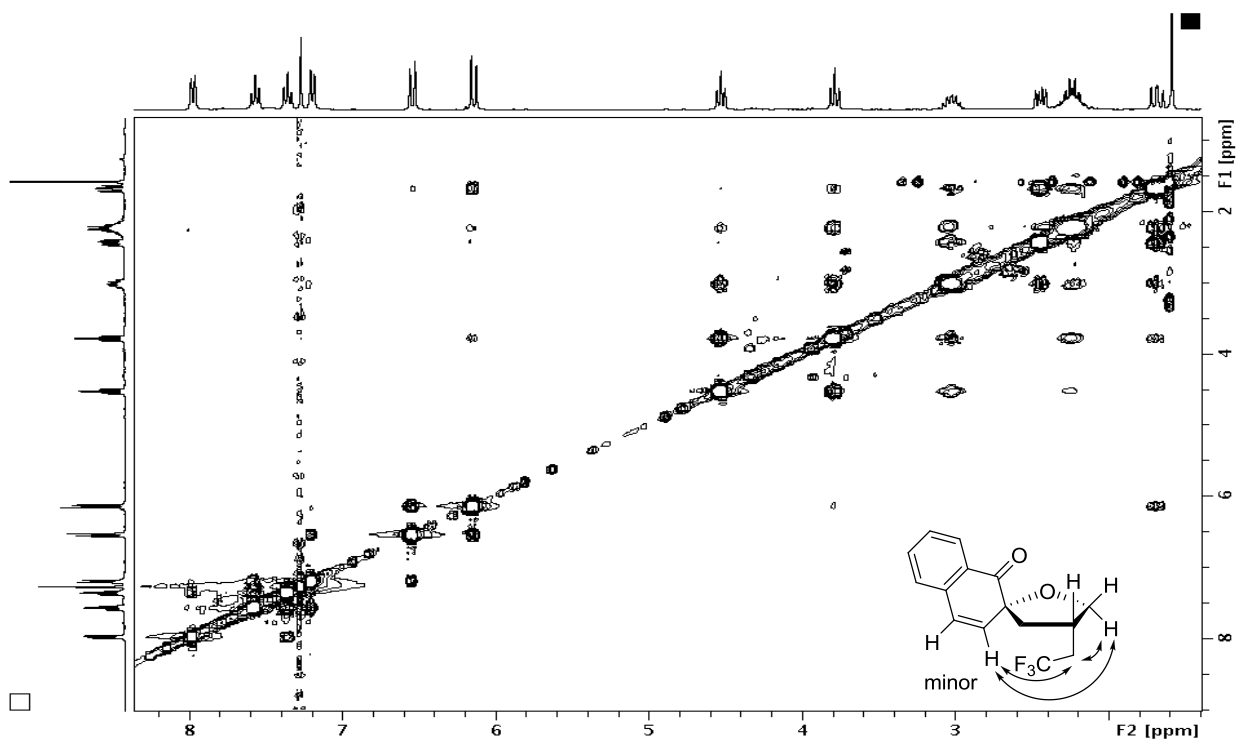
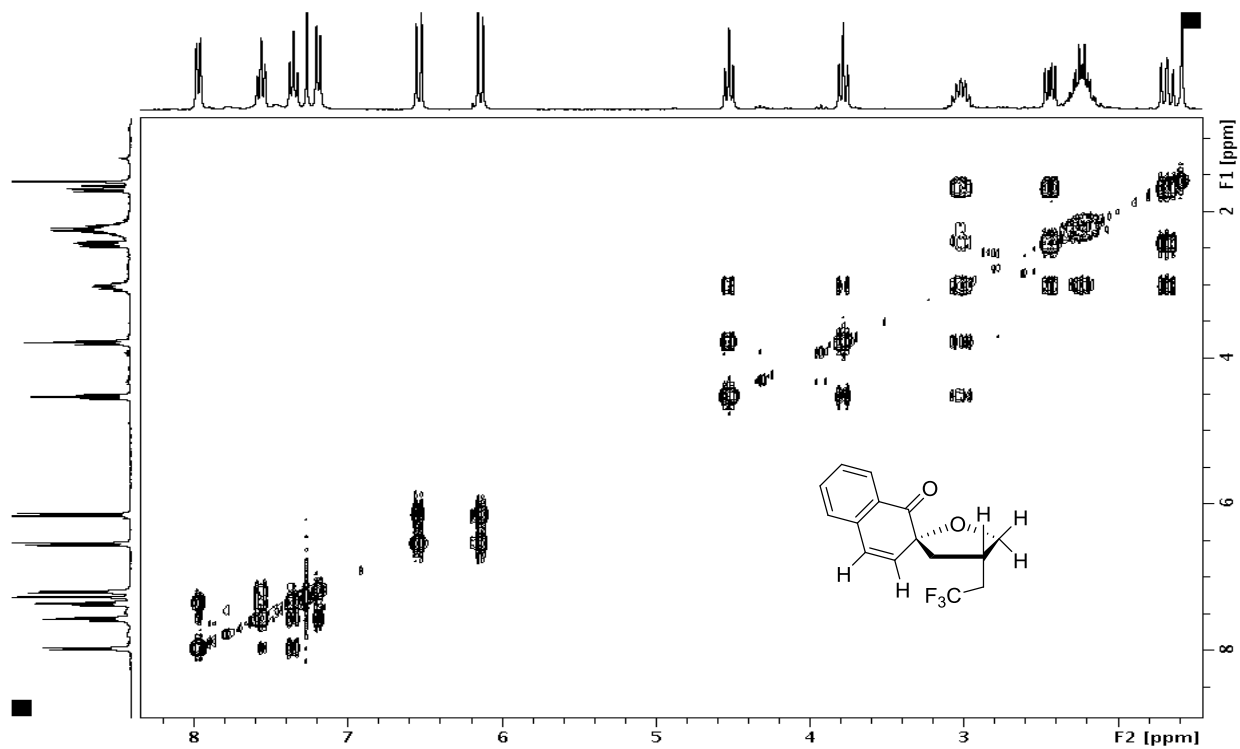


