Studies on C–H-Activation, Organocatalysis, and Synthesis of Amphidinolide Q

Studien zur C–H-Aktivierung, Organokatalyse und Synthese von Amphidinolide Q

Dissertation

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Parts of this work have been published

Publications:

"Formal Total Synthesis of Amphidinolide Q"

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"C–H-Activation approach towards the core structure of the alkaloid γ-lycorane"

Mishra, V. K.; Ravikumar, P. C.; Maier, M. E. *Tetrahedron* **2016**, *72*, 6499-6509.

"TADEADOL-based phosphoric acid Catalyzed Enantioselective Friedel-Crafts Reaction of Indoles with Sulfonimines"

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Oral & Poster presentation:

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This research was carried out from October 2013 to July 2016 at the Institut für Organische Chemie, Mathematisch-Naturwissenschaftliche Fakultät, Eberhard Karls Universität Tübingen, Germany, under the guidance of Prof. Dr. Martin E. Maier in collaboration with Prof. Dr. P. C. Ravikumar (NISER, Bhubaneshwar, Odisa, India).

Other Publication:

"*An Unusual Chemoselective Oxidation Strategy by an Unprecedented Exploration of an Electrophilic Center of DMSO: A New Facet to Classical DMSO Oxidation*"

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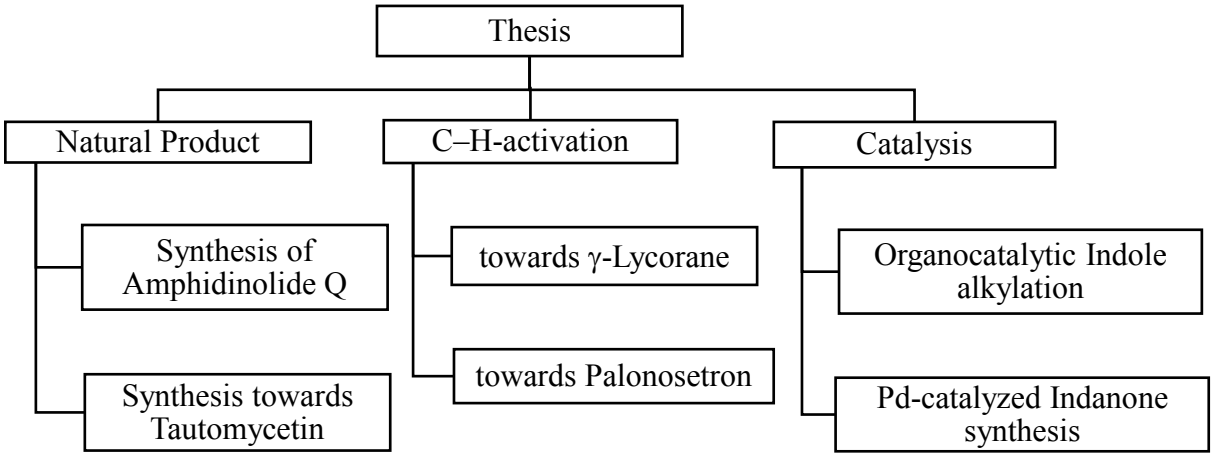
Table of contents

Abstract (English)

This thesis contains several independent projects, covering three aspects of organic chemistry: natural product synthesis, C–H-activation, and organocatalysis. The total synthesis part is concerned about the synthesis of Amphidinolide Q. The C–H-activation part is devoted its application towards natural products γ-Lycorane and Palonosetron. The third part describes the catalysis development and application of a new phosphoric acid based catalyst.

structure of the work



Amphidinolides are a family of cytotoxic macrolides with significant antitumor properties. This family has two 12-membered Amphidinolides, named Amp Q and Amp W. Structurally both Amphidinolides are significantly different. Amp Q was isolated from the cultured dinoflagellate *Amphidinium* sp (Y-5 strain). It exhibits moderate cytotoxicity against murine lymphoma L1210 cells in vitro (IC_{50} = 6.4 μg/mL). It has a very noble structure which contains one α,β-unsaturated ester, one exomethylene, one hydroxy and four methyl units generating all together five stereocenteres, which attracted us for synthesis. Starting from *meso*-2,4-dimethylglutaric anhydride we had successfully completed a formal total synthesis of the Amphidinolide Q. The key steps of this synthesis include a Noyori transfer hydrogenation, Ferringa-Minnaard asymmetric cuprate addition, Mannich reaction, and Yamaguchi macrolactonization.

Tautomycetin is a polyketide, which was isolated from the culture of *Streptomyces griseochromogenes* in 1989. It exhibits cytotoxicity against fungi, yeasts and animal cells. It was synthesized by Oikawa and Shibasaki groups. We were interested in the study of a reductive aldol reaction towards the synthesis of the C1–C18 fragment of tautomycetin.

C–H-activation is a powerful tool towards the synthesis of complex structures. Till the time its application in the synthesis of natural product was rarely known. We have successfully applied this technique in the synthesis of derivatives of γ-Lycorane and a fragment of Palonosetron.

The synthesis of complex bioactive molecules would not be possible without having suitable synthetic methods. Therefore, development of new synthetic methodologies is required. Within

the huge collections of synthetic approaches, the highest diversity and productivity is provided by catalytic methods. We have developed a phosphoric acid based chiral catalyst which is capable to promote enantioselective indole alkylation with imines.

The whole study uses NMR as the main analytical tool. Other methods used in confirmation of the compounds are X-ray structure analysis and high resolution mass spectrometry (ESI-HRMS).

Abstract (German)

Diese Arbeit enthält mehrere unabhängige Projekte, die sich auf drei Aspekte der organischen Chemie beziehen: Synthese von Amphidinolid Q, C–H-Aktivierung und asymmetrische Organokatalyse. Amp Q zeigt in vitro eine mäßige Zytotoxizität gegenüber murinen Lymphom-L1210-Zellen (IC_{50} = 6.4 μg/ml). Wir haben erfolgreich die formale Totalsynthese des Amp Q ausgehend von *meso*-2,4-Dimethylglutarsäureanhydrid realisiert. Die wichtigsten Schritte dieser Synthese sind die Noyori-Transferhydrierung, die asymmetrische Feringa-Minnaard-Cuprat-Addition, die Mannich-Reaktion und die Yamaguchi-Makrolactonisierung. Die C–H-Aktivierung ist ein mächtiges Werkzeug zur Synthese komplexer Strukturen. Bis dahin war seine Anwendung bei der Synthese von Naturprodukten kaum bekannt. Wir haben diese Technik erfolgreich bei der Synthese von Derivaten von γ-Lycoran und einem Fragment von Palonosetron angewendet. Innerhalb der riesigen Sammlung synthetischer Methoden wird die höchste Diversität und Produktivität durch katalytische Ansätze gewährleistet. Wir haben einen chiralen Katalysator auf Phosphorsäurebasis entwickelt, der in zur enantioselektiven Alkylierung von Indolen mit Iminen fähig ist.

Abbreviations

abs	absolute
Ac	Acetyl
ACh	Acetylcholine
AIBN	Azobisisobutyronitrile
aq	aqueous
BBN (9-)	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
br	broad
Cbz	Carboxybenzyl
Con.	Concentration
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
CSA	Camphosulfonic acid
Cy	Cyclohexyl
δ	Chemical shift in ppm (NMR)
d	Doublet (NMR)
DBPO	(Di-)Benzoylperoxid
DBDMH	1,3-Dibromo-5,5-Dimethylhydantoin
DCE	Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	trans
ee	Enantiomeric excess
eq	equation
ESI	Electronspray ionization
Et	Ethyl

Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Fig.	Figure
g	gram
h	Hour(s)
Hex.	Hexane
HMDS	Hexamethyldisilazane
HOMO	Highest occupied molecular orbital
HPLC	high performance liquid chromatography
J	coupling constant
L	Liter(s)
LA	Lewis acid
PCC	Pyridinium chlorochromate
Piv.	Pivaloyl
*i*Pr	isopropyl
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet (NMR)
*m*CPBA	*meta*-perbenzoic acid
Me	methyl
MeOH	Methanol
mg	milligram
µg	microgram
MOM	Methoxymethyl
MVK	Methyl vinyl ketone
m/z	Mass to charge ratio (MS)
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
PPTS	Pyridinium *para*-toluenesulfonate
pTSA	*para*-Toluenesulfonic acid
Py	Pyridine
q	Quartet (NMR)
R_f	Retention factor (TLC)
rt	Room temperature (ca. 23 °C)
s	Singlet (NMR)

t	Triplet (NMR)
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
Tf_2O	Trifluoromethanesulfonic anhydride
TMS	Trimethylsilyl
Tol.	Toluene
Ts	*p*-Toluenesulfonyl
Z	cis

Chapter 1

Formal Total Synthesis of the Macrolide Amphidinolide Q

1 Introduction

Among nature's creation, macrolides are versatile and exciting natural products due to their diverse biological activities such as antibiotic, cytotoxic, or antiangiogenic. Several macrolides and polyketides have been isolated from symbiotic marine dinoflagellates.[1] Many of them show potent cytotoxicity against murine lymphoma L1210 cells. Macrolactones vary in size from 8-membered (octalactins-**1-2**) to 60-membered (quinolidomicins) (**Figure 1**). Erythromycin (**1-1**) a macrolide isolated in 1952 is widely used to treat bacterial infections, and because of its safety and efficacy, it is still a preferred therapeutic agent for the treatment of respiratory infections. Apoptolidin a 20-membered macrolide, selectively induces apoptosis in rat glia cells transformed with adenovirus E1A oncogene in the presence of normal cells and inhibits the mitochondrial F_0F_1-ATPase.[2] Actin-binding marine macrocyclic lactones, and benzolactone enamides are also possessing potent antitumor activity.

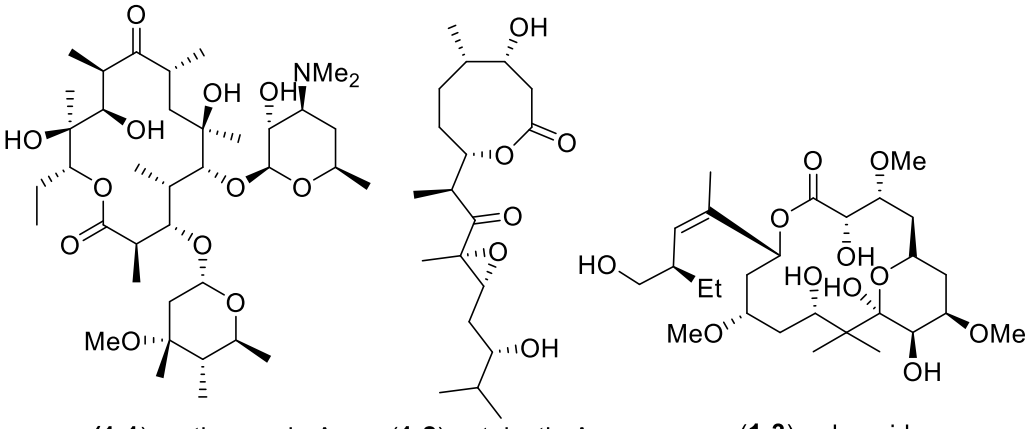


Figure 1. Examples of naturally occurring macrolactones.

A marine microorganism such as bacteria, cyanobacteria, or dinoflagellates produces toxins for their defense mechanism. These toxins are the primary source of fish and algae poisoning. Though these poisons in microgram scale can kill a person but if used in medically administered could be useful for treatment of many fatal diseases such as cancer. Many bioactive substances isolated from marine invertebrates such as sponges, tunicates, and so on have proved to be essential tools in biology for example, neurotoxins like maitotoxins helped to understand the

molecular basis of cellular excitability.[3] Biologically significant secondary metabolites isolated from symbiotic marine dinoflagellates *Amphidinium* sp. called as Amphidinolides. Amp B (**1-6**) increased the ATPase activity of myofibrils and natural actomyosin, resulting increased in contractile responses of myofilaments. Amp H (**1-7**) is a novel F-actin stabilizer that covalently binds on actin.[4] It stabilizes actin similar to phalloidin (**1-9**) but the Amp-H-binding does not compete with phalloidin-binding to F-actin (**Figure 2**).[5]

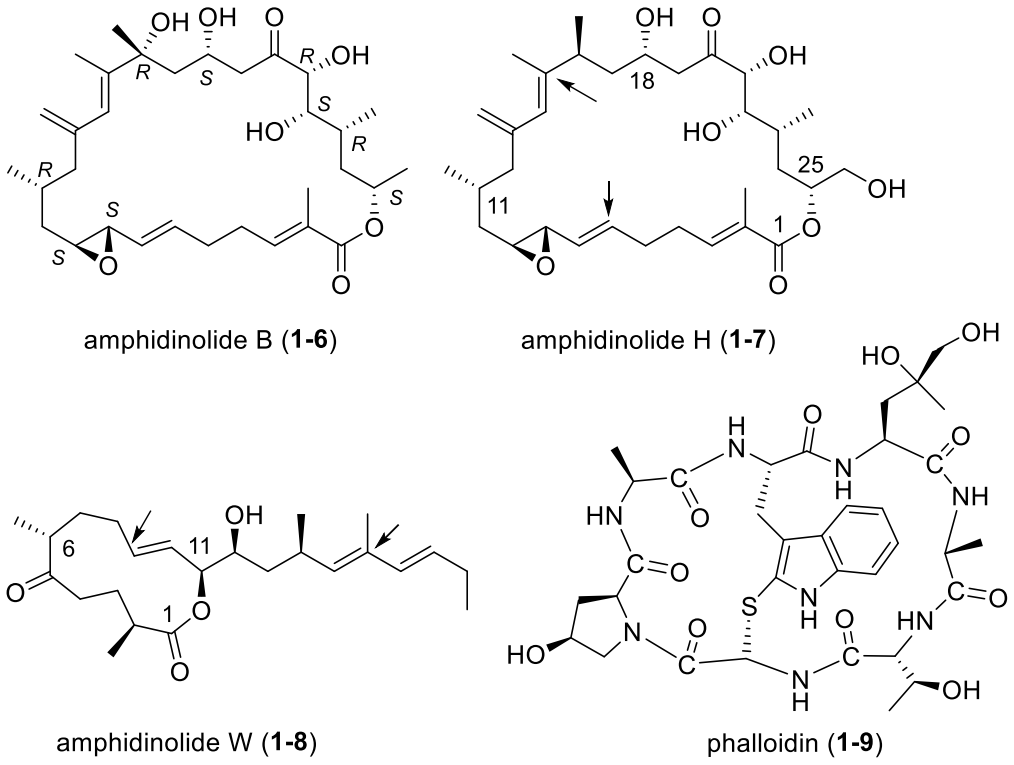


Figure 2. Chemical structure of amphidinolide B, H, W and phalloidin.

Amphidinolide W (**1-8**) and Q (**1-14**) both are 12-membered macrolides and exhibite cytotoxicity against murine lymphoma L1210 cells. Amp W is quite unique as it is the first and only macrolide in its family without an exomethylene unit. The gross structure of the C9–C16 moiety of amphidinolide W corresponds to that of C6–C15 of amp H, which was isolated from strain Y-42, suggesting that amphidinolide W may be biogenetically related to amphidinolide H.[6] Recently four new polyketides, amphidinins C-F have been isolated from the culture broth of symbiotic dinoflagellate *Amphidinium sp* (**Figure 3**). They showed antimicrobial activity against bacteria and/ or fungi. Amphidinin D and F are the first glycosides related to amphidinolides. Spectral analysis led to the suggestion that amphidinins C-F (**1-10**–**1-13**) are 4,5-*seco*-analogues of amp Q (**1-14**).[7]

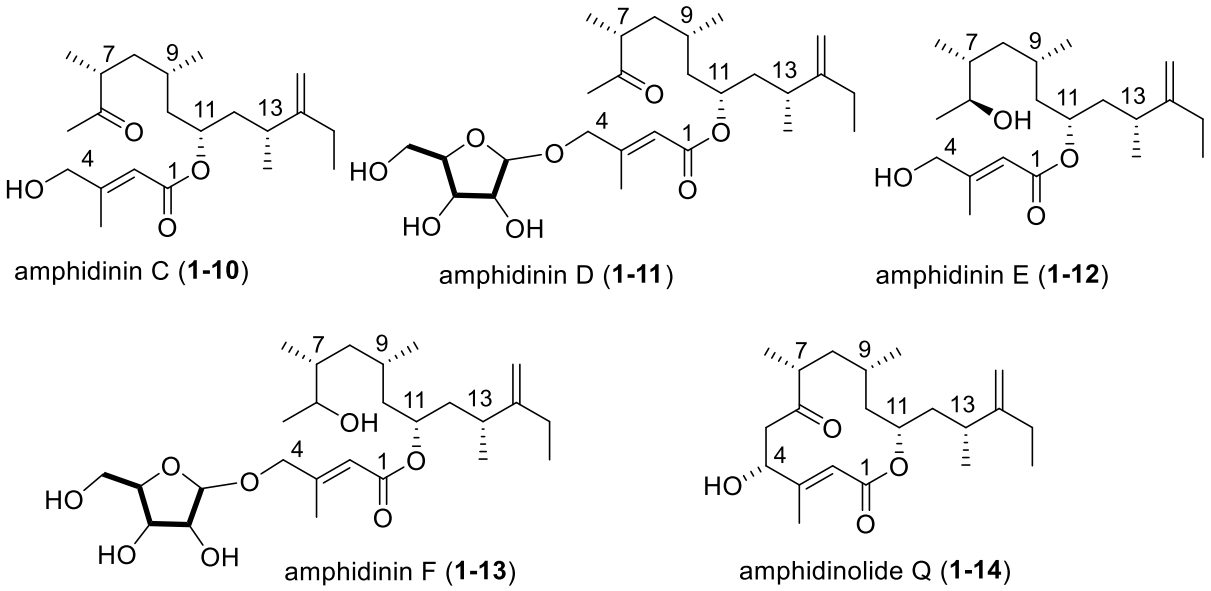


Figure 3. Amphidinins C-F and amphidinolide Q.

Malignancy is a class of epidemic disease related to abnormal cell growth, division and death. Early stage treatment of cancer can decrease the fatality rate. There are several techniques to treat cancer such as surgery, radiotherapy, immunotherapy, chemotherapy etc. In chemotherapy the treatment is done by the use of a pharmaceutical product. It was found, that some amphidinolides exhibits very high cytotoxicity. In this chapter we will discuss about biology of amp H, previous synthesis of amp Q along our investigations.

2 Literature review

2.1 Amphidinolide as anticancer drug

In recent years several proteins have been identified whose overexpression results in several kinds of cancer.[8] The mechanical strength to the cell and its cytoplasmic constituents is provided by the cytoplasmic skeleton. All cytoskeletons contain three constituents units. Microtubules are the largest filament having a diameter of about 25 nm. The structural unit of microtubules is tubulin and the smallest constituent are actin filaments which are 6 nm in diameter and made up of actin protein.

Toxins bind to actin filaments to destabilize it at two distinct regions of actin monomer: (a) the ATP-binding cleft and (b) the barbed end. Actin filaments are dynamic in nature. Amp H forms a residue-specific covalent bond with actin. This interaction occurs between the epoxide and Tyr198 (Tyr200 in mammalian actin) on subdomain 4 of actin. One molecule of toxin seems to bind per actin monomer. Amp H is close to the actin-actin of subdomain 4 of one subunit and subdomain 1 of the diagonally located other subunit in F-actin. This suggests it acts in similar fashion as phalloidin, jasplakinolide and dolastatin do.[9]

2.2 Biosynthesis of amphidinolides

Polyketides were biosynthesized by a complex collection of enzymes known as a polyketide synthase (PKS);[10] the process operates by repeated *thio*-Claisen condensation of malonyl-Co-A and its derivatives [11] in a manner analogous to fatty acid biosynthesis [12] to produce β-ketoester intermediate. The basic enzymatic mechanism involves repetitive arrangement of three fundamental catalytic units such as Ketosynthase (KS), acyltransferase (AT) and acyl carrier protein (ACP). The number of modules present in the PKS is in proportion to the length of the carbon chain of the final product. In addition the modules may also possess modifying domains arranged in various configurations that promote access to the β-hydroxy unit (Ketoreductase, KR), conjugated E alkenes (dehydratase, DH) and fully saturated product (enoyl reductase, ER), terminal thioester domain (TE) responsible for release from enzyme complex depending on the intra or intermolecular availability of nucleophile which may lead the formation of macrolactone or *seco*-acid respectively (**Figure 4**).

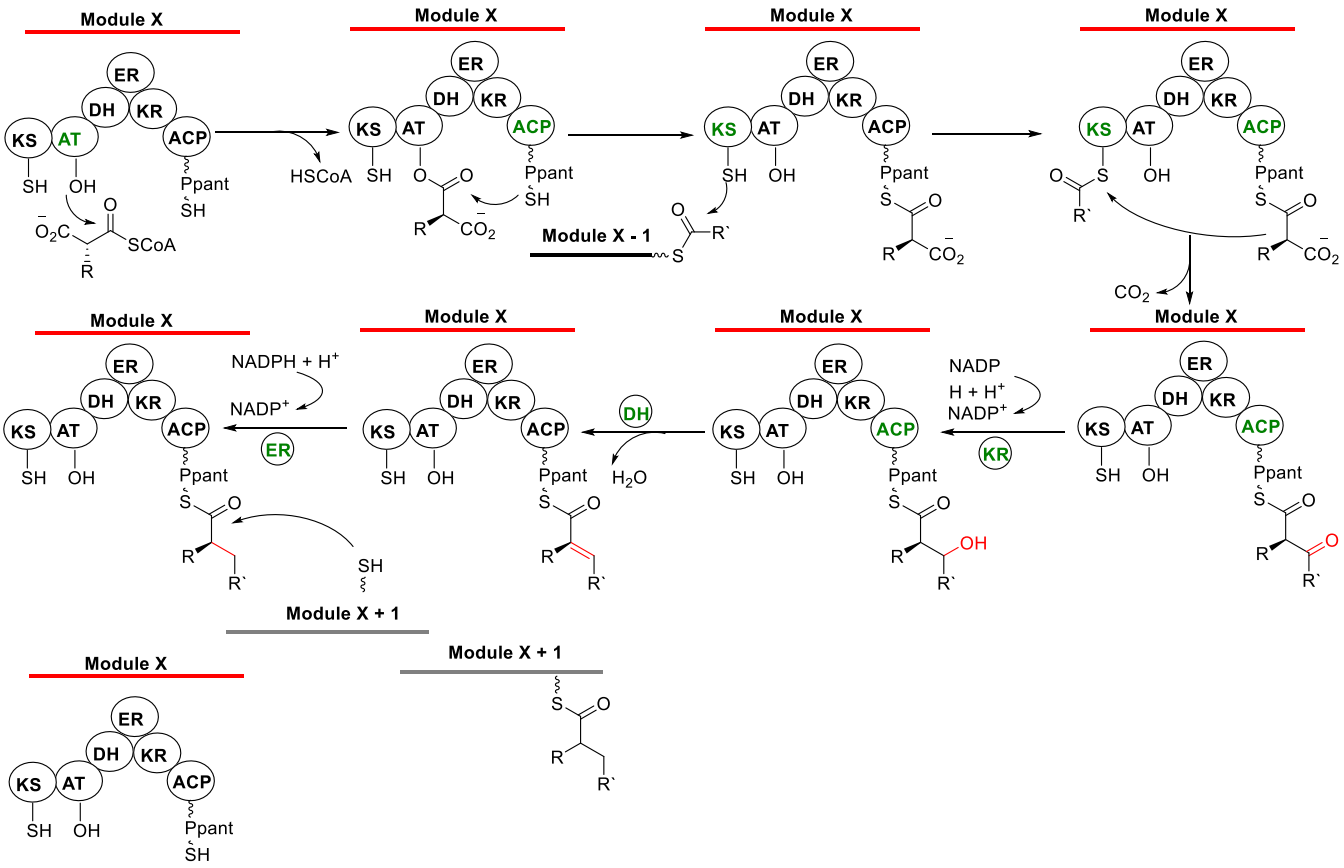


Figure 4. PKS chain elongation of a malonyl-CoA derivative displaying the consensus mechanism for the essential KS-AT-ACP catalytic triad. (R = methyl).

The biosynthetic pattern of amphidinolides were demonstrated[13] on the basis of 2D NMR data of ^{13}C-enriched samples obtained by feeding experiments with [1-^{13}C], [2-^{13}C], and [1,2-$^{13}C_2$] sodium acetates in cultures of a marine dinoflagellate *Amphidinium* sp. These incorporation pattern shows for **1-8 (Figure 5)** that 8 acetate units were directly incorporated for C-3/C-4, C-6/C-7, C-8/C-9, C-10/C-11, C-12/C-13, C-14/C-15, C-16/C-17, and C-19/C-20. The C-6–C-17 portion was likely classical polyketide chains derived from six acetate units, whereas in **1-7** 10 acetate units were directly incorporated for C-3/C-4, C-5/C-6, C-7/C-8, C-9/C-10, C-11/C-12, C-13/C-14, C-17/C-18, C-19/C-20, C-23/C-24, and C-25/C-26 (Fig. 2). These results suggested that three parts from C-3 to C-14, from C-17 to C-20, and from C-23 to C-26 were likely to be classical polyketide chains derived from six, two, and two acetate units, respectively. The four C_1 branches of **1-8** at C-21, C-22, C-23, C-24 and **1-7** at C-27, C-28, C-29, C-30, C-31, and C-32 were all derived from C-2 of acetates, in which the carbonyl carbons were lost. While three irregular labeling patterns (m–m) derived only from C-2 of acetates were observed in **1-7** for C-1/C-2, C-15/C-16, and C-21/C-22.

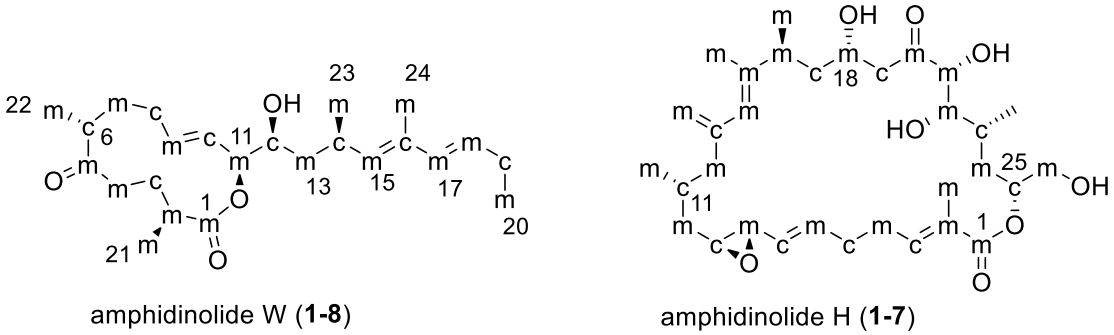
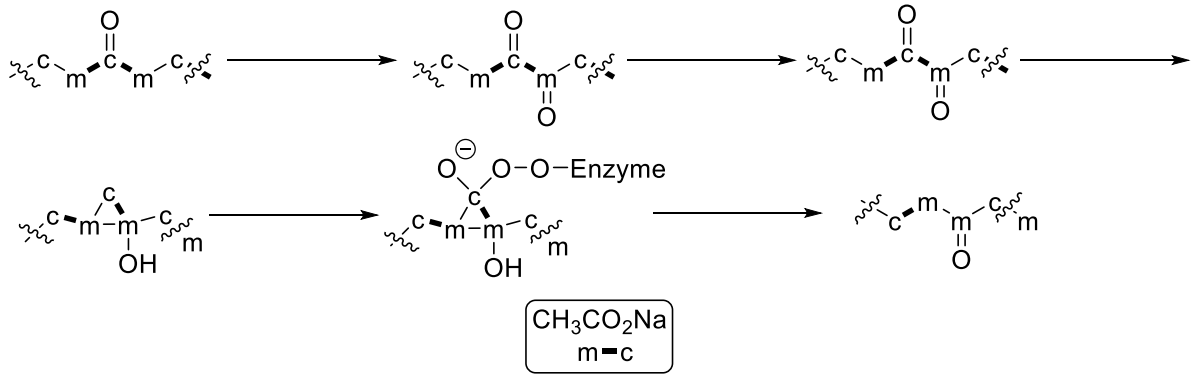


Figure 5. Labeling pattern of amphidinolide W (**1-8**) and amphidinolide H (**1-7**) resulting from feeding experiments with ^{13}C labelled acetates. (m-methyl carbon atom (C1), c-carbonyl carbon atom).

Wright *et al.* postulated the biosynthesis of DTX-4 and amphidinolides J on the basis of isolated carbon atoms from a polyketide chain shown in **Scheme 1**.[14]



Scheme 1. Proposed mechanism for the generation of isolated carbons derived from the methyl group of acetate in the polyketide by Wright *et al*.

2.3 Previous synthesis

The structure of amphidinolide-Q was elucidated by NMR spectroscopy and could be proved by synthesis.[15] The retrosynthesis proposed by Kobayashi *et al*. is outlined in **Figure 6**. Amphidinolide Q was disconnected at the lactone bond; *seco*-acid **2-1** was derived from ketone **2-3** and aldehyde **2-2**.via condensation. The key aldehyde **2-2** containing four stereocenters was prepared from iodide **2-4** via Myers alkylation and Julia coupling of sulfone **2-6** with aldehyde **2-5** could furnish iodide **2-4**.

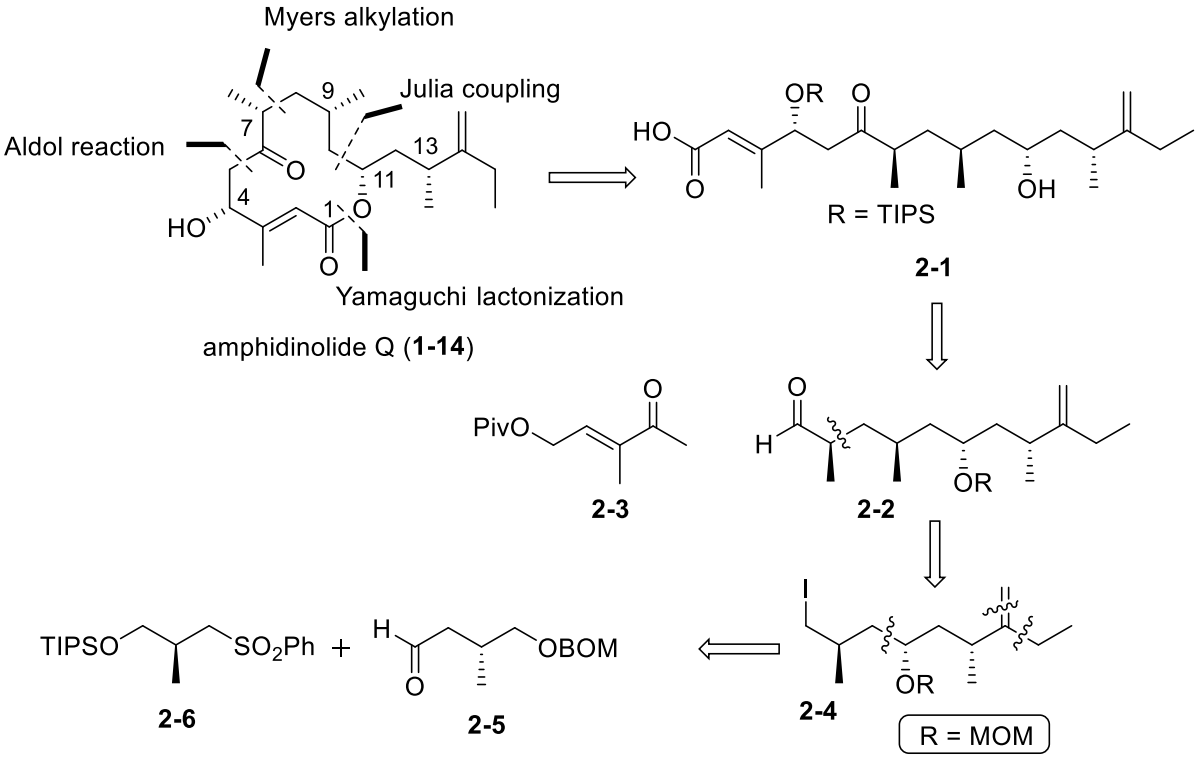
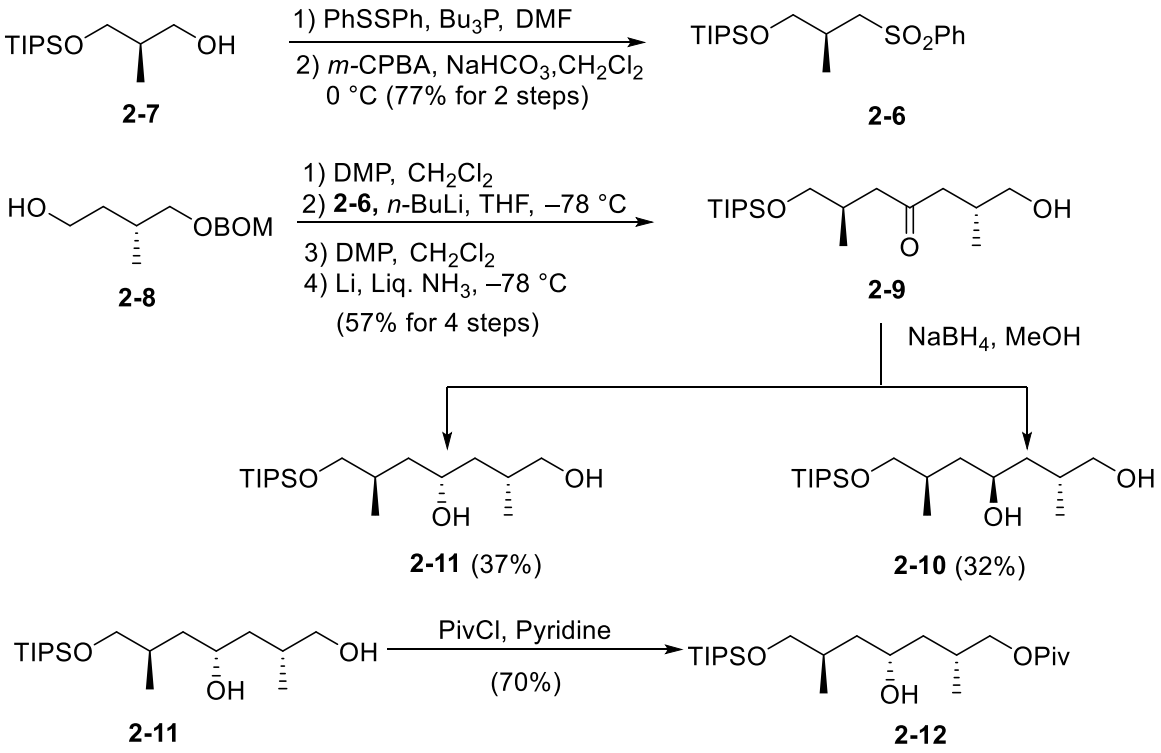


Figure 6. Retrosynthesis of Amphidinolide-Q by Kobayashi *et al.*

The aldehyde obtained from alcohol **2-8** was transformed into a *β*-hydroxy sulfone via Julia coupling with sulfone **2-6**, which after oxidation and reductive removal of the sulfone moiety provide ketone **2-9** (**Scheme 2**).



Scheme 2. Synthesis of the C8-C14 segment of amphidinolide Q.

The configuration of alcohol **2-11** at C11 was elucidated by a modified Mosher's ester analysis (**Figure 7**).

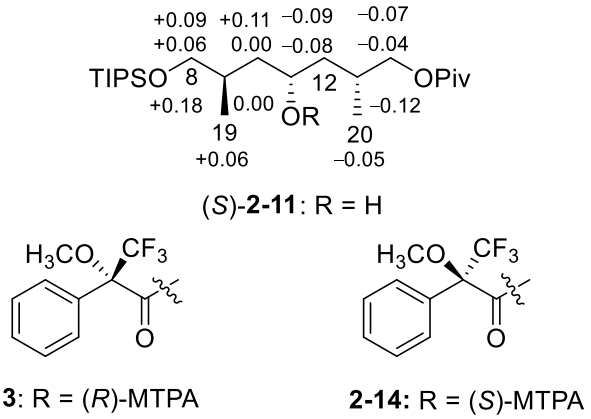
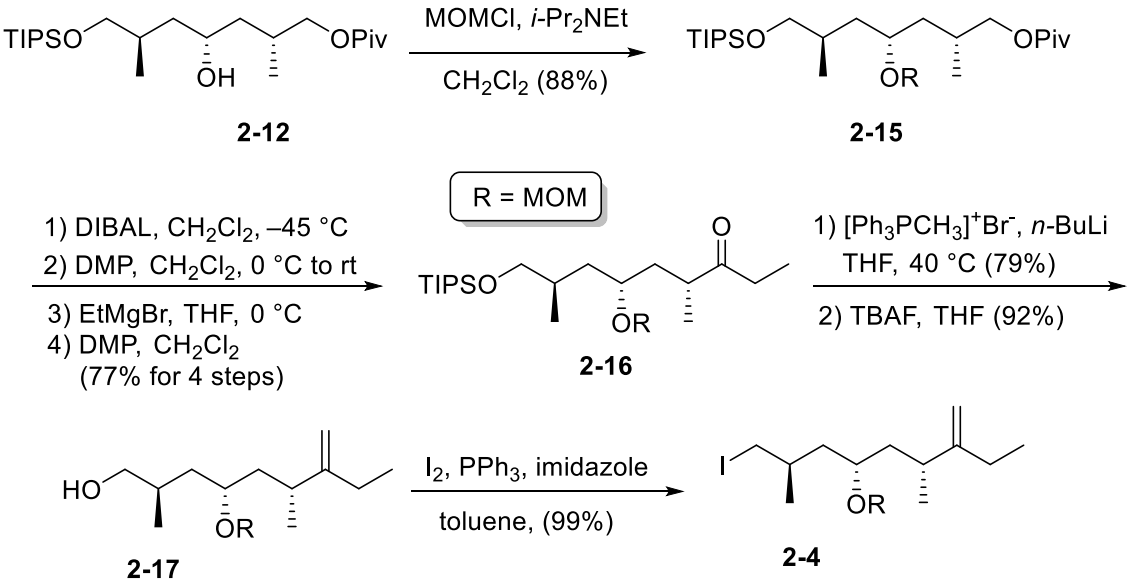


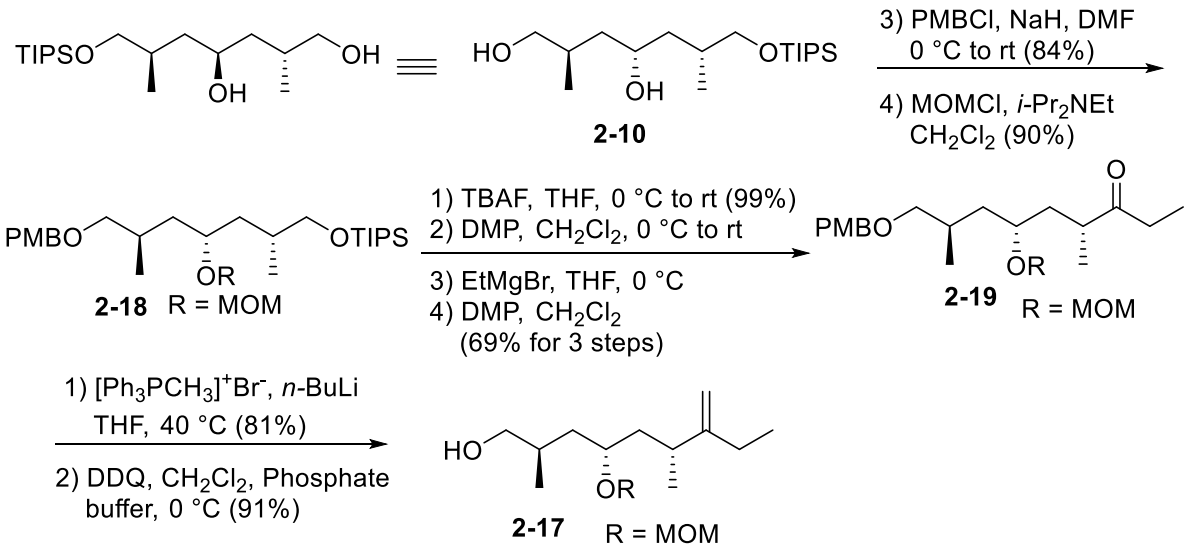
Figure 7. $\Delta\delta$ Values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA ester at C11 (**2-13** and **2-14**, respectively) of alcohol **2-11**.

The exomethylene function was installed in **2-16** by a Wittig reaction followed by Appel reaction to achieve iodide **2-4** (**Scheme 3**).



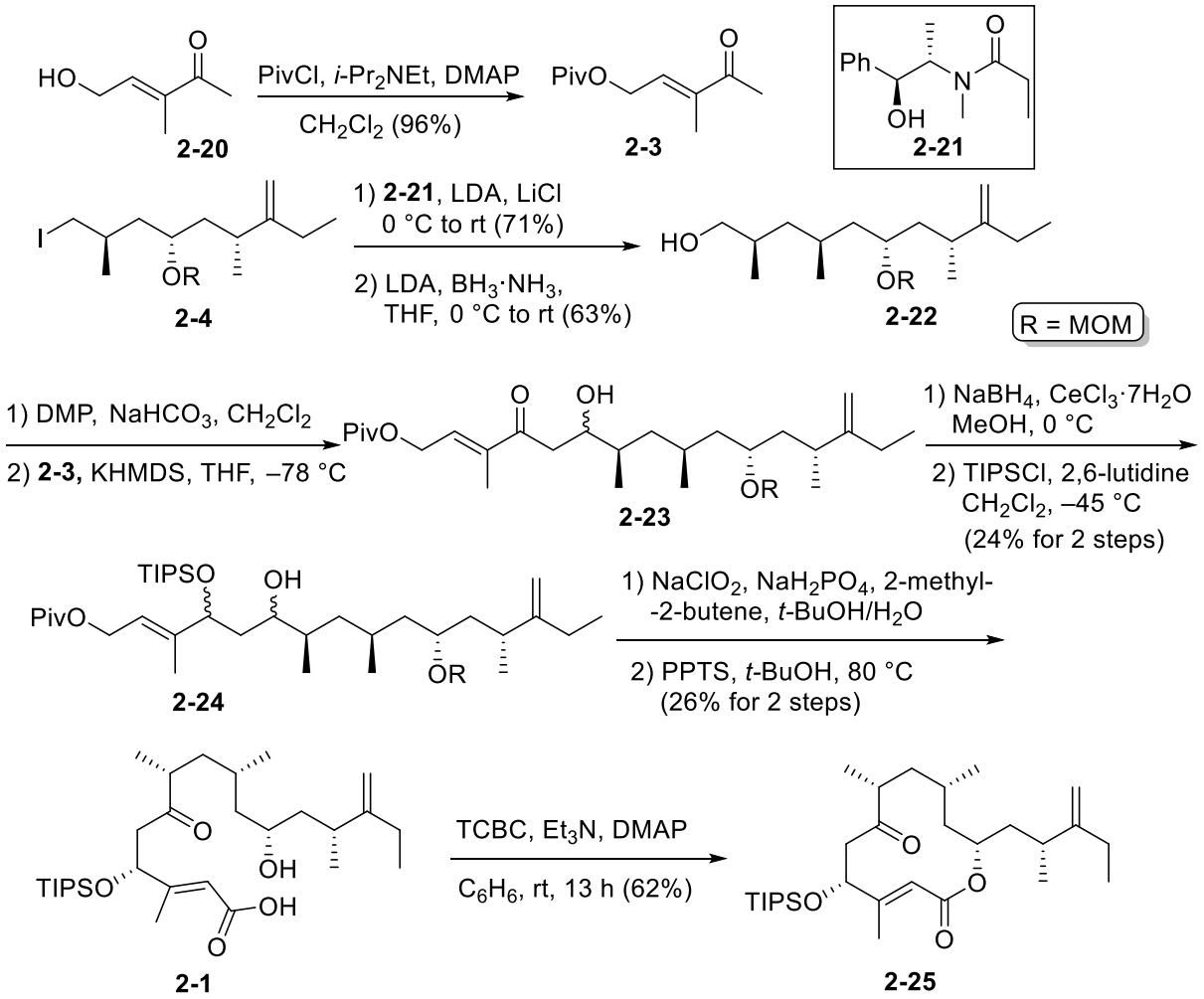
Scheme 3. Synthesis of C8-C16 segment of amp Q from alcohol **2-11**.

The other diastereomer **2-10** was converted to building block **2-17** as shown in **Scheme 4**.



Scheme 4. Synthesis of the C8-C16 segment of amp Q from alcohol **2-10**.

Myers alkylation of iodide **2-4** with propionamide derivative **2-21** gave essentially **2-22** as a single diastereocenter (C7). KHMDS mediated aldol reaction of the aldehyde, obtained after oxidation of **2-22**, with methyl ketone **2-3** produced *β*-hydroxy ketone **2-23**. Luche reduction of ketone **2-23** produced a diastereomeric mixture of allyl alcohol **2-24** (**Scheme 5**). Pinnick oxidation of the aldehyde obtained from alcohol **2-24** followed by Yamaguchi macrolactonization of *seco*-acid **2-1** and TBAF mediated cleavage of silyl ether furnished amp Q (**1-14**).



Scheme 5. Myers alkylation of **2-4** with **2-21**, aldol reaction of **2-3** with **2-2**, and Yamaguchi lactonization of **2-1**.

The synthetic strategy described by Nishiyama *et al.* (**Figure 8**) outlines the possibility of constructing amp Q by joining segment **2-26** and **2-27** followed by macrolactonization.[16]

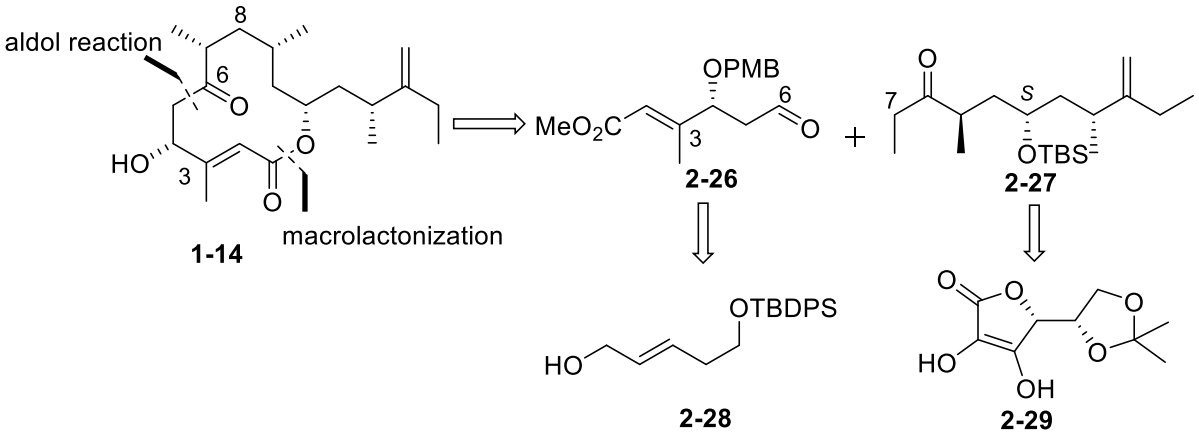
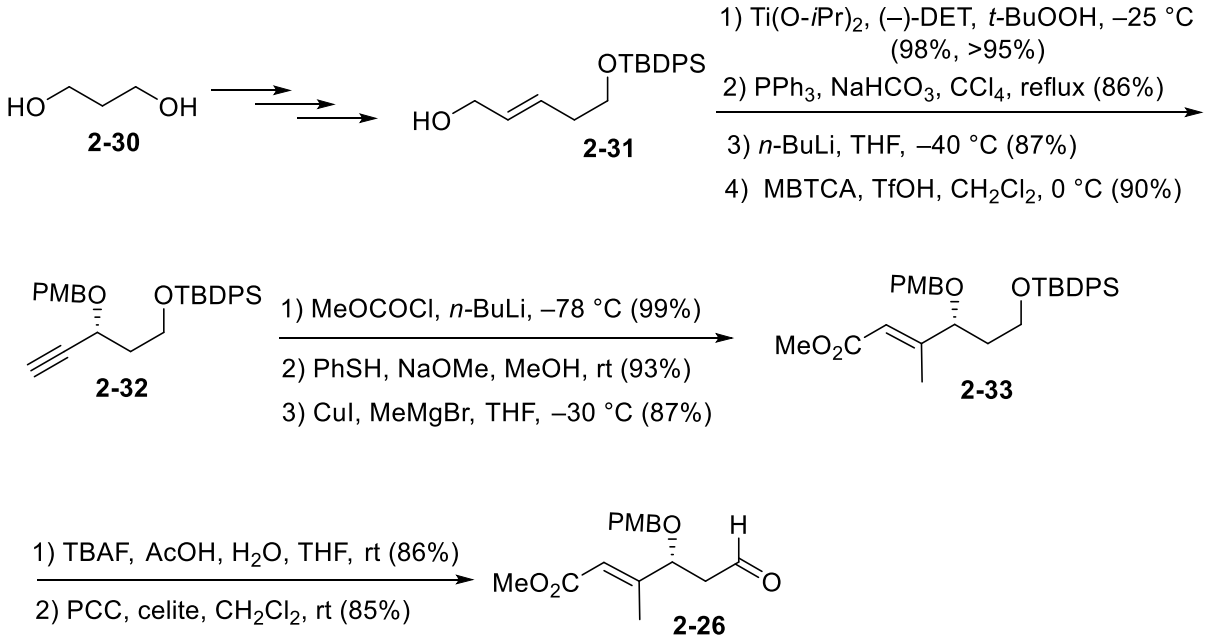


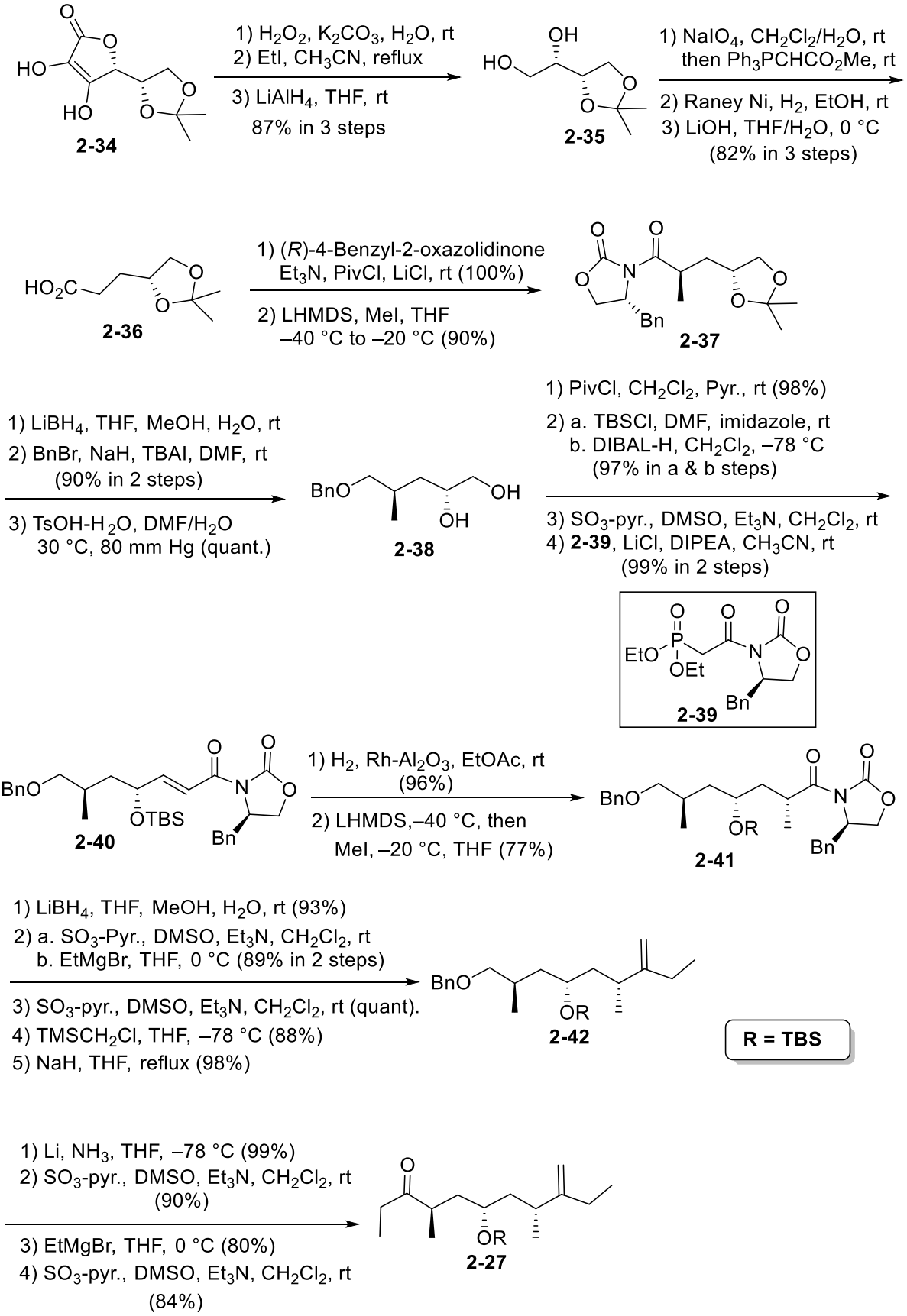
Figure 8. Retrosynthetic analysis by Nishiyama *et al.*

The synthesis of fragment **2-26** began with the epoxidation of alcohol **2-31** obtained from 1,3-propanediol (**2-30**). *E*-selective methylation of the propiolic ester part using a PhS group as an auxiliary,[17] afforded the α,β-unsaturated ester **2-26** (**Scheme 6**).



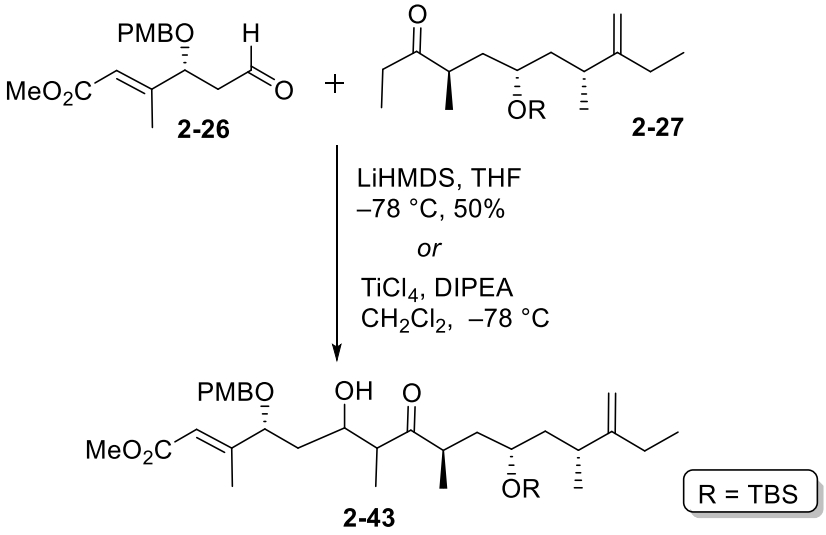
Scheme 6. Synthesis of fragment **2-26** from diol-**2-30**.

The synthesis of ethyl ketone **2-27** was initiated from the ascorbic acid derivative **2-34**. Introduction of the Evans auxiliary in acid **2-36**, followed by methylation leads to the C9 stereocenter. Parikh-Doering oxidation of **2-38** and a Horner-Wadsworth-Emmons reaction gave **2-40**; after routine functional group manipulation and Peterson's olefination introduce the *exo*-methylene function in **2-41** (**Scheme 7**).



Scheme 7. Synthesis of fragment **2-27** from the derivative of ascorbic acid **2-34**.

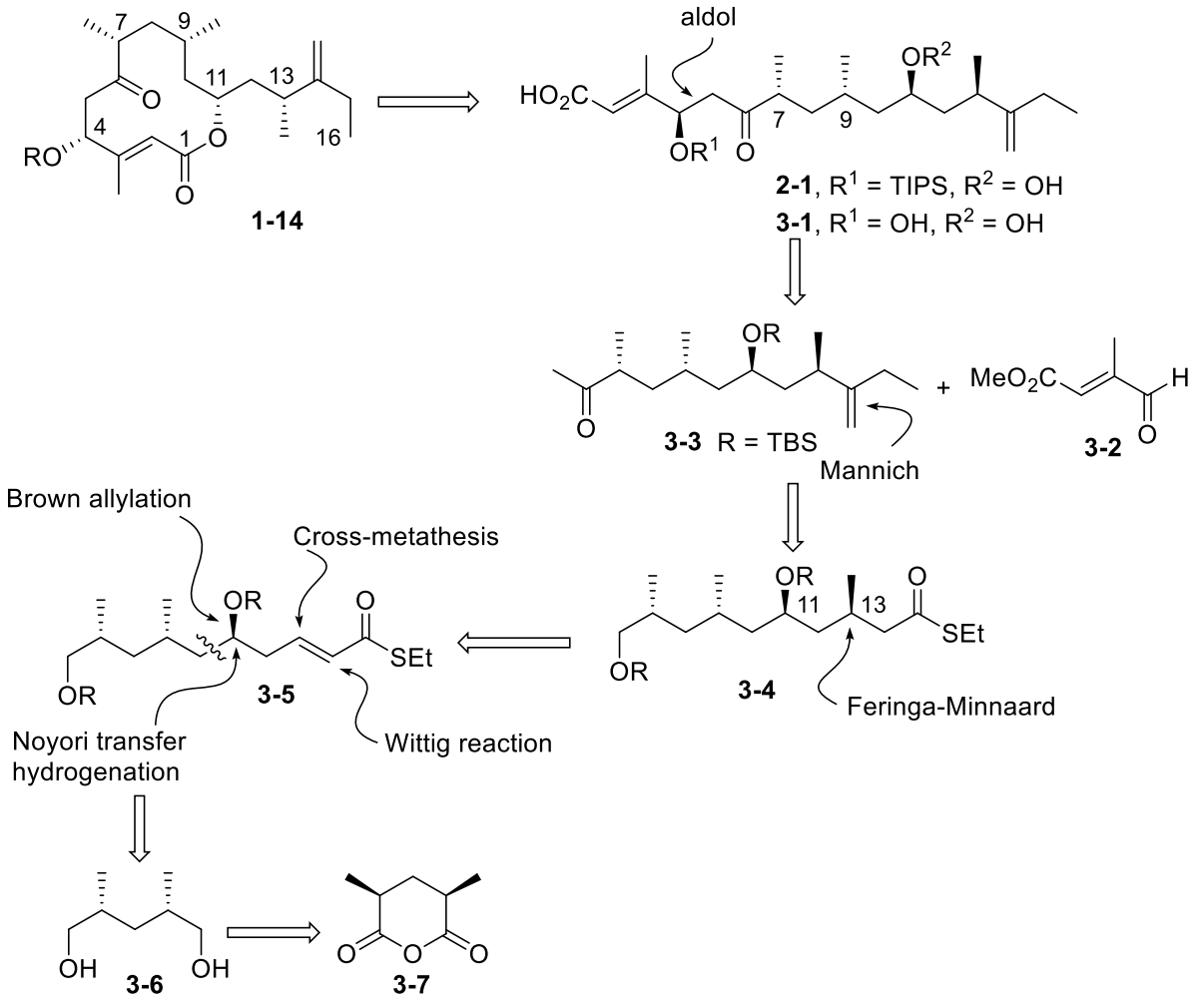
Aldol reaction of both fragments (**2-26 & 2-27**) under acidic condition gave undesirable elimination whereas under basic conditions the reaction suffered from moderate yield. Moreover, the keto function at C8 still has to be removed.



Scheme 8. Aldol reaction of aldehyde **2-26** and ketone **2-27**.

3 Goal of the research

It is evident from the literature that Amphidinolide Q has moderate cytotoxicity. Several analogues of Amp Q are present in nature; some of them have been isolated recently. The analogues are also biologically active compounds. A little modification in the natural macrolide delivered significant changes in the biological activity. As the isolated amounts of the amphidinolides are rather small, total synthesis is the only alternative to secure material for further biological studies.[18] Though Amp Q is rather simple but till the time only one total synthesis was known so far. Therefore we became interested in the synthesis of amp Q (**1-14**).



Scheme 9. Retrosynthetic plan for the synthesis of amphidinolide Q.

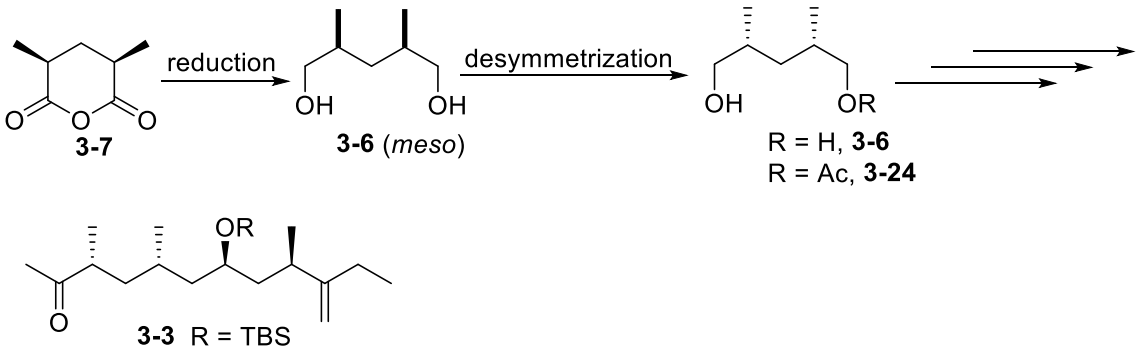
As an initial toehold in the retrosynthetic analysis we recognized the presence of the *syn*-1,3-dimethyl groups at C7 and C9. Accordingly, our aim was to trace back the carbon skeleton of **1-14** to *meso*-diol **3-6**. Thus, seco acid **3-1** could be disconnected to known aldehyde[19] **3-2** and methyl ketone **3-3**. The butenyl fragment attached to C13 was thought to come from a Mannich reaction and a substitution reaction on an allylic alcohol derivative. This led to α,β-unsaturated thioester **3-5** as an advanced precursor. Brown allylation of an aldehyde followed by cross-

metathesis with *S*-ethyl prop-2-enethioate could generate the unsaturated thioester **3-5**. An alternative includes a Noyori transfer hydrogenation on an alkynone to establish the stereocenter at C11 and a Wittig reaction. The thioester **3-4** could be obtained via a Feringa-Minnaard asymmetric methylcuprate addition to an unsaturated thioester.

4 Results and discussion

4.1 Synthesis of methyl ketone 3-3

Methyl ketone **3-3** is the major fragment of this synthesis. It features four stereocenters and one *exo*-methylene unit. The stereocenter's at C7, C9, and C13 are occupied with methyl groups whereas C11 contains hydroxyl function. We have chosen *meso*-diol **3-6** as precursor for this synthesis (**Scheme 10**) therefore it requires desymetrization into a corresponding asymmetric compound.



Scheme 10. Sequence representing synthesis of methyl ketone **3-3** from 2,4-dimethylglutaric anhydride (**3-7**).

4.1.1 Enzymatic desymmetrization

The world contains a vast number of biologically active chiral compounds. The synthesis of enantiomerically pure compounds is always demanding. Enzymes are biocatalysts which accelerate the rate of a reaction. In recent years enzymes have also been used as catalysts for chemical transformations due to the following reasons:

a) Enzymatic reactions are highly chemo, regio, and stereoselective.

b) Enzymes are environmentally benign.

c) Enzymatic transformations complete under mild conditions.

d) Enzymes immobilized on a solid surface can be used several times.

In spite enzymes are very sensitive catalysts and exert their activity mainly in aqueous solutions. Therefore organic chemists hesitate to employ them in synthesis. Recently some advances have been made such as:

a) A broad range of substrates can be transformed in nonaqueous medium.[20]

b) Immobilization techniques have simplified their handling.[21]

There are two main groups of chemical transformations which can be done using enzymes:

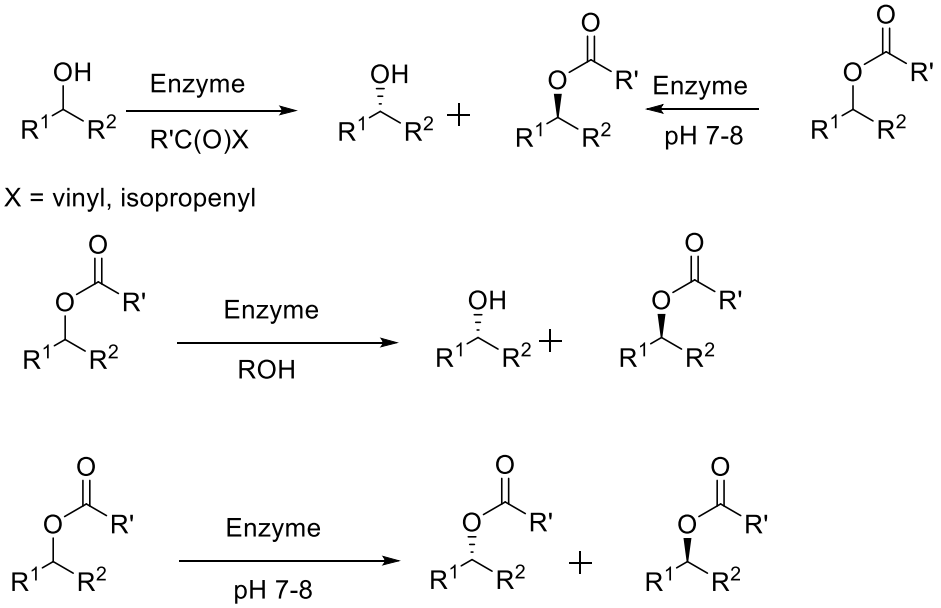
a) Asymmetric synthesis

b) Kinetic resolution of racemic mixtures.

They differ conceptually in the fact that by asymmetric synthesis formation of one or more chirality elements happens within a substrate molecule, whereas by kinetic resolution one of

the enantiomer is converted to a separable derivative. The theoretical yield in the latter case can't exceed 50% and practically is even lower. This could be a significant drawback when only one enantiomer is required. The desymmetrization of symmetric compounds (usually *meso*-compounds) consists of elimination of symmetry elements in the substrate molecule. When these symmetry elements (e.g. mirror plane) preclude chirality, enantioselectivity can be achieved. Desymmetrization belongs to asymmetric synthesis; the maximum yield of theoretically 100% could be achieved.

The most frequent enzymatic transformation includes hydrolysis of ester and *vice versa*. The enzyme responsible for such transformations is lipase (*or* hydrolase). For kinetic resolution esterification, hydrolysis, or transesterification can be chosen (**Scheme 11**).



Scheme 11. Scope of reaction catalyzed by hydrolases.

The mechanism of enzyme catalysis has been thoroughly investigated and found that lipases contain a catalytic triad, a sequence of three amino acids, aspartic acid, histidine and serine[22] The OH residue present in *serine* functions as "nucleophile", imidazole ring of histidine as a "base" and the carboxyl group of aspartic acid works as "acid" (**Figure 9**).

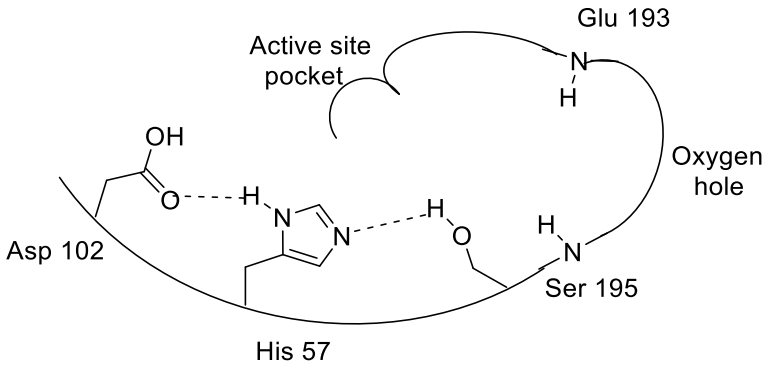


Figure 9. Topographical representation of the active center of a lipase

An ester has been chosen to demonstrate the principle of enzymatic, enantioselective hydrolysis. A covalent bound complex is formed by the attack of the serine hydroxyl function to the carbonyl group (**Figure 10**). The negatively charged oxygen atom of the tetrahedral intermediate forms two hydrogen bonds with the amide proton of serine and glutamine, thus generating an “oxyanion hole”. At the same time alkoxy residue tends to fit in the “active site pocket” of the enzyme. If one enantiomer of alkoxide fits better than the other, this results in an optically enriched product.

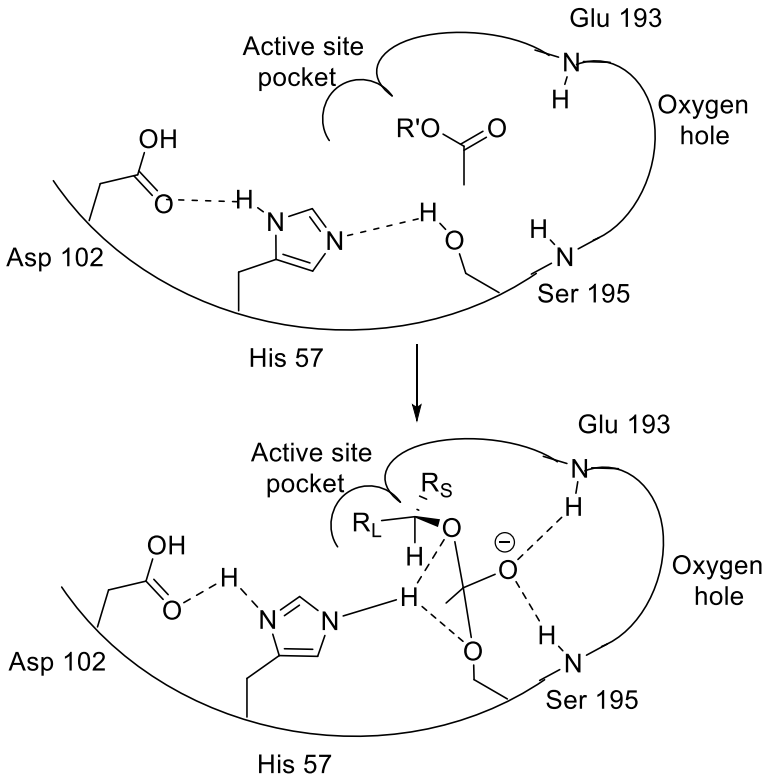


Figure 10. Formation of covalent bound complex between substrate and enzyme.

Alcohol (**Figure 11**) and acylated enzyme will be formed on disruption of the tetrahedral intermediate. The acylated enzyme then reacts with water in a similar way, which releases acetic acid and recovers the serine hydroxyl function.

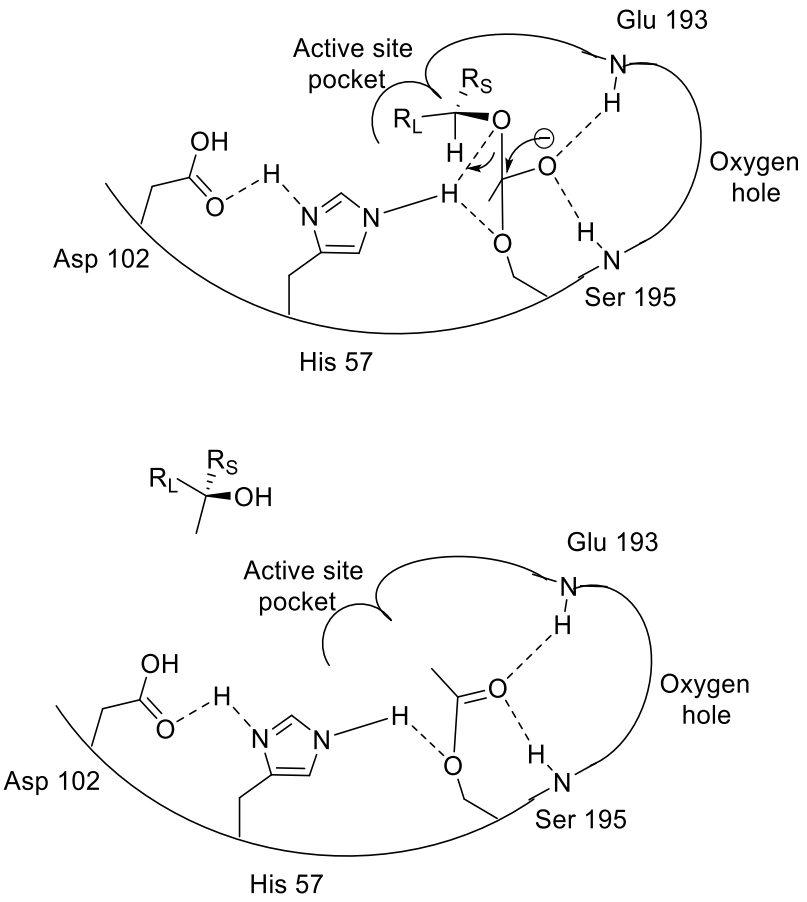
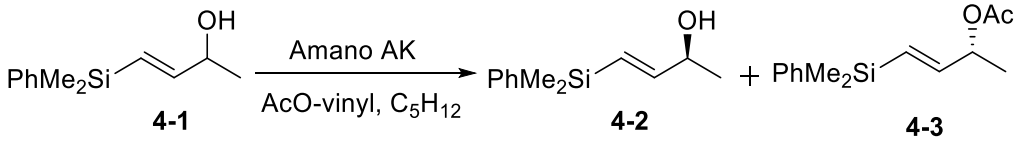


Figure 11. Collapse of the tetrahedral intermediate and release of the alcohol.

A comprehensive review entitled "enantioselective enzymatic desymmetrization in organic synthesis" has been published by Gotor *et al.*[23]

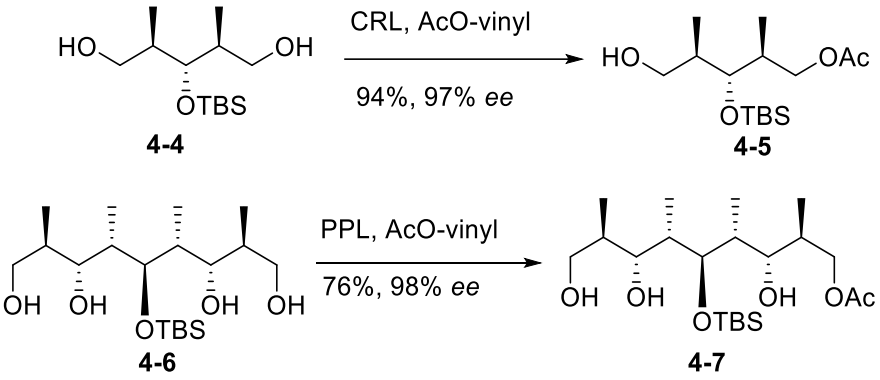
Enzymes are catalysts which increase the rate of reaction by lowering the free energy barrier between reactants and products. As enzymes equilibrate reactants and products therefore, to drive a reaction up to completion, one needs some special acylation agents (e.g. irreversible acyl transfer agents). A recent investigation addresses the use of enol ethers.[24] Vinyl acetate is commonly available and used in polymer synthesis, produced on industrial scale, and would be the simplest acylation agent. The transesterification of an alcohol with vinyl acetate gives unstable ethenol which tautomerizes into acetaldehyde and blocks the reverse reaction. It was also found that active carbonyl compounds such as acetaldehyde or acetone can deactivate enzymes, possibly by reaction with free $-NH_2$ residues present in lysine amino acids, which are located at the surface. To overcome with this adversity use of O-acylated oximes has been suggested.[25]

Panek prepared enantioenriched crotylsilanes by enzymatic resolution of allylic alcohol **4-1** (**Scheme 12**).[26] The alcohol **4-2** and mixed ester **4-3** could be separated and be converted into a useful building block for total synthesis of natural products.



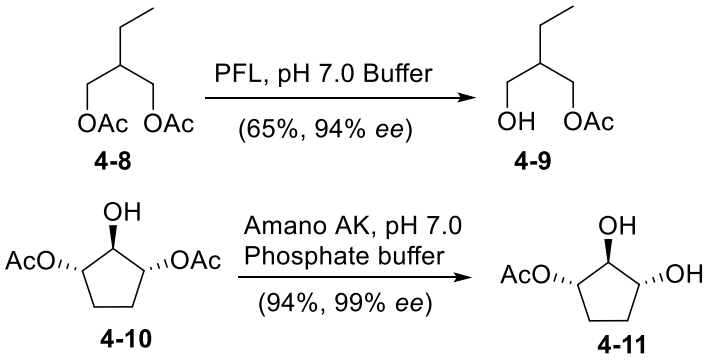
Scheme 12. Kinetic resolution of allyl alcohol.

Dolabrifera, a secondary metabolite present in anaspidean mollusk was synthesized in five steps (58% overall yield) via enzymatic desymmetrization of diol **4-4** catalyzed by *Candida rugosa* lipase (**Scheme 13**).[27] Compound **4-4** on enzymatic esterification gave monoester **4-5** in excellent yield and *ee* when molecular sieves were added to trap the acetaldehyde byproduct from reaction medium. Steroselective acylation of *meso*-polyol **4-6** with vinyl acetate in the presence of lipase from porcine pancreas afforded monoacetate **4-7** in good yield and enantiomeric purity.[28] This reaction seems to be highly regioselective for a primary alcohol end group, the unprotected secondary alcohol functions were left unaffected.



Scheme 13. Preparation of poyketide building blocks by desymmetrization.

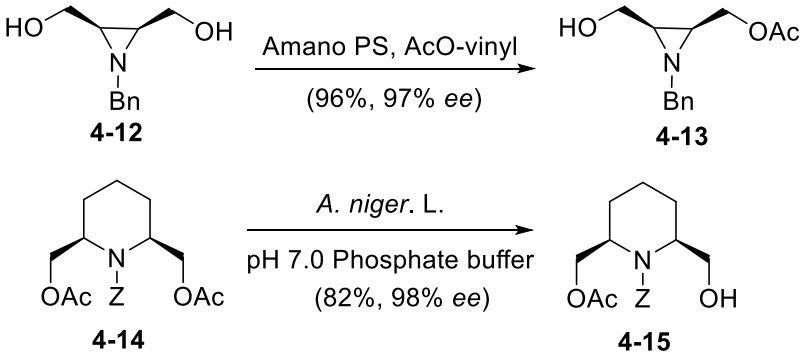
In some cases, hydrolysis of the diacetate was found superior over acylation of the corresponding diol. PFL mediated hydrolysis of 2-ethylpropan-1,3-diol diacetate **4-8** proceeds with 94% *ee* whereas acylation of 2-ethylpropan-1,3-diol only gave 46% ee (**Scheme 14**).[29] In most cases (not for all) hydrolysis of the diacetate would give best enantiomeric purity.[30]



Scheme 14. Desymmetrization of prochiral acetates.

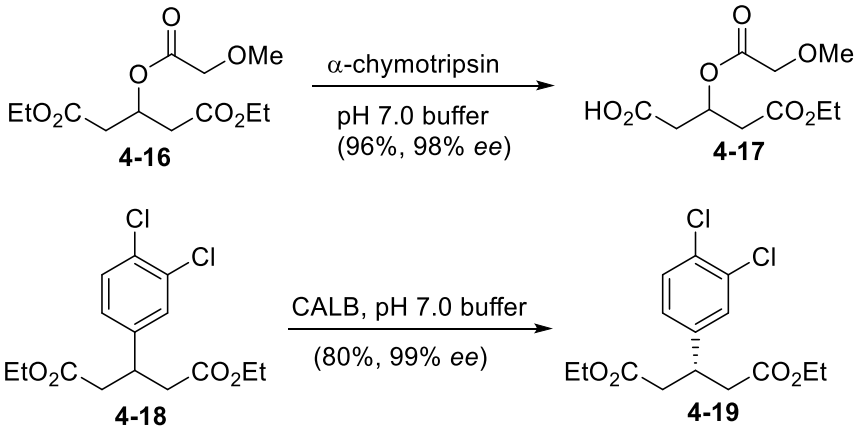
Optically active heterocycles having alcohols function such as aziridine and piperdine are important building blocks in the synthesis of pharmaceutical compounds (**Scheme 15**). The

Amano PS lipase-catalyzed desymetrization of aziridines[31] **4-12** gave monoacylated derivatives in high yield and *ee*. Chenevert & co-workers found good yield and *ee* while investigating desymmetrization of cis-2,6 **4-14** and cis,cis-2,4,6-substituted piperidine derivative.[32]



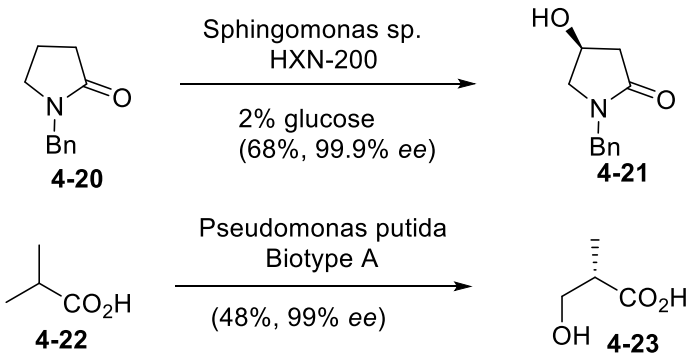
Scheme 15. Desymmetrization of heterocyclic *meso*-compounds.

Different *meso* and prochiral esters possessing a prochirality element in the alkyl chain need to be discussed. Öhrlein and co-workers did desmmetrization of diethyl 3-hydroxyglutarate derivatives **4-16** into **4-17**, which could be a building block of statins.[33] Prochiral diethyl 3-[3′,4′-dichlorophenyl]-glutarate **4-18**, is an intermediate in the synthesis of a series of neurokinin receptor antagonist, has been successfully desymmetrize into **4-19** (**Scheme 16**).[34]



Scheme 16. Desymmetrization of prochiral diesters.

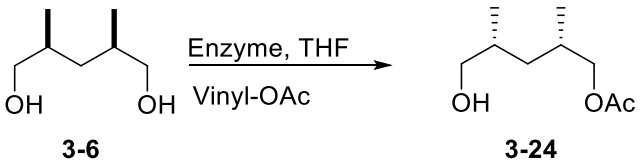
Other useful steroselective enzyme catalyzed reactions include hydrolysis of amides, nitriles, and anhydrides. The scope of steroselective reduction of carbonyl compounds is limited due to stoichiometric requirement of cofactors. Steroselective hydroxylation of methylene **4-22**[35] and methyl **4-20**[36] groups are reported (**Scheme 17**).



Scheme 17. Enzyme catalyzed enantioselective hydroxylation.

As reported in the literature separation of two diastereomers is required at a late stage of Amp Q synthesis therefore we decided to start our synthesis from a chiral building block. Chiral building block **3-24** was developed from 2,4-dimethyl-1,5-pentanediol **3-6**; these compounds have already been reported in literature.[37] Our group has extensively studied this reaction using three different enzymes such as Amano lipase AK, Amano lipase PS and Novazyme 435 in order to get best results.[38] The results are summarized in **Table 1**.

Table 1. Desymmetrization of 2,4-dimethyl-1,5-pentanediol.

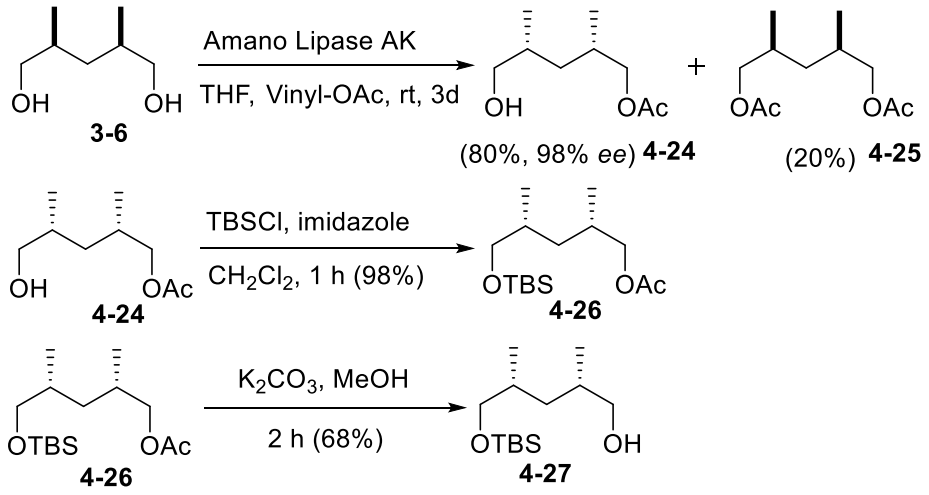


Enzyme	Mono/diacetate	*ee*%
Amano lipase AK	6:1	98
Amano lipase PS	4:1	30
Novozyme 435	2:1	n.d.

The best result was found with Amano lipase AK (Aldrich Cat. No.: 53, 473-10), The enantiomeric excess of the isolated mono-acetate was determined by Chiral GC and cross checked with classical Mosher ester techniques. We found an optical rotation of **3-24** exactly same as reported.

4.1.1.1 Desymmetrization of *meso*-diol 3-6

The standard reaction condition has been used which resulted in competitive formation of the 2,4-dimethylpentane-1,5-diol diacetate **4-25**. At this stage it is easy to separate mono and diacetate since they have large difference in R_f values therefore we decided to separate them by column chromatography to avoid complications in the next step. The monoacetate **4-24** was treated with TBSCl in the presence of imidazole to get silyl ether **4-26**, which on further treatment with potassium carbonate in methanol furnished alcohol **4-27**.

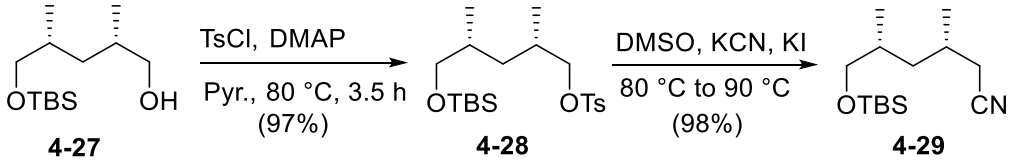


Scheme 18. Enzymatic desymmetrization of 2,4-dimethyl-1,5-lpentanediol (**4-6**).

Finally, in conclusion enantioselective enzymatic desymmetrizations of *meso* and prochiral substrates have proven to be a powerful tool that allows the preparation of a wide range of optically active building blocks in a highly enantioselective fashion and in high yields.

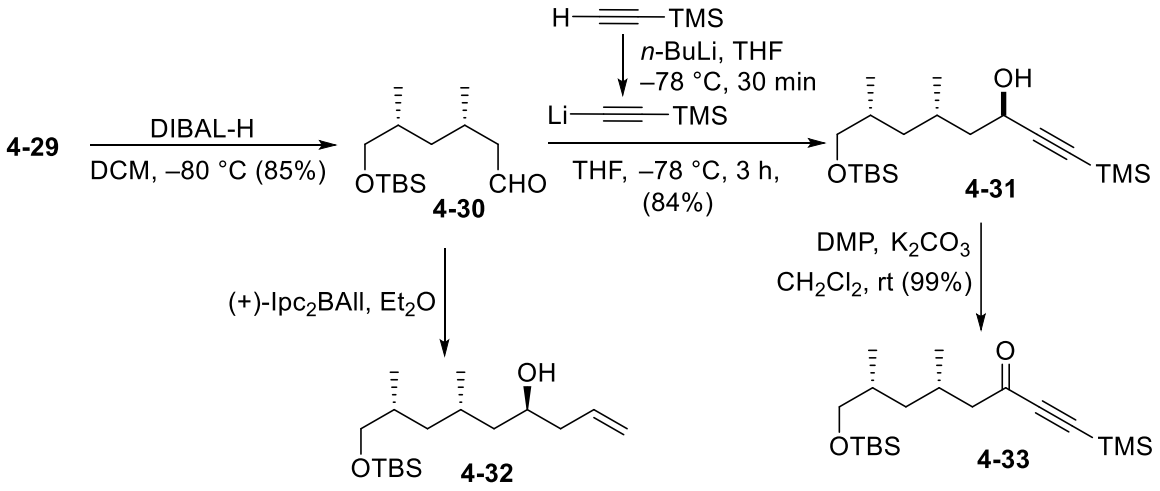
4.1.2 Carbon chain extension

The chain extension of one carbon on alcohol **4-27** was carried out by nucleophilic substitution after tosylation[39] of the alcohol in presence of a catalytic amount of KI. The tosylation was carried out in dichloromethane using pyridine as a base, only a little conversion was observed after 12 h under reflux. The yield was improved by using a catalytic amount of DMAP and excess of pyridine as solvent. Tosylate **4-28** was subjected to reaction with sodium cyanide in DMSO at rt for 18 h, which did not deliver the product, however the described condition in **Scheme 19** gave cyanide **4-29** in quantitative yield.



Scheme 19. Cyanide substitution of alcohol (**4-27**).

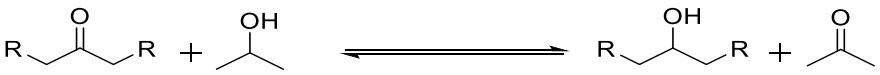
After cyanide reduction with DIBAL-H, the resulting aldehyde **4-30** was subjected for Brown allylation using (+)-B-Allyldiisopinocampheylborane,[40] resulting in a mixture of compounds along with the desired homoallylic alcohol (approx. 15%) together with recovered starting material, which could be explained by mismatch of the chiral centers. Then we started exploration of an alternative strategy explained in retrosynthesis. The aldehyde **4-30** was treated with lithium trimethylacetylide leading to propargyl alcohol **4-31** as a mixture of C11 diastereomers (*S*/*R* : 60/40), which was further oxidized into alkynone **4-33** with Dess-Martin periodinane. First we looked the possibilities of ketone reduction into a chiral alcohol function.



Scheme 20. Brown allylation and acetylation of aldehyde **4-30**.

4.1.3 Noyori reduction

Natural products are rich in having stereocenters with OH and NH_2 functions. They are responsible for bioactivity, which is based on hydrogen bonding with the cellular amino acids to change the function of the cell, only one enantiomer would be active as we discussed in the mechanism of enzyme action. Asymmetric hydrogenation of C=O and C=N bonds is the most fundamental molecular transformation in this aspect. Transfer hydrogenation of ketones using propanol as a hydrogen donor is a well known synthetic operation. A review describing asymmetric hydrogenation using molecular H_2 and Ru-complexes as a catalyst has been published by Noyori.[41] There are also some reports describing the reduction of enolate and enantotopic group using biocatalyst NADH dependent enolate reductase, obtained from yeast and HLADH (horse liver alcohol dehydrogenase) respectively.[42] Asymmetric transfer hydrogenation of ketones has occurred by kinetic discrimination of the enantiofaces and which also stablishes equilibrium (**Scheme 21**).[43]



Scheme 21. Equilibrium between reactant and product.

This problem could be solved by developing such catalysts which lower the reversibility of the reaction in addition to the excellent enantioface-differentiation (**4-34** (k_{Si}/k_{Re}) 99/1).[44] It was proved that **4-35** catalyzes hydrogenation of acetophenone (**4-36**) into (*R*)-benzyl alcohol (**4-37**) 100 times faster than (*S*)-benzyl alcohol (**Figure 12**).

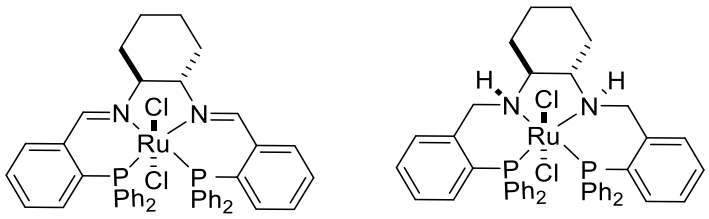
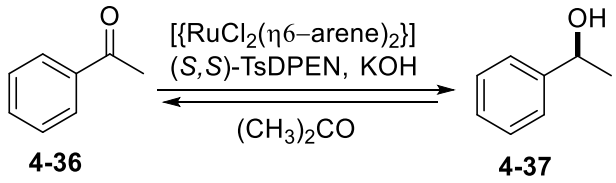


Figure 12. Ru(II) complexes possessing the chiral tetradentate ligands.

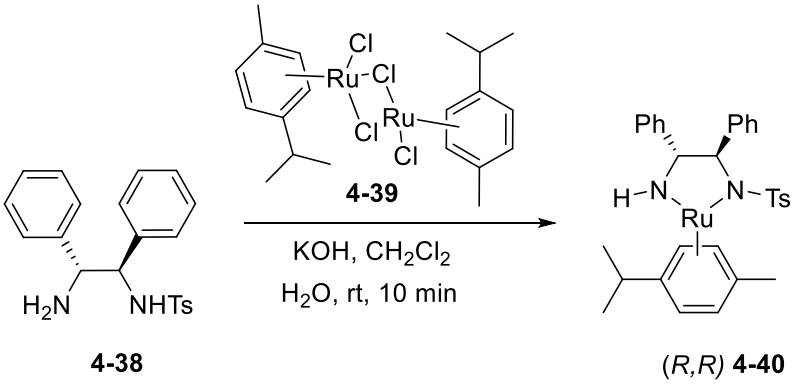
When acetophenone (**4-36**) was allowed to stand 10 h at 28 °C with [$RuCl_2(\eta 6$-arene$)_2$], N-*p*-toluenesulfonyl-1,2-diphenyl ethylenediamine and KOH (Ketone:Ru:diamine:KOH = 200:1:1:2, molar ratio) (*S*)-1-phenylethanol with 97% *ee* and 98% yield was obtaioned (**Scheme 22**),[45] whereas catalyst **4-34** (at 23 °C, 48 h) and **4-35** (at 45 °C, 7 h) gave (*R*)-1-phenylethanol with 18% *ee*, 3% yield and 97% *ee*, 93% yield respectively.



Scheme 22. Conversion of acetophenone into (*S*)-1-phenylethanol.

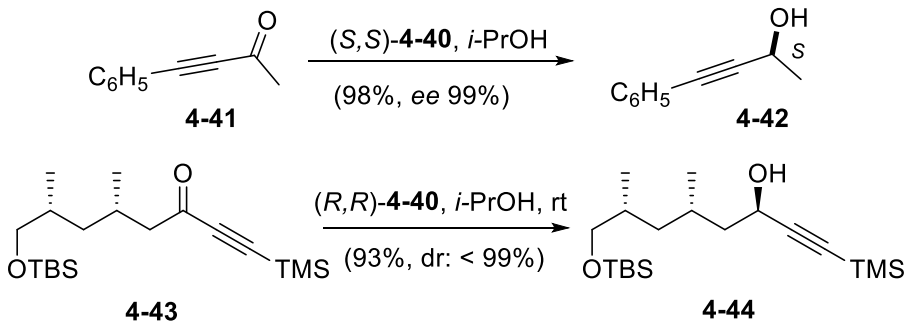
4.1.3.1 Generation of stereocenter C11 on alkynone 4-43

It is clear from above comparative experimental findings that modification in the chiral ligand could lead to high reactivity and enantioselectivity. The catalyst **4-40** generated by the reaction of (*1R,2R*)-(+)-N-*p*-toluenesulfonyl-1,2-diphenylethylene-diamine (**4-38**) and dichloro(*p*-cymene)ruthenium(II) (**4-39**) is now widely used in the reduction of prochiral keto functions (**Scheme 23**).[46]



Scheme 23. Preparation of Noyori catalyst from diamine **4-38** and Ru-dimer **4-39**.

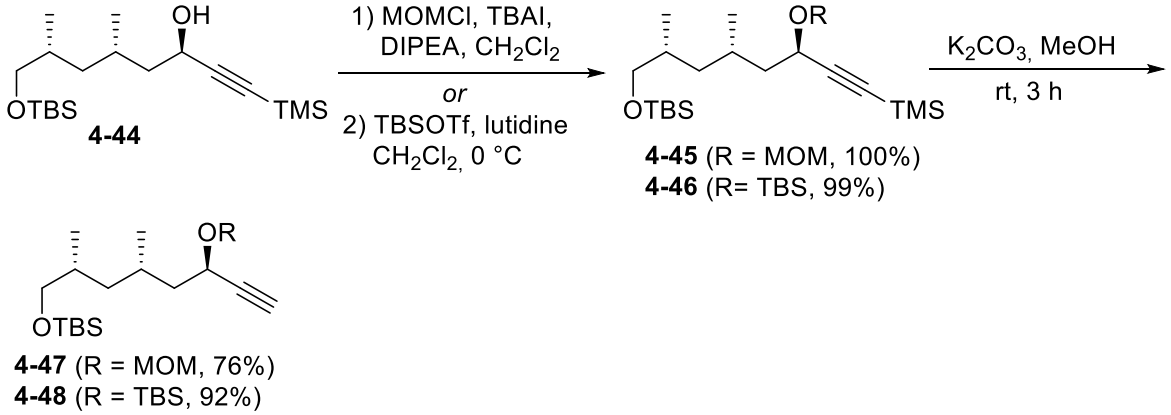
These catalysts allow highly selective reduction of structurally diverse acetylenic ketones to propargylic alcohols of high enantiomeric purity leaving the C≡C bond intact (**Scheme 24**).[47] (*R,R*)-**4-40** catalyst accomplished the formation of alkynol (3*R*)-**4-44** as essentially one diastereomer in high yield. While working on this reduction we observed that even a trace amount of the Dess-Martin periodinane can quench the catalyst, resulting no reaction.



Scheme 24. Enantioselective reduction of ketones **4-41** & **4-43** into propargylic alcohols.

4.1.4 Oxidation of alkyne & Wittig reaction

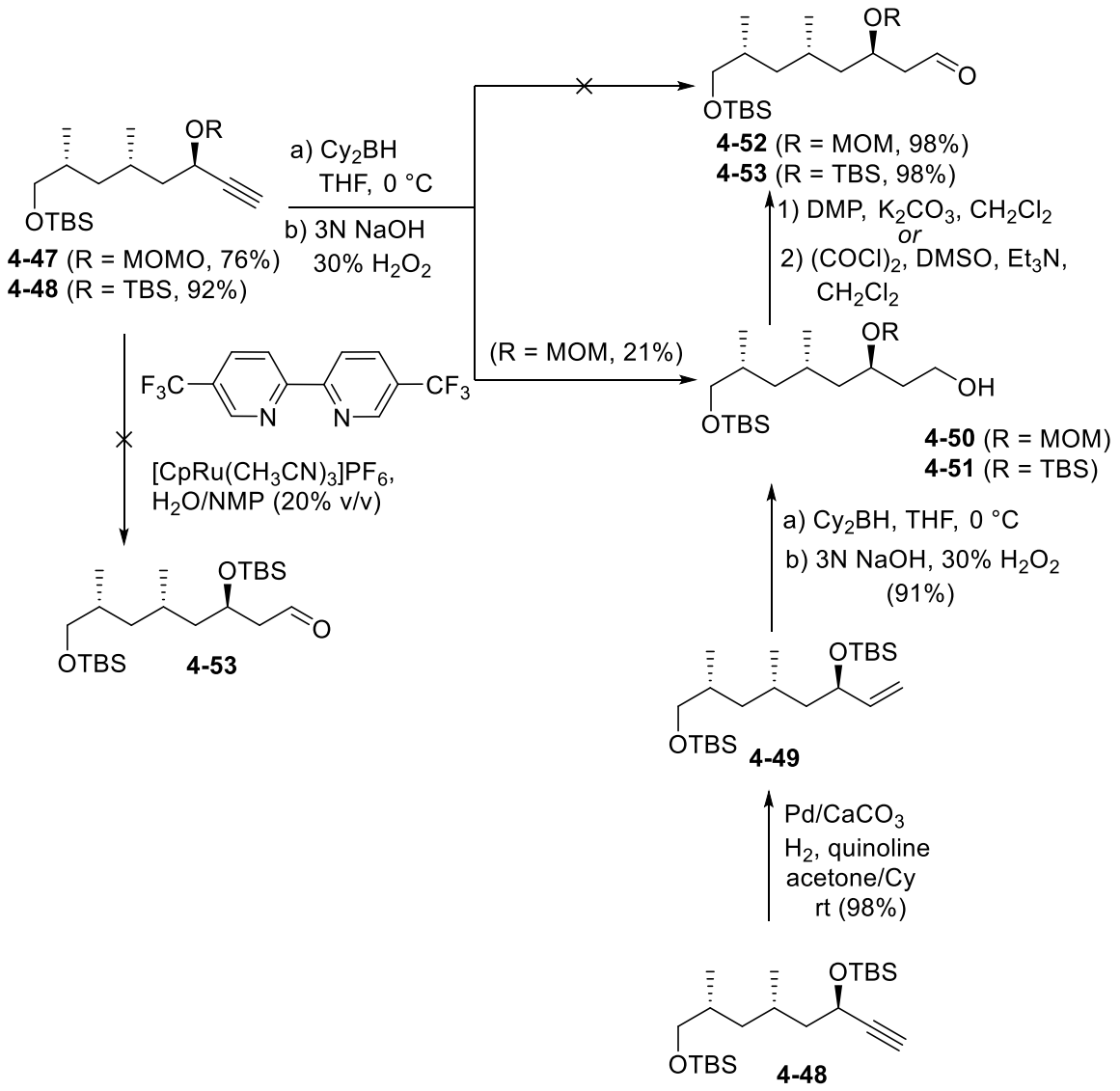
The secondary MOM or TBS group were introduced in the alcohol **4-44** followed by cleavage of the trimethylsilyl group from TMS alkyne in basic medium.



Scheme 25. Etherification of propargyl alcohol **4-44** and desilylation of alkynes **4-45** & **4-46**.

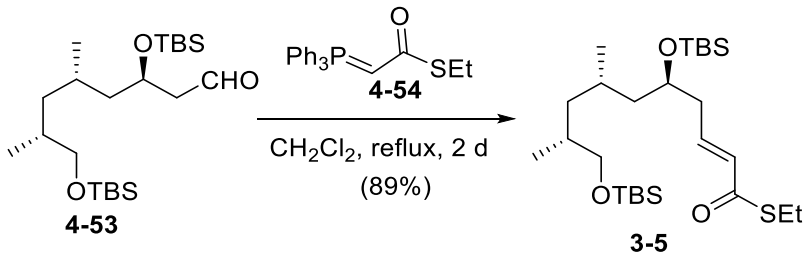
The intermediates **4-47** and **4-48** were subjected for hydroboration oxidation; the MOM derivative **4-47** furnished undesirable alcohol **4-50** with low yield (21%), whereas with **4-48** a complex mixture was observed. Unfortunately we did not observe a reaction when alkyne **4-48** was subjected for a test reaction to the Seth Herzon protocol.[48]

Then we decided to follow a step wise transformation where alkyne **4-48** was first reduced using Lindlar hydrogenation into terminal alkene **4-49**, which on hydroboration of the double bond using dicyclohexylborane followed by oxidative work-up led to primary alcohol **4-51** in good overall yield. The alcohol function was oxidized to aldehyde **4-53** by Swern oxidation (**Scheme 26**).



Scheme 26. Alkyne oxidation via hydroboration-oxidation.

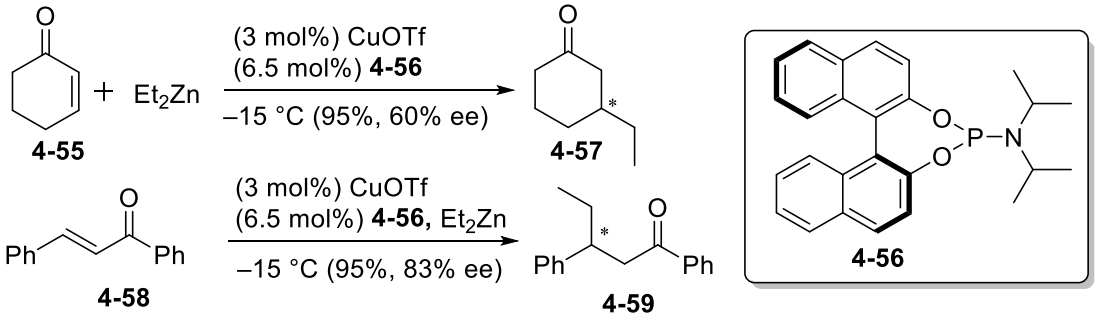
Wittig reagents of general structure $(Ph)_3PCHCO_2R$ are powerful building blocks for two carbon chain extension in organic synthesis. The aldehyde **4-53** produced α,β-unsaturated thioester **4-55** with *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate[49] (**Scheme 27**).



Scheme 27. Wittig reaction of aldehyde **4-53** with **4-54**.

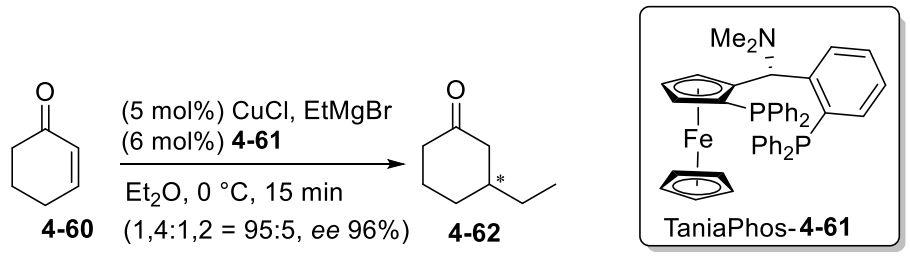
4.1.5 Feringa-Minnaard asymmetric cuprate addition

Once the α,β-unsaturated thioester **3-5** in was hand, a reaction was required which would be stereoselective and add a methyl unit at C13 to generate C13-(*R*)-methyl **3-4** essentially a single diasteromer. The 1,4-addition of organometallic reagents to α,β-unsaturated compounds is one of the most versatile approaches towards C-C bond formation. Hause *et al.* in 1966 revealed that reactive species of conjugate addition is lithium diorganocuprate (I), called "Gilman reagent" and in 1970s a single electron transfer (SET) mechanism for conjugate addition was proposed.[50] The first catalytic approach for conjugate addition (CA) of diethyl zinc using monodentate phosphoramidite ligands **4-56** was developed by Feringa *et al.* in 1996 (**Scheme 28**).[51]



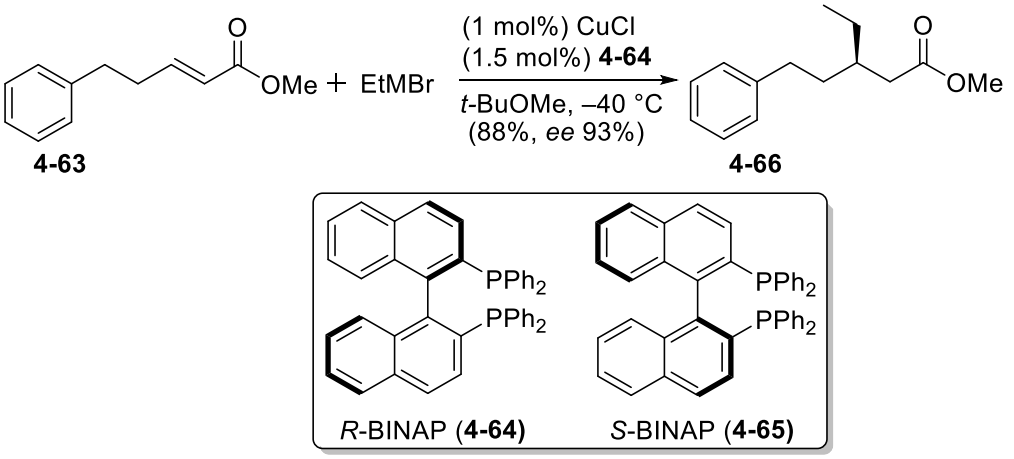
Scheme 28. Enantioselective CuOTf-catalyzed 1,4-addition of Et_2Zn to **4-55** and **4-58** by Feringa and co-workers.

Dialkylzinc reagents have distinct advantages; they show low reactivity in uncatalyzed reaction and high tolerance for functional groups both in the substrate and the zinc reagent. Functionalized organozinc such as alkylzinc halides result in very low enantioselectivities. However, they are easily obtained from the corresponding alkenes through a hydroboration alkyl-transfer procedure.[52] Copper-catalyzed asymmetric conjugate additions of Grignard reagents is rather difficult due to high reactivity of the magnesium reagent which could allow uncatalyzed 1,2-addition. Grignard reagents are inexpensive and readily available, apart from this; there is little issue to use them. (1) How to achieve high *ee* and (2) minimize uncatalyzed reactions; this problem was solved by Feringa *et al.* by using ferrocenyl diphosphines bidentate ligands and CuCl or $CuBr{\cdot}SMe_2$ as a metal source (**Scheme 29**).[53]



Scheme 29. Enantioselective conjugate addition of EtMgBr to cyclohexanone by Feringa and co-workers.

Loh *et al.* used Tol-BINAP and CuI for the enantioselective CA of EtMgBr to *α,β*-unsaturated esters (**Scheme 30**).[54]



Scheme 30. Enantioselective conjugate addition of EtMgBr to *α,β*-unsaturated esters by Loh and co-workers.

A recent review entitled "Highly enantioselective Cu(I)–Tol-BINAP-catalyzed asymmetric conjugate addition of Grignard reagents to *α,β*-unsaturated esters" is published.[55] However, 1,4-addition of less reactive MeMgBr to *α,β*-unsaturated esters gave poor yield [56] which was encountered by using more reactive but equally and readily accessible *α,β*-unsaturated thioesters. The reduced electron delocalization in the thioester moiety, compared to oxoesters, results in a higher reactivity toward conjugate addition reactions.[57] Josiphos/CuBr-catalyzed conjugate addition of Grignard reagents to *α,β*-unsaturated thioesters provided a synthetically very useful methodology. However, it has some drawbacks, (I) addition of sterically hindered Grignard reagents proceeds with poor enantioselectivity and (II) aromatic substrates with substituents on the phenyl ring exhibit low reactivity toward the addition of MeMgBr (**Table 2**).

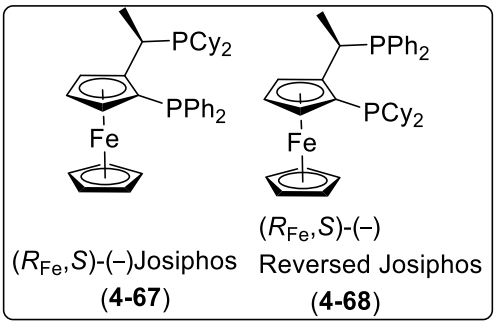
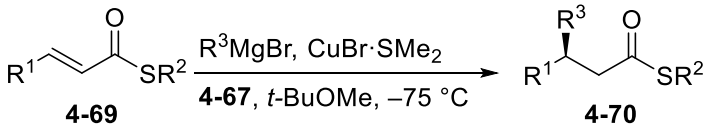


Figure 13. Josiphos and *ent*-Josiphos.

Table 2. Enantioselective conjugate addition of Grignard Reagents (R^3MgBr) to α,β-unsaturated thioesters **4-69** by Feringa-Minnaard.



4-69 **4-70**

entry	R^1	R^2	Grignard	yield **4-70** (%)	*ee* (%)
1	*n*-Pent	Et	MeMgBr	90	96
2	*n*-Pent	Me	MeMgBr	93	96
3	$BnO(CH_2)$	Et	MeMgBr	94	95
4	*n*-Pent	Et	EtMgBr	89	86
5	Et	Et	*n*-PrMgBr	87	85
6	*n*-Pent	Et	*i*-PrMgBr	93	25
7	*n*-Pent	Et	*i*-BuMgBr	80	15

In conjugate addition, it is found that the *ee* of the product depends linearly on the *ee* of the catalyst. Kinetic studies of methyl crotonate and EtMgBr catalyzed by (*R,S*)-Joshiphos (**4-67**) indicated that the rate of the reaction increases on increasing their concentrations. The order of reaction was found 1.1 with respect to the catalyst which suggests involvement of mononuclear species in the catalytic cycle (**Figure 14**). Cu-complex-A was generated by the alkyl transfer from the Grignard reagent which interacts with the carbonyl oxygen of the crotonate **4-72** and forms π–complex **4-73**. Intramolecular rearrangement of π-complex forms σ-complex **4-74**, where Cu forms a σ-bond with β-carbon of enoate and exists in equilibrium with π-complex **4-73**. Reductive elimination of the σ-complex **4-74** delivers the product **4-75** and regenerates complex-A.

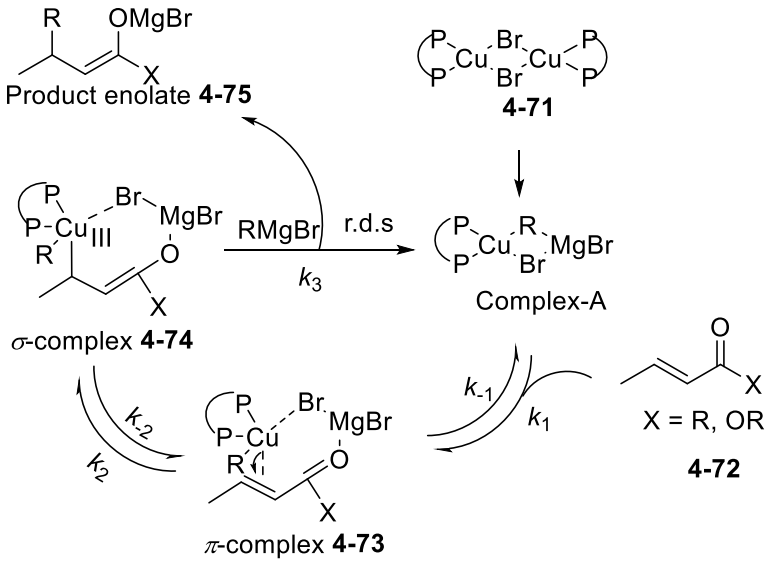


Figure 14. Catalytic cycle of conjugate addition.

Cu-complex-A adopts a distorted tetrahedral geometry which is shown by optimized semiemperical calculations [PM3(tm)]. The Grignard reagent takes the position at the bottom face of the complex, whereas the enone approaches the complex from the least hindered side to form a π-complex with Cu-complex-A using electrons of the sp^2 hybridized carbon atom, this forces the Cu-complex-A to adopt a square pyramidal geometry. Rearrangement of the π-complex leads to a seven membered chair like transition state in which Cu (II) forms a σ-bond with the β-carbon by approaching from the bottom side (**Figure 15**).[58] The methyl group transfer from Cu (III) to the enone unit takes place in such a way that the cyclohexyl moiety present at phosphorous avoids steric interaction.

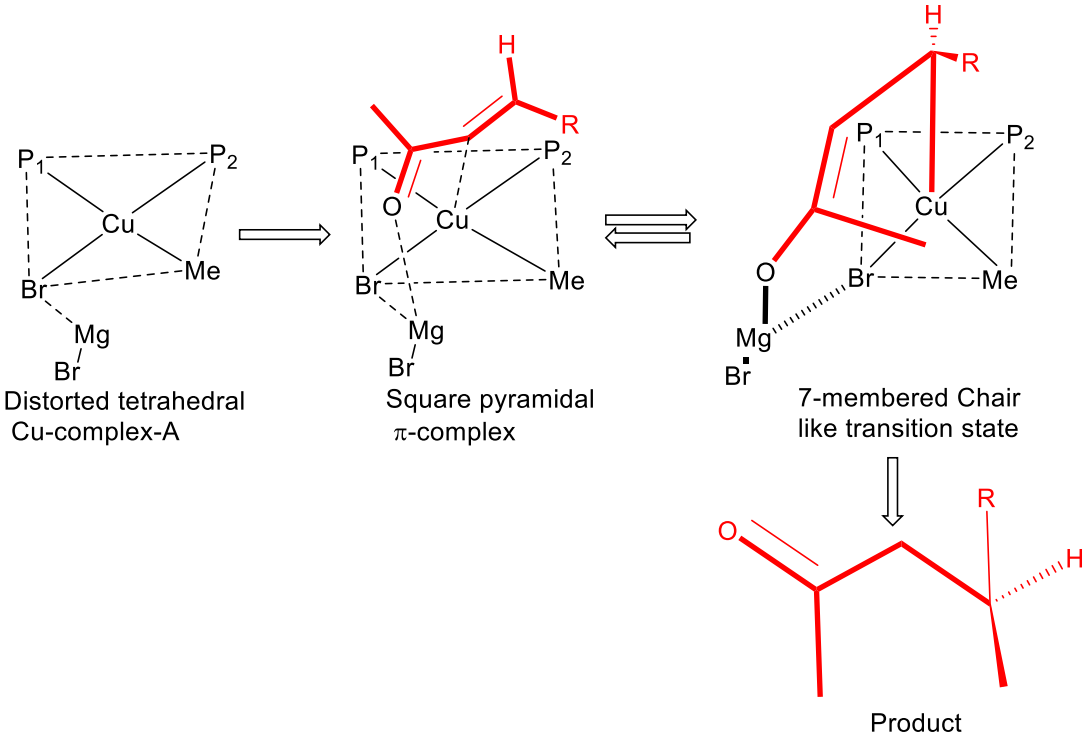
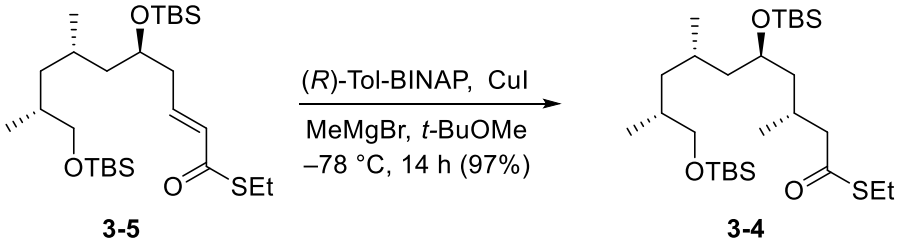


Figure 15. Model for the enantioselective conjugate addition of Grignard reagents (P_1:PPh_2, P_2:PCy_2 of Joshiphos).

4.1.5.1 Conjugate addition of MeMgBr to *α,β*-unsaturated thioester 3-5

Tol-BINAP/CuI-catalyzed conjugate addition of Grignard reagents to *α,β*-unsaturated thioesters attached to an aromatic subunit, and electron donating substituents on the phenyl ring displayed high enantioselectivity but low reactivity.[59] It is believed that conjugation of double bond with aromatic ring reduced the reactivity. The highly desirable addition of MeMgBr to aliphatic *α,β*-unsaturated thioesters **3-5** was achieved in good yield (97%) and high diastereoselectivity (**Scheme 31**).

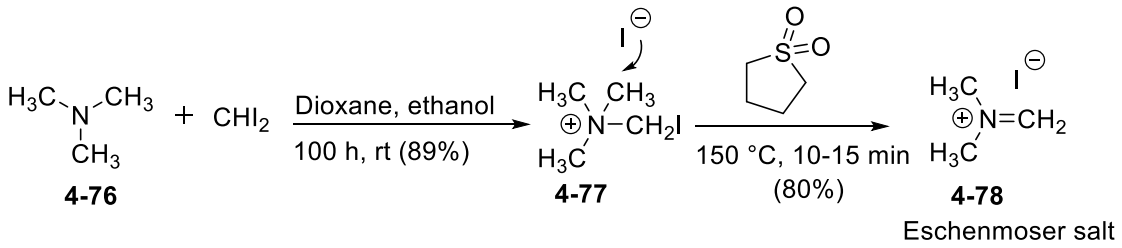


Scheme 31. Synthesis of **3-4** by asymmetric cuprate addition on **3-5**.

4.1.6 Mannich Reaction

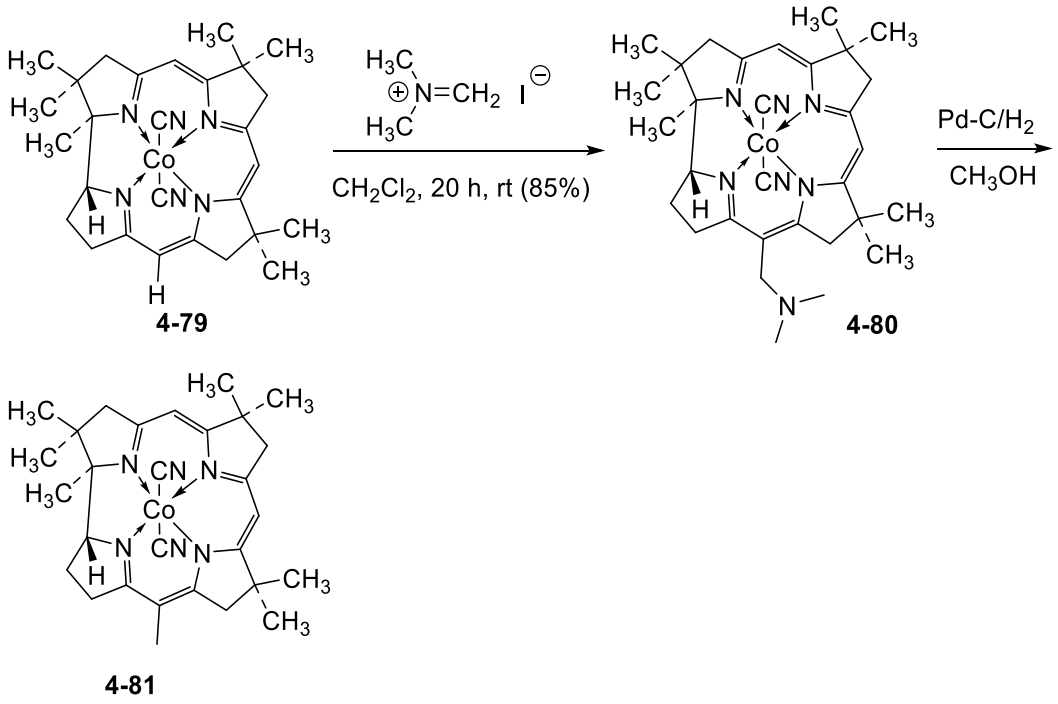
The behavior of dimethyl(methylene)ammonium iodide against nucleophiles was investigated by Eschenmoser [60] in 1971, which had also been used as a highly reactive "Mannich reagent".[61] Originally the Eschenmoser salt was synthesized by heating ammonium salt **4-77** (**Scheme 32**)

in tetrahydrothiophene dioxide at *ca*. 150 °C which formed by dealkylation and elimination of iodide due to ($n \rightarrow \sigma/\sigma \rightarrow \pi$) fragmentation.



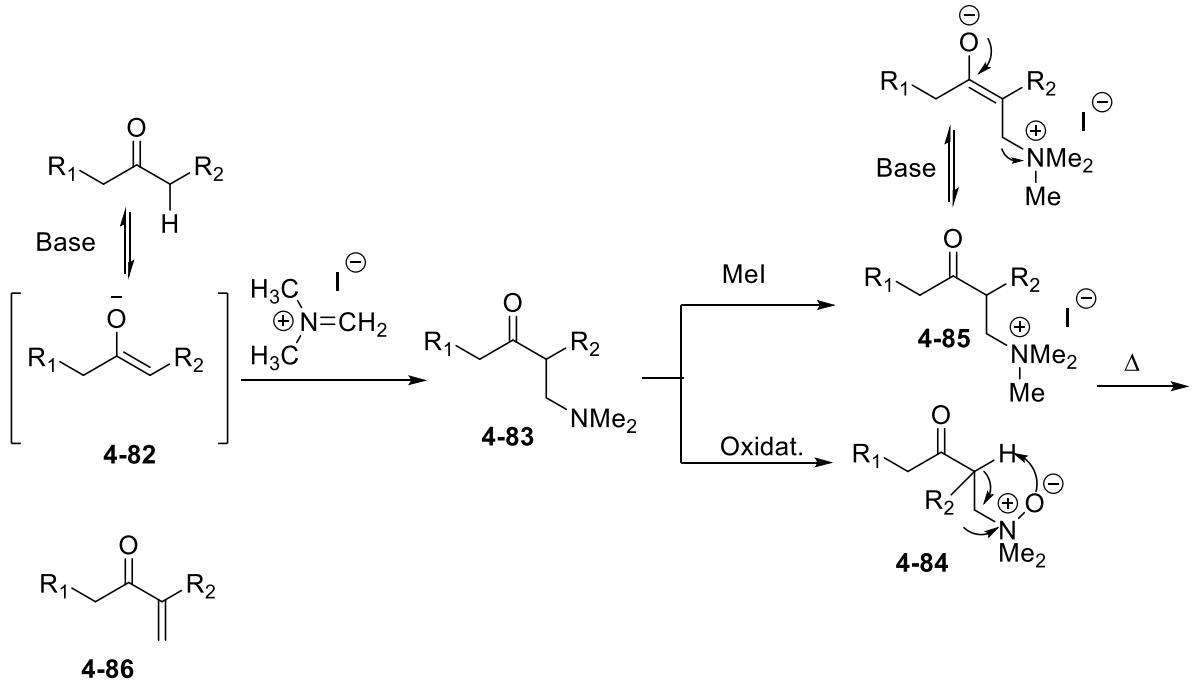
Scheme 32. Synthesis of Eschenmoser salt by Eschenmoser and co-workers.

The Eschenmoser salt is a very strong electrophile, which on reaction with a nucleophile results in aminomethylation. The reaction sequence (**Scheme 33**) shows a simple method of aminomethylation of a sterically unhindered corrin system. Aminomethylated compound **4-80** could be converted into the 15-methylcorrin derivative by hydrogenolysis.



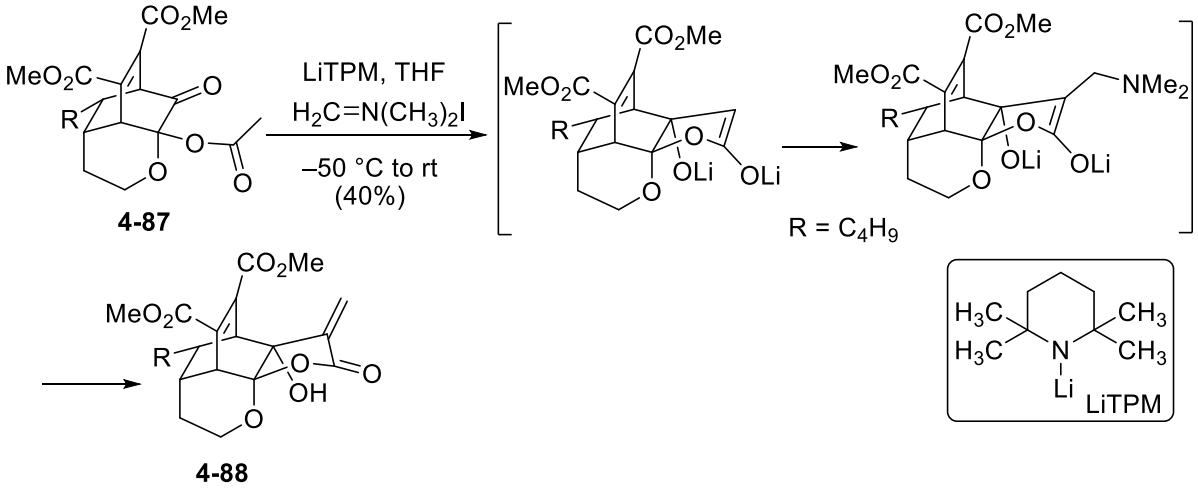
Scheme 33. Preparation of 15-methylcorrin derivative from corrin chromophore by Eschenmoser & co-workers.

Mechanistic studies demonstrate that enolates generated from aldehydes or ketones, are very strong nucleophiles, which attack the iminium ion and furnishes methylated product **4-83**. The amine moiety from **4-83** can be eliminated via heating *N*-oxide **4-84** or ammonium salt **4-85** to get Mannich product **4-86** (**Scheme 34**).



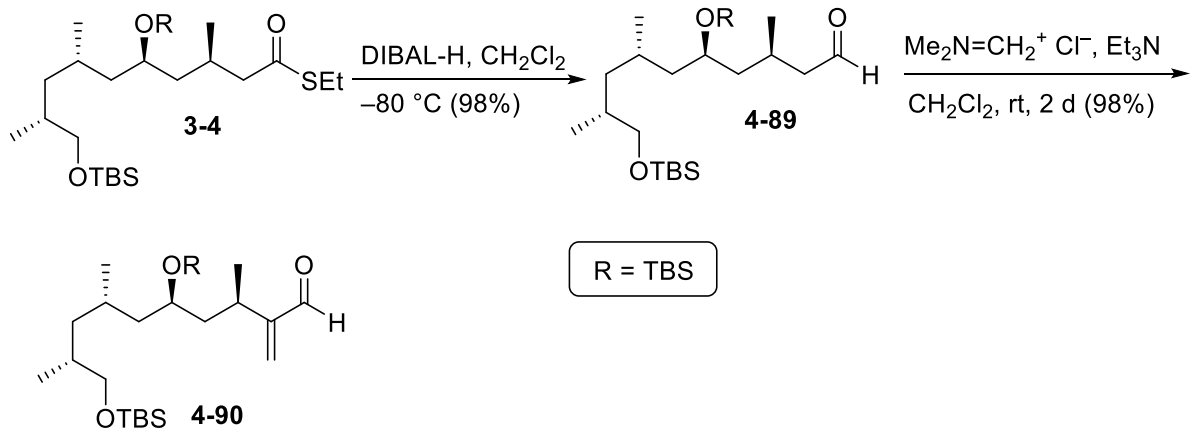
Scheme 34. Mechanism of Mannich reaction.

Exomethylene lactones are cyclic acrylates; which on ring opening polymerization produce polyesters. Exomethylene lactone **4-88** was synthesized during the synthesis of CP-263,114 from **4-87** via the in situ generated lactone.[62]



Scheme 35. One pot lactonization & methylation by Wood and co-workers.

In our case the substrate aldehyde **4-89** was generated by DIBAL-H mediated reduction of thioester **3-4** at low temperature (**Scheme 36**), which on stirring at rt with Eschenmoser salt in CH_2Cl_2 for two days under basic condition produced enal **4-90**. The ^{1}H NMR signals at δ9.51, 6.20, 5.96 ppm corresponding to the C*H*O and *H*$_2$C=CCHO groups, respectively confirmed the enal formation.



Scheme 36. Synthesis of enal **4-90** by Mannich reaction.

4.1.7 Completion of methyl ketone 3-3 synthesis

The DIBAL-H mediated reduction of the aldehyde function of enal **4-90** produced allyl alcohol **4-91** which on further reaction with TsCl in presence of triethyl amine at 0 °C gave a low yield, possibly due to elimination and chloride substitution as shown in **Figure 16**.[63]

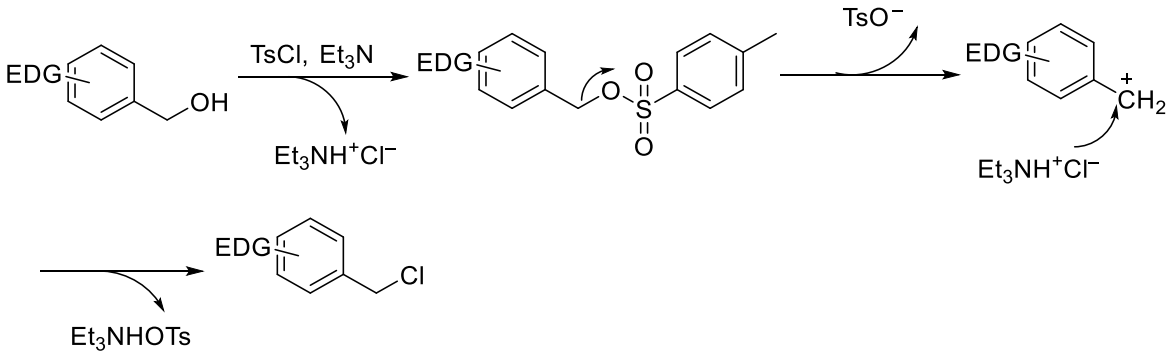
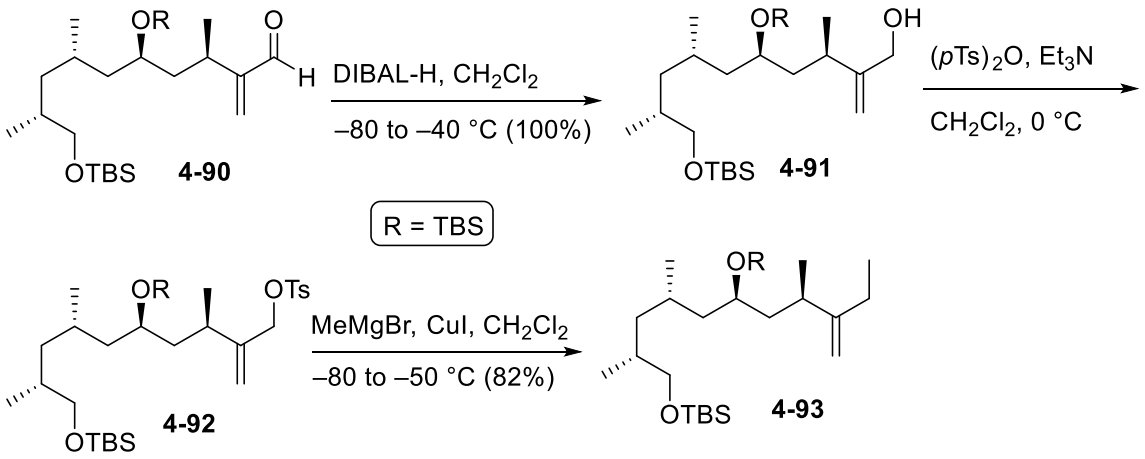


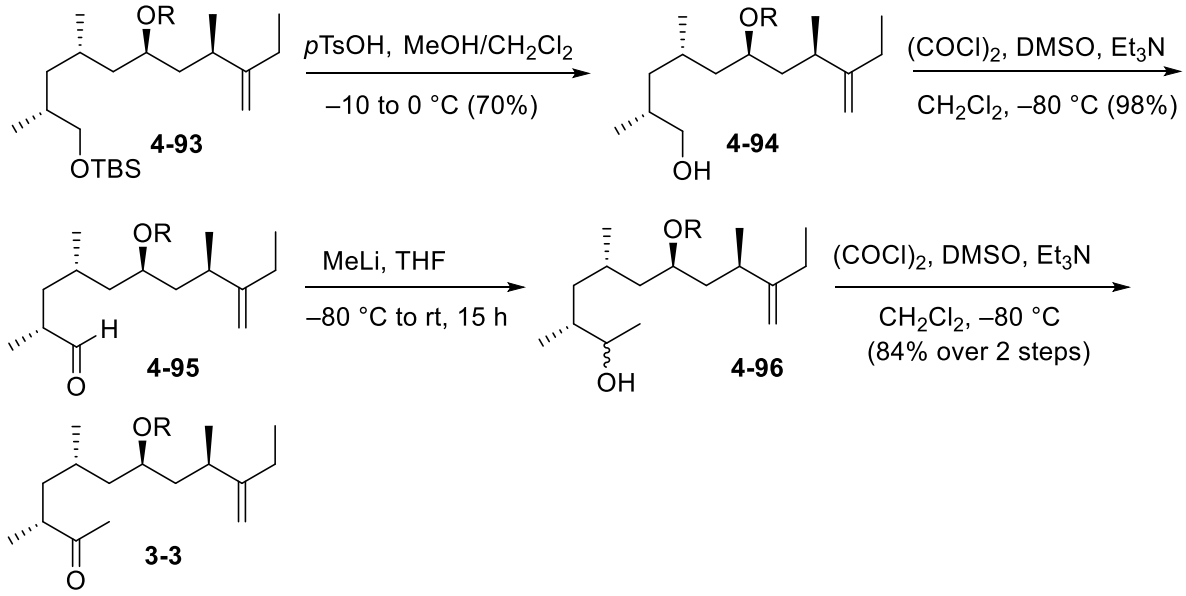
Figure 16. Reaction mechanism of Tosylate substitution by $Et_3N{\cdot}HCl$ proposed by Qi *et al.*

This problem we tackled by using *para*-toluene sulfonic anhydride. The coupling of crude tosylate **4-92** with dimethyl cuprate at low temperature completed the right region of the fragment (**Scheme 37**).



Scheme 37. Introduction of a methyl unit.

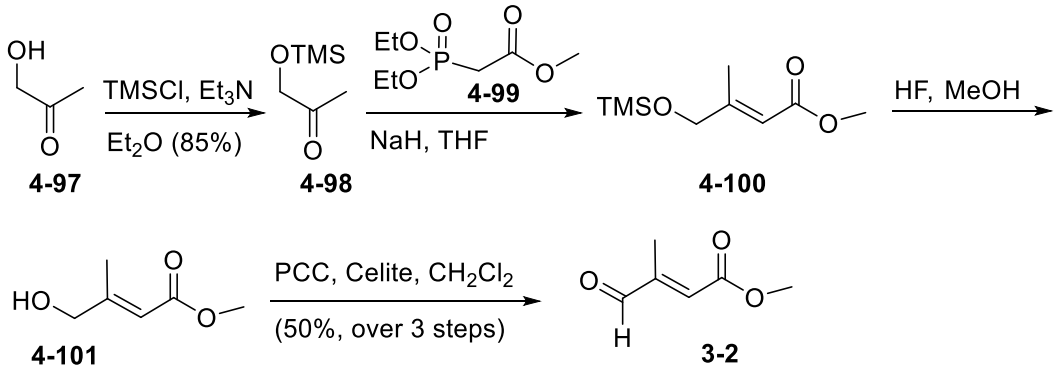
Conversion of **4-93** to methyl ketone **3-3** involved selective cleavage of the primary silyl ether, oxidation of alcohol **4-94** to aldehyde **4-95**, reaction of **4-95** with methyllithium, and Swern oxidation of the intermediate secondary alcohol to ketone **3-3**.



Scheme 38. Synthesis of methyl ketone fragment from primary silyl ether **4-93**.

4.2 Synthesis of methyl 3-methyl-4-oxo-2(*E*)-butenoat (3-2)[64]

The aldehyde **3-2**, which is a second fragment of our synthesis, was synthesized from hydroxyacetone **4-97**. First [(trimethylsilyl)oxy]acetone **4-98** was accomplished on distillation of the filtrate obtained from NaH mediated reaction of hydroxyacetone with TMSCl. The Wadsworth-Emmons reaction of acetone **4-98** with methyl(diethoxyphosphinyl)acetate **4-99** furnished α,β-unsaturated ester **4-100**, which was subjected for the next steps without further purification. Desilylation followed by oxidation with PCC furnished aldehyde **3-2**, which was confirmed by NMR.



Scheme 39. Synthesis of aldehyde **3-2** from hydroxyacetone **4-97**.

4.3 Completion of the formal total synthesis of Amphidinolide Q

4.3.1 Asymmetric aldol reactions

Carbon-carbon bond formation between two carbonyl compounds which is called "aldol reaction" was discovered independently by Charles-Adolphe Wurtz and Alexander Borodin in 1872. Many natural products, mainly poyketides, contain sequences of alternating methyl and hydroxyl groups in the carbon backbone.[65] The relative configuration of vicinal methyl and hydroxyl groups can be controlled by the enolate configuration. *E*-enolates of ketones or ester derivatives produce *anti* aldol whereas *Z*-enolates produce *syn* aldol products provided that the reaction proceeds via a chair-like transition sate (**Figure 17**) known as Zimmerman-Traxler model, proposed by Zimmerman.[66]

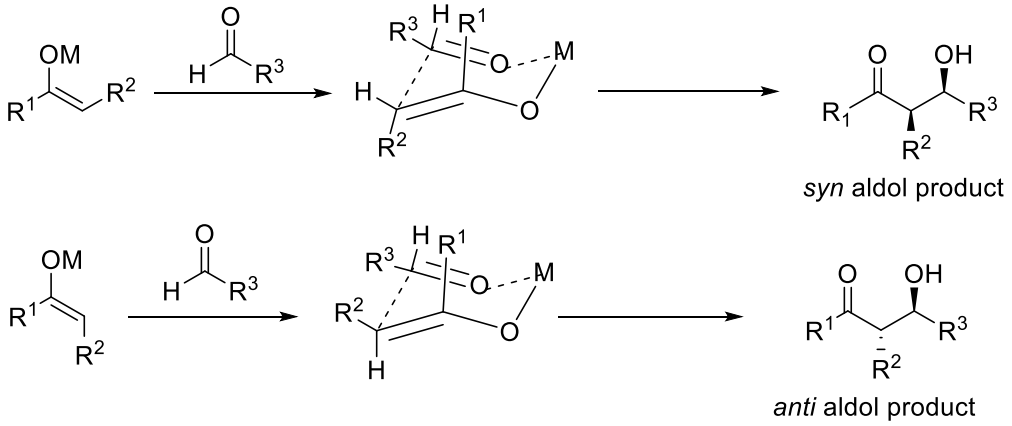


Figure 17. Zimmerman-Traxler transtion states for *E*- and *Z*-enolates.

Chiral adducts could be made by introduction of chirality either in the enolate or in the aldehyde. Evans introduced oxazolidinones as chirals auxiliaries to make diastereoselective *syn* aldol products. [67] The acylated oxazolidinone can only produce the *Z*-enolate on treatment with dibutylboron triflate in presence of a tertiary amine due to a relatively short bond between boron and oxygen, leading to a tight six-membered chair like transition state, which stipulates preferential formation of the *syn* adduct.

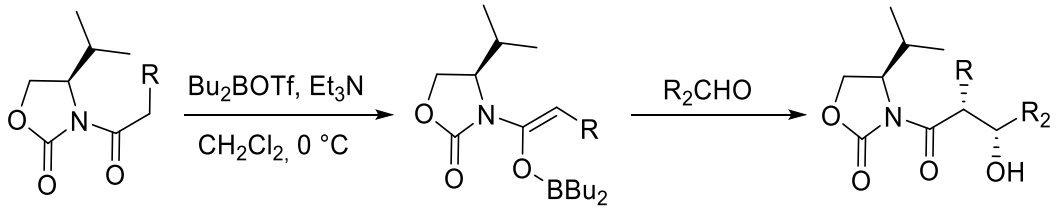


Figure 18. Evans aldol reaction.

Diastereoselectivity is due to the blockage of one side of the enolate by the bulky group in the oxazolidinone ring (**Figure 19**). In the transition state, the carbonyl group of the oxazolidinone and the C-O bond of the enolate tend to arrange in an *anti*-fashion to minimize dipole-dipole repulsions. Therefore, the aldehyde is only allowed to approach the enolate from the less hindered side of the chiral auxiliary.

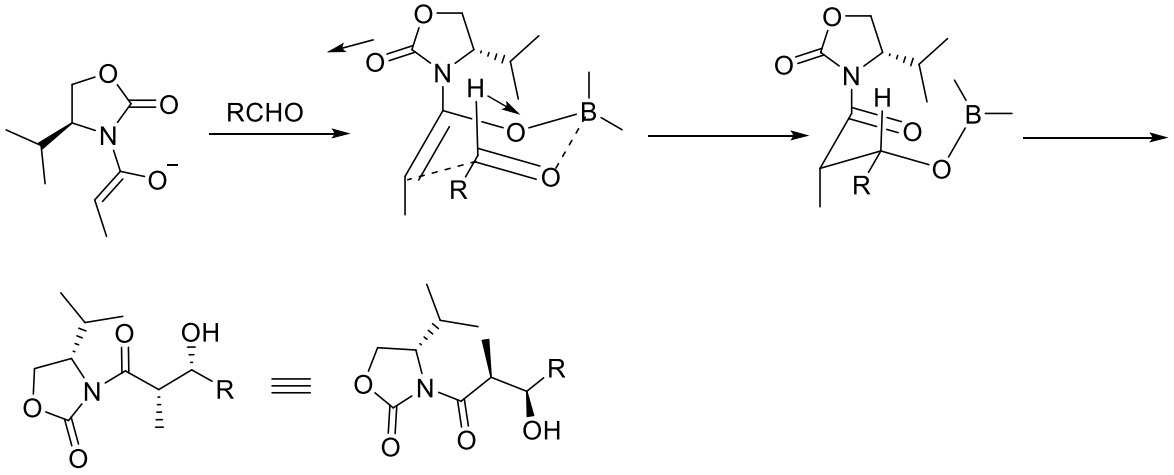
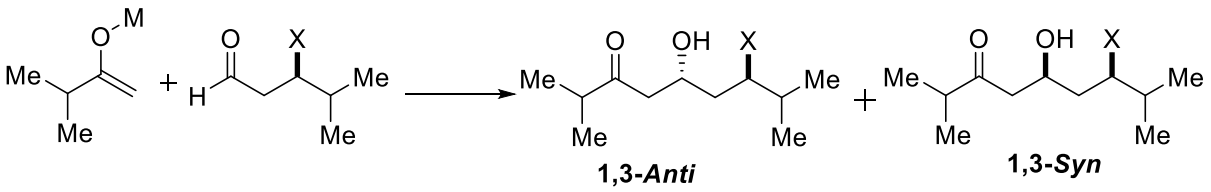


Figure 19. Transition state for Evans aldol reaction.

With chiral aldehydes 1,2- and 1,3-asymmetric induction has been achieved for example during addition of metal enolates and enolsilanes to substituted aldehydes having polar and non-polar substituents at the *β*-position. The best results were obtained with $BF_3 \cdot OEt_2$ in Mukaiyama aldol reactions (**Table 3**).[68] It is believed that cooperative electrostatic and steric effects combine to influence the direction and degree of 1,3-induction.

Table 3. Aldol reaction of 3-methyl-2-butanone enolates with *β*-substituted addehydes by Evans & co-workers.



4-102, X = OPMB ($OCH_2C_6H_4$-*p*-OMe)
4-105, X = OTBS ($OSiMe_2tBu$)

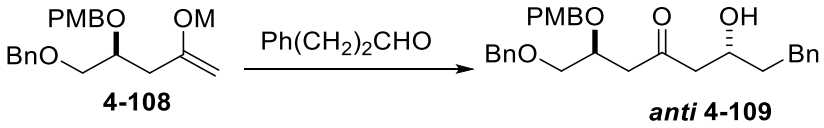
4-103
4-106

4-104
4-107

entry	conditions	metal (M)	**103:104**	**106:107**
			(X = PMB) (%)	(X = TBS) (%)
1	LDA	Li	71:29 (100)	76:24 (91)
2	$TiCl_4$/*i*-Pr_2NEt	$TiCl_n$	60:40 (98)	58:42 (98)
3	9-BBNOTf/*i*-Pr_2NEt	BR_2	42:58 (82)	52:48 (79)
4	$BF_3{\cdot}OEt_2$	$SiMe_3$	92:8 (91)	80:20 (84)

Excellent 1,5 *anti*-diastereoselective induction was observed with dihydrocinnamaldehyde and enolate **4-108**, due to similar steric requirements of the *β*-substituents and partial responsibility of electrostatic effects for enolate face selectivity (**Table 4**).[69]

Table 4. 1,5-Induction with various metal enolates by Evans & co-workers.

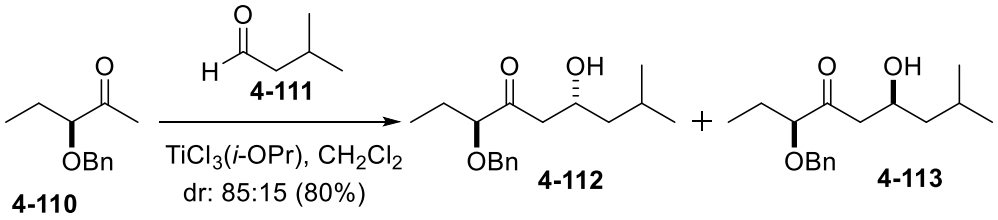


4-108

***anti* 4-109**

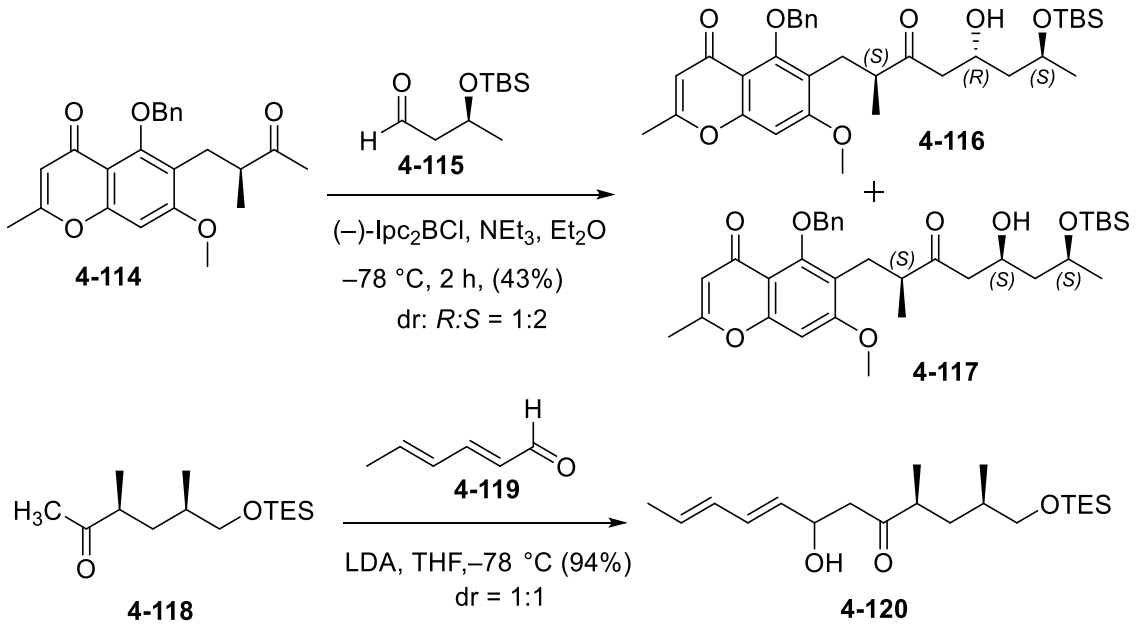
entry	M	*T* (°C)	solvent	yield (%)	*anti*/*syn*
1	Cy_2B	–78	CH_2Cl_2	85	82:18
2	Bu_2B	–78	CH_2Cl_2	80	87:13
3	Bu_2B	–78	PhMe	81	94:06
4	Bu_2B	–78	Et_2O	83	94:06
5	Bu_2B	–115	Et_2O	85	98:02
6	TMS/$BF_3{\cdot}OEt_2$	–78	CH_2Cl_2	85	50:50
7	Li	–78	THF	79	40:60

Good levels of 1,4-*anti* asymmetric induction was obtained in the $TiCl_3$(*i*-PrO)-mediated aldol reaction of *α*-benzyloxy methyl ketone **4-110** with achiral aldehyde **4-111** (**Scheme 40**).[70]



Scheme 40. Titanium-mediated aldol reaction of aldehyde **4-110** and isobutyraldehyde by Urpí & co-workers.

