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# Total Synthesis of (+)-Dendrowardol C

# and

# Investigation of Anti-Inflammatory Epoxyisoprostanes and their Analogs

A thesis submitted to attain the degree of
DOCTOR OF SCIENCES of ETH ZURICH
(Dr. sc. ETH Zurich)

presented by

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Für Daniel und meine Eltern.

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# Publications and Presentations

## List of Publications

H. Wolleb, E. M. Carreira

**Total Synthesis of (+)-Dendrowardol C**

*Angew. Chem. Int. Ed.* **2017**, *56*, 10890–10893.

H. Wolleb, S. Ogawa, M. Schneider, A. Shemet, J. Muri, M. Kopf, E. M. Carreira

**Synthesis and Structure–Activity Relationship Studies of Anti-Inflammatory Epoxyisoprostane Analogues**

*Org. Lett.* **2018**, *20*, 3014–3016.

J. F. Teiber, J. Xiao, G. L. Kramer, S. Ogawa, C. Ebner, H. Wolleb, E. M. Carreira, D. M. Shih, R. W. Haley

**Identification of biologically active δ-lactone eicosanoids as paraoxonase substrates**

*Biochem. Biophys. Res. Commun.* **2018**, *505*, 87–92.

## List of Presentations

10$^{th}$ Symposium of the Scholarship Fund of the Swiss Chemical Industry (SSCI)

Oral presentation: **Total Synthesis of (+)-Dendrowardol C**

January 2018, ETH Zurich, Switzerland

BOSS XVI – 16$^{th}$ Belgian Organic Synthesis Symposium

Poster presentation: **Total Synthesis of (+)-Dendrowardol C**

July 2018, Brussels, Belgium

Syngenta chemistry workshop for talented PhD students

Poster presentation: **Total Synthesis of (+)-Dendrowardol C**

October 2018, Stein Säckingen, Switzerland

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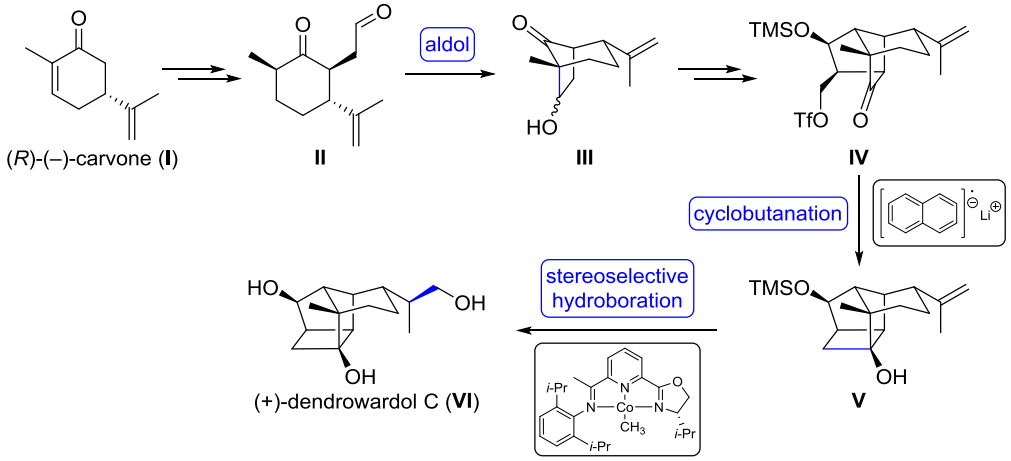
# Abstract

In traditional Chinese medicine, the therapeutic importance of orchids of the genus *Dendrobium* is widely recognized. In 2013, (+)-dendrowardol C (**VI**) was isolated from the stems of *Dendrobium wardianum* Warner, an orchid endemic to southern China and Southeast Asia. This sesquiterpenoid possesses an unprecedented, congested tetracyclic ring system bearing nine contiguous stereogenic centers and thus poses an intriguing synthetic challenge. The first part of this doctoral thesis presents a synthetic analysis of (+)-dendrowardol C (**VI**), which dissects a number of approaches for the construction of the highly bridged carbon framework, including oxy-COPE rearrangements and [2+2] photocycloadditions. The successful route commenced with (*R*)-(–)-carvone (**I**) as an inexpensive chiral starting material and relied on a sequence involving late-stage cyclobutane formation and diastereoselective hydroboration (Scheme I).

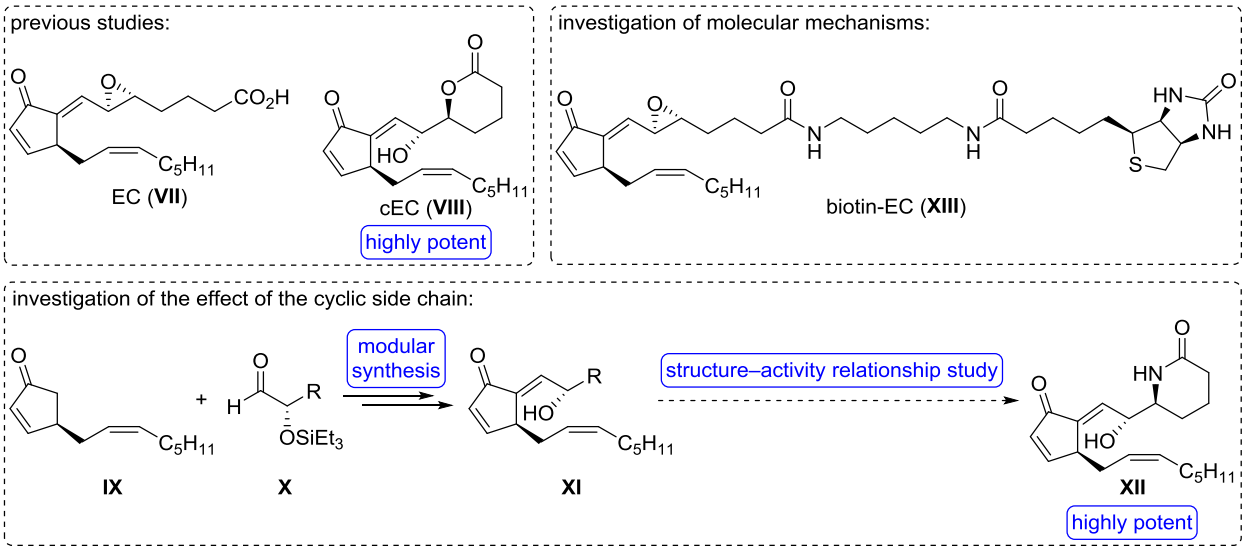



**Scheme I:** Overview of the synthesis of (+)-dendrowardol C (**VI**).

Key features included an intramolecular aldol addition to forge the central bicyclic scaffold **III**, selective homologation of ketone **III**, and 4-*exo*-trig cyclization to form the embedded cyclobutane. Construction of the four-membered carbocycle was enabled by intramolecular epoxide opening followed by formation of the last crucial C–C bond employing umpolung of γ-triflyloxy ketone **IV**. This latter transformation employing lithium naphthalenide as a reducing agent raises mechanistic questions and may be of general use in other cyclization reactions. Finally, the last stereogenic center was set by diastereoselective cobalt-catalyzed hydroboration of the otherwise intractable 1,1-disubstituted double bond in **V**.

The second part of this thesis discusses investigations of anti-inflammatory epoxyisoprostanes and their analogs. Oxidized phospholipids have been recognized as active compounds in inflammation. This class of biomolecules is generated upon exposure of biological membranes to reactive oxygen species, and a majority of investigations suggest oxidized phospholipids to exert proinflammatory effects. However, joint research efforts by the groups of E. M. CARREIRA and M. KOPF have shown that epoxyisoprostane EC (**VII**) acts in an anti-inflammatory fashion, as observed by the reduced secretion of the proinflammatory cytokines IL-6 and IL-12 by bone marrow-derived dendritic cells (Scheme II). Subsequent studies revealed lactone cEC (**VIII**) derived from EC (**VII**) to be even more potent, which prompted further investigations of the effect of the cyclic side chain.

A modular synthesis of analogs was employed, allowing flexible variations of the side chain of parent lactone cEC (**VIII**). The general strategy relied on late-stage coupling of previously described cyclopentenone **IX** with various aldehydes **X** *via* aldol condensation and deprotection to afford the corresponding dienones **XI**. This study identified lactam analog **XII** that retains the high anti-inflammatory activity and is metabolically more stable than cEC (**VIII**). Furthermore, the necessity of the side-chain allylic alcohol for the observed effect was highlighted.

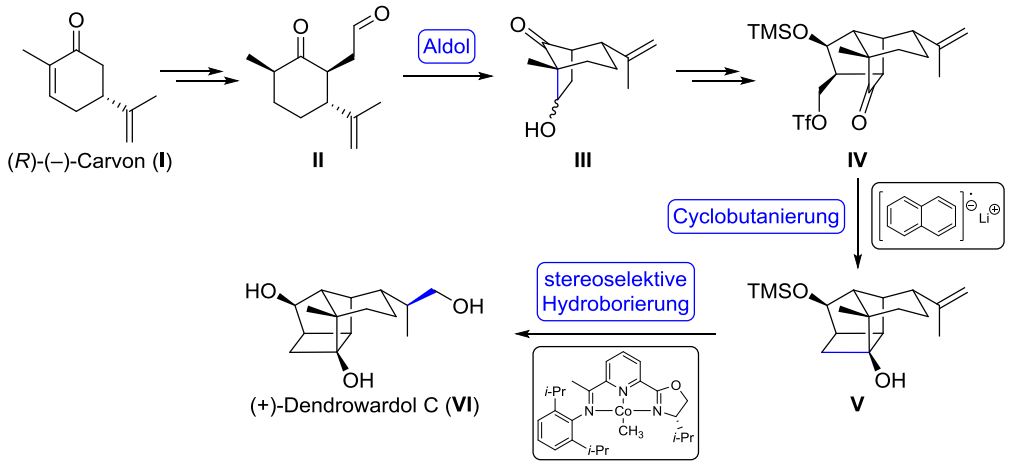



**Scheme II:** Overview of the investigation of anti-inflammatory epoxyisoprostanes and their analogs.

Moreover, a biotinylated analog of EC (**VII**) was synthesized and served as a valuable tool for the investigation of the molecular mechanisms of such epoxyisoprostanes. Biotin-EC (**XIII**) was applied in cell permeabilization experiments and pull-down assays, which confirmed the hypothesis that these cyclopentenone isoprostanes exert their anti-inflammatory activities by signaling through the Keap1/Nrf2 pathway.

# Zusammenfassung

Die therapeutische Wirksamkeit von Orchideen der Gattung *Dendrobium* ist in der traditionellen chinesischen Medizin allgemein bekannt. (+)-Dendrowardol C (**V**) wurde im Jahr 2013 aus den Stängeln von *Dendrobium wardianum* Warner isoliert, einer in Südchina und Südostasien endemischen Orchidee. Das bisher unbekannte, komplexe, tetracyclische Ringsystem dieses Sesquiterpenoids stellt mit seinen neun benachbarten stereogenen Zentren eine faszinierende Syntheseherausforderung dar. Der erste Teil dieser Arbeit präsentiert eine Analyse möglicher Syntheserouten zu (+)-Dendrowardol C (**VI**), wobei verschiedene Herangehensweisen für die Bildung des verbrückten Kohlenstoffgerüstes wie Oxy-COPE-Umlagerungen oder [2+2]-Photocycloadditionen diskutiert werden. Für die erfolgreiche Route, die auf einer späten Cyclobutanierung und einer diastereoselektiven Hydroborierung beruht, wurde (*R*)-(–)-Carvon (**I**) als günstiges, chirales Startmaterial verwendet (Schema I).

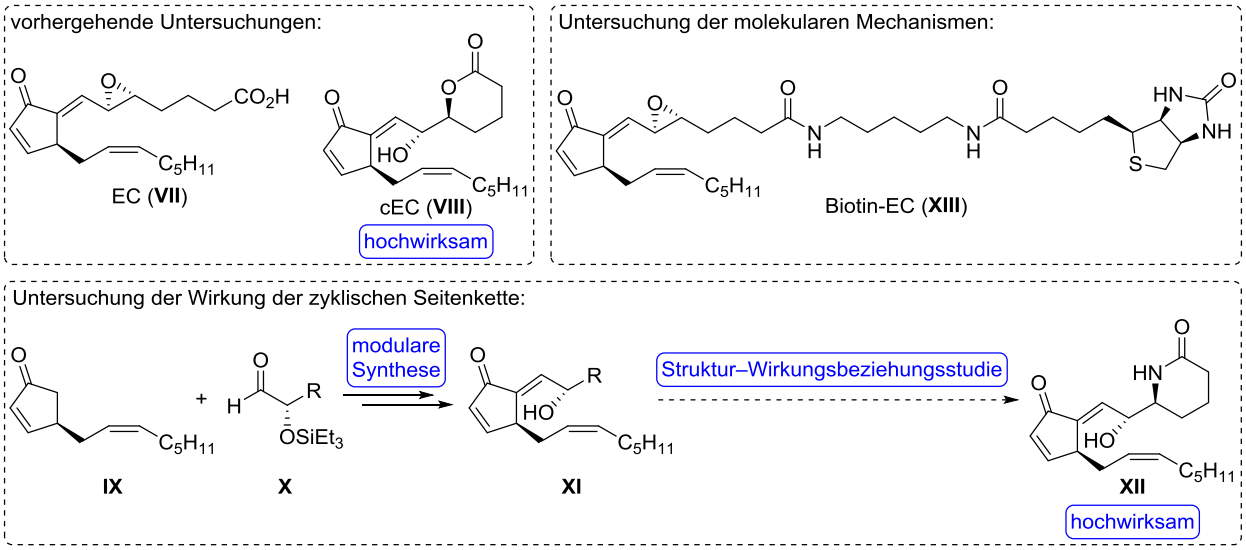



**Schema I:** Überblick über die Synthese von (+)-Dendrowardol C (**VI**).

Eine intramolekulare Aldoladdition, die zum zentralen bicyclischen Gerüst **III** führte, die selektive Homologisierung des Ketons **III** und eine 4-*exo*-trig-Cyclisierung zur Bildung des Cyclobutans in **V** gehören zu den wichtigsten Schritten dieser Synthese. Die Bildung des viergliedrigen Rings wurde durch eine intramolekulare Epoxidöffnung ermöglicht, woraufhin die verbleibende, kritische C–C Bindung durch die Umpolung von γ-Triflyloxyketon **IV** gebildet wurde. Diese Transformation mit Lithiumnaphthalenid als Reduktionsmittel wirft Fragen bezüglich deren Mechanismus auf und könnte sich als generelle Methode für solche Cyclisierungsreaktionen erweisen. In einer anspruchsvollen letzten Transformation wurde das verbleibende stereogene Zentrum mittels einer diastereoselektiven Kobalt-katalysierten Hydroborierung der 1,1-disubstituierten Doppelbindung in **IV** gesetzt.

Der zweite Teil dieser Arbeit diskutiert Untersuchungen von entzündungshemmenden Epoxyisoprostanen und deren Analoga. Oxidierte Phospholipide sind für ihre aktive Rolle während Entzündungen bekannt. Diese Biomoleküle entstehen, wenn biologische Membranen reaktiven Sauerstoffspezies ausgesetzt sind. Eine Mehrzahl von Untersuchungen deuten darauf hin, dass oxidierte Phospholipide entzündungsfördernd wirken. Forschungsarbeiten in den Gruppen von E. M. CARREIRA und M. KOPF haben jedoch gezeigt, dass das Epoxyisoprostan EC (**VII**) entzündungshemmend wirkt, was durch die reduzierte Sekretion der entzündungsfördernden Cytokine IL-6 und IL-12 durch dendritische Knochenmarkzellen beobachtet werden konnte (Schema II). Nachfolgende Studien haben das Lakton cEC (**VIII**) als noch stärker aktiv hervorgehoben, was zur Untersuchung der Wirkung der Seitenkette in cEC (**VIII**) anregte.

Veränderungen der Seitenkette von Lakton cEC (**VIII**) wurden durch eine modulare Synthese von Analoga ermöglicht. Die Strategie beruhte auf einer späten Kupplung des bekannten Cyclopentenons **IX** mit verschiedenen Aldehyden **X** mittels einer Aldolkondensation und nachfolgender Entschützung, wodurch die entsprechenden Dienone **XI** erhalten wurden. Während dieser Studie wurde das Lactam-Analogon **XII** gefunden, das die entzündungshemmende Aktivität beibehält und metabolisch stabiler ist als cEC (**VIII**). Ausserdem wurde die Notwendigkeit des allylischen Alkohols in der Seitenkette für die beobachtete Wirkung gezeigt.




**Schema II:** Überblick über die Untersuchung entzündungshemmender Epoxyisoprostane und deren Analoga.

Ein biotinyliertes Analogon von EC (**VII**) wurde synthetisiert, das als nützliches Hilfsmittel für die Aufklärung der molekularen Mechanismen solcher Epoxyisoprostane diente. Biotin-EC (**XIII**) wurde in Zellpermeabilitätsexperimenten und Pulldown-Assays verwendet, welche die Hypothese bestätigten, dass dise Cyclopentenon-Isoprostane ihre entzündungshemmende Wirkung durch den Keap1/Nrf2-Signalweg ausüben.

# List of Abbreviations, Acronyms, and Symbols

| | |
|---|---|
| Å | Ångstrom |
| ABSA | acetamidobenzenesulfonyl azide |
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | azobisisobutyronitrile |
| app | apparent |
| aq. | aqueous |
| ARE | antioxidant response element |
| ATP | adenosine triphosphate |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BMDC | bone marrow-derived dendritic cell |
| Boc | *tert*-butoxycarbonyl |
| Bp | biphenyl |
| br | broad |
| Bu | butyl |
| °C | degree Celsius |
| CAM | cerium ammonium molybdate |
| cat. | catalytic |
| CDI | 1,1'-carbonyldiimidazole |
| $cm^{-1}$ | 1/centimeter |
| conc. | concentrated |
| COSY | correlation spectroscopy |
| Cp | cyclopentadienyl |
| CSA | 10-camphorsulfonic acid |
| d | day, doublet |
| DBB | 4,4'-di-*tert*-butylbiphenyl |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| $(DHQ)_2PYR$ | hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether |
| DHTL | dihydroxy-eicosatrienoic acid lactone |
| DIBAL-H | diisobutylaluminum hydride |
| DiHET | dihydroxy-eicosatrienoic acid |
| DG | directing group |
| DIAD | diisopropyl azodicarboxylate |
| DMAP | 4-(dimethylamino)pyridine |
| DME | dimethoxyethane |

| | |
|---|---|
| DMF | dimethylformamide |
| DMP | DESS–MARTIN periodinane |
| DMSO | dimethyl sulfoxide |
| d.r. | diastereomeric ratio |
| EC | epoxycyclopentenone isoprostane |
| EDC | *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide |
| EDTA | ethylenediaminetetraacetic acid |
| *ee* | enantiomeric excess |
| EET | epoxyeicosatrienoic acid |
| EI | electron ionization, epoxyisoprostane |
| ELISA | enzyme-linked immunosorbent assay |
| equiv | equivalent |
| ESI | electron spray ionization |
| Et | ethyl |
| FCS | fetal bovine serum |
| g | gram |
| h | hour |
| HEPES | 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid |
| HMBC | heteronuclear multiple bond correlation spectroscopy |
| HMDS | hexamethyldisilazane |
| HMPA | hexamethylphosphoramide |
| HOBt | 1-hydroxybenzotriazole |
| HPLC | high pressure liquid chromatography |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum correlation spectroscopy |
| Hz | Hertz |
| *i* | *iso* |
| IL | interleukin |
| IP | immunoprecipitation |
| Ipc | isopinocampheyl |
| IR | infrared spectroscopy |
| IsoP | isoprostane |
| *J* | coupling constant |
| kcal | kilocalorie |
| Keap1 | Kelch-like ECH-associated protein 1 |
| L | liter |
| LC-MS | liquid chromatography–mass spectrometry |

| | |
|---|---|
| LDA | lithium diisopropylamide |
| M | molar, mega |
| m | multiplet, milli |
| *m*-CPBA | 3-chloroperbenzoic acid |
| Me | methyl |
| min | minute |
| mol | mole |
| mol% | percentage by moles |
| Ms | methanesulfonyl |
| *n* | normal (prefix for alkyl groups) |
| n | nano |
| N | normal |
| NMO | 4-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear OVERHAUSER effect spectroscopy |
| Np | naphthalenide |
| Nrf2 | nuclear factor-erythroid-2-related factor 2 |
| *o* | *ortho* |
| OxPAPC | oxidized 1-palmitoyl-2-arachidonoyl phosphatidylcholine |
| OxPL | oxidized phospholipid |
| *p* | *para* |
| p | quintet |
| PAPC | 1-palmitoyl-2-arachidonoyl phosphatidylcholine |
| PBS | phosphate buffered saline |
| PC | phosphatidylcholine |
| PECPC | epoxycyclopentenone isoprostane phospholipid |
| PEIPC | epoxyisoprostane phospholipid |
| PG | prostaglandin, protecting group |
| Ph | phenyl |
| pH | negative logarithm of hydrogen ion concentration |
| pin | pinacol |
| PMB | 4-methoxybenzyl |
| PON | paraoxonase |
| ppm | parts per million |
| Pr | propyl |
| PUFA | polyunsaturated fatty acid |
| pyr | pyridine |

| | |
|---|---|
| q | quartet |
| quant. | quantitative |
| $R_f$ | retardation factor |
| ROESY | rotating frame nuclear OVERHAUSER effect spectroscopy |
| ROS | reactive oxygen species |
| RPMI | Roswell Park Memorial Institute |
| RT | room temperature |
| *s* | *sec* |
| s | singlet |
| sat. | saturated |
| SDS-PAGE | sodium dodecyl sulfate polyacrylamide gel electrophoresis |
| *t* | *tert* |
| t | triplet |
| TBAF | tetrabutylammonium fluoride |
| TBHP | *tert*-butyl hydroperoxide |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFEF | 2,2,2-trifluoroethyl formate |
| THF | tetrahydrofuran |
| Thx | thexyl |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMEDA | *N*,*N*,*N*',*N*'-tetramethylene-1,2-diamine |
| TMS | trimethylsilyl |
| TPAP | tetrapropylammonium perruthenate |
| Ts | *p*-toluenesulfonyl |
| TS | transition state |
| UV | ultraviolet |
| W | watt |
| WB | western blot |
| WCE | whole cell extract |
| wt% | percentage by weight |
| v/v | volume to volume |
| $\delta$ | chemical shift |
| λ | wavelength |

# 1

# *Total Synthesis of (+)-Dendrowardol C*

# 1. Total Synthesis of (+)-Dendrowardol C

## 1.1 Introduction

### 1.1.1 Isolation and Structural Elucidation

In traditional Chinese medicine, Shi-Hu is an important remedy derived from the stems of the orchid *Dendrobium* nobile, which is used to nourish the stomach, promote saliva secretion, and reduce fever.[1] Five different *Dendrobium* species are recorded in the Chinese Pharmacopoeia, illustrating the therapeutic importance of this genus with 1200 species of epiphytic orchids.[2] Furthermore, *Dendrobium* species are recognized as rich sources of natural products, with several alkaloids associated with the salubrious effects of Shi-Hu and related treatments.

In 2013, the group of J.-M. HU reported the isolation of three novel sesquiterpenoids, dendrowardols A–C (**1**–**3**), from the stems of *Dendrobium wardianum* Warner, an orchid endemic to southern China and Southeast Asia (Figure 1.1).[3,4] While both dendrowardols A (**1**) and B (**2**) possess an unusual 5/7/4 tricyclic ring system, the unprecedented, highly congested tetracyclic scaffold of dendrowardol C (**3**) is structurally even more interesting.

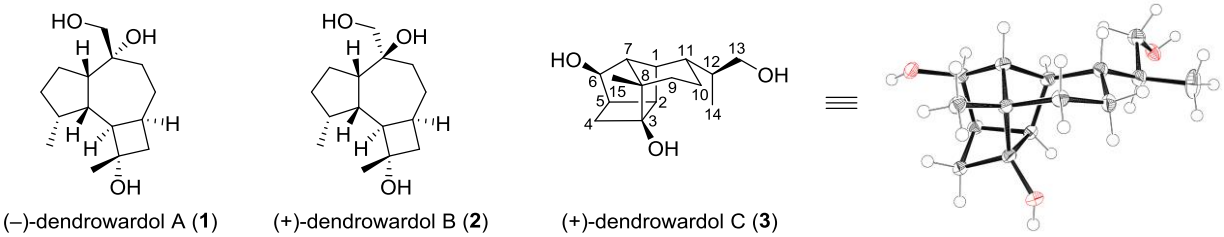



**Figure 1.1:** Structure of dendrowardols A (**1**), B (**2**), and C (**3**), and X-ray crystal structure of **3**; thermal ellipsoids are set at 50% probability.

Dendrowardol C (**3**) was isolated as colorless crystals after extraction of fresh stems of *D. wardianum* Warner with ethanol, subsequent acid-base extraction, repeated column chromatography and final purification by recrystallization from methanol. The molecular formula of the terpenoid was determined on the basis of HRMS to be $C_{15}H_{24}O_3$ (HRMS-ESI: exact mass calculated for $C_{15}H_{24}O_3Na$ [$(M+Na)^+$] 275.1623 *m*/*z*; found 275.1627 *m*/*z*), which indicated four degrees of unsaturation. NMR studies involving $^1H$ NMR, $^{13}C$ NMR, and HSQC experiments were carried out, which revealed the presence of two methyl groups, four

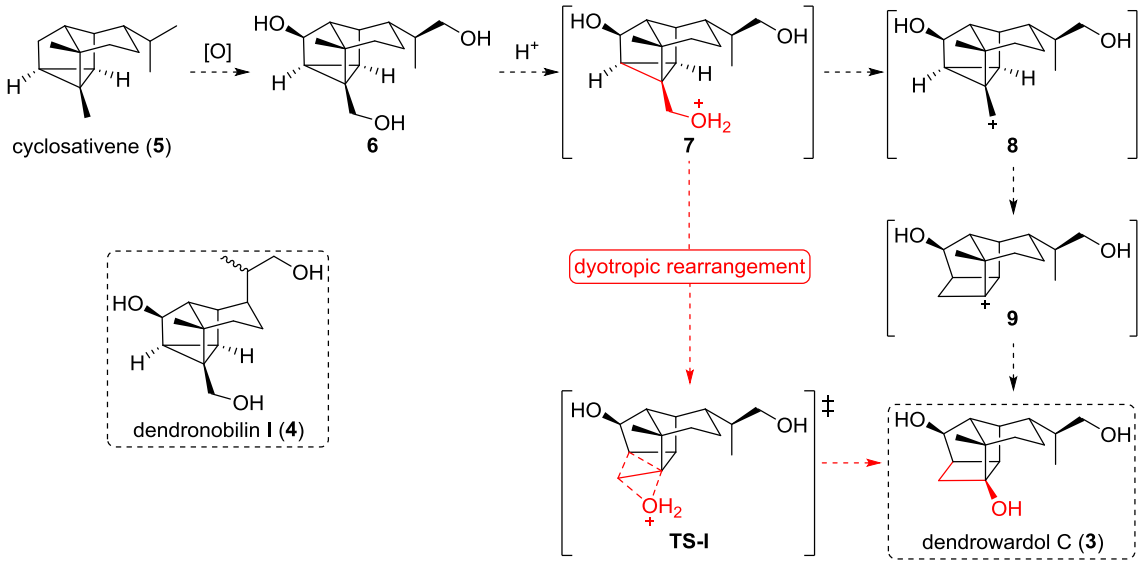
[1] C. J. Bulpitt, Y. Li, P. F. Bulpitt, J. Wang, *J. R. Soc. Med.* **2007**, *100*, 558–563.
[2] R. M. P. Gutiérrez, *J. Med. Plants Res.* **2010**, *4*, 592–638.
[3] W.-W. Fan, F.-Q. Xu, F.-W. Dong, X.-N. Li, X.-Y. Wei, J. Zhou, J.-M. Hu, *Tetrahedron Lett.* **2013**, *54*, 1928–1930.
[4] W.-W. Fan, F.-Q. Xu, F.-W. Dong, X.-N. Li, Y. Li, Y.-Q. Liu, J. Zhou, J.-M. Hu, *Nat. Prod. Bioprospect.* **2013**, *3*, 89–92.

methylenes, seven methines, and two fully substituted carbon atoms with one of them being quaternary. IR and $^{13}C$ NMR spectra indicated the absence of carbonyl groups and alkene double-bonds; therefore, it was concluded that dendrowardol C (**3**) possesses a tetracyclic structure, in accordance with the four degrees of unsaturation. $^{1}H$–$^{1}H$ COSY, HMBC, and ROESY correlations then established the connectivity of the complex scaffold. Finally, the absolute configuration was determined by single crystal X-ray diffractometry.

The group of J.-M. HU also investigated potential biological effects of dendrowardol C (**3**). However, a cytotoxicity assay against five human cancer cell lines revealed no significant activity of this natural product.[4]

### 1.1.2 Proposed Biosynthetis

During the isolation of dendrowardol C (**3**), the known sesquiterpenoid dendronobilin I (**4**) was isolated from the same plant. The presence of this structurally related natural product led to the hypothesis that dendrowardol C (**3**) might be derived from the sesquiterpene cyclosativene (**5**, Scheme 1.1).[4]




**Scheme 1.1:** Proposed biosynthetic pathway of dendrowardol C (**3**).

The original proposal by J.-M. HU and co-workers involves the enzymatic oxidation of cyclosativene (**5**) to an intermediate primary alcohol **6**, which would then be dehydrated under acidic conditions to afford a primary cyclopropylcarbinyl cation **8**. This was proposed to undergo a WAGNER–MEERWEIN rearrangement to cyclobutyl cation **9** followed by recapture of water to

afford dendrowardol C (**3**).[5] However, the generation of first a primary carbocation **8** and then a tertiary bridgehead carbocation **9** seems unlikely, as was pointed out by Y. J. HONG and D. J. TANTILLO in a review on the assembly of cyclobutanes in nature.[6] They suggested a concerted dyotropic rearrangement to replace the stepwise process (Scheme 1.1). Dyotropic rearrangements were defined by M. T. REETZ in 1972 as pericyclic isomerizations in which two $\sigma$-bonds simultaneously migrate intramolecularly.[7] If the two $\sigma$-bonds interchange their positions during the rearrangement, it is of Type I, while in Type II rearrangements, the two σ-bonds do not interchange their positions.[8] A [2,2] Type I dyotropic shift is thermally allowed if one of the migrating groups has a p-orbital available, allowing for inversion at that center.[9] In the above case, such a reaction would involve protonation of the primary alcohol **6** followed by rearrangement via transition state **TS-I**, providing an entry to the 4/5/6/6 ring system and affording dendrowardol C (**3**).

### 1.1.3 Project Outline

Dendrowardol C (**3**) possesses an unprecedented tetracyclic ring system bearing nine contiguous stereogenic centers. This intriguing, highly congested carbon skeleton represented an interesting, yet unsolved synthetic problem and prompted the decision to embark on a synthetic endeavor towards this natural product. The primary goal was to devise an approach that would efficiently forge the challenging tetracyclic scaffold, relying on the strategic disassembly of the caged structure.

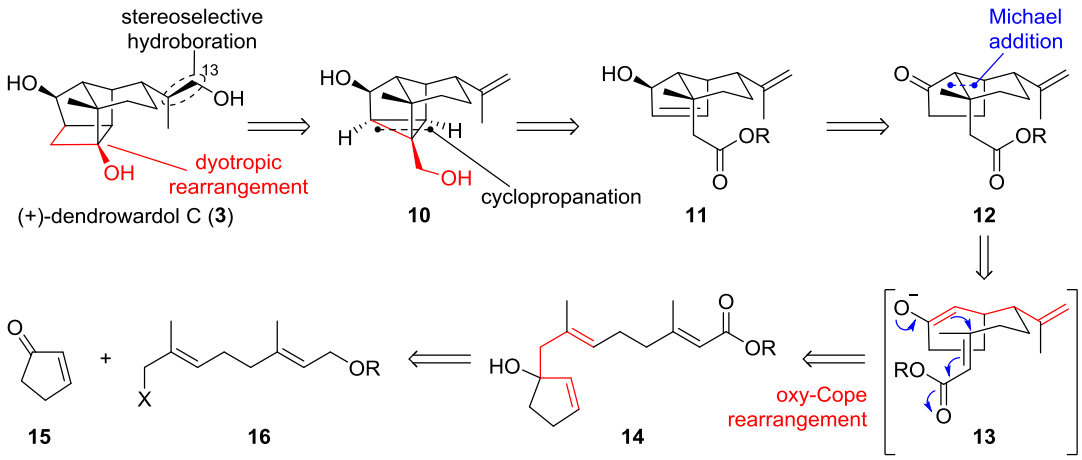
[5] a) G. Wagner, W. Brickner, *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2302–2325; b) H. Meerwein, *Justus Liebigs Ann. Chem.* **1914**, *405*, 129–175.
[6] Y. J. Hong, D. J. Tantillo, *Chem. Soc. Rev.* **2014**, *43*, 5042–5050.
[7] M. T. Reetz, *Angew. Chem. Int. Ed.* **1972**, *11*, 129–130.
[8] M. T. Reetz, *Angew. Chem. Int. Ed.* **1972**, *11*, 130–131.
[9] R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, *8*, 781–853.

## 1.2 First-Generation Approach

### 1.2.1 Retrosynthetic Analysis

The most prominent technique used by organic chemists to design synthetic plans towards complex molecules is the retrosynthetic disconnection approach described by E. J. COREY and co-workers.[10] This type of analysis is a problem-solving technique for tracing back a complex target molecule to a sequence of structures which are increasingly simpler to access. Several types of higher-level strategies are distinguished and can be applied iteratively. Transform-based strategies aim at applying a powerfully simplifying transform, i.e., the reverse of a synthetic reaction, such as for example the DIELS–ALDER transform. Structure–goal strategies target a potential starting material, e.g. a readily available chiral natural substance, while topological strategies identify strategic bond disconnections to retrosynthetically reduce connectivity. Stereochemical strategies remove stereogenic centers under stereocontrol, and finally, functional group-based strategies utilize the latter as keying structural subunits. In the following analyses (Sections 1.2.1 and 1.3.1), both topological and structure–goal strategies will be applied.

Based on the biosynthetic proposal by J.-M. HU and co-workers (Scheme 1.1),[4] the first retrosynthetic analysis of dendrowardol C (**3**) commenced with the suggested dyotropic rearrangement. Furthermore, the primary alcohol at C(13) was envisioned to be installed *via* late-stage stereoselective hydroboration, which traced cyclobutanol **3** back to cyclopropyl carbinol **10**. Further simplification was obtained by disconnecting the three-membered ring in **10**. If successful, such a cyclopropanation would form two of the required four rings in a single step, in accordance with the topological strategy described above. Functional group interconversions would then lead back to cyclopentanone **12**.




**Scheme 1.2:** First-generation retrosynthetic analysis of dendrowardol C (**3**).

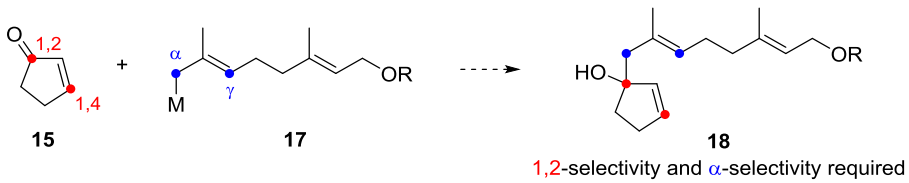
[10] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**.

We envisioned that expeditious access to bicycle **12** could be gained *via* a novel anionic oxy-COPE–MICHAEL addition cascade (**14** to **12**).[11] The first step in this cascade, the anionic oxy-COPE rearrangement, would proceed through a boat-like transition state due to geometrical constraints in the cyclic substrate (*vide infra*) and afford an enolate **13** which could be directly utilized in the second step. Even though investigations by D. A. EVANS and A. M. GOLOB suggested that facile enolate equilibration occurs under the reaction conditions,[12] subsequent MICHAEL addition might preferentially occur from the desired enolate to form a six-membered ring.[13] Regarding the stereoselectivity of the MICHAEL addition, studies by G. STORK and co-workers showed that the stereochemical outcome of internal MICHAEL reactions can be controlled depending on the counterion.[14] Therefore, one-pot stereoselective conversion of allylic alcohol **14** to bicycle **12** appeared viable. Alcohol **14**, in turn, was traced back to cyclopentenone (**15**) and an allyl halide **16**.

With this strategy in hand, the synthetic investigations commenced with the coupling of the two easily accessible fragments **15** and **16** (Section 1.2.2).

### 1.2.2 Synthesis of an Oxy-COPE Precursor

When evaluating the different possibilities to access oxy-COPE precursor **14** (Section 1.2.1), one major challenge was recognized for the coupling of enone **15** with allyl halide **16**. If a reaction involving an allylmetal species **17** derived from the corresponding terminal halide is considered, its α-position would be required to attack cyclopentenone (**15**) in a 1,2-fashion (Scheme 1.3). However, the majority of commonly used metals lead to γ-addition of the corresponding allylmetal species **17** or display poor regioselectivity.[15]



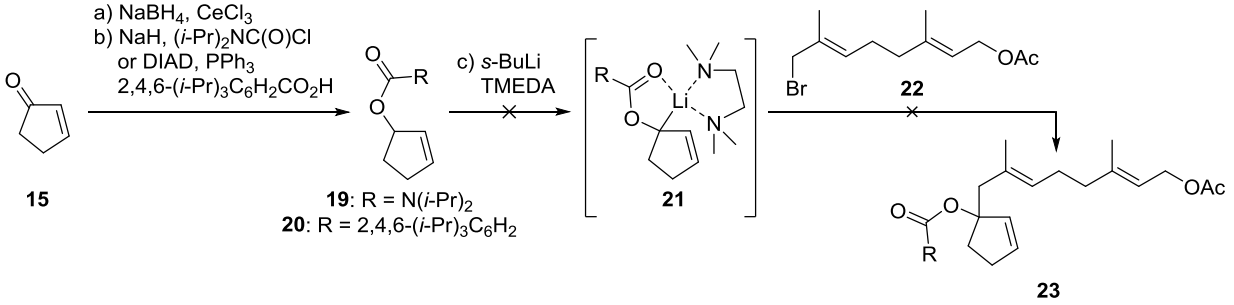

**Scheme 1.3:** Selectivity requirements for the nucleophilic addition of allylmetal **17** to cyclopentenone (**15**).

In order to circumvent this potential problem, a fundamentally different approach was taken into consideration. In 1980, the group of D. HOPPE reported a novel type of 1-oxyallyl anions

[11] An example of an oxy-COPE–MICHAEL cascade with intermediate isomerization: C. S. S. Rao, G. Kumar, K. Rajagopalan, S. Swaminathan, *Tetrahedron* **1982**, *38*, 2195–2199.
[12] D. A. Evans, A. M. Golob, *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.
[13] M. A. Casadei, C. Galli, L. Mandolini, *J. Am. Chem. Soc.* **1984**, *106*, 1051–1056.
[14] G. Stork, C. S. Shiner, J. D. Winkler, *J. Am. Chem. Soc.* **1982**, *104*, 310–312.
[15] Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293.

obtained by lithiation of *N*,*N*-dialkylcarbamic acid allyl esters. In the presence of a chelating diamine ligand, tight ion pairs with the lithium cation complexed at the α-carbon by the proximal carbamoyl oxygen could be generated (Scheme 1.4).[16] In the course of these investigations, D. HOPPE and co-workers could show that such lithiated allylic carbamates reacted with different electrophiles, whereby the α/γ-selectivity on the 1-oxyallyl anion could be modified depending on the substitution pattern; for example, less bulky alkyl groups on the carbamate favored α-selectivity. Such reactivity was considered a viable alternative to the above-mentioned allylmetal approach.

Towards this end, LUCHE reduction of cyclopentenone (**15**) afforded the corresponding allylic alcohol,[17] which was further transformed into carbamate **19** according to a protocol reported by D. HOPPE and co-workers (Scheme 1.4).[18]




**Scheme 1.4:** Attempted alkylation of the 1-oxyallyl anion generated from carbamate **19** or ester **20**. Reagents and conditions: a) $CeCl_3 \cdot 7H_2O$ (1.0 equiv), $NaBH_4$ (2.0 equiv), MeOH, 0 °C to RT, 82%; b) NaH (1.2 equiv), THF, 0 °C to RT, then *N*,*N*-diisopropylcarbamoyl chloride (1.4 equiv), reflux, 74% **19** or DIAD (1.1 equiv), $PPh_3$ (1.1 equiv), 2,4,6-triisopropylbenzoic acid (1.2 equiv), THF, 0 °C, 86% **20**; c) *s*-BuLi (1.1 or 2.0 equiv) or *t*-BuLi (1.1 equiv), TMEDA (1.1 or 2.0 equiv), $Et_2O$, –78 °C or –50 °C, then **22** (1.1 equiv) or allyl chloride (1.1 equiv) or methanol-$d_4$ (excess), no product formation observed.

With this precursor in hand, the lithiation conditions described by the same group were applied (*s*-BuLi, TMEDA, $Et_2O$, –78 °C),[19] followed by the addition of allyl bromide **22**, which could be obtained in two steps from geranyl acetate.[20] Disappointingly, no reaction occurred, and carbamate **19** was recovered. In an attempt to enable the desired reaction, several parameters were varied, including the reaction temperature and time, the nature of the alkyl lithium, and the stoichiometry of the reagents (see caption of Scheme 1.4). Since none of these efforts resulted in any improvement, the lithiation step was probed separately by adding either allyl chloride or deuterated methanol instead of bromide **22**. As before, no reaction occurred, and the fact that no

[16] a) D. Hoppe, R. Hanko, A. Brönneke, *Angew. Chem. Int. Ed.* **1980**, *19*, 625–627; b) D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, *Angew. Chem. Int. Ed.* **1981**, *20*, 1024–1026.
[17] O. Jacquet, T. Bergholz, C. Magnier-Bouvier, M. Mellah, R. Guillot, J.-C. Fiaud, *Tetrahedron* **2010**, *66*, 222–226.
[18] J. Becker, R. Fröhlich, K. Salorinne, D. Hoppe, *Eur. J. Org. Chem.* **2007**, 3337–3348.
[19] A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097–6108.
[20] X.-J. Yu, H. Zhang, F.-J. Xiong, X.-X. Chen, F.-E. Chen, *Helv. Chim. Acta* **2008**, *91*, 1967–1974.

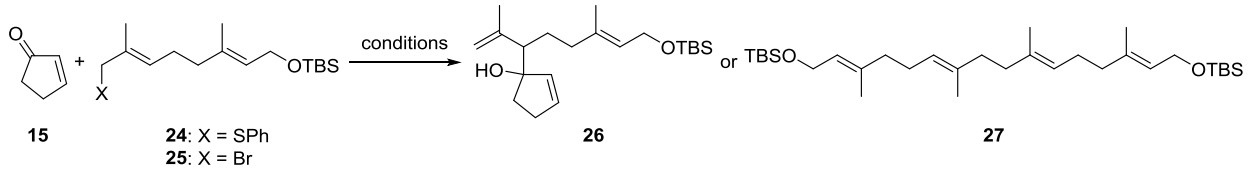
deuterium incorporation was observed under the latter conditions supported the hypothesis that the organolithium species **21** was not formed. This might be attributed to geometric constraints imposed by the five-membered ring.

Following reports by the groups of P. BEAK and V. K. AGGARWAL, the complexing group necessary for the lithiation was changed from carbamate **19** to benzoate **20** (Scheme 1.4).[21] However, only hydrolysis of the ester was observed under the reaction conditions, and the 1-oxyallyl anion approach was dismissed.

Reconsideration of the problem at hand led to the conclusion that using cyclopentenone (**15**) as the electrophile in the desired coupling may be more promising than the 1-oxyallyl anion approach despite the above-mentioned challenges associated with the required 1,2-selectivity / α-selectivity. Based on the comprehensive review by Y. YAMAMOTO and N. ASAO on the chemistry of allylmetal species,[15] a selection of conditions was compiled which appeared promising with respect to the required 1,2-attack on the enone, even though the precedence for α- instead of γ-allylation was very limited. In a first experiment, the behavior of the allyllithium species generated by reductive lithiation of allyl phenyl thioether **24** was examined (Table 1.1, entry 1).[22] Disappointingly, even though literature reports suggested unselective attack with unsymmetrical allylithiums,[23] only the branched product **26** was isolated, which originates from reaction at the γ-position of the allyllithium. Next, addition of the allylic GRIGNARD reagent obtained from allyl bromide **25** to cyclopentenone (**15**) was tested (entry 2).[24] However, only dimer **27** resulting from WURTZ coupling of **25** was observed.[25] Further investigations involved the use of catalytic amounts of titanocene in combination with zinc, a method designed to enable the mild generation of organozinc reagents (entry 3),[26] BARBIER addition with metallic manganese (entry 4),[27] and an *in situ* generated allylchromium(II) reagent (entry 5).[28] The desired product resulting from reaction at the α-position of the allylmetal species was never observed in any of these experiments.

[21] a) P. Beak, L. G. Carter, *J. Org. Chem.* **1981**, *46*, 2363–2373; b) A. P. Pulis, D. J. Blair, E. Torres, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 16054–16057.
[22] a) T. Cohen, M. Bhupathy, *Acc. Chem. Res.* **1989**, *22*, 152–161; b) T. Cohen, M. D. Doubleday, *J. Org. Chem.* **1990**, *55*, 4784–4786.
[23] T. Cohen, B.-S. Guo, *Tetrahedron* **1986**, *42*, 2803–2808.
[24] C. Tanyeli, D. Özdemirhan, *Tetrahedron: Asymmetry* **2014**, *25*, 658–666.
[25] A. Wurtz, *Justus Liebigs Annalen der Chemie* **1855**, *96*, 364–375.
[26] L. M. Fleury, A. D. Kosal, J. T. Masters, B. L. Ashfeld, *J. Org. Chem.* **2013**, *78*, 253–269.
[27] T. Hiyama, M. Sawahata, M. Obayashi, *Chem. Lett.* **1983**, *12*, 1237–1238.
[28] T. Hiyama, Y. Okude, K. Kimura, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561–568.

**Table 1.1:** Testing of different metals for the addition of allyl sulfide **24** or allyl bromide **25** to cyclopentenone (**15**).




**15** **24**: X = SPh **25**: X = Br **26** **27**

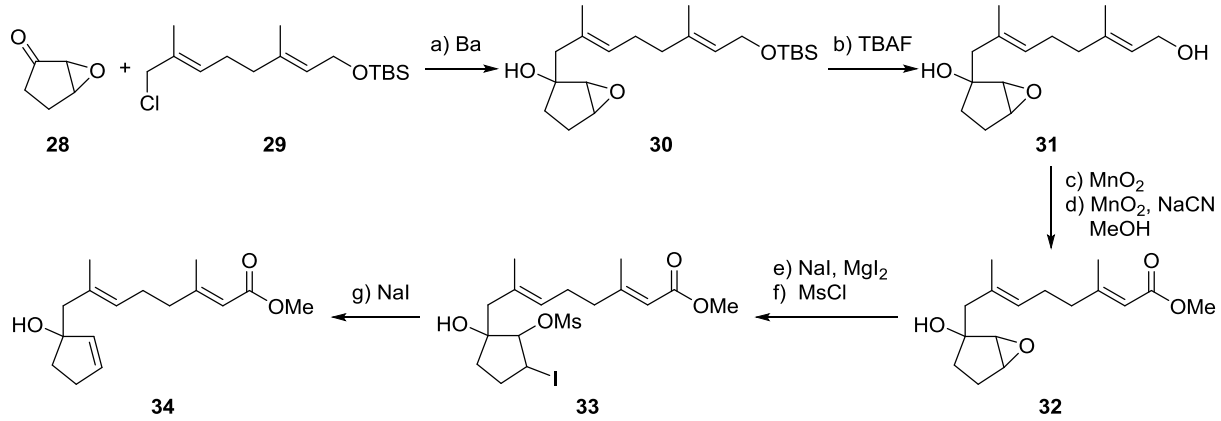
| Entry | Starting Material | Conditions | Product[a] |
|---|---|---|---|
| 1 | **24** | LiDBB (2.0 equiv), THF, –78 °C, then **15** (2.0 equiv), –78 °C | **26** |
| 2 | **25** | Mg (1.5 equiv), $Et_2O$, reflux, then **15** (1.2 equiv), 0 °C to RT | **27** |
| 3 | **25** | $Cp_2TiCl_2$ (1 mol%), Zn (1.0 equiv), **15** (1.0 equiv), THF, RT | **26** |
| 4 | **25** | Mn (1.2 equiv), $I_2$ (20 mol%), **15** (1.0 equiv), THF, reflux | **27** |
| 5 | **25** | $CrCl_2$ (2.5 equiv), **15** (1.0 equiv), THF, RT | **26** |

[a] Yields were not determined.

These unsuccessful results led to a focus on metals which are known to promote α-allylation. In 1994, the group of H. YAMAMOTO reported the use of allylbarium species, which can be prepared by reaction of *in situ* generated barium metal with allylic chlorides, in reactions with aldehydes and ketones with remarkably high α-selectivity.[29] In each of their examples, the double bond geometry of the allylic chloride was retained, and the excellent α-selectivity was not dependent on the substrate. Importantly, an alkyl substituent in the β-position of the allylic barium had no effect on the regioselectivity. However, addition of allylbarium to cyclopentenone (**15**) was reported to be highly selective for 1,4-addition, thus making the direct application of this method for the problem described above impossible.

In order to circumvent this regioselectivity issue, the enone was protected as the corresponding epoxide **28** (Scheme 1.5).[30] With this modified electrophile in hand, the conditions reported by H. YAMAMOTO and co-workers were tested.[29] The required allylchloride **29** was accessible from geraniol in three steps according to literature precedence.[31] Reduction of barium iodide with lithium biphenylide in THF afforded highly reactive RIEKE barium, which, after addition of allylchloride **29**, reacted to a deep red solution of the corresponding allylbarium species. Addition of ketone **28** then afforded tertiary alcohol **30** as a single diastereomer in quantitative yield. Gratifyingly, none of the corresponding branched product was observed, reconfirming the excellent α-selectivity of this method.

[29] A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6130–6141.
[30] Y. Tamura, T. Kawasaki, H. Yasuda, N. Gohda, Y. Kita, *J. Chem. Soc, Perkin Trans. 1* **1981**, 1577–1581.
[31] a) M. Völkert, K. Uwai, A. Tebbe, B. Popkirova, M. Wagner, J. Kuhlmann, H. Waldmann, *J. Am. Chem. Soc.* **2003**, *125*, 12749–12758; b) F. Liu, B. Vijayakrishnan, A. Faridmoayer, T. A. Taylor, T. B. Parsons, G. J. L. Bernardes, M. Kowarik, B. G. Davis, *J. Am. Chem. Soc.* **2014**, *136*, 566–569.




**Scheme 1.5:** Synthesis of oxy-COPE precursor **34**. Reagents and conditions: a) **29** (2.0 equiv), Ba (2.2 equiv), THF, –78 °C, then **28 (**1.0 equiv), quant.; b) TBAF (2.0 equiv), THF, 0 °C, 92%; c) $MnO_2$ (20 equiv), $CH_2Cl_2$, RT; d) $MnO_2$ (20 equiv), NaCN (3.5 equiv), AcOH (1.1 equiv), MeOH, RT, 60% (2 steps); e) NaI (6.0 equiv), $MgI_2$ (6.0 equiv), $CH_2Cl_2$/MeCN (1:1), 0 °C; f) MsCl (1.5 equiv), $NEt_3$ (3.0 equiv), $CH_2Cl_2$, –78 °C to RT, 82% (2 steps); g) NaI (5.0 equiv), $NEt_3$ (5.0 equiv), acetone, RT, 81%.

With coupled product **30** in hand, the required oxy-COPE precursor **34** was accessed in six steps (Scheme 1.5). TBAF-mediated cleavage of the silyl ether in **30** furnished allylic alcohol **31**, which was subjected to a two-step oxidation procedure reported by S. R. ABRAMS and co-workers.[32] In a first step, activated manganese dioxide in $CH_2Cl_2$ promoted the oxidation of the allylic alcohol to the corresponding enal,[33] which was then subjected to COREY–GILMAN–GANEM oxidation conditions:[34] treatment with manganese dioxide in the presence of sodium cyanide and acetic acid in methanol afforded the desired α,β-unsaturated methyl ester **32**. The final task was to unmask the alkene in the five-membered ring to generate an allylic alcohol. Inspired by reports of the groups of E. J. COREY and B. B. SNIDER,[35] the epoxide in **32** was opened at the β-position employing sodium iodide and magnesium iodide in $CH_2Cl_2$/MeCN (1:1) at 0 °C, followed by selective mesylation of the resulting secondary alcohol with methanesulfonyl chloride and triethylamine. Eventually, reduction of the resulting iodo mesylate with sodium iodide and triethylamine in acetone at reflux temperature provided the desired allylic alcohol **34** in 66% yield from hydroxyepoxide **32**, thus setting the stage for the key anionic oxy-COPE–MICHAEL addition cascade (Section 1.2.3).

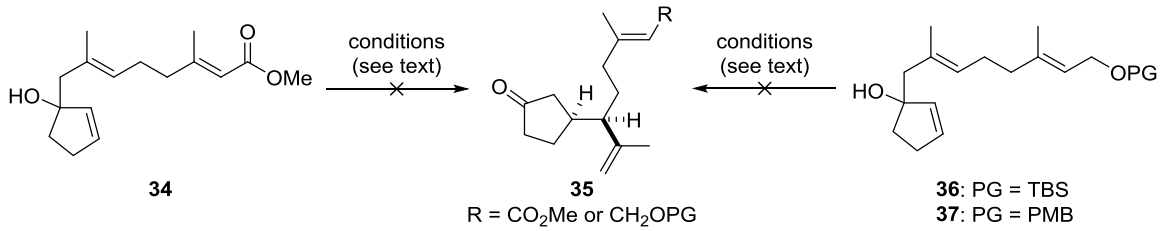
[32] J. M. Nyangulu, M. M. Galka, A. Jadhav, Y. Gai, C. M. Graham, K. M. Nelson, A. J. Cutler, D. C. Taylor, G. M. Banowetz, S. R. Abrams, *J. Am. Chem. Soc.* **2005**, *127*, 1662–1664.
[33] a) A. J. Fatiadi, *Synthesis* **1976**, 65–104; b) A. J. Fatiadi, *Synthesis* **1976**, 133–167.
[34] E. J. Corey, N. W. Gilman, B. E. Ganem, *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617.
[35] a) B. M. Stoltz, T. Kano, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9044–9045; b) X. Gao, B. B. Snider, *J. Org. Chem.* **2004**, *69*, 5517–5527.

### 1.2.3 Investigation of the Anionic Oxy-COPE Rearrangement

The anionic oxy-COPE rearrangement was first described by D. A. EVANS and A. M. GOLOB in 1975.[12,36] They reported that 1,5-hexadiene alkoxides undergo exceptionally facile rearrangements with observed rate accelerations of $10^{10}$–$10^{17}$ compared to the oxy-COPE rearrangement of the corresponding 1,5-diene-3-ols, which can be attributed to the lowering of the bond dissociation energy of the C(3)–C(4) bond.[37] A strong counterion-controlled rate dependence was found: lithium alkoxides did not rearrange, while sodium and potassium alkoxides readily reacted to the expected enolates, the latter displaying a much shorter half-life. Maximum rate acceleration was obtained by the addition of ionophores such as 18-crown-6 to potassium bases.

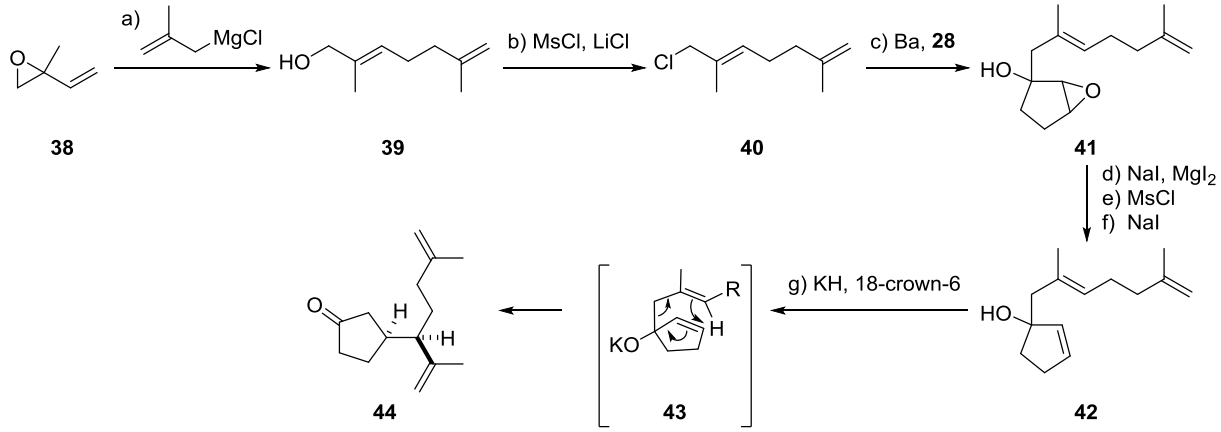
With cyclopentenol **34** in hand, its anionic oxy-COPE rearrangement was investigated (Scheme 1.6). No reaction was observed when employing excess sodium hydride (10 equiv) in THF even at reflux temperature.[38] Change of the base to potassium hydride (1.5 equiv) and addition of 18-crown-6 (1.5 equiv) to achieve significant rate acceleration led to decomposition of the starting material at 0 °C, whereas no conversion was observed at lower temperatures.[39] Furthermore, subjecting allylic alcohol **34** to potassium hexamethyldisilazide (1.0 equiv) and 18-crown-6 (1.0 equiv) in refluxing THF did not lead to any reaction, but addition of more equivalents of the base induced decomposition of the starting material even at ambient temperature.[40] In an attempt to circumvent this lack of reactivity, the anionic oxy-COPE rearrangement was tested with protected allylic alcohols **36** and **37**. With both substrates, decomposition was observed under basic conditions (potassium hydride, 18-crown-6), which led to investigation of the thermal oxy-COPE rearrangement of silyl ether **36**. However, stirring of the substrate in refluxing *o*-xylene, *N*-methylpyrrolidone or *o*-dichlorobenzene only led to slow decomposition of the starting material.[41] Finally, a palladium-catalyzed oxy-COPE rearrangement of silyl ether **36** was tested (10 mol% $PdCl_2(PhCN)_2$ in THF), leading to no improvement.[42]

[36] Selected reviews: a) L. A. Paquette, *Angew. Chem. Int. Ed.* **1990**, *29*, 609–626; b) L. A. Paquette, *Tetrahedron* **1997**, *53*, 13971–14020.
[37] D. A. Evans, D. J. Baillargeon, *Tetrahedron Lett.* **1978**, *19*, 3319–3322.
[38] L. A. Paquette, Z. Gao, Z. Ni, G. F. Smith, *J. Am. Chem. Soc.* **1998**, *120*, 2543–2552.
[39] L. A. Paquette, N. A. Pegg, D. Toops, G. D. Maynard, R. D. Rogers, *J. Am. Chem. Soc.* **1990**, *112*, 277–283.
[40] L. A. Paquette, S. K. Huber, R. C. Thompson, *J. Org. Chem.* **1993**, *58*, 6874–6882.
[41] J. A. Berson, M. Jones, *J. Am. Chem. Soc.* **1964**, *86*, 5019–5020.
[42] N. Bluthe, M. Malacria, J. Gore, *Tetrahedron Lett.* **1983**, *24*, 1157–1160.