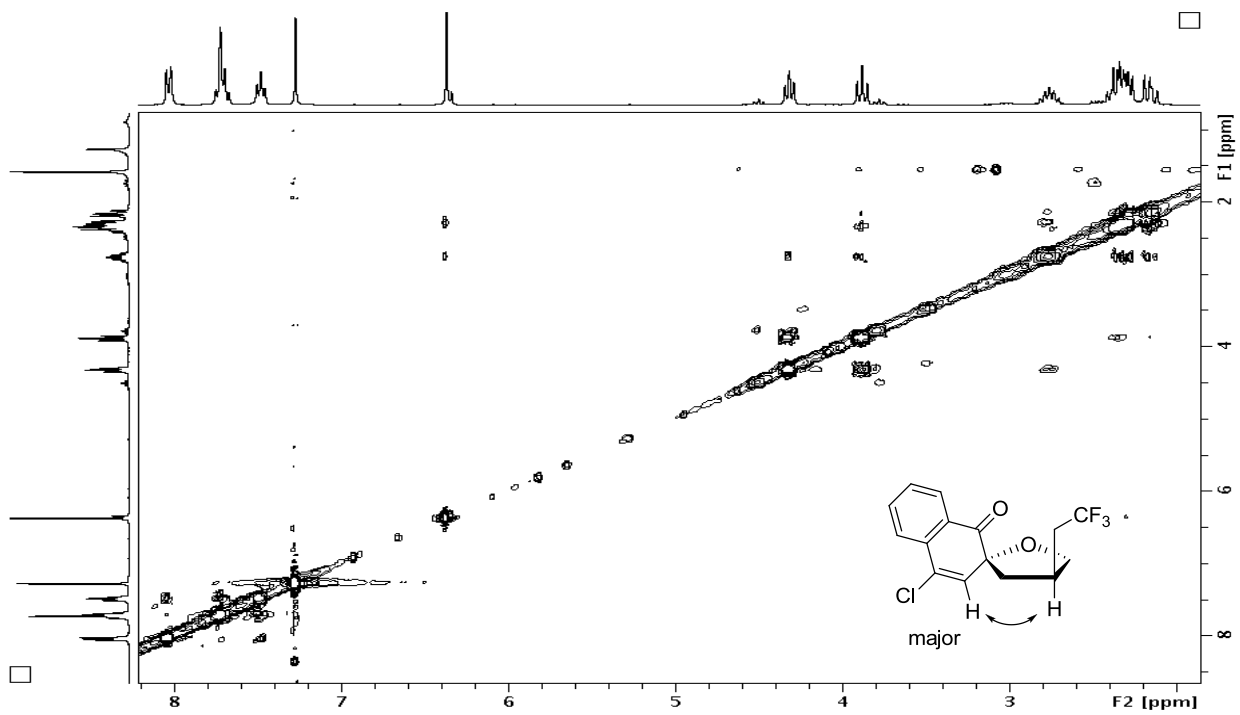
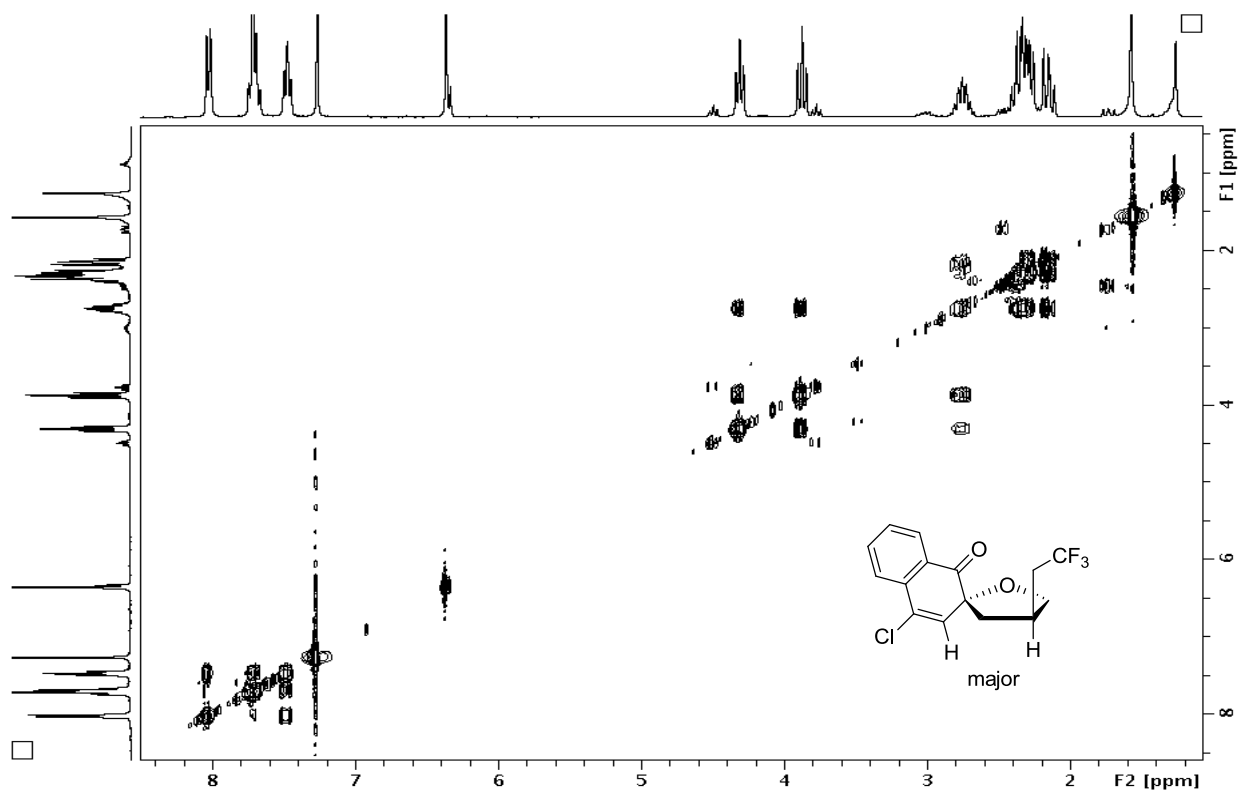


