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# The Total Synthesis of Tetracyclic Meroterpenoid Natural Products

# –

# Gold(I)-Catalyzed Cyclizations of 1-Bromo-1,5-Enynes

von

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## Erklärung

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## Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfsmittel erarbeitet.

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*– Meinen Eltern –*

*Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world.*

*(Louis Pasteur)*

## Parts of this work have been published in peer-reviewed journals.

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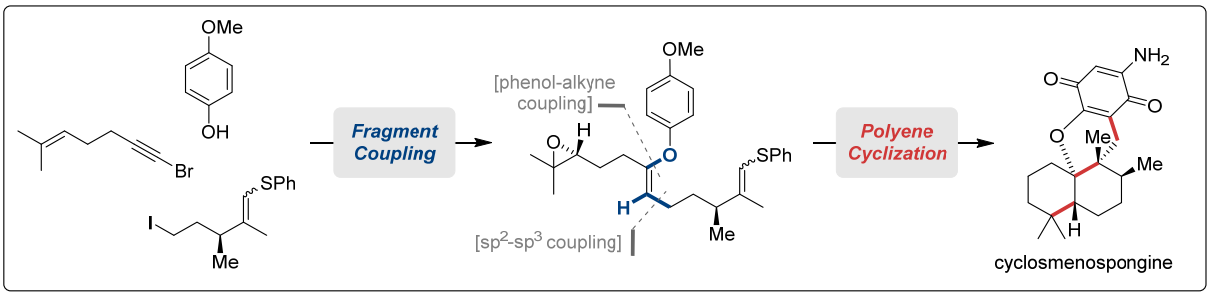
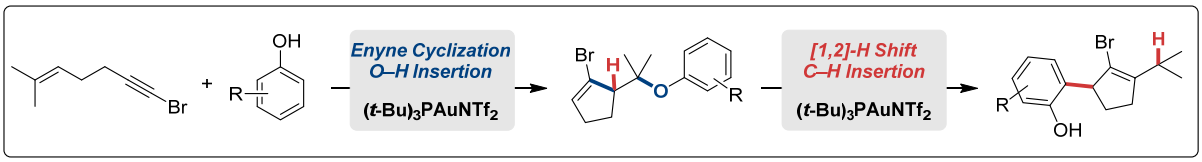
# ABSTRACT

**Part I:** Tetracyclic meroterpenoid natural products are structurally fascinating molecules with intriguing biological activities. Their unique skeleton contains four to five stereogenic centers and bears a decalin ring-system which is fused to diverse aromatic moieties through a dihydropyran. The first part of this thesis presents the evolution of a novel cationic polyene cyclization cascade for the total synthesis of the meroterpenoid natural product (–)-cyclosmenospongine. A highly modular and efficient three fragment coupling strategy permitts the facile synthesis of the key cyclization precursor. The cyclization cascade forms three carbon–carbon bonds and sets four consecutive stereocenters, two of which are tetrasubstituted, to forge the tetracyclic scaffold of cyclosmenospongine in a single step on multi-gram scale. Sequential functionalization and oxidation of the arene allows the synthesis of more than 400 mg of (–)-cyclosmenospongine in one batch.




**Part II:** In the second part of this thesis, the development of a novel gold(I)-catalyzed cyclization cascade of 1-halo-1,5-enynes in the presence of phenols is described. Reactions involving the cyclization of 1,*n*-enynes are of high value as they are capable of generating molecular complexity in a minimal number of steps. The developed one-pot procedure yields 2-halo-cyclopentenes, a structural motif that can be found in several bioactive molecules, through an unprecedented sequential O–H/C–H bond functionalization of phenols under mild reaction conditions. Mechanistic investigations revealed that the reaction cascade proceeds within two constitutive catalytic cycles via the intermediacy of an unstable aryl alkyl ether that collapses at ambient temperature to undergo a [1,2]-hydride shift followed by C–H insertion of the phenol. We found the reaction to be broadly applicable across a range of sterically and electronically diverse substrates by establishing a reaction scope of 18 examples.



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# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AIBN | azoisobutyronitrile |
| Ar | undefined aryl substituent |
| 9-BBN | 9-borobicyclo[3.3.1]nonane |
| Bn | benzyl |
| br | broad (NMR spectroscopy, IR spectroscopy) |
| B.C. | before christ |
| BDSB | bromodiethylsulfonium bromopentachloroantimonat |
| Bu | butyl |
| calc. | calculated |
| CCDC | Cambridge Crystallographic Data Centre |
| COD | 1,5-cylcooctadiene |
| COSY | homonuclear correlation spectroscopy |
| Cp | cyclopentadienyl |
| CSA | camphorsulfonic acid |
| d | doublet (NMR spectroscopy) |
| d.r. | diastereomeric ratio |
| DCTMB | 1,4-dicyanotetramethyl-benzene |
| DDQ | 2,3-dichloro-4,5-dicyano-1,3-benzoquinone |
| $(DHQ)_2Phal$ | bis(dihydroquino)phthalazine |
| $(DHQD)_2Phal$ | bis(dihydroquinidino) phthalazine |
| DIBAL-H | diisobutylaluminum hydride |
| DIPA | *N*,*N*-diisopropylamine |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DMAP | 4-(dimethylamino)pyridine |
| DMAPP | dimethylallyl pyrophosphate |
| $^{3,4}$DMB | 3,4-dimethoxybenzyl |
| DMF | *N*,*N*-dimethylformamide |
| DMP | Dess–Martin periodinane |
| DMPU | *N*,*N*'-dimethylpropyleneurea |
| DMSO | dimethylsulfoxide |
| dppe | 1,2-bis(diphenylphosphino) ethane |
| dppf | 1,1´-bis(diphenylphosphino) ferrocene |
| *ee* | enantiomeric excess |
| EI | electron impact ionization (mass spectrometry) |
| equiv | equivalent(s) |
| ESI | electron spray ionization (mass spectrometry) |
| Et | ethyl |
| FTIR | Fourier-transform infrared spectroscopy |
| g | gram(s) |
| h | hour(s) |
| HMPA | hexamethylphosphoramide |
| HPLC | high-performance liquid chromatography |
| HSQC | heteronuclear single quantum coherence |
| Hz | Hertz (frequency) |
| *i*- | *iso* (isomer) |
| $IC_{50}$ | half maximal inhibitory concentration |
| im | imidazole |
| IMes | 1,3-bis(mesityl)imidazole-2-ylidene |
| IPP | isopentenyl pyrophosphate |
| IPr | 1,3-bis(2,6-diisopropylphenyl) imidazole-2-ylidene |

| | |
|---|---|
| IR | infrared |
| IUPAC | International Union of Pure and Applied Chemistry |
| JohnPhos | (2-biphenyl)di-*tert*-butyl-phosphine |
| HMDS | hexamethyldisilazide |
| LBA | Lewis acid assisted chiral Brønsted acid protonation |
| LDA | lithium *N*,*N*-diisopropylamide |
| $L_n$ | ligand(s) |
| m | medium (IR spectroscopy) |
| m | multiplet (NMR spectroscopy) |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Me | methyl |
| min | minute(s) |
| mL | milliliter |
| mmol | millimole |
| MoOPH | $MoO_5$•pyridine•HMPA |
| MS | mass spectrometry |
| MsCl | methanesulfonyl chloride |
| NBS | *N*-bromosuccinimide |
| NHC | *N*-heterocyclic carbene |
| NIS | *N*-iodosuccinimide |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser effect correlation spectroscopy |
| Nu | nucleophile |
| *p* | *para* (isomer) |
| Ph | phenyl |
| PIFA | phenyliodine bis(trifluoroacetate) |
| pin | pinacol |
| PMB | *para*-methoxybenzyl |
| PMP | *para*-methoxyphenyl |
| ppm | parts per million |
| PPTS | pyridinium *para*-toluenesulfonate |
| *p*-TsOH | *para*-toluenesulfonic acid |
| q | quartet (NMR spectroscopy) |
| R | undefined substituent |
| $R_f$ | retardation factor |
| s | strong (IR spectroscopy) |
| s | singlet (NMR spectroscopy) |
| SPhos | 2-dicyclohexylphospino-2′,6′-dimethoxybiphenyl |
| *T* | temperature |
| t | triplet (NMR spectroscopy) |
| *t*- | (*tert*-) tertiary (isomer) |
| TBAF | tetrabutylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | *para*-toluenesulfonyl |
| w | weak (IR spectroscopy) |
| XPhos | 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl |

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# THEORETICAL SECTION

# PART I:

# TOTAL SYNTHESIS OF

# MEROTERPENOID NATURAL PRODUCTS

# 1.1. General Introduction

## 1.1.1. Natural Products

The simplest definition of a natural product is a molecule that is produced in nature by a living source.[1] Every organism needs these small molecules to live, grow and reproduce. Some of these crucially important and ubiquitous molecules of life are sugars, amino acids, fatty acids and nucleic acids. These compounds are called primary metabolites, and are found in all living organisms as their biosynthesis is highly conserved. In contrast, natural products that are classified as secondary metabolites are often only found in particular organisms to serve a distinct purpose and have increasingly specialized functions.[2] Plants for instance are known to produce a myriad of these highly specialized and unique molecules. The compound responsible for the smell of roses is the natural product damascenone (**1**), whereas anthocyanin (**2**), which was first isolated by Willstätter in the year 1915, gives roses their distinctive red color (Figure 1).[3-4] Another natural product of great importance is indigo (**7**), an ancient natural dye that is now associated with the blue color of jeans.

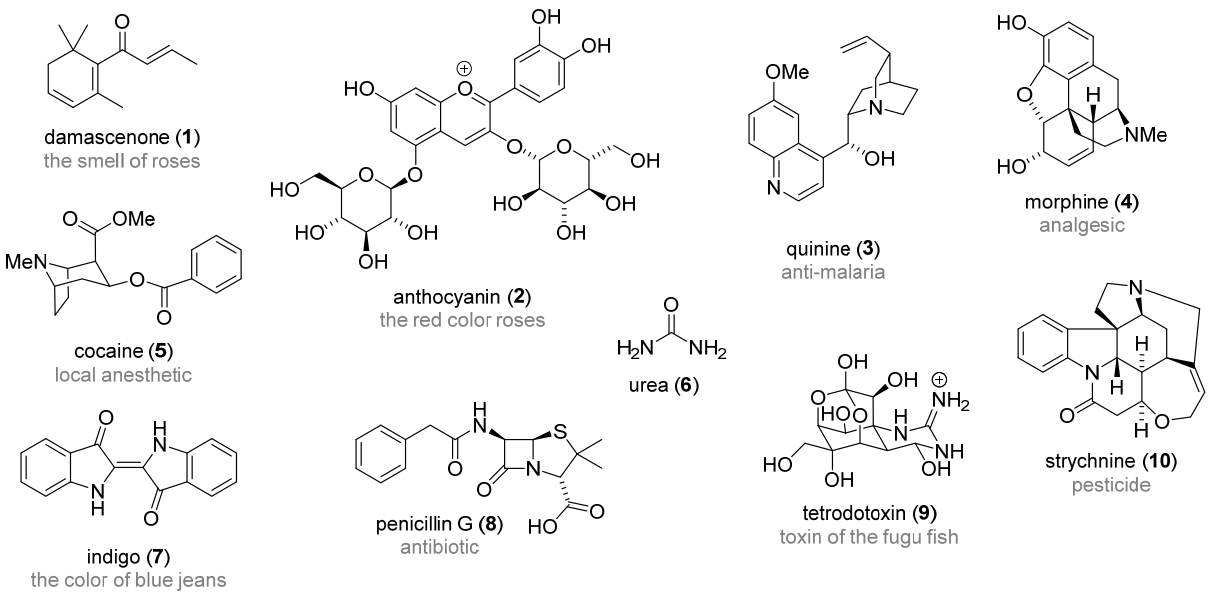



***Figure 1:*** *Selected natural products.*

For thousands of years mankind has benefited from the rich chemical diversity found in nature. Records from Mesopotamia dating back to 2600 B.C. show that extracts of cypress and myrrh were used in traditional medicine to treat the common cold.[5] Natural products have become part of our culture and traditions as is evident from the consumption of coffee, tea or tobacco, and other processed plant products that contain alkaloids with stimulating effects. The alkaloid quinine (**3**), which can be isolated from the bark of the cinchona tree, was historically used to prevent and treat malaria and is used today as the bitterant of tonic water.[5] Drugs like morphine (**4**), cocaine (**5**) or penicillin (**8**) have also had a significant influence on our modern society.[6] For instance, the

discovery of the excellent antibiotic properties of penicillin (**8**), a natural product produced by fungi, saved countless lives. In contrast to cocaine (**4**), which can be isolated in ample quantities from Coca shrubs, there are several natural products with a unique biological profile that cannot be accessed in sufficient quantities to allow for further biological testing and clinical applications. For instance, for the isolation of 18 g of bryostatin I, a natural product with promising biological activity against several types of cancer, more than 12,000 kilogram of the source organism, an aquatic invertebrate, had to be collected.[7-8] Due to the low natural abundance of this and several other potent therapeutic agents, chemical synthesis is the only option to meet the demand.

### 1.1.2. The History of Natural Product Synthesis

The history of natural product synthesis dates back to the beginning of the 19th century. In 1828, the first synthesis of the natural product urea (**6**) was accomplished by Wöhler from ammonium cyanate, a substance regarded as inorganic.[9] This accomplishment shifted the paradigm of natural products, and demonstrated for the first time that chemists can create the molecules of nature. Whether a compound is isolated from natural sources or synthesized in a laboratory makes no difference if the resulting compound is chemically identical.[1]

Initially, the major aim of natural product synthesis was structural elucidation and to prove that one can indeed access these molecules in the laboratory.[10] As early as 1870, Baeyer was able to complete a synthesis of indigo (**7**), whereas the first industrial semi-synthesis of camphor was accomplished by Komppa in 1903. [10-11] However, it was not until the seminal work on the synthesis of cocaine (**5**) by Willstätter, when the term "total synthesis" was introduced for the first time.[12-13] The concept of total synthesis was taken to new heights in 1917, when Robinson disclosed his seminal synthesis of tropinone, heralding a new age of natural product synthesis.[14]

The progress made in the theory of organic chemistry, for example the understanding of the nature of the chemical bond, pioneered by the work of Robinson, Ingold and Pauling and the introduction of the concept of retrosynthetic analysis, formalized by Corey, in combination with the advancement of chromatographic and spectroscopic methods (e.g. column chromatography and NMR spectroscopy) accelerated the advancement of synthetic chemistry to an unprecedented speed.[10] These factors redefined the way synthetic chemists chose their target structures. The focus of total synthesis expanded beyond the mere preparation of the desired compound, but also focused on the invention and implementation of new synthetic methodology, and moreover to prepare new molecules with a potential benefit for society.[10] For example, the war-driven efforts to provide soldiers fighting in Asia with the antimalarial drug quinine (**3**) culminated in its first total synthesis by Woodward and Doering in 1944.[15] Moreover, due to the development of new synthetic methods, such as metal catalyzed bond formations or asymmetric catalysis, more complex molecules like morphine (**4**),[16] strychnine (**9**)[17] or tetrodotoxin (**10**)[18] succumbed to total synthesis.

It is not only due to these developments in the field of organic chemistry that the discipline of total synthesis advanced to its current level of sophistication. It is more likely a synergistic effect that arises from the intrinsic motivation of the synthetic chemist to find new, more elegant and efficient ways to create the molecules provided to us by nature. Nevertheless, synthetic organic chemistry still suffers from several shortcomings, such as the necessity to exploit the reactivity of toxic reagents. In addition, the synthetic sequences to access complex molecules are generally too long and low-yielding to produce many natural products in sufficient quantities to allow for further applications. In order to overcome the drawbacks of synthetic methodology chemists have always strived to mimic nature´s ingenuity and efficiency in constructing these complex molecules.

## 1.2. Polyolefin Cyclizations

### 1.2.1. Learning from Nature

In contrast to the synthetic chemist, who by now is able to choose from a wealth of methods to specifically modify a molecule, biology is generally constrained to a relatively narrow range of conditions that are tolerated by the individual organism.[19] Nevertheless, nature has developed and optimized the synthesis of natural products over millennia and came up with highly efficient ways to build molecular complexity by utilizing enzymes, which are indisputably the most selective catalysts.[20] These highly specialized enzymes are able to perform a variety of transformations under physiological conditions with great efficiency and selectivity.[19] Some of the most fascinating and complex transformations occurring in nature are cascade reactions of simple, linear polyolefinic precursors into diverse polycyclized products. These cascade reactions are capable of generating immense molecular complexity in a rapid and stereoselective manner through multiple subsequently occurring reactions.[20-21]

### 1.2.2. The Concept of Biomimetic Synthesis

Biomimetic synthesis is the approach to synthesize a natural product through transformations or reaction sequences that mimic a biosynthetic proposal. [22] In contrast to biogenetic synthesis, where the synthetic route is planned strictly following a biosynthetic pathway, biomimetic is defined by the attempt to mimic single transformations occurring in nature, such as enzymatic processes.[23] This interplay between biomimicry and total synthesis can provide a deeper understanding of the biogenesis of natural products, and facilitates the development of new reactions and synthetic methodology to allow the construction of natural products in a minimum amount of steps.[20, 24] In traditional syntheses, a target molecule is assembled in a stepwise fashion and the molecular complexity is introduced sequentially with each chemical step. In contrast, a biomimetic approach can dramatically shorten the synthetic sequence as well as reduce the amount of time, labor and waste produced through the implementation of highly efficient and selective cascade reactions.[25]

The first prime example of a biomimetic synthesis employing a cascade was published by Robinson in 1917.[14] In his seminal work he was able to access tropinone (**11**) in a one-pot procedure from the simple compounds acetone dicarboxylic acid, succinic aldehyde and methyl amine via a sequence of Mannich reactions (Figure 1). This remarkable study demonstrated the power and elegance of biomimetic synthesis, as it shortened Willstätter´s preparation of **11** dramatically. Inspired by this pioneering work, researchers have since been able to demonstrate the potential of this concept in numerous total syntheses. This can be exemplified by the elegant cationic cyclization approach to progesterone (**12**) developed by Johnson in 1971, the Heathcock synthesis of several homosecodaphniphyllate natural products starting from the cyclization of squalene-type precursors, or

the masterful endiandric acid C (**13**) synthesis by Nicolaou exploiting an 8π/6π-electrocyclization cascade followed by an intramolecular Diels–Alder reaction. More recently, Trauner synthesized epicolactone (**15**) utilizing a sophisticated reaction cascade including a (5+2) heterodimerization, followed by an intramolecular nucleophilic attack and a vinylogous aldol addition.[26] All of these syntheses highlight the contribution of cascade reactions to both the science and art of organic synthesis. The design and implementation of reaction cascades poses not only a significant intellectual challenge, but also demands a large amount of creativity.[27]

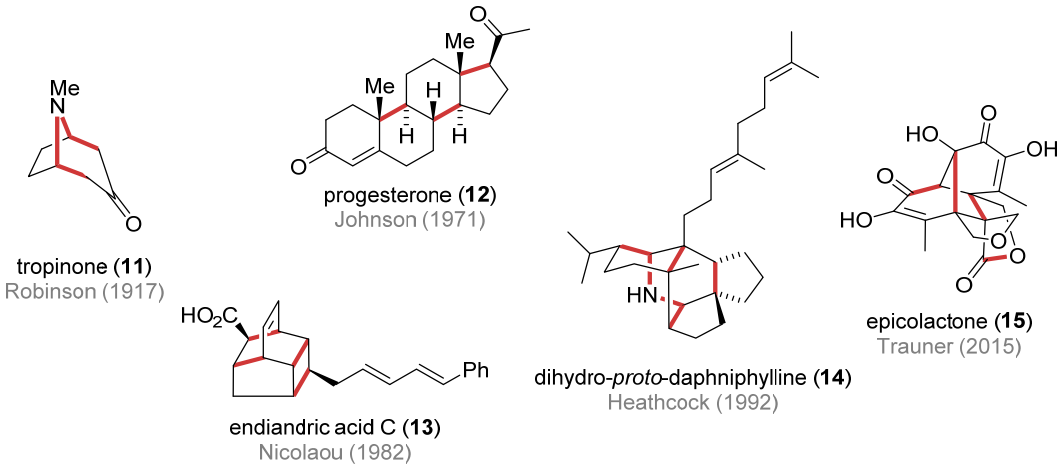


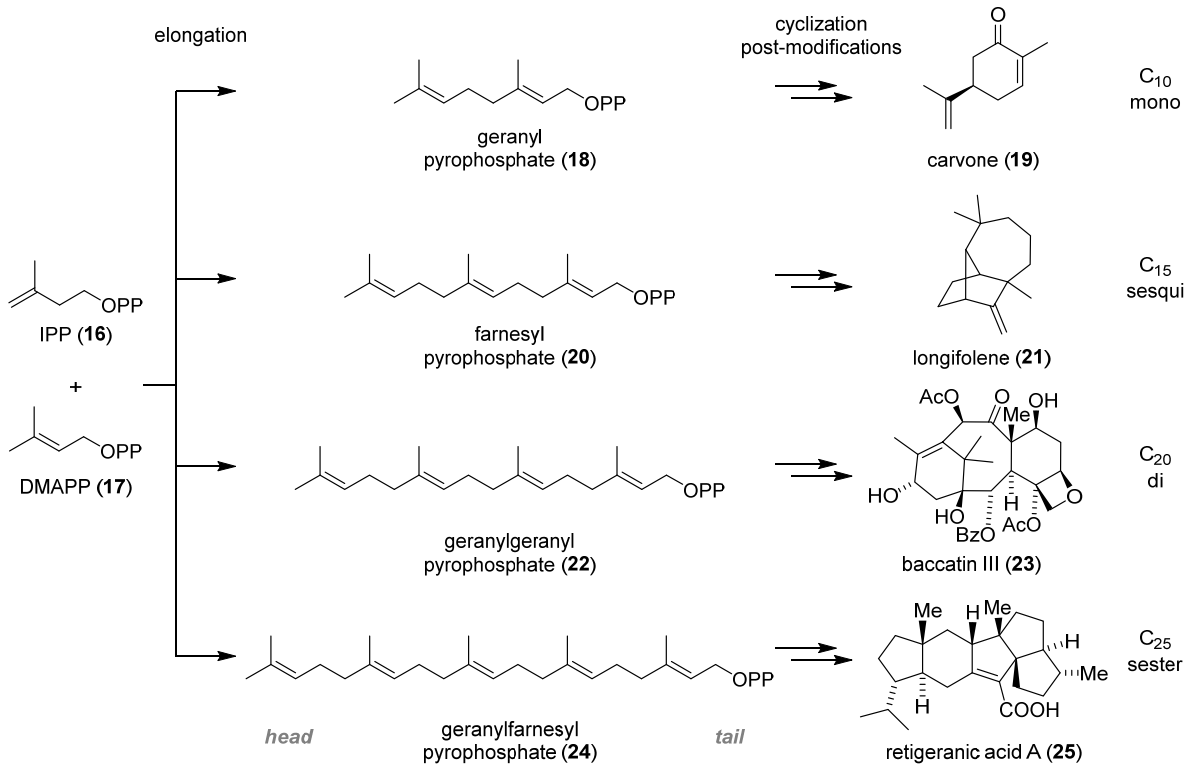

***Figure 2:*** *Landmark biomimetic total syntheses (bonds formed in the biomimetic key-step are highlighted in red).*

### 1.2.3. Terpenoid Natural Products

Terpenoids comprise the largest family of natural products and contain thousands of structurally diverse and unique members.[2] Biosynthetically, all terpenoid natural products originate from the $C_5$ isoprene monomers isopentenyl pyrophosphate (**16**, IPP) and dimethylallyl pyrophosphate (**17**, DMAPP), which are derived from the mevalonate or the mevalonate-independent pathways.[2] These two subunits are fused by prenyltransferases in a tail-to-head fashion to form polyenes of different sizes. Sequential elongation in a head-to-tail fashion gives geranyl pyrophosphate (**18**, $C_{10}$), farnesyl pyrophosphate (**20**, $C_{15}$), geranylgeranyl pyrophosphate (**22**, $C_{20}$) or geranylfarnesyl pyrophosphate (**24**, $C_{25}$), whereas squalene (**26**, $C_{30}$) is derived from the tail-to-tail fusion of two farnesyl subunits.[2] The myriad of natural products arising from these linear precursors are exemplified by carvone (**19**), longifolene (**21**), baccatin III (**23**) and retigeranic acid A (**25**) which can be further classified as mono- ($C_{10}$), sesqui- ($C_{15}$), di- ($C_{20}$), sester ($C_{25}$) or triterpenes ($C_{30}$) (Scheme 1).

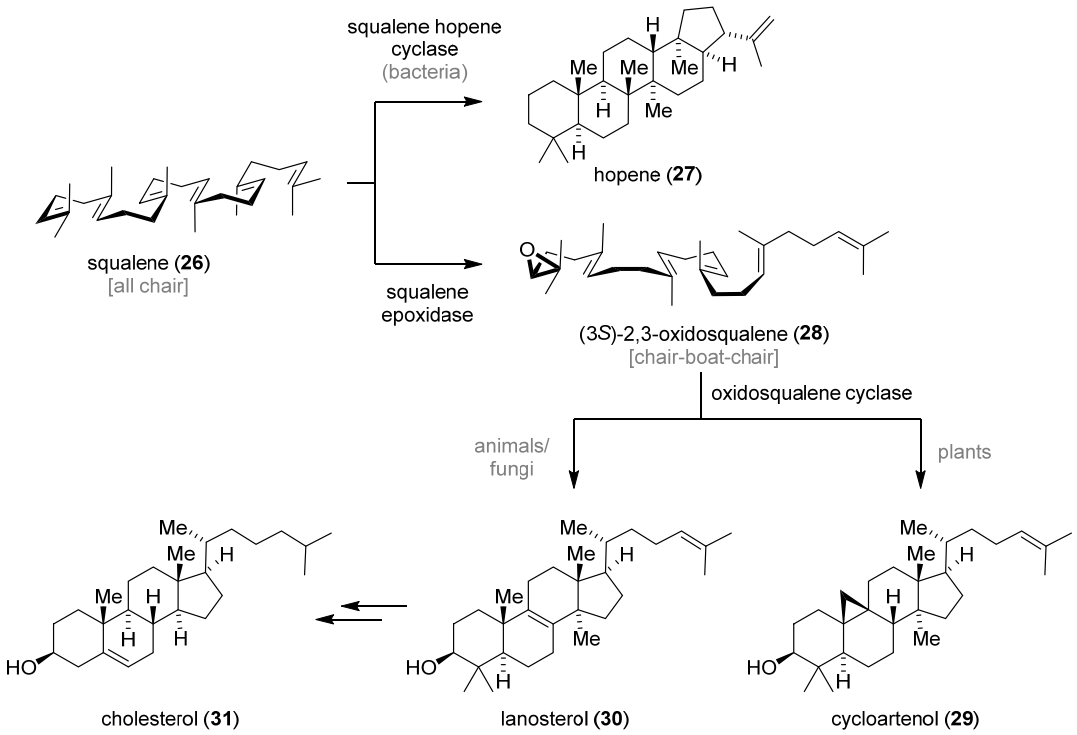
In a typical biosynthesis, these complex molecules are formed in two distinctive phases where the linear and achiral precursors undergo a series of enzymatic transformations.[24] In the first cyclization phase, the unique carbon skeleton is forged through the cyclization of various polyenes by enzymes called cyclases. The second phase is defined by selective, post-cyclase modifications of the

generated molecular framework, usually through a series of oxidations carried out by oxidase enzymes.[24]




***Scheme 1:*** *Biosynthesis of higher terpenoids and their nomenclature including a representative member.*

It is thought that polyene cyclization cascade occurs in a four-step sequence orchestrated by a single cyclase.[22] These intricate polyene cyclizations are typically initiated electrophilically through the generation of a carbocationic intermediate. In the second step, the conformation of the terpenoid is controlled by the cyclase, allowing for the charge to be propagated throughout the molecule in a sequence of stereospecific bond-forming events that can include skeletal rearrangements. Finally, the cascade can be terminated through the loss of a proton, thereby generating an olefin moiety, or by the attack of an external nucleophile such as water to yield an alcohol functionality. These cyclases can be further divided into two subclasses based on their distinct mode of activation.[28-29] Class I cyclases initiate the formation of an allylic cation by cleavage of the pyrophosphate unit (tail), thereby generating an allylic cation, whereas class II terpenoid cyclases initiate carbocation formation through protonation of either the isoprene or the epoxide moiety (head).[29-30] As a result, the direction of the positive charge is propagated differently along the polyene chain. Tail-to-head cyclizations are observed for class I cyclases and give rise to diverse polycyclic skeletons like taxadiene, which is the biogenetic precursor of baccatin III (**23**). In contrast, head-to-tail cyclizations are initiated by class II cyclases and generally furnish poly-decalin frameworks, as can be found in steroids like hopene (**27**).[29]




***Scheme 2:*** *Polycyclic triterpenoids arising from head-to-tail cyclization of squalene (**26**) or oxidosqualene (**28**).*

In the defined environment of an enzymatic active site, squalene (**26**) can be cyclized selectively to different natural products, depending on the cyclase performing the reaction (Scheme 2).[2] There are numerous squalene cyclases known, and each generates a specific polycyclic product. The relative stereochemistry of hopene (**27**) is the result of an all chair-type folding of squalene (**26**) in the enzyme´s active site. In contrast, the stabilization of the chair-boat-chair folding of 2,3-oxidosqualene (**28**) gives rise to the stereochemistry found in cycloartenol (**29**) or lanosterol (**31**), which can be further converted into the ubiquitous steroid cholesterol (**31**). For example, only one out of the 128 possible lanosterol (**30**) stereoisomers that could be formed during cyclization of 2,3-oxidosqualene (**28**) is generated, highlighting the unparalleled stereocontrol of these enzyme-mediated reactions.[31]

The highly variable cyclization patterns of these unique enzymes contribute to the enormous structural diversity of the largest family of natural products. The elucidation of the mechanistic and biosynthetic principles involved during the formation of these complex and structurally diverse natural products has inspired many sophisticated studies.[28] Much of this seminal work was carried out to investigate the constitution of these polycyclic compounds and to shed light on the fundamental basics of 1,5-diene cyclization in order to understand the prevailing mechanism of polyene cyclization cascades.[32]

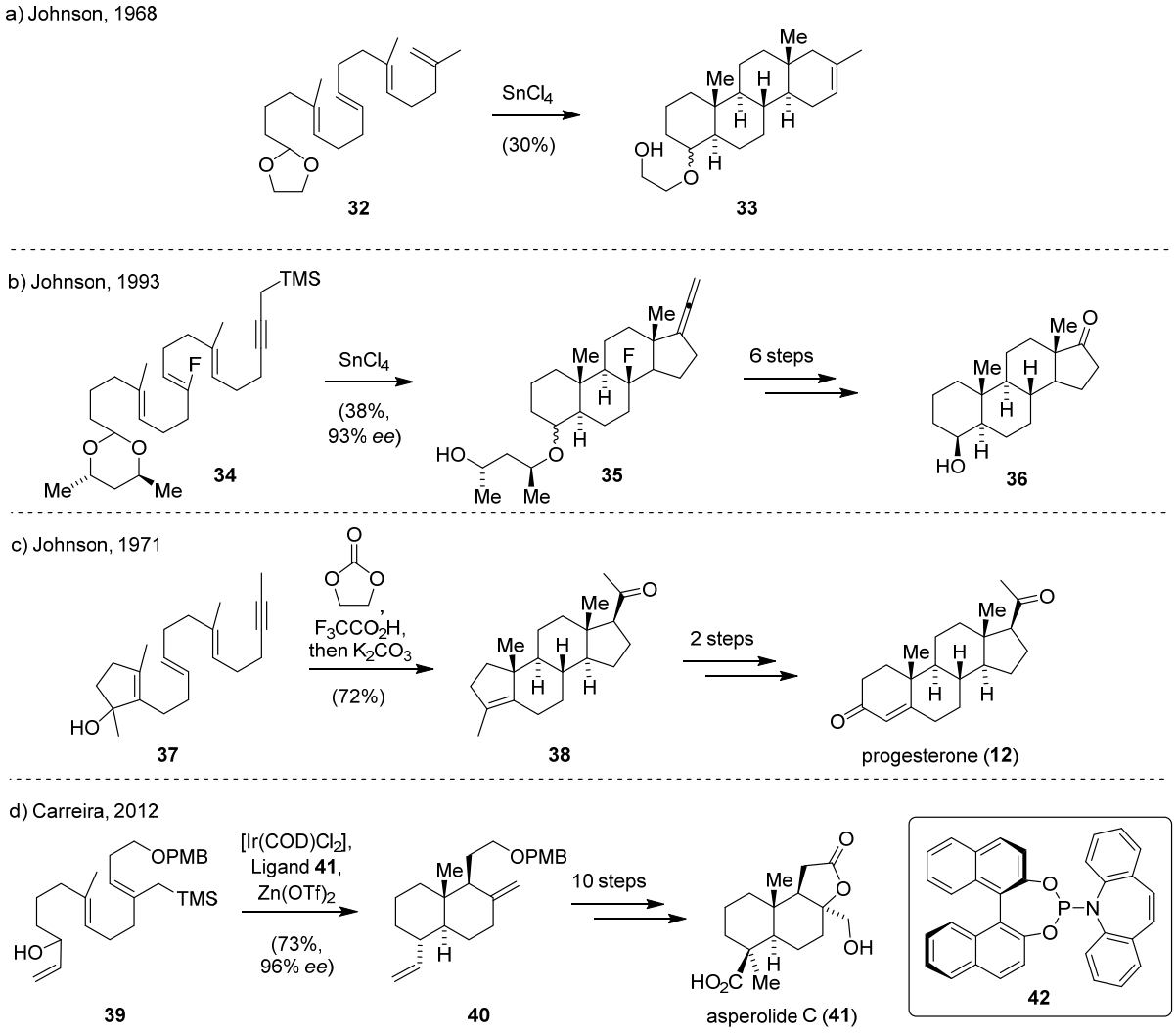
### 1.2.4. Historic Context

The cyclization of isoprenoids is by far the most studied field in biomimetic synthesis as it constitutes one of the most powerful reactions that could be successfully adapted from nature. The first investigations date back to 1945, and were conducted by Bloch and Rittenberg.[33] Their studies aimed to unravel the biosynthetic origin of cholesterol (**31**). They wanted to validate that the triterpenoid squalene (**26**) is a valid biomimetic intermediate through isotopic labelling of acetic acid. After the determination of the structure of lanosterol (**30**) in 1952, and the aforementioned labeling experiments, the biosynthetic connection between squalene (**26**) and cholesterol (**31**) became obvious (Scheme 2).[34-36] On the basis of these findings, Stork and Eschenmoser independently postulated their famous hypothesis of polyalkene cyclizations in 1955.[37-38] Their proposal established the concept that polyalkenes, when aligned in a defined conformation, could be attacked by the adjacent double bond in an antiperiplanar manner, analogous to the stereospecific *trans* addition of bromine to alkenes. This concept allowed for the first time the prediction of the relative stereochemistry of cyclization products and established a complete picture of the biosynthesis of lanosterol (**30**) and its derivatives.[20]

### 1.2.5. Polyene Cyclizations in Total Synthesis

The seminal work of Stork and Eschenmoser inspired chemists to further develop and advance polyene cyclization cascades. To successfully transform this attractive and powerful method into a synthetically useful reaction, several problems had to be addressed. Methods for the stereoselective synthesis of alkenes had to be developed, and suitable functional groups for selective initiation and termination of the cyclization had to found.[39] Although several Brønsted and Lewis acids were shown to sufficiently mediate monocyclizations, initial attempts to initiate the reaction by simple Brønsted acid catalysis proved difficult due to the indiscriminate protonation of the substrate leading to non-productive, competing cyclization pathways.[32, 39]

In his pioneering work on polyene cyclizations, Johnson was not only able to develop excellent initiating groups, he was also able to establish cation stabilizing groups and terminators (Scheme 3a-d) and furthermore apply these findings in the innovative total syntheses of various terpenoid natural products.[39-40] The problem of selective electrophilic activation could be overcome by the introduction of cyclic acetals to the polyolefin. Upon Lewis acid activation of the acetal moiety using tin tetrachloride, the generated oxonium ion serves as an excellent electrophile and triggers the subsequent bond forming events, exemplified by the tetracyclization of tetraenic acetal **32** to **33** (Scheme 3a).[41] Moreover, the use of a chiral acetate and the incorporation of fluorine substituents at the C-8 position of polyene **34** allowed Johnson to access enantioenriched tetracycle **35** in moderate yield (Scheme 3b). The fluorine substituent was introduced as a cation-stabilizing auxiliary in order to favor cyclohexane ring formation over the preferred 5-*exo* ring-closure to yield a cyclopentane.[42]



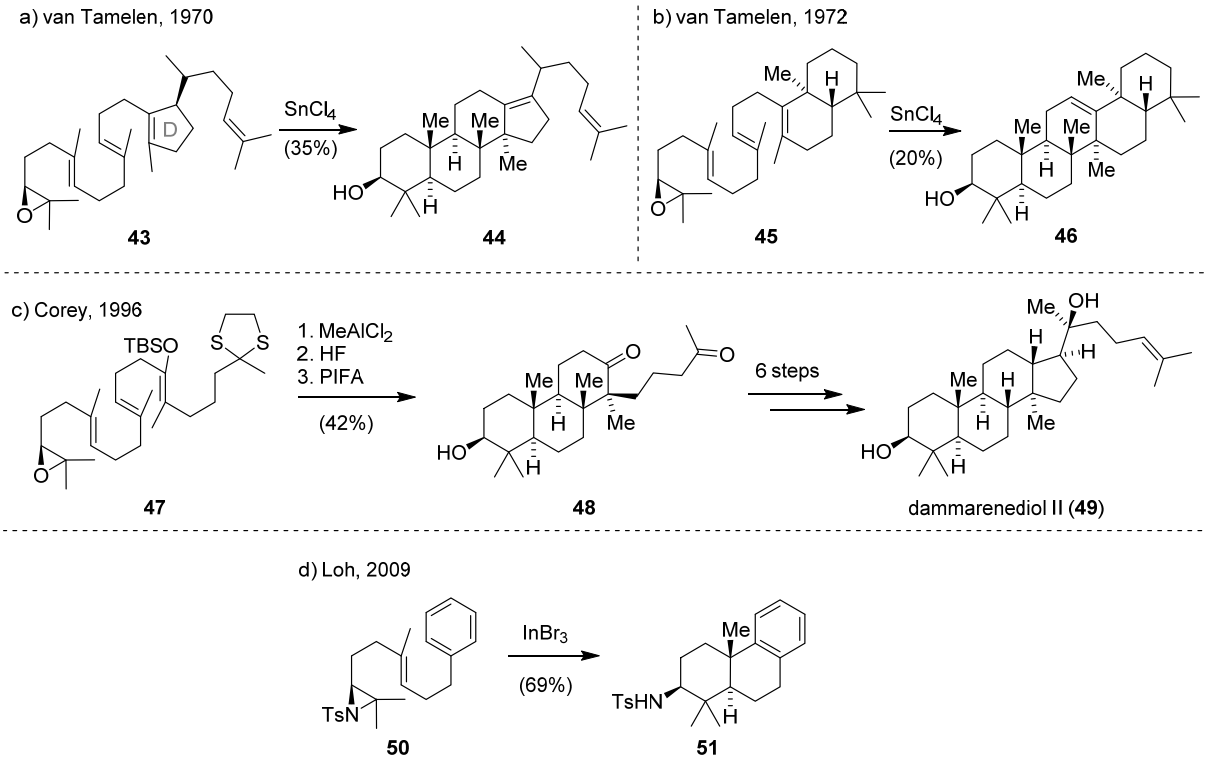

***Scheme 3:*** *a) to c) Seminal contributions of Johnson to the field of polyene cyclization cascades and d) Carreira´s improvement of allylic alcohol activation through chiral iridium catalysis.*

With six further synthetic operations Johnson was able to transform **35** to the known steroid 4β-hydroxyandrostane-17-one (**36**).[43] In addition to the introduction of acetals, Johnson was also able to establish allylic alcohols as suitable functional groups to initiate polyene cyclizations (Scheme 3c). This method of activation was beautifully implemented in his classic synthesis of progesterone (**12**).[44] The electrophilic tertiary allylic cation was generated through cleavage of the carbon-oxygen bond upon exposure of **37** to trifluoroacetic acid, which subsequently participated in the tricyclization cascade. The resulting vinyl cation was then trapped by ethylene carbonate. After basic aqueous work, up tetracycle **38** could be isolated in excellent yield. The final two steps to progesterone (**12**) included an oxidative scission of the pentacyclic double bond, followed by an intramolecular aldol condensation.

In 2012, Carreira reported an enantioselective iridium catalyzed variation of the polyene cyclization initiated by the activation of an allylic alcohol (Scheme 3d).[45] By applying this method, Carreira was able to synthesize the diterpene asperolide C (**41**) in an enantioselective fashion from

allylic alcohol **39**. Exposure of **39** to the chiral iridium(I) catalyst bearing ligand **42** in the presence of zinc triflate generated an iridium-stabilized π-allylic cation, which initiated the polyene cyclization to yield **40** in good yield and excellent enantioselectivity.[46]

The extensive studies of van Tamelen to selectively active polyenes were another major contribution to the field. His attractive approach was inspired by nature´s cyclization of 2,3-oxidosqualene (**28**). In contrast to Johnson, he was more interested in the biochemical aspects of polyene cyclizations.[47] By utilizing an epoxy functional group, he was able to expand the scope of suitable polyene substrates and successfully apply this strategy to the biogenetic synthesis of several natural products (Scheme 4a and b).[48-50]

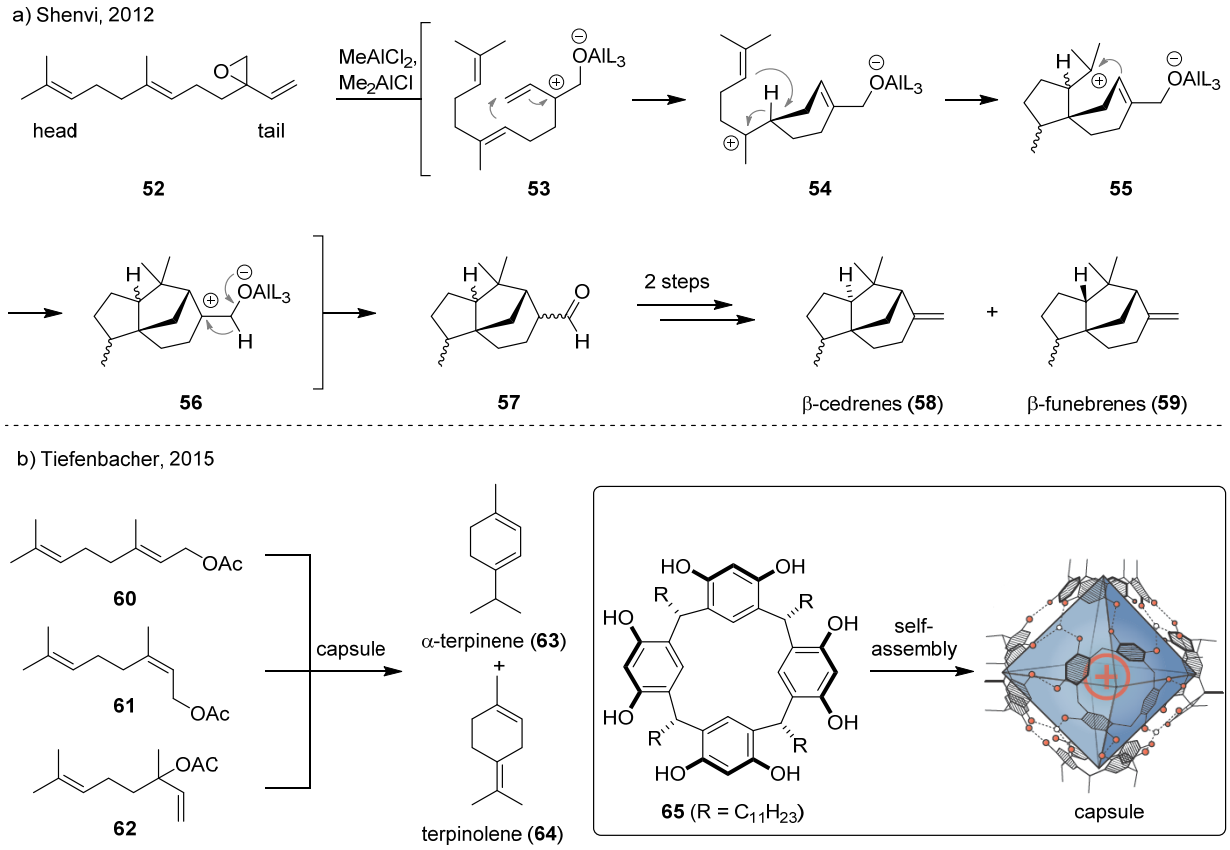



***Scheme 4:*** *Polyene cyclization cascades initiated through epoxide opening.*

In 1970, van Tamelen synthesized the isoeuphenol system **44** through the tricyclization of epoxide **43** (Scheme 4a).[49] He chose **43** as his key intermediate with the preformed five-membered D-ring for two reasons. First the tetrasubstituted double bond of the D-ring should prefer the formation of the six-membered C-ring and additionally serve as an "insulator" to prevent the side chain from participating in the cyclization. Further synthetic efforts culminated in the synthesis the pentacyclic terpenoid $\Delta^{12}$-dehydrotetrahymanol (**46**) from **45** (Scheme 4b). [51]

In contrast to Johnson´s and van Tamelen´s work, Corey´s strategy to selectively gain access to the 6-membered C-ring was based on the reactivity of silylenol ethers (Scheme 4c).[52] After initiation of the polyene cyclization using methyl aluminum dichloride as a Lewis acid, followed by desilylation and oxidative thioacetal cleavage, tricycle **48** could be obtained in good yield from

epoxide **47** and further advanced to dammarenediol II (**49**) in six steps. Numerous modifications of the epoxide opening/polyene cyclization cascade enabled the Corey group to synthesize several other terpenoid natural products.[21] Since the early work of van Tamelen, the epoxide motif has emerged as a valuable initiator for cationic polyene cyclization cascades, and is frequently used in total synthesis.[21] It is noteworthy that this principle could as well be extended to aziridines (Scheme 4d). In 2009, Loh reported the indium bromide-catalyzed opening of aziridine **50** to tricyclic amine **51**[53]

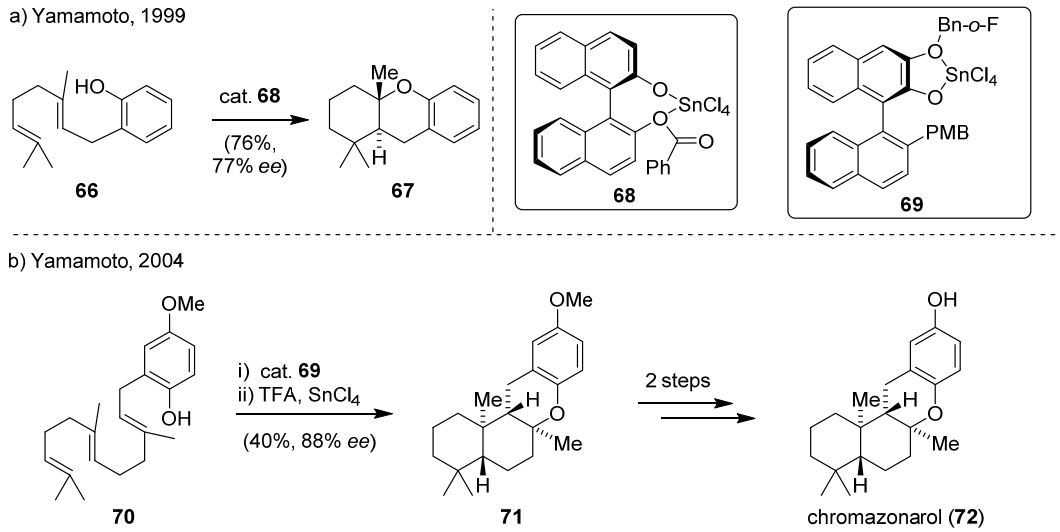



***Scheme 5:*** *Biomimetic tail-to-head cyclizations.*

Although both head-to-tail and tail-to-head polyene cyclizations can be found in nature, it was only recently that the first biomimetic synthesis of a natural product could be accomplished via a tail-to-head cyclization. This underexplored approach allowed Shenvi to synthesize ß-cedrenes (**58**) and ß-funebrenes (**59**) from racemic vinyl epoxide **52** (Scheme 5a).[54] After epoxide activation of **52** through a mixture of methylaluminum dichloride and dimethylaluminum chloride, the generated allylic cation **53** was attacked by the adjacent double bond to yield **54**, which underwent a [1,2]-hydride-shift followed by attack of the isoprene double bond to give **55**. A final carbon–carbon bond formation afforded an epimeric mixture of cation **56**. Aldehyde **57** arose from a terminal hydride shift and was further advanced in two steps into a 2:1 mixture of ß-cedrenes (**58**) and ß-funebrenes (**59**). The key to success was the use of a strong coordinating and non-dissociating Lewis acid to prevent elimination or cation-anion recombination processes to allow non-stop charge propagation.

Tiefenbacher succeeded in combining supramolecular chemistry and tail-to-head polyene cyclizations (Scheme 5b).[55] In his seminal report, he was able to mimic an enzymatic pocket by utilizing a self-assembled supramolecular capsule. Inside the capsule´s cavity, geranyl acetate (**60**), neryl acetate (**61**) or linalyl acetate (**62**) could undergo tail-to-head cyclizations to yield predominantly α-terpinene (**63**) and terpinolene (**64**), along with other fully cyclized monoterpenes.

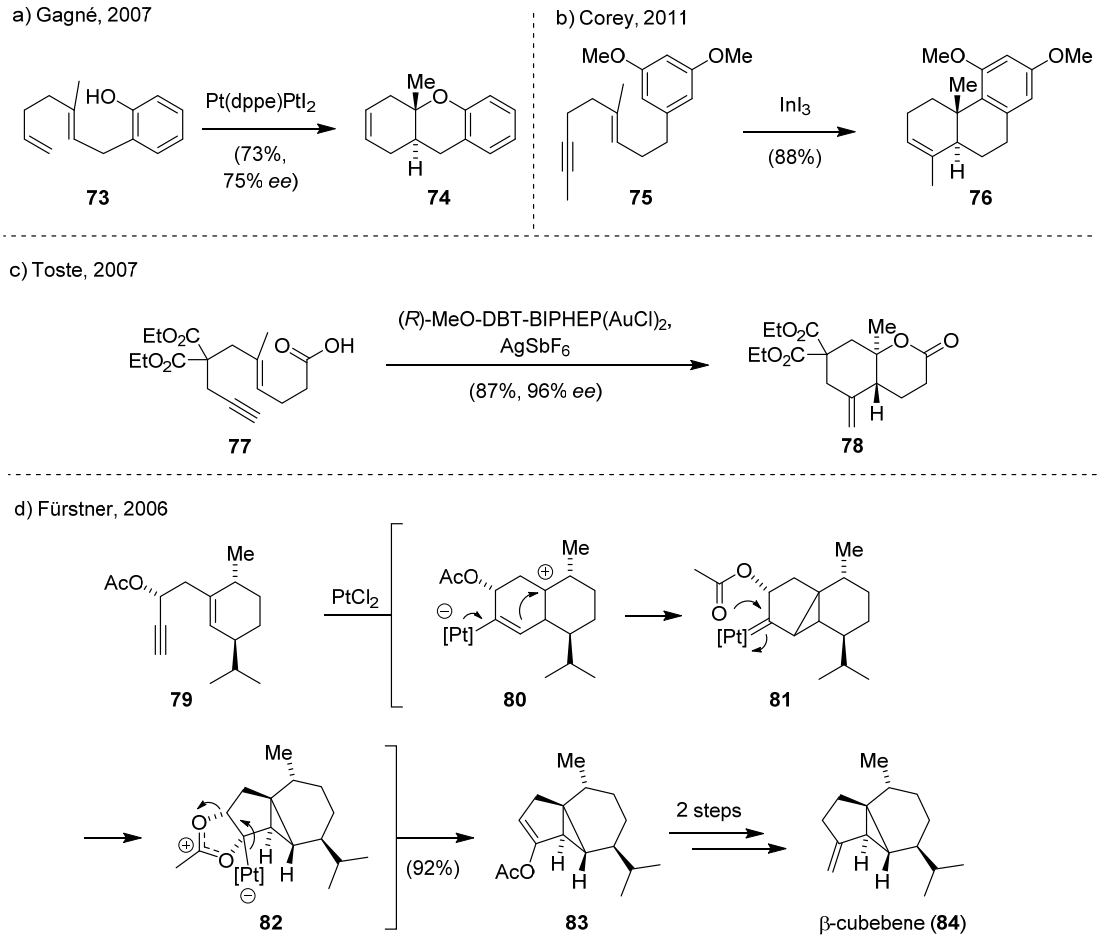
In 1999, Yamamoto reported the first enantioselective proton-induced cyclization of polyenes (Scheme 6a).[56] His pioneering work was based on a Lewis acid-assisted chiral Brønsted acid protonation of an olefin, termed as "LBA". This artificial cyclase is capable of enantioselective protonation of a suitable polyene to initiate the cyclization cascade. In his initial report LBA **68** enabled the isolation of tricyclic ether **67** from diene **66** in good yield and stereocontrol. The utility of this method was demonstrated by its application to the total synthesis of chromazonarol (**72**) from polyene **70**. After successful tricyclization, **71** was deprotected in a two-step sequence to give **72**. Using their optimized LBA **69**, Yamamoto was able to increase the enantiomeric excess from an initial 44% to 88% (Scheme 6b).[57]




***Scheme 6:*** *Lewis acid-assisted chiral Brønsted acid catalyzed polyene cyclization cascades.*

An alternative and equally valuable approach to initiate polyene cycloisomerizations is based on the electrophilicity of transition metal salts. The first reports which exploit the π-acidic character of various mercury(I) salts to induce electrophilic activation of polyenes date back over 40 years.[58-60] Although mercury salts proved to be efficient and reliable initiators to promote the desired cyclizations, stoichiometric quantities of the toxic metal had to be used.[21] To overcome this drawback, Gagné demonstrated the utility of platinum(II) complexes in polyene cyclizations, exemplified by the cyclization of **73** to give enantio-enriched ether **74** (Scheme 7a).[61] In 2007, a report by Corey showed that alkynes, like **75**, can be activated towards nucleophilic addition of an adjacent olefin in a 6-*exo* fashion by catalytic amounts of indium salts to yield polycyclic compounds

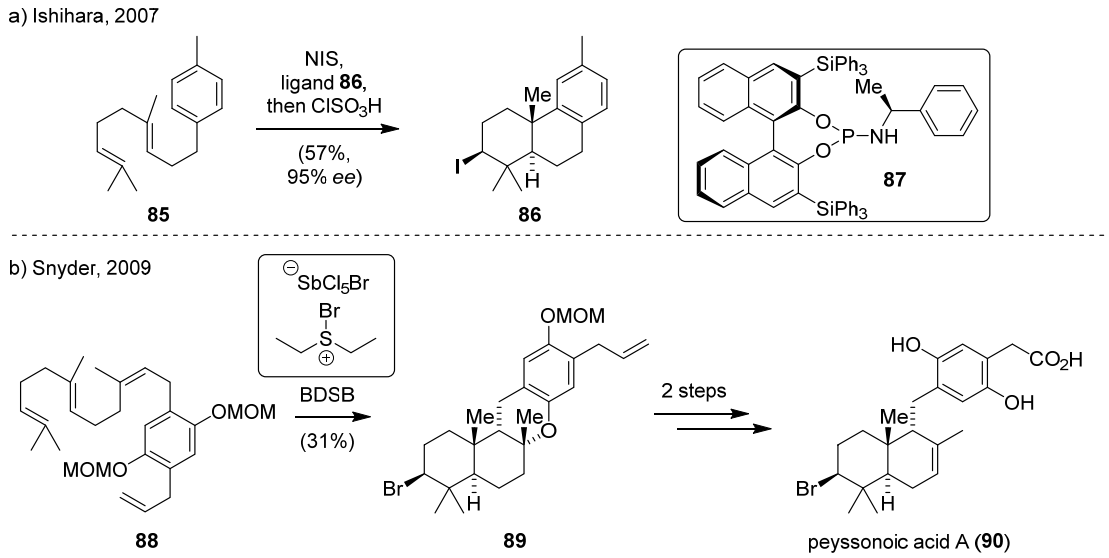
such as **76** (Scheme 7b). Similar to other transition metals, gold(I) species are exceptionally good activating groups for alkynes. Toste exploited this selectivity and developed the first gold(I) catalyzed asymmetric cyclization for enynes (Scheme 7c).[62] Exposure of **77** to the optimized reaction conditions led to the clean formation of **78** in excellent yield and enantiocontrol.




***Scheme 7:*** *Transition metal-catalyzed polyene cyclization cascade.*

A further benefit of the use of transition metals in such cascade reactions lies in their capability to react in a cationic and a "carbenoid-like" fashion.[63] This combined mode of reactivity was beautifully exploited in Fürstner´s total synthesis of β-cubebene (**84**).[64] Exposure of enyne **79** to platinum(II) chloride gave **83** in an impressive 92% yield. After a 6-*endo*-dig cyclization of **79**, the cationic intermediate **80** reacted further to furnish cyclopropyl-carbene complex **81**. Subsequent attack of the adjacent carbonyl group yielded acetate **83** via **82**, which could be transformed to β-cubebene (**84**) in two further steps.

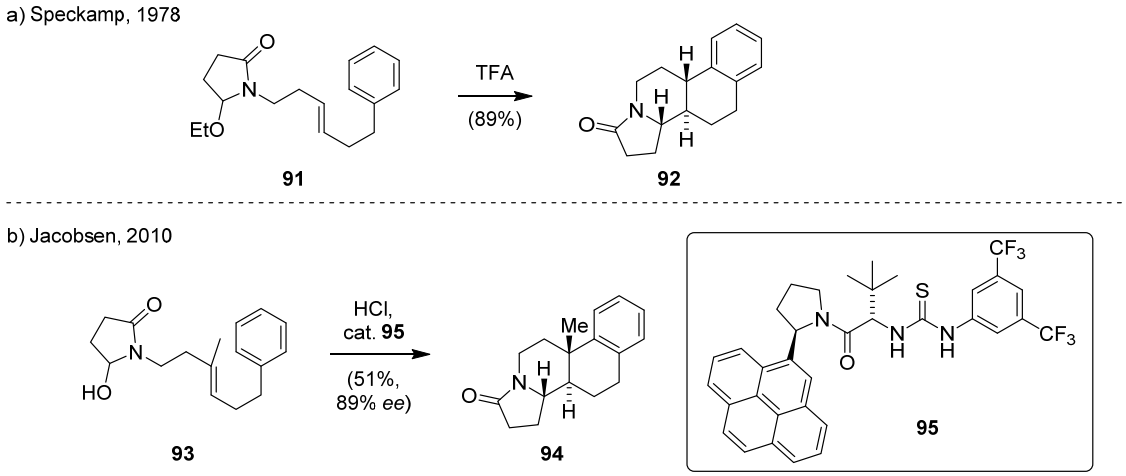
Another landmark achievement in electrophilic polyene initiation was accomplished by Ishihara.[65] Several bio-active marine natural products bear halogenated polycycles and the enantioselective formation of these motifs has been a long standing challenge. Ishihara developed an unprecedented enantioselective halopolyenecyclization by combining the chiral phosphoramidite **87** with *N*-iodosuccinimide (Scheme 8a). The resultant electrophilic chiral iodonium ion serves as an excellent initiating reagent to promote the desired cyclization, exemplified by the formation of **86** from **85** in good yield and enantioselectivity. The exceptional level of stereocontrol can be explained by the formation of a tight ion-pair with a strong hydrogen bonding between the succinimide and the ligand, restricting the P-N bond rotation and constraining the iodonium ion in the sterically hindered region of the chiral pocket formed by the ligand. This method is limited to iodide, as the use of *N*-bromo-succinimide or *N*-chlorosuccinimide gave either significantly diminished reactivity or enantio-selectivity. Regardless, this is unquestionably a major discovery.




***Scheme 8:*** *Halonium-ion induced polyene cyclizations.*

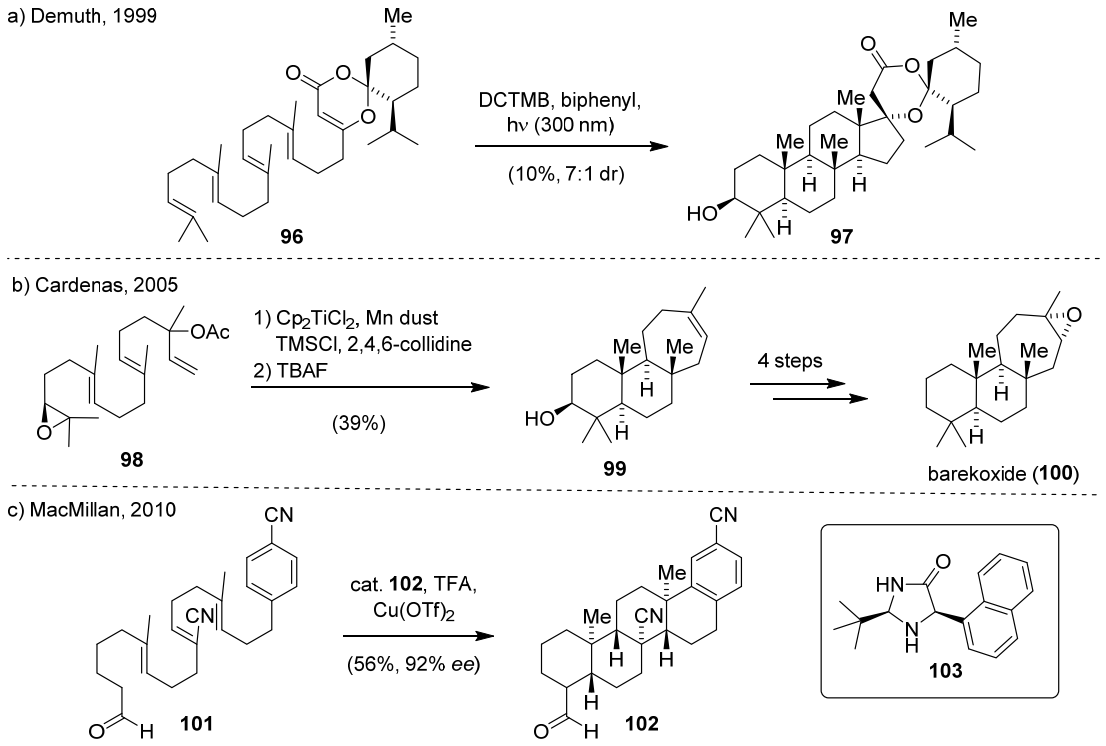
As brominated and chlorinated natural products outnumber the iodinated ones Snyder successfully developed a brominating reagent which allows for fast and selective polyene cyclizations under mild conditions (Scheme 8b).[66-67] A key design element of the initiating reagent BDSB (bromodiethylsulfonium bromopentachloroantimonat) was the use of a non-nucleophilic and non-basic counterion. The utility of this novel reagent was demonstrated in the racemic total syntheses of several brominated natural products. Exposure of polyene **88** to BDSB led to the formation of tetracycle **89**, which could be further converted to peyssonoic acid A (**90**). Unfortunately, attempts to develop an enantioselective variant of BDSB have been unsuccessful so far.

In 1978, Speckamp demonstrated that *N*-acyl iminium ions can serve as the starting point for polyene cyclizations for the first time (Scheme 10a).[68] Upon activation of hemiaminal **91** using a Brønsted acid, polycyclized product **92** could be obtained in excellent yield. Based on this seminal work, Jacobsen extended this method to an enantioselective variant. The use of chiral thiourea organocatalyst **95** provided cyclized products such as **94** from hemiaminal **93** in high yield and with exceptional enantioselectivity (Scheme 9b).[69] During the catalyst optimization studies, Jacobsen observed that larger aryl substituents on the catalyst proved beneficial for enantiocontrol and catalyst turnover. This provided evidence that the catalyst can stabilize the intermediate positive charge developed within the cyclization with cation-π interactions.




***Scheme 9:*** *Organocatalytic cyclization cascades.*

Breslow initially speculated that epoxysqualene (**28**) could be cyclized in a free-radical pathway during the biogenesis of terpenes.[70] This, along with his initial observation that the addition of radical species to the terminal position of polyenes can competently initiate cyclizations, laid the foundation for new remarkable radical-based methods to initiate polyene cyclizations.[70-74] For example Snider developed a manganese(III)-mediated oxidative protocol for the radical polyene cyclization of 1,3-dicarbonyls.[75] Through a photo-induced electron-transfer using 1,4-dicyano-tetramethylbenzene (DCTMB) in the presence of biphenyl, Demuth was able to pentacyclize polyene **96** to alcohol **97**, via the intermediate formation of a radical cation (Scheme 10a).[76] Moreover, by using the remote auxiliary (–)-menthone, he could induce diastereoselectivity during the cyclization step. Mechanistically, the reaction can be divided into two distinctive events. After generation of the radical cation species, the cation was trapped by water to yield the secondary alcohol, whereas the radical species was propagated through the polyene to form the pentacyclic framework of **97**.




***Scheme 10:*** *Radical-based approaches used for polycyclizations.*

In 2005, Cardenas demonstrated the utility of epoxides as initiating groups in radical-based cyclizations.[77] The use of bis(cyclopentadienyl)-titanium(III) chloride, a reagent first introduced by RajanBabu, initiated the polyene cyclization cascade through reductive epoxide opening and led to formation of **99** from epoxide **98** after two 6-*endo* and a final 7-*endo* cyclization.[78] Tricycle **99** was then further converted to barekoxide (**100**) within four additional steps. Even though several radical initiated cyclization cascades were previously reported, it was not until 2010 that an enantioselective variant was developed by MacMillan. He successfully applied his previously developed strategy of using chiral imidazolidinones as catalysts for enamine oxidations for the cyclization of polyenes bearing an aldehyde (Scheme 10c).[79] After enamine formation through condensation of the secondary amine of **103** with aldehyde **101**, a single electron oxidation occurred generating an intermediate α-iminyl radical, which was best propagated through the polyene if the electronic nature of the participating olefins alternates from electron-rich to electron poor, exemplified by the pentacyclization to **102**.

Considering these discoveries, one can clearly see that polyene cyclizations are a powerful tool in organic synthesis. Within a minimum amount of synthetic operations, various structurally complex molecules can be built in a highly efficient and selective manner. Every approach explored addresses different features of the polyene cyclization event and finds application in the synthesis of various natural products. Nevertheless, it seems inevitable that new methods must be developed to further advance the field of cyclization cascades, and to access even more complex molecular architectures with scalable efficiency.

## 1.3. The Aureol Family of Meroterpenoids

### 1.3.1 Overview and Introduction

In recent years, a variety of structurally diverse sesquiterpene natural products have been isolated from marine and terrestrial organisms.[80-83] Since the isolation of avarol (**104**) from the extracts of the marine sponge *Dysidea avara* by Minale in 1974, more than 100 structurally related secondary metabolites have been obtained from various sources (Figure 3).[84-85] In particular, the excellent cytotoxic, antiproliferative and antiviral properties of these sesquiterpenes make them promising lead compounds for further pharmacological studies.[85]

Structurally, one can further distinguish these natural products between "acyclic" congeners, in which the decalin is linked to the various arenes through a methylene bridge, and tetracyclic ones, in which the aromatic phenol forms a second bond to the decalin. Aureol (**105**) was the first member of the tetracyclic subclass and was isolated by Faulkner in 1980.[86] Since then, several natural products with this rare framework have been isolated from both marine sources and microorganisms (Figure 3).

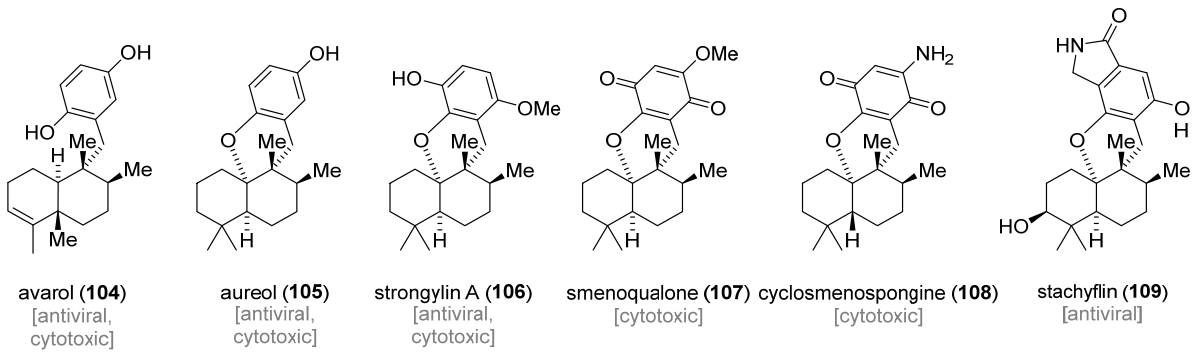



***Figure 3:*** *Selected tetracyclic members of the meroterpenoid family of natural products and their biological activities.*

These meroterpenoids feature a tetracyclic skeleton containing four to five stereogenic centers. The diverse aromatic moieties are fused to the rearranged drimane ring-system by a dihydropyran, thereby forming a benzo[*d*]xanthene. In contrast to aureol (**105**) and strongylin A (**106**), smenoqualone (**107**) and cyclosmenospongine (**108**) bear a unique quinone, whereas a relatively uncommon isoindolinone can be found in stachyflin (**109**). In comparison to these closely related meroterpenoids, which all have a *cis*-decalin incorporated in their skeleton, the decalin-ring system of cyclosmenospongine (**108**) is *trans*-fused.

### 1.3.2 Isolation and Biological Activity

Apart from their appealing structure, most of these natural products possess a wide range of biological activities.[85] Aureol (**105**) was initially isolated from the Caribbean sponge *Smenospongia aurea* by Faulkner in 1980 and subsequently by Pansini from the Caribbean sponge *Verongula gigantea* in 2000.[86-87] This marine natural product shows selective cytotoxicity against human cancer cell lines, including colon adenocarcinoma HT-29 ($IC_{50}$ = 15 μM) and nonsmall cell lung cancer A549 ($IC_{50}$ = 15 μM), antiviral activity against the influenza A strain H1N1($IC_{50}$ = 11 μM) and antimicrobial activity against the *Mycobacterium tuberculosis* strain H37Rv (31% inhibition at 20 μM).[88-90]

In 1991, strongylin A (**106**) was isolated by Wright from the Caribbean sponge *Strongylophora harmani* and was also subsequently isolated from the *Xestospongia wiedenmayeri* Bahamian sponge by the Schering company in 1995.[91-92] Strongylin A (**106**) also displays antiviral activity against the influenza A H1N1 strain ($IC_{50}$ = 19 μM) and shows cytotoxicity against P388 murine leukemia tumor cells ($IC_{50}$ = 48 μM).[91]

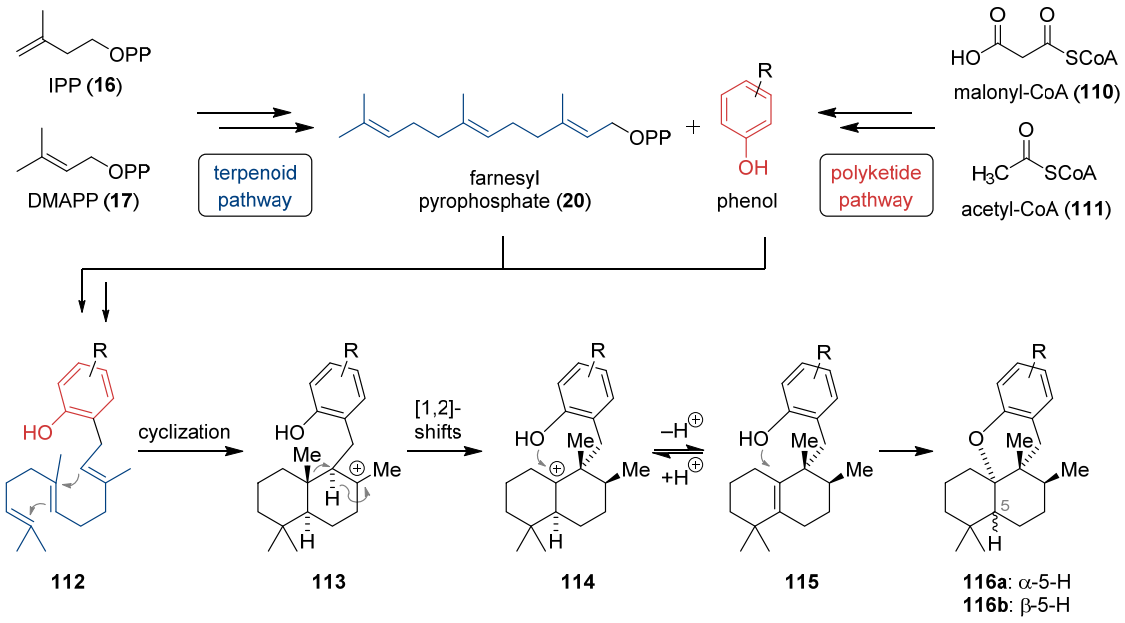
The unique marine meroterpenoid smenoqualone (**107**) was isolated from sponge *Smenospongia* sp. in 1992 by Guyot as a minor product.[93] Although cyclosmenospongine (**108**) can be regarded as the aminoquinone derivative of **107**, it is the only tetracyclic congener bearing a *trans*-fused decalin ring system.[94] Cyclosmenospongine (**108**) was isolated by Utkina from the marine sponge *Spongia* sp. in 2003, and shows low cytotoxic effects ($IC_{50}$ = 0.12 mM) against Ehrlich carcinoma cells.[95-96]

Stachyflin (**109**), by far the most bioactive sesquiterpenoidal natural product of this class, is not of marine origin. It was first isolated by Shionogi & Co., Ltd. in Japan from the fungus *Stachybotrys* sp. RF-7260 by solid state fermentation.[97] With an $IC_{50}$ of 3 nM against the influenza A H1N1 subtype, stachyflin (**109**) outperforms the biological activity of the approved drugs amantadine (Symmetrel®) and zanamivir (Relenza®) by a factor of 250 and 1800, respectively.[98] The observed novel mode of action makes stachyflin (**1**) a promising lead component for future pharmacological studies. Stachyflin (**109**) effectively binds to the viral protein hemagglutinin, thereby preventing virus-cell membrane fusion from occurring.[99] In addition, stachyflin (**109**) displays cytotoxic effects against MDBK cells ($IC_{50}$ = 65μM).[98]

The diverse biological activities that can be found within this class of tetracyclic meroterpenoids offer promising opportunities for the development of new therapeutic agents, which highlights the enormous potential of natural product based drug discovery.

### 1.3.3 Biosynthesis

All members of the aureol family of natural products can be classified as meroterpenoids. This term describes hybrid compounds which share a mixed biosynthetic origin (Scheme 11).[82, 100] In the case of the aureol family, the decalin core can be traced back to farnesyl pyrophosphate (**20**), which itself is derived from the terpenoid pathway.[2] The precise biogenesis of the various aromatic moieties incorporated into the different meroterpenoids probably differs for every congener. Nonetheless, the different phenols most likely originate from malonyl-CoA (**110**) and acetyl-CoA (**111**), which are assembled to the specific aromatic cores via the type I or II polyketide pathway.[2, 101-102] Farnesyl pyrophosphate (**20**), as already mentioned, has its biosynthetic origin in the terpenoid pathway. One molecule of dimethylallyl pyrophosphate (DMAPP, **17**) is elongated sequentially in a tail-to-head manner with two molecules of isopentenyl pyrophosphate (IPP; **16**). This process is catalyzed by enzymes called prenyl transferases and mechanistically resembles the catalytic cycle of class I terpenoid cyclases (*cf.* Chapter 1.2.3.). After enzymatic cleavage of the pyrophosphate unit of DMAPP (**17**) the allylic cation is attacked by the π-bond of IPP (**16**). This is followed by the stereospecific elimination of a proton to furnish the elongated polyene. [28, 31] Both building blocks merge into polyene **112**, the substrate for the polyene cyclization cascade, which is triggered by activation of the isoprene, or in the case of stachyflin (**109**) the corresponding epoxide. After decalin **113** is formed, two sigmatropic and stereospecific [1,2]-hydride and methyl shifts occur to generate cationic intermediate **114**, which could be trapped by the phenolic alcohol to yield the *cis*-fused tetracyclic scaffold of aureol (**105**) and its congeners (**106**, **107** and **109**), or eliminate to **115**. Olefin **115** is considered to be the biosynthetic intermediate for the formation of the *trans*-fused decalin system, which can be found in cyclosmenospongine (**108**).[86, 103-105] A final double bond activation could regenerate the tertiary cation and allow for a diastereoselective ether formation.

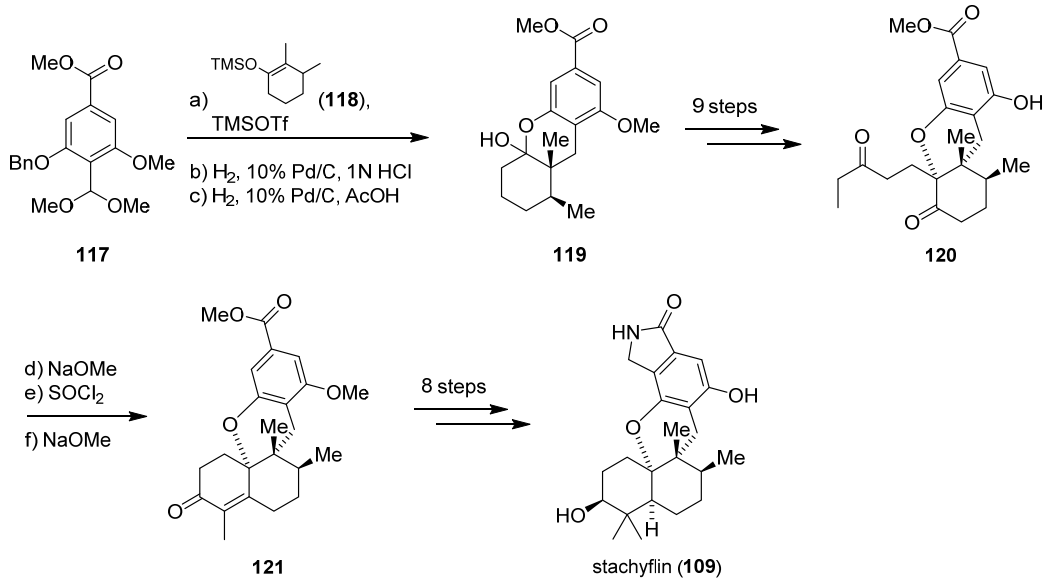



***Scheme 11:*** *Proposed biosynthesis of tetracyclic meroterpenoids (adapted from George).*[106]

### 1.3.4 Previous Work

Because of their diverse and promising biological profiles, along with their intriguing molecular scaffold, several groups have developed elegant syntheses to access these fascinating natural products. These efforts have culminated in a variety of synthetic studies and total syntheses.

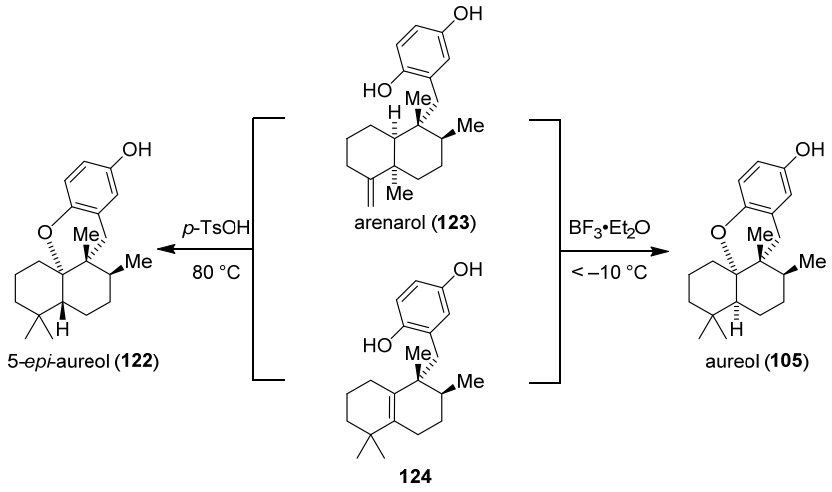
The first racemic total synthesis of the tetracyclic meroterpenoid stachyflin (**109**) was achieved by scientists from the Shionogi research group in 1998 (Scheme 12).[107] Their synthetic endeavor commenced with the preparation of dimethoxy acetal **117** in eight steps from commercially available 3,5-dihydroxybenzoic acid. A Noyori-type aldol condensation of acetal **117** with silylenol ether **118** furnished hemiketal **119** after a subsequent reductive debenzylation and removal of the benzylic methoxy group. Nine further transformations, including a Negishi cross-coupling and iodoetherification gave the advanced intermediate **120**, which is the substrate for an intramolecular aldol cyclization. After dehydration and a base-induced isomerization of the double bond enone **121** was obtained. Completion of the first total synthesis of stachyflin (**109**) included a critical stereoselective hydrogenation to give the desired *cis*-decalin ring system and construction of the γ-lactam.




***Scheme 12:*** *The first racemic synthesis of stachyflin (**109**) by Mori.*

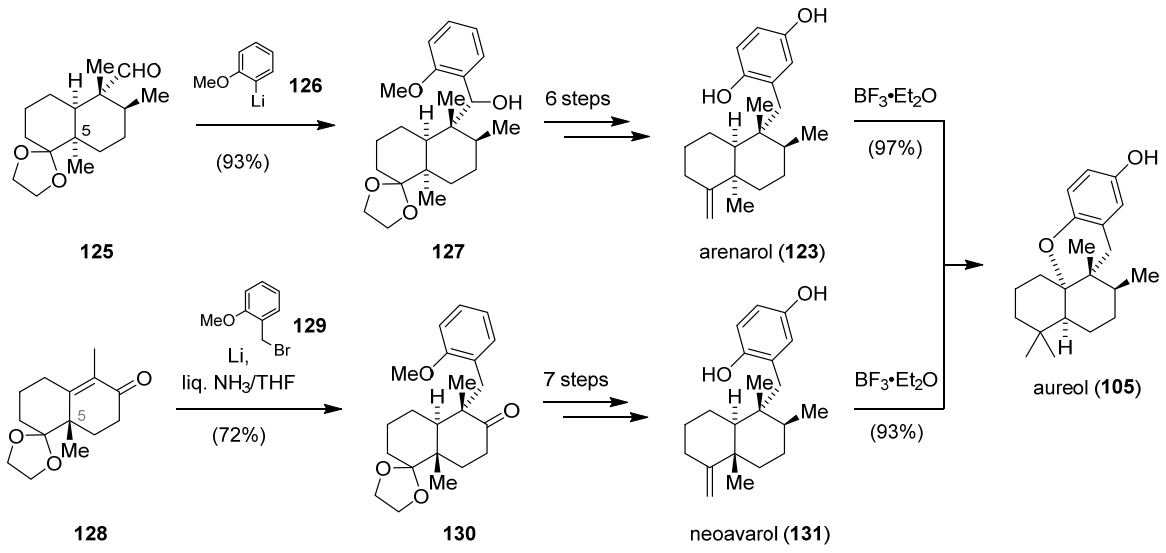
In 2001, Katoh initiated a program for the collective synthesis of this class of natural products using a unified strategy for the assembly of the respective key-intermediates through coupling of different phenols to the preformed decalin, which stems from a Wieland–Miescher ketone derivative.[108] A final bioinspired Lewis-acid induced rearrangement/cyclization cascade was intended to form the *cis*-fused benzo[*d*]xanthene scaffold.[108-109] This cyclization strategy was based on the early work of Faulkner, van der Helm and Capon.[86, 103-105] They showed that upon treatment of arenarol (**123**) or **124** with Lewis- or Brønsted acids the cyclization to aureol (**105**) and 5-*epi*-aureol (**122**) could be accomplished selectively (Scheme 13). Simple variation of the reaction conditions led

to either the kinetically favored *cis*-decalin framework (boron trifluoride etherate, dichloromethane, T < –10 °C), or the thermodynamically more stable *trans*-decalin system (*p*-toluenesulfonic acid, benzene, 80 °C).




***Scheme 13:*** *Selective synthesis of either the cis- or trans-fused decalin-ring system.*

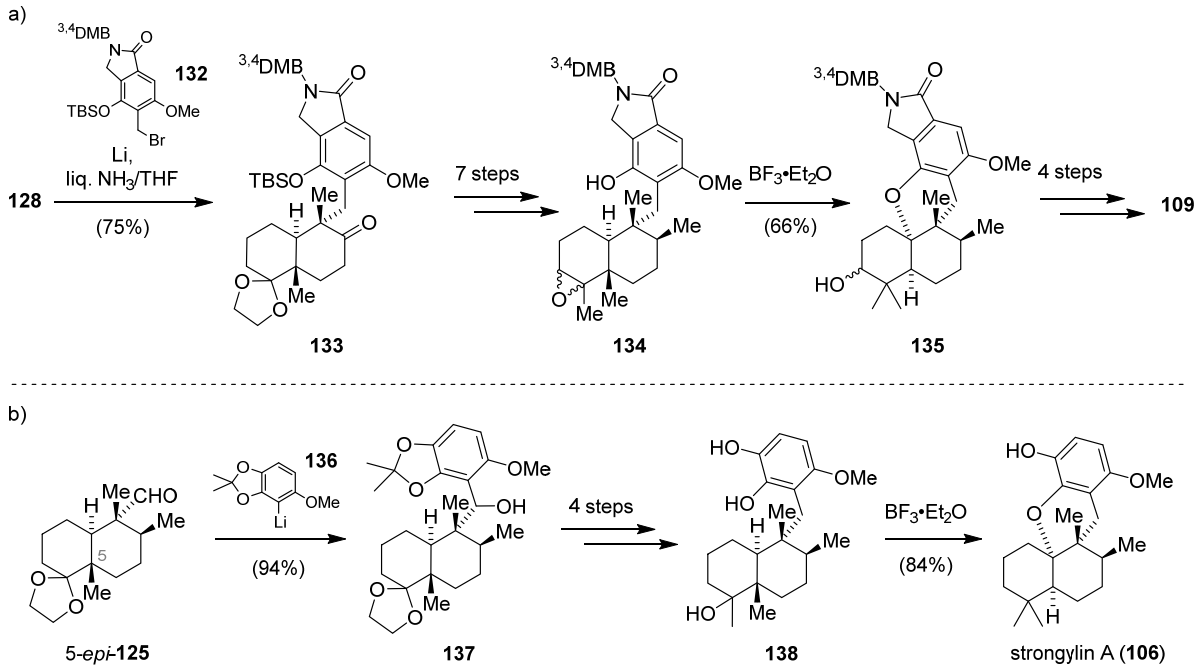
In 2002, the first asymmetric total synthesis of aureol (**105**) was accomplished by Katoh (Scheme 14a).[110] His synthetic approach was based on his previous synthesis of arenarol (**123**).[111] Addition of aryl-lithium **126** onto aldehyde **125**, which was synthesized in 13 steps from 5-*epi*-**128**, gave benzylic alcohol **127**. After conversion of **127** to arenarol (**123**), a boron trifluoride etherate promoted cascade reaction yielded aureol (**105**) in excellent yield. One year later, Katoh developed a more efficient and concise route, based on a reductive alkylation of **129** under Birch conditions with ketone **128**.[112] The use of ketone **128** instead of aldehyde **125** shortened to route tremendously. Exposure of neoavarol (**131**), which was synthesized in seven steps from **130**, to boron trifluoride again resulted in the selective formation of aureol (**105**).




***Scheme 14:*** *Katoh´s 1st and 2nd generation synthesis of aureol (**105**).*

This approach could also be extended to the synthesis of stachyflin (**109**) (Scheme 15a).[113] Reductive coupling of isoindolinone **132** with known ketone **128** yielded **133**, which could be advanced to epoxide **134** within seven synthetic operations. Again the use of boron trifluoride initiated the intended cyclization cascade to afford **135** as an isomeric mixture of alcohols. The final four step sequence to stachyflin (**109**) included deprotection and inversion of the neopentylic alcohol through an oxidation/reduction sequence.

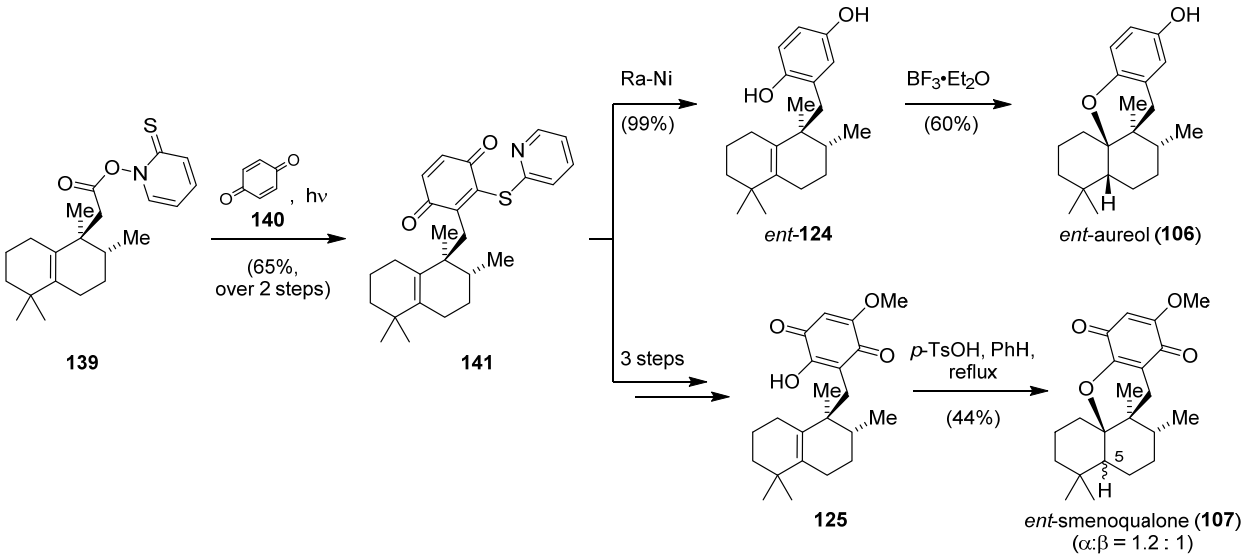
Utilizing the previously describe aldehyde coupling approach, Katoh was also able to synthesize strongylin A (**106**, Scheme 15b).[114] Addition of aryllithium species **136** to 5-*epi*-**125** resulted in the clean formation of **137**. After formation of **138** from **137** within four steps the introduced tertiary alcohol severed as the starting point of the final cyclization cascade. Initiation of the cyclization/rearrangement cascade was again achieved using boron trifluoride and yielded strongylin A (**106**) in excellent yield.




***Scheme 15:*** *The stachyflin (**109**) and strongylin A (**106**) syntheses by Katoh.*

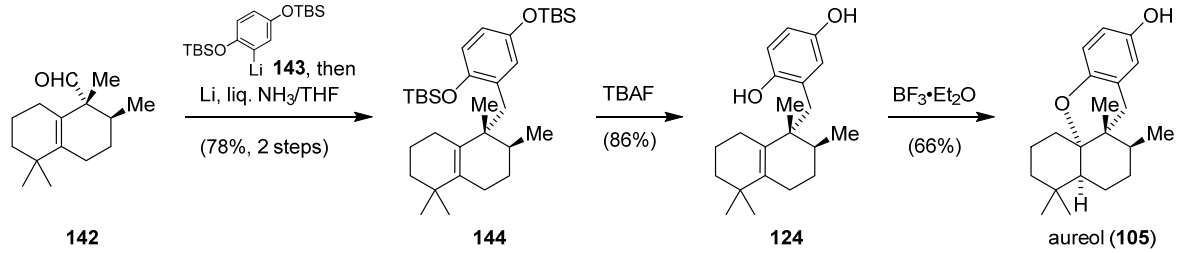
In contrast to the Katoh syntheses, in which the decalin core was accessed from a Wieland–Miescher ketone derivative, Marco´s synthetic strategy was based on a chiral-pool approach (Scheme 16).[115] The synthesis of the first key intermediate **139**, required eleven steps from commercially available *ent*-halimic acid. The first critical step was a previously established light initiated Barton radical decarboxylation/*p*-benzoquinone addition sequence of **139** in the presence of 1,4-benzoquinone (**140**) which gave quinone **141** in good yield over two steps starting from the corresponding carboxylic acid of **139**.[116] From quinone **141**, *ent*-aureol (**105**) was synthesized via reduction of the *p*-quinone to *ent*-**124**, the substrate for the well-established cyclization cascade. Moreover, in the same study Marco concluded the first total synthesis of the natural product smenoqualone (**107**). Quinone **141** was

converted into hydroxyquinone **125** in three additional steps. Carrying out the cyclization under Brønsted acid catalysis and thermodynamic conditions gave a mixture of *ent*-smenoqualone (**107**) and its 5H-epimer in a ratio of 1.2 to 1 in favor of the *cis* fused decalin.




***Scheme 16:*** *Marco´s synthesis of ent-aureol (**105**) and ent-smenoqualone (**107**).*

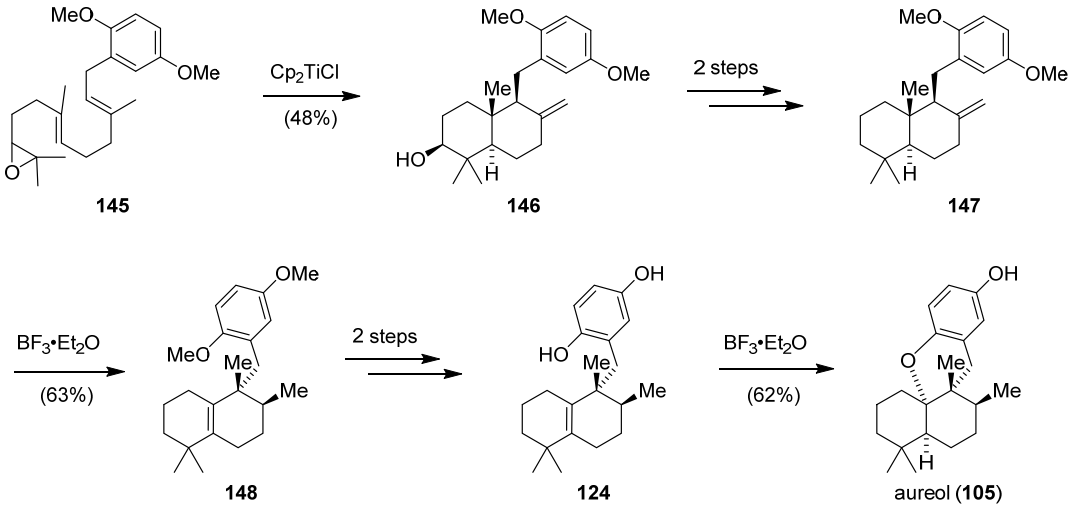
Another synthesis of aureol (**105**) utilizing a chiral pool strategy was developed by George in 2012 (Scheme 17).[106] Starting from commercially available sclareolide, he could synthesize aldehyde **142** in eight steps. To avoid the cumbersome deprotection of the phenol methyl ethers, he chose bis-silyl protected arene **143** as the coupling partner.[110] The resultant benzylic alcohol was subsequently removed under Birch conditions to directly yield **144**. After desilylation, hydroquinone **124** was cyclized under standard Lewis acidic conditions to conclude the synthesis of aureol (**105**).




***Scheme 17:*** *Synthesis of aureol (**105**) by George.*

Recently, Oltra developed a fully biomimetic total synthesis of **105** (Scheme 18).[117] In contrast to the previously reported syntheses, he was able to set the required stereochemistry of the decalin without the need of chiral precursors. A titanium(III) mediated radical cyclization of epoxypolyene **145**, which was derived from farnesol, furnished **146** as a single diastereomer. The obtained bicyclic system was then converted into **147** through a Barton–McCombie deoxygenation

sequence, followed by the first boron trifluoride induced rearrangement to yield methoxy protected **148**. A final demethylation yielded the well-established cyclization precursor **124**, which was again cyclized using boron trifluoride etherate to yield aureol (**105**).



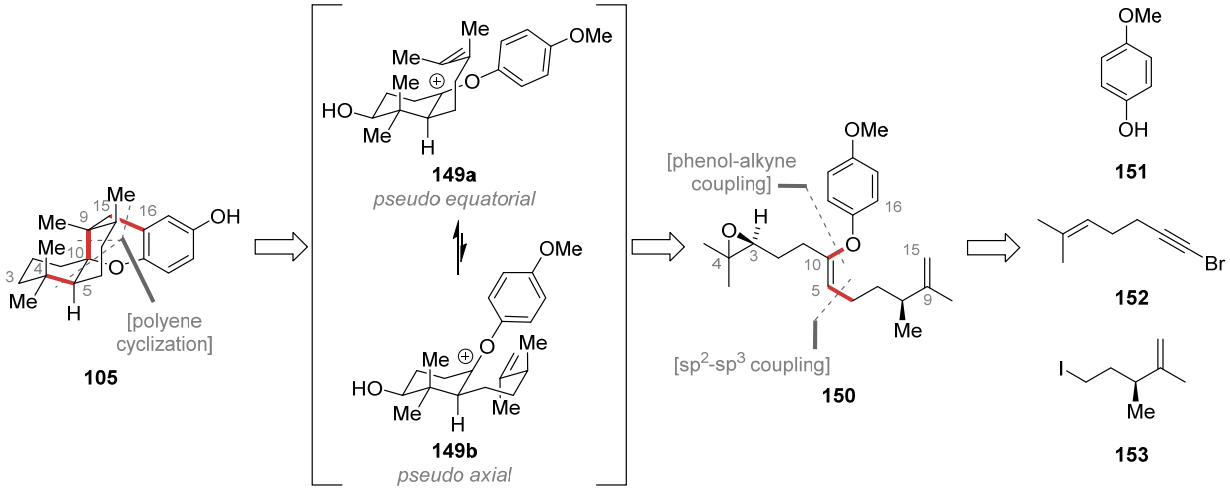

***Scheme 18:*** *Oltra´s biomimetic aureol (**105**) synthesis.*

## 1.4. Results and Discussion

### 1.4.1. Project Outline: Synthesis of Meroterpenoid Natural Products

Due to emerging drug resistance of influenza viruses and the astonishing antiviral and cytotoxic activities of these meroterpenoid natural products, we sought to develop a robust and flexible synthetic platform that would allow us to access a library of natural and non-natural derivatives of this fascinating class of tetracyclic natural products. Since first structure-activity relationship studies revealed that the biological activities can be drastically altered by simple structural modifications, we aimed to develop a highly modular synthesis with respect to possible modifications.[118]

In contrast to the previous syntheses, which were almost exclusively based on the well-established late stage formation of the ether bridge (*cf.* Chapter 1.3.4), we envisioned assembly of the tetracyclic scaffold within one step via an unprecedented, non-biomimetic Lewis acid-promoted polyene cyclization cascade of epoxide **150** (Scheme 19). Our synthetic plan was guided by biosynthetic considerations and previous synthetic studies. It was shown that a polyene cyclization followed by subsequent Wagner–Meerwein rearrangements could produce the unique substitution pattern of these meroterpenoids.[117] Nevertheless, these two independently occurring events can only be performed in a stepwise manner using a traditional polyene cyclization approach. To account for the limitations of synthetic methodology to mimic these two independently occurring events in a single operation, we decided to investigate the cyclization of a polyene which already features the necessary substitution pattern. Based on these considerations we set out to develop a concise and highly modular retrosynthesis.

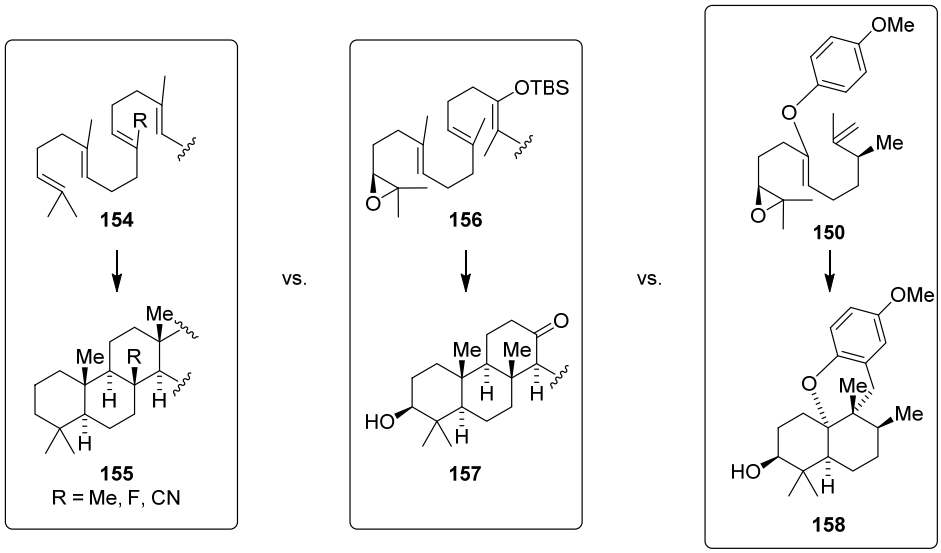



***Scheme 19:*** *Retrosynthesis of aureol (**105**).*

A careful three dimensional analysis of aureol (**105**) allowed us to identify the retrosynthetic bond disconnections highlighted in red. After disconnection of the C4–C5, C9–C10 and the C15–C16

carbon bonds and unfolding of the dissected carbon skeleton, the highly simplified cyclization precursor **150** was revealed. We predicted that epoxide **150** could undergo a non-biomimetic cationic polyene cyclization after Lewis-acid activation. This remarkable and unprecedented transformation could forge the tetracyclic scaffold, and set two quaternary and one tertiary stereocenter in a single reaction. Further dissection of **150** led to identification of three building blocks of equal complexity, which could be united by convergent fragment coupling. A base-mediated phenol alkyne coupling of bromoenyne **152** with phenol **151** should generate the corresponding bromoenol ether, which serves as the substrate for a subsequent $sp^2$-$sp^3$ cross-coupling with iodide **153**.

Although we were uncertain about the influence of the arylenol-ether geometry on the folding and cyclization of **150** due to the lack of literature precedent, we hypothesized that the cyclization would proceed through a highly organized chair-like transition-state as depicted in Scheme 19. After the first bond formation, the sterically demanding aryl ether substituent should favor the pseudo-equatorial alignment **149a** over the energetically unfavored pseudoaxial folding of **149b**. As such, subsequent nucleophilic attack of the adjacent olefin should exclusively occur from the top face to generate the *cis*-decalin framework, which is conserved amongst aureol (**105**) its several congeners.

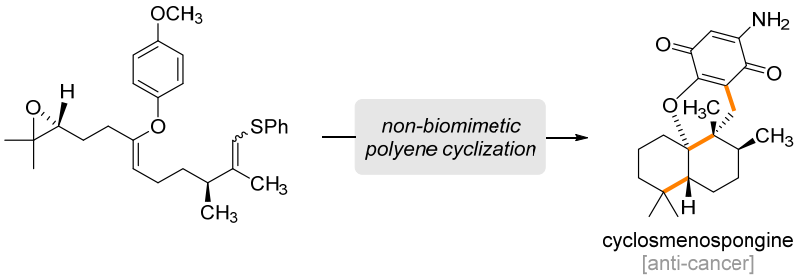



***Scheme 20:*** *Overview of substituted polyenes used in synthesis so far.*

Notably, this polyene cyclization cascade would extend the scope of cationic cyclization cascades tremendously. In a typical polyene cyclization, the double bond substitution pattern has so far been restricted to methyl substituents. Although a variety of terminating groups could be successfully implemented in such cascades, typically arenes, few substrates containing more complex substitutions have been investigated (Scheme 20). Thus far, Johnson utilized a fluoride to favor six versus five-membered ring formation, MacMillan used nitriles to tune the electronics of the participating olefins, whereas Corey exploited the reactivity of silylenol ethers to again favor selective six-membered ring formation and introduce a ketone as a handle for further functionalization.

## 1.4.2. Convergent Assembly of the Tetracyclic Meroterpenoid (–)-Cyclosmenosongine via a Non-Biomimetic Polyene Cyclization





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# Convergent Assembly of the Tetracyclic Meroterpenoid (−)-Cyclosmenospongine by a Non-Biomimetic Polyene Cyclization

*Klaus Speck, Raphael Wildermuth, and Thomas Magauer**

***Abstract:*** *The cationic cyclization of polyenes constitutes a powerful and elegant transformation, which has been utilized by nature's biosynthetic machinery for the construction of complex polycyclic terpenoids. Previous studies by chemists to mimic this cyclization in the laboratory were limited to different modes of activation using biosynthetic-like precursors, which accommodate only simple methyl-derived substituents. Here we describe the development of an unprecedented and highly efficient polyene cyclization of an aryl enol ether containing substrate. The cyclization was shown to proceed in a stepwise manner to generate three rings and three consecutive stereocenters, two of which are tetrasubstituted, in a single flask. The developed transformation is of great synthetic value and has enabled the convergent assembly of the tetracyclic meroterpenoid (−)-cyclosmenospongine.*

Nature utilizes cationic polyene cyclizations as a powerful tool to construct terpenoids of remarkable structural complexity.[1] The carbon decoration of these natural products originates from the individual alkyl substituents along the acyclic polyene precursors and varies depending on the degree of post-modifications. The underlying enzymatic processes have been extensively studied during the last decades[2,3] and the development of methods to mimic these steps in the chemical laboratory have also received great attention.[3] Owing to the substitution pattern of most terpenoids, cyclization precursors with methyl-substituted olefins represent the majority of investigated substrates thus far (Figure 1 a). To the best of our knowledge, precursors that contain more complex substituents or heteroatoms at the central olefin unit have been unexplored (Figure 1 b). We envisaged the investigation of such substrates as part of our program to develop highly convergent and efficient synthetic approaches to polycyclic terpenoids.[4] Herein we describe the first realization of a non-biomimetic cationic polyene cyclization and its application to the convergent assembly of the marine natural product (−)-cyclosmenospongine (**1**),[5] whose tetracyclic carbon framework is conserved among a whole family of meroterpenoids with remarkable biological activities.[6,7] Our studies revealed that subtle modifications within the acyclic precursor proved to be crucial for the successful cyclization, which generates three rings and sets three stereocenters in a single transformation.

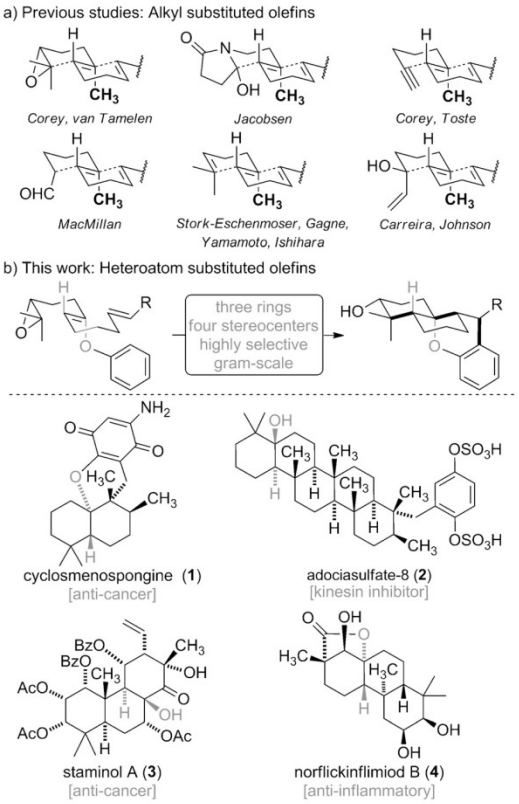


***Figure 1.*** a) Chemists have developed various methods to mimic nature's stereospecific cationic polyene cyclization to assemble complex polycyclic terpenoids. b) The cyclization of aryl enol ether containing substrates has been unexplored and would enable rapid access to hydroxylated decalin subunits of polycyclic terpenoids.

For the realization of this concept, we first analyzed the structure of **1** from several three-dimensional perspectives and thereby identified the retrosynthetic bond disconnections as depicted in Scheme 1. This operation revealed the highly simplified cyclization precursor **5**, itself derived from the convergent component coupling of commercially available phenol **6**, known 1-bromoalkyne **7**,[8] and alkyl iodide **8**. The aryl substituent in **5** not only served as the masked *p*-quinone subunit of **1** but also led to increased chemical stability when compared to alkyl enol ethers.

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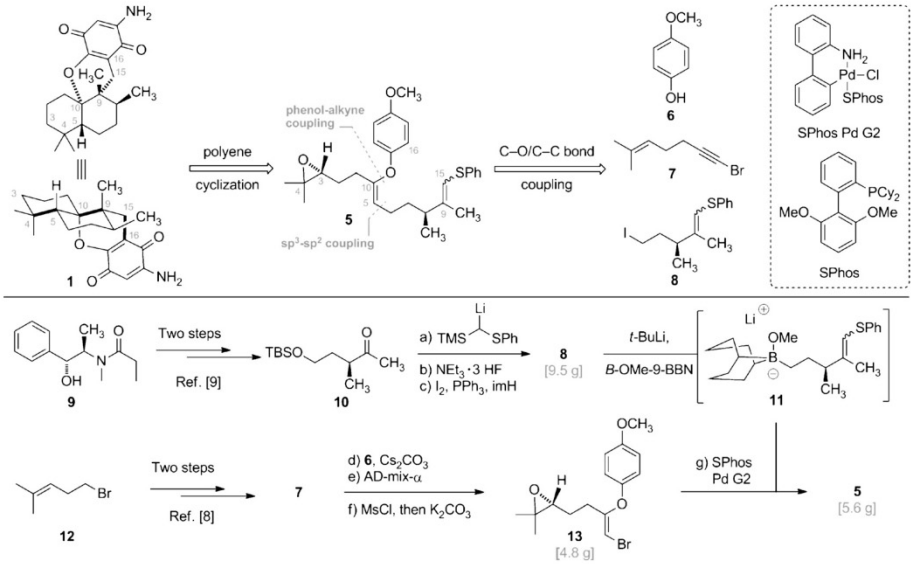


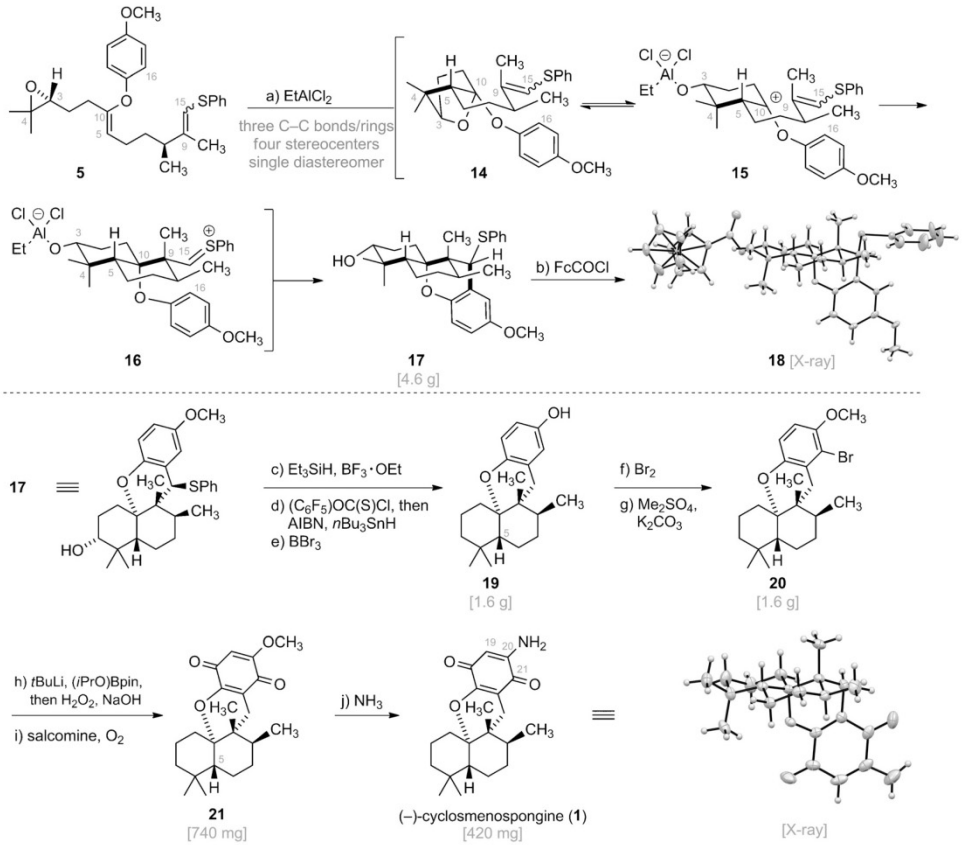

***Scheme 1.*** The non-biomimetic guided retrosynthetic bond disconnection of **1** at C4–C5, C9–C10, and C15–C16 produces enol ether **5**, which can be rapidly assembled by a highly convergent three-component coupling strategy. Reagents and conditions: a) $TMSCH_2SPh$, *n*BuLi, THF, 0 °C to 23 °C, 86%; b) $NEt_3{\cdot}3\,HF$, $CH_3CN$, 23 °C, 95%; c) $I_2$, $PPh_3$, imH, $CH_2Cl_2$, 0 °C, 81%; d) **6** (10 equiv), $Cs_2CO_3$, DMF, 70 °C, 56%; e) AD-mix-α, *t*BuOH, $H_2O$, 0 °C to 23 °C, 94%; f) MsCl, $NEt_3$, $CH_2Cl_2$, 0 °C to 23 °C, then $K_2CO_3$, MeOH, 23 °C, 76%; g) **8**, *t*BuLi, *B*-OMe-9-BBN, THF, −78 °C to 23 °C; SPhos Pd G2 (5 mol%), SPhos (5 mol%), $Cs_2CO_3$, DMF/$H_2O$ (9:1), 40 °C, 85%; *B*-OMe-9-BBN = 9-methoxy-9-borabicyclo[3.3.1]nonane, imH = imidazole, MsCl = methanesulfonyl chloride, THF = tetrahydrofuran, TMS = trimethylsilyl.

To overcome the lack of cation stabilization at C15 upon C9–C10 bond formation, we equipped iodide **8** with a thiophenyl ether unit. While the devised synthetic strategy accounts for maximum modularity and allows rapid structural adjustments, we were uncertain at this stage about the impact of the enol ether geometry on the *cis*/*trans*-decalin selectivity.

We commenced our investigations with the synthesis of iodide **8** from the known ketone **10** (Scheme 1).[9] Subjecting a solution of **10** in tetrahydrofuran to trimethyl((phenylthio)methyl)silane and *n*-butyllithium cleanly afforded the thiophenyl ether as a mixture of double-bond isomers ($E/Z$ = 2:3). Since the double-bond geometry was inconsequential for the subsequent steps, cleavage of the silyl ether and iodination was carried out without further separation of the isomers to give iodide **8** in good yield on multigram scale. Initial attempts to establish a gold(I)-catalyzed addition of *p*-methoxyphenol (**6**) to **7** were unsuccessful due to a competing enyne cyclization.[8] We then adopted a recently reported procedure for the base-mediated addition of phenols to 1-bromoalkynes.[10] Extensive experimentation revealed that the reaction proceeded best in *N*,*N*-dimethylformamide (DMF; 1.0 M) at 70 °C, employing excess phenol (10 equiv) and cesium carbonate as base (3 equiv). The intermediate bromo enol ether, which is surprisingly stable to flash-column chromatography on silica gel, was then converted into **13** by dihydroxylation of the sterically less hindered olefin using freshly prepared AD-mix-α [$K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2Phal$, $K_2CO_3$, $K_3Fe(CN)_6$] and subsequent intramolecular displacement of the secondary alcohol via the corresponding mesylate. Since low yields were encountered in a Negishi cross-coupling reaction between iodide **8** and enol ether **13**, we considered the *B*-alkyl Suzuki–Miyaura coupling reaction[11] as a viable alternative. Under the optimized reaction conditions (5 mol% SPhos Pd G2, 5 mol% SPhos, $Cs_2CO_3$, THF, DMF, $H_2O$, 40 °C), coupling of **11** with **13** proceeded efficiently to afford the cyclization precursor **5** in excellent yield (85%, 5.6 g). Extensive screening revealed that the choice of Buchwald's SPhos ligand[12] in synergism with cesium carbonate was crucial for high conversion and also essential for avoiding β-hydride elimination from the intermediate palladium(II) species. It is noteworthy that an intramolecular coupling process to give the corresponding benzofuran product was not observed in any of these experiments.[10]

With large quantities of **5** in hand, we focused our attention on the crucial polyene cyclization as illustrated in Scheme 2. To our delight, addition of ethylaluminum dichloride ($EtAlCl_2$) to a solution of **5** in dichloromethane at −78 °C resulted in rapid consumption of the starting material and immediate formation of two new products as judged by thin-layer chromatography. After 30 minutes at −78 °C, we observed complete disappearance of the less polar intermediate and accumulation of the lower component as a single product. Isolation of this compound and extensive two-dimensional NMR spectroscopy supported the structure and stereochemistry as depicted for **17**. Further evidence was




***Scheme 2.*** Realization of a stepwise cationic polyene cyclization that creates three rings and sets four stereocenters in a highly efficient manner on gram scale, and advancement of the tetracycle **17** to the natural meroterpenoid (−)-cyclosmenospongine (**1**). Reagents and conditions: a) $EtAlCl_2$, $CH_2Cl_2$, −78 °C, 83%; b) FcCOCl, DMAP, $CH_2Cl_2$, 23 °C, 70%; c) $Et_3SiH$, $CH_2Cl_2$, $BF_3$·OEt, 0 °C, 97%; d) $(C_6F_5)OC(S)Cl$, DMAP, $CH_2Cl_2$, then AIBN, $nBu_3SnH$, benzene, 64%; e) $BBr_3$, $CH_2Cl_2$, −78 °C to 23 °C, 85%; f) $Br_2$, $CH_2Cl_2$, −55 °C, 93%; g) $Me_2SO_4$, $K_2CO_3$, acetone, 23 °C, 87%; h) *t*BuLi, (*i*PrO)Bpin, THF, −78 °C to 0 °C, then $H_2O_2$, NaOH, 0 °C to 23 °C, 75%; i) salcomine, $O_2$, DMF, 23 °C, 77%; j) $NH_3$, MeOH, $H_2O$, pyridine, 23 °C, 60%. Thermal ellipsoids shown at 50% probability.[19] AIBN = azobisisobutyronitrile, DMAP = 4-dimethylaminopyridine, Fc = ferrocene, pin = pinacol.

provided after esterification with ferrocenecarboxylic acid chloride (FcCOCl)[13] and subsequent single-crystal X-ray diffraction of **18**.

The cyclization of **5**, which is remarkable in many ways, produces **17** as a single diastereomer. This highly efficient sequence of carbon–carbon bond forming events leads to the formation of three rings and installation of four stereocenters, three of which are part of the final meroterpenoid skeleton. The excellent stereoselectivity in this transformation can be attributed to a highly organized transition state, which is fully controlled by the double-bond geometry of the enol ether and the stereocenters at C3 and C8. In view of our results and seminal work by Corey,[14] we believe that only epoxide activation and carbon–carbon bond formation between C4–C5 to give **14** might proceed via a concerted process (Scheme 2). Acetal **14**, which is short-lived using ethylaluminum dichloride ($EtAlCl_2$), and was initially only observed by thin-layer chromatography, could be isolated in pure form after exposure of **5** to the less reactive diethylaluminum chloride ($Et_2AlCl$) and hydrolysis of excess Lewis acid at −78 °C. Further cyclization presumably proceeds via a non-concerted, stepwise mechanism and involves the transient species **15** and **16**. Support for this hypothesis also comes from the observation that both thioenol ether double-bond isomers fully equilibrate to give **17** as a single diastereomer. Notably, the presence of the thioenol ether[15] turned out to be critical for successful promotion of the polyene cyclization. Substrates that were lacking this substitution pattern proved to be unreactive, as nucleophilic attack of the remote C9–C15 olefin at C10 would generate an energetically unfavorable primary carbocation at C15, thus suppressing any further productive pathway.

For the final stage of the synthesis, we had to develop a sequence that allowed us to remove the traceless conforma-

tional anchor at C3 and liberate the benzylic position at C15. Desulfurization of **17** using Raney nickel proved to be sluggish in many cases and gave moderate yields (63%) in large-scale experiments. Gratifyingly, we found that removal of the thiophenyl substituent could be accomplished in excellent yield upon exposure of **17** to triethylsilane in the presence of boron trifluoride diethyerate (97%, 3.3 g; Scheme 2). Subsequent Barton deoxygenation[1b] of the secondary alcohol and methyl ether cleavage ($BBr_3$, −78 °C) afforded 5-*epi*-aureol (**19**; 1.6 g), which has yet to be isolated from natural sources.[7e,16] Although efforts to isomerize the *trans*-decalin to the *cis*-form were unsuccessful at this stage, we were able to convert **19** into (−)-cyclosmenospongine (**1**) via sequential functionalization and oxidation of the arene portion.

For this purpose, **19** was first selectively brominated and methylated to give **20** (1.6 g). Exchange of the bromine substituent for a hydroxy group could be best achieved by formation of the boronic ester (*t*BuLi, (*i*PrO)Bpin) followed by oxidation ($H_2O_2$, NaOH). Treating a solution of the phenol in *N*,*N*-dimethylformamide with salcomine under an atmosphere of oxygen[17] led to selective *p*-quinone formation to give 5-*epi*-smenoqualone (**21**; 740 mg), whose spectroscopic data were in full agreement with those reported previously.[7e,18] From there, (−)-cyclosmenospongine **1** (420 mg) was obtained as a dark-red solid after aminolysis ($NH_3$, MeOH, 23 °C)[5] and column chromatography on silica gel. Crystallization from diethyl ether yielded crystals suitable for single-crystal X-ray diffraction and allowed us to unambiguously validate the proposed structure of **1**. However, we were surprised to observe that the $^1H$ and $^{13}C$ NMR data ($CDCl_3$) showed major inconsistencies ($\Delta = 1.0$–$4.7$ ppm) when compared to the values reported for the isolated natural product.[5] To rationalize the exact origin of this discrepancy, we conducted a series of NMR experiments. While concentration effects could be excluded, successive addition of hydrogen chloride led to immediate formation of a deep-purple solution and significant shifts of the key NMR signals, in particular the C17 to C21 region of the aminoquinone subunit of **1**. The so-obtained $^1H$ and $^{13}C$ NMR data were now in better agreement ($\Delta \leq 2.5$ ppm) with those reported in the literature.[5] Interestingly, formation of the hydrogen chloride adducts was reversible as concentration and re-measurement in acid-free chloroform gave the same spectra as before (see the Supporting Information for NMR studies and details).

In summary, we developed a powerful and operationally simple cationic polyene cyclization for the convergent assembly of tetracyclic terpenoids. This work, which enables rapid access to the cyclization precursor via a modular three-fragment coupling strategy, has enabled the total synthesis of the unique meroterpenoid (−)-cyclosmenospongine (**1**). The highlights of this synthesis are a base-mediated phenol–alkyne addition to give a bromoenol ether, a highly efficient $C(sp^2)$–$C(sp^3)$ Suzuki coupling to provide the trisubstituted aryl enol ether and an unprecedented polyene cascade cyclization to forge the crucial benzo[*d*]xanthene skeleton. In the key step, four adjacent stereocenters, two of which are tetrasubstituted, are generated in a highly diastereoselective manner. We hope to stimulate further research in the area of cationic polyene cyclizations and thereby further enhancing the power of organic synthesis. An application of this strategy to other polycylic terpenoids, investigations aimed at the influence of the enol ether geometry on the *cis*/*trans*-decalin selectivity, and detailed biological studies of **1** are currently underway.

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**Keywords:** cations · cyclization · natural products · total synthesis · terpenoids

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[19] CCDC 1499443 (**18**) and 1499442 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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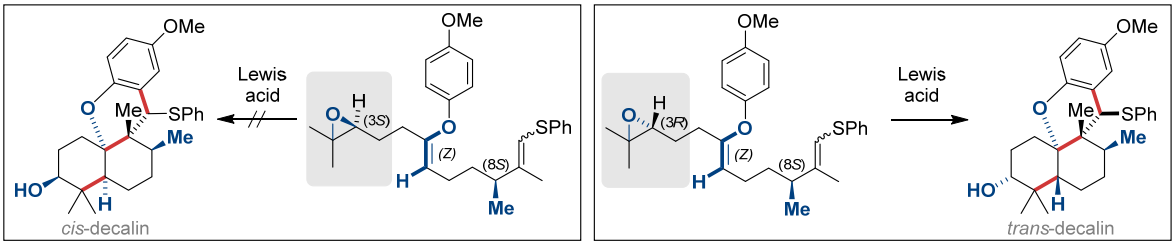
### 1.4.3. Evolution of a Polyene Cyclization Cascade for the Total Synthesis of (–)-Cyclosmenospongine





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# Evolution of a Polyene Cyclization Cascade for the Total Synthesis of (−)-Cyclosmenospongine

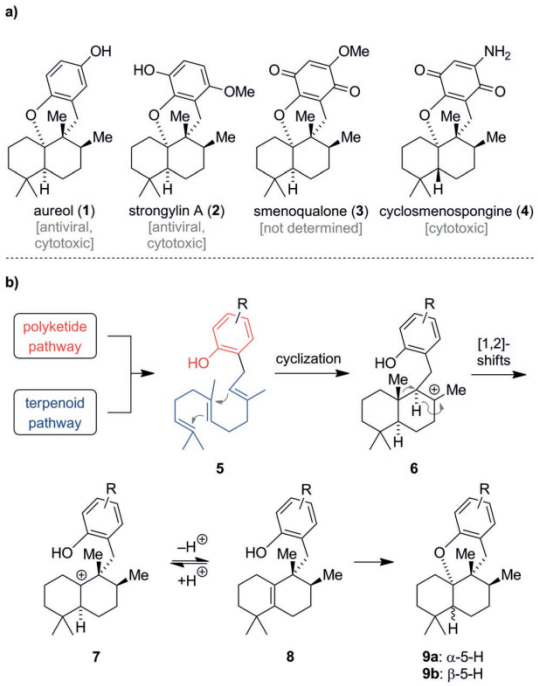
Klaus Speck and Thomas Magauer*[a]

**Abstract:** We report a full account on the development of a unique cationic polyene cyclization for the total synthesis of the tetracyclic meroterpenoid (−)-cyclosmenospongine. A highly convergent three-component coupling strategy enabled rapid access to individual cyclization precursors that were tested for their reactivity. The successful transformation generates three rings and sets four consecutive stereocenters in a single operation proceeding in a highly efficient manner to give exclusively the *trans*-decalin framework. In addition, we found that the enol ether geometry and the relative configuration of C3 and C8 are crucial for the success of the polyene cyclization.

## Introduction

Throughout history, mankind has benefitted from the rich chemical diversity found in nature. While natural products isolated from terrestrial plants have always been an integral part of traditional medicine, marine organisms were long unexplored as a potential source of bioactive molecules.[1] During the past decades, numerous sesquiterpenoids have been isolated from various marine sponges.[2] Within this vast class of natural products, a structurally unique family of tetracyclic meroterpenoids (**1**–**4**) recently drew our interest (Scheme 1 a). Aureol (**1**), the first and eponymous member of this family, was isolated from the Caribbean marine sponge *Smenospongia aurea* by the group of Faulkner in 1980.[3a] Since then, several congeners of this class of tetracyclic meroterpenoids, including strongylin A (**2**), smenoqualone (**3**) and cyclosmenospongine (**4**) have been isolated from various marine sources.[3b–d]

Meroterpenoids are hybrid natural products with a mixed biosynthetic pathway that incorporates polyketide and terpenoid building blocks (Scheme 1 b).[4] The fusion of farnesyl pyrophosphate ($C_{15}$), which originates from the terpene pathway, and a polyketide derived aromatic core gives linear polyene **5**, which undergoes a cationic cyclization cascade to initially produce the key biosynthetic intermediate, drimane **6**.[5] Consecutive [1,2]-hydride and methyl shifts provide cation **7**, which can be either trapped by the adjacent phenol to directly yield the *cis*-fused decalin ring system **9a** (α-5-H) of aureol (**1**) and its congeners (**2** and **3**) or eliminate to give **8**. The latter is considered to be the direct biosynthetic precursor of the *trans*-fused decalin system **9b** (β-5-H), which is present in cyclosmenospongine (**4**).[6,7]




**Scheme 1.** a) Representative members of tetracyclic meroterpenoid natural products and b) their proposed biosynthesis (adapted from George and Faulkner).[3a,9c]

The so-formed tetracycle comprises four consecutive stereocenters, two of which are tetrasubstituted. The aromatic subunit, which can undergo further modifications is fused to either a *cis*- (**1**–**3**) or a *trans*-decalin (**4**) ring system. Although struc-

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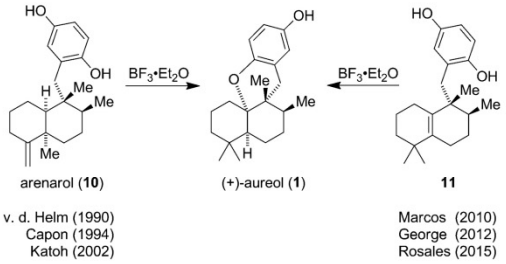
turally closely related, a broad range of biological activities,[2] including antiviral,[3b,8a] anticancer,[4d,8b–h] and antibacterial,[8i] was reported for these natural products.[8i]

Owing to their intriguing structural features and a unique biological profile, several groups have made efforts to develop syntheses of **1**–**4**. As shown in Scheme 2, previous studies towards individual members hinged on the cationic cyclization of biosynthetic-like precursors arenarol (**10**) or **11**.[9a] In the seminal work of Capon and van der Helm, it was shown that exposure of **10** or **11** to Lewis or Brønsted acids promotes cyclization to aureol (**1**) and 5-*epi*-aureol (**38**).[1a,6] By simple variation of the reaction conditions, either the kinetically favoured *cis*-decalin framework ($BF_3{\cdot}OEt_2$, dichloromethane, $T < -10\,^{\circ}C$) or the thermodynamically more stable *trans*-decalin system (*p*TsOH, benzene, 80 °C) were selectively obtained. While the groups of Marcos[9b] and George[9c] developed chiral pool strategies to synthesize **11**, the synthesis of arenarol (**10**) described by the group of Katoh, uses a Wieland–Miescher ketone derivative.[9d–g]

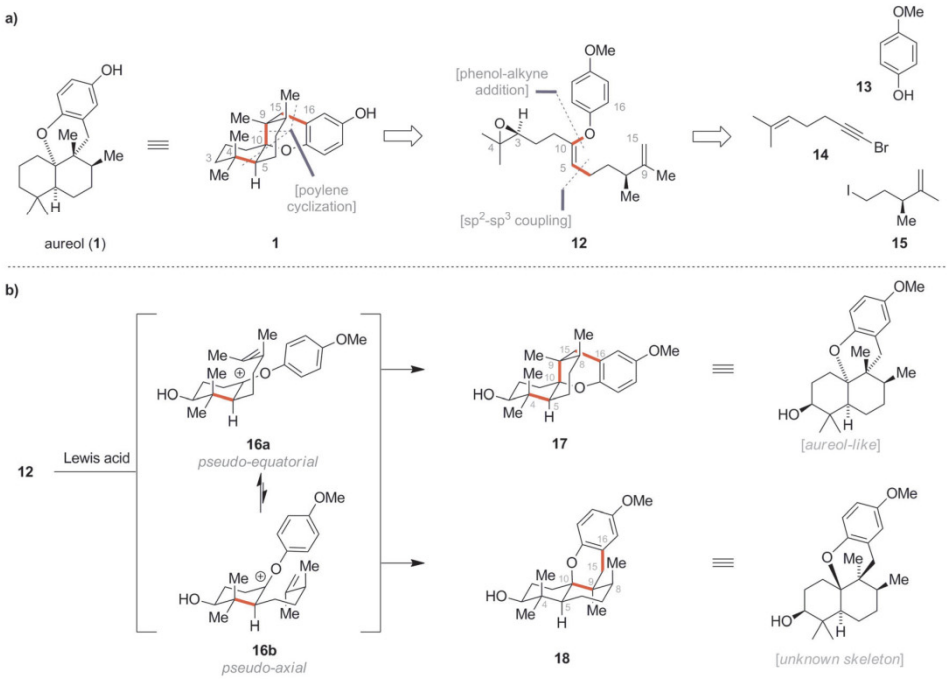



**Scheme 2.** Key intermediates of previous syntheses.

In contrast to these approaches, in which the crucial stereochemistry of the decalin ring system is set in a stepwise manner, Rosales applied a very elegant $Ti^{III}$-mediated reductive epoxide cyclization cascade to construct **11**.[9h] In addition, Cramer reported a ruthenium(III)-catalyzed domino cyclization of a model substrate to access the tetracyclic core of the aureol family of natural products.[9i]

As previous work has shown that formation of the tetracyclic ring system via biomimetic polyene cyclization and Wagner–Meerwein shifts can only occur in a stepwise manner in the laboratory,[9h] we were searching for a strategy to mimic the highly organized environment of an enzymatic active site more efficiently. In order to overcome the current inability of synthetic methodology to mimic these two independently occurring events in a single flask, we recently investigated the cyclization of a well-elaborated polyene.[10] Herein we report the evolution of our idea to assemble the tetracyclic scaffold within one step through an unprecedented polyene cyclization cascade.

Guided by the biosynthesis and inspired by the three-dimensional drawing of aureol (**1**), we identified the retrosynthetic bond disconnections as shown in Scheme 3 a. Scission of the




**Scheme 3.** a) Retrosynthetic analysis of aureol (**1**) and b) hypothetical transition states for the cyclization of **12**.

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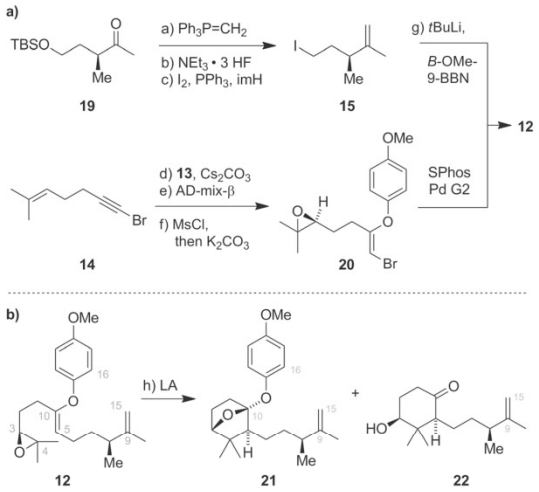
bonds highlighted in red (C4–C5, C9–C10 and C15–C16) revealed the highly simplified cyclization precursor **12**, which was envisioned to undergo the cationic polyene cyclization upon Lewis acid activation of the epoxide. This remarkable transformation would generate three rings and three consecutive stereocenters, two of which are tetrasubstituted, in one step. Further dissection would give three building blocks of equal complexity, which could be united by convergent fragment coupling of phenol **13**, bromoalkyne **14** and iodide **15**.

This modular retrosynthetic approach would allow us to rapidly access a library of both natural and fully synthetic analogues by simple variation of the arene moiety. From a structural point of view, the synthetically most challenging task is the selective formation of the *cis*-decalin. At this point, we were uncertain about the influence of the enol-ether geometry on the folding and cyclization of **15** to either give the desired *cis*-decalin via transition state **16a** or the *trans*-fused decalin ring system resulting from the alternative folding depicted for **16b** (Scheme 3b). At the outset, we hypothesized that the cyclization would proceed in a highly concerted fashion via a chair-like transition state that forces the large aryl ether substituent into the energetically favored pseudo-equatorial position. This would exclusively produce *cis*-decalin framework **18**, which is conserved among aureol (**1**) and several other members of this meroterpenoid family.




**Scheme 4.** a) Synthesis of cyclization precursor **12** and b) attempted cyclization of polyene **12**. Reagents and conditions: a) $PPh_3CH_3Br$, KO*t*Bu, THF, 0 °C to 23 °C, 92%; b) $NEt_3 \cdot 3\,HF$, $CH_3CN$, 23 °C, 95%; c) $I_2$, $PPh_3$, imH, $CH_2Cl_2$, 0 °C, 81%; d) 4-methoxyphenol (**13**) (10 equiv), $Cs_2CO_3$, DMF, 70 °C, 56%; e) AD-mix-β, *t*BuOH, $H_2O$, 0 °C to 23 °C, 88%; f) MsCl, $NEt_3$, $CH_2Cl_2$, 0 °C to 23 °C, then $K_2CO_3$, MeOH, 23 °C, 81%; g) **15**, *t*BuLi, *B*-OMe-9-BBN, THF, −78 °C to 23 °C; SPhos Pd G2 (5 mol%), SPhos (5 mol%), $Cs_2CO_3$, DMF/$H_2O$ (9:1), 40 °C, 72%; h) LA = $Et_2AlCl$, $CH_2Cl_2$, −78 °C, 81% of **21**; LA = $B(C_6F_5)_3$, $CH_2Cl_2$, −78 °C, 54% of **22**; *B*-OMe-9-BBN = 9-methoxy-9-borabicyclo[3.3.1]nonane, imH = imidazole, MsCl = methanesulfonyl chloride, LA = Lewis acid.

## Results and Discussion

We began our synthetic endeavor with the multi-gram synthesis of iodide **15** and bromoenol ether **20** (Scheme 4a). Iodide **15** was prepared starting from the literature known ketone **19**.[11] Wittig olefination of **19**, followed by cleavage of the silyl ether and exposure of the alcohol to Appel 's conditions gave **15** in excellent yield on gram-scale (1.6 g).

Epoxide **20** was synthesized in three steps from 1-bromo-1,5-enyne **14**.[12] Since the previously reported protocol for a base-mediated nucleophilic addition of phenols to 1-bromoalkynes proved to be low yielding and was plagued by side-product formation, we were forced to further optimize the reaction conditions.[13] After extensive screening we found that the addition of 4-methoxyphenol (**13**) to alkyne **14** is best carried out at 70 °C using excess phenol (10 equiv) and cesium carbonate as base (3 equiv) in *N*,*N*-dimethylformamide (1 M). Epoxide **20** was then synthesized through a Sharpless asymmetric dihydroxylation using AD-mix-β and selective mesylation of the secondary alcohol followed by intramolecular nucleophilic displacement. The envisioned palladium-mediated $sp^2$–$sp^3$ cross-coupling of the key building blocks **15** and **20** to give the cyclization precursor **12** proved to be more challenging than anticipated and considerable experimentation was required to establish a mild and efficient protocol that also tolerated the epoxide functionality. As initial attempts to realize the coupling between **15** and **20** using a Negishi cross-coupling were low yielding (ca. 5%), we decided to investigate *B*-alkyl Suzuki–Miyaura coupling conditions. We chose to convert iodide **15** to its corresponding borinate using the "*B*-OMe-9-BBN" variation.[14] The borinate can be conveniently prepared by addition of *tert*-butyl lithium to a premixed solution of **15** and *B*-OMe-9-BBN (1 M in hexanes) in tetrahydrofuran at −78 °C.[15] We found that the use of Buchwald 's Pd SPhos precatalyst system (5 mol% SPhos Pd G2, 5 mol% SPhos, $Cs_2CO_3$, THF, DMF, $H_2O$, 40 °C) was crucial to obtain high yields, short reaction times (typically around 1 h) and to efficiently suppress unwanted β-hydride elimination.[16] The generality of these optimized conditions was also demonstrated for a small array of bromoenol ethers. Electron-rich and electron-poor bromoenol ethers could be efficiently coupled with *n*-butyllithium, an easily available alkyl surrogate, in excellent yields (see Supporting Information for further details).

With our key intermediate **12** in hand, the stage was set to investigate the intended cationic polyene cyclization (Scheme 4b). Addition of either tris(pentafluorophenyl)borane ($B(C_6F_5)_3$),[17] or diethylaluminum chloride ($Et_2AlCl$) to a solution of **12** in dichloromethane at −78 °C effected selective activation of the epoxide and carbon–carbon bond formation between C4 and C5. Unfortunately, the putative oxonium ion **16** (compare Scheme 3b) did not undergo further cyclization but was trapped by the alkoxide to give acetal **21**. All attempts to promote further ring closure of **21** by means of Lewis acid activation resulted in either hydrolysis of the acetal to the ketone **22** or decomposition of the starting material. From this result, we concluded that either steric hindrance around the 1,1-disubstituted olefin or a stepwise mechanism, involving nucleophilic attack of the remote C9–C15 olefin at C10 to generate an energetically unfavorable primary carbocation at C15, pre-

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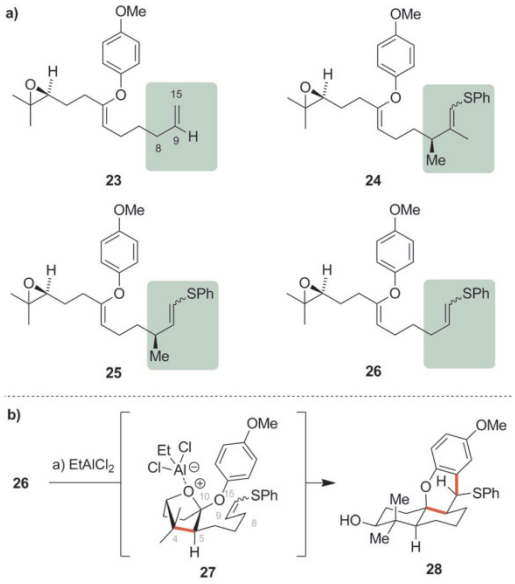


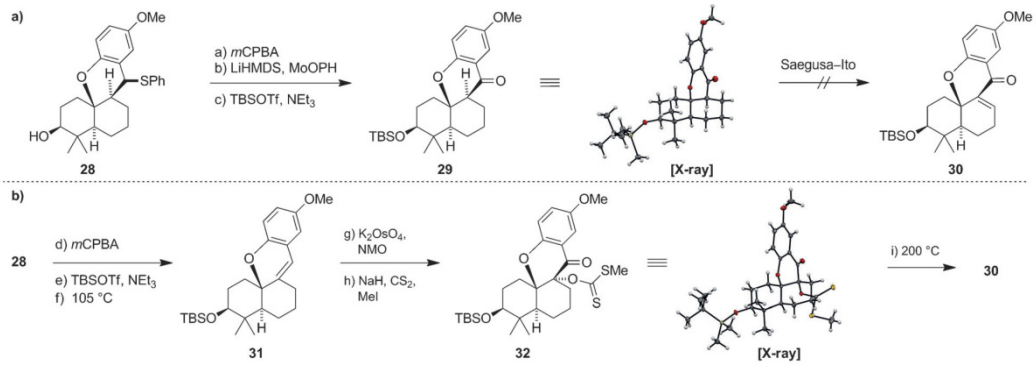

**Scheme 5.** a) Selectively modified cyclization precursors and b) successful cyclization of **26**. Reagents and conditions: a) $EtAlCl_2$, $CH_2Cl_2$, −78 °C, 91 %.

vent acetal **21** from further cyclization. In order to account for these issues and to validate our hypothesis, we decided to modify the C8–C15 substitution pattern of **12** by synthesizing the cyclization precursors depicted in Scheme 5 a according to the chemistry developed before (see Supporting Information for further details).

In a first attempt to rule out any possible steric hindrance around the olefin, including the C8 stereocenter, we investigated compound **23**. Exposure of **23** to ethylaluminumdichloride led to an inseparable mixture of several products, thus validating our hypothesis that low nucleophilicity of the C9–C15 double bond in addition to steric hindrance might impede the cyclization. In order to overcome the lack of cation stabilization without sacrificing the required methyl substituents, we equipped our substrate with a thioenol ether to give **24** (*E*:*Z* = 1:1.2).[18,19] Since this measure was ineffective as well and, in analogy to the activation of **12** and **23**, no fully cyclized product could be observed, we decided to further simplify our system. The first breakthrough resulted from treating a solution of **25**, which lacks the C9 methyl substituent, in dichloromethane with ethylaluminum dichloride at −78 °C. This allowed us to identify a product of which 2D NMR spectra were in full agreement with a tetracyclic structure (see Supporting Information for details). Although, we were unable to increase the low yield (8 %) for this substrate, thioenol ether **26** finally emerged as a substrate that underwent the intended cyclization in a highly efficient (91 %) and stereoselective manner to afford *trans*-decalin **28** as a single product (Scheme 5 b).[20] We believe that the intermediacy of acetal **27** accounts for the selective *trans*-decalin formation by blocking the top face of the molecule, thereby preventing a pseudo-equatorial alignment of the aryl ether substituent (compare Scheme 3 b). The observed equilibration of the phenylthio substituent provides evidence for a non-concerted, stepwise mechanism for the formation of the C9–C10 (decalin) and C15–C16 (tetrahydropyran) single bond.

Having developed a gram-scale synthesis of the full carbon framework, we turned our attention to the selective functionalization of **28**. For the installation of the vicinal-*cis*-dimethyl groups, we envisioned to convert sulfide **28** into enone **30**. With enone **30** in hand, we hoped to add both methyl substituents either through a sequence involving 1,4-addition of a methyl cuprate followed by α-methylation or a 1,3-dipolar cycloaddition using a thiocarbonyl ylide.[21]

For the elaboration of **30**, we investigated two parallel routes. The first approach was based on the conversion of sulfide **28** to ketone **29** followed by a Saegusa–Ito oxidation (Scheme 6 a).[22] The second strategy was based on an elimina-




**Scheme 6.** Formation of enone **30** via a) attempted Saegusa–Ito oxidation and b) styrene **30**. Reagents and conditions: a) *m*CPBA (2.1 equiv), $CH_2Cl_2$, 0 °C, 70 %. b) LiHMDS, MoOPH, THF, 0 °C to 23 °C, 74 %. c) $NEt_3$, TBSOTf, $CH_2Cl_2$, −78 °C to 23 °C, 96 %. d) *m*CPBA (0.95 equiv), $CH_2Cl_2$, 0 °C. e) $NEt_3$, TBSOTf, $CH_2Cl_2$, −78 °C to 23 °C. f) $CHCl_3$, 105 °C, 59 % over 3 steps. g) $K_2OsO_4$, NMO, acetone/$H_2O$, 0 °C to 23 °C, 69 °C%. h) NaH, THF, 0 °C to 23 °C, then $CS_2$, then MeI, 87 %. i) sulfolane, 200 °C, 93 %. *m*CPBA = *meta*-chloroperbenzoic acid, HMPA = hexamethylphosphoramide, MoOPH = $MoO_5$·pyridine·HMPA, NMO = *N*-methylmorpholin-*N*-oxide.

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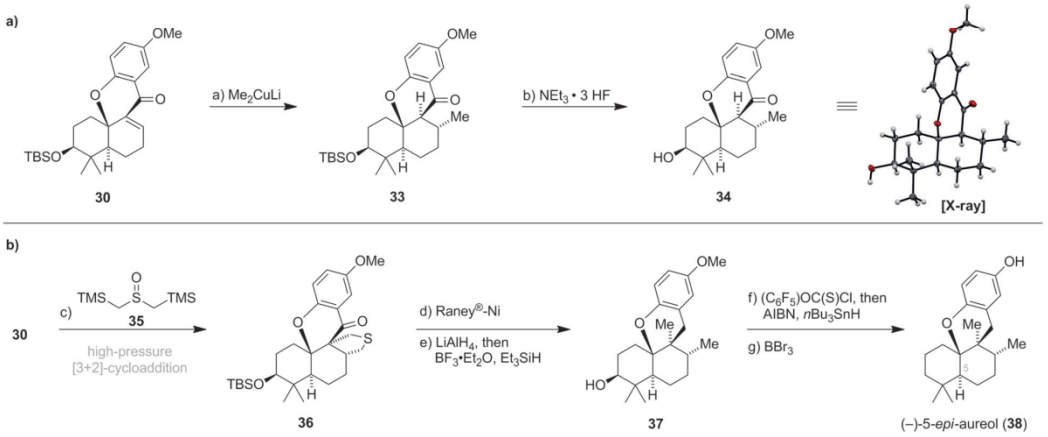
tion/oxidation route via styrene **31** (Scheme 6b). Oxidation of sulfide **28** using excess *m*-chloroperbenzoic acid (*m*CPBA, 2.1 equiv) gave the corresponding sulfone in excellent yield. Modification of a recently reported procedure for oxidative desulfonylation using Vedej 's reagent (MoOPH) allowed us to access the corresponding benzylic ketone.[23] Interestingly, under the reported conditions (*n*BuLi (1.05 equiv), MoOPH (2.00 equiv), −78 °C) the intermediate hydroxy sulfone did not collapse to give the ketone but was left unreacted. We found that only the use of excess lithium bis(trimethylsilyl)amide (LiHMDS) and prolonged stirring of the reaction mixture at 23 °C effected complete elimination. Protection of the secondary alcohol as its silyl ether gave **29**, which provided crystals suitable for X-ray diffraction. This allowed us to unambiguously validate the relative stereochemistry of this key tetracyclic intermediate. Unfortunately, all attempts to further oxidize ketone **29** to enone **30** were unsuccessful. In most experiments, ketone **29** proved to be unreactive and formation of a silyl enol ether, as required for the Saegusa–Ito oxidation, could never be observed.[24] Using more forcing conditions to effect α-deprotonation (LiHMDS, THF, 70 °C) led to β-elimination of the phenol substituent.

Thus, we turned to an alternative strategy that involved elimination of the phenyl thioether via its sulfoxide. Selective oxidation of the phenyl thioether to the sulfoxide could be accomplished using equimolar amounts of *m*CPBA. Protection of the secondary alcohol as its silyl ether followed by thermally-induced elimination (105 °C, $CHCl_3$) furnished styrene **31** in good yield. We were delighted to see that dihydroxylation conditions recently reported by Bräse enabled a successful one-pot oxidation to give an α-hydroxy ketone.[25] For the elimination of the tertiary alcohol, we examined a number of different conditions (e.g. *p*TsOH, Martin 's sulfurane, Burgess reagent, thionyl chloride).[26] We found that only conversion to its xanthate **32** followed by thermal elimination reproducibly afforded **30** in good overall yield (81 %) on large scale.[27]

Having succeeded in forming the enone, we investigated the introduction of the vicinal methyl substituents (Scheme 7). Although conjugate addition of lithium dimethylcuprate ($Me_2CuLi$) to enone **30** occurred with high diastereoselectivity, all attempts to trap the intermediate enolate were unsuccessful. The stereochemistry of **33** could be confirmed by silyl ether cleavage and single-crystal X-ray diffraction of alcohol **34**. Due to the difficulties encountered in the two-step methylation procedure, we searched for alternative alkylation methods that would both avoid possible β-elimination of the phenoxide and allow for *cis*-selectivity. For this purpose, we selected sulfoxide **35**, which was previously developed as an efficient source of thiocarbonyl ylide for the [3+2] cycloaddition reaction with sterically unhindered, electron-poor alkenes.[21a,28] Unfortunately, initial attempts to accomplish the cycloaddition between enone **30** and **35** or modifications thereof failed under a variety of standard conditions. Based on our ongoing efforts to establish high-pressure as a powerful external stimulus to realize otherwise infeasible transformations, we investigated the cycloaddition at 14 kbar.[29] Pleasingly, pressurizing a solution of **30** in a 1:1 mixture of dichloromethane and *N*,*N*′-dimethylpropylene urea (DMPU) in the presence of excess sulfoxide **35** at 23 °C cleanly afforded the tetrahydrothiophene **36** (68 %) along with recovered starting material **30** (16 %).

The best results were obtained when **35** was added in two portions (2×5 equiv) over the course of four hours. In this context, it is important to note that the purity of sulfoxide **35** was crucial to observe high conversion. Traces of *m*-chlorobenzoic acid that are formed during the generation of the sulfoxide have a detrimental effect and inhibit the progress of the reaction. For the completion of the synthesis, we first unmasked the vicinal *cis*-dimethyl group with the aid of Raney nickel.[30]




**Scheme 7.** Installation of the vicinal *cis*-dimethyl group via a) cuprate addition and attempted α-methylation and b) high-pressure [3+2] cycloaddition. Reagents and conditions: a) $Me_2CuLi$, $Et_2O$, 0 °C, 98 %. b) $NEt_3$·3 HF, $CH_3CN$, 40 °C, 59 %. c) **35**, DMPU/$CH_2Cl_2$ (1:1), 23 °C, 14 kbar, 68 % (16 % of **30**). d) Raney Ni, THF, 65 °C, 87 %. e) $LiAlH_4$, THF, 23 °C; then $BF_3$·$OEt_2$, $Et_3SiH$, 0 °C to 23 °C, 88 %. f) $(C_6F_5)OC(S)Cl$, DMAP, $CH_2Cl_2$, 0 to 23 °C, then AIBN, $nBu_3SnH$, benzene, 80 °C, 83 %. g) $BBr_3$, $CH_2Cl_2$, −78 °C to 23 °C, 86 %. DMPU = *N*,*N*′-dimethylpropylene urea, AIBN = azobisisobutyronitrile, DMAP = 4-(dimethyl)aminopyridine.

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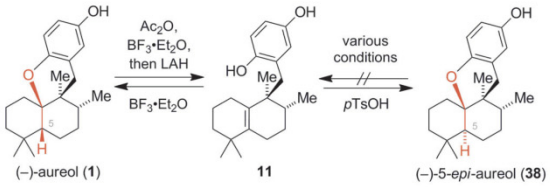
The ketone function was then fully reduced upon exposure to lithium aluminum hydride ($LiAlH_4$) followed by treatment with triethylsilane ($Et_3SiH$) in the presence of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) to give **37**.[31] Deoxygenation according to a recently described protocol and cleavage of the methyl ether with boron tribromide afforded (−)-5-*epi*-aureol (**38**), which has yet to be isolated from natural sources.[6a,9b]

At this stage, we focused on the isomerization of (−)-5-*epi*-aureol (**38**) to (−)-aureol (**1**). Guided by previous results of Faulkner and co-workers for the conversion of **1** to **11**, we initially tried to adopt the reported elimination conditions ($Ac_2O$, $BF_3{\cdot}OEt_2$) for the formation of **11** from **38** (Scheme 8).[3a] Surprisingly, elimination of the phenol of the *trans*-fused decalin ring system of 5-*epi*-aureol (**38**), which is perfectly oriented for an E2-elimination, could not be promoted. Thus far, only monoacetylated **38** could be isolated, which upon heating to 40 °C underwent Fries rearrangement and simultaneous decomposition. The use of trifluoroacetic anhydride in order to suppress the Fries rearrangement and facilitate the elimination step was equally ineffective.[32] Although we conducted an extensive screen of Lewis ($BF_3{\cdot}OEt_2$, $BCl_3$, $AlCl_3$, $B(C_6F_5)_3$, $TiCl_4$, $Er(OTf)_3$, $CeCl_3$)[33] and Brønsted acids (AcOH, TFA, HI, *p*TsOH, $H_2SO_4$, $H_3PO_4$),[9b,34] an array of bases (KO*t*Bu, DBU, pyridine)[35] with and without additional electrophiles to trap the generate phenolate ($Ac_2O$, TFAA, MeI), and several oxidative protocols (CAN, DDQ, $NaIO_4$ supported on silica, PIDA, Fetizon 's reagent),[32a,36] we were unable to observe formation of the elimination product.



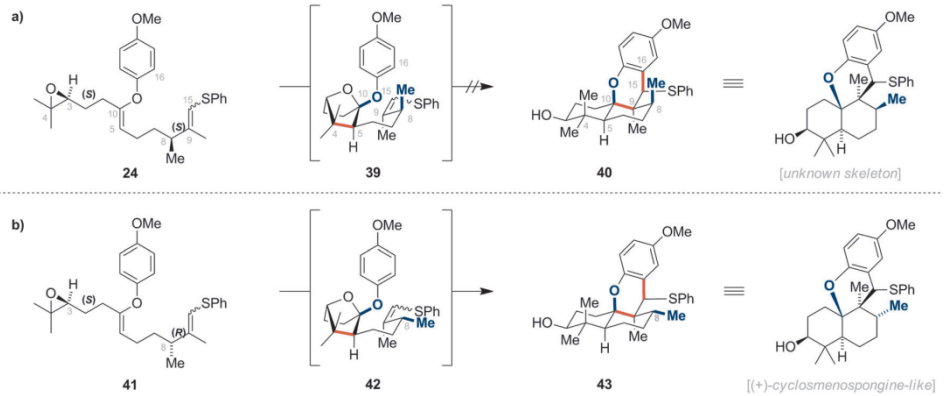

**Scheme 8.** Attempted elimination of 5-*epi*-aureol (**38**) to known intermediate **11**.

Despite the success of promoting this remarkable cyclization and having shown that tetracycle **28** can be advanced to 5-*epi*-aureol (**38**), we faced serious challenges. Firstly, multiple steps were necessary to install the missing vicinal *cis*-dimethyl substitution pattern of C8/C9. Secondly, the overall synthesis was not amenable to large-scale synthesis as the high-pressure cycloaddition reaction was limited to a reaction volume of 8 mL (ca. 80 mg) per batch.

To address these limitations, we revised the design of our cyclization precursor (Scheme 9). From the attempted cyclization of **13** and **23**–**26**, we learned that the cyclization proceeds via the intermediacy of an acetal that is further activated. The formation of this discrete species presumably prevents any top-face approach and forces the vinyl sulfide to adopt an alignment as depicted for **39** (Scheme 9a). From the inspection of **39**, we concluded that the axial aligned C8 methyl group avoids any further cyclization to **40**.

Based on these insights, we hypothesized that generation of the fully-substituted cyclosmenospongine-like framework might be feasible by using polyene **41**. Simple inversion of the relative configuration at C8 should minimize unwanted 1,3-diaxial interactions with the aryl ether and therefore enable the attack of the vinylsulfide to yield tetracycle **43** (Scheme 9b).

To put this idea in practice, we had two options at hand. Either we could exchange the configuration at C8 or adjust the orientation of the epoxide at C3. For practical reasons, we decided to alter the epoxide stereocenter (Scheme 10). Simple exchange of AD-mix-β for AD-mix-α allowed us to synthesize epoxide *ent*-**41** (*E*:*Z* = 1:1.2 at C15) on gram scale (5.6 g) according to the chemistry developed before.[10] Upon exposure of *ent*-**41** to the previously optimized cyclization conditions ($EtAlCl_2$, $CH_2Cl_2$, −78 °C), we were delighted to observe full and clean conversion to the fully cyclized product *ent*-**43**. The occurrence of an acetal intermediate could be validated through the use of less reactive diethylaluminum chloride ($Et_2AlCl$),




**Scheme 9.** Cyclization precursors and hypothetical transition states (bonds formed during the cyclization are highlighted in red). a) Formation of acetal intermediate **39** from **24** (1,3-diaxial interactions are highlighted in blue). b) Formation of acetal **42** from **41** and further cyclization to tetracycle **43**.

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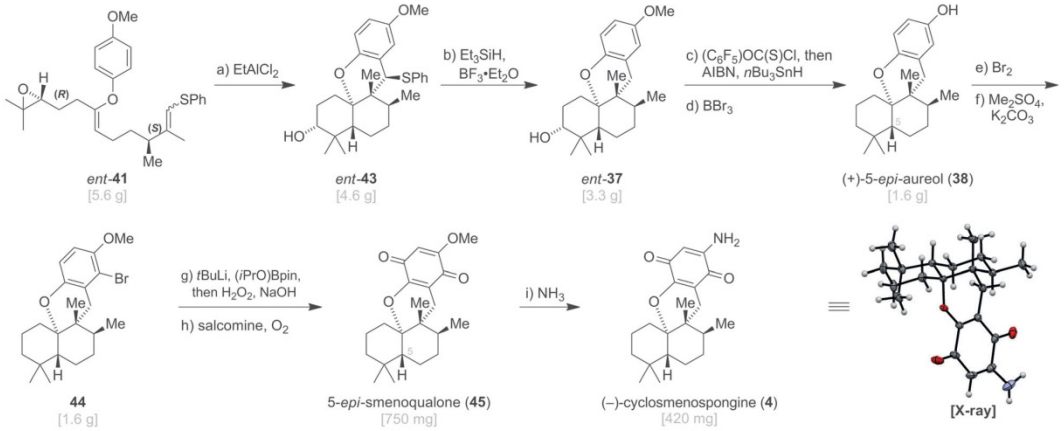


**Scheme 10.** Total synthesis of (−)-cyclosmenospongine (**4**) via the optimized polyene cyclization. Reagents and conditions: a) $EtAlCl_2$, $CH_2Cl_2$, −78 °C, 83 %. b) $Et_3SiH$, $CH_2Cl_2$, $BF_3$-$OEt_2$, 0 °C, 97 %. c) $(C_6F_5)OC(S)Cl$, DMAP, $CH_2Cl_2$, then AIBN, $nBu_3SnH$, benzene, 64 %. d) $BBr_3$, $CH_2Cl_2$, −78 °C to 23 °C, 85 %. e) $Br_2$, $CH_2Cl_2$, −55 °C, 93 %. f) $Me_2SO_4$, $K_2CO_3$, acetone, 23 °C, 87 %. g) *t*BuLi, (*i*PrO)Bpin, THF, −78 °C to 0 °C, then $H_2O_2$, NaOH, 0 °C to 23 °C, 75 %. h) Salcomine, $O_2$, DMF, 23 °C, 77 %. i) $NH_3$, MeOH, $H_2O$, pyridine, 23 °C, 60 %. AIBN = azobisisobutyronitrile, *B*-OMe-9-BBN = *B*-methoxy-9-borabicyclo[3.3.1]nonane, DMAP = 4-dimethylaminopyridine, pin = pinacol.

which allowed us to selectively discontinue the reaction cascade on the acetal level and isolate *ent*-**42** in pure form. Further cyclization of *ent*-**42** was achieved by treatment with ethylaluminum dichloride ($EtAlCl_2$) as before to yield *ent*-**43** in excellent yield (see Supporting Information for further details). This remarkable cyclization generates three rings and sets four stereocenters, three of which are part of the final meroterpenoid skeleton, in a highly stereoselective manner. Although the relative configuration proved crucial to enable successful cyclization of the fully substituted epoxide precursor, we were able to control the absolute stereochemistry of the product by simple adjustment of the epoxide stereocenter.

Desulfurization of *ent*-**43** intersected the previously route to (−)-5-*epi*-aureol (**38**) and afforded *ent*-**37** in good yield on gram-scale (3.3 g). By adjusting the configuration of the epoxide at C3 in order to incorporate both methyl substituents, we could fully bypass the previously developed eight-step sequence required for the conversion of **28** to **37** and thus produce (+)-5-*epi*-(**38**) on a 1.6 gram scale. Moreover, we had enough material to advance 5-*epi*-aureol (**38**) to (−)-cyclosmenospongine (**4**) through sequential functionalization of the aromatic core. Selective bromination and methylation gave **44** in excellent yield.[3a] Conversion of the bromine substituent to the corresponding phenol was best carried out via a boronation–oxidation sequence. The final oxidation to the *p*-quinone moiety of 5-*epi*-smenoqualone (**45**) could be perfomed by exposure of the phenol to salcomine under an oxygen atmosphere.[9d] (−)-Cyclosmenospongine (**4**) was then obtained by aminolysis.[3d,7] Although we could unambiguously validate our synthesized structure by single crystal X-ray analysis, we were surprised to observe remarkable deviations of the $^1H$ and $^{13}C$ NMR data ($CDCl_3$) of synthetic and natural cyclosmenospongine (**4**).[3d] While concentration effects could be excluded, we hypothesized whether residual hydrogen chloride could account for the observed inconsistencies. Indeed, successive addition of a $CDCl_3$ solution saturated with hydrogen chloride to **4** led to formation of a deep-purple solution, the $^1H$ and $^{13}C$ NMR shifts of which were now in better agreement with the literature values. It was interesting to note that formation of the hydrogen chloride adduct could be reversed by simply concentrating the NMR sample (see Supporting Information for NMR studies).

Having successfully investigated the impact of the relative configuration of the epoxide at C3 and the C8 methyl substituent on the cyclization cascade, we finally wanted to extend our strategy to the synthesis of *cis*-fused decalins. According to the Stork–Eschenmoser hypothesis, which postulates that adjacent olefins attack via an *anti*-periplanar fashion, and its beautiful application by Snyder in the synthesis of peyssonoic acid A,[37,38] we anticipated that simple alteration of the enolether geometry (C5–C10) might selectively yield the desired *cis*-decalin (Scheme 11).

These considerations inspired us to investigate the simplified model cyclization precursor **47**, which was synthesized by Ullmann coupling of vinyl iodide **46** with 4-methoxyphenol (**13**).[39,40] Unfortunately, all efforts to realize the cyclization of **47** failed and only bisketone **50**, resulting from hydrolysis of the enol ether and Meinwald rearrangement of the epoxide, could be isolated. We believe that the pseudo-axial alignment of the C5-substituent, as depicted for **48**, is highly unfavorable and therefore might prevent formation of acetal **48** or tetracycle **49**.

## Conclusion

In summary, we were able to develop a highly modular and efficient synthesis of the tetracyclic meroterpenoid cyclosmenspongine (**4**). The establishment of a highly modular three com-

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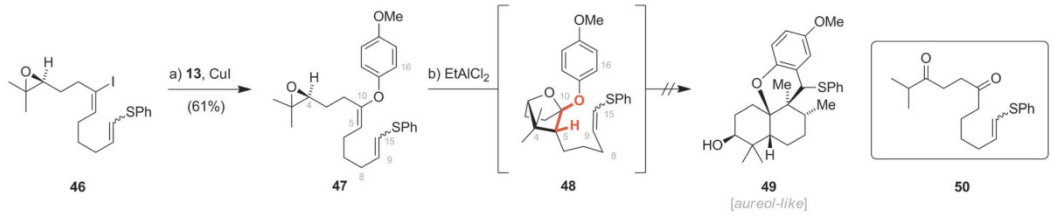


**Scheme 11.** Preparation of cyclization precursor **47** and attempted synthesis of the *cis*-decalin framework **49**. Reagents and conditions: a) CuI, $Cs_2CO_3$, *N*,*N*-dimethylglycine hydrochloride, 1,4-dioxane, 100 °C, 61 %; b) $EtAlCl_2$, $CH_2Cl_2$, −78 °C, 44 % of **50**.

ponent coupling strategy, which is based on a base-mediated phenol–alkyne addition and a highly efficient $sp^2$–$sp^3$ *B*-alkyl Suzuki–Miyaura cross coupling, allowed us to rapidly modify the cyclization precursor in order to investigate the cyclization cascade. Our initial efforts led to the development of an unprecedented cationic polyene cyclization cascade of the simplified polyene **26**. Exposure of **26** to ethylaluminum dichloride initiated the unique cascade, which forged the carbon skeleton of aureol (**1**) in a single step. Further elaboration to 5-*epi*-aureol (**38**) could be achieved by utilizing a Tschugaeff elimination to access the key enone and by implementing an unprecedented high-pressure 1,3-dipolar cycloaddition of a thiocarbonylylide to install the vicinal *cis*-dimethyl group. Careful analysis of the impact of stereochemistry on the cyclization cascade allowed us to further optimize the precursor, thereby shortening the synthesis of (−)-cyclosmenospongine (**4**) by eight steps. The operationally simple and robust cyclization cascade can be performed on multi-gram scale and allowed for the synthesis of more than 400 mg of (−)-cyclosmenospongine (**4**). Although we were unable to adapt the polyene cyclization to the formation of the *cis*-decalin ring system, we hope to stimulate further research in this area and advance polyene cyclizations to the next level of complexity. Application of this concept to other *trans*-decalin natural products and an alternative synthesis of tetracyclic meroterpenoids bearing the *cis*-fused decalin ring system are currently underway in our laboratories and will be reported in due course.

## Experimental Section

Experimental and crystallographic details, as well as compound characterization data and copies of $^1H$ and $^{13}C$ NMR spectra, are available in the Supporting Information.

## *Acknowledgements*

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**Keywords:** cyclization · high-pressure chemistry · natural products · terpenoids · total synthesis

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## 1.5. Conclusion and Outlook

In Part I of this thesis, an unprecedented cationic polyene cyclization cascade was developed and successfully implemented in the first enantioselective total synthesis of the tetracyclic meroterpenoid (–)-cyclosmenospongine. This remarkable cascade generated three carbon–carbon bonds, and set four consecutive stereocenters, two of which are tetrasubstituted, thereby forging the tetracyclic skeleton of (–)-cyclosmenospongine in a single operation.

A highly convergent and modular three-component coupling strategy was established to synthesize the key cyclization precursors. Our strategy was based on a phenol-alkyne addition and an efficient *B*-alkyl Suzuki–Miyaura $sp^2$-$sp^3$ cross-coupling reaction. This modular and scalable synthetic approach allowed for facile modifications of the cyclization precursors, which were sequentially tested for their reactivity. Extensive mechanistic studies of the key cyclization revealed that the intricate reaction cascade proceeds through the intermediacy of an acetal that presumably prevents a top-face approach of the sidechain. This transient acetal species was attacked by the vinylsulfide after further Lewis acid activation to selectively yield the *trans*-fused decalin ring system found in (–)-cyclosmenospongine.

In our first generation synthesis, we were able to cyclize a simplified polyene on multi-gram scale and transform the generated tetracycle to 5-*epi*-aureol, which has yet to be isolated from natural sources. The eleven step procedure included a challenging enone formation via a Tschugaeff elimination, and installation of the missing vicinal *cis*-dimethylgroup through an unprecedented high-pressure [2+3] cycloaddition of a thiocarbonyl ylide.

Careful analysis of the impact of stereochemistry and the resultant steric interactions in the cyclization cascade allowed us to identify an optimized cyclization precursor, which shortened the synthesis of 5-*epi*-aureol by eight steps. Unfortunately, the seemingly trivial isomerization of 5-*epi*-aureol to aureol could not be achieved. Nevertheless, 5-*epi*-aureol was further converted to (–)-cyclosmenospongine through sequential functionalization and oxidation of the arene moiety. The streamlined synthesis allowed us to gain access to 420 mg of (–)-cyclosmenospongine.

Future work will aim to implement the newly developed cyclization cascade in the synthesis of other complex natural products bearing *trans*-fused decalin ring systems. Moreover biological investigations will be carried out in collaboration with the group of Prof. Dr. Mark Brönstrup (Helmholtz Centre for Infection, Braunschweig) and Dr. Susanna Zierler (Walther-Straub Institute for Pharmacology and Toxicology, Munich) to further elucidate their biological activities.

# PART II:

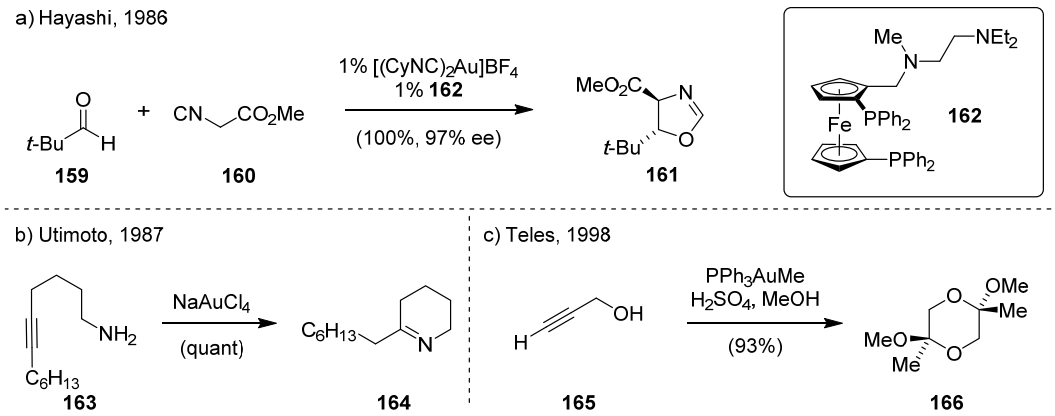
# GOLD(I)-CATALYZED CYCLIZATIONS OF 1,5-ENYNES

# 2.1. General Introduction

## 2.1.1. Gold in Homogenous Catalysis

Within the last 20 years, homogenous gold catalysis has emerged as an extremely dynamic and innovative field in organic chemistry, and has proven to be a versatile tool in the synthetic chemist´s arsenal.[119-122] Although cationic gold was initially considered an inert catalytic species, gold salts and complexes have emerged as powerful catalysts for the selective electrophilic activation of carbon–carbon multiple bonds towards nucleophilic addition.[123-125] The mild reaction conditions, high selectivity and functional group tolerance of gold catalysis has attracted great interest within the scientific community and led to what can be compared to the Californian gold rush of the 19th century.[126-127] This modern gold fever resulted in an exponential growth in the number of publications investigating the reactivity of this precious metal.[128]

In 1986, almost ten years before the aforementioned growth in interest in homogenous gold catalysis began, Hayashi reported the first gold-catalyzed asymmetric aldol condensation of various aldehydes, for example **159**, with isocyano acetate **160** to yield *trans*-oxazolines like **161** in excellent yield and enantioselectivity using the chiral ferrocene ligand **162** (Scheme 21a).[129] Shortly after Hayashi´s seminal work, Utimoto described the formation of tetrahydropyridine **164** from alkyne **163** (Scheme 21b).[130] The activation of carbon–carbon multiple bonds by late transition metals was well known at that time, but in his work he beautifully demonstrated the superiority of gold(III) over other transition metals like palladium(II), which is in a similar $d^8$-configuration. Although the seminal work carried out by Hayashi and Utimoto laid the foundation of homogeneous gold catalysis, the groundbreaking contribution of Teles truly marked a new era in gold catalysis. He discovered that cationic gold catalysts bearing phosphine ligands provide ketals like **168** with exceptional turnover frequencies, outperforming the previously developed methods for the hydration of alkynes by a significant margin.[131-132]

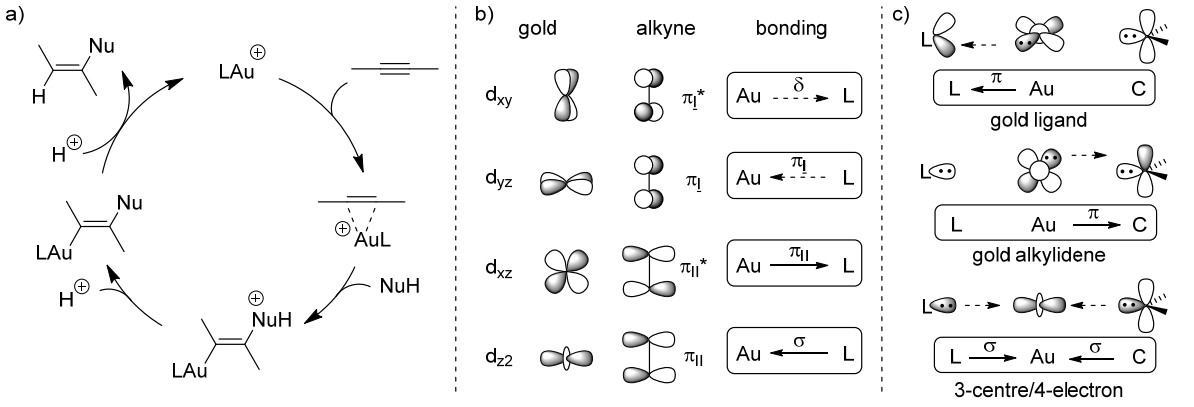



***Scheme 21:*** *Landmark achievements in homogeneous gold catalysis.*

Only recently the long standing paradigm that gold cannot be used in cross-coupling reactions due to the apparent redox stability of gold(I)-species has been overcome.[119, 133-134] Although the gold(III) oxidation state is easily accessible, gold complexes usually do not cycle between oxidation states. By using the external oxidant Selectfluor® in stoichiometric quantities, Zhang demonstrated that the prevalent steps occurring in typical late transition-metal catalysis, such as oxidative addition and reductive elimination, can also be induced for gold catalysis.[135]

### 2.1.2. Mechanistic Aspects

By far the vast majority of reactions developed for homogenous gold catalysis exploit the propensity of gold salts to electrophilically activate carbon–carbon multiple bonds. In a typical reaction, gold(I) is the catalytically active species and acts as a soft π-electrophilic Lewis-acid to form linear bicoordinated $\eta^2$-complexes (Scheme 22a).[136-137] The coordination to the carbon–carbon multiple bond enables attack of a nucleophile. This typically occurs in an *anti*-fashion through an outer-sphere mechanism if a weakly coordinating nucleophile is present, or through an inner-sphere mechanism for strongly coordinating nucleophiles, to yield a *syn*-adduct.[136] Due to the fact that gold(I) typically does not undergo spontaneous β-hydride elimination or oxidative addition a protodeauration is generally the final step of the catalytic cycle.[138-139]




***Scheme 22:*** *a) General catalytic cycle for the electrophilic activation of carbon–carbon multiple bonds through cationic gold and dominant orbital interactions for b) a gold-alkyne complex and c) a gold carbene complex.*

The extraordinary π-affinity of cationic gold species can be explained using relativistic effects.[63, 137] These effects, which are at a maximum for gold, cause a contraction of the atomic s and p orbitals and an expansion of the d and f orbitals in order to decrease the electron-electron repulsion.[140] This relativistic contraction of the 6s orbital is responsible for lowering the energy of the lowest unoccupied molecular orbital (LUMO), which is the primary acceptor of electron density from ligands and the substrates.[63, 120, 137, 139] Because of the relatively low-lying 6s-LUMO, gold is capable of forming strengthened gold-ligand bonds, which explains its high π-acidity compared to other late-transition metals. Moreover, the altered intrinsic energy and expansion of the 5d orbital are responsible

for the "soft" Lewis-acidic character of gold(I) and explain the preferential interaction with soft nucleophiles such as carbon–carbon π bonds, e.g. alkynes.[63]

The binding behavior between gold and its ligands can be described in more detail using the molecular orbital theory (Scheme 22b).[63] The interaction of an alkyne with gold(I) has a σ, π and δ-bond character. The σ-bonding is the result of an overlap of an in-plane $\pi_{II}$-orbital with an unoccupied orbital of gold with corresponding symmetry (M ← L donation). The π-bonding results from a shift of electron density from the metal towards an unoccupied $\pi_{II}$*-orbital through back-donation (M → L), and through π-donation (M ← L) of an out-of-plane $\pi_{\perp}$-orbital. The last interaction a back donation with δ-symmetry can be neglected due to the relatively slight participation in the bonding.[63] The bonding of transient gold carbene species can be explained in a similar manner, and can again be divided into σ and π-character.[120, 139] A 3-centre/4-electron bond with σ-symmetry is proposed which is accompanied by orthogonal back-bonding π-bonds from the gold species to the ligand and the substrate. This back-bonding can be explained by the fact that the 5d electrons of gold are too low in energy to engage in back-donation to anti-bonding ligand orbitals, but are able to delocalize into the lower-energy empty non-bonding orbitals.

Based on this bonding model, the electronic nature of gold(I)-intermediates and their reactivity can be rationalized. Moreover, one can conclude why gold can act in both a π-acidic and a carbenoid-like fashion (*cf*. Chapter 1.2.5). After nucleophilic attack of the alkyne the intermediate vinylgold species stabilizes the resulting positive charge through back-donation. This suggests that carbene formation occurs through an increase in π-bonding character with a concomitant decrease in σ-bonding.[63]

### 2.1.3. Ligand Effects

Initially, simple gold salts like gold(I) and gold(III) chloride, or sodium tetrachloroaurate were used to catalytically activate carbon–carbon multiple bonds.[139] Nevertheless, the seminal work of Teles showed that ancillary ligands can have a significant influence on the reactivity of the cationic gold catalyst.[131] So far, phosphines and *N*-heterocyclic carbenes (NHC) have found the widest applications in gold catalysis as ligands (Figure 4).[122, 139]

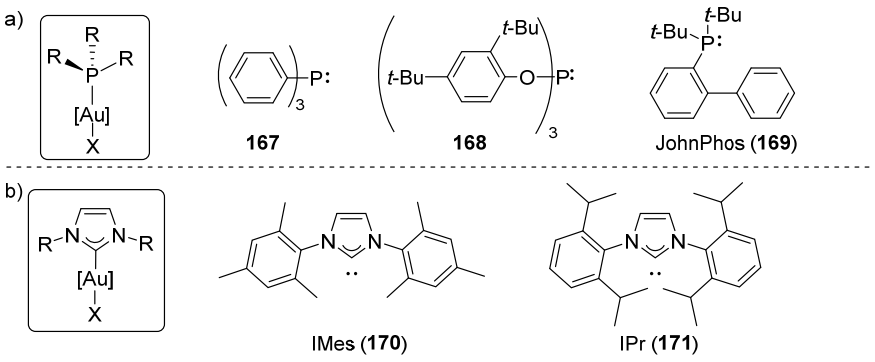



***Figure 4:*** *Typical ligands used in gold catalysis a) phosphorus based and b) N-heterocyclic carbenes.*

The main advantage of the use of ligands in homogenous catalysis is that the reactivity of the catalyst can be easily tuned with respect to the electronic and steric demands. As described above (*cf.* Chapter 2.1.2), the ligand´s back-bonding capability has a direct influence on the electronics of the cationic gold(I)-species. Therefore, the choice of ligand can have a profound effect on the observed reactivity. In general, phosphorus based ligands are strongly π-acidic and generate a more electrophilic gold center, whereas catalysts bearing NHC ligands are especially good in σ-donation and tend to be less electrophilic.[141] Due to the σ-donating properties of these ligands the carbon-gold bond order is decreased which results in a more "carbene-like" intermediate. In contrast, π-acidic ligands decrease the σ-donation, hence a more carbocationic reactivity is observed.[120]

Since gold complexes have a strong preference to form linear bicoordinated complexes precatalyst of the type LAuX, with L being the ligand and X the counterion, are most commonly found in literature. In general, these gold catalysts can be described as a cationic gold center that is stabilized through an anion. The stability of gold-chloride complexes can be explained as a result of the strong coordination of the chloride-ion to the gold center. This results in a diminished catalytic activity as the associative ligand exchange with the substrate is hampered.[139] The catalytically active $LAu^+$ species are therefore generated through chloride abstraction through silver salts with less nucleophilic and bulkier counterions such as tetrafluoroborate ($BF_4$), hexafluoroantimonate ($SbF_4$) or bis(trifluoro-methanesulfonyl)imide ($NTf_2$). However, since silver itself can be catalytically active, silver salts are far from being innocent spectators in gold catalysis.[142-144] Therefore recently silver-free activation protocols have been developed.[145-146] Nolan for instance, utilizes Brønsted acid activation of NHC gold hydroxy complexes, to generate the catalytically active cationic gold(I)-species and producing water as the sole by-product.[147]

Moreover, due to the aforementioned prevailing bicoordination, it is inherently difficult to induce enantioselectivity during gold-catalyzed reactions through the use bidentate ligands, which are arguably the most successful design principle in asymmetric catalysis, or through chiral monodentate ligands, as the chiral information is too distant to be translated to the substrates during the reaction.[63, 122, 139] Nevertheless, by using dinuclear gold complexes or chiral counterions several groups were able to overcome this drawback and develop elegant gold-catalyzed asymmetric reactions.[139, 148-150]

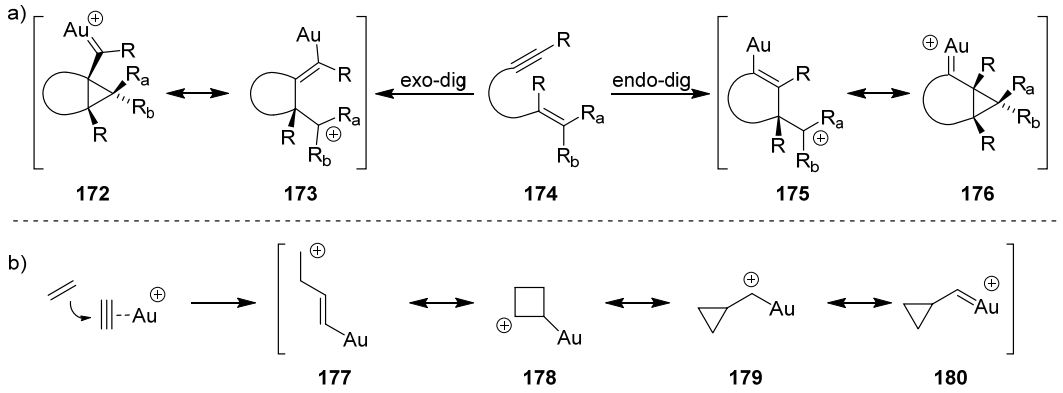
## 2.2. Cyclization of Enynes

### 2.2.1. General Reactivity

Cycloisomerizations of 1,*n*-enynes, especially 1,5- and 1,6-enynes, have emerged as exceptionally valuable reactions as they can provide an atom- and step-economical entry to the synthesis of functionalized cyclic systems in a single synthetic operation with excellent chemoselectivity under mild reaction conditions.[151] Since the pioneering work on palladium catalyzed rearrangement of enynes by Trost in 1984, several metals have been identified that efficiently promote these important transformations.[152-153]

In contrast to other transition metal catalyzed enyne cyclizations, gold(I) is unable to promote cycloisomerization reactions in an Alder–ene fashion. This would require a simultaneous coordination of the cationic gold(I) species with both the alkyne and the alkene, and subsequent formation an intermediate metallacycle through an oxidative addition process. This cyclization mode is highly unfavored by gold(I), as it typically prefers a linear bicoordination and avoids changes in oxidation states. As previously mentioned, cationic gold species selectively activate carbon–carbon multiple bonds towards nucleophilic addition and are able to stabilize the resulting cationic intermediates (*cf.* Chapter 2.1.2.). Most of the early mechanistic studies on the gold catalyzed enyne cyclizations were carried out by Echavarren, Toste and Hashmi.[62, 120, 136, 139, 154]

Their seminal work shed light on these elegant but sometimes promiscuous cascade reactions. The cyclization of 1,*n*-enynes proceed through an initial and chemoselective activation of the alkyne moiety allowing the adjacent alkene to attack the triple bond intramolecularly in either an *exo* or *endo*-fashion, as exemplified for the cyclization of enyne **174** (Scheme 23a). The intermediate carbocationic species **173** or **175**, which are in resonance with their corresponding cyclopropyl gold carbenes **172** and **176**, can subsequently undergo a variety of transformations depending on the exact reaction conditions and the availability of additional nucleophiles.[154-155]

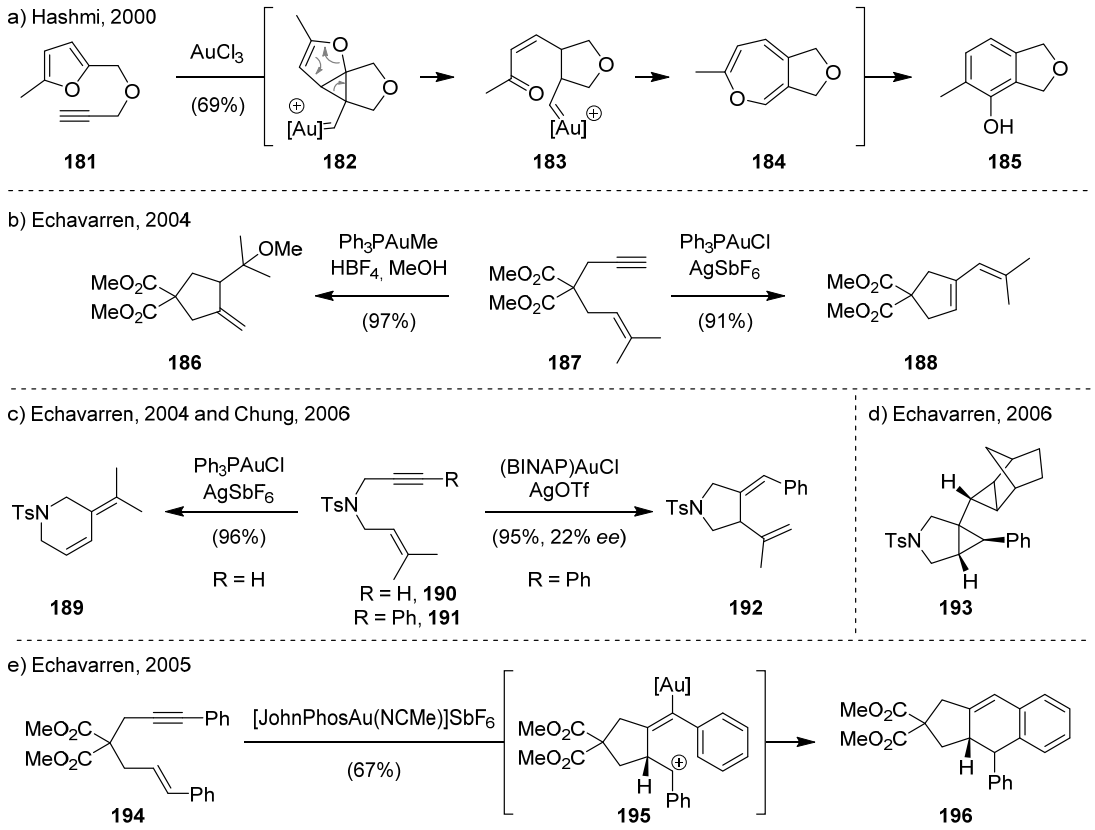



***Scheme 23:*** *Key mechanistic intermediates for the gold-catalyzed cyclization of 1,n-enynes.*

The ability of gold to interconvert between these mesomeric structures explains the occurrence of a variety of skeletally rearranged products found in enyne cycloisomerization reactions. The basic principle of these rearrangements involves the generation of the homoallyl cation **177** after initial attack of an alkene, which can rearrange to cyclobutyl cation **178** or cyclopropylcarbinyl cation **179**, which is in resonance with carbene **180** (Scheme 23b).

### 2.2.2. Cyclization of 1,6-Enynes

The cyclization of 1,6-enynes are probably the best studied substrate class in the field of cycloisomerizations. One of the first examples of a gold-catalyzed 1,6-enyne cyclization was reported by Hashmi in 2000 (Scheme 24 a).[156] Upon exposure of alkyne **181** to gold(III) chloride, the initially formed carbene intermediate **182** underwent several skeletal rearrangements to yield oxepine **184**, which after ring-contraction and aromatization afforded the highly substituted phenol **185** in good yield.