(–)-Ipc$_2$BCl and LDA mediated 1,4-*anti* asymmetric induction was reported during the synthesis of Chaetoquadrins A-C and Abyssomicin C, respectively (**Scheme 41**).[71]

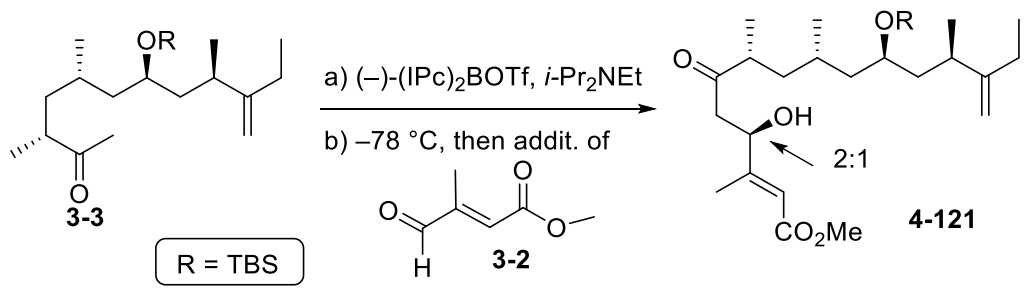


Scheme 41. (–)-Ipc$_2$BCl and LDA mediated aldol reactions by Brimbley & Sorensen.

4.3.1.1 1,4-Asymmetric aldol reactions of methyl ketone 3-3 and aldehyde 3-2

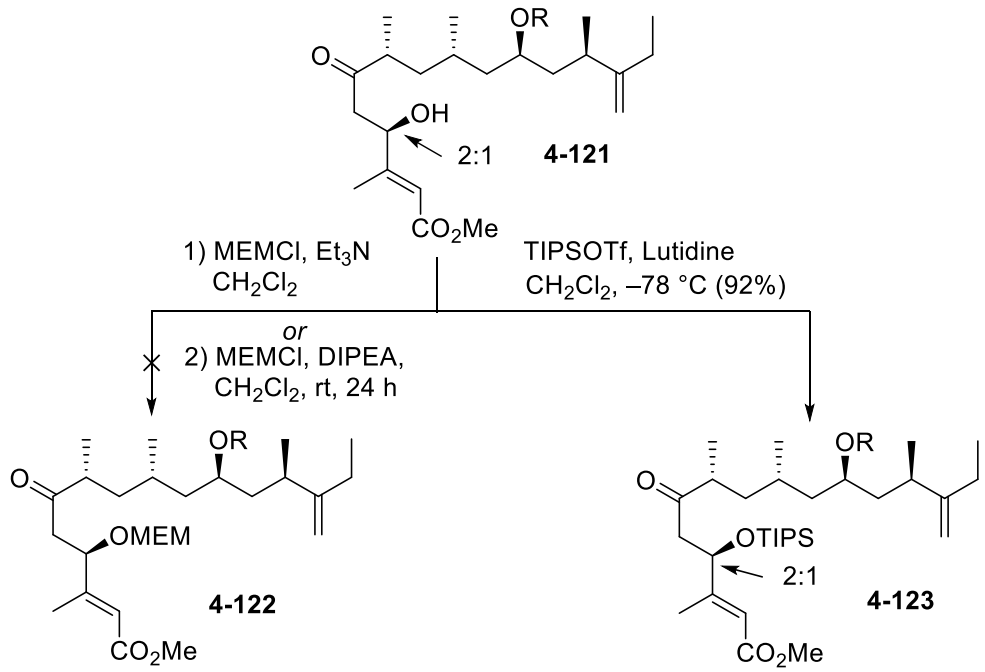
It is clear from the above discussion that there is no evidence which shows very good 1,4-*anti* asymmetric induction without having a stereocenter in the aldehyde. With building block **3-3** in hand, we now could focus on the crucial aldol reaction with aldehyde **3-2**. Using LDA as base in THF at –78 °C a low yield of the hydroxyketones **4-121** was obtained (**Table 5**). The observed diastereoselectivity of 1:1 indicated that there was no substrate control operative. An even lower yield (14%) resulted when trichloro isopropoxy titanium was used for the enolization. Higher chemical yields were realized if boron enolates of methyl ketone **3-3** were employed. Thus, with dicyclohexylboron triflate (Cy_2BOTf)/Et_3N in CH_2Cl_2 the derived enolate reacted with aldehyde **3-2** in 71% yield (dr = 1:1). Even higher yields were observed when (–)-disopinocamphenyl boron triflate/Hünigs base was used for enolate formation. In this case, the desired C4 diastereomer was formed as the major one. Unfortunately, at this stage neither chromatographic separation nor the determination of relative amounts by ^{1}H NMR was possible. We hoped that it would be possible to separate the isomers on the macrolactone stage.

Table 5. Attempted 1,4-asymmetric induction with various metal enolates.



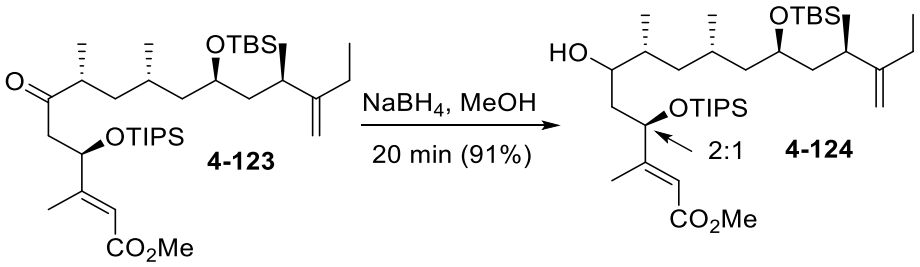
entry	reagent	enolization temp.	yield %	dr
1	$TiCl_3$(*i*PrO)	–78 °C	14	1:1
2	LDA	–78 °C	24	1:1
3	Cy_2BOTf	–78 °C	71	1:1
4	(–)-$(Ipc)_2BOTf$	–78 °C to rt	89	2:1
5	(–)-$(Ipc)_2BOTf$	–78 °C to –50 °C	80	2:1

Once the aldol adduct was in hand, the *β*-hydroxy group of the aldol product required protection to exclude side reactions such as *retro*-aldol and esterification to form a 5-membered lactone. Therefore **4-121** was subjected to methoxyethoxymethyl chloride (MEMCl) under basic conditions at room temperature but product delivery was not observed whereas decomposition was noticed. Then we tried to make silyl ether **4-123** using TIPSOTf under basic conditions at low temperature, but the yield was still poor. Then we noticed if TIPS cation is generated first by mixing TIPSOTf and lutidine at –78 °C, and then allowed to react with alcohol **4-121** the product delivery was excellent without any decomposition. It is believed that decomposition is due to *retro*-aldol reaction.



Scheme 42. Silylation of **4-121** into ketone **4-123**.

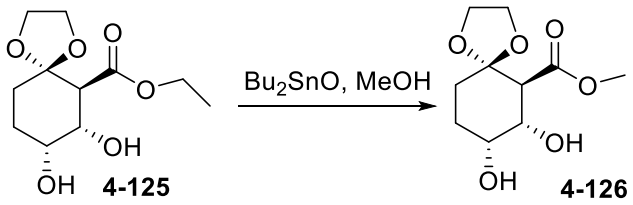
We also have tried reduction of keto function of **4-123** into alcohol **4-124** to separate the diastereomeric mixture at this stage but it was rather difficult. (**Scheme 43**).



Scheme 43. Reduction of ketone **4-123** into alcohol **4-124**.

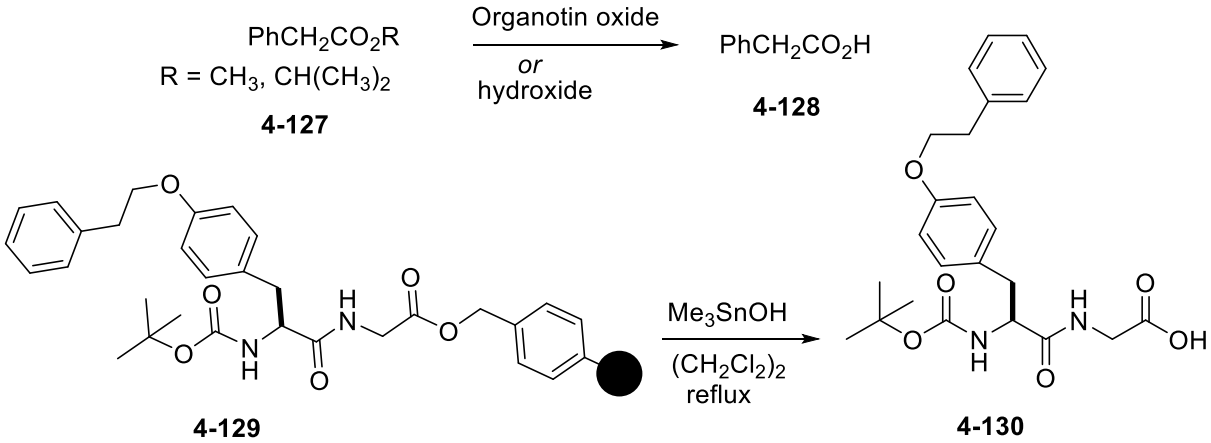
4.3.2 Ester hydrolysis

The base mediated saponification turned out to be difficult. Mild and selective hydrolysis is crucial at late stage of a synthesis. During dibutyltin oxide-mediated O-methylation of compound **4-125** Giannis & co-workers observed the formation of methyl ester **4-126** as a side product without elimination and epimerization at the stereogenic center adjacent to the ester moiety (**Scheme 44**).[72]



Scheme 44. Dibutyltin oxide catalyzed transesterification of ethyl ester **4-125** into methyl ester **4-126** by Giannis & co-workers.

Mascaretti & co-workers have reported the use of bis(tributyltin) oxide (BBTO) and trimethyltin hydroxide (TMTOH) for the chemoselective cleavage of alkyl and aromatic carboxylic esters (**Scheme 45**).[73]



Scheme 45. Trimethyltin hydroxide mediated ester hydrolysis by Mascaretti & co-workers.

Trimethylstannyl 2-phenylacetate ($C_6H_5CH_2CO_2Sn(CH_3)_3$) was isolated in the reaction of Me_3SnOH mediated hydrolysis of methyl 2-phenylacetate and was characterized using IR, ^1H, ^{13}C and ^{119}Sn NMR spectroscopy. On the basis of these findings Mascaretti proposed mechanism of ester hydrolysis which is shown in **Figure 20**.

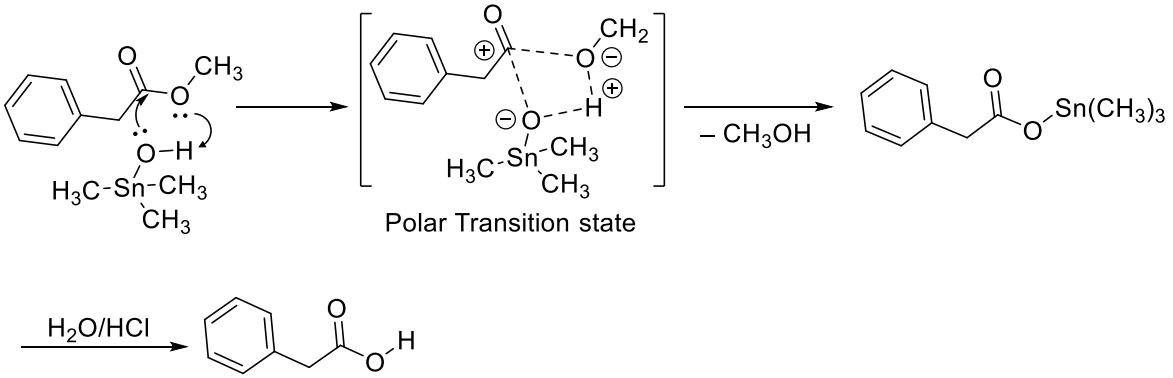
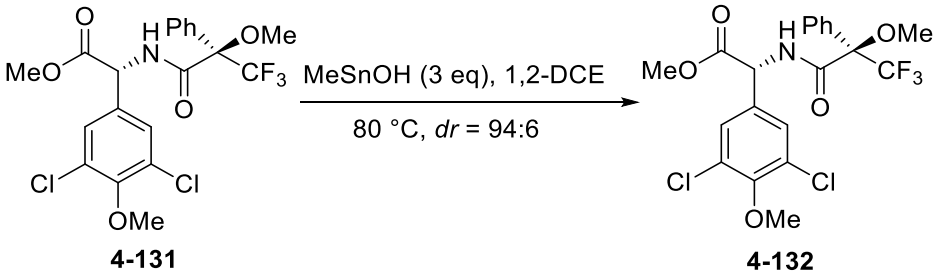


Figure 20. Mechanism of TMTOH mediated ester hydrolysis proposed by Mascaretti.

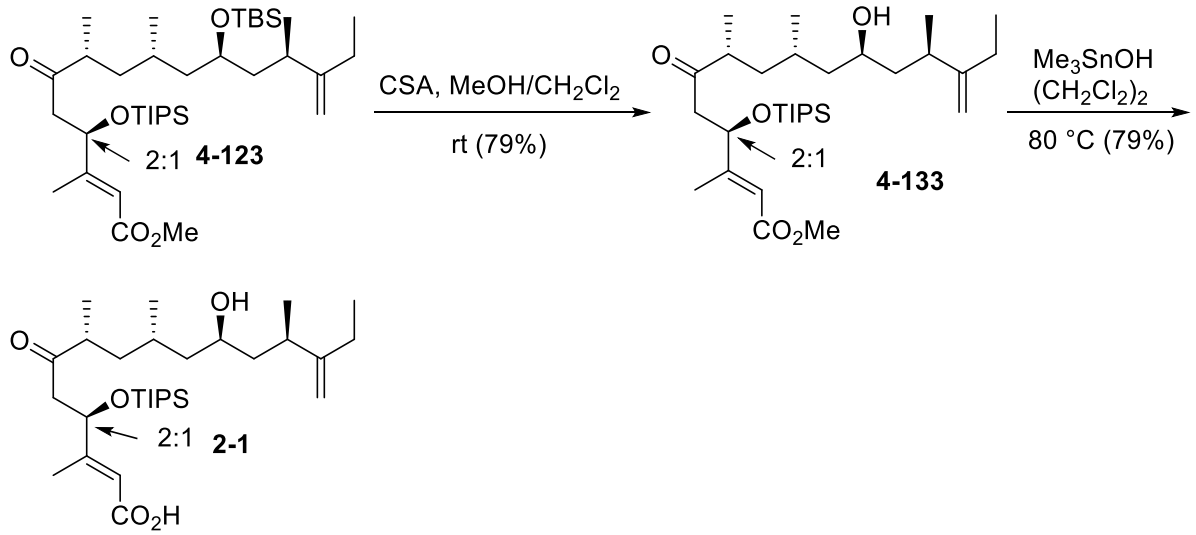
Nicolaou used Me_3SnOH in 1,2-dichloethane at 60-80 °C for the hydrolysis of differently substituted "thiostreptones" and chlorinated (*R*)-Mosher amide-(*R*)-4-hydroxyphenylglycine derivative (**Scheme 46**).[74]



Scheme 46. Methyl ester hydrolysis of chlorinated (*R*)-Mosher amide-(*R*)-4-hydroxyphenylglycine derivative.

4.3.2.1 TMTOH mediated hydrolysis of ester 4-133

It is evident from the above discussion that TMTOH mediated hydrolysis is highly chemoselective. The C11-silyl ether **4-123** was cleaved by acid induced transetherification to get substrate **4-133** for ester hydrolysis. Gratifyingly, at the stage of hydroxyl ester **4-133**, separation of the C4 isomers was possible (2:1 mass ratio), which allowed determination of the ratio by weight (**Scheme 47**).



Scheme 47. Transetherification of **4-123** and hydrolysis of **4-125** into *seco*-acid **3-1**.

4.3.3 Yamaguchi macrolactonization

Now the next step of our synthesis is macrolactonization. Many efficient macrocyclization techniques have been developed over the years such as the RCM, intramolecular cross-coupling, Nozaki-Hiyama-Kishi, and HWE reactions, but lactonization of *seco*-acids is still the most frequently used approach to obtain macrocyclic lactones. Direct cyclization of alcohol and carboxylic acid often is not possible due to entropic and enthalpic factors. Therefore one partner must be activated before cyclization. One of the most frequently used reagent for this purpose is 2,4,6-trichlorobenzoyl chloride (TCBC) which activates the acid part via a mixed anhydride in presence of triethylamine or Hünigs base (**Figure 21**).[75] The mixed anhydride obtained in

this process is dissolved in toluene and slowly added by syringe pump to a highly diluted solution of DMAP (2-5 equiv.) at elevated temperature (80 ºC or reflux).

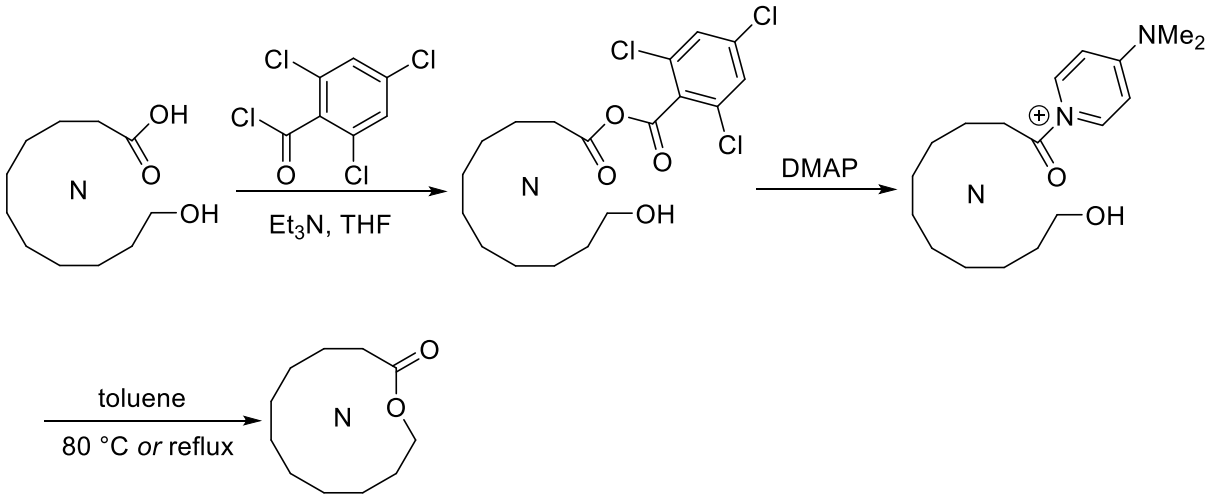
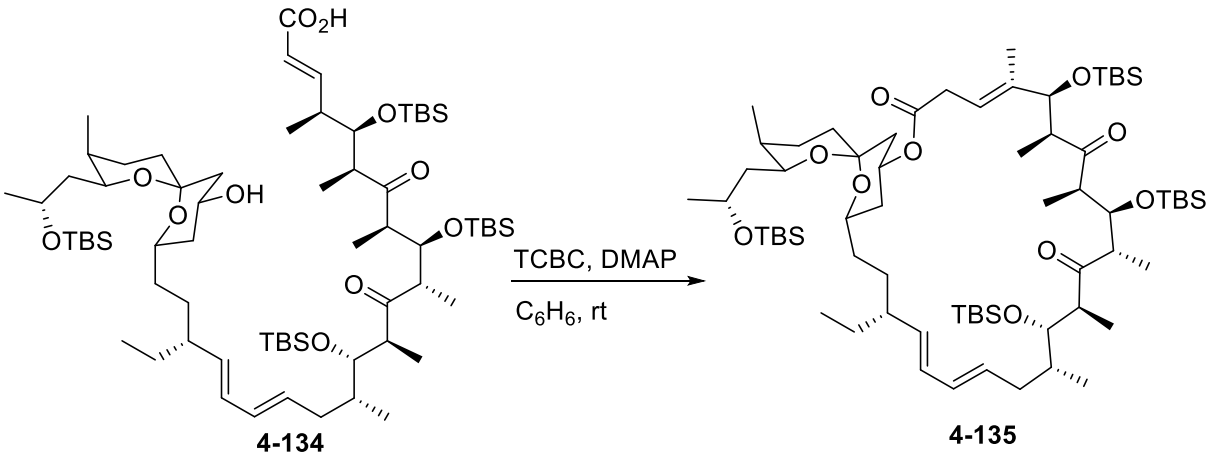


Figure 21. Mechanism of Yamaguchi macrolactonization.

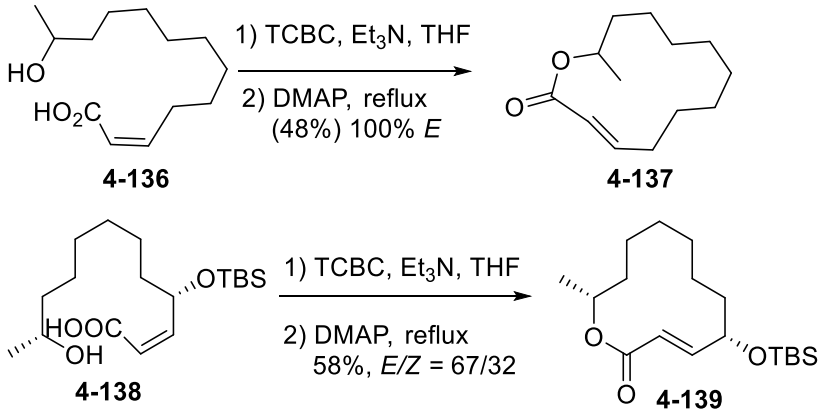
The use of the 2,6-dichloro derivative and pyrrolidinopyridine as supernucleophilic catalyst has also been described.[76] Competitive formation of a symmetrical anhydride was observed during the total synthesis of hygrolidin.[77] Evans reported the necessity of $Et_3N{\cdot}HCl$ filtration in the synthesis of roxaticin to prevent the acid-promoted decomposition of the polyene unit.[78] In the total synthesis of epothilone C a polymer-supported DMAP reagent has been used.[79] There are several variations and modifications of the original Yamaguchi procedure. Two major modifications have been reported by Yonemitsu in several papers.[80] The first modification in the Yamaguchi procedure was reported by Yonemitsu, known as "modified Yamaguchi conditions", where a large amount of DMAP is added to the performed mixed anhydride at room temperature. These conditions have been utilized by Evans in the synthesis of oleandolide [81] and bryostatin.[82] The second modified Yamaguchi procedure is known as "Yonemitsu conditions", in that DMAP is directly introduced at room temperature from the beginning. These less basic conditions became highly efficient and Evans used them in the total synthesis of rutamycin B.[83] Keck, Mukaiyama, and Corey procedures gave mainly the deconjugated *β/γ* lactone as the major product and the classical Yamaguchi procedure gave a 1:1 mixture of the *β/γ* and *α/β* lactones (**Scheme 48**).



4-134 4-135

Scheme 48. Isomerization of the α, β to the β, γ double bond.

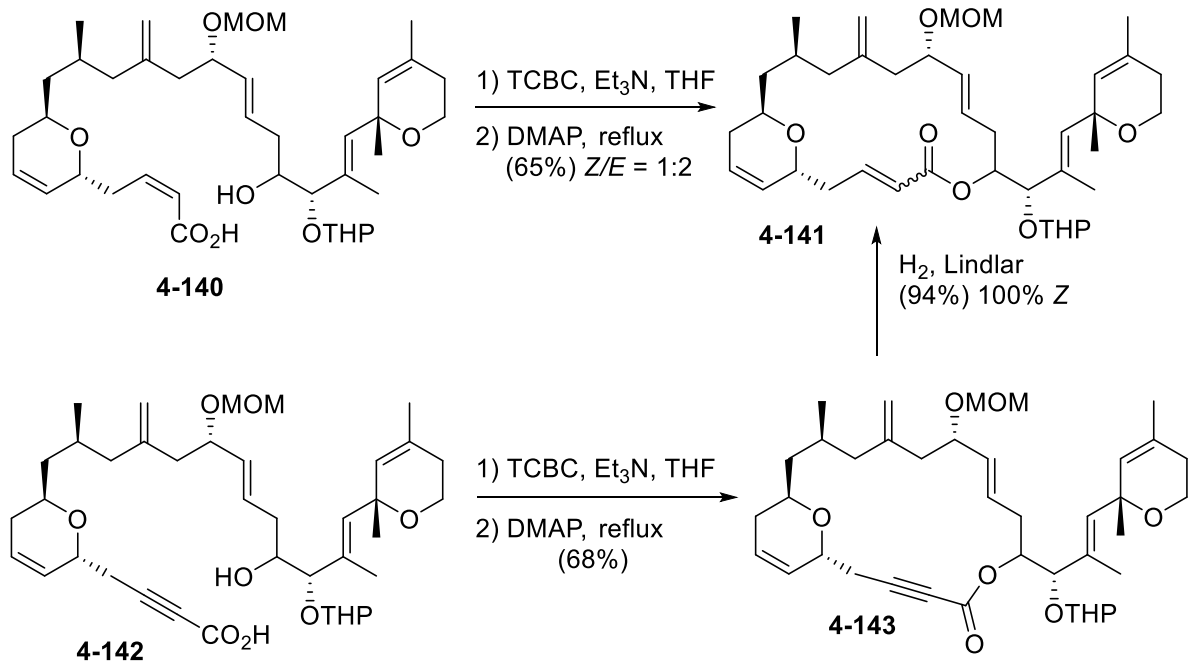
The major disadvantage of the Yamaguchi macrolactonization is the use of the highly basic DMAP and high temperature. These aspects occasionally can lead to obnoxious side reactions such as α,β to β,γ isomerization of conjugated double bonds, epimerization of susceptible chiral centers,[84] and *Z/E* isomerization of conjugated double bonds (**Scheme 49**).[85]



4-136 4-137 4-138 4-139

Scheme 49. Isomerization of conjugated double bonds under Yamaguchi conditions.

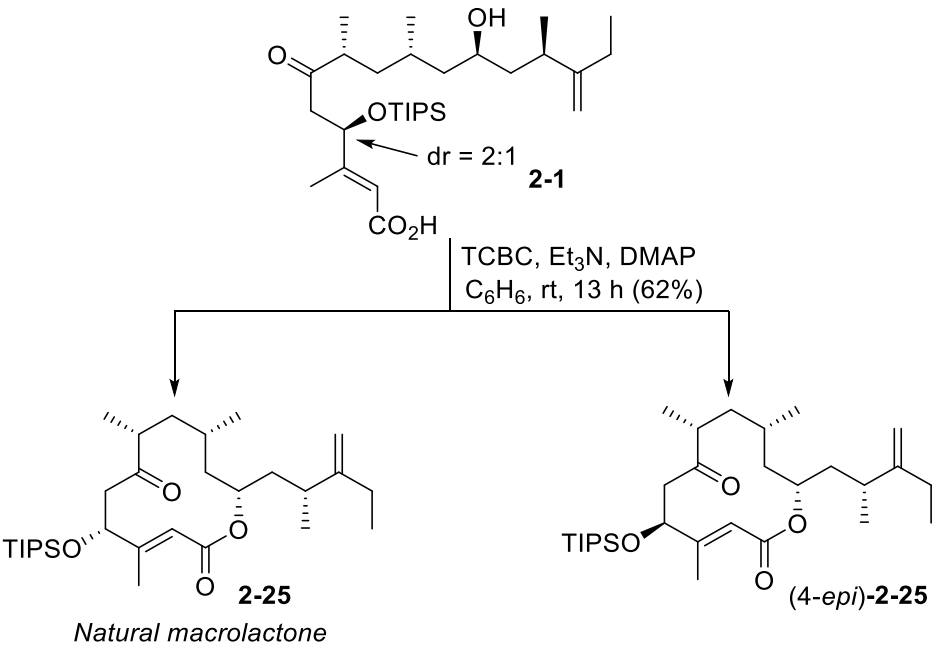
A possible solution for the problem of *Z/E* isomerization could be macrolactonization of the ynoic *seco*-acid followed by hydrogenation of the triple bond (**Scheme 50**).[86] A review partially devoted to the Yamaguchi macrolactonization protocol was composed by Campangne.[87]



Scheme 50. A possible solution to the isomerization of double bonds.

4.3.3.1 Macrolactonization of *seco*-acid 2-1

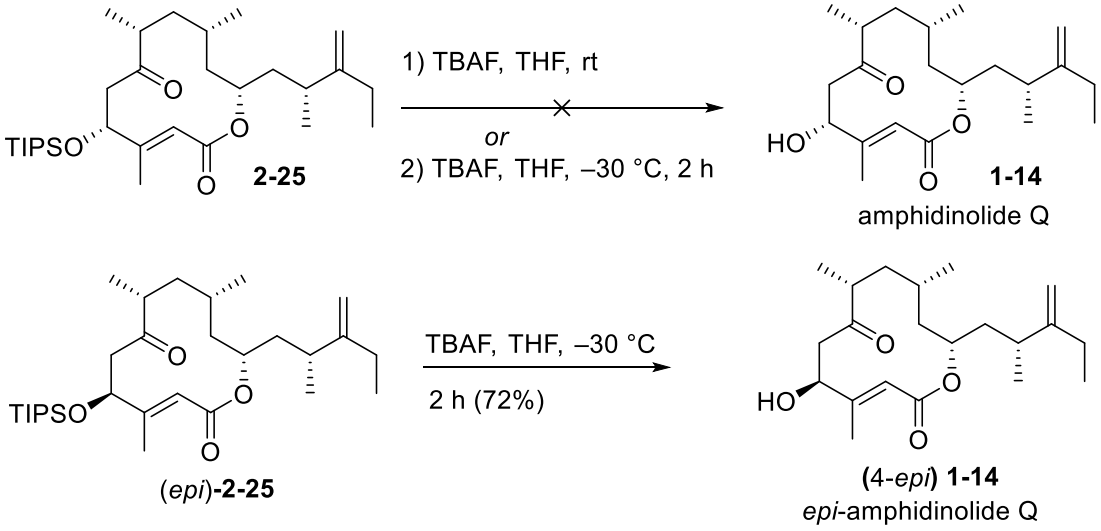
Subjecting the *seco* acid **2-1** to the modified conditions of a Yamaguchi macrolactonization led to two macrolactones **2-26** and (*epi*)-**2-26** that indeed could be separated by chromatography even more easily than hydroxy ester **4-133**. Therefore, in practice, the mixture of diastereomers from the aldol reaction was carried on to the macrolactone stage. The NMR data of the major isomer **2-26** perfectly matched with the published data.[15]



Scheme 51. Yamaguchi macrolactonization of *seco*-acid **2-1** into lactones **2-25** and (4-*epi*)-**2-25**.

4.4 Total synthesis of 4-*epi* Amphidinolide Q

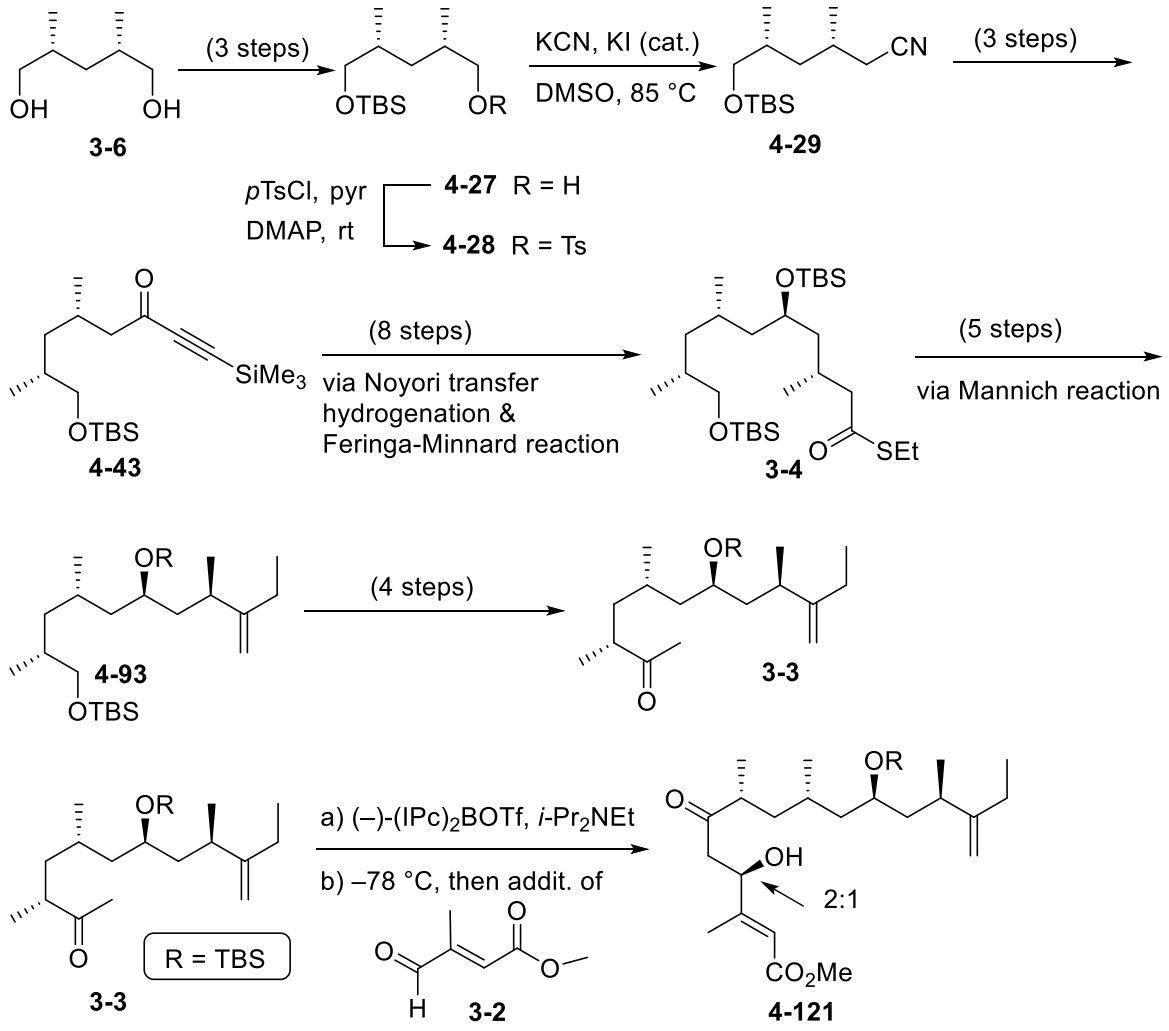
The macrolactone **2-26** was finally subjected for cleavage of silyl ether under strong basic (tetrabutylammonium fluoride) conditions at rt and –30 °C, but in both conditions only decomposition was observed. However, when (4-*epi*)-**2-25** was subjected for deprotection the formation of *epi*-Amp-Q was possible (**Scheme 52**).



Scheme 52. Desilylation of TIPS-ethers **2-25** and (4-*epi*)-**2-25**.

5 Conclusion I

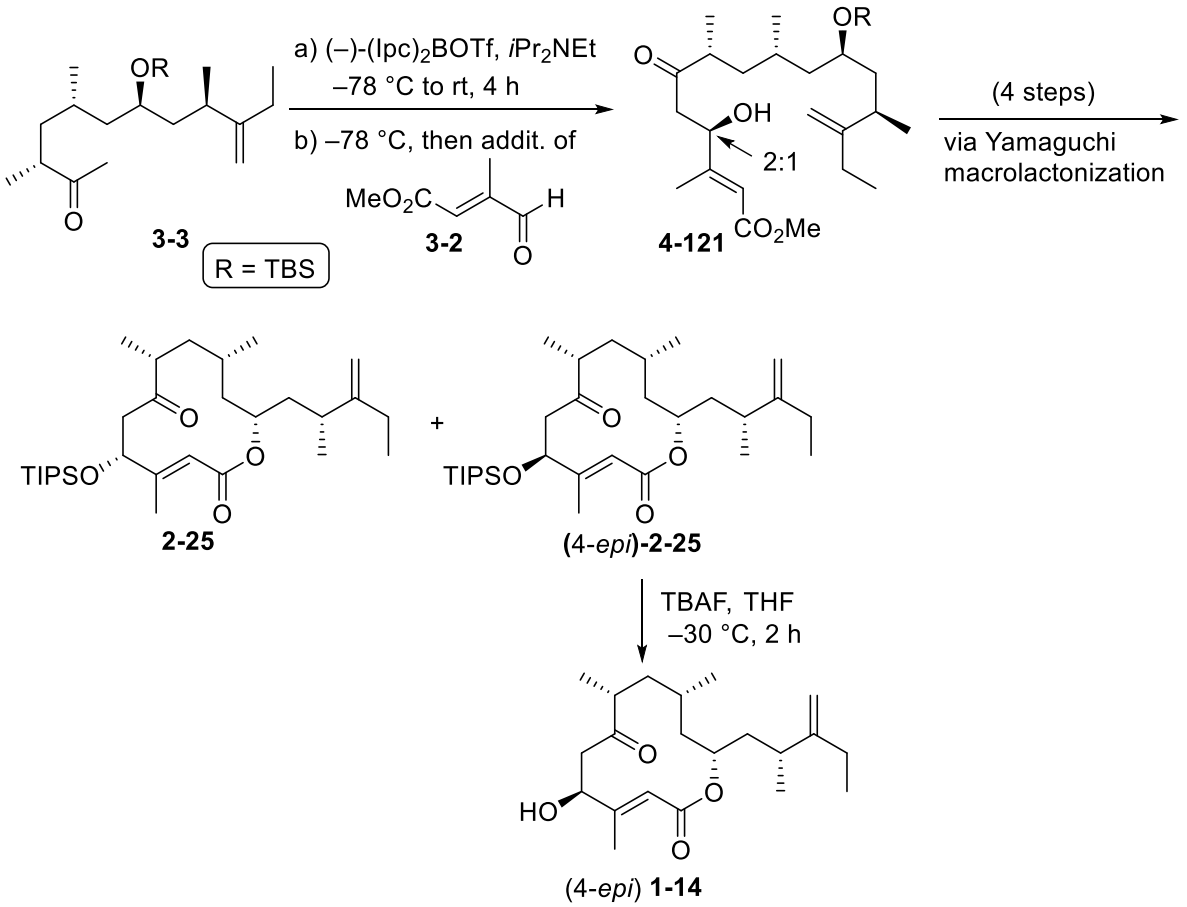
In summary, we developed a short and efficient formal total synthesis of Amphidinolide-Q and a total synthesis of its *epimer*. The *seco* acid **3-1** has been disconnected into fragments of unequal sizes suitable for an aldol reaction which is not common. The C5-C16 fragment **3-3** was efficiently prepared from known alcohol **4-27**, which itself is easily available from *meso*-diol **3-6** via enzymatic desymmetrization. In a sequence of 22 steps key transformations include a Noyori transfer hydrogenation on alkynone **4-43**, as we faced an unexpected problem during hydroboration oxidation of alkyne **4-48** into aldehyde **4-53**. A Feringa-Minnard asymmetric cuprate addition was performed on gram scale on thioester **3-5** and a Mannich reaction on aldehyde **4-89**. The resulting enal **4-90** served as entry point to create the butenyl terminus of this natural product. The derived allylic alcohol **4-91** was converted to the corresponding tosylate which upon reaction with dimethyl cuprate gave the required functionality.



Scheme 53. Key intermediates in the synthesis of major fragment of Amphidinolide Q.

Several reaction conditions have been screened for aldol reaction but unfortunately none of them had delivered good diastereoselectivity. The combination (–)-diisopinocampheylboron

triflate/Hünig base has been used for further studies which delivered 2:1 diastereoselection. At this stage the diastereomeric mixture was not possible to separate. We believed that it would be separable after macrolactonizatuion. The mixture after TBS-ether desilylation was separated for weight determination of both isomers. The separation at this stage is not that easy. Therefore, separation at the stage of the macrolactonization is recommended.



Scheme 54. Aldol reaction and Yamaguchi macrolactonization along with cleavage silyether.

Modified Yamaguchi macrolactonization conditions of *seco*-acid led to the formation of two C4 diasteromers (2:1 ratio). Both isomers have been subjected for ether cleavage but only (4-*epi*)**-2-25** delivered the product (4-*epi*) **1-14** whereas the major isomer was found unexpectedly decomposed.

Chapter 2

C–H-Activation Approach towards the Core Structure of the Alkaloid γ-Lycorane

6 Introduction

Plants are used for the treatment of medical conditions from the ages as traditional medicines. They are rich sources of biologically active compounds such as alkaloids, terpenes etc. Amaryllidaceae, a family of herbaceous, perennial and bulbous (rarely rhizomatous) flowering plants (**Figure 22**), is an owner of an exclusive group of alkaloids; they have been isolated from the plants of all genera of the family. The Amaryllidaceae alkaloids represent a large group of tyrosine and phenyl alanine derived alkaloids.

Figure 22. Amaryllidaceae species from genera such as Galanthus (snowdrops, left) and Narcissus (daffodils, right).

A large number of structurally diverse Amaryllidaceae alkaloids could be classified mainly into eight skeletal systems (**Figure 23**).[88] Crinine (**6-1**) alkaloids comprise a 2,3,4,4a-tetrahydro-1*H*,6*H*-5,10b-ethanophenanthridine (*cis*-3a-aryloctahydroindole nucleus). They have been synthesized by the cyclizations of a bicyclic amine via an intramolecular Heck reaction followed by oxidation generating a tetracyclic spirocyclohexadione.[89] They display interesting biological property such as immune-stimulatory, cytotoxic, antimalarial, and anticholinergic activities. Lycorine (**6-2**) alkaloids are tetracyclic pyrrolo-[*d,e*]phenanthridine frameworks (galanthan ring system) whereas galanthamine (**6-3**) type of alkaloids feature (4a*S*, 6*R*, 8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a, 3, 2-*ef*][*2*]benzazepin-6-ol and wear three chiral centers. Galanthamine hydrobromide is a tertiary alkaloid drug that has been developed and approved in the USA and several countries in Europe as a treatment for mild-to-moderate Alzheimer's disease.[90] Phenanthridine (**6-4**) alkaloids include (±)-pancratistatin and 3-*epi*-pancratistatin, structurally they have a B/C-trans fused ring junction. It was proved that pancratistatin selectively induces apoptotic cell death in a variety of human

cancer cells without affecting non-cancerous cells.[91] Plicamine (**6-5**) is rare dinitrogenous alkaloids of the Amarayllidaceae family. It has an unusual tetracyclic core containing a 6,6-spirocyclic system defining three stereogenic centers.[92] At present there is no evidence for useful biological activity. Montanine (**6-6**) alkaloids are characterized by an unique 5,11-methanomorphanthridine skeleton, they include brunsvigine, pancracine, montanine, coccinine, manthine and nangustine. Homolycorine (**6-7**) alkaloids are lactones with B/C-*cis* fused rings. Gracilamine (**6-8**) is a dinitrogenous alkaloid, which has a complex structure.

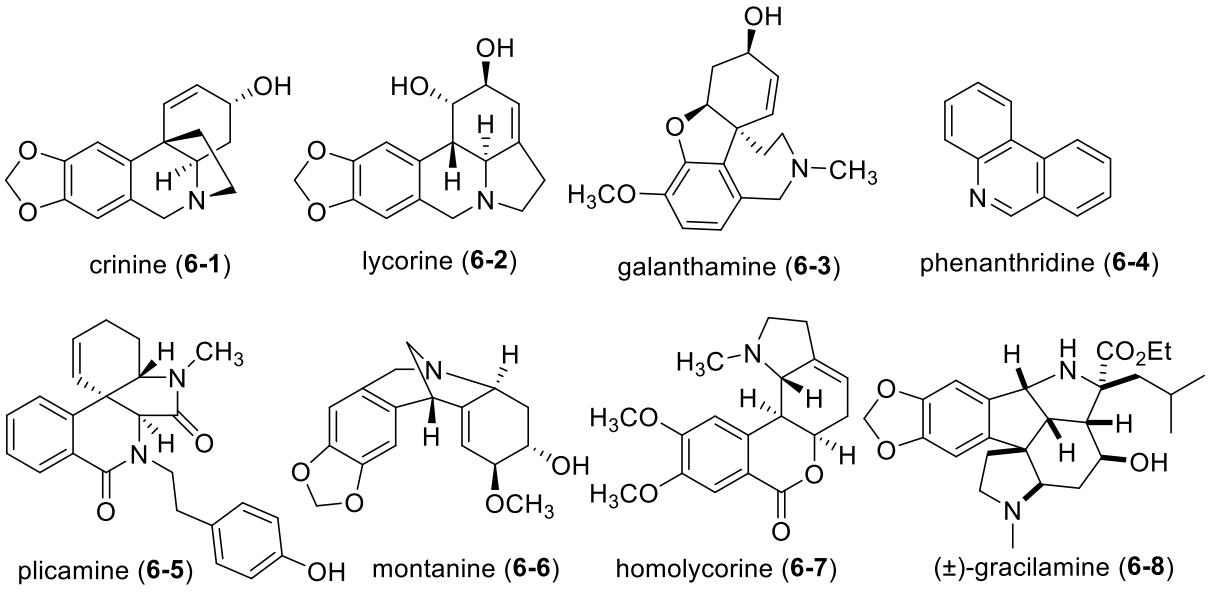


Figure 23. Eight different ring systems found in amaryllidaceae alkaloids.

The alkaloids isolated from the extract of *Amarryllidaceae sp*, have been investigated and chemically synthesized by various research groups in past three decades. They have been tested against diseases, some of them were found active against serious diseases such as cancer, pertussis, allergies etc.

In this chapter we discuss the biosynthesis, biological activity and various synthesis related to lycorane along with our own invetigations.

7 Literature review

7.1 Biosynthetic pathways

In the biosynthesis of Amaryllidaceae alkaloids L-phenylalanine (**7-1**) and L-tyrosine (**7-3**) serve as primary precursors. Barton and Cohen postulated Amaryllidaceae alkaloids are the derivative of a common precursor "norbelladine" (**Figure 24**).[93] The C6–C1 unit of the ring A comes from the phenylalanine whereas the ring C and the two-carbon side chain C6–C2–N originate from the tyrosine unit. The loss of NH_3 is antiperiplaner from L-Phe, which is mediated by the enzyme phenylalanine ammonia lyase (PAL)[94] to secure the trans-cinnamic acid (**7-2**). Hydroxylation of the benzene ring was catalyzed by cytochrome (P450s), cinnamate-4-hydroxylase (Ca4H) and coumarate 3-hydroxylase (Ca3H), thereafter, loss of two carbon atoms leads to the formation of the C6–C1 precursor protocatechuic aldehyde (**7-4**). L-tyr degrades into tyramine (**7-5**) just before the formation of a Schiff base, which is reduced to norbelladine (**7-6**).

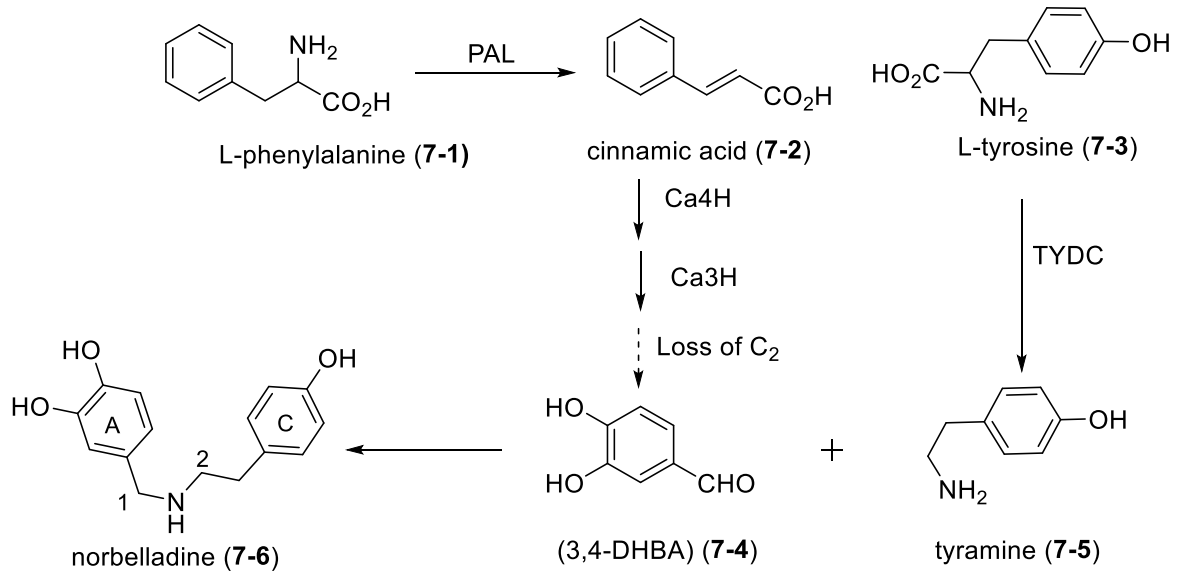


Figure 24. Biosynthetic pathway to norbelladine.

Methylation of one alcohol function of ring A generates *O*-methylnorbelladine (**7-7**) which undergoes oxidative coupling to generate intermediates for various alkaloids of the family. Labelling studies with [^{3}H] at the third position of the aromatic ring in L-tyr appear later in norpluvine (**7-11**) at C2 (**Figure 26**), and which is subsequently retained in lycorine.[95] Epoxide **7-12** ring opening and allyl rearrangement provides the alcohol function at C2 with an inversion of tritium configuration in **7-13**. The final step of the biosynthesis would be the conversion of the *O*-methoxyphenol to the methylenedioxy.

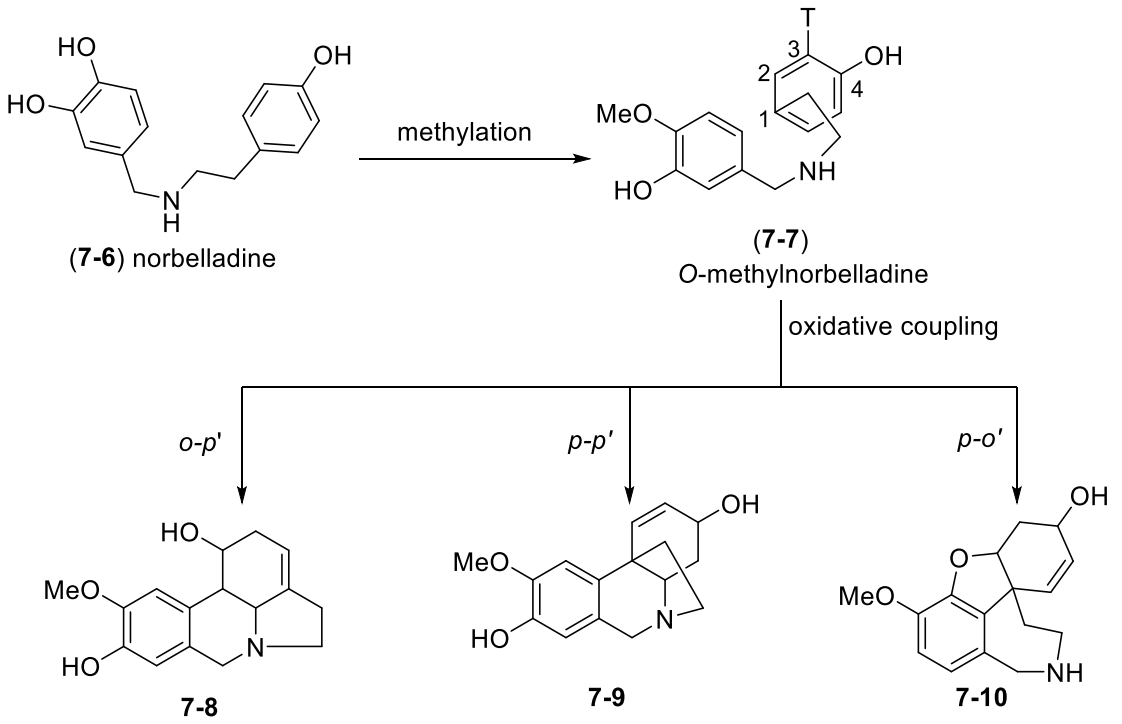


Figure 25. O-methylation and oxidative coupling of norbelladine (**7-6**).

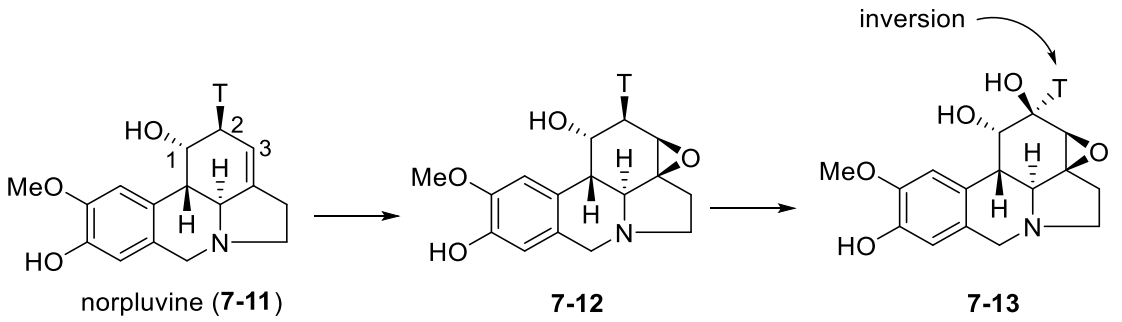


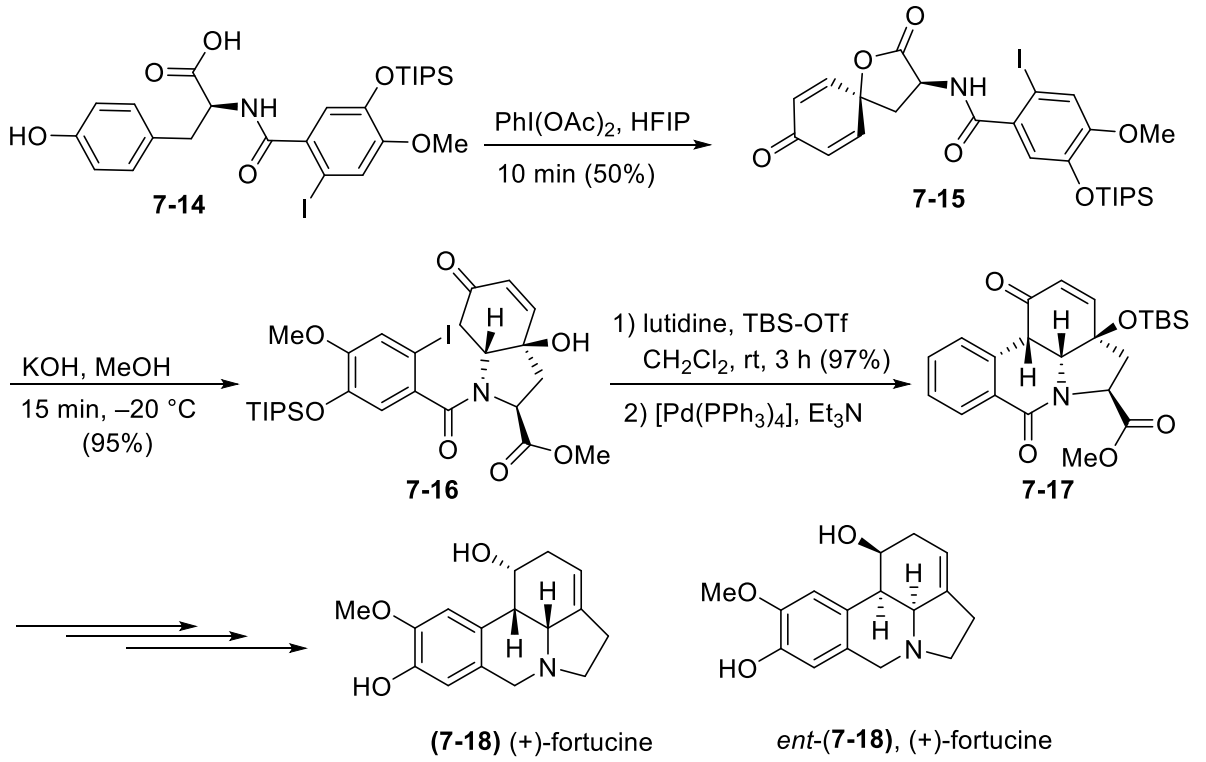
Figure 26. Lycorine biosynthesis via epoxidation and inversion of the configuration at C2.

7.2 Biological activity of lycorine Alkaloids

Lamoral-Theys, D. *et al*. have investigated 22 lycorine-related compounds for in *vitro* antitumor activity using four cancer cell lines displaying different levels of resistance to proapoptotic stimuli and two cancer cell lines sensitive to proapoptotic stimuli. They found that lycorine is more active than the other compounds. It also exhibits the highest potential (in *vitro*) therapeutic ratio, which is 15 times more active against cancer than normal cells.[96] The presence of the diol functionality in the C-ring, stereochemistry of the C/D-ring junction and conformational freedom of the C-ring are crucial for anticancer activity. Both incorporation of an oxo group in the B-ring and quaternization of the amine reduce the activity. Lycorine is able to cross the blood brain barrier with respect to narciclasine[97]. In *vivo* lycorine seemed to be better than narciclasine, because it is less toxic and therefore easier to manage clinically.

7.3 Absolute configuration of a lycorine alkaloid of *cis-cis* fusion (Fortucine)

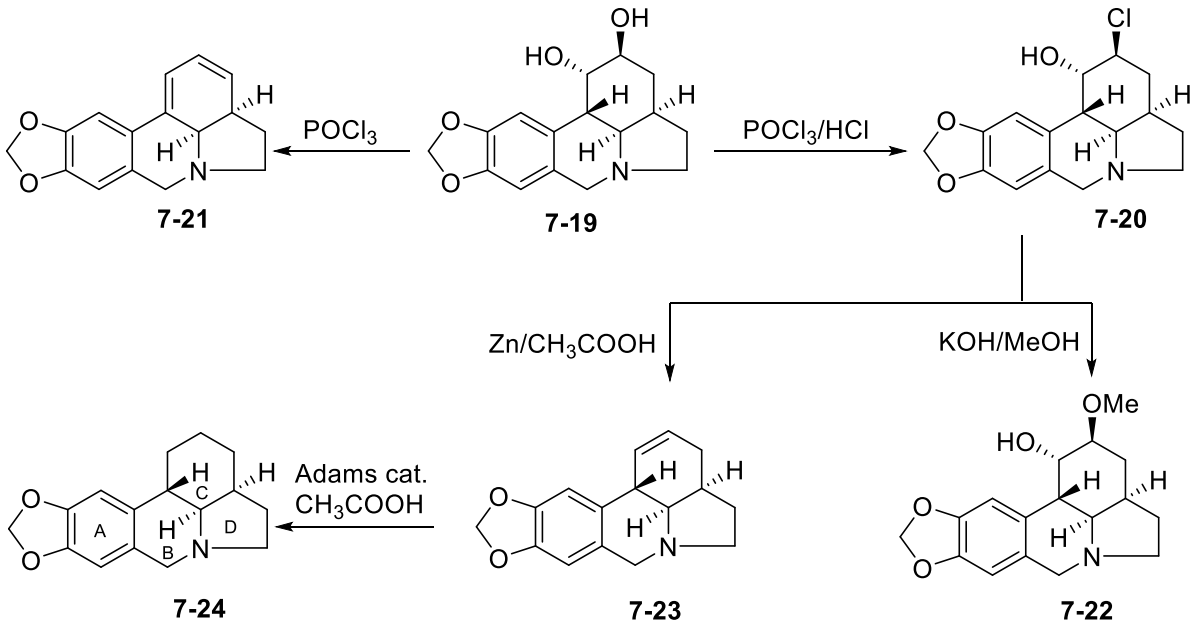
The absolute configuration of fortucine was recently clasified by total synthesis.[98] The precursor **7-14** was prepared using a Schotten-Baumann reaction from L-tyrosine methyl ester and an acid chloride. Dearomatization and subsequent stereoselective transformation led to bicyclic **7-15**. Carbopalladation on TBS-O-vinyl ether derived from enone **7-16** *cis*-tetracyclic pyrrolo[*d,e*]phenanthridine skeleton **7-17** was generated. The *cis* stereochemistry was elucidated by the planar geometry upon lactam segment. The synthesized enantiomer has opposite sign of optical rotation and Cotton effect which suggest that the natural and synthesized compounds are mirror images (**Scheme 55**).



Scheme 55 Synthesis of (+)-fortucine from L-tyrosine methyl ester.

7.4 Degradation studies on lycorine

The deoxygenated product of lycorine obtained after degradation is called α-lycorane (**7-24**).[99] Lycorine on treatment with phosphoryl chloride loses two molecules of water and it forms anhydrodihydrolycorine (**7-21**) whereas under milder conditions ($POCl_3$ and dil. HCl) it produces dihydrolycorinechlorohydrin (**7-20**), which on treatment with methanolic potassium hydroxide and zinc dust/acetic acid produces methyl ether **7-22** and monoene **7-23,** respectively. The formation of (–)-α-lycorane was achieved by reduction of monoene **7-23** with Adams catalyst in presence of acetic acid (**Scheme 56**).



Scheme 56. Degradation of lycorine (**7-19**).

Most of the lycorine alkaloids contain a *trans*-B/C ring junction, theire de-oxygenated product would be "α-lycorane" whereas few lycorine alkaloids contain a *cis*-B/C junction such as (+)-fortucine (**7-18**), (+)-kirkine (**7-25**) and (–)-siculinine (**7-26**).

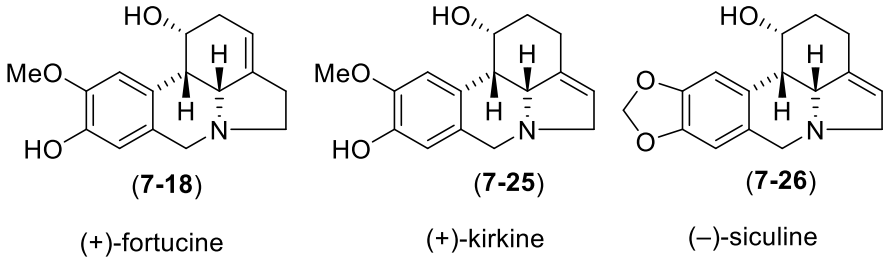


Figure 27. Lycorine type alkaloids having a *cis*-B/C ring fusion.

The degradation products of cis-B/C ring fused alkaloids are called γ-lycorane (**Figure 28**).[100]

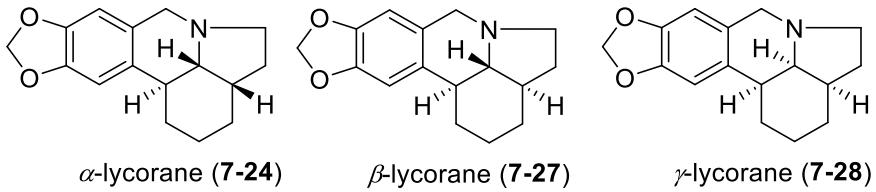
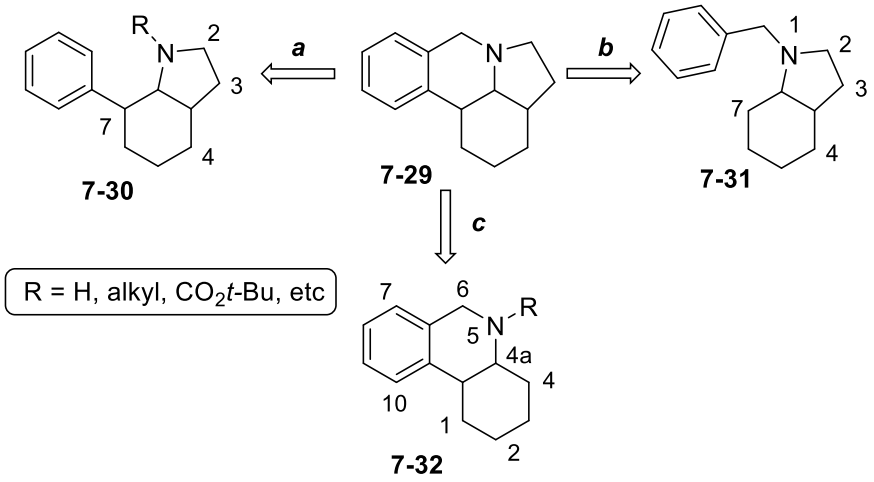


Figure 28. Lycoranes with galanthane ring system.

7.5 Privileged structures

The main strategies towards lycorane skeletones **7-29** can be grouped according to formation of the final ring (**Scheme 57**).



Scheme 57. Major strategies for formation of the last ring of the galanthan ring system.

7.5.1 Route "*a*" towards *γ*-lycoranes

The major approach is to generate intermediate phenyl-octahydro-1*H*-indole derivatives **7-30** and close ring B, for example by Pictet-Spengler cyclization (**Scheme 58**).[101] The first approach towards the hydroindol demonstrated the utilization of triene **7-33** which was generated via cheletropic extrusion of SO_2 from trihydrothiophene oxide, and then underwent [4+2] cycloaddition to produce *cis* & *trans* hydroindoles in 1:1.5 ratio.[102] Condensation of aldehyde **7-34** with *α*-carboxy amine produces an iminium ylide, which is an unstable compound and undergoes [3+2] intramolecular cycloaddition to give *trans-cis* lycorane.[103] In an association with Li_2CuCl_4 an aryl Grignard reagent favored *γ*-attack to the allylhalide, which enabled Bäckvall to introduce an aromatic unit into the hydroindol **7-35**.[104] Azides are used in the synthesis of triazoles. Thermal intramolecular 1,3-dipolar cycloaddition of **7-36** produced the triazoline intermediate **7-41** (**Figure 29**), with the all three rings *cis* fused, it decomposed into **7-42**. Internal alkylation from imine **7-43** to iminium ion **7-44** and reduction from the least crowded face furnished *γ*-lycorane.[105]

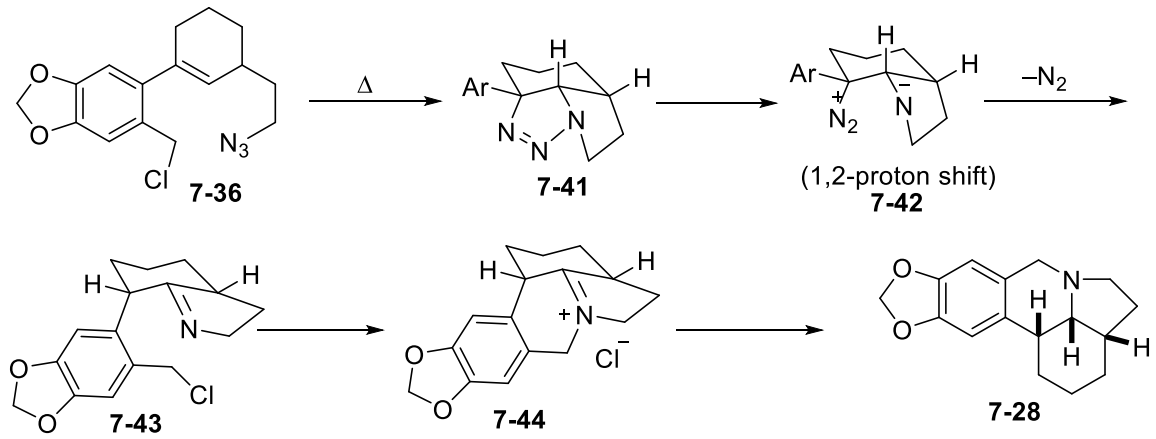
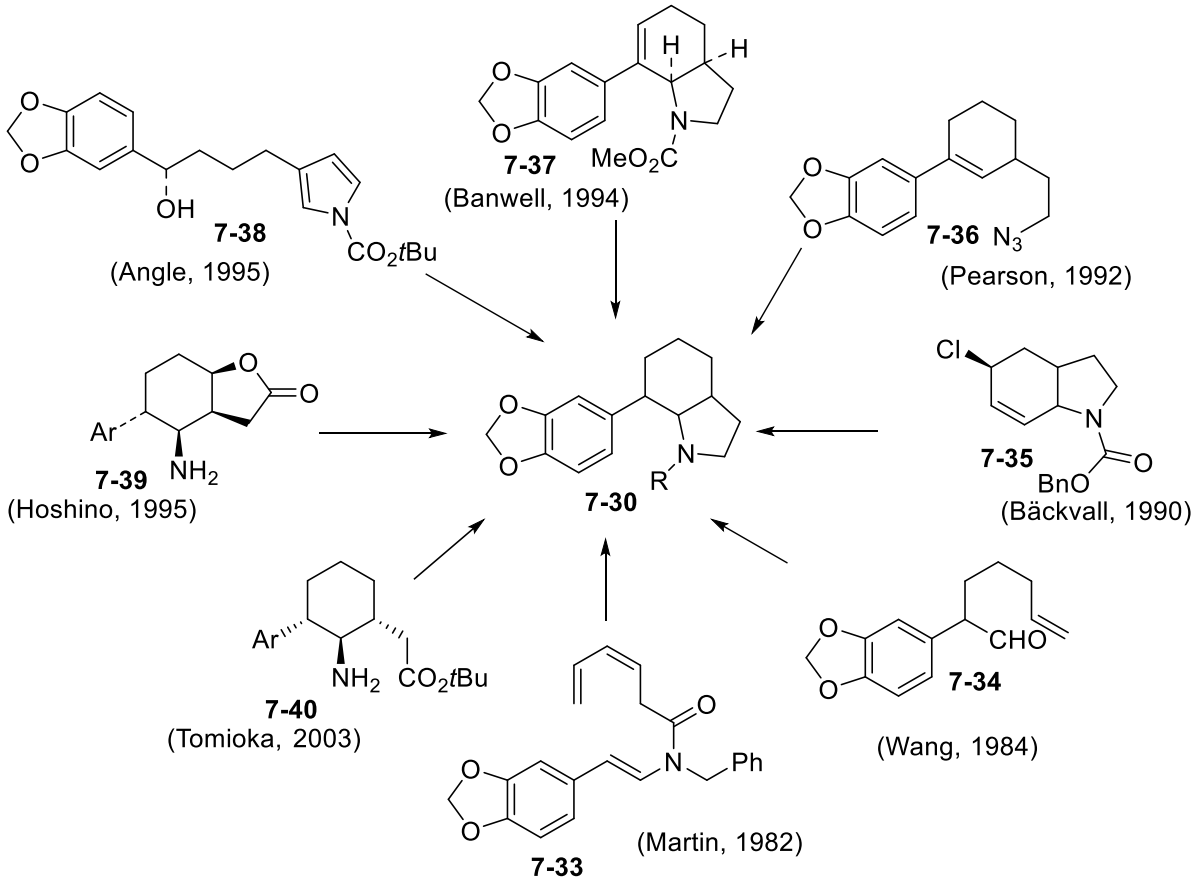
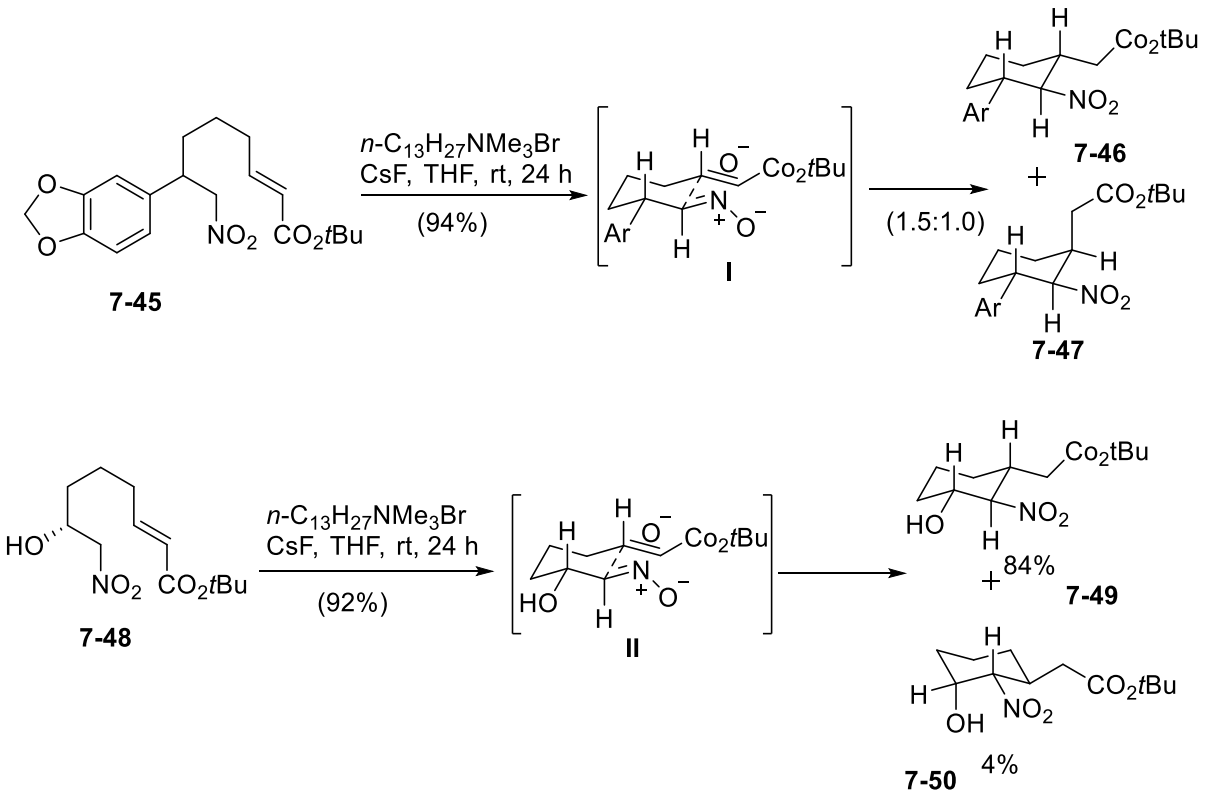


Figure 29. Mechanism of triazoline decomposition and the formation of *γ*-lycorane (**7-28**).



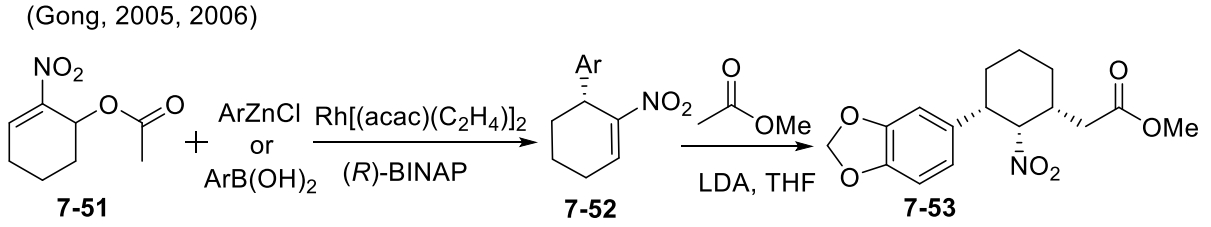
Scheme 58. Different approaches to achieve hydroindol **7-30** for Pictet-Spengler cyclization.

Silver mediated ring expansion of *gem*-dibromocyclopropane led to the formation of vinylbromohydroindole which after Suzuki cross-coupling and catalytic hydrogenation secured hydroindole derivative **7-37**.[106] The regioselective cyclization of a benzylalcohol into hydroindole opens a new synthetic approach to lycoranes.[107] Lactone **7-39** in basic medium rearranged into a β-hydroxy γ-lactam.[108] Chemoselective conjugate addition of an aryllithium to the nitro-olefin moiety of a ω-nitro-α,β,ψ,ω-unsaturated ester led to unsaturated ester **7-45**, which underwent a stereoselective nitro-Michael cyclization. Nitronate (**I**, **Scheme 59**) anion approaches the unsatuaretd ester moiety *anti* to an Ar–C bond, producing a diastereomeric mixture of **7-46** and **7-47,** however higher selectivity was observed with a β-hydroxy nitronate (**II, Scheme 59**) generated from **7-48**.[109]



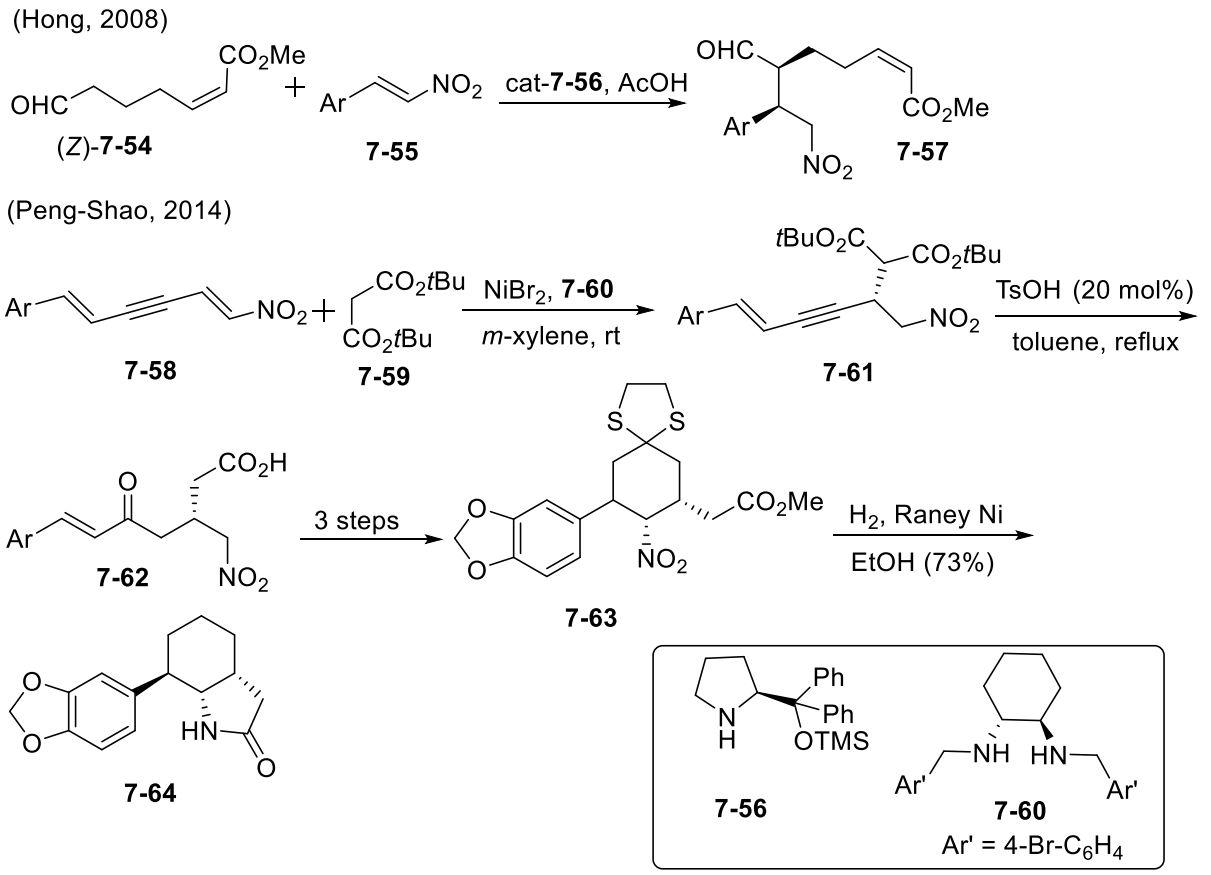
Scheme 59. Chemoselective conjugate addition and stereoselective nitro-Michael cyclization.

After the advent of asymmetric nitroallylation of arylboronic acids with nitroallyl acetate Gong demonstrated the asymmetric total synthesis of optically pure (+)-γ-lycorane shown in **Scheme 60**.[110]



Scheme 60. Asymmetric nitroallylation of an arylboronic acid or aryl zinc chloride with nitroallylacetate **7-52** and conjugate addition of ester to the nitroalkene **7-52**.

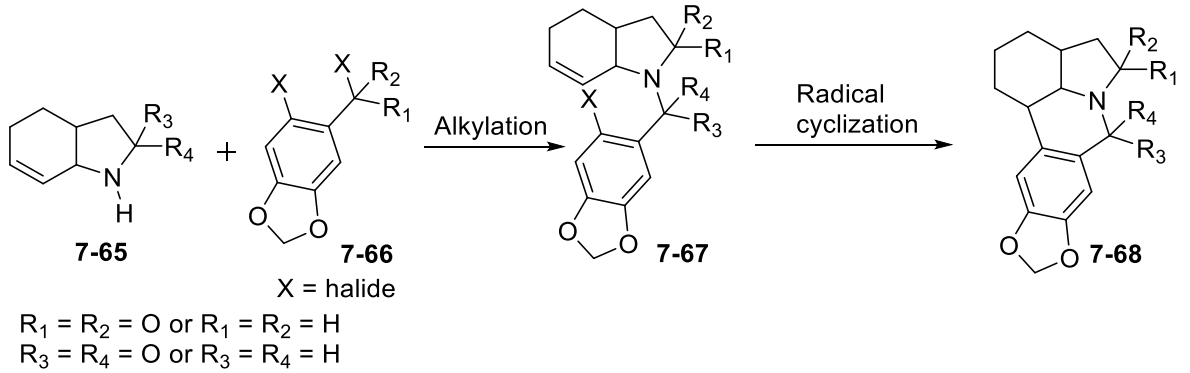
Several catalysts have been developed for asymmetric nitro-Michael addition; pyrolidine catalyst **7-56** is selectively promoting the reaction between aldehyde **7-54** and nitroalkene **7-55** to give the product **7-57**.[111] 1,4-Conjugate addition of nitro dienyne **7-58** with di-*tert*-butyl malonate **7-59** in the presence of chiral diamine-$NiBr_2$ complex provides 1,3-enyne **7-61** in 93% *ee*. In the presence of a catalytic amount of TsOH (20 mol%) 1,3-enyne underwent hydration regioselectively to deliver enone **7-62** (**Scheme 61**).[112] After reduction of the nitro function of ester **7-63** lactam formation led to hydroindol **7-64**.



Scheme 61. Synthesis of hydroindole derivative **7-64** from **7-54** and **7-58**.

7.5.2 Route "*b*" towards *γ*-lycoranes

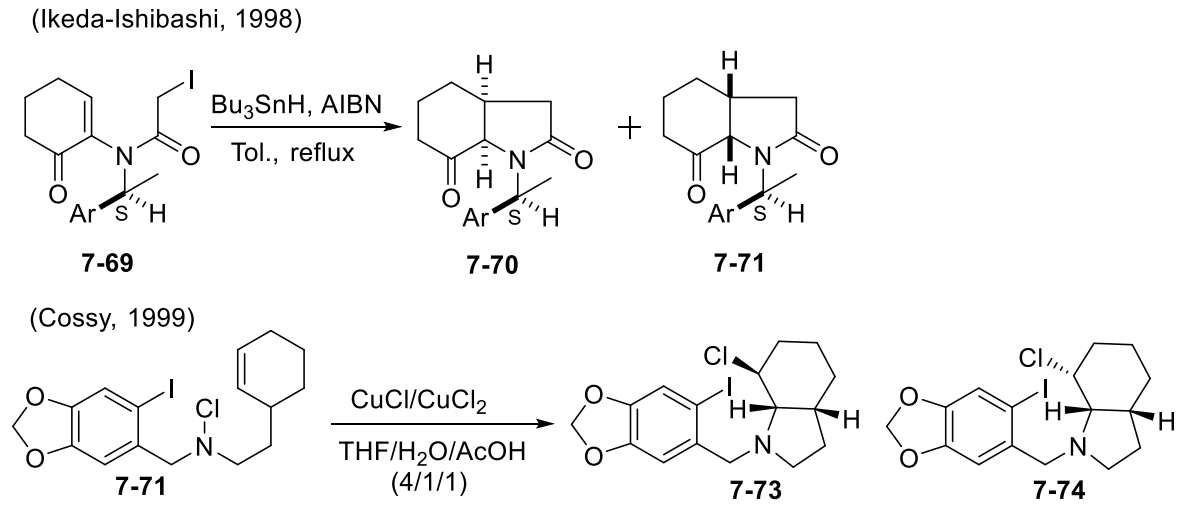
It involves the *N*-alkylation of hydroindol **7-65** followed by Heck coupling or radical cyclization of compound **7-67** (**Scheme 62**).[113] Several synthetic approaches to hydroindol **7-65** have been demonstrated.



Scheme 62. General synthetic approach of route "*b*".

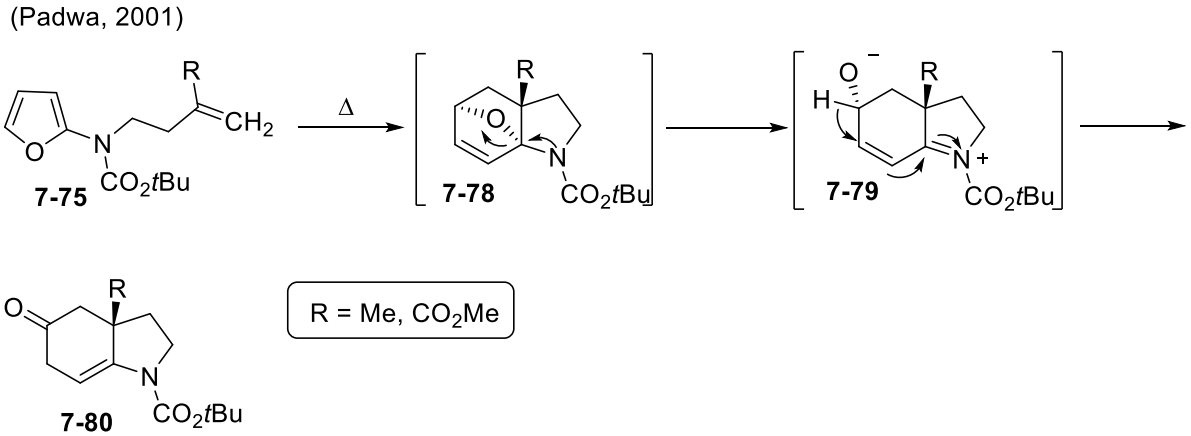
The radical precursor **7-69** was synthesized by condensation of cyclohexane-1,2-dione and (–)-(*S*)-1-phenylethyl amine followed by reaction with chloroacetyl iodide. Radical cyclization of iodoacetamide **7-69** provided an inseparable diasteromeric mixture of hydroindalones **7-70**

and **7-71**.[114] The 5-*exo-trig* cyclization of haloamine **7-71** also gave a mixture of **7-73** and **7-74** (**Scheme 63**).[115]



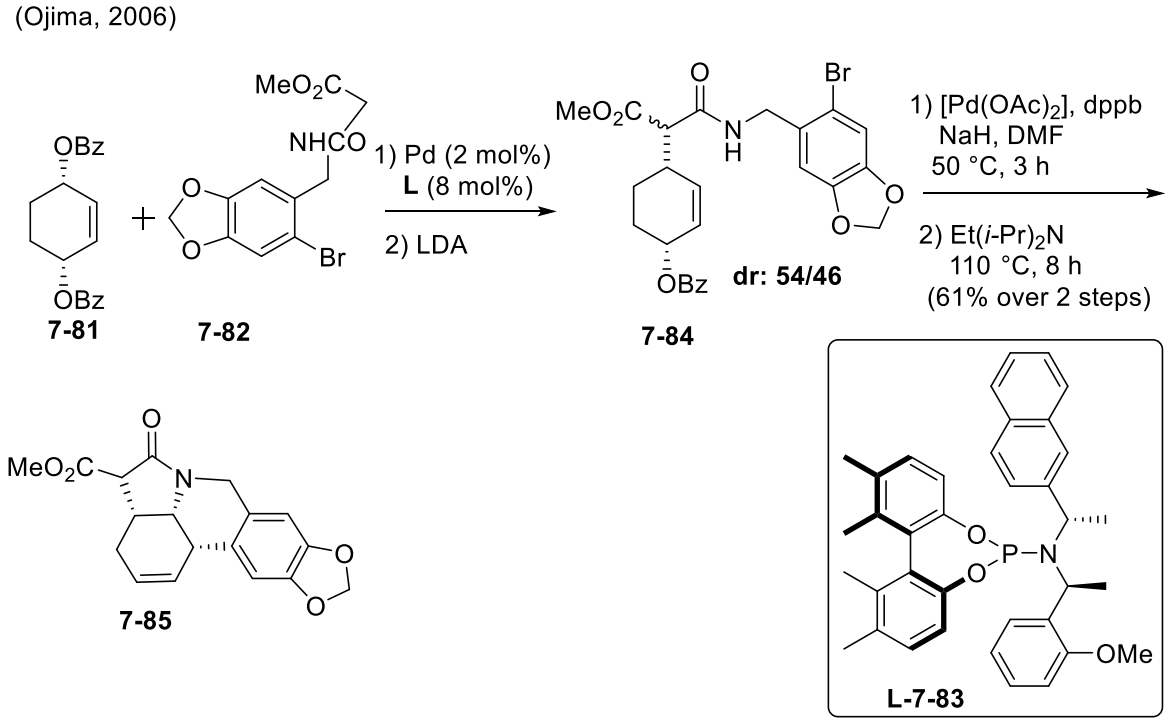
Scheme 63. Synthesis of hydroindoles from **7-69** and **7-71**.

Padwa and co-workers synthesized hydroindol derivate **7-80** from furanyl carbamate **7-75** via nitrogen assisted ring opening of Diels-Alder adduct **7-78** demonstrated in **Scheme 64**.[116]



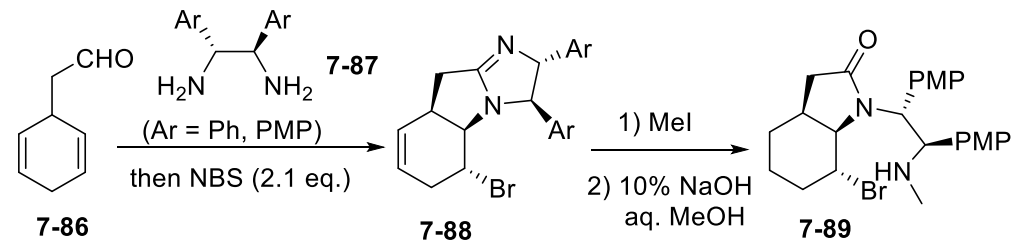
Scheme 64. Diels-Alder reaction of **7-75** and nitrogen assisted ring opening of **7-78**.

Asymmetric allylic alkylation was first demonstrated by Mori and co-workers in 1995 using (*S*)-BINAPO.[117] Later the work was extended by Ojima and co-workers for the synthesis of (+)-*γ*-lycorane. Palladium-catalyzed alylic alkylation of allylic benzoate **7-81** with activated ester **7-82** gave malonate half amide **7-84** as diastereomeric mixture (54/46) due to epimerization of the acidic methine of the malonate half amide moiety. However, it provided up to 99% enantiomerically pure one malonate half amide **7-84** determined on the basis of chiral HPLC analysis of compound **7-85,** obtained from **7-84** via one-pot tandem allylic amination-intramolecular Heck reaction.[118]



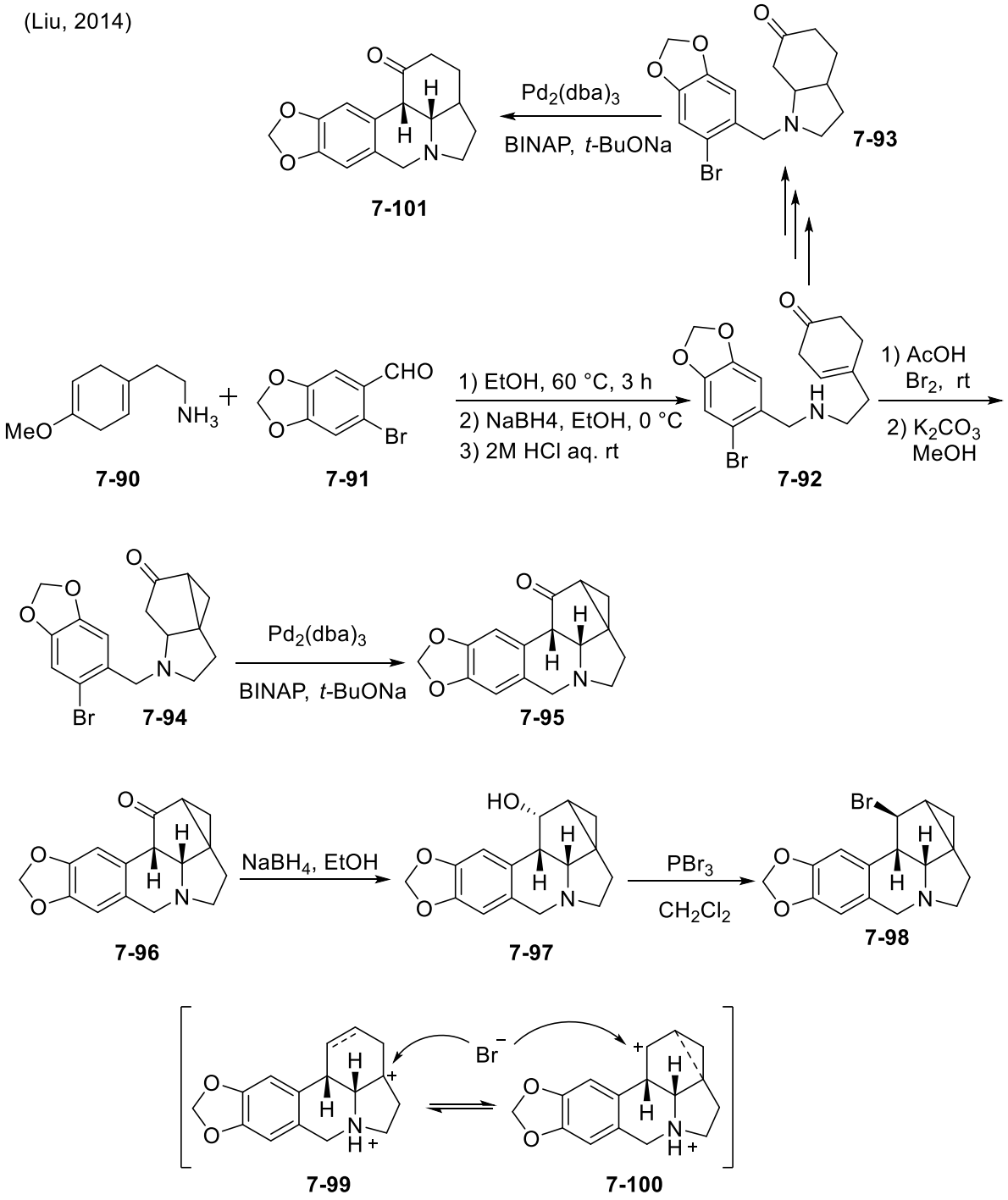
Scheme 65. Pd-catalyzed allylic alkylation & desymmetrization of **7-81**.

The aminal derived from aldehyde **7-86** and diamine **7-87** could be transformed into cyclic aminal **7-88** by treating it with required amount of NBS, which on hydrolysis delivered hydoindol **7-89** and opened the path for asymmetric synthesis of (–)-γ-lycorane.[119]



Scheme 66. Desymmetrization of amine **7-87** and hydrolysis of **7-88** into hexahydoindolone **7-89**.

Another approach to hydroindolone **7-93**, which includes aminocyclization of compound **7-92** did not lead directly hydroindolone **7-93**. However, the formation of cyclopropyl ketone **7-94** was observed due to the presence of carbonyl function in ring C which activates the α-position to attack the carbocation generated after bromination (**Scheme 67**).[120]

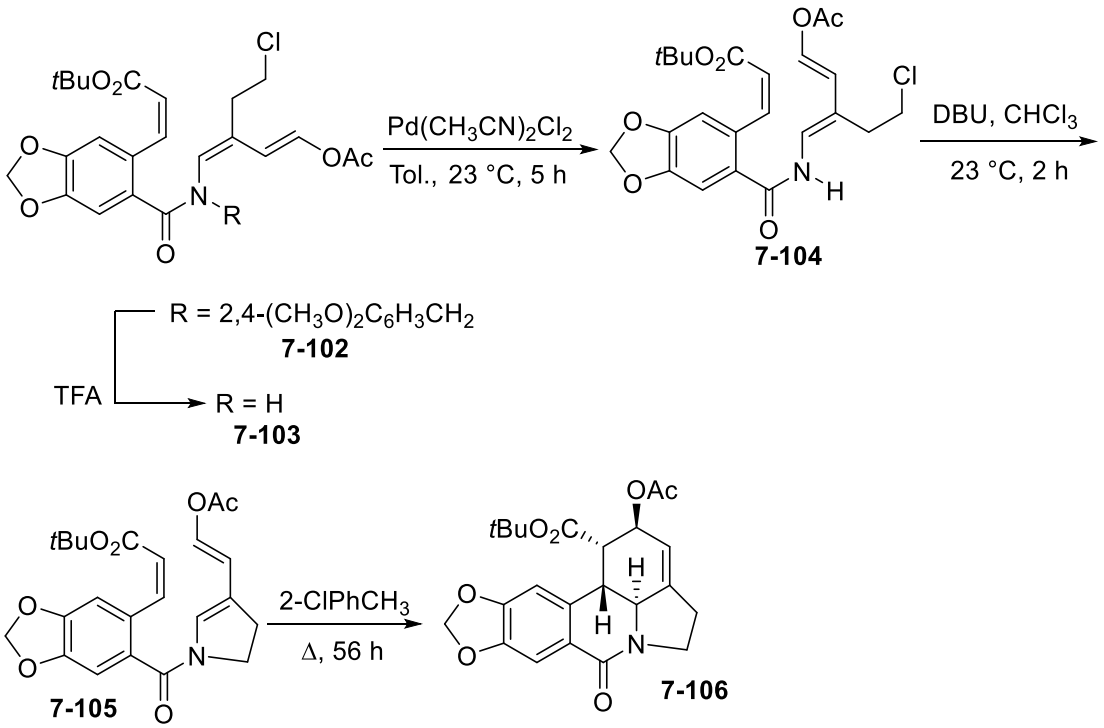


Scheme 67. Construction of the lycorine skeleton from intermediate **7-93** and nonclassical carbocation rearrangement.

7.5.3 Route "*c*" towards *γ*-lycoranes

A quite unique synthesis of lycorine (**6-2**) features an intramolecular Diels-Alder reaction to simultaneously create the B and C rings starting from **7-102** (**Scheme 68**).[121]

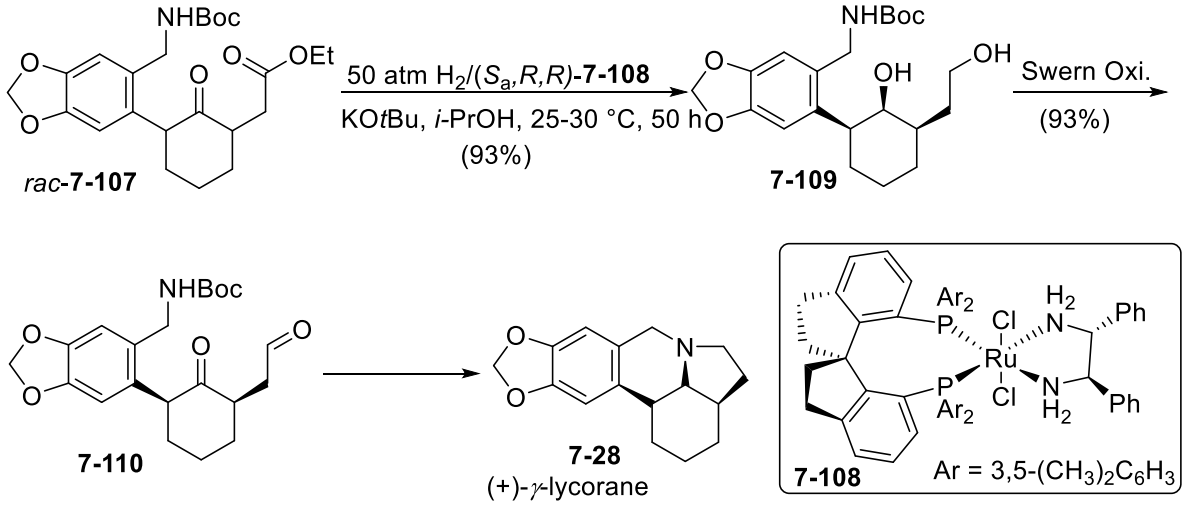
(Boeckman, 1981)



Scheme 68. Synthesis of lycorine derivative **7-106** from **7-102** via Diels-Alder reaction.

Transition metal catalyzed asymmetric hydrogenation of configurationally labile substrate **7-107** through dynamic kinetic resolution (DKR)[122] enabled Zhou and co-workers to convert racemic α-ethoxycarbonyl alkyl-α'-arylcycloketone **7-107** into the corresponding diol **7-109**, a precursor for (+)-γ-lycorane (**Scheme 69**)[123] and (–)-α-lycorane.[124]

(Xie-Zhou, 2013)

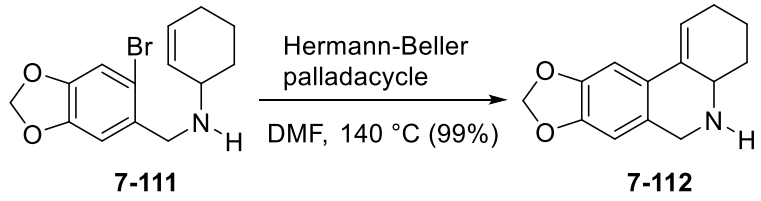


Scheme 69. Catalytic enantioselective synthesis of (+)-γ-lycorane.

In approach "*c*", a phenanthridine nucleus is the core structure which is found in several natural products. It contains all three rings of the lycorane alkaloids except ring D and therefore it needs

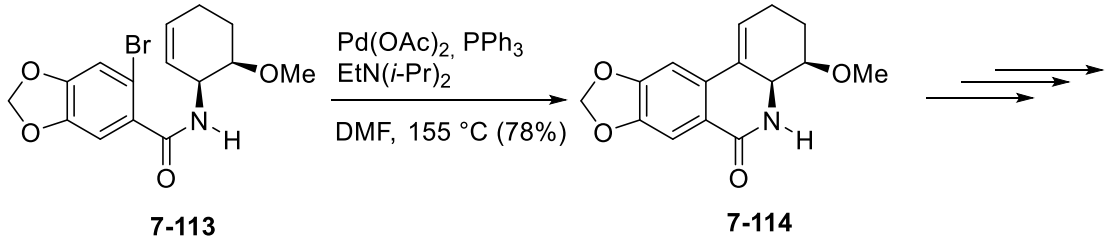
to be ring D installed. There are several approaches towards the synthesis of phenanthridines such as Heck cyclization used in the synthesis of 7-deoxypancreastatin **7-115** (**Scheme 70**)[125] and C–H-activation strategies.

(Hulme, 2011)

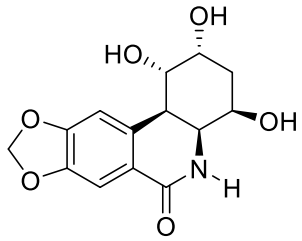


7-111 **7-112**

(Sutherland, 2012)



7-113 **7-114**



7-115-analogue of
(+)-7-deoxypancratistatin

Scheme 70. Synthesis of phenanthridine rings **7-112** and **7-114** fom **7-111** and **7-113** respectively, via Heck coupling.

7.6 C–H-activation towards isoquinolines

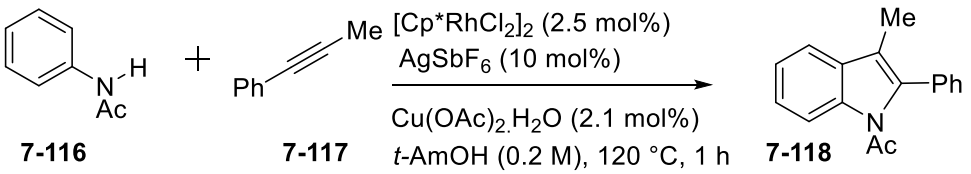
Isoquinolines are present in several alkaloids and regarded as privileged structure. Rhodium catalyzed activation of aromatic C–H bonds with unsaturated substrates such as alkynes and alkenes provides a simple solution to isoquinoline synthesis starting from benzamides, benzimines, acetophenones etc. C–H-activation can be divided into two major categories sp^2- and sp^3 C–H-bond functionalization. Aromatic compounds are very common with functional groups such as ketones, aldehydes, carboxylic acids, alcohols, amides and imines. These functional groups could coordinate with the metal and the resulting complex would be thermodynamically less stable, which enabled functional groups to regulate the catalytic annulation on a particular position of the aromatic ring. Cp*Rh(III) complexes are regarded as catalysts for C–H bond annulation due to the following reasons: (a) Rh(III) is a good π-acceptor (b) Cp* is a bulky and electronically rich species which stabilizes the organorhodium intermediate via coordination to the Rh center in one hand and on the other hand feciliates

reductive elimination.[126] Several reviews on the Rh(III)-catalyzed C–H functionalization have been published.[127] Here we describe the directional aspect of some functional groups in the annulation of alkynes, alkenes etc.

7.6.1 Annulation of alkynes

Larock demonstrated that substrates having both a nitrogen containing moiety and a carbon halide bond can undergo annulation with alkynes. Later strategies were developed where a C–H bond was exploited in place of a C–X bond. In this view two types of methodologies have been ripened, one involving external oxidants (oxidative strategy) to re-activate the catalyst and the other exploiting the labile nature of a group present in the molecule undergoing annulation to activate the catalyst internally (redox strategy). Fagnou developed a regioselective indol synthesis from *N*-acetyl amines, utilizing its orthometalation property under cationic Rh(III) condition (**Scheme 71**).[128] C–H-activation was observed on the less hindered C–H-bond of *N*-acetyl amines. The regioselectivty was affected by the temperature and alkyne concentration. The catalyst was found more active when an external oxidant, $Cu(OAc)_2$ in combination with molecular oxygen was used. Huang demonstrated the use of molecular O_2 as a sole oxidant in Rh(III) catalyzed annulations of alkynes. O_2 as a sole oxidant is very attractive since it allowed to substite the stoichiometric amounts of metal oxidant.[129]

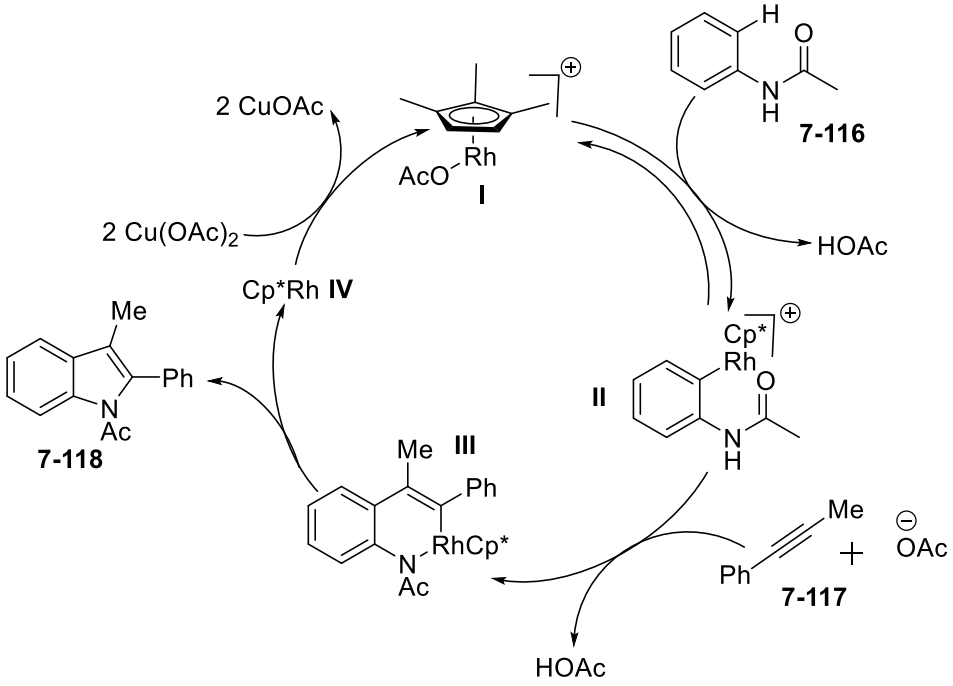
(Fagnou, 2008, Stuart, 2010)



7-116 **7-117** **7-118**

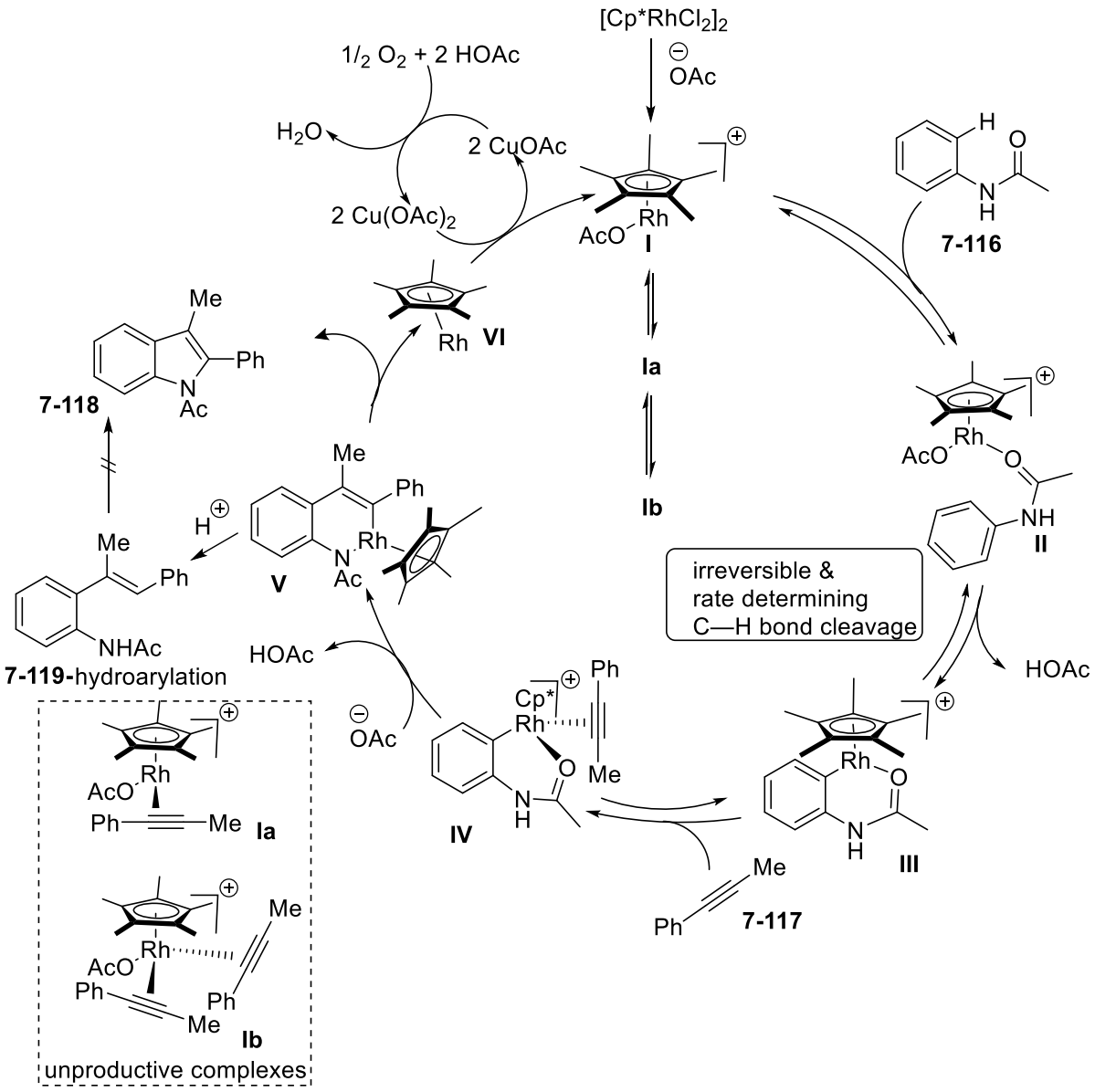
Scheme 71. Alkyne insertion to acetanilide under external oxidant.

The mechanism for acetanilide annulation proposed by Stuart is shown in **Scheme 72**. Jones admitted that the active metalating agent of benzylimines is a cationic complex.[130] Alkyne coordination with the cationic complex and 1,2-migration of rhodium-carbon bond facilitates the formation of six-membered metallacycle **III**. Reductive elimination delivers the product and RhCp* (**IV**) complex, which is further reoxidized into active complex **I** by the Cu(II) oxidant.



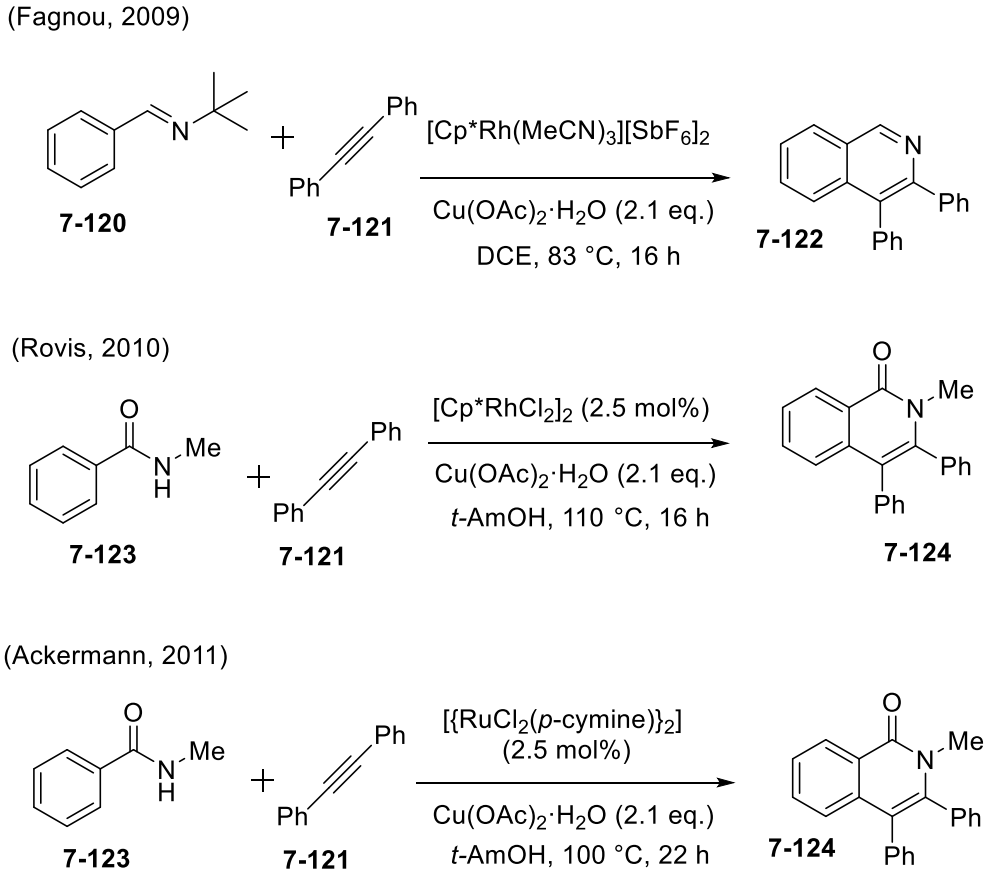
Scheme 72. Proposed catalytic cycle under first-generation conditions**.**

On the basis of kinetic data Stuart proposed revised mechanism showing the possibility of the formation of side product during oxidative C–H bond functionalization which is devised in **Scheme 73**.[128(b)] $[RhCp^*Cl_2]_2$ complex reacts with one equivalent of acetate to generate active Rh species **I**, this could react with alkyne **7-117** first and generate unproductive complexes **Ia** and **Ib**, or after the coordination with the oxygen of the Lewis basic amide and C–H bond cleavage. Then the complex rearranges into six-membered rhodacycle **V**, which could undergo normal reductive elimination to give the compound **7-118** or may produce hydroarylation product **7-119** in presence of acid.



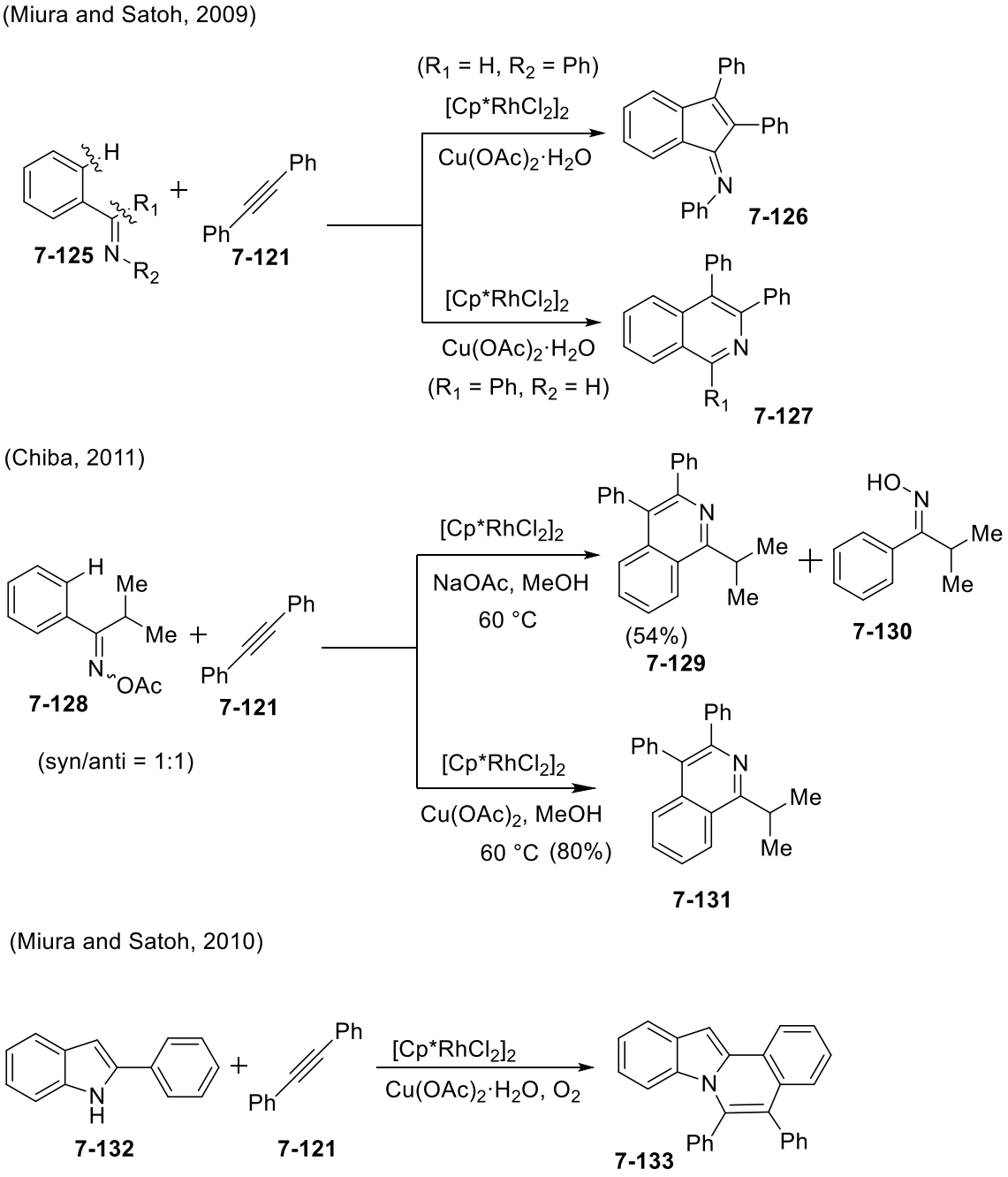
Scheme 73. Revised catalytic cycle for first and second generation conditions.

The nitrogen of amides could also coordinate with rhodium since its loan pair is delocalized. Whenever the amide is tertiary the coordination of the metal with the oxygen is more favored. Fangau reported the oxidative annulation of *N*-tert-butylbenzaldimines **7-120** with internal alkynes which furnished isoquinoline **7-122**.[131] Rovis and Ackermann have successfully demonstrated the use rhodium and ruthenium metals for similar transformations (**Scheme 74**).[132]



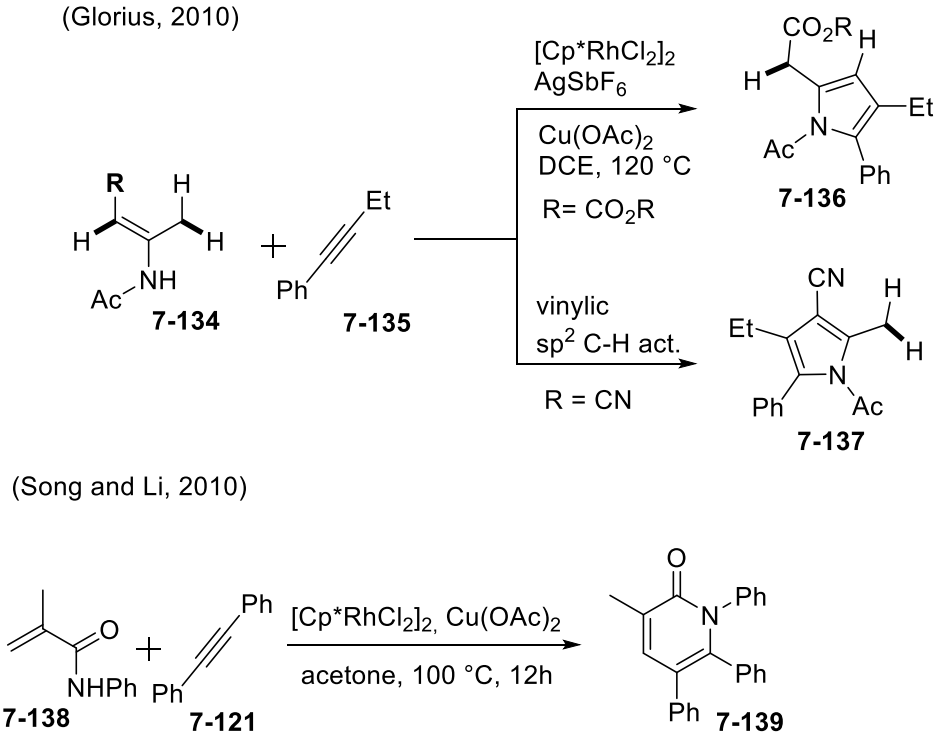
Scheme 74. Synthesis of isoquinoline **7-122** and isoquinolone **7-124** from **7-120** and **7-123** respectively.

The sp^2 nitrogen of the imine has played a directing role in numerous oxidative coupling reactions via C–H bond cleavage. Imine **7-125** having α-hydrogen undergoes alkyne insertion to cyclize into **7-126** whereas α-substituted imines give isoquinoline derivatives like **7-127**.[133] Similar results were obtained when aryl ketone *O*-acetyl oxime **7-128** and internal alkyne **7-121** were treated with $[Cp^*RhCl_2]_2$, NaOAc in MeOH at 60 °C, this mixture is able to differentiate between *syn* and *anti*-oxime, only the *syn*-oxime undergoes cyclization leaving behind the *anti* isomer unreacted in a "kinetic resolution". A catalytic amount of $Cu(OAc)_2$ changes the reaction pathway and both *syn* & *anti*-oximes delivered the product **7-131**.[134]



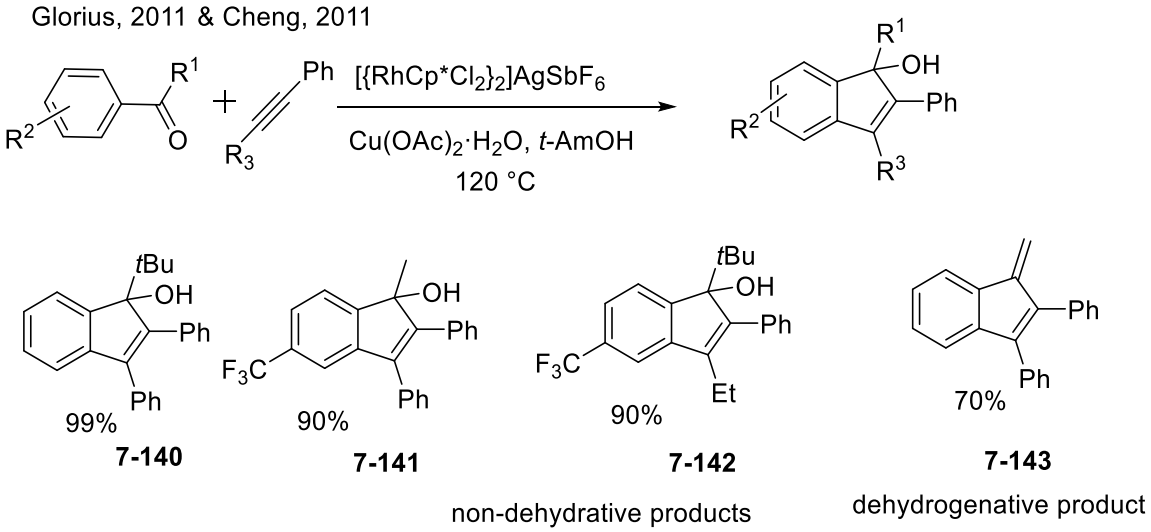
Scheme 75. Alkyne **7-121** insertion to benzylimine **7-125** and indole derivative **7-132**.

Alkyne insertion to the enamine **7-134** is affected by the presence of CO_2R and CN at the *β*-position of enamine; one goes under sp^3 C–H activation whereas other follows the path of sp^2 C–H functionalization (**Scheme 76**).[135] Pyridones were synthesized in the same line of the synthesis (**Scheme 76**).[136]



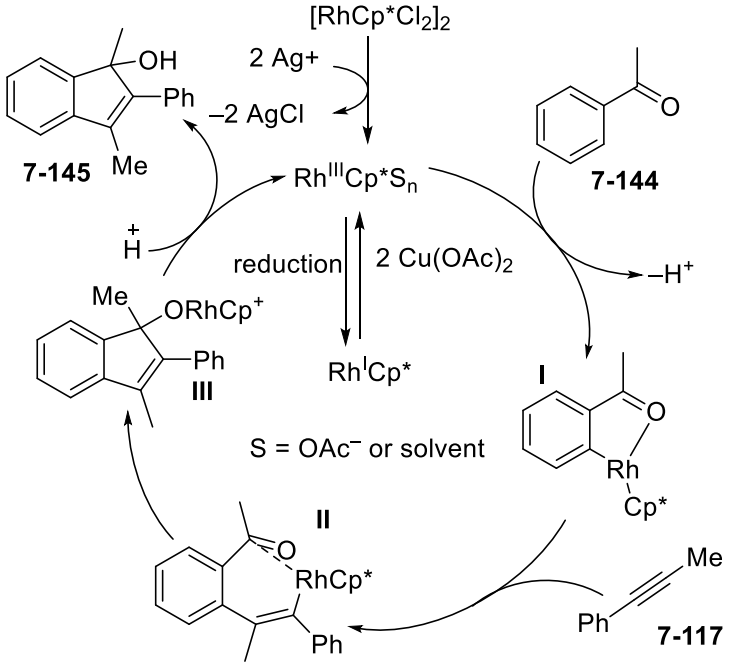
Scheme 76. Scope of alkyne insertion under external oxidant condition.

Aldehydes and ketones have week coordination ability. Therefore they are not a very good choice for directing ability. Examples of catalytic annulation of aromatic aldehydes and ketones were described by Glorius and Cheng in 2011 as shown in **Scheme 77**. Ketones as a directing group were used in the synthesis of indenols via ketone assisted C–H-activation/carbocyclization (**Scheme 77**).[137] Intersting results were obtained; ketones having no α-hydrogen gave indenols, whereas ketones having α-hydrogen and electron rich phenones undergo dehydrogenation to give fulvenes. Phenones with electron withdrawing groups having a α-hydrogen also furnished indenoles without undergoing dehydrogenation.



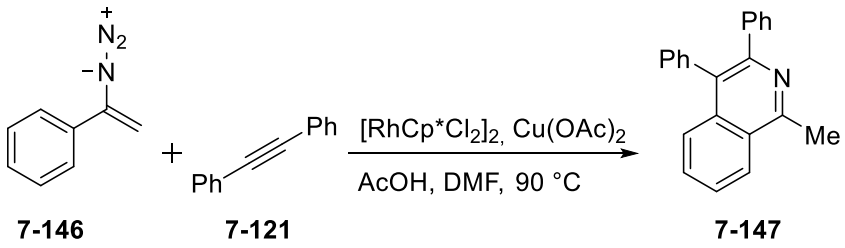
Scheme 77. Carbocyclization of aryl ketones with alkynes.

The mechanism for indenol formation described by Cheng *et al.* is shown in **Scheme 78**. The catalytic cycle starts with Cl^- ion removal from the precatalyst $[RhCp^*Cl_2]_2$ by Ag^+. Coordination of the catalyst to acetophenone **7-144** and subsequent C–H bond cleavage forms the five membered rhodacycle **I**. Alkyne insertion to rhodacycle transforms it into a seven membered rhodacycle **II** having π-bonded keto-rhodium functionality. Then the carbonyl function gets inserted to produce rhodium alkoxide intermediate **III**, which on protonation delievered the indenol **7-143** and regenerates the active catalyst.



Scheme 78. Proposed mechanistic pathway for the formation of indenol derivatives.

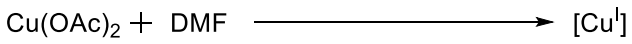
Vinyl azides thermally decompose into strained three membered cyclic imines, 2*H*-azirines, which would be the equivalent to a vinyl nitrene. Chiba explored the directional property of vinyl nitrenes (**Scheme 79**).[138]



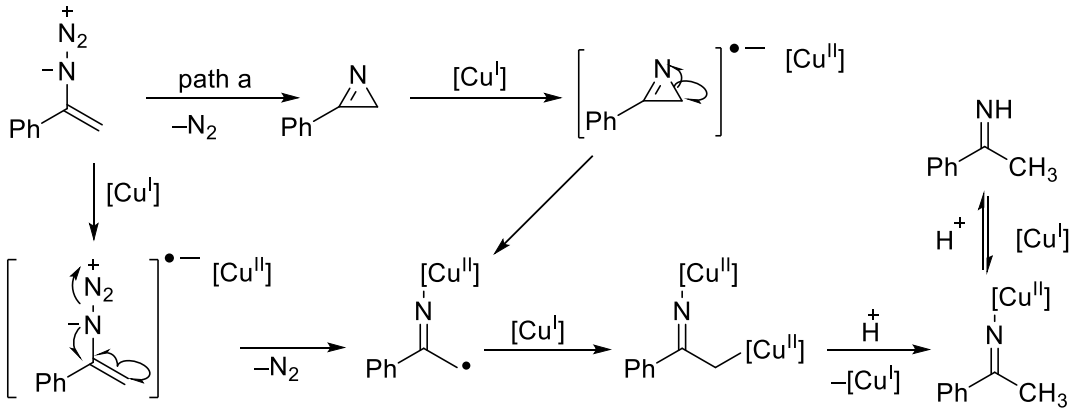
Scheme 79. Isoquinoline synthesis from vinyl nitrene.

The proposed mechanism for the formation of isoquinolines from azides is demonstrated in **Scheme 80**.

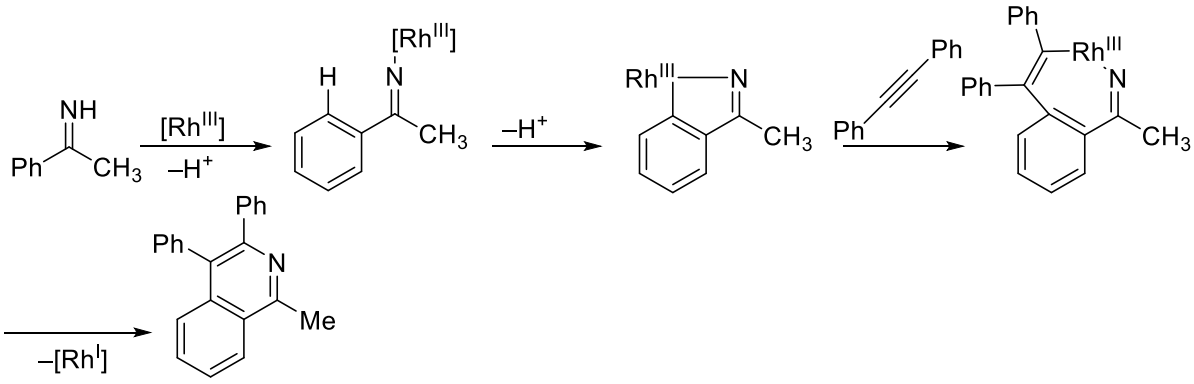
step A: generation of Cu(I) species from $Cu(OAc)_2$ by reduction with DMF



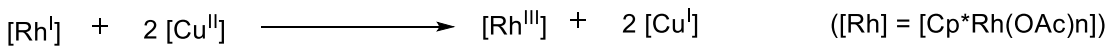
step B: reductive formation of N–H imines from vinyl azides and Cu^I species



step C: ortho C–H rhodation, alkyne insertion, and C–N reductive elimination



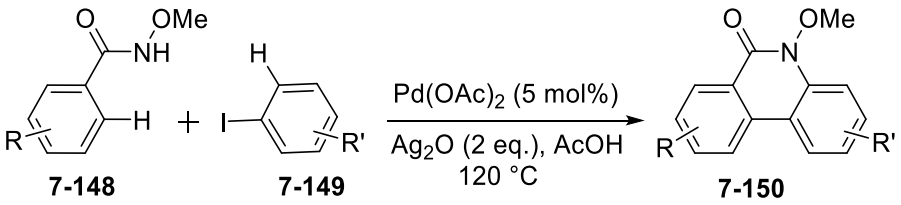
step D: Redox regeneration of Rh(III) and Cu(I)



Scheme 80. Proposed reaction pathway for isoquinoline from vinyl nitrine.

7.6.2 Annulation of phenyl ring

A palldium mediated intermolecular C–C bond formation was coupled with another intramolecular C–N bond formation by Wang and co-workers. Phenanthridinone **7-150**, a biologically important compound was prepared by the reaction of benzamide **7-148** and iodobenzene (**7-149**). In the course of the reaction, formation of palladacycles was directed by benzamide, thereafter aryl halide insertion takes place (**Scheme 81**).[139]

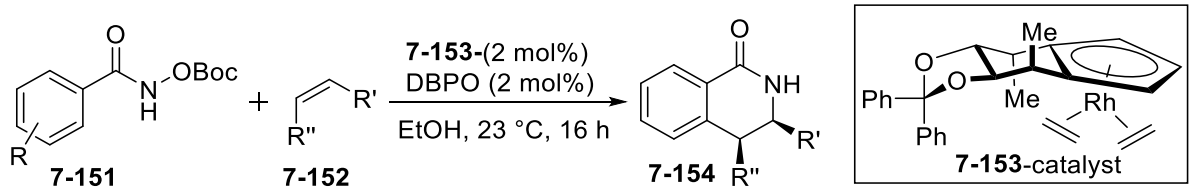


7-148 7-149 7-150

Scheme 81. Synthesis of phenanthridinones by palladium catalyzed reaction of N-methoxybenzamides with aryl iodides**.**

7.4.4 Annulation of alkenes

Cramer and co-workers designed a C_2-symmetric cyclopentadienyl (Cp) derivative, which could control the spatial arrangement of the transiently coordinated reactants around the central metal atom.[140] They considered three criteria for developing the catalyst: (i) C_2-symmetric Cp derivative could avoid formation of the diastereomer in coordination of the metal to either ligand face; (ii) restriction of rotation around the Cp-moiety and (iii) steric blocking perpendicular to the to the Cp plane to ensure approaching of the reactant from one side only. The performance of the catalyst is shown in **Scheme 82**.

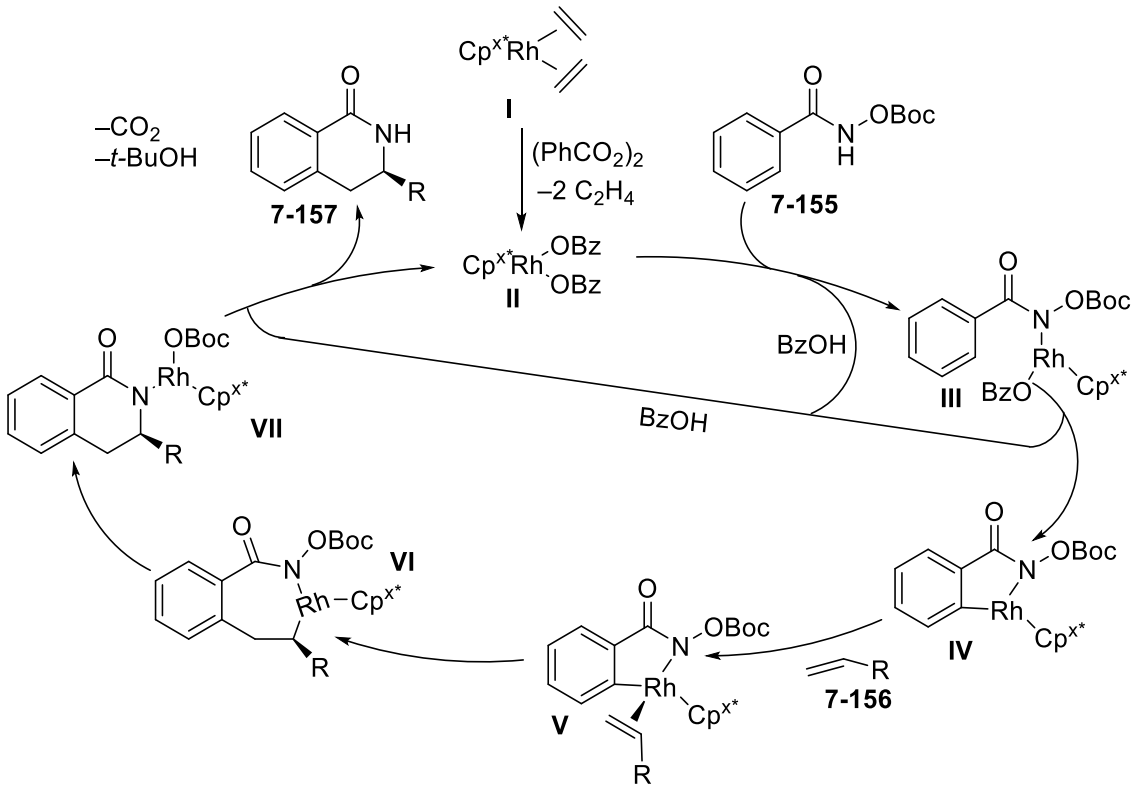


R = H, 3-Me, 4-NO_2, 4-F etc.
R' = 4-Me-C_6H_4, 4-F-C_6H_4, Ph etc.
R'' = H, $SiMe_3$ etc.

ee: 85-97

Scheme 82. Enantioselective annulation of alkene **7-151**.

The catalytic cycle of alkene annulation is shown in **Scheme 83**. The Rh(I) complex in oxidized with dibenzoxyperoxide into **II**, which converts into **III** by ligand exchange. Concerted cyclometalation/deprotonation and the loss of benzoic acid lead to a crucial cyclometalated 16-electron intermediate **IV.** Olefin coordination takes place in a highly diastereoselective manner leading to 18-electron chiral-metal complex **V**, which converts into **VI**. Then ligand exchange/protonation by BzOH present in the system regenerates catalyst **II** and delivers the product. Generated *t*-$BuHCO_3$ collapses into CO_2 and *t*-BuOH without affecting the acidity of the system.

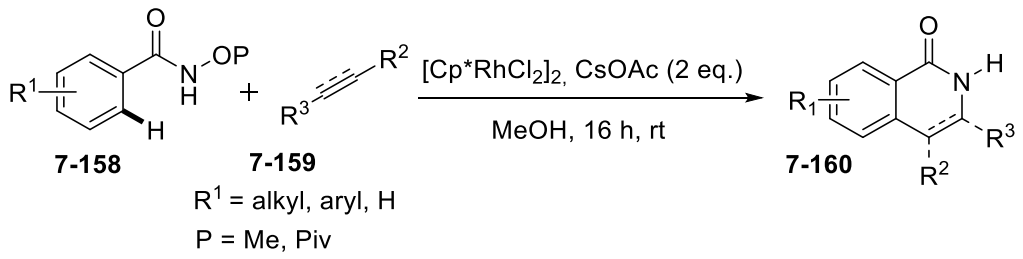


Scheme 83. Presumed catalytic cycle for the insertion and cyclization of alkenes.

7.6.3 Redox C–H activation:

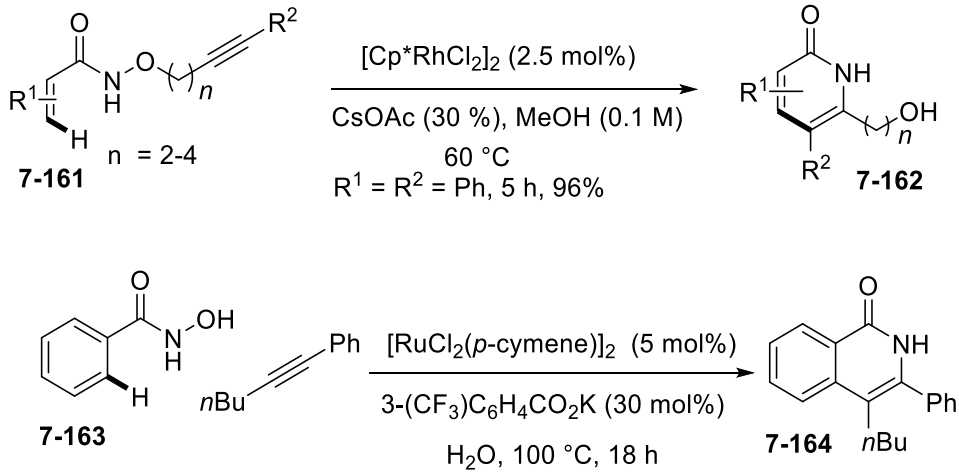
Internal alkynes produce disubstituted heterocycles. However, $Cu(OAc)_2 \cdot H_2O$ mediated dimerization of terminal alkynes is well known. Therefore, the terminal alkynes under the disccused conditions could not be annulated. In order to avoid alkyne dimeration Cu(II) free conditions are required. Guimond reported isoquinoline synthesis from benzamide **7-158**[141] and found external oxidant was not required to re-oxidize the rhodium catalyst. The N–O bond was cleaved during the course of reaction. The concept was also used in palladium catalyzed C–H-functionalization by Hartwig, Cui and Wu.[142] Terminal alkynes under this condition produce monosubstituted heterocycles in moderate to high yield. The regioselctivety is quite predictable, as the terminal end of the alkene is located at 4-position (**Scheme 84**).

Guimond, 2011 & Glorius, 2011



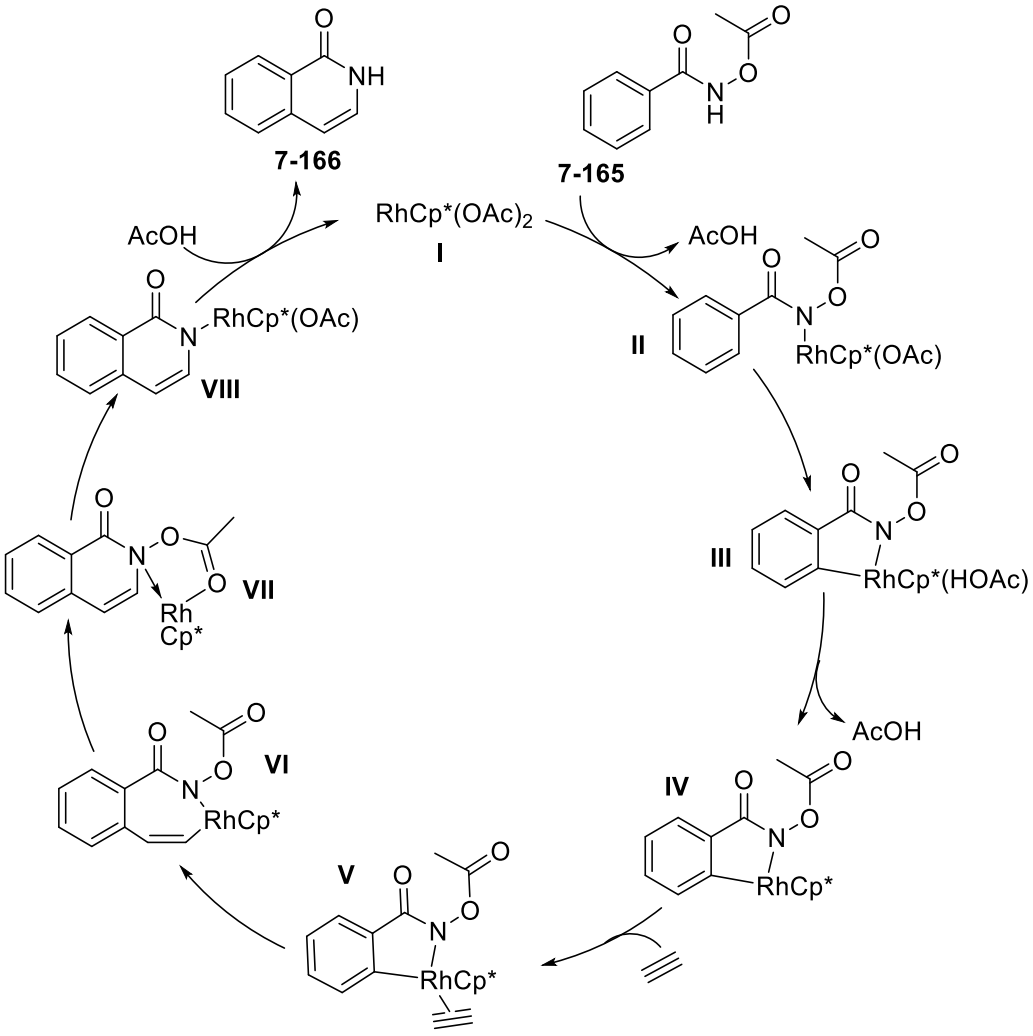
Scheme 84. Benzamide annulation with alkenes and alkynes.

C(sp^2)-Rh species would be nucleophilic to attack on C=O or α-halo ketones to produce α-aryl ketones. Glorious and co-workers have annulated benzamides with α-halo and pseudohalo ketones.[143] Intramolecular rhodium catalyzed C–H annulation reaction provides isoquinolones with reverse regioselectivity.[144] Ackerman demonstrated dehydrative alkyne annulation with free hydroxamic acid under Ru(II) catalysis in aqueous medium.[145]



Scheme 85. Intra- and intermolecular annulation of **7-161** and hydroxamic acid **7-163**, respectively.

The mechanism for redox C–H activation is shown in **Scheme 86**. The catalyst **I** coordinates with **7-165** with the loss of attached acetate ion which is followed by C–H bond cleavage through concerted metalation-deprotonation to produce intermediate **III**. The bound acetic acid molecule is lost and acelylene is inserted. The reductive elimination allows C–N bond formation resulting in intermediate **VII.** Consequently a fast oxidative addition generates intermediate **VIII,** which is protonated by acetic acid to give product **7-124** and active catalyst **I**.