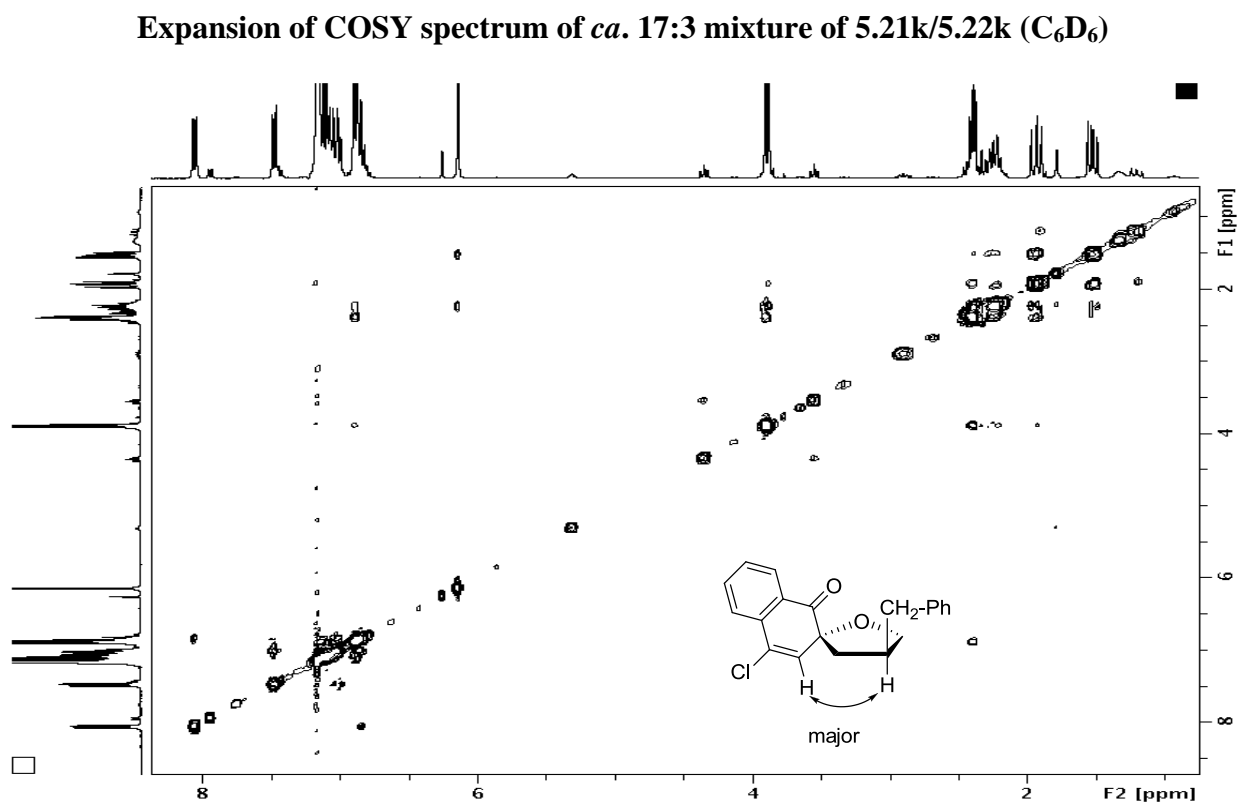
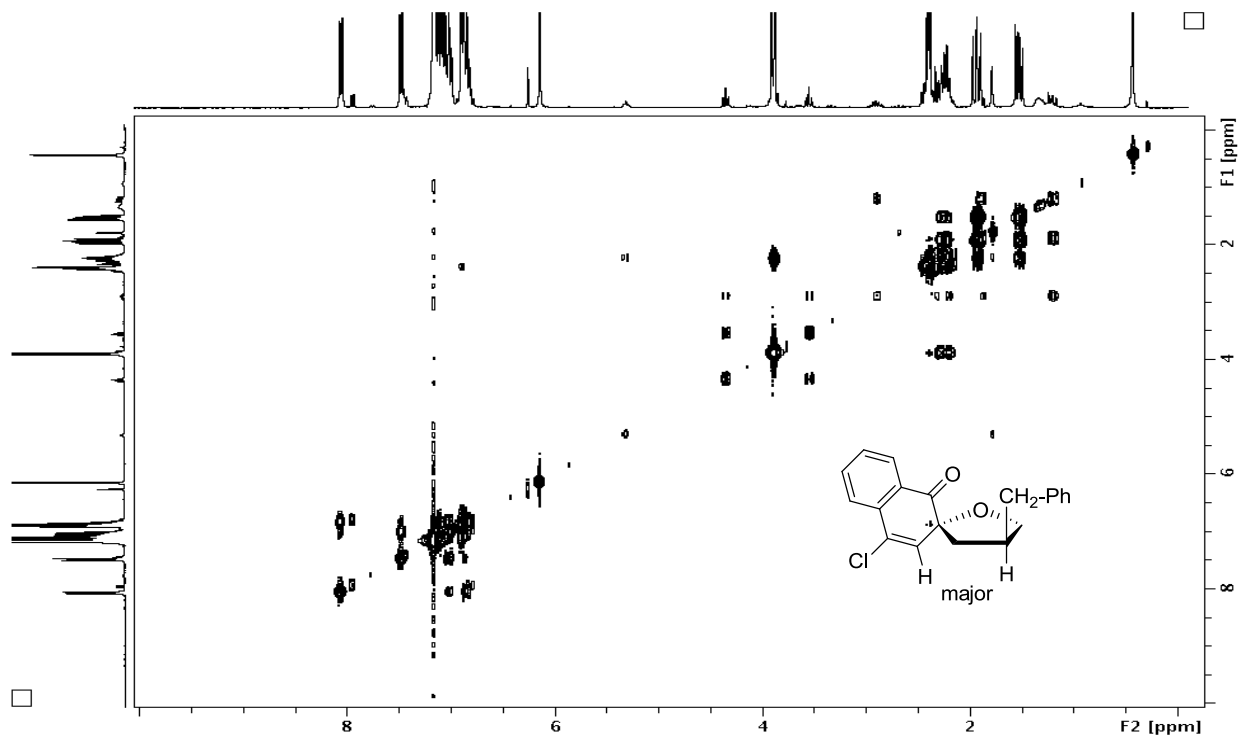
Expansion of COSY spectrum of 5.21n (CDCl₃)