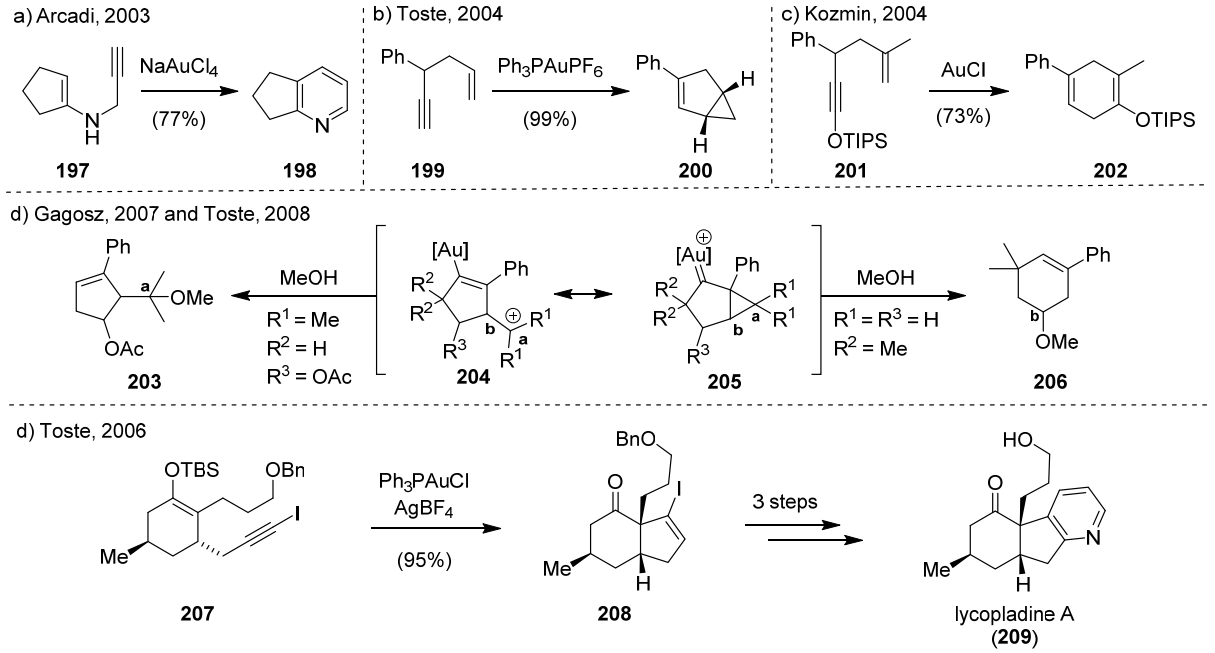

***Scheme 24:*** *Selected gold-catalyzed cycloisomerizations of 1,6-enynes.*

In seminal work, Echavarren beautifully demonstrated the versatility of enyne cyclizations, and moreover validated the superiority of gold catalysis for the cyclization of various 1,6-enynes (Scheme 24b).[157] By simple variation of the reaction conditions, the gold mediated cyclization of enyne **187** yielded either **186** if methanol was present as an external nucleophile, or the skeletally

rearranged 1,3-diene **188** in its absence. In the same study, Echavarren also showed that the *N*-substituted enyne **190** selectively cyclized through a 6-*endo* process to yield piperidine **189** (Scheme 24c). A simple exchange of the catalyst and the substitution of the terminal alkyne allowed Chung to access enantioenriched 1,4-diene **192** from **191**.[158] The intermediacy of a gold-carbene could be unambiguously confirmed through interception of the cyclization cascade with norbornene to yield cyclopropanated **193** (Scheme 24d).[159] By using the σ-donating NHC ligand IMes (**170**), the gold-carbene was sufficiently stabilized to allow for an insertion into the norbornene double bond. Another mode of reactivity was observed for arylated enyne **194**. The intermediate homoallylic cation **195** could be trapped by the arene to give tricyclic compound **196** (Scheme 24d).[160]

### 2.2.3. Cyclization of 1,5-Enynes

The first gold-initiated 1,5-enyne cyclization cascade was developed by Arcadi in 2003.[161] By establishing a one-pot procedure, he was able to synthesize a variety of substituted pyridine derivatives in excellent yields (Scheme 25a). Condensation of propargylamine with various ketones resulted in the formation of *N*-substituted 1,5-enynes, which upon heating in the presence of sodium tetrachloroaurate gave the desired pyridines as exemplified by the conversion of **197** to **198**. In 2004, Toste reported the gold(I)-catalyzed cycloisomerization of enyne **199** to bicycle **200** (Scheme 25b).[162] This report was directly followed by a study of Kozmin on the cyclization of O-substituted 1,5-enynes (Scheme 25c).[163] The exposure of enyne **201** to gold(I) chloride led to the clean formation of cyclohexadiene **202** via a sequence of several rearrangements. It is interesting to note the simple alkyne substitution led to the formation of completely different products, which again showcases the mechanistic diversity which can occur during the cycloisomerization of enynes.



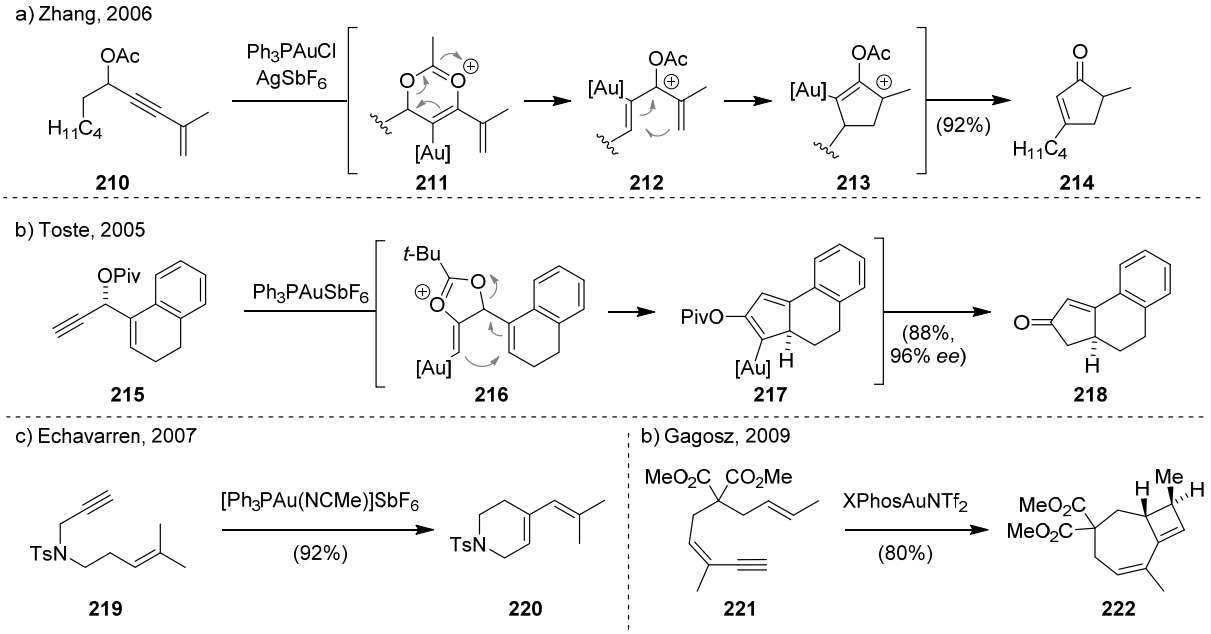

***Scheme 25:*** *Selected cycloisomerizations of 1,5-enynes.*

In analogy to 1,6-enynes, the cyclization of 1,5-enynes also proceeds through species that are intermediate between a bicyclic gold-carbene, like **204**, and an open gold-stabilized homoallylic carbocation such as **205**, but occur typically in an *endo*-fashion.[164] As previously described, the choice of ancillary ligands can influence the equilibrium of these mesomeric structures and thereby dramatically affect the reaction outcome. The same holds true for substituents on the enyne, which are able to alter the equilibrium between **204** and **205** through subtle electronic effects.[155] Depending on the substitution pattern the cationic intermediate can be attacked by a nucleophile on different sites (a or b, Scheme 25a). Gagosz observed that the cyclization of an enyne bearing an acetate ($R^3$) yields **203**, whereas studies carried out by Toste demonstrated that an enyne with methyl substitution ($R^2$) gives selectively the rearranged methoxy adduct **206**.[122, 165]

A beautiful synthetic application of a 1,5-enyne cyclization was reported by Toste in 2006.[166] A gold(I)-initiated 5-*endo*-dig cyclization of silyl enol ether **207** resulted in the clean formation of *cis*-hydrindane **208**, which was further advanced to the natural product lycopladine A (**209**) within three additional steps.

### 2.2.3. Miscellaneous 1,*n*-Enyne Cyclizations

Whereas numerous cycloisomerization reactions of 1,5- and 1,6-enynes have been reported, the gold catalyzed cyclizations of other enynes are far less common. In 2006, Zhang succeeded in developing a cyclopentenone synthesis starting from 1,3-enynes (Scheme 26a).[167] After a gold-initiated [1,3]-acetate migration of **210** to **211**, the resultant bis-vinyl cation **212** underwent a Nazarov-type electrocyclization to yield **213**. A final [1,2]-hydride shift followed by protodeauration gave **214** in excellent yield.




***Scheme 26:*** *Selected examples for 1,n-enyne cyclizations.*

The cyclization of 1,4-enynes that bear an adjacent carboxylate proceed through a similar mechanism, generally referred to as the Rautenstrauch reaction, as depicted in Scheme 26b.[168-169] Upon exposure of **215** to a gold catalyst, a [1,2]-acyl-shift occurs and the resultant cationic intermediate **216** cyclizes to **217**, which after proteolysis and tautomerization gives ketone **218**. The reaction occurs with remarkable chirality transfer and allows the efficient and enantiospecific synthesis of highly substituted cyclopentenones.

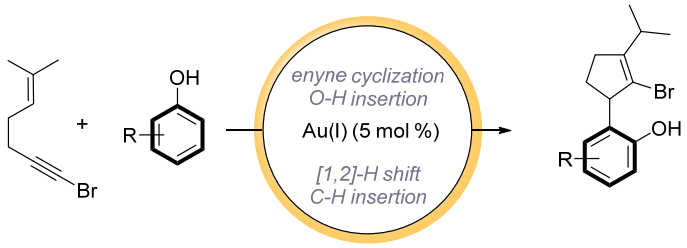
Whereas the cyclization of 1,7-enynes generally give cyclization products arising from a 6-*endo* pathway, as shown for the conversion of **219** to **220** (Scheme 26c), the cyclization of 1,8-enynes, like **221**, can proceed via a formal [2+2] cycloaddition to from cyclobutene derivatives such as **222** (Scheme 26d).[170-171] Although the [2+2] cycloaddition can also be observed for smaller 1,*n*-enynes, it is much less common due to the presence of other skeletal rearrangements which lead to potentially less strained cyclic products.[154] This mode of reactivity could also be observed for higher enynes and was beautifully utilized by Echavarren for the macrocyclization of various 1,*n*-enynes, (n = 10–16).[172]

The enormous diversity of products which can arise from the cyclization of various 1,*n*-enynes, along with the profound influence the exact reaction conditions on the reaction outcome renders these transformations highly valuable and worthwhile to investigate. The discovery of novel cycloisomerization pathways will allow to construct polyfunctionalized cyclic frameworks with extraordinary efficiency and elegance from simple acyclic compounds and enable unprecedented retrosynthetic disconnections.

## 2.3. Results and Discussion

### 2.3.1. Sequential O–H/C–H Bond Insertion of Phenols Initiated by the Gold(I)-Catalyzed Cyclization of 1-Bromo-1,5-Enynes





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# Sequential O–H/C–H Bond Insertion of Phenols Initiated by the Gold(I)-Catalyzed Cyclization of 1-Bromo-1,5-enynes

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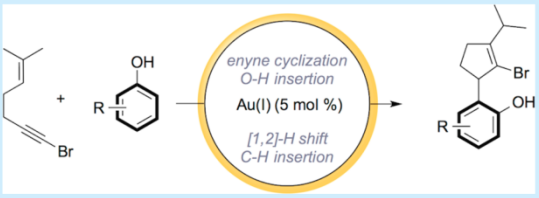
Supporting Information

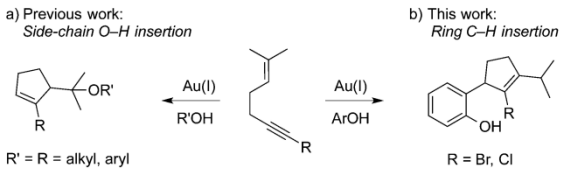
**ABSTRACT:** The development of a sequential O–H/C–H bond functionalization of phenols initiated by the cationic gold(I)-catalyzed cyclization of 1-bromo-1,5-enynes to produce (2-bromocyclopent-2-en-1-yl)phenols is reported. This unprecedented domino transformation efficiently proceeds under mild conditions (5 mol % of $(t\text{-Bu})_3PAuNTf_2$, $CH_2Cl_2$, 0–23 °C) via an intermediate aryl alkyl ether which collapses at ambient temperature to undergo a 1,2-hydride shift followed by C–H insertion of the phenol.




Reactions involving the cyclization of 1,*n*-enynes are highly valuable as they can generate molecular complexity under mild conditions in one synthetic operation.[1] Within this general reaction class, chemical processes based on the gold(I)-catalyzed cyclization of 1,5- and 1,6-enynes have emerged as a reliable and efficient strategy for the synthesis of functionalized cycloalkane derivatives.[2] Although the overall reaction mechanism of these transformations is strongly dependent upon the exact experimental conditions and reaction partners, a few intermediates were proposed to play a key-role.[3]

The way these transient structures interact with an external nucleophile has a profound influence on the reaction pathway and the substitution pattern of the products.[2c,4] Carbon (arenes, heteroarenes, 1,3-dicarbonyls)[4d] and oxygen ($H_2O$, ROH, RCOOH) nucleophiles[4e−h] typically attack the putative enyne–cyclization intermediates to give products carrying the former nucleophile in their side-chain (Scheme 1a, Nu = R′OH, R′ = R = alkyl, aryl).[3d]

**Scheme 1. Gold(I)-Promoted Cyclization of 1,5-Enynes in the Presence of External Oxygen Nucleophiles**




Herein, we describe a mild experimental procedure for the realization of an unexplored reaction pathway[4d] that is operative for 1-halo-1,5-enynes in the presence of phenols (Scheme 1b, Nu = ArOH, R = Br, Cl). This strategy constitutes a facile entry to synthetically useful (2-halocyclopent-2-en-1-yl)phenols whose underlying (cyclopentyl)phenol structural motif can be found in several biologically active molecules (Figure 1).[5]

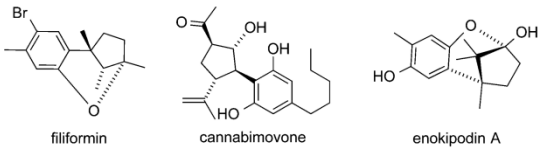



**Figure 1.** Selected natural products containing the (cyclopentyl)phenol structural motif.

As part of our efforts to study the gold(I)-catalyzed addition of phenols to 1-bromoalkynes for the synthesis of aryl bromoenol ethers, we discovered that Nolan's [(IPr)Au(OH)] $HBF_4{\cdot}OEt_2$ catalyst[6] (5 mol %) promotes the cycloisomerization of 1-bromo-6-methylhept-5-en-1-yne **1a** followed by C–H insertion of *p*-cresol to provide **2a** (37%) and traces of the bis-alkylated phenol **3a** (Table 1, entry 1). Careful reaction monitoring revealed that both products had only formed after concentration of the yellow reaction solution at 50 °C to give the product mixture as a red-orange residue. The expected *trans*-addition of *p*-cresol across the alkyne, to give the bromo enol ether, was not observed. Excited by this unexpected result, we evaluated a series of different catalytic systems to optimize the transformation of enyne **1a** to **2a**. We found that the electronic nature of the spectator ligand (phosphine, phosphite, or *N*-heterocyclic carbene ligand) had little effect on the reactivity of the catalyst (entries 2–4).[7] However, exchange of the counterion led to a dramatic change in reaction yield (entries 1 and 5–7).[8] It was interesting to note that the catalytic system containing either the triflate or triflimide anion showed similar efficiency, whereas a sharp drop was observed for hexafluoroantimonate. Chloride failed to catalyze the transformation at all. Finally, by increasing the amount of phenol to 5 equiv, the byproduct **3a** could be further diminished to give **2a** in 76% yield (entry 8). The recently

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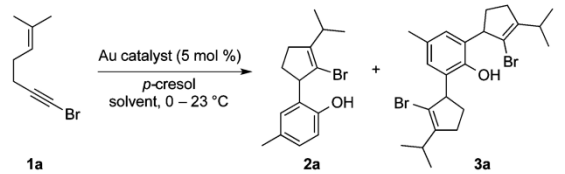
**Table 1. Gold(I)-Catalyzed Cycloisomerization of 1-Bromo-1,5-enyne 1a in the Presence of *p*-Cresol. Optimization of Reaction Parameters[a]**



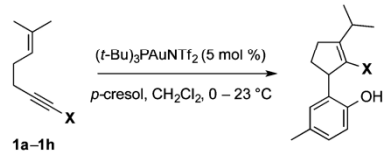

| entry[a] | catalyst | solvent | yield **2a**/**3a** (%) |
|---|---|---|---|
| 1 | (IPr)Au(OH), $HBF_4$·$OEt_2$ | toluene | 37/6[b] |
| 2 | IPrAuNTf$_2$ | $CH_2Cl_2$ | 62/5 |
| 3 | (2,4-*t*-BuPhO)$_3$PAuNTf$_2$ | $CH_2Cl_2$ | 64/4 |
| 4 | (*t*-Bu)$_3$PAuNTf$_2$ | $CH_2Cl_2$ | 66/4 |
| 5 | (*t*-Bu)$_3$PAuCl | $CH_2Cl_2$ | 0 |
| 6 | (*t*-Bu)$_3$PAuCl, $AgSbF_6$ | $CH_2Cl_2$ | 39/4 |
| 7 | (*t*-Bu)$_3$PAuCl, AgOTf | $CH_2Cl_2$ | 65 |
| 8 | **(*t*-Bu)$_3$PAuNTf$_2$** | $CH_2Cl_2$ | **76**[c] |
| 9 | $InI_3$, $AgSbF_6$ | $CH_2Cl_2$ | 43/4 |

[a]Reaction conditions: **1** (0.25 mmol), *p*-cresol (0.38 mmol), catalyst (5 mol %), $CH_2Cl_2$ (1 mL), 23 °C. Yields of **2a**/**3a** were determined by $^1$H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]**1** (0.49 mmol), *p*-cresol (0.54 mmol), catalyst (5 mol %), toluene (1.8 mL), 50 °C. [c]*p*-Cresol (5 equiv), isolated yield. IPr = (2,6-diisopropylphenyl)-1,3-imidazol-2-ylidene; $NTf_2$ = bis[(trifluoromethane)sulfonyl]amide].

described yneophile diodoindium(II) cation[9] promoted this reaction as well but showed significantly lower conversion (entry 9). For a full analysis of reaction conditions, promoters, and control experiments, see Table 1 in the Supporting Information.

After having performed these initial experiments, we speculated that the 1-bromo substituent might exert a unique steric and electronic effect on this transformation. To prove this hypothesis, several substrates differing in the alkyne substitution were prepared (Scheme 2).

**Scheme 2. Influence of the Alkyne Substituent on the Overall Reaction Sequence**

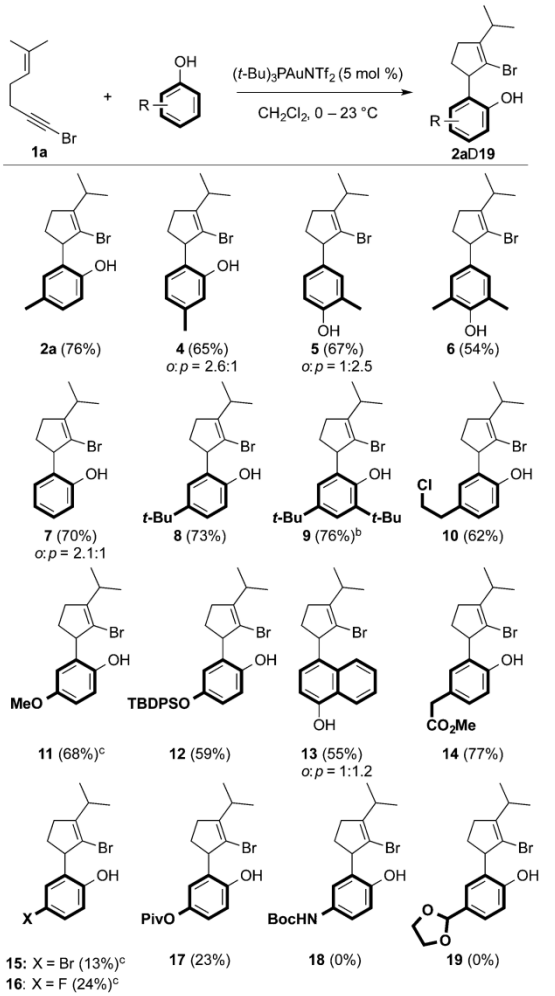



**2a**, X = Br (76%)
**2b**, X = Cl (56%)
**2c**, X = I (6%)
**2d**, X = $CO_2$Me (0%)
**2e**, X = Me (0%)
**2f**, X = H (0%)
**2g**, X = Ph (8%)
**2h**, X = TMS (0%)

The unique behavior of **1a** was immediately evident, as product formation for nonhalogenated substrates could only be observed for **2g** (X = Ph, 8%). Exchange for chlorine decreased the yield to 56%, whereas only a 6% yield was obtained for 1-iodoalkyne **1c**, which was unstable under the reaction conditions.[10] The reactions of **1d**–**g** led to the formation of side products (see Supporting Information for details), and for **1h** decomposition occurred.

Having established the optimized reaction conditions, the substrate scope was investigated with a panel of phenols. As shown in Scheme 3, electron-rich phenols react smoothly to give **2a** and **4**–**13** in good yields. Although exclusive chemoselectivity was observed for the C–H bond, the site-selectivity was less predictable. For **5** and **13**, the *para* position was favored, and for **4** and **7** the *ortho* products were predominantly formed. This ratio was also not altered when the catalyst (2,4-*t*-BuPhO)$_3$PAuNTf$_2$, previously reported for the gold(I)-catalyzed site-specific C–H bond functionalization of phenols,[11] was used. When *para*-substituted phenols were employed, the *ortho* C–H functionalization products could be isolated in yields up to 76%.

**Scheme 3. Substrate Scope and Functional-Group Tolerance[a]**




[a]Reaction conditions according to entry 8 of Table 1. Yields of the isolated product. Average of two runs. [b]*p*-Fluorophenol (1.05 equiv) was added prior to the addition of 2,4-di-*tert*-butylphenol. [c]*p*-Methoxyphenol, *p*-fluorophenol, and *p*-bromophenol were used in excess (10 equiv).

Substrates containing functional groups such as halides (**10**), alkyl ethers (**11**), silyl ethers (**12**), and esters (**14**, **17**) were also tolerated under the reaction conditions. Unfortunately, the less electron-rich compounds **15**–**17** were formed in low yields even in the presence of a large excess of phenol (10 equiv).[12] For **16**, the O–H insertion product according to the pathway shown in Scheme 1a could be isolated in 75% yield (see the Supporting Information for details). However, the low reactivity of *p*-fluorophenol in the consecutive C–H insertion step made the overall transformation inefficient.



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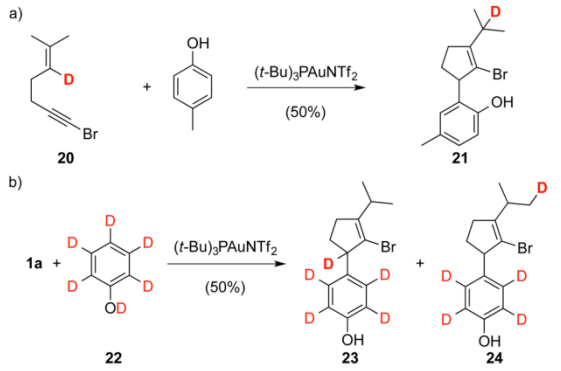
For sterically hindered phenols, which reacted sluggishly with **1a**, we could take advantage of this observation. Addition of 2,4-di-*tert*-butylphenol (5 equiv) to the aforementioned O−H insertion product in the presence of catalyst gave **9** in good yield.[13] The electron-poor substrates *p*-(trifluoromethyl)phenol, methyl *p*-hydroxybenzoate, and *p*-hydroxyacetophenone were unreactive under the reaction conditions, and for substrates containing nitrogen (**18**) or acid-labile groups (**19**), no C−H insertion could be observed.

To obtain a more detailed insight into the reaction mechanisms, the deuterium-labeled 1-bromo-1,5-enyne **20** was exposed to the standard reaction conditions (Scheme 4a).

**Scheme 4. Mechanistic Investigations**



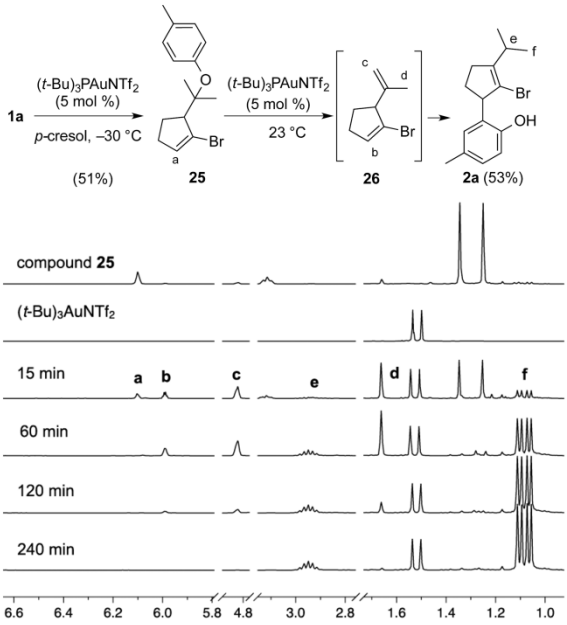

Isolation of **21** confirmed that deuterium underwent a [1,2]-shift prior to C−H insertion. The HR-MS and $^2$H NMR analysis of the product mixture obtained from the reaction of **1a** with phenol-$d_6$ revealed that incorporation of deuterium has occurred as depicted for **23** and **24** (Scheme 4b). These results are consistent with a reaction pathway that includes a protodeauration step after enyne cyclization and the occurrence of a transient isopropyl cation. The latter would be in equilibrium with an isopropenyl group which, in the presence of traces of $DNTf_2$, accounts for the formation of **24**.[14]

Further evidence for the pathway leading to **24** was obtained from a time-resolved $^1$H NMR experiment (Scheme 5). Lowering the reaction temperature to −30 °C led to the formation of aryl alkyl ether **25** as a single compound. Rapid purification by flash column chromatography on silica gel gave **25** in 51% yield. When a solution of **25** in dichloromethane-$d_2$ was treated with gold(I) complex $(t\text{-Bu})_3PAuNTf_2$ at 23 °C, clean formation of **26** and **2a** could be observed within 15 min.

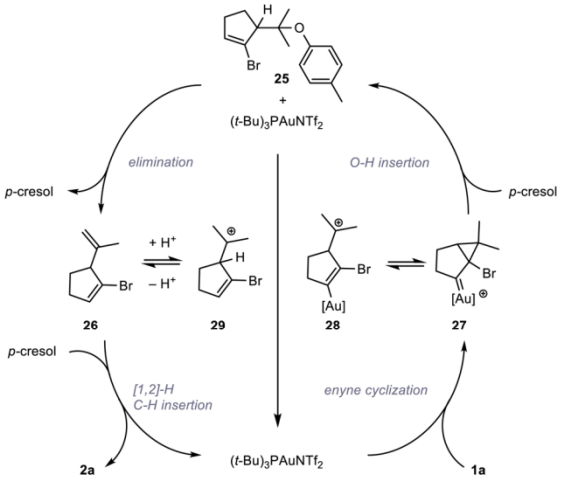
A proposed reaction mechanism that is consistent with the experimental data and literature[3,4g,h] is provided in Scheme 6. Site-selective addition of *p*-cresol to the gold-stabilized carbocation[15] **27** or **28**,[16] obtained via the enyne−cycloisomerization of **1a** produces the aryl alkyl ether **25**.[17] Monitoring the reaction via $^1$H and $^{31}$P NMR revealed that the catalyst was fully regenerated after the formation of **25** at low temperature (−30 °C). The unstable alkyl aryl ether collapses under the reactions conditions at ambient temperature with concomitant expulsion of *p*-cresol to give **26** which, in the presence of traces of acid, is in equilibrium with **29**.

The subsequent [1,2]-hydride shift of **29** should be favored due to the formation of a tertiary allylic cation (not shown) which could be further stabilized by the adjacent bromine substituent. Addition of *p*-cresol (C−H insertion step) to the allylic system

**Scheme 5. Synthesis of Aryl Ether 25 and Monitoring Its Conversion to 2a via $^1$H NMR Spectroscopy ($CD_2Cl_2$, 400 MHz)**




**Scheme 6. Proposed Catalytic Cycle**




leads to **2a**. In a separate experiment, it was found that the overall rearrangement from **25** to **2a** can be promoted in the presence of catalytic amounts of $HNTf_2$ (5 mol %, 51% yield).[14,18] This explains why the overall reaction outcome is dominated by the counterion and not the ligand on the gold(I) catalyst.

The site-selectivity is controlled by the substrate structure. The unique feature that only 1-halo-1,5-enynes **1a** and **1b** efficiently undergo this transformation is noteworthy, too.[19] However, the exact role of the halogen substituent is still unclear.

In summary, we have developed a domino transformation which converts 1-halo-1,5-enynes in the presence of phenols to 2-(halocyclopent-2-en-1-yl)phenols which are valuable precursors for the elaboration of more complex structures. This



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carbon−carbon bond-forming reaction is catalyzed by cationic gold(I) complexes, proceeds via a sequential O−H/C−H functionalization of phenols, and extends the product range typically observed for simple 1,5-enynes. An application of this method for the synthesis of bioactive molecules is currently underway in our laboratories.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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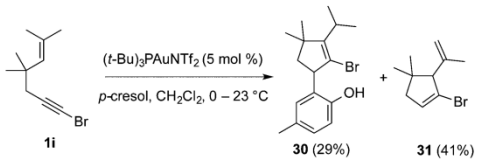
(17) A similar ether adduct could be observed when methanol was used; however, the obtained dialkyl ether did not undergo further reactions.

(18) For a related allylic alkylation see: Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426−2433.

(19) The corresponding 1-bromo-1,4-enyne and 1-bromo-1,6-enyne led to the formation of complex product mixtures. Substitution of the alkene was not tolerated, but modification of the alkyl chain linking the alkene and alkyne was possible:


**1i** **30** (29%) **31** (41%)



DOI: 10.1021/acs.orglett.5b00738
*Org. Lett.* 2015, 17, 1982−1985

## 2.4. Conclusions and Outlook

In Part II of this thesis, a novel gold(I)-catalyzed domino reaction of 1-halo-1,5-enynes in the presence of phenols is described. The newly developed reaction constitutes a facile entry to highly functionalized halocyclopentenes, a structural motif that can be found in several biologically active compounds.

Detailed mechanistic investigations, including deuterium labelling, cross-over experiments of reactive intermediates and NMR-studies, shed light on this unexplored transformation. The unprecedented cascade reaction proceeds through a dual catalytic cycle which requires a π-acidic cationic gold species and a Brønsted-acidic counterion. The initial step, a gold(I)-catalyzed 5-*endo*-cyclization of the enyne, generates an intermediate aryl alkyl ether which collapses at ambient temperatures through trace amounts of Brønsted-acid to undergo a [1,2]-hydride shift followed by subsequent C–H insertion of the phenol.

The developed one-pot procedure proceeds efficiently under mild reaction conditions and was found to tolerate a variety of substituted phenols resutling in a total scope of 18 examples. The developed cascade beautifully highlights the profound influence of external nucleophiles and experimental conditions on the reaction pathway of gold(I)-catalyzed cyclization of enynes. In future work we aim to expand this methodology to the synthesis of bioactive molecules.

# EXPERIMENTAL SECTION

# 3.1. General Experimental Details

## 3.1.1. General Working Methods

All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), $H_2O$/ice (0 °C). Reaction temperatures above room temperature were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminum plates percolated with silica gel (0.25 mm, 60-Å pore size, *Merck*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$), ceric ammonium molybdate solution (CAM) or *p*-anisaldehyde solution (Anis), and were developed by heating with a heat gun. Flash-column chromatography was performed as described by Still employing silica gel (60 Å, 40–63 µm, *Merck KGaA*).[173] The yields refer to chromatographically and spectroscopically ($^1H$ and $^{13}C$ NMR) pure material.

## 3.1.2. Materials

Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were distilled under $N_2$ atmosphere from sodium and benzophenone prior to use. Dichloromethane ($CH_2Cl_2$), triethylamine ($Et_3N$), diisopropylamine (DIPA) and Hünig's base (DIPEA) were distilled under nitrogen atmosphere from $CaH_2$ prior to use. Dimethyl sulfoxide (DMSO), acetonitrile (MeCN), acetone, toluene, chloroform ($CHCl_3$) and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, ABCR) and were used as received. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. Lithium chloride was dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4−5 min immediately prior to use. The molarity of *n*-butyllithium and *t*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[174] The concentration of freshly prepared dimethyldioxirane solutions[175] was determined by iodometric titration as follows: A 0.02 M aqueous stock solution of sodium thiosulfate pentahydrate (124 mg $Na_2S_2O_3 \cdot 5\ H_2O$ in 25 mL $H_2O$) was prepared in a 25 mL graduated cylinder. A 100 mL flask was charged with water (30 mL), sodium iodide (2.00 g) and glacial acetic acid (1 mL), whereupon the dimethyldioxirane solution (2 mL) was added. The resulting

brown mixture was rapidly titrated with the sodium thiosulfate stock solution until disappearance of the yellow iodine color occurred. The concentration of the dimethyldioxirane solution was calculated according to the following equation:

$$c(DMDO) = \frac{M(titrant)\ x\ V(titrant)}{V(DMDO)\ x\ 2}$$

and was generally in the range of 0.04 M to 0.06 M.

### 3.1.3. NMR Spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, *Bruker* AXR300, *Varian* VXR400 S, *JOEL* ECX400, *Bruker* AMX600 and *Bruker* Avance HD 800. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual proton in the NMR solvent ($CHCl_3$: δ 7.26, $C_6D_5H$: δ 7.16, $CDHCl_2$: δ 5.32). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, $C_6D_6$: δ 128.06, $CD_2Cl_2$: δ 54.00). $^1H$ NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Additionally to $^1H$ and $^{13}C$ NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. Coupling constants *J* are reported in Hz. All raw fid files were processed and the spectra analyzed using the program *MestReNOVA 9.0* from *Mestrelab Research S. L*.

### 3.1.4. Mass Spectroscopy

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. Mass spectra were recorded on the following spectrometers (ionization mode in brackets): MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan GmbH* or MS-700 (DEI) from *JOEL*. Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

### 3.1.5. IR Spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. If required, substances were dissolved in $CH_2Cl_2$ prior to direct application on the ATR unit. Data are represented as follows: frequency of absorption ($cm^{-1}$), and intensity of absorption (*vs* = very strong, *s* = strong, *m* = medium, *w* = weak, *br* = broad).

### 3.1.6. Optical Rotation

Optical rotation values were recorded on a *PerkinElmer* 241 or *Anton Paar* MCP 200 polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

Thereby, the wave length λ is reported in nm and the measuring temperature ϕ in °C. α represents the recorded optical rotation at the apparatus, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in $10^{-1} \cdot deg \cdot cm^2 \cdot g^{-1}$. Usage of the sodium D line ($\lambda$ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

### 3.1.7. Melting Points

Melting points were determined on a B-450 melting point apparatus from *BÜCHI Labortechnik AG*. The values are uncorrected.

### 3.1.8. High-pressure Reactions

The high pressure reactions were performed in self-made Teflon reaction vials in an emulsion high pressure machine from *Andreas Hofer Hochdrucktechnik GmbH* (max. 14 kbar, piston Ø 25 mm, stroke 95 mm) equipped with a *Julabo* MA-4 circulation thermostat.

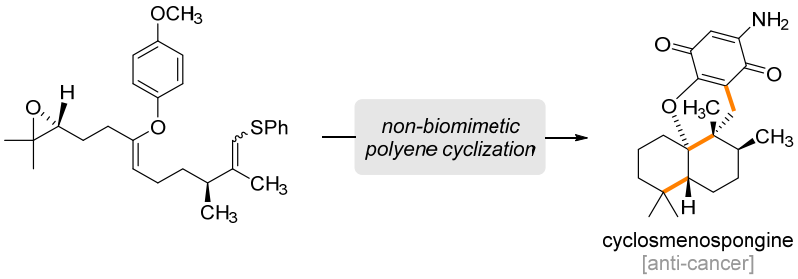
### 3.1.9. Elemental Analysis

Elemental analyses were performed in the micro analytical laboratory of the Department of Chemistry, *Ludwig-Maximilians-Universität München*, on an *Elementar Vario EL* apparatus.

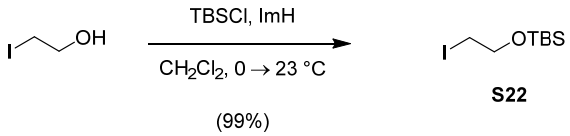
## 3.2. Supporting Information for Chapter 1.4.2.

# Convergent Assembly of the Tetracyclic Meroterpenoid (–)-Cyclosmenosongine via a Non-Biomimetic Polyene Cyclization

K. Speck, R. Wildermuth, T. Magauer, *Angew. Chem. Int. Ed.* **2016**, *55*, 14131–14135.

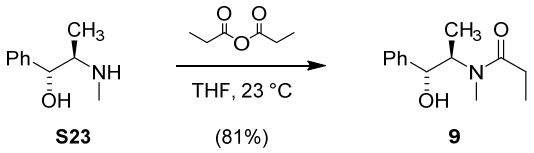


### 3.2.1. Experimental Procedures



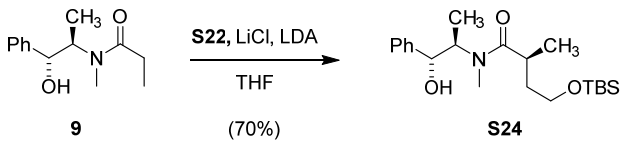

**Iodide S22**

To a solution of 2-iodoethanol (25.0 g, 145 mmol, 1 equiv) in dichloromethane (360 mL) and imidazole (19.8 g, 291 mmol, 2.00 equiv) was added *tert*-butyldimethylsilyl chloride (21.9 g, 145 mmol, 1.00 equiv) at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the reaction mixture was diluted with dichloromethane (200 mL) and the organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 200 mL) and with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give iodide **S22** (41.4 g, 99%) as a colorless oil. The crude product was directly used without further purification. Characterization data obtained for **S22** were in full agreement with values previously reported.[176]



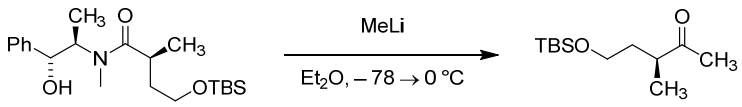

**(–)-(1*R*,2*R*)-pseudoephedrine propionylamide 9**

Propionic anhydride (21.2 mL, 165 mmol, 1.07 equiv) was added dropwise to a solution of (–)-(1*R*,2*R*)-pseudoepedrine (**S23**) (25.5 g, 154 mmol, 1 equiv) in tetrahydrofuran (300 mL) at 23 °C. After 30 min, excess propionic anhydride was quenched by the addition of saturated aqueous sodium bicarbonate solution (150 mL). The resulting biphasic mixture was partitioned between water (200 mL) and ethyl acetate (250 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was recrystallized from toluene to afford amide **9** (32.1 g, 94%) as a white solid. The obtained characterization data were in full agreement with those reported in literature.[177]




**Amide S24**

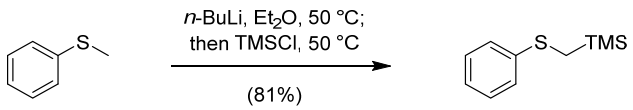
*N*,*N*-Diisopropylamime (23.0 mL, 163 mmol, 2.25 equiv) was added dropwise to a suspension of lithium chloride (18.4 g, 434 mmol, 6.00 equiv) in tetrahydrofuran (72 mL) at 23 °C and the resulting suspension was cooled to –78 °C. A solution of *n*-butyllithium (2.52 M in hexanes, 60.3 mL, 152 mmol, 2.10 equiv) was added via syringe. The reaction mixture was briefly warmed to 0 °C for 5 min, then cooled to –78 °C. An ice-cooled solution of amide **9** (16.0 g, 72.3 mmol, 1 equiv) in tetrahydrofuran (180 mL) was added by cannula to the inner wall of the flask. The transfer was quantitated with tetrahydrofuran (15 mL). The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min and at 23 °C for 5 min. Then the reaction mixture was cooled to 0 °C, whereupon iodide **S22** (41.4 g, 145 mmol, 2.00 equiv) was added. Stirring was continued at 23 °C for 3.5 h. Saturated aqueous ammonium chloride solution (20 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (200 mL) and aqueous hydrochloric acid solution (1 M, 150 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (40% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to give amide **S24** (22.8 g, 83%) as a viscous yellow oil. Characterization data obtained for **S24** were in full agreement with previously reported values.[177]




**S24** (83%) **10**

**Ketone 10**

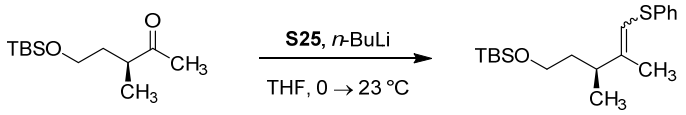
Amide **S24** was dried by azeotropic distillation (benzene, 2 × 40 mL) prior to use. To a solution of **S24** (22.8 g, 60.1 mmol, 1 equiv) in diethyl ether (400 mL) was added methyllithium (1.6 M in diethyl ether, 97.6 mL, 156 mmol, 2.60 equiv) via syringe at –78 °C. The reaction mixture was allowed to warm to 0 °C. After 45 min, excess methyllithium was quenched at 0 °C by the addition of *N*,*N*-diisopropylamine (8.49 mL, 60.1 mmol, 1.00 equiv). A solution of acetic acid in diethyl ether (20% v/v, 75 mL) was added and the reaction mixture (pH = 6 to 7) was partitioned between diethyl ether (100 mL) and water (200 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 10% ethyl acetate in hexanes) to provide ketone 10 (11.9 g, 83%) as a colorless oil. The obtained characterization data were in full agreement with those reported in literature.[177]




**S25**

**Trimethyl((phenylthio)methyl)silane S25**

*Peterson reagent **S25** was prepared according to the procedure described by D. J. Ager:*[178] To a solution of *n*-butyllithium (2.52 M in hexanes, 34.7 mL, 87.4 mmol, 1.01 equiv) in diethyl ether (30 mL) was added thioanisole (10.2 mL, 86.6 mmol, 1 equiv) at 23 °C, then the mixture was heated to 50 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C, chlorotrimethylsilane (13.3 mL, 104 mmol, 1.20 equiv) was added dropwise to the now white suspension and heated to 50 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C and poured into saturated aqueous ammonium chloride solution (40 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by distillation to give sulfide **S25** (13.7 g, 81%) as a colorless oil (boiling point: 125–128 °C, 20 mbar). The obtained analytical data were in full agreement with those reported in literature.[178]




**10** **S26**

**Vinylsulfide S26**

To a solution of Peterson reagent **S25** (11.9 g, 60.8 mmol, 1.40 equiv) in tetrahydrofuran (100 mL) was added a solution of *n*-butyllithium (2.45 M in hexanes, 23.9 mL, 58.6 mmol, 1.35 equiv) at 0 °C. After 30 min, a solution of ketone **10** (10.0 g, 43.4 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added and stirring was continued at 0°C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 5 h, the reaction mixture was diluted with diethyl ether (100 mL) and the organic layer was washed with saturated aqueous ammonium chloride solution (200 mL). The aqueous phase was extracted with diethyl ether (2 × 200 mL) and the combinded organic extracts were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially grading to 2% ethyl acetate in hexanes) to provide vinylsulfide **S26** as an inseparable mixture of double bond isomers (12.6 g, 86%, *E*:*Z* = 2:3) as a colorless oil.

**TLC** (5% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, CAM).

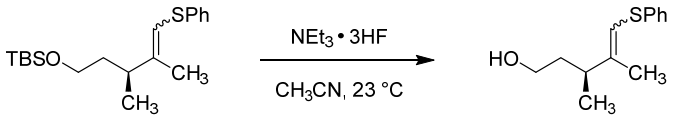
**$^1$H NMR** ($CDCl_3$, 400 MHz): (*Z*): δ = 7.33–7.24 (m, 4H), 7.20–7.12 (m, 1H), 5.89 (q, *J* = 1.2 Hz, 1H), 3.66–3.49 (m, 2H), 3.19–3.04 (m, 1H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.73–1.49 (m, 2H), 1.04 (d, *J* = 6.9

Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); (*E*): δ = 7.32–7.22 (m, 4H), 7.19–7.13 (m, 1H), 5.98–5.95 (m, 1H), 3.68–3.48 (m, 2H), 2.58–2.43 (m, 1H), 1.79 (d, *J* = 1.1 Hz, 3H), 1.74–1.51 (m, 2H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 146.6, 137.7, 129.0, 128.1, 125.7, 115.8, 61.8, 37.8, 33.0, 26.1, 19.0, 18.5, 18.4, –5.1, –5.1; (*E*): δ = 146.5, 137.5, 129.0, 128.1, 125.8, 115.6, 61.4, 39.3, 38.0, 26.1, 19.7, 18.5, 14.7, –5.1, –5.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2955 (*m*), 2927 (*m*), 2855 (*m*), 1584 (*w*), 1479 (*m*), 1251 (*m*), 1090 (*s*), 833 (*vs*), 773 (*vs*), 736 (*vs*), 689 (*vs*).

**HRMS** (EI) calc. for $C_{19}H_{32}O^{32}S^{28}Si$ $[M]^+$: 336.1938 found: 336.1933.




**S26** (77%) **S27**

**Alcohol S27**

To a solution of silylether **S26** (12.5 g, 37.3 mmol, 1 equiv) in acetonitrile (120 mL) was added triethylamine trihydrofluoride (10.6 mL, 65.2 mmol, 1.75 equiv) at 23 °C. After 8 h, the reaction mixture was portioned between diethyl ether (150 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution (200 mL) and saturated aqueous sodium chloride solution (200 mL). The aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) to yield alcohol **S27** (7.87 g, 95%, *E*:*Z* = 2:3) as a colorless oil.

An analytical sample was purified by flash-column chromatography (10% ethyl acetate in hexanes) to give pure alcohol **(*Z*)-27** and alcohol **(*E*)-27** as colorless oils. *Note: Since the double bond geometry is inconsequential for the subsequent steps the following transformations were performed using the mixture of double bond isomers.*

**(*Z*)-27**:

**TLC** (40% ethyl acetate in hexane): $R_f$ = 0.38 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.37–7.26 (m, 4H), 7.24–7.17 (m, 1H), 5.96 (q, *J* = 1.4 Hz, 1H), 3.71–3.54 (m, 2H), 3.29–3.09 (m, 1H), 1.91 (s, 1H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.74–1.59 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 145.4, 136.9, 129.0, 128.4, 126.0, 116.5, 61.2, 37.4, 32.7, 19.0, 18.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3340 (*br w*), 2958 (*w*), 2930 (*w*), 2870 (*w*), 1582 (*m*), 1478 (*m*), 1438(*m*), 1046 (*s*), 1024 (*m*), 809 (*m*), 735 (*vs*), 688 (*vs*).

**HRMS** (EI) calc. for $C_{13}H_{18}O^{32}S$ $[M]^+$: 222.1073 found: 222.1070.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 45.8° (*c* = 1.00, $CH_2Cl_2$).

**(*E*)-27**:

**TLC** (40% ethyl acetate in hexane): $R_f$ = 0.31 (UV, $KMnO_4$).

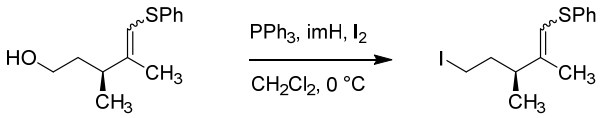
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.34–7.27 (m, 4H), 7.21–7.14 (m, 1H), 6.02–6.00 (m, 1H), 3.64 (td, *J* = 6.8, 1.2 Hz, 2H), 2.59–2.45 (m, 1H), 1.80 (d, *J* = 1.1 Hz, 3H), 1.78–1.68 (m, 1H), 1.68–1.57 (m, 1H), 1.36 (br s, 1H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 145.5, 137.1, 129.1, 128.3, 125.9, 116.3, 61.4, 39.6, 37.7, 19.8, 14.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3324 (*br w*), 2958 (*m*), 2928 (*m*), 2870 (*w*), 1582 (*m*), 1478 (*s*), 1438 (*m*), 1376 (*w*), 1047 (*s*), 816 (*m*), 736 (*vs*), 689 (*s*).

**HRMS** (EI) calc. for $C_{13}H_{18}O^{32}S$ $[M]^+$: 222.1073 found: 222.1072.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 5.4° (*c* = 1.00, $CH_2Cl_2$).




**S27** **8**

**Iodide 8**

To a solution of imidazole (2.87 g, 42.1 mmol, 1.20 equiv) and triphenylphosphine (11.0 g, 42.1 mmol, 1.20 equiv) in dichloromethane (180 mL) was added iodide (10.7 gg, 42.1 mmol, 1.20 equiv) at 0 °C. After 15 min, a solution of alcohol **S27** (7.80 g, 35.1 mmol, 1 equiv) in dichloromethane (60 mL) was added to the reaction mixture. After 30 min, the mixture was diluted with hexanes (200 mL) and the organic layer was washed with saturated aqueous sodium thiosulfate solution (200 mL). The aqueous phase was extracted with a 1:1 mixture of diethyl ether and hexanes (3 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 10% ethyl acetate in hexanes) to give iodide **8** (9.46 g, 81%, *E*:*Z* = 1:1.2) as a pale yellow oil.

*To obtain analytical pure samples, alcohol **(Z)-27** and alcohol **(E)-27** were converted to the corresponding analytical pure iodides **(Z)-8** and **(E)-8** using the above described procedure.*

**(*Z*)-8:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.78 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.16–7.04 (m, 4H), 7.04–6.95 (m, 1H), 5.79 (q, *J* = 1.3 Hz, 1H), 2.94–2.89 (m, 3H), 1.91–1.67 (m, 2H), 1.58 (d, *J* = 1.3 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 143.9, 137.2, 129.0, 128.4, 126.0, 117.9, 39.1, 37.6, 18.4, 18.2, 3.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2960 (*m*), 2929 (*w*), 2362 (*w*), 1538 (*m*), 1478 (*m*), 1438 (*m*), 1238 (*w*), 1024 (*m*), 738 (*s*), 689 (*m*).

**$[\alpha]^{25}_{D}$** = –38.7° (*c* = 1.00, $CHCl_3$).

**HRMS** (EI) calc. for $C_{13}H_{17}{}^{127}I^{32}S$ $[M]^+$: 332.0090 found: 332.0084.

**(*E*)-8:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.78 (UV, $KMnO_4$).

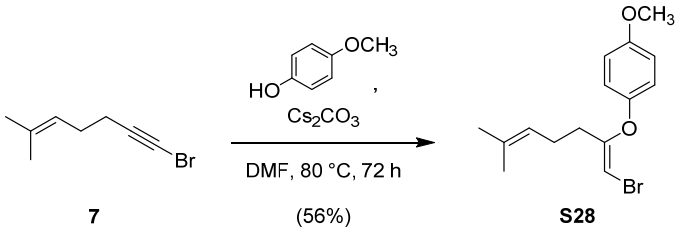
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.36–7.27 (m, 4H), 7.23–7.15 (m, 1H), 6.08 (s, 1H), 3.24–3.14 (m, 1H), 3.11–3.00 (m, 1H), 2.60–2.45 (m, 1H), 2.02–1.79 (m, 2H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 143.0, 136.9, 129.1, 128.4, 126.0, 117.8, 43.4, 38.2, 19.1, 14.2, 5.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*m*), 1582 (*m*), 1478 (*s*), 1438 (*m*), 1377 (*w*), 1236 (*w*), 1024 (*m*), 821 (*w*), 737 (*s*), 689 (*s*).

$[\alpha]_D^{20}$ = +7.2° (*c* = 1.00, $CHCl_3$).

**HRMS** (EI) calc. for $C_{13}H_{17}{}^{127}I^{32}S$ $[M]^+$: 332.0090 found: 332.0104.




**7** (56%) **S28**

**Bromoenolether S28**

A suspension of bromoalkyne **7**[179] (7.00 g, 37.4 mmol, 1 equiv), cesium carbonate (36.6 g, 112 mmol, 3.00 equiv) and 4-methoxyphenol (**6**) (46.4 g, 374 mmol, 10.0 equiv) in *N*,*N*-dimethylformamide (38 mL) was heated to 80 °C in a pressure flask. After 72 h, the reaction mixture was partitioned between ethyl acetate (300 mL) and water (300 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 300 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The

residue was purified by flash-column chromatography on silica gel (2% ethyl aceate in hexanes initially, grading to 10% ethyl acetate in hexanes) to provide bromoenol ether **S28** as a yellow oil (6.52 g, 56%).

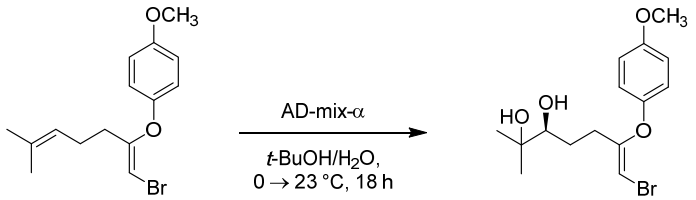
**TLC** (10% ethyl acetate in hexanes): $R_f = 0.55$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.94–6.88 (m, 2H), 6.87–6.79 (m, 2H), 5.65 (t, *J* = 0.9 Hz, 1H), 5.05–4.99 (m, 1H), 3.78 (s, 3H), 2.23–2.12 (m, 4H), 1.66 (s, 3H), 1.54 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 155.7, 155.5, 148.8, 133.2, 122.5, 118.6, 114.8, 90.4, 55.8, 32.2, 25.8, 25.2, 17.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3333 (*w*), 2922 (*w*), 2833 (*w*), 1633 (*m*), 1547 (*m*), 1501 (*vs*), 1243 (*m*), 1208 (*vs*), 1036 (*m*), 803 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{18}{}^{79}BrO_2$ $[M–H]^+$: 309.0490 found: 309.0491.




**S28** (94%) **3(*S*)-S29**

**Diol 3(*S*)-S29**

Potassium hexacyanoferrate (III (41.4 g, 126 mmol, 6.00 equiv), potassium carbonate (17.4 g, 126 mmol, 6.00 equiv) and $(DHQ)_2Phal$ (676 mg, 0.84 mmol, 0.04 equiv) were grinded to a fine powder and were added to a 1:1 mixture of *t*-butanol and water (210 mL). Potassium osmate (IV) dihydrate (61.8 mg, 0.17 mmol, 0.8 mol%) was added to the orange suspension at 23 °C. After 30 min, the reaction mixture was cooled to 0 °C and methanesulfonamide (3.99 g, 41.9 mmol, 2.00 equiv) was added in one portion followed by a solution of alkene **S28** (6.52 g, 20.9 mmol, 1 equiv) in *t*-butanol (110 mL). After 5 min, the reaction mixture was allowed to warm to 23 °C. After 15 h, sodium sulfate (26.4 g, 209 mmol, 10.0 equiv) was added. After 30 min, 5% aqueous sodium hydroxide solution (150 mL) was added and the mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% methanol in dichloromethane) to give diol **3(*S*)-S29** (6.76 g, 94%) as a yellow oil.

**TLC** (5% MeOH in dichloromethane): $R_f = 0.31$ (UV; CAM).

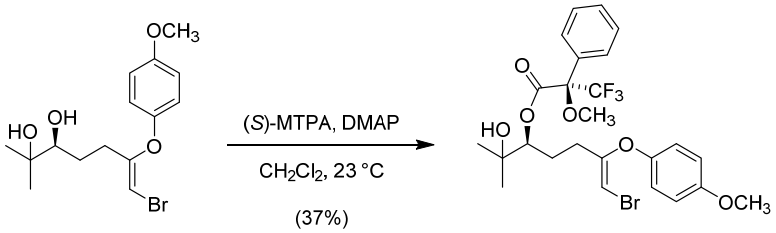
**$^1$H NMR** ($C_6D_6$, 800 MHz): δ = 6.87–6.82 (m, 2H), 6.67–6.63 (m, 2H), 5.47 (t, *J* = 0.9 Hz, 1H), 3.25 (s, 3H), 3.00 (d, *J* = 10.8 Hz, 1H), 2.41–2.34 (m, 1H), 2.16–2.10 (m, 1H), 1.75 (br d, *J* = 3.1 Hz, 1H), 1.48–1.43 (m, 1H), 1.26–1.20 (m, 1H), 1.02 (br s, 1H), 0.88 (s, 3H), 0.87 (s, 3H).

**$^{13}$C NMR** ($C_6D_6$, 201 MHz): δ = 156.0, 155.9, 149.2, 118.7, 115.1, 91.0, 77.1, 72.5, 55.1, 29.4, 28.5, 26.4, 23.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3405 (*w*), 2972 (*w*), 2359 (*w*), 1645 (*w*), 1503 (*vs*), 1207 (*s*), 1034 (*w*), 830 (*w*).

**HRMS** (EI) calc. for $C_{15}H_{21}{}^{79}BrO_4$ $[M]^+$: 344.0618; found: 344.0612.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +18.4 (c = 1.00, $CH_2Cl_2$).




**3(*S*)-S29** **3(*S*)-S30**

**Mosher Ester 3(*S*)-S30**

The enantiomeric excess of **3(*S*)-S29** was determined as 94% by $^1$H analysis of its corresponding mono-(*S*)-MTPA esters **3(*S*)-S30** and **3(*R*)-S30**.

**3(*R*)-S30** was synthesized in an analogous fashion to **3(*S*)-S29** using AD-mix-β. The analytical data obtained were in full agreement with those of **3(*R*)-S29**. ($[\alpha]_D^{20}$ = –5.9 (c = 1.00, $CH_2Cl_2$)).

**3(*S*)-S30**

To a solution of diol **3(*S*)-S29** (5.00 mg, 14.5 µmol, 1 equiv) and 4-dimethylaminopyridine (7.08 mg, 57.9 µmol, 4.00 equiv) in dichloromethane (0.8 ml) was added (*S*)-Mosher´s acid chloride (5.4 µL, 2.90 µmol, 2.00 equiv) at 23 °C. After 1h, 4-dimethylaminopyridine (7.08 mg, 57.9 µmol, 4.00 equiv) and (*S*)-Mosher´s acid chloride (5.4 µL, 2.90 µmol, 2.00 equiv) were added. After 1h, water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethylacetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to yield mono-MTPA ester **3(*S*)-S30** (3.0 mg, 37%) as a colorless oil.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.26 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.56–7.50 (m, 2H), 7.42–7.39 (m, 1H), 7.39–7.37 (m, 2H), 6.88–6.84 (m, 2H), 6.84–6.80 (m, 2H), 5.67 (s, 1H), 4.90 (dd, *J* = 9.8, 2.3 Hz, 1H), 3.78 (s, 3H), 3.44 (s, 3H), 2.27–2.21 (m, 1H), 2.20–2.14 (m, 1H), 1.96–1.89 (m, 1H), 1.75–1.65 (m, 1H), 1.40 (s, 1H), 1.12 (s, 3H), 1.09 (s, 3H).

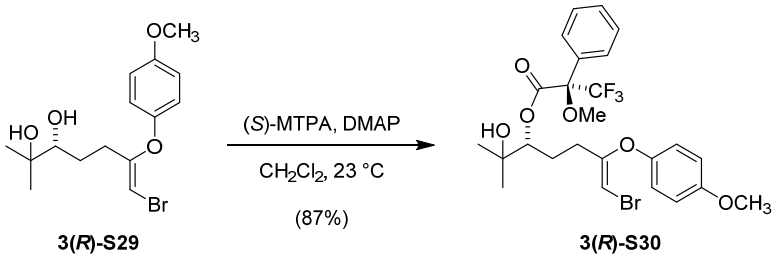
**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 166.5, 155.7, 154.4, 148.4, 132.1, 129.9, 128.7, 127.4, 123.5 (q, *J* = 290 Hz), 118.3, 114.9, 91.8, 84.6 (q, *J* = 27.5 Hz), 81.9, 72.4, 55.8, 55.5, 29.0, 27.4, 26.2, 24.9.

**$^{19}$F NMR** ($CDCl_3$, 377 MHz): δ = –70.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3519 (br *w*), 2948 (*m*), 1744 (*m*), 1503 (*vs*), 1247 (*m*), 1206 (*s*), 1168 (*s*), 1033 (*m*), 829 (*w*), 718 (*m*).

**HRMS** (ESI) calc. for $C_{25}H_{32}{}^{79}BrF_3NO_6[M+NH_4]^+$: 578.1360; found: 578.1364.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +12.8 (c = 0.30, $CH_2Cl_2$).




**Mosher Ester 3(*S*)-S30**

To a solution of diol **3(*R*)-S29** (5.00 mg, 14.5 μmol, 1 equiv) and 4-dimethylaminopyridine (7.08 mg, 57.9 μmol, 4.00 equiv) in dichloromethane (0.8 ml) was added (*S*)-Mosher´s acid chloride (5.4 μL, 2.90 μmol, 2.00 equiv) at 23 °C. After 1.5 h, water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethylacetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to yield mono-MTPA ester **3(*S*)-S30** (7.1 mg, 87%) as a colorless oil.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.27 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.58–7.55 (m, 2H), 7.44–7.34 (m, 3H), 6.87–6.83 (m, 2H), 6.83–6.78 (m, 2H), 5.61 (s, 1H), 4.90 (dd, *J* = 10.3, 2.2 Hz, 1H), 3.77 (s, 3H), 3.47 (s, 3H), 2.17–2.12 (m, 1H), 2.12–2.06 (m, 1H), 1.86–1.81 (m, 1H), 1.66–1.60 (m, 1H), 1.42 (s, 1H), 1.17 (s, 3H), 1.11 (s, 3H).

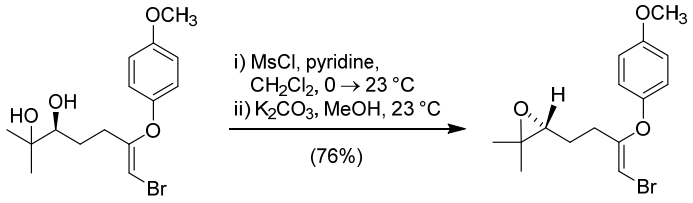
**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 167.0, 155.7, 154.4, 148.4, 132.0, 129.9, 128.7, 127.8, 123.5 (q, *J* = 288.7 Hz), 118.2, 114.9, 91.7, 84.9 (q, *J* = 27.8 Hz), 81.7, 72.60, 55.8, 55.5, 28.7, 27.4, 26.9, 24.1.

**$^{19}$F NMR** ($CDCl_3$, 377 MHz): δ = –70.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3452 (br *w*), 2948 (*w*), 1743 (*m*), 1503 (*vs*), 1247 (*m*), 1206 (*s*), 1168 (*s*), 1033 (*m*), 828 (*w*), 717 (*m*).

**HRMS** (EI) calc. for $C_{25}H_{28}{}^{79}BrF_3O_6[M]^+$: 560.1016; found: 560.1002.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +38.0 (c = 0.33, $CH_2Cl_2$).




**3(*S*)-S29** **13**

**Epoxide 13**

To a solution of diol **3(*S*)-S29** (6.76, 19.6 mmol, 1 equiv) and pyridine (7.92 mL, 97.9 mmol, 5.00 equiv) in dichloromethane (100 mL) was added methanesulfonyl chloride (2.23 mL, 29.4 mmol, 1.50 equiv) dropwise at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 15 h, water (150 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 150 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated and the residue was dried azeotropically with benzene (2 × 30 mL). To a solution of the crude mesylate in methanol (100 mL) was added potassium carbonate (5.41 g, 39.2 mmol, 2.00 equiv) at 23 °C. After 1 h, the reaction mixture was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to yield epoxide **13** (4.84 g, 76%) as a yellow oil.

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.53 (UV, $KMnO_4$).

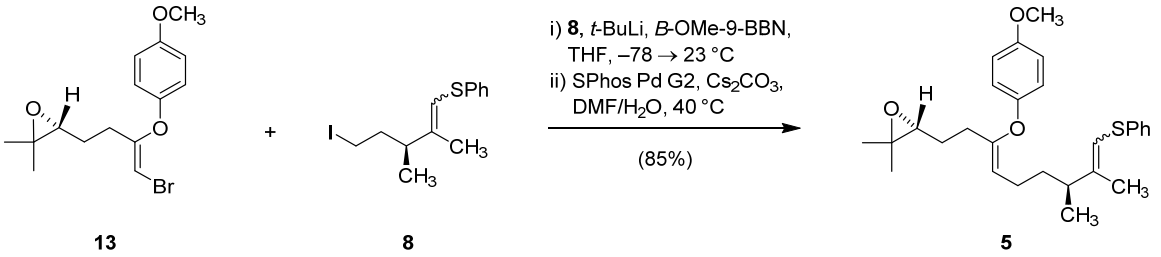
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.98–6.88 (m, 2H), 6.87–6.81 (m, 2H), 5.74 (s, 1H), 3.78 (s, 3H), 2.67 (dd, *J* = 7.0, 5.5 Hz, 1H), 2.47–2.36 (m, 1H), 2.35–2.25 (m, 1H), 1.79–1.68 (m, 1H), 1.68–1.57 (m, 1H), 1.28 (s, 3H), 1.22 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 155.6, 154.9, 148.5, 118.4, 114.9, 91.1, 63.2, 58.7, 55.8, 29.0, 26.2, 24.9, 18.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1645 (*w*), 1502 (*m*), 1246 (*w*), 1205 (*m*), 1034 (*w*), 903 (*s*), 829 (*w*), 724 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO_3[M]^+$: 326.0512; found: 326.0509.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.9 (c = 0.50, $CH_2Cl_2$).




**13** **8** **5**

**Enolether 5**

To a solution of iodide **8** (6.34 g, 19.1 mmol, 1.30 equiv) in tetrahydrofuran (76 mL) and *B*-methoxy-9-BBN (1.0 M in hexanes, 44.0 mL, 44.0 mmol, 3.00 equiv) was added a solution of *t*-butyllithium (1.65 M in hexanes, 34.7 mL, 57.2 mmol, 3.90 equiv) dropwise at –78 °C. After 5 min, the yellow solution was allowed to warm to 23 °C upon it turned colorless again. After 30 min, the reaction mixture was transferred to a suspension of bromoenol ether **13** (4.80 g, 14.7 mmol, 1 equiv), cesium carbonate (9.56 g, 29.3 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (529 mg, 0.73 mmol, 0.05 equiv) and SPhos (301 mg, 0.73 mmol, 0.05 equiv) in a 9:1 mixture of *N*,*N*-dimethylformamide and water (140 mL) and heated to 40 °C. After 2 h, water (300 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give enolether **5** (5.61 g, 85%) as a yellow oil.

*To obtain analytical pure samples, iodides **(Z)-8** and **(E)-8** were coupled separately under the same conditions to yield **(Z)-5** and **(E)-5** .*

**(*Z*)-5:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.23 (UV, Anis).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.31–7.23 (m, 4H), 7.20–7.13 (m, 1H), 6.88–6.84 (m, 2H), 6.81 (d, *J* = 9.2 Hz, 2H), 5.87 (q, *J* = 1.3 Hz, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 3.07–2.96 (m, 1H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.34–2.23 (m, 1H), 2.23–2.13 (m, 1H), 2.12–2.02 (m, 1H), 2.02–1.92 (m, 1H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.70–1.62 (m, 2H), 1.49–1.39 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.6, 150.4, 150.4, 146.9, 137.7, 129.0, 128.1, 125.7, 117.2, 115.9, 115.8, 114.8, 63.8, 58.6, 55.8, 35.8, 34.6, 29.2, 26.6, 25.0, 23.3, 18.8, 18.8, 18.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*w*), 2925 (*w*), 1681 (*w*), 1584 (*w*), 1503 (*vs*), 1377 (*w*), 1209 (*s*), 1038 (*w*), 828 (*w*), 740 (*w*).

**HRMS** (ESI) calc. for $C_{28}H_{37}O_3{}^{32}S$ $[M+H]^+$: 453.2458 found: 453.2466.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –13.4° (*c* = 1.00, $CH_2Cl_2$).

**(*E*)-5:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.23 (UV, Anis).

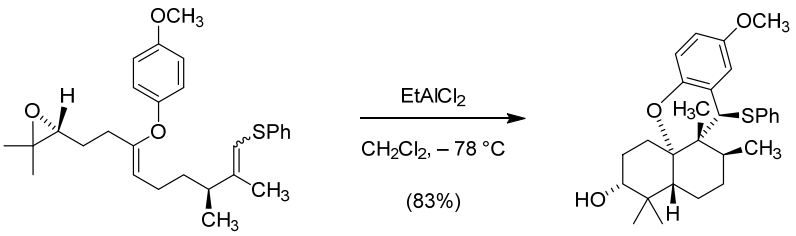
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.33–7.23 (m, 4H), 7.22–7.12 (m, 1H), 6.90–6.79 (m, 4H), 5.94 (s, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 2.72 (t, *J* = 6.3 Hz, 1H), 2.38–2.28 (m, 2H), 2.28–2.16 (m, 1H), 2.08–1.96 (m, 2H), 1.74 (d, *J* = 1.1 Hz, 3H), 1.73–1.62 (m, 2H), 1.55–1.47 (m, 1H), 1.45–1.35 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.6, 150.5, 150.3, 146.5, 137.5, 129.0, 128.1, 125.7, 117.2, 115.9, 115.6, 114.8, 63.8, 58.6, 55.8, 42.6, 34.8, 29.2, 26.6, 25.0, 23.4, 19.7, 18.8, 14.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*w*), 2924 (*w*), 1681 (*w*), 1583 (*w*), 1502 (*vs*), 1377 (*w*), 1208 (*s*), 1037 (*w*), 827 (*w*), 739 (*m*).

**HRMS** (ESI) calc. for $C_{28}H_{37}O_3{}^{32}S$ $[M+H]^+$: 453.2458 found: 453.2466.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –16.0° (*c* = 1.00, $CH_2Cl_2$).




**5** **17**

**Tetracycle 17**

*Note: The cyclization was carried out in two parallel 2.8 g batches.*

To a solution epoxide **5** (2.80 g, 6.19 mmol, 1 equiv) in dichloromethane (620 mL) was added a solution of ethylaluminum dichloride (1.0 M in hexanes, 12.4 mL, 12.4 mmol, 2.00 equiv) in dichloromethane (30 mL) dropwise at –78 °C over a period of 5 min. After 30 min, saturated aqueous potassium sodium tartrate solution (300 mL) was added and the reaction mixture was allowed to warm to 23 °C under vigorous stirring. Water (150 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 200 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residues were combined and purified by flash-column chromatography on silica gel (15% ethyl acetate in hexanes) to yield decalin **17** (4.64 g, 83%) as an off white foam.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.36 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 7.53 (dd, *J* = 8.3 Hz, 1.1, 2H), 7.38–7.33 (m, 2H), 7.28–7.24 (m, 1H), 6.75–6.68 (m, 3H), 4.36 (s, 1H), 3.65 (s, 3H), 3.31–3.24 (m, 1H), 2.09–2.04 (m, 1H), 1.87–1.80 (m,

1H), 1.75–1.70 (m, 2H), 1.70–1.65 (m, 1H), 1.61–1.52 (m, 3H), 1.43 (dd, *J* = 12.7, 3.3 Hz, 1H), 1.39–1.32 (m, 2H), 1.23 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.3, 144.3, 140.2, 131.2, 129.5, 127.0, 124.7, 118.2, 115.7, 114.4, 80.5, 78.2, 55.7, 55.0, 45.3, 44.5, 39.2, 33.6, 31.3, 28.6, 27.6, 26.4, 21.2, 16.8, 15.8, 15.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3376(*br w*), 2956 (*m*), 1494 (*vs*), 1438 (*m*), 1236 (*s*), 1156 (*m*), 1041 (*m*), 808 (*m*), 737 (*s*), 691 (*s*).

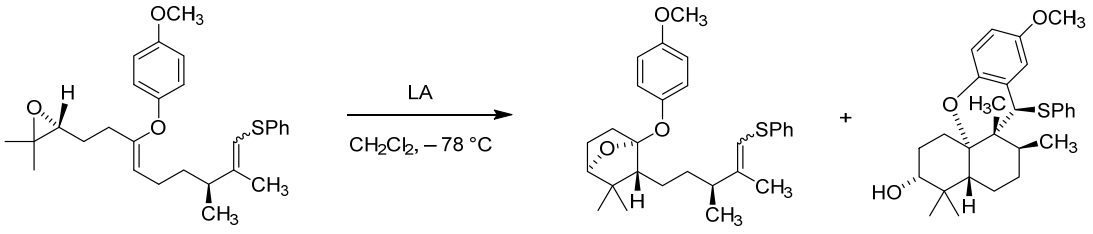
**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380; found: 452.2370.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –193.8° (*c* = 1.00, $CH_2Cl_2$).

**Lewis Acid screen:**

To a solution epoxide **5** (10.0 mg, 0.02 mmol, 1 equiv) in dichloromethane (2.20 mL) was added a solution of the Lewis acid (Table 1, 0.44 mmol, 2.00 equiv) in dichloromethane (0.50 mL) dropwise at –78 °C. After the time indicated, water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield the tetracycle **17** or acetal **14**.

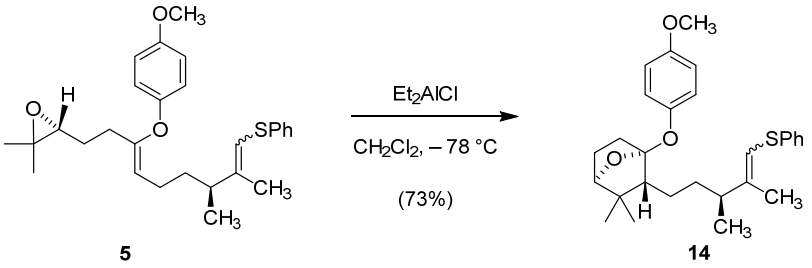
***Table 1:*** *Lewis acid screening.*




**5** **14** **17**

| Entry | Lewis acid | Time [min] | Yield 14 [%] | Yield 17 [%] |
|---|---|---|---|---|
| 1 | $EtAlCl_2$ | 10 | 83 | – |
| 2 | $Et_2AlCl$ | 150 | 51 | 39 |
| 3 | $SnCl_4$ | 10 | – | 66* |
| 4 | $B(C_6F_5)_3$ | 30 | – | 59 |

* along with inseperable impurities




5 14

**Acetal 14**

*Note: The acetal formation was carried out with pure **(Z)-5** and **(E)-5** separately. The procedure is described for (**Z**)-5. Diethylaluminum chloride was used instead of ethylaluminum dichloride.*

To a solution epoxide **(*Z*)-5** (10.0 mg, 0.02 mmol, 1 equiv) in dichloromethane (2.20 mL) was added a solution of diethylaluminum chloride (1.0 M in hexanes, 44.2 µL, 0.44 mmol, 2.00 equiv) in dichloromethane (0.50 mL) dropwise at –78 °C. After 10 min, water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield acetal **(*Z*)-14** (7.3 mg, 73%) as a colorless oil.

**(*Z*)-14:**

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.29 (dt, *J* = 7.7, 1.1 Hz, 2H), 7.25–7.22 (m, 2H), 7.14–7.11 (m, 1H), 7.10–7.07 (m, 2H), 6.81–6.77 (m, 2H), 5.88 (q, *J* = 1.3 Hz, 1H), 3.77 (s, 3H), 3.68 (d, *J* = 5.5 Hz, 1H), 3.09–3.02 (m, 1H), 1.96–1.88 (m, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.76–1.73 (m, 2H), 1.73–1.64 (m, 2H), 1.58–1.55 (m, 1H), 1.42–1.37 (m, 1H), 1.37–1.33 (m, 1H), 1.29–1.23 (m, 1H), 1.05 (s, 3H), 1.05–1.04 (m, 6H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 155.8, 148.6, 148.1, 137.9, 128.9, 128.0, 125.6, 122.5, 115.4, 114.2, 113.2, 81.4, 56.9, 55.7, 44.6, 36.8, 35.2, 29.9, 26.3, 25.4, 24.3, 24.0, 19.3, 18.3.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (*m*), 1505 (*vs*), 1440 (*w*), 1299 (*w*), 1243 (*m*), 1213 (*s*), 1010 (*w*), 836 (*m*), 739 (*w*), 690 (*w*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380 found: 452.2378.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +3.1° (*c* = 0.37, $CH_2Cl_2$).

**(*E*)-14:**

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, CAM).

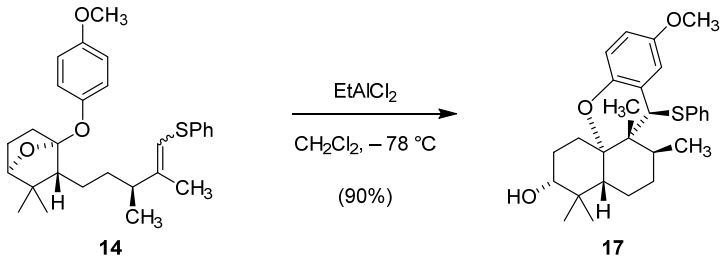
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.30–7.28 (m, 2H), 7.23–7.20 (m, 2H), 7.11 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.09–7.03 (m, 2H), 6.81–6.75 (m, 2H), 5.96 (s, 1H), 3.77 (s, 3H), 3.70 (d, *J* = 5.4 Hz, 1H), 2.35–2.29 (m, 1H), 1.95–1.89 (m, 1H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.78–1.67 (m, 4H), 1.57 (t, *J* = 6.9 Hz, 1H), 1.38–1.34 (m, 2H), 1.32–1.26 (m, 1H), 1.10 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 155.8, 148.5, 147.9, 137.7, 129.0, 128.1, 125.6, 122.6, 115.1, 114.2, 113.1, 81.4, 57.0, 55.7, 44.6, 43.9, 35.3, 29.9, 26.4, 25.3, 24.4, 23.9, 19.9, 14.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2958 (*m*), 1504 (*vs*), 1439 (*w*), 1297 (*m*), 1242 (*m*), 1212 (*s*), 1009 (*m*), 835 (*m*), 738 (*m*), 690 (*w*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380 found: 452.2374.

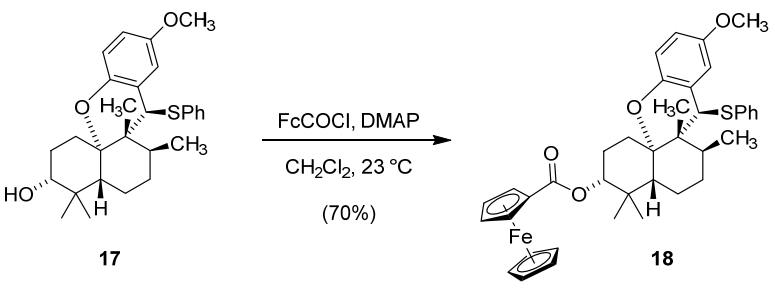
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –58.7° (*c* = 0.32, $CH_2Cl_2$).




**Tetracycle 17**

*Note: A 1:1 mixture of acetal **(Z)-14** and **(E)-14** was used.*

To a solution acetal **14** (7.00 mg, 15.5 μmol, 1 equiv) in dichloromethane (1.5 mL) was added a solution of ethylaluminum dichloride (1.0 M in hexanes, 30.9 μL, 30.9 μmol, 2.00 equiv) in dichloromethane (0.3 mL) dropwise at –78 °C. After 15 min, water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residues were combined and purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield decalin **17** (6.3 mg, 90%) as a white foam.




**Ferrocene 18**

To a suspension of ferrocene carboxylic acid (10.0 mg, 43.5 μmol, 2.00 equiv) in dichloromethane (1.0 mL) was added oxalyl chloride solution (2 M in dichloromethane, 23.9 μL, 47.8 μmol, 2.20 equiv), followed by 1 drop of *N*,*N*-dimethylformamide at 23 °C. After 45 min, toluene (1.0 mL) was added and the mixture was concentrated. To a solution of tetracycle **17** (10.0 mg, 22.1 μmol, 1 equiv) and 4-dimethylaminopyridine (27.0 mg, 0.22 mmol, 10.0 equiv) in dichloromethane (0.5 mL) was added a solution of the freshly prepared ferrocenecarboxylic acid chloride in dichloromethane (0.5 mL) at 23 °C. After 2 h, the reaction mixture was directly purified by flash-column chromatography on silica gel (dichloromethane) to yield ferrocene **18** (10.2 mg, 70%) as an orange foam. Crystallization from diethyl ether gave crystals suitable for X-ray diffraction.

**TLC** (dichloromethane): $R_f$ = 0.63 (UV, CAM).

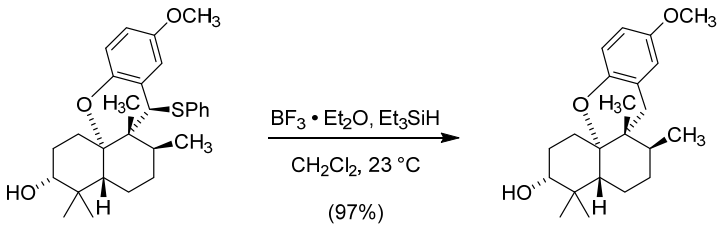
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.55–7.52 (m, 2H), 7.38–7.35 (m, 2H), 7.28–7.25 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.75–6.71 (m, 2H), 4.86–4.80 (m, 2H), 4.67 (dd, *J* = 11.6, 3.9 Hz, 1H), 4.43–4.38 (m, 2H), 4.38 (s, 1H), 4.20 (s, 5H), 3.65 (s, 3H), 2.15–2.07 (m, 1H), 1.94–1.79 (m, 3H), 1.73–1.68 (m, 2H), 1.63–1.57 (m, 3H), 1.46–1.32 (m, 1H), 1.27 (s, 6H), 1.04 (s, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 171.5, 153.4, 144.3, 140.1, 131.3, 129.5, 127.0, 124.8, 118.2, 115.8, 114.4, 80.4, 79.5, 72.2, 71.3, 71.2, 70.4, 70.1, 69.8, 55.7, 54.9, 45.5, 44.5, 38.2, 33.7, 31.2, 28.4, 27.6, 23.3, 21.1, 16.8, 16.6, 15.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2958 (*m*), 1707 (*s*), 1495 (*s*), 1459 (*m*), 1374 (*w*), 1275 (*s*), 1140 (*s*), 1040 (*m*), 963 (*w*), 821 (*w*).

**HRMS** (EI) calc. for $C_{39}H_{44}{}^{56}FeO_4{}^{32}S$ $[M]^+$: 664.2310 found: 664.2307.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –96.6° (c = 1.00, $CH_2Cl_2$).




**17** **S31**

**Alcohol S31**

To a solution of sulfide **17** (4.50 g, 9.94 mmol, 1 equiv) in dichloromethane (45 mL) and triethylsilane (8.03 mL, 49.7 mmol, 5.00 equiv) was added boron trifluoride etherate (48%, 6.53 mL, 24.9 mmol, 2.50 equiv) at 23 °C. After 15 min, saturated sodium bicarbonate solution (250 mL) was added and the mixture was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was

concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to afford **S31** (3.34 g, 97%) as a white solid.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.36 (UV, CAM).

**melting point**: 173–175 °C

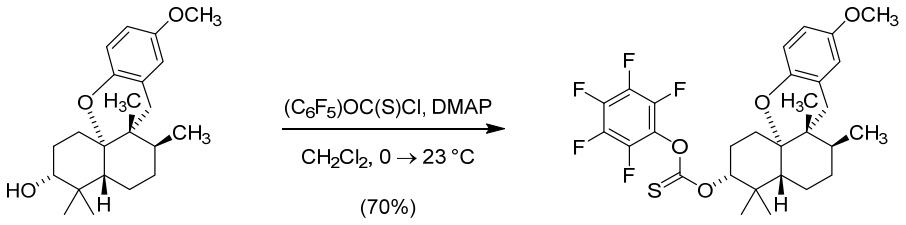
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.72 (d, *J* = 8.8 Hz, 1H), 6.68 (dd, *J* = 8.8 Hz, 3.0, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.26 (dd, *J* = 11.9, 3.7 Hz, 1H), 2.59 (d, *J* = 17.3 Hz, 1H), 2.52 (d, *J* = 17.3 Hz, 1H), 1.85–1.77 (m, 2H), 1.77–1.70 (m, 1H), 1.69–1.64 (m, 1H), 1.60–1.56 (m, 1H), 1.53–1.47 (m, 3H), 1.41 (dd, *J* = 12.7, 3.5 Hz, 1H), 1.35 (br s, 1H), 1.34–1.28 (m, 1H), 1.08 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.2, 146.3, 121.7, 117.5, 114.1, 113.3, 80.5, 78.6, 55.8, 45.5, 39.2, 37.5, 33.9, 31.7, 30.7, 27.6, 27.1, 26.5, 21.5, 17.0, 16.2, 15.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3263 (*br w*), 2943 (*m*), 1499 (*vs*), 1430 (*m*), 1222 (*s*), 1165 (*m*), 1044 (*s*), 933 (*m*), 858 (*w*), 800 (*m*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_3$ $[M]^+$: 344.2346; found: 344.2347.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –14.0° (*c* = 1.00, $CH_2Cl_2$).




**S31** **S32**

**Thiocarbonate S32**

To a solution of alcohol **S31** (3.20 g, 9.29 mmol, 1 equiv) in dichloromethane (60 mL) and 4-dimethylaminopyridine (3.41 g, 27.9 mmol, 3.00 equiv) was added pentafluorophenyl chlorothionoformate (2.98 mL, 18.6 mmol, 2.00 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (200 mL) was added and the mixture was extracted with dichloromethane (4 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (4% ethyl acetate in hexanes) to furnish thiocarbonate **S32** (3.72 g, 70%) as a colorless solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.59 (UV, CAM).

**melting point**: 189–191 °C

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.76 (d, *J* = 8.8 Hz, 1H), 6.70 (dd, *J* = 8.8 Hz, 2.9 Hz, 1H), 6.55 (d, *J* = 2.9 Hz, 1H), 4.98 (dd, *J* = 11.9 , 4.0 Hz, 1H), 3.75 (s, 3H), 2.63 (d, *J* = 17.5 Hz, 1H), 2.53 (d, *J* = 17.5 Hz, 1H), 2.04–1.95 (m, 1H), 1.94–1.78 (m, 3H), 1.74–1.66 (m, 1H), 1.64–1.50 (m, 4H), 1.42–1.29 (m, 1H), 1.26 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($^1$H decoupled, $CDCl_3$, 101 MHz): δ = 191.9, 153.4, 145.9, 142.94–139.87 (m), 141.63–138.42 (m), 139.71–136.17 (m), 128.14–127.20 (m), 121.6, 117.6, 114.2, 113.5, 94.7, 80.0, 55.8, 45.8, 38.9, 37.5, 33.9, 31.7, 30.4, 27.2, 26.9, 21.6, 21.2, 17.0, 16.8, 16.1.

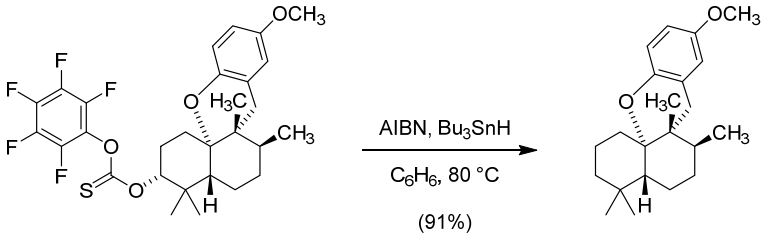
**$^{13}$C NMR** ($^{19}$F decoupled, $CDCl_3$, 101 MHz): δ = 191.9 (d, *J* = 4.2 Hz), 141.3, 140.0, 138.1, 127.7, 56.5, 55.1.

**$^{19}$F NMR** ($CDCl_3$, 376 MHz): δ = –152.25– –152.40 (m), –157.15 (t, *J* = 21.7 Hz), –162.18– –162.41.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2955 (*w*), 1520 (*vs*), 1496 (*s*), 1311 (*m*), 1222 (*m*), 1142 (*s*), 997 (*s*), 954 (*s*), 736 (*w*).

**HRMS** (EI) calc. for $C_{29}H_{31}F_5O_4{}^{32}S$ $[M]^+$: 570.1858; found: 570.1859.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –41.8° (*c* = 1.00, $CH_2Cl_2$).




**S32** **S33**

**Methoxy-5-*epi*-aureol S33**

A solution of thiocarbonate **S32** (3.72 g, 6.52 mmol, 1 equiv), tributyltin hydride (5.27 mL, 19.6 mmol, 3.00 equiv) and azobisisobutyronitrile (214 mg, 1.30 mmol, 0.20 equiv) in benzene (150 mL) was heated to 80 °C in a pressure flask. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to give **S33** (1.95 g, 91%) as a white solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.54 (UV, CAM).

**melting point**: 143–146 °C

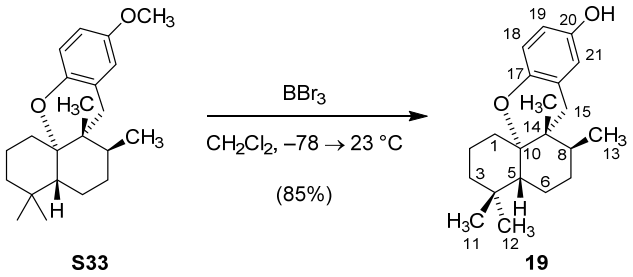
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.73 (d, *J* = 8.7 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.53 (d, *J* = 2.9 Hz, 1H), 3.74 (s, 3H), 2.57 (d, *J* = 17.3 Hz, 1H), 2.53 (d, *J* = 17.3 Hz, 1H), 1.75–1.70 (m, 2H), 1.69–1.63 (m, 2H), 1.56–1.54 (m, 1H), 1.50–1.45 (m, 1H), 1.45–1.41 (m, 1H), 1.38 (dd, *J* = 12.7, 3.5 Hz, 1H), 1.35–1.24 (m, 3H), 1.21–1.14 (m, 1H), 1.11 (s, 3H), 0.91 (s, 3H), 0.91 (s, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.0, 146.8, 122.0, 117.5, 114.1, 113.2, 81.2, 55.8, 45.7, 42.2, 37.4, 33.9, 33.6, 32.8, 31.9, 30.7, 28.7, 22.6, 22.0, 18.0, 17.0, 16.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2936 (*m*), 1496 (*vs*), 1250 (*m*), 1234 (*s*), 1223 (*s*), 1171 (*m*), 1151 (*w*), 1043 (*m*), 933 (*w*), 801 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_2$ $[M]^+$: 328.2402; found: 328.2395.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +13.1 (c = 1.00, $CH_2Cl_2$).




**S33** **19**

**5-*epi*-Aureol (19)**

To a solution of methyl ether **S33** (1.90 g, 5.78 mol, 1 equiv) in dichloromethane (55 mL) was added boron tribromide (1 M in hexanes, 57.8 mL, 57.8 mmol, 10.0 equiv) at –78 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 1.5 h, methanol (20 mL) was carefully added and the mixture was partitioned between saturated aqueous sodium bicarbonate solution (300 mL) and dichloromethane (150 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl aceate in hexanes) to give 5-*epi*-aureol (**19**) (1.55 g, 85%) as a colorless solid.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.46 (UV, CAM).

**melting point:** 114–116 °C (reported 115–116 °C)[104]

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.67 (d, $^3J_{18/16}$ = 8.6 Hz, 1H, H-18), 6.58 (dd, $^3J_{19/18}$ = 8.6 Hz, $^4J_{19/21}$ = 3.0 Hz, 1H, H-19), 6.47 (d, $^4J_{21/19}$ = 3.0 Hz, 1H, H-21), 4.26 (br s, 1H, OH), 2.54 (d, $^2J_{15A/15B}$ = 17.3 Hz, 1H, H-$15_A$), 2.50 (d, $^2J_{15B/15A}$ = 17.3 Hz, 1H, $15_B$), 1.75–1.69 (m, 2H; H-$1_A$, H-$6_A$), 1.69–1.63 (m,

2H, H-$2_A$, H-8), 1.58–1.52 (m, 1H, H-$6_B$), 1.50–1.45 (m, 1H, H-$7_A$), 1.45–1.42 (m, 1H, H-$3_A$), 1.38 (dd, $^3J_{5/6A}$ = 12.7 Hz, $^3J_{5/6B}$ = 3.6 Hz, 1H, H-5), 1.35–1.24 (m, 3H, H-$1_B$, H-$2_B$, H-$7_B$), 1.21–1.16 (m, 1H, H-$3_B$), 1.10 (s, 3H, H-11), 0.91 (s, 3H, H-12), 0.90 (s, 3H, H-14), 0.75 (d, $^3J_{13/8}$ = 6.8 Hz, 3H, H-13).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 148.5 (C-20), 146.8 (C-17), 122.2 (C-16), 117.6 (C-18), 115.5 (C-21), 114.4 (C-19), 81.2 (C-10), 45.7 (C-5), 42.2 (C-3), 37.4 (C-9), 33.7 (C-15), 33.6 (C-4), 32.8 (C-12), 31.9 (C-8), 30.7 (C-7), 28.7 (C-1), 22.6 (C-11), 22.0 (C-6), 18.0 (C-2), 17.0 (C-14), 16.4 (C-13).

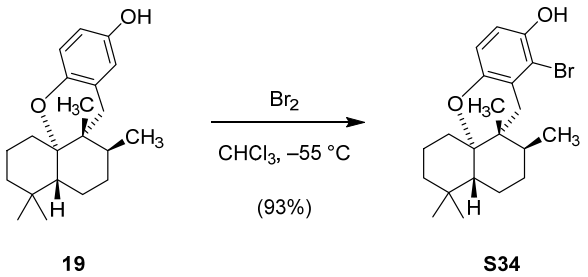
**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3350 (*br w*), 2927 (*vs*), 2854 (*s*), 1710 (*w*), 1495 (*s*), 1454 (*s*), 1234 (*s*), 1222 (*vs*), 1171 (*s*), 965 (*m*), 807 (*m*).

**HRMS** (EI) calc. for $C_{21}H_{30}O_2$ $[M]^+$: 314.2240; found: 314.2243.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +10.6 (c = 1.00, $CHCl_3$); +12.5 (c = 0.17, $CHCl_3$; (+)-5-*epi*-Aureol)[105]

***Table 2:*** *Comparison of $^1$H NMR data for reported and synthetic 5-epi-Aureol (**19**).*

| Proton | Synthetic (800 MHz, $CDCl_3$) | Marcos (200 MHz, $CDCl_3$)[115] | Δδ (ppm) | v. d. Helm (270 MHz, $CDCl_3$)[104] | Δδ (ppm) |
|---|---|---|---|---|---|
| **1A** | 1.75–1.69 (m) | 2.10–1.36 (m, 12H) | | not reported | |
| **1B** | 1.35–1.24 | | | | |
| **2A** | 1.69–1.63 (m) | | | | |
| **2B** | 1.35–1.24 (m) | | | | |
| **3A** | 1.45–1.42 (m) | | | | |
| **3B** | 1.21–1.16 (m) | | | | |
| **5** | 1.37 (dd, 12.7, 3.6 Hz) | | | | |
| **6A** | 1.75–1.69 (m) | | | | |
| **6B** | 1.58–1.52 (m) | | | | |
| **7A** | 1.50–1.45 (m) | | | | |
| **7B** | 1.35–1.24 (m) | | | | |
| **8** | 1.69–1.63 (m) | | | | |
| **11** | 1.10 (s) | 1.10 (s) | ± 0.00 | 1.13 (s) | – 0.03 |
| **12** | 0.91 (s) | 0.96 (s, 6H) | – 0.05 | 0.92 (br s, 6H) | – 0.01 |
| **13** | 0.75 (d, 6.8 Hz) | 0.75 (d, 6.8 Hz) | ± 0.00 | 0.77 (d, 7.5 Hz) | – 0.02 |
| **14** | 0.90 (s) | 0.96 (s, 6H) | – 0.06 | 0.92 (br s, 6H) | – 0.02 |
| **15A** | 2.54 (d, 17.3 Hz) | 2.52 (s, 2H) | + 0.02 | 2.54 (s,2H) | ± 0.00 |
| **15B** | 2.50 (d, 17.3 Hz) | | – 0.02 | | – 0.04 |
| **18** | 6.67 (d, 8.6 Hz) | 6.69 (d, 9.0 Hz) | – 0.02 | 6.69 (d, 9Hz) | – 0.02 |
| **19** | 6.59 (dd, 8.6, 3.0 Hz) | 6.60 (dd, 9.0, 3.1 Hz) | – 0.01 | 6.60 (dd, 9.0, 3.0 Hz) | – 0.01 |
| **21** | 6.47 (d, 3.0 Hz) | 6.49 (d, 3.1 Hz) | – 0.02 | 6.48 (d, 3 Hz) | – 0.01 |
| **OH** | 4.26 (br s) | 4.26 (s) | ± 0.00 | 4.30 (br s) | – 0.04 |




**19** **S34**

**Bromide S34**

To a solution of 5-*epi*-aureol (**19**) (1.55 g, 4.93 mmol, 1 equiv) in chloroform (150 mL) was added a solution of bromide in chloroform (0.22 M, 22.7 mL, 4.93 mmol, 1.00 equiv) dropwise at –55 °C over a period of 15 min. After 30 min, saturated aqueous sodium thiosulfate solution (100 mL) and saturated aqueous sodium chloride solution (100 mL) were added and the mixture was extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl aceate in hexanes) to give bromide **S34** (1.80 g, 93%) as a white solid.

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.47 (UV, CAM).

**melting point**: 158–160 °C

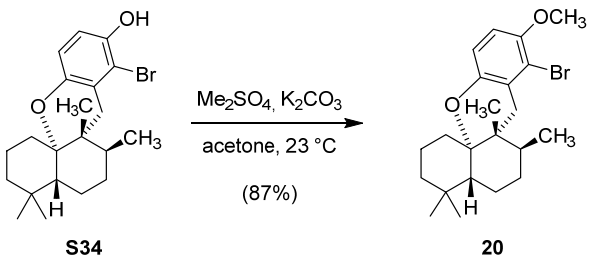
**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 6.82 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 5.11 (s, 1H), 2.71 (d, *J* = 17.8 Hz, 1H), 2.31 (d, *J* = 17.8 Hz, 1H), 1.74–1.65 (m, 2H), 1.63–1.54 (m, 3H), 1.51–1.46 (m, 1H), 1.45–1.42 (m, 1H), 1.40 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.35–1.24 (m, 3H), 1.22–1.15 (m, 1H), 1.10 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 147.0, 145.8, 121.3, 117.1, 114.0, 112.3, 81.2, 45.6, 42.1, 37.9, 35.1, 33.6, 32.7, 32.3, 30.6, 28.5, 22.5, 21.9, 17.9, 16.9, 16.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3487 (*w*), 2952 (*m*), 1475 (*vs*), 1431 (*m*), 1247 (*m*), 1193 (*m*), 1170 (*s*), 949 (*m*), 881 (*w*), 810 (*m*), 740 (*w*).

**HRMS** (EI) calc. for $C_{21}H_{29}O_2{}^{79}Br$ $[M]^+$: 392.1345; found: 392.1358.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 9.6 (c = 1.00, $CH_2Cl_2$).




**S34** **20**

**Methyl ether 20**

To a suspension of phenol **S34** (1.77 g, 4.50 mmol, 1 equiv) and potassium carbonate (2.18 g, 15.7 mmol, 3.50 equiv) in acetone (25 mL) was added dimethyl sulfate (1.07 mL, 11.2 mmol, 2.50 equiv) at 23 °C. After 15 h, the reaction mixture was filtered through a plug of Celite® and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl aceate in hexanes) to give methyl ether **20** (1.60 g, 87%) as a white solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.54 (UV, CAM).

**melting point**: 202–204 °C

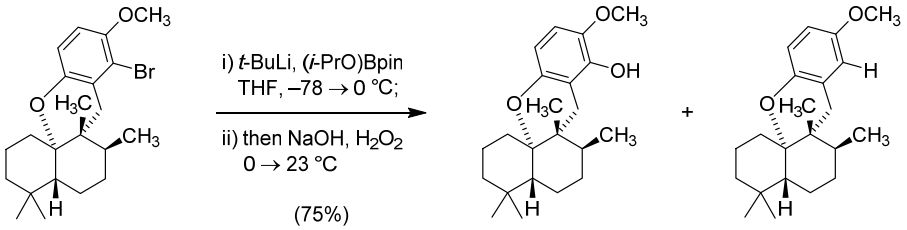
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 6.76 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 2.82 (d, *J* = 17.9 Hz, 1H), 2.32 (d, *J* = 17.9 Hz, 1H), 1.74–1.64 (m, 2H), 1.65–1.55 (m, 3H), 1.50–1.46 (m, 1H), 1.45–1.42 (m, 1H), 1.40 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.36–1.26 (m, 3H), 1.21–1.16 (m, 1H), 1.11 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 149.7, 147.7, 123.0, 115.9, 114.2, 111.3, 81.2, 57.1, 45.6, 42.1, 37.9, 35.2, 33.6, 32.7, 32.3, 30.6, 28.6, 22.6, 21.9, 18.0, 16.9, 16.5.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930 (*m*), 1476 (*vs*), 1435 (*m*), 1387 (*w*), 1247 (*s*), 1170 (*m*), 1069 (*m*), 949 (*m*), 873 (*w*), 804 (*m*), 739 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{31}O_2{}^{79}Br$ $[M]^+$: 406.1502; found: 406.1503.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 5.0 (c = 1.00, $CH_2Cl_2$).




**Phenol S35**

Isopropyl pinacol borate was dried by azeotropic distillation (benzene, 2 × 20 mL) prior to use. To a solution of bromide **20** (1.50 g, 3.68 mmol, 1 equiv) and isopropyl pinacol borate (3.01 mL, 14.7 mmol, 4.00 equiv) in tetrahydrofuran (37 mL) was added a solution of *t*-butyllithium (1.60 M in hexanes, 6.91 mL, 11.0 mmol, 3.00 equiv) at –78 °C. After 1.5 h, the reaction mixture was allowed to warm to 0 °C. After 15 min, aqueous sodium hydroxide solution (10%; 15 mL) and aquoues hydrogen peroxide solution (30%; 30 mL) were added and the reaction mixture was allowed to warm to 23 °C. After 45 min, saturated aqueous ammonium chloride solution (200 mL) was added and the mixture was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were dried over sodium

sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl aceate in hexanes) to give phenol **S35** (949 mg, 75%) as a white solid and methyl ether **S33** (259 mg, 21%) as a white solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.33 (UV, CAM).

**melting point**: 197–200 °C

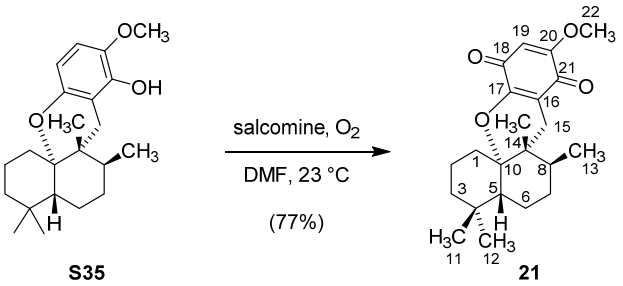
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.67 (d, *J* = 8.7 Hz, 1H), 6.33 (d, *J* = 8.7 Hz, 1H), 5.63 (s, 1H), 3.83 (s, 3H), 2.79 (d, *J* = 17.6 Hz, 1H), 2.28 (d, *J* = 17.6 Hz, 1H), 1.79–1.74 (m, 1H), 1.74–1.69 (m, 1H), 1.69–1.61 (m, 2H), 1.57–1.53 (m, 1H), 1.50–1.46 (m, 1H), 1.45–1.41 (m, 1H), 1.39 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.35–1.25 (m, 3H), 1.22–1.16 (m, 1H), 1.11 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 147.6, 143.6, 139.5, 109.7, 109.2, 106.7, 81.0, 56.8, 45.7, 42.2, 36.8, 33.6, 32.8, 32.2, 30.7, 28.6, 28.1, 22.6, 22.0, 18.0, 17.1, 16.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3526 (*w*), 2949 (*m*), 1488 (*vs*), 1439 (*s*), 1242 (*vs*), 1170 (*s*), 1040 (*s*), 1027 (*s*), 925 (*m*), 795 (*m*), 738 (*m*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_2$ $[M]^+$: 344.2346; found: 344.2352.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –3.5 (c = 1.00, $CH_2Cl_2$).




**5-*epi*-Smenoqualone (21)**

*N*,*N*′-Bis(salicylidene)ethylenediaminocobalt(II) (444 mg, 1.36 mmol, 0.50 equiv) was added to a solution of phenol **S35** (940 mg, 2.73 mmol, 1 equiv) in *N*,*N*-dimethylformamide (90 mL) at 23 °C and oxygen was bubbled through the reaction mixture for 30 min. After 30 min, water (200 mL) was added and the mixture was extracted with diethyl ether (4 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to give 5-*epi*-smenoqualone (**21**) (749 mg, 77%) as a yellow foam. Crystallization from diethyl ether gave **21** as yellow crystals.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.36 (UV, CAM).

**melting point:** 166–167 °C

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 5.73 (s, 1H, H-19), 3.81 (s, 3H, H-22), 2.57 (d, $^2J_{15A/15B}$ = 18.8 Hz, 1H, H-15$_A$), 2.00 (d, $^2J_{15B/15A}$ = 18.8 Hz, 1H, H-15$_B$), 1.70–1.66 (m, 1H, H-1$_A$), 1.64–1.57 (m, 3H, H-6, H-2$_A$), 1.52–1.48 (m, 1H, H-7$_A$), 1.48–1.45 (m, 1H, H-3$_A$), 1.45–1.40 (m, 2H, H-5, H-8), 1.39–1.33 (m, 2H, H-1$_B$, H-2$_B$), 1.32–1.24 (m, 1H, H-7$_B$), 1.22–1.19 (m, 1H, H-3$_B$), 1.17 (s, 3H, H-11), 0.95 (s, 3H, H-14), 0.93 (s, 3H, H-12), 0.77 (d, $^3J_{13/8}$ = 6.7 Hz, 3H, H-13).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 181.6 (C-18), 181.5 (C-21), 159.6 (C-20), 152.8 (C-17), 115.3 (C-16), 105.0 (C-19), 86.6 (C-10), 56.5 (C-22), 45.8 (C5), 41.8 (C-3), 37.4 (C-9), 33.6 (C-4), 32.6 (C-12), 32.5 (C-8), 30.4 (C-7), 29.5 (C-1), 26.8 (C-15), 22.3 (C-11), 22.0 (C-6), 17.9 (C-2), 17.0 (C-14), 16.5 (C-13).

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2942 (*w*), 1661 (*m*), 1639 (*w*), 1599 (*vs*), 1456 (*w*), 1353 (*w*), 1353 (*w*), 1227 (*m*), 1213 (*m*), 1161 (*w*), 1049 (*m*), 840 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{30}O_4$ $[M]^+$: 358.2139; found: 358.2140.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –83.4 (c = 1.00, $CHCl_3$); –75.6 (c = 0.16, $CHCl_3$; (–)-5-*epi*-Smenoqualone)[103]; +69.3 (c = 0.10, $CHCl_3$; (+)-5-*epi*-Smenoqualone).[115]

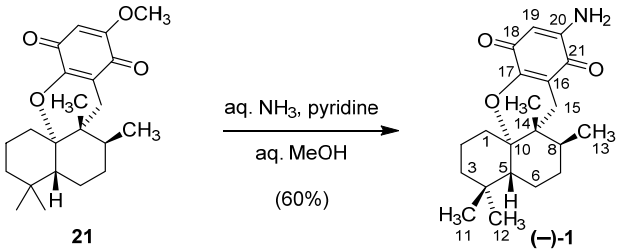
***Table 3:*** *Comparison of $^1$H NMR data for reported and synthetic 5-epi-smenoqualone (**21**).*

| Proton | Synthetic (800 MHz, $CDCl_3$) | Marcos (200 MHz, $CDCl_3$)[115] | Δδ (ppm) | Capon (400 MHz, $CDCl_3$)[103] | Δδ (ppm) |
|---|---|---|---|---|---|
| **1A** | 1.70–1.66 (m) | | | | |
| **1B** | 1.39–1.33 (m) | | | | |
| **2A** | 1.64–1.57 (m) | | | | |
| **2B** | 1.39–1.33 (m) | | | | |
| **3A** | 1.48–1.45 (m) | | | | |
| **3B** | 1.22–1.19 (m) | 1.98–1.36 (m, 12H) | | not reported | |
| **5** | 1.45–1.40 (m) | | | | |
| **6** | 1.64–1.57 (m) | | | | |
| **7A** | 1.52–1.48 (m) | | | | |
| **7B** | 1.32–1.24 (m) | | | | |
| **8** | 1.45–1.40 (m) | | | | |
| **11** | 1.17 (s) | 1.17 (s) | ± 0.00 | 1.17 | ± 0.00 |
| **12** | 0.93 (s) | 0.94 | + 0.01 | 0.94 | + 0.01 |
| **13** | 0.77 (d, 6.7 Hz) | 0.77 (d, 6.0 Hz) | ± 0.00 | 0.77 (d, 6.0 Hz) | ± 0.00 |
| **14** | 0.95(s) | 0.96 (s) | + 0.01 | 0.96 | + 0.01 |
| **15A** | 2.57 (d, 18.8 Hz) | 2.57 (d, 20.0 Hz) | ± 0.00 | 2.57 (d, 20.0 Hz | ± 0.00 |
| **15B** | 2.00 (d, 18.8 Hz) | 2.00 (d, 20.0 Hz) | ± 0.00 | 2.00 (d, 20.0 Hz) | ± 0.00 |
| **19** | 5.73 (s) | 5.74 (s) | + 0.01 | 5.74 | + 0.01 |
| **22** | 3.81 (s) | 3.80 (s) | – 0.01 | 3.81 | ± 0.00 |

***Table 4:*** *Comparison of $^{13}C$ NMR data for reported and synthetic 5-epi-smenoqualone (**21**).*

| Carbon | Synthetic (201 MHz, $CDCl_3$) | Marcos (50 MHz, $CDCl_3$)[115] | Δδ (ppm) | Capon (100 MHz, $CDCl_3$)[103] | Δδ (ppm) |
|---|---|---|---|---|---|
| **1** | 29.5 | 29.5* | ± 0.0 | 29.4 | + 0.1 |
| **2** | 17.9 | 17.8 | + 0.1 | 17.8 | + 0.1 |
| **3** | 41.8 | 41.7 | + 0.1 | 41.7 | + 0.1 |
| **4** | 33.6 | 33.5 | + 0.1 | 33.5 | + 0.1 |
| **5** | 45.8 | 45.5 | + 0.3 | 45.6 | + 0.2 |
| **6** | 22.0 | 22.0 | ± 0.0 | 21.9 | + 0.1 |
| **7** | 30.4 | 30.3* | + 0.1 | 30.3 | + 0.1 |
| **8** | 32.5 | 32.4 | + 0.1 | 32.4 | + 0.1 |
| **9** | 37.4 | 37.0 | + 0.4 | 37.2 | + 0.2 |
| **10** | 86.6 | 86.5 | + 0.1 | 86.4 | + 0.2 |
| **11** | 22.3 | 22.3 | ± 0.0 | 22.2 | + 0.1 |
| **12** | 32.6 | 32.5 | + 0.1 | 32.5 | + 0.1 |
| **13** | 16.5 | 16.4 | + 0.1 | 16.4 | + 0.1 |
| **14** | 17.0 | 17.0 | ± 0.0 | 17.0 | ± 0.0 |
| **15** | 26.8 | 26.7* | + 0.1 | 26.7 | + 0.1 |
| **16** | 115.3 | 115.1 | + 0.2 | 115.2 | + 0.1 |
| **17** | 152.8 | 152.5 | + 0.3 | 152.7 | + 0.1 |
| **18** | 181.6 | 181.5 | + 0.1 | 181.4 | + 0.2 |
| **19** | 105.0 | 105.0 | ± 0.0 | 104.9 | + 0.1 |
| **20** | 159.6 | 159.5 | + 0.1 | 159.5 | + 0.1 |
| **21** | 181.5 | 181.5 | ± 0.0 | 181.5 | ± 0.0 |
| **22** | 56.5 | 56.4 | + 0.1 | 56.4 | + 0.1 |

* Carbon was reassigned by us on the basis of 2D NMR studies.




**(–)-Cyclosmenospongine (1)**

To a solution of 5-*epi*-smenoqualone (**21**) (740 mg, 2.06 mmol, 1 equiv) and pyridine (60 mL) in aqueous methanol (50%, 500 mL) was added aqueous ammonia (25%, 60 mL) at 23 °C. After 16h, the reaction mixture was concentrated and the residue was extracted with diethyl ether (5 × 300 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes initially, grading to 30% ethyl acetate in hexanes) to yield (–)-cyclosmenospongine (**1**) (423 mg, 60%) as a dark red crystalline solid. Recrystallization from ether gave crystals suitable for X-ray diffraction.

**TLC** (30% ethyl acetate in hexanes): $R_f = 0.21$ (UV, CAM).

**melting point:** 240–242 °C

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 5.54 (s, 1H, H-19), 5.05 (s, 2H, $NH_2$), 2.52 (d, $^2J_{15A/15B}$ = 18.3 Hz, 1H, H-$15_A$), 1.97 (d, $^2J_{15B/15A}$ = 18.3 Hz, 1H, H-15B), 1.74–1.69 (m, 1H, H-$1_A$), 1.67–1.58 (m, 3H, H-6, H-$2_A$), 1.52–1.44 (m, 3H, H-$7_A$, H-8, H-$3_A$), 1.42 (dd, $^3J_{5/6A}$ = 12.2 Hz, $^3J_{5/6B}$ = 4.1 Hz, 1H, H-5), 1.39–1.32 (m, 2H, H-$1_B$, H-$2_B$), 1.32–1.25 (m, 1H, H-$7_B$), 1.22–1.16 (m, 4H, H-$3_B$, H-11), 0.95 (s, 3H, H-14), 0.93 (s, 3H, H-12), 0.78 (d, $^3J_{13/8}$ = 6.6 Hz, 3H, H-13).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 182.6 (C-21), 180.3 (C-18), 154.8 (C-17), 147.6 (C-20), 113.0 (C-16), 99.5 (C-19), 86.6 (C-10), 45.8 (C-5), 41.9 (C-3), 37.3 (C-9), 33.6 (C-4), 32.6 (C-12), 32.4 (C-8), 30.4 (C-7), 29.7 (C-1), 26.7 (C-15), 22.3 (C-11), 22.0 (C-6), 18.0 (C-2), 17.0 (C-14), 16.5 (C-13).

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3452 (*w*), 3335 (*w*), 2947 (*w*), 1640 (*w*), 1595 (*vs*), 1456 (*w*), 1371 (*w*), 1215 (*m*), 1161 (*m*), 979 (*w*), 896 (*w*), 732 (*w*).

**HRMS** (EI) calc. for $C_{21}H_{29}O_3N$ $[M]^+$: 343.2142; found: 343.2140.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –346.6 (c = 0.12, $CHCl_3$); –18.0 (c = 0.10, $CHCl_3$; (–)-cyclosmenospongine).[95]

**Elemental Analysis** calc. (%) for $C_{21}H_{29}O_3N$: C 73.44, H 8.51, N 4.08; found: C 72.90, H 8.51, N 3.94.

***Table 5:*** *Comparison of $^1$H NMR data for natural and synthetic (–)-cyclosmenospongine (**1**).*

| Proton | Synthetic (800 MHz, $CDCl_3$)* | Natural (300 MHz, $CDCl_3$)[95] | Δδ (ppm) |
|---|---|---|---|
| 1A | 1.74–1.69 (m) | 1.84 (m) | – 0.12 |
| 1B | 1.39–1.32 (m) | 1.49 (m) | – 0.13 |
| 2A | 1.67–1.58 (m) | 1.59 (m) | + 0.04 |
| 2B | 1.39–1.32 (m) | 1.51 (m) | – 0.15 |
| 3A | 1.52–1.44 (m) | 1.51 (m) | – 0.03 |
| 3B | 1.22–1.16 (m) | 1.25 (m) | – 0.06 |
| 5 | 1.42 (dd, 12.2, 4.1 Hz) | 1.51 (m) | – 0.09 |
| 6 | 1.67–1.58 (m) | 1.66 (m), 1.51 (m) | |
| 7A | 1.52–1.44 (m) | 1.54 (m) | – 0.06 |
| 7B | 1.32–1.25 (m) | 1.29 (m) | ± 0.00 |
| 8 | 1.52–1.44 (m) | 0.98 (m) | + 0.50 |
| 11 | 1.19 (s) | 1.02 (s) | + 0.17 |
| 12 | 0.93 (s) | 0.98 (s) | – 0.05 |
| 13 | 0.78 (d, 6.6 Hz) | 0.78 (d, 6.4 Hz) | ± 0.00 |
| 14 | 0.95 (s) | 0.97 (s) | – 0.02 |
| 15A | 2.52 (d, 18.3 Hz) | 2.57 (d, 18.8 Hz) | – 0.05 |
| 15B | 1.97 (d, 18.3 Hz) | 2.06 (d, 18.8 Hz) | – 0.09 |
| 19 | 5.54 (s) | 5.54 (s) | ± 0.00 |
| $NH_2$ | 5.05 (br s) | 5.65 (br) | – 0.50 |

* acid-free $CDCl_3$ was used for the NMR measurement.

***Table 6:*** *Comparison of $^{13}C$ NMR data for natural and synthetic (–)-cyclosmenospongine (**1**).*

| Carbon | Synthetic (201 MHz, $CDCl_3$)* | Natural (76 MHz, $CDCl_3$)[95] | Δδ (ppm) |
|---|---|---|---|
| 1 | 29.7 | 29.1 | + 0.6 |
| 2 | 18.0 | 17.8 | + 0.2 |
| 3 | 41.9 | 40.9 | + 1.0 |
| 4 | 33.6 | 33.2 | + 0.4 |
| 5 | 45.8 | 45.7 | + 0.1 |
| 6 | 22.0 | 22.0 | ± 0.0 |
| 7 | 30.4 | 30.1 | + 0.3 |
| 8 | 32.4 | 32.3 | + 0.1 |
| 9 | 37.3 | 37.6 | – 0.3 |
| 10 | 86.6 | 88.6 | – 2.0 |
| 11 | 22.3 | 22.4 | – 0.1 |
| 12 | 32.6 | 32.4 | + 0.2 |
| 13 | 16.5 | 16.3 | + 0.2 |
| 14 | 17.0 | 17.1 | – 0.1 |
| 15 | 26.7 | 26.7 | ± 0.0 |
| 16 | 113.0 | 113.3 | – 0.3 |
| 17 | 154.8 | 153.6 | + 1.2 |
| 18 | 180.3 | 177.6# | + 2.7 |
| 19 | 99.5 | 98.1 | + 1.4 |
| 20 | 147.6 | 152.3 | – 4.7 |
| 21 | 182.6 | 180.5# | + 2.1 |

* acid-free $CDCl_3$ was used for the NMR measurement.

# Carbon was reassigned by us on the basis of 2D-NMR studies.

### 3.2.2. NMR studies of (–)-Cyclosmenospongine (1)

#### 3.2.2.1. Concentration effects:

A $^{1}H$ NMR spectrum was recorded with different amounts of (–)-cyclosmenospongine (**1**) (1 mg, 5 mg, 10 mg, 30 mg) in $CDCl_3$ (0.7 mL).

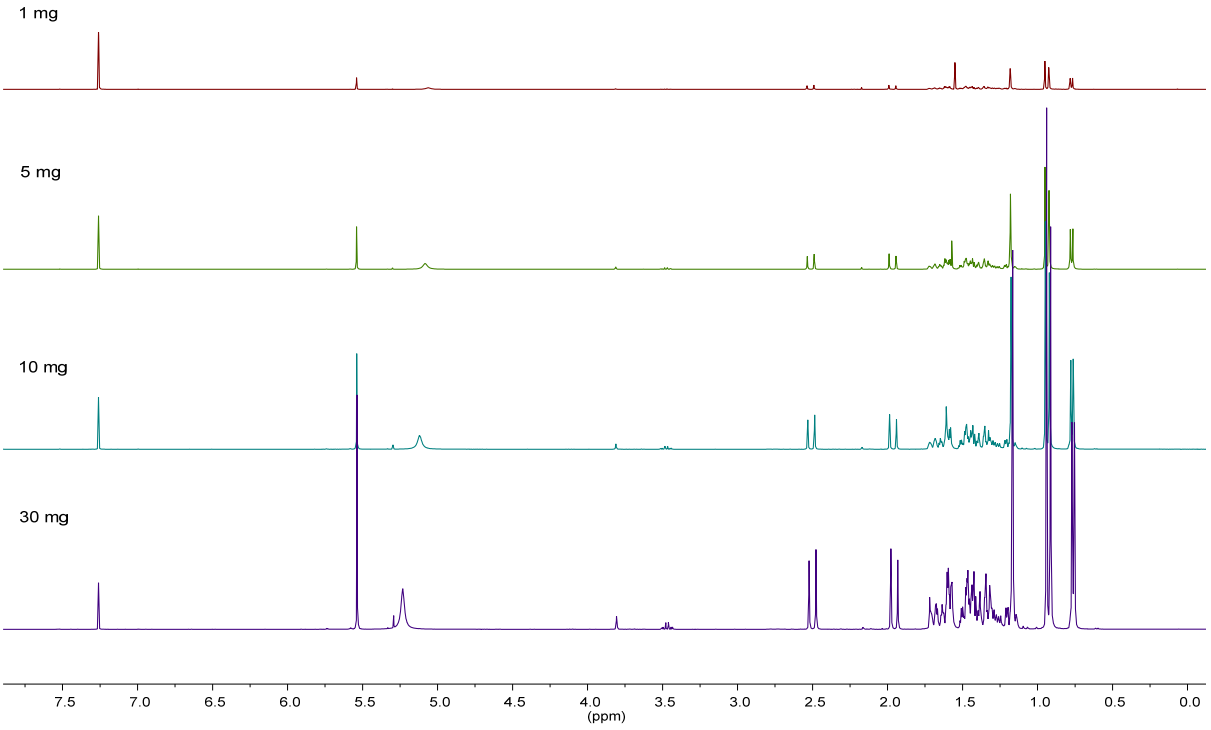



***Figure 5:*** *$^{1}H$ NMR (400MHz) of (–)-cyclosmenospongine (**1**) at different concentrations.*

#### 3.2.2.2. Addition of HCl:

Preparation of $HCl/CDCl_3$ solution:

Deuterated chloroform ($CDCl_3$) was purged with hydrogen chloride gas (freshly prepared by the slow dropwise addition of concentrated aqueous sulfuric acid to a vigorously stirred suspension of sodium chloride and concentrated aqueous hydrogen chloride solution) for 15 min.

To a solution of (–)-cyclosmenospongine (**1**) (30 mg) in $CDCl_3$ (0.5 mL) was sequentially added a freshly prepared $HCl/CDCl_3$ solution (50 µL, 50 µL, 100 µL, 100 µL and 200 µL). After every addition a $^{1}H$ and $^{13}C$ NMR spectrum was recorded.

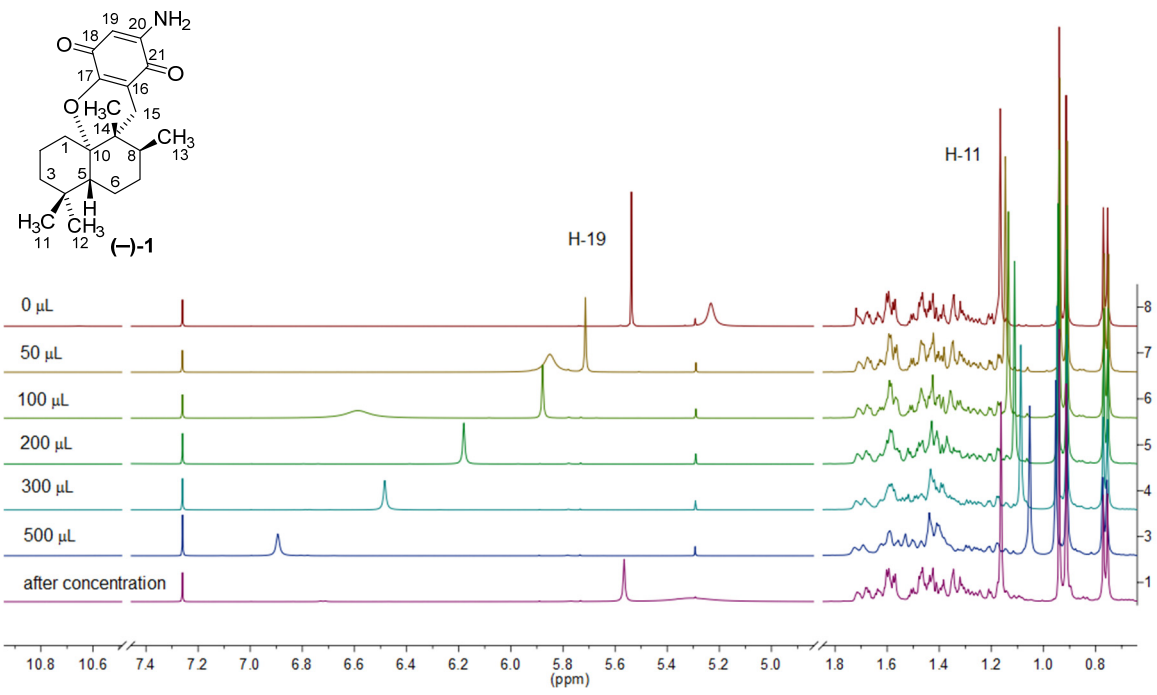



***Figure 6:*** *$^{1}$H NMR (400 MHz) spectra of **1** after the addition of $CDCl_3$ saturated with HCl.*

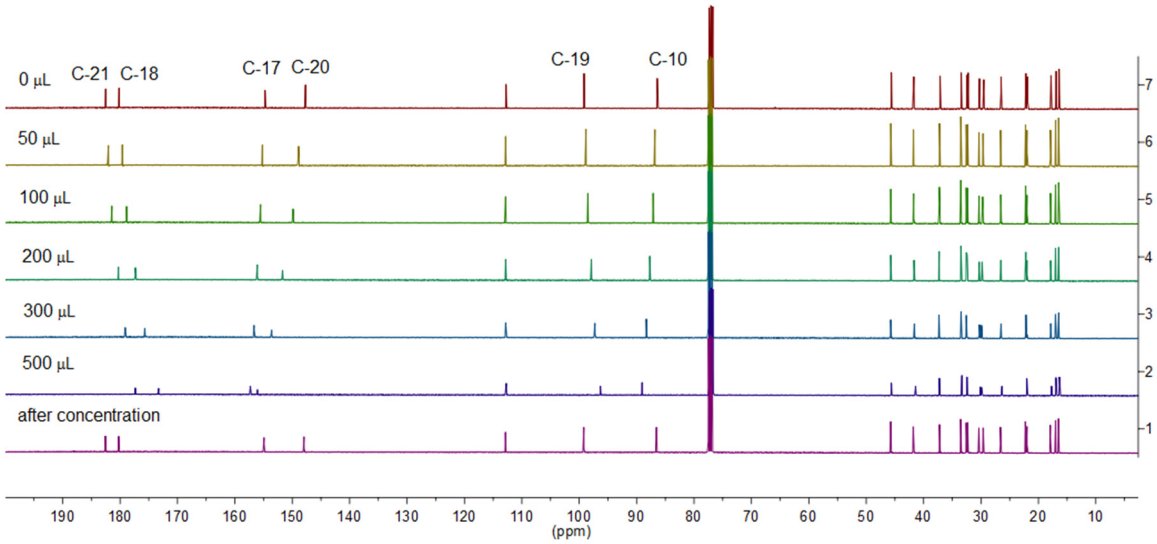



***Figure 7:*** *$^{13}$C NMR (101 MHz) spectra of **1** after the addition of $CDCl_3$ saturated with HCl.*

***Table 7:*** *$^{13}C$ NMR shifts of **1** after the addition of $CDCl_3$ saturated with HCl and shift differences to the reported spectrum of natural **1**.[95]*

| Carbon | Natural (76 MHz, $CDCl_3$)[95] | Synthetic (201 Hz, $CDCl_3$) | Δ | Synthetic (50 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (100 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (200 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (300 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (500 µL; 101 Hz, $CDCl_3$) | Δ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 29.1 | 29.7 | 0.6 | 29.7 | 0.6 | 29.7 | 0.6 | 29.8 | 0.7 | 29.9 | 0.8 | 29.9 | 0.8 |
| 2 | 17.8 | 18.0 | 0.2 | 17.9 | 0.1 | 17.9 | 0.1 | 17.9 | 0.1 | 17.9 | 0.1 | 17.7 | –0.1 |
| 3 | 40.9 | 41.9 | 1.0 | 41.8 | 0.9 | 41.7 | 0.8 | 41.7 | 0.8 | 41.6 | 0.7 | 41.4 | 0.5 |
| 4 | 33.2 | 33.6 | 0.4 | 33.5 | 0.3 | 33.5 | 0.3 | 33.5 | 0.3 | 33.5 | 0.3 | 33.3 | 0.1 |
| 5 | 45.7 | 45.8 | 0.1 | 45.7 | 0.0 | 45.7 | 0.0 | 45.7 | 0.0 | 45.7 | 0.0 | 45.6 | –0.1 |
| 6 | 22.0 | 22.0 | 0.0 | 22.0 | 0.0 | 22.0 | 0.0 | 22.0 | 0.0 | 22.0 | 0.0 | 21.9 | –0.1 |
| 7 | 30.1 | 30.4 | 0.3 | 30.3 | 0.2 | 30.3 | 0.2 | 30.3 | 0.2 | 30.3 | 0.2 | 30.1 | 0.0 |
| 8 | 32.3 | 32.4 | 0.1 | 32.3 | 0.0 | 32.4 | 0.1 | 32.4 | 0.1 | 32.5 | 0.2 | 32.4 | 0.1 |
| 9 | 37.6 | 37.3 | –0.3 | 37.2 | –0.4 | 37.3 | –0.3 | 37.3 | –0.3 | 37.3 | –0.3 | 37.2 | –0.4 |
| 10 | 88.6 | 86.6 | –2.0 | 86.8 | –1.8 | 87.1 | –1.5 | 87.7 | –0.9 | 88.3 | –0.3 | 89.0 | 0.4 |
| 11 | 22.4 | 22.3 | –0.1 | 22.2 | –0.2 | 22.2 | –0.2 | 22.2 | –0.2 | 22.2 | –0.2 | 22.0 | –0.4 |
| 12 | 32.4 | 32.6 | 0.2 | 32.6 | 0.2 | 32.6 | 0.2 | 32.6 | 0.2 | 32.6 | 0.2 | 32.4 | 0.0 |
| 13 | 16.3 | 16.5 | 0.2 | 16.5 | 0.2 | 16.5 | 0.2 | 16.5 | 0.2 | 16.5 | 0.2 | 16.3 | 0.0 |
| 14 | 17.1 | 17.0 | –0.1 | 17.0 | –0.1 | 17.0 | –0.1 | 17.0 | –0.1 | 17.0 | –0.1 | 16.9 | –0.2 |
| 15 | 26.7 | 26.7 | 0.0 | 26.6 | –0.1 | 26.6 | –0.1 | 26.5 | –0.2 | 26.5 | –0.2 | 26.4 | –0.3 |
| 16 | 113.3 | 113.0 | –0.3 | 112.8 | –0.5 | 112.8 | –0.5 | 112.8 | –0.5 | 112.8 | –0.5 | 112.7 | –0.6 |
| 17 | 153.6 | 154.8 | 1.2 | 155.2 | 1.6 | 155.5 | 1.9 | 156.1 | 2.5 | 156.7 | 3.1 | 157.3 | 3.7 |
| 18 | 177.6 | 180.3 | 2.7 | 179.6 | 2.0 | 178.9 | 1.3 | 177.3 | –0.3 | 175.7 | –1.9 | 173.3 | –4.3 |
| 19 | 98.1 | 99.2 | 1.1 | 98.8 | 0.7 | 98.5 | 0.4 | 97.9 | –0.2 | 97.3 | –0.8 | 96.3 | –1.8 |
| 20 | 152.3 | 147.6 | –4.7 | 148.9 | –3.4 | 149.9 | –2.4 | 151.7 | –0.6 | 153.6 | 1.3 | 156.1 | 3.8 |
| 21 | 180.5 | 182.6 | 2.1 | 182.0 | 1.5 | 181.4 | 0.9 | 180.3 | –0.2 | 179.1 | –1.4 | 177.3 | –3.2 |

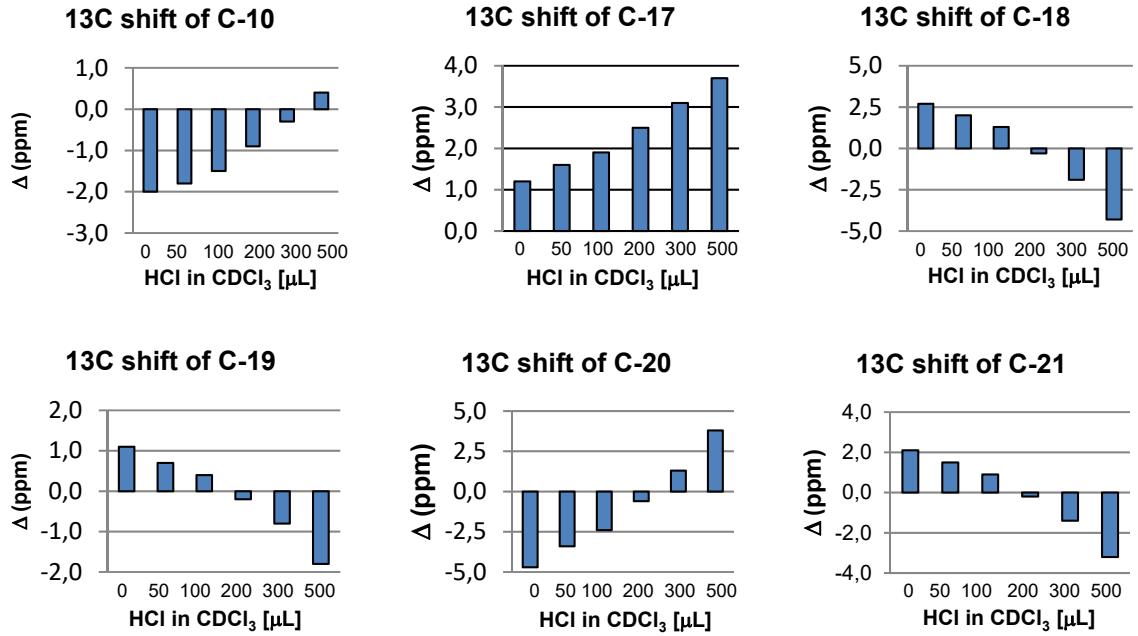



***Figure 8:*** *Selected carbon atoms of (–)-cyclosmenospongine (**1**) and the influence of protonation on their $^{13}C$ NMR shifts.*

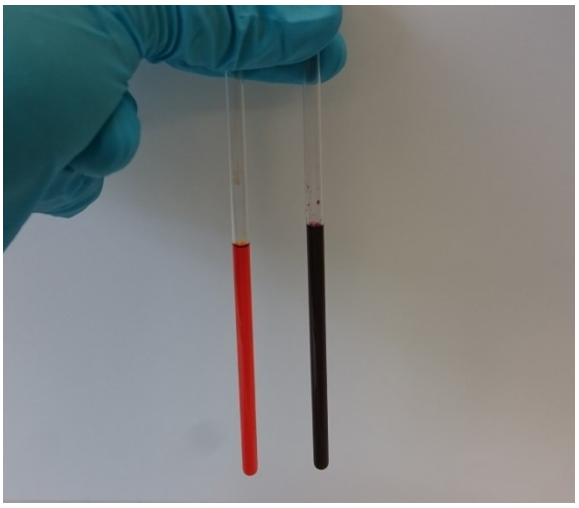
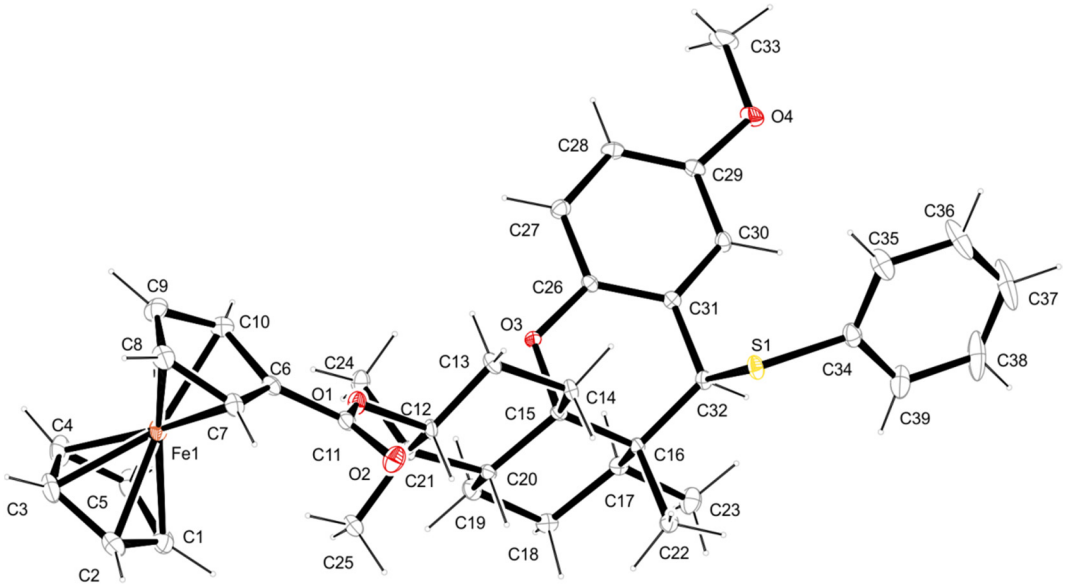


***Figure 9:*** *left: (–)-cyclosmenospongine* ***(1)*** *in $CDCl_3$ (bright red); right: (–)-cyclosmenospongine* ***(1)*** *in $HCl/CDCl_3$ (purple, reported as wine-red[95])*

### 3.2.3. X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[S8] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[180] and refined by least-squares methods against *F*2 with SHELXL-97.[181] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

#### 3.2.3.1. Ferrocenecarboxylate ester 18



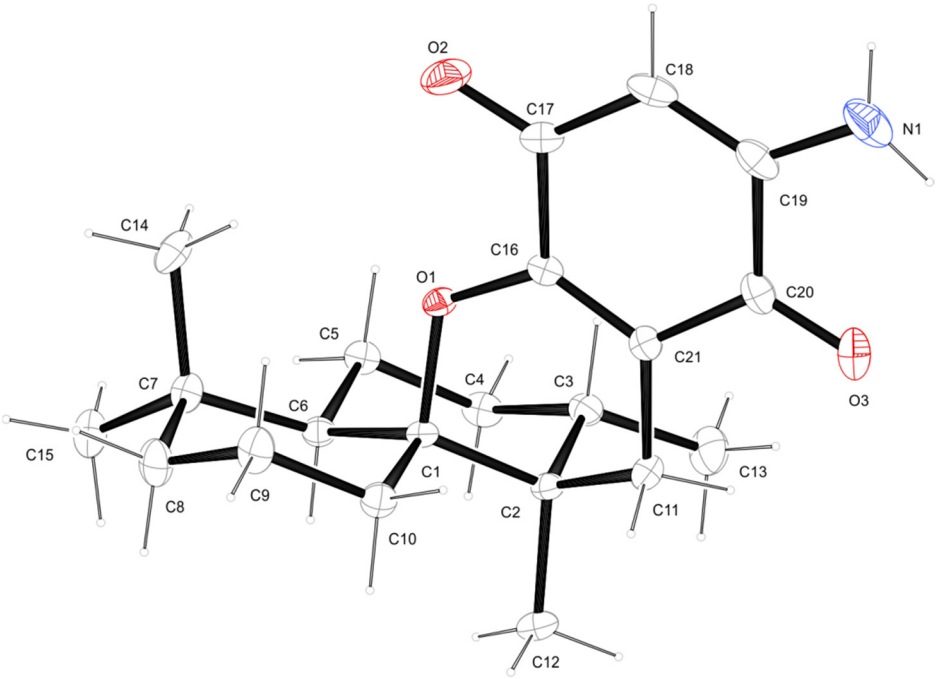

**CCDC 1499443** contains the supplementary crystallographic data for ferrocenecarboxylate ester **18**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

**Table 8:** Ferrocenecarboxylate ester **18**.

| | |
|---|---|
| net formula | $C_{39}H_{44}FeO_4S$ |
| $M_r$/g mol$^{-1}$ | 664.65 |
| crystal size/mm | 0.100 × 0.030 × 0.010 |
| *T*/K | 153.(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8 Venture TXS' |
| crystal system | monoclinic |
| space group | 'P 1 21 1' |
| *a*/Å | 14.3768(19) |

| | |
|---|---|
| *b*/Å | 7.3244(9) |
| *c*/Å | 17.1643(19) |
| α/° | 90 |
| β/° | 111.981(4) |
| γ/° | 90 |
| $V$/Å$^3$ | 1676.0(4) |
| $Z$ | 2 |
| calc. density/g cm$^{-3}$ | 1.317 |
| μ/mm$^{-1}$ | 0.552 |
| absorption correction | Multi-Scan |
| transmission factor range | 0.6807–0.7454 |
| refls. measured | 23821 |
| $R_{int}$ | 0.0775 |
| mean σ($I$)/$I$ | 0.0749 |
| θ range | 3.168–26.371 |
| observed refls. | 5507 |
| $x$, $y$ (weighting scheme) | 0.0267, 0.3292 |
| hydrogen refinement | constr |
| Flack parameter | 0.008(10) |
| refls in refinement | 6743 |
| parameters | 411 |
| restraints | 1 |
| $R(F_{obs})$ | 0.0447 |
| $R_w(F^2)$ | 0.0844 |
| $S$ | 1.039 |
| shift/error$_{max}$ | 0.001 |
| max electron density/e Å$^{-3}$ | 0.317 |
| min electron density/e Å$^{-3}$ | −0.433 |

### 3.2.3.2. (–)-Cyclosmenospongine (1)

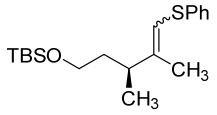


**CCDC 1499442** contains the supplementary crystallographic data (–)-Cyclosmenospongine (**1**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***Table 9:*** *(–)-Cyclosmenospongine (**1**).*

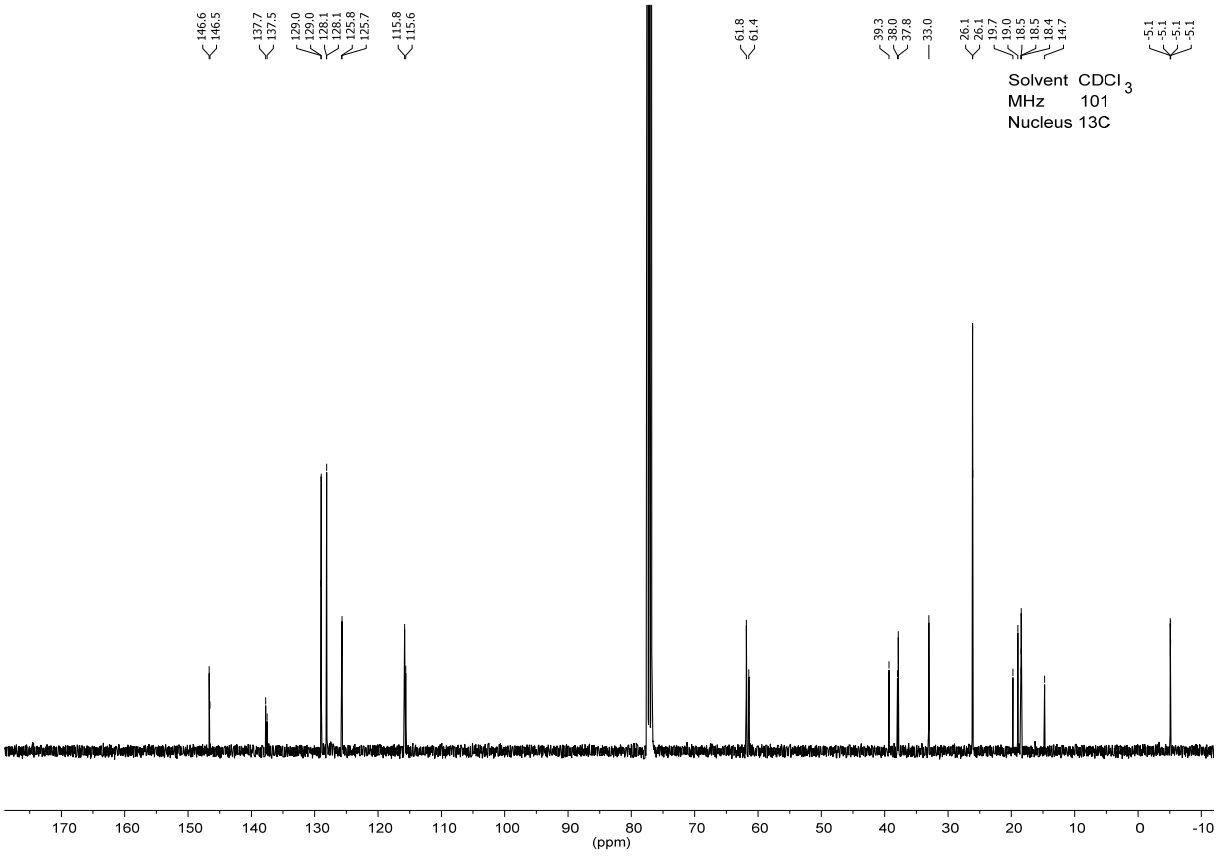
| | |
|---|---|
| net formula | $C_{21}H_{29}NO_3$ |
| $M_r$/g mol$^{-1}$ | 343.45 |
| crystal size/mm | 0.100 × 0.060 × 0.050 |
| $T$/K | 153.(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8 Venture TXS' |
| crystal system | orthorhombic |
| space group | 'P 21 21 21' |
| $a$/Å | 10.7772(8) |
| $b$/Å | 11.6369(8) |
| $c$/Å | 14.6780(10) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| $V$/Å$^3$ | 1840.8(2) |
| $Z$ | 4 |
| calc. density/g cm$^{-3}$ | 1.239 |
| μ/mm$^{-1}$ | 0.082 |
| absorption correction | Multi-Scan |
| transmission factor range | 0.9033–0.9590 |
| refls. measured | 42454 |
| $R_{int}$ | 0.0806 |
| mean σ($I$)/$I$ | 0.0501 |
| θ range | 3.358–27.484 |
| observed refls. | 3522 |
| $x$, $y$ (weighting scheme) | 0.0379, 0.4490 |
| hydrogen refinement | C-H: constr, N-H: refall |
| Flack parameter | 0.1(2) |
| refls in refinement | 4086 |
| parameters | 238 |
| restraints | 0 |
| $R(F_{obs})$ | 0.0489 |
| $R_w(F^2)$ | 0.0947 |
| $S$ | 1.074 |
| shift/error$_{max}$ | 0.001 |
| max electron density/e Å$^{-3}$ | 0.232 |
| min electron density/e Å$^{-3}$ | −0.191 |

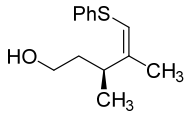
### 3.2.4. $^{1}H$ and $^{13}C$ NMR Spectra




**S26**

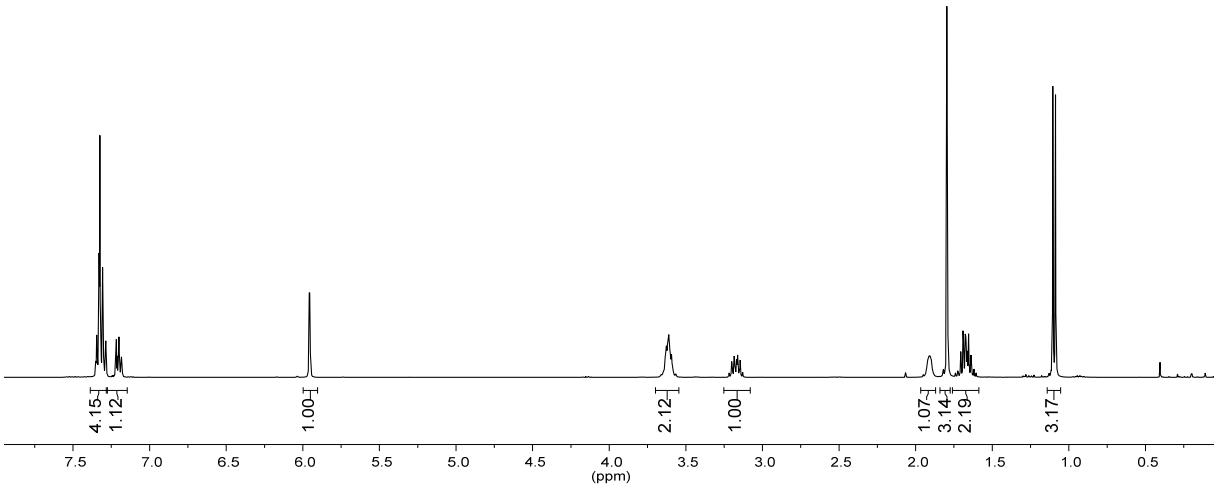




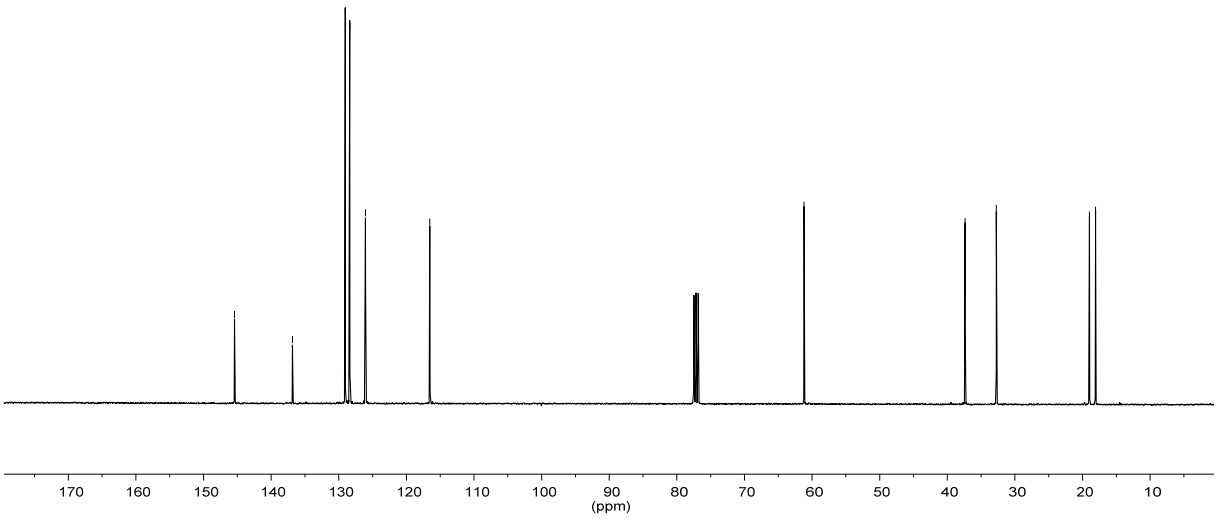

**(*Z*)-S27**

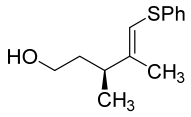
Solvent CDCl3
MHz 400
Nucleus 1H





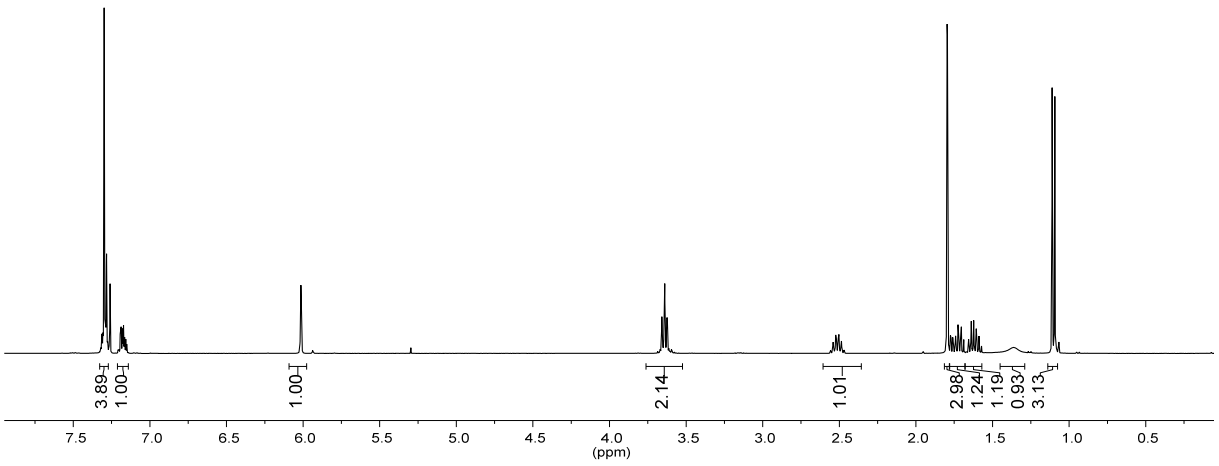
Solvent CDCl3
MHz 101
Nucleus 13C

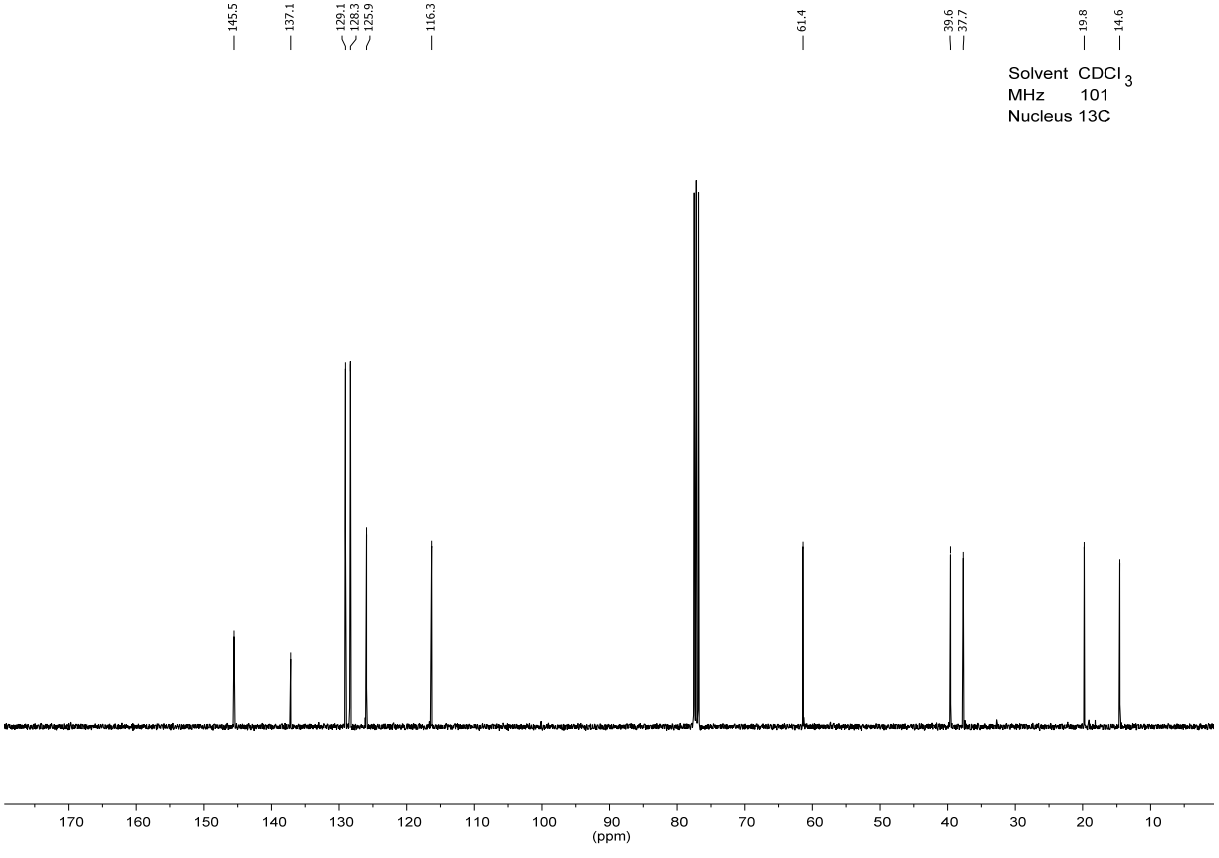


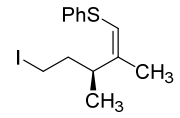



**(*E*)-S27**

Solvent CDCl 3
MHz 400
Nucleus 1H

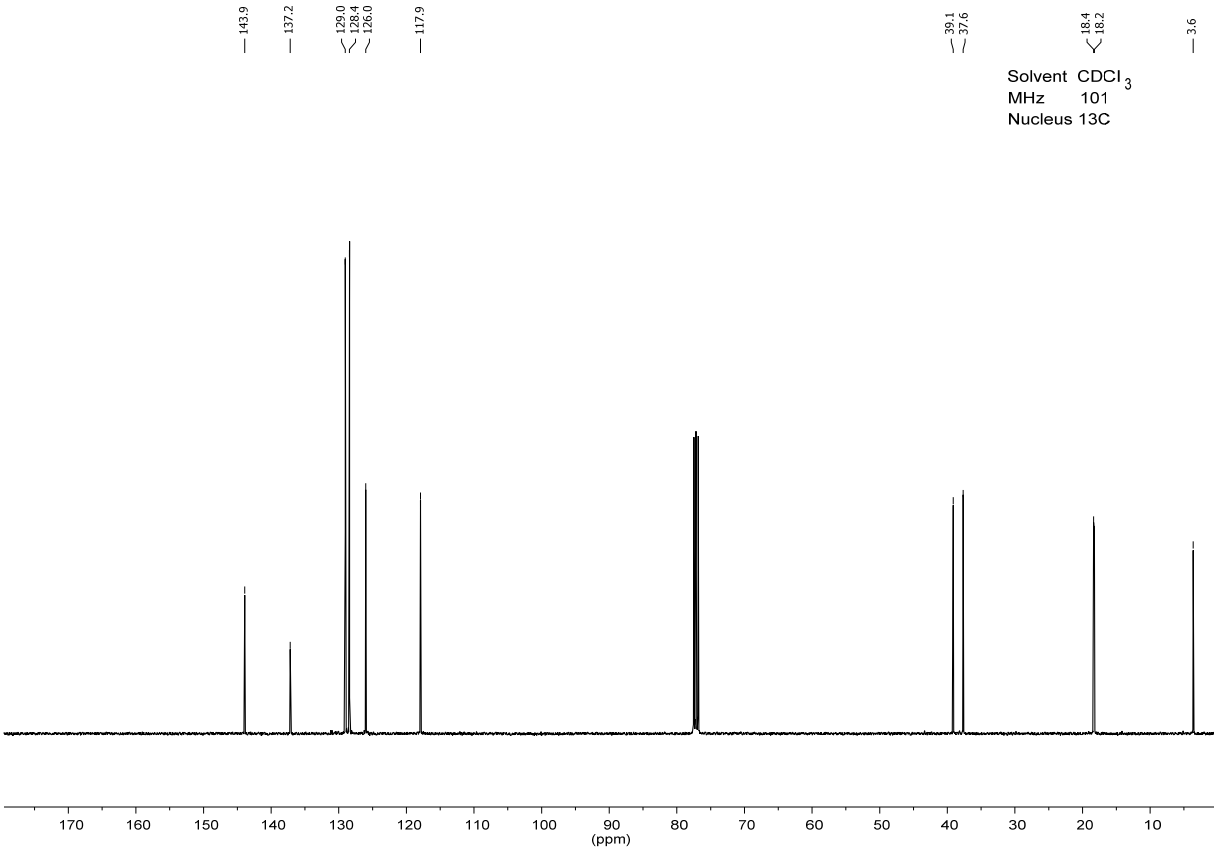


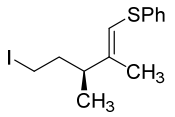




PhS
I
CH3
CH3

**(*Z*)-8**

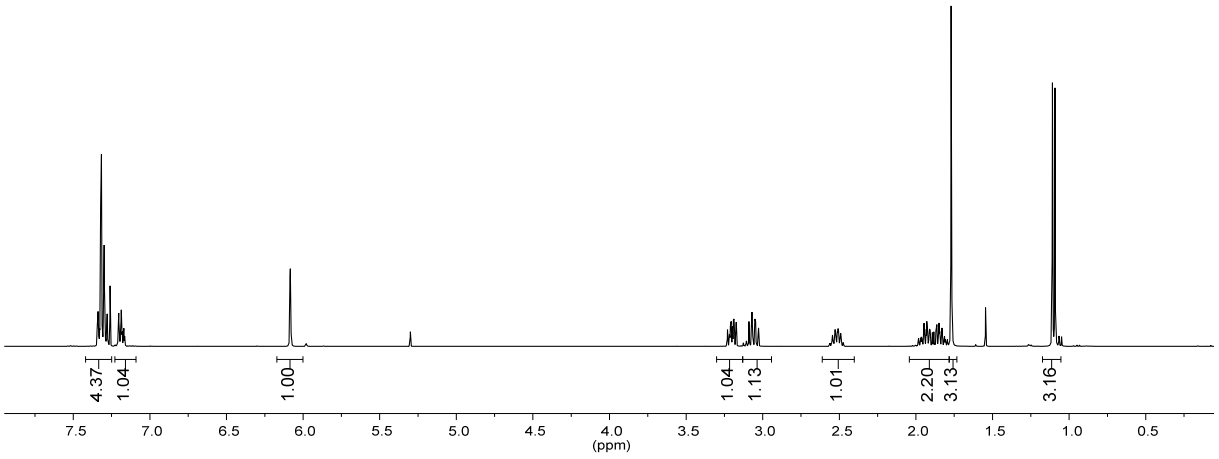

Solvent CDCl3
MHz 400
Nucleus 1H
4.14
1.00
0.98
3.04
2.11
3.15
3.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

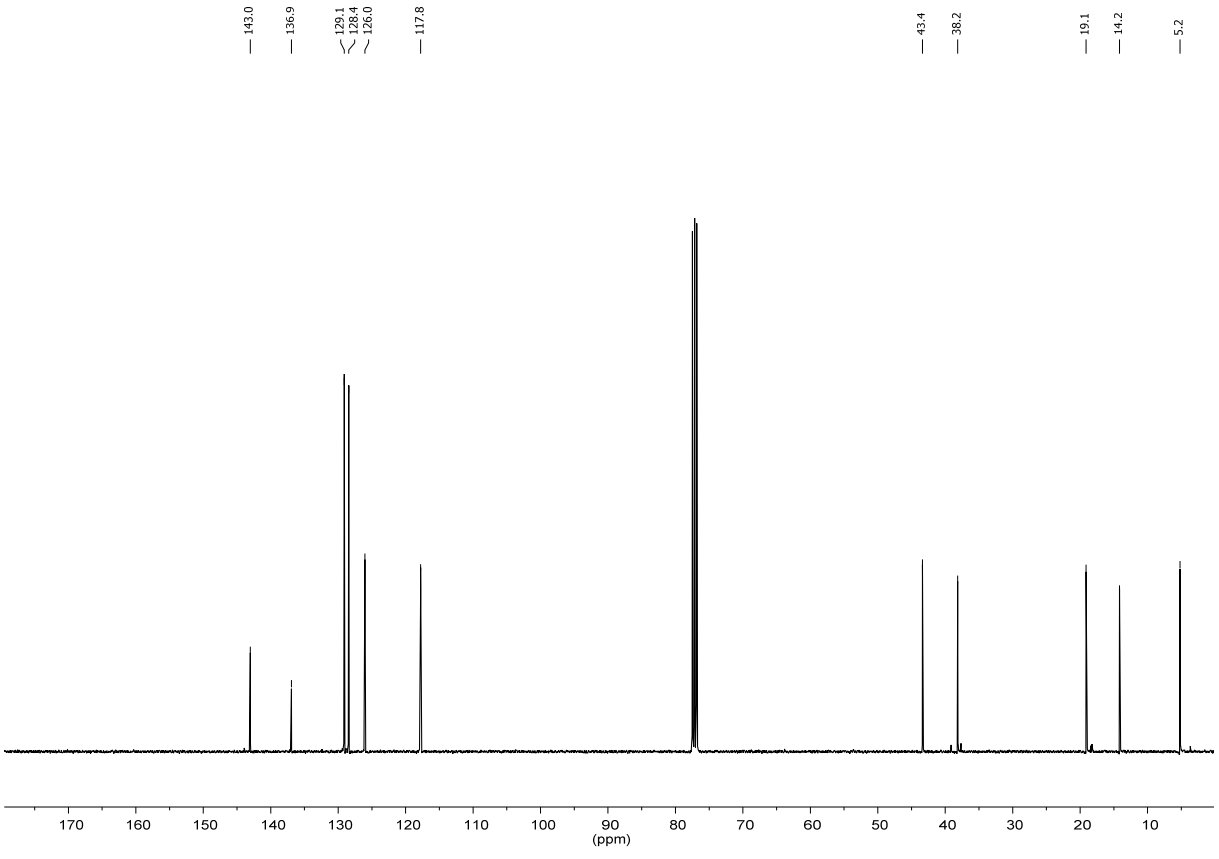

143.9
137.2
129.0
128.4
126.0
117.9
39.1
37.6
18.4
18.2
3.6
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

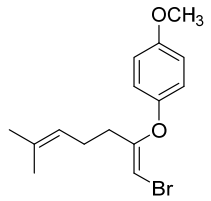



**(*E*)-8**

Solvent CDCl 3
MHz 400
Nucleus 1H

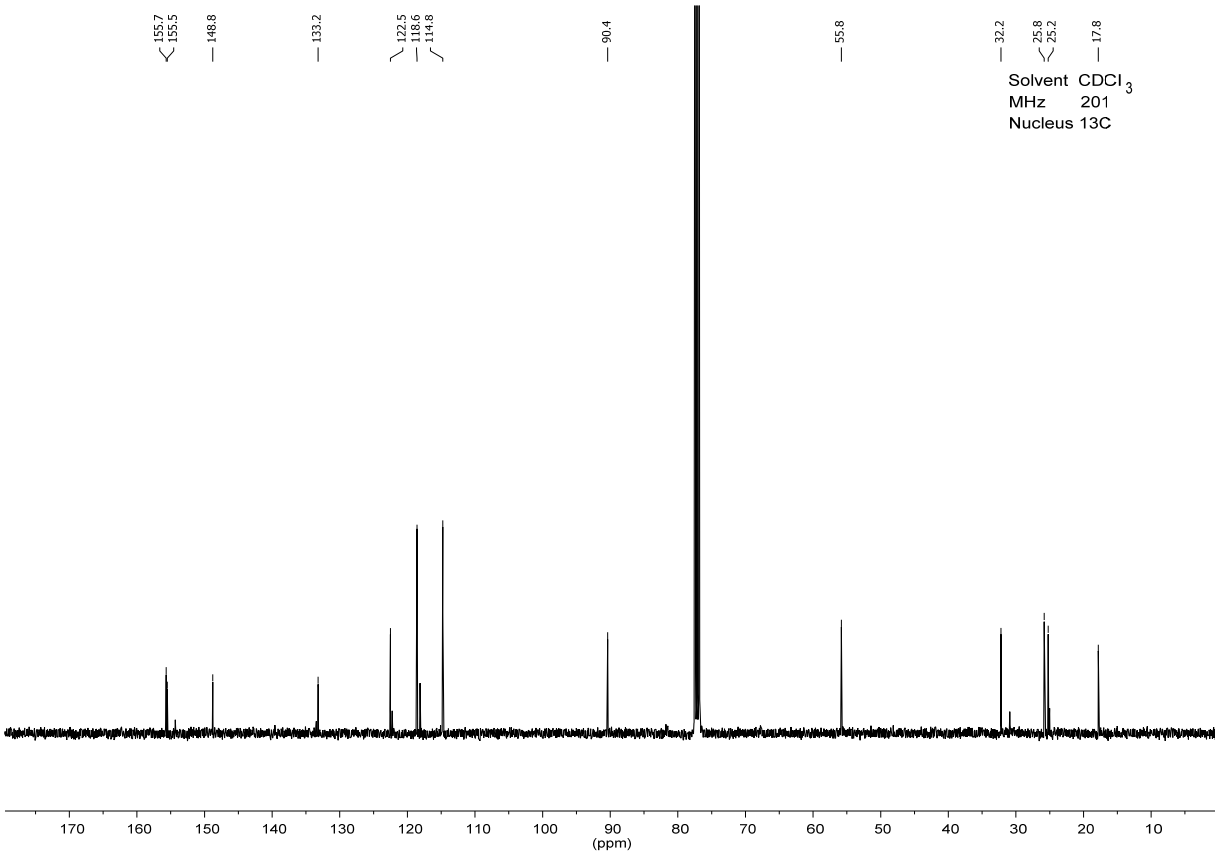


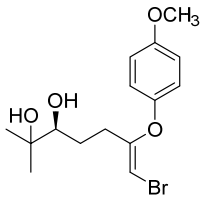




OCH3
O
Br

**S28**

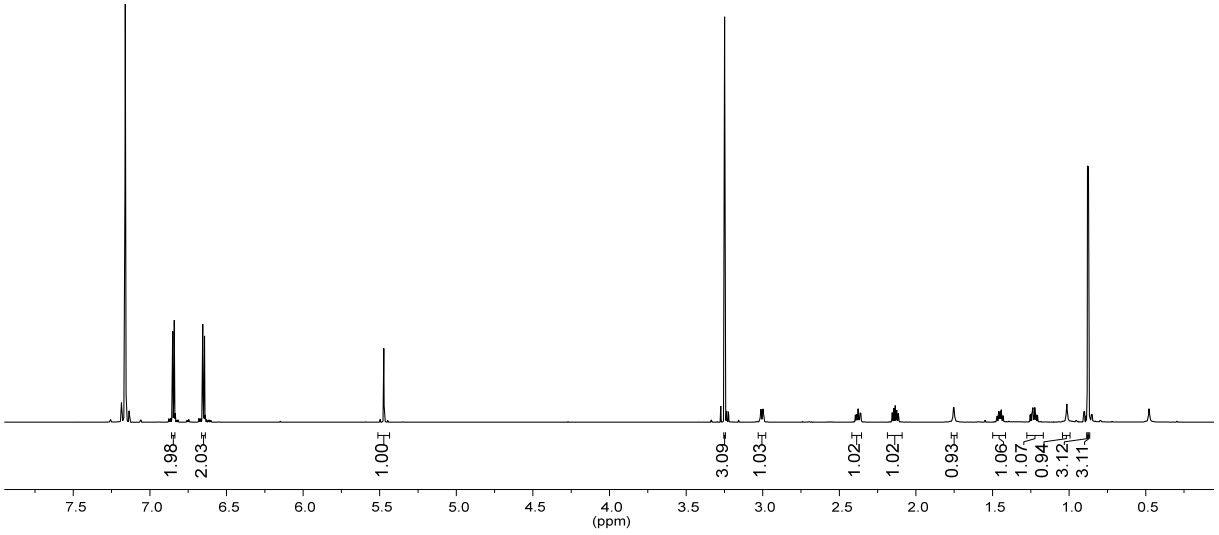

Solvent CDCl3
MHz 400
Nucleus 1H
1.93
2.03
0.94
1.00
3.07
4.00
3.08
3.17
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

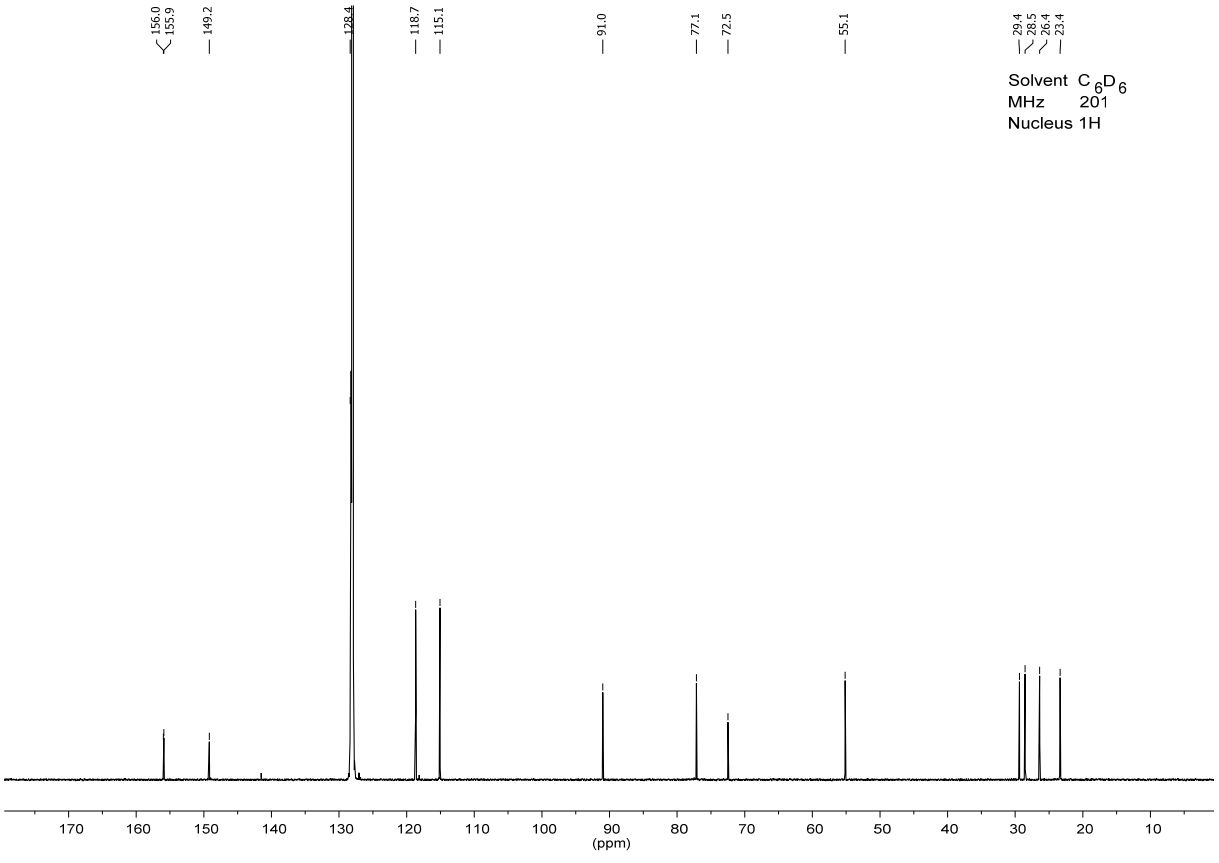

155.7
155.5
148.8
133.2
122.5
118.6
114.8
90.4
55.8
32.2
25.8
25.2
17.8
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



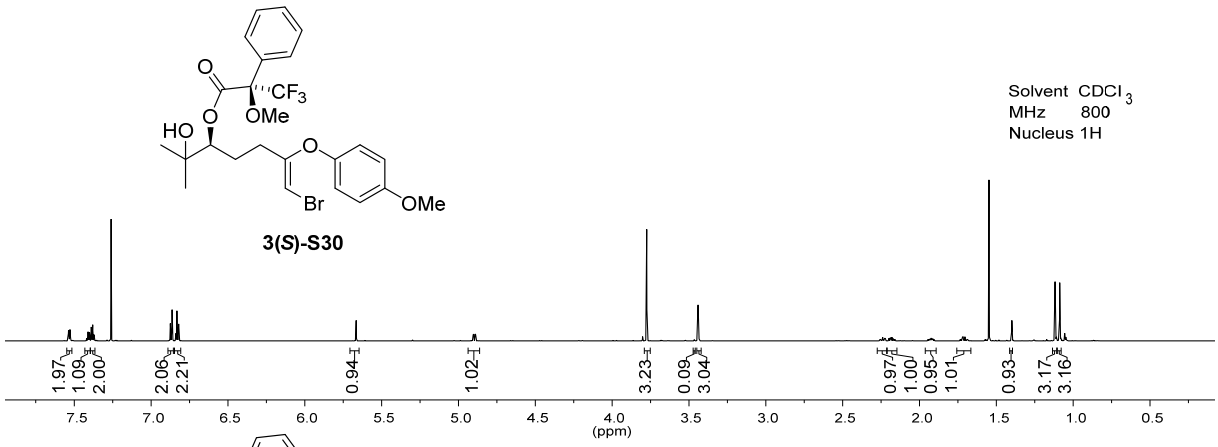

**3(*S*)-S29**

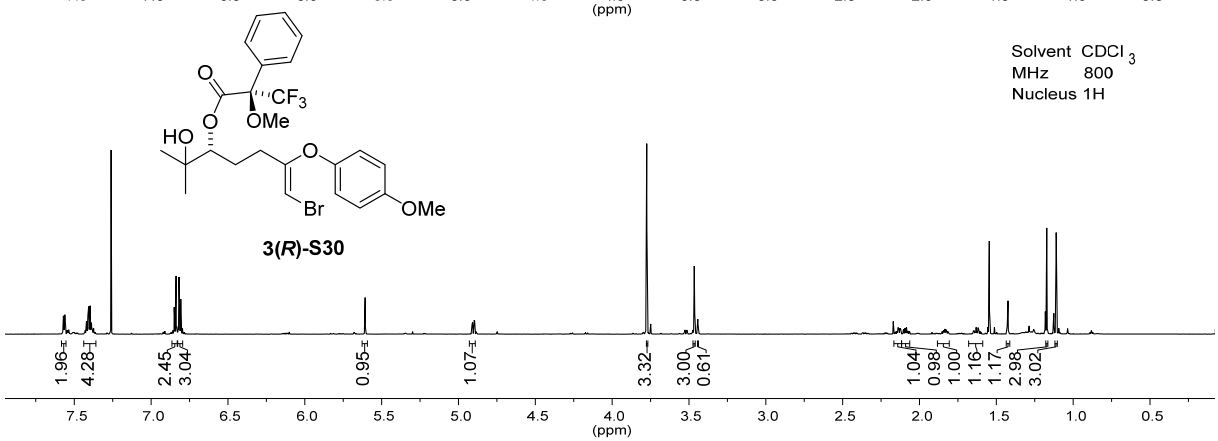
Solvent $C_6D_6$
MHz 800
Nucleus 1H

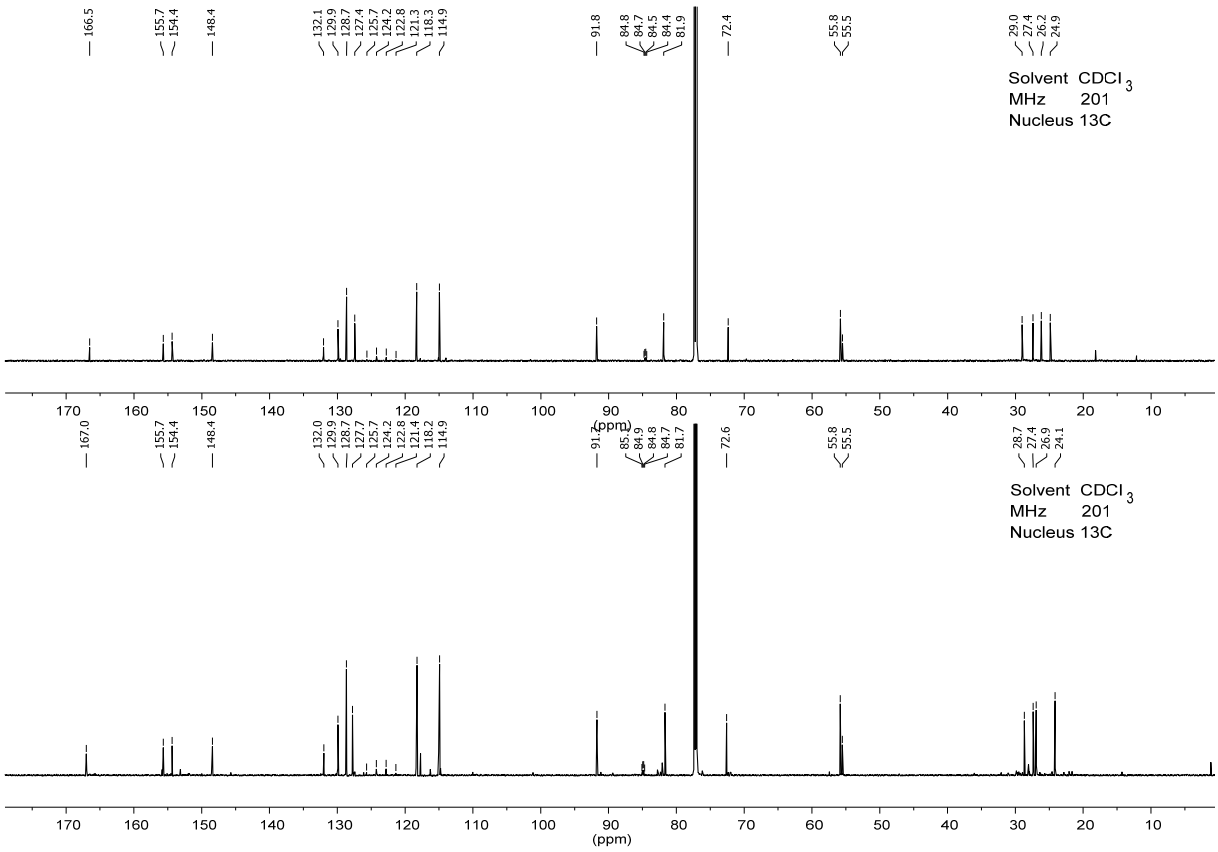


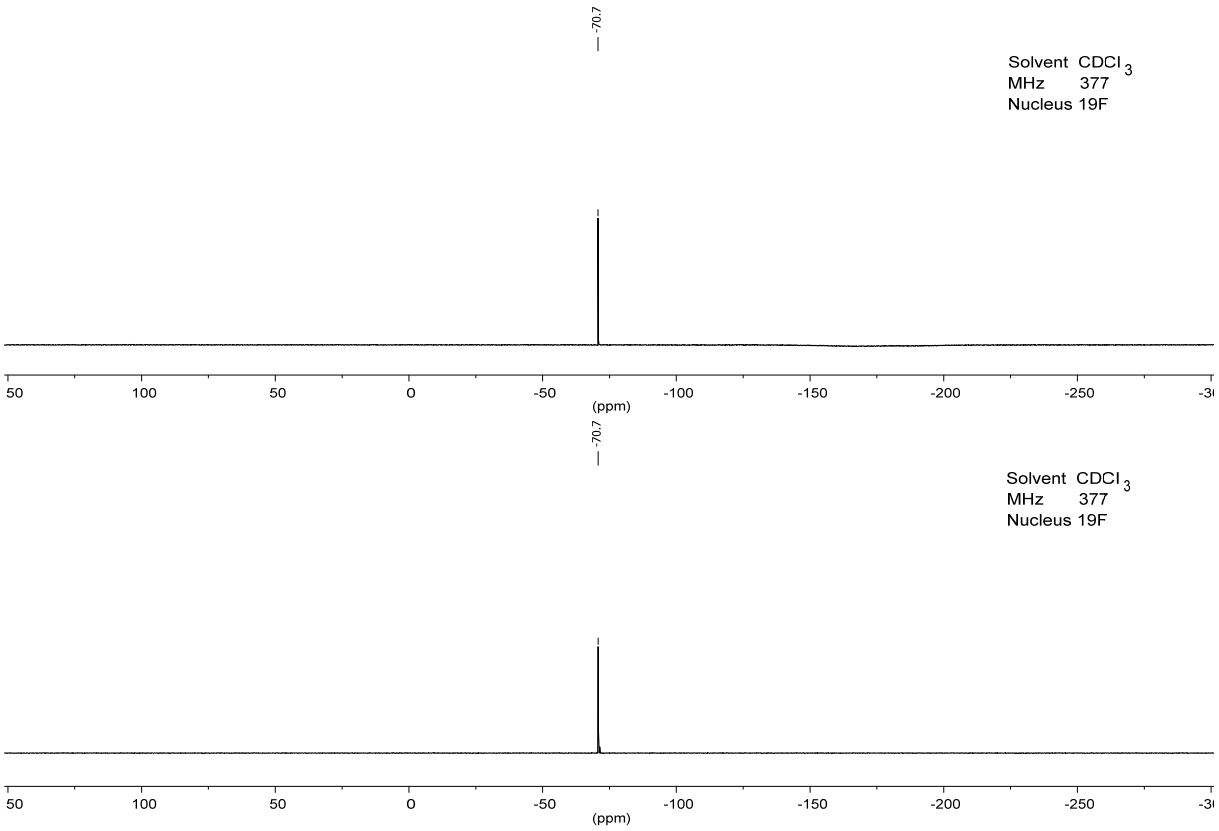

Solvent $C_6D_6$
MHz 201
Nucleus 1H

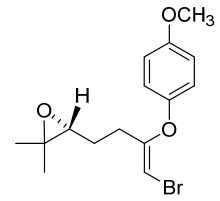

Solvent CDCl3
MHz 800
Nucleus 1H
3(S)-S30


Solvent CDCl3
MHz 800
Nucleus 1H
3(R)-S30


Solvent CDCl3
MHz 201
Nucleus 13C

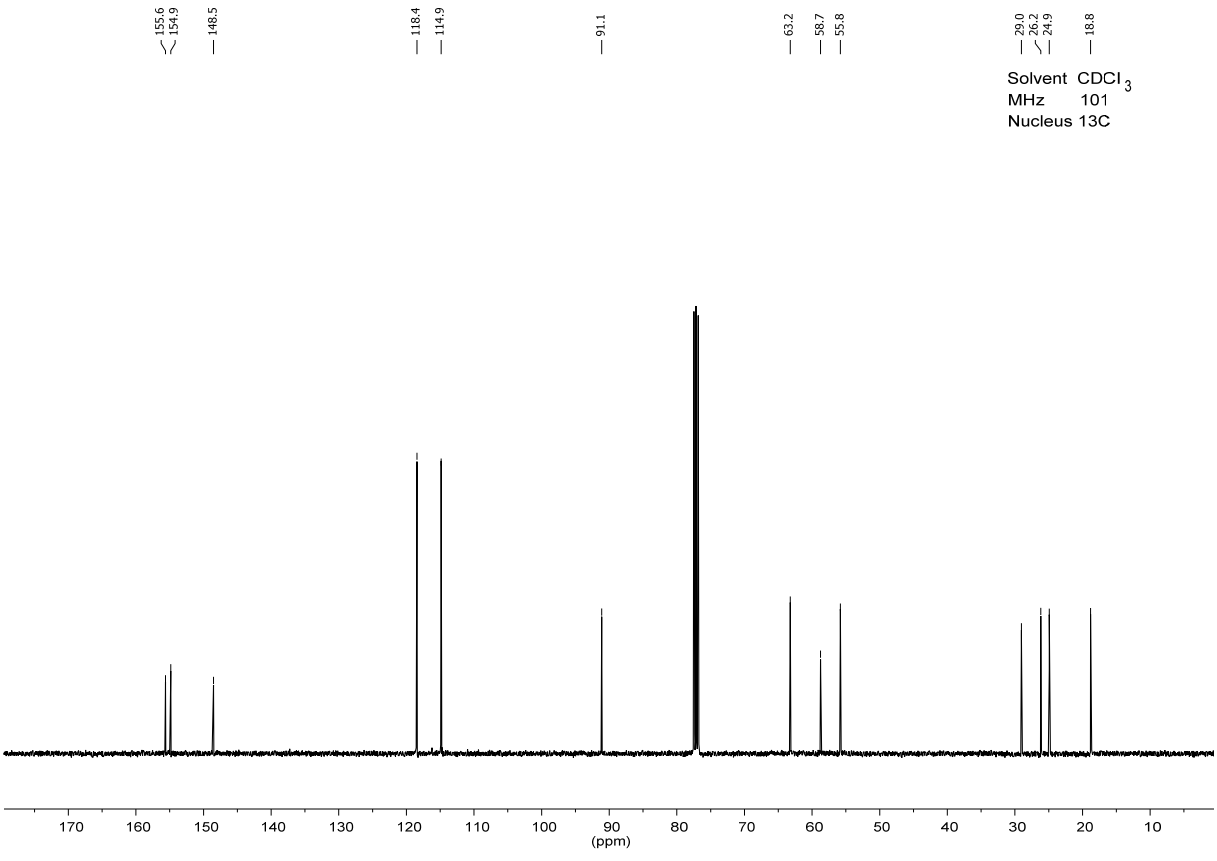

Solvent CDCl3
MHz 201
Nucleus 13C

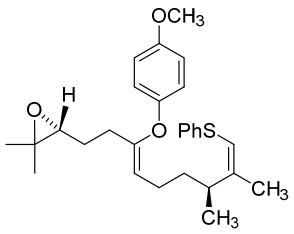

-70.7
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
(ppm)
-70.7
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
(ppm)