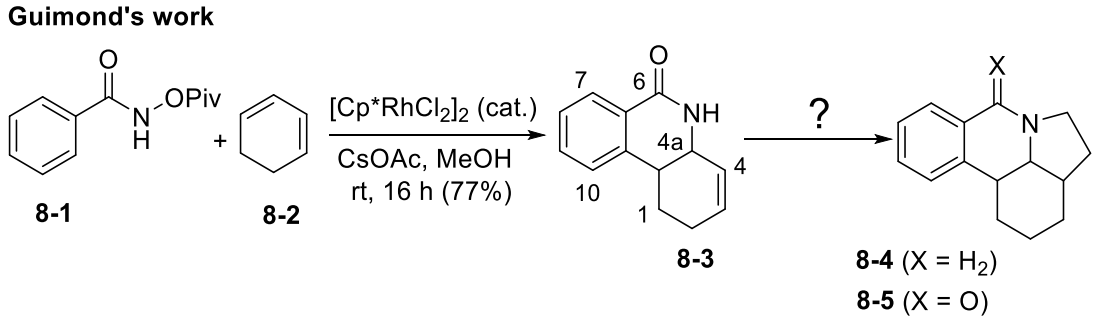


Scheme 86. DFT calculated catalytic cycle proposed by Guimond *et al.*

A recent review entitled "designing catalysts for functionalization of unactivated C–H bonds based on the C–H activation Reaction" describes the different metal catalyst for C–H functionalization.[146] Carboxylate-assisted Ru-catalyzed alkyne annulation is worthy to note.[147]

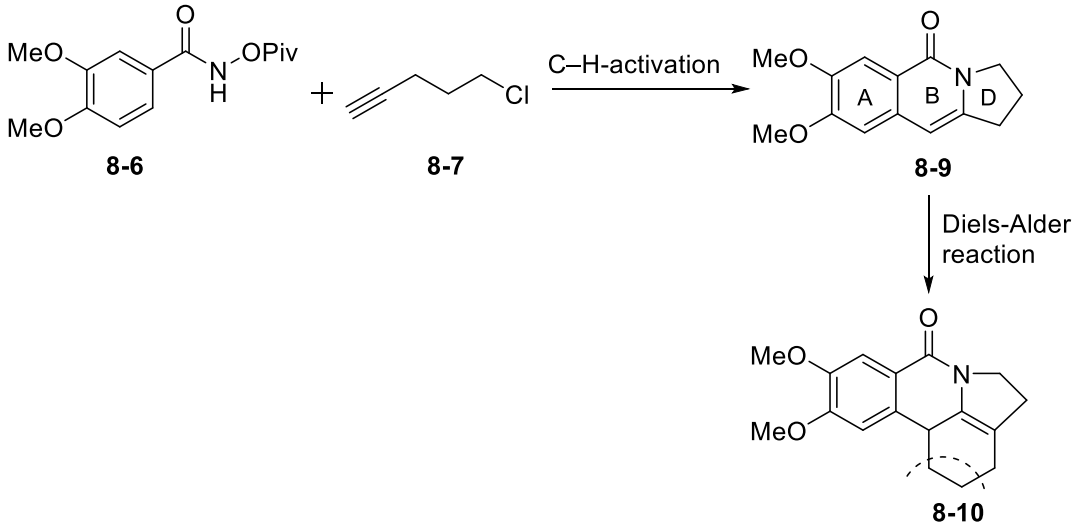
8 Goal of the research

C–H-activation is the finest approach towards the synthesis of complex structures in a single shot. It is evident from the literature that a huge number of approaches have been published for lycorane synthesis. However, a close insight of literature indicates that synthesis of complex alkaloids such as lycorine, fortucine etc. utilizing lycorane synthetic techniques failed at some instances either in synthesis of desired alkaloid or delivery of the correct stereocenter. Here our approach is to develop such a method which could be applicable for a broad range of alkaloids with known stereochemistry at carbons. While lycoranes are not biologically active compounds though, they are the timeless synthetic targets for demonstrating potential of new strategies towards such polycyclic alkaloids. The C–H-activation generates B/C-*cis* fused tricyclic systems. The synthesis of lycorane like structures seemed to be possible by annexing the D-ring to a properly substituted tetrahydrophenanthridinone (**Scheme 87**). However, this would require to study the effect of substituted benzamide derivatives on this Rh(III)-catalyzed phenanthridinone synthesis.



Scheme 87. Possible route to lycorane derivatives via Rh(III)-catalyzed C–H-activation on benzamide derivatives with annulation of cyclohexadienes followed by formation of ring D.

Our second approach is to generate first the A–B–D ring system of lycorane by C–H-activation and then annex the ring C on a dihydropyrrolo-isoquinolinone by Diels-Alder reaction. In this approach one would require a detailed study of allylic oxidation, Wittig reaction and Diels-Alder cyclization.



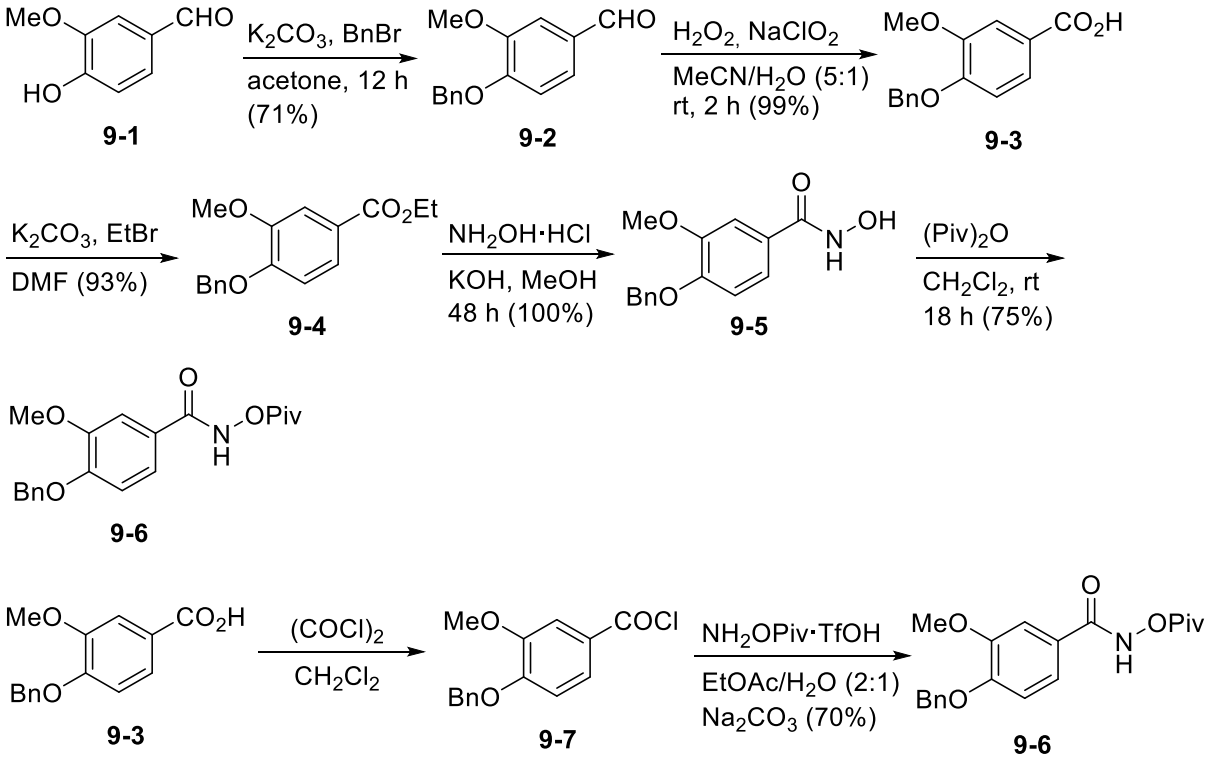
Equation 88. A second possible route to lycorane derivatives via Rh(III)-catalyzed C–H-activation on benzamide derivatives with annulation of alkyne **8-7** followed by formation of ring C by Diels-Alder reaction.

In the next section we describe our findings towards the goal.

9 Results and discussion

9.1 Preparation of model compound

With a view towards the synthesis of lycorane using this strategy, 3,4-dialkoxy-substituted *N*-(pivaloyloxy)-benzamide **9-6** was prepared as a model compound. The synthesis of this amide from vanillin is summarized in **Scheme 89**.



Scheme 89. Synthesis of benzamide derivative **9-6** from vanillin (**9-1**).

Thus, benzylation of 4-hydroxy-3-methoxy-benzaldehyde (vanillin, **9-1**) to benzyl ether[148] **9-2** was followed by oxidation[149] of the aldehyde function to benzoic acid[150] **9-3**. For the conversion of benzoic acid **9-3** to *N*-pivaloyloxy amide **9-6** two variants was explored. In the first one, acid **9-3** was converted to ethyl benzoate[151] **9-4** under alkylating conditions. Subsequent reaction of **9-4** with hydroxylamine led to hydroxamic acid **9-5**.[152] A final reaction with pivalic anhydride provided benzamide derivative **9-6**. The second variant utilizes the acid chloride, derived from **9-3**. Its reaction with, *O*-pivaloylhydroxylamine,[153] generated from its triflate salt with Na_2CO_3 gave amide **9-6** as well.

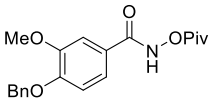
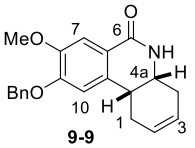
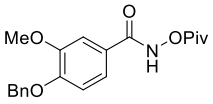
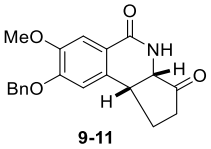
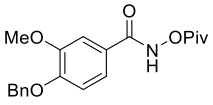
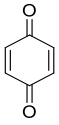
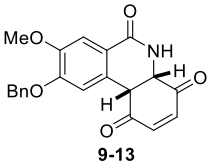
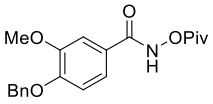
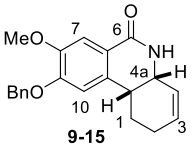
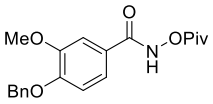
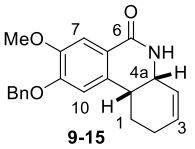
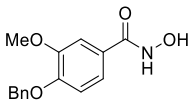
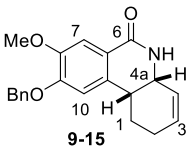
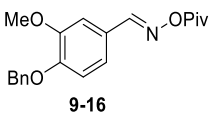
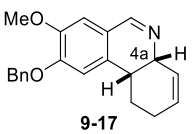
9.2 Model studies on C–H-activation

9.2.1 Reaction screaning & optimization

In order to do annulation of amide **9-6**, diene and enones were screend. The results are summarized in **Table 6**. Annulation of amide **9-6** was not observed with 1,4-cyclohexadiene,

cyclopentenone and benzoquinone with high loading of the catalyst $[RhCp^*Cl_2]_2$ (10 mol%). Using 1,3-cyclohexadiene with amide **9-6** underwent Rh(III) catalyzed annulation though the yield (10 %) was poor, but the palladium mediated annulation was not observed. Then we screaned varrients of benzamide such as hydroxamic acid **9-5** and benzylimine **9-17** with 1,3-cyclohexadiene using $[RhCp^*Cl_2]_2$ as a catalyst along the additives. However, none of them delivered the product.

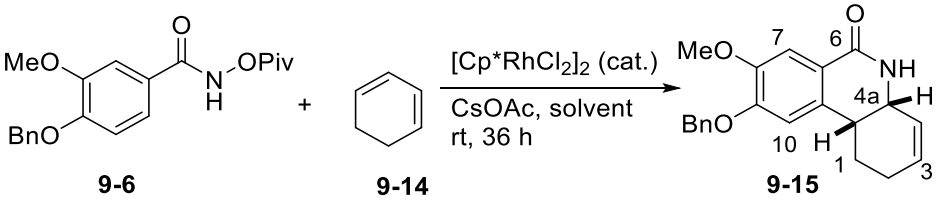
Table 6. Screening of benzamide and benzimine annulation.

entry	benzamide	diene	reaction condition	time (h)	product (expected)	yield (%)
1	 **9-6**	 **9-8**	$[RhCp^*Cl_2]_2$ (10 mol%), (2.0 eq.) CsOAc, MeOH (0.2 M), rt	12	 **9-9**	00
2	 **9-6**	 **9-10**	$[RhCp^*Cl_2]_2$ (10 mol%)., (2.0 eq.) CsOAc, MeOH (0.2 M), rt	17	 **9-11**	00
3	 **9-6**	 **9-12**	$[RhCp^*Cl_2]_2$ (10 mol%)., (2.0 eq.) CsOAc, MeOH (0.2 M), rt	120	 **9-13**	00
4	 **9-6**	 **9-14**	$Pd(OAc)_2$ (10 mol%), (20 mol%) $P(tol)_3$, (2.0 eq.) CsOAc, toluene, rt	18	 **9-15**	00
5	 **9-6**	 **9-14**	$[RhCp^*Cl_2]_2$ (10 mol%), (2.0 eq.) CsOAc, MeOH (0.2 M), rt	18	 **9-15**	10
6	 **9-5**	 **9-14**	$[RhCp^*Cl_2]_2$ (10 mol%), (2.0 eq.) CsOAc, toluene, rt	24	 **9-15**	00
			Additive: PPh_3, rt	24		
7	 **9-16**	 **9-14**	$[RhCp^*Cl_2]_2$ (10 mol%), (2.0 eq.) CsOAc, THF, rt	37	 **9-17**	00
			Additive: CH_3COOH (2 drops), 60 °C	30		

We observed annulation of benzamide **9-6** with 1,3-cyclohexadiene in 10% yield. Therefore a brief survey of reaction conditions was performed to enhance the isolated yield. The results

obtained on amount of catalyst $[Cp^*RhCl_2]_2$,[154] loading in different solvents are shown in **Table 7**. In methanol the reaction led to successful C–H-activation, cross-coupling and cyclization. However, despite relatively high catalyst loadings (up to 5 mol%) the yield of tricyclic amide **9-15** did not exceed 20%. Acetonitrile as solvent was even worse with a 10% yield of **9-15** in presence of 5 mol% catalyst. Much better results were obtained in ethanol as solvent. Here up to 55% of **9-15** (2.5 mol% of catalyst) could be obtained.

Table 7. Screening of conditions for the Rhodium(III)-catalyzed synthesis of phenanthridinone **9-15**.

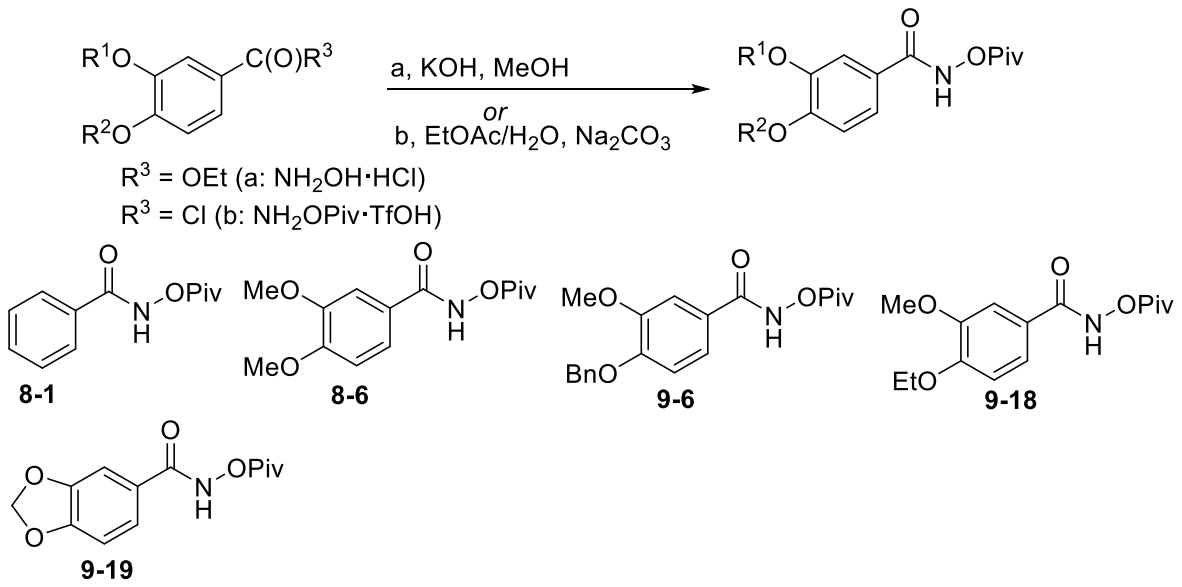


entry	Catalyst (mol%)	solvent	yield of **9-15** (%)
1	5	MeOH	20
2	2.5	MeOH	20
3	1	MeOH	10
4	5	MeCN	10
5	2.5	MeCN	5
6	1	MeCN	0
7	5	EtOH	50
8	2.5	EtOH	55
9	1	EtOH	40

In a larger scale reaction besides the *cis*-product **9-15** a small amount of the corresponding *trans*-fused compound could be isolated (*cis*/*trans* = 98:02). As can be seen, the C–H activation is regioselective with the insertion taking place only at 6-H.

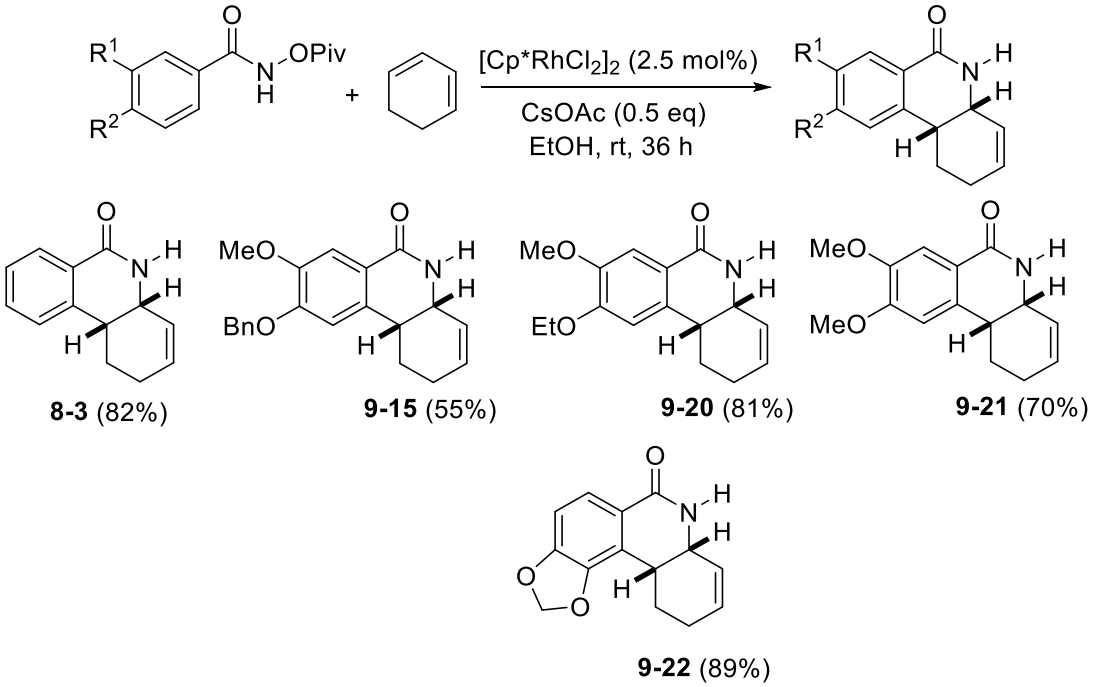
9.2.2 Synthesis of Phenanthridinones & their reduction

With a view towards delineating the scope of this reaction, various 3,4-dialkoxy-substituted *N* (pivaloyloxy)benzamides were prepared (**Scheme 90**) analogously to **9-6** as mentioned before using both ethylbenzoate and acid chloride pathways.



Scheme 90. Synthesis of benzamide derivative from corresponding benzoic acid ester or chloride.

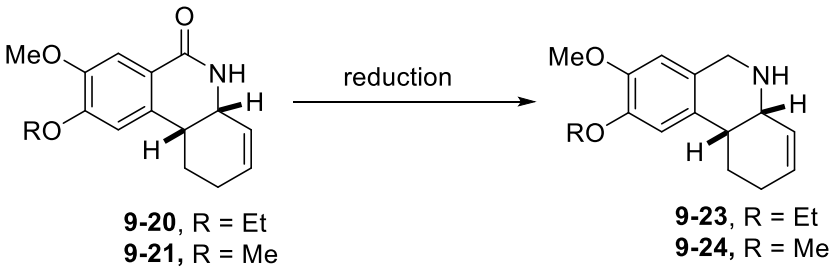
The benzamides were reacted reacted with cyclohexadiene (**9-14**) utilizing the optimized conditions (2.5 mol% of catalyst, 0.5 equiv of (CsOAc, EtOH 0 °C to rt, 36 h). The results are summarized in **Scheme 91**. With the exception of **9-15**, all annulations proceeded in quite good yields. In all cases essentially only the *cis*-fused products were obtained (dr > 98:02). A surprising result was obtained with the amide **9-19** derived from 3,4-(methylendioxy)benzoic acid. In this case only the isomer resulting from activation of 2-H was observed. This was clearly evident from observation of two doublets for the aromatic protons. As is known, the electron-donating effect of the methylenedioxy function is significantly reduced due to conformational reasons, since the free election pairs of the oxygen atoms cannot be in line with the π-system. Moreover, the steric demand of the methylenedioxy group might be less. Similar regioselectivtiy has been observed for other Rh(III)-catalyzed reactions of **9-19**.[155] Therefore, access to the lycorane skeleton would not be possible from **9-19** via this strategy. Thus, it seems that electronic factors govern the regiochemistry in the C–H activation step.



Scheme 91. Rhodium(III)-catalyzed synthesis of phenanthridinones using the optimized conditions from **Table 7**.

In order to construct ring D, amide would have to be reduced into amine. The direct reduction of the amide function of **9-15** with $LiAlH_4$ did not deliver the product. Charette's amide reduction also failed (entry 3-6, **Table 8**), which is a mild reduction condition for hindered tertiary and secondary amide via activation of amides with Tf_2O.[156] However, the reagent combination $LiAlH_4/AlCl_3$ towards reduction was successful.[157]

Table 8. Reduction of amide to *sec*-amine.



9-20, R = Et
9-21, R = Me

9-23, R = Et
9-24, R = Me

entry	R	reagent	solvent	temp. (°C)	time (h)	yield (%)
1.	Bn	$LiAlH_4$	THF	0 °C–rt	12	00
2	Bn	$LiAlH_4$	THF	0 °C–reflux	20	00
3	Bn	Tf_2O then $NaBH_4$	CH_2Cl_2	0 °C–rt	02	00
4	Bn	Tf_2O then $NaBH_4$	CH_2Cl_2	0 °C–rt	12	00
5	Bn	Tf_2O then $NaBH_4$	CH_2Cl_2	0 °C–50 °C	18	00
6	Et	Tf_2O then $NaBH_4$	CH_2Cl_2	0 °C–50 °C	18	00
7	Et	$LiAlH_4/AlCl_3$	THF	0 °C–rt °C	12	10
8	Et	$LiAlH_4/AlCl_3$	THF	0 °C–40 °C	08	60
9	Me	$LiAlH_4/AlCl_3$	THF	0 °C–40 °C	08	75

The reduction of amide **9-21** with $LiAlH_4/AlCl_3$ at 40 °C led to secondary amines **9-24** with 75% yield whereas reduction of **9-20** gave lesser yield (60%). The structure of **9-23**·HCl was secured by X-ray analysis, which proved the B/C-*cis*-function in the phenanthridinones (**Figure 30**).

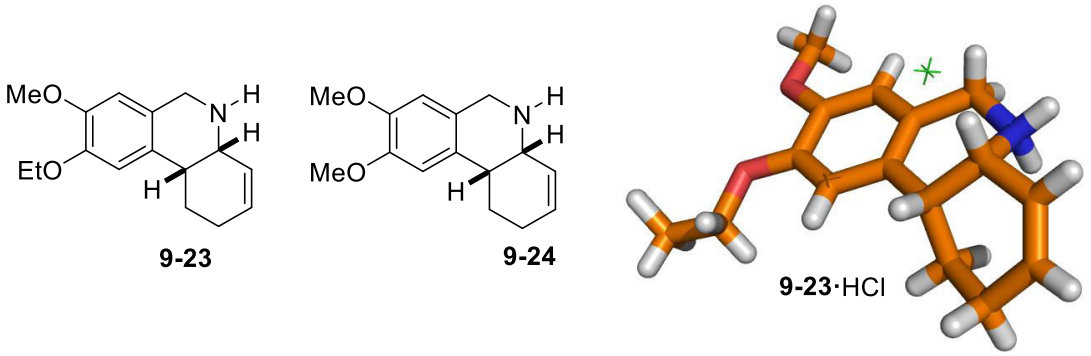
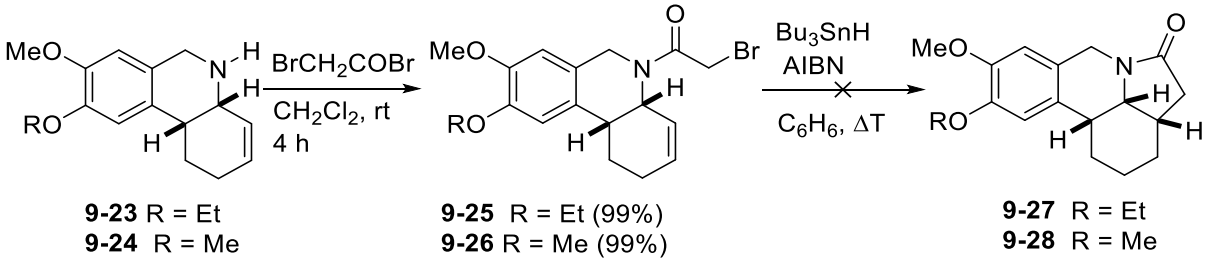


Figure 30. Amine **9-23** and **9-24** obtained from reduction of **9-20** and **9-21**, respectvely and X-ray structure of amine **9-23** (as hydrochloride) showing the *cis*-fusion.

9.3 Studies on construction of ring-D of γ-lycorane

Accordingly, studies were carried on tetrahydrophenanthridines **9-23** and **9-24** towards the formation of ring D. However, this turned out to be rather difficult. Some of these experiments with **9-23** and **9-24** are summarized in **Scheme 92**. Amines **9-23** and **9-24** could be acylated

with bromoacetyl bromide to the corresponding amides **9-25**, **9-26**. However, neither radical conditions[158] nor reaction in presence of $Pd(OAc)_2$ (30 mol%), *t*-Bu_3P (40 mol%), Et_3N (2 equiv), toluene, 110 °C, 12 h, led to the desired tetracycles **9-27** or **9-28**. Rather decomposition of these bromoacetamides with the formation of a complex mixture was observed.



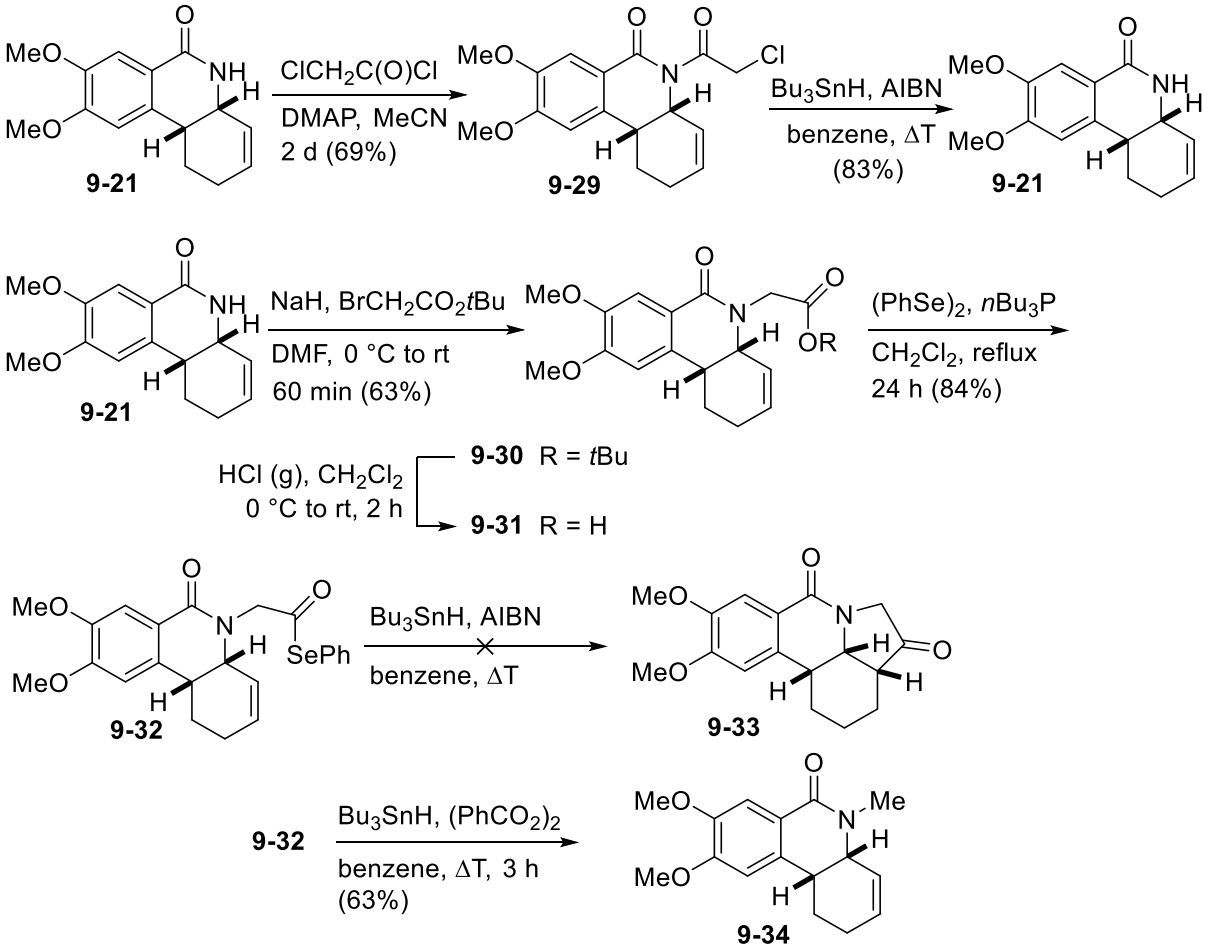
9-23 R = Et
9-24 R = Me

9-25 R = Et (99%)
9-26 R = Me (99%)

9-27 R = Et
9-28 R = Me

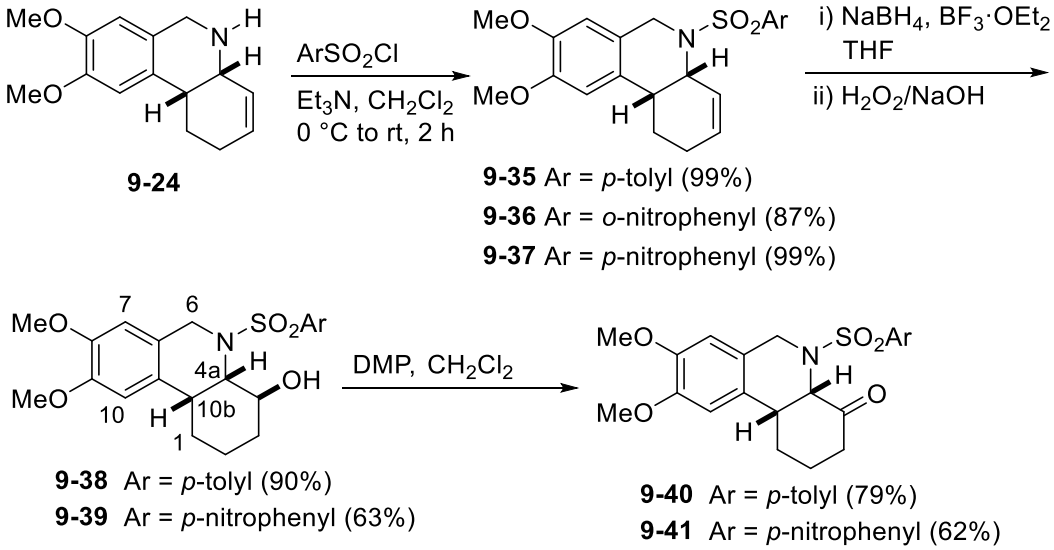
Scheme 92. Attempts to form lactams **9-27, 28** by radical cyclization.

Diacylamine **9-29**, obtained from amide **9-21**, underwent cleavage of the acylic amide bond upon reaction with Bu_3SnH given back the starting amide **9-21** (**Scheme 93**). As it is known that phenyl selenoesters can serve as precursors for acyl radicals, selenoester **9-32** was prepared from amide **9-21** in three steps. However, reaction of **9-32** with Bu_3SnH in presence of AIBN did not lead to the desired tetracyclic compound. Here only starting material (16 mg of 25 mg) was recovered. Using benzoylperoxide as radical initiator led to formation of the intermediate acyl radical followed by decarbonylation and formation of *N*-methylamide **9-34**.



Scheme 93. Attempts to cyclize amide derivatives **9-29** and **9-32** to the corresponding galanthan ring systems.

Our next plans focused on derivatization reactions of the double bond of ring C. This might open additional options for creation of ring D. Initially, amine **9-24** was converted to sulfonamides (**Scheme 94**). As it turned out, hydroboration[159] of the double bond was highly selective, with the borane attacking the double bond at the more hindered position. The alcohol derivatives were not further purified (purified for characterization only) but rather oxidized to the α-aminoketone derivatives **9-38** and **9-39** using the Dess-Martin periodinane reagent. The regiochemistry of the hydroboration was inferred from the ^{1}H NMR spectra. Indicative of the regiochemistry was the signal for 4a-H in alcohol **9-38** which appeared as a doublet of doublet (δ = 3.90, J = 8.0, 4.0 Hz). The hydroboration was also diastereoselective. While this was not further investigated, we assume attack of the borane from the *exo* face, *syn* to 4a-H and 10b-H. For the other regioisomer a multiplet would be expected instead.



Scheme 94. Conversion of tricyclic amine **9-24** to sulfonamides and the regioselective hydroboration of the ring C double bond.

In order to attach ring D, extension of the ketone by a suitable C2-building block is required. Ketone **9-41** has been screened with phosphonoesters shown in **Figure 31** under different reaction condition. The results obtained from this reaction are presented in **Table 9**. Under these conditions desired compound formation was not observed.

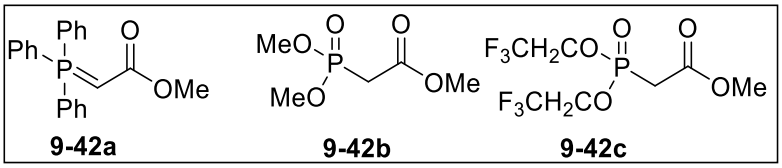
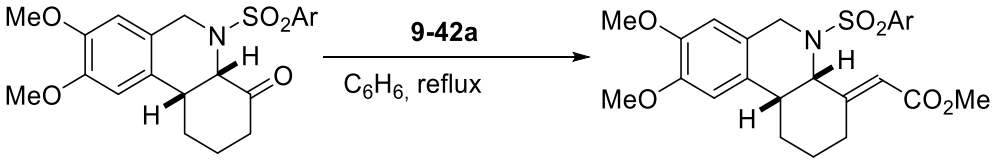


Figure 31. Phosphonoester reagents for Wittig-Horner and Wittig reaction.

Table 9. Optimization of Wittig reaction of **9-41** under different condition.



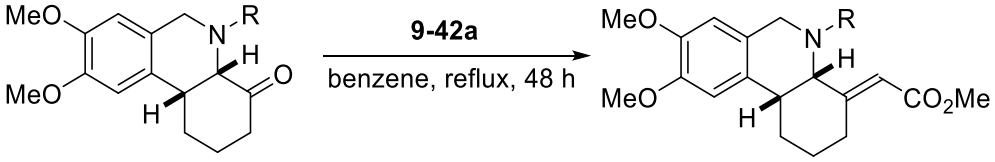
9-41 Ar = *p*-nitrophenyl

9-44 Ar = *p*-nitrophenyl (5%)

entry	reagent	solvent	temp. (°C)	time (h)	yield (%)
1.	**9-42a**, $LiOH·H_2O$, PPh_3	THF	rt	12	00
2	**9-42b**, NaH/MeOH	MeOH	rt	12	00
3	**9-42b**, KHMDS	THF	rt	05	00
4	**9-42b**, *t*BuOK	THF	rt	12	00
5	**9-42c**, KHMDS, 18-crown-6	THF	rt	12	00
6	**9-42c**, LiCl, DBU	CH_3CN	rt	1 to 24	00
7	**9-42a**	benzene	reflux	48	5

Reaction of the two ketones **9-40** and **9-41** with methyl 2-(triphenylphosphoranylidine) acetate **9-42a** gave the desired enoates **9-43** and **9-44**, respectively. However, the yields were too low to be of practical value.

Table 10. Optimization of Wittig reaction on **9-40** under different conditions.

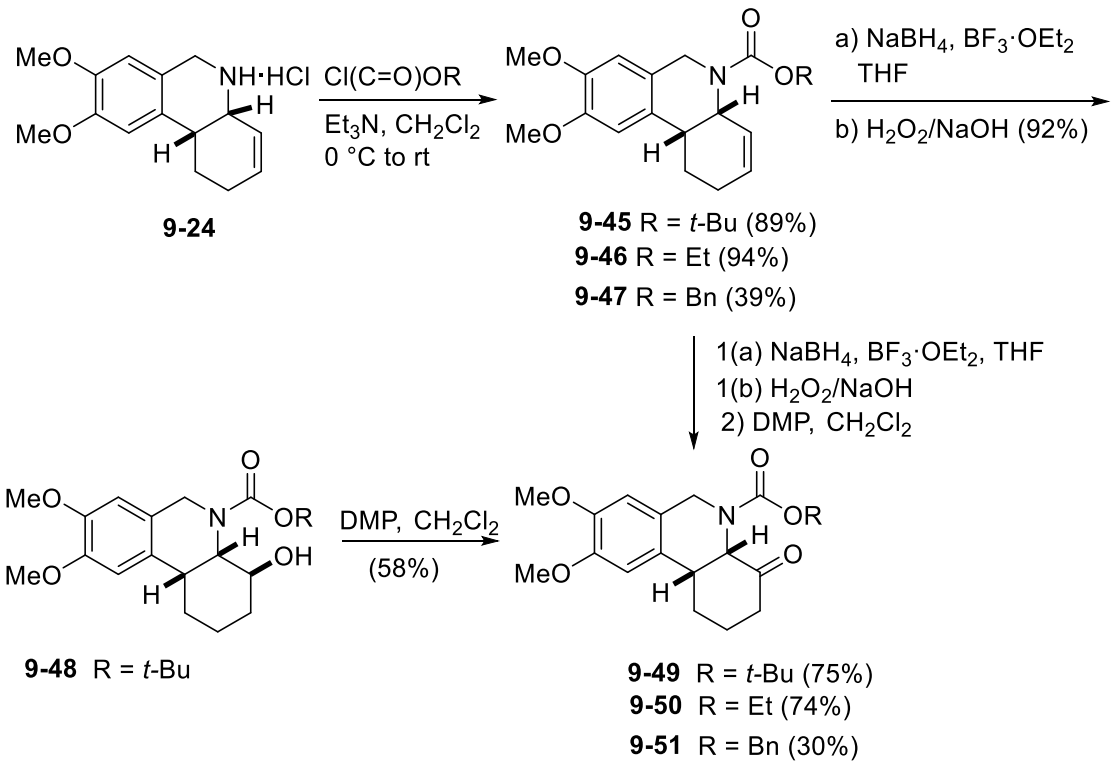


9-40 Ar = *p*-tosyl

9-43 Ar = *p*-tosyl (11%)

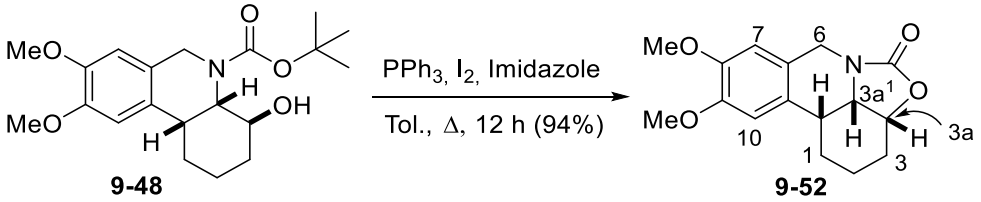
entry	reagent	Ar	solvent	temp. (°C)	time (h)	yield (%)
1	**9-42a**	*p*-tosyl	benzene	rt	48	00
2	**9-42c**, KH	*p*-tosyl	THF	rt	12	00
3	**9-42a**	*p*-tosyl	benzene	reflux	48	11

In order to check whether the protecting group on the nitrogen influences the regiochemistry of the hydroboration reaction, amine **9-24** was converted to the carbamates **9-45** – **9-47** (**Scheme 95**). On subjecting these carbamates to the hydroboration/oxidation sequence led to the α-aminoketone derivatives **9-48**–**9-50**, respectively.



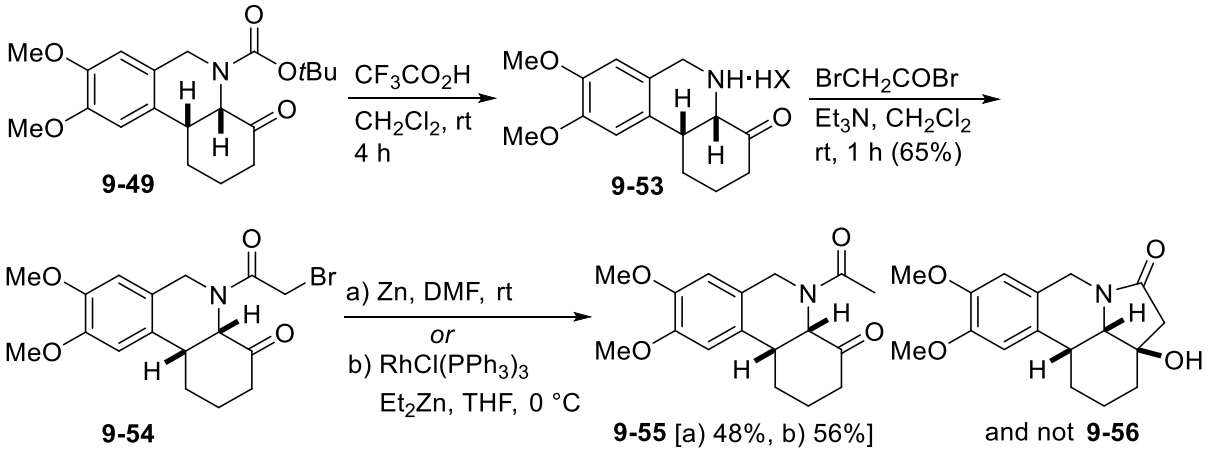
Scheme 95. Conversion of tricyclic amine **9-24** to carbamates and their regioselective hydroboration of the ring C double bond followed by oxidation into ketones.

In order to understand the regioselectivity of the hydroboration oxidation, we subjected hydroxyl-carbamate **9-48** for Appel reaction conditions which delivered cyclic carbamate **9-52** (oxy-lycorane) as a single diastereomer. The diastereoselectivity of the cyclic carbamate **9-52** was inferred from the ^{1}H NMR spectra (3a^1-H, J = 4.3, 7.6 Hz). It confirmed that hydroboration is regioselective as well as diastereoselective.



Scheme 96. Synthesis of oxy-lycorane (**9-52**) from hydroxyl-carbamate **9-48**.

Carbamate **9-49** was deprotected under acid conditions giving amine salt **9-53**. Then it was acylated with 2-bromoacetyl bromide into 2-bromoacetamide **9-54** and then subjected to conditions for a Reformatsky reaction. However instead of the desired intramolecular aldol reaction, only reductive dehalogenation to acetamide **9-55** could be observed. The reasons for the failure of the above-mentioned cyclizations are unclear, as visual inspection of amine **9-23** indicates that cyclization of an amide derivative via attack at the double bond should be possible. Most likely, the tricyclic ring system already suffers from some strain so the additional ring D would increase the ring strain even more.



Scheme 97. Attempts on intramolecular Reformatsky reaction of keto amide **9-54**.

Eventually we turned to transition metal catalyzed cyclization where the cyclization would be initiated from a vinylmetal species. Delgado and co-workers described the reaction of amino-tethered halodienes with $Ni(COD)_2$ followed by trapping of the presumably formed σ-alkylmetal intermediates.[160] Vinyl bromide containing a distal nitrogen atom displays high selectivity in the product **9-60** whereas compounds **9-61** without nitrogen atom undergoes elimination and does not exhibit selectivity in the cyclized product **9-62**.

The mechanism of the process is demonstrated in **Figure 32**. The alkylnickel intermediate **III** originating after oxidative addition and alkene insertion, which after treating with a strong nucleophile delievered the product **IV**.

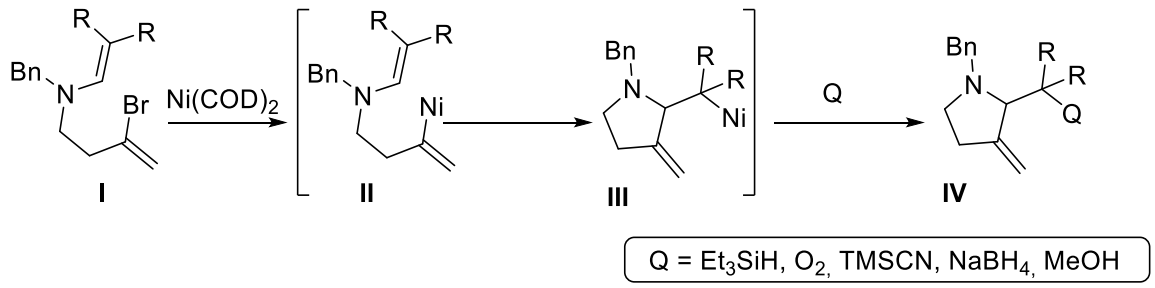


Figure 32. Mechanism of nickel promoted cyclization of amino-tethered vinyl bromides.

The increased stability of the intermediate nickel complex is due to the coordination of amino function which ceases the β-elimination process. The trapping reagent also affects the elimination; therefore a delicate balance is required to obtain high yields of cyclic products. The high selectivity could also be coming from assistance of the amino group (**Figure 33**).

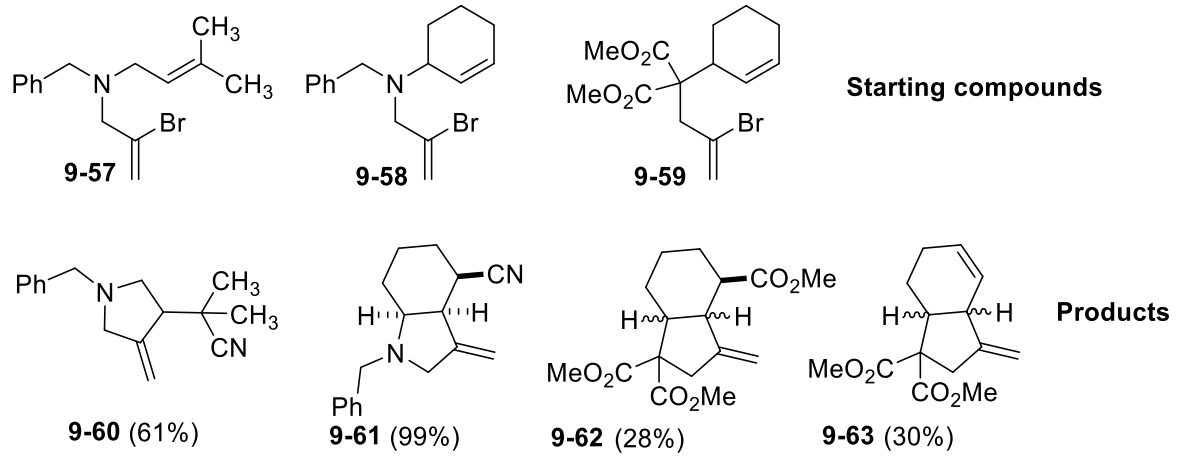
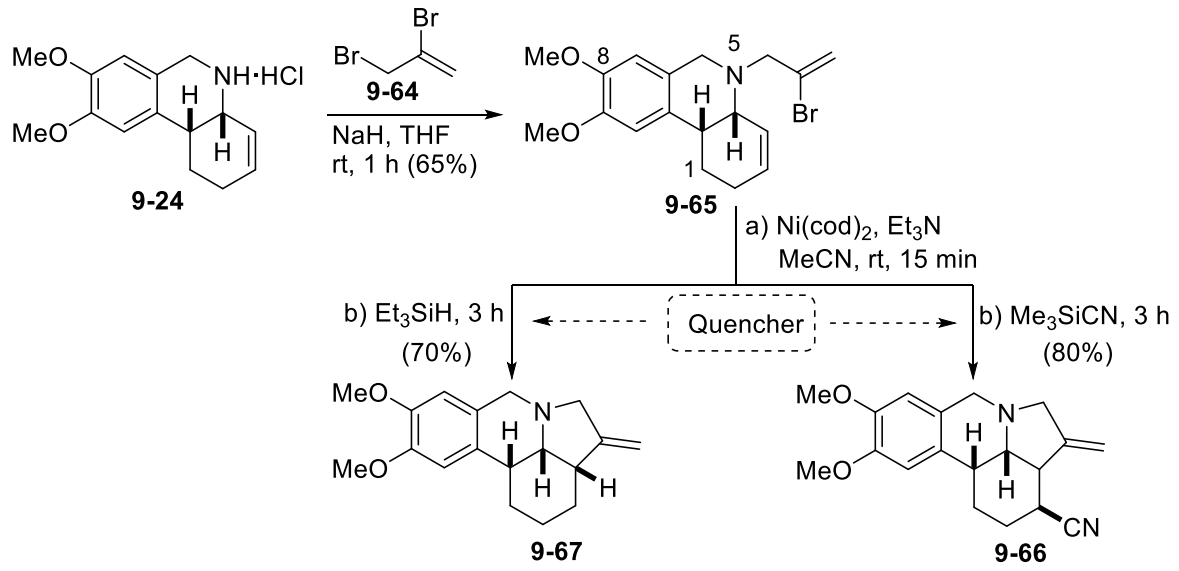


Figure 33. Cyclic products obtained from nickel promoted cyclization of vinyl bromides.

Accordingly, amine **9-24** was alkylated with 2-bromoallyl bromide (**9-64**) to yield allylamine **9-65** (**Scheme 98**). With this substrate successful cyclization was observed in presence of $Ni(COD)_2$, Et_3N and a suitable nucleophile, like trimethylsilyl cyanide or triethylsilane. This way the two tetracyclic compounds **9-66** and **9-67** were obtained. Both feature the *cis*/*cis*-ring fusion of the *γ*-lycorane ring system.

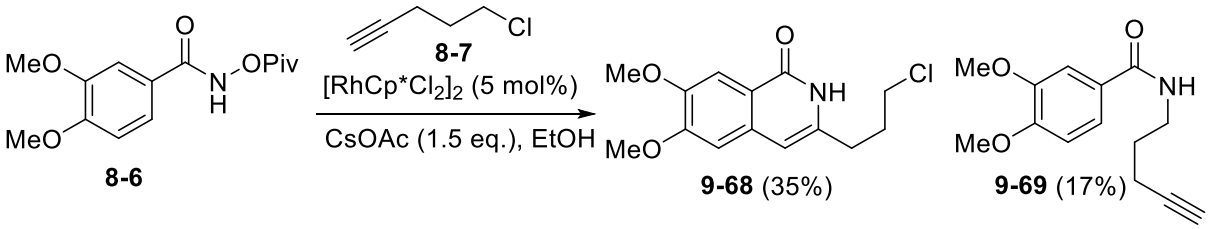


Scheme 98. Conversion of amine **9-24** to 5-(2-bromoallyl)-hexahydrophenanthridine derivative **9-65** and its nickel-mediated cyclization to 4-methylene-octahydro-1*H*-pyrrolo[3,2,1-de]phenanthridines **9-66** and **9-67**.

Brief attempts to epoxidation of **9-67** or oxidative cleavage (O_3) were unsuccessful.

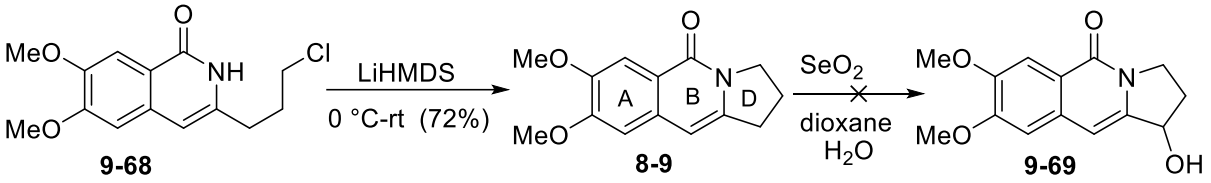
In view to construct ring D, we explored other possibility. Thus, a $[RhCp^*Cl_2]_2$ mediated annulation reaction of benzamide **8-6** with alkyne **8-7** (Across) gave cyclic product **9-68** along with the *N*-alkylated benzamide **9-69** (**Scheme 99**).[144] The presence of three singlets in the aromatic region of ^1H NMR confirms the formation of cyclized product **9-68**, whereas in case

of no cyclization two doublets in aromatic region along the singlet of acetylenic proton at 2.1 ppm were found.



Scheme 99. Benzamide **8-6** annulation with alkyne **8-7**.

Though the yield of cyclic product **9-68** was quite low, we tried to cyclize it into tricyclic amide using LiHMDS in THF at 0 °C, which delivered desired product **8-9**.



Scheme 100. Intramolecular amide alkylation.

In order to introduce ring C, a brief attempts toward allylic oxidation of alkene **8-9** into allylic alcohol **9-69** were unsuccessful.

10 Conclusion II

We developed a new approach to lycorane-like structures. Several *N*-(pivaloyloxy)benzamides were reacted with cyclohexa-1,3-diene in presence of a rhodium(III) catalyst which resulted via C–H activation in the corresponding tetrahydrophenanthridinones (**Figure 34**).

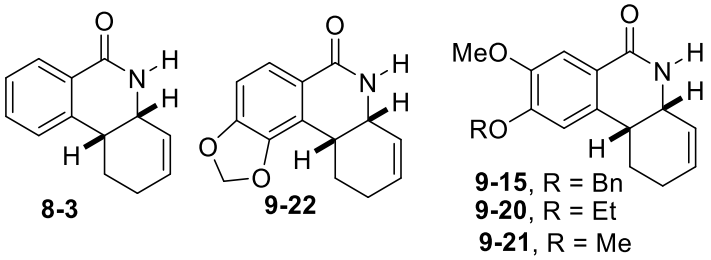


Figure 34. Tetrahydrophenanthridinones.

They were reduced into secondary amines using a combination of $LiAlH_4/AlCl_3$. Subsequently, various strategies were explored to convert these tricyclic phenanthridines to the tetracyclic core structure of the lycoranes. However, radical based approaches and Reformatsky reaction were unsuccessful. Further tricyclic secondary amine was alkylated with 2-bromoallyl bromide and a Ni-induced cyclization led to the tetracyclic *γ*-lycorane analogs **9-67** and **9-66**.

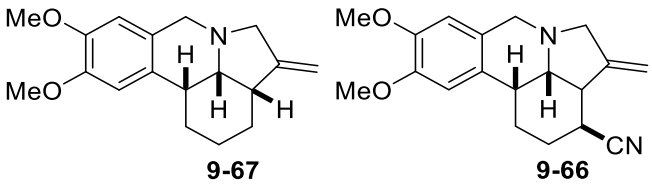
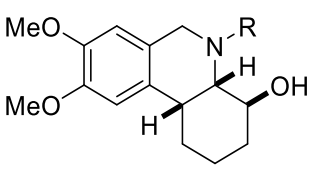


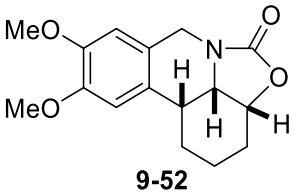
Figure 35. Analogs of *γ*-lycorane.

In the course of this study we discovered a strong influence of the type of the 3,4-dialkoxy substituents on the regiochemistry of the C–H-activation. While for the non-constrained N-(pivaloyloxy) benzamides activation of 6-H takes place, 1,3-cyclohexadiene insertion to 3,4-methylendioxyamide occurs selectively at 2-H (**9-22**).

Furthermore *N*-protected phenanthridine derivatives underwent a regio- and stereoselective hydroboration/oxidation to the corresponding *α*-aminoketone compounds, which was confirmed by the formation oxy-lycorane (**9-52**) from carbamate **9-48.**



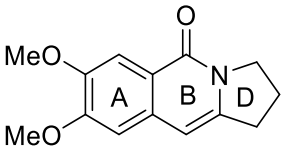
9-38 R = tosyl
9-39 R= *p*-nosyl
9-48 R = Boc



9-52

Figure 36. Alkanolamine and oxy-lycorane.

We also have shown the synthesis of tricyclic amide **8-9** via rhodium catalyzed C–H annulation, containg the A,B,D ring system of *γ*-lycorane.



8-9

Figure 37. Tricyclic amide **8-9**.

Chapter 3

Enantioselective Organocatalytic Friedel-Crafts Indole Alkylation

11 Introduction

Synthetic chemistry has been revolutionized over the last decades by the advent of enantioselective catalysis in the development of asymmetric reactions.[161] Activation of a substrate by a chiral catalyst became a powerful strategy. Asymmetric metal complexes have been used as catalysts in the synthesis of chiral compounds.[162] For, example many commercial therapeutics have been developed using asymmetric hydrogenation.[161(a),(b)] Organocatalysis is distictally advantageous over conventional metal catalysis. Metals are hazardous materials. Whereas, very little is known about the toxicity of organo catalyst. Metal catalyzed reactions are very sensitive to water and air. Organocatalytic reactions are able to tolerate the presence of a little amount of moisture and air.[163] Therefore, organocatytic reactions are easy to handle. A substance which can cause physiological changes in the body is known as drug. It can be injected to the body in different ways such as injection, oral, or through respiration. Antibiotics a class of drugs, is used in the treatment or prevention of bacterial infections. Some antibiotics are also active against protozoans and viruses. Antibiotics could be obtained from bacteria by genomic modification. Though the natural products isolated from plants, animals, fungi and bacteria are potentially active against infection. They are present in organisms in ultra-low quantities. Their isolation from natural sources could provide insufficient amount, which would be the obstacle in clinical trials. Therefore, an alternative route is demanding. Chemical synthesis could provide a required amount. Natural product synthesis requires suitable reaction sequences which can generate the assigned stereocenters of the natural product. Mostly natural products contain a carbon core. Many C–C bond forming reactions have been developed. In 1877 Charles Friedel and James Craft developed alkylation and acylation of aromatic rings using $FeCl_3$. This was the first time when a Lewis acid was used in organic synthesis and became a choice of chemists for the alkylation of arenes and heteroarenes. The reaction proceeds through electrophilic aromatic substitution. A large group among the alkaloids containing an indole unit is known as “indole alkaloids”. The indole framework has been recognized as a “privileged” structure, representing more than 3000 isolated natural products where 40 of them are used as therapeutic agents. The first indole alkaloid, strychnine was isolated in 1818 and its structural formula was stablished in 1947. The asymmetric Friedel-Craft alkylation of indoles with imines provides enantiopure indol-3-ylmethamines, which serve as precursors of many biologically important natural products.[164]

3-Substituted-3-hydroxy-2-oxindoles are biologically important scaffolds, which are present in numerous alkaloids, shown in **Figure 38**. Convolutamydine A (**11-3**) induces the appearance of characteristic features to the differentiated tumor cell line HL-60.[165] Maremycins B (**11-4**) is a diketopiperazine alkaloid, which was isolated from the culture broth of marine Streptomyces species B 9173.[166] Biological studies of TMC-95A (**11-6**) showed that it inhibits the chymotrypsin-like (CT-L), trypsin-like (TL), and post-glutamyl peptide hydrolytic (PGPH) activities of the proteasome with IC_{50} values of 5.4, 200, and 60 nM, respectively.[167] A oxindole derivative of **11-1** was synthesized by palladium-mediated intramolecular Heck reaction of

substituted N-acyl-2,6-dibromoaniline.[168] 3-Hydroxy-*N*-methyl-welwitindolone C isonitrile (**11-5**) is present in blue green algae.[169]

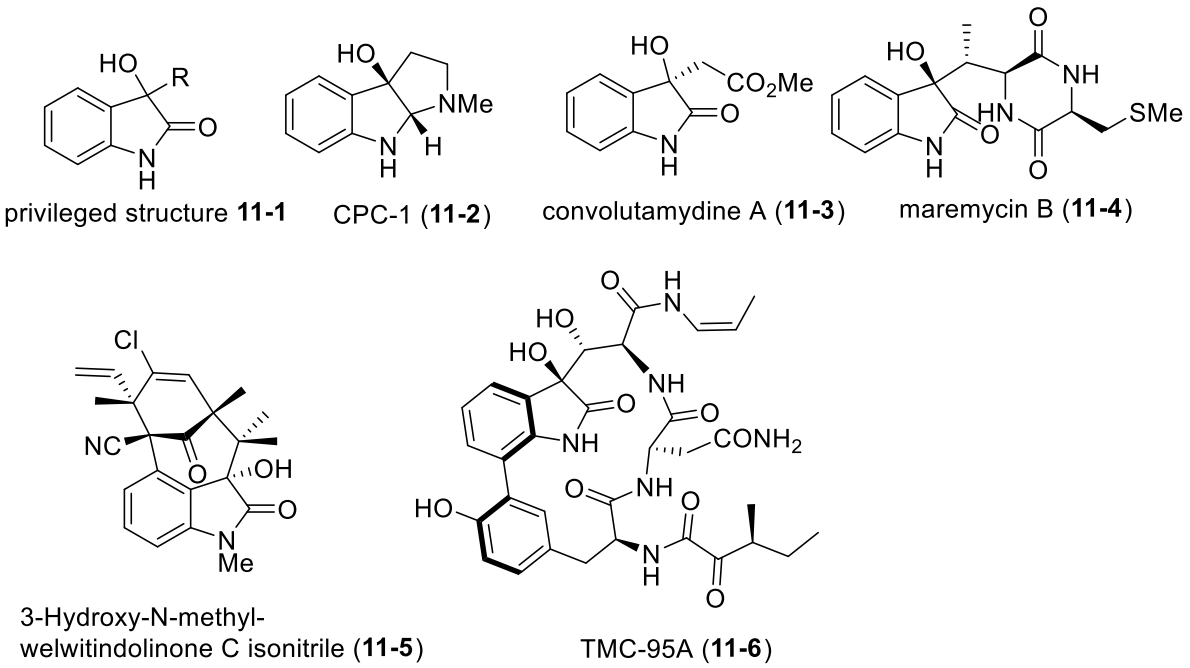


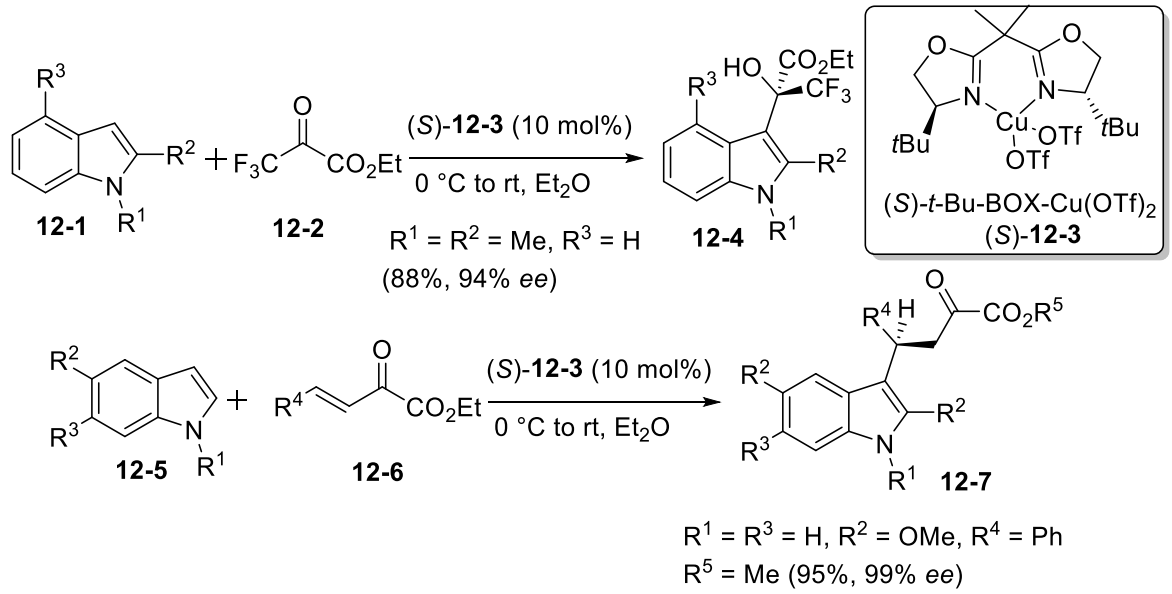
Figure 38. 3-Substituted-3-hydroxy-2-oxindoles embodied in natural products.

12 Literature review

A Friedel-Craft reaction introduces an alkyl or acyl group into the aromatic system under Lewis-acid conditions. In the last decade, much attention has been paid on the development of catalytic use of Lewis acid. Alkylation using benzyl-, propargyl- and allyl alcohols, imines or styrenes has been employed in place of toxic benzyl halides.[170]

12.1 Metal-based chiral complex catalysis

The chiral bisoxazoline-copper(II) complex (*S*)-**12-3** was deployed as a Lewis acid in catalytic enantioselective Friedel-Crafts alkylation of heteroaromatics and aromatics.[171] It has been established that a pyrrole π-system is quite much more active towards electrophilic substitution reactions than indole.[172] Catalyst (*S*)-**12-3** could also catalyze enantioselective addition of electron rich aromatics **12-1** to activated carbonyls.[173]



Scheme 101. Addition of indoles to activated carbonyl compounds.

Phosphorous based ligands in combination with Lewis acid for Friedel-Crafts alkylation were to be found inefficient whereas bisoxazoline based chiral catalyst **12-10** shown in **Figure 39** gave surprising results are summarized in **Table 11**.[174]

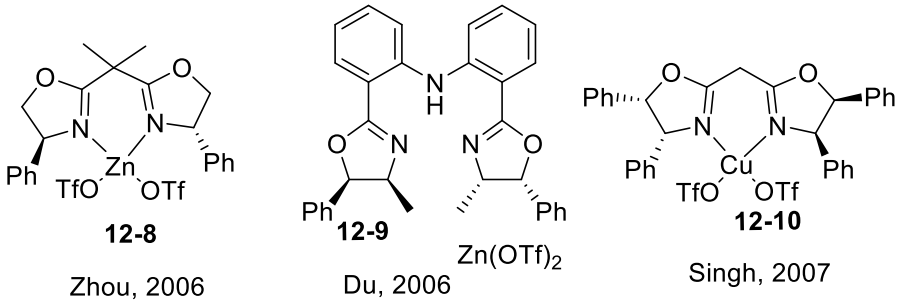
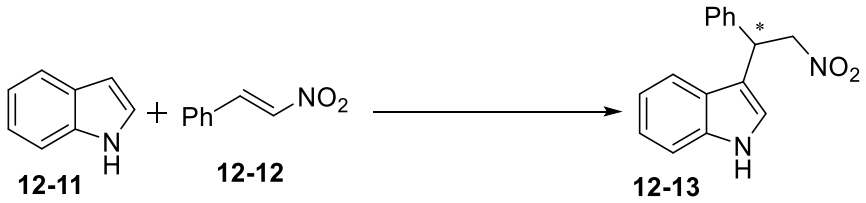


Figure 39. Bisoxazoline based ligands and Lewis acids.

Toluene turned out to be the best solvent for such particular transformations. The tridentate ligand **12-9** could activate the nitroalkene through coordination of the nitro group to the Lewis acid center. The NH group present in between to two phenyl rings of **12-9** would engage in NH $\cdots$ π (indole) interaction and direct the indole to attack the nitroalkene preferentially from *si*-face.

Table 11. Indole alkylation with nitrostyrene under different catalyst conditions.



entry	ligand	cat. (mol%)	solvent	time (h)	yield (%)	*ee* (%)
1	**12-8**	12	toluene	5	93	73
2	**12-9**	10	toluene	8	99	83
3	**12-10**	10	$CHCl_3$	12	79	81

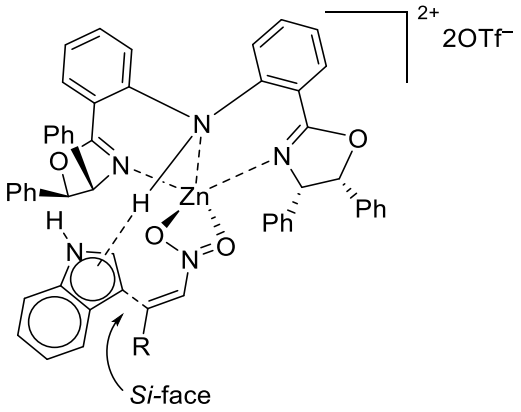
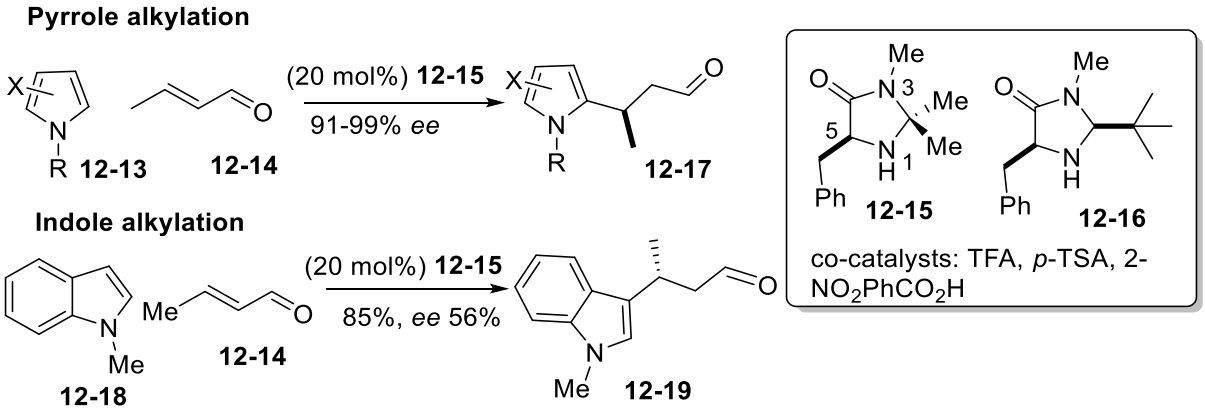


Figure 40. Possible bifunctional mode in the transition state of the catalyst **12-9**-$Zn(OTf)_2$.

Small organic molecules could be used as catalyst to catalyze some organic reactions without the involvement of co-catalyst such as Lewis acids. The process of such catalysis is known as organocatalysis.[175]

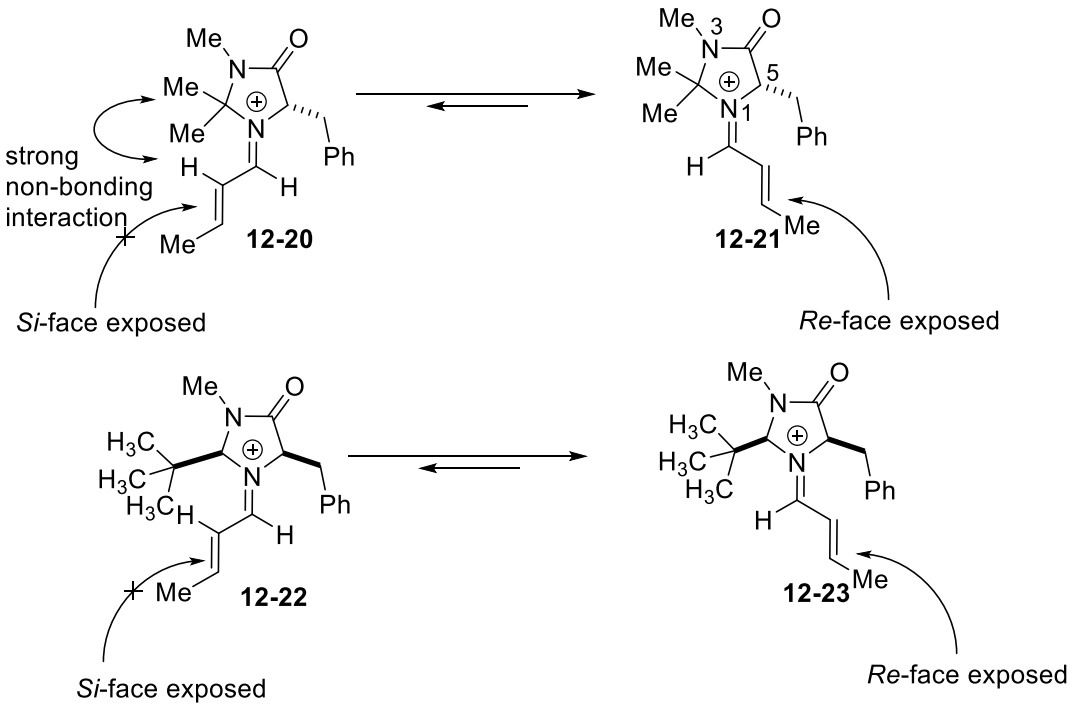
12.2 Iminium and SOMO Catalysis

MacMillan found poor reaction rates and enantioselectivities when *N*-methylindole (**12-18**) were treated with (*E*)-crotonaldehyde (**12-14**) using imidazolidinone **12-15** as a catalyst. Since the overall rate of iminium-catalyzed reactions depends upon the iminium formation as well as on the C–C bond formation.[176] In the enal and enone activation mode the energy of the lowest unoccupied molecular orbital of substrate gets lowered resulting enantioselective C–C and C–N conjugate additions, cycloadditions, hydrogenations, and Friedel-Crafts alkylations. The lone pair on nitrogen in catalyst **12-16** is better exposed whereas in catalyst **12-15** it is hidden under the methyl unit at C_2. Alkylation of *N*-methylindole with (*E*)-crotonaldehyde using catalyst **12-16** in combination with TFA and *p*-TSA gave better yield and enantioselectivity.



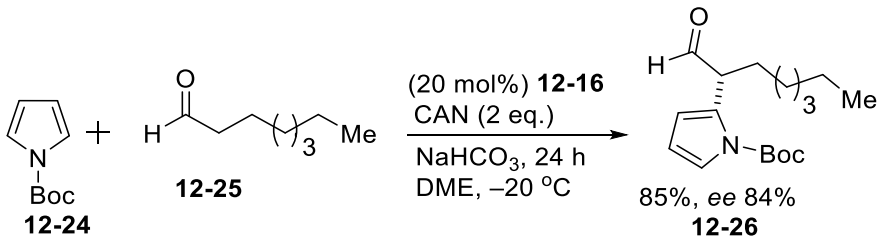
Scheme 102. Pyrole & *N*-methylindole alkylation with crotonaldehyde.

Now the question is? Why enantioselectivity is improved with catalyst **12-16**. The iminium ion geometry is controlled by the size difference of substituents at C2 and C5 positions of the imidazolidinone. The increased reactivity of the iminium ion **12-22** towards the C–C bond formation is due to selectively increased population of (*E*)-isomer **12-23** to overcome from the non-bonding interaction between the olefin of the substrate and the *t*-butyl unit. Therein benzyl unit in (*E*)-isomer shields the *si*-face and leaving free *re*-face for indole addition (**Scheme 103**).



Scheme 103. Iminium ion geometry and selectivity towards C–C bond formation.

The other process of aldehyde and ketone activation via enamine formation raises the energy of the highest occupied molecular orbital (HOMO) to promote enantioselective α-carbonyl functionalization.[177] MacMillan hypothesized a three-π-electron radical cation which is a singly occupied molecular orbital (SOMO) and active for a range of enantioselective catalytic transformations (**Figure 41**).[178] The pyrrole alkylation using aldehyde **12-25** is shown in **Scheme 104**.



Scheme 104. Enantioselective α-heteroarylation of aldehyde via SOMO catalysis.

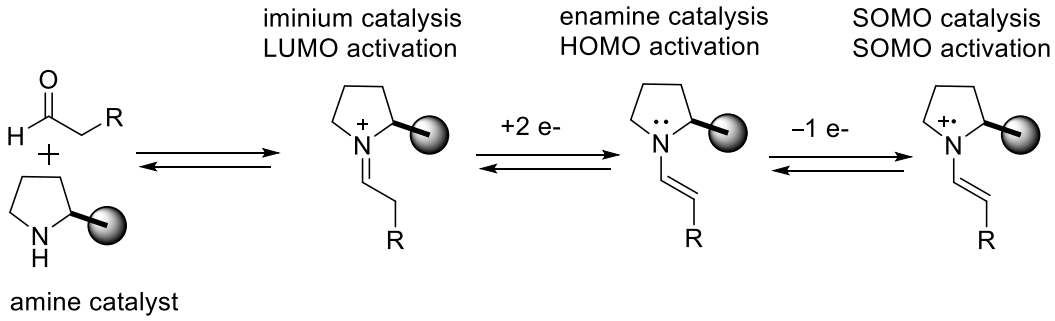
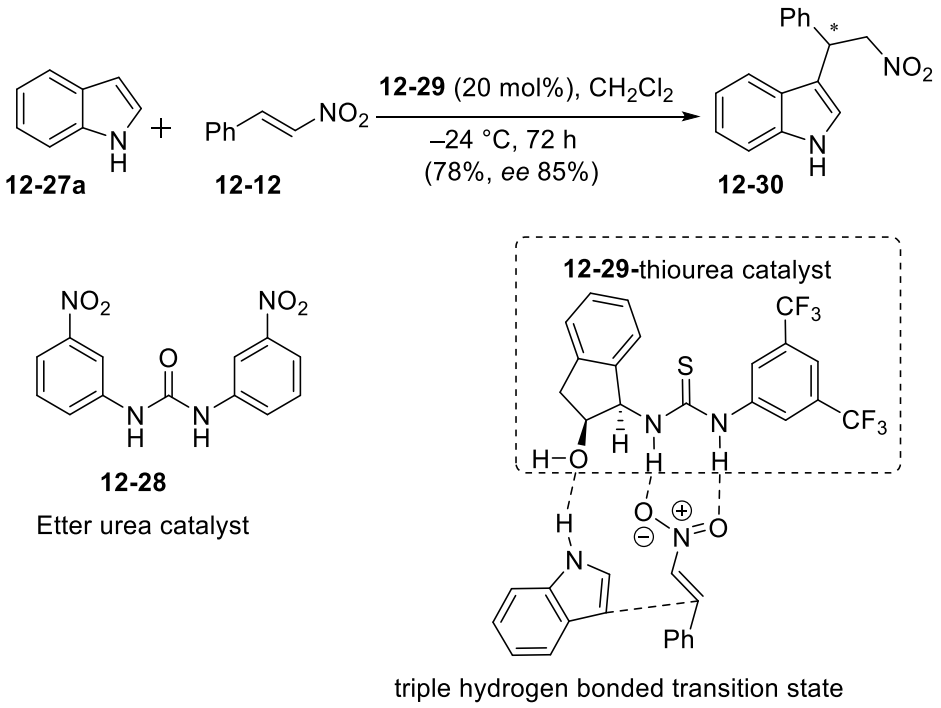


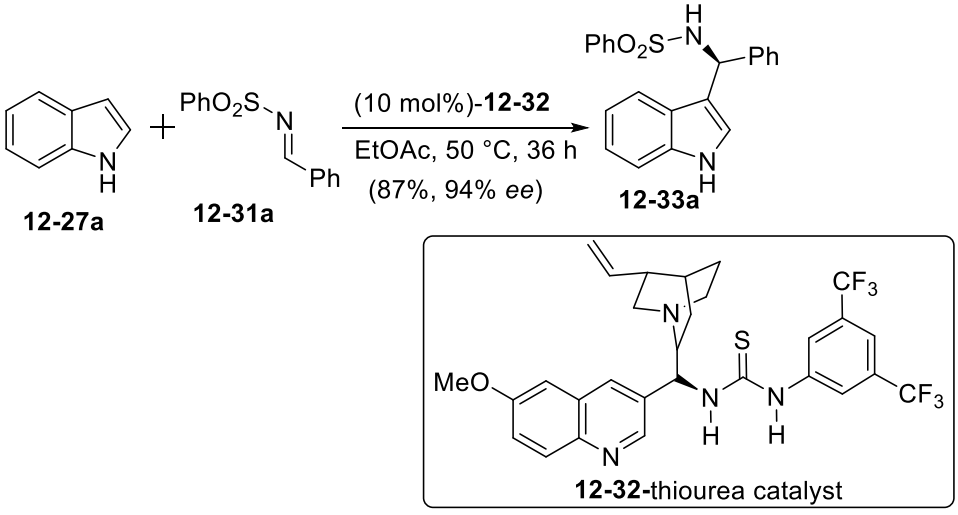
Figure 41. Hypothetical representation of single-electron oxidation of transiently formed enamine.

12.3 Organocatalysis via hydrogen bond-activation

Carbonyl group and related compounds could be activated by the introduction of double hydrogen-bonding.[179] The discovery of Etter and co-workers towards diaryl ureas such as **12-28** bearing electron-withdrawing substituents readily form co-crystals with variety of proton acceptors, including carbonyl compounds, inspired the development of urea catalysts.[180] Ricci and co-workers developed different thiourea catalysts for asymmetric alkylation of indole **12-27a** with electronically poor nitroalkenes **12-12** and found best results with the catalyst **12-29**. The transition state shown in **Scheme 105** seems to be more compact due to the hydrogen bonding interaction of the alcohol function in the catalyst **12-29** and the indole N–H, bringing both substrates closer, together leading to better selectivity. It is also clear from the transition state that *N*-alkylated indole could not interact with the hydroxyl unit of the catalyst **12-29** therefore the reaction would be less efficient. Thiourea based catalyst **12-32** is used to alkylate indole **12-27a** with imine **12-31a** (**Scheme 106**).[181]



Scheme 105. Friedel-Crafts alkylation of indole **12-27a** in presence of **12-29** catalyst and it's triply hydrogen bonded transition state.

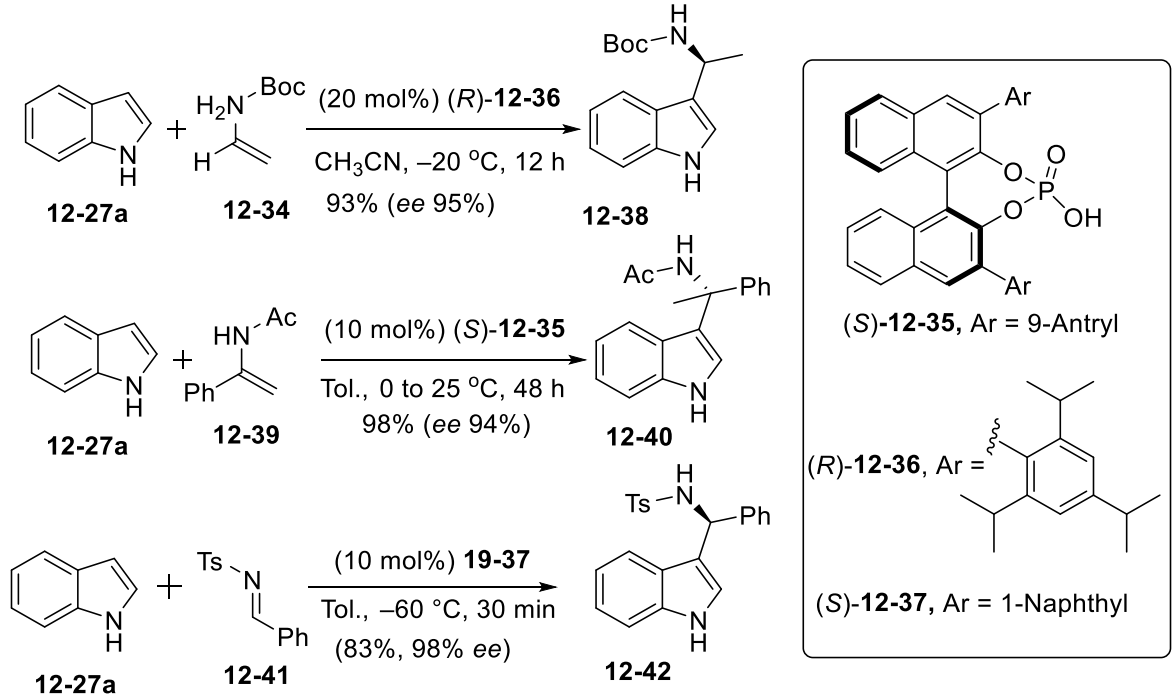


Scheme 106. Indole addition to aldimine.

12.4 Chiral Brønsted acid catalysis

A recent review "Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates" describes different aspects of catalysis is worthy noting.[182] The catalysis described before proceeds via activation of electron deficient multiple bonds. A highly enantioselective F-C alkylation of electron-rich alkenes, activated by chiral Brønsted acid is shown **Scheme 107**.[183] An important class of asymmetric F-C reaction of indole with imines could be catalyzed by phosphoric acid based organocatalysts (**Scheme**

107). The product of this reaction gives an opportunity to access enantiopure 3-indolyl methylamine derivatives, which are present in numerous alkaloids having significant biological activities.[184]



Scheme 107. Chiral Brønsted acid catalyzed asymmetric Friedel-Crafts reaction of indole **12-27a** with enamides **12-34**, **12-39** and imine **12-41**.

The transition state of enamide addition to indole is shown in **Figure 42**.

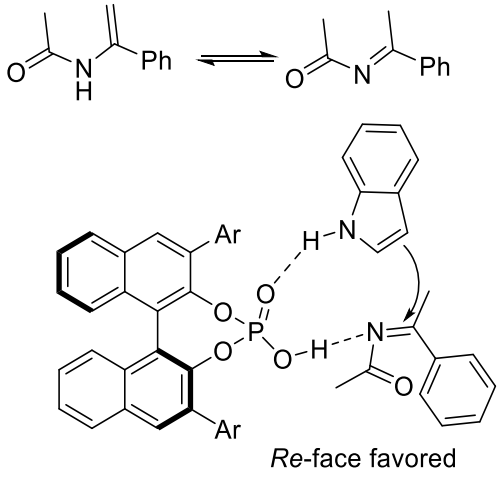
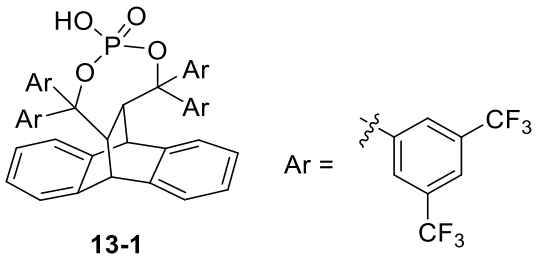


Figure 42. Proposed reaction model for reaction of indole and α-aryl enamides.

13 Goal of the research

Numerous natural and unnatural products with significant biological activities contain an indolyl methylamine unit. Several chiral phosphoric acid based catalysts have been developed and employed in asymmetric F-C reactions of indoles and imines to get 3-indolyl methylamine derivatives. From the literature review it is clear that known catalysts are delivering better selectivity at lower temperatures but higher temperatures are required for better conversion.

Our group (Dr. Anton Khartulyari) has designed a catalyst for indole alkylation with imines considering the following points. (1) Moderate acidity, which might bring the lower reaction temperature to ambient temperature. (2) Better capability of hydrogen bonding, which could engage indole and imine in a tight transition state and (3) a C_2 symmetry of the catalyst, would block one face for approach of reactants.

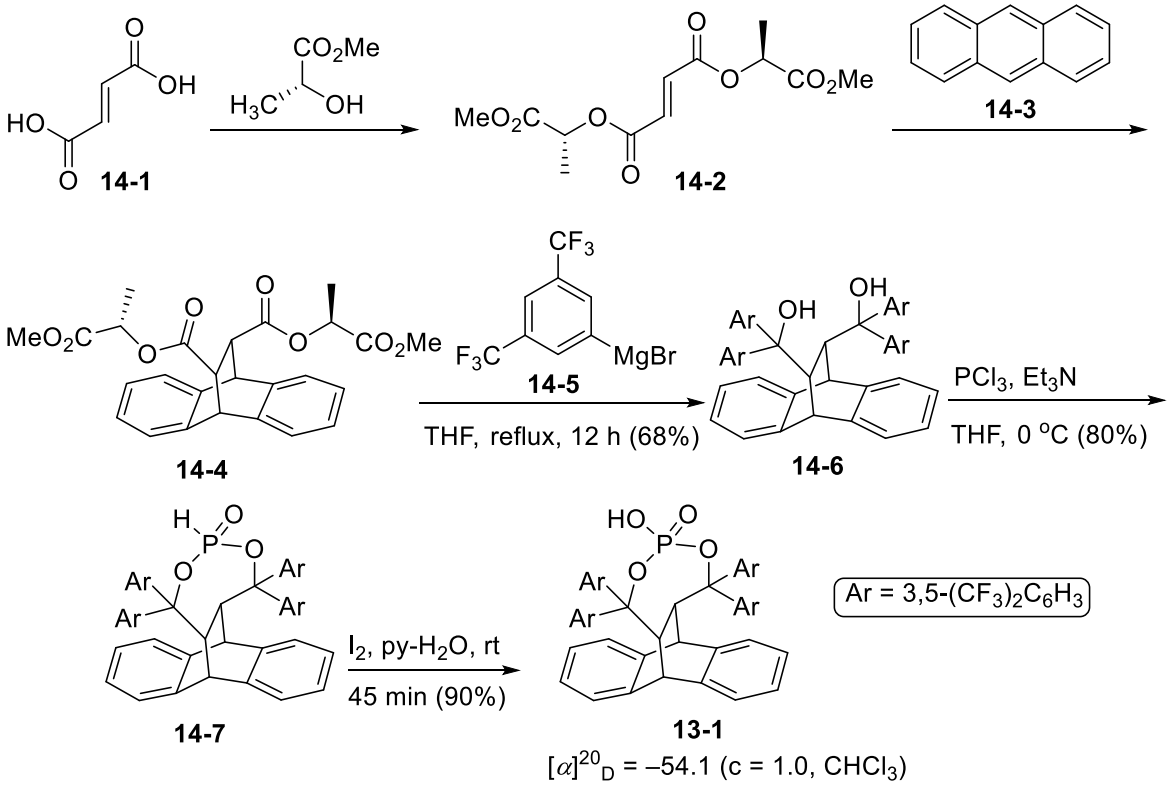


13-1

Figure 43. A C_2 symmetric phosphoric acid based chiral catalyst.

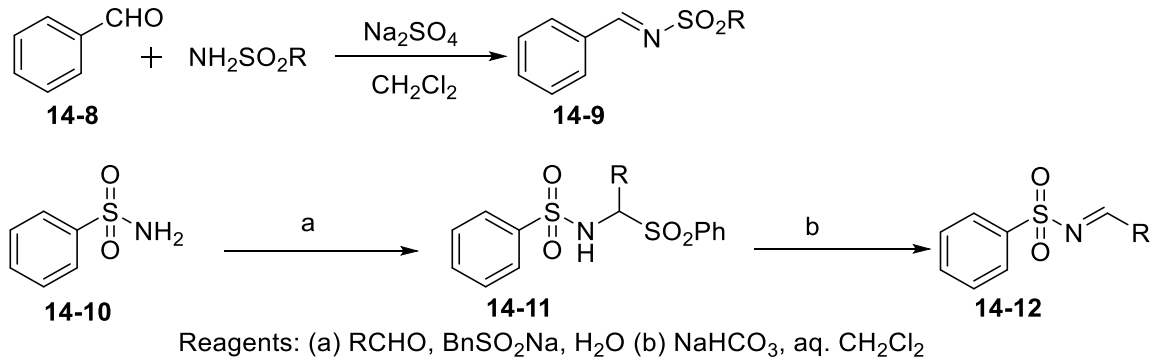
14 Results and discussion

The catalyst **13-1** was prepared by few synthetic operations involving a Diels-Alder reaction as a key step (**Scheme 108**). Helmchen's technique[185] using a chiral fumarate derivative **14-2** provides Diels-Alder adduct **14-4** in enantiomerically pure form after a single recrystallization. Ester **14-4** was subjected to react with Grignard reagent **14-3** (excess) to get diol **14-6**.[186] Phosphorylation of diol **14-3** with PCl_3 in basic medium provides phosphite **14-7** which after oxidation furnished catalyst **13-1** [$[\alpha]^{20}_D$ = –54.1 (c = 1.0, $CHCl_3$)] as a slightly yellow powder.[187]



Scheme 108. Preparation of phosphoric acid based catalyst **13-1**.

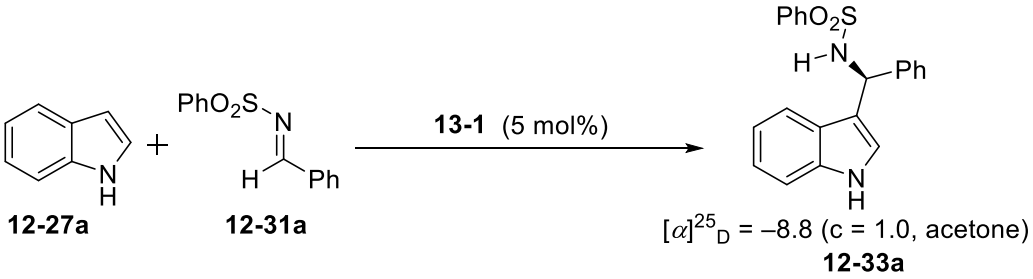
With the view toward the indole alkylation several aromatic and aliphatic aldimines were prepared by reaction of an aldehyde with benzenesulfonamide. Aromatic aldehydes and aliphatic aldehydes (having no enolizable α-hydrogen) derived sulfonylimines are very easy to prepare as shown in **Scheme 109**, whereas aliphatic imines could be prepared by addition-elimination to avoid enolization of imine into enamine.[188]



Scheme 109. Synthesis of *N*-sulfonyl aldimines from aldehydes and benzenesulfonamide.

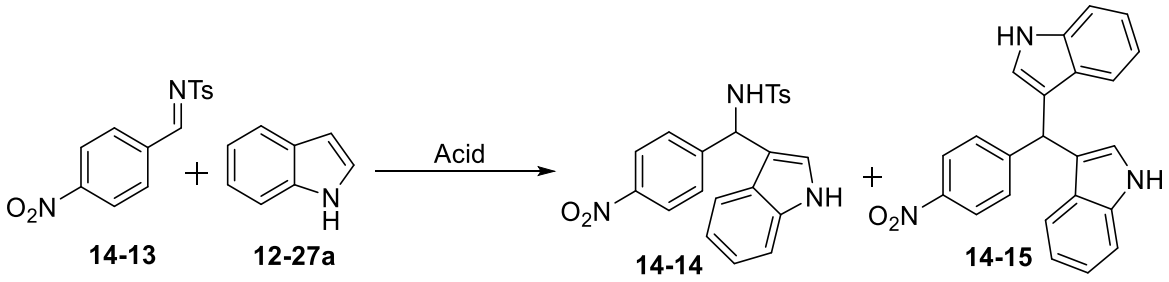
In order to test the scope of the catalyst, reaction conditions were optimized which are shown in **Table 12**. Equimolar amounts of indole **12-27a** and imine **12-31a** were reacted in presence of catalyst **13-1** (5 mol%), the delivery of desired product **12-33a** was either low or reaction was not proceeding. Then the indole concentration was increased up to 2.5 equiv to get better yield. Less polar aromatic solvents such as toluene were found useful for a chiral monophosphoric acid-catalyzed F-C reaction via the activation of an electron deficient double bond (C=NR),[189] whereas in the case of carbamate activation a marked retardation was observed with non-polar as well highly polar and protophilic solvents (**Scheme 107**).[183] We screened the reaction in hexane and toluene. The lower yield in hexane is due to poor solubility whereas in toluene reaction is faster forming the bis-indole byproduct. The best yield and enantioselectivity were found when toluene and hexane were used in equal ratio (1:1, v/v).

Table 12. Screening of conditions for the F-C reaction of **12-27a** and **12-31a** catalyzed by PA **13-1**.



entry	solvent	T (°C)	time	yield (%)	*ee* (%)
1	hexane	rt	15	20	–
2	toluene	rt	15	50	–
3	Toluene/Hexane, (1:1)	rt	15	90	96.5
5	Toluene/hexane, (1:1), 4 A° MS	0 °C to rt	15	97	96.5

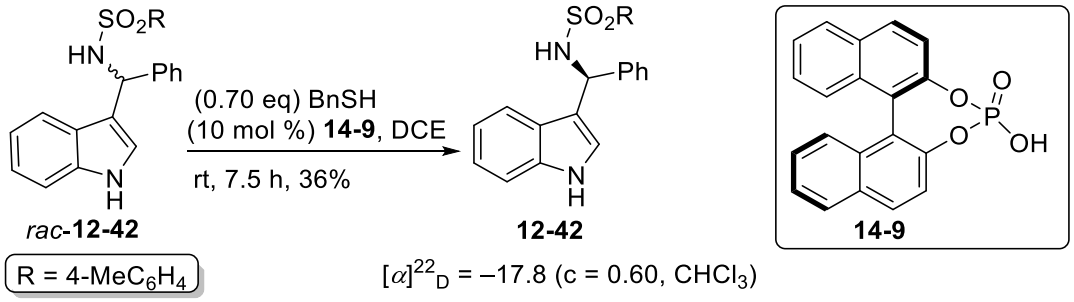
It is well known that 3-indolyl methylamines **14-14** in presence of acid provoke a SN^1 reaction with indoles to form bis-indole **14-15** derivatives.[190]



Scheme 110. Formation of bis-indole adduct.

Determination of the absolute configuration of the indolyl methylamine

Simon and Goodman demonstrated the use of computation models and analytical data in identification of the specific indolyl methylamine product obtained from Friedel-Crafts reactions of indole with *N*-tosylimines catalyzed by BINOL-phosphoric acids.[191] Tian and co-workers treated racemic sulfonamide **12-42** with benzyl thiol and chiral phosphoric acid **14-9** at room temperature which led to formation of racemic thioether in 60% yield and remaining 36% enantiomerically (98% *ee*) pure sulfonamide was recovered unreacted (**Scheme 111**).[192] This could be explained from the transition state shown in **Figure 44**.



Scheme 111. Kinetic resolution of racemic *N*-(3-indolyl)(phenyl)methylsulfonamide with benzyl thiol.

The N–H groups present in the indole and sulfonamide of **12-42** engage themselves with the chiral phosphoric acid through hydrogen bonding and therefore chiral phosphoric acid is able to discriminate between two enantiomers of the indolyl-methyl by recognizing the steric repulsion between R^1 and the Ar unit. In case of (**Figure 44**,TS-**I**) the steric repulsion is less therefore the sp^3 C–N bond cleavage is faster, whereas the other enantiomer (**Figure 44**, TS-**II**) could feel stronger repulsion, which makes slower C–N bond cleavage to become unreacted.

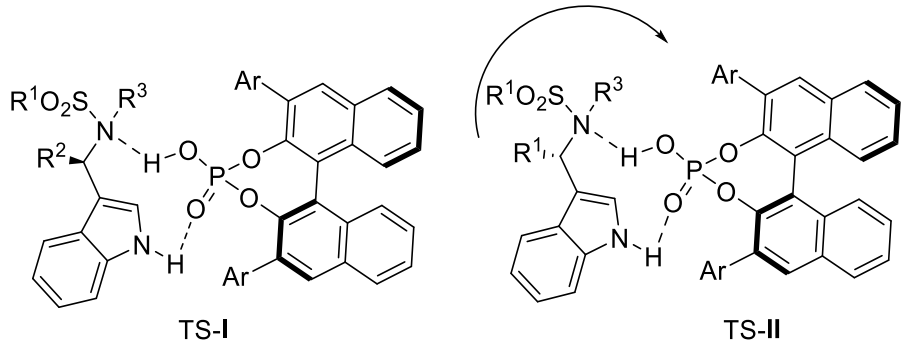


Figure 44. Possible transition states for the chiral phosphoric acid-catalyzed sp^3 C–N bond cleavage.

On the basis of the above discussion, we propose a possible model for the asymmetric induction with our catalyst, shown in **Figure 45**. The bifunctional catalyst binds with the substrate through hydrogen bonding making preferentially the *re*-face free to indole addition, leading to a (*S*)-configuration adduct.

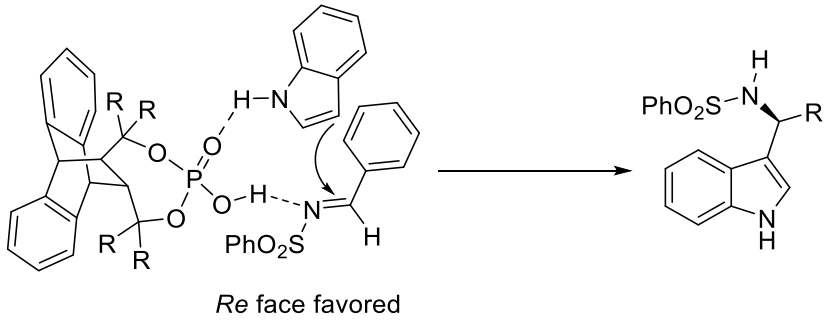
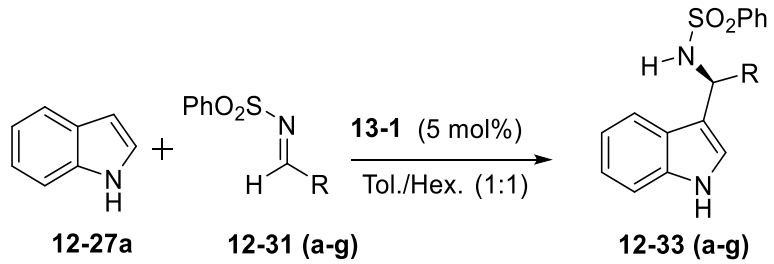


Figure 45. Proposed Reaction Model.

The chiral phosphoric acid and Tol-BINAP-$CuPF_6$ catalysis is only efficient with electron rich substrates.[193] In order to test the scope of the reaction first we have chosen indole and differently substituted aldimines. As evident from **Table 13** all the addition reactions give the 3-substituted indole derivative. The addition to the electron-rich substrates (**Table 13**, entry 1–4) gave the products up to 99% yield and 98% *ee*. The aldimines with electron withdrawing substituents (**Table 13**, entry 5, 6) also reacted very well except for bromide substituted (**Table 13**, entry 7) which gave low selectivity as well as yield (36% yield and 87% *ee*). Hindered aldimine (**Table 13**, entry 8–10) did not deliver product with increased catalyst loading (10 mol%) and temperature (up to 90 °C).

Table 13. Organocatalyzed enantioselective alkylation of indole with different aldimines, showing the effect of substituents on the aldimines.



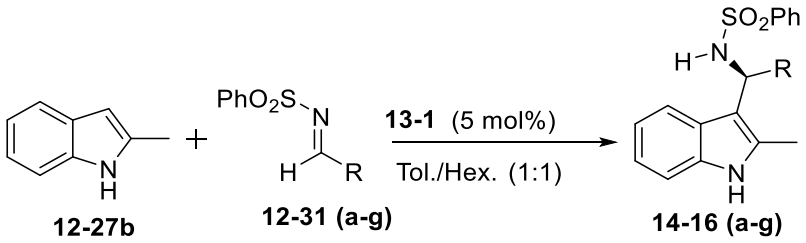
12-27a **12-31 (a-g)** **12-33 (a-g)**

entry	R	solvent	temp (^oC)	time (h)	yield (%)	*ee* (%)
1	Ph (**12-31a**)	Tol/Hex	0 ^{o}C–rt	15	97	97
2	Np (**12-31b**)	Tol/Hex	0 ^{o}C–rt	24	97	97
3	3,4-O_2CH_2Ph (**12-31c**)	Tol/Hex	0 ^{o}C–rt	18	99	98
4	4-OMePh (**12-31d**)	Tol/Hex	0 ^{o}C–rt	18	79	96
5	4-CF_3Ph (**12-31e**)	Tol/Hex	0 ^{o}C–rt	15	86	96
6	4-CO_2Me (**12-31f**)	Tol/Hex	0 ^{o}C–rt	15	83	90
7	4-BrPh (**12-31g**)	Tol/Hex	0 ^{o}C–rt	35	36	87
8	2,6-Me_2Ph (**12-31h**)	Tol/Hex	0 ^{o}C–rt	35	00	
9	2,6-Me_2Ph (**12-31h**)	Tol	rt–60 ^{o}C	35	00	
10	2,6-Me_2Ph (**12-31h**)	Tol	90 ^{o}C	18	00	

Abbreviations used in table: Tol = Toluene, Hex = Hexane.

The steric effect on this Friedel-Crafts reaction was evaluated using 2-methyl indole (**12-27b**) and imines **12-31** (**a-g**); the results are summarized in **Table 14**. Interestingly, both the reactivity and the enantioselectivity were enhanced with electron withdrawing substituents on the imine to match excess electron density produced by the 2-methyl group in the indole (**Table 14**, entries 5–7). On the other hand, for imines having relatively big electron donating groups (**Table 14**, entries 3–4), reactivity and selectivity were found to be decreased. Therefore in the first case inductive and in other case steric factors are operative.

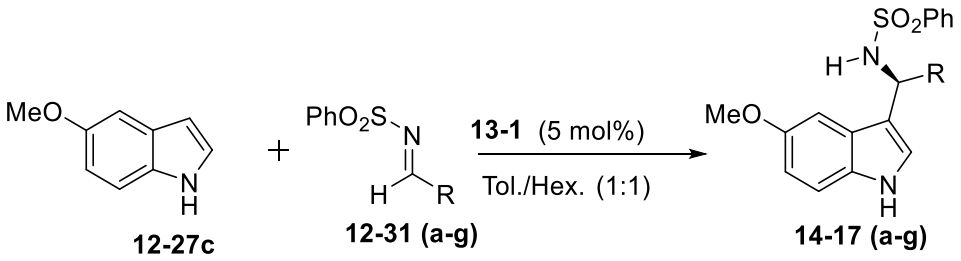
Table 14. Organocatalytic enantioselective alkylation of methylindole with different aldimines to delineate steric effect and week electron donation.



entry	R	solvent	temp (^oC)	time (h)	yield (%)	*ee* (%)
1	Ph (**12-31a**)	Tol/Hex	0 ºC–rt	15	99	92
2	Np (**12-31b**)	Tol/Hex	0 ºC–rt	24	84	93
3	3,4-O_2CH_2Ph (**12-31c**)	Tol/Hex	0 ºC–rt	18	97	84
4	4-OMePh (**12-31d**)	Tol/Hex	0 ºC–rt	18	86	83
5	4-CF_3Ph (**12-31e**)	Tol/Hex	0 ºC–rt	15	88	93
6	4-CO_2Me (**12-31f**)	Tol/Hex	0 ºC–rt	15	99	97
7	4-BrPh (**12-31g**)	Tol/Hex	0 ºC–rt	35	80	92

In order to understand the effect imposed on this F-C reaction by higher electron density on indole, 5-methoxy indole (**12-27c**) was examined with various imines **12-31** (**a-g**). Since the methoxy group is away from the N–H of indole, therefore it is expected that it would not be interfering in hydrogen bonding with the catalyst. For aryl imines (**Table 15**, entry 1–6), the reactions went smoothly to give the corresponding products in 91-99% yield and 93-98% *ee*. In the case of the imine sustituted with bromide (**Table 15**, entry 7), a strong electron withdrawing substituent, lowering of the reactivity as well as selectivity (78%, 65% *ee*) was observed. These results indicate that the methoxy unit does not play any steric role in the reaction and only inductive effects seem to be operative.

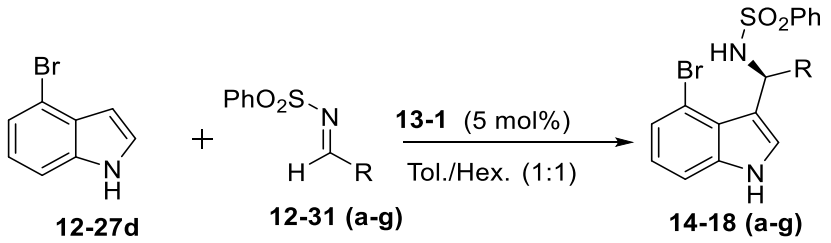
Table 15. Organocatalytic enantioselective alkylation of 5-methoxyindole with aldimines and effect of strong electron donation.



entry	R	solvent	temp (^oC)	time (h)	yield (%)	*ee* (%)
1	Ph (**12-31a**)	Tol/Hex	0 ºC–rt	15	99	94
2	Np (**12-31b**)	Tol/Hex	0 ºC–rt	24	91	95
3	3,4-O_2CH_2Ph (**12-31c**)	Tol/Hex	0 ºC–rt	18	99	98
4	4-OMePh (**12-31d**)	Tol/Hex	0 ºC–rt	18	97	98
5	4-CF_3Ph (**12-31e**)	Tol/Hex	0 ºC–rt	15	99	98
6	4-CO_2Me (**12-31f**)	Tol/Hex	0 ºC–rt	15	94	93
7	4-BrPh (**12-31g**)	Tol/Hex	0 ºC–rt	35	78	65

Our next goal stands to study the effect of an electron-withdrawing group on the indole ring which led to a lower reactivity (**Table 16**, entries 1-7). For aryl imines (**Table 16**, entries 1, 3, 4, 6), the reactions did not take place. In the case of imine **12-31e** having an electron withdrawing unit good results (73%, 94% *ee*) were obtained.

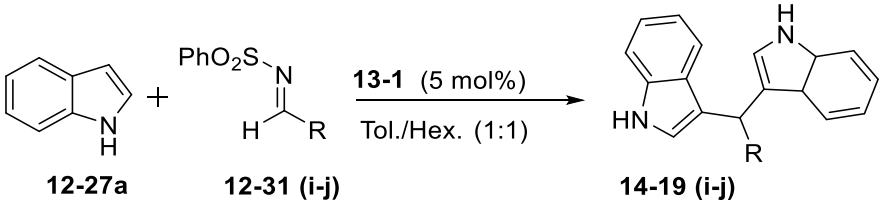
Table 16. Organocatalytic enantioselective alkylation of 4-bromoindole with aldimines and an effect of electron-withdrawing group on the reaction.



entry	R	solvent	temp (^oC)	time (h)	yield (%)	*ee* (%)
1	Ph (**12-31a**)	Tol/Hex	0 °C–rt	55	–	–
2	Np (**12-31b**)	Tol/Hex	0 °C–rt	55	51	63
3	3,4-O_2CH_2Ph (**12-31c**)	Tol/Hex	0 °C–rt	55	–	–
4	4-OMePh (**12-31d**)	Tol/Hex	0 °C–rt	55	–	–
5	4-CF_3Ph (**12-31e**)	Tol/Hex	0 °C–rt	55	73	94
6	4-CO_2Me (**12-31f**)	Tol/Hex	0 °C–rt	55	–	–
7	4-BrPh (**12-31g**)	Tol/Hex	0 °C–rt	55	11	–

In order to test the scope of the reaction, we screened two aliphatic aldimines **12-31** (**i-j**). The aliphatic aldimines (**Table 17**, entry 1–5) did not react at low temperature; when they were allowed to react at elevated temperature (up to 90 °C) or at room temperature for longer (up to 35 days), the formation of bisindole derivatives **14-19i** and **14-19j** were observed.

Table 17. Organocatalyzed alkylation of indole with different aldimines



entry	R	solvent	temp (^oC)	time (h)	yield (%)	*ee* (%)
1	Cy (**12-31i**)	Tol/Hex	0 °C–rt	22	00	
2	Cy (**12-31i**)	Tol	90 °C	18	60	
3	*t*-Bu (**12-31j**)	Tol/Hex	0 °C–rt	22	50	
4	*t*-Bu (**12-31j**)	Tol/Hex	90 °C	18	99	
5	*t*-Bu (**12-31j**)	Tol/Hex	0 °C–rt	840 (35 d)	99	

Abbreviations used in table: Cy = cyclohexy, *t*-Bu = tertiary butyl.

15 Conclusion III

Indoles were alkylated with imines using a novel C_2 symmetric catalyst. The reaction features a metal free approach, high efficiency of the catalyst, mild reaction conditions, high yields up to 99%, and excellent enantioselectivities up to 98%

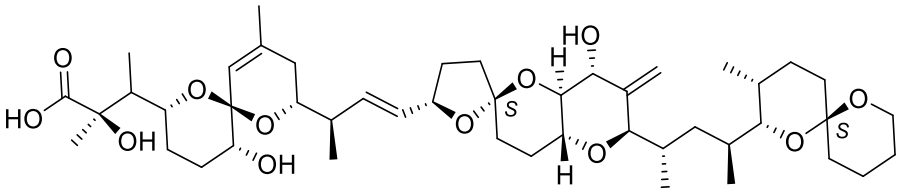
Chapter 4

Progress towards Tautomycetin, Palonosetron, and Indanones

16 Progress towards the synthesis of tautomycetin fragment

16.1 Tautomycetin

Physiological functions of cells are governed by protein regulation, known as phosphorylation/dephosphorylation. They are directed by the balance between kinases and phosphatases. Protein kinases are responsible for transfer of a phosphate unit from ATP to the protein (phosphorylation), whereas the reverse process is catalyzed by protein phosphatases (dephosphorylation). It is estimated that 2% of the eukaryotic genome is responsible for kinases.[194] There are 15 proteins and 13 genes in the PPP family along the additional 10 genes in the PPM family. The largest class of protein phosphatase is the phosphoprotein phosphatase (PPP) family involving PP1, PP2A, PP2B, PP4, PP5, PP6 and PP7, and the protein phosphatase Mg^{2+}- or Mn^{2+}-dependent (PPM) family, composed primarily of PP2C.[195] Less than 0.1% of human genome covers serine/threonine protein phosphatases. Basically every disease is an outcome of defect in cellular signaling. Protein phosphatases had played a role in disease detection as well as in treatment. Okadaic acid (OA) is known for its strong inhibitory action against protein phosphatases, specifically serine/threonine phosphatases.[196]



Okadaic acid (**16-1**)

Figure 46. Structure of okadaic acid.

Tautomycin (**16-2**) and tautomycetin (**16-3**) are two related polyketides that have been known from several years. Tautomycin was discovered in 1987,[197] whereas tautomycetin was isolated from the culture of *Streptomyces griseochromogenes* in 1989.[198] They exhibit cytotoxicity against fungi, yeasts and animal cells; it is named as tautomycin because of its existence as tautomeric form in solution. In the meantime they turned out to be protein phosphatase 1 and 2 (PP1, PP2) inhibitors. Therefore they are analogous to okadaic acid. Tautomycin was found to have more than threefold (serine/threonine phosphatase) inhibitory activity than tautomycetin. They also seem to have antitumor activity, inducing morphological changes in human leukemia cells K5621. In addition, antiviral activity has been noted. Structurally, these two polyketide contains a somewhat unusual dialkylmaleic anhydride subunit[199] that is attached to the remaining part via an ester bond.

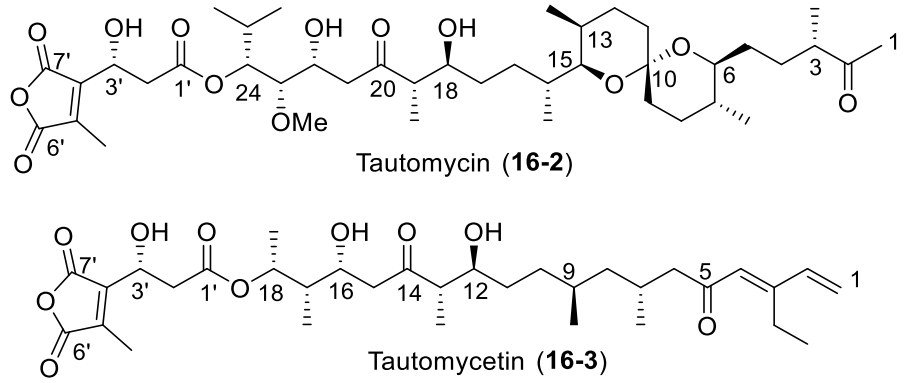
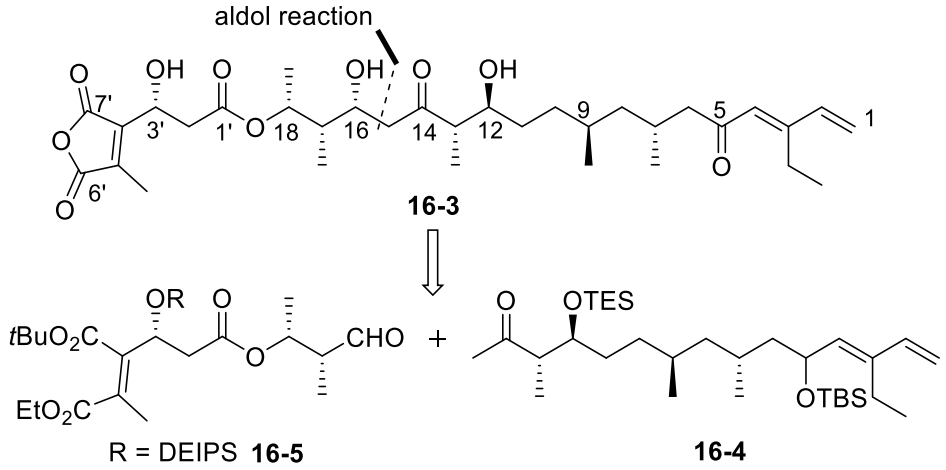


Figure 47. Structure of tautomycin and tautomycetin.

16.2 Current state of research

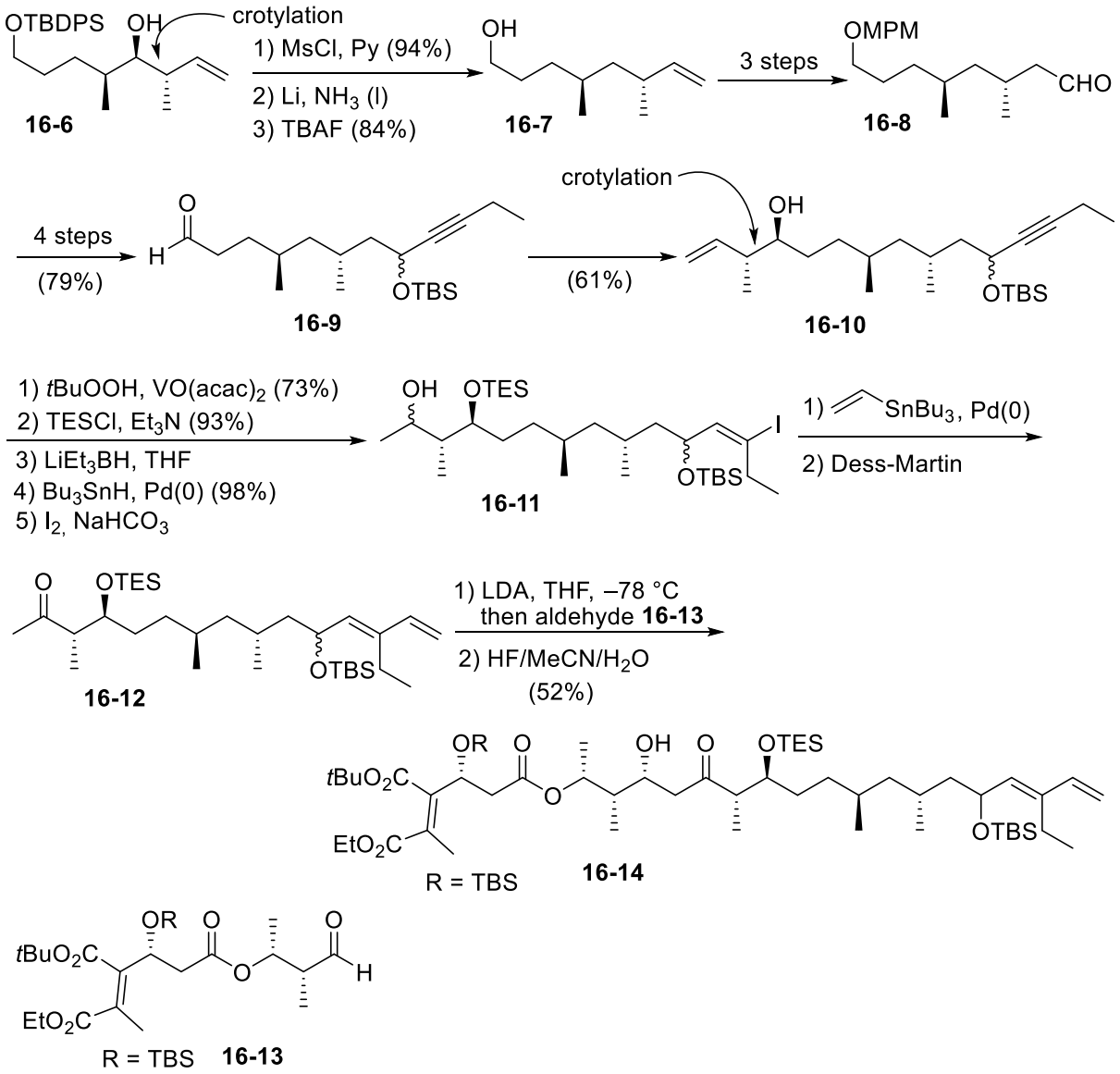
While a total synthesis for tautomycin is known,[200] the synthesis of tautomycetin could not be finished due to problems in late stage deprotection steps.[201]

Oikawa and co-workers a proposed a retrosynthesis of tautomycetin (**16-3**) as shown in **Scheme 112**.



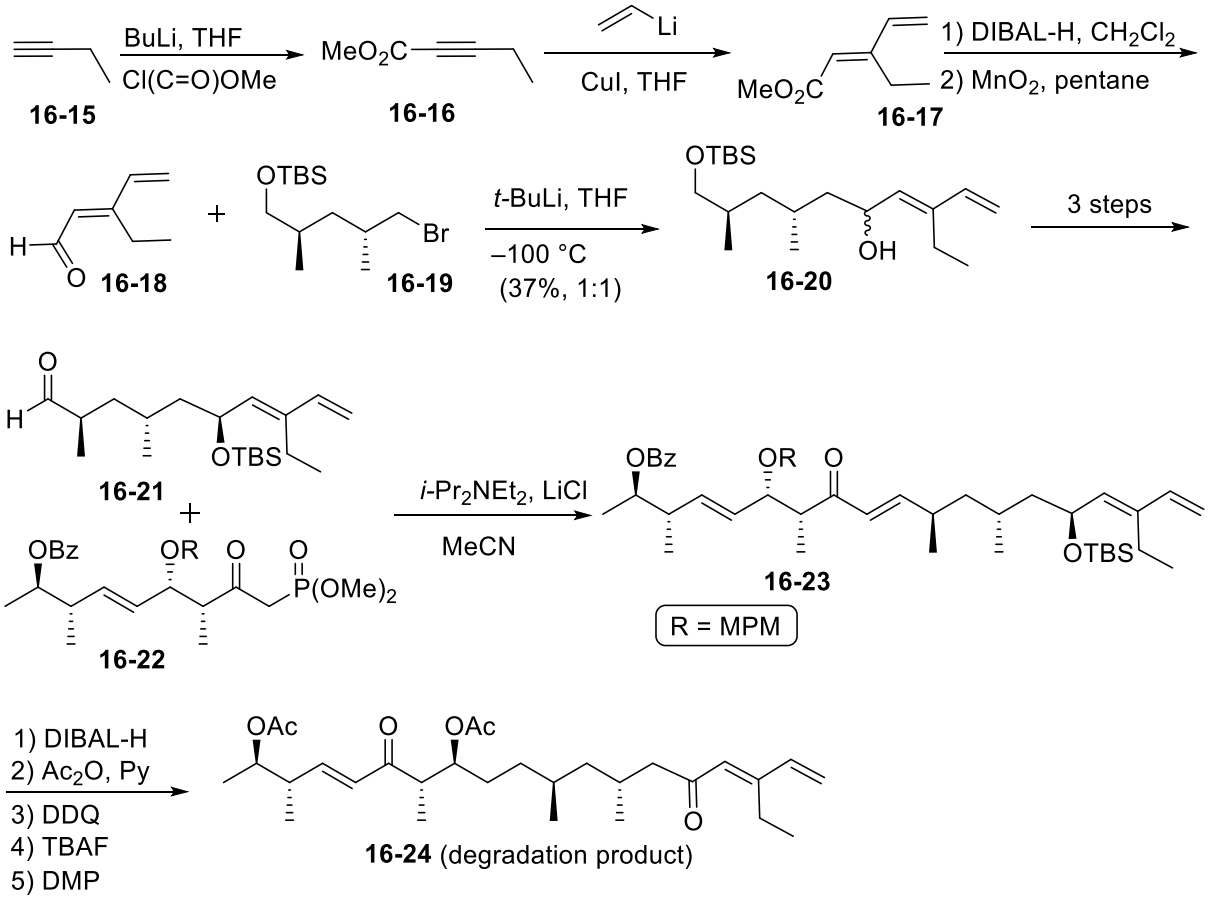
Scheme 112. Retrosynthesis proposed by the Oikawa group.

The alkenol **16-6**, which was prepared by Roush crotylation reaction, was deoxygenated to give the anti-1,3-dimethyl pattern (**Scheme 113**). Functionlization of the terminal double bond of **16-7** led to aldehyde **16-8**. The aldehyde **16-8** was extended to propargylic ether **16-9**. From here a chain extension on the other terminus and refunctionlization of the double bond from the crotylation reaction followed by hydrostannylation of the triple bond allowed for access to vinyl iodide **16-11**. The vinyl substituent could then be introduced by Stille cross-coupling reaction. A final aldol reaction of methyl ketone **16-12** with aldehyde **16-13** furnished hydroxyketone **16-14** as a 2:1 mixture of diastereomers.[201]



Scheme 113. Approach towards tautomycetin by the Oikawa group.

Shibasaki and co-workers published the synthesis of the degradation product **16-24**.[202] Key steps of this route include an organolithium addition to dienal **16-18** (C5–C6 bond) and a HWE reaction between ketophosphonate **16-22** and aldehyde **16-21** to form C10–C11 (**Scheme 114**). The organolithium addition led to a mixture of diastereomers at C5. They were separated and the synthesis was continued with one of them. The dienal **16-18** was prepared by vinylcuprate addition to alkynoate **16-16**.

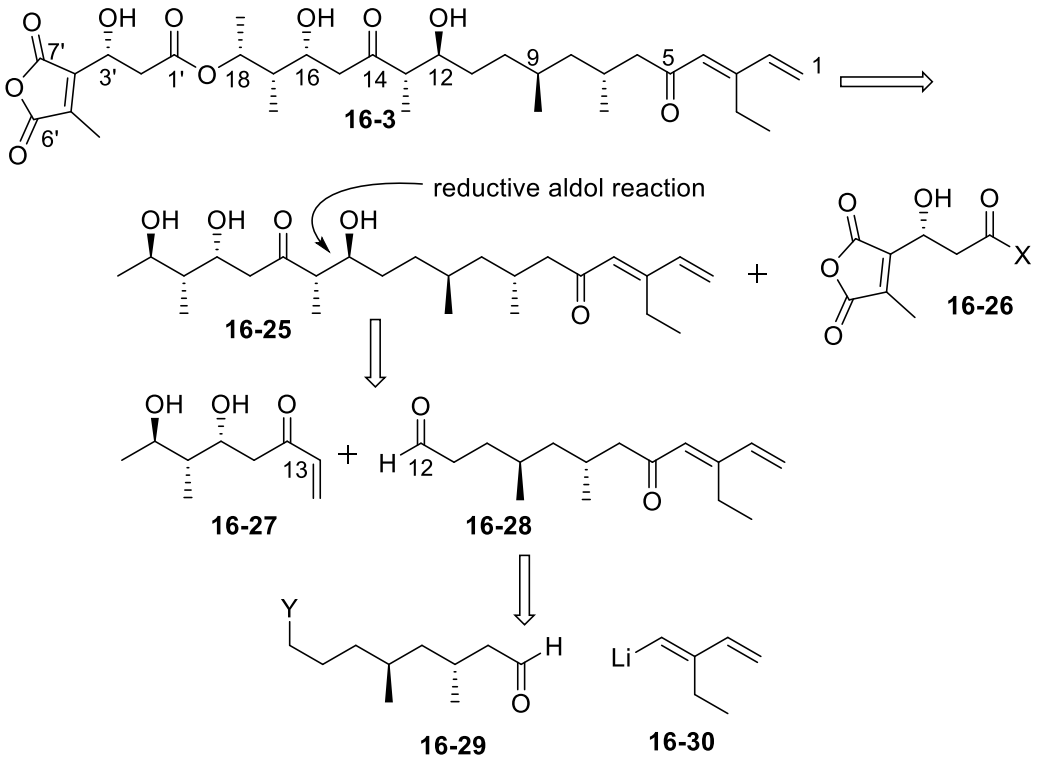


Scheme 114. Synthetic study towards tautomycetin by Shibasaki *et al.*

From the synthetic work on tautomycin it turned out that smaller fragments were essentially inactive. In particular the region around C12–C16 seems quite important.[203] The anhydride region serves to enhance the biological activity. Regarding the apoptosis inducing activity, the C1–C18 moiety turned out to be essential. The authors of this article suggest that different parts of tautomycin are responsible for protein phosphatase inhibition and the apoptosis inducing property. Futher biological studies including an X-ray structure of tautomycin with protein phosphatase-1 have been published.[204] Because of the unusual structure and the lacking biological studies with tautomycetin, the synthesis of this compound appears as worthwhile undertaking.

16.3 Retrosynthetic plan

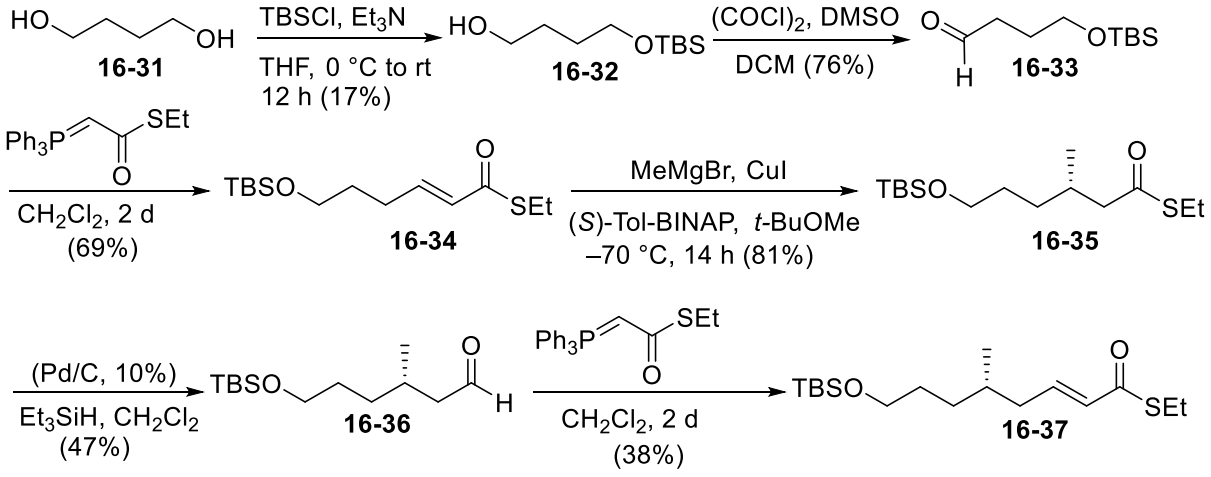
After removal of the anhydride unit, the polyketide might be broken up into fragments **16-27** and **16-28** (**Scheme 115**), which could be coupled by reductive aldol reaction using chiral boranes. The fragment **16-28** is challenging because of the dienone part that as Michael acceptor might be sensitive to nucleophiles. Therefore, it would be best to introduce this part late in the synthesis.



Scheme 115. Retrosynthesis of tautomycetin.

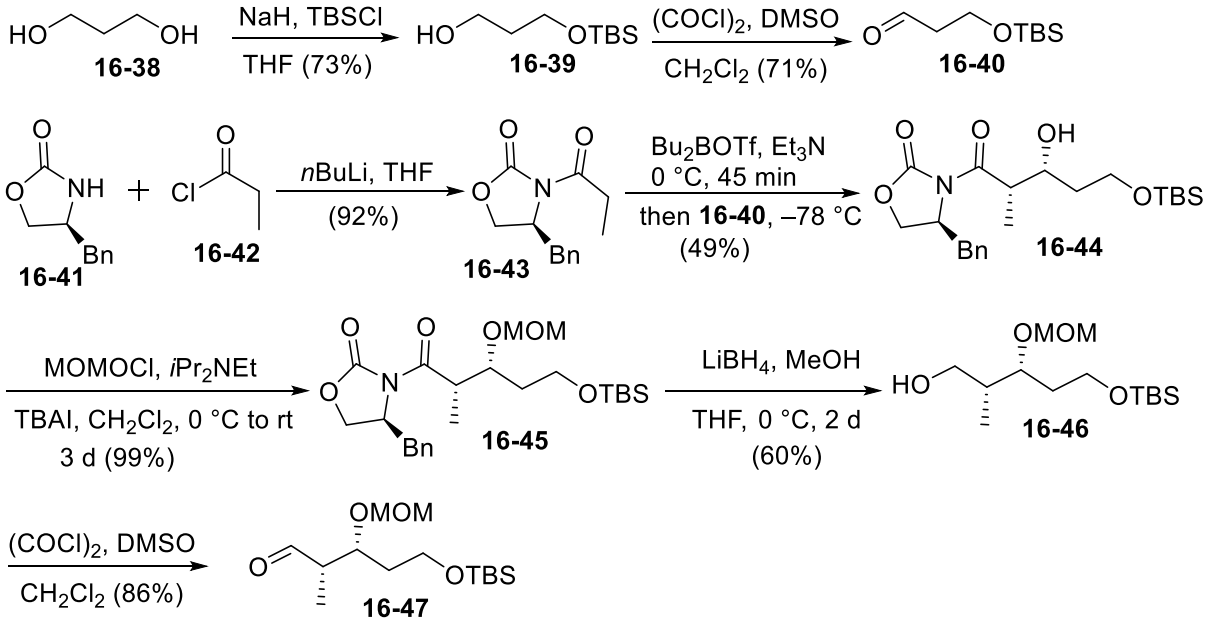
16.4 Results and discussion

With a view towards of fragment **16-29**, diol **16-31** was selectively protected as silyl ether **16-32**, the alcohol function was oxidized to aldehyde 16-33 which was subjected to chain extension with *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate giving rise to unsaturated thioester **16-34**, the asymmetric methyl cuprate addition, in presence of (*S*)-Tol-BINAP provided thioester **16-35**. For iterative asymmetric cuprate addition,[205] first the ester function of **16-35** was reduced into aldehyde and chain extension with *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate furnished thioester **16-37**.



Scheme 116. Synthesis of thioester from **16-37** from 1,4-butanediol (**16-31**).

The second fragment **16-27** we envisioned to be prepared by Evans-aldol reaction of oxazolidinone **16-43** and aldehyde **16-40**. The selectively protection of the inexpensive 1,3-propanediol (**16-38**) into silyl ether **16-39** and further oxidation gave aldehyde **16-40** with very good yield. Acylation of oxazolidine **16-41** in presence of *n*-BuLi gave oxazolidinone **16-43** which on reaction with aldehyde **16-40** furnished exclusively the single *syn*-diastereomer **16-44**. First the alcohol was reacted with MOMCl in presence of Huenig's base and tetrabutylammonium iodide, which produced ether **16-45** in the quantitative yield. The reduction of oxazolidinone **16-45** with $LiBH_4$ followed by oxidation produced aldehyde **16-47**.



Scheme 117. Aldehyde synthesis from diol **16-47** via aldol reaction.

17 Intramolecular C–H-activation towards Palonosetron

17.1 Palonosetron

Phenanthridone derivatives are present in the antineoplatic Amarylldaceae natural products.[206] Palonosetron is a 5-HT(3) antagonist used in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV).[207] There are several traditional syntheses along the C–H-activation approach.

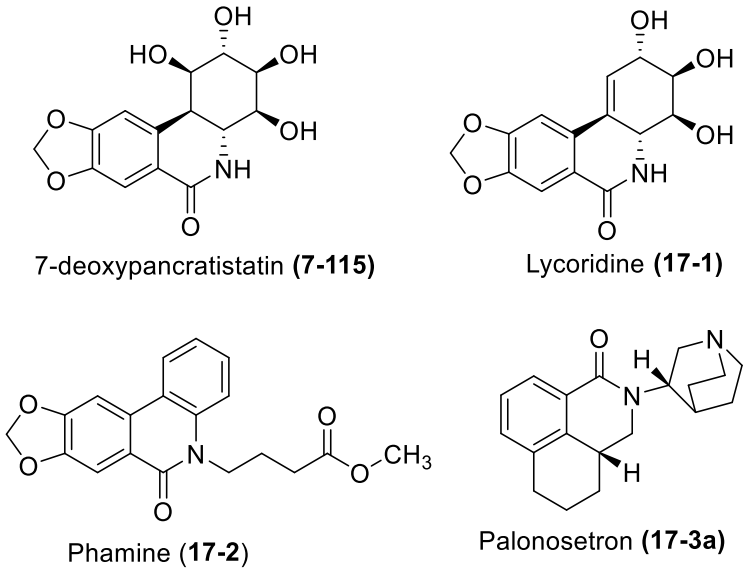
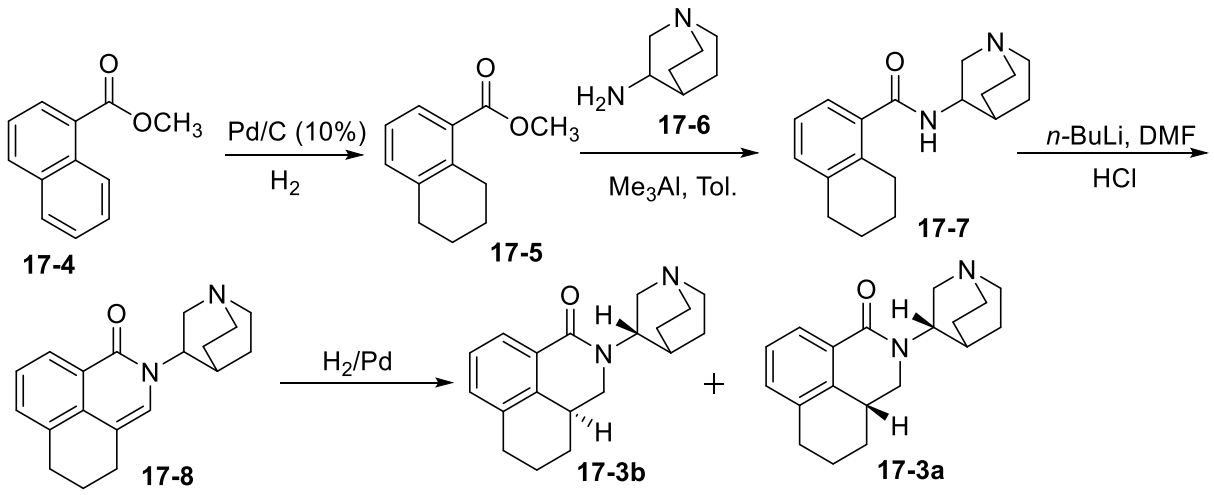


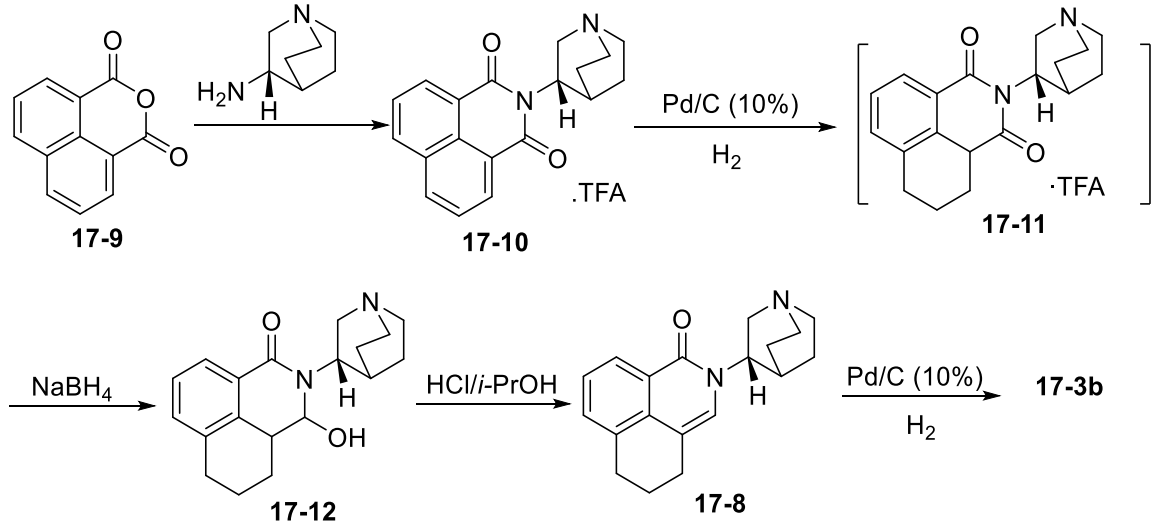
Figure 48. Phenantridinone alkaloids.

The synthesis of palonosteron proposed by Clark and co-workers is demonstrated in **Scheme 118**.[208] Treatment of the *N*-quinuclidin-3-yl amides **17-7** with 2 equiv of *n*-BuLi generates the dilithio derivatives which on quenching with *N*,*N*-dimethylformamide produced 3-hydroxy derivative which and dehydration and catalytic hydrogenation of furnished palonosterons.



Scheme 118. Synthesis of palonosteron (**17-3**) from from methyl-1-naphthoate (**17-4**) by Clark and co-workers.

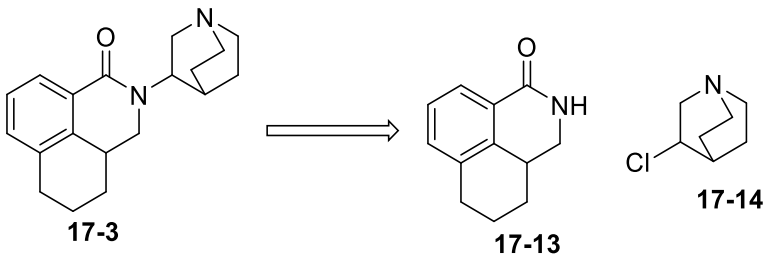
The above synthesis has several drawbacks such as reduction of 1-naphthoic acid into 5,6,7,8-tetrahydro-1-naphthoic acid, which is very sensitive to reduction and the generation of dianion of **17-7** required excess *n*-BuLi which could be difficult to handle at production scale. The improved synthesis of palonosteron by Kowalczyk *et al.* is shown in **Scheme 119**.[209] They observed reduction of **17-10** with H_2 at 50 °C and they found selective reduction of imide **17-11** with $NaBH_4$ in alcohol at low temperature gave best results.



Scheme 119. Synthesis of palonosteron from 1,8-naphthalic anhydride (**17-9**).

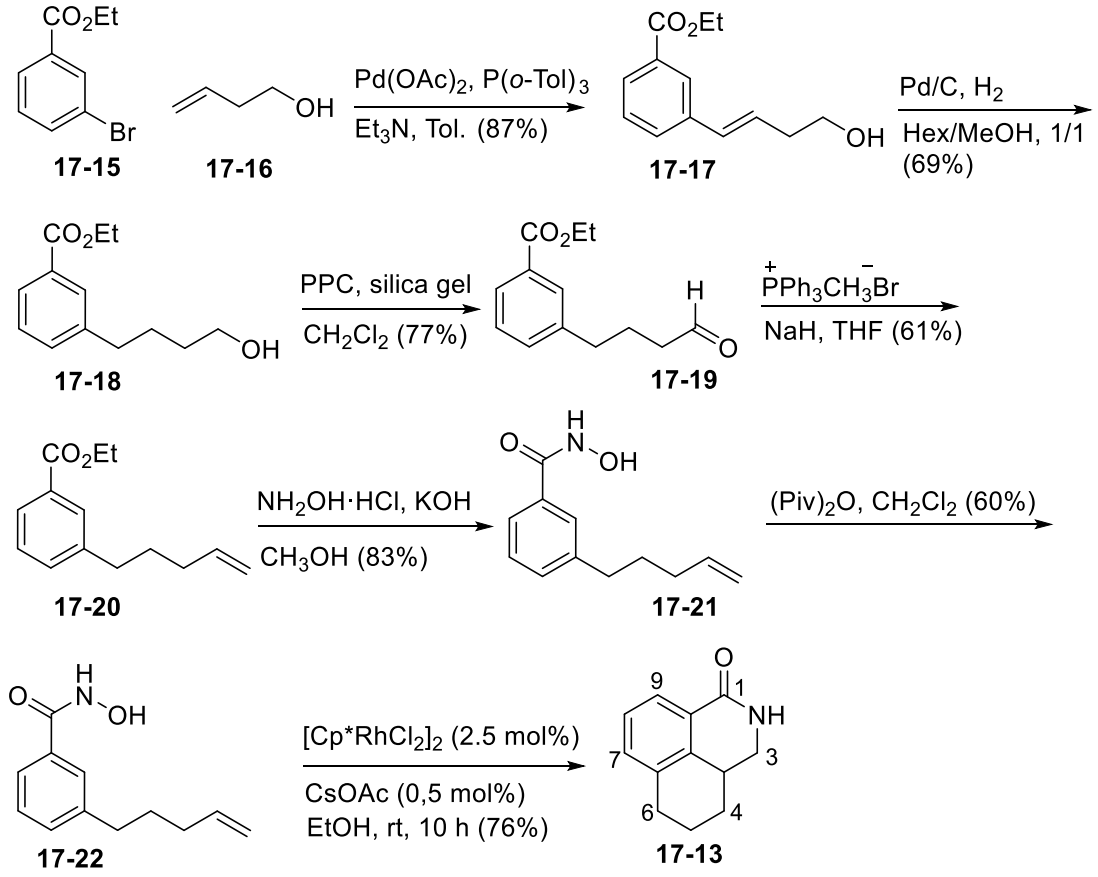
17.2 Results and discussion

In an alternative plan palanosteron could be fragmented into amide **17-13** and halide **17-14**. Intramolecular C–H-activation could generate amide fragment **17-13**, which after *N*-alkylation with 3-chloroquinuclidine would produce palonosteron (**Scheme 120**).



Scheme 120. Framentation of palonosteron.

The C–H-activation strategies are advantageous over traditional strategies because of obviation of prefunctionalization.[210] We synthesized *N*-pivaloxy benzamide in six steps (**Scheme 121**). Thus, Heck reaction of ethyl-3-bromobenzoate (**17-15**) with 3-butenol (**17-16**) provided *E*-alkene **17-17** which on reduction under Landlar's condition following PCC oxidation gave aldehyde **17-19**. The chain extension on aldehyde **17-19** was carried out using a Wittig reaction. *N*-OPiv benzamide **17-22** was prepared from benzoic acid ester **17-20** using our optimized procedure in chapter 2 (procedure 3). The intramolecular alkene annulation gave benzamide **17-13** in 76% yield. The cross peaks between 3a-H and 4-H in COSY spectrum (**Figure 49**) of compound **17-13** confirms its formation.



Scheme 121. Intramolecular C–H-activation to generate the core structure of Palanosteron.

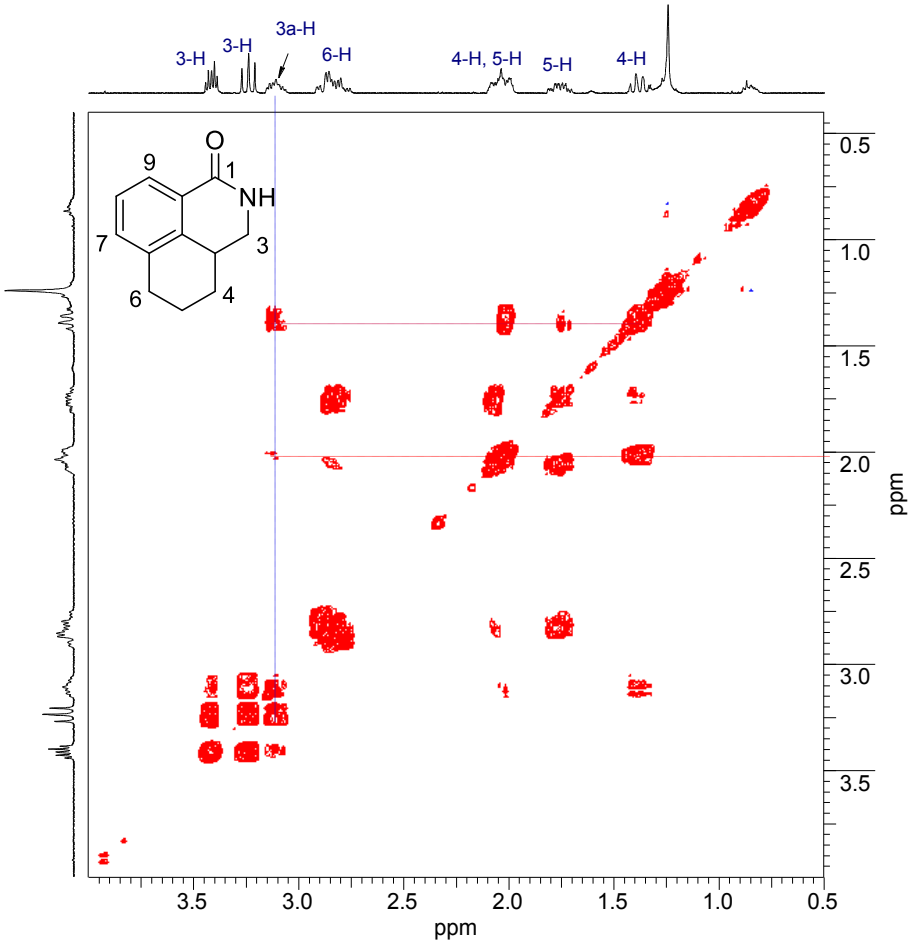
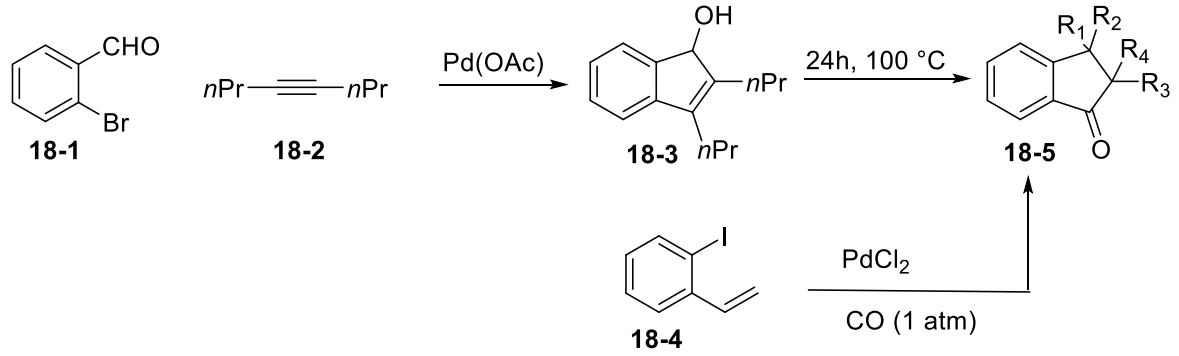


Figure 49. COSY spectrum of **17-13** (0.5 ppm to 4.0 ppm).