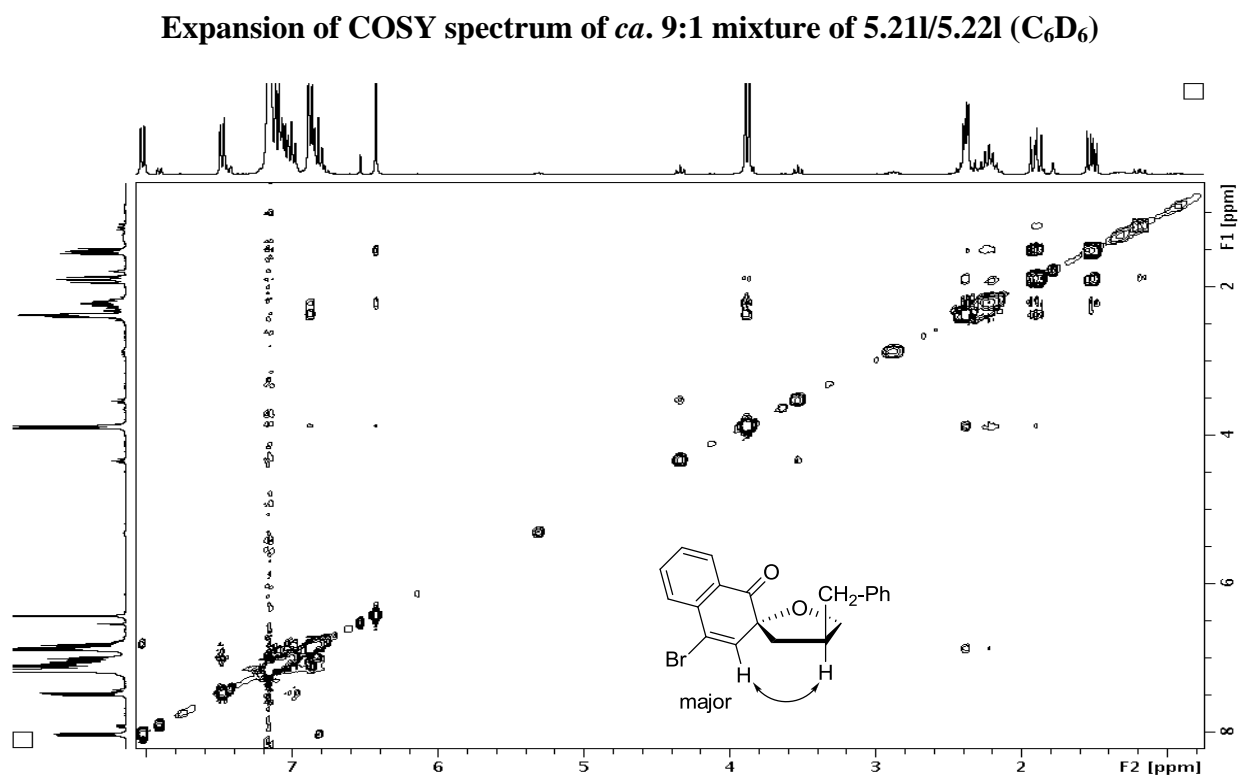
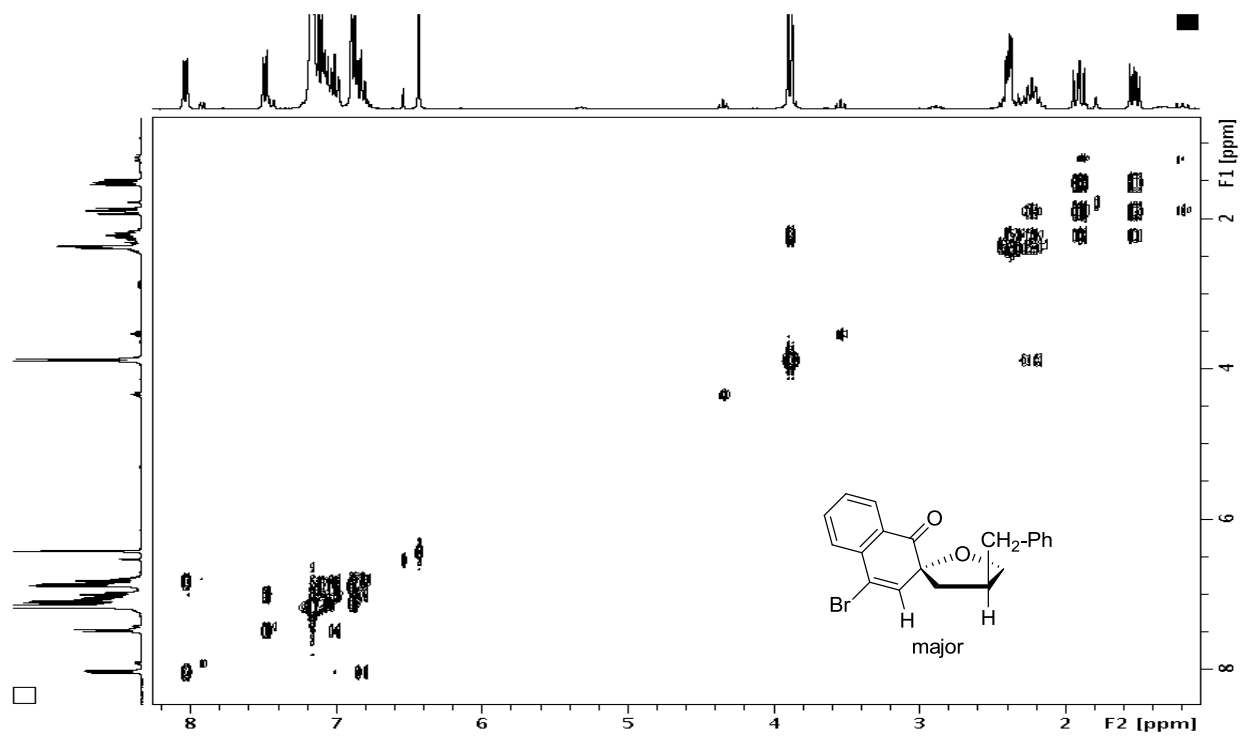