**Scheme 1.6:** Attempted anionic oxy-COPE rearrangement of cyclopentenols **34**, **36** and **37**.

Based on a successful oxy-COPE test reaction with 1-(2-methylallyl)cyclopent-2-enol, which was obtained from the addition of 2-methylallylmagnesium chloride to cyclopentenone (**15**),[43] it was hypothesized that the polar moiety in the side chain in **34**, **36**, and **37** might be detrimental to the oxy-COPE rearrangement. Accordingly, truncated substrate **42** was synthesized in a sequence very similar to the one described above (Scheme 1.7).




**Scheme 1.7:** Successful oxy-COPE rearrangement of cyclopentenol **42**. Reagents and conditions: a) (2-methallyl)-magnesium chloride (1.4 equiv), CuI (5 mol%), THF, –30 °C, 60%; b) MsCl (3.0 equiv), LiCl (3.0 equiv), 2,4,6-trimethylpyridine (4.0 equiv), DMF, 0 °C, 72%; c) **40** (1.3 equiv), Ba (1.5 equiv), THF, –78 °C, then **28** (1.0 equiv), 95%; d) NaI (4.0 equiv), $MgI_2$ (4.0 equiv), $CH_2Cl_2$/MeCN (1:1), 0 °C; e) MsCl (1.5 equiv), $NEt_3$ (3.0 equiv), $CH_2Cl_2$, –78 °C to RT, 73% (2 steps); f) NaI (5.0 equiv), $NEt_3$ (5.0 equiv), acetone, RT, 93%; g) KH (1.5 equiv), 18-crown-6 (1.5 equiv), THF, –40 °C to RT, 27%.

(2-Methylallyl)magnesium chloride was added to 2-methyl-2-vinyloxirane (**38**) in the presence of catalytic amounts of CuI to afford allylic alcohol **39** in 60% yield.[44] Allylchloride **40** was then accessed by treating alcohol **39** with excess MsCl and 2,4,6-trimethylpyridine in the presence of LiCl in DMF at 0 °C and was subsequently converted to the corresponding allylbarium species. *In situ* addition of ketone **28** (*vide supra*) to this allylmetal species afforded cyclopentenol **41** in 95% yield. Application of the same sequence as above (Scheme 1.5) to unmask the cyclopentenol then furnished oxy-COPE precursor **42** in 67% yield over three steps. Finally, this allylic alcohol **42** was subjected to the standard oxy-COPE

[43] S. P. Moore, S. C. Coote, P. O'Brien, J. Gilday, *Org. Lett.* **2006**, *8*, 5145–5148.
[44] J. M. Botubol-Ares, M. J. Durán-Peña, A. J. Macías-Sánchez, J. R. Hanson, I. G. Collado, R. Hernández-Galán, *Org. Biomol. Chem.* **2014**, *12*, 5304–5310.

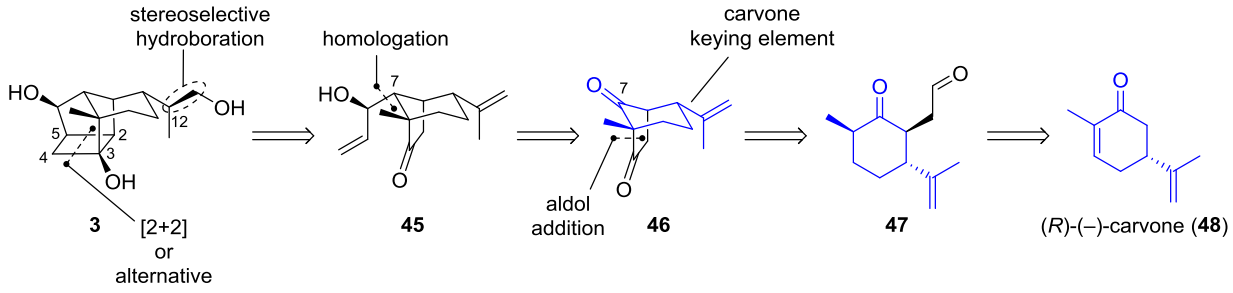
conditions (potassium hydride, 18-crown-6). Surprisingly, the desired rearrangement occurred, furnishing ketone **44** in modest yield after acidic work-up. The stereochemistry of this diene was tentatively assigned based on the expected boat-like geometry adopted by alkoxide **43** in the rearrangement step.

As the envisioned anionic oxy-COPE–MICHAEL addition cascade was made impossible by the substrate requirements of the first step, the direct conversion of an acyclic intermediate such as **34** to a bicyclic system **12** (Scheme 1.2) could not be realized. Thereby, the efficiency of this synthetic plan was significantly reduced, which led to a reevaluation of the retrosynthetic analysis of dendrowardol C (**3**).

## 1.3 Second-Generation Approach

### 1.3.1 Retrosynthetic Analysis

A new strategy towards dendrowardol C (**3**) was devised. Considering its intriguing fused ring system, this second retrosynthetic analysis was envisioned to be guided by a topological strategy,[10] which would not be influenced by the biosynthetic proposal by J.-M. HU and co-workers.[4] E. J. COREY's guidelines state that in fused ring systems, cocyclic pairs of bonds should be disconnected, leading to the cleavage of two rings. Furthermore, all possible [2+2] disconnections of fused four-membered rings are claimed to be strategic. In agreement with these rules, the second-generation approach rooted in late-stage cyclobutane formation (Scheme 1.8). Retrosynthetic disconnection of the C(2)–C(5) and C(3)–C(4) bonds reduced the complex tetracyclic scaffold to a bridged bicyclic structure. Also, the stereogenic center at C(12) was envisaged to be set *via* diastereoselective hydroboration of the corresponding alkene at the end of the synthesis, thereby decoupling this stereogenic center from the others in the target molecule. This analysis led back to bicyclic ketone **45**, which was envisioned to enable the investigation of various approaches to the cyclobutane moiety and which was anticipated to arise from the corresponding diketone **46** *via* homologation at C(7).



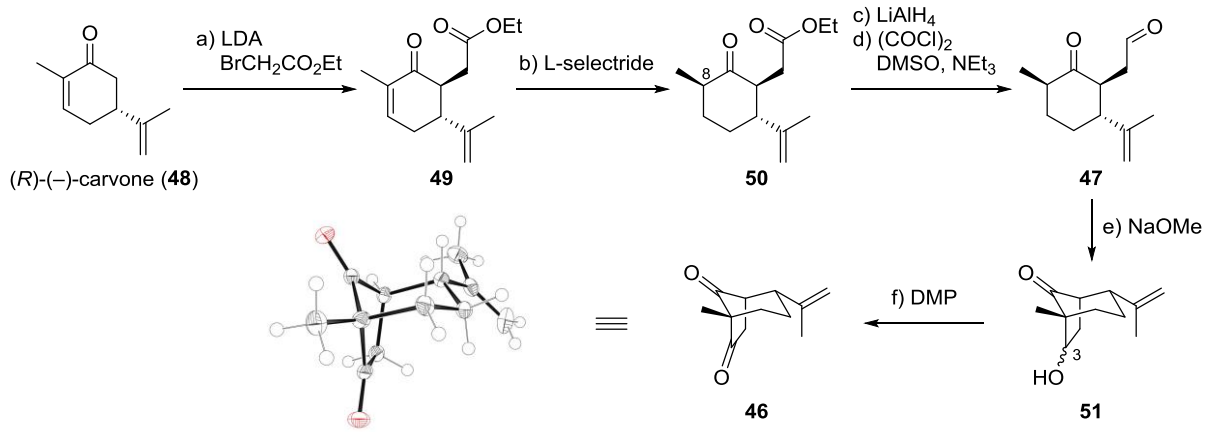

**Scheme 1.8:** Second-generation retrosynthetic analysis of dendrowardol C (**3**).

Recognition of the structural similarity of diketone **46** with carvone prompted the development of a synthetic plan utilizing (*R*)-(–)-carvone (**48**) as a suitable starting material (Scheme 1.8, highlighted in blue). It was reasoned that straightforward access to bicycle **46** could be gained from ketoaldehyde **47** employing an aldol addition to form the bridging C–C bond. Aldehyde **47**, in turn, would be readily accessible from monocyclic (*R*)-(–)-carvone (**48**). The use of such chiral terpenes as inexpensive and abundant starting materials for the synthesis of natural products and pharmaceutical agents has been exploited in numerous applications.[45]

[45] a) S. Hanessian, *Total Synthesis of Natural Products: The ‚Chiron' Approach*, Pergamon, Oxford, **1983**; b) T.-L. Ho, *Enantioselective Synthesis. Natural Products from Chiral Terpenes*, Wiley, New York, **1992**; c) T. Gaich, J. Mulzer in *Comprehensive Chirality, Vol. 2* (Eds.: E. M. Carreira, H. Yamamoto), Elsevier,

### 1.3.2 Synthesis of a Cyclobutanation Precursor

Following this newly devised strategy (Section 1.3.1), the synthesis of a versatile cyclobutanation precursor was approached. Literature-known ketoester **50** was synthesized following a report by Z. YANG and co-workers (Scheme 1.9).[46] Diastereoselective alkylation of (*R*)-(–)-carvone (**48**) with ethyl bromoacetate afforded ester **49** in 79% yield, which was then subjected to conjugate reduction employing L-selectride in THF at –78 °C. The desired saturated ketoester **50** was isolated as an inconsequential mixture of diastereomers at C(8) (d.r. = 3:1). As selective reduction of the ethyl ester in **50** in the presence of the ketone could not be achieved using DIBAL-H in $CH_2Cl_2$ at–78 °C,[47] a two-step protocol was applied, involving global reduction to the corresponding diol with $LiAlH_4$ and subsequent oxidation. A survey of the literature suggested the SWERN oxidation as the method of choice for the oxidation of 1,4-diols to the corresponding ketoaldehydes, presumably due to the impossibility of overoxidation to the lactone ensured by the stepwise mechanism. Accordingly, oxidation under SWERN conditions afforded ketoaldehyde **47** in 84% yield over two steps.[48]




**Scheme 1.9:** Synthesis of diketone **46** and its crystal structure; thermal ellipsoids are set at 50% probability. Reagents and conditions: a) LDA (1.1 equiv), THF, –78 °C, then $BrCH_2CO_2Et$ (1.2 equiv), –78 °C to RT, 79%; b) L-selectride (1.1 equiv), THF, –78 °C, 83%, d.r. = 3:1; c) $LiAlH_4$ (3.0 equiv), THF, 0 °C to RT; d) $(COCl)_2$ (3.0 equiv), DMSO (10 equiv), $NEt_3$ (10 equiv), $CH_2Cl_2$, –78 °C to RT, 84% (2 steps), d.r. = 4:1; e) NaOMe (0.5 equiv), MeOH, reflux, 59%; f) DMP (2.0 equiv), *t*-BuOH (1.0 equiv), $CH_2Cl_2$, RT, 70%.

With desired precursor **47** in hand, the stage was set for the investigation of the key aldol reaction (Scheme 1.9). K. MORI and co-workers described the intramolecular aldol addition of a related system bearing an isopropyl instead of an isopropenyl group in β-position to the

Amsterdam, **2012**, pp. 163–206; d) Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753–11795.

[46] L.-L. Shi, H.-J. Shen, L.-C. Fang, J. Huang, C.-C. Li, Z. Yang, *Chem. Commun.* **2013**, *49*, 8806–8808.

[47] H. Usuda, M. Kanai, M. Shibasaki, *Org. Lett.* **2002**, *4*, 859–862.

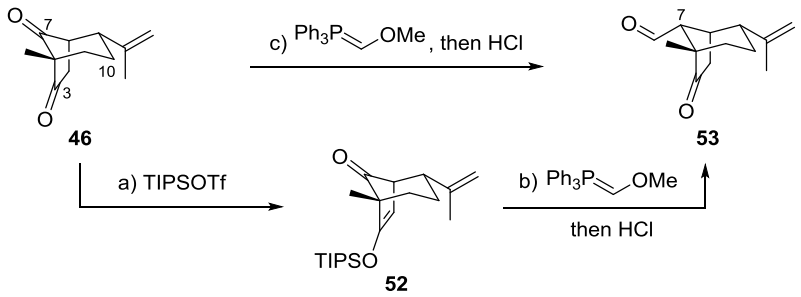
[48] a) K. Mori, S. Takayama, M. Kido, *Bioorg. Med. Chem.* **1994**, *2*, 395–401; b) C. Liu, J.-H. Xie, Y.-L. Li, J.-Q. Chen, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 593–596.

ketone.[49] Interestingly, they observed a clear temperature dependence for this reaction: while subjecting the ketoaldehyde to sodium methoxide (0.5 equiv) in methanol at ambient temperature afforded the product diastereomer with the isopropyl group in the axial position, heating of the same reaction mixture to reflux temperature furnished a 2.8:1 mixture of equatorial vs. axial substitution. These results stem from epimerization of the stereogenic centers in α-position to the ketone under the reaction conditions. Inspired by this report, ketoaldehyde **47** was treated with sodium methoxide (0.5 equiv) in methanol and heated to reflux temperature for 4 hours. The reaction was conducted in high dilution (20 mM) in order to avoid intermolecular reactions. Reproducibly, the following outcome was observed: the desired bicycle **51** was isolated in 59% yield as an inconsequential 1:1 mixture of diastereomers at C(3), along with recovered starting material **47** (26% yield) and a small amount of undesired diastereomers with the isopropenyl side chain in the axial position (4% yield). This distribution did not change upon prolongation of the reaction time. Alcohol **51** was then oxidized uneventfully using DESS–MARTIN periodinane with *t*-BuOH as an additive to furnish the desired diketone **46** in 70% yield.[50] On large scale, this oxidation protocol gave higher yields than the JONES oxidation, which had been reported for a similar system.[51] Crystals suitable for X-ray crystallography could be obtained *via* slow evaporation of a solution in diethyl ether, and the desired absolute stereochemistry could be confirmed (Scheme 1.9).[52]

In line with the retrosynthetic analysis (Section 1.3.1), construction of one C–C bond on the central six-membered ring remained. Upon first examination, the ketones at C(3) and C(7) in **46** appeared to reside in a very similar environment, and it was not clear whether differentiation between them would be possible in a reaction involving nucleophilic attack (Scheme 1.10). In order to circumvent this potential problem, one feature distinguishing the two sites was recognized: only the C(3) ketone is enolizable. However, attempted enol acetate formation by treatment with NaHMDS followed by addition of acetic anhydride exclusively formed dimerized products.[53] Therefore, the corresponding silyl enol ether **52** was targeted instead, which was formed in excellent yield upon reaction of diketone **46** with excess triethylamine and TIPSOTf in $CH_2Cl_2$, thereby avoiding the intermediate formation of an enolate.[54] From alcohol **51**, this protected diketone **52** could also be obtained in 64% yield in a one-pot operation involving LEY–

[49] H. Watanabe, T. Onoda, T. Kitahara, K. Mori, *Tetrahedron Lett.* **1997**, *38*, 6015–6018.
[50] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) G. Tojo, M. Fernández, *Oxidation of Alcohols to Aldehydes and Ketones. A Guide to Current Common Practice*, Springer, Boston, **2006**, pp. 181–214.
[51] H. Hagiwara, M. Fukushima, K. Kinugawa, T. Matsui, T. Hoshi, T. Suzuki, *Tetrahedron* **2011**, *67*, 4061–4068.
[52] The absolute stereochemistry was assigned based on the enantiopure starting material (*R*)-(–)-carvone (**48**).
[53] Y. Luo, A. J. Carnell, *J. Org. Chem.* **2010**, *75*, 2057–2060.
[54] J.-Q. Yu, H.-C. Wu, E. J. Corey, *Org. Lett.* **2005**, *7*, 1415–1417.

GRIFFITH oxidation with tetrapropylammonium perruthenate and NMO followed by direct addition of the above reagents.[55] With one of the ketones thus protected, the WITTIG homologation of **52** with *in situ* generated methoxymethylenetriphenylphosphine was investigated.[56] Interestingly, while rapid consumption of the starting material was observed by TLC analysis (full consumption within one hour), the spot corresponding to the product only emerged very slowly, and long stirring times (72 hours) were crucial to obtain good yields. An attempt to accelerate the reaction by increasing the excess of WITTIG reagent was unsuccessful and led to the formation of unidentified side products. The intermediate methyl enol ether was directly hydrolyzed upon treatment of the reaction mixture with aqueous HCl, and the desired homologated aldehyde **53** was isolated in 73% yield as a 4:1 mixture of diastereomers at C(7). It was essential to allow the system to reach thermodynamic equilibrium during hydrolysis: when worked up after 1 hour, a 1:4 mixture of equatorial vs. axial aldehyde was isolated, whereas when stirred for 12 h, the abovementioned ratio of 4:1 was observed. Also, the isolated 1:4 mixture was converted to a 4:1 mixture when resubjected to the reaction conditions and stirred overnight. The two diastereomers could be easily distinguished by $^1$H NMR: the aldehyde proton appeared as a doublet for the equatorial aldehyde ($^3J$ = 2.3 Hz), but as a singlet for the axial aldehyde. This finding was in good agreement with a literature-known related structure.[51]



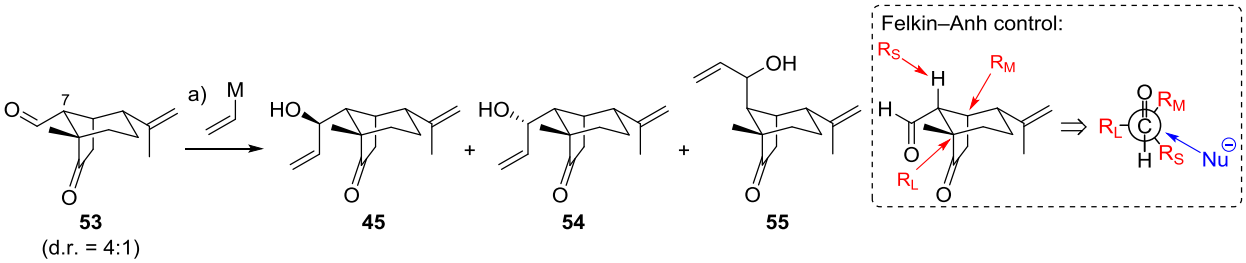

**Scheme 1.10:** Homologation of diketone **46**. Reagents and conditions: a) $NEt_3$ (6.0 equiv), TIPSOTf (4.0 equiv), $CH_2Cl_2$, 0 °C to RT, 93%; b) $MeOCH_2PPh_3Cl$ (1.5 equiv), *n*-BuLi (1.4 equiv), THF, 0 °C to RT, then HCl aq., 0 °C to RT, 73%, d.r. = 4:1; c) $MeOCH_2PPh_3Cl$ (1.5 equiv), *n*-BuLi (1.4 equiv), THF, 0 °C to RT, then HCl aq., 0 °C to RT, 70%, d.r. = 4:1.

During efforts to streamline the synthetic route, the direct WITTIG homologation of diketone **46** was tested (Scheme 1.10). Surprisingly, the reaction took place exclusively at C(7), leaving the C(3) ketone unaffected. This may be explained by the additional steric hindrance imposed on the C(3) ketone by the axial proton at C(10). Furthermore, the reaction time could be reduced to 14 hours without significant loss of yield. This finding represented a significant

[55] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
[56] a) S. G. Levine, *J. Am. Chem. Soc.* **1958**, *80*, 6150–6151; b) C. Spino, C. Godbout, C. Beaulieu, M. Harter, T. M. Mwene-Mbeja, L. Boisvert, *J. Am. Chem. Soc.* **2004**, *126*, 13312–13319.

amelioration: the number of steps and purifications was reduced, the atom economy improved, and the overall yield was slightly higher.

The selective addition of suitable vinyl nucleophiles to aldehyde **53** was explored next (Scheme 1.11). First experiments focused on the use of vinylmagnesium bromide in THF at –78 °C,[57] which led to the isolation of a separable mixture of three diastereomers. While initially no information on the relative configuration of the three isomers was available, **45** and **54** converged to the same enone upon oxidation of each of the allylic alcohols with excess manganese dioxide. In contrast, the enone obtained from alcohol **55** was clearly different, indicating that no epimerization had taken place during oxidation and that **45** and **54** have the same configuration at C(7). Furthermore, taking into account the FELKIN–ANH model for diastereofacial selectivity in nucleophilic additions to aldehydes and ketones (Scheme 1.11, box),[58] the major product of the addition to aldehyde **53** was predicted to be allylic alcohol **45**. Later experiments allowed to unambiguously assign structures **45**, isolated in 37% yield, and **54**, obtained in 18% yield (*vide infra*). In an attempt to improve the selectivity of the reaction and the yield of the desired isomer **45**, vinyl lithium in diethyl ether was employed as the nucleophile.[59] Indeed, the addition now proceeded with a diastereomeric ratio of 4:1 (**45** vs. **54**), the desired alcohol **45** was isolated in 56% yield, and none of the axial isomer **55** was observed. This last finding was attributed to epimerization at C(7) under the basic reaction conditions in combination with a faster consumption of the equatorial aldehyde. Thereby, the diastereomeric mixture obtained in the WITTIG homologation proved to be inconsequential.




**Scheme 1.11:** Addition of vinyl nucleophiles to aldehyde **53** and illustration of the stereochemical course of the reaction. Reagents and conditions: a) vinylmagesium bromide (2.0 equiv), THF, –78 °C, 37% **45**, 18% **54**, yield not determined for **55**; or vinyllithium (1.5 equiv), $Et_2O$, –78 °C, 56% **45**.

With allylic alcohols **45** and **54** in hand and all the carbon atoms of dendrowardol C (**3**) in place, the stage was now set for the exploration of various cyclobutanation reactions (Sections 1.3.3 and 1.3.4).

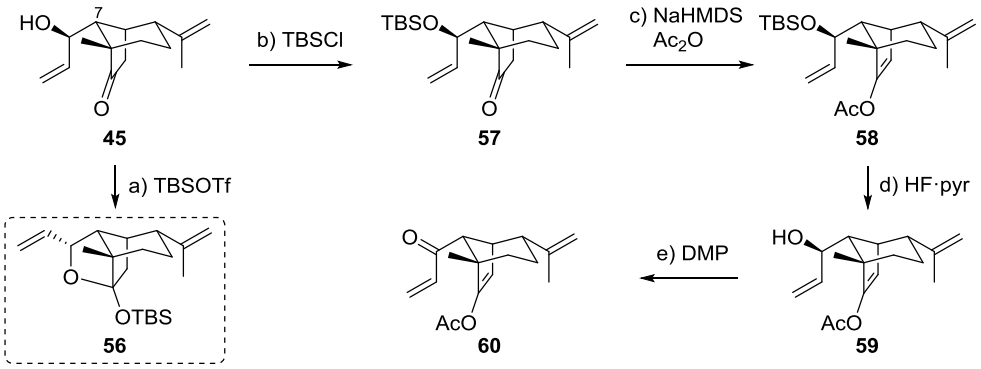
[57] Y. Shimizu, S.-L. Shi, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2010**, *49*, 1103–1106.
[58] a) M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *9*, 2199–2204; b) N. T. Anh, O. Eisenstein, *Tetrahedron Lett.* **1976**, *17*, 155–158; c) N. T. Anh, *Top. Curr. Chem.* **1980**, *88*, 145–142.
[59] P. A. Wade, J. F. Bereznak, B. A. Palfey, P. J. Carroll, W. P. Dailey, S. Sivasubramanian, *J. Org. Chem.* **1990**, *55*, 3045–3051.

### 1.3.3 [2+2] Photocycloaddition Approach

Considering the efficiency of cycloaddition reactions in the buildup of complexity,[10] formation of the four-membered ring in dendrowardol C (**3**) employing a [2+2] photocycloaddition appeared beneficial. Arguably, the [2+2] photocycloaddition of alkenes is the most prominent photochemical reaction, and such transformations often employ cyclic α,β-unsaturated ketones or carboxylic acid derivatives.[60] Generally, direct excitation of an olefin to the $S_1$ state (typically requiring $\lambda = 300–350$ nm for enones) followed by rapid intersystem crossing to the respective triplet state allows the attack of another olefin to generate a 1,4-diradical intermediate from which the products are formed. Conveniently, olefinic substrates with the double bond conjugated to a carbonyl group possess a long-lived excited triplet state, which is usually of $\pi\pi^*$ character. Furthermore, population of the excited triplet state can be induced not only by direct excitation, but also by energy transfer from another photoexcited molecule, typically an aliphatic or aromatic ketone. This process is called sensitization and requires a photosensitizer with a higher triplet energy than that of the substrate.

The structure of dendrowardol C (**3**) appeared to be ideally set up for an enone olefin photocycloaddition according to the retrosynthetic analysis described above (Section 1.3.1). One major concern was recognized, however: the regioselectivity of [2+2] photocycloadditions of enones to alkenes does not follow a simple rule and is hard to predict.[61] In order to extenuate this uncertainty, several possible modifications such as the introduction of additional substituents were anticipated, which might allow to influence the regiochemical outcome (*vide infra*). The synthesis of the required photocycloaddition precursor commenced with protection of allylic alcohol **45** as a silyl ether (Scheme 1.12). In a first experiment, alcohol **45**, which was at that point still of unknown configuration, was treated with TBSOTf and 2,6-lutidine in $CH_2Cl_2$. At 0 °C, the starting material was fully consumed within 15 minutes. Interestingly, not the desired silyl ether **57** was observed, but instead, protected hemiacetal **56** was isolated in excellent yield. While not providing the desired silyl ether, this reactivity confirmed the hypothesis that the two diastereomers **45** and **54** obtained by addition of vinylmagnesium bromide to aldehyde **53** (Scheme 1.11) had indeed the desired configuration at C(7). No such hemiacetal formation would be possible for diastereomers with the side chain in the axial position.

[60] S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, 9748–9815.
[61] D. I. Schuster, G. Lem, N. A. Kaprinidis, *Chem. Rev.* **1993**, *93*, 3–22.



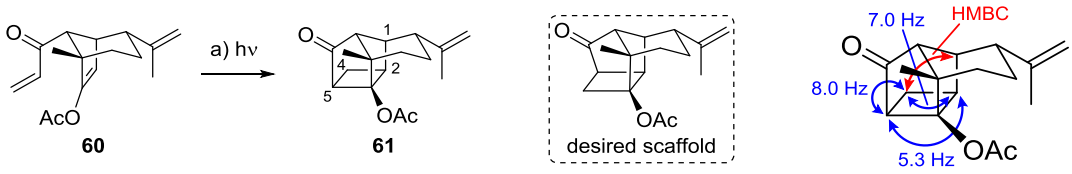

**Scheme 1.12:** Synthesis of [2+2] photocycloaddition precursor **60**. Reagents and conditions: a) TBSOTf (2.5 equiv), 2,6-lutidine (5.0 equiv), $CH_2Cl_2$, 0 °C, 92%; b) TBSCl (5.0 equiv), imidazole (7.5 equiv), DMAP (1.0 equiv), DMF, RT, 75%; c) NaHMDS (3.0 equiv), THF, 0 °C, then $Ac_2O$ (7.0 equiv), 0 °C, 73%; d) HF·pyridine (12 equiv), THF, 0 °C to RT, 87%; e) DMP (2.0 equiv), *t*-BuOH (1.0 equiv), $CH_2Cl_2$, RT, 75%.

Since TBSOTf had been shown to be too LEWIS acidic to leave the ketone in **45** unaffected, the desired protection of allylic alcohol **45** was effected by subjecting the substrate to an excess of less reactive TBSCl and imidazole in DMF in the presence of one equivalent of DMAP. The reaction was sluggish and required the use of DMF instead of $CH_2Cl_2$ as well as long stirring times (overnight or longer). Gratifyingly, under these optimized conditions, TBS ether **57** was isolated in 75% yield. The olefinic moiety required for the photocycloaddition step was then generated by converting ketone **57** to the corresponding enol acetate **58**.[53] The reaction proceeded smoothly *via* deprotonation of the ketone with NaHMDS in THF at 0 °C followed by trapping of the resulting enolate with acetic anhydride.[53] Subsequent cleavage of the silyl ether in **58** was first attempted employing TBAF,[62] but unfortunately, concomitant cleavage of the enol acetate occurred, furnishing ketone **45**. In contrast, reaction of **58** with HF·pyridine in THF cleanly produced the desired alcohol **59** in 87% yield.[63] Finally, DESS–MARTIN oxidation of **59** with *t*-BuOH as an additive furnished photocycloaddition precursor **60** in 75% yield.[50]

Photochemical reactions often require deoxygenated solvents to help minimize radical side reactions, but any solvent can be utilized as long as the reactants are soluble and the absorbance of the solvent does not hamper the desired excitation.[64] In a first experiment, a solution of enone **60** in carefully degassed deuterated benzene was placed in a quartz NMR tube. The reaction mixture was irradiated at ambient temperature with a 365 nm handheld UV lamp, but no conversion of the starting material was observed by NMR. Employing more forcing conditions, irradiation was continued with a 150-W medium-pressure mercury lamp ($\lambda$ = 260–600 nm) for

[62] F. Meng, B. Jung, F. Haeffner, A. H. Hoveyda, *Org. Lett.* **2013**, *15*, 1414–1417.
[63] S. P. Kotun, G. K. S. Prakash, J. Hu in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2007**, pp. 1–6.
[64] M. T. Crimmins, T. L. Reinhold in *Organic Reactions, Vol. 44* (Ed.: L. A. Paquette), Wiley, New York, **1993**, pp. 297–335.

1 hour, but no product formation occurred. Replacing the solvent with degassed $CD_2Cl_2$ did not lead to any observable change. The recovery of starting material indicated that excitation of this enone was challenging. Based on this finding, one equivalent of benzophenone was added to a solution of enone **60** in degassed deuterated benzene to enable access to the required excited triplet state of the enone. With this commonly used photosensitizer, clean conversion of **60** took place upon irradiation with a 365 nm UV lamp for 15 h, yielding one single product. Upon scale-up, cyclobutane **61** was isolated in 20% yield (Scheme 1.13). Disappointingly, careful NMR analysis confirmed the structure of **61** to be the opposite regioisomer of the desired scaffold (cf. structure in the box). This became evident upon studying the $^3J$ and $^4J$ coupling constants between the C(2), C(4) and C(5) protons, as highlighted in blue in Scheme 1.13. The two larger values of 7.0 Hz and 8.0 Hz were assigned to the three-bond couplings between the C(2)/C(4) and C(4)/C(5) protons, respectively. While normally, long-range couplings across saturated carbons are too small to be easily detected, the four-bond coupling constant between the C(2) and C(5) protons was measured to be 5.3 Hz. This high value resulted from a so-called W-coupling, arising from a favorable alignment of the four connecting bonds with the H–C and the C–H fragments close to coplanar in an "zigzag"-arrangement, which is often observed in four-membered rings.[65] Considering HSQC correlations, the methylene in the four-membered ring was not part of the W-coupling, which ruled out the desired scaffold. Moreover, HMBC correlations between one of the C(4) protons and C(1) (highlighted in red) further corroborated structure **61**.



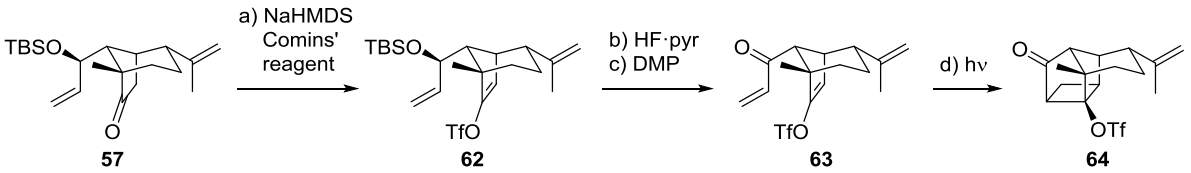

**Scheme 1.13:** [2+2] Photocycloaddition of enone **60** and structural elucidation with key NMR correlations ($^3J$ and $^4J$ couplings highlighted in blue). Reagents and conditions: a) hν (λ = 365 nm, handheld UV lamp), benzophenone (1.0 equiv), $C_6D_6$, RT, 20%.

In theory, the desired scaffold is energetically favored over tetracycle **61** by 1.5 kcal/mol (B3PW91/6-311++G**).[66] The exclusive formation of **61** suggested that a kinetic effect was operative, which could stem from the conformation adopted upon excitation of the enone.

With this first unfruitful result in hand, several strategies to circumvent the undesired regioselectivity in the [2+2] photocycloaddition were devised. Firstly, the electronic properties of the olefinic part were modified by replacing the enol acetate with the corresponding triflate

[65] A. Gamba, R. Mondelli, *Tetrahedron Lett.* **1971**, *12*, 2133–2138.
[66] Calculations were performed by S. Rössler.

(Scheme 1.14). To this end, ketone **57** was subjected to deprotonation with NaHMDS followed by trapping of the corresponding enolate with COMINS' reagent to furnish enol triflate **62** in 73% yield.[67] Application of the same protocol as described above (Scheme 1.12), namely cleavage of the silyl ether with HF·pyridine followed by DESS–MARTIN oxidation, afforded enone **63**. When this [2+2] photocycloaddition precursor was dissolved in degassed deuterated benzene and irradiated with a medium-pressure mercury lamp in the presence of benzophenone as a photosensitizer, cyclobutane **64** was formed exclusively.[68] Disappointingly, NMR analysis as described above confirmed its undesired regiochemistry.



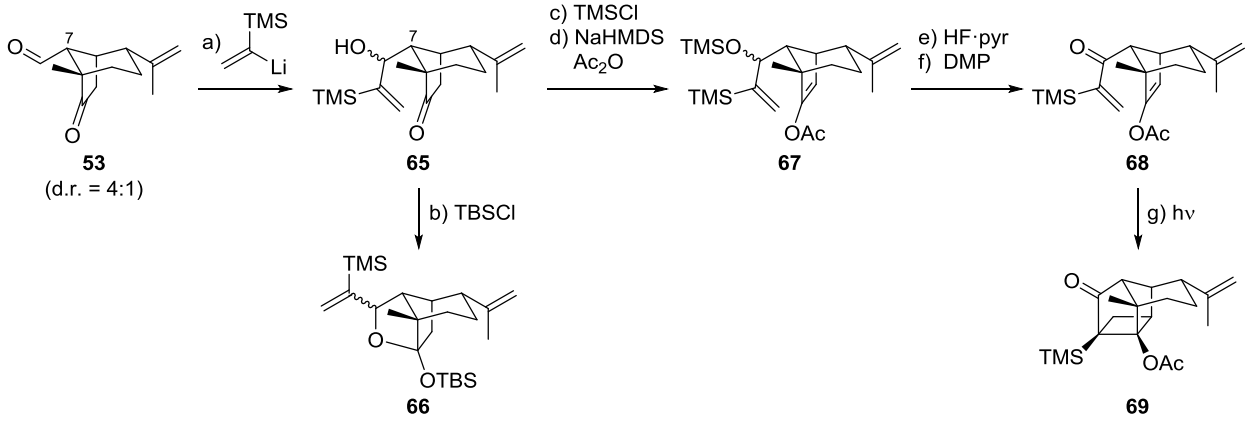

**Scheme 1.14:** [2+2] Photocycloaddition of enol triflate **63**. Reagents and conditions: a) NaHMDS (2.1 equiv), THF, 0 °C, then COMINS' reagent (2.1 equiv), 0 °C, 73%; b) HF·pyridine (12 equiv), THF, 0 °C to RT, 85%; c) DMP (2.0 equiv), *t*-BuOH (1.0 equiv), $CH_2Cl_2$, RT, 86%; d) hν (λ = 260–600 nm, mercury lamp), benzophenone (1.0 equiv), $C_6D_6$, RT, yield not determined.

In a second attempt to reverse the regioselectivity of the [2+2] photocycloaddition, the steric properties of the enone were altered. When a DREIDING model of the enone precursor was examined, it appeared reasonable to introduce steric bulk in the α-position of the enone in order to force the system to adopt a different conformation during the excitation. Interestingly, in 1980, the group of J. S. SWENTON reported the use of trimethylsilyl groups as removable directing groups in photochemistry.[69] In the photocycloaddition of 2-(trimethylsilyl)cyclopentenone with various olefins, they almost exclusively observed the head-to-tail photoadduct, in contrast to the low regioselectivity obtained with unsubstituted cyclopentenone. A preferred orientation in the excited-state complex leading to the formation of only one cycloaddition product was proposed.

This approach was adopted for the system at hand. The trimethylsilyl directing group was introduced by addition of *in situ* generated 1-(trimethylsilyl)vinyllithium to aldehyde **53**, furnishing allylic alcohol **65** as a 2.5:1 mixture of diastereomers (Scheme 1.15).[70] Protection of the free alcohol **65** as the corresponding TBS ether was not possible under the conditions established above (Scheme 1.12); even with TBSCl, the undesired protected hemiacetal **66** was formed, albeit very sluggishly and upon heating to 50 °C. However, this acetalization once more

[67] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
[68] Irradiation with a 365 nm UV lamp resulted in decomposition of the starting material.
[69] C. Shih, E. L. Fritzen, J. S. Swenton, *J. Org. Chem.* **1980**, *45*, 4462–4471.
[70] D. Labrecque, T.-H. Chan in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2001**, pp. 1–3.

confirmed the desired configuration at C(7) for both isolated diastereomers of alcohol **65**. Reasoning that the TBS group was too bulky to be introduced adjacently to the vinylsilane, the allylic alcohol was TMS protected using excess TMSCl and imidazole with one equivalent of DMAP in $CH_2Cl_2$ at ambient temperature. Without purification, the resulting silyl ether was directly treated with NaHMDS and acetic anhydride to furnish the corresponding enol acetate **67**, which was isolated in 46% yield over two steps (d.r. = 1.5:1). The silyl ether was cleaved selectively in the presence of the vinylsilane when subjected to HF·pyridine in THF at ambient temperature for 15 min. At this point, the diastereomers could be separated, but their relative configurations were not determined. DESS–MARTIN oxidation finally furnished the desired [2+2] photocycloaddition precursor **68**. In analogy to the experiments described above, a solution of **68** and benzophenone in degassed deuterated benzene was irradiated with a medium-pressure mercury lamp, resulting in the exclusive formation of cyclobutane **69**. This product again displayed the undesired connectivity observed in all the [2+2] photocycloadditions carried out so far, as was determined by 2D NMR analysis. COSY and HMBC correlations confirmed structure **69**.

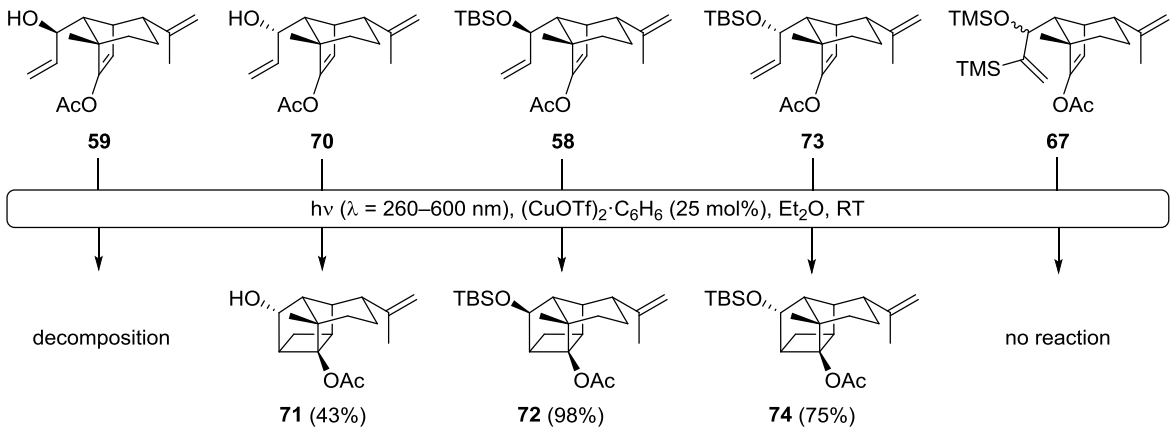



**Scheme 1.15:** [2+2] Photocycloaddition of enone **68**. Reagents and conditions: a) (1-bromovinyl)trimethylsilane (1.2 equiv), *t*-BuLi (2.4 equiv), $Et_2O$, –78 °C, 75%, d.r. = 2.5:1; b) TBSCl (5.0 equiv), imidazole (7.5 equiv), DMAP (1.0 equiv), DMF, RT to 50 °C, 28%, d.r. = 6:1; c) TMSCl (5.0 equiv), imidazole (7.5 equiv), DMAP (1.0 equiv), $CH_2Cl_2$, RT; d) NaHMDS (5.0 equiv), THF, 0 °C, then $Ac_2O$ (12 equiv), 0 °C, 46% (2 steps), d.r. = 1.5:1; e) HF·pyridine (11 equiv), THF, 0 °C to RT, 95%; f) DMP (2.0 equiv), *t*-BuOH (1.0 equiv), $CH_2Cl_2$, RT, 88%; g) hν (λ = 260–600 nm, mercury lamp), benzophenone (1.0 equiv), $C_6D_6$, RT, yield not determined.

At this point, the [2+2] photocycloaddition strategy was reconsidered. While the reaction employing an enone seemed to inherently display undesired regioselectivity, a change in the underlying reaction mechanism might lead to a different product. Enones can be excited directly, whereas unactivated olefins require high energy for excitation, which cannot be provided by conventional light sources. However, upon complexation to a transition metal, the UV absorption maxima of such olefins shift to values around 240 nm, thus enabling excitation.[60] Copper(I) salts, in particular CuOTf, have been established as the most typical catalysts for a subsequent

[2+2] photocycloaddition.[71] Such a reaction takes place *via* a complex in which the copper(I) cation is coordinatively linked with two alkene units. In 1982, the group of R. G. SALOMON reported the Cu(I)-catalyzed photocycloaddition of alkenylallyl alcohols.[72] The high-yielding photobicyclization of 1,6-heptadien-3-ols in the presence of CuOTf in diethyl ether to furnish the corresponding bicyclo[3.2.0]heptan-2-ols was described. Based on the stereochemical outcome of this reaction, the authors proposed a pathway involving the coordination of two C=C bonds and the hydroxyl group with a single copper(I) cation.

This reactivity of allylic alcohols was considered a viable approach to the desired cyclobutane *en route* to dendrowardol C (**3**). In a first experiment, enol acetate **59** was subjected to reaction conditions similar to the ones described by R. G. SALOMON and co-workers (Scheme 1.16).[72] A suspension of **59** and 25 mol% of $(CuOTf)_2 \cdot C_6H_6$[73] in degassed diethyl ether was irradiated with a medium-pressure mercury lamp for 2.5 days. Disappointingly, a complex mixture was isolated upon aqueous work-up. Reasoning that the configuration of the allylic alcohol may be crucial for the successful tridentate complexation to copper(I), enol acetate **70** was synthesized from the minor product **54** resulting from the addition of vinylmagnesium bromide to aldehyde **53** (Scheme 1.11). Interestingly, when this allylic alcohol **70** was subjected to the same reaction conditions as described above, a single product was formed in moderate yield. Careful NMR analysis revealed the product to be cyclobutane **71**, which was further confirmed by DESS–MARTIN oxidation of the secondary alcohol in **71**, which furnished the same ketone **61** as obtained in the enone [2+2] photocycloaddition (Scheme 1.13). Again, no trace of the desired cyclobutane was formed.




**Scheme 1.16:** Cu(I)-catalyzed photocycloaddition of allylic alcohols **59**, **70**, **58**, **73**, and **67**.

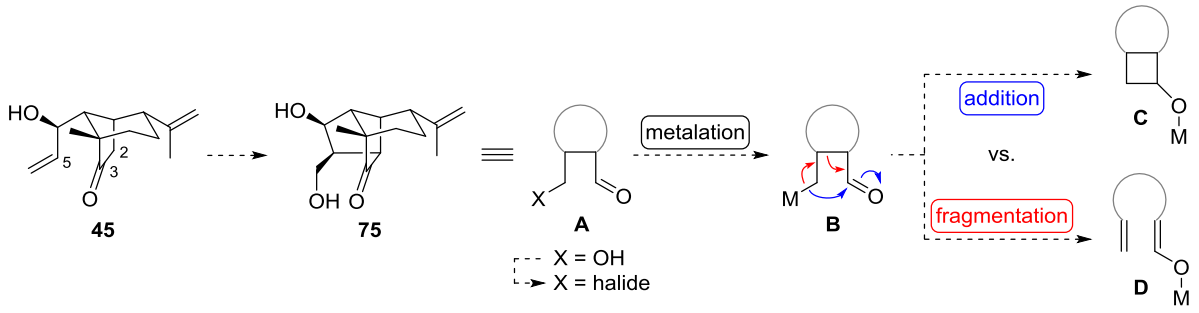
[71] a) R. G. Salomon, *Tetrahedron* **1983**, *39*, 485–575; b) S. Ghosh in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Eds.: W. M. Horspool, F. Lenci), CRC Press, Boca Raton, **2004**, pp. 18-1–18-24.
[72] R. G. Salomon, D. J. Coughlin, S. Ghosh, M. G. Zagorski, *J. Am. Chem. Soc.* **1982**, *104*, 998–1007.
[73] R. G. Solomon, J. K. Kochi, *J. Chem. Soc., Chem. Commun.* **1972**, 559–560.

It was considered that a highly defined arrangement was obtained prior to the cycloaddition of allylic alcohol **70** upon coordination of both C=C double bonds and the hydroxyl group to copper(I). This might be changed by preventing the coordination of the free alcohol, allowing more flexibility in the system and possibly leading to a different regioselectivity. Following this reasoning, diastereomeric TBS ethers **58** and **73** were irradiated in the presence of $(CuOTf)_2 \cdot C_6H_6$ as described above. The assumption that in these systems, copper(I) does not coordinate to the TBS protected alcohol is supported by the fact that here, the configuration at the alcohol stereogenic center did not influence the outcome, as opposed to the case of the free allylic alcohols **59** and **70**. However, this strategy proved unfruitful: cyclobutanes **72** and **74** were isolated in good yields, without any traces of the desired regioisomers detected. Again, the structures were confirmed by NMR analysis as well as by cleavage of the silyl ethers followed by oxidation to known cyclobutane **61**. In a last attempt to utilize the Cu(I)-catalyzed photocycloaddition, vinyl silane **67** was subjected to the reaction conditions described above. However, no conversion of the starting material was observed, possibly due to the trimethylsilyl group preventing coordination of copper(I) to the olefin.

The observations made during this study of [2+2] photocycloaddition reactions, namely the absence of even trace amounts of the desired cyclobutane products, suggested that the desired transformation might be intrinsically impossible and made the success of further screenings appear unlikely.

### 1.3.4 Synthesis of (+)-Dendrowardol C

After ruling out the use of [2+2] cycloaddition strategies to access the cyclobutane core of dendrowardol C (**3**), a route designed to form the two crucial C–C bonds in a stepwise manner was envisaged. To this end, cyclobutanation precursor **45** (Scheme 1.11) was revisited, leading to the identification of a strategic transformation which would forge the C(2)–C(5) bond of the natural product (Scheme 1.17). Namely, epoxidation of allylic alcohol **45** followed by opening of the resulting epoxide with the enolate of the C(3) ketone would furnish an entry to the desired scaffold **75**, provided the appropriate stereochemistry of the epoxide. Hypothesizing that a γ-halogenated carbonyl compound **A** could thus be accessed, an organometal intermediate such as **B** was envisioned, which could intramolecularly add to the ketone to furnish desired cyclobutanol **C**. Similar cyclobutanol formations have been reported previously, furnishing the desired products in good yields upon treatment of the corresponding γ-halogenated ketones with magnesium, samarium diiodide, or *t*-BuLi.[74] However, a competing reaction pathway could lead to C–C bond scission and fragmentation, furnishing an alkene **D**. It was not clear whether the rigid ring system and attendant orbital overlap would render one of the two pathways favorable. Nevertheless, this approach appeared viable when considering that carbon leaving groups are known to be slow as nucleofuges.[75]



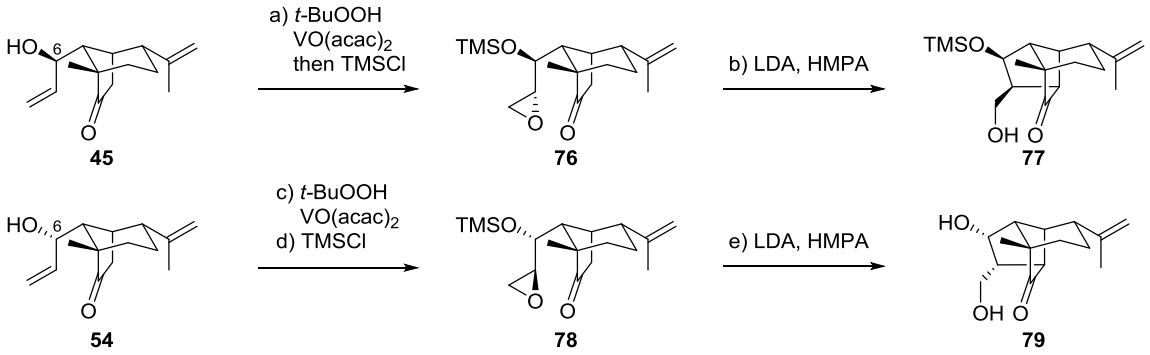

**Scheme 1.17:** Envisioned stepwise cyclobutanation approach.

The first step in this new synthetic plan involved epoxidation of allylic alcohol **45**. Since this substrate also possesses an unactivated alkene which would be prone to oxidation with peracids, the vanadium-catalyzed epoxidation of allylic alcohols reported by the group of K. B. SHARPLESS was considered the method of choice.[76] Such directed epoxidations have been shown to exhibit remarkable reactivity towards allylic alcohols and to proceed with high stereoselectivity. The same group proposed a transition state model to permit an estimation of the stereochemical

[74] a) W. M. Dadson, T. Money, *Can. J. Chem.* **1980**, *58*, 2524–2526; b) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1991**, *56*, 4112–4120; c) I. Cornella, J. Pérez Sestelo, A. Mouriño, L. A. Sarandeses, *J. Org. Chem.* **2002**, *67*, 4707–4714.
[75] C. J. M. Stirling, *Acc. Chem. Res.* **1979**, *12*, 198–203.
[76] K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

outcome of such transformations,[77] which, in the case of allylic alcohol **45**, leads to the prediction of the formation of the desired epoxide.

Allylic alcohol **45** was treated with an excess of *tert*-butyl hydroperoxide and catalytic amounts of $VO(acac)_2$ in $CH_2Cl_2$ (Scheme 1.18). During initial studies, the reaction mixture was worked up, and the desired epoxide was isolated in 69% yield as a single diastereomer. Protection of the resulting secondary alcohol was deemed necessary for the successful execution of the subsequent steps. In analogy to the protected intermediates described above (Section 1.3.3), TBS protection was attempted, but this sterically demanding group could not be installed; instead, the corresponding protected chlorohydrin was isolated upon prolonged treatment with TBSCl, imidazole and DMAP in DMF. In contrast, TMS ether **76** could be easily synthesized employing TMSCl. In an effort to streamline the synthesis, the two steps were combined into a one-pot protocol: allylic alcohol **45** was epoxidized and then directly protected by adding TMSCl, triethylamine and DMAP to the reaction mixture. Thus, TMS ether **76** was isolated in 76% yield.




**Scheme 1.18:** Cyclization of epoxides **76** and **78**. Reagents and conditions: a) *t*-BuOOH (3.0 equiv), $VO(acac)_2$ (10 mol%), $CH_2Cl_2$, 0 °C to RT, then TMSCl (8.0 equiv), $NEt_3$ (10 equiv), DMAP (50 mol%), 0 °C, 76%; b) LDA (5.0 equiv), HMPA (10 equiv), THF, 0 °C to RT, 53% (along with 27% **76**); c) *t*-BuOOH (3.0 equiv), $VO(acac)_2$ (10 mol%), $CH_2Cl_2$, 0 °C to RT, 55%; d) TMSCl (2.5 equiv), $NEt_3$ (5.0 equiv), DMAP (50 mol%), $CH_2Cl_2$, 0 °C to RT, 85%; e) LDA (5.0 equiv), HMPA (10 equiv), THF, –78 °C to 0 °C, yield not determined.

With this precursor in hand, the cyclization outlined above (Scheme 1.17) was tackled. Relatively few 5-(*C-enolexo*)-*exo*-tet cyclizations of this type involving the opening of an epoxide have been reported in the literature.[78,79] In the present case, this transformation proved capricious upon scaling up (*vide infra*). In a first experiment, epoxide **76** was treated with two

[77] a) B. E. Rossiter, T. R. Verhoeven, K. B. Sharpless, *Tetrahedron Lett.* **1979**, *20*, 4733–4736; b) K. B. Sharpless, T. R. Verhoeven, *Aldrichimica Acta* **1979**, *12*, 63–74.

[78] J. E. Baldwin, L. I. Kruse, *J. Chem. Soc., Chem. Commun.* **1977**, 233–235.

[79] Selected examples of such cyclizations: a) J. Shin, W. Fenical, *J. Org. Chem.* **1991**, *56*, 3392–3398; b) L. A. Paquette, D. R. Sauer, S. D. Edmondson, D. Friedrich, *Tetrahedron* **1994**, *50*, 4071–4086; c) K. Ohe, K. Miki, S.-i. Yanagi, T. Tanaka, S. Sawada, S. Uemura, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3627–3634; d) D. B. Ushakov, V. Navickas, M. Ströbele, C. Maichle-Mössmer, F. Sasse, M. E. Maier, *Org. Lett.* **2011**, *13*, 2090–2093.

equivalents of freshly prepared LDA in THF at –78 °C, following a procedure reported by the group of L. A. PAQUETTE.[79] Since no conversion of the starting material could be detected by TLC analysis, additional ten equivalents of LDA were added, and the mixture was allowed to warm to ambient temperature. Only 30% conversion was reached after a total stirring time of 13 hours at ambient temperature.[80] However, despite the sluggish reactivity, the desired primary alcohol **77** could be isolated in 20% yield. In an attempt to make this reaction more efficient, HMPA was used as an additive, which is known for its ability to induce a substantial increase in reaction rates for the electrophilic trapping of enolates.[81] Indeed, the addition of ten equivalents of HMPA led to full consumption of the starting material **76** and a substantial increase in yield. Several experiments led to the conclusion that the reaction only occurred upon warming to ambient temperature, but that prolonged reaction times induced cleavage of the silyl ether. Taking these issues into consideration, the optimal reaction conditions were identified as shown in Scheme 1.18: a solution of epoxide **76** in THF was treated with ten equivalents LDA and HMPA at 0 °C, and the resulting reaction mixture was stirred at ambient temperature for 1 hour prior to acidic work-up. Following this procedure, tricycle **77** was isolated in 53% yield along with 27% of recovered starting material **76**.

As mentioned before, the relative configuration of allylic alcohol **45** had not been experimentally determined so far, implying that also the structure of primary alcohol **77** needed to be confirmed. To this end, allylic alcohol **54** with the opposite stereochemistry at C(6) was subjected to the same reaction sequence as performed with alcohol **45** (Scheme 1.18). Vanadium-catalyzed directed epoxidation of **54** proceeded with complete diastereoselectivity in 55% yield. The resulting epoxide was tentatively assigned to possess (*S*) configuration at C(5), based on the transition state model proposed by B. K. SHARPLESS.[77] Protection of the resulting secondary alcohol employing TMSCl then furnished epoxide **78** in 85% yield. When this substrate was subjected to the cyclization conditions established before, it was observed that the reaction proceeded to full conversion already at 0 °C. Furthermore, only the deprotected product **79** could be isolated, which might be attributed to the reduced steric encumbrance around the silyl group in this configuration.

With the two primary alcohols **77** and **79** in hand, the proposed structures could finally be confirmed by nuclear OVERHAUSER effect spectroscopy (Figure 1.2). For **77**, the NOESY correlations between the C(1) and C(6) and between the C(5) and C(6) protons were decisive,

[80] Determined by $^1$H NMR analysis of the crude reaction mixture.

[81] R. D. Dykstra in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2001**, pp. 1–8.

along with the correlation between the methyl group and the C(4) protons. In contrast, **79** displayed NOESY correlations between the methyl group and the C(6) proton and between the C(4) and both the C(2) and C(9) protons. All of these highlighted correlations could only be explained by the two structures having the configurations proposed earlier. Thus, the relative configurations at C(5) and C(6) were proven unambiguously and it was demonstrated that the major isomer **45** led to the formation of desired tricycle **77**.