18 Palladium-catalyzed redox indanone synthesis

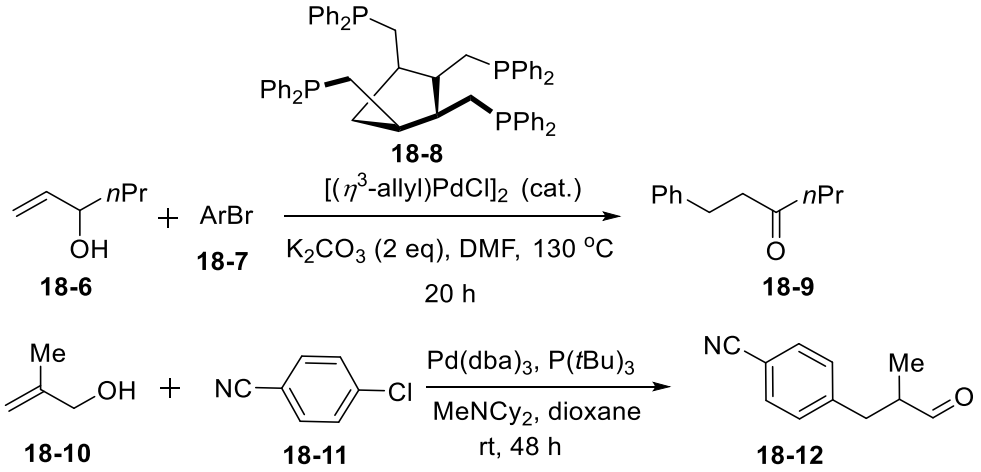
18.1 Indanones

Indanones are attractive intermediates in the synthesis of various natural products[211] and its derivative such as indanocine, which is a potent microtubule-destabilizing agent, binds to the colchicine binding site of tubulin.[212] A huge number of palladium-catalyzed annulation reactions are reported towards the synthesis of carbo- and heterocycles.[213] Palladium-catalyzed annulation of internal alkynes with aromatic aldehydes and carbonylative annulation of *o*-iodostyrenes would deliver indanones (**Scheme** 122).[214,215] The oxidation of benzylic and allylic alcohols was achieved in DMSO.[216] Gold catalyzed cycloisomerzation reactions were also reported.[217] There are no such documented reports or examples to make cyclocarbonyles in one shot from aryl-allyalcohol halides. In this topic we demonstrate the electronic and steric dependency on this reaction.



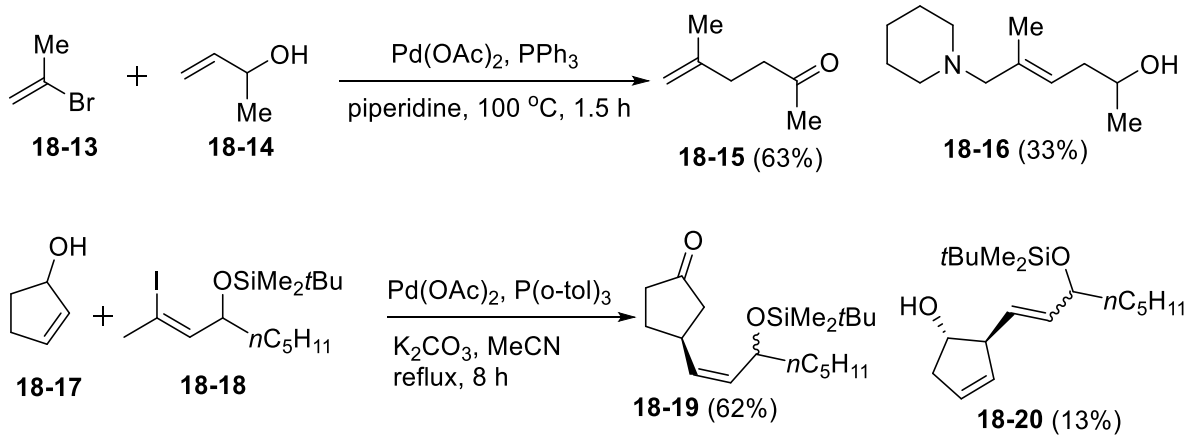
Scheme 122. Palladium-catalyzed annulation of internal alkyne with o-bromobenzaldehydes by carbonylatio of and *o*-iodostyrenes.

$[(\eta^3\text{-allyl})PdCl]_2$ catalyzed arylation of alkenols with a range of aryl halides led to the formation of the corresponding ketone **18-9**.[218] Aryl halides like **18-11** having mild activating functions efficiently undergo Pd(0) redox oxidation.[219]



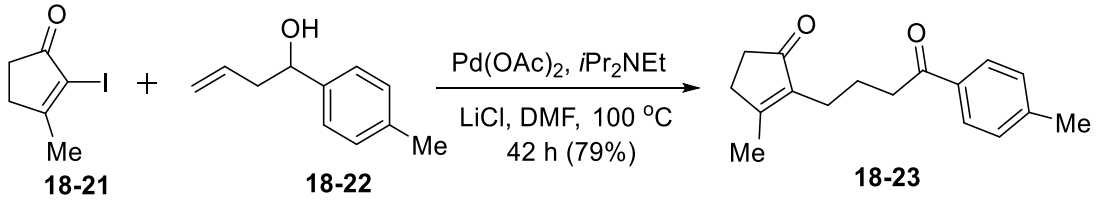
Scheme 123. Arylation of allyl alcohols with aryl halides under Pd(0) condition.

Piperidine and morpholine were found better acid acceptors over trimethylamine in the coupling of vinyl halide **18-13** with allyl alcohol **18-14** (**Scheme 124**).[220] In the absence of secondary amines, alkenylation of 2-cyclopentenol occurs at both olefinic carbons.[221]



Scheme 124. Addition of vinyl halides to allyl alcohols.

β-Substituted ketones were obtained in Pd(II) mediated coupling of vinyl, aryl and heteroaryl halides with homoallylic alcohols (**Scheme 125**).[222] A review describing palladium catalyzed reactions of alcohols was published by Muzart.[223]



Scheme 125. Addition of vinyl halide **18-21** to homoallylic alcohol **18-22**.

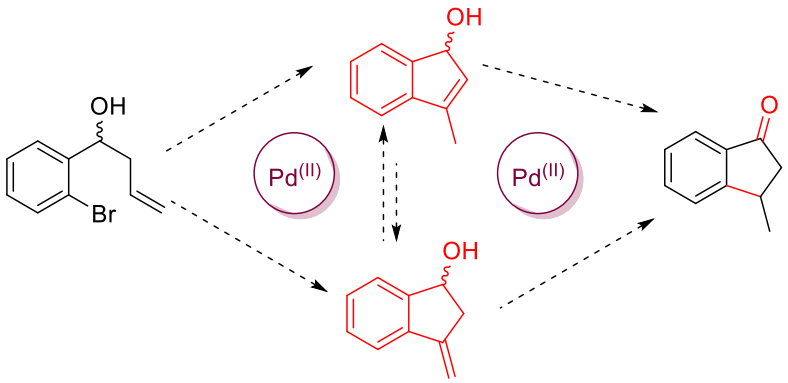


Figure 50. Our work "palladium mediated redox indanone synthesis".

18.2 Results and discussion

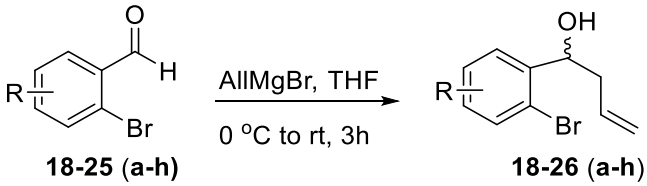
We began our investigation by making benzyl alcohols from differently substituted 2-bromobenzaldehydes with allylmagnesium chloride which furnished the corresponding

homoallyl alcohols (**Scheme 127**).[224] The pipronol (**18-24e**) was oxidized into corresponding 2-bromopipronaldehyde (**18-25e**) using DBDMH.[225]

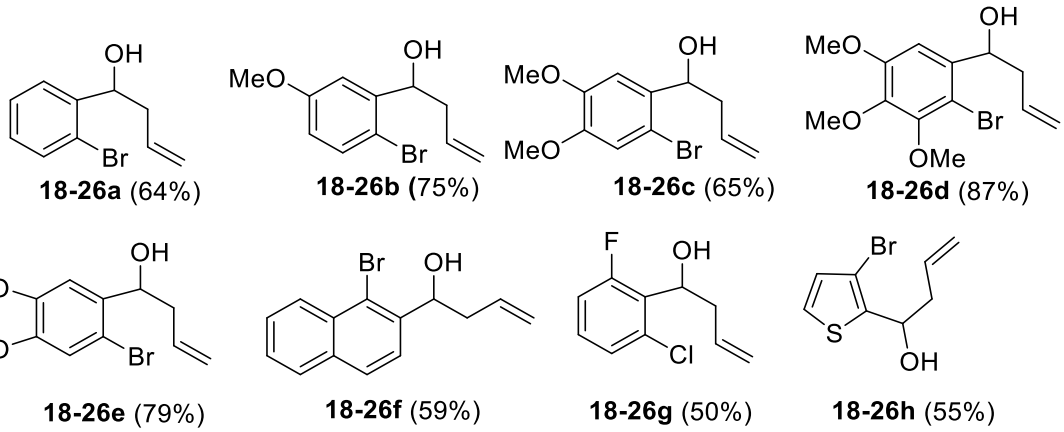
18-24e **18-25e**

Scheme 126. Oxidation of pipronol (**18-24e**) into 2-bromopipronaldehyde (**18-25e**).

The addition of allylmagnesium bromide to the electronically rich 2-bromo-3,4,5-trimethoxy benzaldehyde (**18-25d**) furnished homoallylic alcohol **18-26d** in 87% yield whereas addition to the electronically poor 2-chloro-6-flurobenzaldehyde (**18-25g**) delivered benzylic alcohol **18-26g** in 50% yield. The addition of Grignard reagent to the the 3-bromothiophene carboxaldehyde (**18-25h**) led to the formation of homoallylic alcohol **18-26h**.



18-25 (**a-h**) **18-26** (**a-h**)

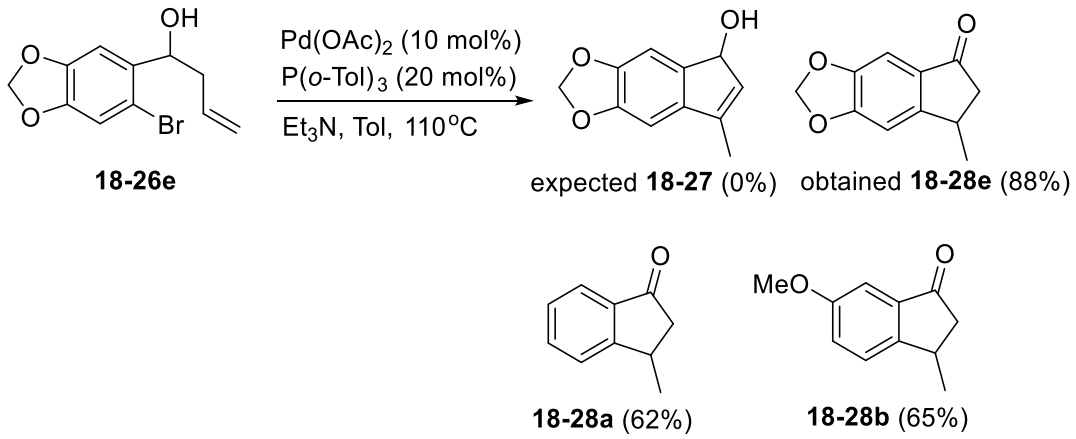


18-26a (64%) **18-26b** (75%) **18-26c** (65%) **18-26d** (87%)

18-26e (79%) **18-26f** (59%) **18-26g** (50%) **18-26h** (55%)

Scheme 127. Allylation of aldehydes **18-25** (**a-h**) with AllMgBr into homoallylic alcohols **18-26** (**a-h**).

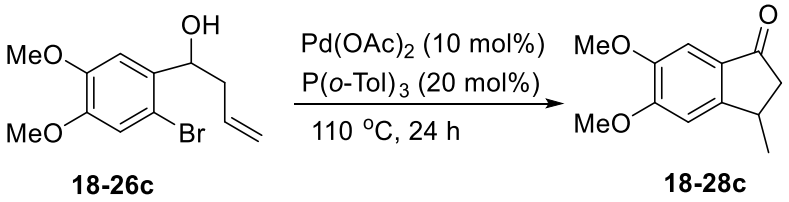
We selected methylenedioxy substituted homoallyl alcohol **18-26e** as a starting material and subjected it to 10 mol% [$Pd(OAc)_2$], 20 mol% P(*o*-Tol)$_3$ as an additive and Et_3N as a base, at 110 °C under N_2 atmosphere in toluene. This set of conditions afforded the unexpected product **18-28e** in 88% yield after 6 h. The doublet of methyl protons at 1.34 ppm in the ^{1}H NMR and a resonance at 204.2 of the carbonyl function in ^{13}C spectrum confirm the formation of redox product **18-28e**. Analogously, other homoallyl alcohols were subjected for this reaction, however only **18-28a** and **18-28b** furnished the redox products. It is expected that in case of **18-26c** and **18-26d** palladacycle formation is rather difficult whereas in case of **18-26g** benzene ring is electron deficient.



Scheme 128. Palladium mediated redox synthesis of indanones from corresponding homoallylic alcohols.

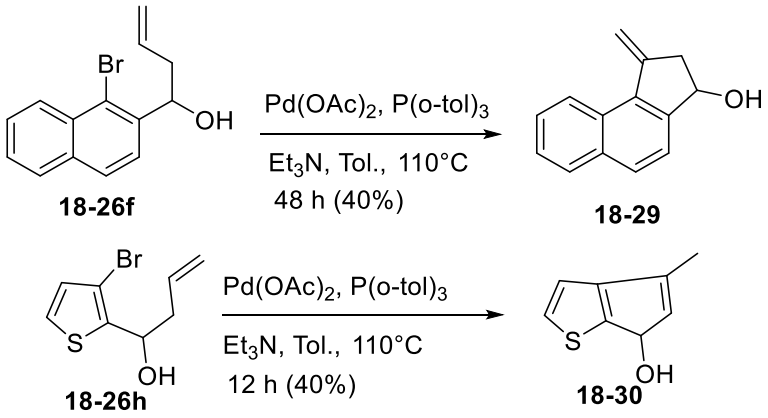
We again tried to optimize the reaction condition for hindered homoallylic alcohols, choosing **18-26c** as a model compound. A brief analysis of solvent and base is depicted in **Table 18**.

Table 18. Effect of base and polarity of solvent on palladium mediated redox reaction.



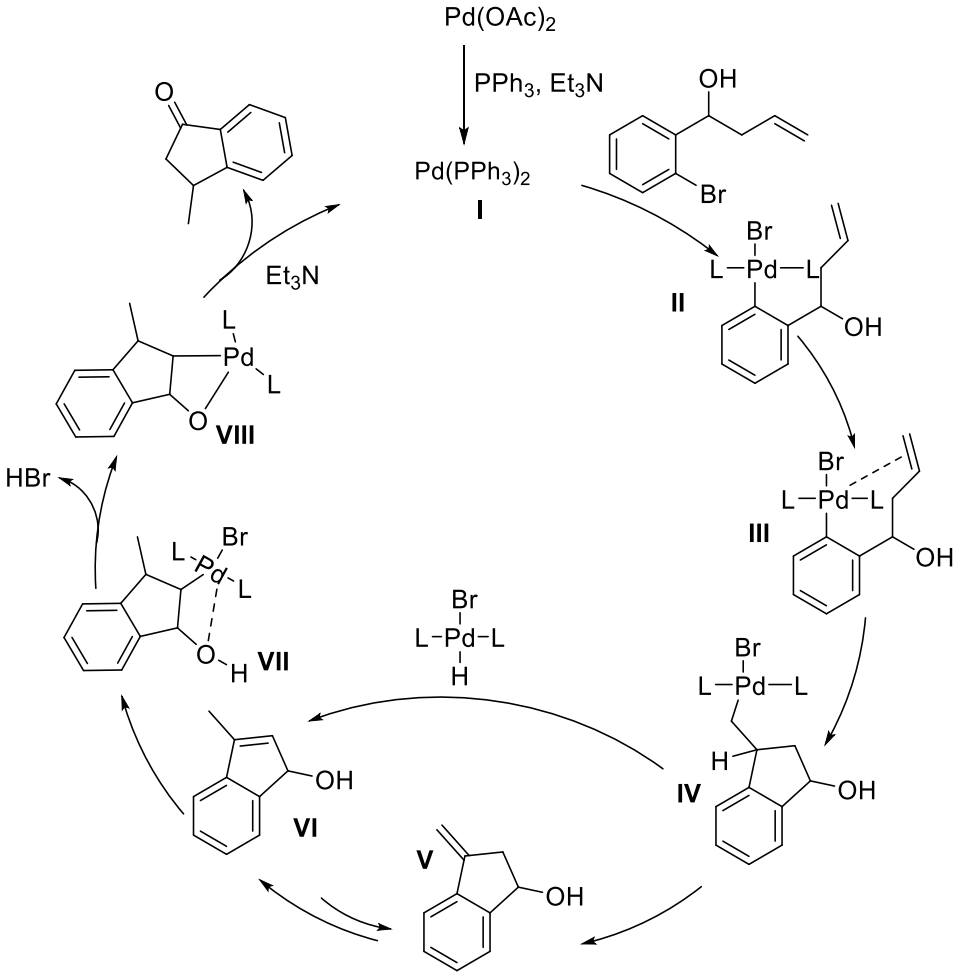
entry	base	solvent	yield (%)
1	TEA	toluene	00
2	TEA	DMSO	00
3	TEA	DMSO	00
4	DIPEA	DMSO	00
5	DIPEA	DMSO	00

The homoallylic alcohols **18-26f** undergoes intramolecular Heck reaction to produce indenol **18-29,** whereas the cyclization product from alcohol **18-26h** with an *exo*-cyclic double bond rearranges to give the indenol **18-30**.



Scheme 129. Heck reaction of homoallylic alcohols **18-26f** and **18-26h**.

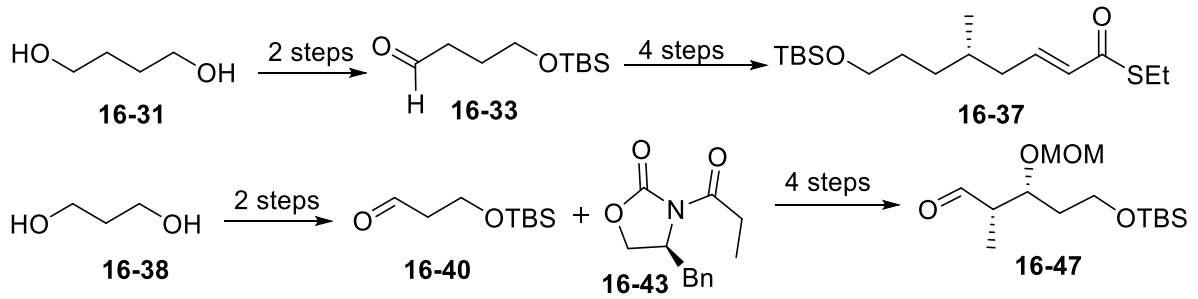
The proposed mechanism of the formation of indanones from the derivative of *o*-bromo benzyl alcohols is demonstrated in **Scheme 130**.



Scheme 130. Proposed mechanistic pathway for the formation of indanone.

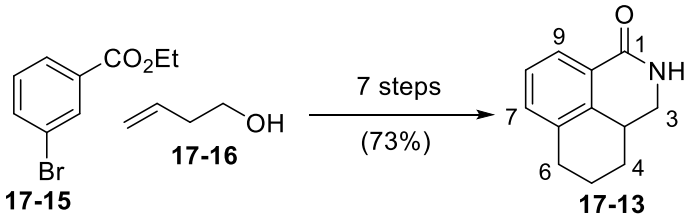
19 Conclusion IV

A little progress we made towards the synthesis of a Tautomycetin fragment. The ester segment **16-37** we synthesized from a commercially available and cheap alcohol **16-31** demonstrating successful use of Swern-oxidation on a four carbon alcohol. Whereas, the aldehyde segment **16-47** we synthesized by employing Swern oxidation on three carbon alcohol **16-38**. Oxazolidine chiral auxiliary enabled us to make *syn*-alcohol **16-**47 via an Evans aldol reaction.



Scheme 131. Synthesis of thioester **16-37** and aldehyde **16-47** from 1,4-butandiol and 1,3-propanediol, respectively.

We have successfully synthesized the fragment of palonosteron **17-13** via intramolecular C–H-activation approach. In 2014 Glorius and co-workers disclosed the intramolecular C–H-activation towards such valuable compounds.[210] Therefore, we discontinued this work.



Scheme 132. Synthesis of palonosteron fragment **17-13**.

During the intramolecular Heck reaction of some aryl halides, we observed redox products (**Figure 51**). These observations attract us to further investigate this work. Unfornately, the developed protocol is operating only on less hindered and mild activated aromatic rings. This work needs a further investigation to improve the protocol for a range of aromatics.

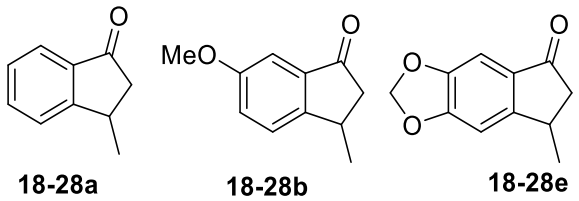


Figure 51. 3-Methyl indanones.

20 Experimental Section

20.1 General remarks

20.1.1 Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, and Merck. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

16.1.2 NMR-spectroscopy

All the spectra were measured on a Bruker Avance 400 spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): spectra were recorded at 295 K either in $CDCl_3$ or [D_4]MeOH; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ H = 7.25 ppm, δ C = 77.0 ppm), [D_4]MeOH (δ H = 2.49 ppm, δ C = 39.5 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, J = coupling constant (Hz), integration, peak assignment in italic form).

16.1.3 Mass Spectrometry

High-resolution mass spectra (HRMS) were recorded on an instrument (Brucker maXis 4G) with electron spray ionization (ESI) and a TOF mass detector (mass range: 50−20000 m/z, mass accuracy: 600 ppb RMS error). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}. High

resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

16.1.4 Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020. They are reported as follows: [α]temperature D (concentration, solvent). The unit of c is g/100 mL. Anhydrous CH_2Cl_2, $CHCl_3$ or EtOH were used as solvents. For the measurement the sodium D line = 589 nm was used.

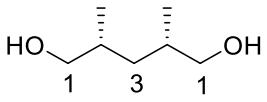
16.1.5 Chromatographic Methods

High performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using a Eurocell Knauer (250 × 4.6 mm). UV absorption was monitored at 220 nm or at 254 nm. Hexanes/isopropanol (65/25) mixture was used for elution (0.8 ml/min). Flash column chromatography was performed using flash silica gel (40-63 μm, 230-400 mesh ASTM) from Macherey-Nagel. Analytical thin layer chromatography (TLC) and preparative thin layer chromatography were performed on precoated silica gel 60 F254 plates (Merck) or Polygram Sil G/UV254 (Macherey Nagel). The compounds were visualized by UV254 light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$] and 0.4 g $Ce(SO_4)_2\cdot 4H_2O$ were dissolved in 400 mL of 10% H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL H_2O.

20.2 Experimental procedures

All the experimental procedures are arranged in the ascending order of number of the compound.

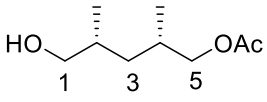
meso-2,4-Dimethylpentane-1,5-diol (3-6)



3-6

To a 0 °C solution of *meso*-2,4-dimethylglutaric anhydride (10.00 g, 50.35 mmol) in anhydrous THF (200 mL), $LiAlH_4$ (8.00 g, 211.00 mmol, 3 equiv) was added in equal portions. The reaction was warmed to rt in 5 min., and then heated at reflux for 24 h. The reaction was cooled to 0 °C and the excess $LiAlH_4$ was cautiously quenched by the sequential addition of water (150 mL) and HCl (6N, 60 mL). The resulting white suspension was warmed to rt and the aqeous layers was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The diol was purified by flash chromatography (ethyl acetate/petroleum ether, 1/1, 3/1, 4/1) to afford product (9.47 g) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76-0.86 (m, 1H, 3-H), 0.88 (d, J = 6.8 Hz, 6H, 2-CH_3), 1.50-1.59 (m, 1H, 3-H), 1.61-1.72 (m, 2H, 2-H), 3.35 (dd, J = 5.8, 10.8 Hz, 2H, 1-H), 4.43 (dd, J = 5.3, 10.6 Hz, 2H, 1-H), 3.53 (br, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (2-CH_3), 32.9 (C-3), 36.8 (C-2), 67.3 (C-1); HRMS (ESI): calcd for $C_7H_{16}O_2$ $[M+Na]^+$: 155.10425, found 155.10436.

(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl acetate (4-24)

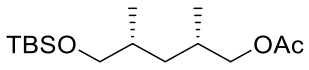


4-24

To a solution of *meso*-diol **3-6** (14.0 g, 0.107 mol) and vinyl acetate (9.5 g, 10 mL, 0.11 mol) in THF (300 mL) was added Amano Lipase AK from Pseudomonas fluorescence, 100 mg, (Aldrich Cat. Nr. 53,473-0), and the resulting suspension was stirred at room temperature using a mechanical stirrer. After 24 h additional vinyl acetate (2 mL) was added, and stirring continued for a total of 80 h. Then the reaction mixture was filtered through a Celite pad (2 cm), and the filtrate concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (150 mL), and the solution washed with 15% NaCl water solution (2 × 50 mL), aquous saturated NaCl solution (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield mono-acetate **4-24** (17.2 g, 80%) as a colorless oil. Our group has performed analytical studies of this compound, results are summerized here. The analysis by chiral GC [(column: heptakis(2,3-diacetyl-6-TBDMS)-β-cyclodextrin (30%) PS 86 (70%), df = 0.13 μ, size: 25 m × 0.25 mm), mobile phase: H_2, 90/2/4/140, pressure: 80 kPa, retention time (main): 11.1 min, (minor): 11.3 min] showed 98% *ee*, which was confirmed by NMR of Mosher ester. R_f = 0.2 (EtOAc/petroleum ether, 1:5); $[\alpha]^{22}{}_D$ = +7.7 (c = 1.0 in CH_2Cl_2); ^{1}HNMR (400 MHz, $CDCl_3$):

δ= 0.88-0.94 (m, 6H, 2-CH_3, 4-CH_3), 0.95-1.0 (m, 1H, 3-H), 1.35-1.45 (m, 1H, 3-H), 1.62-1.76 (m, 1H, 2-H), 1.78-1.95 (m, 2H, OH, 4-H), 3.32-3.41 (m, 1H, 1-H), 3.42-3.49 (m, 1H, 1-H), 3.80 (dd, J = 6.8, 10.8 Hz, 1H, 5-H), 3.93 (dd, J = 5.4, 10.8 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2 (2-CH_3), 17.8 (4-CH_3), 20.9 ($COCH_3$), 29.9 (C-4), 33.0 (C-3), 37.2 (C-2), 67.9 (C-1), 69.1 (C-5), 171.3 ($OCOCH_3$); HRMS (ESI): calcd for $C_9H_{18}O_3$ $[M+Na]^+$ 197.11482, found 197.11486.

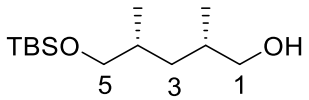
(2*S*,4*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentyl acetate (4-26)



4-26

To a solution of acetate **4-24** (2.0 g, 9.4 mmol) from the previous step and imidazole (1.4 g, 20 mmol, 2 equiv) in CH_2Cl_2 (6 mL) was added *tert*-butyldimethylchlorsilane (1.5 g, 10 mmol, 1.05 equiv) in small portions over 15 min, and the reaction mixture was stirred for additional 40 min. The imidazole hydrochloride was filtered off, and the filtrate washed with water (2 × 20 mL), 3% HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethylacetate/petroleum ether, 100:2) to afford pure product **4-26** (3.0 g 98%) as colorless oil. R_f = 0.5 (ethylacetate/petroleum ether, 1/20)

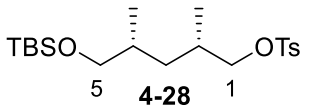
(2*S*,4*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (4-27)



4-27

To a solution of the silyl ether **4-26** (3.0 g) from the previous step in MeOH (12 mL) was added powdered K_2CO_3 (1.68 g, 12 mmol) and the mixture was stirred for 2 h. Thereafter the solid was removed by filtration and the filtrate was concentrated in *vacuo*. The residue was redissolved in petroleum ether (15 mL), washed with water (3 × 10 mL), saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo* affording the alcohol **4-27** as a colorless oil (2.1 g, 75% from 2,4-dimethylpentane-1,5-diol). R_f = 0.7 (EtOAc/petroleum ether, 1:5); $[\alpha]^{22}_D$ = –3.3 (c 1.0 in CH_2Cl_2); ^{1}HNMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.87-0.90 (m, 4H, 3-H, 4-CH_3), 0.92 (d, J = 6.8 Hz, 3H, 2-CH_3), 1.37-1.46 (m, 1H, 3-H), 1.63-1.75 (m, 3H, 2-H, 4-H), 3.32-3.52 (m, 4H, 1-H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($(CH_3)_2Si$), 17.7, 17.8 (CH_3), 18.3 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 33.2, 33.3 (C-2, C-4), 37.3 (C-3), 68.2, 68.3 (C-1, C-5); HRMS (ESI): calcd for $C_{13}H_{30}O_2Si$ $[M+Na]^+$: 269.19073, found 269.19097.

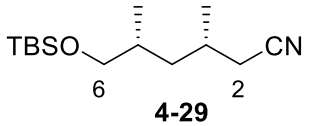
(2*S*,4*R*)-5-{(*tert*-Butyldimethylsilyl)oxy}-2,4-dimethylpentyl-4-methylbenzenesulfonate (4-28)



4-28

To a solution of alcohol **4-27** (1.00 g, 4.06 mmol) in pyridine (2 mL) was added *para*-toluenesulfonyl chloride (0.97 g, 5.07 mmol, 1.25 equiv) and DMAP (0.008 g, 0.08 mmol, 0.02 equiv) at 0 °C. The reaction mixture was allowed to warm and stirred for 3 h at room temperature, before it was quenched with HCl (1N, 7 mL), and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with saturated Na_2CO_3 solution (2 × 7 mL), saturated NaCl solution (1 × 7 ml), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 1.60 g (99%) of tosylate **4-28** as a yellow oil. The crude product was used in next step without further purification. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6H, $(CH_3)_2Si$), 0.82 (d, J = 6.8 Hz, 3H, 4-CH_3), 0.86 (s, 9H, $(CH_3)_2Si$), 0.90 (d, J = 6.8 Hz, 3H, 2-CH_3), 0.88-0.93 (m, 1H, 3-H), 1.29-1.40 (m, 1H, 3-H), 1.50-1.64 (m, 1H, 4-H), 1.82-1.95 (m, 1H, 2-H), 2.44 (s, 3H, *p*-CH_3), 3.29 (dd, J = 6.1, 9.8.Hz, 1H, 1-H), 3.36 (dd, J = 5.6, 9.8 Hz, 1H, 1-H), 3.73 (dd, J = 7.1, 9.3 Hz, 1H, 5-H), 3.89 (dd, J = 5.0, 9.3 Hz, 1H, 5-H), 7.33 (d, J = 8.6 Hz, 2H, *m*-H), 7.77 (d, J = 8.3 Hz, 2H, *o*-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($(CH_3)_2Si$), 17.36, 17.40 (4-CH_3, 2-CH_3), 18.2 ($(CH_3)_2CSi$), 21.6 (*p*-CH_3), 25.8 ($(CH_3)_3CSi$), 30.4 (C-2), 32.8 (C-3), 36.8 (C-4), 67.8 (C-5), 75.1 (C-1), 127.0 (Ar), 127.9 (Ar), 129.8 (Ar), 130.2 (Ar), 133.1 (Ar).

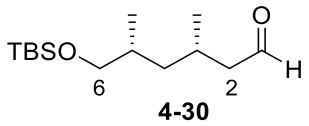
(3*S*,5*R*)-6-{(*tert*-Butyldimethylsilyl)oxy}-3,5-dimethylhexanenitrile (4-29).



4-29

To a solution of tosylate **4-28** (1.54 g, 3.84 mmol) in dry DMSO (12 mL) were added KCN (0.626 g, 9.61 mmol, 2.5 equiv) and a small amount of potassium iodide (catalytic amount, about 10 mg) at room temperature. The reaction mixture was then stirred for 2 h at 85 °C, before it was cooled to 0 °C, diluted with water (10 mL), and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and saturated NaCl solution (10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to afford pure nitrile **4-29** (0.90 g, 98%) as a colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{22}_D$ = +10.8 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_2Si$) (d, J = 6.7 Hz, 3H, 5-CH_3), 1.07 (d, J = 6.7 Hz, 3H, 3-CH_3), 1.01-1.13 (m, 1H, 4-H), 1.41-1.49 (m, 1H, 4-H), 1.56-1.69 (m, 1H, 3-H), 1.89-2.03 (m, 1H, 5-H), 2.16 (dd, J = 7.1, 16.7 Hz, 1H, 2-H), 2.31 (dd, J = 5.0, 16.7 Hz, 1H, 2-H), 3.34-3.43 (m, 2H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($(CH_3)_2Si$), 17.1 (5-CH_3), 18.2 ($(CH_3)_2CSi$), 20.1 (3-CH_3), 24.3 (C-3), 25.8 ($(CH_3)_3CSi$), 28.0 (C-2), 33.1 (C-5), 40.0 (C-4), 67.9 (C-6), 118.7 (CN); HRMS (ESI) : calcd for $C_{14}H_{29}NOSi$ $[M+Na]^+$ 278.19106, found 278.19131.

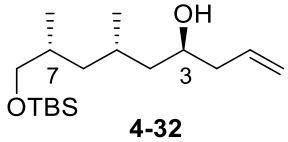
(3*S*,5*R*)-6-{(*tert*-Butyldimethylsilyl)oxy}-3,5-dimethylhexanal (4-30)



4-30

To a solution of nitrile **4-29** (0.825 g, 3.23 mmol) in CH_2Cl_2 (35 mL) at –80 °C was added DIBAL-H in hexane (1m, 6.5 mL, 6.46 mmol, 2.0 equiv) in a dropwise fashion. After stirring the mixture at –80 °C for 3.5 h, excess DIBAL-H was quenched with ethyl acetate (2 mL) before saturated NH_4Cl solution (30 mL) was added. The mixture was transferred to a separation funnel and both layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude aldehyde was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give pure aldehyde **4-30** (0.705 g, 85%) as colorless oil. R_f = 0.4 (petroleum ether/ethyl acetate, 20:1); $[\alpha]^{22}_D$ = +0.5 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_2Si$) (d, *J* = 6.7 Hz, 3H, 5-CH_3), 0.95 (d, *J* = 6.7 Hz, 3H, 3-CH_3), 0.97-1.04 (m, 1H, 4-H), 1.31-1.41 (m, 1H, 4-H), 1.57-1.68 (m, 1H, 5-H), 2.10-2.19 (m, 2H, 3-H, 2-H), 2.32-2.42 (m, 1H, 2-H), 3.35 (dd, *J* = 6.1, 9.6 Hz, 1H, 6-H), 3.41 (dd, *J* = 5.6, 9.6 Hz, 1H, 6-H), 9.73 (t, *J* = 2.0 Hz, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($(CH_3)_2Si$), 17.3 (5-CH_3), 18.3 ($(CH_3)_2CSi$), 20.7 (3-CH_3), 25.7 (C-3), 25.9 ($(CH_3)_3CSi$), 33.1 (C-5), 40.9 (C-4), 50.8 (C-2), 67.98 (C-6) 203.0 (CHO); HRMS (ESI): calcd for $C_{14}H_{30}O_2Si$ $[M+Na]^+$ 313.21694, found 313.21723.

(4*S*,6*S*,8*R*)-9-((*tert*-Butyldimethylsilyl)oxy)-6,8-dimethylnon-1-en-4-ol (4-32)



4-32

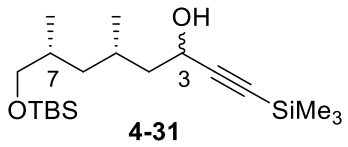
Preparation of Ipc$_2$BOMe. (a) To a 0 °C cooled solution $BH_3{\cdot}SMe_2$ (50 mmol) and THF (18 mL) in a 250 mL flask was added (+)-α-pinene (18.3 mL, 115 mmol, $[\alpha]^{23}_D$ –48.1° (neat), 91.3% *ee*) dropwise. After the mixture was stirred at 0 °C for 1 h (Ipc$_2$BH separated as white solid during this time), the flask was kept in a cold refrigerater at 0 °C for 2 d. The solid was filtered and washed with cold Et_2O, and then dried. The crystalline solid was dissolved in THF (18 mL) and treated with methanol (4.0 mL, 100 mmol) at 0 °C. After complete addition of methanol, the reaction mixture was warmed to rt and stirred at rt for 1 h. The solvents were removed under vacuum and the crude product was stored under nitrogen at –4 °C. Pure Ipc$_2$BOMe became a transparent solid.

Preparation of Ipc$_2$B(allyl). (b) Allylmagnesium bromide in ether (1.6 mL 3M, 4.87 mmol, 1.2 equiv) was added dropwise to a well-stirred solution of B-methoxybis(2-isocamphanyl)borane (1.60 g, 5.07 mmol) at 0 °C. After complete addition, the reaction mixture was vigorously stirred for 1 h at rt, and the solvents were pumped off under vacuum. The residue was extracted with pentane (2 × 5 mL) under nitrogen, and the extract was kept without

disturbing to settle down the salt MgBr(OMe). The clear supernatant pentane extract (free from the magnesium salts) was transferred into another flask using a syringe.

Allylation of aldehyde 4-30. (c). The $Ipc_2Ballyl$ in Et_2O (10 mL) was cooled at –80 °C and aldehyde **4-30** (1.0 g, 3.9 mmol) in Et_2O was added along the wall of the flask. After complete addition, the reaction mixture was stirred for 2 h at –80 °C, and then methanol (0.4 mL) was added. The reaction mixture was brought to rt within 1 h, and treated with 3N NaOH (3 mL) and 60% H_2O_2 (30 mL) followed by stirring of the resulting mixture overnight. The mixture was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alcohol **4-32** (160 mg) and aldehyde (345 mg unreacted) as colorless oil. R_f = 0.2 (petroleum ether/diethyl ether, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.83-0.95 (m, 6H, 7-CH_3, 5-CH_3), 1.05-1.21 (m, 1H, 7-H), 1.24-1.51 (m, 3H, 5H, 6-H, 7-H), 1.61-1.81 (m, 3H, 5-H, OH), 2.05-2.18 (m, 1H, 3-H), 2.20-2.32 (m, 1H, 3-H), 3.27-3.38 (m, 1H, 9-H), 3.40-3.47 (m, 1H, 9-H), 3.69-3.80 (m, 1H, 4-H), 5.07-5.10 (m, 1H, 1-H), 5.11-5.14 (m, 1H, 1-H), 5.75-5.88 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= –5.4 $(CH_3)_2Si$), 17.4, 17.9, 18.3, 20.1, 21.1, 25.9, 26.6, 27.2, 33.0, 40.8, 41.8, 41.9, 42.8, 44.0, 44.4, 67.9, 68.2, 68.3, 68.7, 118.0, 134.9.

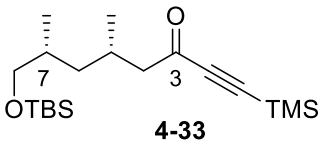
(5*S*,7*R*)-8-{(*tert*-Butyldimethylsilyl)oxy}-5,7-dimethyloct-1-yn-3-ol (4-31)



4-31

A solution of trimethylsilylacetylene (0.463 mL, 3.25 mmol, 1.2 equiv) in dry THF (9 mL), cooled to –78 °C, was treated dropwise with *n*-BuLi (2.5m in hexane, 1.3 mL, 3.25 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min at –78 °C, before a solution of aldehyde **4-30** (0.70 g, 2.71 mmol) in THF (15 mL) was added dropwise via cannula. After 3 h of stirring at –78 °C, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and the cooling system was removed. The mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alkynol **4-31** (0.810 g, 84%) as colorless oil (mixture of diastereomers at C3).

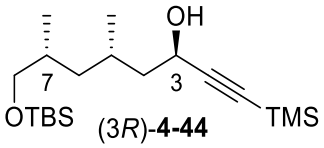
(5*S*,7*R*)-8-{(*tert*-Butyldimethylsilyl)oxy}-5,7-dimethyl-1-(trimethylsilyl)oct-1-yn-3-one (4-33)



4-33

To a solution of alkynol **4-31** (0.810 g, 2.27 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMP (0.963 g, 2.27 mmol, 1.0 equiv) and $NaHCO_3$ (0.191 g, 2.27 mmol, 1.0 equiv). After addition, the cooling bath was removed and the mixture stirred for 4 h at room temperature. Most of the solvent was removed in vacuo and the crude ketone purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give pure alkynone **4-33** (0.80 g, 99%) as colorless oil. $[\alpha]^{22}_D$ = –8.4 (*c* = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.21 (s, 9H, TMS), 0.87 (s, 9H, $(CH_3)_3CSi$), (d, *J* = 6.7 Hz, 3H, 7-CH_3), 0.92 (d, *J* = 6.3 Hz, 3H, 5-CH_3), 0.98 (td, *J* = 6.3, 12.9 Hz, 1H, 6-H), 1.31 (td, *J* = 6.3, 13.6 Hz, 1H, 6-H), 1.57-1.69 (m, 1H, 7-H), 2.11-2.21 (m, 1H, 5-H), 2.25 (dd, *J* = 9.0, 15.0 Hz, 1H, 4-H), 2.54 (dd, *J* = 4.0, 15.0 Hz, 1H, 4-H), 3.32 (dd, *J* = 6.6, 9.8 Hz, 1H, 8-H), 3.42 (dd, *J* = 5.3, 9.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), 0.80 (TMS), 17.2 (7-CH_3), 18.3 ($(CH_3)_2CSi$), 20.6 (5-CH_3), 25.9 ($(CH_3)_3CSi$), 27.2 (C-5), 33.2 (C-7), 40.7 (C-6), 52.5 (C-4), 68.1 (C-8), 97.3 (C-1), 102.3 (C-2), 187.7 (C=O).

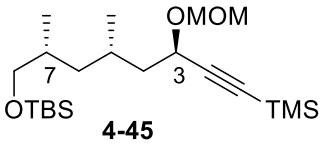
(3*R*,5*S*,7*R*)-8-{(*tert*-Butyldimethylsilyl)oxy}-5,7-dimethyl-1-(trimethylsilyl)oct-1-yn-3-ol [((3*R*)-4-44]



(3*R*)-**4-44**

To a solution of alkynone **4-33** (0.266 g, 0.75 mmol) in isopropanol (25 mL) was added dropwise RuCl[*R*,*R*]-NTsCH(Ph)CH(Ph)NH_2(η^6-cymene) (*R*,*R*)-**4-40** (0.016 g, 10 mol%) in CH_2Cl_2 (0.5 mL) at room temperature. After stirring of the mixture for 50 min at this temperature, most of the isopropanol was removed in vacuo. The crude propargylic alcohol was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alkynol (3*R*)-**4-44** (0.250 g, 93%) as colorless oil. $[\alpha]^{22}_D$ = +10.9 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.21 (s, 9H, TMS), 0.88 (s, 9H, $(CH_3)_3CSi$), (d, *J* = 7.6 Hz, 3H, 7-CH_3), 0.92 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 0.92-0.95 (m, 1H, 6-CH), 1.27-1.44 (m, 2H, 6-H, 7-H), 1.68-1.88 (m, 4H, 5-H, 4-H), 3.30 (dd, *J* = 6.8, 9.6 Hz, 1H, 8-H), 3.45 (dd, *J* = 5.0, 9.6 Hz, 1H, 8-H), 4.40 (dd, *J* = 5.0, 8.0 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), –0.14 (TMS), 17.5 (7-CH_3), 18.3 ($(CH_3)_2CSi$), 20.3 (5-CH_3), 25.9 ($(CH_3)_3CSi$), 26.6 (C-5), 33.1 (C-7), 41.2 (C-6), 45.0 (C-4), 60.9 (C-3), 68.2 (C-8), 88.9 (C-1), 107.4 (C-2); HRMS (ESI): calcd for $C_{19}H_{40}O_2Si$ $[M+Na]^+$ 379.24590, found 379.24597.

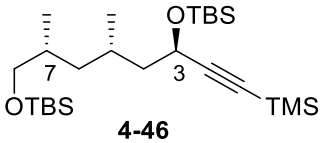
(5*R*,7*S*,9*R*)-7,9,12,12,13,13-Hexamethyl-5-((trimethylsilyl)ethynyl)-2,4,11-trioxa-12-silatetradecane (4-45)



4-45

To a solution of alcohol (3*R*)-**4-44** (0.210 g, 0.59 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C *N*-*N*-diisopropylethylamin (1.1 mL, 5.9 mmol, 10 equiv) and tetrabutylammonium iodide (22 mg, 0.059 mmol, 0.1 equiv), followed by MOMCl (240 µL, 2.94 mmol, 5 equiv). After stirring of the mixture overnight, saturated $NaHCO_3$ solution (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude MOM-ether was purified by flash chromatography (Et_2O/petroleum ether, 1:20) to give product **4-45** (240 mg, 100%) as colorless oil. R_f = 0.7 (petroleum ether/diethyl ether, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.14 (s, 9H, TMS), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.84-0.97 (m, 6H, 5-CH_3, 7-CH_3, 6-H), 1.22-1.44 (m, 2H, 6-H, 5-H), 1.62-1.86 (m, 3H, 4-H, 7-H), 3.29 (dd, *J* = 7.1, 9.6 Hz, 1H, 8-H), 3.36 (s, 3H, OMe), 3.45 (dd, *J* = 5.3, 9.6 Hz, 1H, 8-H), 4.37 (dd, *J* = 4.0, 9.1 Hz, 1H, 3-H), 4.56 (d, *J* = 6.6 Hz, 1H, OCH_2O), 4.94 (d, *J* = 6.6 Hz, 1H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$),–0.1 (TMS), 17.5 (7-CH_3), 18.3 ($(CH_3)_2CSi$, 20.1 (5-CH_3), 26.0 ($(CH_3)_3CSi$) 26.6 (C-5), 33.1 (C-7), 41.3 (C-6), 45.9 (C-4), 55-7 (OMe), 64.2 (C-3), 68.3 (C-8), 89.8 (C-1), 94.1 (OCH_2O), 104.9 (C-2).

(3*R*,5*S*,7*R*)-3,8-Di{(*tert*-butyldimethylsilyl)oxy}-5,7-dimethyl-1-(trimethylsilyl)-1-octyne (4-46)

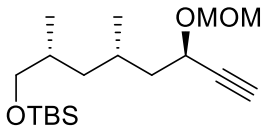


4-46

To a solution of alcohol (3*R*)-**4-44** (0.840 g, 2.35 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C 2,6-lutidine (0.615 mL, 5.17 mmol, 2.2 equiv), followed by TBSOTf (0.69 mL, 2.60 mmol, 1.1 equiv). After stirring of the mixture for 2.5 h at 0 °C, saturated $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed successively with saturated $NaHSO_4$ solution (2 × 10 mL), saturated $NaHCO_3$ solution (20 mL), saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude silyl ether was purified by flash chromatography (petroleum ether/diethyl ether, 50:1) to give product **4-46** (1.100 g, 99%) as a colorless oil. R_f = 0.7 (petroleum ether/diethyl ether, 49:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.10 (s, 6H, $(CH_3)_2Si$), 0.13 (s, 6H, $(CH_3)_2Si$), 0.14 (s, 9H, TMS), 0.86 (d, *J* = 5.8 Hz, 6H, 5-CH_3, 7-CH_3), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.84-0.91 (m, 1H, 6-H), 1.22-1.32 (m, 2H, 6-H, 5-H), 1.62-1.86 (m, 3H, 4-H, 7-H), 3.29 (dd, *J* = 7.1, 9.6 Hz, 1H, 8-H), 3.45

(dd, J = 5.3, 9.6 Hz, 1H, 8-H), 4.39 (dd, J = 4.0, 9.1 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 $(CH_3)_2Si$), –5.0 $(CH_3)_2Si$), –4.3 $(CH_3)_2Si$), –0.16 (TMS), 17.2 (7-CH_3), 18.2 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.0 (5-CH_3), 25.7, 25.8 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$) 26.2 (C-5), 33.1 (C-7), 41.2 (C-6), 45.5 (C-4), 61.2 (C-3), 68.4 (C-8), 88.1 (C-1), 108.4 (C-2); HRMS (ESI): calcd for $C_{25}H_{54}O_2Si_3$ $[M+Na]^+$ 493.33238, found 493.33259.

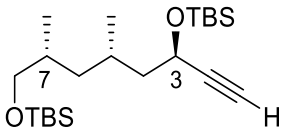
(5*R*,7*S*,9*R*)-5-Ethynyl-7,9,12,12,13,13-hexamethyl-2,4,11-trioxa-12-silatetradecane (4-47)



4-47

A solution of alkyne **4-45** (210 mg, 0.52 mmol) in methanol (2.5 mL) was treated with dry K_2CO_3 (85 mg, 0.62 mmol, 1.2 equiv) and the mixture was stirred at room temperature for 3 h. Most of the methanol was removed in vacuo before the residue was re-dissolved in Et_2O (10 mL) and the solution was washed with water (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude alkyne was purified by flash chromatography (Et_2O/petroleum ether, 20:1) to give product **4-47** (130 mg, 76%) as colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 25:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.84-0.97 (m, 6H, 5-CH_3, 7-CH_3, 6-H), 1.22-1.46 (m, 2H, 6-H, 5-H), 1.62-1.88 (m, 3H, 4-H, 7-H),2.38 (d, J = 2.0 Hz, 1H, 1-H) 3.31 (dd, J = 6.6, 9.6 Hz, 1H, 8-H), 3.37 (s, 3H, OMe), 3.45 (dd, J = 5.3, 9.6 Hz, 1H, 8-H), 4.36-4.42 (m, 1H, 3-H), 4.57 (d, J = 6.8 Hz, 1H, OCH_2O), 4.94 (d, J = 6.8 Hz, 1H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), 17.5 (7-CH_3), 18.3 ($(CH_3)_2CSi$, 20.1 (5-CH_3), 25.9 ($(CH_3)_3CSi$) 26.6 (C-5), 33.1 (C-7), 41.2 (C-6), 43.0 (C-4), 55-7 (OMe), 63.6 (C-3), 68.2 (C-8), 73.1 (C-1), 83.1(C-2). 94.1 (OCH_2O).

(3*R*,5*S*,7*R*)-3,8-Di{(*tert*-butyldimethylsilyl)oxy}-5,7-dimethyl-1-octyne (4-48)

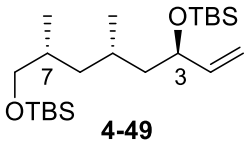


4-48

A solution of alkyne **4-46** (3.150 g, 6.69 mmol) in methanol (13 mL) was treated with dry K_2CO_3 (1.11 g, 8.03 mmol, 1.2 equiv) and the mixture was stirred at room temperature for 3 h. Most of the methanol was removed in vacuo before the residue was re-dissolved in Et_2O (30 mL) and the solution was washed with water (30 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude alkyne was purified by flash chromatography (Et_2O/petroleum ether, 50:1) to give product **4-48** (2.445 g, 92%) as a colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 49:1); $[\alpha]^{22}_D$ = +110.1 (c = 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.10 (s, 3H, $(CH_3)_2Si$), 0.14 (s, 3H, $(CH_3)_2Si$) 0.88 (s, 9H,

$(CH_3)_3CSi$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.84-0.96 (m, 7H, 7-CH_3, 5-CH_3, 6-H), 1.22-1.36 (m, 2H, 6-H, 5-H), 1.63-1.72 (m, 1H, 7-H), 1.73-1.83 (m, 2H, 4-H), 2.35 (d, J = 2.3 Hz, 1H, 1-H), 3.31 (dd, J = 6.8, 9.8 Hz, 1H, 8-H), 3.44 (dd, J = 5.3, 9.8 Hz, 1H, 8-H), 4.39 (ddd, J = 2.0, 4.3, 8.8 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), –5.2 $(CH_3)_2Si$), –4.4 ($(CH_3)_2Si$), 17.3 (7-CH_3), 18.1 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.1 (5-CH_3), 25.7 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.2 (C-5), 33.1 (C-7), 41.2 (C-6), 45.0 (C-4), 60.6 (C-3), 68.2 (C-8), 71.8 (C-1), 86.2 (C-2); HRMS (ESI): calcd for $C_{22}H_{46}O_2Si_2$ $[M+Na]^+$ 421.29285, found 421.29314.

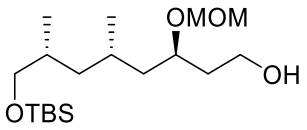
(3*R*,5*S*,7*R*)-3,8-Di{(*tert*-butyldimethylsilyl)oxy}-5,7-dimethyl-1-octene (4-49)



4-49

To a solution of alkyne **4-48** (2.445 g, 6.13 mmol) in a mixture of acetone/cyclohexene (65 mL, 50:15) was added quinoline (7.2 mL, 61.3 mmol, 10 equiv). This solution was flushed with N_2 and treated with (5% Pd) palladium/calcium carbonate (0.526 g, 0.24 mmol, 4 mol%) before hydrogen gas was bubbled through the solution via a hydrogen balloon through an inlet needle and keeping the thin outlet needle free. The reaction progress was monitored by TLC (petroleum ether/diethyl ether, 49:1). After completion of the reaction (after about 30 min), the catalyst was filtered off and the filtrate concentrated in vacuo. The residue was re-dissolved in Et_2O (20 mL) and this solution washed successively with saturated $NaHSO_4$ solution (2 × 10 mL), saturated $NaHCO_3$ solution (10 mL), saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude alkene was purified by flash chromatography (Et_2O/petroleum ether, 50:1) to give alkene **4-49** (2.40 g, 98%) as a colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 49:1); $[\alpha]^{22}_D$ = +2.8 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H, $(CH_3)_2Si$), 0.02 (s, 6H, $(CH_3)_2Si$), 0.40 (s, 3H, $(CH_3)_2Si$), 0.88 (s, 18H, $(CH_3)_3CSi$), 0.85-0.90 (m, 6H, 7-CH_3, 5-CH_3), 0.90-0.95 (m, 1H, 6-H), 1.00-1.09 (m, 1H, 6-H), 1.21-1.29 (m, 1H, 7-H), 1.49-1.58 (m, 1H, 5-H), 1.63-1.75 (m, 2H, 4-H), 3.28 (dd, J = 6.8, 9.6 Hz, 1H, 8-H), 3.45 (dd, J = 5.3, 9.6 Hz, 1H, 8-H), 4.11-4.18 (m, 1H, 3-H), 4.98 (ddd, J = 1.0, 1.8, 10.4 Hz, 1H, 1-H), 5.11 (ddd, J = 1.0, 1.5, 16.9 Hz, 1H, 1-H), 5.70-5.83 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 $(CH_3)_2Si$), –4.9 ($(CH_3)_2Si$), –4.1 ($(CH_3)_2Si$), 17.4 (7-CH_3), 18.2 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.4 (5-CH_3), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.1 (C-5), 33.1 (C-7), 41.2 (C-6), 45.0 (C-4), 68.4 (C-8), 71.9 (C-3), 113.2 (C-1), 142.6 (C-2); HRMS (ESI): calcd for $C_{22}H_{48}O_2Si_2$ $[M+Na]^+$ 423.30850, found 423.30881.

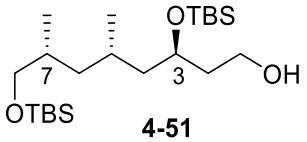
(3*R*,5*S*,7*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-5,7-dimethyloctan-1-ol (4-50)



4-50

To a solution of $BH_3 \cdot SMe_2$ complex (22 μL, 0.37 mmol, 1.1 equiv) in THF (2 mL) was added cyclohexene (76 μL, 00.74 mmol, 2.2 equiv) dropwise at 0 °C followed by stirring of the mixture for 30 min. Then the ice bath was removed and the mixture was allowed to stir at room temperature for 1 h. It was re-cooled to 0 °C before alkyne **4-47** (110 mg, 0.33 mmol, 1 equiv) in THF (1 mL) was added dropwise. After 3 h of stirring at 0 °C, NaOH (3N, 6 mL) and H_2O_2 solution (30%, 6 mL) were added and the mixture stirred for 3 h. Thereafter, the mixture was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give alcohol **4-50** (25 mg, 21%) as colorless oil. R_f = 0.3 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.84-0.97 (m, 6H, 5-CH_3, 7-CH_3, 6-H), 1.22-1.38 (m, 2H, 6-H, 5-H), 1.48-1.90 (m, 6H, 4-H, 7-H), 3.29 (dd, J = 6.6, 9.6 Hz, 1H, 8-H), 3.39 (s, 3H, OMe), 3.45 (dd, J = 5.3, 9.6 Hz, 1H, 8-H), 3.65-3.73 (m, 1H, 3-H), 3.76-3.89 (m, 2H, 1-H), 4.85 (d, J = 1.5 Hz, 2H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), 17.6 (7-CH_3), 18.3 ($(CH_3)_2CSi$, 20.6 (5-CH_3), 25.9 ($(CH_3)_3CSi$) 26.7(C-5), 33.0 (C-7), 37.4 (C-2), 41.4 (C-6), 42.5 (C-4), 55.8 (OMe), 59.7 (C-1), 68.1 (C-8), 74.7 (C-3), 96.2 (OCH_2O).

(3*R*,5*S*,7*R*)-3,8-Bis{(*tert*-butyldimethylsilyl)oxy}-5,7-dimethyloctan-1-ol (4-51)

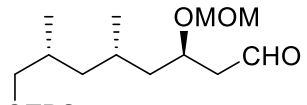


4-51

To a solution of $BH_3 \cdot SMe_2$ complex (2M in THF, 36 mL, 18.00 mmol, 3 equiv) in THF (50 mL) was added cyclohexene (3.65 mL, 36.00 mmol, 6 equiv) dropwise at 0 °C followed by stirring of the mixture for 30 min. Then the ice bath was removed and the mixture was allowed to stir at room temperature for 1 h. It was re-cooled to 0 °C before alkene **4-49** (2.31 g, 5.76 mmol, 1 equiv) in THF (30 mL) was added dropwise. After 3 h of stirring at 0 °C, NaOH (3N, 60 mL) and H_2O_2 solution (30%, 60 mL) were added and the mixture stirred for 3 h. Thereafter, the mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give alcohol **4-51** (2.20 g, 91%) as a colorless oil. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{22}_D$ = –2.0 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.07 (s, 6H, $(CH_3)_2Si$), 0.09 (s, 3H, $(CH_3)_2Si$), 0.88 (s, 18H, $(CH_3)_3CSi$), 0.85-0.91 (m, 6H, 7-

CH_3, 5-CH_3, 6-H), 1.14-1.22 (m, 2H, 6-H), 1.26-1.36 (m, 1H, 5-H), 1.49-1.72 (m, 4H, 2-H, 7-H, 4-H), 1.89-1.91 (m, 1H, 2-H), 3.22 (dd, J = 6.5, 9.8 Hz, 1H, 8-H), 3.43 (dd, J = 5.3, 9.8 Hz, 1H, 8-H), 3.65-3.72 (m, 1H, 3-H), 3.81-3.89 (m, 1H, 1-H), 3.96-4.04 (m, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), –4.5 ($(CH_3)_2Si$), –4.4 ($(CH_3)_2Si$), 17.7 (7-CH_3), 17.9 ($(CH_3)_2CSi$), 18.3 ($(CH_3)_2CSi$), 20.7 (5-CH_3), 25.8 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 26.6 (C-5), 33.0 (C-7), 38.5 (C-6), 44.2 (C-4), 44.2 (C-2), 60.1 (C-1), 67.9 (C-8), 69.8 (C-3); HRMS (ESI): calcd for $C_{22}H_{50}O_3Si$ $[M+Na]^+$ 441.31907, found 441.31939.

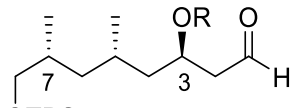
(3*R*,5*S*,7*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-5,7-dimethyloctanal (4-52)



4-52

To a solution of alcohol **4-50** (20 mg, 0.57 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added DMP (48 mg, 0.114 mmol, 2.0 equiv) and K_2CO_3 (15 mg, 0.114 mmol, 2.0 equiv). After addition, the cooling bath was removed and the mixture stirred for 2 h at room temperature. Most of the solvent was removed in vacuo and the crude aldehyde purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give pure aldehyde **4-52** (15 mg, 98%) as colorless oil. R_f = 0.5 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.02 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.84-0.97 (m, 7H, 5-CH_3, 7-CH_3, 6-H), 1.23-1.35 (m, 2H, 6-H, 5-H), 1.62-1.78 (m, 3H, 4-H, 7-H), 2.15-2.67 (m, 2H, 2-H), 3.34 (s, 3H, OMe), 3.28-3.48 (m, 2H, 8-H), 4.10-4.20 (m, 1H, 3-H), 4.65 (d, J = 1.3 Hz, 2H, OCH_2O), 9.78 (dd, J = 2.0, 2.8 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), 17.5 (7-CH_3), 18.3 $(CH_3)_2CSi$, 20.2 (5-CH_3), 25.9 ($(CH_3)_3CSi$) 26.6(C-5), 33.0 (C-7), 41.4 (C-6), 42.8 (C-4), 49.6 (C-2), 55.7 (OMe), 68.1 (C-3), 71.5 (C-8), 96.1 (OCH_2O), 200.2 (CHO).

(3*R*,5*S*,7*R*)-3,8-Bis{(*tert*-butyldimethylsilyl)oxy}-5,7-dimethyloctan-1-al (4-53)

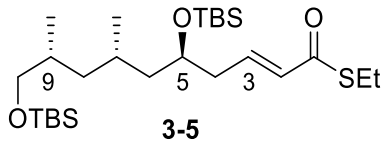


4-53 R = TBS

To a solution of oxalyl chloride (0.67 mL, 7.83 mmol, 1.6 equiv) in CH_2Cl_2 (30 mL) at –80 °C was added DMSO (1.11 mL, 15.65 mmol, 3.2 equiv) dropwise. The resulting mixture was stirred for 15 min before alcohol **4-51** (2.050 g, 4.89 mmol) in CH_2Cl_2 (8 mL) was added dropwise within 15 min. After stirring the mixture for 1 h at –80 °C, Et_3N (4.23 mL, 29.34 mmol, 6 equiv) was added slowly. Then the reaction mixture was allowed to warm to room temperature. For work-up water (20 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give aldehyde **4-53** (1.98 g, 98%) as a colorless oil. R_f = 0.6 (petroleum ether/ethyl acetate, 9:1);

$[\alpha]^{22}_D$ = +15.9 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.05 (s, 3H, $(CH_3)_2Si$), 0.60 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.86 (d, *J* = 6.6 Hz, 3H, 7-CH_3), 0.88 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 1.08-1.17 (m, 1H, 6-H), 1.19-1.32 (m, 2H, 6-H, 5-H), 1.54-1.71 (m, 3H, 4-H, 7-H), 2.47 (ddd, *J* = 3.0, 5.3, 15.7 Hz, 1H, 2-H), 2.54 (ddd, *J* = 3.0, 5.6, 15.7 Hz, 1H, 2-H), 3.31 (dd, *J* = 6.6, 9.6 Hz, 1H, 8-H), 3.42 (dd, *J* = 5.3, 9.6 Hz, 1H, 8-H), 4.20-4.27 (m, 1H, 3-H), 9.80 (t, *J* = 3.0 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($(CH_3)_2Si$), –5.4 ($(CH_3)_2Si$), –4.5 ($(CH_3)_2Si$), –4.4 ($(CH_3)_2Si$), 17.5 (7-CH_3), 17.9 ($(CH_3)_2CSi$), 18.3 ($(CH_3)_2CSi$), 20.3 (5-CH_3), 25.8 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 26.4 (C-5), 33.0 (C-7), 41.3 (C-6), 45.3 (C-4), 51.8 (C-2), 66.1 (C-3), 68.0 (C-8), 200.2 (CHO); HRMS (ESI): calcd for $C_{22}H_{48}O_3Si_2$ $[M+Na]^+$ 471.32963, found 471.32998.

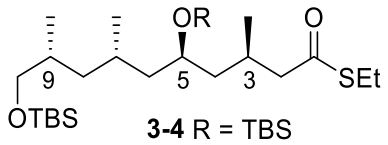
_S_-Ethyl (3_R_,5_S_,7_R_)-3,10-bis{(_tert_-butyldimethylsilyl)oxy}-7,9-dimethyldec-2-enethioate (3-5)



3-5

To a solution of aldehyde **4-53** (1.94 g, 4.65 mmol) in CH_2Cl_2 (50 mL) was added *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene) ethanethioate (**4-54**) (2.04 g, 5.58 mmol, 1.2 equiv). The resulting solution was refluxed for 2 d, and then cooled to room temperature before it was concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:50) to give enoate **3-5** (2.08 g, 89%) as a yellow oil. R_f = 0.5 (petroleum ether/diethyl ether, 40:1); $[\alpha]^{22}_D$ = +22.5 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.40 (s, 3H, $(CH_3)_2Si$), 0.85 (d, *J* = 6.8 Hz, 6H, 9-CH_3, 7-CH_3), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.88-0.93 (m, 1H, 8-H), 0.98-1.07 (m, 1H, 8-H), 1.27 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$S), 1.20-1.32 (m, 1H, 6-H), 1.42-1.52 (m, 1H, 6-H), 1.58-1.72 (m, 2H, 7-H, 9-H), 2.25-2.38 (m, 2H, 4-H), 2.93 (q, *J* = 7.5 Hz, 2H, CH_3C*H*$_2$S), 3.29 (dd, *J* = 6.8, 9.8 Hz, 1H, 10-H), 3.43 (dd, *J* = 5.0, 9.8 Hz, 1H, 10-H), 3.81-3.90 (m, 1H, 5-H), 6.09 (dt, *J* = 1.3, 15.7 Hz, 1H, 2-H), 6.81-6.92 (m, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($(CH_3)_2Si$), –5.3 ($(CH_3)_2Si$), –4.6 ($(CH_3)_2Si$), –4.2 ($(CH_3)_2Si$), 14.6 (*C*H$_3$CH$_2$S), 17.4 (9-CH_3), 18.0 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.4 (7-CH_3), 23.0 (CH$_3$*C*H$_2$S), 25.8 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.2 (C-7), 33.0 (C-9), 41.1 (C-8), 41.5 (C-4), 44.7 (C-6), 68.2 (C-10), 69.0 (C-5), 130.6 (C-2), 141.7 (C-3), 189.9 (C-1); HRMS (ESI): calcd for $C_{26}H_{54}O_3SSi_2$ $[M+Na]^+$ 525.32244, found 525.32296.

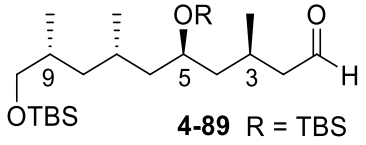
S-Ethyl (3*R*,5*R*,7*S*,9*R*)-5,10-Bis{(*tert*-butyldimethylsilyl)oxy}-3,7,9 trimethyldecanethioate (3-4)



3-4 R = TBS

To a solution of (*R*)-Tol-BINAP (0.045 g, 0.065 mmol, 0.016 equiv) in dry *tert*-butyl methyl ether (15 mL) was added copper iodide (0.008 g, 0.043 mmol, 0.010 equiv). This suspension was stirred for 1 h at room temperature turning into a dark yellow solution. The solution was cooled to –78 °C and treated dropwise with a solution of MeMgBr in Et_2O (3m 7.4 mL, 26.22 mmol, 6.6 equiv). The resulting mixture was stirred for 30 min before a solution of enoate **3-5** (2.000 g, 3.98 mmol) in *tert*-butyl methyl ether (7 mL) was added dropwise using a syringe pump within 2 h. The mixture was stirred overnight during at –78 °C. The reaction was quenched with MeOH (1 mL) and saturated NH_4Cl solution (10 mL), the cooling system was removed, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/petroleum ether, 1:50) afforded pure ester **3-4** (2.00 g, 97%) as colorless oil. R_f = 0.6 (petroleum ether/diethyl ether, 40:1); $[\alpha]^{22}_D$ = +23.1 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 12H, $(CH_3)_2Si$), 0.03 (s, 3H, $(CH_3)_2Si$), 0.05 (s, 3H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.83-0.90 (m, 7H, 7-CH_3, 9-CH_3, 8-H), 0.92 (d, *J* = 6.6 Hz, 3H, 3-CH_3), 1.03-1.12 (m, 1H, 8-H), 1.23 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$S), 1.18-1.26 (m, 1H, 6-H), 1.29-1.46 (m, 3H, 6-H, 4-H), 1.62-1.73 (m, 2H, 9-H, 7-H), 2.01-2.16 (m, 1H, 3-H), 2.33 (dd, *J* = 8.3, 14.6 Hz, 1H, 2-H), 2.55 (dd, *J* = 5.6, 14.6 Hz, 1H, 2-H), 2.86 (q, *J* = 7.3 Hz, 2H, CH$_3$C*H*$_2$S), 3.28 (dd, *J* = 7.0, 9.6 Hz, 1H, 10-H), 9.60 (dd, *J* = 5.1, 9.6 Hz, 1H, 10-H), 3.71-3.80 (m, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($(CH_3)_2Si$), –4.4 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 14.6 (*C*H$_3$CH$_2$S), 17.4 (9-CH_3), 18.0 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 19.6 (7-CH_3), 20.4 (3-CH_3), 23.3 (CH$_3$*C*H$_2$S), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.1 (C-7), 27.8 (C-3), 33.0 (C-9), 41.8 (C-8), 44.1 (C-4), 44.3 (C-6), 51.8 (C-2), 68.1 (C-10), 68.4 (C-5), 198.9 (C-1); HRMS (ESI): calcd for $C_{27}H_{58}O_3SSi_2$ $[M+Na]^+$ 541.35374, found 541.35411.

(3*R*,5*R*,7*S*,9*R*)-5,10-Bis{(*tert*-butyldimethylsilyl)oxy}-3,7,9-trimethyldecanal (4-89)

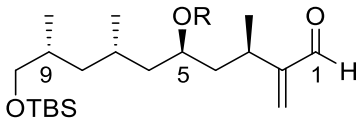


4-89 R = TBS

To a solution of thioester **3-4** (2.00 g, 3.85 mmol) in CH_2Cl_2 (70 mL) at –80 °C was added DIBAL-H in hexane (1m, 4.04 mL, 4.04 mmol, 1.05 equiv) dropwise. After 30 min of stirring at –80 °C the excess DIBAL-H was quenched with ethyl acetate (1 mL) and saturated NH_4Cl solution (5 mL). After having reached room temperature, the layers were separated and the

aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give pure aldehyde **4-89** (1.73 g, 98%) as colorless oil. R_f = 0.4 (petroleum ether/diethyl ether, 40:1); $[\alpha]^{22}_D$ = +36.4 (*c* = 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.03 (s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.84-0.89 (m, 6H, 7-CH_3, 9-CH_3), 0.89-0.92 (m, 1H, 8-H), 1.40 (d, *J* = 6.6 Hz, 3H, 3-CH_3), 1.05-1.16 (m, 1H, 8-H), 1.18-1.28 (m, 1H, 6-H), 1.36-1.46 (m, 3H, 6-H, 4-H), 1.62-1.74 (m, 2H, 9-H, 7-H), 2.07-2.17 (m, 1H, 3-H), 2.21 (ddd, *J* = 2.8, 8.3, 16.2 Hz, 1H, 2-H), 2.24 (ddd, *J* = 1.7, 4.8, 16.2 Hz, 1H, 2-H), 3.28 (dd, *J* = 6.8, 9.6 Hz, 1H, 10-H), 3.44 (dd, *J* = 5.3, 9.6 Hz, 1H, 10-H), 3.74-3.84 (m, 1H, 3-H), 9.73 (t, *J* = 2.0, Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($(CH_3)_2Si$), –4.4 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 17.4 (9-CH_3), 18.0 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.2 (3-CH_3), 20.4 (7-CH_3), 24.8 (C-3), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.2 (C-7), 33.0 (C-9), 41.8 (C-8), 44.2 (C-4), 45.4 (C-6), 51.5 (C-2), 68.1 (C-5), 68.4 (C-10), 200.3 (CHO).

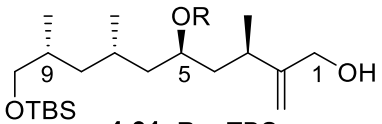
(3*R*,5*R*,7*S*,9*R*)-5,10-Bis{(*tert*-butyldimethylsilyl)oxy}-3,7,9-trimethyl-2-methylenedecanal (4-90)



4-90 R = TBS

To a solution of aldehyde **4-89** (1.60 g, 2.53 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (1.1 mL, 7.59 mmol, 3 equiv) and Eschenmoser's salt ($Me_2N{=}CH_2^+$ Cl^-) (0.59 g, 6.32 mmol, 2.5 equiv). The reaction mixture was stirred at room temperature for 2 d and then concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 1:20) gave pure enal **4-90** (1.18 g, 99%) as a colorless oil. R_f = 0.5 (petroleum ether/ethyl acetate, 33:1). $[\alpha]^{22}_D$ = +34.0 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H, $(CH_3)_2Si$), 0.02 (s, 9H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.83-0.96 (m, 7H, 7-CH_3, 9-CH_3, 8-H), 1.05 (d, *J* = 6.8 Hz, 3H, 3-CH_3), 1.09-1.26 (m, 2H, 8-H, 6-H), 1.35-1.52 (m, 2H, 6-H, 4-H), 1.57-1.74 (m, 3H, 9-H, 7-H, 4-H), 2.67-2.78 (m, 1H, 3-H), 3.27 (dd, *J* = 7.1, 9.6 Hz, 1H, 10-H), 3.46 (dd, *J* = 5.3, 9.8 Hz, 1H, 10-H), 3.68-3.78 (m, 1H, 5-H), 5.96 (s, 1H, H_2C=CCHO), 6.20 (s, 1H, H_2C=CCHO), 9.51 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($(CH_3)_2Si$), –4.4 ($(CH_3)_2Si$), –4.1 ($(CH_3)_2Si$), 17.4 (9-CH_3), 18.0 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 19.8 (3-CH_3), 20.4 (7-CH_3), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.2 (C-7), 28.3 (C-3), 33.1 (C-9), 41.8 (C-8), 43.9 (C-4), 44.3 (C-6), 68.4 (C-5), 68.5 (C-10), 132.8 (CH_2=CCHO), 155.7 (CH_2=CCHO), 194.4 (CHO); HRMS (ESI): calcd for $C_{26}H_{54}O_3Si_2$ $[M+Na]^+$ 493.35037, found 493.35065.

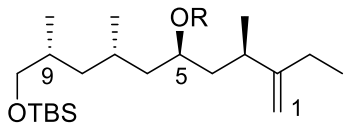
(3*R*,5*R*,7*S*,9*R*)-5,10-Bis{(*tert*-butyldimethylsilyl)oxy}-3,7,9-trimethyl-2-methylenedecan-1-ol (4-91)



4-91 R = TBS

To a solution of enal **4-90** (1.180 g, 2.50 mmol) in CH_2Cl_2 (25 mL) at –80 °C was added DIBAL-H in hexane (1M 2.62 mL, 2.62 mmol, 1.05 equiv) dropwise. After complete addition, the reaction mixture was allowed to warm to –40 °C within 1 h. Excess DIBAL-H was quenched with ethyl acetate (1 mL) and saturated NH_4Cl solution (3 mL), and after having reached room temperature, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give pure allyl alcohol **4-91** (1.18 g, 100%) as a colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate, 20:1); $[\alpha]^{22}_D$ = +9.6 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $(CH_3)_2Si$), 0.04 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.83-0.95 (m, 7H, 7-CH_3, 9-CH_3, 8-H), 1.04 (d, J = 6.8 Hz, 3H, 3-CH_3), 1.07-1.16 (m, 1H, 8-H), 1.18-1.28 (m, 1H, 6-H), 1.36-1.50 (m, 2H, 6-H, 7-H), 1.52-1.74 (m, 4H, 9-H, 4-H), 2.18-2.28 (m, 1H, 3-H), 3.27 (dd, J = 7.1, 9.8 Hz, 1H, 10-H), 3.45 (dd, J = 5.3, 9.8 Hz, 1H, 10-H), 3.72-3.80 (m, 1H, 5-H), 4.10 (s, 2H, 1-H), 4.88 (m, 1H, CH_2=CCH$_2$OH), 5.03 (m, 1H, CH_2=CCH$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 $(CH_3)_2Si$), –4.3 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 17.4 (9-CH_3), 18.1 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.3 (3-CH_3), 20.6 (7-CH_3), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.3 (C-7), 33.1 (C-3), 33.1 (C-9), 41.8 (C-8), 44.3 (C-4), 44.5 (C-6), 64.9 (C-1), 66.5 (C-10), 68.9 (C-5), 108.0 (*C*H$_2$=CCH$_2$OH), 154.4 (CH$_2$=*C*CH$_2$OH); HRMS (ESI): calcd for $C_{26}H_{56}O_3Si_2$ $[M+Na]^+$ 495.36602, found 495.36595.

(3*R*,5*R*,7*S*,9*R*)-5,10-Bis{(*tert*-butyldimethylsilyl)oxy}-2-ethyl-3,7,9-trimethyl-1-decene (4-93)



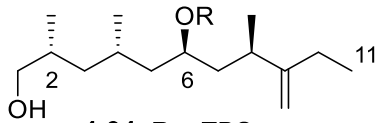
4-93 R = TBS

a) **Tosylate 4-92**: To a cooled (0 °C) solution of alcohol **4-91** (0.250 g, 0.53 mmol) and Et_3N (0.076 mL, 0.53 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added *para*-toluenesulfonic anhydride (0.175 g, 0.53 mmol, 1.0 equiv). After being stirred for 30 min at 0 °C, water (2 mL) was added to the reaction mixture, the layers were separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give crude tosylate **4-92** (0.320 g, 96%) which was used for the next step without further purification.

b) **Substitution of tosylate**: The crude tosylate **4-92** was dissolved in CH_2Cl_2 (5 mL) and CuI (0.010 g, 0.051 mmol, 10 mol%) was added. This mixture was cooled to –80 °C and treated

with a solution of MeMgBr in diethyl ether (3M 0.7 mL, 2.04 mmol, 4 equiv) in a dropwise fashion. The reaction mixture was allowed to warm to –50 °C within 1.5 h before it was quenched with MeOH (0.2 mL) and saturated NH_4Cl solution (1 mL). The cooling system was removed, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (Et_2O/petroleum ether, 1/50) to afford pure alkene **4-93** (0.205 g, 82%) as a colorless oil. R_f = 0.6 (petroleum ether/diethyl ether, 49:1); $[\alpha]^{20}_D$ = +21.8 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $(CH_3)_2Si$), 0.04 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.83-0.96 (m, 7H, 7-CH_3, 9-CH_3, 8-H), 0.98-1.13 (m, 7H, 8-H, 3-CH_3, C*H*$_3$CH$_2$), 1.17-1.29 (m, 1H, 6-H), 1.35-1.46 (m, 2H, 6-H, 7-H), 1.52-1.62 (m, 1H, 4-H), 1.63-1.77 (m, 2H, 4-H, 9-H), 1.94-2.06 (m, 2H, C*H*$_2$CH$_3$), 2.09-2.21 (m, 1H, 3-H), 3.27 (dd, *J* = 7.1, 9.8 Hz, 1H, 10-H), 3.46 (dd, *J* = 5.3, 9.8 Hz, 1H, 10-H), 3.68-3.78 (m, 1H, 5-H), 4.66-4.77 (m, 2H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($(CH_3)_2Si$), –4.3 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 12.4 (*C*H$_3$CH$_2$), 17.4 (9-CH_3), 18.1 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.0 (3-CH_3), 20.5 (7-CH_3), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.3 (C-7), 26.4 (*C*H$_2$CH$_3$), 33.1 (C-3), 36.8 (C-9), 42.0 (C-8), 44.5 (C-4), 44.6 (C-6), 68.5 (C-10), 68.9 (C-5), 106.3 (C-1), 156.4 (C-2); HRMS (ESI): calcd for $C_{27}H_{58}O_2Si_2$ $[M+Na]^+$ 493.38675, found 493.38692.

(2*R*,4*S*,6*R*,8*R*)-6-{(*tert*-Butyldimethylsilyl)oxy}-2,4,8-trimethyl-9-methyleneundecan-1-ol (4-94)

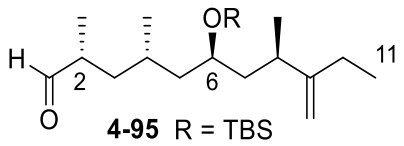


4-94 R = TBS

To a stirred solution of disilyl ether **4-93** (0.190 g, 0.403 mmol) in MeOH/CH_2Cl_2 (5:1, 6 mL) at –10 °C was added *p*TsOH·H_2O (0.010 g, 0.05 mmol, 0.13 equiv). The temperature was maintained between –10 °C and 0 °C throughout the reaction which was stirred for 4 h. Solid $NaHCO_3$ (10 mg) was added and most of the solvent was removed in vacuo. This solid was re-dissolved in ethyl acetate (5 mL) and the solution was washed with water (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alcohol **4-94** (0.100 g, 70%) as colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{21}_D$ = +33.7 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.88-0.92 (m, 6H, 2-CH_3, 11-H), 0.93-0.98 (m, 1H, 3-H), 0.98-1.05 (m, 6H, 4-CH_3, 8-CH_3), 1.06-1.15 (m, 1H, 3-H), 1.98-1.30 (m, 2H, 5-H), 1.34-1.45 (m, 1H, 7-H), 1.51-1.60 (m, 1H, 4-H), 1.65-1.78 (m, 2H, 2-H), 1.95-2.02 (m, 2H, 10-H), 2.09-2.19 (m, 1H, 8-H), 3.36 (dd, *J* = 6.8, 10.6 Hz, 1H, 1-H), 3.49 (dd, *J* = 5.3, 10.6 Hz, 1H, 1-H), 3.67-3.77 (m, 1H, 6-H), 4.66-4.77 (m, 2H, C=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 12.4 (C-11), 17.4 (2-CH_3), 18.1 ($(CH_3)_2CSi$), 20.0 (8-CH_3), 20.4 (4-CH_3), 25.9 ($(CH_3)_3CSi$), 26.2 (C-4), 26.4 (C-10), 33.0 (C-8), 36.8 (C-2), 41.8 (C-3), 44.3 (C-7), 44.6 (C-5), 68.5 (C-1), 68.9

(C-6), 106.3 (9-CCH_2), 156.4 (C-9); HRMS (ESI): calcd for $C_{21}H_{44}O_2Si$ $[M+Na]^+$ 379.30028, found 379.30052.

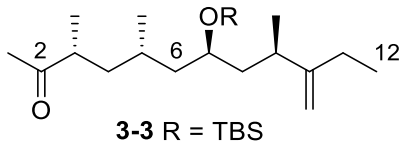
(2*R*,4*S*,6*R*,8*R*)-6-{(*tert*-Butyldimethylsilyl)oxy}-2,4,8-trimethyl-9-methyleneundecanal (4-95)



4-95 R = TBS

To a solution of oxalyl chloride (0.036 mL, 0.42 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) at –80 °C was added DMSO (0.060 mL, 0.84 mmol, 3.0 equiv) in a dropwise fashion. The resulting mixture was stirred 15 min at this temperature. Then alcohol **4-94** (0.100 g, 0.28 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise within 15 min. After stirring the mixture for 1 h, Et_3N (0.242 mL, 1.68 mmol, 6 equiv) was added slowly before the reaction mixture was allowed to warm to room temperature. Subsequently, water (1 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give aldehyde **4-95** (0.098 g, 98%) as colorless oil. R_f = 0.6 (petroleum ether/ethyl acetate, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.86-0.94 (m, 3H, 11-CH_3), 0.97-1.09 (m, 9H, 2-CH_3, 4-CH_3, 8-CH_3), 1.12-1.22 (m, 2H, 5-H), 1.32-1.45 (m, 2H, 4-H, 5-H), 1.51-1.77 (m, 4H, 3-H, 7-H),1.91-2.06 (m, 2H, 10-H), 2.08-2.20 (m, 1H, 8-H), 2.26-2.49 (m, 1H, 2-H), 3.36-3.82 (m, 1H, 6-H), 4.68-4.75 (m, 2H, C=CH_2), 9.57 (d, J = 2.3 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 12.4 (C-11), 13.8 (2-CH_3), 18.0 ($(CH_3)_2CSi$), 20.0 (8-CH_3), 20.1 (4-CH_3), 25.9 ($(CH_3)_3CSi$), 26.2 (C-10), 26.5 (C-4), 36.8 (C-8), 38.7 (C-3), 44.0 (C-7), 44.2 (C-2), 44.5 (C-5), 68.7 (C-6), 106.0 (C=*C*H_2), 156.4 (C-9), 205.3 (CHO).

(3*R*,5*S*,7*R*,9*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-3,5,9-trimethyl-10-methylenedodecan-2-one (3-3)



3-3 R = TBS

a) **Addition of MeLi to aldehyde 4-95**: To a solution of aldehyde **4-95** (0.382 g, 1.08 mmol) in THF (8 mL) at –80 °C was added a solution of MeLi·LiBr in diethyl ether (2.2m, 2.45 mL, 5.40 mmol, 5 equiv). The reaction mixture was allowed to warm to room temperature within 15 h. Before quenching with saturated NH_4Cl (2 mL) the reaction mixture was re-cooled to –80 °C, then the mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to the give crude secondary alcohol **4-96** (0.411 g)

as colorless oil. This material was subjected to the subsequent oxidation without further purification. HRMS (ESI): calcd for $C_{22}H_{46}O_2Si$ $[M+Na]^+$ 393.31565, found 393.31607.

b) **Oxidation to ketone 3-3**: To a solution of oxalyl chloride (0.260 mL, 3.0 mmol, 2.78 equiv) in CH_2Cl_2 (10 mL) at –80 °C was added DMSO (0.430 mL, 6.0 mmol, 5.5 equiv) dropwise. The resulting mixture was stirred for 15 min at this temperature before the foregoing alcohol **4-96** (0.411 g) in CH_2Cl_2 (2.5 mL) was added dropwise within 15 min. After stirring of the mixture for 1 h at –80 °C, Et_3N (1.73 mL, 12.0 mmol) was added slowly. Thereafter, the reaction mixture was allowed to warm to room temperature, water (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give methyl ketone **3-3** (0.336 g, 84%, 2 steps) as colorless oil. R_f = 0.6 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{21}_D$ = +30.6 (c = 1.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.87-0.94 (m, 3H, 12-H), 0.97-1.08 (m, 9H, 3-CH_3, 5-CH_3, 9-CH_3), 1.10-1.19 (m, 2H, 6-H), 1.31-1.45 (m, 2H, 5-H, 4-H), 1.51-1.71 (m, 3H, 8-H, 4-H), 1.94-2.04 (m, 2H, 11-H), 2.11 (s, 3H, 1-H), 2.12-2.18 (m, 1H, 9-H), 2.54-2.66 (m, 1H, 3-H), 3.66-3.77 (m, 1H, 7-H), 4.67-4.75 (m, 2H, 10-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3 $(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 12.4 (C-12), 16.7 (3-CH_3), 18.0 ($(CH_3)_2CSi$), 19.9 (9-CH_3), 20.0 (5-CH_3), 25.9 ($(CH_3)_3CSi$), 26.3 (C-11), 26.8 (C-5), 27.7 (C-9), 36.8 (C-1), 41.1 (C-4), 44.4 (C-8), 44.5 (C-6), 44.8 (C-3), 68.7 (C-7), 106.0 (10-CH_2), 156.4 (C-10), 212.9 (C-2); HRMS (ESI): calcd for $C_{22}H_{44}O_2Si$ $[M+Na]^+$ 391.30028, found 391.30024.

The aldol reaction

The aldol reaction between methyl ketone **3-3** and aldehyde **3-2** was carried out using the following reaction conditions:

Enolate generation with trichloroisopropoxytitanium(IV) [$TiCl_3$(O*i*Pr)]: To solution of $TiCl_4$ (0.006 mL, 0.06 mmol, 0.82 equiv) in CH_2Cl_2 (0.02 mL) was added Ti(O*i*Pr)$_4$] (0.006 mL, 0.02 mmol, 0.27 equiv) at 0 °C. The solution turned to white and was stirred at 0 °C for 15 min and at room temperature for 10 min to complete the metathesis. Then it was diluted with CH_2Cl_2 (0.02 mL), resulting in a colorless solution. This colorless solution was added dropwise to a cooled solution of methyl ketone **3-3** (0.030 g, 0.07 mmol) and *i*Pr_2NEt (0.015 mL, 0.08 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) at –78 °C. The resulting dark red solution was stirred for 30 min at –78 °C. Then neat aldehyde **3-2** (0.022 g, 0.18 mmol, 2.6 equiv) was added dropwise and stirring was continued for 30 min at this temperature. The reaction was quenched with saturated NH_4Cl solution (1 mL), allowed to warm to room temperature and diluted with Et_2O (10 mL) before the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution (3 mL), saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give the hydroxy ketone **4-121** (5 mg, 14%, dr 1:1) as colorless oil.

Enolate generation with lithium diisopropylamide (LDA): To a solution of diisopropylamine (0.014 mL, 0.10 mmol, 2.5 equiv) in THF (0.5 mL) was added *n*BuLi (1.6M in hexanes, 0.05 mL, 0.08 mmol, 2 equiv) at –78 °C. The solution was stirred for 15 min at 0 °C and then cooled again to –78 °C. Next, a solution of methyl ketone **3-3** (0.015 g, 0.04 mmol) in THF (0.5 mL) was added to the LDA solution and the mixture stirred for 3 h at –78 °C before neat aldehyde **3-2** (0.010 g, 0.08 mmol, 2.0 equiv) was added to the enolate solution. The reaction was left to stir overnight at –78 °C. The temperature was allowed to rise to 0 °C and then the reaction was quenched with saturated aqueous NH_4Cl solution (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 3mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give hydroxyl ketone **4-121** (5 mg, 24%, dr 1:1) as colorless oil.

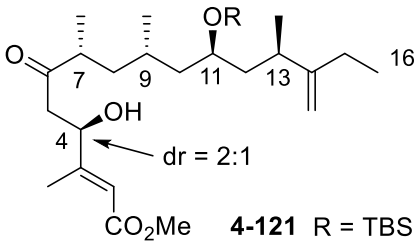
Enolate generation with dicyclohexylboron trifluoromethanesulfonate (Cy_2BOTf): To a cooled solution of methyl ketone **3-3** (0.020 g, 0.054 mmol) and Et_3N (0.034 mL, 0.235 mmol, 4.3 equiv) at –78 °C was added a pre-cooled (–78 °C) solution of *c*Hex_2BOTf {0.062 g, 0.19 mmol, 3.5 equiv, dissolved in hexane (0.020 mL) and diluted with CH_2Cl_2 (0.040 mL)} dropwise. After 3 h of stirring at –78 °C, neat aldehyde **3-2** (0.025 g, 0.19 mmol, 2 equiv) was added and the reaction mixture was stirred overnight, while it was allowed to warm to 0 °C. For work-up phosphate buffer (pH 7, 1 mL) and 30% H_2O_2 (1 mL) were added and stirring was continued for the next 2 h. The reaction mixture was diluted with water (1 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 mL), saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give unreacted ketone **3-3** (0.010 g, 0.027 mmol) and the product **4-121** (0.010 g, 71%, dr 1:1) as colorless oils.

Enolate generation with diisopinocampheylboron triflate (–)-$(Ipc)_2BOTf$: To a suspension of (–)-$(Ipc)_2BH$ (0.500 g, 1.75 mmol) in hexane (0.5 mL) at 0 °C was added trifluoromethanesulfonic acid (0.154 mL, 1.75 mmol) dropwise. The resulting two phase mixture was stirred at room temperature until completion of the reaction (about 1 h). The upper colorless hexane solution was used for the aldol reaction assuming 60% conversion (0.6 mL of 1.7M solution of the triflate).

To a cooled solution of methyl ketone **3-3** (0.030 g, 0.07 mmol) and *i*Pr_2NEt (0.04 mL, 0.21 mmol, 2.4 equiv) in CH_2Cl_2 (0.5 mL) at –78 °C was added a pre-cooled (–78 °C) solution of the above (–)-$(Ipc)_2BOTf$ (1.7M in hexane, 0.1 mL, 0.17 mmol) dropwise. After stirring of the mixture at –78 °C to –50 °C for 4 h, neat aldehyde **3-2** (0.022 g, 0.18 mmol, 2.6 equiv) was added at –78 °C and the reaction mixture was stirred overnight, allowing it to warm to 0 °C. Thereafter, phosphate buffer (pH 7, 1 mL) and 30% H_2O_2 (1 mL) were added, and stirring was continued for the next 2 h. The reaction mixture was diluted with water (1 mL), and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 mL), saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl

acetate/petroleum ether, 1:9) to give unreacted ketone **3-3** (0.010 g, 0.027 mmol) and the aldol product **4-121** (0.025 g, 89%, dr 2:1) as a colorless oil.

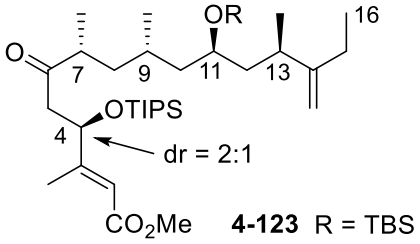
(7*R*,9*S*,11*R*,13*R*,*E*)-Methyl 11-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3,7,9,13-tetramethyl-14-methylene-6-oxohexadec-2-enoate (4-121)



4-121 R = TBS

R_f = 0.5 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.81-0.90 (m, 3H, 9-CH_3), 0.97-1.16 (m, 10H, 7-CH_3, 13-CH_3, 16-H, 8-H), 1.28-1.47 (m, 2H, 8-H, 10-H), 1.49-1.68 (m, 4H, 9-H, 10-H, 12-H), 1.91-2.04 (m, 2H, 15-H), 2.11 (s, 3H, 3-CH_3), 2.11-2.19 (m, 2H, 13-H), 2.52-2.68 (m, 2H, 5-H), 2.68-2.78 (m, 1H, 7-H), 3.70-3.76 (m, 1H, 11-H), 3.69 (s, 3H, OMe), 4.46-4.56 (m, 1H, 4-H), 4.68-4.76 (m, 2H, 14-CH_2), 6.02 (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3 ($(CH_3)_2Si$), –4.0 ($(CH_3)_2Si$), 12.4 (C-16), 15.4 (3-CH_3), 16.5, 18.0 ($(CH_3)_2CSi$), 20.0, 25.9 ($(CH_3)_3CSi$), 26.3, 26.7, 36.8, 40.8, 44.2, 44.5, 44.6, 44.7, 45.59, 45.3 (C-5, C-7), 51.0 (OMe), 68.4 (C-11), 71.7 (C-4), 106.4 (14-CH_2), 115.0 (C-2), 156.3 (C-14), 157.9 (C-3), 167.2 (CO_2Me), 215.0 (C-6); HRMS (ESI): calcd for $C_{31}H_{58}O_5Si$ $[M+Na]^+$ 561.39457, found 561.39459.

(7*R*,9*S*,11*R*,13*R*,*E*)-Methyl 11-((*tert*-butyldimethylsilyl)oxy)-3,7,9,13-tetramethyl-14-methylene-6-oxo-4-((triisopropylsilyl)oxy)hexadec-2-enoate (4-123)

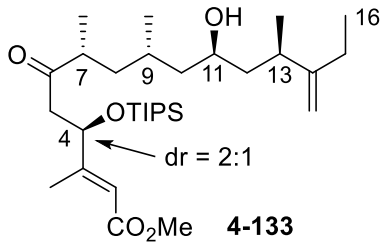


4-123 R = TBS

To a solution of TIPSOTf (0.065 mL, 0.24 mmol, 4 equiv) in CH_2Cl_2 (0.5 mL) at –78 °C was added 2,6-lutidine (0.035 mL, 0.30 mmol, 5 equiv) dropwise followed by the addition of hydroxy ketone **4-121** (0.030 g, 0.06 mmol) in CH_2Cl_2 (0.025 mL). The mixture was stirred for 3 h at –78 °C then warmed to –40 °C and stirred at this temperature for 45 h. Thereafter, water (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with saturated NH_4Cl solution (3 mL), saturated $NaHCO_3$ solution (3 mL), saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:50) to give unreacted alcohol **4-121** (5 mg) and silyl ether **4-123** (30 mg, 92%) as colorless oils. R_f = 0.5 (petroleum ether/ethyl acetate, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.81-0.90 (m, 3H, 9-CH_3), 0.96-1.05

(m, 29H, ((*CH*$_3$)$_2$CH)$_3$Si, 7-CH$_3$, 13-CH$_3$, 16-H, 8-H), 1.06-1.14 (m, 3H, ((CH$_3$)$_2$C*H*)$_3$Si), 1.30-1.45 (m, 2H, 9-H, 10-H), 1.46-1.59 (m, 2H, 10-H, 12-H), 1.60-1.70 (m, 1H, 12-H), 2.00 (q, J = 7.5 Hz, 2H, 15-H), 2.10 (d, J = 1.1 Hz, 3H, 3-CH$_3$), 2.10-2.17 (m, 1H, 13-H), 2.45-2.66 (m, 2H, 5-H, 7-H), 2.68-2.78 (m, 1H, 5-H), 3.67 (s, 3H, OMe), 3.68-3.76 (m, 1H, 11-H), 4.68-4.76 (m, 2H, 14-CH$_2$), 4.77 (t, J = 5.9 Hz, 1H, 4-H), 5.90-5.96 (m, 1H, 2-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = –4.3 ((CH$_3$)$_2$Si), –4.0 ((CH$_3$)$_2$Si), 12.4, 14.5, 15.8, 18.0 ((CH$_3$)$_2$CSi), 20.0, 20.3, 25.9 ((CH$_3$)$_3$CSi), 26.3, 26.7, 36.8, 40.4, 43.9, 44.5, 44.6, 48.1, 48.7 (C-5), 51.0 (OMe), 68.7 (C-11), 73.3 (C-4), 106.4 (14-CH$_2$), 115.4 (C-2), 156.3 (C-14), 160.1 (C-3), 167.2 (C-1), 211.0 (C-6); HRMS (ESI): calcd for C$_{37}$H$_{72}$O$_5$Si$_2$ [M+Na]$^+$ 675.48105, found 675.48158.

(7*R*,9*S*,11*R*,13*R*,*E*)-Methyl 11-hydroxy-3,7,9,13-tetramethyl-14-methylene-6-oxo-4-((triisopropylsilyl)oxy)hexadec-2-enoate (4-133)



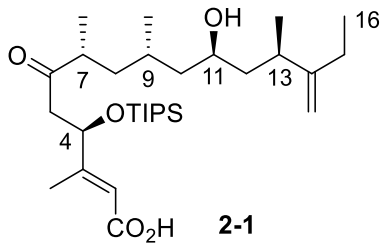
To a solution of silyl ether **4-123** (0.023 g, 0.035 mmol) in CH$_3$OH/CH$_2$Cl$_2$ (0.3 mL, 2:1) was added camphorsulfonic acid (2 mg, 0.007 mmol, 0.2 equiv). After 50 min of stirring at room temperature, Et$_3$N (0.020 mL) was added to the mixture, and then the volatiles solvent were removed in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9, 1:5) to give hydroxy ester **4-133** (15 mg, 79%, 10 mg major isomer, 5 mg minor isomer) as a colorless oil. The chromatographic separation on this stage is possible, but it is more convenient to perform the separation on the stage of the macrolactones **4-133a** and **4-133b** due to larger difference in their retention factors.

Major isomer (4-133a): R$_f$ = 0.5 (petroleum ether/ethyl acetate, 5:1); $[\alpha]^{20}_D$ = +1.8 (c = 0.83, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.87 (d, J = 6.4 Hz, 3H, 9-CH$_3$), 0.96-1.10 (m, 31H, 3 x SiCH(CH$_3$)$_2$, 16-H, 7-CH$_3$, 13-CH$_3$, 8-H), 1.34-1.45 (m, 2H, 12-H, 10-H), 1.46-1.54 (m, 1H, 12-H), 1.60-1.67 (m, 3H, 8-H, 9-H, 10-H), 1.92-2.06 (m, 2H, 15-H), 2.10 (d, J = 1.1 Hz, 3H, 3-CH$_3$), 2.36-2.47 (m, 1H, 13-H), 2.50-2.59 (m, 1H, 7-H), 2.68 (dd, J = 1.8, 5.8 Hz, 2H, 5-H), 3.59-3.74 (m, 1H, 11-H), 3.67 (s, 3H, OMe), 4.73-4.82 (m, 3H, 14-CH$_2$, 4-H), 5.90-5.96 (m, 1H, 2-H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.3 (C-16), 14.4 (3-CH$_3$), 16.4 (7-CH$_3$), 18.0 (SiCH(CH$_3$)$_2$), 20.0 (13-CH$_3$), 20.8 (9-CH$_3$), 25.5 (C-15), 27.3 (C-9), 37.3 (C-13), 40.4 (C-10), 43.8 (C-12), 44.8 (C-7), 48.1 (C-5), 51.0 (OMe), 67.6 (C-11), 73.1 (C-4), 107.3 (14-CH$_2$), 115.4 (C-2), 155.8 (C-14), 160.1 (C-3), 167.2 (C-1), 211.3 (C-6); HRMS (ESI): calcd for C$_{31}$H$_{58}$O$_5$Si [M+Na]$^+$ 561.39457, found 561.39459.

Minor isomer (4-133b): R$_f$ = 0.6 (petroleum ether/ethyl acetate, 5:1); $[\alpha]^{22}_D$ = - 13.8 (c = 0.38, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.84 (d, J = 6.4 Hz, 3H, 9-CH$_3$), 0.97-1.07 (m, 31H, 3 x SiCH(CH$_3$)$_2$, 16-H, 7-CH$_3$, 13-CH$_3$, 8-H), 1.33-1.46 (m, 2H, 12-H, 10-H), 1.47-1.54 (m, 1H, 12-H), 1.56-1.68 (m, 3H, 8-H, 9-H, 10-H), 1.93-2.06 (m, 2H, 15-H), 2.11 (d, J = 1.1 Hz, 3H, 3-CH$_3$), 2.36-2.48 (m, 1H, 13-H), 2.50-2.78 (m, 3H, 7-H, 5-H), 3.59-3.71 (m, 1H, 11-H),

3.68 (s, 3H, OMe), 4.73-4.82 (m, 3H, 14-CH_2, 4-H), 5.89-5.94 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 14.4 (3-CH_3), 16.5 (7-CH_3), 17.7, 18.0 (SiCH(CH_3)$_2$), 20.0 (13-CH_3), 20.8 (9-CH_3), 25.5 (C-15), 27.3 (C-9), 37.2 (C-13), 40.5 (C-10), 43.7 (C-12), 44.8 (C-8), 44.9 (C-7), 48.7 (C-5), 51.0 (OMe), 67.5 (C-11), 73.2 (C-4), 107.3 (14-CH_2), 115.4 (C-2), 155.8 (C-14), 160.1 (C-3), 167.2 (C-1), 211.3 (C-6).

(7*R*,9*S*,11*R*,13*R*,*E*)-11-Hydroxy-3,7,9,13-tetramethyl-14-methylene-6-oxo-4-((triisopropylsilyl)oxy)hexadec-2-enoic acid (2-1)

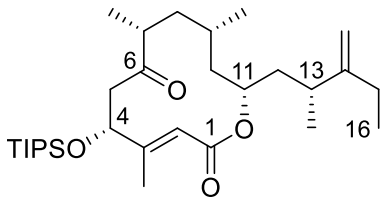


2-1

To a solution of ester **4-133** (0.012 g, 0.022 mmol) in 1,2-dichloroethane (0.4 mL) was added Me_3SnOH (0.017 g, 0.11 mmol, 5 equiv). After stirring for 2 d at 80 °C, the reaction mixture was diluted with $KHSO_4$ solution (1 mL, 5% in water) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 3 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to give seco acid **2-1** (8 mg, 69%) as a colorless oil. R_f = 0.4 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 4.0 Hz, 3H, 9-CH_3), 0.99-1.08 (m, 30H, 3 x SiCH(CH_3)$_2$, 16-H, 7-CH_3, 13-CH_3), 1.25-1.33 (m, 2H, 8-H, 12-H), 1.35-1.46 (m, 2H, 12-H, 10-H), 1.47-1.54 (m, 1H, 10-H), 1.56-1.69 (m, 2H, 8-H, 9-H), 1.93-2.07 (m, 2H, 15-H), 2.11 (s, 3H, 3-CH_3), 2.36-2.47 (m, 1H, 13-H), 2.50-2.60 (m, 1H, 7-H), 2.62-2.76 (m, 2H, 5-H), 3.59-3.71 (m, 1H, 11-H), 4.73-4.84 (m, 3H, 14-CH_2, 4-H), 5.90-5.96 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 14.8 (3-CH_3), 16.5 (7-CH_3), 17.8, 18.0 (SiCH(CH_3)$_2$), 20.0 (13-CH_3), 20.8 (9-CH_3), 25.4 (C-15), 27.3 (C-9), 37.3 (C-13), 40.4 (C-10), 43.7 (C-12), 44.8 (C-7), 48.1 (C-5), 67.6 (C-11), 73.1 (C-4), 107.4 (14-CH_2), 115.4 (C-2), 155.7 (C-14), 162.8 (C-3), 170.8 (C-1), 211.1 (C-6); HRMS (ESI): calcd for $C_{30}H_{56}O_5Si$ $[M+Na]^+$ 547.37892, found 547.37870.

4-*O*-Triisopropylsilyl-amphidinolide Q (2-25 and ***epi*-2-25**): To a solution of hydroxy acid **2-1** (5 mg, 0.009 mmol) in benzene (25 mL) were added Et_3N (0.021 mL, 0.148 mmol, 16 equiv) and 2,4,6-trichlorobenzoyl chloride (TCBC) (0.011 mL, 0.072 μmol, 8 equiv). The reaction mixture was stirred at room temperature for 1.5 h before DMAP (0.017 g, 0.142 mmol) was added and the reaction mixture was stirred overnight. It was diluted with Et_2O (70 mL) and washed with saturated NH_4Cl solution (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude lactone mixture was purified (Et_2O/petroleum ether, 2:50) to give macrolactones **2-25** and ***epi*-2-25** (2 mg, 1 mg, 62%) as colorless oils. The NMR spectra of **2-25** matched with the published one.

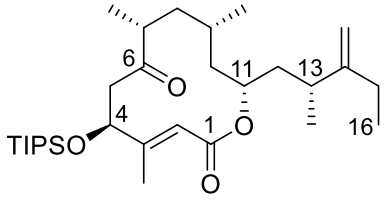
4-(*R*)-*O*-Triisopropylsilyl-amphidinolide Q (2-25)



2-25

R_f = 0.2 (petroleum ether/ethyl acetate, 33:1); $[\alpha]^{21}_D$ = –32.3 (c = 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.6 Hz, 3H, 19-H), 1.00-1.09 (m, 32H, 3 x $SiCH(CH_3)_2$, 16-H, 18-H, 8-H, 9-H), 1.29 (ddd, J = 1.7, 3.2, 18.5 Hz, 1H, 10-H), 1.43 (ddd, J = 7.5, 11.2, 18.5 Hz, 1H, 10-H), 1.50-1.62 (m, 2H, 12-H), 1.90 (dd, J = 2.9, 14.4, 1H, 8-H), 1.94-2.05 (m, 2H, 15-H), 2.06-2.12 (m, 1H, 7-H), 2.14 (d, J = 1.0 Hz, 3H, 17-H), 2.26 (dd, J = 7.1, 14.3 Hz, 1H, 13-H), 2.60 (dd, J = 6.2, 12.6 Hz, 1H, 5-H), 2.79 (dd, J = 3.2, 12.6 Hz, 1H, 5-H), 4.58 (dd, J = 3.1, 6.1 Hz, 1H, 4-H), 4.75-4.79 (m, 2H, 21-H), 4.88-5.00 (m, 1H, 11-H), 6.05 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (C-16), 16.7 (C-17), 18.0 ($SiCH(CH_3)_2$), 18.2 (C-18), 21.1 (C-20), 23.6 (C-19), 26.2 (C-15), 29.7 (C-9), 37.0 (C-13), 39.9 (C-8), 41.3 (C-12), 44.9 (C-10), 46.3 (C-5), 49.6 (C-7), 73.9 (C-4), 75.1 (C-11), 107.1 (C-21), 117.6 (C-2), 155.3 (C-14), 155.9 (C-3), 168.1 (C-1), 211.5 (C-6); HRMS (ESI): calcd for $C_{30}H_{54}O_4Si$ $[M+Na]^+$ 529.36836, found 529.36842.

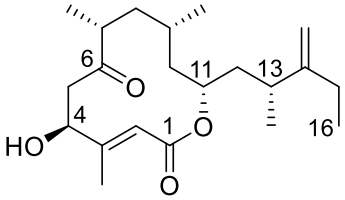
4-(*S*)-O-Triisopropylsilyl-amphidinolide Q (*epi*-2-25)



(*epi*)-**2-25**

R_f = 0.3 (petroleum ether/ethyl acetate, 33:1); $[\alpha]^{22}_D$ = –78.7 (c = 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.6 Hz, 3H, 19-H), 0.98-1.07 (m, 30H, 3 x $SiCH(CH_3)_2$, 16-H, 18-H), 1.27-1.30 (8-H, 9-H), 1.35-1.49 (m, 2H, 10-H) 1.52-1.58 (m, 2H, 12-H), 1.90-2.11 (m, 4H, 15-H, 8-H, 7-H), 2.18 (d, J = 1.1 Hz, 3H, 17-H), 2.15-2.27 (m, 1H, 13-H), 2.51 (dd, J = 5.0, 11.0 Hz, 1H, 5-H), 2.94 (t, J = 11.0 Hz, 1H, 5-H), 4.50 (dd, J = 4.9, 10.6 Hz, 1H, 4-H), 4.73-4.79 (m, 2H, 21-H), 4.98-5.07 (m, 1H, 11-H), 5.59 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 17.7 (C-17), 17.9 ($SiCH(CH_3)_2$), 18.0 (C-18), 21.1 (C-20), 23.7 (C-19), 26.1 (C-15), 29.7 (C-9), 33.0 (C-13), 37.0 (C-7), 39.9 (C-12), 41.3 (C-10), 44.5 (C-5), 49.5 (C-8), 74.3 (C-4), 76.8 (C-11), 107.1 (C-21), 116.8 (C-2), 155.1 (C-14), 155.8 (C-3), 166.8 (C-1), 213.6 (C-6); HRMS (ESI): calcd for $C_{30}H_{54}O_4Si$ $[M+Na]^+$ 529.36836, found 529.36860.

4-*epimer*-Amphidinolide Q (*epi*-1-14)



(*epi*)-**1-14**

To a solution of silyl ether (*epi*)-**2-25** (2 mg, 4.0 μmol) in THF (1 mL) was added a solution of TBAF (50 μL, 50 μmol) in THF (1.0 M) at –30 °C. After complete addition the color of the reaction mixture became milky. It was allowed to stir at the same temperature for 2 h before it was quenched with aqueous NH_4Cl (1 mL), and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether/ethyl acetate, 5:1) provided *epi*-amphidinolide Q (1.0 mg, 72%) as a colorless oil. R_f = 0.3 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.98-1.11 (m, 14H), 1.37-1.44 (m, 2H), 1.56-1.65 (m, 2H), 1.75 (d, J = 6.3 Hz, 1H), 1.94-2.02 (m, 1H), 2.07-2.14 (m, 2H), 2.15-2.25 (m, 4H), 2.31-2.39 (m, 1H), 2.59-2.65 (m, 1H), 2.92 (t, J = 11.0 Hz, 1H), 4.48-4.53 (m, 1H), 4.74-4.78 (m, 2H), 4.95-5.02 (m, 1H), 5.67 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 12.3, 17.7, 21.1, 23.3, 26.2, 29.7, 32.6, 36.9, 40.3, 41.3, 44.5, 47.7, 49.8, 74.7, 75.6, 107.1, 118.0, 139.1, 155.1, 166.8, 213.7; HRMS (ESI): calcd for $C_{21}H_{34}O_4$ $[M+Na]^+$ 373.23493, found 373.23475.

Table 19: ^{13}C Chemical shift (δ, ppm) comparison of Amphidinolide Q, 4-(*R*)-O-Triisopropylsilyl-amphidinolide Q, reported and synthesized.

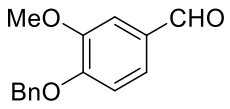
C (No)	Q (δ)	reported (δ)	synthetic (δ)	Δ(δ)
1	169.6	168.05	168.05	0.0
2	117.4	117.54	117.59	+0.05
3	155.4	155.87	155.86	–0.01
4	73.1	73.83	73.86	+0.03
5	44.6	46.26	46.26	+0.04
6	215.1	211.59	211.53	–0. 06
7	50.5	49.61	49.59	–0.02
8	40.3	39.84	39.89	+0. 05
9	33.0	29.69	29.69	0.0
10	45.5	44.86	44.88	+0.02
11	74.3	75.09	75.13	+0.04
12	41.8	41.21	41.26	+0.05
13	37.2	36.94	36.96	+0.02
14	155.5	155.21	155.25	+0.04
15	27.0	26.11	26.15	+0.03
16	12.6	12.09	12.11	+0.02
17	16.6	16.69	16.68	–0.01
18	17.9		18.16	-
19	23.0	23.57	23.55	–0.02
20	21.5	21.07	21.07	0.0
21	107.3	107.05	107.06	+0. 01

Abbreviation: Q = Amphidinolide Q

Preparation of catalyst [Cp*RhCl$_2$]$_2$

To a stirred solution of $RhCl_3$ (0.5 g, 1.95 mmol) in MeOH (12 mL) was added excess pentamethylcyclopentadiene (0.5 mL). The mixture was reflux for 21 h, cooled to room temperature, and filtered through a sintered funnel. The filter cake washed with diethyl ether (2 × 5 mL), and dried under vacuum to give the rhodium catalyst (1.02 g, 85%) as dark brown powder.

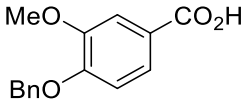
4-(Benzyloxy)-3-methoxybenzaldehyde (9-2)



9-2

To a suspension of vanilin (5.0 g, 32.9 mmol, 1.0 equiv) and K_2CO_3 (11.4 g, 82.2 mmol, 2.5 equiv) in acetone (50 mL), benzyl bromide (4.3 mL, 36.1 mmol, 1.1 equiv) was added and the resulting mixture was refluxed for 10 h. After being cooled to room temperature, the suspension was filtered through a sintered funnel. The filtrate was evaporated to dryness and treated with (50 mL) water and extracted with ethyl actate (3 × 20 mL). The combined organic layers were washed with (20 mL) saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to afford the pure benzyl ether **9-2** (6.66 g, 82%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3H, OMe), 5.25 (s, 2H, OCH_2Ph), 6.98 (d, J = 8.1Hz, 1H, 5-H), 7.30-7.36 (m, 1H, 2-H), 7.36-7.42 (m, 3H, Ar), 7.42-7.48 (m, 3H, Ar), 9.84 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0 (OMe), 70.8 (CH_2Ph), 109.3 (C-2), 112.3 (C-5), 126.5 (Ar), 127.2 (Ar), 128.2 (Ar), 128.7 (Ar), 130.2 (Ar), 136.0 (Ar), 150.0 (Ar), 153.5 (Ar), 190.9 (CHO).

4-(Benzyloxy)-3-methoxybenzoic acid (9-3)

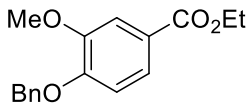


9-3

To a stirred solution of aldehyde **9-2** (2.5 g, 10.33 mmol, 1.0 equiv), $NaH_2PO_4 \cdot 2H_2O$ (0.483 g, 3.10 mmol, 0.3 equiv) and H_2O_2 (60%, 0.31 mL, 10.84 mmol, 1.04 equiv) in MeCN/H_2O (60 mL, 5:1, v/v) was added a solution of $NaClO_2$ (1.64 g, 14.46 mmol, 1.4 eq) in H_2O (15 mL) dropwise while keeping the temperature of the mixture below 10 °C with a water bath. The mixture was stirred at room temperature for 90 min, before solid $Na_2S_2O_3$ (0.254 g, 1.6 mmol) was added followed by stirring of the mixture at room temperature for 5 min to decompose excess H_2O_2. The mixture was diluted with saturated NaCl solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (2 × 20 mL) and with saturated $NaHCO_3$ solution (3 × 20 mL). The organic layers were discarded. The combined aqueous layers were acidified with concentrated HCl until pH4 followed by extraction with EtOAc (3 × 20 mL). These organic extracts were dried over

Na_2SO_4, filtered and concentrated in *vacuo* to give the crude acid (2.55 g, 99%) as white solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3H, OMe), 5.23 (s, 2H, CH_2Ph), 6.92 (d, J = 8.6 Hz, 1H, 5-H), 7.28-7.34 (m, 1H, Ar), 7.35-7.40 (m, 2H, Ar), 7.41-7.46 (m, 2H, Ar), 7.61(d, J = 2.0 Hz, 2-H), 7.70 (dd, J = 2.0, 8.3 Hz, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0 (OMe), 70.7 (CH_2Ph), 112.3 (C-5), 112.7 (C-2), 121.9 (C-6), 124.4 (Ar), 127.2 (Ar), 128.1 (Ar), 128.7 (Ar), 136.2 (Ar), 149.1 (Ar), 152.8 (Ar), 172.0 (CO_2H).

Ethyl 4-(benzyloxy)-3-methoxybenzoate (9-4)



9-4

To the stirred solution of acid **9-3** (0.5 g, 1.94 mmol, 1.0 equiv) and K_2CO_3 (0.655 g, 4.75 mmol, 2.5 equiv) in DMF (10 mL) was added bromoethane (350 µL, 4.75 mmol, 2.5 equiv). The reaction mixture was stirred at room temperature overnight under N_2 atmosphere. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and saturated NaCl solution (20 mL). They were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude ester was purified by flash chromatography (ethyl acetate/petroleum ether, 5:1) to afford pure ester **9-4** (0.508 g, 93%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.92 (s, 3H, OMe), 4.33 (q, J = 7.3, 14.4 Hz, 2H, OCH_2CH_3), 5.20 (s, 2H, CH_2Ph), 6.88 (d, J = 8.3 Hz, 1H, 5-H), 7.26-7.32 (m, 1H, Ar), 7.33-7.38 (m, 2H, Ar), 7.39-7.45 (m, 2H, Ar), 7.56 (d, J = 2.0 Hz, 1H, 2-H), 7.60 (dd, J = 2.0, 8.3 Hz, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 56.0 (OMe), 60.7 (OCH_2CH_3), 70.7 (CH_2Ph), 112.3 (C-5), 123.2 (C-2), 123.2 (Ar), 127.1 (Ar), 128.0 (Ar), 128.6 (Ar), 136.3 (Ar), 149.0 (Ar), 151.9 (Ar), 166.3 (CO_2Et).

Preparation of *O*-pivaloyl hydroxamic acids

(Procedure 1, via hydroxamic acid)

(a) To a stirred solution of ethyl benzoate (1.0 equiv) and hydroxylamine hydrochloride (4.0 equiv) in MeOH (2 mL per mmol of benzoate) was added KOH solution (1M in methanol, 5.0 equiv) in a dropwise fashion. The resulting solution was stirred 48 h at room temperature. Thereafter most of the MeOH was distilled out in vacuo and the solid residue was dissolved in a mixture of acetic acid/water (1/1, 4 mL per mmol of benzoate). The mixture was extracted with EtOAc (3 × 5 mL (per mmol of benzoate)). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude hydroxamic acid which was washed with diethyl ether (5 mL per mmol of benzoate) to afford the pure hydroxamic acid as transparent solid.

(b) To the suspension of hydroxamic acid (1.0 equiv) in CH_2Cl_2 (5 mL per mmol of acid) was added pivalic anhydride (0.8 equiv). The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with saturated $NaHCO_3$ (4 mL per mmol of acid) and extracted with EtOAc (2 × 5 mL (per mmol of acid)). The combined organic layers were

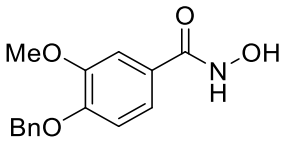
washed with saturated $NaHCO_3$ solution (4 mL per mmol of acid), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography to afford the pure *O*-pivaloyl hydroxamic acid.

Procedure 2 (reaction of acid chloride with *O*-pivaloylhydroxylamine)

To a solution of benzoic acid (1.0 equiv) in dry CH_2Cl_2 (3 mL per mmol of acid) was added $SOCl_2$ (5.0 equiv) at room temperature followed by the addition of a catalytic amount of DMF (4 drops per 10 mmol of acid). The mixture was refluxed for 8 h. After cooling, solvent and excess reagent were removed in *vacuo* to afford the crude acid chloride, which was used in the next step without further purification.

O-Pivaloylhydroxylamine triflate (1.2 equiv) was added to a biphasic mixture of Na_2CO_3 (2.0 equiv) in EtOAc/H_2O (9 mL per mmol of acid chloride, 2:1). To the cooled mixture containing the pivaloylhydroxylamine at 0 °C was added crude acid chloride (1.0 equiv) in EtOAc (1 mL per mmol of acid chloride) dropwise. The reaction mixture was allowed to reach room temperature within 5 h. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL (per mmol of acid chloride)). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to provide. The crude product was purified by flash chromatography to afford pure *O*-pivaloyl hydroxamic acid.

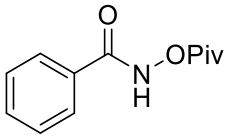
4-(Benzyloxy)-N-hydroxy-3-methoxybenzamide (9-5)



9-5

Prepared from benzoic acid **9-3** (300 mg, 1.05 mmol) according to procedure 1 (a). The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:2) to give hydroxamic acid **9-5** (280 mg, 95%) as colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.78 (s, 3H, OMe), 5.11 (s, 2H, CH_2Ph), 7.1 (d, J = 8.3 Hz, 1H, Ar), 7.28-7.47 (m, 7H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.8 (OMe), 70.0 (CH_2Ph), 110.6 (C-5), 112.8 (C-2), 120.1 (C-6), 125.4 (Ar), 128.14 (Ar), 128.3 (Ar), 128.7 (Ar), 136.9 (Ar), 148.8 (Ar), 150.3 (Ar), 164.2 (CONHOH); HRMS (ESI): calcd for $C_{15}H_{15}NO_4$ $[M+Na]^+$ 296.08933, found 296.08989.

***N*-(Pivaloyloxy)benzamide (8-1)**

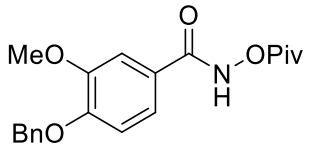


8-1

Prepared from the corresponding *N*-hydroxybenzamide (850 mg, 6.20 mmol) according to procedure 1 (b). The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give pure *N*-(pivaloyloxy)benzamide **8-1** (1.260 g, 92%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H, OPiv), 7.39-7.46 (m, 2H, Ar),

7.50-7.57 (m, 1H, Ar), 7.76-7.82 (m, 2H, Ar), 9.48 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0 (OPiv), 38.4 (*t*Bu), 127.4 (Ar), 128.8 (Ar), 130.8 (Ar), 132.6 (Ar), 166.7 (CONH), 177.0 (*t*Bu*C*O$_2$).

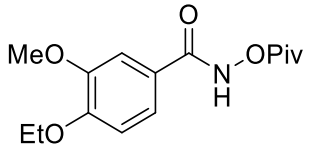
4-(Benzyloxy)-3-methoxy-N-(pivaloyloxy)benzamide (9-6)



9-6

Prepared from *N*-hydroxybenzamide **9-5** (250 mg, 0.91 mmol) according to procedure 1 (b). The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give pure *N*-(pivaloyloxy)benzamide **9-6** (240 mg, 75%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, OPiv), 3.91 (s, 3H, OMe), 5.21 (s, 2H, CH_2Ph), 6.87 (d, J = 8.6 Hz, 1H, 5-H), 7.28-7.47 (m, 7H, Ar), 9.24 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0 (OPiv), 38.4 (*t*Bu), 56.1 (OMe), 70.84 (CH_2Ph), 111.0 (C-5), 112.7 (C-2), 120.3 (C-6), 123.5 (Ar), 127.2 (Ar), 128.1 (Ar), 128.7 (Ar), 136.2 (Ar), 149.7 (Ar), 151.9 (Ar), 177.3 (CONH), 177.7 (*t*Bu*C*O$_2$); HRMS (ESI): calcd for $C_{20}H_{23}NO_5$ $[M+Na]^+$ 380.14684, found 380.14715.

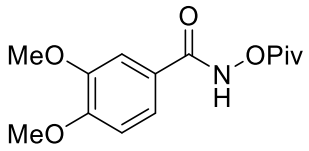
4-Ethoxy-3-methoxy-*N*-(pivaloyloxy)benzamide (9-18)



9-18

Prepared from the corresponding benzoic acid (1.00 g, 5.09 mmol) according to procedure 2. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give pure *N*-(pivaloyloxy)benzamide **9-18** (1.5 g, 98%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H, OPiv), 1.41 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.79 (s, 3H, OMe), 4.05 (q, J = 7.1 Hz, OCH_2CH_3), 6.71-6.77 (m, 1H, Ar), 7.29-7.35 (m, 2H, Ar), 9.79 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (OCH_2CH_3), 26.9 (OPiv), 38.3 (*t*Bu), 55.7 (OMe), 64.2 (OCH_2CH_3), 110.5 (Ar), 111.17 (Ar), 120.5 (Ar), 122.7 (Ar), 148.9 (Ar), 151.8 (Ar), 166.5 (CONH), 177.0 (*t*Bu*C*O$_2$); HRMS (ESI): calcd for $C_{15}H_{21}NO_5$ $[M+Na]^+$ 318.13119, found 318.13121.

3,4-(Dimethoxy)-*N*-(pivaloyloxy)benzamide (8-6)

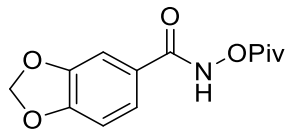


8-6

Prepared either from the corresponding *N*-hydroxybenzamide (3.00 g, 15.2 mmol, procedure 1) or the benzoic acid (3.0 g, 14.48 mmol, procedure 2). The crude product was purified by flash

chromatography (ethyl acetate/petroleum ether, 1:3) to give pure *N*-(pivaloyloxy)benzamide **8-6** (3.70 g, 86%, procedure 1; 3.70 g, 80%, procedure 2) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H, OPiv), 3.75 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.65-6.73 (m, 1H, 5-H), 7.26-7.36 (m, 2H, 2-H, 3-H), 9.65 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (OPiv), 38.2 (*t*Bu), 55.6 (OMe), 55.7 (OMe), 110.1 (Ar), 110.2 (Ar), 120.5 (Ar), 122.9 (Ar), 148.6 (Ar), 152.2 (Ar), 166.3 (CONH), 176.9 (*t*Bu*C*O$_2$); HRMS (ESI): calcd for $C_{14}H_{19}NO_5$ $[M+Na]^+$ 304.11554, found 304.11566.

***N*-(pivaloyloxy) benzo[*d*][1,3]dioxole-5-carboxamide (9-19)**



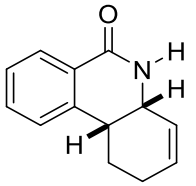
9-19

Prepared from the corresponding benzoyl chloride (500 mg, 2.71 mmol) according to procedure 2. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to give pure *N*-(pivaloyloxy)benzamide **9-19** (650 mg, 90%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H, OPiv), 5.99 (s, 2H, OCH_2O), 6.76 (d, J = 8.3 Hz, 5-H), 7.21 (d, J = 2.0 Hz, 2-H), 7.22 (dd, J = 8.3, 2.0 Hz, 1H, 6-H), 9.58 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9 (OPiv), 38.5 (*t*Bu), 101.8 (OCH_2O), 107.8 (C-5), 108.1 (C-2), 122.6 (C-6), 124.6 (Ar), 147.9 (Ar), 151.2 (Ar), 166.2 (CONH), 177.1 (*t*Bu*C*O$_2$); HRMS (ESI): calcd for $C_{13}H_{15}NO_5$ $[M+Na]^+$ 288.08424, found 288.08450.

Rhodium catalyzed annulation (Procedure 3)

An oven dried, cooled Schlenk tube under N_2, was charged with *N*-(pivaloyloxy)benzamide (1.0 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol%), CsOAc (50 mol%) and dry EtOH (1 mL per mmol of amide). The mixture was cooled to 0 °C, whereupon 1,3-cyclohexadiene (1.3 equiv) was added in one shot. The screw cap was closed tightly under positive pressure of N_2 followed by stirring of the reaction mixture at room temperature for 35 h (TLC control). The mixture was concentrated in vacuo and the residue purified by flash chromatography to afford the pure annulation product.

1,4a,5,10b-Tetrahydrophenanthridin-6(2*H*)-one (8-3)

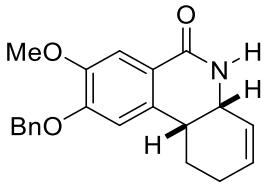


8-3

Prepared from *N*-(pivaloyloxy)benzamide **8-1** (100 mg, 0.45 mmol) according to procedure 3. TLC showed consumption of starting material after 19 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to give pure phenanthridinone **8-3** (74 mg, 82%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.73 (m, 1H, 1-H), 1.88-2.05 (m, 1H, 2-H), 2.10-2.28 (m, 2H, 1-H, 2-H), 2.92 (td, J = 3.8, 12.2 Hz, 1H, 10b-H), 4.22-

4.30 (m, 1H, 4a-H), 5.79 (ddt, *J* = 2.1, 4.5, 9.3 Hz, 1H, 4-H), 5.94-6.06 (m, 1H, 3-H), 6.26 (s, br, 1H, NH), 6.23 (d, *J* = 7.5 Hz, 1H, Ar), 7.33 (td, *J* = 1.1, 7.6 Hz, 1H, Ar), 7.46 (td, *J* = 1.3, 7.5 Hz, 1H, Ar), 8.06 (dd, *J* = 1.2, 7.8 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (C-2), 25.1 (C-1), 37.7 (C-10b), 47.9 (C-4a), 124.4 (Ar), 127.0 (Ar), 127.2 (Ar), 127.5 (Ar), 127.9 (Ar) 132.2 (C-4), 132.5 (C-3), 142.7 (Ar), 165.4 (CONH); HRMS (ESI): calcd for $C_{13}H_{13}NO$ $[M+Na]^+$ 222.08893, found 222.08894.

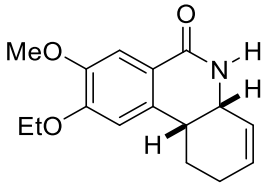
9-(Benzyloxy)-8-methoxy-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one (9-15)



9-15

Prepared from *N*-(pivaloyloxy)benzamide **9-6** (50 mg, 0.14 mmol) according to procedure 3. TLC showed consumption of starting material after 39 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to give pure phenanthridinone **9-15** (26 mg, 55%) as slightly yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54-1.65 (m, 1H, 1-H), 1.82-1.97 (m, 1H, 1-H), 2.06-2.26 (m, 2H, 1-H), 2.78 (td, *J* = 3.3, 12.1 Hz, 1H, 10a-H), 3.92 (s, 3H, OMe), 4.21 (m, 1H, 4a-H), 5.20 (OCH_2Ph), 5.57 (s, br, NH), 5.68-5.78 (m, 1H, 4-H), 5.94-6.05 (m, 1H, 3-H), 6.70 (s, 1H, 10-H), 7.28-7.34 (m, 1H, Ar), 7.34-7.41 (m, 2H, Ar), 7.41-7.48 (m, 2H, Ar), 7.58 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (C-2), 25.0 (C-1), 37.4 (C-10b), 48.2 (C-4a), 56.1 (OMe), 70.9 (OCH_2Ph), 110.4 (C-7), 111.6 (C-10), 120.4 (Ar), 124.4, 127.2, 128.0, 128.6, 132.2, 136.2, 136.4, 148.6 (Ar), 151.6 (Ar), 164.9 (CONH); HRMS (ESI): calcd for $C_{21}H_{21}O_3$ $[M+H]^+$ 336.159420, found 336.159327.

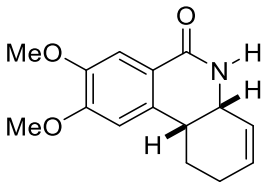
9-Ethoxy-8-methoxy-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one (9-20)



9-20

Prepared from *N*-(pivaloyloxy)benzamide **9-18** (100 mg, 0.34 mmol) according to procedure 3. TLC showed consumption of starting material after 20 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 2:1) to give pure phenanthridinone **9-20** (75 mg, 81%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 6.8 Hz, 3H, OCH_2CH_3), 1.58-1.68 (m, 1H, 1-H), 1.82-1.95 (m, 1H, 1-H), 2.11-2.21 (m, 2H, 2-H), 2.78 (td, *J* = 3.3, 12.4 Hz, 1H, 10a-H), 3.87 (s, 3H, OMe), 4.11 (q, *J* = 6.8 Hz, 2H, OCH_2CH_3), 4.18-4.23 (m, 1H, 4a-H), 5.72-5.80 (m, 1H, 4-H), 5.93-6.01 (m, 1H, 3-H), 6.40 (s, 1H, NH), 6.65 (s, 1H, 10-H), 7.51 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (OCH_2CH_3), 24.9 (C-2), 25.1 (C-1), 37.4 (C-10b), 48.1 (C-4a), 56.0 (OMe), 64.3 (OCH_2CH_3), 110.0 (C-7), 110.2 (C-10), 119.6 (Ar), 124.3 (C-4), 132.0 (Ar), 136.5 (C-3), 148.1 (Ar), 151.9 (Ar), 165.4 (CONH).

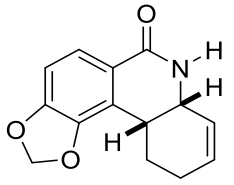
8,9-Dimethoxy-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one (9-21)



9-21

Prepared from *N*-(pivaloyloxy)benzamide **8-6** (500 mg, 1.78 mmol) according to procedure 3. TLC showed consumption of starting material after 55 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 4:1) to give pure phenanthridinone **9-21** (325 mg, 70%) as slightly brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61-1.71 (m, 1H, 1-H), 1.84-1.99 (m, 1H, 1-H), 2.15-2.24 (m, 2H, 2-H), 2.82 (td, J = 4.0, 12.4 Hz, 1H, 10b-H), 3.91 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.23 (t, J = 4.0 Hz, 1H, 4a-H), 5.72-5.84 (m, 2H, 4-H, NH), 5.97-6.05 (m, 1H, 3-H), 6.67 (s, 1H, 10-H), 7.51 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (C-2), 25.2 (C-1), 37.7 (C-10b), 48.2 (C-4a), 56.0 (OMe), 56.1 (OMe), 109.3 (C-7), 109.9 (C-10), 120.0 (Ar), 124.4 (C-4), 132.2 (Ar), 136.6 (C-3), 148.0 (Ar), 152.5 (Ar), 164.9 (CONH); HRMS (ESI): calcd for $C_{15}H_{17}NO_3$ $[M+Na]^+$ 282.11006, found 282.11030.

7a,8,9,11a-Tetrahydro-[*1,3*]dioxolo[*4,5-k*]phenanthridin-6(7*H*)-one (9-22)



9-22

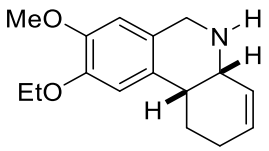
Prepared from *N*-(pivaloyloxy)benzamide **9-19** (500 mg, 2.00 mmol) according to procedure 3. TLC showed consumption of starting material after 35 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 4:1) to give pure phenanthridinone **9-22** (435 mg, 89%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69-1.78 (m, 1H, 11-H), 1.80-1.97 (m, 1H, 11-H), 2.14-2.26 (m, 2H, 10-H_2), 2.98-3.12 (m, 1H, 11a-H), 4.14-4.26 (m, 1H, 7a-H), 5.68-5.85 (m, 2H, 8-H, NH), 6.00-6.11 (m, 1H, 9-H), 6.02 (d, J = 1.3 Hz, 2-H), 6.79 (d, J = 1.3 Hz, 2-H), 6.79 (d, J = 8.2 Hz, 1H, 4-H), 7.68 (d, J = 8.3 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (C-10), 25.2 (C-11), 32.4 (C-11a), 47.6 (C-7a), 101.9 (C-2), 107.1 (C-4), 121.7 (Ar), 123.4 (C-5), 123.9 (Ar), 124.0 (C-8), 132.6 (C-9), 143.9 (Ar), 150.6 (Ar), 164.6 (CONH); HRMS (ESI): calcd for $C_{14}H_{13}NO_3$ $[M+Na]^+$ 266.07876, found 266.07918.

Reduction of the tetrahydrophenanthridinones to hexahydrophenanthridines (Procedure 4)

To a cooled (0 °C) solution of $AlCl_3$ (1 equiv) in THF (10 mL per mmol $AlCl_3$) under N_2 was added $LiAlH_4$ (3 equiv). The mixture was allowed to stir at room temperature for 1 h, before it was added dropwise via cannula to a separately stirred solution of the amide (1 equiv) in THF (20 mL per mmol of amide). The reaction mixture was allowed to reach room temperature

within 1 h. Then the flask was moved to a preheated oil bath (40 °C) and the mixture stirred for 8 h. Thereafter, the reaction mixture was cooled to 0 °C and quenched with saturated NH_4Cl solution (10 mL per mmol of $AlCl_3$). The organic layer was separated and the aqueous semisolid washed with diethyl ether (10 mL per mmol of amide). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was dissolved in diethyl ether (10 mL per mmol of amide) and cooled to 0 °C, and then ethereal HCl (3m, 0.5 mL per mmol of amide) was added dropwise. The white solid amine salt which precipitated was collected by filtration through a G4 frit. It was found to be of sufficient purity.

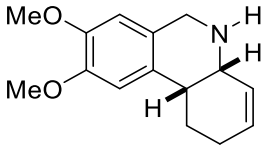
9-Ethoxy-8-methoxy-1,2,4a,5,6,10b-hexahydrophenanthridin-5-iumchloride (9-23)



9-23

Prepared from tetrahydrophenanthridinone **9-20** (127 mg, 0.46 mmol) according to procedure 4 to give pure hydrochloride **9-23** (115 mg, 80%) as colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.40 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.79-1.91 (m, 1H, 1-H), 2.04-2.12 (m, 1H, 1-H), 2.16-2.35 (m, 2H, 2-H), 3.16 (dt, J = 4.3, 12.1 Hz, 1H, 10b-H), 3.82 (s, 3H, OMe), 4.06 (q, J = 7.1 Hz, 3H, OCH_2CH_3, 4a-H), 4.28 (dd, J = 11.4, 15.4 Hz, 2H, 6-H), 5.86-5.93 (m, 1H, 4-H), 6.28-6.34 (m, 1H, 3-H), 6.79 (s, 1H, 10-H), 6.93 (s, 1H, 7-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 15.2 (OCH_2CH_3), 25.8 (C-2), 27.8 (C-1), 35.5 (C-10b), 45.2 (C-6), 52.2 (C-4a), 56.7 (OMe), 65.8 (OCH_2CH_3), 110.7 (C-7), 114.2 (C-10), 120.5 (Ar), 122.0 (C-4), 129.2 (Ar), 138.2 (C-3), 150.2 (Ar), 150.3 (Ar); HRMS (ESI): calcd for $C_{16}H_{22}ClNO_2$ $[M]^+$ 260.164505, found 260.164354.

8,9-Dimethoxy-1,2,4a,5,6,10b-hexahydrophenanthridin-5-iumchloride (9-24)



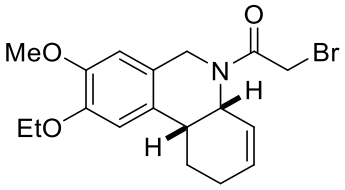
9-24

Prepared from tetrahydrophenanthridinone **9-21** (500 mg, 1.90 mmol) according to procedure 4 to give pure hydrochloride **9-24** (425 mg, 75%) as colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.77-1.93 (m, 1H, 1-H), 2.04-2.17 (m, 1H, 1-H), 2.18-2.37 (m, 2H, 2-H), 3.18 (dt, J = 4.0, 12.0 Hz, 1H, 10b-H), 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.02-4.10 (m, 1H, 4a-H), 4.29 (dd, J = 14.4, 15.7 Hz, 2H, 6-H), 5.84-5.91 (m, 1H, 4-H), 6.28-6.37 (m, 1H, 3-H), 6.78 (s, 1H, 10-H), 6.95 (s, 1H, 7-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 25.8 (C-2), 27.8 (C-1), 35.6 (C-10b), 45.2 (C-6), 52.3 (C-4a), 56.6 (OMe), 56.7 (OMe), 110.5 (C-7), 112.9 (C-10), 120.5 (Ar), 121.9 (C-4), 129.3 (Ar), 138.3 (C-3), 150.2 (Ar), 151.0 (Ar); HRMS (ESI): calcd for $C_{15}H_{20}ClNO_2$ $[M+Na]^+$ 246.14886, found 246.14873.

Preparation of α-haloamides from amine hydrochlorides (Procedure 5)

To a stirred solution of the amine·HCl (1 equiv) and trimethylamine (2 equiv) in THF (3 mL per mmol of salt) at 0 °C was added 2-bromoacetyl bromide (2 equiv). The stirred reaction mixture was allowed to reach room temperature within 1 h. For work-up the mixture was diluted with saturated $NaHCO_3$ solution (20 mL per mmol of salt) and extracted with Et_2O (3 × 15 mL (per mmol of salt). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude amide was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to provide pure product.

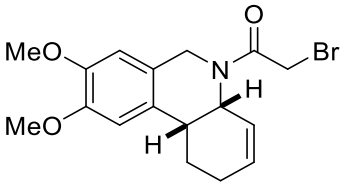
2-Bromo-1-(9-ethoxy-8-methoxy-2,4a,6,10b-tetrahydrophenanthridin-5(1*H*)-yl)ethan-1-one (9-25)



9-25

Prepared from amine hydrochloride **9-23** (50 mg, 0.16 mmol) according to procedure 5 to give pure bromoacetylamide **9-25** (67 mg, 99%) as brown solid. R_f = 0.5 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 1.43 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.68-1.93 (m, 2H, 1-H, 2-H), 1.93-2.09 (m, 1H, 1-H), 2.21-2.43 (m, 1H, 2-H), 3.16-3.43 (m, 1H, 10b-H), 3.81 (s, 3H, OMe), 4.00-4.23 (m, 5H, OCH_2CH_3, CH_2Br, 4a-H), 4.40-4.64 (m, 1H, 6-H), 5.12-5.46 (m, 1H, 6-H), 5.46-5.58 (m, 1H, 4-H), 5.70-5.85 (m, 1H, 3-H), 6.54 (s, 1H, 7-H), 6.80 (s, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 20.1, 25.3, 33.1, 34.4, 40.7, 41.1, 41.5, 44.6, 48.6, 53.4, 55.8, 64.5, 64.6, 108.5, 108.9, 111.0, 111.2, 124.4, 125.2, 125.6, 126.0, 132.1, 132.6, 147.3, 147.7, 147.8, 148.0, 165.3 (CO); HRMS (ESI): calcd for $C_{18}H_{22}BrNO_3$ $[M]^+$ 402.067527, found 402.067526.

2-Bromo-1-(8,9-dimethoxy-2,4a,6,10b-tetrahydrophenanthridin-5(1*H*)-yl)ethan-1-one (9-26)

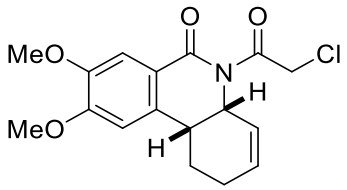


9-26

Prepared from amine hydrochloride **9-24** (200 mg, 0.71 mmol) according to procedure 5 to give pure bromoacetylamide **9-26** (145 mg, 56%) as brown solid. R_f = 0.2 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 1.66-1.92 (m, 2H, 1-H, 2-H), 1.93-2.11 (m, 1H, 1-H), 2.22-2.48 (m, 1H, 2-H), 3.13-3.48 (m, 1H, 10b-H), 3.81 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.97-4.24 (m, 1H, 4a-H), 4.15 (s, 2H, CH_2Br), 4.43-4.83 (m, 1H, 6-H), 5.12-5.45 (m, 1H, 6-H), 5.46-5.60 (m, 1H, 4-H), 5.71-5.88 (m, 1H, 3-H), 6.53 (s, 1H, 7-H), 6.78 (s, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 25.3, 33.2, 34.4, 40.7, 41.1, 41.4,

44.6, 48.6, 53.4, 55.7, 56.0, 108.2, 108.7, 109.2, 109.5, 124.4, 125.1, 125.6, 125.9, 132.1, 132.6, 148.1, 148.5, 165.4 (CO); HRMS (ESI): calcd for $C_{17}H_{20}BrNO_3$ $[M+Na]^+$ 388.05188, found 388.05197.

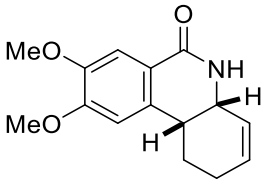
5-(2-Chloroacetyl)-8,9-dimethoxy-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one (9-29)



9-29

To a solution of amide **9-21** (40 mg, 0.15 mmol) and 2-dimethylaminopyridine (37 µL, 0.30 mmol) in CH_3CN (0.5 mL) at 0 °C was added dropwise chloroacetyl chloride (24 µL, 0.30 mmol), then the mixture was allowed to warm to room temperature and stirred for 2 d. The solvent was removed in vacuo, and the remainder diluted with EtOAc (1.0 mL). The solution was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude amide was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) to provide pure amide **9-29** (35 mg, 69%), as a yellow amorphous solid. R_f = 0.4 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86-2.04 (m, 2H, 1-H, 2-H), 2.05-2.17 (m, 1H, 1-H), 2.41-2.51 (m, 1H, 2-H), 3.40-3.48 (m, 1H, 10b-H), 3.89 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.78 (d, J = 16.2 Hz, 1H, $COCH_2Cl$), 4.93 (d, J = 16.2 Hz, 1H, $COCH_2Cl$), 5.31-5.41 (m, 1H, 4a-H), 5.46-5.53 (m, 1H, 4-H), 5.56-5.65 (m, 1H, 3-H), 6.81 (s, 1H, 10-H), 7.57 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (C-2), 23.8 (C-1), 33.3 (C-10b), 47.4 ($COCH_2Cl$), 53.3 (C-4a), 55.9 (OMe), 56.1 (OMe), 107.5 (C-7), 111.1 (C-10), 120.0 (Ar), 126.5 (C-4), 129.6 (C-3), 134.9 (Ar), 148.0 (Ar), 154.0 (Ar), 164.6 (CON), 169.9 ($NCOCH_2Cl$); HRMS (ESI): calcd for $C_{17}H_{18}ClNO_4$ [M+Na]+ 358.08166, found 358.08153.

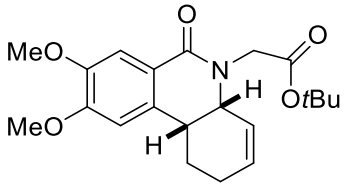
8,9-Dimethoxy-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one (9-21)



9-21

To a boiling solution of chloroacetyl amide **9-29** (20 mg, 60 µmol) in benzene (6 mL) was added dropwise a solution of Bu_3SnH (19 µL, 70 µmol, 1.2 equiv), Bu_3SnCl (81 µL, 0.30 mmol, 5 equiv) and AIBN (2 mg, 12 µmol, 20 mol%) in benzene (3 mL) over 3 h by employing a syringe pump. After complete addition, the reaction mixture was refluxed for further 2 h. The solvent was evaporated in vacuo and the remainder diluted with Et_2O (5 mL). This solution was washed with 10% aqueous solution of KF (2 × 5 mL), dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give pure amide **9-21** (13 mg, 83%), as a brown solid.