OCH3
H
O
O
Br

**13**

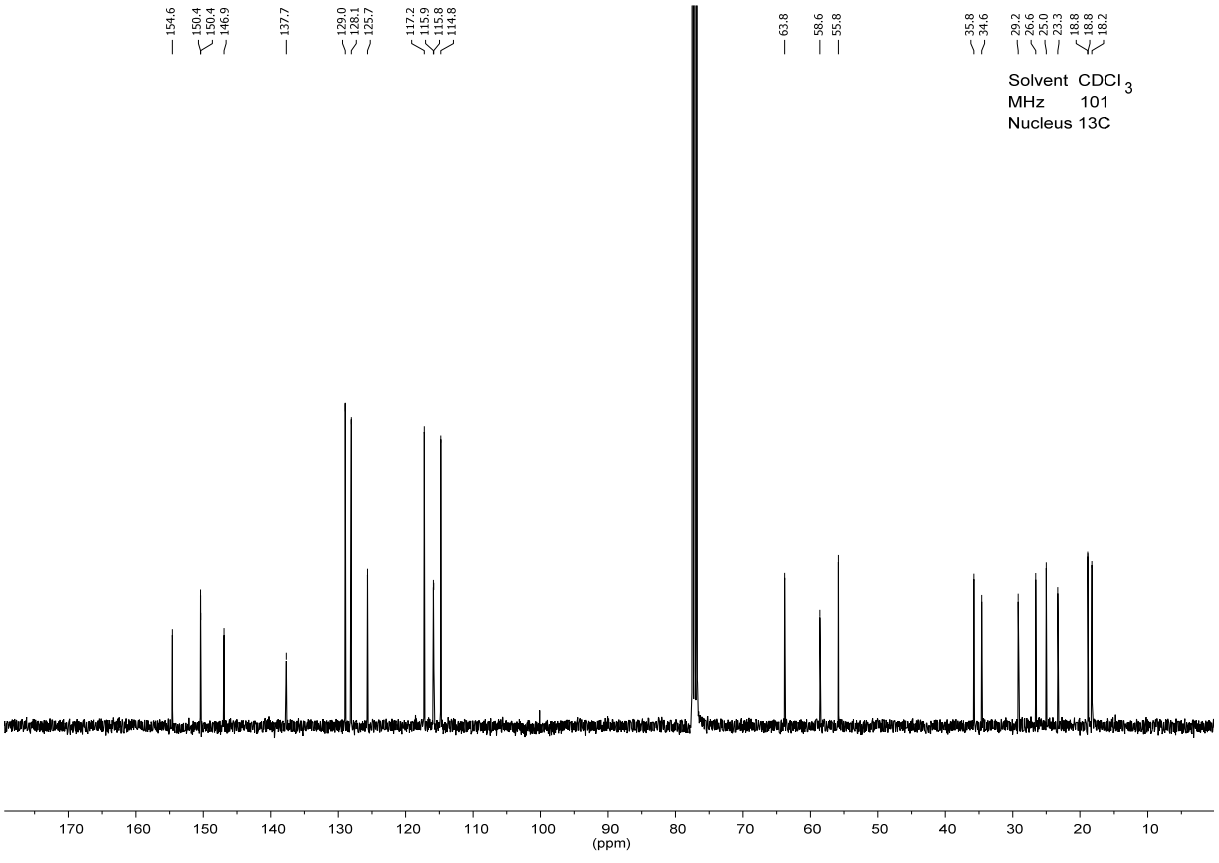

Solvent CDCl3
MHz 400
Nucleus 1H
2.04
2.10
1.00
3.19
0.99
1.03
1.07
1.09
1.17
3.05
2.96
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

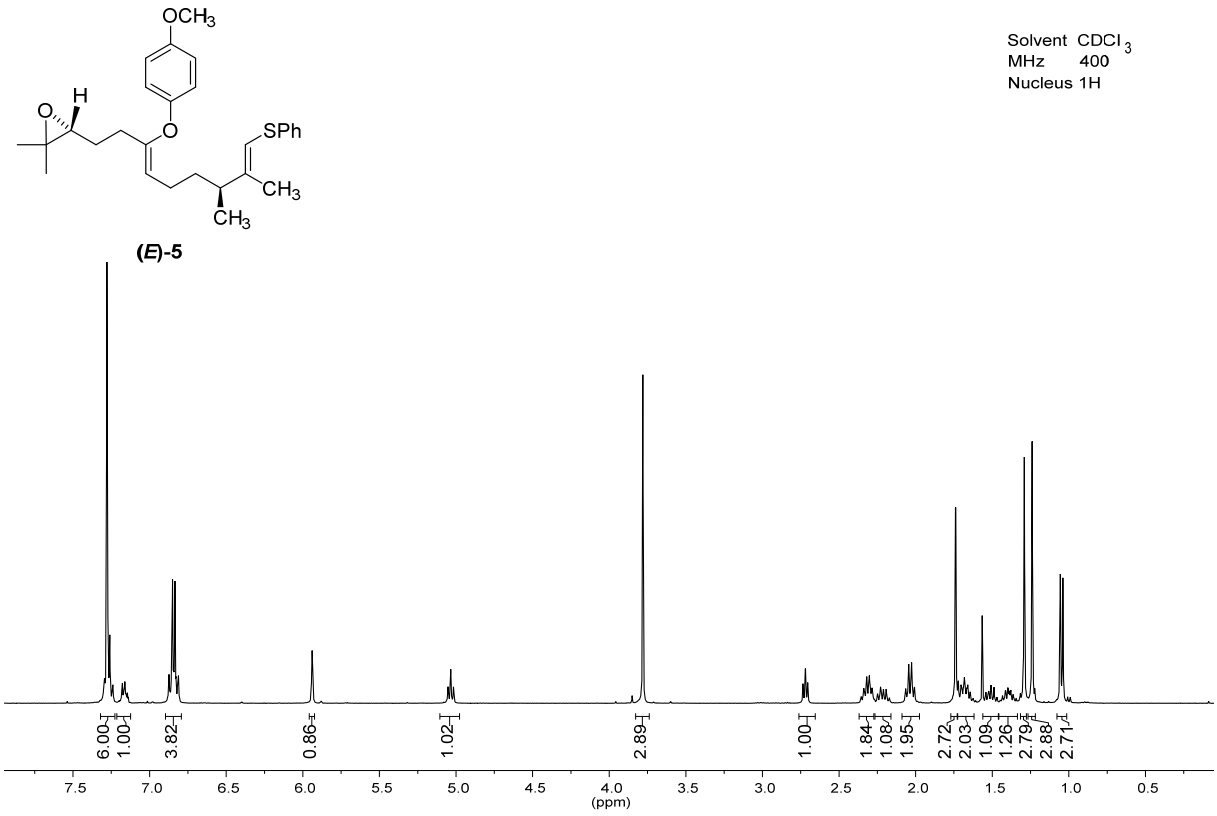

155.6
154.9
148.5
118.4
114.9
91.1
63.2
58.7
55.8
29.0
26.2
24.9
18.8
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OCH3
H
O
O PhS
CH3
CH3

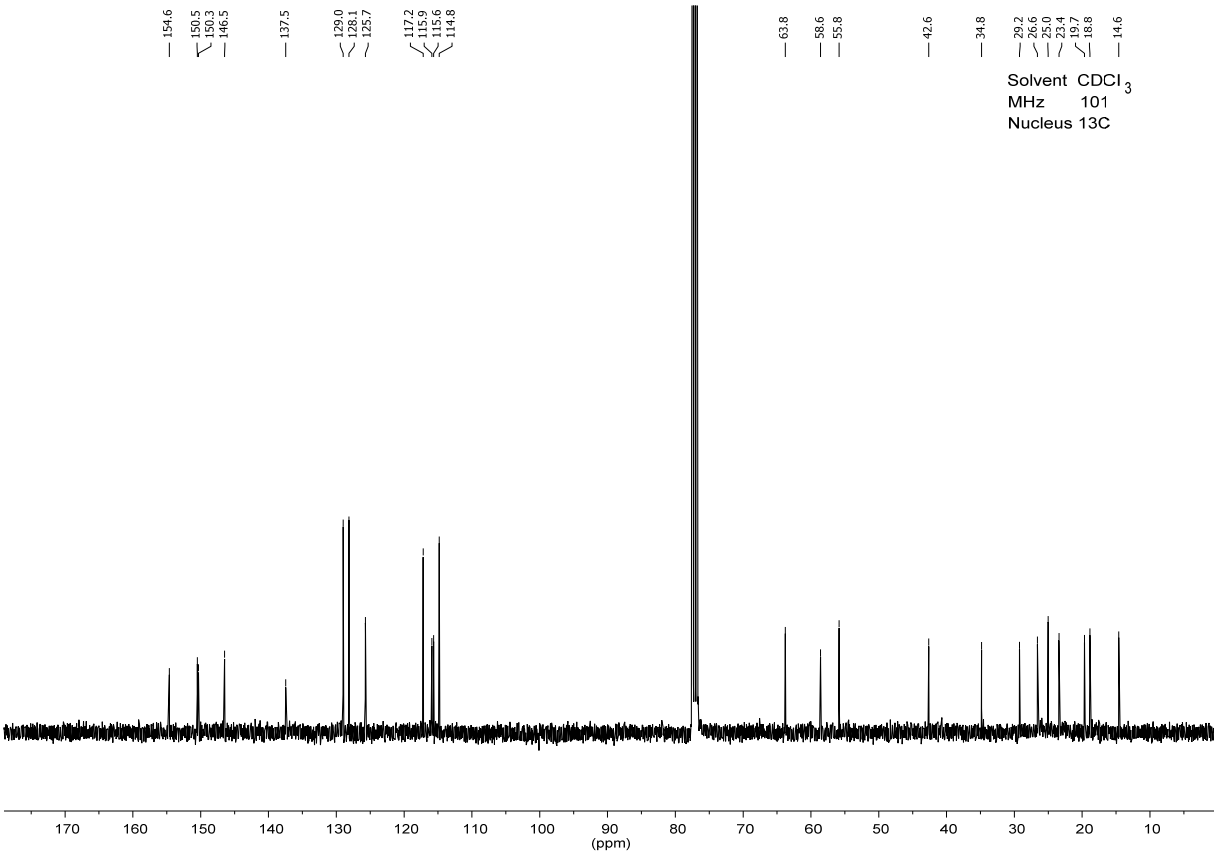
**(*Z*)-5**

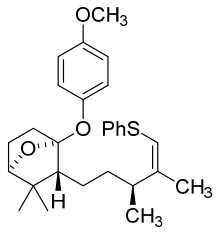

Solvent CDCl3
MHz 400
Nucleus 1H
4.94
1.06
1.96
2.02
1.00
1.00
2.87
1.01
0.98
1.02
1.06
1.04
1.07
2.89
1.99
1.97
3.05
2.99
2.90
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


154.6
150.4
150.4
146.9
137.7
129.0
128.1
125.7
117.2
115.9
115.8
114.8
63.8
58.6
55.8
35.8
34.6
29.2
26.6
25.0
23.3
18.8
18.8
18.2
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OCH3
H
O
O
SPh
CH3
CH3
Solvent CDCl3
MHz 400
Nucleus 1H
6.00
1.00
3.82
0.86
1.02
2.89
1.00
1.84
1.08
1.95
2.72
2.03
1.09
1.26
2.79
2.88
2.71
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

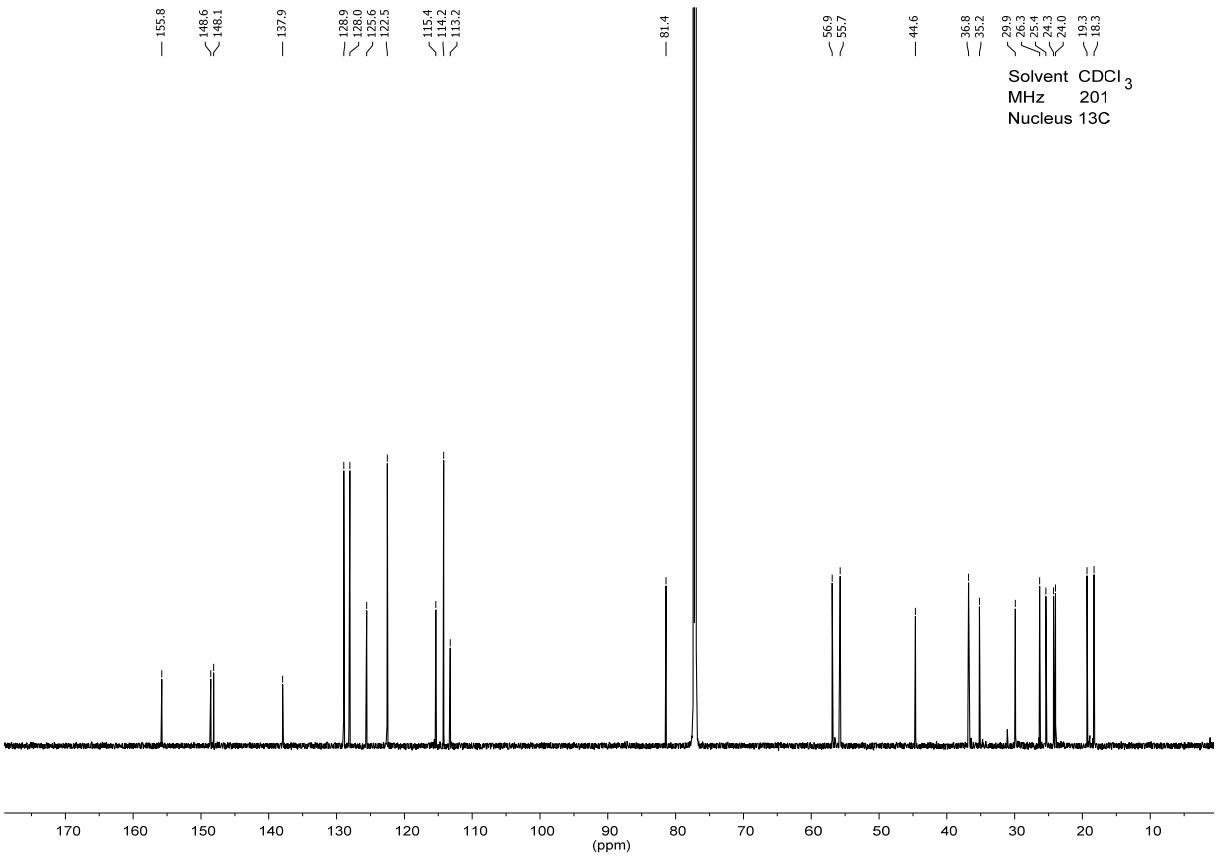
(*E*)-5

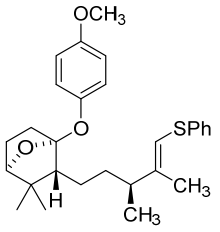

154.6
150.5
150.3
146.5
137.5
129.0
128.1
125.7
117.2
115.9
115.6
114.8
63.8
58.6
55.8
42.6
34.8
29.2
26.6
25.0
23.4
19.7
18.8
14.6
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


OCH3
O PhS
O
H
CH3
CH3

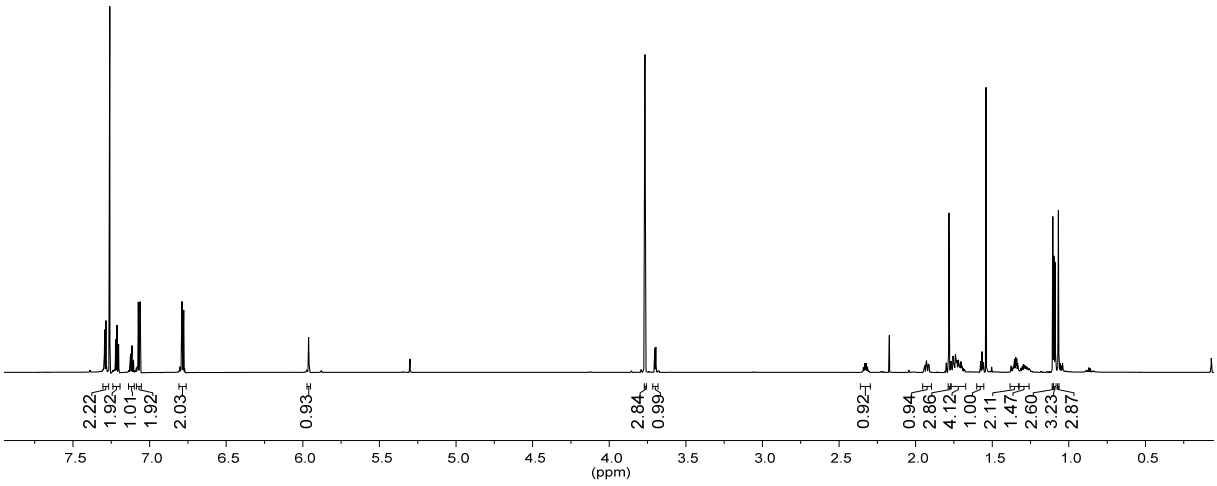
**(*Z*)-14**

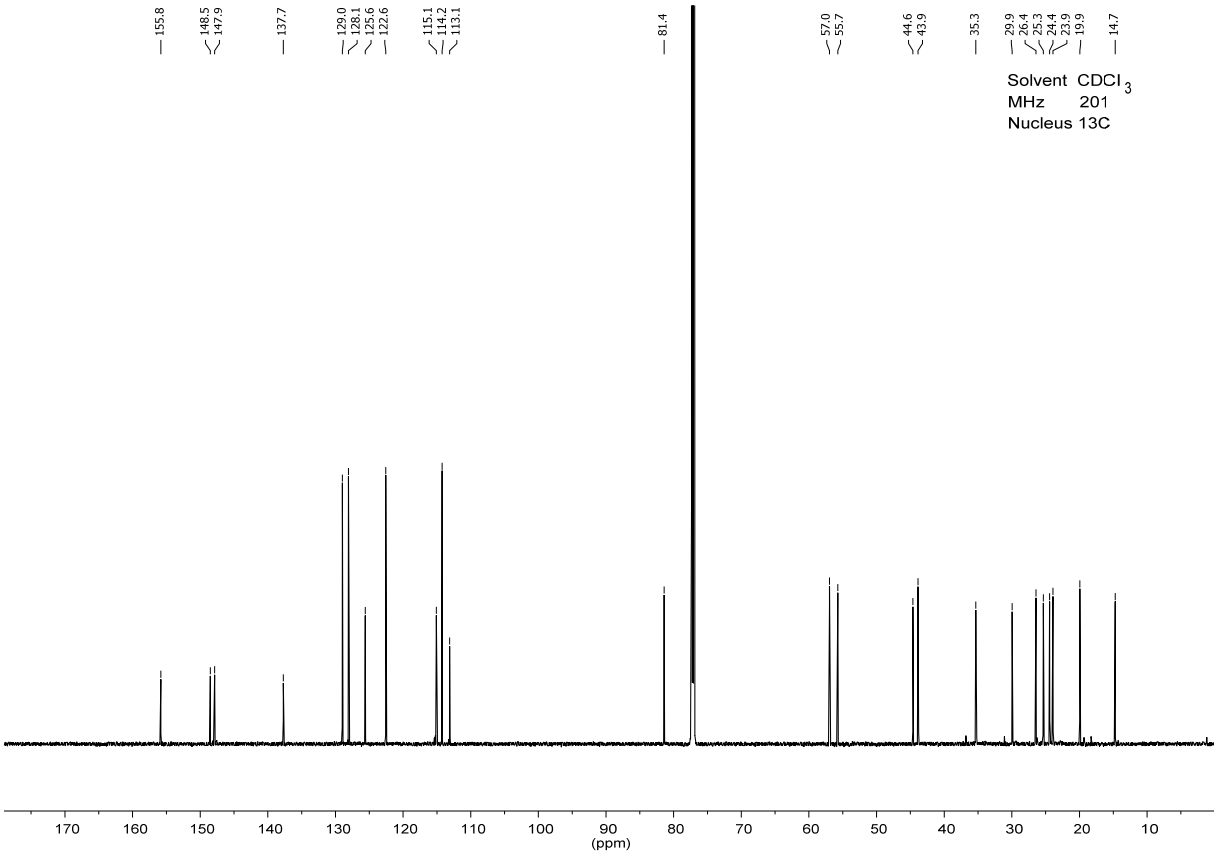

Solvent CDCl3
MHz 800
Nucleus 1H
2.13
1.89
1.00
1.78
1.97
0.91
3.08
0.98
0.93
0.96
2.98
1.84
2.26
1.12
1.00
1.11
1.46
2.70
5.93
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

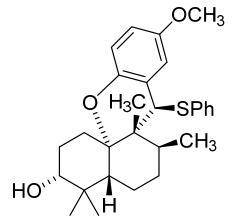

155.8
148.6
148.1
137.9
128.9
128.0
125.6
122.5
115.4
114.2
113.2
81.4
56.9
55.7
44.6
36.8
35.2
29.9
26.3
25.4
24.3
24.0
19.3
18.3
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OCH3
O
SPh
O
CH3
H
CH3

**(*E*)-14**

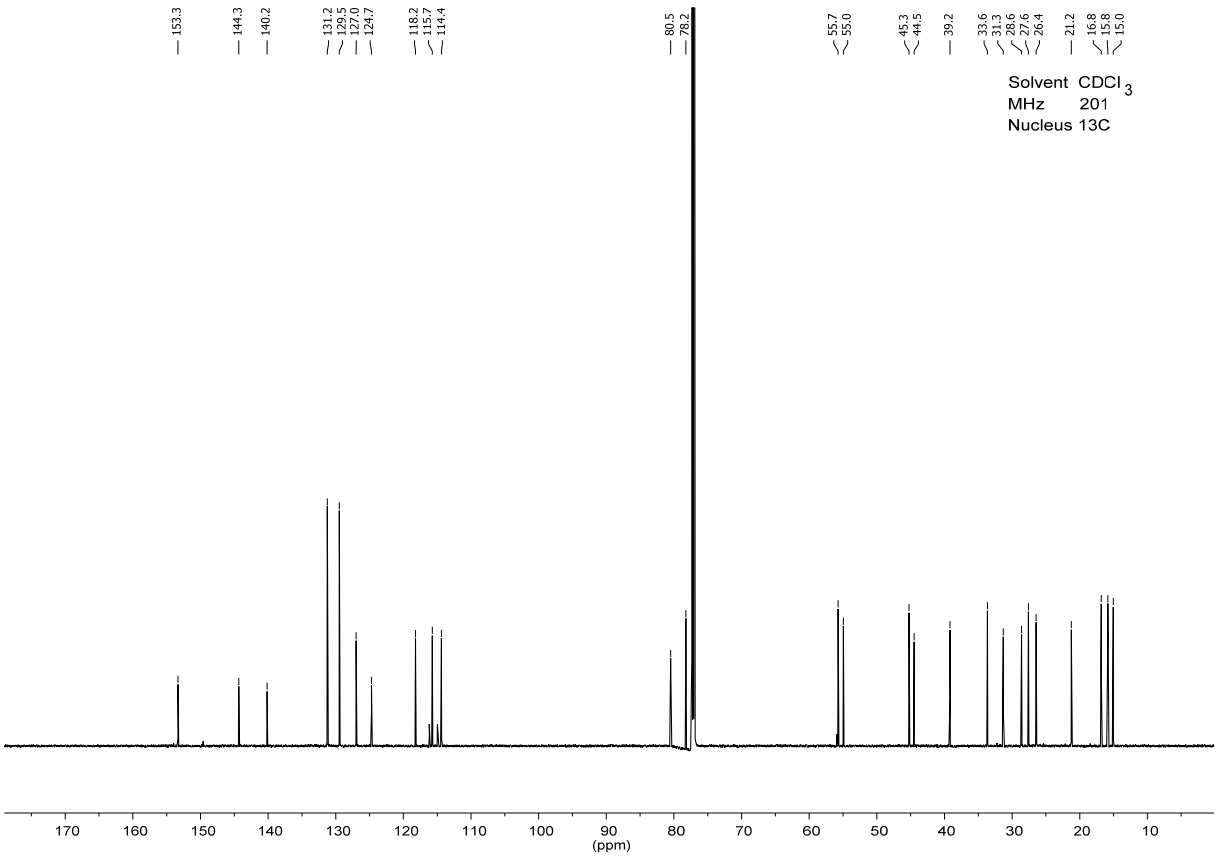

Solvent CDCl3
MHz 800
Nucleus 1H
2.22
1.92
1.01
1.92
2.03
0.93
2.84
0.99
0.92
0.94
2.86
4.12
1.00
2.11
1.47
2.60
3.23
2.87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

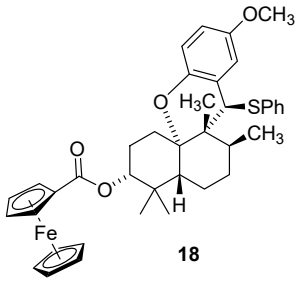

155.8
148.5
147.9
137.7
129.0
128.1
125.6
122.6
115.1
114.2
113.1
81.4
57.0
55.7
44.6
43.9
35.3
29.9
26.4
25.3
24.4
23.9
19.9
14.7
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


OCH3
O
H3C
SPh
CH3
HO
H

**17**

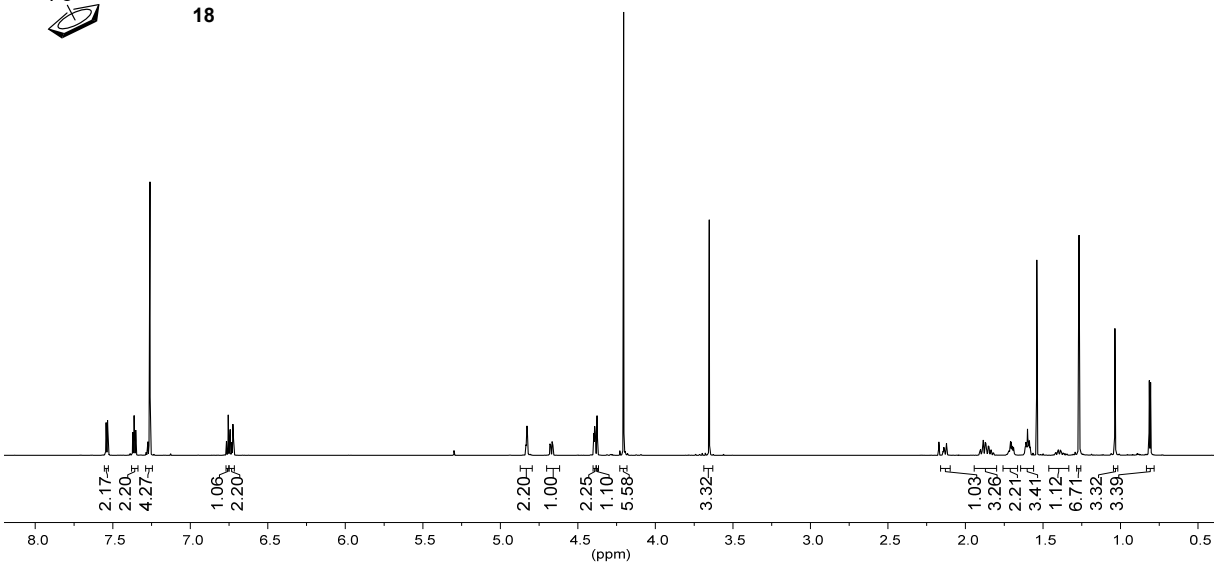

Solvent CDCl3
MHz 800
Nucleus 1H
1.90
1.94
2.38
3.00
0.94
3.03
0.91
0.89
1.00
1.91
1.18
3.03
1.02
1.89
3.03
3.05
3.11
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

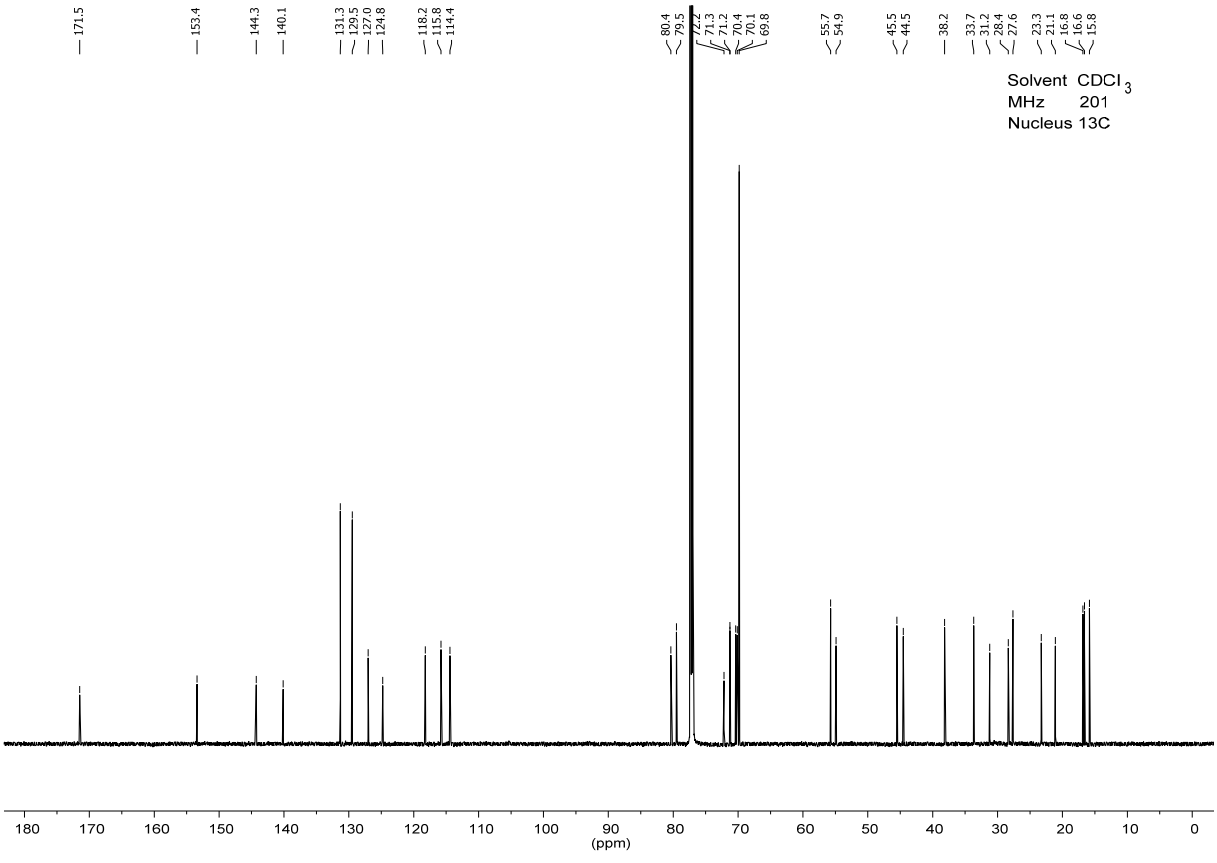

153.3
144.3
140.2
131.2
129.5
127.0
124.7
118.2
115.7
114.4
80.5
78.2
55.7
55.0
45.3
44.5
39.2
33.6
31.3
28.6
27.6
26.4
21.2
16.8
15.8
15.0
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

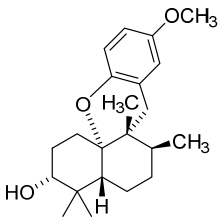



**18**

Solvent CDCl3
MHz 800
Nucleus 1H

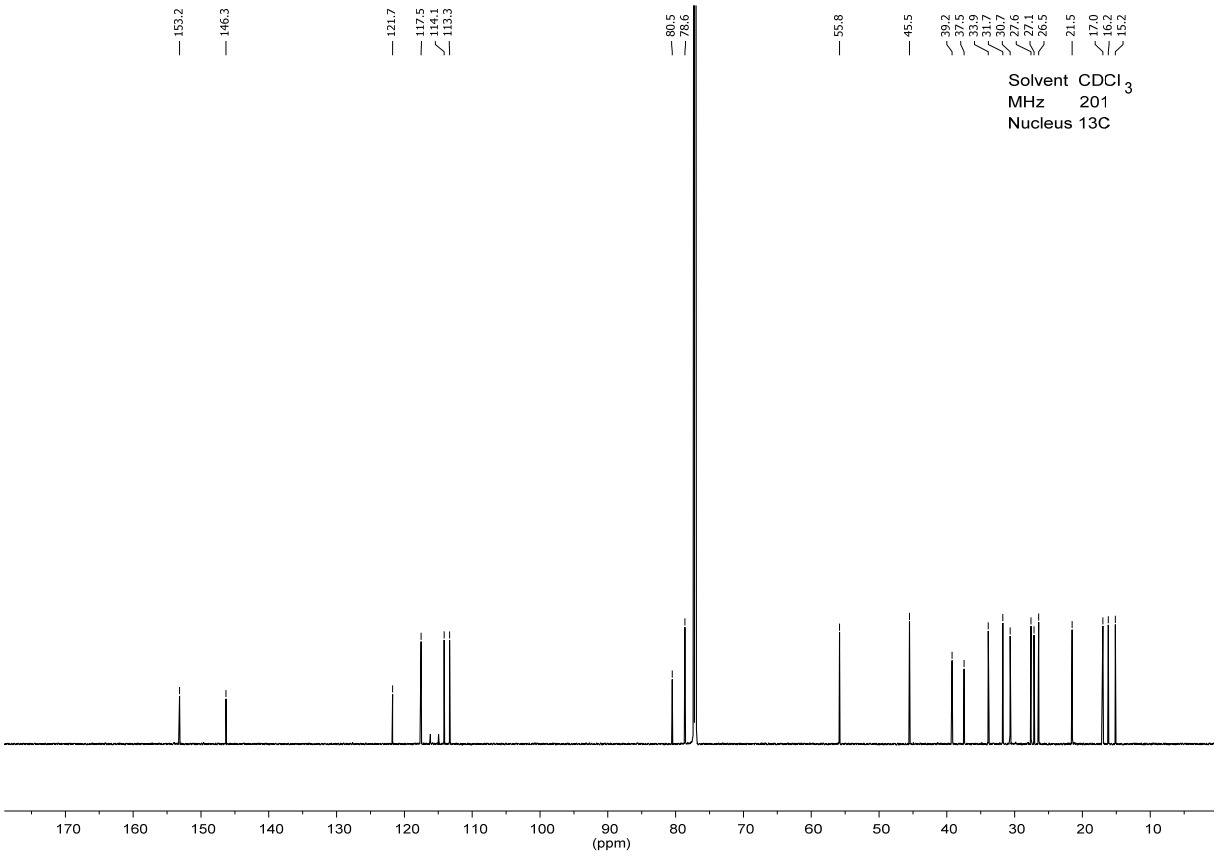


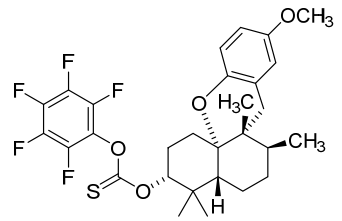




OCH3
O
H3C
CH3
HO
H

**S31**

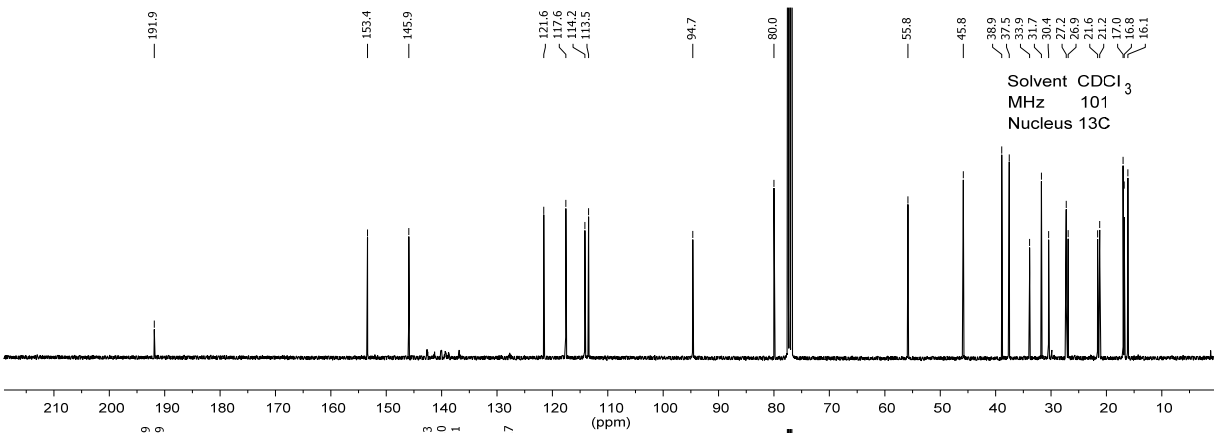

Solvent CDCl3
MHz 800
Nucleus 1H
1.00
0.99
1.01
3.16
0.99
0.99
0.98
2.12
1.00
1.09
2.50
3.31
1.14
0.76
1.28
3.19
3.02
3.16
3.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

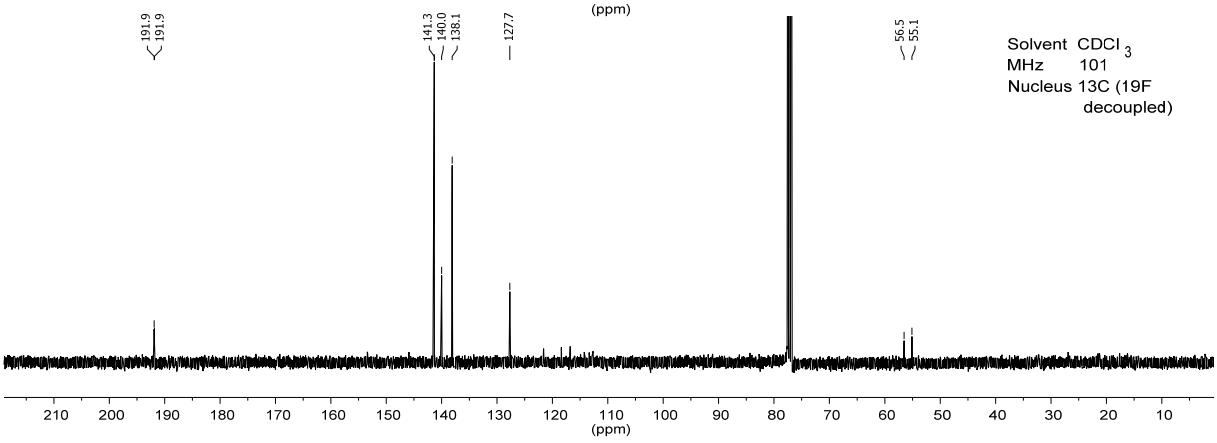

153.2
146.3
121.7
117.5
114.1
113.3
80.5
78.6
55.8
45.5
39.2
37.5
33.9
31.7
30.7
27.6
27.1
26.5
21.5
17.0
16.2
15.2
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

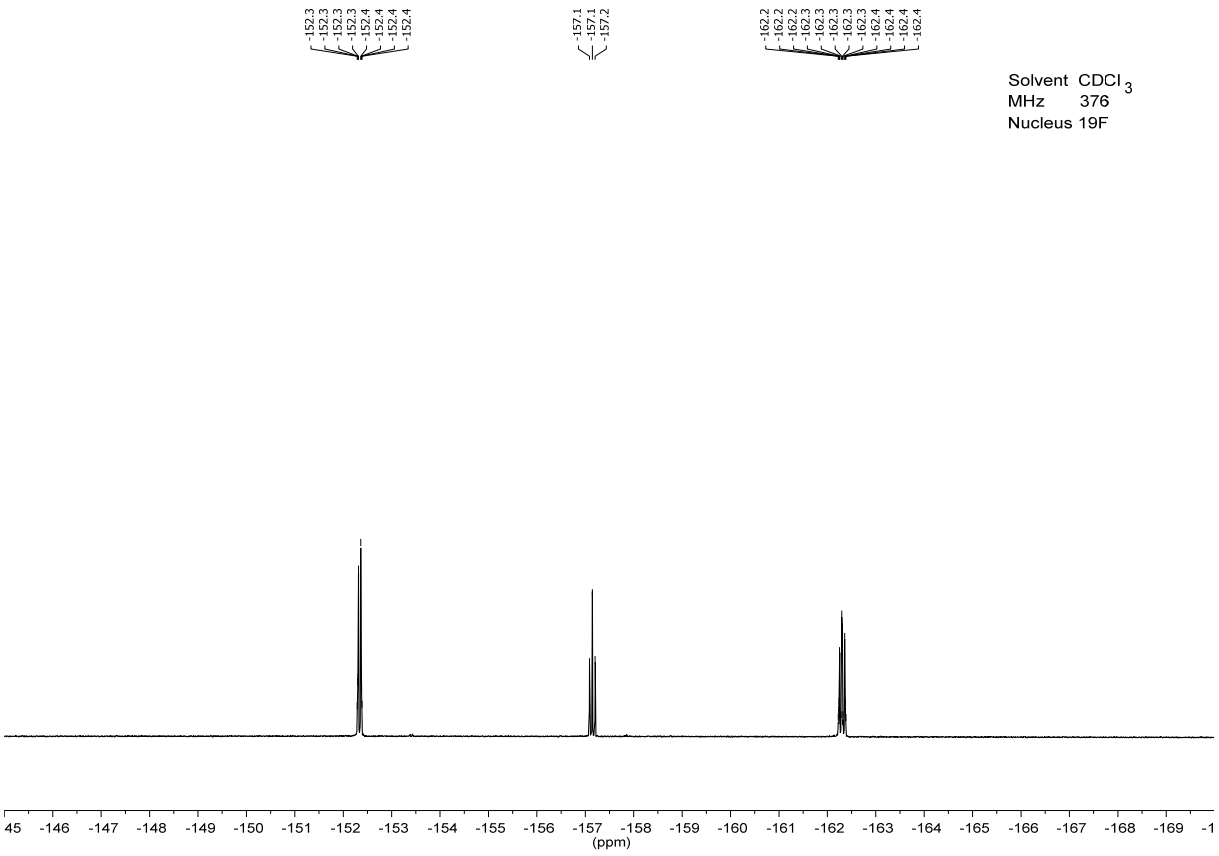

OCH3
F
F
F
F
O
H3C
CH3
O
S
O
H

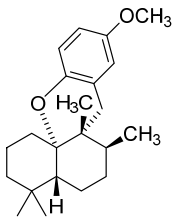
**S32**


Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.03
1.00
1.03
2.74
1.07
1.13
1.06
3.30
1.16
5.34
1.44
2.98
2.74
2.67
2.77
(ppm)

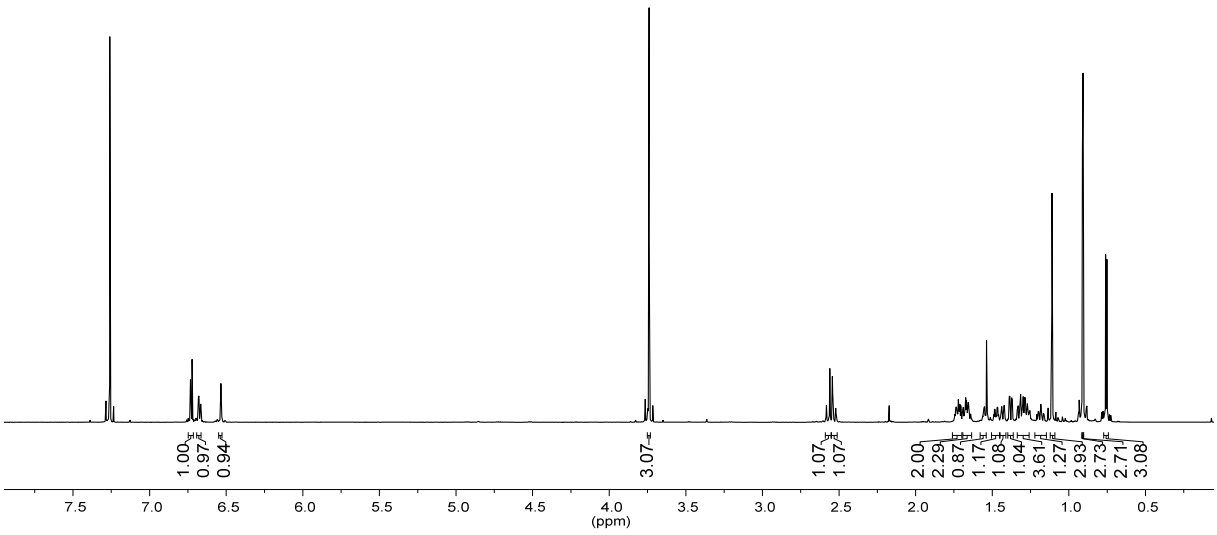

191.9
153.4
145.9
121.6
117.6
114.2
113.5
94.7
80.0
55.8
45.8
38.9
37.5
33.9
31.7
30.4
27.2
26.9
21.6
21.2
17.0
16.8
16.1
Solvent CDCl3
MHz 101
Nucleus 13C
(ppm)

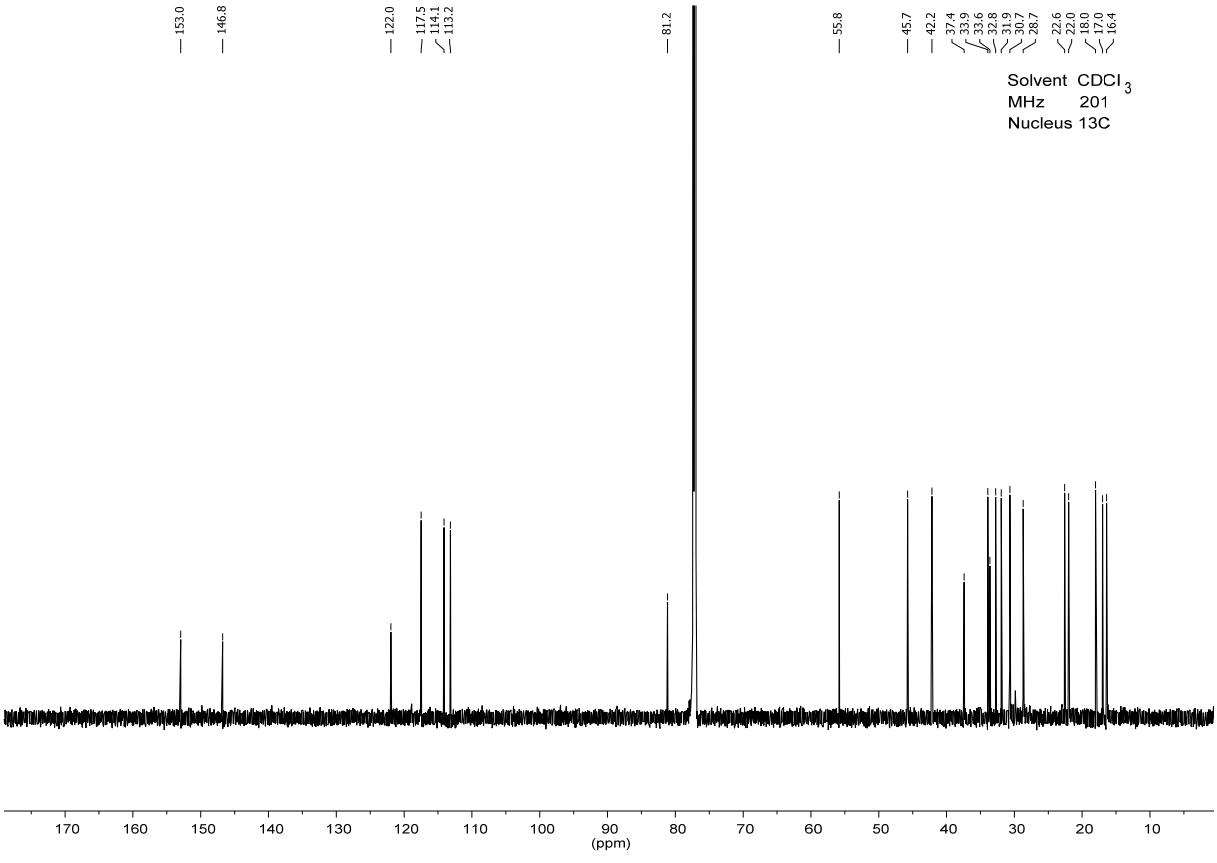

191.9
191.9
141.3
140.0
138.1
127.7
56.5
55.1
Solvent CDCl3
MHz 101
Nucleus 13C (19F
decoupled)
(ppm)

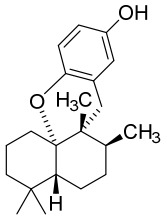

-152.3
-152.3
-152.3
-152.3
-152.4
-152.4
-152.4
-152.4
-157.1
-157.1
-157.2
-162.2
-162.2
-162.2
-162.3
-162.3
-162.3
-162.3
-162.4
-162.4
-162.4
-162.4
Solvent CDCl3
MHz 376
Nucleus 19F
45 -146 -147 -148 -149 -150 -151 -152 -153 -154 -155 -156 -157 -158 -159 -160 -161 -162 -163 -164 -165 -166 -167 -168 -169 -1
(ppm)


OCH3
O
H3C
CH3
H

**S33**

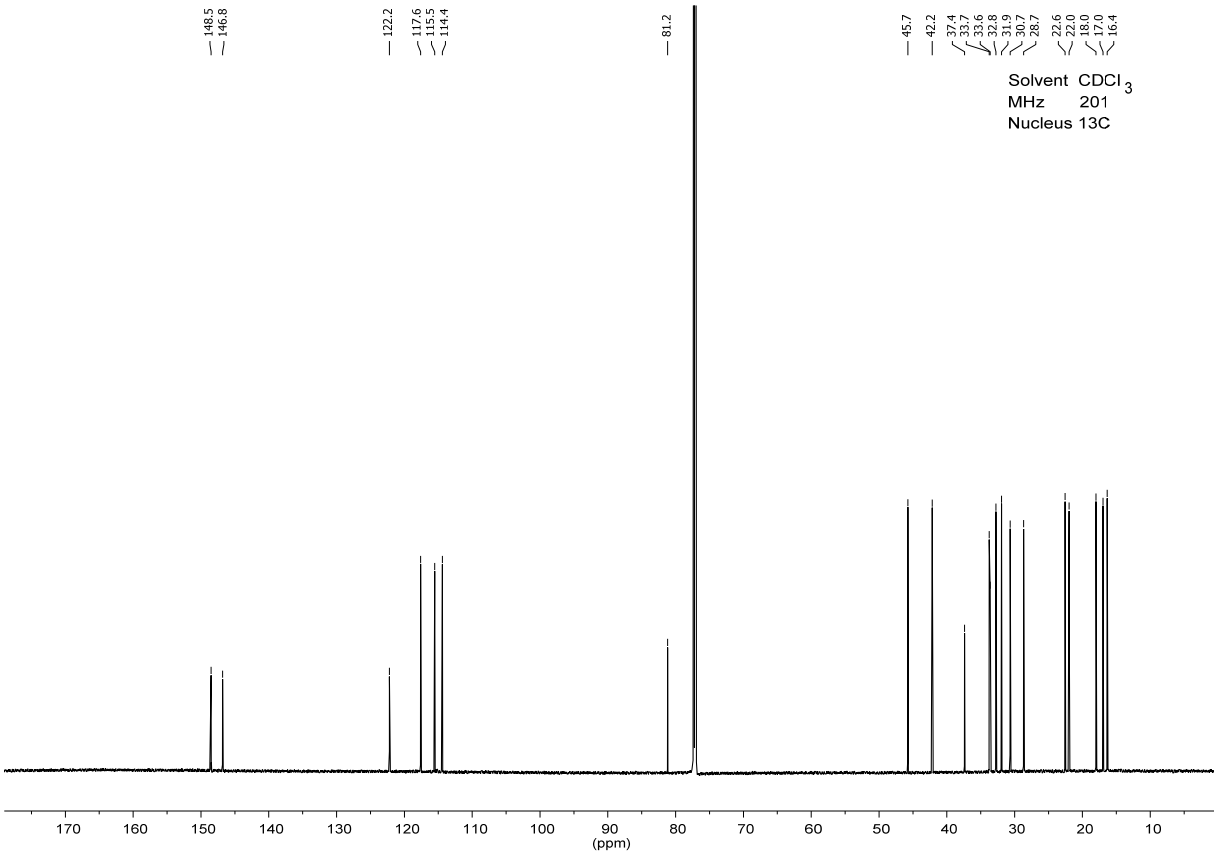

Solvent CDCl3
MHz 800
Nucleus 1H
1.00
0.97
0.94
3.07
1.07
1.07
2.00
2.29
0.87
1.17
1.08
1.04
3.61
1.27
2.93
2.73
2.71
3.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

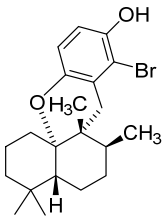

153.0
146.8
122.0
117.5
114.1
113.2
81.2
55.8
45.7
42.2
37.4
33.9
33.6
32.8
31.9
30.7
28.7
22.6
22.0
18.0
17.0
16.4
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


OH
O
H3C
CH3
H

**19**

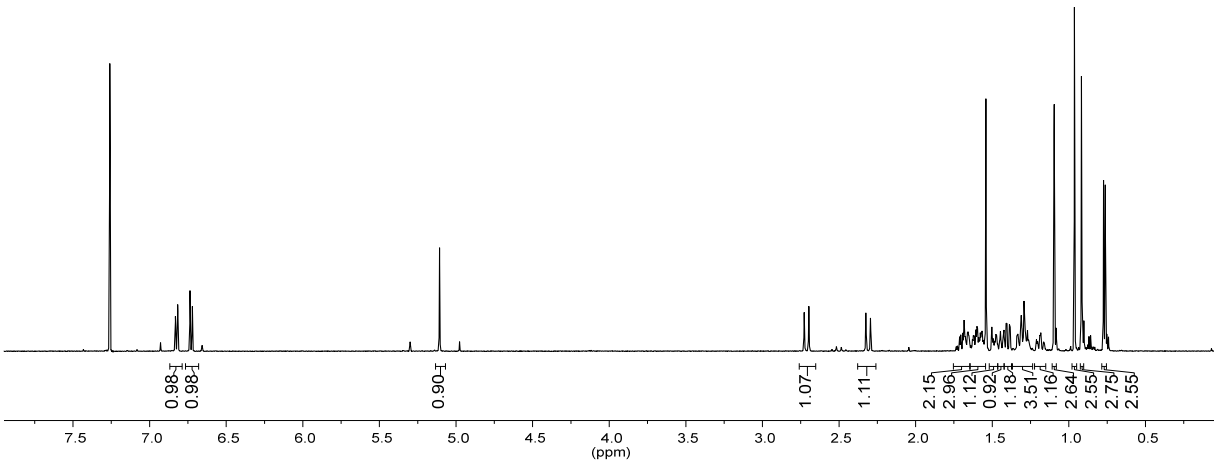

Solvent CDCl3
MHz 800
Nucleus 1H
1.00
1.00
0.92
0.99
1.10
1.00
2.02
2.30
1.06
1.07
1.08
1.08
3.30
1.08
3.13
3.22
3.09
3.10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

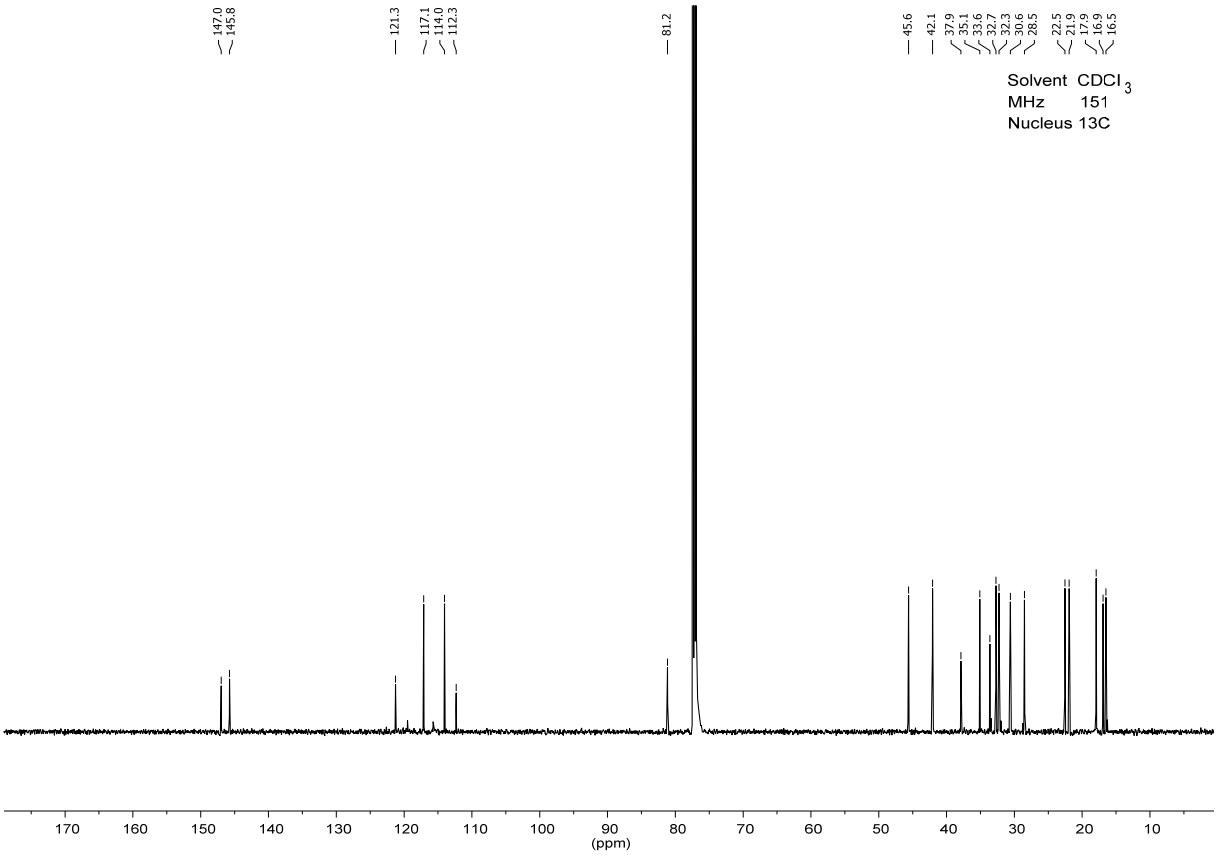

148.5
146.8
122.2
117.6
115.5
114.4
81.2
45.7
42.2
37.4
33.7
33.6
32.8
31.9
30.7
28.7
22.6
22.0
18.0
17.0
16.4
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

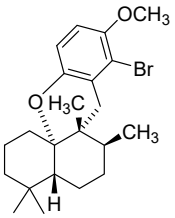



**S34**

Solvent CDCl3
MHz 599
Nucleus 1H

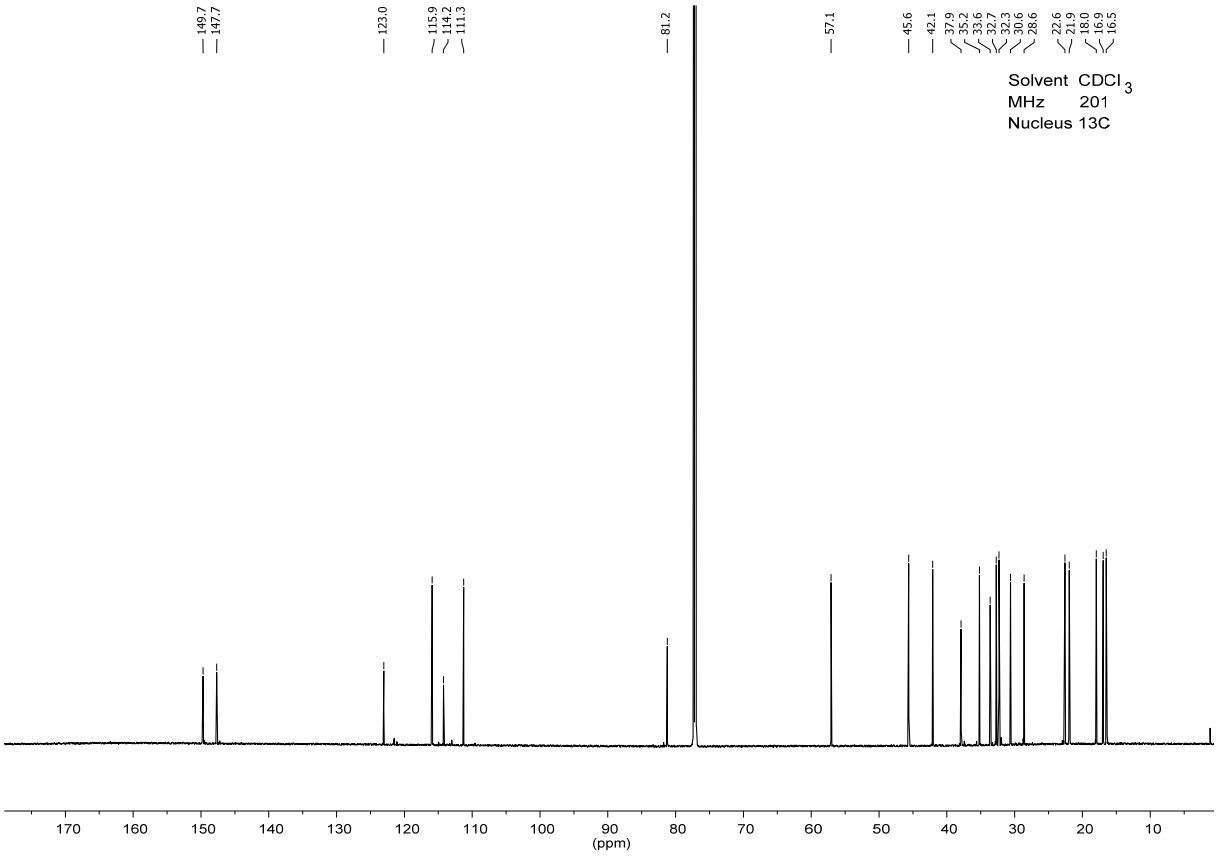


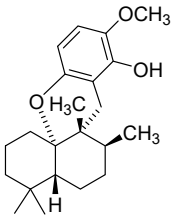




OCH3
Br
O H3C
CH3
H

**20**

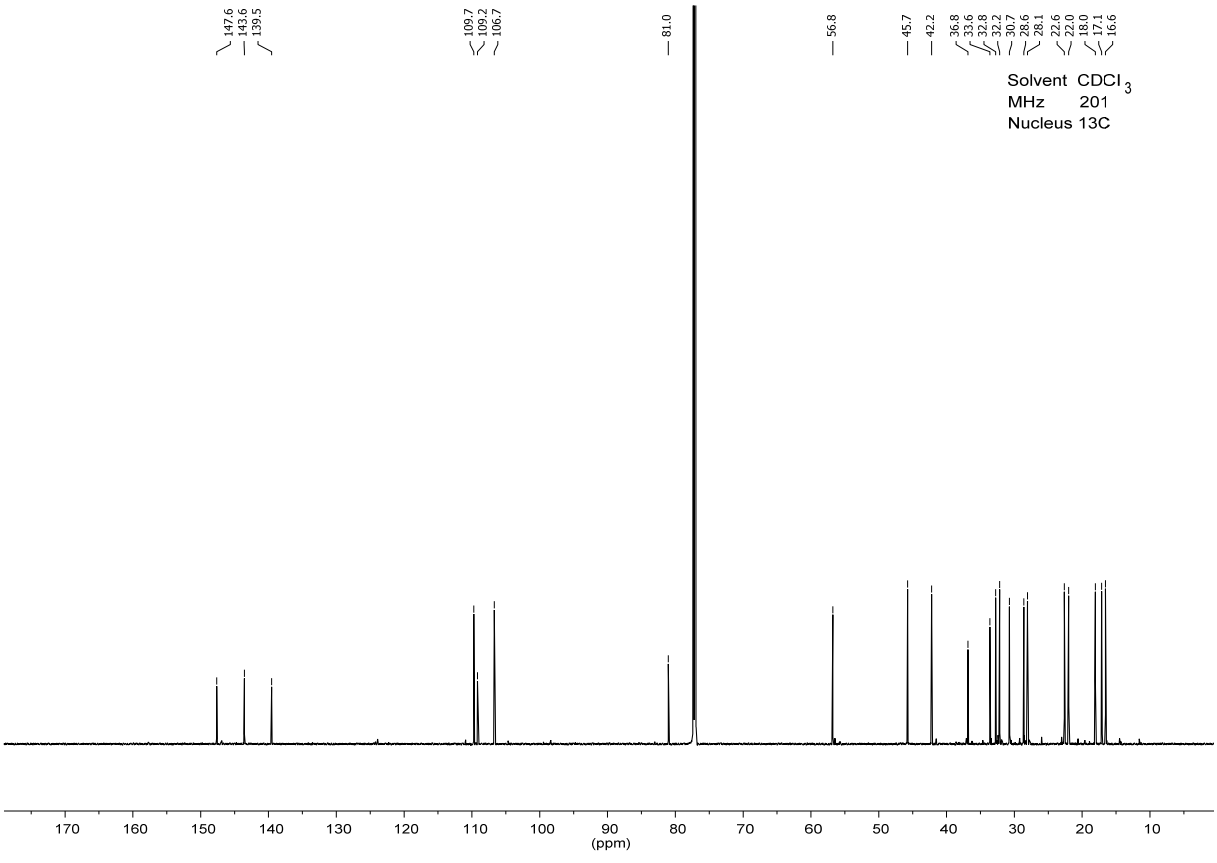

Solvent CDCl 3
MHz 800
Nucleus 1H
1.00
0.95
3.04
0.93
0.93
1.97
3.09
1.05
1.02
1.02
3.36
1.04
3.00
3.02
3.07
3.10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

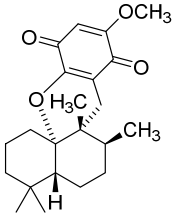

149.7
147.7
123.0
115.9
114.2
111.3
81.2
57.1
45.6
42.1
37.9
35.2
33.6
32.7
32.3
30.6
28.6
22.6
21.9
18.0
16.9
16.5
Solvent CDCl 3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OCH3
OH
O
H3C
CH3
H

**S35**

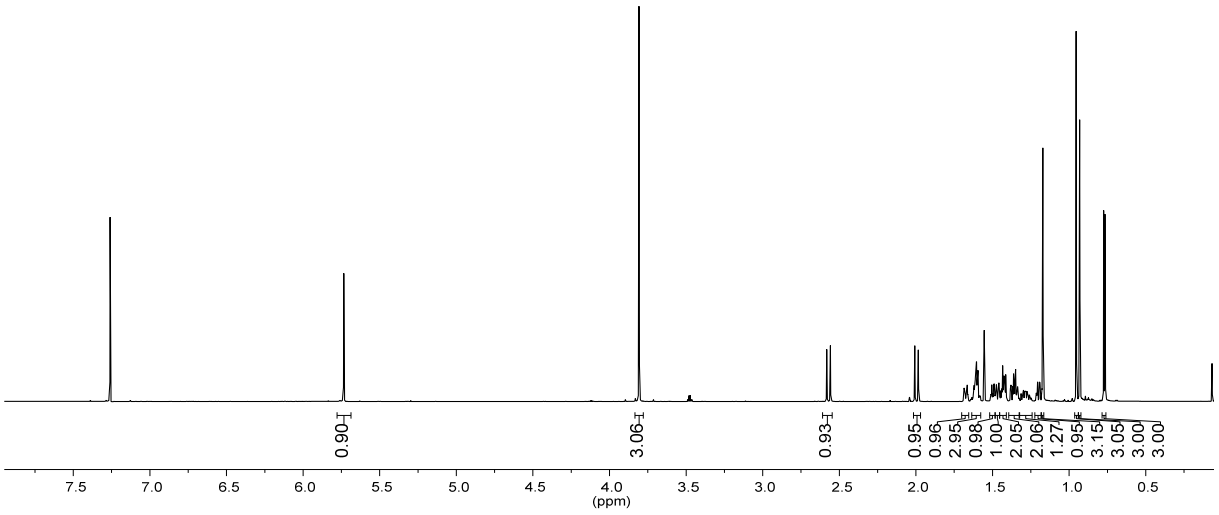

Solvent CDCl3
MHz 800
Nucleus 1H
0.83
0.81
0.76
2.87
0.75
0.79
0.91
1.00
1.84
1.99
1.04
1.02
0.99
3.45
1.06
2.85
3.00
2.87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

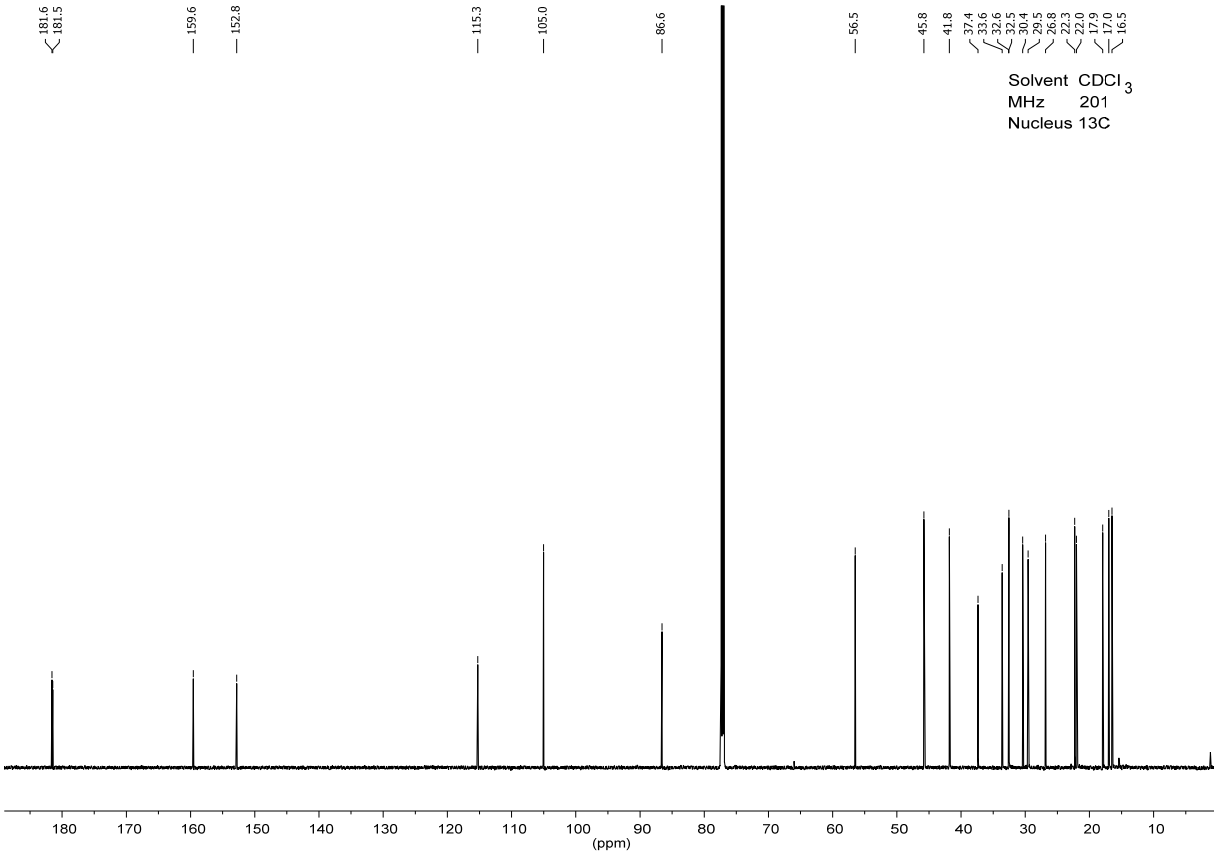

147.6
143.6
139.5
109.7
109.2
106.7
81.0
56.8
45.7
42.2
36.8
33.6
32.8
32.2
30.7
28.6
28.1
22.6
22.0
18.0
17.1
16.6
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



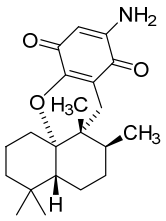

**21**

Solvent CDCl 3
MHz 800
Nucleus 1H



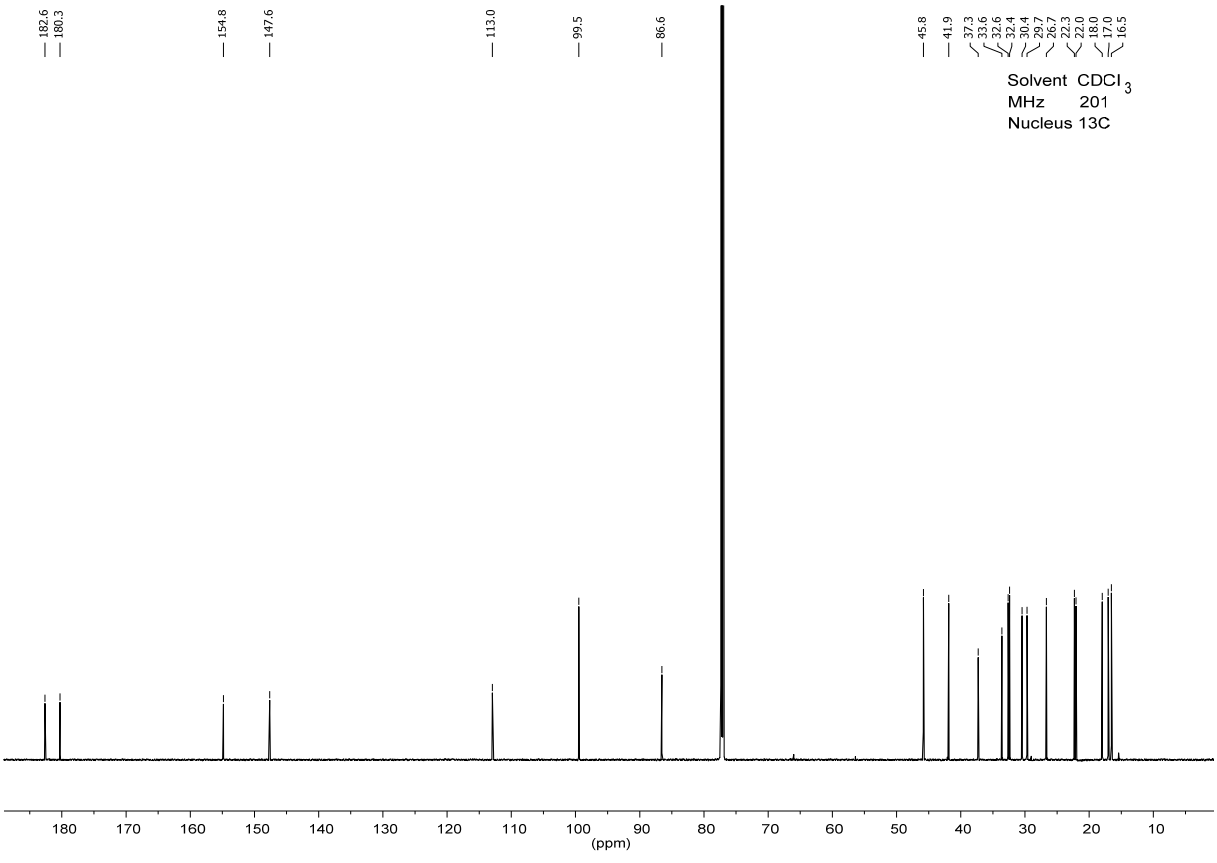




Solvent CDCl 3
MHz 201
Nucleus 13C


NH2
O
O
O
H3C
CH3
H

**(–)-1**


Solvent CDCl3
MHz 800
Nucleus 1H
1.00
1.83
1.06
1.09
1.19
3.56
3.52
1.17
2.29
1.19
4.74
3.53
3.32
3.32
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


182.6
180.3
154.8
147.6
113.0
99.5
86.6
45.8
41.9
37.3
33.6
32.6
32.4
30.4
29.7
26.7
22.3
22.0
18.0
17.0
16.5
Solvent CDCl3
MHz 201
Nucleus 13C
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

## 3.3. Supporting Information for Chapter 1.4.3.

# Evolution of a Polyene Cyclization Cascade for the Total Synthesis of (–)-Cyclosmenospongine

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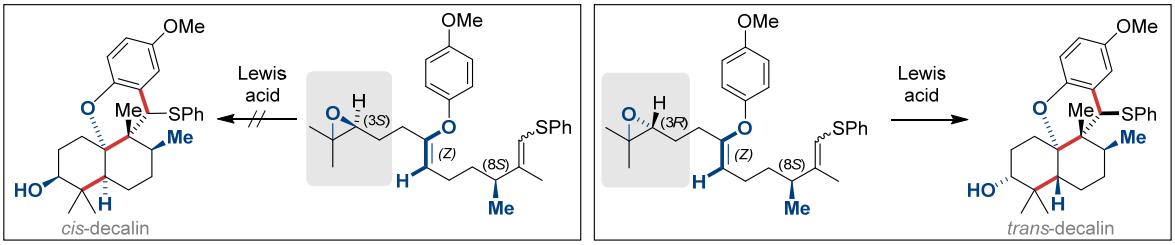
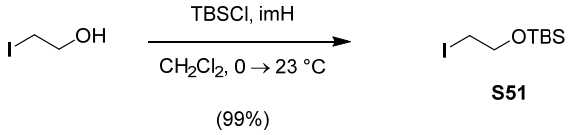
K. Speck, T. Magauer, *Chem. Eur. J.* **2016**, *DOI: 10.1002/chem.201605029.*





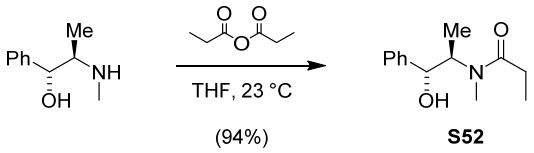
## 3.3.1. Experimental Procedures

### 3.3.1.1. Synthesis of Iodides




**Iodide S51**

To a solution of 2-iodoethanol (25.0 g, 145 mmol, 1 equiv) in dichloromethane (360 mL) and imidazole (19.8 g, 291 mmol, 2.00 equiv) was added *t*-butyldimethylsilyl chloride (21.9 g, 145 mmol, 1.00 equiv) at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the reaction mixture was diluted with dichloromethane (200 mL) and the organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 200 mL) and with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give iodide **S51** (41.4 g, 99%) as a colorless oil. The crude product was directly used without further purification. Characterization data obtained for **S51** were in full agreement with values previously reported.[176]

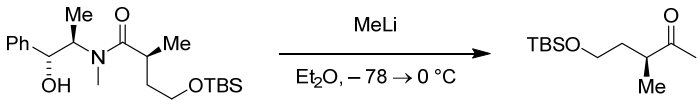



**(–)-(1*R*,2*R*)-pseudoephedrine propionylamide S52**

Propionic anhydride (21.2 mL, 165 mmol, 1.07 equiv) was added dropwise to a solution of (–)-(1*R*,2*R*)-pseudoepedrine (25.5 g, 154 mmol, 1 equiv) in tetrahydrofuran (300 mL) at 23 °C. After 30 min, excess propionic anhydride was quenched by the addition of saturated aqueous sodium bicarbonate solution (150 mL). The resulting biphasic mixture was partitioned between water (200 mL) and ethyl acetate (250 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was recrystallized from toluene to afford amide **S52** (32.1 g, 94%) as a white solid. The obtained characterization data were in full agreement with those reported in literature.[177]


**Amide S53**

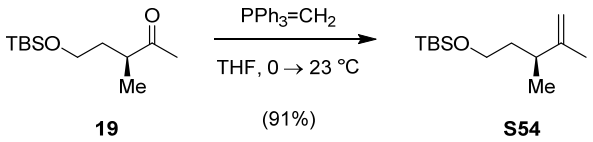
*N*,*N*-Diisopropylamime (23.0 mL, 163 mmol, 2.25 equiv) was added dropwise to a suspension of lithium chloride (18.4 g, 434 mmol, 6.00 equiv) in tetrahydrofuran (72 mL) at 23 °C and the resulting suspension was cooled to –78 °C. A solution of *n*-butyllithium (2.52 M in hexanes, 60.3 mL, 152 mmol, 2.10 equiv) was added via syringe. The reaction mixture was briefly warmed to 0 °C for 5 min, then cooled to –78 °C. An ice-cooled solution of amide **S52** (16.0 g, 72.3 mmol, 1 equiv) in tetrahydrofuran (180 mL) was added by cannula onto the inner wall of the flask. The transfer was quantitated with tetrahydrofuran (15 mL). The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min and at 23 °C for 5 min. Then the reaction mixture was cooled to 0 °C, whereupon iodide **S51** (41.4 g, 145 mmol, 2.00 equiv) was added. Stirring was continued at 23 °C for 3.5 h. Saturated aqueous ammonium chloride solution (20 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (200 mL) and aqueous hydrochloric acid solution (1 M, 150 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (40% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to give amide **S53** (22.8 g, 83%) as a viscous yellow oil. Characterization data obtained for **S53** were in full agreement with previously reported values.[177]




**S53** (83%) **19**

**Ketone 19**

Amide **S53** was dried by azeotropic distillation (benzene, 2 × 40 mL) prior to use. To a solution of **S53** (22.8 g, 60.1 mmol, 1 equiv) in diethyl ether (400 mL) was added a solution of methyllithium (1.60 M in diethyl ether, 97.6 mL, 156 mmol, 2.60 equiv) via syringe at –78 °C. The reaction mixture was allowed to warm to 0 °C. After 45 min, excess methyllithium was quenched at 0 °C by the addition of *N*,*N*-diisopropylamine (8.49 mL, 60.1 mmol, 1.00 equiv). A solution of acetic acid in diethyl ether (20% v/v, 75 mL) was added and the reaction mixture (pH = 6 to 7) was partitioned between diethyl ether (100 mL) and water (200 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 10% ethyl acetate in hexanes) to provide ketone **19** (11.9 g, 83%) as a colorless oil. The obtained characterization data were in full agreement with those reported in literature.[177]




**19** **S54**

**Alkene S54**

To a suspension of methyltriphenylphosphonium bromide (29.5 g, 82.5 mmol, 2.00 equiv) in tetrahydrofuran (160 mL) was added potassium *t*-butoxide (6.94 g, 61.8 mmol, 1.50 equiv) at 0 °C. The yellow suspension was stirred for 30 min at 0 °C and then 10 min at 23 °C. The suspension was cooled to 0 °C and a solution of ketone **19** (9.50 g, 41.2 mmol, 1 equiv) in tetrahydrofuran (80 mL) was added dropwise. Stirring was continued for 10 min at 0 °C, then the reaction mixture was allowed to warm to 23 °C. After 1 h, the mixture was diluted with a mixture of hexane and diethyl ether (1:1, 50 mL) and saturated aqueous ammonium chloride solution (20 mL) was added. The aqueous layer was separated and extracted with a mixture of hexane and diethyl ether (1:1, 3 × 10 mL). The organic layers were combined and dried over sodium sulfate. The dried solution was filtered through a plug of silica gel and the filtrate was concentrated. The residue was suspended in hexane and the mixture was filtered through a pad of Celite (the filtration was repeated twice). The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel (hexanes) to provide alkene **S54** (8.60 g, 91%) as a colorless oil.

**TLC** (hexane), $R_f$ = 0.50 (CAM).

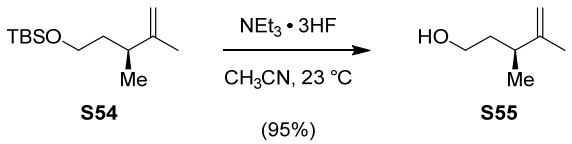
**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 4.69–4.67 (m, 2H), 3.58–3.54 (m, 2H), 2.35–2.22 (m, 1H), 1.66 (t, *J* = 1.1 Hz, 3H), 1.66–1.58 (m, 1H), 1.52–1.45 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 150.0, 109.5, 61.7, 38.1, 37.7, 26.1, 19.9, 19.2, 18.5, –5.1, –5.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2928 (*w*), 2857 (*w*), 1472 (*w*), 1255 (*m*), 1100 (*m*), 884 (*m*), 833 (*s*), 773 (*s*).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = + 0.60° (*c* = 1.00, $CHCl_3$).

**HRMS** (EI) calc. for $C_{13}H_{27}O^{28}Si$ $[M–H]^+$: 227.1837 found: 227.1830.




**S54** **S55**

**Alcohol S55**

To a solution of the alkene **S54** (8.20 g, 35.9 mmol, 1 equiv) in acetonitrile (40 mL) was added triethylamine trihydrofluoride (10.3 mL, 62.9 mmol, 1.75 equiv) at 23 °C to give a colorless solution. After 18 h, the reaction mixture was diluted with diethyl ether (200 mL) and saturated aqueous sodium

bicarbonate solution (150 mL) and saturated aqueous sodium chloride solution (150 mL) were added. The aqueous layer was separated and extracted with diethyl ether (8 × 80 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (80 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated at 23 °C (300 mbar). The residue was purified by flash-column chromatography (20% diethyl ether in pentane initially, grading to 50% diethyl ether in pentane) to yield alcohol **S55** (3.90 g, 95%) as a colorless oil.

**TLC** (40% ethyl acetate in hexane), $R_f$ = 0.63 (CAM).

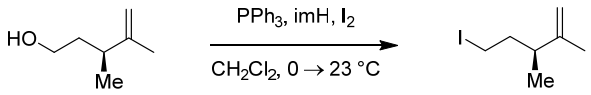
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 4.77–4.67 (m, 2H), 3.62 (t, *J* = 6.7 Hz, 2H), 2.43–2.25 (m, 1H), 1.72–1.63 (m, 4H), 1.67–1.50 (m, 1H), 1.37 (s, 1H), 1.04 (d, *J* = 7.0 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 150.1, 110.0, 61.7, 38.3, 37.7, 19.9, 18.9.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3327 (*br w*), 2961 (*m*), 2932 (*m*), 1645 (*m*), 1455 (*m*), 1375 (*m*), 1050(*s*), 1000 (*s*), 886 (*s*).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 1.90° (*c* = 1.00, $CHCl_3$).

**HRMS** (EI) calc. for $C_7H_{14}O$ $[M]^+$: 114.1039 found: 114.1043.




**S55** (81%) **15**

**Iodide 15**

To a solution of S55 (1.00 g, 8.76 mmol, 1 equiv), imidazole (0.76 g, 10.5 mmol, 1.20 equiv) and triphenylphosphine (2.76 g, 10.5 mmol, 1.20 equiv) in dichloromethane (40 mL) was added iodine (2.67 g, 10.5 mmol, 1.20 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 30 min, the mixture was diluted with pentane (200 mL) and the organic layer was washed with water (2 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (pentane) to give **15** (1.58 g, 81%) as a colorless oil.

**TLC** (hexane), $R_f$ = 0.76 (CAM).

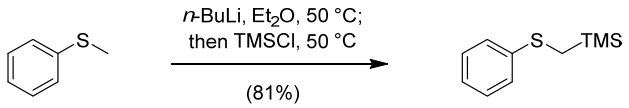
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 4.76 (dq, *J* = 1.1, 0.3 Hz, 2H), 3.24–3.00 (m, 2H), 2.41–2.22 (m, 1H), 2.00–1.71 (m, 2H), 1.66 (t, *J* = 1.1 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 148.0, 111.0, 42.0, 38.7, 19.2, 18.8, 5.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2961 (*m*), 1644 (*m*), 1453 (*m*), 1435 (*m*), 1375 (*m*), 1235 (*m*), 1175 (*s*), 890 (*vs*).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +15.6° (*c* = 1.00, $CHCl_3$).

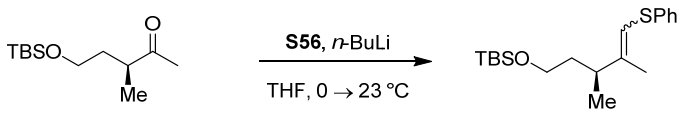
**HRMS** (EI) calc. for $C_7H_{13}{}^{127}I$ $[M]^+$: 224.0056 found: 224.0051.




**S56**

**Trimethyl((phenylthio)methyl)silane S56**

*Peterson reagent **S56** was prepared according to the procedure described by D. J. Ager[178].* To a solution of *n*-butyllithium (2.52 M in hexanes, 34.7 mL, 87.4 mmol, 1.01 equiv) in diethyl ether (30 mL) was added thioanisole (10.2 mL, 86.6 mmol, 1 equiv) at 23 °C, then the mixture was heated to 50 °C. After 16 h, the reaction mixture was allowed to cool to 23 °C, chlorotrimethylsilane (13.3 mL, 104 mmol, 1.20 equiv) was added dropwise to the now white suspension and heated to 50 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C and poured into saturated aqueous ammonium chloride solution (40 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by distillation to give sulfide **S56** (13.7 g, 81%) as a colorless oil (boiling point: 125–128 °C, 20 mbar). The obtained analytical data were in full agreement with those reported in literature.[178]




**19** **S57**

**Vinylsulfide S57**

To a solution of Peterson reagent **S57** (11.9 g, 60.8 mmol, 1.40 equiv) in tetrahydrofuran (100 mL) was added a solution of *n*-butyllithium (2.45 M in hexanes, 23.9 mL, 58.6 mmol, 1.35 equiv) at 0 °C. After 30 min, a solution of ketone **19** (10.0 g, 43.4 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added and stirring was continued at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 5 h, the reaction mixture was diluted with diethyl ether (100 mL) and the organic layer was washed with saturated aqueous ammonium chloride solution (200 mL). The aqueous phase was extracted with diethyl ether (2 × 200 mL) and the combinded organic extracts were washed with saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (hexanes

initially, grading to 2% ethyl acetate in hexanes) to provide vinylsulfide **S57** as an inseparable mixture of double bond isomers (12.6 g, 86%, *E*:*Z* = 2:3) as a colorless oil.

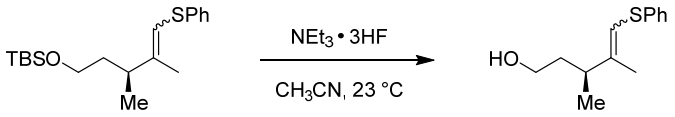
**TLC** (5% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 400 MHz): (*Z*): δ = 7.33–7.24 (m, 4H), 7.20–7.12 (m, 1H), 5.89 (q, *J* = 1.2 Hz, 1H), 3.66–3.49 (m, 2H), 3.19–3.04 (m, 1H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.73–1.49 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); (*E*): δ = 7.32–7.22 (m, 4H), 7.19–7.13 (m, 1H), 5.98–5.95 (m, 1H), 3.68–3.48 (m, 2H), 2.58–2.43 (m, 1H), 1.79 (d, *J* = 1.1 Hz, 3H), 1.74–1.51 (m, 2H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 146.6, 137.7, 129.0, 128.1, 125.7, 115.8, 61.8, 37.8, 33.0, 26.1, 19.0, 18.5, 18.4, –5.1, –5.1; (*E*): δ = 146.5, 137.5, 129.0, 128.1, 125.8, 115.6, 61.4, 39.3, 38.0, 26.1, 19.7, 18.5, 14.7, –5.1, –5.1.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*m*), 2927 (*m*), 2855 (*m*), 1584 (*w*), 1479 (*m*), 1251 (*m*), 1090 (*s*), 833 (*vs*), 773 (*vs*), 736 (*vs*), 689 (*vs*).

**HRMS** (EI) calc. for $C_{19}H_{32}O^{32}S^{28}Si$ $[M]^+$: 336.1938 found: 336.1933.




**S57** **S58**

**Alcohol S58**

To a solution of silylether **S57** (12.5 g, 37.3 mmol, 1 equiv) in acetonitrile (120 mL) was added triethylamine trihydrofluoride (10.6 mL, 65.2 mmol, 1.75 equiv) at 23 °C. After 8 h, the reaction mixture was portioned between diethyl ether (150 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution (200 mL) and saturated aqueous sodium chloride solution (200 mL). The aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) to yield alcohol **S58** (7.87 g, 95%, *E*:*Z* = 1:1.5) as a colorless oil.

An analytical sample was purified by flash-column chromatography (10% ethyl acetate in hexanes) to give pure alcohol **(*Z*)-58** and alcohol **(*E*)-58** as colorless oils. *Note: Since the double bond geometry is inconsequential for the subsequent steps the following transformations were performed using the mixture of double bond isomers.*

**(*Z*)-S58:**

**TLC** (40% ethyl acetate in hexane): $R_f$ = 0.38 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.37–7.26 (m, 4H), 7.24–7.17 (m, 1H), 5.96 (q, *J* = 1.4 Hz, 1H), 3.71–3.54 (m, 2H), 3.29–3.09 (m, 1H), 1.91 (s, 1H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.74–1.59 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 145.4, 136.9, 129.0, 128.4, 126.0, 116.5, 61.2, 37.4, 32.7, 19.0, 18.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3340 (*br w*), 2958 (*w*), 2930 (*w*), 2870 (*w*), 1582 (*m*), 1478 (*m*), 1438(*m*), 1046 (*s*), 1024 (*m*), 809 (*m*), 735 (*vs*), 688 (*vs*).

**HRMS** (EI) calc. for $C_{13}H_{18}O^{32}S$ $[M]^+$: 222.1073 found: 222.1070.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 45.8° (*c* = 1.00, $CH_2Cl_2$).

**(*E*)-S58:**

**TLC** (40% ethyl acetate in hexane): $R_f$ = 0.31 (UV, $KMnO_4$).

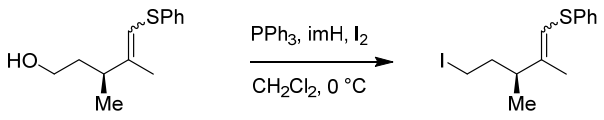
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.34–7.27 (m, 4H), 7.21–7.14 (m, 1H), 6.02–6.00 (m, 1H), 3.64 (td, *J* = 6.8, 1.2 Hz, 2H), 2.59–2.45 (m, 1H), 1.80 (d, *J* = 1.1 Hz, 3H), 1.78–1.68 (m, 1H), 1.68–1.57 (m, 1H), 1.36 (br s, 1H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 145.5, 137.1, 129.1, 128.3, 125.9, 116.3, 61.4, 39.6, 37.7, 19.8, 14.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3324 (*br w*), 2958 (*m*), 2928 (*m*), 2870 (*w*), 1582 (*m*), 1478 (*s*), 1438 (*m*), 1376 (*w*), 1047 (*s*), 816 (*m*), 736 (*vs*), 689 (*s*).

**HRMS** (EI) calc. for $C_{13}H_{18}O^{32}S$ $[M]^+$: 222.1073 found: 222.1072.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = + 5.4° (*c* = 1.00, $CH_2Cl_2$).




**S58** **S59**

**Iodide S59**

To a solution of imidazole (2.87 g, 42.1 mmol, 1.20 equiv) and triphenylphosphine (11.0 g, 42.1 mmol, 1.20 equiv) in dichloromethane (180 mL) was added iodine (10.7 g, 42.1 mmol, 1.20 equiv) at 0 °C. After 15 min, a solution of alcohol **S58** (7.80 g, 35.1 mmol, 1 equiv) in dichloromethane (60 mL) was added to the reaction mixture. After 30 min, the mixture was diluted with hexanes (200 mL) and the organic layer was washed with saturated aqueous sodium thiosulfate solution (200 mL). The aqueous phase was extracted with a mixture of diethyl ether and hexanes (1:1, 3 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography

on silica gel (hexanes initially, grading to 10% ethyl acetate in hexanes) to give iodide **S59** (9.46 g, 81%, *E*:*Z* = 1:1.2) as a pale yellow oil.

*To obtain analytical pure samples, alcohol **(Z)-S58** and alcohol **(E)-S58** were converted to the corresponding analytical pure iodides **(Z)-S59** and **(E)-S59** using the above described procedure.*

**(*Z*)-S59:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.78 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.16–7.04 (m, 4H), 7.04–6.95 (m, 1H), 5.79 (q, *J* = 1.3 Hz, 1H), 2.94–2.89 (m, 3H), 1.91–1.67 (m, 2H), 1.58 (d, *J* = 1.3 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 143.9, 137.2, 129.0, 128.4, 126.0, 117.9, 39.1, 37.6, 18.4, 18.2, 3.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2960 (*m*), 2929 (*w*), 2362 (*w*), 1538 (*m*), 1478 (*m*), 1438 (*m*), 1238 (*w*), 1024 (*m*), 738 (*s*), 689 (*m*).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –38.7° (*c* = 1.00, $CHCl_3$).

**HRMS** (EI) calc. for $C_{13}H_{17}{}^{127}I^{32}S$ $[M]^+$: 332.0090 found: 332.0084.

**(*E*)-S59:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.78 (UV, $KMnO_4$).

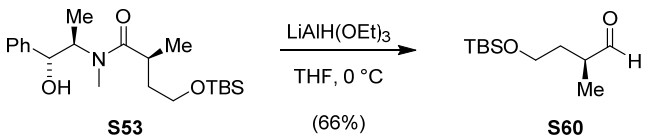
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.36–7.27 (m, 4H), 7.23–7.15 (m, 1H), 6.08 (s, 1H), 3.24–3.14 (m, 1H), 3.11–3.00 (m, 1H), 2.60–2.45 (m, 1H), 2.02–1.79 (m, 2H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 143.0, 136.9, 129.1, 128.4, 126.0, 117.8, 43.4, 38.2, 19.1, 14.2, 5.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*m*), 1582 (*m*), 1478 (*s*), 1438 (*m*), 1377 (*w*), 1236 (*w*), 1024 (*m*), 821 (*w*), 737 (*s*), 689 (*s*).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.2° (*c* = 1.00, $CHCl_3$).

**HRMS** (EI) calc. for $C_{13}H_{17}{}^{127}I^{32}S$ $[M]^+$: 332.0090 found: 332.0104.

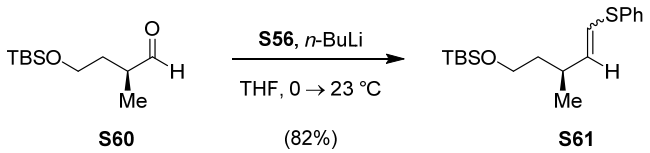



**S53** **S60**

**Aldehyde S60**

Ethyl acetate (0.88 mL, 8.96 mmol, 3.40 equiv) was added dropwise to a suspension of lithium aluminum hydride (230 mg, 6.06 mmol, 2.30 equiv) in hexanes (16 mL) at 0 °C over a period of 30 min. After 1 h, the reaction mixture was cooled to –78 °C and a solution of amide **S53** (1.00 g,

2.63 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added dropwise within 5 min. After 10 min, the reaction was allowed to warm to 0 °C. After 2 h, the reaction mixture was transferred to a solution of trifluoroacetic acid (1.96 mL, 26.3 mmol, 10.0 equiv) in aqueous hydrogen chloride solution (1 N, 40 mL). The transfer was quantitated with tetrahydrofuran (10 mL) and the biphasic mixture was stirred at 23 °C. After 5 min, the mixture was diluted with aqueous hydrogen chloride solution (60 mL) and diethyl ether (100 mL). The layers were separted and the aqueous phase was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to afford aldehyde **S60** (379 mg, 66%) as a colorless oil. The obtained analytical data were in full agreement with the data previously reported.[182]




**S60** (82%) **S61**

**Vinylsulfide S61**

To a solution of Peterson reagent **S56** (462 mg, 2.35 mmol, 1.50 equiv) in tetrahydrofuran (4 mL) was added a solution of *n*-butyllithium (2.34 M in hexanes, 0.97 mL, 2.28 mmol, 1.45 equiv) at 0 °C. After 30 min, a solution of aldehyde **S60** (340 mg, 1.57 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added and stirring was continued at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 1.5 h, the reaction mixture was diluted with diethyl ether (20 mL) and the organic layer was washed with saturated aqueous ammonium chloride solution (20 mL). The aqueous phase was extracted with diethyl ether (2 × 40 mL) and the combinded organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (1% ethyl acetate in hexanes initially grading to 2% ethyl acetate in hexanes) to provide vinylsulfide **S61** as an inseparable mixture of double bond isomers (415 mg, 82%, *E*:*Z* = 1:1.5) as a colorless oil.

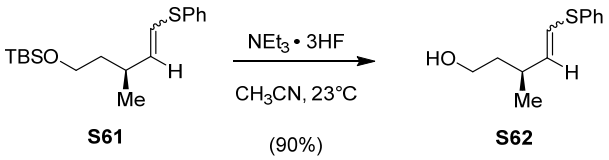
**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.37 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 599 MHz): (*Z*): δ = 7.36–7.27 (m, 4H), 7.21–7.15 (m, 1H), 6.14 (dd, *J* = 9.2, 0.7 Hz, 1H), 5.66–5.57 (m, 1H), 3.71–3.57 (m, 2H), 2.85–2.77 (m, 1H), 1.69–1.49 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H); (*E*): δ = 7.36–7.28 (m, 4H), 7.21–7.15 (m, 1H), 6.11 (dd, *J* = 15.0, 1.0 Hz, 1H), 5.88 (dd, *J* = 15.0, 8.1 Hz, 1H), 3.69–3.60 (m, 2H), 2.53–2.44 (m, 1H), 1.67–1.52 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): (Z): δ = 139.1, 136.8, 129.1, 128.9, 126.2, 121.8, 61.6, 40.2, 30.9, 26.1, 20.7, 18.5, –5.1, –5.1; (*E*): δ = 142.7, 136.7, 129.1, 128.6, 126.2, 119.9, 61.1, 39.7, 34.2, 26.1, 20.5, 18.5, –5.1, –5.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2955 (*m*), 2927 (*m*), 2856 (*w*), 1584 (*m*), 1471 (*m*), 1253 (*m*), 1094 (*vs*), 833 (*vs*), 773 (*vs*), 736 (*vs*), 688i (*s*).

**HRMS** (EI) calc. for $C_{18}H_{30}O^{32}S^{28}Si$ $[M]^+$: 322.1781 found: 322.1799.




**S61** **S62**

**Alcohol S62**

To a solution of the silylether **S61** (400 mg, 1.24 mmol, 1 equiv) in acetonitrile (4 mL) was added triethylamine trihydrofluoride (0.35 mL, 2.17 mmol, 1.75 equiv) at 23 °C. After 6 h, the reaction mixture was portioned between diethyl ether (30 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution (20 mL) and saturated aqueous sodium chloride solution (20 mL). The aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by flash-column chromatography (30% ethyl acetate in hexanes) to yield alcohol **S62** (233 mg, 90%, *E*:*Z* = 1:1.5) as a colorless oil.

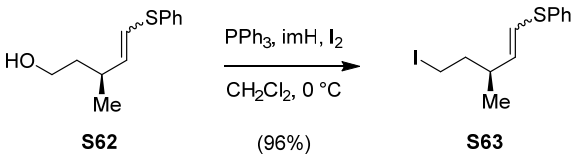
**TLC** (20% ethyl acetate in hexane), $R_f$ = 0.22 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): (*E*): δ = 7.38–7.27 (m, 4H), 7.24–7.17 (m, 1H), 6.17 (dd, *J* = 15.0, 0.9 Hz, 1H), 5.86 (dd, *J* = 15.0, 8.2 Hz, 1H), 3.73–3.64 (m, 2H), 2.54–2.45 (m, 1H), 1.66–1.58 (m, 2H), 1.23 (br s, 1H), 1.09 (d, *J* = 6.8 Hz, 3H); (*Z*): δ = 7.39–7.26 (m, 4H), 7.24–7.16 (m, 1H), 6.19 (dd, *J* = 9.2, 0.7 Hz, 1H), 5.68–5.55 (m, 1H), 3.74–3.64 (m, 2H), 2.94–2.80 (m, 1H), 1.80–1.67 (m, 1H), 1.58–1.48 (m, 1H), 1.23 (br s, 1H), 1.08 (d, *J* = 6.7 Hz, 3H)

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 138.4, 136.1, 129.2, 128.8, 126.6, 122.6, 61.3, 39.9, 30.9, 20.9; (*E*): δ = 141.6, 136.4, 129.1, 126.6, 126.4, 120.6, 61.1, 39.6, 34.5, 20.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3339 (*br w*), 2957 (*m*), 2926 (*m*), 1583 (*m*), 1478 (*m*), 1439 (*m*), 1050(*m*), 956 (*w*), 737 (*s*), 689 (*s*).

**HRMS** (EI) calc. for $C_{12}H_{16}O^{32}S$ $[M]^+$: 208.0916 found: 208.0918.




**S62** **S63**

**Iodide S63**

To a solution of imidazole (84.5 mg, 1.24 mmol, 1.20 equiv) and triphenylphosphine (326 mg, 1.24 mmol, 1.20 equiv) in dichloromethane (4.8 mL) was added iodine (315 mg, 1.24 mmol, 1.20 equiv) at 0 °C. After 15 min, a solution of alcohol **S62** (230 mg, 1.03 mmol, 1 equiv) in dichloromethane (2.0 mL) was added to the reaction mixture. After 40 min, the mixture was diluted with hexanes (40 mL) and the organic layer was washed with saturated aqueous sodium thiosulfate solution (40 mL). The aqueous phase was extracted with hexanes (3 × 40 mL) and diethyl ether (3 × 40 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give **S63** (331 mg, 96%) as a pale yellow oil

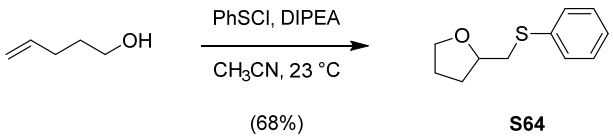
**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.63 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): (*E*): δ = 7.31–7.21 (m, 4H), 7.17–7.11 (m, 1H), 6.22–6.14 (m, 1H), 5.66 (dd, *J* = 15.0, 8.5 Hz, 1H), 3.23–3.00 (m, 2H), 2.47–2.34 (m, 1H), 1.98–1.69 (m, 2H), 1.01 (d, *J* = 6.9 Hz, 3H); (*Z*): δ = 7.31–7.21 (m, 4H), 7.17–7.11 (m, 1H), 6.22–6.14 (m, 1H), 5.51–5.44 (m, 1H), 3.23–3.00 (m, 2H), 2.81–2.67(m, 1H), 1.98–1.69 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 136.7, 136.3, 129.2, 129.2, 126.5, 123.9, 41.3, 35.5, 20.1, 3.9; (*E*): δ = 139.4, 136.1, 129.2, 129.0, 126.5, 122.0, 40.0, 38.6, 20.1, 5.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2957 (*m*), 2926 (*m*), 1583 (*m*), 1478 (*m*), 1438 (*m*), 1024 (*m*), 737 (*s*), 689 (*s*).

**HRMS** (EI) calc. for $C_{12}H_{15}{}^{127}I^{32}S$ $[M]^+$: 317.9934 found: 317.9945.



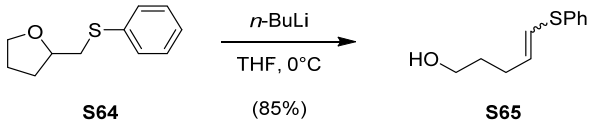

**S64**

**Furan S64**

*Furan S64 was prepared according to the procedure described by A. G. Fallis.*[183]

To a solution of diphenyldisulfide (9.51 g, 43.5 mmol, 0.50 equiv) and pyridine (50 µL) in acetonitrile (150 mL) was added sulfuryl chloride (3.60 mL, 44.4 mmol, 0.51 equiv) dropwise at 0 °C. After 20 min, the orange solution was added to a solution of 4-penten-1-ol (7.50 g, 87.1 mmol, 1 equiv) in acetonitrile (150 mL) at 23 °C. After 1 h, a solution of *N*,*N*-diisopropylethylamine (18.1 mL, 104 mmol, 1.20 equiv) in acetonitrile (75 mL) was added dropwise to the reaction mixture. After

30 min, the reaction mixture was concentrated and the residue was extracted with diethyl ether (400 mL). The organic extract was washed with water (3 × 300 mL) and saturated aqueous ammonium chloride solution (2 × 200 mL). The washed solution was dried over sodium sulfate, the dried solution was filtred and the filtrate was concentrated. The residue was purified by distillation to yield furan **S64** (11.5 g, 68%) as a yellow oil (boiling point 144 °C, 7 mbar). The obtained characterization data were in full agreement with those reported in literature.[183]

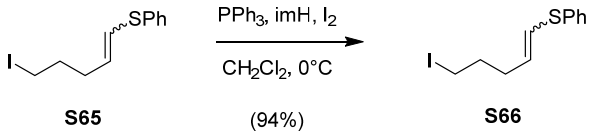



**S64** **S65**

**Alcohol S65**

*Alcohol **S64** was prepared according to the procedure described by A. G. Fallis.[183]*

To a solution of tetrahydrofuran **S64** (11.5 g, 59.4 mmol, 1 equiv) in tetrahydrofuran (60 mL) was added a solution of *n*-butyllithium (2.40 M in hexanes, 29.7 mL, 71.3 mmol, 1.20 equiv) dropwise at 0 °C within 30 min. After 45 min, water (100 mL) was added and the mixture was extracted with diethyl ether (4 × 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by bulb-to-bulb distillation (Set up: 1st bulb filled with crude product, 2nd outside the heating device as trap at 23 °C, 3rd bulb cooled to 0 °C, mantle temperature 270 °C, high vacuum < 1 mbar) to give alcohol **S65** (9.76 g, 85%; *E*:*Z* = 1.4:1) as a yellow oil. The obtained characterization data were in full agreement with those reported in literature.[183]




**S65** **S66**

**Iodide S66**

To a solution of imidazole (4.08 g, 59.9 mmol, 1.20 equiv) and triphenylphosphine (15.7 g, 59.9 mmol, 1.20 equiv) in dichloromethane (260 mL) was added iodine (15.2 g, 59.9 mmol, 1.20 equiv) at 0 °C. After 25 min, a solution of alcohol **S65** (9.70 mg, 49.9 mmol, 1 equiv) in dichloromethane (20 mL) was added to the reaction mixture. After 40 min, the mixture was diluted with hexanes (300 mL) and the organic layer was washed with saturated aqueous sodium thiosulfate solution (300 mL). The aqueous phase was extracted with hexanes (2 × 300 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to give iodide **S66** (14.2 g, 94%) as a pale yellow oil.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.71 (UV, $KMnO_4$).

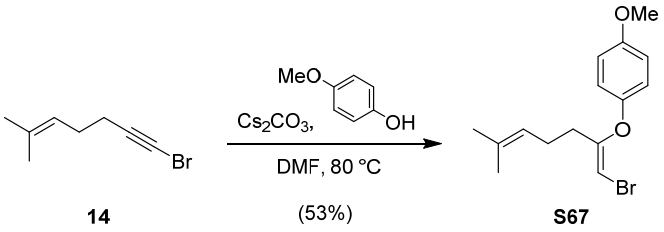
**$^1$H NMR** ($CDCl_3$, 400 MHz): (*Z*): δ = 7.40–7.28 (m, 4H), 7.25–7.16 (m, 1H), 6.31–6.20 (m, 1H), 5.76 (dt, *J* = 9.3, 7.3 Hz, 1H), 3.27–3.15 (m, 2H), 2.42–2.34 (m, 2H), 2.04–1.97 (m, 2H); (*E*): δ = 7.40–7.28 (m, 4H), 7.25–7.16 (m, 1H), 6.31–6.20 (m, 1H), 5.87 (dt, *J* = 15.0, 7.1 Hz, 1H), 3.27–3.15 (m, 2H), 2.34–2.24 (m, 2H), 1.97–1.89 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 136.1, 130.5, 129.2, 129.0, 126.5, 125.0, 33.0, 30.2, 5.9; (*E*): δ = 136.0, 133.6, 129.2, 129.0, 126.5, 123.4, 33.7, 32.5, 6.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3057 (*w*), 3006 (*w*), 2930 (*w*), 2836 (*w*), 1583 (*m*), 1478 (*s*), 1438 (*s*), 1205 (*vs*), 1166 (*m*), 945 (*m*), 737 (*vs*), 689 (*vs*).

**HRMS** (EI) calc. for $C_{11}H_{13}{}^{127}I^{32}S$ $[M]^+$: 303.9777 found: 303.9782.

### 3.3.1.2. Synthesis of Bromoenol Ethers




**Bromoenol ether S67**

A suspension of bromoalkyne **14**[179] (7.00 g, 37.4 mmol, 1 equiv), cesium carbonate (36.6 g, 112 mmol, 3.00 equiv) and 4-methoxyphenol (46.4 g, 374 mmol, 10.0 equiv) in *N*,*N*-dimethylformamide (38 mL) was heated to 80 °C in a pressure flask. After 2 d, the reaction mixture was partitioned between ethyl acetate (300 mL) and water (300 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 300 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (2% ethyl aceate in hexanes initially, grading to 15% ethyl acetate in hexanes) to provide bromoenol ether **S67** as a yellow oil (6.20 g, 53%).

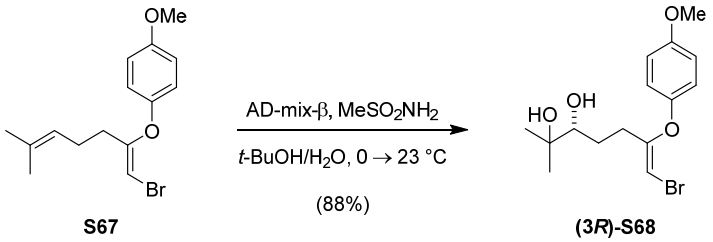
**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.55 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.94–6.88 (m, 2H), 6.87–6.79 (m, 2H), 5.65 (t, *J* = 0.9 Hz, 1H), 5.05–4.99 (m, 1H), 3.78 (s, 3H), 2.23–2.12 (m, 4H), 1.66 (s, 3H), 1.54 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 155.7, 155.5, 148.8, 133.2, 122.5, 118.6, 114.8, 90.4, 55.8, 32.2, 25.8, 25.2, 17.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3333 (*w*), 2922 (*w*), 2833 (*w*), 1633 (*m*), 1547 (*m*), 1501 (*vs*), 1243 (*m*), 1208 (*vs*), 1036 (*m*), 803 (*s*).

**HRMS** (EI) calc. for $C_{10}H_{18}{}^{79}BrO_2$ $[M–H]^+$: 309.0490 found: 309.0491.




**S67** **(3*R*)-S68**

**Diol (3*R*)-S68**

Potassium hexacyanoferrate (III) (39.4 g, 120 mmol, 6.00 equiv), potassium carbonate (16.5 g, 120 mmol, 6.00 equiv) and $(DHQD)_2Phal$ (621 mg, 0.80 mmol, 0.04 equiv) were grinded to a fine powder and were added to a mixture of *t*-butanol and water (1:1, 200 mL). Potassium osmate (VI) dihydrate (58.7 mg, 0.16 mmol, 0.8 mol%) was added to the orange suspension at 23 °C. After 30 min, the reaction mixture was cooled to 0 °C and methanesulfonamide (3.79 g, 39.8 mmol, 2.00 equiv) was added in one portion followed by a solution of alkene **S67** (6.20 g, 19.9 mmol, 1 equiv) in *t*-butanol (100 mL). After 5 min, the reaction mixture was allowed to warm to 23 °C. After 18 h, sodium sulfite (25.1 g, 199 mmol, 10.0 equiv) was added. After 30 min, aqueous sodium hydroxide solution (5%, 300 mL) was added and the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% methanol in dichloromethane) to give diol **(3*R*)-S68** (6.07g, 88%) as a yellow oil.

**TLC** (5% MeOH in dichloromethane), $R_f$ = 0.31 (UV; CAM).

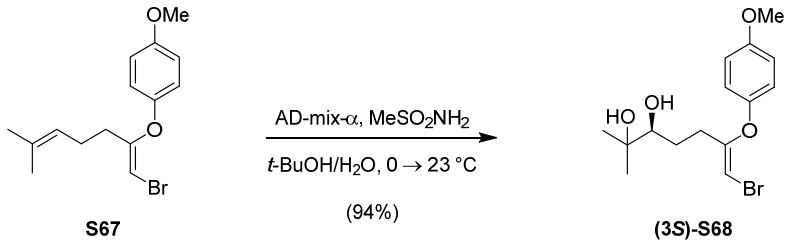
**$^1$H NMR** ($C_6D_6$, 800 MHz): δ = 6.87–6.82 (m, 2H), 6.67–6.63 (m, 2H), 5.47 (t, *J* = 0.9 Hz, 1H), 3.25 (s, 3H), 3.00 (d, *J* = 10.8 Hz, 1H), 2.41–2.34 (m, 1H), 2.16–2.10 (m, 1H), 1.75 (br d, *J* = 3.1 Hz, 1H), 1.48–1.43 (m, 1H), 1.26–1.20 (m, 1H), 1.02 (br s, 1H), 0.88 (s, 3H), 0.87 (s, 3H).

**$^{13}$C NMR** ($C_6D_6$, 201 MHz): δ = 156.0, 155.9, 149.2, 118.7, 115.1, 91.0, 77.1, 72.5, 55.1, 29.4, 28.5, 26.4, 23.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3405 (*w*), 2972 (*w*), 2359 (*w*), 1645 (*w*), 1503 (*vs*), 1207 (*s*), 1034 (*w*), 830 (*w*).

**HRMS** (EI) calc. for $C_{15}H_{21}{}^{79}BrO_4$ $[M]^+$: 344.0618; found: 344.0612.

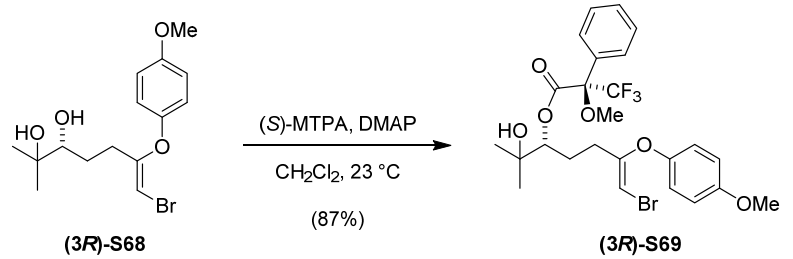
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –5.9 (c = 1.00, $CH_2Cl_2$).




**Diol (3*S*)-S68**

Potassium hexacyanoferrate (III) (41.4 g, 126 mmol, 6.00 equiv), potassium carbonate (17.4 g, 126 mmol, 6.00 equiv) and $(DHQ)_2Phal$ (676 mg, 0.84 mmol, 0.04 equiv) were grinded to a fine powder and were added to a mixture of *t*-butanol and water (1:1, 210 mL). Potassium osmate (VI) dihydrate (61.8 mg, 0.17 mmol, 0.8 mol%) was added to the orange suspension at 23 °C. After 30 min, the reaction mixture was cooled to 0 °C and methanesulfonamide (3.99 g, 41.9 mmol, 2.00 equiv) was added in one portion followed by a solution of alkene **S67** (6.52 g, 20.9 mmol, 1 equiv) in *t*-butanol (110 mL). After 5 min, the reaction mixture was allowed to warm to 23 °C. After 15 h, sodium sulfite (26.4 g, 209 mmol, 10.0 equiv) was added. After 30 min, aqueous sodium hydroxide solution (5%, 150 mL) was added and the mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% methanol in dichloromethane) to give diol **(3*S*)-S68** (6.76 g, 94%) as a yellow oil. The obtained characterization data were in full agreement with those of **(3*R*)-S68**.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +18.4 (c = 1.00, $CH_2Cl_2$).




**Mosher Ester (3*R*)-S69**

*The enantiomeric excess of **(3S)-S68** was determined as 67% by $^1H$ analysis of its corresponding mono-(S)-MTPA esters **(3S)-S69** and **3(3R)-S69**.*

To a solution of diol **(3*R*)-S68** (5.00 mg, 14.5 µmol, 1 equiv) and 4-dimethylaminopyridine (7.08 mg, 57.9 µmol, 4.00 equiv) in dichloromethane (0.8 ml) was added (*S*)-Mosher´s acid chloride (5.4 µL, 2.90 µmol, 2.00 equiv) at 23 °C. After 1.5 h, water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by

flash-column chromatography on silica gel (10% ethylacetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to yield mono-MTPA ester **(3*S*)-S69** (7.1 mg, 87%) as a colorless oil.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.27 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.58–7.55 (m, 2H), 7.44–7.34 (m, 3H), 6.87–6.83 (m, 2H), 6.83–6.78 (m, 2H), 5.61 (s, 1H), 4.90 (dd, *J* = 10.3, 2.2 Hz, 1H), 3.77 (s, 3H), 3.47 (s, 3H), 2.17–2.12 (m, 1H), 2.12–2.06 (m, 1H), 1.86–1.81 (m, 1H), 1.66–1.60 (m, 1H), 1.42 (s, 1H), 1.17 (s, 3H), 1.11 (s, 3H).

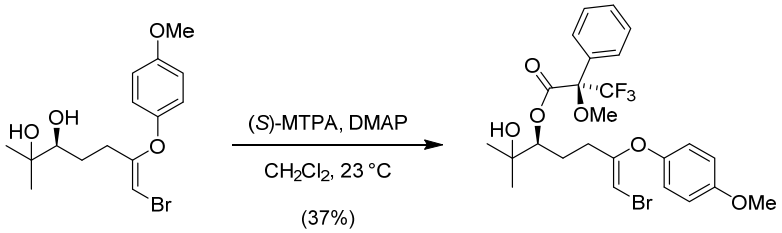
**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 167.0, 155.7, 154.4, 148.4, 132.0, 129.9, 128.7, 127.8, 123.5 (q, *J* = 288.7 Hz), 118.2, 114.9, 91.7, 84.9 (q, *J* = 27.8 Hz), 81.7, 72.60, 55.8, 55.5, 28.7, 27.4, 26.9, 24.1.

**$^{19}$F NMR** ($CDCl_3$, 377 MHz): δ = –70.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3452 (br *w*), 2948 (*w*), 1743 (*m*), 1503 (*vs*), 1247 (*m*), 1206 (*s*), 1168 (*s*), 1033 (*m*), 828 (*w*), 717 (*m*).

**HRMS** (EI) calc. for $C_{25}H_{28}{}^{79}BrF_3O_6$ $[M]^+$: 560.1016; found: 560.1002.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +38.0 (c = 0.33, $CH_2Cl_2$).




**(3*S*)-S68** **(3*S*)-S69**

**Mosher Ester (3*S*)-S69**

*The enantiomeric excess of **(3S)-S68** was determined as 94% by $^1$H analysis of its corresponding mono-(S)-MTPA esters **(3S)-S69** and **(3R)-S69**.*

To a solution of diol **(3*S*)-S68** (5.00 mg, 14.5 µmol, 1 equiv) and 4-dimethylaminopyridine (7.08 mg, 57.9 µmol, 4.00 equiv) in dichloromethane (0.8 ml) was added (*S*)-Mosher´s acid chloride (5.4 µL, 2.90 µmol, 2.00 equiv) at 23 °C. After 1h, 4-dimethylaminopyridine (7.08 mg, 57.9 µmol, 4.00 equiv) and (*S*)-Mosher´s acid chloride (5.4 µL, 2.90 µmol, 2.00 equiv) were added. After 1h, water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethylacetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to yield mono-MTPA ester **(3*S*)-S69** (3.0 mg, 37%) as a colorless oil.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.26 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.56–7.50 (m, 2H), 7.42–7.39 (m, 1H), 7.39–7.37 (m, 2H), 6.88–6.84 (m, 2H), 6.84–6.80 (m, 2H), 5.67 (s, 1H), 4.90 (dd, *J* = 9.8, 2.3 Hz, 1H), 3.78 (s, 3H), 3.44 (s, 3H), 2.27–2.21 (m, 1H), 2.20–2.14 (m, 1H), 1.96–1.89 (m, 1H), 1.75–1.65 (m, 1H), 1.40 (s, 1H), 1.12 (s, 3H), 1.09 (s, 3H).

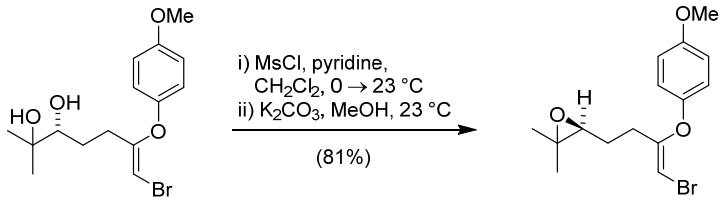
**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 166.5, 155.7, 154.4, 148.4, 132.1, 129.9, 128.7, 127.4, 123.5 (q, *J* = 290 Hz), 118.3, 114.9, 91.8, 84.6 (q, *J* = 27.5 Hz), 81.9, 72.4, 55.8, 55.5, 29.0, 27.4, 26.2, 24.9.

**$^{19}$F NMR** ($CDCl_3$, 377 MHz): δ = –70.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3519 (br *w*), 2948 (*m*), 1744 (*m*), 1503 (*vs*), 1247 (*m*), 1206 (*s*), 1168 (*s*), 1033 (*m*), 829 (*w*), 718 (*m*).

**HRMS** (ESI) calc. for $C_{25}H_{32}{}^{79}BrF_3NO_6$ $[M+NH_4]^+$: 578.1360; found: 578.1364.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.8 (c = 0.30, $CH_2Cl_2$).




**(3*R*)-S68** **(3*S*)-20**

**Epoxide (3*S*)-20**

To a solution of diol **(3*R*)-S68** (6.07 g, 17.6 mmol, 1 equiv) and pyridine (7.11 mL, 87.9 mmol, 5.00 equiv) in dichloromethane (79 mL) was added methanesulfonyl chloride (2.04 mL, 26.4 mmol, 1.50 equiv) dropwise at 0 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 19 h, water (150 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 150 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated and the residue dried by azeotropic distillation with benzene (2 × 30 mL).

To a solution of the crude mesylate in methanol (80 mL) was added potassium carbonate (4.86 g, 35.2 mmol, 2.00 equiv) at 23 °C. After 2.5 h, the reaction mixture was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in hexane) to yield epoxide **(3*S*)-20** (4.63 g, 81%) as a yellow oil.

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.53 (UV, $KMnO_4$).

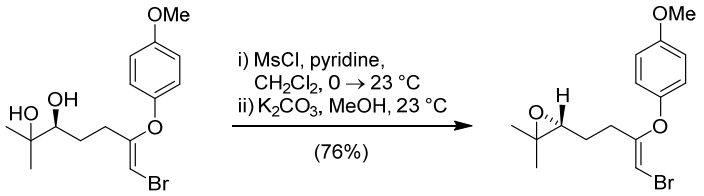
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.98–6.88 (m, 2H), 6.87–6.81 (m, 2H), 5.74 (s, 1H), 3.78 (s, 3H), 2.67 (dd, *J* = 7.0, 5.5 Hz, 1H), 2.47–2.36 (m, 1H), 2.35–2.25 (m, 1H), 1.79–1.68 (m, 1H), 1.68–1.57 (m, 1H), 1.28 (s, 3H), 1.22 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 155.6, 154.9, 148.5, 118.4, 114.9, 91.1, 63.2, 58.7, 55.8, 29.0, 26.2, 24.9, 18.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1645 (*w*), 1502 (*m*), 1246 (*w*), 1205 (*m*), 1034 (*w*), 903 (*s*), 829 (*w*), 724 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO_3$ $[M]^+$: 326.0512; found: 326.0509.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +0.5 (c = 1.00, $CH_2Cl_2$).




**(3*S*)-S68** **(3*R*)-20**

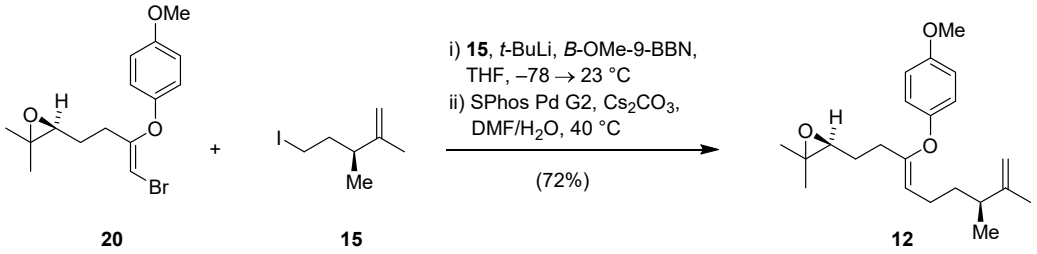
**Epoxide (3*R*)-20**

To a solution of diol **(3*S*)-S68** (6.76 g, 19.6 mmol, 1 equiv) and pyridine (7.92 mL, 97.9 mmol, 5.00 equiv) in dichloromethane (100 mL) was added methanesulfonyl chloride (2.23 mL, 29.4 mmol, 1.50 equiv) dropwise at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 15 h, water (150 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 150 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated and the residue was dried by azeotropic distillation with benzene (2 × 30 mL).

To a solution of the crude mesylate in methanol (100 mL) was added potassium carbonate (5.41 g, 39.2 mmol, 2.00 equiv) at 23 °C. After 1 h, the reaction mixture was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to yield epoxide **(3*R*)-20** (4.84 g, 76%) as a yellow oil. The obtained characterization data were in full agreement with those of **(3*S*)-20**.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.9 (c = 0.50, $CH_2Cl_2$).

### 3.3.1.3. Synthesis of Cylization Precursors and Cyclization Studies




**Enol Ether 12**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of iodide **15** (178 mg, 0.90 mmol, 1.30 equiv) in tetrahydrofuran (3.2 mL) and *B*-methoxy-9-BBN (1.00 M in hexanes, 1.83 mL, 1.83 mmol, 3.00 equiv) was added a solution of *t*-butyllithium (1.70 M in pentane, 1.40 mL, 2.38 mmol, 3.90 equiv) dropwise a –78 °C. After 5 min, the yellow solution solution was allowed to warm to 23 °C upon it turned colorless again. After 15 min, the reaction mixture was transferred to a suspension of bromoenol ether **20** (200 mg, 0.61 mmol, 1 equiv), cesium carbonate (398 mg, 1.22 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (22.0 mg, 0.03 mmol, 0.05 equiv) and SPhos (12.5 mg, 0.03 mmol, 0.05 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 6.0 mL) and heated to 40 °C. After 1 h, water (75 mL) was added the mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (initially 5% ethyl acetate in hexanes, grading to 10% ethyl acetate in hexanes) to furnish enol ether **12** (152 mg, 72%) as a colorless oil.

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.58 (UV, Anis).

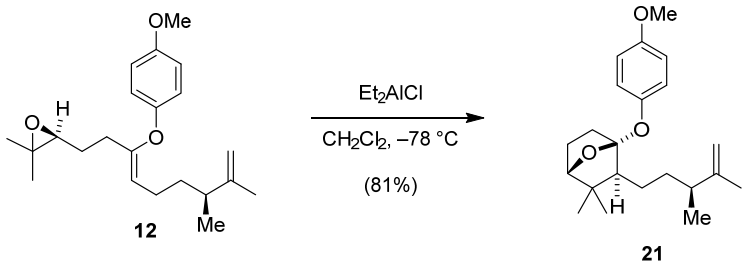
**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 6.93–6.74 (m, 4H), 5.01 (t, *J* = 7.3 Hz, 1H), 4.65–4.63 (m, 2H), 3.77 (s, 3H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.33–2.25 (m, 1H), 2.22–2.16 (m, 1H), 2.15–2.09 (m, 1H), 2.02–1.96 (m, 2H), 1.72–1.63 (m, 2H), 1.61 (t, *J* = 1.2 Hz, 3H), 1.47–1.40 (m, 1H), 1.35–1.29 (m, 1H), 1.28 (s, 3H), 1.23 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 154.6, 150.4, 150.2, 150.0, 117.2, 116.3, 114.8, 109.6, 63.8, 58.6, 55.9, 40.9, 35.0, 29.2, 26.6, 25.0, 23.3, 19.7, 19.1, 18.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2960 (*w*), 1682 (*w*), 1503 (*vs*), 1442 (*w*), 1377 (*w*), 1296 (*w*), 1209 (*s*), 1038 (*m*), 888 (*w*), 828 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_3$ $[M]^+$: 344.2346; found: 344.2345.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 0.0° (*c* = 0.60, $CHCl_3$).




**Acetal 21**

To a solution of epoxide **12** (9.5 mg, 0.03 mmol, 1 equiv) in dichloromethane (3.0 mL) was added a solution of diethylaluminumchloride solution (1.00 M in hexanes, 82.7 µL, 0.08 mol, 3.00 equiv) in dichloromethane (0.5 mL) dropwise onto the inner wall of the flask at –78 °C. After 45 min, saturated aquoues ammonium chloride solution (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield acetal **21** (7.7 mg, 81%) as a colorless oil.

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.58 (UV, CAM).

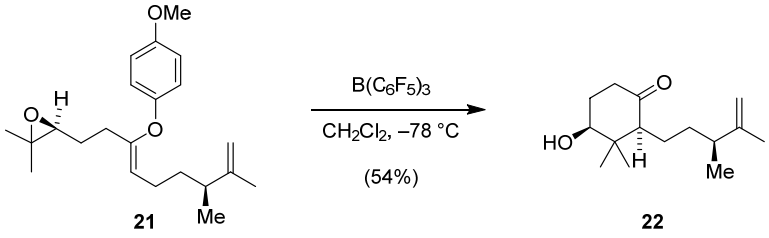
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.16–7.01 (m, 2H), 6.86–6.74 (m, 2H), 4.73–4.64 (m, 2H), 3.77 (s, 3H), 3.72–3.62 (m, 1H), 2.21–2.09 (m, 1H), 1.96–1.87 (m, 1H), 1.78–1.63 (m, 6H), 1.57–1.53 (m, 1H), 1.53–1.38 (m, 2H), 1.36–1.17 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H), 1.02 (d, $J$ = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 155.7, 150.5, 148.6, 122.5, 114.2, 113.1, 109.4, 81.4, 57.1, 55.7, 44.6, 42.0, 35.4, 30.0, 26.5, 25.3, 24.0, 23.9, 19.8, 19.3.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2960 (*m*), 1505 (*vs*), 1463 (*w*), 1299 (*w*), 1213 (*s*), 1037 (*w*), 1009 (*m*), 886 (*w*), 836 (*m*), 751 (*w*).

**HRMS** (ESI) calc. for $C_{22}H_{33}O_3$ $[M+H]^+$: 345.2424; found: 345.2424.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –29.0° ($c$ = 0.39, $CH_2Cl_2$).




**Ketone 22**

To a solution of epoxide **21** (15.0 mg, 0.04 mmol, 1 equiv) in dichloromethane (4.5 mL) was added a solution of tris(pentafluorophenyl)borane (33.4 mg, 0.07 mmol, 1.50 equiv) in

dichloromethane (1.0 mL) dropwise onto the inner wall of the flask at –78 °C. After 30 min, water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield ketone **22** (5.6 mg, 54%) as a colorless oil.

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.13 (UV, $KMnO_4$).

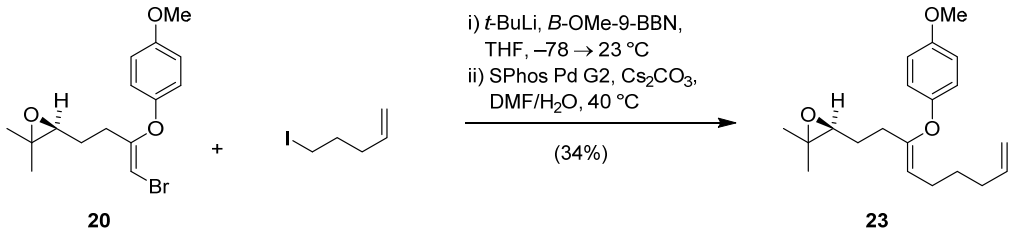
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 4.68 (s, 2H), 3.78 (dd, *J* = 10.9, 4.4 Hz, 1H), 2.43–2.35 (m, 2H), 2.18–2.10 (m, 2H), 2.02 (dd, *J* = 10.3, 1.9 Hz, 1H), 1.87–1.77 (m, 1H), 1.75–1.65 (m, 1H), 1.64 (s, 3H), 1.55 (s, 1H), 1.41–1.29 (m, 1H), 1.27–1.15 (m, 1H), 1.10 (s, 3H), 1.08–1.03 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.70 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 211.2, 150.2, 109.6, 76.2, 58.8, 43.7, 41.7, 39.4, 34.8, 31.0, 26.0, 21.3, 19.8, 19.1, 14.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3399 (*br s*), 2963 (*s*), 1703 (*vs*), 1644 (*m*), 1456 (*m*), 1368 (*m*), 1163 (*w*), 1030 (*m*), 1014 (*m*), 887 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{27}O_2$ $[M+H]^+$: 239.2006; found: 239.2005.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +19.2° (*c* = 0.28, $CH_2Cl_2$).




**Enol ether 23**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of 5-iodopentene[184] (27.0 mg, 0.14 mmol, 1.50 equiv) in tetrahydrofuran (0.55 mL) and *B*-methoxy-9-BBN (1.00 M in hexanes, 0.32 mL, 0.32 mmol, 3.50 equiv) was added a solution of *t*-butyllithium (1.70 M in pentane, 0.243 mL, 0.413 mmol, 4.50 equiv) dropwise at –78 °C. After 5 min, the yellow solution solution was allowed to warm to 23 °C upon it turned colorless again. After 15 min, the reaction mixture was transferred to a suspension of bromoenol ether **20** (30 mg, 0.09 mmol, 1 equiv), cesium carbonate (59.7 mg, 018 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (3.3 mg, 4.58 µmol, 0.05 equiv) and SPhos (1.9 mg, 4.58 µmol, 0.05 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 0.9 mL) and heated to 40 °C. After 3 d, water (20 mL) was added the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by

flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to furnish epoxide **23** (9.9 mg, 34%) as a pale yellow oil.

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.44 (UV, Anis).

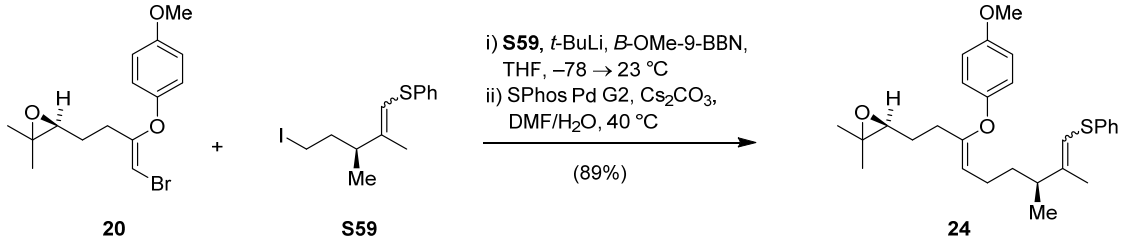
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.93–6.76 (m, 4H), 5.90–5.74 (m, 1H), 5.12–4.91 (m, 3H), 3.80 (s, 3H), 2.73 (t, *J* = 6.2 Hz, 1H), 2.37–2.28 (m, 1H), 2.27–2.17 (m, 1H), 2.15–2.01 (m, 4H), 1.77–1.63 (m, 2H), 1.53–1.41 (m, 2H), 1.31 (s, 3H), 1.25 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.6, 150.3, 150.3, 138.8, 117.2, 116.1, 114.8, 114.6, 63.8, 58.6, 55.8, 33.6, 29.2, 29.0, 26.6, 25.0, 24.8, 18.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2924 (*w*), 1683 (*w*), 1501 (*vs*), 1441 (*w*), 1206 (*s*), 1036 (*m*), 909 (*m*), 826 (*m*), 730 (*w*).

**HRMS** (EI) calc. for $C_{20}H_{28}O_3$ $[M]^+$: 316.2038; found: 316.2033.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –12.1° (*c* = 0.50, $CH_2Cl_2$).




**20** **S59** **24**

**Enol ether 24**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of iodide **S59** (152 mg, 0.92 mmol, 1.50 equiv) in tetrahydrofuran (1.2 mL) and *B*-methoxy-9-BBN (1.00 M in hexanes, 1.07 mL, 1..07 mmol, 3.50 equiv) was added a solution of *t*-butyllithium (1.60 M in pentane, 0.86 mL, 1.38 mmol, 4.50 equiv) dropwise at –78 °C. After 5 min, the yellow solution was allowed to warm to 23 °C upon it turned colorless again. After 15 min, the reaction mixture was transferred to a suspension of bromoenol ether **20** (100 mg, 0.31 mmol, 1 equiv), cesium carbonate (199 mg, 0.61 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (11.0 mg, 0.02 mmol, 0.05 equiv) and SPhos (6.3 mg, 0.02 mmol, 0.05 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 3.1 mL) and heated to 40 °C. After 2 h, the reaction mixture was diluted with ethyl acetate (50 mL) and filtered through a plug of celite. The organic layer was washed with water (50 mL) and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give epoxide **24** (123 mg, 89%) as a yellow oil.

*To obtain analytical pure samples, iodides **(Z)-S59** and **(E)-S59** were coupled separately under the same conditions to yield **(Z)-24** and **(E)-24**.*

**(*Z*)-24:**

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.26 (UV, Anis).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.39–7.20 (m, 4H), 7.18–7.11 (m, 1H), 6.91–6.74 (m, 4H), 5.86 (q, *J* = 1.3 Hz, 1H), 5.04 (t, *J* = 7.3 Hz, 1H), 3.77 (s, 3H), 3.08–2.91 (m, 1H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.34–2.21 (m, 1H), 2.22–2.11 (m, 1H), 2.10–1.88 (m, 2H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.69–1.57 (m, 2H), 1.52–1.34 (m, 2H), 1.27 (s, 3H), 1.21 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.6, 150.4, 150.4, 146.9, 137.7, 129.0, 128.1, 125.7, 117.3, 115.8, 115.8, 114.8, 63.8, 58.6, 55.8, 35.8, 34.6, 29.2, 26.6, 25.0, 23.3, 18.8, 18.8, 18.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*m*), 2925 (*m*), 1584 (*w*), 1503 (*vs*), 1440 (*m*), 1209 (*s*), 1037 (*m*), 828 (*m*), 740 (*m*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380; found: 452.2385.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –15.6° (*c* = 1.00, $CH_2Cl_2$)

**(*E*)-24:**

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.26 (UV, Anis).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.29–7.21 (m, 4H), 7.17–7.12 (m, 1H), 6.85–6.83 (m, 2H), 6.82–6.79 (m, 2H), 5.93–5.92 (m, 1H), 5.02 (t, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.34–2.27 (m, 2H), 2.23–2.17 (m, 1H), 2.05–1.99 (m, 2H), 1.73 (d, *J* = 1.1 Hz, 3H), 1.72–1.61 (m, 2H), 1.54–1.47 (m, 1H), 1.43–1.35 (m, 1H), 1.28 (s, 3H), 1.22 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 154.7, 150.5, 150.4, 146.5, 137.5, 129.0, 128.2, 125.7, 117.2, 115.8, 115.7, 114.8, 63.8, 58.6, 55.8, 42.6, 34.9, 29.3, 26.6, 25.0, 23.4, 19.6, 18.8, 14.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2958 (*m*), 2924 (*m*), 1583 (*w*), 1501 (*vs*), 1439 (*m*), 1206 (*vs*), 1036 (*m*), 826 (*m*), 737 (*m*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380; found: 452.2381.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –14.6° (*c* = 1.00, $CH_2Cl_2$)

**Cyclization Studies of Enol ether 24:**

To a solution of epoxide **24** (20.0 mg, 0.04 mmol, 1 equiv) in dichloromethane (4.5 mL) was added a solution of Lewis acid (Table 1, 0.09 mmol, 2.00 equiv) in dichloromethane (0.5 mL) dropwise onto the inner wall of the flask at –78 °C. After the time indicated, water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield the products indicated in Table 1.

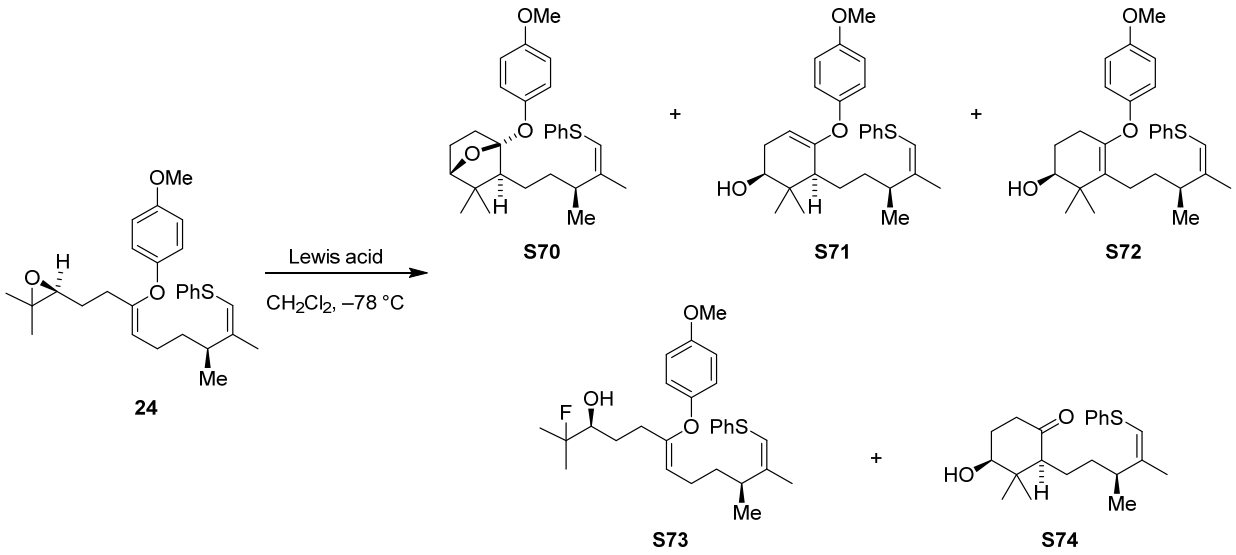



***Table 10:*** *Conditions tested for the cyclization of 24.*

| Entry | Lewis acid | Solvent | T[°C] | Yield S70 [%] | Yield S71 [%] | Yield S72 [%] | Yield S73 [%] | Yield S74 [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | $EtAlCl_2$ | $CH_2Cl_2$ | –78 | 10 | – | 59 | – | – |
| 2 | $BF_3$•$Et_2O$ | MTBE | –78 to 0 | – | – | – | 62 | 3 |
| 3 | $B(C_6F_5)_3$ | $CH_2Cl_2$ | 23 | 9 | – | – | – | 32 |
| 4 | $B(C_6F_5)_3$ | $CH_2Cl_2$ | –78 | 45 | 12 | – | – | – |

**Acetal S70:**

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.52 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 7.32–7.29 (m, 2H), 7.26–7.21 (m, 2H), 7.14–7.11 (m, 1H), 7.08–7.04 (m, 2H), 6.80–6.76 (m, 2H), 5.91 (q, *J* = 1.3 Hz, 1H), 3.77 (s, 3H), 3.69–3.67 (m, 1H), 3.09–3.01 (m, 1H), 1.95–1.89 (m, 1H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.78–1.74 (m, 1H), 1.73–1.65 (m, 2H), 1.64–1.56 (m, 2H), 1.50–1.41 (m, 1H), 1.35–1.30 (m, 1H), 1.30–1.23 (m, 1H), 1.10 (s, 3H), 1.07 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 155.8, 148.6, 147.6, 137.8, 129.0, 128.2, 125.6, 122.6, 115.6, 114.2, 113.0, 81.4, 56.5, 55.7, 44.6, 36.4, 34.7, 29.9, 26.5, 25.3, 23.9, 23.9, 18.9, 18.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*m*), 1584 (*w*), 1505 (*vs*), 1439 (*w*), 1299 (*w*), 1214 (*s*), 1010 (*w*), 836 (*w*), 739 (*w*), 690 (*w*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380; found: 455.2383.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –41.4° (*c* = 0.45, $CH_2Cl_2$).

**Enol ether S71:**

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.15 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.32–7.26 (m, 4H), 7.18–7.14 (m, 1H), 6.92–6.89 (m, 2H), 6.85–6.82 (m, 2H), 5.91 (d, *J* = 1.4 Hz, 1H), 4.47–4.45 (m, 1H), 3.78 (s, 3H), 3.54–3.46 (m, 1H), 3.01–2.94 (m, 1H), 2.26–2.20 (m, 1H), 2.06–2.03 (m, 1H), 2.00–1.94 (m, 1H), 1.81–1.77 (m, 1H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.58–1.52 (m, 2H), 1.42–1.35 (m, 2H), 1.04 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 157.8, 155.7, 149.6, 147.7, 137.9, 129.0, 128.0, 125.6, 121.4, 115.5, 114.7, 98.3, 74.8, 55.8, 47.9, 38.9, 36.9, 36.5, 29.8, 26.3, 25.4, 18.9, 18.4, 15.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3415 (*br w*), 2959 (*m*), 1667 (*w*), 1584 (*w*), 1503 (*vs*), 1211 (*vs*), 1089 (*m*), 1037 (*m*), 841 (*m*), 738 (*m*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380; found: 452.2379.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –77.3° (*c* = 0.23, $CH_2Cl_2$).

**Enol ether S72:**

**TLC** (30% ethyl acetate in hexanes), $R_f$ = 0.33 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.25–7.20 (m, 4H), 7.13 (tt, *J* = 7.2, 1.8 Hz, 1H), 6.83–6.80 (m, 2H), 6.79–6.75 (m, 2H), 5.84 (q, *J* = 1.4 Hz, 1H), 3.77 (s, 3H), 3.59–3.53 (m, 1H), 2.99–2.89 (m, 1H), 2.19–2.13 (m, 1H), 2.10–2.05 (m, 1H), 1.96–1.86 (m, 3H), 1.85–1.77 (m, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.52–1.46 (m, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 154.5, 150.5, 147.3, 144.2, 137.9, 129.6, 128.9, 128.0, 125.6, 117.0, 115.7, 114.8, 75.4, 55.8, 40.0, 37.0, 35.2, 26.6, 26.5, 24.8, 23.2, 21.9, 19.0, 18.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3410 (*br w*), 2959 (*w*), 1502 (*vs*), 1439 (*w*), 1209 (*s*), 1104 (*w*), 1037 (*m*), 825 (*w*), 739 (*m*), 690 (*w*).

**HRMS** (EI) calc. for $C_{30}H_{39}O_5{}^{32}S$ $[M+OAc]^-$: 511.2524; found: 511.2516.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –56.6° (*c* = 0.36, $CH_2Cl_2$).

**Fluorohydrine S73:**

**TLC** (30% ethyl acetate in hexanes), $R_f$ = 0.57 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 7.291–7.22 (m, 4H), 7.18–7.11 (m, 1H), 6.88–6.83 (m, 2H), 6.82–6.79 (m, 2H), 5.86 (q, *J* = 1.4 Hz, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 3.58–3.49 (m, 1H), 3.07–2.93 (m, 1H), 2.43–2.34 (m, 1H), 2.21–2.13 (m, 1H), 2.12–2.01 (m, 1H), 2.01–1.90 (m, 2H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.65–1.57 (m, 1H), 1.48–1.33 (m, 3H), 1.31 (d, *J* = 4.2 Hz, 3H), 1.27 (d, *J* = 4.2 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 154.6, 150.8, 150.5, 146.9, 137.7, 129.0, 128.2, 125.7, 117.2, 116.0, 115.9, 114.8, 98.1 (d, *J* = 164.8 Hz), 76.1 (d, *J* = 22.7 Hz), 55.9, 35.7, 34.6, 29.1, 28.6 (d, *J* = 2.8 Hz), 23.8 (d, *J* = 24.7 Hz), 23.3, 21.3 (d, *J* = 24.6 Hz), 18.7, 18.2.

**$^{19}$F NMR** ($CDCl_3$, 377 MHz): δ = –145.2

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3483 (*br w*), 2929 (*m*), 1503 (*vs*), 1440 (*m*), 1296 (*w*), 1209 (*s*), 1086 (*m*), 1038 (*m*), 829 (*m*), 740 (*m*).

**HRMS** (ESI) calc. for $C_{30}H_{40}FO_5{}^{32}S$ $[M+OAc]^-$: 531.2586; found: 531.2575.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –9.5° (*c* = 0.42, $CH_2Cl_2$).

**Ketone S74:**

**TLC** (30% ethyl acetate in hexanes), $R_f$ = 0.18 (UV, CAM).

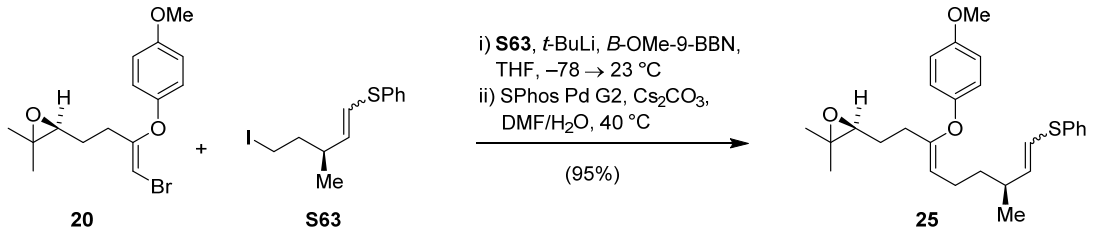
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.32–7.24 (m, 4H), 7.19–7.12 (m, 1H), 5.89 (q, *J* = 1.4 Hz, 1H), 3.79–3.72 (m, 1H), 3.06–2.93 (m, 1H), 2.41–2.28 (m, 2H), 2.13–2.08 (m, 1H), 2.08–2.04 (m, 1H), 1.82–1.76 (m, 2H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.54 (d, *J* = 5.0 Hz, 1H), 1.49–1.42 (m, 1H), 1.23–1.17 (m, 1H), 1.11 (s, 3H), 1.10–1.06 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.68 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 211.0, 147.6, 137.7, 129.0, 128.0, 125.7, 115.5, 76.1, 58.5, 43.7, 39.3, 36.4, 34.4, 31.0, 26.0, 21.3, 18.6, 18.4, 14.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3444 (*br w*), 2960 (*s*), 1709 (*vs*), 1584 (*m*), 1478 (*s*), 1439 (*s*), 1037 (*m*), 1024 (*s*), 739 (*vs*), 690 (*s*).

**HRMS** (EI) calc. for $C_{21}H_{30}O_2{}^{32}S$ $[M]^+$: 346.1961; found: 346.1958.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –11.6° (*c* = 1.00, $CH_2Cl_2$).




**Enol ether 25**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of iodide **S63** (120 mg, 0.37 mmol, 1.50 equiv) in tetrahydrofuran (1.5 mL) and *B*-methoxy-9-BBN (1.00 M in hexanes, 0.88 mL, 0.88 mmol, 3.50 equiv) was added a solution of *t*-butyllithium (1.70 M in pentane, 0.67 mL, 1.13 mmol, 4.50 equiv) dropwise at –78 °C. After 5 min, the yellow solution was allowed to warm to 23 °C upon it turned colorless again. After 15 min, the reaction mixture was transferred to a suspension of bromoenol ether **20** (82.0 mg, 0.25 mmol, 1 equiv), cesium carbonate (164 mg, 0.50 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (9.1 mg, 0.01 mmol, 0.05 equiv) and SPhos (5.2 mg, 0.01 mmol, 0.05 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 2.5 mL) and heated to 40 °C. After 3 h, the reaction mixture was diluted with water (50 mL) and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give enol ether **25** (105 mg, 95%) as a yellow oil.

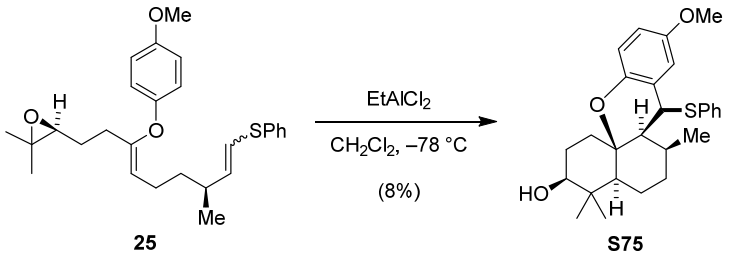
**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.30 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 599 MHz): (*Z*): δ = 7.33–7.22 (m, 4H), 7.21–7.13 (m, 1H), 6.87–6.84 (m, 2H), 6.83–6.79 (m, 2H), 6.12 (dd, *J* = 9.2, 0.8 Hz, 1H), 5.58 (dd, *J* = 9.2, 9.2 Hz, 1H), 5.05 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 2.73–2.62 (m, 2H), 2.33–2.25 (m, 1H), 2.23–2.16 (m, 1H), 2.15–2.02 (m, 2H), 1.71–1.62 (m, 2H), 1.46–1.33 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H); (*E*): δ = 7.33–7.22 (m, 4H), 7.21–7.13 (m, 1H), 6.87–6.84 (m, 2H), 6.83–6.79 (m, 2H), 6.08 (dd, *J* = 15.0, 1.0 Hz, 1H), 5.83 (dd, *J* = 15.0, 8.0 Hz, 1H), 5.00 (t, *J* = 7.3 Hz, 1H), 3.77 (s, 3H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.33–2.25 (m, 2H), 2.23–2.16 (m, 1H), 2.15–2.02 (m, 2H), 1.71– 1.62 (m, 2H), 1.46–1.33 (m, 2H), 1.28 (s, 3H), 1.23 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): (*Z*): δ = 154.6, 150.4, 150.3, 139.4, 136.7, 129.1, 128.8, 126.2, 121.7, 117.2, 115.8, 114.8, 63.8, 58.6, 55.8, 36.9, 33.7, 29.2, 26.6, 25.0, 23.1, 20.4, 18.8; (*E*): δ = 154.7, 150.6, 150.4, 142.7, 136.7, 129.0, 128.6, 126.1, 119.9, 117.3, 115.9, 114.8, 63.8, 58.6, 55.8, 37.3, 36.6, 29.2, 26.6, 25.0, 23.1, 20.3, 18.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2958 (*w*), 2923 (*w*), 1683 (*w*), 1584 (*w*), 1502 (*vs*), 1440 (*w*), 1209 (*s*), 1037 (*m*), 828 (*w*), 739 (*m*).

**HRMS** (EI) calc. for $C_{27}H_{34}{}^{32}SO_3$ $[M]^+$: 438.2229; found: 438.2218.




**Tetracycle S75**

To a solution epoxide **25** (10.0 mg, 0.02 mmol, 1 equiv) in dichloromethane (2.2 mL) was added a solution of ethylaluminum dichloride (1.00 M in hexanes, 0.07 mL, 0.07 mmol, 3.00 equiv) in dichloromethane (0.5 mL) dropwise at –78 °C. After 20 min, water (10 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to obtain **S75** (0.8 mg, 8%) as a colorless oil.

**TLC** (30% ethyl acetate in hexanes), $R_f$ = 0.26 (UV, CAM).

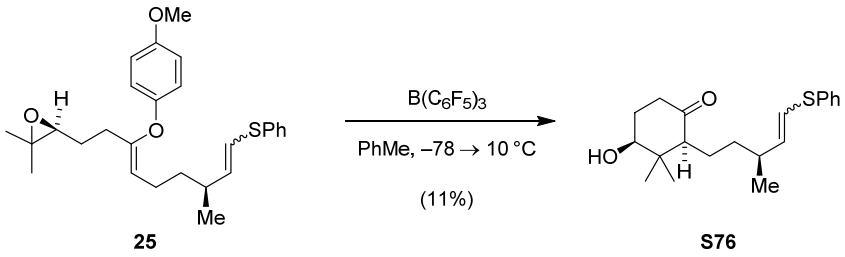
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.50–7.46 (m, 2H), 7.34–7.31 (m, 2H), 7.27 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.24 (tt, *J* = 7.1, 1.2 Hz, 1H), 6.72–6.70 (m, 1H), 6.69 (s, 1H), 4.86 (d, *J* = 6.4, 1H), 3.73 (s, 3H), 3.33–3.27 (m, 1H), 2.53–2.45 (m, 1H), 2.15–2.11 (m, 1H), 1.87–1.80 (m, 1H), 1.76 (dd, *J* = 6.6, 5.3 Hz, 1H), 1.74–1.66 (m, 2H), 1.53–1.49 (m, 3H), 1.27–1.25 (m, 1H), 1.20–1.14 (m, 1H), 1.09 (s, 3H), 1.07 (dd, *J* = 12.6 Hz, 3.1, 1H), 1.05 (s, 3H), 0.77 (d, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.6, 147.8, 137.4, 130.3, 129.4, 126.8, 123.9, 118.0, 114.6, 113.0, 78.3, 78.3, 55.8, 53.2, 47.5, 44.0, 39.4, 34.2, 32.4, 29.3, 27.6, 26.4, 16.5, 15.9, 15.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3425 (*br w*), 2942 (*m*), 1582 (*w*), 1490 (*vs*), 1221 (*s*), 1156 (*m*), 1043 (*s*), 1023 (*m*), 952 (*m*), 734 (*m*).

**HRMS** (EI) calc. for $C_{27}H_{34}O_3{}^{32}S$ $[M]^+$: 438.2223; found: 438.2224.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +7.6° (*c* = 0.26, $CH_2Cl_2$).




**25** **S76**

**Ketone S76**

To a solution epoxide **25** (5.0 mg, 11.4 μmol, 1 equiv) in toluene (1.1 mL) was added a solution of tris(pentafluorophenyl)borane (8.75 mg, 17.1 μmol, 1.50 equiv) in toluene (0.25 mL) dropwise at –78 °C. After 40 min, the reaction mixture was slowly allowed to warm to 10 °C within 3h. After 1h, saturated aqueous ammonium chloride solution (10 mL) was added and mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel (15% ethyl acetate in hexanes initially, grading to 25% ethyl acetate in hexanes) to obtain ketone **S76** (0.4 mg, 11%) as a colorless oil.

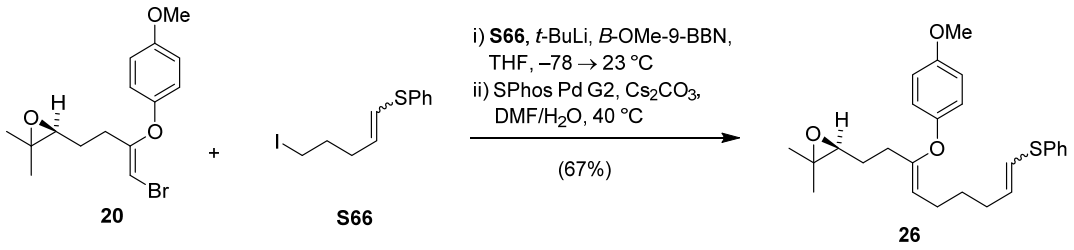
**TLC** (30% ethyl acetate in hexanes), $R_f$ = 0.32 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 400 MHz): (*Z*): δ = 7.37–7.26 (m, 4H), 7.23–7.14 (m, 1H), 6.18–6.08 (m, 1H), 5.61 (dd, *J* = 9.4, 9,4 Hz, 1H), 3.78 (dd, *J* = 10.7, 3.6 Hz, 1H), 2.73–2.59 (m, 1H), 2.43–2.33 (m, 2H), 2.18–2.10 (m, 1H), 2.09–2.01 (m, 1H), 1.87–1.72 (m, 2H), 1.50–1.40 (m, 1H), 1.38–1.24 (m, 1H), 1.12 (s, 3H), 1.08–0.99 (m, 4H), 0.70 (s, 3H); (*E*): δ = (*Z*): 7.37–7.26 (m, 4H), 7.23–7.14 (m, 1H), 6.18–6.08 (m, 1H), 5.86 (dd, *J* = 15.0, 8.1 Hz, 1H), 3.78 (dd, *J* = 10.7, 3.6 Hz, 1H), 2.43–2.33 (m, 2H), 2.32–2.22 (m, 1H), 2.18–2.10 (m, 1H), 2.09–2.01 (m, 1H), 1.87–1.72 (m, 2H), 1.50–1.40 (m, 1H), 1.38–1.24 (m,1H), 1.12 (s, 3H), 1.08–0.99 (m, 4H), 0.72 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 211.0, 139.8, 136.7, 129.1, 128.8, 126.2, 121.6, 76.2, 58.5, 43.7, 39.3, 36.7, 34.5, 31.0, 26.0, 21.3, 20.5, 14.9; (*E*): δ = 211.0, 143.2, 136.8, 129.1, 128.6, 126.2, 119.8, 76.1, 58.7, 43.7, 39.3, 38.3, 36.5, 31.0, 26.1, 21.4, 20.6, 15.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3422 (*br m*), 2964 (*m*), 1708 (*s*), 1583 (*w*), 1477 (*m*), 1439 (*m*), 1367 (*m*), 1024 (*m*), 741 (*s*), 690 (*s*).

**HRMS** (EI) calc. for $C_{20}H_{28}O_2{}^{32}S$ $[M]^+$: 332.1805; found: 332.1801.




**Enol ether 26**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of iodide **S66** (5.56 g, 18.3 mmol, 1.30 equiv) in tetrahydrofuran (74 mL) and *B*-methoxy-9-BBN (1.00 M in hexanes, 42.2 mL, 42.2 mmol, 3.00 equiv) was added a solution of *t*-butyllithium (1.60 M in pentane, 34.3 mL, 54.8 mmol, 3.90 equiv) dropwise at –78 °C. After 10 min, the yellow solution was allowed to warm to 23 °C upon it turned colorless again. After 25 min, the reaction mixture was transferred to a suspension of bromoenol ether **20** (4.60 g, 14.1 mmol, 1 equiv), cesium carbonate (9.16 g, 28.1 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (507 mg, 0.70 mmol, 0.05 equiv) and SPhos (289 mg, 0.70 mmol, 0.05 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 140 mL) and heated to 40 °C. After 19 h, water (400 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give enol ether **26** (4.01 g, 67%) as a yellow oil.

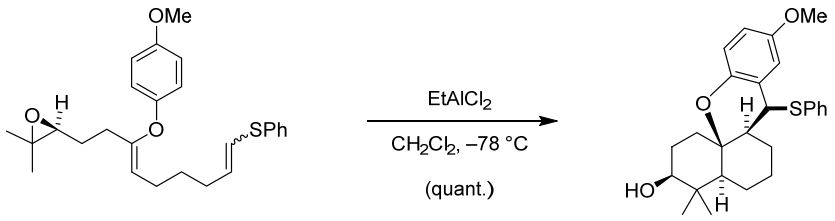
**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.47 (UV, anis).

**$^1$H NMR** ($CDCl_3$, 400 MHz): (*Z*): δ = 7.37–7.24 (m, 4H), 7.24–7.15 (m, 1H), 6.93–6.84 (m, 4H), 6.20 (d, *J* = 9.2 Hz, 1H), 5.86–5.77 (m, 1H), 5.08 (t, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 2.73 (t, *J* = 6.2 Hz, 1H), 2.39–2.05 (m, 6H), 1.78–1.62 (m, 2H), 1.58–1.47 (m, 2H), 1.31 (s, 3H), 1.25 (s, 3H); (*E*): δ = 7.37–7.24 (m, 4H), 7.24–7.15 (m, 1H), 6.93–6.84 (m, 4H), 6.14 (d, *J* = 14.6, 1H), 5.97 (dt, *J* = 14.6, 6.9 Hz, 1H), 5.04 (t, *J* = 5.7 Hz, 1H), 3.79 (s, 3H), 2.73 (t, *J* = 6.2 Hz, 1H), 2.39–2.05 (m, 6H), 1.78–1.62 (m, 2H), 1.58–1.47 (m, 2H), 1.31 (s, 3H), 1.25 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*): δ = 154.6, 150.6, 150.3, 136.5, 133.2, 129.1, 128.9, 126.2, 123.0, 117.3, 114.8, 114.8, 63.8, 58.6, 55.8, 29.2, 29.0, 28.9, 26.6, 25.0, 24.8, 18.8; (*E*): δ = 154.6, 150.7, 150.2, 137.1, 136.6, 129.0, 128.5, 126.2, 121.2, 117.2, 115.7, 114.8, 63.8, 58.6, 55.8, 32.8, 29.2, 29.0, 26.6, 25.0, 24.7, 18.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2926 (*w*), 1683 (*w*), 1584 (*w*), 1503 (*vs*), 1440 (*w*), 1209 (*s*), 1037 (*m*), 829 (*w*), 739 (*m*), 690 (*w*).

**HRMS** (EI) calc. for $C_{26}H_{32}O_3{}^{32}S$ $[M]^+$: 424.2072; found: 424.2064.




**26** **28**

**Tetracycle 28**

To a solution epoxide **26** (1.90 g, 4.47 mmol, 1 equiv) in dichloromethane (450 mL) was added a solution of ethylaluminum dichloride (1.00 M in hexanes, 4.92 mL, 4.92 mmol, 1.15 equiv) in dichloromethane (20 mL) dropwise at –78 °C over a period of 5 min. After 15 min, saturated aqueous ammonium chloride solution (500 mL) and saturated aqueous sodium chloride solution (200 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 500 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica, the filtrate was concentrated and the crude tetracycle **28** was directly used in the following reactions.

*Note: When performing the reaction on 60 mg scale tetracycle **28** (55 mg, 91%) was isolated as a colorless foam after flash-column chromatography on silca gel (20% ethyl acetate in hexanes).*

**TLC** (30% ethyl acetate in hexanes), $R_f$ = 0.52 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.47 (t, *J* = 8.6 Hz, 1.1, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.24 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.21–7.20 (m, 1H), 6.77–6.74 (m, 2H), 4.77 (d, *J* = 5.2 Hz, 1H), 3.72 (s, 3H), 3.29 (dd, *J* = 11.8, 3.4 Hz, 1H), 2.13–2.09 (m, 1H), 2.04–2.00 (m, 1H), 1.88–1.83 (m, 1H), 1.79–1.69 (m, 1H), 1.68–1.61 (m, 3H), 1.58–1.53 (m, 1H), 1.36 (br s, 1H), 1.29–1.23 (m, 1H), 1.22–1.16 (m, 1H), 1.12–1.07 (m, 1H), 1.06 (s, 3H), 1.06–1.03 (m, 1H), 1.02 (s, 3H).

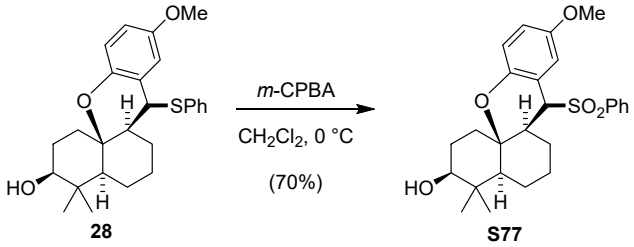
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.4, 146.3, 136.8, 130.3, 129.3, 126.8, 121.4, 118.1, 115.3, 113.6, 78.2, 77.3, 55.8, 52.0, 47.8, 43.0, 39.2, 31.6, 27.3, 26.4, 25.9, 23.3, 21.3, 15.1.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3424 (*br w*), 2939 (*s*), 1582 (*w*), 1489 (*vs*), 1271 (*m*), 1220 (*s*), 1038 (*s*), 909 (*m*), 736 (*s*), 691 (*m*).

**HRMS** (EI) calc. for $C_{26}H_{32}O_3{}^{32}S$ $[M]^+$: 424.2072; found: 424.2066.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –3.2° (*c* = 1.00, $CH_2Cl_2$).

### 3.3.1.4. Synthesis of Enone 30




**Sulfone S77**

To a solution of crude tetracycle **28** (550 mg, 1.30 mmol, 1 equiv) in dichloromethane (19 mL) was added *m*-chloroperbenzoic acid (626 mg, 2.72 mmol, 2.10 equiv) at 0 °C. After 2 h, saturated aqueous sodium bicarbonate solution (75 mL) was added and the mixture was extracted with dichloromethane (3 × 75 mL). The combined oranic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel (50% ethyl acetate in hexanes) to yield sulfone **S77** (416 mg, 70%) as a white foam.

**TLC** (50% ethyl acetate in hexanes), $R_f$ = 0.24 (UV, CAM).

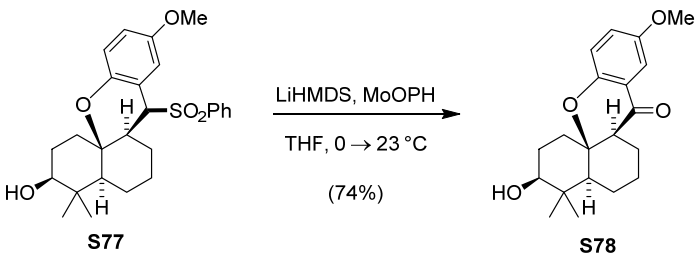
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 8.07–7.94 (m, 2H), 7.72–7.68 (m, 1H), 7.64–7.61 (m, 2H), 7.32 (d, *J* = 2.6 Hz, 1H), 6.82 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 4.85 (d, *J* = 4.8 Hz, 1H), 3.69 (s, 3H), 3.26 (dd, *J* = 11.9, 4.0 Hz, 1H), 2.10–2.05 (m, 1H), 1.98–1.93 (m, 1H), 1.84–1.78 (m, 1H), 1.71–1.63 (m, 2H), 1.63–1.59 (m, 2H), 1.55–1.51 (m, 1H), 1.34–1.28 (m, 1H), 1.26 (s, 1H), 1.16–1.10 (m, 2H), 1.03 (s, 3H), 1.01–1.00 (m, 1H), 0.99 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.4, 146.6, 140.9, 134.0, 129.6, 128.1, 119.0, 117.1, 113.2, 112.3, 77.9, 76.8, 62.7, 55.9, 51.8, 40.6, 39.3, 31.3, 27.1, 26.3, 25.4, 23.2, 21.0, 15.0.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3536 (*br w*), 2939 (*m*), 1492 (*s*), 1446 (*m*), 1306 (*m*), 1224 (*s*), 1141 (*vs*), 1085 (*m*), 1038 (*s*), 910 (*m*), 726 (*vs*).

**HRMS** (ESI) calc. for $C_{26}H_{31}O_5{}^{32}S$ $[M–H]^-$: 455.1898; found: 455.1901.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +31.9° (*c* = 0.84, $CH_2Cl_2$).




**Ketone S78**

To a solution of sulfone **S77** (200 mg, 0.44 mmol, 1 equiv) in tetrahydrofuran (26 mL) was added lithium bis(trimethylsilyl)amine solution (1.00 M in tetrahydrofuran, 2.63 mL, 2.63 mmol, 6.00 equiv) at 0 °C. After 30 min, a solution of MoOPH[185] (228 mg, 0.53 mmol, 1.20 equiv) in tetrahydrofuran (13 mL) was added at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 3 h, saturated aqueous sodium sulfite solution (60 mL) was added and the mixture was extracted with diethyl ether (3 × 60 mL). The combined oranic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel (30% ethyl acetate in hexanes) to yield ketone **S78** (107 mg, 74%) as an off-white foam.

**TLC** (40% ethyl acetate in hexanes), $R_f$ = 0.21 (UV, CAM).

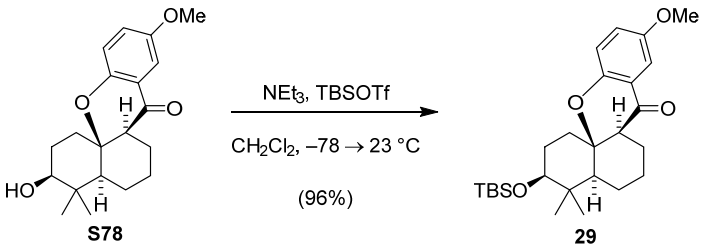
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.27 (d, *J* = 3.2 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.34 (dd, *J* = 11.8, 3.9 Hz, 1H), 2.22–2.18 (m, 1H), 2.13 (dd, *J* = 12.9, 4.7 Hz, 1H), 1.94–1.89 (m, 1H), 1.78–1.73 (m, 2H), 1.73–1.68 (m, 1H), 1.68–1.63 (m, 1H), 1.54–1.47 (m, 2H), 1.40 (s, 1H), 1.37–1.32 (m, 1H), 1.21–1.15 (m, 1H), 1.11 (s, 3H), 1.10–1.07 (m, 1H), 1.07 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 196.4, 154.0, 152.8, 125.3, 119.7, 119.4, 107.5, 80.6, 78.2, 55.9, 54.4, 50.9, 39.3, 30.6, 27.3, 26.9, 26.5, 25.4, 21.2, 15.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3451 (*br w*), 2939 (*m*), 1678 (*m*), 1486 (*vs*), 1431 (*s*), 1282 (*s*), 1216 (*s*), 1126 (*m*), 1035 (*s*), 914 (*m*), 731 (*s*).

**HRMS** (ESI) calc. for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1904; found: 331.1907.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –49.6° (*c* = 1.00, $CH_2Cl_2$).




**Silyl ether 29**

To a solution of alcohol **S78** (50.0 mg, 0.15 mmol, 1 equiv) in dichloromethane (2.5 mL) and triethylamine (84.1 µL, 0.61 mmol, 4.00 equiv) was added freshly distilled (over $CaH_2$) *t*-butyldimthylsilyl trifluoromethanesulfonate (76.5 µL, 0.33 mmol, 2.20 equiv) at –78 °C. After 15 min, the reaction mixture was allowed to warm to 23 °C. After 15 min, saturated aqueous sodium bicarbonate solution (20 mL) was added and the mixture was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was

filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel (10% ethyl acetate in hexanes) to give silyl ether **29** (64.7 mg, 96%) as an off-white foam. Crystallization from dichloromethane gave crystals suitable for X-ray diffraction.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.36 (UV, CAM).

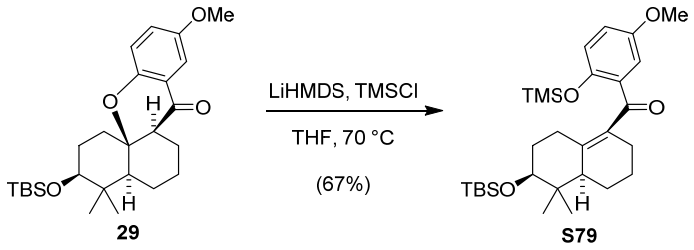
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.27–7.25 (m, 1H), 7.08 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.29 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.18–2.05 (m, 2H), 1.94–1.84 (m, 1H), 1.83–1.61 (m, 4H), 1.56–1.44 (m, 1H), 1.42–1.30 (m, 2H), 1.17–1.09 (m, 1H), 1.08 (s, 3H), 1.06–1.00 (m, 1H), 0.97 (s, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 196.7, 153.8, 153.0, 125.3, 119.9, 119.3, 107.3, 80.6, 78.7, 55.9, 54.4, 50.9, 39.9, 30.5, 27.7, 26.9, 26.9, 26.0, 25.4, 21.3, 18.2, 15.9, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2935 (*m*), 1687 (*m*), 1486 (*vs*), 1430 (*m*), 1280 (*s*), 1216 (*m*), 1099 (*s*), 944 (*m*), 879 (*s*), 934 (*s*), 773 (*s*).

**HRMS** (ESI) calc. for $C_{26}H_{41}O_4Si$ $[M+H]^+$: 445.2769; found: 445.2768.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –44.3° (*c* = 0.32, $CH_2Cl_2$).




**Enone S79**

To a solution of ketone **29** (5.0 mg, 0.01 mmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added lithium bis(trimethylsilyl)amine solution (1.00 M in tetrahydrofuran, 67.5 mL, 0.07 mmol, 6.00 equiv) at 23 °C and heated to 70 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C and freshly distilled (over $CaH_2$) trimethylsilyl chloride (14.4 mL, 0.11 mmol, 10.0 equiv) was added. After 10 min saturated aqueous sodium bicarbonate solution (10 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give enone **S79** (3.9 mg, 67%) as pale yellow oil.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.41 (UV, CAM).

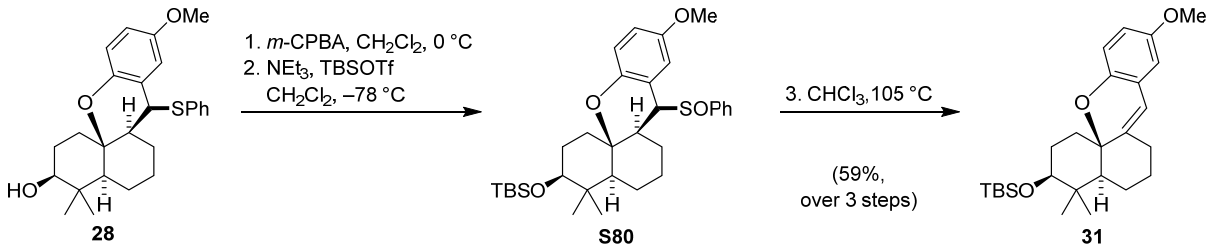
**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 6.98 (d, *J* = 3.2 Hz, 1H), 6.90 (dd, *J* = 8.8, 3.2 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 3H), 3.39 (dd, *J* = 11.3, 4.6 Hz, 1H), 2.59 (ddd, *J* = 14.4, 4.3, 2.7 Hz, 1H), 2.33–2.23 (m, 1H), 1.98–1.92 (m, 1H), 1.86–1.61 (m, 4H), 1.52–1.31 (m, 4H), 0.99 (s, 3H), 0.88 (s, 9H), 0.80 (s, 3H), 0.21 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ = 199.9, 154.4, 148.2, 142.4, 136.3, 133.2, 122.1, 119.0, 115.1, 78.6, 56.2, 47.3, 42.8, 31.6, 30.0, 28.2, 26.2, 25.7, 24.5, 23.1, 18.5, 14.9, 0.6, –3.7, –4.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2952 (*m*), 1655 (*w*), 1488 (*s*), 1251 (*s*), 1218 (*m*), 1101 (*m*), 1075 (*m*), 1042 (*m*), 913 (*m*), 835 (*vs*), 773 (*m*).

**HRMS** (EI) calc. for $C_{29}H_{48}O_4Si_2$ $[M]^+$: 516.3086; found: 516.3091.

$[\alpha]_D^{20}$ = –56.9° (*c* = 0.13, $CH_2Cl_2$).




**Stryrene 31**

To a solution of crude tetracycle **28** (1.90 g, 4.47 mmol, 1 equiv) in dichloromethane (53 mL) was added *m*-chloroperbenzoic acid (978 mg, 4.25 mmol, 0.95 equiv) at 0 °C. After 15 min, saturated aqueous sodium bicarbonate solution (250 mL) was added and the mixture was extracted with dichloromethane (3 × 250 mL). The combined oranic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica, the filtrate was concentrated and the crude sulfoxide (obtained as an inconsequential diastereomeric mixture) was directly used in the next reaction.

To a solution of the crude sulfoxide (1.81 g, 4.11 mmol, 1 equiv) in dichloromethane (22 mL) and triethylamine (2.29 mL, 16.5 mmol, 4.00 equiv) was added freshly distilled (over $CaH_2$) *t*-butyl-dimethylsilyl trifluoromethanesulfonate (1.89 mL, 8.23 mmol, 2.00 equiv) at –78 °C. After 1 h, saturated aqueous sodium bicarbonate solution (300 mL) was added and the mixture was extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was filtered through a short plug of silica, the filtrate was concentrated and the crude silyl ether **S80** (obtained as an inconsequential diastereomeric mixture) was directly used in the next reaction.

A solution of crude sulfoxide **S80** (1.80 g, 3.24 mmol, 1 equiv) in chloroform (45 mL) in a pressure flask was heated to 105 °C. After 24 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silca gel (10% ethyl acetate in hexanes) to furnish styrene **31** (1.13 g, 59%, over 3 steps) as a yellow oil.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.53 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 6.83 (d, *J* = 8.6 Hz, 1H), 6.64 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.57 (d, *J* = 3.0 Hz, 1H), 6.12 (d, *J* = 1.8 Hz, 1H), 3.75 (s, 3H), 3.35 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.32–2.24 (m,

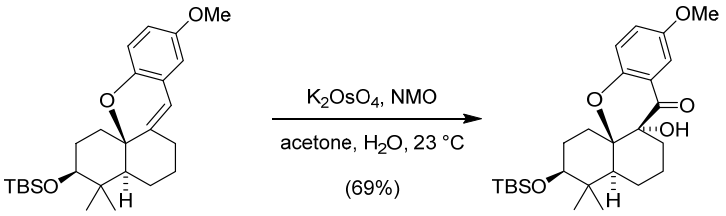
1H), 2.17–2.12 (m, 1H), 2.01–1.94 (m, 1H), 1.91–1.81 (m, 1H), 1.79–1.71 (m, 1H), 1.71–1.58 (m, 3H), 1.49–1.45 (m, 1H), 1.42 –1.36 (m, 1H), 1.22–1.15 (m, 1H), 1.08 (s, 3H), 0.99 (s, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 154.0, 146.0, 141.4, 125.0, 118.4, 117.2, 113.2, 110.9, 79.3, 78.6, 55.9, 48.0, 39.9, 29.2, 28.4, 27.6, 26.5, 26.1, 22.2, 18.3, 16.6, 16.4, –3.6, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2933 (*s*), 1609 (*w*), 1490 (*s*), 1361 (*w*), 1226 (*s*), 1102 (*s*), 1066 (*s*), 953 (*m*), 881 (*s*), 835 (*vs*).

**HRMS** (EI) calc. for $C_{26}H_{40}O_3{}^{28}Si$ $[M]^+$: 428.2747; found: 428.2741.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –18.0° (*c* = 0.27, $CH_2Cl_2$).




**31** **S81**

**Hydroxyketone S81**

To a solution of styrene **31** (1.13 g, 2.64 mmol, 1 equiv) in acetone/water mixture (12 mL, 5:1 v/v%) was added *N*-methylmorpholin-*N*-oxide (1.54 g, 13.2 mmol, 5.00 equiv), followed by potassium oxmate(VI) dihydrate (48.6 mg, 0.13 mmol, 0.05 equiv) at 0 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 18 h, sodium sulfite (6.65 g, 52.7 mmol, 20.0 equiv) was added. After 30 min, the reaction mixture was separated between water (200 mL) and dichloromethane (200 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give α-hydroxyketone **S81** (841 mg, 69%) as a white foam.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.46 (UV, CAM).

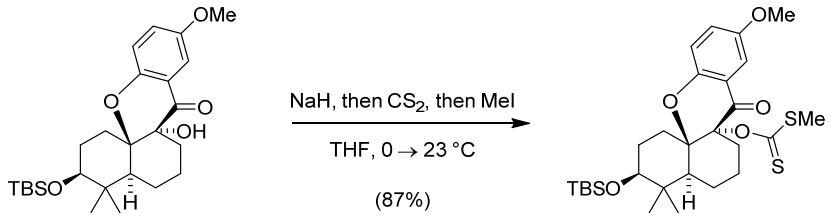
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.23 (d, *J* = 3.1 Hz, 1H), 7.13 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 3H), 3.59 (s, 1H), 3.30 (dd, *J* = 10.9, 4.2 Hz, 1H), 1.86–1.78 (m, 2H), 1.78–1.68 (m, 4H), 1.69–1.61 (m, 2H), 1.54 (dd, *J* = 12.1, 3.1 Hz, 1H), 1.39–1.32 (m, 2H), 1.06 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), –0.00 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 197.8, 154.0, 153.1, 126.2, 120.2, 118.1, 107.4, 84.9, 78.3, 75.9, 56.0, 45.7, 39.7, 33.2, 27.6, 26.6, 26.0, 24.4, 21.0, 20.7, 18.2, 15.7, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3485 (*w*), 2952 (*m*), 1685 (*m*), 1487 (*vs*), 1433 (*m*), 1220 (*s*), 1085 (*s*), 942 (*m*), 883 (*s*), 838 (*s*), 773 (*s*).

**HRMS** (ESI) calc. for $C_{26}H_{41}O_5{}^{28}Si$ $[M+H]^+$: 461.2718; found: 461.2724.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –111.2° (*c* = 0.53, $CH_2Cl_2$).




**S81** **32**

**Xanthogenate 32**

To a solution of α-hydroxyketone **S81** (841 mg, 1.83 mmol, 1 equiv) in tetrahydrofuran (25 mL) was added sodium hydride (60% dispersion in mineral oil, 730 mg, 18.3 mmol, 10.0 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 1 h, carbon disulfide (3.30 mL, 54.8 mmol, 30.0 equiv) was added to the grey suspension. After 1 h, methyl iodide (1.71 mL, 27.4 mL, 15.0 equiv) was added to the orange suspension. After 1.5 h, saturated aqueous ammonium chloride solution (200 mL) was added to the now yellow mixture and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel (5% ethyl acetate in hexanes) to give xanthogenate **32** (876 mg, 87%) as a yellow crystalline solid. Crystallization from dichloromethane gave crystals suitable for X-ray diffraction.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.51 (UV, CAM).

**melting point:** 114–116 °C

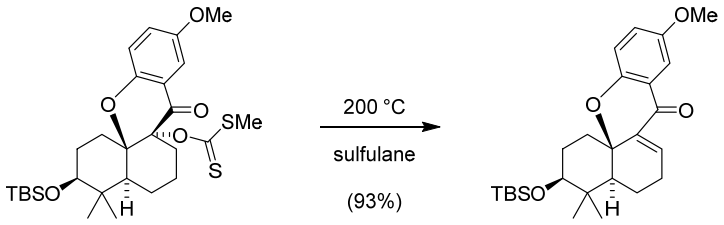
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.23 (d, *J* = 3.2 Hz, 1H), 7.10 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 3.78 (s, 3H), 3.75–3.72 (m, 1H), 3.31 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.60 (s, 3H), 1.98 (ddd, *J* = 14.7, 13.5, 4.0 Hz, 1H), 1.93–1.84 (m, 2H), 1.79–1.73 (m, 2H), 1.72–1.64 (m, 2H), 1.57–1.53 (m, 1H), 1.53–1.49 (m, 1H), 1.44–1.41 (m, 1H),1.09 (s, 3H), 1.00 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 214.0, 190.1, 154.4, 151.2, 125.4, 120.4, 119.6, 108.2, 92.4, 84.8, 78.3, 55.9, 45.6, 40.1, 27.8, 26.7, 26.5, 26.0, 24.9, 20.7, 20.4, 20.2, 18.2, 15.7, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2953 (*m*), 1707 (*m*), 1618 (*w*), 1488 (*vs*), 1430 (*m*), 1276 (*m*), 1218 (*s*), 1036 (*s*), 834 (*m*), 774 (*m*).

**HRMS** (EI) calc. for $C_{28}H_{42}O_5{}^{32}S_2{}^{28}Si$ $[M]^+$: 550.2243; found: 550.2239.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +46.1° (*c* = 0.46, $CH_2Cl_2$).




**32** **30**

**Enone 30**

A suspension of xanthogenate **32** (870 mg, 1.58 mmol, 1 equiv) in sulfulane (2 mL) was heated to 200 °C, whereupon the mixture becomes a clear solution. After 15 min, the reaction mixture is directly purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes, initially, grading to 15% ethyl acetate in hexanes) to furnish enone **30** (648 mg, 93%) as a white foam.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.29 (UV, CAM).