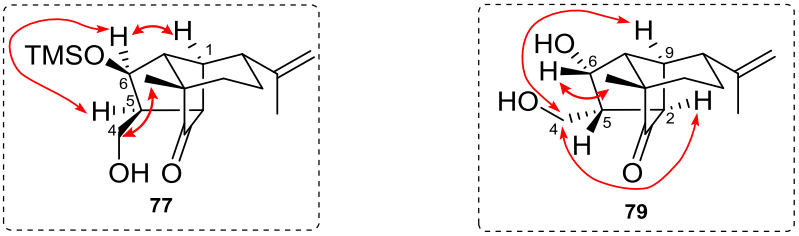
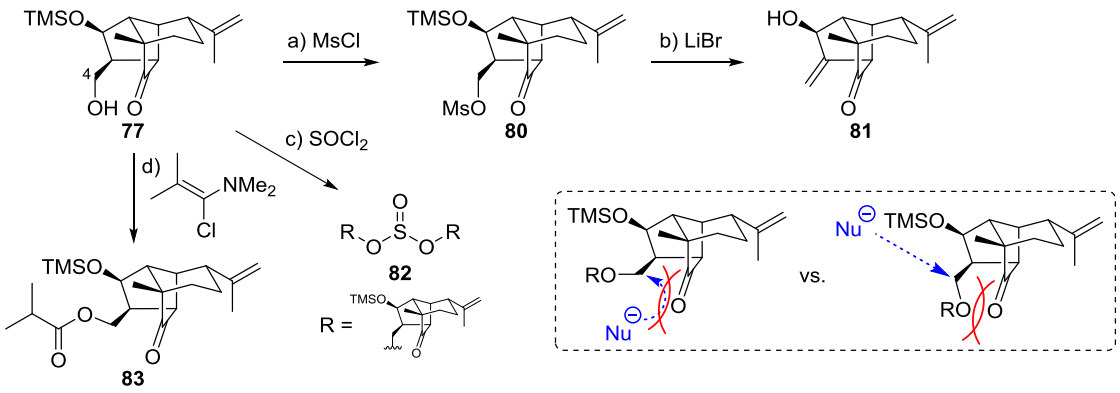



**Figure 1.2:** Key NOESY correlations for the confirmation of the relative configurations of alcohols **77** and **79.**

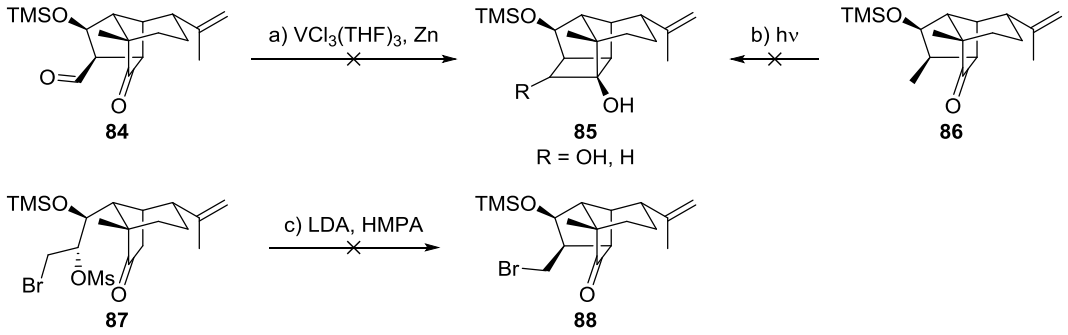
In accordance with the synthetic plan discussed above (Scheme 1.17), the strategy for cyclobutane ring closure called for the conversion of alcohol **77** into a primary halide as a suitable precursor for metalation. In a first experiment, the APPEL reaction was investigated.[82] Disappointingly, treatment of alcohol **77** with triphenylphosphine (1.5 equiv) and carbon tetrabromide (1.5 equiv) in $CH_2Cl_2$ resulted in a complex mixture of products. Switching to a combination of triphenylphosphine, iodine, and imidazole did not improve this result. Therefore, the primary alcohol was transformed into the corresponding mesylate **80** upon treatment with excess MsCl and trietylamine, and $S_N2$ displacement with LiBr was attempted (Scheme 1.19). However, while refluxing mesylate **80** with 20 equivalents of LiBr in acetone did not induce any reaction, changing to refluxing DMF led to the formation of elimination product **81** in 72% yield. At this point, the high steric encumbrance around C(4) was considered, which seemed to make the backside attack required for an $S_N2$ reaction very difficult (Scheme 1.19, box). Nevertheless, chlorination of the primary alcohol **77** with thionyl chloride was tested.[83] Interestingly, reaction of **77** with $SOCl_2$ and triethylamine in $CH_2Cl_2$ at ambient temperature furnished thionocarbonate **82**, again illustrating the difficulty of the required $S_N2$ displacement. Finally, 1-chloro-*N*,*N*,2-trimethylpropenylamine, a reagent developed by the group of L. GHOSEZ for the mild chlorination of alcohols,[84] was examined. Similar to the result obtained with thionyl chloride, the last part of the reaction, namely the $S_N2$ displacement, did not take place, and isobutyrate **83** was isolated in 53% yield.

[82] a) J. B. Lee, *J. Am. Chem. Soc.* **1966**, *88*, 3440–3441; b) R. Appel, *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811.
[83] D. D. Wirth, V. Sikervar, J. Pabba in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2017**, pp. 1–6.
[84] F. Munyemana, A.-M. Frisque-Hesbain, A. Devos, L. Ghosez, *Tetrahedron Lett.* **1989**, *30*, 3077–3080.




**Scheme 1.19:** Attempted conversion of alcohol **77** to a primary halide and rationale for its failure. Reagents and conditions: a) MsCl (3.0 equiv), $NEt_3$ (4.0 equiv), $CH_2Cl_2$, 0 °C to RT, quant.; b) LiBr (20 equiv), DMF, reflux, 72%; c) $SOCl_2$ (2.0 equiv), $NEt_3$ (1.5 equiv), $CH_2Cl_2$, 0 °C to RT, yield not determined; d) 1-chloro-*N*,*N*,2-trimethylpropenylamine (3.0 equiv), $CHCl_3$, 0 °C to RT, then $NEt_3$, 53%.

After these first unsuccessful attempts, different strategies towards the cyclobutane in dendrowardol C (**3**) were investigated. These included tests of a vanadium(II)-catalyzed intramolecular pinacol coupling of the corresponding 4-oxo aldehyde **84**,[85] a NORRISH Type II reaction of ketone **86** obtained after BARTON–MCCOMBIE radical deoxygenation of alcohol **77**,[86] and cyclobutanation of bromohydrin **87** resulting from opening of epoxide **76** (Scheme 1.18) with $MgBr_2$ followed by mesylation (Scheme 1.20). None of these efforts led to any useful result.[87]

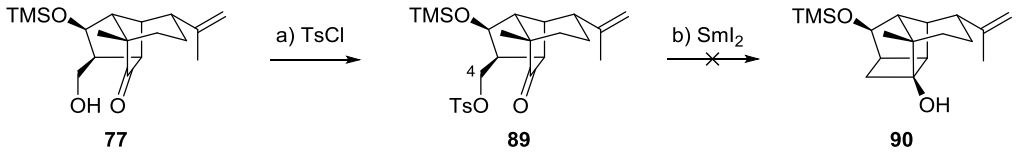



**Scheme 1.20:** Attempted cyclization of aldehyde **84**, ketone **86**, and bromide **87**. Reagents and conditions: a) $VCl_3(THF)_3$ (2.3 equiv), Zn (1.4 equiv), HMPA (5.7 equiv), $CH_2Cl_2$, RT; b) hν (λ = 260–600 nm, mercury lamp), $C_6D_6$, RT; c) LDA (5.0 equiv), HMPA (10 equiv), THF, 0 °C to RT.

In a further study, the reactivity of samarium diiodide was explored, following a report by H. B. KAGAN and co-workers.[88] They described the use of $SmI_2$ to promote the alkylation of ketones by alkyl sulfonates to afford tertiary alcohols in good yields. Based on the observation that tosylates can be reduced to the corresponding hydrocarbons upon treatment with $SmI_2$, it

[85] A. S. Raw, S. F. Pedersen, *J. Org. Chem.* **1991**, *56*, 830–833.
[86] a) H. R. Sonawane, B. S. Nanjundiah, S. I. Rajput, M. U. Kumar, *Tetrahedron Lett.* **1986**, *27*, 6125–6128. b) A. Ogura, K. Yamada, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2012**, *14*, 1632–1635.
[87] a) No conversion observed; b) Decomposition of the starting material; c) Treatment with LDA and HMPA afforded the corresponding alkene resulting from elimination.
[88] P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

was proposed that this reaction occurs *via* reduction of the alkyl sulfonate and subsequent attack at the ketone. Disappointingly, when tosylate **89** obtained from treatment of alcohol **77** with excess TsCl and pyridine in the presence of DMAP in $CH_2Cl_2$ was subjected to the conditions described by the group of H. B. KAGAN, the desired cyclization product **90** was not observed (Scheme 1.21). Instead, treatment with $SmI_2$ induced partial desulfonylation, and a mixture of primary alcohol **77** and starting material **89** was obtained. The fact that H. B. KAGAN and co-workers detected a small amount of alkyl iodide when reducing alkyl tosylates with $SmI_2$ indicated that the reaction probably involves replacement of the tosylate with an iodide and subsequent reduction. Therefore, in analogy to the observations made above (Scheme 1.19), the impossibility of an $S_N2$ attack at C(4) rendered the application of this reaction fruitless.

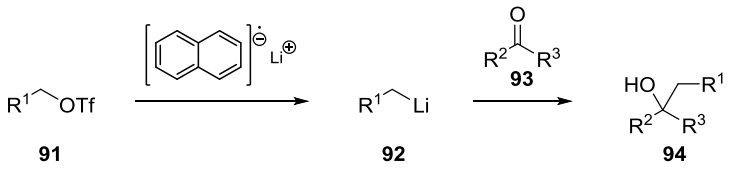



**Scheme 1.21:** Attempted cyclobutanation employing samarium diiodide. Reagents and conditions: a) TsCl (3.0 equiv), pyridine (8.0 equiv), DMAP (50 mol%), $CH_2Cl_2$, 0 °C to reflux, 91%; b) $SmI_2$ (2.0 equiv), THF, reflux.

With these unfruitful results in hand, an alternative for the transformation of the primary alcohol in **77** to an organometal intermediate was sought. Ideally, this would involve metalation of an activated alcohol derivative, which would obviate the need to execute a displacement reaction. Examination of the literature showed that such transformations are rare. However, the group of M. YUS published a number of articles on this subject, especially focusing on lithiation reactions.[89] In 1992, this group reported on the naphthalene-catalyzed lithiation of dialkyl sulfates and the use of the resulting alkyl lithium reagents in the addition to different electrophiles.[90] Thereby, an indirect way for transforming alcohols into organolithium compounds was disclosed, which complements the widely used halogen–lithium exchange. At the same time, a second report appeared which illustrated the use of the same methodology for the lithiation of allylic and benzylic mesylates.[91] Two years later, the same group described a related approach, namely the direct transformation of trialkyl phosphates into organolithium compounds catalyzed by 4,4'-di-*tert*-butylbiphenyl.[92] Again, the versatility of the resulting alkyl lithium species in C–C bond forming reactions with various electrophiles was demonstrated.

[89] M. Yus in *PATAI's Chemistry of Functional Groups* (Ed.: Z. Rappoport), Wiley, New York, **2009**, pp. 1–101.
[90] a) D. Guijarro, B. Mancheño, M. Yus, *Tetrahedron Lett.* **1992**, *33*, 5597–5600; b) D. Guijarro, G. Guillena, B. Mancheño, M. Yus, *Tetrahedron* **1994**, *50*, 3427–3436.
[91] D. Guijarro, B. Mancheño, M. Yus, *Tetrahedron* **1992**, *48*, 4593–4600.
[92] D. Guijarro, B. Mancheño, M. Yus, *Tetrahedron* **1994**, *50*, 8551–8558.

None of the methods described above was directly applicable to the system at hand, either due to the requirement of an allylic alcohol or to the necessity of forming dialkyl sulfates or trialkyl phosphates. In 1996, M. YUS and co-workers disclosed another possible solution to this problem when they reported the naphthalene-catalyzed direct transformation of alkyl triflates into organolithium compounds (Scheme 1.22).[93] Simple, commercially available triflates **91** like ethyl or methyl triflate were treated with an excess of lithium powder in the presence of a catalytic amount of naphthalene and an electrophile **93**. Thus, the reagent was generated in the presence of the coupling partner under BARBIER-type reaction conditions, reasoning that this allowed to prevent WURTZ-like side reactions.[94] With aldehydes, imines or ketones as electrophiles, C–C bond formation occurred in moderate to good yields, furnishing the corresponding alcohols **94**.



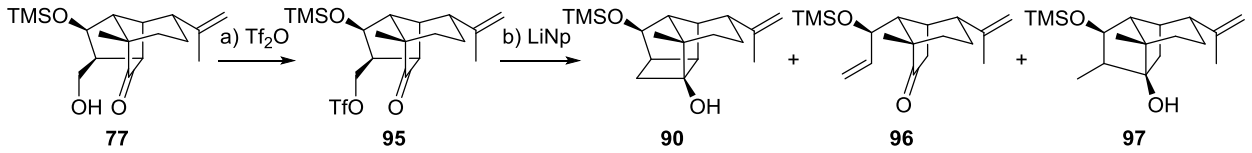

**Scheme 1.22:** Lithiation of alkyl triflates and BARBIER-type reaction with carbonyl electrophiles reported by YUS.

While this formal umpolung was considered a viable option, it had never been used to form a cyclobutane or applied in a complex synthesis setting.[95] The triflate required for the lithiation step was synthesized from alcohol **77** employing triflic anhydride and pyridine in $CH_2Cl_2$ (Scheme 1.23). When this reaction was carried out at ambient temperature, deprotection of the TMS protected alcohol and isomerization of the isopropenyl double bond was observed. Even when the reaction was executed at –78 °C, the diol resulting from cleavage of the silyl ether in **77** could be observed in the crude reaction mixture (ca. 3:1 ratio of desired product to diol). Interestingly, this diol did not undergo triflation and could be easily separated by column chromatography, resulting in the isolation of triflate **95** in 65% yield.

The first test of the lithiation reaction with triflate **95** was based on the literature procedure reported by M. YUS and co-workers.[93] However, since the reaction was carried out on a 10 mg scale, conducting it with catalytic naphthalene appeared to be difficult. Instead, a lithium naphthalenide solution in THF with known concentration was prepared following a literature-known procedure by S. YANAGIDA and co-workers in which ultrasound irradiation is used to

[93] E. Alonso, D. J. Ramón, M. Yus, *Tetrahedron* **1996**, *52*, 14341–14348.
[94] C. Blomberg, F. A. Hartog, *Synthesis* **1977**, 18–30.
[95] D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239–258.

promote the formation of aromatic anion radicals and to shorten the induction time. [96] At first, two equivalents of this freshly prepared lithium naphthalenide solution were added to a solution of triflate **95** in THF at –78 °C, resulting in instantaneous decoloring, but TLC analysis indicated incomplete consumption of the starting material. Therefore, the reaction mixture was titrated with the lithium naphthalenide solution, and after addition of a total of four equivalents, the dark color persisted. Aqueous work-up and purification by column chromatography furnished three products, including the desired cyclobutanol **90** as a minor product (16% yield of isolated material). The major product was isolated in 43% yield and was identified as alkene **96**. Furthermore, tricycle **97** was isolated in 28% yield. To further corroborate this analysis, the silyl ether in cyclobutanol **90** was cleaved with HF·pyridine, and encouragingly, the chemical shifts in the $^{13}$C NMR spectrum of the resulting diol were very similar to the ones reported for dendrowardol C (**3**).[4]




**Scheme 1.23:** First attempt to lithiate alkyl triflate **95**. Reagents and conditions: a) $Tf_2O$ (1.8 equiv), pyridine (2.1 equiv), $CH_2Cl_2$, –78 °C, 65%; b) LiNp (4.0 equiv), THF, –78 °C, 16% **90**, 43% **96**, 28% **97**.

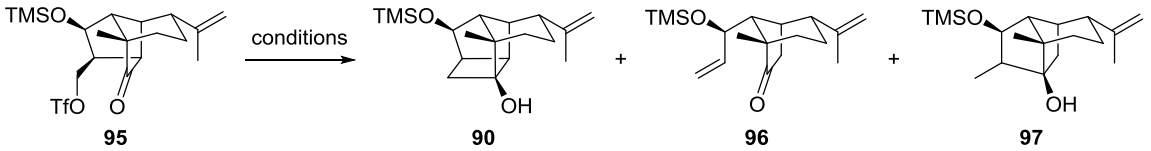
Thus, the first test of the reaction of triflate **95** with lithium naphthalenide furnished the desired cyclobutanol **90**, albeit in only 16% yield. This result was encouraging, but necessitated an extensive optimization study (Table 1.2). Under an inert atmosphere, the reaction of triflate **95** was evaluated in diverse solvents at variable temperatures. Different reducing agents were added slowly until the dark color of the reagent persisted; this required four to five equivalents of reductant. The ratio of products in each run was evaluated by $^1$H NMR analysis of the crude reaction mixtures.

First, the reaction temperature was varied (entries 1–3). Since M. YUS and co-workers reported that their catalytic reactions were warmed to 0 °C and lithium naphthalenide is known to be stable at ambient temperature if stored in solution,[93,96] the reaction was carried out in THF at 0 °C (entry 2). Even though this had no marked positive effect on the reaction outcome, it showed that higher temperatures favor the formation of tricycle **97** at the expense of alkene **96**. Lower temperatures did not improve the product ratio, and even at –100 °C, instantaneous decoloring of lithium naphthalenide was observed upon addition (entry 3). This led to the

[96] a) T. Azuma, S. Yanagida, H. Sakurai, S. Sasa, K. Yoshino, *Synth. Commun.* **1982**, *12*, 137–140; b) P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924–1930; c) K. M. Short, A. Wei, P. Padungros in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2014**, pp. 1–6.

conclusion that the reaction occurred so fast that favorable selectivity could not be achieved by varying the temperature. Next, reverse addition was tested by adding a solution of triflate **95** to a precooled solution of lithium naphthalenide in THF, but while the product distribution changed to strongly favor alkene **96**, the ratio of cyclobutanol **90** remained unchanged (entry 4).

**Table 1.2:** Optimization of the reaction conditions for the ring closure to **90**.




**95** **90** **96** **97**

| Entry | Reducing Agent[a] | Additive, Solvent | *T* [°C] | Ratio **90**:**96**:**97**[b] | Yield **90**[c] |
|---|---|---|---|---|---|
| 1 | LiNp | THF | –78 | 26:44:29 | 16% |
| 2 | LiNp | THF | 0 | 32:15:53 | n.d. |
| 3 | LiNp | THF | –100 | 22:78:0 | n.d. |
| 4 | LiNp[d] | THF | –78 | 18:81:1 | n.d. |
| 5 | LiBp | THF | –78 | 18:77:5 | n.d. |
| 6 | NaNp | THF | –78 | only **96** | n.d. |
| 7 | LiNp | HMPA (7 equiv), THF | –78 | only **96** | n.d. |
| 8 | LiNp | TMEDA, benzene | 10 | 28:27:45 | n.d. |
| 9 | LiNp | THF/benzene (1:5) | 10 | 39:22:39 | n.d. |
| 10 | LiNp | THF/benzene (1:10) | 10 | 42:38:20 | 27% |
| 11 | LiNp | THF/toluene (1:5) | 0 | 44:45:11 | n.d. |
| 12 | LiNp | THF/hexane (1:5) | 0 | 42:48:10 | n.d. |
| **13** | **LiNp** | **2-MeTHF/benzene (1:10)** | **10** | **58:30:12** | **40%**[e] |

[a] A solution of the reducing agent was added until the color persisted (4–5 equivalents) and the mixture was quenched after 5 min; Np = naphthalenide, Bp = biphenylide. [b] Estimated by $^1$H NMR analysis of the crude reaction mixture. [c] n.d. = not determined. [d] Reverse addition. [e] On a preparative scale, the yield of cyclobutanol **90** was 46%.

In an attempt to investigate the influence of the nature of the reducing agent, naphthalene was substituted with biphenyl, which smoothly reacted to lithium biphenylide under the same conditions as employed with naphthalene.[96] However, using this reducing agent under otherwise identical reaction conditions did not lead to an increase in the ratio of cyclobutanol **90** (entry 5). When the metal employed in the reduction of the arene was changed to sodium, the resulting sodium naphthalenide furnished fragmentation product **96** exclusively, thus completely shutting down the desired pathway to form **90** (entry 6).[97] Considering that this change may be related to the interaction between the formal carbanion at C(4) and the metal cation, an experiment employing lithium naphthalenide with an excess HMPA as additive was carried out (entry 7).[81] Interestingly, as with sodium naphthalenide, exclusive formation of the fragmented

[97] G. A. Molander, C. R. Harris in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2001**, pp. 1–3.

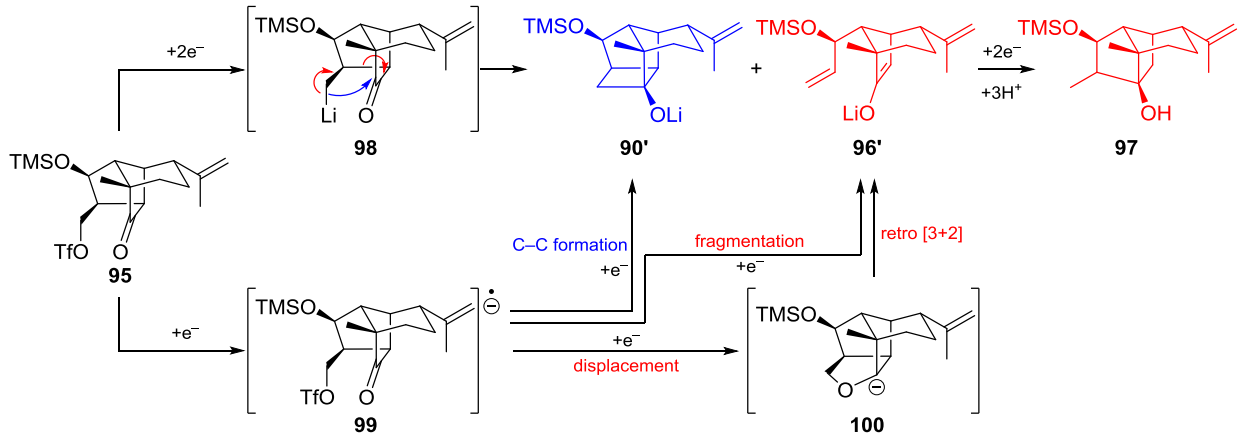
product **96** was observed, leading to the hypothesis that the desired pathway to cyclobutanol **90** is favored by a formal carbanion that is strongly coordinated to the metal cation, i.e., a more "naked" carbanion is detrimental.

Building on this assumption, it was considered that solvent changes may have strong effects on selectivity. The space for variation was limited by the fact that generation of lithium naphthalenide has been reported to require specific ethereal solvents.[96] Typically, THF and DME have been employed while diethyl ether has been shown not to be effective. However, one report by the groups of K. SUGAHARA and H. HASHIMOTO described the preparation of lithium naphthalenide in non-ethereal solvents such as benzene in the presence of one equivalent of TMEDA.[98] Following this report, benzene with TMEDA as an additive was employed, but this unconventional mixture afforded the same results as THF (entry 8). Therefore, binary solvent mixtures were considered. Given the reported solubility of lithium naphthalenide in benzene, the reagent was prepared in THF and then added to a solution of triflate **95** in benzene (entry 9). Encouragingly, the ratio of cyclobutane **90** improved significantly, indicating that the desired reaction is rendered more favorable in less polar media. This finding is in accordance with the observation made before, namely that coordination of the metal cation to the formal carbanion is preferable. However, further increasing the ratio of benzene (entry 10) or switching the less polar solvent component to toluene or hexane (entries 11 and 12) did not lead to a pronounced improvement. Therefore, other ethereal solvents such as methyl *tert*-butyl ether, tetrahydropyran, 2-methyltetrahydrofuran, and 2,5-dimethyltetrahydrofuran were evaluated for the generation of lithium naphthalenide. Of these, only 2-MeTHF allowed the formation of the reagent, demonstrating the importance of subtle differences in the solvation properties. In analogy to the experiment with the THF/benzene solvent mixture (entry 10), lithium naphthalenide was generated in 2-MeTHF and added to a solution of triflate **95** in benzene (entry 13). Gratifyingly, the product ratio improved significantly, resulting in the isolation of desired cyclobutanol **90** in 40% yield.

Even though M. YUS and co-workers reported that only allyl or benzyl mesylates could be subjected to their arene-catalyzed lithiation and that alkyl mesylates did not undergo the desired transformation,[93] the reactions in entries 2 and 10 in Table 1.2 were repeated with mesylate **80** (Scheme 1.19) instead of triflate **95**. In contrast to the reported finding, subjecting this mesylate to lithium naphthalenide resulted in the formation of the three products **90**, **96**, and **97** in very similar ratios as found for triflate **95**.

[98] K. Sugahara, T. Fujita, S. Watanabe, H. Hashimoto, *J. Chem. Tech. Biotechnol.* **1987**, *37*, 95–99.

The results described in Table 1.2 were in partial accordance with the hypothesis that two reaction pathways were possible for a γ-lithiated ketone, furnishing either a cyclobutanol or a fragmented alkene (Scheme 1.17). For the system at hand, the picture was more complex because in principle, each of the observed products could arise from different reaction pathways (Scheme 1.24). Firstly, it was observed by TLC that tricycle **97** was formed from alkene **96**. Furthermore, it was shown that higher temperatures favor the formation of tricycle **97** at the expense of alkene **96** (Table 1.2, entries 1, 2, and 3). Therefore, an initial analysis would have to account for the formation of cyclobutanol **90** and fragmented alkene **96**. The first reaction pathway is in accordance with the mechanistic proposal suggested by M. YUS and co-workers:[93] direct lithiation of triflate **95** affords organolithium **98**, which following C=O addition (highlighted in blue) or fragmentation (highlighted in red) furnishes alkoxide **90'** or enolate **96'**, respectively. Alternatively, **95** could be reduced to ketyl **99**, which could subsequently undergo C–C bond formation and reduction to afford alkoxide **90'**. Ketyl **99** could also lead to the formation of enolate **96'** *via* fragmentation and reduction. A third pathway involves ketyl **99** undergoing C–O bond formation and reduction to give **100**, which would be expected to undergo retro [3+2] cycloaddition, in analogy to 2-lithio-THF, to furnish enolate **96'**.[99]




**Scheme 1.24:** Possible reaction pathways for the transformation of triflate **95** with lithium naphthalenide.

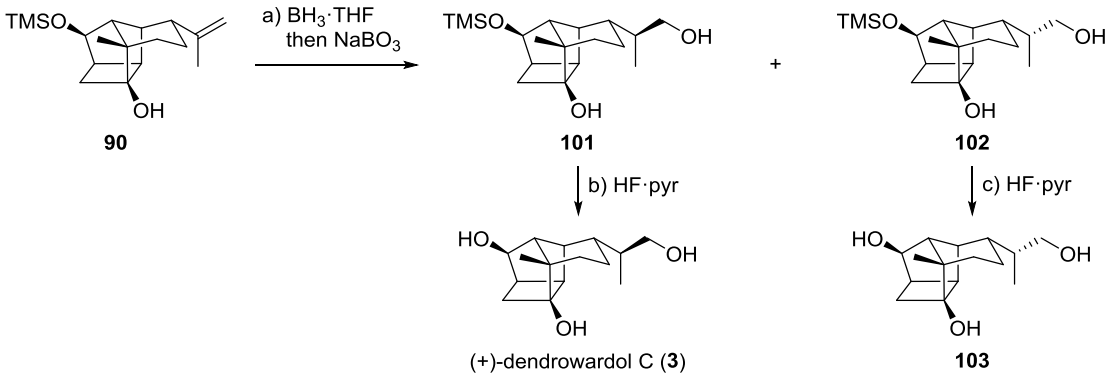
Only vague assumptions could be made to account for the formation of tricycle **97**. The observation that it arises from alkene **96** suggests that its formation involves reduction of the ketone to afford another ketyl moiety, which would then attack the alkene in a 5-*exo* fashion.

In an attempt to establish whether one of the two reduction modes of γ-triflyloxy ketone **95** could be ruled out, lithium naphthalenide was added to a solution of ethyl triflate in THF at –78 °C, which led to instantaneous decoloring. Cyclohexanone was added to the mixture after two minutes, but could be recovered after work-up. On the other hand, when lithium

[99] R. B. Bates, L. M. Kroposki, D. E. Potter, *J. Org. Chem.* **1972**, *37*, 560–562.

naphthalenide was added to a solution of cyclohexanone in THF at –78 °C, instantaneous decoloring was observed and doubly alkylated dihydronaphthalene was isolated,[96,100] illustrating that indeed, ketones could also be reduced under the reaction conditions. Therefore, neither of the two pathways for the initial reduction of triflate **95** could be excluded.

Having successfully obtained the tetracyclic ring system of the natural product, the remaining challenge of setting the stereogenic center at C(12) was addressed. According to the retrosynthetic analysis detailed above (Scheme 1.8), a stereoselective hydroboration of the C(12)=C(13) double bond was evaluated. In an initial experiment, tetracycle **90** was subjected to standard hydroboration–oxidation conditions employing $BH_3$·THF followed by sodium perborate (Scheme 1.25).[101] Encouragingly, the desired transformation took place cleanly to afford the two diastereomeric primary alcohols **101** and **102** in 35% and 29% yield, respectively, which were easily separable by column chromatography. In order to assign their relative structures, the silyl ethers in both tetracycles **101** and **102** were cleaved with HF·pyridine. Thus, synthetic (+)-dendrowardol C (**3**) was isolated for the first time upon deprotection of the major diastereomer **101**. The spectroscopic data obtained were in full agreement with those reported for the natural product. Furthermore, 12-*epi*-dendrowardol C (**103**) was obtained after deprotection of **102**. In subsequent experiments, the additional step for deprotection was saved by adding concentrated HCl directly to the reaction mixture after oxidative work-up of the hydroboration, thus enabling conversion of alkene **90** to dendrowardol C (**3**) in a one-pot procedure.

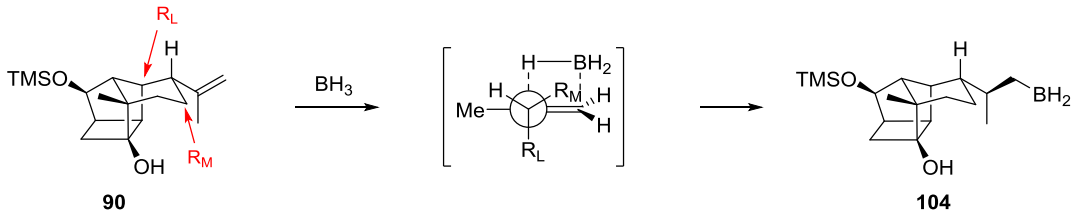



**Scheme 1.25:** Hydroboration of alkene **90** and first synthesis of (+)-dendrowardol C (**3**). Reagents and conditions: a) $BH_3$·THF (7.2 equiv), THF, 0 °C, then $NaBO_3$·$4H_2O$ (20 equiv), $H_2O$, RT, 64%, d.r. = 1.2:1; b) HF·pyridine (15 equiv), THF, 0 °C to RT, 55%; c) HF·pyridine (25 equiv), THF, 0 °C to RT, 60%.

[100] 1,1'-(1,4-Dihydronaphthalene-1,4-diyl)dicyclohexanol was isolated in 82% yield.

[101] a) H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695; b) G. W. Kabalka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, *54*, 5930–5933.

While this result was highly promising, one problem remained. The diastereomeric ratio of the key hydroboration step was 1.2:1 in favor of the desired diastereomer **101**, which, even though the yield was good, was unsatisfactory in terms of selectivity. This outcome could be rationalized by taking into account the model described by the group of Y. KISHI for the acyclic stereocontrol operative in the hydroboration of an olefin incorporating a stereogenic center at the allylic position, as displayed in Scheme 1.26.[102] This model leads to the prediction of the desired diastereomer **104** as the major product.




**Scheme 1.26:** Prediction of the formation of the desired diastereomer **104** upon hydroboration of **90** using KISHI's model for acyclic stereocontrol.

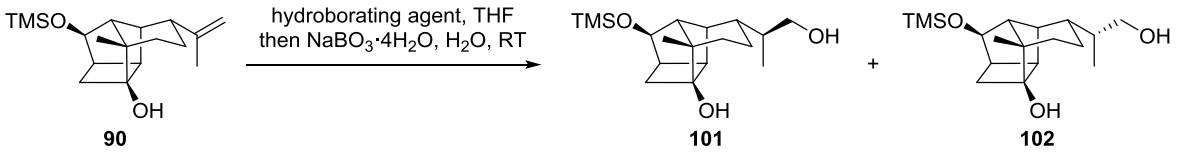
When examining this model, it became evident that the two moieties designated as $R_L$ and $R_M$ in Scheme 1.26 are rather similar in size, resulting in poor diastereoselectivity. In order to explore the behavior of alkene **90** in hydroboration reactions employing various conditions, the effect of temperature was investigated first (Table 1.3, entries 1 and 2). However, no marked difference in diastereoselectivity could be observed. Since it is known that the use of a bulky borane affects the diastereofacial preferences of a given olefin, 9-BBN was employed instead of $BH_3$·THF (entry 3). The diastereoselectivity of the hydroboration of alkene **90** was reversed, but again, no pronounced preference for either of the diastereomers was observed. This was in contrast to a finding by the group of M. M. MIDLAND, who reported the hydroboration of a 1,1-disubstituted alkene where 9-BBN furnished good diastereoselectivity while the use of borane led to a 1:1 mixture.[103]

Given these initial unfruitful attempts to improve diastereoselectivity with conventional boranes, asymmetric hydroborations employing chiral boranes were explored. In 1961, H. C. BROWN and G. ZWEIFEL published a landmark report describing the asymmetric hydroboration of *cis*-but-2-ene using diisopinocampheylborane.[104] Even though $Ipc_2BH$ has been shown to furnish low enantioselectivities for 1,1-disubstituted alkenes,[105] the groups of S. MASAMUNE and D. C. HARROWVEN reported diastereoselective hydroborations of such olefins

[102] a) Y. Kishi, *Aldrichimica Acta* **1980**, *13*, 23–29; b) H. Nagaoka, Y. Kishi, *Tetrahedron* **1981**, *37*, 3873–3888; c) K. N. Houk, N. G. Rondan, Y.-D. Wu, J. T. Metz, M. N. Paddon-Row, *Tetrahedron* **1984**, *40*, 2257–2274.
[103] M. M. Midland, Y. C. Kwon, *J. Am. Chem. Soc.* **1983**, *105*, 3725–3727.
[104] H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 486–487.
[105] S. P. Thomas, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2009**, *48*, 1896–1898.

with the chiral $Ipc_2BH$ reagent.[106] Encouraged by this finding, both enantiomers of $Ipc_2BH$ were tested on alkene **90** (entries 4 and 5), but unfortunately, hardly any induction of diastereoselectivity could be detected.[107]

**Table 1.3:** Screening of different hydroborating agents for the diastereoselective synthesis of alcohol **101**.




90 101 102

| Entry | Hydroborating Agent | *T* [°C] | d.r.[a] |
|---|---|---|---|
| 1 | $BH_3$·THF (7.2 equiv) | 0 °C | 1.2:1 |
| 2 | $BH_3$·THF (5.0 equiv) | RT | 1.1:1 |
| 3 | 9-BBN (5.0 equiv) | RT | 1:1.4 |
| 4 | (+)-$Ipc_2BH$ (5.0 equiv) | RT | 1:1 |
| 5 | (–)-$Ipc_2BH$ (5.0 equiv) | RT | 1.2:1 |
| 6 | $ThxBH_2$ (1.0 equiv) | RT | 1:1.4 |

[a] Estimated by $^1H$ NMR analysis of the crude reaction mixture.

In a last attempt to achieve a diastereoselective hydroboration relying on substrate control, the reaction with thexyl borane was explored (entry 6). The group of T. A. BRYSON reported a boron annulation strategy involving the intramolecular delivery of borane by a hydroxyl group in the δ-position to a 1,1-disubstituted alkene.[108] Thus, they could alter the facial selectivity with sterically small boranes and obtained the best diastereomeric ratios employing thexyl borane. Conjecturing that the hydroxyl group in cyclobutanol **90** might be in a position suitable to direct the hydroboration of the 1,1-disubstituted alkene, thexyl borane was prepared following a procedure by E. NEGISHI and H. C. BROWN.[109] However, when alcohol **90** was treated with one equivalent of this reagent at ambient temperature, a 1:1 mixture of diastereomers **101** and **102** was isolated, suggesting that the hydroboration occurred faster than the reaction of the borane with the free alcohol. Following up on this idea, hydroxyl-directed hydrosilylations were explored, relying on reports by the groups of S. A. KOZMIN, L. A. PAQUETTE, and W. R. ROUSH.[110] Disappointingly, the tentatively assigned silyl ether obtained from reaction of

[106] a) S. Masamune, L. D.-L. Lu, W. P. Jackson, T. Kaiho, T. Toyoda, *J. Am. Chem. Soc.* **1982**, *104*, 5523–5526; b) D. C. Harrowven, D. D. Pascoe, D. Demurtas, H. O. Bourne, *Angew. Chem. Int. Ed.* **2005**, *44*, 1221–1222.

[107] The reagent was prepared according to: M. Lautens, M. L. Maddess, E. L. O. Sauer, S. G. Ouellet, *Org. Lett.* **2002**, *4*, 83–86.

[108] M. C. Welch, T. A. Bryson, *Tetrahedron Lett.* **1989**, *30*, 523–526.

[109] E. Negishi, H. C. Brown, *Synthesis* **1974**, 77–89.

[110] a) S. A. Kozmin, *Org. Lett.* **2001**, *3*, 755–758; b) L. A. Paquette, J. Yang, Y. O. Long, *J. Am. Chem. Soc.* **2002**, *124*, 6542–6543; c) F. Li, W. R. Roush, *Org. Lett.* **2009**, *11*, 2932–2935.

alcohol **90** with 1,1,3,3-tetramethyldisilazane failed to undergo the desired reaction in the presence of either $H_2PtCl_6 \cdot H_2O$ or KARSTEDT's catalyst.[111]

These unsuccessful experiments prompted a closer examination of recent literature on asymmetric hydroborations of 1,1-disubstituted alkenes.[105] In reactions with chiral boranes, this class of olefins stands out as being highly challenging. This can be explained by the fact that such a substrate is barely prochiral, thus making it difficult for the reagent to differentiate between the two enantiotopic faces. For example, the chiral borane developed in the group of S. MASAMUNE gives high enantioselectivities in the majority of cases, but fails for 1,1-disubstituted olefins.[112] Also, a recently reported method by J. A. SODERQUIST and co-workers employing 9-borabicyclo[3.3.2]decanes was deemed unsuitable, since in the case of chiral substrates, the catalyst was unable to override the substrate selectivity.[113] Moreover, enantioselective Rh-catalyzed hydroborations with catecholborane have been shown to exhibit low regio- and enantioselectivity in the case of 1,1-disubstituted alkenes.[114]

Having ruled out the above approaches, recent advances in cobalt-catalyzed asymmetric transformations promised a possible solution.[115] In 2014, Z. HUANG and co-workers reported the use of cobalt(I) complexes of novel iminopyridine–oxazoline ligands **106** in the asymmetric hydroboration of 1,1-disubstituted aryl alkenes **105** with pinacolborane (Scheme 1.27).[116] Their report focused on the high enantioselectivities observed for styrene derivatives; for example, boronic ester **108** was obtained in excellent yield and enantioselectivity.

[111] H. Lebel in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2011**, pp. 1–4.

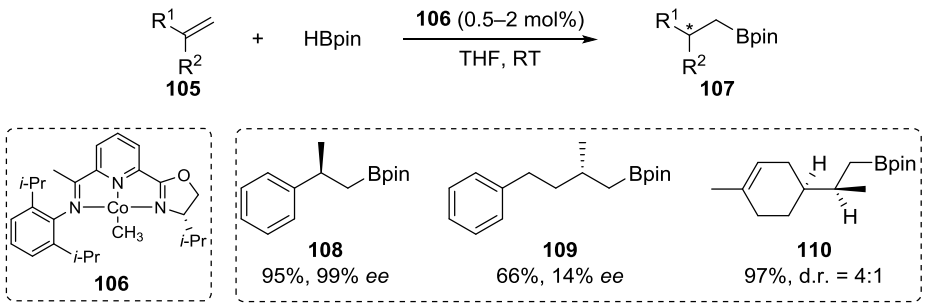
[112] S. Masamune, B. M. Kim, J. S. Petersen, T. Sato, S. J. Veenstra, T. Imai, *J. Am. Chem. Soc.* **1985**, *107*, 4549–4551.

[113] A. Z. Gonzalez, J. G. Román, E. Gonzalez, J. Martinez, J. R. Medina, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2008**, *130*, 9218–9219.

[114] a) K. Burgess, M. J. Ohlmeyer, *J. Org. Chem.* **1988**, *53*, 5178–5179; b) M. Sato, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1990**, *31*, 231–234; c) T. Hayashi, Y. Matsumoto, Y. lto, *Tetrahedron: Asymmetry* **1991**, *2*, 601–612.

[115] Selected reviews: a) A. Pfaltz in *Modern Synthetic Methods, Vol. 5* (Ed.: R. Scheffold), Springer, Heidelberg, **1989**, pp. 199–248; b) H. Pellissier, H. Clavier, *Chem. Rev.* **2014**, *114*, 2775–2823; c) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498–525.

[116] a) L. Zhang, Z. Zuo, X. Wan, Z. Huang, *J. Am. Chem. Soc.* **2014**, *136*, 15501–15504; b) L. Zhang, Z. Zuo, X. Leng, Z. Huang, *Angew. Chem. Int. Ed.* **2014**, *53*, 2696–2700.

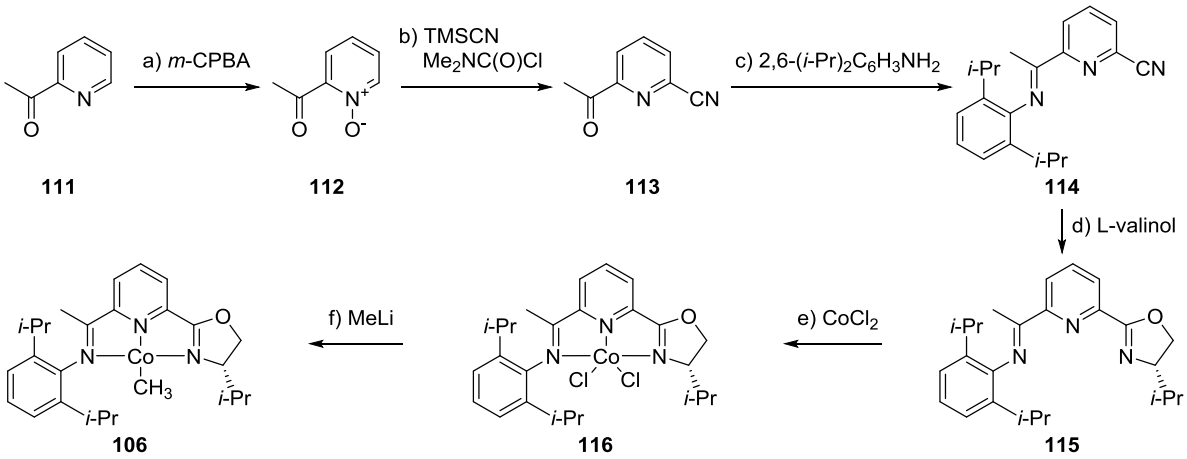



**Scheme 1.27:** Cobalt(I)-catalyzed enantioselective hydroboration of 1,1-disubstituted alkenes reported by HUANG.

The hydroboration of an alkene with aliphatic substitutents was included as a negative example, resulting in only 14% *ee* for boronic ester **109**, demonstrating the limits of the novel method (Scheme 1.27). Nonetheless, the reaction of chiral (*S*)-(–)-limonene in the presence of stereochemically matched catalyst **106** afforded the corresponding boronic ester **110** in a diastereomeric ratio of 4:1. Therefore, a stereogenic center in the α-position of the 1,1-disubstituted alkene can lead to improved diastereoinduction. Recognizing the similarities between limonene and alkene **90**, this approach was considered a viable option.

Cobalt(I) complex **106** was prepared following the procedure by Z. HUANG and co-workers (Scheme 1.28). 2-Acetylpyridine (**111**) was oxidized with *m*-CBPA in $CH_2Cl_2$ to afford the corresponding *N*-oxide **112** in 67% yield.[117] Regioselective cyanation was achieved employing a modified REISSERT–HENZE reaction with trimethylsilyl cyanide and dimethylcarbamoyl chloride in $CH_2Cl_2$.[118] The desired 6-acetylpicolinonitrile (**113**) was isolated in only 24% yield, a fact which was attributed to the sluggish elimination of the intermediate carbamate as observed by LC-MS. Iminopyridine **114** was subsequently formed upon treatment of acetylpyridine **113** with 2,6-diisopropylaniline and catalytic amounts of *p*-toluenesulfonic acid monohydrate in refluxing toluene. The resulting bright yellow crystals were condensed with L-valinol in the presence of catalytic $Zn(OTf)_2$ in refluxing toluene to produce the chiral iminopyridine–oxazoline ligand **115** in 62% yield. The neutral Co(II) dichloride complex **116** was then formed in 90% yield by the addition of ligand **115** to $CoCl_2$ in THF. Finally, the Co(II) dichloride species **116** was reduced to Co(I) methyl complex **106** upon treatment with two equivalents of MeLi in pentane. A very distinct color change from greenish to deep purple was observed upon warming the reaction mixture from –35 °C to RT. Careful filtration through a nitrogen-flushed syringe, removal of the solvent under inert conditions and transfer to a nitrogen-filled glovebox were necessary to prevent oxidation of the highly air-sensitive Co(I) complex.

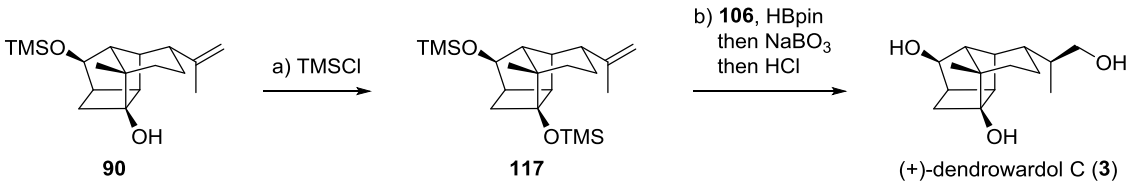
[117] M. Holmquist, G. Blay, M. C. Muñoz, J. R. Pedro, *Org. Lett.* **2014**, *16*, 1204–1207.
[118] W. K. Fife, *J. Org. Chem.* **1983**, *48*, 1375–1377.




**Scheme 1.28:** Synthesis of cobalt(I) complex **106**. Reagents and conditions: a) *m*-CPBA (3.2 equiv), $CH_2Cl_2$, 0 °C to RT, 67%; b) TMSCN (1.1 equiv), dimethylcarbamoyl chloride (1.0 equiv), $CH_2Cl_2$, RT, 24%; c) 2,6-diisopropyl-aniline (1.2 equiv), *p*-TsOH·$H_2O$ (5 mol%), toluene, reflux, 72%; d) L-valinol (1.5 equiv), $Zn(OTf)_2$ (5 mol%), toluene, reflux, 62%; e) $CoCl_2$ (1.0 equiv), THF, RT, 90%; f) MeLi (2.0 equiv), pentane, –35 °C to RT, yield not determined.

With these two cobalt complexes in hand, the stage was set for the exploration of their behavior as catalysts for the hydroboration of the 1,1-disubstituted alkene *en route* to (+)-dendrowardol C (**3**). Towards this end, cyclobutanol **90** was protected as the corresponding TMS ether to afford alkene **117** in 64% yield (Scheme 1.29). Due to the difficult handling of Co(I) complexes resulting from their air-sensitivity, the key hydroboration step was first tested with Co(II) dichloride complex **116**. Z. HUANG and co-workers reported only slightly diminished yields and enantioselectivities when using this Co(II) complex as a precatalyst and activating it with $NaBEt_3H$.[116] However, when this protocol was tested with alkene **117**, reduction of the isopropenyl group to the corresponding isopropyl group was observed. When therefore the Co(I) methyl complex **106** was investigated, initial results were discouraging: with freshly distilled pinacolborane, solvent degassed by sparging with nitrogen, and standard Schlenk techniques, the purple color indicating the presence of the Co(I) catalyst vanished within one hour and seemingly no conversion of alkene **117** took place. However, upon careful examination of the $^1$H NMR spectrum of the crude reaction mixture, small bumps in the baseline indicated the formation of a new alcohol. Therefore, the reaction was repeated in a nitrogen-filled glovebox: a solution of alkene **117** in carefully degassed THF was added to a vial containing one tip of a spatula of catalyst **106**, followed by a solution of freshly distilled pinacolborane in THF. Encouragingly, no decoloring was observed, and indeed, full conversion was indicated by TLC after 14 hours. The reaction mixture was oxidatively quenched with sodium perborate and water. Then, global deprotection was effected by the addition of HCl to the reaction mixture. $^1$H NMR analysis of the crude reaction mixture indicated that the hydroboration of **117** had occurred in a diastereomeric ratio of 4:1, similar to the limonene

example reported by Z. HUANG and co-workers. After column chromatography, pure (+)-dendrowardol C (**3**) was isolated in 60% yield.



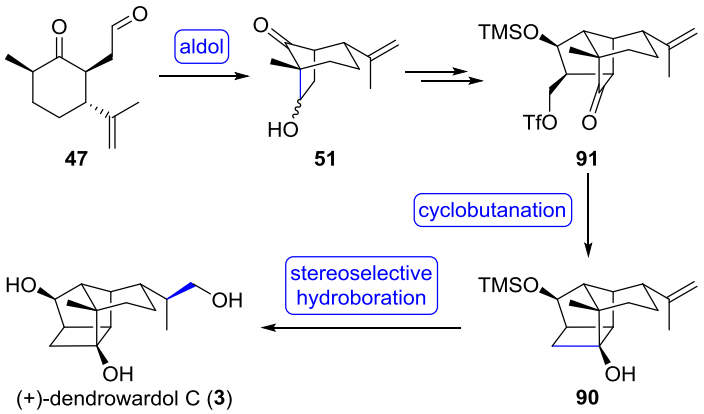

**Scheme 1.29:** Co(I)-catalyzed diastereoselective hydroboration of alkene **117**. Reagents and conditions: a) TMSCl (5.1 equiv), $NEt_3$ (11 equiv), DMAP (1.0 equiv), $CH_2Cl_2$, 0 °C to RT, 64%; b) **106** (cat.), HBpin (1.2 equiv), THF, RT, then $NaBO_3 \cdot 4H_2O$ (10 equiv), $H_2O$, RT, then HCl aq., RT, 60%.

To investigate the effect of a free hydroxyl group on the Co(I)-catalyzed hydroboration, the reaction was tested on cyclobutanol **90**. The same hydroboration–oxidation–deprotection sequence could be effected in a similar diastereomeric ratio (4:1), albeit in only 41% yield.

With the success of this novel hydroboration method, the investigations on the total synthesis of (+)-dendrowardol C were concluded.

## 1.4 Conclusion

In conclusion, the first total synthesis of (+)-dendrowardol C (**3**) was achieved (Scheme 1.30). Key features included an intramolecular aldol addition to forge the central bicyclic scaffold **51**, selective homologation of the resulting ketone, and stepwise cyclobutane formation. The latter was enabled by intramolecular epoxide opening followed by formation of the last crucial C–C bond employing the cyclization of γ-triflyloxy ketone **91**. This formal umpolung employing lithium naphthalenide as a reducing agent raised interesting mechanistic questions and may be of general use in cyclization reactions. Finally, the last stereogenic center was set by diastereoselective cobalt-catalyzed hydroboration of a 1,1-disubstituted double bond.




**Scheme 1.30:** Summary of the total synthesis of (+)-dendrowardol C (**3**).

# 2

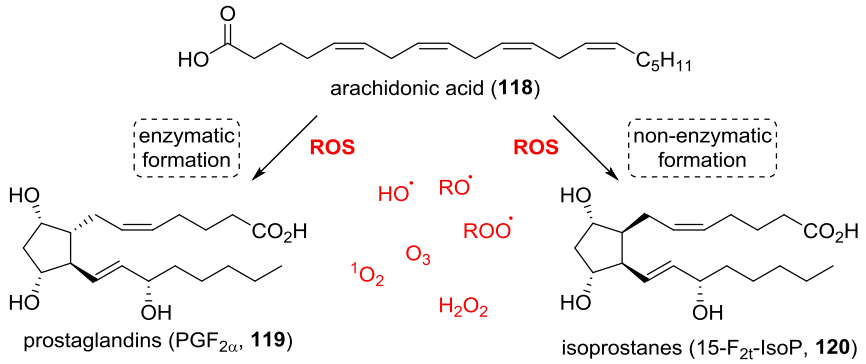
# *Investigation of Anti-Inflammatory Epoxyisoprostanes and their Analogs*

# 2. Investigation of Anti-Inflammatory Epoxyisoprostanes and their Analogs

## 2.1 Introduction

### 2.1.1 Origin and Classification of Oxidized Phospholipids

Since the emergence of life in an oxidizing atmosphere, evolution has provided a complex array of antioxidation mechanisms in order to prevent the oxidation of critical biomolecules.[119] Nevertheless, reactive oxygen species (ROS) represent a constant challenge for the cell, which uses compartmentalization by membranes to protect critical components. The membrane lipids are therefore the initial barriers to prevent free diffusion of ROS and can themselves become the subjects of oxidation reactions.[120] Importantly, polyunsaturated fatty acids (PUFAs), which modulate the membrane structure and are therefore abundant in the cell membrane, display highly increased reactivity compared to saturated and mono-unsaturated fatty acids.[121] This is illustrated by the well-studied enzymatic oxidative conversion of arachidonic acid (**118**) into prostaglandins (PGs), which act as local hormones and, among other functions, mediate inflammation (Scheme 2.1).[122] These natural products were first discovered in the 1930s as compounds with the ability to reduce the blood pressure in animals,[123] but only three decades later could their structures be determined unambiguously.[124]




**Scheme 2.1:** Formation of prostaglandins and isoprostanes from arachidonic acid (**118**).

[119] An excellent introduction to prostaglandins and isoprostanes: J. Egger, Diss. ETH No. 21363.
[120] W. L. Smith, R. C. Murphy, *J. Biol. Chem.* **2008**, *283*, 15513–15514.
[121] U. Jahn, J.-M. Galano, T. Durand, *Angew. Chem. Int. Ed.* **2008**, *47*, 5894–5955.
[122] a) R. J. Kulmacz in *CRC Handbook of Eicosanoids, Vol. 1A* (Ed.: A. L. Willis), CRC Press, Boca Raton, **1987**, pp. 163–172; b) J. A. Salmon, G. A. Higgs, *Br. Med. Bull.* **1987**, *43*, 285–296.
[123] a) M. W. Goldblatt, *J. Physiol.* **1935**, *84*, 208–218; b) U. S. von Euler, *J. Physiol.* **1936**, *88*, 213–234.
[124] a) S. Bergström, R. Ryhage, B. Samuelsson, J. Sjövall, *Acta Chem. Scand.* **1962**, *16*, 501–502; b) D. H. Nugteren, D. A. Van Dorp, S. Bergström, M. Hamberg, B. Samuelsson, *Nature* **1966**, *212*, 38–39.

While the biosynthesis of the prostaglandins is mediated by enzymes and thus leads to products as single regio- and stereoisomers, the group of L. J. ROBERTS discovered a series of prostaglandin $F_2$-like compounds that are produced *in vivo* in humans by a non-enzymatic mechanism involving the free radical peroxidation of arachidonic acid (Scheme 2.1).[125] Such reactions can be initiated by ROS such as hydroxyl radicals, superoxide radical anions, alkoxyl radicals, peroxyl radicals, singlet oxygen, ozone, and hydrogen peroxide.[121] The resulting compounds, termed isoprostanes (IsoPs), were proposed to be formed through stochastic processes determined by C–H bond strengths and were isolated as mixtures of isomers.

In general, oxidized phospholipids (OxPLs) originate from the major PUFAs present in living organisms, namely α-linolenic acid, arachidonic acid (**118**, Scheme 2.1), eicosapentaenoic acid, and docosahexaenoic acid.[121] The metabolites resulting from these lipids can be divided into acyclic and cyclic structures and further classified as enzymatic or non-enzymatic, depending on their mode of formation. Prostaglandins are enzymatically formed cyclic metabolites, while isoprostanes are the corresponding cyclic compounds resulting from an autoxidative pathway. Both occur in regioisomeric series depending on the site of the initial radical generation, which, for the isoprostanes, determines the position of the oxygen in the side chain (Figure 2.1).

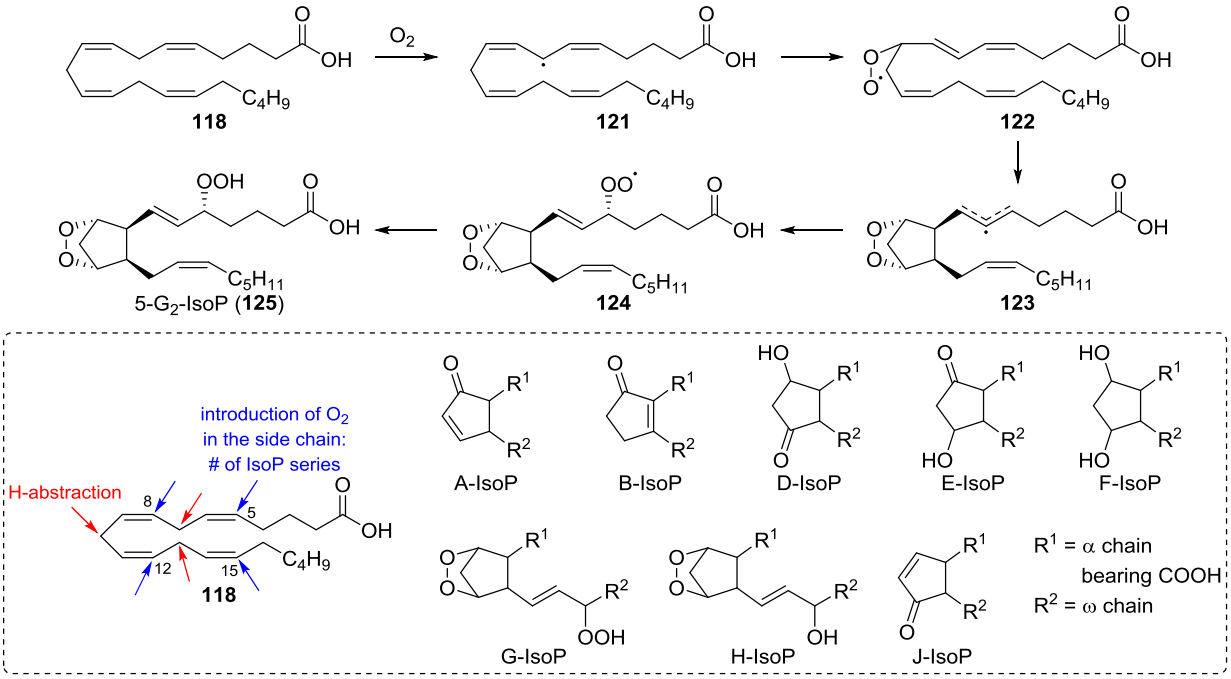


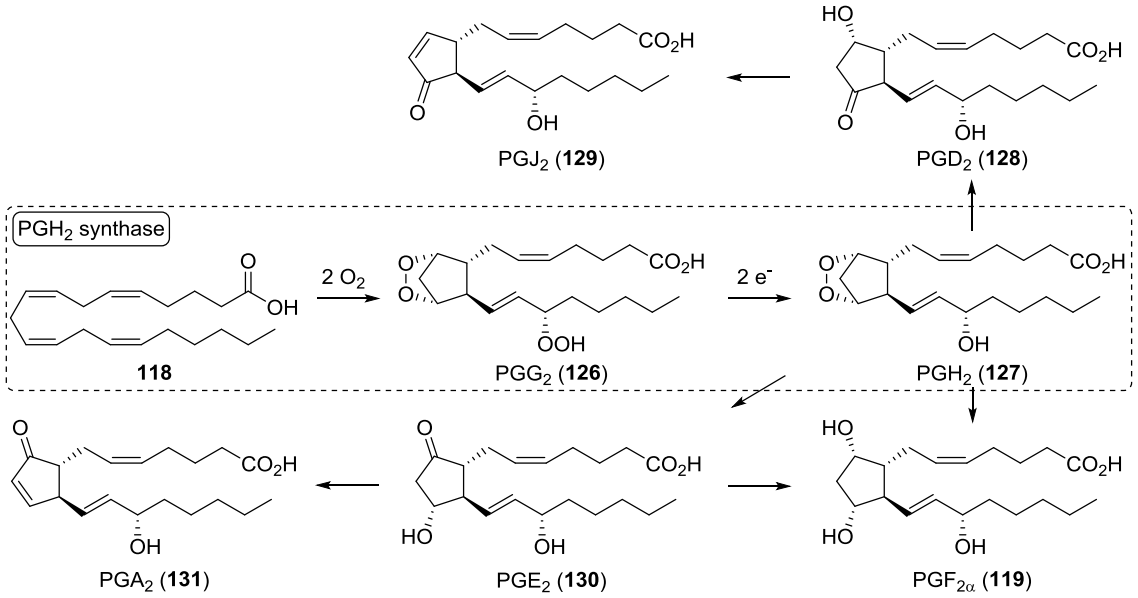

**Figure 2.1:** Mechanism of the free radical-initiated peroxidation of arachidonic acid (**118**), origin of regioisomeric products upon oxidation of arachidonic acid (**118**), and nomenclature of the isoprostanes.