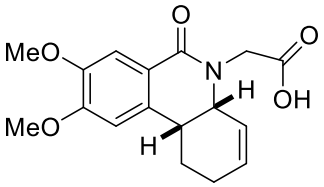
tert-Butyl 2-(8,9-dimethoxy-6-oxo-2,4a,6,10b-tetrahydrophenanthridin-5(1*H*)-yl)acetate (9-30)



9-30

Sodium hydride (20 mg, 0.50 mmol, 1.3 equiv, 60% dispersion in mineral oil) was added to a stirred, cold (0 °C) solution of amide **9-21** (100 mg, 0.38 mmol) in dry DMF (2 mL). The solution was allowed to warm to room temperature for 20 min and then cooled to 0 °C, before *tert*-butyl bromoacetate (86 μL, 0.57 mmol, 1.5 equiv) was added. Then the reaction mixture was warmed to room temperature within 45 min. The reaction mixture was diluted with water (30 mL) and the aqueous phase was basified (10% NaOH, 5 mL) and extracted with ether (5 × 10 mL). The combined ether extracts were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to provide pure *N*-alkyation product **9-30** (90 mg, 63%) as an amorphous solid. R_f = 0.6 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H, *t*Bu), 1.70-1.80(m, 1H, 1-H), 2.03-2.20 (m, 3H, 1-H, 2-H), 2.99-3.09 (m, 1H, 10b-H), 3.86 (d, J = 17.2 Hz, 1H, NCH_2CO), 3.89 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.33 (m, 1H, 4a-H), 4.70 (d, J = 17.2 Hz, 1H, NCH_2CO), 5.66-5.72 (m, 1H, 4-H), 5.91-5.99 (m, 1H, 3-H), 6.67 (s, 1H, 10-H), 7.58 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (C-2), 24.4 (C-1), 28.0 (*t*Bu), 36.7 (C-10b), 46.0 (NCH_2CO), 53.5 (C-4a), 56.0 (OMe), 81.6 (C-$(CH_3)_3$), 108.5 (C-7), 110.7 (C-10), 120.6 (Ar), 123.8 (C-4), 132.6 (C-3), 135.2 (Ar), 147.8 (Ar), 152.2 (Ar), 164.3 (CON), 169.0 (CO_2tBu); HRMS (ESI): calcd for $C_{21}H_{27}NO_5$ $[M+Na]^+$ 396.17814, found 396.17849.

2-(8,9-Dimethoxy-6-oxo-2,4a,6,10b-tetrahydrophenanthridin-5(1*H*)-yl)acetic acid (9-31)

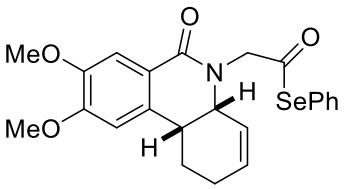


9-31

Through a solution of ester **9-30** (67 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was bubbled HCl gas at 0 °C for 5 h. The solution was stirred for additional 1.5 h at 0 °C, warmed to room temperature over 30 min, and evaporated to dryness. This way acid **9-31** was obtained as a white solid in pure form; ^{1}H NMR (400 MHz, CD_3OD): δ = 1.73-1.92 (m, 1H, 1-H), 2.08-2.30 (m, 3H, 1-H, 2-H), 3.06-3.22 (m, 1H, 10b-H), 3.84 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.07 (d, J = 17.4 Hz, 1H, NCH_2CO), 4.35-4.42 (m, 1H, 4a-H), 4.62 (d, J = 17.4 Hz, 1H, NCH_2CO), 5.74-5.81 (m, 1H, 4-H), 5.94-6.01 (m, 1H, 3-H), 6.91 (s, 1H, 10-H), 7.41 (s, 1H, 7-H); ^{13}C NMR (100 MHz, CD_3OD): δ = 25.3 (C-2), 25.3 (C-1), 37.7 (C-10b), 46.0 (NCH_2CO), 55.8 (C-4a), 56.6 (OMe),

56.7 (OMe), 110.5 (C-7), 111.8 (C-10), 121.4 (Ar), 124.9 (C-4), 133.9 (C-3), 137.6 (Ar), 149.5 (Ar), 154.5 (Ar), 166.3 (CON), 173.1 (CO_2H).

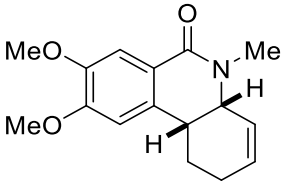
_Se_-phenyl 2-(8,9-dimethoxy-6-oxo-2,4a,6,10b-tetrahydrophenanthridine-5(1*H*)-yl)ethaneselenoate (9-32)



9-32

$(PhSe)_2$ (60 mg, 0.20 mmol, 1.5 equiv) was added to a solution of acid **9-31** in CH_2Cl_2 (10 mL). The solution was cooled to 0 °C before *n*-Bu_3P (66 μL, 0.26 mmol, 2.0 equiv) was added. The reaction mixture was refluxed for 24 h, poured into water (20 mL) and then the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to provide pure selenoester **9-32** (50 mg, 84%), as an amorphous solid. R_f = 0.5 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75-1.94 (m, 1H, 1-H), 2.06-2.28 (m, 3H, 1-H, 2-H), 3.18-3.37 (m, 1H, 10b-H), 3.91 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.11 (d, *J* = 16.9 Hz, 1H, NCH_2CO), 4.37-4.44 (m, 1H, 4a-H), 5.05 (d, *J* = 16.9 Hz, 1H, NCH_2CO), 5.64-5.73 (m, 1H, 4-H), 5.92-6.01 (m, 1H, 3-H), 6.72 (s, 1H, 10-H), 7.32-7.40 (m, 3H, Ar), 7.46-7.53 (m, 2H, Ar), 7.62 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8 (C-2), 24.3 (C-1), 36.2 (C-10b), 54.7 (NCH_2CO), 56.0 (OMe), 56.05 (OMe), 56.5 (C-4a), 108.3 (C-7), 110.8 (C-10), 120.1 (Ar), 123.4 (C-4), 125.4 (Ar), 128.9 (C-3), 129.1 (Ar),129 (Ar), 131.4 (Ar), 132.8 (Ar), 135.0 (Ar), 136.0 (Ar), 148.0 (Ar), 152.6 (Ar), 164.8 (CON), 199.0 (COSePh); HRMS (ESI): calcd for $C_{23}H_{23}NO_4Se$ $[M+Na]^+$ 480.06845, found 480.06836.

8,9-Dimethoxy-5-methyl-1,4a,5,10b-tetrahydrophenanthridin-6(2*H*)-one (9-34)



9-34

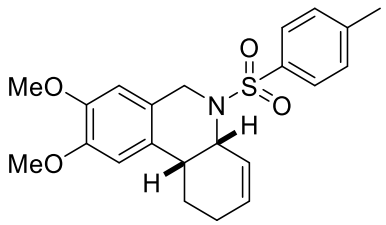
To a boiling solution of compound selenoester **9-32** (16 mg, 0.035 mmol) in benzene (2 mL) was added dropwise a solution of Bu_3SnH (14 μL, 0.052 mmol, 1.5 equiv), and benzoyl peroxide (2 mg, 0.008 mmol, 23 mol%) in benzene (1 mL) over 1 h by employing a syringe pump. After complete addition, the reaction mixture was further refluxed for 2 h. The solvent was evaporated in vacuo, and the residue diluted with Et_2O (3 mL). This solution was washed with 10% aqueous solution of KF (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:2) to provide *N*-methylamide **9-34** (6 mg, 63%), as a colorless solid. R_f = 0.1 (petroleum

ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79-1.92(m, 1H, 1-H), 2.02-2.15 (m, 2H, 1-H, 2-H), 2.16-2.27 (m, 1H, 2-H), 3.14 (s, 3H, NCH_3), 3.17-3.28 (m, 1H, 10b-H), 3.91 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.08-4.20 (m, 1H, 4a-H), 5.64-5.75 (m, 1H, 4-H), 5.78-5.90 (m, 1H, 3-H), 6.71 (s, 1H, 10-H), 7.60 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9 (C-2), 24.0 (C-1), 32.2 (NCH_3), 35.3 (C-10b), 56.0 (OMe), 56.2 (C-4a), 107.9 (C-7), 110.7 (C-10), 121.5 (Ar), 124.5 (C-4), 130.6 (C-3), 133.4 (Ar), 147.8 (Ar), 151.9 (Ar), 164.1 (CON); HRMS (ESI): calcd for $C_{16}H_{19}NO_2$ $[M+Na]^+$ 296.12571, found 296.12582.

Preparation of sulfonamides from amine hydrochlorides (Procedure 6)

To a cooled (0 °C) suspension of amine·HCl (1.0 equiv) in CH_2Cl_2 (9 mL per mmol of hydrochloride) were added Et_3N (2.0 equiv) and arylsulfonyl chloride (1.5 equiv). The stirred reaction mixture was allowed reach room temperature within 2 h. Thereafter, saturated $NaHCO_3$ solution (9 mL per mmol of hydrochloride) was added. After separation of the layers the aqueous layer was extracted with CH_2Cl_2 (2 × 9 mL per mmol of hydrochloride). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography to afford the pure sulfonamides.

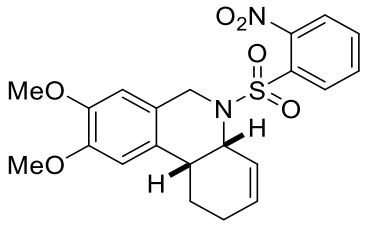
8,9-Dimethoxy-5-tosyl-1,2,4a,5,6,10b-hexahydrophenanthridine (9-35)



9-35

Prepared from amine hydrochloride **9-24** (305 mg, 1.03 mmol) according to procedure 6 to give pure sulfonamide **9-35** (435 mg, 99%) as colorless solid. R_f = 0.3 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55-1.83 (m, 2H, 1-H, 2-H), 1.85-1.98 (m, 1H, 1-H), 2.18-2.31 (m, 1H, 2-H), 2.38 (s, 3H, SO_2CH_2Ph), 3.07-3.21 (m, 1H, 10b-H), 3.81 (s, 6H, 2 OMe), 4.13 (d, J = 15.6 Hz, 1H, 6-H), 4.59 (d, J = 15.6 Hz, 1H, 6-H), 4.76-4.88 (m, 1H, 4a-H), 5.10-5.20 (m, 1H, 4-H), 5.56-5.73 (m, 1H, 3-H), 6.48 (s, 1H, 7-H), 6.69 (s, 1H, 10-H), 7.22 (d, J = 8.0 Hz, 2H, Ar), 7.69 (d, J = 8.0 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (C-2), 21.4 (Me), 25.5 (C-1), 34.0 (C-10b), 43.2 (C-6), 52.4 (C-4a), 55.7 (OMe), 56.0 (OMe), 108.4 (C-8), 109.4 (C-10), 124.7 (Ar), 125.2 (C-4), 126.5 (Ar), 127.1 (Ar), 129.6 (Ar), 132.6 (C-3), 137.4 (Ar), 143.2 (Ar), 147.3 (Ar), 148.2 (Ar); HRMS (ESI): calcd for $C_{22}H_{25}NO_4S$ $[M+Na]^+$ 422.13965, found 422.13960.

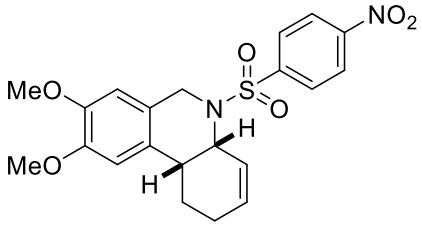
8,9-Dimethoxy-5-((2-nitrophenyl)sulfonyl)-1,2,4a,5,6,10b-hexahydrophenanthridine (9-36)



9-36

Prepared from amine hydrochloride **9-24** (350 mg, 1.01 mmol) according to procedure 6 to give pure sulfonamide **9-36** (377 mg, 87%) as yellow amorphous solid. R_f = 0.2 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63-1.87 (m, 2H, 1-H, 2-H), 1.93-2.03 (m, 1H, 1-H), 2.25-2.37 (m, 1H, 2-H), 3.26-3.36 (m, 1H, 10b-H), 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.39 (d, J = 16.2 Hz, 1H, 6-H), 4.56 (d, J = 16.2 Hz, 1H, 6-H), 4.81-4.89 (m, 1H, 4a-H), 5.34-5.43 (m, 1H, 4-H), 5.68-5.79 (m, 1H, 3-H), 6.52 (s, 1H, 7-H), 6.76 (s, 1H, 10-H), 7.58-7.70 (m, 3H, Ar), 8.01-8.08 (m, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (C-2), 25.5 (C-1), 33.9 (C-10b), 43.5 (C-6), 52.9 (C-4a), 55.8 (OMe), 56.0 (OMe), 108.4 (C-7), 109.4 (C-10), 124.7 (Ar), 124.2 (Ar), 124.7 (Ar), 126.2 (Ar), 130.7 (C-4), 131.7 (C-3), 133.1 (Ar), 133.3 (Ar), 133.7 (Ar), 147.4 (Ar), 147.9 (Ar), 148.3 (Ar); HRMS (ESI): calcd for $C_{21}H_{22}N_2O_6S$ $[M+Na]^+$ 453.10908, found 453.10940.

8,9-Dimethoxy-5-((4-nitrophenyl)sulfonyl)-1,2,4a,5,6,10b-hexahydrophenanthridine (9-37)



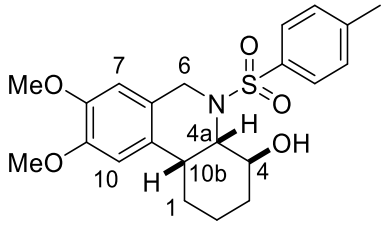
9-37

Prepared from amine hydrochloride **9-24** (100 mg, 0.35 mmol) according to procedure 6 to give pure sulfonamide **9-37** (140 mg, 99%) as yellow amorphous solid. R_f = 0.2 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.73 (m, 1H, 1-H), 1.74-1.85 (m, 1H, 2-H), 1.85-1.98 (m, 1H, 1-H), 2.18-2.31 (m, 1H, 2-H), 2.99-3.13 (m, 1H, 10b-H), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.23 (d, J = 15.9 Hz, 1H, 6-H), 4.64 (d, J = 15.9 Hz, 1H, 6-H), 4.81-4.89 (m, 1H, 4a-H), 5.14-5.21 (m, 1H, 4-H), 5.67-5.75 (m, 1H, 3-H), 6.49 (s, 1H, 7-H), 6.66 (s, 1H, 10-H), 7.97 (d, J = 8.8 Hz, 2H, Ar), 8.26 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (C-2), 25.5 (C-1), 33.8 (C-10b), 43.4 (C-6), 52.8 (C-4a), 55.8 (OMe), 56.0 (OMe), 108.4 (C-7), 109.4 (C-10), 124.7 (Ar), 124.2 (Ar), 124.7 (C-4), 126.5 (Ar), 128.2 (Ar), 133.5 (C-3), 146.4 (Ar), 147.6 (Ar), 148.5 (Ar), 149.8 (Ar); HRMS (ESI): calcd for $C_{21}H_{22}N_2O_6S$ $[M+Na]^+$ 453.10908, found 453.10940.

Directed hydroboration of arylsulfonyl)-hexahydrophenanthridines and carbamates (Procedure 8)

To a magnetically stirred suspension of $NaBH_4$ (6.0 equiv) in dry THF (3 mL per mmol of $NaBH_4$) was added neat $BF_3{\cdot}OEt_2$ (5.5 equiv) at 0 °C. The reaction mixture was allowed to stir at room temperature for 30 min before the alkene **9-(35, 37)** or **9-(45-47)** (1.0 equiv) respectively, in dry THF (30 mL per mmol of alkene) was added dropwise to the mixture at 0 °C. Thereafter, the mixture was allowed to reach room temperature within 1.5 h. For work-up 3n aqueous NaOH (30 mL per mmol of alkene) and 30% H_2O_2 (30 mL per mmol of alkene) were added sequentially to the reaction mixture at 0 °C. The mixture was stirred at room temperature for 5 h, before it was extracted with Et_2O (3 × 50 mL per mmol of alkene). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography gave the pure secondary alcohol.

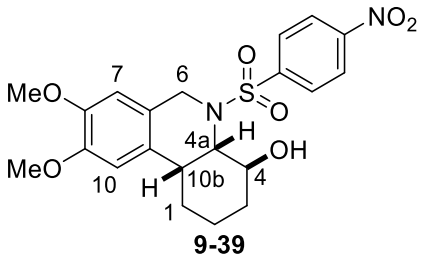
8,9-Dimethoxy-5-tosyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-4-ol (9-38)



9-38

Prepared from alkene **9-35** (220 mg, 0.55 mmol) according to procedure 8 to give alcohol **9-38** (206 mg, 90%) as colorless solid. R_f = 0.4 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11-1.26 (m, 1H, 2-H), 1.29-1.43 (m, 1H, 2-H), 1.48-1.68 (m, 2H, 1-H), 1.94-2.05 (m, 1H, 3-H), 2.23-2.33 (m, 1H, 3-H), 2.36 (s, 3H, CH_3), 2.87-2.98 (m, 1H, 10b-H), 3.44 (td, J = 10.6, 4.8 Hz, 1H, 4-H), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.90 (dd, J = 8.0, 4.0 Hz, 1H, 4a-H), 4.41 (d, J = 16.0 Hz, 1H, 6-H), 4.64 (d, J = 16.0 Hz, 1H, 6-H), 6.53 (s, 1H, 7-H), 6.64 (s, 1H, 10-H), 7.23 (d, J = 8.1 Hz, 2H, Ar), 7.71 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (C-2), 21.5 (CH_3), 27.6 (C-1), 33.9 (C-3), 36.0 (C-10b), 43.5 (C-6), 55.8 (OMe), 56.0 (OMe), 60.6 (C-4), 66.3 (C-4a), 108.6 (C-7), 108.9 (C-10), 123.8 (Ar), 126.4 (Ar), 127.1 (Ar), 129.7 (Ar), 137.0 (Ar), 143.5 (Ar), 147.6 (Ar), 148.2 (Ar); HRMS (ESI): calcd for $C_{22}H_{27}NO_5S$ $[M+Na]^+$ 440.15021, found 440.15022.

8,9-Dimethoxy-5-((4-nitrophenyl)sulfonyl)-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-4-ol (9-39)



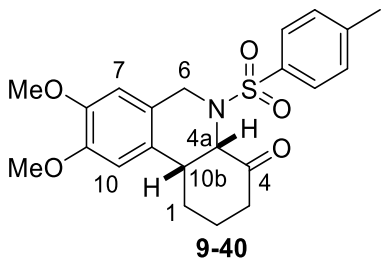
9-39

Prepared from alkene **9-37** (120 mg, 0.29 mmol) according to procedure 8 to give alcohol **9-39** (80 mg, 63%) as yellow solid. R_f = 0.4 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15-1.30 (m, 1H), 1.34-1.48 (m, 1H), 1.54-1.75 (m, 3H), 1.97-2.08 (m, 1H), 2.31-2.43 (m, 1H), 3.01-3.10 (m, 1H, 4a-H), 3.5 (td, *J* = 10.4, 4.5 Hz, 1H, 4-H), 3.81 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.90 (dd, *J* = 10.1, 5.0 Hz, 1H, 4a-H), 4.40 (d, *J* = 16.4 Hz, 1H, 6-H), 4.72 (d, *J* = 16.4 Hz, 1H, 6-H), 6.53 (s, 1H, 7-H), 6.67 (s, 1H, 10-H), 8.04 (d, *J* = 8.8 Hz, 2H, Ar), 8.28 (d, *J* = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (C-2), 27.7 (C-1), 34.5 (C-3), 36.8 (C-10b), 43.5 (C-6), 55.9 (OMe), 56.0 (OMe), 60.9 (C-4), 66.2 (C-4a), 108.6 (C-7), 108.7 (C-10), 123.2 (Ar), 124.2 (Ar), 126.1 (Ar), 128.3 (Ar), 146.2 (Ar), 147.8 (Ar), 148.5 (Ar).

Oxidation of the secondary alcohols to the corresponding ketones using Dess-Martin periodinane (Procedure 9)

To a stirred solution of alcohol (1 equiv) in CH_2Cl_2 (50 mL per mmol of alcohol) was added DMP (1.5 equiv) and the mixture was allowed to stir at room temperature for 1.5 h. Then it was diluted with saturated $NaHCO_3$ solution (30 mL per mmol of alcohol) and concentrated sodium thiosulfate solution (30 mL per mmol of alcohol). This mixture was stirred until both the organic and aqueous layers appeared clear. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL per mmol of alcohol). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Purification of the residue by flash chromatography afforded the pure ketone.

8,9-Dimethoxy-5-tosyl-2,3,4,4a,5,6,10b-hexahydrophenanthridin-4-(1*H*)-one (9-40)

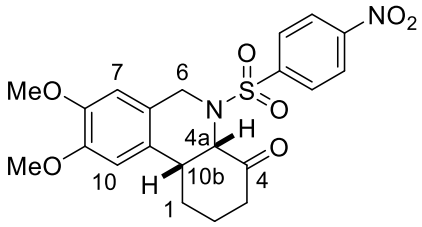


9-40

Prepared from alcohol **9-38** (120 mg, 0.30 mmol) according to procedure 9 to give ketone **9-40** (98 mg, 79%) as colorless solid. R_f = 0.5 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45-1.96 (m, 2H, 2-H), 2.07-2.24 (m, 1H, 1-H), 2.25-2.36 (m, 2H, 1-H, 3-H), 2.42 (s, 3H, CH_3), 2.52-2.66 (m, 1H, 3-H), 3.59-3.72 (m, 1H, 10b-H), 3.81 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.47 (d, *J* = 15.2 Hz, 1H, 6-H), 4.58 (d, *J* = 15.2 Hz, 1H, 6-H), 4.79 (d, *J* =

5.6 Hz, 1H, 4a-H), 6.49 (s, 1H, 7-H), 6.70 (s, 1H, 10-H), 7.29 (d, J = 8.1 Hz, 2H, Ar), 7.73 (d, J = 8.1 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C-1), 21.5 (CH_3), 27.6 (C-2), 41.0 (C-3), 41.1 (C-10b), 44.2 (C-6), 55.7 (OMe), 56.0 (OMe), 62.5 (C-4a), 108.1 (C-7), 108.8 (C-10), 124.5 (Ar), 125.0 (Ar), 127.4 (Ar), 129.4 (Ar), 136.2 (Ar), 143.3 (Ar), 148.0 (Ar), 148.1 (Ar), 205.1 (CO); HRMS (ESI): calcd for $C_{22}H_{25}NO_5S$ $[M+Na]^+$ 438.13456, found 438.13454.

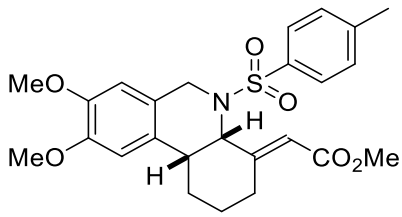
8,9-Dimethoxy-5-((4-nitrophenyl)sulfonyl)-2,3,4,4a,5,6,10b-hexahydrophenanthridin-4-(1*H*)-one (41)



9-41

Prepared from alcohol **9-39** (50 mg, 0.10 mmol) according to procedure 9 to give ketone **9-41** (47 mg, 99%) as yellow amorphous solid, R_f = 0.5 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54-1.61 (m, 1H, 2-H), 1.82-1.92 (m, 1H, 2-H), 2.12-2.34 (m, 3H, 1-H, 3-H), 2.56-2.67 (m, 1H, 3-H), 3.70-3.77 (m, 1H, 10b-H), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.39 (d, J = 14.6 Hz, 1H, 6-H), 4.68 (d, J = 14.6 Hz, 1H, 6-H), 4.85 (d, J = 6.1 Hz, 1H, 4a-H), 6.48 (s, 1H, 7-H), 6.70 (s, 1H, 10-H), 8.00 (d, J = 8.8 Hz, 2H, Ar), 8.34 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C-1), 27.6 (C-2), 40.9 (C-10b), 41.0 (C-3), 44.3 (C-6), 55.8 (OMe), 56.1 (OMe), 62.8 (C-4a), 108.1 (C-7), 108.8 (C-10), 124.1 (Ar), 124.3 (Ar), 128.6 (Ar), 144.9 (Ar), 148.4 (Ar), 150.0 (Ar), 204.9 (CO). HRMS (ESI): calcd for $C_{21}H_{22}N_2O_7S$ $[M+Na]^+$ 469.10399, found 469.10415.

Methyl (*E*)-2-(8,9-dimethoxy-5-tosyl-2,3,4a,5,6,10b-hexahydrophenanthridin-4(1*H*)-ylidene)acetate (9-43)



9-43

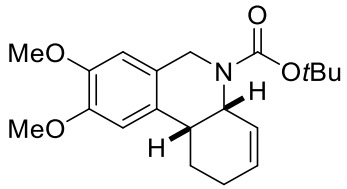
To a stirred solution of ketone 9-40 (82 mg, 0.2 mmol) in benzene (2 mL) was added methyl 2-(triphenyl-λ5-phosphanylidene)acetate (330 mg, 0.99 mmol, 5 equiv) followed by refluxing of the mixture for 48 h. After cooling, the mixture was concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to afford the pure enoate **9-43** (10 mg, 11%) as yellow solid. R_f = 0.6 (ethyl acetate/petroleum ether, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32-1.50 (m, 2H, 2-H), 1.63-1.74 (m, 1H, 1-H), 1.85-2.08 (m, 2H, 1-H, 3-H), 2.40 (s, 3H, CH_3), 2.35-2.47 (m, 1H, 3-H), 2.97-3.07 (m, 1H, 10b-H), 3.58 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.36 (d, J = 15.4 Hz, 1H, 6-H), 4.48 (d, J =

15.4 Hz, 1H, 6-H), 4.73 (dd, J = 5.6, 2.2 Hz, 1H, 4a-H), 5.66-5.70 (m, 1H, $CHCO_2Me$), 6.55 (s, 1H, 7-H), 6.62 (s, 1H, 10-H), 7.28 (d, J = 8.3 Hz, 2H, Ar), 7.73 (d, J = 8.3 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (two signals in DEPT-135, C-1, CH_3), 27.5 (C-2), 28.6 (C-3), 39.5 (C-10b), 44.8 (C-6), 50.9 (CO_2CH_3), 55.9 (OMe), 56.0 (OMe), 59.4 (C-4a), 108.5 (C-7), 109.2 (C-10), 114.4 ($CHCO_2Me$), 124.1 (Ar), 126.0 (Ar), 127.2 (Ar), 129.8 (Ar), 136.3 (Ar), 143.6 (Ar), 147.7 (Ar), 148.2 (Ar), 157.5 (Ar), 166.6 (CO_2Me).

Preparation of carbamates from amine hydrochlorides (Procedure 7)

To a cooled (0 °C) suspension of amine·HCl (1.0 equiv) in CH_2Cl_2 (9 mL per mmol of hydrochloride) were added Et_3N (2.0 equiv) and the corresponding chloroformate (2.0 equiv) or Boc_2O (2.5 equiv). The stirred reaction mixture was allowed reach room temperature within 1 h (in case chloroformate) or 2 h (in case of Boc_2O), respectively. Thereafter, saturated $NaHCO_3$ solution (9 mL per mmol of hydrochloride) was added. After separation of the layers the aqueous layer was extracted with CH_2Cl_2 (2 × 9 mL per mmol of hydrochloride). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography to afford the pure carbamates.

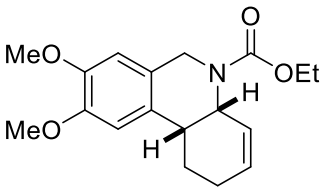
***tert*-Butyl (4a*R*,10b*R*)-8,9-dimethoxy-2,4a,6,10b-tetrahydrophenanthridine-5(1*H*)-carboxylate (9-45)**



9-45

Prepared from amine hydrochloride **9-24** (173 mg, 0.68 mmol) according to procedure 7 to give pure carbamate **9-45** (210 mg, 89%) as colorless amorphous solid. R_f = 0.3 (petroleum ether/ethyl acetate, 2:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9H, O*t*Bu), 1.69-1.89 (m, 2H, 1-H, 2-H), 1.91-2.06 (m, 1H, 1-H), 2.26-2.38 (m, 1H, 2-H), 3.16-3.26 (m, 1H, 10b-H), 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.12 (d, J = 16.7 Hz, 6-H), 4.75 (d, J = 16.7 Hz, 1H, 6-H), 4.87-5.20 (m, 1H, 4a-H), 5.41-5.53 (m, 1H, 4-H), 5.63-5.76 (m, 1H, 3-H), 6.52 (s, 1H, 7-H), 6.81 (s, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (C-2), 25.4 (C-1), 28.4 (O*t*Bu), 33.6 (C-10b), 42.2 (C-6), 55.7 (OMe), 56.0 (C-4a), 56.1 (OMe), 79.8 (O*t*Bu), 108.6 (C-7), 109.5 (C-10), 127.6 (C-4), 130.8 (C-3), 147.3 (Ar), 147.9 (Ar), 154.8 (CO). HRMS (ESI): calcd for $C_{20}H_{27}NO_4$ $[M+Na]^+$ 368.18323, found 368.18325.

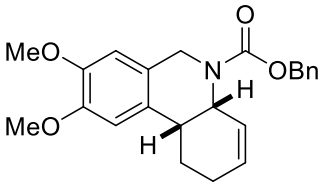
Ethyl 8,9-dimethoxy-2,4a,6,10b-tetrahydrophenanthridine-5(1*H*)-carboxylate (9-46)



9-46

Prepared from amine hydrochloride **9-24** (10 mg, 0.03 mmol) according to procedure 7 to give pure carbamate **9-46** (9 mg, 94%) as colorless amorphous solid. R_f = 0.5 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.71-1.91 (m, 2H, 1H, 2-H), 1.94-2.08 (m, 1H, 1-H), 2.28-2.38 (m, 1H, 2-H), 3.19-3.29 (m, 1H, 10b-H), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.18 (q, J = 7.1 Hz, 3H, OCH_2, 6-H) 4.81 (d, J = 15.7 Hz, 1H, 6-H), 4.96-5.28 (m, 1H, 4a-H), 5.44-5.55 (m, 1H, 4-H), 5.65-5.78 (m, 1H, 3-H), 6.52 (s, 1H, 7-H), 6.81 (s, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (OCH_2CH_3), 20.3 (C-2), 25.3 (C-1), 33.5 (C-10b), 42.2 (C-6), 50.3 (C-4a), 55.8 (OMe), 56.1 (OMe), 61.5 (OCH_2), 108.5 (C-7), 109.5 (C-10), 127.3 (C-4), 131.2 (C-3), 147.4 (Ar), 148.0 (Ar), 155.4 (CO).

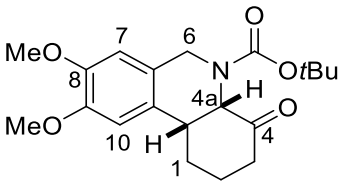
Benzyl 8,9-Dimethoxy-2,4a,6,10b-tetrahydrophenanthridine-5(1*H*)-carboxylate (9-47)



9-47

Prepared from amine hydrochloride **9-24** (100 mg, 0.34 mmol) according to procedure 7 to give pure carbamate **9-47** (50 mg, 39%) as colorless amorphous solid. R_f = 0.2 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69-1.90 (m, 2H, 1-H, 2-H), 1.91-2.09 (m, 1H, 1-H), 2.26-2.41 (m, 2H, 2-H), 3.18-3.35 (m, 1H, 10b-H), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.21 (d, J = 16.0 Hz, 1H, 6-H), 4.84 (d, J = 16.0 Hz, 1H, 6-H), 5.02-5.26 (m, 1H, 4a-H), 5.17 (s, 2H, OCH_2Ph), 5.46-5.55 (m, 1H, 4-H), 5.67-5.77 (m, 1H, 3-H), 6.52 (s, 1H, 7-H), 6.81 (s, 1H, 10-H), 7.28-7.34 (m, 1H, Ar), 7.35-7.44 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (C-2), 25.2 (C-1), 33.4 (C-10b), 42.3 (C-6), 50.4 (C-4a), 55.7 (OMe), 56.0 (OMe), 67.2 (OCH_2Ph), 108.5 (C-7), 109.4 (C-10), 127.6 (C-4), 128.4 (Ar), 128.9 (Ar), 131.8 (C-3), 136.6 (Ar), 147.3 (Ar), 148.0 (Ar), 155.4 (CO); HRMS (ESI): calcd for $C_{23}H_{25}NO_4$ $[M+Na]^+$ 402.16758, found 402.16774.

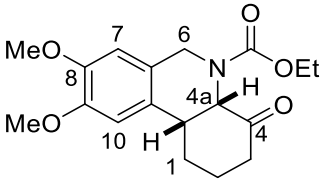
tert-Butyl 8,9-dimethoxy-4-oxo-2,3,4,4a,6,10b-hexahydrophenanthridine-5(1*H*)-carboxylate (9-49)



9-49

Prepared from alkene **9-45** (112 mg, 0.324 mmol) according to procedures 8 and 9 to give ketone **9-49** (88 mg, 75%, 2 steps) as colorless amorphous solid. R_f = 0.4 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9H, O*t*Bu), 1.57-1.79 (m, 1H, 2-H), 1.82-2.00 (m, 1H, 2-H), 2.08-2.25 (m, 1H, 1-H), 2.26-2.43 (m, 2H, 1-H, 3-H), 2.52-2.66 (m, 1H, 3-H), 3.54-3.68 (m, 1H, 10b-H), 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.46-4.80 (m, 2H, 6-H2), 5.02 (d, J = 6.1 Hz, 1H, 4a-H), 6.54 (s, 1H, 7-H), 6.71 (s, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C-1), 27.3 (C-2), 28.4 (O*t*Bu), 39.5 (C-10b), 40.8 (C-3), 44.5 (C-6), 55.8 (OMe), 56.1 (OMe), 60.8 (C-4a), 80.4 (O*t*Bu), 107.9 (C-7), 109.1 (C-10), 124.8 (Ar), 126.4 (Ar), 147.9 (Ar), 148.1, 206.4 (CO); HRMS (ESI): calcd for $C_{20}H_{27}NO_5$ $[M+Na]^+$ 384.17814, found 384.17828.

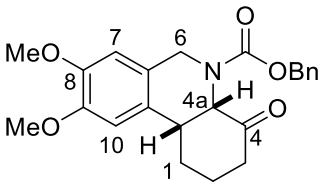
Ethyl 8,9-Dimethoxy-4-oxo-2,34,4a,6,10b-tetrahydrophenanthridine-5(1*H*)-carboxylate (9-50)



9-50

Prepared from alkene **9-46** (5 mg, 0.016 mmol) according to procedures 8 and 9 to give ketone **9-50** (4 mg, 74%, 2 steps) as colorless amorphous solid. R_f = 0.6 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.86-1.95 (m, 1H, 2-H), 2.14-2.27 (m, 1H, 1-H), 2.29-2.43 (m, 2H, 1-H, 3-H), 2.54-2.65 (m, 1H, 3-H), 3.58-3.66 (m, 1H, 10b-H), 3.83 (s,3H, OMe), 3.84 (s, 3H, OMe), 4.20 (q, J = 7.1 Hz, OCH_2CH_3), 4.58 (d, J = 16.4 Hz, 1H, 6-H), 4.67 (d, J = 16.4 Hz, 1H, 6-H), 5.05 (d, J = 6.1 Hz, 1H, 4a-H), 6.55 (s, 1H, 7-H), 6.72 (s, 1H, 10-H); HRMS (ESI): calcd for $C_{18}H_{23}NO_5$ $[M+Na]^+$ 365.14684, found 356.14695.

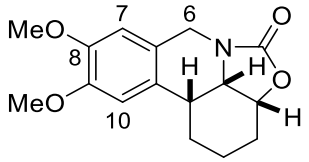
Benzyl 8,9-dimethoxy-4-oxo-2,3,4,4a,6,10b-hexahydrophenanthridine-5(1*H*)-carboxylate (9-51)



33b

Prepared from alkene **9-47** (19 mg, 0.05 mmol) according to procedures 8 and 9 to give ketone **9-51** (6 mg, 30%, 2 steps) as colorless amorphous solid. R_f = 0.5 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.70 (m, 2H, 2-H), 1.82-1.99 (m, 1H, 1-H), 2.30-2.45 (m, 2H, 1-H, 3-H), 2.54-2.66 (m, 1H, 3-H), 3.56-3.69 (m, 1H, 10b-H), 3.84 (s, 6H, 2 × OMe), 4.53-4.76 (m, 2H, 6-H), 5.07 (d, J = 6.1Hz, 1H, 4a-H), 5.14-5.26 (m, 2H, OCH_2Ph), 6.52 (s, 1H, 7-H), 6.72 (s, 1H, 10-H), 7.28-7.45 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (C-1), 27.2 (C-2), 39.4 (C-10b), 40.8 (C-3), 44.3 (C-6), 55.8 (OMe), 56.1 (OMe), 61.4 (C-4a), 67.6 (OCH_2Ph), 108.0 (C-7), 109.1 (C-10), 124.5(Ar), 125.9 (Ar), 127.9 (Ar), 128.0 (Ar), 128.1 (Ar), 128.5 (Ar), 136.5 (Ar), 148.0 (Ar), 148.2 (Ar), 156.3 (NCO_2Ph), 206.0 (CO); HRMS (ESI): calcd for $C_{23}H_{25}NO_5$ $[M+Na]^+$ 418.16249, found 418.16264.

(3a*S*,3a1*R*,11b*R*)-9,10-Dimethoxy-2,3,3a,3a1,4,5,7,11b-octahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (9-52)

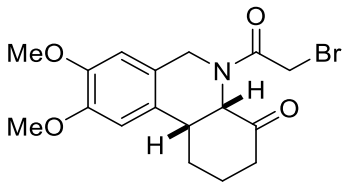


***oxy*-lycorane (9-52)**

Iodine (84 mg, 0.33 mmol, 4.0 equiv) was added to a solution of Ph_3P (115 mg, 0.44 mmol, 4.0 equiv) in toluene (3 mL) and the mixture was stirred at rt for 10 min. A solution of the alcohol (40 mg, 0.11 mmol) in toluene (1 mL) was then added and the mixture was further stirred at room temperature overnight, TLC shows only starting material, then the reaction mixture was heated up to 80 °C for 4 h, the reaction was monitored by TLC. Saturated aqueous $Na_2S_2O_3$ (5 mL) was added and the mixture was stirred up to 10 min. It was then diluted with EtOAc (10 mL), organic phase was separated and washed with H_2O (2 × 5 mL) and saturated aqueous NaCl (10 mL) successively, after which it was dried with anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to give carbamate **9-52** (30 mg, 94%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31-1.48 (m, 2H, 1-H 2-H), 1.62-1.91 (m, 3H, 1-H, 2-H, 3-H), 2.01-2.17 (m, 1H, 3-H), 2.75-2.92 (m, 1H, 11b-H), 3.84 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.93 (dd, J = 4.3, 7.6 Hz, 1H, 3a^1-H), 4.25 (d, J = 16.2 Hz, 1H, 6-H), 4.63 (d, J = 16.2 Hz, 1H, 6-H), 4.77 (q, J = 7.6 Hz, 1H, 3a-H), 6.58 (s, 1H, 7-H), 6.60 (s, 1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (C-2), 26.4 (C-3), 28.9 (C-1), 37.4 (C-11b), 42.8 (C-6), 53.4 (C-3a^1), 55.9 (OMe), 56.0 (OMe), 74.1 (C-3a), 109.0

(C-7), 111.6 (C-10), 122.1 (Ar), 128.6 (Ar), 148.1 (Ar), 148.3 (Ar), 158.3 (C-5); HRMS (ESI): calcd for $C_{16}H_{19}NO_4$ $[M+Na]^+$ 312.12063, found 312.12086.

5-(2-Bromoacetyl)-8,9-dimethoxy-2,3,4a,5,6,10b-hexahydrophe-nanthridin-4(1*H*)-one (9-54)

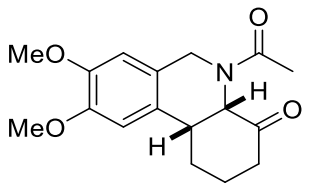


9-54

To a cooled (0 °C) stirred solution of carbamate **9-49** (30 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL). The reaction mixture was allowed to stir at room temperature for 4 h. Excess solvent and TFA were removed on a rotavapor in vacuo and the residual TFA was removed by adding several times CH_2Cl_2 and concentration of the solution in vacuo to give the solid amine salt, which was directly used in next step without further purification.

To a cooled (0 °C) solution of salt and Et_3N (36 μL, 0.25 mmol, 3 equiv) in CH_2Cl_2 (1 mL) was added bromoacetyl bromide (8 μL, 0.10 mmol, 1.2 equiv) dropwise. The stirred reaction mixture was allowed to reach room temperature within 1 h. For work-up, the mixture was treated with saturated $NaHCO_3$ (2 mL), and this mixture was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude amide was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) to provide pure amide **9-54** (20 mg, 65% over two steps) as yellow solid. R_f = 0.3 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 1.53-1.81 (m, 2H, 2-H), 1.82-2.01 (m, 1H, 2-H), 2.13-2.27 (m, 2H, 1-H), 2.28-2.46 (m, 2H, 1-H, 3-H), 2.54-2.75 (m, 1H, 3-H), 3.52-3.67 (m, 1H, 10b-H), 3.78-3.86 (6H, 2 OMe), 3.90-4.08 (s, 1H, $COCH_2Br$), 4.14-4.31 (m, 1H, $COCH_2Br$), 4.59-4.73 (m, 1H, 6-H), 4.76-4.92 (m, 1H, 6-H), 5.44 (d, J = 6.1 Hz, 1H, 4a-H), 6.52-6.59 (1H, 7-H), 6.68-6.75 (1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.1, 25.9, 26.1, 27.0, 27.2, 38.9, 40.8, 41.2, 45.4, 45.8, 55.8, 55.8, 56.0, 56.1, 59.6, 59.64, 107.8, 107.9, 108.8, 109.2, 123.5, 124.4, 124.5, 124.7, 124.7, 148.3, 148.4, 166.5, 166.8, 205.1, 205.2; HRMS (ESI): calcd for $C_{17}H_{20}BrNO_4$ $[M+Na]^+$ 404.04679, found 404.04670.

5-Acetyl-8,9-dimethoxy-2,3,4a,5,6,10b-hexahydrophenanthridin-4(1*H*)-one (9-55)



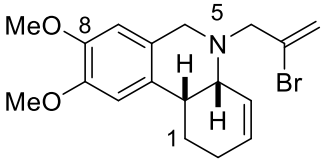
9-55

(a) Using $(RhCl(PPh_3)_3$ and Et_2Zn: To a stirred solution of $(RhCl(PPh_3)_3$ (8 mg, 9 μmol, 17.5 mol%) in THF (250 μL) at 0 °C were added α-bromo amide **9-54** (18 mg, 0.047 mmol), and a

solution of Et_2Zn (1M in hexane 100 µL, 0.10 mmol, 2.2 equiv). After stirring of the mixture for 5 min at 0 °C, saturated $NaHCO_3$ solution (2 mL) was added and the mixture extracted with Et_2O (3 × 3mL). The combined extracts were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave pure acetamide **9-55** (8 mg, 56%) as colorless oil.

(b) Using zinc dust: To zinc dust (34 mg, 0.52 mmol, 5 equiv, activated by diluted HCl) at 0 °C was added dropwise a solution of α-bromo amide **9-54** (40 mg, 0.10 mmol) in DMF (0.5 mL). The resulting paste was allowed to stir for 1 h at room temperature, before saturated $NaHCO_3$ solution (5 mL) was added and the mixture extracted with Et_2O (3 × 5mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried with anhydrous Na_2SO_4, filtered, concentrated in *vacuo*. Purification by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave pure acetamide **9-55** (15 mg, 49%) as a colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 1.78-1.92 (m, 2H, 2-H), 1.96-2.02 (m, 1H, 2-H), 2.09-2.21 (m, 1H, 1-H), 2.24 (s, 3H, $COCH_3$), 2.28-2.46 (m, 2H, 1-H, 3-H), 2.50-2.72 (m, 1H, 3-H), 3.49-3.65 (m, 1H, 10b-H), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.54 (d, J = 15.4 Hz, 1H, 6-H), 4.78 (d, J = 15.4 Hz, 1H, 6-H), 5.53 (d, J = 6.1 Hz, 1H, 4a-H), 6.54 (s, 1H, 7-H), 6.73 (1H, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 21.3 ($COCH_3$), 21.7 (C-1), 27.2 (C-2), 39.2 (C-10b), 40.9 (C-3), 46.1 (C-6), 55.8 (OMe), 56.1 (OMe), 59.1 (C-4a), 110.0 (C-7), 109.0 (C-10), 125.1 (Ar), 125.3 (Ar), 148.2 (Ar), 170.7 (NCOCH3), 205.8 (CO); HRMS (ESI): calcd for $C_{17}H_{21}NO_4$ $[M+Na]^+$ 326.13628, found 326.13639.

5-(2'-Bromoallyl)-8,9-dimethoxy-1,2,4a,5,6,10b-hexahydro phenanthridine (9-65)

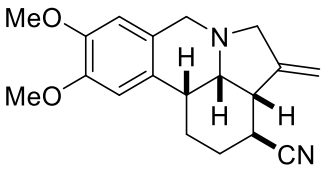


9-65

To a stirred solution of amine·HCl **9-24** (110 mg, 0.34 mmol) in DMF (1 mL) was added NaH (60% dispersion in oil, 35 mg, 0.85 mmol, 2.5 equiv) and bromoallyl bromide (51 µL, 0.51 mmol, 1.5 equiv). The reaction mixture was allowed to stir at room temperature for 1 h, before it was cooled to 0 °C and quenched with H_2O (2 mL). The mixture was extracted with EtOAc (3 × 3mL). The combined organic layers were washed with H_2O (3 × 3 mL) and saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 3:1) provided pure allylamine **9-65** (80 mg, 65%) as yellow oil. R_f = 0.6 (petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80-1.89 (m, 1H, 1-H), 1.92-2.03 (m, 2H, 2-H), 2.11-2.24 (m, 1H, 1-H), 2.92-3.01 (m, 1H, 10b-H), 3.40 (d, J = 16.0 Hz, 1H, 1'-H), 3.46-3.50 (m, 1H, 4a-H), 3.53 (d, J = 16.0 Hz, 1H, 1'-H), 3.58 (d, J = 15.2 Hz, 1H, 6-H), 3.81 (s, 3H, OMe), 3.84 (d, J = 15.2 Hz, 6-H), 3.85 (s, 3H, OMe), 5.57 (s, 1H, 3'-H), 5.71-5.79 (m, 1H, 4-H), 5.82-5.89 (m, 1H, 3-H), 5.91 (s, 1H, 3'-H), 6.48 (s, 1H, 10-H), 6.74 (s, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (C-2), 26.6 (C-1), 35.2 (C-10b), 51.3 (C-6), 55.7 (OMe), 55.9 (C-1'), 56.0 (OMe), 60.9

(C-4a), 109.0 (C-7), 110.2 (C-10), 117.8 (C-2'), 126.0 (C-3'), 126.6 (Ar), 129.1 (Ar), 131.7 (C-4), 132.1 (C-3), 147.1 (Ar), 147.8 (Ar).

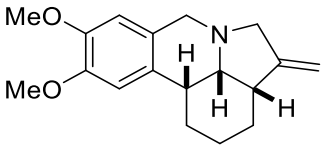
9,10-Dimethoxy-4-methylene-2,3,3a,3a,1,4,5,7,11b-octahydro-1*H*-pyrrolo[*3,2,1-de*]phenanthridine-3-carbonitrile (9-66)



9-66

To a solution of $Ni(COD)_2$ (149 mg, 0.54 mmol, 2.0 equiv) in dry acetonitrile (1 mL), at room temperature and under nitrogen atmosphere, was added a solution of vinyl bromide **9-65** (100 mg, 0.27 mmol) and Et_3N (117 µL, 0.81 mmol, 3.0 equiv) in dry acetonitrile (1 mL). The reaction mixture was stirred at room temperature for about 15 min, resulting in a color change from yellow to black. When all starting material had been consumed (checked by TLC), the quencher TMSCN (100 µL, 0.66 mmol, 2.5 equiv) was added and the mixture stirred for additional 3 h. It was filtered through Celite and the filter cake washed several times with CH_2Cl_2. The filtrate was washed with saturated Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH, 9/1) afforded the cyclization product **9-66** (67 mg, 80%) as yellow solid. R_f = 0.6 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (tt, J = 3.3, 13.6 Hz, 1H, 1-H), 1.75-2.87 (m, 1H, 2-H), 1.91-2.02 (m, 1H, 1-H), 2.02-2.13 (m, 1H, 2-H), 2.68 (t, J = 4.8 Hz, 1H, 3a-H), 2.72-2.82 (m, 2H, 3-H, 11b-H), 2.94 (d, J = 14.1 Hz, 1H, 5-H), 3.00-3.07 (m, 1H, 3b-H), 3.28 (d, J = 14.1 Hz, 1H, 5-H), 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.09 (d, J = 14.4 Hz, 1H, 7-H), 4.11 (d, J = 14.4 Hz, 1H, 7-H), 5.08 (s, 1H, 4-CH_2), 5.13 (s, 1H, 4-CH_2), 6.52 (s, 1H, 11-H), 6.62 (s, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6 (C-3), 27.3 (C-2), 31.1 (C-1), 38.1 (C-11b), 44.8 (C-3a), 55.7 (C-7), 55.89 (OMe), 55.92 (OMe), 59.5 (C-5), 61.1 (C-3b), 107.6 (4-CH_2), 109.2 (C-8), 111.2 (C-11), 121.6 (CN), 126.0 (Ar), 129.9 (Ar), 147.5 (Ar), 147.6 (Ar), 148.4 (C-4); HRMS (ESI): calcd for $C_{19}H_{22}N_2O_2$ $[M+H]^+$ 311.17540, found 311.17548.

9,10-Dimethoxy-4-methylene-2,3,3a,3a,1,4,5,7,11b-octahydro-1*H*-pyrrolo[*3,2,1-de*]phenanthridine (9-67)

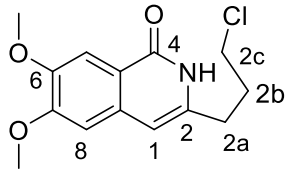


9-67

To a solution of $Ni(COD)_2$ (149 mg, 0.54 mmol, 2.0 equiv) in dry acetonitrile (1 mL), at room temperature and under nitrogen atmosphere, was added a solution of vinyl bromide **9-65** (100 mg, 0.27 mmol) and Et_3N (117 µL, 0.81 mmol, 3.0 equiv) in dry acetonitrile (1 mL). The reaction mixture was stirred at room temperature for about 15 min, resulting in a color change

from yellow to black. When all starting material had been consumed (checked by TLC), the quencher Et_3SiH (137 µL, 0.85 mmol, 3.2 equiv) was added and the mixture stirred for additional 3 h. It was filtered through Celite and the filter cake washed several times with CH_2Cl_2. The filtrate was washed with saturated Na_2CO_3 solution. The organic laywer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH, 9/1) afforded the cyclization product **9-67** (54 mg, 70%) as yellow solid. R_f = 0.5 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23-1.48 (m, 3H, 3-H, 2-H), 1.55-1.80 (m, 3H, 2-H, 1-H), 2.48-2.59 (m, 2H, 3a-H, 11b-H), 2.64-2.75 (m, 1H, 3b-H), 2.83 (d, J = 14.0 Hz, 1H, 5-H), 3.20 (d, J = 14.0 Hz, 1H, 5-H), 3.75 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.88 (d, J = 14.0 Hz, 1H, 7-H), 3.97 (d, J = 14.0 Hz, 1H, 7-H), 4.81 (s, 1H, 4-H), 4.82 (s, 1H, 4-H), 6.45 (s, 1H, 11-H), 6.57 (s, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (C-2), 29.8 (C-3), 31.4 (C-1), 38.5 (C-11b), 43.5 (C-3a), 55.8 (OMe), 56.4 (C-7), 59.9 (C-5), 62.9 (C-3b), 103.9 (4-*C*H_2), 109.2 (C-8), 111.3 (C-11), 125.7 (Ar), 131.5 (Ar), 147.2 (Ar), 147.6 (Ar), 152.2 (C-4); HRMS (ESI): calcd for $C_{18}H_{23}NO_2$ $[M+H]^+$ 286.18016, found 286.18043.

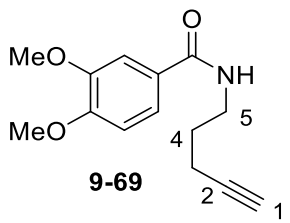
3-(3-Chloropropyl)-6,7-dimethoxyisoquinolin-1(2*H*)-one (9-68)



9-68

Prepared from *N*-(pivaloyloxy)benzamide **8-6** (200 mg, 0.71 mmol) according to procedure 3. TLC showed consumption of starting material after 35 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 2:1) to give pure isoquinolone **9-68** (70 mg, 35%) along the *N*-alkylation product **9-69** (30 mg, 17%) as colorless solids. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21-2.35 (m, 2H, 2b-H), 2.83 (t, J = 7.6 Hz, 2H, 2a-H), 3.62 (t, J = 6.3 Hz, 2H, 2c-H), 3.97 (s, 3H, OMe), 4.00 (s, 3H, OMe), 6.30 (s, 1H, 1-H), 6.84 (s, 1H, 5-H), 6.84 (s, 1H, 8-H), 11.92 (NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4 (C-2b), 31.1 (C-2a), 44.0 (C-2c), 56.0 (OMe), 56.1 (OMe), 104.3 (C-1), 105.8 (C-5), 106.9 (C-8), 118.1, 134.2, 138.8, 148.8, 153.8, 164.2 (C-4).

3,4-Dimethoxy-N-(pent-4-yn-1-yl)benzamide (9-69)

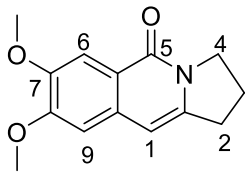


9-69

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 1H, 1-H), 2.20-2.37 (m, 2H, 4-H), 2.77-2.93 (m, 2H, 3-H), 3.62 (t, J = 6.2 Hz, 2H, 5-H), 3.89 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.62 (s, 1H, Ar), 7.09 (d, J = 8.8 Hz, 1H, Ar), 8.12 (d, J = 8.8 Hz, 1H, Ar), 11.68 (s, 1H, NH); ^{13}C NMR (100

MHz, $CDCl_3$): δ = 30.8 (C-4), 31.1 (C-3), 44.0 (C-5), 56.0 (OMe), 61.0 (C-1), 98.6, 111.6, 124.2, 133.7, 140.4, 141.8, 154.9, 164.6 (CONH).

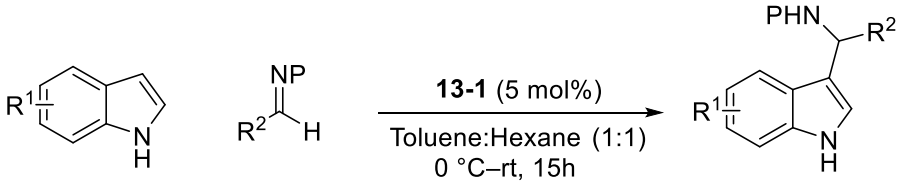
7,8-dimethoxy-2,3-dihydropyrrolo[1,2-*b*]isoquinolin-5(1*H*)-one (8-9)



8-9

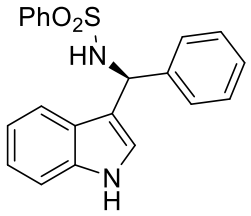
To the cooled (0 °C) solution of compound **9-68** (50 mg, 0.18 mmol) in THF (3 mL) was added LiHMDS (0.27 mmol, 1.5 equiv) dropwise, then the reaction mixture was allowed to reach at rt in overnight. Excess of LiHMDS was quenched with saturated solution of NH_4Cl (5 mL) at 0 °C, and then the mixture was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with saturated NaCl (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (ethylacetate/petroleum ether, 1:3) to get pure compound **8-9** (32 mg, 72%) as colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15-2.21 (m, 2H, 3-H), 3.07 (td, J = 1.3, 7.8 Hz, 2H, 2-H), 3.95 (s, 3H, OMe), 3.98 (s, 3H, OMe), 4.16 (t, J = 7.1 Hz, 2H, 4-H), 6.32 (s, 1H, 1-H), 6.80 (s, 1H, 6-H), 7.74 (s, 1H, 9-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (C-3), 31.1 (C-2), 48.0 (C-4), 56.0 (OMe), 56.1 (OMe), 99.8 (C-1), 105.8 (C-6), 107.2 (C-9), 118.5, 133.6, 142.3, 148.4, 153.2, 160.9 (C-5); HRMS (ESI): calcd for $C_{12}H_{15}NO_3$ $[M+Na]^+$ 268.09441 found 268.09477.

Asymmetric addition of indoles to *N*-Sulfonyl imines (procedure 10)



A hot oven dried Schlenk tube (10 cm) equipped with magnetic stir bar and rubber septum, was cooled under nitrogen atmosphere. Thereafter, it was charged with *N*-sulfonyl imine (0.1 mmol), catalyst **13-1** (5 mol%) and molecular sieves (0.4 nm, 50 mg). Then the mixture was allowed to stir for 2 min under N_2 before dry toluene and hexane (1 mL, 1:1 mixture) were added. The reaction mixture was cooled to 0 °C and indole (2.5 mmol) was added in one portion. The reaction was allowed to stir for 15 h (0 °C to rt), diluted with EtOAc (2 mL) and the mixture was syringed out and filtered through a PTFE-20/25 (0.20 μm) filter. The Schlenk tube was rinsed with EtOAc (2 × 2 mL), which was also filtered. The filtrates were combined and concentrated in *vacuo*. The residue was purified by preparative TLC (solvent mixture is mentioned along the compounds).

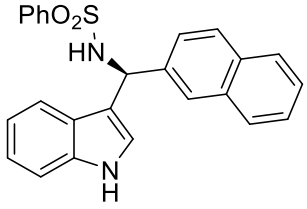
(*S*)-*N*-((1*H*-indol-3-yl)(phenyl)methyl)benzenesulfonamide (12-33a)



12-33a

Prepared from imine **12-31a** (25 mg, 0.1 mmol) and indole (**12-27a**) (29 mg, 0.25 mmol) according to procedures 10 to give product **12-33a** as colorless amorphous solid (33 mg, 97%). R_f = 0.3 (petroleum ether/EtOAc, 1:3); *ee* = 97% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 31.0 min, t (minor) = 19.8 min]; $[\alpha]_D^{25}$ = –8.8 (c 1.0, Acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 5.86 (s, 1H), 6.64 (s, 1H), 6.89 (td, *J* = 7.1, 1.0 Hz, 1H), 7.05 (td, *J* = 7.1, 1.0 Hz, 1H), 7.10-7.18 (m, 3H), 7.20-7.32 (m, 6H), 7.35-7.43 (m, 1H), 7.63 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 56.4, 112.4, 116.9, 120.9, 120.1, 120.3, 122.8, 125.2, 127.3, 128.0, 128.2, 128.6, 129.2, 129.7, 133.1, 138.4, 142.6, 142.9; HRMS (ESI): calcd for $C_{21}H_{18}N_2O_2S$ $[M+Na]^+$ 385.09812; found 385.09874.

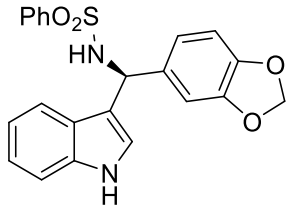
(*S*)-*N*-((1*H*-indol-3-yl)(naphthalen-2-yl)methyl)benzenesulfonamide (12-33b)



12-33b

Prepared from imine **12-31b** (30 mg, 0.1 mmol) and indole (**12-27a**) (29 mg, 0.25 mmol) according to procedures 10 to give product **12-33b** (40 mg, 97%) as colorless amorphous pink. R_f = 0.3 (petroleum ether/EtOAc, 3:1); *ee* = 97% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 36.7 min, t (minor) = 27.5 min]; $[\alpha]_D^{25}$ = –18.1 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 6.02 (s, 1H), 6.69 (d, *J* = 1.0 Hz, 1H), 6.89 (td, *J* = 7.1, 1.0 Hz 1H), 7.06 (td, *J* = 7.1, 1.0 Hz, 1H), 7.13-7.20 (m, 2H), 7.23-7.30 (m, 2H), 7.31-7.38 (m, 2H), 7.40 (d, *J* = 3.5 Hz, 1H), 7.42 (d, *J* = 3.0 Hz 1H), 7.60-7.71 (m, 5H), 7.75 (dd, *J* = 5.6, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 56.6, 112.4, 116.8, 120.1, 120.3, 122.8, 125.3, 126.9, 127.0, 127.1, 127.3, 127.4, 128.1, 128.6, 129.0, 129.1, 129.6, 133.0, 134.2, 134.7, 138.5, 139.9, 143.0; HRMS (ESI): calcd for $C_{25}H_{20}N_2O_2S$ $[M+Na]^+$ 435.11377; found 435.11382.

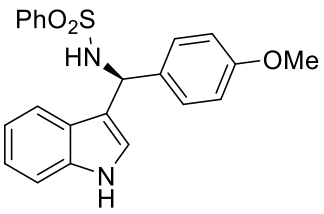
(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl(1*H*-indol-3-yl)methyl)benzenesulfonamide (12-33c)



12-33c

Prepared from imine **12-31c** (30 mg, 0.1 mmol) and indole (**12-27a**) (29 mg, 0.25 mmol) according to procedures 10 to give product **12-33c** (42 mg, 99%) as colorless amorphous solid. R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 98% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 46.2 min, t (minor) = 40.2 min]; $[\alpha]_D^{25}$= –7.7 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 5.77 (s, 1H), 5.82 (d, *J* = 8.1 Hz, 2H), 6.58 (d, *J* = 7.8 Hz 1H), 6.65-6.74 (m, 3H), 6.91 (td, *J* = 7.8, 1.0 Hz, 1H), 7.06 (td, *J* = 8.0, 1.0 Hz, 1H), 7.23-7.36 (m, 4H), 7.41 (t, *J* = 7.1 Hz, 1H), 7.63 (dd, *J* = 8.1, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 56.5, 102.3, 108.7, 109.1, 112.4, 116.9, 120.1, 120.4, 122.2, 122.8, 125.0, 127.2, 128.1, 129.7, 130.1, 133.0, 136.5, 138.5, 143.0, 148.0, 148.2, 149.0; HRMS (ESI): calcd for $C_{22}H_{18}N_2O_2S$ $[M+Na]^+$ 415.10868; found 415.10936.

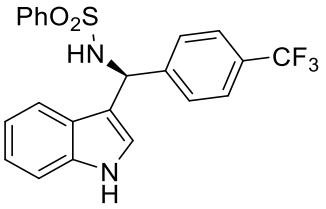
(*S*)-*N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)benzenesulfonamide (12-33d)



12-33d

Prepared from imine **12-31d** (28 mg, 0.1 mmol) and indole (**12-27a**) (29 mg, 0.25 mmol) according to procedures 10 to give product **12-33d** (31 mg, 79%) as colorless solid. yield:. R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 96% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 46.0 min, t (minor) = 275 min]; $[\alpha]_D^{25}$= –12.7 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.72 (s, 3H), 5.80 (s, 1H), 6.66-6.72 (m, 3H), 6.89 (td, *J* = 7.07, 1.0 Hz, 1H), 7.05 (td, *J* = 8.1, 1.0 Hz, 1H), 7.09-7.15 (m, 2H), 7.24-7.32 (m, 4H), 7.40 (tt, *J* = 7.3, 1.8 Hz, 1H), 7.59-7.65 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ = 55.8, 56.1, 112.3, 114.6, 117.2, 120.0, 120.4, 122.7, 125.1, 127.2, 128.1, 129.7, 129.8, 133.0, 134.7, 138.5, 143.1, 160.3; HRMS (ESI): calcd for $C_{22}H_{20}N_2O_3S$ $[M+Na]^+$ 415.10868; found 415.10936.

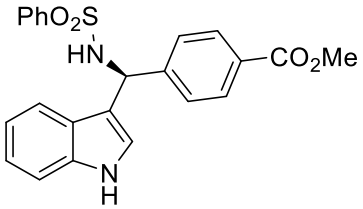
(*S*)-*N*-((1*H*-Indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)benzenesulfonamide (12-33e)



12-33e

Prepared from imine **12-31e** (31 mg, 0.1 mmol) and indole (**12-27a**) (32 mg, 0.26 mmol) according to procedures 10 to give product **12-33e** (37 mg, 86%) as colorless solid, yield: R_f = 0.2 (petroleum ether/EtOAc, 2:1); *ee* = 96% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 28.7 min, t (minor) = 19.5 min]; $[\alpha]_D^{25}$= –19.3 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 5.93 (s, 1H), 6.62 (s, 1H), 6.91 (td, *J* = 7.1, 1.0 Hz, 1H), 7.07 (td, *J* = 7.1, 1.0 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.8 Hz 2H), 7.40-7.50 (m, 5H), 7.65 (dd, *J* = 8.8, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 56.0, 112.5, 116.0, 120.1, 120.3, 123.0, 125.3, 126.1 (q, *J* = 4.1 Hz), 127.1, 128.1, 128.4 (CF_3, *J* = 267.0 Hz), 129.3, 129.8, 133.2, 138.5, 142.8, 147.3; HRMS (ESI): calcd for $C_{22}H_{17}F_3N_2O_2S$ $[M+Na]^+$ 453.08550; found 453.08577.

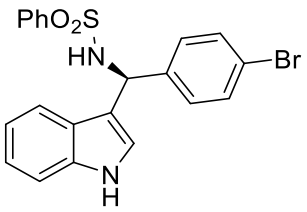
Methyl (*S*)-4-((1*H*-indol-3-yl)(phenylsulfonamido)methyl)benzoate (12-33f)



12-33f

Prepared from imine **12-31f** (30 mg, 0.1 mmol) and indole (**12-27a**) (22 mg, 0.25 mmol) according to procedures 10 to give product **12-33f** (40 mg, 52%) as colorless amorphous pink. R_f = 0.2 (petroleum ether/EtOAc, 2:1); *ee* = 90% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 47.4 min, t (minor) = 26.9 min]; $[\alpha]_D^{25}$= –15.7 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3H), 5.38 (d, *J* = 6.8 Hz, 1H), 5.92 (d, *J* = 6.8 Hz, 1H), 6.55 (s, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 7.15-7.23 (m, 2H), 7.28-7.36 (m, 5H), 7.44-7.50 (m, 1H), 7.67-7.72 (m, 2H), 7.85-7.89 (m, 2H), 8.13 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.1, 54.6, 111.37, 111.4, 115.37, 115.4, 118.9, 120.1, 120.1, 122.7, 123.7, 123.8, 125.0, 125.1, 127.1, 127.1, 128.8, 129.2, 129.6, 132.5, 136.3, 136.4, 140.1, 140.14, 145.3, 166.8; HRMS (ESI): calcd for $C_{23}H_{20}N_2O_4S$ $[M+Na]^+$ 443.10360; found 443.10358.

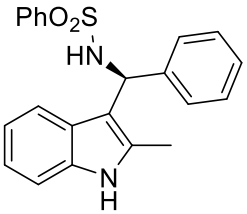
(*S*)-4-Bromo-*N*-((4-bromophenyl)(1*H*-indol-3-yl)methyl)benzenesulfonamide (12-33g)



12-33g

Prepared from imine **12-31g** (32 mg, 0.1 mmol) and indole (**12-27a**) (29 mg, 0.25 mmol) according to procedures 10 to give product **12-33g** (16 mg, 36%) as brown amorphous solid. R_f = 0.2 (petroleum ether/EtOAc, 2:1); *ee* = 87% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 34.0 min, t (minor) = 22.2 min]; $[\alpha]_D^{25}$= –18.7 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (d, *J* = 6.6, 1H), 5.84 (d, *J* = 6.6 Hz, 1H), 6.63 (m, 1H), 7.06-7.00 (m, 1H), 7.23-7.13 (m, 4H), 7.40-7.31 (m, 5H), 7.55-7.49 (m, 1H), 7.72-7.68 (m, 2H), 8.04 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.5, 111.4, 115.7, 119.0, 120.2, 121.4, 122.8, 123.7, 125.0, 127.1, 128.8, 128.9, 131.4, 132.4, 136.5, 139.2, 140.2; HRMS (ESI): calcd for $C_{21}H_{17}BrN_2O_2S$ $[M+Na]^+$ 463.00863; found 463.00818.

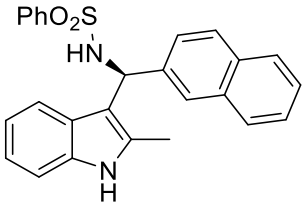
(*S*)-4-bromo-*N*-((2-methyl-1*H*-indol-3-yl)(phenyl)methyl)benzenesulfonamide (14-16a)



14-16a

Prepared from imine **12-31a** (25 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (33 mg, 0.25 mmol) according to procedures 10 to give product **14-16a** (45 mg, 99%) as yellow amorphous solid. R_f = 0.3 (petroleum ether/EtOAc, 3:1); *ee* = 92% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 18.1 min, t (minor) = 12.0 min]; $[\alpha]_D^{25}$= –20.6 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.07 (s, 3H), 5.85 (s, 1H), 6.75 (t, *J* = 7.1 Hz, 1H), 6.91 (t, *J* = 7.1, 1H), 7.12-7.04 (m, 2H), 7.26-7.13 (m, 5H), 7.40-7.29 (m, 3H), 7.50-7.45 (m, 1H), 7.57-7.51 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 11.7, 54.0, 111.4, 111.7, 119.6, 120.0, 121.5, 127.7, 127.8, 128.1, 128.4, 129.1, 129.3, 132.6, 134.4, 143.1, 143.4; HRMS (ESI): calcd for $C_{22}H_{20}N_2O_2S$ $[M+Na]^+$ 399.11377; found 399.11403.

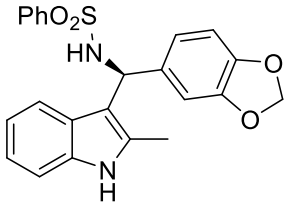
(*S*)-*N*-((2-Methyl-1*H*-indol-3-yl)(naphthalen-2-yl)methyl)benzenesulfonamide (14-16b)



14-16b

Prepared from imine **12-31b** (28 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (33 mg, 0.25 mmol) according to procedures 10 to give product **14-16b** (34 mg, 84%) as yellow amorphous solid. R_f = 0.7 (petroleum ether/EtOAc, 2:1); *ee* = 93% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 28.1 min, t (minor) = 17.6 min]; $[\alpha]_D^{25}$= –38.9 (c 0.25, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H), 5.39 (d, *J* = 7.1 Hz, 1H), 5.90 (d, *J* = 7.33 Hz, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.89-6.97 (m, 2H), 7.02-7.15 (m, 3H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.29-7.36 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.56-7.62 (m, 2H), 7.64-7.68 (m, 1H), 7.71 (br, 1H), 7.81 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 53.9, 110.3, 110.4, 118.3, 119.7, 121.4, 125.3, 125.4, 125.9, 126.0, 126.1, 126.8, 127.4, 128.0, 128.1, 128.4, 132.1, 132.5, 132.8, 133.0, 135.2, 137.8, 140.1; HRMS (ESI): calcd for $C_{26}H_{22}N_2O_2S$ $[M+Na]^+$ 449.12942; found 449.12924.

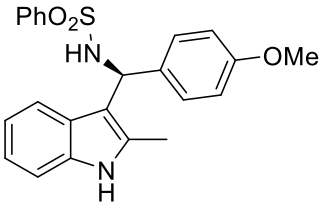
(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl(2-methyl-1*H*-indol-3-yl)methyl)benzenesulfonamide (14-16c)



14-16c

Prepared from imine **12-31c** (30 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (33 mg, 0.25 mmol) according to procedures 10 to give product **14-16c** (42 mg, 97%) as yellow amorphous solid. yield: R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 84% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 29.4 min, t (minor) = 21.6 min]; $[\alpha]_D^{25}$= –14.9 (c 0.8, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.08 (s, 3H), 5.75 (s, 1H), 5.86 (dd, *J* = 6.3, 1.0 Hz, 2H), 6.64 (dd, *J* = 6.1, 2.3 Hz, 1H), 6.75-6.86 (m, 3H), 6.92 (td, *J* = 7.1, 1.0 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.30 (tt, *J* = 7.6, 1.0 Hz 1H), 7.51 (dd, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 11.7, 54.6, 102.2, 108.5, 108.9, 110.9, 111.3, 119.7, 119.8, 121.5, 121.6, 127.5, 129.2, 132.7, 134.3, 136.5, 137.0, 142.1, 147.8, 148.9; HRMS (ESI): calcd for $C_{23}H_{20}N_2O_4S$ $[M+Na]^+$ 443.10360; found 443.10357.

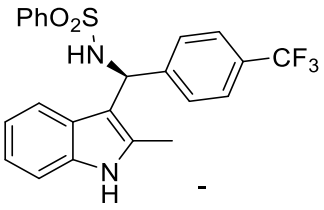
(*S*)-*N*-((4-methoxyphenyl)(2-methyl-1*H*-indol-3-yl)methyl)benzenesulfonamide (14-16d)



14-16d

Prepared from imine **12-31d** (26 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (33 mg, 0.25 mmol) according to procedures 10 to give product **14-16d** (33 mg, 86%) as yellow foam. R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 83% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 28.8 min, t (minor) = 16.7 min]; $[\alpha]_D^{25}$= –11.7 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.08 (s, 3H), 3.72 (s, 3H), 5.80 (s, 1H), 6.76 (t, *J* = 8.1 Hz, 3H), 6.91 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.13 (t, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ= 11.7, 54.5, 55.8, 111.2, 111.4, 114.5, 119.7, 120.0, 121.6, 127.6, 128.0, 129.2, 129.6, 132.8, 134.4, 134.6, 137.2, 142.5, 160.2; HRMS (ESI): calcd for $C_{23}H_{22}N_2O_3S$ $[M+Na]^+$ 429.12433; found 429.12438.

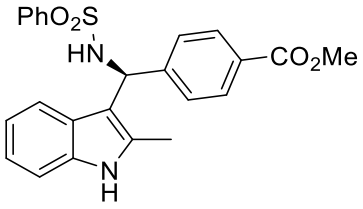
(*S*)-*N*-((2-methyl-1*H*-indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)benzenesulfonamide (14-16e)



14-16e

Prepared from imine **12-31e** (33 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (36 mg, 0.25 mmol) according to procedures 10 to give product **14-16a** (39 mg, 88%) as yellow amorphous solid. R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 93% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 21.7 min, t (minor) = 10.6 min]; $[\alpha]_D^{25}$= –37 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.73 (d, J = 6.8 Hz, 1H), 6.78-6.92 (m, 2H), 6.99 (td, *J* = 8.0, 1.0 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.17-7.24 (m, 2H), 7.33-7.39 (m, 1H), 7.44 (q, *J* = 8.6 Hz, 4H), 7.53-7.58 (m, 2H), 7.75 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.4, 53.4, 110.0, 110.6, 118.1, 120.0, 121.8, 125.2, 125.2, 125.3, 125.5, 126.9, 127.4, 128.6, 129.0, 129.1, 132.4, 132.8, 135.3, 139.8, 144.6; HRMS (ESI): calcd for $C_{23}H_{19}F_3N_2O_2S$ $[M+Na]^+$ 467.10115; found 467.10152.

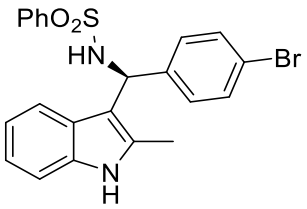
Methyl (*S*)-4-((2-methyl-1*H*-indol-3-yl)(phenylsulfonamido)methyl)benzoate (14-16f)



14-16f

Prepared from imine **12-31f** (31 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (34 mg, 0.25 mmol) according to procedures 10 to give product **14-16f** (49 mg, 99%) as yellow amorphous amorphous solid. R_f = 0.3 (petroleum ether/EtOAc, 3:1); *ee* = 97% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 33.2 min, t (minor) = 16.8 min]; $[\alpha]_D^{25}$= –33.1 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.95 (s, 3H), 3.80 (s, 3H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.75 (d, *J* = 7.1 Hz, 1H), 6.79 (td, *J* = 8.1, 1.0 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.96 (td, *J* = 8.1, 1.0 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.16-7.22 (m, 2H), 7.34 (tt, *J* = 7.6, 1.0 Hz, 1H), 7.40 (d, *J* = 7.8, 2H), 7.53-7.57 (m, 2H), 7.79-7.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.5, 52.1, 53.6, 110.1, 110.5, 118.1, 119.9, 121.6, 125.6, 126.9, 127.0, 128.6, 128.9, 129.5, 132.8, 132.3, 135.2, 139.9, 145.9, 166.9; HRMS (ESI): calcd for $C_{24}H_{22}N_2O_4S$ $[M+Na]^+$ 457.11925; found 457.11944.

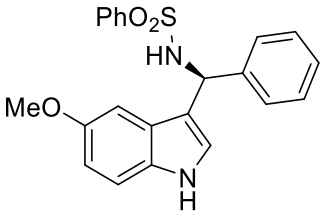
(*S*)-*N*-((4-Bromophenyl)(2-methyl-1*H*-indol-3-yl)methyl)benzenesulfonamide (14-16g)



14-16g

Prepared from imine **12-31g** (32 mg, 0.1 mmol) and 2-methylindole (**12-27b**) (32 mg, 0.25 mmol) according to procedures 10 to give product **14-16g** (39 mg, 80%) as brown amorphous solid. R_f = 0.4 (petroleum ether/EtOAc, 3:1); *ee* = 92% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 23.0 min, t (minor) = 11.9 min]; $[\alpha]_D^{25}$= –14.4 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ= 2.05 (s, 3H), 5.78 (s, 1H), 6.77 (td, *J* = 7.1, 1.0 Hz, 1H), 6.92 (td, *J* = 7.3, 1.0 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.25-7.40 (m, 5H), 7.55 (dd, *J* = 8.1, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ= 11.6, 54.4, 110.6, 111.5, 119.7, 119.9, 121.7, 121.8, 127.7, 129.4, 130.4, 132.2, 133.0, 134.7, 137.2, 142.3; HRMS (ESI): calcd for $C_{22}H_{19}BrN_2O_2S$ $[M+Na]^+$ 477.02428; found 477.02422.

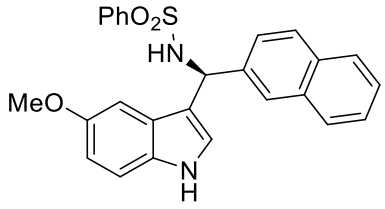
(*S*)-*N*-((5-methoxy-1*H*-indol-3-yl)(phenyl)methyl)benzenesulfonamide (14-17a)



14-17a

Prepared from imine **12-31a** (25 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (37 mg, 0.25 mmol) according to procedures 10 to give product **14-17a** (40 mg, 99%) as colorless amorphous solid. R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 94% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 68.1 min, t (minor) = 15.0 min]; $[\alpha]_D^{25}$ = –19.6 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.69 (s, 3H), 5.83 (s, 1H), 6.59 (s, 1H), 6.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 7.11-7.20 (m, 4H), 7.22-7.30 (m, 4H), 7.38 (tt, *J* = 7.6, 1.0 Hz, 1H), 7.63 (dd, *J* = 8.3, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 56.3, 56.5, 102.2, 113.0, 113.2, 116.7, 125.9, 127.7, 128.0, 128.2, 128.6, 129.2, 129.7, 133.1, 133.6, 142.7, 143.0, 155.1; HRMS (ESI): calcd for $C_{22}H_{20}N_2O_3S$ $[M+Na]^+$ 415.10868; found 415.10841.

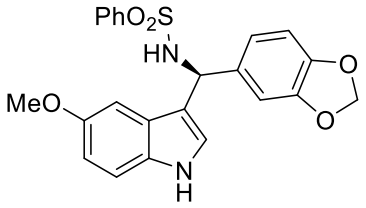
(*S*)-*N*-((5-methoxy-1*H*-indol-3-yl)(naphthalen-2-yl)methyl)benzenesulfonamide (14-17b)



14-17b

Prepared from imine **12-31b** (28 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (37 mg, 0.25 mmol) according to procedures 10 to give product **14-17b** (38 mg, 91%) as yellow amorphous solid. R_f = 0.3 (petroleum ether/EtOAc, 3:1); *ee* = 95% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 66.7 min, t (minor) = 20.2 min]; $[\alpha]_D^{25}$ = –52.7 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (s, 3H), 5.38 (d, *J* = 7.3 Hz, 1H), 6.43-6.47 (m, 1H), 6.73 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 7.02-7.09 (m, 3H), 7.14-7.23 (m, 2H), 7.30-7.39 (m, 2H), 7.50-7.58 (m, 5H), 7.63-7.69 (m, 1H), 7.85 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 55.8, 100.9, 112.1, 112.9, 115.7, 124.6, 125.2, 125.8, 125.9, 126.0, 126.1, 126.3, 126.9, 127.5, 127.9, 128.1, 128.5, 129.1, 131.5, 133.0, 137.2, 140.4, 154.2; HRMS (ESI): calcd for $C_{26}H_{22}N_2O_3S$ $[M+Na]^+$ 465.12433; found 465.12446.

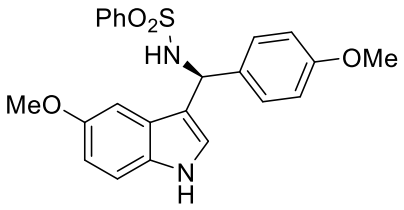
(*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl(5-methoxy-1*H*-indol-3-yl)methyl)benzenesulfonamide (14-17c)



14-17c

Prepared from imine **12-31c** (30 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (37 mg, 0.25 mmol) according to procedures 10 to give product **14-17c** (45 mg, 99%) as colorless crystalline solid. R_f = 0.2 (petroleum ether/EtOAc, 3:1); recrystallized (CH_2Cl_2/petroleum ether, 2:1); *ee* = 98% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 93.1 min, t (minor) = 27.1 min]; $[\alpha]_D^{25}$= –17.5 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 5.05 (d, *J* = 6.8 Hz, 1H), 5.78 (d, *J* = 6.8 Hz, 1H), 5.90 (dd, *J* = 6.8, 1.3 Hz,2H), 6.62-6.77 (m, 4H), 6.82-6.89 (m, 2H), 7.21 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.3, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.91 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.0, 55.8, 101.0, 101.0, 107.7, 107.9, 112.0, 113.0, 116.0, 120.7, 124.2, 125.7, 127.1, 128.6, 131.6, 132.2, 134.0, 140.6, 146.9, 147.6, 154.3; HRMS (ESI): calcd for $C_{23}H_{20}N_2O_5S$ $[M+Na]^+$ 459.09851; found 459.09862.

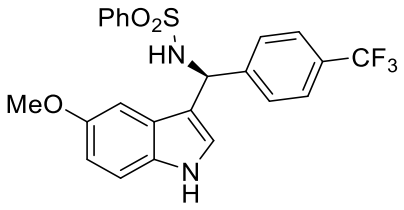
(*S*)-*N*-((5-methoxy-1*H*-indol-3-yl)(4-methoxyphenyl)methyl)benzenesulfonamide (14-17d)



14-17d

Prepared from imine **12-31d** (28 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (37 mg, 0.25 mmol) according to procedures 10 to give product **14-17d** (41 mg, 97%) as colorless amorphous solid. R_f = 0.2 (petroleum ether/EtOAc, 2:1); *ee* = 98% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 94.4 min, t (minor) = 20.6 min]; $[\alpha]_D^{25}$= –16.8 (c 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3H), 3.67 (s, 3H), 5.19 (d, *J* = 7.1, 1H), 5.73 (d, *J* = 7.1 Hz, 1H), 6.53 (d, *J* = 2 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.72-6.77 (m, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 54.7, 55.2, 55.8, 101.0, 112.0, 112.8, 113.7, 116.1, 124.3, 125.8, 126.3, 127.0, 128.3, 128.6, 129.1, 131.6, 132.1, 140.5, 154.1, 158.8; HRMS (ESI): calcd for $C_{23}H_{22}N_2O_4S$ $[M+Na]^+$ 445.11925; found 445.11920.

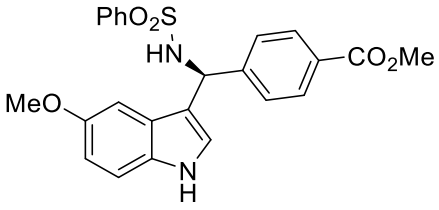
(*S*)-*N*-((5-Methoxy-1*H*-indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)benzenesulfonamide (14-17e)



14-17e

Prepared from imine **12-27e** (31 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (37 mg, 0.25 mmol) according to procedures 10 to give product **14-17e** (46 mg, 99%) as red solid. R_f = 0.2 (petroleum ether/EtOAc, 3:1); *ee* = 98% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 65.7 min, t (minor) = 11.7 min]; $[\alpha]_D^{25}$= –37.5 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ= 3.69 (s, 3H), 5.91 (s, 1H), 6.56 (s, 1H), 6.74 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.24-7.31 (m, 5H), 7.64 (dd, *J* = 8.1, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ= 56.1, 56.3, 101.0, 113.2, 113.4, 115.7, 125{(q, *J* = 271.2 Hz) 121.8, 124.4, 127.1, 129.9}, 125.9, 126.1 (q, *J* = 4.1 Hz), 127.5, 128.1, 129.1, 128.8, 130 {-CF_3 (q, *J* = 32.3 Hz), 129.8, 130.1, 130.5, 130.9}, 133.2, 133.6, 142.8, 147.1, 155.3; HRMS (ESI): calcd for $C_{23}H_{19}F_3N_2O_3S$ $[M+Na]^+$ 483.09607; found: 483.09635.

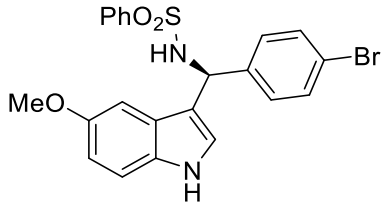
Methyl (*S*)-4-((5-methoxy-1*H*-indol-3-yl)(phenylsulfonamido)methyl)benzoate (14-17f)



14-17f

Prepared from imine **12-31f** (28 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (36 mg, 0.25 mmol) according to procedures 10 to give product **14-17f** (39 mg, 94%) as a slightly yellow solid. R_f = 0.2 (petroleum ether/EtOAc, 2:1); *ee* = 93% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 113.9 min, t (minor) = 23.3 min]; $[\alpha]_D^{25}$= –28.4 (c 1.06, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.62 (s, 3H), 3.81 (s, 3H), 5.48 (d, *J* = 6.8 Hz, 1H), 5.80 (d, *J* = 6.8 Hz, 1H), 6.37 (s, 1H), 6.73 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.13-7.21 (m, 4H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 8.03 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 52.1, 54.7, 55.8, 100.6, 112.2, 113.0, 115.0, 124.5, 125.6, 126.9, 127.1, 128.7, 129.1, 129.6, 131.5, 132.4, 140.2, 145.3, 154.2, 166.8; HRMS: calcd for $C_{24}H_{22}N_2O_5S$ $[M+Na]^+$ 473.11416; found 473.11457.

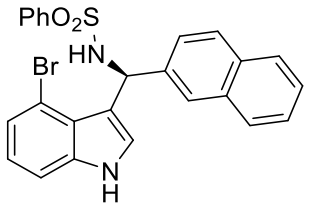
(*S*)-*N*-((4-Bromophenyl)(5-methoxy-1*H*-indol-3-yl)methyl)benzenesulfonamide (14-17g)



14-17g

Prepared from imine **12-31g** (32 mg, 0.1 mmol) and 5-methoxyindole (**12-27c**) (37 mg, 0.25 mmol) according to procedures 10 to give product **14-17g** (37 mg, 78%) as brown solid. R_f = 0.3 (petroleum ether/EtOAc, 3:1); *ee* = 65% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 78.9 min, t (minor) = 14.3 min]; $[\alpha]_D^{25}$= –21.3 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.73 (s, 3H), 5.83 (s, 1H), 6.61 (s, 1H), 6.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 7.23-7.17 (m, 3H), 7.36-7.28 (m, 4H), 7.45 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.63-7.52 (m, 1H), 7.7-7.64 (m, 2H), 7.96-7.91 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 55.7, 56.1, 101.9, 112.9, 113.1, 115.8, 121.7, 125.6, 127.0, 127.3, 127.8, 129.6, 129.9, 130.4, 132.0, 132.9, 133.1, 133.4, 141.8, 142.7, 145.0, 155.0; HRMS (ESI): calcd for $C_{22}H_{19}BrN_2O_3S$ $[M+Na]^+$ 493.01920; found 493.01888.

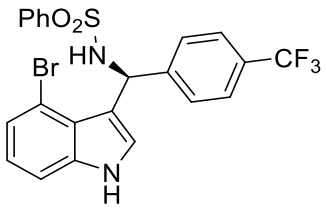
(*S*)-*N*-((4-bromo-1*H*-indol-3-yl)(naphthalen-2-yl)methyl)benzenesulfonamide (14-18b)



14-18b

Prepared from imine **12-31b** (30 mg, 0.1 mmol) and 4-bromoindole (**12-27d**) (50 mg, 0.25 mmol) according to procedures 10 to give product **14-18b** (30 mg, 51%) as a brown solid; Reaction time 55 h; R_f = 0.4 (petroleum ether/EtOAc, 3:1); *ee* = 63% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 30.8 min, t (minor) = 16.2 min]; $[\alpha]_D^{25}$= +1.0 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ = 6.83 (s, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 7.12 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.18-7.24 (m, 2H), 7.27-7.43 (m, 5H), 7.49 (s, 1H), 7.60 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.64-7.71 (m, 3H), 7.76 (dd, *J* = 7.1, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 55.2, 112.1, 114.4, 117.0, 123.7, 124.9, 125.7, 127.0, 127.2, 127.5, 127.6, 128.1, 128.6, 128.9, 129.1, 129.6, 130.1, 133.1, 133.3, 134.2, 134.7, 139.4, 141.4, 143.0; HRMS (ESI): calcd for $C_{25}H_{19}BrN_2O_2S$ $[M+Na]^+$ 513.02428; found 513.02396.

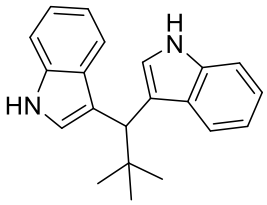
(*S*)-*N*-((4-Bromo-1H-indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)benzenesulfonamide (14-18e)



14-18e

Prepared from imine **12-31e** (33 mg, 0.11 mmol) and 4-bromoindole (**12-27e**) (50 mg, 0.25 mmol) according to procedures 10 to give product **14-18e** (39 mg, 73%) as a brown solid; Reaction time 55 h; R_f = 0.3 (petroleum ether/EtOAc, 3:1); *ee* = 94% [*n*-hexanes/2-propanol = 75/25, 0.8 mL/min, λ = 254 nm, t (major) = 25.6 min, t (minor) = 9.4 min]; $[\alpha]_D^{25}$= +1.0 (c 1.0, acetone); ^{1}H NMR (400 MHz, CD_3OD): δ: 6.74 (s, 1H), 6.94 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 0.5 Hz, 1H), 7.13 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.26-7.21 (m, 2H), 7.28 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.40-7.34 (m, 3H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.67-7.62 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 54.6, 112.2, 114.2, 123.7, 125.0, 125.5, 126.1 (q, *J* = 4.1 Hz), 127.2, 128.1, 128.8 {-CF_3 (*J* = 271.2 Hz), 127.4, 130.1}, 129.6, 129.7, 133.2, 139.4, 142.9, 148.5; HRMS (ESI): calcd for $C_{22}H_{16}BrF_3N_2O_2S$ $[M+Na]^+$ 530.99602; found 530.99614.

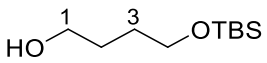
3,3'-(2,2-dimethylpropane-1,1-diyl)bis(1H-indole) (14-19j)



14-19j

Prepared from imine **12-31j** (23 mg, 0.1 mmol) and indole **12-27a** (29 mg, 0.25 mmol) according to procedures 10 to give product **14-19j** (35 mg, 99%) as colorless amorphous solid, R_f = 0.2 (petroleum ether/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9H), 4.57 (s, 1H), 7.17-7.07 (m, 4H), 7.22 (d, *J* = 2.5 Hz, 2H), 7.33-7.29 (m, 2H), 7.73 (d, *J* = 7.88, 2H), 7.97 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.0, 35.8, 43.0, 110.7, 119.1, 119.2, 119.4, 121.6, 121.9, 128.7, 135.3.

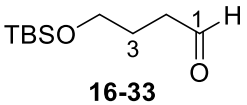
4-((*tert*-Butyldimethylsilyl)oxy)butan-1-ol (16-31)



16-32

To a stirred solution of 1,4-butanediol (16.0 g, 174.0 mmol) in CH_2Cl_2 (500 mL) at room temperature was added TBSCl (21.7 g, 144.0 mmol, 0.83 equiv). The resulting mixture was cooled to 0 °C before Et_3N (20.0 mL, 144.0 mmol, 0.83 equiv) was slowly added. The resulting mixture was warmed to room temperature and stirred for 3 h, then quenched with saturated aqueous NH_4Cl (250 mL). The layers were separated and the organic layer was washed with H_2O (200 mL), dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give mono-protected alcohol (6.0 g, 17%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_2Si$), 1.55-1.66 (m, 4H, 2-H, 3-H), 2.75 (br, 1H, OH), 3.60 (t, J = 5.8 Hz, 2H, 1-H), 3.63 (t, J = 5.6 Hz, 2H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 $(CH_3)_2Si$), 18.2 ($(CH_3)_3CSi$), 25.4 ($(CH_3)_3CSi$), 29.8 (C-2), 30.1 (C-3), 62.6, 63.3; HRMS (ESI): calcd for $C_{10}H_{24}O_2Si$ $[M+Na]^+$ 227.14378, found 227.14410.

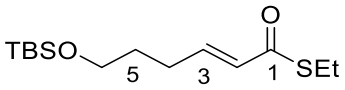
4-((*tert*-Butyldimethylsilyl)oxy)butanal (16-33)



16-33

To a solution of oxalyl chloride (2.55 mL, 29.78 mmol, 1.3 equiv) in CH_2Cl_2 (120 mL) at –80 °C was added DMSO (2.68 mL, 34.36 mmol, 1.5 equiv) dropwise. The resulting mixture was stirred for 15 min before alcohol **16-32** (4.683 g, 22.91 mmol) in CH_2Cl_2 (25 mL) was added dropwise within 15 min. After stirring the mixture for 1 h at –80 °C, Et_3N (17.19 mL, 119.12 mmol, 4 equiv) was added slowly. Then the reaction mixture was allowed to warm to room temperature. For work-up water (50 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give aldehyde **16-33** (3.536 g, 76%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.85 (s, 9H, $(CH_3)_3CSi$), 1.78-1.87 (m, 2H, 3-H), 2.47 (td, J = 1.5, 7.1 Hz, 2H, 2-H), 3.62 (t, J = 6.0 Hz, 2H, 4-H), 9.7 (t, J = 1.8 Hz, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($(CH_3)_2Si$), 18.2 (C-3), 18.3 (C-3), 25.4 ($(CH_3)_2CSi$), 25.8 ($(CH_3)_3CSi$), 40.7 (C-2), 62.0 (C-4), 202.5 (C-1).

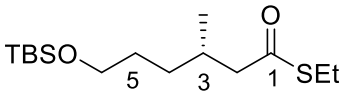
_S_-Ethyl (_E_)-6-((_tert_-butyldimethylsilyl)oxy)hex-2-enethioate (16-34)



16-34

To a solution of aldehyde **16-33** (3.54 g, 17.47 mmol) in CH_2Cl_2 (270 mL) was added *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate (8.28 g, 22.71 mmol, 1.3 equiv). The resulting solution was refluxed for 2 d, and then cooled to room temperature before it was concentrated in *vacuo*. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:50) to give enoate **16-34** (3.50 g, 69%) as yellow oil. R_f = 0.5 (petroleum ether/diethyl ether, 33:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_2CSi$), 1.25 (t, J = 7.3 Hz, 3H, SCH_2CH_3), 1.60-1.70 (m, 2H, 5-H), 2.25 (ddd, J = 1.5, 7.1, 13.4 Hz, 2H, 4-H), 2.92 (q, J = 7.3 Hz, 2H, SCH_2CH_3), 3.61 (t, J = 6.1 Hz, 2H, 6-H, 6.09 (dt, J = 1.5, 15.7 Hz, 1H, 2-H), 6.89 (dt, J = 7.1, 15.7 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.38 ($(CH_3)_2Si$), 14.8 (SCH_2CH_3), 18.2 ($(CH_3)_3CSi$), 23.0 (SCH_2CH_3), 25.9 ($(CH_3)_3CSi$), 28.6 (C-4), 31.02 (C-5), 62.1 (C-6), 128.8 (C-2); 144.9 (C-3), 190.0 (C-1); HRMS (ESI): calcd for $C_{14}H_{28}O_2SSi$ $[M+Na]^+$ 311.14715, found 311.14758.

_S_-Ethyl (_R_)-6-((_tert_-butyldimethylsilyl)oxy)-3-methylhexanethioate (16-35)

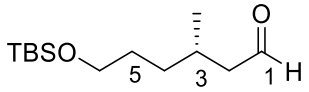


16-35

To a solution of (*S*)-Tol-BINAP (0.036 g, 0.052 mmol, 0.015 equiv) in dry *tert*-butyl methyl ether (7 mL) was added copper iodide (0.007 g, 0.035 mmol, 0.010 equiv). This suspension was stirred for 1 h at room temperature turning into a dark yellow solution. The solution was cooled to –70 °C and treated dropwise with a solution of MeMgBr in Et_2O (3M 5.8 mL, 17.5 mmol, 5.0 equiv). The resulting mixture was stirred for 30 min before a solution of enoate **16-34** (1.000 g, 3.5 mmol) in *tert*-butyl methyl ether (2 mL) was added dropwise using a syringe pump within 2 h. The mixture was stirred overnight at –40 °C. The reaction was quenched with MeOH (1 mL) and saturated NH_4Cl solution (5 mL), the cooling system was removed, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Purification of the residue by flash chromatography (Et_2O/petroleum ether, 1:50) afforded pure ester **16-35** (0.868 g, 81%) as colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 33:1); $[\alpha]^{20}_D$ = –5.1 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_2Si$), 0.92 (d, J = 6.6 Hz, 3H, 3-CH_3), 1.14-1.21(m, 1H, 4-H), 1.22 (t, J = 7.6 Hz, 3H, SCH_2CH_3), 1.30-1.40 (m, 1H, 4-H), 1.42-1.57 (m, 2H, 5-H), 1.91-2.12 (m, 1H, 3-H), 2.33 (dd, J = 8.1, 14.4 Hz, 1H, 2-H), 2.51 (dd, J = 6.1, 14.4 Hz, 1H, 2-H), 2.84 (q, J = 7.6 Hz, 2H, SCH_2CH_3), 3.56 (t, J = 6.6 Hz, 2H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.31 ($(CH_3)_2Si$), 14.8 (SCH_2CH_3), 18.3 ($(CH_3)_3CSi$), 19.5 (3-CH_3),

23.2 (S*CH*$_2$CH$_3$) 25.9 ((CH$_3$)$_3$CSi), 30.1 (C-5), 30.9 (C-3), 32.7 (C-4), 51.3 (C-2), 63.2 (C-6), 199.1 (C-1); HRMS (ESI): calcd for $C_{15}H_{32}O_2SSi$ $[M+Na]^+$ 327.17845, found 327.17875.

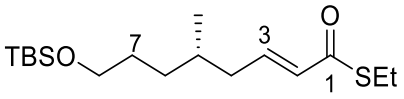
(*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-methylhexanal (16-36)



16-36

To a stirred mixture of the thioester **16-35** (800 mg, 2.6 mmol) and Pd/C (138 mg, 10% wt) in CH_2Cl_2 (5 mL) was added Et_3SiH (1.25 mL, 7.8 mmol, 3 equiv) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 30 min. The catalyst was filtered off through a pad of Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give the pure aldehyde **16-36** (300 mg, 47%) as slightly yellow oil.

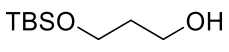
***S*-Ethyl (*S,E*)-8-((*tert*-butyldimethylsilyl)oxy)-5-methyloct-2-enethioate (16-37)**



16-37

To a solution of aldehyde **16-36** (0.30 g, 1.23 mmol) in CH_2Cl_2 (18 mL) was added *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate (0.57 g, 1.56 mmol, 1.3 equiv). The resulting solution was refluxed for 2 d, and then cooled to room temperature before it was concentrated in *vacuo*. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:50) to give enoate **16-37** (0.15 g, 69%) as yellow oil. R_f = 0.6 (petroleum ether/diethyl ether, 33:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, (CH$_3$)$_2$Si), 0.88 (s, 9H, (CH$_3$)$_2$Si), 0.90 (d, J = 6.6 Hz, 3H, 5-CH$_3$), 1.10-1.22 (m, 1H, 6-H), 1.26 (t, J = 7.3 Hz, 3H, SCH$_2$*CH$_3$*), 1.30-1.41 (m, 1H, 6-H), 1.43-1.57 (m, 2H, 5-H, 7-H), 1.57-1.67 (m, 1H, 7-H), 1.96-2.07 (m, 1H, 4-H), 2.13-2.25 (m, 1H, 4-H), 2.93 (q, J = 7.3 Hz, 2H, S*CH*$_2$CH$_3$), 3.57 (t, J = 6.6 Hz, 2H, 8-H), 6.80 (dt, J = 1.3, 15.4 Hz, 1H, 2-H), 6.85 (m, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ((CH$_3$)$_2$Si), 14.8 (SCH$_2$*CH$_3$*), 18.3((CH$_3$)$_3$CSi), 19.6 (5-CH$_3$), 25.9 ((CH$_3$)$_3$CSi), 23.0 (S*CH*$_2$CH$_3$), 30.3 (C-7), 32.4 (C-5), 32.7 (C-6), 39.6 (C-4), 63.3 (C-8), 129.8 (C-2), 144.1 (C-3), 190.0 (C-1).

3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol (16-39)

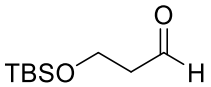


16-39

To a stirred solution of 1,3-propanediol (10.0 g, 131.42 mmol) in THF (225 mL) at 0 °C was added NaH (5.04 g, 131.42 mmol, 1.0 equiv) in five equal proportions at every 5 min duration, followed by the addition of TBSCl (19.51 g, 129.42 mmol, 0.98 equiv). The resulting reaction mixture was warmed to room temperature and stirred for 1 h, then quenched with saturated

aqueous NH_4Cl (5 mL) at 0 °C and then excess of saturated aqueous NH_4Cl solution (100 mL) was added. The layers were separated, and the organic layer was dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give mono-protected alcohol **16-39** (11.00 g, 44%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.84 (s, 9H, $(CH_3)_3CSi$), 1.72 (m, 2H, 2-H), 2.91 (br, 1H, OH), 3.72 (t, J = 6.0 Hz, 2H, 1-H), 3.76 (t, J = 6.0 Hz, 2H, 3-H

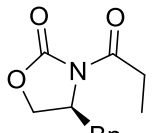
3-((*tert*-Butyldimethylsilyl)oxy)propanal (16-40)



16-40

To a solution of oxalyl chloride (2.23 mL, 26.03 mmol, 1.5 equiv) in CH_2Cl_2 (150 mL) at –80 °C was added DMSO (3.70 mL, 52.10 mmol, 3.0 equiv) dropwise. The resulting mixture was stirred 15 min before alcohol **16-39** (3.300 g, 17.35 mmol) in CH_2Cl_2 (40 mL) was added dropwise within 15 min. After stirring the mixture for 1 h at –80 °C, Et_3N (15.00 mL, 104.1 mmol, 6 equiv) was added slowly. Then the reaction mixture was allowed to warm to room temperature. For work-up water (30 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:25) to give aldehyde **16-40** (2.330 g, 71%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $(CH_3)_2Si$), 0.85 (s, 9H, $(CH_3)_3CSi$), 2.57 (td, J = 2.0, 6.1 Hz, 2H, 2-H), 3.96 (t, J = 6.1 Hz, 2H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($(CH_3)_2Si$), 18.2 ($(CH_3)_3CSi$), 25.8 ($(CH_3)_3CSi$), 46.5 (C-2), 57.4 (C-3), 201.9 (C-1); HRMS (ESI): calcd for $C_9H_{20}O_2Si$ [M+ MeOH+Na]$^+$ 243.13869, found 243.13887.

(*S*)-4-Benzyl-3-propionyloxazolidin-2-one (16-43)

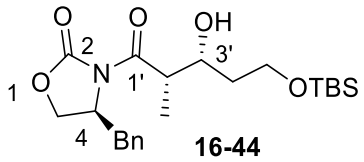


16-43

To the solution of (*S*)-4-benzyloxazolidin-2-one (0.42 g, 2.37 mmol) in THF (4 mL) was added dropwise a solution of *n*-BuLi (1.3 mL, 2.0 M, 2.63 mmol, 1.1 equiv) at –78 °C for 30 min. The resulting reaction mixture was further stirred for 30 min before the dropwise addition of propionyl chloride (320 µL, 3.41 mmol, 1.4 equiv). The reaction was allowed to warm to rt within 1 h, quenched with saturated aqueous NH_4Cl (2 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with aqueous NaOH (5 mL, 1N), dried over anhydrous Na_2SO_4 and filtered concentrated in *vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to afford compound **16-43** as a colorless oil (0.51 g, 92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.3 Hz, 3H, CH_3), 2.78 (dd, J = 9.4, 13.1 Hz, 1H, CH_2Ph), 2.88-3.06 (m, 2H, $COCH_2$), 3.31 (dd, J = 9.4, 13.1 Hz,

1H, CH_2Ph), 4.14-4.24 (m, 2H, OCH_2), 4.64-4.72 (m, 1H, NCH), 7.19-7.24 (m, 2H, Ar), 7.25-7.30 (m, 1H, Ar), 7.31-7.37 (m, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.2 (CH_3), 29.1 ($COCH_2$), 37.9 (CH_2Ph), 55.1 (NHCH), 66.2 (OCH_2), 127.3 (Ar), 128.9 (Ar), 129.4 (Ar), 135.3 (Ar), 153.4 (OCON), 174.0 (NCO); HRMS (ESI): calcd for $C_{13}H_{15}NO_3$ $[M+Na]^+$ 256.09441, found 256.09452.

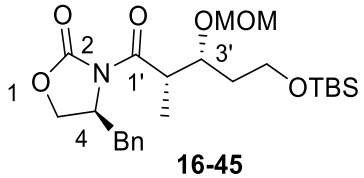
(*S*)-4-Benzyl-3-((2*S*,3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one (16-44)



16-44

To a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (**16-43)** (0.48 g, 2.06 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise Bu_2BOTf solution (2.7 mL, 1M, 2.67 mmol, 1.3 equiv) and triethylamine (0.43 mL, 3.01 mmol, 1.4 equiv). The obtained red solution was stirred at 0 °C for 45 min and cooled to –78 °C. To this solution aldehyde **16-40** (0.35 g, 1.87 mmol, and 0.9 equiv) was added dropwise. The reaction was stirred at –78 °C for 30 min, and then allowed to stir at 0 °C overnight. Aqueous phosphate buffer (2.0 mL, 1.0 M, pH 4) and methanol (6 mL) were added, followed by slow addition of mixture of methanol/H_2O_2 (15 mL, 2:1). The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:2 to 1:1) to afford the aldol product **16-44** (0.426 g, 49%); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.27 (d, J = 7.1 Hz, 3H, 2'-CH_3), 1.59-1.67 (m, 1H, 4'-H), 1.71-1.82 (m, 1H, 4'-H) 2.76 (dd, J = 9.6, 13.4 Hz, 1H, CH_2Ph), 3.26 (dd, J = 3.0, 13.4 Hz, 1H, CH_2Ph), 3.55 (br, 1H, OH), 3.75-3.89 (m, 3H, 3'-H, 5'-H), 4.12-4.24 (m, 3H, 2-H, 5-H), 4.64-4.73 (m, 1H, 4-H), 7.17-7.22 (m, 2H, Ar), 7.25-7.35 (m, 3H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 $(CH_3)_2Si$), 11.2 (2-CH_3), 18.2 $(CH_3)_3CSi$), 25.9 $(CH_3)_3CSi$), 35.9 (C-4'), 37.8 (CH_2Ph), 42.8 (C-2'), 55.3 (C-4), 61.9 (C-5'), 66.1 (C-5), 71.2 (C-3'), 127.3 (Ar), 128.9 (Ar), 129.4 (Ar), 135.2 (Ar), 153.1 (C-2), 176.4 (C-1'); HRMS (ESI): calcd for $C_{22}H_{35}NO_5Si$ $[M+Na]^+$ 444.21767, found 444.21811.

(*S*)-4-benzyl-3-((2*S*,3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-(methoxymethoxy)-2-methylpentanoyl)oxazolidin-2-one (16-45)

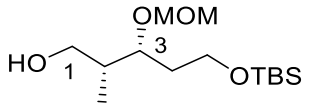


16-45

To a solution of alcohol (3*S*)-**16-44** (0.324 g, 0.77 mmol) in CH_2Cl_2 (7 mL) was added at 0 °C *N*-*N*-diisopropylethylamin (1.3 mL, 7.7 mmol, 10 equiv) and tetrabutylammonium iodide (28 mg, 0.077 mmol, 0.1 equiv), followed by MOMCl (310 µL, 3.85 mmol, 5 equiv). After stirring

of the mixture for 2 d, saturated $NaHCO_3$ solution (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (10 mL), saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude MOM-ether was purified by flash chromatography (Et_2O/petroleum ether, 1:5) to give product **16-45** (412 mg, 99%) as colorless oil. R_f = 0.6 (petroleum ether/diethyl ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 1.23 (d, J = 6.8 Hz, 3H, 2'-CH_3), 1.71-1.89 (m, 2H, 4'-H), 2.76 (dd, J = 9.6, 13.4 Hz, 1H, CH_2Ph), 3.37-3.40 (m, 1H, CH_2Ph), 3.63-3.76 (m, 2H, 3'-H, 5'-H), 3.92-4.06 (m, 2H, 2'-H, 5'-H), 4.11-4.20 (m, 2H, 5-H), 4.61 (s, 2H, OCH_2O), 7.17-7.23 (m, 2H, Ar), 7.25-7.35 (m, 3H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), 11.9 (2'-CH_3), 18.2 $(CH_3)_3CSi$), 25.9 $(CH_3)_3CSi$), 35.8 (C-4'), 37.7 (CH_2Ph), 41.6 (C-2'), 55.9 (C-4) 56.0 (OCH_3), 59.5 (C-5'), 66.1 (C-5), 76.4 (C-3'), 96.7 (OCH_2O), 127.3 (Ar), 128.9 (Ar), 129.4 (Ar), 135.4 (Ar), 153.2 (C-2), 174.9 (C-1'); HRMS (ESI) : calcd for $C_{24}H_{39}NO_6Si$ $[M+Na]^+$ 488.24389, found 488.24423.

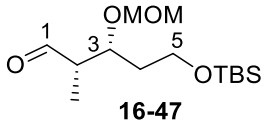
(2*R*,3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-(methoxymethoxy)-2-methylpentan-1-ol (16-46)



16-46

To a solution of compound **16-45** (0.41 g, 0.88 mmol) in THF (20 mL) at 0 °C was added solid $LiBH_4$ (97 mg, 4.4 mmol, 5 equiv) and MeOH (180 μL, 4.4 mmol, 5 equiv) dropwise. The resulting solution was allowed to stir for 3 d. Thereafter, aqueous NaOH solution (1N 2 mL) was added and after 30 min of stirring at rt, the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude alcohol was purified by flash chromatography (petroleum ether/diethyl ether, 3:1) to give pure alcohol **16-46** (155 mg, 60%) as a colorless liquid. R_f = 0.4 (petroleum ether/diethyl ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $(CH_3)_2Si$), 0.82 (d, J = 7.1 Hz, 3H, 2-CH_3), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.61-1.80 (m, 2H, 2-H, 4-H), 1.89-2.00 (m, 1H, 4-H), 3.40 (s, 3H, OMe), 3.52 (dd, J = 5.4, 11.1 Hz, 1H, 1-H), 3.57-3.73 (m, 3H, 1-H, 3-H, 5-H), 3.85-3.93 (m, 1H, 5-H), 4.64 (d, J = 6.6 Hz, 1H, OCH_2O), 4.69 (d, J = 6.6 Hz, 1H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 $(CH_3)_2Si$), –5.3 $(CH_3)_2Si$), 11.2 (2-CH_3), 18.2 $(CH_3)_3CSi$), 25.9 $(CH_3)_3CSi$), 34.6 (C-4), 38.5 (C-2), 55.9 (OCH_3), 59.7 (C-5), 65.3 (C-1), 76.9 (C-3), 97.0 (OCH_2O).

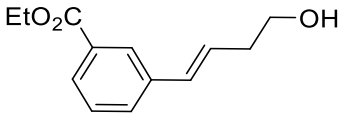
(2*S*,3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-(methoxymethoxy)-2-methylpentanal (16-47)



16-47

To a solution of oxalyl chloride (60 μL, 0.72 mmol, 1.5 equiv) in CH_2Cl_2 (3 mL) at –80 °C was added DMSO (100 μL, 1.44 mmol, 3.0 equiv) dropwise. The resulting mixture was stirred 15 min before alcohol **16-46** (140 mg, 0.48 mmol) in CH_2Cl_2 (1 mL) was added dropwise within 15 min. After stirring the mixture for 1 h at –80 °C, Et_3N (415 μL, 2.87 mmol, 6 equiv) was added slowly. Then the reaction mixture was allowed to warm to room temperature. For work-up water (5 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo* to get crude aldehyde **16-47** (120 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, crude): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 1.08 (d, J = 7.0 Hz, 3H, 2-CH_3), 1.64-1.82 (m, 2H), 2.51-2.60 (m, 1H), 2.59 (s, 2H), 3.29 (s, 3H), 3.67 (dd, J = 5.1, 6.9 Hz, 2H), 4.15-4.23 (m, 1H), 4.58 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5, 7.8, 25.8, 35.2, 40.9, 50.3, 55.6, 59.3, 74.9, 96.6, 204.3; HRMS (ESI): calcd for $C_{14}H_{30}O_4Si$ $[M+Na]^+$ 345.20677, found 345.20702.

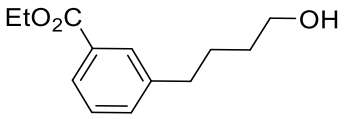
Ethyl (*E*)-3-(4-hydroxybut-1-en-1-yl)benzoate (17-18)



17-18

To a stirred solution of the aryl bromide **17-16** (3.00 g, 13.1 mmol) in Et_3N (3.7 mL, 25.6 mmol, 2.0 equiv) were successively added 3-buten-1-ol (**17-17**) (1.9 mL, 22.9 mmol, 1.8 equiv), $Pd(OAc)_2$ (295 mg, 1.37 mmol, 0.1 equiv), and P(*o*-tol)$_3$ (0.834 g, 2.74 mmol, 0.2 equiv), and the mixture was stirred at 75 °C for 21 h, cooled, and concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with saturated solution of NaCl (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:2) afforded pure ester **17-18** (2.515 g, 87%) as colorless oil. R_f = 0.5 (EtOAc/petroleum ether, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.27 (br, 1H, OH), 2.46 (qd, J = 1.3, 6.6 Hz, 2H, 2-H), 3.73 (t, J = 6.3 Hz, 2H, 1-H), 4.34 (q, J = 7.1, Hz, 2H, OCH_2CH_3), 6.27 (dt, J = 7.1, 16.0 Hz, 1H, 3-H), 6.47 (d, J = 16.0 Hz, 1H, 4-H), 7.31 (t, J = 7.6 Hz, 1H, Ar), 7.47 (dt, J = 1.3, 7.6 Hz, 1H, Ar), 7.84 (dt, J = 1.3, 7.8 Hz, 1H, Ar), 7.99 (t, J = 2.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_3), 36.2 (C-2), 60.9 (OCH_2CH_3), 61.8 (C-1), 126.9, 127.9, 128.0, 128.4, 130.2, 130.6, 131.4, 137.5, 166.6 (CO); HRMS (ESI): calcd for $C_{13}H_{16}O_3$ $[M+Na]^+$ 243.09917, found 243.09911.

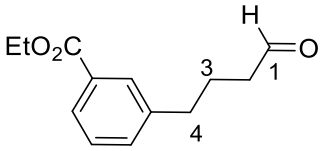
Ethyl 3-(4-hydroxybutyl)benzoate (17-19)



17-19

To a gently stirred solution of styrene derivative **17-18** (1.211 g, 5.5 mmol) in MeOH/hexane (60 mL, 1:1) was added Pd/C (10%, 267 mg), then the septum having a needle inlet (normal capillary) and an outlet (fine capillary) was closed. The reaction flask was first purged with N_2 for 2 min then with H_2 for 10 min at room temperature. The outlet needle was removed and a hydrogen balloon was attached to the inlet needle. Thereafter, the reaction mixture was allowed to stir at rt for 2 h. The mixture was filtered through Celite, and the filtrate concentrated in *vacuo*. The residue was purified by flash chromatography (EtOAc/petroleum ether, 1:2 to 1:1) which afforded pure ester **17-19** (0.848 g, 69%) as colorless oil. R_f = 0.4 (EtOAc/petroleum ether, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.55-1.66 (m, 2H, 2-H), 1.67-1.76 (m, 2H, 3-H), 2.69 (t, J = 7.6 Hz, 2H, 4-H), 3.66 (t, J = 6.3 Hz, 2H, 1-H), 4.36 (q, J = 7.1, Hz, 2H, $O\mathit{CH_2}CH_3$), 7.30-7.40 (m, 2H, Ar), 7.82-7.90 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 ($OCH_2\mathit{CH_3}$), 27.5 (C-3), 32.2 (C-2), 35.4 (C-4), 60.9 ($O\mathit{CH_2}CH_3$), 62.7 (C-1), 127.1, 128.3, 129.4, 130.5, 132.9, 142.6, 166.8 (CO); HRMS (ESI): calcd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.11482, found 245.11502.

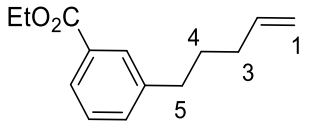
Ethyl 3-(4-oxobutyl)benzoate (17-20)



17-20

A flask was charged with PCC (0.29 g, 1.35 mmol, 3.0 equiv) and silica gel (0.29 g). The contents were mixed with the help of glass rod until a homogenous mixture was formed. To this, alcohol **17-19** (100 mg, 0.45 mmol) in CH_2Cl_2 (3 mL) was added dropwise within 30 min, then the reaction mixture was filtered through a small silica gel column using CH_2Cl_2 as eluent, the obtained filtrate was concentrated in *vacuo* and the crude residue was purified by flash chromatography (EtOAc/petroleum ether, 1:20) to give aldehyde **17-20** (76 mg, 77%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.92-2.05 (m, 2H, 3-H), 2.45 (td, J = 1.5, 7.3 Hz, 2H, 2-H), 2.70 (t, J = 7.6 Hz, 2H, 4-H), 4.32 (q, J = 7.1, Hz, 2H, $O\mathit{CH_2}CH_3$), 7.32-7.38 (m, 2H, Ar), 7.82-7.91 (m, 2H, Ar), 9.75 (t, J = 1.5 Hz, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 ($OCH_2\mathit{CH_3}$), 23.5 (C-3), 34.7 (C-4), 43.0 (C-2), 60.9 ($O\mathit{CH_2}CH_3$), 127.4, 128.4, 129.4, 130.6, 132.9, 141.5, 166.7 (CO_2Et), 202.0 (C-1); HRMS (ESI): calcd for $C_{13}H_{16}O_3$ (dimer, 2 × $C_{13}H_{16}O_3$) $[2M+Na]^+$ 463.20911, found 463.20927.

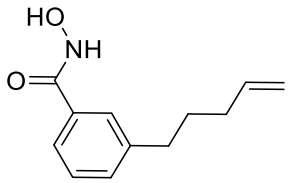
Ethyl 3-(pent-4-en-1-yl)benzoate (17-21)



17-21

To a solution of CH_3PPh_3Br (3.243 g, 9.0 mmol, 2.0 equiv) in THF (40 mL) at 0 °C was added NaH (0.194 g, 8.1 mmol, 1.8 equiv). The resulting mixture was allowed to reach rt within 2 h. Thereafter, the reaction mixture was re-cooled to 0 °C and before aldehyde **17-20** (1.00 g, 4.5 mmol) in THF (10 mL) was added dropwise. After complete addition, the reaction mixture was stirred for 2 h, quenched with water (1 mL) at 0 °C, then excess water (10 mL) was added, and the mixture extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with saturated solution of NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:20) afforded aldehyde **17-20** (0.50 g, 2.25 mmol) and pure alkene-ester **17-21** (0.300 g, 61%) as colorless oil. R_f = 0.6 (EtOAc/petroleum ether, 1:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 1.67-1.81 (m, 2H, 4-H), 2.09 (q, J = 5.6 Hz, 2H, 3-H), 2.67 (t, J = 7.6 Hz, 5H), 4.37 (q, J = 7.1, Hz, 2H, $O\mathit{CH_2}CH_3$), 4.92-5.08 (m, 2H, 1-H), 5.63-5.89 (m, 1H, 2-H), 7.30-7.43 (m, 2H, Ar), 7.83-7.94 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 ($OCH_2\mathit{CH_3}$), 29.7 (C-4), 30.5 (C-3), 33.2 (C-5), 60.9 ($O\mathit{CH_2}CH_3$), 114.9 (C-1), 127.0, 128.2, 129.5, 130.5, 133.0, 138.3, 147.7, 166.8 (CO_2Et); HRMS (ESI): calcd for $C_{17}H_{23}NO_3$ $[M+Na]^+$ 312.15701, found 312.15728.

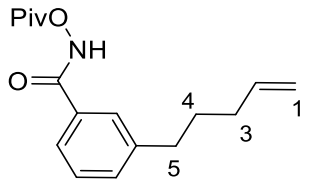
***N*-Hydroxy-3-(pent-4-en-1-yl)benzamide (17-22)**



17-22

To a stirred solution of ethyl benzoate **17-21** (0.300 g, 1.4 mmol) and hydroxylamine hydrochloride (0.382 g, 5.5 mmol, 4.0 equiv) in MeOH (3 mL) was added KOH solution (1M in methanol, 7 mL, 5.0 equiv) in a dropwise fashion. The resulting solution was stirred 48 h at room temperature. Thereafter most of the MeOH was distilled out in vacuo and the solid residue was dissolved in a mixture of acetic acid/water (1/1, 5 mL). The mixture was extracted with EtOAc (3 × 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude hydroxamic acid which was washed with diethyl ether (7 mL) to afford the pure hydroxamic acid **17-22** as transparent solid (0.24 g, 89%); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3 (C-4), 32.9 (C-3), 34.7 (C-4), 115.3 (C-1), 124.6, 127.1, 128.6, 131.5, 132.9, 137.1, 138.6, 142.6, 164.7 (CONH).

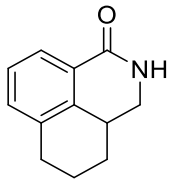
3-(pent-4-en-1-yl)-N-(pivaloyloxy)benzamide (17-23)



17-23

To the suspension of hydroxamic acid **17-22** (0.24 g, 1.2 mmol) in CH_2Cl_2 (6 mL) was added pivalic anhydride (0.22 mL, 1.1 mmol, 0.9 equiv). The resulting mixture was stirred for 35 h at room temperature. The reaction mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (2 × 6 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatography to afford the pure O-pivaloyl hydroxamic acid **17-23** (0.20 g, 60%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H, OPiv), 1.58 (pent, J = 7.6 Hz, 2H, 4-H), 2.06 (q, J = 7.1 Hz, 2H, 3-H), 2.62 (t, J = 7.8 Hz, 2H, 5-H), 4.90-5.06 (m, 2H, 1-H), 5.58-5.87 (m, 1H, 2-H), 7.27-7.40 (m, 2H, Ar), 7.55-7.69 (m, 2H, Ar), 9.57 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0 (C(*CH*)$_3$), 30.3 (C-4), 33.1 (C-3), 35.0 (C-5), 38.3 (*C*(CH)$_3$), 115.0 (C-1), 124.7, 127.5, 128.6, 130.8, 132.8, 138.2, 143.2, 169.9 (CONH), 177.0 (OC(O)*t*Bu).

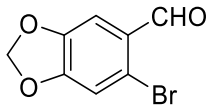
2,3,3a,4,5,6-Hexahydro-1*H*-benzo[*de*]isoquinolin-1-one (17-14)



17-14

An oven dried, cooled Schlenk tube under N_2, was charged with N-(pivaloyloxy)benzamide **17-23** (20 mg, 0.07 mmol), $[Cp^*RhCl_2]_2$ (2 mg, 2.5 mol%), CsOAc (32 mg, 0.17 mmol, 2.5 equiv) and dry EtOH (0.1 mL). The screw cap was closed tightly under positive pressure of N_2 followed by stirring of the reaction mixture at room temperature for 8 h (TLC control). The mixture was concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to afford the pure annulation product **17-14** (10 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31-1.45 (m, 1H, 4-H), 1.68-1.83 (m, 1H, 5-H), 1.96-2.11 (m, 2H, 4-H, 5-H), 2.74-2.95 (m, 2H, 6-H), 3.05-3.17 (m, 1H, 3a-H), 3.24 (dd, J = 11.6, 13.1 Hz, 1H, 3-H), 3.41 (dd, J = 6.1, 11.6 Hz, 1H, 3-H), 6.07 (br, 1H, HN), 7.26 (d, J = 4.6 Hz, 2H, 7-H, 9-H), 7.88 (t, J = 4.6 Hz, 8-H); HRMS m/z (ESI): calcd for $C_{12}H_{13}NO$ $(M+H)^+$ 188.10699, found 188.10692.

6-Bromobenzo[*d*][1,3]dioxole-5-carbaldehyde (18-25e)

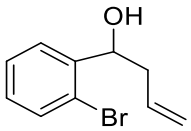


18-25e

To a mixture of piperonal (152 mg, 0.66 mmol) in CH_2Cl_2 (20ml) was added DBDMH (286 mg, 1.0 mmol) at room temperature. Then the reaction mixture was stirred for 0.5 h, washed with water (3 × 30 ml), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1) to afford the aldehyde **18-25e** as light yellow solid (70 mg, 46% yield). R_f = 0.7 (EtOAc/petroleum ether, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 2H, OCH_2O), 7.03 (s, 1H, Ar), 7.33 (s, 1H, Ar), 10.15 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.7, 108.1, 113.2, 121.5, 128.0, 148.1, 153.3, 190.3.

Addition of allylMgBr to the *o*-bromoaldehydes (Procedure 11): To a solution of aldehyde (1.0 equiv) in THF (3.5 mL per mmol of aldehyde) at 0 °C was added a solution of allylMgBr (1 M in Et_2O, 3 equiv). The reaction mixture was allowed to warm to room temperature. Before quenching with saturated NH_4Cl (5 mL), the reaction mixture was re-cooled to 0 °C, then the mixture was extracted with ethyl acetate (2 × 10 mL per mmol of aldehyde). The combined organic layers were washed with saturated aqueous NaCl solution (10 mL per mmol of aldehyde), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to the give crude secondary alcohol.

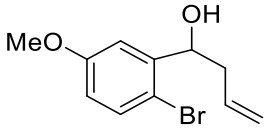
1-(2-Bromophenyl)but-3-en-1-ol (18-26a)



18-26a

Prepared from 2-bromobenzaldehyde (1.00 g, 5.5 mmol) according to general procedure. Reaction time 2 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give alcohol **18-26a** (0.80 g, 64%) as brown oil.

1-(2-Bromo-5-methoxyphenyl)but-3-en-1-ol (18-26b)

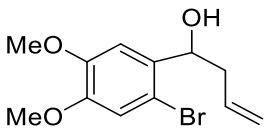


18-26b

Prepared from 2-bromo-5-methoxybenzaldehyde (0.50 g, 2.32 mmol) according to general procedure 11. Reaction time 1 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give alcohol **18-26b** (0.390 g, 65%) as brown oil. R_f = 0.7 (EtOAc/petroleum ether, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (br, 1H), 2.26-2.36 (m, 1H), 2.56-2.65 (m, 1H), 3.79 (s, 3H), 5.03 (dd, J = 3.5, 8.6 Hz, 1H), 5.13-5.23 (m, 2H),

5.80-5.93 (m, 1H), 6.68 (dd, J = 3.0, 8.6 Hz, 1H), 7.11 (d, 3.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.0, 55.4, 71.8, 111.9, 112.5, 114.8, 118.6, 133.2, 134.3, 143.8, 159.2; HRMS (ESI): calcd for $C_{11}H_{13}BrO_2$ $[M+Na]^+$ 278.99911, found 278.99934.

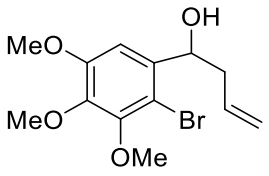
1-(2-Bromo-4,5-dimethoxyphenyl)but-3-en-1-ol (18-26c)



18-26c

Prepared from 2-bromo-4,5-dimethoxybenzaldehyde (0.500 g, 2.04 mmol) according to general procedure 11. Reaction time 1 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give alcohol **18-26c** (0.390 g, 75%) as brown oil. R_f = 0.5 (EtOAc/petroleum ether, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21-2.61 (br, 3H), 3.80 (s, 6H), 4.91-5.00 (m, 1H), 5.06-5.19 (m, 2H), 5.74-5.89 (m, 1H), 6.90 (s, 1H), 7.0 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.2, 55.9, 56.0, 71.6, 109.6, 111.3, 115.0, 118.2, 118.3, 134.3, 134.8, 148.5.

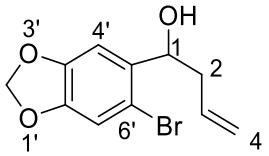
1-(2-Bromo-3,4,5-trimethoxyphenyl)but-3-en-1-ol (18-26d)



18-26d

Prepared from 2-bromo-3,4,5-trimethoxybenzaldehyde (0.400 g, 1.45 mmol) according to general procedure 11. Reaction time 1 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give alcohol **18-26d** (0.400 g, 87%) as brown oil. R_f = 0.4 (EtOAc/petroleum ether, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (br, 1H), 2.23-2.33 (m, 1H), 2.56-2.66 (m, 1H), 3.83-3.90 (3s, 9H), 5.07 (dd, J = 3.5, 8.6 Hz, 1H), 5.13-5.23 (m, 2H), 5.81-5.95 (m, 1H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.0, 56.1, 61.0, 71.8, 105.8, 107.8, 118.6, 134.4, 138.4, 142.1, 150.4, 153.0; HRMS (ESI): calcd for $C_{13}H_{17}BrO_4$ $[M+Na]^+$ 339.02024, found 339.02044.

1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)but-3-en-1-ol (18-26e)

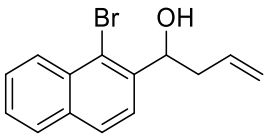


18-26e

Prepared from piperonal (65 mg, 0.28 mmol) according to general procedure 11. Reaction time 2 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether,

1:10) to give alcohol **18-26e** (60 mg, 79%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.20 (br, 1H, OH), 2.25-2.37 (m, 1H, 2-H), 2.48-2.59 (m, 1H, 2-H), 5.01 (dd, J = 3.8, 8.3 Hz, 1H, 4-H), 5.13-5.21 (m, 2H, 1-H, 4-H), 5.78-5.91 (m, 1H, 3-H), 5.95 (d, J = 1.5 Hz, 1H, 2'-H), 5.96 (d, J = 1.5 Hz, 1H, 2'-H), 6.94 (s, 1H, 7'-H), 7.03 (s, 1H, 4'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.2 (C-2), 71.7 (C-1), 101.7 (C-2'), 107.2, 111.9, 112.4, 118.6, 134.2, 136.1, 147.4, 147.6.

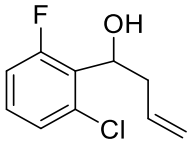
1-(1-Bromonaphthalen-2-yl)but-3-en-1-ol (18-26f)



18-26f

Prepared from 1-bromo-2-naphthaldehyde (0.50 g, 1.83 mmol) according to general procedure 11. Reaction time 1 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give alcohol **18-26f** (0.300 g, 59%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.26 (br, 1H), 2.40-2.52 (m, 1H), 2.63-2.73 (m, 1H), 5.14-5.30 (m, 2H), 5.45 (dd, J = 3.9, 8.4 Hz, 1H), 5.86-5.98 (m, 1H), 7.48-7.54 (m, 1H), 7.56-7.62 (m, 1H), 7.69 (dd, J = 4.0, 8.6 Hz, 1H), 7.77-7.86 (m, 1H), 8.32 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.2, 72.6, 118.7, 121.5, 124.3, 126.5, 127.3, 127.4, 128.0, 128.1, 132.1, 134.1, 134.2, 140.7; HRMS (ESI): calcd for $C_{14}H_{13}BrO$ $[M+Na]^+$ 299.00420, found 299.00439.

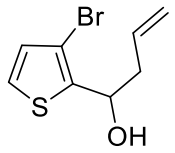
1-(2-Chloro-6-fluorophenyl)but-3-en-1-ol (18-26g)



18-26g

Prepared from 2-chloro-6-fluorobenzaldehyde (2.00 g, 12.6 mmol) according to general procedure 11. Reaction time 12 h. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give alcohol **18-26g** (1.258 g, 50%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.56 (br, 1H), 2.58-2.66 (m, 1H), 2.70-2.80 (m, 1H), 5.04-5.17 (m, 2H), 5.26 (t, J = 7.1 Hz, 1H), 5.73-5.86 (m, 1H), 6.91-7.02 (s, 1H), 7.11-7.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 41.0, 69.3, 114.8, 115.0, 118.3, 125.7, 128.4, 128.5, 129.0, 129.1, 133.4, 133.5, 133.6, 160.4, 162.9; HRMS (ESI): calcd for $C_{10}H_{10}ClFO$ $[M+Na]^+$ 223.02964, found 223.03007.

1-(3-Bromothiophen-2-yl)but-3-en-1-ol (18-26h)



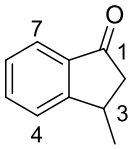
18-26h

Prepared from 3-bromothiophene-2-carbaldehyde (0.200 g, 1.05 mmol) according to general procedure 11. Reaction time 10 min. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give alcohol **18-26h** (0.135 g, 55%) as yellow oil. R_f = 0.5 (EtOAc/petroleum ether, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 1H), 2.48-2.68 (m, 2H), 5.09 (dd, J = 5.3, 7.5 Hz, 1H), 5.13-5.23 (m, 1H), 5.77-7.90 (m, 1H), 6.92 (d, J = 5.3 Hz, 1H), 7.23 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.6, 68.8, 107.3, 119.1, 124.7, 129.8, 133.4, 142.1; HRMS (ESI): calcd for C_8H_9BrOS $[M+Na]^+$ 254.94497, found 254.94488.

Redox cyclization (Procedure 12)

To a stirred solution of the aryl bromide (1.0 equiv) in toluene (2.5 mL per mmol) under N_2 atm was added Et_3N (2.0 equiv), $Pd(OAc)_2$ (0.1 equiv), and P(*o*-tol)$_3$ (0.2 equiv), and the reaction mixture was stirred at 110 °C for 6 h, then cooled, and concentrated in vacuo. The residue was dissolved in EtOAc (10 mL per mmol of aryl bromide) and H_2O (10 mL per mmol of aryl bromide). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL (per mmol of aryl bromide)),.The combined extracts were washed with saturated NaCl solution (20 mL per mmol of aryl bromide), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to afford crude product.

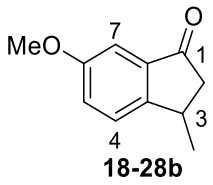
3-Methyl-2,3-dihydro-1*H*-inden-1-one (18-28a)



18-28a

Prepared from aryl bromide **18-26a** (100 mg, 0.44 mmol) according to general procedure 12. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give indanone **18-28a** (40 mg, 62%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, J = 7.1 Hz, 3H, 3-CH_3), 2.26 (dd, J = 3.3, 19.0 Hz, 1H, 2-H), 2.92 (dd, J = 7.6, 19.0 Hz, 1H, 2-H), 3.36-3.48 (m, 1H, 3-H), 7.35 (dd, J = 7.3, 7.6 Hz, 1H, Ar), 7.49 (dd, J = 1.0, 7.8 Hz, 1H, Ar), 7.59 (ddd, J = 1.3, 7.6, 8.6 Hz, 1H, Ar), 7.35 (dd, J = 7.8 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (3-CH_3), 32.7 (C-3), 45.3 (C-2), 123.4, 125.2, 127.3, 134.7, 136.4, 159.9 (Ar), 206.4 (C-1).

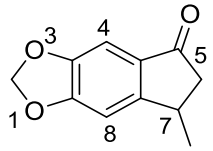
6-methoxy-3-methyl-2,3-dihydro-1*H*-inden-1-one (18-28b)



18-28b

Prepared from aryl bromide **18-26b** (100 mg, 0.39 mmol) according to general procedure 12. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give indanone **18-28b** (46 mg, 72%) as colorless oil. R_f = 0.7 (EtOAc/petroleum ether, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, J = 7.1 Hz, 3H, 3-CH_3), 2.27 (dd, J = 3.3, 19.0 Hz, 1H, 2-H), 2.94 (dd, J = 7.3, 19.0 Hz, 1H, 2-H), 3.30-3.41 (m, 1H, 3-H), 3.81 (s, 3H, OCH_3), 7.10-7.20 (m, 2H, Ar), 7.35-7.39 (m, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (3-CH_3), 32.1 (C-3), 46.0 (C-2), 55.6 (OCH_3), 104.0 (Ar), 124.1, 126.0, 137.6, 152.9, 159.4 (Ar), 206.3 (C-1); HRMS (ESI): calcd for $C_{11}H_{12}O_2$ $[M+Na]^+$ 199.07295, found 199.07324.

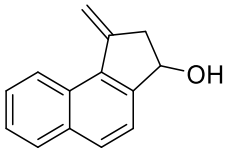
7-Methyl-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one (18-28e)



18-28e

Prepared from aryl bromide **18-26e** (50 mg, 1.05 mmol) according to general procedure 12. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:5) to give indanone **18-28e** (30 mg, 88%) as colorless oil. R_f = 0.3 (EtOAc/petroleum ether, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, J = 7.1 Hz, 3H, 7-CH_3), 2.24 (dd, J = 3.0, 19.0 Hz, 1H, 6-H), 2.90 (dd, J = 7.3, 19.0 Hz, 1H, 6-H), 3.30 (dq, J = 3.0, 7.1 Hz, 7-H), 6.05 (s, 2H, 2-H), 6.84 (s, 1H, 8-H), 7.05 (s, 1H, 4-H; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (7-CH_3), 32.6 (C-7), 45.7 (C-6), 102.0 (Ar), 102.2 (C-2), 104.5 (Ar), 131.1 (Ar), 148.3 (Ar), 154.3 (Ar), 157.7 (Ar), 204.2 (C-5); HRMS (ESI): calcd for $C_{11}H_{10}O_3$ $[M+Na]^+$ 213.05221, found 213.05221.

1-methylene-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-3-ol (18-29)



18-29

Prepared from aryl bromide **18-26f** (100 mg, 0.36 mmol) according to general procedure 12. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to give indenol **18-29** (30 mg, 42%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (br, 1H, OH), 2.62-2.71 (m, 1H, 2-H), 3.19 (ddt, J = 1.7, 7.0, 15.5 Hz, 1H, 2-H), 5.20 (dd, J = 4.4,

7.0 Hz, 1H, 3-H), 5.27 (t, J = 1.7 Hz, 1H, 1-CH_2), 5.80 (t, J = 2.1 Hz, 1H, 2-CH_2), 7.38-2.56 (m, 4H, Ar), 7.68 (d, J = 8.3 Hz, 1H, Ar), 7.79 (dd, J = 1.0, 8.0 Hz, 1H, Ar), 8.35 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.6 (C-2), 73.1 (C-3), 108.1 (1-CH_2), 122.3, 122.6, 124.4, 125.8, 126.5, 126.9, 127.1, 128.5, 129.1, 130.1, 146.6.

21 Appendix

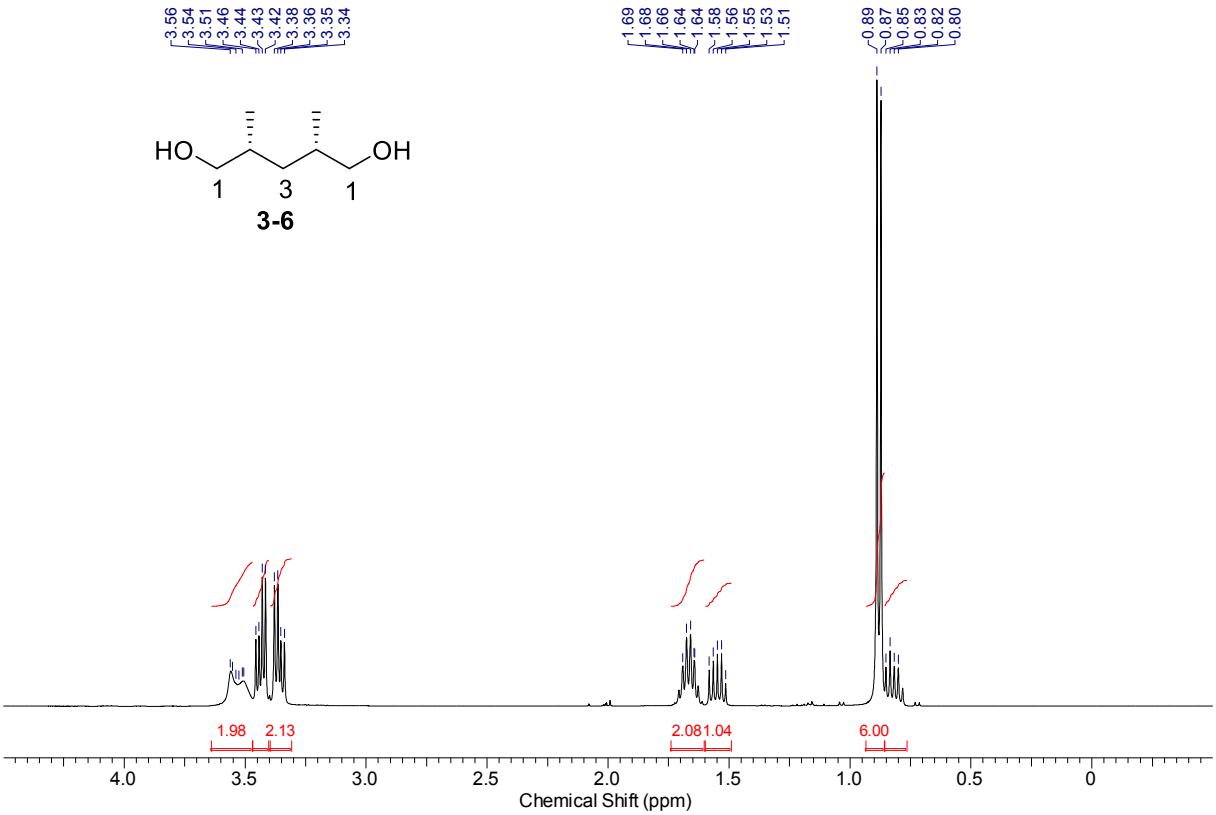
21.1 NMR-Spectra

Not all NMR spectra are included here. The remaining ones can be found in the supporting information from the following publications:

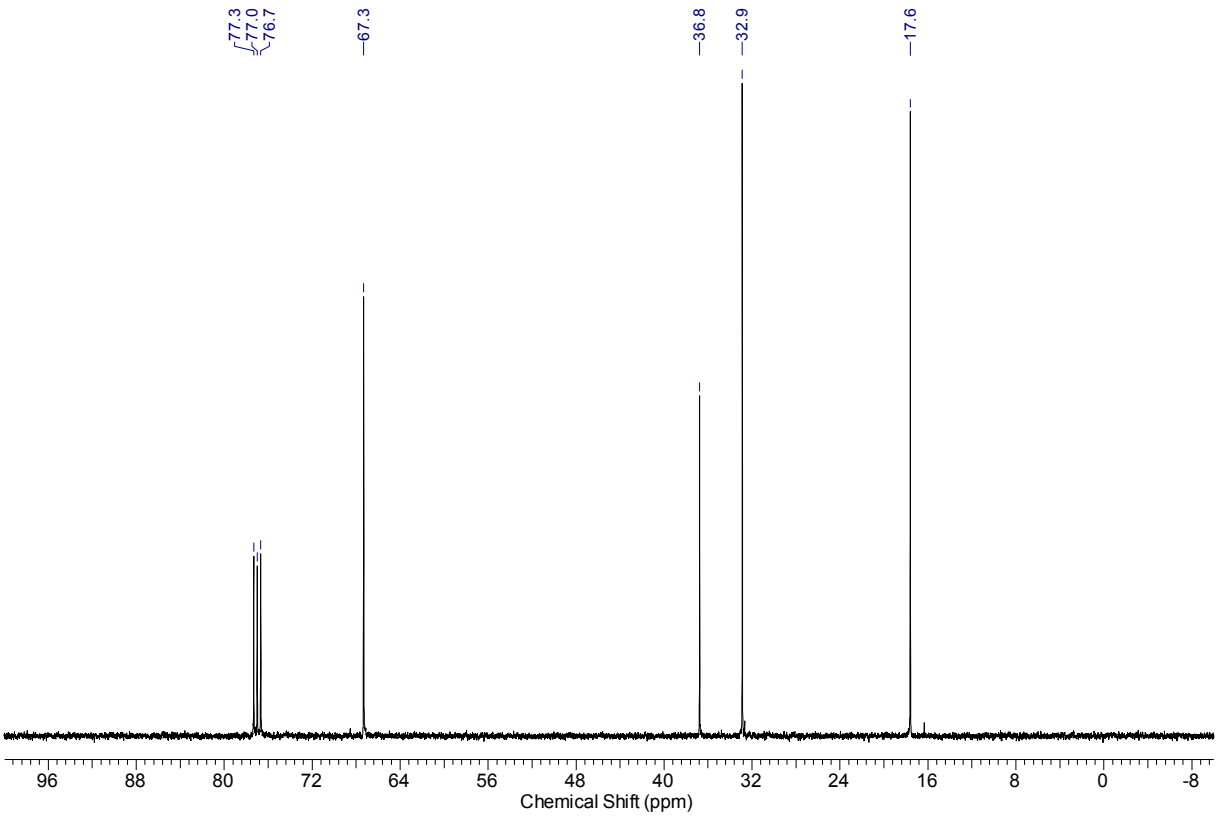
Chapter 1. Formal Total Synthesis of Amphidinolide Q. *J. Org. Chem.* **2016**, *81*, 9728-9737.

Chapter 2. C–H-Activation approach towards the core structure of the alkaloid γ-lycorane *Tetrahedron* **2016**, *72*, 6499-6509.

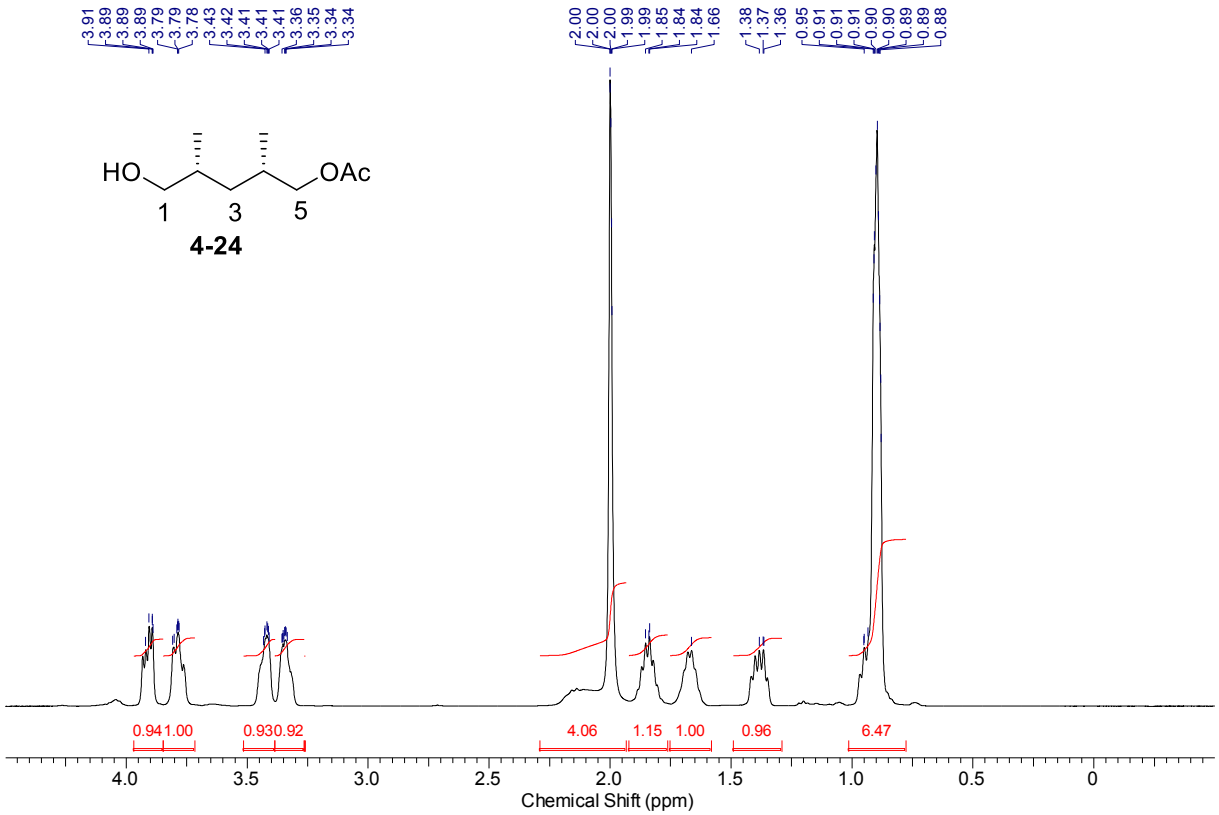
Chapter 3. All NMR spectra along with few chromatograms are included here.