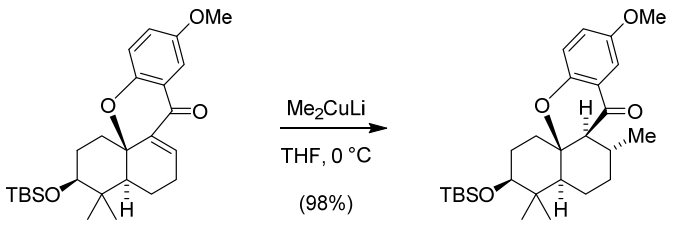
**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 7.35 (d, *J* = 3.2 Hz, 1H), 7.07 (dd, *J* = 8.9, 3.2 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.69 (d, *J* = 5.2 Hz, 1H), 3.80 (s, 3H), 3.36 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.48–2.39 (m, 1H), 2.37–2.32 (m, 1H), 2.16 – 2.07 (m, 1H), 1.86–1.79 (m, 1H), 1.78–1.71 (m, 1H), 1.67–1.58 (m, 1H), 1.48–1.41 (m, 1H), 1.31–1.27 (m, 1H), 1.23–1.16 (m, 1H), 1.11 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 186.0, 154.0, 153.5, 140.3, 138.0, 124.9, 122.9, 120.1, 107.5, 79.2, 78.7, 56.0, 50.5, 40.0, 30.1, 28.3, 28.0, 27.4, 26.0, 18.8, 18.3, 16.4, –3.6, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2954 (*m*), 1679 (*m*), 1640 (*m*), 1485 (*vs*), 1428 (*m*), 1282 (*s*), 1109 (*m*), 1074 (*s*), 882 (*s*), 835 (*s*), 776 (*s*).

**HRMS** (EI) calc. for $C_{26}H_{38}O_4{}^{28}Si$ $[M]^+$: 442.2539; found: 442.2539.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +133.6° (*c* = 1.00, $CH_2Cl_2$).




**30** **33**

**Ketone 33**

A suspension of copper(I) iodide (258 mg, 1.36 mmol, 10.0 equiv) in diethyl ether (6.0 mL) was added a solution of methyl lithium (1.60 M in diethyl ether, 1.69 mL, 2.71 mmol, 20.0 equiv) dropwise at 0 °C. After 30 min, a solution of enone **30** (60.0 mg, 0.14 mmol, 1 equiv) in diethyl ether (2.5 mL) was added to the reaction mixture at 0 °C. The transfer was quantitated with diethyl ether (2 × 0.5 mL). After 30 min, saturated aqueous ammonium chloride solution (40 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acete in hexanes) to give ketone **33** (60.1 mg, 98%) as a white foam.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.40 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.25 (d, *J* = 3.2 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.28 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.14–2.06 (m, 1H), 1.92–1.77 (m, 2H), 1.78–1.60 (m, 4H), 1.40–1.30 (m, 1H), 1.18–1.08 (m, 1H), 1.09–1.00 (m, 5H), 0.97 (s, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 6.0 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H).

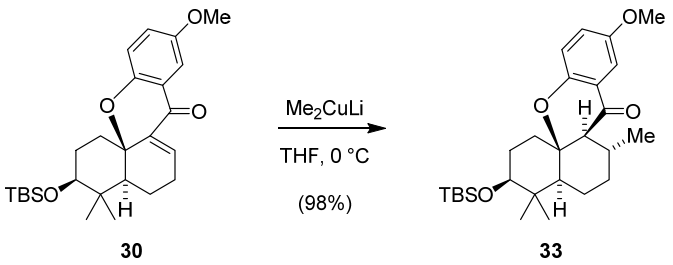
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 196.0, 153.7, 152.8, 125.0, 119.6, 119.6, 107.4, 81.0, 78.6, 61.1, 55.9, 51.0, 39.8, 34.7, 31.1, 30.5, 27.7, 26.9, 26.0, 21.3, 19.6, 18.2, 15.9, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*m*), 2854 (*w*), 1686 (*m*), 1485 (*vs*), 1429 (*m*), 1280 (*s*), 1175 (*m*), 1101 (*s*), 879 (*s*), 834 (*s*), 772 (*s*).

**HRMS** (EI) calc. for $C_{27}H_{42}O_4{}^{28}Si$ $[M]^+$: 458.2847; found: 458.2851.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –37.3° (*c* = 0.23, $CH_2Cl_2$).

### 3.3.1.5. Installation of the vicinal *cis*-Dimethylgroup




**30** **33**

**Ketone 33**

A suspension of copper(I) iodide (258 mg, 1.36 mmol, 10.0 equiv) in diethyl ether (6.0 mL) was added a solution of methyl lithium (1.60 M in diethyl ether, 1.69 mL, 2.71 mmol, 20.0 equiv) dropwise at 0 °C. After 30 min, a solution of enone **30** (60.0 mg, 0.14 mmol, 1 equiv) in diethyl ether (2.5 mL) was added to the reaction mixture at 0 °C. The transfer was quantitated with diethyl ether (2 × 0.5 mL). After 30 min, saturated aqueous ammonium chloride solution (40 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acete in hexanes) to give ketone **33** (60.1 mg, 98%) as a white foam.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.40 (UV, CAM).

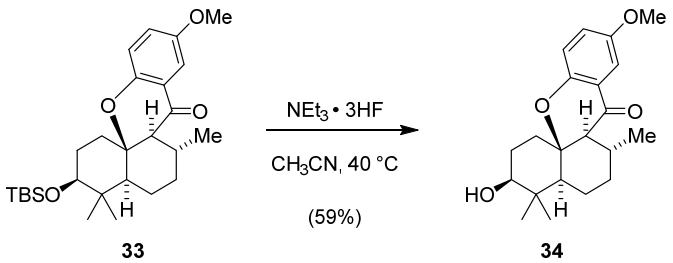
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.25 (d, *J* = 3.2 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.28 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.14–2.06 (m, 1H), 1.92–1.77 (m, 2H), 1.78–1.60 (m, 4H), 1.40–1.30 (m, 1H), 1.18–1.08 (m, 1H), 1.09–1.00 (m, 5H), 0.97 (s, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 6.0 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 196.0, 153.7, 152.8, 125.0, 119.6, 119.6, 107.4, 81.0, 78.6, 61.1, 55.9, 51.0, 39.8, 34.7, 31.1, 30.5, 27.7, 26.9, 26.0, 21.3, 19.6, 18.2, 15.9, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2951 (*m*), 2854 (*w*), 1686 (*m*), 1485 (*vs*), 1429 (*m*), 1280 (*s*), 1175 (*m*), 1101 (*s*), 879 (*s*), 834 (*s*), 772 (*s*).

**HRMS** (EI) calc. for $C_{27}H_{42}O_4{}^{28}Si$ $[M]^+$: 458.2847; found: 458.2851.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –37.3° (*c* = 0.23, $CH_2Cl_2$).




**Alcohol 34**

To a solution of silyl ether **33** (12.0 mg, 0.03 mmol, 1 equiv) in acetonitrile (0.2 mL) was added triethylamine trihydrofluoride (93.2 µL, 0.53 mmol, 20.0 equiv) at 40 °C. After 7 days, saturated aqueous sodium bicarbonate solution (10 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acete in hexanes initially, grading to 40% ethyl acetate in hexanes) to give alcohol **34** (5.3 mg, 59%) as a white foam. Crystallization from diethyl ether gave crystals suitable for X-ray diffraction.

**TLC** (40% ethyl acetate in hexanes), $R_f$ = 0.23 (UV, CAM).

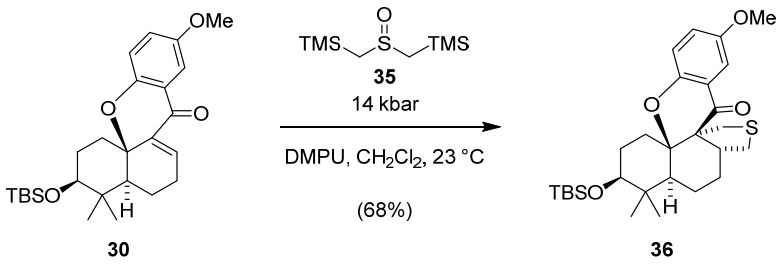
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.26 (d, *J* = 3.2 Hz, 1H), 7.08 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.33 (dd, *J* = 11.8, 4.1 Hz, 1H), 2.18–2.12 (m, 1H), 1.91–1.80 (m, 2H), 1.78–1.72 (m, 2H), 1.71–1.62 (m, 2H), 1.53–1.49 (m, 1H), 1.25 (s, 1H), 1.21–1.15 (m, 1H), 1.10 (s, 3H), 1.09–1.04 (m, 5H), 0.84 (d, *J* = 6.4 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 195.7, 153.9, 152.6, 125.1, 119.7, 119.5, 107.5, 81.0, 78.2, 61.0, 55.9, 50.9, 39.2, 34.6, 31.0, 30.6, 27.3, 26.5, 21.1, 19.6, 15.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3448 (*w*), 2938 (*w*), 1681 (*m*), 1486 (*vs*), 1430 (*m*), 1283 (*s*), 1216 (*m*), 1035 (*m*), 941 (*w*), 733 (*w*).

**HRMS** (EI) calc. for $C_{21}H_{28}O_4$ $[M]^+$: 344.1982; found: 344.1982.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –50.6° (*c* = 0.32, $CH_2Cl_2$).




**Tetrahydrothiophene 36**

Preparation of bis(trimethylsilylmethyl) sulfoxide **35**:

To a solution of bis(trimethylsilylmethyl) sulfide (350 mg, 1.69 mmol, 1 equiv) in dichloromethane (3.5 mL) was added a solution of *m*-chloroperoxybenzoic acid (77%, 418 mg, 1.86 mmol, 1.10 equiv) in dichloromethane (3.5 mL) dropwise at –78 °C. After 30 min, the reaction mixture was briefly allowed to warm to 0 °C. After 2 min, the mixture was diluted with dichloromethane (10 mL) and the organic phase was washed with ice-cold water (10 mL) and saturated aqueous sodium bicarbonate solution (2 × 10 mL). The washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated at 10 °C to give crude sulfoxide **35**.

*Note*: *it is of crucial importance for a successful dipolar cycloaddition to remove any residual m-chlorobenzoic acid; the sulfoxide can be stored at 10 °C for several hours*.

To a solution of enone **30** (75 mg, 0.17 mmol, 1 equiv) in dichloromethane and *N*,*N*'-dimethylpropyleneurea (1:1, 7.5 mL) in a high pressure Teflon vial was added freshly prepared sulfoxide **35** (188 mg, 0.85 mmol, 5.00 equiv). The closed vial was shaken and put under 14 kbar at 20 °C. After 3 h, the pressure was released and sulfoxide **35** (188 mg, 0.85 mmol, 5.00 equiv) was added. After 3 h, the reaction mixture was partitioned between 10% aqueous lithium chloride solution (30 mL) and diethyl ether (30 mL). The aquoues phase was extracted with diethyl ether (2 × 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel to yield tetrahydrothiophene **36** (58.2 mg, 68%) and starting enone **30** (11.7 mg, 16%) as a colorless foam. (*Note*: *The scale of the reaction is limited by the size of the teflon vial (max. 8.0 mL)).*


***Figure 1:*** *Left: Teflon vials used to carry out the high pressure reactions. Right: High Pressure apparatus by Andreas Hofer Hochdrucktechnik GmbH with a Julabo MA-4 circulation thermostat.*

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.37 (UV, CAM).

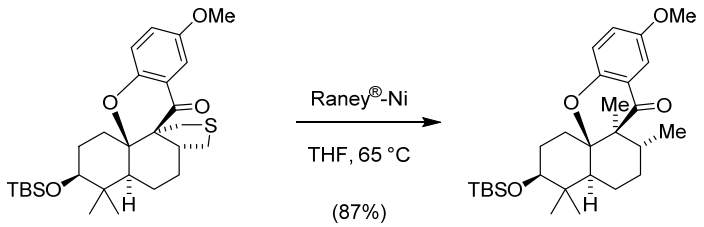
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 7.28 (d, *J* = 3.2 Hz, 1H), 7.09 (dd, *J*=9.0, 3.2 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.24 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.22 (d, *J* = 10.3 Hz, 1H), 2.74 (d, *J* = 10.3 Hz, 1H), 2.69 (dd, *J* = 10.9, 4.8 Hz, 1H), 2.48–2.44 (m, 2H), 2.01–1.96 (m, 2H), 1.81–1.72 (m, 3H), 1.68–1.62 (m, 1H), 1.40 (dd, *J* = 12.2, 3.0 Hz, 1H), 1.36–1.31 (m, 1H), 1.24–1.18 (m, 1H), 1.09 (s, 3H), 1.00 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 194.9, 153.9, 151.9, 125.4, 119.5, 118.5, 108.0, 84.1, 78.5, 63.8, 55.9, 46.0, 44.6, 39.8, 36.2, 31.1, 28.4, 28.2, 27.6, 26.6, 26.0, 20.4, 18.2, 15.8, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2951(*m*), 1683 (*m*), 1618 (*w*), 1488 (*vs*), 1430 (*m*), 1288 (*s*), 1223 (*m*), 1105 (*m*), 1035 (*m*), 835 (*m*).

**HRMS** (EI) calc. for $C_{28}H_{42}O_4{}^{32}S^{28}Si$ $[M]^+$: 502.2573; found: 502.2572.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –32.8° (*c* = 0.25, $CH_2Cl_2$).




**36** **S82**

**Ketone S82**

To a solution of tetrahydrothiophene **36** (160 mg, 0.32 mmol, 1 equiv) in tetrahydrofuran (19 mL) Raney®-Nickel (2800, slurry in water, 1.00 g) was added and the reaction mixture was heated to 65 °C. After 2 h, the reaction mixture was filtered through a plug of Celite® which was washed thoroughly with diethyl ether (50 mL). The filtrate was washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give ketone **S82** (134.5 mg, 87%) as a white foam.

**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.45 (UV, CAM).

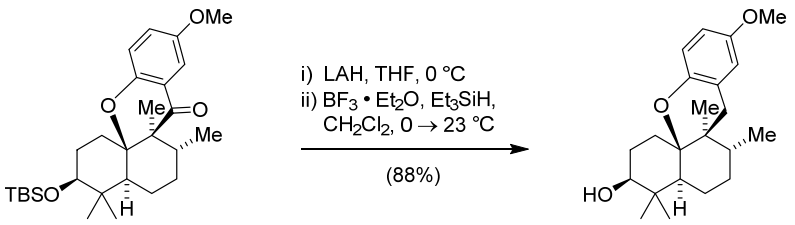
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.27 (d, *J* = 3.2 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 3.23 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.05–1.99 (m, 1H), 1.96–1.89 (m, 1H), 1.85–1.80 (m, 1H), 1.73–1.64 (m, 2H), 1.63–1.59 (m, 1H), 1.44–1.39 (m, 1H), 1.36 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.34–1.27 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.66 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 197.8, 153.7, 151.9, 124.7, 119.5, 119.4, 108.0, 85.6, 78.9, 55.9, 53.1, 45.5, 39.9, 32.8, 29.6, 28.1, 26.8, 26.6, 26.0, 21.7, 18.3, 16.2, 15.7, 9.7, –3.7, –4.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2956 (*m*), 1683 (*m*), 1488 (*vs*), 1429 (*m*), 1287 (*m*), 1222 (*m*), 1104 (*m*), 878 (*m*), 835 (*s*), 773 (*m*).

**HRMS** (EI) calc. for $C_{28}H_{44}O_4{}^{28}Si$ $[M]^+$: 472.3009; found: 472.2999.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –48.1° (*c* = 1.00, $CH_2Cl_2$).




**S82** **37**

**Alcohol 37**

To a suspension of lithium aluminum hydride (41.7 mg, 1.10 mmol, 4.00 equiv) in tetrahydrofuran (1.5 mL) was added a solution of ketone **S82** (130 mg, 0.28 mmol, 1 equiv) at 23 °C. After 15 min, the reaction mixture was diluted with diethyl ether (5 mL) then aqueous sodium hydroxide solution (10%, 25 μL) was added, followed by water (25 μL), After 10 min, sodium sulfate was added. The dried solution was filtered and the filtrate was concentrated to give the corresponding crude benzylic alcohol.

To a solution of benzylic alcohol and triethylsilane (88.4 μL, 0.55 mmol, 2.00 equiv) in dichloromethane (8.0 mL) was added boron trifluoride etherate (47% in diethyl ether, 0.14 mL, 0.55 mmol, 2.00 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, triethylsilane (0.11 mL, 0.69 mmol, 2.50 equiv) and boron trifluoride etherate (47% in diethyl ether, 0.18 mL, 0.69 mmol, 2.50 equiv) were added. After 45 min, saturated aqueous sodium bicarbonate solution (40 mL) was added and the mixture was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetae in hexanes) to furnish alcohol **37** (87 mg, 92%) as a white solid.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.36 (UV, CAM).

**melting point**: 173–175 °C

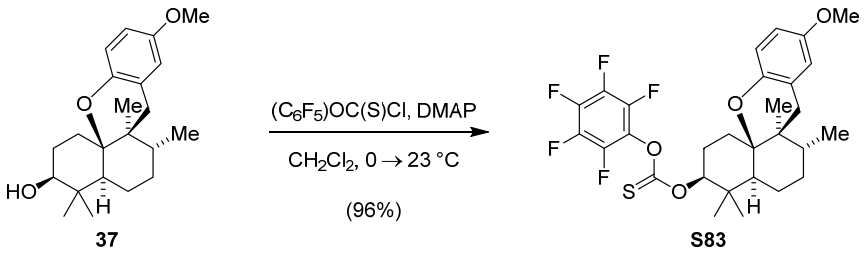
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.72 (d, *J* = 8.8 Hz, 1H), 6.68 (dd, *J* = 8.8 Hz, 3.0, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.26 (dd, *J* = 11.9, 3.7 Hz, 1H), 2.59 (d, *J* = 17.3 Hz, 1H), 2.52 (d, *J* = 17.3 Hz, 1H), 1.85–1.77 (m, 2H), 1.77–1.70 (m, 1H), 1.69–1.64 (m, 1H), 1.60–1.56 (m, 1H), 1.53–1.47 (m, 3H), 1.41 (dd, *J* = 12.7, 3.5 Hz, 1H), 1.35 (br s, 1H), 1.34–1.28 (m, 1H), 1.08 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.2, 146.3, 121.7, 117.5, 114.1, 113.3, 80.5, 78.6, 55.8, 45.5, 39.2, 37.5, 33.9, 31.7, 30.7, 27.6, 27.1, 26.5, 21.5, 17.0, 16.2, 15.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3263 (*br w*), 2943 (*m*), 1499 (*vs*), 1430 (*m*), 1222 (*s*), 1165 (*m*), 1044 (*s*), 933 (*m*), 858 (*w*), 800 (*m*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_3$ $[M]^+$: 344.2346; found: 344.2347.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +11.3° (*c* = 0.74, $CH_2Cl_2$).




**Thiocarbonate S83**

To a solution of alcohol **37** (80.0 mg, 0.23 mmol, 1 equiv), pyridine (93.9 µl, 1.16 mmol, 5.00 equiv) in dichloromethane (11.0 mL) and 4-dimethylaminopyridine (2.84 mg, 0.02 mmol, 0.10 equiv) was added pentafluorophenyl chlorothionoformate (93.2 µL, 0.58 mmol, 2.50 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 3.5 h, saturated aqueous sodium bicarbonate solution (30 mL) was added and the mixture was extracted with dichloromethane (4 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to furnish thiocarbonate **S83** (127.4 mg, 96%) as a colorless solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.59 (UV, CAM).

**melting point:** 189–191 °C

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.76 (d, *J* = 8.8 Hz, 1H), 6.70 (dd, *J* = 8.8 Hz, 2.9 Hz, 1H), 6.55 (d, *J* = 2.9 Hz, 1H), 4.98 (dd, *J* = 11.9 , 4.0 Hz, 1H), 3.75 (s, 3H), 2.63 (d, *J* = 17.5 Hz, 1H), 2.53 (d, *J* = 17.5 Hz, 1H), 2.04–1.95 (m, 1H), 1.94–1.78 (m, 3H), 1.74–1.66 (m, 1H), 1.64–1.50 (m, 4H), 1.42–1.29 (m, 1H), 1.26 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($^1$H decoupled, $CDCl_3$, 101 MHz): δ = 191.9, 153.4, 145.9, 142.94–139.87 (m), 141.63–138.42 (m), 139.71–136.17 (m), 128.14–127.20 (m), 121.6, 117.6, 114.2, 113.5, 94.7, 80.0, 55.8, 45.8, 38.9, 37.5, 33.9, 31.7, 30.4, 27.2, 26.9, 21.6, 21.2, 17.0, 16.8, 16.1.

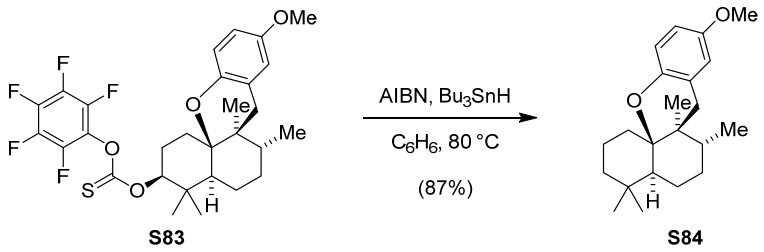
**$^{13}$C NMR** ($^{19}$F decoupled, $CDCl_3$, 101 MHz): δ = 191.9 (d, *J* = 4.2 Hz), 141.3, 140.0, 138.1, 127.7, 56.5, 55.1.

**$^{19}$F NMR** ($CDCl_3$, 376 MHz): δ = –152.25– –152.40 (m), –157.15 (t, *J* = 21.7 Hz), –162.18– –162.41.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (*w*), 1520 (*vs*), 1496 (*s*), 1311 (*m*), 1222 (*m*), 1142 (*s*), 997 (*s*), 954 (*s*), 736 (*w*).

**HRMS** (EI) calc. for $C_{29}H_{31}F_5O_4{}^{32}S$ $[M]^+$: 570.1858; found: 570.1855.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +30.8° (*c* = 0.24, $CH_2Cl_2$).




**S83** **S84**

**Methoxy-5-*epi*-aureol S84**

A solution of thiocarbonate **S83** (127.0 mg, 0.22 mmol, 1 equiv), tributyltin hydride (0.18 mL, 0.67 mmol, 3.00 equiv) and azobisisobutyronitrile (7.31 mg, 0.04 mmol, 0.20 equiv) in benzene (5.2 mL) was heated to 80 °C in a pressure flask. After 3 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to give **S84** (63.8 mg, 87%) as a white solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.54 (UV, CAM).

**melting point:** 143–146 °C

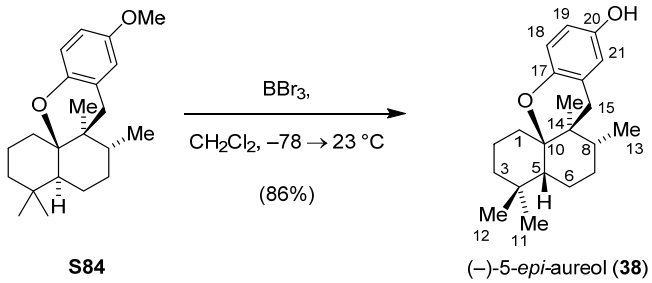
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.73 (d, *J* = 8.7 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.53 (d, *J* = 2.9 Hz, 1H), 3.74 (s, 3H), 2.57 (d, *J* = 17.3 Hz, 1H), 2.53 (d, *J* = 17.3 Hz, 1H), 1.75–1.70 (m, 2H), 1.69–1.63 (m, 2H), 1.56–1.54 (m, 1H), 1.50–1.45 (m, 1H), 1.45–1.41 (m, 1H), 1.38 (dd, *J* = 12.7, 3.5 Hz, 1H), 1.35–1.24 (m, 3H), 1.21–1.14 (m, 1H), 1.11 (s, 3H), 0.91 (s, 3H), 0.91 (s, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.0, 146.8, 122.0, 117.5, 114.1, 113.2, 81.2, 55.8, 45.7, 42.2, 37.4, 33.9, 33.6, 32.8, 31.9, 30.7, 28.7, 22.6, 22.0, 18.0, 17.0, 16.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2936 (*m*), 1496 (*vs*), 1250 (*m*), 1234 (*s*), 1223 (*s*), 1171 (*m*), 1151 (*w*), 1043 (*m*), 933 (*w*), 801 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_2$ $[M]^+$: 328.2402; found: 328.2395.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –7.4 (c = 1.00, $CH_2Cl_2$).




**S84** (–)-5-*epi*-aureol (**38**)

**(–)-5-*epi*-Aureol (38)**

To a solution of methyl ether **S84** (58.0 mg, 0.18 mmol, 1 equiv) in dichloromethane (1.8 mL) was added boron tribromide (1.00 M in hexanes, 1.80 mL, 1.77 mmol, 10.0 equiv) at –78 °C. After

10 min, the reaction mixture was allowed to warm to 23 °C. After 50 min, methanol (2 mL) was carefully added and the mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (20 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give (–)-5-*epi*-aureol (**38**) (47.5 mg, 86%) as a colorless solid.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.46 (UV, CAM).

**melting point:** 114–116 °C (reported 115–116 °C)[104]

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.67 (d, $^3J_{18/16}$ = 8.6 Hz, 1H, H-18), 6.58 (dd, $^3J_{19/18}$ = 8.6 Hz, $^4J_{19/21}$ = 3.0 Hz, 1H, H-19), 6.47 (d, $^4J_{21/19}$ = 3.0 Hz, 1H, H-21), 4.26 (br s, 1H, OH), 2.54 (d, $^2J_{15A/15B}$ = 17.3 Hz, 1H, H-15$_A$), 2.50 (d, $^2J_{15B/15A}$ = 17.3 Hz, 1H, 15$_B$), 1.75–1.69 (m, 2H; H-1$_A$, H-6$_A$), 1.69–1.63 (m, 2H, H-2$_A$, H-8), 1.58–1.52 (m, 1H, H-6$_B$), 1.50–1.45 (m, 1H, H-7$_A$), 1.45–1.42 (m, 1H, H-3$_A$), 1.38 (dd, $^3J_{5/6A}$ = 12.7 Hz, $^3J_{5/6B}$ = 3.6 Hz, 1H, H-5), 1.35–1.24 (m, 3H, H-1$_B$, H-2$_B$, H-7$_B$), 1.21–1.16 (m, 1H, H-3$_B$), 1.10 (s, 3H, H-11), 0.91 (s, 3H, H-12), 0.90 (s, 3H, H-14), 0.75 (d, $^3J_{13/8}$ = 6.8 Hz, 3H, H-13).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 148.5 (C-20), 146.8 (C-17), 122.2 (C-16), 117.6 (C-18), 115.5 (C-21), 114.4 (C-19), 81.2 (C-10), 45.7 (C-5), 42.2 (C-3), 37.4 (C-9), 33.7 (C-15), 33.6 (C-4), 32.8 (C-12), 31.9 (C-8), 30.7 (C-7), 28.7 (C-1), 22.6 (C-11), 22.0 (C-6), 18.0 (C-2), 17.0 (C-14), 16.4 (C-13).

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3350 (*br w*), 2927 (*vs*), 2854 (*s*), 1710 (*w*), 1495 (*s*), 1454 (*s*), 1234 (*s*), 1222 (*vs*), 1171 (*s*), 965 (*m*), 807 (*m*).

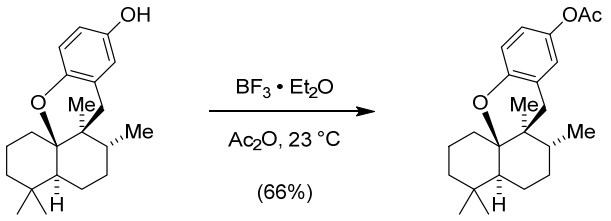
**HRMS** (EI) calc. for $C_{21}H_{30}O_2$ $[M]^+$: 314.2240; found: 314.2243.

$[\alpha]_D^{20}$ = –12.7 (c = 0.57, $CHCl_3$). +15.5 (c = 0.17, $CHCl_3$; (+)-5-*epi*-Aureol[105])

**Table 11:** Comparison of $^1$H NMR data for reported and synthetic 5-*epi*-aureol (**38**).

| Proton | Synthetic (800 MHz, $CDCl_3$) | Marcos (200 MHz, $CDCl_3$)[115] | Δδ (ppm) | v. d. Helm (270 MHz, $CDCl_3$)[104] | Δδ (ppm) |
|---|---|---|---|---|---|
| **1A** | 1.75–1.69 (m) | | | | |
| **1B** | 1.35–1.24 | | | | |
| **2A** | 1.69–1.63 (m) | | | | |
| **2B** | 1.35–1.24 (m) | | | | |
| **3A** | 1.45–1.42 (m) | | | | |
| **3B** | 1.21–1.16 (m) | 2.10–1.36 (m, 12H) | | not reported | |
| **5** | 1.37 (dd, 12.7, 3.6 Hz) | | | | |
| **6A** | 1.75–1.69 (m) | | | | |
| **6B** | 1.58–1.52 (m) | | | | |
| **7A** | 1.50–1.45 (m) | | | | |
| **7B** | 1.35–1.24 (m) | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **8** | 1.69–1.63 (m) | | | | |
| **11** | 1.10 (s) | 1.10 (s) | ± 0.00 | 1.13 (s) | – 0.03 |
| **12** | 0.91 (s) | 0.96 (s, 6H) | – 0.05 | 0.92 (br s, 6H) | – 0.01 |
| **13** | 0.75 (d, 6.8 Hz) | 0.75 (d, 6.8 Hz) | ± 0.00 | 0.77 (d, 7.5 Hz) | – 0.02 |
| **14** | 0.90 (s) | 0.96 (s, 6H) | – 0.06 | 0.92 (br s, 6H) | – 0.02 |
| **15A** | 2.54 (d, 17.3 Hz) | 2.52 (s, 2H) | + 0.02 | 2.54 (s,2H) | ± 0.00 |
| **15B** | 2.50 (d, 17.3 Hz) | | – 0.02 | | – 0.04 |
| **18** | 6.67 (d, 8.6 Hz) | 6.69 (d, 9.0 Hz) | – 0.02 | 6.69 (d, 9Hz) | – 0.02 |
| **19** | 6.59 (dd, 8.6, 3.0 Hz) | 6.60 (dd, 9.0, 3.1 Hz) | – 0.01 | 6.60 (dd, 9.0, 3.0 Hz) | – 0.01 |
| **21** | 6.47 (d, 3.0 Hz) | 6.49 (d, 3.1 Hz) | – 0.02 | 6.48 (d, 3 Hz) | – 0.01 |
| **OH** | 4.26 (br s) | 4.26 (s) | ± 0.00 | 4.30 (br s) | – 0.04 |




**38** **S85**

**Acetate S85**

To a solution of 5-*epi*-aureol (**38**) (2.0 mg, 6.36 μmol, 1 equiv) in acetic anhydride (0.4 mL) was added boron trifluoride etherate (47% in diethyl ether, 1 drop) at 23 °C. After 60 min, water (10 mL) was added and mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give acetate **S85** (1.5 mg, 66%) as a colorless oil. The obtained characterization data were in full agreement with those reported in literature.[115]

**TLC** (5% ethyl acetate in hexanes): $R_f$ = 0.35 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.79–6.76 (m, 2H), 6.71–6.68 (m, 1H), 2.55 (s, 2H), 2.26 (s, 3H), 1.77–1.59 (m, 4H), 1.59–1.55 (m, 1H), 1.51–1.41 (m, 2H), 1.38 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.35–1.23 (m, 3H), 1.23–1.13 (m, 1H), 1.10 (s, 3H), 0.91 (s, 3H), 0.91 (s, 3H), 0.74 (d, *J* = 6.8 Hz, 3H).

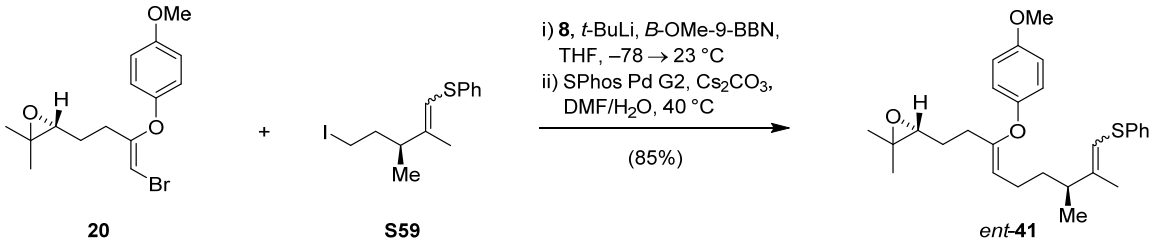
**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 170.2, 150.5, 143.4, 122.0, 121.8, 120.2, 117.5, 81.8, 45.8, 42.1, 37.3, 33.6, 33.6, 32.7, 31.9, 30.6, 28.9, 22.5, 22.0, 21.3, 18.0, 17.0, 16.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2941 (*m*), 1761 (*m*), 1494 (*m*), 1367 (*w*), 1202 (*s*), 1170 (*m*), 1140 (*w*), 1015 (*w*), 932 (*w*), 814 (*w*).

**HRMS** (EI) calc. for $C_{23}H_{32}O_3$ $[M]^+$: 356.2346; found: 356.2348.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –28.0 (c = 0.10, $CHCl_3$); –42.0 (c = 0.10, $CHCl_3$)[115]

### 3.3.1.6. 2nd Generation Synthesis




**Enol ether *ent*-41**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of iodide **S59** (6.34 g, 19.1 mmol, 1.30 equiv) in tetrahydrofuran (76 mL) and *B*-methoxy-9-BBN (1.00 M in hexanes, 44.0 mL, 44.0 mmol, 3.00 equiv) was added a solution of *t*-butyllithium (1.65 M in pentane, 34.7 mL, 57.2 mmol, 3.90 equiv) dropwise at –78 °C. After 5 min, the yellow solution was allowed to warm to 23 °C upon it turned colorless again. After 30 min, the reaction mixture was transferred to a suspension of bromoenol ether **20** (4.80 g, 14.7 mmol, 1 equiv), cesium carbonate (9.56 g, 29.3 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (529 mg, 0.73 mmol, 0.05 equiv) and SPhos (301 mg, 0.73 mmol, 0.05 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 140 mL) and heated to 40 °C. After 2 h, water (300 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (200 mL), the washed organic solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give enol ether *ent*-**41** (5.61 g, 85%) as a yellow oil.

*To obtain analytical pure samples, iodides (Z)-**S59** and (E)-**S59** were coupled separately under the same conditions to yield (Z)-ent-**41** and (E)-ent-**41**.*

**(*Z*)-*ent*-41:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.23 (UV, Anis).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.31–7.23 (m, 4H), 7.20–7.13 (m, 1H), 6.88–6.84 (m, 2H), 6.81 (d, *J* = 9.2 Hz, 2H), 5.87 (q, *J* = 1.3 Hz, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 3.07–2.96 (m, 1H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.34–2.23 (m, 1H), 2.23–2.13 (m, 1H), 2.12–2.02 (m, 1H), 2.02–1.92 (m, 1H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.70–1.62 (m, 2H), 1.49–1.39 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.6, 150.4, 150.4, 146.9, 137.7, 129.0, 128.1, 125.7, 117.2, 115.9, 115.8, 114.8, 63.8, 58.6, 55.8, 35.8, 34.6, 29.2, 26.6, 25.0, 23.3, 18.8, 18.8, 18.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*w*), 2925 (*w*), 1681 (*w*), 1584 (*w*), 1503 (*vs*), 1377 (*w*), 1209 (*s*), 1038 (*w*), 828 (*w*), 740 (*w*).

**HRMS** (ESI) calc. for $C_{28}H_{37}O_3{}^{32}S$ $[M+H]^+$: 453.2458 found: 453.2466.

$[\alpha]_D^{20}$ = –13.4° (*c* = 1.00, $CH_2Cl_2$).

**(*E*)-ent-41:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.23 (UV, Anis).

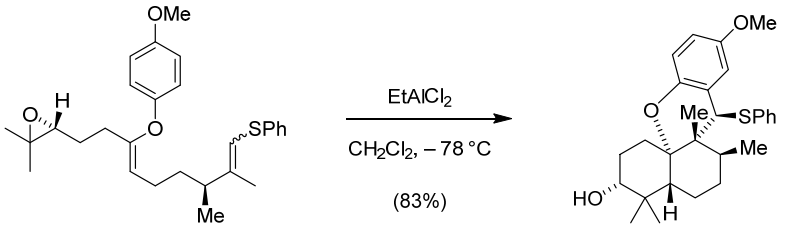
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.33–7.23 (m, 4H), 7.22–7.12 (m, 1H), 6.90–6.79 (m, 4H), 5.94 (s, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 2.72 (t, *J* = 6.3 Hz, 1H), 2.38–2.28 (m, 2H), 2.28–2.16 (m, 1H), 2.08–1.96 (m, 2H), 1.74 (d, *J* = 1.1 Hz, 3H), 1.73–1.62 (m, 2H), 1.55–1.47 (m, 1H), 1.45–1.35 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.6, 150.5, 150.3, 146.5, 137.5, 129.0, 128.1, 125.7, 117.2, 115.9, 115.6, 114.8, 63.8, 58.6, 55.8, 42.6, 34.8, 29.2, 26.6, 25.0, 23.4, 19.7, 18.8, 14.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*w*), 2924 (*w*), 1681 (*w*), 1583 (*w*), 1502 (*vs*), 1377 (*w*), 1208 (*s*), 1037 (*w*), 827 (*w*), 739 (*m*).

**HRMS** (ESI) calc. for $C_{28}H_{37}O_3{}^{32}S$ $[M+H]^+$: 453.2458 found: 453.2466.

$[\alpha]_D^{20}$ = –16.0° (*c* = 1.00, $CH_2Cl_2$).




*ent*-**41** *ent*-**43**

**Tetracycle *ent*-43**

*Note: The cyclization was carried out in two parallel 2.8 g batches.*

To a solution epoxide *ent*-**41** (2.80 g, 6.19 mmol, 1 equiv) in dichloromethane (620 mL) was added a solution of ethylaluminum dichloride (1.00 M in hexanes, 12.4 mL, 12.4 mmol, 2.00 equiv) in dichloromethane (30 mL) dropwise at –78 °C over a period of 5 min. After 30 min, saturated aqueous potassium sodium tartrate solution (300 mL) was added and the reaction mixture was allowed to warm to 23 °C under vigorous stirring. Water (150 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 200 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residues were combined and purified by flash-column chromatography on silica gel (15% ethyl acetate in hexanes) to yield decalin *ent*-**43** (4.64 g, 83%) as an off white foam.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.36 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 7.53 (dd, *J* = 8.3 Hz, 1.1, 2H), 7.38–7.33 (m, 2H), 7.28–7.24 (m, 1H), 6.75–6.68 (m, 3H), 4.36 (s, 1H), 3.65 (s, 3H), 3.31–3.24 (m, 1H), 2.09–2.04 (m, 1H), 1.87–1.80 (m,

1H), 1.75–1.70 (m, 2H), 1.70–1.65 (m, 1H), 1.61–1.52 (m, 3H), 1.43 (dd, *J* = 12.7, 3.3 Hz, 1H), 1.39–1.32 (m, 2H), 1.23 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 153.3, 144.3, 140.2, 131.2, 129.5, 127.0, 124.7, 118.2, 115.7, 114.4, 80.5, 78.2, 55.7, 55.0, 45.3, 44.5, 39.2, 33.6, 31.3, 28.6, 27.6, 26.4, 21.2, 16.8, 15.8, 15.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3376(*br w*), 2956 (*m*), 1494 (*vs*), 1438 (*m*), 1236 (*s*), 1156 (*m*), 1041 (*m*), 808 (*m*), 737 (*s*), 691 (*s*).

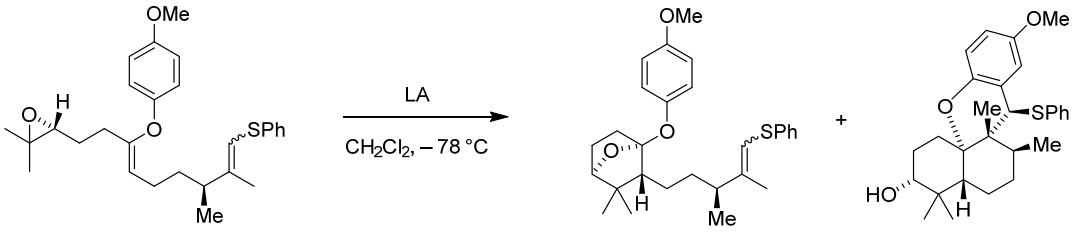
**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380; found: 452.2370.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –193.8° (*c* = 1.00, $CH_2Cl_2$).

**Lewis Acid screen:**

To a solution epoxide *ent*-**41** (10.0 mg, 0.02 mmol, 1 equiv) in dichloromethane (2.2 mL) was added a solution of the Lewis acid (Table 1, 0.44 mmol, 2.00 equiv) in dichloromethane (0.5 mL) dropwise at –78 °C. After the time indicated, water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield the tetracycle *ent*-**43** or acetal *ent*-**42**.

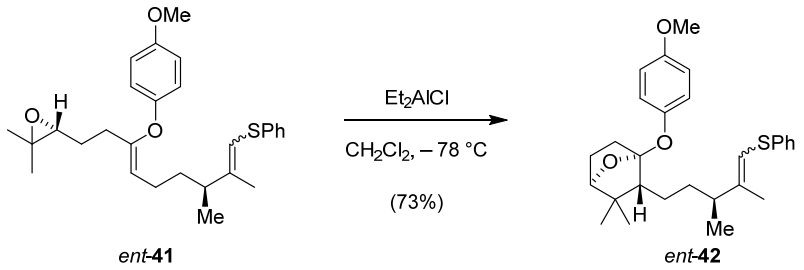
***Table 12:*** *Lewis acid screen for the cyclization of ent-**41**.*




*ent*-**41** *ent*-**42** *ent*-**43**

| Entry | Lewis acid | Time [min] | Yield ent-42 [%] | Yield ent-43 [%] |
|---|---|---|---|---|
| 1 | $EtAlCl_2$ | 10 | – | 83 |
| 2 | $Et_2AlCl$ | 150 | 51 | 39 |
| 3 | $SnCl_4$ | 10 | – | 66* |
| 4 | $B(C_6F_5)_3$ | 30 | – | 59 |

* along with inseperable impurities




*ent*-**41** *ent*-**42**

**Acetal *ent*-42**

*Note: The acetal formation was carried out with pure (Z)-ent-**41b** and (E)-ent-**41b** separately. The procedure is described for (Z)-ent-**42**. Diethylaluminum chloride was used instead of ethylaluminum dichloride.*

To a solution epoxide (*Z*)-*ent*-**41** (10.0 mg, 0.02 mmol, 1 equiv) in dichloromethane (2.2 mL) was added a solution of diethylaluminum chloride (1.00 M in hexanes, 44.2 µL, 0.44 mmol, 2.00 equiv) in dichloromethane (0.5 mL) dropwise at –78 °C. After 10 min, water (10 mL) was added. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield acetal (*Z*)-*ent*-**42** (7.3 mg, 73%) as a colorless oil.

**(*Z*)-*ent*-42:**

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.29 (dt, *J* = 7.7, 1.1 Hz, 2H), 7.25–7.22 (m, 2H), 7.14–7.11 (m, 1H), 7.10–7.07 (m, 2H), 6.81–6.77 (m, 2H), 5.88 (q, *J* = 1.3 Hz, 1H), 3.77 (s, 3H), 3.68 (d, *J* = 5.5 Hz, 1H), 3.09–3.02 (m, 1H), 1.96–1.88 (m, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.76–1.73 (m, 2H), 1.73–1.64 (m, 2H), 1.58–1.55 (m, 1H), 1.42–1.37 (m, 1H), 1.37–1.33 (m, 1H), 1.29–1.23 (m, 1H), 1.05 (s, 3H), 1.05–1.04 (m, 6H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 155.8, 148.6, 148.1, 137.9, 128.9, 128.0, 125.6, 122.5, 115.4, 114.2, 113.2, 81.4, 56.9, 55.7, 44.6, 36.8, 35.2, 29.9, 26.3, 25.4, 24.3, 24.0, 19.3, 18.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*m*), 1505 (*vs*), 1440 (*w*), 1299 (*w*), 1243 (*m*), 1213 (*s*), 1010 (*w*), 836 (*m*), 739 (*w*), 690 (*w*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380 found: 452.2378.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +3.1° (*c* = 0.37, $CH_2Cl_2$).

**(*E*)-*ent*-42:**

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.30–7.28 (m, 2H), 7.23–7.20 (m, 2H), 7.11 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.09–7.03 (m, 2H), 6.81–6.75 (m, 2H), 5.96 (s, 1H), 3.77 (s, 3H), 3.70 (d, *J* = 5.4 Hz, 1H), 2.35–2.29

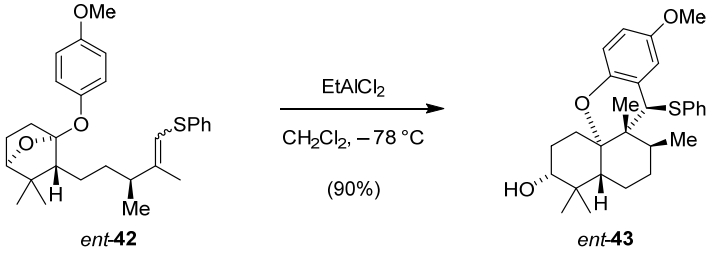
(m, 1H), 1.95–1.89 (m, 1H), 1.78 (d, $J$ = 1.1 Hz, 3H), 1.78–1.67 (m, 4H), 1.57 (t, $J$ = 6.9 Hz, 1H), 1.38–1.34 (m, 2H), 1.32–1.26 (m, 1H), 1.10 (s, 3H), 1.09 (d, $J$ = 6.8 Hz, 3H), 1.07 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 155.8, 148.5, 147.9, 137.7, 129.0, 128.1, 125.6, 122.6, 115.1, 114.2, 113.1, 81.4, 57.0, 55.7, 44.6, 43.9, 35.3, 29.9, 26.4, 25.3, 24.4, 23.9, 19.9, 14.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2958 (*m*), 1504 (*vs*), 1439 (*w*), 1297 (*m*), 1242 (*m*), 1212 (*s*), 1009 (*m*), 835 (*m*), 738 (*m*), 690 (*w*).

**HRMS** (EI) calc. for $C_{28}H_{36}O_3{}^{32}S$ $[M]^+$: 452.2380 found: 452.2374.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –58.7° (*c* = 0.32, $CH_2Cl_2$).

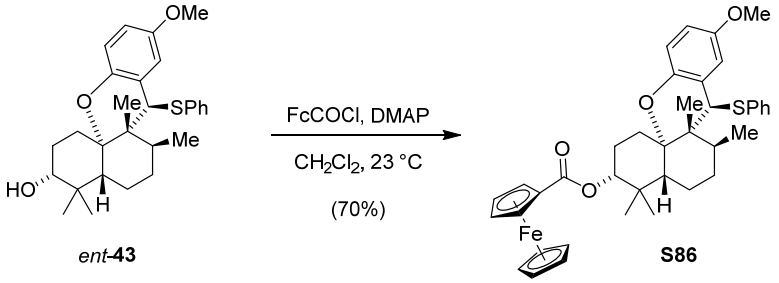



*ent*-**42** *ent*-**43**

**Tetracycle *ent*-43**

*Note: A 1:1 mixture of acetal (Z)-ent-**42** and (E)-ent-**42** was used.*

To a solution acetal *ent*-**42** (7.00 mg, 15.5 μmol, 1 equiv) in dichloromethane (1.5 mL) was added a solution of ethylaluminum dichloride (1.00 M in hexanes, 30.9 μL, 30.9 μmol, 2.00 equiv) in dichloromethane (0.3 mL) dropwise at –78 °C. After 15 min, water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residues were combined and purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes) to yield *ent*-**43** (6.3 mg, 90%) as a white foam.




*ent*-**43** **S86**

**Ferrocene S86**

To a suspension of ferrocene carboxylic acid (10.0 mg, 43.5 μmol, 2.00 equiv) in dichloromethane (1.0 mL) was added oxalyl chloride solution (2.00 M in dichloromethane, 23.9 μL, 47.8 μmol, 2.20 equiv), followed by 1 drop of *N*,*N*-dimethylformamide at 23 °C. After 45 min, toluene

(1.0 mL) was added and the mixture was concentrated. To a solution of tetracycle *ent*-**43** (10.0 mg, 22.1 μmol, 1 equiv) and 4-dimethylaminopyridine (27.0 mg, 0.22 mmol, 10.0 equiv) in dichloromethane (0.5 mL) was added a solution of the freshly prepared ferrocenecarboxylic acid chloride in dichloromethane (0.5 mL) at 23 °C. After 2 h, the reaction mixture was directly purified by flash-column chromatography on silica gel (dichloromethane) to yield ferrocene **S86** (10.2 mg, 70%) as an orange foam. Crystallization from diethyl ether gave crystals suitable for X-ray diffraction.

**TLC** (dichloromethane): $R_f$ = 0.63 (UV, CAM).

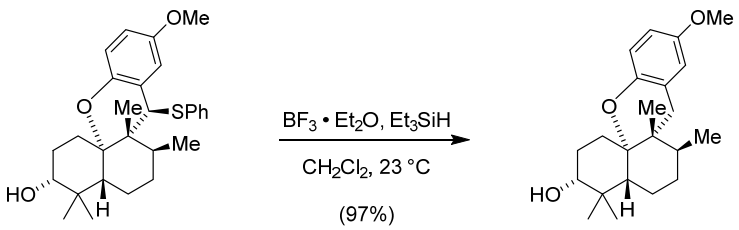
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 7.55–7.52 (m, 2H), 7.38–7.35 (m, 2H), 7.28–7.25 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.75–6.71 (m, 2H), 4.86–4.80 (m, 2H), 4.67 (dd, *J* = 11.6, 3.9 Hz, 1H), 4.43–4.38 (m, 2H), 4.38 (s, 1H), 4.20 (s, 5H), 3.65 (s, 3H), 2.15–2.07 (m, 1H), 1.94–1.79 (m, 3H), 1.73–1.68 (m, 2H), 1.63–1.57 (m, 3H), 1.46–1.32 (m, 1H), 1.27 (s, 6H), 1.04 (s, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 171.5, 153.4, 144.3, 140.1, 131.3, 129.5, 127.0, 124.8, 118.2, 115.8, 114.4, 80.4, 79.5, 72.2, 71.3, 71.2, 70.4, 70.1, 69.8, 55.7, 54.9, 45.5, 44.5, 38.2, 33.7, 31.2, 28.4, 27.6, 23.3, 21.1, 16.8, 16.6, 15.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2958 (*m*), 1707 (*s*), 1495 (*s*), 1459 (*m*), 1374 (*w*), 1275 (*s*), 1140 (*s*), 1040 (*m*), 963 (*w*), 821 (*w*).

**HRMS** (EI) calc. for $C_{39}H_{44}{}^{56}FeO_4{}^{32}S$ $[M]^+$: 664.2310 found: 664.2307.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –96.6° (*c* = 1.00, $CH_2Cl_2$).



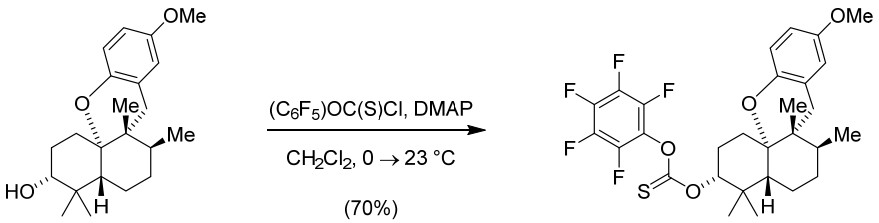

*ent*-**43** *ent*-**37**

**Alcohol *ent*-37**

To a solution of sulfide *ent*-**43** (4.50 g, 9.94 mmol, 1 equiv) in dichloromethane (45 mL) and triethylsilane (8.03 mL, 49.7 mmol, 5.00 equiv) was added boron trifluoride etherate (47% in diethyl ether, 6.53 mL, 24.9 mmol, 2.50 equiv) at 23 °C. After 15 min, saturated sodium bicarbonate solution (250 mL) was added and the mixture was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to afford *ent*-**37**

(3.34 g, 97%) as a white solid. The obtained characterization data were in full agreement with those of **37** (see page172).

$[\alpha]_D^{20}$ = –14.0° (*c* = 1.00, $CH_2Cl_2$).

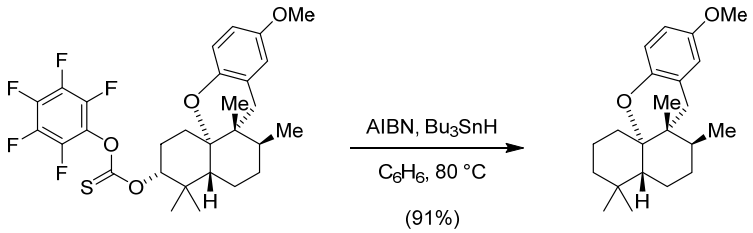



*ent*-**37** *ent*-**S83**

**Thiocarbonate *ent*-S83**

To a solution of alcohol *ent*-**37** (3.20 g, 9.29 mmol, 1 equiv) in dichloromethane (60 mL) and 4-dimethylaminopyridine (3.41 g, 27.9 mmol, 3.00 equiv) was added pentafluorophenyl chlorothionoformate (2.98 mL, 18.6 mmol, 2.00 equiv) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (200 mL) was added and the mixture was extracted with dichloromethane (4 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (4% ethyl acetate in hexanes) to furnish thiocarbonate *ent*-**S83** (3.72 g, 70%) as a colorless solid. The obtained characterization data were in full agreement with those of **S83** (see page 173).

$[\alpha]_D^{20}$ = –41.8° (*c* = 1.00, $CH_2Cl_2$).

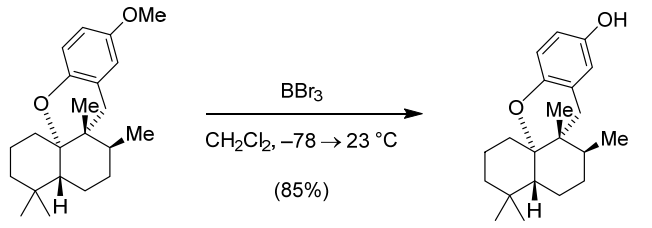



*ent*-**S83** *ent*-**S84**

**Methoxy-5-*epi*-aureol *ent*-S84**

A solution of thiocarbonate *ent*-**S83** (3.72 g, 6.52 mmol, 1 equiv), tributyltin hydride (5.27 mL, 19.6 mmol, 3.00 equiv) and azobisisobutyronitrile (214 mg, 1.30 mmol, 0.20 equiv) in benzene (150 mL) was heated to 80 °C in a pressure flask. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 2% ethyl acetate in hexanes) to give *ent*-**S84** (1.95 g, 91%) as a white solid. The obtained characterization data were in full agreement with those of **S84** (see page 174).

$[\alpha]_D^{20}$ = +13.1 (c = 1.00, $CH_2Cl_2$).

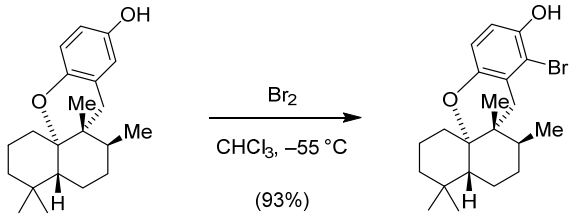



*ent*-**S84** (+)-5-*epi*-aureol (**38**)

**(+)-5-*epi*-Aureol (38)**

To a solution of methyl ether *ent*-**S84** (1.90 g, 5.78 mol, 1 equiv) in dichloromethane (55 mL) was added boron tribromide (1.00 M in hexanes, 57.8 mL, 57.8 mmol, 10.0 equiv) at –78 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 1.5 h, methanol (20 mL) was carefully added and the mixture was partitioned between saturated aqueous sodium bicarbonate solution (300 mL) and dichloromethane (150 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl aceate in hexanes) to give (+)-5-*epi*-aureol (**38**) (1.55 g, 85%) as a colorless solid. The obtained characterization data were in full agreement with those of (–)-5-*epi*-aureol (**38**) (see page 175).

$[\alpha]_D^{20}$ = +10.6 (c = 1.00, $CHCl_3$); +12.5 (c = 0.17, $CHCl_3$; (+)-5-*epi*-Aureol)[105]




**38** **S87**

**Bromide S87**

To a solution of (+)-5-*epi*-aureol (**38**) (1.55 g, 4.93 mmol, 1 equiv) in chloroform (150 mL) was added a solution of bromide in chloroform (0.22 M, 22.7 mL, 4.93 mmol, 1.00 equiv) dropwise at –55 °C over a period of 15 min. After 30 min, saturated aqueous sodium thiosulfate solution (100 mL) and saturated aqueous sodium chloride solution (100 mL) were added and the mixture was extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl aceate in hexanes) to give bromide **S87** (1.80 g, 93%) as a white solid.

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.47 (UV, CAM).

**melting point:** 158–160 °C

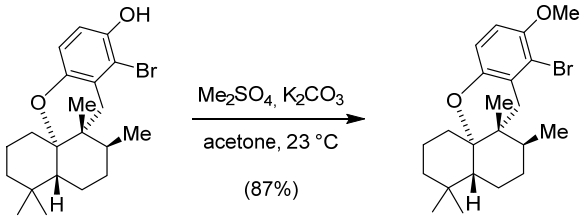
**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 6.82 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 5.11 (s, 1H), 2.71 (d, *J* = 17.8 Hz, 1H), 2.31 (d, *J* = 17.8 Hz, 1H), 1.74–1.65 (m, 2H), 1.63–1.54 (m, 3H), 1.51–1.46 (m, 1H), 1.45–1.42 (m, 1H), 1.40 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.35–1.24 (m, 3H), 1.22–1.15 (m, 1H), 1.10 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 147.0, 145.8, 121.3, 117.1, 114.0, 112.3, 81.2, 45.6, 42.1, 37.9, 35.1, 33.6, 32.7, 32.3, 30.6, 28.5, 22.5, 21.9, 17.9, 16.9, 16.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3487 (*w*), 2952 (*m*), 1475 (*vs*), 1431 (*m*), 1247 (*m*), 1193 (*m*), 1170 (*s*), 949 (*m*), 881 (*w*), 810 (*m*), 740 (*w*).

**HRMS** (EI) calc. for $C_{21}H_{29}O_2{}^{79}Br$ $[M]^+$: 392.1345; found: 392.1358.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = 9.6 (c = 1.00, $CH_2Cl_2$).




**S87** **44**

**Methyl ether 44**

To a suspension of phenol **S87** (1.77 g, 4.50 mmol, 1 equiv) and potassium carbonate (2.18 g, 15.7 mmol, 3.50 equiv) in acetone (25 mL) was added dimethyl sulfate (1.07 mL, 11.2 mmol, 2.50 equiv) at 23 °C. After 15 h, the reaction mixture was filtered through a plug of Celite® and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl aceate in hexanes) to give methyl ether **44** (1.60 g, 87%) as a white solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.54 (UV, CAM).

**melting point:** 202–204 °C

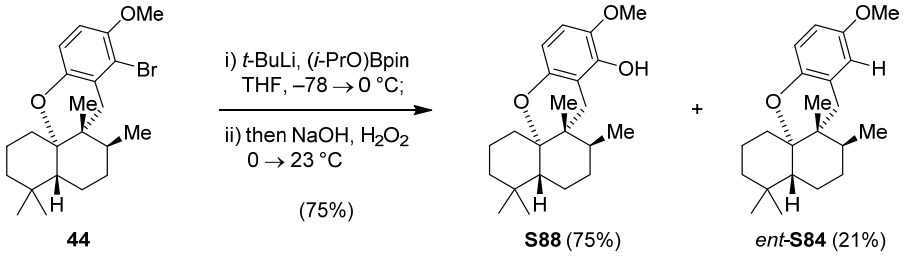
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 6.76 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 2.82 (d, *J* = 17.9 Hz, 1H), 2.32 (d, *J* = 17.9 Hz, 1H), 1.74–1.64 (m, 2H), 1.65–1.55 (m, 3H), 1.50–1.46 (m, 1H), 1.45–1.42 (m, 1H), 1.40 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.36–1.26 (m, 3H), 1.21–1.16 (m, 1H), 1.11 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 149.7, 147.7, 123.0, 115.9, 114.2, 111.3, 81.2, 57.1, 45.6, 42.1, 37.9, 35.2, 33.6, 32.7, 32.3, 30.6, 28.6, 22.6, 21.9, 18.0, 16.9, 16.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2930 (*m*), 1476 (*vs*), 1435 (*m*), 1387 (*w*), 1247 (*s*), 1170 (*m*), 1069 (*m*), 949 (*m*), 873 (*w*), 804 (*m*), 739 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{31}O_2{}^{79}Br$ $[M]^+$: 406.1502; found: 406.1503.

$[\alpha]_D^{20}$ = 5.0 (c = 1.00, $CH_2Cl_2$).




**44** **S88** (75%) *ent*-**S84** (21%)

**Phenol S88**

Isopropyl pinacol borate was dried by azeotropic distillation (benzene, 2 × 20 mL) prior to use. To a solution of bromide **44** (1.50 g, 3.68 mmol, 1 equiv) and isopropyl pinacol borate (3.01 mL, 14.7 mmol, 4.00 equiv) in tetrahydrofuran (37 mL) was added a solution of *t*-butyllithium (1.60 M in pentane, 6.91 mL, 11.0 mmol, 3.00 equiv) at –78 °C. After 1.5 h, the reaction mixture was allowed to warm to 0 °C. After 15 min, aqueous sodium hydroxide solution (10%; 15 mL) and aquoues hydrogen peroxide solution (30%; 30 mL) were added and the reaction mixture was allowed to warm to 23 °C. After 45 min, saturated aqueous ammonium chloride solution (200 mL) was added and the mixture was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl aceate in hexanes) to give phenol **S88** (949 mg, 75%) as a white solid and methyl ether *ent*-**S84** (259 mg, 21%) as a white solid.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.33 (UV, CAM).

**melting point:** 197–200 °C

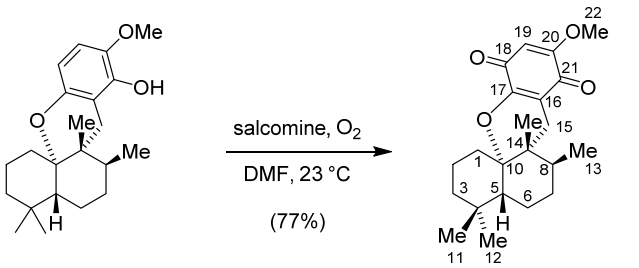
**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 6.67 (d, *J* = 8.7 Hz, 1H), 6.33 (d, *J* = 8.7 Hz, 1H), 5.63 (s, 1H), 3.83 (s, 3H), 2.79 (d, *J* = 17.6 Hz, 1H), 2.28 (d, *J* = 17.6 Hz, 1H), 1.79–1.74 (m, 1H), 1.74–1.69 (m, 1H), 1.69–1.61 (m, 2H), 1.57–1.53 (m, 1H), 1.50–1.46 (m, 1H), 1.45–1.41 (m, 1H), 1.39 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.35–1.25 (m, 3H), 1.22–1.16 (m, 1H), 1.11 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 147.6, 143.6, 139.5, 109.7, 109.2, 106.7, 81.0, 56.8, 45.7, 42.2, 36.8, 33.6, 32.8, 32.2, 30.7, 28.6, 28.1, 22.6, 22.0, 18.0, 17.1, 16.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3526 (*w*), 2949 (*m*), 1488 (*vs*), 1439 (*s*), 1242 (*vs*), 1170 (*s*), 1040 (*s*), 1027 (*s*), 925 (*m*), 795 (*m*), 738 (*m*).

**HRMS** (EI) calc. for $C_{22}H_{32}O_2$ $[M]^+$: 344.2346; found: 344.2352.

$[\alpha]_D^{20}$ = –3.5 (c = 1.00, $CH_2Cl_2$).




**S88** 5-*epi*-smenoqualone (**45**)

**5-*epi*-Smenoqualone (45)**

*N*,*N*′-Bis(salicylidene)ethylenediaminocobalt(II) (444 mg, 1.36 mmol, 0.50 equiv) was added to a solution of phenol **S88** (940 mg, 2.73 mmol, 1 equiv) in *N*,*N*-dimethylformamide (90 mL) at 23 °C and oxygen was bubbled through the reaction mixture for 30 min. After 30 min, water (200 mL) was added and the mixture was extracted with diethyl ether (4 × 200 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to give 5-*epi*-smenoqualone (**45**) (749 mg, 77%) as a yellow foam. Crystallization from diethyl ether gave **45** as yellow crystals.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.36 (UV, CAM).

**melting point**: 166–167 °C

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ 5.73 (s, 1H, H-19), 3.81 (s, 3H, H-22), 2.57 (d, $^2J_{15A/15B}$ = 18.8 Hz, 1H, H-$15_A$), 2.00 (d, $^2J_{15B/15A}$ = 18.8 Hz, 1H, H-$15_B$), 1.70–1.66 (m, 1H, H-$1_A$), 1.64–1.57 (m, 3H, H-6, H-$2_A$), 1.52–1.48 (m, 1H, H-$7_A$), 1.48–1.45 (m, 1H, H-$3_A$), 1.45–1.40 (m, 2H, H-5, H-8), 1.39–1.33 (m, 2H, H-$1_B$, H-$2_B$), 1.32–1.24 (m, 1H, H-$7_B$), 1.22–1.19 (m, 1H, H-$3_B$), 1.17 (s, 3H, H-11), 0.95 (s, 3H, H-14), 0.93 (s, 3H, H-12), 0.77 (d, $^3J_{13/8}$ = 6.7 Hz, 3H, H-13).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 181.6 (C-18), 181.5 (C-21), 159.6 (C-20), 152.8 (C-17), 115.3 (C-16), 105.0 (C-19), 86.6 (C-10), 56.5 (C-22), 45.8 (C5), 41.8 (C-3), 37.4 (C-9), 33.6 (C-4), 32.6 (C-12), 32.5 (C-8), 30.4 (C-7), 29.5 (C-1), 26.8 (C-15), 22.3 (C-11), 22.0 (C-6), 17.9 (C-2), 17.0 (C-14), 16.5 (C-13).

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942 (*w*), 1661 (*m*), 1639 (*w*), 1599 (*vs*), 1456 (*w*), 1353 (*w*), 1353 (*w*), 1227 (*m*), 1213 (*m*), 1161 (*w*), 1049 (*m*), 840 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{30}O_4$ $[M]^+$: 358.2139; found: 358.2140.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –83.4 (c = 1.00, $CHCl_3$); –75.6 (c = 0.16, $CHCl_3$; (–)-5-*epi*-Smenoqualone)[103]; +69.3 (c = 0.10, $CHCl_3$; (+)-5-*epi*-Smenoqualone).[115]

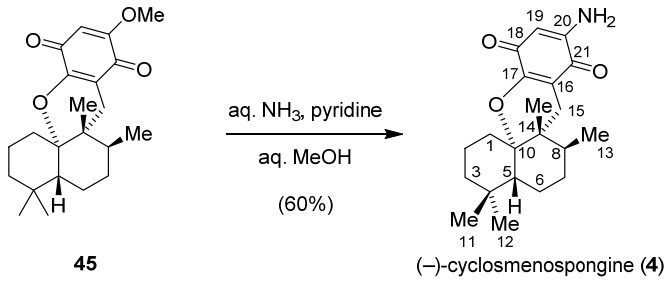
***Table 13:*** *Comparison of $^{1}H$ NMR data for reported and synthetic 5-epi-smenoqualone (**21**).*

| Proton | Synthetic (800 MHz, $CDCl_3$) | Marcos (200 MHz, $CDCl_3$)[115] | Δδ (ppm) | Capon (400 MHz, $CDCl_3$)[103] | Δδ (ppm) |
|---|---|---|---|---|---|
| **1A** | 1.70–1.66 (m) | | | | |
| **1B** | 1.39–1.33 (m) | | | | |
| **2A** | 1.64–1.57 (m) | | | | |
| **2B** | 1.39–1.33 (m) | | | | |
| **3A** | 1.48–1.45 (m) | | | | |
| **3B** | 1.22–1.19 (m) | 1.98–1.36 (m, 12H) | | not reported | |
| **5** | 1.45–1.40 (m) | | | | |
| **6** | 1.64–1.57 (m) | | | | |
| **7A** | 1.52–1.48 (m) | | | | |
| **7B** | 1.32–1.24 (m) | | | | |
| **8** | 1.45–1.40 (m) | | | | |
| **11** | 1.17 (s) | 1.17 (s) | ± 0.00 | 1.17 | ± 0.00 |
| **12** | 0.93 (s) | 0.94 | + 0.01 | 0.94 | + 0.01 |
| **13** | 0.77 (d, 6.7 Hz) | 0.77 (d, 6.0 Hz) | ± 0.00 | 0.77 (d, 6.0 Hz) | ± 0.00 |
| **14** | 0.95(s) | 0.96 (s) | + 0.01 | 0.96 | + 0.01 |
| **15A** | 2.57 (d, 18.8 Hz) | 2.57 (d, 20.0 Hz) | ± 0.00 | 2.57 (d, 20.0 Hz | ± 0.00 |
| **15B** | 2.00 (d, 18.8 Hz) | 2.00 (d, 20.0 Hz) | ± 0.00 | 2.00 (d, 20.0 Hz) | ± 0.00 |
| **19** | 5.73 (s) | 5.74 (s) | + 0.01 | 5.74 | + 0.01 |
| **22** | 3.81 (s) | 3.80 (s) | – 0.01 | 3.81 | ± 0.00 |

***Table 14:*** *Comparison of $^{13}C$ NMR data for reported and synthetic 5-epi-smenoqualone (**21**).*

| Carbon | Synthetic (201 MHz, $CDCl_3$) | Marcos (50 MHz, $CDCl_3$)[115] | Δδ (ppm) | Capon (100 MHz, $CDCl_3$)[103] | Δδ (ppm) |
|---|---|---|---|---|---|
| **1** | 29.5 | 29.5* | ± 0.0 | 29.4 | + 0.1 |
| **2** | 17.9 | 17.8 | + 0.1 | 17.8 | + 0.1 |
| **3** | 41.8 | 41.7 | + 0.1 | 41.7 | + 0.1 |
| **4** | 33.6 | 33.5 | + 0.1 | 33.5 | + 0.1 |
| **5** | 45.8 | 45.5 | + 0.3 | 45.6 | + 0.2 |
| **6** | 22.0 | 22.0 | ± 0.0 | 21.9 | + 0.1 |
| **7** | 30.4 | 30.3* | + 0.1 | 30.3 | + 0.1 |
| **8** | 32.5 | 32.4 | + 0.1 | 32.4 | + 0.1 |
| **9** | 37.4 | 37.0 | + 0.4 | 37.2 | + 0.2 |
| **10** | 86.6 | 86.5 | + 0.1 | 86.4 | + 0.2 |
| **11** | 22.3 | 22.3 | ± 0.0 | 22.2 | + 0.1 |
| **12** | 32.6 | 32.5 | + 0.1 | 32.5 | + 0.1 |
| **13** | 16.5 | 16.4 | + 0.1 | 16.4 | + 0.1 |
| **14** | 17.0 | 17.0 | ± 0.0 | 17.0 | ± 0.0 |
| **15** | 26.8 | 26.7* | + 0.1 | 26.7 | + 0.1 |
| **16** | 115.3 | 115.1 | + 0.2 | 115.2 | + 0.1 |
| **17** | 152.8 | 152.5 | + 0.3 | 152.7 | + 0.1 |
| **18** | 181.6 | 181.5 | + 0.1 | 181.4 | + 0.2 |
| **19** | 105.0 | 105.0 | ± 0.0 | 104.9 | + 0.1 |
| **20** | 159.6 | 159.5 | + 0.1 | 159.5 | + 0.1 |
| **21** | 181.5 | 181.5 | ± 0.0 | 181.5 | ± 0.0 |
| **22** | 56.5 | 56.4 | + 0.1 | 56.4 | + 0.1 |

* Carbon was reassigned by us on the basis of 2D NMR studies.




**(–)-Cyclosmenospongine (4)**

To a solution of 5-*epi*-smenoqualone (**45**) (740 mg, 2.06 mmol, 1 equiv) and pyridine (60 mL) in aqueous methanol (50%, 500 mL) was added aqueous ammonia (25%, 60 mL) at 23 °C. After 16h, the reaction mixture was concentrated and the residue was extracted with diethyl ether (5 × 300 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (20% ethyl acetate in hexanes initially, grading to 30% ethyl acetate in hexanes) to yield (–)-cyclosmenospongine (**4**) (423 mg, 60%) as a dark red crystalline solid. Recrystallization from diethyl ether gave crystals suitable for X-ray diffraction.

**TLC** (30% ethyl acetate in hexanes): $R_f$ = 0.21 (UV, CAM).

**melting point:** 240–242 °C

**$^1$H NMR** ($CDCl_3$, 800 MHz): δ = 5.54 (s, 1H, H-19), 5.05 (s, 2H, $NH_2$), 2.52 (d, $^2J_{15A/15B}$ = 18.3 Hz, 1H, H-15$_A$), 1.97 (d, $^2J_{15B/15A}$ = 18.3 Hz, 1H, H-15B), 1.74–1.69 (m, 1H, H-1$_A$), 1.67–1.58 (m, 3H, H-6, H-2$_A$), 1.52–1.44 (m, 3H, H-7$_A$, H-8, H-3$_A$), 1.42 (dd, $^3J_{5/6A}$ = 12.2 Hz, $^3J_{5/6B}$ = 4.1 Hz, 1H, H-5), 1.39–1.32 (m, 2H, H-1$_B$, H-2$_B$), 1.32–1.25 (m, 1H, H-7$_B$), 1.22–1.16 (m, 4H, H-3$_B$, H-11), 0.95 (s, 3H, H-14), 0.93 (s, 3H, H-12), 0.78 (d, $^3J_{13/8}$ = 6.6 Hz, 3H, H-13).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): δ = 182.6 (C-21), 180.3 (C-18), 154.8 (C-17), 147.6 (C-20), 113.0 (C-16), 99.5 (C-19), 86.6 (C-10), 45.8 (C-5), 41.9 (C-3), 37.3 (C-9), 33.6 (C-4), 32.6 (C-12), 32.4 (C-8), 30.4 (C-7), 29.7 (C-1), 26.7 (C-15), 22.3 (C-11), 22.0 (C-6), 18.0 (C-2), 17.0 (C-14), 16.5 (C-13).

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3452 (*w*), 3335 (*w*), 2947 (*w*), 1640 (*w*), 1595 (*vs*), 1456 (*w*), 1371 (*w*), 1215 (*m*), 1161 (*m*), 979 (*w*), 896 (*w*), 732 (*w*).

**HRMS** (EI) calc. for $C_{21}H_{29}O_3N$ $[M]^+$: 343.2142; found: 343.2140.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –346.6 (c = 0.12, $CHCl_3$); –18.0 (c = 0.10, $CHCl_3$; (–)-cyclosmenospongine).[95]

**Elemental Analysis** calc. (%) for $C_{21}H_{29}O_3N$: C 73.44, H 8.51, N 4.08; found: C 72.90, H 8.51, N 3.94.

***Table 15:*** *Comparison of $^{1}H$ NMR data for natural and synthetic (–)-cyclosmenospongine (**4**).*

| Proton | Synthetic (800 MHz, $CDCl_3$)* | Natural (300 MHz, $CDCl_3$)[95] | Δδ (ppm) |
|---|---|---|---|
| 1A | 1.74–1.69 (m) | 1.84 (m) | – 0.12 |
| 1B | 1.39–1.32 (m) | 1.49 (m) | – 0.13 |
| 2A | 1.67–1.58 (m) | 1.59 (m) | + 0.04 |
| 2B | 1.39–1.32 (m) | 1.51 (m) | – 0.15 |
| 3A | 1.52–1.44 (m) | 1.51 (m) | – 0.03 |
| 3B | 1.22–1.16 (m) | 1.25 (m) | – 0.06 |
| 5 | 1.42 (dd, 12.2, 4.1 Hz) | 1.51 (m) | – 0.09 |
| 6 | 1.67–1.58 (m) | 1.66 (m), 1.51 (m) | |
| 7A | 1.52–1.44 (m) | 1.54 (m) | – 0.06 |
| 7B | 1.32–1.25 (m) | 1.29 (m) | ± 0.00 |
| 8 | 1.52–1.44 (m) | 0.98 (m) | + 0.50 |
| 11 | 1.19 (s) | 1.02 (s) | + 0.17 |
| 12 | 0.93 (s) | 0.98 (s) | – 0.05 |
| 13 | 0.78 (d, 6.6 Hz) | 0.78 (d, 6.4 Hz) | ± 0.00 |
| 14 | 0.95 (s) | 0.97 (s) | – 0.02 |
| 15A | 2.52 (d, 18.3 Hz) | 2.57 (d, 18.8 Hz) | – 0.05 |
| 15B | 1.97 (d, 18.3 Hz) | 2.06 (d, 18.8 Hz) | – 0.09 |
| 19 | 5.54 (s) | 5.54 (s) | ± 0.00 |
| $NH_2$ | 5.05 (br s) | 5.65 (br) | – 0.50 |

* acid-free $CDCl_3$ was used for the NMR measurement.

***Table 16:*** *Comparison of $^{13}C$ NMR data for natural and synthetic (–)-cyclosmenospongine (**4**).*

| Carbon | Synthetic (201 MHz, $CDCl_3$)* | Natural (76 MHz, $CDCl_3$)[95] | Δδ (ppm) |
|---|---|---|---|
| 1 | 29.7 | 29.1 | + 0.6 |
| 2 | 18.0 | 17.8 | + 0.2 |
| 3 | 41.9 | 40.9 | + 1.0 |
| 4 | 33.6 | 33.2 | + 0.4 |
| 5 | 45.8 | 45.7 | + 0.1 |
| 6 | 22.0 | 22.0 | ± 0.0 |
| 7 | 30.4 | 30.1 | + 0.3 |
| 8 | 32.4 | 32.3 | + 0.1 |
| 9 | 37.3 | 37.6 | – 0.3 |
| 10 | 86.6 | 88.6 | – 2.0 |
| 11 | 22.3 | 22.4 | – 0.1 |
| 12 | 32.6 | 32.4 | + 0.2 |
| 13 | 16.5 | 16.3 | + 0.2 |
| 14 | 17.0 | 17.1 | – 0.1 |
| 15 | 26.7 | 26.7 | ± 0.0 |
| 16 | 113.0 | 113.3 | – 0.3 |
| 17 | 154.8 | 153.6 | + 1.2 |
| 18 | 180.3 | 177.6# | + 2.7 |
| 19 | 99.5 | 98.1 | + 1.4 |
| 20 | 147.6 | 152.3 | – 4.7 |
| 21 | 182.6 | 180.5# | + 2.1 |

* acid-free $CDCl_3$ was used for the NMR measurement.

# Carbon was reassigned by us on the basis of 2D-NMR studies.

### 3.3.2. NMR studies of (–)-Cyclosmenospongine (4)

#### 3.3.2.1 Concentration effects:

A $^{1}H$ NMR spectrum was recorded with different amounts of (–)-cyclosmenospongine (**4**) (1 mg, 5 mg, 10 mg, 30 mg) in $CDCl_3$ (0.7 mL).

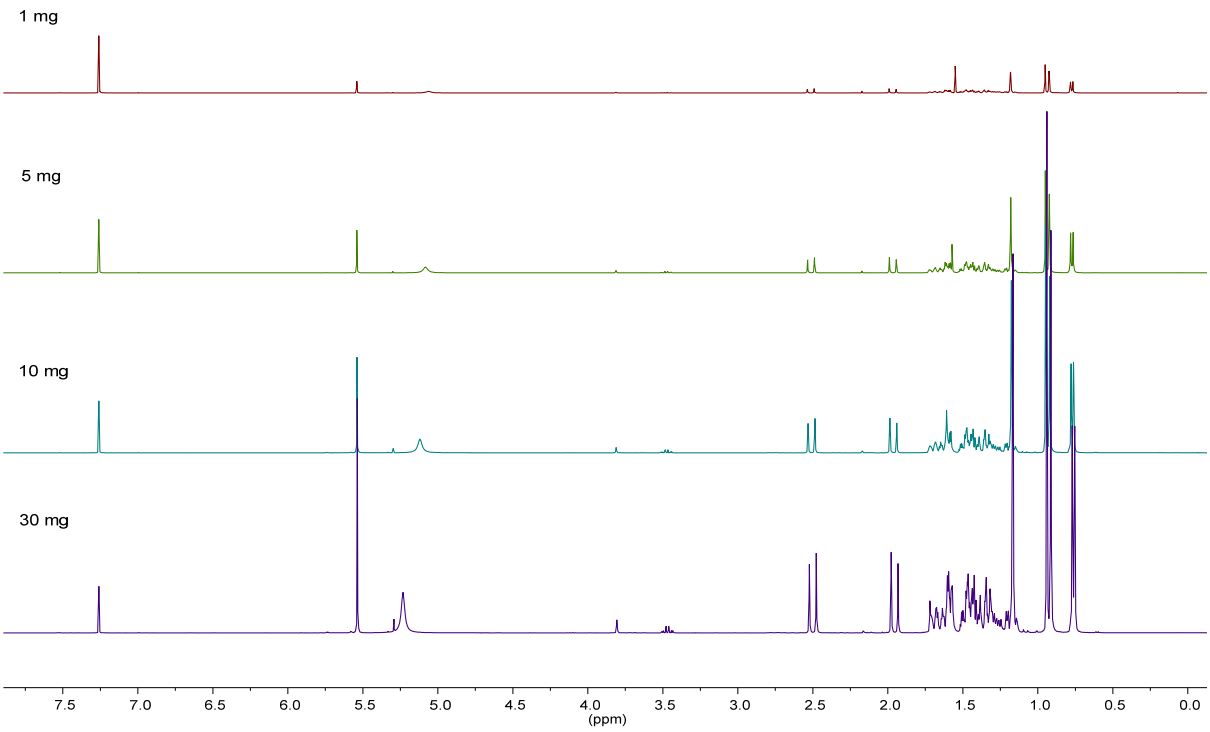



***Figure 10:*** *$^{1}H$ NMR (400MHz) of (–)-cyclosmenospongine (**4**) at different concentrations.*

#### 3.3.2.2.Addition of HCl:

Preparation of $HCl/CDCl_3$ solution:

Deuterated chloroform ($CDCl_3$) was purged with hydrogen chloride gas (freshly prepared by the slow dropwise addition of concentrated aqueous sulfuric acid to a vigorously stirred suspension of sodium chloride and concentrated aqueous hydrogen chloride solution) for 15 min.

To a solution of (–)-cyclosmenospongine (**4**) (30 mg) in $CDCl_3$ (0.5 mL) was sequentially added a freshly prepared $HCl/CDCl_3$ solution (50 µL, 50 µL, 100 µL, 100 µL and 200 µL). After every addition a $^{1}H$ and $^{13}C$ NMR spectrum was recorded.

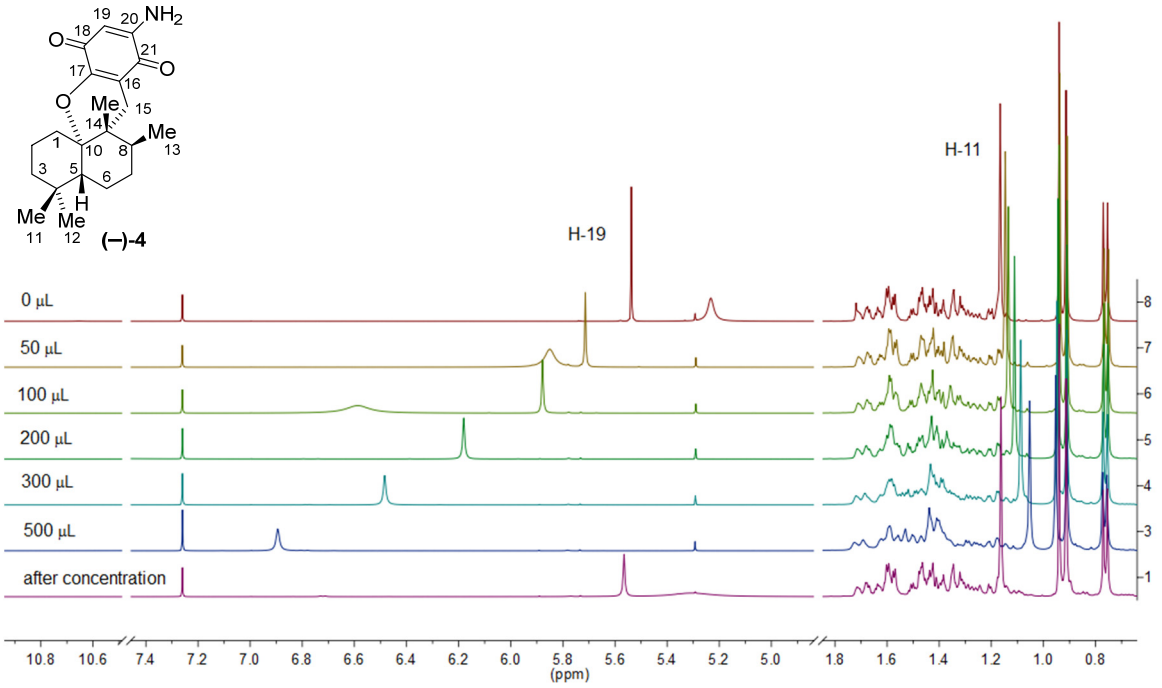



***Figure 11:*** *$^{1}$H NMR (400 MHz) spectra of **4** after the addition of $CDCl_3$ saturated with HCl.*

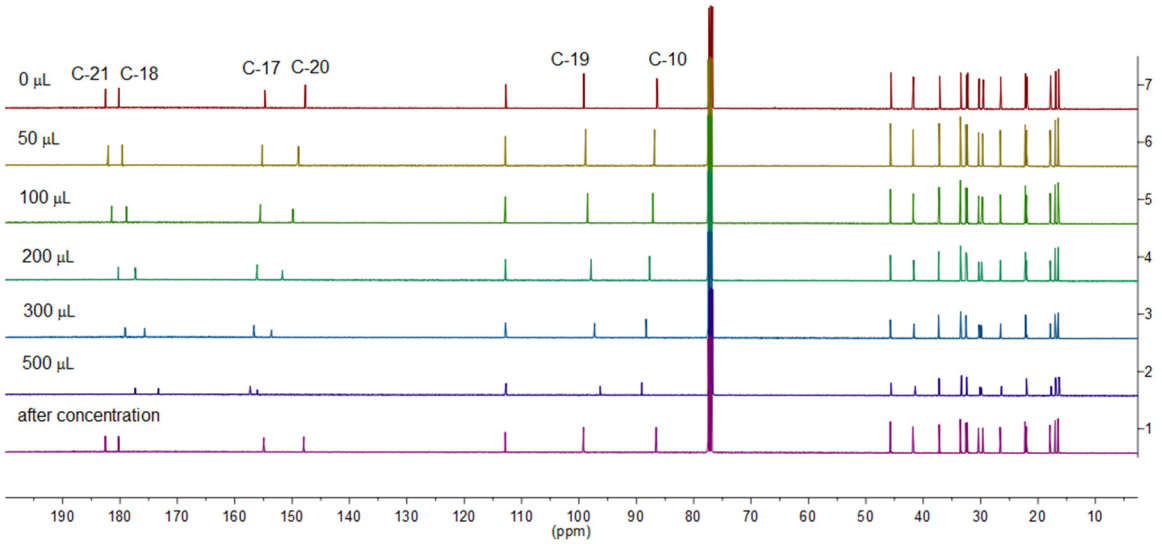



***Figure 12:*** *$^{13}$C NMR (101 MHz) spectra of **4** after the addition of $CDCl_3$ saturated with HCl.*

***Table 17:*** *$^{13}C$ NMR shifts of **4** after the addition of $CDCl_3$ saturated with HCl and shift differences to the reported spectrum of natural **4**.*[95]

| Carbon | Natural (76 MHz, $CDCl_3$)[95] | Synthetic (201 Hz, $CDCl_3$) | Δ | Synthetic (50 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (100 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (200 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (300 µL; 101 Hz, $CDCl_3$) | Δ | Synthetic (500 µL; 101 Hz, $CDCl_3$) | Δ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 29.1 | 29.7 | 0.6 | 29.7 | 0.6 | 29.7 | 0.6 | 29.8 | 0.7 | 29.9 | 0.8 | 29.9 | 0.8 |
| 2 | 17.8 | 18.0 | 0.2 | 17.9 | 0.1 | 17.9 | 0.1 | 17.9 | 0.1 | 17.9 | 0.1 | 17.7 | –0.1 |
| 3 | 40.9 | 41.9 | 1.0 | 41.8 | 0.9 | 41.7 | 0.8 | 41.7 | 0.8 | 41.6 | 0.7 | 41.4 | 0.5 |
| 4 | 33.2 | 33.6 | 0.4 | 33.5 | 0.3 | 33.5 | 0.3 | 33.5 | 0.3 | 33.5 | 0.3 | 33.3 | 0.1 |
| 5 | 45.7 | 45.8 | 0.1 | 45.7 | 0.0 | 45.7 | 0.0 | 45.7 | 0.0 | 45.7 | 0.0 | 45.6 | –0.1 |
| 6 | 22.0 | 22.0 | 0.0 | 22.0 | 0.0 | 22.0 | 0.0 | 22.0 | 0.0 | 22.0 | 0.0 | 21.9 | –0.1 |
| 7 | 30.1 | 30.4 | 0.3 | 30.3 | 0.2 | 30.3 | 0.2 | 30.3 | 0.2 | 30.3 | 0.2 | 30.1 | 0.0 |
| 8 | 32.3 | 32.4 | 0.1 | 32.3 | 0.0 | 32.4 | 0.1 | 32.4 | 0.1 | 32.5 | 0.2 | 32.4 | 0.1 |
| 9 | 37.6 | 37.3 | –0.3 | 37.2 | –0.4 | 37.3 | –0.3 | 37.3 | –0.3 | 37.3 | –0.3 | 37.2 | –0.4 |
| 10 | 88.6 | 86.6 | –2.0 | 86.8 | –1.8 | 87.1 | –1.5 | 87.7 | –0.9 | 88.3 | –0.3 | 89.0 | 0.4 |
| 11 | 22.4 | 22.3 | –0.1 | 22.2 | –0.2 | 22.2 | –0.2 | 22.2 | –0.2 | 22.2 | –0.2 | 22.0 | –0.4 |
| 12 | 32.4 | 32.6 | 0.2 | 32.6 | 0.2 | 32.6 | 0.2 | 32.6 | 0.2 | 32.6 | 0.2 | 32.4 | 0.0 |
| 13 | 16.3 | 16.5 | 0.2 | 16.5 | 0.2 | 16.5 | 0.2 | 16.5 | 0.2 | 16.5 | 0.2 | 16.3 | 0.0 |
| 14 | 17.1 | 17.0 | –0.1 | 17.0 | –0.1 | 17.0 | –0.1 | 17.0 | –0.1 | 17.0 | –0.1 | 16.9 | –0.2 |
| 15 | 26.7 | 26.7 | 0.0 | 26.6 | –0.1 | 26.6 | –0.1 | 26.5 | –0.2 | 26.5 | –0.2 | 26.4 | –0.3 |
| 16 | 113.3 | 113.0 | –0.3 | 112.8 | –0.5 | 112.8 | –0.5 | 112.8 | –0.5 | 112.8 | –0.5 | 112.7 | –0.6 |
| 17 | 153.6 | 154.8 | 1.2 | 155.2 | 1.6 | 155.5 | 1.9 | 156.1 | 2.5 | 156.7 | 3.1 | 157.3 | 3.7 |
| 18 | 177.6 | 180.3 | 2.7 | 179.6 | 2.0 | 178.9 | 1.3 | 177.3 | –0.3 | 175.7 | –1.9 | 173.3 | –4.3 |
| 19 | 98.1 | 99.2 | 1.1 | 98.8 | 0.7 | 98.5 | 0.4 | 97.9 | –0.2 | 97.3 | –0.8 | 96.3 | –1.8 |
| 20 | 152.3 | 147.6 | –4.7 | 148.9 | –3.4 | 149.9 | –2.4 | 151.7 | –0.6 | 153.6 | 1.3 | 156.1 | 3.8 |
| 21 | 180.5 | 182.6 | 2.1 | 182.0 | 1.5 | 181.4 | 0.9 | 180.3 | –0.2 | 179.1 | –1.4 | 177.3 | –3.2 |

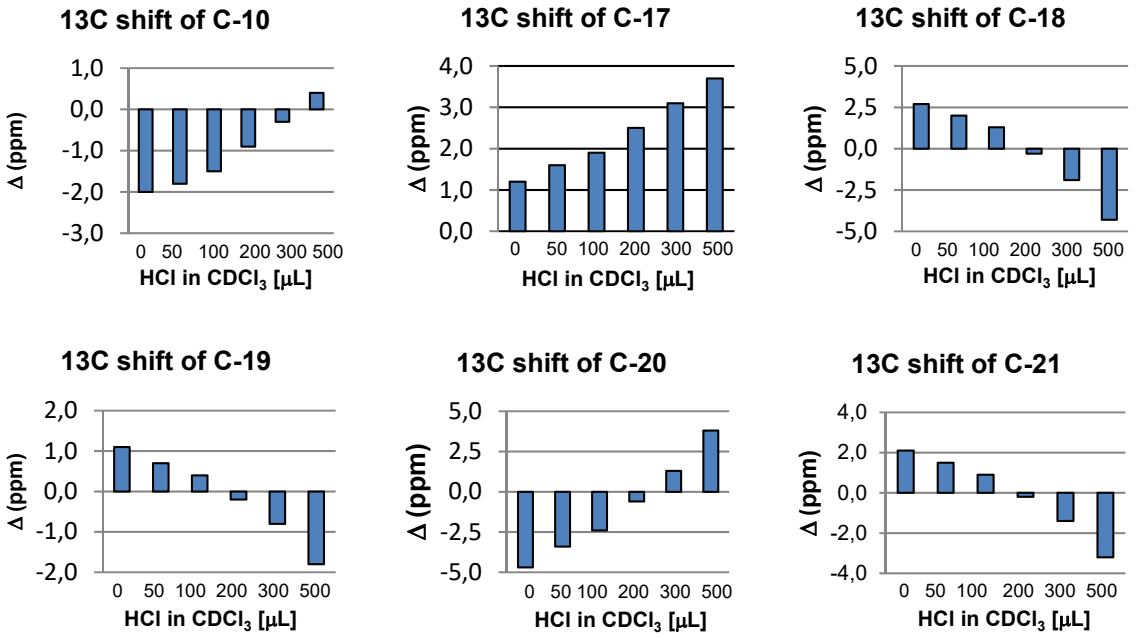



***Figure 13:*** *Selected carbon atoms of (–)-cyclosmenospongine (**4**) and the influence of protonation on their $^{13}C$ NMR shifts.*

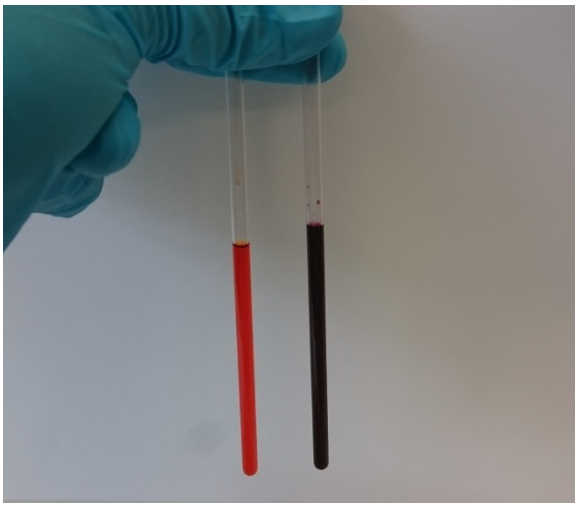
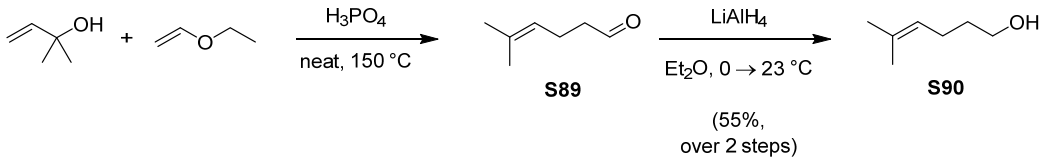


***Figure 14:*** *left: (–)-cyclosmenospongine* ***(1)*** *in $CDCl_3$ (bright red); right: (–)-cyclosmenospongine* ***(1)*** *in $HCl/CDCl_3$ (purple, reported as wine-red[95])*

### 3.3.3. (*E*)-Enol Ether Synthesis



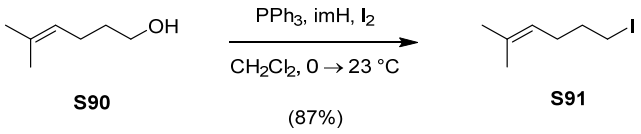

**Alcohol S90**

*Aldehyde **S89** was prepared according to the procedure described by Dulcère.*[186]

To a solution of 2-methyl-3-buten-2-ol (21.8 mL, 209 mmol, 1 equiv) and vinyl ethyl ether (42.0 mL, 439 mmol, 2.10 equiv) in a pressure tube was added concentrated phosphoric acid (61.0 µL, 1.04 mmol, 0.01 equiv) and the reaction mixture was heated to 150 °C. After 2 h, the mixture was allowed to cool to 23 °C. The crude aldehyde **S89** (22.4 g) was used in the next step without further purification.

*Alcohol **S90** was prepared according to the procedure described by Corey.*[187]

A solution of crude aldehyde **S89** (22.4 g, 200 mmol, 1 equiv) in diethyl ether (100 mL) was added to a suspension of lithium aluminum hydride (9.28 g, 220 mmol, 1.10 equiv) in diethyl ether (200 mL) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the mixture was cooled to 0 °C and aqueous sodium hydroxide solution (10%, 10 mL) and water (10 mL) were added carefully. The mixture was allowed to warm to 23 °C and sodium sulfate was added. After 10 min, the dried solution was filtrated and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes initially, grading to 50% ethyl acetate in hexanes) to yield alcohol **S90** (13.0 g, 55% over two steps) as a colourless oil. Characterization data obtained for **S90** were in full agreement with values previously reported.[187]

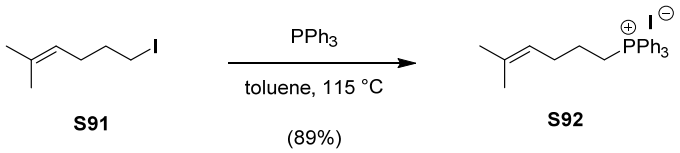



**Iodide S91**

*Iodide **S91** was prepared according to the procedure described by Heathcock.*[188]

To a solution of alcohol **S90** (13.0 g, 114 mmol, 1 equiv) in dichloromethane (240 mL) was added triphenylphosphine (32.9 g, 125 mmol, 1.10 equiv) and imidazole (9.31 g, 137 mmol, 1.20 equiv) at 23 °C. After 30 min, the reaction mixture was cooled to 0 °C and iodide (39.1 g, 154 mmol, 1.35 equiv) was added in small portions. After 2 h, saturated aqueous sodium thiosulfate solution (300 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 150 mL).The combined organic extracts were dried over sodium sulfate, the dried solution was filtrated and the filtrate was concentrated. The residue was dissolved in a minimum amount of dichloromethane (20 mL) and a mixture of hexanes and diethyl ether (1:1, 200 mL) was added. The precipitating

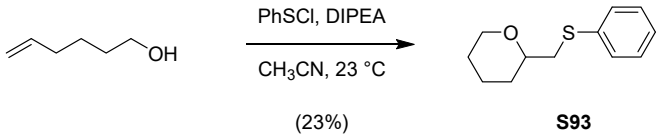
triphenylphosphine oxide was removed by filtration through a pad of Celite®. The filtrate was concentrated the residue was purified by flash-column chromatography on silica gel (hexanes) to yield iodide **S91** (22.3 g, 87%) as a yellowish oil. Characterization data obtained for **S91** were in full agreement with values previously reported.[189]




**S91** **S92**

**Phosphonium salt S92**

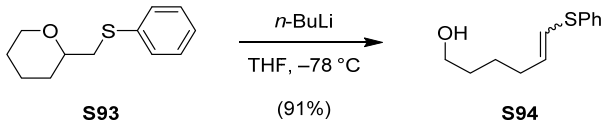
*Phosphonium iodide **S92** was prepared according to the procedure described by Ksander.[190]* To a solution of iodide **S91** (12.0 g, 53.6 mmol, 1.10 equiv) in toluene (100 mL) was added triphenylphosphine (12.8 g, 48.7 mmol, 1 equiv) in a pressure tube and the reaction mixture was heated to 115 °C. After 19 h, the mixture was allowed to cool to 23 °C and the mixture was concentrated. The residue was washed with ethyl acetate (3 × 5 mL) and diethyl ether (3 × 5 mL). The washed solid was dried by azeotropic distillation with toluene (2 × 5 mL). The residue was dried under high vacuum to yield phosphonium salt **S92** (21.1 g, 89%) as an off-white solid. Characterization data obtained for **S92** were in full agreement with values previously reported.[190]




**S93**

**Pyran S93**

*Pyran **S93** was prepared according to the procedure described by A. G. Fallis.[183]*
To a solution of diphenyldisulfide (5.45 g, 25.0 mmol, 0.50 equiv) and pyridine (40 μL) in acetonitrile (75 mL) was added sulfuryl chloride (2.06 mL, 25.5 mmol, 0.51 equiv) dropwise at 0 °C. After 20 min, the orange solution was added to a solution of 5-hexen-1-ol (5.00 g, 49.9 mmol, 1 equiv) in acetonitrile (75 mL) at 23 °C. After 2 h, a solution of *N*,*N*-diisopropylethylamine (10.4 mL, 59.9 mmol, 1.20 equiv) in acetonitrile (30 mL) was added dropwise to the reaction mixture. After 30 min, the reaction mixture was concentrated and the residue was extracted with diethyl ether (200 mL). The organic extract was washed with water (3 × 100 mL) and saturated aqueous ammonium chloride solution (2 × 75 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give pyran **S93** (2.35 g, 23%) as a yellow oil. The obtained characterization data were in full agreement with those reported in literature.[183]




**S93** (91%) **S94**

**Alcohol S94**

*Alcohol **S94** was prepared according to the procedure described by S. Takano.[191]*

To a solution of pyran **S93** (2.18 g, 10.5 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added a solution of *n*-butyllithium (2.31 M in hexanes, 5.44 mL, 12.6 mmol, 1.20 equiv) dropwise at –78 °C within 10 min. After 20 min, water (30 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (30% ethyl acetate in hexanes) to give alcohol **S94** (1.99 g, 91%, *E*:*Z* = 1.8:1) as a yellow oil.

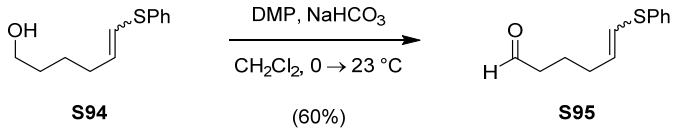
**TLC** (40% ethyl acetate in hexanes), $R_f$ = 0.31 (UV, $KMnO_4$)

**$^1$H NMR** ($CDCl_3$, 599 MHz): (*E*): $\delta$ = 7.37–7.27 (m, 4H), 7.24–7.15 (m, 1H), 6.16 (dt, *J* = 14.9, 1.4 Hz, 1H), 5.98 (dt, *J* = 14.9, 7.0 Hz, 1H), 3.71–3.64 (m, 2H), 2.24–2.18 (m, 2H), 1.67–1.58 (m, 2H), 1.57–1.48 (m, 2H), 1.27 (br s, 1H); (*Z*): $\delta$ = 7.37–7.27 (m, 4H), 7.24–7.15 (m, 1H), 6.22 (dt, *J* = 9.2, 1.4 Hz, 1H), 5.82 (dt, *J* = 9.2, 7.3 Hz, 1H), 3.70–3.63 (m, 2H), 2.36–2.26 (m, 2H), 1.66–1.58 (m, 2H), 1.57–1.48 (m, 2H), 1.27 (br s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): (*E*): $\delta$ = 136.8, 136.5, 129.1, 128.7, 126.3, 121.5, 62.9, 32.9, 32.3, 25.4. (*Z*): $\delta$ = 136.5, 133.1, 129.1, 128.9, 126.3, 123.3, 62.9, 32.4, 28.9, 25.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3331 (*br m*), 2933 (*m*), 2859 (*m*), 1583 (*m*), 1479 (*m*), 1439 (*m*), 1089 (*m*), 1068 (*m*), 1025 (*m*), 952 (*m*), 738 (*s*), 690 (*s*).

**HRMS** (ESI) calc. for $C_{12}H_{16}OS$ $[M]^+$: 208.0916 found: 208.0908.




**S94** (60%) **S95**

**Aldehyde S95**

To a suspenion of alcohol **S94** (900 mg, 4.32 mmol, 1 equiv) and sodium bicarbonate (1.81 g, 21.6 mmol, 5.00 equiv) in dichloromethane (20 mL) was added Dess–Martin-periodinane (2.38 g, 5.62 mmol, 1.30 equiv) at 0 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 1 h, saturated aqueous sodium bicarbonate solution (100 mL) was added and the mixture was extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by

flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give the aldehyde **S95** (540 mg, 60%, *E*:*Z* = 1.2:1) as a colorless oil.

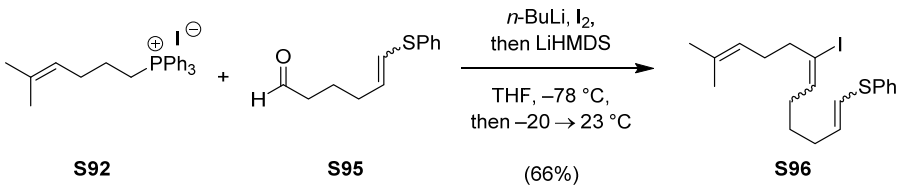
**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.31 (UV, $KMnO_4$)

**$^1$H NMR** ($CDCl_3$, 599 MHz): (*Z*): δ = 9.80 (t, *J* = 1.6 Hz, 1H), 7.36–7.27 (m, 4H), 7.24–7.18 (m, 1H), 6.26 (dt, *J* = 9.3, 1.3 Hz, 1H), 5.77 (dt, *J* = 9.3, 7.3 Hz, 1H), 2.53–2.46 (m, 2H), 2.24–2.19 (m, 2H), 1.84–1.74 (m, 2H); (*E*): δ = 9.79 (t, *J* = 1.5 Hz, 1H), 7.36–7.27 (m, 4H), 7.24–7.18 (m, 1H), 6.18 (dt, *J* = 15.0, 1.4 Hz, 1H), 5.90 (dt, *J* = 15.0, 7.1 Hz, 1H), 2.53–2.46 (m, 2H), 2.35–2.28 (m, 2H), 1.84–1.74 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): (*Z*): *δ* = 202.4, 136.2, 131.6, 129.2, 129.1, 126.5, 124.6, 43.4, 28.5, 21.5; (*E*): *δ* = 202.2, 136.1, 134.8, 129.2, 129.1, 126.5, 122.9, 43.2, 32.4, 21.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2933 (*w*), 2722 (*w*), 1722 (v*s*), 1583 (*w*), 1479 (*m*), 1439 (*m*), 1089 (*w*), 1024 (*w*), 953 (*w*), 739 (*s*), 690 (*m*).

**HRMS** (EI) calc. for $C_{12}H_{14}O^{32}S$ $[M]^+$: 206.0760 found: 206.0770.

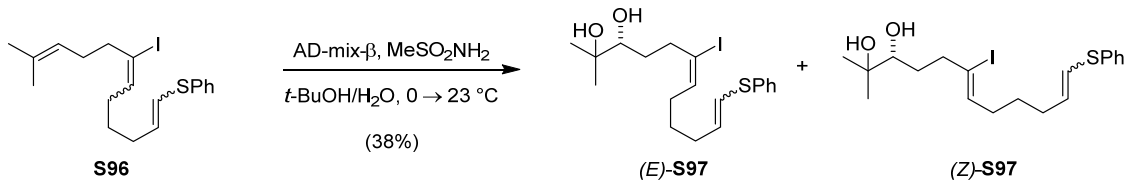



**S92** **S95** (66%) **S96**

**Vinyl iodide S96**

To a suspension of phosphonium iodide **S92** (1.77 g, 3.64 mmol, 1.50 equiv) in tetrahydrofuran (16 mL) was added a solution of *n*-butyl lithium (2.31 M in hexanes, 1.52 mL, 3.51 mmol, 1.45 equiv) at –78 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 30 min, the mixture was cooled to –78 °C and a solution of iodide (800 mg, 3.15 mmol, 1.30 equiv) was added. After 20 min, a solution of lithium bis(trimethylsilyl)amine solution (1.00 M in tetrahydrofuran, 0.64 mL, 3.39 mmol, 1.40 equiv) was added and the mixture was allowed to warm to –20 °C. After 30 min, the reaction mixture was cooled to –78 °C and a solution of aldehyde **S95** (500 mg, 2.42 mmol, 1 equiv) in tetrahydrofuran (4.5 mL) was added. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 3 h, saturated aqueous sodium thiosulfate solution (75 mL) was added and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (2% ethyl acetate in hexanes) to yield vinyl iodide **S96** (664 mg, 66%) as an inseparable mixture of double bond isomers (664 mg, 66% *E*:*Z* = 1:2.2, for vinyl iodide) as a pale yellow oil.

*Note: Since the reaction afforded an inseparable mixture of four diastereomers purified **S96** was directly used in the next reaction without further characterization.*




**Diol S97**

Potassium hexacyanoferrate (III) (3.16 g, 9.60 mmol, 6.00 equiv), potassium carbonate (1.33 g, 9.60 mmol, 6.00 equiv) and $(DHQD)_2Phal$ (49.9 mg, 0.06 mmol, 0.04 equiv) were grinded to a fine powder and were added to a mixture of *t*-butanol and water (1:1, 200 mL). Potassium osmate (VI) dihydrate (4.72 mg, 12.8 µmol, 0.8 mol%) was added to the orange suspension at 23 °C. After 30 min, the reaction mixture was cooled to 0 °C and methanesulfonamide (304 mg, 3.20 mmol, 2.00 equiv) was added in one portion followed by a solution of alkene **S96** (660 mg, 1.60 mmol, 1 equiv) in *t*-butanol (8 mL). After 5 min, the reaction mixture was allowed to warm to 23 °C. After 22 h, sodium sulfite (2.01 g, 16.0 mmol, 10.0 equiv) was added. After 20 min, aqueous sodium hydroxide solution (5%, 75 mL) was added and the mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (0.5% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to give diol **(*E*)-S97** (105 mg, 15%, *E*:*Z* = 1:1.2) as a pale yellow oil and diol **(Z)-S97** (166 mg, 23%, *E*:*Z* = 1:1.2) as a pale yellow oil.

**(*E*)-S97:**

**TLC** (2% methanol in dichloromethane): $R_f$ = 0.39 (UV, $KMnO_4$).

**$^1$H NMR** ($C_6D_6$, 599 MHz): (*Z*): δ = 7.34–7.30 (m, 1H), 7.30–7.26 (m, 1H), 7.08–7.02 (m, 1H), 7.02–6.98 (m, 1H), 6.97–6.89 (m, 1H), 6.20 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.16–6.10 (m, 1H), 5.53 (dt, *J* = 9.2 7.2 Hz, 1H), 3.18–3.10 (m, 1H), 2.61–2.54 (m, 1H), 2.53–2.44 (m, 1H), 2.19–2.12 (m, 2H), 2.00–1.90 (m, 3H), 1.74–1.67 (m, 1H), 1.39–1.23 (m, 3H), 1.02 (br s, 1H), 0.98 (s, 3H), 0.95 (s, 3H); (*E*): δ = 7.34–7.30 (m, 1H), 7.30–7.26 (m, 1H), 7.08–7.02 (m, 1H), 7.02–6.98 (m, 1H), 6.97–6.89 (m, 1H), 6.16–6.10 (m, 1H), 6.01 (dt, *J* = 15.0, 1.4 Hz, 1H), 5.80 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.18–3.10 (m, 1H), 2.61–2.54 (m, 1H), 2.53–2.44 (m, 1H), 1.99–1.92 (m, 1H), 1.92–1.83 (m, 2H), 1.82–1.76 (m, 2H), 1.74–1.67 (m, 1H), 1.39–1.23 (m, 1H), 1.17–1.08 (m, 2H), 1.02 (br s, 1H), 0.97 (s, 3H), 0.94 (s, 3H).

**$^{13}$C NMR** ($C_6D_6$, 151 MHz): (*Z*): δ = 142.1, 136.9, 132.5, 129.3, 129.3, 126.4, 124.1, 104.1, 76.6, 72.6, 35.7, 31.3, 30.6, 28.8, 28.7, 26.7, 23.2; (*E*): δ = 142.0, 137.0, 136.1, 129.3, 129.2, 126.4, 122.4, 104.1, 76.6, 72.6, 35.7, 32.4, 31.3, 30.3, 28.5, 26.7, 23.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3418 (*br w*), 2927 (*w*), 2280 (*m*), 1584 (*w*), 1453 (*w*), 1330 (*m*), 1161 (*w*), 957 (*w*), 812 (*vs*), 739 (*m*).

**HRMS** (EI) calc. for $C_{19}H_{27}O_2{}^{127}I\,{}^{32}S$ $[M]^+$: 446.0771 found: 446.0771.

**(*Z*)-S97:**

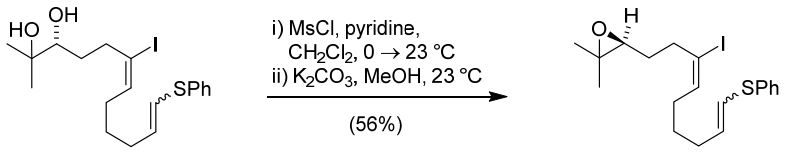
**TLC** (2% methanol in dichloromethane): $R_f$ = 0.35 (UV, $KMnO_4$).

**$^1$H NMR** ($C_6D_6$, 599 MHz): (*Z*): δ = 7.36–7.32 (m, 1H), 7.31–7.26 (m, 1H), 7.06–7.01 (m, 1H), 7.01–6.97 (m, 1H), 6.95–6.90 (m, 1H), 6.14 (dt, *J* = 9.3, 1.4 Hz, 1H), 5.59 (dt, *J* = 9.3, 7.3 Hz, 1H), 5.40 (t, *J* = 6.8 Hz, 1H), 3.19–3.11 (m, 1H), 2.77–2.65 (m, 1H), 2.61–2.48 (m, 1H), 2.28–2.20 (m, 2H), 2.18–2.11 (m, 2H), 1.86–1.81 (m, 1H), 1.76–1.66 (m, 1H), 1.44–1.34 (m, 3H), 1.11 (br s, 1H), 0.97 (s, 3H), 0.95 (s, 3H). (*E*): δ = 7.36–7.32 (m, 1H), 7.31–7.26 (m, 1H), 7.06–7.01 (m, 1H), 7.01–6.97 (m, 1H), 6.95–6.90 (m, 1H), 6.06 (dt, *J* = 14.9, 1.3 Hz, 1H), 5.85 (dt, *J* = 14.9, 7.0 Hz, 1H), 5.33 (t, *J* = 6.7 Hz, 1H), 3.19–3.11 (m, 1H), 2.77–2.65 (m, 1H), 2.61–2.48 (m, 1H), 2.08–2.01 (m, 2H), 1.91–1.81 (m, 3H), 1.76–1.66 (m, 1H), 1.44–1.34 (m, 1H), 1.28–1.20 (m, 2H), 1.06 (s, 1H), 0.96 (s, 3H), 0.95 (s, 3H).

**$^{13}$C NMR** ($C_6D_6$, 151 MHz): (*Z*): δ = 136.9, 135.3, 132.7, 129.3, 129.3, 126.4, 124.0, 110.3, 76.8, 72.6, 42.5, 36.3, 31.7, 28.9, 28.0, 26.6, 23.4; (*E*): δ = 137.1, 136.3, 135.3, 129.3, 129.2, 126.4, 122.4, 110.3, 76.7, 72.6, 42.5, 36.2, 32.7, 31.7, 27.9, 26.6, 23.4.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3395 (*br m*), 2926 (*m*), 1583 (*w*), 1478 (*m*), 1439 (*m*), 1157 (*m*), 1070 (*m*), 948 (*m*), 737 (*vs*), 689 (*s*).

**HRMS** (EI) calc. for $C_{19}H_{27}O_2{}^{127}I\,{}^{32}S$ $[M]^+$: 446.0771 found: 446.0791.




*(E)*-**S97** **46**

**Epoxide 46**

To a solution of diol **(*E*)-S97** (92.0 mg, 0.19 mmol, 1 equiv) and pyridine (78.4 µL, 0.97 mmol, 5.00 equiv) in dichloromethane (1 mL) was added methanesulfonyl chloride (22.5 µL, 0.29 mmol, 1.50 equiv) at 0 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 14 h, water (10 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated and the residue was dried by azeotropic distillation with benzene (2 × 5 mL). To a solution of the crude mesylate in methanol (1 mL) was added potassium carbonate (53.6 mg, 0.39 mmol, 2.00 equiv) at 23 °C. After 2 h, the reaction mixture was partitioned between water (10 mL) and dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography

on silica gel (10% ethyl acetate in hexanes) to yield epoxide **46** (49.6 mg, 56%, *E*:*Z* = 1:1.2) as a colorless oil.

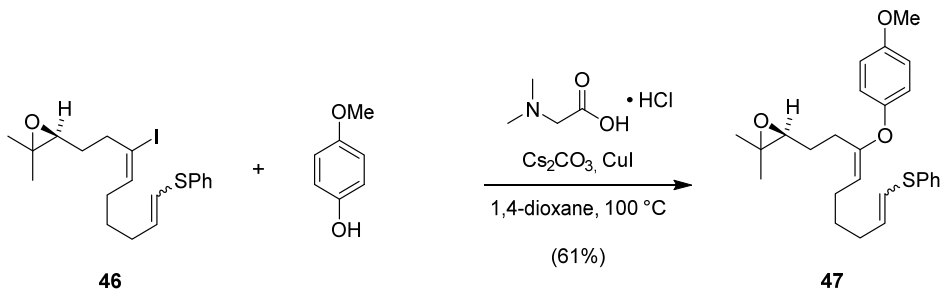
**TLC** (20% ethyl acetate in hexanes): $R_f = 0.52$ (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 800 MHz): (*Z*): δ = 7.35–7.33 (m, 1H), 7.31–7.28 (m, 3H), 7.22–7.18 (m, 1H), 6.27–6.21 (m, 2H), 5.78 (dt, *J* = 9.3, 7.2 Hz, 1H), 2.76–2.71 (m, 1H), 2.61–2.52 (m, 2H), 2.29–2.23 (m, 2H), 2.15–2.10 (m, 2H), 1.84–1.77 (m, 1H), 1.70–1.62 (m, 1H), 1.55–1.50 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H); (*E*): δ = 7.35–7.33 (m, 1H), 7.31–7.28 (m, 3H), 7.22–7.18 (m, 1H), 6.27–6.21 (m, 1H), 6.16 (dt, *J* = 15.0, 1.4 Hz, 1H), 5.93 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.76–2.71 (m, 1H), 2.61–2.52 (m, 2H), 2.21–2.15 (m, 2H), 2.15–2.10 (m, 2H), 1.84–1.77 (m, 1H), 1.70–1.62 (m, 1H), 1.55–1.50 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 201 MHz): (*Z*): δ = 141.9, 136.4, 132.3, 129.1, 129.0, 126.4, 123.9, 101.9, 63.0, 58.8, 35.9, 30.6, 28.7, 28.7, 28.5, 25.0, 19.1; (*E*): δ =141.7, 136.3, 135.9, 129.1, 128.9, 126.4, 122.1, 102.0, 62.9, 58.8, 35.9, 32.5, 30.4, 28.7, 28.5, 25.0, 19.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2923 (*s*), 1734 (*w*), 1583 (*w*), 1478 (*m*), 1456 (*m*), 1439 (*m*), 1376 (*m*), 1024 (*w*), 875 (*w*), 737 (*s*), 689 (*m*).

**HRMS** (EI) calc. for $C_{19}H_{25}O^{127}I^{32}S$ $[M]^+$: 428.0665 found: 428.0641.




**46** **47**

**Enol ether 47**

*Note: 1,4-dioxane was degassed via freeze-pump-thaw (three cycles) prior to use.*

A suspension of vinyl iodide **46** (31.0 mg, 67.9 μmol, 1 equiv) 4-methoxyphenol (12.6 mg, 0.10 mmol, 1.50 equiv), cesium carbonate (99.6 mg, 0.31 mmol, 4.50 equiv), *N*,*N*-dimethylglycine hydrochloride (28.4 mg, 0.20 mmol, 3.00 equiv) and copper(I) iodide (12.9 mg, 67. 9 μmol, 1.00 equiv) in 1,4-dioxane (1.2 mL) was heated to 100 °C. After 20 h, the reaction mixture was allowed to cool to 23 °C, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield enol ether **47** (18.8 mg, 61%, *E*:*Z* = 1:1.1) as a colorless oil and vinyl iodide **46** (10 mg, 32%) as a colorless oil.

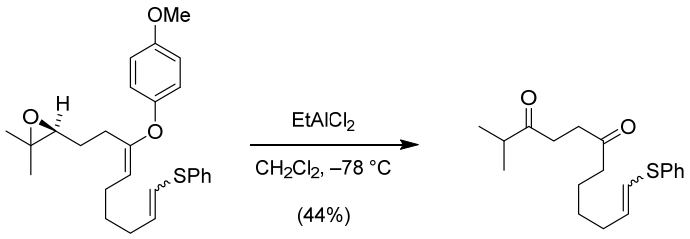
**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.42 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 599 MHz): (*Z*): δ 7.35–7.32 (m, 1H), 7.32–7.27 (m, 3H), 7.22–7.16 (m, 1H), 6.92–6.87 (m, 2H), 6.86–6.79 (m, 2H), 6.20 (dt, *J* = 9.2, 1.4 Hz, 1H), 5.79 (dt, *J* = 9.2, 7.2 Hz, 1H), 4.66 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 2.83–2.75 (m, 1H), 2.50–2.35 (m, 2H), 2.27–2.21 (m, 2H), 2.10–2.01 (m, 2H), 1.86–1.75 (m, 2H), 1.52–1.42 (m, 2H), 1.32 (s, 3H), 1.29 (s, 3H); (*E*): δ = 7.35–7.32 (m, 1H), 7.32–7.27 (m, 3H), 7.22–7.16 (m, 1H), 6.92–6.87 (m, 2H), 6.86–6.79 (m, 2H), 6.13 (dt, *J* = 15.0, 1.4 Hz, 1H), 5.95 (dt, *J* = 14.9, 7.0 Hz, 1H), 4.62 (t, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 2.83–2.75 (m, 1H), 2.50–2.35 (m, 2H), 2.18–2.12 (m, 2H), 2.10–2.01 (m, 2H), 1.86–1.75 (m, 2H), 1.52–1.42 (m, 2H), 1.32 (s, 3H), 1.29 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): (*Z*): δ = 155.6, 155.0, 149.5, 136.5, 133.0, 129.1, 128.9, 126.3, 123.3, 120.8, 114.7, 107.9, 63.9, 58.6, 55.8, 29.8, 28.8, 26.9, 26.3, 26.0, 25.1, 18.9; (*E*): δ = 155.6, 155.1, 149.5, 136.8, 136.5, 129.1, 128.7, 126.3, 121.5, 120.9, 114.8, 107.5, 63.9, 58.6, 55.7, 32.7, 29.8, 26.9, 26.2, 26.0, 25.1, 18.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2926 (*w*), 1670 (*w*), 1502 (*vs*), 1440 (*m*), 1208 (*vs*), 1099 (*m*), 1036 (*m*), 830 (*m*), 738 (*s*), 690 (*s*).

**HRMS** (EI) calc. for $C_{26}H_{32}O_3{}^{32}S$ $[M]^+$: 424.2067 found: 424.2055.




**47** **50**

**Ketone 50**

To a solution epoxide **47** (9.0 mg, 0.02 mmol, 1 equiv) in dichloromethane (2.0 mL) was added a solution of ethylaluminum dichloride (1.00 M in hexanes, 0.06 mL, 0.06 mmol, 3.00 equiv) in dichloromethane (0.5 mL) dropwise at –78 °C. After 30 min, water (10 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silca gel (10% ethyl acetate in hexanes) to obtain **50** (3.0 mg, 44%, *E*:*Z* = 1.1:1) as a colorless oil.

**TLC** (20% ethyl acetate in hexanes), $R_f$ = 0.33 (UV, CAM).

**$^1$H NMR** ($CDCl_3$, 400 MHz): (*Z*) δ = 7.36–7.26 (m, 4H), 7.22–7.16 (m, 1H), 6.20 (dt, *J* = 9.2, 1.4 Hz, 1H), 5.80 (dt, *J* = 9.2, 7.3 Hz, 1H), 2.77–2.69 (m, 2H), 2.69–2.60 (m, 3H), 2.53–2.45 (m, 2H), 2.30–2.23 (m, 2H), 1.70–1.56 (m, 2H), 1.51–1.39 (m, 2H), 1.12 (d, *J* = 6.9 Hz, 3H); 1.11 (d, *J* = 6.9 Hz,

3H); (*E*) δ = 7.36–7.26 (m, 4H), 7.22–7.16 (m, 1H), 6.14 (dt, *J* = 14.9 Hz, 1.3, 1H), 5.95 (dt, *J* = 14.9, 6.9 Hz, 1H), 2.77–2.69 (m, 2H), 2.69–2.60 (m, 3H), 2.53–2.45 (m, 2H), 2.21–2.13 (m, 2H), 1.70–1.56 (m, 2H), 1.51–1.39 (m, 2H), 1.12 (d, *J* = 6.9 Hz, 3H); 1.11 (d, *J* = 6.9 Hz, 3H).

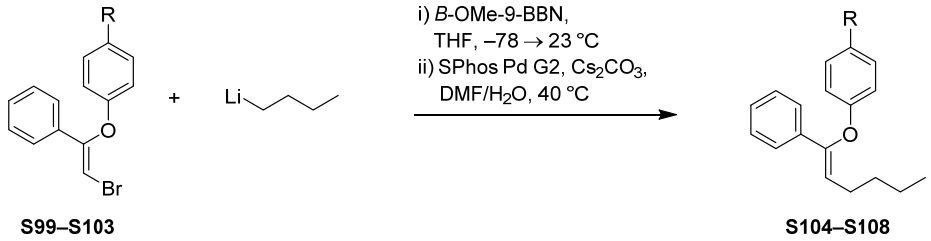
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): (*Z*) δ = 213.5, 209.7, 136.5, 133.0, 129.1, 128.9, 126.3, 123.3, 42.7, 41.0, 36.2, 34.0, 28.9, 28.6, 23.4, 18.5, 18.5; (*E*) δ = 213.5, 209.6, 136.8, 136.6, 129.1, 128.7, 126.2, 121.4, 42.7, 41.0, 36.2, 33.9, 33.0, 28.7, 23.4, 18.5, 18.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2930 (*m*), 1709 (*s*), 1583 (*w*), 1479 (*w*), 1439 (*w*), 1216 (*w*), 1089 (*w*), 1025 (*w*), 740 (*m*), 691 (*w*).

**HRMS** (EI) calc. for $C_{19}H_{26}O_2{}^{32}S$ $[M]^+$: 318.1648; found: 318.1664.

### 3.3.4. Suzuki–Miyaura Cross-Coupling Scope

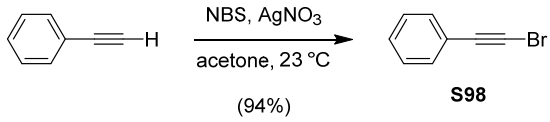
#### 3.3.4.1. Reaction Scope




**S99–S103** **S104–S108**

| Entry | R | Yield [%] |
|---|---|---|
| 1 | H | 96 |
| 2 | NO2 | 78 |
| 3 | CN | 90 |
| 4 | F | 94 |
| 5 | OMe | 93 |

#### 3.3.4.2. Bromoenol Ether Synthesis

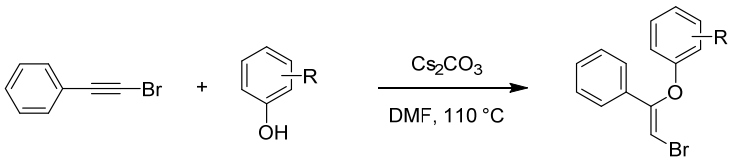



**S98**

**Bromo alkyne S98**

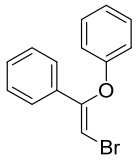
To a solution of ethynylbenzene (5.00 g, 49.0 mmol, 1 equiv) in acetone (160 mL) were sequentially added silver nitrate (0.83 g, 4.90 mmol, 0.10 equiv) and *N*-bromosuccinimide (10.5 g, 59.0 mmol, 1.20 equiv) at 23 °C. After 1.5 h, the grey suspension was poured into water (100 mL). The aqueous phase was extracted with hexanes (4 × 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexanes) to yield bromo alkyne **S98** (8.30 g, 94%) as a yellow oil. The obtained data were in full agreement with those reported in literature.[192]

**General Procedure A:**




**S98** **S99–S103**

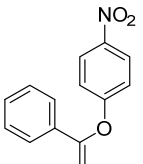
A glass vial equipped with a screw cap was charged with the corresponding phenol (3.30 mmol, 1.10 equiv), cesium carbonate (1.96 g, 6.00 mmol, 2.00 equiv), bromo alkyne **S98** (543 mg, 3.00 mmol, 1 equiv) and *N*,*N*-dimethylformamide (6.0 mL). The obtained suspension was heated to 110 °C. After complete conversion, the reaction mixture was cooled to 23 °C, diluted with ethyl acetate and filtered through a plug of Celite®, which was thoroughly washed with ethyl acetate. The filtrate was concentrated and the residue was purified by flash-column chromatography on silica gel.




**S99**

**Bromoenol ether S99**

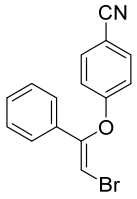
Bromoenol ether **S99** was prepared by following general procedure A. After 3.5 h, the standard work-up procedure was performed. The residue was purified by flash-column chromatography on silica gel (5% toluene in hexanes) to yield bromoenol ether **S99** (209 mg, 25%) as a pale gray solid. The obtained characterization data were in full agreement with the values previously reported.[193]




**S100**

**Bromoenol ether S100**

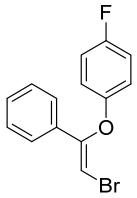
Bromoenol ether **S100** was prepared by following general procedure A. After 3.5 h, the standard work-up procedure was performed. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield bromoenol ether **S100** (397 mg, 41%) as a yellow oil. The obtained characterization data were in full agreement with the values previously reported.[193]




**S101**

**Bromoenol ether S101**

Compound **S101** was prepared by following general procedure A. After 3 h, the standard work-up procedure was performed. The residue was purified by flash-column chromatography on silica gel (1% acetone in toluene) to yield bromoenol ether **S101** (484 mg, 54%) as a yellow oil. The obtained data were in full agreement with those reported in literature.[193]




**S102**

**Bromoenol ether S102**

Compound **S102** was prepared by following general procedure A. After 3 h, the standard work-up procedure was performed. The residue was purified by flash-column chromatography on silica gel (2% toluene in hexanes) to yield bromoenol ether **S102** (183 mg, 21%) as a pale yellow solid.

**TLC** (2% toluene in hexanes), $R_f$ = 0.18 (UV, $KMnO_4$)

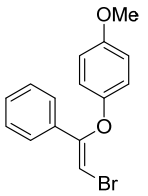
**$^1$H NMR** ($CDCl_3$, 300 MHz): δ = 7.48–7.42 (m, 2H), 7.35–7.29 (m, 3H), 6.94–6.93 (m, 2H), 6.92–6.91 (m, 2H), 6.48 (s, 1H).

**$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ = 159.9, 156.7, 153.6, 151.9, 133.5, 129.5, 129.0, 126.1, 117.4, 117.3, 116.4, 116.1, 95.3.

**$^{19}$F NMR** ($CDCl_3$; 282 MHz): δ = –121.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 1626 (*w*), 1498 (*vs*), 1444 (*w*), 1277 (*w*), 1192 (*s*), 1092 (*w*), 1045 (*m*), 830 (*m*), 726 (*s*), 694 (*w*).

**HRMS** (EI) calc. for $C_{14}H_{10}BrFO$ $[M]^+$: 291.9899; found: 291.9902.



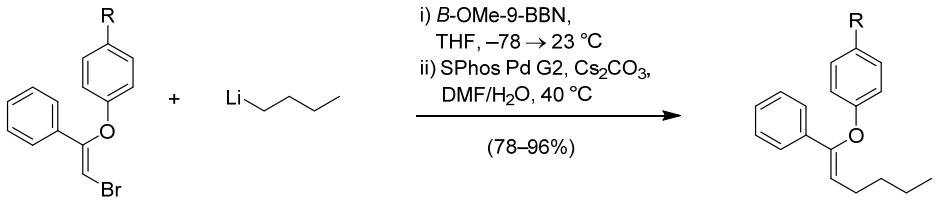

**S103**

**Bromoenol ether S103**

Compound **S103** was prepared by following general procedure A. After 3.5 h, the standard work-up procedure was performed. The residue was purified by flash-column chromatography on silica gel (40% toluene in hexanes) to yield bromoenol ether **S103** (202 mg, 27%) as a yellow oil. The obtained data were in full agreement with those reported in literature.[193]

### 3.3.4.3. Suzuki–Miyaura Coupling

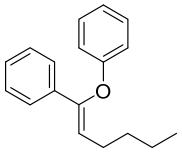
**General Procedure B:**




**S99–S103** **S104–S108**

*Note: All solvents were degassed via freeze-pump-thaw (three cycles) prior to use.*

To a solution of *B*-methoxy-9-BBN (1.00 M in hexanes, 1.00 mL, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (3.2 mL) was added a solution of *n*-butyllithium (2.30 M in hexanes, 0.33 mL, 0.75 mmol, 1.50 equiv) dropwise at –78 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 10 min, the borinate solution was added dropwise to a suspension of the corresponding bromoenol ether **S99–S103** (0.50 mmol, 1 equiv), cesium carbonate (326 mg, 1.00 mmol, 2.00 equiv), SPhos Pd G2 precatalyst (7.2 mg, 0.01 mmol, 0.02 equiv) and SPhos (4.1 mg, 0.01 mmol, 0.02 equiv) in a mixture of *N*,*N*-dimethylformamide and water (9:1, 6.0 mL) at 23 °C and heated to 40 °C. After 1 h, the reaction mixture was cooled to 23 °C water (60 mL) was added and the mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (60 mL), the washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel.



**S104**

**Enol ether S104**

Compound **S104** was prepared by following general procedure B. After the standard work-up procedure was performed, the residue was purified by column chromatography on silica gel (3% ethyl acetate in hexanes) to yield enol ether **S104** (122 mg, 96%) as a colorless oil.

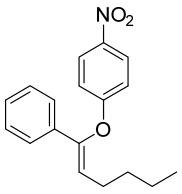
**TLC** (3% ethyl acetate in hexanes), $R_f = 0.49$ (UV, $KMnO_4$)

**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 7.49 (d, $J$ = 7.6 Hz, 2H), 7.29–7.25 (m, 2H), 7.25–7.20 (m, 3H), 6.98–6.91 (m, 3H), 5.87 (t, $J$ = 7.4 Hz, 1H), 2.24–2.19 (m, 2H), 1.46–1.40 (m, 2H), 1.38–1.31 (m, 2H), 0.89 (t, $J$ = 7.2 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 157.6, 148.8, 135.7, 129.6, 128.6, 127.9, 125.4, 121.4, 118.5, 115.6, 31.6, 25.7, 22.6, 14.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2925 (*w*), 1595 (*m*), 1488 (*vs*), 1446 (*m*), 1216 (*vs*), 1163 (*m*), 1041 (*m*), 749 (*vs*), 689 (*vs*).

**HRMS** (EI) calc. for $C_{18}H_{20}O$ $[M]^+$: 252.1509; found: 252.1502.



**S105**

**Enol ether S105**

Compound **S105** was prepared by following general procedure B. After the standard work-up procedure was performed, the residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to yield enol ether **S105** (116 mg, 78%) as a yellow oil.

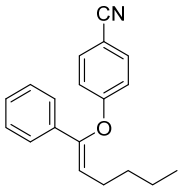
**TLC** (5% ethyl acetate in hexanes), $R_f = 0.49$ (UV, $KMnO_4$)

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 8.18–8.11 (m, 2H), 7.45–7.41 (m, 2H), 7.33–7.27 (m, 3H), 7.06–7.01 (m, 2H), 5.94 (t, $J$ = 7.4 Hz, 1H), 2.21–2.13 (m, 2H), 1.46–1.38 (m, 2H), 1.37–1.30 (m, 2H), 0.88 (t, $J$ = 7.2 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 162.8, 148.4, 142.2, 134.4, 128.8, 128.5, 126.1, 125.1, 119.1, 115.7, 31.3, 25.7, 22.5, 14.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2927 (*w*), 1590 (*s*), 1514 (*s*), 1489 (*s*), 1339 (*vs*), 1239 (*vs*), 1162 (*s*), 1110 (*s*), 1037 (*m*), 847 (*s*), 750 (*s*), 693 (*vs*).

**HRMS** (EI) calc. for $C_{18}H_{19}NO_3$ $[M]^+$: 297.1359; found: 297.1368.




**S106**

**Enol ether S106**

Compound **S106** was prepared by following general procedure B. After the standard work-up procedure was performed, the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to yield enol ether **S106** (125 mg, 90%) as a pale yellow solid.

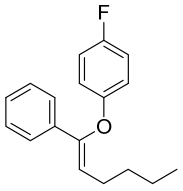
**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.44 (UV, $KMnO_4$)

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.45–7.40 (m, 2H), 7.36–7.31 (m, 2H), 7.22–7.13 (m, 3H), 6.94–6.90 (m, 2H), 5.83 (t, *J* = 7.4 Hz, 1H), 2.14–1.97 (m, 2H), 1.37–1.18 (m, 4H), 0.78 (t, *J* = 7.2 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 161.0, 148.2, 134.5, 134.2, 128.7, 128.4, 125.0, 119.1, 119.0, 116.3, 104.9, 31.3, 25.6, 22.5, 13.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2927 (*w*), 2225 (*m*), 1601 (v*s*), 1501 (v*s*), 1446 (*m*), 1238 (*vs*), 1164 (*s*), 1038 (*w*), 835 (*s*), 766 (*m*), 693 (*m*).

**HRMS** (EI) calc. for $C_{19}H_{19}NO$ $[M]^+$: 277.1461; found: 277.1465.




**S107**

**Enol ether S107**

Compound **S107** was prepared by following general procedure B. After the standard work-up procedure was performed, the residue was purified by column chromatography on silica gel (3% ethyl acetate in hexanes) to yield enol ether **S107** (126 mg, 94%) as a colorless oil.

**TLC** (3% ethyl acetate in hexanes), $R_f$ = 0.42 (UV, $KMnO_4$)

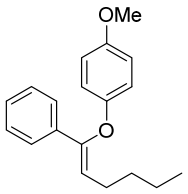
**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 7.47–7.45 (m, 2H), 7.30–7.26 (m, 2H), 7.25–7.21 (m, 1H), 6.93–6.86 (m, 4H), 5.84 (t, *J* = 7.4 Hz, 1H), 2.23–2.19 (m, 2H), 1.45–1.39 (m, 2H), 1.38–1.31 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 151 MHz): δ = 158.5, 156.9, 153.6, 149.1, 135.5, 128.6, 128.0, 125.4, 118.5, 116.5, 116.5, 116.1, 115.9, 31.6, 25.7, 22.6, 14.0.

**$^{19}$F NMR** ($CDCl_3$; 282 MHz): δ = –123.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2926 (*w*), 1499 (*vs*), 1446 (*w*), 1197 (*s*), 1092 (w), 1041 (*w*), 829 (*m*), 737 (*m*), 692 (*m*).

**HRMS** (EI) calc. for $C_{18}H_{19}FO$ $[M]^+$: 270.1414; found: 270.1405.




**S108**

**Enol ether S108**

Compound **S108** was prepared by following general procedure B. After the standard work-up procedure was performed, the residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to yield enol ether **S108** (131 mg, 93%) as a yellow oil.

**TLC** (5% ethyl acetate in hexanes), $R_f$ = 0.49 ($KMnO_4$, UV).

**$^1$H NMR** ($CDCl_3$, 599 MHz): δ = 7.48 (d, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.89–6.86 (m, 2H), 6.78–6.75 (m, 2H), 5.81 (t, *J* = 7.4 Hz, 1H), 3.73 (s, 3H), 2.25–2.20 (m, 2H), 1.46–1.40 (m, 2H), 1.39–1.32 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ = 154.3, 151.6, 149.3, 135.9, 128.5, 127.9, 125.5, 118.3, 116.3, 114.8, 55.8, 31.7, 25.7, 22.6, 14.1.

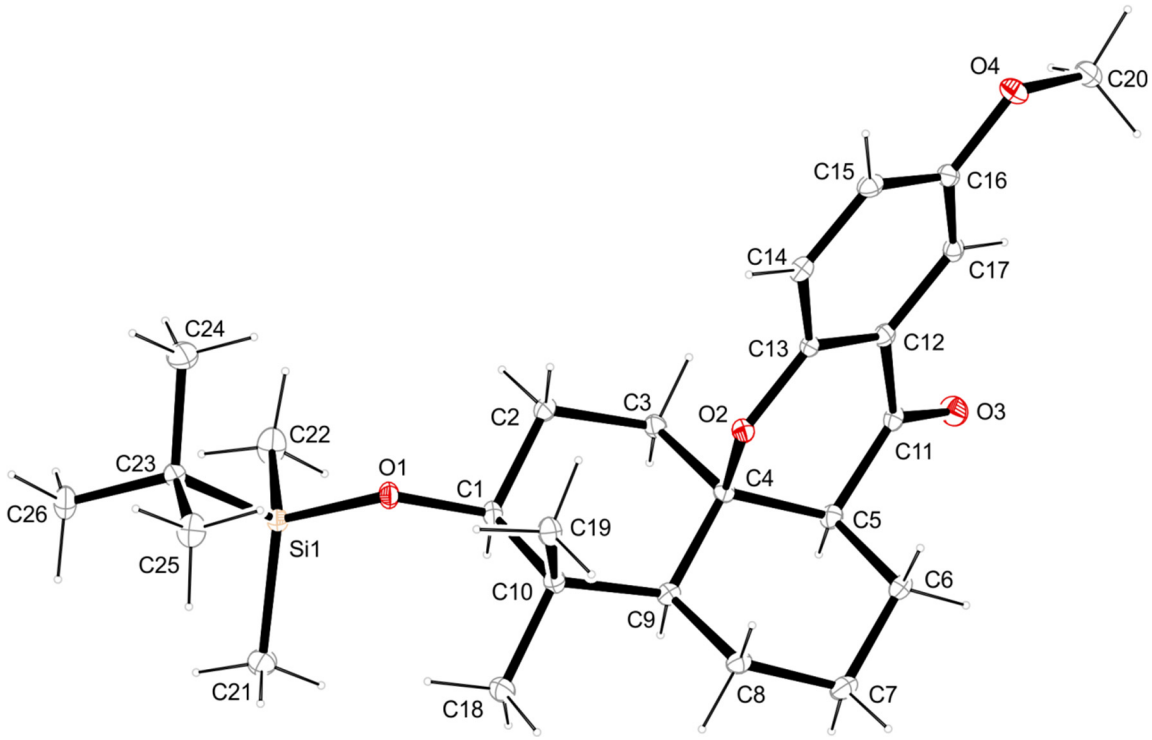
**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2926 (*w*), 2855 (*w*), 1501 (*vs*), 1445 (*m*), 1206 (*vs*), 1179 (*m*), 1040 (*m*), 825 (*s*), 730 (*s*), 692 (*m*).

**HRMS** (EI) calc. for $C_{19}H_{22}O_2$ $[M]^+$: 282.1614; found: 282.1629

### 3.3.5. X-Ray Crystallographic Data

The data collections were performed either on an *Oxford Diffraction* Xcalibur diffractometer, on a *Bruker* D8Quest diffractometer or on a *Bruker* D8Venture at 100 K or at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[180] and refined by least-squares methods against *F*2 with SHELXL-97.[181] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in the tables at the different sections.

#### 3.3.5.1.Ketone 29



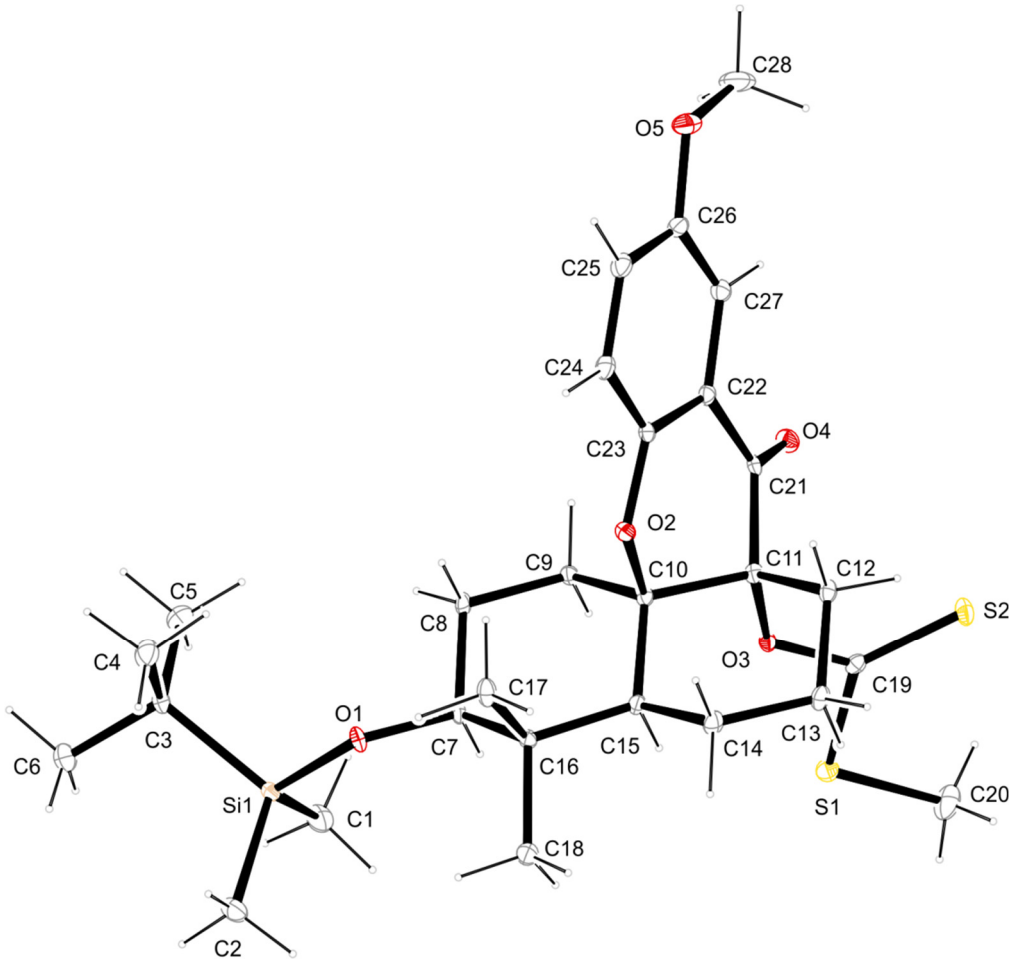

**CCDC 1510948** contains the supplementary crystallographic data for ketone 29. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***Table 18.*** *Crystallographic data for ketone* ***29****.*

| | |
|---|---|
| net formula | C26H40O4Si |
| Mr/g mol−1 | 444.67 |
| crystal size/mm | 0.090 × 0.070 × 0.050 |
| T/K | 100(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8Venture' |
| crystal system | monoclinic |

| | |
|---|---|
| space group | 'P 21' |
| a/Å | 7.7016(3) |
| b/Å | 13.7604(5) |
| c/Å | 12.1094(5) |
| α/° | 90 |
| β/° | 101.7470(11) |
| γ/° | 90 |
| V/Å3 | 1256.44(8) |
| Z | 2 |
| calc. density/g cm−3 | 1.175 |
| μ/mm−1 | 0.122 |
| absorption correction | multi-scan |
| transmission factor range | 0.9165–0.9585 |
| refls. measured | 22027 |
| Rint | 0.0326 |
| mean σ(I)/I | 0.0302 |
| θ range | 3.080–26.38 |
| observed refls. | 4663 |
| x, y (weighting scheme) | 0.0450, 0.1910 |
| hydrogen refinement | constr |
| Flack parameter | 0.02(4) |
| refls in refinement | 5132 |
| parameters | 288 |
| restraints | 1 |
| R(Fobs) | 0.0313 |
| Rw(F2) | 0.0782 |
| S | 1.037 |
| shift/errormax | 0.001 |
| max electron density/e Å−3 | 0.259 |
| min electron density/e Å−3 | −0.163 |

### 3.3.5.2.Xanthogenate 32



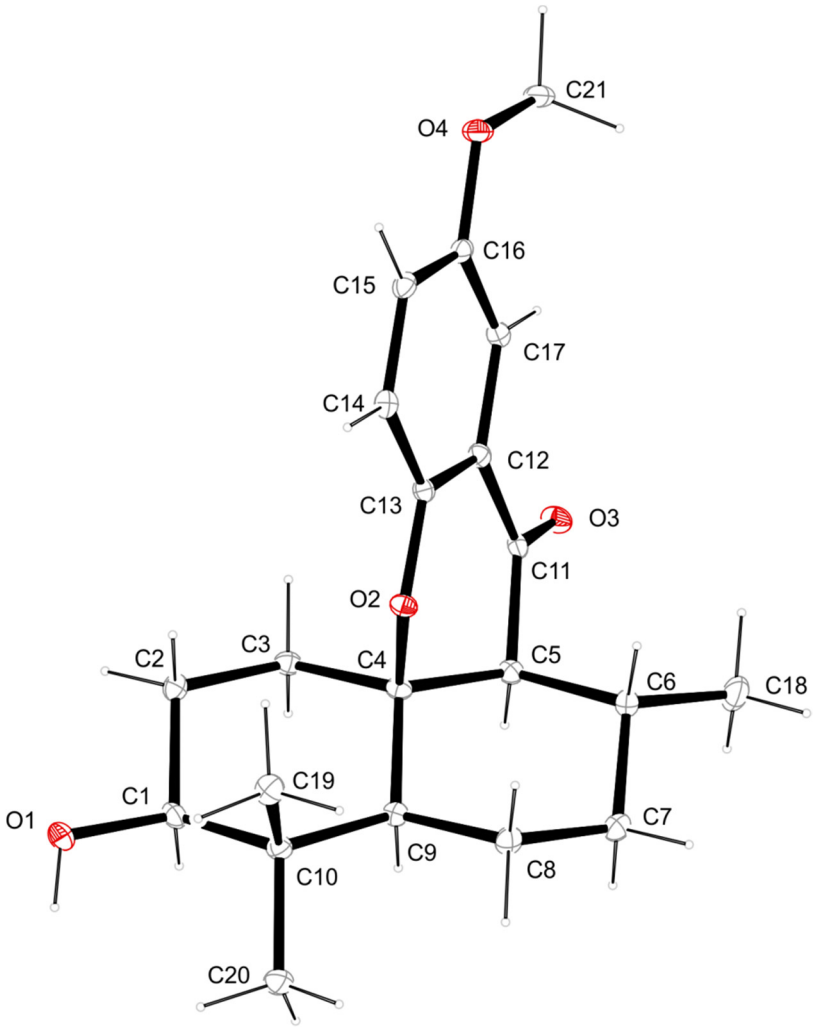

**CCDC 1510949** contains the supplementary crystallographic data for xanthogenate **32**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***Table 19***. *Crystallographic data for xanthgenate **32**.*

| | |
|---|---|
| net formula | C28H42O5S2Si |
| Mr/g mol−1 | 550.82 |
| crystal size/mm | 0.100 × 0.090 × 0.080 |
| T/K | 100(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8Venture' |
| crystal system | orthorhombic |
| space group | 'P 21 21 21' |
| a/Å | 6.9050(2) |
| b/Å | 12.1975(4) |
| c/Å | 34.5705(11) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| V/Å3 | 2911.66(16) |

| | |
|---|---|
| Z | 4 |
| calc. density/g cm−3 | 1.257 |
| μ/mm−1 | 0.259 |
| absorption correction | multi-scan |
| transmission factor range | 0.8834–0.9281 |
| refls. measured | 27302 |
| Rint | 0.0298 |
| mean σ(I)/I | 0.0280 |
| θ range | 3.177–26.41 |
| observed refls. | 5582 |
| x, y (weighting scheme) | 0.0272, 0.9303 |
| hydrogen refinement | constr |
| Flack parameter | −0.019(17) |
| refls in refinement | 5959 |
| parameters | 334 |
| restraints | 0 |
| R(Fobs) | 0.0286 |
| Rw(F2) | 0.0645 |
| S | 1.074 |
| shift/errormax | 0.001 |
| max electron density/e Å−3 | 0.239 |
| min electron density/e Å−3 | −0.194 |

**3.3.5.3.Ketone 34**



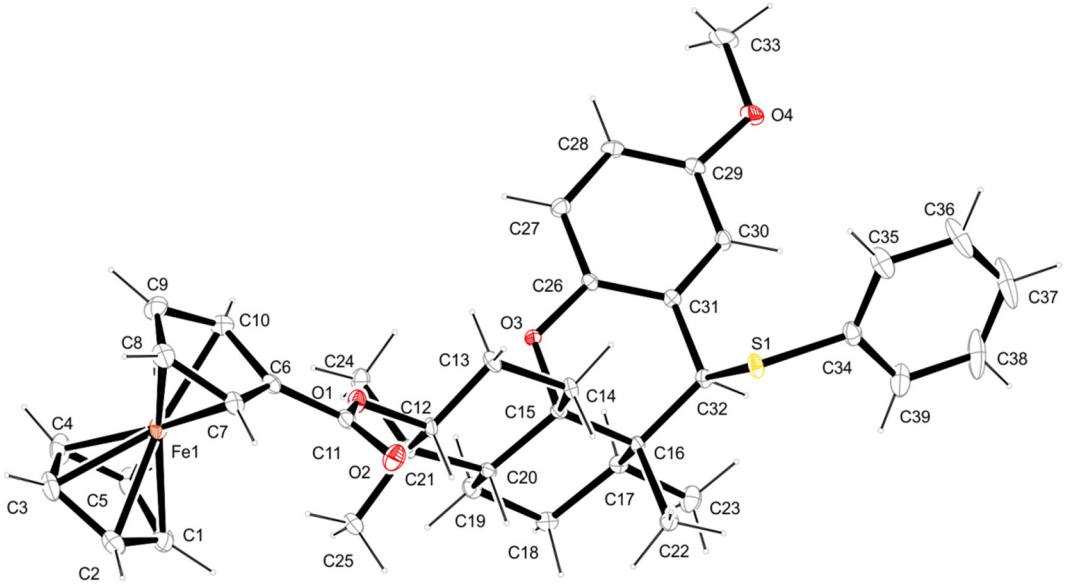
**CCDC 1510950** contains the supplementary crystallographic data for ketone **34**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***Table 20**. Crystallographic data for ketone **34**.*

| | |
|---|---|
| net formula | C21H28O4 |
| Mr/g mol−1 | 344.43 |
| crystal size/mm | 0.100 × 0.090 × 0.020 |
| T/K | 100(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8Venture' |
| crystal system | orthorhombic |
| space group | 'P 21 21 21' |
| a/Å | 10.1322(3) |
| b/Å | 10.7189(3) |
| c/Å | 16.5723(4) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| V/Å3 | 1799.85(9) |
| Z | 4 |
| calc. density/g cm−3 | 1.271 |
| μ/mm−1 | 0.086 |
| absorption correction | multi-scan |
| transmission factor range | 0.8781–0.9582 |
| refls. measured | 22043 |
| Rint | 0.0623 |
| mean σ(I)/I | 0.0384 |
| θ range | 3.027–25.69 |
| observed refls. | 3179 |
| x, y (weighting scheme) | 0.0269, 0.8345 |
| hydrogen refinement | mixed |
| Flack parameter | 0.1(5) |
| refls in refinement | 3382 |
| parameters | 234 |
| restraints | 0 |
| R(Fobs) | 0.0380 |
| Rw(F2) | 0.0874 |
| S | 1.091 |
| shift/errormax | 0.001 |
| max electron density/e Å−3 | 0.218 |
| min electron density/e Å−3 | −0.189 |

C-H: constr, O-H: refall.

### 3.3.3.4. Ferrocenecarboxylate ester S86



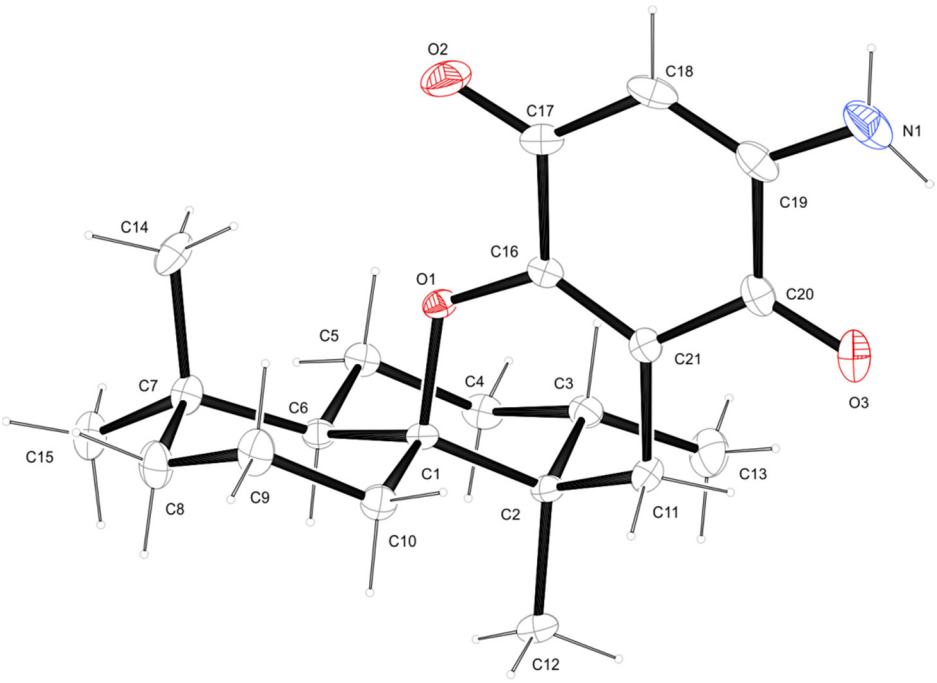

**CCDC 1499443** contains the supplementary crystallographic data for ferrocenecarboxylate ester **S86**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

**Table 21:** Ferrocenecarboxylate ester **S86**.

| | |
|---|---|
| net formula | $C_{39}H_{44}FeO_4S$ |
| $M_r$/g mol$^{-1}$ | 664.65 |
| crystal size/mm | 0.100 × 0.030 × 0.010 |
| $T$/K | 153.(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8 Venture TXS' |
| crystal system | monoclinic |
| space group | 'P 1 21 1' |
| $a$/Å | 14.3768(19) |
| $b$/Å | 7.3244(9) |
| $c$/Å | 17.1643(19) |
| α/° | 90 |
| β/° | 111.981(4) |
| γ/° | 90 |
| $V$/Å$^3$ | 1676.0(4) |
| $Z$ | 2 |
| calc. density/g cm$^{-3}$ | 1.317 |
| μ/mm$^{-1}$ | 0.552 |
| absorption correction | Multi-Scan |
| transmission factor range | 0.6807–0.7454 |
| refls. measured | 23821 |
| $R_{int}$ | 0.0775 |
| mean σ($I$)/$I$ | 0.0749 |
| θ range | 3.168–26.371 |
| observed refls. | 5507 |
| $x$, $y$ (weighting scheme) | 0.0267, 0.3292 |
| hydrogen refinement | constr |
| Flack parameter | 0.008(10) |

| | |
|---|---|
| refls in refinement | 6743 |
| parameters | 411 |
| restraints | 1 |
| $R(F_{obs})$ | 0.0447 |
| $R_w(F^2)$ | 0.0844 |
| $S$ | 1.039 |
| shift/error$_{max}$ | 0.001 |
| max electron density/e Å$^{-3}$ | 0.317 |
| min electron density/e Å$^{-3}$ | −0.433 |

### 3.3.3.5. (–)-Cyclosmenospongine (4)



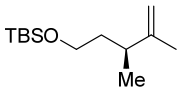

**CCDC 1499442** contains the supplementary crystallographic data (–)-Cyclosmenospongine (**4**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***Table 22:*** *(–)-Cyclosmenospongine (4).*

| | |
|---|---|
| net formula | $C_{21}H_{29}NO_3$ |
| $M_r$/g mol$^{-1}$ | 343.45 |
| crystal size/mm | 0.100 × 0.060 × 0.050 |
| $T$/K | 153.(2) |
| radiation | MoKα |
| diffractometer | 'Bruker D8 Venture TXS' |
| crystal system | orthorhombic |
| space group | 'P 21 21 21' |
| $a$/Å | 10.7772(8) |
| $b$/Å | 11.6369(8) |
| $c$/Å | 14.6780(10) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |

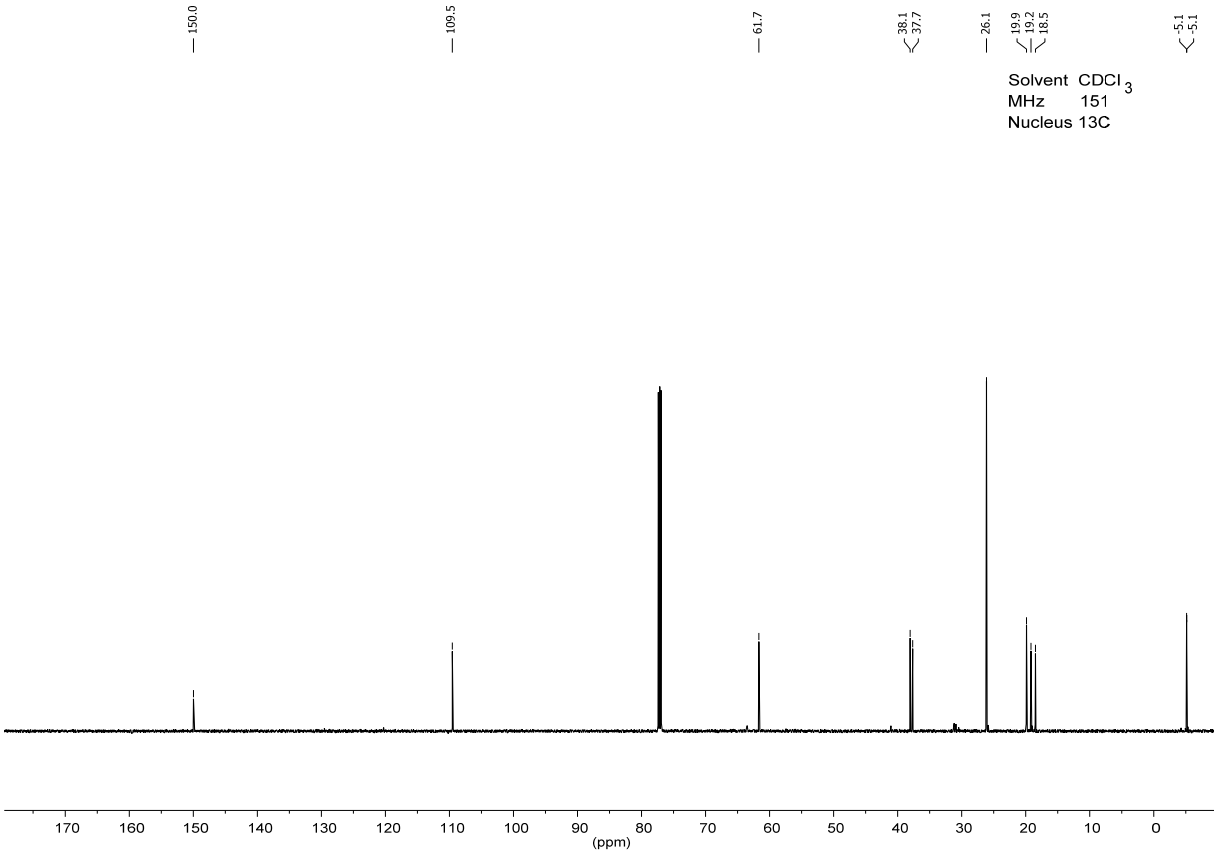
| | |
|---|---|
| $V$/Å$^3$ | 1840.8(2) |
| $Z$ | 4 |
| calc. density/g cm$^{-3}$ | 1.239 |
| μ/mm$^{-1}$ | 0.082 |
| absorption correction | Multi-Scan |
| transmission factor range | 0.9033–0.9590 |
| refls. measured | 42454 |
| $R_{int}$ | 0.0806 |
| mean σ($I$)/$I$ | 0.0501 |
| θ range | 3.358–27.484 |
| observed refls. | 3522 |
| $x$, $y$ (weighting scheme) | 0.0379, 0.4490 |
| hydrogen refinement | C-H: constr, N-H: refall |
| Flack parameter | 0.1(2) |
| refls in refinement | 4086 |
| parameters | 238 |
| restraints | 0 |
| $R(F_{obs})$ | 0.0489 |
| $R_w(F^2)$ | 0.0947 |
| $S$ | 1.074 |
| shift/error$_{max}$ | 0.001 |
| max electron density/e Å$^{-3}$ | 0.232 |
| min electron density/e Å$^{-3}$ | −0.191 |

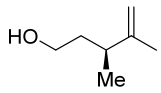
### 3.3.6. $^{1}H$ and $^{13}C$ NMR Spectra




**S54**

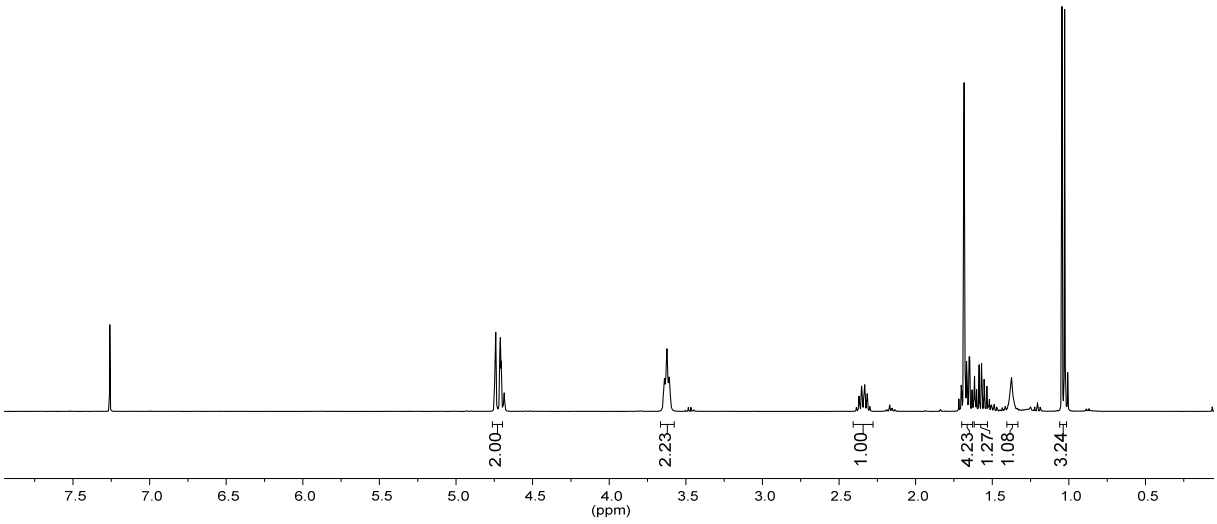




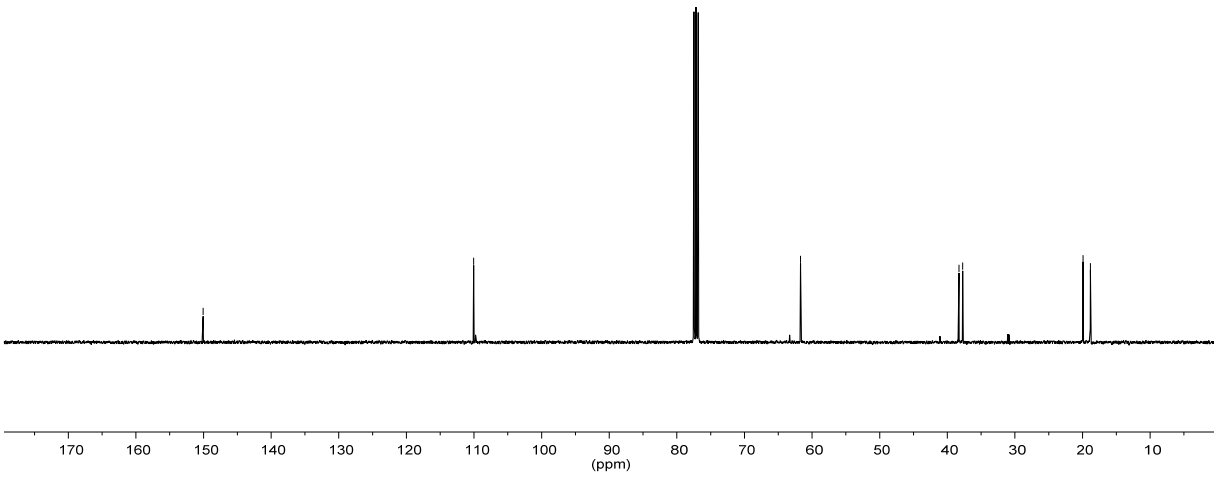

**S55**

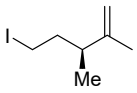
Solvent CDCl 3
MHz 400
Nucleus 1H




150.1
110.0
61.7
38.3
37.7
19.9
18.8

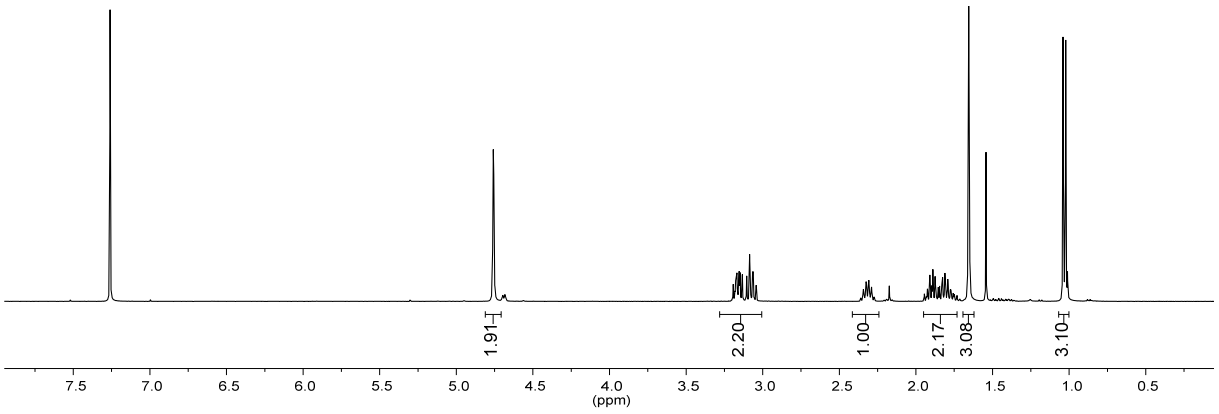
Solvent CDCl 3
MHz 101
Nucleus 13C

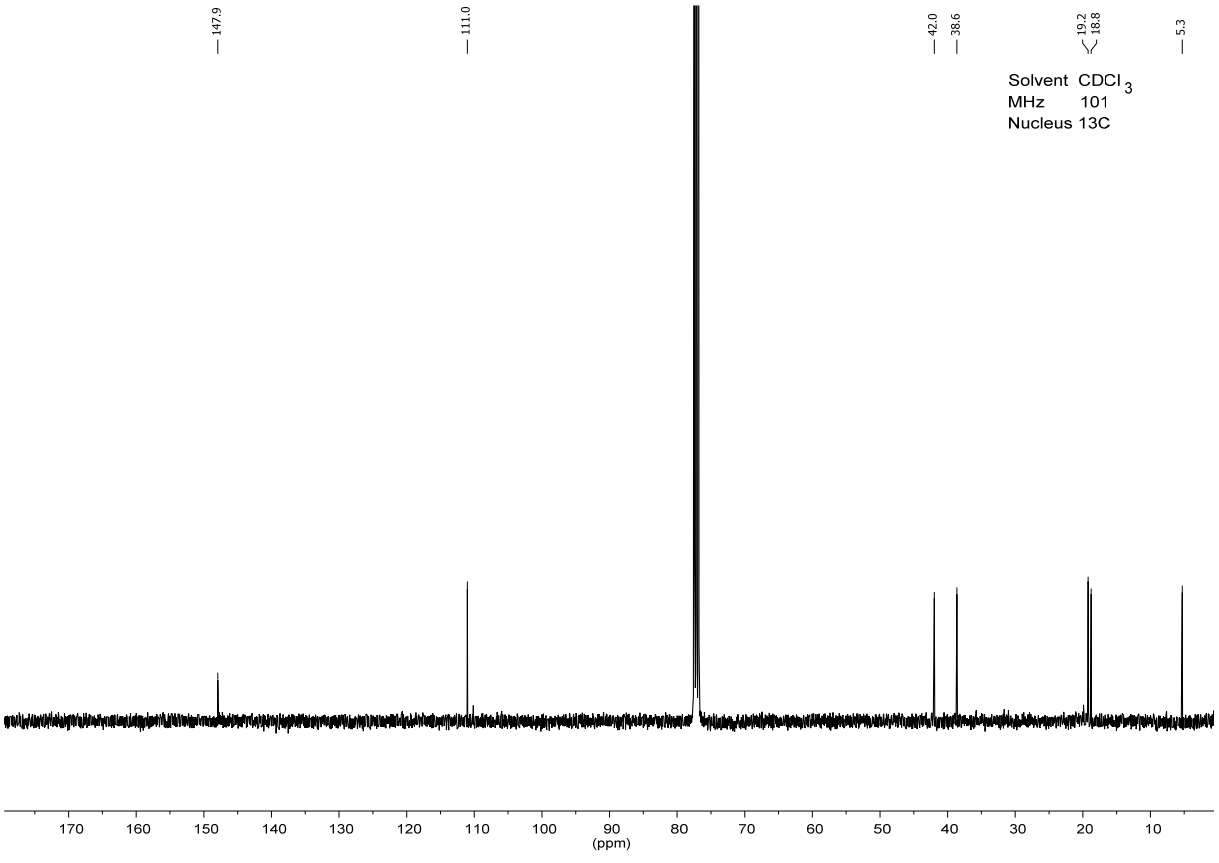




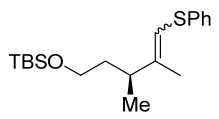

**15**

Solvent $CDCl_3$
MHz 400
Nucleus 1H



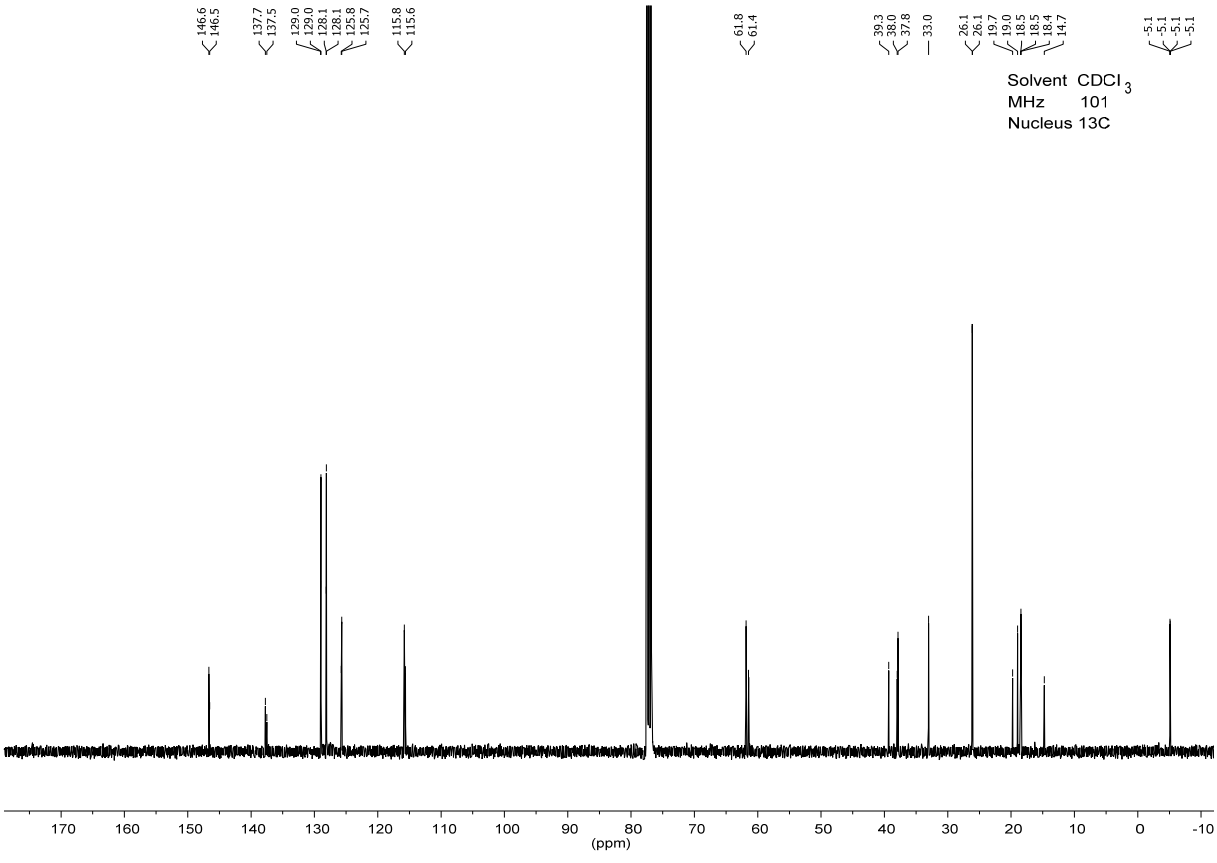



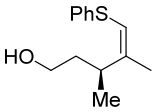

Solvent $CDCl_3$
MHz 101
Nucleus 13C


SPh
TBSO
Me

**S57**

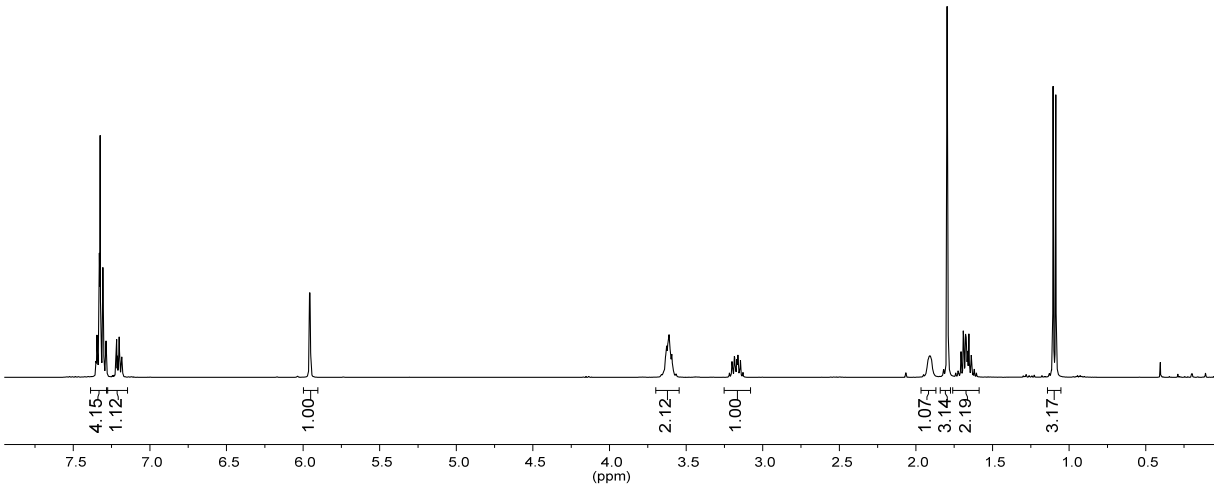

Solvent CDCl3
MHz 400
Nucleus 1H
3.46
0.96
0.37
0.61
2.05
0.62
0.38
2.29
2.64
1.15
1.92
9.11
3.80
(ppm)


146.6
146.5
137.7
137.5
129.0
128.0
128.1
125.8
125.7
115.8
115.6
61.8
61.4
39.3
38.0
37.8
33.0
26.1
26.1
19.7
19.0
18.5
18.5
18.4
14.7
-5.1
-5.1
-5.1
-5.1
Solvent CDCl3
MHz 101
Nucleus 13C
(ppm)