[125] a) J. D. Morrow, T. M. Harris, L. J. Roberts, *Anal. Biochem.* **1990**, *184*, 1–10; b) J. D. Morrow, K. E. Hill, R. F. Burk, T. M. Nammour, K. F. Badr, L. J. Roberts, *Proc. Natl. Acad. Sci. U. S. A.* **1990**, *87*, 9383–9387; c) G. L. Milne, H. Yin, K. D. Hardy, S. S. Davies, L. J. Roberts, *Chem. Rev.* **2011**, *111*, 5973–5996.

The mechanism of the free radical-initiated peroxidation of arachidonic acid (**118**) to the 5-series IsoPs is depicted in Figure 2.1.[125] Initially, a bis-allylic hydrogen atom is abstracted. Addition of oxygen then affords peroxyl radical **122** which undergoes 5-*exo* cyclization to furnish allyl radical **123**. Addition of a second molecule of oxygen to the backbone then leads to 5-$G_2$-IsoP (**125**). The nomenclature applied to this class of natural products was first introduced by L. J. ROBERTS and co-workers, following the nomenclature for prostaglandins (Figure 2.1).[126] For example, in 5-$G_2$-IsoP (**125**), the number 5 refers to the regioisomeric series of IsoPs, the letter G defines the substitution pattern on the prostane ring, and the subscript 2 stands for two double bonds in the side chains.

### 2.1.2 Biosynthesis of Prostaglandins

Arachidonic acid (**118**) is the predominant precursor for the prostaglandins. In the initial step of the biosynthesis, phospholipase $A_2$ catalyzes the hydrolysis of the *sn*-2 fatty acyl bond of the phospholipid to liberate the free fatty acid **118** (Scheme 2.2).[127] Then, two subsequent reactions are catalyzed by $PGH_2$ synthase: first the oxidative transformation to hydroperoxide $PGG_2$ (**126**) with consumption of two molecules of oxygen, and second a two-electron reduction to $PGH_2$ (**127**).[128]




**Scheme 2.2:** Enzymatic formation of $PGH_2$ (**127**) from arachidonic acid (**118**) and subsequent formation of various prostaglandins.

[126] a) D. F. Taber, J. D. Morrow, L. J. Roberts, *Prostaglandins* **1997**, *53*, 63–67; b) N. A. Nelson, *J. Med. Chem.* **1974**, *17*, 911–918.

[127] E. A. Dennis, *J. Biol. Chem.* **1994**, *269*, 13057–13060.

[128] a) L. J. Marnett, S. W. Rowlinson, D. C. Goodwin, A. S. Kalgutkar, C. A. Lanzo, *J. Biol. Chem.* **1999**, *274*, 22903–22906; b) W. L. Smith, D. L. DeWitt, R. M. Garavito, *Ann. Rev. Biochem.* **2000**, *69*, 145–182.

The first reaction is initiated by the highly selective abstraction of a bis-allylic hydrogen from arachidonic acid (**118**) by a nearby *O*-centered tyrosine radical. This could be shown *via* X-ray crystal structure analysis of $PGH_2$ synthase with arachidonic acid (**118**) bound in a chemically productive conformation.[129] Two isoforms of $PGH_2$ synthase exist: the first is expressed constitutively in response to hormonal stimuli to fine-tune physiological processes, the second transiently in response to physiological stresses such as infection and inflammation.

Endoperoxide $PGH_2$ (**127**) is then transformed into other prostanoids either by the action of various enzymes such as isomerases and ketoreductases or *via* direct dehydration or isomerization (examples displayed in Scheme 2.2).[130] The resulting prostaglandins act as local hormones, performing tissue-specific functions such as the mediation of pain and inflammation. They are found in virtually all peripheral organs as well as in the central nervous system, exerting their biological actions through binding to cell surface receptors.

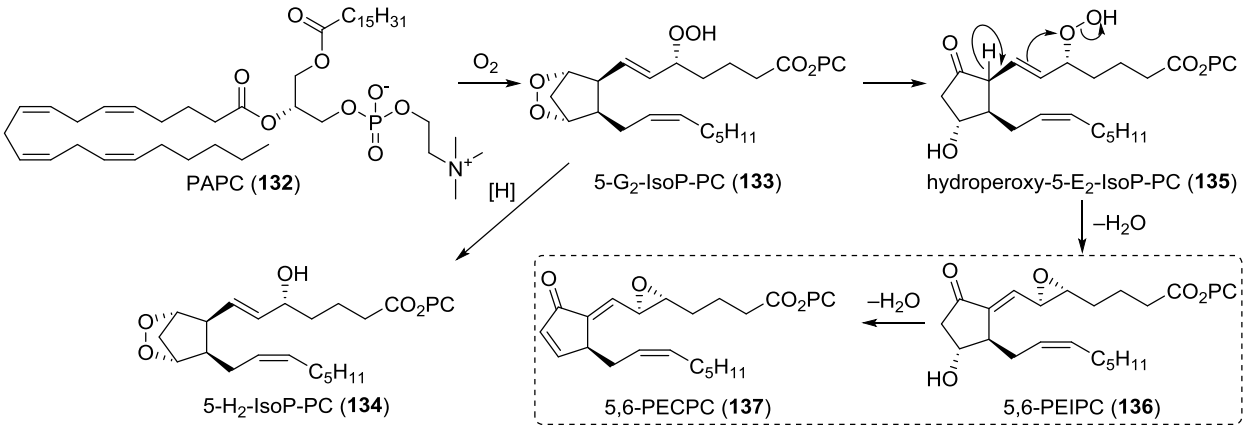
### 2.1.3 Biosynthesis of Isoprostanes

Given the structural similarity of prostaglandins and isoprostanes, a related mechanism for their formation was proposed early on.[125] In contrast to the biosynthesis of prostaglandins, which involves free arachidonic acid (**118**), isoprostanes are formed from PUFAs bound in the cell membrane as phospholipids, before the metabolite is released from the membrane.[131] In general, the initial event in the oxidative metabolization of PUFAs is hydrogen abstraction as shown in Figure 2.1, which occurs at an increased rate if the production of initiating species, such as ROS, cannot be sufficiently suppressed.[121] The bis-allylic positions are prone to hydrogen abstraction, resulting in carbon-centered radicals which rapidly react with molecular oxygen to afford peroxyl radicals, which can themselves abstract hydrogen from other PUFAs. The resulting peroxyl radicals and hydroperoxides undergo subsequent reactions producing a plethora of different OxPLs.[132] C–C bond scissions lead to fragmented OxPLs,[133] which are highly reactive entities able to form covalent adducts with other biomolecules.[134] On the other

[129] M. G. Malkowski, S. L. Ginell, W. L. Smith, R. M. Garavito, *Science* **2000**, *289*, 1933–1937.
[130] S. Das, S. Chandrasekhar, J. S. Yadav, R. Grée, *Chem. Rev.* **2007**, *107*, 3286–3337.
[131] J. D. Morrow, J. A. Awad, H. J. Boss, I. A. Blair, L. J. Roberts, *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 10721–10725.
[132] V. N. Bochkov, O. V. Oskolkova, K. G. Birukov, A.-L. Levonen, C. J. Binder, J. Stöckl, *Antioxid. Redox Signaling* **2010**, *12*, 1009–1059.
[133] A. A. Frimer, *Chem. Rev.* **1979**, *79*, 359–387.
[134] a) E. A. Podrez, E. Poliakov, Z. Shen, R. Zhang, Y. Deng, M. Sun, P. J. Finton, L. Shan, M. Febbraio, D. P. Hajjar, R. L. Silverstein, H. F. Hoff, R. G. Salomon, S. L. Hazen, *J. Biol. Chem.* **2002**, *277*, 38517–38523; b) H. H. Hoff, J. O'Neil, Z. Wu, G. Hoppe, R. L. Salomon, *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 275–282.

hand, if the initial hydroperoxides contain further sites of unsaturation, additional peroxidation is possible, furnishing advanced oxidation products bearing various combinations of hydroxyl-, hydroperoxy-, keto-, and epoxy groups. Furthermore, peroxyl radicals can cyclize and then undergo further rearrangements and oxidations. Depending on the oxygen concentration within the tissue and the nature of the parent PUFA, different OxPLs are formed preferentially.

In particular, the biosynthetic pathway for the formation of the isoprostanes is illustrated in Scheme 2.3.[121,135] The palmitoyl-phosphatidylcholine (PC) ester of arachidonic acid, PAPC (**132**), is oxidized non-enzymatically with two equivalents of oxygen in a twofold cyclization to furnish $G_2$-IsoPs as a mixture of regioisomers (cf. Figure 2.1). One marked difference to the prostaglandins lies in the relative stereochemistry on the prostane ring: for IsoPs, bicycloendoperoxide intermediates like 5-$G_2$-IsoP-PC (**133**) contain side chains in *cis* configuration due to the kinetically favored formation of these stereoisomers.




**Scheme 2.3:** Non-enzymatic oxidation of PAPC (**132**) to 5-$G_2$-IsoP-PC (**133**) and further transformation into 5-$H_2$-IsoP-PC (**134**), 5,6-PEIPC (**136**), and 5,6-PECPC (**137**).

In the presence of reducing agents, the biosynthesis proceeds to form $H_2$-IsoPs such as 5-$H_2$-IsoP-PC (**134**, Scheme 2.3). Interestingly, when no reducing agents are available, rearranged species such as hydroperoxy-$E_2$-IsoPs are formed.[136] From these intermediates, which possess an acidic α-keto hydrogen, 1,5-dehydration can occur to afford epoxy-$E_2$-IsoPs. This is illustrated in Scheme 2.3 with the conversion of hydroperoxy-5-$E_2$-IsoP-PC (**135**) to 5,6-PEIPC (**136**). Dehydration of these β-hydroxy ketones can then lead to the formation of epoxy-$A_2$-IsoPs, as in the case of the transformation of 5,6-PEIPC (**136**) to 5,6-PECPC (**137**).

[135] L. Gao, W. E. Zackert, J. J. Hasford, M. E. Danekis, G. L. Milne, C. Remmert, J. Reese, H. Yin, H.-H. Tai, S. K. Dey, N. A. Porter, J. D. Morrow, *J. Biol. Chem.* **2003**, *278*, 28479–28489.

[136] G. Subbanagounder, J. W. Wong, H. Lee, K. F. Faull, E. Miller, J. L. Witztum, J. A. Berliner, *J. Biol. Chem.* **2002**, *277*, 7271–7281.

### 2.1.4 Biological Effects of Isoprostanes

Inflammation is an innate immune response to tissue damage initiated upon activation of specialized pattern-recognition receptors, which are mainly expressed by cells of the innate immune system.[137] The immune defenses are promoted upon encountering either pathogen-associated molecular patterns or self-encoded molecules which are released during cell damage or death (damage-associated molecular patterns).[138] If the resulting response can successfully remove the inducing stimuli, only a transient reduction of tissue function is caused, while a protracted inflammatory response can lead to permanent defects and chronic disease.[139]

Transient increases in intracellular levels of reactive oxygen species (ROS) are important both for innate host defense by inflammatory cells and for signaling pathways involved in cellular differentiation and death programs.[137] However, excessive ROS production leads to the oxidative modification of critical biomolecules, as discussed above (Section 2.1.1). PUFAs are highly susceptible to radical-mediated oxidation.[132] The resulting OxPLs are generated as a large array of structurally diverse species due to the non-enzymatic nature of peroxidation and have been recognized to assist in the initiation, amplification, and resolution of inflammation.[137] The formation of OxPLs *in vivo* has been shown for diseases with an inflammatory component such as atherosclerosis or acute lung injury.[140] Intriguingly, OxPLs have been reported to mediate both pro- and anti-inflammatory effects, with the majority of studies documenting strong proinflammatory bioactivities of OxPLs.[137] The latter can be attributed to the ability of OxPLs to interact with pattern recognition receptors of the innate immune system, such as Toll-like receptors and scavenger-receptors.[140,141] These receptors are responsible for an array of immune responses through the induction of inflammatory cytokines and other cell signaling molecules.[142]

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[137] S. Freigang, *Eur. J. Immunol.* **2016**, *46*, 1818–1825.
[138] T. Pradeu, E. L. Cooper, *Front. Immunol.* **2012**, *3*, 287-1–287-9.
[139] R. Medzhitov, *Cell* **2010**, *140*, 771–776.
[140] a) J. A. Berliner, A. D. Watson, *N. Engl. J. Med.* **2005**, *353*, 9–11; b) Y. Imai, K. Kuba, G. G. Neely, R. Yaghubian-Malhami, T. Perkmann, G. van Loo, M. Ermolaeva, R. Veldhuizen, Y. H. C. Leung, H. Wang, H. Liu, Y. Sun, M. Pasparakis, M. Kopf, C. Mech, S. Bavari, J. S. M. Peiris, A. S. Slutsky, S. Akira, M. Hultqvist, R. Holmdahl, J. Nicholls, C. Jiang, C. J. Binder, J. M. Penninger, *Cell* **2008**, *133*, 235–249.
[141] a) C. R. Stewart, L. M. Stuart, K. Wilkinson, J. M. van Gils, J. Deng, A. Halle, K. J. Rayner, L. Boyer, R. Zhong, W. A. Frazier, A. Lacy-Hulbert, J. E. Khoury, D. T. Golenbock, K. J. Moore, *Nat. Immunol.* **2010**, *11*, 155–162; b) T. A. Seimon, M. J. Nadolski, X. Liao, J. Magallon, M. Nguyen, N. T. Feric, M. L. Koschinsky, R. Harkewicz, J. L. Witztum, S. Tsimikas, D. Golenbock, K. J. Moore, I. Tabas, *Cell Metab.* **2010**, *12*, 467–482; c) E. A. Podrez, E. Poliakov, Z. Shen, R. Zhang, Y. Deng, M. Sun, P. J. Finton, L. Shan, B. Gugiu, P. L. Fox, H. F. Hoff, R. G. Salomon, S. L. Hazen, *J. Biol. Chem.* **2002**, *277*, 38503–38516; d) K. Gillotte-Taylor, A. Boullier, J. L. Witztum, D. Steinberg, O. Quehenberger, *J. Lipid Res.* **2001**, *42*, 1474–1482.
[142] H. Kumar, T. Kawai, S. Akira, *Int. Rev. Immunol.* **2011**, *30*, 16–34.

In contrast to these proinflammatory bioactivities of OxPLs, also anti-inflammatory effects have been described, which result from interference with proinflammatory Toll-like receptor signaling.[137,143] It was hypothesized that the local concentration of OxPLs might determine whether they exert pro- or anti-inflammatory effects.[144] However, for thorough exploration of the relationship between OxPL structure and biological effects, the study of distinct, isolated OxPL species appeared to be essential. During research efforts directed towards this goal, cyclopentenone-containing OxPLs emerged as important mediators for the anti-inflammatory properties of bulk OxPLs, as will be discussed in Section 2.1.5.

### 2.1.5 Cyclopentenone Isoprostanes as Anti-Inflammatory Lipid Mediators

Cyclopentenone IsoPs, such as PECPC (**137**, Scheme 2.3), are reactive electrophiles and undergo conjugate addition reactions with other molecules in the cell. In 2004, V. M. DARLEY-USMAR and co-workers reported that two cyclopentenone-containing oxidized phospholipid derivatives react with the cysteine-rich protein Keap1.[145] This cytoplasmic protein plays a key role for the adaptation of cells to oxidative stress through interaction with the transcription factor Nrf2, which is the key regulator of the antioxidant response (Figure 2.2).[132] Under non-stressed conditions, Nrf2 is bound to Keap1, ubiquitinated and rapidly degraded in proteasomes. In contrast, oxidative stress evokes an antioxidant response by inducing alkylation of reactive cysteines in Keap1. Thereupon, Nrf2 dissociates from the protein and translocates to the nucleus where it activates antioxidant-responsive elements (ARE), which in turn regulate the transcription of several cytoprotective genes.[146]

[143] a) N. Leitinger, T. R. Tyner, L. Oslund, C. Rizza, G. Subbanagounder, H. Lee, P. T. Shih, N. Mackman, G. Tigyi, M. C. Territo, J. A. Berliner, D. K. Vora, *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 12010–12015; b) V. N. Bochkov, A. Kadl, J. Huber, F. Gruber, B. R. Binder, N. Leitinger, *Nature* **2002**, *419*, 77–81; c) S. Blüml, S. Kirchberger, V. N. Bochkov, G. Krönke, K. Stuhlmeier, O. Majdic, G. J. Zlabinger, W. Knapp, B. R. Binder, J. Stöckl, N. Leitinger, *J. Immunol.* **2005**, *175*, 501–508; d) S. Knapp, U. Matt, N. Leitinger, T. van der Poll, *J. Immunol.* **2007**, *178*, 993–1001.

[144] O. V. Oskolkova, T. Afonyushkin, B. Preinerstorfer, W. Bicker, E. von Schlieffen, E. Hainzl, S. Demyanets, G. Schabbauer, W. Lindner, A. D. Tselepis, J. Wojta, B. R. Binder, V. N. Bochkov, *J. Immunol.* **2010**, *185*, 7706–7712.

[145] A.-L. Levonen, A. Landar, A. Ramachandran, E. K. Ceaser, D. A. Dickinson, G. Zanoni, J. D. Morrow, V. M. Darley-Usmar, *Biochem. J.* **2004**, *378*, 373–382.

[146] K. Taguchi, H. Motohashi, M. Yamamoto, *Genes to Cells* **2011**, *16*, 123–140.

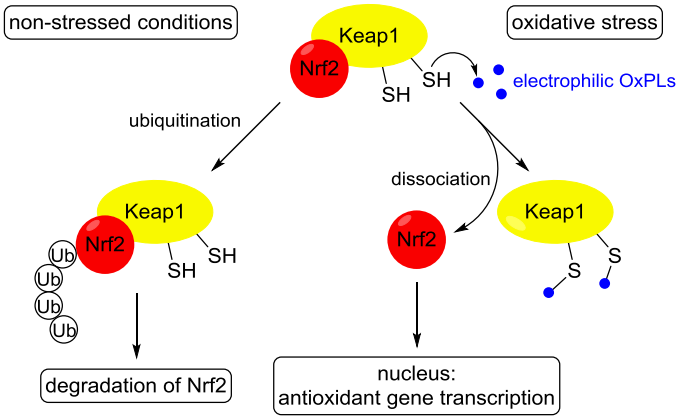



**Figure 2.2:** Antioxidant stress response *via* the Keap1/Nrf2 pathway induced by the alkylation of Keap1.

The interaction between 15d-$PGJ_2$ (**138**) and 15-$A_{2t}$-IsoP (**139**) with Keap1 was proven by treating human endothelial cells expressing tagged Keap1 with biotinylated OxPL analogs **140** and **141**, followed by cell lysis and western blot analysis (Figure 2.3).[145] Thus, evidence for a covalent adduct between Keap1 and the biotinylated cyclopentenone OxPL analogs could be provided. Furthermore, it could be shown that the reactive cysteine residues $Cys^{257}$, $Cys^{273}$, $Cys^{288}$, and $Cys^{297}$ are most likely the targets of the modification by the electrophilic cyclopentenones.

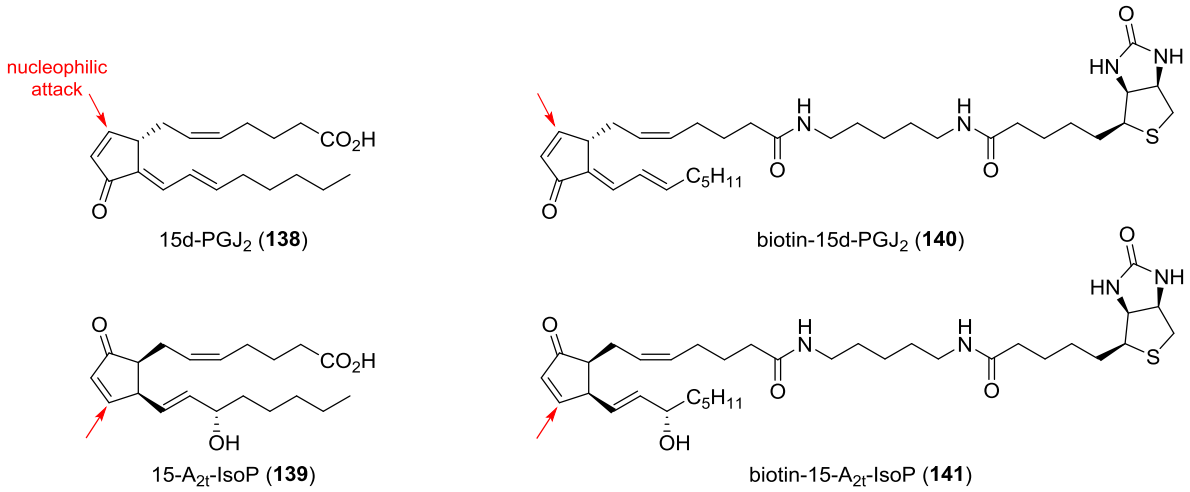



**Figure 2.3:** Structures of cyclopentenone OxPLs **138** and **139** and of their biotinylated analogs **140** and **141**. Red arrows indicate the sites of nucleophilic attack by reactive cysteine residues.

Importantly, several studies have suggested that the anti-inflammatory bioactivity of OxPL mixtures can predominantly be attributed to cyclopentenone-containing oxidizided phospholipids operating through this Keap1/Nrf2 pathway.[137]

### 2.1.6 Previous Studies on Epoxyisoprostanes in the Groups of CARREIRA and KOPF

In 2015, the groups of E. M. CARREIRA and M. KOPF disclosed an investigation of the spectrum of OxPL species which is generated upon oxidation of esterified arachidonic acid PAPC (**132**, Scheme 2.3).[147] Synthetic PAPC was oxidized either by metal-catalyzed oxidation or by exposure to air, and the resulting oxidized PAPC (OxPAPC) was evaluated *in vitro*. Intriguingly, exposure of bone marrow-derived dendritic cells (BMDCs) to OxPAPC induced a distinct reduction in the secretion of the proinflammatory cytokines IL-6 and IL-12 in response to stimulation of the Toll-like receptor 7, thus demonstrating the anti-inflammatory properties of this mixture of OxPLs. It was reasoned that the overall bioactivity of a given OxPAPC mixture likely results from the combined properties of its components. Since the composition of an OxPAPC mixture depends on the oxidation conditions, PAPC (**132**) was oxidized following different protocols. The resulting OxPL mixtures were tested for their ability to reduce IL-6 and IL-12 secretion and analyzed by mass spectrometry for their composition. Then, it was investigated whether the overall bioactivity of these complex mixtures correlated with the abundance of any of the individual OxPL species. During these studies, PEIPC (**136**) and PECPC (**137**, Scheme 2.3) were suggested as potential anti-inflammatory OxPAPC components. However, further studies of these compounds necessitated access to synthetic material.

The unique molecular architecture and biological activity of the prostaglandins and isoprostanes have called forth numerous synthetic efforts towards these intriguing molecules. Since the landmark total syntheses of the prostaglandins $PGF_{2\alpha}$ and $PGE_2$ by the group of E. J. COREY in 1969, which relied on a brilliant bicycloheptane strategy,[148] an extensive number of PG syntheses have been reported.[130,149] For the isoprostanes, different strategies had to be devised due to the *cis*-relationship of the side chains on the prostane core of this class of compounds, which is in contrast to the *trans*-arrangement in the prostaglandins. These efforts resulted in several elegant synthetic routes.[150] In particular, epoxyisoprostanes PEIPC (**136**) and PECPC (**137**, Scheme 2.3) were targets of interest, as only trace amounts of these natural products could be isolated and the structural assignment upon isolation remained tentative.[136] In 2005, H. P. ACHARYA and Y. KOBAYASHI reported the first total synthesis of PECPC (**137**)

[147] P. Bretscher, J. Egger, A. Shamshiev, M. Trötzmüller, H. Köfeler, E. M. Carreira, M. Kopf, S. Freigang, *EMBO Mol. Med.* **2015**, *7*, 593–607.

[148] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.

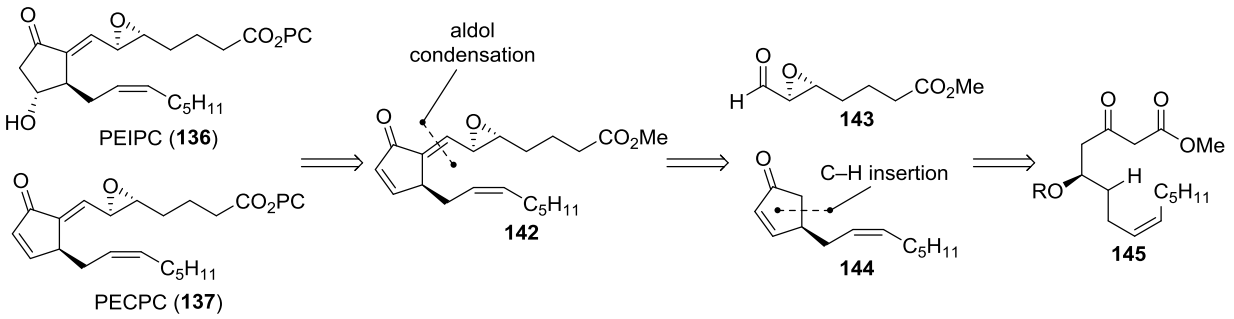
[149] a) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533–1564; b) H. Peng, F.-E. Chen, *Org. Biomol. Chem.* **2017**, *15*, 6281–6301.

[150] a) L. G. Quan, J. K. Cha, *Chem. Phys. Lipids* **2004**, *128*, 3–14; b) J.-M. Galano, E. Mas, A. Barden, T. A. Mori, C. Signorini, C. De Felice, A. Barrett, C. Opere, E. Pinot, E. Schwedhelm, R. Benndorf, J. Roy, J.-Y. Le Guennec, C. Oger, T. Durand, *Prostaglandins Other Lipid Mediators* **2013**, *107*, 95–102.

relying on a WITTIG olefination to introduce the ω-chain and an aldol reaction followed by (*E*)-selective elimination to install the α-chain.[151] During this investigation, the relative stereochemistry of the epoxyisoprostane could be assigned unambiguously. In concurrent studies, the group of M. E. JUNG disclosed two very similar synthetic routes to PEIPC (**136**), which also furnished PECPC (**137**) as a side product.[152]

The exploration of the biological activity of PEIPC (**136**) and PECPC (**137**), which had emerged as potential anti-inflammatory OxPAPC components, necessitated preparation of significant quantities of the material for *in vitro* and *in vivo* studies. However, the synthetic routes described by the groups of Y. KOBAYASHI and M. E. JUNG appeared to be too laborious and low-yielding to furnish ample material. To meet this requirement, E. M. CARREIRA and co-workers devised an efficient and flexible synthetic strategy towards these natural products.[153]

In their retrosynthetic analysis, both PEIPC (**136**) and PECPC (**137**) were traced back to the common precursor dienone **142** (Scheme 2.4). The epoxide side chain was envisaged to be introduced *via* aldol reaction between aldehyde **143** and cyclopentenone **144**, thus enabling a highly convergent synthesis. While epoxyaldehyde **143** would be accessible by JØRGENSEN epoxidation of the corresponding enal,[154] cyclopentenone **144** was envisioned to arise from a stereoselective C–H insertion of an acyclic intermediate **145**.

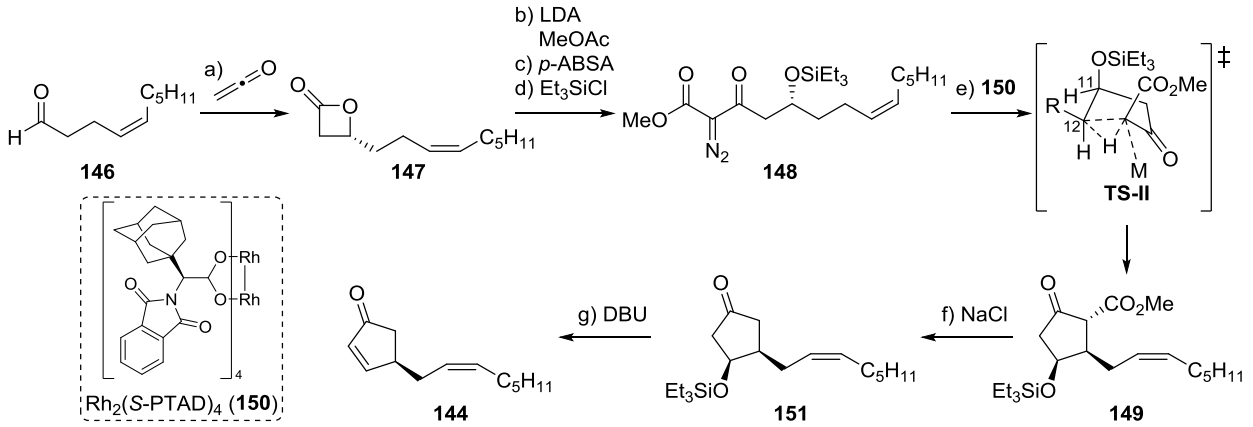



**Scheme 2.4:** Retrosynthetic analysis of PEIPC (**136**) and PECPC (**137**).

According to this synthetic plan, the synthesis commenced with the enantioselective [2+2] cycloaddition of (*Z*)-decenal **146** with *in situ* generated ketene in the presence of the chiral catalyst TMS-quinidine (Scheme 2.5).[155] The resulting β-lactone **147** was opened with the lithium enolate of methyl acetate to furnish the corresponding β-ketoester, which, upon

[151] a) H. P. Acharya, Y. Kobayashi, *Angew. Chem. Int. Ed.* **2005**, *44*, 3481–3484; b) H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2005**, *46*, 8435–8438.
[152] a) M. E. Jung, J. A. Berliner, D. Angst, D. Yue, L. Koroniak, A. D. Watson, R. Li, *Org. Lett.* **2005**, *7*, 3933–3935; b) M. E. Jung, J. A. Berliner, L. Koroniak, B. G. Gugiu, A. D. Watson, *Org. Lett.* **2008**, *10*, 4207–4209.
[153] J. Egger, P. Bretscher, S. Freigang, M. Kopf, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 5382–5385.
[154] M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965.
[155] C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352–5353.

diazotization and silyl protection of the secondary alcohol, was transformed into diazoketoester **148**. With this acyclic precursor in hand, the key homoallylic C–H insertion was explored. In a first experiment, $Rh(OAc)_2$ was used as the catalyst, which resulted in the formation of the desired cyclized product **149** in a 4:1 mixture of diastereomers, revealing a preference for the desired C(11)–C(12) *cis* product. This desired selectivity could be significantly improved by employing bulkier rhodium catalysts, as could be predicted by analyzing the putative transition state **TS-II**. Under optimized reaction conditions, a 9:1 diastereomeric ratio was reached employing commercially available $Rh_2$(*S*-PTAD)$_4$ (**150**), and cyclopentanone **149** was isolated in 71% yield. Upon subsequent KRAPCHO decarboxylation,[156] the major *cis*-diastereomer **151** could be separated from the *trans*-product by column chromatography. Finally, elimination of triethylsilanol mediated by DBU afforded cyclopentenone **144** in 60% yield over two steps.

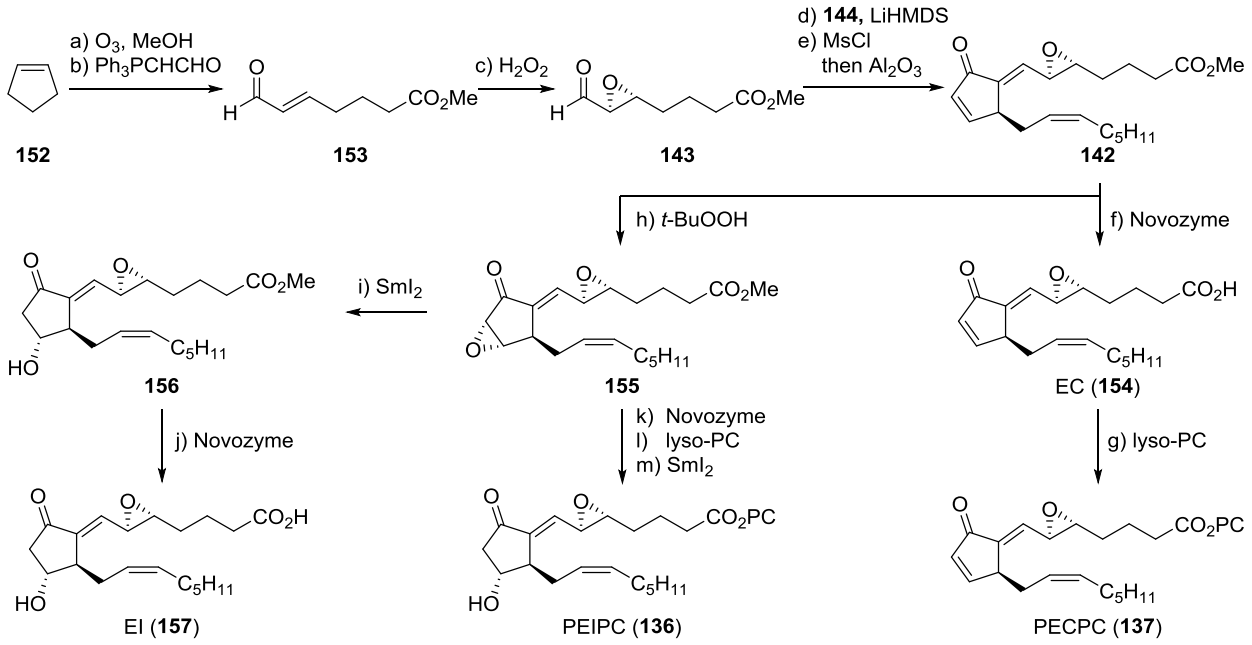



**Scheme 2.5:** Synthesis of cyclopentenone **144** as reported by CARREIRA and co-workers.[153] Reagents and conditions: a) $LiClO_4$ (3.0 equiv), TMS-quinidine (12 mol%), (*i*-Pr)$_2$NEt (2.5 equiv), AcCl (2.5 equiv), $Et_2O/CH_2Cl_2$ (1:2), –78 °C, 62%, 92% *ee*; b) LDA (3.8 equiv), methyl acetate (3.8 equiv), THF, –78 °C, 77%; c) *p*-ABSA (1.3 equiv), $NEt_3$ (2.0 equiv), MeCN, 0 °C to RT, 97%; d) $Et_3SiCl$ (1.5 equiv), imidazole (2.0 equiv), DMF, 0 °C to RT, 98%; e) $Rh_2$(*S*-PTAD)$_4$ (1 mol%), $CH_2Cl_2$, reflux, 71%, d.r. = 9:1; f) NaCl (30 equiv), DMSO, 140 °C, 65%; g) DBU (10 equiv), $CH_2Cl_2$, 0 °C, 93%.

The aldehyde coupling partner **143** was accessed as illustrated in Scheme 2.6. Following a report by the group of M. A. CUIFOLINI, ozonolysis of cyclopentene (**152**) in the presence of MeOH afforded an intermediate δ-oxoester. Subsequent WITTIG olefination furnished *trans*-α,β-unsaturated aldehyde **153** in 55% yield over two steps,[157] which was subjected to the enantioselective epoxidation conditions developed by the group of K. A. JØRGENSEN to afford epoxyaldehyde **143** in 51% yield and 92% *ee*.[154] The installation of the α-side chain on the cyclopentenyl ring was then conducted using a modification of the procedure reported by H. P. ACHARYA and Y. KOBAYASHI.[151] Aldol addition of epoxyaldehyde **143** and

[156] A. P. Krapcho, G. A. Glynn, B. J. Grenon, *Tetrahedron Lett.* **1967**, *8*, 215–217.
[157] M. A. Ciufolini, S. Zhu, *J. Org. Chem.* **1998**, *63*, 1668–1675.

cyclopentenone **144** occurred upon deprotonation of **144** with LiHMDS in THF at –78 °C followed by addition of aldehyde **143**. The required (*E*)-selective elimination was then induced by mesylation of the intermediate secondary alcohol and subsequent treatment with neutral alumina, furnishing the desired dienone **142**. Finally, acid- and base-sensitive ester **142** was enzymatically hydrolyzed under neutral conditions to obtain EC (**154**) in 70% yield. Furthermore, PECPC (**137**) could be accessed in 69% yield by coupling of EC (**154**) with lyso-PC employing YAMAGUCHI's conditions.[152]




**Scheme 2.6:** Synthesis of EC (**154**), PECPC (**137**), EI (**157**), and PEIPC (**136**) as reported by CARREIRA and co-workers.[153] Reagents and conditions: a) $O_3$, $NaHCO_3$ (0.3 equiv), $MeOH/CH_2Cl_2$ (1:5), –78 °C, then $NEt_3$ (2.0 equiv), $Ac_2O$ (2.0 equiv), benzene, 0 °C; b) $Ph_3PCHCHO$ (2.1 equiv), toluene, 70 °C, 55% (2 steps), d.r. = 5:1; c) (*S*)-2-(diphenyl-[(trimethylsilyl)oxy]methyl)pyrrolidine (10 mol%), $H_2O_2$ (1.3 equiv), $CH_2Cl_2$, RT, 51%, d.r. = 10:1, 92% *ee*; d) **144** (1.0 equiv), LiHMDS (1.2 equiv), THF, –78 °C, then **143** (2.0 equiv); e) MsCl (3.0 equiv), $NEt_3$ (6.0 equiv), $CH_2Cl_2$, –78 °C, then $Al_2O_3$, $CH_2Cl_2$, RT, 64% (2 steps); f) Novozyme, phosphate buffer pH 7/THF (4:1), RT, 70%; g) 2,4,6-$Cl_3C_6H_2COCl$ (10 equiv), DMAP (10 equiv), lyso-PC (3.0 equiv), $CHCl_3$, RT, 69%; h) *t*-BuOOH (1.0 equiv), DBU (1.0 equiv), THF, 0 °C, 74%; i) $SmI_2$ (2.0 equiv), THF/MeOH (4:1), –90 °C, 54%; j) Novozyme, phosphate buffer pH 7/THF (4:1), RT, 60%; k) Novozyme, phosphate buffer pH 7/THF (4:1), RT, 74%; l) 2,4,6-$Cl_3C_6H_2COCl$ (10 equiv), DMAP (10 equiv), lyso-PC (3.0 equiv), $CHCl_3$, RT, 69%; m) $SmI_2$ (2.0 equiv), THF/MeOH (4:1), –90 °C, 43%.

Cyclopentenone **142** also served as a common intermediate for the synthesis of both EI (**157**) and PEIPC (**136**, Scheme 2.6). Diastereoselective WEITZ–SCHEFFER epoxidation of the endocyclic enone in **142** with *tert*-butyl hydroperoxide and DBU followed by reductive opening of the resulting epoxide **155** with samarium diiodide at –90 °C furnished β-hydroxyketone **156** in 40% yield over two steps.[158,159] Enzymatic hydrolysis of the methyl ester in **156** under careful

[158] a) E. Weitz, A. Scheffer, *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2327–2344; b) A study of the electrophilicity of the endo- and exocyclic enones in prostaglandins: M. Suzuki, M. Mori, T. Niwa, R. Hirata, K. Furuta, T. Ishikawa, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 2376–2385.

control of the pH in order to preclude elimination afforded EI (**157**) in 60% yield. In analogy, hydrolysis of epoxyketone **155** followed by esterification with lyso-PC and reductive epoxide opening furnished PEIPC (**136**) in 22% yield over three steps.

With an efficient route to the epoxyisoprostanes in hand, the anti-inflammatory effects of PEIPC (**136**) and PECPC (**137**) as well as of the free acids EI (**157**) and EC (**154**) were investigated in the laboratory of M. KOPF.[153] Towards this end, bone marrow-derived dendritic cells (BMDCs) were incubated with the synthetic epoxyisoprostanes at defined concentrations in supplemented RPMI (Roswell Park Memorial Institute) medium for one hour. The cells were then washed and stimulated with Toll-like receptor ligand R837 for 18 hours to induce the secretion of proinflammatory cytokines. The supernatants were subsequently collected for analysis. Gratifyingly, a dose-dependent decrease in secretion of the proinflammatory cytokines IL-6 and IL-12 was observed (Figure 2.4). While the original target structures PEIPC (**136**) and PECPC (**137**) displayed moderate anti-inflammatory activities, their free acid counterparts EI (**157**) and EC (**154**) were significantly more active. Furthermore, comparison of the effects induced by hydroxylated isoprostane EI (**157**) with its dehydrated analog EC (**154**) indicated a stronger activity of the latter. This finding is in agreement with the hypothesis for the mode of action of cyclopentenone isoprostanes formulated above (Section 2.1.5), stating the requirement for an electrophilic endocyclic enone. Possibly, EI (**157**) undergoes elimination to form EC (**154**) before exerting its biological activity.

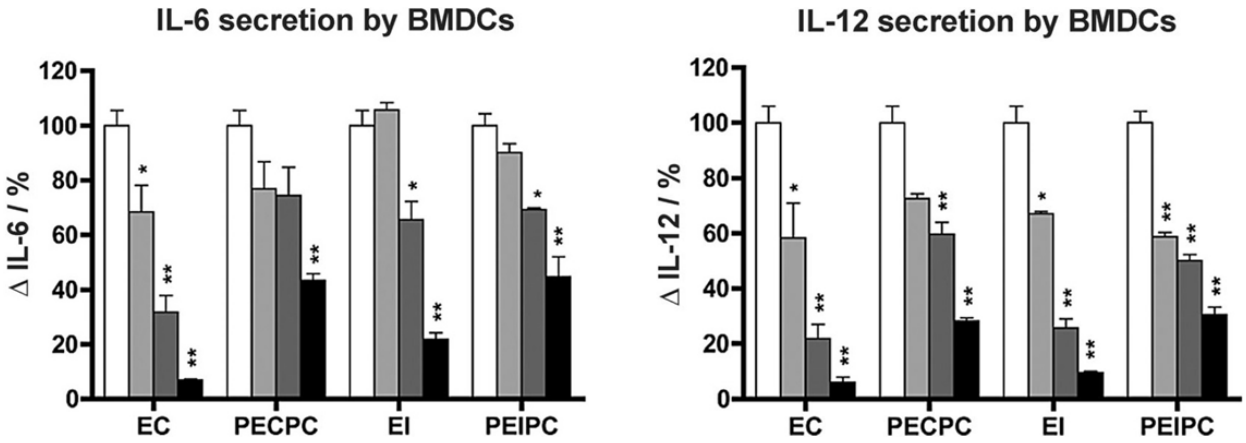
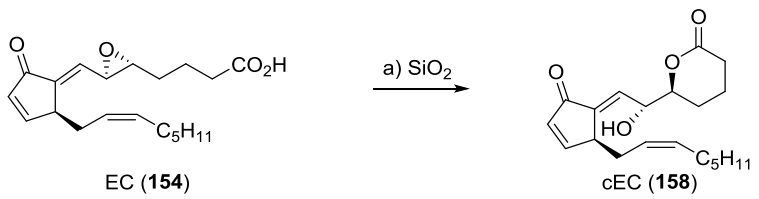



**Figure 2.4:** Comparison of the activity of EC (**154**), PECPC (**137**), EI (**157**), and PEIPC (**136**) in inhibiting secretion of the proinflammatory cytokines IL-6 and IL-12. Concentrations (from left to right) for EC, PECPC, and EI: 0, 0.37, 1.11, and 3.33 µM; for PEIPC: 0, 1.52, 3.04, and 6.07 µM. Picture taken with permission from reference.[153]

[159] G. A. Molander, G. Hahn, *J. Org. Chem.* **1986**, *51*, 2596–2599.

Having demonstrated the potent anti-inflammatory activity of epoxyisoprostane EC (**154**), the mode of action of this class of oxidized lipids was further investigated. Importantly, it could be shown that the bioactivity of both OxPAPC and EC (**154**) was abrogated in the absence of Nrf2,[147] thus demonstrating that EC (**154**) signals through Nrf2 to mediate its anti-inflammatory effect and therefore functions similar to other cyclopentenone-containing OxPLs.[145]

During the synthetic studies directed at the total synthesis of PECPC (**137**), it was observed that the free acid EC (**154**) underwent isomerization to lactone **158**, later termed cEC, upon exposure to silica gel (Scheme 2.7). This serendipitous finding was exploited by subjecting EC (**154**) to silica gel in $CHCl_3$ at ambient temperature, which furnished cEC (**158**) in 65% yield.[160] A similar 6-*exo*-tet cyclization had been observed before by the group of Y. KOBAYASHI when exposing a diastereomer of EC (**154**) to silica gel.[151]




EC (**154**) cEC (**158**)

**Scheme 2.7:** Conversion of EC (**154**) to cEC (**158**). Reagents and conditions: a) $SiO_2$, $CHCl_3$, RT, 65%.

The evaluation of the anti-inflammatory effects of cEC (**158**) showed a remarkable result: the lactone derivative of EC (**154**) exhibited a significantly higher activity than all the compounds tested before. This observation sparked the interest to investigate the contribution of the structure of the α-side chain to the biological effects of these isoprostanes. Towards this end, several analogs of EC (**154**) were synthesized by the group of E. M. CARREIRA to systematically probe the influence of this side chain (Figure 2.5).[160,161] Acid **159** results from switching the position of the carboxylic acid to the other side chain, thus rendering lactonization unlikely. Trienone **160**, displaying structural similarities to 15d-$PGJ_2$ (**138**, Figure 2.3), was designed to explore the effect of the electrophilic epoxide, while diol **161** was investigated to determine whether cEC (**158**) is a precursor to an even more active seco-acid derivative. However, upon testing of their biological activity, none of **159**–**161** was more potent than the parent compound EC (**154**). In particular, the reduced activity of diol **161** indicated that the lactone incorporated in the side chain of cEC (**158**) possesses a distinct advantage compared to the other analogs, which is not a result of lactone hydrolysis.

[160] J. Egger, P. Bretscher, S. Freigang, M. Kopf, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 17382–17385.
[161] A related structure–activity relationship study on 15d-$PGJ_2$: J. Egger, S. Fischer, P. Bretscher, S. Freigang, M. Kopf, E. M. Carreira, *Org. Lett.* **2015**, *17*, 4340–4343.

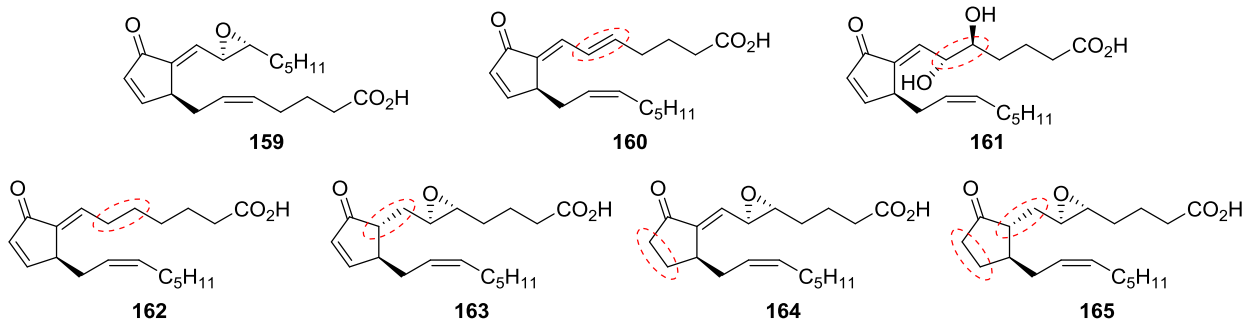



**Figure 2.5:** Synthetic analogs of EC (**154**) investigated by CARREIRA and KOPF.[160]

Having established the superiority of cEC (**158**), the electrophilic sites in EC (**154**) necessary for bioactivity were then examined (Figure 2.5). Analogs **162**, **163**, **164**, and **165** were synthesized following similar strategies as outlined above (Scheme 2.6). In the subsequent biological assay, dienone **162** and cyclopentenone **163** displayed similar and considerable potencies, although they were less active than the parent EC (**154**). Thus, it was demonstrated that both the exocyclic enone and the epoxide only have a reinforcing effect. In contrast, exocyclic enone **164** exhibited drastically diminished potency compared to EC (**154**), and cyclopentanone **165** showed no biological activity. These results showcased the importance of the endocyclic enone for the observed anti-inflammatory effects.

In conclusion, the research efforts conducted in the groups of E. M. CARREIRA and M. KOPF disclosed the anti-inflammatory activities of epoxyisoprostanes EI (**157**) and EC (**154**) as well as, to a lesser extent, their phosphatidylcholine derivatives PEIPC (**136**) and PECPC (**137**).[153] It could be demonstrated that the endocyclic enone present in cyclopentenone isoprostanes is crucial for their biological activity.[160] Furthermore, the studies revealed the surprising anti-inflammatory activity of cEC (**158**), which surpassed the one displayed by EC (**154**) and was the highest observed for any of the investigated analogs. This observation elicited the hypothesis that the lactone cEC (**158**), as the most active agent, may be responsible for the observed effects of both EI (**157**) and EC (**154**) through the formation of cEC (**158**) under physiological conditions (Figure 2.6).

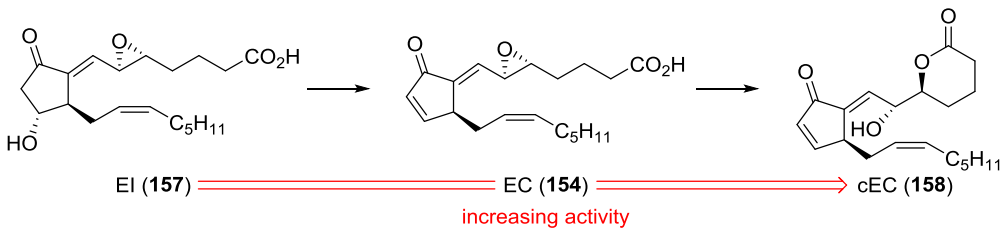



**Figure 2.6:** Hypothesized conversion of EI (**157**) and EC (**154**) to cEC (**158**) under physiological conditions.

### 2.1.7 Project Outline

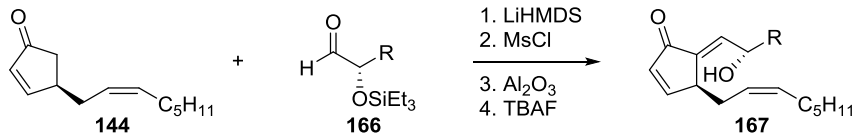
The work described in this thesis was sparked by the intriguing biological activity of cEC (**158**), which prompted further studies on the influence of the cyclic α-side chain. The promising activity of cEC (**158**) suggested this class of cyclopentenone isoprostane derivatives as a potential scaffold for future anti-inflammatory therapeutics, thus making further structure–activity relationship studies appear a worthwhile target. Moreover, an investigation of the molecular mechanisms involved in the signaling of this class of isoprostanes was undertaken, aiming at the determination of their fate on a molecular level. Therefore, the synthesis of suitable bioorganic tools was envisioned.

## 2.2 Structure–Activity Relationship Studies

Following the motivation outlined above (Section 2.1.7), S. OGAWA set out to prepare a selection of analogs of cEC (**158**) which were then tested for their anti-inflammatory activities by J. MURI in the laboratory of M. KOPF.[162] Soon after the beginning of this endeavor, the author of this thesis joined the project. In this section, the joint research efforts will be described. However, the syntheses of the analogs prepared by S. OGAWA, i.e., **178**, **185**, **186**, **194**, **195**, **196**, **197**, **198**, **199**, and **200**, will not be depicted in detail.[163]

### 2.2.1 Synthesis of Lactam Analog 168

While previous studies had shown that the endo- and the exocyclic enone as well as the allylic epoxide in EC (**154**) are crucial for the observed high activity,[160] the role of the cyclic side chain in cEC (**158**) vis-à-vis its anti-inflammatory effects had not been investigated. The structure–activity relationship studies described herein aimed at the exploration of this question and relied on the rapid access to a variety of different analogs granted by the flexible synthetic route described above (Scheme 2.6). Namely, the general strategy involved late-stage coupling of the previously described cyclopentenone **144** with various aldehydes **166** *via* aldol condensation reactions to afford dienones **167** bearing diverse side chains (Scheme 2.8). This approach allowed for the modular synthesis of a variety of analogs.

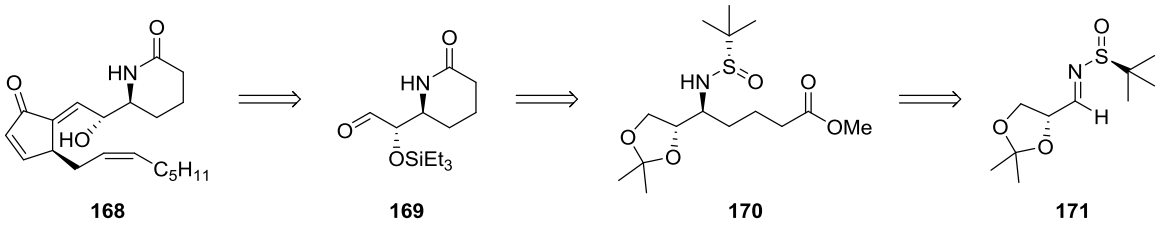



**Scheme 2.8:** General synthetic plan to access dienones **167**.

The presence of a lactone in cEC (**158**) was shown to be beneficial for the observed anti-inflammatory activity. However, it also generates ambiguity with respect to the generation of seco-acid **161** (Figure 2.5) under physiological conditions. Therefore, the targeted analogs included replacements for the lactone with potentially higher hydrolytic stability, such as lactams, sultams, and other rings.[164]

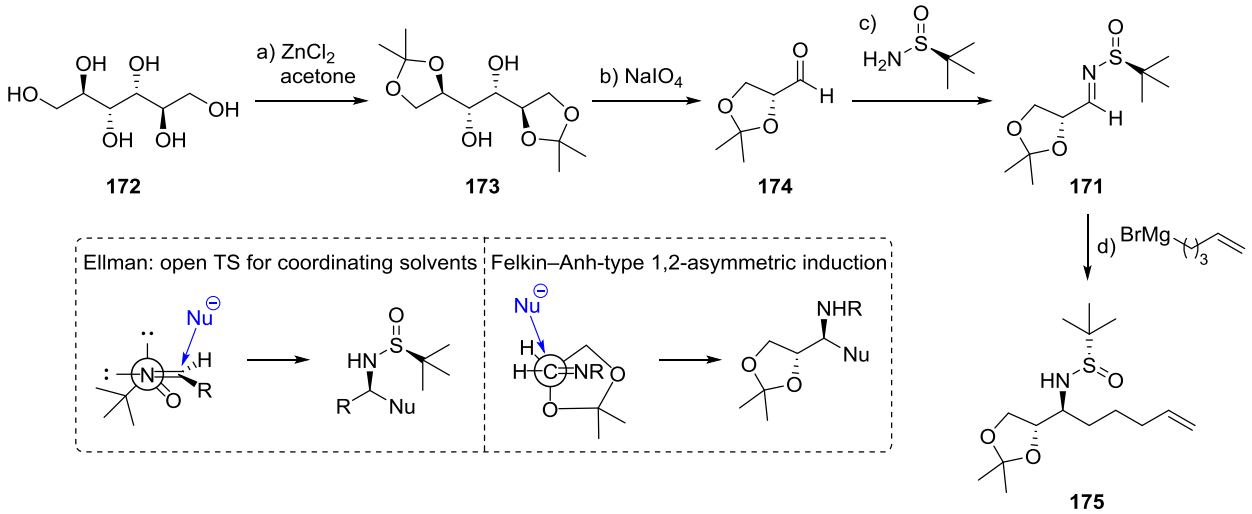
[162] S. Ogawa was a visiting researcher in the group of E. M. Carreira from 2017 to 2018.
[163] Detailed synthetic routes to all of the prepared analogs: H. Wolleb, S. Ogawa, M. Schneider, A. Shemet, J. Muri, M. Kopf, E. M. Carreira, *Org. Lett.* **2018**, *20*, 3014–3016.
[164] B. Testa, J. M. Mayer, *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry and Enzymology*, Verlag Helvetica Chimica Acta, Zürich, **2003**, pp. 163–234.

First, lactam analog **168** of cEC (**158**) was targeted, following previous investigations carried out by M. SCHNEIDER during his master thesis (Scheme 2.9).[165] The relative stereochemistry of the required protected α-hydroxyaldehyde **169** was envisioned to be installed employing the chiral sulfinamide approach developed by the group of J. A. ELLMAN,[166] thus tracing back aldehyde **169** to sulfinamide **170**. Aldimine **171** was identified as a suitable starting material.