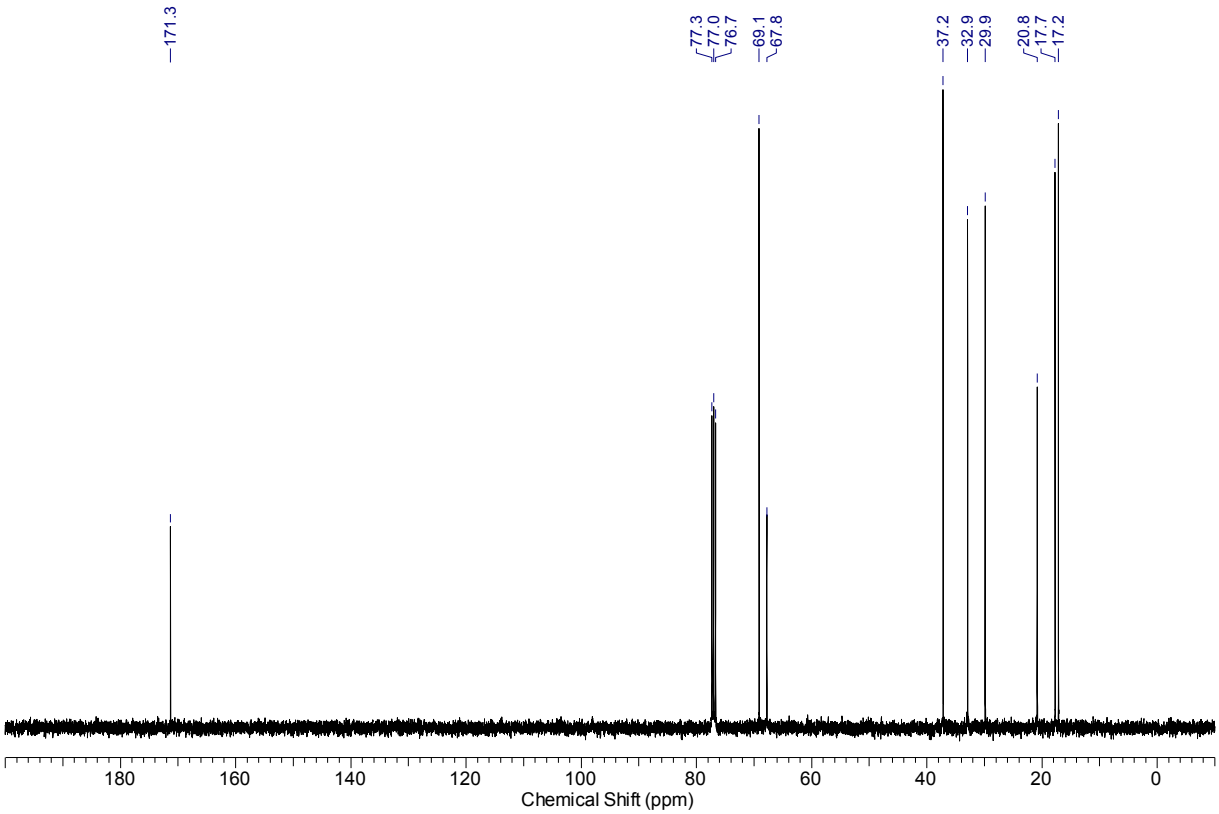
^{1}H NMR (400 MHz) spectrum of diol **3-6** in $CDCl_3$.



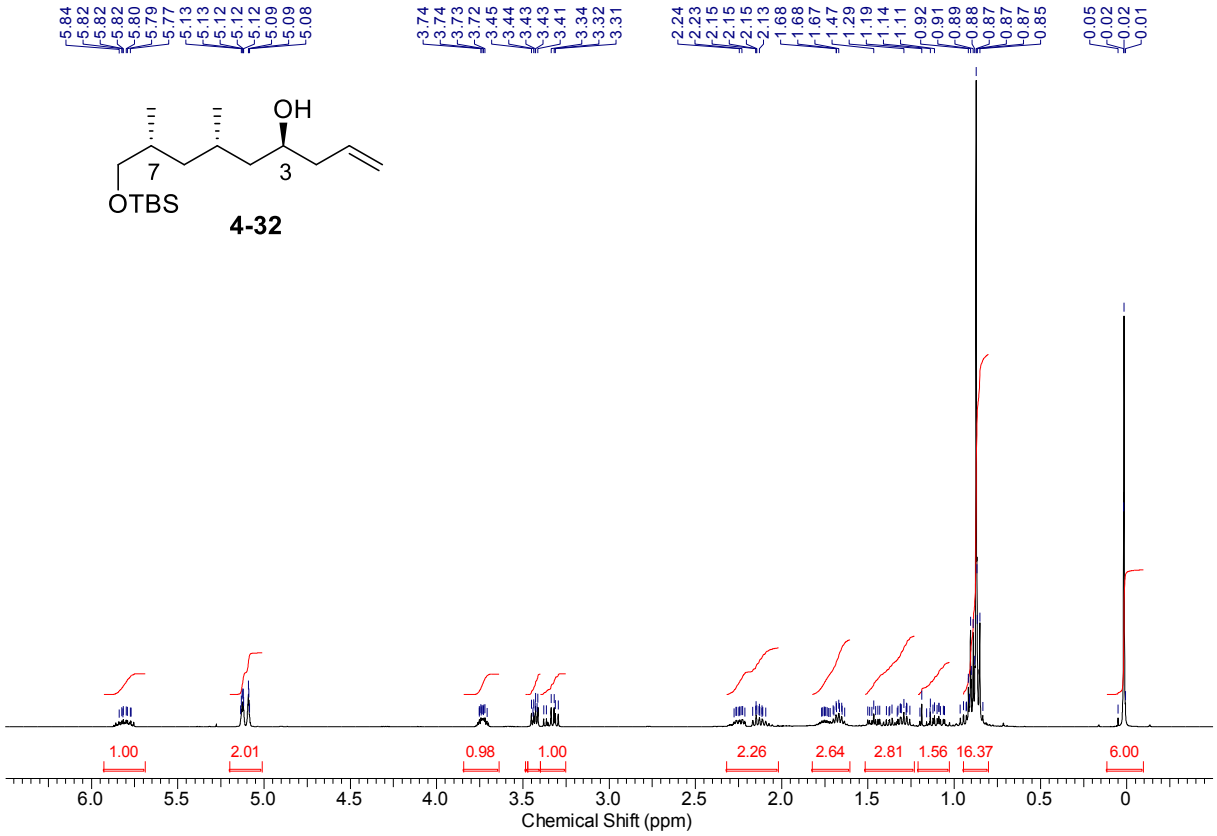
^{13}C NMR (100 MHz) spectrum of diol **3-6** in $CDCl_3$.



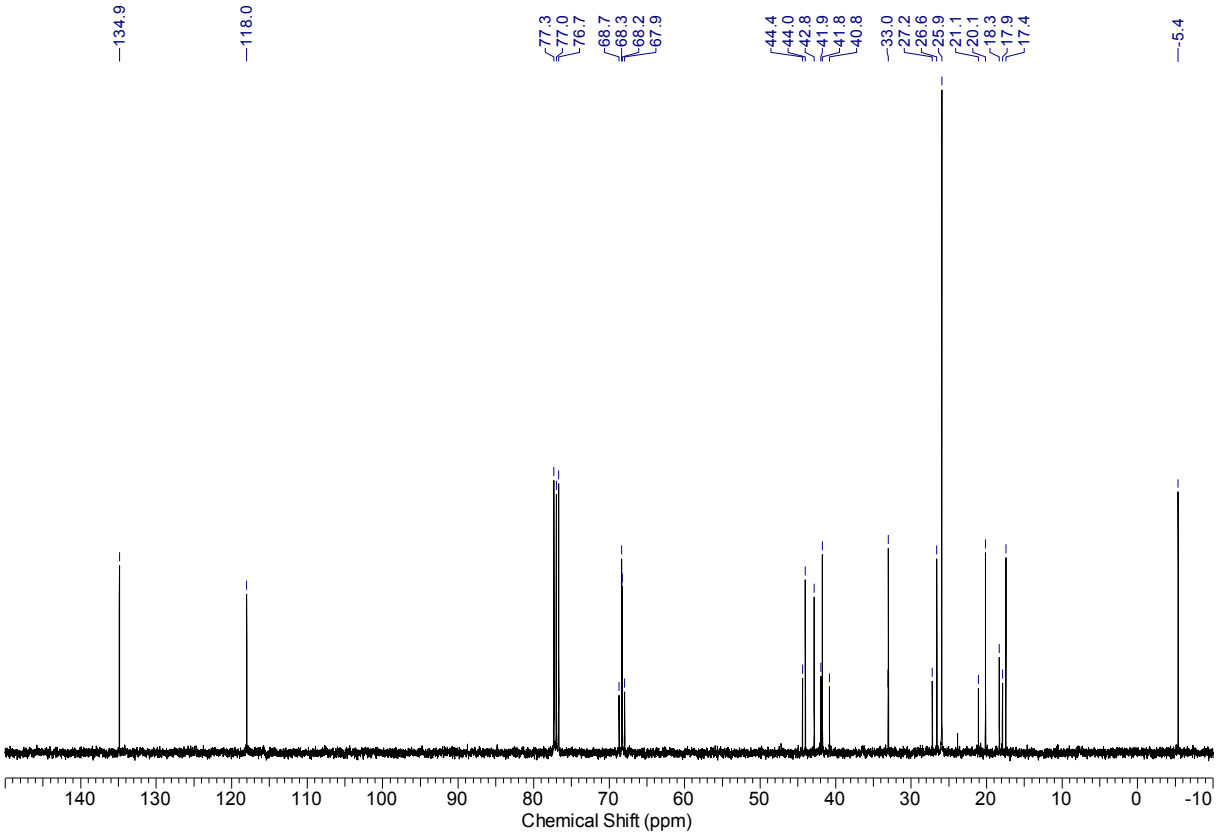
^{1}H NMR (400 MHz) spectrum of alcohol **4-24** in $CDCl_3$.



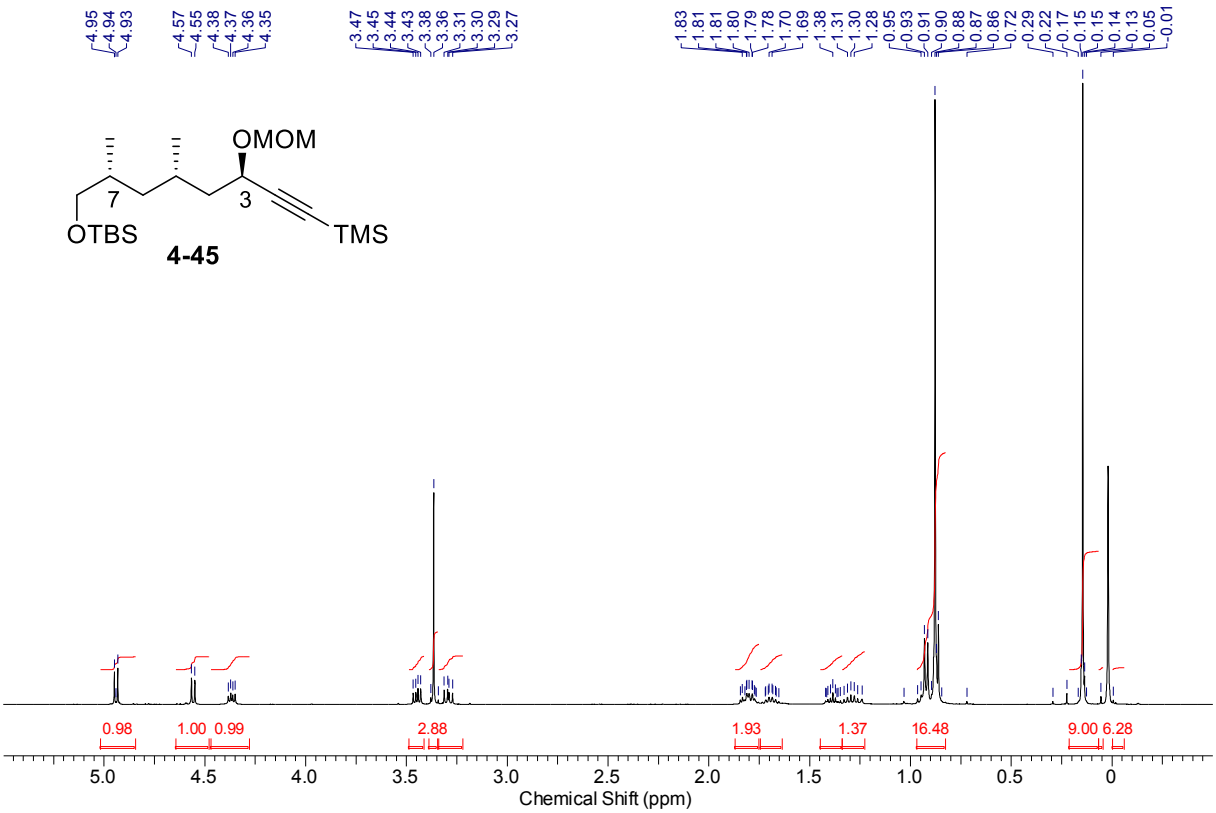
^{13}C NMR (100 MHz) spectrum of alcohol **4-24** in $CDCl_3$.



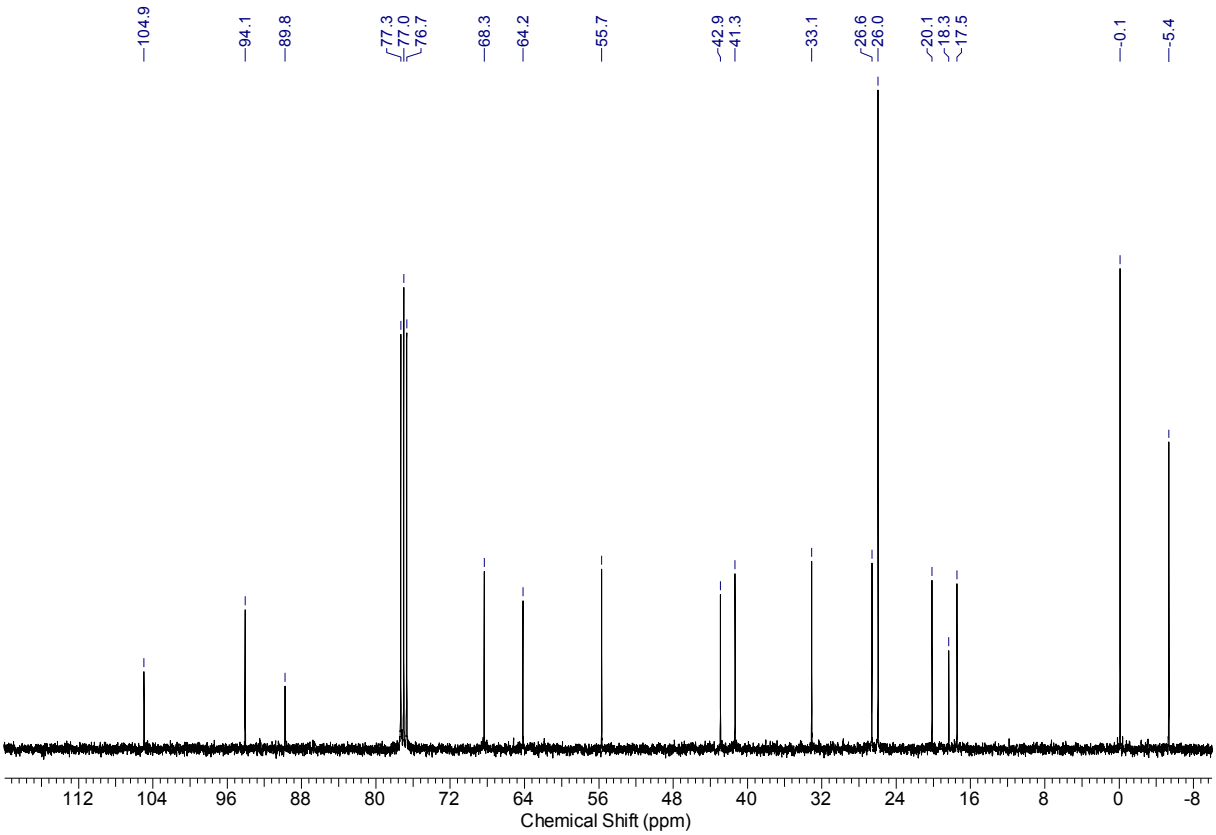
^{1}H NMR (400 MHz) spectrum of hydroxyl-alkene **4-32** in $CDCl_3$.



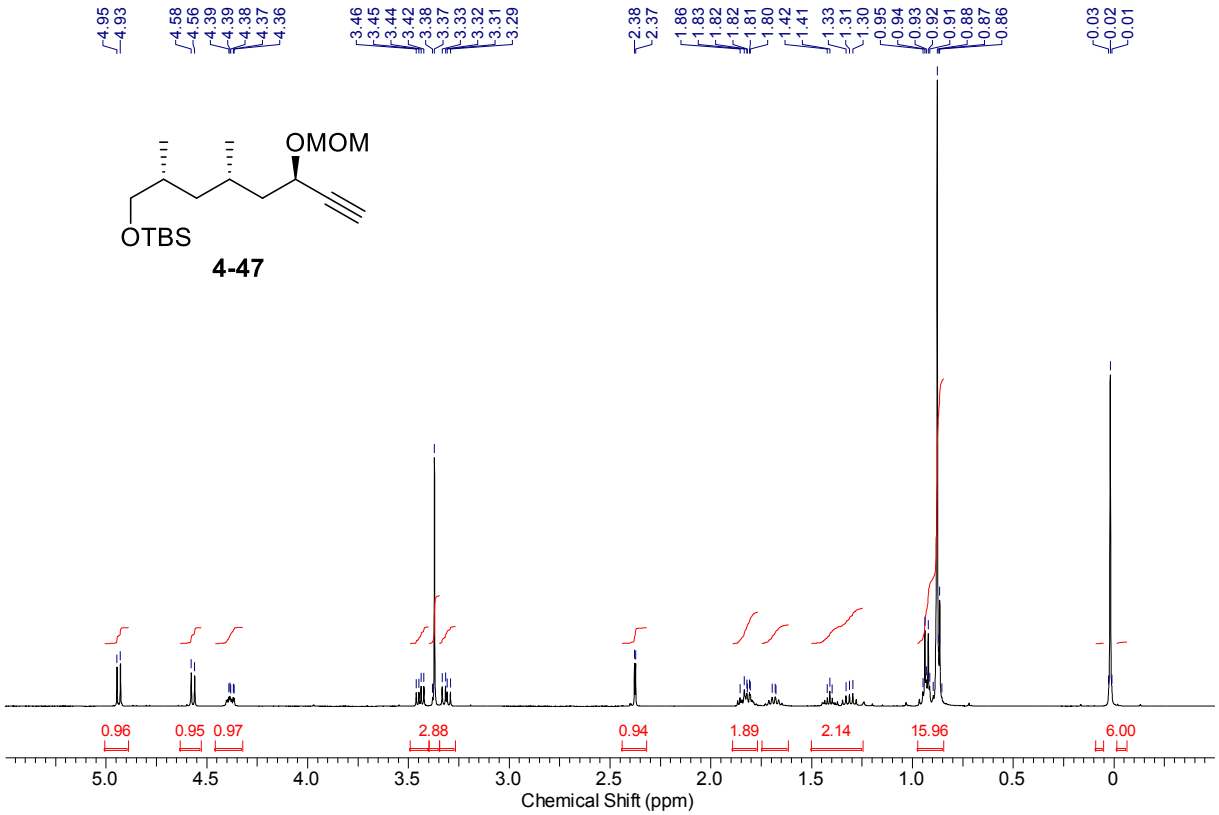
^{13}C NMR (100 MHz) spectrum of hydroxyl-alkene **4-32** in $CDCl_3$.



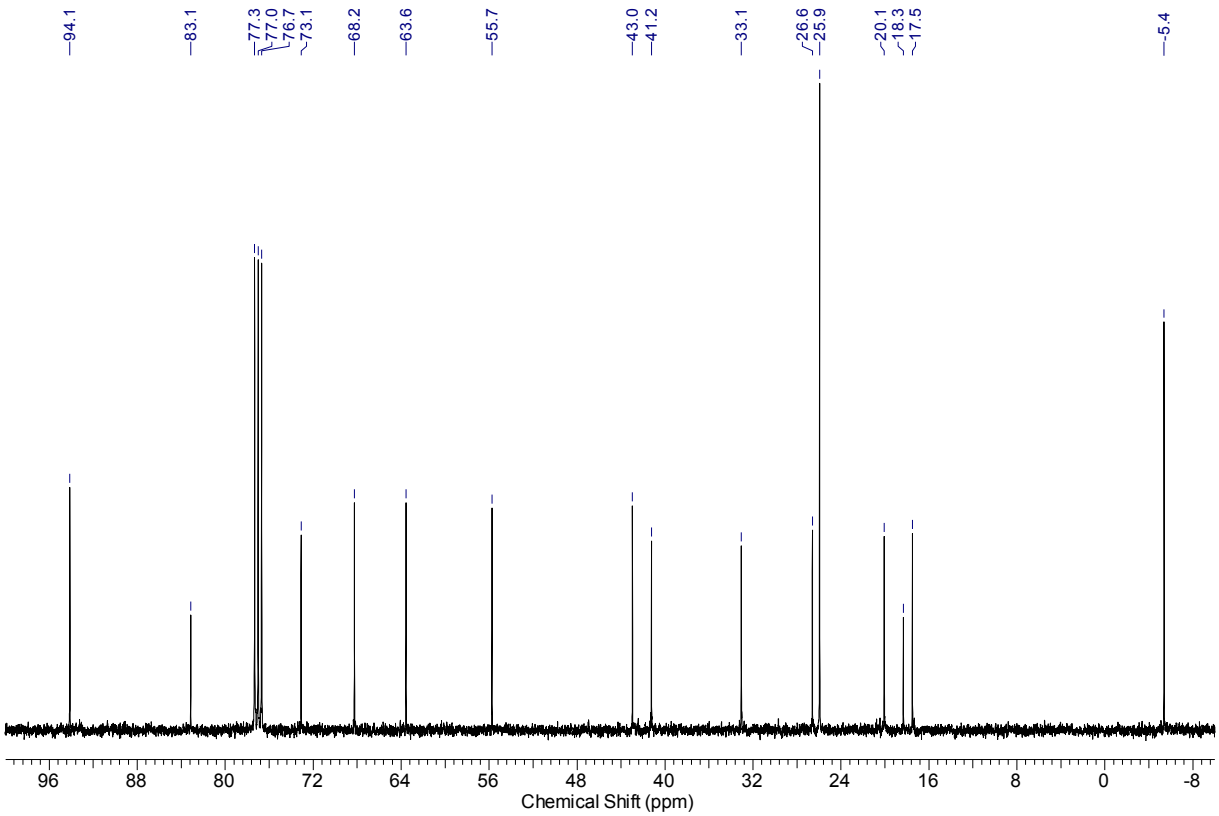
^{1}H NMR (400 MHz) spectrum of alkyne **4-45** in $CDCl_3$.



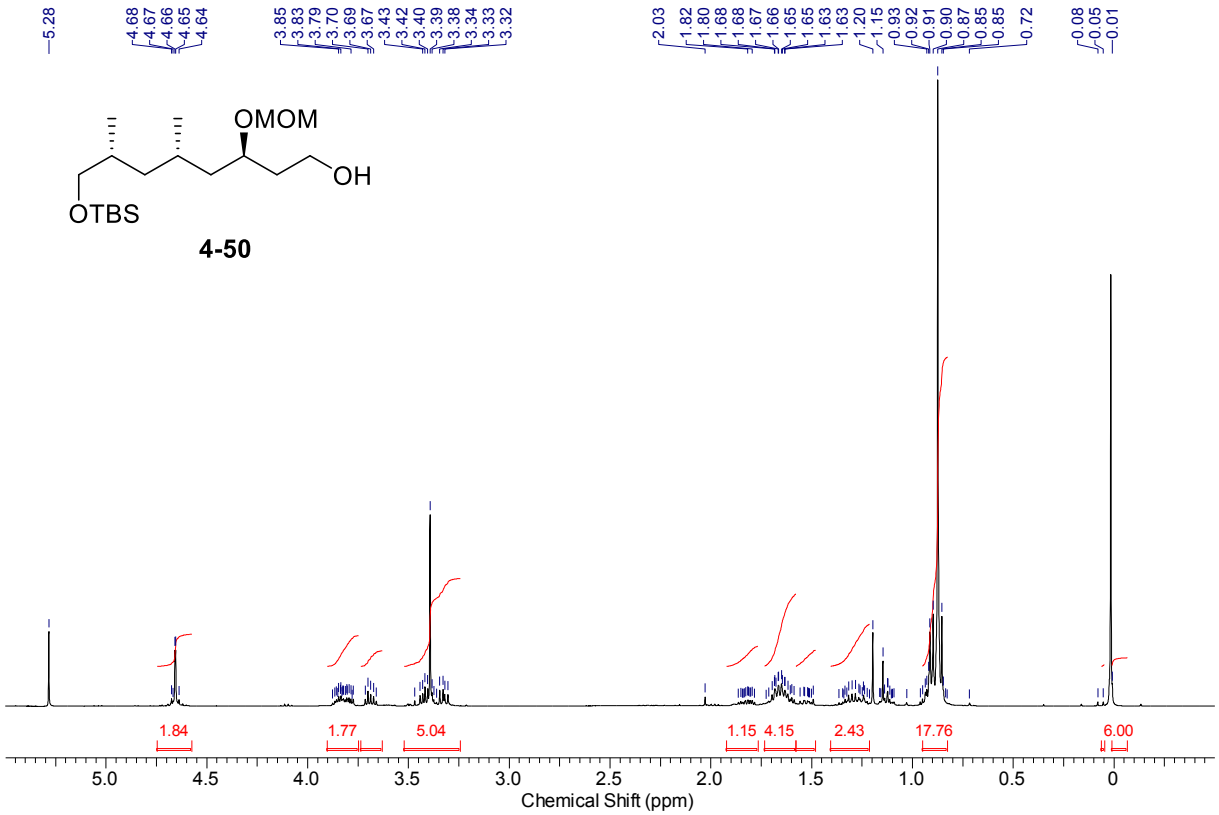
^{13}C NMR (100 MHz) spectrum of internal-alkyne **4-45** in $CDCl_3$.



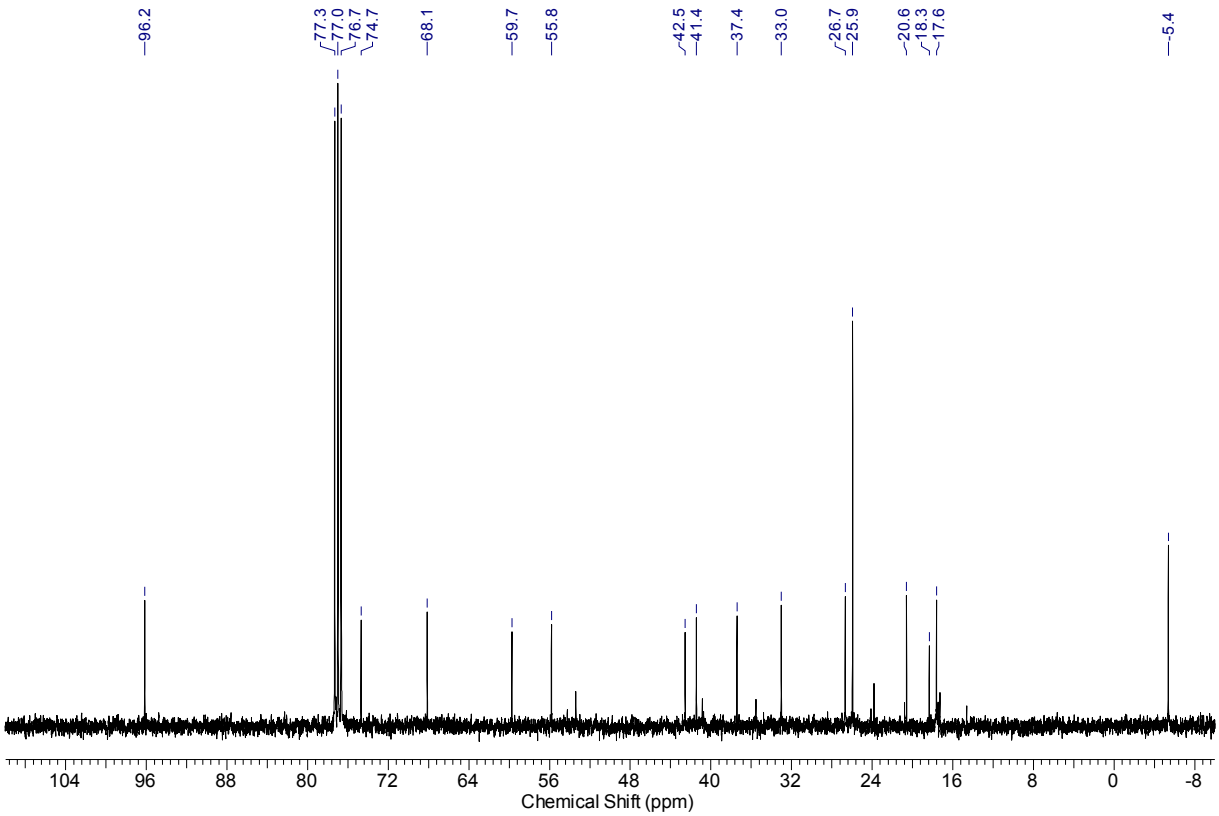
^{1}H NMR (400 MHz) spectrum of terminal-alkyne **4-47** in $CDCl_3$.



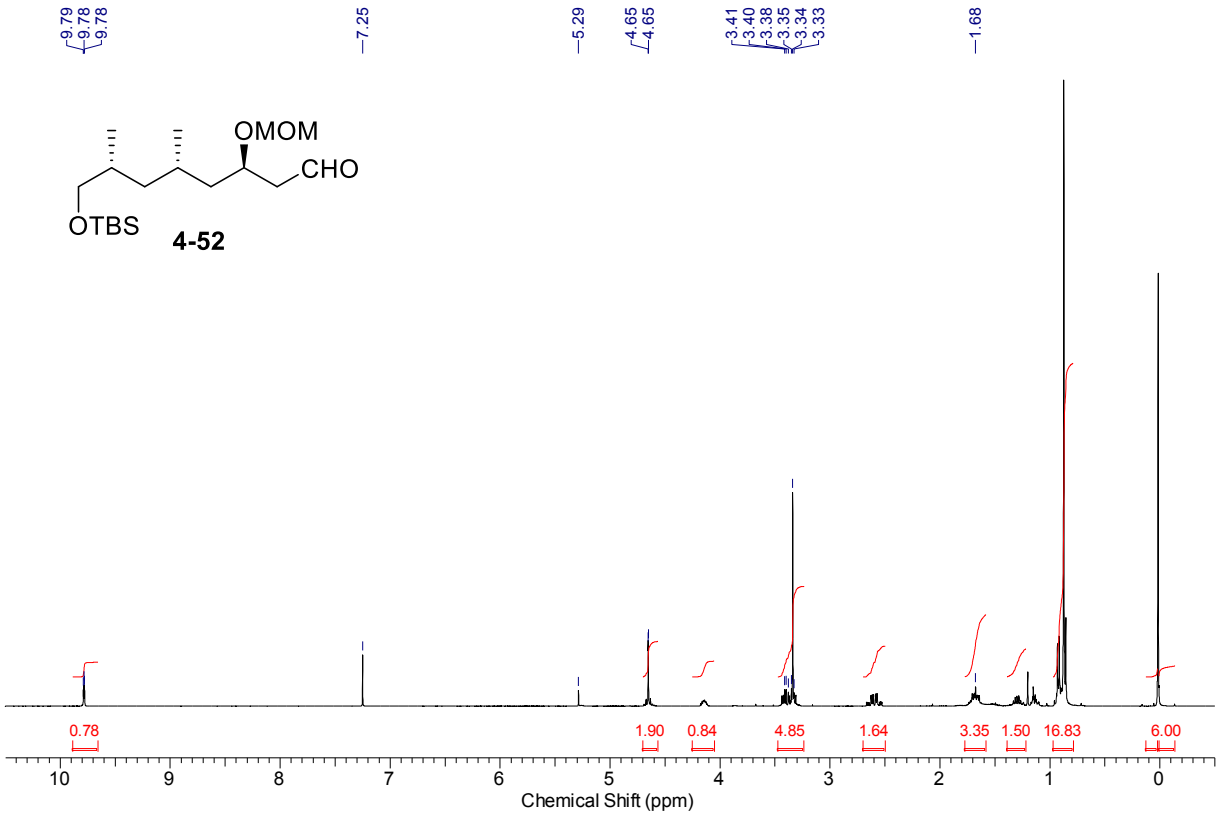
^{13}C NMR (100 MHz) spectrum of terminal-alkyne **4-47** in $CDCl_3$.



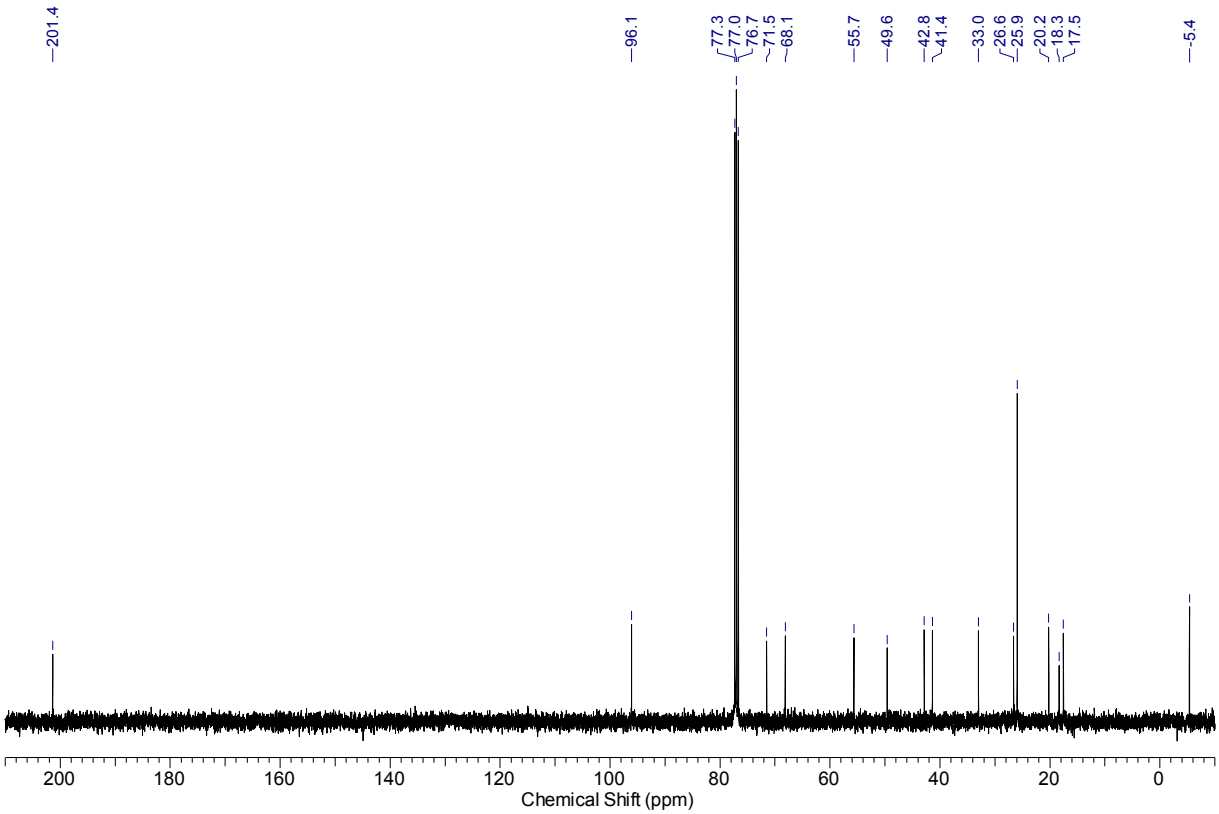
^{1}H NMR (400 MHz) spectrum of alcohol **4-50** in $CDCl_3$.



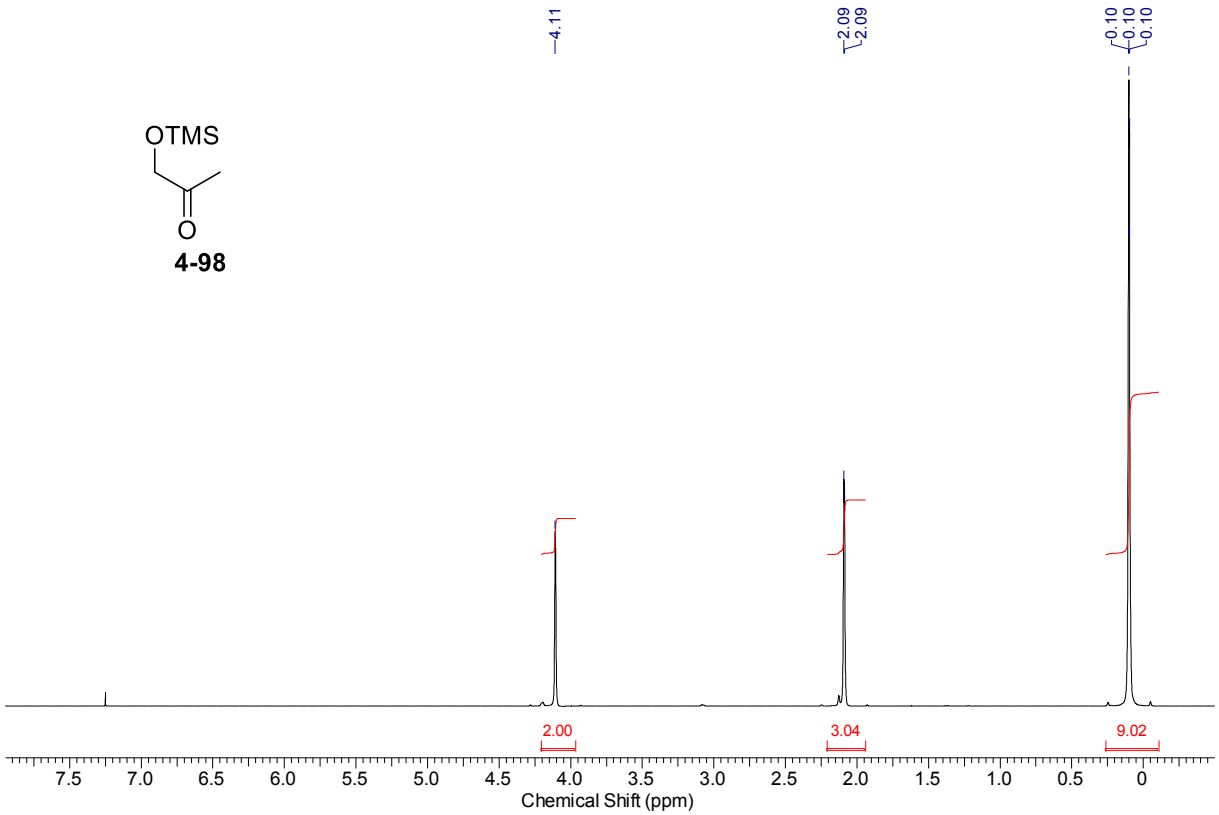
^{13}C NMR (100 MHz) spectrum of alcohol **4-50** in $CDCl_3$.



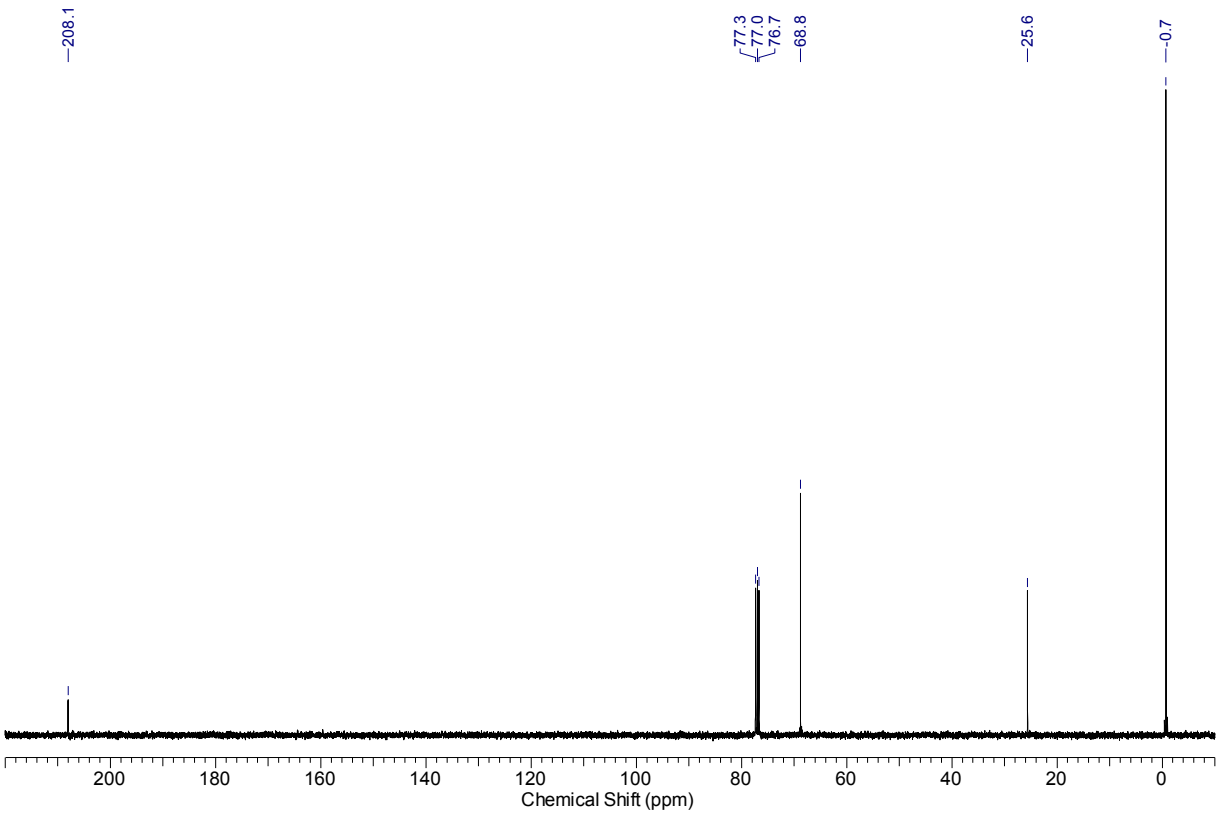
^{1}H NMR (400 MHz) spectrum of aldehyde **4-52** in $CDCl_3$.



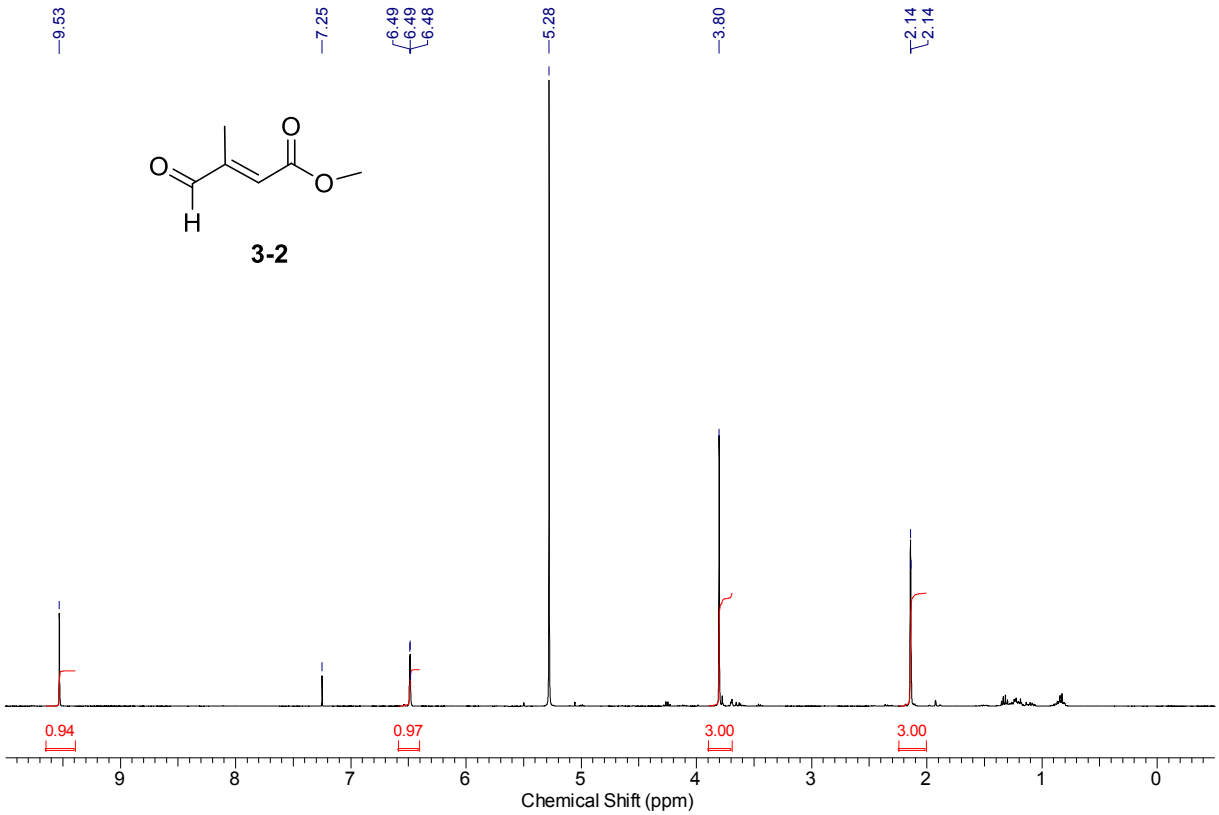
^{13}C NMR (100 MHz) spectrum of aldehyde **4-52** in $CDCl_3$.



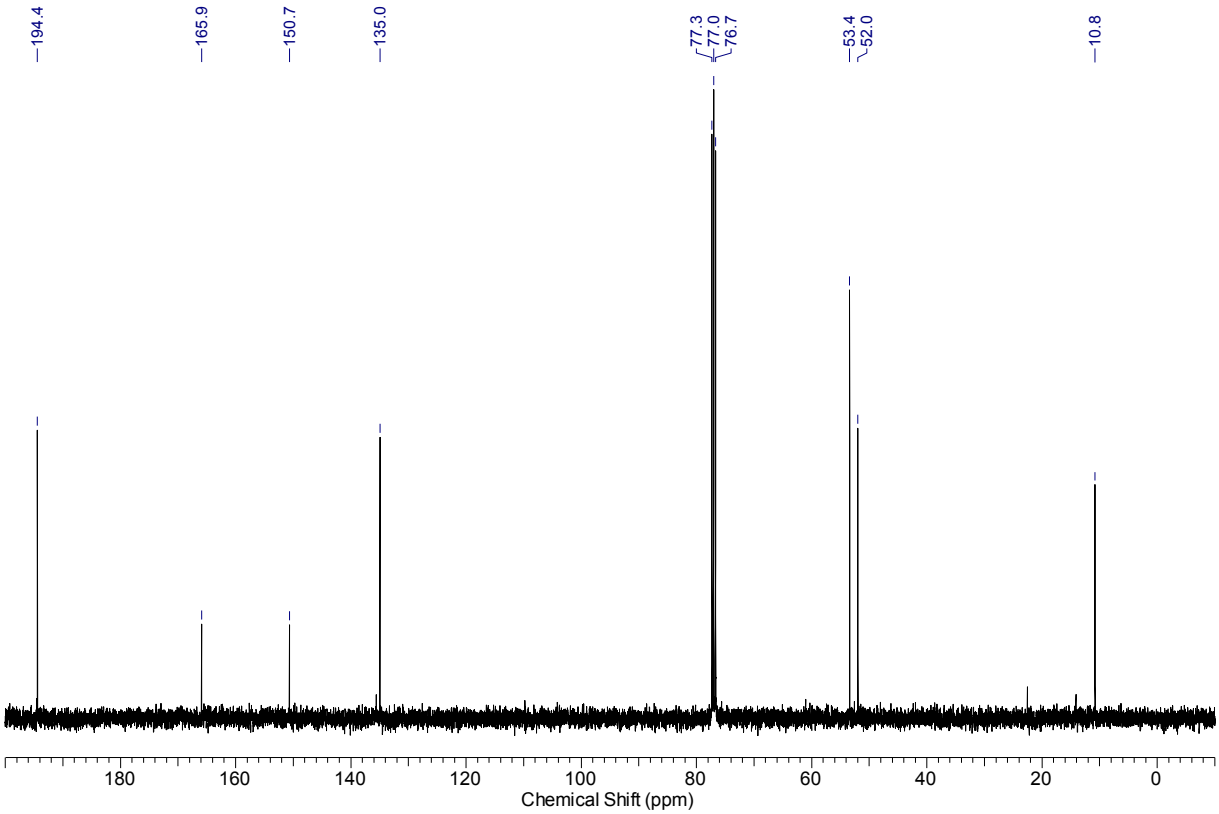
^{1}H NMR (400 MHz) spectrum of OTMS-acetone **4-98** in $CDCl_3$.



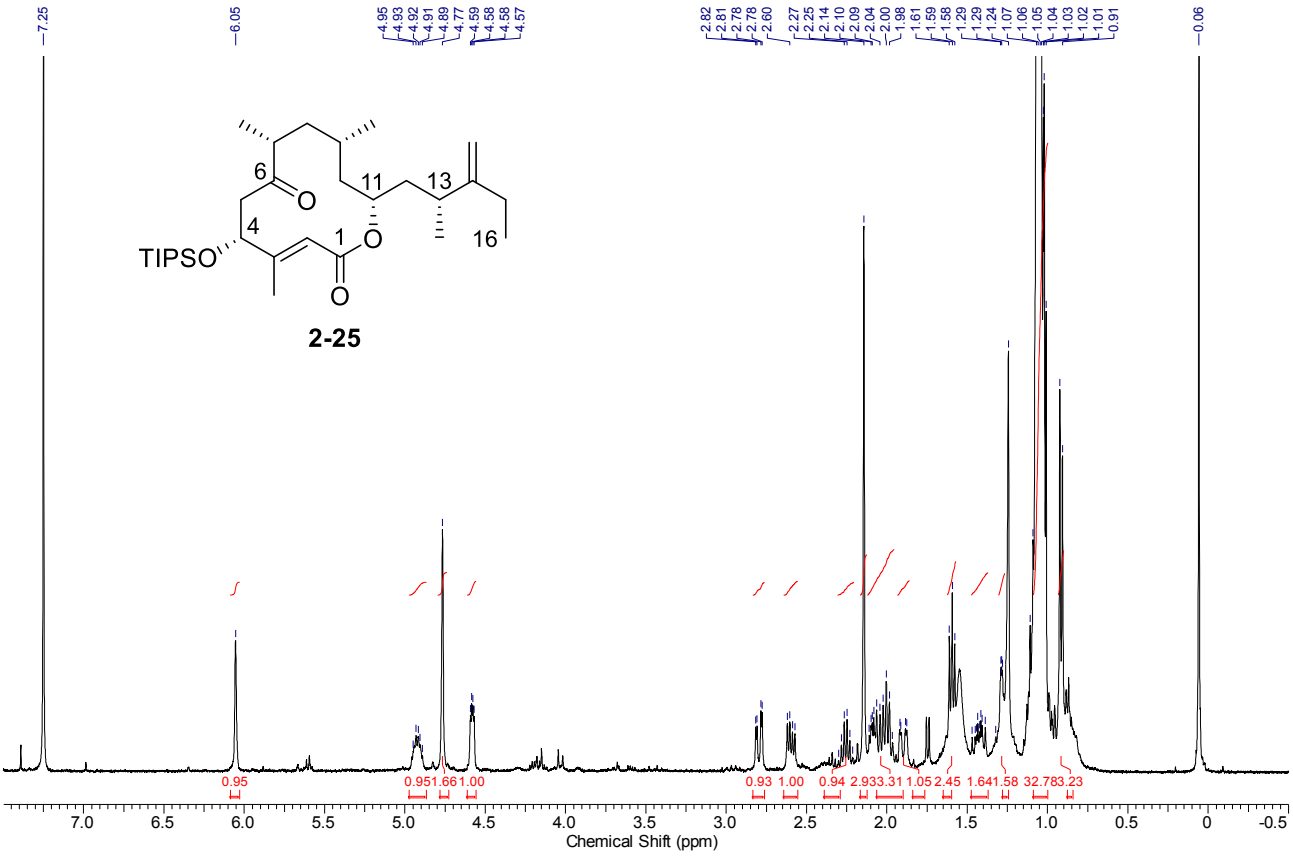
^{13}C NMR (100 MHz) spectrum of OTMS-acetone **4-98** in $CDCl_3$.



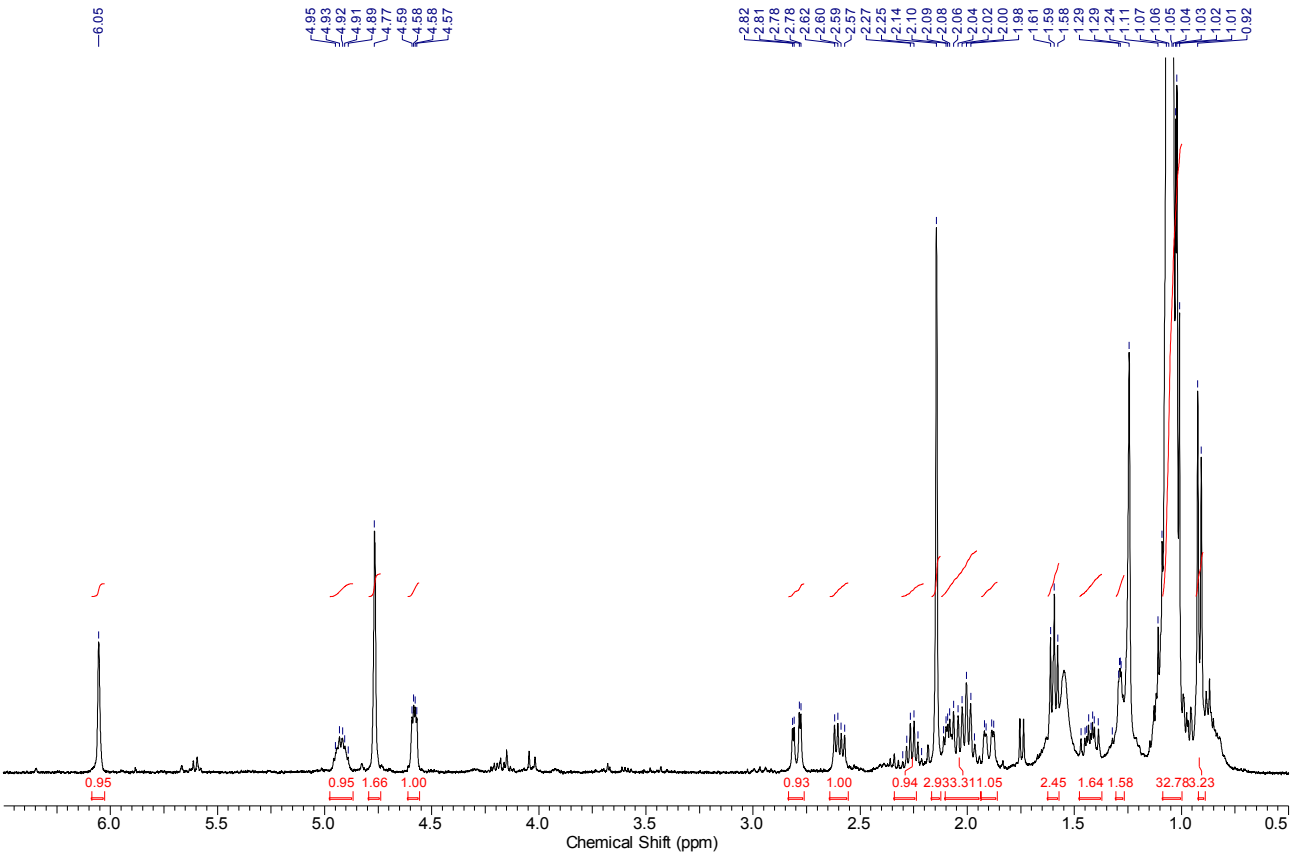
^{1}H NMR (400 MHz) spectrum of oxo-ester **3-2** in $CDCl_3$.



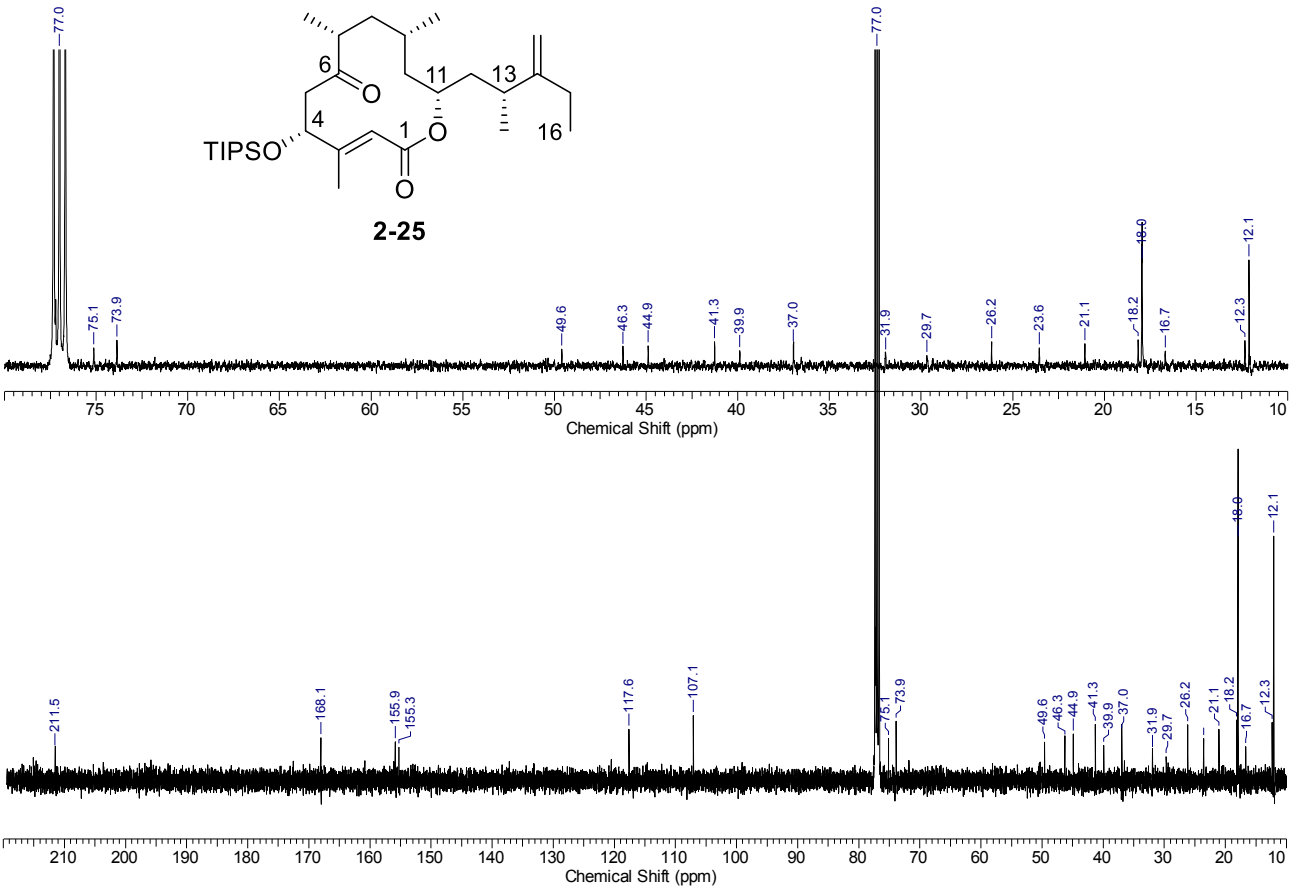
^{13}C NMR (100 MHz) spectrum of oxo-ester **3-2** in $CDCl_3$.



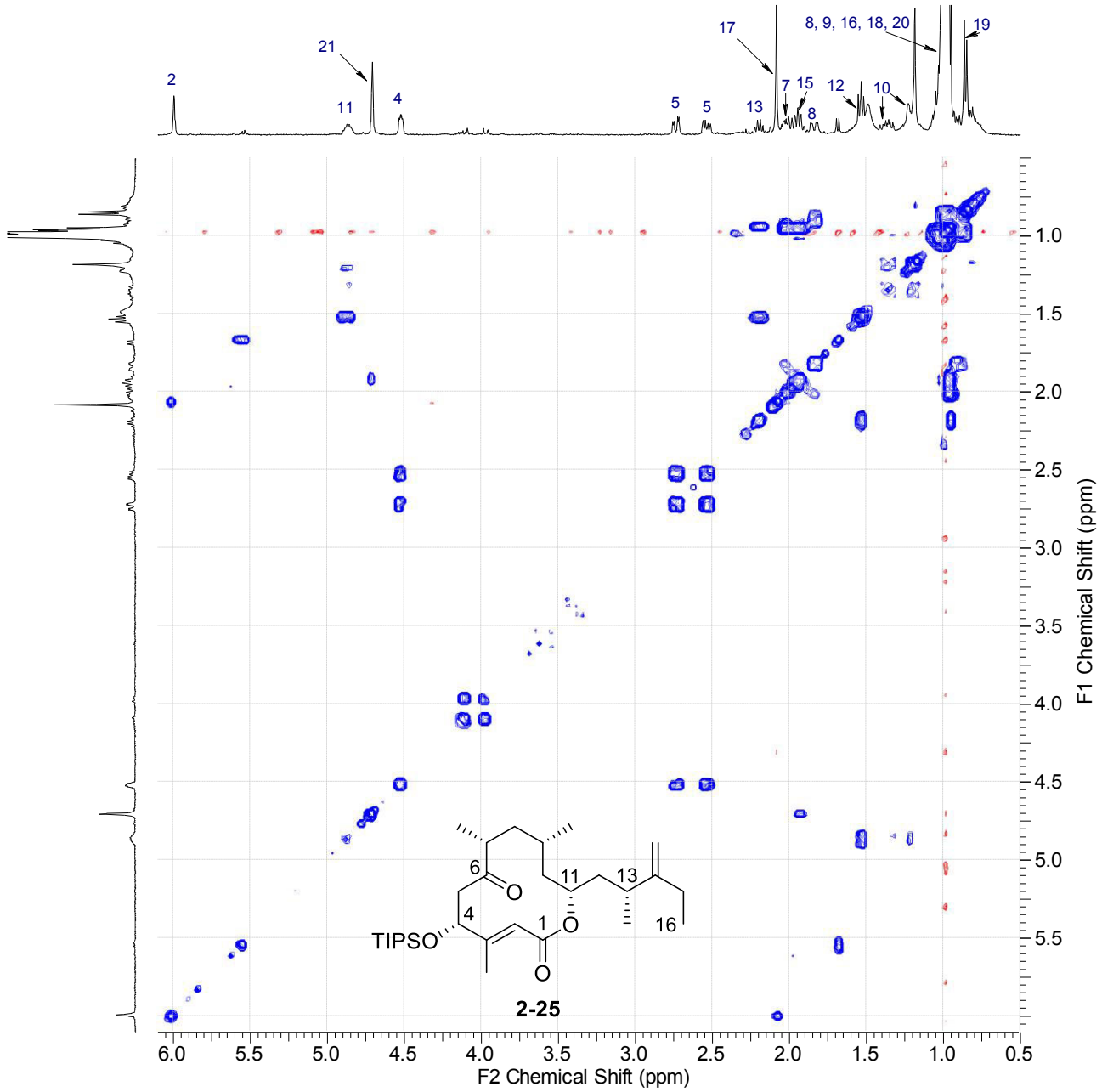
^{1}H NMR (400 MHz) spectrum of macrolactone **2-25** in $CDCl_3$ (–0.5 – 7.5 ppm).



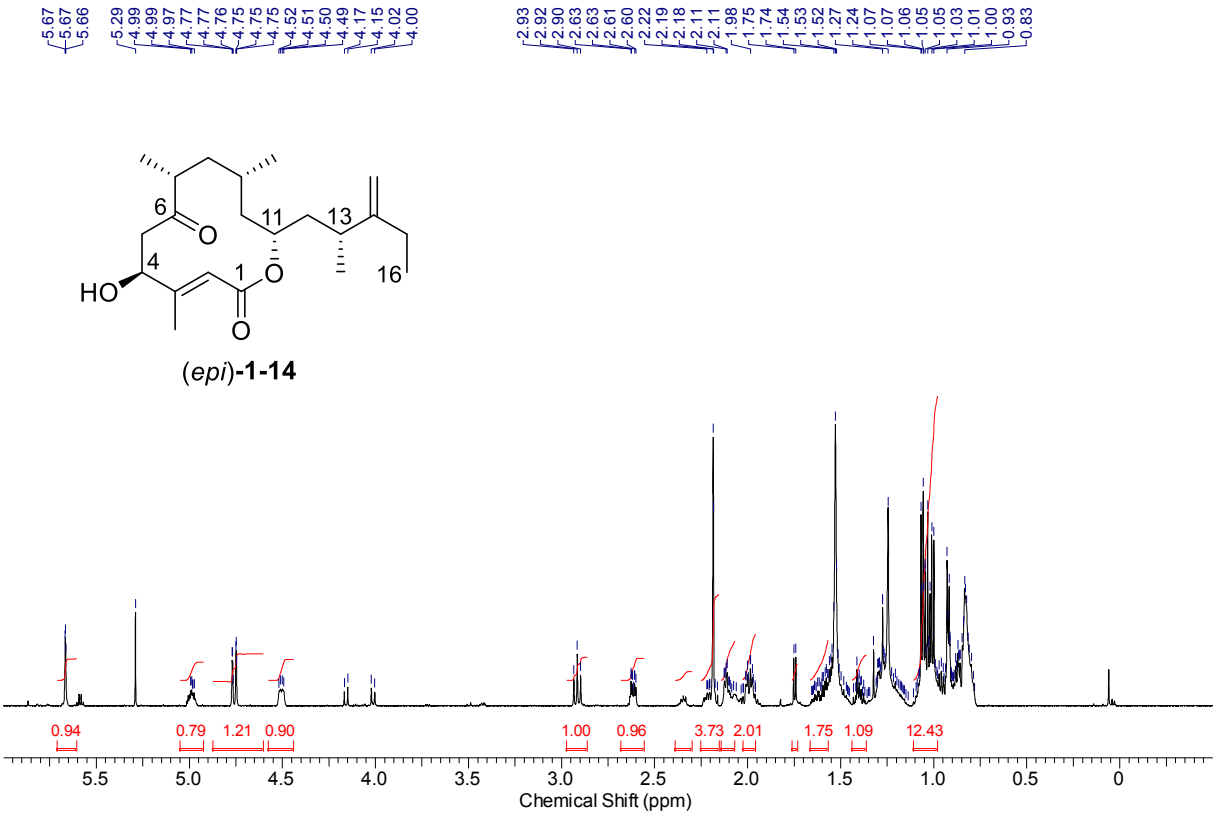
^{1}H NMR (400 MHz) spectrum of macrolactone **2-25** in $CDCl_3$ (–0.5 – 6.5 ppm).



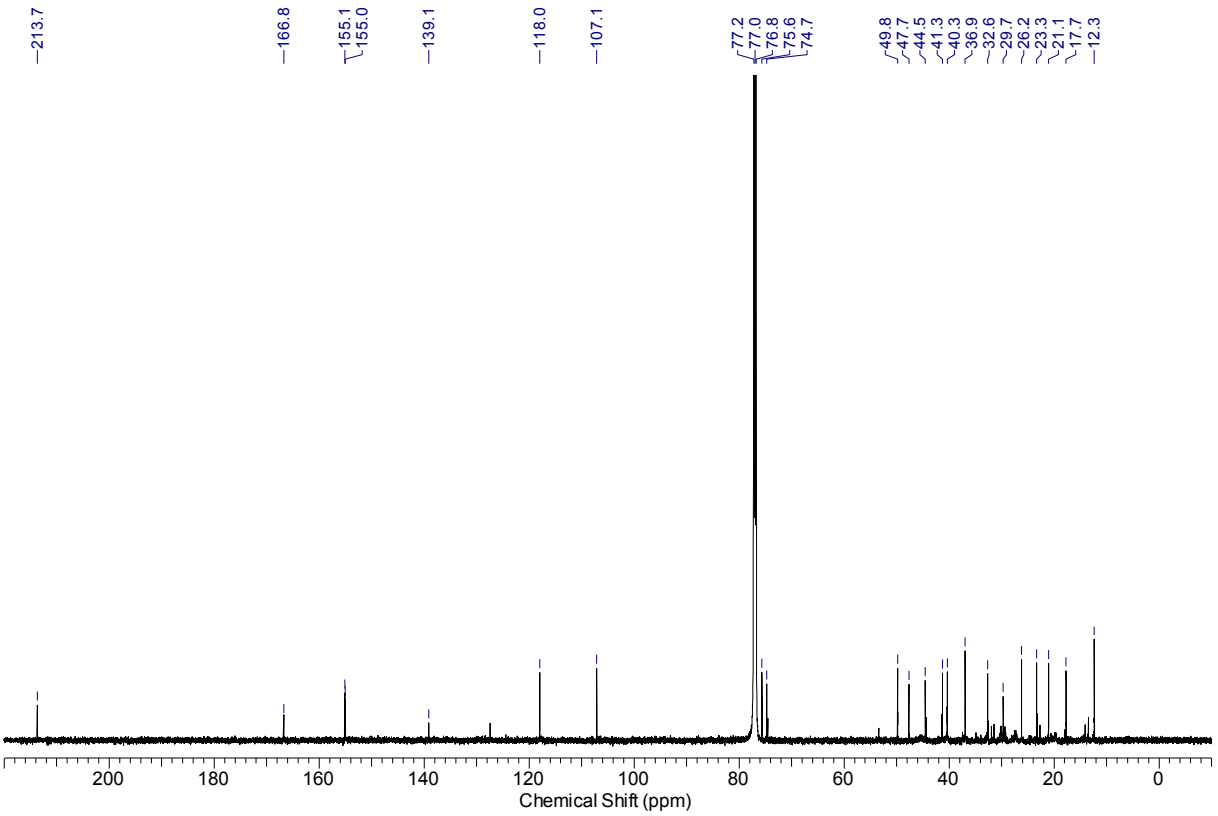
^{13}C NMR (100 MHz) spectrum of macrolactone **2-25** in $CDCl_3$.



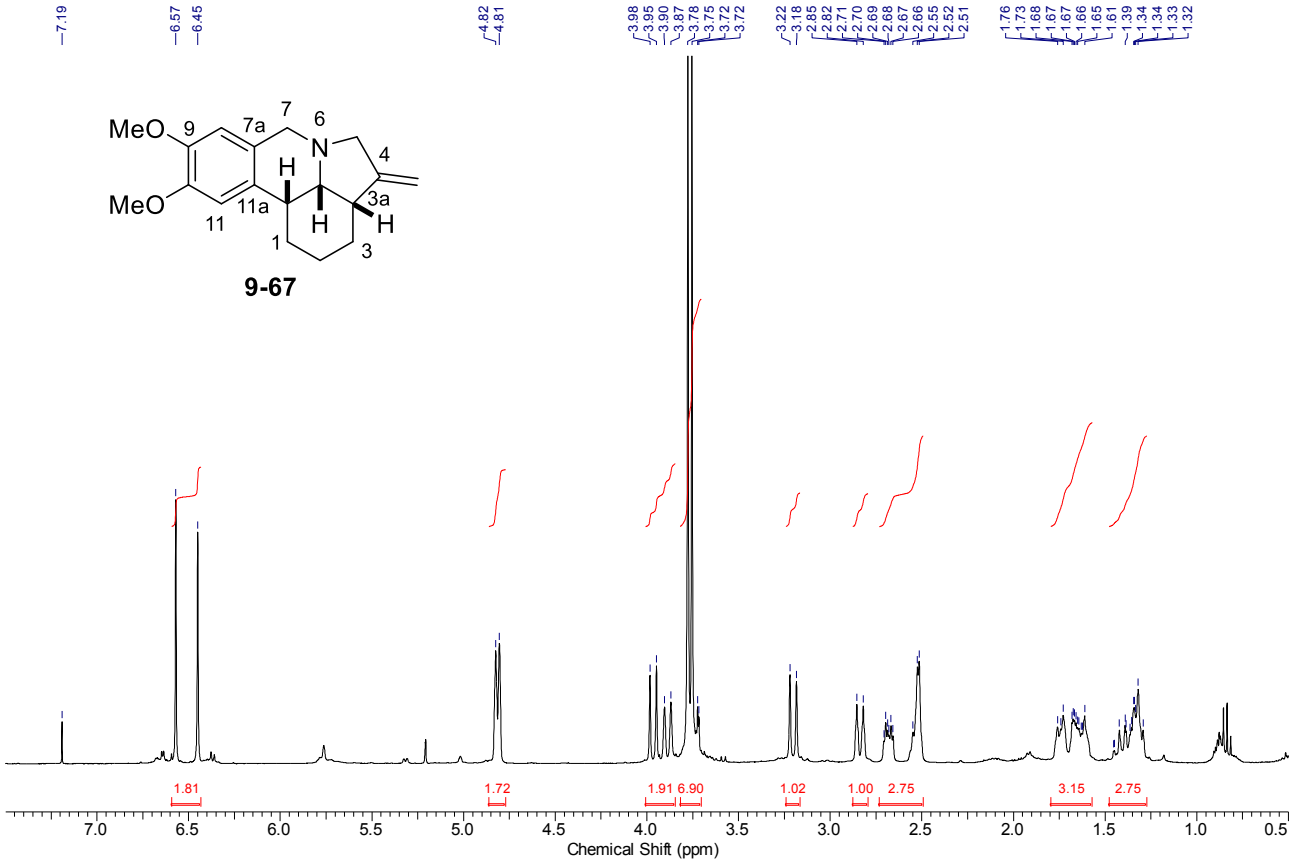
COSY (400 MHz) spectrum of macrolactone **2-25** in $CDCl_3$ (0.5 – 6.1 ppm).



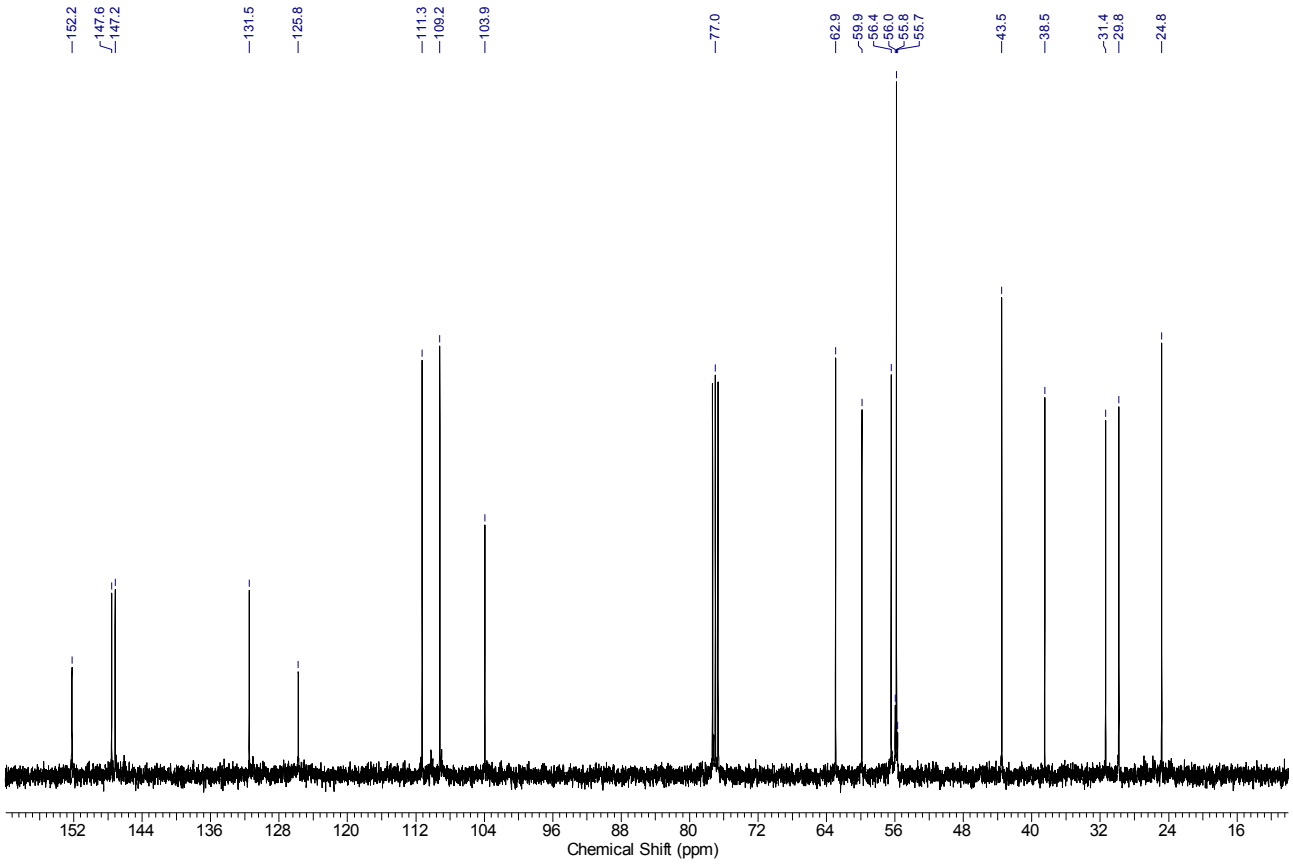
^{1}H NMR (600 MHz) spectrum of 4-*epi*-amphidinolide Q (***epi*-1-14**) in $CDCl_3$.



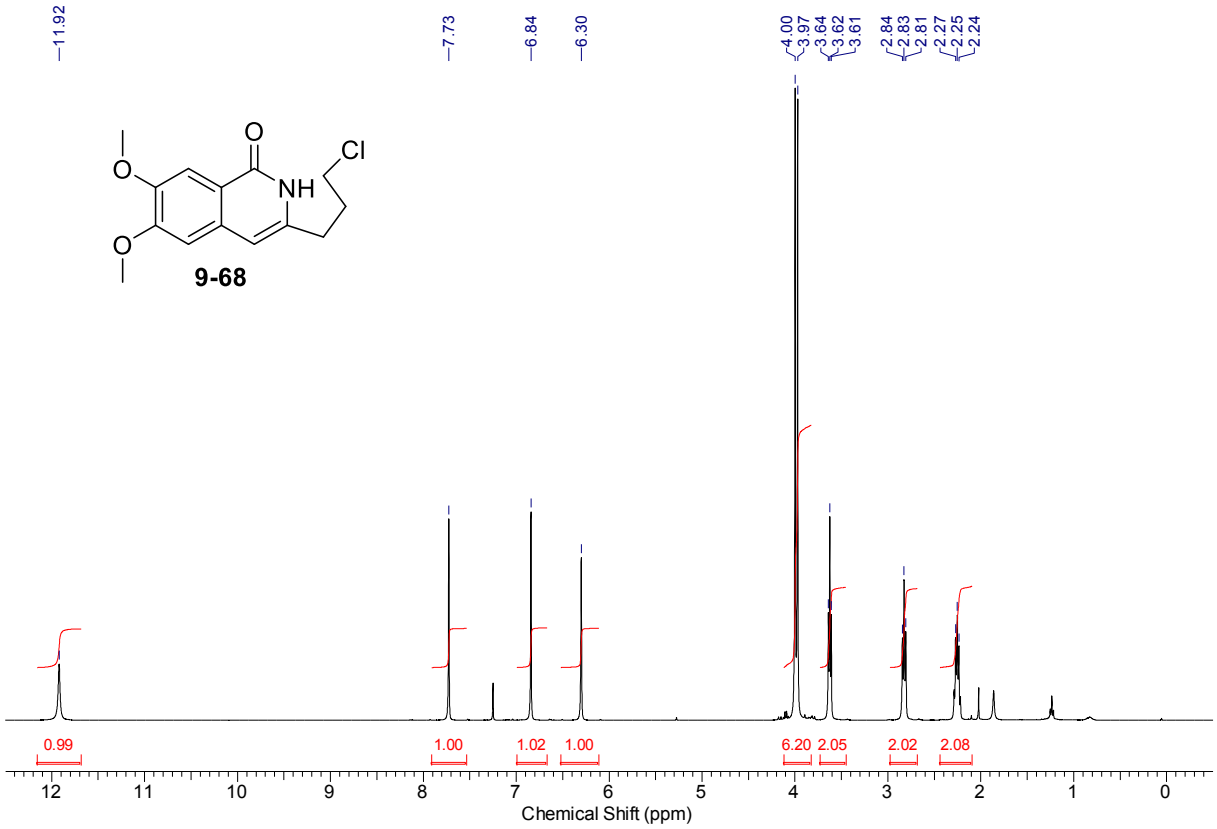
^{13}C NMR (150 MHz) spectrum of 4-*epi*-amphidinolide Q (***epi*-1-14**) in $CDCl_3$.



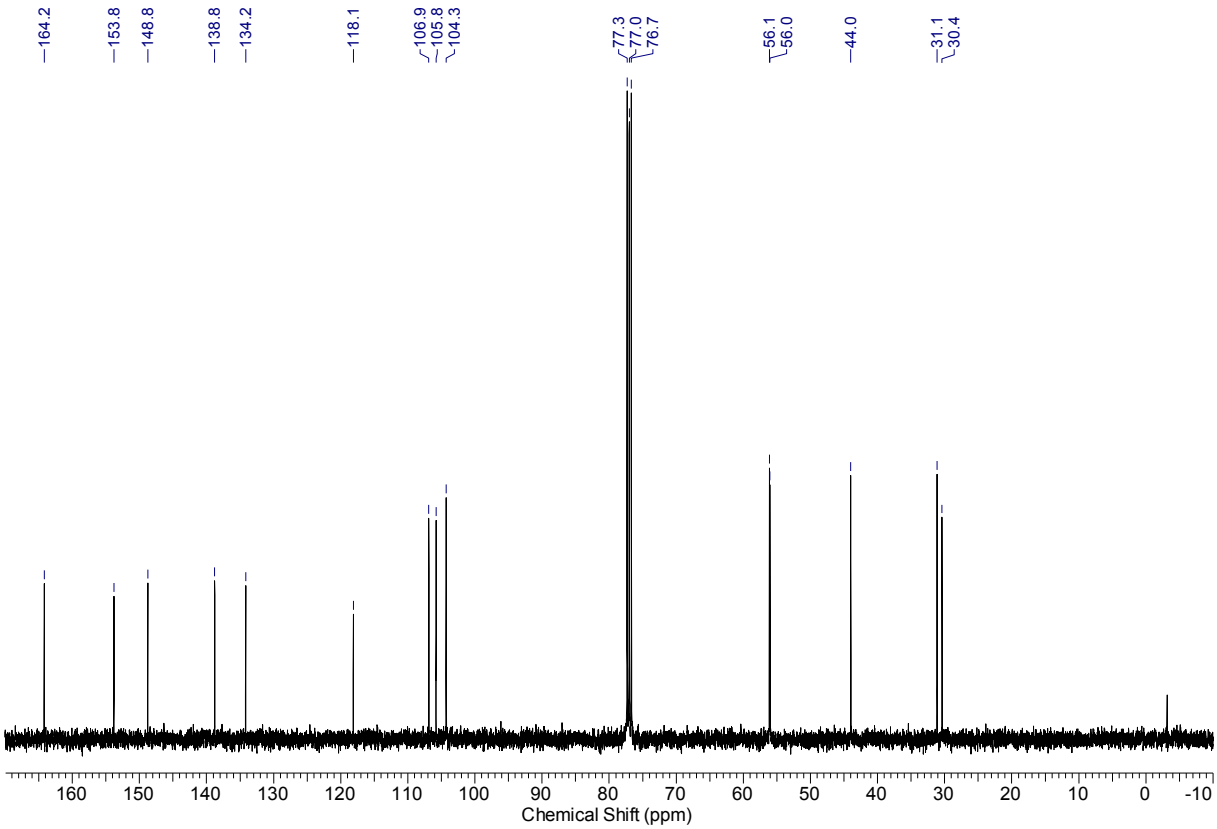
^{1}H NMR (400 MHz) spectrum of tetracycle **9-67** in $CDCl_3$.



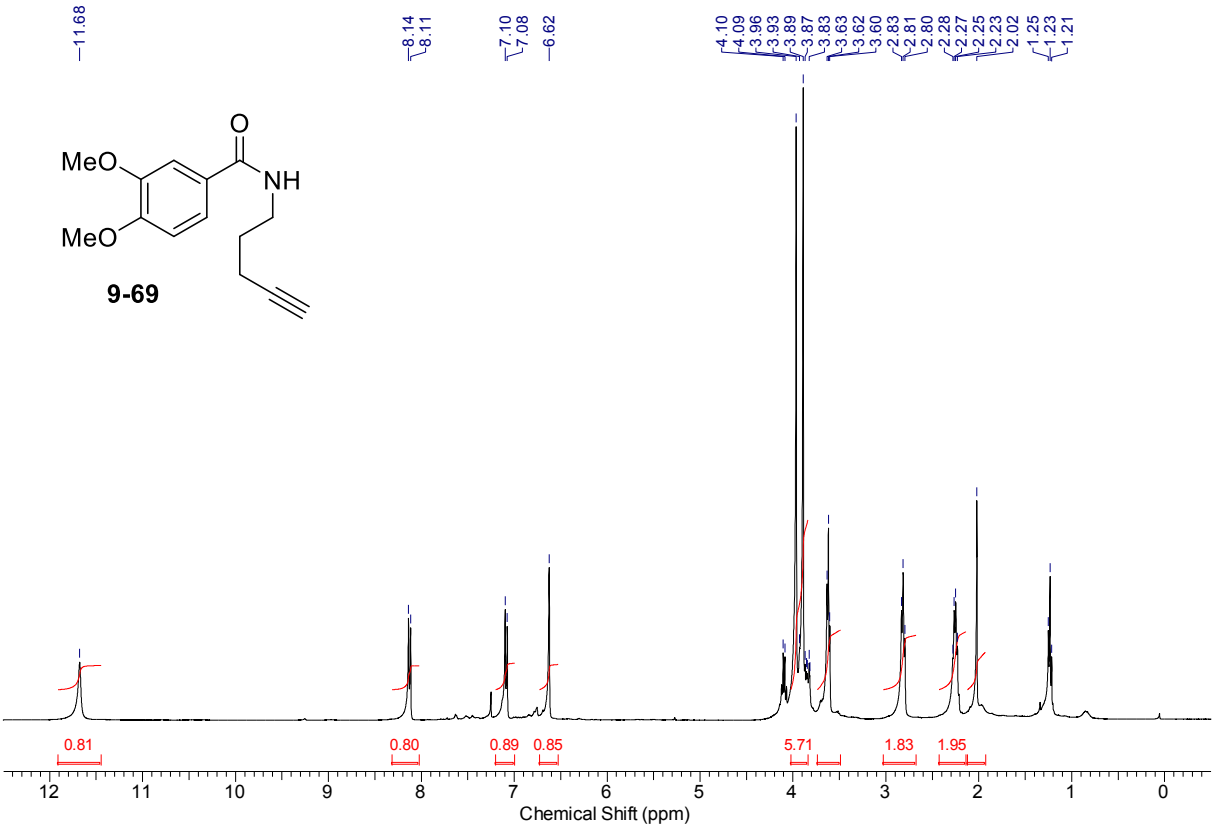
^{13}C NMR (100 MHz) spectrum of tetracycle **9-67** in $CDCl_3$.



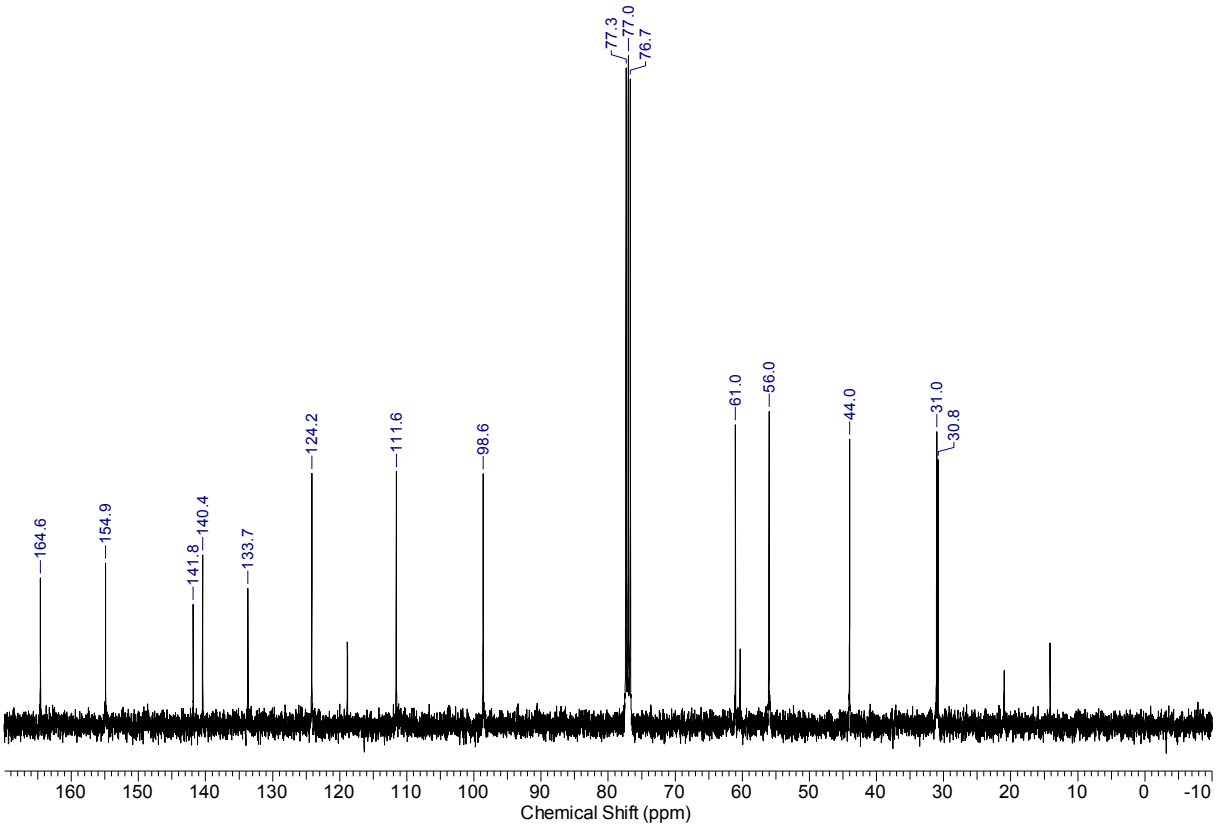
^{1}H NMR (400 MHz) spectrum of iso-indole **9-68** in $CDCl_3$.



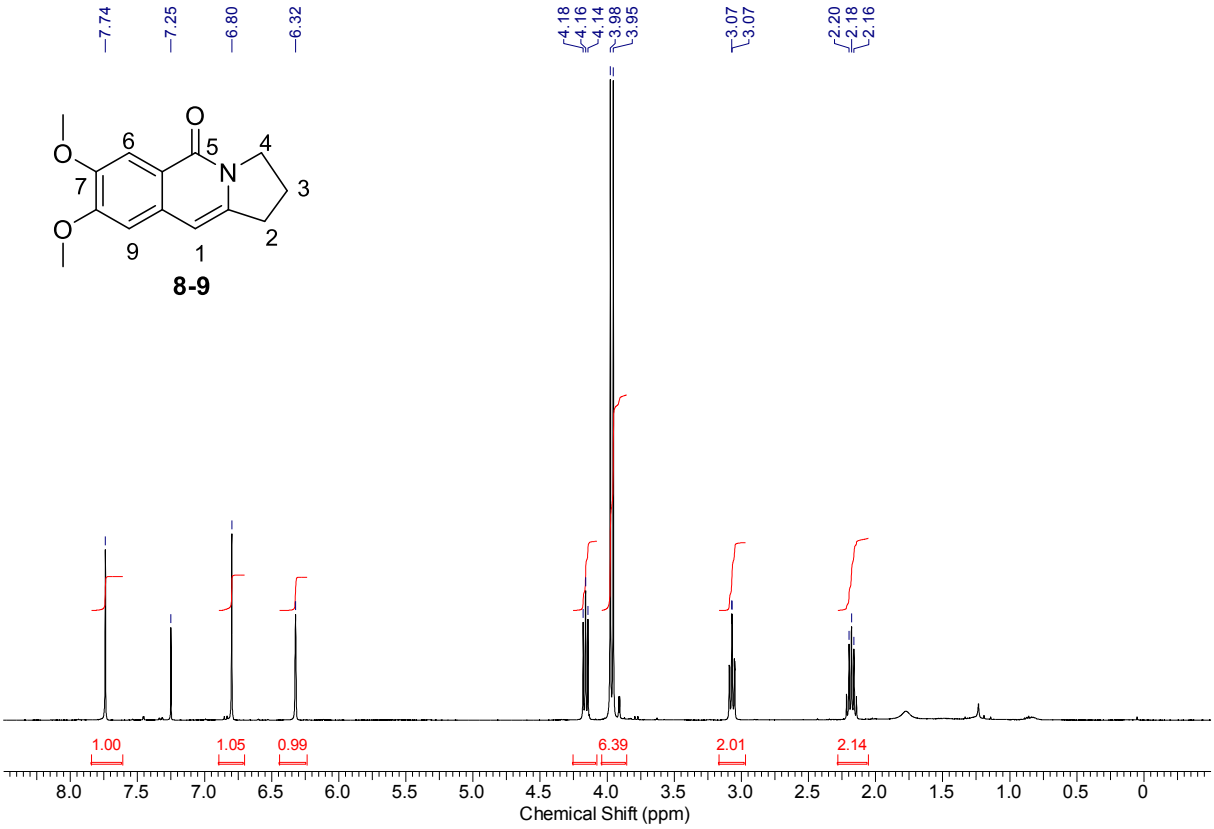
^{13}C NMR (100 MHz) spectrum of iso-indole **9-68** in $CDCl_3$.



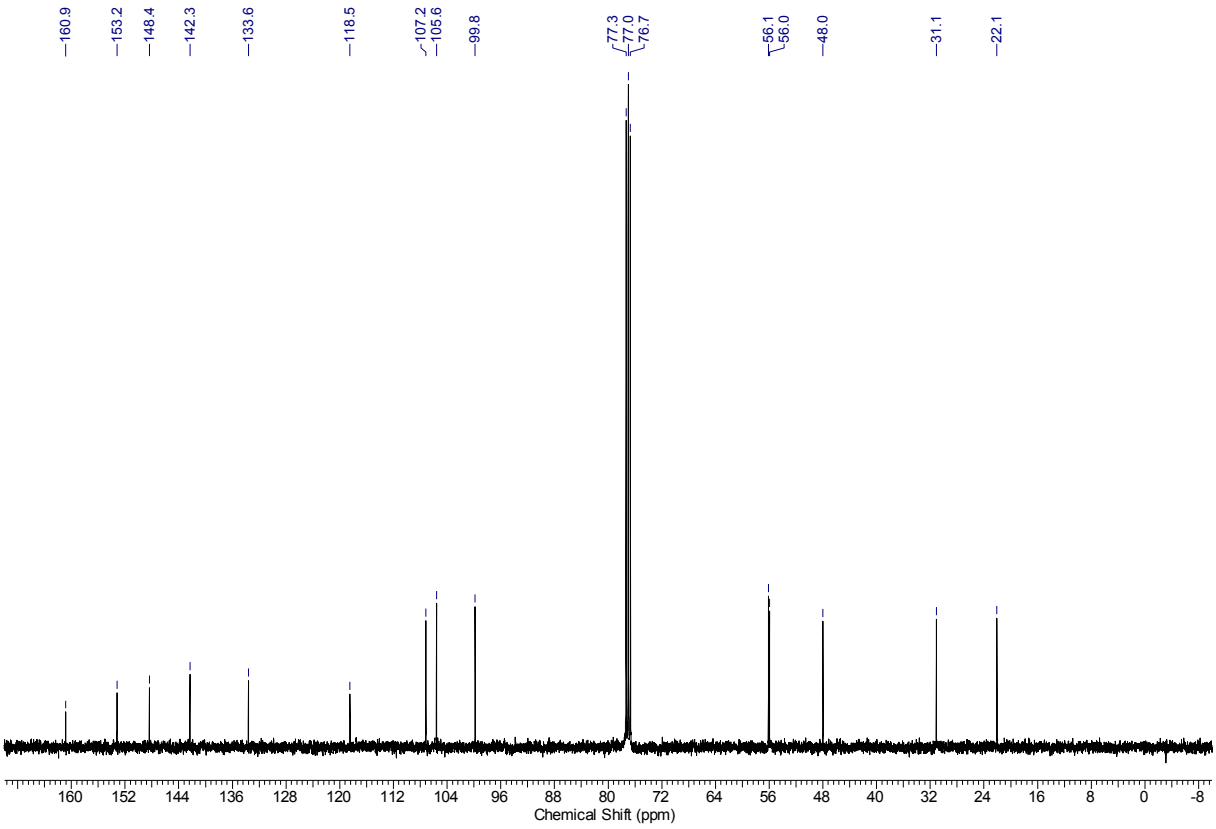
^{1}H NMR (400 MHz) spectrum of amide **9-69** in $CDCl_3$.



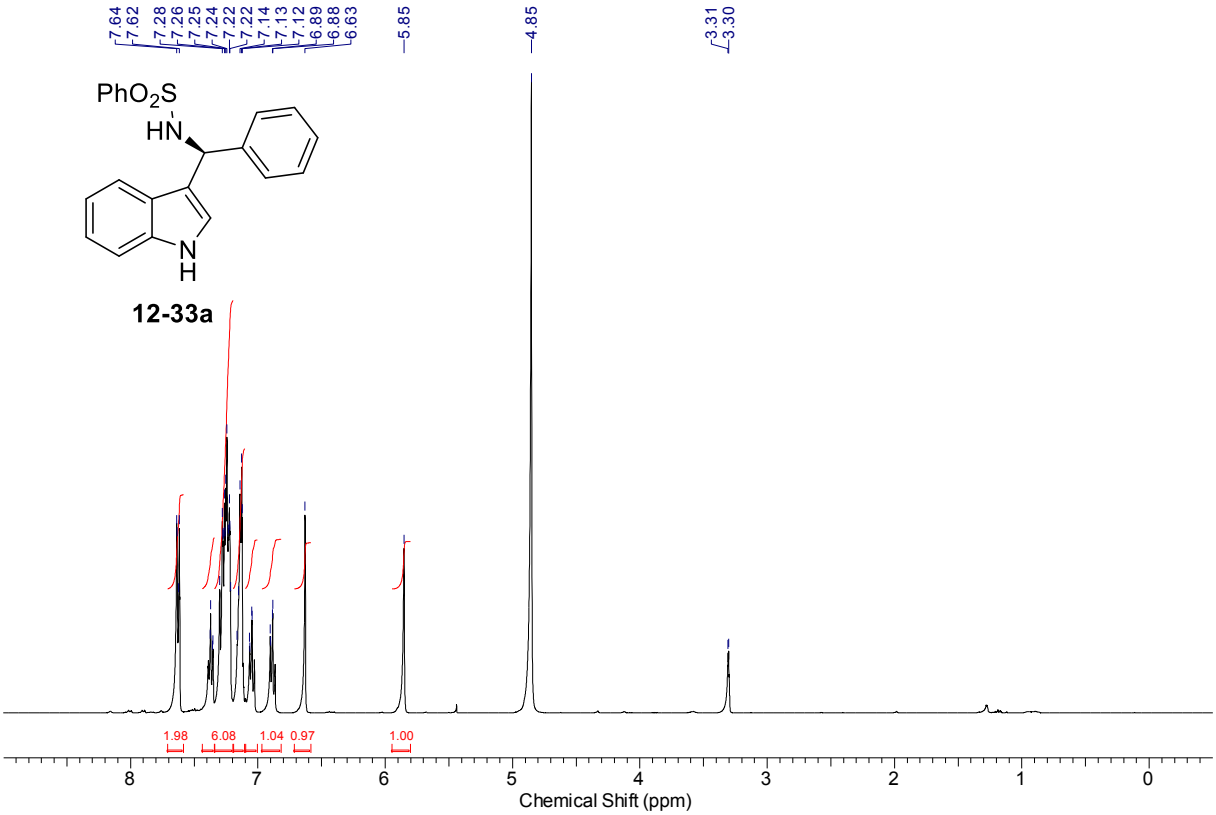
^{13}C NMR (100 MHz) spectrum of amide **9-69** in $CDCl_3$.



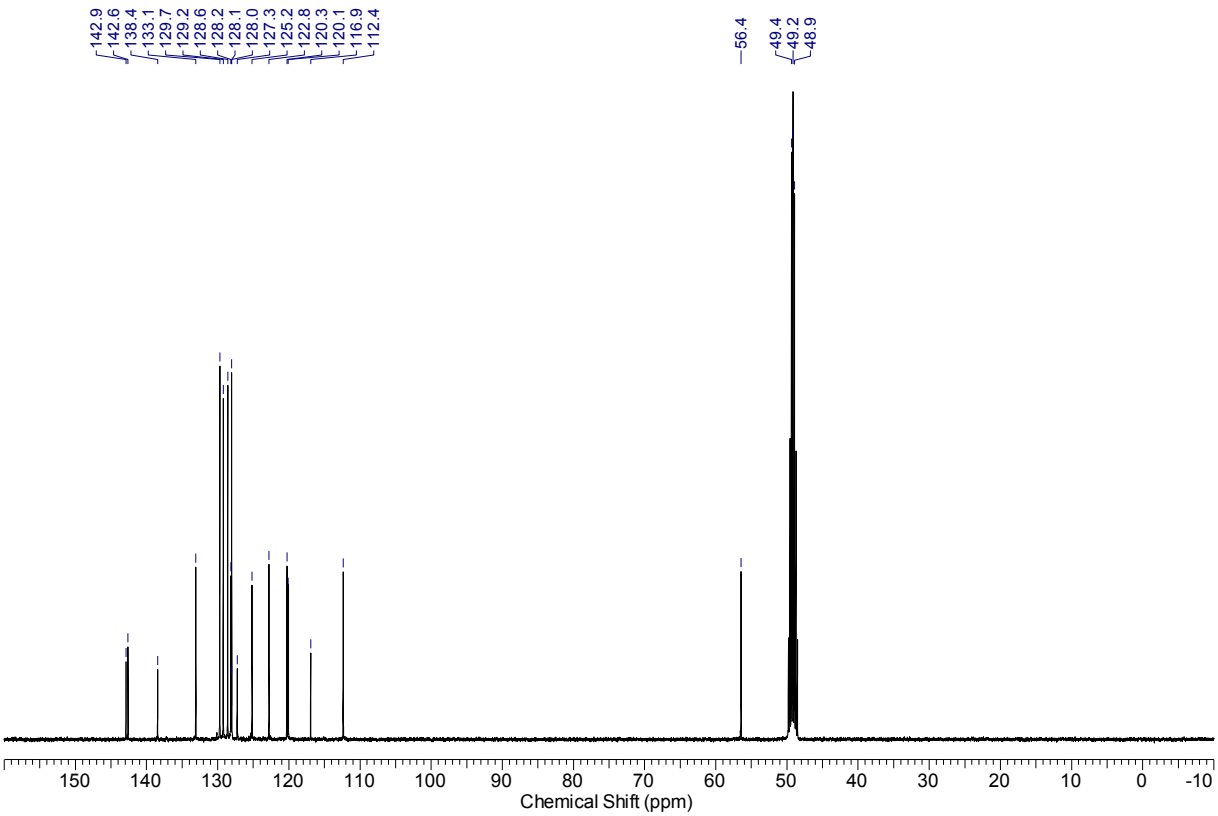
^{1}H NMR (400 MHz) spectrum of pyrolo-isoquinoline **8-9** in $CDCl_3$.



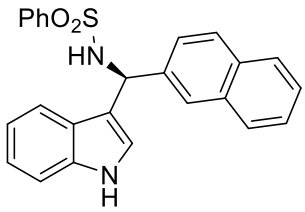
^{13}C NMR (100 MHz) spectrum of pyrolo-isoquinoline **8-9** in $CDCl_3$.



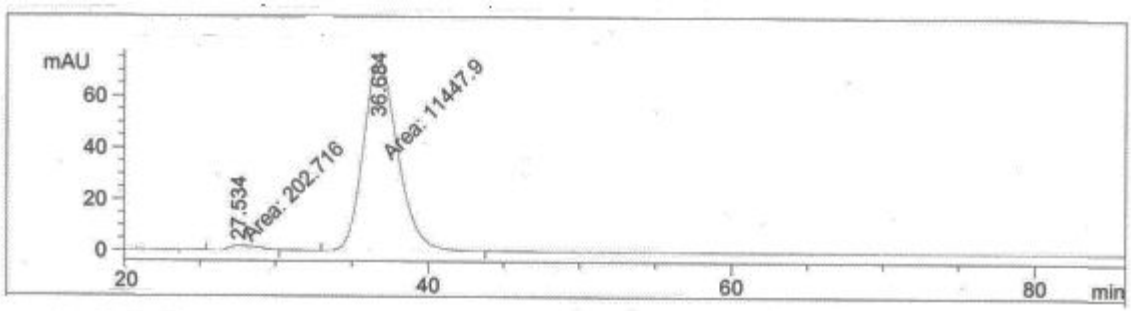
^{1}H NMR (400 MHz) spectrum of **12-33a** in CD_3OD.



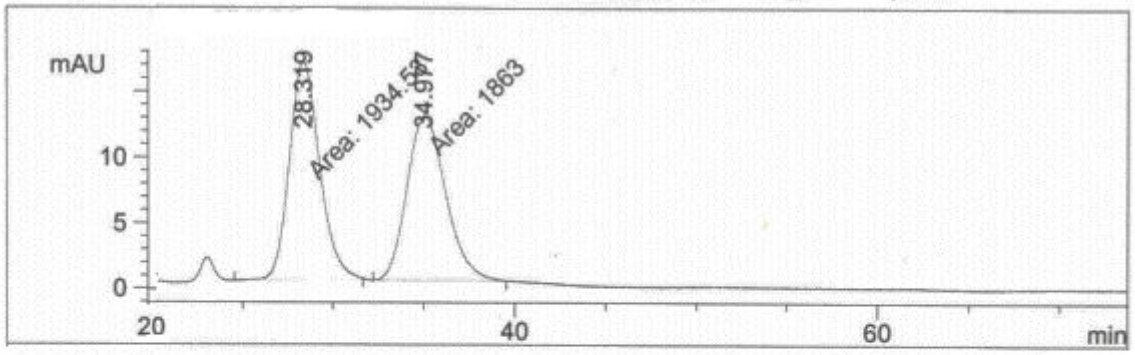
^{13}C NMR (100 MHz) spectrum of **12-33a** in CD_3OD.



12-33b

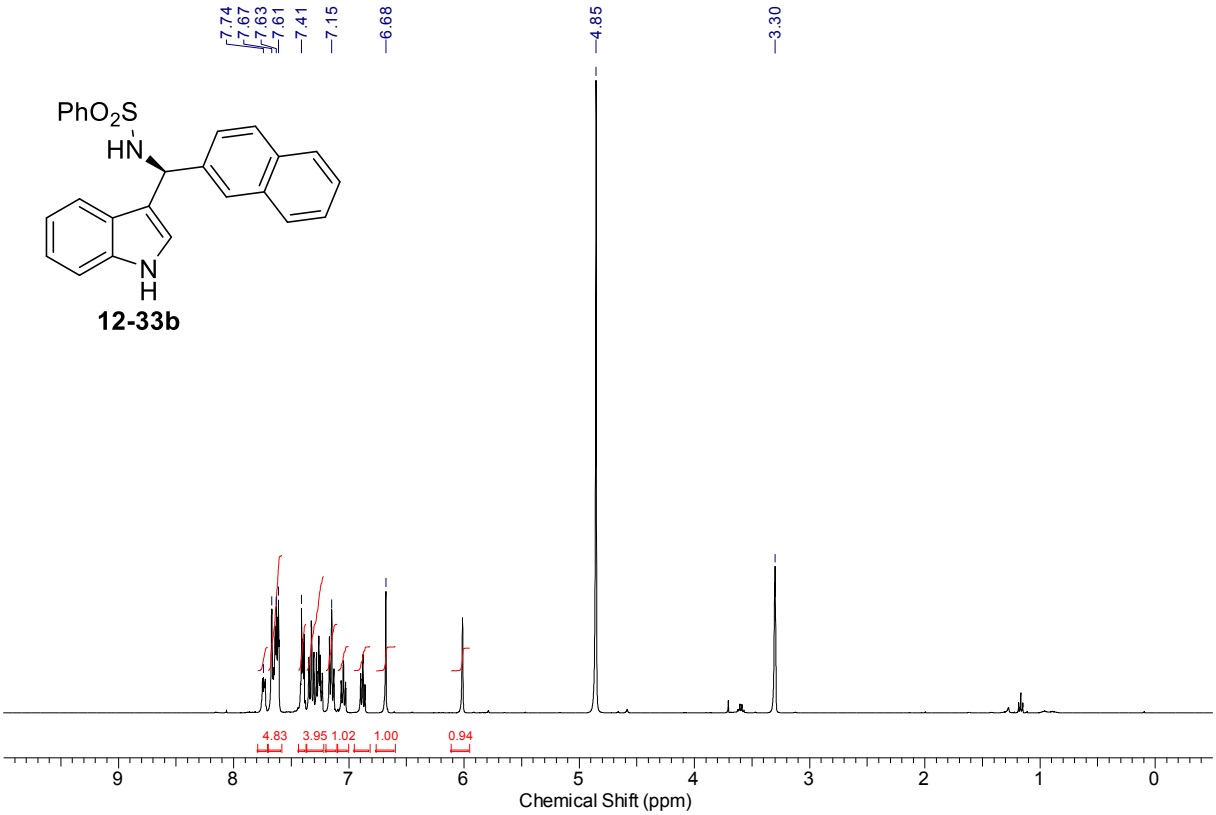


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	27.534	MM	1.9950	202.71628	1.69350	1.7400
2	36.684	MM	2.5981	1.14479e4	73 43687	98.2600
Totals :				1.16506e4	75.13037	

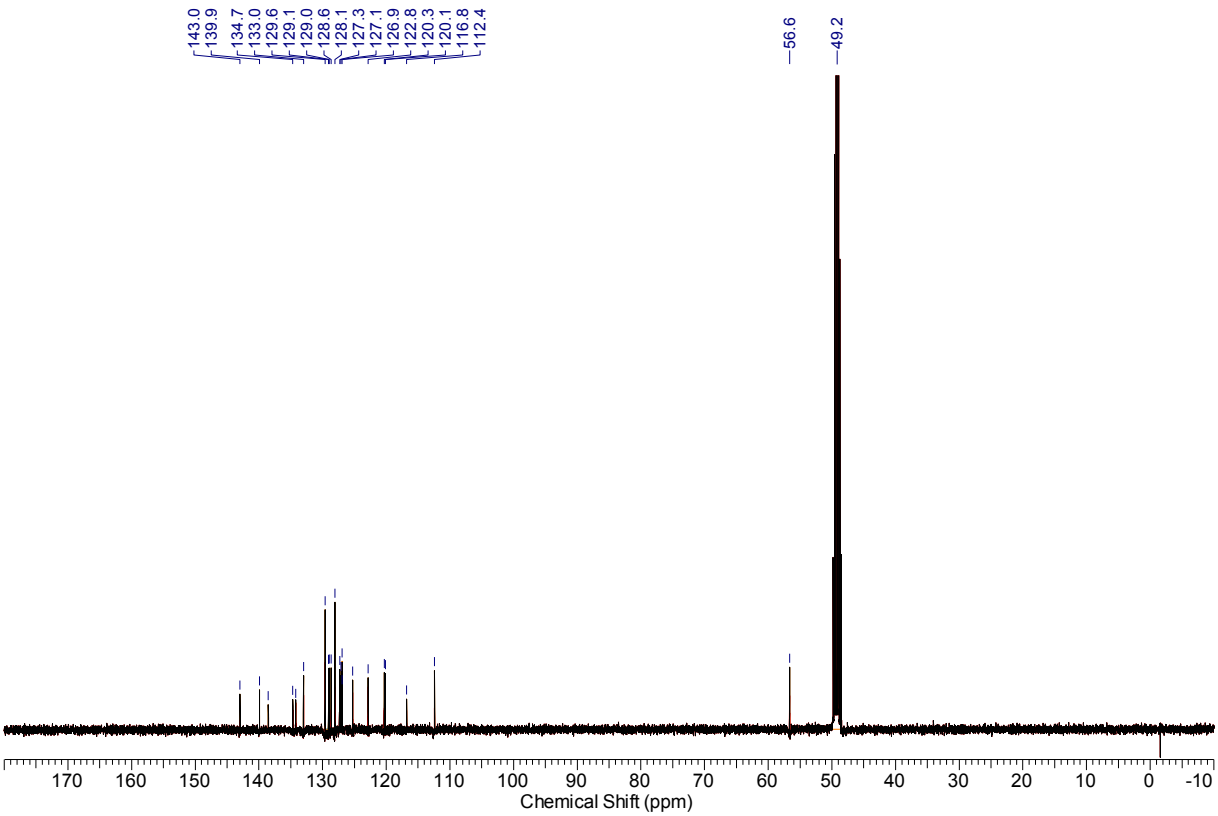


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.670	PB	0.1660	55.64733	4.84686	1.4442
2	28.319	MM	1.9455	1934.52563	16.57290	50.2060
3	34.977	MM	2.4688	1863.00476	12.57718	48.3498
Totals :				3853.17772	33.99693	

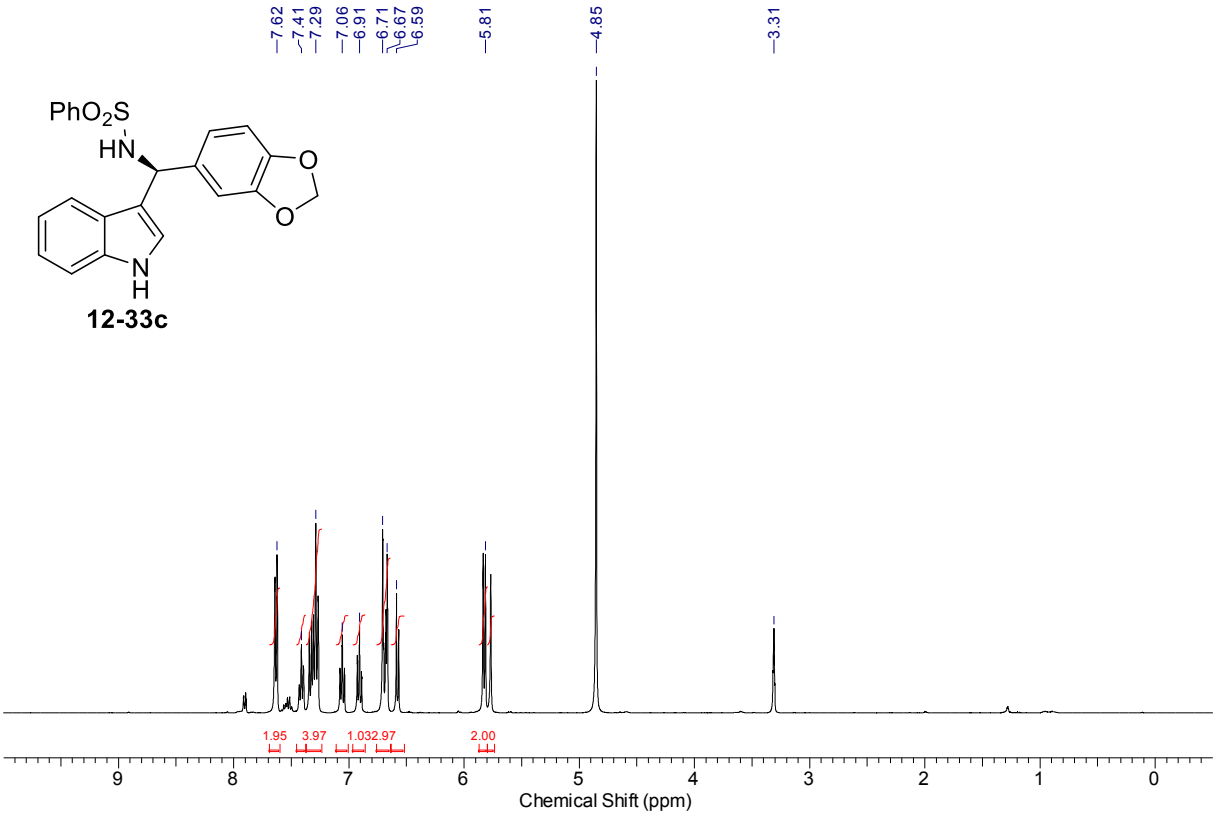
Chromatograms of compounds (−) & (±) **12-33b**.



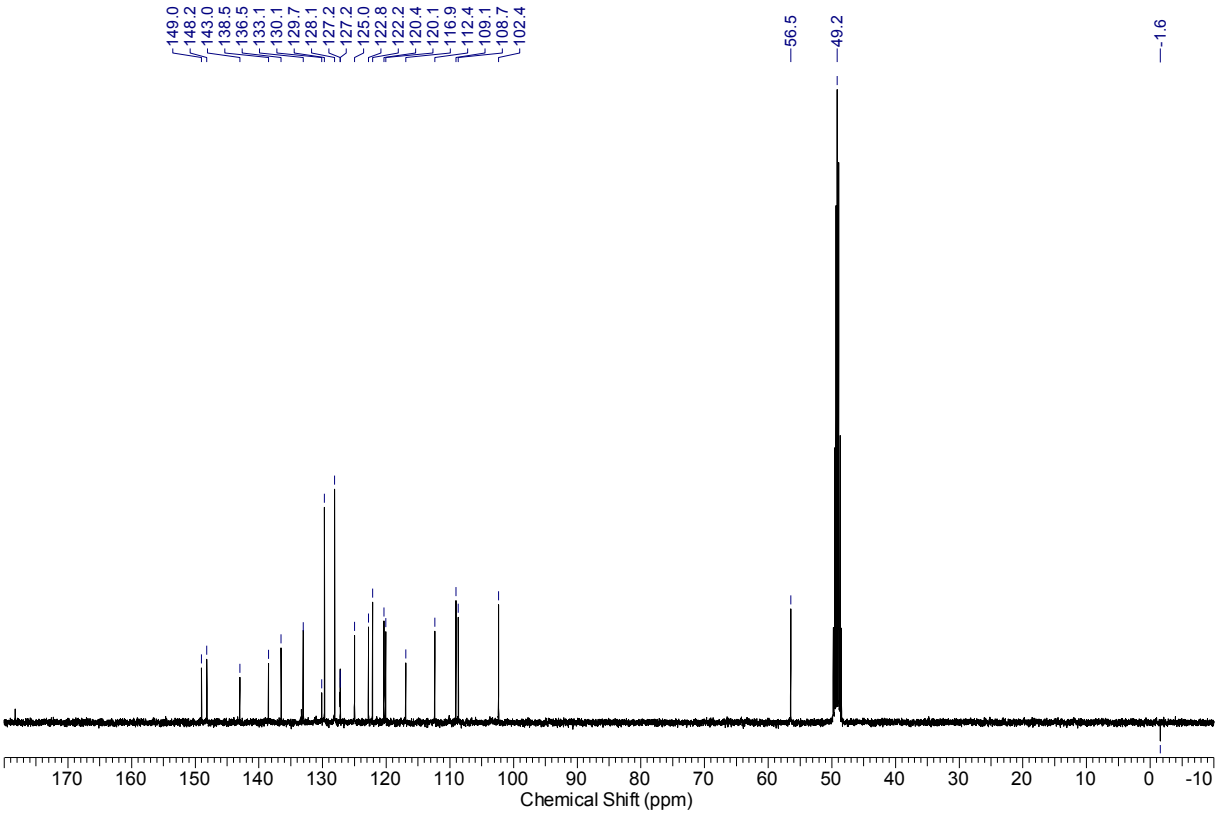
^{1}H NMR (400 MHz) spectrum of **12-33b** in CD_3OD.



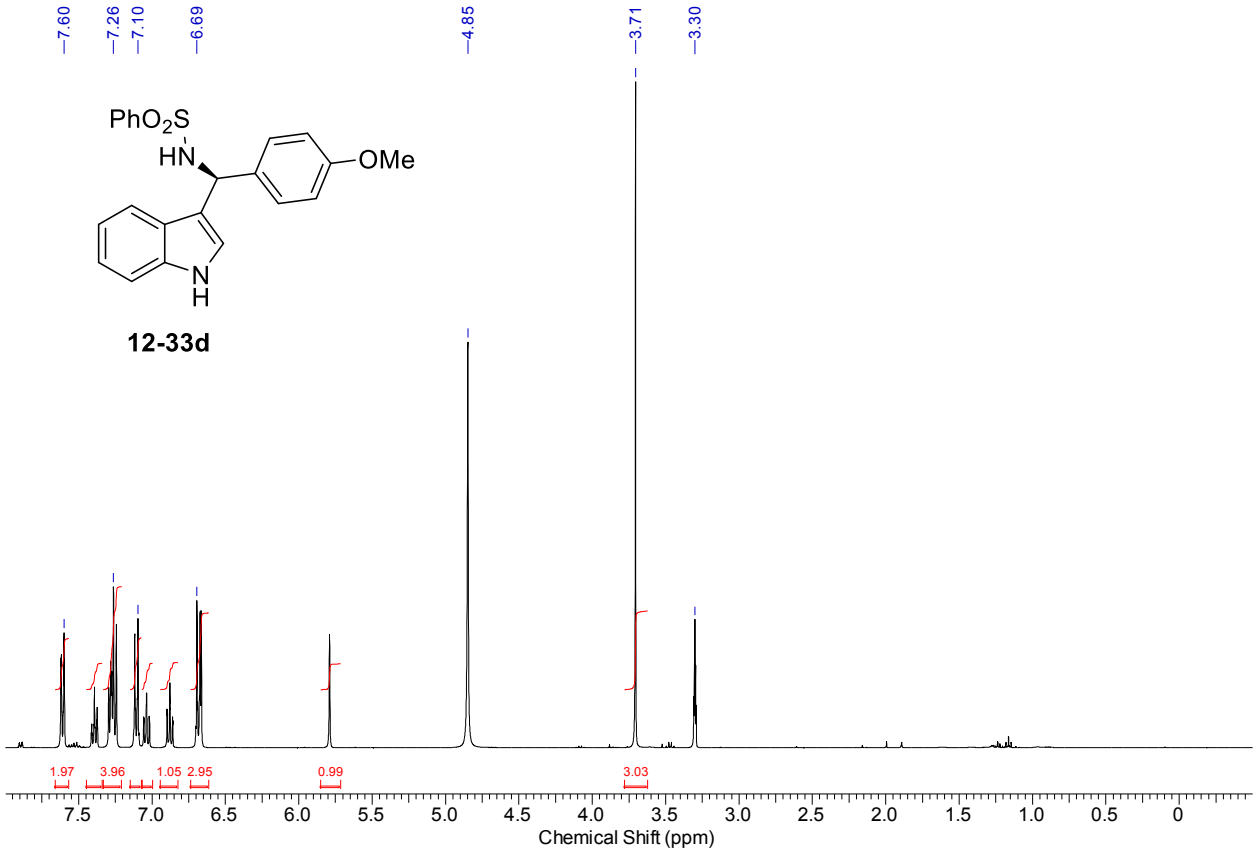
^{13}C NMR (100 MHz) spectrum of **12-33b** in CD_3OD.



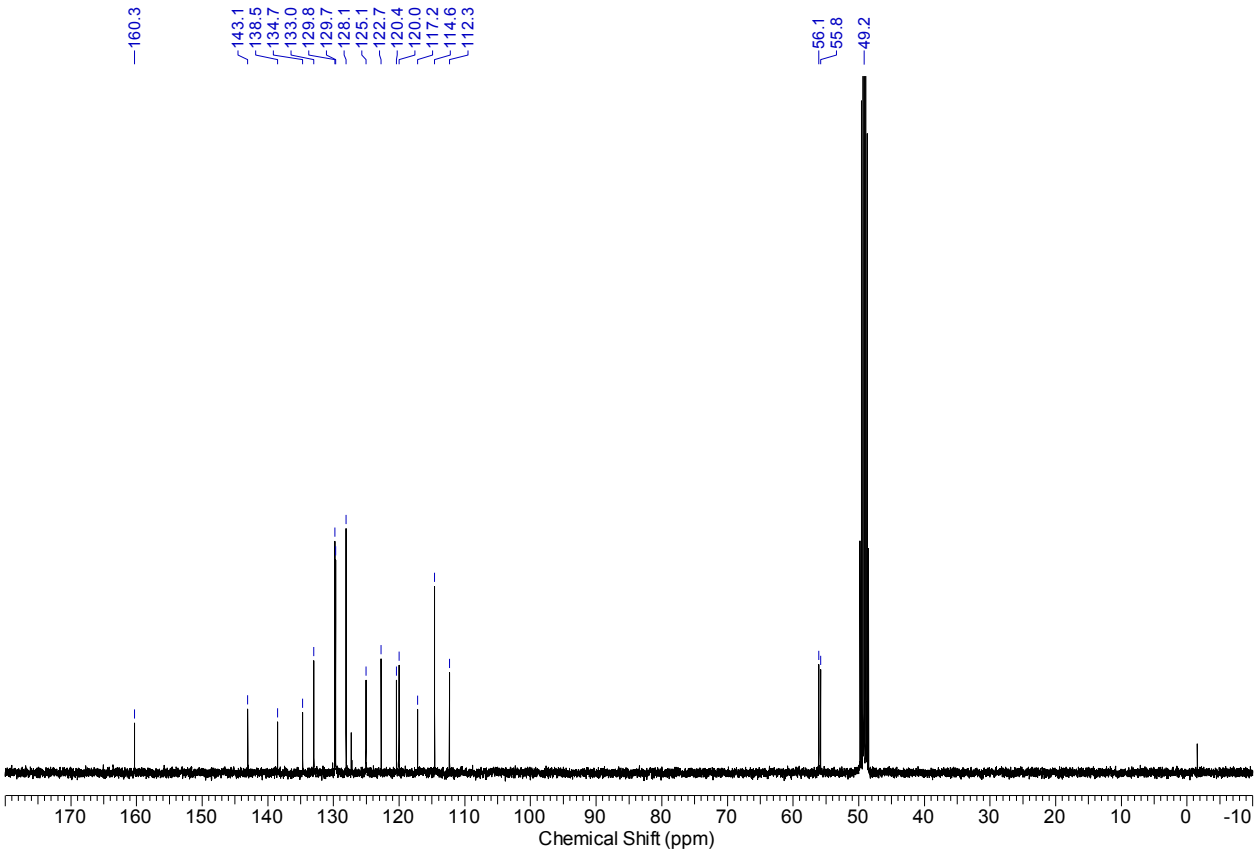
^{1}H NMR (400 MHz) spectrum of **12-33c** in CD_3OD.



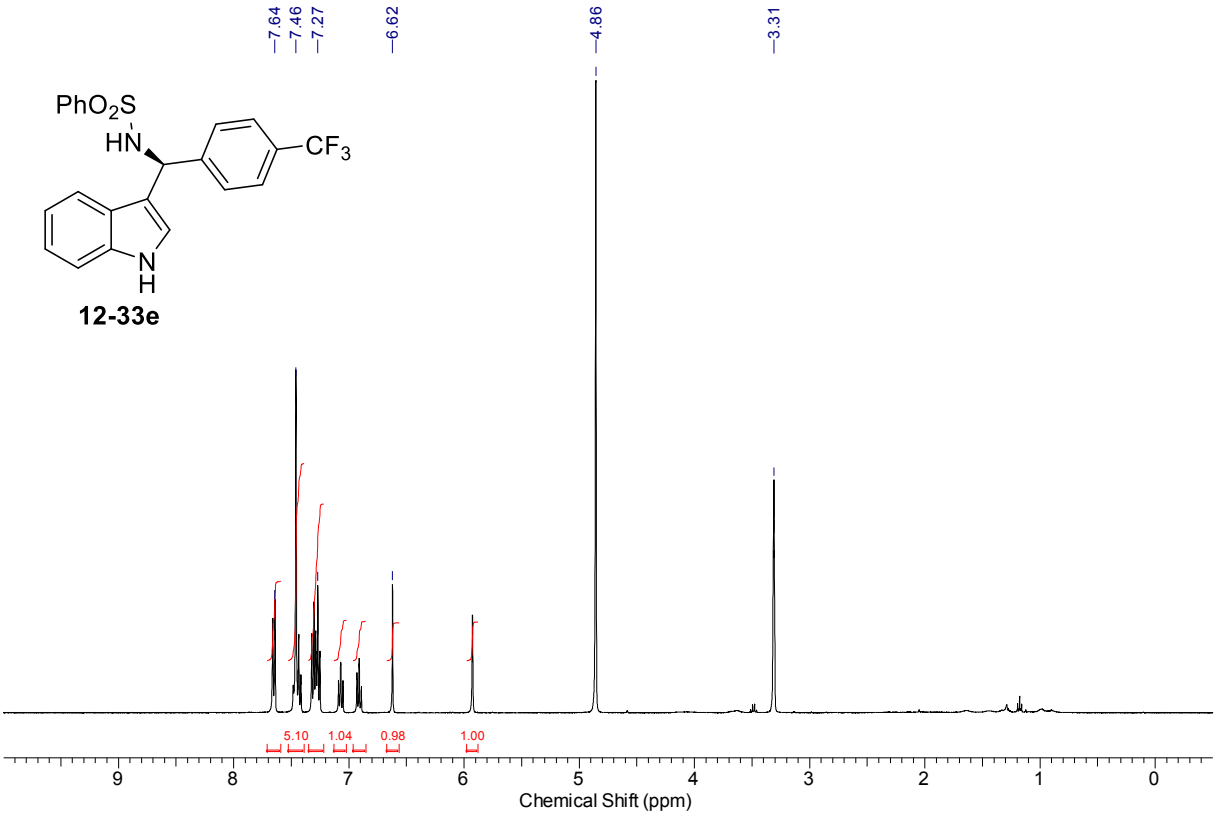
^{13}C NMR (100 MHz) spectrum of **12-33c** in CD_3OD.



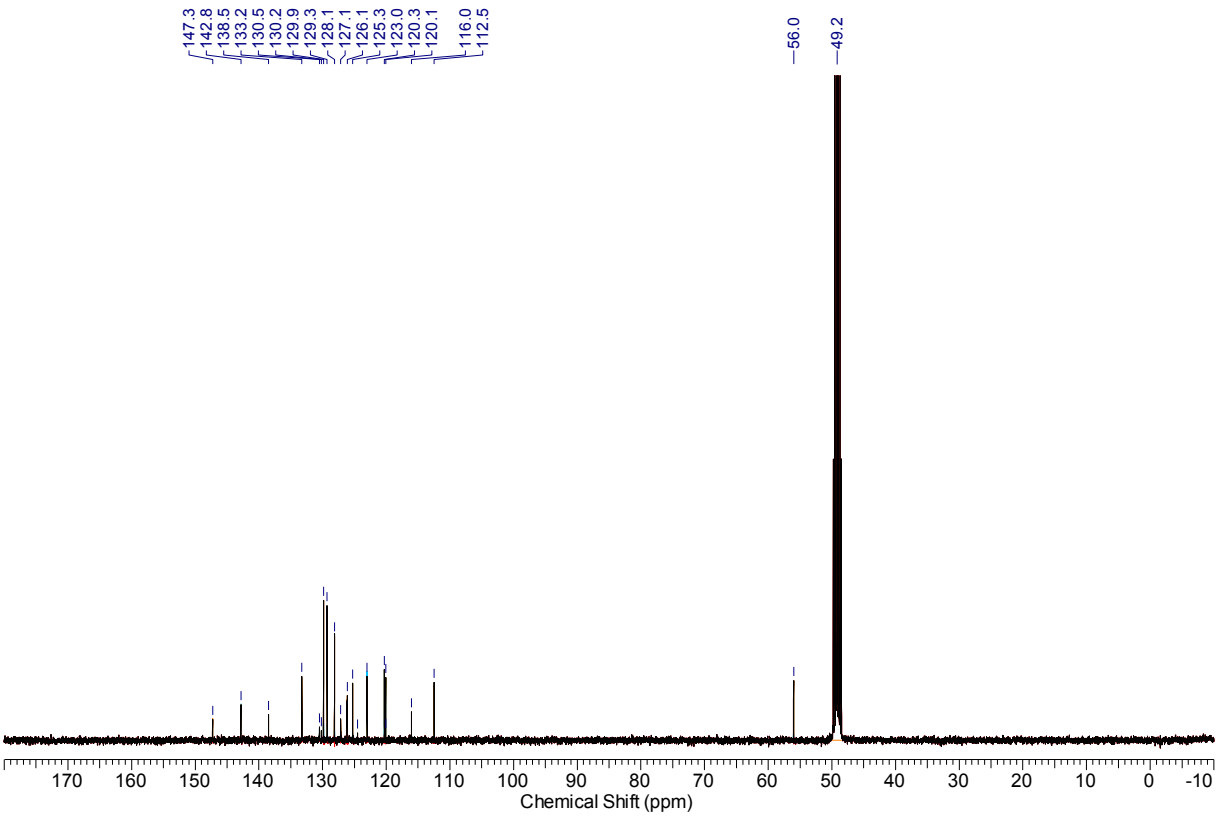
^{1}H NMR (400 MHz) spectrum of **12-33d** in CD_3OD.



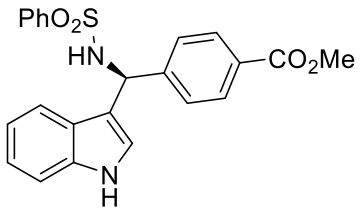
^{13}C NMR (100 MHz) spectrum of **12-33d** in CD_3OD.



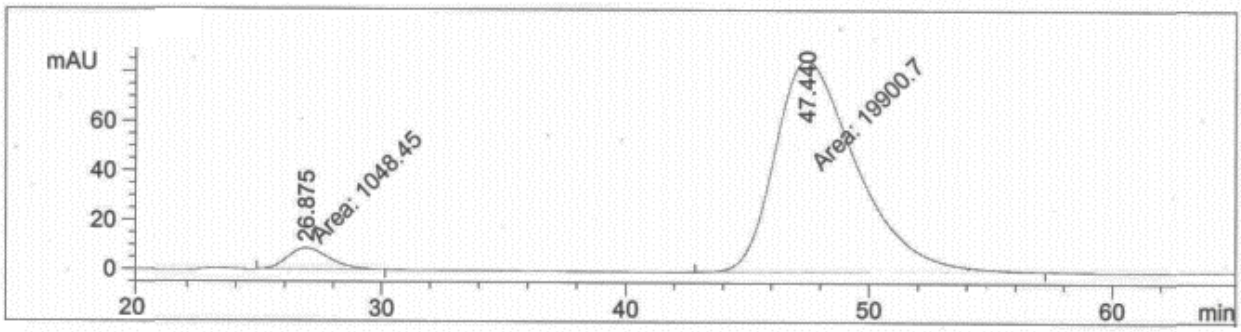
^{1}H NMR (400 MHz) spectrum of **12-33e** in CD_3OD.



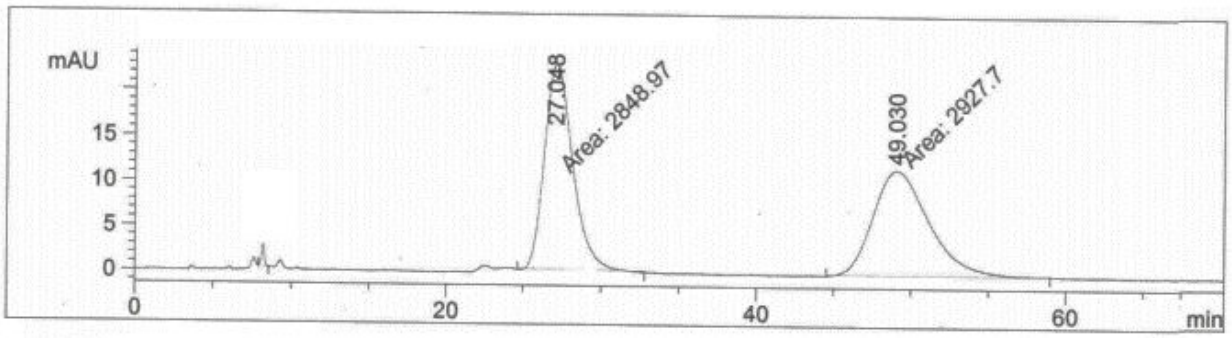
^{13}C NMR (100 MHz) spectrum of **12-33e** in CD_3OD.



12-33f

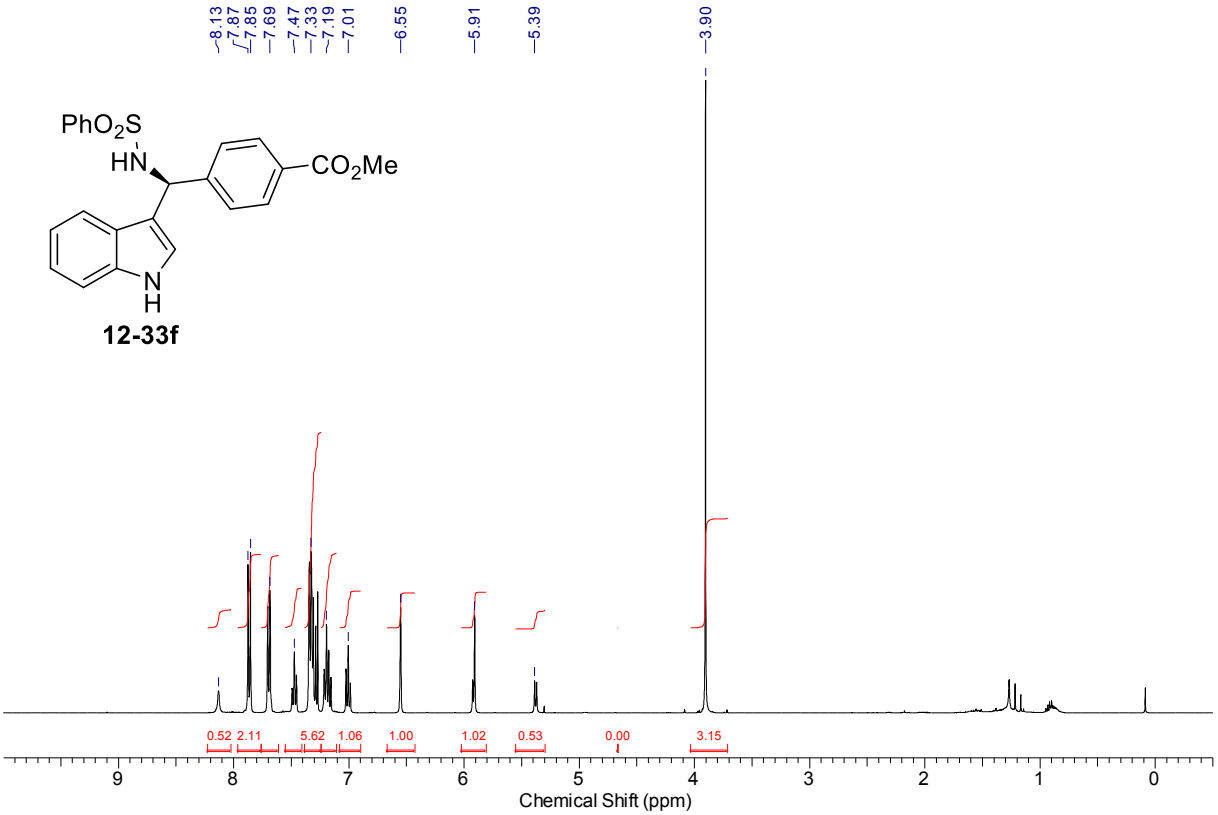


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.875	MM	2.0045	1048.44946	8.71758	5.0047
2	47.440	MM	3.8801	1.99007e4	85.48148	94.9953
Totals :				2.09491e4	94.19906	

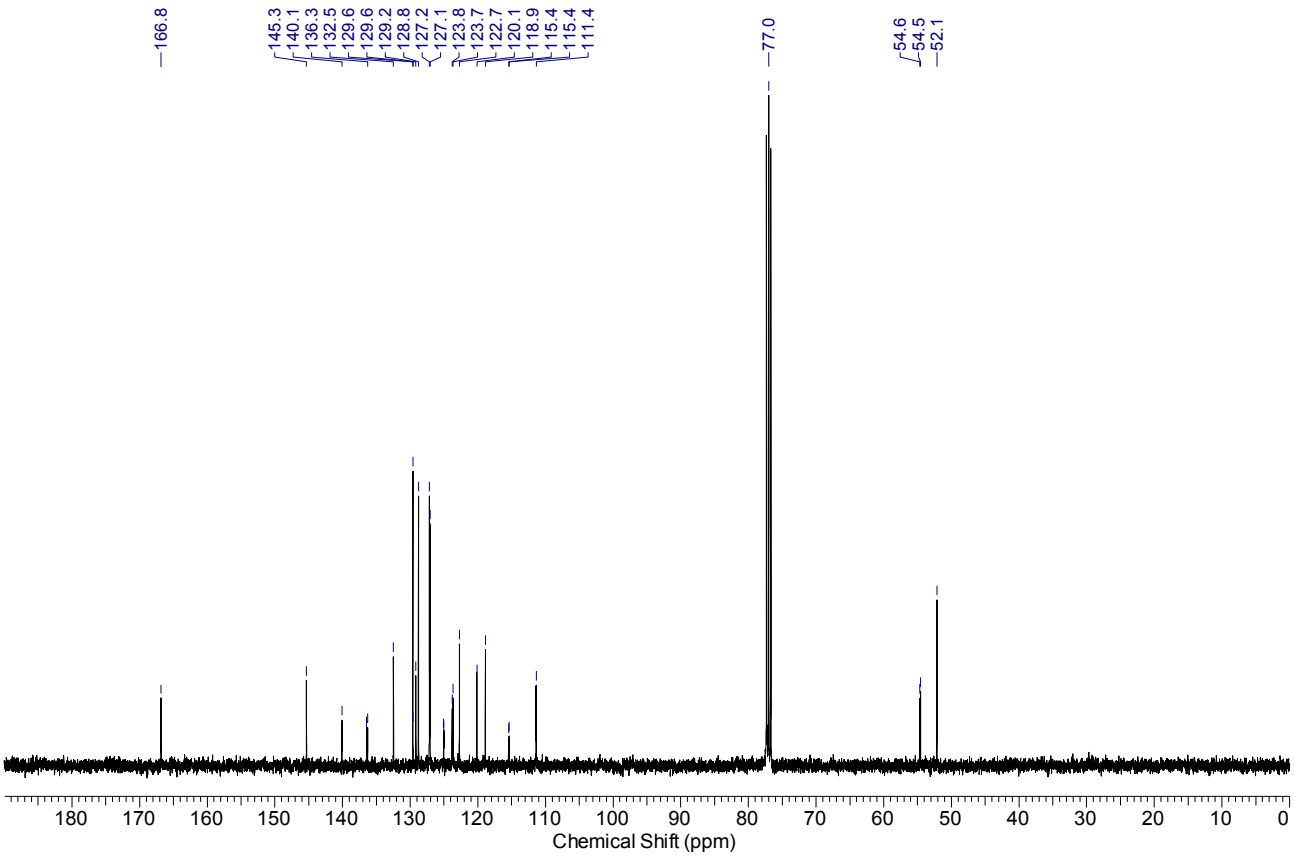


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	27.048	MM	2.0870	2848.96704	22.75183	49.0063
2	49.030	MM	4.1757	2927.70337	11.68536	50.3607
Totals :				5813.46632	36.98431	

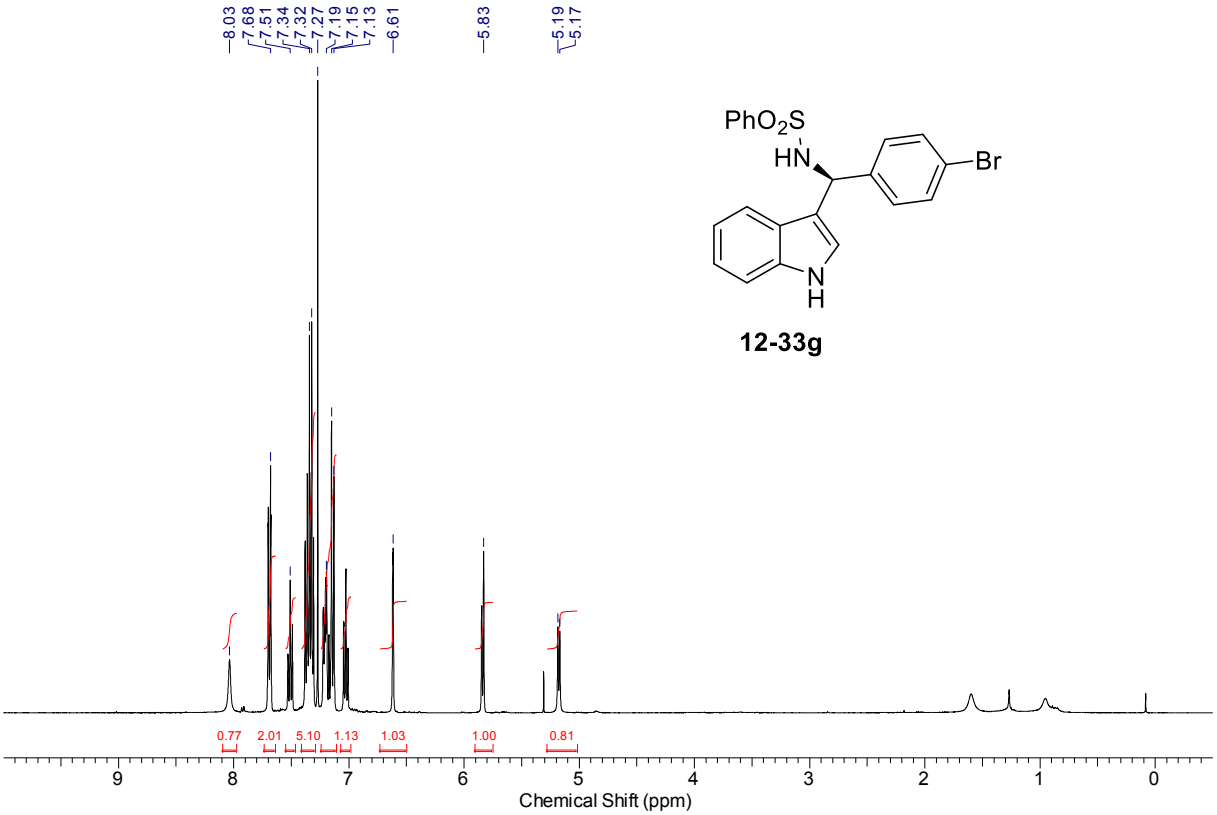
Chromatograms of compounds (−) & (±) **12-33f**.