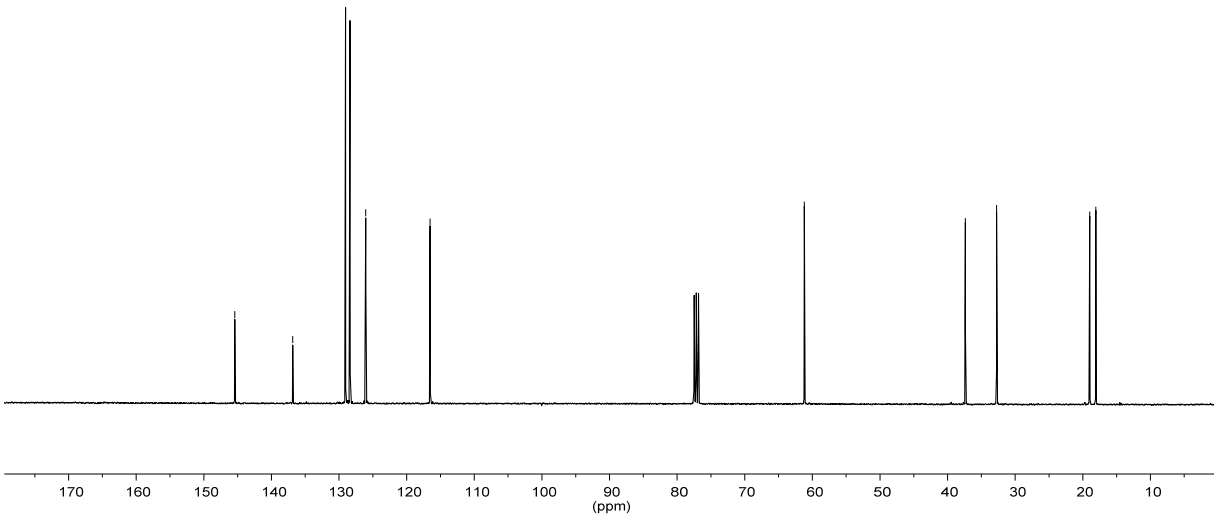

**(*Z*)-S58**

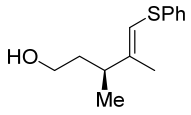
Solvent CDCl 3
MHz 400
Nucleus 1H





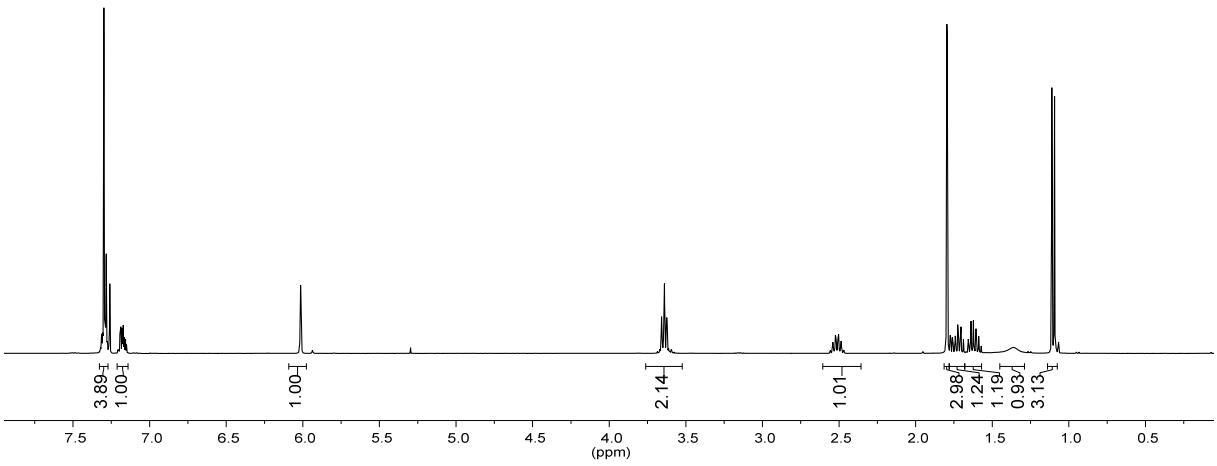
Solvent CDCl 3
MHz 101
Nucleus 13C





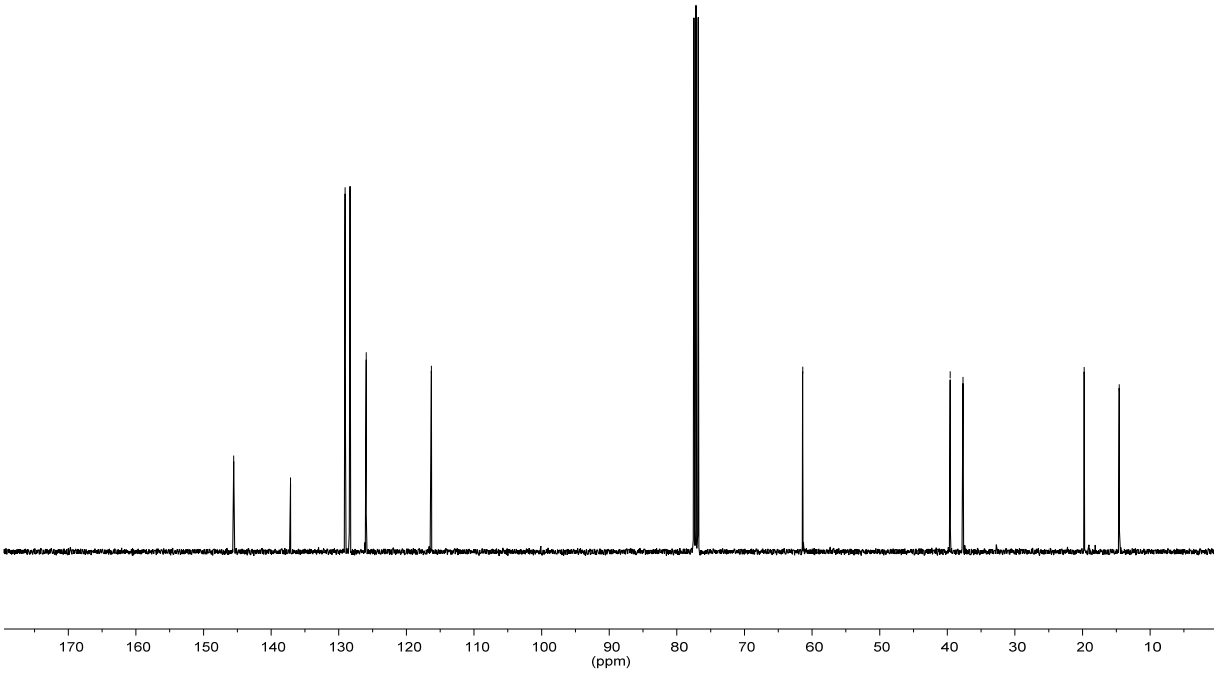

**(*E*)-S58**

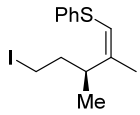
Solvent CDCl 3
MHz 400
Nucleus 1H





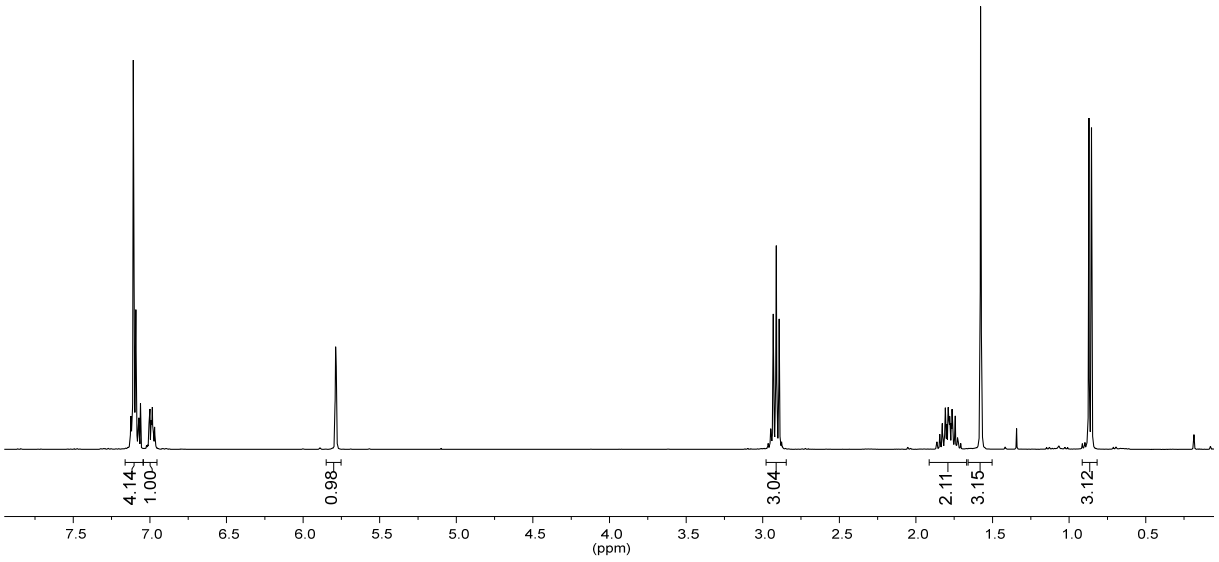
Solvent CDCl 3
MHz 101
Nucleus 13C





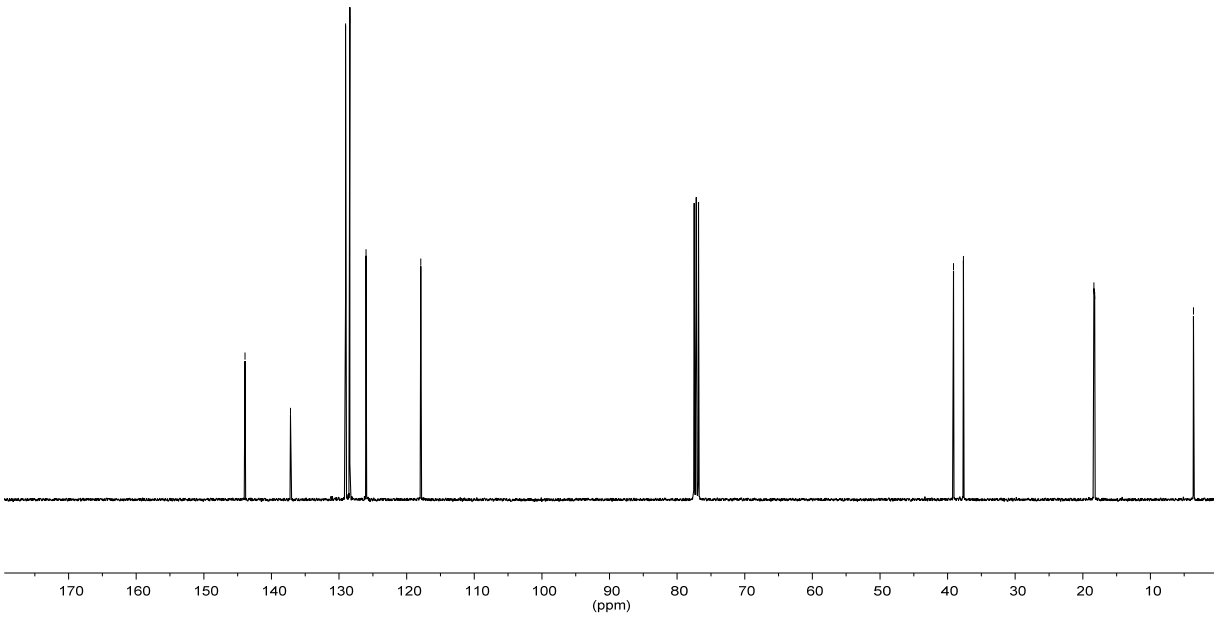

**(*Z*)-S59**

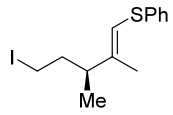
Solvent CDCl 3
MHz 400
Nucleus 1H





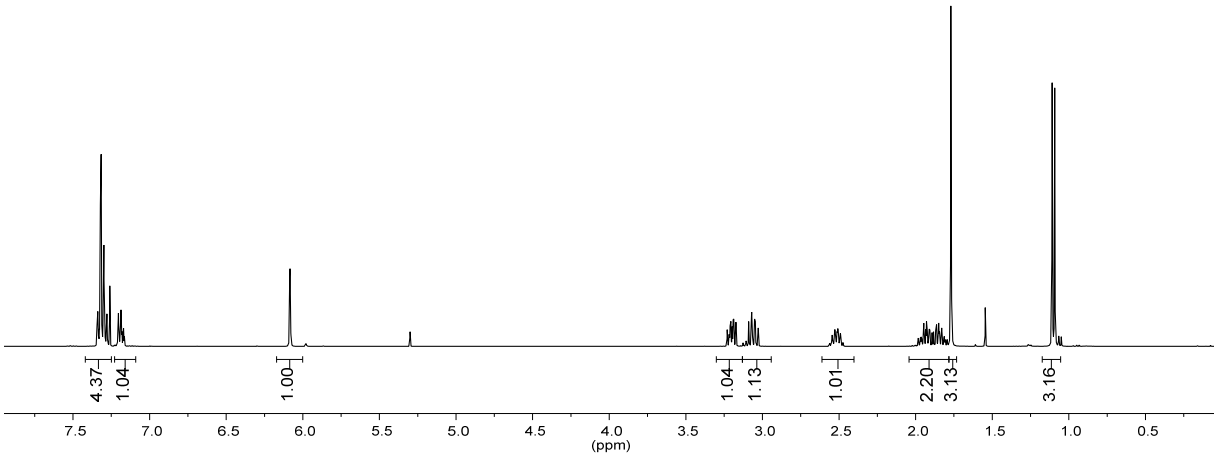
Solvent CDCl 3
MHz 101
Nucleus 13C





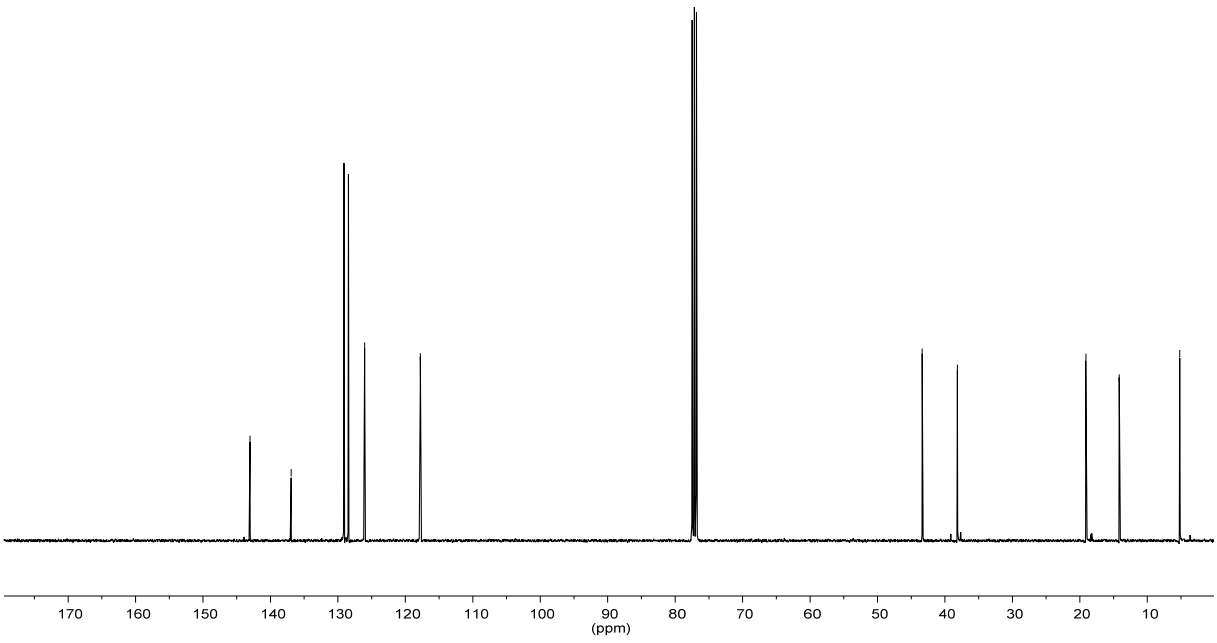

**(*E*)-S59**

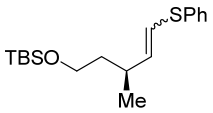
Solvent CDCl 3
MHz 400
Nucleus 1H





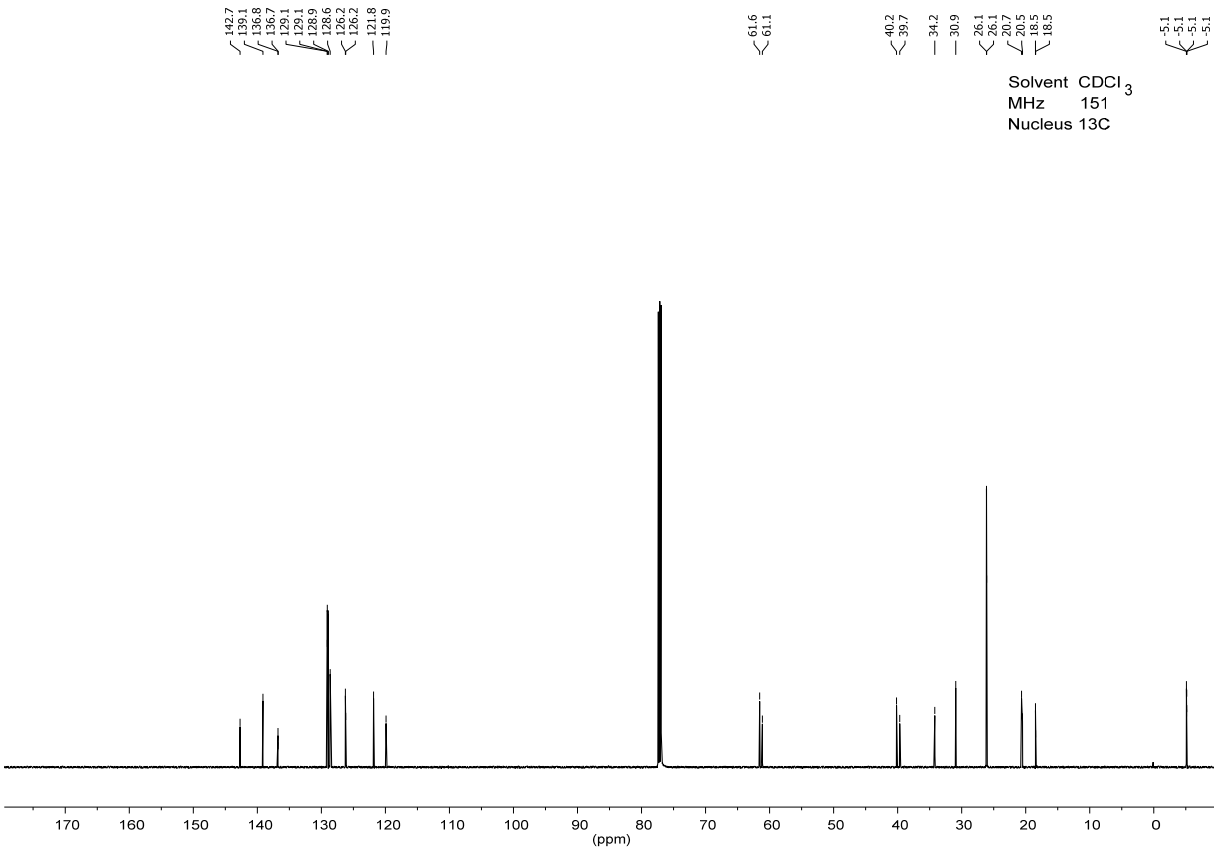
Solvent CDCl 3
MHz 101
Nucleus 13C

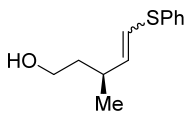



SPh
TBSO
Me

**S61**

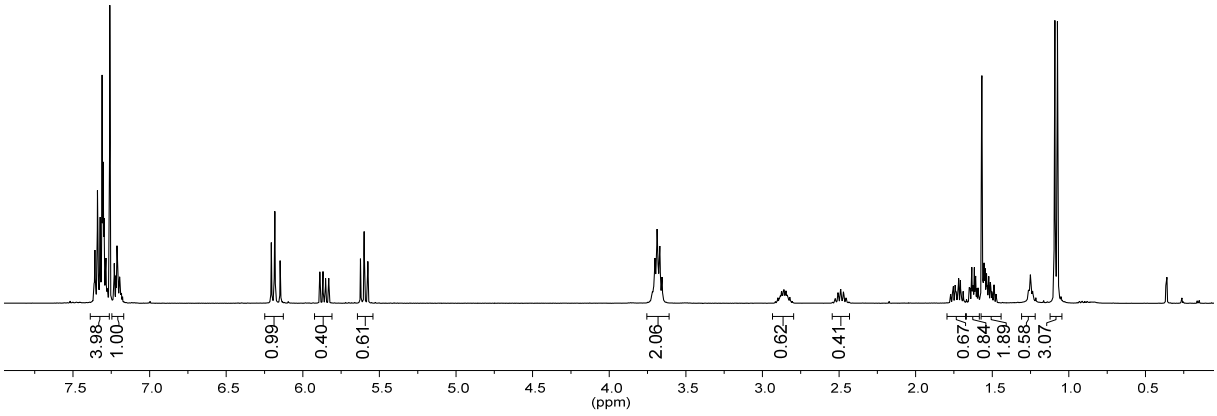

Solvent CDCl3
MHz 599
Nucleus 1H
4.14
1.00
0.96
0.52
0.78
1.88
0.83
0.59
0.65
1.76
0.96
1.54
7.41
4.61
(ppm)

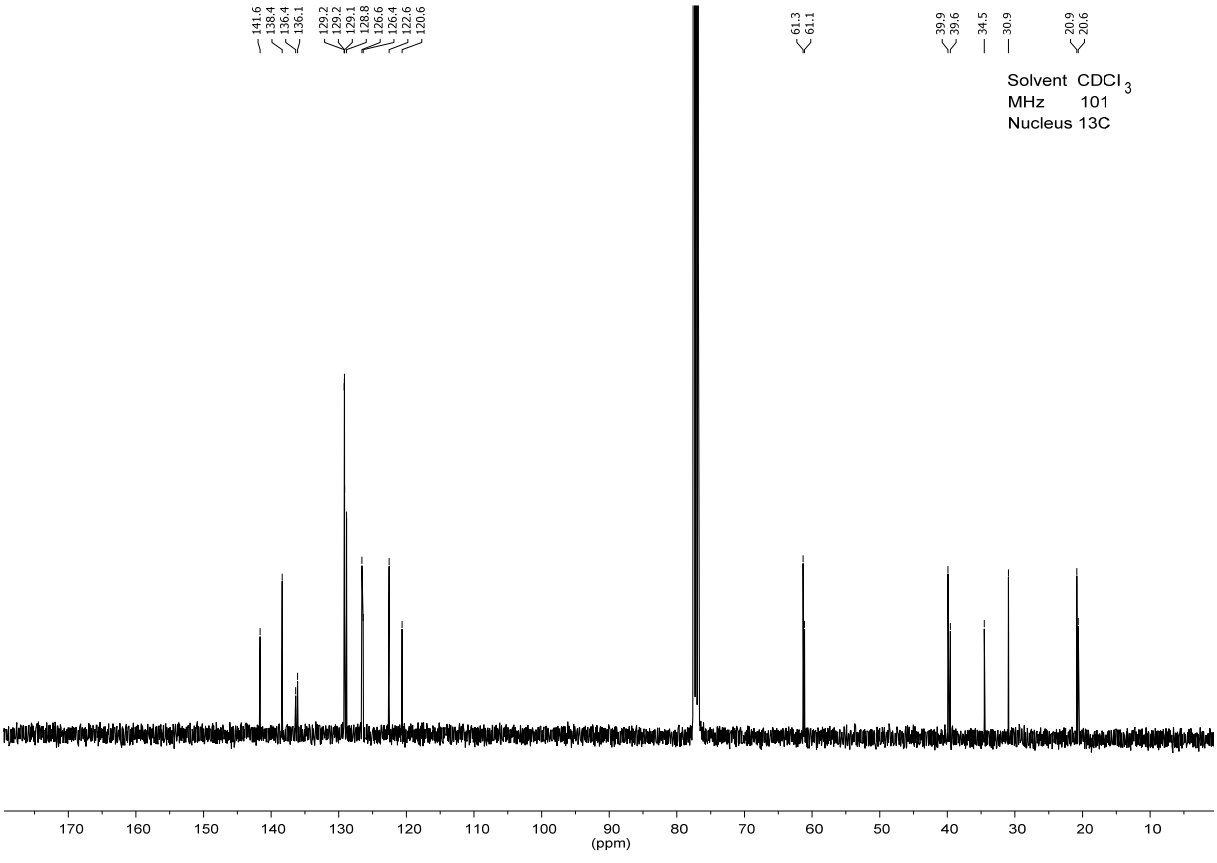

142.7
139.1
136.8
136.7
129.1
129.1
128.9
128.6
126.2
126.2
121.8
119.9
61.6
61.1
40.2
39.7
34.2
30.9
26.1
26.1
20.7
20.5
18.5
18.5
-5.1
-5.1
-5.1
-5.1
Solvent CDCl3
MHz 151
Nucleus 13C
(ppm)

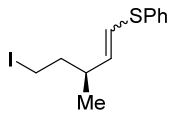



**S62**

Solvent CDCl3
MHz 400
Nucleus 1H

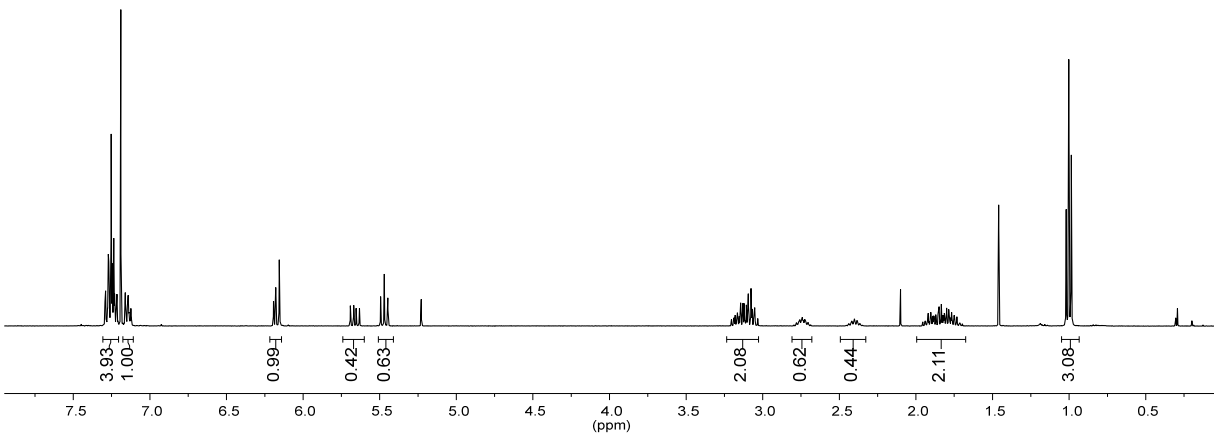


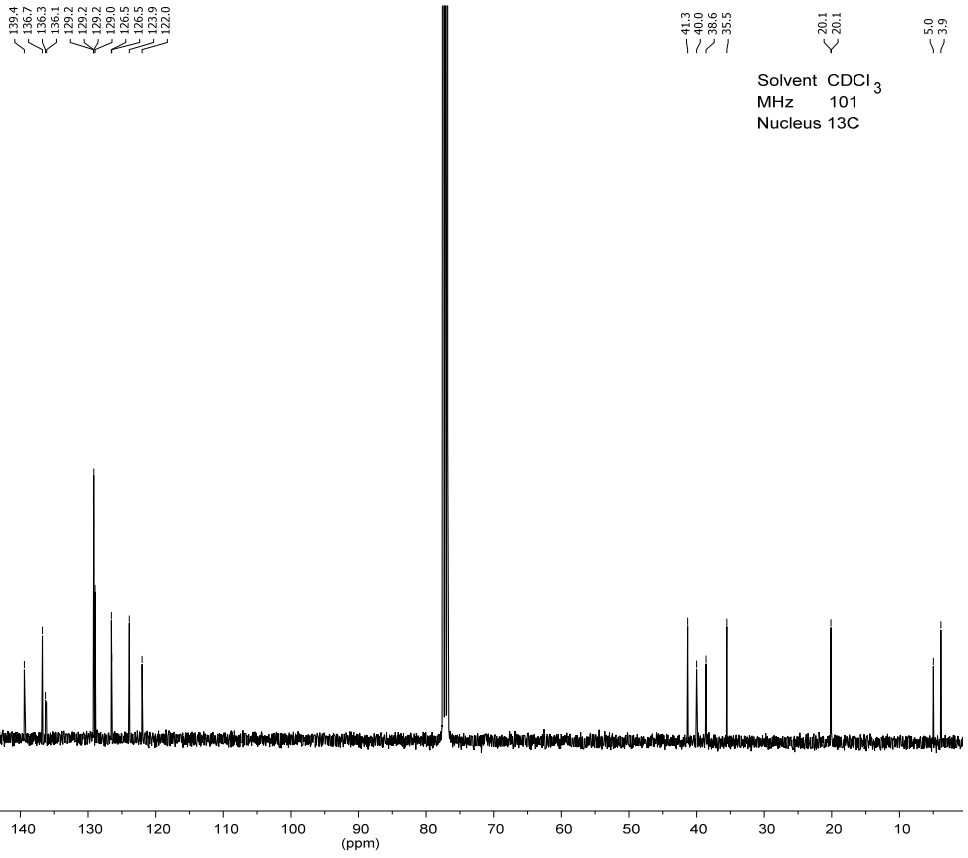



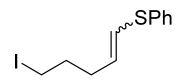



**S63**

Solvent CDCl 3
MHz 400
Nucleus 1H

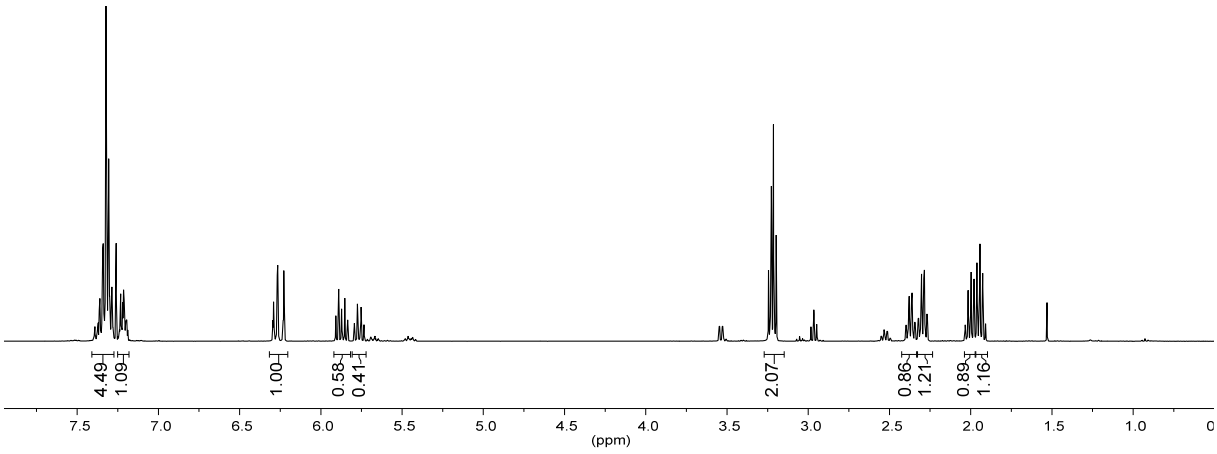


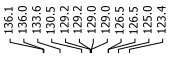






**S66**

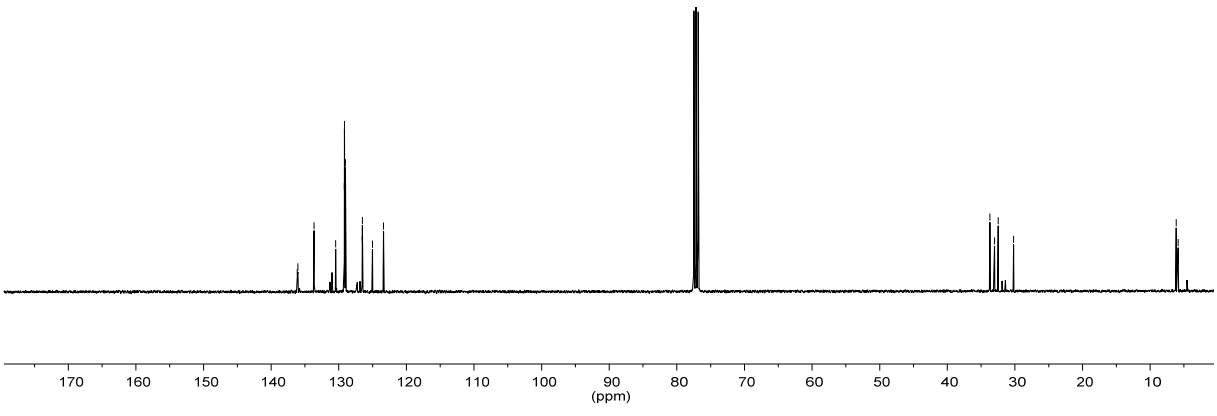
Solvent CDCl 3
MHz 400
Nucleus 1H

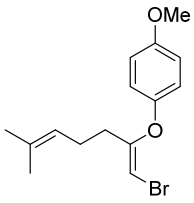




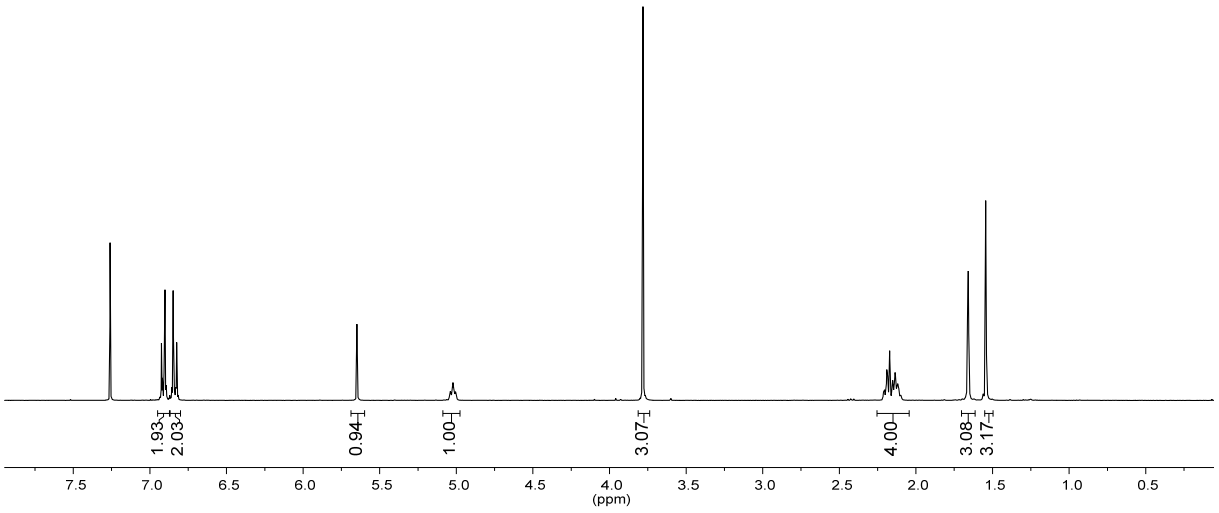
Solvent CDCl 3
MHz 101
Nucleus 13C

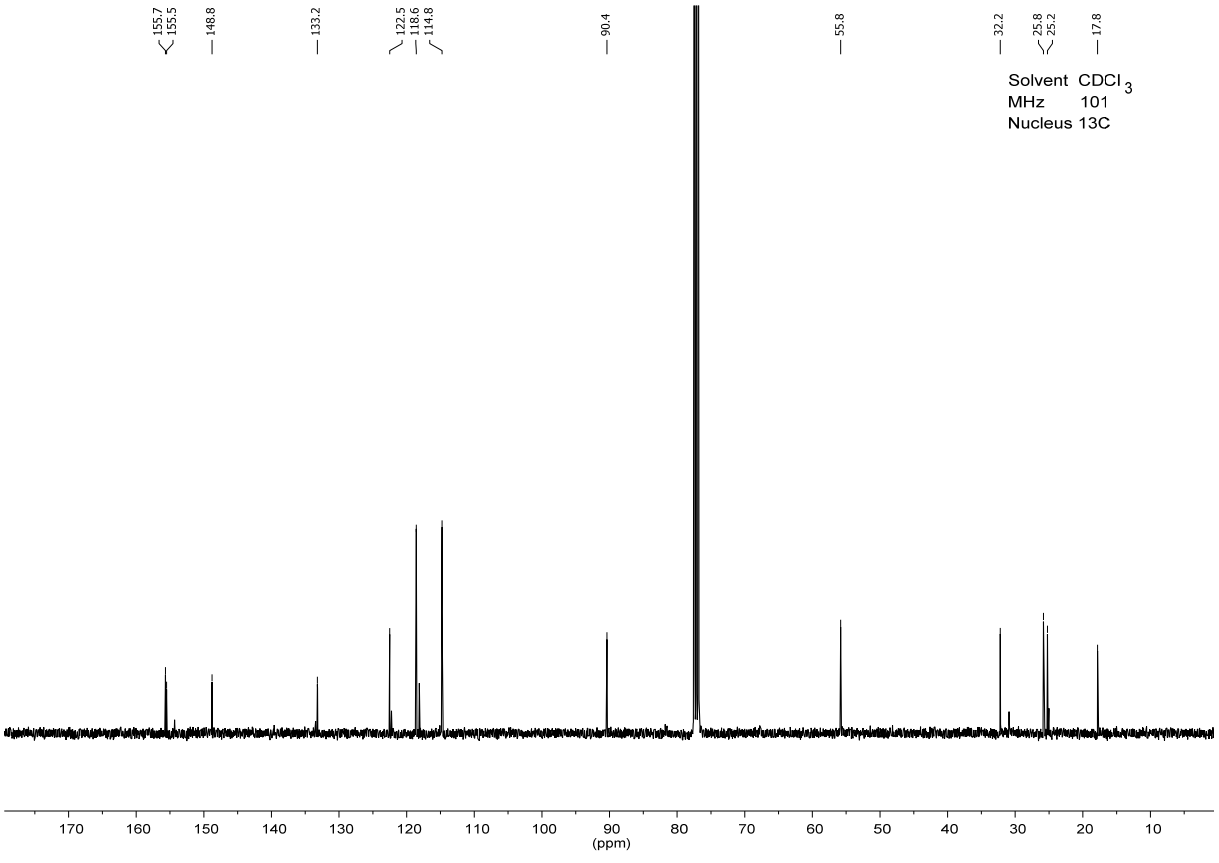




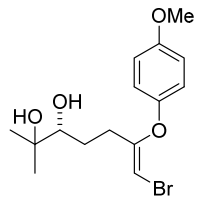

**S67**

Solvent CDCl 3
MHz 400
Nucleus 1H



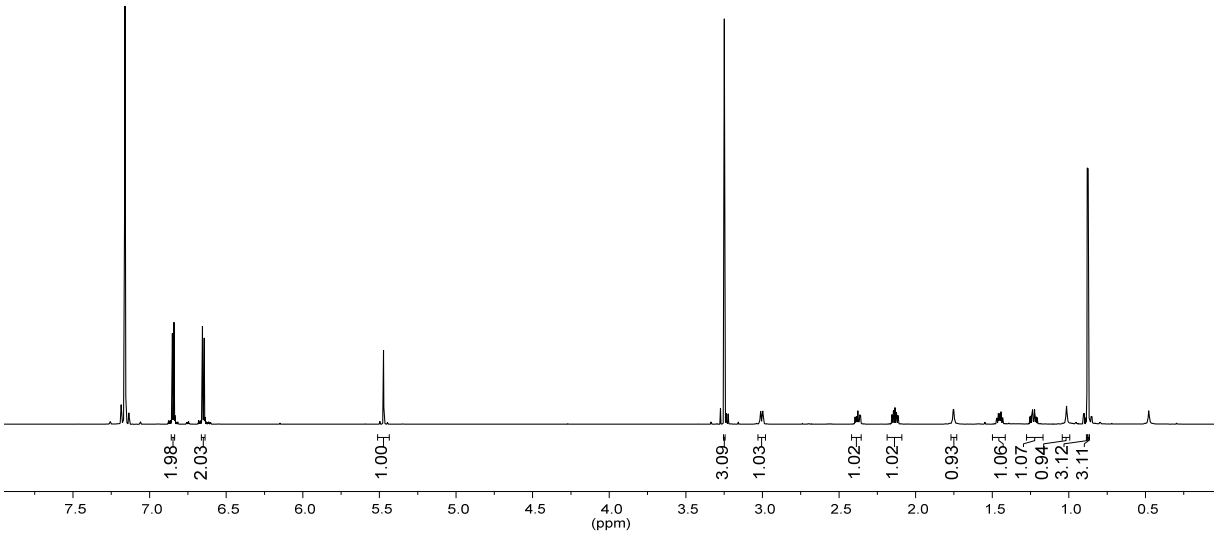



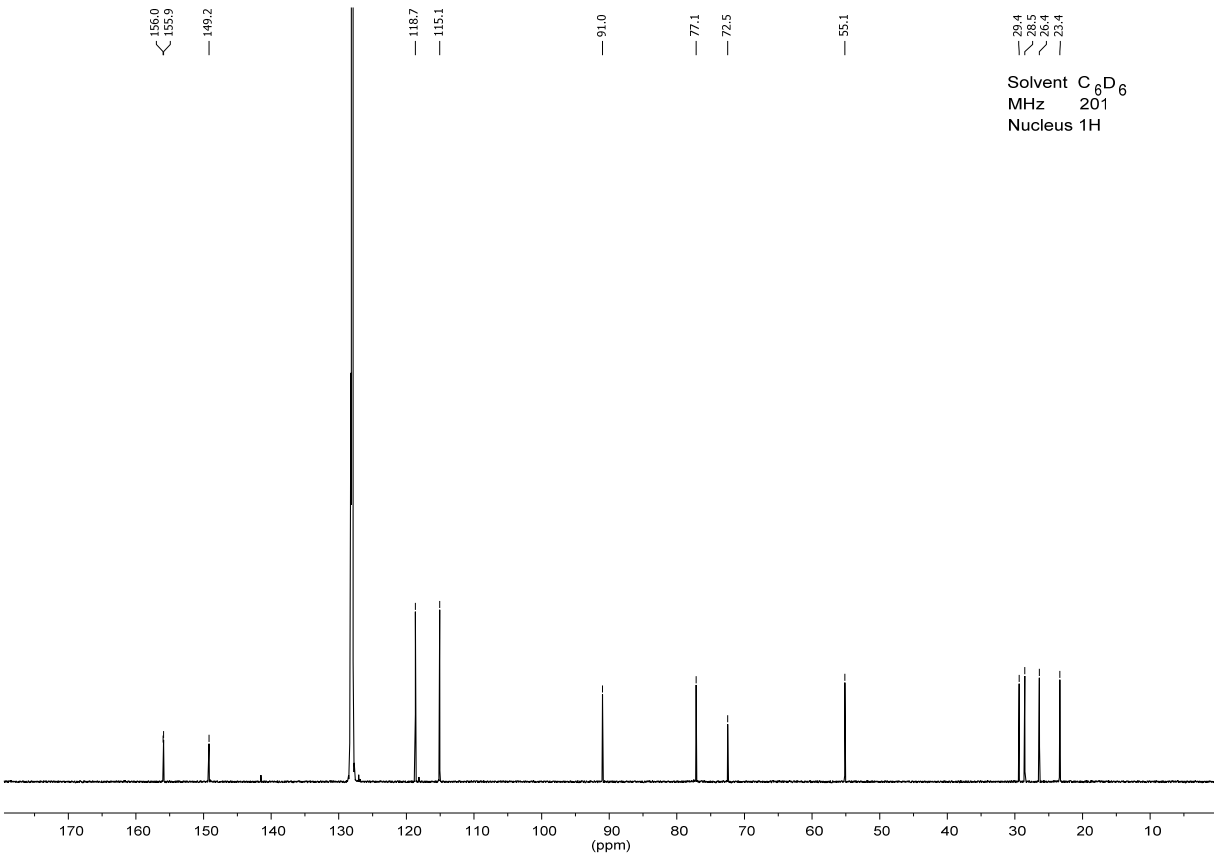

Solvent CDCl 3
MHz 101
Nucleus 13C

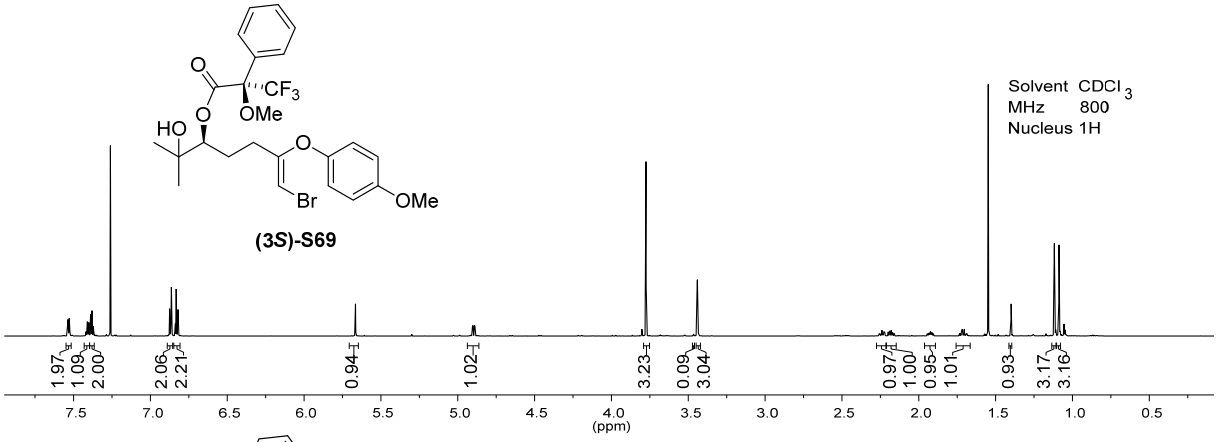



**(3*R*)-S68**

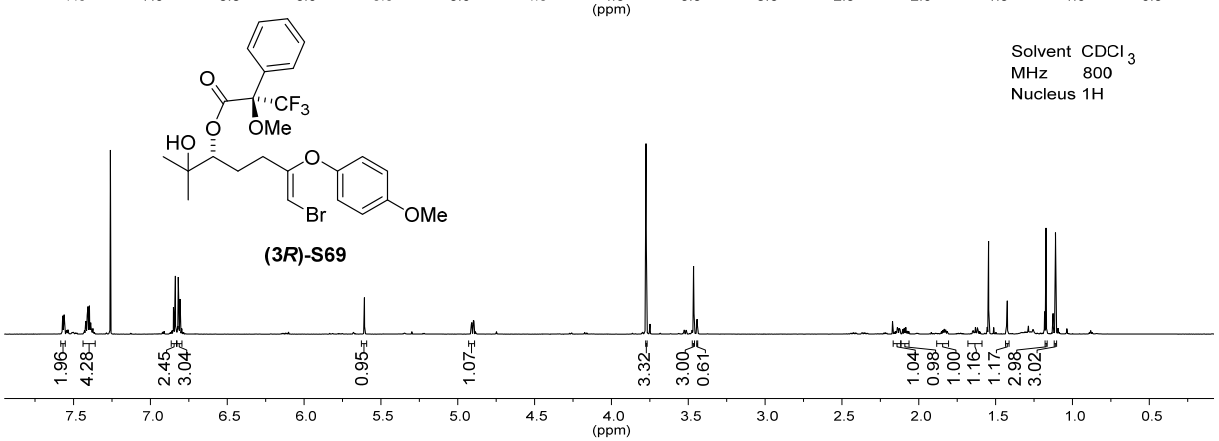
Solvent $C_6D_6$
MHz 800
Nucleus 1H



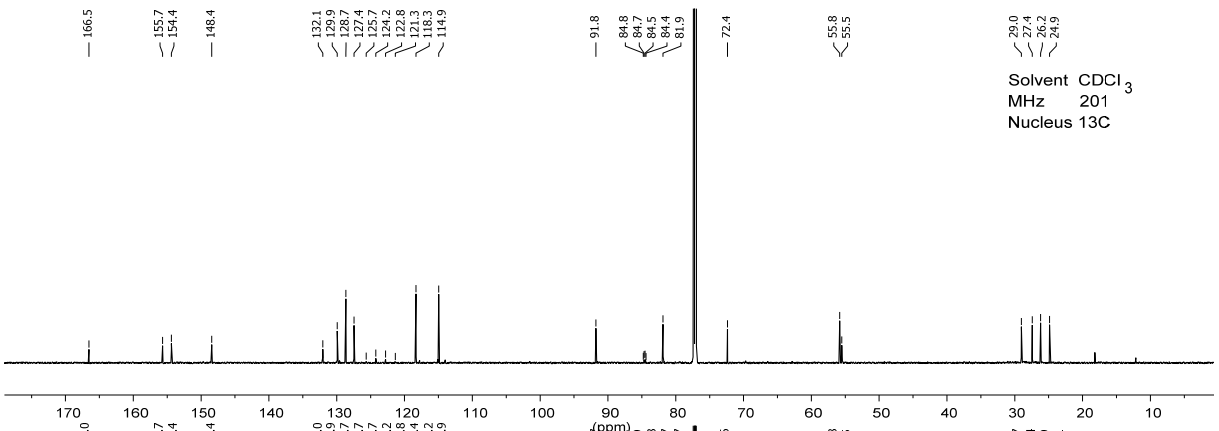



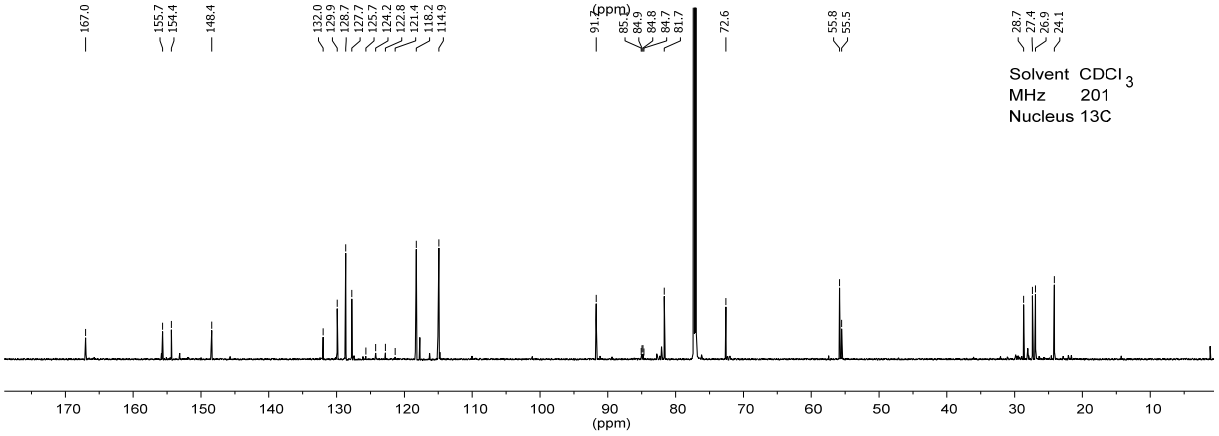

Solvent CDCl3
MHz 800
Nucleus 1H
(ppm)

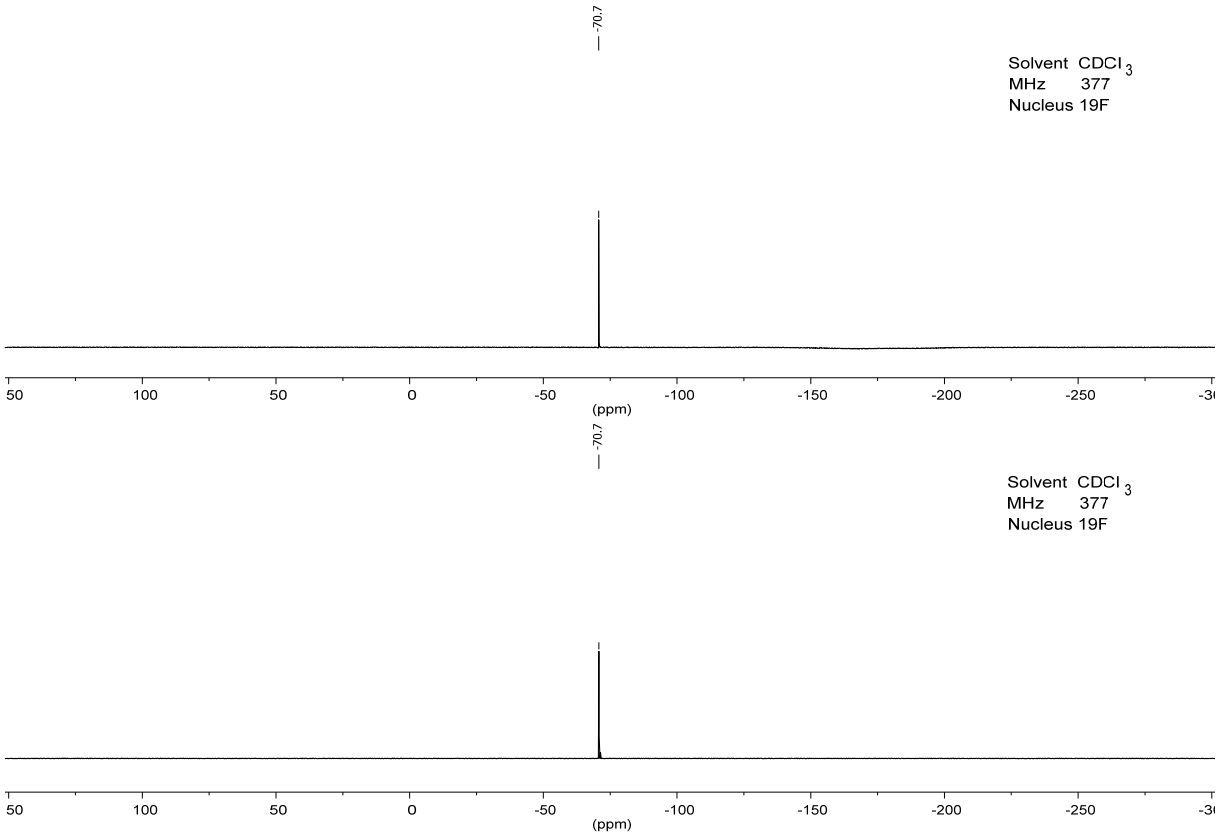
**(3*S*)-S69**

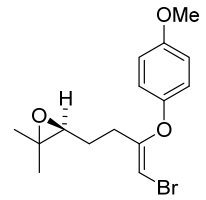

Solvent CDCl3
MHz 800
Nucleus 1H
(ppm)

**(3*R*)-S69**


Solvent CDCl3
MHz 201
Nucleus 13C
(ppm)

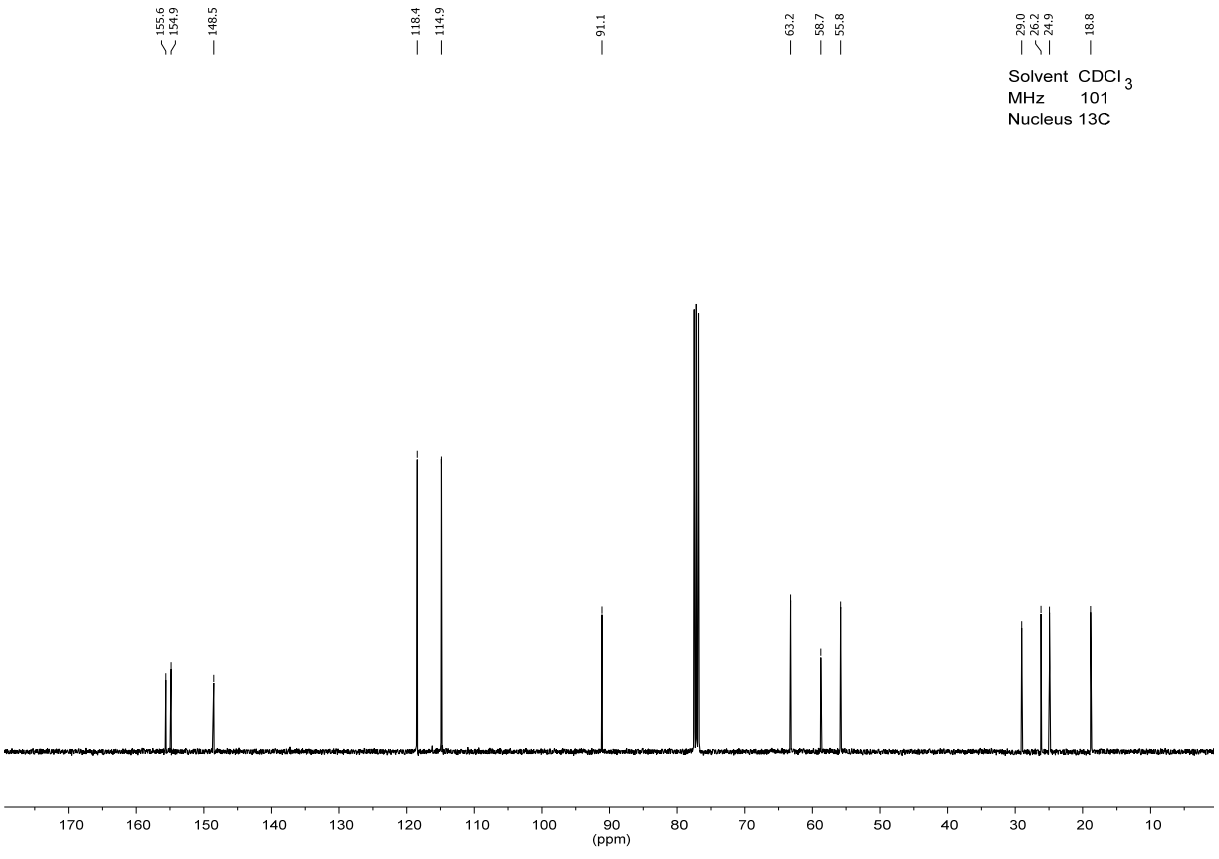

Solvent CDCl3
MHz 201
Nucleus 13C
(ppm)

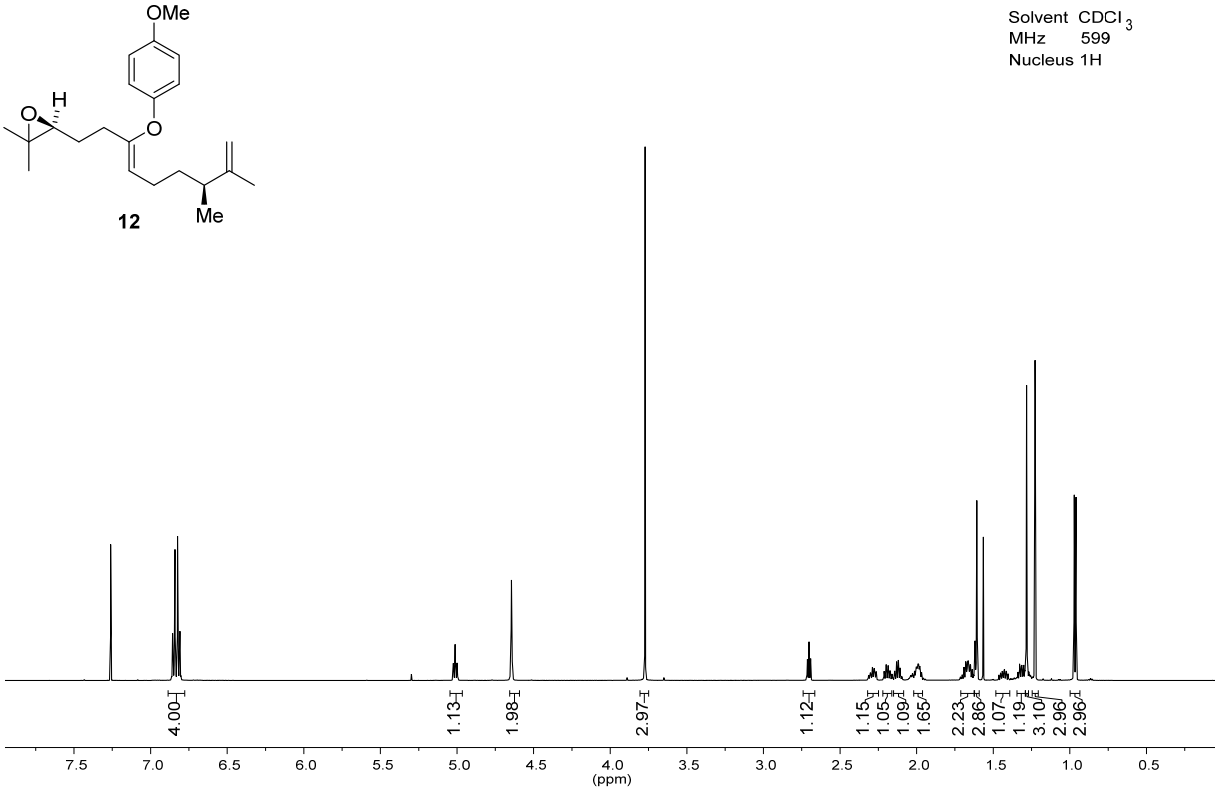

-70.7
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
(ppm)
-70.7
Solvent CDCl3
MHz 377
Nucleus 19F
50
100
50
0
-50
-100
-150
-200
-250
(ppm)

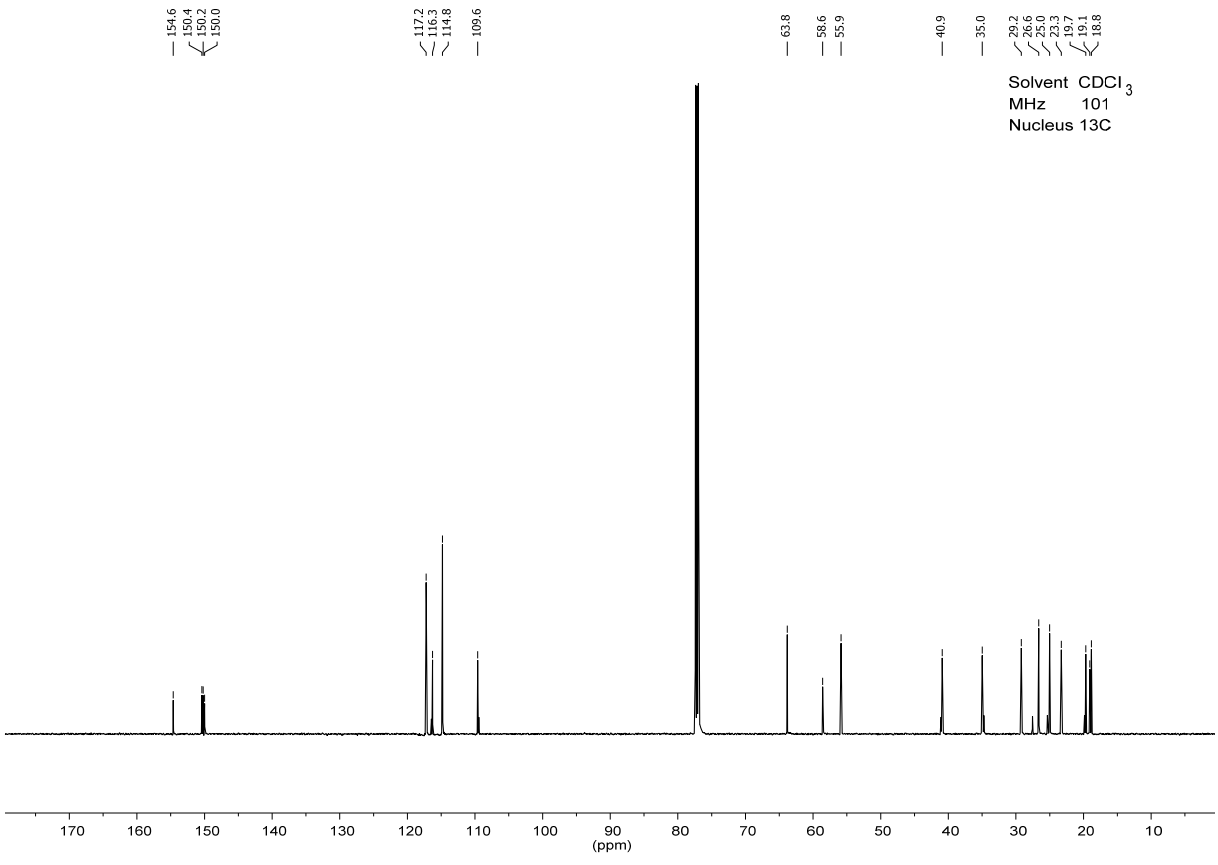

OMe
H
O
O
Br

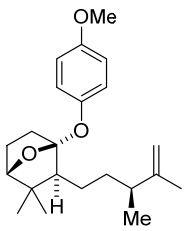
**(3*S*)-20**


Solvent CDCl3
MHz 400
Nucleus 1H
2.04
2.10
1.00
3.19
0.99
1.03
1.07
1.09
1.17
3.05
2.96
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


155.6
154.9
148.5
118.4
114.9
91.1
63.2
58.7
55.8
29.0
26.2
24.9
18.8
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

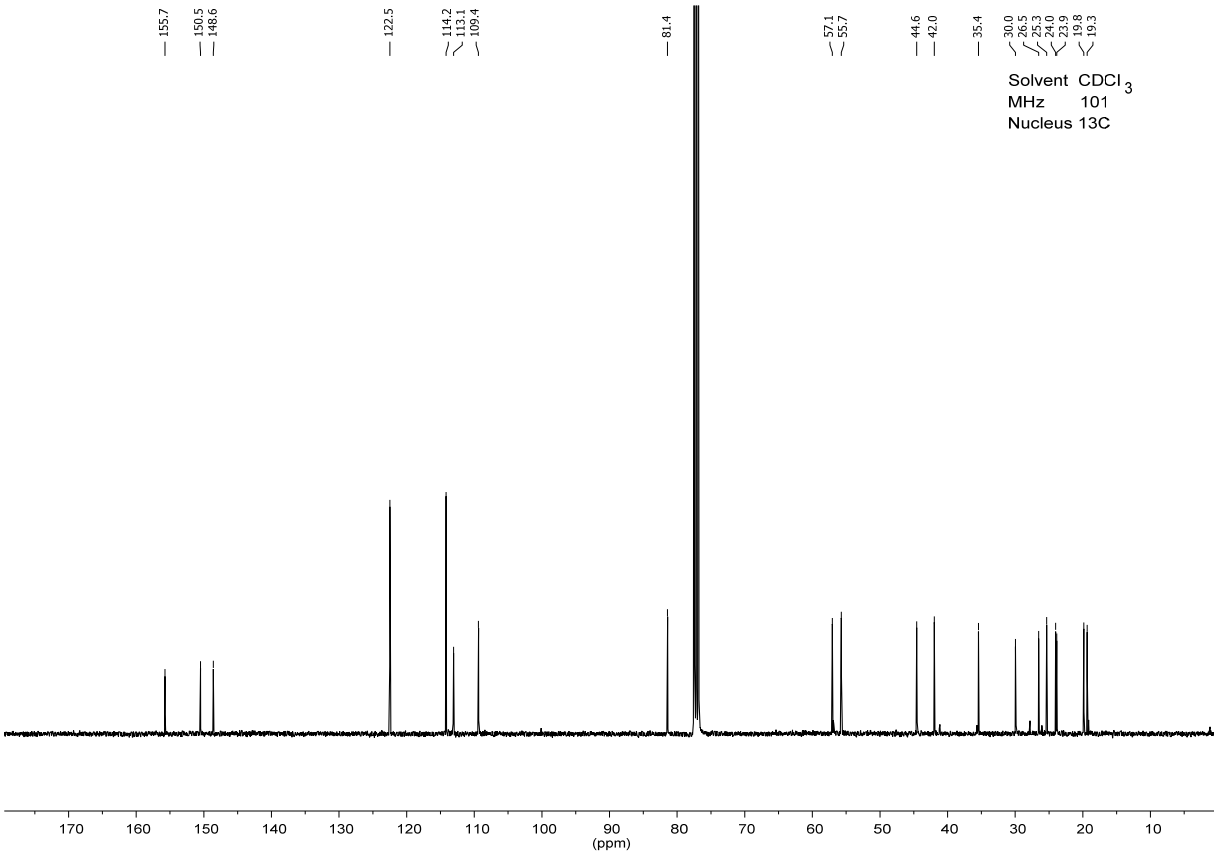

OMe
H
O
O
Me
12
Solvent CDCl3
MHz 599
Nucleus 1H
4.00
1.13
1.98
2.97
1.12
1.15
1.05
1.09
1.65
2.23
2.86
1.07
1.19
3.10
2.96
2.96
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

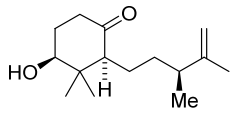

154.6
150.4
150.2
150.0
117.2
116.3
114.8
109.6
63.8
58.6
55.9
40.9
35.0
29.2
26.6
25.0
23.3
19.7
19.1
18.8
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OMe
O
O
H
Me

**21**

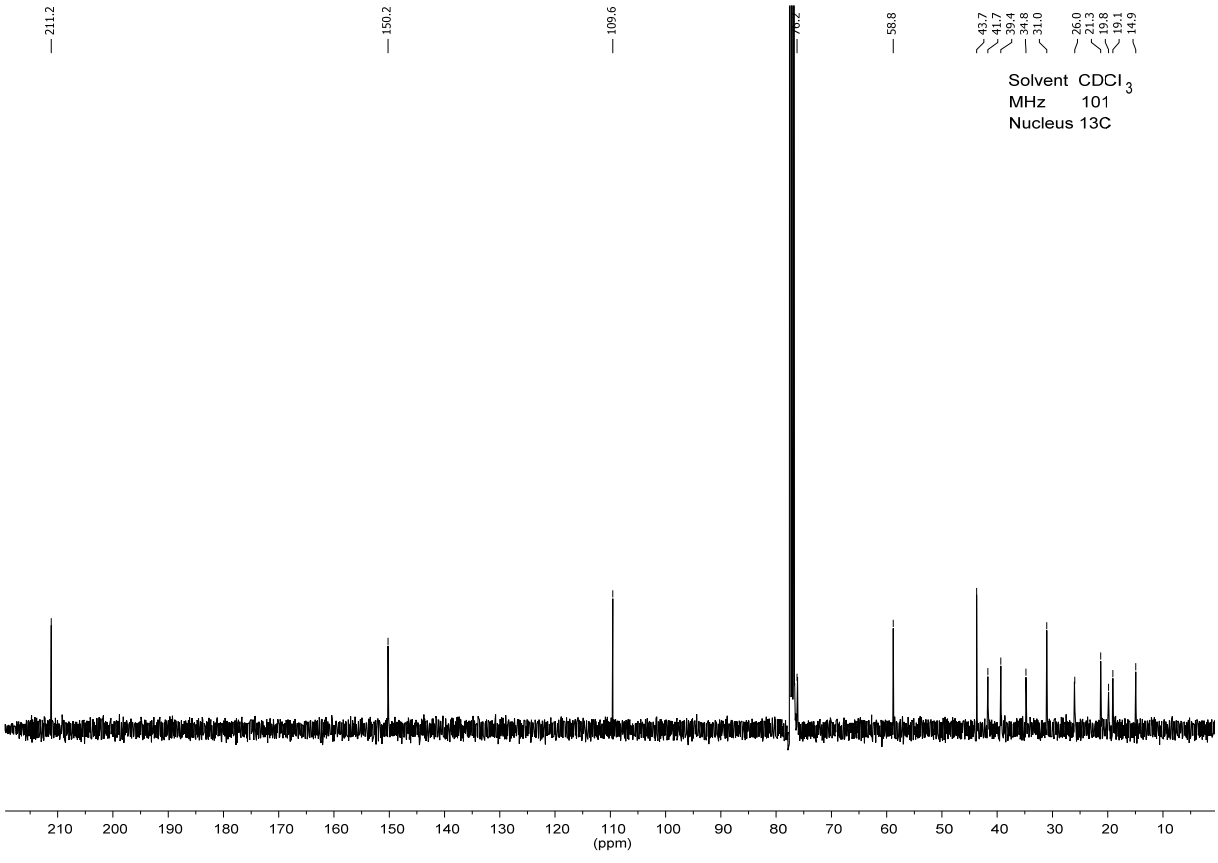

Solvent CDCl3
MHz 400
Nucleus 1H
2.04
2.09
1.99
3.02
1.00
1.05
1.02
6.31
1.23
2.03
2.57
2.80
3.07
2.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

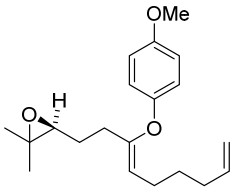

155.7
150.5
148.6
122.5
114.2
113.1
109.4
81.4
57.1
55.7
44.6
42.0
35.4
30.0
26.5
25.3
24.0
23.9
19.8
19.3
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


O
HO
H
Me

**22**

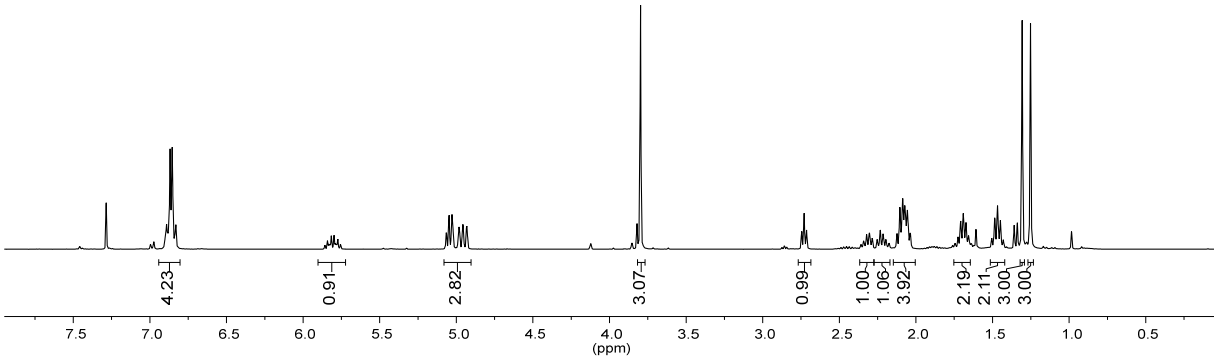

Solvent CDCl3
MHz 400
Nucleus 1H
1.78
1.00
1.94
1.84
1.06
1.24
1.27
3.27
2.42
1.17
1.44
3.12
0.50
2.83
2.89
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


211.2
150.2
109.6
58.8
43.7
41.7
39.4
34.8
31.0
26.0
21.3
19.8
19.1
14.9
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



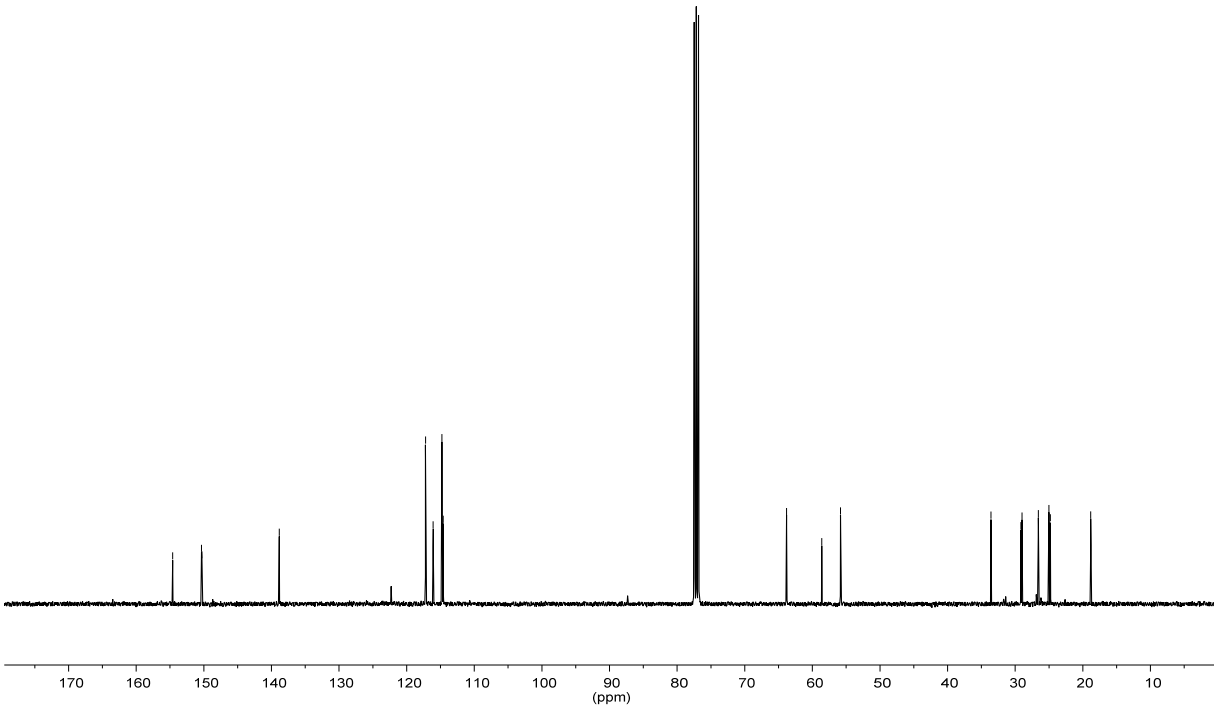

**23**

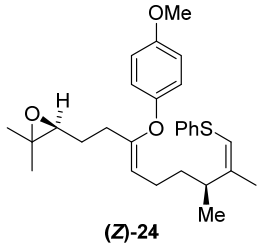
Solvent $CDCl_3$
MHz 400
Nucleus 1H




154.6
150.3
150.3
138.8
117.2
116.1
114.8
114.6
63.8
58.6
55.8
33.6
29.2
29.0
26.6
25.0
24.8
18.8

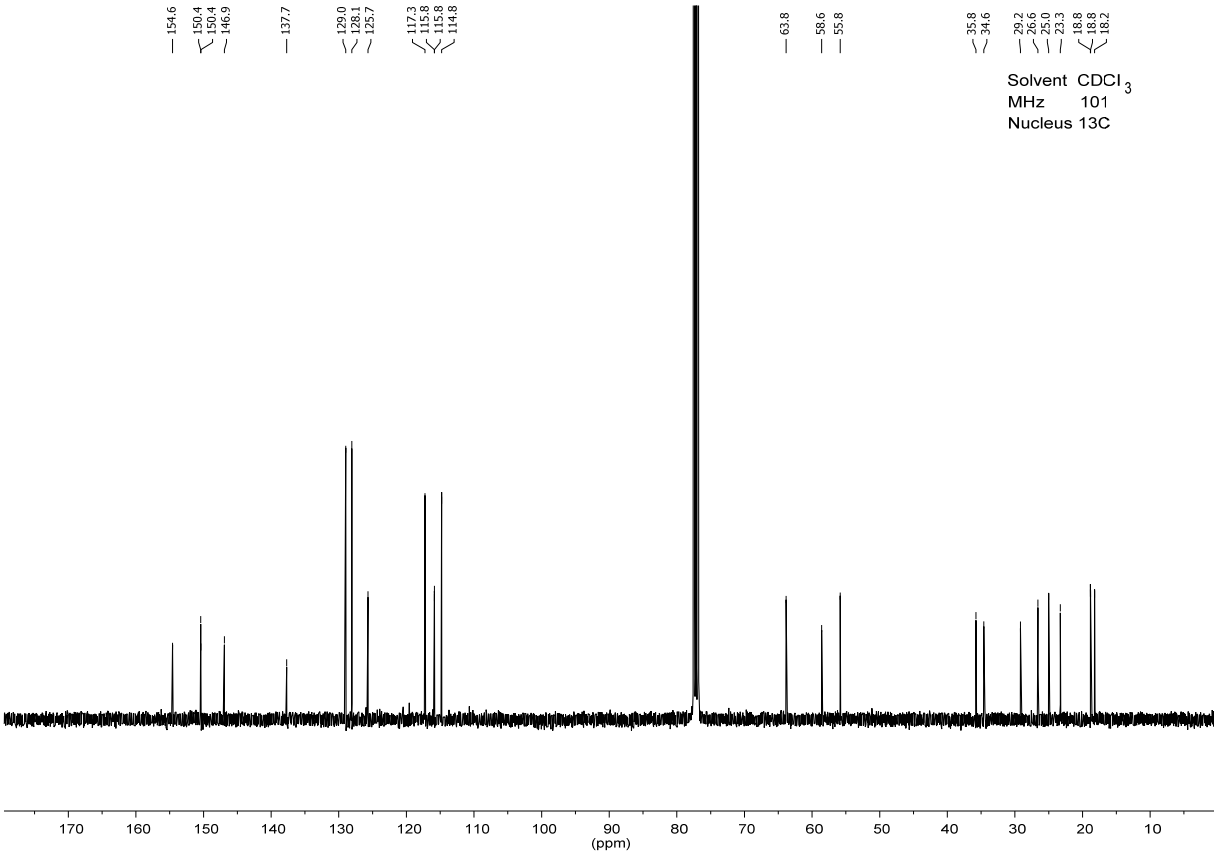
Solvent $CDCl_3$
MHz 101
Nucleus 13C

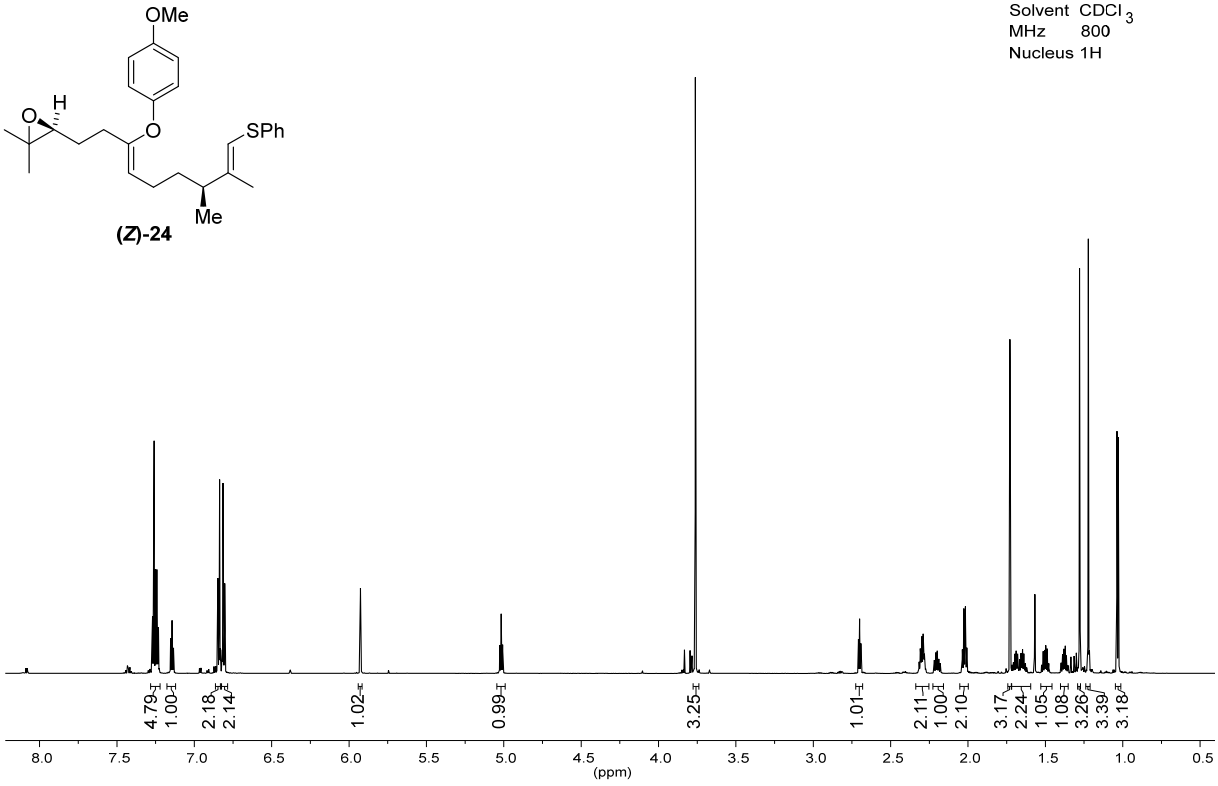


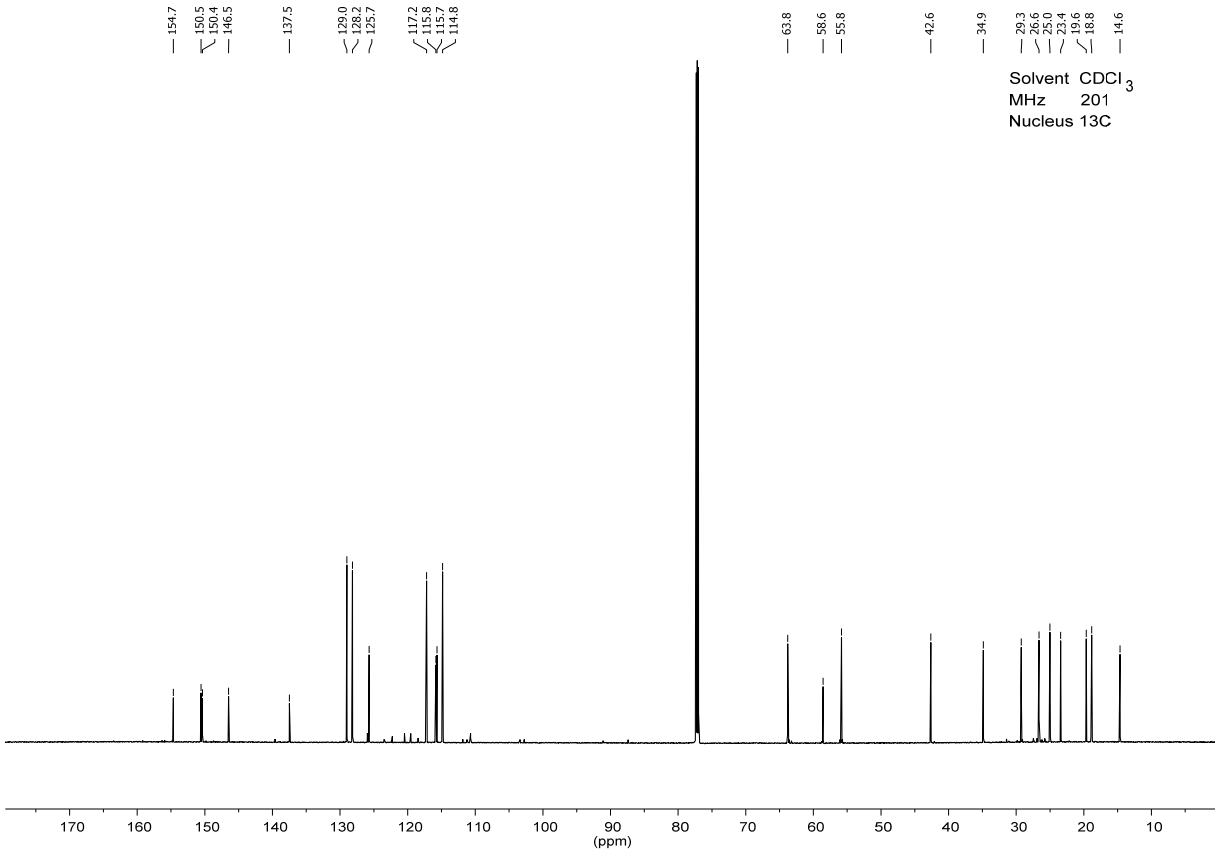

OMe
H
O
O
PhS
Me

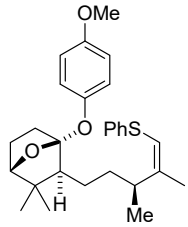
**(*Z*)-24**


Solvent CDCl3
MHz 400
Nucleus 1H
6.00
1.00
3.85
0.96
0.98
2.89
1.01
0.98
1.01
1.08
1.00
1.08
2.77
2.03
1.97
3.39
3.03
2.84
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


154.6
150.4
150.4
146.9
137.7
129.0
128.1
125.7
117.3
115.8
115.8
114.8
63.8
58.6
55.8
35.8
34.6
29.2
26.6
25.0
23.3
18.8
18.8
18.2
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

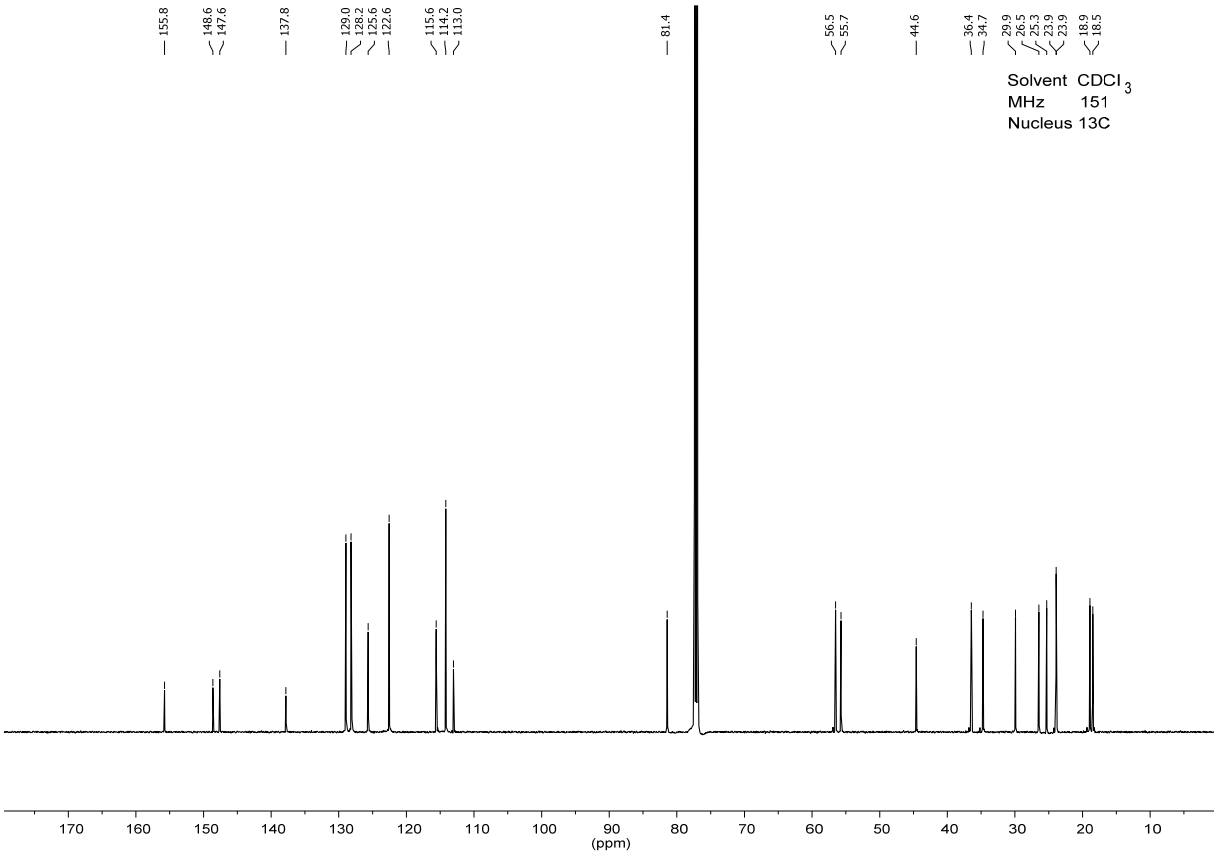

OMe
H
O
O
SPh
Me
(Z)-24
Solvent CDCl3
MHz 800
Nucleus 1H
4.79
1.00
2.18
2.14
1.02
0.99
3.25
1.01
2.11
1.00
2.10
3.17
2.24
1.05
1.08
3.26
3.39
3.18
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

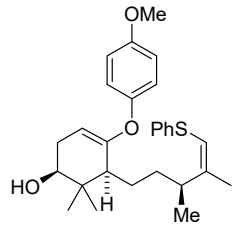

154.7
150.5
150.4
146.5
137.5
129.0
128.2
125.7
117.2
115.8
115.7
114.8
63.8
58.6
55.8
42.6
34.9
29.3
26.6
25.0
23.4
19.6
18.8
14.6
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OMe
O
PhS
O
H
Me

**S70**

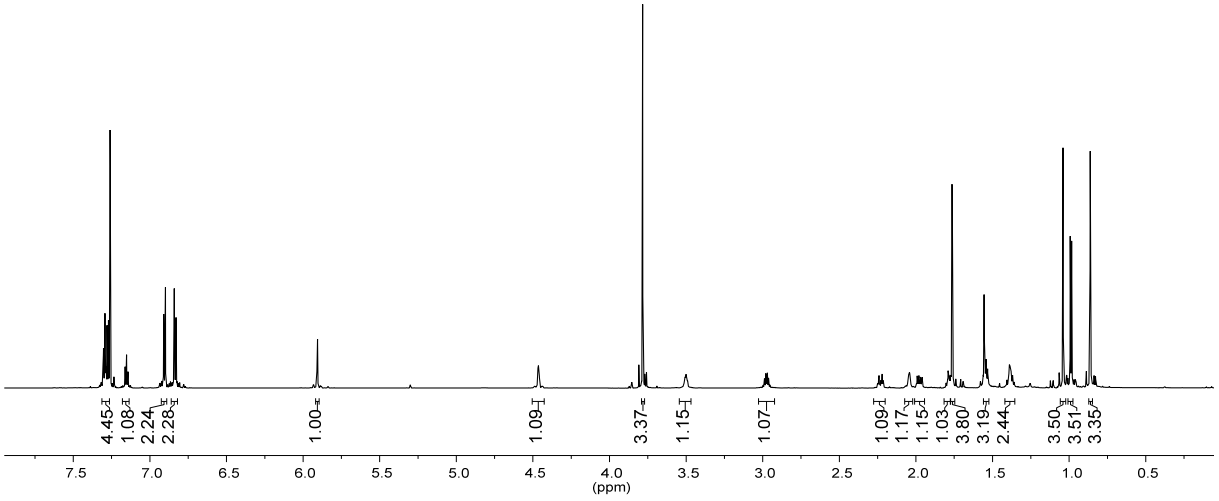

Solvent CDCl3
MHz 599
Nucleus 1H
1.78
1.77
1.00
1.69
1.88
0.82
2.51
0.99
1.13
0.91
2.84
1.06
1.78
2.00
1.18
0.97
1.02
2.53
2.40
2.73
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

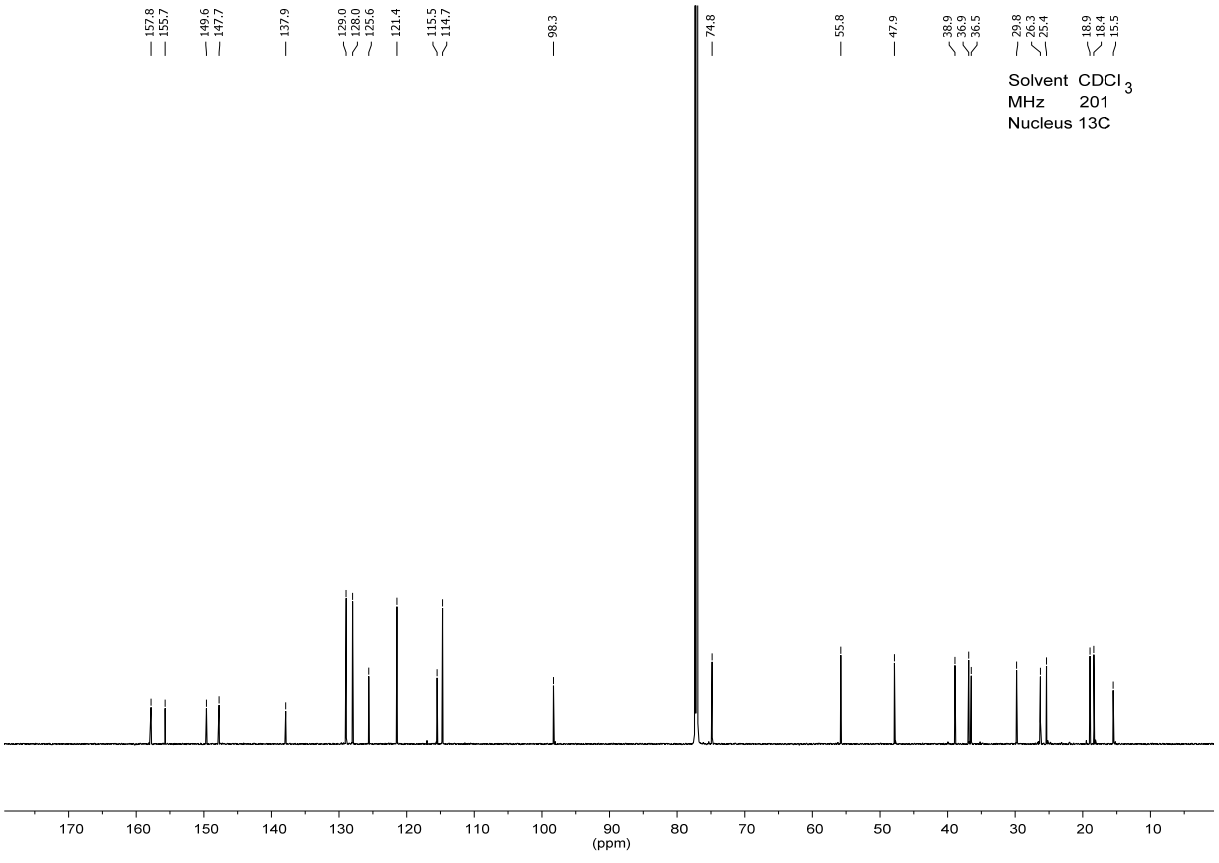

155.8
148.6
147.6
137.8
129.0
128.2
125.6
122.6
115.6
114.2
113.0
81.4
56.5
55.7
44.6
36.4
34.7
29.9
26.5
25.3
23.9
23.9
18.9
18.5
Solvent CDCl3
MHz 151
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

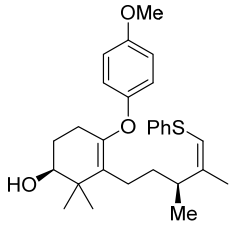



**S71**

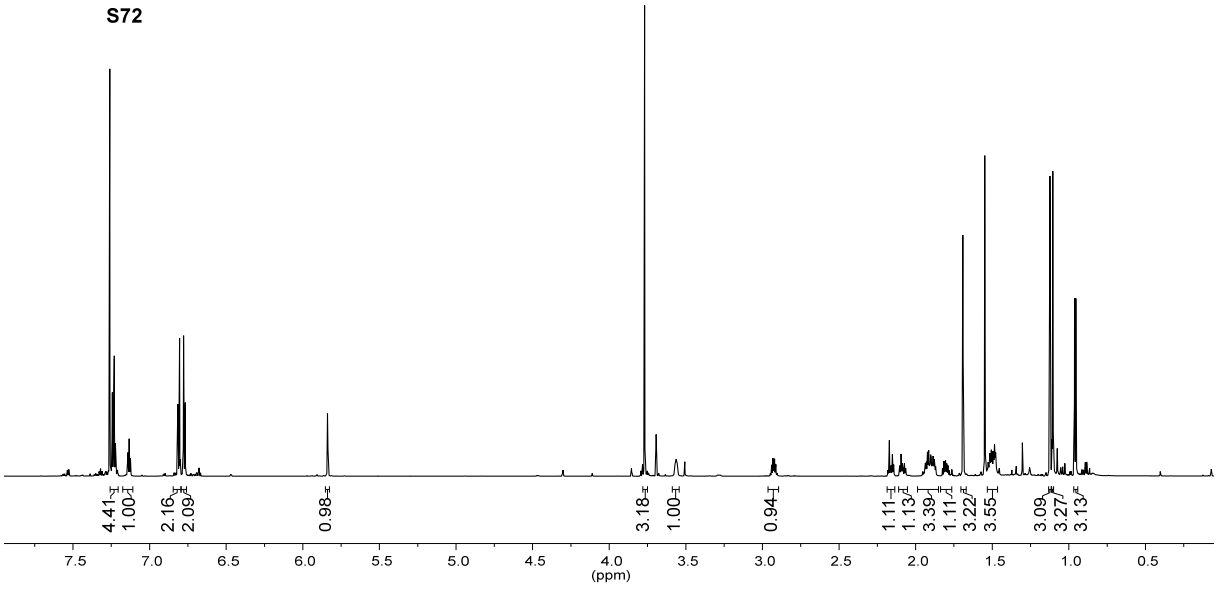
Solvent CDCl 3
MHz 800
Nucleus 1H

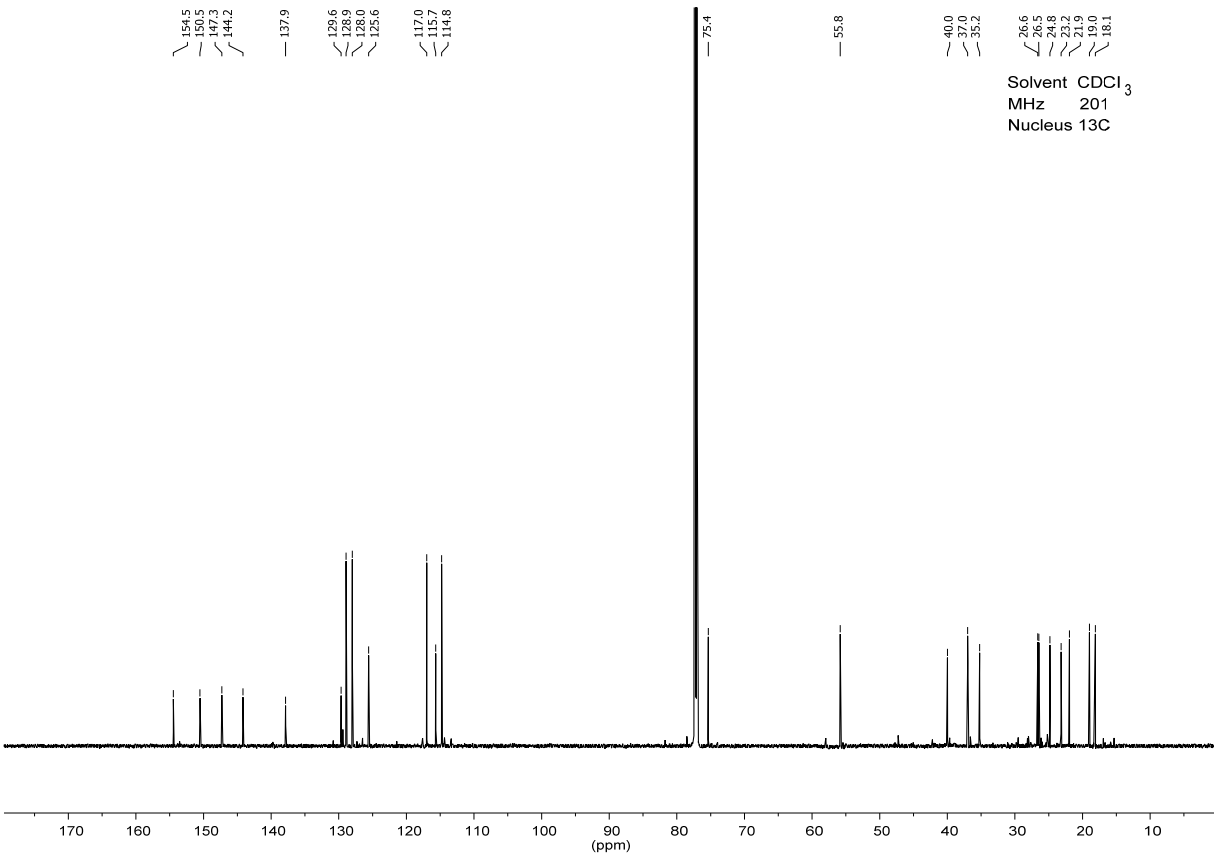


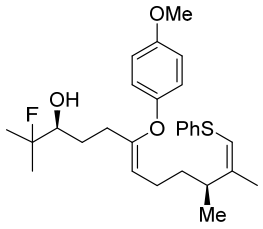




OMe
O PhS
HO
Me

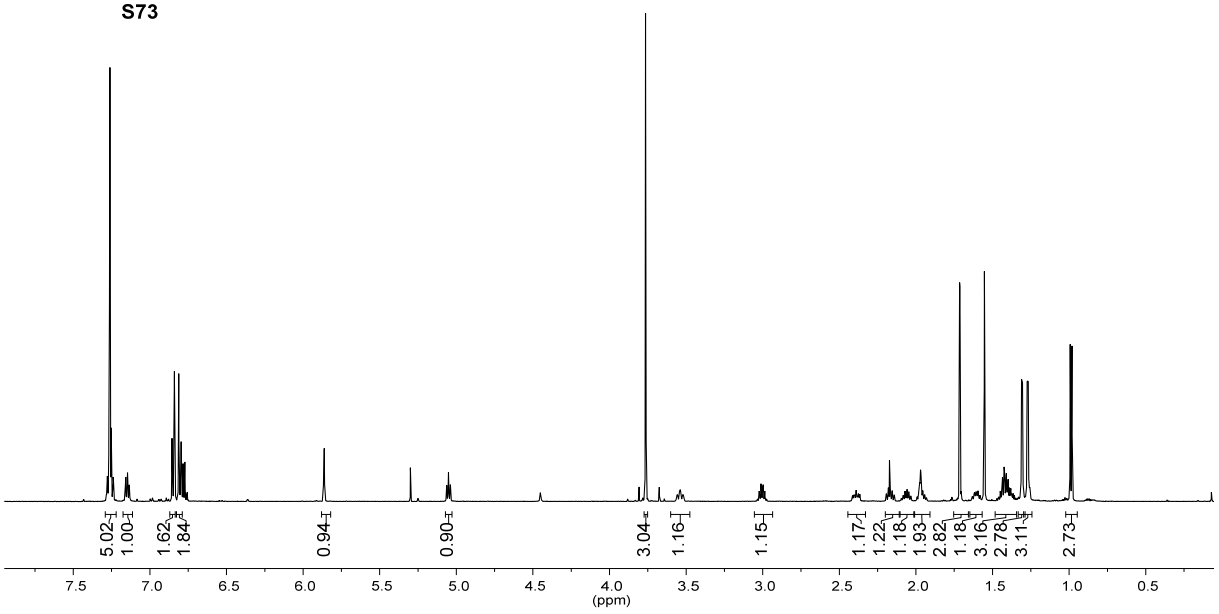
**S72**

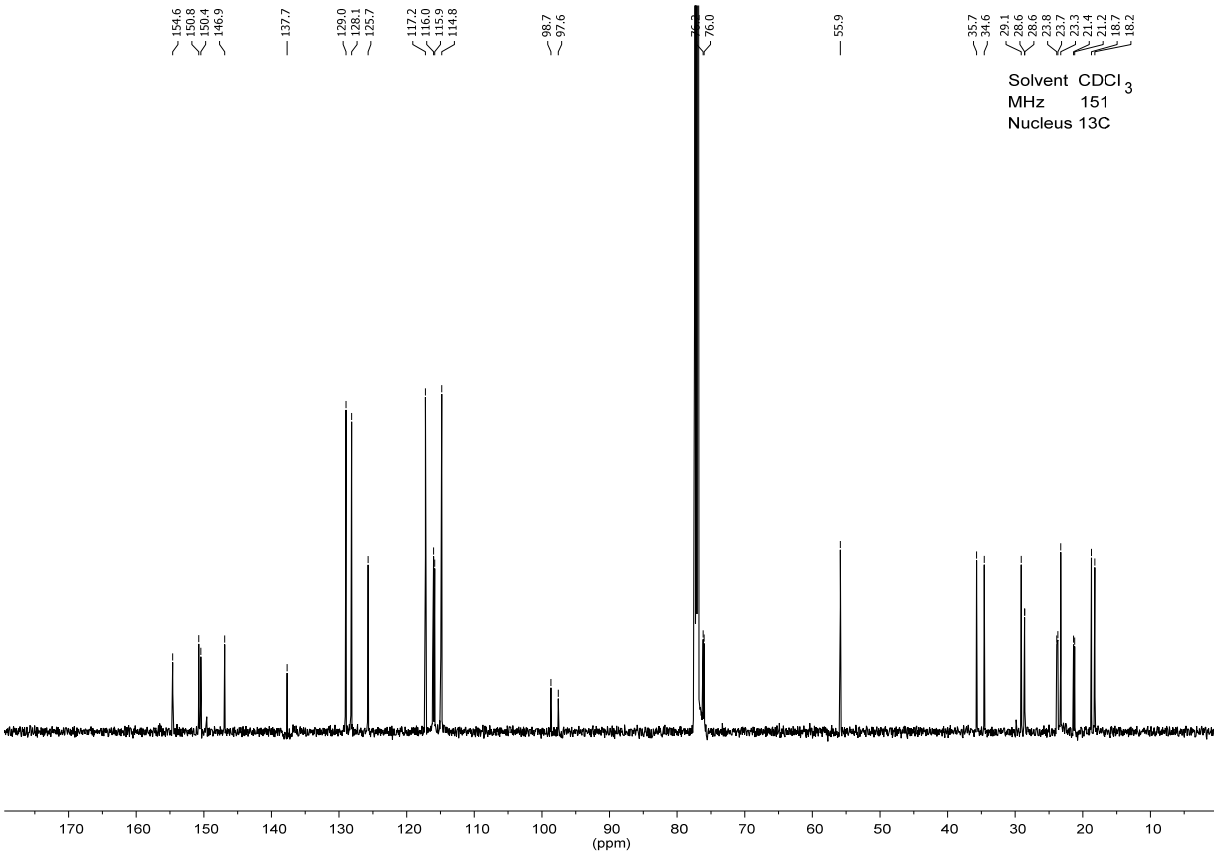

Solvent CDCl3
MHz 800
Nucleus 1H
4.41
1.00
2.16
2.09
0.98
3.18
1.00
0.94
1.11
1.13
3.39
1.11
3.22
3.55
3.09
3.27
3.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

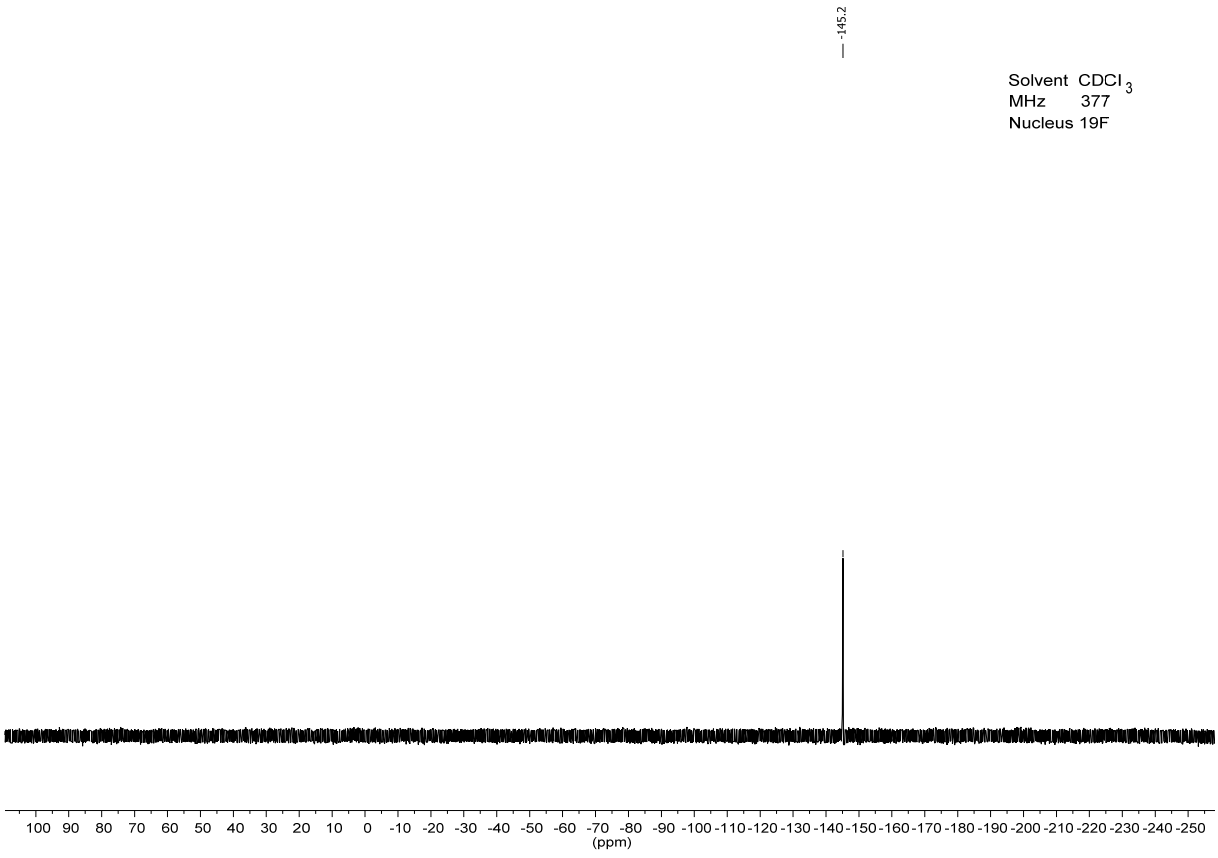

154.5
150.5
147.3
144.2
137.9
129.6
128.9
128.0
125.6
117.0
115.7
114.8
75.4
55.8
40.0
37.0
35.2
26.6
26.5
24.8
23.2
21.9
19.0
18.1
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

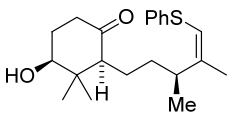

OMe
OH
F
O
PhS
Me

**S73**


Solvent CDCl3
MHz 599
Nucleus 1H
5.02
1.00
1.62
1.84
0.94
0.90
3.04
1.16
1.15
1.17
1.22
1.18
1.93
2.82
1.18
3.16
2.78
3.11
2.73
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

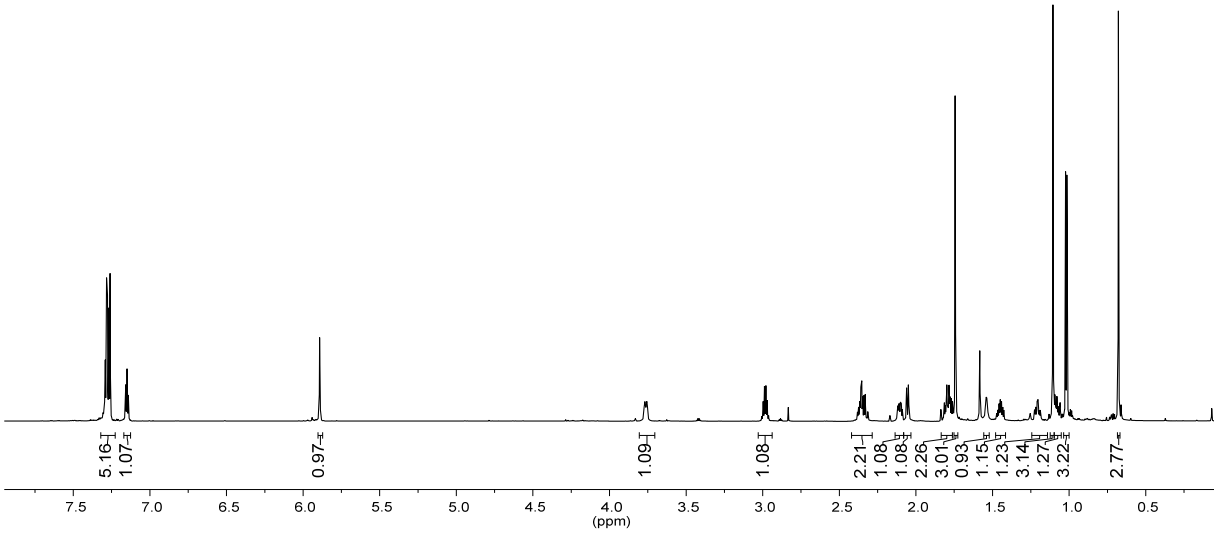

154.6
150.8
150.4
146.9
137.7
129.0
128.1
125.7
117.2
116.0
115.9
114.8
98.7
97.6
76.0
55.9
35.7
34.6
29.1
28.6
28.6
23.8
23.7
23.3
21.4
21.2
18.7
18.2
Solvent CDCl3
MHz 151
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

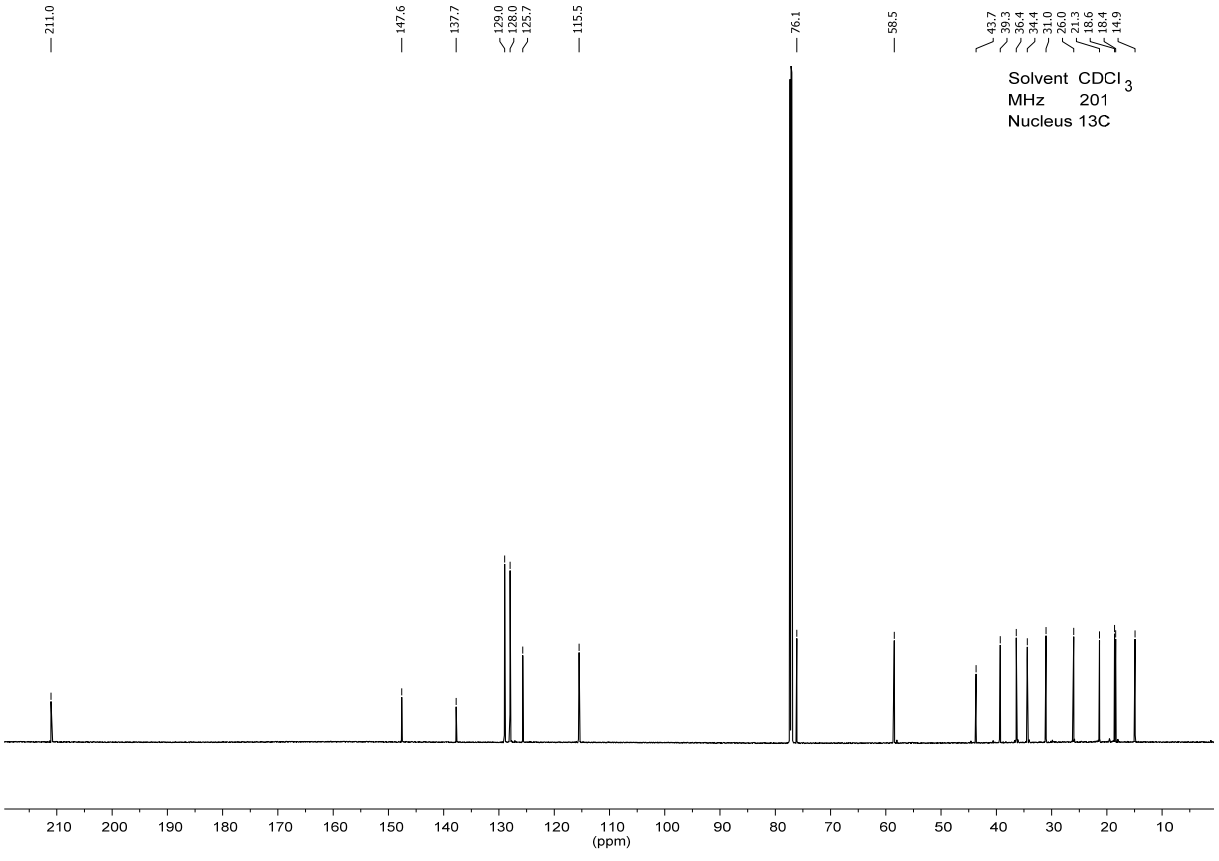

-145.2
Solvent CDCl3
MHz 377
Nucleus 19F
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
(ppm)

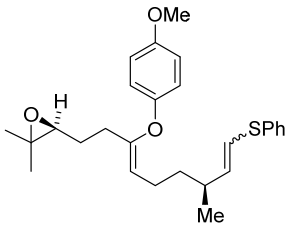



**S74**

Solvent $CDCl_3$
MHz 800
Nucleus 1H

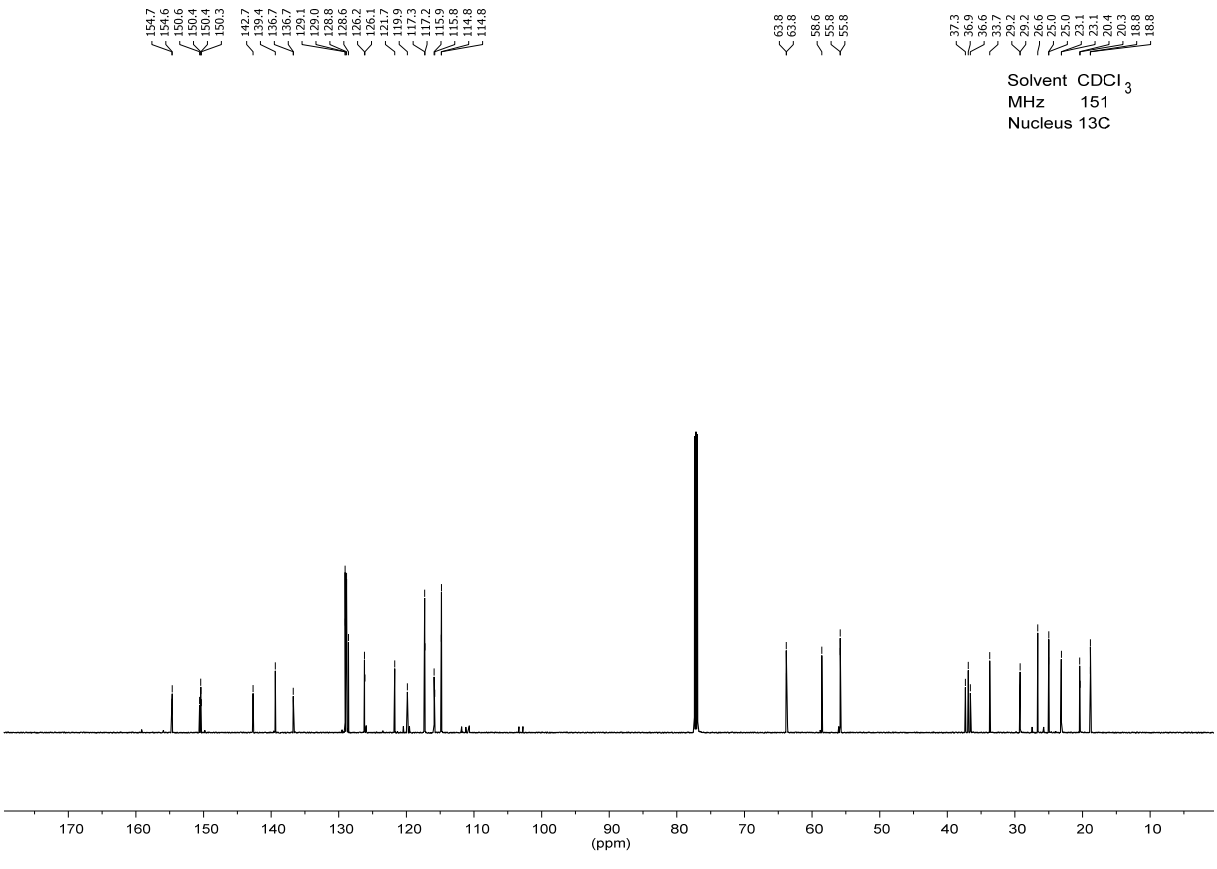


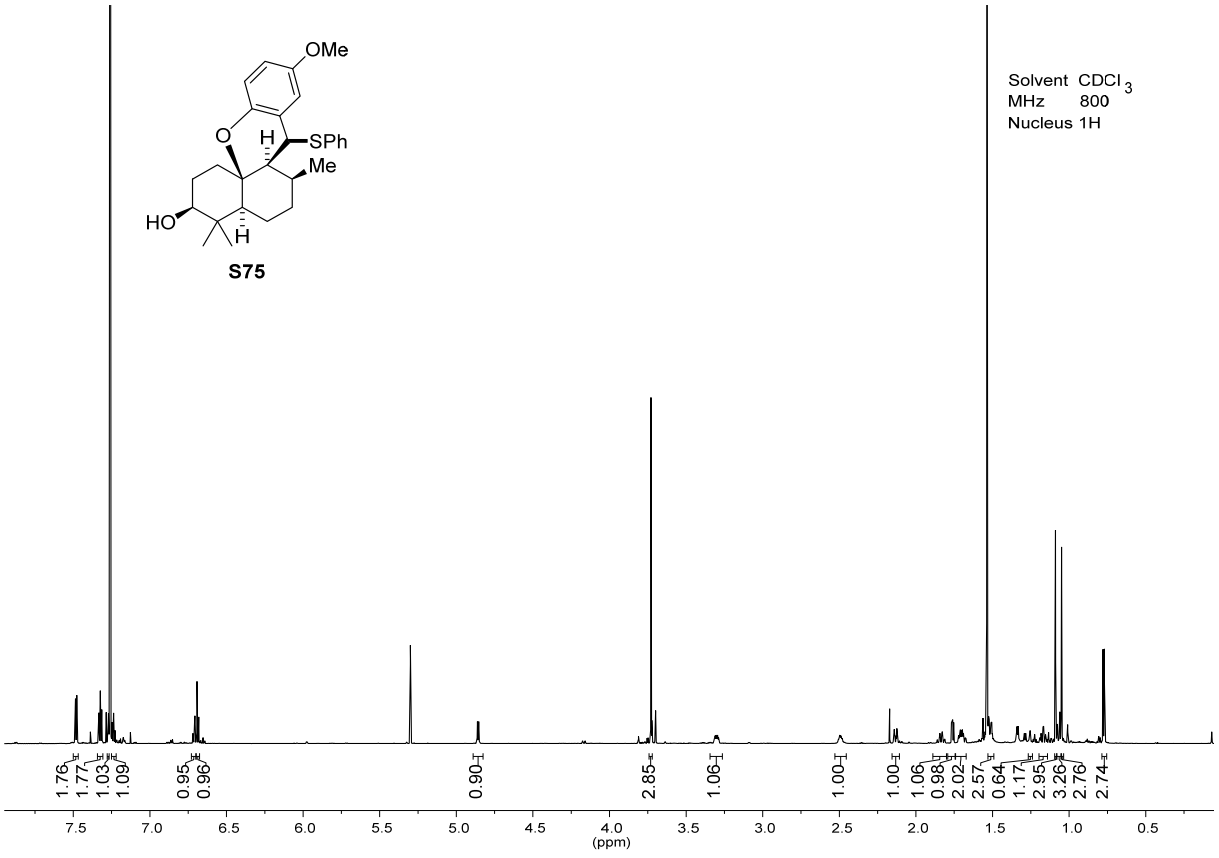



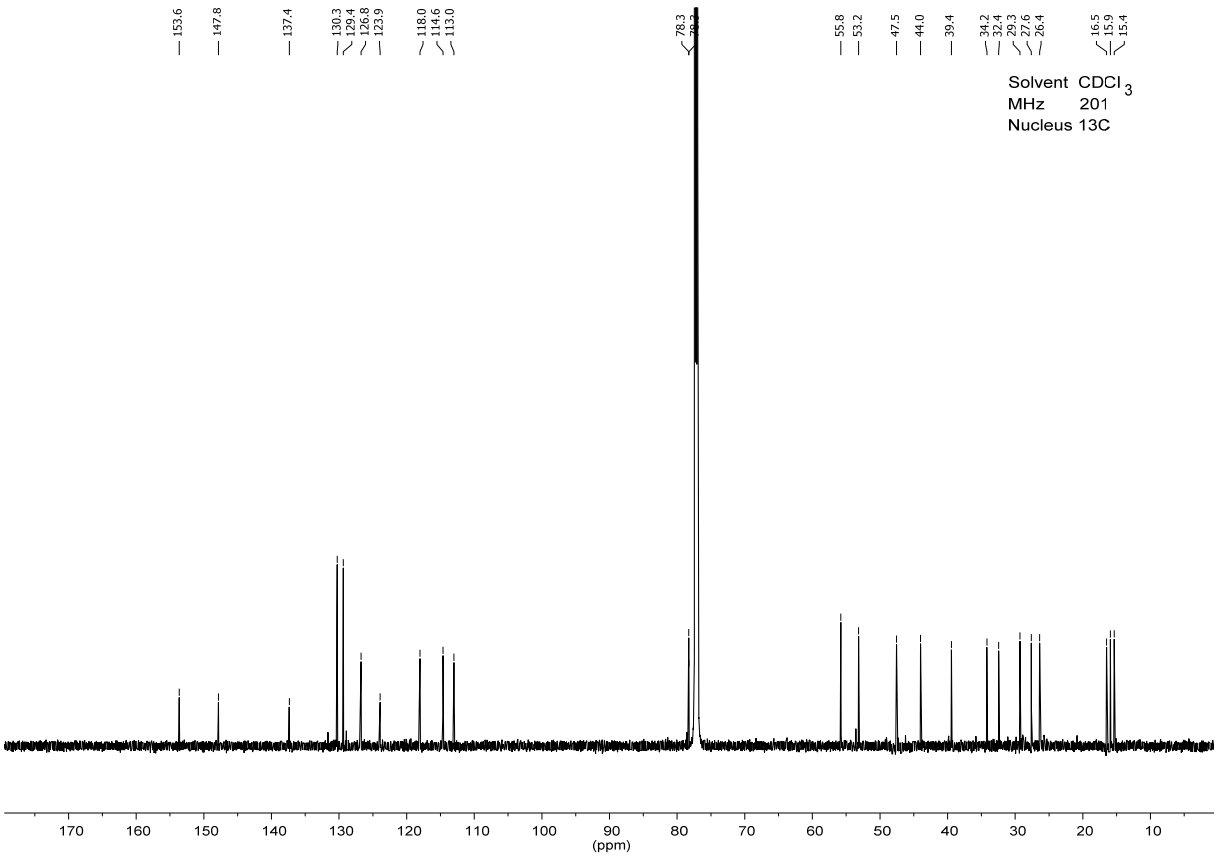

OMe
H
O
O
SPh
Me

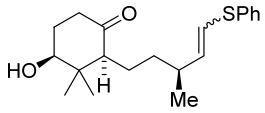
**25**


Solvent CDCl3
MHz 599
Nucleus 1H
3.66
1.00
1.68
1.78
0.57
0.44
0.48
0.65
0.62
0.45
0.88
1.39
1.07
0.30
1.48
1.18
1.96
1.96
2.19
0.99
1.56
0.88
1.51
0.98
1.49
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


154.7
154.6
150.6
150.4
150.4
150.3
142.7
139.4
136.7
136.7
129.1
129.0
128.8
128.6
126.2
126.1
121.7
119.9
117.3
117.2
115.9
115.8
114.8
114.8
63.8
63.8
58.6
55.8
55.8
37.3
36.9
36.6
33.7
29.2
29.2
26.6
25.0
25.0
23.1
23.1
20.4
20.3
18.8
18.8
Solvent CDCl3
MHz 151
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

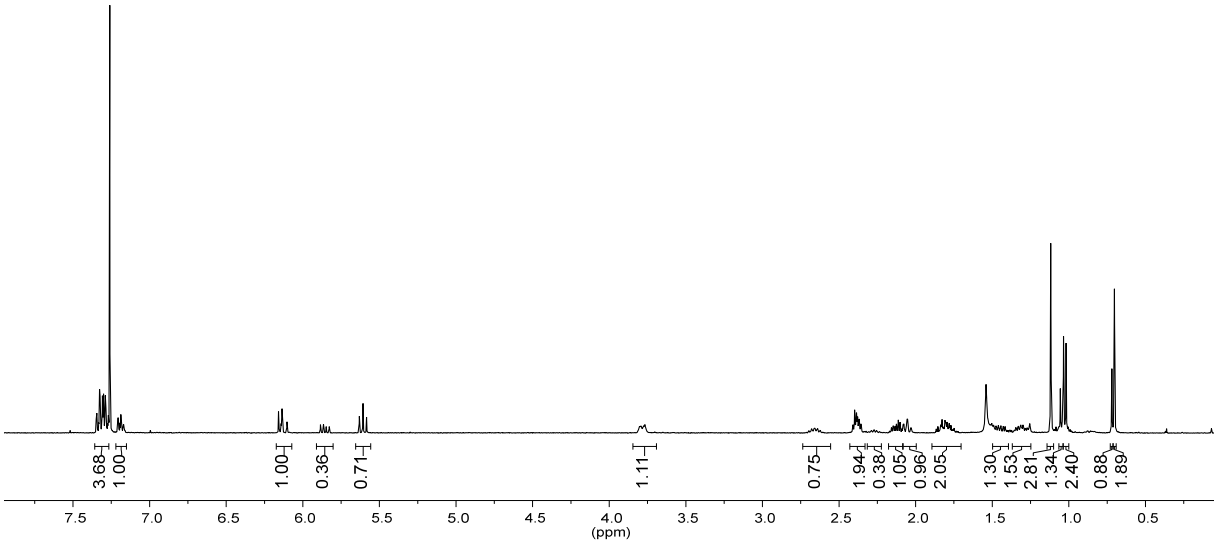

OMe
O
H
SPh
Me
HO
H
S75
Solvent CDCl3
MHz 800
Nucleus 1H
1.76
1.77
1.03
1.09
0.95
0.96
0.90
2.85
1.06
1.00
1.00
1.06
0.98
2.02
2.57
0.64
1.17
2.95
3.26
2.76
2.74
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

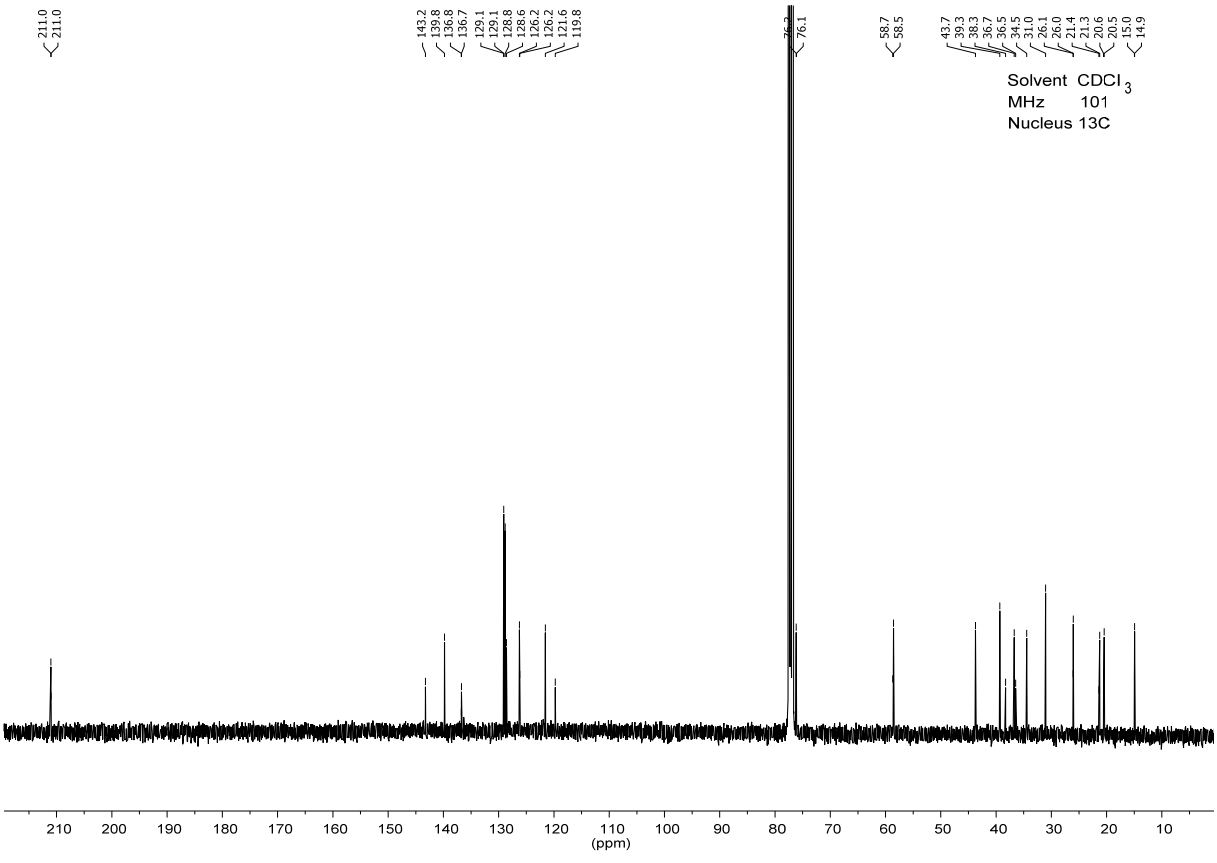

153.6
147.8
137.4
130.3
129.4
126.8
123.9
118.0
114.6
113.0
78.3
55.8
53.2
47.5
44.0
39.4
34.2
32.4
29.3
27.6
26.4
16.5
15.9
15.4
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

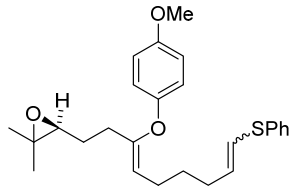



**S76**

Solvent CDCl 3
MHz 400
Nucleus 1H

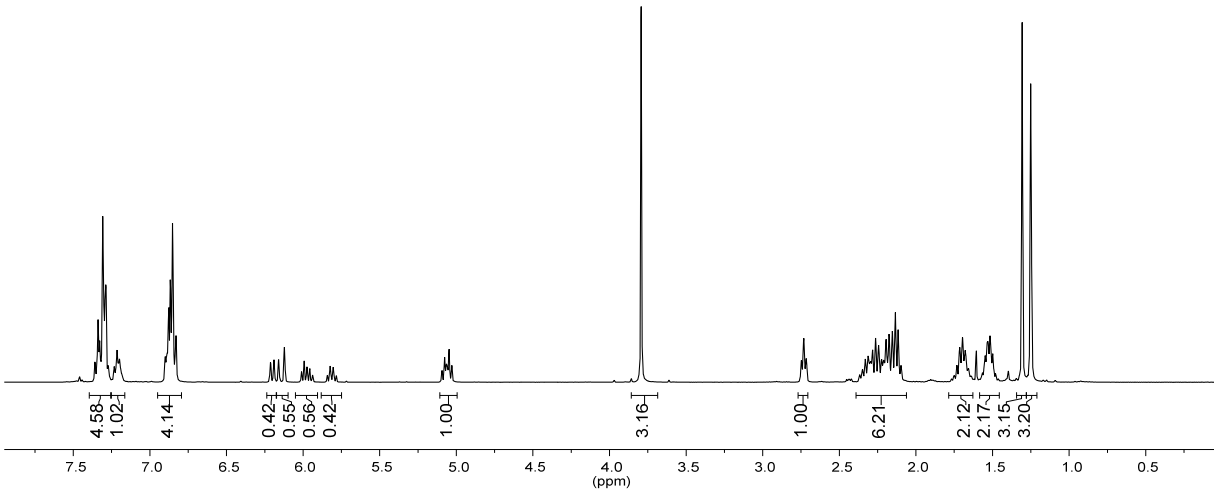


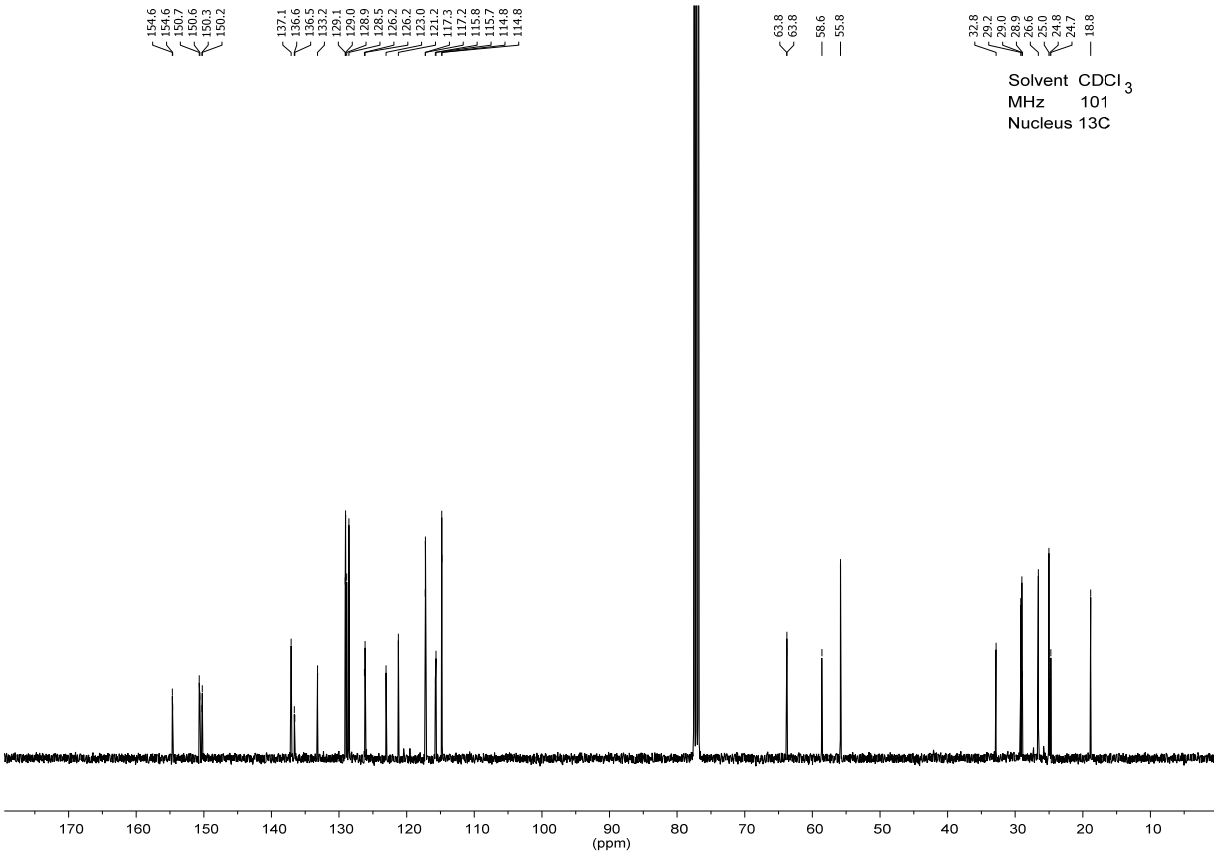



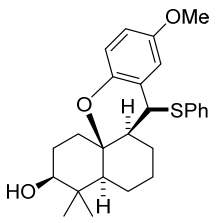



**26**

Solvent $CDCl_3$
MHz 400
Nucleus 1H

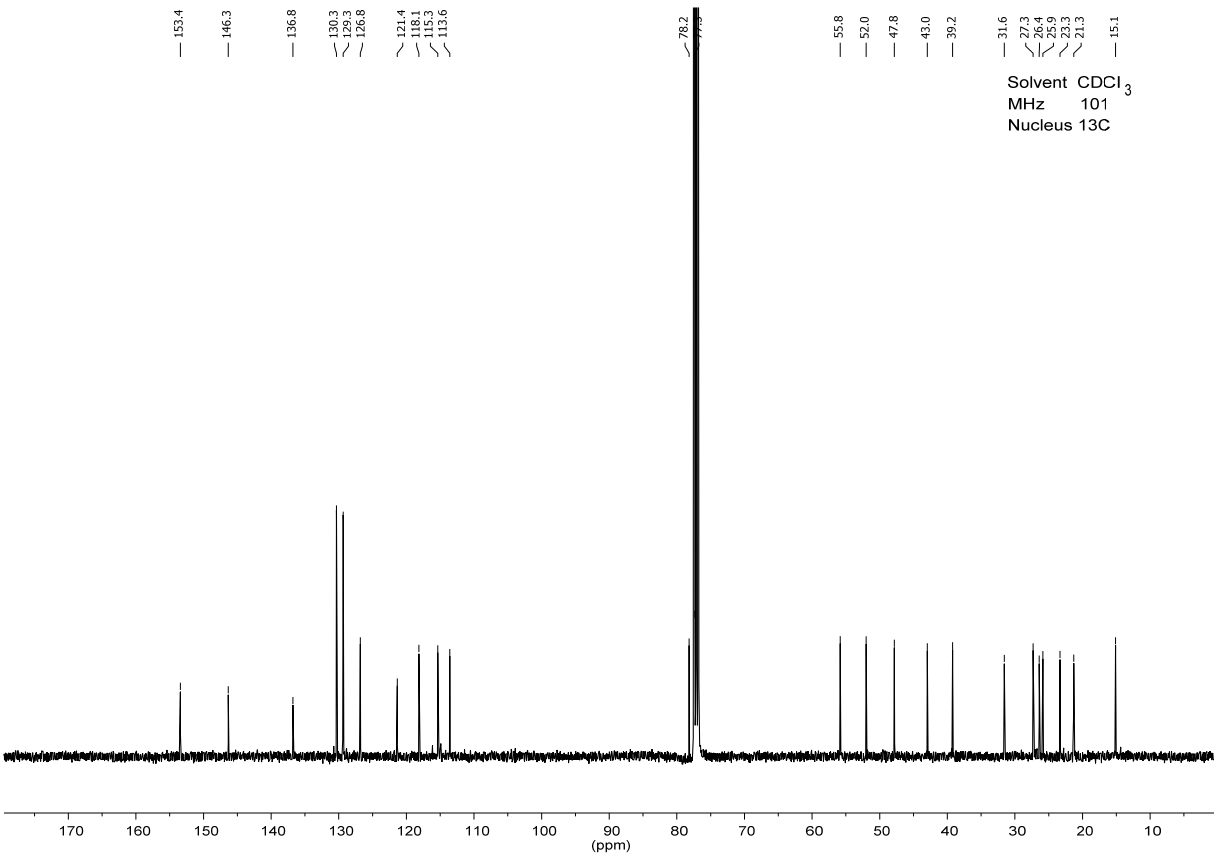


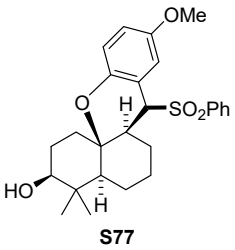




OMe
O
H
SPh
HO
H

**28**

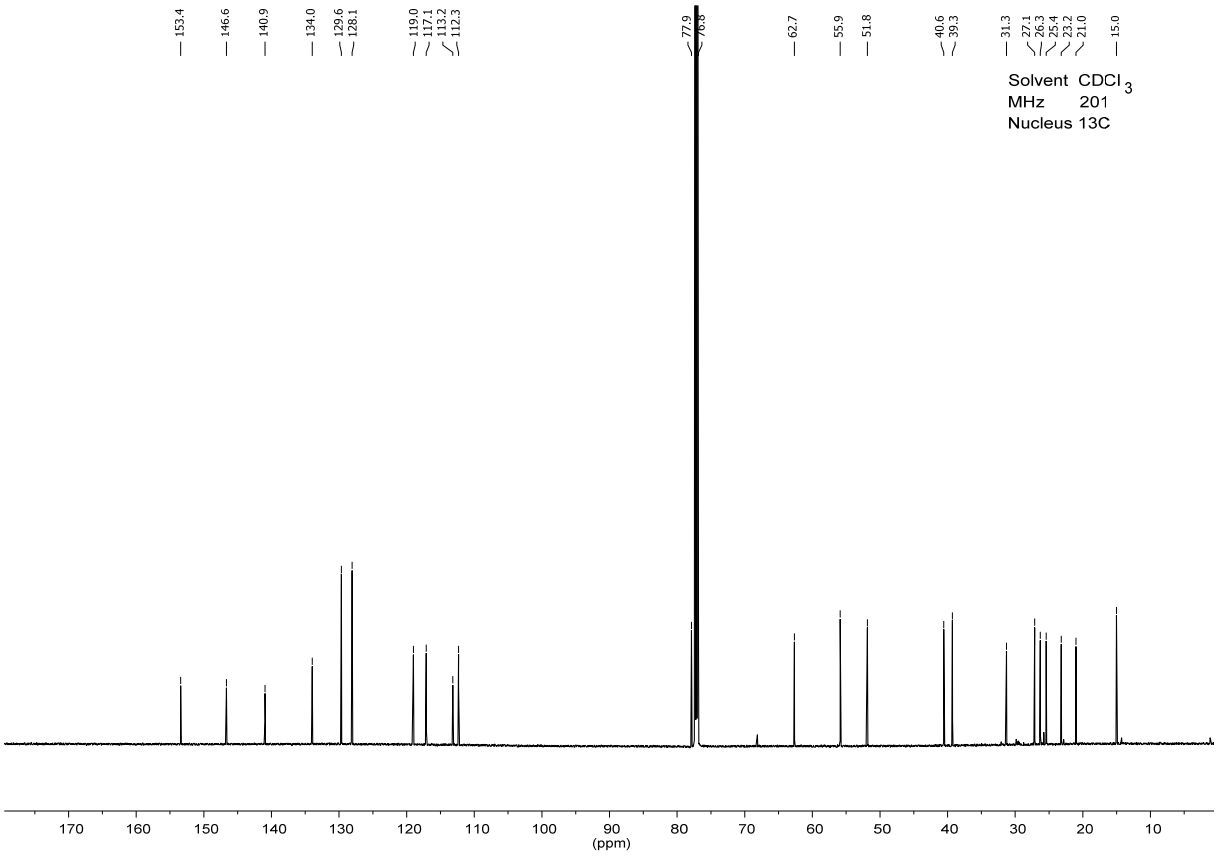

Solvent CDCl3
MHz 800
Nucleus 1H
1.98
1.92
0.95
1.00
2.15
0.90
3.07
0.92
1.02
1.02
1.04
1.10
3.20
2.28
1.20
1.53
1.20
5.64
3.31
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

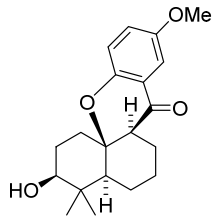

153.4
146.3
136.8
130.3
129.3
126.8
121.4
118.1
115.3
113.6
78.2
55.8
52.0
47.8
43.0
39.2
31.6
27.3
26.4
25.9
23.3
21.3
15.1
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


OMe
O
H
SO2Ph
HO
H

**S77**

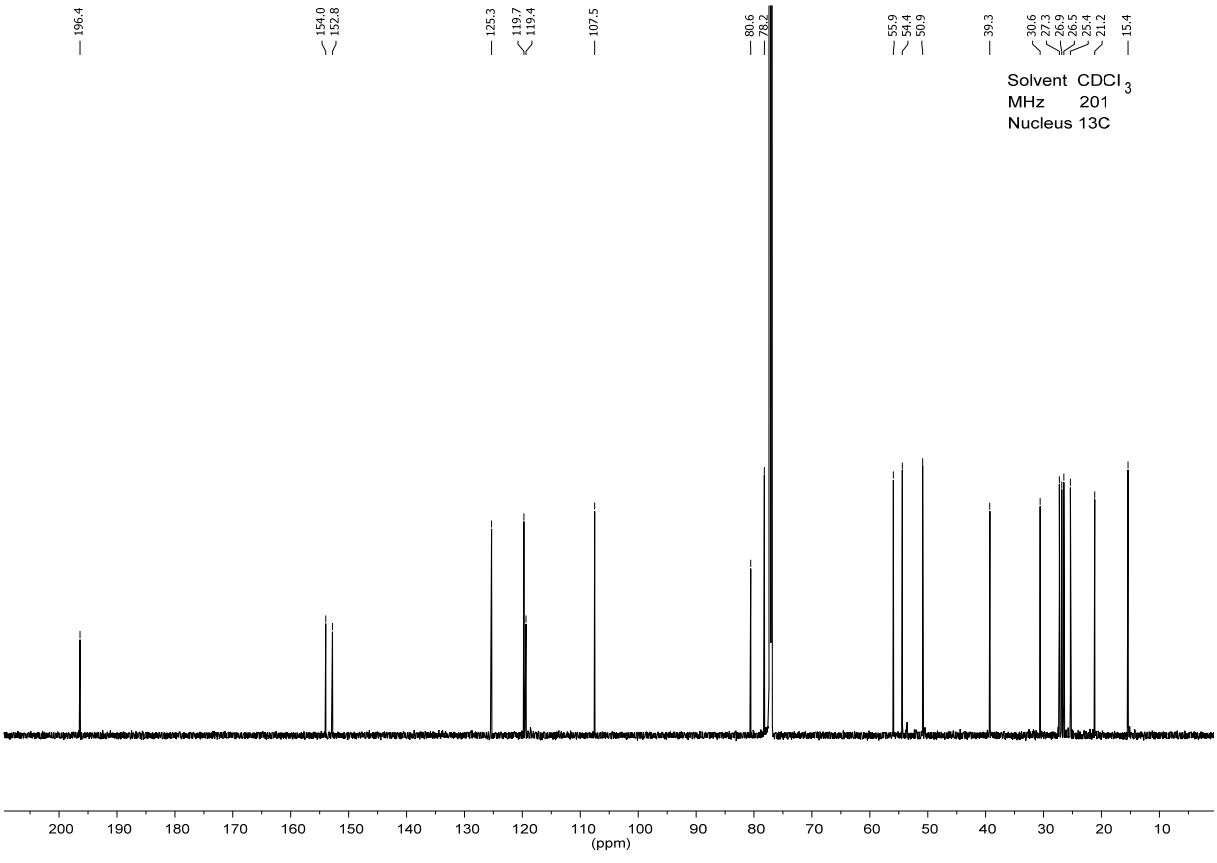

Solvent CDCl3
MHz 800
Nucleus 1H
2.13
1.03
2.15
1.00
1.05
1.04
3.13
1.03
1.02
1.06
1.06
2.10
2.30
1.30
1.59
0.88
2.33
3.14
0.99
3.39
(ppm)

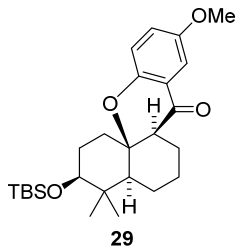

153.4
146.6
140.9
134.0
129.6
128.1
119.0
117.1
113.2
112.3
77.9
76.8
62.7
55.9
51.8
40.6
39.3
31.3
27.1
26.3
25.4
23.2
21.0
15.0
Solvent CDCl3
MHz 201
Nucleus 13C
(ppm)


OMe
O
H
O
HO
H

**S78**

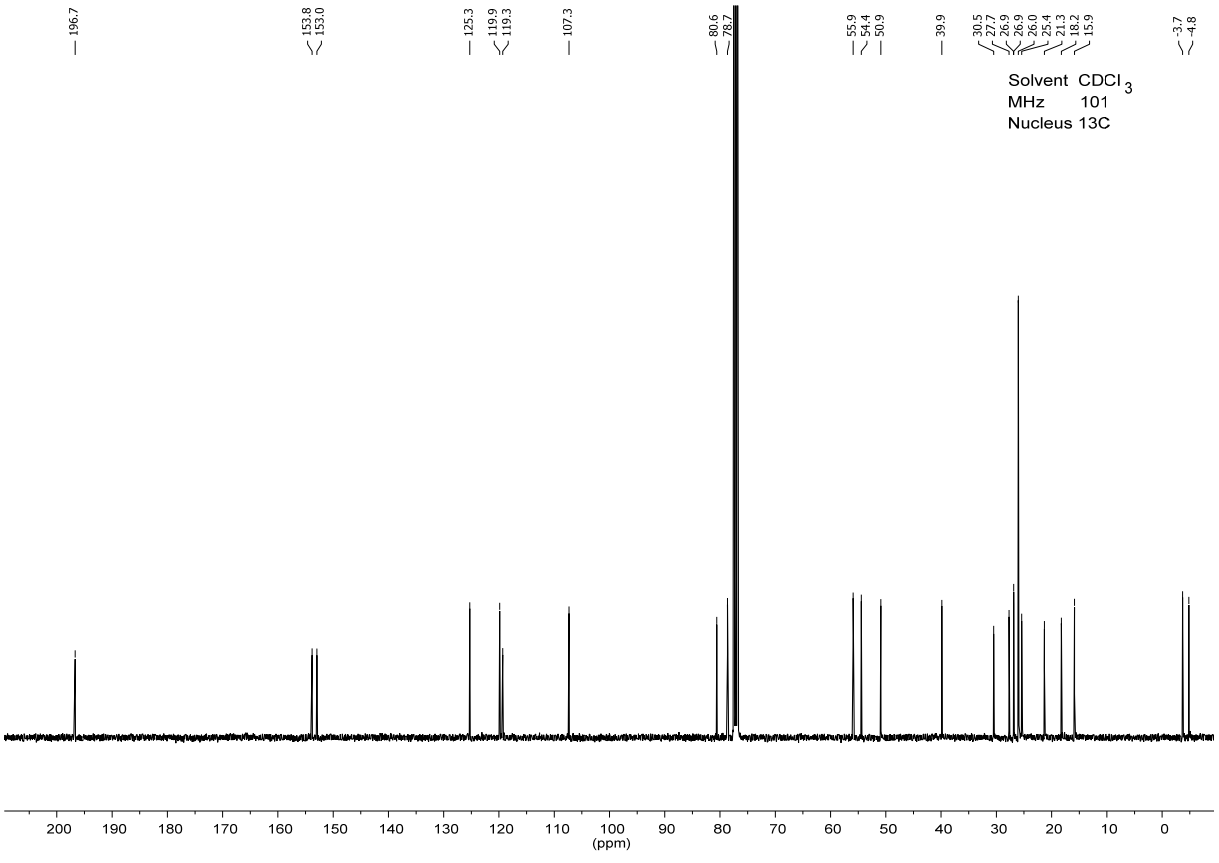

Solvent CDCl3
MHz 800
Nucleus 1H
0.99
0.87
0.98
2.75
0.95
0.90
0.93
1.00
1.85
1.13
1.19
2.12
0.80
1.18
1.28
2.77
4.40
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

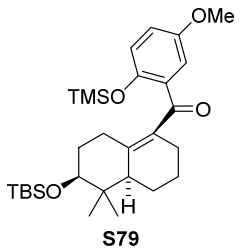

196.4
154.0
152.8
125.3
119.7
119.4
107.5
80.6
78.2
55.9
54.4
50.9
39.3
30.6
27.3
26.9
26.5
25.4
21.2
15.4
Solvent CDCl3
MHz 201
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


OMe
O
H
O
TBSO
H

**29**

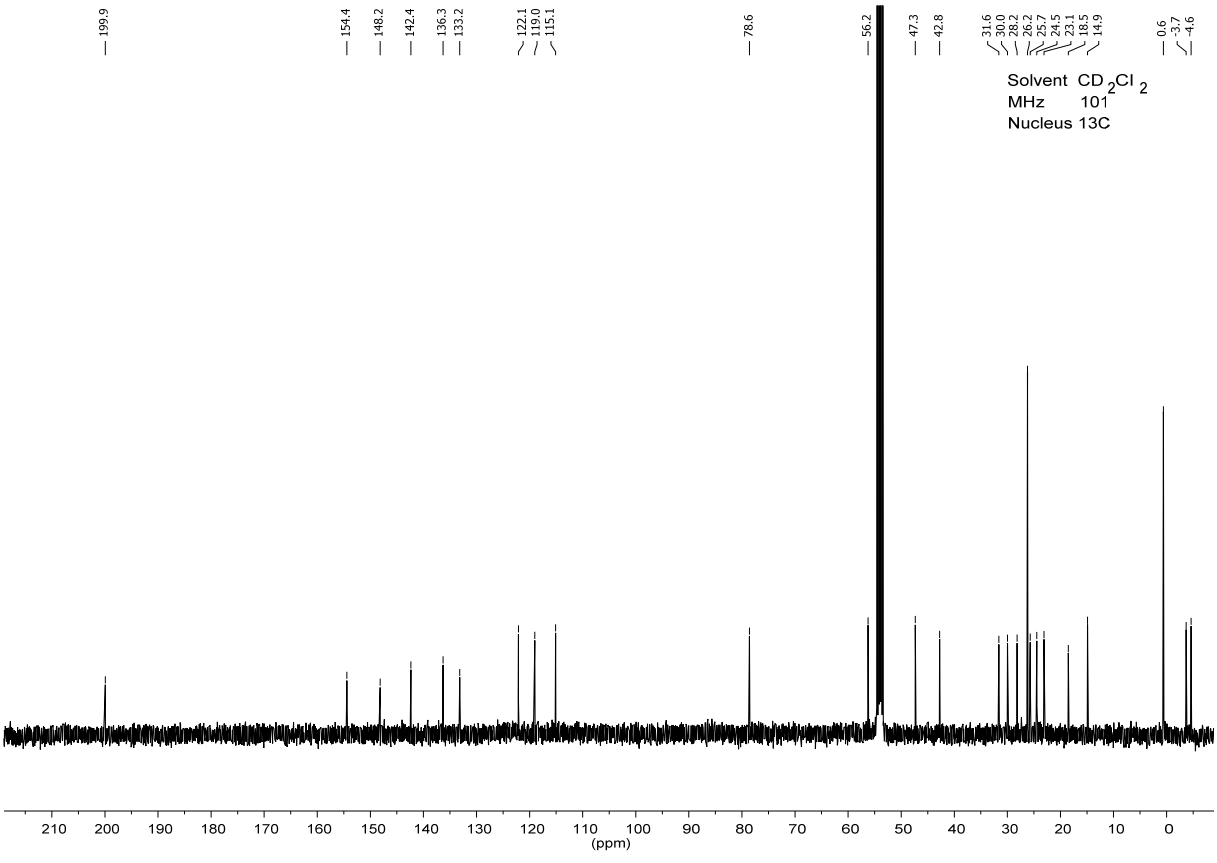

Solvent CDCl3
MHz 400
Nucleus 1H
1.63
1.03
1.00
3.05
1.03
2.07
1.12
4.39
1.28
2.02
1.06
3.31
1.32
3.33
10.66
3.04
3.26
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

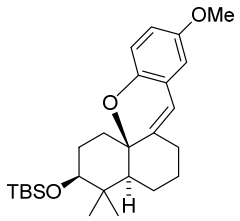

196.7
153.8
153.0
125.3
119.9
119.3
107.3
80.6
78.7
55.9
54.4
50.9
39.9
30.5
27.7
26.9
26.9
26.0
25.4
21.3
18.2
15.9
-3.7
-4.8
Solvent CDCl3
MHz 101
Nucleus 13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


OMe
TMSO
O
TBSO
H

**S79**

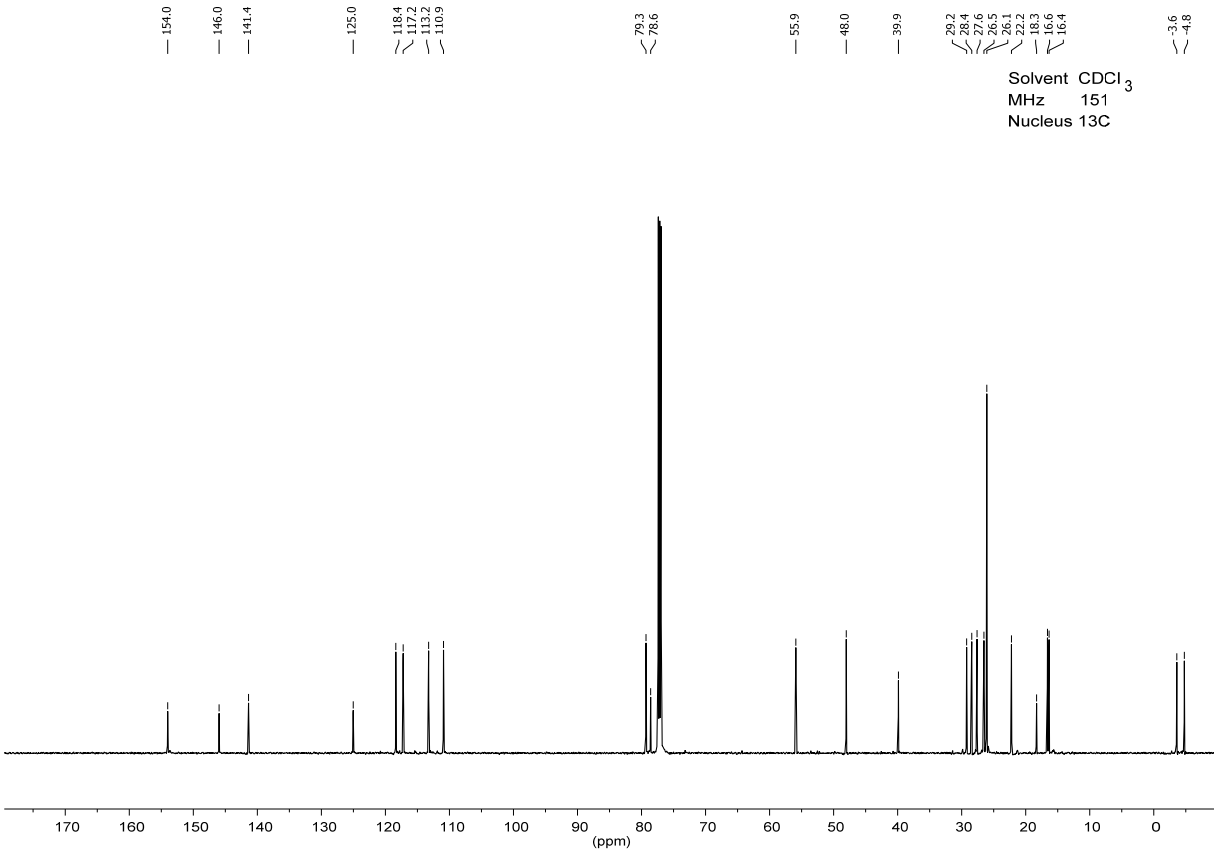

Solvent CD2Cl2
MHz 400
Nucleus 1H
0.90
0.97
0.95
2.75
1.05
1.00
1.02
1.31
3.61
4.03
3.12
9.95
2.83
8.62
3.67
3.25
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

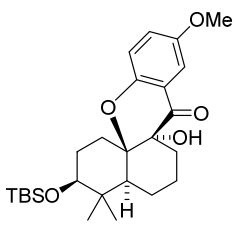

199.9
154.4
148.2
142.4
136.3
133.2
122.1
119.0
115.1
78.6
56.2
47.3
42.8
31.6
30.0
28.2
26.2
25.7
24.5
23.1
18.5
14.9
0.6
-3.7
-4.6
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


OMe
O
TBSO
H

**31**

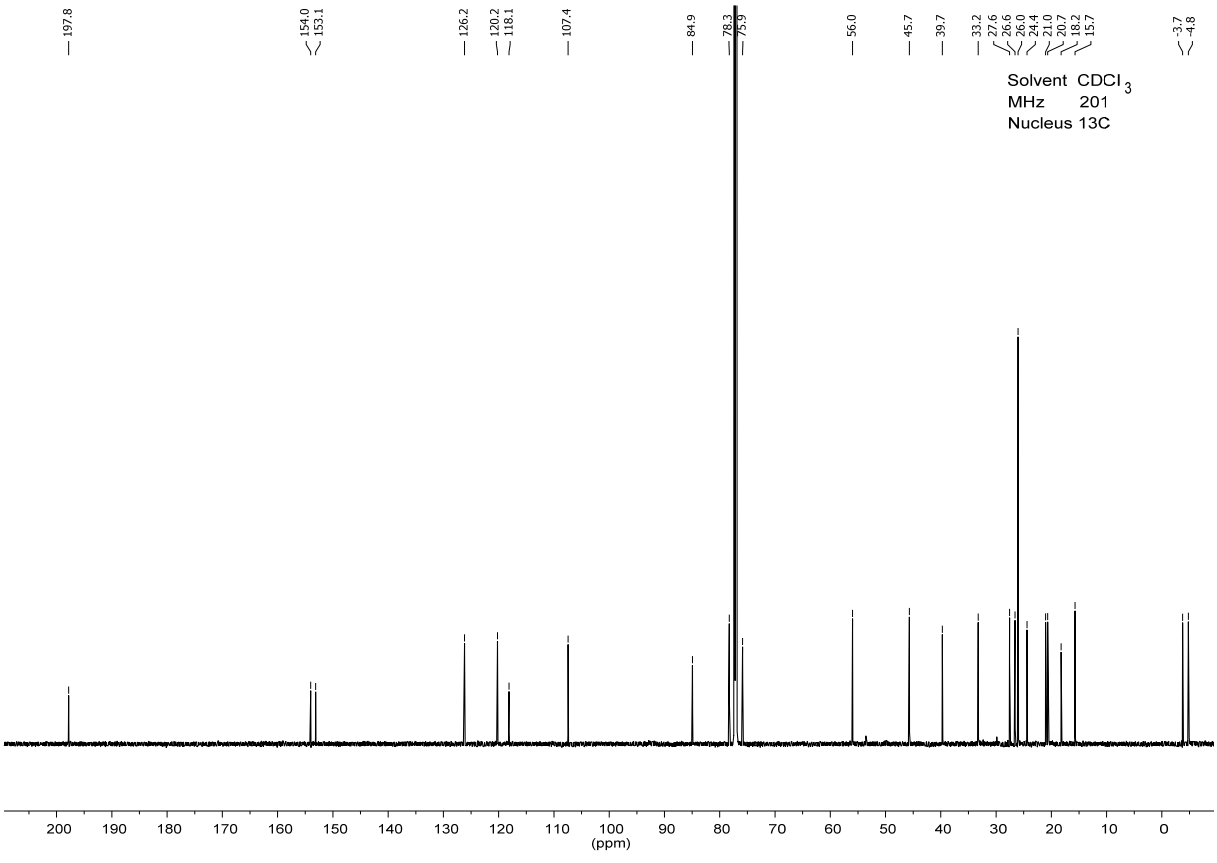

Solvent CDCl3
MHz 599
Nucleus 1H
1.00
0.92
0.98
0.98
2.81
0.99
1.12
1.10
1.09
1.10
1.05
2.94
1.00
1.04
1.17
2.62
2.45
7.33
2.57
2.87
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

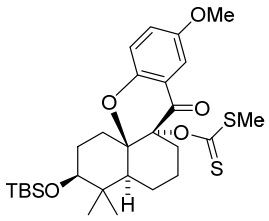

154.0
146.0
141.4
125.0
118.4
117.2
113.2
110.9
79.3
78.6
55.9
48.0
39.9
29.2
28.4
27.6
26.5
26.1
22.2
18.3
16.6
16.4
-3.6
-4.8
Solvent CDCl3
MHz 151
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


OMe
O
O
OH
TBSO
H

**S81**

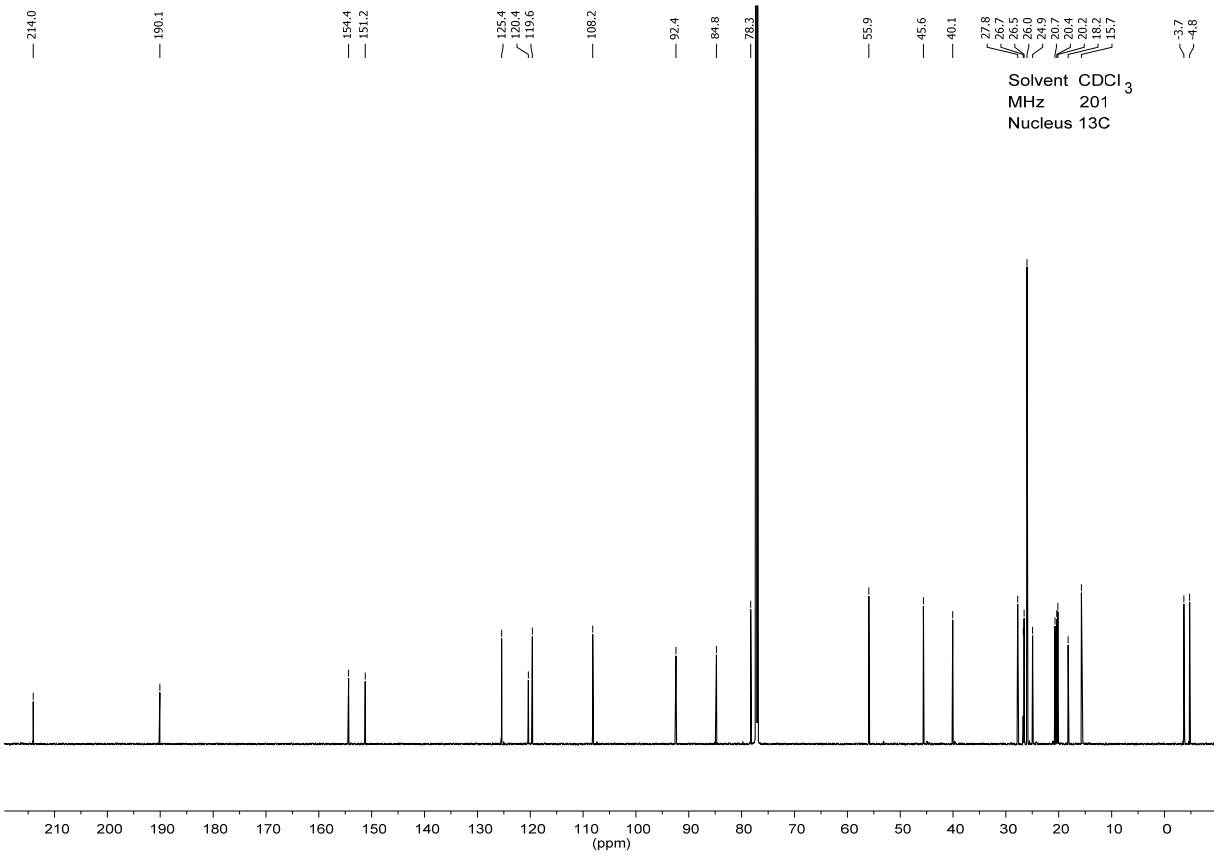

Solvent CDCl3
MHz 800
Nucleus 1H
0.98
0.97
0.98
3.27
0.95
1.00
2.32
4.40
2.29
1.15
2.41
3.39
3.29
10.05
3.35
3.07
(ppm)

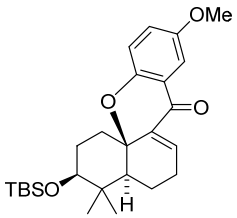

197.8
154.0
153.1
126.2
120.2
118.1
107.4
84.9
78.3
75.9
56.0
45.7
39.7
33.2
27.6
26.6
26.0
24.4
21.0
20.7
18.2
15.7
-3.7
-4.8
Solvent CDCl3
MHz 201
Nucleus 13C
(ppm)


OMe
O
O
SMe
O
S
TBSO
H

**32**

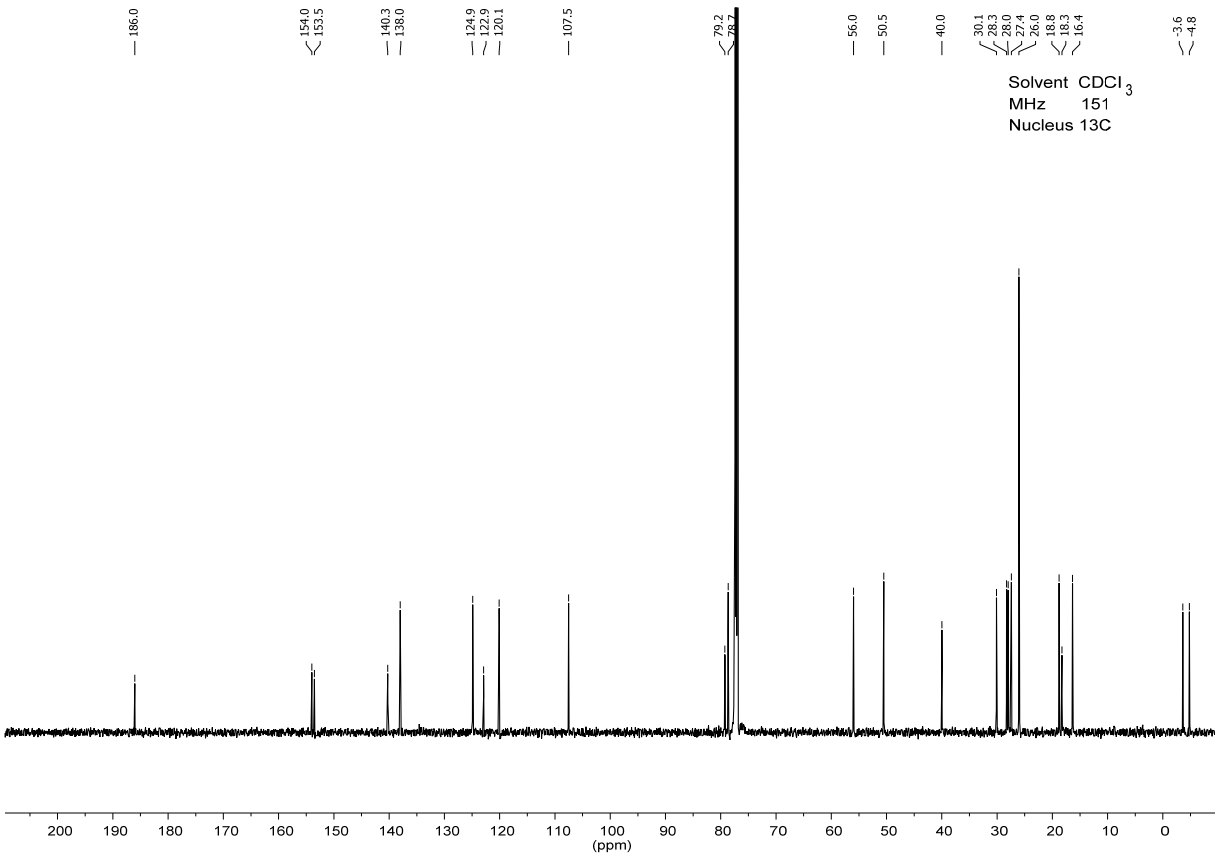

Solvent CDCl3
MHz 800
Nucleus 1H
1.00
0.99
0.99
3.21
1.01
1.00
3.12
1.01
2.03
2.14
2.07
1.34
0.95
0.99
3.15
3.11
9.40
3.19
3.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

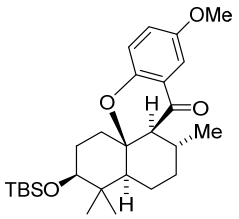

214.0
190.1
154.4
151.2
125.4
120.4
119.6
108.2
92.4
84.8
78.3
55.9
45.6
40.1
27.8
26.7
26.5
26.0
24.9
20.7
20.4
20.2
18.2
15.7
-3.7
-4.8
Solvent CDCl3
MHz 201
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


OMe
O
O
TBSO
H

**30**

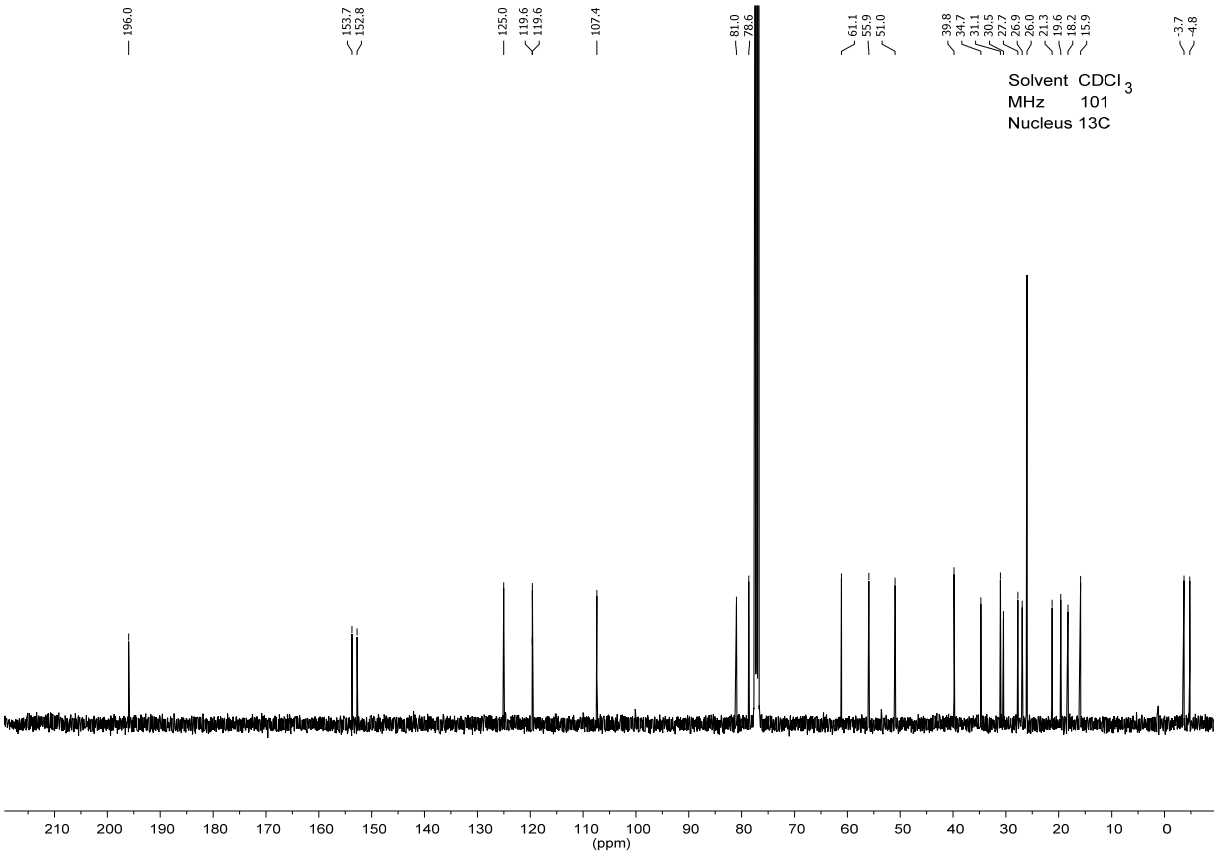

Solvent CDCl3
MHz 599
Nucleus 1H
0.77
0.82
0.81
0.83
2.39
0.89
1.00
0.96
0.99
0.90
1.03
1.05
0.95
1.21
1.16
2.32
2.29
6.99
2.42
2.29
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

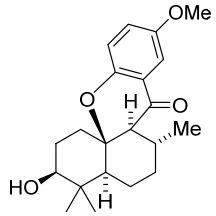

186.0
154.0
153.5
140.3
138.0
124.9
122.9
120.1
107.5
79.2
78.7
56.0
50.5
40.0
30.1
28.3
28.0
27.4
26.0
18.8
18.3
16.4
-3.6
-4.8
Solvent CDCl3
MHz 151
Nucleus 13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


OMe
O
H
O
Me
TBSO
H

**33**

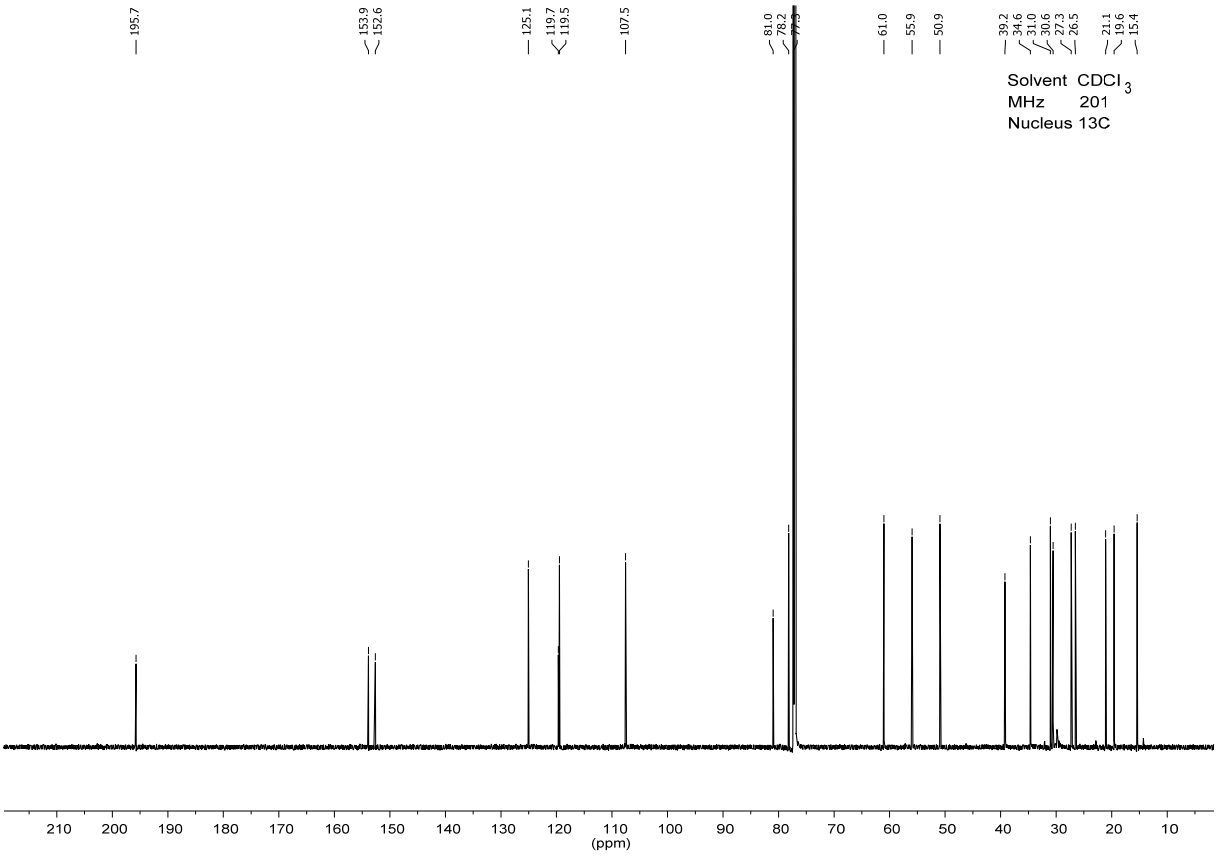

Solvent CDCl3
MHz 400
Nucleus 1H
1.10
1.00
1.00
2.94
1.02
1.00
2.00
4.09
1.13
1.05
5.08
2.72
8.59
3.01
2.85
2.85
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

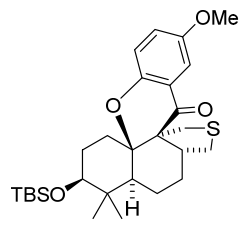

196.0
153.7
152.8
125.0
119.6
119.6
107.4
81.0
78.6
61.1
55.9
51.0
39.8
34.7
31.1
30.5
27.7
26.9
26.0
21.3
19.6
18.2
15.9
-3.7
-4.8
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


OMe
O
H
O
Me
HO
H

**34**

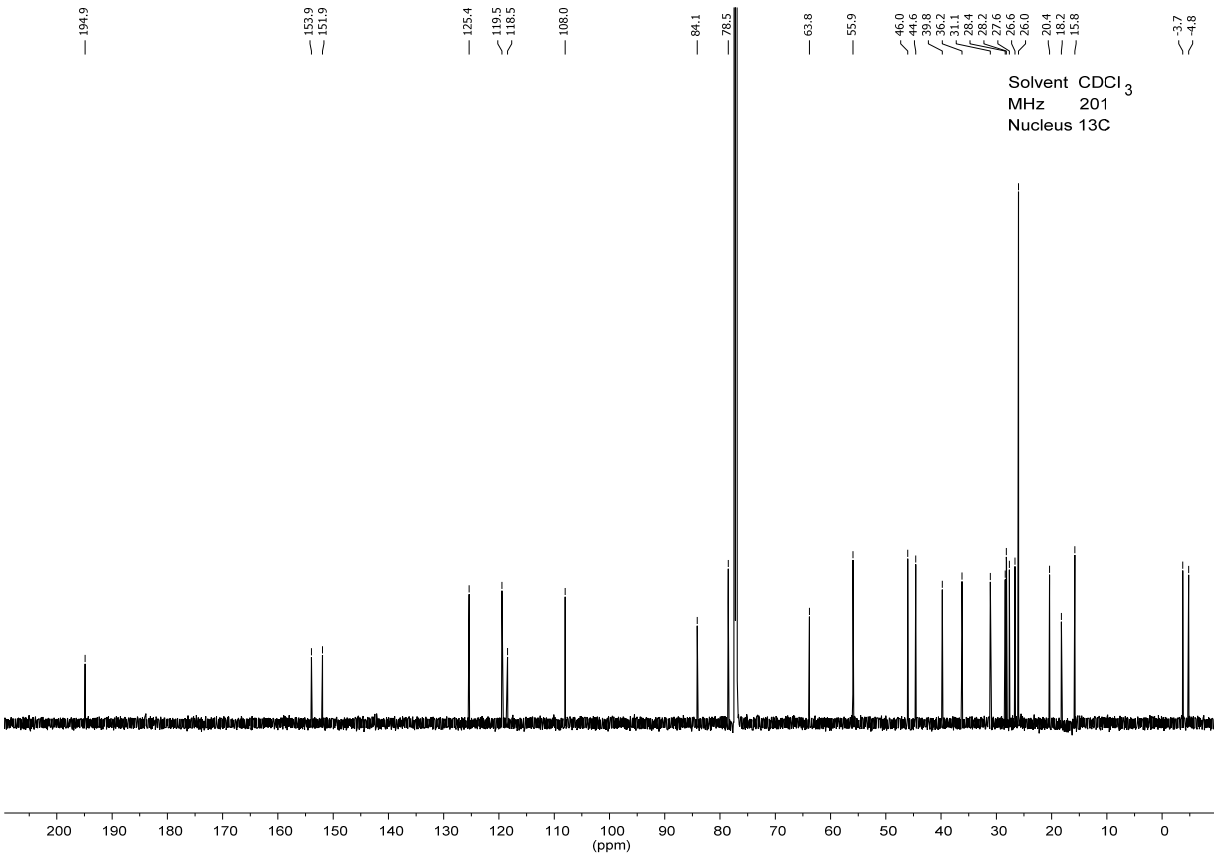

Solvent CDCl3
MHz 800
Nucleus 1H
1.07
0.96
1.00
3.17
0.96
0.95
2.03
2.10
2.33
1.18
0.93
1.15
3.10
5.23
3.38
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

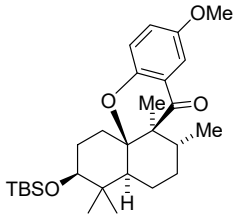

195.7
153.9
152.6
125.1
119.7
119.5
107.5
81.0
78.2
77.3
61.0
55.9
50.9
39.2
34.6
31.0
30.6
27.3
26.5
21.1
19.6
15.4
Solvent CDCl3
MHz 201
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OMe
O
O
S
TBSO
H

**36**

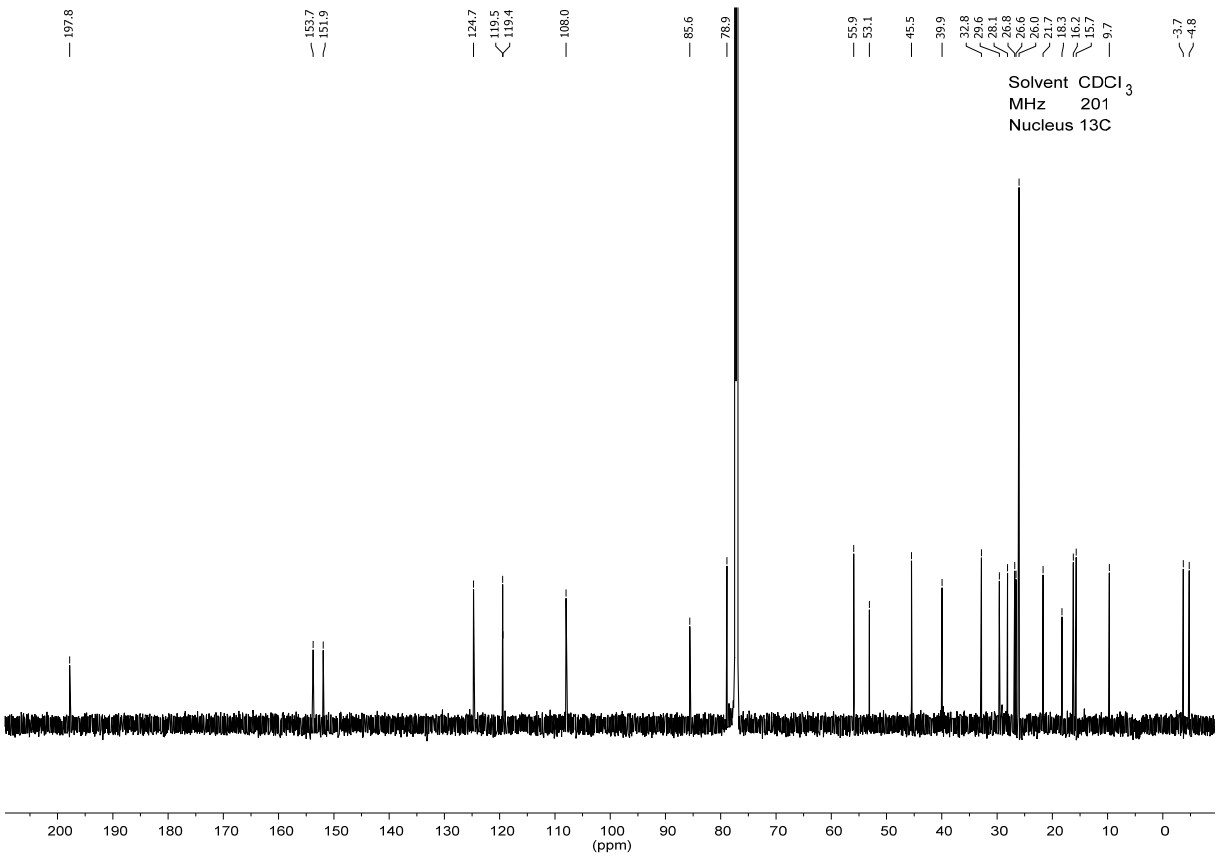

Solvent CDCl 3
MHz 800
Nucleus 1H
1.00
0.96
1.00
3.11
1.07
1.04
0.98
1.00
1.90
1.92
3.22
1.04
0.97
1.04
1.07
3.11
3.12
9.60
3.23
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

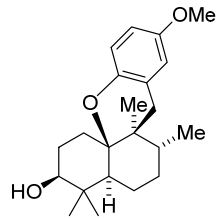

194.9
153.9
151.9
125.4
119.5
118.5
108.0
84.1
78.5
63.8
55.9
46.0
44.6
39.8
36.2
31.1
28.4
28.2
27.6
26.6
26.0
20.4
18.2
15.8
-3.7
-4.8
Solvent CDCl 3
MHz 201
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


OMe
O
Me
O
Me
TBSO
H

**S82**

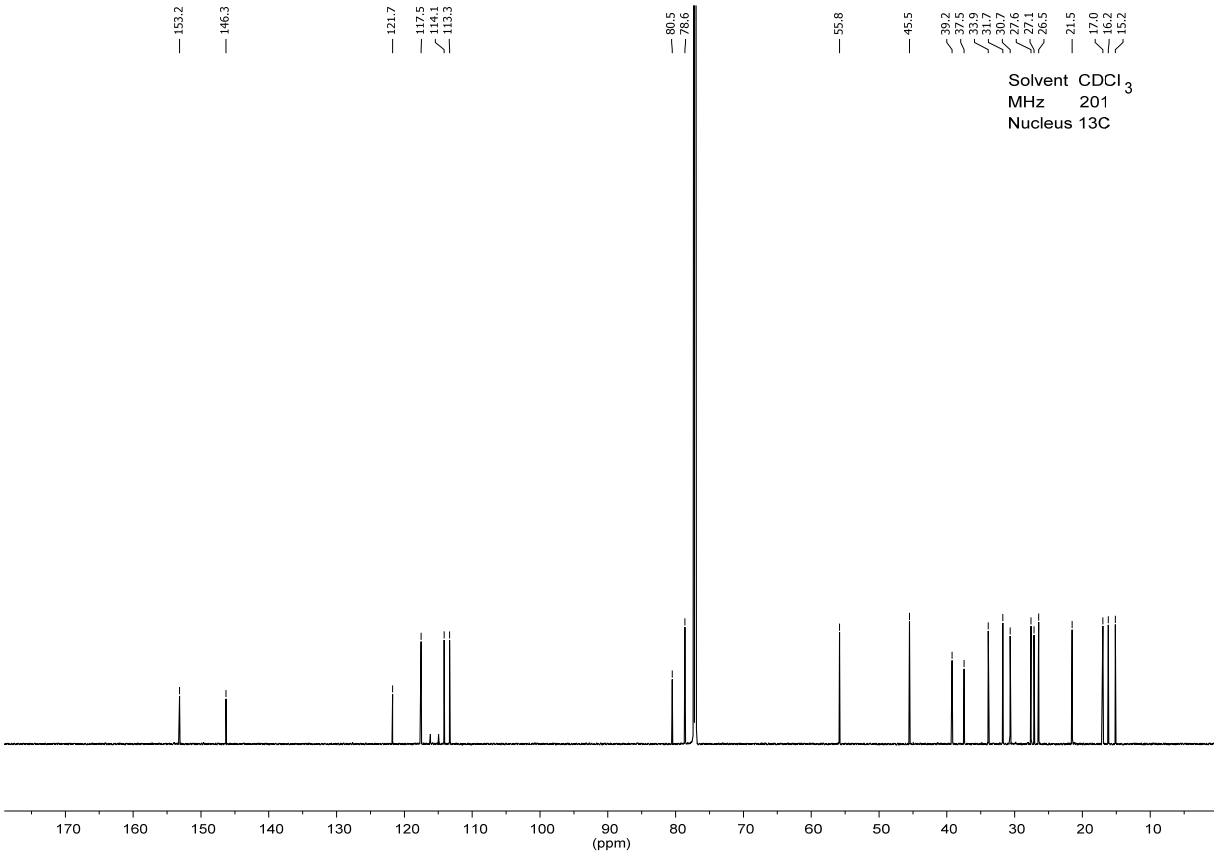

Solvent CDCl3
MHz 800
Nucleus 1H
0.93
0.86
0.92
3.26
1.00
1.00
0.90
0.93
2.06
0.97
1.28
1.12
2.41
2.83
2.84
2.71
9.64
2.87
3.13
2.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

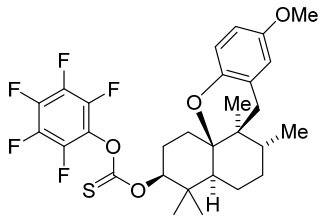

197.8
153.7
151.9
124.7
119.5
119.4
108.0
85.6
78.9
55.9
53.1
45.5
39.9
32.8
29.6
28.1
26.8
26.6
26.0
21.7
18.3
16.2
15.7
9.7
-3.7
-4.8
Solvent CDCl3
MHz 201
Nucleus 13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