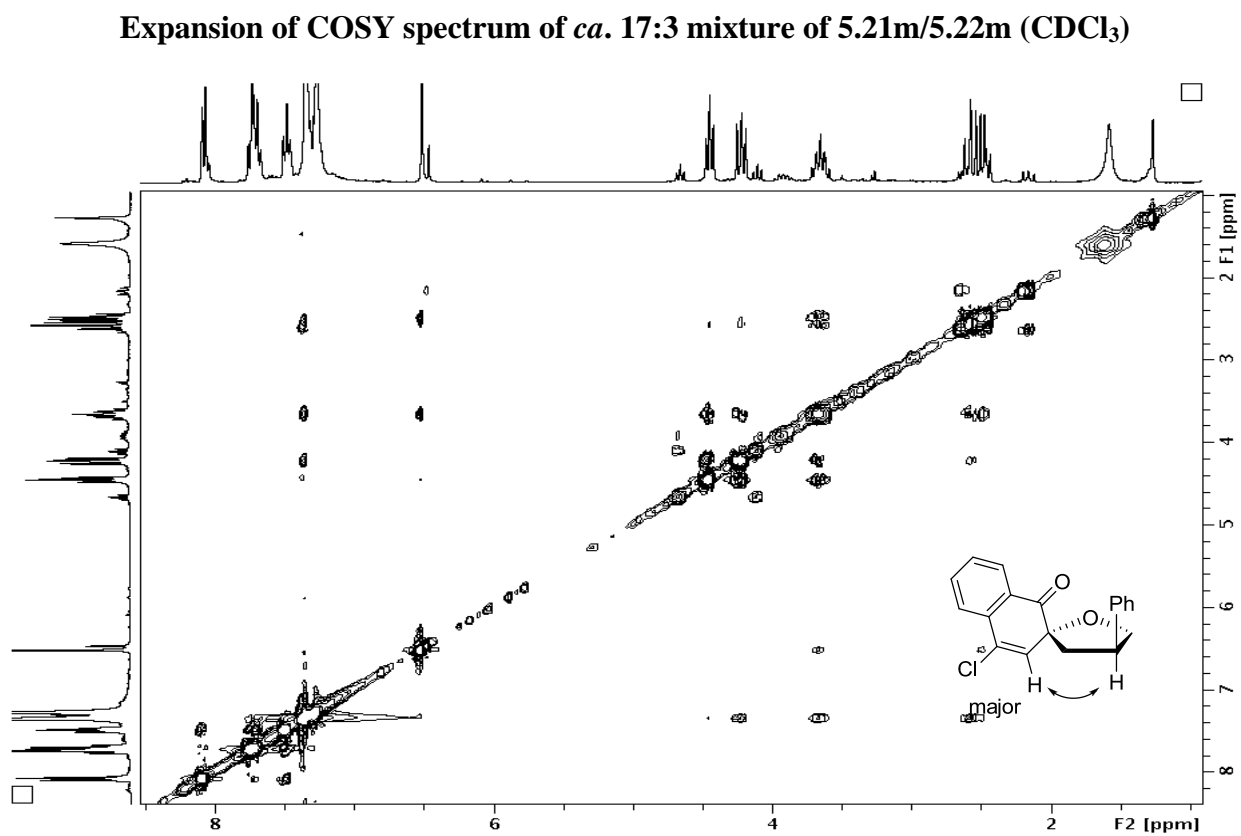
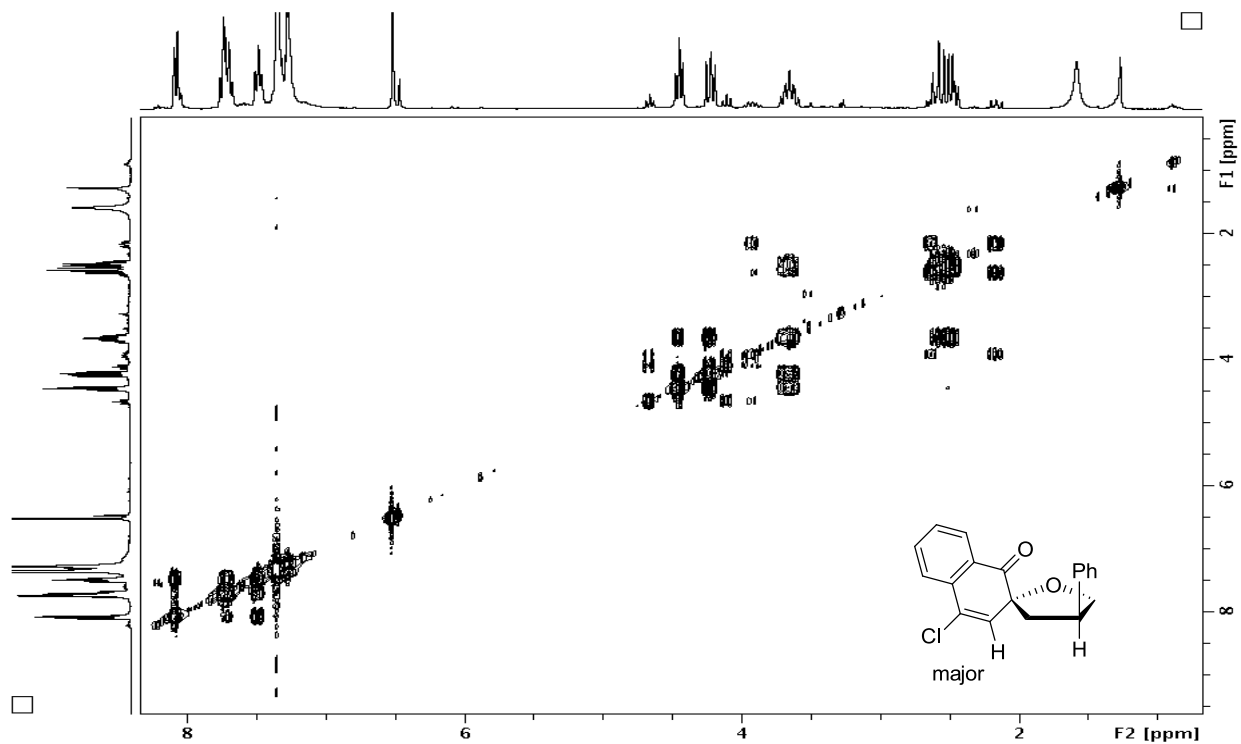
Expansion of NOESY spectrum of 5.21n (CDCl₃)





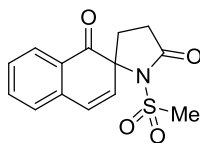
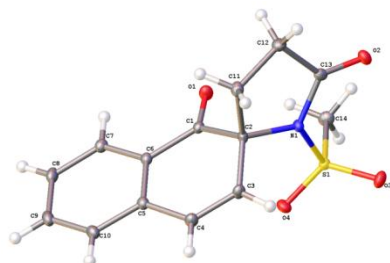






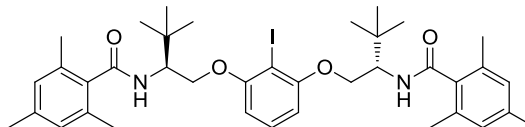
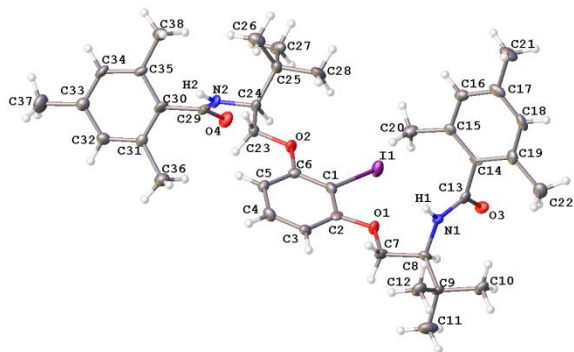
E. X-ray Crystal Data

X-ray crystal data of (±)-4.9a



Empirical Formula	C ₁₄ H ₁₃ NO ₄ S
Formula Weight	291.31
Crystal Colour, Habit	colourless, irregular
Crystal Dimensions	0.13 x 0.25 x 0.26 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 7.3286(4) Å b = 8.1385(4) Å c = 11.4208(6) Å α = 88.802(1)° β = 80.059(1)° γ = 73.259(1)° V = 642.22(6) Å ³
Space Group	<i>P</i> -1 (#2)
Z value	2
D _{calc}	1.506 g/cm ³
F ₀₀₀	304.00
μ (Mo-Kα)	2.65 cm ⁻¹
Diffractometer	Bruker APEX DUO
Radiation	Mo-Kα (λ = 0.71073 Å)
Data Images	2088 exposures @ 2.0 seconds
Detector Position	40.17 mm
2θ _{max}	60.1°
No. of Reflections Measured	Total: 15696 Unique: 3764 (R _{int} = 0.027)
Residuals (refined on F ² , all data): R1; wR2	0.034; 0.083
Residuals (refined on F ²): R1; wR2	0.030; 0.080
Goodness of Fit Indicator	1.05