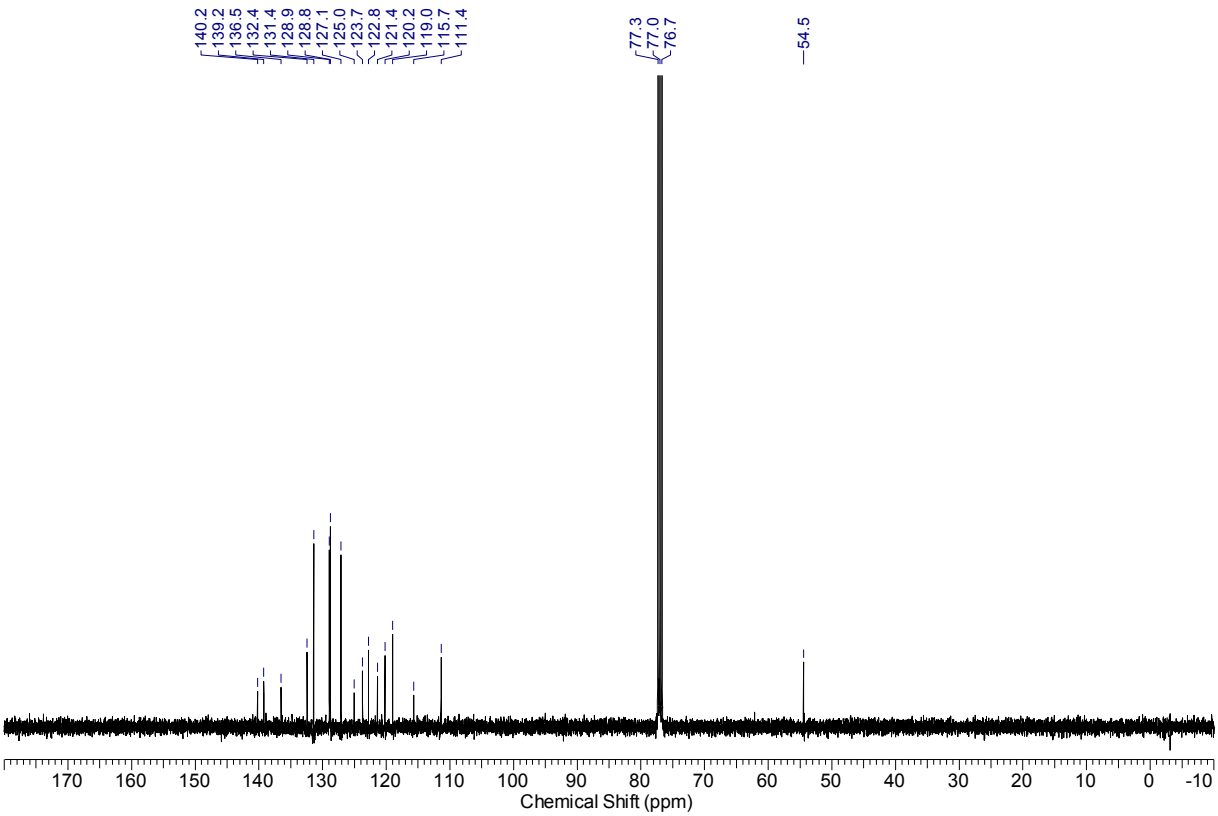
^{1}H NMR (400 MHz) spectrum of **12-33f** in $CDCl_3$.



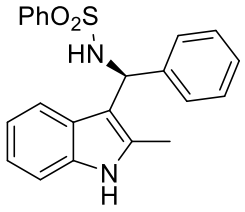
^{13}C NMR (100 MHz) spectrum of **12-33f** in $CDCl_3$.



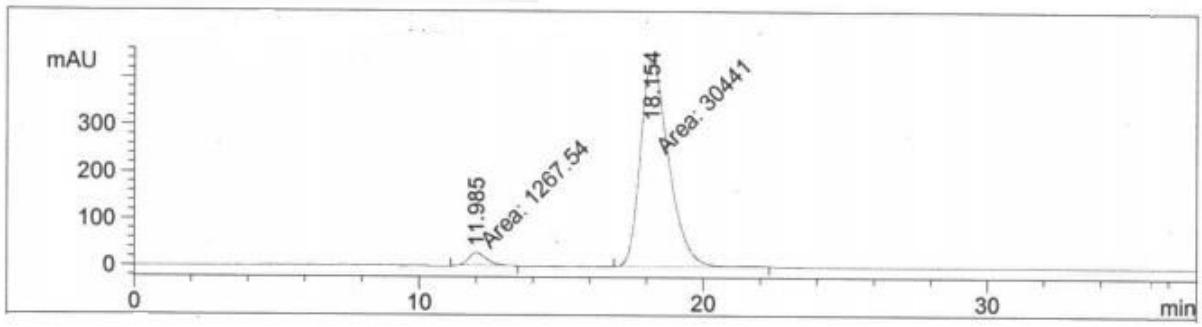
^{1}H NMR (400 MHz) spectrum of **12-33g** in $CDCl_3$.



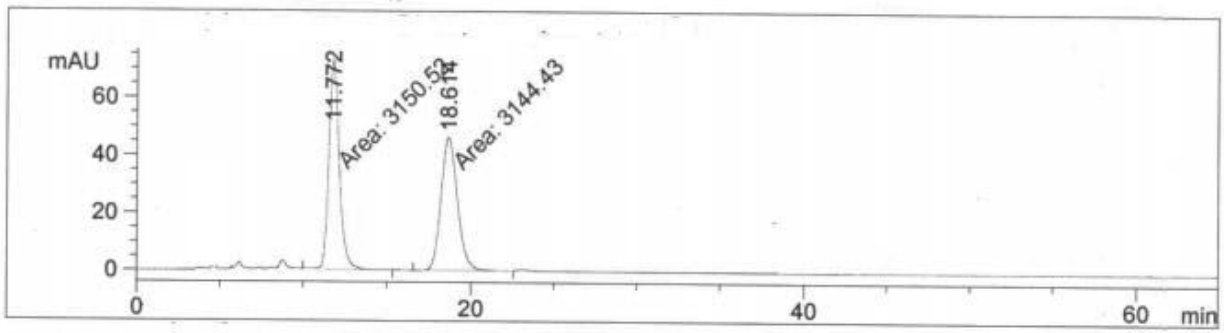
^{13}C NMR (100 MHz) spectrum of **12-33g** in $CDCl_3$.



14-16a

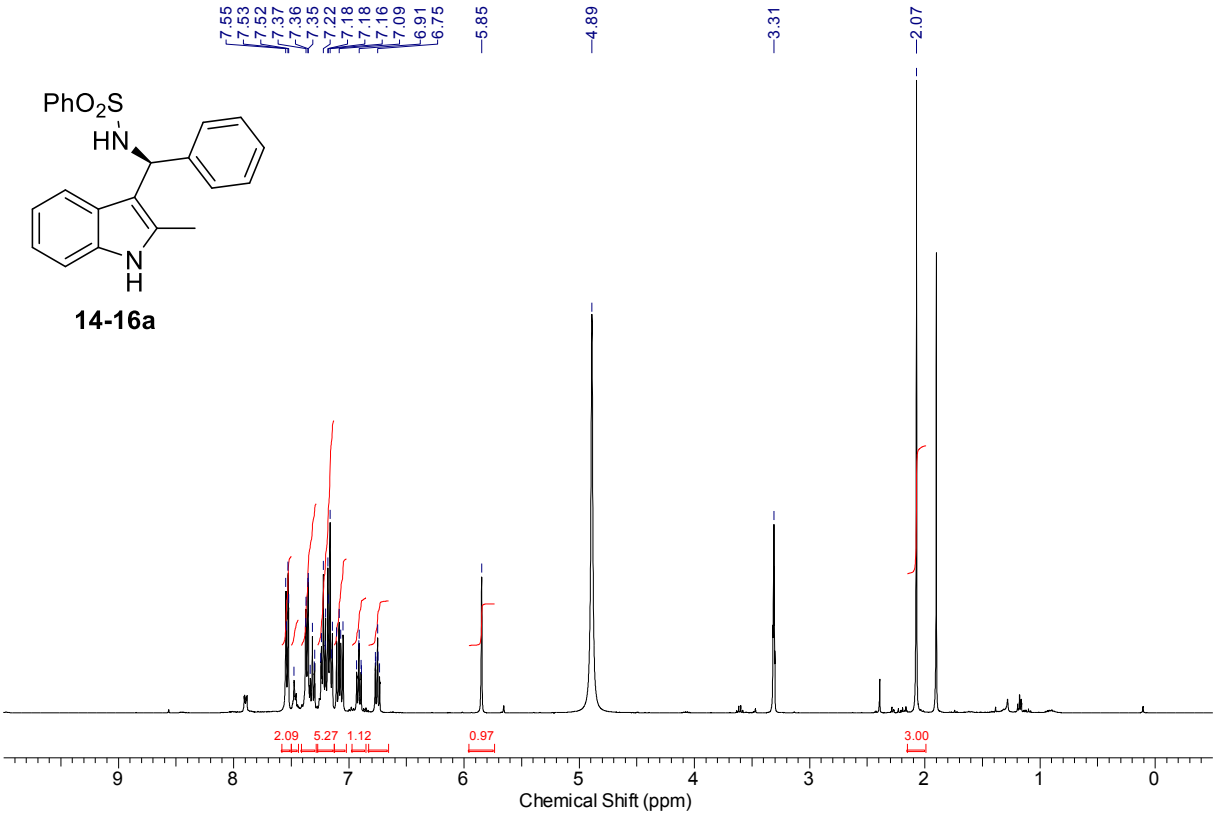


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.985	MM	0.7641	1267.54248	27.64603	3.9975
2	18.154	MM	1.1581	3.04410e4	438.10474	96.0025
Totals :				3.17085e4	465.75077	

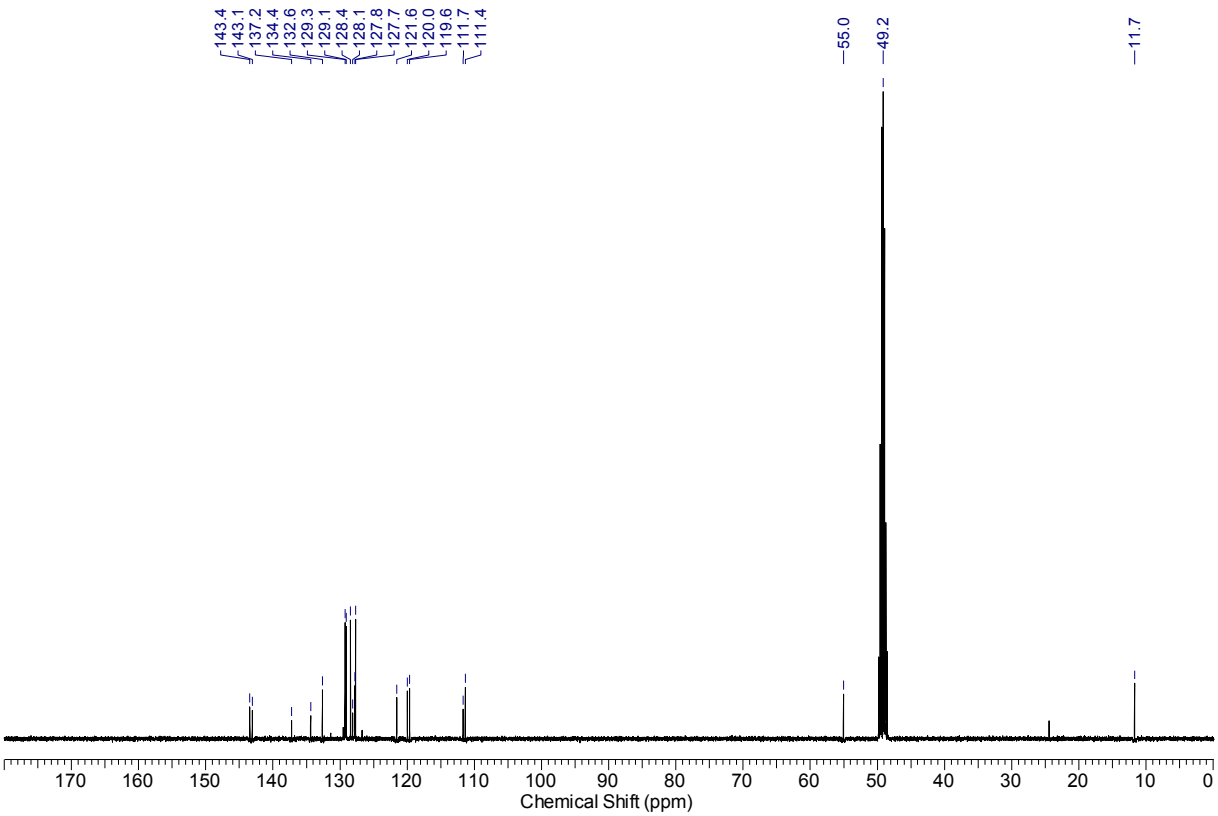


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.772	MM	0.7258	3150.52246	72.34541	50.0484
2	18.614	MM	1.1367	3144.43335	46.10390	49.9516
Totals :				6294.95581	118.44930	

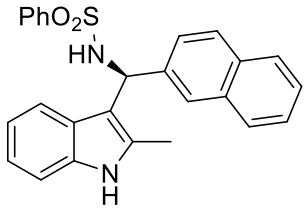
Chromatograms of compounds (−) & (±) **14-10a**.



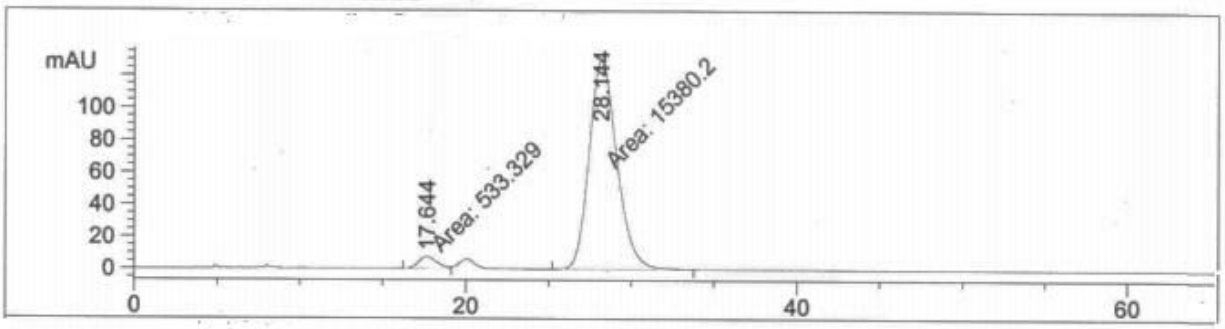
^{1}H NMR (400 MHz) spectrum of **14-16a** in CD_3OD.



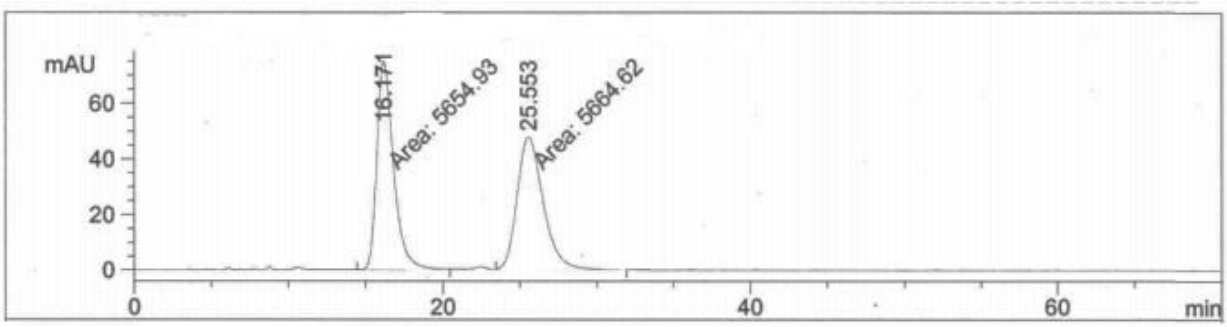
^{13}C NMR (100 MHz) spectrum of **14-16a** in CD_3OD.



14-16b

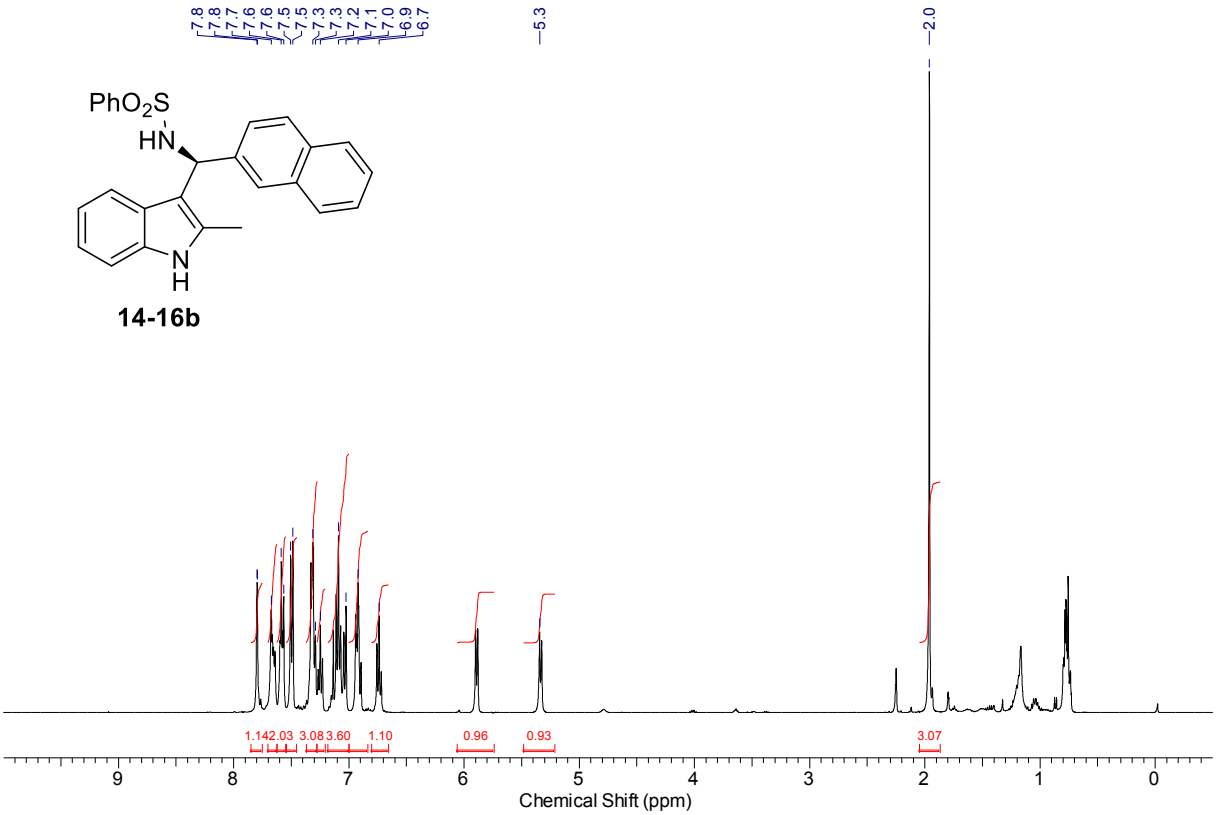


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.644	MM	1.2337	533.32910	7.20521	3.3514
2	28.144	MM	1.9743	1.53802e4	129.83688	96.6486
Totals :				1.59135e4	137.04210	

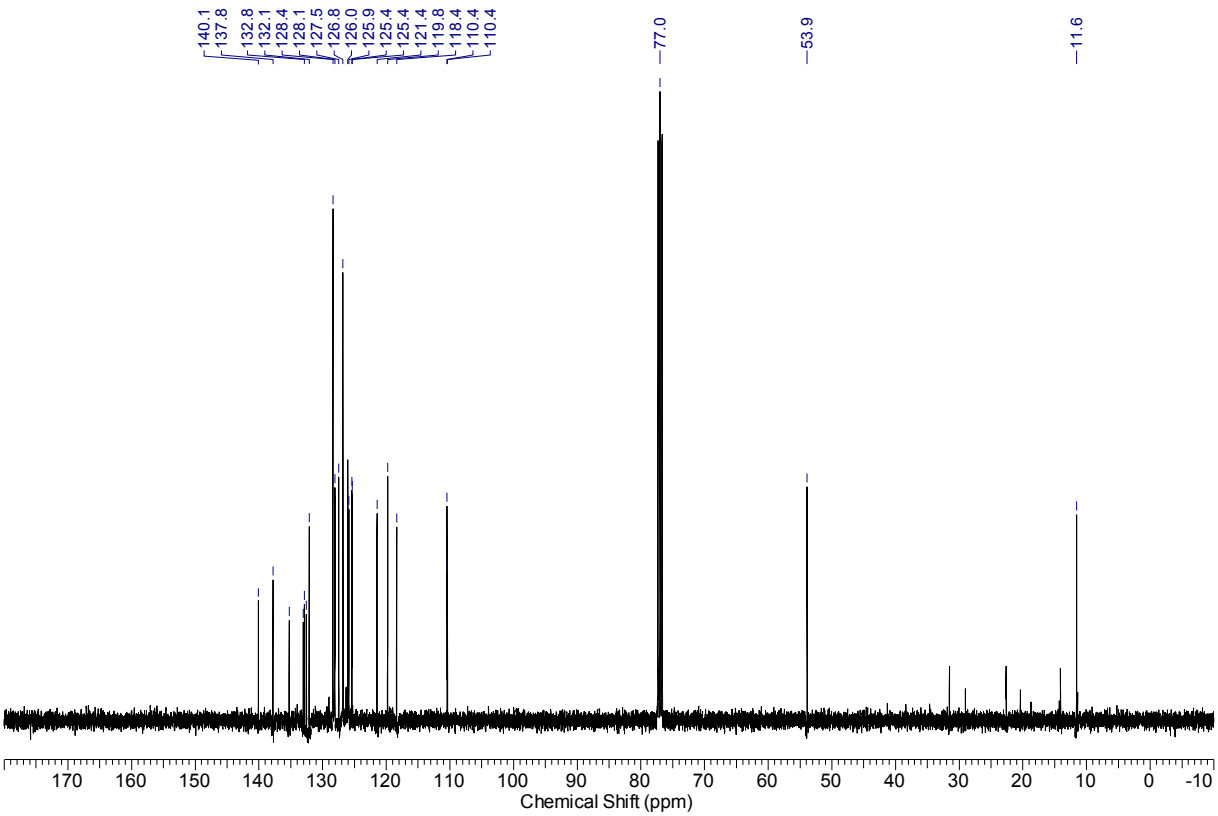


Peak #	RetTime [min]	Type	Width [mir]	Area mAU *s	Height [mAU]	Area %
1	16.171	MM	1.2571	5654.92578	74.97263	49.9572
2	25.553	MM	1.9737	5664.62061	47.83390	50.0428
Totals :				1.13195e4	122.80653	

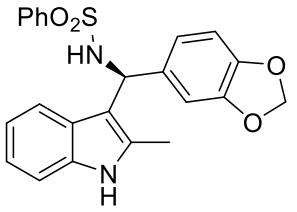
Chromatogrms of compounds (−) & (±) **14-16b**.



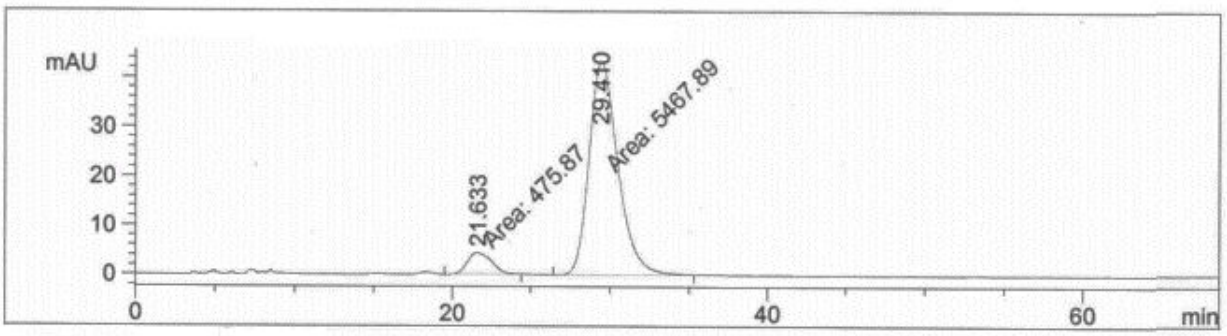
^{1}H NMR (400 MHz) spectrum of **14-16b** in $CDCl_3$.



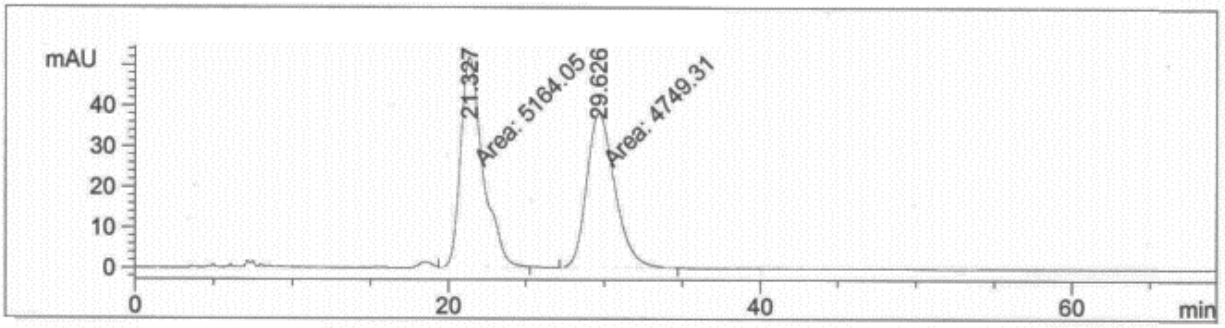
^{13}C NMR (100 MHz) spectrum of **14-16b** in $CDCl_3$.



14-16c

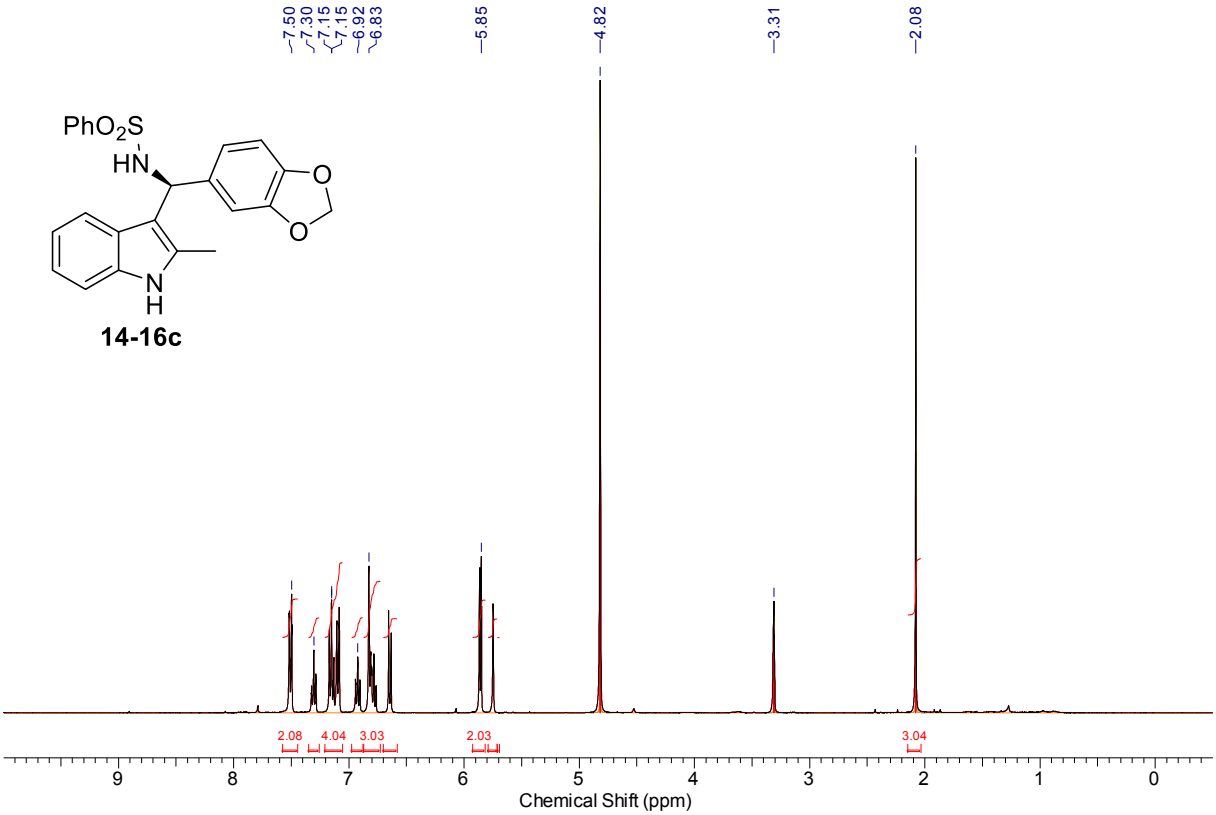


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	21.633	MM	1.7947	475.86990	4.41914	8.0062
2	29.410	MM	2.1106	5467.88672	43.17885	91.9938
Totals :				5943.75662	47.59800	

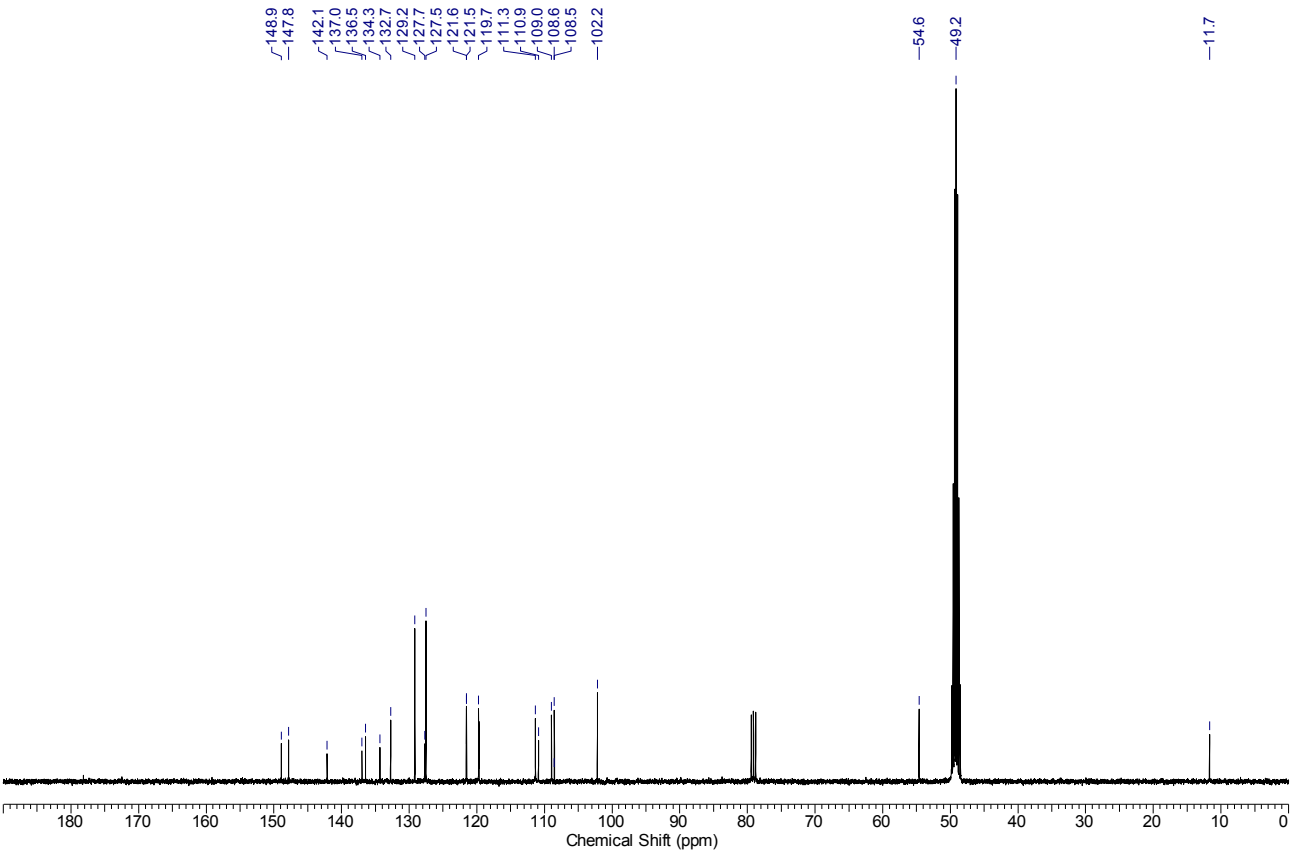


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	21.327	MM	1.6658	5164.04932	51.66678	52.0918
2	29.626	MM	2.0848	4749.30518	37.96683	47.9082
Totals :				9913.35449	89.63361	

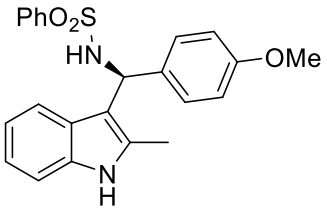
Chromatogrms of compounds (−) & (±) **14-16c**.



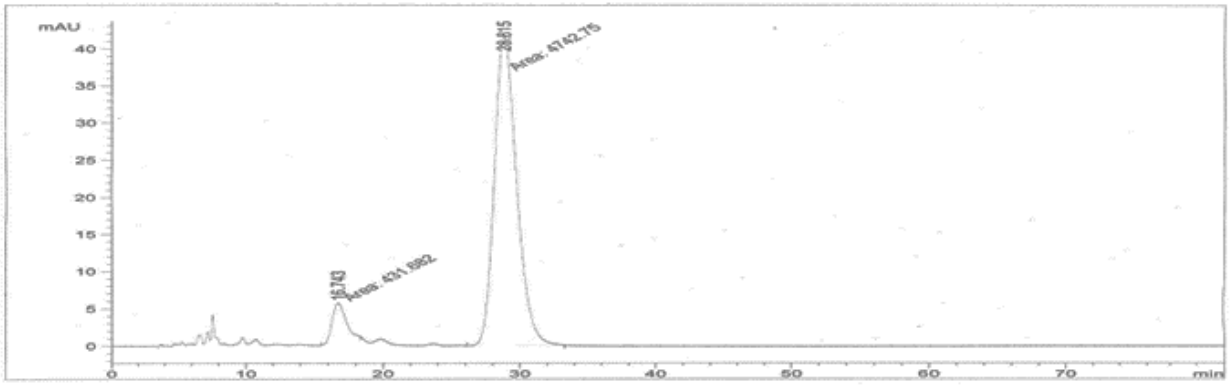
^{1}H NMR (400 MHz) spectrum of **14-16c** in CD_3OD.



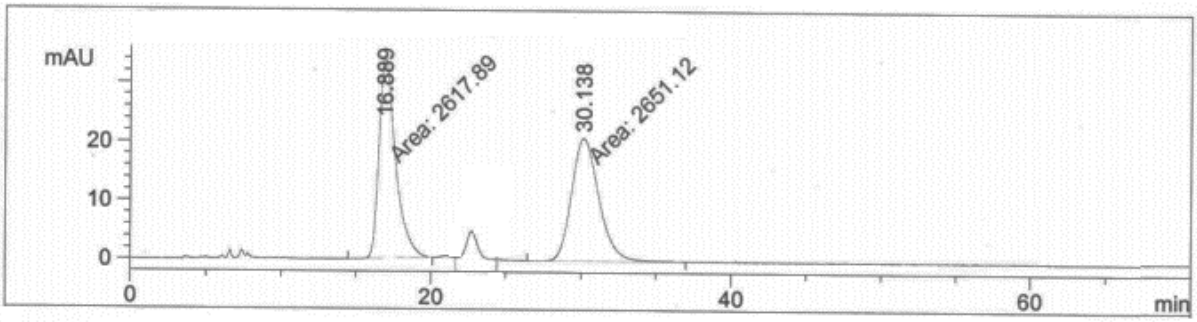
^{13}C NMR (100 MHz) spectrum of **14-16c** in CD_3OD.



14-16d

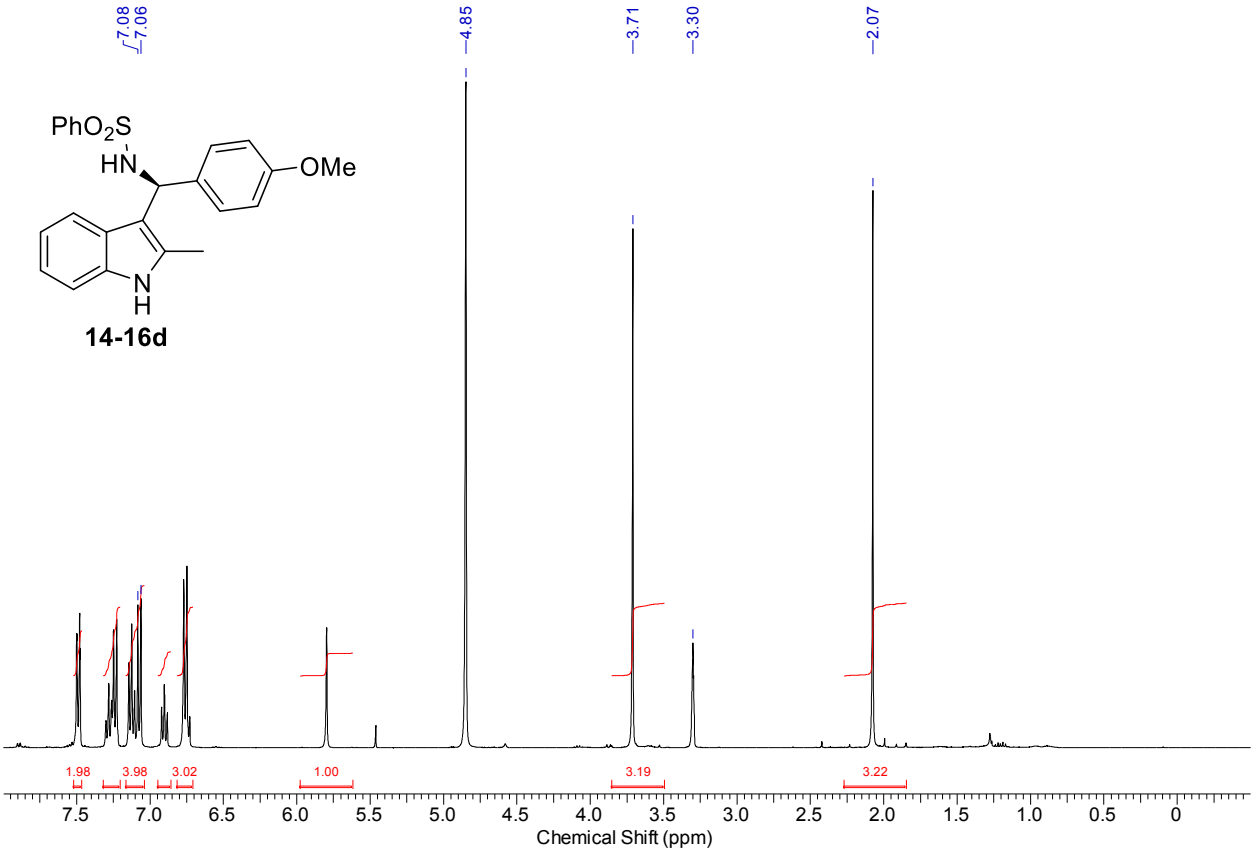


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.743	MM	1.2931	431.68228	5.56391	8.3426
2	28.815	MM	1.9022	4742.75293	41.55535	91.6574
Totals :				5174.43521	47.11926	

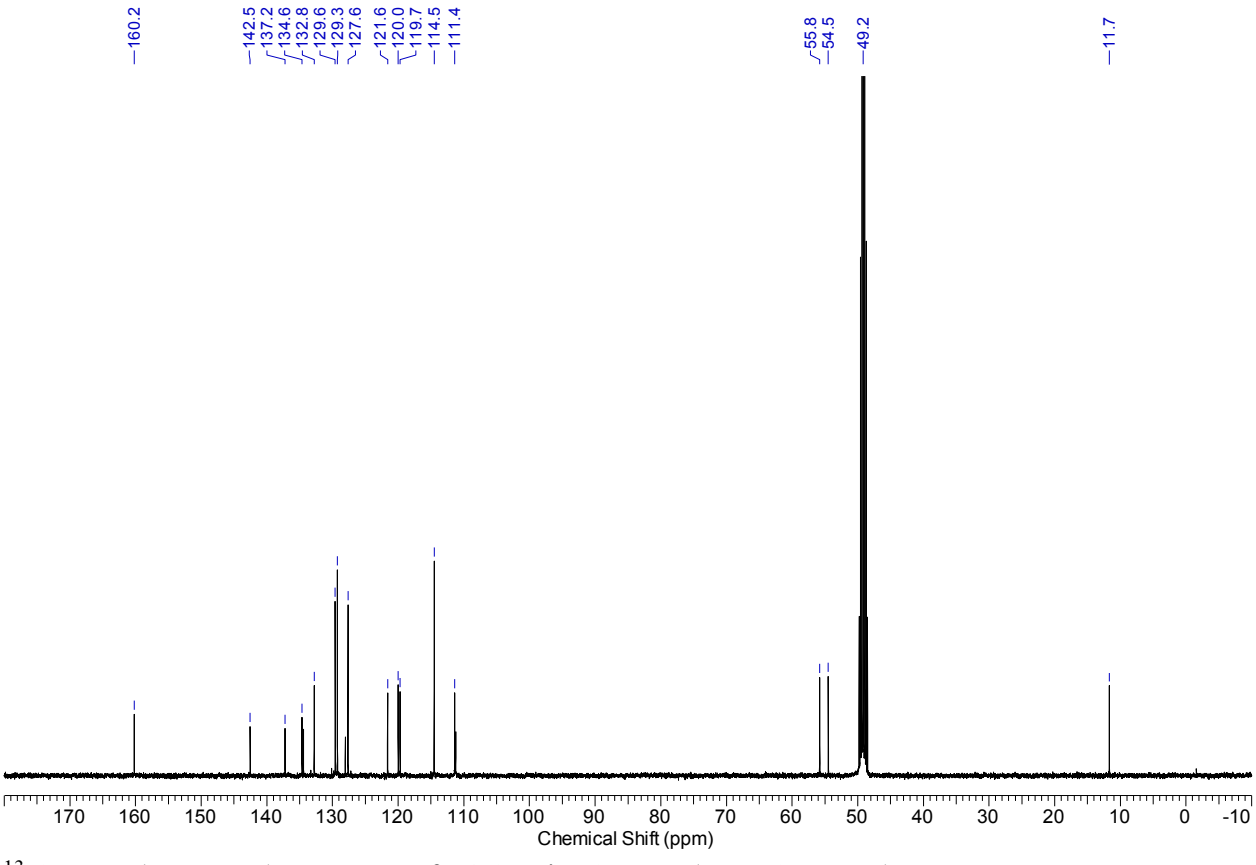


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.889	MM	1.2840	2617.88770	33.98180	49.6846
2	30.138	MM	2.1145	2651.12207	20.89652	50.3154
Totals :				5269.00977	54.87831	

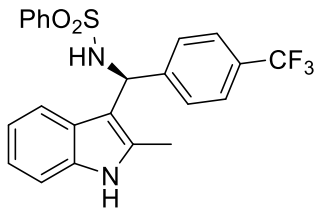
Chromatogrms of compounds (−) & (±) **14-16d**.



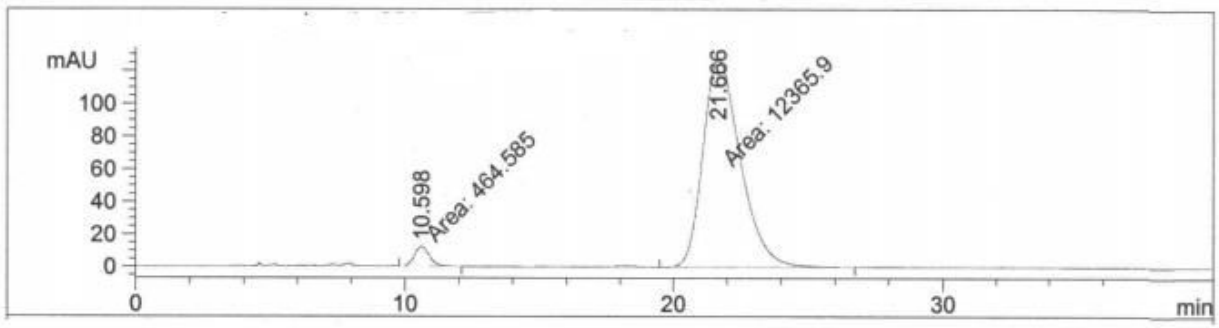
^{1}H NMR (400 MHz) spectrum of **14-16d** in CD_3OD (00 – 10.0 ppm).



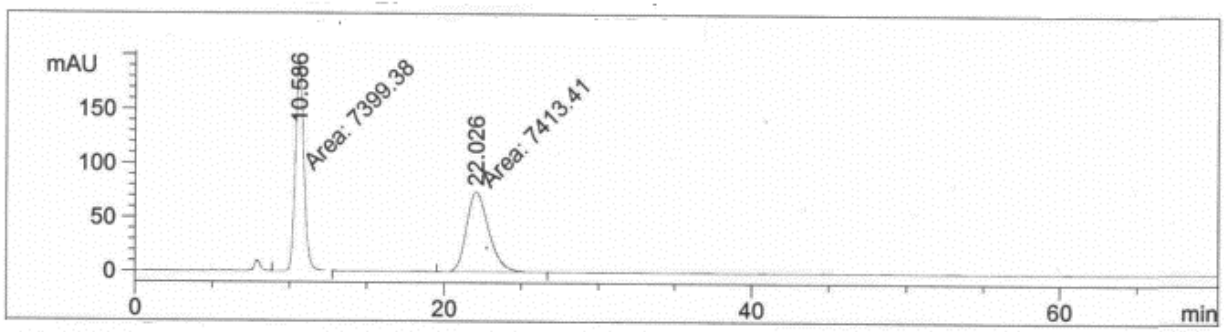
^{13}C NMR (100 MHz) spectrum of **14-16d** in CD_3OD (0.0 – 190 ppm).



14-16e

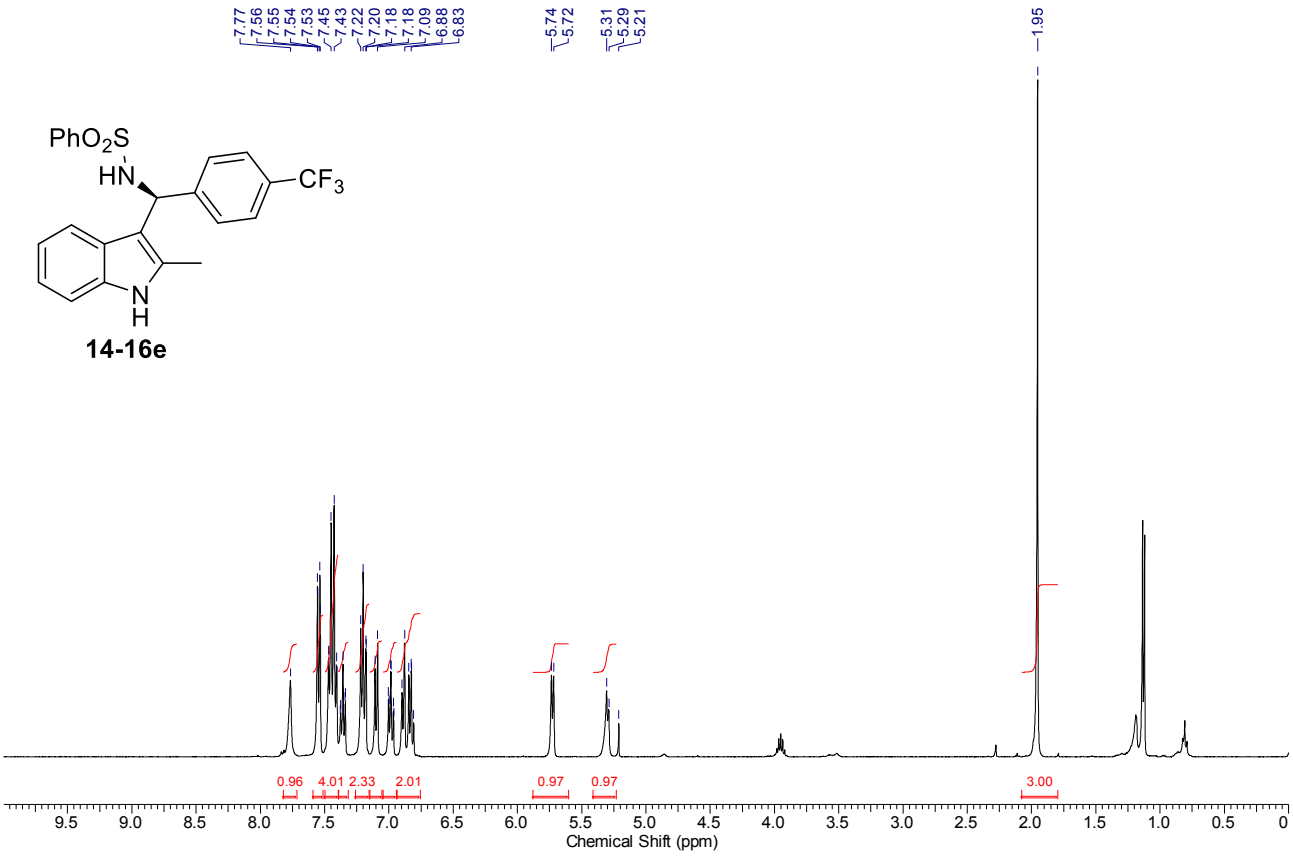


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.598	MM	0.6422	464.58514	12.05668	3.6209
2	21.666	MM	1.6135	1.23659e4	127.73050	96.3791
Totals :				1.28305e4	139.78718	

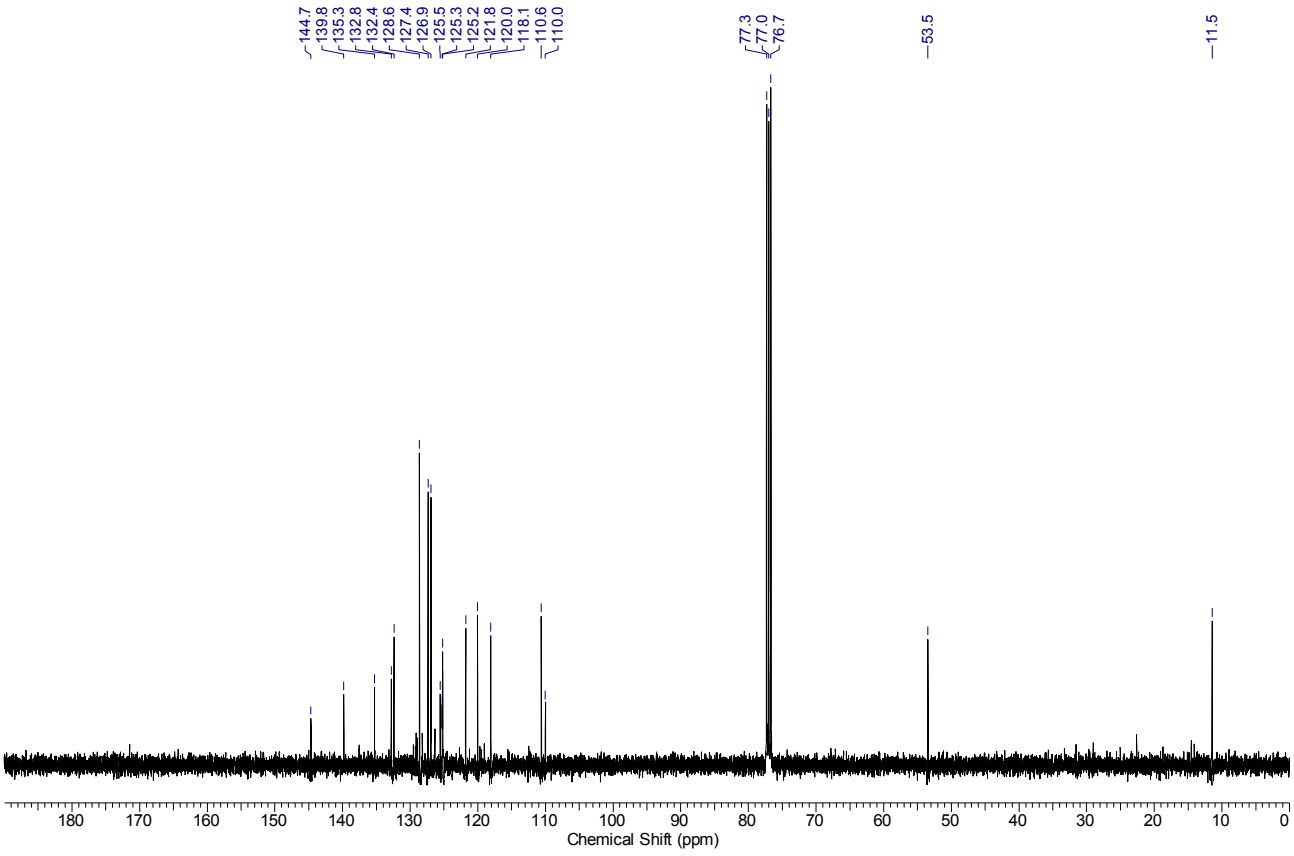


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.586	MM	0.6399	7399.37744	192.71036	49.9526
2	22.026	MM	1.6651	7413.40820	74.20424	50.0474
Totals :				1.48128e4	266.91460	

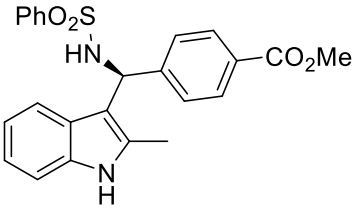
Chromatogrms of compounds (−) & (±) **14-16e**.



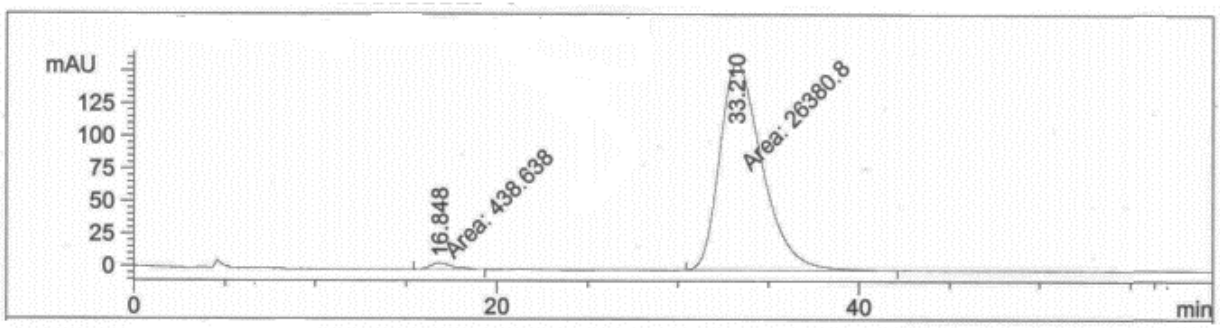
^{1}H NMR (400 MHz) spectrum of **14-16e** in $CDCl_3$.



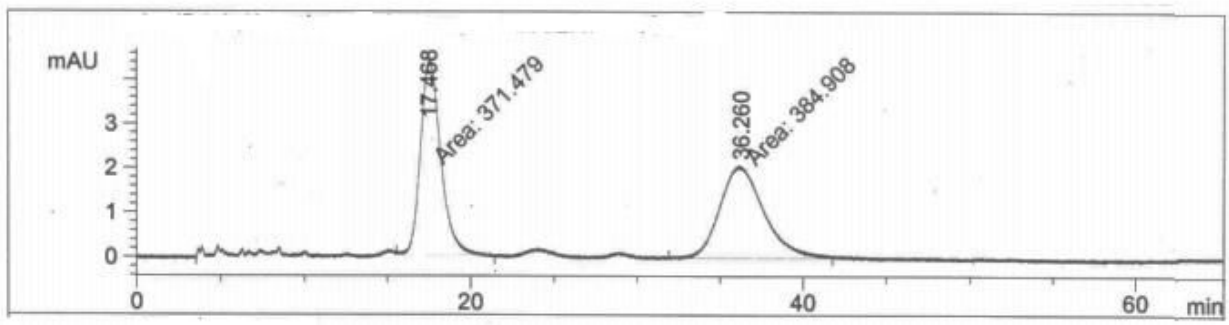
^{13}C NMR (100 MHz) spectrum of **14-16e** in $CDCl_3$.



14-16f

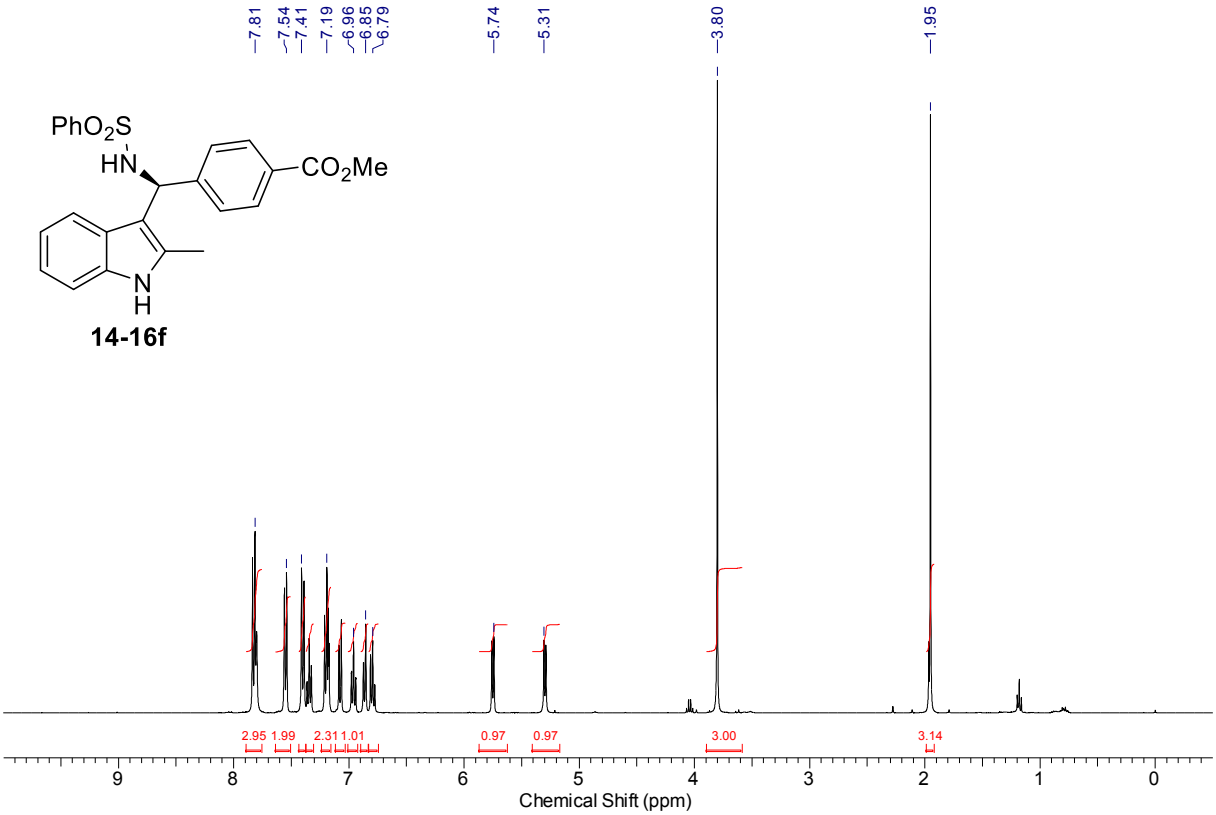


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.848	MM	1.4717	438.63815	4.96752	1.6355
2	33.210	MM	2.7594	2.63808e4	159.33727	98.3645
Totals :				2.68194e4	164.30478	

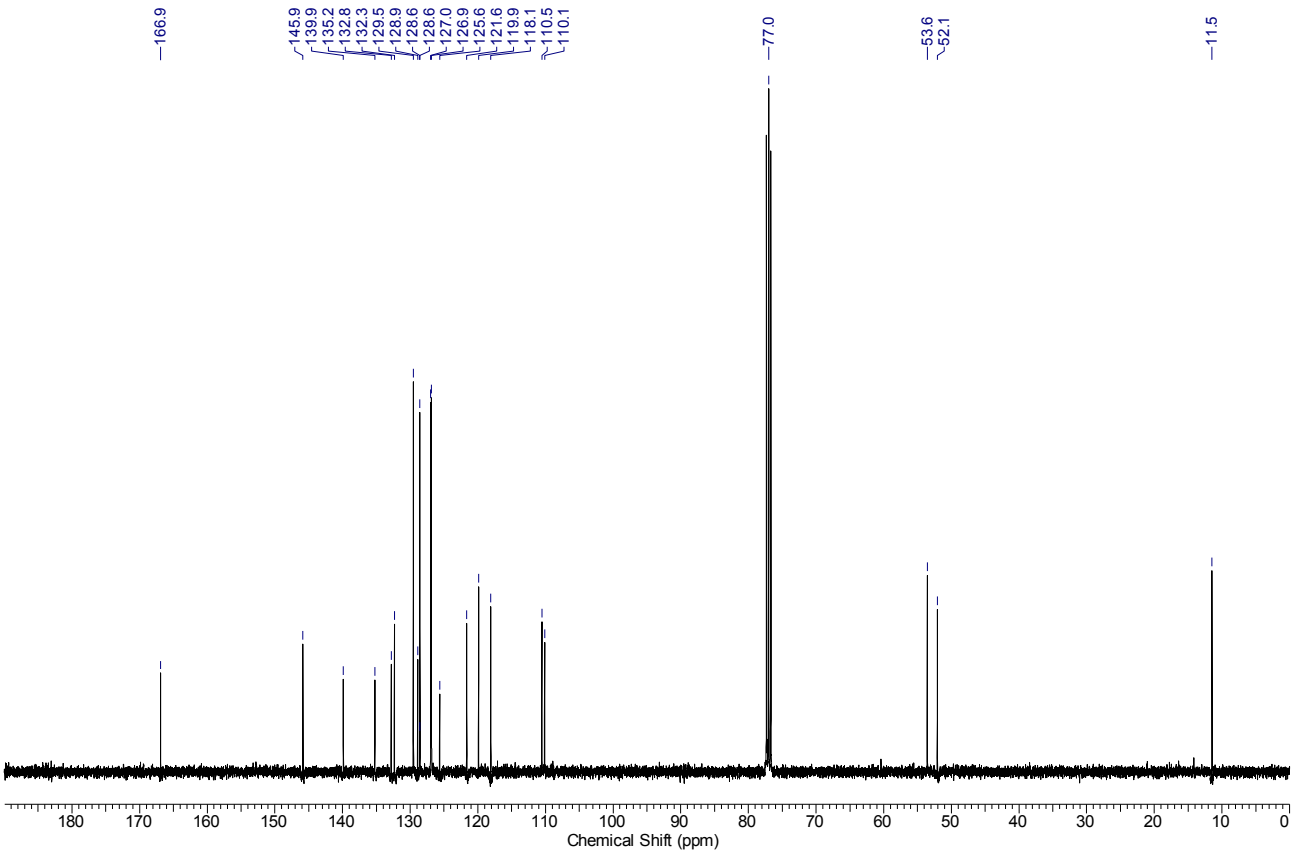


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.468	MM	1.4007	371.47852	4.42016	49.1122
2	36.260	MM	3.0803	384.90820	2.08262	50.8878
Totals :				756.38672	6.50278	

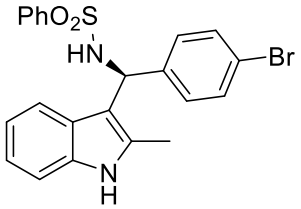
Chromatograms of compounds (−) & (±) **14-16f**.



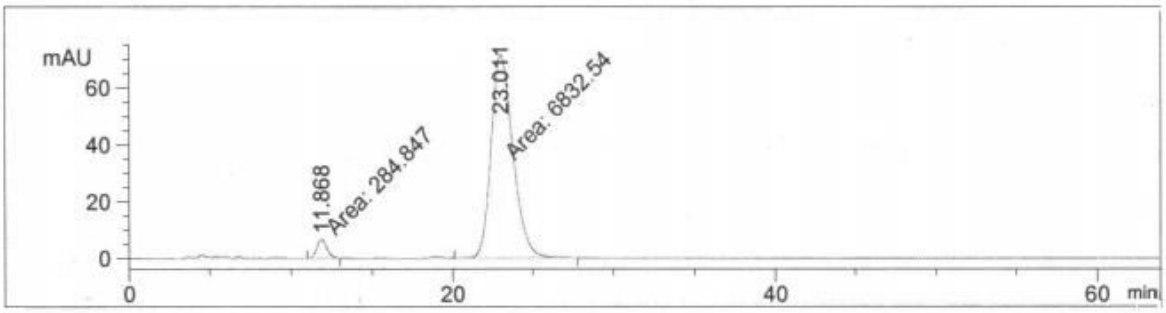
^{1}H NMR (400 MHz) spectrum of **14-16f** in $CDCl_3$.



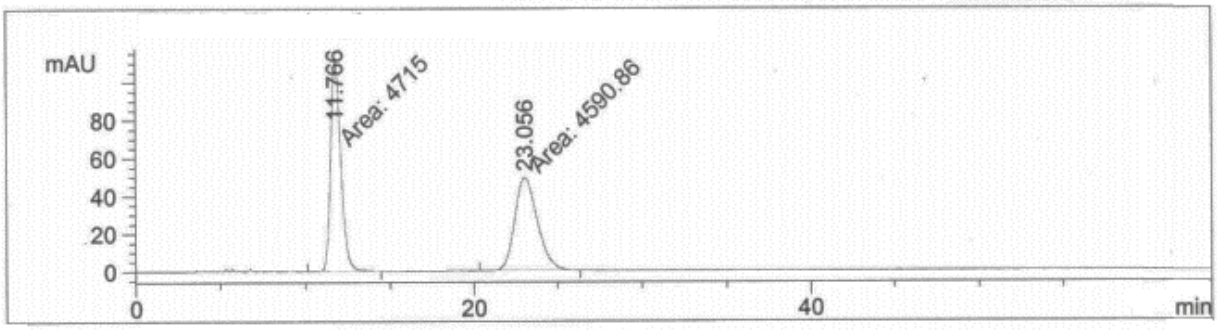
^{13}C NMR (100 MHz) spectrum of **14-16f** in $CDCl_3$.



14-16g

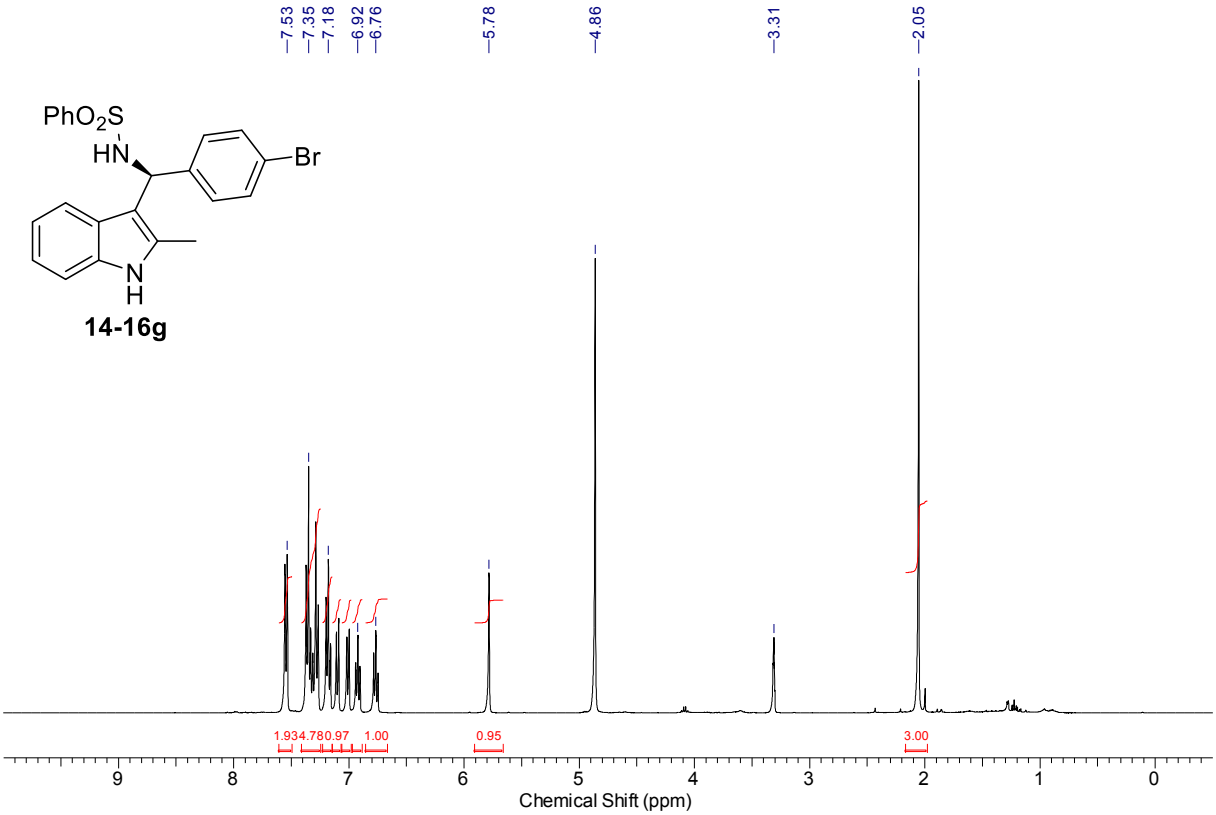


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.868	MM	0.7110	284.84732	6.67748	4.0021
2	23.011	MM	1.5900	6832.54346	71.62121	95.9979
Totals :				7117.39078	78.29868	

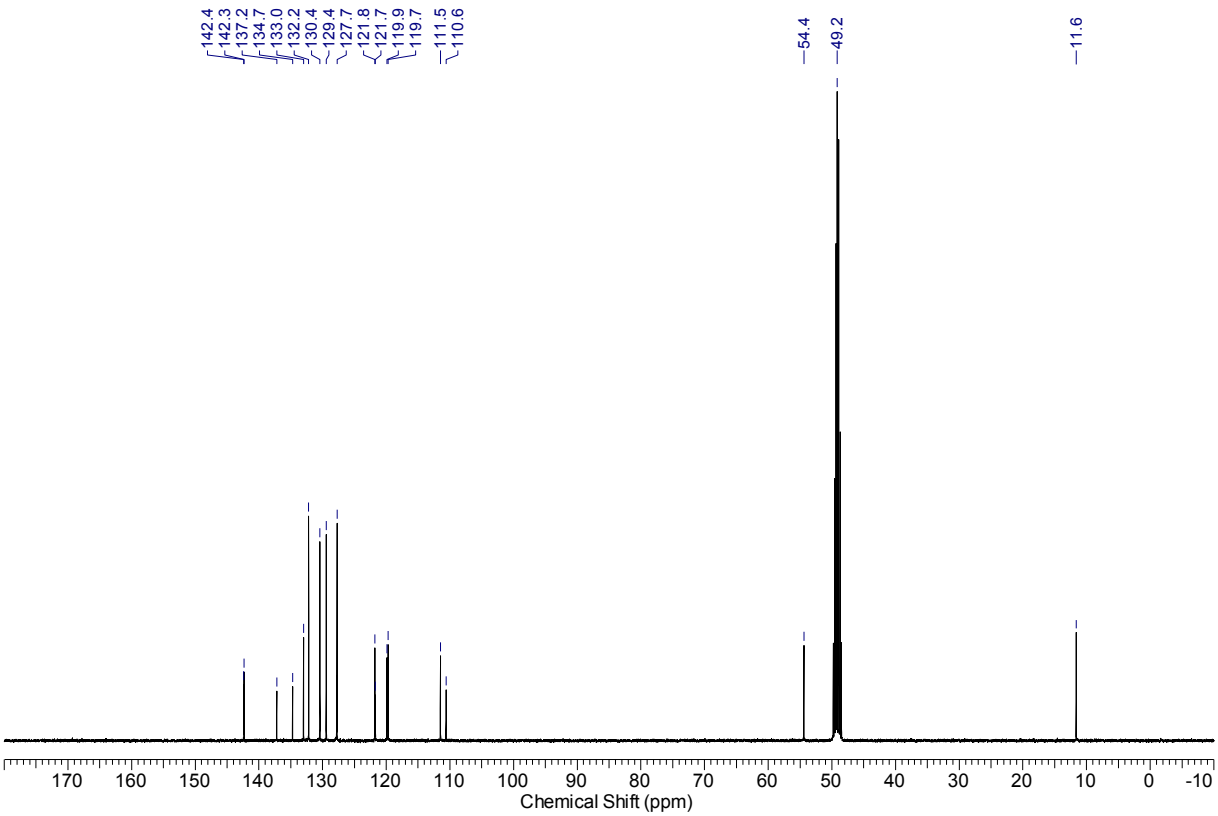


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.766	MM	0.7014	4715.00098	112.03199	50.6670
2	23.056	MM	1.5593	4590.85547	49.06917	49.3330
Totals :				9305.85645	161.10116	

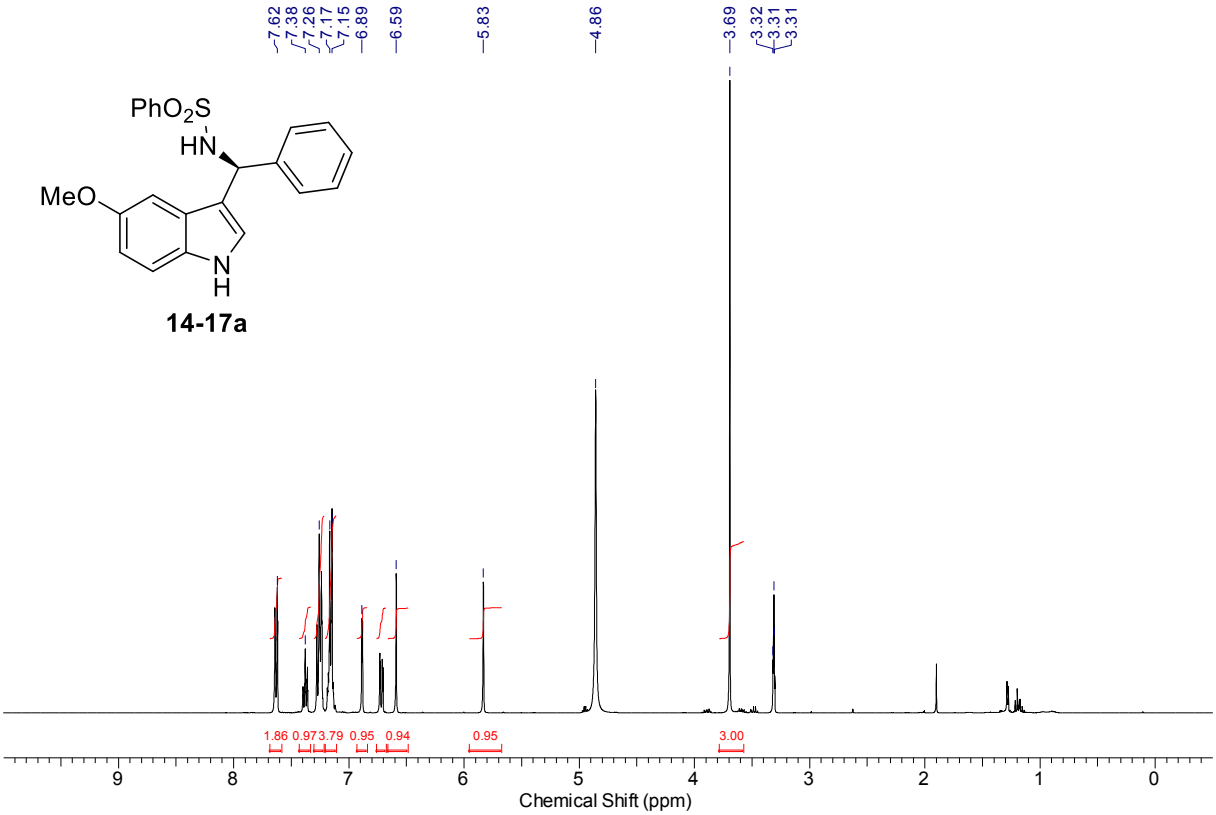
Chromatograms of compounds (−) & (±) **14-16g**.



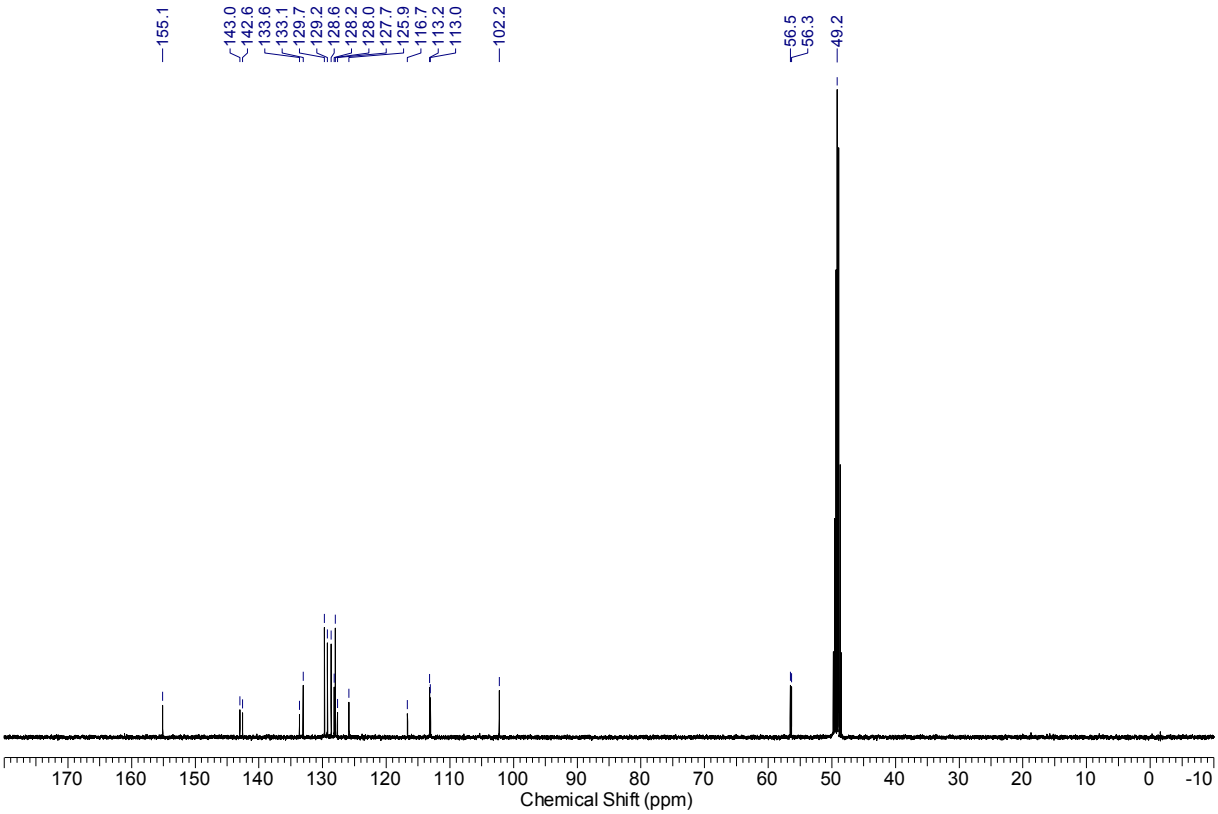
^{1}H NMR (400 MHz) spectrum of **14-16g** in CD_3OD.



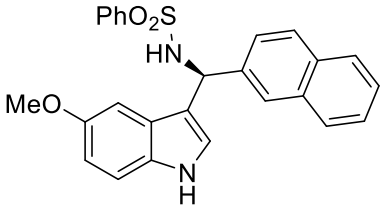
^{13}C NMR (100 MHz) spectrum of **14-16g** in CD_3OD.



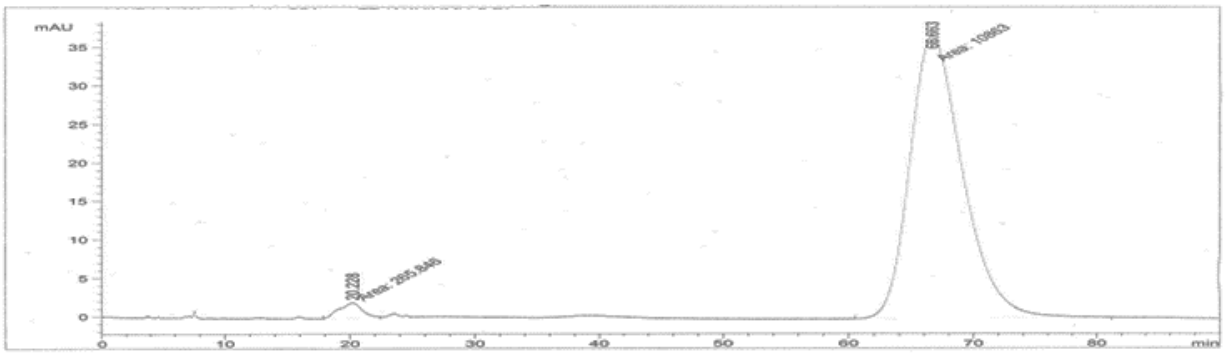
^{1}H NMR (400 MHz) spectrum of **14-17a** in CD_3OD.



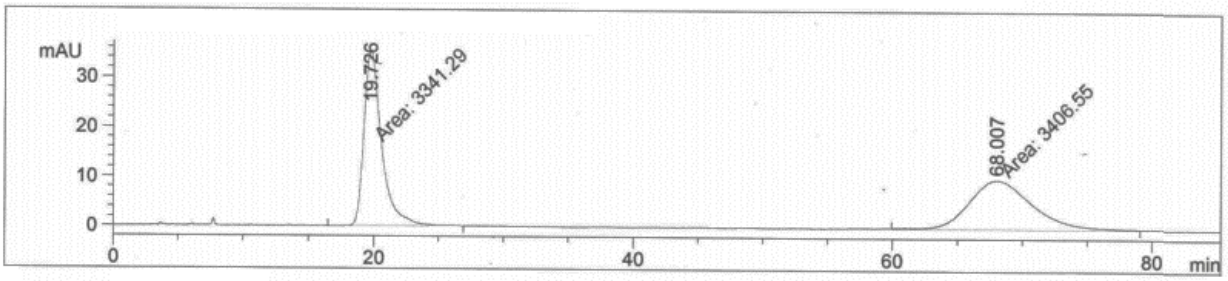
^{13}C NMR (100 MHz) spectrum of **14-17a** in CD_3OD.



14-17b

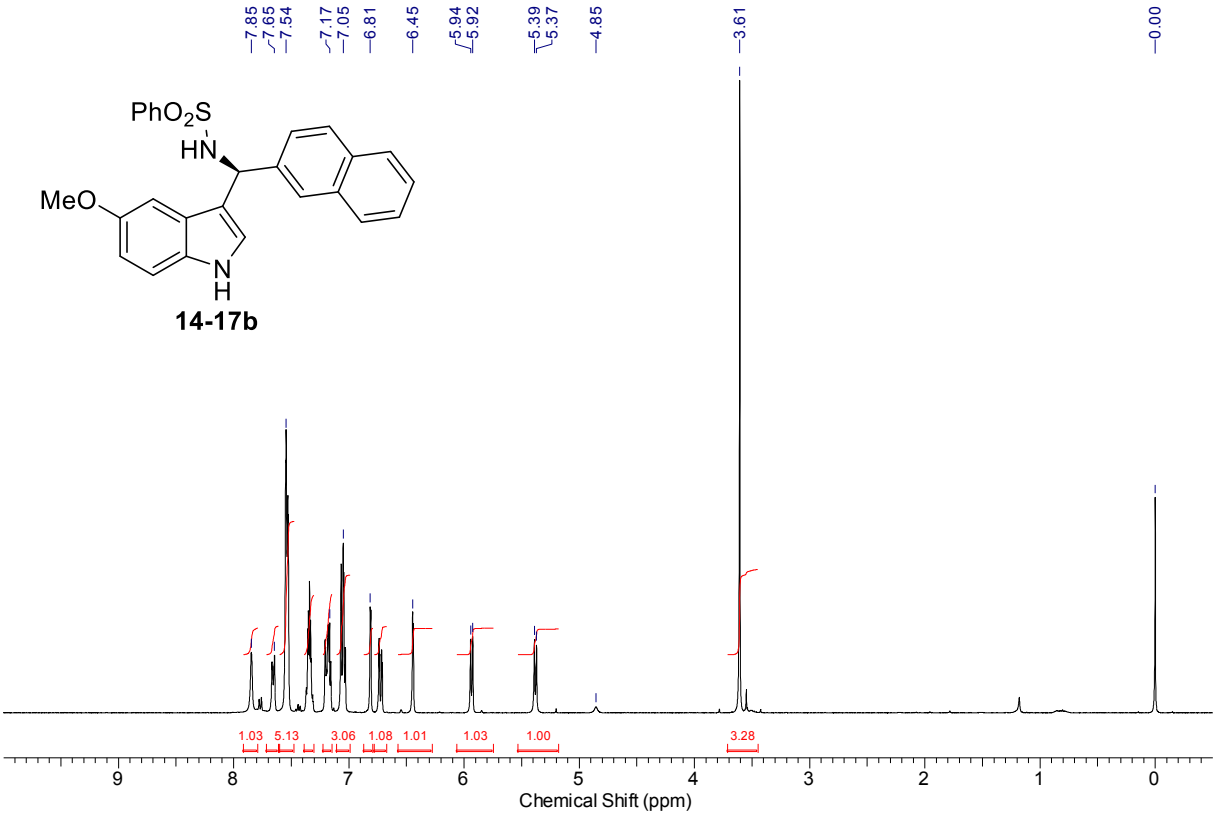


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.228	MM	2.1312	265.84613	2.07900	2.3888
2	66.663	MM	4.9253	1.08630e4	36.75920	97.6112
Totals :				1.11288e4	38.83820	

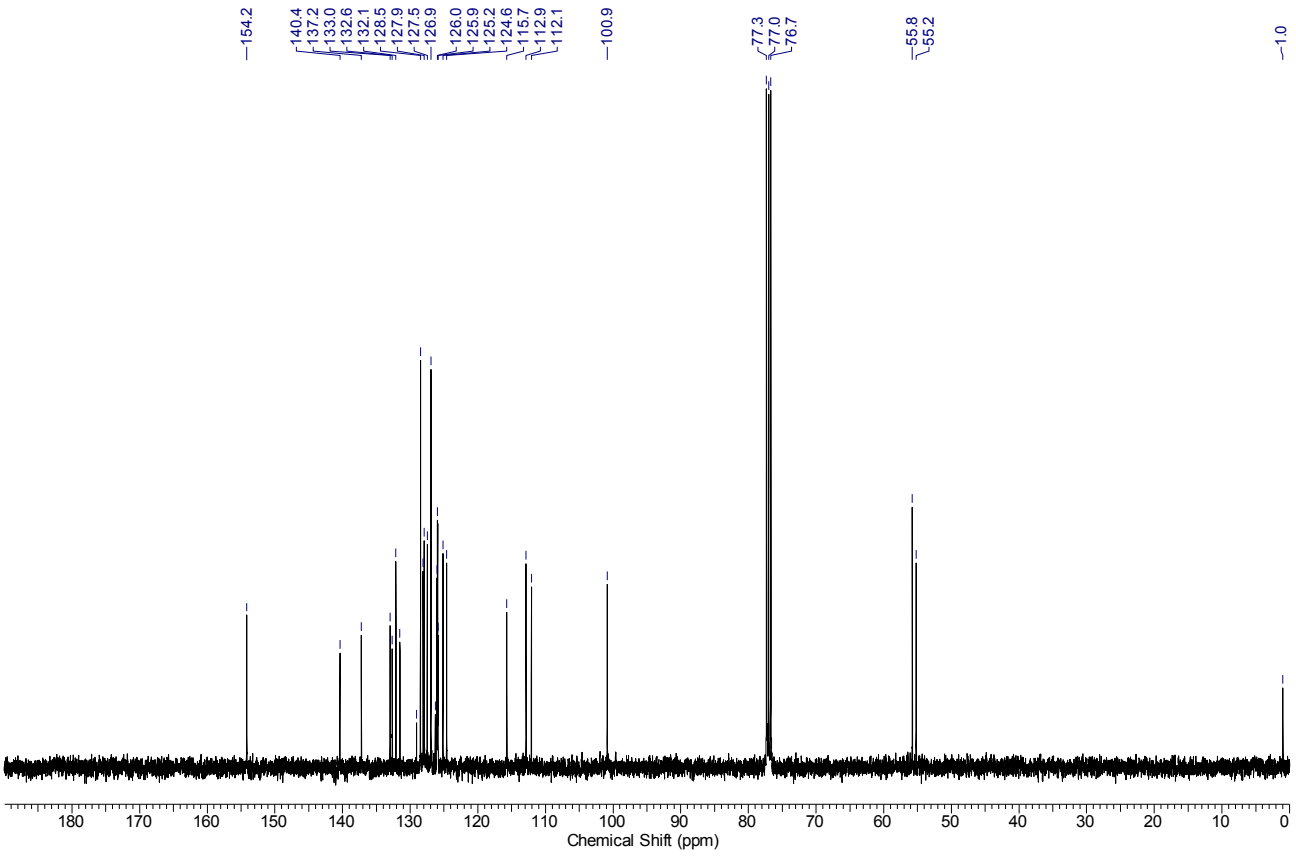


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	19.726	MM	1.5812	3341.28979	35.21814	49.5164
2	68.007	MM	5.7198	3406.55249	9.92619	50.4836
Totals :				6747.84229	45.14433	

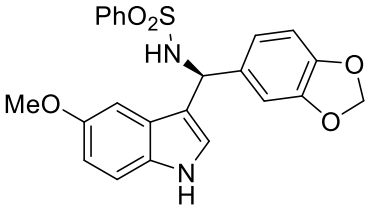
Chromatograms of compounds (−) & (±) **14-17b**.



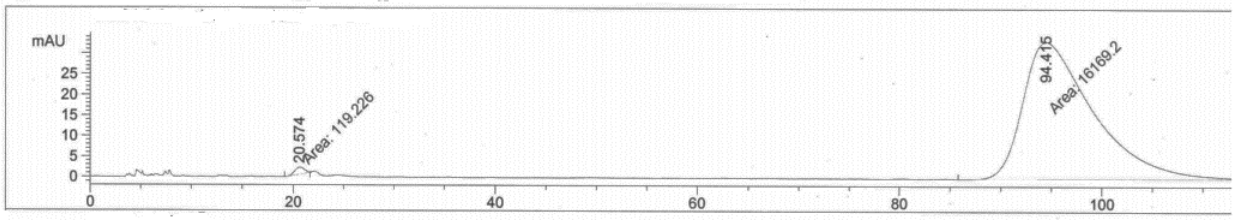
^{1}H NMR (400 MHz) spectrum of **14-17b** in $CDCl_3$.



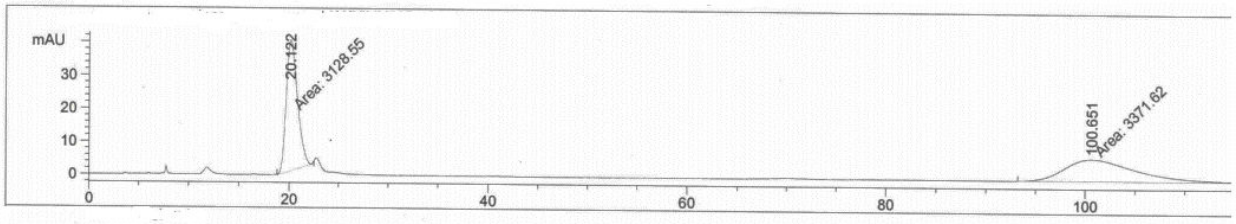
^{13}C NMR (100 MHz) spectrum of **14-17b** in $CDCl_3$.



14-17c

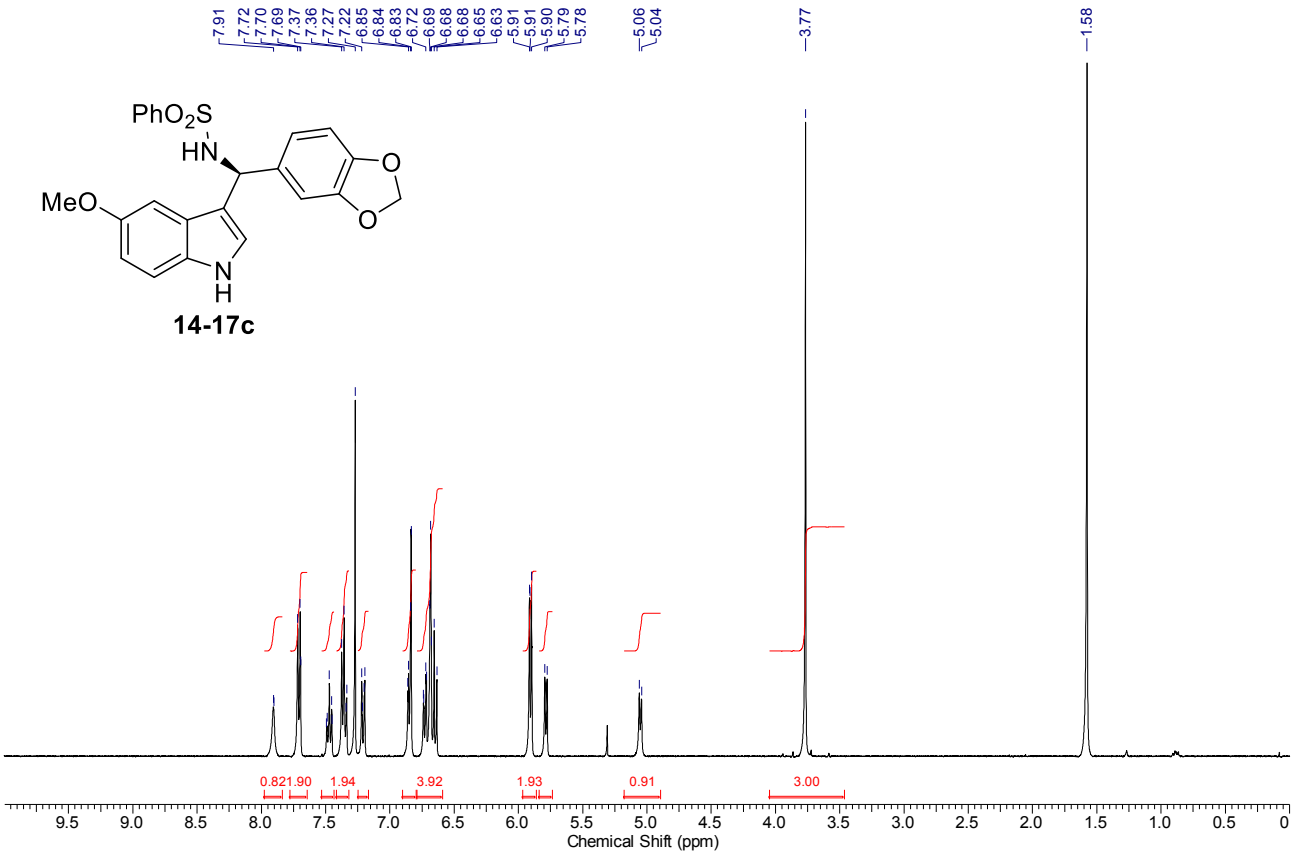


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.574	MM	1.1319	119.22604	1.75551	0.7320
2	94.415	MM	8.0965	1.61692e4	33.28428	99.2680
Totals :				1.62884e4	35.03978	

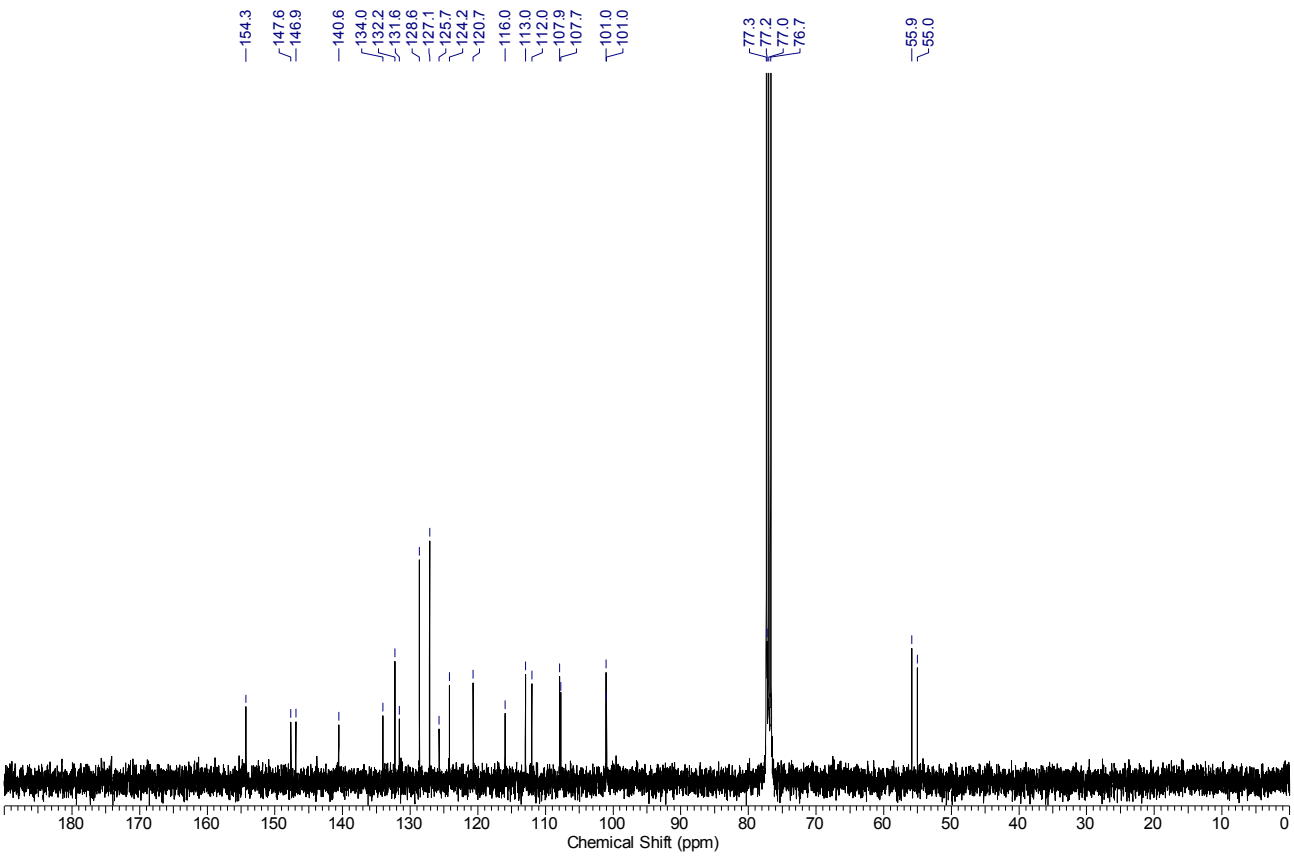


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.122	MM	1.3168	3128.55151	39.59771	48.1303
2	100.651	MM	8.3233	3371.62134	6.75139	51.8697
Totals :				6500.17285	46.34910	

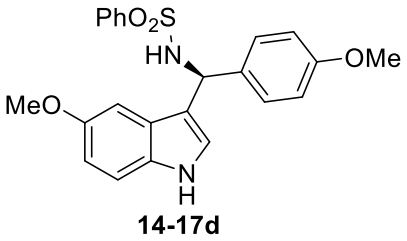
Chromatograms of compounds (−) & (±) **14-17c**.



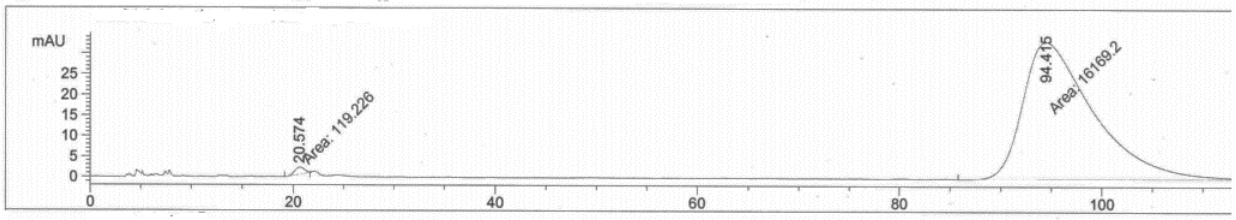
^{1}H NMR (400 MHz) spectrum of **14-17c** in $CDCl_3$.



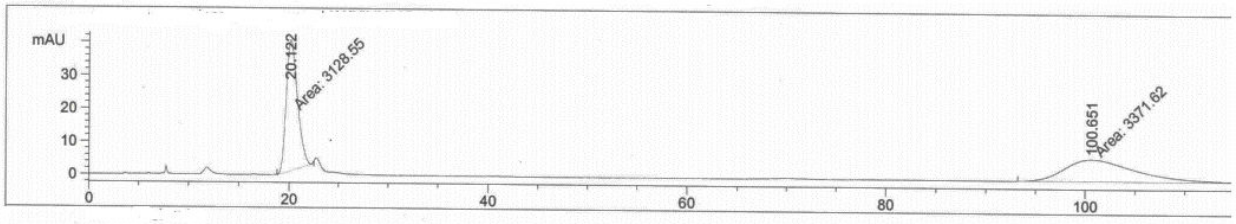
^{13}C NMR (100 MHz) spectrum of **14-17c** in $CDCl_3$.



14-17d

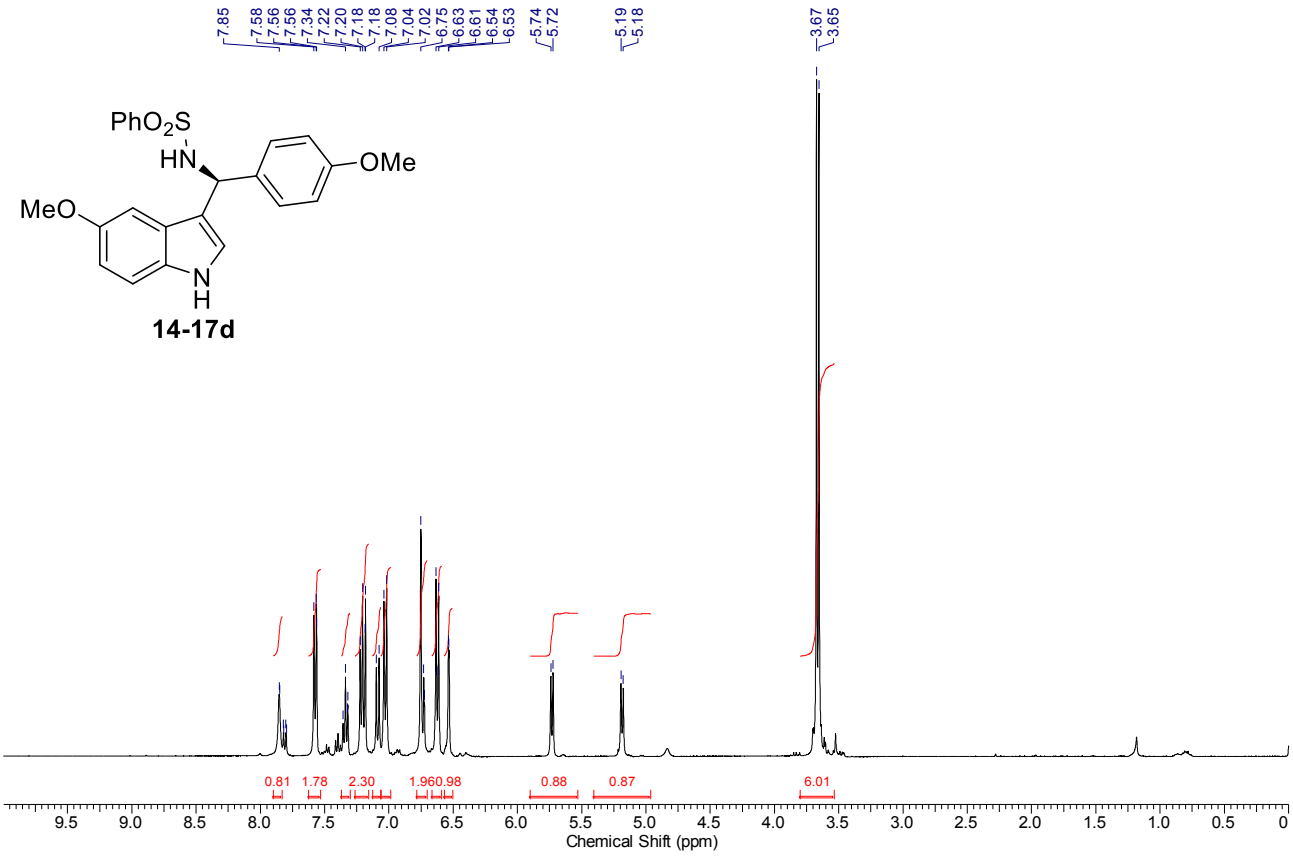


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.574	MM	1.1319	119.22604	1.75551	0.7320
2	94.415	MM	8.0965	1.61692e4	33.28428	99.2680
Totals :				1.62884e4	35.03978	

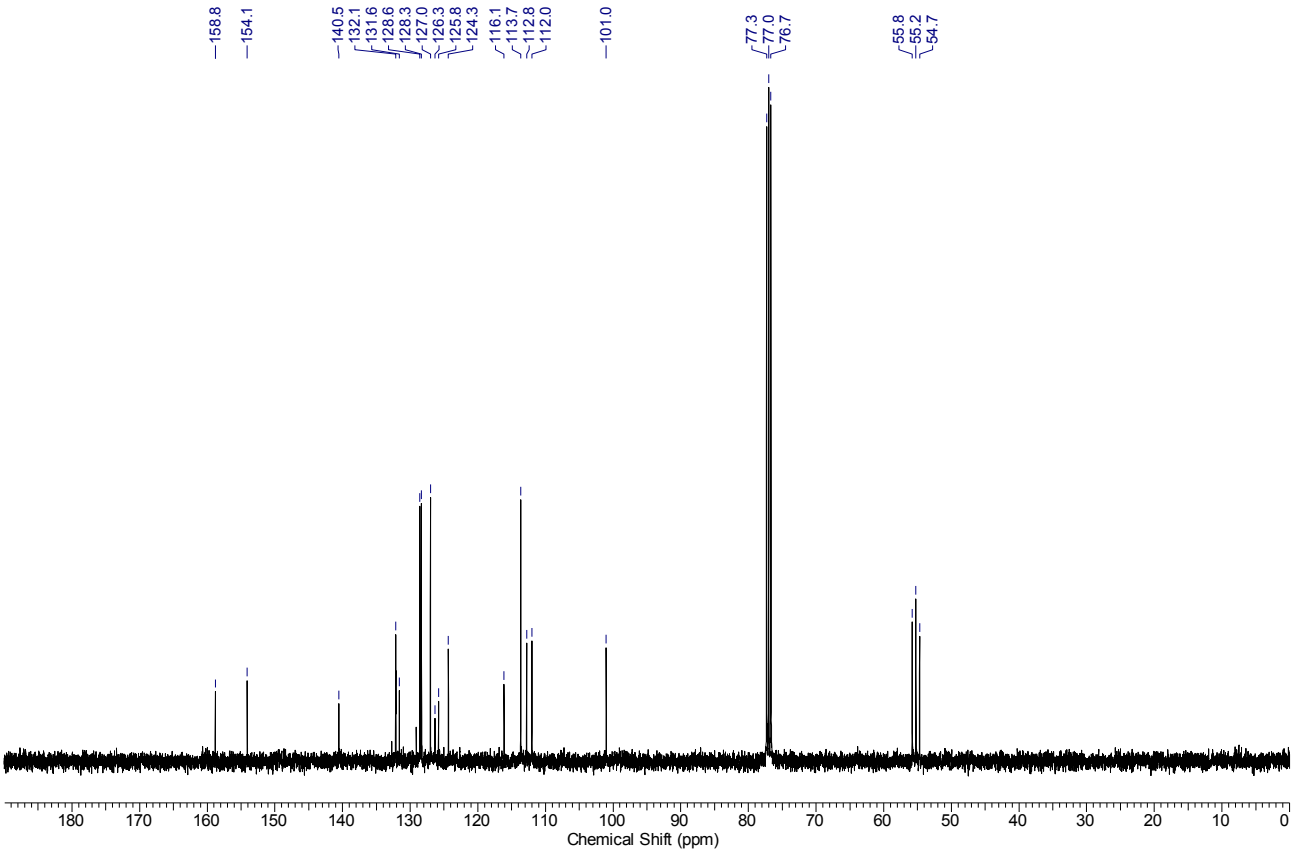


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	20.122	MM	1.3168	3128.55151	39.59771	48.1303
2	100.651	MM	8.3233	3371.62134	6.75139	51.8697
Totals :				6500.17285	46.34910	

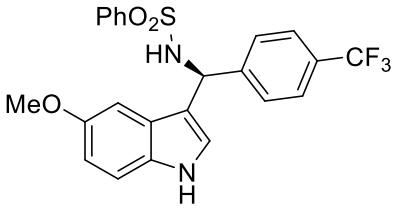
Chromatograms of compounds (−) & (±) **14-17d**.



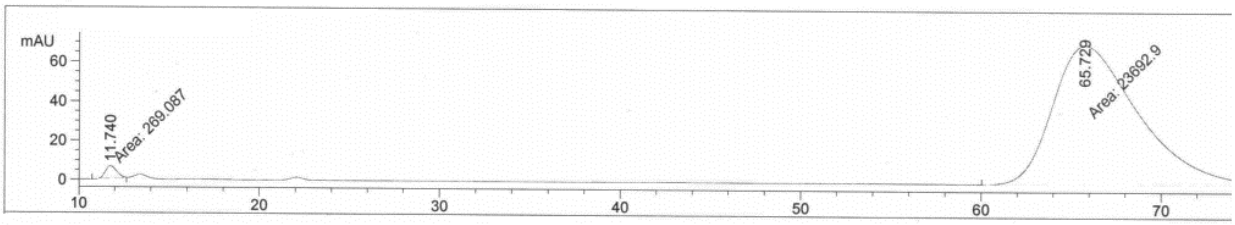
^{1}H NMR (400 MHz) spectrum of **14-17d** in $CDCl_3$.



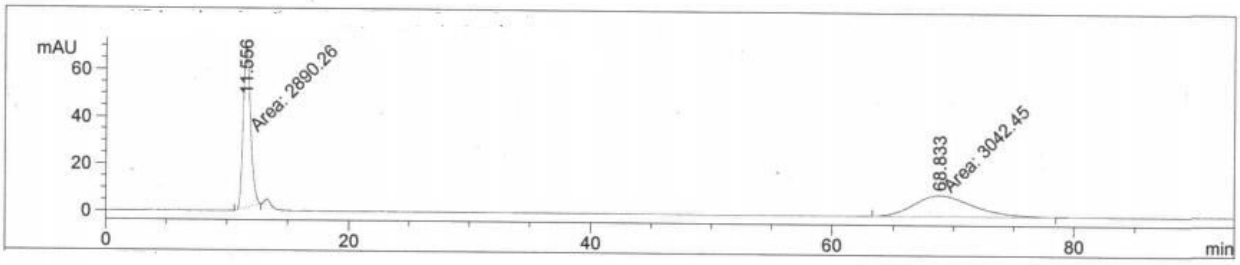
^{13}C NMR (100 MHz) spectrum of **14-17d** in $CDCl_3$.



14-17e

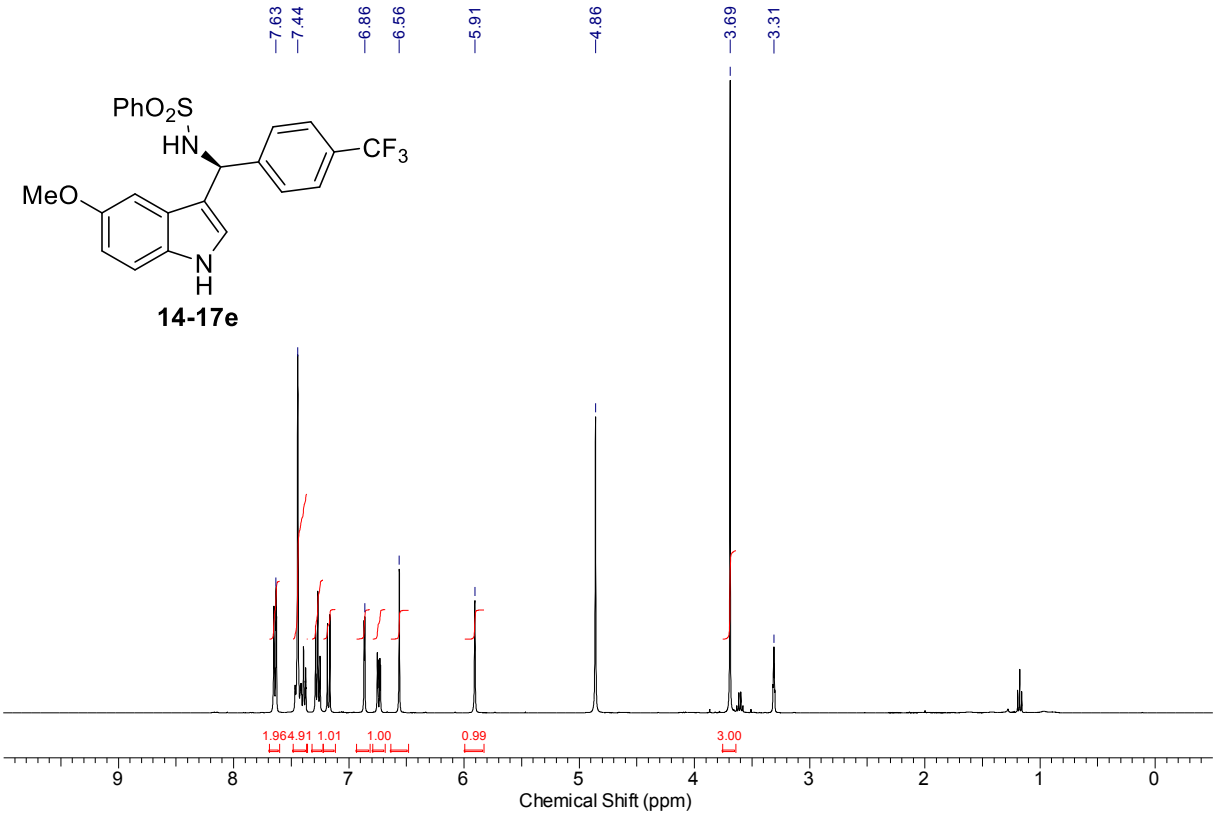


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.740	MM	0.7066	269.08707	6.34657	1.1216
2	65.729	MM	5.5897	2.36929e4	70.64452	98.7594
Totals :				2.39905e4	80.90391	

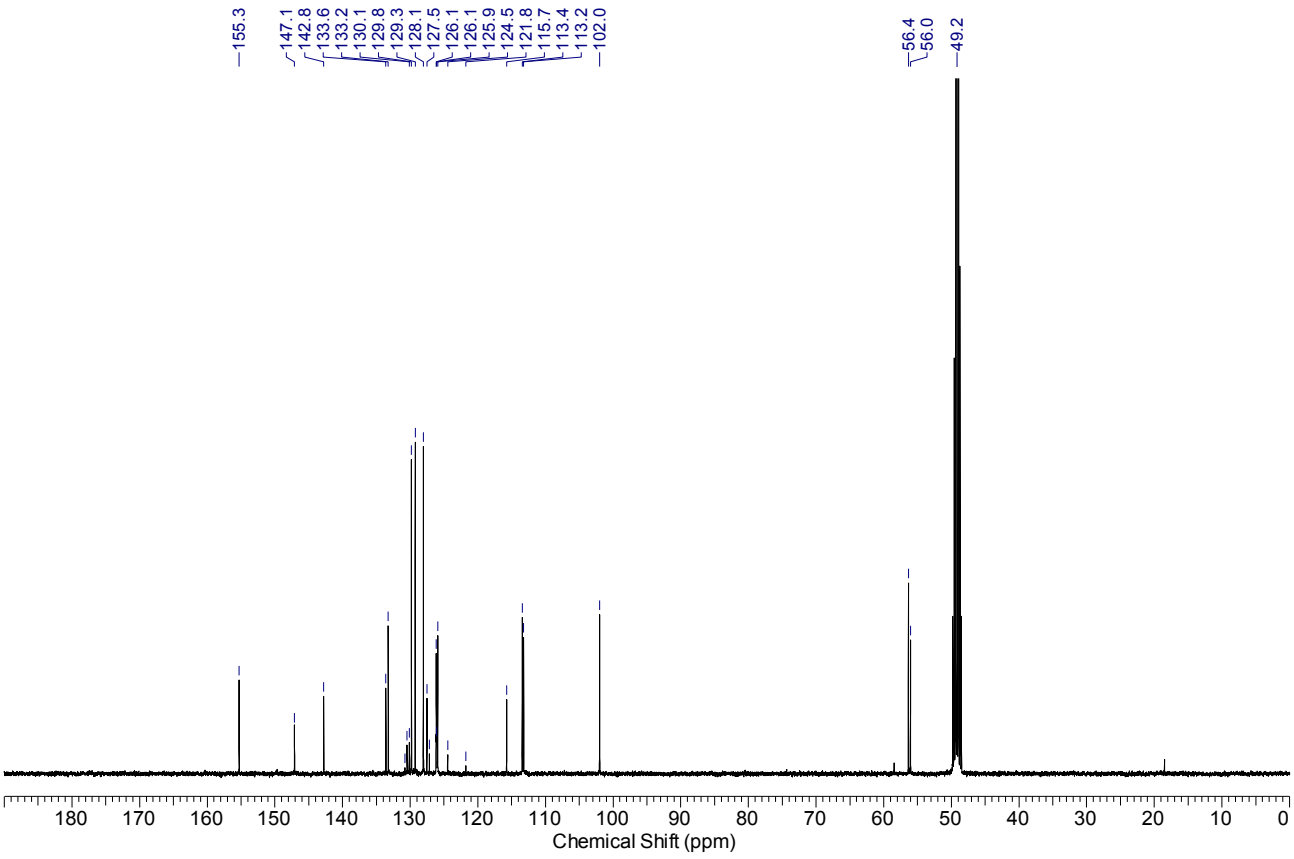


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.556	MM	0.7063	2890.26270	68.20457	48.7174
2	68.833	MM	5.6864	3042.45166	8.91738	51.2826
Totals :				5932.71436	77.12196	

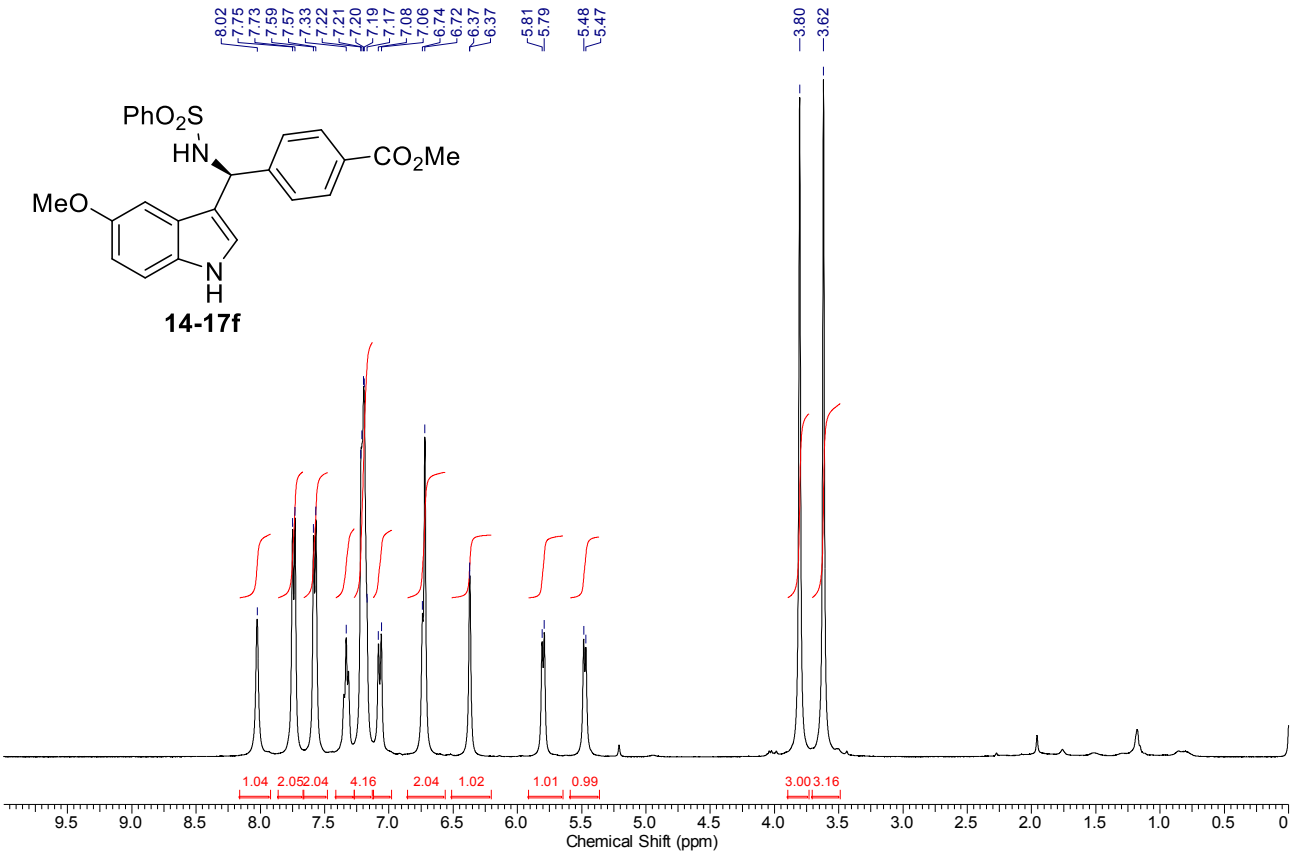
Chromatograms of compounds (−) & (±) **14-17e**.



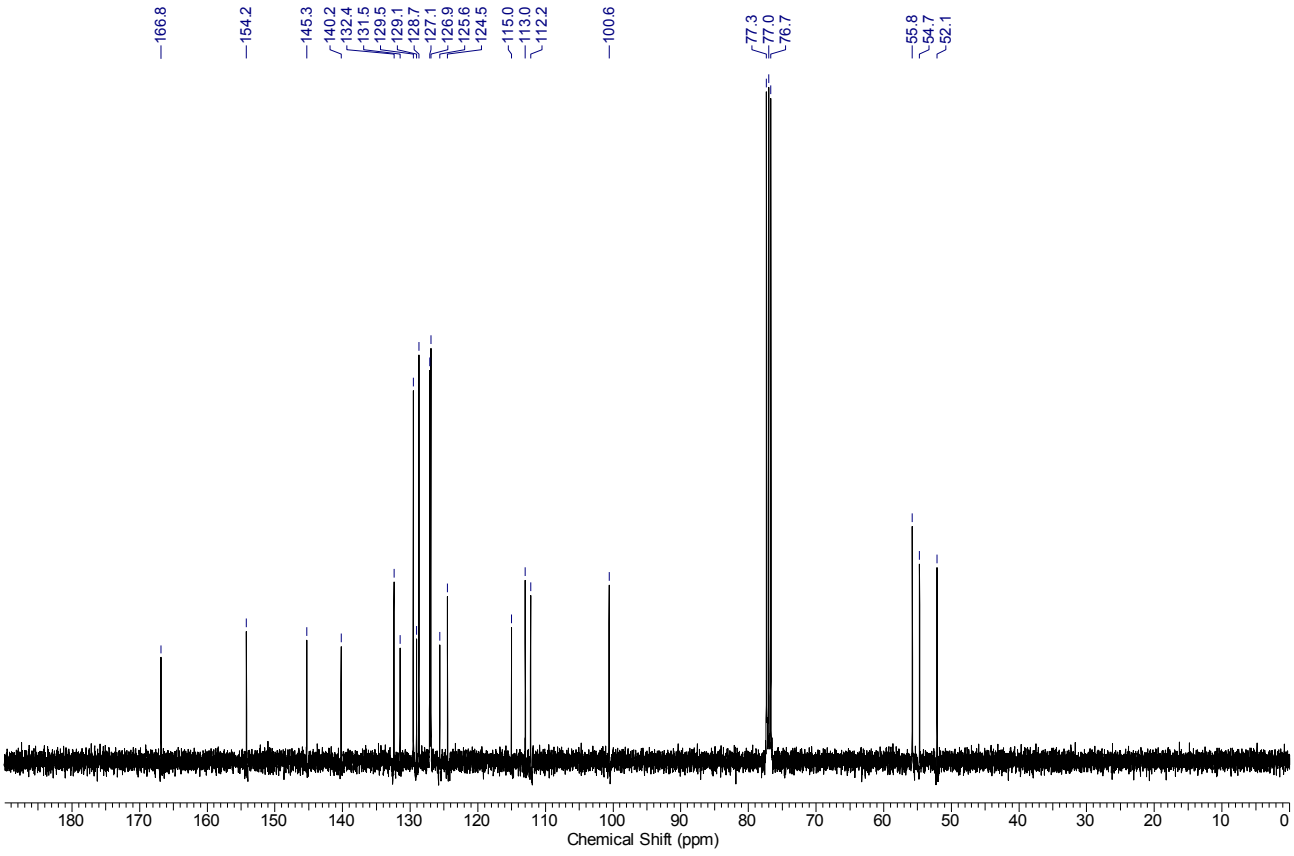
^{1}H NMR (400 MHz) spectrum of **14-17e** in CD_3OD.



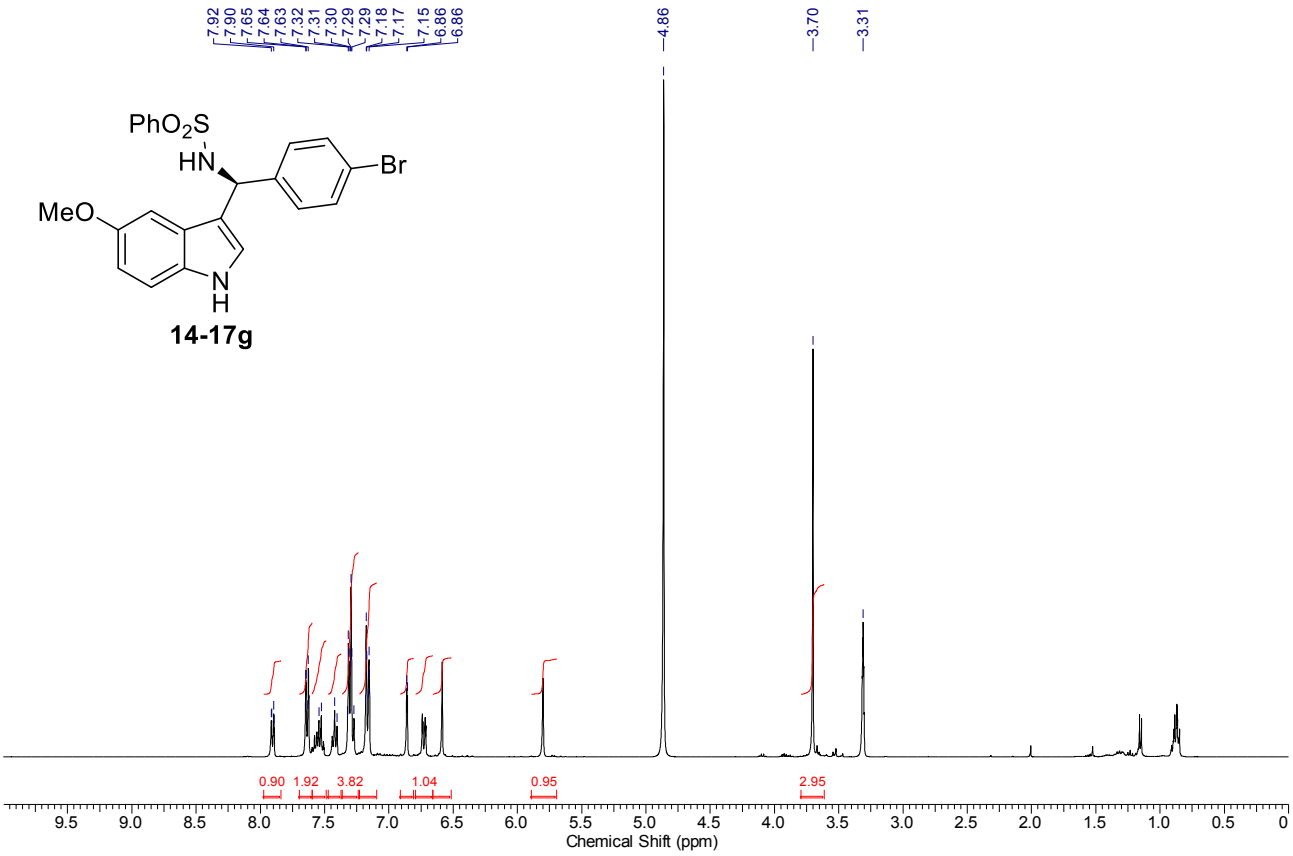
^{13}C NMR (100 MHz) spectrum of **14-17e** in CD_3OD.



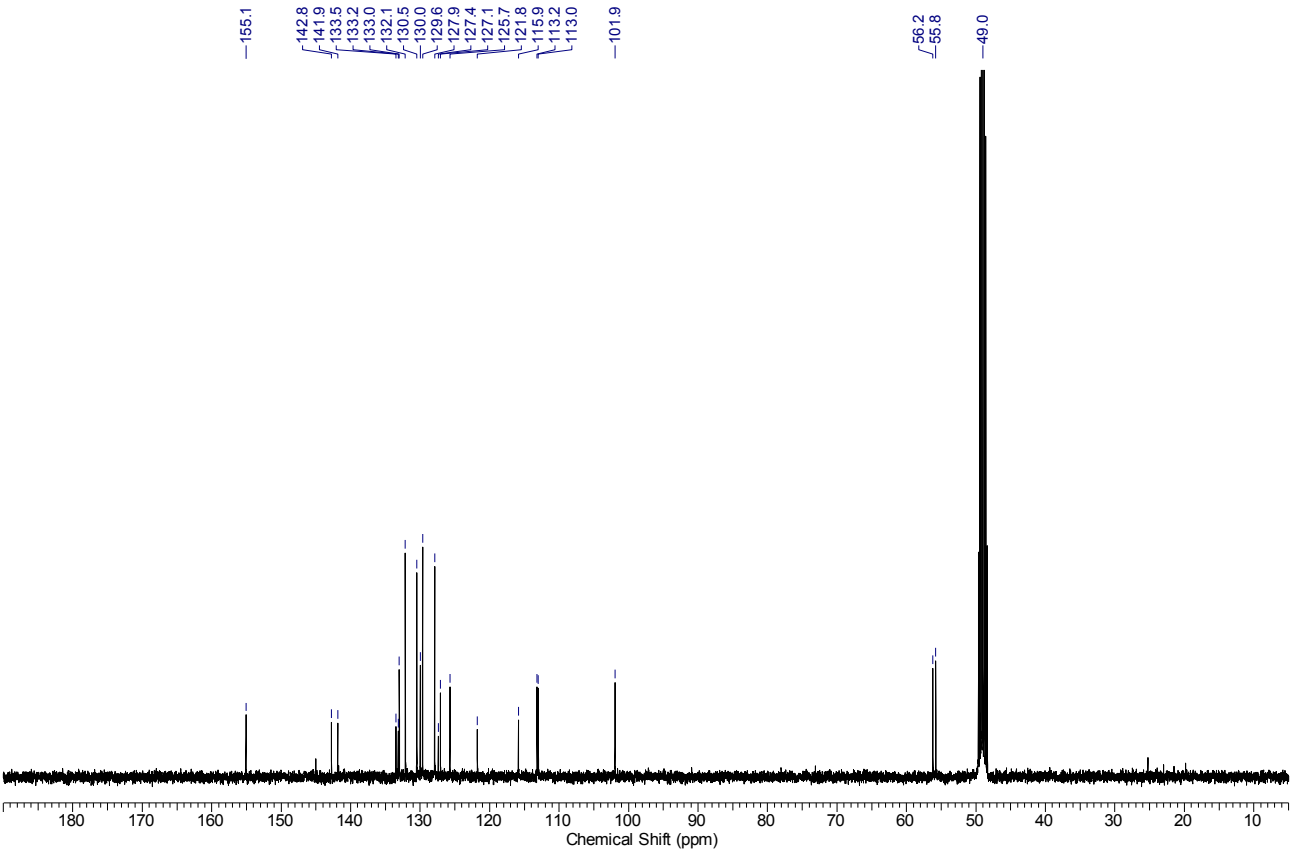
^{1}H NMR (400 MHz) spectrum of **14-17f** in $CDCl_3$.



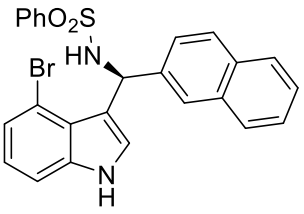
^{13}C NMR (100 MHz) spectrum of **14-17f** in $CDCl_3$.



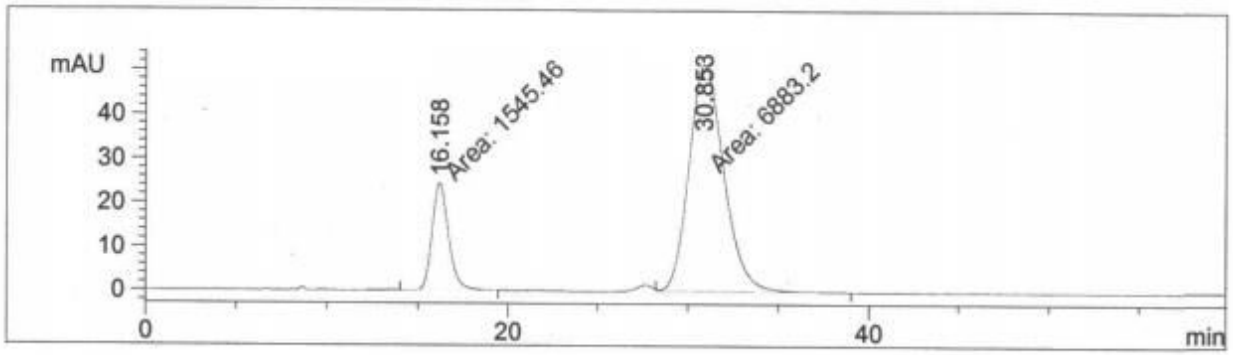
^{1}H NMR (400 MHz) spectrum of **14-17g** in CD_3OD.



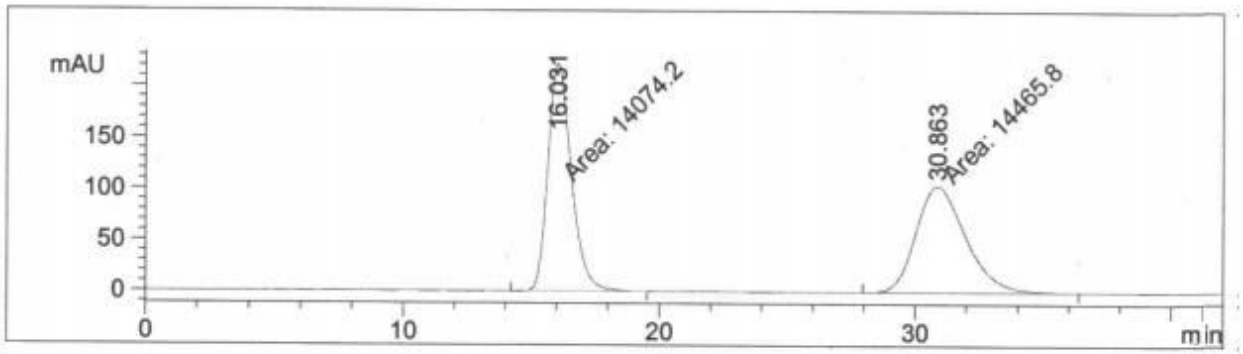
^{13}C NMR (100 MHz) spectrum of **14-17g** in CD_3OD.



14-18b

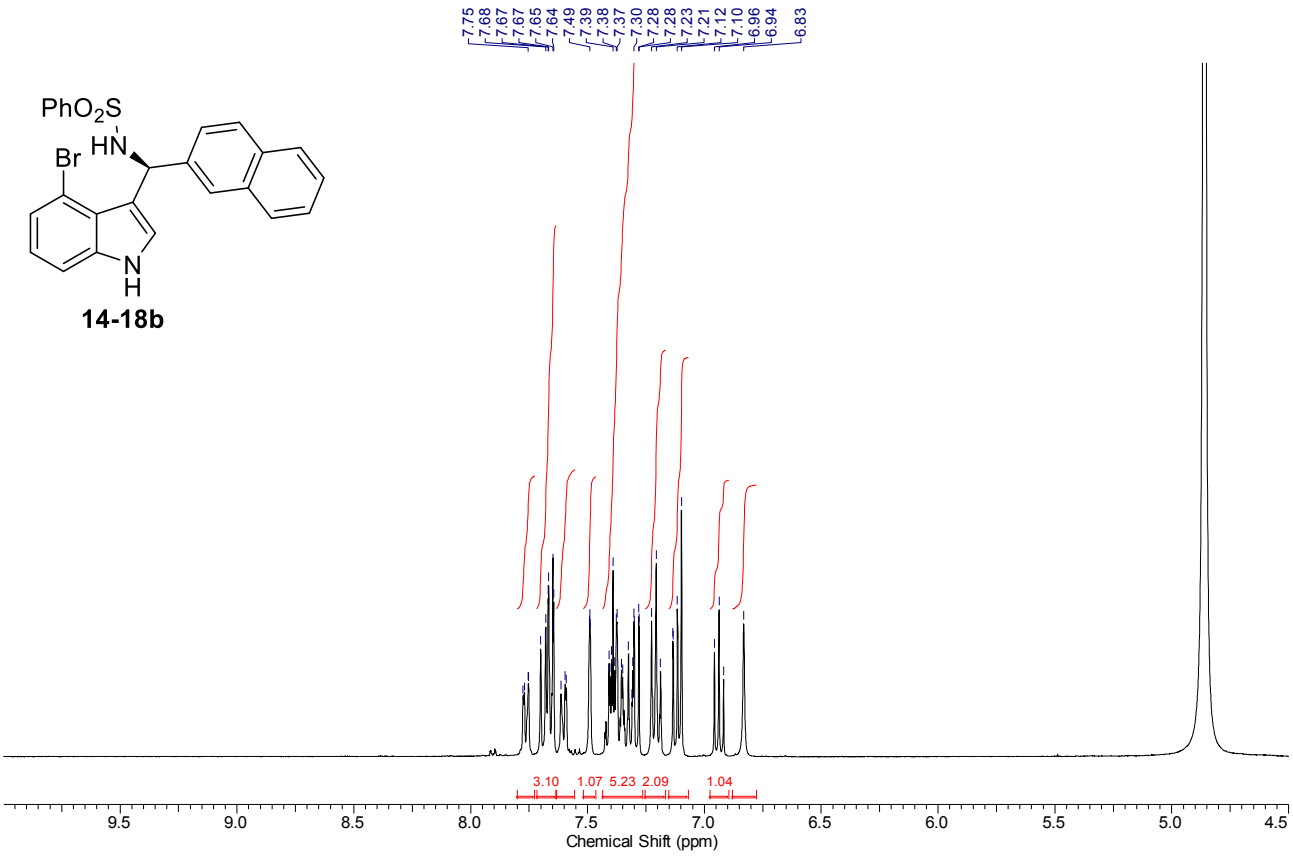


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.158	MM	1.0543	1545.46423	24.43146	18.3358
2	30.853	MM	2.2335	6883.19824	51.36246	81.6642
Totals :				8428.66248	75.79392	

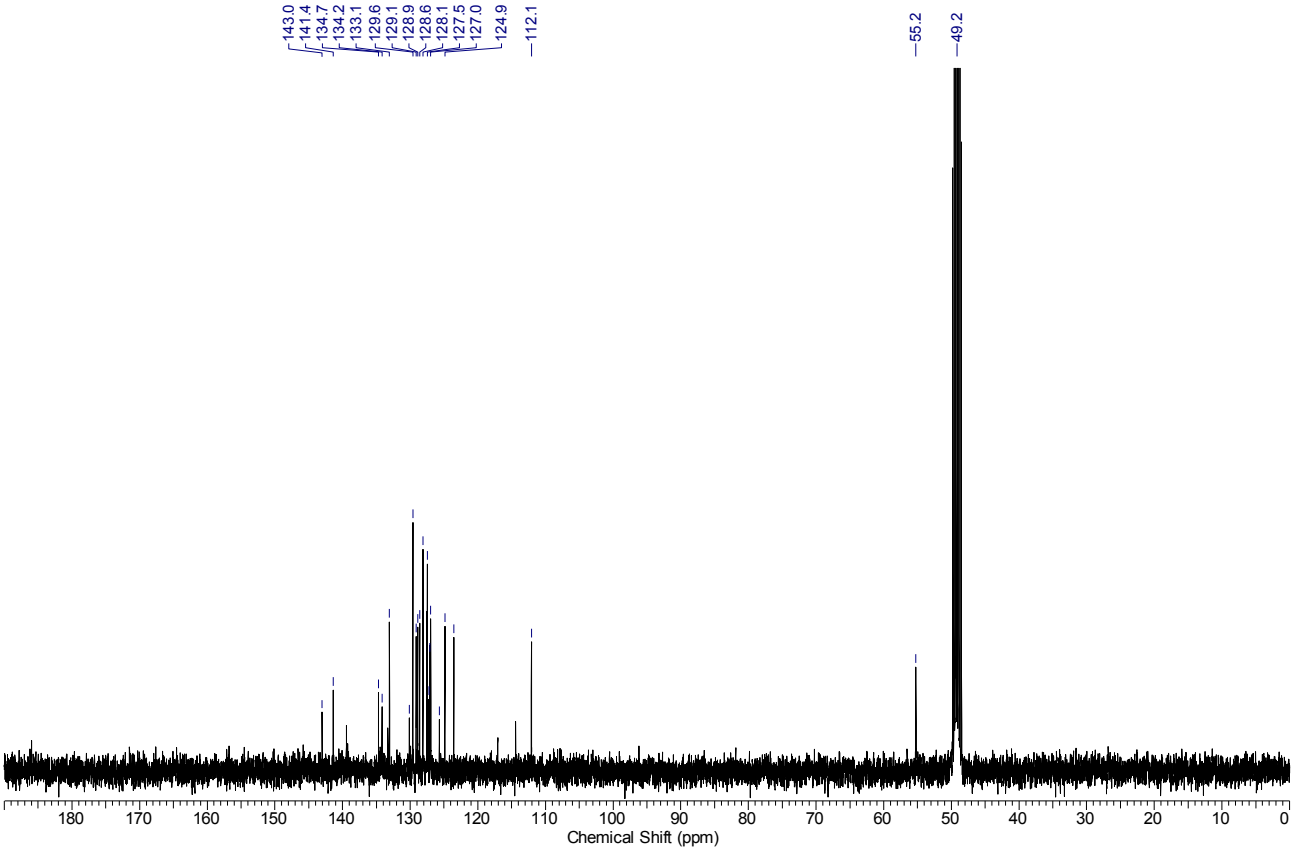


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.031	MM	1.0601	1.40742e4	221.28078	49.3139
2	30.863	MM	2.3088	1.44658e4	104.42770	50.6861
Totals :				2.85401e4	325.70847	

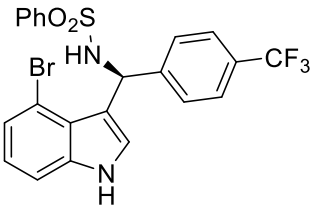
Chromatograms of compounds (−) & (±) **14-18b**.



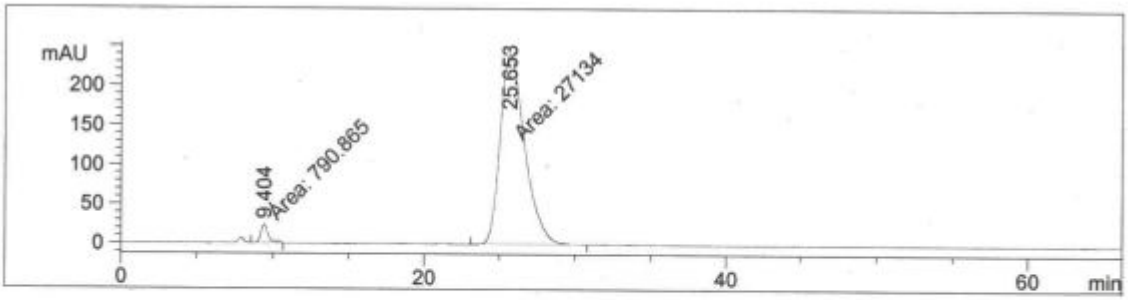
^{1}H NMR (400 MHz) spectrum of **14-18b** in CD_3OD (4.5 – 10.0 ppm).



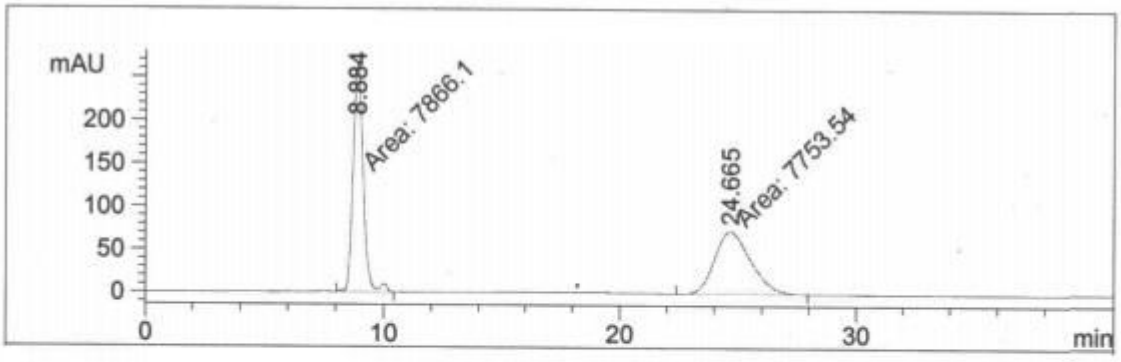
^{13}C NMR (100 MHz) spectrum of **14-18b** in CD_3OD (0.0 – 190 ppm).