**Scheme 2.9:** Retrosynthetic analysis of lactam **168**.

Analysis of the stereochemical properties of aldimine **171** indicated that the required 1,2-addition of a suitable organometal species would occur with the desired diastereoselectivity (box, Scheme 2.10). J. A. ELLMAN and co-workers proposed transition state models for the 1,2-addition of organometallic reagents to such aldimines, suggesting an open transition state to be favored by the use of coordinating solvents such as THF.[167] As illustrated, such an open transition state leads to the desired configuration of the amine. Secondly, FELKIN–ANH-type 1,2-asymmetric induction reinforces the preference for the formation of the desired amine.[58]

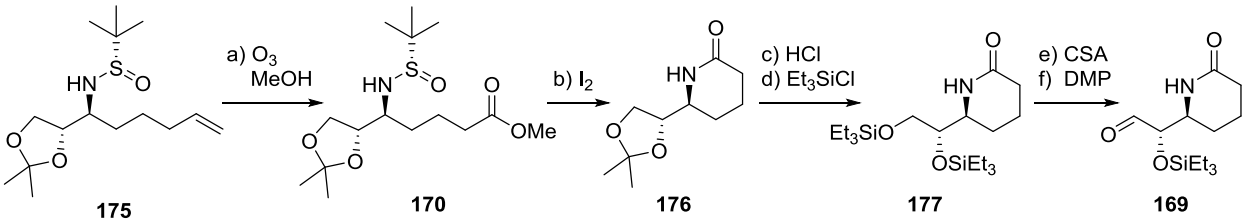



**Scheme 2.10:** Synthesis of sulfinamide **175** and rationale for the stereochemical outcome of the GRIGNARD addition. Reagents and conditions: a) $ZnCl_2$ (2.1 equiv), acetone, 0 °C to RT, 41%; b) $NaIO_4$ (2.0 equiv), aq. $NaHCO_3$, $CH_2Cl_2$, RT, 42%; c) (*S*)-(–)-2-methyl-2-propanesulfinamide (1.5 equiv), $Ti(OEt)_4$ (4.9 equiv), $CH_2Cl_2$, RT, 77%; d) pent-4-en-1-ylmagnesium bromide (2.5 equiv), $Et_2O$/THF (1:3), 55 °C, 69%.

[165] M. Schneider carried out initial studies towards the synthesis of lactam analog **168** using a chiral sulfinimine in the group of E. M. Carreira in 2015.
[166] G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
[167] M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740.

Following literature procedures, D-mannitol (**172**) was converted to diol **173** upon reaction with zinc chloride in acetone,[168] followed by oxidative cleavage with sodium periodate to afford protected D-glyceraldehyde **174** in moderate yield (Scheme 2.10).[169] Condensation with (*S*)-(–)-2-methyl-2-propanesulfinamide in the presence of $Ti(OEt)_4$ as a LEWIS acid catalyst and water scavenger then furnished literature-known sulfinimine **171** in 77% yield.[170] Addition of pent-4-en-1-ylmagnesium bromide in diethyl ether to a solution sulfinimine **171** in THF followed by stirring at 55 °C afforded the desired sulfinamide **175** in a diastereomeric ratio of 10:1 as indicated by $^1$H NMR analysis of the crude reaction mixture. The two diastereomers could be readily separated by column chromatography, resulting in the isolation of **175** as a single diastereomer in 69% yield.

With sulfinamide **175** in hand, the stage was set for the investigation of the required lactam formation (Scheme 2.11). According to a procedure reported by J. A. MARSHALL and co-workers for the direct conversion of olefins into esters,[171] ozonolysis of terminal alkene **175** in the presence of methanol and sodium hydroxide furnished methyl ester **170**. Care had to be taken to interrupt the reaction after ten minutes in order to avoid oxidation of the sulfinamide to the corresponding sulfonamide.



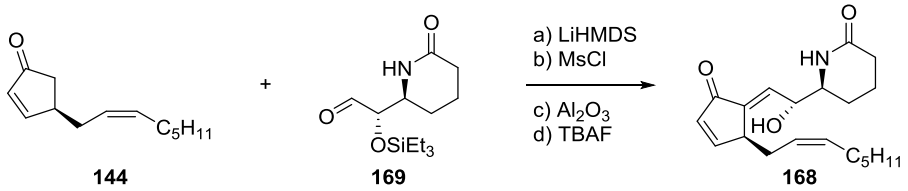

**Scheme 2.11:** Synthesis of aldehyde **169** from sulfinamide **175**. Reagents and conditions: a) $O_3$, NaOH (5.0 equiv), $CH_2Cl_2$/MeOH (3:1), –78 °C, then $PPh_3$ (1.5 equiv), –78 °C to RT; b) $Na_2CO_3$ (3.0 equiv), DMAP (20 mol%), $I_2$ (2.5 equiv), THF/$H_2O$ (1:1), RT; c) 2 M HCl, EtOH, RT; d) $Et_3SiCl$ (6.0 equiv), imidazole (10 equiv), $CH_2Cl_2$, 0 °C to RT, 19% (4 steps); e) CSA (1.0 equiv), $CH_2Cl_2$/MeOH (1:1), –40 °C; f) DMP (1.2 equiv), $CH_2Cl_2$, 0 °C to RT, yield not determined.

Ester **170** was then treated with iodine, sodium carbonate, and DMAP in a mixture of THF and water, which induced removal of the auxiliary with concomitant amide bond formation to furnish lactam **176** (Scheme 2.11). This mild iodine-mediated deprotection protocol was devised by the group of H. ZHANG to provide a functional group compatible method for this transformation.[172] Harsher reaction conditions, such as the attempted deprotection with aqueous

[168] H. Yokoyama, K. Otaya, H. Kobayashi, M. Miyazawa, S. Yamaguchi, Y. Hirai, *Org. Lett.* **2000**, *2*, 2427–2429.
[169] C. H. Sugisaki, Y. Ruland, M. Baltas, *Eur. J. Org. Chem.* **2003**, 672–688.
[170] A. W. Buesking, T. D. Baguley, J. A. Ellman, *Org. Lett.* **2011**, *13*, 964–967.
[171] a) J. A. Marshall, A. W. Garofalo, R. C. Sedrani, *Synlett* **1992**, 643–645; b) J. A. Marshall, A. W. Garofalo, *J. Org. Chem.* **1993**, *58*, 3675–3680.
[172] W. Chen, J. Ren, M. Wang, L. Dang, X. Shen, X. Yang, H. Zhang, *Chem. Commun.* **2014**, *50*, 6259–6262.

HCl, only led to decomposition of sulfinamide **170**. The relative stereochemistry of lactam **176** was confirmed by comparison with its literature-known diastereomer.[173] Finally, acetonide **176** had to be converted to protected α-hydroxyaldehyde **169**. To this end, deprotection of **176** with aqueous HCl in ethanol at ambient temperature furnished the corresponding diol, which was then doubly protected to afford silyl ether **177** in 19% yield from alkene **175**. The primary alcohol was selectively deprotected by treating silyl ether **177** with camphorsulfonic acid in a 1:1 mixture of $CH_2Cl_2$ and MeOH at –40 °C.[174] Required aldehyde **169** was finally obtained upon DESS–MARTIN oxidation and was used in the subsequent aldol condensation without purification (*vide infra*).[50]

According to the general strategy outlined above (Scheme 2.8), aldehyde **169** was coupled to cyclopentenone **144** following the protocol reported by the group of E. M. CARREIRA (Scheme 2.12).[153,175] Deprotonation of **144** with LiHMDS followed by addition of aldehyde **169** furnished the intermediate aldol adduct as a mixture of diastereomers. Without separation, this mixture was converted to the corresponding mesylate, which was then exposed to $Al_2O_3$ in $CH_2Cl_2$ to effect (*E*)-selective elimination.[176] Finally, cleavage of the silyl ether mediated by TBAF furnished the desired lactam **168** in moderate yield, which was then used for biological testing.




**Scheme 2.12:** Synthesis of lactam analog **168**. Reagents and conditions: a) **144** (3.9 equiv), LiHMDS (3.5 equiv), THF, –78 °C, then **169** (1.0 equiv); b) MsCl (7.0 equiv), $NEt_3$ (14 equiv), $CH_2Cl_2$, –78 °C to –50 °C; c) $Al_2O_3$, $CH_2Cl_2$, RT; d) TBAF (4.2 equiv), THF, 0 °C, 6% (6 steps from **177**).

[173] S. C. Deshmukh, A. Roy, P. Talukdar, *Org. Biomol. Chem.* **2012**, *10*, 7536–7544.
[174] J. W. Winkler, J. Uddin, C. N. Serhan, N. A. Petasis, *Org. Lett.* **2013**, *15*, 1424–1427.
[175] The coupling of **144** and **169** to afford lactam **168** was carried out by S. OGAWA. It is described here to convey a coherent illustration of the synthesis of this analog. Of note, aldehyde **169** was used as the limiting reagent, in contrast to the original procedure which employs an excess of the aldehyde coupling partner.
[176] H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**, *45*, 1199–1202.

### 2.2.2 Biological Testing

The analogs of cEC (**158**), which were all accessed employing approaches closely related to the one described in the previous section, were tested for their ability to inhibit the secretion of the proinflammatory cytokine IL-6 by bone marrow-derived dendritic cells (BMDCs). These tests were carried out in the laboratory of M. KOPF following the same protocol as described for the evaluation of EC (**154**) and cEC (**158**, Section 2.1.6).[153]

In a first comparative experiment, lactam **168** was tested together with its diastereomer **178** and the two known isoprostanes EC (**154**) and cEC (**158**, Figure 2.7). Gratifyingly, substitution of the lactone for a lactam resulted in an epoxyisoprostane analog exhibiting slightly higher anti-inflammatory activity, along with potentially higher hydrolytic stability. Lactam **168** therefore replaced cEC (**158**) as the most potent compound in the series, further highlighting the importance of the cyclic side chain. Comparison with diastereomeric lactam **178**, which also displayed considerable activity, indicated that the stereogenic center in the six-membered ring only had a minor impact on the anti-inflammatory effect.

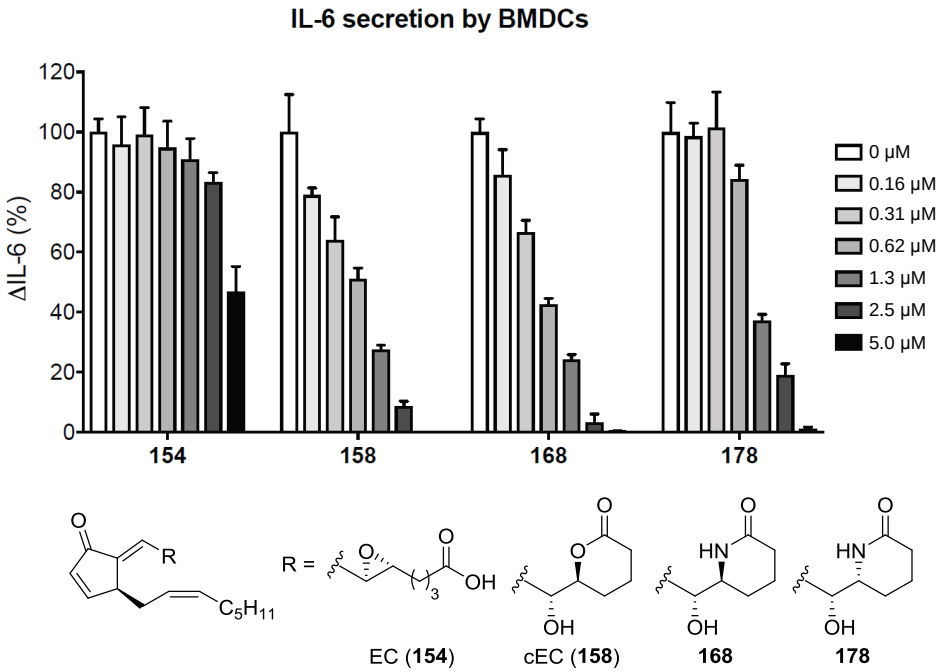


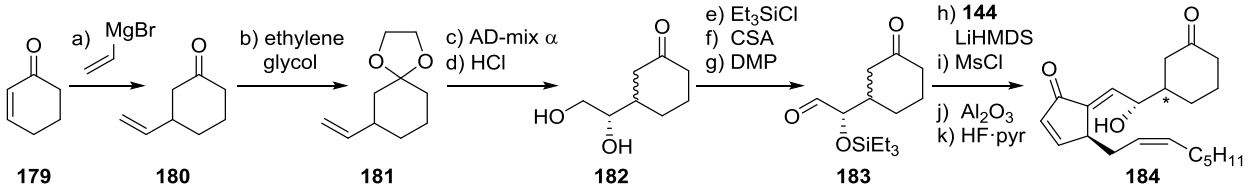

**Figure 2.7:** Comparison of the activity of EC (**154**), cEC (**158**), and lactams **168** and **178** in inhibiting secretion of the proinflammatory cytokine IL-6.

With this encouraging result in hand, ester and amide surrogates were further investigated. Such bioisosteres, i.e., compounds with similar molecular shapes and distribution of electrons exhibiting similar physical properties,[177] have been widely studied in the context of medicinal chemistry. Amide isosteres are of interest for the modulation of polarity and bioavailability,

[177] A. Burger in *Progress in Drug Research* (Ed.: E. Jucker), Birkhäuser Basel, Basel, **1991**, pp. 287–371.

while ester isosteres have been used to address metabolism issues.[178] For the exploration of epoxyisoprostane analogs, the ester moiety was envisioned to be replaced by ketone or sulfonamide groups.

The synthesis of ketone **184** was envisaged to involve enantioselective installation of the secondary alcohol *via* SHARPLESS asymmetric dihydroxylation of a suitable alkene.[179] Towards this end, CuI-catalyzed addition of vinylmagnesium bromide to 2-cyclohexenone (**179**) afforded the corresponding ketone **180**,[180] which was examined as a substrate for the required dihydroxylation (Scheme 2.13). Surprisingly, when the reaction conditions reported by the group of K. B. SHARPLESS were applied, no conversion of the starting material was observed. The same result was obtained when using catalytic $OsO_4$ in combination with NMO, leading to the conjecture that the carbonyl moiety may lead to unproductive coordination to the metal. Therefore, literature-known dioxolane **181** was accessed by reaction of ketone **180** with ethylene glycol in the presence of catalytic *p*-toluenesulfonic acid monohydrate in THF.[181] With this substrate, SHARPLESS dihydroxylation employing AD-mix α uneventfully afforded the corresponding diol as a 1:1 mixture of diastereomers, which was directly converted to ketone **182** upon treatment with aqueous HCl in ethanol. The newly formed stereogenic center was tentatively assigned based on the expected diastereofacial selectivity of AD-mix α.[179]




**Scheme 2.13:** Synthesis of ketone **184**. Reagents and conditions: a) vinylmagnesium bromide (2.0 equiv), CuI (17 mol%), THF, 0 °C, 55%; b) ethylene glycol (4.0 equiv), *p*-TsOH·$H_2O$ (20 mol%), THF, RT, 88%; c) AD-mix α, *t*-BuOH/$H_2O$ (1:1), 0 °C; d) 2 M HCl, EtOH, RT, 78% (2 steps), d.r. = 1:1; e) $Et_3SiCl$ (6.0 equiv), imidazole (10 equiv), $CH_2Cl_2$, 0 °C to RT, 87%, d.r. = 1:1; f) CSA (1.0 equiv), $CH_2Cl_2$/MeOH (1:1), –78 °C, 38%, d.r. = 1:1; g) DMP (1.2 equiv), $CH_2Cl_2$, 0 °C to RT, d.r. = 1:1, yield not determined; h) **144** (1.0 equiv), LiHMDS (1.2 equiv), THF, –78 °C, then **183** (2.5 equiv); i) MsCl (6.9 equiv), $NEt_3$ (12 equiv), $CH_2Cl_2$, –78 °C to RT; j) $Al_2O_3$ (40 equiv), $CH_2Cl_2$, RT, 14% (3 steps); k) HF·pyridine (14 equiv), THF, 0 °C to RT, quant.

Application of the protection–monodeprotection–oxidation protocol developed for the synthesis of lactam **168** (Scheme 2.11) then gave access to the desired aldehyde **183**, which was isolated as an inseparable 1:1 mixture of diastereomers (Scheme 2.13). Of note, the CSA-mediated deprotection of the intermediate primary silyl ether had to be conducted at lower temperatures than in the case of the analogous silyl ether **177** in order to avoid double

[178] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.
[179] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
[180] F. A. J. Kerdesky, S. P. Schmidt, J. H. Holms, R. D. Dyer, G. W. Carter, D. W. Brooks, *J. Med. Chem.* **1987**, *30*, 1177–1186.
[181] Z.-K. Yang, Q.-H. Chen, F.-P. Wang, *Tetrahedron* **2011**, *67*, 4192–4195.

deprotection. Subsequently, aldehyde **183** was coupled to cyclopentenone **144** employing the conditions established for this aldol addition–elimination sequence. In line with an observation by C. EBNER, the practicability of the protocol could be improved by introducing an aqueous work-up step after mesylation of the aldol adduct.[182] Interestingly, only one product diastereomer was formed, which represents resolution of aldehyde **183**. Deprotection of the secondary alcohol employing HF·pyridine finally afforded desired ketone **184** quantitatively. When the same transformation was attempted with TBAF, decomposition of the starting material was observed. For this epoxyisoprostane analog **184**, the relative configuration of the stereogenic center in the six-membered ring (marked with an asterisk) to the other stereogenic centers was not established.

As discussed above, diastereomeric sultams **185** and **186**, which were prepared following a similar approach as described above, as well as ketone **184** were examined as ester surrogates (Figure 2.8). All three compounds were isolated as single diastereomers, and the absolute configuration of sultam **185** was determined by X-ray crystallography. While one stereogenic center remained unassigned in ketone **184**, the relative configuration of the amide and alcohol stereogenic centers in sultam **186** was established to be *anti*, but the relationship to the γ-stereogenic center in the cyclopentenone was not determined. However, since the comparison of lactams **168** and **178** (Figure 2.7) showed that the stereogenic center in the six-membered ring was not crucial for the observed activity, these ambiguities were considered admissible.

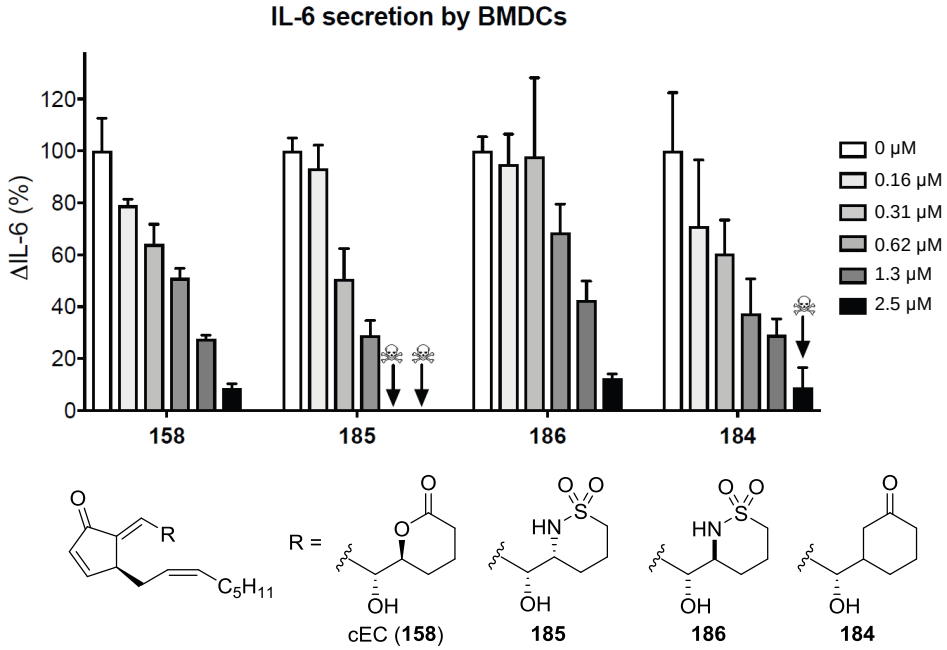
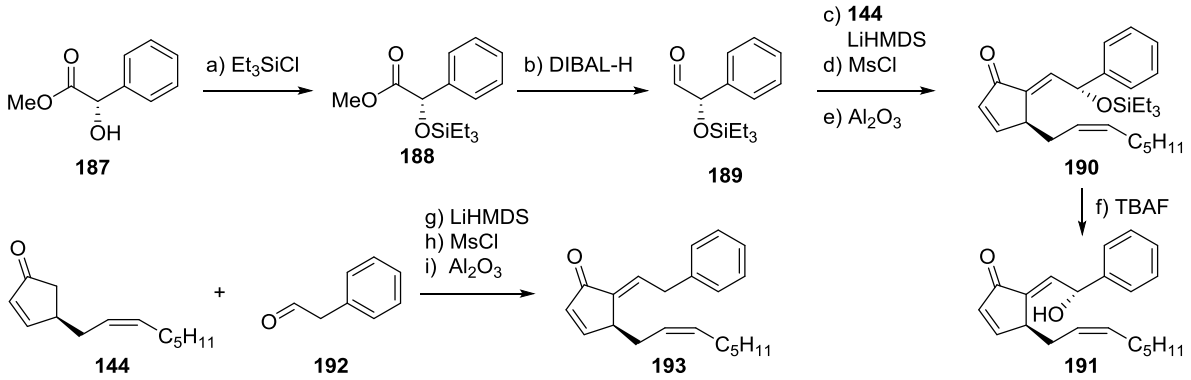



**Figure 2.8:** Comparison of the activity of cEC (**158**), sultams **185** and **186**, and ketone **184** in inhibiting secretion of the proinflammatory cytokine IL-6. Skull and crossbones indicate cytotoxicity at a specific concentration.

[182] C. Ebner, Diss. ETH No. 23711.

When subjected to the biological assay, sultam **185** displayed activity comparable to cEC (**158**), but cytotoxicity was observed at concentrations larger than 1 µM (Figure 2.8). Cytotoxicity at different concentrations was assessed with a viability dye that irreversibly labels intracellular proteins in dead cells and can be analyzed by flow cytometry. In contrast, diastereomeric sultam **186** was slightly less active, but not cytotoxic in the observed concentration range. Furthermore, ketone **184** also displayed potent anti-inflammatory activity as well as cytotoxicity at concentrations exceeding 2 µM. These results illustrate that the lactone in cEC (**158**) can indeed be replaced by a bioisosteric moiety, thus opening up possibilities for the design of potential therapeutics.

In follow-up studies, the effect of the secondary alcohol in the side chain of cEC (**158**) on the observed anti-inflammatory activity was examined. The deoxy derivatives **194** and **195** of cEC (**158**) and lactam **168**, the two most active compounds identified, were synthesized to systematically probe the importance of this allylic alcohol (Figure 2.9). Furthermore, in an attempt to isolate the effect of the latter moiety, the δ-lactone in both cEC (**158**) and its deoxy version was replaced by a phenyl group. The two phenyl compounds **191** and **193** were synthesized as illustrated in Scheme 2.14.




**Scheme 2.14:** Synthesis of phenyl analogs **191** and **193**. Reagents and conditions: a) $Et_3SiCl$ (1.5 equiv), imidazole (1.7 equiv), DMF, RT, 94%; b) DIBAL-H (1.2 equiv), $CH_2Cl_2$, –78 °C, 90%; c) **144** (1.0 equiv), LiHMDS (1.2 equiv), THF, –78 °C, then **189** (2.5 equiv); d) MsCl (5.7 equiv), $NEt_3$ (11 equiv), $CH_2Cl_2$, –78 °C to RT; e) $Al_2O_3$ (30 equiv), $CH_2Cl_2$, RT, 15% (3 steps); f) TBAF (1.2 equiv), THF, –40 °C, 90%; g) **144** (1.0 equiv), LiHMDS (1.2 equiv), THF, –78 °C, then **192** (2.5 equiv); h) MsCl (6.5 equiv), $NEt_3$ (10 equiv), $CH_2Cl_2$, –78 °C to RT; i) $Al_2O_3$ (20 equiv), $CH_2Cl_2$, RT, 15% (3 steps).

Commercially available alcohol **187** was protected as the corresponding silyl ether **188**.[183] Literature-known aldehyde **189** was then obtained upon reduction with DIBAL-H, and application of the standard aldol condensation protocol furnished silyl ether **190** in 15% yield.[184] Finally, the silyl ether was cleaved employing TBAF, affording dienone **191** in

[183] G. D. Joly, E. N. Jacobsen, *Org. Lett.* **2002**, *4*, 1795–1798.
[184] S. R. Angle, I. Choi, F. S. Tham, *J. Org. Chem.* **2008**, *73*, 6268–6278.

90% yield. Its deoxy analog **193** was obtained *via* aldol condensation of cyclopentenone **144** with 2-phenylacetaldehyde (**192**) in 15% yield.

Analysis of the data for cEC (**158**), deoxy-cEC **194**, lactam **168**, its deoxy analog **195**, and the two phenyl analogs **191** and **193** clearly showed that the presence of the allylic alcohol is crucial for potent activity (Figure 2.9). It is interesting to note that the phenyl analog **191** exhibited noticeable activity, while its deoxy version **193** was virtually inactive.

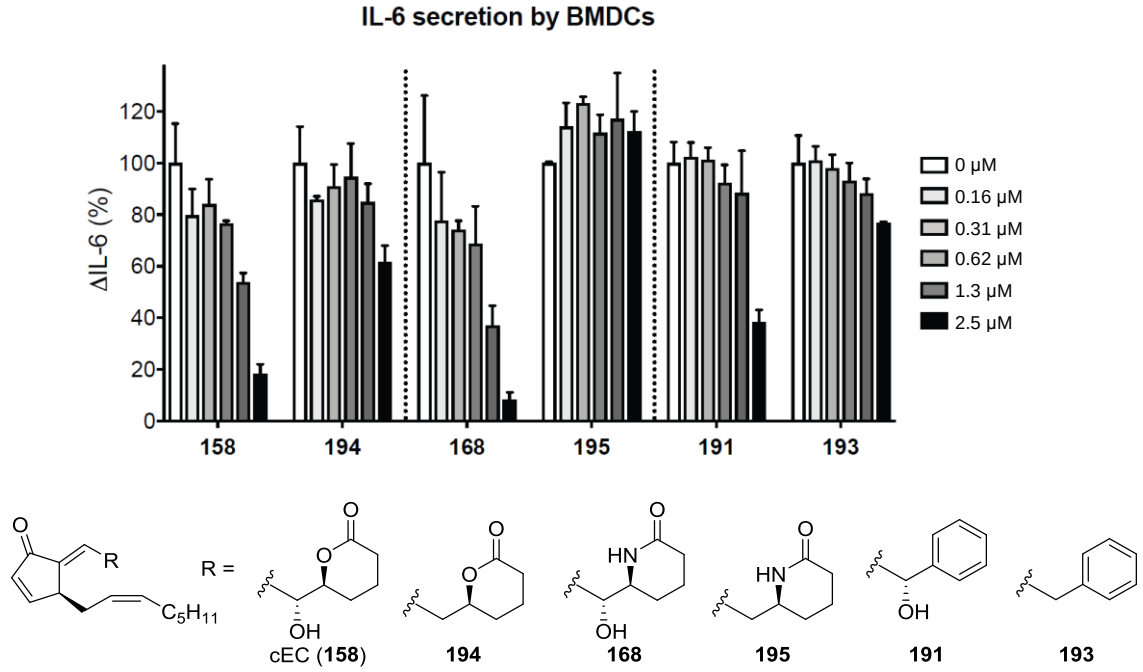



**Figure 2.9:** Comparison of the activity of cEC (**158**), **168**, and **191** and their deoxy analogs **194**, **195**, and **193** in inhibiting secretion of the proinflammatory cytokine IL-6.

Having explored the polar groups in the α-side chain of cEC (**158**), attention was next turned to the investigation of substituted, homologated or truncated analogs in order to assess the importance of the spatial arrangement of these functional groups (Figure 2.10). *N*-methylated lactam **196** was significantly less active than cEC (**158**), suggesting that additional steric bulk on the six-membered ring was not well tolerated. Furthermore, this analog displayed cytotoxicity at concentrations exceeding 2 μM. In contrast, γ-lactam **197** exhibited similar cytotoxic effects, but was almost as potent as cEC (**158**) in the non-toxic concentration range. Homologated lactones **198** and **199** were less active than their $C_{20}$ analog cEC (**158**), but interestingly, the configuration of the allylic alcohol appears to have no significant effect on the anti-inflammatory activity. Finally, exocyclic (*Z*)-enone **200** displayed decrease in potency, which was attributed to the profound change in the spatial arrangement of this compound.

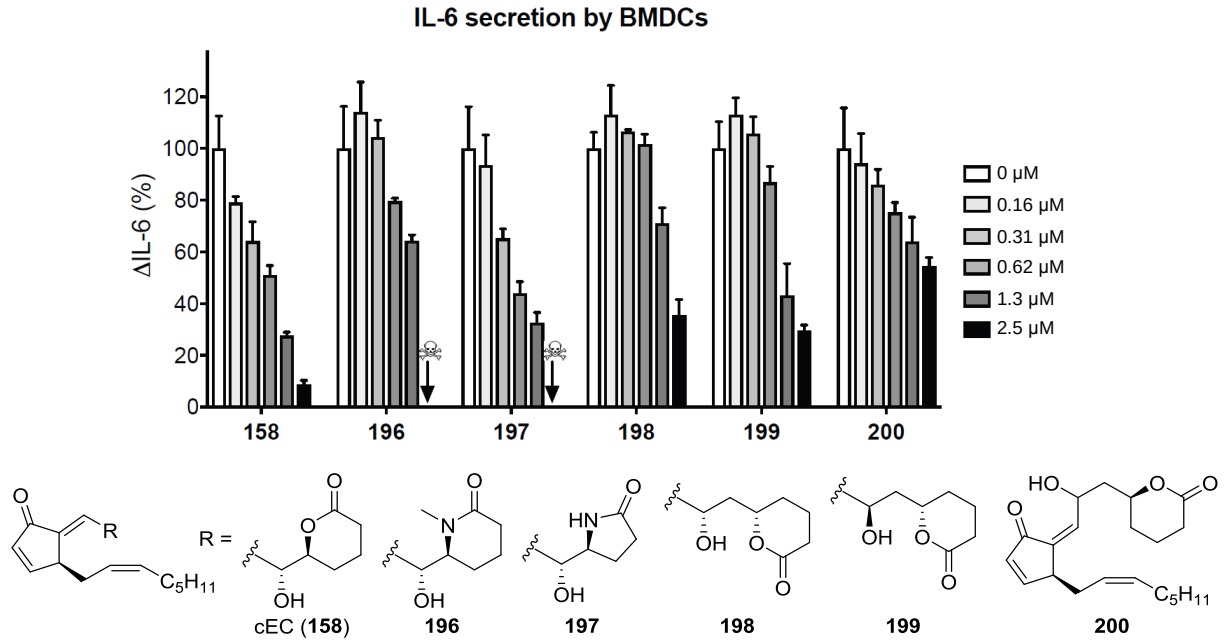
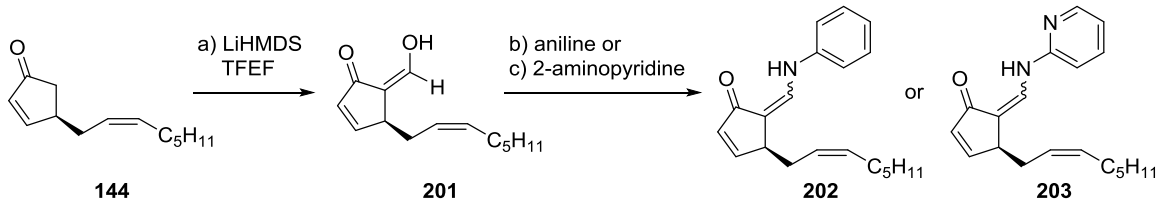



**Figure 2.10:** Comparison of the activity of cEC (**158**), **196**, **197**, **198**, **199**, and **200** in inhibiting secretion of the proinflammatory cytokine IL-6.

In an additional attempt to simplify the structure of the active compounds, exocyclic enaminones were investigated.[185] Their synthesis commenced with the formylation of cyclopentenone **144** (Scheme 2.15). As deprotonation of **144** with LiHMDS followed by addition of ethyl formate only resulted in decomposition or dimerization of the starting material, the protocol for direct formylation of ketone enolates reported by G. H. ZAYIA was investigated.[186] This method enables α-functionalization under conditions of kinetic control employing 2,2,2-trifluoroethyl formate (TFEF) as the formylating agent. Using these conditions, cyclopentenone **144** could be converted to enol **201**, albeit in only 26% yield. The latter was unstable and had to be used in the following transformation as quickly as possible. Condensation with aniline in the presence of catalytic *p*-toluenesulfonic acid monohydrate in ethanol then furnished enaminone **202** in 72% yield. $^1$H NMR analysis in $CDCl_3$ indicated that only the (*Z*)-enaminone was present. However, when the same measurement was repeated in DMSO-$d_6$, a (*Z*)/(*E*) ratio of 3:1 was observed, and at 80 °C, this ratio changed to 1.5:1. This finding indicates that the configuration adopted by enaminone **202** strongly depends on the environment. Also enaminone **203** was accessed, representing the only pyridine-containing analog in the series.

[185] I. O. Edafiogho, S. B. Kombian, K. V. V. Ananthalakshmi, N. N. Salama, N. D. Eddington, T. L. Wilson, M. S. Alexander, P. L. Jackson, C. D. Hanson, K. R. Scott, *J. Pharm. Sci.* **2007**, *96*, 2509–2531.
[186] G. H. Zayia, *Org. Lett.* **1999**, *1*, 989–991.




**Scheme 2.15:** Synthesis of enaminones **202** and **203**. Reagents and conditions: a) LiHMDS (1.2 equiv), TFEF (10 equiv), THF, –78 °C, 26%; b) aniline (1.0 equiv), *p*-TsOH·$H_2O$ (10 mol%), EtOH, RT, 72%; c) 2-aminopyridine (1.0 equiv), *p*-TsOH·$H_2O$ (10 mol%), EtOH, RT, yield not determined.

When these novel enaminone analogs were tested for their anti-inflammatory activity, no effect on the secretion of IL-6 was observed. Interestingly, phenyl analog **191** (Figure 2.9) is significantly more active than enaminone **202**, highlighting the importance of the spatial arrangement and of the allylic alcohol for the observed biological activity.

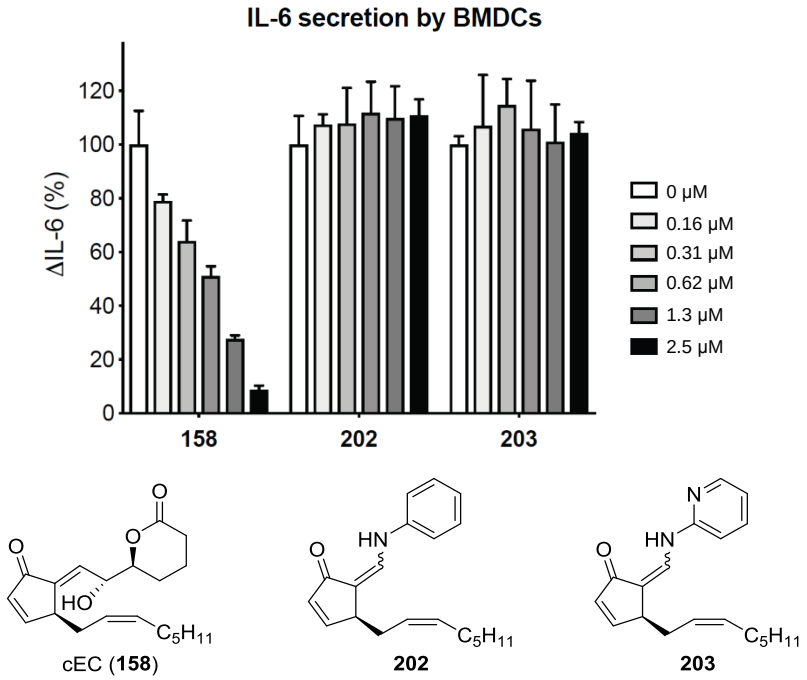



**Figure 2.11:** Comparison of the activity of cEC (**158**) and enaminones **202** and **203** in inhibiting secretion of the proinflammatory cytokine IL-6.

With this experiment, the structure–activity relationship studies designed to investigate the effect of the α-side chain of cEC (**158**) on the anti-inflammatory properties of this epoxyisoprostane derivative were concluded. It was demonstrated that lactam **168** slightly exceeds the high anti-inflammatory activity of cEC (**158**), and diastereomeric lactam **178**, ketone **184**, sultam **185**, as well as γ-lactam **197** displayed comparable potency. The study also emphasized the necessity of the side chain allylic alcohol for activity. Unfortunately, since no X-ray crystal structure of the relevant domain of the putative receptor Keap1 has been reported to date, molecular modeling studies were not possible. This circumstance hampered further investigations of the interactions responsible for the high activity of cEC (**158**).

### 2.2.3 Look from a Different Angle: Study with PONs

cEC (**158**) was investigated as a substrate of mammalian paraoxonases, a family of calcium-dependent esterases comprising the three isozymes PON 1, 2, and 3, in collaboration with the group of J. F. TEIBER.[187] All three PONs display antioxidative properties, but their physiological roles are uncertain. These enzymes, which are highly conserved within and between species, hydrolyze various esters including lactones and display distinct substrate specificities. Their native substrates are expected to be naturally occurring and to be efficiently metabolized by the corresponding PONs. However, no such compounds could be identified so far. Structure–activity relationship studies suggested that all three PONs share activity for lipophilic γ- and δ-lactones. Interestingly, it was shown that two endogenous oxidized PUFAs are efficiently metabolized by PON3, suggesting that such compounds may be native PON substrates.[188]

J. F. TEIBER and co-workers tested the ability of PON1, PON2, and PON3 to hydrolyze two derivatives of arachidonic acid (**118**), cEC (**158**) and 5,6-DHTL (**205**, Figure 2.12). While PON3 hydrolyzed both cEC (**158**) and 5,6-DHTL (**205**) with high efficiency as shown by HPLC analysis, PON2 was virtually inactive and PON1 exhibited moderate activity towards 5,6-DHTL (**205**), but none towards cEC (**158**). Furthermore, it was found that lactam analog **168** was not a substrate for PONs. The relative contribution of PONs to the hydrolysis of cEC (**158**) *in vivo* was tested by comparing the metabolic activity of human and mouse liver fractions towards lactone **158** in the presence and absence of EDTA. This chelating agent inhibits metal-dependent esterases such as the PONs. This experiment indicated that 80% of the cEC (**158**) hydrolytic activity in the liver is attributed to PON-mediated hydrolysis. This finding was further supported by the determination of the direct contribution of PON3 to cEC (**158**) hydrolysis. Wild type and PON3 knockout mouse liver homogenates were compared for their ability to hydrolyze cEC (**158**), demonstrating that the PON3 knockout liver homogenates only retained 20% of the wild type activity.

[187] D. I. Draganov, J. F. Teiber, A. Speelman, Y. Osawa, R. Sunahara, B. N. La Du, *J. Lipid Res.* **2005**, *46*, 1239–1247.

[188] a) J. F. Teiber, D. I. Draganov, B. N. L. Du, *Biochem. Pharmacol.* **2003**, *66*, 887–896; b) O. Khersonsky, D. S. Tawfik, *Biochemistry* **2005**, *44*, 6371–6382.

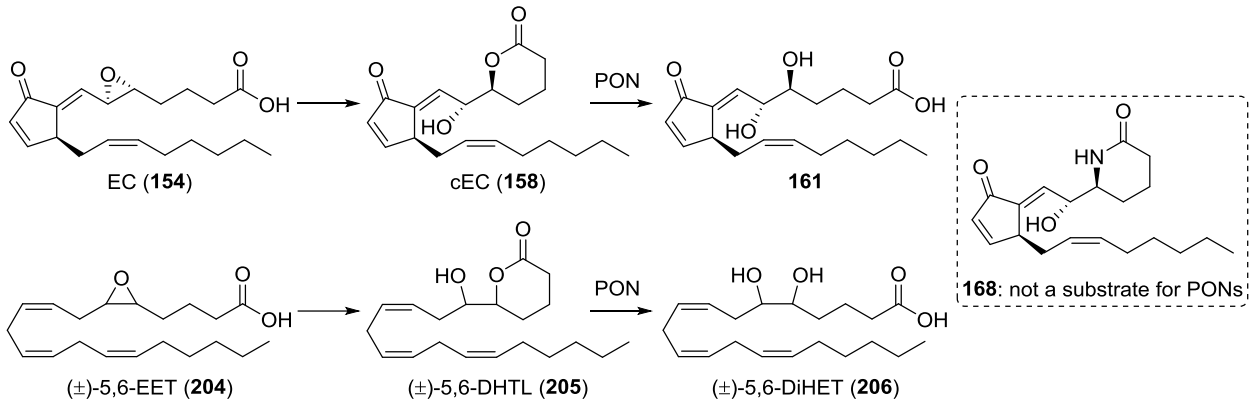



**Figure 2.12:** Evaluation of cEC (**158**) and 5,6-DHTL (**205**) as substrates for PONs.

These findings suggest that the ability of PONs to mediate inflammatory responses may result from their ability to metabolize a distinct class of signaling molecules. While the lactonization of EC (**154**) to cEC (**158**) has never been observed *in vivo*, 5,6-DHTL (**205**) was identified in mouse kidney, thereby demonstrating that such lactonizations can indeed occur under physiological conditions.[189] Hydrolysis by PON3 may thus be an important regulator of the activity of cEC (**158**), provided its natural occurrence. In combination with the fact that lactam **168** is not metabolized by PONs, this finding is important in view of future anti-inflammatory therapeutics. It might be possible to control the levels of anti-inflammatory lipid mediators by using metabolically stable synthetic analogs such as lactam **168**.

### 2.2.4 Conclusion

A structure–activity relationship study designed to investigate the effect of the cyclic side chain in cEC (**158**) on its anti-inflammatory properties was carried out. Lactam **168** was identified as an analog which retains the high activity. Furthermore, this analog was demonstrated to exhibit increased metabolic stability, thus representing an interesting scaffold for further investigation. However, such research efforts would greatly benefit from molecular modeling studies, which have so far been hampered by the lack of a suitable X-ray crystal structure of relevant receptor Keap1.

[189] S. Eryanni-Levin, S. Khatib, R. Levy-Rosenzvig, S. Tamir, A. Szuchman-Sapir, *Biochim. Biophys. Acta* **2015**, *1851*, 1118–1122.

## 2.3 Synthesis and Application of a Biotinylated EC Derivative

### 2.3.1 Synthesis of Biotinylated Analogs

While the structure–activity relationship study described in Section 2.2 provided insight into the structural requirements for active anti-inflammatory epoxyisoprostane analogs, elucidation of the molecular mechanisms involved in the signaling of this class of molecules derived from EC (**154**) required further investigation. Biotin has been established as a versatile tag for immunoprecipitation, a method using the specificity of antibodies to isolate target proteins from complex mixtures (*vide infra*), and other applications.[190] The success of this tool roots in the high binding affinity of biotin to streptavidin, which enables the formation of irreversible and specific linkages between biomolecules.[191] As a consequence, biotinylated EC analogs were identified as suitable bioorganic tools for the exploration of interaction partners of such isoprostanes in the cell.

Initial studies focused on the introduction of biotin on the ω side chain of lactam **158**, thus aiming to preserve the lactam moiety which had proven to induce excellent anti-inflammatory activity (Section 2.2.2). Biotin was envisioned to be installed *via* a copper-catalyzed azide–alkyne cycloaddition.[192] Such click reactions are easy to perform, are relatively unaffected by the nature of the substrates, and the resulting 1,2,3-triazoles display high chemical stability.[193] The synthesis commenced with terminal alkyne **207**, which was prepared by A. TRAJKOVSKI during his master thesis employing a route developed by C. EBNER (Scheme 2.16).[182,194] Aldol condensation with aldehyde **169** followed by deprotection as described above (Scheme 2.12) afforded lactam **208** in 13% yield over four steps. Required biotin derivative **209** was synthesized in two steps following a procedure reported by the group of S. LIU.[195] Finally, treatment of a mixture of alkyne **208** and azide **209** in $CH_2Cl_2$/MeOH (1:1) with a stoichiometric amount of $Cu(MeCN)_4PF_6$ at 40 °C furnished the corresponding triazole **210** in 94% yield as a yellowish solid.[196]

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[190] B. Kaboord, M. Perr in *2D PAGE: Sample Preparation and Fractionation* (Ed.: A. Posch), Humana Press, Totowa, NJ, **2008**, pp. 349–364.

[191] P. C. Weber, D. H. Ohlendorf, J. J. Wendoloski, F. R. Salemme, *Science* **1989**, *243*, 85–88.

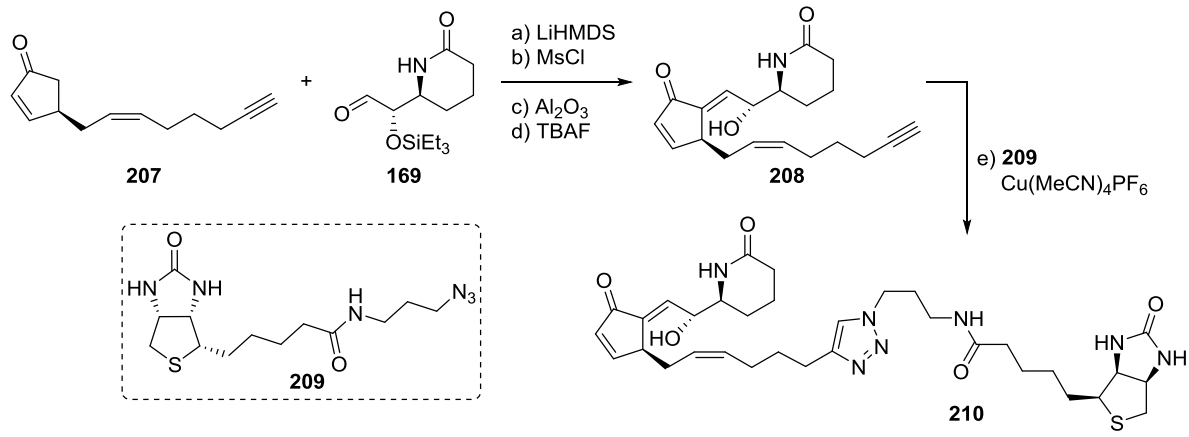
[192] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; b) P.-C. Lin, S.-H. Ueng, M.-C. Tseng, J.-L. Ko, K.-T. Huang, S.-C. Yu, A. K. Adak, Y.-J. Chen, C.-C. Lin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4286–4290.

[193] J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315.

[194] A. Trajkovski carried out synthetic studies towards Raman-active EC analogs in the group of E. M. Carreira in 2017.

[195] X. Wan, G. Zhang, Z. Ge, R. Narain, S. Liu, *Chem. Asian J.* **2011**, *6*, 2835–2845.

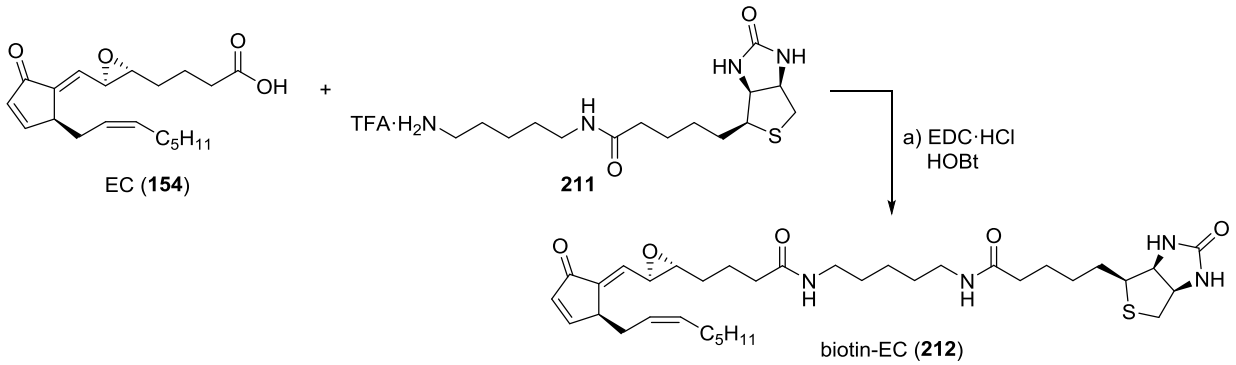
[196] F. Wang, P. Chen, G. Liu in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: A. Charette), Wiley, Chichester, **2017**, pp. 1–4.




**Scheme 2.16:** Synthesis of biotinylated lactam analog **210**. Reagents and conditions: a) **207** (1.0 equiv), LiHMDS (1.2 equiv), THF, –78 °C, then **169** (2.3 equiv); b) MsCl (6.0 equiv), $NEt_3$ (10 equiv), $CH_2Cl_2$, –78 °C to RT; c) $Al_2O_3$ (10 equiv), $CH_2Cl_2$, RT; d) TBAF (1.2 equiv), THF, –40 °C, 13% (4 steps); e) **209** (2.0 equiv), $Cu(MeCN)_4PF_6$ (1.0 equiv), $CH_2Cl_2$/MeOH (1:1), 40 °C, 94%.

Retention of activity is a prerequisite for biotinylated probes. Disappointingly, when biotinylated lactam analog **210** was tested for its ability to inhibit the secretion of the proinflammatory cytokine IL-6 by bone marrow-derived dendritic cells, no effect was observed (*vide infra*), thus rendering lactam **210** unusable for further investigations. Based on a report by the group of V. M. DARLEY–USMAR on the use of biotinylated 15d-$PGJ_2$ (**140**, Figure 2.3), biotinylation of EC (**154**) was envisaged as a viable alternative.[145]

In line with this plan, literature-known 5-(biotinamido)pentylamine (**211**) was accessed in two steps from D-bitoin following a procedure reported by K. TACHIBANA and co-workers (Scheme 2.17).[197] Coupling with EC (**154**) was mediated by EDC·HCl, HOBt, and triethylamine in DMF at ambient temperature. Due to difficulties encountered during chromatographic purification, biotin-EC (**212**) was isolated in 8% yield only.[198]




**Scheme 2.17:** Synthesis of biotin-EC (**212**). Reagents and conditions: a) EDC·HCl (2.0 equiv), HOBt·$H_2O$ (2.0 equiv), $NEt_3$ (24 equiv), DMF, RT, 8%.

[197] K. Konoki, N. Sugiyama, M. Murata, K. Tachibana, Y. Hatanaka, *Tetrahedron* **2000**, *56*, 9003–9014.
[198] HOBt was difficult to remove by normal-phase chromatography; preparative HPLC may be preferable.

Gratifyingly, biotin-EC (**212**) inhibited the secretion of IL-6 by bone marrow-derived dendritic cells (BMDCs), thus displaying the desired anti-inflammatory activity (Figure 2.13). While this analog was less potent than the parent EC (**154**), it was considered active enough for use in subsequent studies (*vide infra*).

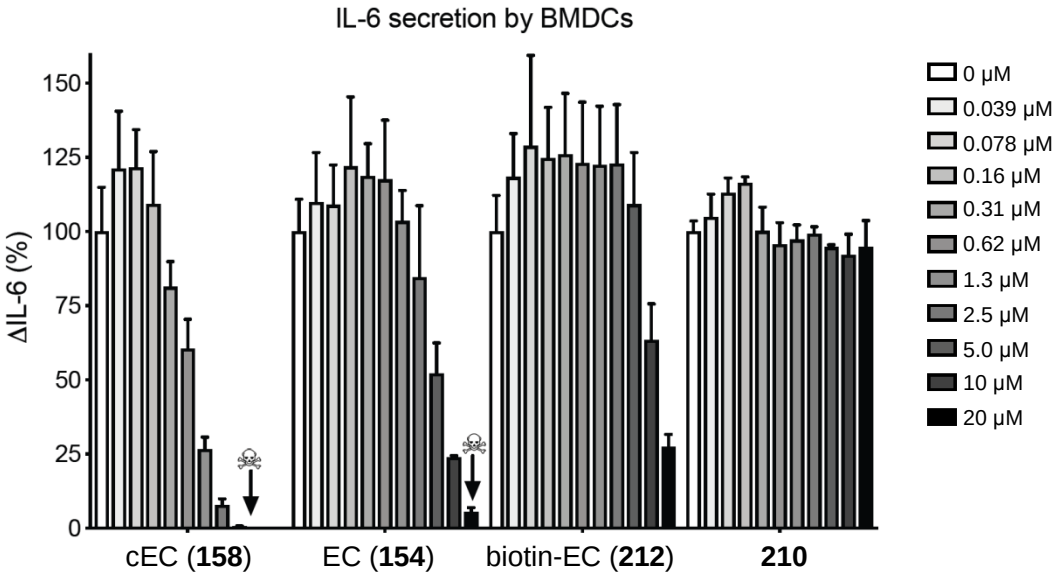



**Figure 2.13:** Comparison of the activity of cEC (**158**), EC (**154**), biotin-EC (**212**), and biotinylated lactam **210** in inhibiting secretion of the proinflammatory cytokine IL-6.

### 2.3.2 Cell Permeability Studies

The investigation of the molecular interactions of epoxyisoprostanes in the cell commenced with an experiment designed to disclose whether the oxidized lipids are taken up by BMDCs or whether they interacted with the cell surface.[199] Membrane permeabilization of fixed cells employing organic solvents or detergents is a common method to detect intracellular antigens.[200] Saponin, a detergent widely used for this purpose, interacts with membrane cholesterol and removes it, thus leaving holes in the membrane. Applying this method, BMDCs were treated with biotin-EC (**212**) for 5 minutes before being fixed with formaldehyde (Figure 2.14). Streptavidin conjugated to a fluorophore (peridinin-chlorophyll-protein) was added together with (*permeabilization*) or without (*control*) saponin. Thereby, the accessible biotinylated molecules were labeled with the fluorophore, taking advantage of the strong interaction of biotin with streptavidin. Subsequently, flow cytometric analysis was used to measure fluorophore intensity in and on the cells.[201] In the control experiment (Figure 2.14,

[199] This experiment was carried out by J. Muri in the laboratory of M. Kopf.
[200] M. C. Jamur, C. Oliver in *Immunocytochemical Methods and Protocols* (Eds.: C. Oliver, M. C. Jamur), Humana Press, Totowa, NJ, **2010**, pp. 63–66.
[201] J. Picot, C. L. Guerin, C. Le Van Kim, C. M. Boulanger, *Cytotechnology* **2012**, *64*, 109–130.

left), no fluorescence was detected, indicating that no biotin-EC (**212**) was bound to the cell surface. In contrast, fluorescence was detected in the permeabilized cells depending on the concentration of biotin-EC (**212**), demonstrating that the uptake of biotin-EC was very fast and complete within 5 minutes. It could therefore be concluded that epoxyisoprostanes rapidly enter the cells, which suggests that they exert their anti-inflammatory effects *via* interaction with intracellular receptors.

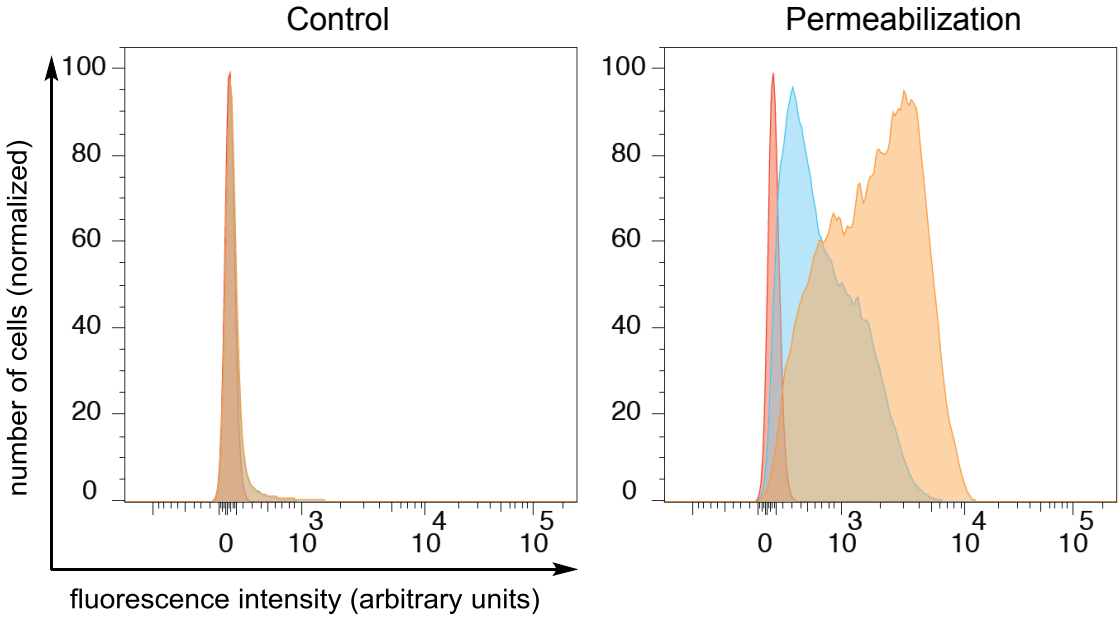



**Figure 2.14:** Cellular uptake of biotin-EC (**212**)**.** BMDCs were treated with biotin-EC (**212**) for 5 minutes and fixed with 1.6% formaldehyde for 10 minutes. Cells were subsequently stained with peridinin-chlorophyll-protein-conjugated streptavidin in staining buffer containing either none (*control*) or 0.5% saponin (*permeabilization*), and finally analyzed by flow cytometry. Red, blue and orange colors indicate none, 5 µM, and 15 µM biotin-EC (**212**). Data are representative of two independent experiments.

### 2.3.3 Pull-down Assay

Having demonstrated that epoxyisoprostanes can enter cells, it was tested whether they interact with intracellular target proteins. A pull-down assay was used to determine whether Keap1 was the relevant receptor as suggested by previous investigations.[147,202] Based on the report by V. M. DARLEY–USMAR and co-workers on the investigation of biotin-15d-$PGJ_2$ (**140**),[145] BMDCs were treated with biotin-EC (**212**) for one hour followed by cell lysis and immunoprecipitation using neutravidin beads, an immobilized modified version of avidin. Thereby, the proteins containing biotin were separated from the lysate due to the strong biotin–avidin interaction. The resulting biotin-containing proteins were subjected to SDS-PAGE, a variant of gel electrophoresis, thus separating them by their molecular masses in an electric

[202] A. Louche, S. P. Salcedo, S. Bigot in *Bacterial Protein Secretion Systems: Methods and Protocols* (Eds.: L. Journet, E. Cascales), Springer, New York, **2017**, pp. 247–255.

field. Subsequently, Keap1 was detected by western blotting.[203] In this method, a primary antibody, in this case anti-Keap1, labels the bands corresponding to the target protein. The labeled bands are then made visible using a secondary antibody conjugated to a protein that can be observed by spectrophotometric methods.

The results of this experiment are shown in Figure 2.15. Immunoprecipitation of biotin-containing proteins followed by western blot with anti-Keap1 antibody demonstrated that biotin-EC (**212**) binds to Keap1 (**A**, Figure 2.15). Importantly, when the cells were not treated with biotin-EC (**212**) prior to immunoprecipitation (0 µM), no Keap1 was detected by western blotting, confirming that the pull-down procedure selectively precipitated biotin-containing proteins. In a control experiment without immunoprecipitation (whole cell extract, **B**, Figure 2.15), Keap1 was detected in all cells, independently of the concentration of biotin-EC (**212**).

In summary, Keap1 was identified as a target protein of biotin-EC (**212**), thus confirming the hypothesis that such epoxyisoprostanes signal through the Keap1/Nrf2 pathway by alkylation of Keap1. However, other possible targets of biotin-EC (**212**) could not be detected by this method.