X-ray crystal data of (*R,R*)-4.52



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{38}H_{51}N_2O_4I$
726.70
colourless, blade
0.06 x 0.10 x 0.23 mm
monoclinic
Primitive
 $a = 9.7410(6) \text{ \AA}$
 $b = 31.6135(18) \text{ \AA}$
 $c = 12.9116(8) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 110.980(1)^\circ$
 $\gamma = 90^\circ$
 $V = 3712.5(4) \text{ \AA}^3$

Space Group
Z value
 D_{calc}
F000

$P 2_1 (\#4)$
4
1.300 g/cm³
1512.00

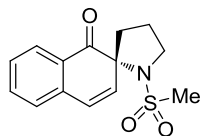
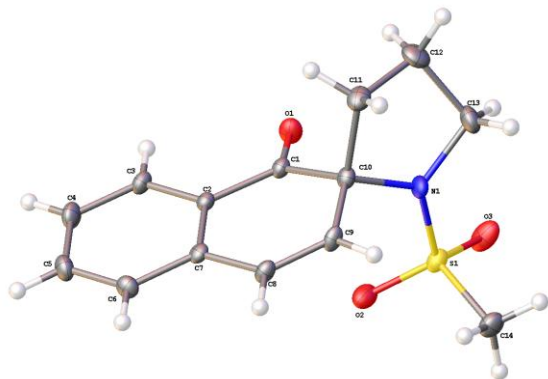
μ (Mo-K α)
Diffractometer
Radiation
Data Images
Detector Position
 $2\theta_{\text{max}}$
No. of Reflections Measured

9.02 cm⁻¹
Bruker APEX DUO
Mo-K α ($\lambda = 0.71073 \text{ \AA}$)
1754 exposures @ 10.0 seconds
40.12 mm
50.8 $^\circ$
Total: 46324
Unique: 13589 ($R_{\text{int}} = 0.058$)

Residuals (refined on F^2 , all data): R1; wR2
Residuals (refined on F^2): R1; wR2
Goodness of Fit Indicator

0.052; 0.068
0.039; 0.065
1.05

X-ray crystal data of (+)-(R)-4.2a



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{14}H_{15}NO_3S$
277.33
colourless, prism
0.15 x 0.18 x 0.20 mm
tetragonal
Primitive
 $a = 7.0473(6) \text{ \AA}$
 $b = 7.0473 \text{ \AA}$
 $c = 53.220(5) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 90^\circ$
 $\gamma = 90^\circ$
 $V = 2643.1(5) \text{ \AA}^3$

Space Group
Z value
D_{calc}
F₀₀₀

$P 4_1 2_1 2$ (#2)
8
1.394 g/cm³
1168.00

μ (Mo-K α)
Diffractometer
Radiation
Data Images
Detector Position
 $2\theta_{\text{max}}$

2.48 cm⁻¹
Bruker APEX DUO
Mo-K α ($\lambda = 0.71073 \text{ \AA}$)
2802 exposures @ 6.0 seconds
69.81 mm
60.3°

No. of Reflections Measured

Total: 21399
Unique: 3868 ($R_{\text{int}} = 0.065$)

Residuals (refined on F^2 , all data): R1; wR2

0.053; 0.106

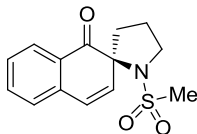
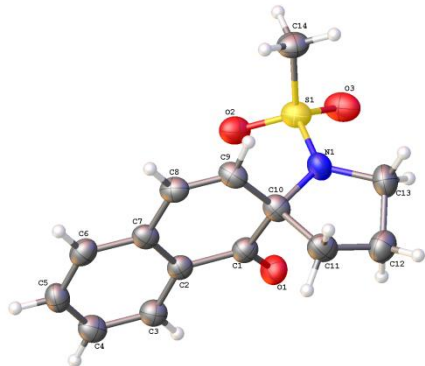
Residuals (refined on F^2): R1; wR2

0.048; 0.105

Goodness of Fit Indicator

1.15

X-ray crystal data of (-)-(S)-4.2a



Empirical Formula

Formula Weight

Crystal Colour, Habit

Crystal Dimensions

Crystal System

Lattice Type

Lattice Parameters

$C_{14}H_{15}NO_3S$

277.33

colourless, irregular

0.08 x 0.12 x 0.13 mm

tetragonal

primitive

$a = 7.0495(3) \text{ \AA}$

$b = 7.0495(3) \text{ \AA}$

$c = 53.102(3) \text{ \AA}$

$\alpha = 90^\circ$

$\beta = 90^\circ$

$\gamma = 90^\circ$

$V = 2638.9(3) \text{ \AA}^3$

$P 4_32_12(\#96)$

8

1.396 g/cm^3

1168.00

22.20 cm^{-1}

Bruker APEX DUO

Cu-K α ($\lambda = 1.54178 \text{ \AA}$)

2258 exposures @ 5.0 seconds

49.84 mm

115.9°

Total: 43862

Unique: 1830 ($R_{\text{int}} = 0.077$)

Space Group

Z value

D_{calc}

F000

μ (Mo-K α)

Diffractometer

Radiation

Data Images

Detector Position

$2\theta_{\text{max}}$

No. of Reflections Measured

Residuals (refined on F^2 , all data): R1; wR2

Residuals (refined on F^2): R1; wR2

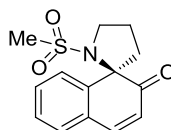
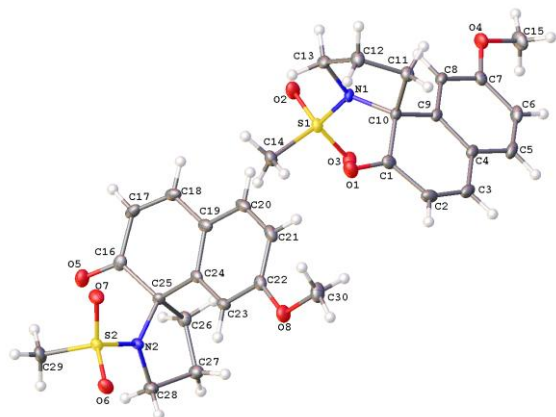
Goodness of Fit Indicator

0.049; 0.110

0.045; 0.108

1.06

X-ray crystal data of (+)-(*R*)-4.5b



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{15}H_{17}NO_4S$
307.35
colourless, plate
0.13 x 0.21 x 0.52 mm
monoclinic
primitive
 $a = 7.0932(8) \text{ \AA}$
 $b = 12.206(2) \text{ \AA}$
 $c = 16.105(2) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 91.429(5)^\circ$
 $\gamma = 90^\circ$
 $V = 1393.9(4) \text{ \AA}^3$
 $P 2_1(\#4)$