14-18e

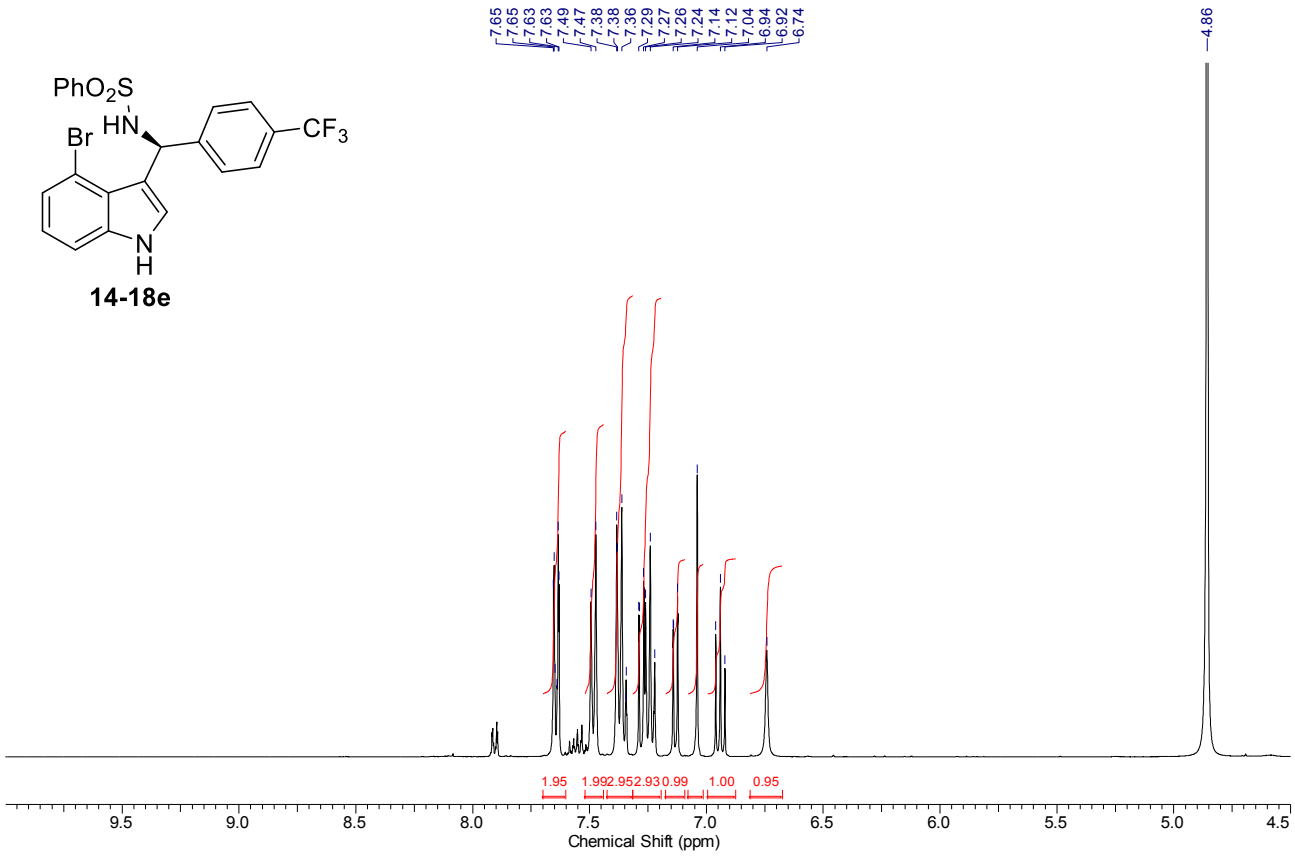


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.404	MM	0.5591	790.86456	23.57382	2.8321
2	25.653	MM	1.8756	2.71340e4	241.10884	97.1679
Totals :				2.79249e4	264.68266	

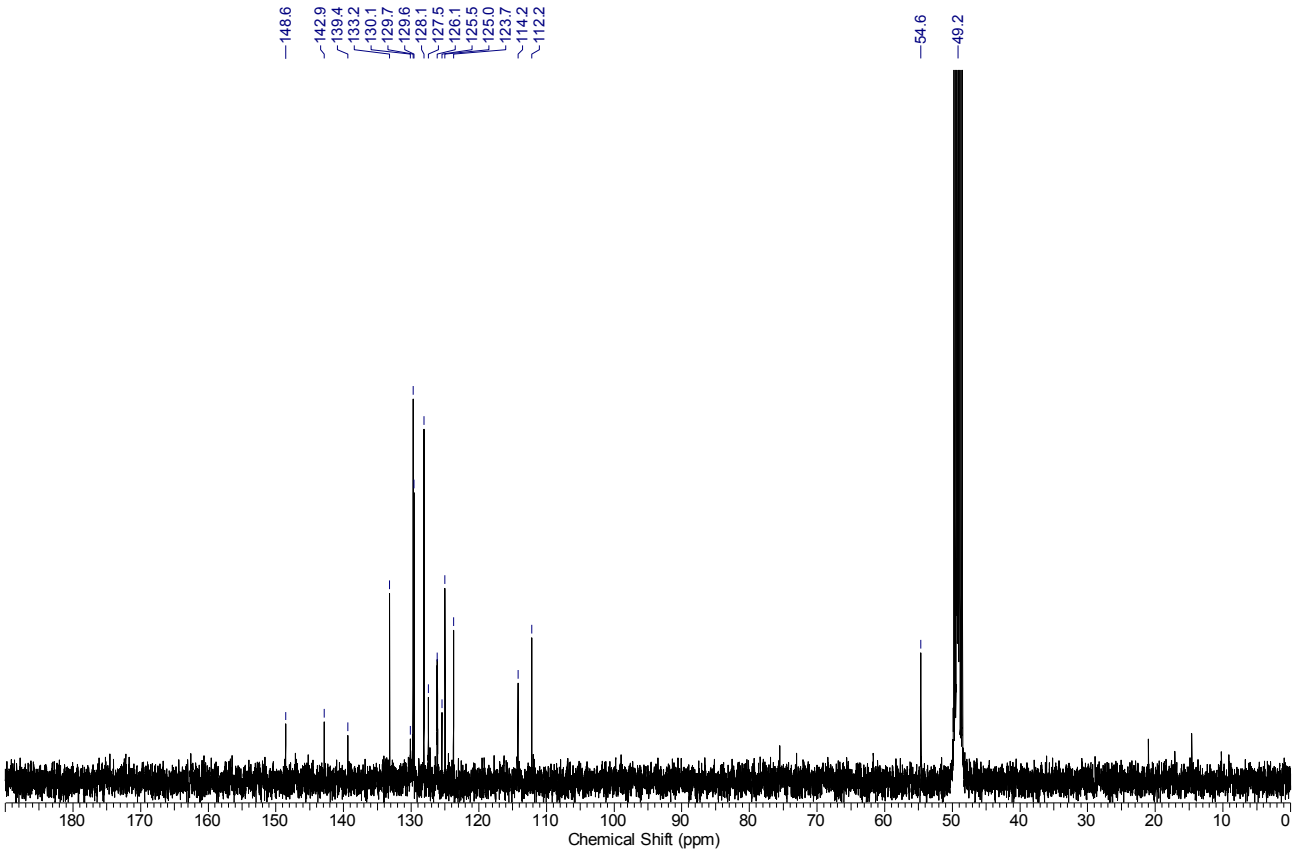


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.884	MM	0.4925	7866.10449	266.20837	50.3603
2	24.665	MM	1.7766	7753.53955	72.73925	49.6397
Totals :				1.56196e4	338.94762	

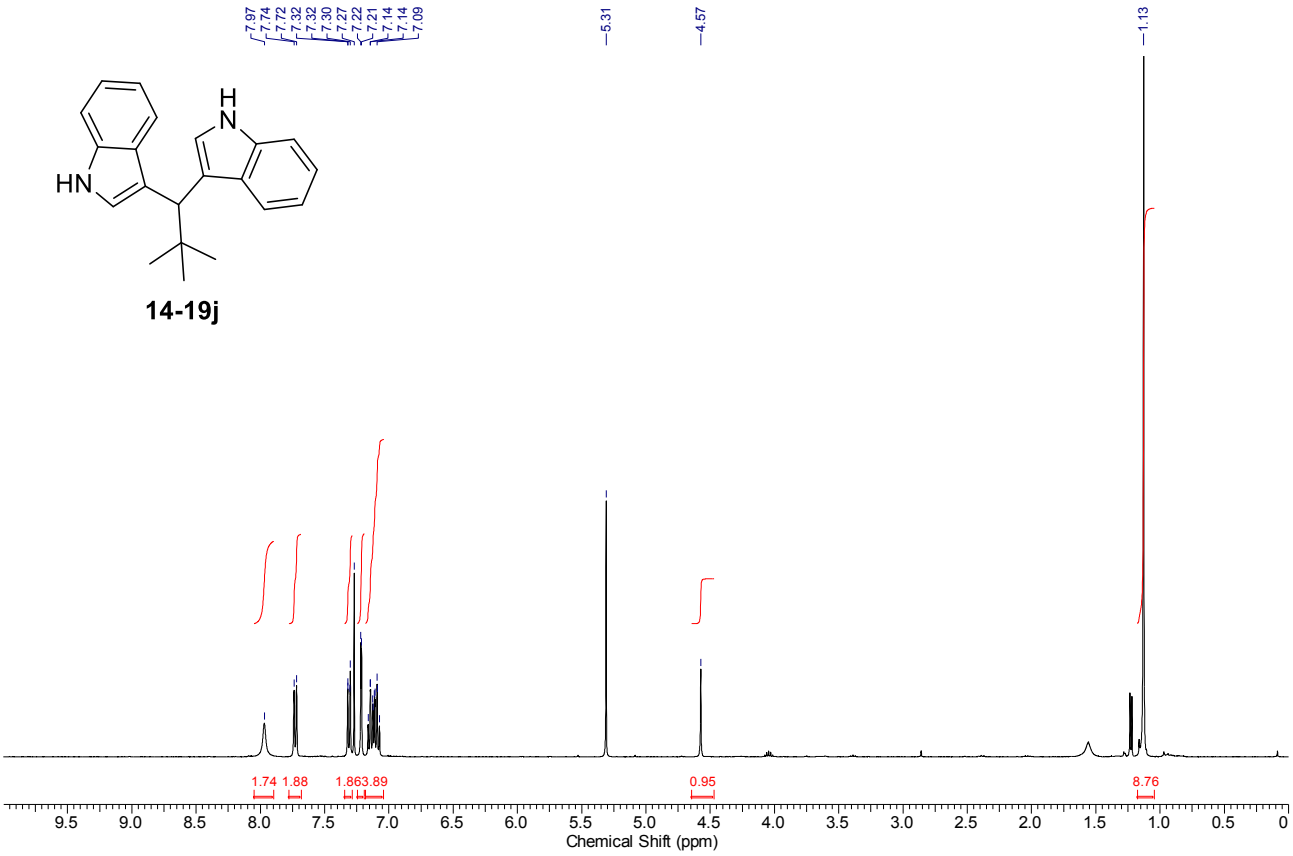
Chromatograms of compounds (−) & (±) **14-18e**.



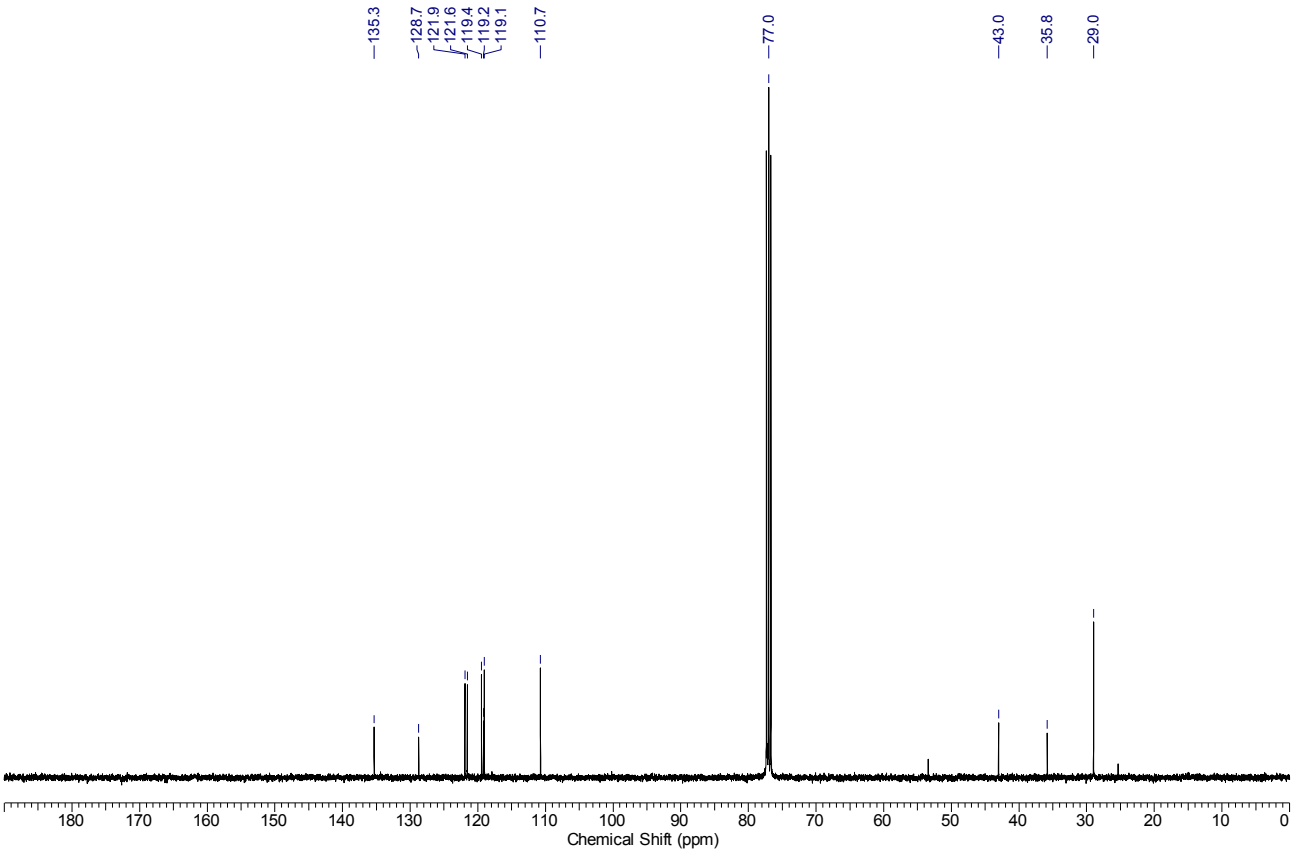
^{1}H NMR (400 MHz) spectrum of **14-12e** in CD_3OD (4.5 – 10.0 ppm).



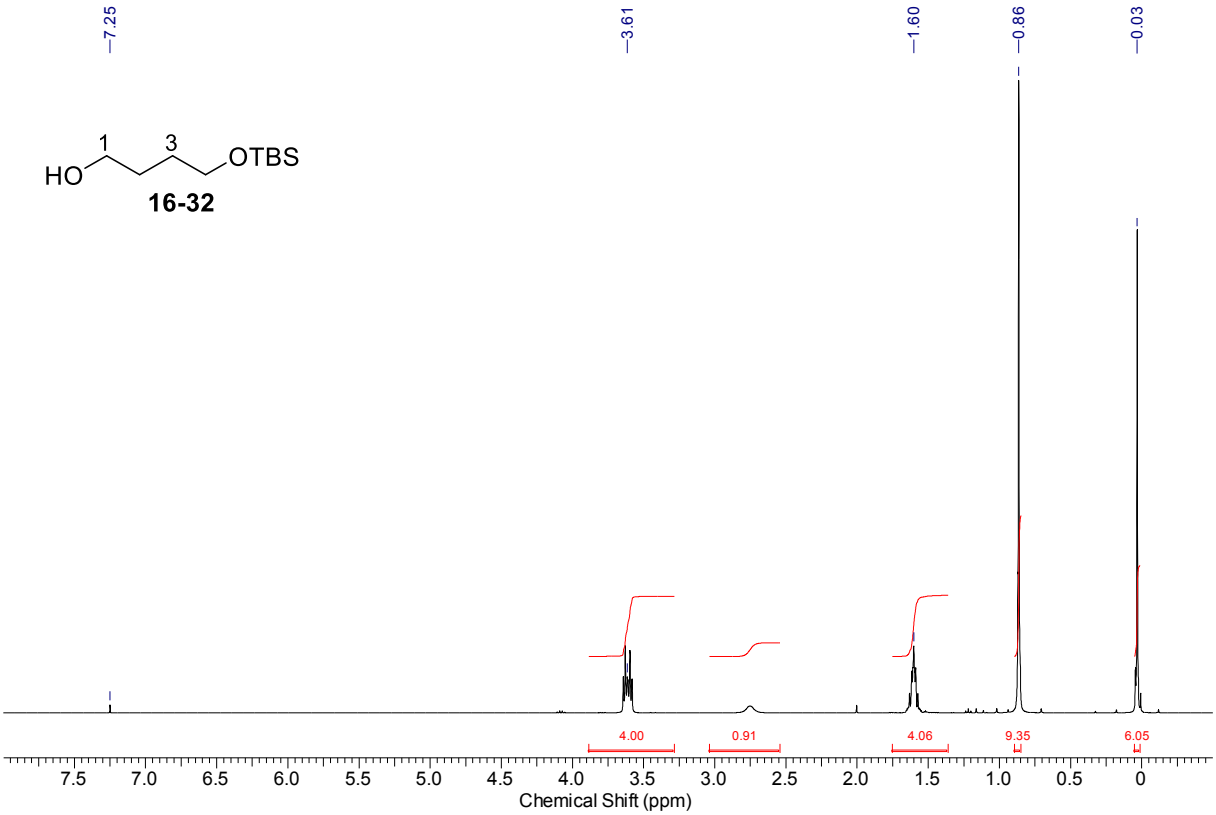
^{13}C NMR (100 MHz) spectrum of **14-18e** in CD_3OD (0.0 – 190 ppm).



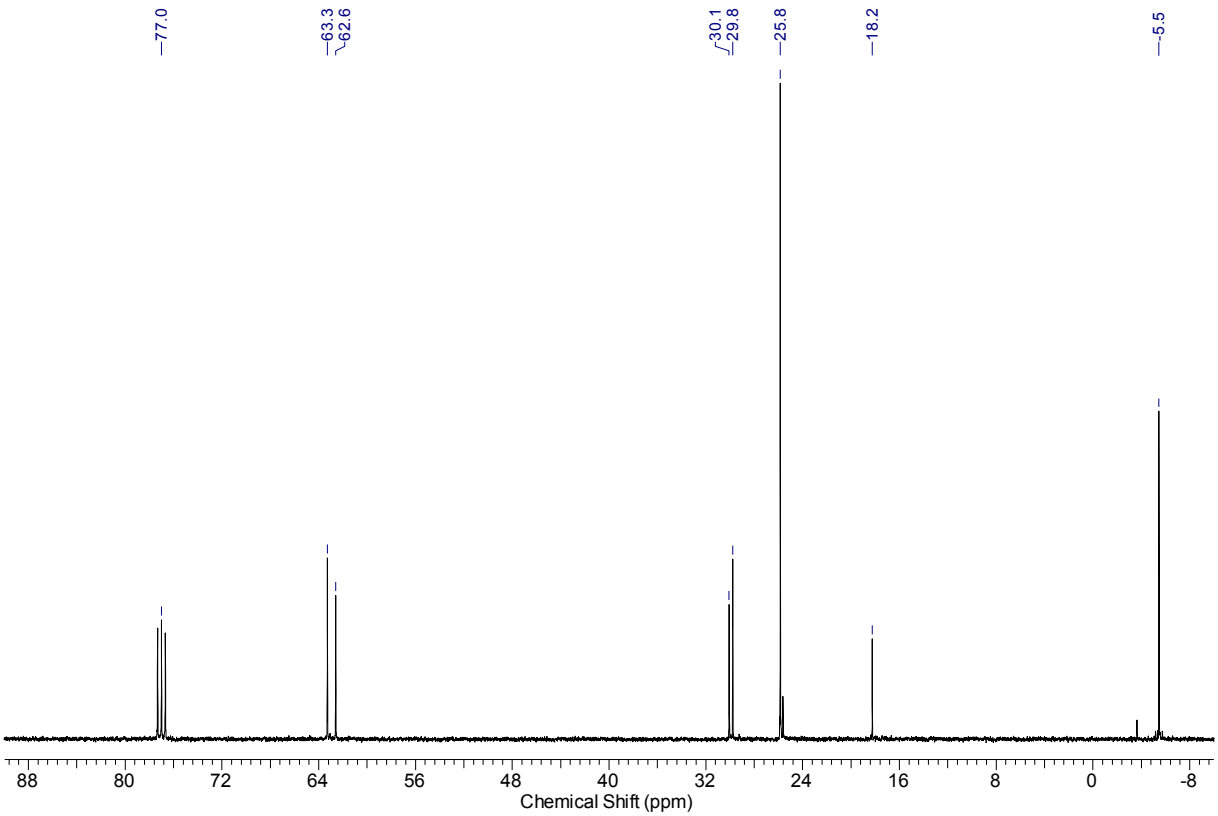
^{1}H NMR (400 MHz) spectrum of **14-19j** in $CDCl_3$.



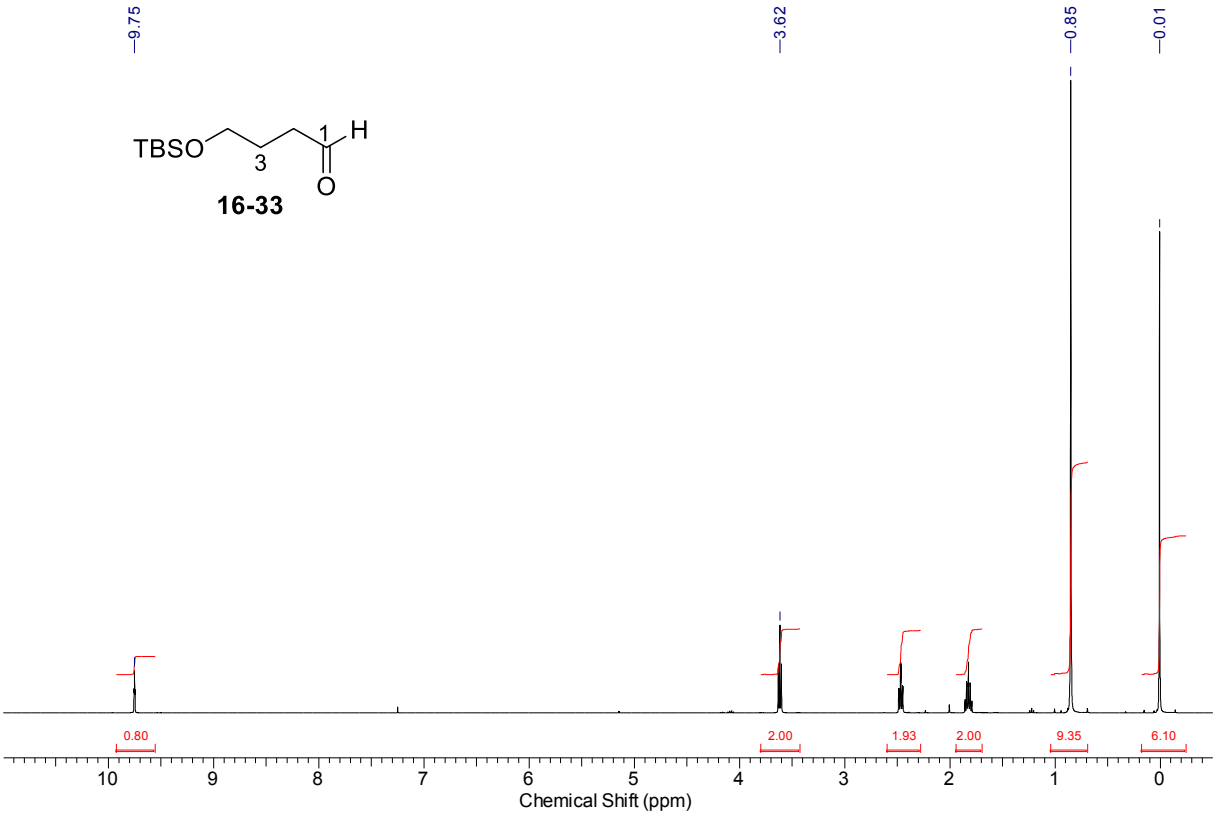
^{13}C NMR (100 MHz) spectrum of **14-19j** in $CDCl_3$.



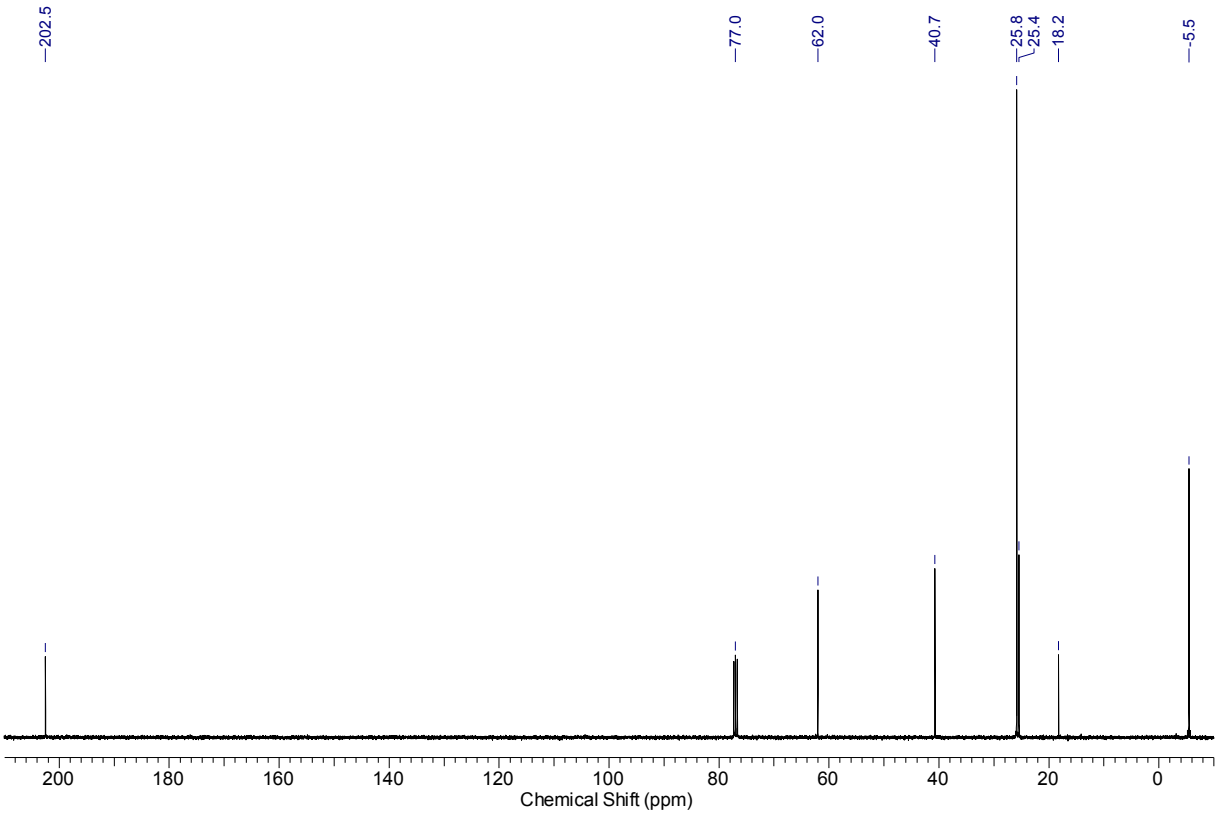
^{1}H NMR (400 MHz) spectrum of alcohol **16-32** in $CDCl_3$.



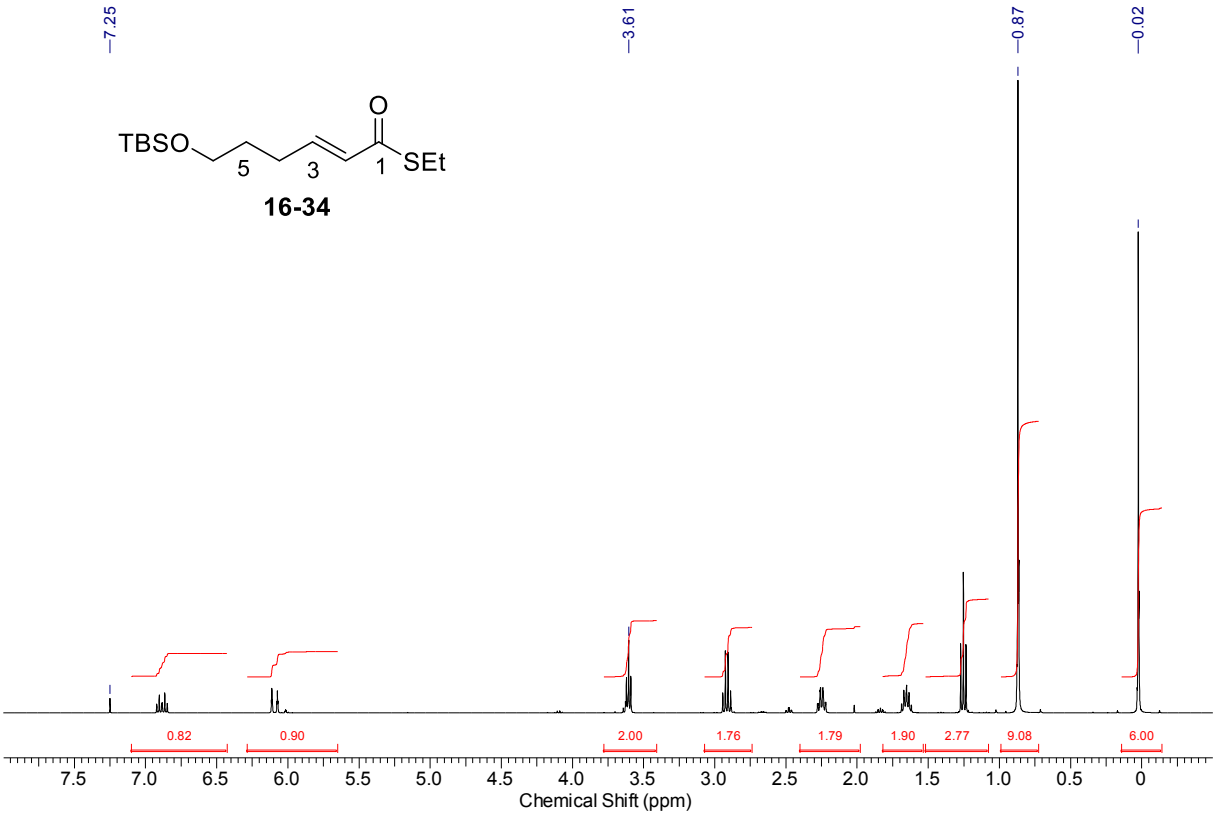
^{13}C NMR (100 MHz) spectrum of alcohol **16-32** in $CDCl_3$.



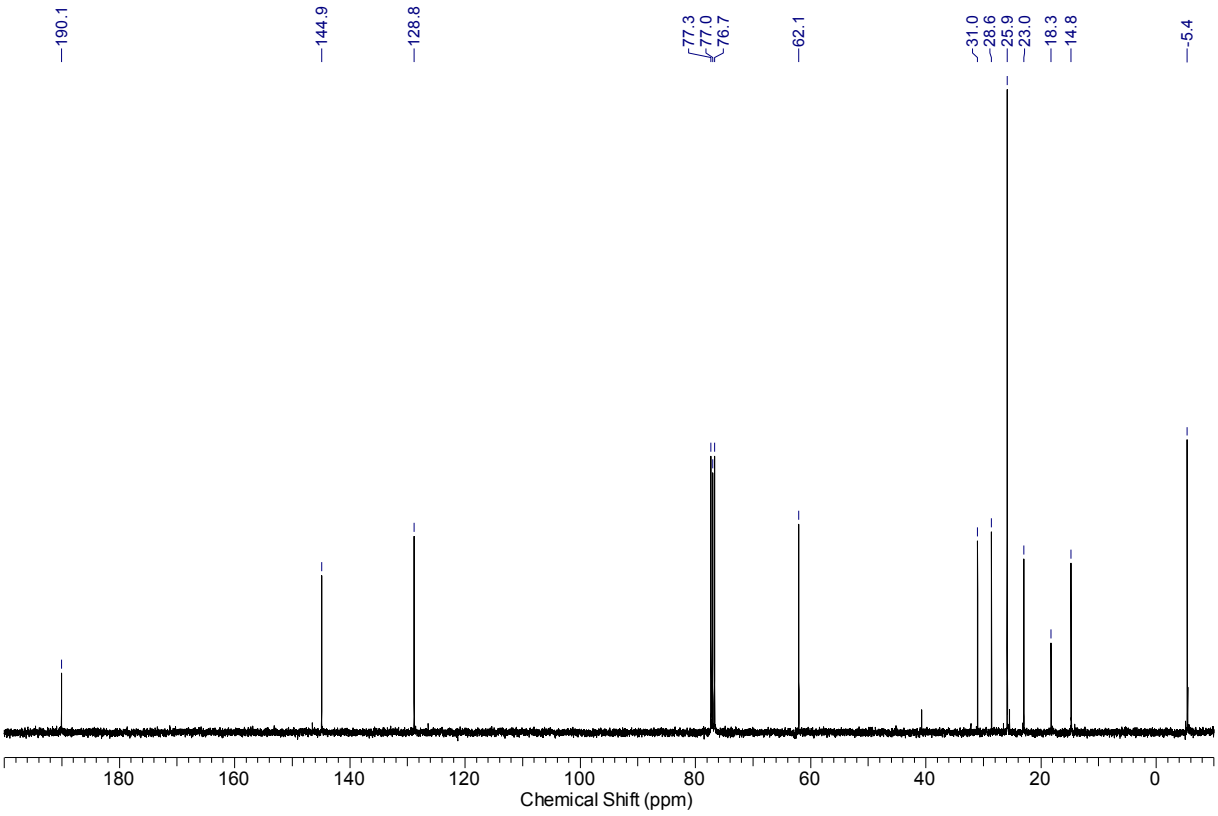
^{1}H NMR (400 MHz) spectrum of aldehyde **16-33** in $CDCl_3$.



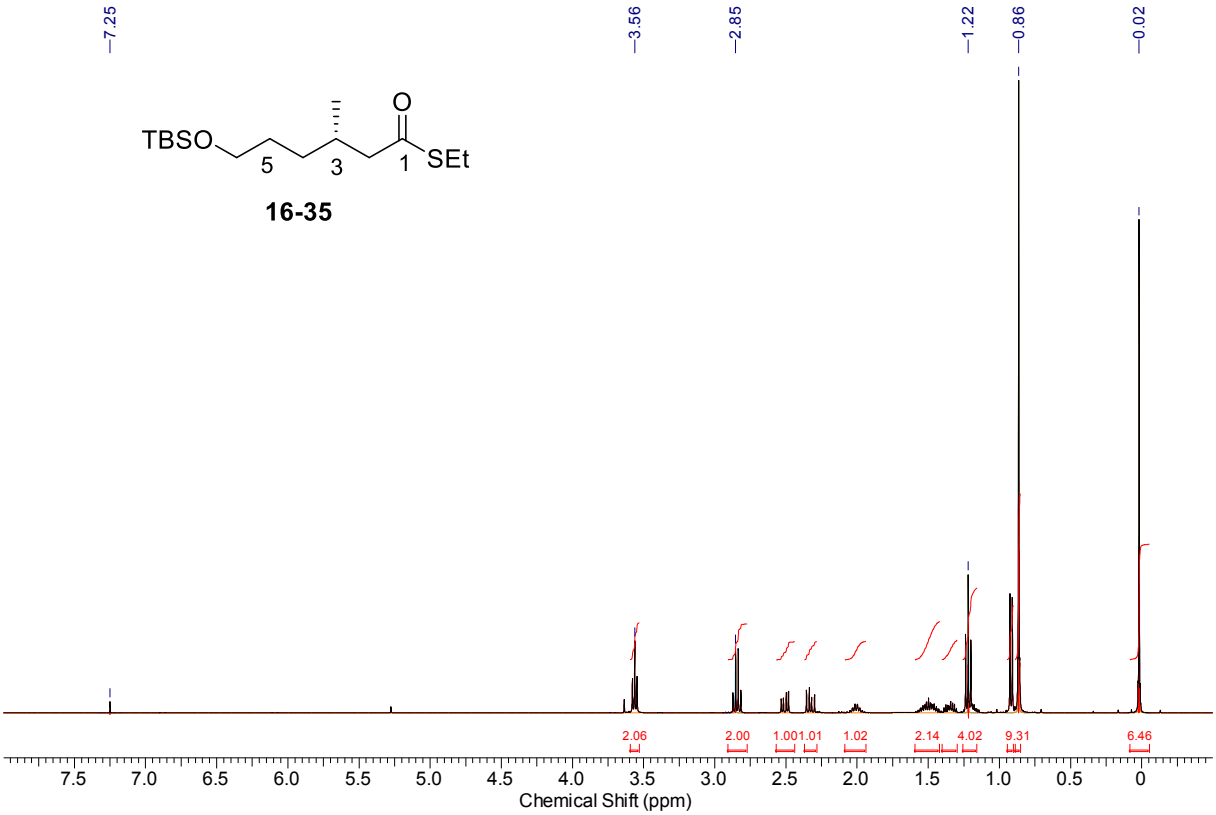
^{13}C NMR (100 MHz) spectrum of aldehyde **16-33** in $CDCl_3$.



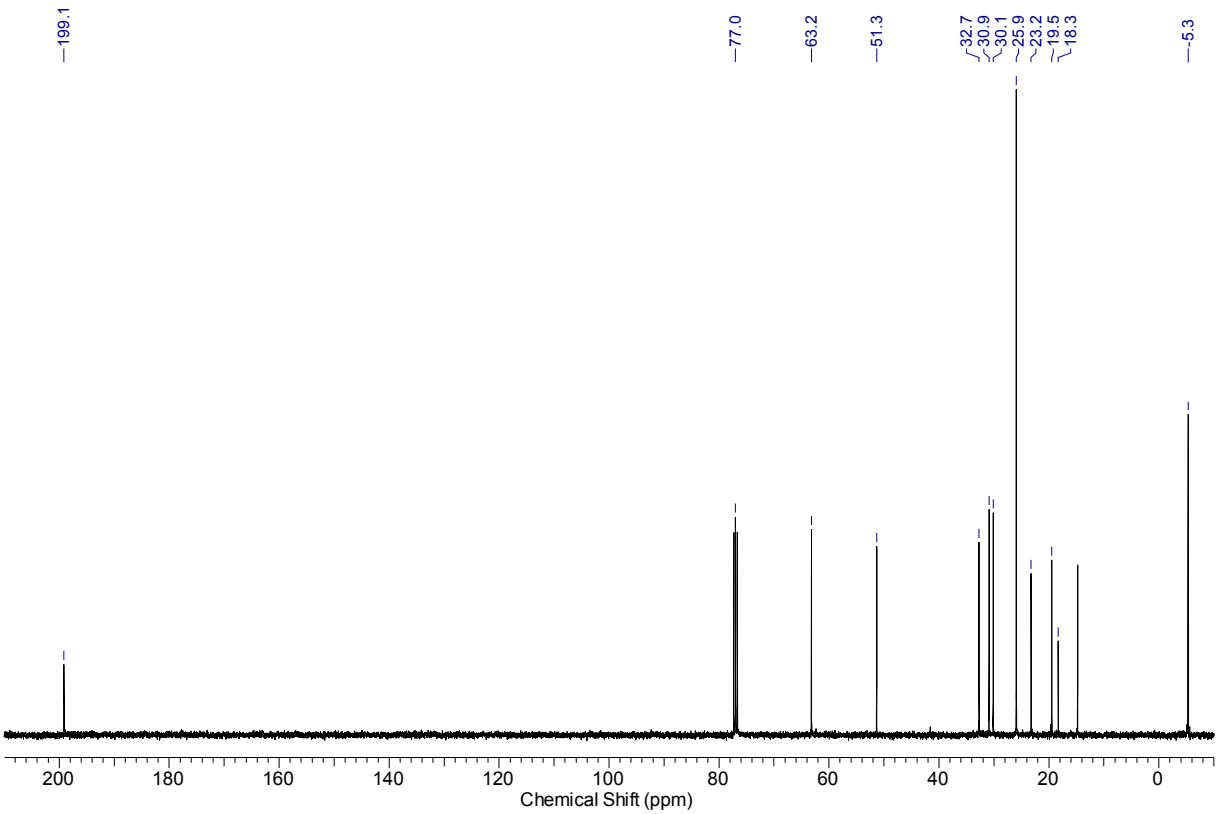
^{1}H NMR (400 MHz) spectrum of unsaturated thioester **16-34** in $CDCl_3$.



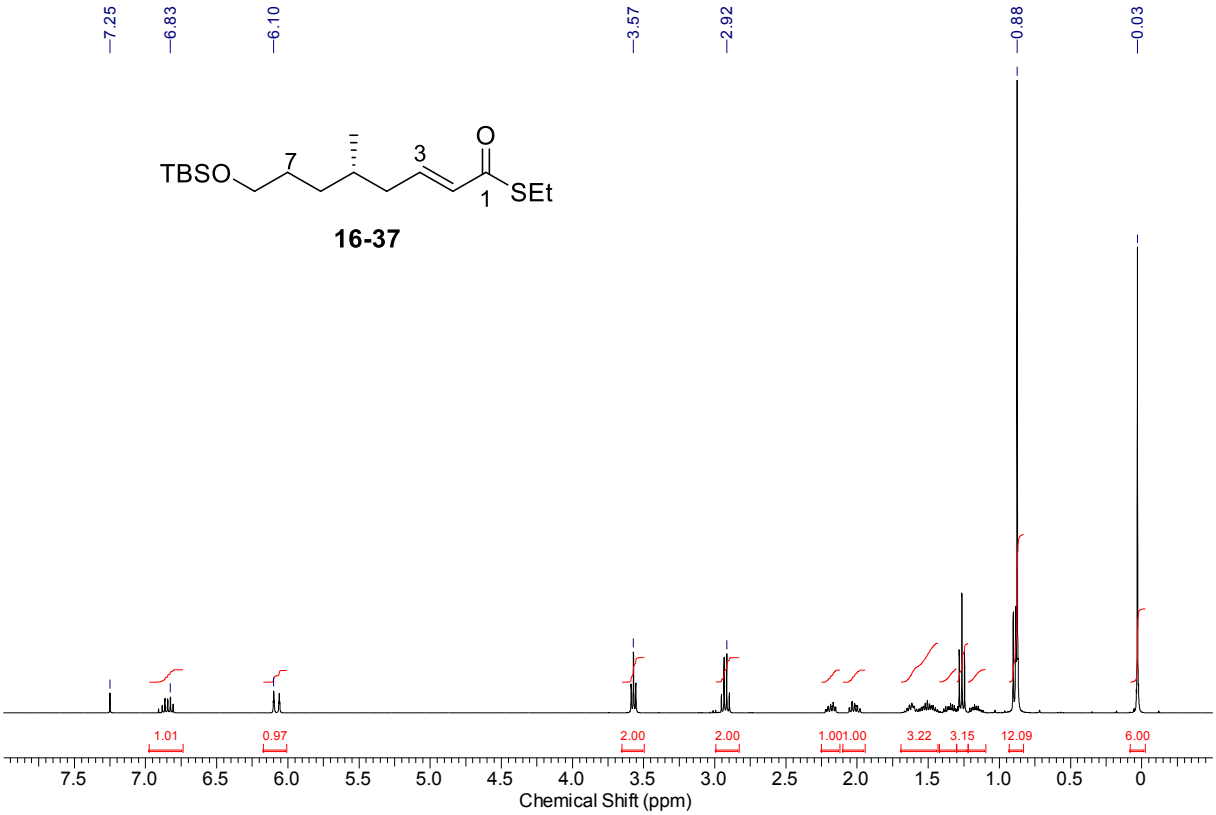
^{13}C NMR (100 MHz) spectrum of unsaturated thioester **16-34** in $CDCl_3$.



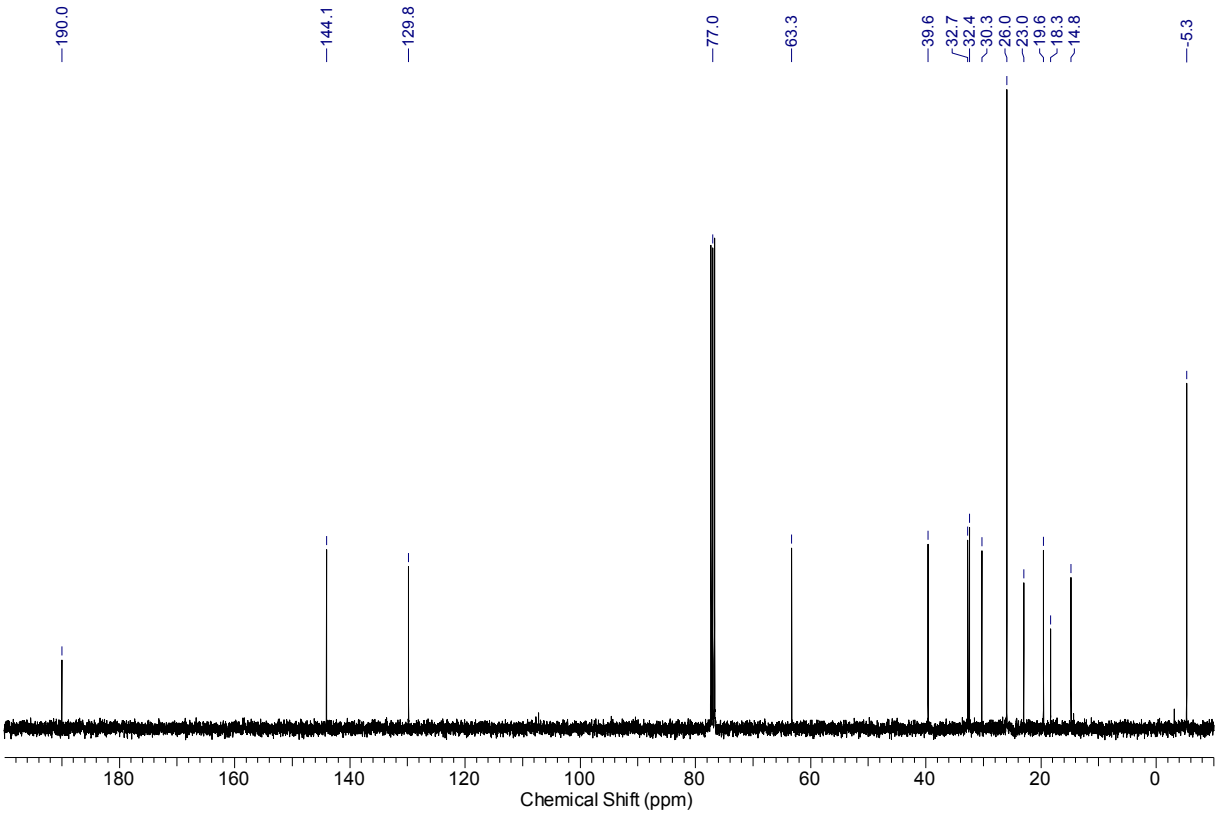
^{1}H NMR (400 MHz) spectrum of thioester **16-35** in $CDCl_3$.



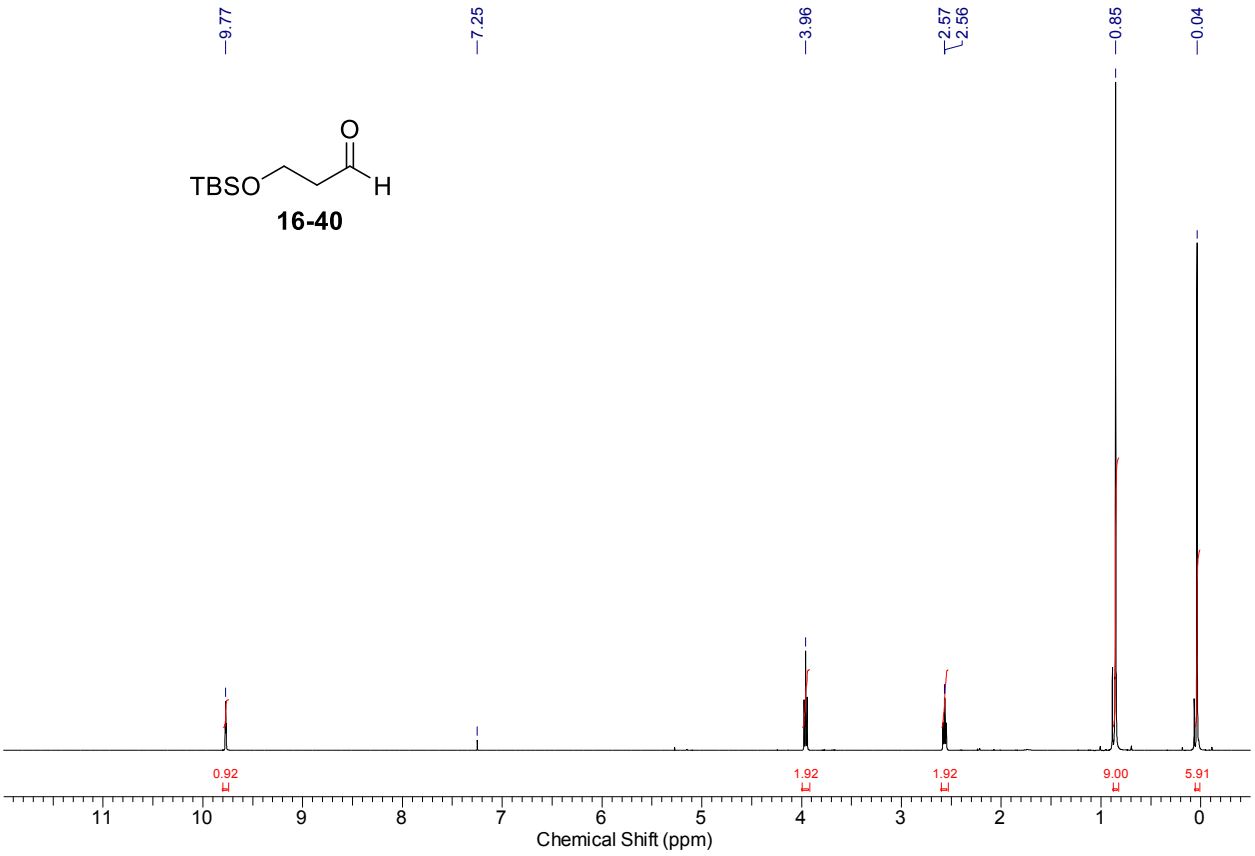
^{13}C NMR (100 MHz) spectrum of thioester **16-35** in $CDCl_3$.



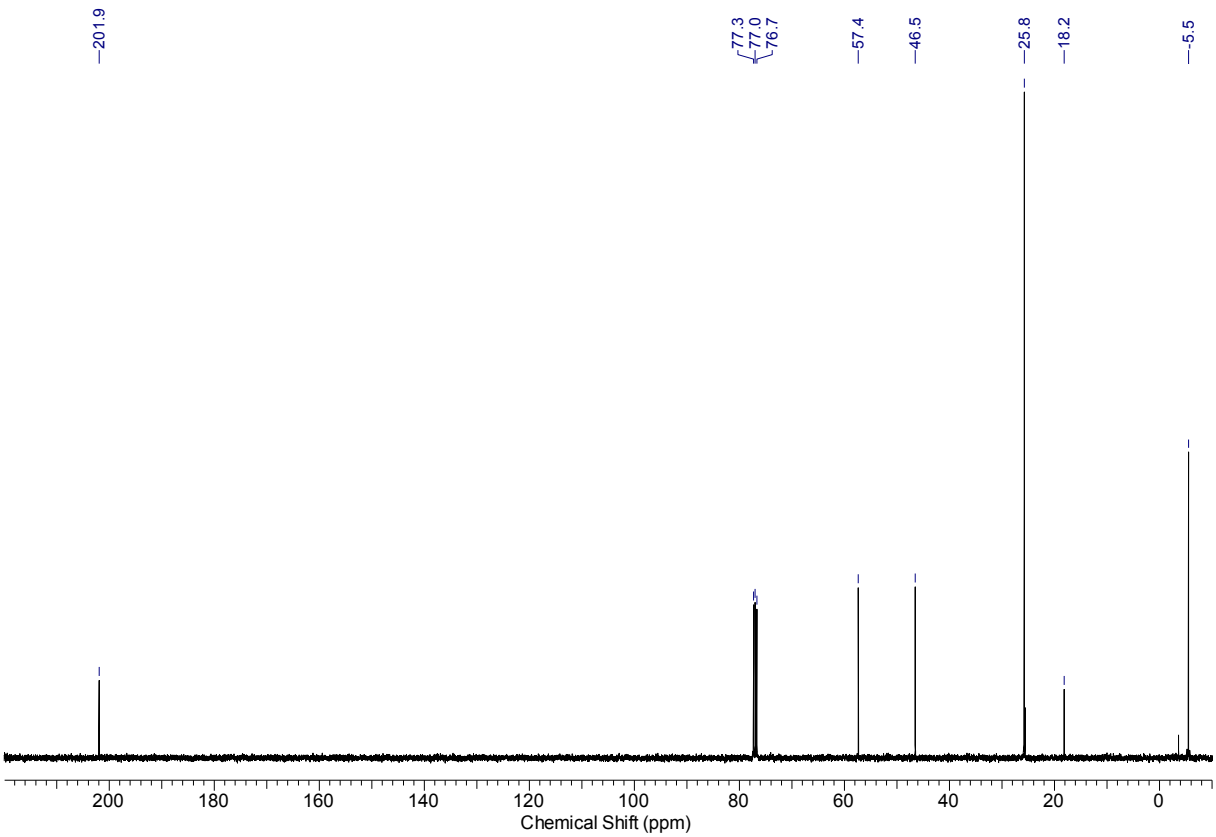
^{1}H NMR (400 MHz) spectrum of unsaturated thioester **16-37** in $CDCl_3$.



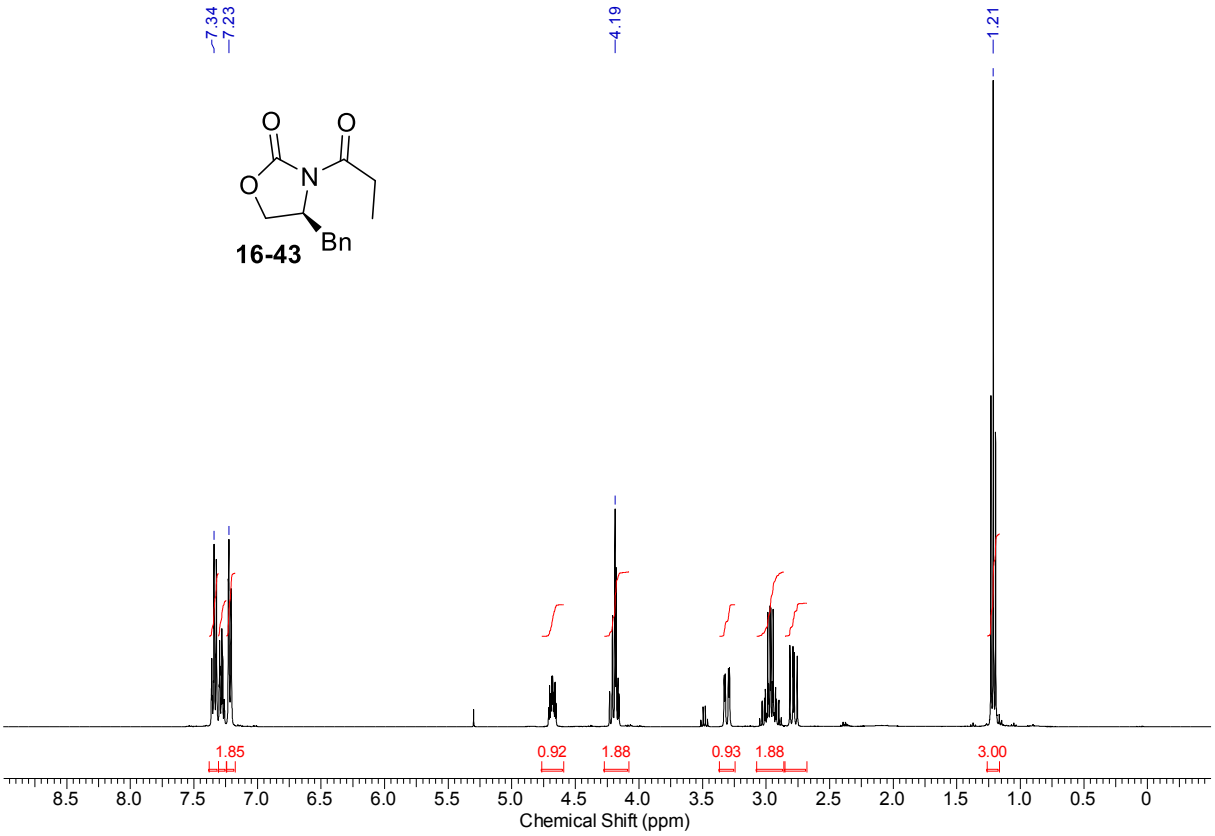
^{13}C NMR (100 MHz) spectrum of unsaturated thioester **16-37** in $CDCl_3$.



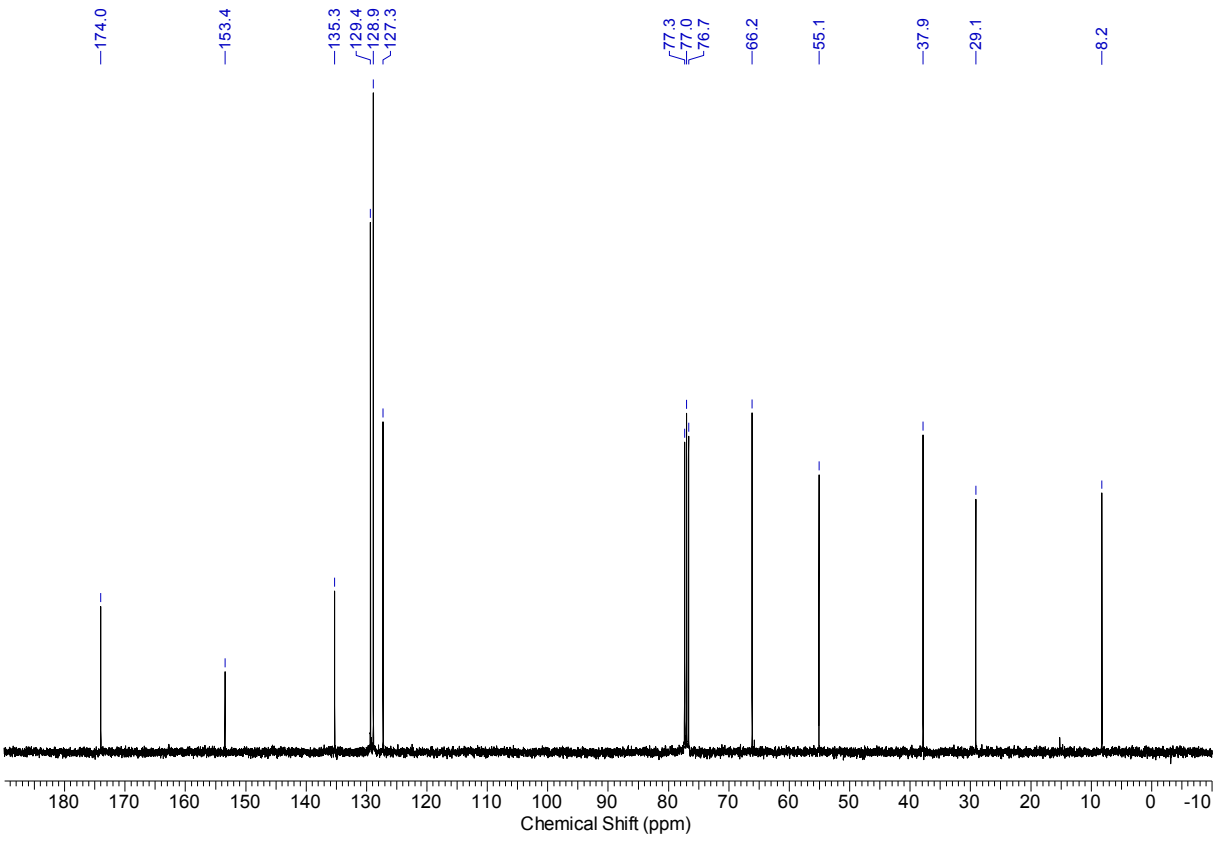
^{1}H NMR (400 MHz) spectrum of aldehyde **16-40** in $CDCl_3$.



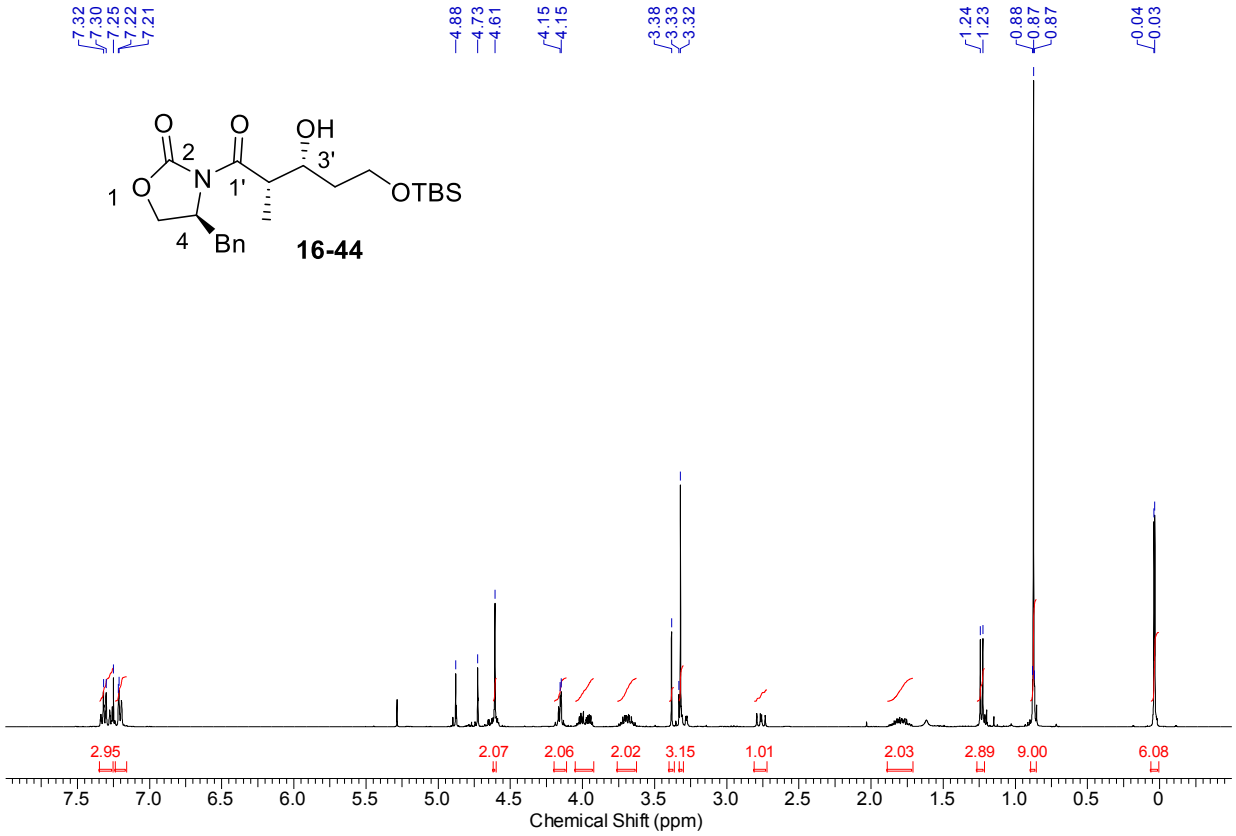
^{13}C NMR (100 MHz) spectrum of aldehyde **16-40** in $CDCl_3$.



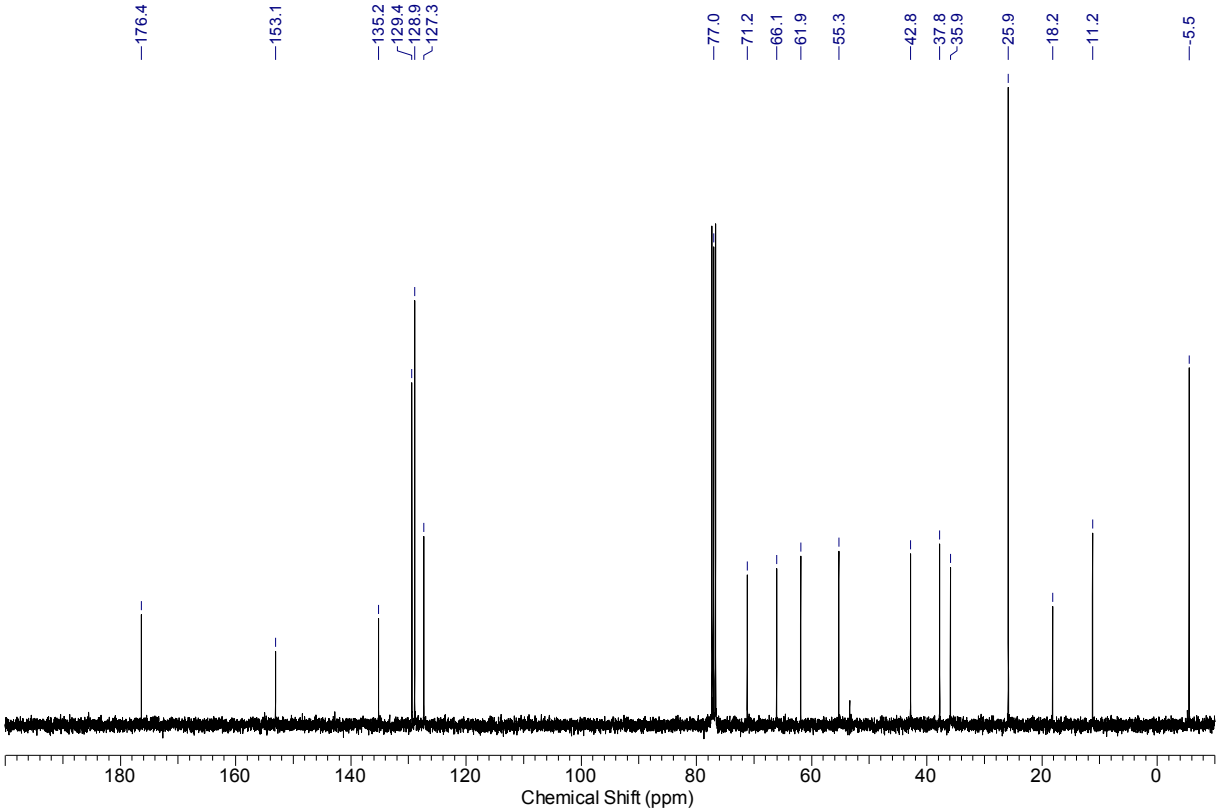
^{1}H NMR (400 MHz) spectrum of oxazolidinone **16-43** in $CDCl_3$.



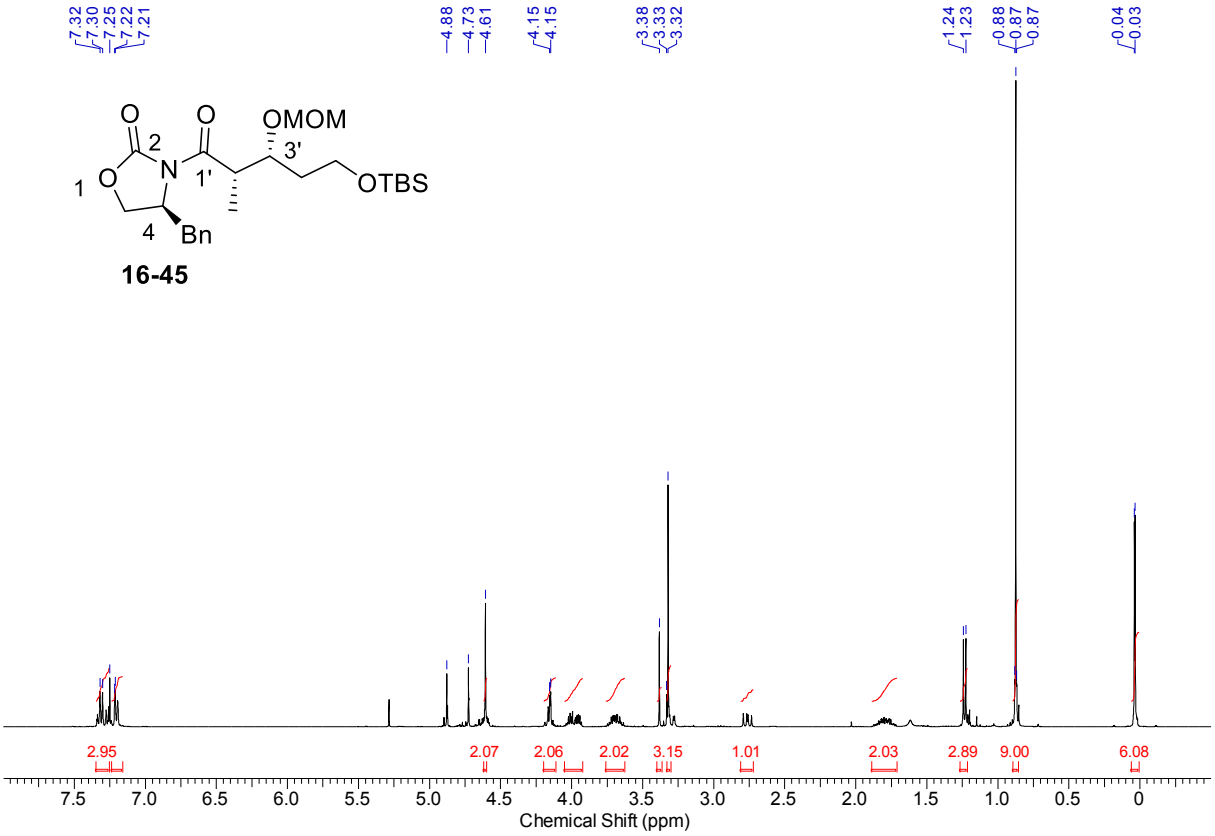
^{13}C NMR (100 MHz) spectrum of oxazolidinone **16-43** in $CDCl_3$.



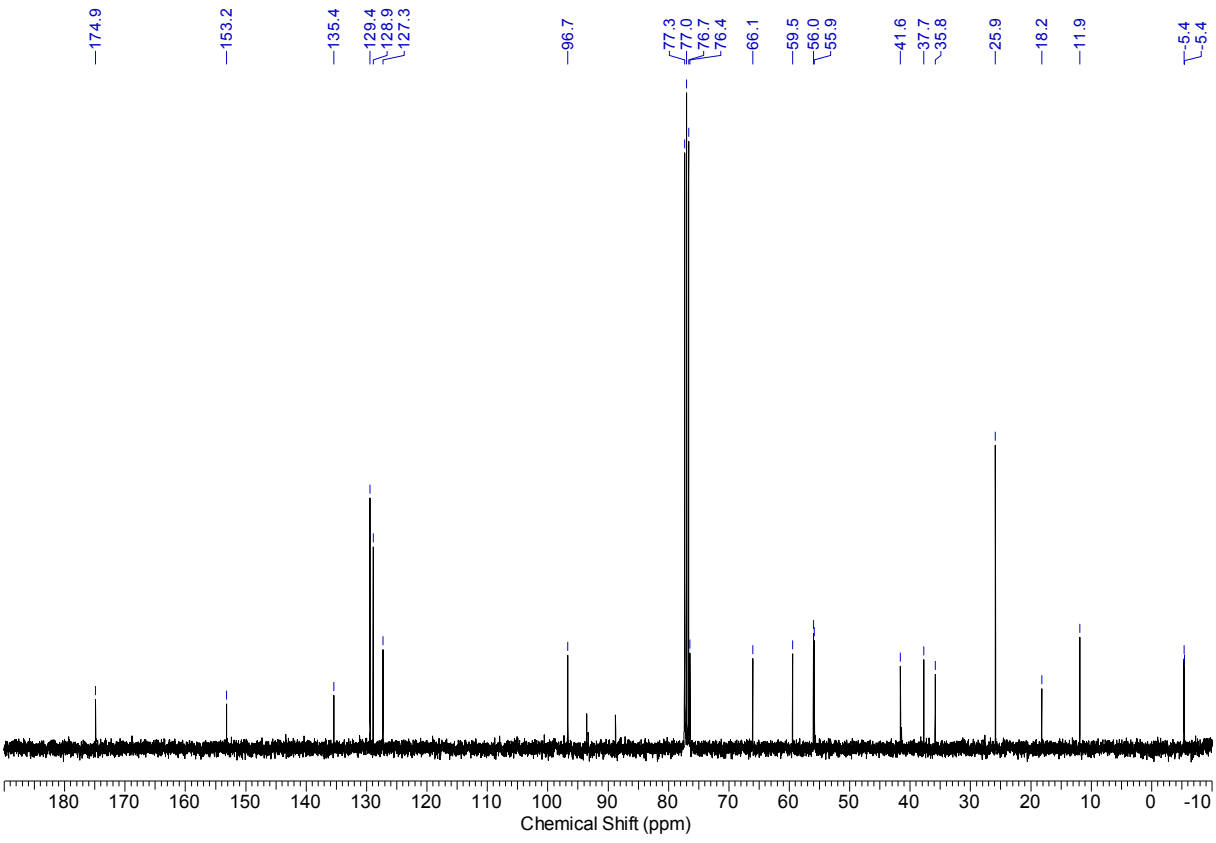
^{1}H NMR (400 MHz) spectrum of aldol-adduct **16-44** in $CDCl_3$.



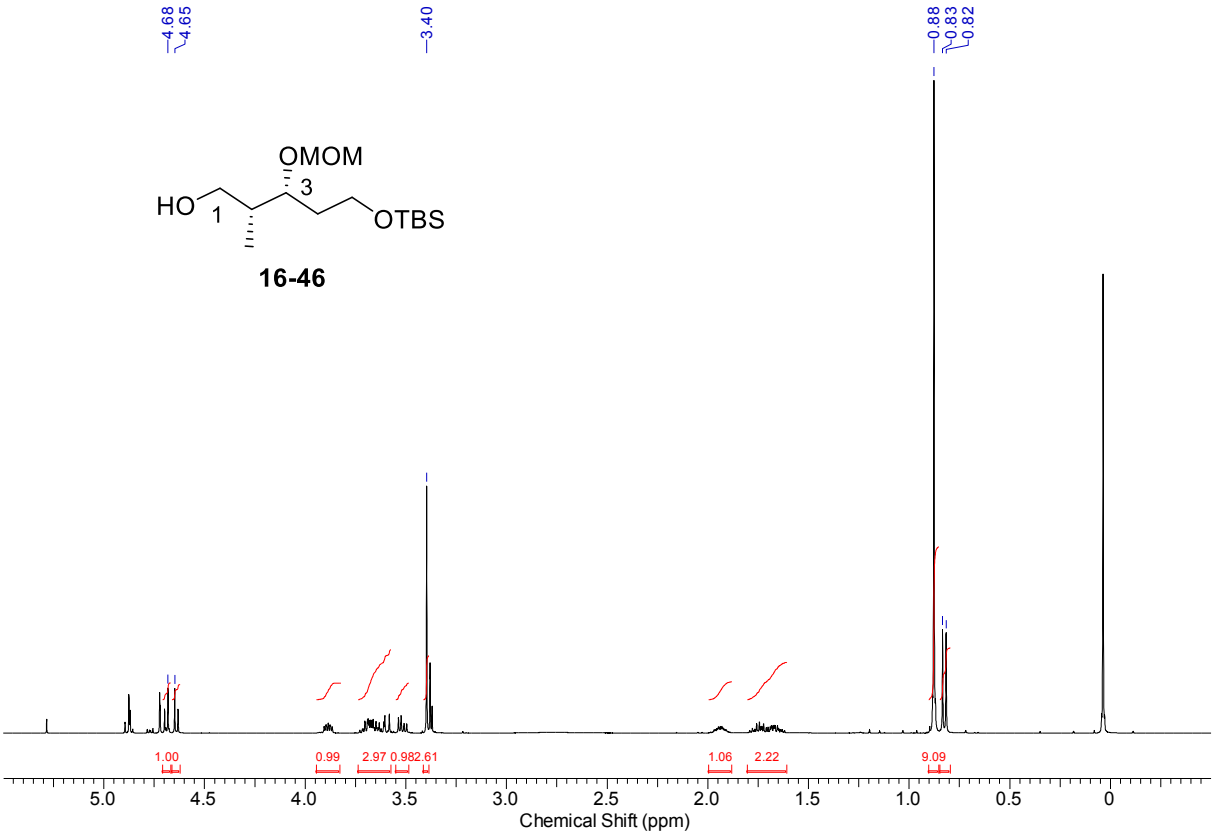
^{13}C NMR (100 MHz) spectrum of aldol-adduct **16-44** in $CDCl_3$.



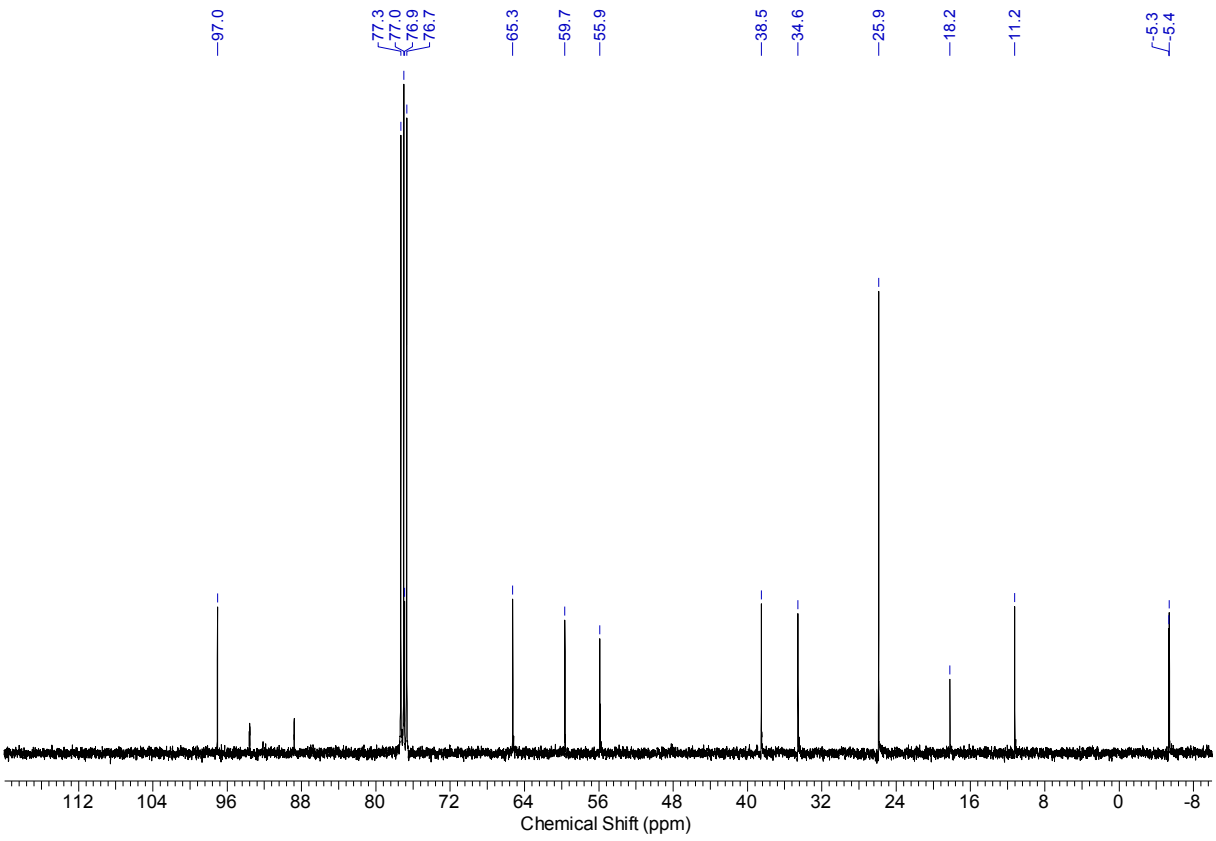
^{1}H NMR (400 MHz) spectrum of adduct-ether **16-45** in $CDCl_3$.



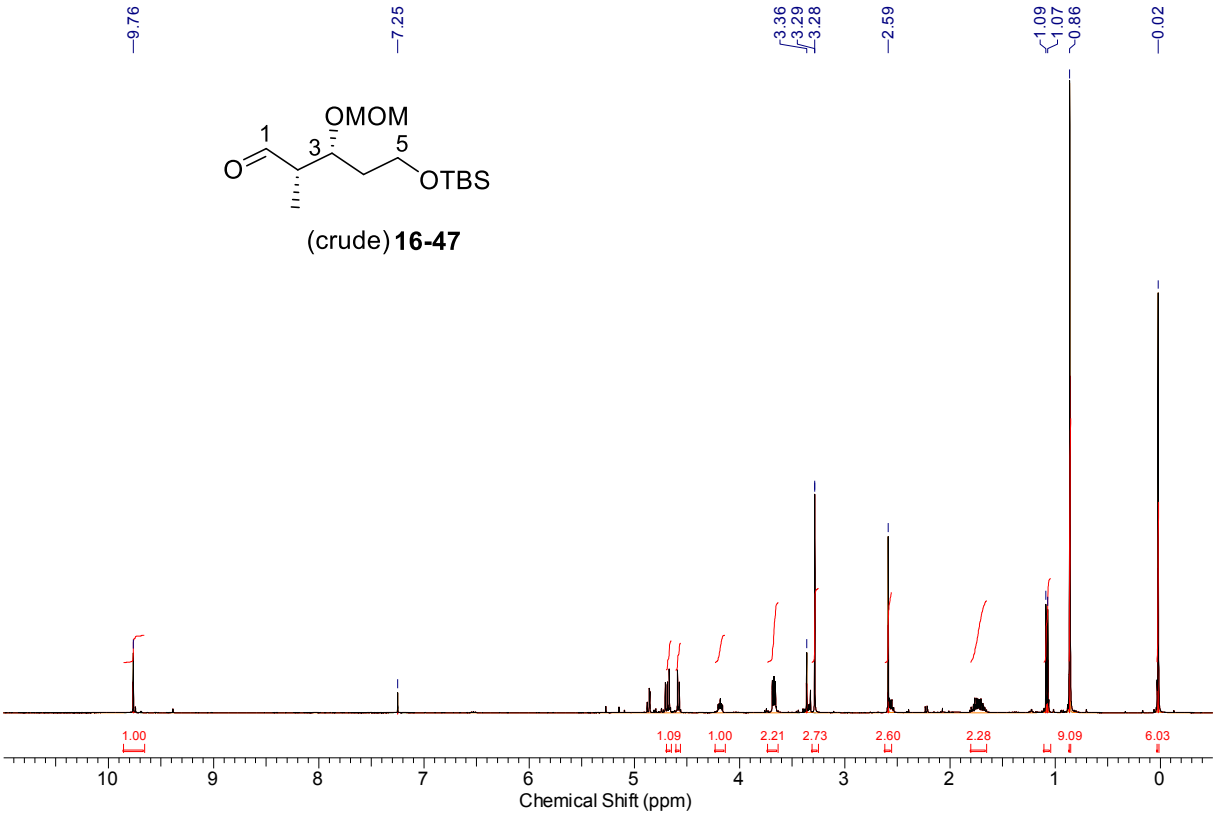
^{13}C NMR (100 MHz) spectrum of adduct-ether **16-45** in $CDCl_3$.



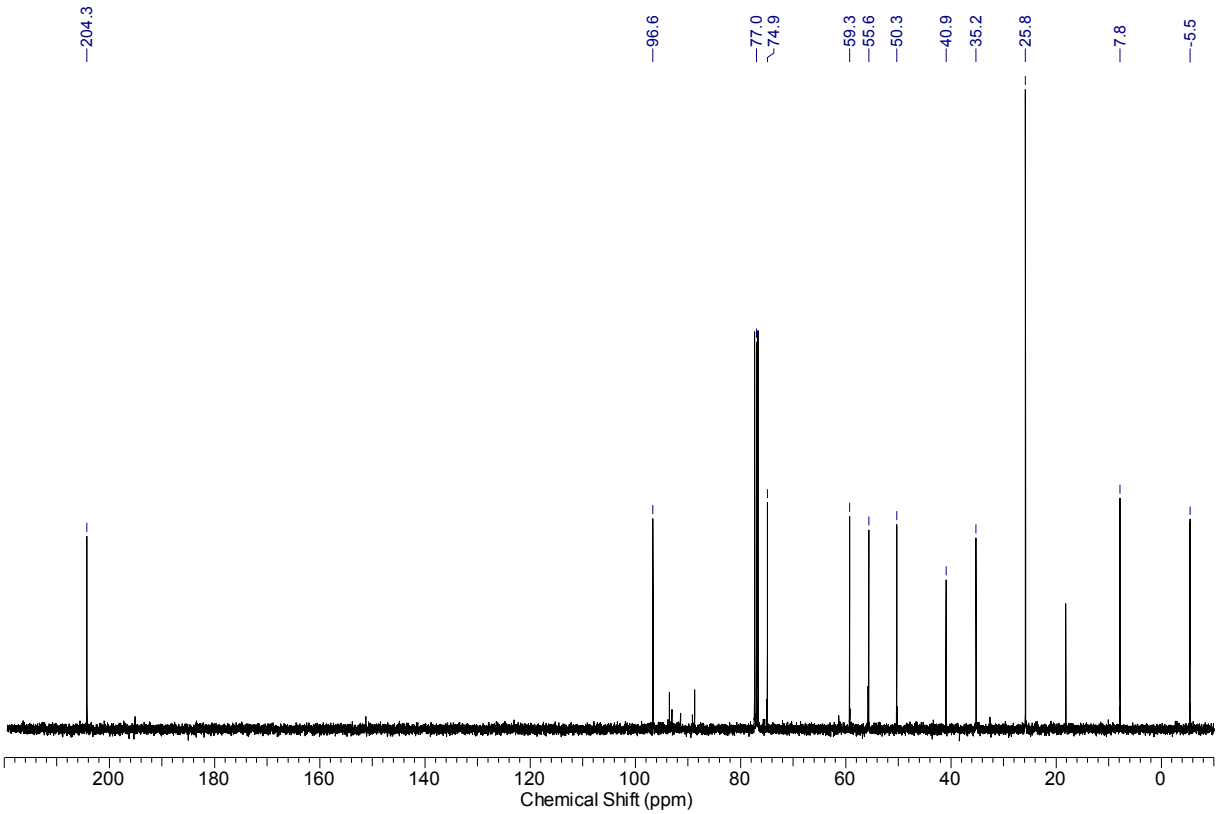
^{1}H NMR (400 MHz) spectrum of alcohol **16-46** in $CDCl_3$.



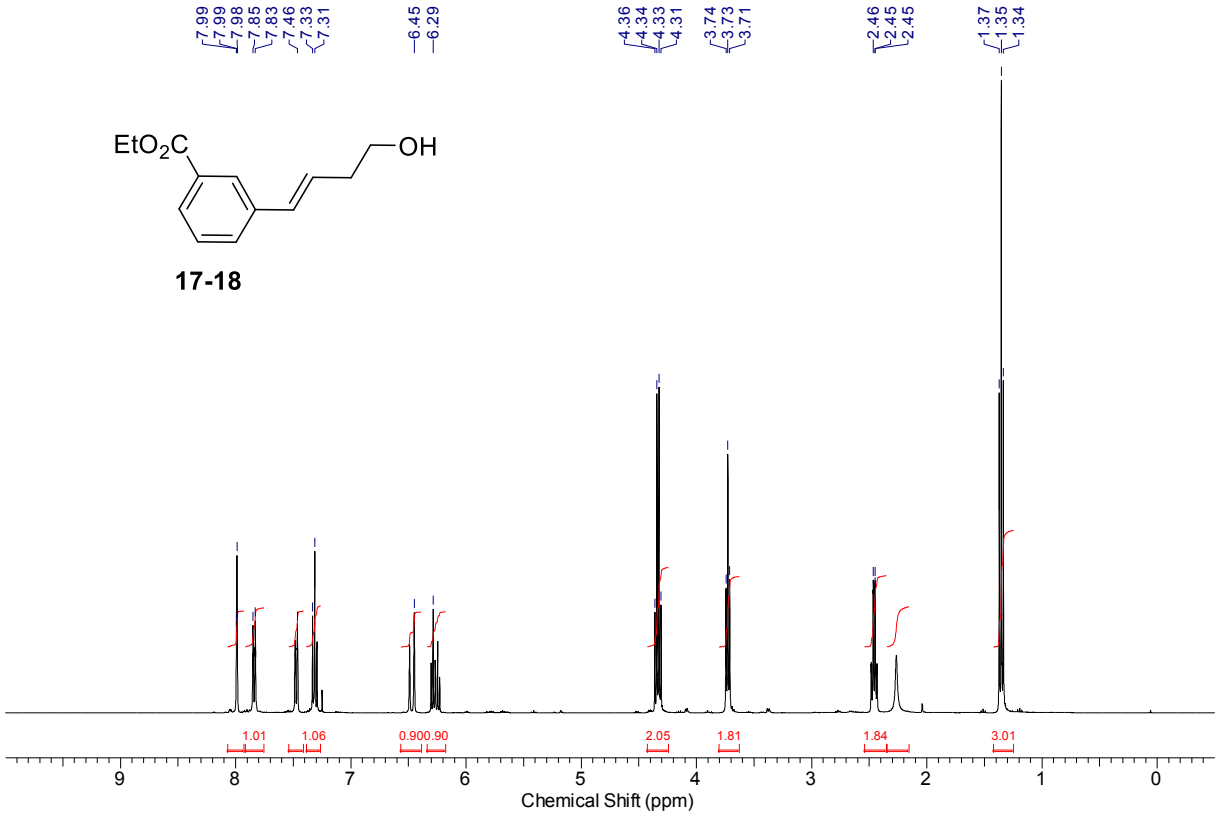
^{13}C NMR (100 MHz) spectrum of alcohol **16-46** in $CDCl_3$.



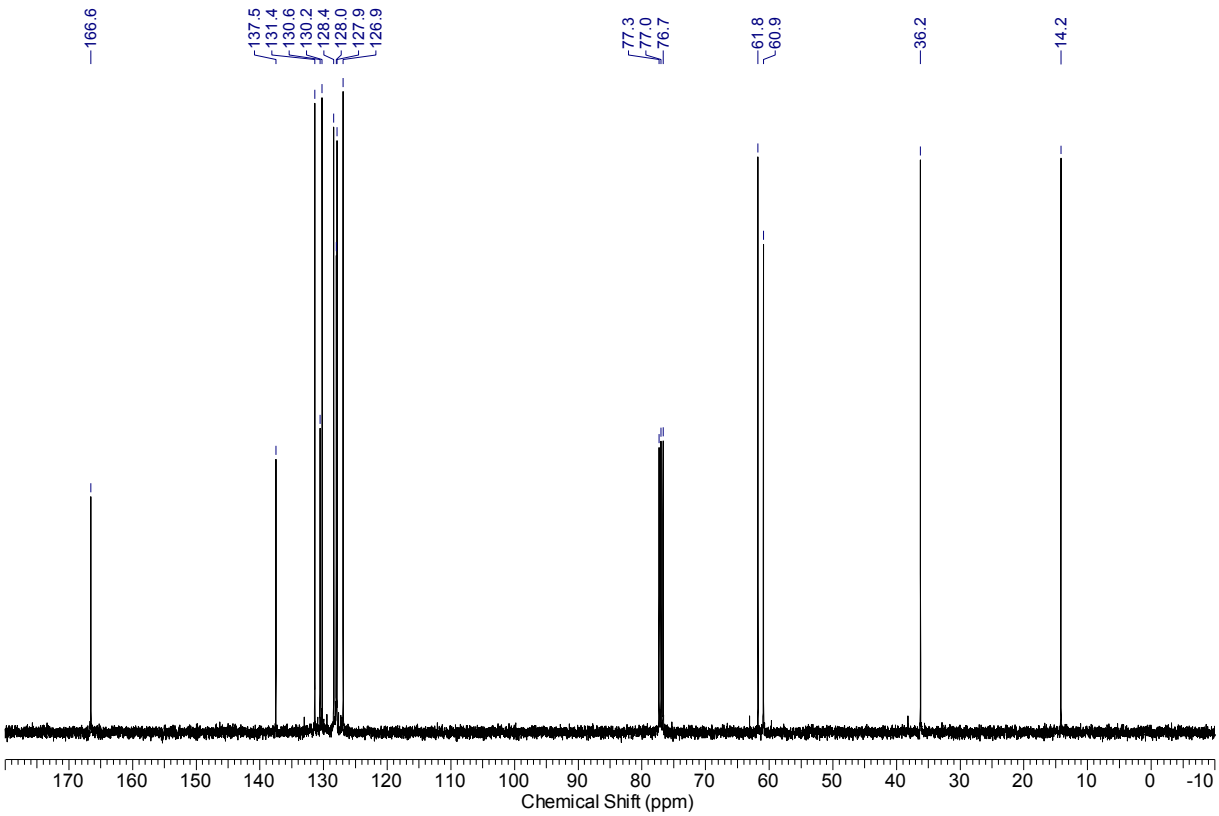
^{1}H NMR (400 MHz) spectrum of crude aldehyde **16-47** in $CDCl_3$.



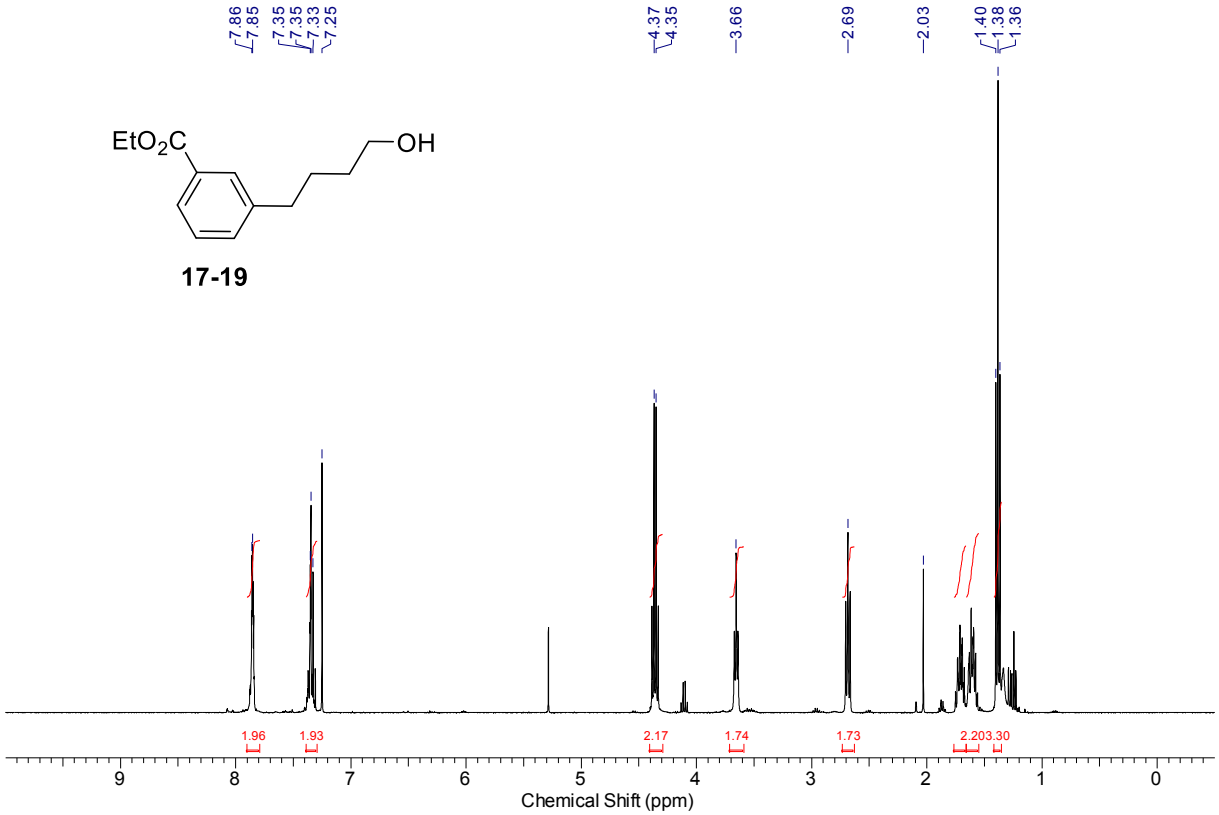
^{13}C NMR (100 MHz) spectrum of crude aldehyde **16-47** in $CDCl_3$.



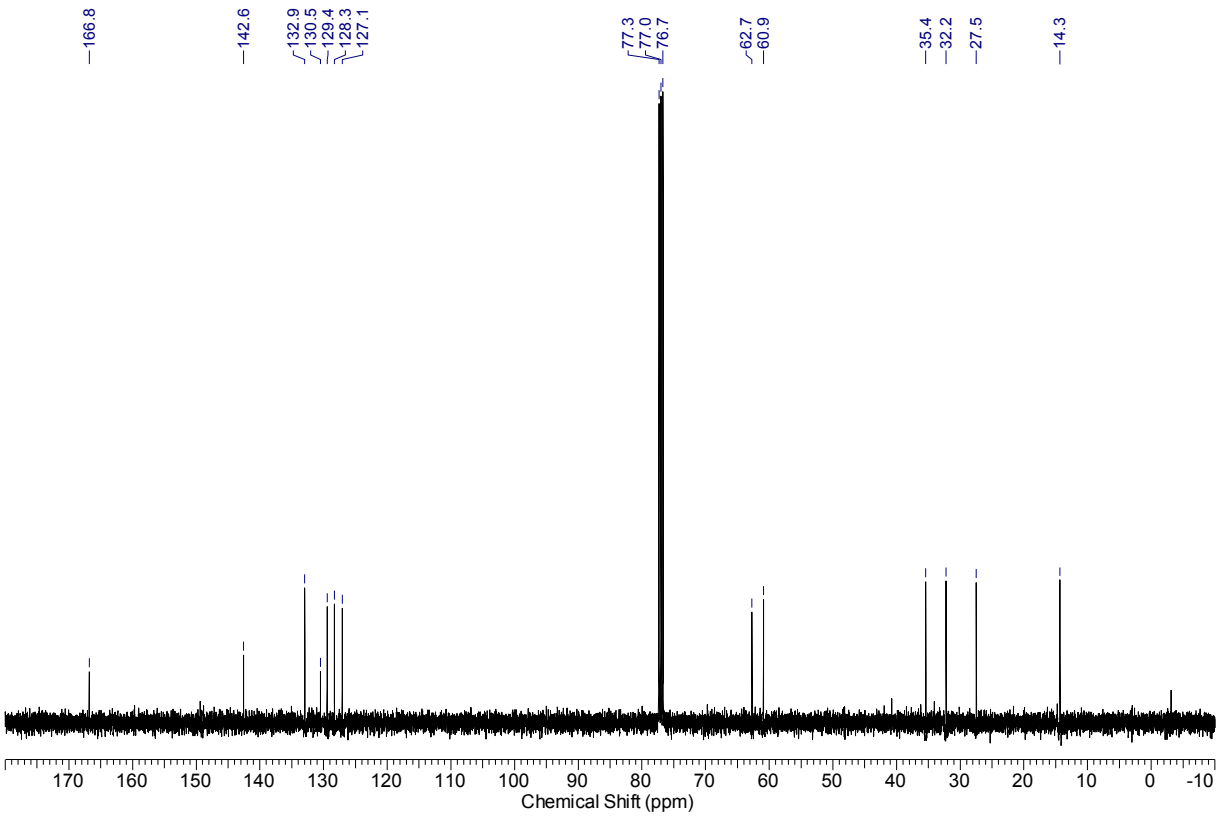
^{1}H NMR (400 MHz) spectrum of alkenol **17-18** in $CDCl_3$.



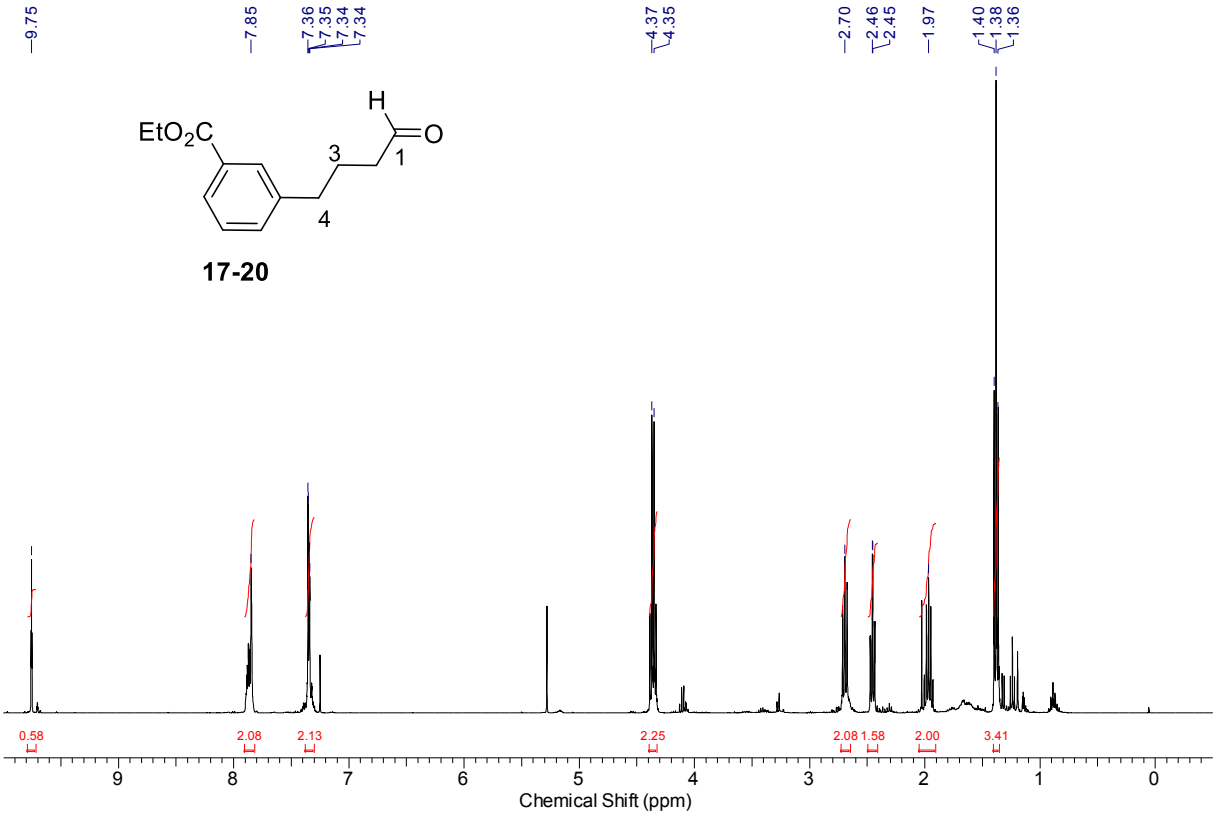
^{13}C NMR (400 MHz) spectrum of alkenol **17-18** in $CDCl_3$.



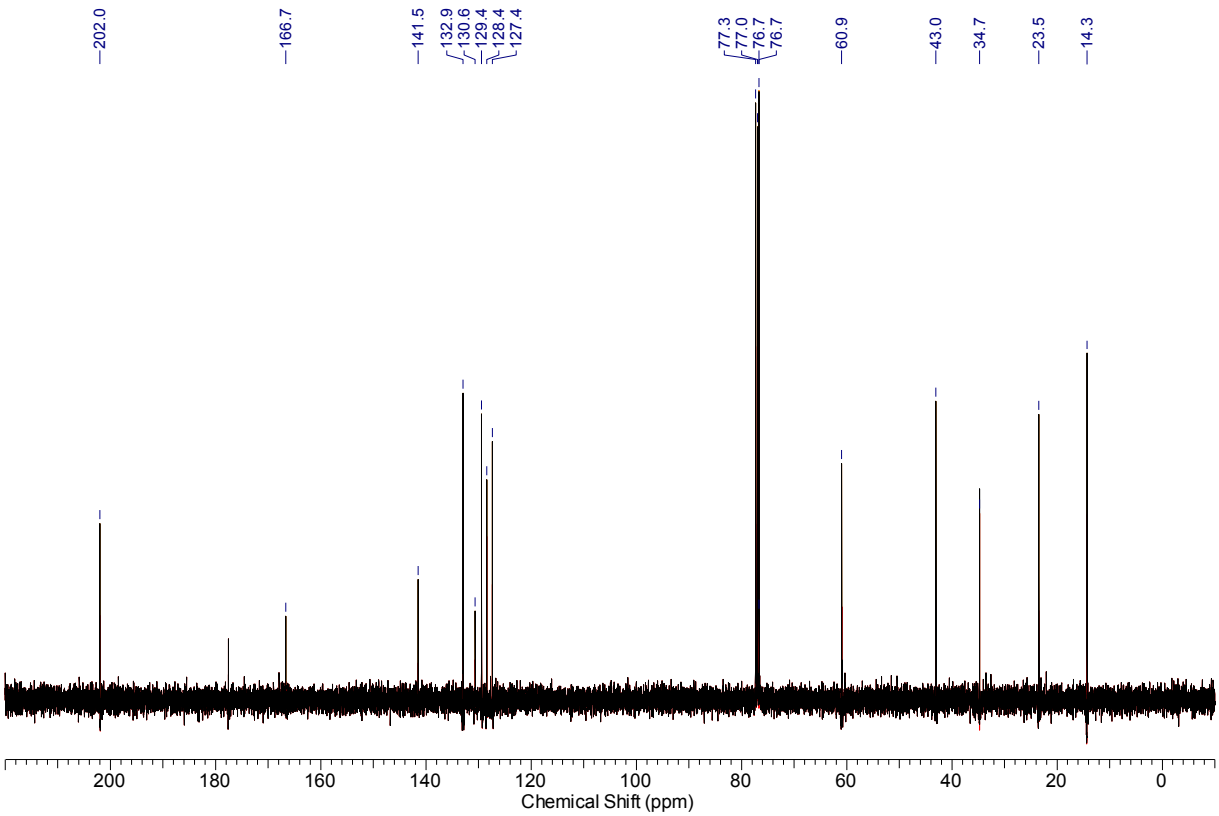
^{1}H NMR (400 MHz) spectrum of alcohol **17-19** in $CDCl_3$.



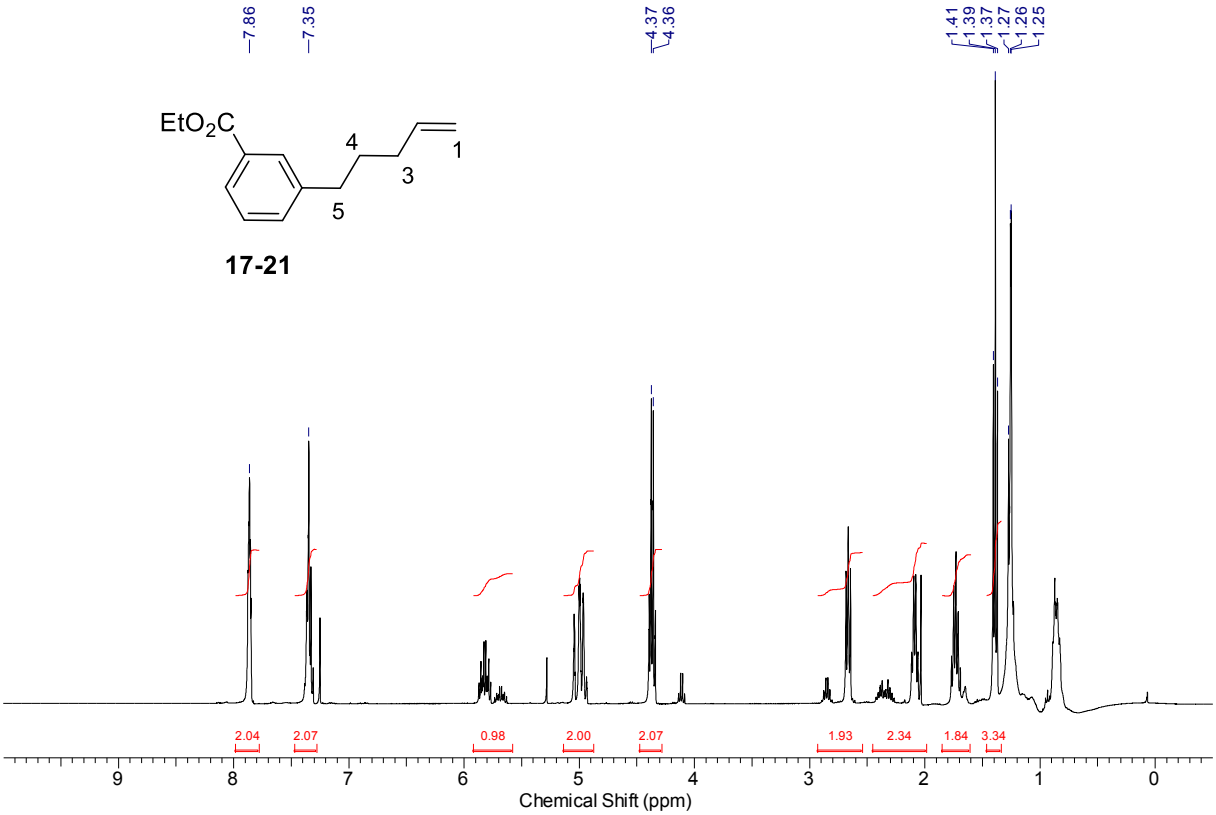
^{13}C NMR (100 MHz) spectrum of alcohol **17-19** in $CDCl_3$.



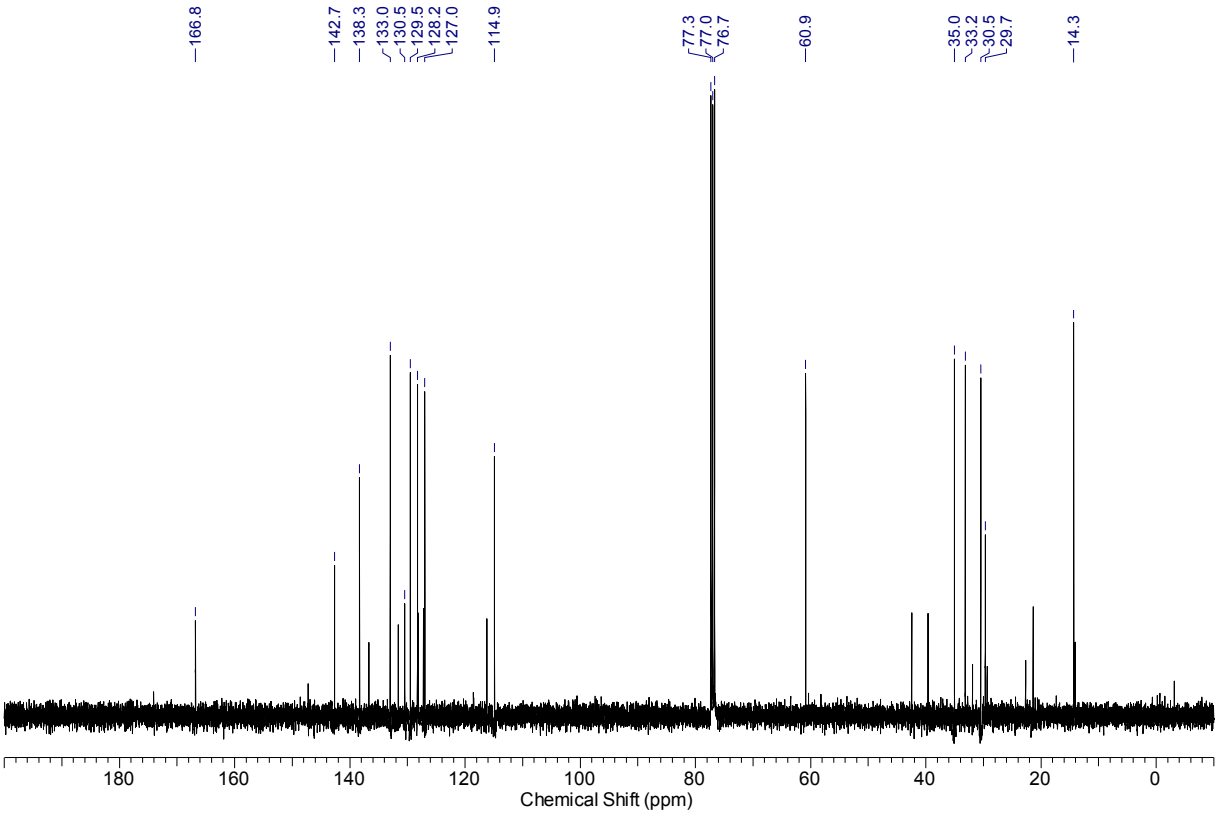
^{1}H NMR (400 MHz) spectrum of aldehyde **17-20** in $CDCl_3$.



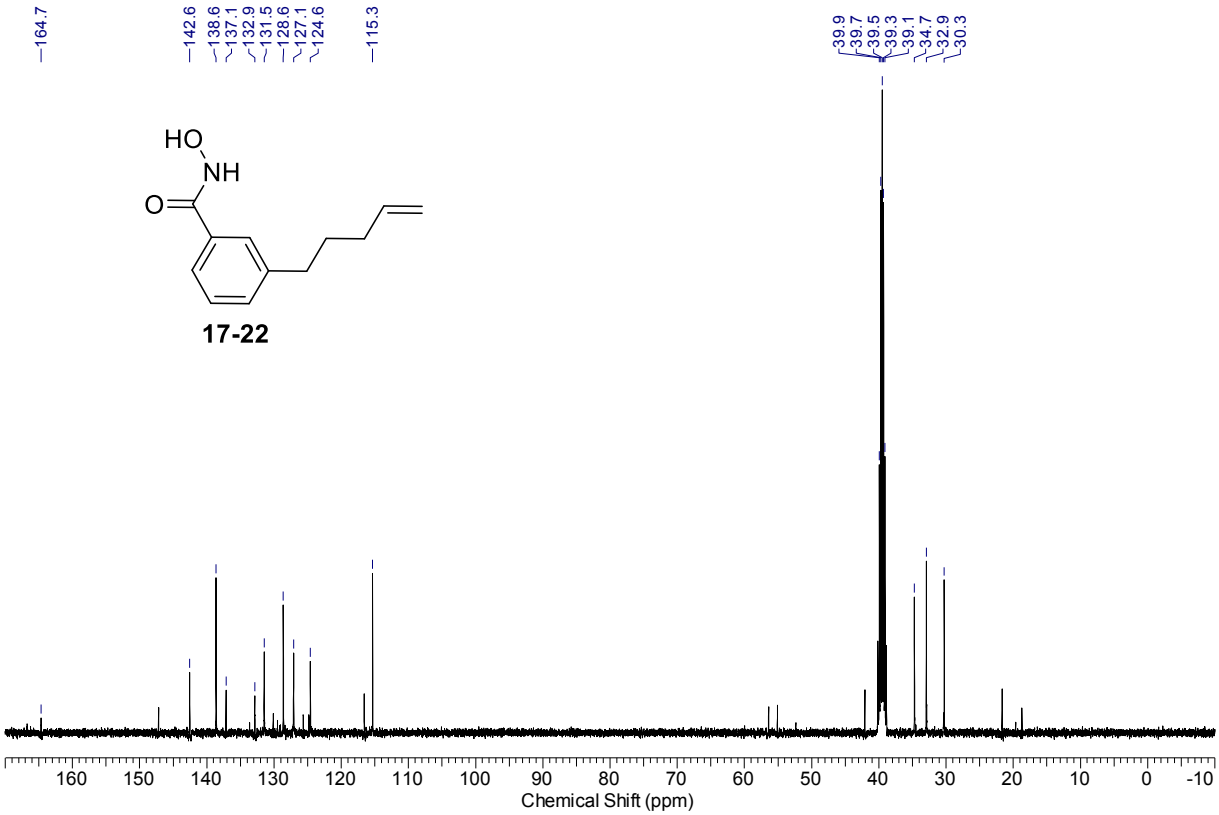
^{13}C NMR (100 MHz) spectrum of aldehyde **17-20** in $CDCl_3$.



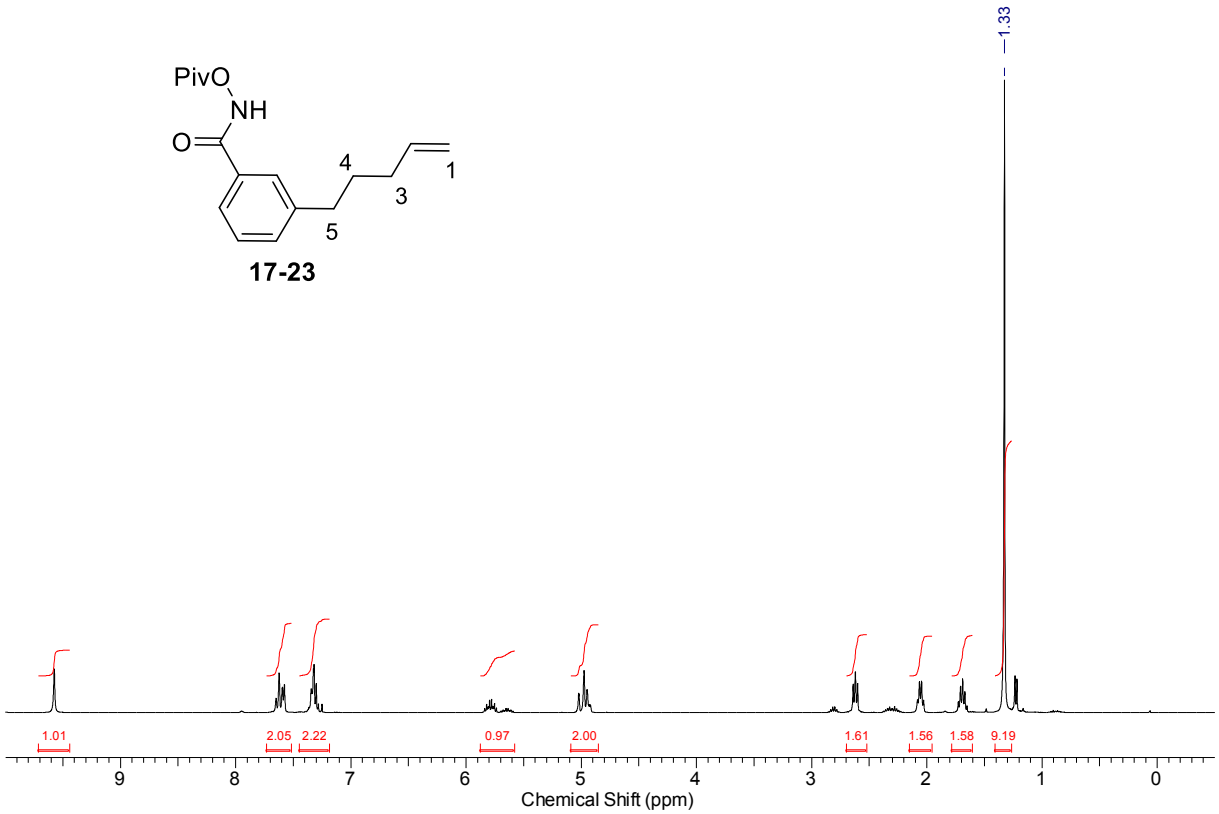
^{1}H NMR (400 MHz) spectrum of alkene **17-21** in $CDCl_3$.



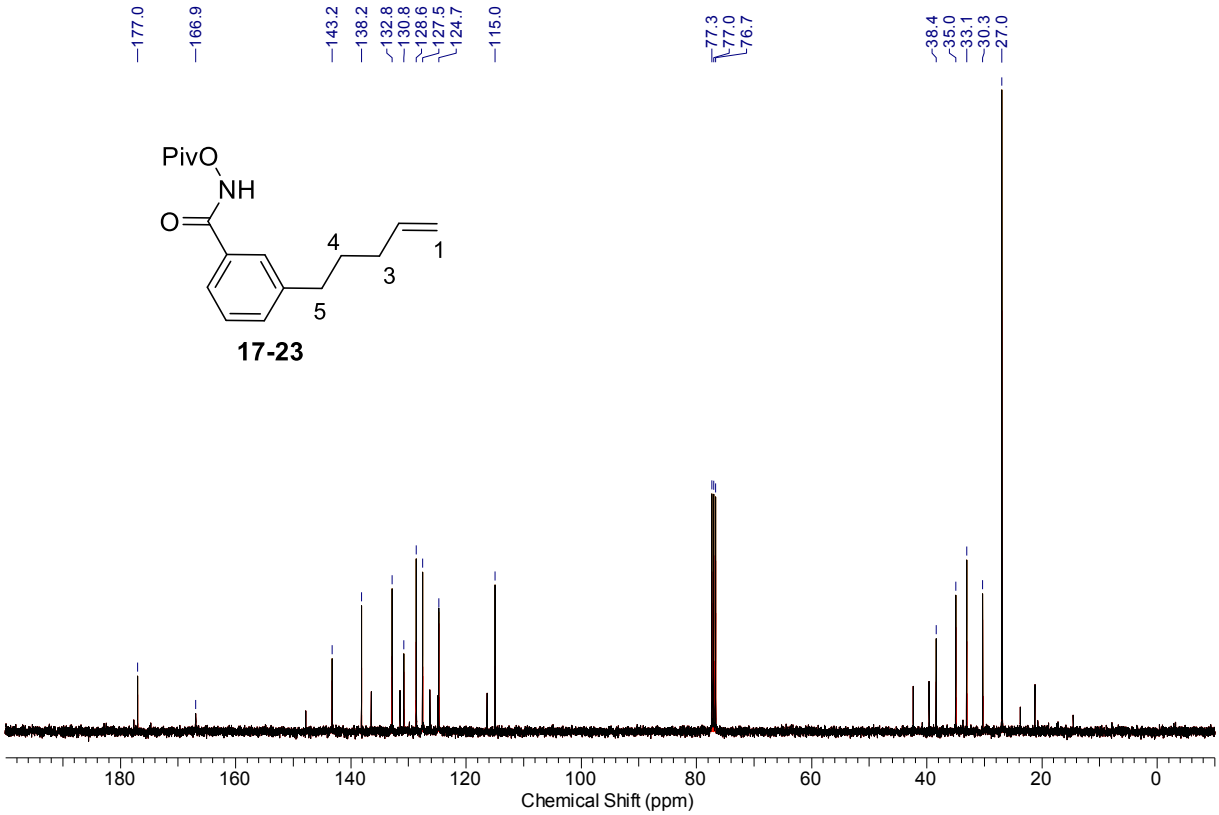
^{13}C NMR (100 MHz) spectrum of alkene **17-21** in $CDCl_3$.



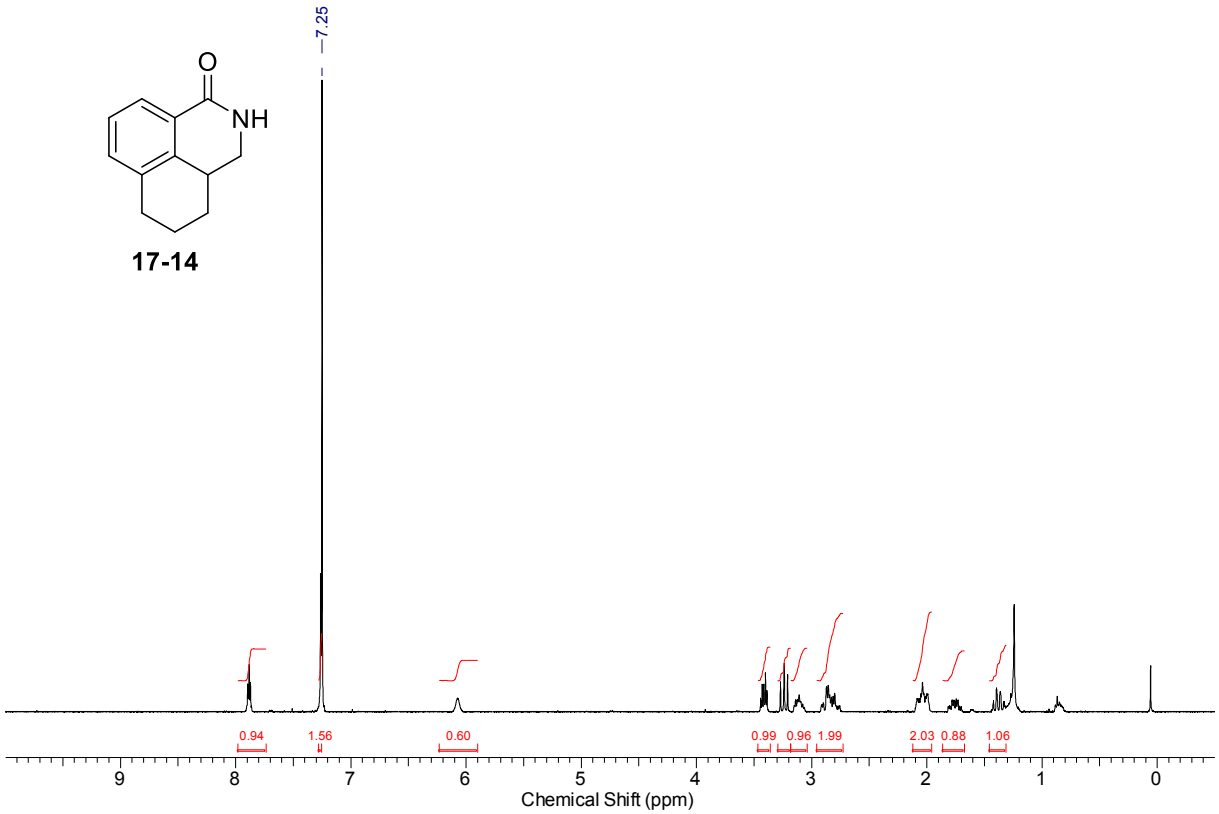
^{13}C NMR (100 MHz) spectrum of hydroxamic acid **17-22** in DMSO.



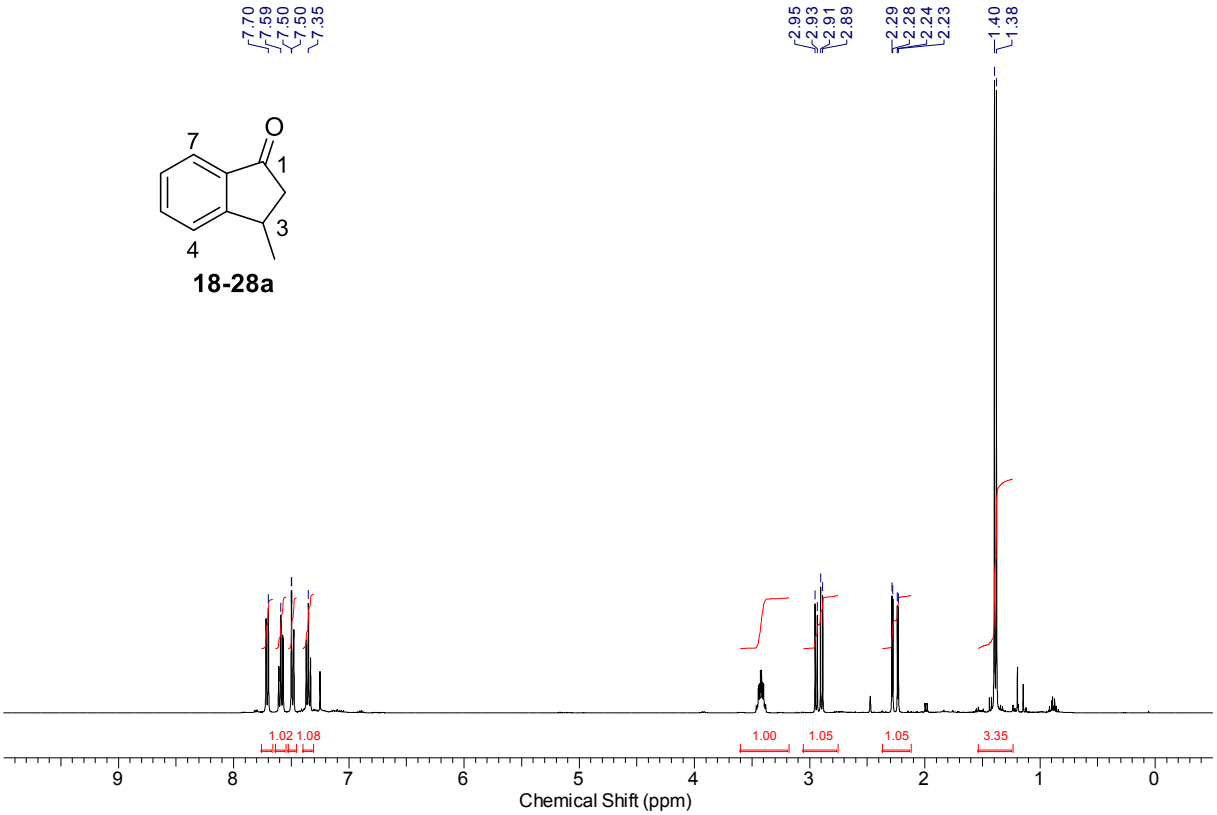
^{1}H NMR (400 MHz) spectrum of O-Pivaloate **17-23** in $CDCl_3$.



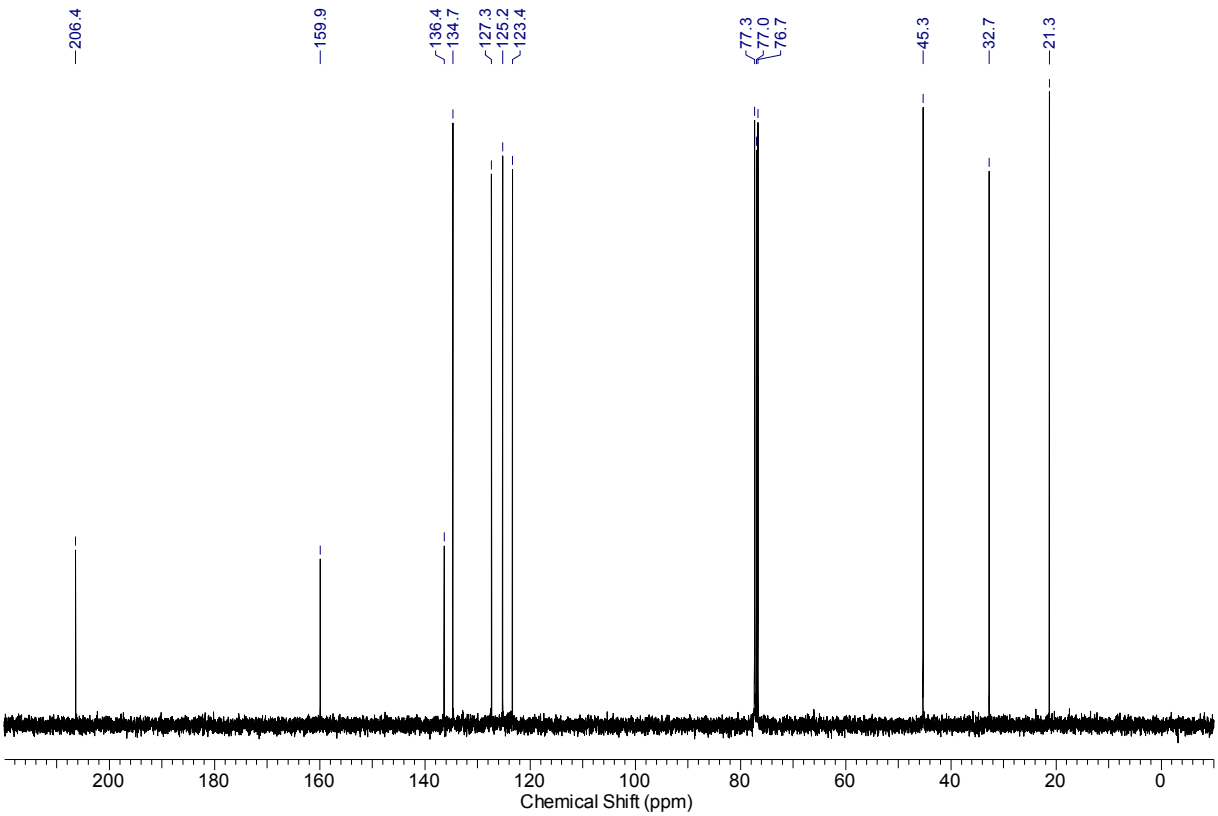
^{13}C NMR (100 MHz) spectrum of O-Pivaloate **17-23** in $CDCl_3$.



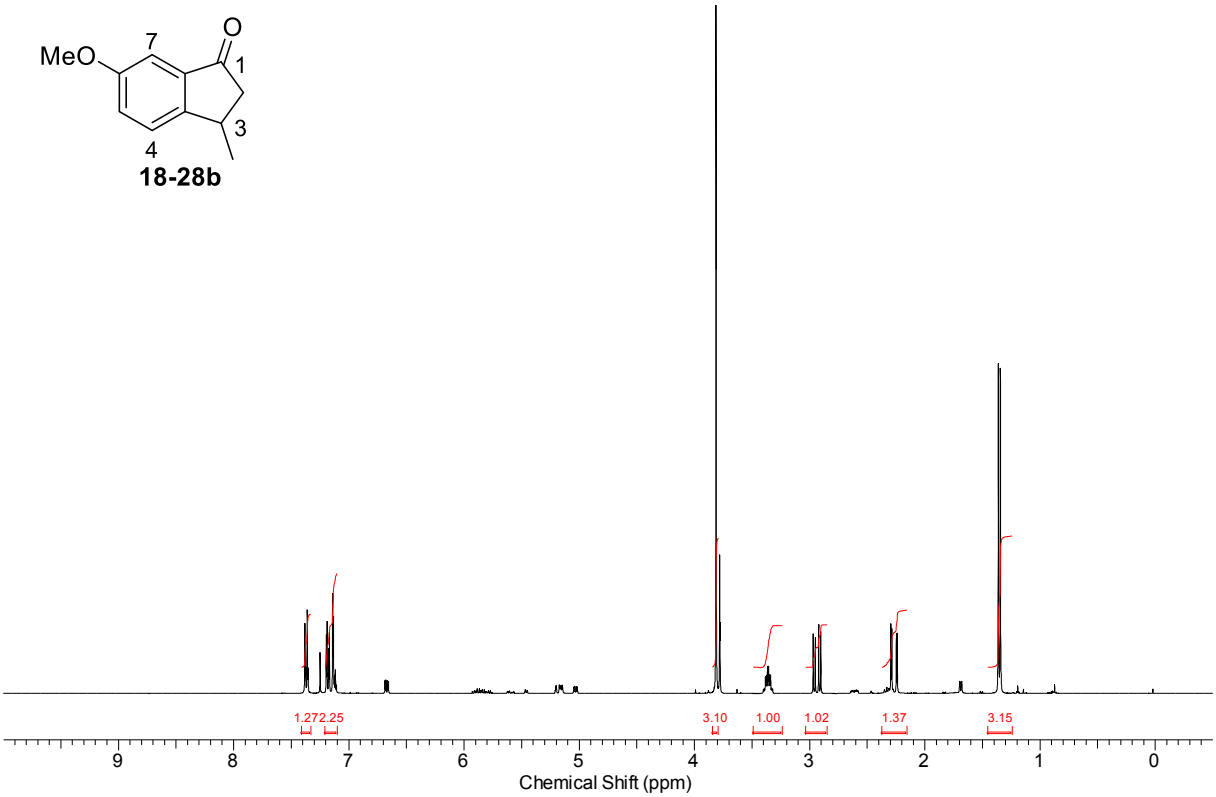
^{1}H NMR (400 MHz) spectrum of **17-14** in $CDCl_3$.



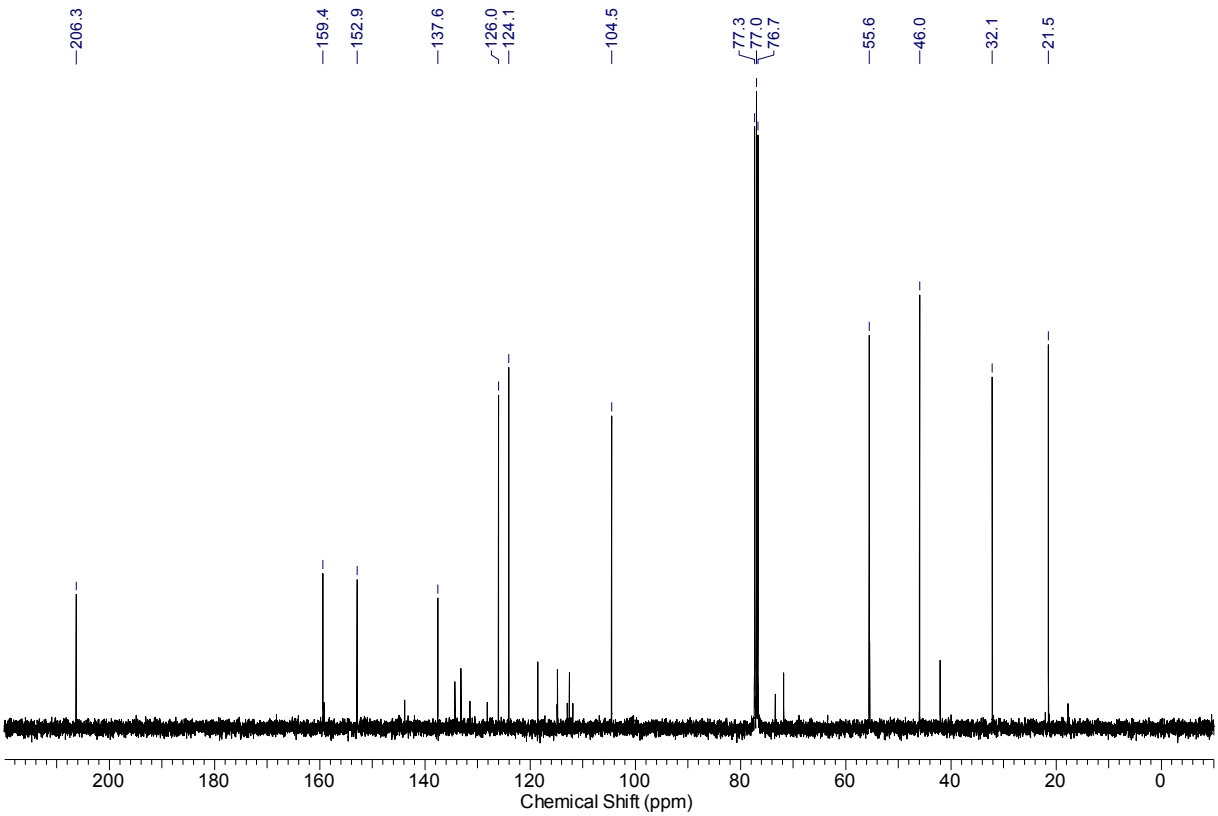
^{1}H NMR (400 MHz) spectrum of 3-methyl indanone **18-28a** in $CDCl_3$.



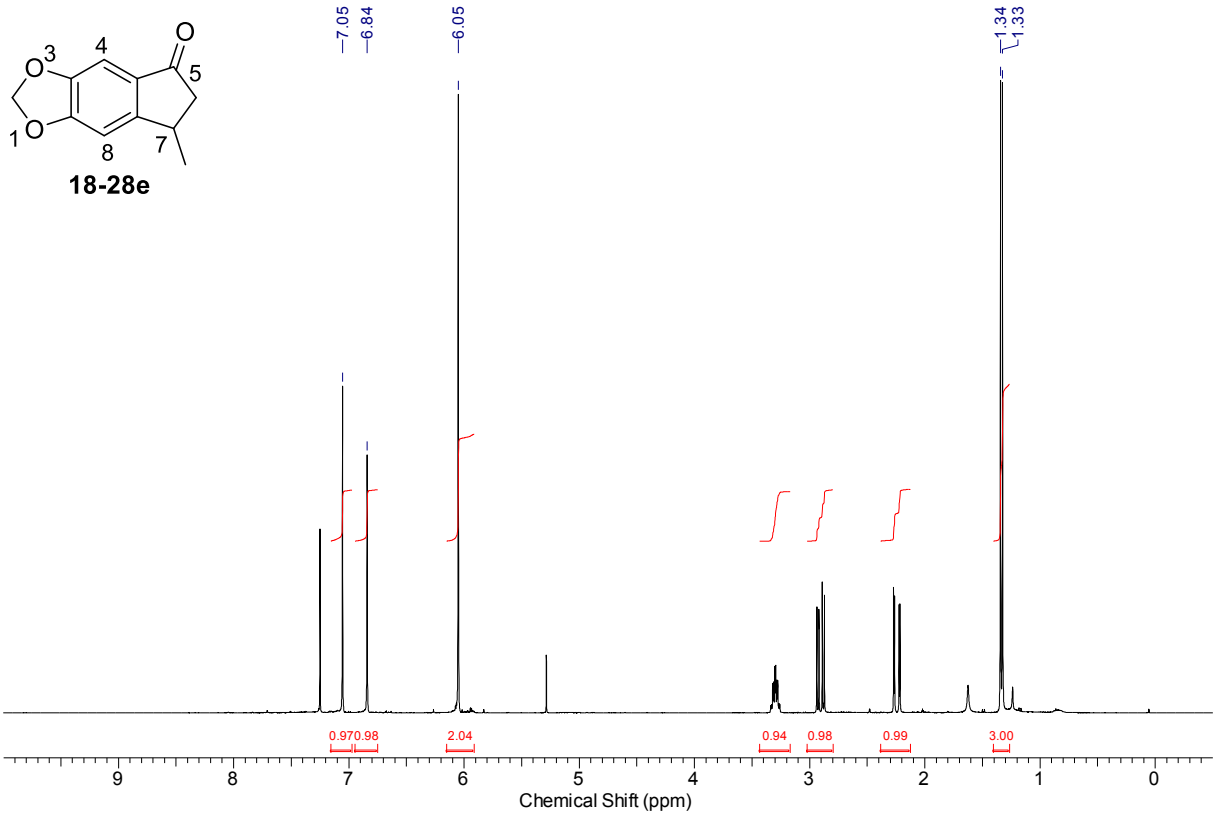
^{13}C NMR (100 MHz) spectrum of 3-methyl indanone **18-28a** in $CDCl_3$.



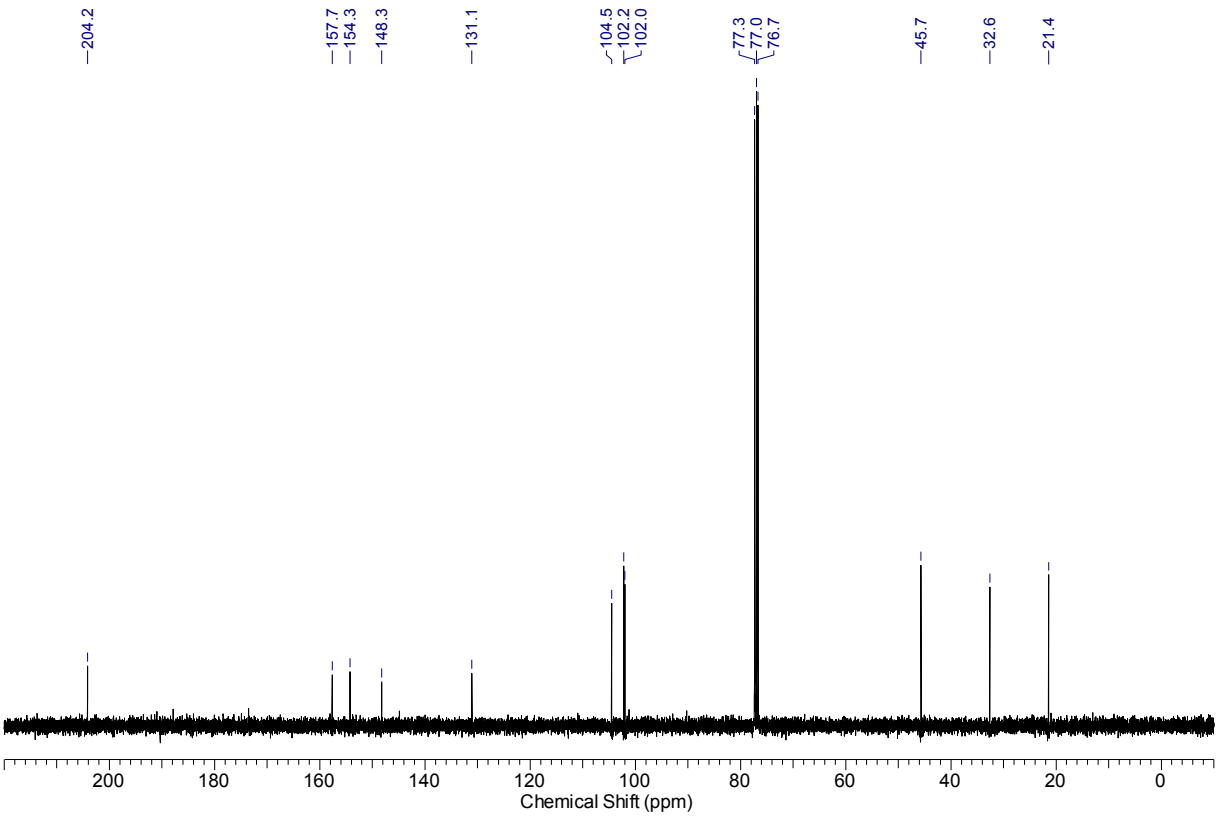
^{1}H NMR (400 MHz) spectrum of 3-methyl-6-methoxy indanone **18-28b** in $CDCl_3$.



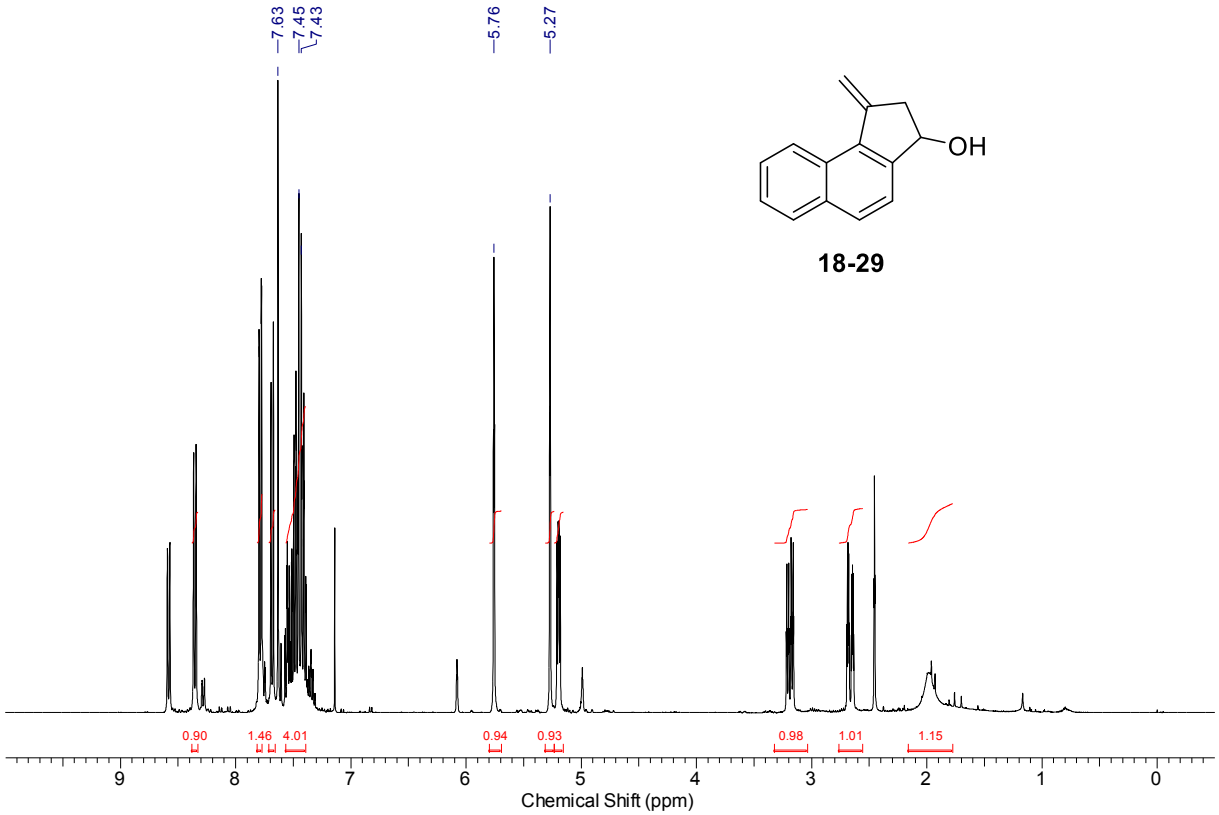
^{13}C NMR (100 MHz) spectrum of 3-methyl-6-methoxy indanone **18-28b** in $CDCl_3$.



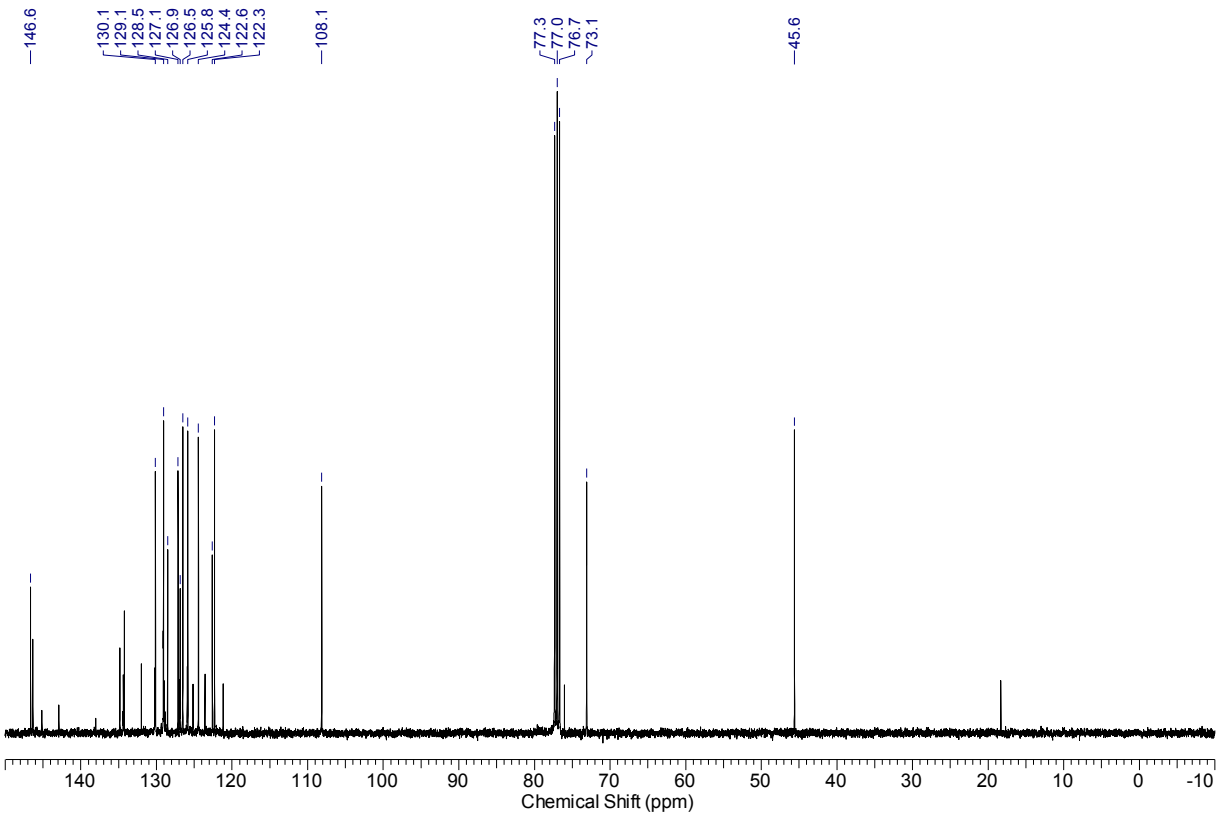
^{1}H NMR (400 MHz) spectrum of 7-methyl-1,3-methylenedioxy indanone **18-28e** in $CDCl_3$.



^{13}C NMR (100 MHz) spectrum of 7-methyl-1,3-methylenedioxy indanone **18-28e** in $CDCl_3$.



^{1}H NMR (400 MHz) spectrum of naphthyl indenone **18-29** in $CDCl_3$.



^{13}C NMR (100 MHz) spectrum of naphthyl indenone **18-29** in $CDCl_3$.

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