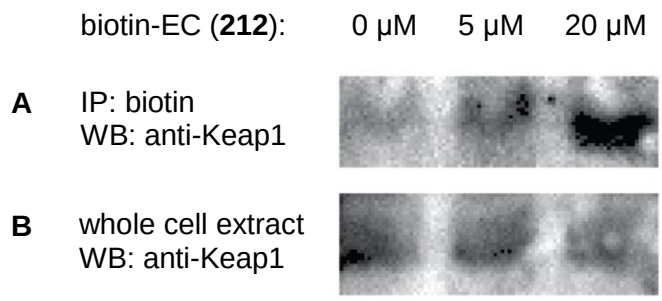



**Figure 2.15:** Co-immunoprecipitation of biotin-EC (**212**) and the Nrf2 inhibitor Keap1. BMDCs were treated for 1 hour with biotin-EC (**212**). Immunoprecipitation and western blotting were performed using neutravidin beads [Neutravidin Plus UltraLink Resin (#53151, ThermoScientific)] and a rabbit polyclonal anti-Keap1 antibody. Blot is a representative of two independent experiments. IP = immunoprecipitation; WB = western blot.

### 2.3.4 Comparison with Itaconate

In 2018, L. A. O'NEILL and co-workers reported a study on itaconate, an anti-inflammatory metabolite which activates Nrf2 *via* alkylation of Keap1.[204] The cell-permeable itaconate surrogate 4-octyl itaconate (**213**, Figure 2.16) was used to investigate the mechanism for the

[203] a) U. K. Laemmli, *Nature* **1970**, *227*, 680–685; b) H. Towbin, T. Staehelin, J. Gordon, *Proc. Natl. Acad. Sci. U. S. A.* **1979**, *76*, 4350–4354.

[204] E. L. Mills, D. G. Ryan, H. A. Prag, D. Dikovskaya, D. Menon, Z. Zaslona, M. P. Jedrychowski, A. S. H. Costa, M. Higgins, E. Hams, J. Szpyt, M. C. Runtsch, M. S. King, J. F. McGouran, R. Fischer, B. M. Kessler, A. F. McGettrick, M. M. Hughes, R. G. Carroll, L. M. Booty, E. V. Knatko, P. J. Meakin, M. L. J. Ashford, L. K. Modis, G. Brunori, D. C. Sévin, P. G. Fallon, S. T. Caldwell, E. R. S. Kunji, E. T. Chouchani, C. Frezza, A. T. Dinkova-Kostova, R. C. Hartley, M. P. Murphy, L. A. O'Neill, *Nature* **2018**, *556*, 113–117.

action of this endogenous metabolite, which has emerged as a regulator of macrophage function. It was demonstrated that 4-octyl itaconate (**213**) increases Nrf2 levels in mouse macrophages and exerts anti-inflammatory effects when used at non-cytotoxic concentrations. Interestingly, tandem mass spectrometry experiments revealed that 4-octyl itaconate modifies the Keap1 cysteine residues $Cys^{151}$, $Cys^{257}$, $Cys^{273}$, and $Cys^{288}$. Of note, this observation is in agreement with previous studies by the group of V. M. DARLEY–USMAR, who suggested $Cys^{273}$ and $Cys^{288}$ in Keap1 to be critical for sensing oxidative stress.

4-Octyl itaconate (**213**) and cEC (**158**) therefore exert their anti-inflammatory effects through the same Keap1/Nrf2 pathway. A comparative experiment was carried out to assess the relative activities of the two compounds (Figure 2.16).[199,205]

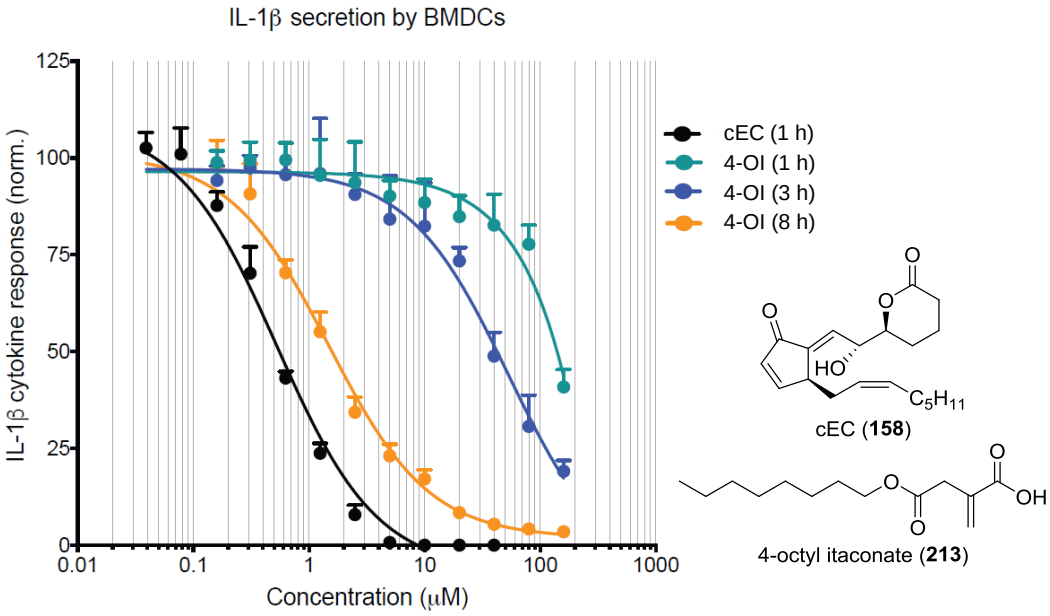



**Figure 2.16:** Anti-inflammatory activity of cEC (**158**) and 4-octyl itaconate (4-OI, **213**)**.** BMDCs were treated for the indicated time with either cEC (**158**) or 4-octyl itaconate (**213**) and stimulated with R837 (5 mg/mL) for 3 hours and with ATP (2 mM) for additional 45 minutes. Shown is the dose–response curve displaying Il-1β production. Mean + standard deviation of a triplicate is displayed. Data are representative of two independent experiments.

In contrast to all the previous experiments, which measured secretion of IL-6 and IL-12, the production of the proinflammatory cytokine IL-1β was analyzed. The dose–response curve of cEC (**158**) displaying the secretion of IL-1β by BMDCs is represented in black (Figure 2.16). Importantly, the cells were treated with cEC (**158**) for one hour prior to stimulation, which led to very efficient inhibition of IL-1β secretion. In contrast, when the cells were exposed to 4-octyl itaconate (**213**) for one hour, inhibition of the interleukin was only observed at very high concentrations (green). Increasing the exposure time to three or eight hours (blue or orange) enhanced the activity of 4-octyl itaconate (**213**), but even for long pre-treatments, the activity

[205] 4-Octyl itaconate (**213**) was prepared according to the procedure reported by L. A. O'Neill and co-workers.

was much lower than that of cEC (**158**). This finding once more demonstrated the pronounced anti-inflammatory properties of cEC (**158**).

### 2.3.5 Conclusion

Biotin-EC (**212**) served as a valuable tool for the investigation of the molecular mechanisms of this epoxyisoprostane. In a first experiment, cell permeabilization studies showed that biotin-EC (**212**) rapidly enters bone marrow-derived dendritic cells, suggesting that the isoprostanes exert their anti-inflammatory activities by interacting with intracellular receptors. Secondly, a pull-down assay confirmed Keap1 as a target protein of biotin-EC (**212**), a finding which is in accordance with previous studies on cyclopentenone isoprostanes. Having gained insight into the mechanisms for the action of these oxidized lipids, cEC (**158**) was compared to 4-octyl itaconate (**213**), which was reported to act through the same pathway. This comparative study further confirmed the high potency of cEC (**158**).

## 2.4 Conclusion and Outlook

In conclusion, the studies directed at the investigation of the anti-inflammatory epoxyisoprostane EC (**154**) and its highly potent lactone derivative cEC (**158**) provided numerous valuable insights. A structure–activity relationship study directed at the exploration of the cyclic side chain in cEC (**158**) was enabled by the modular synthesis of analogs, which allowed flexible variations of the parent lactone. This study identified a lactam analog **168** that retains the high activity and is metabolically more stable than cEC (**158**), thus representing a potential scaffold for future anti-inflammatory therapeutics. Furthermore, the allylic alcohol in the side chain was demonstrated to be crucial for anti-inflammatory activity. In a second part, a biotinylated analog of EC (**154**) was synthesized and served as a useful tool for the investigation of the molecular mechanisms of such epoxyisoprostanes. Namely, biotin-EC (**212**) was applied in cell permeabilization experiments and pull-down assays, which confirmed the hypothesis that these cyclopentenone isoprostanes exert their anti-inflammatory activities by signaling through the Keap1/Nrf2 pathway.

Further investigations of this intriguing family of natural products are ongoing in the laboratories of E. M. CARREIRA and M. KOPF. While the ability of cEC (**158**) and OxPAPC to inhibit secretion of the proinflammatory cytokines IL-6 and IL-12 has been demonstrated and explored,[147] a publication by the group of J. C. KAGAN in 2016 led to a shift in research focus.[206] In this report, OxPAPC was described to induce production of the proinflammatory cytokine IL-1β and to thus have the opposite effect to the anti-inflammatory activity described by the group of M. KOPF. Furthermore, this release of IL-1β was reported to be dependent on caspase 11, a receptor protease which is activated by Toll-like receptor signaling. Caspases are involved in the release of IL-1β from its precursor pro-IL-1β.[207] Moreover, J. C. KAGAN and co-workers reported OxPAPC to induce IL-1β production without concomitant cell death through pyroptosis.

Recently, the group of M. KOPF set out to investigate whether cEC (**158**) also exerted the aforementioned proinflammatory activities. However, when bone marrow-derived dendritic cells were treated with either cEC (**158**) or OxPAPC for one hour prior to stimulation with Toll-like receptor ligand R837 or lipopolysaccharide, IL-1β production was inhibited similarly to IL-6 and

[206] a) I. Zanoni, Y. Tan, M. Di Gioia, A. Broggi, J. Ruan, J. Shi, C. A. Donado, F. Shao, H. Wu, J. R. Springstead, J. C. Kagan, *Science* **2016**, *352*, 1232–1236; b) I. Zanoni, Y. Tan, M. Di Gioia, J. R. Springstead, J. C. Kagan, *Immunity* **2017**, *47*, 697–709.

[207] a) R. G. Snodgrass, S. Huang, I.-W. Choi, J. C. Rutledge, D. H. Hwang, *J. Immunol.* **2013**, *191*, 4337–4347; b) C. L. Evavold, J. C. Kagan, *J. Mol. Biol.* **2018**, *430*, 217–237.

IL-12, which contrasted the work by J. C. KAGAN. On the other hand, when the cells were first stimulated with lipopolysaccharide for three hours and subsequently treated with cEC (**158**) in high concentrations (10 μM) for 16 hours, IL-1β production was induced. Intriguingly, the cells died during IL-1β production, a finding which contradicts the report by J. C. KAGAN and co-workers. These observations may be explained by the following mechanism. First, a Toll-like receptor is activated, which induces production of pro-IL-1β. Second, cEC (**158**) mediates the activation of the inflammasome, a multiprotein oligomer activating inflammatory responses,[208] which leads to the release of a caspase that then cleaves the pro-form to IL-1β. The observation that no IL-1β production occurred in the presence of caspase inhibitors supported this hypothesis. Interestingly, IL-1β production induced by cEC (**158**) was found to be independent of caspases 1 and 11, which is in disagreement with the work of J. C. KAGAN. The possibility of caspase 8 being active in the observed pathway is currently under investigation in the laboratory of M. KOPF.

These new findings demonstrate that cEC (**158**) can elicit different contrasting biological activities depending on the concentrations and conditions employed during an experiment. This intriguing property is the subject of ongoing studies, which will result in a deeper understanding of this interesting class of lipid mediators.

[208] F. Martinon, K. Burns, J. Tschopp, *Molecular Cell* **2002**, *10*, 417-426.

# 3

# *Experimental Part*

# 3. Experimental Part

## 3.1 General Methods and Materials

**General Procedures.** All non-aqueous reactions were performed under an inert atmosphere of dry nitrogen in flame dried glassware sealed with a rubber septum unless stated otherwise. Nitrogen was supplied through a glass manifold. Reactions were stirred magnetically and monitored by thin layer chromatography (TLC). Analytical thin layer chromatography was performed using MERCK Silica Gel F254 TLC glass plates and visualized by ultraviolet light (UV). Additionally, TLC plates were stained with aqueous potassium permanganate ($KMnO_4$) [1.5 g $KMnO_4$, 200 mL $H_2O$, 10 g $K_2CO_3$, 1.25 mL 10% NaOH], cerium ammonium molybdate (CAM) [0.5 g $Ce(NH_4)_2(NO_3)_6$, 12 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 235 mL $H_2O$, 15 mL conc. $H_2SO_4$] or dinitrophenylhydrazine (DNP) [12 g 2,4-dinitrophenylhydrazine, 60 mL conc. $H_2SO_4$, 80 mL $H_2O$, 200 mL EtOH]. Concentration under reduced pressure was performed by rotator evaporation at 40 °C at the appropriate pressure. Chromatographic purification was performed as flash chromatography on SIGMA-ALDRICH silica gel 60 Å (230–400 mesh) at 0.2–0.5 bar overpressure.[209] Purified compounds were dried further under high vacuum (0.01–0.1 mbar). Yields refer to the purified compound.

**Chemicals.** All chemicals and solvents were purchased from ABCR, ACROS, ALFA-AESAR, COMBI-BLOCKS, FLUKA, FLUOROCHEM, MERCK, TCI or SIGMA-ALDRICH and were used as received from the commercial supplier without further purification unless mentioned otherwise. THF, $Et_2O$, MeCN, and $CH_2Cl_2$ were dried using an LC TECHNOLOGY SOLUTIONS *SP-1* solvent purification system under an atmosphere of dry $N_2$. Deuterated solvents were obtained from ARMAR CHEMICALS. Pyridine and diisopropylamine were distilled from KOH under an atmosphere of dry nitrogen. Triethylamine was distilled from $CaH_2$ under an atmosphere of dry nitrogen.

**Analytics.** Nuclear Magnetic Resonance (NMR) spectra were recorded on VARIAN MERCURY (300 MHz), BRUKER AV and DRX (400 MHz), BRUKER AV (500 MHz) or BRUKER AVIII (600 MHz with cryoprobe) spectrometers. Measurements were carried out at ambient temperature (ca. 22 °C). Chemical shifts ($\delta$) are reported in ppm with the residual solvent signal as internal standard (chloroform: 7.26 and 77.00 ppm for $^1$H NMR and $^{13}$C NMR spectroscopy, respectively; benzene: 7.16 and 128.06 ppm; methanol: 3.31 and 49.00 ppm; pyridine: 7.22 and 123.87 ppm). The data is reported as $\delta$ (s = singlet, d = doublet, t = triplet, q = quartet,

[209] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

p = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). $^{13}$C NMR spectra were recorded with broadband $^{1}$H decoupling. Service measurements were performed by the NMR service team of the *Laboratorium für Organische Chemie* at ETH ZURICH by Mr. RENÉ ARNOLD, Mr. RAINER FRANKENSTEIN and Mr. STEPHAN BURKHARDT under direction of Dr. MARC-OLIVIER EBERT.

Infrared (IR) spectra were recorded on a PERKIN ELMER TWO-FT-IR (UATR) as thin films. Absorptions are given in wavenumbers ($cm^{-1}$).

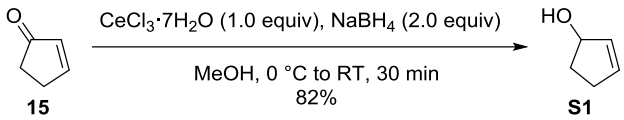
High resolution mass spectrometry (HRMS) analyses were performed as EI measurements on a WATERS MICROMASS AUTOSPEC ULTIMA at 70 eV, as ESI measurements on a BRUKER DALTONICS MAXIS (UHR-TOF) or as MALDI measurements on a BRUKER DALTONICS SOLARIX instrument by the mass spectrometry service of the *Laboratorium für Organische Chemie* at ETH ZURICH by Mr. LOUIS BERTSCHI, Mr. OSWALD GRETER, Mr. ROLF HÄFLIGER and Mr. DANIEL WIRZ under direction of Dr. BERTRAN RUBI and Dr. XIANGYANG ZHANG.

Optical rotations ($[\alpha]_D^T$) were measured on a JASCO P-2000 polarimeter at the indicated temperature and concentration (c = 1.00 corresponding to 10.0 mg/mL) and with the specified solvent.

X-ray diffraction experiments were carried out by Dr. NIELS TRAPP and Mr. MICHAEL SOLAR on a BRUKER APEX2 DUO (Cu) diffractometer at the *Laboratorium für Organische Chemie* at ETH ZURICH. The data obtained was deposited at the Cambridge Crystallographic Data Centre.

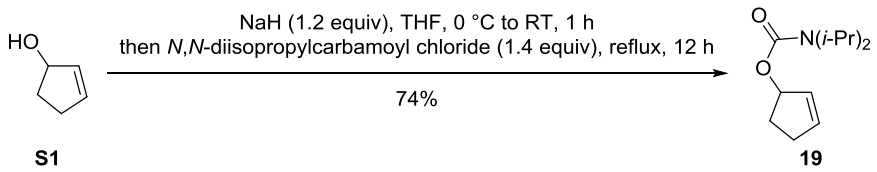
## 3.2 Experimental Part for the Total Synthesis of (+)-Dendrowardol C

### 3.2.1 Experimental Procedures for the First-Generation Approach




**Cyclopent-2-en-1-ol (S1).** According to a procedure reported by J.-C. FIAUD and co-workers,[17] cyclopent-2-enone (**15**) (2.04 mL, 24.4 mmol, 1.0 equiv) was added to a solution of $CeCl_3 \cdot 7H_2O$ (9.2 g, 24.7 mmol, 1.0 equiv) in MeOH (40 mL). The resulting yellowish solution was stirred at ambient temperature for 5 min before it was cooled to 0 °C and sodium borohydride (1.84 g, 48.7 mmol, 2.0 equiv) was added in portions over a period of 10 min. The resulting white suspension was then stirred at ambient temperature for 15 min. Water (40 mL) was added until the mixture became clear. It was extracted with diethyl ether (3 x 100 mL), and the combined organic phases were washed with NaCl solution (50 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford alcohol **S1** (1.7 g, 82%) as a yellow oil.

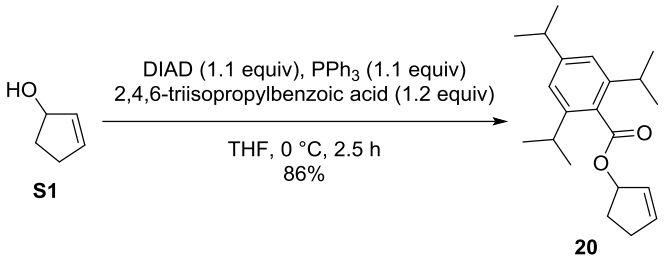
**TLC:** $R_f$ = 0.44 (EtOAc/hexane, 10:90; DNP); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.99 (dd, $J$ = 5.5, 2.5 Hz, 1H), 5.84 (dd, $J$ = 5.5, 2.4 Hz, 1H), 4.87 (d, $J$ = 6.5 Hz, 1H), 2.61–2.38 (m, 1H), 2.37–2.07 (m, 2H), 1.92–1.30 (m, 2H). According to the spectral data reported in the literature.[17]




**Cyclopent-2-en-1-yl diisopropylcarbamate (19).** A solution of alcohol **S1** (419 mg, 4.98 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 239 mg, 5.98 mmol, 1.2 equiv) in THF (10 mL) at 0 °C. The resulting suspension was stirred at ambient temperature for 1 h. Then, *N*,*N*-diisopropylcarbamoyl chloride (1.14 g, 6.97 mmol, 1.4 equiv) was added in portions over 5 min, and the resulting turbid brown reaction mixture was stirred at reflux temperature for 12 h. It was then cooled to 0 °C and quenched with phosphate buffer pH 7 (10 mL). The mixture was brought to pH 7 by the addition of 1 M HCl, and the organic solvent was removed under reduced pressure. The remaining mixture was extracted with diethyl ether (3 x 20 mL), and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced

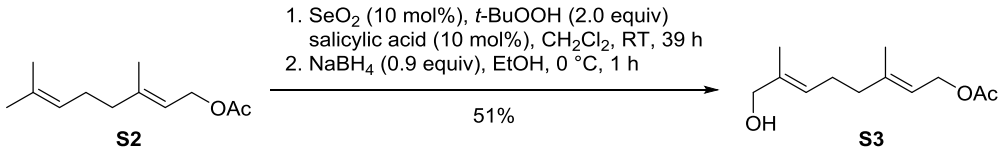
pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded carbamate **19** (783 mg, 74%) as a clear oil.

**TLC:** $R_f$ = 0.40 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 6.04 (dt, $J$ = 5.2, 2.2 Hz, 1H), 5.89–5.83 (m, 1H), 5.71–5.63 (m, 1H), 4.23–3.44 (m, 2H), 2.48 (dddd, $J$ = 15.5, 8.7, 3.9, 1.7 Hz, 1H), 2.36–2.18 (m, 2H), 1.90–1.74 (m, 1H), 1.17 (dd, $J$ = 6.8, 2.7 Hz, 12H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 155.8, 136.3, 130.3, 80.2, 45.4, 31.0, 30.1, 21.0; **IR** (thin film): 2969, 2935, 1683, 1435, 1367, 1343, 1286, 1132, 1048, 1039, 772 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{12}H_{21}NNaO_2$ [$(M+Na)^+$] 234.1464, found 234.1461.




**Cyclopent-2-en-1-yl 2,4,6-triisopropylbenzoate (20).** Over a period of 10 min, DIAD (1.27 mL, 6.54 mmol, 1.1 equiv) was added dropwise to a solution of alcohol **S1** (0.500 g, 5.94 mmol, 1.0 equiv), triphenylphosphine (1.72 g, 6.56 mmol, 1.1 equiv) and 2,4,6-triisopropylbenzoic acid (1.70 g, 6.84 mmol, 1.2 equiv) in THF (9 mL) at 0 °C. The resulting clear colorless reaction mixture was stirred at 0 °C for 2.5 h before it was concentrated under reduced pressure. The residue was taken up in pentane (10 mL), stirred for 5 min, filtered to remove triphenylphosphine oxide and washed with pentane (60 mL). The filtrate was concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded ester **20** (1.61 g, 86%) as a colorless oil.

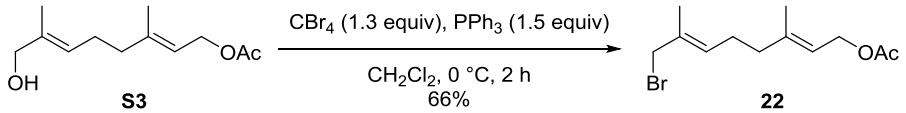
**TLC:** $R_f$ = 0.59 (EtOAc/hexane, 5:95; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 6.99 (s, 2H), 6.15 (dt, $J$ = 5.3, 2.1 Hz, 1H), 6.01–5.91 (m, 2H), 2.97–2.81 (m, 3H), 2.60–2.45 (m, 1H), 2.43–2.26 (m, 2H), 2.05–1.89 (m, 1H), 1.28–1.20 (m, 18H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 170.7, 150.0, 144.7, 138.0, 130.7, 129.1, 120.8, 81.0, 34.4, 31.3, 31.1, 29.8, 24.1, 24.1, 24.0; **IR** (thin film): 2960, 2930, 2870, 1720, 1607, 1460, 1250, 1137, 1075, 1027, 877 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{21}H_{30}NaO_2$ [$(M+Na)^+$] 337.2138, found 337.2139.




**S2** **S3**

**(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (S3).** Similar to a procedure reported by F.-E. CHEN and co-workers,[20] selenium dioxide (283 mg, 2.55 mmol, 10 mol%) and *tert*-butyl hydroperoxide (70% in water, 7.1 mL, 51 mmol, 2.0 equiv) were added sequentially to a solution of salicylic acid (352 mg, 2.55 mmol, 10 mol%) in $CH_2Cl_2$ (30 mL). The resulting turbid mixture was stirred at ambient temperature for 15 min before a solution of acetate **S2** (5.16 mL, 25.5 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) was added dropwise. The resulting reaction mixture was stirred at ambient temperature for 39 h. It was then diluted with diethyl ether (300 mL) and sequentially washed with 10% KOH solution (3 x 100 mL), water (3 x 100 mL) and NaCl solution (2 x 100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil. This crude product was taken up in EtOH (44 mL) and cooled to 0 °C. Sodium borohydride (825 mg, 21.8 mmol, 0.9 equiv) was added in portions over 10 min and the resulting clear yellow reaction mixture was stirred at 0 °C for 1 h. It was then quenched with $NH_4Cl$ solution (50 mL, sat. aqueous) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with water (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 40:60) afforded primary alcohol **S3** (2.78 g, 51%) as a colorless oil.

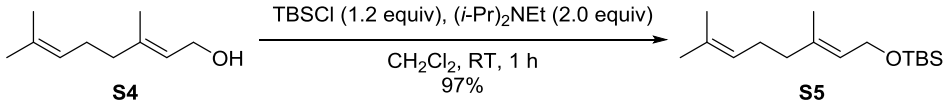
**TLC:** $R_f$ = 0.43 (EtOAc/hexane, 40:60; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.40–5.28 (m, 2H), 4.58 (d, $J$ = 7.1 Hz, 2H), 3.99 (s, 2H), 2.22–2.07 (m, 4H), 2.05 (s, 3H), 1.70 (d, $J$ = 1.2 Hz, 3H), 1.66 (d, $J$ = 1.2 Hz, 3H), 1.45 (s, br, 1H). According to the spectral data reported in the literature.[20]




**S3** **22**

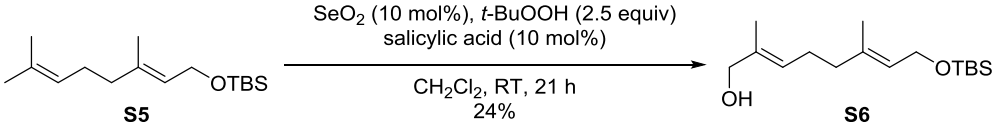
**(2*E*,6*E*)-8-Bromo-3,7-dimethylocta-2,6-dien-1-yl acetate (22).** Carbon tetrabromide (1.13 g, 3.40 mmol, 1.3 equiv) and triphenylphosphine (1.03 g, 3.93 mmol, 1.5 equiv) were added sequentially to a solution of alcohol **S3** (555 mg, 2.61 mmol, 1.0 equiv) in $CH_2Cl_2$ (6 mL) at 0 °C. The resulting turbid orange reaction mixture was stirred at 0 °C for 2 h before it was filtered through a short plug of celite eluting with $CH_2Cl_2$ and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded bromide **22** (474 mg, 66%) as a yellow oil.

**TLC:** $R_f$ = 0.46 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.63–5.50 (m, 1H), 5.34 (ddt, $J$ = 8.4, 7.1, 1.3 Hz, 1H), 4.58 (d, $J$ = 7.0 Hz, 2H), 3.96 (s, 2H), 2.22–2.04 (m, 7H), 1.75 (d, $J$ = 1.2 Hz, 3H), 1.70 (d, $J$ = 1.2 Hz, 3H). According to the spectral data reported in the literature.[20]




**(E)-*tert*-Butyl((3,7-dimethylocta-2,6-dien-1-yl)oxy)dimethylsilane (S5).** According to a procedure reported by H. WALDMANN and co-workers,[31] to a solution of geraniol (**S4**) (10 mL, 57 mmol, 1.0 equiv) in $CH_2Cl_2$ (57 mL) at ambient temperature was added diisopropylethylamine (20 mL, 114 mmol, 2.0 equiv), followed by *tert*-butyldimethylsilyl chloride (10 g, 69 mmol, 1.2 equiv). The resulting clear colorless reaction mixture was stirred at ambient temperature for 1 h before it was quenched with $NH_4Cl$ solution (40 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with $CH_2Cl_2$ (3 x 100 mL) and the combined organic extracts were washed with NaCl solution (100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane to EtOAc/hexane, 10:90) afforded silyl ether **S5** (15 g, 97%) as a yellowish oil.

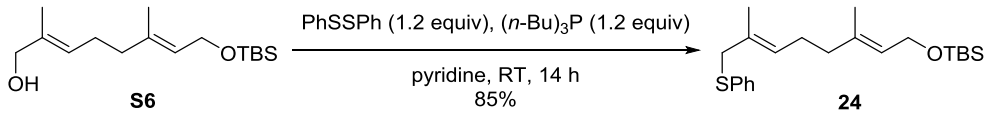
**TLC:** $R_f$ = 0.88 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.37–5.24 (m, 1H), 5.16–5.02 (m, 1H), 4.19 (dd, $J$ = 6.3, 0.9 Hz, 2H), 2.16–1.94 (m, 4H), 1.68 (d, $J$ = 1.2 Hz, 3H), 1.62 (d, $J$ = 1.2 Hz, 3H), 1.61–1.59 (m, 3H), 0.91 (s, 9H), 0.07 (s, 6H). According to the spectral data reported in the literature.[31]




**(2*E*,6*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylocta-2,6-dien-1-ol (S6).** Similar to a procedure reported by F.-E. CHEN and co-workers,[20] selenium dioxide (0.36 g, 3.2 mmol, 10 mol%) and *tert*-butyl hydroperoxide (70% in water, 11 mL, 81 mmol, 2.5 equiv) were added sequentially to a solution of salicylic acid (0.45 g, 3.2 mmol, 10 mol%) in $CH_2Cl_2$ (30 mL). The resulting turbid mixture was stirred at ambient temperature for 15 min before a solution of silyl ether **S5** (8.7 g, 32 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) was added dropwise. The resulting reaction mixture was stirred at ambient temperature for 21 h. It was then diluted with diethyl ether (300 mL) and sequentially washed with $NaHCO_3$ solution (100 mL, sat. aqueous), water

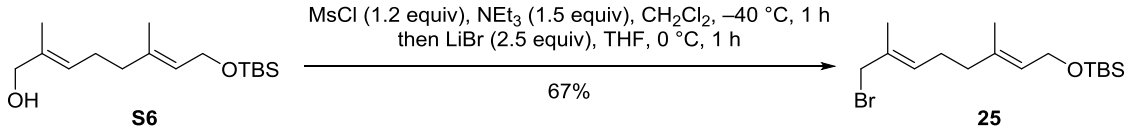
(100 mL) and NaCl solution (100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography (EtOAc/hexane, 10:90) afforded primary alcohol **S6** (2.2 g, 24%).

**TLC:** $R_f$ = 0.12 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.43–5.34 (m, 1H), 5.34–5.26 (m, 1H), 4.19 (dd, $J$ = 6.4, 0.9 Hz, 2H), 3.98 (s, 2H), 2.21–1.99 (m, 4H), 1.69–1.64 (m, 3H), 1.62 (d, $J$ = 0.8 Hz, 3H), 1.39 (s, br, 1H), 0.90 (s, 9H), 0.07 (s, 6H). According to the spectral data reported in the literature.[31]




***tert*-Butyl(((2*E*,6*E*)-3,7-dimethyl-8-(phenylthio)octa-2,6-dien-1-yl)oxy)dimethylsilane (24).** A solution of alcohol **S6** (0.500 g, 1.78 mmol, 1.0 equiv) in pyridine (0.3 mL) was added dropwise to a solution of diphenyl disulfide (460 mg, 2.11 mmol, 1.2 equiv) and tri-*n*-butylphosphine (0.52 mL, 2.1 mmol, 1.2 equiv) in pyridine (0.3 mL) at ambient temperature. The resulting clear yellow reaction mixture was stirred at ambient temperature for 14 h before it was cooled to 0 °C and quenched with water (5 mL). The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were sequentially washed with $NH_4Cl$ solution (20 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96, then again 2:98) afforded sulfide **24** (564 mg, 85%) as a colorless oil.

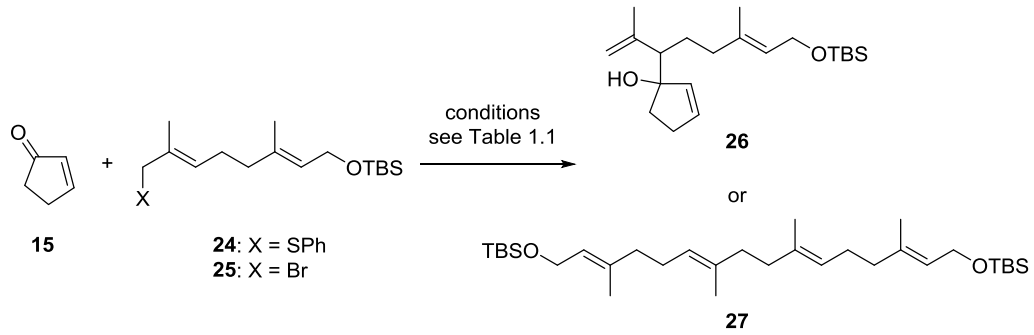
**TLC:** $R_f$ = 0.61 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 7.37–7.32 (m, 2H), 7.32–7.25 (m, 2H), 7.20 (dd, $J$ = 7.6, 6.9 Hz, 1H), 5.32–5.20 (m, 2H), 4.20 (dd, $J$ = 6.3, 0.9 Hz, 2H), 3.51 (d, $J$ = 1.0 Hz, 2H), 2.14–2.05 (m, 2H), 1.93 (dd, $J$ = 8.9, 6.6 Hz, 2H), 1.79–1.73 (m, 3H), 1.62–1.59 (m, 3H), 0.93 (s, 9H), 0.09 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 136.5, 136.5, 130.5, 130.4, 128.6, 128.5, 126.2, 124.6, 60.3, 44.3, 39.0, 26.4, 26.0, 18.4, 16.3, 15.2, –5.0; **IR** (thin film): 2954, 2928, 2856, 1438, 1253, 1108, 1060, 834, 775, 738, 690 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{22}H_{36}NaOSSi$ [$(M+Na)^+$] 399.2148, found 399.2145.




**(((2*E*,6*E*)-8-Bromo-3,7-dimethylocta-2,6-dien-1-yl)oxy)(tert-butyl)dimethylsilane (25).** Methanesulfonyl chloride (0.13 mL, 1.7 mmol, 1.2 equiv) was added dropwise to a solution of

alcohol **S6** (400 mg, 1.41 mmol, 1.0 equiv) and triethylamine (0.29 mL, 2.1 mmol, 1.5 equiv) in $CH_2Cl_2$ (2.8 mL) at –40 °C. The resulting white suspension was stirred at this temperature for 1 h before it was allowed to warm to 0 °C and a solution of lithium bromide (305 mg, 3.51 mmol, 2.5 equiv) in THF (1.7 mL) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 1 h and then poured on water (3 mL). The phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were washed with NaCl solution (10 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded bromide **25** (326 mg, 67%) as a colorless oil.

**TLC:** $R_f$ = 0.84 (EtOAc/hexane, 10:90; UV, CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.58 (t, $J$ = 6.2 Hz, 1H), 5.34–5.27 (m, 1H), 4.19 (dd, $J$ = 6.2, 0.9 Hz, 2H), 3.96 (s, 2H), 2.17–2.12 (m, 2H), 2.05 (dd, $J$ = 8.9, 6.2 Hz, 2H), 1.75 (d, $J$ = 1.1 Hz, 3H), 1.62 (d, $J$ = 1.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 136.0, 132.1, 130.9, 125.0, 60.3, 41.7, 38.6, 26.5, 26.0, 18.4, 16.3, 14.7, –5.0; **IR** (thin film): 2954, 2928, 2856, 1439, 1253, 1109, 1060, 834, 775 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{16}H_{32}BrOSi$ [$(M+H)^+$] 347.1400, found 347.1394.

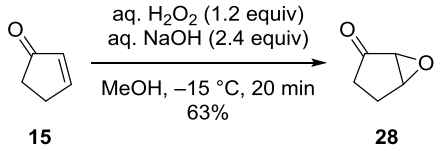



**(*E*)-1-(8-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylocta-1,6-dien-3-yl)cyclopent-2-en-1-ol (26).** Allylic alcohol **26** was isolated as a 1.2:1 mixture of diastereomers.

**$^1$H NMR** (400 MHz, $CDCl_3$, all peaks reported): $\delta$ 5.91 (ddt, $J$ = 8.0, 5.6, 2.3 Hz, 1H), 5.78 (dt, $J$ = 5.7, 2.2 Hz, 0.54H), 5.62 (dt, $J$ = 5.7, 2.2 Hz, 0.44H), 5.29 (ddt, $J$ = 7.8, 4.9, 1.3 Hz, 1H), 5.03–4.92 (m, 1H), 4.85–5.80 (m, 1H), 4.18 (d, $J$ = 6.3 Hz, 2H), 2.59–2.41 (m, 1H), 2.34–2.20 (m, 2H), 2.11 (dddd, $J$ = 13.4, 8.7, 7.1, 4.9 Hz, 1H), 2.03–1.92 (m, 1H), 1.90–1.68 (m, 5H), 1.64–1.48 (m, 5H), 0.90 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, all peaks reported): $\delta$ 145.3, 145.3, 136.8, 136.8, ,136.1, 135.0, 134.0, 133.9, 124.6, 124.6, 115.6, 115.5, 87.2, 87.2, 60.3, 56.2, 55.4, 37.6, 37.6, 37.3, 35.7, 31.5, 31.0, 26.1, 26.0, 25.7, 21.1, 21.0, 18.4, 16.4, 16.3, –5.0; **IR** (thin film): 3461, 2951, 2928, 2855, 1639, 1462, 1375, 1253, 1058, 834, 774 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{21}H_{38}NaO_2Si$ [$(M+Na)^+$] 373.2533, found 373.2537.

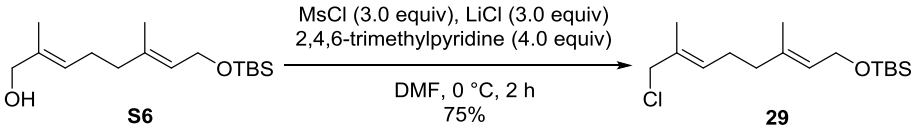
**(6*E*,10*E*,14*E*,18*E*)-2,2,3,3,7,11,14,18,22,22,23,23-Dodecamethyl-4,21-dioxa-3,22-disila-tetracosa-6,10,14,18-tetraene (27).**

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.35–5.26 (m, 2H), 5.18–5.02 (m, 2H), 4.22–4.16 (m, 4H), 2.14–1.95 (m, 12H), 1.64–1.58 (m, 12H), 0.91 (s, 18H), 0.07 (s, 12H); **HRMS** (MALDI): exact mass calculated for $C_{32}H_{66}NO_2Si_2$ $[(M+NH_4)^+]$ 552.4627, found 552.4623.




**6-Oxabicyclo[3.1.0]hexan-2-one (28).** According to a procedure reported by Y. TAMURA and co-workers,[30] hydrogen peroxide (30% in water, 4.4 mL, 43 mmol, 1.2 equiv) was added to a solution of cyclopent-2-enone (**15**) (3.0 mL, 36 mmol, 1.0 equiv) in MeOH (180 mL) at –15 °C. 6 N NaOH (14 mL, 86 mmol, 2.4 equiv) was added dropwise, while care was taken not to let the temperature rise above –10 °C. The resulting colorless reaction mixture was stirred at –15 °C for 20 min before it was poured into ice-cold water (150 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 200 mL). The combined organic phases were washed with NaCl solution (100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (diethyl ether/pentane, 40:60) afforded epoxide **28** (2.2 g, 63%) as a yellowish oil.

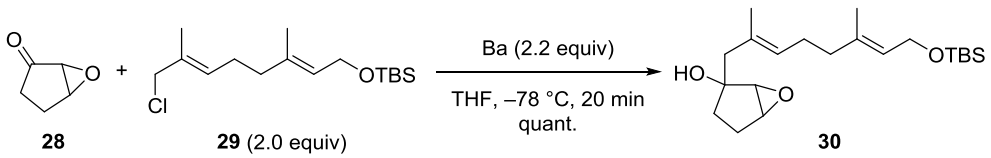
**TLC:** $R_f$ = 0.40 (diethyl ether/pentane, 40:60; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 3.92–3.88 (m, 1H), 3.30 (d, $J$ = 2.3 Hz, 1H), 2.45–2.20 (m, 2H), 2.15–1.93 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 210.0, 57.8, 54.8, 30.5, 23.1; **IR** (thin film): 2942, 1742, 1448, 1410, 1371, 1258, 1199, 1176, 967, 840, 803 $cm^{-1}$; **HRMS** (EI): exact mass calculated for $C_5H_6O_2$ $[M^+]$ 98.0363, found 98.0367.




***tert*-Butyl(((2*E*,6*E*)-8-chloro-3,7-dimethylocta-2,6-dien-1-yl)oxy)dimethylsilane (29).** Similar to a procedure reported by B. G. DAVIS and co-workers,[31] methanesulfonyl chloride (1.23 mL, 15.8 mmol, 3.0 equiv) was added dropwise to a mixture of alcohol **S6** (1.5 g, 5.3 mmol, 1.0 equiv), lithium chloride (0.67 g, 16 mmol, 3.0 equiv) and 2,4,6-trimethylpyridine (2.8 mL, 21 mmol, 4.0 equiv) in DMF (20 mL) at –3 °C. The resulting yellow suspension was stirred at 0 °C for 2 h. It was then poured onto ice-cold $NaHCO_3$ solution (20 mL, sat. aqueous) and the

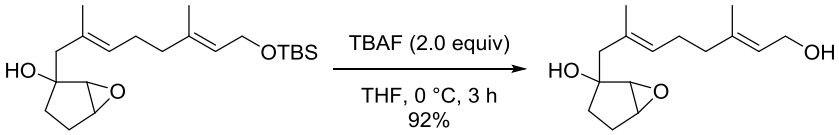
aqueous phase was extracted with hexane/diethyl ether (1:1 v/v, 3 x 80 mL). The combined organic phases were sequentially washed with $NH_4Cl$ solution (80 mL, sat. aqueous) and NaCl solution (80 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded chloride **29** (1.2 g, 75%) as a yellowish oil.

**TLC:** $R_f$ = 0.84 (EtOAc/hexane, 10:90; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.51 (dddt, $J$ = 8.1, 6.7, 2.3, 1.0 Hz, 1H), 5.31 (ddq, $J$ = 7.6, 4.6, 1.3 Hz, 1H), 4.22–4.17 (m, 2H), 4.01 (d, $J$ = 0.7 Hz, 2H), 2.21–2.12 (m, 2H), 2.09–2.00 (m, 2H), 1.76–1.72 (m, 3H), 1.65–1.61 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 136.1, 131.8, 130.4, 124.9, 60.3, 52.5, 38.7, 26.3, 26.0, 18.4, 16.3, 14.1, –5.1; **IR** (thin film): 2929, 2856, 1669, 1472, 1463, 1387, 1361, 1254, 1109, 1061, 1006, 834, 813, 774, 684 cm$^{-1}$.




**2-((2*E*,6*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)-6-oxabicyclo-[3.1.0]hexan-2-ol (30).** Biphenyl (723 mg, 4.69 mmol, 4.6 equiv) and lithium (31 mg, 4.5 mmol, 4.4 equiv) were placed in a Schlenk flask under argon atmosphere. THF (10 mL) was added, and the resulting mixture was sonicated at ca. 10 °C for 2 h to afford a dark blue-green solution. In a separate Schlenk flask, barium iodide (877 mg, 2.24 mmol, 2.2 equiv) was dissolved in THF (10 mL) and stirred for 5 min at ambient temperature. To the resulting clear solution was added the lithium biphenylide solution via cannula. The reaction mixture was stirred at ambient temperature for 30 min to afford a dark brown suspension which was then cooled to –78 °C. A solution of chloride **29** (618 mg, 2.04 mmol, 2.0 equiv) in THF (3.4 mL) was added dropwise, and the resulting deep red reaction mixture was stirred at –78 °C for 20 min. Then, a solution of ketone **28** (100 mg, 1.02 mmol, 1.0 equiv) in THF (2 mL) was added dropwise, and the clear reaction mixture became less intensely red. The reaction mixture was stirred at –78 °C for 20 min before it was quenched with $NH_4Cl$ solution (25 mL, sat. aqueous), allowed to warm to ambient temperature and extracted with diethyl ether (3 x 100 mL). The combined organic phases were sequentially washed with 1 N $Na_2S_2O_3$ solution (50 mL) and NaCl solution (80 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane to EtOAc/hexane, 10:90 to 20:80) afforded tertiary alcohol **30** (371 mg, quant.) as a clear yellow oil.

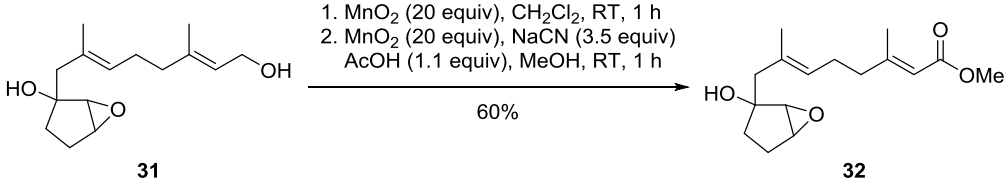
**TLC:** $R_f$ = 0.33 (EtOAc/hexane, 40:60; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.30 (tdd, $J$ = 5.6, 5.1, 2.6, 1.4 Hz, 1H), 5.25–5.17 (m, 1H), 4.21–4.16 (m, 2H), 3.47–3.43 (m, 1H), 3.26 (d, $J$ = 2.7 Hz, 1H), 2.29–2.20 (m, 2H), 2.20–2.11 (m, 1H), 2.11–2.00 (m, 4H), 1.92 (s, br, 1H), 1.78–1.67 (m, 4H), 1.65–1.50 (m, 4H), 1.39–1.28 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 136.5, 131.1, 129.4, 124.7, 80.2, 61.8, 60.3, 56.4, 46.2, 39.3, 31.9, 26.3, 26.3, 26.0, 18.4, 18.3, 16.3, –5.1; **IR** (thin film): 2934, 1738, 1416, 1246, 1207, 1148, 1126, 944, 890, 877, 845, 612 cm$^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{21}H_{39}O_3Si$ [$(M+H)^+$] 367.2663, found 367.2665.




**30** **31**

**2-((2*E*,6*E*)-8-Hydroxy-2,6-dimethylocta-2,6-dien-1-yl)-6-oxabicyclo[3.1.0]hexan-2-ol (31).** TBAF (1 M in THF, 0.61 mL, 0.61 mmol, 2.0 equiv) was added dropwise to a solution of silyl ether **30** (111 mg, 0.303 mmol, 1.0 equiv) in THF (5.5 mL) at 0 °C. The resulting clear colorless reaction mixture was stirred at 0 °C for 3 h before it was quenched with $NH_4Cl$ solution (5 mL, sat. aqueous), diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 70:30) afforded alcohol **31** (70 mg, 92%) as a yellowish oil.

**TLC:** $R_f$ = 0.47 (EtOAc/hexane, 70:30; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.40 (ddq, $J$ = 6.9, 5.4, 1.4 Hz, 1H), 5.26–5.13 (m, 1H), 4.16–4.12 (m, 2H), 3.45 (d, $J$ = 2.7 Hz, 1H), 3.27 (d, $J$ = 2.7 Hz, 1H), 2.25–2.14 (m, 4H), 2.14–2.05 (m, 3H), 1.75 (d, $J$ = 1.2 Hz, 3H), 1.70–1.64 (m, 4H), 1.64–1.51 (m, 1H), 1.42–1.30 (m, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 139.0, 131.3, 129.3, 124.1, 80.0, 61.6, 59.3, 56.3, 46.2, 39.2, 31.9, 26.2, 26.1, 18.4, 16.0; **IR** (thin film): 3383, 2923, 1441, 1383, 1177, 1118, 983, 925, 852, 552 cm$^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{15}H_{25}O_3$ [$(M+H)^+$] 253.1798, found 253.1800.



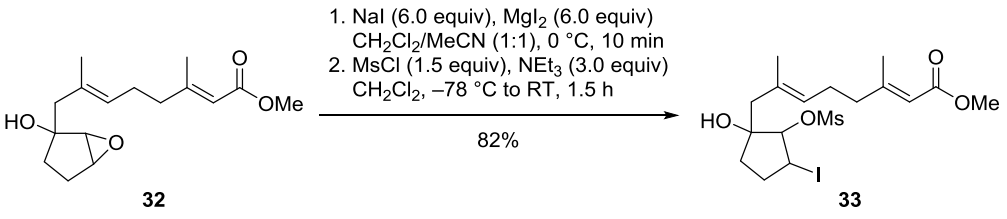

**31** **32**

**Methyl (2*E*,6*E*)-8-(2-hydroxy-6-oxabicyclo[3.1.0]hexan-2-yl)-3,7-dimethylocta-2,6-dienoate (32).** Manganese dioxide (517 mg, 5.94 mmol, 20 equiv) was added to a solution of alcohol **31**

(75 mg, 0.30 mmol, 1.0 equiv) in $CH_2Cl_2$ (2.3 mL) at ambient temperature. The resulting black suspension was stirred at ambient temperature for 1 h and then filtered through a short plug of celite eluting with $CH_2Cl_2$. The resulting solution was concentrated under reduced pressure to afford the corresponding aldehyde (63 mg). The crude product was used in the next transformation without further purification.

The above product was dissolved in MeOH (2.3 mL), and manganese dioxide (517 mg, 5.94 mmol, 20 equiv), sodium cyanide (51 mg, 1.0 mmol, 3.5 equiv) and acetic acid (19 µL, 0.33 mmol, 1.1 equiv) were added sequentially. The resulting black suspension was stirred at ambient temperature for 1 h before it was filtered through a short plug of celite eluting with $CH_2Cl_2$ and concentrated under reduced pressure. The resulting residue was taken up in water (10 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic phases were washed with NaCl solution (30 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 40:60) afforded methyl ester **32** (50 mg, 60% over two steps) as a yellow oil.

**TLC:** $R_f$ = 0.56 (EtOAc/hexane, 70:30; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.67 (d, $J$ = 1.2 Hz, 1H), 5.22–5.13 (m, 1H), 3.68 (s, 3H), 3.45 (ddd, $J$ = 2.6, 1.3, 0.6 Hz, 1H), 3.26 (d, $J$ = 2.8 Hz, 1H), 2.29–2.18 (m, 6H), 2.16 (d, $J$ = 1.3 Hz, 3H), 2.12–2.01 (m, 1H), 1.88–1.82 (m, 1H), 1.79–1.72 (m, 3H), 1.73–1.66 (m, 1H), 1.56 (dddd, $J$ = 14.2, 10.0, 8.6, 1.3 Hz, 1H), 1.38–1.21 (m, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 167.1, 159.6, 132.2, 128.0, 115.5, 80.3, 61.8, 56.5, 50.8, 46.1, 40.6, 32.0, 26.3, 25.9, 18.7, 18.2; **IR** (thin film): 3485, 2948, 2926, 2856, 1716, 1648, 1435, 1385, 1358, 1223, 1146, 1079, 852, 551 cm$^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{16}H_{25}O_4$ [$(M+H)^+$] 281.1747, found 281.1749.




32 33

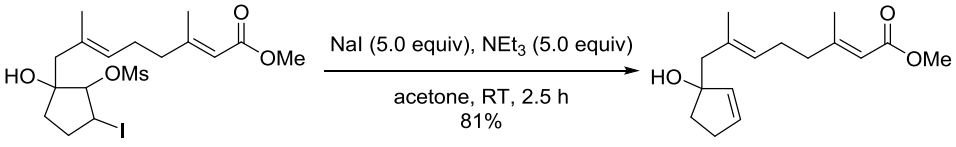
**Methyl (2*E*,6*E*)-8-(1-hydroxy-3-iodo-2-((methylsulfonyl)oxy)cyclopentyl)-3,7-dimethyl-octa-2,6-dienoate (33).** To a solution of epoxide **32** (40 mg, 0.14 mmol, 1.0 equiv) in $CH_2Cl_2$/MeCN (1:1 v/v, 16 mL) at 0 °C was added sodium iodide (128 mg, 0.856 mmol, 6.0 equiv), followed by magnesium iodide (238 mg, 0.856 mmol, 6.0 equiv). The resulting yellowish reaction mixture was stirred in the dark at 0 °C for 10 min. It was then filtered through a short plug of silica gel eluting with EtOAc/hexane (70:30) and concentrated under reduced

pressure to afford the corresponding iodide (54 mg) as a yellow oil. The crude product was used in the following step without further purification.

**TLC:** $R_f$ = 0.74 (EtOAc/hexane, 70:30; UV, $KMnO_4$); **HRMS** (MALDI): exact mass calculated for $C_{16}H_{26}IO_4$ [$(M+H)^+$] 409.0870, found 409.0870.

The above product (54 mg) was dissolved in $CH_2Cl_2$ (1.2 mL) and cooled to –78 °C. A solution of methanesulfonyl chloride (17 µL, 0.21 mmol, 1.5 equiv) in $CH_2Cl_2$ (0.4 mL) was added, and the mixture was stirred at –78 °C for 5 min. Then, a solution of triethylamine (60 µL, 0.43 mmol, 3.0 equiv) in $CH_2Cl_2$ (0.8 mL) was added dropwise over 10 min, and the resulting colorless reaction mixture was stirred at –78 °C for 1 h. It was then allowed to warm to ambient temperature over 30 min. The reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ solution (2 mL, sat. aqueous), diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were sequentially washed with $Na_2S_2O_3$ solution (10 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 40:60) afforded mesylate **33** (57 mg, 82% over two steps) as a yellow oil.

**TLC:** $R_f$ = 0.18 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.71–5.62 (m, 1H), 5.25–5.16 (m, 1H), 4.85 (d, $J$ = 8.5 Hz, 1H), 4.32 (app q, $J$ = 8.5 Hz, 1H), 3.68 (s, 3H), 3.28 (s, 3H), 2.60–2.42 (m, 2H), 2.25–2.17 (m, 5H), 2.15 (d, $J$ = 1.3 Hz, 3H), 2.11–2.00 (m, 1H), 2.00–1.95 (m, 1H), 1.95–1.83 (m, 1H), 1.78 (dd, $J$ = 9.0, 5.2 Hz, 1H), 1.72 (d, $J$ = 1.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 167.1, 159.6, 131.8, 128.8, 115.5, 94.2, 78.5, 50.8, 48.2, 40.5, 40.0, 34.2, 32.8, 26.0, 21.9, 18.7, 18.0; **IR** (thin film): 3504, 2947, 2855, 1716, 1648, 1436, 1358, 1224, 1175, 1147, 957, 849, 532 $cm^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{17}H_{28}IO_6S$ [$(M+H)^+$] 487.0646, found 487.0648.

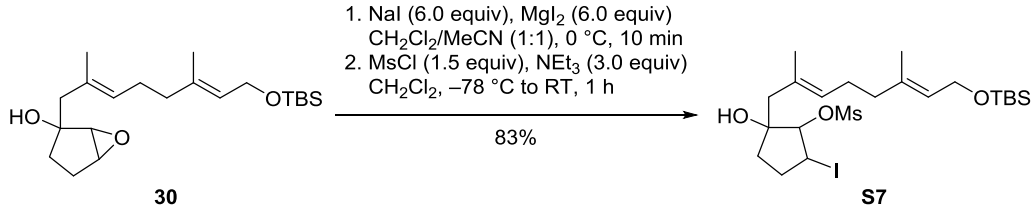



**33** **34**

**Methyl (2*E*,6*E*)-8-(1-hydroxycyclopent-2-en-1-yl)-3,7-dimethylocta-2,6-dienoate (34).** Triethylamine (43 µL, 0.31 mmol, 5.0 equiv) and sodium iodide (46 mg, 0.31 mmol, 5.0 equiv) were added to a solution of iodide **33** (30 mg, 62 µmol, 1.0 equiv) in acetone (2.7 mL) at ambient temperature. The resulting first colorless, then dark orange reaction mixture was stirred at ambient temperature for 2.5 h before it was concentrated under reduced pressure and the residue was taken up in EtOAc (100 mL). The organic phase was sequentially washed with $Na_2S_2O_3$ solution (30 mL, sat. aqueous), $NH_4Cl$ solution (30 mL, sat. aqueous) and NaCl

solution (30 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 30:70) afforded alkene **34** (13 mg, 81%) as a yellow oil.

**TLC:** $R_f$ = 0.67 (EtOAc/hexane, 70:30; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.78 (q, $J$ = 1.3 Hz, 1H), 5.66–5.59 (m, 2H), 5.05 (app ddt, $J$ = 7.1, 5.9, 1.3 Hz, 1H), 3.43 (s, 3H), 2.33–2.21 (m, 3H), 2.17 (d, $J$ = 1.3 Hz, 3H), 2.11–2.01 (m, 1H), 2.01–1.81 (m, 5H), 1.74 (ddd, $J$ = 13.3, 8.6, 4.7 Hz, 1H), 1.67–1.60 (m, 3H), 1.32 (s, br, 1H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 166.8, 159.5, 137.8, 133.9, 132.3, 127.7, 116.1, 85.3, 50.9, 50.5, 40.7, 38.3, 31.2, 26.2, 18.7, 18.3; **IR** (thin film): 3427, 2925, 2852, 1719, 1649, 1435, 1358, 1223, 1146, 1057, 746 cm$^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{16}H_{25}O_3$ [(M+H)$^+$] 265.1799, found 265.1798.



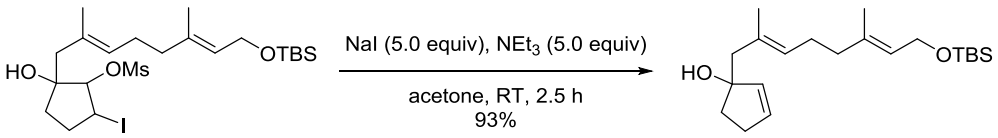

**2-((2*E*,6*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)-2-hydroxy-5-iodocyclopentyl methanesulfonate (S7).** To a solution of epoxide **30** (40 mg, 0.11 mmol, 1.0 equiv) in $CH_2Cl_2$/MeCN (1:1 v/v, 12 mL) at 0 °C was added sodium iodide (98 mg, 0.67 mmol, 6.0 equiv), followed by magnesium iodide (182 mg, 0.655 mmol, 6.0 equiv). The resulting yellowish reaction mixture was stirred in the dark at 0 °C for 10 min. It was then filtered through a short plug of silica gel eluting with EtOAc/hexane (70:30) and concentrated under reduced pressure to afford the corresponding iodide (50 mg) as a yellow oil. The crude product was used in the following step without further purification.