Space Group
Z value

4
1.465 g/cm³

D_{calc}
F000

648.00

μ (Mo-K α)

2.48 cm⁻¹

Diffractometer

Bruker APEX DUO

Radiation

Mo-K α ($\lambda = 0.71073 \text{ \AA}$)

Data Images

2319 exposures @ 10.0 seconds

Detector Position

39.70 mm

$2\theta_{\text{max}}$

55.9 $^\circ$

No. of Reflections Measured

Total: 34959

Unique: 10906 ($R_{\text{int}} = 0.038$)

Residuals (refined on F^2 , all data): R1; wR2

0.039; 0.091

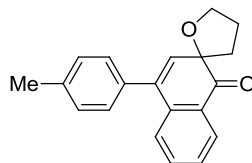
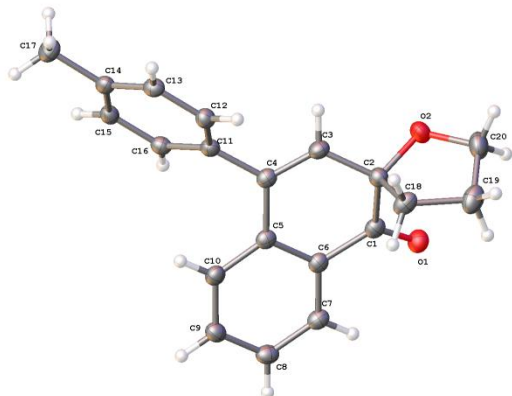
Residuals (refined on F^2): R1; wR2

0.034; 0.086

Goodness of Fit Indicator

1.04

X-ray crystal data of (±)-5.2e



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{20}H_{18}O_2$
290.34
colourless, irregular
0.12 x 0.18 x 0.23 mm
monoclinic
Primitive
 $a = 12.3309(11) \text{ \AA}$
 $b = 16.2475(14) \text{ \AA}$
 $c = 7.4239(6) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 100.837(5)^\circ$
 $\gamma = 90^\circ$
 $V = 1460.8(2) \text{ \AA}^3$
 $P2_1/c$ (#14)

Space Group
Z value

4

D_{calc}

1.320 g/cm³

F000

616.00

μ (Mo-K α)

6.62 cm⁻¹

Diffractometer

Bruker APEX DUO

Radiation

Cu-K α ($\lambda = 1.54178 \text{ \AA}$)

Data Images

1344 exposures @ 5.0 seconds

Detector Position

59.81 mm

$2\theta_{\text{max}}$

136.7 $^\circ$

No. of Reflections Measured

Total: 9993

Unique: 2626 ($R_{\text{int}} = 0.039$)

Residuals (refined on F^2 , all data): R1; wR2

0.058; 0.145

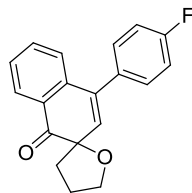
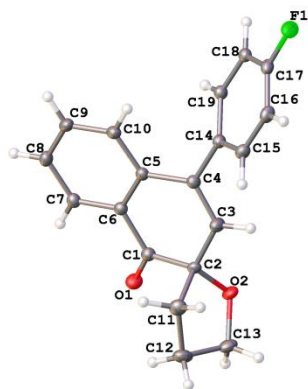
Residuals (refined on F^2): R1; wR2

0.052; 0.137

Goodness of Fit Indicator

1.05

X-ray crystal data of (±)-5.2h



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{19}H_{15}O_2F$
294.31
colourless, irregular
0.12 x 0.16 x 0.26 mm
monoclinic
primitive
 $a = 7.3019(3) \text{ \AA}$
 $b = 11.2896(5) \text{ \AA}$
 $c = 17.3944(8) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 100.618(2)^\circ$
 $\gamma = 90^\circ$
 $V = 1409.36(11)(5) \text{ \AA}^3$

Space Group
Z value
 D_{calc}
F000

$P 2_1/c$ (#14)
4
 1.387 g/cm^3
616.00

μ (Mo- $K\alpha$)
Diffractometer
Radiation
Data Images
Detector Position

0.98 cm^{-1}
Bruker X8 APEX II
Mo $K\alpha$ ($\lambda = 0.71073 \text{ \AA}$)
4407 exposures @ 5.0 seconds
39.84 mm

$2\theta_{\text{max}}$
No. of Reflections Measured

60.1°
Total: 66169
Unique: 4115 ($R_{\text{int}} = 0.036$)

Residuals (refined on F^2 , all data): R1; wR2

0.052; 0.119

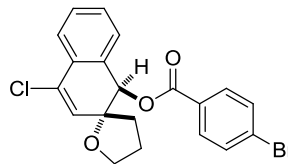
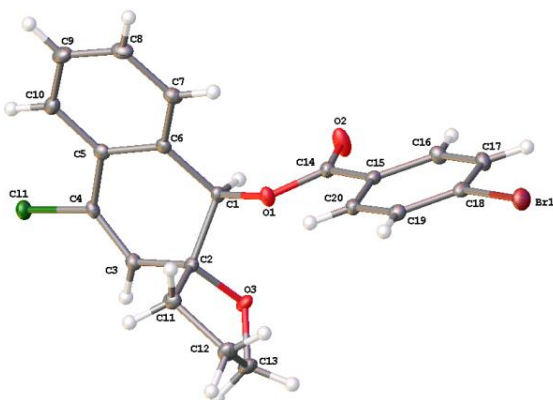
Residuals (refined on F^2): R1; wR2

0.050; 0.118

Goodness of Fit Indicator

1.20

X-ray crystal data of (-)-(R,R)-5.13



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{20}H_{16}BrClO_3$
419.69
colourless, plate
0.12 x 0.20 x 0.23 mm
orthorhombic
Primitive
 $a = 9.3570(3) \text{ \AA}$
 $b = 10.8815(3) \text{ \AA}$
 $c = 17.3083(5) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 90^\circ$
 $\gamma = 90^\circ$
 $V = 1762.30(9) \text{ \AA}^3$
 $P 2_12_12_1$ (#19)

Space Group
Z value

4

D_{calc}

1.582 g/cm^3

F000

848.00

μ (Mo-K α)

25.00 cm^{-1}

Diffractometer

Bruker APEX DUO

Radiation

Mo-K α ($\lambda = 0.71073 \text{ \AA}$)

Data Images

1302 exposures @ 3.0 seconds

Detector Position

60.01 mm

$2\theta_{\text{max}}$

60.0°

No. of Reflections Measured

Total: 20702

Unique: 5138 ($R_{\text{int}} = 0.027$)