OMe
O
Me
Me
HO
H

**37**

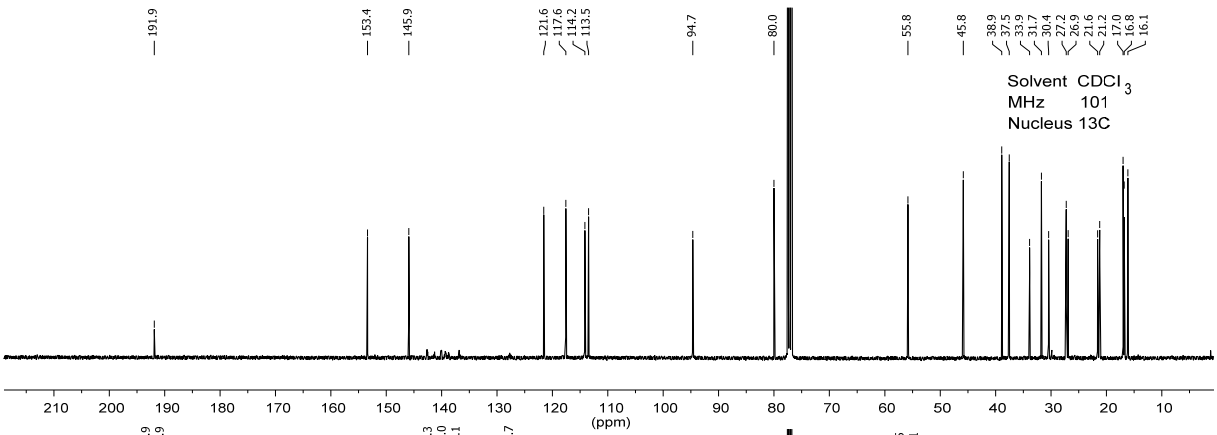

Solvent CDCl3
MHz 800
Nucleus 1H
1.00
0.99
1.01
3.16
0.99
0.99
0.98
2.12
1.00
1.09
2.50
3.31
1.14
0.76
1.28
3.19
3.02
3.16
3.16
(ppm)

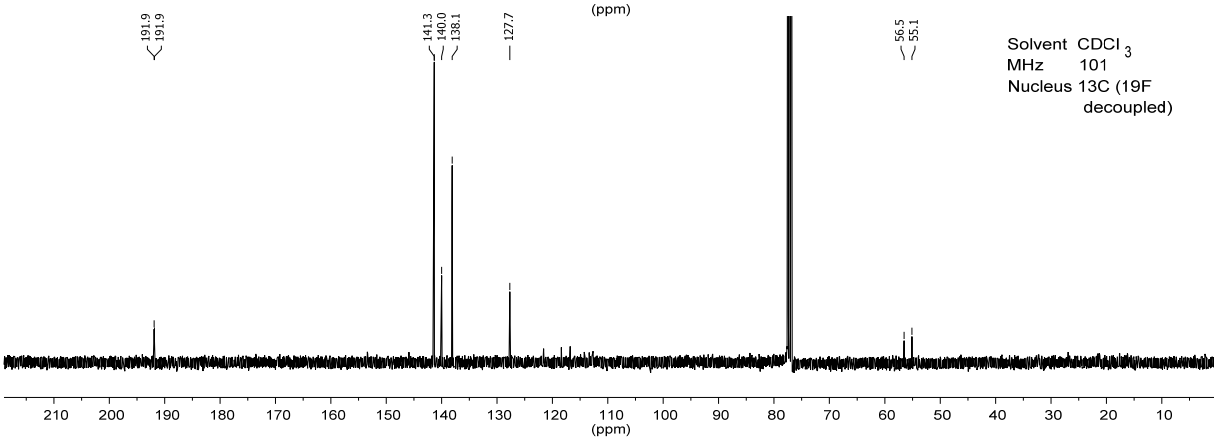

153.2
146.3
121.7
117.5
114.1
113.3
80.5
78.6
55.8
45.5
39.2
37.5
33.9
31.7
30.7
27.6
27.1
26.5
21.5
17.0
16.2
15.2
Solvent CDCl3
MHz 201
Nucleus 13C
(ppm)

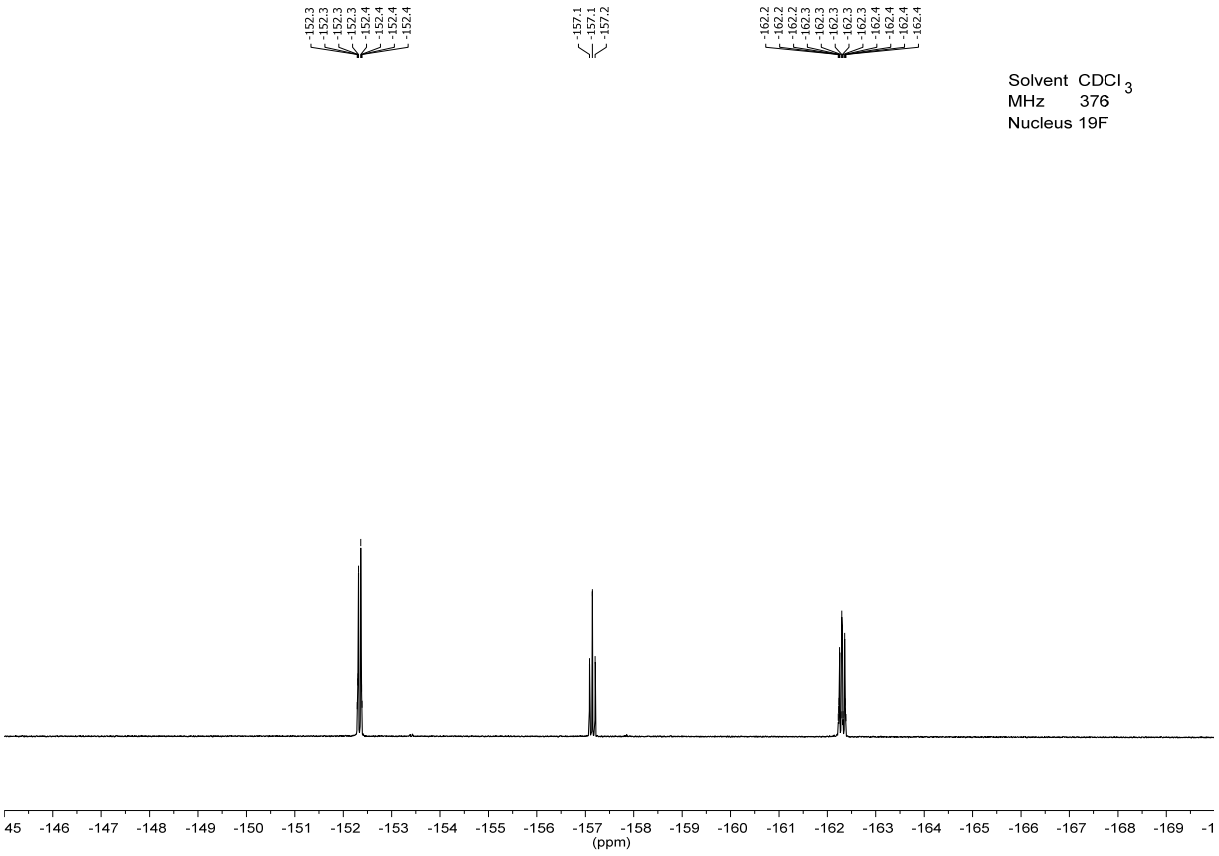

OMe
F
F
F
F
F
O
Me
Me
O
S
O
H

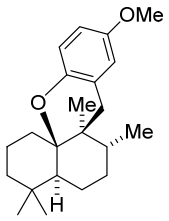
**S83**


Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.03
1.00
1.03
2.74
1.07
1.13
1.06
3.30
1.16
5.34
1.44
2.98
2.74
2.67
2.77
(ppm)


191.9
153.4
145.9
121.6
117.6
114.2
113.5
94.7
80.0
55.8
45.8
38.9
37.5
33.9
31.7
30.4
27.2
26.9
21.6
21.2
17.0
16.8
16.1
Solvent CDCl3
MHz 101
Nucleus 13C
(ppm)

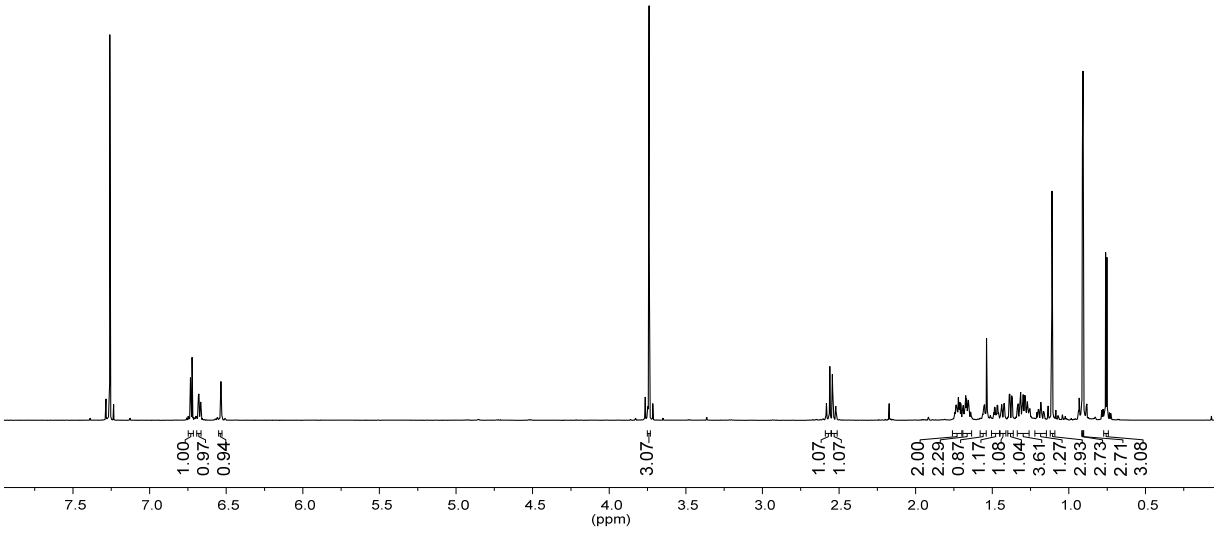

191.9
191.9
141.3
140.0
138.1
127.7
56.5
55.1
Solvent CDCl3
MHz 101
Nucleus 13C (19F
decoupled)
(ppm)


-152.3
-152.3
-152.3
-152.3
-152.4
-152.4
-152.4
-152.4
-157.1
-157.1
-157.2
-162.2
-162.2
-162.2
-162.3
-162.3
-162.3
-162.3
-162.4
-162.4
-162.4
-162.4
Solvent CDCl3
MHz 376
Nucleus 19F
45 -146 -147 -148 -149 -150 -151 -152 -153 -154 -155 -156 -157 -158 -159 -160 -161 -162 -163 -164 -165 -166 -167 -168 -169 -1
(ppm)

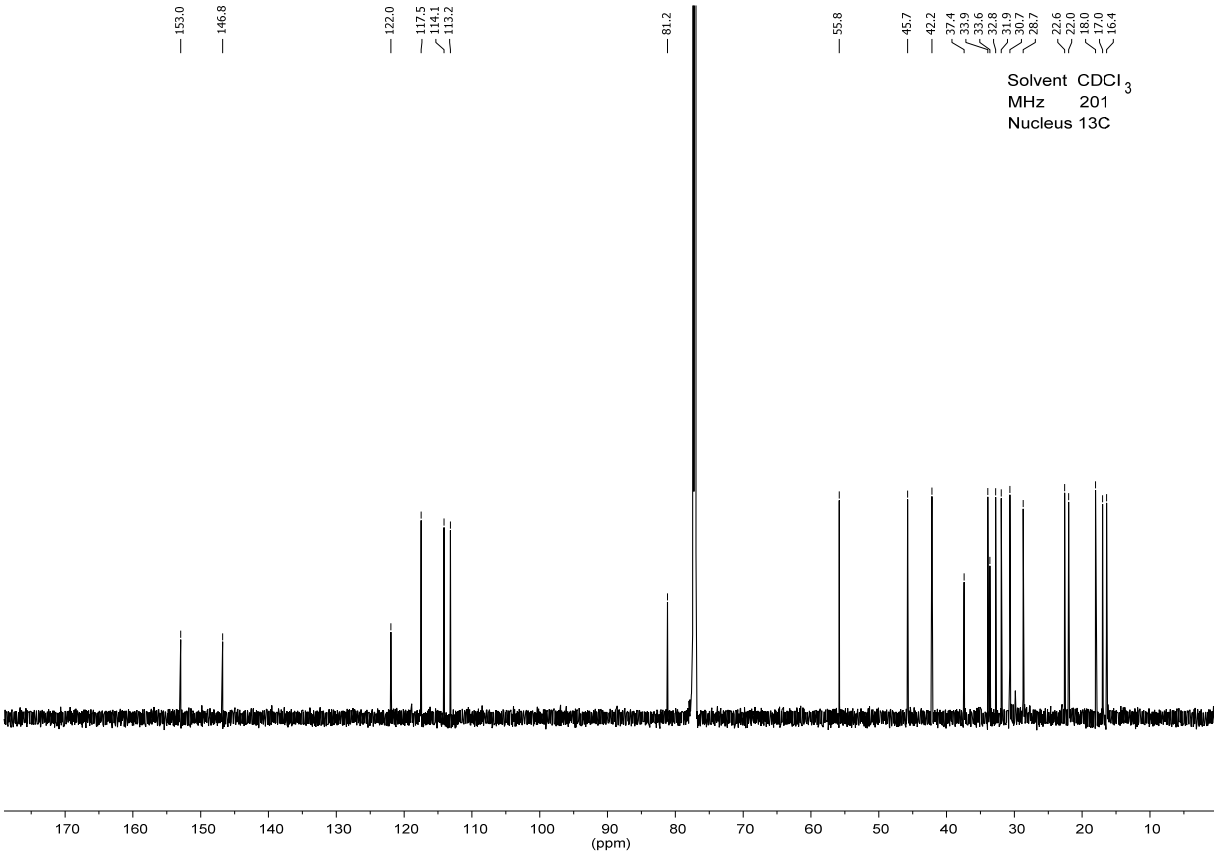


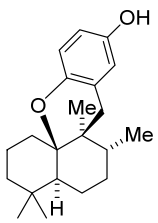

**S84**

Solvent CDCl 3
MHz 800
Nucleus 1H



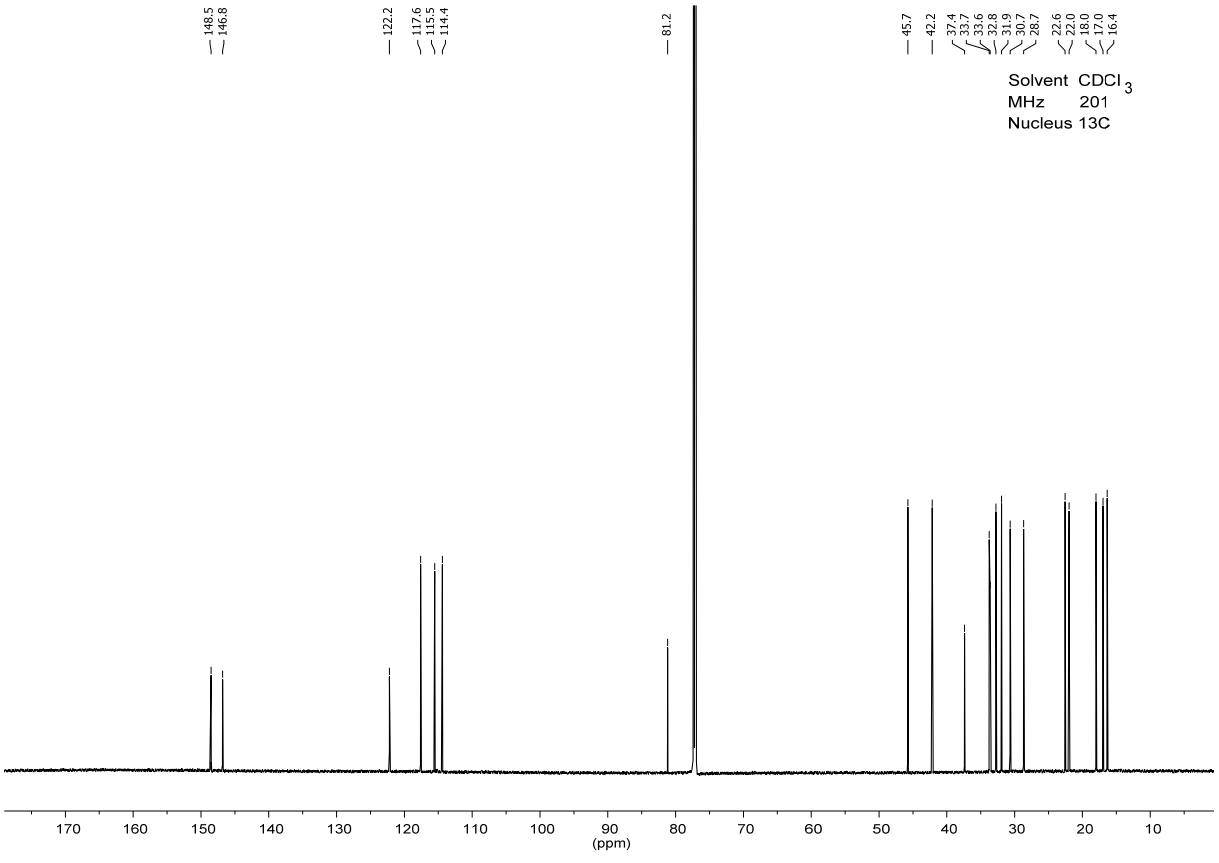

Solvent CDCl 3
MHz 201
Nucleus 13C

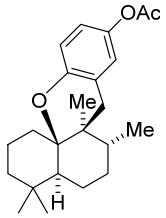





5-*epi*-Aureol (**35**)

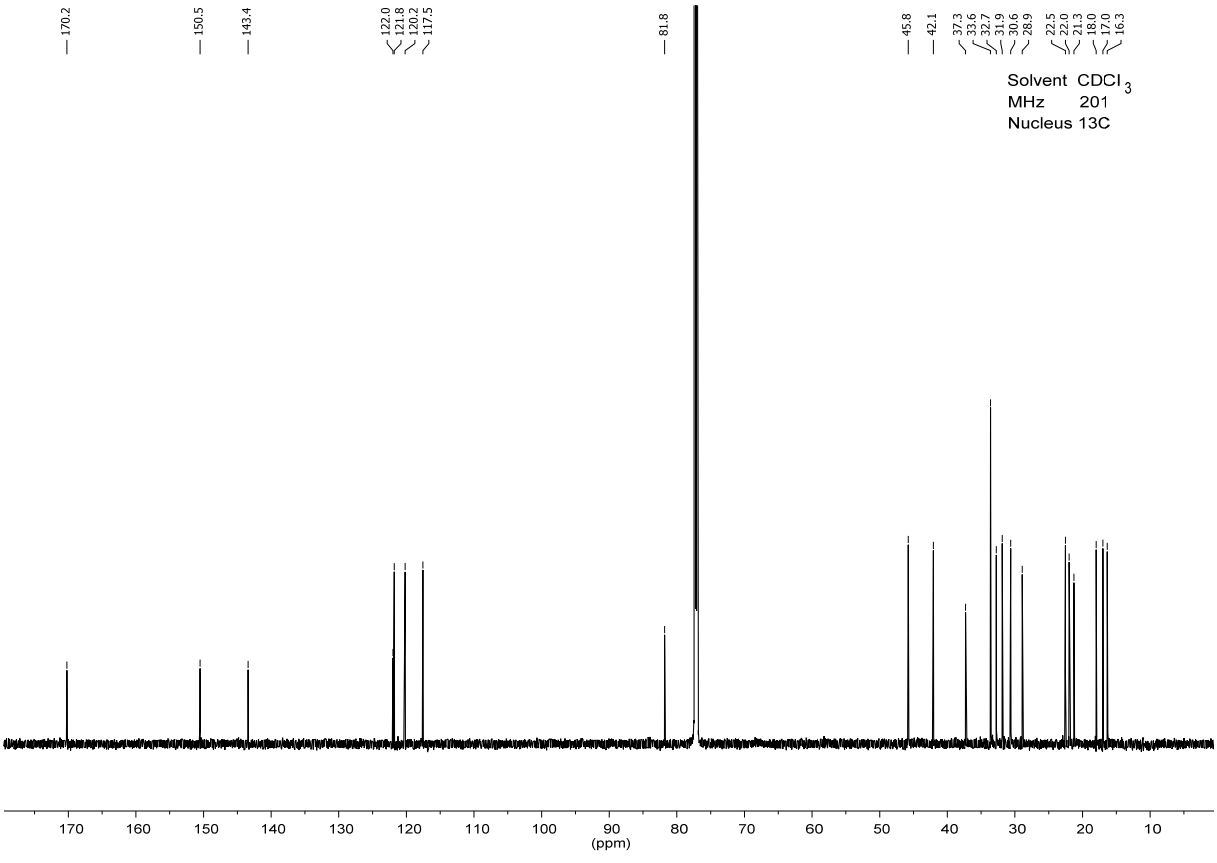


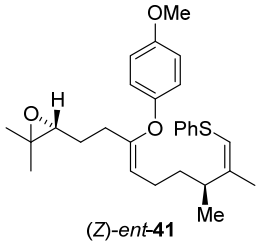




OAc
O
Me
Me
H

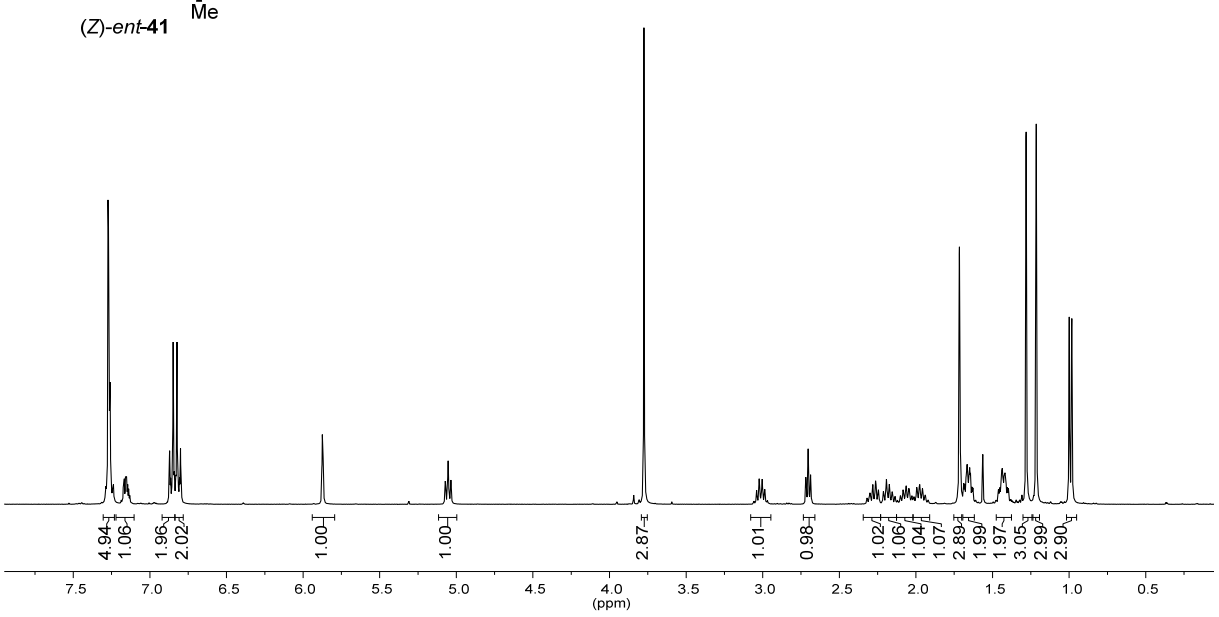
**S85**

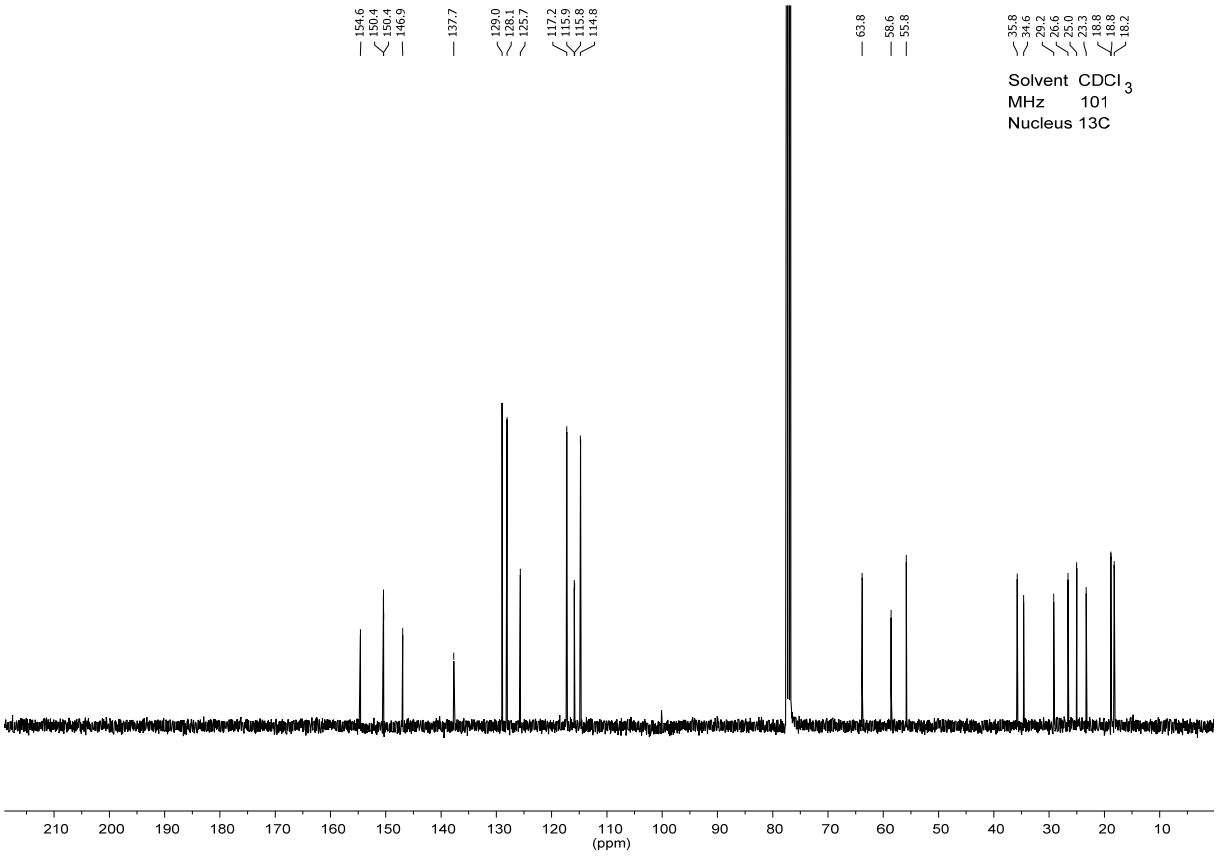

Solvent CDCl3
MHz 400
Nucleus 1H
1.80
0.99
1.89
3.00
4.35
1.01
2.26
1.39
3.83
1.21
2.94
2.43
2.30
3.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

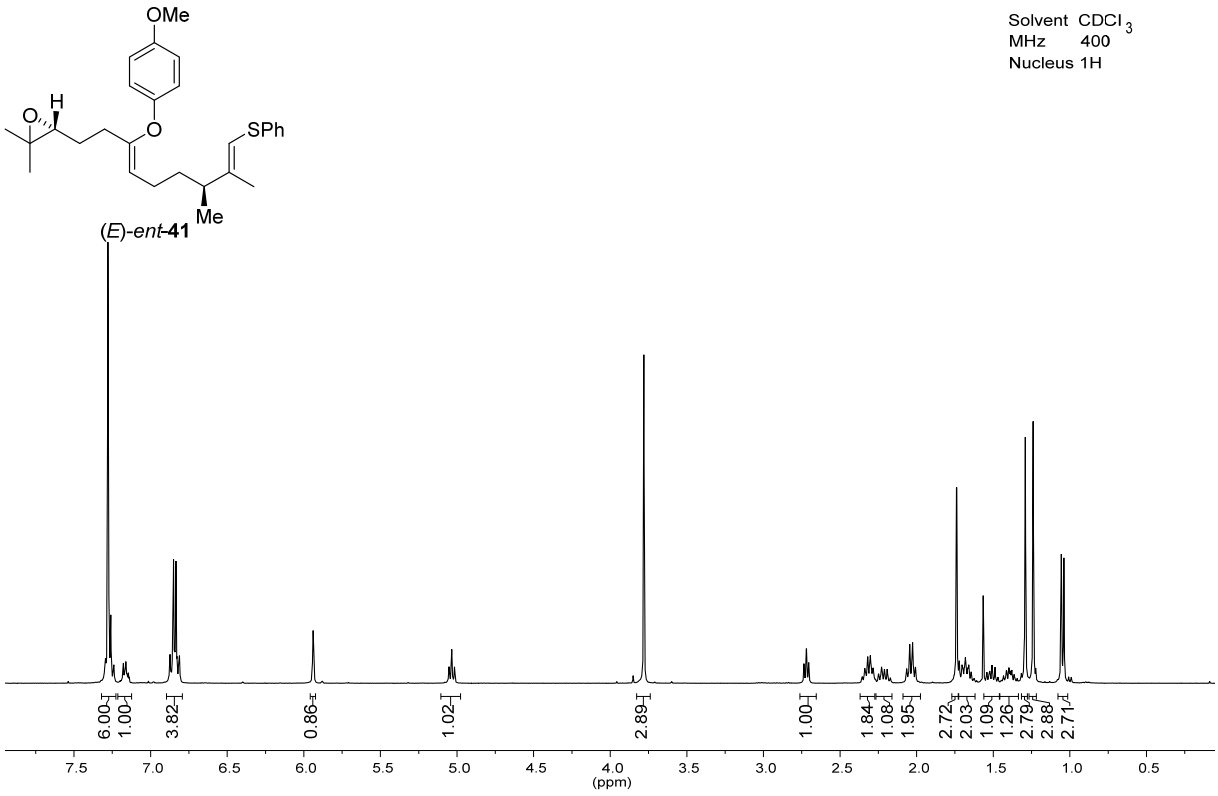

170.2
150.5
143.4
122.0
121.8
120.2
117.5
81.8
45.8
42.1
37.3
33.6
32.7
31.9
30.6
28.9
22.5
22.0
21.3
18.0
17.0
16.3
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

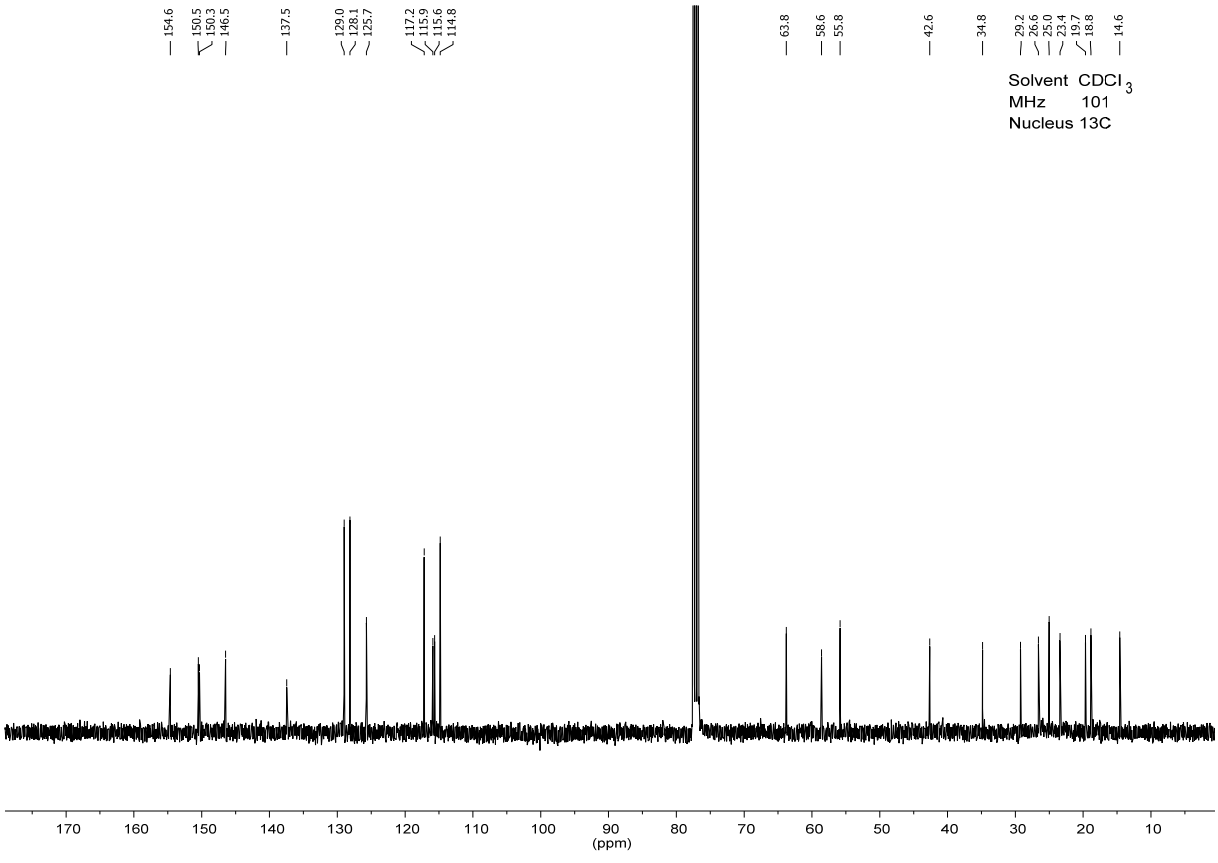

OMe
H
O
O
PhS
Me

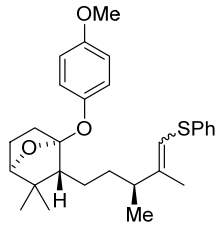
(*Z*)-*ent*-**41**


Solvent CDCl3
MHz 400
Nucleus 1H
4.94
1.06
1.96
2.02
1.00
1.00
2.87
1.01
0.98
1.02
1.06
1.04
1.07
2.89
1.99
1.97
3.05
2.99
2.90
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


154.6
150.4
150.4
146.9
137.7
129.0
128.1
125.7
117.2
115.9
115.8
114.8
63.8
58.6
55.8
35.8
34.6
29.2
26.6
25.0
23.3
18.8
18.8
18.2
Solvent CDCl3
MHz 101
Nucleus 13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

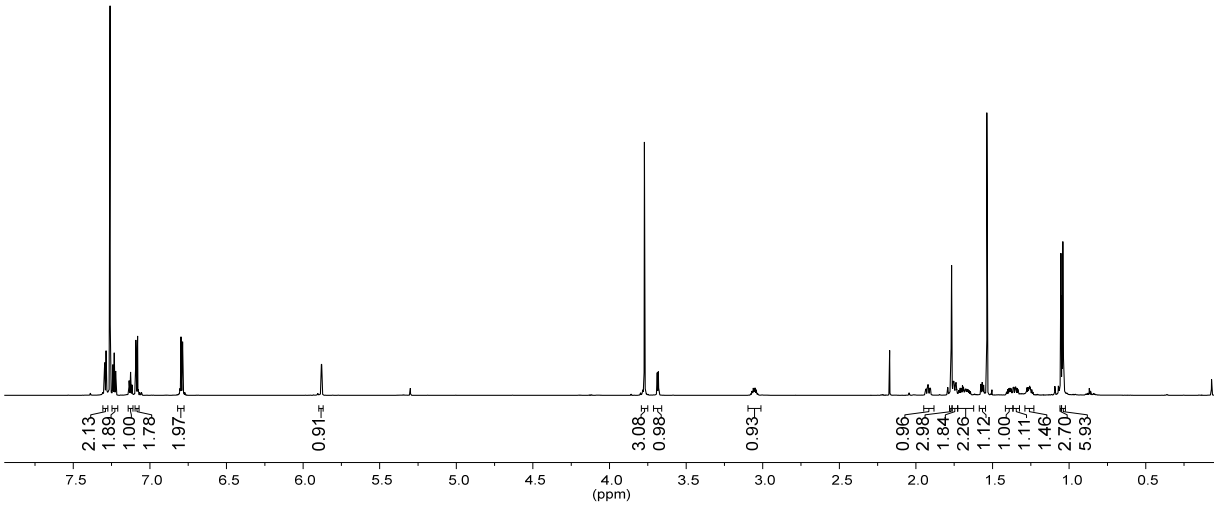

OMe
H
O
O
SPh
Me
(*E*)-*ent*-**41**
Solvent CDCl3
MHz 400
Nucleus 1H
6.00
1.00
3.82
0.86
1.02
2.89
1.00
1.84
1.08
1.95
2.72
2.03
1.09
1.26
2.79
2.88
2.71
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

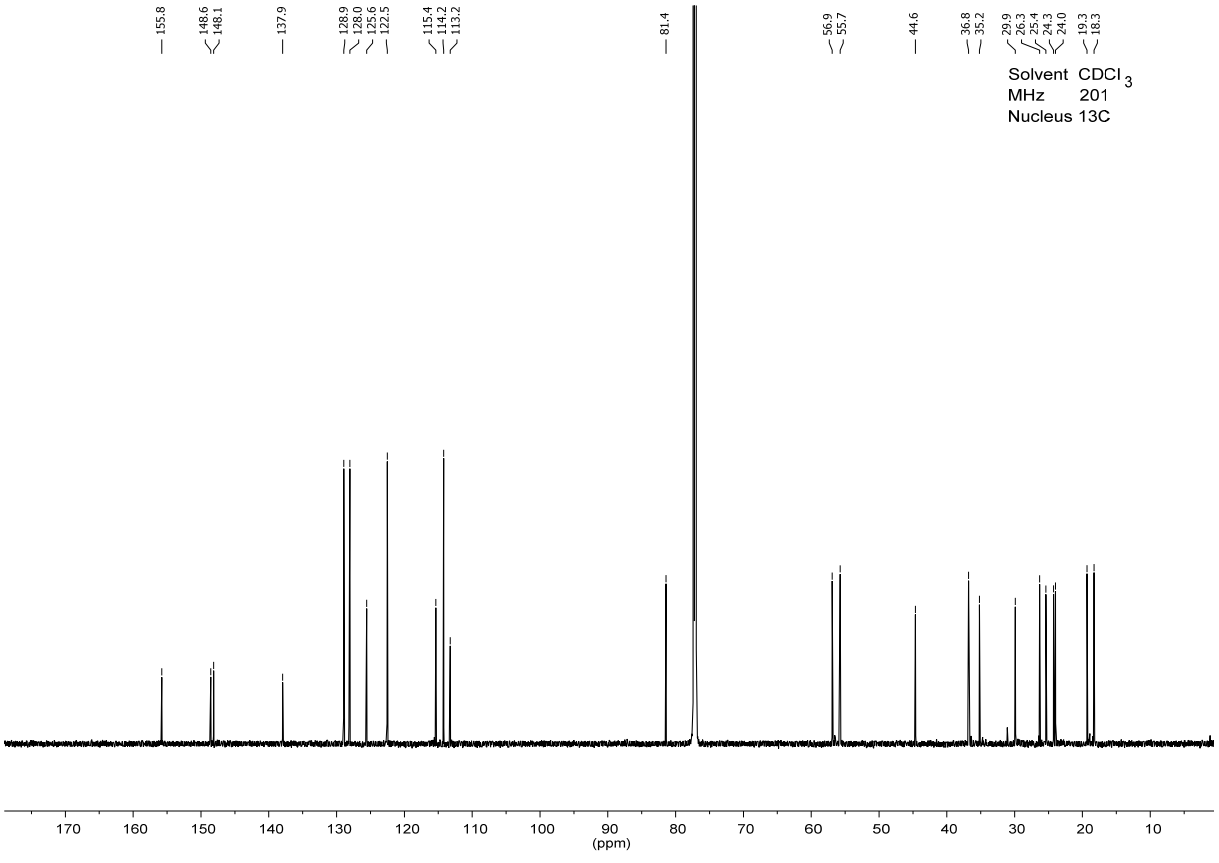

154.6
150.5
150.3
146.5
137.5
129.0
128.1
125.7
117.2
115.9
115.6
114.8
63.8
58.6
55.8
42.6
34.8
29.2
26.6
25.0
23.4
19.7
18.8
14.6
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

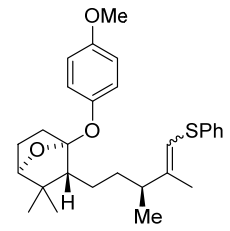



(*Z*)-*ent*-**42**

Solvent CDCl 3
MHz 800
Nucleus 1H

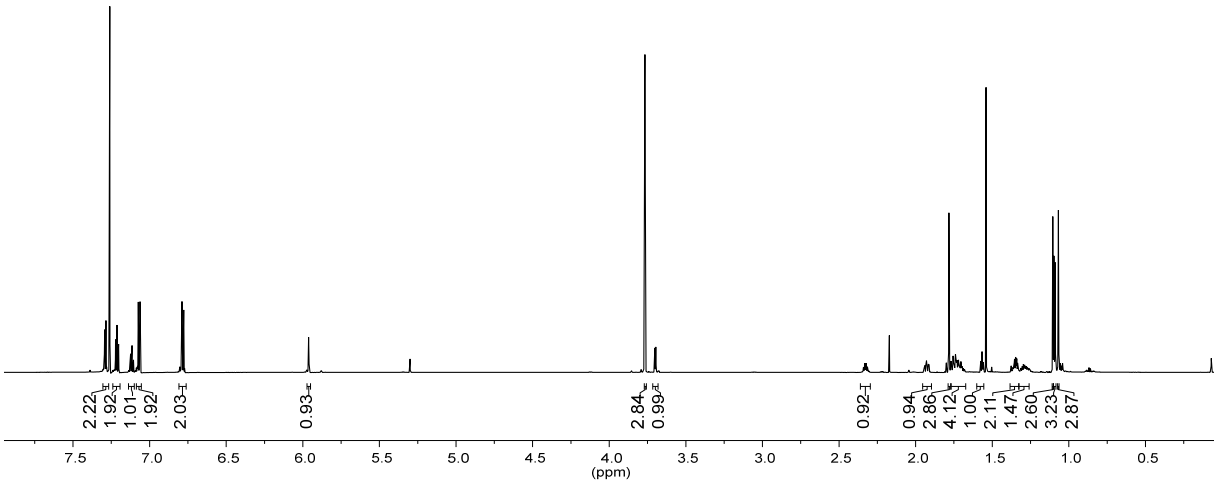


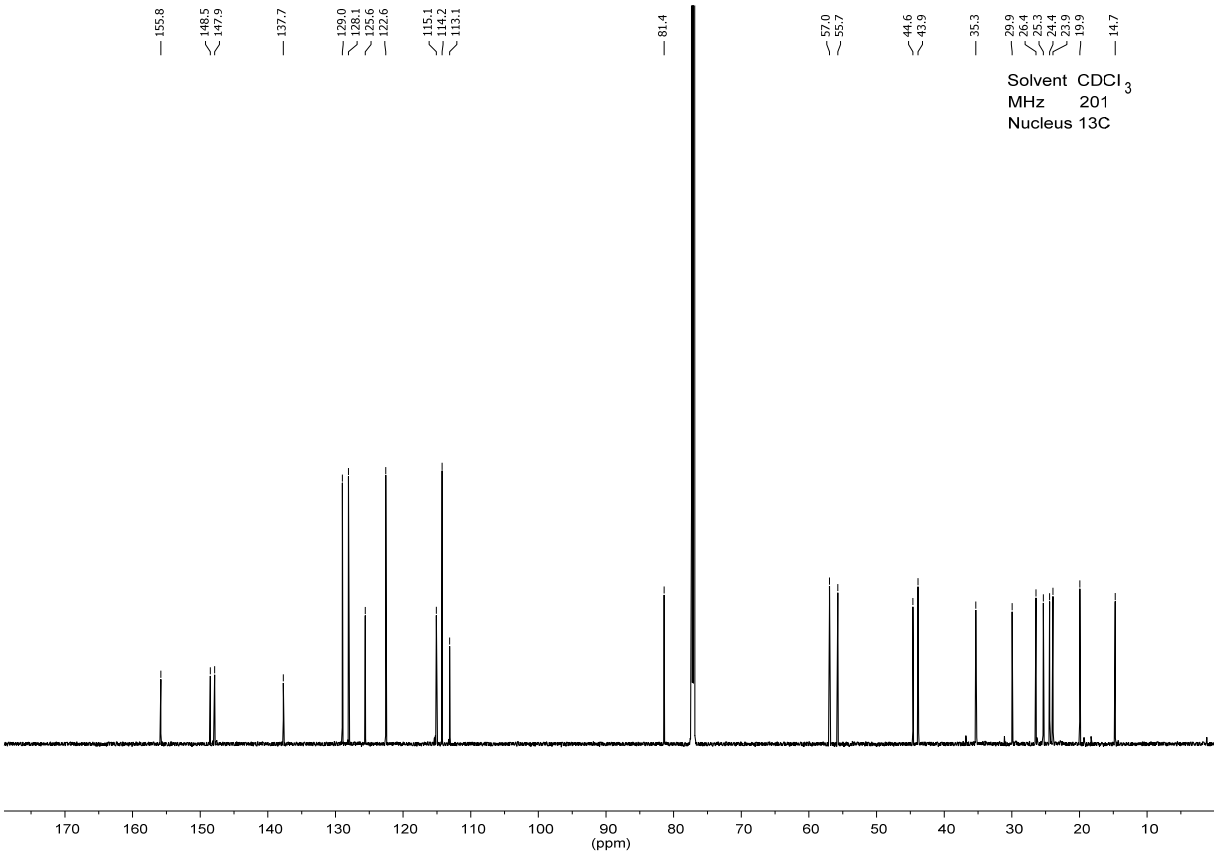





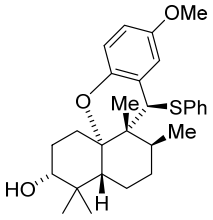

(*E*)-*ent*-**42**

Solvent CDCl 3
MHz 800
Nucleus 1H



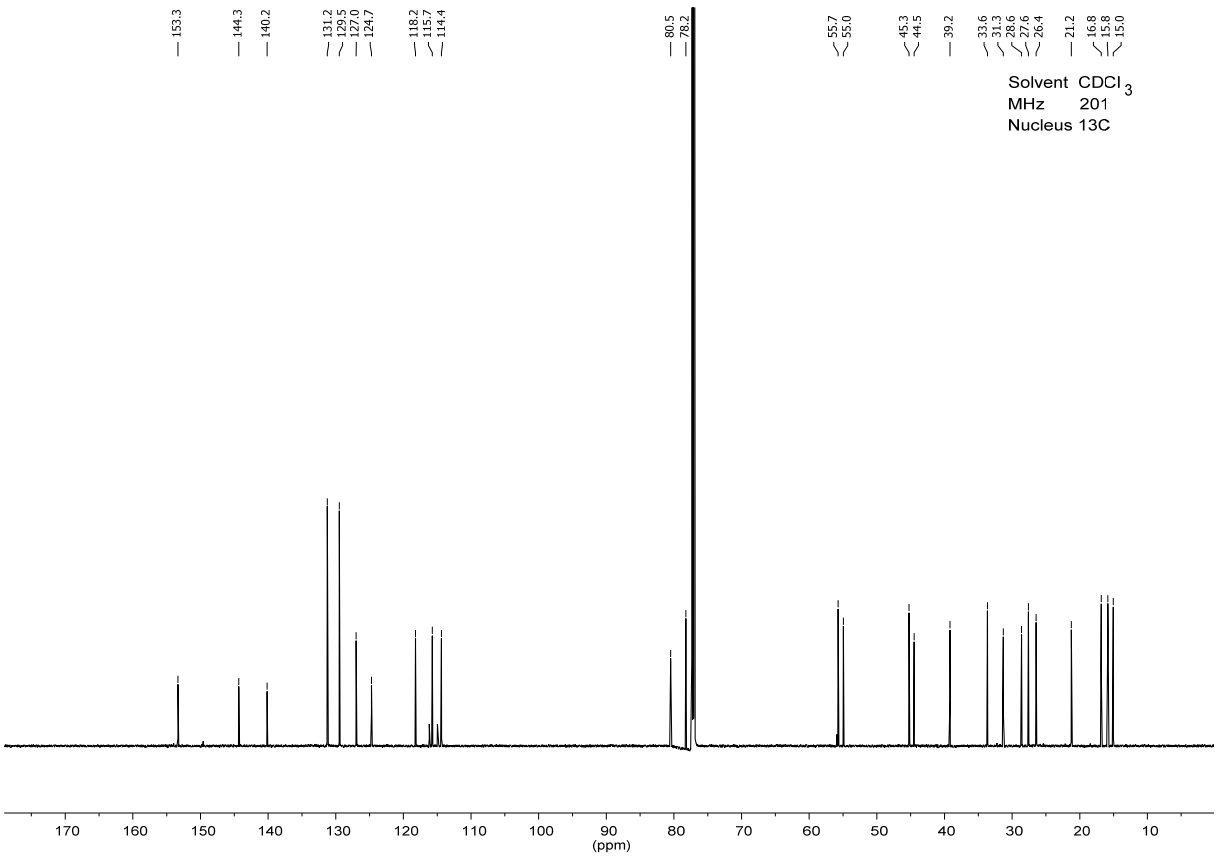



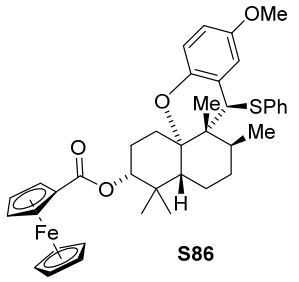

Solvent CDCl 3
MHz 201
Nucleus 13C


OMe
O
Me
SPh
Me
HO
H

*ent*-**43**

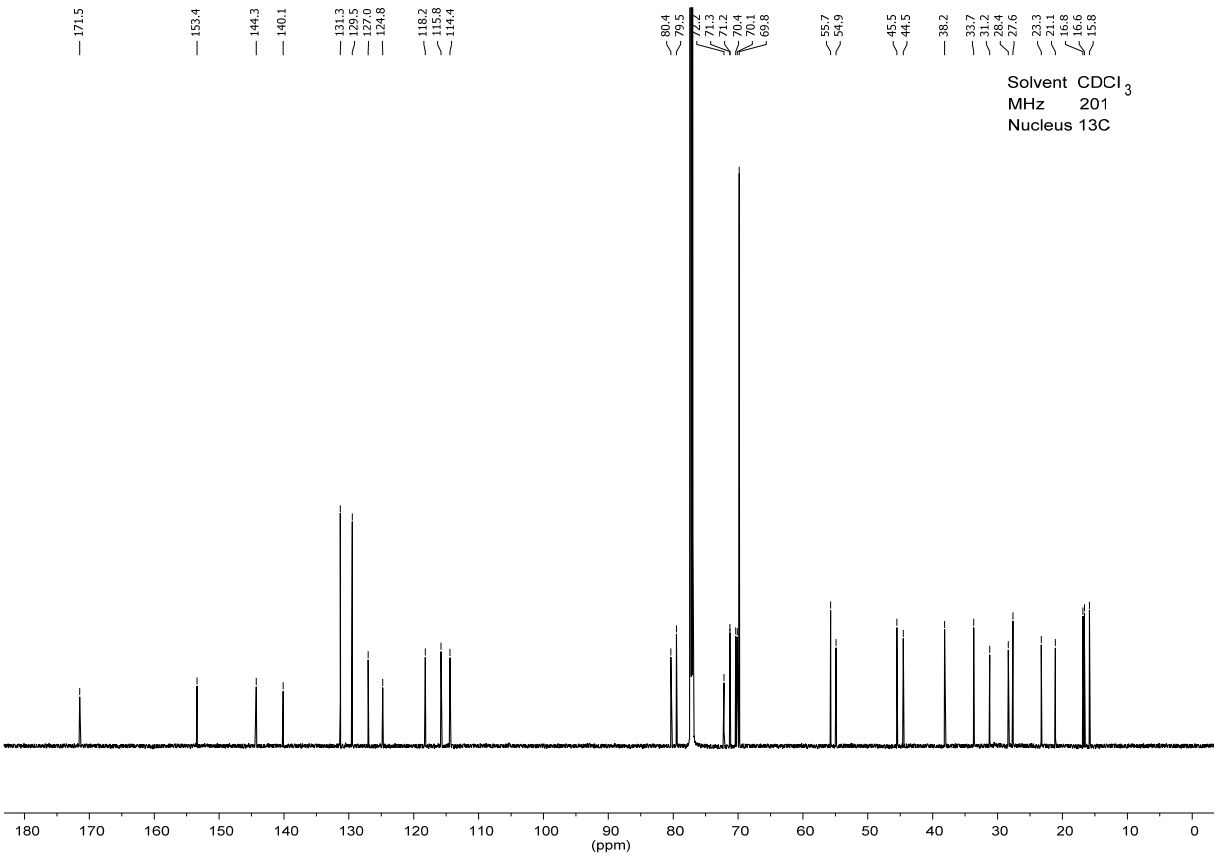

Solvent CDCl3
MHz 800
Nucleus 1H
1.90
1.94
2.38
3.00
0.94
3.03
0.91
0.89
1.00
1.91
1.18
3.03
1.02
1.89
3.03
3.05
3.11
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

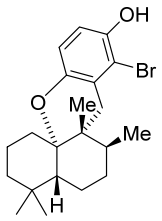

153.3
144.3
140.2
131.2
129.5
127.0
124.7
118.2
115.7
114.4
80.5
78.2
55.7
55.0
45.3
44.5
39.2
33.6
31.3
28.6
27.6
26.4
21.2
16.8
15.8
15.0
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OMe
O
Me
SPh
Me
O
O
H
Fe

**S86**

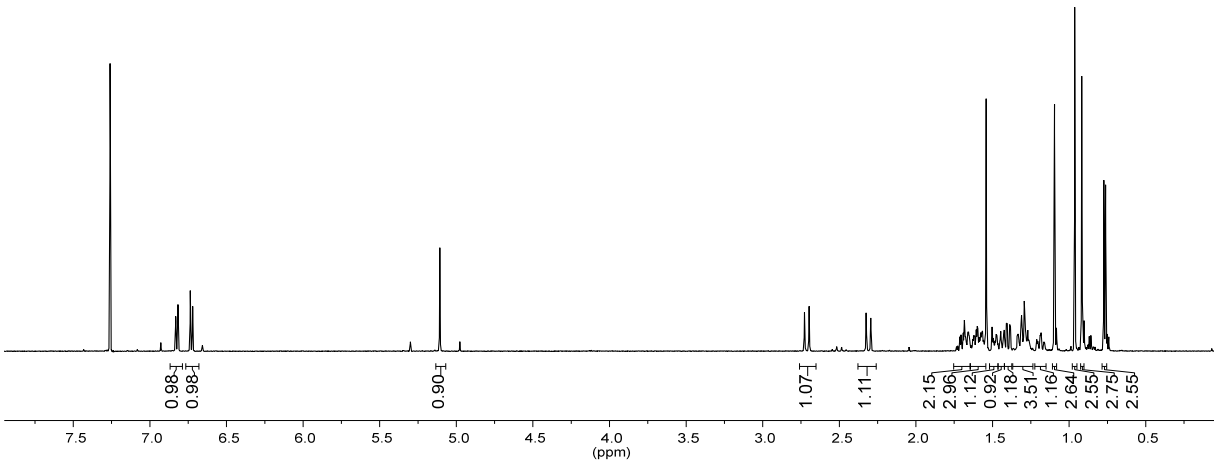

Solvent CDCl3
MHz 800
Nucleus 1H
2.17
2.20
4.27
1.06
2.20
2.20
1.00
2.25
1.10
5.58
3.32
1.03
3.26
2.21
3.41
1.12
6.71
3.32
3.39
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

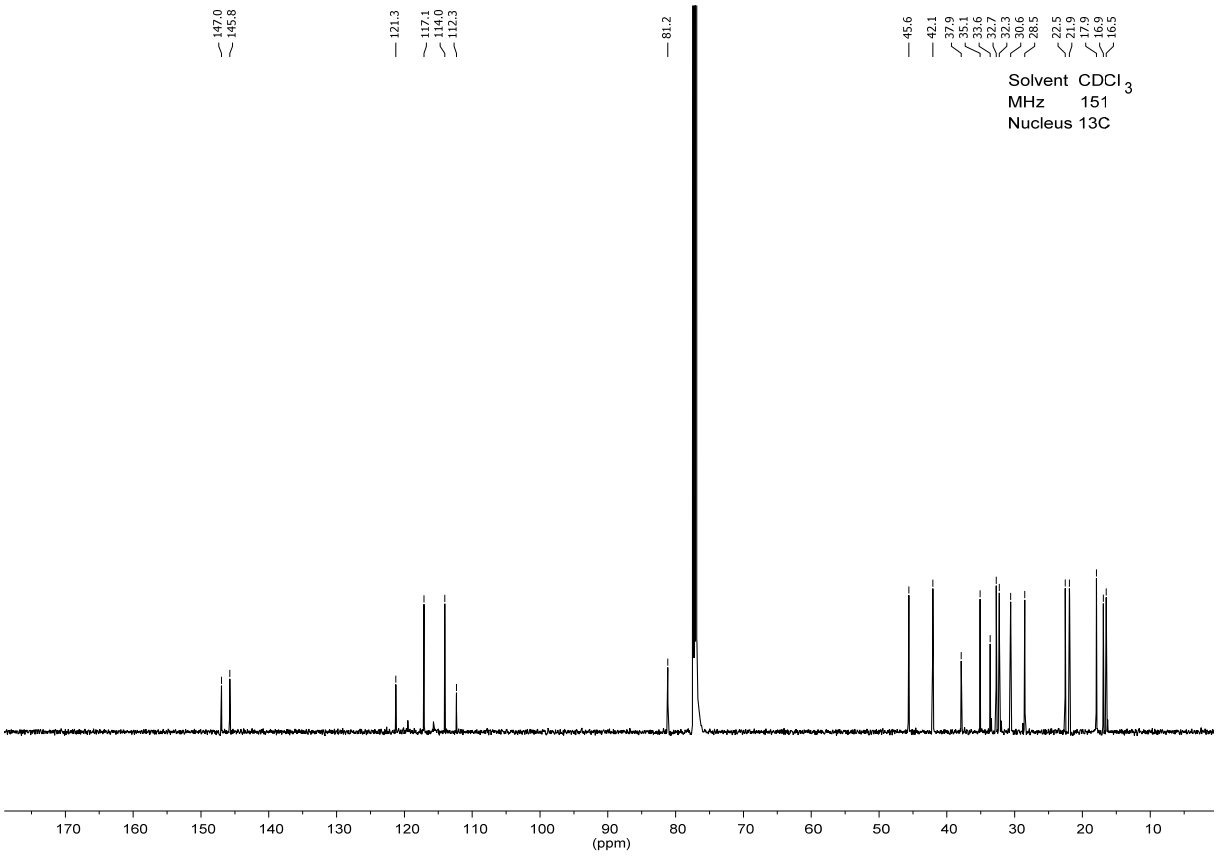

171.5
153.4
144.3
140.1
131.3
129.5
127.0
124.8
118.2
115.8
114.4
80.4
79.5
72.2
71.3
71.2
70.4
70.1
69.8
55.7
54.9
45.5
44.5
38.2
33.7
31.2
28.4
27.6
23.3
21.1
16.8
16.6
15.8
Solvent CDCl3
MHz 201
Nucleus 13C
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

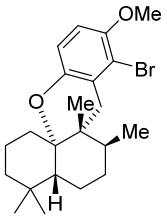



**S87**

Solvent CDCl 3
MHz 599
Nucleus 1H

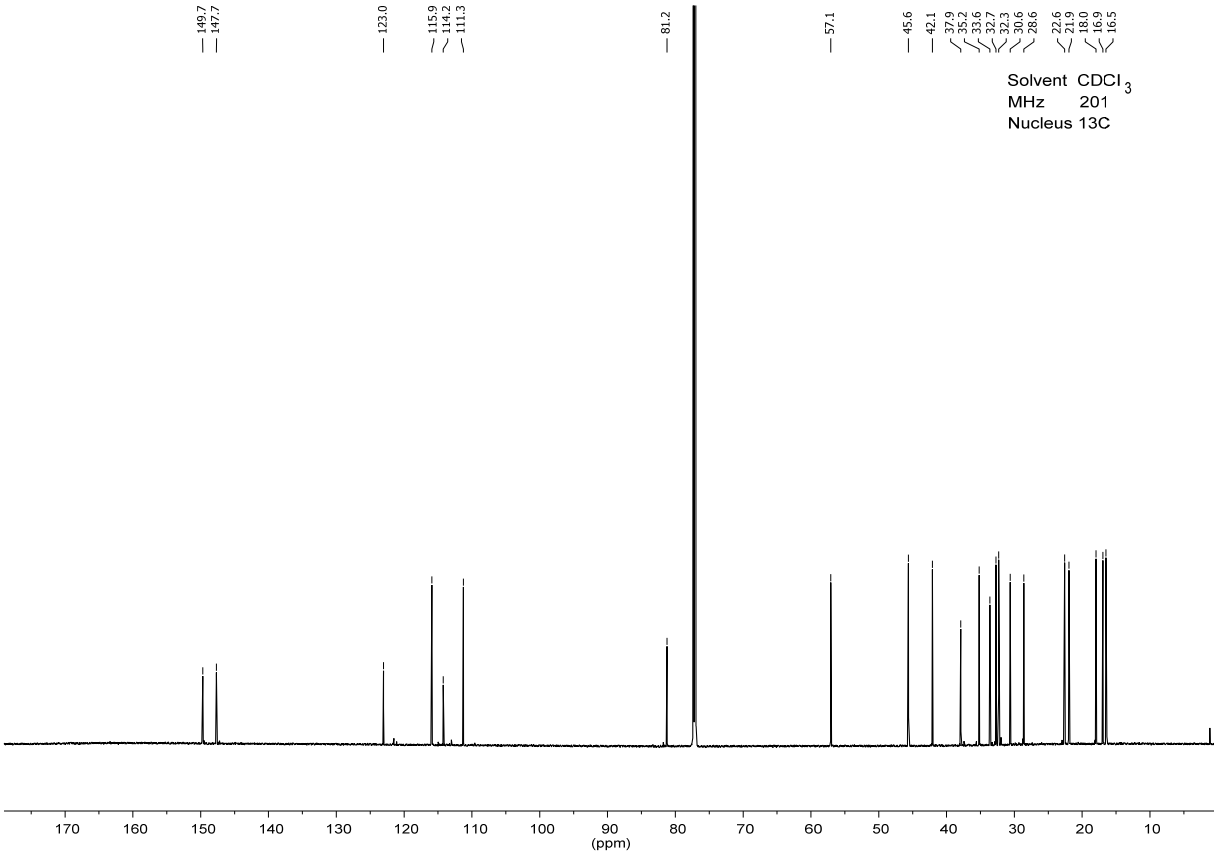


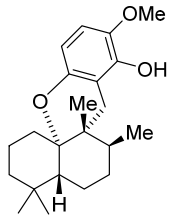




OMe
Br
O
Me
Me
H

**44**

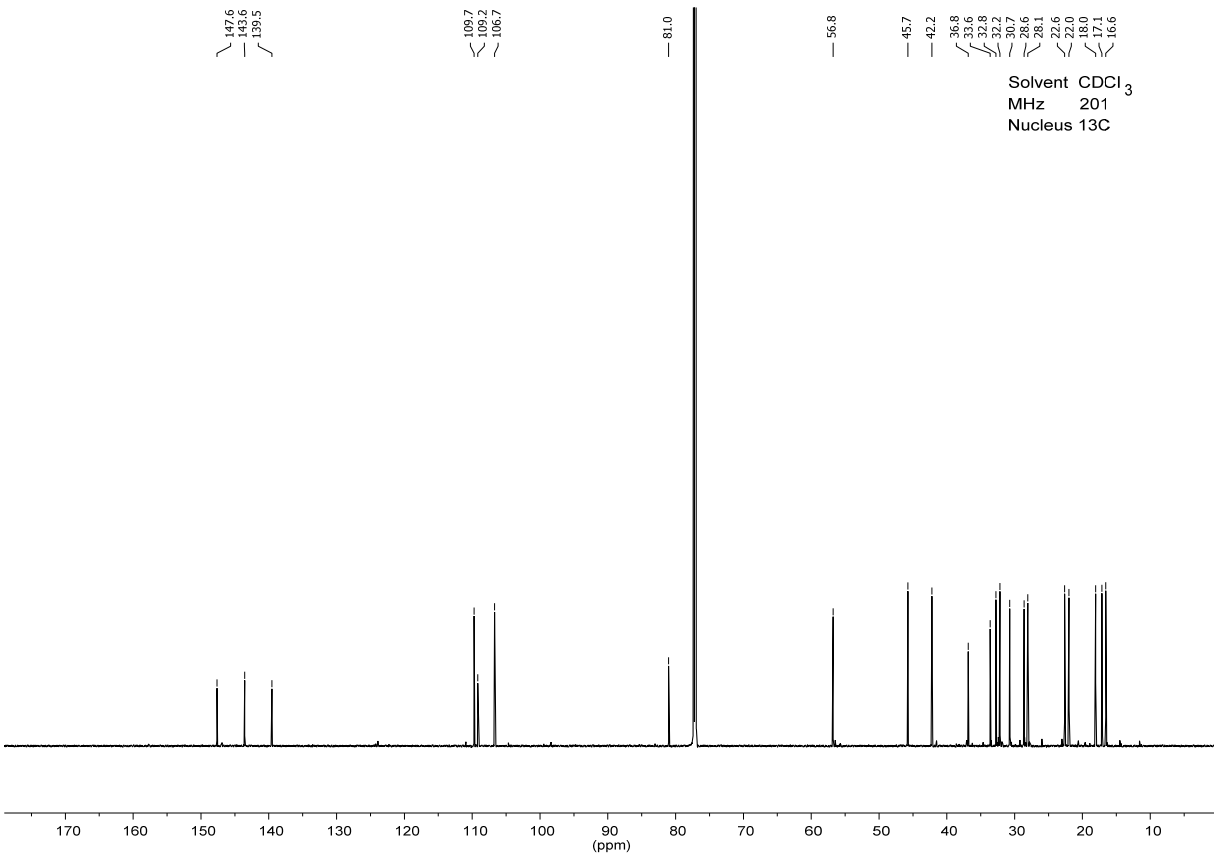

Solvent CDCl3
MHz 800
Nucleus 1H
1.00
0.95
3.04
0.93
0.93
1.97
3.09
1.05
1.02
1.02
3.36
1.04
3.00
3.02
3.07
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

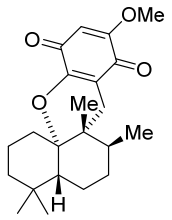

149.7
147.7
123.0
115.9
114.2
111.3
81.2
57.1
45.6
42.1
37.9
35.2
33.6
32.7
32.3
30.6
28.6
22.6
21.9
18.0
16.9
16.5
Solvent CDCl3
MHz 201
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


OMe
OH
O
Me
Me
H

**S88**

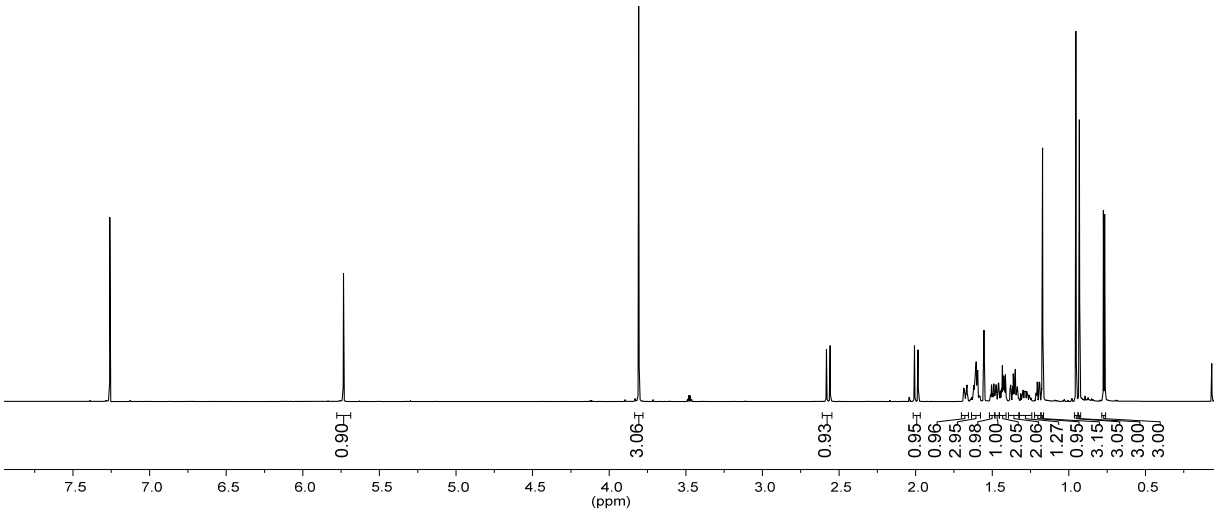

Solvent CDCl3
MHz 800
Nucleus 1H
0.83
0.81
0.76
2.87
0.75
0.79
0.91
1.00
1.84
1.99
1.04
1.02
0.99
3.45
1.06
2.85
3.00
3.00
2.87
(ppm)

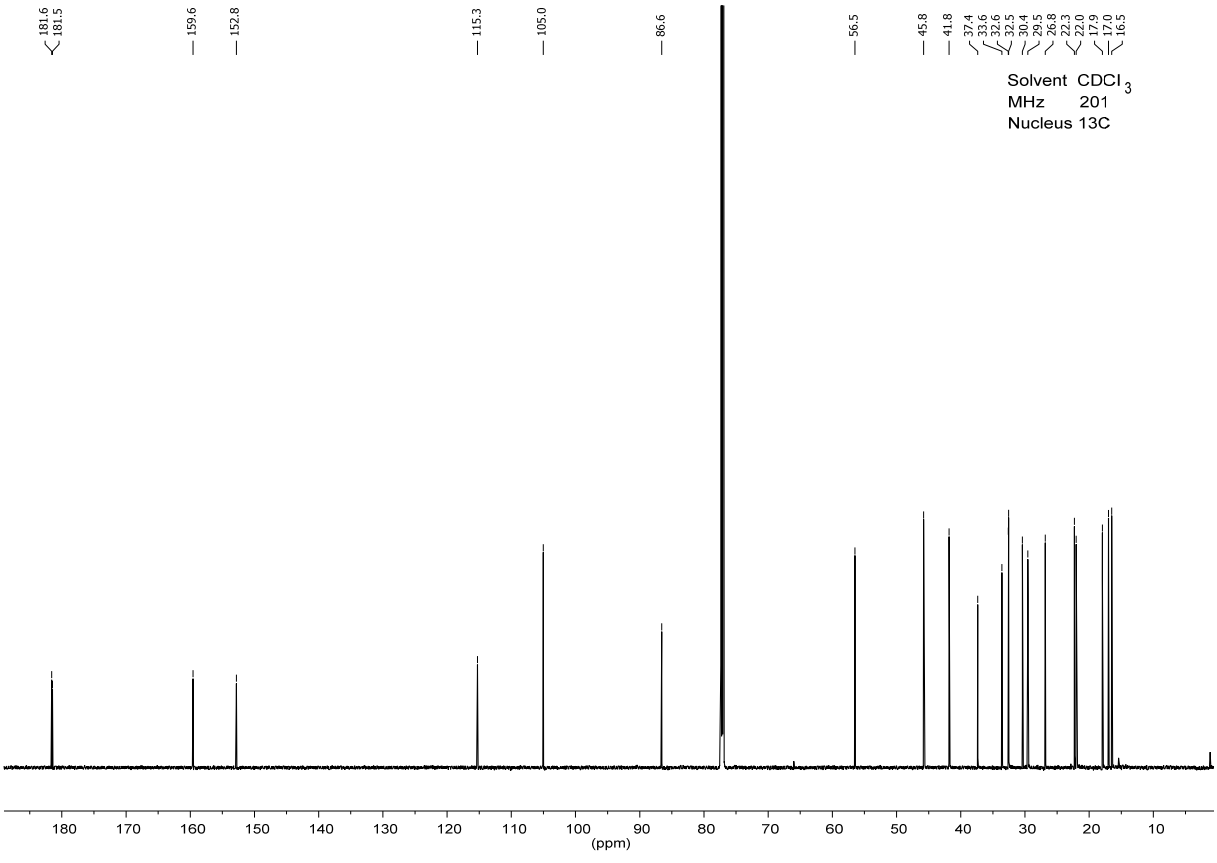

147.6
143.6
139.5
109.7
109.2
106.7
81.0
56.8
45.7
42.2
36.8
33.6
32.8
32.2
30.7
28.6
28.1
22.6
22.0
18.0
17.1
16.6
Solvent CDCl3
MHz 201
Nucleus 13C
(ppm)

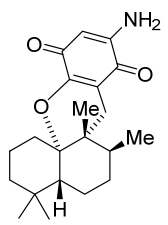



5-*epi*-smenoqualone (**45**)

Solvent CDCl 3
MHz 800
Nucleus 1H

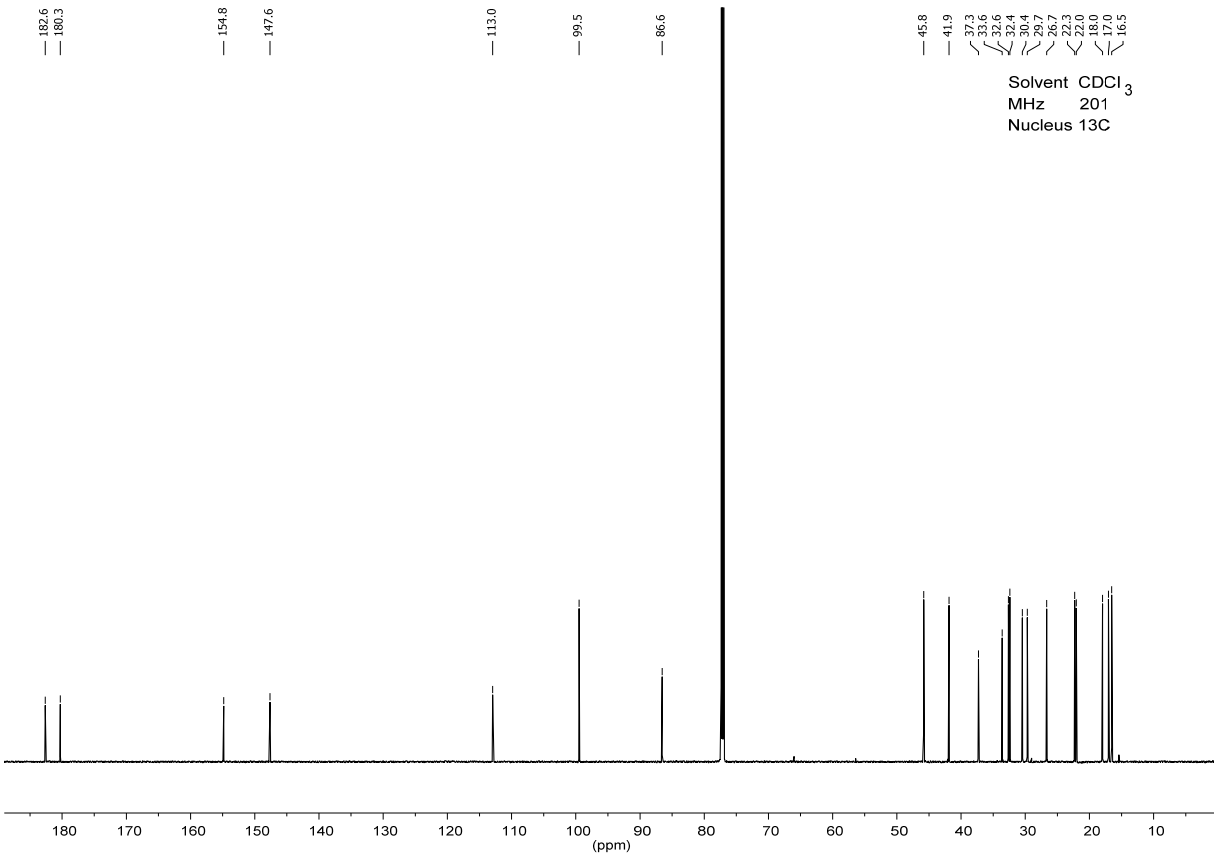


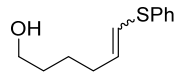






(–)-cyclosmenospongine (**4**)

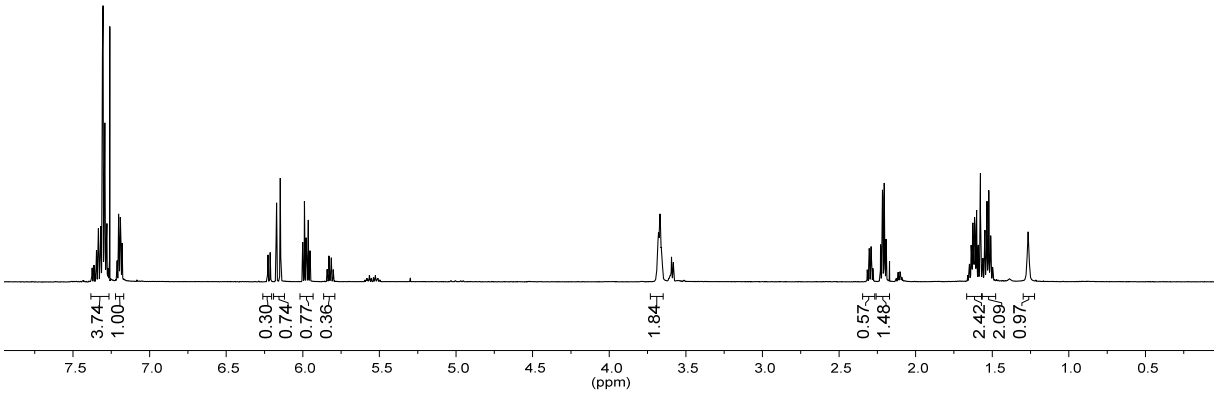


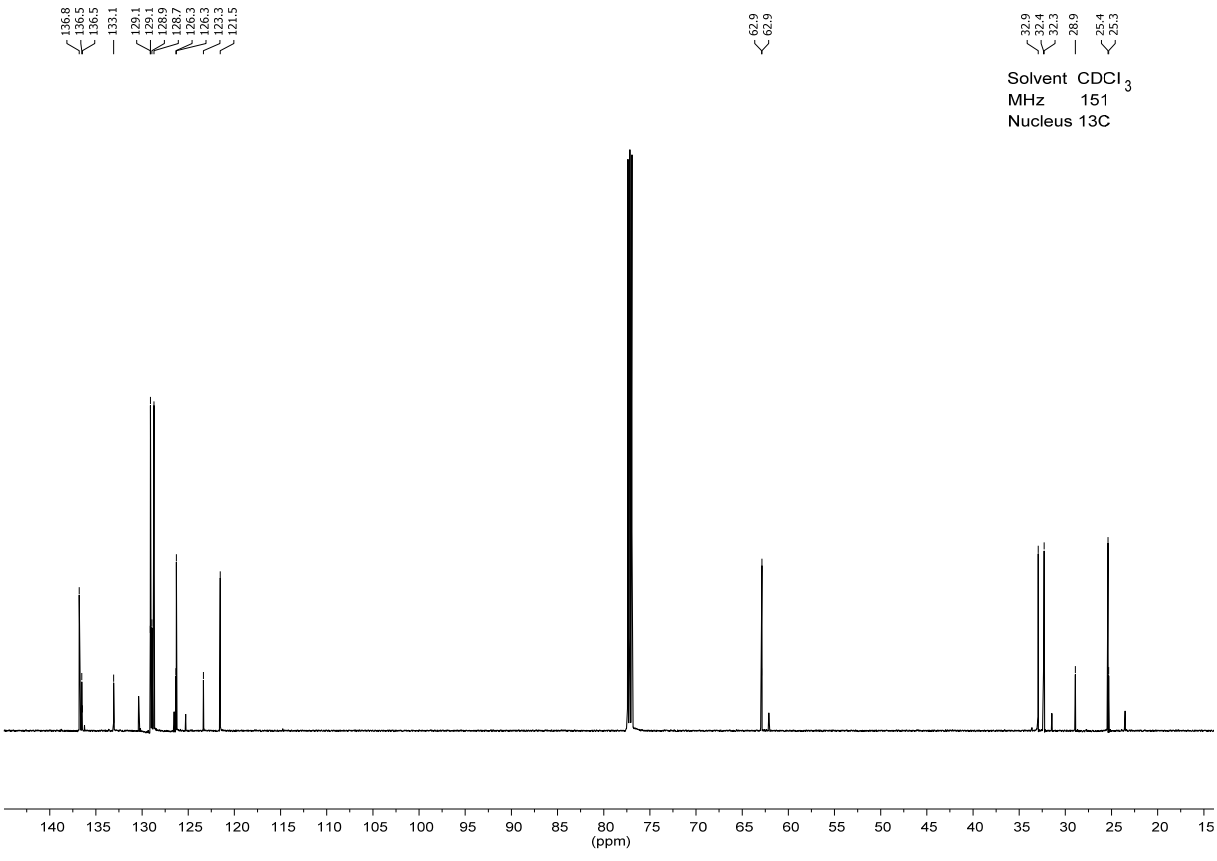





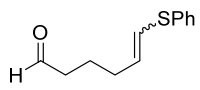

**S94**

Solvent CDCl 3
MHz 599
Nucleus 1H



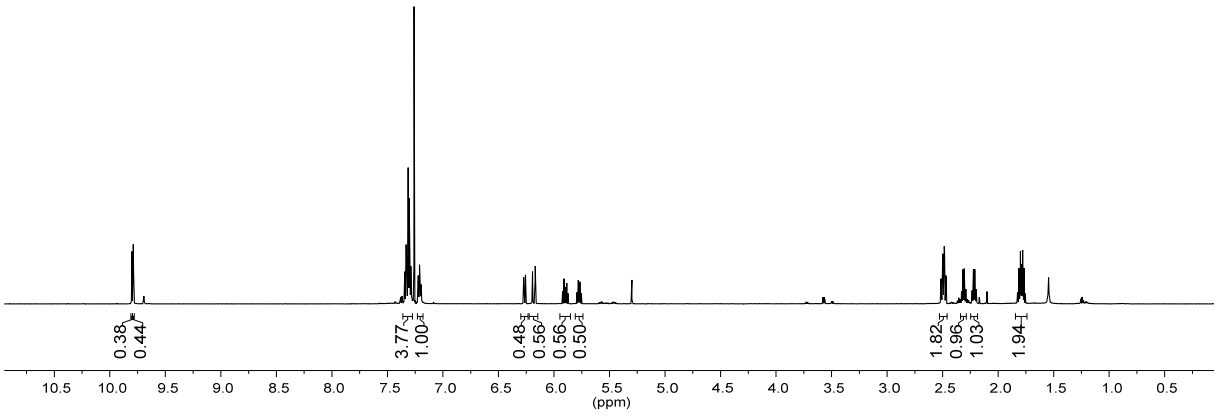



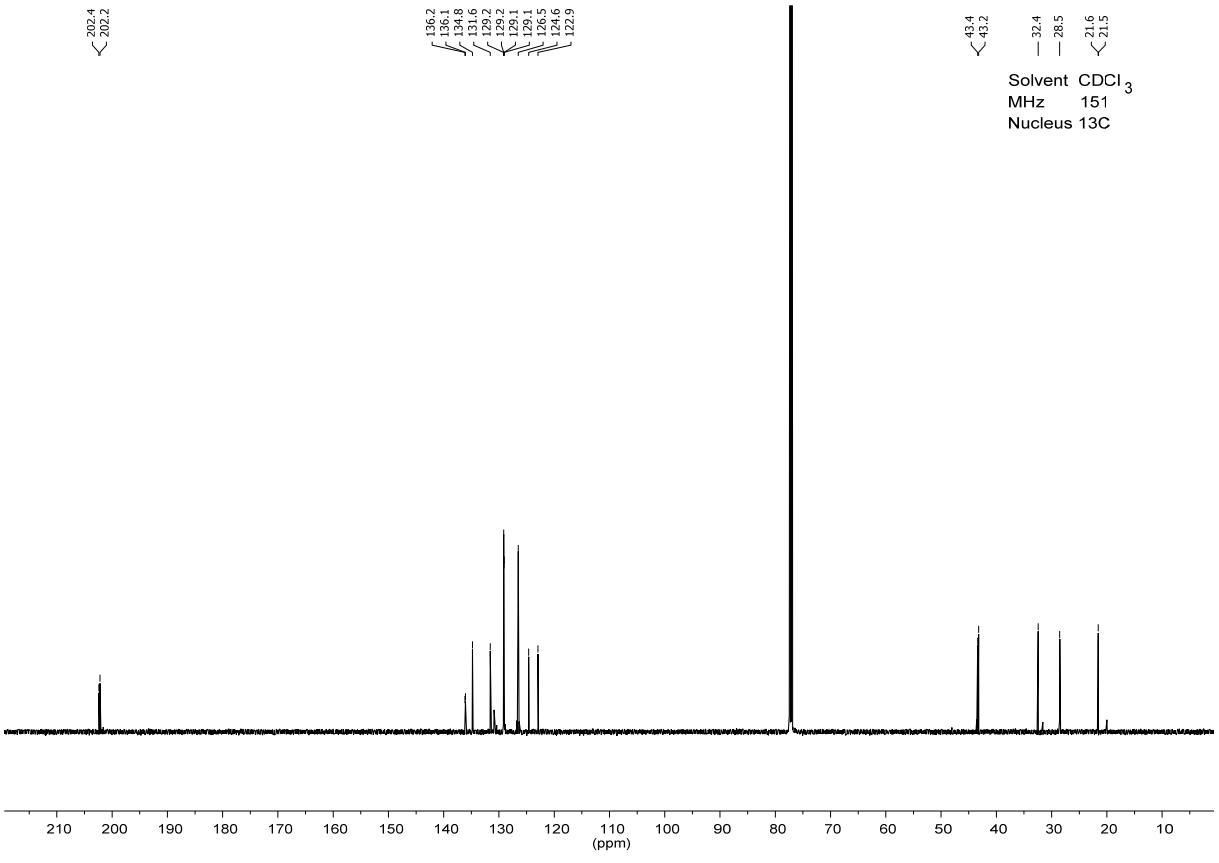

Solvent CDCl 3
MHz 151
Nucleus 13C

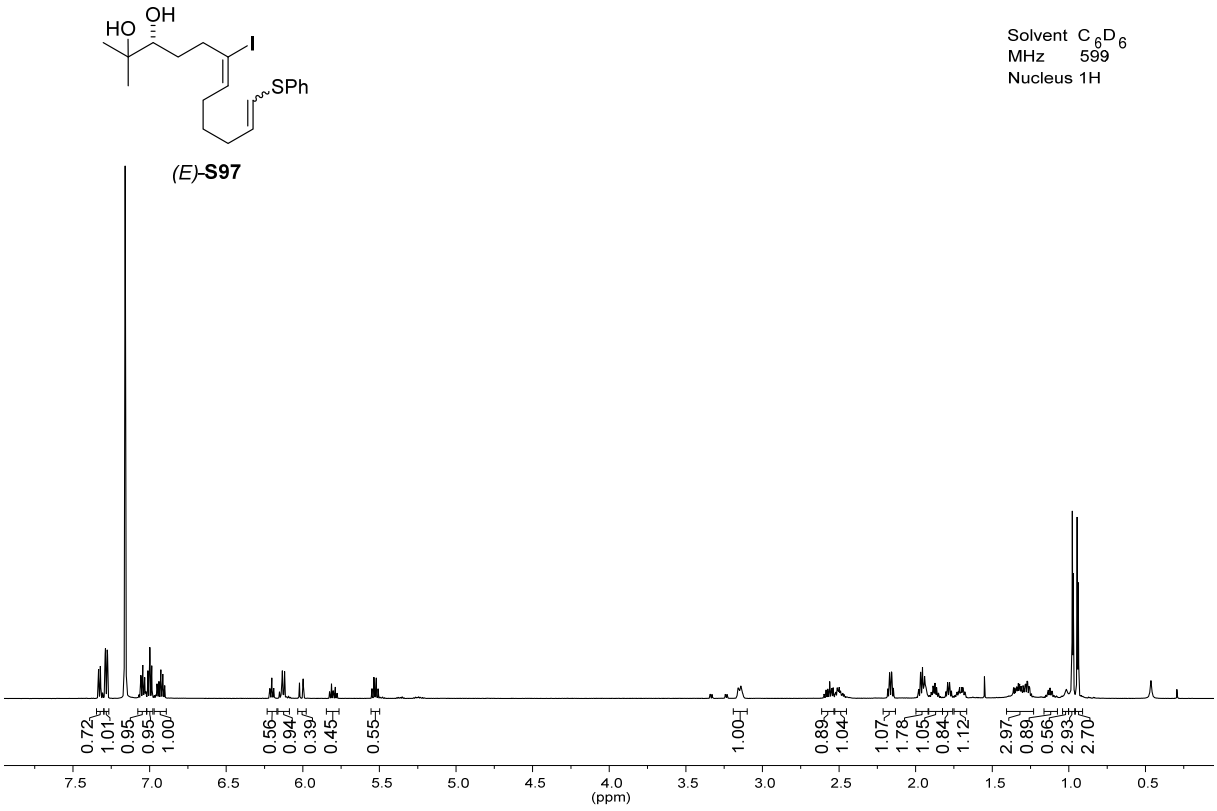



**S95**

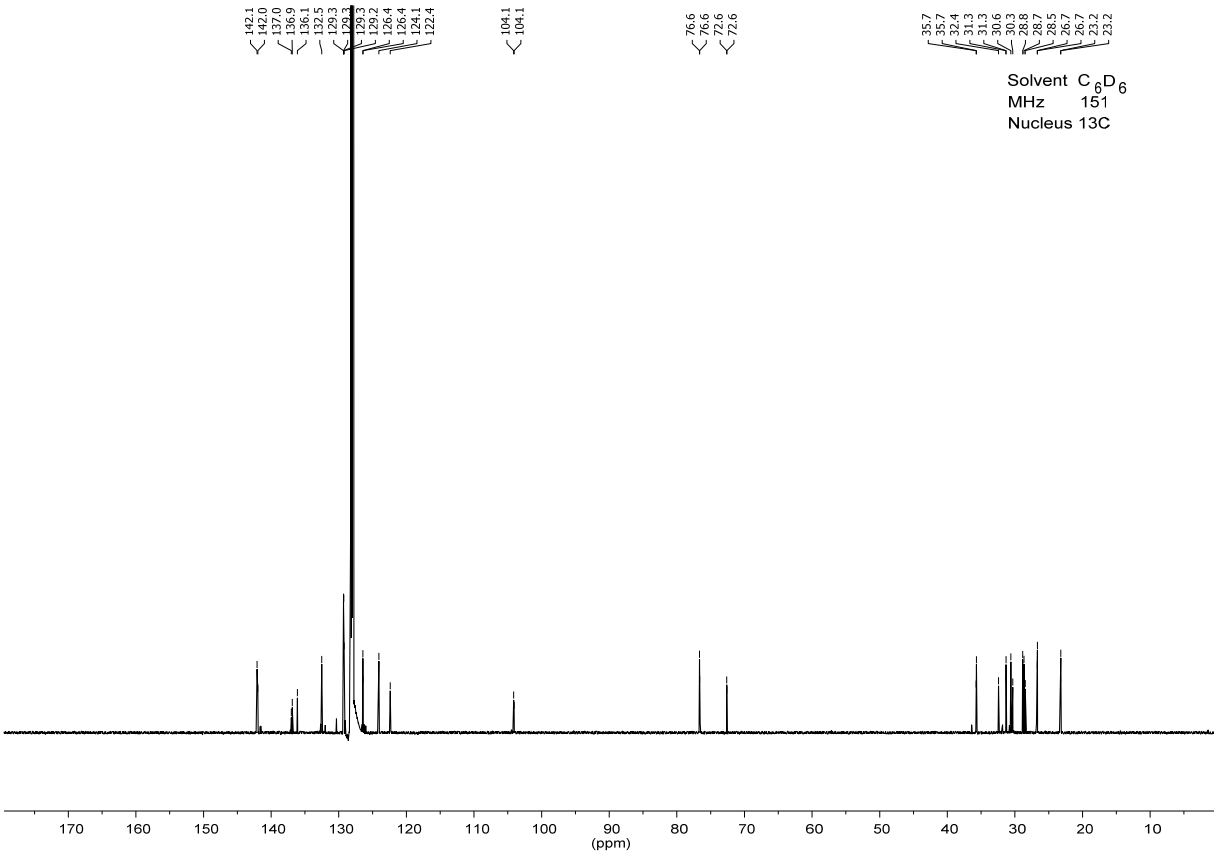
Solvent CDCl 3
MHz 599
Nucleus 1H

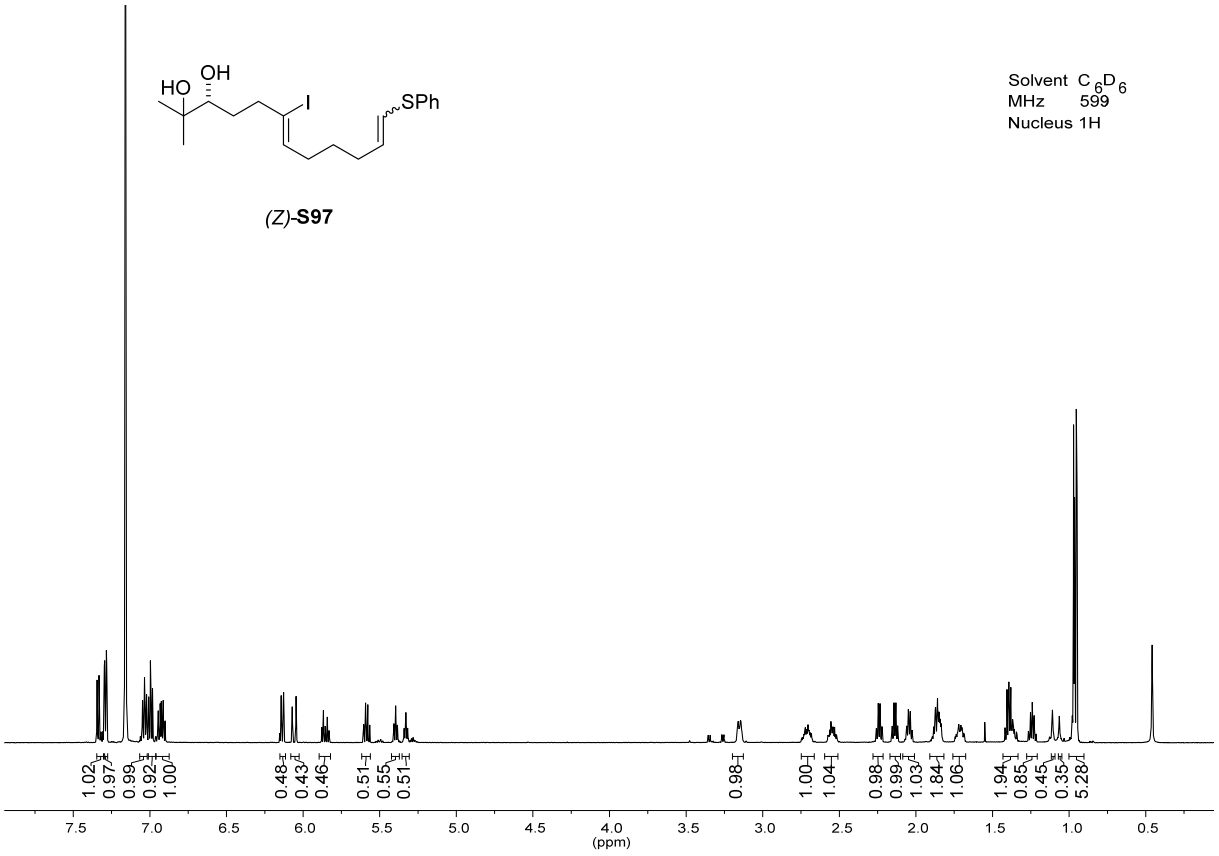


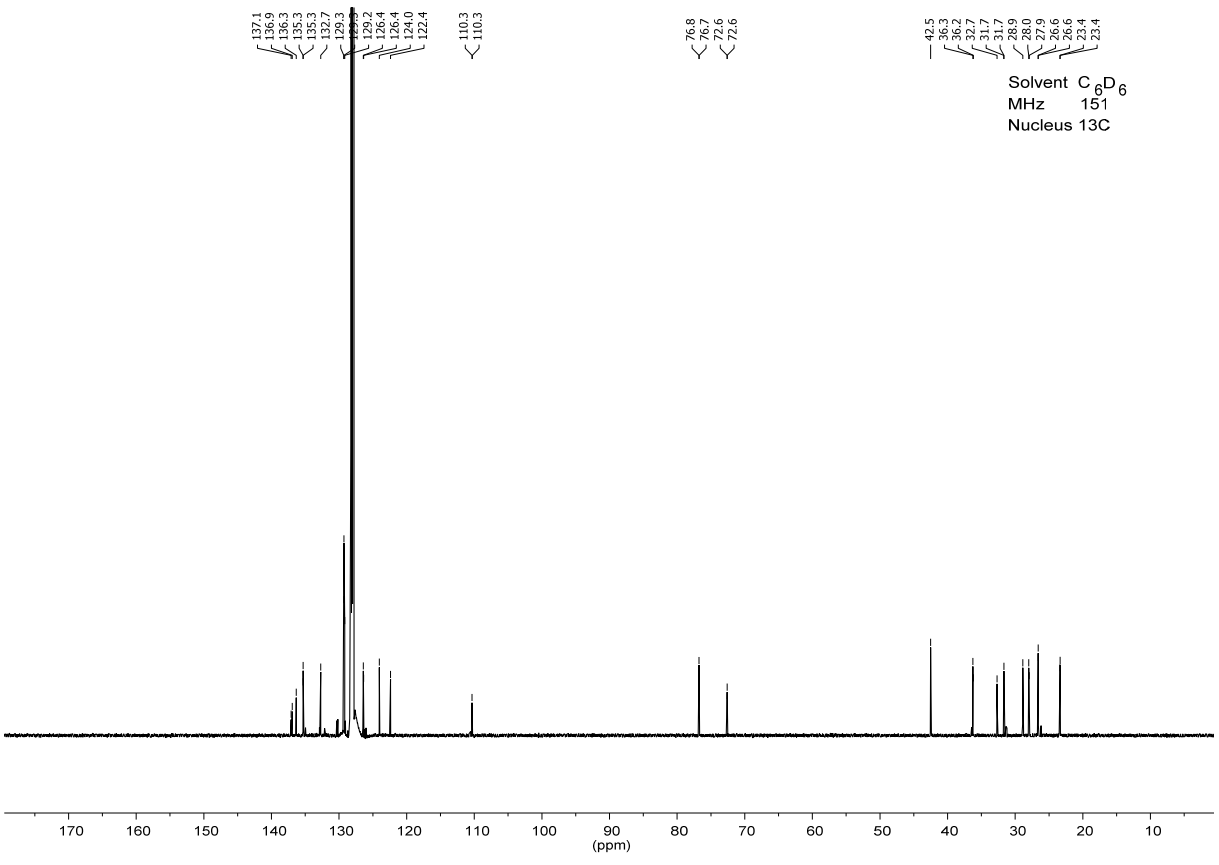

HO
OH
I
SPh
Solvent C6D6
MHz 599
Nucleus 1H
0.72
1.01
0.95
0.95
1.00
0.56
0.94
0.39
0.45
0.55
1.00
0.89
1.04
1.07
1.78
1.05
0.84
1.12
2.97
0.89
0.56
2.93
2.70
(ppm)

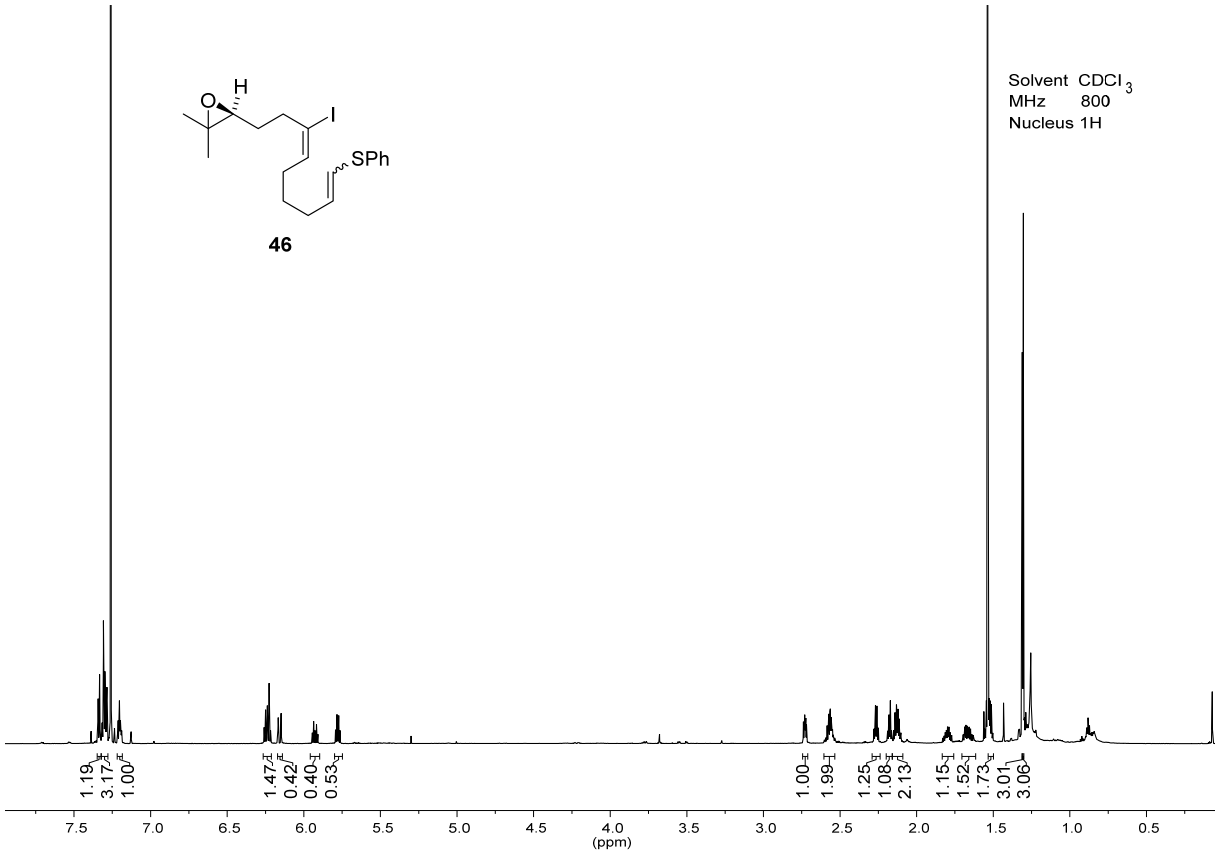
*(E)*-**S97**

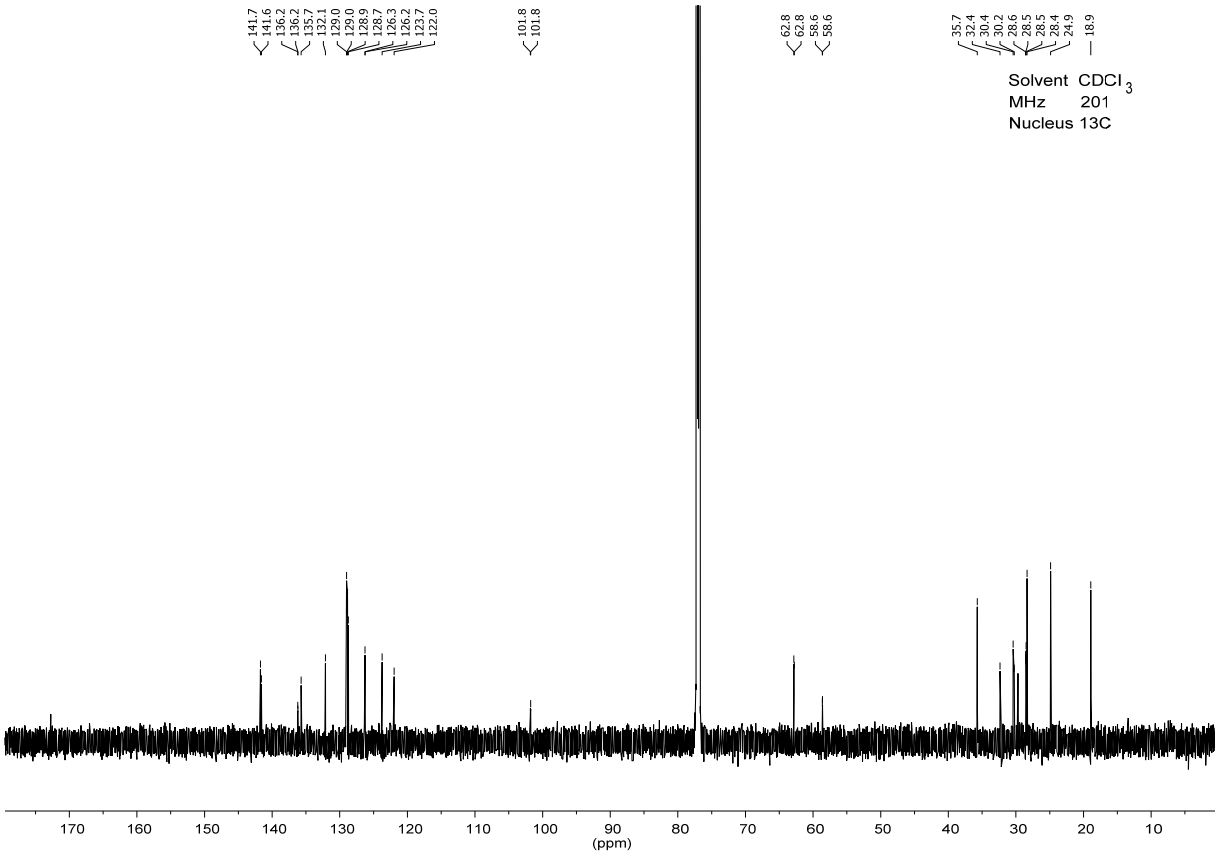

142.1
142.0
137.0
136.9
136.1
132.5
129.3
129.3
129.3
129.2
126.4
126.4
124.1
122.4
104.1
104.1
76.6
76.6
72.6
72.6
35.7
35.7
32.4
31.3
31.3
30.6
30.3
28.8
28.7
28.5
26.7
26.7
23.2
23.2
Solvent C6D6
MHz 151
Nucleus 13C
(ppm)

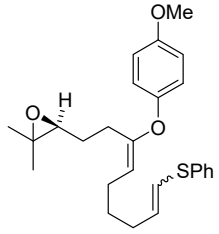

HO
OH
I
SPh
Solvent C6D6
MHz 599
Nucleus 1H
1.02
0.97
0.99
0.92
1.00
0.48
0.43
0.46
0.51
0.55
0.51
0.98
1.00
1.04
0.98
0.99
1.03
1.84
1.06
1.94
0.85
0.45
0.35
5.28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

*(Z)*-**S97**


137.1
136.9
136.3
135.3
135.3
132.7
129.3
129.2
126.4
126.4
124.0
122.4
110.3
110.3
76.8
76.7
72.6
72.6
42.5
36.3
36.2
32.7
31.7
31.7
28.9
28.0
27.9
26.6
26.6
23.4
23.4
Solvent C6D6
MHz 151
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

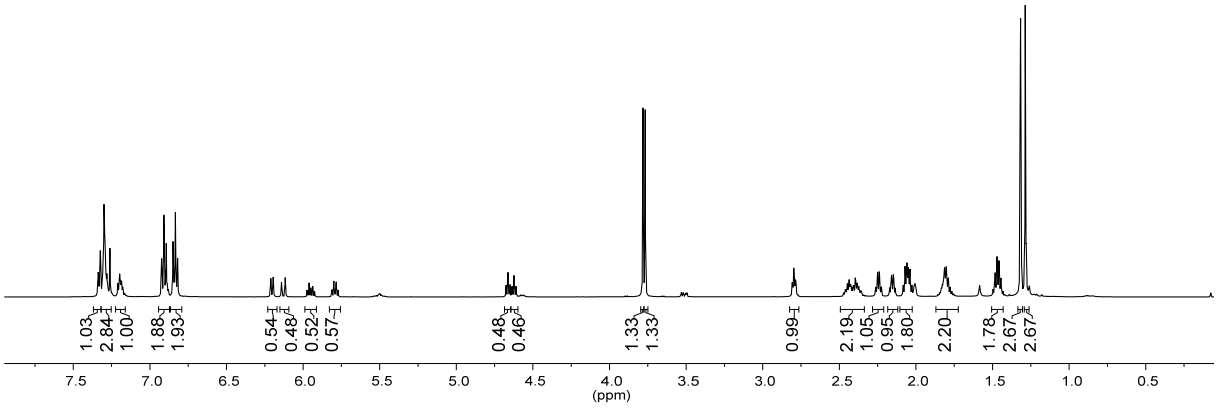

O
H
I
SPh
46
Solvent CDCl3
MHz 800
Nucleus 1H
1.19
3.17
1.00
1.47
0.42
0.40
0.53
1.00
1.99
1.25
1.08
2.13
1.15
1.52
1.73
3.01
3.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


141.7
141.6
136.2
136.2
135.7
132.1
129.0
129.0
128.9
128.7
126.3
126.2
123.7
122.0
101.8
101.8
62.8
62.8
58.6
58.6
35.7
32.4
30.4
30.2
28.6
28.5
28.5
28.4
24.9
18.9
Solvent CDCl3
MHz 201
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



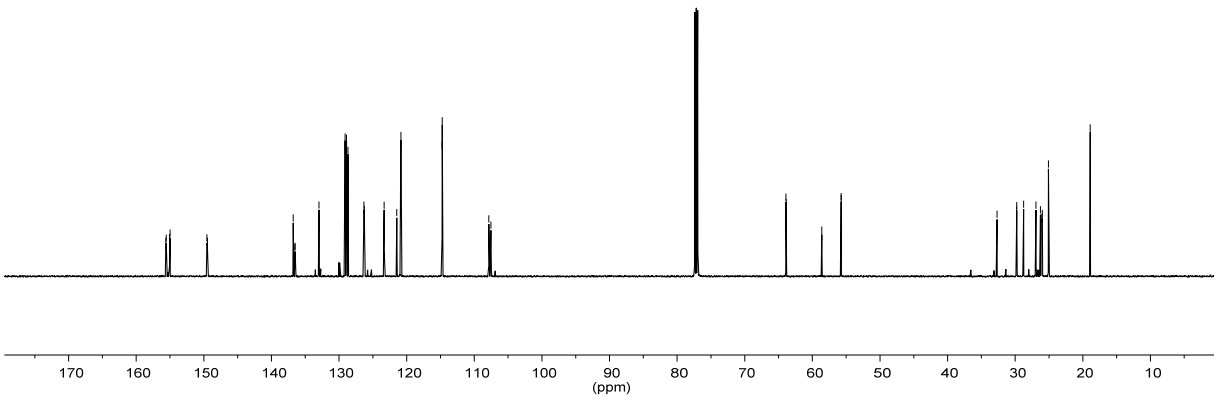

**47**

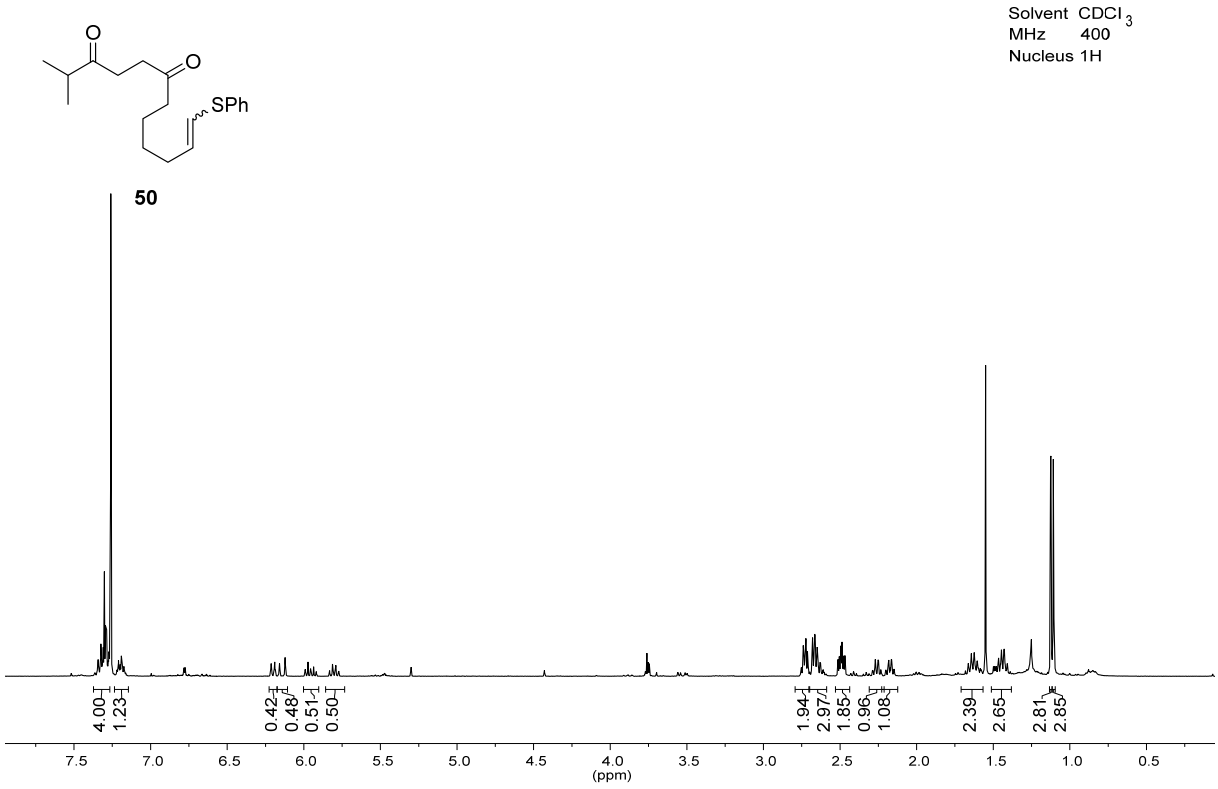
Solvent $CDCl_3$
MHz 599
Nucleus 1H



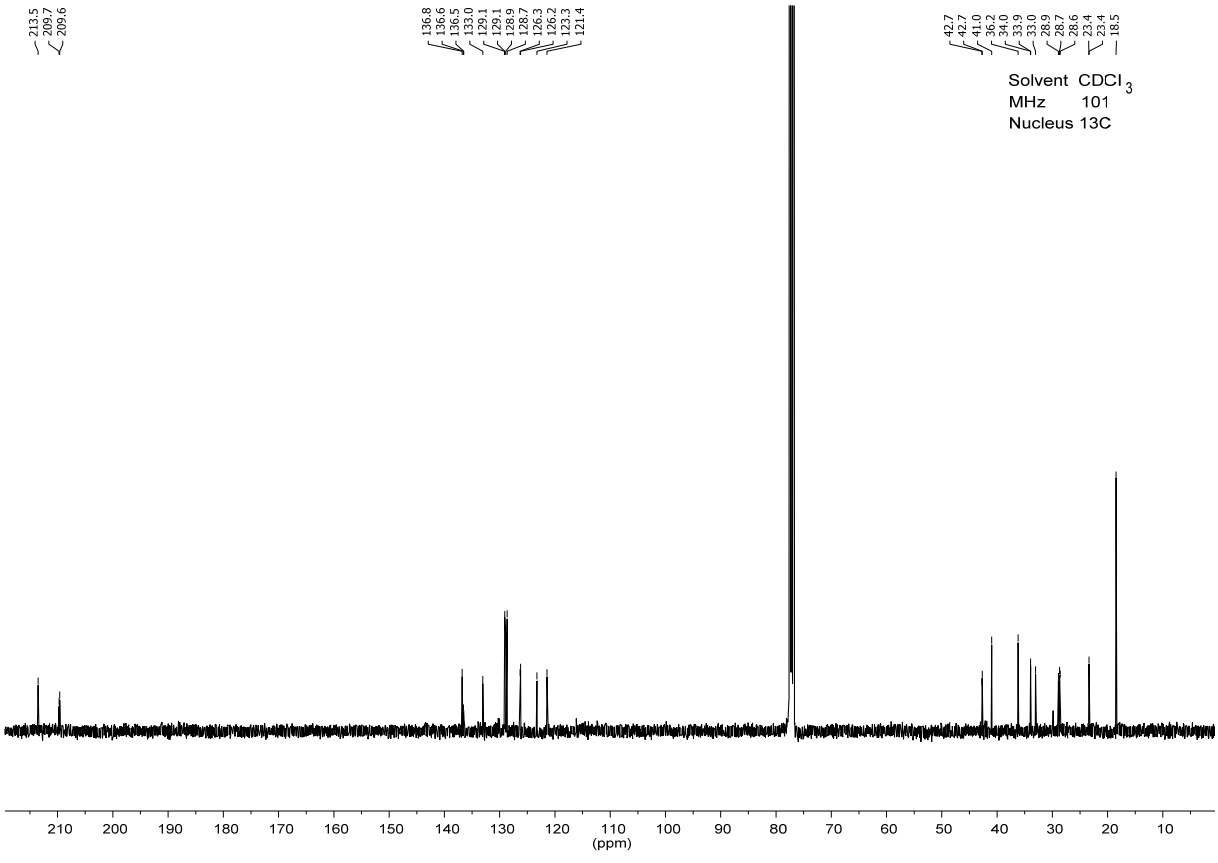


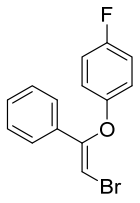
Solvent $CDCl_3$
MHz 151
Nucleus 13C




O
O
SPh
Solvent CDCl3
MHz 400
Nucleus 1H
4.00
1.23
0.42
0.48
0.51
0.50
1.94
2.97
1.85
0.96
1.08
2.39
2.65
2.81
2.85
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

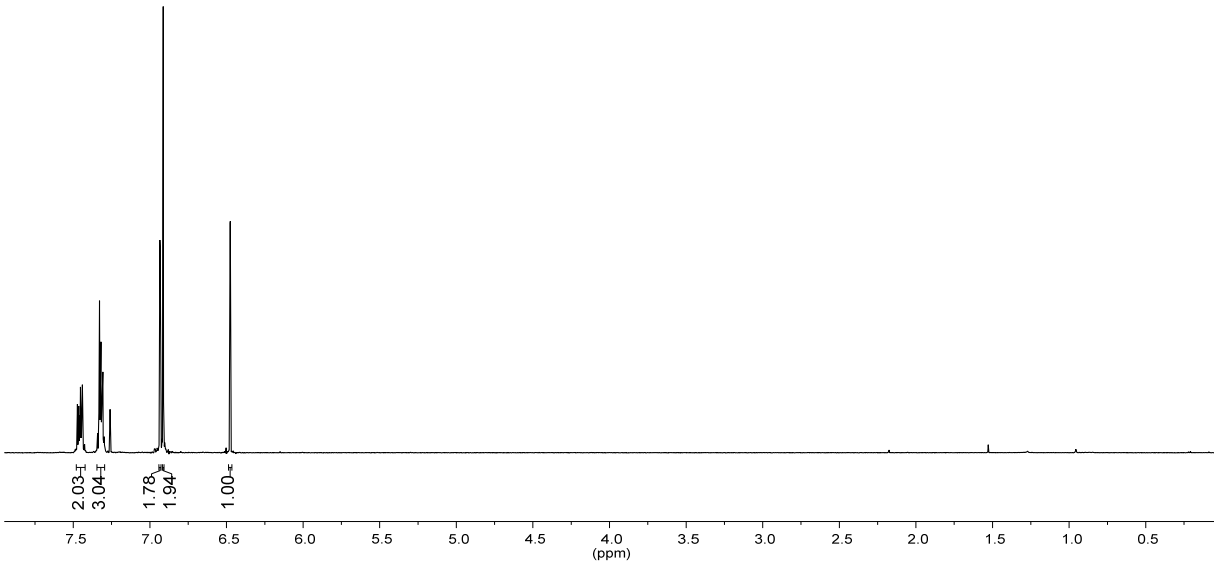
**50**


213.5
209.7
209.6
136.8
136.6
136.5
133.0
129.1
129.1
128.9
128.7
126.3
126.2
123.3
121.4
42.7
42.7
41.0
36.2
34.0
33.9
33.0
28.9
28.7
28.6
23.4
23.4
18.5
Solvent CDCl3
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



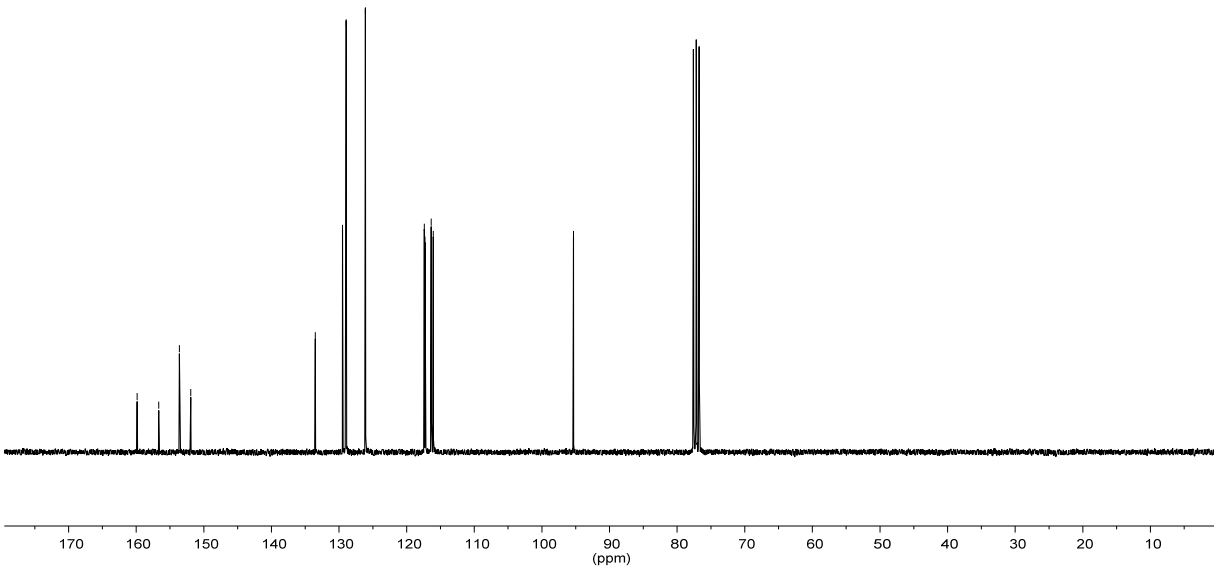

**S102**

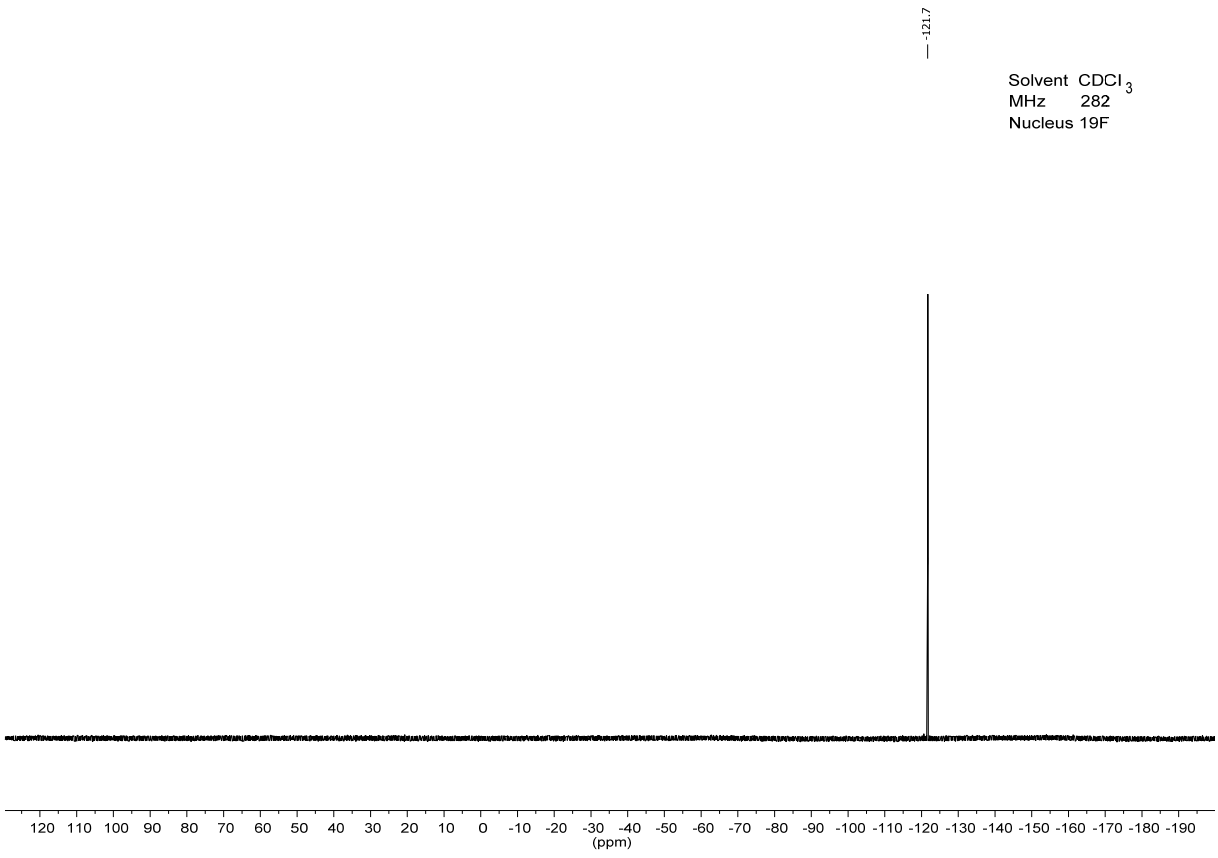
Solvent CDCl 3
MHz 300
Nucleus 1H

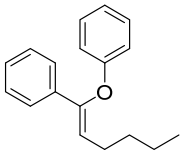



159.9
156.7
153.6
151.9
133.5
129.5
129.0
126.1
117.4
117.3
116.4
116.1
95.3

Solvent CDCl 3
MHz 75
Nucleus 13C

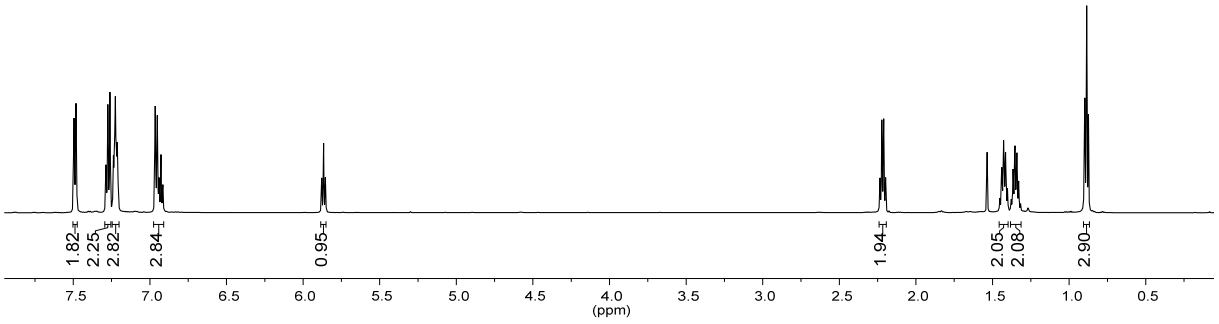


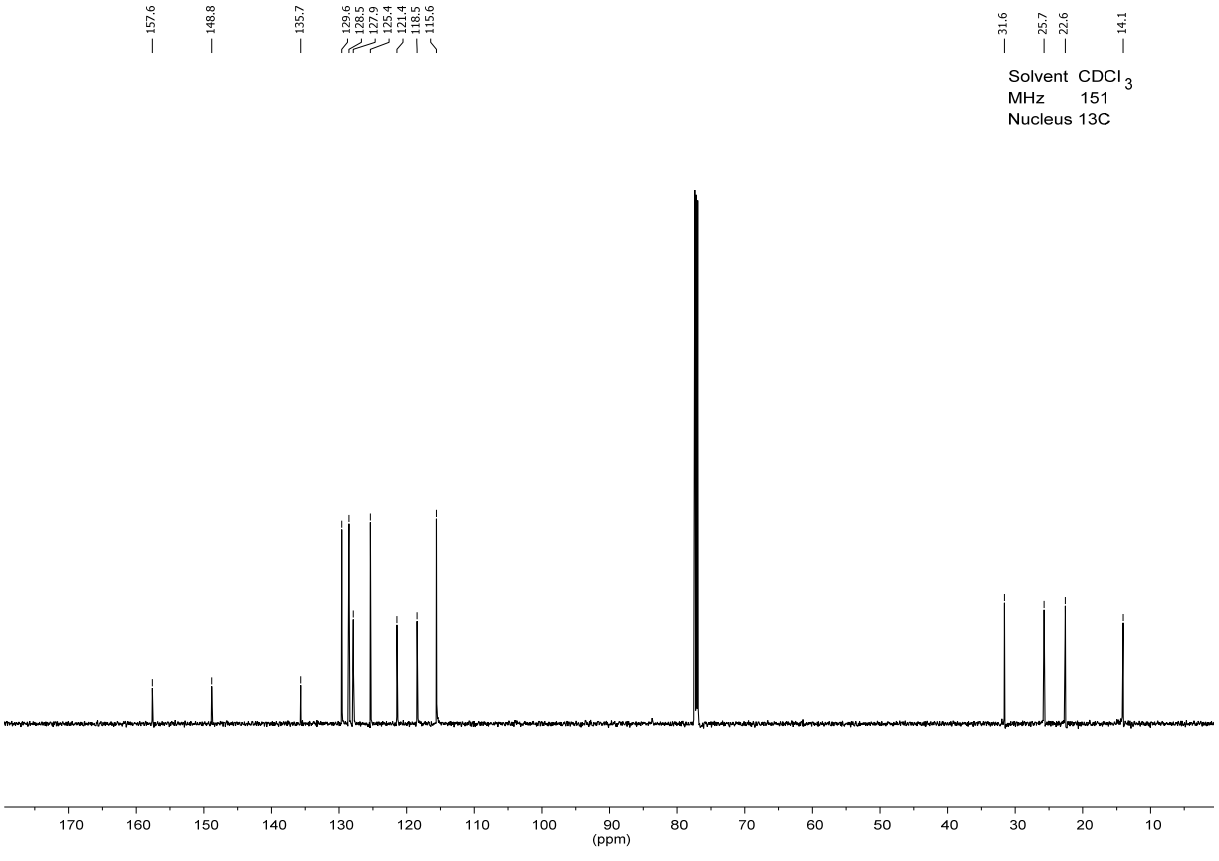

-121.7
Solvent CDCl3
MHz 282
Nucleus 19F
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
(ppm)

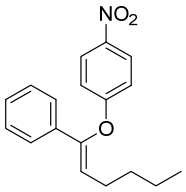


**S104**

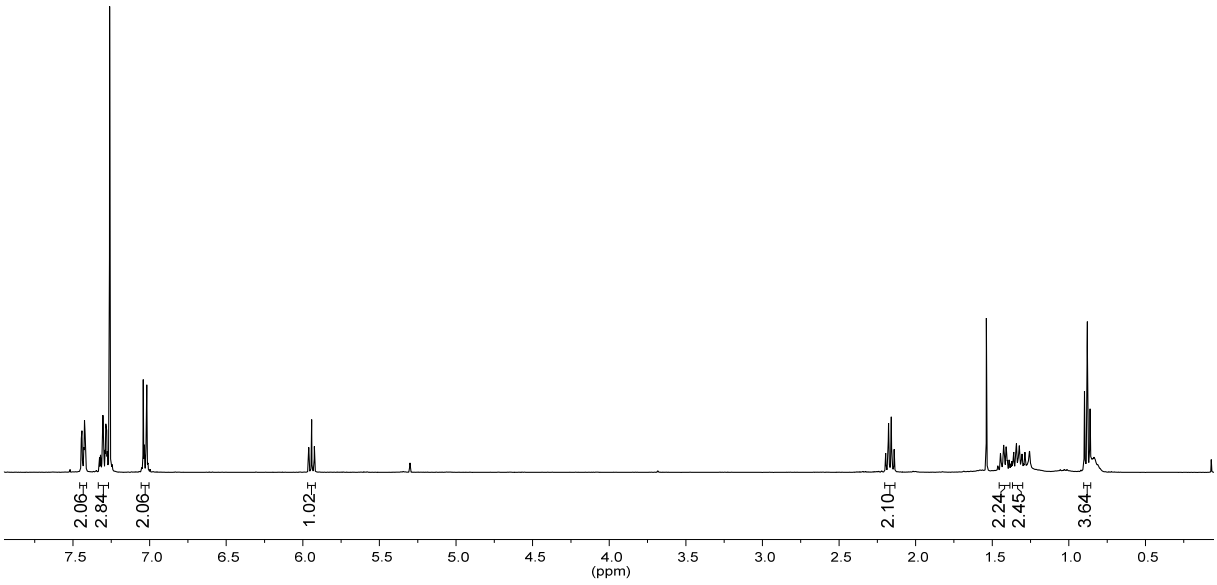
Solvent CDCl 3
MHz 599
Nucleus 1H

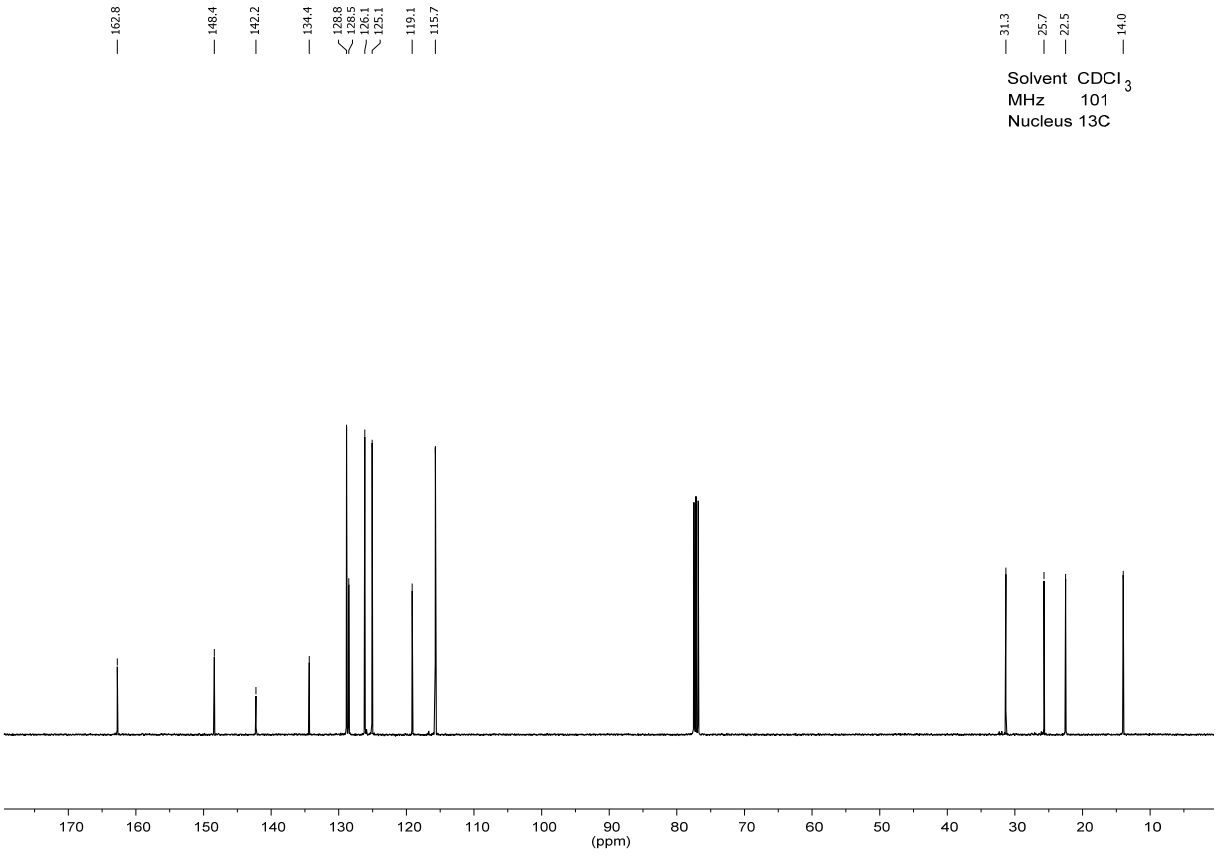


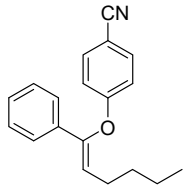




NO2
O

**S105**

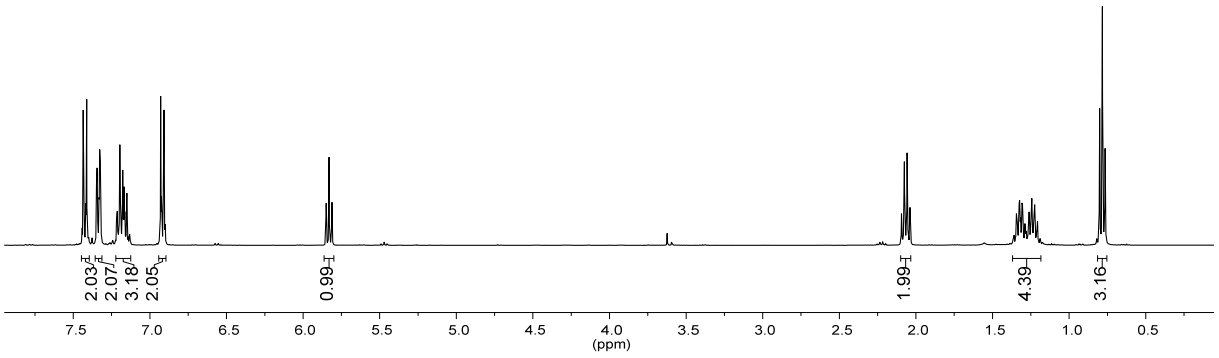

Solvent CDCl3
MHz 400
Nucleus 1H
2.06
2.84
2.06
1.02
2.10
2.24
2.45
3.64
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


162.8
148.4
142.2
134.4
128.8
128.5
126.1
125.1
119.1
115.7
31.3
25.7
22.5
14.0
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



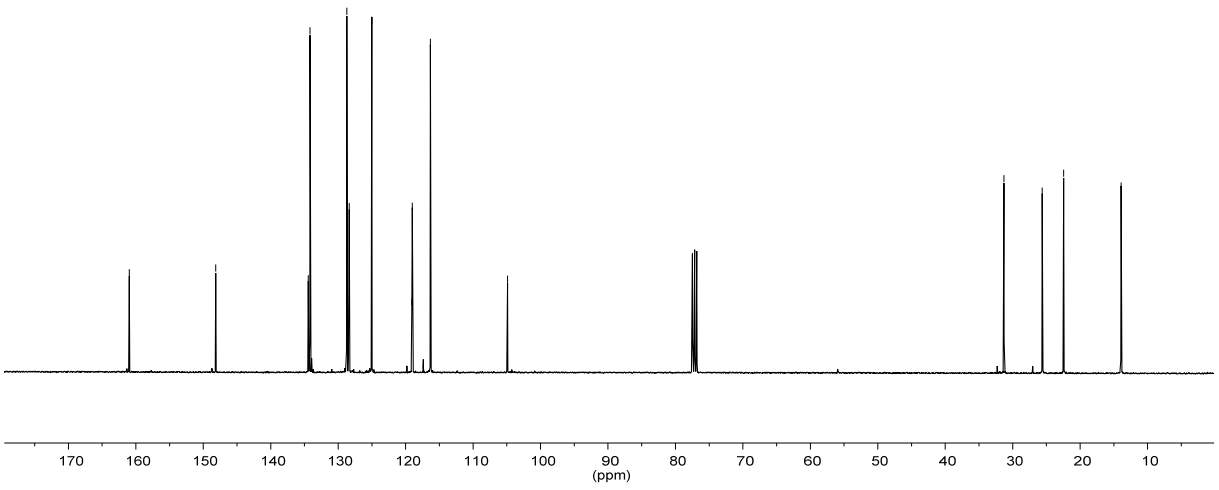

**S106**

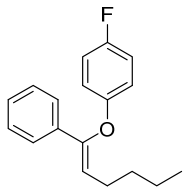
Solvent CDCl 3
MHz 400
Nucleus 1H





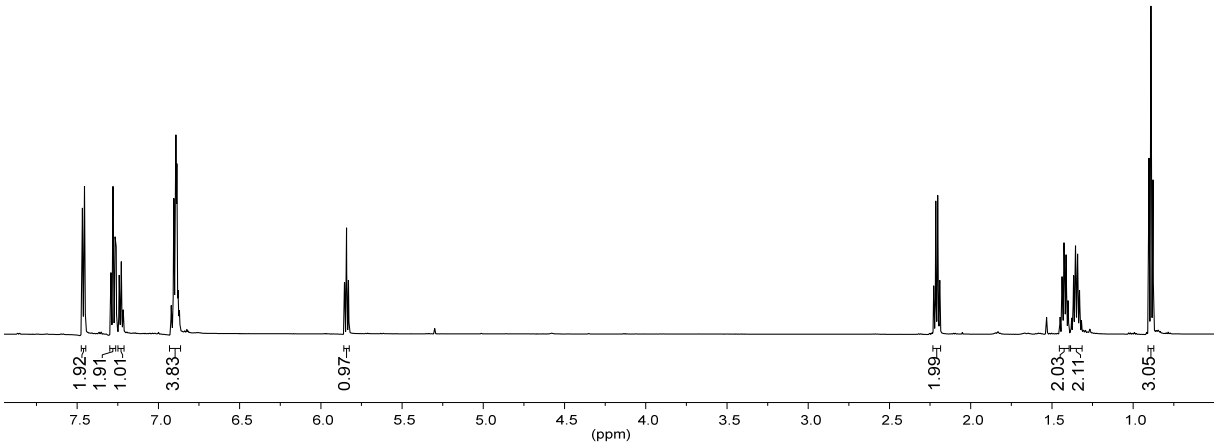
Solvent CDCl 3
MHz 101
Nucleus 13C



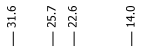



**S107**

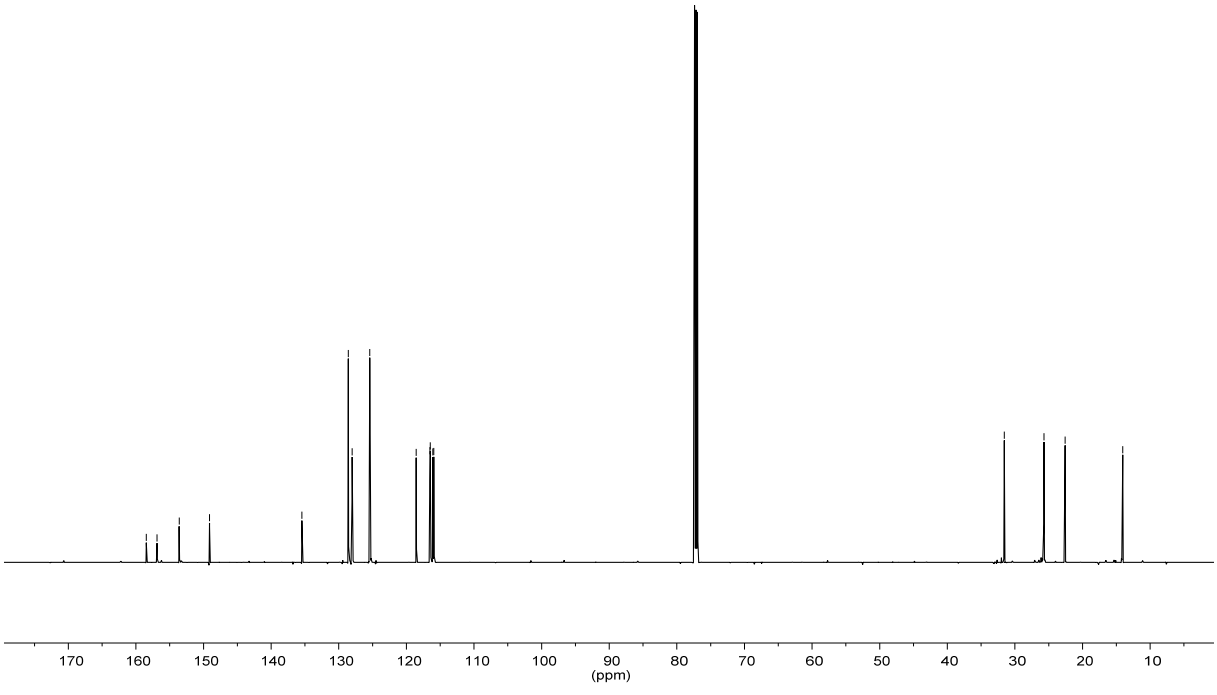
Solvent CDCl 3
MHz 599
Nucleus 1H

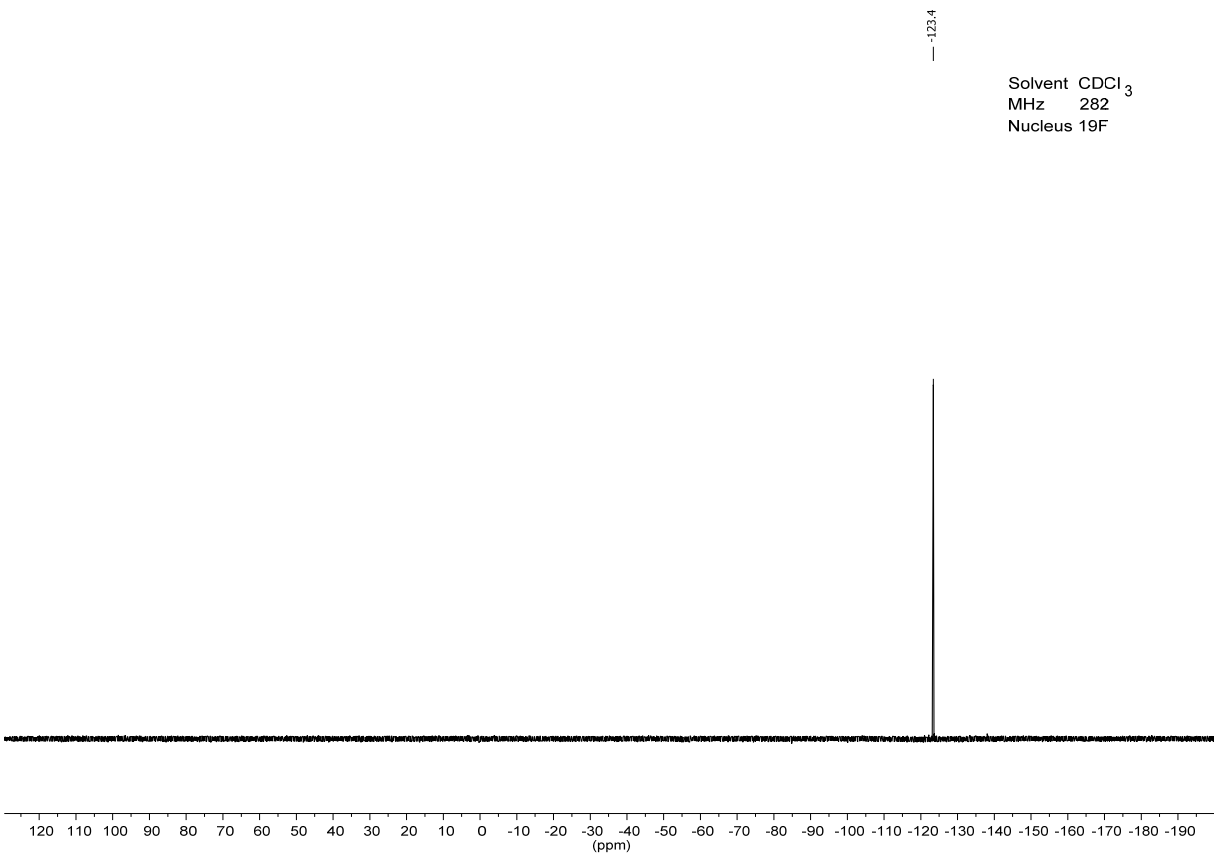


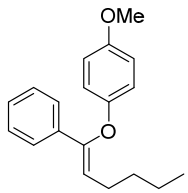





Solvent CDCl 3
MHz 151
Nucleus 13C

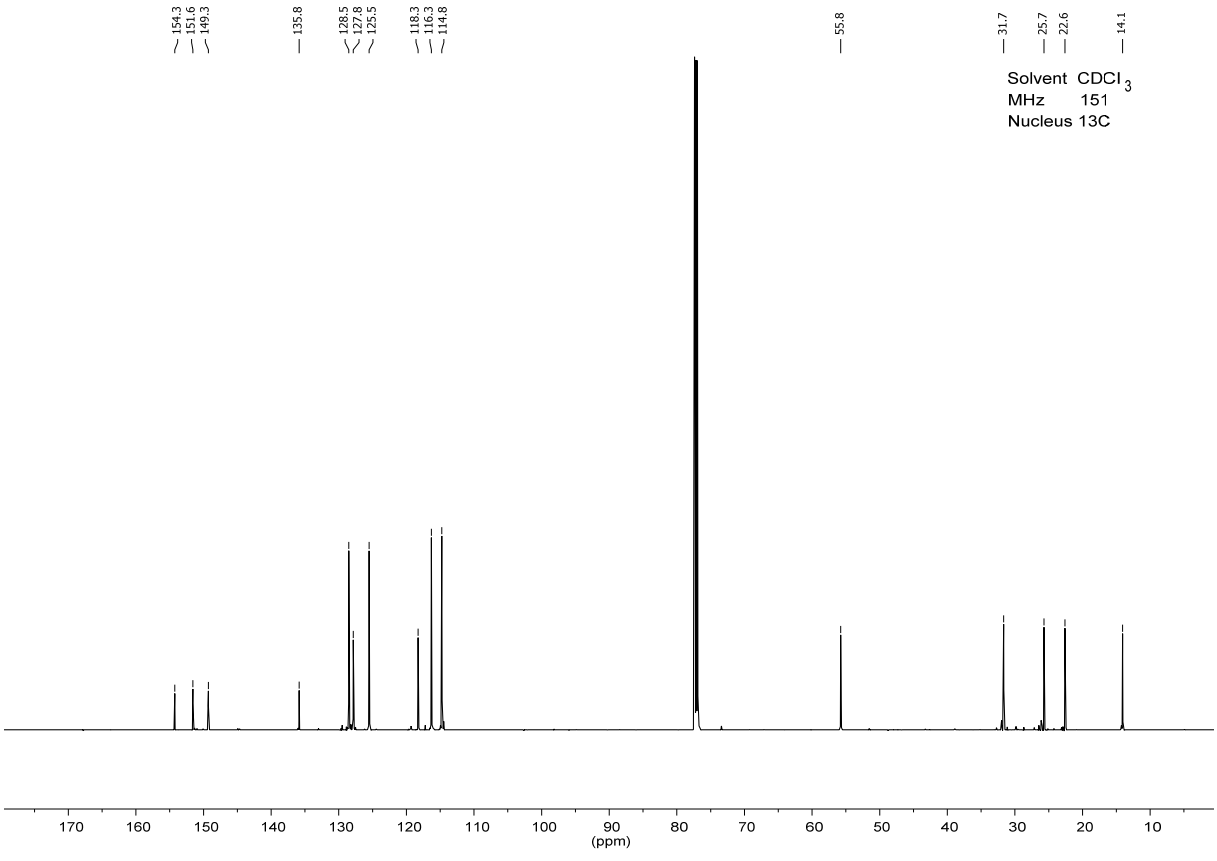



-123.4
Solvent CDCl3
MHz 282
Nucleus 19F
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
(ppm)


OMe
O

**S108**


Solvent CDCl3
MHz 599
Nucleus 1H
1.92
2.39
1.00
1.92
2.00
1.00
2.86
2.07
2.27
2.36
3.28
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


154.3
151.6
149.3
135.8
128.5
127.8
125.5
118.3
116.3
114.8
55.8
31.7
25.7
22.6
14.1
Solvent CDCl3
MHz 151
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

## 3.4. Supporting Information for Chapter 2.3.1.

# Sequential O–H/C–H Bond Insertion of Phenols Initiated by the Gold(I)-Catalyzed Cyclization of 1-Bromo-1,5-Enynes

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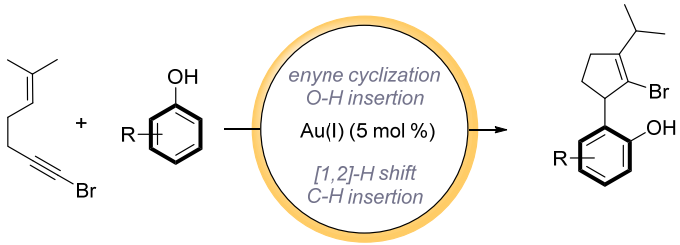
K. Speck, K. Karaghiosoff, T. Magauer, *Org. Lett.* **2015**, *17*, 1982–1985.



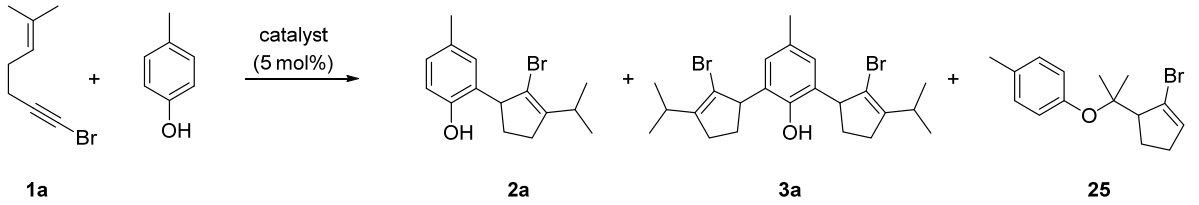


### 3.4.1. Optimization Studies

#### 3.4.1.1. Catalyst Screening:

To a solution of *p*-cresol (40.6 mg, 0.38 mmol, 1.50 equiv) and catalyst (Table 1, 5 mol %) in dichloromethane (1.0 mL) was added bromide **1a** (46.8 mg, 0.25 mmol, 1 equiv) at 23 °C. After complete consumption of bromide **1a** (judged by TLC analysis) the reaction mixture was filtered through a short plug of silica and the filtrate was concentrated. 1,3,5-trimethoxybenzene (2.00 mg, 11.9 μmol) was added and the yield for **2a** /**3a** was calculated from the $^{1}$H-NMR spectrum.

***Table 23: Catalyst screening.***

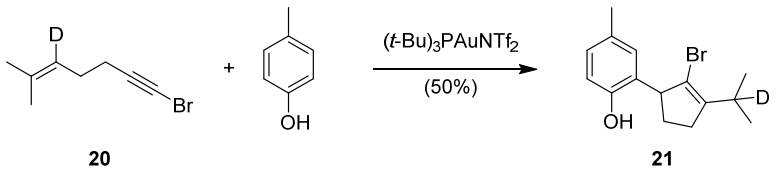



**1a** **2a** **3a** **25**

| Entry | Catalyst | Time [h] | Yield 2a / 3a [%] |
|---|---|---|---|
| 1 | $IPrAuNTf_2$ | 2.0 | 62 / 5 |
| 2 | $(t\text{-}Bu)_3PAuNTf_2$ | 2.0 | 66 / 4 |
| 3 | $Ph_3PAuNTf_2$ | 2.0 | 62 / 5 |
| 4 | $(PhO)_3PAuNTf_2$ | 1.5 | 62 / 5 |
| 5 | $(2,4\text{-}t\text{-}BuPhO)_3PAuNTf_2$ | 1.5 | 64 / 4 |
| 6 | $HNTf_2$ | 24 | 0 |
| 7 | AuCl | 3.0 | 7 of **25** |
| 8 | $AuCl_3$ | 3.0 | 11 of **25** |
| 9 | $PtCl_2$ | 3.0 | 0 |
| 10 | $InI_3/AgSbF_6$ –20 °C to 0 °C | 3.0 | 43 / 4 |
| 11 | $InI_3$ | 3.0 | 44 / 8 |
| 12 | $InI_3$/ $AgNTf_2$ | 3.5 | 47 / 9 |
| 13 | $(t\text{-}Bu)_3PAuCl$ | 5.0 | 0 |
| 14 | $(t\text{-}Bu)_3PAuBF_4$ | 5.0 | 11 of **25** |
| 15 | $(t\text{-}Bu)_3PAuSbF_6$ | 4.0 | 39 / 4 |
| 16 | $(t\text{-}Bu)_3PAuOTf$ | 0.5 | 65 |

### 3.4.2. Mechanistic Studies

#### 3.4.2.1. Deuterium Labeling




**20** **21**

**Phenol 21**

To a solution of *p*-cresol (17.2 mg, 0.16 mmol, 1.50 equiv) and $(t\text{-Bu})_3PAuNTf_2$ (3.61 mg, 5.32 µmol, 5 mol %) was added bromide **20** (20.0 mg, 0.11 mmol, 1 equiv) at 23 °C. After 3.5 h, the reaction mixture was filtered through a short plug of silica and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to afford phenol **21** (15.8 mg, 50%) as a pale yellow oil.

**TLC** (20% ethyl acetate in hexanes): $R_f = 0.37$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 300 MHz): δ = 6.93 (dd, *J* = 8.1 Hz, 2.2 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.80 (s, 1H), 4.27–4.11 (m, 1H), 2.61–2.30 (m, 3H), 2.27 (s, 3H), 2.01–1.81 (m, 1H), 1.10 (s, 3H), 1.06 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ = 151.7, 149.5, 130.2, 129.7, 129.0, 128.5, 117.0, 116.1, 51.7, 30.3, 29.3, 29.0 (t, *J* = 19.9 Hz), 20.8, 20.5, 20.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3446 (*br w*), 2960 (*s*), 2686 (*m*), 1611 (*w*), 1507 (*s*), 1461 (*m*), 1260 (*m*), 1192 (*m*), 1106 (*m*), 867 (*w*), 810 (*m*).

**HRMS** (EI) calc. for $C_{15}H_{18}D^{79}BrO$ $[M]^+$: 295.0682; found: 295.0680.

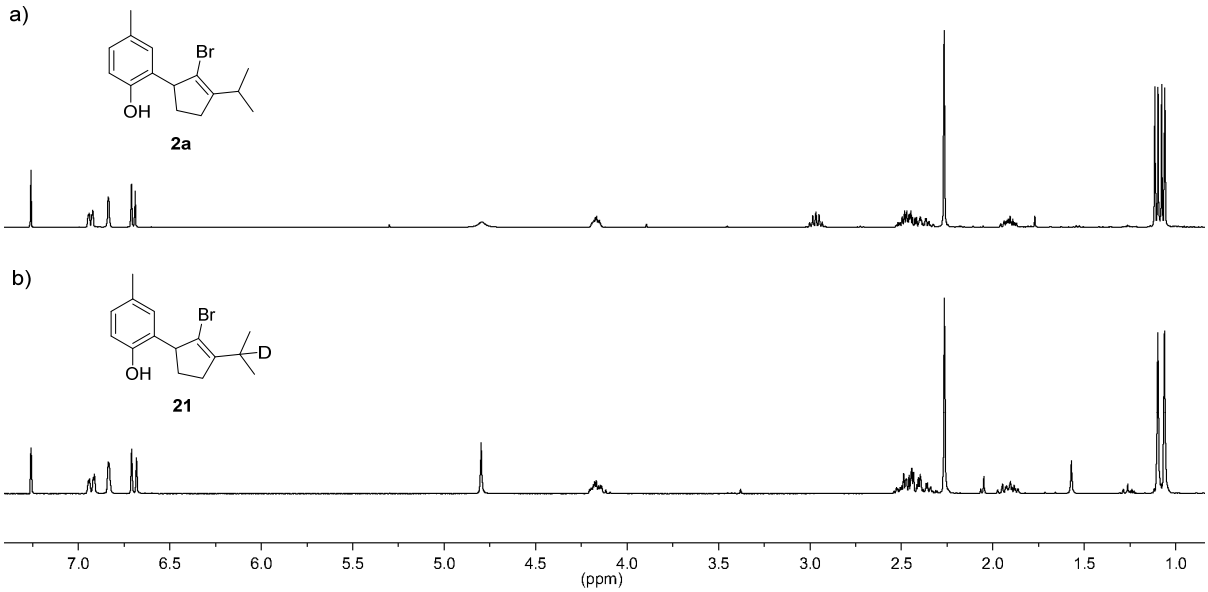
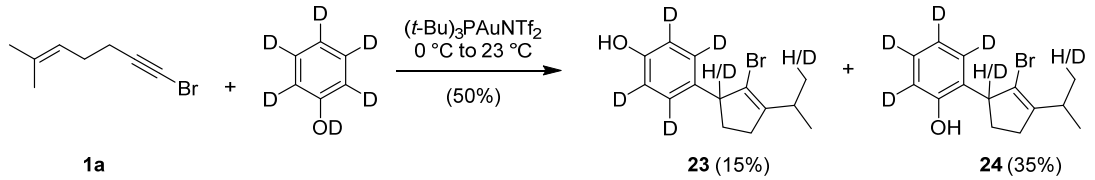



***Figure 15:*** *Comparison of $^1$H-NMR spectra of **2a** and **21** (400 MHz, $CDCl_3$).*




**1a** **23** (15%) **24** (35%)

**Phenols 23 and 24**

To a solution of phenol-$d_6$ (37.6 mg, 0.38 mmol, 1.50 equiv) and $(t\text{-Bu})_3PAuNTf_2$ (8.49 mg, 0.01 mmol, 5 mol %) was added bromide **1a** (46.8 mg, 0.25 mmol, 1 equiv) at 23 °C. After 3 h, the reaction mixture was filtered through a short plug of silica and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to furnish *ortho*-substituted **24** (24.9 mg, 35%) as a pale yellow oil. To obtain an analytical pure sample, **24** was further purified by preparative TLC (3% acetone in toluene). The fractions containing starting phenol and *para*-substituted **23** were further purified on silica gel (dichloromethane) to yield *para*-substituted **23** (11.1 mg, 15%) as a white solid.

**23:**

**TLC** (dichloromethane): $R_f = 0.30$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 4.84 (s, 1H), 3.89–3.80 (m, 0.5H; 0.5D), 2.91 (hept, $J$ = 6.9 Hz, 1H), 2.52–2.37 (m, 2H), 2.37–2.26 (m, 1H), 1.88–1.72 (m, 1H), 1.09 (d, $J$ = 6.9 Hz, 2.6H, 0.4D), 1.05 (d, $J$ = 6.9 Hz, 2.7H, 0.3D).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.8, 148.5, 148.5, 137.0, 136.9, 128.81 (t, $J$ = 23.3 Hz), 118.7, 118.6, 115.6, 115.3, 115.1, 56.3, 32.7, 32.5, 31.2, 29.7, 29.6, 29.4, 20.8, 20.7, 20.6, 20.5, 20.3 (t, $J$ = 19.6 Hz).

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3330 (*br w*), 2960 (*m*), 1643 (*w*), 1577 (*m*), 1434 (*s*), 1400 (*m*), 1310 (*m*), 1205 (*s*), 911 (*w*), 730 (*w*).

**HRMS** (EI) calc. for $C_{14}H_{13}D_4{}^{79}BrO$ $[M]^+$: 284.0714; found: 284.0698;
calc. for $C_{14}H_{12}D_5{}^{79}BrO$ $[M]^+$: 285.0777; found: 285.0757;
calc. for $C_{14}H_{11}D_6{}^{79}BrO$ $[M]^+$: 286.0839; found: 286.0848.

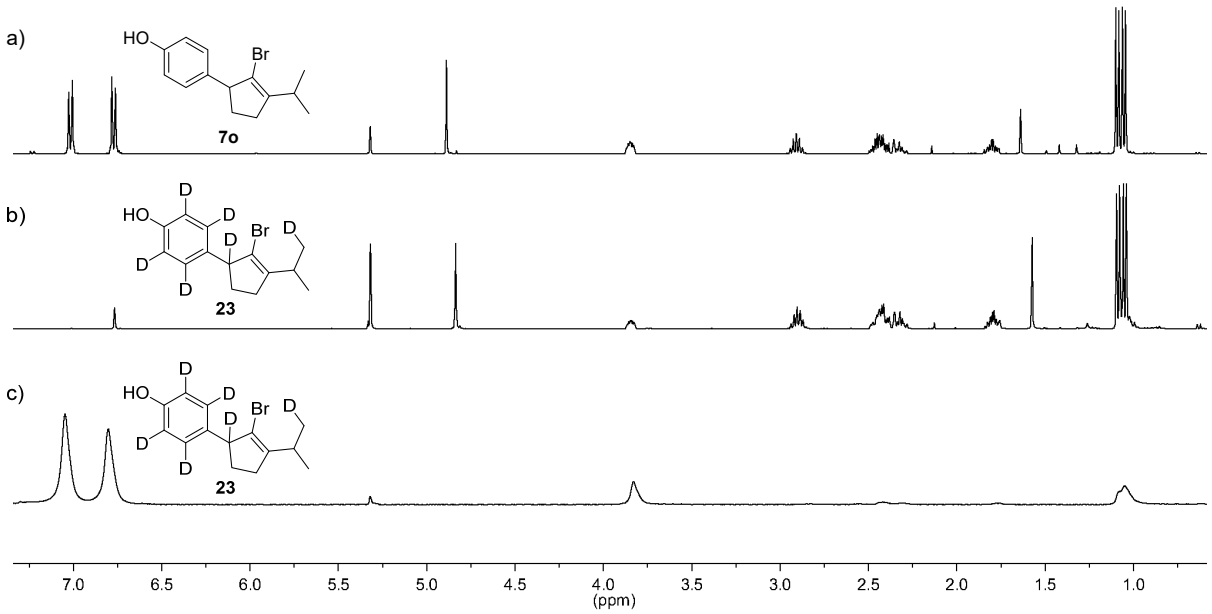



***Figure 16:*** *a) $^{1}$H-NMR spectrum of **7p** (400 MHz, $CD_2Cl_2$); b) $^{1}$H-NMR spectrum of **23** (400 MHz, $CD_2Cl_2$); c) $^{2}$H-NMR spectrum of **23** (400 MHz, $CH_2Cl_2$).*

**24:**

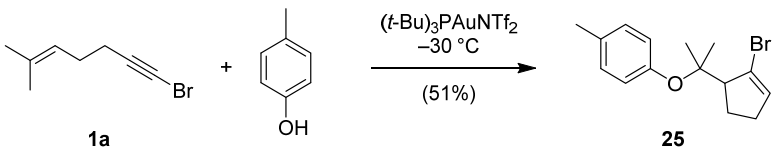
**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.49 (UV, $KMnO_4$).

**$^{1}$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 5.02 (s, 1H), 4.26–4.20 (m, 0.5H; 0.5D), 2.95 (hept, *J* = 6.9 Hz, 1H), 2.52–2.41 (m, 2H), 2.40–2.31 (m, 1H), 1.91–1.79 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 2.5H; 0.5D), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.2, 150.0, 129.9, 121.1, 121.1, 120.8, 120.6, 117.0, 117.0, 116.1, 115.9, 115.6, 51.2, 30.9, 30.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 20.7, 20.7, 20.5, 20.4.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3422 (*br w*), 2960 (*vs*), 1644 (*w*), 1568 (*m*), 1457 (*m*), 1382 (*m*), 1234 (*m*), 1172 (*s*), 910 (*w*), 857 (*w*).

**HRMS** (EI) calc. for $C_{14}H_{13}D_4{}^{79}BrO$ $[M]^+$: 284.0714; found: 284.0695;
calc. for $C_{14}H_{12}D_5{}^{79}BrO$ $[M]^+$: 285.0777; found: 285.0753;
calc. for $C_{14}H_{11}D_6{}^{79}BrO$ $[M]^+$: 286.0839; found: 286.0698.




**Ether 25**

To a solution of *p*-cresol (170 mg, 1.57 mmol, 1.05 equiv) and and $(t\text{-Bu})_3PAuNTf_2$ (51.0 mg, 0.08 mmol, 5 mol %) was added bromide **1a** (281 mg, 1.50 mmol, 1 equiv) at –30 °C. After 2 h, the

reaction mixture was filtered through a short plug of silica and the filtrate was concentrated. The residue was purified via column chromatography on silica gel (5% ethyl acetate in pentane) to yield ether **25** (223 mg, 51%) as a pale yellow oil.

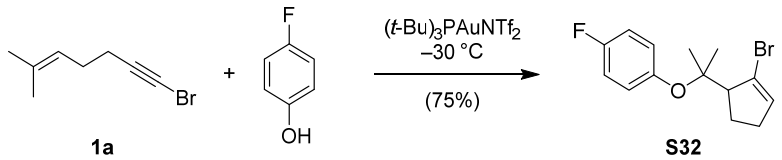
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.58 (UV, $KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 7.06 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.14–6.06 (m, 1H), 3.18–3.06 (m, 1H), 2.40–2.10 (m, 7H), 1.34 (s, 3H), 1.25 (s, 3H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ = 153.0, 136.5, 133.4, 129.9, 124.6, 122.1, 83.0, 59.0, 31.5, 27.4, 25.3, 24.0, 21.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2978 (*w*), 2934 (*w*), 1611 (*w*), 1506 (*vs*), 1461 (*w*), 1368 (*w*), 1224 (*s*), 1267 (*m*), 946 (*w*), 829 (*w*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO$ $[M]^+$: 294.0619; found: 294.0621.




**Ether S32**

To a solution of *p*-flurophenol (88.3 mg, 0.79 mmol, 1.05 equiv) and $(t\text{-Bu})_3PAuNTf_2$ (51.0 mg, 0.08 mmol, 5 mol %) in dichloromethane (13 mL) was added bromide **1a** (140 mg, 0.75 mmol, 1 equiv) at –30 °C. After 4 h, saturated aqueous sodium bicarbonate solution (25 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified via column chromatography on silica gel (10% ethyl acetate in hexanes) to yield ether **S32** (168 mg, 75%) as a pale yellow oil.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.60 (UV, $KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 7.04–6.92 (m, 4H), 6.15–6.09 (m, 1H), 3.17–3.02 (m, 1H), 2.40–2.23 (m, 2H), 2.23–2.10 (m, 2H), 1.33 (s, 3H), 1.25 (s, 3H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ = 159.6 (d, *J* = 240.6 Hz), 151.3 (d, *J* = 2.6 Hz), 136.6, 126.2 (d, *J* = 8.3 Hz), 122.0, 115.8 (d, *J* = 22.8 Hz), 83.5, 58.9, 31.5, 27.4, 25.0, 24.0.

**$^{19}$F NMR** ($CD_2Cl_2$, 376 MHz): δ = –121.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2979 (*w*), 2937 (*w*), 1613 (*w*), 1500 (*vs*), 1367 (*w*), 1204 (*s*), 1125 (*m*), 889 (*w*), 856 (*m*), 801 (*w*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrFO$ $[M]^+$: 298.0369; found: 298.0362.

### 3.4.2.2. NMR Studies

a) Low Temperature $^1$H NMR studies

To a solution of bromide **1a** (13.1 mg, 0.07 mmol, 1 equiv) and *p*-cresol (11.4 mg, 0.11 mmol, 1.5 equiv) in dichloromethane-$D_2$ (0.7 mL) in an NMR-tube was added (*t*-Bu)$_3$PAuNTf$_2$ (2.38 mg, 3.50 µmol, 5 mol %) at –35 °C. After complete conversion to **25** (1.5 h), the reaction mixture was allowed to warm to 25 °C. An $^1$H-NMR spectrum was measured at the indicated times. After completion of the reaction 1,3,5-trimethoxybenzene (1.00 mg, 5.95 µmol) was added and the yield was calculated from the $^1$H-NMR spectrum.

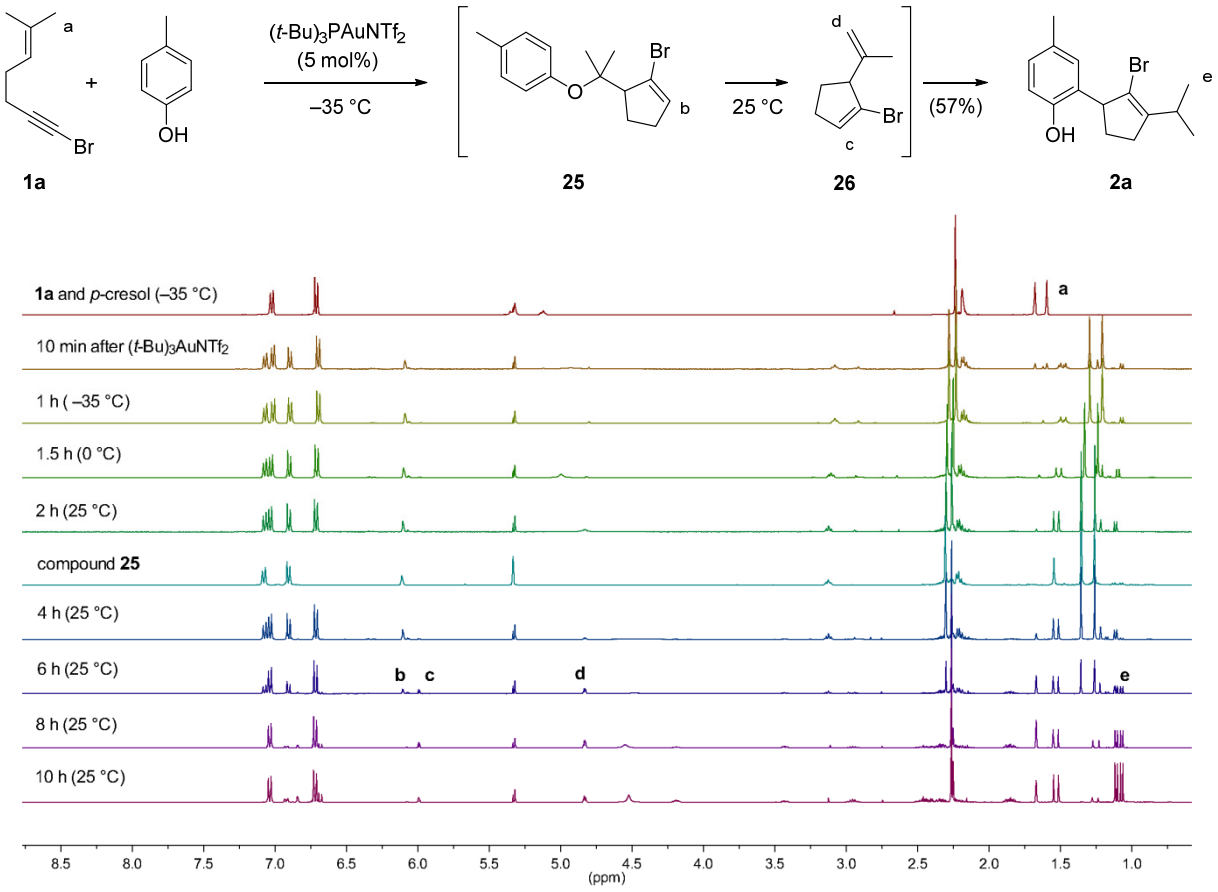



***Figure 17:*** *Selective synthesis of ether **25** at –35 °C and its conversion to **2a** via the intermediacy of **26** ($^1$H NMR, $CD_2Cl_2$, 400 MHz).*

b) Conversion of **25** to **1a**

To a solution of (*t*-Bu)$_3$PAuNTf$_2$ (2.30 mg, 3.50 µmol, 5 mol %) in dichloromethane-$D_2$ (0.5 mL) in an NMR-tube was added a solution of ether **25** (20.0 mg, 0.07 mmol, 1 equiv) in dichloromethane-$D_2$ (0.2 mL) at 23 °C. An $^1$H-NMR spectrum was measured at the indicated times. After completion of the reaction 1,3,5-trimethoxybenzene (1.00 mg, 5.95 µmol) was added and the yield was calculated from the $^1$H-NMR spectrum.

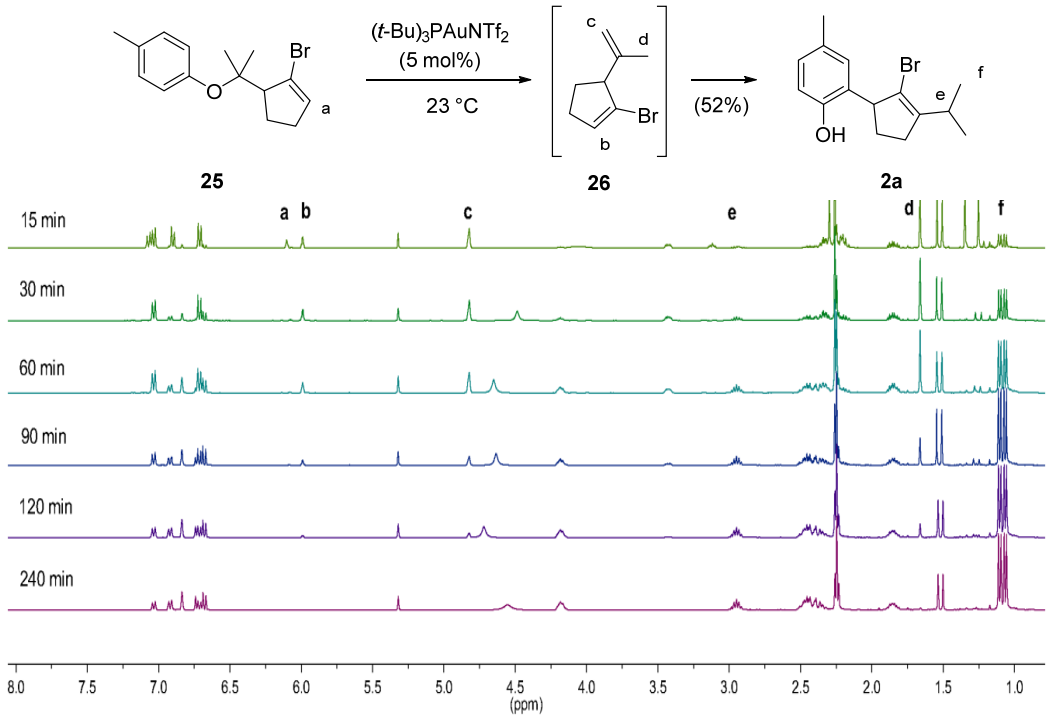



***Figure 18:*** *Monitoring the conversion of ether **25** to **2a** via the intermediacy of **26** ($^1$H NMR, $CD_2Cl_2$, 400 MHz).*

c) $^{31}$P NMR studies

To a solution of bromide **1a** (13.1 mg, 0.07 mmol, 1 equiv) and *p*-cresol (11.4 mg, 0.11 mmol, 1.5 equiv) in dichloromethane-$D_2$ (0.7 mL) in an NMR-tube was added (*t*-Bu)$_3$PAuNTf$_2$ (2.38 mg, 3.50 µmol, 5 mol %) at –50 °C. After complete conversion to ether **25** (3.5 h) the reaction mixture was allowed to warm to 25 °C.

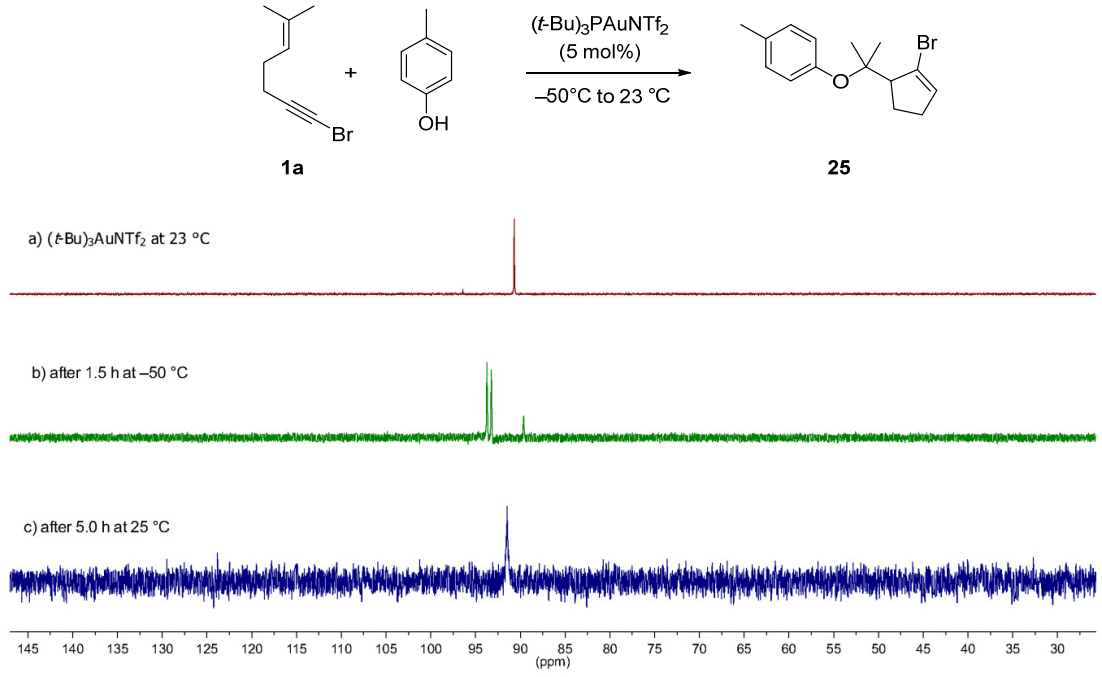
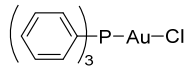



***Figure 19:*** *a) $^{31}$P-NMR spectrum of (t-Bu)$_3$PAuNTf$_2$ (23 °C, $CD_2Cl_2$, 162 MHz), b) $^{31}$P-NMR after 1.5 h (–50 °C, $CD_2Cl_2$, 162 MHz), c) $^{31}$P-NMR spectrum after 5.0 h (25 °C, $CD_2Cl_2$, 162 MHz). The spectrum shows that the catalyst was fully regenerated after complete formation of **25**.*

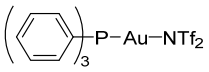
### 3.4.3. Experimental Procedures

#### 3.4.3.1. Synthesis of Gold Catalysts



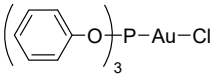
**Chloro(triphenylphosphine)gold(I) S33**

To a solution of sodium tetrachloroaurate (100 mg, 0.25 mmol, 1 equiv) in water (3 mL) 2,2′-thiodiethanol (75.5 µL, 0.75 mmol, 3.00 equiv) was added dropwise at 0 °C over a period of 45 min, followed by a solution of triphenylphosphite (65.9 mg, 0.25 mmol. 1.00 equiv) in ethanol (3 mL). The resulting white suspension was allowed to warm to 23 °C. After 30 min, the reaction mixture was filtered and the filtrate was washed with methanol (5 mL). The residue was dissolved in a minimum amount of dichloromethane and the product was precipitated with pentane to give **S33** (95.7 mg, 77%) as a colorless microcrystalline powder. The obtained analytical data were in full agreement with the data previously reported.[194]



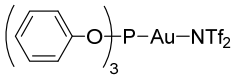
**[Bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold(I) S34**

To a solution of silver bis(trifluoromethanesulfonyl)imide (38.8 mg, 0.10 mmol, 1.00 equiv) in dichloromethane (0.5 mL) was added a solution of **S33** (49.5 mg. 0.10 mmol, 1 equiv) in dichloromethane (1 mL) at 23 °C. After 15 min, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated. The residue was dissolved in a minimum amount of dichloromethane and the product was precipitated by the addition of pentane (15 mL). The formed suspension was filtered to give **S34** (54 mg, 73%) as a white microcrystalline solid. The obtained analytical data were in full agreement with the data previously reported.[194]



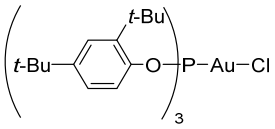
**Chloro(triphenylphosphite)gold(I) S35**

To a solution of sodium tetrachloroaurate (100 mg, 0.25 mmol, 1 equiv) in water (3 mL) was added 2,2′-thiodiethanol (75.5 µL, 0.75 mmol, 3.00 equiv) dropwise at 0 °C over a period of 45 min, followed by a solution of triphenylphosphite (78.0 mg, 0.25 mmol. 1.00 equiv) in pentane (3 mL). The resulting white suspension was allowed to warm to 23 °C. After 30 min, the reaction mixture was filtered and washed with methanol (5 mL). The residue was dissolved in a minimum amount of dichloromethane and the product precipitated with pentane to give **S35** (92.0 mg, 67%) as a white powder. The obtained data were in full agreement with those reported in literature.[195]



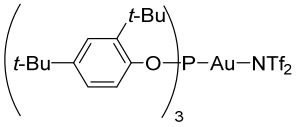
**[Bis(trifluoromethanesulfonyl)imidate](triphenylphosphite)gold(I) S36**

To a solution of silver bis(trifluoromethanesulfonyl)imide (38.8 mg, 0.10 mmol, 1.00 equiv) in dichloromethane (0.5 mL) was added a solution of **S35** (54.3 mg. 0.10 mmol, 1 equiv) in dichloromethane (1 mL) at 23 °C. After 3 h, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated to give **S36** (78 mg, 99%) as a pale yellow solid. The obtained analytical data were in full agreement with the data previously reported.[195]



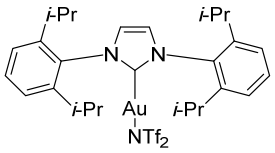
**Chloro[tris(2,4-di-*tert*-butylphenyl)phosphite]gold(I) S37**

To a solution of sodium tetrachloroaurate (100 mg, 0.25 mmol, 1 equiv) in water (1 mL) was added 2,2′-thiodiethanol (75.5 μL, 0.75 mmol, 3.00 equiv) dropwise at 0 °C over a period of 45 min, followed by a solution of tris(2,4-di-*tert*-butylphenyl)phosphite (163 mg, 0.25 mmol. 1.00 equiv) in pentane (3 mL). The resulting white suspension was allowed to warm to 23 °C. After 30 min, the reaction mixture was filtered and the residue was washed with methanol (5 mL) to give **S37** (169 mg, 77%) as a white powder. The obtained analytical data were in full agreement with the data previously reported.[196]



**[Bis(trifluoromethanesulfonyl)imidate](2,4-di-*tert*-butylphenyl)phosphite)gold(I) S38**

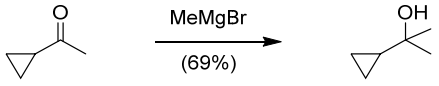
To a solution of silver bis(trifluoromethanesulfonyl)imide (38.8 mg, 0.10 mmol, 1.00 equiv) in dichloromethane (0.5 mL) was added a solution of **S37** (54.3 mg. 0.10 mmol, 1 equiv) in dichloromethane (2 mL) at 23 °C. After 30 min, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated to give **S38** (51.9 mg, 46%) as a white solid. The obtained analytical data were in full agreement with the data previously reported.[197]



**IPrAuNTf$_2$ S39**

To a solution of IPrAuCl (62.2 mg, 0.10 mmol, 1 equiv) in dichloromethane (2 mL) was added silver bis(trifluoromethanesulfonyl)imide (38.8 mg, 0.10 mmol, 1.00 equiv) at 23 °C. After 5 min, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated. The residue was dissolved in a minimum amount of dichloromethane and precipitated with pentane (15 mL). The resulting white solid was filtered to give **S39** (78 mg, 90%) as a white powder. The obtained analytical data were in full agreement with the data previously reported.[198]

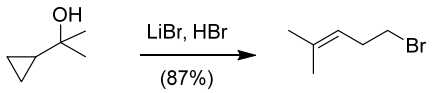
### 3.4.3.2. Synthesis of Enynes




**S40**

**2-Cyclopropylpropan-2-ol S40**

To a solution of cyclopropyl methyl ketone (50.0 g, 594 mmol, 1 equiv) in ether (200 mL) was added dropwise a solution of methyl magnesium bromide (3.0 M in ether, 258 mL, 773 mmol, 1.30 equiv) at 0 °C over a period of 1 h. The cooling bath was removed and the mixture was allowed to warm to 23 °C. After 1 h, excess methyl magnesium bromide was carefully quenched with saturated aqueous ammonium chloride solution (400 mL). The layers were separated and the aqueous phase was extracted with ether (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (400 mL), the washed solution was dried over potassium carbonate, the dried solution was filtered and the filtrate was carefully concentrated (700 mbar). The residue was subjected to distillation to yield 2-cyclopropylpropan-2-ol **S40** (41.2 g, 69%) as a colorless oil (boiling point 121–122 °C, 1013 mbar). Characterization data obtained for **S40** were in full agreement with values previously reported.[199]

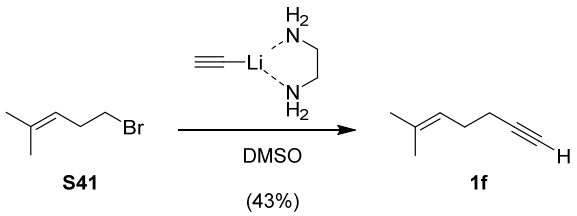



**S40** **S41**

**Bromide S41**

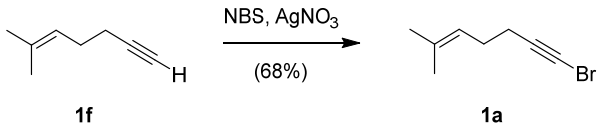
Lithium bromide (37.4 g, 430 mmol, 1.16 equiv) was added to neat alcohol **S40** (39.2 g, 391 mmol, 1 equiv) and the resulting suspension was cooled to 0 °C. Hydrobromic acid (48 %, 42 mL, 1.05 equiv) was added dropwise over a period of 10 min and the resulting solution was stirred at 0 °C. After 45 min, the reaction mixture was diluted with ether (600 mL) and saturated aqueous sodium bicarbonate solution (200 mL) was added to the resulting biphasic mixture. The phases were separated and the organic layer was sequentially washed with saturated aqueous sodium bicarbonate solution (200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic extract was dried over sodium sulfate, the dried solution was filtered and the filtrate was carefully concentrated on

a rotary evaporator (600 mbar, 40 °C) and by careful distillation (600 mbar, 80 °C oil bath). Distillation of the residue afforded 5-bromo-2-methylpent-2-ene **S41** (55.3 g, 87%) as a colorless oil (boiling point: 59–61 °C, 35 mbar). The obtained data were in full agreement with those reported in the literature.[199]




**Akyne 1f**

To a suspension of lithium acetylide ethylenediamine complex (39.7 g, 388 mmol, 1.15 equiv in dimethyl sulfoxide (200 mL) was added dropwise bromide **S41** (55.0 g, 337 mmol, 1 equiv) under vigorous stirring at 0 °C over a period of 35 min. After 15 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, the mixture was cooled to 15 °C and excess lithium acetylide was carefully quenched by the addition of water (800 mL). The aqueous phase was extracted with pentane (3 × 200 mL), the combined organic extracts were filtered through a plug of Celite and the filtrate was carefully concentrated. Distillation of the residue afforded alkyne **1f** (15.8 g, 43%) as a colorless oil (boiling point: 120–125 °C, 1013 mbar). Characterization data obtained for **1f** were in full agreement with the values previously reported.[200]




**Bromo alkyne 1a**

To a solution of alkyne **1f** (3.00 g, 27.7 mmol, 1 equiv) in acetone (90 mL) were sequentially added silver nitrate (471 mg, 2.77 mmol, 0.10 equiv) and *N*-bromosuccinimide (5.92 g, 33.3 mmol, 1.20 equiv) at 23 °C. After 30 min, the blue-greyish suspension was poured into water (30 mL). The aqueous layer was extracted with hexanes (3 × 50 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford bromide **1a** (4.10 g, 79%) as a colorless oil.