**TLC:** $R_f$ = 0.38 (EtOAc/hexane, 50:50; UV, $KMnO_4$).

The above product (50 mg) was dissolved in $CH_2Cl_2$ (0.9 mL) and cooled to –78 °C. A solution of methanesulfonyl chloride (13 µL, 0.16 mmol, 1.5 equiv) in $CH_2Cl_2$ (0.3 mL) was added, and the mixture was stirred at –78 °C for 5 min. Then, a solution of triethylamine (46 µL, 0.33 mmol, 3.0 equiv) in $CH_2Cl_2$ (0.6 mL) was added dropwise over 10 min, and the resulting colorless reaction mixture was stirred at –78 °C for 30 min. It was then allowed to warm to ambient temperature over 15 min. The reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ solution (1.5 mL, sat. aqueous), diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were sequentially washed with $Na_2S_2O_3$ solution (10 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and

concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded mesylate **S7** (52 mg, 83% over two steps) as a yellowish oil.

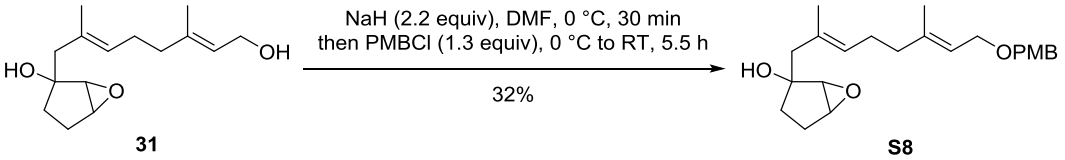
**TLC:** $R_f$ = 0.17 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.33–5.27 (m, 1H), 5.27–5.20 (m, 1H), 4.85 (d, $J$ = 8.3 Hz, 1H), 4.33 (dt, $J$ = 9.2, 8.1 Hz, 1H), 4.21–4.16 (m, 2H), 3.28 (s, 3H), 2.62–2.50 (m, 1H), 2.47 (d, $J$ = 13.9 Hz, 1H), 2.19 (d, $J$ = 13.9 Hz, 1H), 2.17–2.11 (m, 2H), 2.11–1.99 (m, 4H), 1.91 (ddd, $J$ = 13.9, 10.0, 6.7 Hz, 1H), 1.81–1.73 (m, 1H), 1.71 (d, $J$ = 1.3 Hz, 3H), 1.62 (d, $J$ = 1.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 136.6, 130.7, 130.1, 124.7, 94.1, 78.4, 60.3, 48.2, 39.9, 39.2, 34.3, 32.9, 26.3, 26.0, 22.0, 18.4, 18.0, 16.3, –5.1.




**S7** **36**

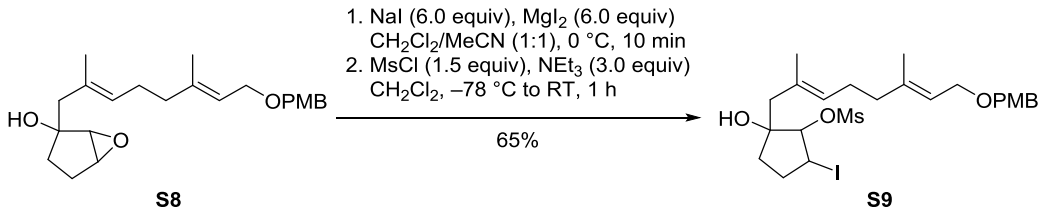
**1-((2*E*,6*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)cyclopent-2-en-1-ol (36).** Triethylamine (0.16 mL, 1.2 mmol, 5.0 equiv) and sodium iodide (174 mg, 1.16 mmol, 5.0 equiv) were added to a solution of iodide **S7** (133 mg, 0.232 mmol, 1.0 equiv) in acetone (10 mL) at ambient temperature. The resulting first colorless, then yellow reaction mixture was stirred at ambient temperature for 2.5 h before it was concentrated under reduced pressure and the residue was taken up in EtOAc (30 mL). The organic phase was sequentially washed with $Na_2S_2O_3$ solution (10 mL, sat. aqueous), $NH_4Cl$ solution (10 mL, sat. aqueous) and NaCl solution (10 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 30:70) afforded alkene **36** (76 mg, 93%) as a yellow oil.

**TLC:** $R_f$ = 0.60 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.67 (dt, $J$ = 5.6, 2.0 Hz, 1H), 5.63 (dt, $J$ = 5.6, 2.2 Hz, 1H), 5.52 (tq, $J$ = 6.3, 1.3 Hz, 1H), 5.21 (ddt, $J$ = 7.0, 5.8, 1.2 Hz, 1H), 4.25 (dd, $J$ = 6.3, 0.9 Hz, 2H), 2.33 (s, 2H), 2.31–2.22 (m, 1H), 2.15–2.02 (m, 3H), 2.01–1.91 (m, 3H), 1.79 (ddd, $J$ = 13.4, 8.6, 4.8 Hz, 1H), 1.73–1.66 (m, 3H), 1.55–1.48 (m, 3H), 1.46 (s, 1H), 1.01 (s, 9H), 0.11 (s, 6H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 137.9, 136.5, 133.1, 132.1, 128.9, 125.6, 85.2, 60.5, 51.1, 39.7, 38.4, 31.3, 26.7, 26.2, 18.6, 18.3, 16.2, –4.8; **HRMS** (MALDI): exact mass calculated for $C_{21}H_{39}O_2Si$ [$(M+H)^+$] 351.2714, found 351.2715.




**2-((2*E*,6*E*)-8-((4-Methoxybenzyl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)-6-oxabicyclo[3.1.0]-hexan-2-ol (S8).** A solution of alcohol **31** (30 mg, 0.12 mmol, 1.0 equiv) in DMF (0.4 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 10 mg, 0.26 mmol, 2.2 equiv) in DMF (1.8 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 30 min before PMBCl (18 µL, 0.13 mmol, 1.1 equiv) was added. The reaction mixture was stirred at ambient temperature for 3.5 h. Then, another portion of PMBCl (3 µL, 20 µmol, 0.2 equiv) was added. After another 2 h, the reaction mixture was quenched with MeOH (0.5 mL). The mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with water (4 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 40:60) afforded epoxide **S8** (14 mg, 32%) as a pink oil.

**TLC:** $R_f$ = 0.59 (EtOAc/hexane, 70:30; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 7.34–7.22 (m, 3H), 6.94–6.83 (m, 2H), 5.44–5.33 (m, 1H), 5.25–5.15 (m, 1H), 4.43 (s, 2H), 3.98 (d, $J$ = 6.8 Hz, 2H), 3.80 (s, 3H), 3.44 (d, $J$ = 2.8 Hz, 1H), 3.26 (d, $J$ = 2.8 Hz, 1H), 2.25–2.12 (m, 4H), 2.12–2.00 (m, 3H), 1.74 (d, $J$ = 1.3 Hz, 3H), 1.72–1.65 (m, 1H), 1.64 (d, $J$ = 1.2 Hz, 3H), 1.55 (dddd, $J$ = 14.0, 9.8, 8.4, 1.3 Hz, 1H), 1.40–1.23 (m, 1H); **HRMS** (MALDI): exact mass calculated for $C_{23}H_{33}O_4$ [$(M+H)^+$] 373.2373, found 373.2372.

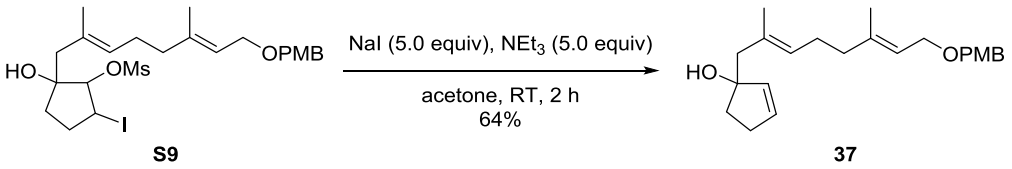



**2-Hydroxy-5-iodo-2-((2*E*,6*E*)-8-((4-methoxybenzyl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)-cyclopentyl methanesulfonate (S9).** To a solution of epoxide **S8** (14 mg, 38 µmol, 1.0 equiv) in $CH_2Cl_2$/MeCN (1:1 v/v, 4 mL) at 0 °C was added sodium iodide (34 mg, 0.23 mmol, 6.0 equiv), followed by magnesium iodide (63 mg, 0.23 mmol, 6.0 equiv). The resulting yellowish reaction mixture was stirred in the dark at 0 °C for 10 min. It was then filtered through a short plug of silica gel eluting with EtOAc/hexane (70:30) and concentrated under reduced pressure to afford the corresponding iodide (20 mg) as a yellow oil. The crude product was used in the following step without further purification.

**TLC:** $R_f$ = 0.61 (EtOAc/hexane, 70:30; UV, $KMnO_4$).

The above product (20 mg) was dissolved in $CH_2Cl_2$ (0.3 mL) and cooled to –78 °C. A solution of methanesulfonyl chloride (4.4 µL, 56 µmol, 1.5 equiv) in $CH_2Cl_2$ (0.1 mL) was added, and the mixture was stirred at –78 °C for 5 min. Then, a solution of triethylamine (16 µL, 0.11 mmol, 3.0 equiv) in $CH_2Cl_2$ (0.2 mL) was added dropwise over 10 min, and the resulting colorless reaction mixture was stirred at –78 °C for 30 min. It was then allowed to warm to ambient temperature over 30 min. The reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ solution (0.5 mL, sat. aqueous), diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were sequentially washed with $Na_2S_2O_3$ solution (10 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 30:70) afforded mesylate **S9** (14 mg, 65% over two steps) as a yellow oil.

**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 7.27 (dd, $J$ = 6.5, 2.1 Hz, 2H), 6.95–6.83 (m, 2H), 5.44–5.31 (m, 1H), 5.28–5.16 (m, 1H), 4.84 (d, $J$ = 8.6 Hz, 1H), 4.43 (s, 2H), 4.30 (dt, $J$ = 9.4, 8.0 Hz, 1H), 3.98 (d, $J$ = 6.7 Hz, 2H), 3.81 (s, 3H), 3.27 (s, 2H), 2.58–2.39 (m, 2H), 2.22–2.12 (m, 3H), 2.11–1.97 (m, 4H), 1.96–1.84 (m, 1H), 1.80–1.72 (m, 1H), 1.70 (d, $J$ = 1.2 Hz, 3H), 1.63 (d, $J$ = 1.3 Hz, 3H).

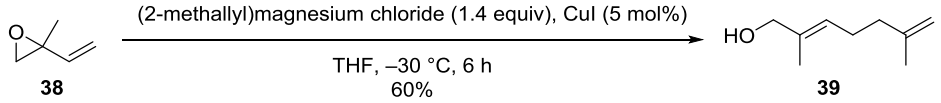



**S9** **37**

**1-((2*E*,6*E*)-8-((4-Methoxybenzyl)oxy)-2,6-dimethylocta-2,6-dien-1-yl)cyclopent-2-en-1-ol (37).** Triethylamine (17 µL, 0.12 mmol, 5.0 equiv) and sodium iodide (18 mg, 0.12 mmol, 5.0 equiv) were added to a solution of iodide **S9** (14 mg, 24 µmol, 1.0 equiv) in acetone (1 mL) at ambient temperature. The resulting first colorless, then orange reaction mixture was stirred at ambient temperature for 2 h before it was concentrated under reduced pressure and the residue was taken up in EtOAc (30 mL). The organic phase was sequentially washed with $Na_2S_2O_3$ solution (10 mL, sat. aqueous), $NH_4Cl$ solution (10 mL, sat. aqueous) and NaCl solution (10 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded alkene **37** (5.5 mg, 64%) as a yellow oil.

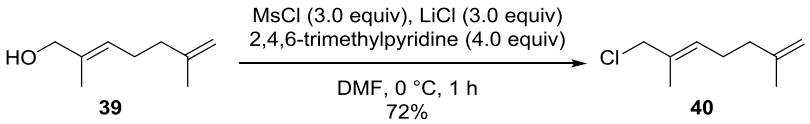
**TLC:** $R_f$ = 0.54 (EtOAc/hexane, 70:30; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ 7.33–7.24 (m, 2H), 6.86–6.77 (m, 2H), 5.69 (dt, $J$ = 5.6, 2.0 Hz, 1H), 5.63 (dt, $J$ = 5.6, 2.2 Hz, 1H), 5.60–5.50 (m, 1H), 5.29–5.12 (m, 1H), 4.41 (s, 2H), 4.02 (d, $J$ = 6.6 Hz, 2H), 3.30 (s, 3H), 2.36–2.31 (m, 2H), 2.31–2.22 (m, 1H), 2.17–2.05 (m, 3H), 2.05–1.96 (m, 2H), 1.93 (dd, $J$ = 8.5, 4.6 Hz,

1H), 1.80 (ddd, *J* = 13.3, 8.5, 4.7 Hz, 1H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.51 (d, *J* = 1.2 Hz, 3H), 1.42–1.27 (m, 1H).




**(*E*)-2,6-Dimethylhepta-2,6-dien-1-ol (39).** According to a procedure reported by R. HERNÁNDEZ-GALÁN and co-workers,[44] precooled (2-methallyl)magnesium chloride (0.5 M in THF, 143 mL, 71.3 mmol, 1.4 equiv, at –30 °C) was added to a mixture of epoxide **38** (5.0 mL, 51 mmol, 1.0 equiv) and CuI (485 mg, 2.6 mmol, 5 mol%) in THF (55 mL) at –30 °C. The resulting clear yellowish reaction mixture was stirred at –30 °C for 6 h. It was then quenched with $NH_4Cl$ solution (150 mL, sat. aqueous) and allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 300 mL). The combined organic phases were sequentially washed with 1 N HCl (300 mL), $NaHCO_3$ solution (300 mL, sat. aqueous), water (300 mL) and NaCl solution (300 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (diethyl ether/pentane, 10:90 to 20:80) afforded alcohol **39** (4.3 g, 60%) as a yellowish oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.45–5.37 (m, 1H), 4.72 (td, *J* = 1.5, 0.7 Hz, 1H), 4.70–4.65 (m, 1H), 3.99 (d, *J* = 1.2 Hz, 2H), 2.18 (dddt, *J* = 8.8, 6.9, 5.9, 1.0 Hz, 2H), 2.06 (dd, *J* = 9.2, 6.2 Hz, 2H), 1.72 (d, *J* = 1.2 Hz, 3H), 1.70–1.65 (m, 3H), 1.51–1.39 (m, 1H). According to the spectral data reported in the literature.[210]

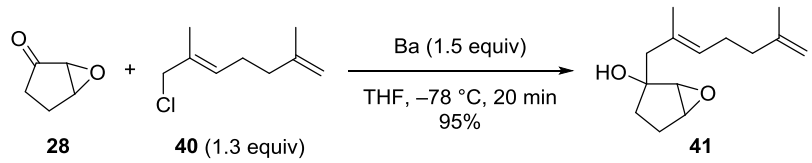



**(*E*)-7-Chloro-2,6-dimethylhepta-1,5-diene (40).** Methanesulfonyl chloride (7.0 mL, 90 mmol, 3.0 equiv) was added dropwise to a mixture of alcohol **39** (4.2 g, 30 mmol, 1.0 equiv), lithium chloride (3.8 g, 90 mmol, 3.0 equiv) and 2,4,6-trimethylpyridine (16 mL, 120 mmol, 4.0 equiv) in DMF (110 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 1 h. It was then poured onto ice-cold $NaHCO_3$ solution (100 mL, sat. aqueous) and the aqueous phase was extracted with pentane/diethyl ether (1:1 v/v, 3 x 300 mL). The combined organic phases were sequentially washed with $NH_4Cl$ solution (200 mL, sat. aqueous) and NaCl solution (200 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification

[210] D. Yang, M. Xu, *Org. Lett.* **2001**, *3*, 1785–1788.

by column chromatography (pentane to diethyl ether/pentane, 1:99) afforded chloride **40** (3.4 g, 72%) as a yellowish oil.

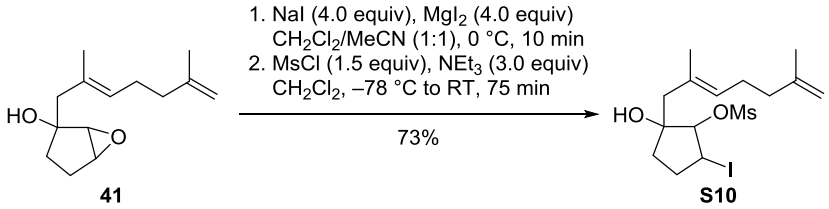
**TLC:** $R_f$ = 0.99 (EtOAc/hexane, 20:80; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.57–5.49 (m, 1H), 4.73 (td, $J$ = 1.5, 0.7 Hz, 1H), 4.68 (dd, $J$ = 2.1, 1.0 Hz, 1H), 4.02 (d, $J$ = 0.7 Hz, 2H), 2.23–2.14 (m, 2H), 2.11–2.03 (m, 2H), 1.77–1.74 (m, 3H), 1.74–1.70 (m, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 145.1, 131.8, 130.4, 110.2, 52.5, 37.0, 26.2, 22.4, 14.1; **IR** (thin film): 3075, 2969, 2936, 2856, 1650, 1441, 1374, 1263, 887, 682 cm$^{-1}$.




**(*E*)-2-(2,6-Dimethylhepta-2,6-dien-1-yl)-6-oxabicyclo[3.1.0]hexan-2-ol (41).** Biphenyl (2.89 g, 18.8 mmol, 3.1 equiv) and lithium (125 mg, 17.9 mmol, 2.9 equiv) were placed in a Schlenk flask under argon atmosphere. THF (40 mL) was added, and the resulting mixture was sonicated at ca. 10 °C for 2 h to afford a dark blue-green solution. In a separate Schlenk flask, barium iodide (3.51 g, 8.97 mmol, 1.5 equiv) was dissolved in THF (40 mL) and stirred for 5 min at ambient temperature. To the resulting clear solution was added the lithium biphenylide solution via cannula. The reaction mixture was stirred at ambient temperature for 30 min to afford a dark green suspension which was then cooled to –78 °C. A solution of chloride **40** (1.29 g, 8.15 mmol, 1.3 equiv) in THF (13.6 mL) was added dropwise, and the resulting deep red reaction mixture was stirred at –78 °C for 20 min. Then, a solution of ketone **28** (0.600 g, 6.12 mmol, 1.0 equiv) in THF (8 mL) was added dropwise, and the clear reaction mixture became less intensely red. The reaction mixture was stirred at –78 °C for 20 min before it was quenched with $NH_4Cl$ solution (150 mL, sat. aqueous), allowed to warm to ambient temperature and extracted with diethyl ether (3 x 300 mL). The combined organic phases were sequentially washed with 1 N $Na_2S_2O_3$ solution (150 mL) and NaCl solution (200 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane to EtOAc/hexane, 10:90 to 20:80) afforded tertiary alcohol **41** (1.3 g, 95%) as a clear yellow oil.

**TLC:** $R_f$ = 0.17 (diethyl ether/pentane, 40:60; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.26–5.19 (m, 1H), 4.74–4.70 (m, 1H), 4.67 (dd, $J$ = 2.3, 1.1 Hz, 1H), 3.46–3.42 (m, 1H), 3.27 (d, $J$ = 2.7 Hz, 1H), 2.23 (d, $J$ = 4.1 Hz, 2H), 2.22–2.15 (m, 2H), 2.12–2.02 (m, 3H), 2.02–1.96 (m, 1H), 1.77–1.74 (m, 3H), 1.73–1.69 (m, 4H), 1.64–1.51 (m, 1H), 1.40–1.29 (m, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 145.5, 131.1, 129.5, 110.2, 80.1, 61.7, 56.4, 46.3, 37.5, 31.9, 26.3, 26.2,

22.3, 18.3; **IR** (thin film): 3451, 2926, 1648, 1442, 1374, 1174, 1118, 983, 885, 852 $cm^{-1}$; **HRMS** (EI): exact mass calculated for $C_{14}H_{22}O_2$ [$M^+$] 222.1615, found 222.1618.



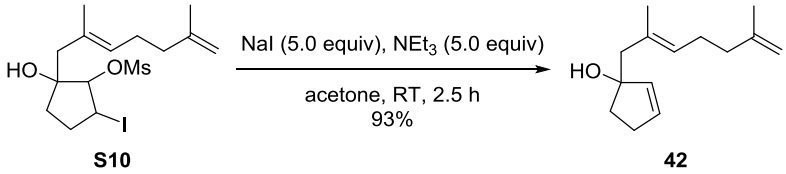

**(*E*)-2-(2,6-Dimethylhepta-2,6-dien-1-yl)-2-hydroxy-5-iodocyclopentyl methanesulfonate (S10).** To a solution of epoxide **41** (1.45 g, 6.52 mmol, 1.0 equiv) in $CH_2Cl_2$/MeCN (1:1 v/v, 260 mL) at 0 °C was added sodium iodide (3.91 g, 26.1 mmol, 4.0 equiv), followed by magnesium iodide (7.23 g, 26.1 mmol, 4.0 equiv). The resulting yellowish reaction mixture was stirred in the dark at 0 °C for 10 min. It was then filtered through a short plug of silica gel eluting with EtOAc/hexane (70:30) and concentrated under reduced pressure to afford the corresponding iodide (1.95 g) as a brown oil. The crude product was used in the following step without further purification.

**TLC:** $R_f$ = 0.66 (EtOAc/hexane, 60:40; UV, $KMnO_4$).

The above product (1.95 g) was dissolved in $CH_2Cl_2$ (50 mL) and cooled to –78 °C. A solution of methanesulfonyl chloride (0.76 mL, 9.8 mmol, 1.5 equiv) in $CH_2Cl_2$ (10 mL) was added, and the mixture was stirred at –78 °C for 5 min. Then, a solution of triethylamine (2.73 mL, 19.6 mmol, 3.0 equiv) in $CH_2Cl_2$ (20 mL) was added dropwise over 10 min, and the resulting colorless reaction mixture was stirred at –78 °C for 1 h. It was then allowed to warm to ambient temperature over 15 min. The reaction mixture was quenched at 0 °C with $NaHCO_3$ solution (20 mL, sat. aqueous), diluted with water (50 mL) and extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic phases were sequentially washed with $Na_2S_2O_3$ solution (100 mL, sat. aqueous) and NaCl solution (200 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded mesylate **S10** (2.0 g, 73% over two steps) as a yellow oil.

**TLC:** $R_f$ = 0.19 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.25 (ddt, $J$ = 7.0, 5.9, 1.2 Hz, 1H), 4.87 (d, $J$ = 8.4 Hz, 1H), 4.72 (td, $J$ = 1.5, 0.7 Hz, 1H), 4.67 (dd, $J$ = 2.2, 1.1 Hz, 1H), 4.34 (dt, $J$ = 9.2, 8.2 Hz, 1H), 3.28 (s, 3H), 2.62–2.50 (m, 1H), 2.50–2.45 (m, 1H), 2.24–2.13 (m, 3H), 2.13–2.01 (m, 3H), 1.92 (ddd, $J$ = 14.0, 10.1, 6.7 Hz, 1H), 1.82–1.74 (m, 2H), 1.74–1.69 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 145.5, 130.6, 130.2, 110.2, 94.0, 78.3, 48.1, 39.9, 37.5, 34.4, 32.8, 26.2, 22.3, 22.0, 18.0; **IR** (thin film): 3522, 2935, 1648,

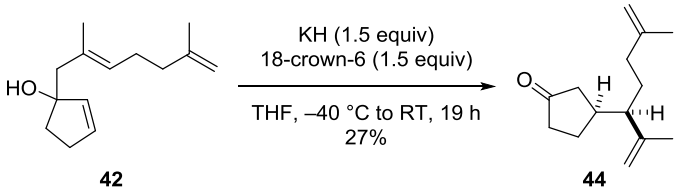
1444, 1342, 1175, 1068, 1008, 957, 848, 531 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{15}H_{25}INaO_4S$ [$(M+Na)^+$] 451.0410, found 451.0407.




**S10** **42**

**(*E*)-1-(2,6-Dimethylhepta-2,6-dien-1-yl)cyclopent-2-en-1-olate (42).** Triethylamine (3.25 mL, 23.4 mmol, 5.0 equiv) and sodium iodide (3.50 g, 23.4 mmol, 5.0 equiv) were added to a solution of iodide **S10** (2.0 g, 4.7 mmol, 1.0 equiv) in acetone (200 mL) at ambient temperature. The resulting first colorless, then yellow reaction mixture was stirred at ambient temperature for 2.5 h before it was concentrated under reduced pressure and the residue was taken up in EtOAc (300 mL). The organic phase was sequentially washed with $Na_2S_2O_3$ solution (100 mL, sat. aqueous), $NH_4Cl$ solution (100 mL, sat. aqueous) and NaCl solution (100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded alkene **42** (897 mg, 93%) as a yellow oil.

**TLC:** $R_f$ = 0.55 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.67 (dt, $J$ = 5.6, 2.1 Hz, 1H), 5.62 (dt, $J$ = 5.6, 2.2 Hz, 1H), 5.27–5.18 (m, 1H), 4.83–4.77 (m, 2H), 2.33 (d, $J$ = 0.9 Hz, 2H), 2.27 (dddd, $J$ = 16.4, 8.5, 4.3, 2.2 Hz, 1H), 2.17–1.90 (m, 6H), 1.84–1.75 (m, 1H), 1.71–1.68 (m, 3H), 1.62 (t, $J$ = 1.1 Hz, 3H), 1.48 (s, br, 1H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 145.5, 137.9, 133.1, 132.1, 129.0, 110.7, 85.2, 51.1, 38.3, 38.0, 31.3, 26.6, 22.4, 18.3; **IR** (thin film): 3379, 3052, 2966, 2926, 2850, 1649, 1443, 1373, 1055, 954, 885, 746 $cm^{-1}$.



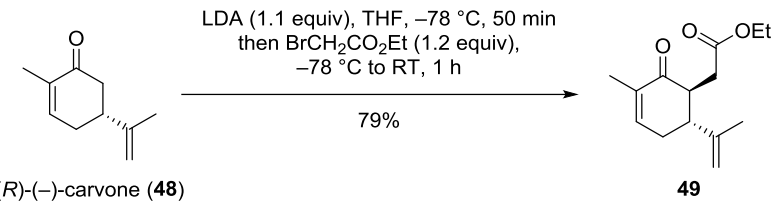

**42** **44**

**3-(2,6-Dimethylhepta-1,6-dien-3-yl)cyclopentan-1-one (44).** 18-Crown-6 (29 mg, 0.11 mmol, 1.5 equiv) was added to a suspension of potassium hydride (4.4 mg, 0.11 mmol, 1.5 equiv) in THF (2 mL) and the resulting mixture was cooled to –40 °C. A solution of alcohol **42** (15 mg, 73 µmol, 1.0 equiv) in THF (0.25 mL) was added dropwise, and the resulting yellowish reaction mixture was stirred at –20 °C for 20 min. It was then allowed to warm to 0 °C and stirred for 30 min before it was stirred at ambient temperature for 18 h. The now dark brown reaction mixture was cooled to 0 °C and quenched with MeOH (0.5 mL) and $NH_4Cl$ solution (1 mL, sat. aqueous). The resulting mixture was diluted with water (10 mL) and extracted with diethyl ether

(3 x 20 mL). The combined organic phases were washed with NaCl solution (10 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography afforded ketone **44** (4.0 mg, 27%).

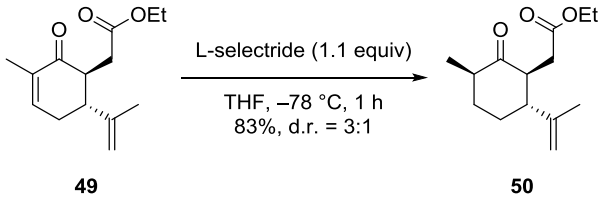
**TLC:** $R_f$ = 0.50 (EtOAc/hexane, 50:50; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.84 (dd, $J$ = 2.4, 1.4 Hz, 1H), 4.74 (dt, $J$ = 2.3, 0.7 Hz, 1H), 4.70 (ddt, $J$ = 2.2, 1.4, 0.7 Hz, 1H), 4.65 (dd, $J$ = 2.3, 1.1 Hz, 1H), 2.45 (dddd, $J$ = 18.0, 7.2, 2.0, 1.0 Hz, 1H), 2.33–2.23 (m, 1H), 2.19–2.04 (m, 2H), 2.03–1.91 (m, 2H), 1.90–1.78 (m, 3H), 1.70 (s, 3H), 1.64 (dd, $J$ = 1.5, 0.8 Hz, 3H), 1.59–1.48 (m, 1H), 1.48–1.36 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 219.3, 145.7, 145.0, 113.5, 109.9, 53.6, 44.3, 40.0, 38.7, 35.4, 29.3, 28.5, 22.5, 17.9; **IR** (thin film): 3072, 2966, 2931, 1742, 1646, 1445, 1403, 1375, 1160, 886 $cm^{-1}$; **HRMS** (EI): exact mass calculated for $C_{14}H_{22}O$ [$M^+$] 206.1666, found 206.1666.

### 3.2.2 Experimental Procedures for the Second-Generation Approach




**Ethyl 2-((1*S*,6*R*)-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-en-1-yl)acetate (49).** Similar to the procedure reported by Z. YANG and co-workers,[46] to a solution of diisopropylamine (10.0 mL, 70.2 mmol, 1.1 equiv) in THF (200 mL) at 0 °C was slowly added *n*-BuLi (1.6 M in hexane, 44 mL, 0.070 mol, 1.1 equiv) and the resulting yellowish solution was stirred at 0 °C for 15 min before it was cooled to –78 °C. (*R*)-(–)-Carvone (**48**) (10.0 mL, 63.8 mmol, 1.0 equiv) was added dropwise and stirring was continued at –78 °C for 50 min. Then, a solution of ethyl bromoacetate (8.5 mL, 77 mmol, 1.2 equiv) in THF (20 mL) was added dropwise and the reaction mixture was allowed to warm to ambient temperature and stirred for 1 h before it was quenched with $NH_4Cl$ solution (200 mL, sat. aqueous) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 200 mL) and the combined organic phases were sequentially washed with $NH_4Cl$ solution (200 mL, sat. aqueous) and NaCl solution (200 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98; then 4:96) afforded ketoester **49** (11.9 g, 79%) as a colorless oil.

**TLC:** $R_f$ = 0.38 (EtOAc/hexane, 10:90; UV, CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 6.74–6.68 (m, 1H), 4.87–4.81 (m, 2H), 4.15 (qd, *J* = 7.1, 1.9 Hz, 2H), 2.88 (ddd, *J* = 13.3, 6.6, 4.8 Hz, 1H), 2.74 (ddd, *J* = 13.3, 11.2, 4.6 Hz, 1H), 2.55–2.42 (m, 3H), 2.30 (dddd, *J* = 18.4, 6.0, 4.6, 1.3 Hz, 1H), 1.80–1.75 (m, 3H), 1.71 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **Optical rotation:** $[\alpha]_D^{22}$ +29.8° (c = 1.00, $CHCl_3$). According to the spectral data reported in the literature.[46]



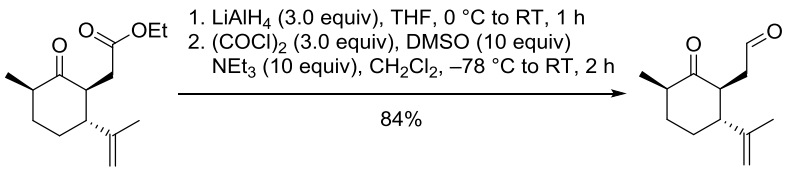

**Ethyl 2-((1*S*,3*R*,6*R*)-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohexyl)acetate (50).** Similar to the procedure reported by Z. YANG and co-workers,[46] L-selectride (1.0 M in THF, 26 mL, 26 mmol, 1.1 equiv) was added dropwise to a solution of enone **49** (5.9 g, 25 mmol, 1.0 equiv) in THF (50 mL) at –78 °C. The resulting clear yellowish reaction mixture was stirred at this

temperature for 1 h, then allowed to warm to 0 °C and quenched with $NH_4Cl$ solution (100 mL, sat. aqueous). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with NaCl solution (100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded ketoester **50** (4.9 g, 83%, d.r. = 3:1) as a yellowish oil. Analytical samples of both diastereomers could be obtained by careful column chromatography.

Diastereomeric mixture: **Optical rotation:** $[\alpha]_D^{22}$ +20.6° (c = 1.00, $CHCl_3$).

Major diastereomer: **TLC:** $R_f$ = 0.35 (EtOAc/hexane, 10:90; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.80 (app t, $J$ = 1.6 Hz, 1H), 4.75 (app dt, $J$ = 1.9, 0.8 Hz, 1H), 4.15–4.06 (m, 2H), 2.94–2.84 (m, 1H), 2.61–2.44 (m, 2H), 2.24–2.14 (m, 2H), 2.14–2.05 (m, 1H), 1.95–1.83 (m, 1H), 1.78 (app dtd, $J$ = 13.5, 3.9, 2.9 Hz, 1H), 1.71 (dd, $J$ = 1.5, 0.8 Hz, 3H), 1.44–1.30 (m, 1H), 1.24 (t, $J$ = 7.1 Hz, 3H), 1.03 (d, $J$ = 6.5 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 211.8, 173.0, 145.5, 113.0, 60.3, 53.3, 49.4, 45.0, 35.2, 32.1, 31.1, 18.1, 14.5, 14.2. According to the spectral data reported in the literature.[46]

Minor diastereomer: **TLC:** $R_f$ = 0.35 (EtOAc/hexane, 10:90; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.80 (app t, $J$ = 1.6 Hz, 1H), 4.77–4.74 (m, 1H), 4.10 (q, $J$ = 7.2 Hz, 2H), 3.07 (ddd, $J$ = 12.5, 9.2, 3.6 Hz, 1H), 2.61 (ddd, $J$ = 7.5, 4.8, 2.9 Hz, 1H), 2.50 (dd, $J$ = 16.8, 9.2 Hz, 1H), 2.27–2.18 (m, 2H), 2.04–1.74 (m, 3H), 1.72 (s, 3H), 1.62 (dt, $J$ = 12.7, 3.9 Hz, 1H), 1.28–1.20 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 214.3, 172.7, 145.5, 113.0, 60.3, 51.9, 45.1, 43.9, 32.0, 31.5, 25.7, 18.3, 16.7, 14.1; **IR** (thin film): 2973, 2934, 2866, 1733, 1708, 1457, 1354, 1214, 1182, 1155, 1034, 896 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{14}H_{22}NaO_3$ $[(M+Na)^+]$ 261.1461, found 261.1462.




**50** (d.r. = 3:1) → **47** (d.r. = 4:1)

**2-((1*S*,3*R*,6*R*)-3-Methyl-2-oxo-6-(prop-1-en-2-yl)cyclohexyl)acetaldehyde (47).** A solution of ketoester **50** as a mixture of diastereomers (7.2 g, 0.030 mol, 1.0 equiv) in THF (30 mL) was added dropwise to a solution of $LiAlH_4$ (2.0 M in THF, 45 mL, 91 mmol, 3.0 equiv) in THF (110 mL) at 0 °C. The resulting clear colorless reaction mixture was stirred at ambient temperature for 1 h, before it was cooled to 0 °C. Water (3.5 mL) was added carefully, followed by the addition of 15% NaOH (3.5 mL) and again water (10.5 mL). The white slurry was stirred

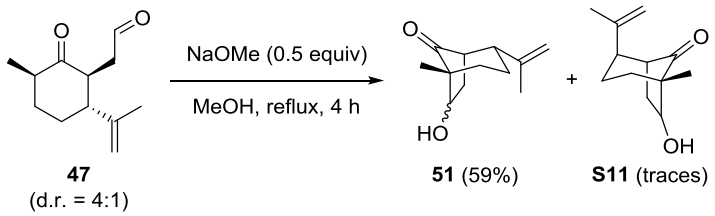
for at ambient temperature for 30 min, then $Na_2SO_4$ was added and stirring was continued for 20 min before the mixture was filtered through a short plug of celite eluting with EtOAc. Concentration under reduced pressure afforded a yellowish oil which was used in the following transformation without further purification.

A solution of DMSO (21.5 mL, 303 mmol, 10.0 equiv) in $CH_2Cl_2$ (25 mL) was slowly added to a solution of oxalyl chloride (8.0 mL, 91 mmol, 3.0 equiv) in $CH_2Cl_2$ (250 mL) at –78 °C. The resulting mixture was stirred at this temperature for 15 min, before a solution of the above product (30 mmol, 1.0 equiv) in $CH_2Cl_2$ (25 mL) was added dropwise. After stirring the resulting turbid white reaction mixture at –78 °C for 1 h, triethylamine (42 mL, 300 mmol, 10 equiv) was added *via* syringe and the turbid yellow mixture was allowed to warm to ambient temperature and stirred for 1 h. It was then poured on $NaHCO_3$ solution (250 mL, sat. aqueous) and the phases were separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 250 mL), and the combined organic phases were sequentially washed with $NH_4Cl$ solution (250 mL, sat. aqueous) and NaCl solution (300 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 15:85) afforded ketoaldehyde **47** (4.9 g, 84 %, d.r. = 4:1) as a reddish oil.

Diastereomeric mixture: **Optical rotation:** $[\alpha]_D^{22}$ +16.0° (c = 1.00, $CHCl_3$).

Major diastereomer: **TLC:** $R_f$ = 0.94 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 9.81 (dd, $J$ = 1.3, 0.5 Hz, 1H), 4.81 (app t, $J$ = 1.6 Hz, 1H), 4.76 (app dt, $J$ = 1.7, 0.8 Hz, 1H), 3.00 (dddd, $J$ = 12.3, 9.2, 3.2, 1.3 Hz, 1H), 2.83 (ddd, $J$ = 17.8, 9.2, 1.3 Hz, 1H), 2.50 (dddd, $J$ = 13.2, 6.6, 5.7, 1.2 Hz, 1H), 2.29–2.07 (m, 3H), 1.91–1.76 (m, 2H), 1.70–1.67 (m, 3H), 1.38 (app qd, $J$ = 13.0, 4.1 Hz, 1H), 1.03 (d, $J$ = 6.6 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 211.4, 201.1, 145.6, 113.1, 53.4, 48.3, 44.9, 41.2, 35.2, 31.1, 18.1, 14.5; **IR** (thin film): 2969, 2932, 2861, 1707, 1451, 1378, 1014, 896 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{12}H_{18}O_2$ [$M^+$] 194.1302, found 194.1299.

Minor diastereomer (spectra obtained from a different route): **TLC:** $R_f$ = 0.94 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 9.78 (dd, $J$ = 1.3, 0.6 Hz, 1H), 4.81 (app p, $J$ = 1.5 Hz, 1H), 4.75 (app dt, $J$ = 1.8, 0.8 Hz, 1H), 3.18 (ddd, $J$ = 12.2, 8.7, 3.5 Hz, 1H), 2.75 (ddd, $J$ = 17.7, 8.7, 1.3 Hz, 1H), 2.63 (ddd, $J$ = 7.8, 4.1, 2.0 Hz, 1H), 2.32–2.19 (m, 2H), 2.04–1.77 (m, 3H), 1.70 (dd, $J$ = 1.5, 0.8 Hz, 3H), 1.67–1.61 (m, 1H), 1.27 (d, $J$ = 7.8 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 214.0, 200.7, 145.6, 113.1, 52.1, 44.1, 43.7, 41.0, 31.5, 25.6, 18.2, 16.9; **IR** (thin film): 2970, 2934, 2862, 1721, 1703, 1456, 1378, 1226, 895 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{12}H_{18}O_2$ [$M^+$] 194.1302, found 194.1301.




**(1*R*,4*R*,5*R*)-7-Hydroxy-1-methyl-4-(prop-1-en-2-yl)bicyclo[3.2.1]octan-8-one (51).** A solution of sodium methoxide (5.4 M in MeOH, 1.9 mL, 0.010 mol, 0.5 equiv) in MeOH (100 mL) was added *via* cannula to a solution of aldehyde **47** as a mixture of diastereomers (4.00 g, 20.6 mmol, 1.0 equiv) in MeOH (900 mL). The resulting clear yellow reaction mixture was stirred at reflux temperature for 4 h before it was cooled to 0 °C and quenched with $NH_4Cl$ solution (200 mL, sat. aqueous). After partial concentration under reduced pressure, the mixture was diluted with water (200 mL) and extracted with diethyl ether (3 x 300 mL). The combined organic phases were washed with water (2 x 200 mL) and NaCl solution (300 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded alcohol **51** (2.37 g, 59%) as a colorless oil (ca. 1:1 mixture of diastereomers) along with trace amounts of alcohol **S11**. Analytical samples of all three diastereomers could be obtained by careful column chromatography.

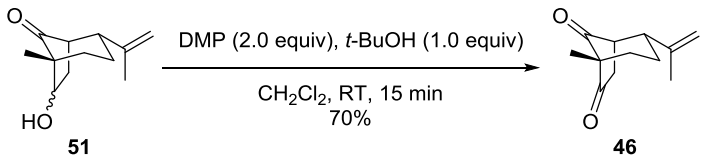
First diastereomer: **TLC:** $R_f$ = 0.56 (EtOAc/hexane, 60:40; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.86 (q, $J$ = 1.3 Hz, 1H), 4.80–4.75 (m, 1H), 4.06 (app dt, $J$ = 10.6, 4.2 Hz, 1H), 2.60–2.48 (m, 2H), 2.23 (ddd, $J$ = 14.5, 10.6, 7.8 Hz, 1H), 2.14–1.96 (m, 2H), 1.81 (d, $J$ = 4.2 Hz, 1H), 1.75–1.67 (m, 4H), 1.63–1.46 (m, 2H), 1.01 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.7, 145.0, 110.9, 73.5, 52.3, 51.5, 49.2, 36.5, 30.1, 22.5, 22.4, 17.1; **IR** (thin film): 3440, 2964, 2937, 1731, 1453, 1376, 1100, 1079, 893 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{12}H_{18}O_2$ [$M^+$] 194.1302, found 194.1307.

Second diastereomer: **TLC:** $R_f$ = 0.44 (EtOAc/hexane, 60:40; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.86 (q, $J$ = 1.3 Hz, 1H), 4.75–4.71 (m, 1H), 4.07 (dd, $J$ = 8.2, 2.5 Hz, 1H), 2.60–2.55 (m, 1H), 2.51–2.43 (m, 1H), 2.33 (ddd, $J$ = 14.7, 8.2, 0.9 Hz, 1H), 1.82–1.75 (m, 2H), 1.73–1.70 (m, 3H), 1.68–1.54 (m, 4H), 1.03 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.6, 145.0, 110.8, 73.1, 51.6, 51.0, 47.7, 39.9, 31.2, 22.4, 22.1, 13.6; **IR** (thin film): 3450, 2935, 1733, 1452, 1376, 1055, 893 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{12}H_{18}O_2$ [$M^+$] 194.1302, found 194.1296.

**(1S,4R,5S)-7-Hydroxy-1-methyl-4-(prop-1-en-2-yl)bicyclo[3.2.1]octan-8-one (S11).**

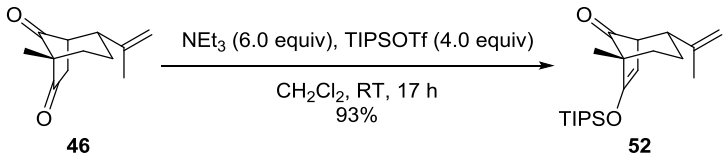
**TLC:** $R_f$ = 0.31 (EtOAc/hexane, 60:40; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.87 (q, $J$ = 1.4 Hz, 1H), 4.83–4.79 (m, 1H), 4.24–4.14 (m, 1H), 2.74–2.66 (m, 1H), 2.65–2.57 (m, 1H), 2.47–2.36 (m, 1H), 1.97–1.82 (m, 3H), 1.82–1.70 (m, 5H), 1.47 (s, br, 1H), 0.98 (s, 3H);

**$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 144.6, 111.2, 72.6, 52.7, 51.3, 47.1, 39.6, 36.2, 22.5, 20.9, 13.9 (carbonyl-C not detected); **IR** (thin film): 3453, 2929, 1736, 1644, 1452, 1043.




**(1*R*,2*R*,5*R*)-5-Methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]octane-6,8-dione (46).** To a solution of alcohol **51** as a mixture of diastereomers (2.37 g, 12.2 mmol, 1.0 equiv) in $CH_2Cl_2$ (120 mL) at ambient temperature was added DESS–MARTIN periodinane (10.4 g, 24.4 mmol, 2.0 equiv). The resulting orange suspension was stirred for 5 min before *t*-BuOH (1.17 mL, 12.2 mmol, 1.0 equiv) was added. Stirring was continued for 15 min, then the reaction mixture was quenched with $Na_2S_2O_3$ solution (100 mL, sat. aqueous), stirred vigorously for 5 min and poured on $NaHCO_3$ solution (300 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 200 mL) and the combined organic phases were washed with NaCl solution (200 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded diketone **46** (1.63 g, 70%) as off-white needles. Crystals suitable for X-ray crystallography could be obtained via slow evaporation of a solution in diethyl ether.

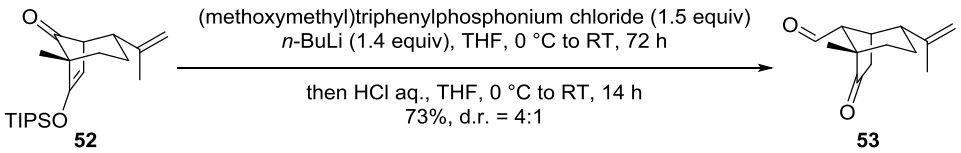
**TLC:** $R_f$ = 0.66 (EtOAc/hexane, 50:50; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 4.94 (q, $J$ = 1.2 Hz, 1H), 4.80–4.76 (m, 1H), 3.03–2.96 (m, 1H), 2.75 (dd, $J$ = 11.0, 5.9 Hz, 1H), 2.65 (dd, $J$ = 19.4, 0.8 Hz, 1H), 2.46 (dd, $J$ = 19.4, 7.7 Hz, 1H), 1.98 (ddd, $J$ = 11.4, 4.7, 1.7 Hz, 1H), 1.88–1.76 (m, 4H), 1.76–1.66 (m, 2H), 1.08 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 216.8, 212.1, 144.2, 111.7, 58.9, 51.2, 48.3, 41.5, 39.6, 22.4, 22.4, 11.8; **IR** (thin film): 2967, 2931, 2861, 1767, 1725, 1451, 1283, 1046, 899, 699 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{21}$ +35.1° (c = 1.00, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{12}H_{16}O_2$ [$M^+$] 192.1145, found 192.1142; **X-Ray Crystallography:** See Section 4.2.




**(1*R*,4*R*,5*S*)-1-Methyl-4-(prop-1-en-2-yl)-7-((triisopropylsilyl)oxy)bicyclo[3.2.1]oct-6-en-8-one (52).** To a solution of diketone **46** (1.63 g, 8.48 mmol, 1.0 equiv) in $CH_2Cl_2$ (85 mL) at 0 °C was added triethylamine (7.1 mL, 51 mmol, 6.0 equiv), followed by triisopropylsilyl trifluoromethanesulfonate (9.2 mL, 34 mmol, 4.0 equiv). The resulting orange reaction mixture

was stirred at ambient temperature for 17 h, then cooled to 0 °C and quenched with $NaHCO_3$ solution (50 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 100 mL), and the combined organic phases were sequentially washed with $NH_4Cl$ solution (100 mL, sat. aqueous) and NaCl solution (100 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded enol ether **52** (2.74 g, 93%) as a colorless oil.

**TLC:** $R_f$ = 0.79 (EtOAc/hexane, 20:80; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.79 (d, $J$ = 3.1 Hz, 1H), 4.76 (app t, $J$ = 1.6 Hz, 1H), 4.75–4.72 (m, 1H), 3.04 (dd, $J$ = 3.2, 1.8 Hz, 1H), 2.18 (app ddt, $J$ = 12.4, 4.4, 1.4 Hz, 1H), 1.73 (app dtd, $J$ = 13.7, 12.4, 6.2 Hz, 1H), 1.57–1.54 (m, 3H), 1.54–1.48 (m, 1H), 1.41–1.27 (m, 1H), 1.27–1.16 (m, 4H), 1.16–0.96 (m, 21H), 1.04 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 212.8, 155.2, 147.2, 110.1, 95.8, 53.4, 51.9, 46.9, 33.3, 24.2, 22.2, 18.1, 13.5, 12.8; **IR** (thin film): 2945, 2867, 1762, 1615, 1455, 1354, 1295, 1275, 1248, 1185, 1114, 881, 845, 789, 756, 684 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ +76.7° (c = 1.00, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{21}H_{36}O_2Si$ [$M^+$] 348.2479, found 348.2485.

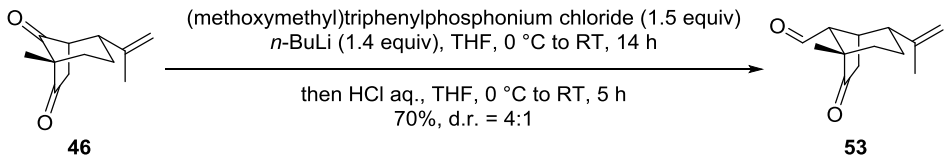



**(1*S*,4*R*,5*R*,8*R*)-1-Methyl-7-oxo-4-(prop-1-en-2-yl)bicyclo[3.2.1]octane-8-carbaldehyde (53).** *n*-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol, 1.4 equiv) was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (876 mg, 2.56 mmol, 1.5 equiv) in THF (14 mL) at 0 °C. The resulting deep red mixture was stirred at 0 °C for 30 min, before a solution of ketone **52** (594 mg, 1.70 mmol, 1.0 equiv) in THF (5.6 mL) was added dropwise. After stirring the resulting turbid yellow reaction mixture at ambient temperature for 72 h, it was cooled to 0 °C and HCl (conc., 0.6 mL) was added. Stirring was continued at ambient temperature for 14 h. The clear yellow reaction mixture was then diluted with water (40 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with $NaHCO_3$ solution (100 mL sat. aqueous) and NaCl solution (100 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded aldehyde **53** (258 mg, 73%, d.r. = 4:1) as a colorless oil. The analytical data were extracted from the spectra of the diastereomeric mixture; for the analysis of the minor diastereomer, the hydrolysis was interrupted after 15 min, which resulted in d.r. = 2:7.

Diastereomeric mixture: **TLC:** $R_f$ = 0.23 (EtOAc/hexane, 10:90; $KMnO_4$); **IR** (thin film): 2928, 2855, 1739, 1717, 1454, 1376, 1050, 892 $cm^{-1}$; **HRMS** (EI): exact mass calculated for $C_{13}H_{18}O_2$ $[M^+]$ 206.1302, found 206.1302; **Optical rotation:** $[\alpha]_D^{23}$ –51.9° (c = 1.00, $CHCl_3$).

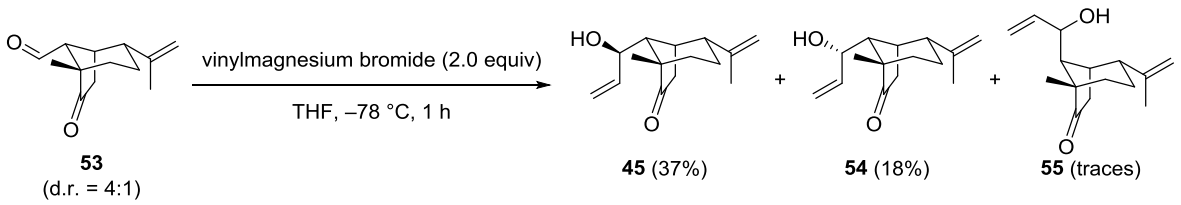
Major diastereomer: **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 9.83 (d, $J$ = 2.3 Hz, 1H), 4.87 (q, $J$ = 1.3 Hz, 1H), 4.69–4.66 (m, 1H), 2.85–2.80 (m, 1H), 2.80–2.77 (m, 1H), 2.36–2.23 (m, 2H), 2.11 (ddd, $J$ = 19.1, 1.9, 1.0 Hz, 1H), 1.79–1.76 (m, 3H), 1.75–1.69 (m, 1H), 1.66–1.60 (m, 2H), 1.53–1.39 (m, 1H), 1.15 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 218.1, 202.1, 145.5, 110.7, 65.2, 50.2, 46.3, 38.1, 37.5, 33.5, 23.1, 22.7, 16.8.

Minor diastereomer: **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 9.41 (s, 1H), 4.71 (q, $J$ = 1.4 Hz, 1H), 4.42 (d, $J$ = 1.9 Hz, 1H), 2.43 (ddd, $J$ = 7.0, 4.5, 1.9 Hz, 1H), 2.12 (app dt, $J$ = 10.9, 2.7 Hz, 1H), 2.05 (d, $J$ = 18.5 Hz, 1H), 1.73 (dd, $J$ = 4.5, 2.0 Hz, 1H), 1.62 (dd, $J$ = 18.5, 7.0 Hz, 1H), 1.52–1.48 (m, 4H), 1.24–1.16 (m, 3H), 1.12 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 216.6, 200.9, 146.4, 110.5, 60.0, 48.4, 40.4, 39.9, 34.2, 31.4, 23.2, 22.5, 19.3.



**46** **53**

**(1*S*,4*R*,5*R*,8*R*)-1-Methyl-7-oxo-4-(prop-1-en-2-yl)bicyclo[3.2.1]octane-8-carbaldehyde (53).** *n*-BuLi (1.6 M in hexane, 0.91 mL, 1.5 mmol, 1.4 equiv) was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (535 mg, 1.56 mmol, 1.5 equiv) in THF (9 mL) at 0 °C. The resulting deep red mixture was stirred at 0 °C for 30 min, before a solution of diketone **46** (0.200 g, 1.04 mmol, 1.0 equiv) in THF (3 mL) was added dropwise. After stirring the resulting turbid orange reaction mixture at ambient temperature for 14 h, it was cooled to 0 °C and HCl (conc., 20 drops) was added. Stirring was continued at ambient temperature for 5 h. The clear yellow reaction mixture was then diluted with water (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic phases were washed with $NaHCO_3$ solution (40 mL sat. aqueous) and NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded aldehyde **53** (149 mg, 70%, d.r. = 4:1) as a colorless oil.

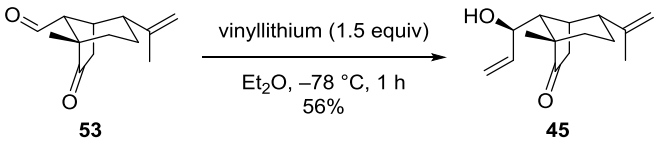



**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-Hydroxyallyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]octan-6-one (45), (1*R*,2*R*,5*S*,8*R*)-8-((*S*)-1-hydroxyallyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]-octan-6-one (54).** Vinylmagnesium bromide (1.0 M in THF, 2.9 mL, 2.9 mmol, 2.0 equiv) was added dropwise to a solution of aldehyde **53** as a mixture of diastereomers (0.300 g, 1.45 mmol, 1.0 equiv) in THF (14 mL) at –78 °C and the resulting yellowish reaction mixture was stirred at this temperature for 1 h. It was quenched with $NH_4Cl$ solution (10 mL, sat. aqueous) and allowed to warm to ambient temperature. The phases were separated, the aqueous phase was extracted with EtOAc (3 x 80 mL) and the combined organic phases were washed with NaCl solution (80 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded allylic alcohol **45** (126 mg, 37%) as a white solid and its diastereomer **54** (60 mg, 18%) as a colorless oil. The yield for the undesired diastereomer **55** was not determined.

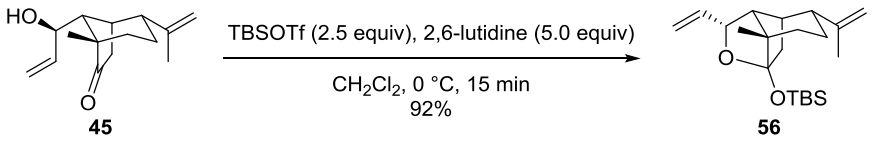
Major diastereomer **45**: **TLC:** $R_f$ = 0.21 (EtOAc/hexane, 50:50; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.99 (ddd, $J$ = 17.2, 10.5, 5.0 Hz, 1H), 5.30 (app dt, $J$ = 17.2, 1.5 Hz, 1H), 5.24 (app dt, $J$ = 10.5, 1.5 Hz, 1H), 4.81 (q, $J$ = 1.4 Hz, 1H), 4.64–4.61 (m, 1H), 4.46–4.39 (m, 1H), 2.71–2.64 (m, 1H), 2.49 (dd, $J$ = 18.7, 7.9 Hz, 1H), 2.24–2.16 (m, 1H), 1.91 (dd, $J$ = 18.7, 1.9, 1H), 1.79–1.72 (m, 4H), 1.71–1.55 (m, 3H), 1.51–1.41 (m, 1H), 1.40–1.37 (m, 1H), 1.13 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 221.8, 146.7, 139.9, 115.1, 109.8, 71.7, 57.8, 50.0, 48.0, 38.8, 38.7, 33.1, 23.4, 22.7, 16.8; **IR** (thin film): 3441, 2932, 2854, 1726, 1643, 1450, 1406, 1375, 1142, 992, 890 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ –57.2° (c = 1.00, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{15}H_{22}O_2$ [$M^+$] 234.1615, found 234.1619.

Minor diastereomer **54**: **TLC:** $R_f$ = 0.12 (EtOAc/hexane, 50:50; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.91 (ddd, $J$ = 17.1, 10.3, 7.3 Hz, 1H), 5.25–5.14 (m, 2H), 4.81 (q, $J$ = 1.4 Hz, 1H), 4.63 (dq, $J$ = 1.6, 0.8 Hz, 1H), 4.06 (app t, $J$ = 7.0 Hz, 1H), 2.50 (dd, $J$ = 7.4, 1.5 Hz, 1H), 2.34–2.26 (m, 1H), 2.21–2.10 (m, 1H), 1.99 (ddd, $J$ = 19.2, 2.1, 0.7 Hz, 1H), 1.92 (d, $J$ = 6.5, 2.1 Hz, 1H), 1.76 (app dt, $J$ = 1.4, 0.7 Hz, 3H), 1.72–1.64 (m, 2H), 1.64–1.56 (m, 2H), 1.47–1.38 (m, 1H), 1.16 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 221.7, 146.5, 139.5, 116.2, 110.0, 75.2, 58.7, 51.3, 47.4, 39.1, 37.7, 36.1, 23.3, 22.8, 18.0; **IR** (thin film): 3442, 2931, 1729, 1643, 1452, 1377, 994, 922, 891 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{15}H_{22}O_2$ [$M^+$] 234.1615, found 234.1617.