Residuals (refined on F^2 , all data): R1; wR2

0.023; 0.049

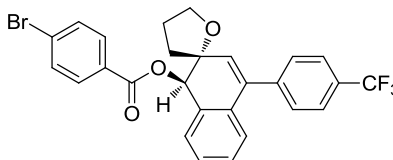
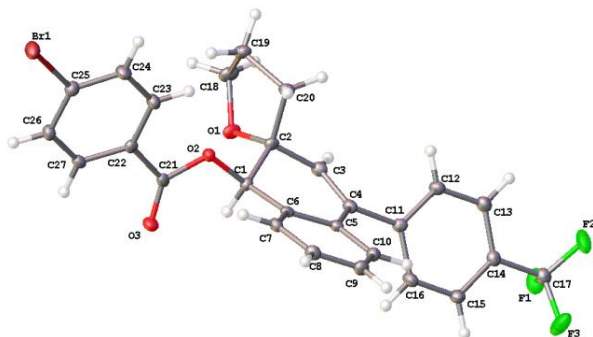
Residuals (refined on F^2): R1; wR2

0.021; 0.148

Goodness of Fit Indicator

1.05

X-ray crystal data of (-)-(R,R)-5.16



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{27}H_{20}F_3O_3Br$
529.34
colourless, blade
0.12 x 0.15 x 0.31 mm
monoclinic
Primitive
 $a = 8.9303(4) \text{ \AA}$
 $b = 9.5597(5) \text{ \AA}$
 $c = 13.7624(6) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 103.8250(10)^\circ$

$\gamma = 90^\circ$
 $V = 1140.87(9) \text{ \AA}^3$

Space Group

$P 2_1 (\#2)$

Z value

2

D_{calc}

1.541 g/cm^3

F000

3616.00

μ (Mo- $K\alpha$)

18.54 cm^{-1}

Diffractometer

Bruker APEX DUO

Radiation

Mo- $K\alpha$ ($\lambda = 0.71073 \text{ \AA}$)

Data Images

1829 exposures @ 3.0 seconds

Detector Position

40.14 mm

$2\theta_{max}$

60.1°

No. of Reflections Measured

Total: 24565

Unique: 6691 ($R_{int} = 0.027$)

Residuals (refined on F^2 , all data): R1; wR2

0.028; 0.058

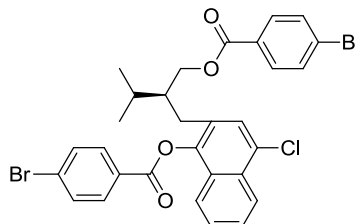
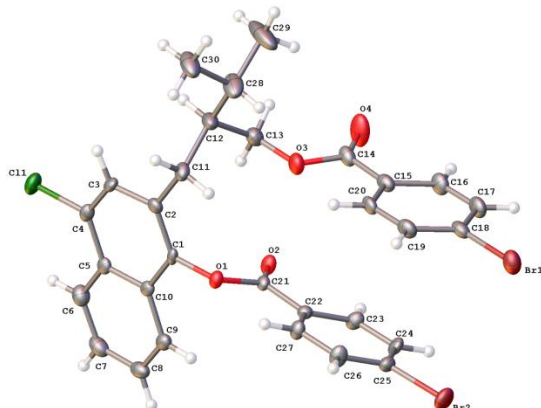
Residuals (refined on F^2): R1; wR2

0.025; 0.057

Goodness of Fit Indicator

1.02

X-ray crystal data of (-)-(S)-5.27



Empirical Formula
Formula Weight
Crystal Colour, Habit
Crystal Dimensions
Crystal System
Lattice Type
Lattice Parameters

$C_{30}H_{25}Br_2O_4Cl$
644.77
colourless, blade
0.02 x 0.10 x 0.60 mm
orthorhombic
Primitive
 $a = 6.3355(3) \text{ \AA}$
 $b = 18.8615(10) \text{ \AA}$
 $c = 22.9044(11) \text{ \AA}$

$\alpha = 90^\circ$
 $\beta = 90^\circ$
 $\gamma = 90^\circ$
 $V = 2737.0(2) \text{ \AA}^3$
 $P 2_12_12_1$ (#19)

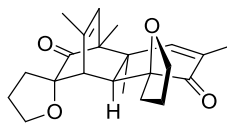
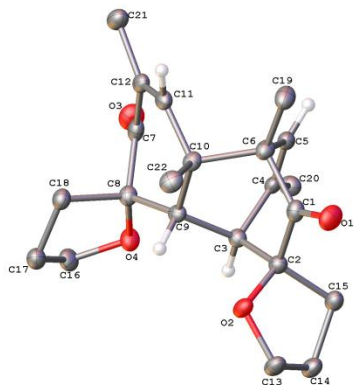
Space Group
Z value
 D_{calc}
F000
 μ (Mo-K α)
Diffractometer
Radiation
Data Images
Detector Position
 $2\theta_{\text{max}}$
No. of Reflections Measured

4
1.565 g/cm³
1296.00
30.94 cm⁻¹
Bruker APEX DUO
Mo-K α ($\lambda = 0.71073 \text{ \AA}$)
1016 exposures @ 30.0 seconds
50.12 mm
50.8 $^\circ$
Total: 19498
Unique: 5028 ($R_{\text{int}} = 0.043$)

Residuals (refined on F^2 , all data): R1; wR2
Residuals (refined on F^2): R1; wR2
Goodness of Fit Indicator

0.040; 0.058
0.030; 0.055
1.02

X-ray crystal data of (-)-(S,S)-5.5



Empirical Formula	C ₂₂ H ₂₈ O ₄
Formula Weight	356.44
Crystal Colour, Habit	colourless, tablet
Crystal Dimensions	0.08 x 0.18 x 0.35 mm
Crystal System	monoclinic
Lattice Type	primitive
Lattice Parameters	a = 10.3039(5) Å b = 13.7016(6) Å c = 13.1209(7) Å α = 90° β = 91.850(2)° γ = 90° V = 1851.4(2) Å ³
Space Group	P 2 ₁ (#4)
Z value	4
D _{calc}	1.279 g/cm ³
F ₀₀₀	768.00
μ (Mo-Kα)	6.94 cm ⁻¹
Diffractometer	Bruker APEX DUO
Radiation	Cu-Kα (λ = 1.54178 Å)
Data Images	3093 exposures @ 2.0 and 5.0 seconds
Detector Position	49.90 mm
2θ _{max}	133.0°
No. of Reflections Measured	Total: 22844 Unique: 10875 (R _{int} = 0.041)
Residuals (refined on F ² , all data): R1; wR2	0.037; 0.099
Residuals (refined on F ²): R1; wR2	0.036; 0.094
Goodness of Fit Indicator	1.10