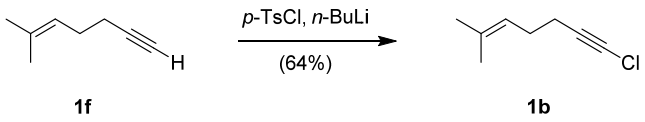
**TLC** (pentane), $R_f$ = 0.52 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 300 MHz): δ = 5.19–5.07 (m, 1H), 2.25–2.13 (m, 4H), 1.69 (s, 3H), 1.60 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ = 133.6, 122.6, 80.5, 37.9, 27.3, 25.9, 20.4, 18.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2968 (*s*), 2913 (*vs*), 2865 (*m*), 1674 (*w*), 1444 (*vs*), 1376 (*vs*), 1320 (*m*), 1108 (*m*), 983 (*m*), 822 (*vs*).

**HRMS** (EI) calc. for $C_8H_{11}{}^{79}Br$ $[M]^+$: 186.0044; found: 186.0043.




**1f** **1b**

**Chloro alkyne 1b**

To a solution of alkyne **1f** (200 mg, 1.85 mmol, 1 equiv) in tetrahydrofuran (6.0 mL) was added *n*-butyllithium (2.48 M in hexanes, 0.78 mL, 1.94 mmol, 1.05 equiv) at –78 °C. After 1 h, a solution of *para*-toluenesulfonyl chloride (370 mg, 1.94 mmol, 1.05 equiv) in tetrahydrofuran (2.5 mL) was added dropwise at this temperature. The mixture was then allowed to warm to –40 °C over 2 h and then was warmed to 24 °C. After 1 h, the mixture was diluted with water (10 mL) and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give chloro enyne **1b** (169 mg, 64%) as a pale yellow oil.

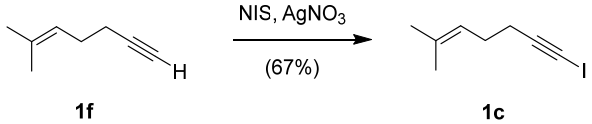
**TLC** (hexanes), $R_f$ = 0.58 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.19–5.09 (m, 1H), 2.23–2.14 (m, 4H), 1.71 (s, 3H), 1.62 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.5, 122.5, 69.7, 57.2, 27.3, 25.9, 19.4, 17.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2969 (*m*), 2916 (*s*), 2858 (*m*), 1450 (*m*), 1432 (*m*), 1378 (*m*), 1323 (*w*), 1078 (*m*), 983 (*w*), 823 (*m*).

**HRMS** (EI) calc. for $C_8H_{11}{}^{35}Cl$ $[M]^+$: 142.0549; found: 142.0532.




**1f** **1c**

**Iodo alkyne 1c**

To a solution of alkyne **1f** (200 mg, 1.85 mmol, 1 equiv) in acetone (6.0 mL) were sequentially added silver nitrate (31.4 mg, 0.19 mmol, 0.10 equiv) and *N*-iodosuccinimide (499 mg, 2.22 mmol, 1.20 equiv) at 23 °C under exclusion of light. After 1 h, the suspension was poured into water (20 mL). The aqueous layer was extracted with hexanes (3 × 30 mL) and the combined organic

extracts were washed with saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (2% ethyl acetate in hexanes) to afford iodide **1c** (289 mg, 67%) as a colorless oil.

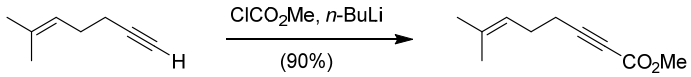
**TLC** (hexanes), $R_f$ = 0.33 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.22–5.05 (m, 1H), 2.40–2.31 (m, 2H), 2.25–2.15 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.5, 122.4, 94.8, 27.4, 25.9, 21.4, 17.9, –7.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2966 (*s*), 2912 (*vs*), 1673 (*w*), 1446 (*s*), 1375 (*s*), 1319 (*m*), 1252 (*w*), 1107 (*m*), 983 (*m*), 822 (*s*).

**HRMS** (EI) calc. for $C_7H_8{}^{127}I$ $[M–CH_3]^+$: 218.9671; found: 218.9660.




**1f** **1d**

**Enyne 1d**

To a solution of alkyne **1f** (250 mg, 2.31 mmol, 1 equiv) in tetrahydrofuran (5.0 mL) was added *n*-butyllithium (2.48 M in hexanes, 0.98 mL, 2.43 mmol, 1.05 equiv) at –78 °C. After 1 h, methyl chloroformate (0.19 mL, 2.43 mmol, 1.05 equiv) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was slowly allowed to warm to –30 °C. After 1.5 h, saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to give enyne **1d** (345 mg, 90%) as colorless oil.

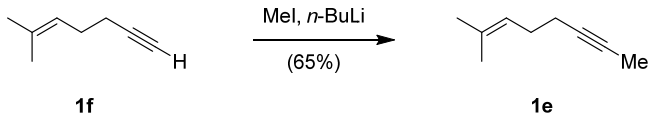
**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.38 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.12 (t, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 2.36–2.21 (m, 4H), 1.69 (s, 3H), 1.61 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.4, 134.1, 121.8, 89.8, 72.9, 52.7, 26.4, 25.8, 19.3, 17.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2917 (*w*), 2238 (*m*), 1712 (*vs*), 1434 (*m*), 1377 (*w*), 1247 (*vs*), 1070 (*s*), 901 (*w*), 752 (*s*).

**HRMS** (EI) calc. for $C_{10}H_{14}O_2$ $[M]^+$: 166.0994; found: 166.0996.




**1f** **1e**

**Enyne 1e**

To a solution of alkyne **1f** (200 mg, 1.85 mmol, 1 equiv) in tetrahydrofuran (6.0 mL) was added *n*-butyllithium (2.24 M in hexanes, 0.87 mL, 1.94 mmol, 1.05 equiv) at –78 °C. After 1 h, methyl iodide (345 mL, 5.55 mmol, 3.00 equiv) was added dropwise to the reaction mixture at –78 °C. The cooling bath was then removed and the reaction mixture was allowed to warm to 24 °C. After 20 min, saturated aqueous ammonium chloride solution (10 mL) was added and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (2% ether in pentane) to give enyne **1e** (147 mg, 65%) as a colorless oil.

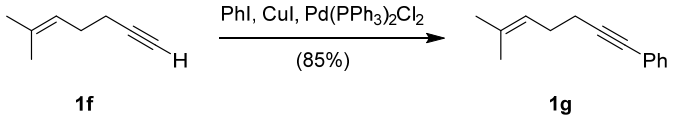
**TLC** (hexanes), $R_f$ = 0.34 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.19–5.13 (m, 1H), 2.20–2.09 (m, 4H), 1.78 (t, *J* = 2.4 Hz, 3H), 1.70 (s, 3H), 1.62 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 132.9, 123.2, 79.4, 75.6, 28.0, 25.9, 19.4, 17.9, 3.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2968 (*m*), 2919 (*s*), 2858 (*m*), 1436 (*s*), 1377 (*m*), 1326 (*w*), 1107 (*m*), 984 (*w*), 824 (*m*).

**HRMS** (EI) calc. for $C_9H_{14}$ $[M]^+$: 122.1096; found: 122.1085.




**1f** **1g**

**Enyne 1g**

To a solution of alkyne **1f** (200 mg, 1.85 mmol, 1 equiv) in a mixture of diisopropylamine (5.0 mL) and dichloromethane (1.0 mL) was added copper (I) iodide (35.2 mg, 0.19 mmol, 0.10 equiv), *bis*(triphenylphosphine)palladium(II) chloride (13 mg, 0.02 mmol, 0.01 equiv) and iodobenzen (453 mg, 2.22 mmol, 1.20 equiv) at 23 °C. After 5 h, water (30 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexanes) to give enyne **1g** (289 mg, 85%) as a colorless oil.

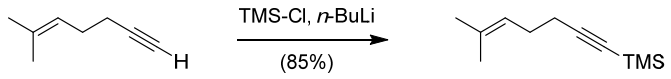
**TLC** (hexanes), $R_f$ = 0.23 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.42–7.36 (m, 2H), 7.31–7.24 (m, 3H), 5.23 (t, *J* = 7.0 Hz, 1H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.34–2.26 (m, 2H), 1.73 (s, 3H), 1.66 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.3, 131.7, 128.3, 127.6, 124.2, 122.9, 90.4, 80.7, 27.7, 25.9, 20.1, 18.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2969 (*w*), 2914 (*m*), 1599 (*w*), 1490 (*m*), 1442 (*m*), 1376 (*w*), 1070 (*w*), 824 (*w*), 755 (*vs*), 691 (*s*).

**HRMS** (EI) calc. for $C_{14}H_{16}$ $[M]^+$: 184.1252; found: 184.1238.




**1f** **1h**

**Enyne 1h**

To a solution of alkyne **1f** (200 mg, 1.85 mmol, 1 equiv) in tetrahydrofuran (6.0 mL) was added *n*-butyllithium (2.48 M in hexanes, 0.87 mL, 1.94 mmol, 1.05 equiv) at –78 °C. After 1 h, chlorotrimethylsilane (0.26 mL, 2.03 mmol, 1.10 equiv) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was then slowly allowed to warm to 24 °C. After 3 h, water (10 mL) was added to the reaction mixture and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (2% ethyl acetate in hexanes) to give enyne **1h** (284 mg, 85%) as a colorless oil.

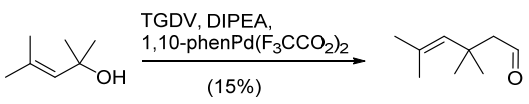
**TLC** (hexanes), $R_f$ = 0.32 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.18–5.12 (m, 1H), 2.23–2.19 (m, 4H), 1.70 (s, 3H), 1.62 (s, 3H), 0.15 (s, 9H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.2, 122.8, 107.6, 84.4, 27.6, 25.9, 20.5, 18.0, 0.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2963 (*w*), 2172 (*w*), 1265 (*m*), 1250 (*m*), 1046 (*w*), 895 (*w*), 841 (*vs*), 736 (*vs*), 704 (*s*).

**HRMS** (EI) calc. for $C_{11}H_{20}{}^{28}Si$ $[M]^+$: 180.1334; found: 180.1312.




**S42** **S43**

**Aldheyde S43**

Aldehyde **S43** was preapared according to a literature procedure.[201] To a solution of tertiary alcohol[202] **S42** (1.70 g, 15.0 mmol, 1 equiv) and *N*,*N*-diisoproylethylamine (130 μL, 0.75 mmol, 0.05 equiv) in triethyleneglycol divinyl ether (4.5 mL) in a pressure tube was added 1,10-phenathroline-$Pd(OAc)_2$ (38.4 mg, 0.08 mmol, 0.5 mol %) at 23 °C and reaction mixture was heated to 85 °C. After 15 h, the mixture was heated to 125 °C. After 24 h, the mixture was allowed to cool to 23 °C and the residue was directly purified by column chromatography on silica gel (10% ether in pentane) to afford aldehyde **S43** (307 mg, 15%) as a colorless oil.

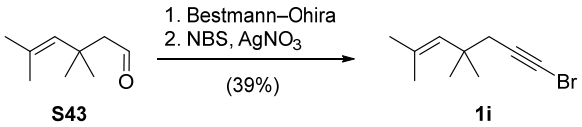
**TLC** (pentane), $R_f$ = 0.47 ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 9.70 (t, *J* = 3.0 Hz, 1H), 5.23 (s, 1H), 2.41 (d, *J* = 3.0 Hz, 2H), 1.73 (s, 3H), 1.69 (s, 3H), 1.21 (s, 6H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ= 204.1, 133.2, 132.1, 56.5, 34.6, 30.0, 28.2, 19.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2962 (*m*), 2730 (*w*), 1720 (*vs*), 1632 (*w*), 1449 (*w*), 1366 (*w*), 1172 (*w*), 1045 (*w*), 820 (*w*).

**HRMS** (EI) calc. for $C_9H_{16}O$ $[M]^+$: 140.1201; found: 140.1190.




**Enyne 1i**

To a solution of aldehyde **S43** (260 mg, 1.85 mmol, 1 equiv) in methanol (9 mL) was added potassium carbonate (384 mg, 2.78 mmol, 1.50 equiv) and Bestmann–Ohira´s reagent[203] (dimethyl (1-diazo-2-oxopropyl)phosphonate) (534 mg, 2.78 mmol, 1.50 equiv) at 23 °C. After 3h, water (30 mL) was added to the reaction mixture and the aqueous phase was extracted with pentane (4 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was carefully concentrated (23 °C, 500 mbar). The residue was dissolved in acetone (8 mL) and silver nitrate (31.4 mg, 0.19 mmol, 0.01 equiv) was added followed by *N*-bromosuccinimide (379 mg, 2.13 mmol, 1.15 equiv) at 23 °C. After 3 h, the blue-greyish suspension was poured into water (40 mL). The aqueous layer was extracted with pentane (3 × 30 mL) and the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford bromide **1i** (156 mg, 39%) as a colorless oil.

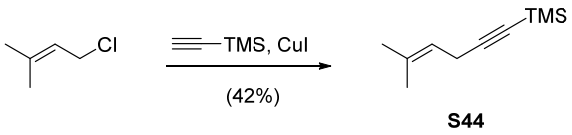
**TLC** (pentane), $R_f$ = 0.72 ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 5.18–5.13 (m, 1H), 2.25 (s, 2H), 1.72 (s, 3H), 1.69 (s, 3H), 1.16 (s, 6H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ= 132.6, 132.5, 79.6, 38.6, 35.8, 35.1, 28.3, 28.3, 19.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2964 (*s*), 2928 (*m*), 1664 (*w*), 1466 (*m*), 1447 (*m*), 1364 (*m*), 1072 (*m*), 981 (*m*), 818 (*s*).

**HRMS** (DEI) calc. for $C_{10}H_{15}{}^{79}Br$ $[M]^+$: 214.0357; found: 214.0353.




**S44**

**Enyne S44**

According to a literature procedure[204], potassium carbonate (1.13 g, 8.16 mmol, 1.00 equiv), sodium sulphite (514 mg, 4.08 mmol, 0.50 equiv), copper(I) iodide (31.1 mg, 0.16 mmol 0.02 equiv) and 1,8-diazabicyclo[5.4.0)undec-7-ene (DBU) (1.30 mg, 0.01 mmol, 1 mol %) were added to a solution of 3,3-dimethylallyl chloride (1.28 g, 12.2mmol, 1 equiv) and ethynynltrimethylsilane in dimethylformamide (15 mL) at 23 °C. After 22 h, the reaction mixture was partitioned between saturated aqueous ammonium chloride solution (90 mL) and pentane (90 mL). The aqueous phase was extracted with pentane (2 × 90 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was carefully concentrated (23 °C, 500 mbar). The residue was purified by column chromatography on silica gel (pentane) to afford alkyne **S44** (570 mg, 42%) as a colorless oil.

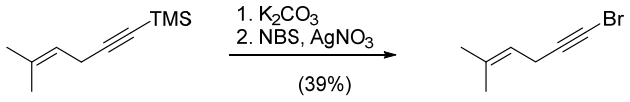
**TLC** (pentane), $R_f$ = 0.20 ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 5.18–5.12 (m, 1H), 2.92 (d, *J* = 6.8 Hz, 2H), 1.71 (s, 3H), 1.62 (s, 3H), 0.13 (s, 9H)

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ = 134.5, 119.1, 106.4, 84.0, 25.8, 19.5, 17.9, 0.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2961 (*w*), 2176 (*m*), 1450 (*w*), 1283 (*w*), 1248 (*m*), 1031 (*w*), 1004 (*w*), 836 (*vs*), 758 (*s*).

**HRMS** (EI) calc. for $C_{10}H_{18}{}^{28}Si$ $[M]^+$: 166.1178; found: 166.1174.




**S44** **S45**

**Enyne S45**

To a solution of TMS-alkyne **S44** (100 mg, 0.60 mmol, 1 equiv) in methanol (2 mL) was added potassium carbonate (91.4 mg, 0.66 mmol, 1.10 equiv) at 23 °C. After 3.5 h, water (5 mL) was added to the reaction mixture and the aqueous phase was extracted with pentane (3 × 5 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was carefully concentrated (23 °C water bath, 500 mbar). The residue was dissolved in acetone (2 mL) and silver nitrate (10.2 mg, 0.06 mmol, 0.01 equiv), followed by *N*-bromosuccinimide (123 mg, 0.69 mmol, 1.15 equiv) were added at 23 °C. After 1.5 h, the suspension was poured into water (5 mL). The aqueous layer was extracted with pentane (3 × 10 mL) and the combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford bromide **S45** (53.6 mg, 52%) as a colorless oil.

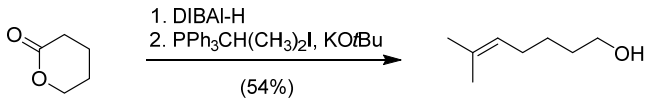
**TLC** (pentane), $R_f$ = 0.56 ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 5.19–5.11 (m, 1H), 2.90 (d, *J* = 6.9 Hz, 2H), 1.71 (s, 3H), 1.62 (s, 3H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ = 135.2, 118.2, 79.6, 37.6, 25.7, 19.2, 17.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2970 (*m*), 2914 (*m*), 1673 (*w*), 1447 (*s*), 1376 (*s*), 1286 (*s*), 1102 (*s*), 917 (*m*), 832 (*vs*).

**HRMS** (EI) calc. for $C_7H_9{}^{79}Br$ $[M]^+$: 171.9888; found: 171.9876.



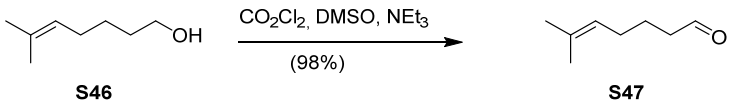

**S46**

**Alcohol S46**

To a solution of δ-valerolactone (2.00 g, 20.0 mmol, 1 equiv) in dichloromethane (2 mL) was added diisobutylaluminum hydride (1.00 M in dichloromethane, 24.0 mL, 24.0 mmol, 1.20 equiv) at –78 °C dropwise over a period of 20 min. After 40 min, ethyl acetate (5 mL) was added to the reaction mixture, followed by a saturated aqueous solution of potassium sodium tartrate (5 mL). The biphasic mixture was allowed to warm to 23 °C. After 3 h, water (10 mL) was added and the mixture was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give the crude lactol.

Potassium *tert*-butoxide (2.58 g, 23 mmol, 1.15 equiv) was added to a suspension of

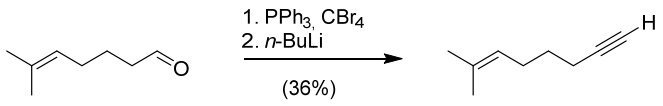
isopropyltriphenylphosphonium iodide (9.08 g, 21 mmol, 1.05 equiv) in tetrahydrofuran (40 mL) at –78 °C. After 5 min, the dark red mixture was allowed to warm to 0 °C. After 30 min, a solution of the crude lactol in tetrahydrofuran (10 mL) was added to the reaction mixture. The mixture was allowed to warm to 23 °C and after 23 h, water (50 mL) was added and the reaction mixture was extracted with ether (3 × 75 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in hexanes) to yield alcohol **S46** (1.39 g, 54%) as a pale yellow oil. The obtained analytical data for **S46** were in full agreement with those previously reported.[205]




**S46** **S47**

**Aldehyde S47**

A solution of dimethyl sulfide (2.08 mL, 29.2 mmol, 3.00 equiv) in dichloromethane (11 mL) was added to a solution of oxalylchloride (2 M in dichloromethane, 7.31 mL, 14.6 mmol, 1.10 equiv) in dichloromethane (11 mL) at –78 °C. After 10 min, a solution of alcohol **S42** (1.25 g, 9.75 mmol, 1 equiv) in dichloromethane (16 mL) was added dropwise to the reaction mixture at –78 °C over a period of 15 min. After 30 min, triethylamine (8.13 mL, 58.5 mmol, 6.00 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 30 min, water (50 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (20% ether in pentane) to yield aldehyde **S47** (1.20 g, 98%) as a pale yellow oil. The obtained analytical data were in full agreement with the ones previously reported.[205]




**S47** **S48**

**Enyne S48**

To a solution of carbon tetrabromide (6.31 g, 19.0 mmol, 2.00 equiv) in dichloromethane (7.0 mL) was added triphenylphosphine (9.98 g, 38.0 mmol, 4.00 equiv) at 0 °C. After 30 min, a solution of aldehyde **S47** (1.20 g, 9.51 mmol, 1 equiv) in dichloromethane (4.5 mL) was added at 0 °C and the reaction mixture was allowed to warm to 23 °C. After 1 h, the mixture was filtered through a short plug of silica, the filter cake was washed with a 1:5 mixture of ether in pentane (400 mL) and the filtrate was concentrated to give the crude dibromoolefin.

To a solution of the crude dibromoolefin in tetrahydrofuran (24 mL) was added *n*-butyllithium (2.31 M in hexanes, 9.06 mL, 20.9 mmol, 2.20 equiv) at –78 °C. After 20 min, saturated aqueous

ammonium chloride solution (50 mL) was added and the aqueous phase was extracted with ether (3 × 75 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (pentane) to afford enyne **S48** (412 mg, 36%) as a colorless oil.

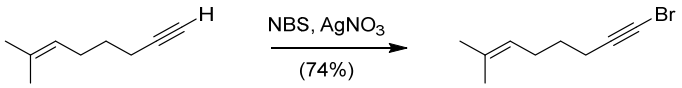
**TLC** (pentane), $R_f$ = 0.38 ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 5.09 (t, *J* = 6.9 Hz, 1H), 2.16 (td, *J* = 7.2 Hz, 2.5 Hz, 2H), 2.08 (q, *J* = 7.3 Hz, 2H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.54 (q, *J* = 7.4 Hz, 2H).

**$^{13}$C NMR** ($CD_2Cl_2$, 101 MHz): δ = 133.0, 124.0, 85.2, 68.5, 29.3, 27.5, 26.0, 18.3, 17.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3308 (*m*), 2967 (*m*), 2930 (*s*), 1450 (*s*), 1377 (*m*), 1235 (*w*), 1108 (*w*), 852 (*w*), 825 (*w*).

**HRMS** (EI) calc. for $C_9H_{13}$ $[M–H]^+$: 121.1017; found: 121.0998.




**S48** **S49**

**Enyne S49**

To a solution of alkyne **S48** (350 mg, 2.86 mmol, 1 equiv) in acetone (11 mL) was added silver nitrate (48.6 mg, 0.29 mmol, 0.01 equiv) followed by *N*-bromosuccinimide (586 mg, 3.29 mmol, 1.15 equiv) at 23 °C. After 45 min, the suspension was poured into water (40 mL). The aqueous layer was extracted with pentane (3 × 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford bromide **S49** (426 mg, 74%) as a colorless oil.

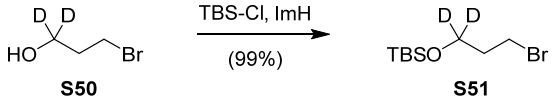
**TLC** (pentane), $R_f$ = 0.45 ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.07 (tq, *J* = 7.2 Hz, 1.5 Hz, 1H), 2.19 (t, *J* = 7.1 Hz, 2H), 2.07 (q, *J* = 7.4 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.55 (p, *J* = 7.3 Hz, 2H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 132.8, 123.5, 80.5, 37.7, 28.5, 27.1, 25.9, 19.3, 17.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2967 (*m*), 2929 (*vs*), 2860 (*m*), 1673 (*w*), 1447 (*s*), 1376 (*m*), 1108 (*w*), 984 (*w*), 856 (*w*).

**HRMS** (DEI) calc. for $C_9H_{12}{}^{79}Br$ $[M–H]^+$: 199.0122; found: 199.0109.




**Silyl ether S51**

To a solution of alcohol **S50**[206] (1.18 g, 8.37 mmol, 1 equiv) in dichloromethane (7 mL) was added imidazole (1.00 g, 14.6 mmol, 1.75 equiv) and *tert*-butyldimethylsilyl chloride (1.45 g, 9.62 mmol, 1.15 equiv) at 0 °C. After 15 min, the reaction mixture was allowed to warm to 23 °C. After further 1 h, the mixture was diluted with dichloromethane (40 mL) and the organic layer was washed with saturated aqueous sodium chloride solution (30 ml). The aqueous phase was extracted with dichloromethane (40 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to give silyl protected alcohol **S51** (2.14 g, 99%) as a colorless oil, which was used without further purification.

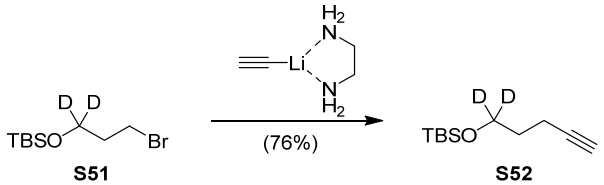
**TLC** (10% ethyl acetate in hexanes), $R_f$ = 0.69 ($KMnO_4$, UV).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 3.51 (t, *J* = 6.4 Hz, 2H), 2.02 (t, *J* = 6.4 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 59.9 (p, *J* = 21.9 Hz), 35.5, 30.8, 26.1, 18.5, –5.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2953 (*m*), 2928 (*m*), 2855 (*m*), 1471 (*w*), 1253 (*s*), 1177 (*s*), 1086 (*s*), 1045 (*s*), 8632 (v*s*), 775 (*s*).

**MS** (EI) calc. for $C_5H_{10}D_2{}^{79}BrO^{28}Si^+$ [M–*t*-Bu]$^+$: 196.9966; found: 1960.9973.




**Alkyne S52**

To a suspension of lithium acetylide ethylenediamine complex (0.89 g, 9.63 mmol, 1.15 equiv) in dimethylsulfoxide (6 mL) was added bromide **S51** (2.14 g, 8.37 mmol, 1 equiv) dropwise at 0 °C under vigorous stirring. After 30 min, the reaction mixture was allowed to warm to 23 °C. After 3 h, excess lithium acetylide was carefully quenched by the addition of water (20 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (10% ether in pentane) to yield alkyne **S52** (1.28 g, 76%) as a colorless oil.

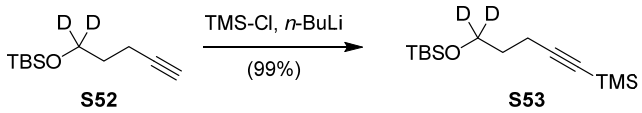
**TLC** (10% ether in pentane): $R_f$ = 0.69 ($KMnO_4$, UV).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.27 (td, *J* = 7.1, 2.7 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.71 (t, *J* = 7.1 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 84.4, 68.4, 60.9 (p, *J* = 21.6 Hz), 31.4, 26.1, 18.5, 14.9, –5.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3310 (*w*), 2928 (*w*), 1471 (*w*), 1254 (*m*), 1152 (*m*), 1099 (*m*), 1051 (*m*), 908 (*s*), 832 (*s*), 775 (*s*), 731 (*s*).

**MS** (DEI) calc. for $C_7H_{15}D_2O^{28}S$ $[M–C_4H_5]^+$: 147.1; found: 147.1, calc. $C_7H_{11}D2O^{28}S$ $[M–t\text{-Bu}]^+$: 143.1; found: 143.1.



**S52** **S53**

**TMS alkyne S53**

*n*-Butyllithium (2.20 M in hexanes, 2.98 mL, 6.55 mmol, 1.05 equiv) was added dorpwise to a solution of alkyne **S52** (1.25 g, 6.24 mmol, 1 equiv) in tetrahydrofuran (18 mL) at –78 °C. After 30 min, chlorotrimethylsilane (0.88 mL, 6.86 mmol, 1.10 equiv) was added dropwise to the reaction mixture over a period of 10 min. The reaction mixture was then allowed to warm to 0 °C. After 30 min, saturated ammonium chloride solution (50 mL) was added to the reaction mixture and the aqueous solution was extracted with ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic extract was dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated to yield TMS-alkyne **S53** (1.72 g, 99%) as a yellow oil, which was used in the next reaction without further purification.

**TLC** (5% ether in hexanes): $R_f$ = 0.56 ($KMnO_4$, UV).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.30 (t, *J* = 7.0 Hz, 2H), 1.69 (t, *J* = 7.0 Hz, 2H), 0.90 (s, 9H), 0.14 (s, 9H), –0.06 (s, 6H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 107.2, 84.7, 77.5, 60.9 (p, *J* = 21.6 Hz), 31.5, 26.11, 18.5, 16.3, 0.3, –5.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2956 (*w*), 2176 (*w*), 1472 (*w*), 1249 (*m*), 1153 (*m*), 1099 (*m*), 1051 (*m*), 831 (*vs*), 774 (*s*), 758 (*s*), 698 (*m*).

**HRMS** (EI) calc. for $C_{13}H_{25}D_2O^{28}Si_2$ $[M–CH_3]^+$: 257.1726; found: 257.1706.

**S53** **S54**

**Alcohol S54**

To a solution of silyl ether **S53** (1.70 mg, 6.24 mmol, 1 equiv) in a 1:1 mixture of dichloromethane and methanol (16 mL) was added camphorsulfonic acid (725 mg, 3.12 mmol, 0.50 equiv) at 0 °C. After 1.5 h, triethylamine (0.87 mL, 6.24 mmol, 1.00 equiv) was added to the reaction mixture and the mixture was concentrated. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to give alcohol **S54** (857 mg, 87%) as a colorless oil.

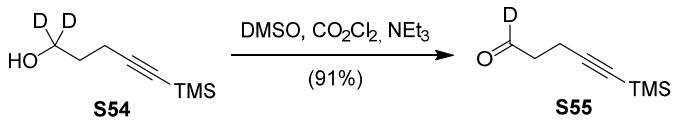
**TLC** (40% ethyl acetate in hexanes): $R_f$ = 0.22 ($KMnO_4$, UV).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.35 (t, *J* = 6.9 Hz, 2H), 1.76 (t, *J* = 6.9 Hz, 2H), 1.52 (br s, 1H), 0.15 (s, 9H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 106.8, 85.4, 61.2 (p, *J* = 22.6 Hz), 31.1, 16.7, 0.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3334 (*br w*), 2958 (*w*), 2174 (*m*), 1248 (*s*), 1202 (*w*), 1135 (*w*), 966 (*m*), 836 (*vs*), 758 (*s*), 697 (*m*).

**HRMS** (EI) calc. for $C_7H_{10}D_2O_2{}^{28}Si$ $[M–CH_3]^+$: 143.0861; found: 143.0862.




**Aldehyde S55**

To a solution of oxalylchloride (2.0 M in dichloromethane, 4.05 mL, 8.10 mmol, 1.5 equiv) in dichloromethane (6.0 mL) was added a solution of dimethylsulfoxide (1.15 mL, 16.2 mmol, 3.00 equiv) in dichloromethane (6.0 mL) at –78 °C. After 10 min, a solution of alcohol **S54** (855 mg, 5.40 mmol, 1 equiv) in dichloromethane (12 mL) was added dropwise at –78 °C. After 30 min, triethylamine (4.50 mL, 32.4 mmol, 6.00 equiv) was added and the reaction mixture was allowed to warm to 23 °C. After 15 min, water (50 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (10% ether in pentane) to yield aldehyde **S55** (763 mg, 91%) as a colorless oil.

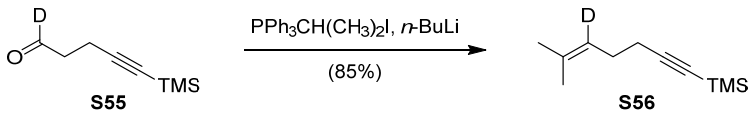
**TLC** (20% ether in pentane): $R_f$ = 0.32 ($KMnO_4$, UV).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.71–2.64 (m, 2H), 2.58–2.50 (m, 2H), 0.14 (s, 9H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 200.2 (t, *J* = 26.7 Hz), 104.9, 85.9, 42.5, 13.2, 0.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2959 (*w*), 2177 (*w*), 2083 (*w*), 1714 (*m*), 1407 (*w*), 1249 (*m*), 1093 (*w*), 910 (*w*), 836 (*vs*), 758 (*s*).

**HRMS** (EI) calc. for $C_7H_{11}DO^{28}Si$ $[M–CH_3]^+$: 140.0642; found: 140.0633.




**Enyne S56**

To a yellow suspension of *iso*-propyltriphenylphosphonium iodide (1.47 g, 3.41 mmol, 1.30 equiv) in tetrahydrofuran (20 mL) was added *n*-butyllithium (2.31 M in hexanes, 1.36 mL, 3.15 mmol, 1.20 equiv) at 0 °C. After 30 min, a solution of aldehyde **S55** (406 mg, 2.62 mmol, 1 equiv) in tetrahydrofuran (3.0 mL) was added to the dark red suspension. Stirring was continued at 0 °C for 5 min and the reaction mixture was then allowed to warm to 23 °C. After 40 min, the mixture was diluted with water (50 mL). The aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5% ether in pentane) to furnish enyne **S56** (404 mg, 85%) as a colorless oil.

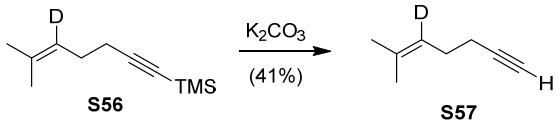
**TLC** (10% ethyl acetate in hexanes): $R_f = 0.67$ ($KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.25–2.16 (m, 4H), 1.70 (s, 3H), 1.62 (s, 3H), 0.15 (s, 9H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.0, 122.5 (t, $J$ = 23.1 Hz), 107.6, 84.4, 27.5, 25.8, 20.5, 18.0, 0.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2961 (*w*), 2175 (*w*), 1448 (*w*), 1248 (*m*), 1044 (*w*), 887 (*m*), 837 (*vs*), 758 (*s*), 734 (*s*), 697 (*m*).

**HRMS** (EI) calc. for $C_{11}H_{19}D^{28}Si$ $[M]^+$: 181.1397; found: 181.1385.




**Enyne S57**

To a solution of TMS-alkyne **S56** (404 mg, 2.23 mmol, 1 equiv) in methanol (7.5 mL) was added potassium carbonate (339 mg, 2.45 mmol, 1.10 equiv) at 23 °C. After 10 h, water (20 mL) was and the aqueous phase was extracted with pentane (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, the dried solution was filtered and the filtrate was carefully concentrated (23 °C water bath, 500 mbar). The residue was purified by column chromatography on silica gel (2% ether in pentane) to afford alkyne **S57** (98.9 mg, 41%) as a colorless oil.

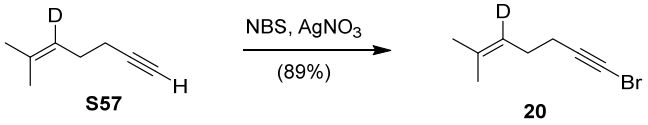
**TLC** (pentane): $R_f = 0.26$ ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 2.19 (s, 4H), 1.98–1.94 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.6, 122.7 (t, *J* = 23.4 Hz), 85.0, 68.4, 27.7, 25.8, 19.32, 18.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2954 (*s*), 2928 (*s*), 2857 (*s*), 2174 (*m*), 1463 (*m*), 1249 (*m*), 838 (*s*), 826 (*s*), 775 (*s*), 680 (*w*).

**HRMS** (EI) calc. for $C_8H_{11}D$ $[M]^+$: 109.1002; found: 109.1003.




**S57** **20**

**Enyne 20**

To a solution of alkyne **S57** (40 mg, 0.37 mmol, 1 equiv) in acetone (1.2 mL) was added silver nitrate (6.22 mg, 0.04 mmol, 0.01 equiv) followed by *N*-bromosuccinimide (75.0 mg, 0.42 mmol, 1.15 equiv) at 23 °C. After 45 min, the suspension was poured into water (10 mL). The aqueous layer was extracted with pentane (3 × 10 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford bromide **20** (61.4 mg, 89%) as a colorless oil.

**TLC** (pentane), $R_f$ = 0.72 ($KMnO_4$).

**$^1$H NMR** ($CD_2Cl_2$, 400 MHz): δ = 2.22–2.17 (m, 4H), 1.70 (s, 3H), 1.62 (s, 3H).

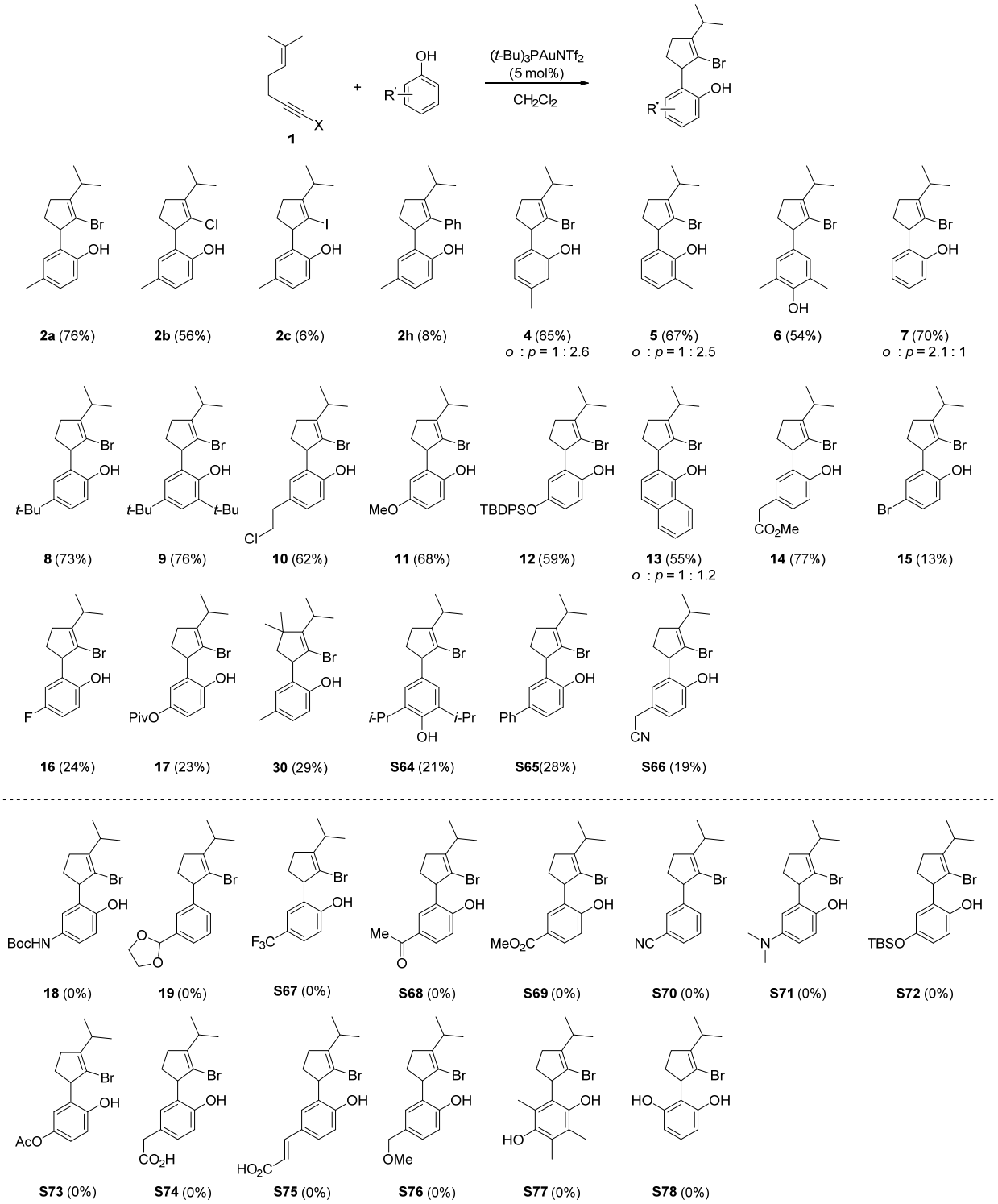
**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 133.8, 122.5 (t, *J* = 23.1 Hz), 80.9, 37.7, 27.4, 25.9, 20.6, 18.0.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2967 (*m*), 2912 (*s*), 2855 (*m*), 1663 (*w*), 1447 (*s*), 1373 (*m*), 1336 (*w*), 1134 (*m*), 682 (*m*).

**HRMS** (EI) calc. for $C_8H_{10}D^{79}Br$ $[M]^+$: 187.0107; found: 187.0110.

### 3.4.3.3. Cyclization Products

***Scheme 27:*** *Complete reaction scope.*



**General Procedure A:**

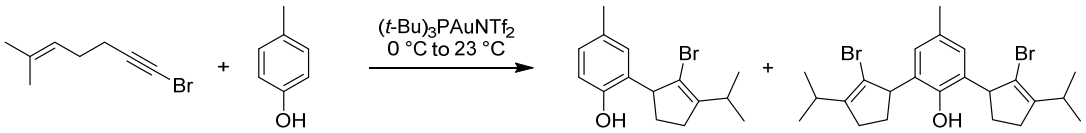
To a solution of the 1,5-enyne (0.25 mmol, 1 equiv) and phenol (1.25 mmol, 5.00 equiv) in dichloromethane (1.0 mL) was added ($t$-Bu)$_3$PAuNTf$_2$ (5 mol %) at 0 °C under an argon atmosphere. After complete consumption of the 1,5-enyne, the mixture was allowed to warm to 23 °C and the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was concentrated and the residue was purified by flash column chromatography on silica gel (ethyl acetate in hexanes or dichloromethane) to afford the title compound.

**General Procedure B:**

To a solution of the 1,5-enyne (0.25 mmol, 1 equiv) and phenol (2.50 mmol, 10.0 equiv) in dichloromethane (1.0 mL) was added ($t$-Bu)$_3$PAuNTf$_2$ (5 mol %) at –20 °C under an argon atmosphere. After complete consumption of the 1,5-enyne, the mixture was allowed to warm to 23 °C and the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was concentrated and the residue was purified by flash column chromatography on silica gel (ethyl acetate in hexanes or dichloromethane) to afford the title compound.

**General Procedure C:**

To a solution of the 1,5-enyne (0.25 mmol, 1 equiv) and $p$-fluorophenol (0.26 mmol, 1.05 equiv) in dichloromethane (1.0 mL) was added ($t$-Bu)$_3$PAuNTf$_2$ (5 mol %) at –20 °C under an argon atmosphere. After complete consumption of the 1,5-enyne, the phenol (1.25 mmol, 5.00 equiv) was added and the mixture was allowed to warm to 23 °C. The reaction was monitored by thin layer chromatography chromatography. After completion of the reaction, the mixture was concentrated and the residue was purified by flash column chromatography on silica gel (ethyl acetate in hexanes or dichloromethane) to afford the title compound.




**1a** **2a** (76%) **3a** (5%)

**Phenol 2a**

Phenols **2a** and **3a** were prepared according to General Procedure A. After 1 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to furnish bis-alkylated phenol **3a** (3.0 mg, 5%, d.r. = 1.7:1) as a pale yellow oil and phenol **2a** (56.2 mg, 76%) as a pale yellow oil.

**2a:**

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.47 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.93 (dd, *J* = 8.1 Hz, 2.2 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.79 (s, 1H), 4.21–4.12 (m, 1H), 2.97 (hept, *J* = 6.9 Hz, 1H), 2.57–2.30 (m, 3H), 2.27 (s, 3H), 1.98–1.84 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 151.7, 149.6, 130.1, 129.7, 128.9, 128.5, 117.0, 116.1, 51.8, 30.3, 29.4, 29.3, 20.8, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3429 (*br w*), 2959 (*s*), 1610 (*w*), 1504 (*vs*), 1458 (*m*), 1256 (*m*), 1105 (*m*), 1037 (*m*), 808 (*vs*), 734 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO$ $[M]^+$: 294.0619; found: 294.0603.

**3a:**

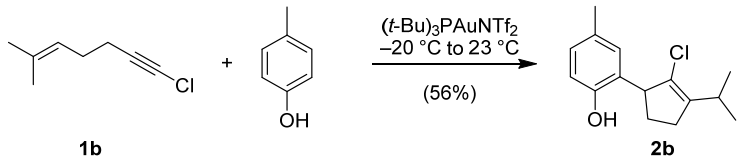
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.48 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz, major diastereomer marked with *): δ = 6.73 (s, 2H), 5.11* (s, 1H), 5.04 (s, 1H), 4.23–4.10 (m, 2H), 2.96 (hept, *J* = 6.9 Hz, 2H), 2.53–2.29 (m, 6H), 2.25 (s, 3H), 2.00–1.85 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.9 Hz, 6H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz, major diastereomer marked with *): δ = 150.2*, 150.1, 149.6*, 149.4, 129.6, 129.4, 128.1*, 127.9, 117.2, 117.2*, 52.0, 30.3, 29.4*, 29.4, 29.2, 21.0, 21.0*, 20.6, 20.4, 20.3*.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3507 (*br w*), 2960 (*vs*), 1645 (*w*), 1474 (*vs*), 1310 (*m*), 1200 (*s*), 908 (*m*), 864 (*s*), 734 (*s*), 610 (*w*).

**HRMS** (ESI) calc. for $C_{23}H_{29}{}^{79}Br_2O_2$ $[M–H]^-$: 479.0663; found: 479.0591.




1b 2b

**Phenol 2b**

Phenol **2b** was prepared according to General Procedure B. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to give phenol **2b** (34.8 mg, 56%) as a pale yellow oil.

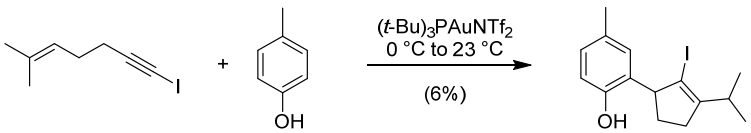
**TLC** (20% ethyl acetate in hexanes): $R_f = 0.61$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.93 (dd, *J* = 8.1 Hz, 1.9 Hz, 1H), 6.85 (d, *J* = 1.9 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.83 (s, 1H), 4.23–4.09 (m, 1H), 2.99 (hept, *J* = 6.9 Hz, 1H), 2.59–2.33 (m, 3H), 2.27 (s, 3H), 1.96–1.78 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 151.7, 146.0, 130.2, 129.5, 128.7, 128.4, 125.6, 116.0, 49.9, 29.9, 28.6, 27.6, 20.8, 20.6, 20.4.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3398 (*br w*), 2962 (*s*), 1612 (*w*), 1509 (*s*), 1462 (*m*), 1259 (*m*), 1204 (*m*), 1086 (*m*), 931 (*w*), 811 (*m*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{35}ClO$ $[M]^+$: 250.1124; found: 250.1116.




1c 2c

**Phenol 2c**

Phenol **2c** was prepared according to General Procedure A under the exclusion of light. After 8 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield phenol **2c** (5.5 mg, 6%) as a pale yellow oil.

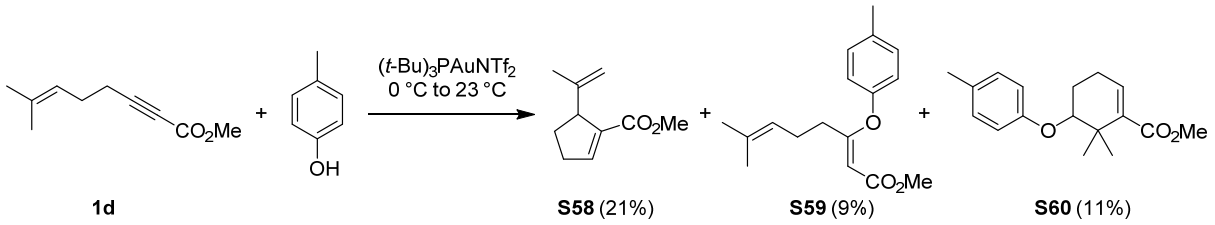
**TLC** (10% ethyl acetate in hexanes): $R_f = 0.26$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.94 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.79 (s, 1H), 4.19–4.04 (m, 1H), 2.86 (hept, *J* = 6.9 Hz, 1H), 2.67–2.32 (m, 3H), 2.27 (s, 3H), 2.02–1.91 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 156.2, 151.8, 130.1, 130.0, 129.4, 128.6, 116.2, 95.2, 55.1, 32.8, 30.6, 30.1, 20.8, 20.6, 20.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3444 (*br w*), 2960 (*s*), 1611 (*w*), 1502 (*s*), 1459 (*m*), 1257 (*m*), 1193 (*m*), 1103 (*m*), 1103 (*m*), 917 (*w*), 810 (*w*).

**HRMS** (EI) calc. $C_{15}H_{19}{}^{127}IO$ $[M]^+$: 342.0481; found: 342.0475.




**1d** **S58** (21%) **S59** (9%) **S60** (11%)

**Compounds S58, S59 and S60**

Compounds **S58**, **S59** and **S60** were prepared according to General Procedure A. After 19 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (2% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to yield cyclopentene **S58** (9.1 mg, 21%) as a pale yellow oil, enolether **S59** (6.1 mg, 9 %) as a colorless oil and ether **S60** (7.8 mg, 11%) as a pale yellow oil.

**Cyclopentene S58:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.32 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.89 (s, 1H), 4.72 (s, 1H), 4.68 (s, 1H), 3.71 (s, 3H), 3.57 (d, *J* = 9.8 Hz, 1H), 2.62–2.39 (m, 2H), 2.29–2.15 (m, 1H), 1.86–1.74 (m, 1H), 1.71 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 165.6, 147.2, 145.2, 138.2, 109.9, 51.5, 32.2, 30.6, 20.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2948 (*w*), 1720 (*s*), 1630 (*w*), 1506 (*w*), 1436 (*m*), 1280 (*m*), 1195 (*s*), 1097 (*m*), 890 (*w*), 753 (*w*).

**HRMS** (EI) calc. $C_{10}H_{14}O_2$ $[M]^+$: 166.0994; found: 166.0980.

**Enolether S59:**

**TLC** (5% ethyl acetate in hexanes): $R_f$ = 0.41 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.17 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.24 (t, *J* = 7.2 Hz, 1H), 4.78 (s, 1H), 3.61 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.45–2.37 (m, 2H), 2.34 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 176.7, 167.9, 151.3, 135.4, 132.7, 130.6, 123.2, 121.4, 95.2, 50.9, 31.6, 26.2, 25.9, 21.0, 17.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2926 (*w*), 1715 (*vs*), 1631 (*s*), 1505 (*s*), 1435 (*m*), 1206 (*m*), 1153 (*s*), 1121 (*vs*), 1034 (*m*), 836 (*m*).

**HRMS** (EI) calc. $C_{17}H_{22}O_3$ $[M]^+$: 274.1569; found: 274.1554.

**Ether S60:**

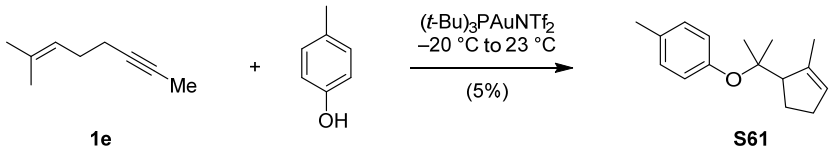
**TLC** (5% ethyl acetate in hexanes): $R_f$ = 0.24 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.04 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 6.82–6.79 (m, 1H), 3.70 (s, 3H), 3.35 (d, *J* = 9.4 Hz, 1H), 2.65–2.49 (m, 1H), 2.48–2.35 (m, 1H), 2.29 (s, 3H), 2.28–2.23 (m, 1H), 2.21–2.10 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 167.2, 152.7, 145.2, 138.1, 132.9, 129.5, 124.2, 83.6, 54.3, 51.6, 32.8, 27.6, 24.6, 24.1, 20.9.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2979 (*w*), 1718 (*vs*), 1630 (*w*), 1507 (*vs*), 1435 (*m*), 1293 (*m*), 1224 (*vs*), 1194 (*s*), 1092 (*s*), 840 (*m*).

**HRMS** (EI) calc. $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1642; found: 275.1630.




**Ether S61**

Ether **S61** was prepared according to General Procedure B. After 8 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to yield ether **S61** (3.0 mg, 5%) as a colorless oil.

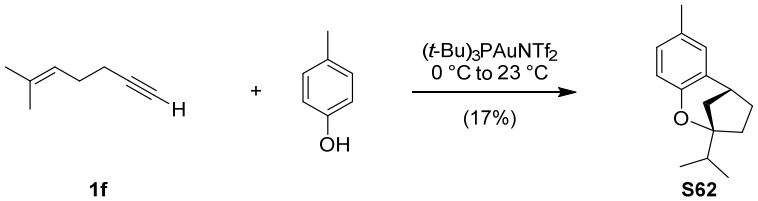
**TLC** (hexanes): $R_f$ = 0.13 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.05 (d, *J* = 8.3 Hz , 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.53–5.50 (m, 1H), 2.98–2.90 (m, 1H), 2.30 (s, 3H), 2.29–2.13 (m, 2H), 2.14–2.01 (m, 1H), 1.90 (s, 3H), 1.86–1.75 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 152.9, 141.5, 132.5, 129.5, 128.8, 124.1, 83.5, 58.2, 30.9, 27.9, 25.1, 22.8, 20.9, 18.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2976 (*w*), 2851 (*w*), 1610 (*w*), 1507 (*s*), 1382 (*w*), 1226 (*s*), 1146 (*m*), 1123 (*m*), 907 (*w*), 835 (*w*).

**HRMS** (EI) calc. $C_{16}H_{21}O$ $[M–H]^+$: 229.1592; found: 229.1569.



**Ether S62**

Etherl **S62** was prepared according to General Procedure A. After 2.5 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to yield phenol **S62** (9.0 mg, 17%) as a yellow oil.

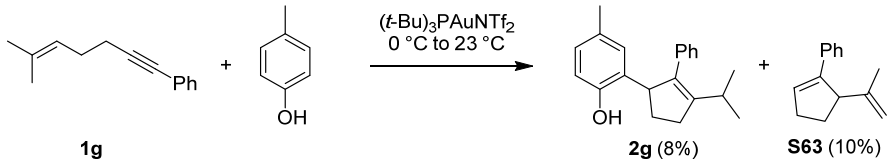
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.75 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.87 (dd, *J* = 8.2 Hz, 1.8 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 3.10–1.77 (m, 1H), 2.23 (s, 3H), 2.04–1.77 (m, 6H), 1.68 (dd, *J* = 11.7 Hz, 4.0 Hz, 1H), 1.07 (d, *J* = 4.5 Hz, 3H), 1.05 (d, *J* = 4.4 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 151.9, 130.5, 128.2, 128.0, 127.6, 115.6, 89.4, 39.8, 36.2, 36.1, 35.3, 34.6, 20.6, 18.1, 17.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2962 (*m*), 1494 (*s*), 1468 (*m*), 1365 (*w*), 1234 (*m*), 1162 (*m*), 1040 (*w*), 979 (*w*), 920 (*m*), 913 (*m*).

**HRMS** (EI) calc. $C_{15}H_{19}O$ $[M–H]^+$: 215.1436; found: 215.1440.




**Phenol 2g**

Phenol **2g** was prepared according to General Procedure A. After 5.5 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (hexanes initially, grading to 10% ethyl acetate in hexanes) to furnish phenol **2h** (6.0 mg, 8%) as a pale yellow oil and ether **S63** (9.6 mg, 10%) as a colorless yellow oil.

**2g:**

**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.41 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.22 (t, *J* = 7.5 Hz, 2H), 7.17–7.10 (m, 3H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.26 (s, 1H), 4.39–4.32 (m, 1H), 2.93 (hept, *J* = 6.8 Hz, 1H), 2.75–2.64 (m, 1H), 2.63–2.40 (m, 2H), 2.17 (s, 3H), 1.95–1.83 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 152.1, 149.5, 137.3, 136.3, 130.3, 129.9, 129.5, 128.2, 128.1, 128.0, 126.6, 116.0, 52.1, 31.0, 30.6, 27.8, 21.9, 21.4, 20.7.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3456 (*br w*), 2958 (*s*), 1599 (*w*), 1500 (*s*), 1465 (*m*), 1258 (*m*), 1195 (*m*), 810 (*m*), 766 (*m*), 699 (*vs*).

**HRMS** (EI) calc. for $C_{21}H_{24}O$ $[M]^+$: 292.1827; found: 292.1824.

**S63:**

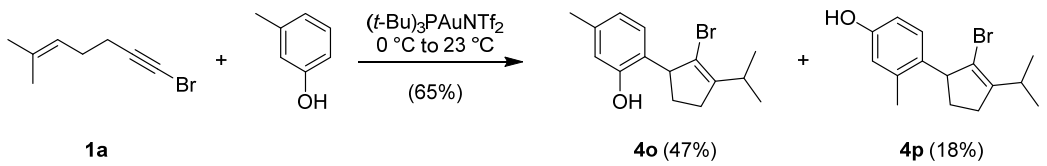
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.66 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.32–7.24 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.27 (dt, *J* = 3.3 Hz, 1.8 Hz, 1H) 4.78 (s, 1H), 4.72 (s, 1H), 3.78 (d, *J* = 9.0 Hz, 1H), 2.65–2.38 (m, 2H), 2.37–2.21 (m, 1H), 1.94–1.76 (m, 1H), 1.64 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 147.9, 143.9, 136.6, 128.6, 128.3, 126.9, 126.1, 111.0, 53.4, 32.1, 31.1, 19.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3058 (*w*), 2940 (*m*), 1646 (*w*), 1496 (*m*), 1446 (*m*), 1034 (*w*), 890 (*m*), 817 (*w*), 755 (*s*), 69s (*s*).

**HRMS** (EI) calc. for $C_{14}H_{16}[M]^+$: 184.1252; found: 184.1245.




**1a** **4o** (47%) **4p** (18%)

**Phenols 4o and 4p**

Phenols **4o** and **4p** were prepared according to General Procedure A. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to furnish *ortho*-substituted **4o** (69.0 mg, 47%) as a colorless oil. The fractions containing starting phenol and *para*-substituted **4p** were further purified on silica gel (dichloromethane) to yield *para*-substituted **4p** (26.0 mg, 18%) as a colorless oil.

**4o:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.93 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.63 (s, 1H), 4.86 (s, 1H), 4.23–4.08 (m, 1H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.53–2.31 (m, 3H), 2.29 (s, 3H), 1.96–1.83 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.7, 149.5, 138.1, 128.9, 126.2, 121.8, 117.1, 116.9, 51.2, 30.4, 29.3, 29.2, 21.2, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3499 (*br w*), 2960 (*vs*), 1619 (*w*), 1457 (*s*), 1417 (*s*), 1284 (*s*), 1209 (*s*), 1105 (*s*), 910 (*m*), 810 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO$ $[M]^+$: 294.0619; found: 294.0605.

**4p:**

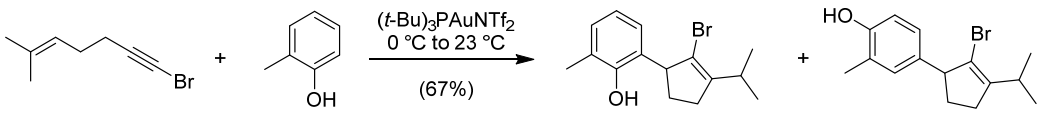
**TLC** (dichloromethane): $R_f$ = 0.29 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.91 (d, *J* = 8.7 Hz, 1H), 6.68–6.60 (m, 2H), 4.59 (s, 1H), 4.17–4.03 (m, 1H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.50–2.24 (m, 6H), 1.80–1.66 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.8, 148.3, 137.7, 134.5, 128.0, 117.8, 117.3, 113.0, 51.7, 31.2, 29.2, 28.7, 20.6, 20.5, 19.8.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3325 (*br w*), 2960 (*s*), 1609 (*m*), 1586 (*m*), 1499 (*s*), 1458 (*s*), 1243 (*s*), 1197 (*s*), 952 (*m*), 856 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO$ $[M]^+$: 294.0619; found: 294.0609.




**1a** **5o** (19%) **5p** (48%)

**Phenols 5o and 5p**

Phenols **5o** and **5p** were prepared according to General Procedure A. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to furnish *ortho*-substituted **5o** (9.7 mg, 19%) as a colorless oil. The fractions containing starting phenol and *para*-substituted **5p** were further purified on silica gel (dichloromethane) to yield *para*-substituted **5p** (35.1 mg, 48%) as a pale yellow oil.

**5o:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.52 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.04 (d, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 4.97 (s, 1H), 4.26–4.12 (m, 1H), 2.97 (hept, *J* = 6.9 Hz, 1H), 2.59–2.32 (m, 3H), 2.25 (s, 3H), 2.01–1.81 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 152.4, 149.8, 129.5, 128.6, 126.9, 124.2, 120.5, 117.0, 30.2, 29.4, 29.3, 20.6, 20.3, 16.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3507 (*br w*), 2961 (*s*), 1594 (*w*), 1467 (*vs*), 1326 (*m*), 1260 (*m*), 1188 (*m*), 1084 (*m*), 834 (*m*), 744 (*s*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO$ $[M]^+$: 294.0619; found: 294.0609.

**5p:**

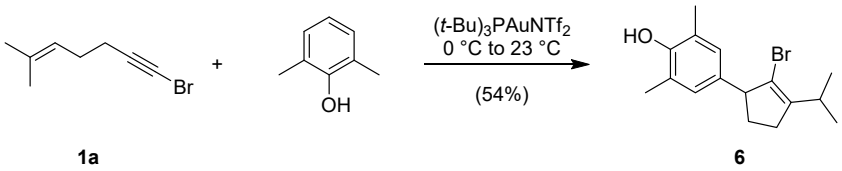
**TLC** (dichloromethane): $R_f$ = 0.43 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.90 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.1 Hz, 2.0 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 4.65 (s, 1H), 3.91–3.78 (m, 1H), 2.92 (hept, *J* = 6.9 Hz, 1H), 2.55–2.36 (m, 2H), 2.36–2.28 (m, 1H), 2.24 (s, 3H), 1.92–1.74 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 152.6, 147.8, 136.6, 130.4, 126.1, 123.8, 118.5, 115.1, 56.0, 32.4, 29.3, 29.0, 20.7, 20.5, 16.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3401 (*br m*), 2960 (*vs*), 1612 (*w*), 1505 (*vs*), 1460 (*m*), 1265 (*s*), 1203 (*s*), 1115 (*vs*), 817 (*m*), 756 (*w*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO$ $[M]^+$: 294.0619; found: 294.0618.




**1a** **6**

**Phenol 6**

Phenol **6** was prepared according to General Procedure A. After 2.5 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (dichloromethane) to give phenol **6** (41.8 mg, 54%) as a pale yellow oil.

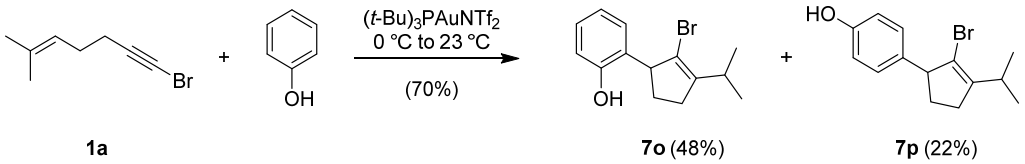
**TLC** (dichloromethane): $R_f$ = 0.57 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.75 (s, 2H), 4.50 (s, 1H), 3.84–3.74 (m, 1H), 2.93 (hept, *J*= 6.9 Hz, 1H), 2.51–2.26 (m, 3H), 2.24 (s, 6H), 1.87–1.75 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 151.0, 147.7, 135.9, 127.8, 123.1, 118.5, 56.0, 32.5, 29.3, 29.1, 20.7, 20.5, 16.2.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3572 (*br w*), 2961 (*s*), 1643 (*w*), 1487 (*vs*), 1463 (*m*), 1310 (*m*), 1196 (*vs*), 1154 (*m*), 871 (*m*), 733 (*w*).

**HRMS** (EI) calc. for $C_{16}H_{21}{}^{79}BrO$ $[M]^+$: 308.0776; found: 308.0782.




**1a** **7o** (48%) **7p** (22%)

**Phenols 7o and 7p**

Phenols **7o** and **7p** were prepared according to General Procedure A. After 1 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel

(10% ethyl acetate in hexanes) to furnish *ortho*-substituted **7o** (33.8 mg, 48%) as a pale yellow oil. The fractions containing starting phenol and *para*-substituted **7p** were further purified on silica gel (dichloromethane) to yield *para*-substituted **7p** (15.2 mg, 22%) as a pale yellow oil.

**7o:**

**TLC** (20% ethyl acetate in hexanes): $R_f = 0.48$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.14 (td, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.06 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 6.91 (td, *J* = 7.4 Hz, 0.9 Hz, 1H), 6.80 (dd, *J* = 8.0 Hz, 0.9 Hz, 1H), 5.01 (s, 1H), 4.27–4.21 (m, 1H), 2.98 (hept, *J* = 6.9 Hz, 1H), 2.55–2.31 (m, 3H), 1.98–1.85 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.9, 149.6, 129.4, 129.0, 128.0, 121.1, 116.8, 116.1, 51.3, 30.3, 29.3, 29.2, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3445 (*br w*), 2961 (*s*), 1593 (*m*), 1502 (*m*), 1456 (*vs*), 1327 (*m*), 1097 (*m*), 911 (*w*), 861 (*m*), 751 (*vs*).

**HRMS** (EI) calc. for $C_{14}H_{17}{}^{79}BrO$ $[M]^+$: 280.0463; found: 280.0464.

**7p:**

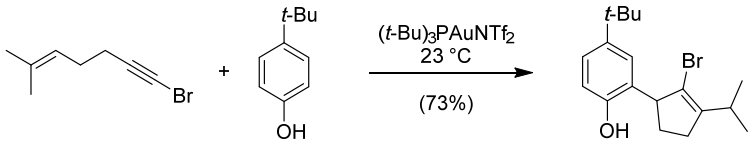
**TLC** (dichloromethane): $R_f = 0.38$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.02 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 4.72 (s, 1H), 3.90–3.82 (m, 1H), 2.92 (hept, *J* = 6.9 Hz, 1H), 2.51–2.37 (m, 2H), 2.37–2.26 (m, 1H), 1.88–1.77 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 154.3, 147.9, 136.7, 128.8, 118.4, 115.5, 55.9, 32.3, 29.2, 29.1, 20.7, 20.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3327 (*br m*), 2961 (*s*), 1613 (*m*), 1512 (*vs*), 1458 (*m*), 1362 (*w*), 1235 (*s*), 1172 (*m*), 912 (*w*), 830 (*s*).

**HRMS** (EI) calc. for $C_{14}H_{17}{}^{79}BrO$ $[M]^+$: 280.0463; found: 280.0459.




**1a** **8**

**Phenol 8**

Phenol **8** was prepared according to a modified General Procedure A (catalyst was added to the reaction mixture at 23 °C). After 1 h, the reaction mixture was concentrated and the residue was

purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to furnish phenol **8** (61.8 mg, 73%) as a pale yellow oil.

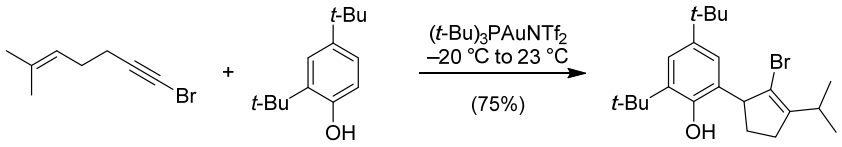
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.46 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.13 (dd, *J* = 8.3 Hz, 2.5, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 4.79 (br s, 1H), 4.23–4.15 (m, 1H), 2.99 (hept, *J* = 6.9 Hz, 1H), 2.53–2.29 (m, 3H), 1.97–1.86 (m, 1H), 1.28 (s, 9H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 151.5, 149.5, 143.5, 128.4, 126.0, 124.6, 117.1, 115.5, 51.6, 34.2, 31.7, 30.4, 29.3, 29.1, 20.7, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3432 (*br w*), 2962 (*vs*), 1610 (*w*), 1506 (*s*), 1464 (*m*), 1362 (*m*), 1264 (*s*), 1124 (*m*), 891 (*w*), 818 (*m*).

**HRMS** (EI) calc. for $C_{18}H_{25}{}^{79}BrO$ $[M]^+$: 336.1089; found: 336.1072.




**1a** **9**

**Phenol 9**

Phenol **9** was prepared according to General Procedure C. After 1 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to furnish phenol **9** (75.1 mg, 76%) as a pale yellow oil.

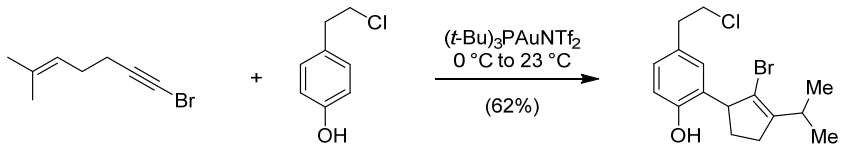
**TLC** (5% ethyl acetate in hexanes): $R_f$ = 0.41 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.23 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 5.07 (s, 1H), 4.14–4.04 (m, 1H), 3.00 (hept, *J* = 6.9 Hz, 1H), 2.60–2.32 (m, 3H), 2.09–1.94 (m, 1H), 1.43 (s, 9H), 1.30 (s, 9H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 150.8, 150.3, 142.1, 135.8, 127.9, 124.2, 122.7, 117.2, 53.3, 35.0, 34.4, 31.8, 30.1, 29.9, 29.4, 29.3, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3503 (*br w*), 2951 (*vs*), 2869 (*m*), 1654 (*w*), 1478 (*s*), 1362 (*s*), 1236 (*m*), 1200 (*s*), 878 (*m*), 767 (*w*).

**HRMS** (EI) calc. for $C_{22}H_{33}{}^{79}BrO$ $[M]^+$: 392.1715; found: 392.1716.




1a 10

**Phenol 10**

Phenol **10** was prepared according to General Procedure A. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to give phenol **10** (53.5 mg, 62%) as a pale yellow oil.

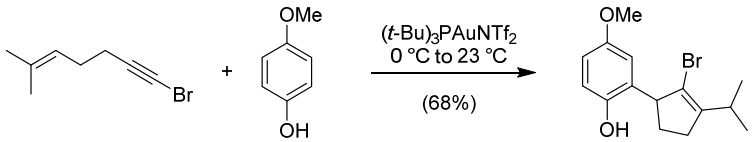
**TLC** (20% ethyl acetate in hexanes): $R_f = 0.30$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.98 (dd, *J* = 8.1 Hz, 2.0, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 4.93 (br s, 1H), 4.25–4.12 (m, 1H), 3.66 (t, *J* = 7.3 Hz, 2H), 3.06–2.91 (m, 3H), 2.55–2.29 (m, 3H), 1.95–1.82 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 152.8, 149.8, 130.5, 129.5, 129.4, 128.2, 116.6, 116.3, 51.5, 45.4, 38.7, 30.3, 29.3, 29.2, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3524 (*br w*), 2959 (*s*), 2360 (*w*), 1610 (*m*), 1504 (*vs*), 1432 (*s*), 1259 (*s*), 1187 (*s*), 1103 (*s*), 816 (*s*).

**HRMS** (EI) calc. for $C_{16}H_{20}{}^{79}Br^{35}ClO$ $[M]^+$: 342.0386; found: 342.0381.




1a 11

**Phenol 11**

Phenol **11** was prepared according to General Procedure A with using an excess of 10 equivalents of anisol. After 1 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to furnish phenol **11** (52.8 mg, 68%) as a pale yellow oil.

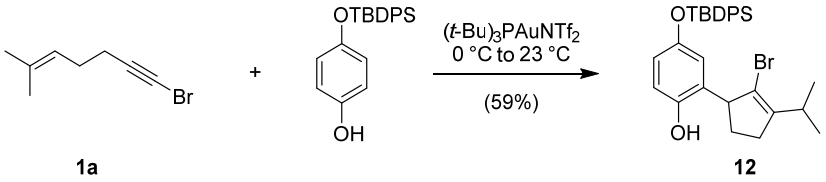
**TLC** (20% ethyl acetate in hexanes): $R_f = 0.31$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.74 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.7 Hz, 3.0 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 4.65 (s, 1H), 4.25–4.16 (m, 1H), 3.75 (s, 3H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.54–2.41 (m, 2H), 2.41–2.29 (m, 1H), 1.95–1.85 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 53.9, 149.7, 147.7, 130.7, 116.8, 116.6, 114.6, 112.5, 55.8, 51.4, 30.3, 29.3, 29.2, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3395 (*br w*), 2960 (*m*), 1609 (*w*), 1503 (*vs*), 1431 (*s*), 1266 (*m*), 1200 (*vs*), 1039 (*s*), 857 (*m*), 804 (*m*).

**HRMS** (EI) calc. for $C_{15}H_{19}{}^{79}BrO_2$ $[M]^+$: 310.0568; found: 310.0562.




**1a** **12**

**Phenol 12**

Phenol **12** was prepared according to General Procedure A. After 3 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 15% ethyl acetate in hexanes) to give phenol **12** (78.9 mg, 59%) as a yellow oil.

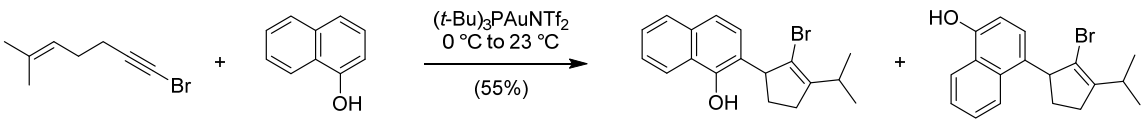
**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.33 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.73–7.64 (m, 4H), 7.47–7.28 (m, 6H), 6.62–6.52 (m, 2H), 6.39 (d, *J* = 2.7 Hz, 1H), 4.43 (s, 1H), 4.10–3.98 (m, 1H), 2.76 (hept, *J* = 6.9 Hz, 1H), 2.35–2.22 (m, 1H), 2.22–2.02 (m, 2H), 1.65–1.52 (m, 1H), 1.09 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 149.7, 149.0, 147.5, 135.7, 135.7, 133.3, 133.3, 130.3, 129.8, 129.8, 127.8, 127.7, 119.6, 118.6, 116.6, 116.5, 50.4, 30.3, 29.1, 28.8, 26.7, 20.3, 20.3, 19.6.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3388 (*br w*), 2960 (*w*), 2858 (*w*), 1497 (*m*), 1427 (*m*), 1186 (*m*), 971 (*m*), 907 (*s*), 730 (*vs*), 698 (*vs*).

**HRMS** (EI) calc. for $C_{30}H_{35}{}^{79}BrO_2{}^{28}Si$ $[M]^+$: 534.1590; found: 534.1574.




**1a** **13o** (25%) **13p** (30%)

**Phenols 13o and 13p**

Phenols **13o** and **13p** were prepared according to General Procedure A. After 1.5 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes) to furnish *ortho*-substituted **13o** (21.0 mg, 25%) as a pale yellow oil and *para*-substituted **13p** (25.0 mg, 30%) as a pale yellow oil.

**13o:**

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.26 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 8.17–8.12 (m, 1H), 7.82–7.76 (m, 1H), 7.50–7.44 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 5.62 (s, 1H), 4.39–4.26 (m, 1H), 3.00 (hept, *J* = 6.9 Hz, 1H), 2.67–2.52 (m, 2H), 2.52–2.40 (m, 1H), 2.11–1.96 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 150.3, 149.2, 133.8, 127.8, 127.2, 126.0, 125.5, 125.1, 122.6, 121.4, 120.6, 117.1, 52.6, 30.2, 29.7, 29.5, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3491 (*br w*), 2961 (*vs*), 1655 (*m*), 1575 (*s*), 1464 (*m*), 1383 (*s*), 1268 (*s*), 1072 (*m*), 807 (*vs*), 746 (*s*).

**HRMS** (EI) calc. for $C_{18}H_{19}{}^{79}BrO$ $[M]^+$: 330.0619; found: 330.0613.

**13p:**

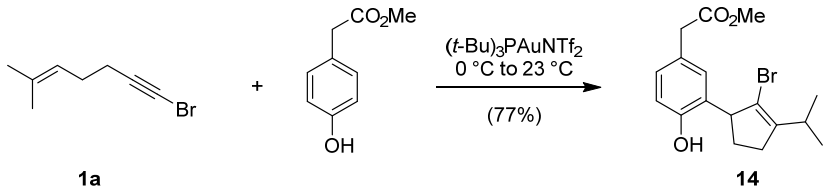
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.17 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 8.25 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.61–7.45 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.19 (s, 1H), 4.75–4.60 (m, 1H), 3.06 (hept, *J* = 6.9 Hz, 1H), 2.69–2.50 (m, 1H), 2.36 (br s, 2H), 1.85 (br s, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 150.3, 149.6, 133.0, 131.7, 126.6, 125.0, 125.0, 123.6, 123.4, 122.5, 116.6, 108.3, 76.8, 51.2, 31.9, 29.3, 28.5, 20.7, 20.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3410 (*br m*), 2960 (*s*), 1626 (*m*), 1587 (*s*), 1381 (*vs*), 1274 (*s*), 1052 (*s*), 907 (*m*), 823 (*m*), 759 (*vs*).

**HRMS** (EI) calc. for $C_{18}H_{19}{}^{79}BrO$ $[M]^+$: 330.0619; found: 330.0615.




**1a** **14**

**Phenol 14**

Phenol **14** was prepared according to General Procedure A. After 4 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in hexanes) to give phenol **14** (68.2 mg, 77%) as a pale yellow oil.

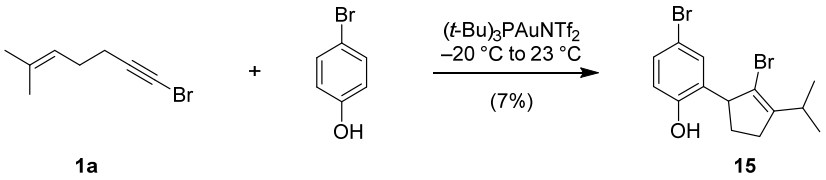
**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.22 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.02 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.29 (s, 1H), 4.25–4.15 (m, 1H), 3.69 (s, 3H), 3.55 (s, 2H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.56–2.22 (m, 3H), 1.94–1.82 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 172.8, 153.2, 149.7, 129.9, 129.4, 128.7, 126.1, 116.7, 116.3, 52.2, 51.3, 40.6, 30.3, 29.3, 29.2, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3412 (*br w*), 2959 (*m*), 1714 (*s*), 1611 (*w*), 1508 (*m*), 1435 (*s*), 1262 (*s*), 1147 (*s*), 1015 (*m*), 806 (*m*).

**HRMS** (EI) calc. for $C_{17}H_{21}{}^{79}BrO_3$ $[M]^+$: 352.0674; found: 352.0669.




**1a** **15**

**Phenol 15**

Phenol **15** was prepared according to General Procedure B. After 1 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (dichloromethane) to give phenol **15** (12.0 mg, 7%) as a pale yellow oil.

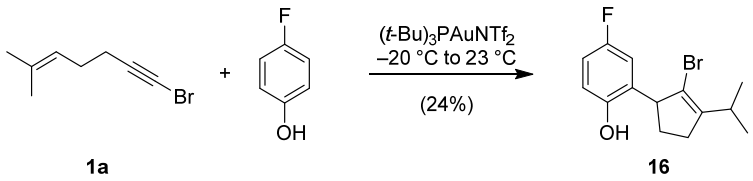
**TLC** (dichloromethane): $R_f$ = 0.48 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.22 (dd, *J* = 8.6 Hz, 2.5 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 5.02 (s, 1H), 4.21–4.12 (m, 1H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.54–2.41 (m, 2H), 2.41–2.31 (m, 1H), 1.93–1.80 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.1, 150.4, 131.8, 131.7, 130.7, 117.9, 115.9, 113.1, 51.4, 30.2, 29.3, 29.3, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3438 (*br w*), 2962 (*s*), 1489 (*s*), 1431 (*s*), 1324 (*m*), 1266 (*s*), 1167 (*m*), 1109 (*m*), 873 (*w*), 810 (*m*).

**HRMS** (EI) calc. for $C_{14}H_{16}{}^{79}Br_2O$ $[M]^+$: 357.9568; found: 357.9553.




**1a** **16**

**Phenol 16**

Phenol **16** was prepared according to General Procedure B. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (3% ethyl acetate in hexanes) to yield phenol **16** (17.4 mg, 24%) as a pale yellow oil.

**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.25 (UV, $KMnO_4$).

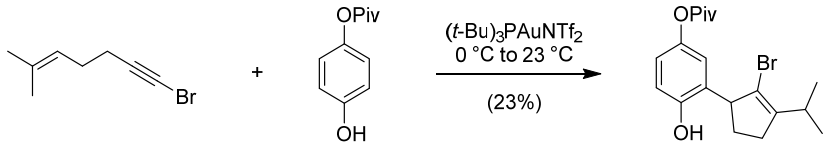
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.86–6.78 (m, 1H), 6.78–6.70 (m, 2H), 4.80 (br s, 1H), 4.26–4.16 (m, 1H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.54–2.30 (m, 3H), 1.95–1.79 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 157.4 (d, *J* = 238 Hz), 150.2, 149.7 (d, *J* = 2.0 Hz), 131.2 (d, *J* = 6.6 Hz), 116.9 (d, *J* = 8.1 Hz), 116.0, 115.3 (d, *J* = 23.4 Hz), 114.1 (d, *J* = 23.2 Hz), 51.1, 30.3, 29.3, 29.1, 20.6, 20.3.

**$^{19}$F NMR** ($CDCl_3$, 282 MHz): δ = –123.5.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3426 (*br w*), 2962 (*s*), 1619 (*w*), 1504 (*vs*), 1434 (*s*), 1258 (*s*), 1172 (*s*), 873 (*m*), 809 (*m*), 749 (*w*).

**HRMS** (EI) calc. for $C_{14}H_{16}{}^{79}BrFO$ $[M]^+$: 298.0369; found: 298.0356.




**Phenol 17**

Phenol **17** was prepared according to General Procedure A. After 2.5 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to give phenol **17** (22.0 mg, 23%) as a pale yellow oil.

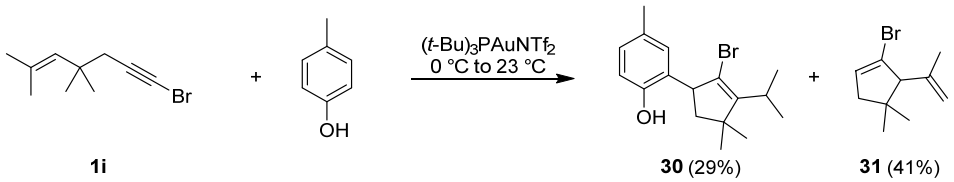
**TLC** (20% ethyl acetate in hexanes): $R_f$ = 0.43 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.80 (dd, *J* = 8.6 Hz, 2.7 Hz, 1H), 6.75–6.68 (m, 2H), 5.09 (s, 1H), 4.24–4.12 (m, 1H), 2.95 (hept, *J* = 6.9 Hz, 1H), 2.52–2.39 (m, 2H), 2.39–2.30 (m, 1H), 1.97–1.83 (m, 1H), 1.34 (s, 9H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 177.8, 151.5, 150.0, 144.7, 130.3, 121.7, 120.6, 116.7, 116.3, 51.6, 39.2, 30.2, 29.3, 29.2, 27.3, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3443 (*br w*), 2962 (*m*), 1723 (*s*), 1504 (*m*), 1434 (*s*), 1262 (*s*), 1141 (*vs*), 1030 (*m*), 900 (*m*), 799 (*w*).

**HRMS** (EI) calc. for $C_{19}H_{25}{}^{79}BrO_3$ $[M]^+$: 380.0987; found: 380.0985.



**Phenol 30 and cyclopentene 31**

Phenol **2c** and cyclopentene **31** were prepared according to General Procedure A. After 8 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (10% ethyl acetate in hexanes) to yield phenol **30** (23.3 mg, 29%) as a pale yellow oil and bromide **31** (23.4 mg, 41%) as a colorless oil.

**30:**

**TLC** (10% ethyl acetate in hexanes): $R_f = 0.33$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ 6.94 (dd, $J$ = 8.1 Hz, 2.0 Hz, 1H), 6.86 (d, $J$ = 2.0 Hz, 1H), 6.70 (d, $J$ = 8.1 Hz, 1H), 4.90 (s, 1H), 4.13 (t, $J$ = 8.4 Hz, 1H), 2.61 (hept, $J$ = 7.1 Hz, 1H), 2.28 (s, 3H), 2.27–2.20 (m, 1H), 1.83 (dd, $J$ = 13.0 Hz, 8.0 Hz, 1H), 1.31 (d, $J$ = 7.1 Hz, 3H), 1.32 (d, $J$ = 7.1 Hz, 3H), 1.18 (s, 3H), 1.14 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 155.5, 152.0, 130.3, 130.0, 128.8, 128.5, 117.0, 116.2, 50.4, 48.0, 47.2, 27.8, 27.5, 27.3, 20.8, 20.6, 20.4.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3442 (*br w*), 2957 (*s*), 1611 (*w*), 1502 (*s*), 1462 (*m*), 1363 (*s*), 1258 (*s*), 1199 (*s*), 1098 (*s*), 810 (*vs*).

**HRMS** (EI) calc. $C_{17}H_{23}{}^{79}BrO$ $[M]^+$: 322.0932; found: 322.0924.

**31:**

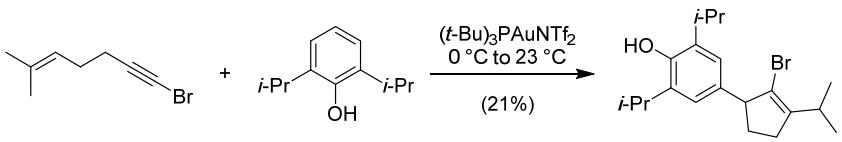
**TLC** (10% ethyl acetate in hexanes): $R_f = 0.72$ (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 5.93 (s, 1H), 4.95 (s, 1H), 4.76 (s, 1H), 2.83 (d, $J$ = 2.6 Hz, 1H), 2.20 (d, $J$ = 16.1 Hz, 1H), 2.03 (dd, $J$ = 16.1 Hz, 2.9 Hz, 1H), 1.65 (s, 3H), 1.13 (s, 3H), 1.00 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 144.0, 131.8, 123.6, 114.9, 69.9, 47.3, 42.3, 32.5, 25.0. 21.1.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2957 (*vs*), 2926 (*s*), 1644 (*w*), 1618 (*w*), 1464 (*m*), 1371 (*m*), 1167 (*w*), 895 (*m*), 862 (*m*), 816 (*s*).

**HRMS** (EI) calc. $C_{10}H_{15}{}^{79}BrO$ $[M]^+$: 214.0357; found: 214.0369.




**1a** **S64**

**Phenol S64**

Phenol **S64** was prepared according to General Procedure A. After 2 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel

(1% dichloromethane in hexanes initially, grading to 20% dichloromethane in hexanes) to give phenol **S64** (20.0 mg, 21%) as a pale yellow oil.

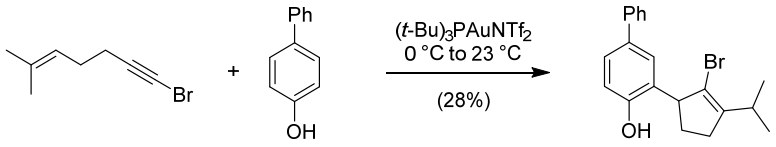
**TLC** (30% dichloromethane in hexanes): $R_f$ = 0.25 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 6.81 (s, 2H), 4.66 (s, 1H), 3.87–3.78 (m, 1H), 3.13 (hept, *J* = 6.8 Hz, 2H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.50–2.24 (m, 3H), 1.89–1.78 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 148.7, 147.7, 135.9, 133.6, 122.5, 118.8, 56.4, 32.5, 29.3, 28.9, 27.4, 22.9, 22.9, 20.7, 20.4.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3578 (*br w*), 2961 (*vs*), 2689 (*m*), 1643 (*m*), 1468 (*s*), 1309 (*m*), 1199 (*s*), 1152 (*m*), 876 (*w*), 764 (*w*).

**HRMS** (EI) calc. for $C_{20}H_{29}{}^{79}BrO$ $[M]^+$: 364.1402; found: 364.1387.




**1a** **S65**

**Phenol S65**

Phenol **S65** was prepared according to General Procedure A. After 3.5 h, the reaction mixture was concentrated and the residue was purified by flash-column chromatography on silica gel (5% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to give phenol **S65** (51.2 mg, 28%) as a pale yellow oil.

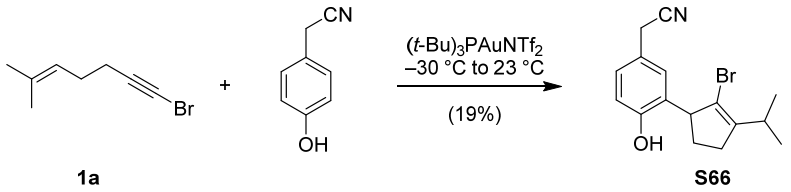
**TLC** (10% ethyl acetate in hexanes): $R_f$ = 0.33 (UV, $KMnO_4$).

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.54 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.37 (dd, *J* = 8.3 Hz, 2.3 Hz, 1H), 7.33–7.27 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.05 (s, 1H), 4.36–4.20 (m, 1H), 3.00 (hept, *J* = 6.9 Hz, 1H), 2.61–2.45 (m, 2H), 2.44–2.33 (m, 1H), 2.03–1.89 (m, 1H), 1.12 (d, *J* =6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.5, 149.9, 141.1, 134.1, 129.5, 128.8, 127.9, 126.9, 126.7, 126.6, 116.7, 116.5, 51.6, 30.4, 29.4, 29.3, 20.7, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3430 (*br w*), 2960 (*m*), 1608 (*m*), 1485 (*vs*), 1454 (*m*), 1265 (*s*), 1109 (*m*), 821 (*m*), 762 (*vs*), 698 (*s*).

**HRMS** (EI) calc. for $C_{20}H_{21}{}^{79}BrO$ $[M]^+$: 356.0776; found: 356.0771.




1a S66

**Phenol S66**

Phenol **S66** was prepared according to a modified General Procedure C. $(t\text{-Bu})_3PAuNTf_2$ (3.61 mg, 5.32 μmol, 5 mol %) was added to a solution of bromide **1a** (46.8 mg, 0.25 mmol, 1 equiv) and *p*-fluorophenol (29.4 mg, 0.26 mmol, 1.05 equiv) in dichloromethane (1 mL) at –30 °C. After 45 min, 4-hydroxyphenylacetonitrile (172 mg, 1.25 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to 0 °C. After 1 h, methanesulfonic acid (81.1 μL, 1.25 mmol, 5 equi) was slowly added and the reaction mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes initially, grading to 30% ethyl acetate in hexanes) to give phenol **S66** (15.4 mg, 19%) as a white solid.

**TLC** (30% ethyl acetate in hexanes): $R_f = 0.33$ (UV, $KMnO_4$).

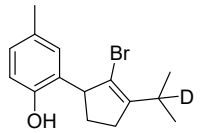
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 7.08 (d, *J* = 8.2 Hz, 1H), 6.97 (s, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 1H), 4.26–4.15 (m, 1H), 3.67 (s, 2H), 2.97 (hept, *J* = 6.8 Hz, 1H), 2.58–2.42 (m, 2H), 2.42–2.31 (m, 1H), 1.95–1.80 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ = 153.8, 150.3, 130.2, 128.7, 127.6, 122.1, 118.4, 116.9, 116.1, 51.6, 30.2, 29.4, 29.3, 23.1, 20.6, 20.3.

**IR** (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3368 (*s*), 2961 (*m*), 1611 (*w*), 1509 (*s*), 1438 (*m*), 1270 (*s*), 1118 (*m*), 900 (*w*), 807 (*s*), 740 (*w*).

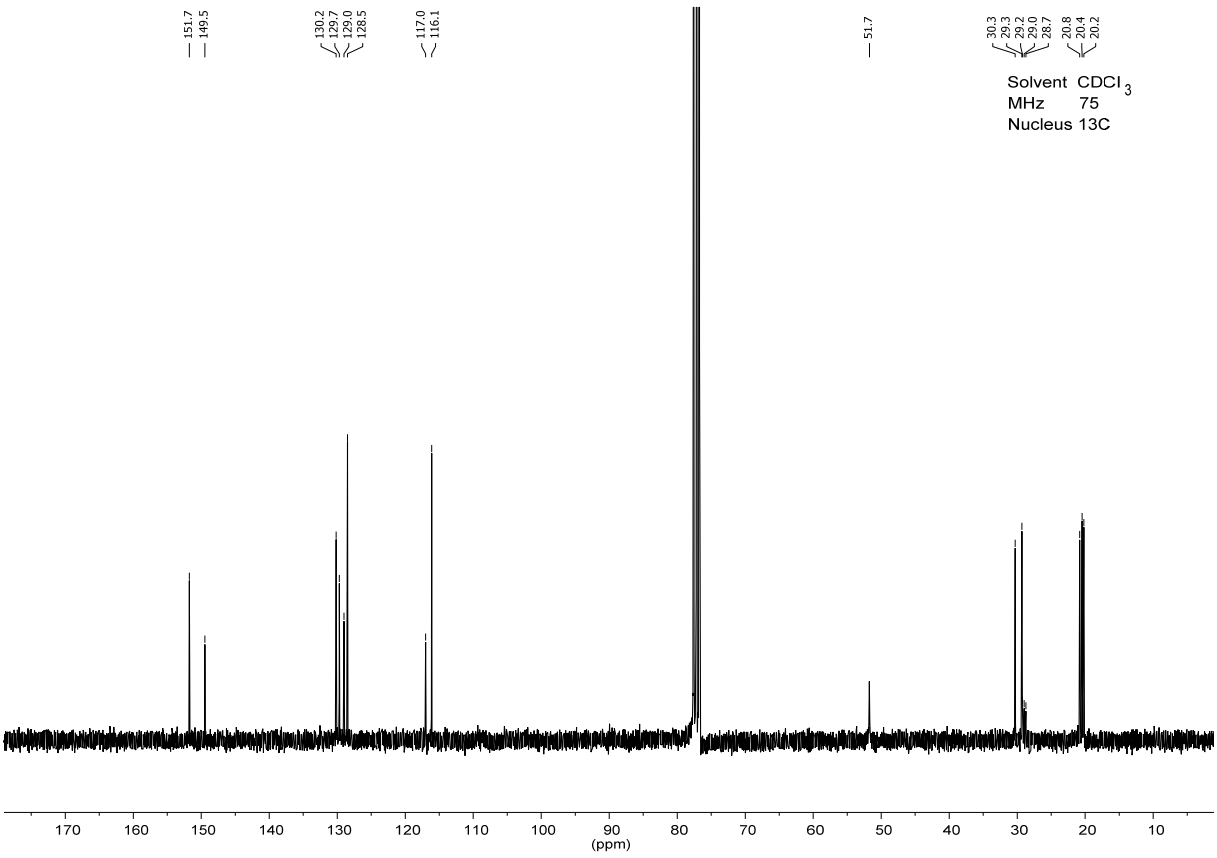
**HRMS** (EI) calc. for $C_{16}H_{18}{}^{79}BrNO$ $[M]^+$: 319.0527; found: 319.0564.

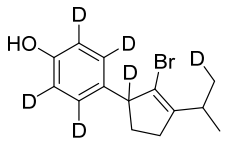
### 3.4.4. $^{1}H$ and $^{13}C$ NMR Spectra




**21**

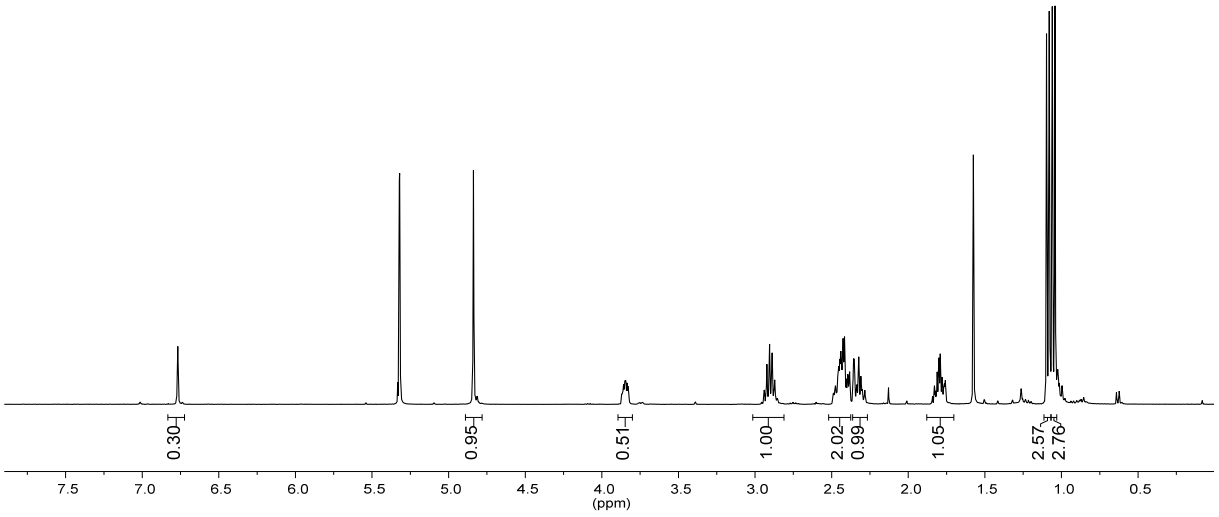


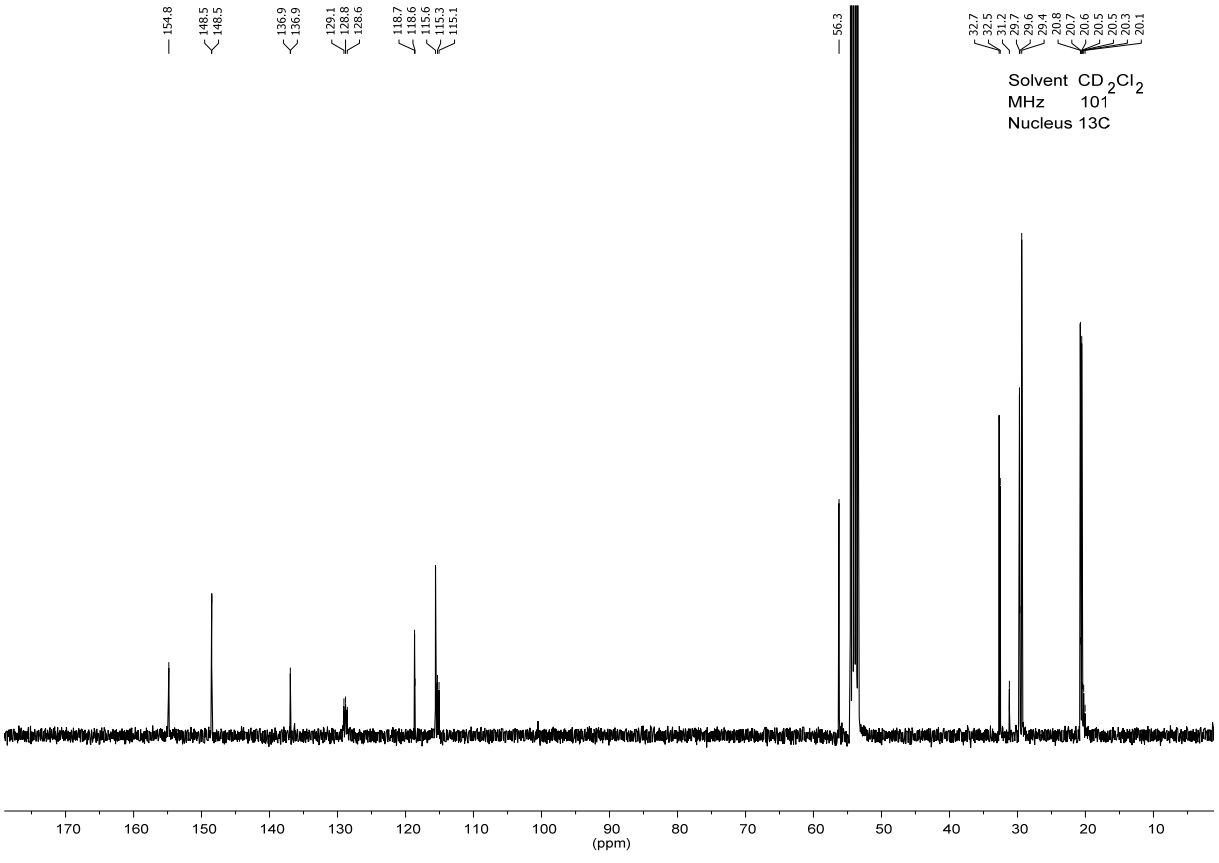



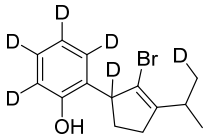



**23**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H

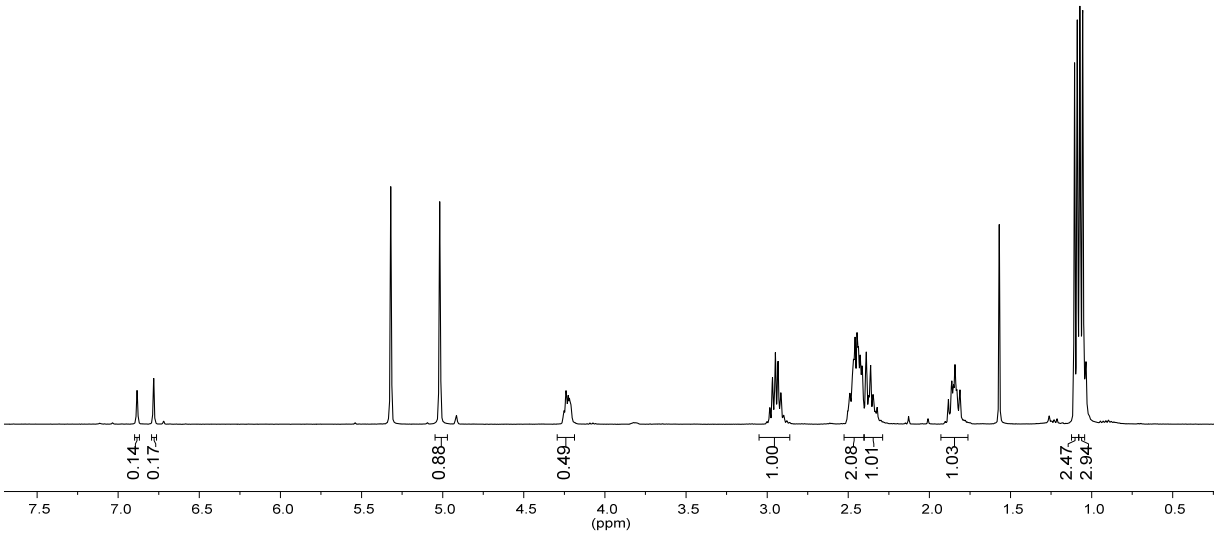


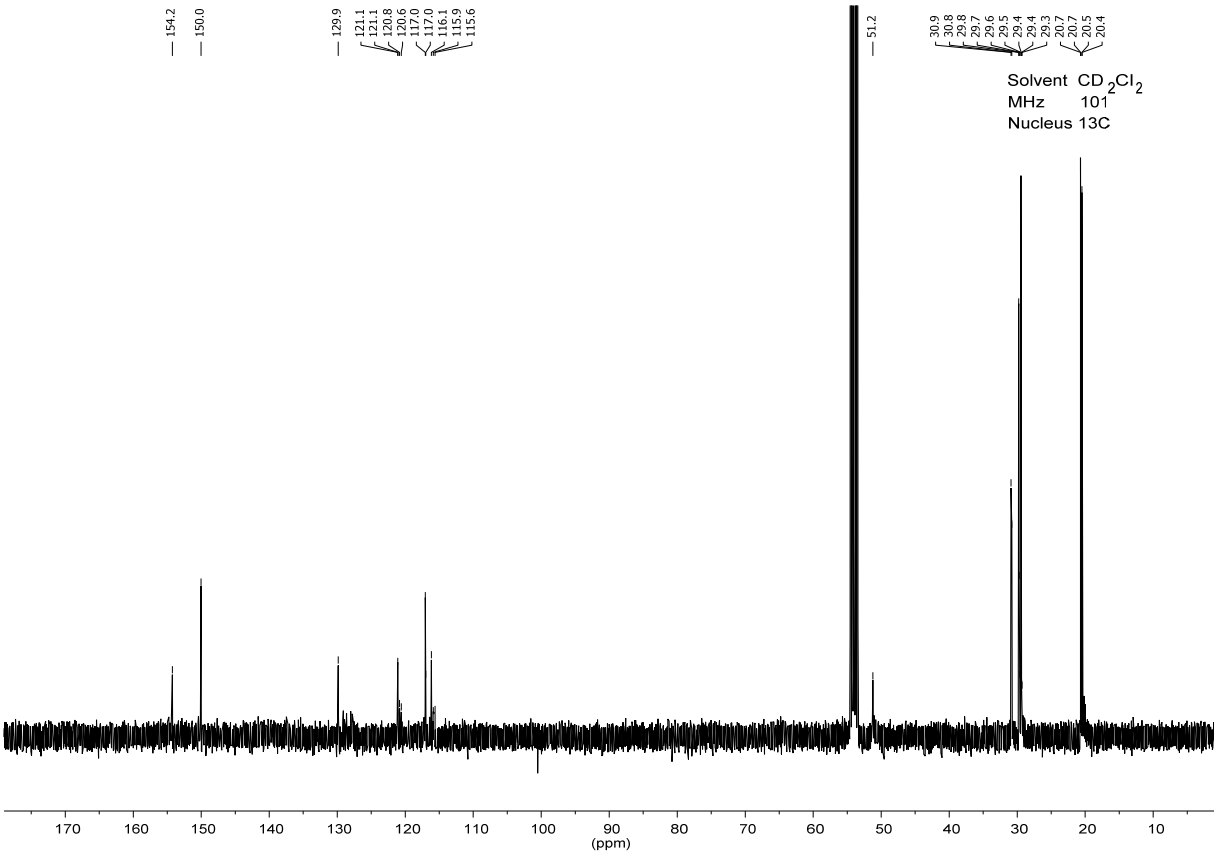


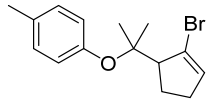

**24**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H



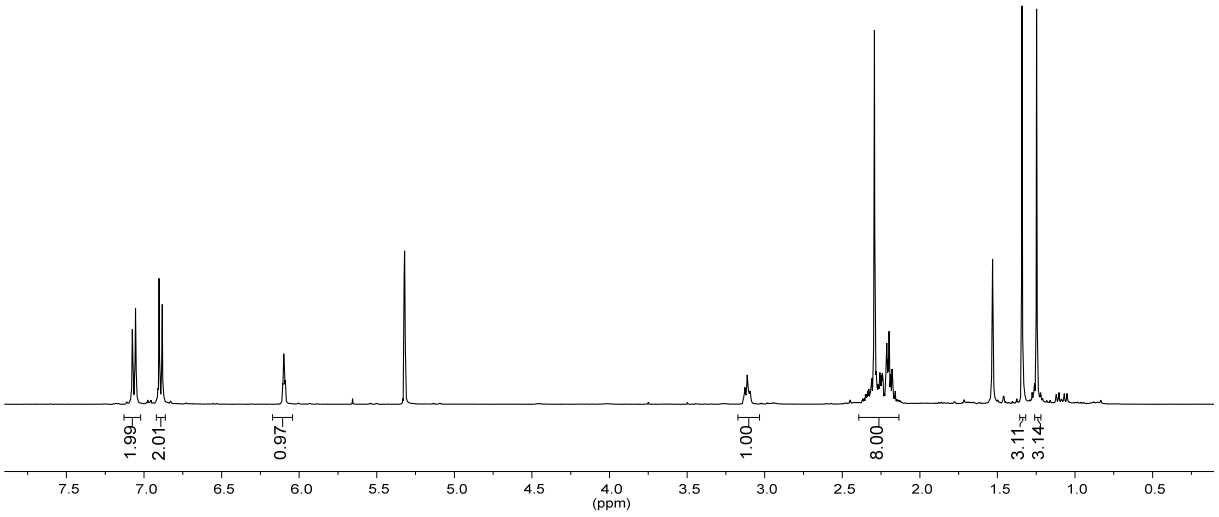

Solvent $CD_2Cl_2$
MHz 101
Nucleus 13C

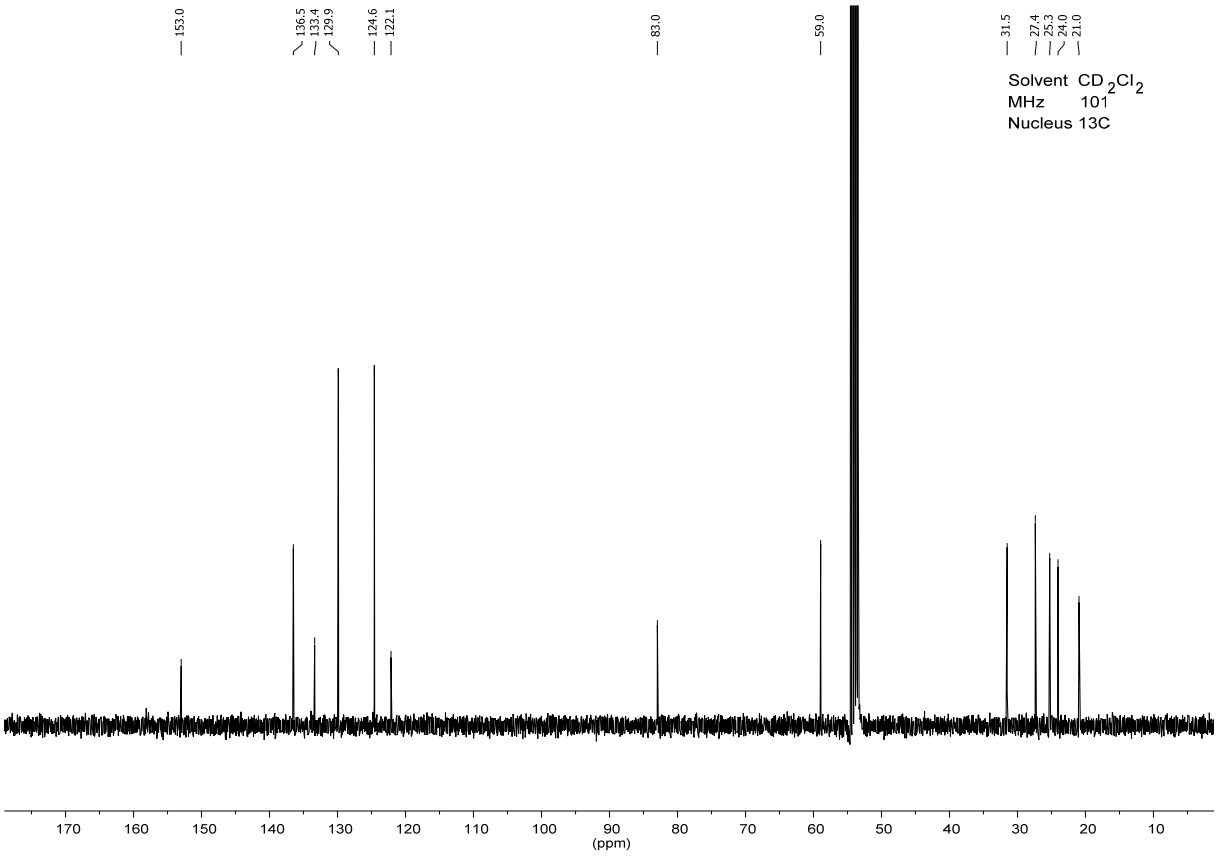




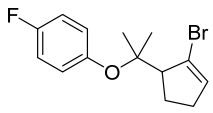

**25**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H



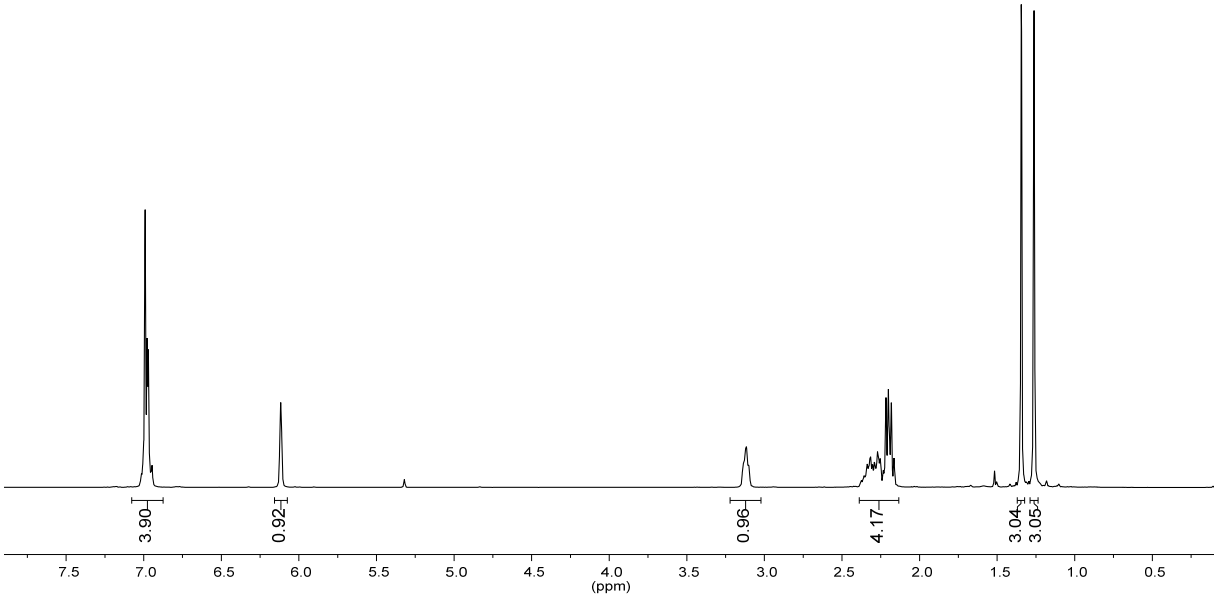




Solvent $CD_2Cl_2$
MHz 101
Nucleus 13C



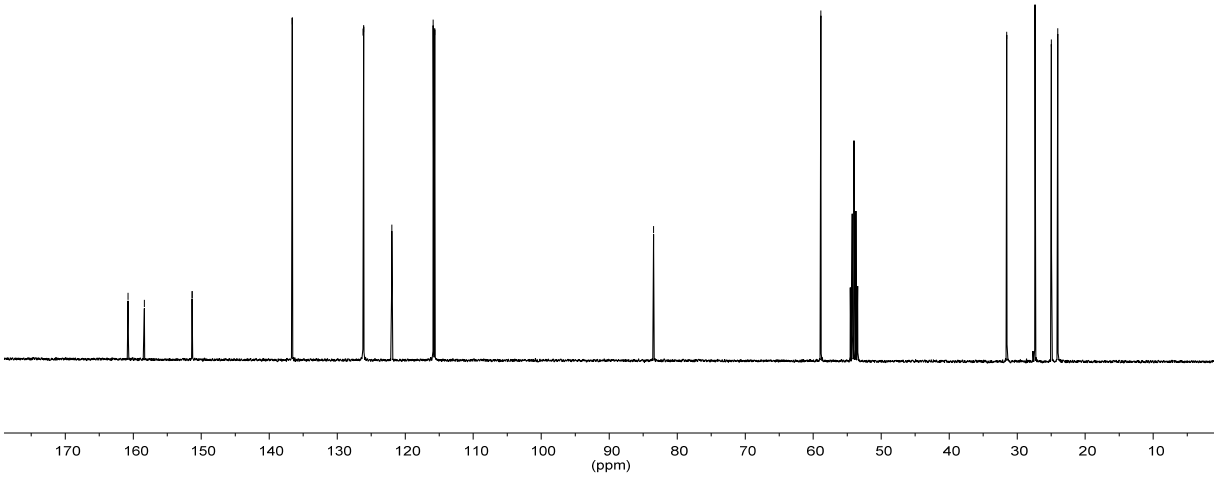

**S32**

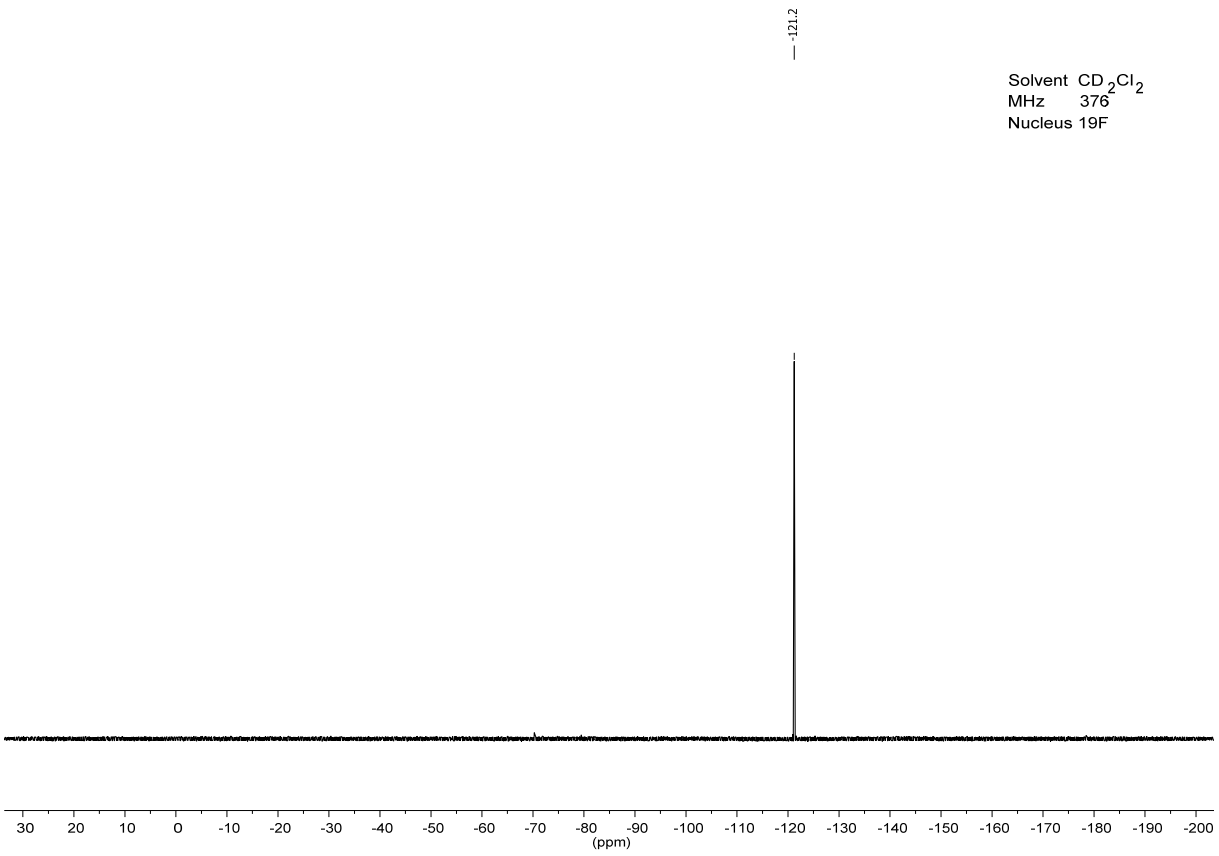
Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H

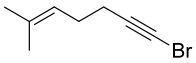



160.8
158.4
151.3
151.3
136.6
126.2
126.1
122.0
115.9
115.7
83.5
58.9
31.5
27.4
25.0
24.0

Solvent $CD_2Cl_2$
MHz 101
Nucleus 13C

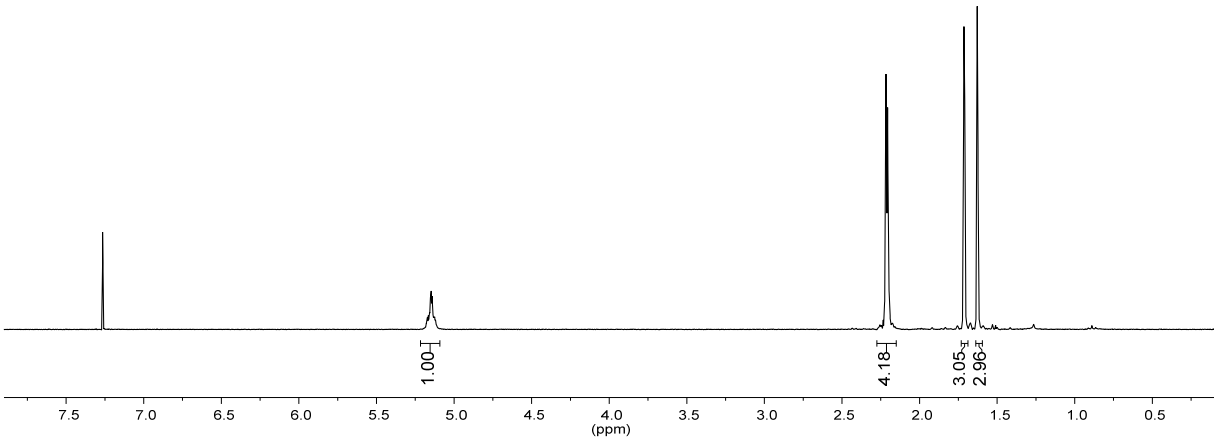


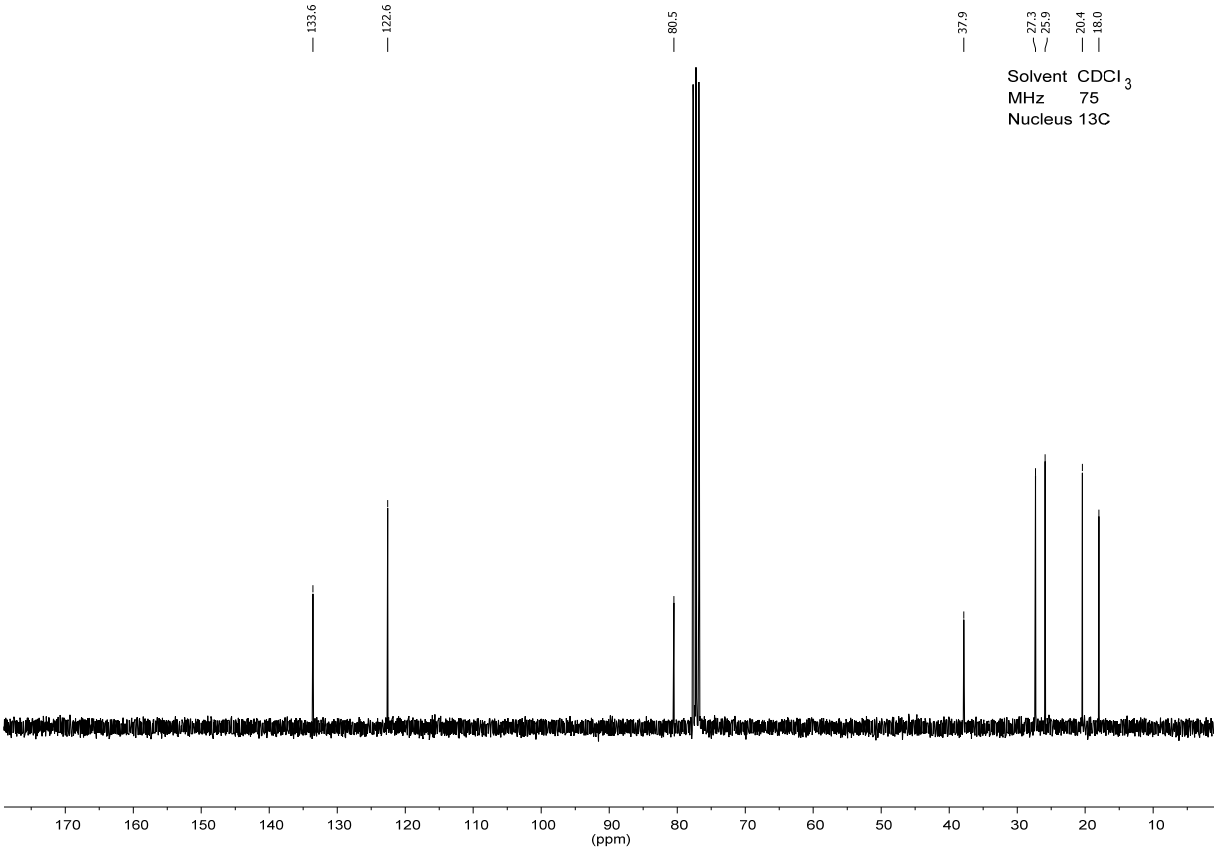

-121.2
Solvent CD2Cl2
MHz 376
Nucleus 19F
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
(ppm)

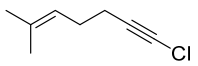



**1a**

Solvent CDCl 3
MHz 300
Nucleus 1H

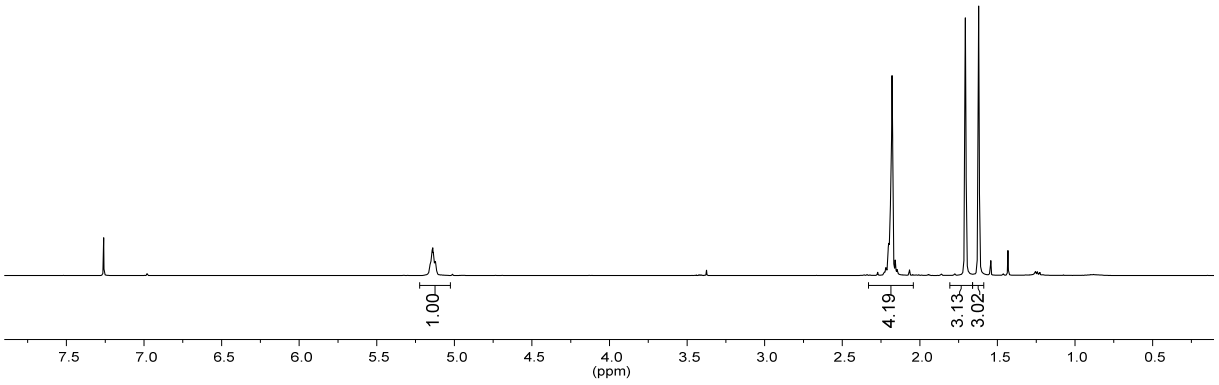


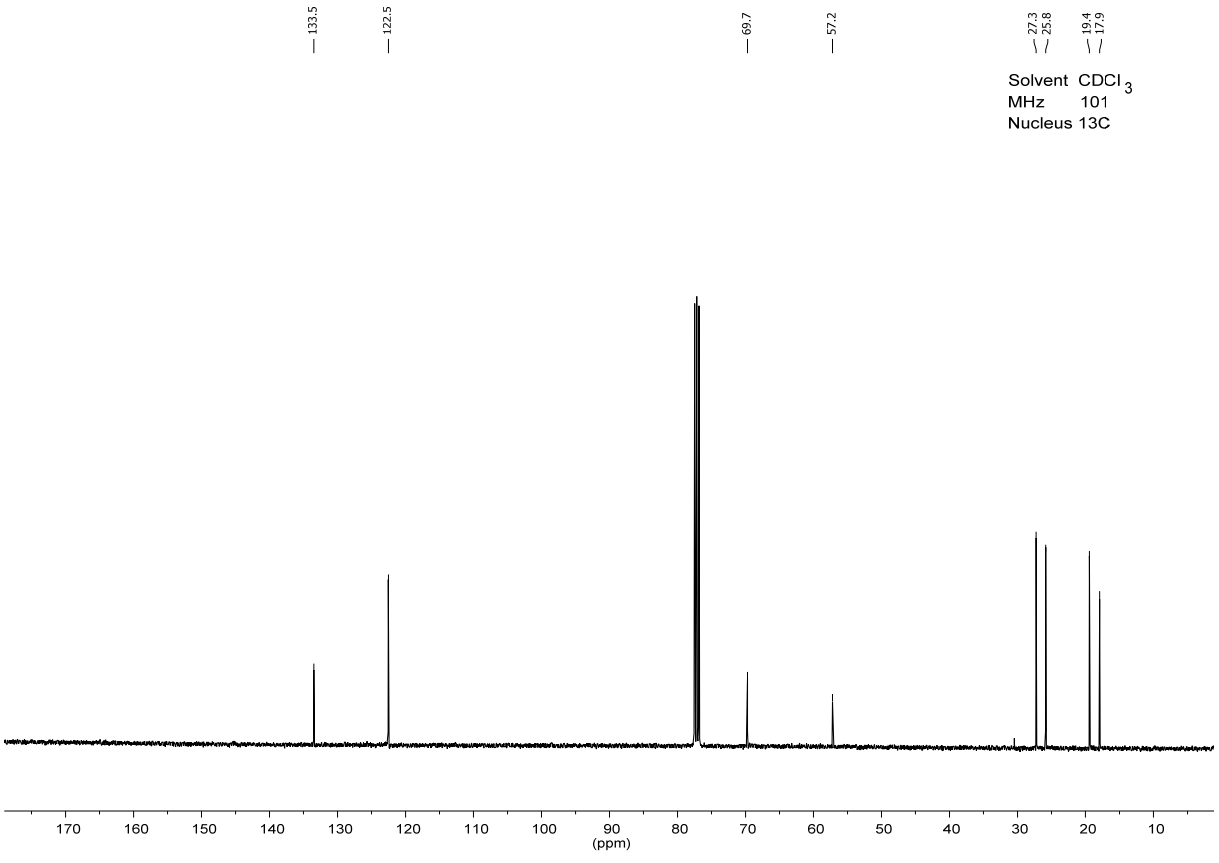



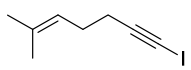



**1b**

Solvent CDCl 3
MHz 400
Nucleus 1H

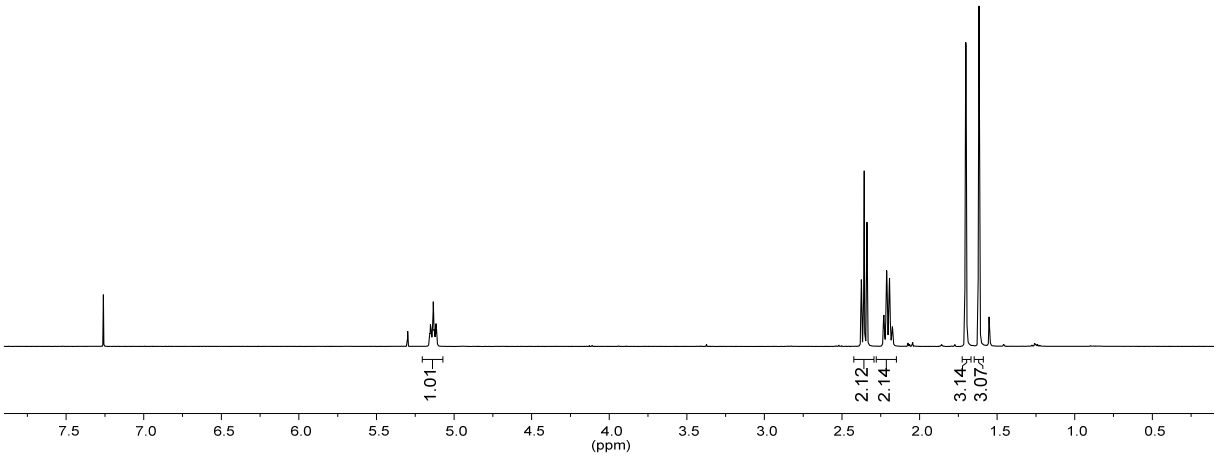




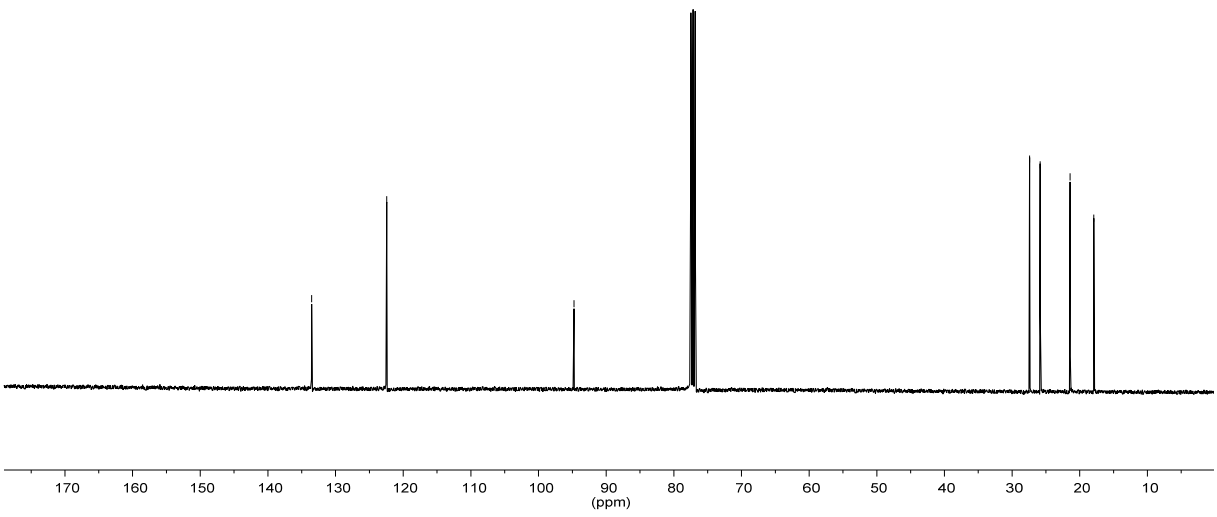
**1c**

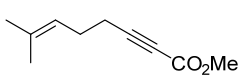
Solvent CDCl 3
MHz 400
Nucleus 1H




133.5
122.4
94.8
27.4
25.9
21.4
17.9

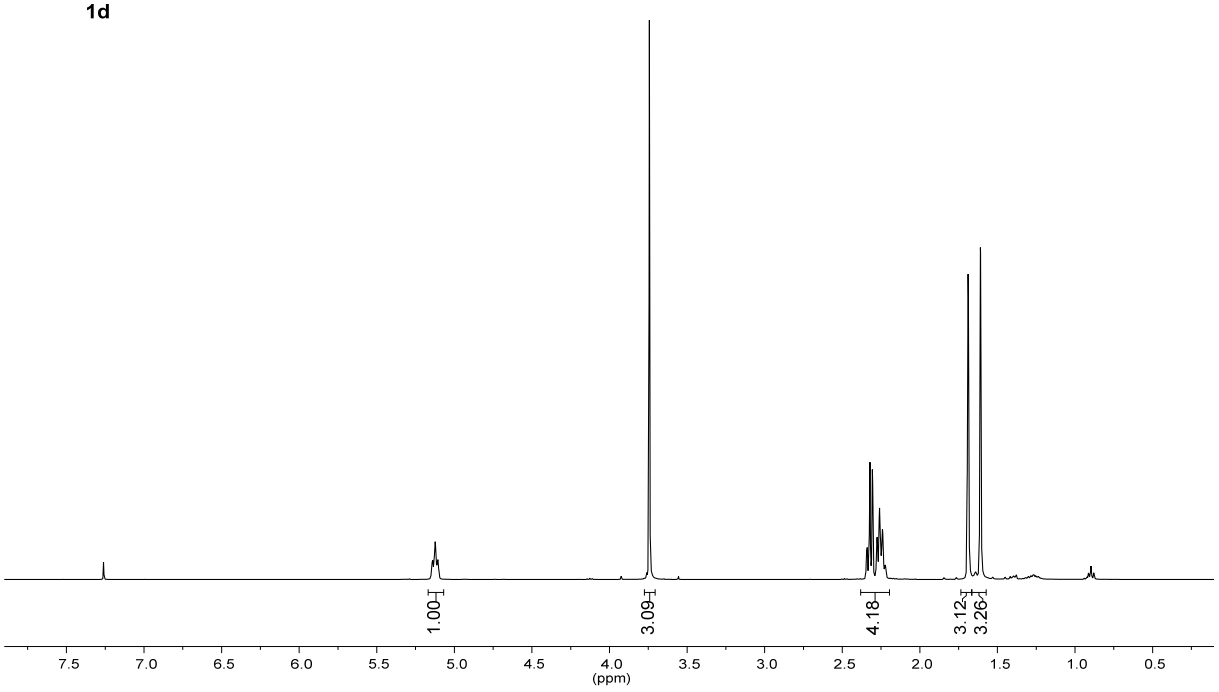
Solvent CDCl 3
MHz 101
Nucleus 13C





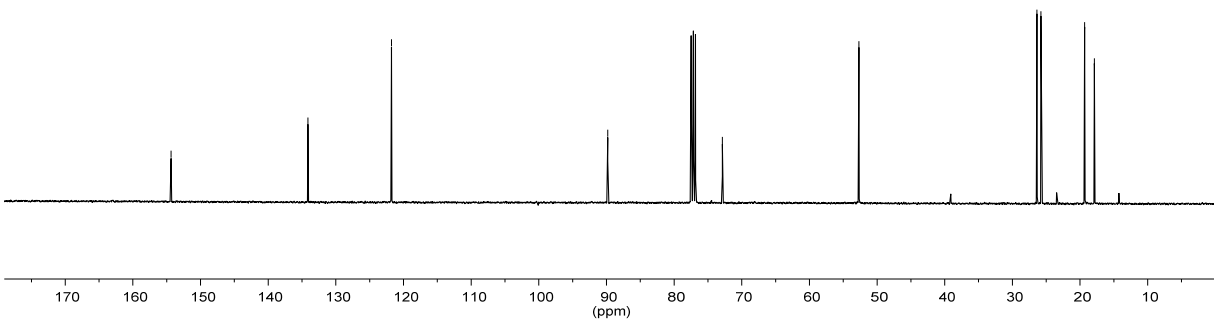

**1d**

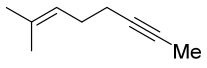
Solvent CDCl 3
MHz 400
Nucleus 1H




154.4
134.1
121.8
89.8
72.9
52.7
26.4
25.8
19.3
17.9

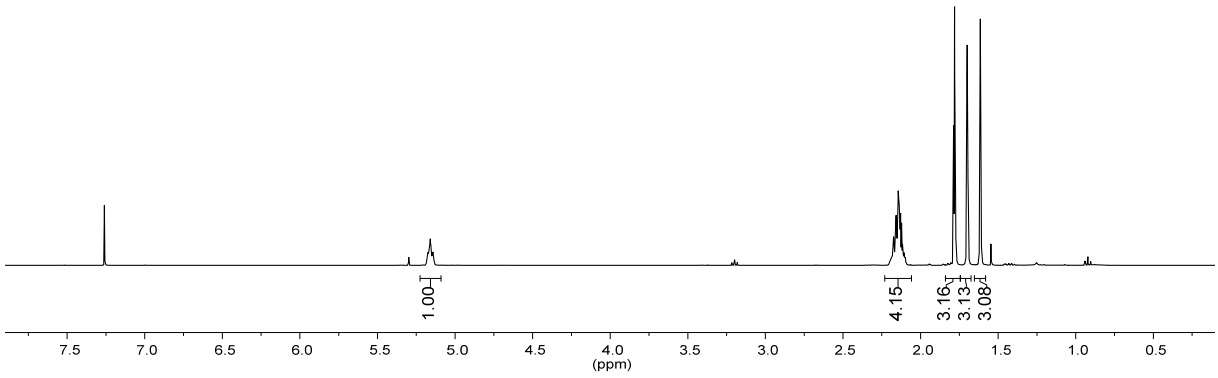
Solvent CDCl 3
MHz 101
Nucleus 13C





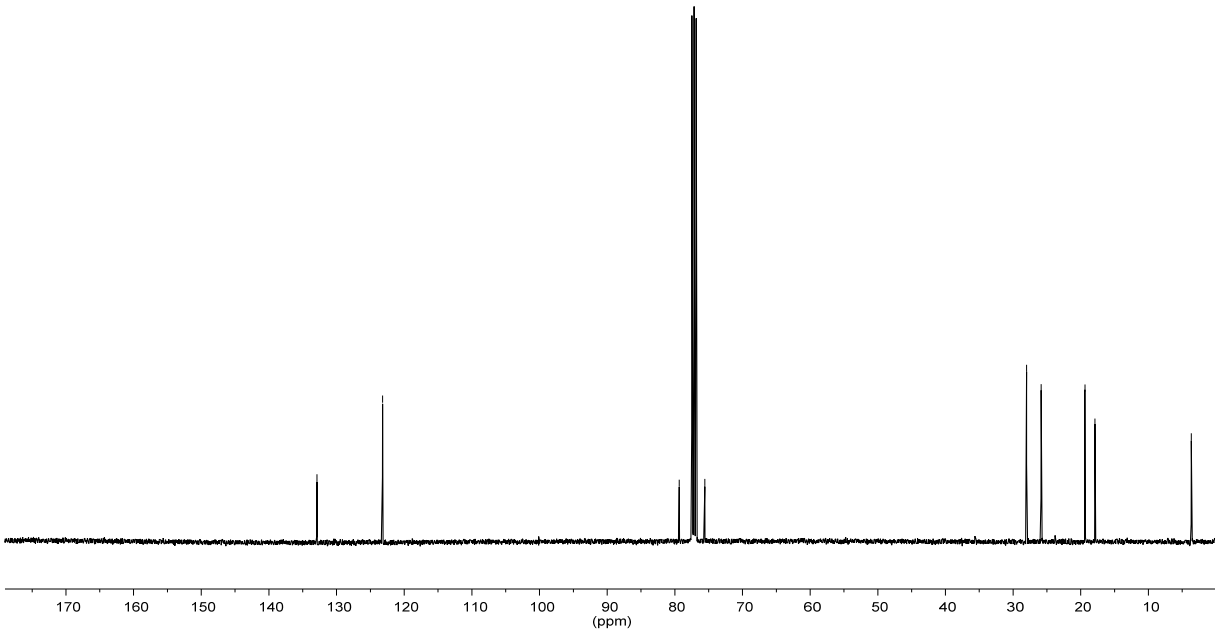

**1e**

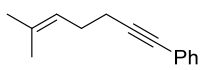
Solvent $CDCl_3$
MHz 400
Nucleus 1H




132.9
123.2
79.4
75.6
28.0
25.9
19.4
17.9
3.7

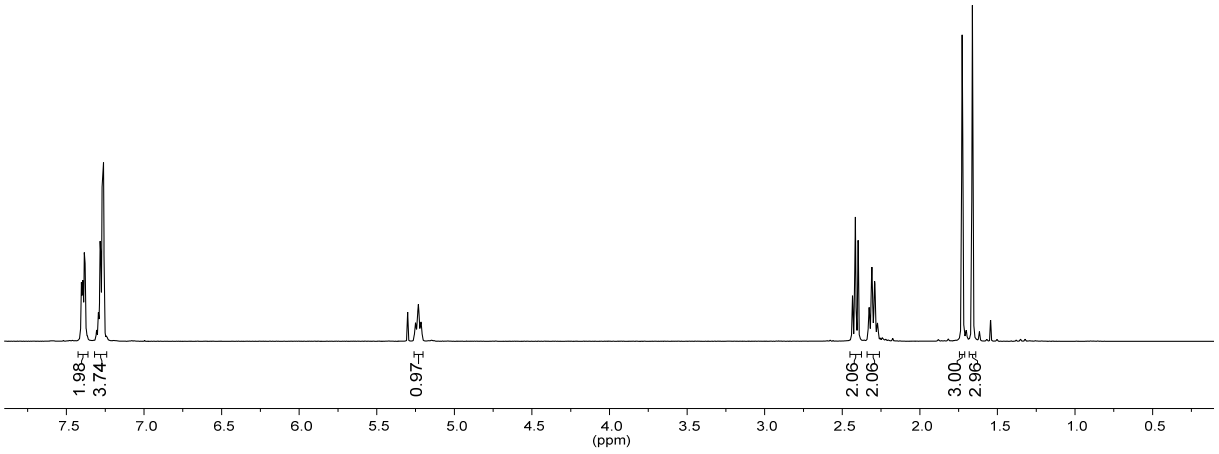
Solvent $CDCl_3$
MHz 101
Nucleus 13C

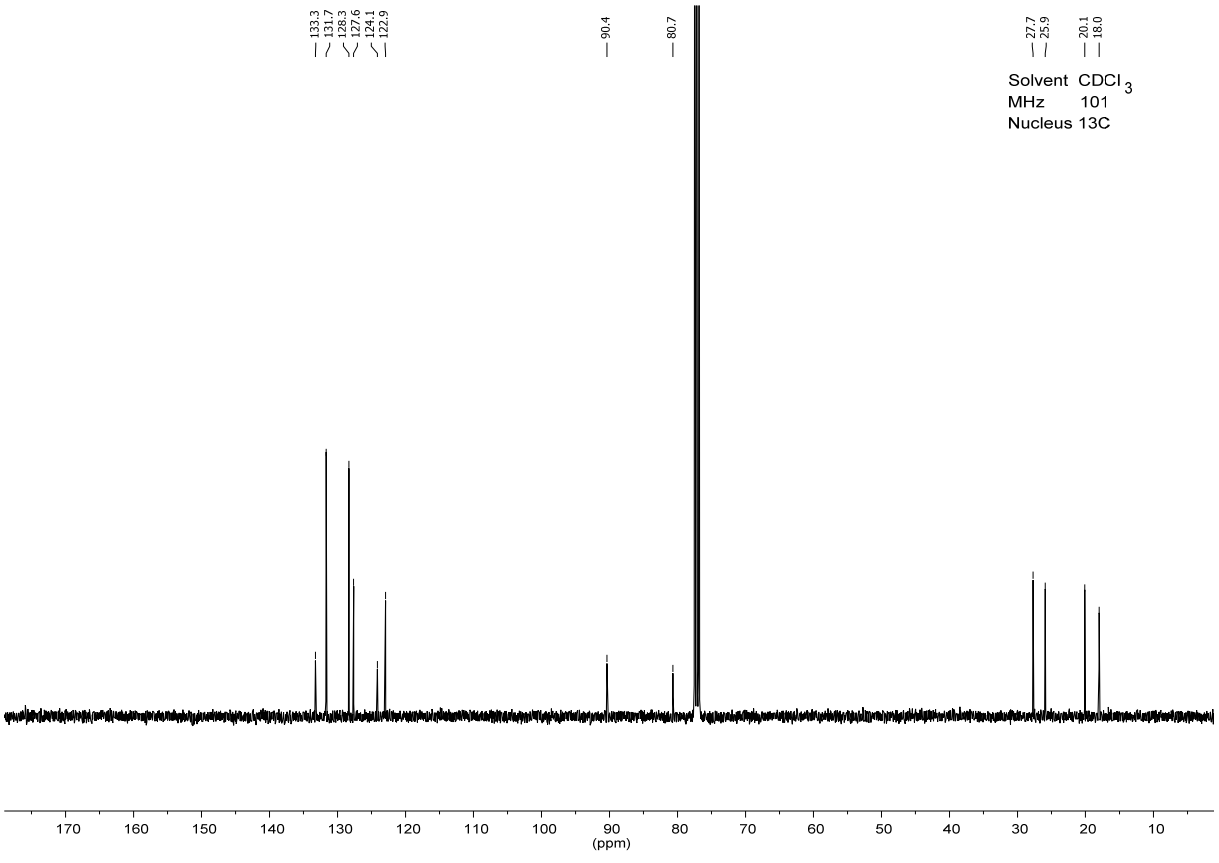


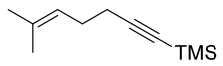



**1g**

Solvent CDCl 3
MHz 400
Nucleus 1H

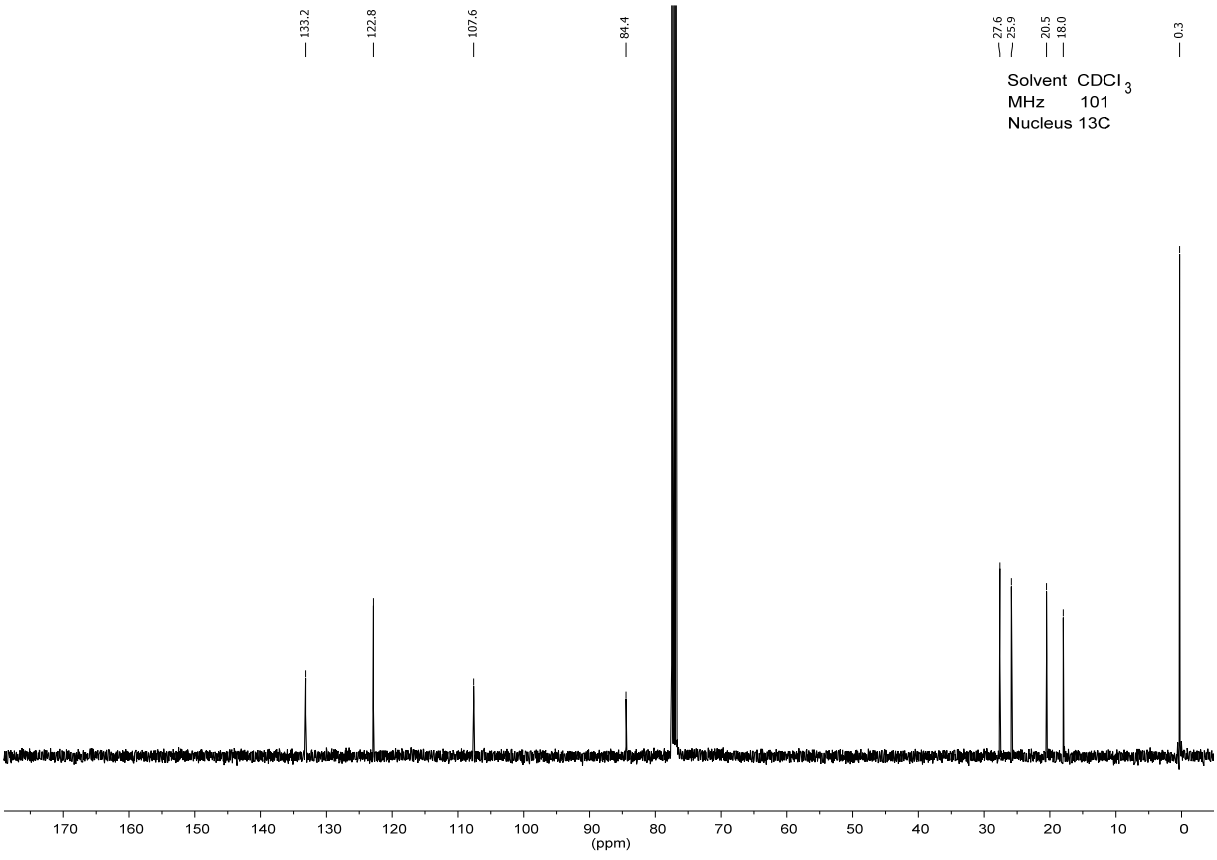


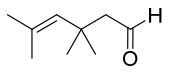




TMS

**1h**

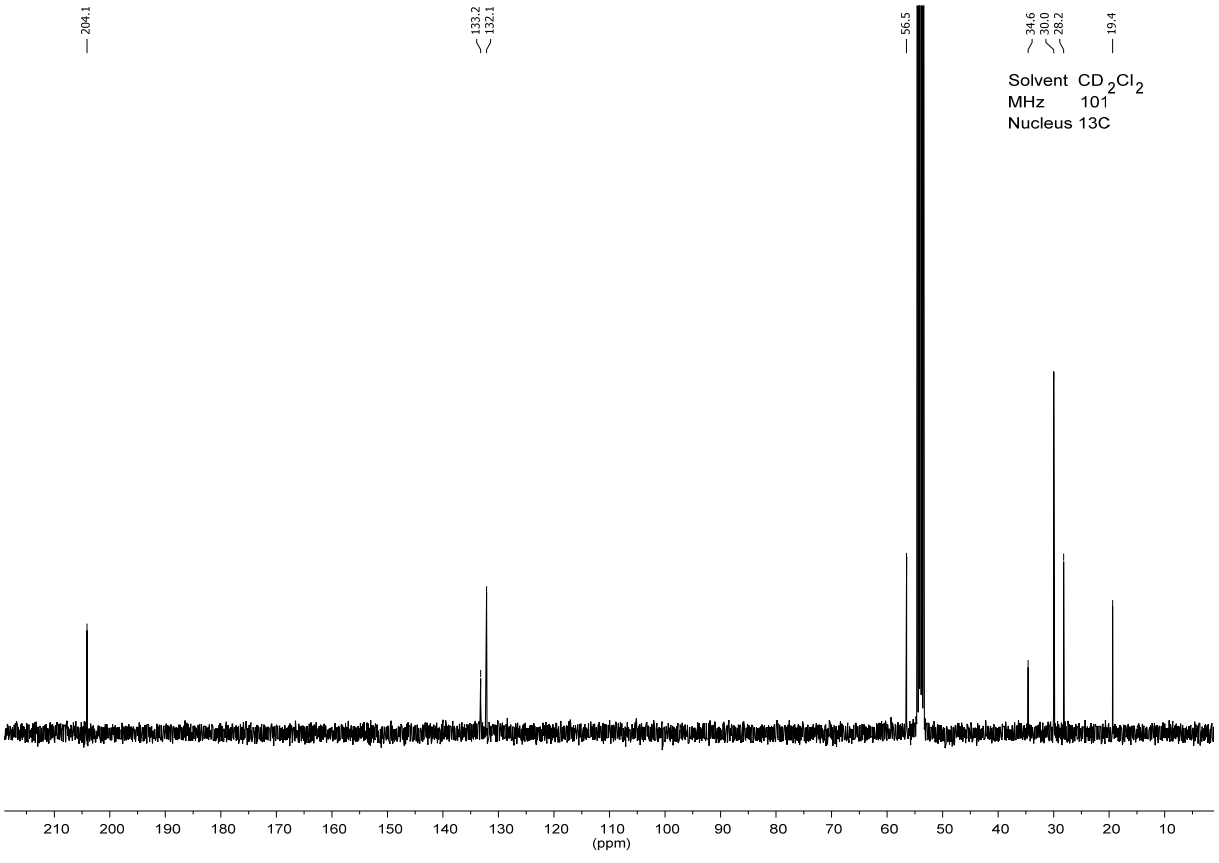

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
4.17
3.13
3.06
9.25
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

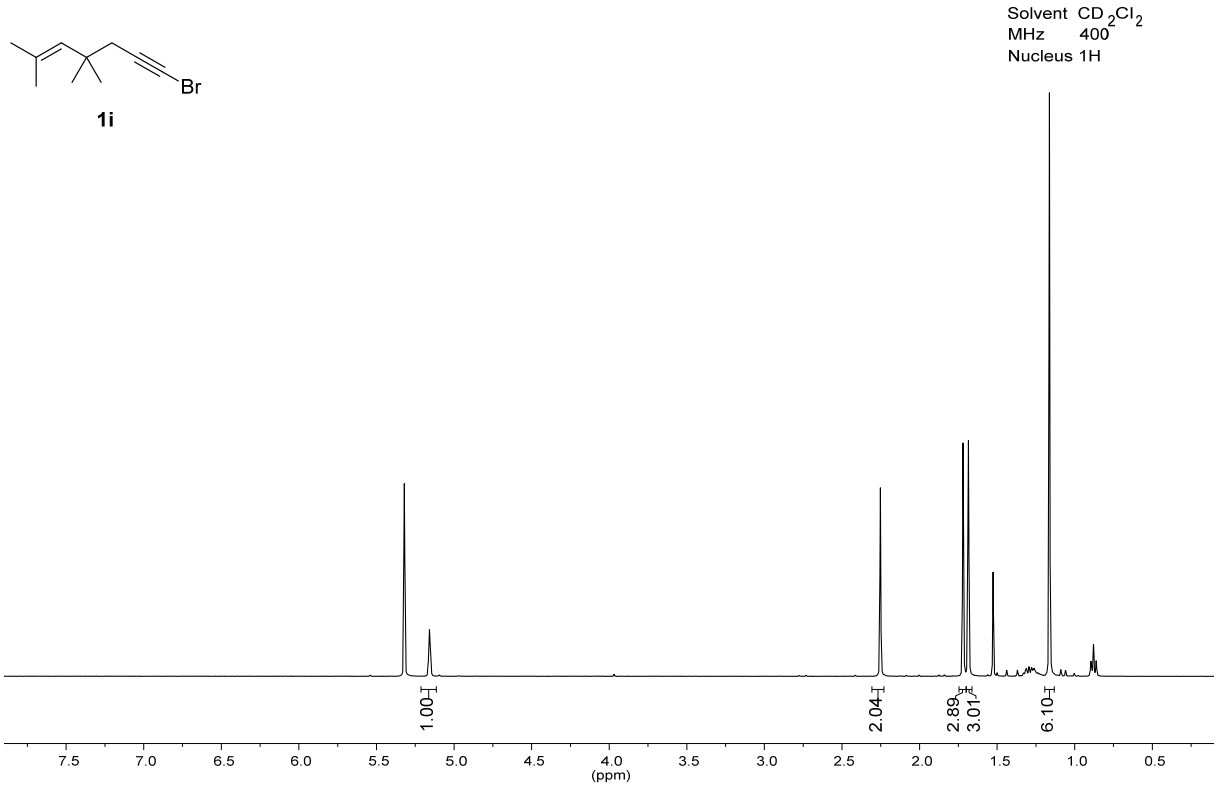

133.2
122.8
107.6
84.4
27.6
25.9
20.5
18.0
0.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

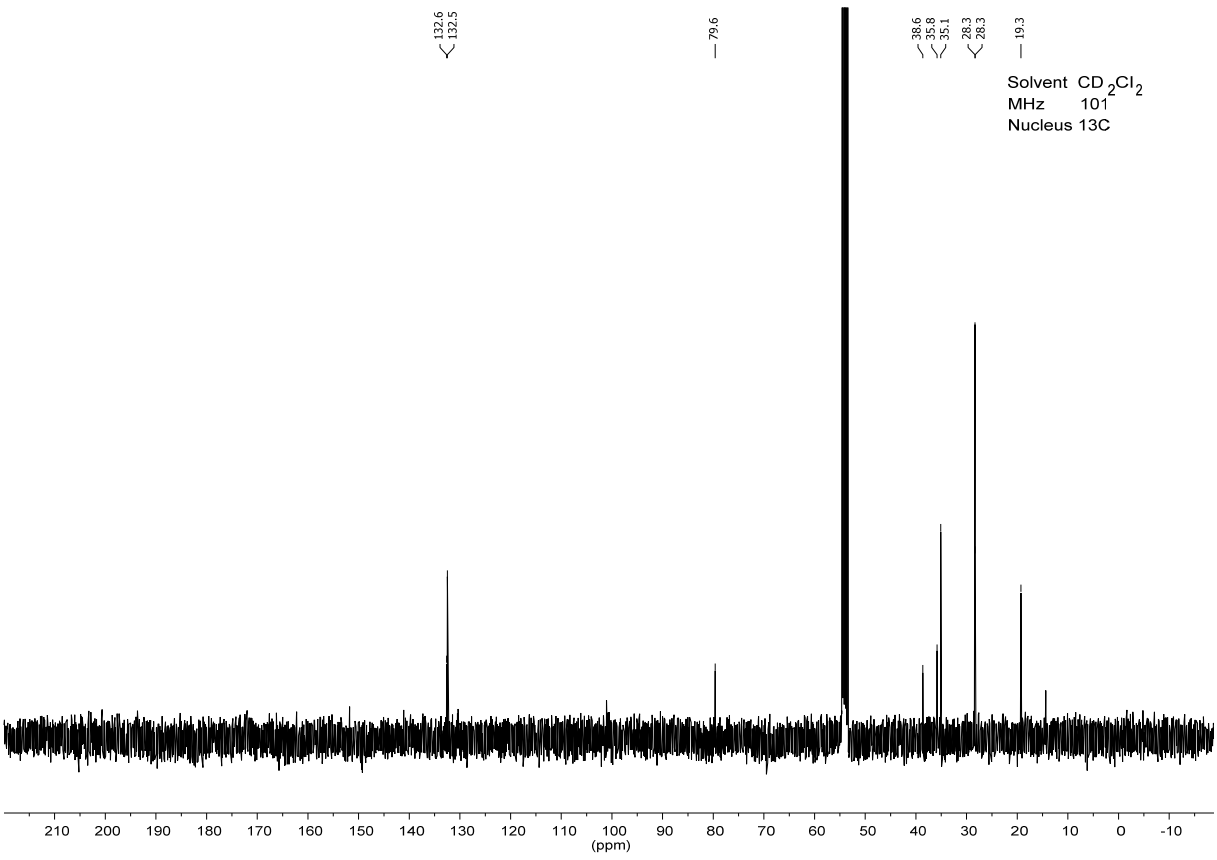


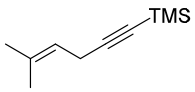
**S43**


Solvent CD2Cl2
MHz 400
Nucleus 1H
1.00
1.04
2.11
2.96
3.08
6.35
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


204.1
133.2
132.1
56.5
34.6
30.0
28.2
19.4
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

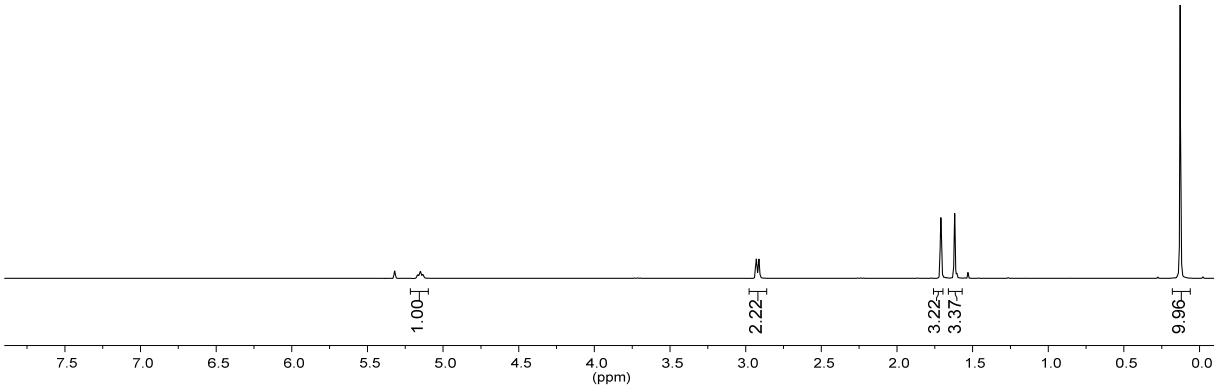

Br
1i
Solvent CD2Cl2
MHz 400
Nucleus 1H
1.00
2.04
2.89
3.01
6.10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

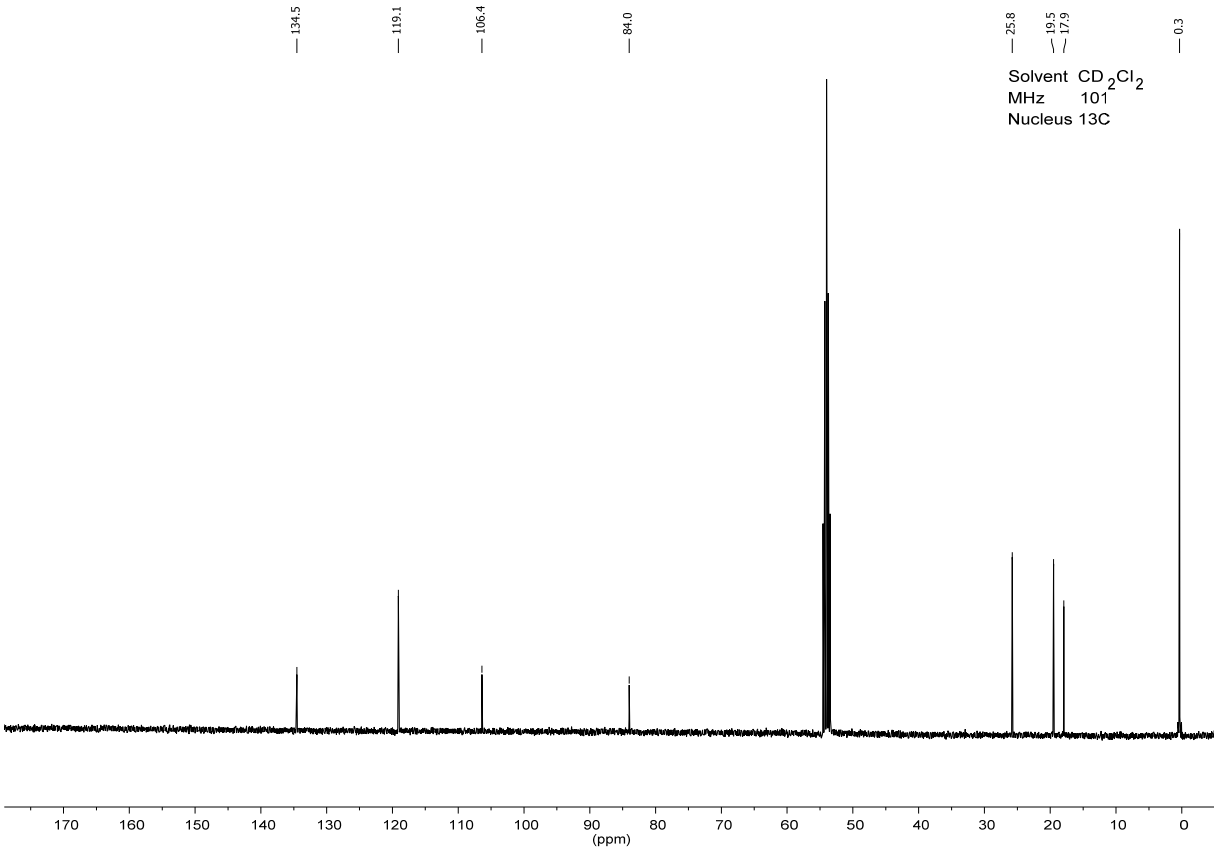

132.6
132.5
79.6
38.6
35.8
35.1
28.3
28.3
19.3
Solvent CD2Cl2
MHz 101
Nucleus 13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

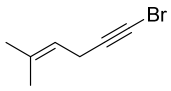



**S44**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H

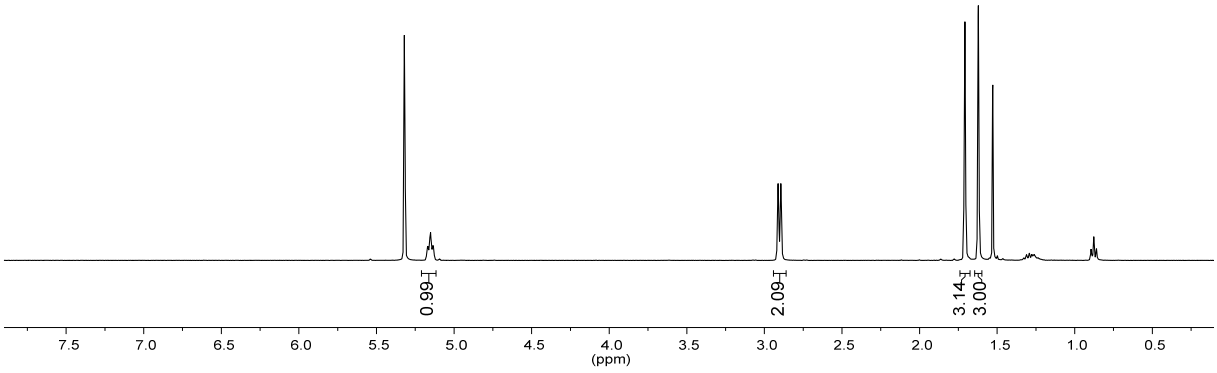


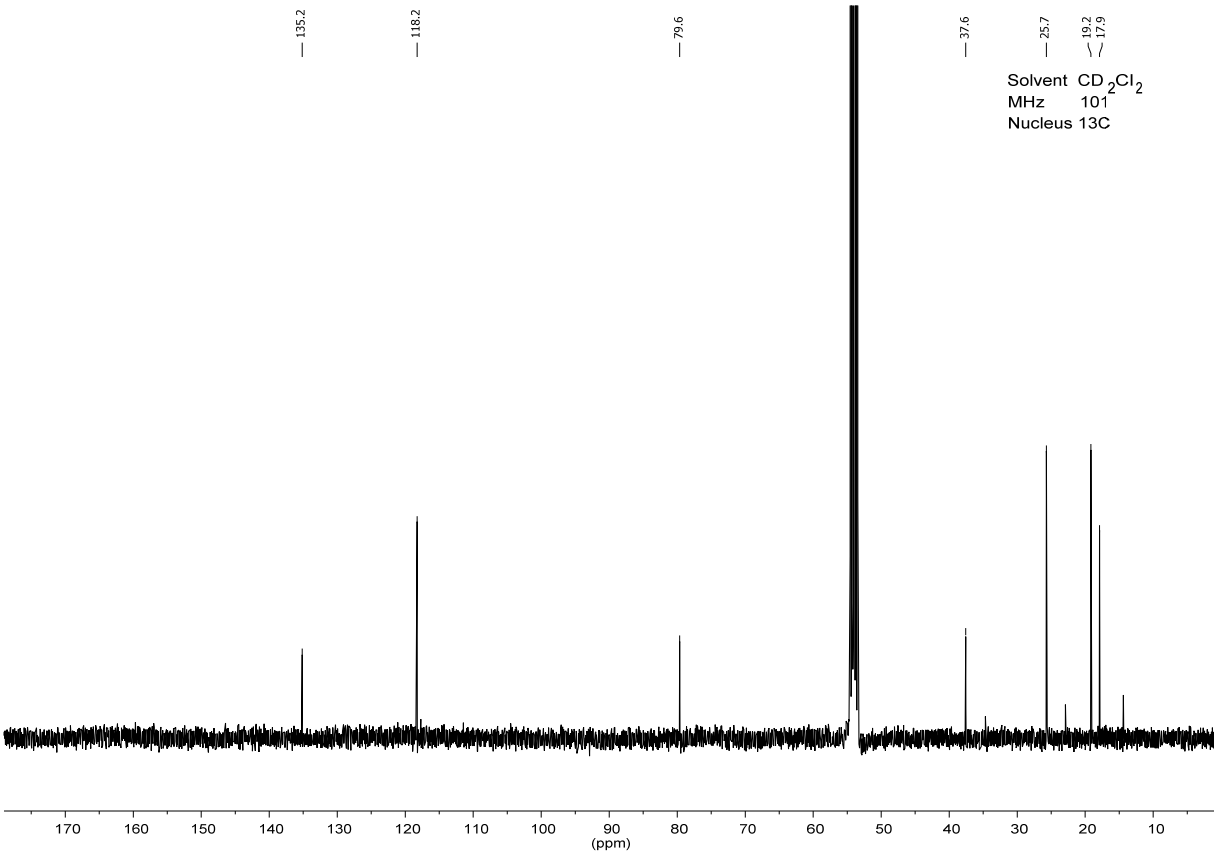



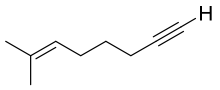



**S45**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H

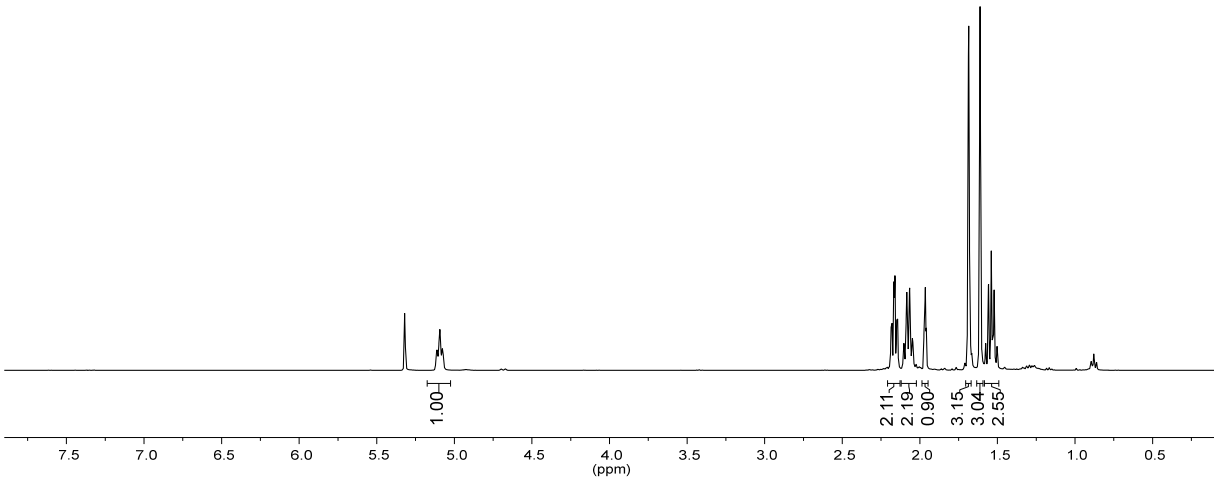


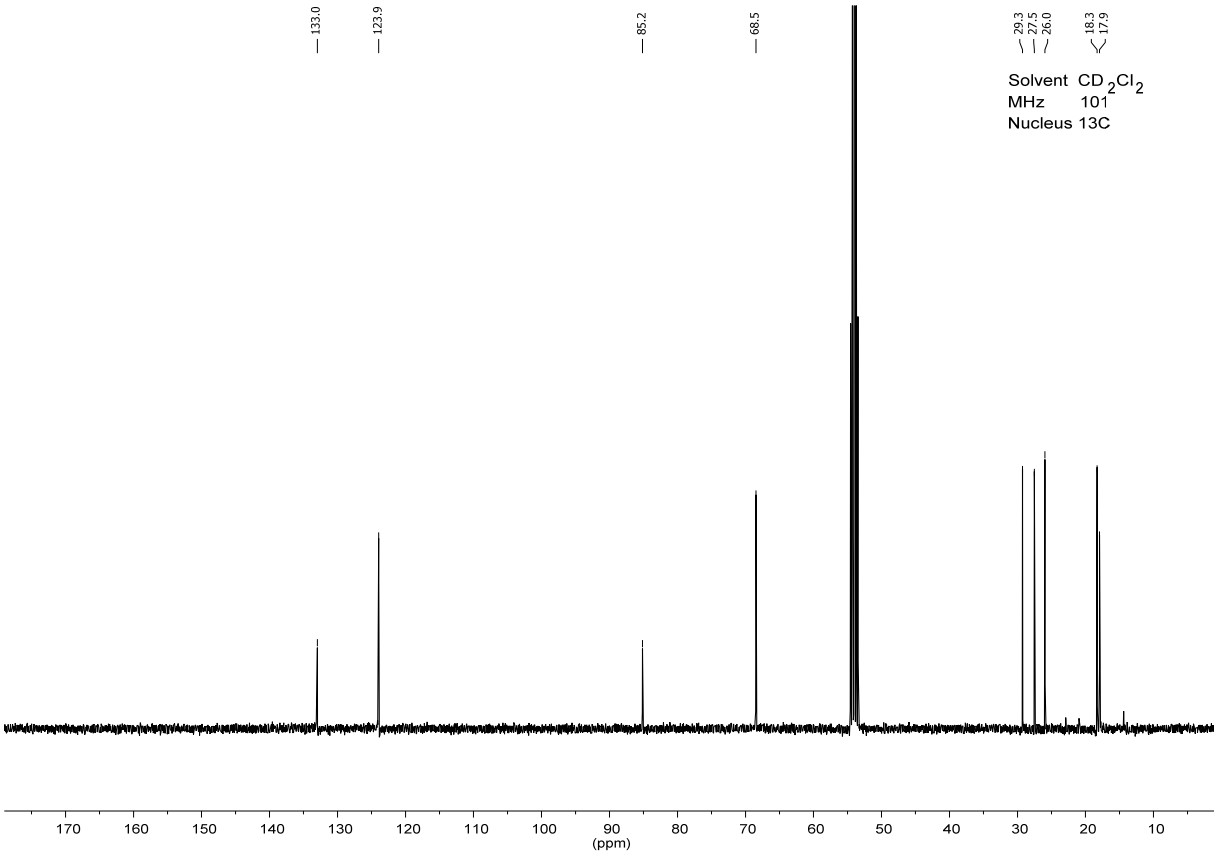



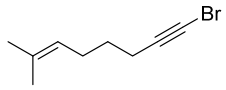


**S48**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H

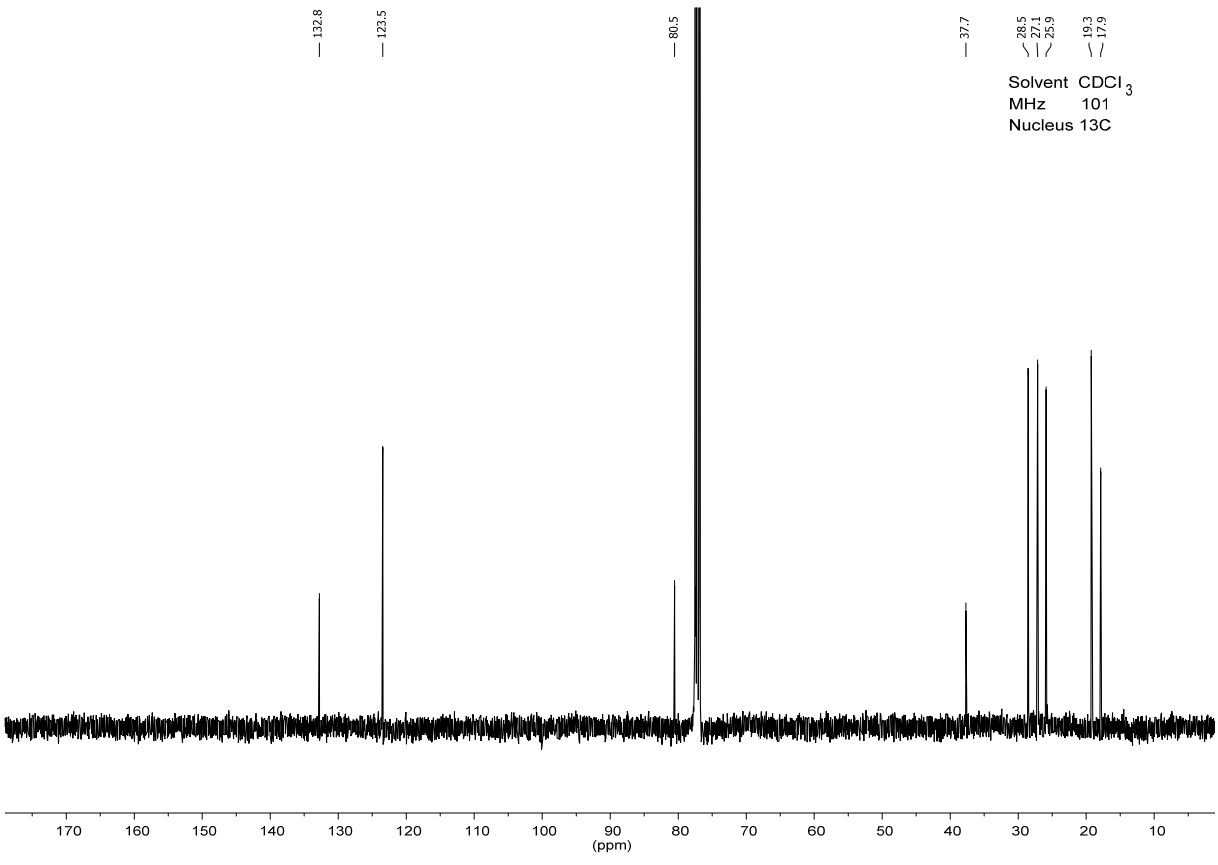


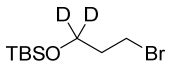




Br

**S49**

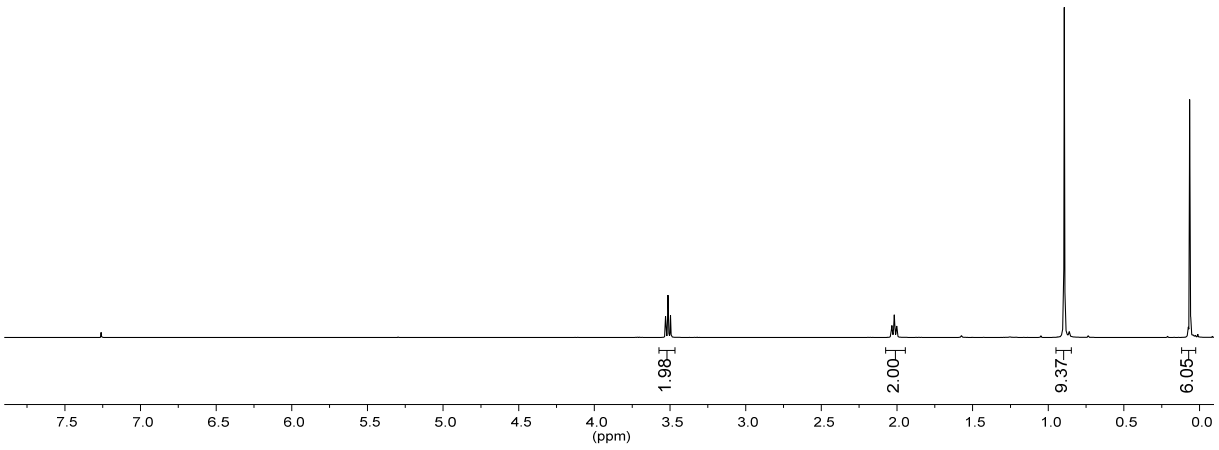

Solvent CDCl3
MHz 400
Nucleus 1H
0.97
2.00
1.99
2.96
2.83
2.47
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

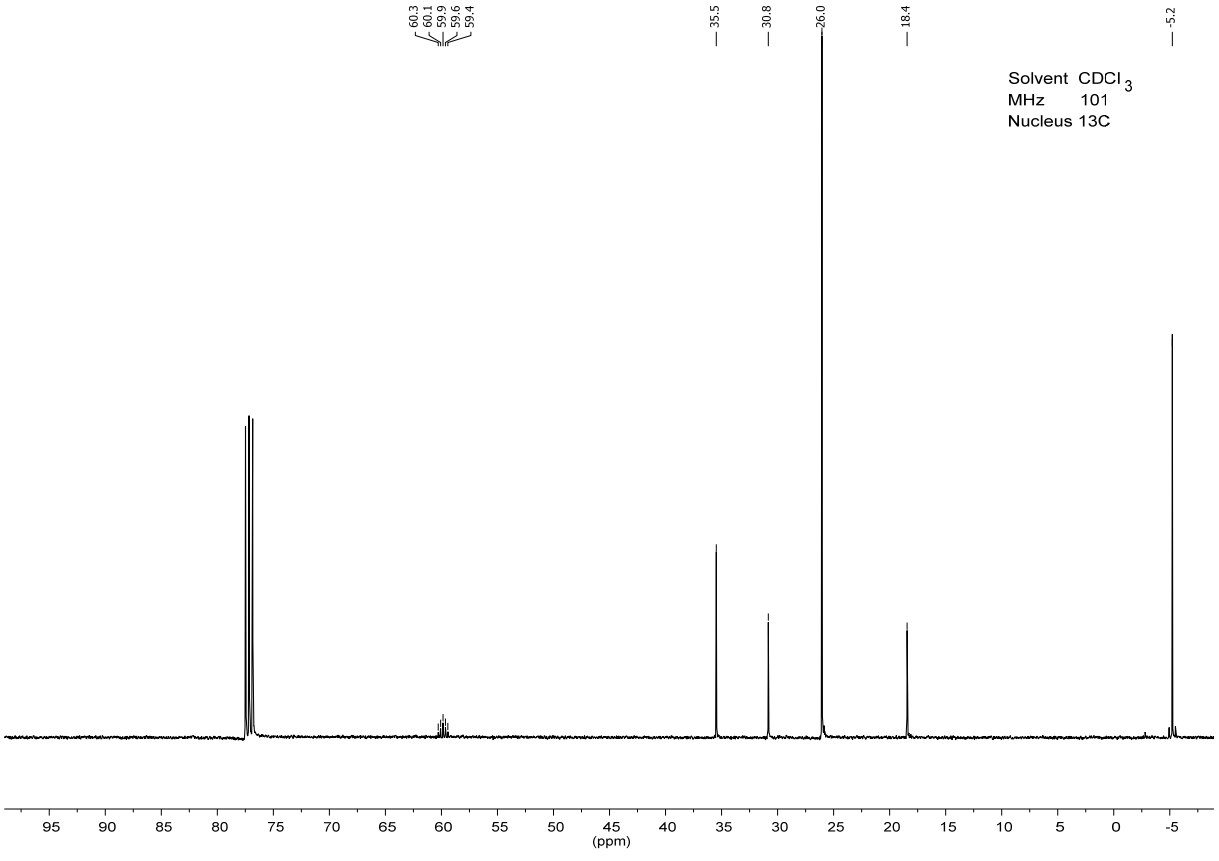

132.8
123.5
80.5
37.7
28.5
27.1
25.9
19.3
17.9
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



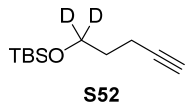

**S51**

Solvent CDCl 3
MHz 400
Nucleus 1H



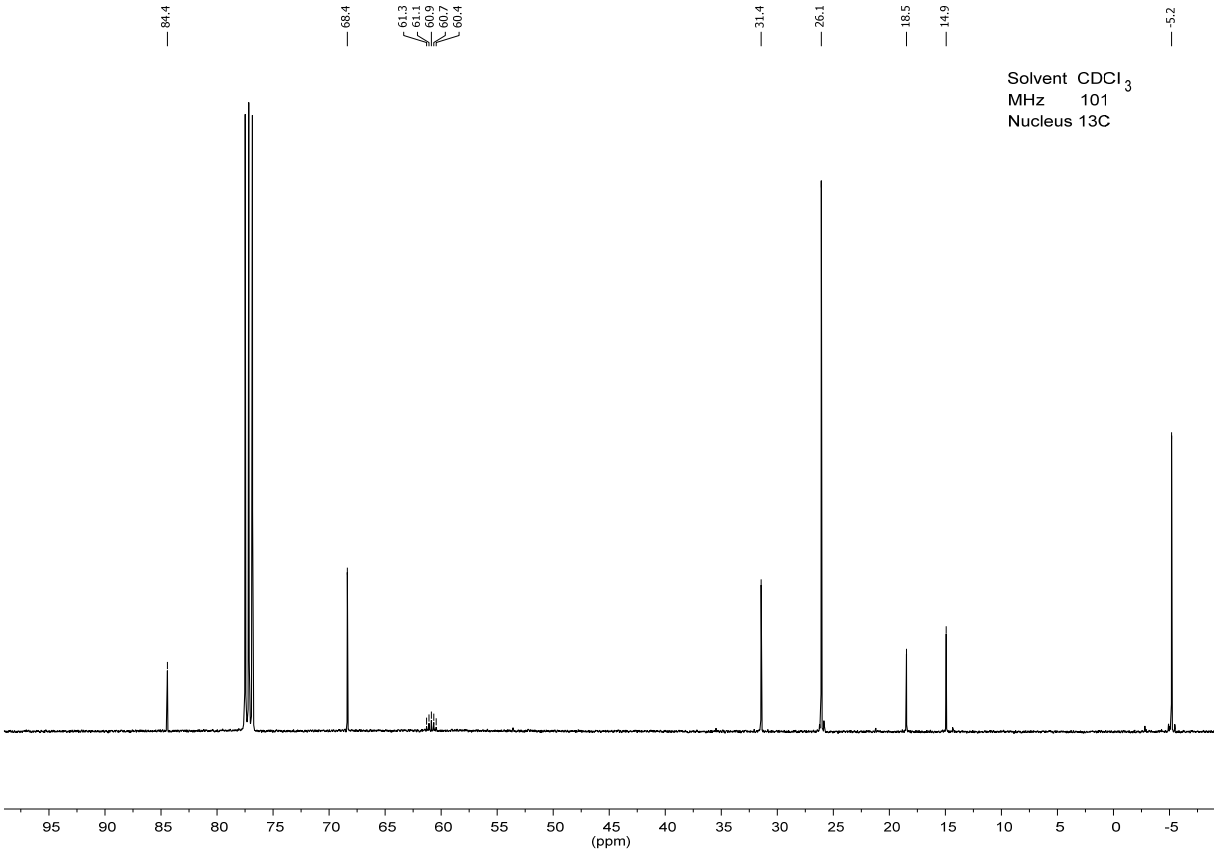



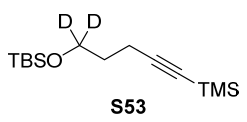

Solvent CDCl 3
MHz 101
Nucleus 13C


D D
TBSO

**S52**

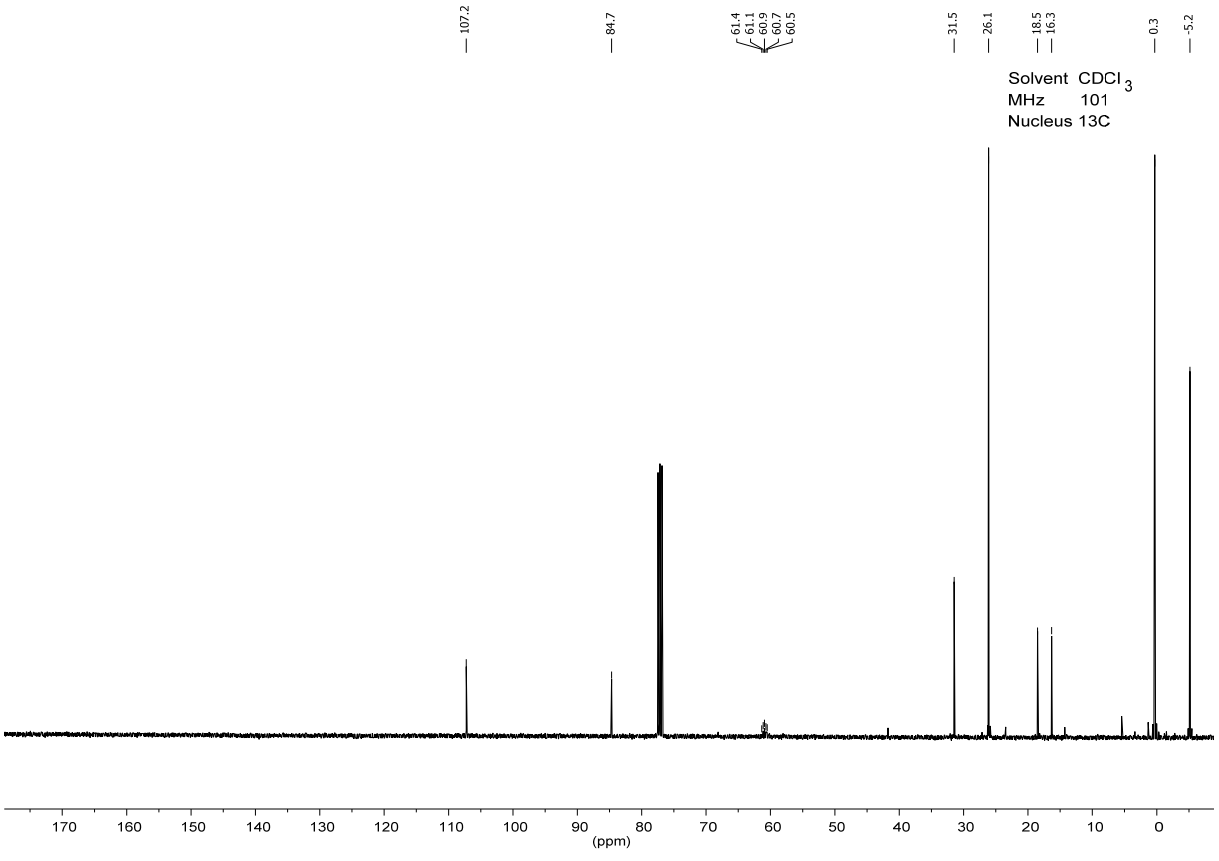

Solvent CDCl3
MHz 400
Nucleus 1H
2.17
1.00
2.19
10.25
6.88
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

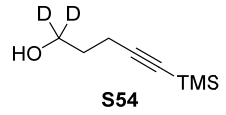

84.4
68.4
61.3
61.1
60.9
60.7
60.4
31.4
26.1
18.5
14.9
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5
(ppm)


D D
TBSO
TMS

**S53**

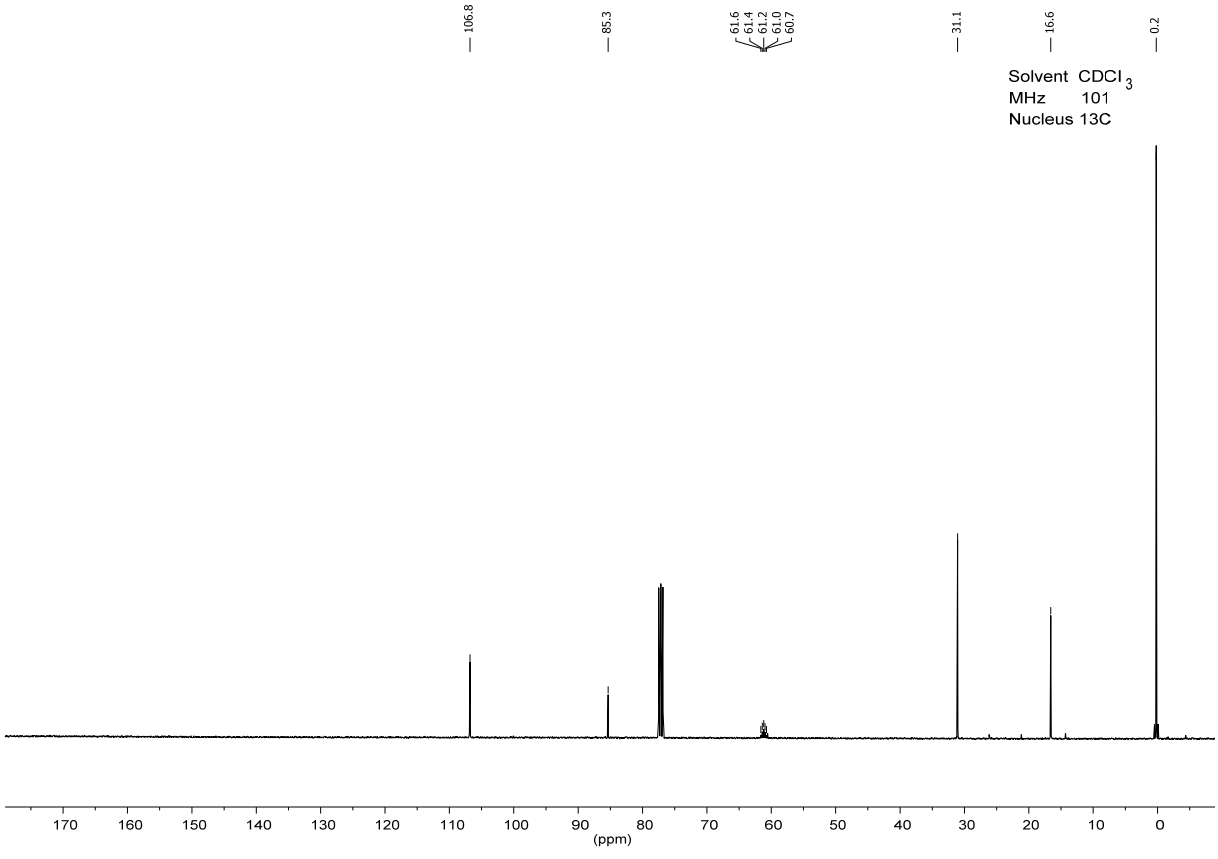

Solvent CDCl3
MHz 400
Nucleus 1H
1.98
2.00
10.06
8.91
6.70
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

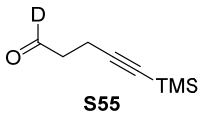

107.2
84.7
61.4
61.1
60.9
60.7
60.5
31.5
26.1
18.5
16.3
0.3
-5.2
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


D D
HO
TMS

**S54**

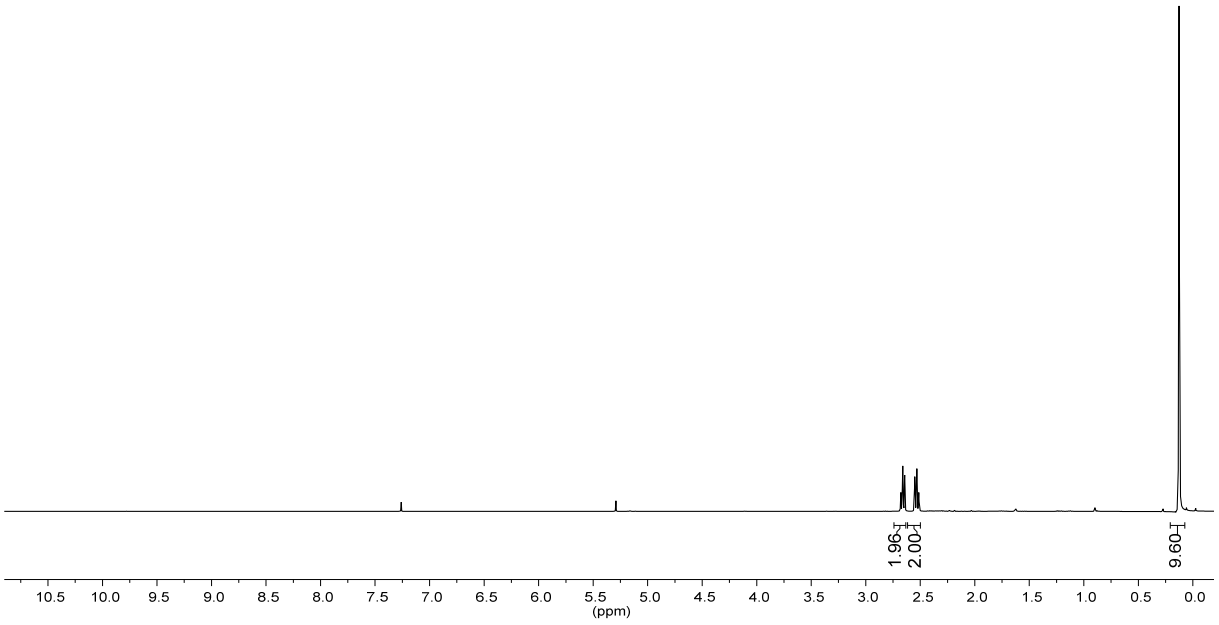

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
2.02
0.98
8.54
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


106.8
85.3
61.6
61.4
61.2
61.0
60.7
31.1
16.6
0.2
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

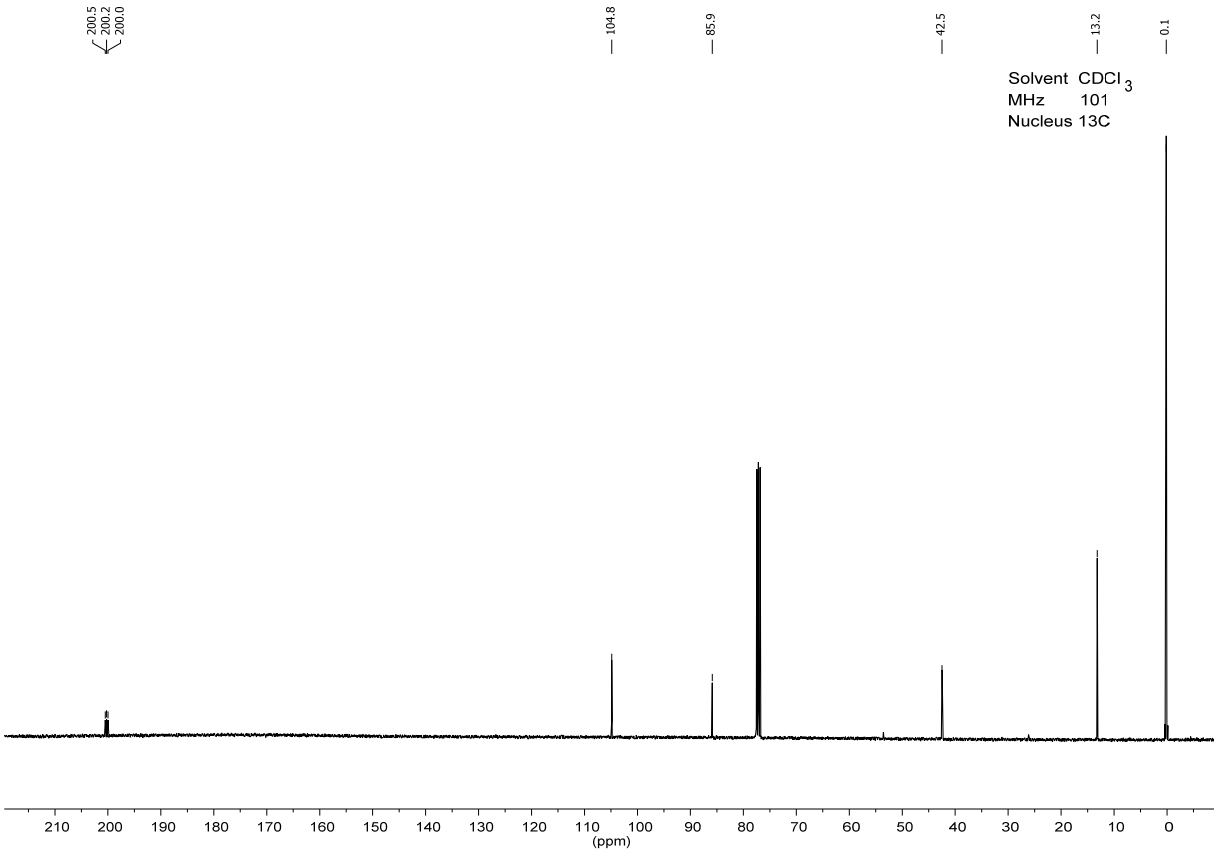


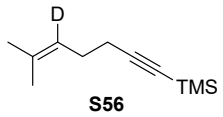

**S55**

Solvent CDCl 3
MHz 400
Nucleus 1H



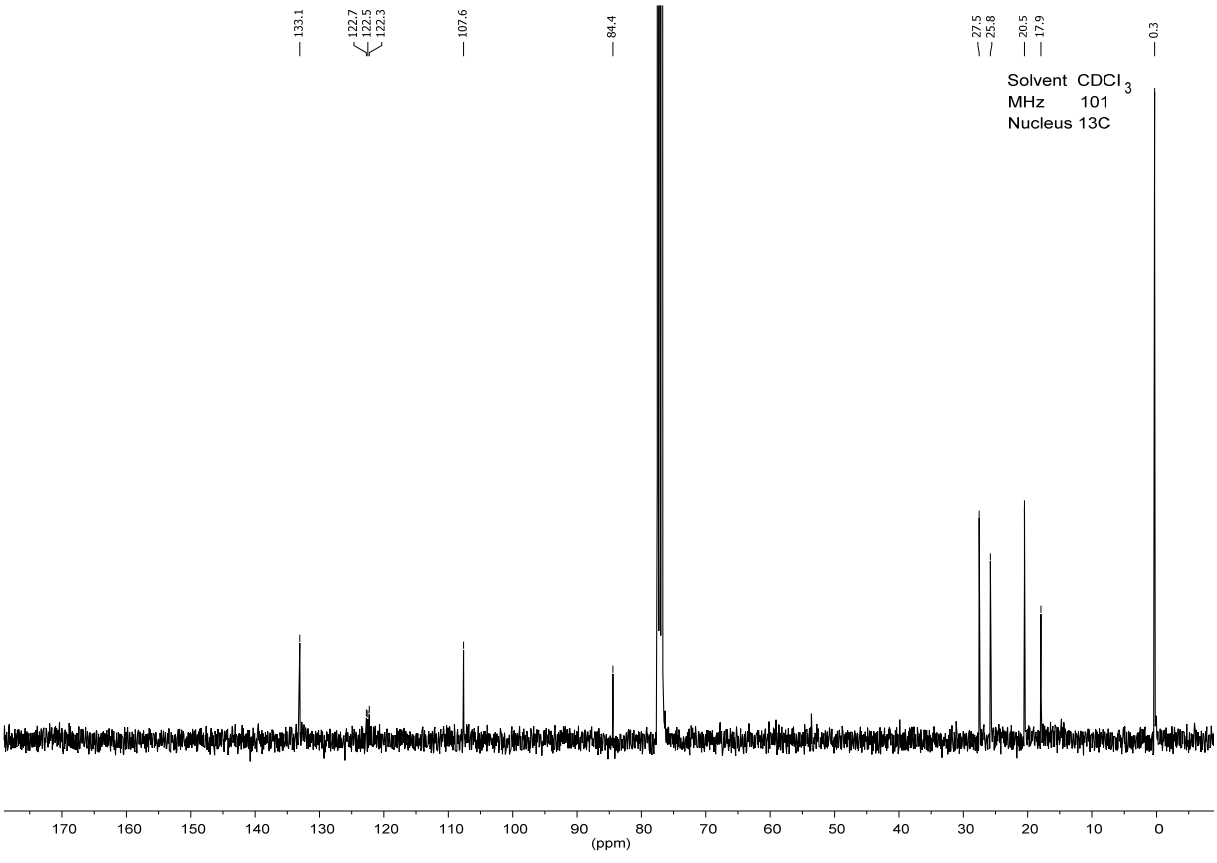

Solvent CDCl 3
MHz 101
Nucleus 13C

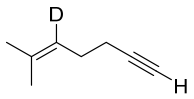



D
TMS

**S56**

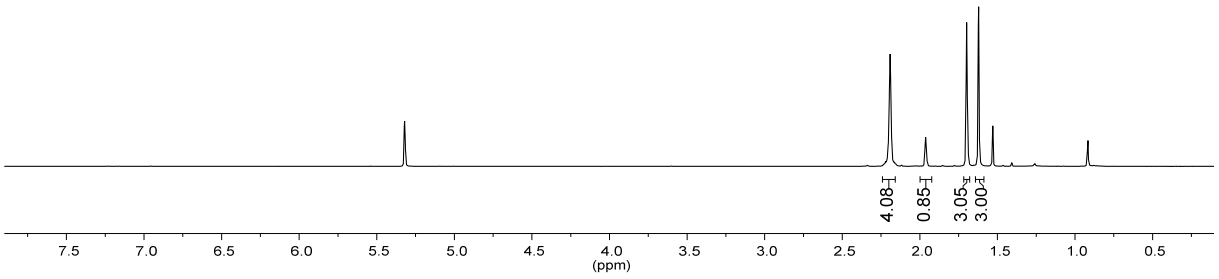

Solvent CDCl3
MHz 400
Nucleus 1H
4.41
3.00
2.96
9.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

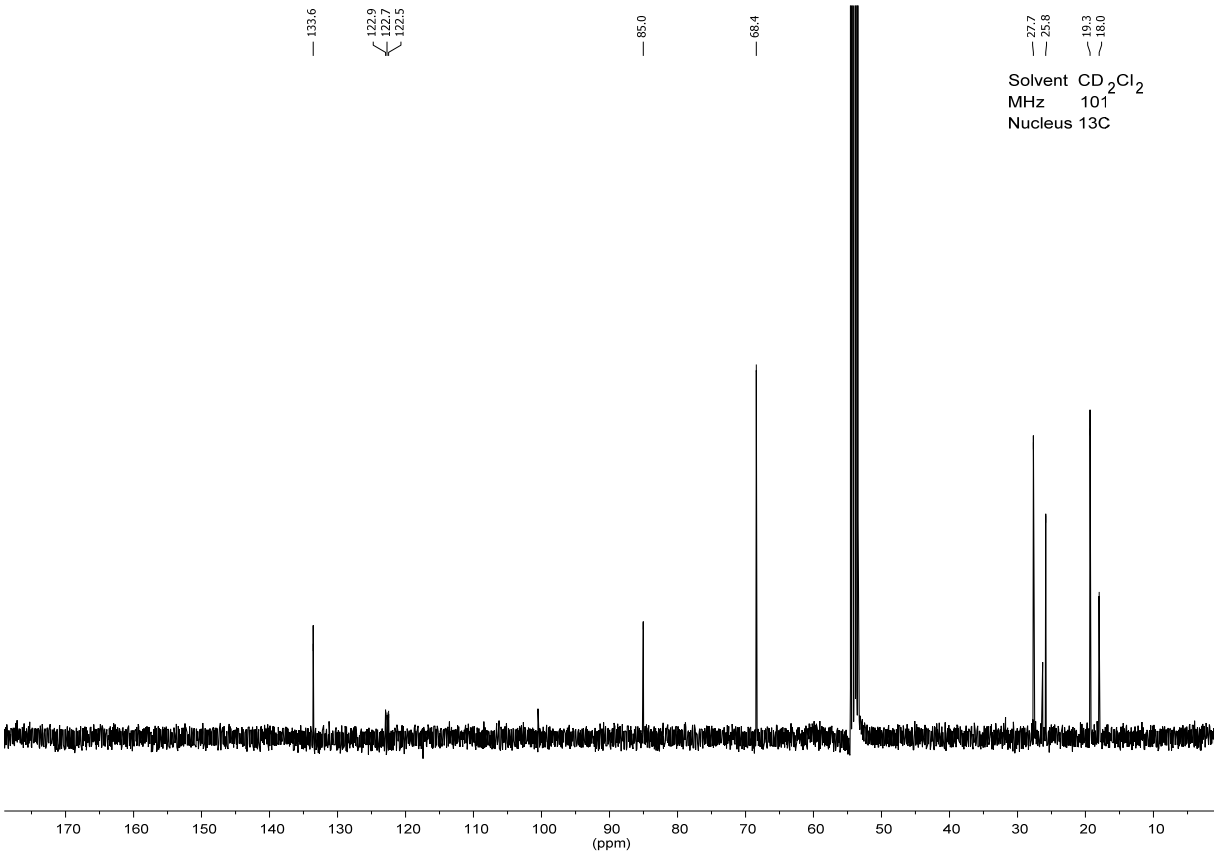

133.1
122.7
122.5
122.3
107.6
84.4
27.5
25.8
20.5
17.9
0.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

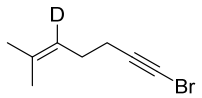



**S57**

Solvent $CD_2Cl_2$
MHz 400
Nucleus 1H

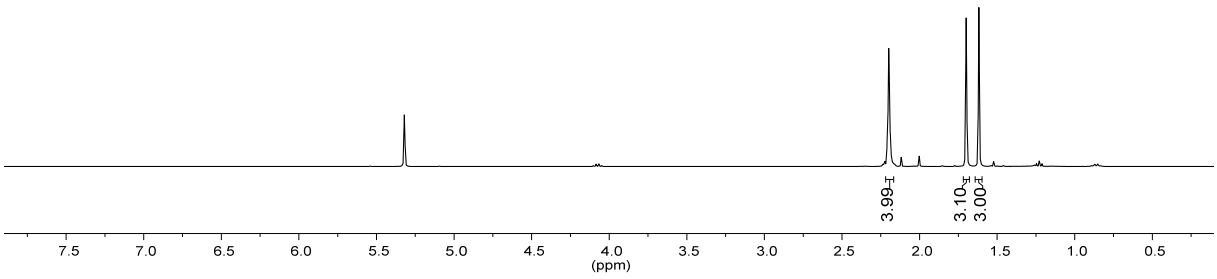


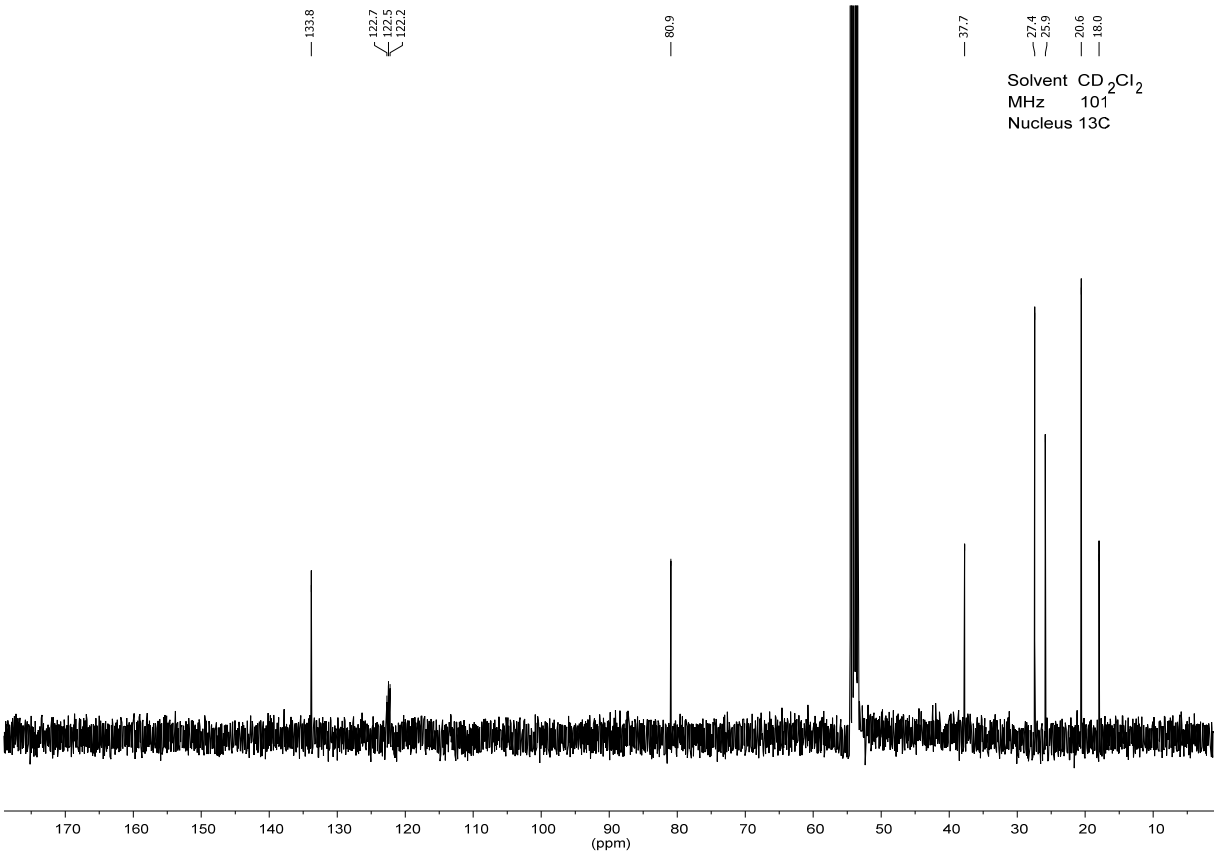



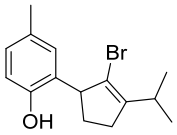



**20**

Solvent $CD_2Cl_2$
MHz 101
Nucleus 13C

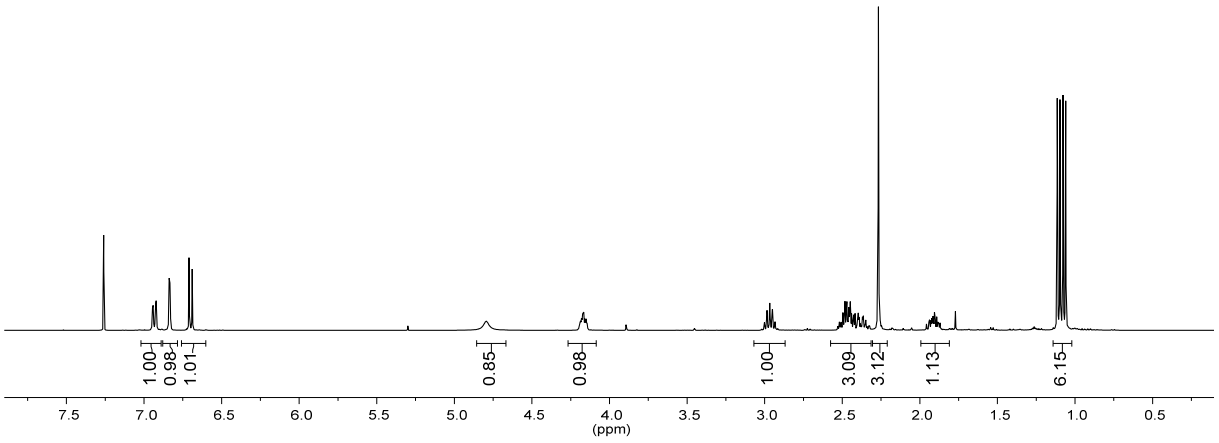


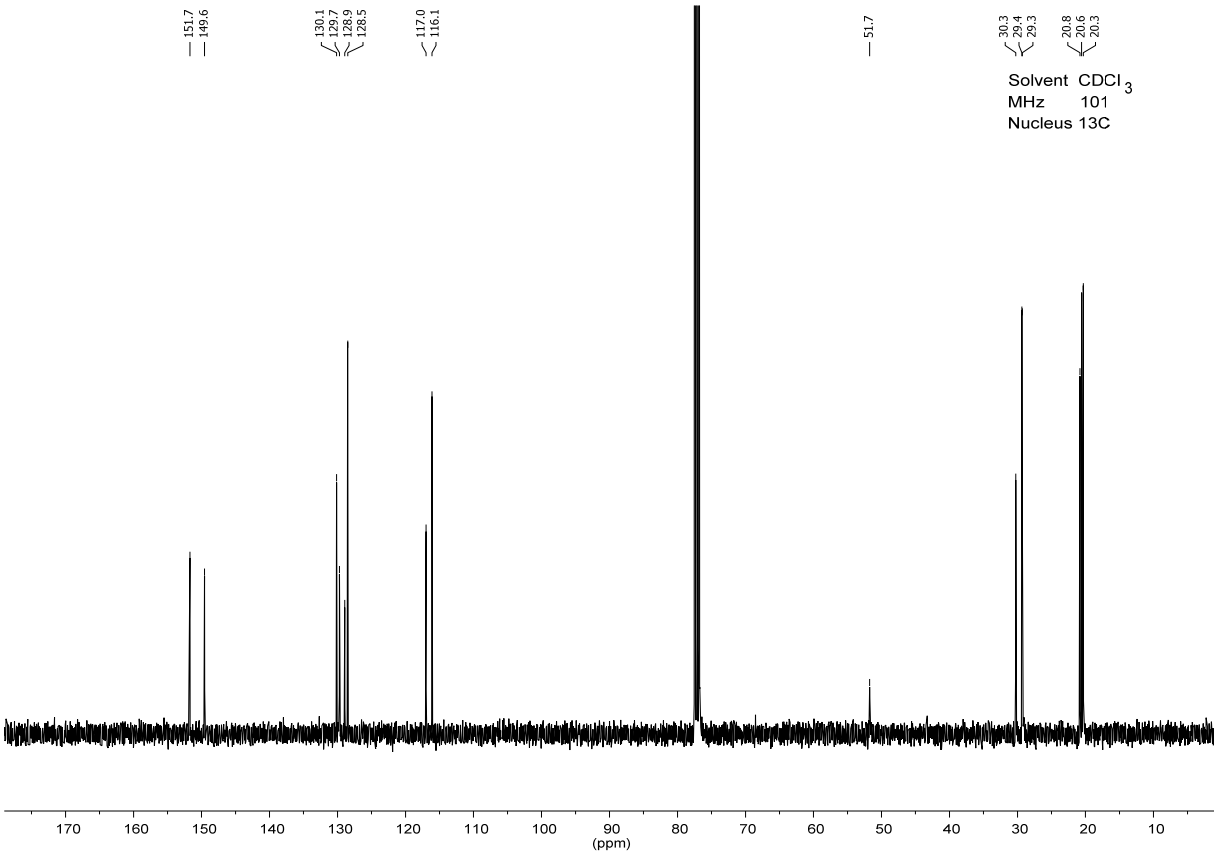



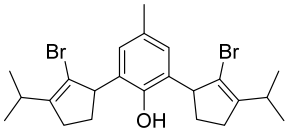



**2a**

Solvent CDCl 3
MHz 400
Nucleus 1H

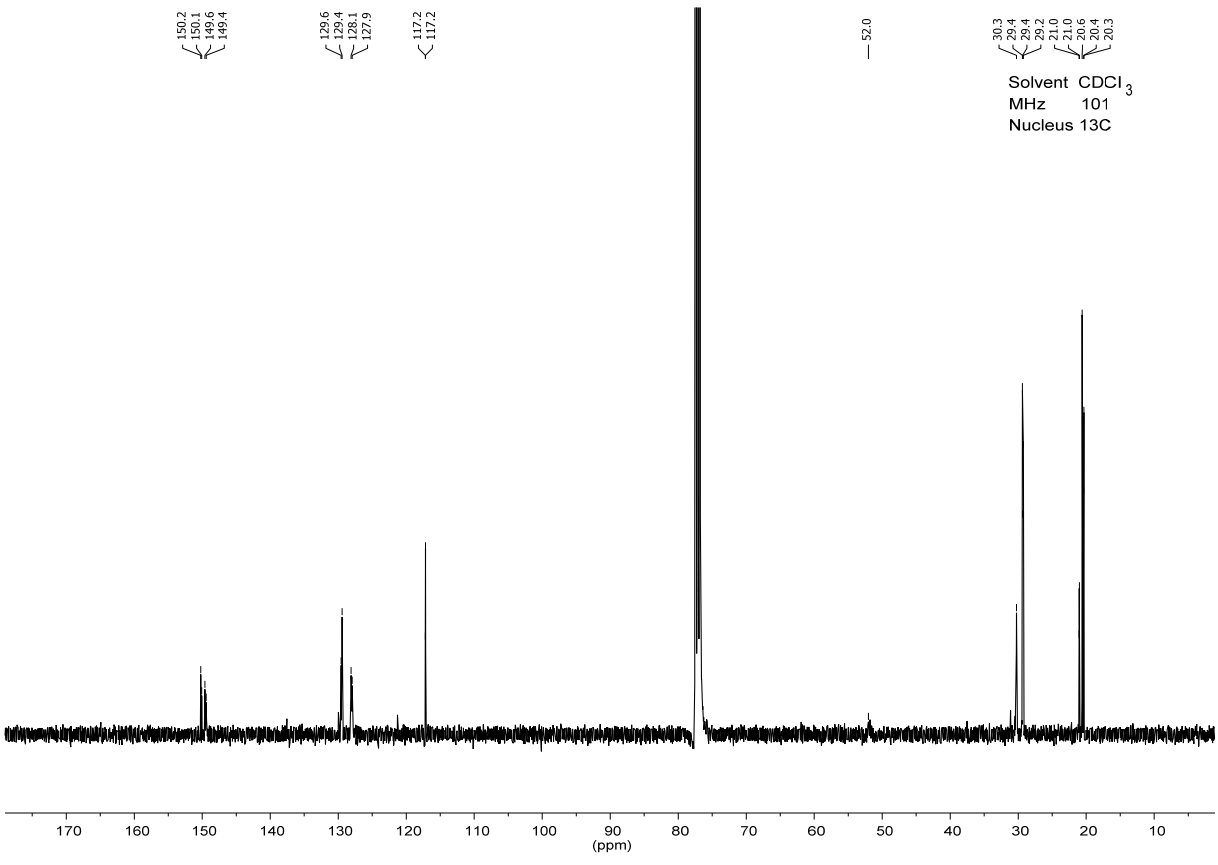


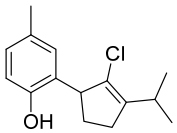




Br
Br
OH

**3a**

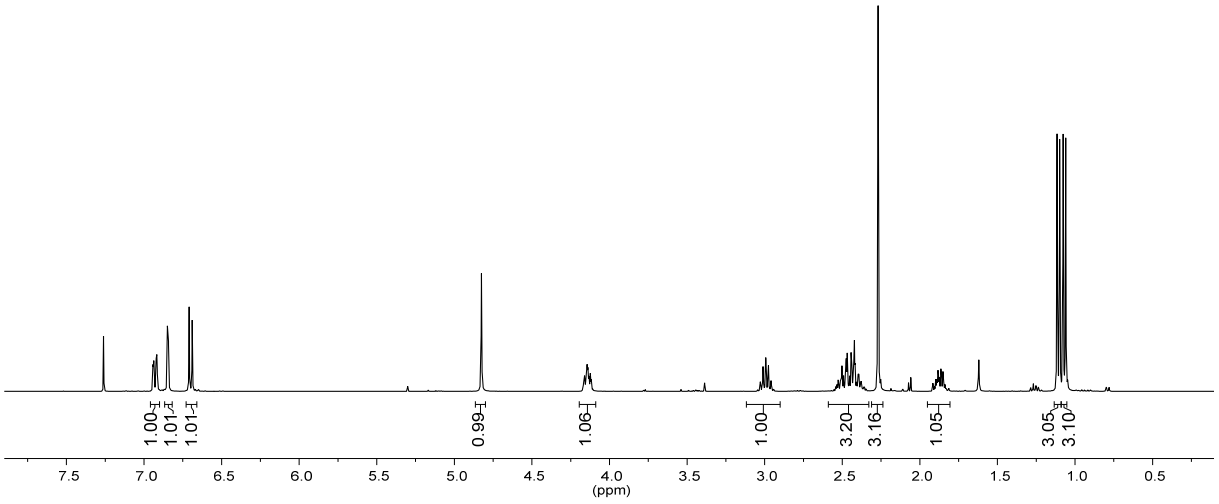

Solvent CDCl3
MHz 400
Nucleus 1H
1.94
0.54
0.31
1.87
2.00
6.01
3.04
2.17
5.77
5.91
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

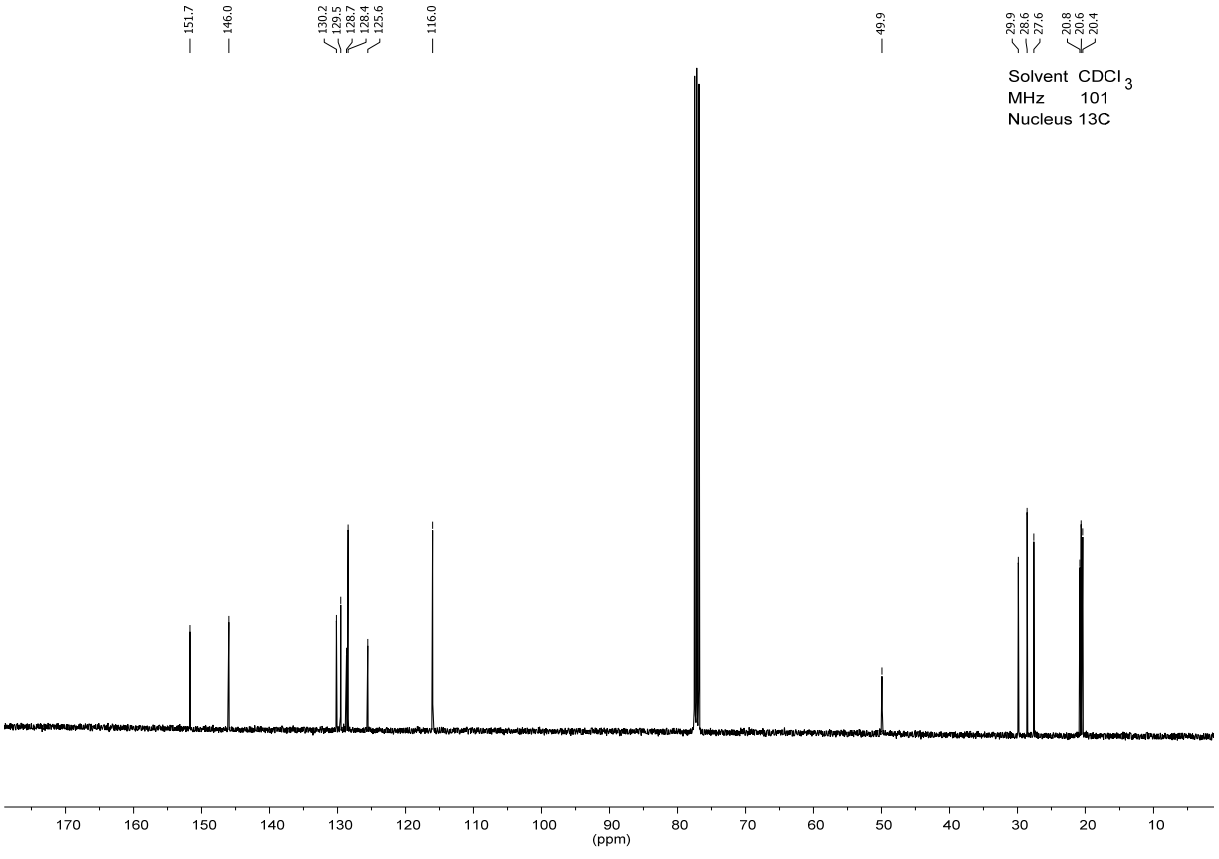

150.2
150.1
149.6
149.4
129.6
129.4
128.1
127.9
117.2
117.2
52.0
30.3
29.4
29.4
29.2
21.0
21.0
20.6
20.4
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



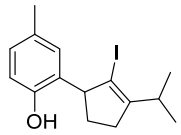

**2b**

Solvent CDCl 3
MHz 400
Nucleus 1H



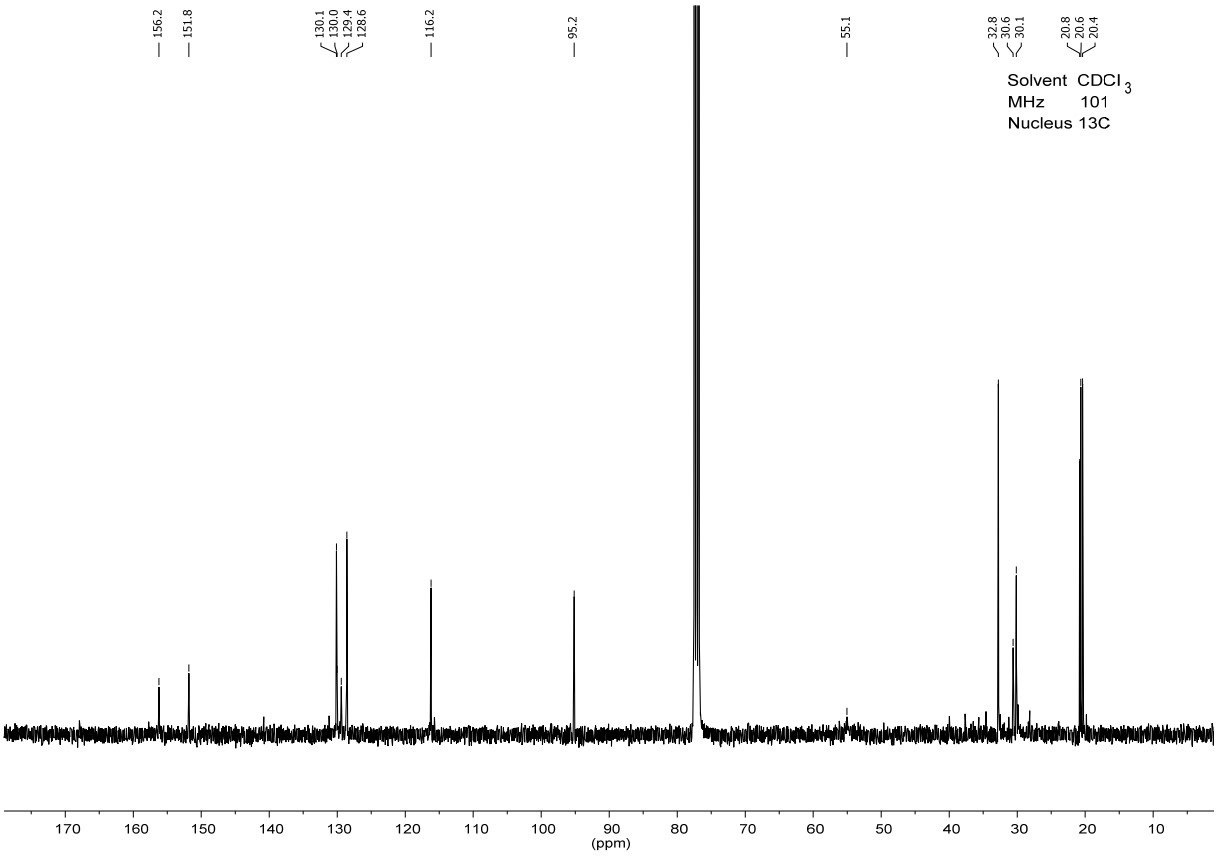



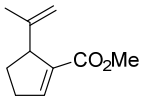

Solvent CDCl 3
MHz 101
Nucleus 13C


I
OH

**2c**

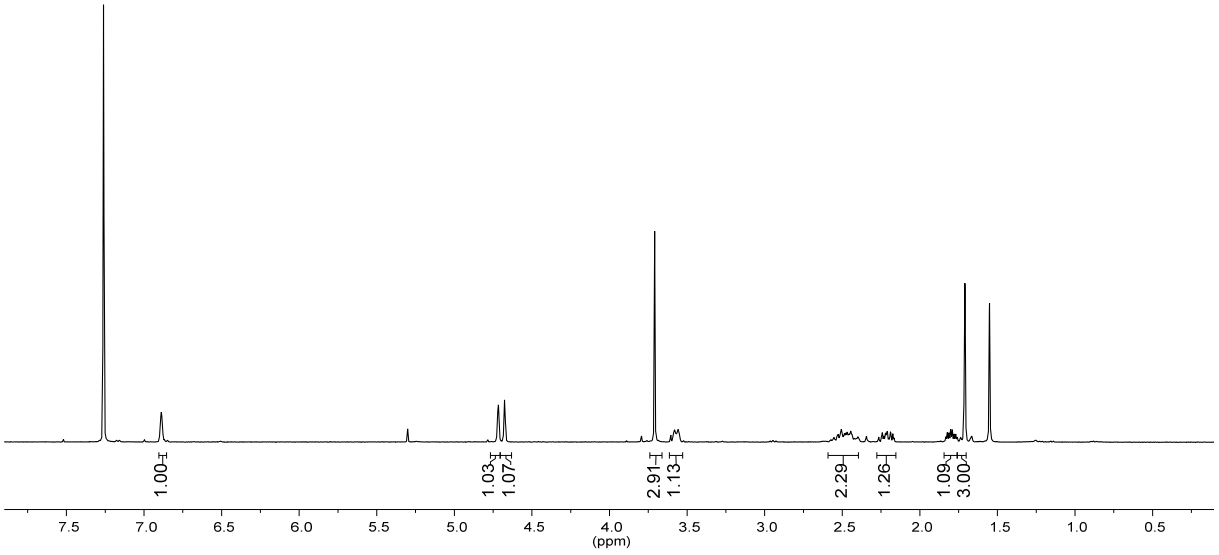

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.05
1.04
0.90
1.02
1.08
3.28
3.43
1.11
3.03
3.08
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

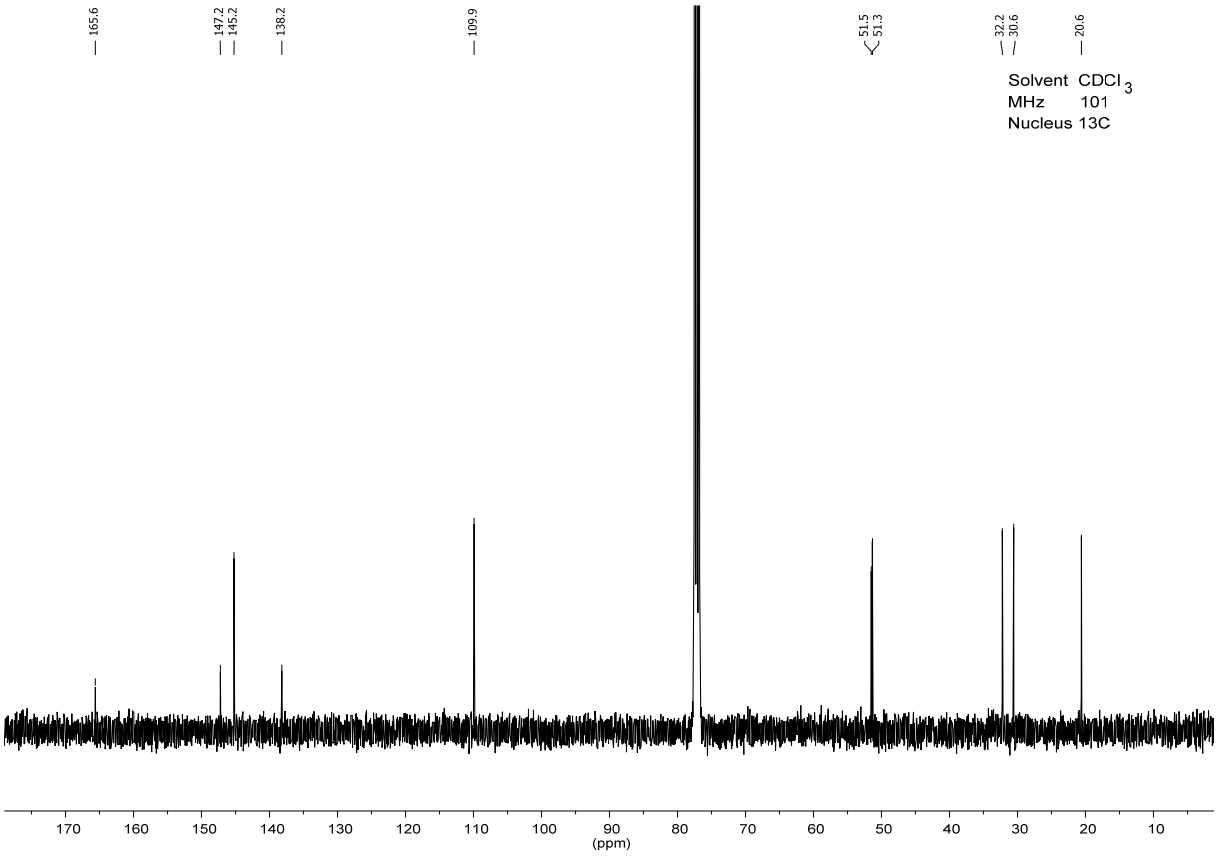

156.2
151.8
130.1
130.0
129.4
128.6
116.2
95.2
55.1
32.8
30.6
30.1
20.8
20.6
20.4
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



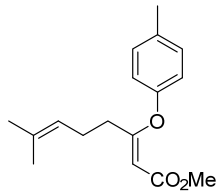

**S58**

Solvent CDCl 3
MHz 400
Nucleus 1H



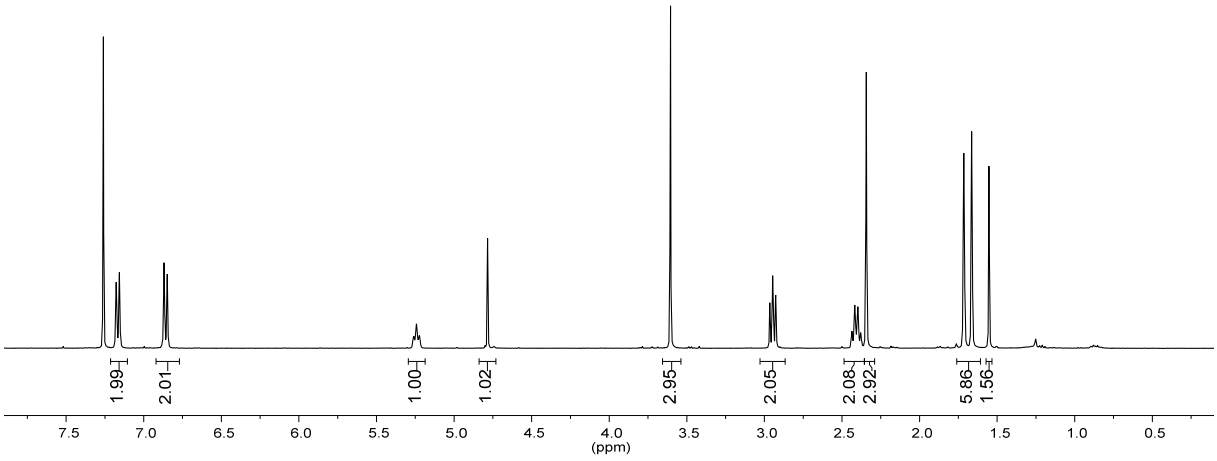



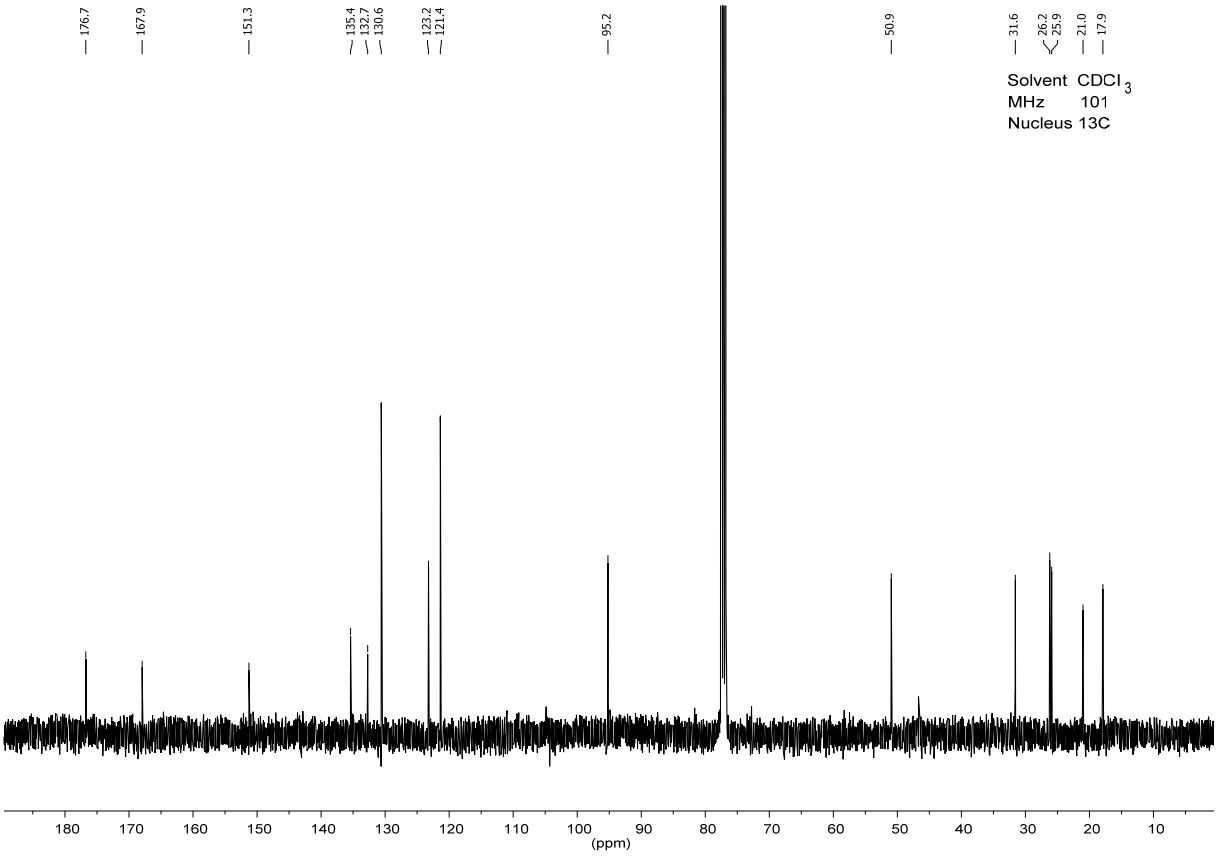

Solvent CDCl 3
MHz 101
Nucleus 13C

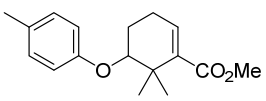



**S59**

Solvent CDCl3
MHz 400
Nucleus 1H

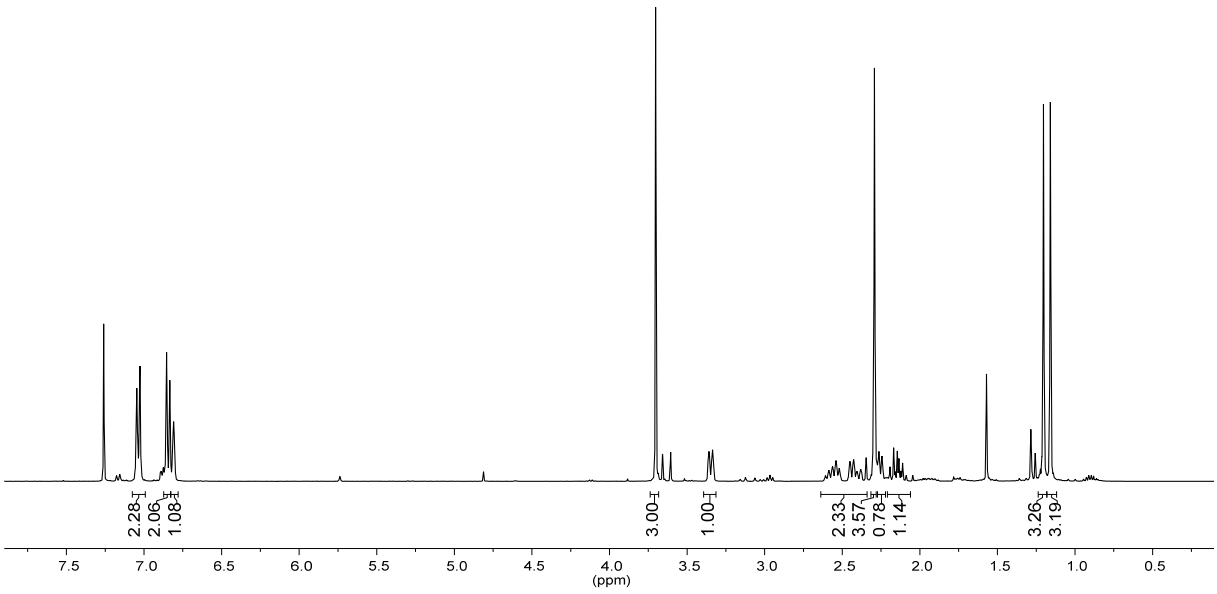


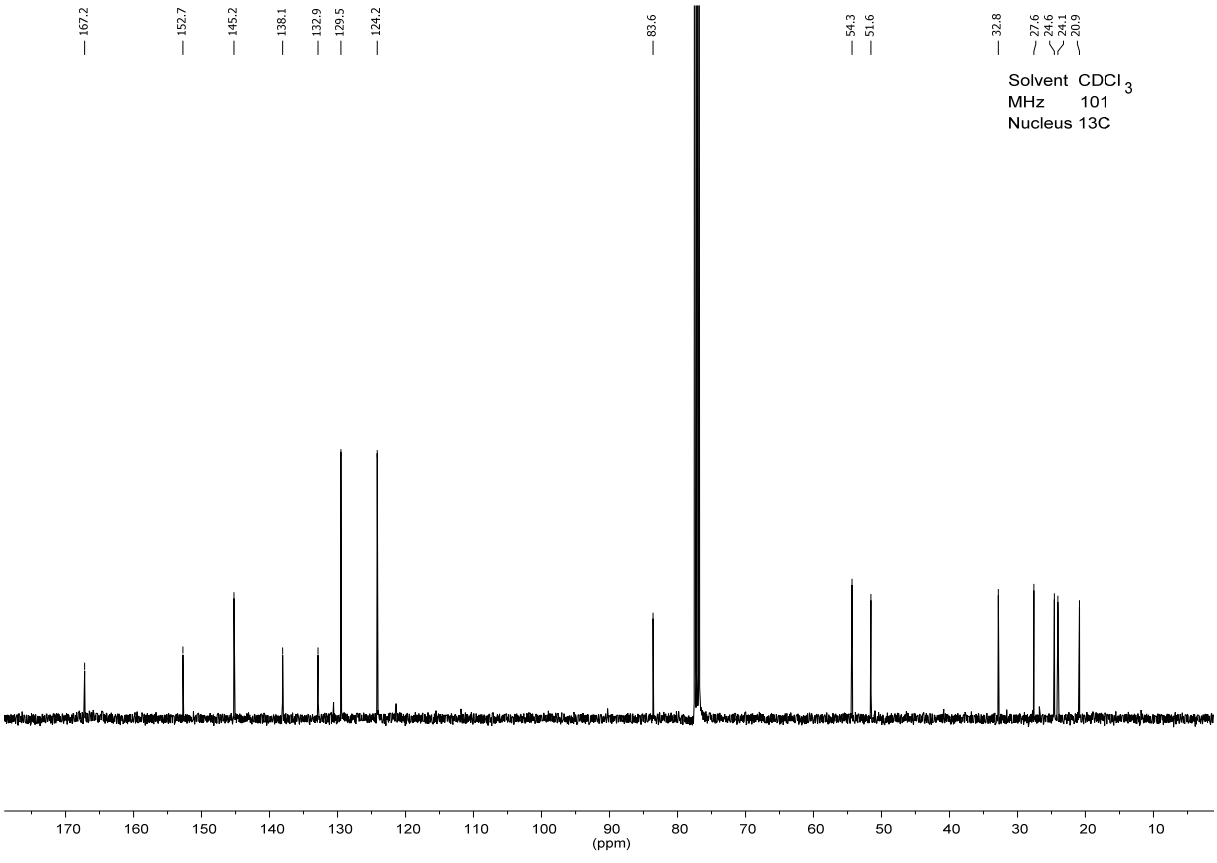





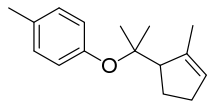

**S60**

Solvent CDCl 3
MHz 400
Nucleus 1H



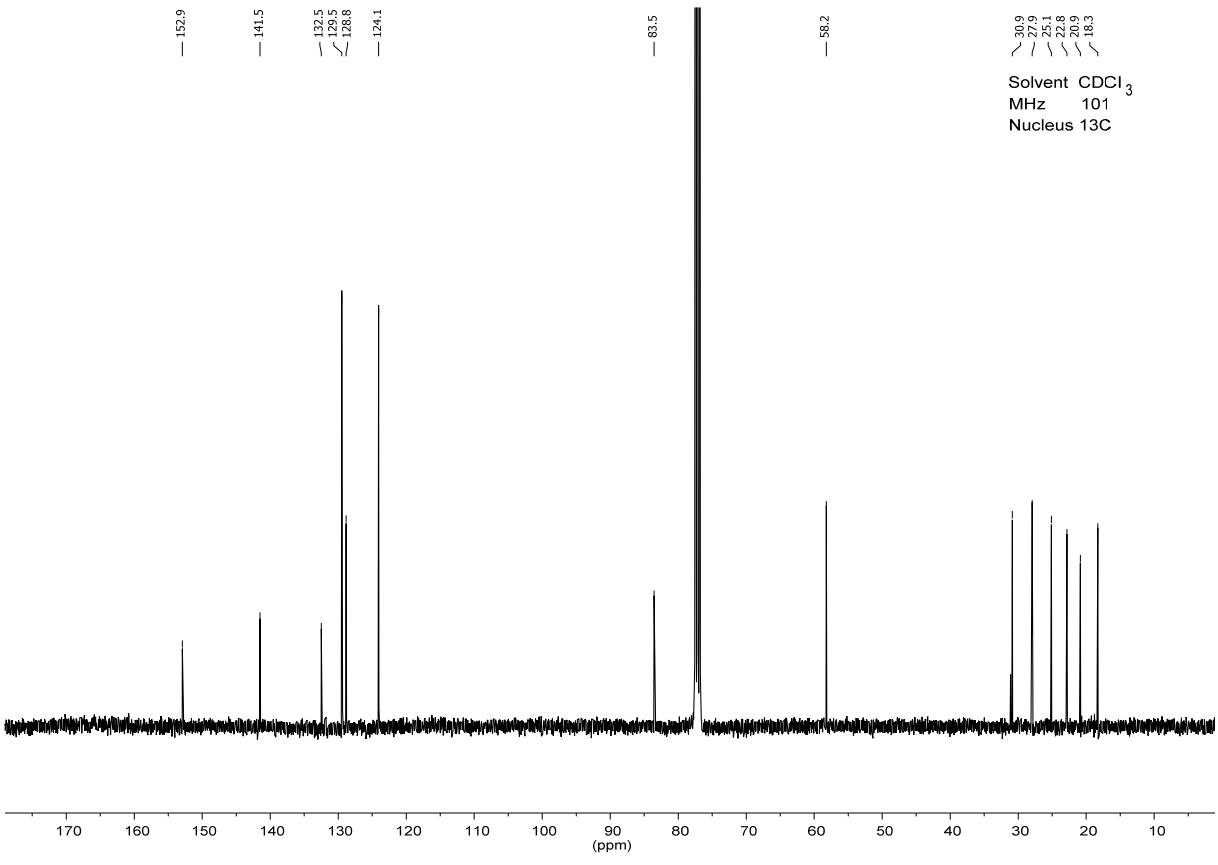



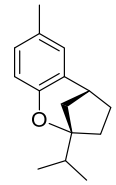

Solvent CDCl 3
MHz 101
Nucleus 13C



**S61**

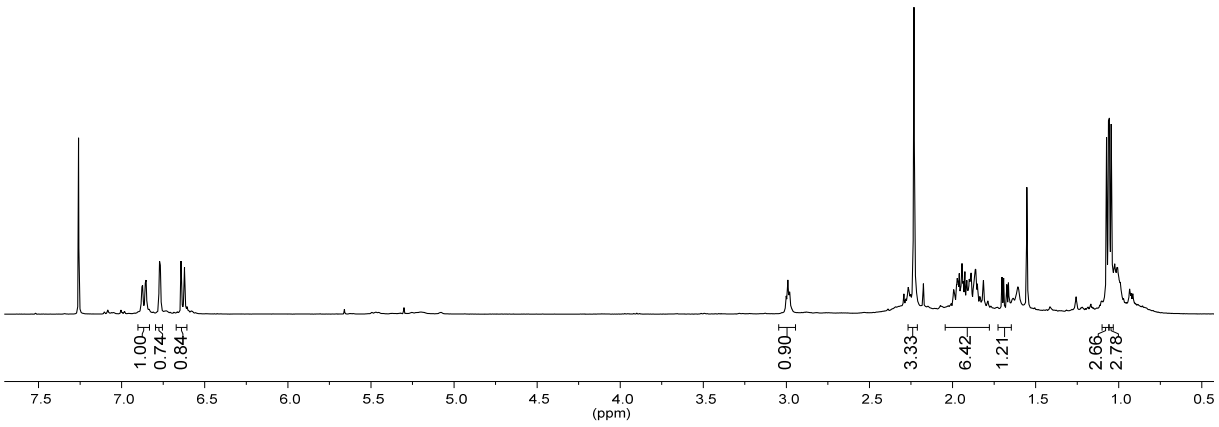

Solvent CDCl3
MHz 400
Nucleus 1H
2.03
2.03
0.95
1.03
3.17
2.18
1.20
3.00
1.19
3.12
3.20
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

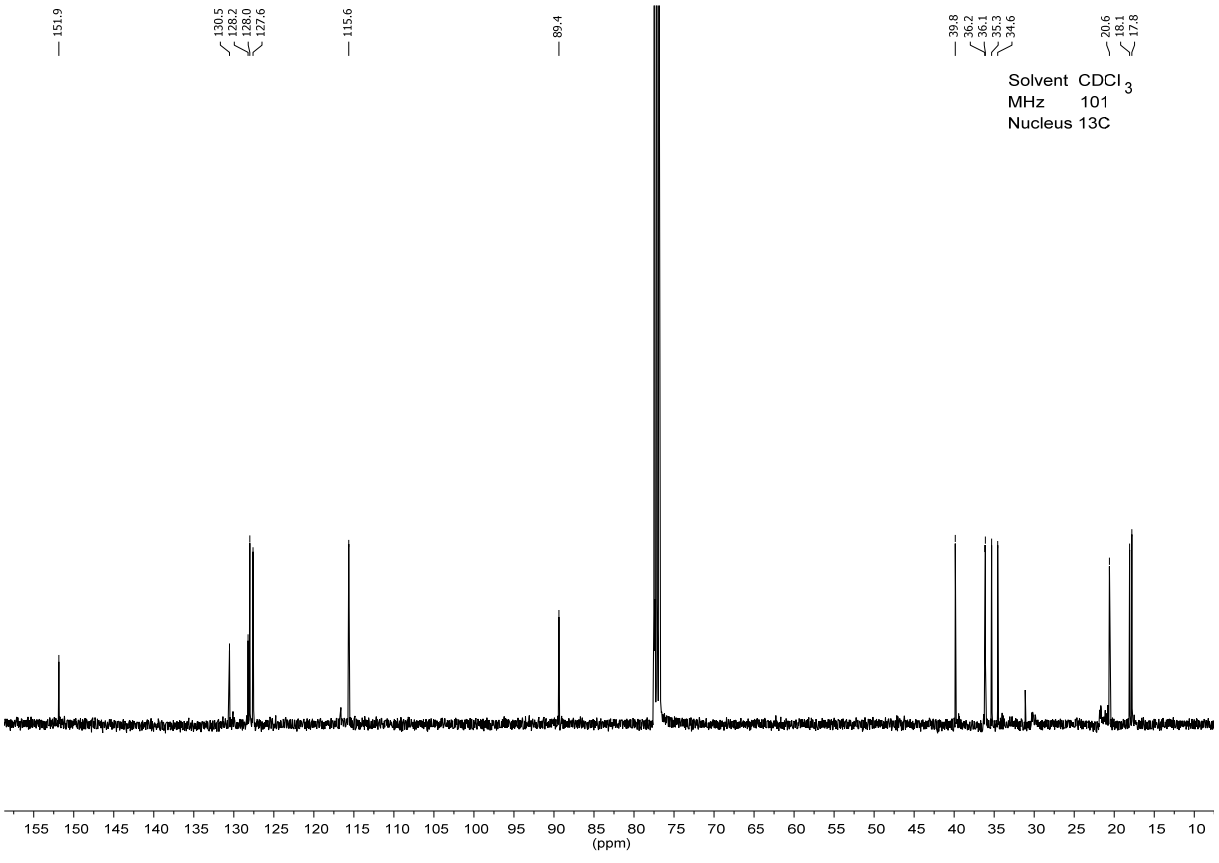

152.9
141.5
132.5
129.5
128.8
124.1
83.5
58.2
30.9
27.9
25.1
22.8
20.9
18.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



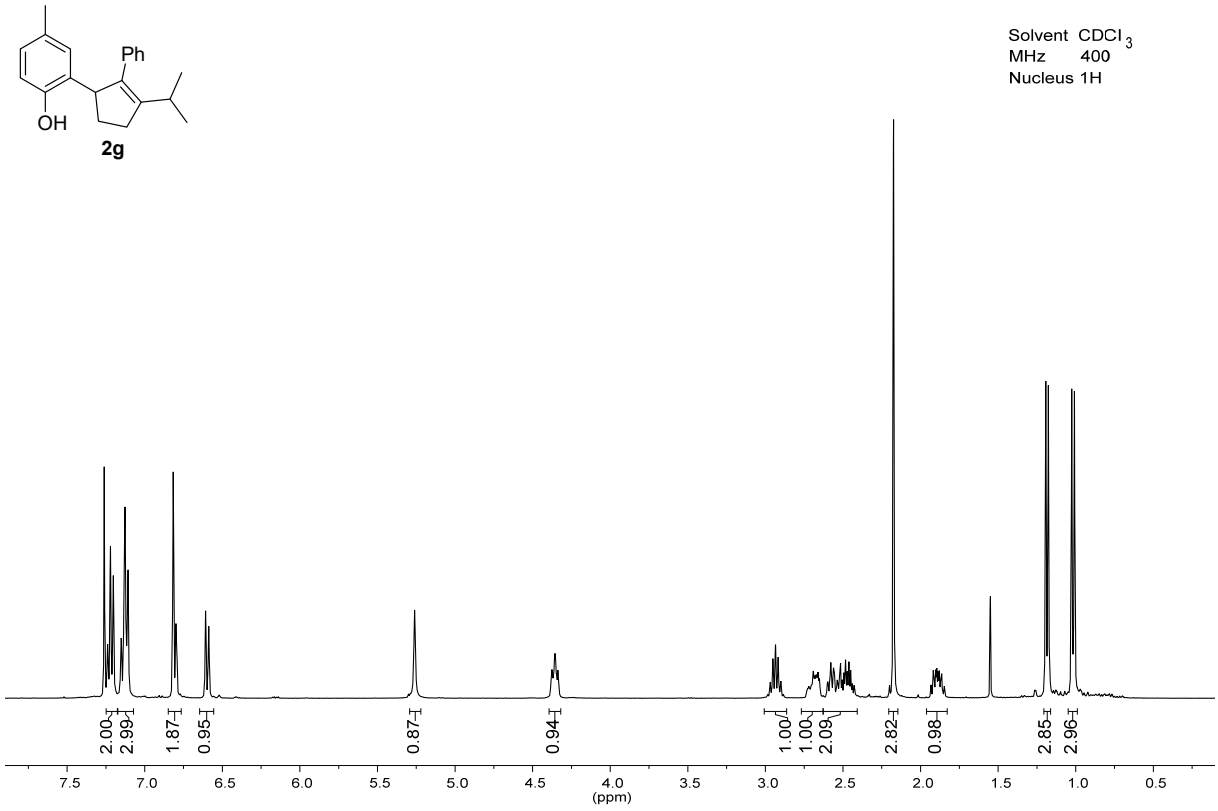
**S62**

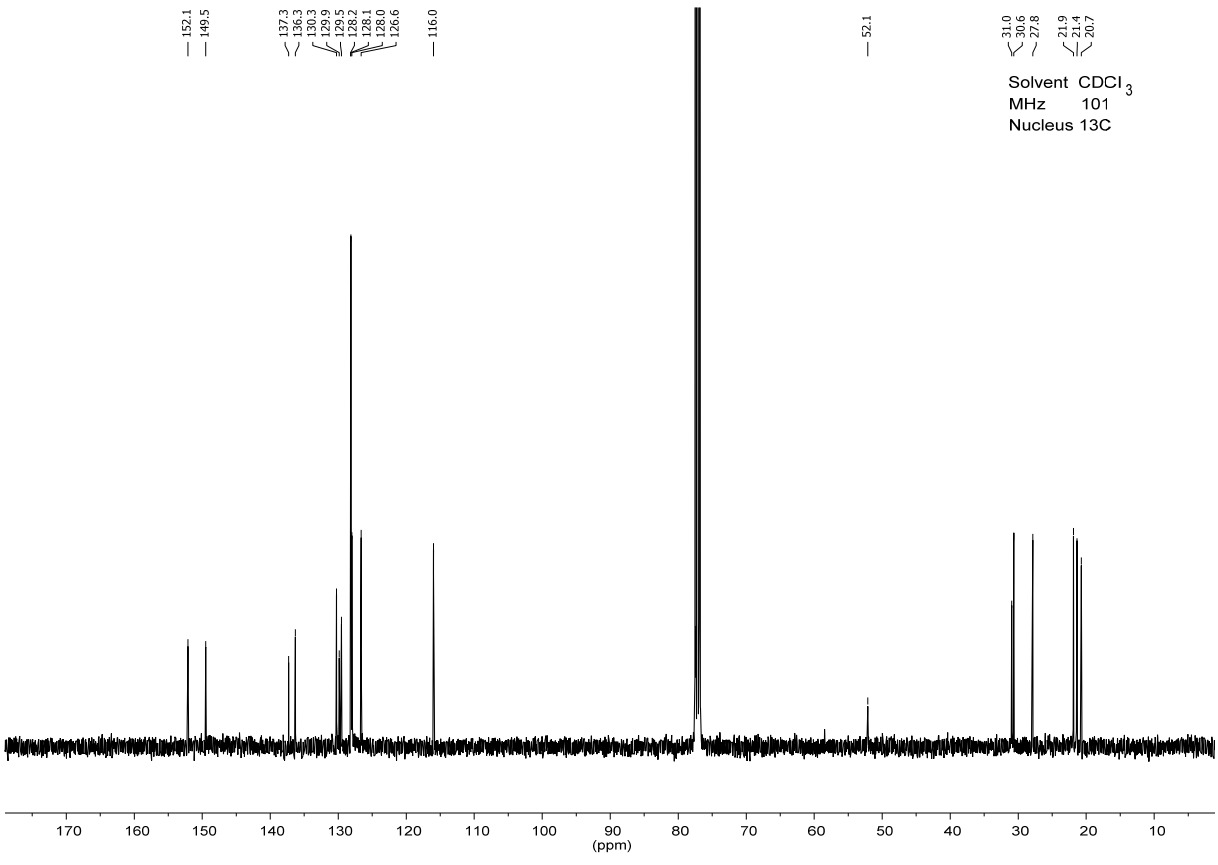
Solvent CDCl 3
MHz 400
Nucleus 1H

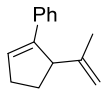



Solvent CDCl 3
MHz 101
Nucleus 13C

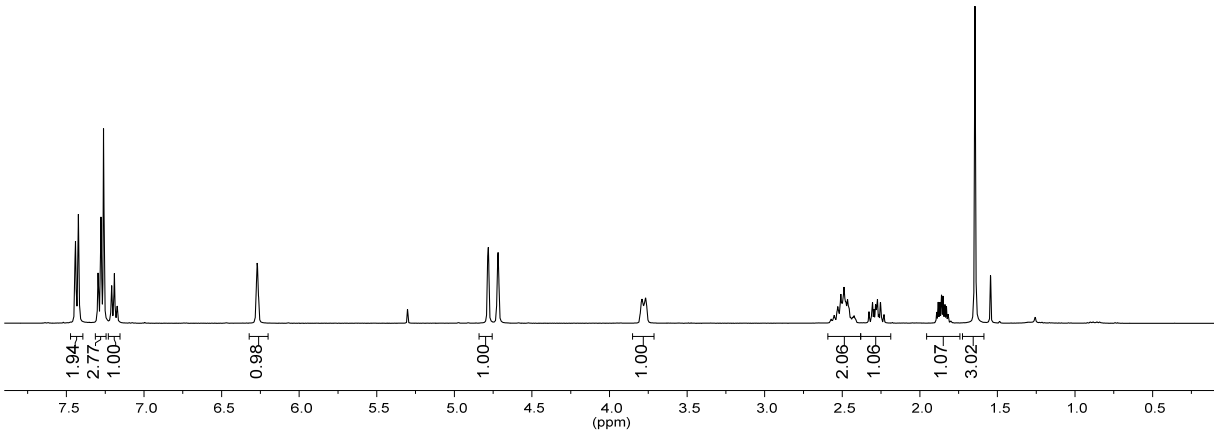

Ph
OH
2g
Solvent CDCl3
MHz 400
Nucleus 1H
2.00
2.99
1.87
0.95
0.87
0.94
1.00
1.00
2.09
2.82
0.98
2.85
2.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

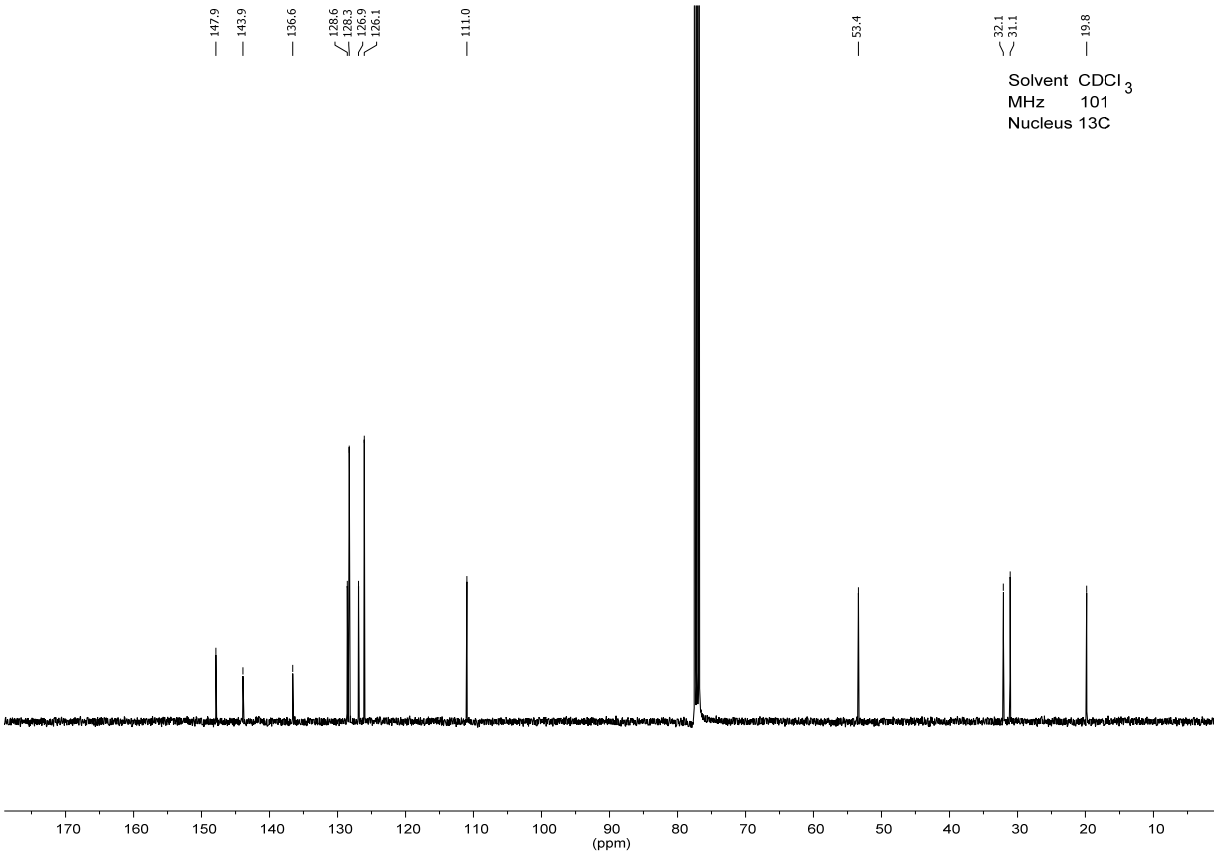

152.1
149.5
137.3
136.3
130.3
129.9
129.5
128.2
128.1
128.0
126.6
116.0
52.1
31.0
30.6
27.8
21.9
21.4
20.7
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

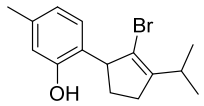



**S63**

Solvent CDCl 3
MHz 400
Nucleus 1H

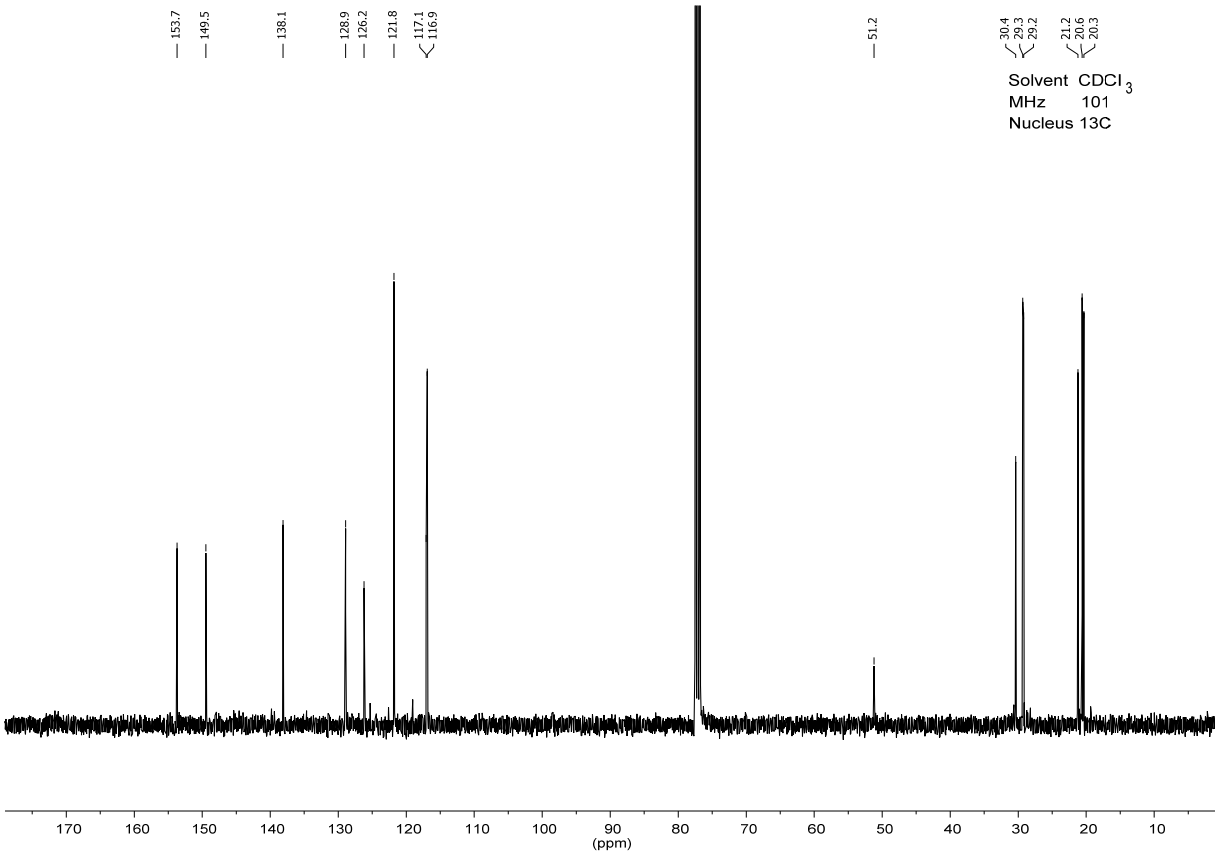


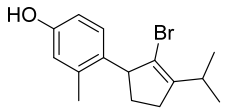




Br
OH

**4o**

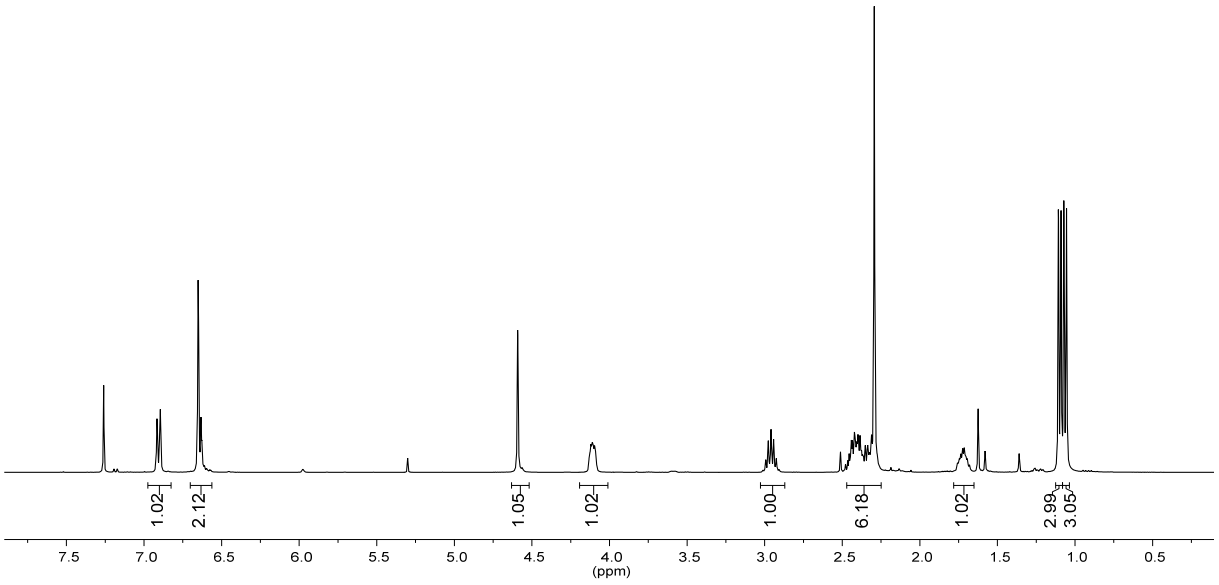

Solvent CDCl3
MHz 400
Nucleus 1H
0.96
1.00
1.04
0.80
1.04
1.11
3.32
2.96
1.07
3.05
3.17
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

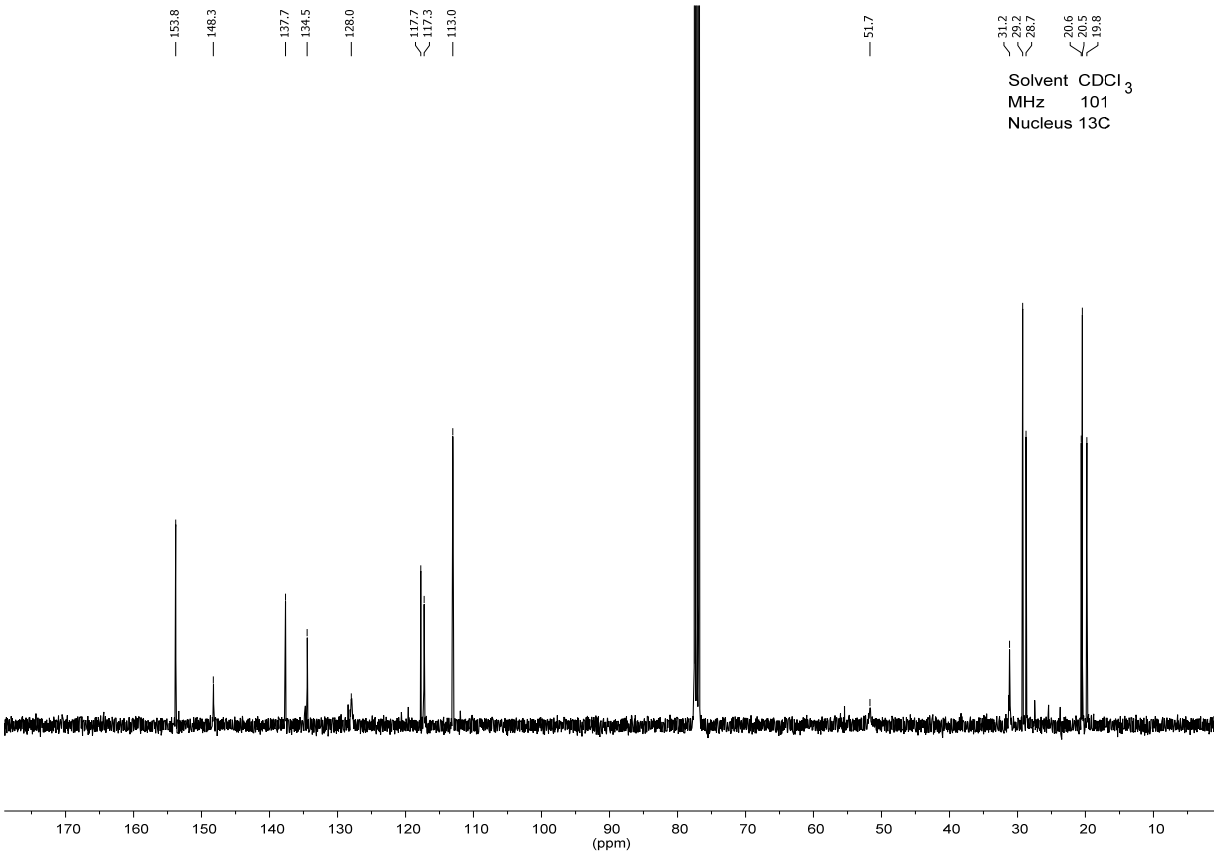

153.7
149.5
138.1
128.9
126.2
121.8
117.1
116.9
51.2
30.4
29.3
29.2
21.2
20.6
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



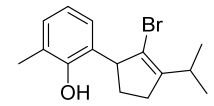

**4p**

Solvent CDCl 3
MHz 400
Nucleus 1H



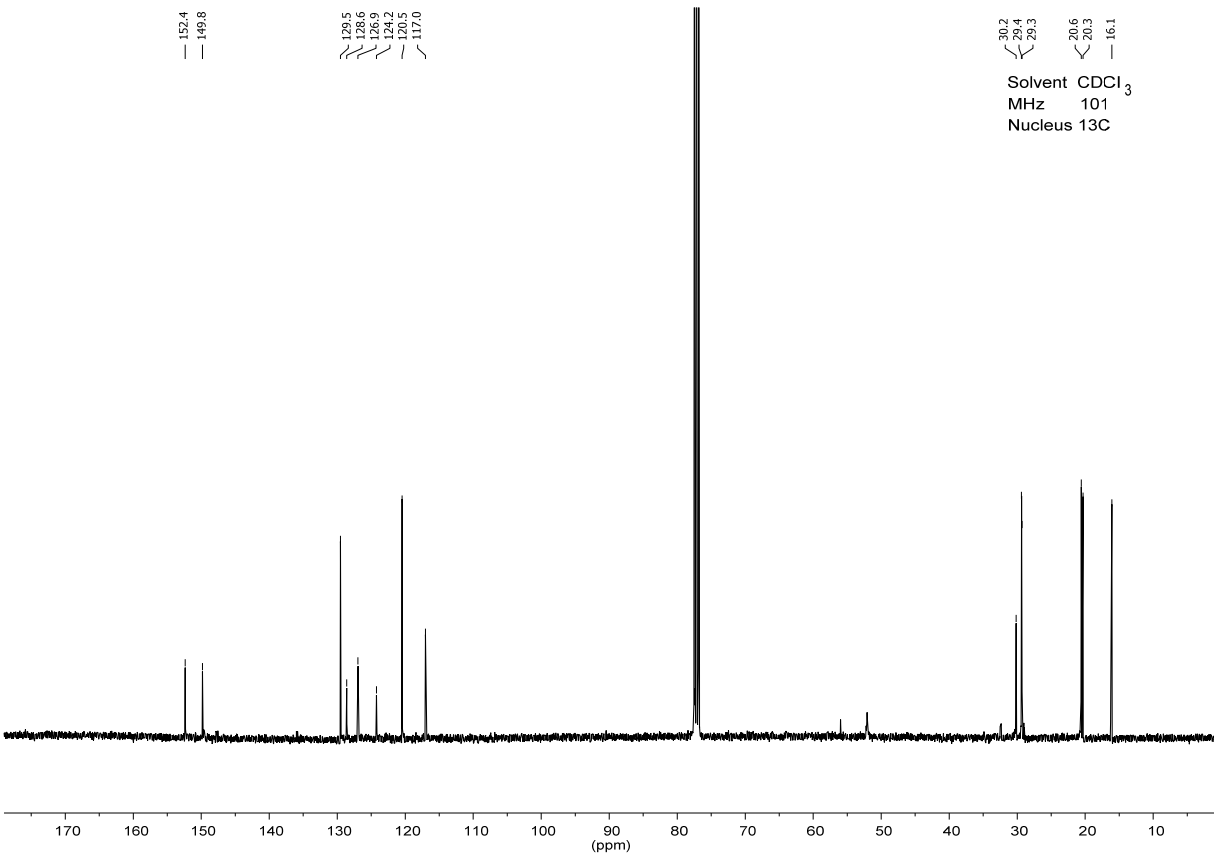



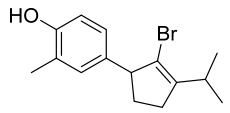

Solvent CDCl 3
MHz 101
Nucleus 13C


Br
OH

**5o**

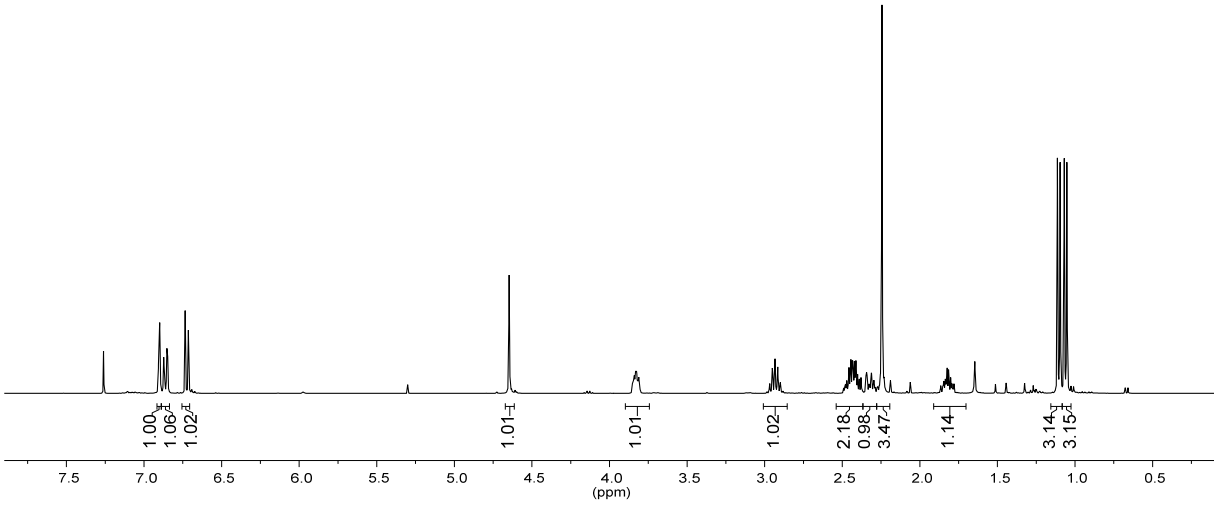

Solvent CDCl3
MHz 400
Nucleus 1H
0.85
0.85
0.93
0.82
0.93
1.00
3.10
2.86
0.97
2.86
3.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

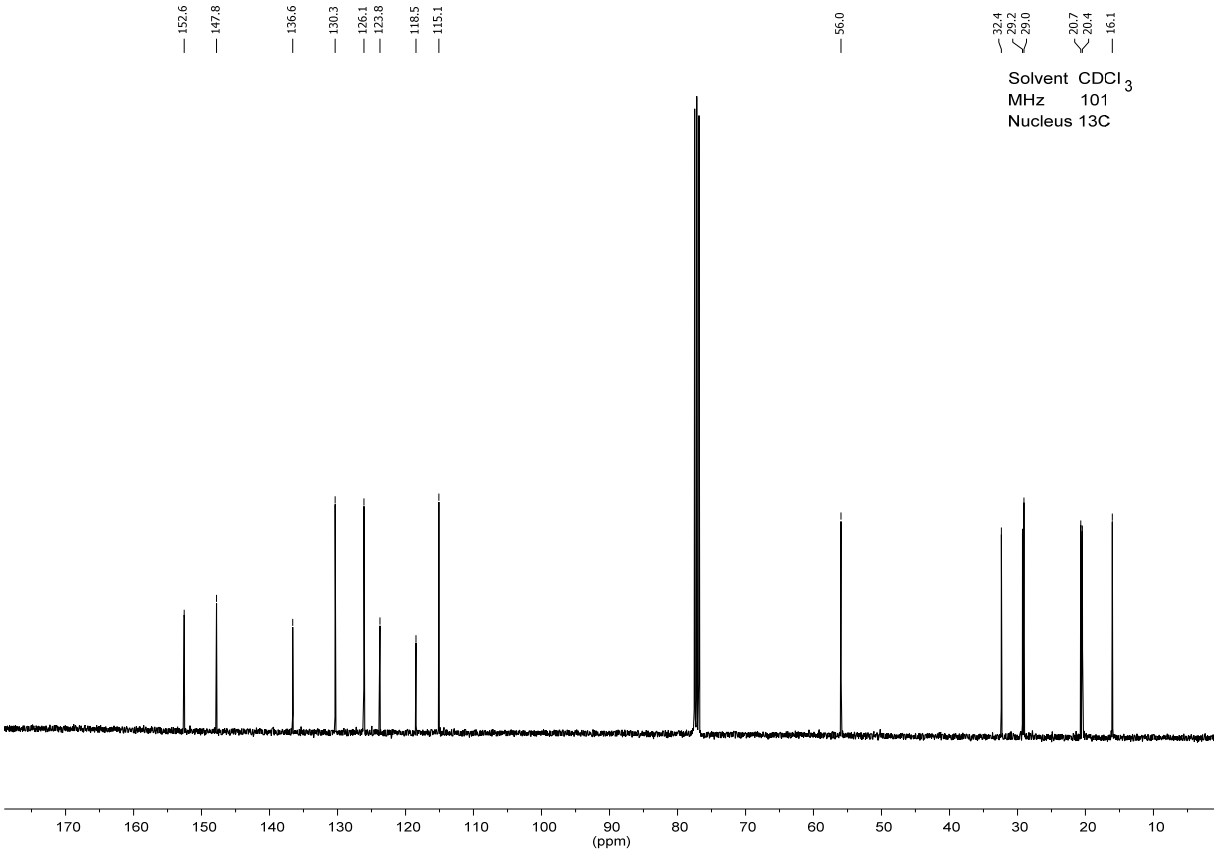

152.4
149.8
129.5
128.6
126.9
124.2
120.5
117.0
30.2
29.4
29.3
20.6
20.3
16.1
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

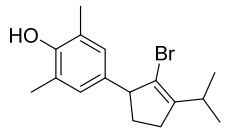



**5p**

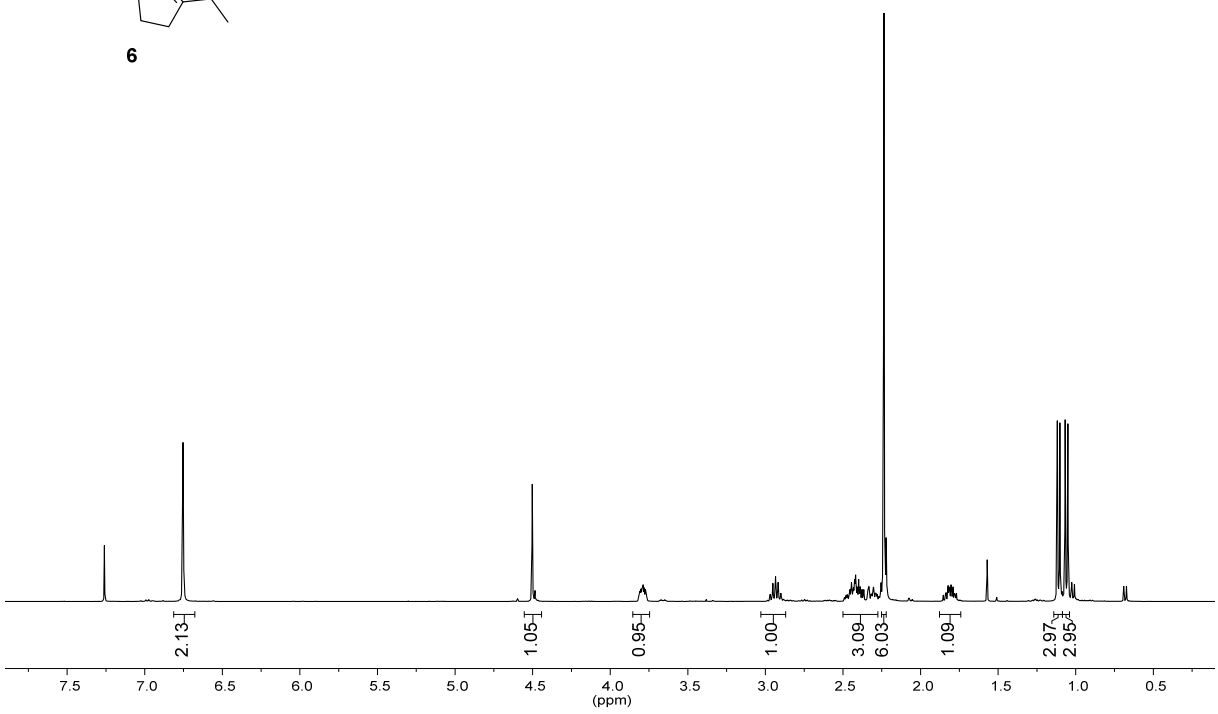
Solvent CDCl 3
MHz 400
Nucleus 1H

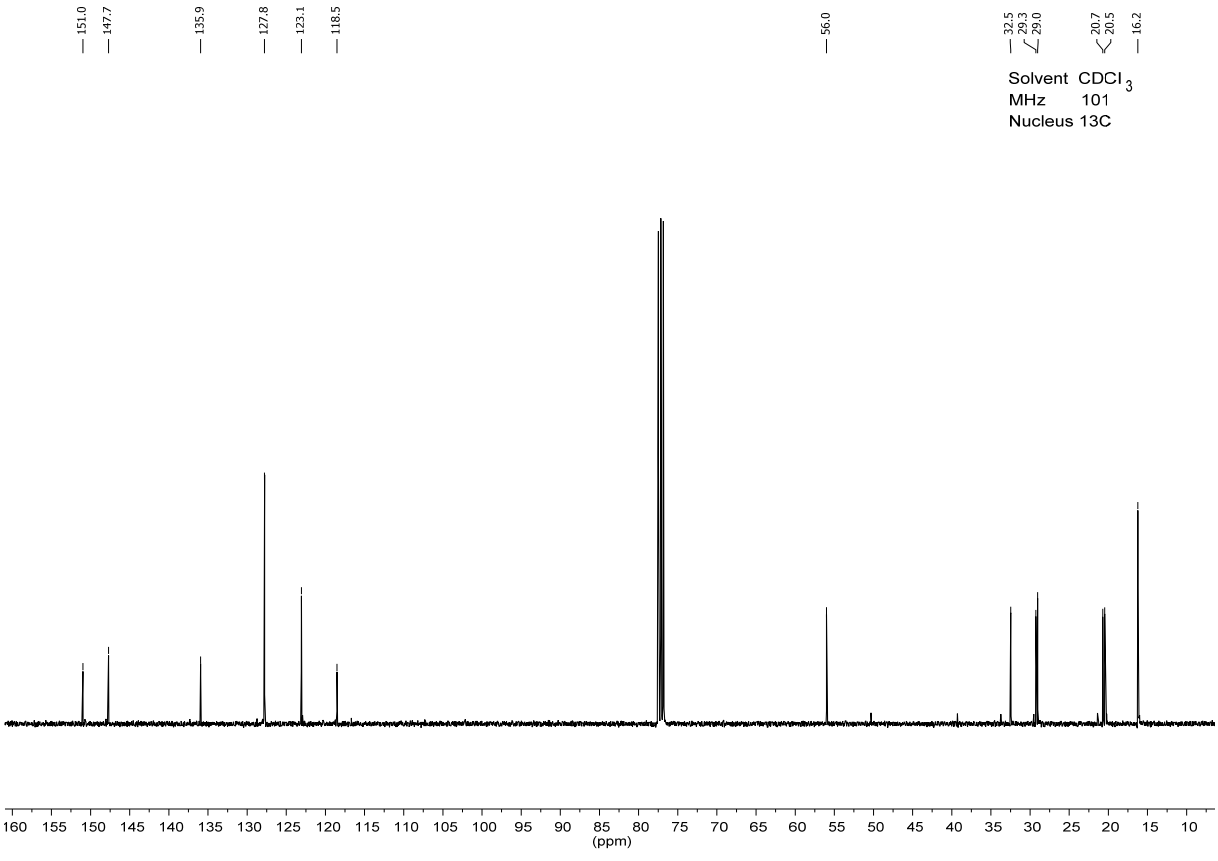


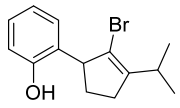




HO
Br

**6**

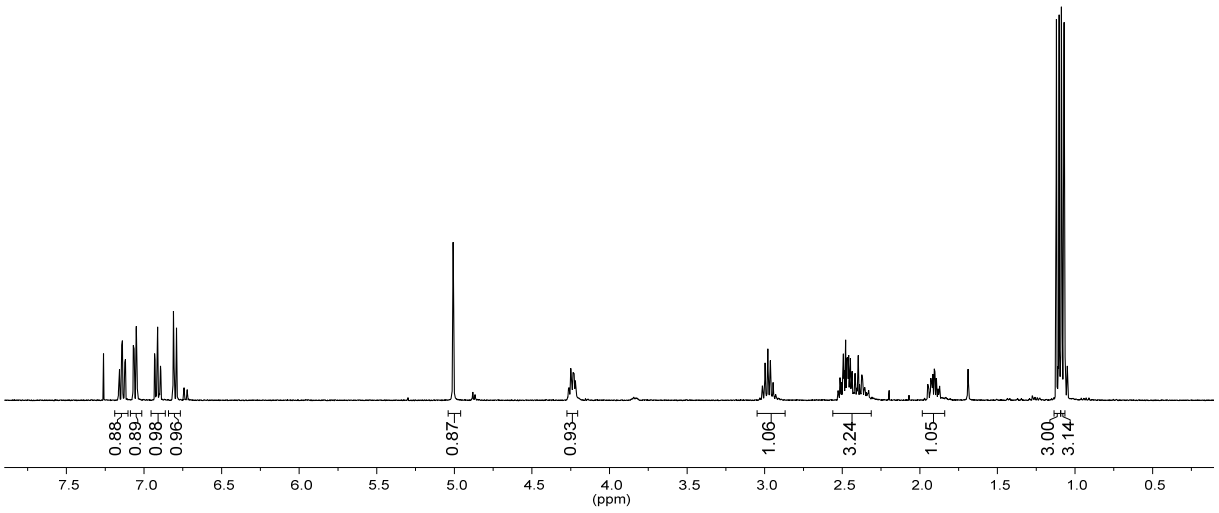

Solvent CDCl3
MHz 400
Nucleus 1H
2.13
1.05
0.95
1.00
3.09
6.03
1.09
2.97
2.95
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


151.0
147.7
135.9
127.8
123.1
118.5
56.0
32.5
29.3
29.0
20.7
20.5
16.2
Solvent CDCl3
MHz 101
Nucleus 13C
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
(ppm)



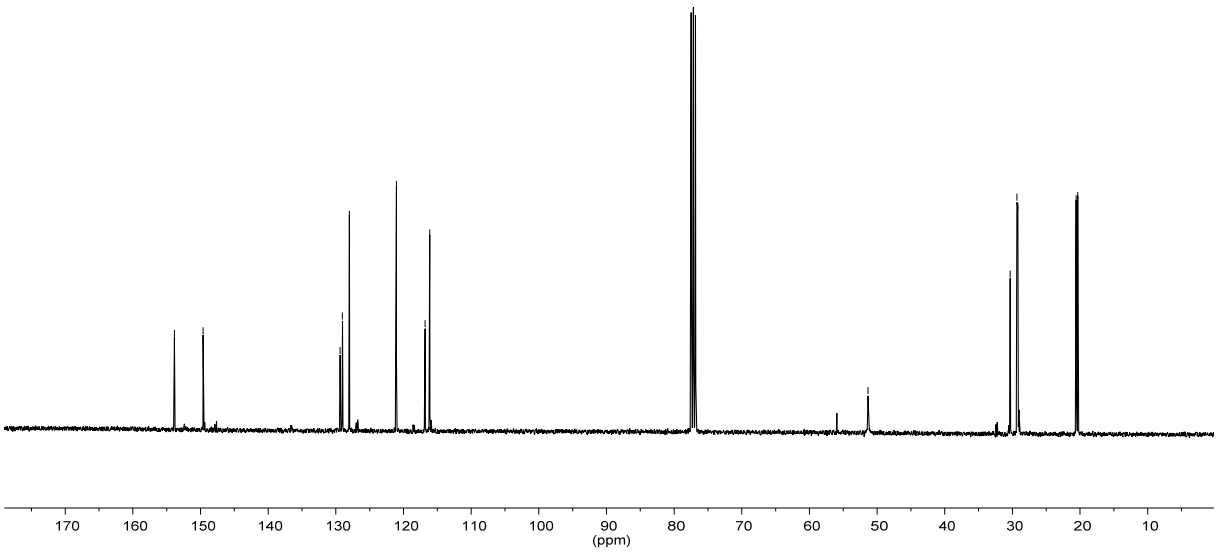

**7o**

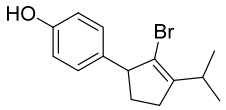
Solvent CDCl 3
MHz 400
Nucleus 1H




153.9
149.6
129.4
129.0
128.0
121.0
116.8
116.1
51.3
30.3
29.3
29.2
20.6
20.3

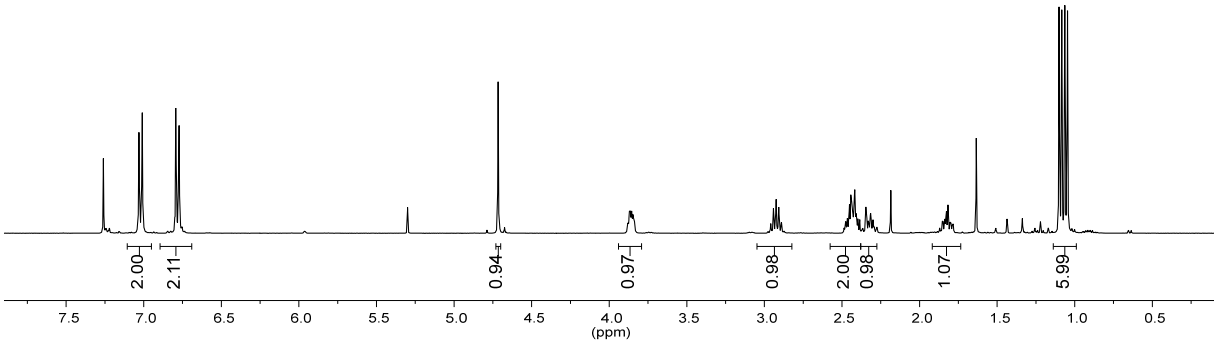
Solvent CDCl 3
MHz 101
Nucleus 13C

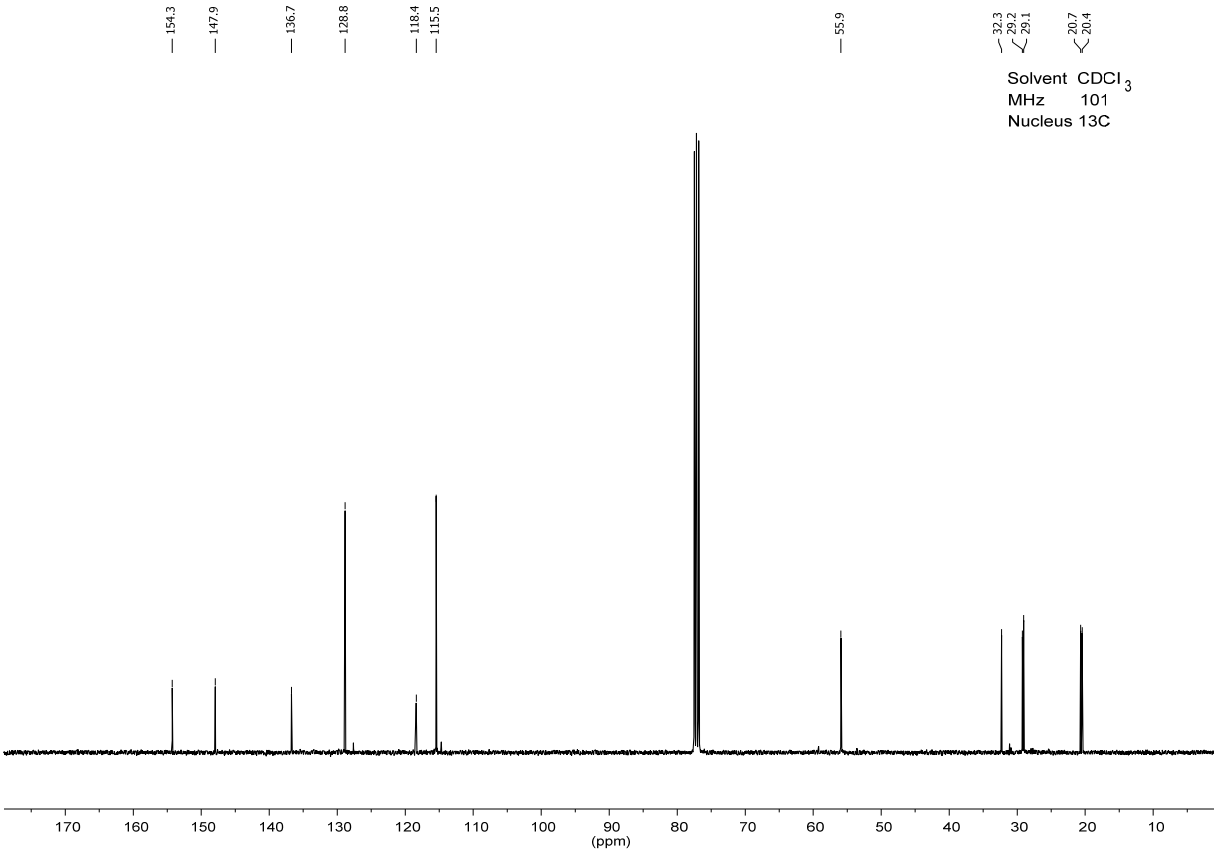


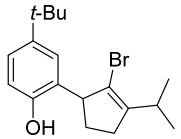



**7p**

Solvent CDCl 3
MHz 400
Nucleus 1H

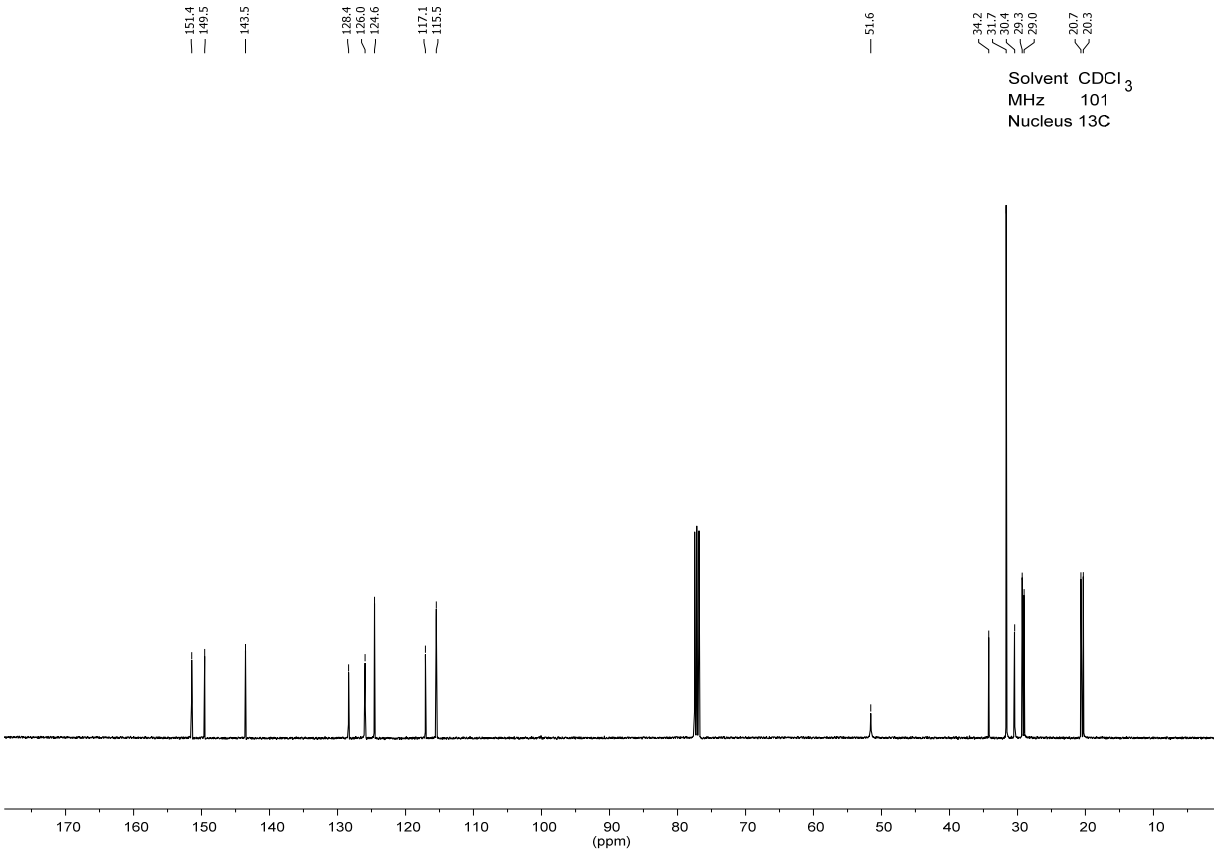


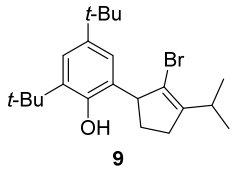




t-Bu
Br
OH

**8**

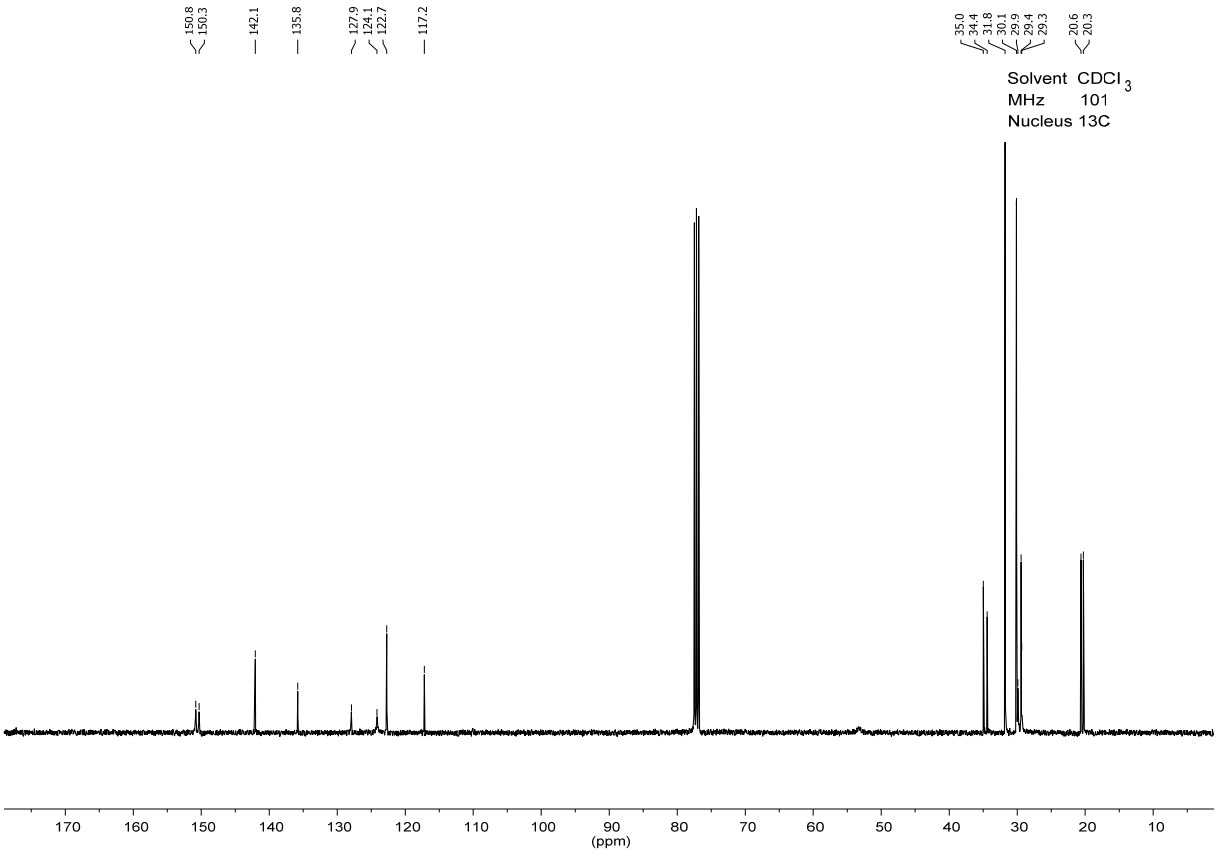

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.00
0.99
0.76
0.98
0.97
3.05
1.05
9.12
3.02
2.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

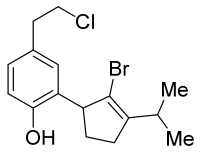

151.4
149.5
143.5
128.4
126.0
124.6
117.1
115.5
51.6
34.2
31.7
30.4
29.3
29.0
20.7
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


t-Bu
Br
t-Bu
OH

**9**

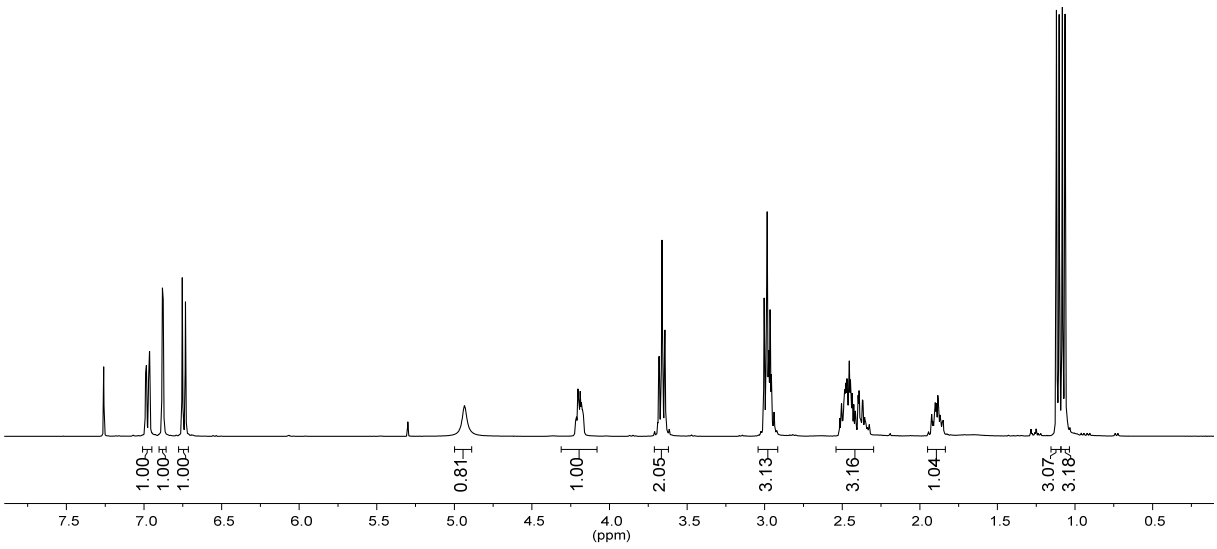

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
0.99
0.95
1.02
1.01
3.13
1.02
9.31
9.49
3.17
3.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

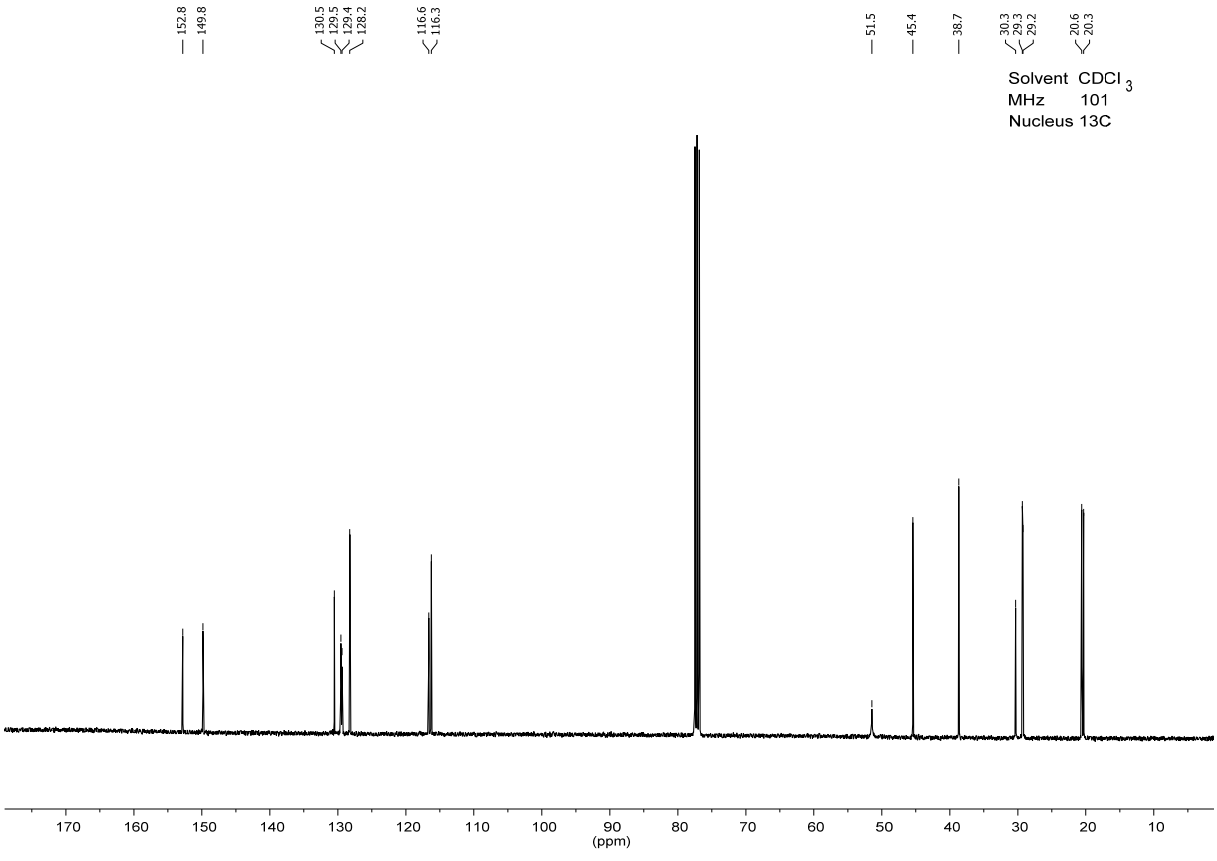

150.8
150.3
142.1
135.8
127.9
124.1
122.7
117.2
35.0
34.4
31.8
30.1
29.9
29.4
29.3
20.6
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

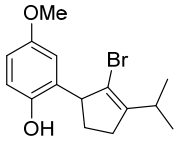



**10**

Solvent CDCl 3
MHz 400
Nucleus 1H

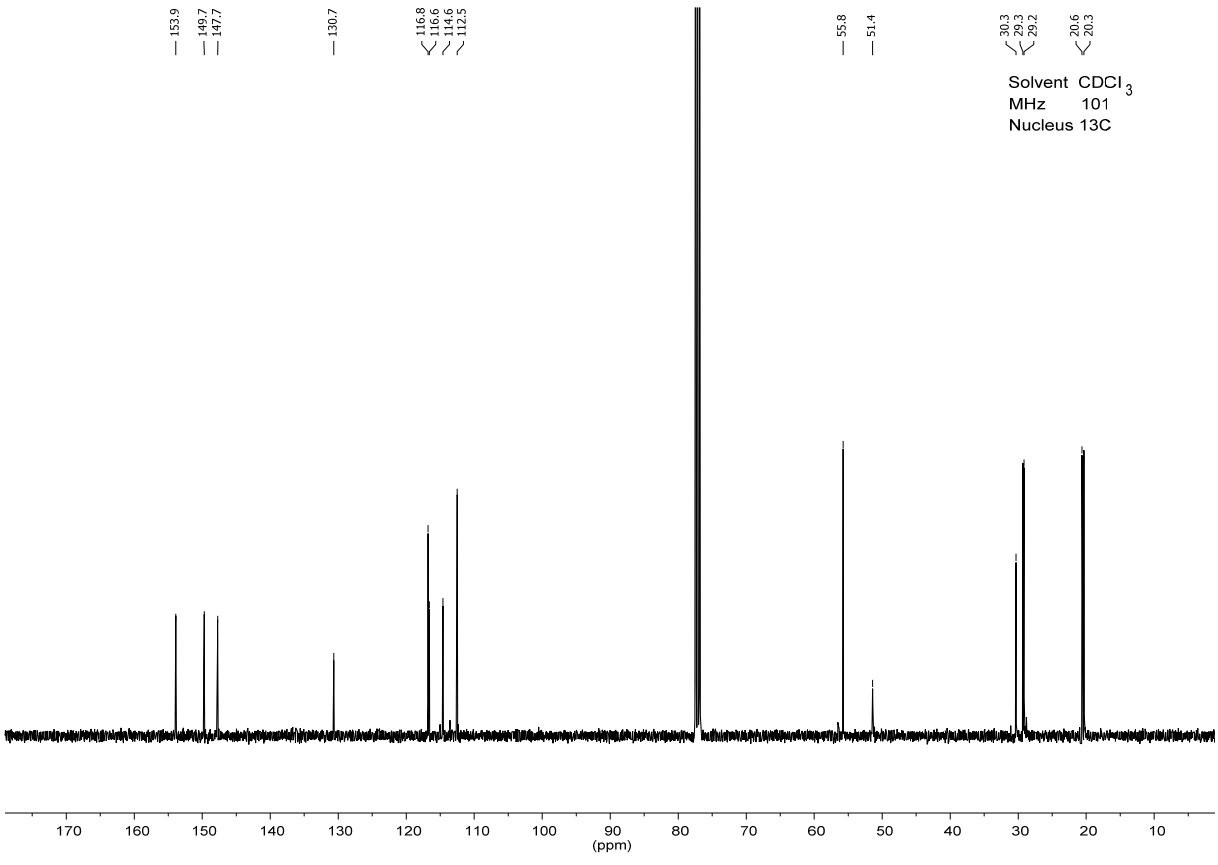


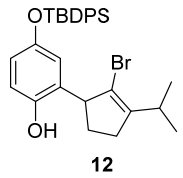




OMe
Br
OH

**11**

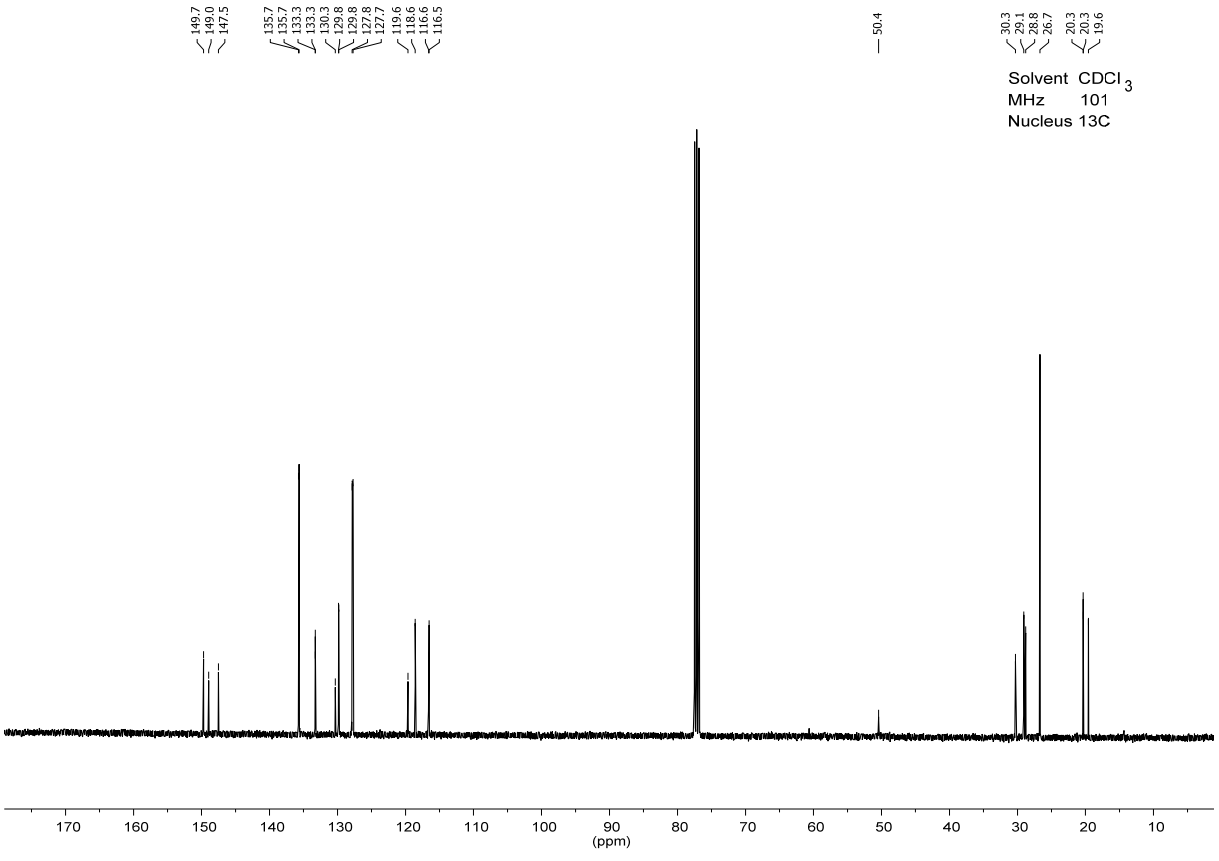

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.05
0.98
0.94
0.97
3.08
1.04
2.08
1.16
1.00
3.21
3.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

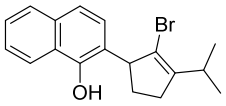

153.9
149.7
147.7
130.7
116.8
116.6
114.6
112.5
55.8
51.4
30.3
29.3
29.2
20.6
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


OTBDPS
Br
OH

**12**

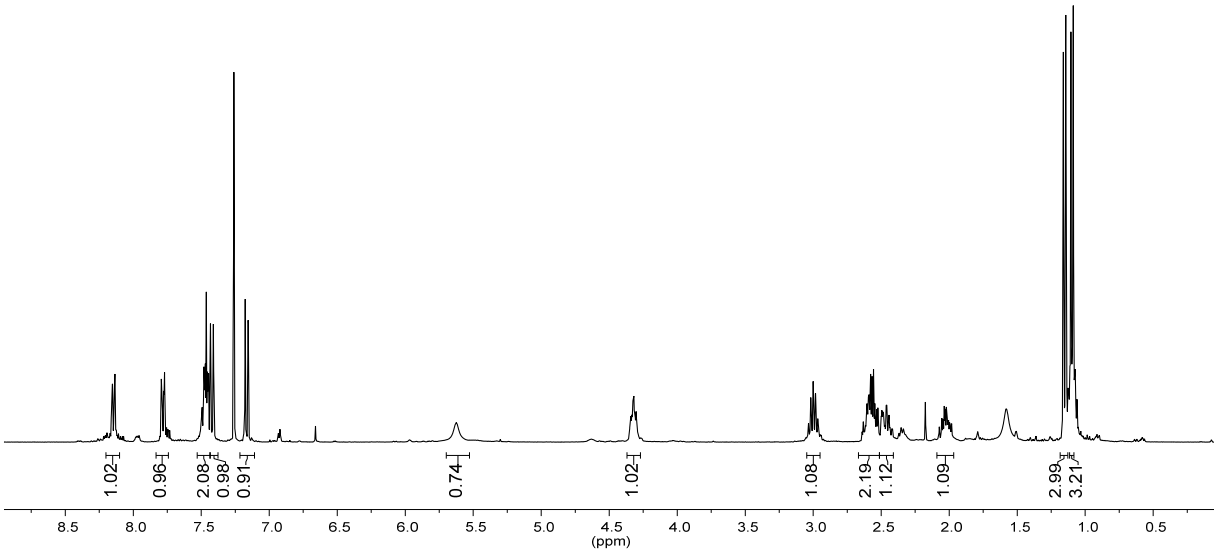

Solvent CDCl3
MHz 400
Nucleus 1H
4.13
6.26
2.00
0.97
0.98
1.01
1.00
1.07
2.13
1.47
9.66
3.10
3.02
(ppm)

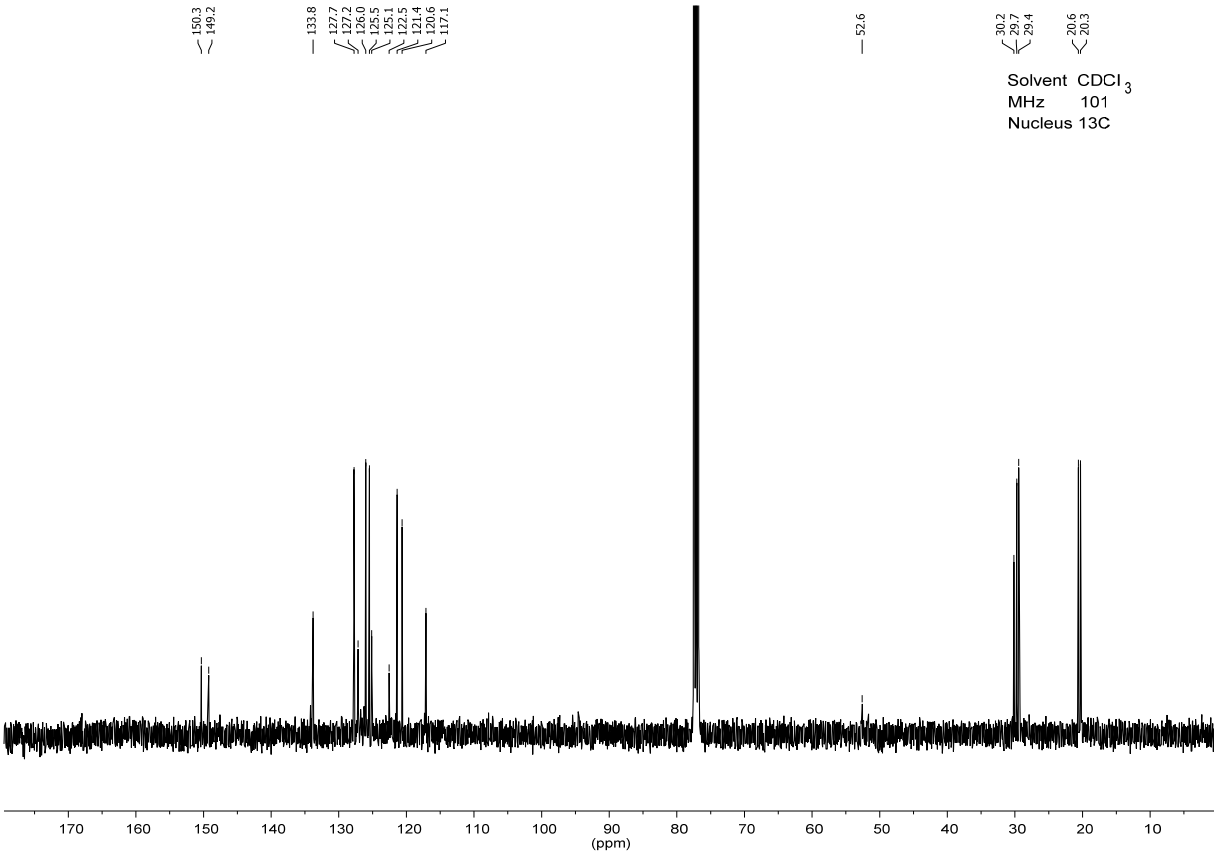

149.7
149.0
147.5
135.7
135.7
133.3
133.3
130.3
129.8
129.8
127.8
127.7
119.6
118.6
116.6
116.5
50.4
30.3
29.1
28.8
26.7
20.3
20.3
19.6
Solvent CDCl3
MHz 101
Nucleus 13C
(ppm)

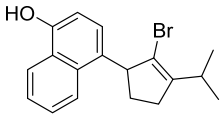



**13o**

Solvent CDCl 3
MHz 400
Nucleus 1H

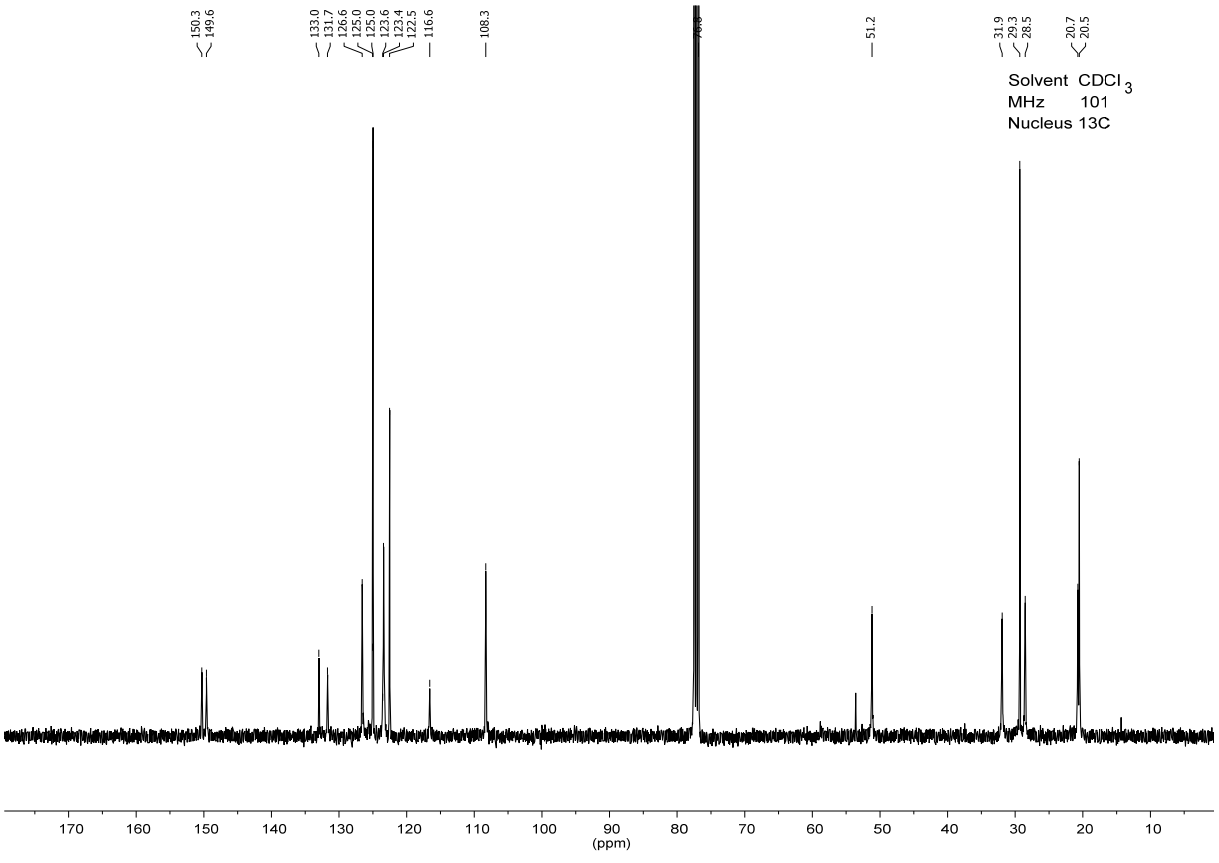


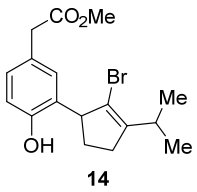




HO
Br

**13p**

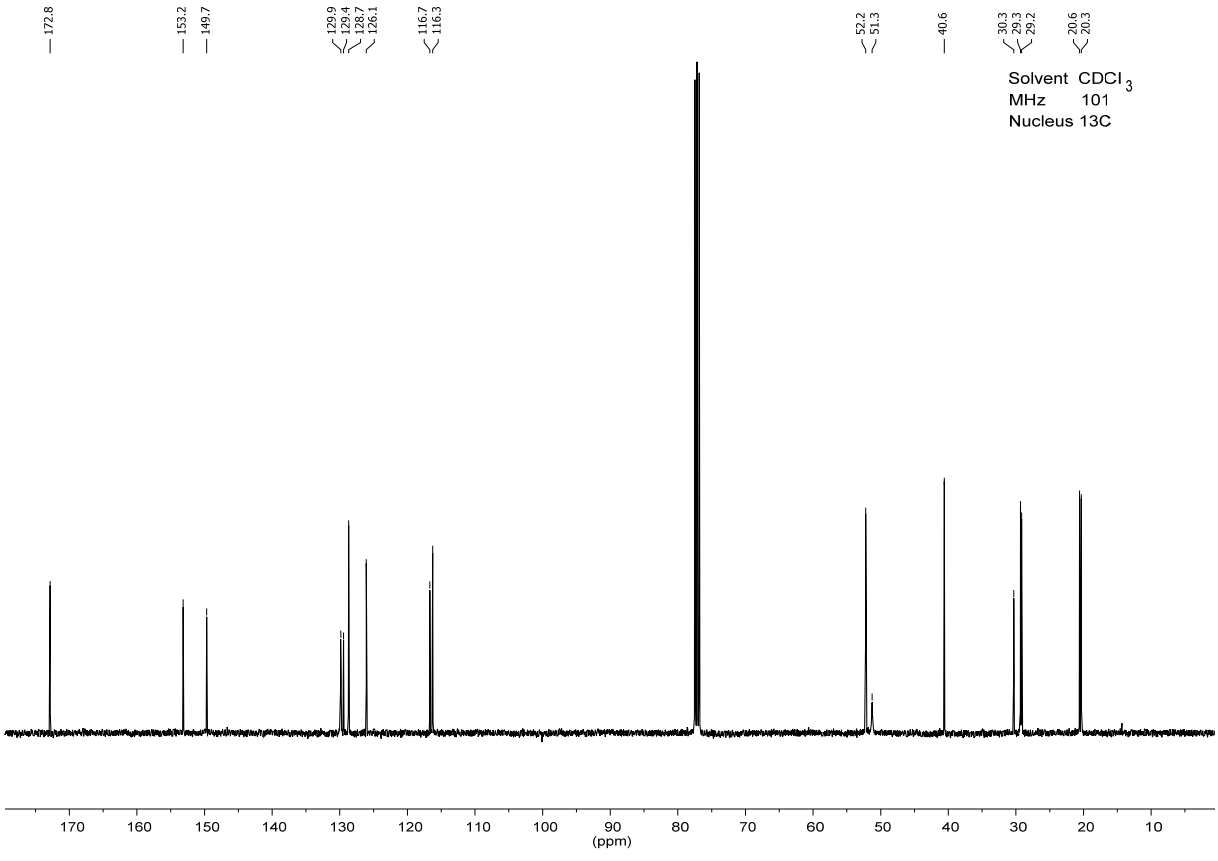

Solvent CDCl3
MHz 400
Nucleus 1H
0.99
1.06
2.05
0.98
0.96
1.00
0.86
1.00
1.18
1.95
0.90
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

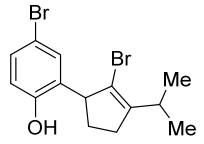

150.3
149.6
133.0
131.7
126.6
125.0
125.0
123.6
123.4
122.5
116.6
108.3
76.8
51.2
31.9
29.3
28.5
20.7
20.5
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


CO2Me
Br
Me
OH
Me

**14**

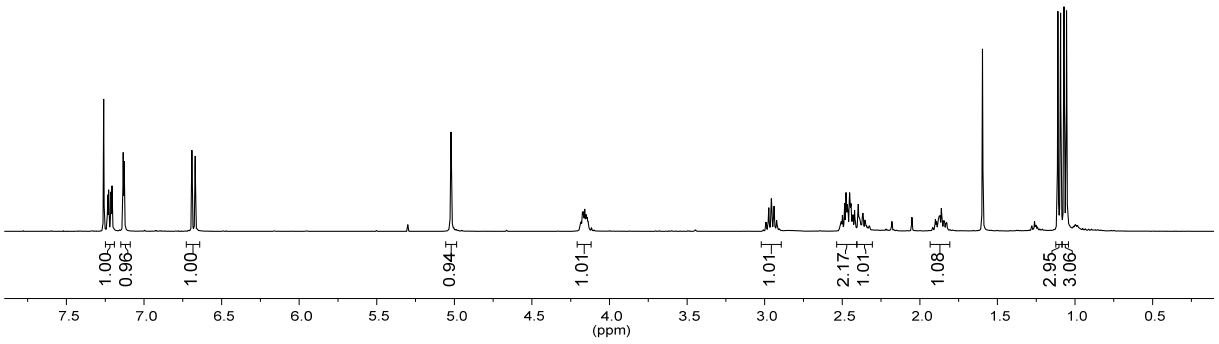

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
0.95
1.00
1.09
1.01
3.05
1.95
1.01
3.13
1.03
3.02
3.15
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

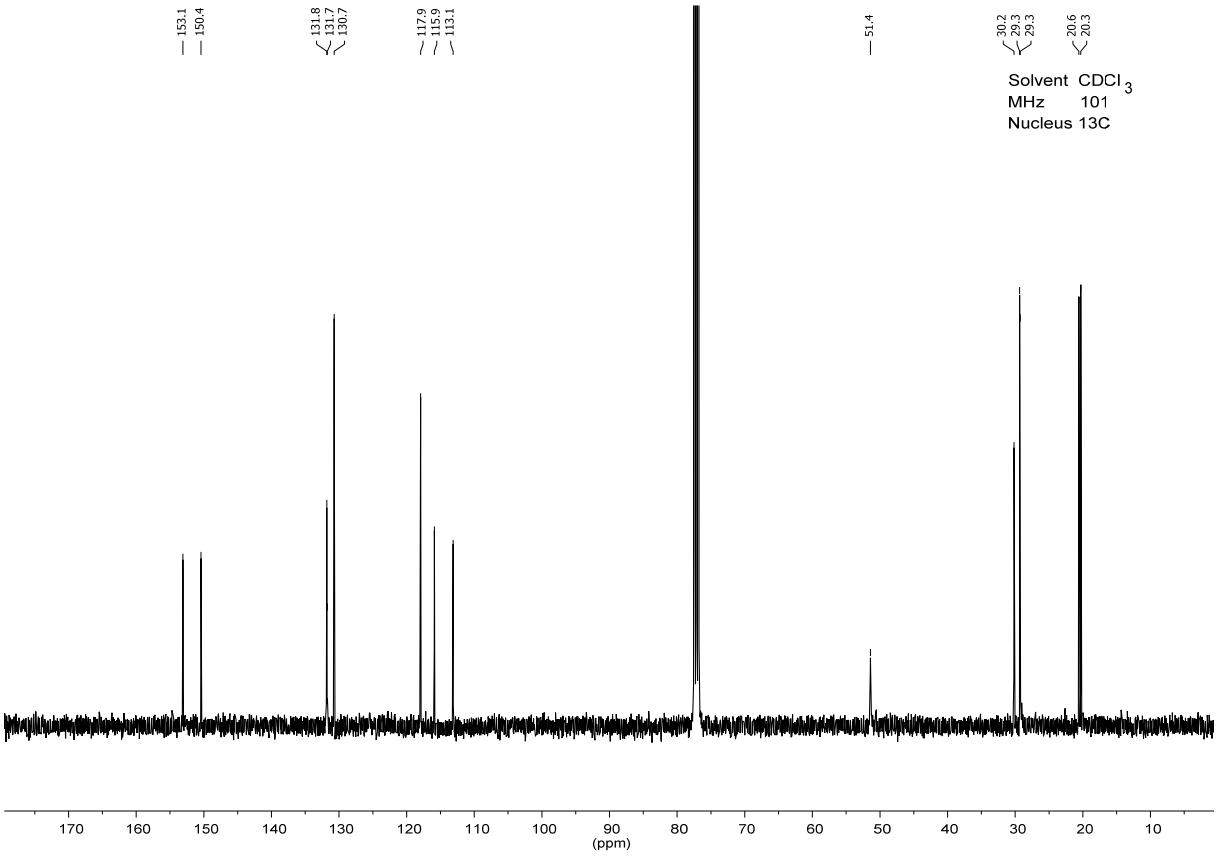

172.8
153.2
149.7
129.9
129.4
128.7
126.1
116.7
116.3
52.2
51.3
40.6
30.3
29.3
29.2
20.6
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

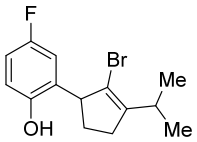



**15**

Solvent $CDCl_3$
MHz 400
Nucleus 1H

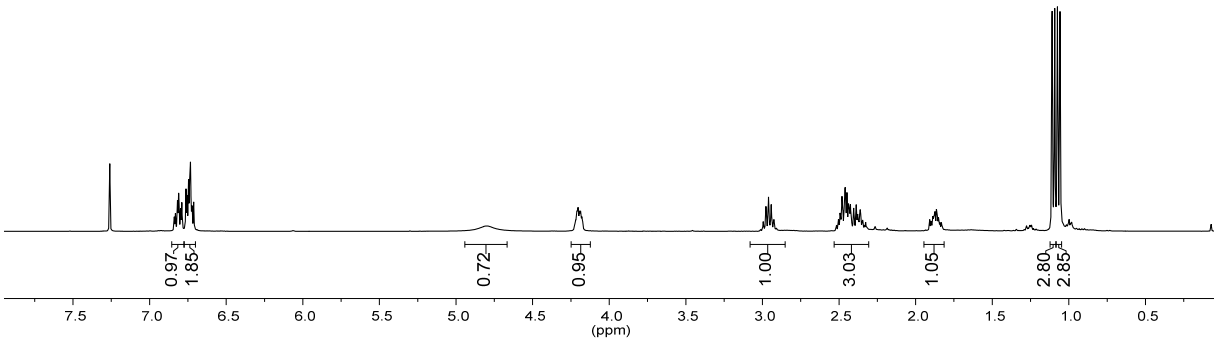


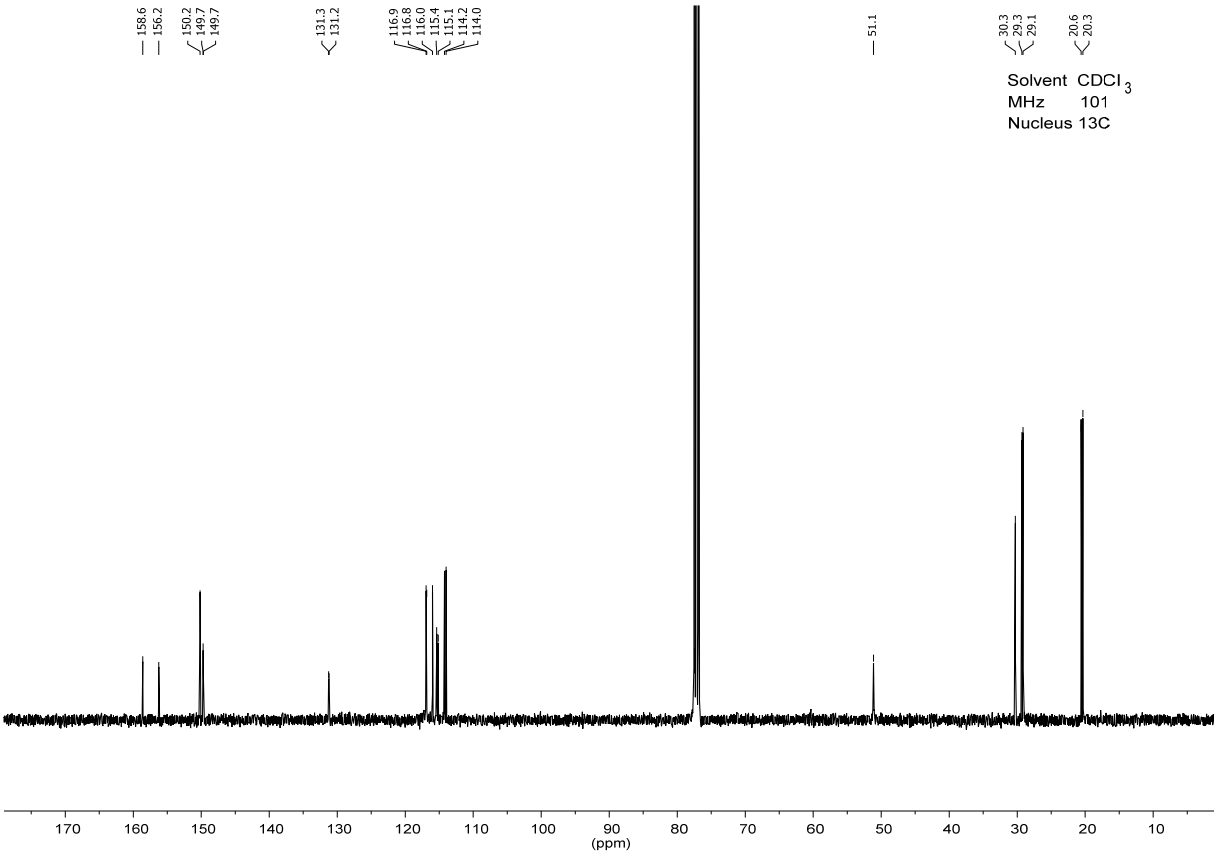



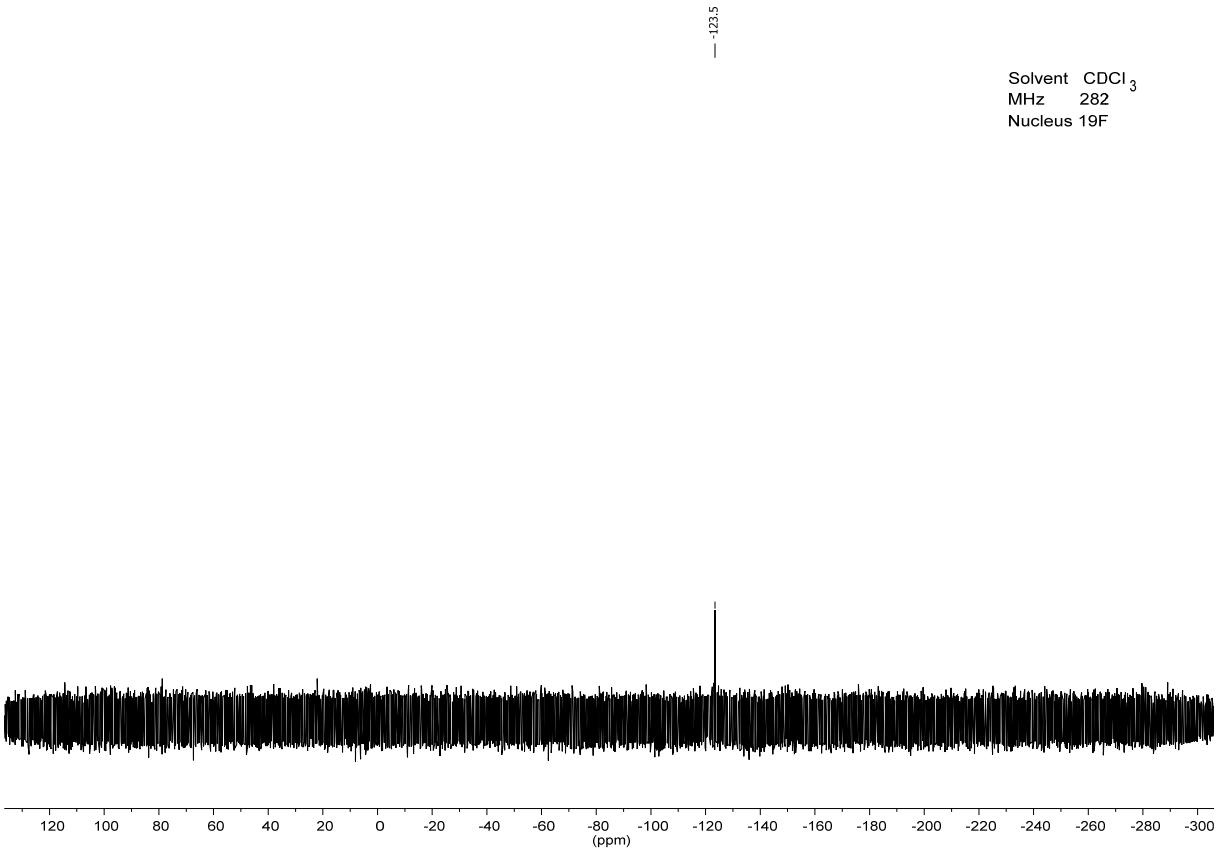


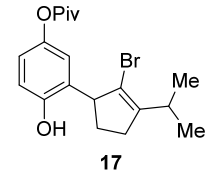

**16**

Solvent CDCl 3
MHz 400
Nucleus 1H



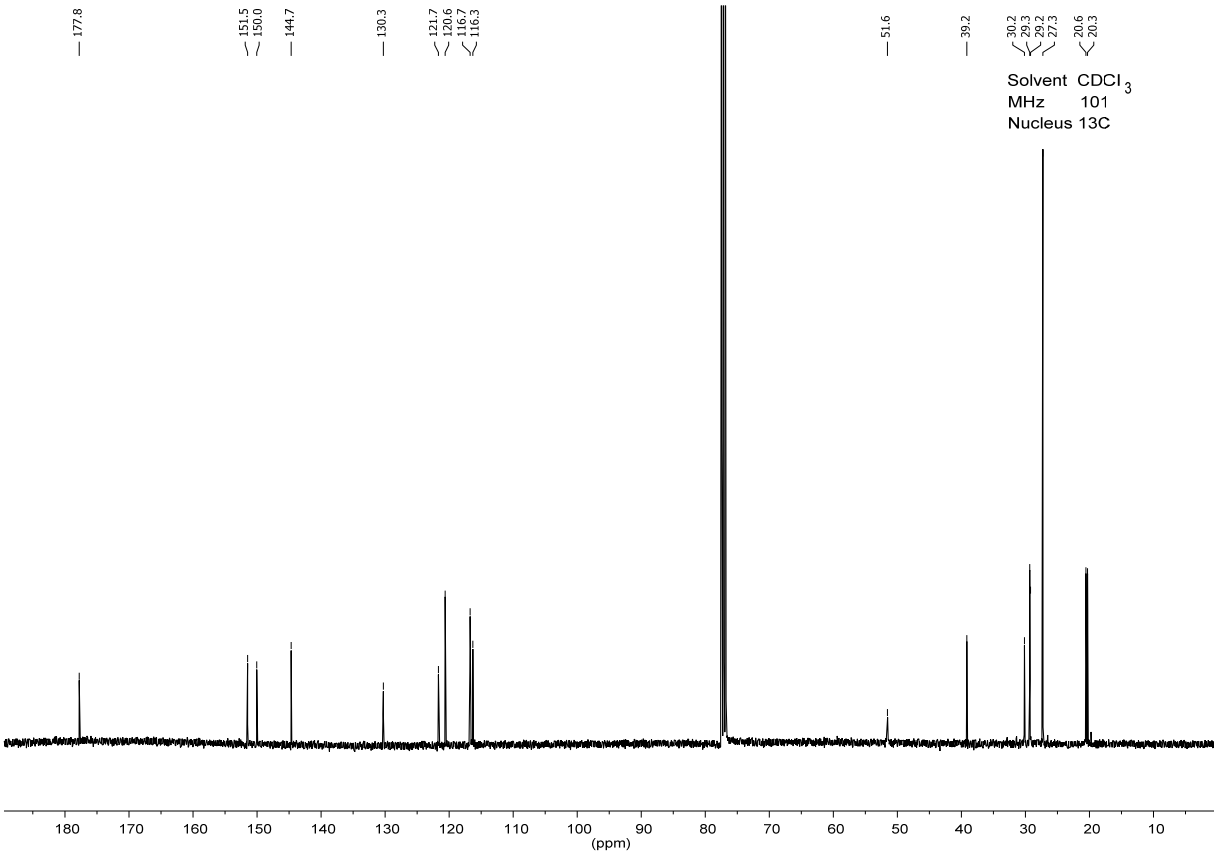



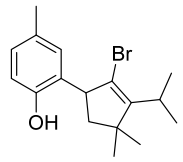

-123.5
Solvent CDCl3
MHz 282
Nucleus 19F
120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260 -280 -300
(ppm)


OPiv
Br
Me
OH
Me

**17**

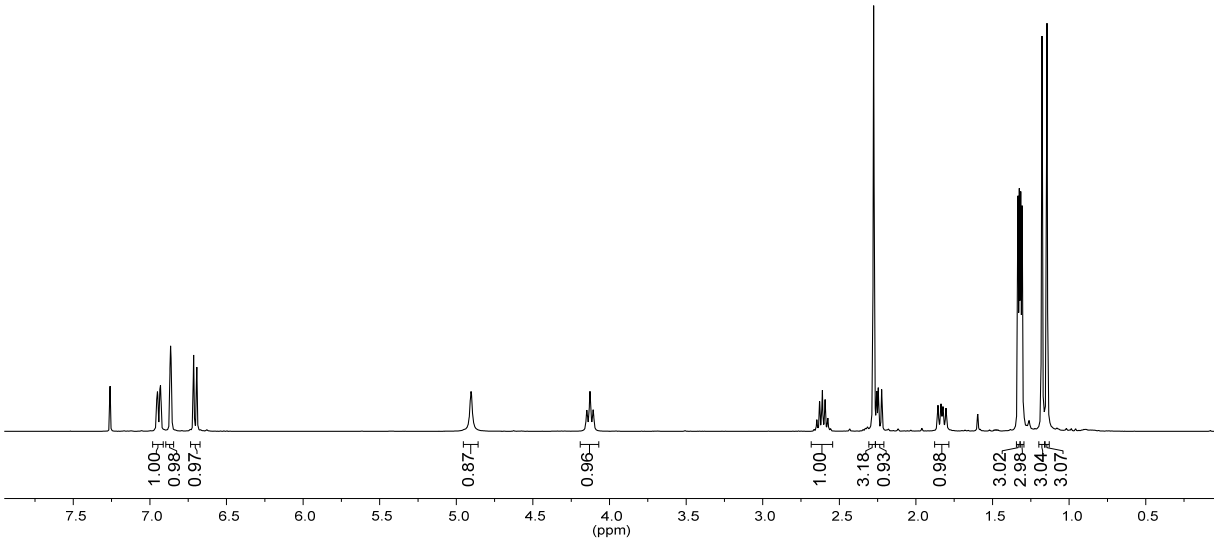

Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.98
0.98
1.01
1.02
2.12
0.99
1.02
9.40
2.95
3.12
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

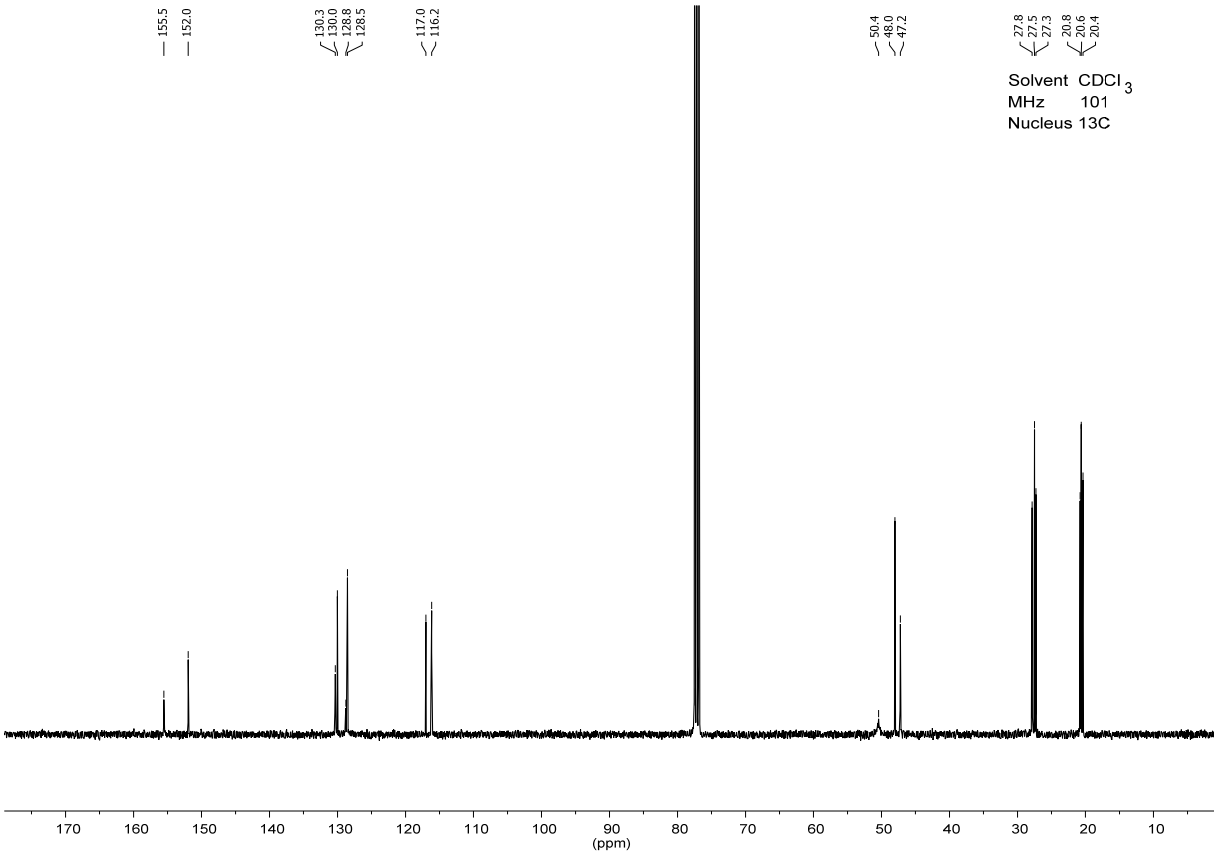

177.8
151.5
150.0
144.7
130.3
121.7
120.6
116.7
116.3
51.6
39.2
30.2
29.3
29.2
27.3
20.6
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



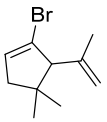

**30**

Solvent CDCl 3
MHz 400
Nucleus 1H

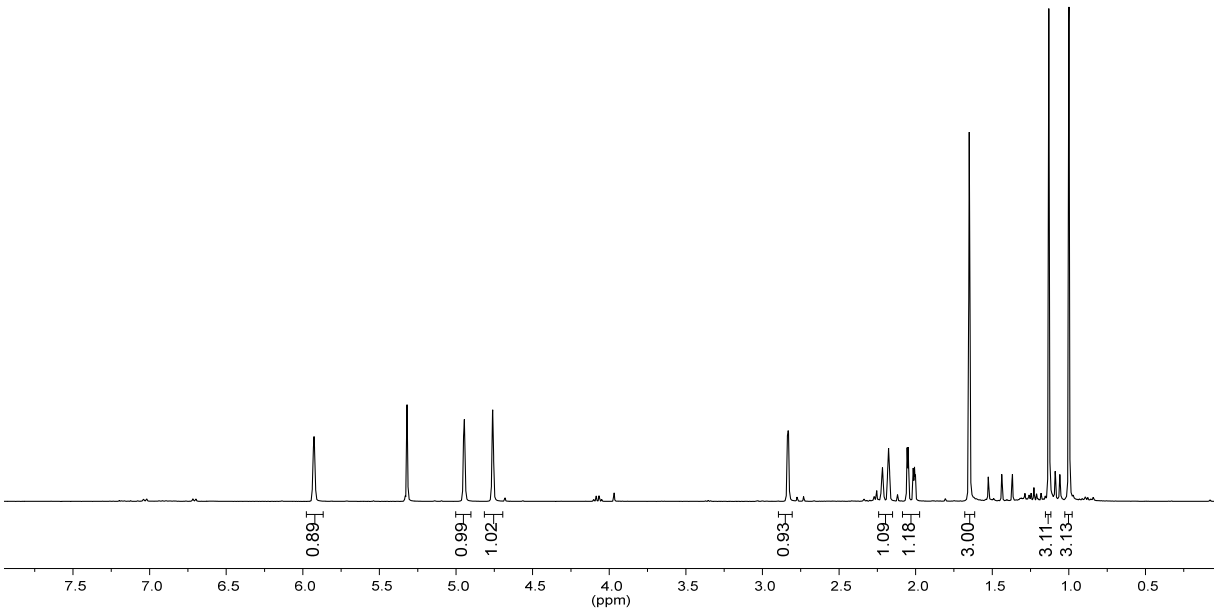


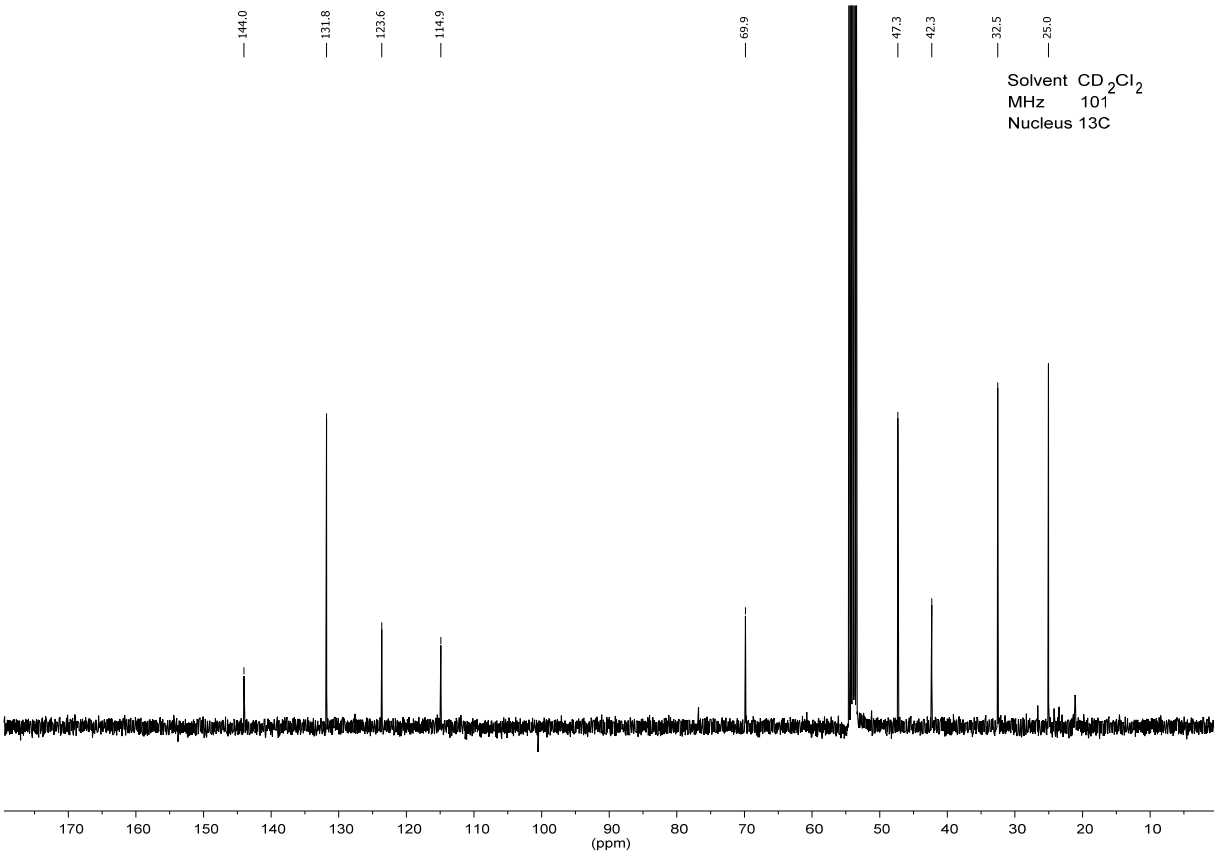



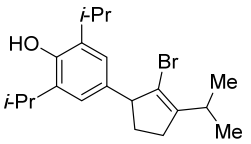

Solvent CDCl 3
MHz 101
Nucleus 13C


Br

**31**

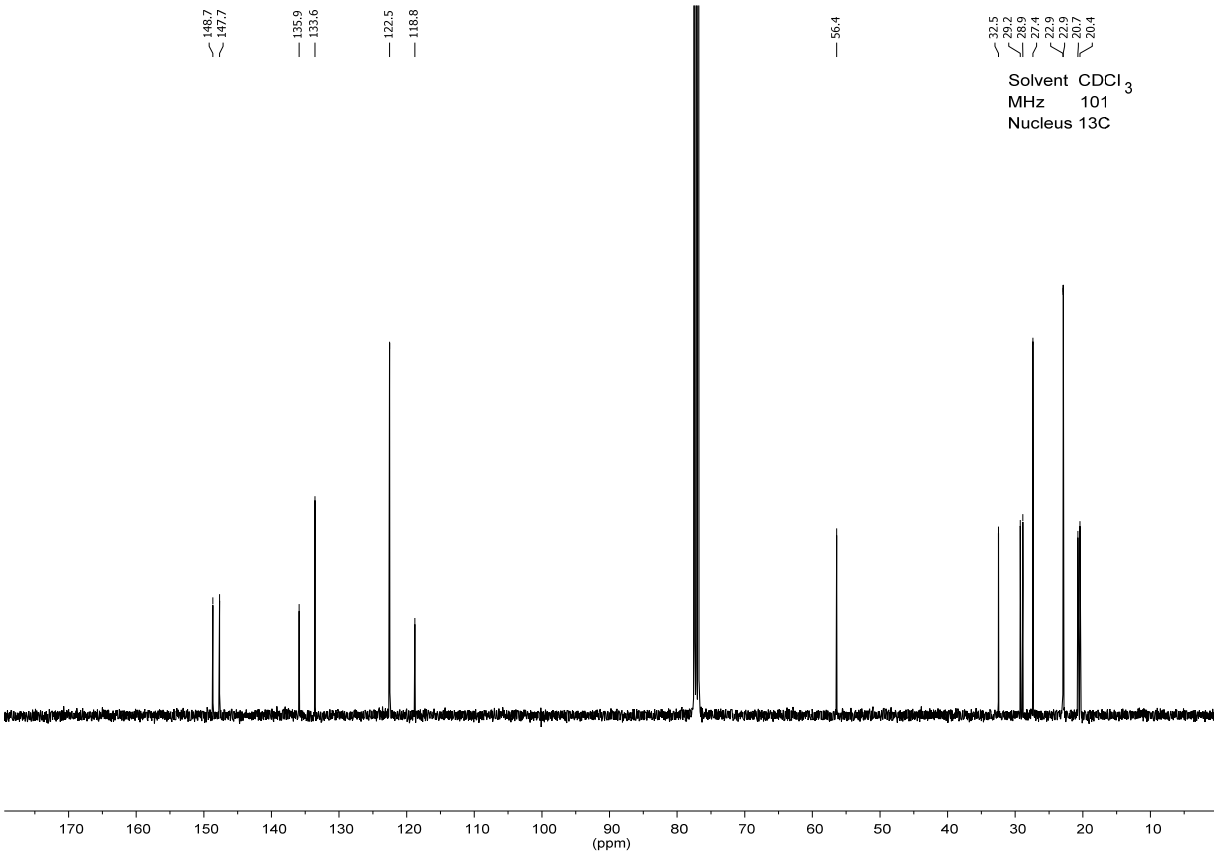

Solvent CD2Cl2
MHz 400
Nucleus 1H
0.89
0.99
1.02
0.93
1.09
1.18
3.00
3.11
3.13
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

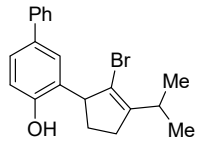

144.0
131.8
123.6
114.9
69.9
47.3
42.3
32.5
25.0
Solvent CD2Cl2
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


i-Pr
HO
Br
Me
i-Pr
Me

**S64**

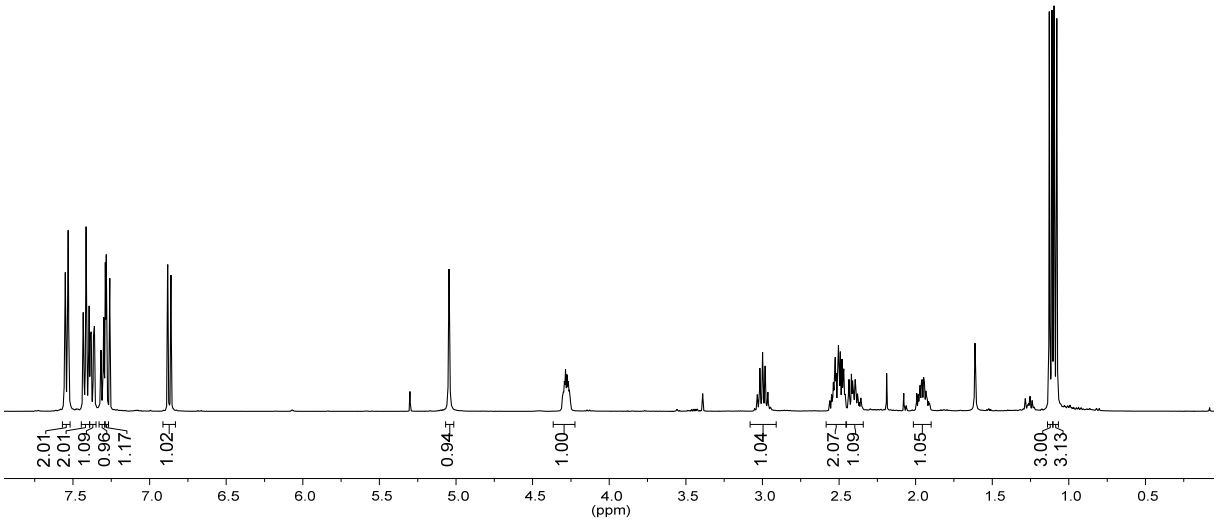

Solvent CDCl3
MHz 400
Nucleus 1H
2.00
0.95
2.10
1.03
3.06
0.99
6.09
5.89
3.09
3.09
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

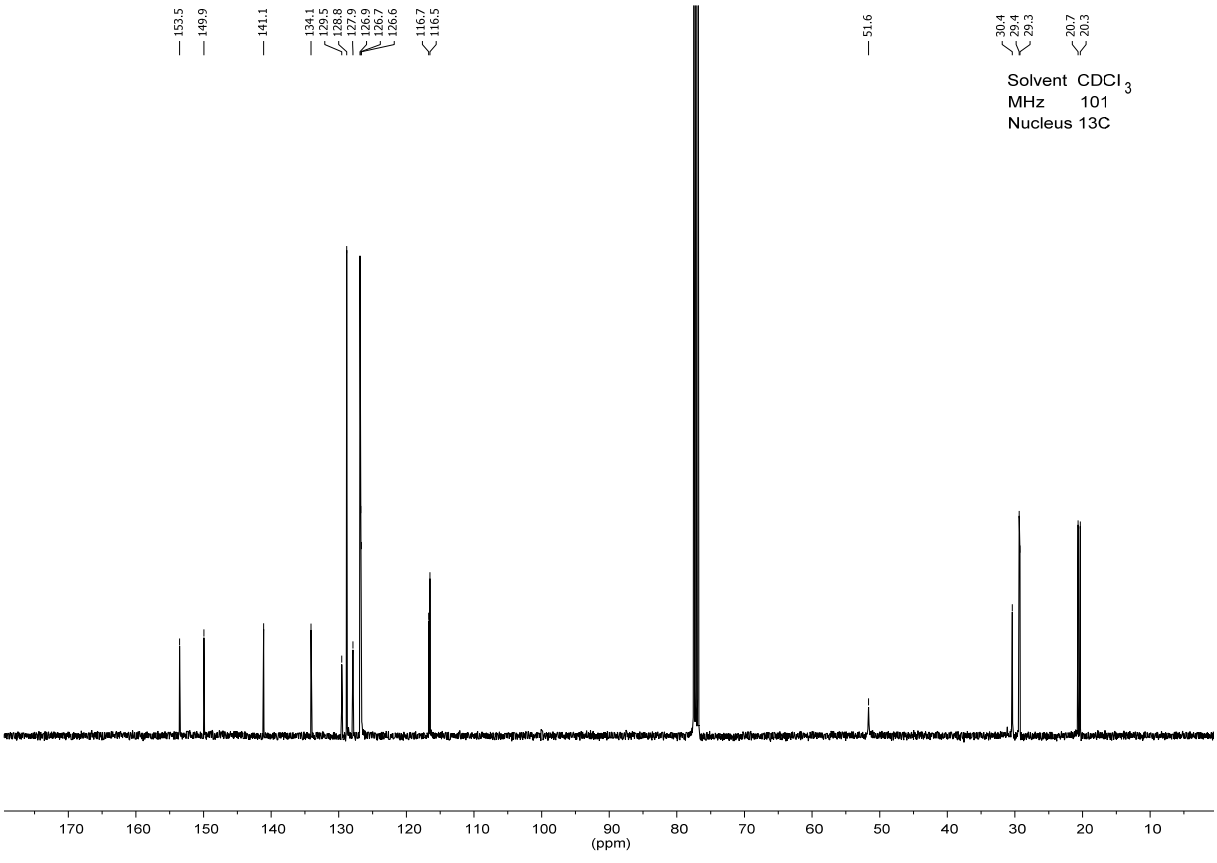

148.7
147.7
135.9
133.6
122.5
118.8
56.4
32.5
29.2
28.9
27.4
22.9
22.9
20.7
20.4
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)



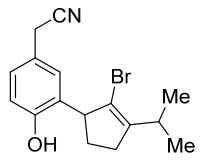

**S65**

Solvent CDCl 3
MHz 400
Nucleus 1H



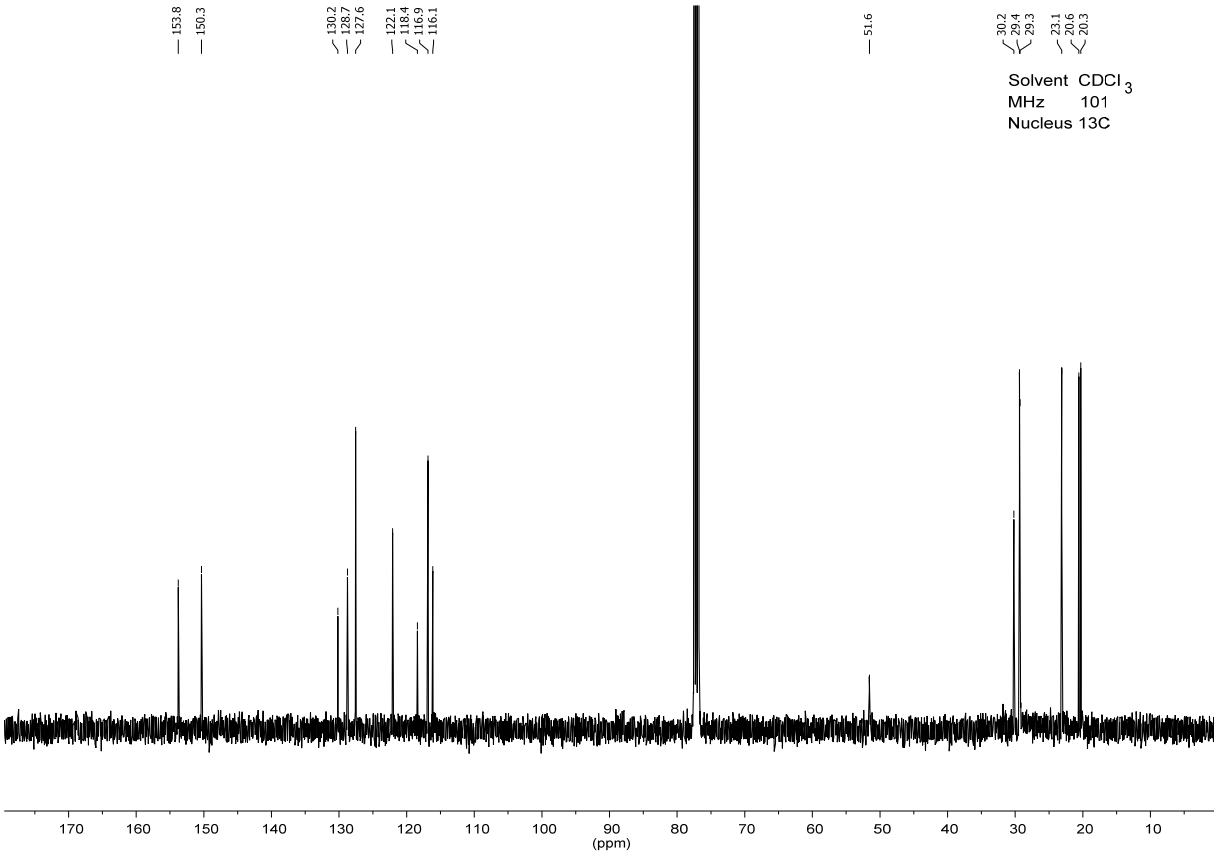




Solvent CDCl 3
MHz 101
Nucleus 13C


CN
Br
Me
Me
OH

**S66**


Solvent CDCl3
MHz 400
Nucleus 1H
1.00
1.00
1.03
0.99
1.01
2.01
1.02
2.16
0.92
1.03
2.98
3.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


153.8
150.3
130.2
128.7
127.6
122.1
118.4
116.9
116.1
51.6
30.2
29.4
29.3
23.1
20.6
20.3
Solvent CDCl3
MHz 101
Nucleus 13C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

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