Axial diastereomer **55**: **$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.99 (ddd, $J$ = 17.1, 10.2, 7.6 Hz, 1H), 5.45–5.25 (m, 2H), 4.82 (q, $J$ = 1.4 Hz, 1H), 4.72–4.65 (m, 1H), 4.65–4.60 (m, 1H), 2.47–2.39 (m, 1H), 2.33–2.26 (m, 1H), 2.21–2.08 (m, 2H), 1.88–1.80 (m, 1H), 1.80–1.74 (m, 1H), 1.69–1.65 (m, 3H), 1.63–1.57 (m, 1H), 1.48–1.36 (m, 2H), 1.17 (s, 3H).; **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 221.7, 146.5, 139.2, 116.7, 110.3, 71.7, 53.7, 49.6, 40.5, 38.0, 34.5, 30.2, 22.6, 22.5, 20.6; **IR** (thin film): 3454, 2930, 2869, 1729, 1643, 1453, 1376, 1016, 995, 890 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{15}H_{22}O_2$ [$M^+$] 234.1615, found 234.1629.



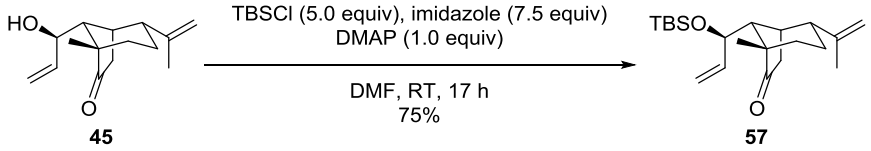

**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-Hydroxyallyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]octan-6-one (45).** To a solution of aldehyde **53** as a mixture of diastereomers (0.300 g, 1.45 mmol, 1.0 equiv) in diethyl ether (12 mL) at –78 °C was added dropwise vinyllithium (1 M in diethyl ether, 2.2 mL, 2.2 mmol, 1.5 equiv) prepared according to a procedure reported by S. SIVASUBRAMANIAN and co-workers.[59] The resulting clear yellowish reaction mixture was stirred at –78 °C for 1 h before it was quenched with $NH_4Cl$ solution (13 mL, sat. aqueous) and allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phases were sequentially washed with $NH_4Cl$ solution (40 mL, sat. aqueous) and NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded allylic alcohol **45** as a single diastereomer (190 mg, 56%) as a white solid.




***tert*-Butyldimethyl(((3*R*,3a*R*,4*R*,5*R*,7a*S*)-7a-methyl-5-(prop-1-en-2-yl)-3-vinyloctahydro-1,4-methanoisobenzofuran-1-yl)oxy)silane (56).** To a solution of alcohol **45** (8.0 mg, 34 µmol, 1.0 equiv) in $CH_2Cl_2$ (0.5 mL) at 0 °C were sequentially added 2,6-lutidine (20 µL, 0.17 mmol, 5.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (20 µL, 87 µmol, 2.5 equiv), and the resulting yellowish reaction mixture was stirred at 0 °C for 15 min. It was quenched with $NaHCO_3$ solution (0.5 mL, sat. aqueous), diluted with water (5 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were sequentially washed with $NH_4Cl$ solution

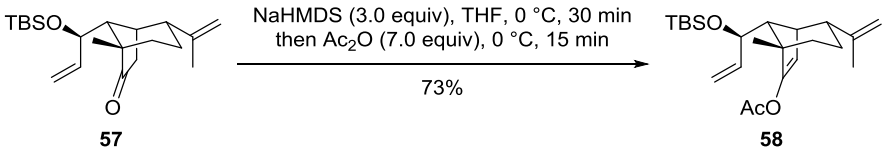
(20 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded acetal **56** (11 mg, 92%) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.87 (ddd, $J$ = 17.1, 10.6, 4.4 Hz, 1H), 5.39 (app dt, $J$ = 17.1, 2.0 Hz, 1H), 5.16 (app dt, $J$ = 10.7, 2.0 Hz, 1H), 4.69 (app h, $J$ = 1.6 Hz, 1H), 4.61–4.53 (m, 2H), 2.25–2.18 (m, 1H), 2.01 (dd, $J$ = 10.1, 4.6 Hz, 1H), 1.75–1.51 (m, 10H), 0.99 (s, 3H), 0.89 (s, 9H), 0.15 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 148.4, 138.0, 114.6, 109.9, 108.6, 76.9, 52.0, 47.7, 45.0, 36.3, 35.0, 30.1, 25.8, 23.7, 22.2, 17.9, 17.0, –3.0; **IR** (thin film): 2928, 2855, 1644, 1471, 1463, 1316, 1249, 1221, 982, 882, 838, 781 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{21}H_{37}O_2Si$ [$(M+H)^+$] 349.2557, found 349.2556.




**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]octan-6-one (57).** To a mixture of alcohol **45** (143 mg, 0.610 mmol, 1.0 equiv), imidazole (312 mg, 4.58 mmol, 7.5 equiv), DMAP (74.5 mg, 0.610 mmol, 1.0 equiv) and *tert*-butyldimethylsilyl chloride (460 mg, 3.95 mmol, 5.0 equiv) was added DMF (2.3 mL), and the resulting turbid reaction mixture was stirred at ambient temperature for 17 h. It was then diluted with water (20 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic phases were sequentially washed with water (50 mL) and NaCl solution (50 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded ketone **57** (160 mg, 75%) as a colorless oil.

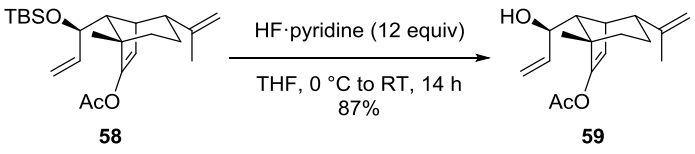
**TLC:** $R_f$ = 0.80 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.98 (ddd, $J$ = 17.1, 10.4, 7.7 Hz, 1H), 5.23–5.21 (m, 2H), 4.81 (q, $J$ = 1.4 Hz, 1H), 4.64 (q, $J$ = 0.8 Hz, 1H), 4.31 (dd, $J$ = 7.7, 3.1 Hz, 1H), 2.76–2.68 (m, 1H), 2.52 (dd, $J$ = 18.6, 7.9 Hz, 1H), 2.23–2.15 (m, 1H), 1.90 (dd, $J$ = 18.6, 1.8 Hz, 1H), 1.76 (app dt, $J$ = 1.3, 0.6 Hz, 3H), 1.68 (app t, $J$ = 2.4 Hz, 1H), 1.65–1.37 (m, 4H), 1.08 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.8, 146.8, 140.8, 115.7, 109.7, 74.2, 60.6, 49.9, 48.0, 39.1, 38.8, 33.3, 25.8, 23.3, 22.8, 18.0, 16.6, –3.3, –5.0; **IR** (thin film): 2929, 2857, 1740, 1644, 1463, 1374, 1252, 1087, 1038, 928, 883, 838, 775 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{21}H_{37}O_2Si$ [$(M+H)^+$] 349.2557, found 349.2555.



**57** **58**

**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl acetate (58).** NaHMDS (1.0 M in THF, 1.4 mL, 1.4 mmol, 3.0 equiv) was added to a solution of ketone **57** (0.160 g, 0.459 mmol, 1.0 equiv) in THF (7.5 mL) at 0 °C, and the resulting yellow reaction mixture was stirred at this temperature for 30 min. Acetic anhydride (0.30 mL, 3.2 mmol, 7.0 equiv) was added dropwise, and stirring was continued at 0 °C for 15 min before the reaction mixture was quenched with $NH_4Cl$ solution (7.5 mL, sat. aqueous). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 40 mL). The combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:100) afforded enol acetate **58** (130 mg, 73%) as a yellowish oil.

**TLC:** $R_f$ = 0.58 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.95 (ddd, $J$ = 17.3, 10.3, 7.0 Hz, 1H), 5.67 (dd, $J$ = 3.3, 1.0 Hz, 1H), 5.21 (ddd, $J$ = 17.3, 1.9, 1.0 Hz, 1H), 5.02 (ddd, $J$ = 10.3, 2.1, 0.7 Hz, 1H), 4.89 (app p, $J$ = 1.0 Hz, 1H), 4.84 (app t, $J$ = 1.7 Hz, 1H), 4.42–4.33 (m, 1H), 3.22 (app t, $J$ = 2.3 Hz, 1H), 2.04–1.96 (m, 1H), 1.96–1.85 (m, 1H), 1.76 (app t, $J$ = 1.0 Hz, 3H), 1.66–1.59 (m, 5H), 1.51–1.42 (m, 1H), 1.24–1.12 (m, 1H), 1.07 (s, 3H), 1.03 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 168.2, 152.2, 148.6, 142.9, 115.2, 110.6, 109.4, 73.4, 65.5, 46.9, 44.1, 41.9, 34.8, 26.2, 25.0, 22.8, 20.5, 19.7, 18.5, –3.7, –4.4; **IR** (thin film): 2956, 2929, 2856, 1763, 1644, 1462, 1368, 1251, 1194, 1090, 1049, 836, 775 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{23}H_{39}O_3Si$ [$(M+H)^+$] 391.2663, found 391.2662.

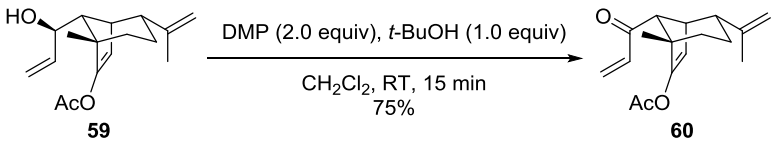


**58** **59**

**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-Hydroxyallyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl acetate (59).** To a solution of enol acetate **58** (0.130 g, 0.333 mmol, 1.0 equiv) in THF (3.3 mL) in a 15 mL polypropylene tube at 0 °C was slowly added hydrogen fluoride pyridine (70 wt% HF, 0.51 mL, 4.0 mmol, 12 equiv). The resulting reaction mixture was stirred at ambient temperature for 14 h before it was cooled to 0 °C and carefully quenched with $KHCO_3$ solution (10 mL, sat. aqueous). The phases were separated, the aqueous layer was extracted with

diethyl ether (3 x 40 mL) and the combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded allylic alcohol **59** (80 mg, 87%) as a colorless oil.

**TLC:** $R_f$ = 0.22 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.82 (ddd, $J$ = 17.1, 10.5, 4.3 Hz, 1H), 5.60 (app dt, $J$ = 17.1, 2.0 Hz, 1H), 5.50–5.44 (m, 1H), 5.19 (app dt, $J$ = 10.5, 2.0 Hz, 1H), 4.75 (dd, $J$ = 1.5, 0.8 Hz, 1H), 4.73 (dd, $J$ = 1.5, 0.8 Hz, 1H), 4.54 (app q, $J$ = 2.4 Hz, 1H), 3.10 (s, br, 1H), 2.98–2.93 (m, 1H), 1.88 (dd, $J$ = 12.1, 5.1 Hz, 1H), 1.77–1.64 (m, 1H), 1.64–1.60 (m, 3H), 1.58 (s, 3H), 1.57–1.51 (m, 1H), 1.45–1.36 (m, 2H), 1.14–1.05 (m, 1H), 1.02 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 169.9, 152.0, 148.2, 140.8, 114.5, 114.5, 109.5, 70.8, 64.0, 46.1, 44.3, 39.9, 34.1, 25.2, 22.4, 20.0, 17.4; **IR** (thin film): 3514, 2931, 2854, 1744, 1644, 1455, 1439, 1370, 1218, 1195, 1174, 1087, 990, 918, 887 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{17}H_{24}NaO_3$ [$(M+Na)^+$] 299.1618, found 299.1615.

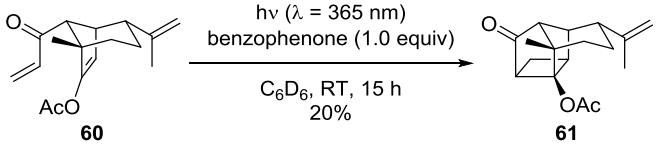


**59** **60**

**(1*S*,2*R*,5*S*,8*R*)-8-Acryloyl-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl acetate (60).** To a solution of allylic alcohol **59** (0.030 g, 0.11 mmol, 1.0 equiv) in $CH_2Cl_2$ (2 mL) at ambient temperature was added DESS–MARTIN periodinane (92 mg, 0.22 mmol, 2.0 equiv). The resulting colorless mixture was stirred for 5 min before *t*-BuOH (0.010 mL, 0.11 mmol, 1.0 equiv) was added. Stirring was continued for 15 min, then the reaction mixture was quenched with $Na_2S_2O_3$ solution (1.2 mL, sat. aqueous), stirred vigorously for 5 min and poured on $NaHCO_3$ solution (6 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded enone **60** (22 mg, 74%) as a colorless oil.

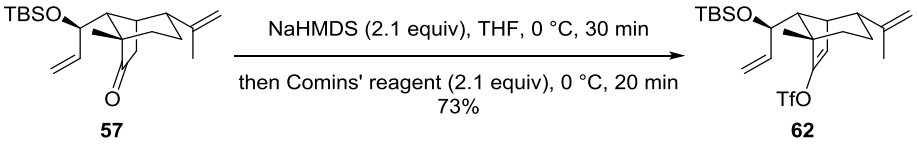
**TLC:** $R_f$ = 0.84 (EtOAc/hexane, 50:50; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 6.29 (dd, $J$ = 17.3, 10.4 Hz, 1H), 6.10 (dd, $J$ = 17.3, 1.8 Hz, 1H), 5.76 (dd, $J$ = 3.3, 0.7 Hz, 1H), 5.18 (dd, $J$ = 10.4, 1.8 Hz, 1H), 4.80 (app q, $J$ = 0.9 Hz, 1H), 4.78 (app t, $J$ = 1.6 Hz, 1H), 2.87–2.80 (m, 1H), 2.33 (app s, 1H), 1.99–1.83 (m, 2H), 1.61 (app t, $J$ = 1.0 Hz, 3H), 1.56 (s, 3H), 1.54–1.44 (m, 2H), 1.19 (s, 3H), 1.15–1.06 (m, 1H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 197.9, 167.8, 151.3, 147.7, 136.2, 126.6, 110.1, 109.2, 68.6, 47.0, 44.0, 43.5, 33.9, 25.1, 22.3, 20.5, 18.6; **IR** (thin

film): 2926, 2854, 1761, 1698, 1679, 1644, 1611, 1455, 1400, 1369, 1190, 1068, 885 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{17}H_{23}O_3$ [$(M+H)^+$] 275.1642, found 275.1644.




**(1*S*,2*S*,3a*R*,4*S*,5*R*,7a*S*,8*S*)-7a-Methyl-3-oxo-5-(prop-1-en-2-yl)octahydro-1H-1,4,2-(epietha-ne[1,1,2]triyl)inden-1-yl acetate (61).** A solution of enone **60** (0.020 g, 73 µmol, 1.0 equiv) and benzophenone (13 mg, 73 µmol, 1.0 equiv) in degassed deuterated benzene (8 mL, degassed by freeze-pump-thaw, three cycles) was placed in a quartz round-bottomed flask and irradiated with a 365 nm UV lamp (365 nm, BioGlow Handheld UV Lamp) at ambient temperature for 15 h. The reaction was monitored by $^1$H NMR (disappearance of the signal at 5.76 ppm, appearance of the signal at 2.77 ppm). The colorless reaction mixture was then concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded tetracycle **61** (4 mg, 20%) as a yellowish oil.

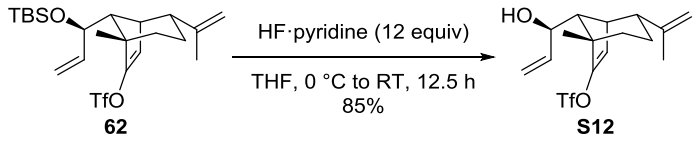
**TLC:** $R_f$ = 0.29 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.78–4.74 (m, 1H), 4.64–4.59 (m, 1H), 3.21–3.14 (m, 1H), 2.91 (ddd, $J$ = 10.4, 8.0, 7.0 Hz, 1H), 2.77 (ddd, $J$ = 7.0, 5.3, 1.6 Hz, 1H), 2.12 (d, $J$ = 1.4 Hz, 1H), 2.09 (app q, $J$ = 1.6 Hz, 1H), 1.73–1.65 (m, 2H), 1.63 (s, 3H), 1.59–1.56 (m, 1H), 1.52–1.49 (m, 3H), 1.40–1.31 (m, 3H), 0.83 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 209.6, 169.0, 146.6, 110.2, 92.4, 64.3, 49.5, 49.5, 45.9, 44.5, 41.4, 32.0, 30.7, 23.5, 22.7, 20.9, 18.0; **IR** (thin film): 2923, 2853, 1750, 1644, 1451, 1367, 1222, 1079, 1049, 892, 803, 700 $cm^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{17}H_{22}NaO_3$ [$(M+Na)^+$] 297.1461, found 297.1461.




**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl trifluoromethanesulfonate (62).** NaHMDS (1.0 M in THF, 0.12 mL, 0.12 mmol, 2.1 equiv) was added to a solution of ketone **57** (20 mg, 57 µmol, 1.0 equiv) in THF (1 mL) at 0 °C, and the resulting reaction mixture was stirred at this temperature for 30 min. A solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfon-imide) (COMINS' reagent, 47 mg, 0.12 mmol, 2.1 equiv) in THF (0.2 mL) was added dropwise, and stirring was continued at 0 °C for 20 min before the reaction mixture was quenched with $NH_4Cl$ solution (1 mL, sat. aqueous).

The mixture was diluted with water (5 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:100) afforded enol triflate **62** (20 mg, 73%) as a yellowish oil.

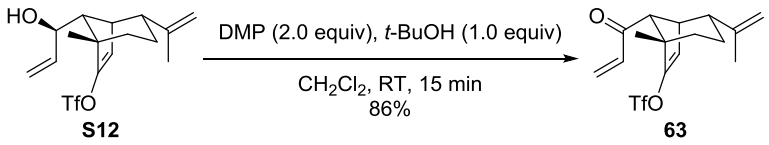
**TLC:** $R_f$ = 0.86 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.84 (ddd, $J$ = 17.3, 10.3, 7.2 Hz, 1H), 5.47–5.43 (m, 1H), 5.22–5.07 (m, 2H), 4.75 (app td, $J$ = 1.5, 0.8 Hz, 1H), 4.66 (q, $J$ = 0.7 Hz, 1H), 4.15–4.08 (m, 1H), 3.03 (dd, $J$ = 3.5, 2.0 Hz, 1H), 2.10–2.02 (m 1H), 1.74 (app dt, $J$ = 1.3, 0.6 Hz, 3H), 1.70–1.60 (m, 3H), 1.53–1.47 (m, 1H), 1.41–1.31 (m, 1H), 1.05 (s, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 150.9, 147.7, 141.5, 115.8, 113.7, 109.3, 72.5, 64.7, 46.5, 43.2, 40.9, 33.5, 25.8, 24.0, 22.5, 18.5, 18.1, –4.0, –4.9 (*C*$F_3$ not detected); **IR** (thin film): 2955, 2929, 2857, 1641, 1462, 1423, 1250, 1212, 1141, 1047, 861, 836, 775, 607 cm$^{-1}$; **HRMS** (MALDI): exact mass calculated for $C_{22}H_{35}F_3NaO_4SSi$ [$(M+Na)^+$] 503.1870, found 503.1870.




**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-1-Hydroxyallyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl trifluoromethanesulfonate (S12).** To a solution of silyl ether **62** (88 mg, 0.18 mmol, 1.0 equiv) in THF (1.8 mL) in a 15 mL polypropylene tube at 0 °C was slowly added hydrogen fluoride pyridine (70 wt% HF, 0.28 mL, 2.2 mmol, 12 equiv). The resulting reaction mixture was stirred at ambient temperature for 12.5 h before it was cooled to 0 °C and carefully quenched with $KHCO_3$ solution (10 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 40 mL) and the combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 6:94) afforded alcohol **S12** (57 mg, 85%) as a colorless oil.

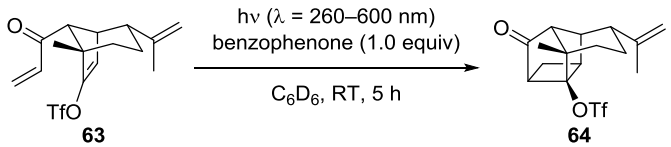
**TLC:** $R_f$ = 0.25 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.89 (ddd, $J$ = 17.2, 10.4, 5.7 Hz, 1H), 5.60–5.53 (m, 1H), 5.37–5.17 (m, 2H), 4.76 (app td, $J$ = 1.5, 0.8 Hz, 1H), 4.67 (dq, $J$ = 1.5, 0.8 Hz, 1H), 4.36–4.29 (m, 1H), 2.97–2.92 (m, 1H), 2.08 (dd, $J$ = 11.7, 5.3 Hz, 1H), 1.77–1.68 (m, 4H), 1.68–1.60 (m, 2H), 1.60–1.54 (m, 1H), 1.51 (d, $J$ = 4.4 Hz, 1H), 1.40 (ddd, $J$ = 13.2, 11.6, 6.1 Hz, 1H), 1.13 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 151.2, 147.4, 140.2, 116.0, 114.3, 109.6, 71.1, 63.2, 46.2, 43.6, 39.9, 33.2, 24.2, 22.3, 17.5 (*C*$F_3$ not

detected); **IR** (thin film): 3432, 2925, 2857, 1640, 1421, 1212, 1140, 1047, 869, 851, 605 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{16}H_{21}F_3NaO_4S$ [$(M+Na)^+$] 389.1005, found 389.1006.




**(1*S*,2*R*,5*S*,8*R*)-8-Acryloyl-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl trifluoromethanesulfonate (63).** To a solution of allylic alcohol **S12** (49 mg, 0.13 mmol, 1.0 equiv) in $CH_2Cl_2$ (1.3 mL) at ambient temperature was added DESS–MARTIN periodinane (113 mg, 0.27 mmol, 2.0 equiv). The resulting colorless mixture was stirred for 5 min before *t*-BuOH (13 µL, 0.13 mmol, 1.0 equiv) was added. Stirring was continued for 15 min, then the reaction mixture was quenched with $Na_2S_2O_3$ solution (1 mL, sat. aqueous), stirred vigorously for 5 min and poured on $NaHCO_3$ solution (5 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 40 mL) and the combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded enone **63** (42 mg, 86%) as a colorless oil.

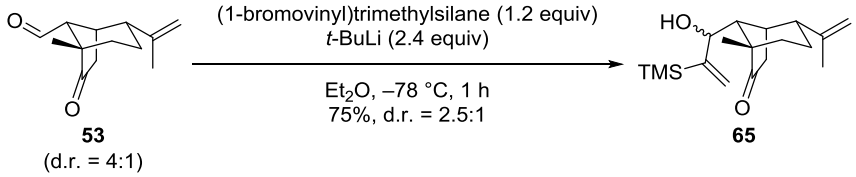
**TLC:** $R_f$ = 0.39 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 6.06–5.91 (m, 2H), 5.49 (dd, $J$ = 3.5, 0.8 Hz, 1H), 5.14 (dd, $J$ = 8.9, 3.1 Hz, 1H), 4.71–4.68 (m, 1H), 4.63–4.60 (m, 1H), 2.68–2.63 (m, 1H), 2.16 (s, 1H), 1.73–1.55 (m, 2H), 1.48 (app t, $J$ = 1.0 Hz, 3H), 1.44–1.24 (m, 2H), 1.01 (s, 3H), 0.96–0.86 (m, 1H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 196.6, 150.0, 146.8, 136.0, 127.2, 113.7, 110.4, 67.7, 47.1, 43.3, 42.7, 32.8, 24.4, 22.1, 17.9 ($CF_3$ not detected); **IR** (thin film): 2928, 2857, 1698, 1642, 1422, 1248, 1212, 1140, 1052, 853, 606 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{16}H_{20}F_3O_4S$ [$(M+H)^+$] 365.1029, found 365.1025.




**(1*S*,2*S*,3a*R*,4*S*,5*R*,7a*S*,8*S*)-7a-Methyl-3-oxo-5-(prop-1-en-2-yl)octahydro-1H-1,4,2-(epiethane[1,1,2]triyl)inden-1-yl trifluoromethanesulfonate (64).** A solution of enone **63** (5.0 mg, 14 µmol, 1.0 equiv) and benzophenone (2.5 mg, 14 µmol, 1.0 equiv) in degassed deuterated benzene (1.4 mL, degassed by freeze-pump-thaw, three cycles) was placed in a quartz test tube and the resulting clear colorless reaction mixture was irradiated with a 150-W medium-pressure mercury lamp (Wisag TQ 150) at ambient temperature for 5 h. The reaction was monitored by

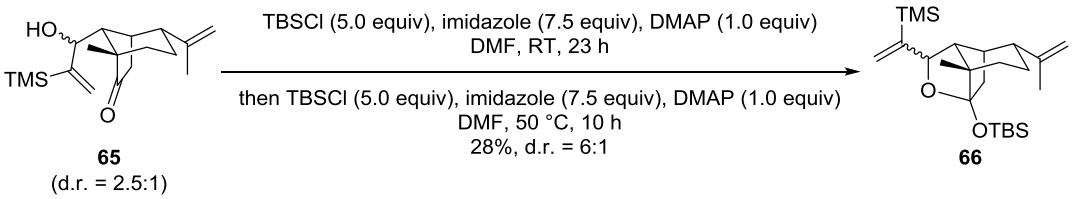
$^1$H NMR. The now yellow solution was concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 3:97) afforded cyclobutane **64** (yield not determined) as a colorless film.

**TLC:** $R_f$ = 0.46 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.69 (q, $J$ = 1.3 Hz, 1H), 4.47 (q, $J$ = 1.1 Hz, 1H), 2.98 (ddd, $J$ = 7.8, 5.9, 2.0 Hz, 1H), 2.76 (ddd, $J$ = 7.5, 5.9, 1.7 Hz, 1H), 2.68 (app dt, $J$ = 11.0, 7.4 Hz, 1H), 1.94 (app q, $J$ = 1.7 Hz, 1H), 1.91 (d, $J$ = 1.5 Hz, 1H), 1.59–1.41 (m, 2H), 1.41–1.39 (m, 3H), 1.37–1.28 (m, 3H), 1.14 (d, $J$ = 10.9 Hz, 1H), 0.68 (s, 3H); **IR** (thin film): 2925, 2855, 1760, 1458, 1414, 1213, 1144, 1008, 877, 613 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{16}H_{20}F_3O_4S$ [(M+H)$^+$] 365.1029, found 365.1038.



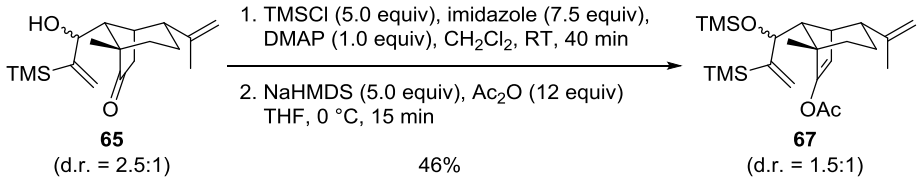

**(1*R*,2*R*,5*S*,8*R*)-8-(1-Hydroxy-2-(trimethylsilyl)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo-[3.2.1]octan-6-one (65).** *t*-BuLi (1.7 M in pentane, 0.75 mL, 1.3 mmol, 2.4 equiv) was added dropwise to a solution of (1-bromovinyl)trimethylsilane (0.10 mL, 0.64 mmol, 1.2 equiv) in diethyl ether (2 mL) at –78 °C, and the resulting yellowish solution was stirred at this temperature for 1 h. Then, a solution of aldehyde **53** as a mixture of diastereomers (110 mg, 0.533 mmol, 1.0 equiv) in diethyl ether (1 mL) was slowly added, and stirring was continued at –78 °C for 1 h. The reaction mixture was quenched with $NH_4Cl$ solution (2 mL, sat. aqueous), allowed to warm to ambient temperature, diluted with water (5 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 7/93) afforded vinyl silane **65** (123 mg, d.r. = 2.5:1) as a colorless oil.

Only the major diastereomer is reported: **TLC:** $R_f$ = 0.56 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.92 (app t, $J$ = 2.2 Hz, 1H), 5.60 (app td, $J$ = 1.6, 0.8 Hz, 1H), 4.79 (d, $J$ = 1.3 Hz, 1H), 4.71–4.66 (m, 1H), 4.63–4.60 (m, 1H), 2.51–2.41 (m, 2H), 2.18–2.09 (m, 1H), 1.88–1.79 (m, 1H), 1.74–1.72 (m, 1H), 1.72–1.70 (m, 3H), 1.69–1.43 (m, 4H), 1.18 (s, 3H), 0.16 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 221.8, 153.6, 146.6, 123.6, 109.8, 72.9, 56.5, 50.1, 47.9, 38.8, 38.8, 32.5, 23.3, 22.7, 16.7, –0.9; **IR** (thin film): 3451, 2954, 2928, 2854, 1728, 1643, 1451, 1407, 1375, 1248, 891, 853, 835, 758, 690 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{31}O_2Si$ [(M+H)$^+$] 307.2088, found 307.2089.




***tert*-Butyldimethyl(((3a*R*,4*R*,5*R*,7a*S*)-7a-methyl-5-(prop-1-en-2-yl)-3-(1-(trimethylsilyl)vinyl)octahydro-1,4-methanoisobenzofuran-1-yl)oxy)silane (66).** To a mixture of alcohol **65** as a mixture of diastereomers (18 mg, 59 µmol, 1.0 equiv), imidazole (30 mg, 0.44 mmol, 7.5 equiv), DMAP (7.2 mg, 59 µmol, 1.0 equiv) and *tert*-butyldimethylsilyl chloride (44 mg, 0.29 mmol, 5.0 equiv) was added DMF (0.2 mL), and the resulting turbid reaction mixture was stirred at ambient temperature for 23 h. It was then diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (2 x 20 mL) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. A $^1$H NMR indicated only 30% conversion of the starting material, which was therefore again treated with imidazole (30 mg, 0.44 mmol, 7.5 equiv), DMAP (7.2 mg, 59 µmol, 1.0 equiv) and *tert*-butyldimethylsilyl chloride (44 mg, 0.29 mmol, 5.0 equiv) in DMF (0.2 mL) and stirred at 50 °C for 10 h. Work-up as above and purification by column chromatography (EtOAc/hexane, 1:99) afforded acetal **66** (28%, d.r. = 6:1) as a colorless oil.

Only the major diastereomer is reported: **TLC:** $R_f$ = 0.88 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 6.11 (dd, $J$ = 3.6, 2.3 Hz, 1H), 5.46 (dd, $J$ = 3.6, 2.1 Hz, 1H), 4.77 (app dt, $J$ = 3.4, 2.2 Hz, 1H), 4.70–4.66 (m, 1H), 4.58–4.54 (m, 1H), 2.02–1.95 (m, 2H), 1.71–1.51 (m, 10H), 1.02 (s, 3H), 0.90 (s, 9H), 0.16 (s, 6H), 0.11 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 150.2, 148.1, 122.9, 109.8, 108.6, 79.0, 51.8, 47.7, 44.9, 35.7, 35.1, 30.1, 25.8, 23.5, 22.4, 17.9, 17.1, –0.9, –2.8, –3.0; **IR** (thin film): 2954, 2928, 2856, 1644, 1471, 1462, 1322, 1315, 1248, 1218, 935, 887, 835, 780, 756 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{24}H_{45}O_2Si_2$ [$(M+H)^+$] 421.2953, found 421.2950.



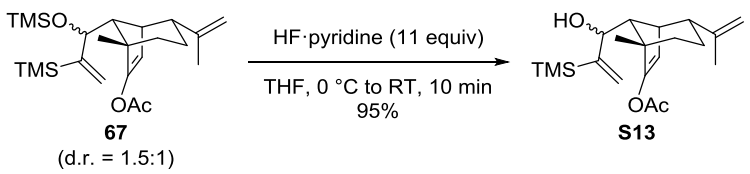

**(1*R*,2*R*,5*S*,8*R*)-5-Methyl-2-(prop-1-en-2-yl)-8-(2-(trimethylsilyl)-1-((trimethylsilyl)oxy)allyl)bicyclo[3.2.1]oct-6-en-6-yl acetate (67).** To a solution of allylic alcohol **65** as a mixture of diastereomers (30 mg, 98 µmol, 1.0 equiv) in $CH_2Cl_2$ (1.5 mL) at 0 °C were sequentially added imidazole (50 mg, 0.73 mmol, 7.5 equiv), DMAP (12 mg, 98 µmol, 1.0 equiv) and trimethylsilyl

chloride (0.06 mL, 0.5 mmol, 5 equiv). The resulting slightly turbid reaction mixture was stirred at ambient temperature for 40 min before it was quenched with $NH_4Cl$ solution (1.5 mL, sat. aqueous), diluted with water (5 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford a yellow oil which was used in the following transformation without further purification.

Only the major diastereomer is reported: **TLC:** $R_f$ = 0.61 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.86 (dd, $J$ = 2.9, 1.7 Hz, 1H), 5.62 (dd, $J$ = 2.9, 1.3 Hz, 1H), 4.79–4.75 (m, 1H), 4.65 (d, $J$ = 1.8 Hz, 1H), 4.60 (s, 1H), 2.55 (d, $J$ = 8.0 Hz, 1H), 2.44 (dd, $J$ = 18.2, 8.0 Hz, 1H), 2.32–1.89 (m, 3H), 1.70 (s, 3H), 1.64–1.45 (m, 4H), 1.10 (s, 3H), 0.14 (s, 9H), 0.01 (s, 9H); **IR** (thin film): 2955, 2928, 2854, 1740, 1644, 1450, 1407, 1374, 1250, 1092, 893, 838, 757 cm$^{-1}$.

NaHMDS (1.0 M in THF, 0.49 mL, 0.49 mmol, 5.0 equiv) was added to a solution of the above product (98 µmol, 1.0 equiv) in THF (0.7 mL) at 0 °C, and the resulting yellow reaction mixture was stirred at this temperature for 2 h. Acetic anhydride (0.11 mL, 1.2 mmol, 12 equiv) was added dropwise, and stirring was continued at 0 °C for 15 min before the reaction mixture was quenched with $NH_4Cl$ solution (1.5 mL, sat. aqueous), diluted with water (5 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded enol acetate **67** (19 mg, 46% over two steps, d.r. = 1.5:1) as a yellowish oil.

Only the major diastereomer is reported: **TLC:** $R_f$ = 0.79 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.80 (dd, $J$ = 2.7, 0.9 Hz, 1H), 5.70 (dd, $J$ = 3.5, 0.9 Hz, 1H), 5.41 (dd, $J$ = 2.7, 0.6 Hz, 1H), 4.91–4.88 (m, 1H), 4.84–4.82 (m, 1H), 4.64 (d, $J$ = 7.4 Hz, 1H), 3.24 (dd, $J$ = 3.5, 1.6 Hz, 1H), 2.11–1.87 (m, 3H), 1.75–1.73 (m, 3H), 1.67 (s, 3H), 1.59–1.48 (m, 2H), 1.33–1.24 (m, 1H), 1.10 (s, 3H), 0.24 (s, 9H), 0.16 (s, 9H); **IR** (thin film): 2955, 2854, 1764, 1645, 1368, 1249, 1193, 1051, 877, 836, 757 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{23}H_{41}O_3Si_2$ [$(M+H)^+$] 421.2589, found 421.2586.

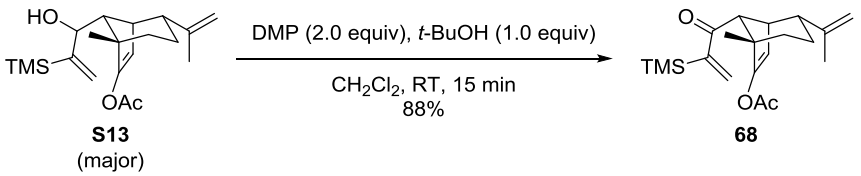



**(1*R*,2*R*,5*S*,8*R*)-8-(1-Hydroxy-2-(trimethylsilyl)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo-[3.2.1]oct-6-en-6-yl acetate (S13).** To a solution of silyl ether **67** as a mixture of diastereomers

(23 mg, 55 µmol, 1.0 equiv) in THF (0.8 mL) in a 15 mL polypropylene tube at 0 °C was slowly added hydrogen fluoride pyridine (70 wt% HF, 0.08 mL, 0.6 mmol, 11 equiv). The resulting reaction mixture was stirred at ambient temperature for 10 min before it was cooled to 0 °C and carefully quenched with $KHCO_3$ solution (7 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 3:97) afforded alcohol **S13** as two diastereomers (major: 12 mg, 63%; minor: 6 mg, 32%).

Major diastereomer: **TLC:** $R_f$ = 0.41 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 6.18 (dd, $J$ = 2.9, 1.9 Hz, 1H), 5.63 (dd, $J$ = 2.9, 1.8 Hz, 1H), 5.51–5.45 (m, 1H), 4.89 (app t, $J$ = 2.5 Hz, 1H), 4.79–4.74 (m, 2H), 3.42 (d, $J$ = 3.2 Hz, 1H), 2.94 (app t, $J$ = 2.6 Hz, 1H), 1.99 (dd, $J$ = 12.0, 5.2 Hz, 1H), 1.82–1.68 (m, 2H), 1.65–1.63 (m, 3H), 1.60–1.54 (m, 4H), 1.47 (ddd, $J$ = 13.1, 6.5, 1.3 Hz, 1H), 1.19–1.13 (m, 1H), 1.11 (s, 3H), 0.21 (s, 9H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 170.1, 153.7, 152.2, 148.1, 124.4, 114.9, 109.5, 72.8, 63.1, 46.3, 44.4, 39.4, 34.4, 25.2, 22.5, 20.0, 17.3, –0.1; **IR** (thin film): 3523, 2954, 2924, 2854, 1748, 1645, 1457, 1371, 1247, 1196, 1088, 888, 854, 836, 756 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{20}H_{32}NaO_3Si$ [(M+Na)$^+$] 371.2013, found 371.2012.

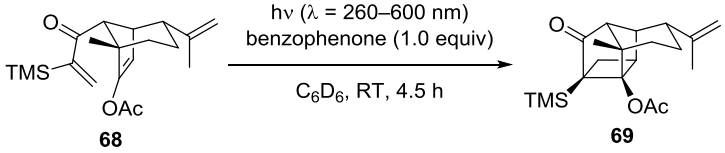
Minor diastereomer: **TLC:** $R_f$ = 0.34 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 5.63 (dd, $J$ = 2.9, 0.9 Hz, 1H), 5.57 (dd, $J$ = 3.3, 1.0 Hz, 1H), 5.36 (d, $J$ = 2.9 Hz, 1H), 4.84–4.82 (m, 1H), 4.78 (app p, $J$ = 1.7 Hz, 1H), 4.53–4.44 (m, 1H), 2.52 (app t, $J$ = 2.5 Hz, 1H), 2.08–2.00 (m, 1H), 1.91 (app dtd, $J$ = 13.5, 12.1, 6.3 Hz, 1H), 1.72–1.65 (m, 7H), 1.63–1.52 (m, 3H), 1.32–1.29 (m, 3H), 0.21 (s, 9H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 168.3, 154.8, 153.3, 148.4, 126.5, 110.3, 109.7, 80.5, 63.8, 48.4, 44.3, 43.9, 34.3, 25.0, 22.6, 20.5, 19.1, 0.3; **IR** (thin film): 2955, 2924, 2854, 1767, 1644, 1457, 1368, 1246, 1194, 888, 838 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{20}H_{32}NaO_3Si$ [(M+Na)$^+$] 371.2013, found 371.2014.




**(1*S*,2*R*,5*S*,8*R*)-5-Methyl-2-(prop-1-en-2-yl)-8-(2-(trimethylsilyl)acryloyl)bicyclo[3.2.1]-oct-6-en-6-yl acetate (68).** To a solution of allylic alcohol **S13** (major diastereomer, 8.0 mg, 23 µmol, 1.0 equiv) in $CH_2Cl_2$ (0.5 mL) at ambient temperature was added DESS–MARTIN periodinane (19 mg, 45 µmol, 2.0 equiv). The resulting colorless mixture was stirred for 5 min before *t*-BuOH (2 µL, 20 µmol, 1 equiv) was added. Stirring was continued for 15 min, then the

reaction mixture was quenched with $Na_2S_2O_3$ solution (0.2 mL, sat. aqueous), stirred vigorously for 5 min and poured on $NaHCO_3$ solution (1 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded enone **68** (7.0 mg, 88%) as a colorless oil.

**TLC:** $R_f$ = 0.45 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 6.07 (d, $J$ = 1.7 Hz, 1H), 5.82 (d, $J$ = 1.7 Hz, 1H), 5.78–5.74 (m, 1H), 4.85–4.83 (m, 1H), 4.78 (app t, $J$ = 1.4 Hz, 1H), 2.93–2.87 (m, 1H), 2.83 (s, 1H), 2.09–1.94 (m, 2H), 1.66–1.59 (m, 4H), 1.58 (s, 3H), 1.58–1.52 (m, 1H), 1.24 (s, 3H), 1.22–1.12 (m, 1H), 0.21 (s, 9H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 203.9, 167.8, 155.2, 151.4, 147.8, 133.5, 110.2, 108.2, 64.6, 46.7, 44.7, 44.3, 33.9, 25.2, 22.3, 20.5, 19.0, –0.9; **IR** (thin film): 2955, 2930, 2854, 1758, 1663, 1646, 1453, 1368, 1246, 1189, 1088, 1068, 884, 857, 841, 765 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{20}H_{31}O_3Si$ [$(M+H)^+$] 347.2037, found 347.2036.

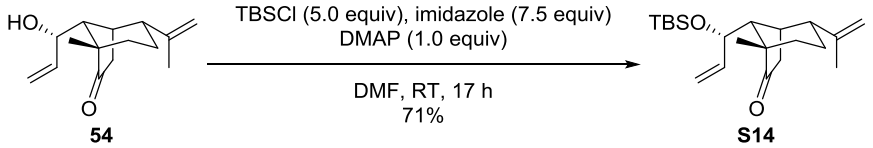


**68** **69**

**(1*R*,2*R*,3a*R*,4*S*,5*R*,7a*S*,8*S*)-7a-Methyl-3-oxo-5-(prop-1-en-2-yl)-2-(trimethylsilyl)octa-hydro-1H-1,4,2-(epiethane[1,1,2]triyl)inden-1-yl acetate (69).** A solution of enone **68** (5.3 mg, 15 µmol, 1.0 equiv) and benzophenone (2.8 mg, 15 µmol, 1.0 equiv) in degassed deuterated benzene (1.4 mL, degassed by freeze-pump-thaw, three cycles) was placed in a quartz test tube and the resulting clear colorless reaction mixture was irradiated with a 150-W medium-pressure mercury lamp (Wisag TQ 150) at ambient temperature for 4.5 h. The reaction was monitored by $^1$H NMR. The resulting solution was then concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:99, then 2:98) afforded cyclobutane **69** (yield not determined) as a colorless oil.

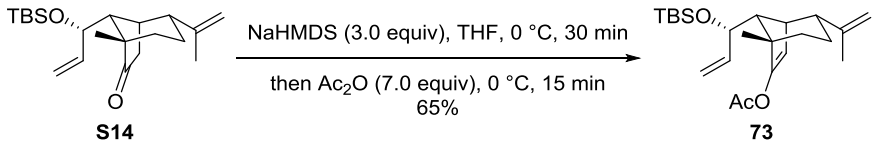
**TLC:** $R_f$ = 0.22 (EtOAc/hexane, 5:95; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.80 (app td, $J$ = 1.5, 1.0 Hz, 1H), 4.73 (dq, $J$ = 1.6, 0.8 Hz, 1H), 3.44–3.38 (m, 1H), 3.01 (dd, $J$ = 10.1, 6.5 Hz, 1H), 2.23 (d, $J$ = 1.5 Hz, 1H), 2.19–2.16 (m, 1H), 1.87 (app qd, $J$ = 12.9, 5.9 Hz, 1H), 1.75–1.69 (m, 1H), 1.68 (s, 3H), 1.61–1.53 (m, 4H), 1.41–1.31 (m, 2H), 1.12 (ddd, $J$ = 13.8, 12.4, 6.0 Hz, 1H), 0.82 (s, 3H), 0.20 (s, 9H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 212.9, 169.0, 146.8, 110.2, 95.9, 64.6, 51.3, 49.0, 47.1, 44.6, 40.9, 35.9, 30.9, 23.5, 22.7, 21.3, 17.8, –2.0; **IR** (thin film): 2956, 2933, 2852, 1748, 1729, 1451, 1368, 1246, 1231, 1199, 1191, 1055, 890, 841,

693 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{20}H_{31}O_3Si$ [$(M+H)^+$] 347.2037, found 347.2037.




**(1*R*,2*R*,5*S*,8*R*)-8-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]octan-6-one (S14).** To a mixture of alcohol **54** (84 mg, 0.36 mmol, 1.0 equiv), imidazole (183 mg, 2.69 mmol, 7.5 equiv), DMAP (43.8 mg, 0.358 mmol, 1.0 equiv) and *tert*-butyldimethylsilyl chloride (270 mg, 1.79 mmol, 5.0 equiv) was added DMF (1.3 mL), and the resulting turbid reaction mixture was stirred at ambient temperature for 19 h. It was then diluted with water (5 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (20 mL) and NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 2:98) afforded silyl ether **S14** (89 mg, 71%) as a colorless oil.

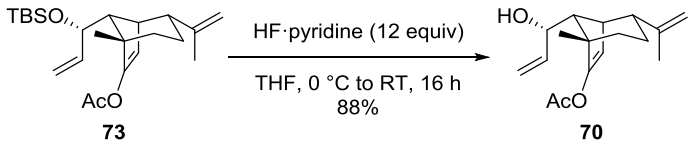
**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.68 (ddd, $J$ = 17.0, 10.3, 6.5 Hz, 1H), 5.08 (app dt, $J$ = 17.2, 1.6 Hz, 1H), 4.97 (app dt, $J$ = 10.3, 1.5 Hz, 1H), 4.70 (q, $J$ = 1.3 Hz, 1H), 4.52 (s, 1H), 4.19–4.10 (m, 1H), 2.49 (dd, $J$ = 8.0, 1.6 Hz, 1H), 2.15 (dd, $J$ = 19.3, 7.7 Hz, 2H), 1.86–1.75 (m, 2H), 1.67 (d, $J$ = 1.3 Hz, 3H), 1.60–1.41 (m, 4H), 1.01 (s, 3H), 0.79 (s, 9H), –0.05 (s, 3H), –0.08 (s, 3H); **HRMS** (ESI): exact mass calculated for $C_{21}H_{37}O_2Si$ [$(M+H)^+$] 349.2557, found 349.2558.




**(1*R*,2*R*,5*S*,8*R*)-8-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)allyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl acetate (73).** NaHMDS (1.0 M in THF, 0.75 mL, 0.75 mmol, 3.0 equiv) was added to a solution of ketone **S14** (87 mg, 0.25 mmol, 1.0 equiv) in THF (4.2 mL) at 0 °C, and the resulting yellow reaction mixture was stirred at this temperature for 30 min. Acetic anhydride (0.17 mL, 1.8 mmol, 7.2 equiv) was added dropwise, and stirring was continued at 0 °C for 15 min before the reaction mixture was quenched with $NH_4Cl$ solution (4 mL, sat. aqueous). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 40 mL). The combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by

column chromatography (EtOAc/hexane, 1:100) afforded enol acetate **73** (63 mg, 65%) as a yellowish oil.

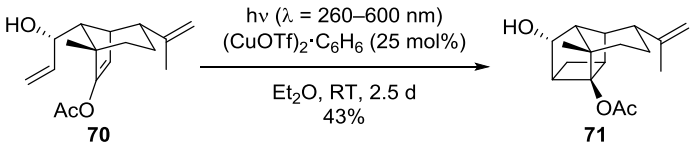
**TLC:** $R_f$ = 0.74 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ 5.84 (ddd, $J$ = 17.5, 10.2, 7.6 Hz, 1H), 5.62 (d, $J$ = 3.0 Hz, 1H), 5.12–5.02 (m, 1H), 4.96 (dd, $J$ = 10.2, 2.1 Hz, 1H), 4.86 (s, 1H), 4.80 (app t, $J$ = 1.6 Hz, 1H), 4.46 (dd, $J$ = 7.6, 6.0 Hz, 1H), 2.86 (app t, $J$ = 2.3 Hz, 1H), 2.07–1.86 (m, 2H), 1.73–1.66 (m, 4H), 1.66–1.61 (m, 4H), 1.61–1.49 (m, 2H), 1.22 (s, 3H), 1.03 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); **HRMS** (ESI): exact mass calculated for $C_{23}H_{39}O_3Si$ [$(M+H)^+$] 391.2663, found 391.2658.



**73** **70**

**(1*R*,2*R*,5*S*,8*R*)-8-((*S*)-1-Hydroxyallyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo[3.2.1]oct-6-en-6-yl acetate (70).** To a solution of enol acetate **73** (30 mg, 77 µmol, 1.0 equiv) in THF (0.76 mL) in a 15 mL polypropylene tube at 0 °C was slowly added hydrogen fluoride pyridine (70 wt% HF, 0.12 mL, 0.92 mmol, 12 equiv). The resulting reaction mixture was stirred at ambient temperature for 16 h before it was cooled to 0 °C and carefully quenched with $KHCO_3$ solution (3 mL, sat. aqueous). The phases were separated, the aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 5:95) afforded allylic alcohol **70** (19 mg, 88%) as a colorless oil.

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ 5.76 (ddd, $J$ = 17.4, 10.2, 7.2 Hz, 1H), 5.61 (d, $J$ = 3.2 Hz, 1H), 5.07 (app dt, $J$ = 17.1, 1.5 Hz, 1H), 4.95 (dd, $J$ = 10.2, 1.9 Hz, 1H), 4.83–4.74 (m, 2H), 4.31–4.19 (m, 1H), 2.67 (app t, $J$ = 2.3 Hz, 1H), 1.99–1.90 (m, 2H), 1.90–1.77 (m, 1H), 1.66–1.64 (m, 3H), 1.63 (s, 3H), 1.61–1.46 (m, 3H), 1.31–1.20 (m, 4H); **HRMS** (ESI): exact mass calculated for $C_{17}H_{24}NaO_3$ [$(M+Na)^+$] 299.1618, found 299.1615.

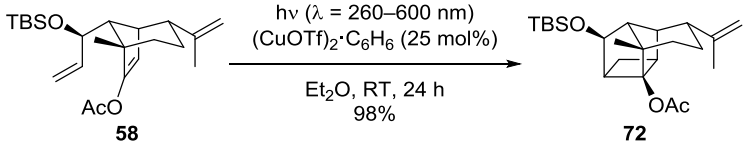


**70** **71**

**(1*S*,2*R*,3*R*,3a*R*,4*R*,5*R*,7a*S*,8*S*)-3-Hydroxy-7a-methyl-5-(prop-1-en-2-yl)octahydro-1H-1,4,2-(epiethane[1,1,2]triyl)inden-1-yl acetate (71).** A solution of allylic alcohol **70** (10 mg, 36 µmol, 1.0 equiv) and copper(I) trifluoromethanesulfonate benzene complex (4.6 mg,

9.0 µmol, 25 mol%) in degassed diethyl ether (0.4 mL, degassed by freeze-pump-thaw, three cycles) was placed in a quartz NMR tube. While stirring, the resulting greenish reaction mixture was irradiated with a 150-W medium-pressure mercury lamp (Wisag TQ 150) at ambient temperature for 2.5 d. The now turbid mixture was poured on water (2 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 7:93, then 20:80) afforded cyclobutane **71** (4.3 mg, 43%) as a colorless oil.

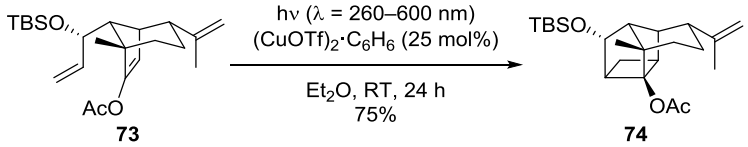
**TLC:** $R_f$ = 0.26 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.83 (app q, $J$ = 1.3 Hz, 1H), 4.78 (app dt, $J$ = 1.7, 0.8 Hz, 1H), 4.38 (dd, $J$ = 7.7, 3.6 Hz, 1H), 3.01 (app dtd, $J$ = 7.7, 6.5, 1.2 Hz, 1H), 2.73–2.64 (m, 2H), 2.43–2.32 (m, 1H), 2.02 (d, $J$ = 10.0 Hz, 1H), 1.92–1.83 (m, 2H), 1.73 (s, 3H), 1.69–1.65 (m, 3H), 1.65–1.60 (m, 1H), 1.52–1.42 (m, 2H), 1.38–1.24 (m, 1H), 0.95 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 169.4, 147.7, 109.5, 96.7, 70.8, 55.3, 47.7, 45.8, 42.7, 42.3, 41.1, 33.1, 25.2, 24.1, 22.8, 21.3, 19.9; **IR** (thin film): 3424, 2933, 2850, 1743, 1726, 1643, 1452, 1439, 1368, 1224, 1059, 1050, 990, 888 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{17}H_{24}NaO_3$ [$(M+Na)^+$] 299.1618, found 299.1622.




**(1*S*,2*R*,3*S*,3a*R*,4*R*,5*R*,7a*S*,8*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-7a-methyl-5-(prop-1-en-2-yl)-octahydro-1H-1,4,2-(epiethane[1,1,2]triyl)inden-1-yl acetate (72).** A solution of silyl ether **58** (10 mg, 26 µmol, 1.0 equiv) and copper(I) trifluoromethanesulfonate benzene complex (3.2 mg, 6.4 µmol, 25 mol%) in degassed diethyl ether (0.3 mL, degassed by freeze-pump-thaw, three cycles) was placed in a quartz NMR tube. While stirring, the resulting greenish reaction mixture was irradiated with a 150-W medium-pressure mercury lamp (Wisag TQ 150) at ambient temperature for 24 h. The now turbid mixture was poured on water (2 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:100) afforded cyclobutane **72** (9.8 mg, 98%) as a colorless oil.

**$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.87–4.82 (m, 1H), 4.81–4.78 (m, 1H), 3.97–3.91 (m, 1H), 2.94 (app td, $J$ = 6.7, 2.1 Hz, 1H), 2.80 (app td, $J$ = 6.6, 1.4 Hz, 1H), 2.65 (app dt, $J$ = 10.1, 7.0 Hz, 1H), 2.10–2.00 (m, 1H), 2.00–1.96 (m, 2H), 1.84–1.80 (m, 1H), 1.77–1.71 (m, 4H), 1.66 (app dt,

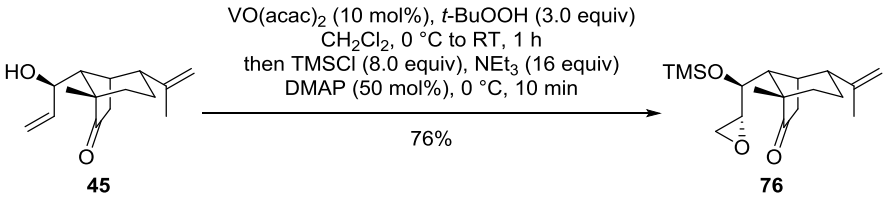
$J$ = 1.3, 0.9 Hz, 3H), 1.58–1.45 (m, 2H), 1.37 (s, 3H), 1.23 (d, $J$ = 10.1 Hz, 1H), 0.99 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 169.3, 147.7, 109.6, 95.7, 81.6, 57.5, 51.3, 50.2, 46.2, 45.8, 39.7, 34.2, 31.6, 26.0, 23.9, 22.8, 21.3, 20.8, 18.2, –4.7; **IR** (thin film): 2929, 2856, 1747, 1644, 1454, 1366, 1222, 1240, 1188, 1112, 1077, 1057, 1047, 1006, 889, 877, 851, 834, 773 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{23}H_{39}O_3Si$ [$(M+H)^+$] 391.2663, found 391.2668.



**73** **74**

**(1*S*,2*R*,3*R*,3a*R*,4*R*,5*R*,7a*S*,8*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-7a-methyl-5-(prop-1-en-2-yl)-octahydro-1H-1,4,2-(epiethane[1,1,2]triyl)inden-1-yl acetate (74).** A solution of silyl ether **73** (10 mg, 26 µmol, 1.0 equiv) and copper(I) trifluoromethanesulfonate benzene complex (3.2 mg, 6.4 µmol, 25 mol%) in degassed diethyl ether (0.3 mL, degassed by freeze-pump-thaw, three cycles) was placed in a quartz NMR tube. While stirring, the resulting greenish reaction mixture was irradiated with a 150-W medium-pressure mercury lamp (Wisag TQ 150) at ambient temperature for 24 h. The now turbid mixture was poured on water (2 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:100) afforded cyclobutane **74** (7.5 mg, 75%) as a colorless oil.

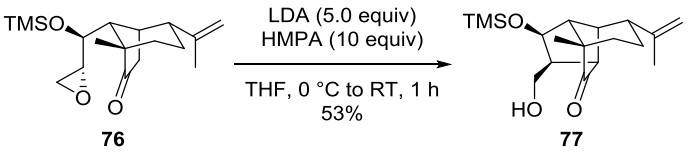
**TLC:** $R_f$ = 0.74 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ 4.86–4.83 (m, 1H), 4.82–4.80 (m, 1H), 4.75 (dd, $J$ = 7.6, 3.6 Hz, 1H), 3.17 (app dtd, $J$ = 7.6, 6.5, 1.2 Hz, 1H), 2.82–2.77 (m, 1H), 2.73–2.66 (m, 1H), 2.41 (app dt, $J$ = 9.8, 7.0 Hz, 1H), 2.17 (d, $J$ = 9.8 Hz, 1H), 1.98–1.86 (m, 2H), 1.75 (s, 3H), 1.72–1.69 (m, 3H), 1.67–1.64 (m, 1H), 1.63–1.60 (m, 1H), 1.51–1.43 (m, 1H), 1.41–1.34 (m, 1H), 1.03 (s, 3H), 0.99 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); **$^{13}$C NMR** (101 MHz, $C_6D_6$): $\delta$ 169.4, 147.6, 109.5, 96.3, 71.9, 56.3, 47.6, 45.9, 42.8, 42.7, 41.1, 33.2, 26.2, 25.7, 24.0, 22.9, 21.3, 19.9, 18.5, –4.7; **IR** (thin film): 2953, 2930, 2856, 1747, 1644, 1463, 1367, f1239, 1223, 1101, 1082, 887, 874, 836 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{23}H_{42}NO_3Si$ [$(M+NH_4)^+$] 408.2928, found 408.2924.




45 76

**(1*R*,2*R*,5*S*,8*R*)-5-Methyl-8-((*S*)-((*R*)-oxiran-2-yl)((trimethylsilyl)oxy)methyl)-2-(prop-1-en-2-yl)bicyclo[3.2.1]octan-6-one (76).** To a solution of allylic alcohol **45** (185 mg, 0.789 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at 0 °C was added vanadyl acetylacetonate (21 mg, 79 µmol, 10 mol%), followed by *tert*-butyl hydroperoxide (5.5 M in decane, 0.43 mL, 2.4 mmol, 3.0 equiv). The resulting deep red reaction mixture was stirred at ambient temperature for 1 h before it was cooled to 0 °C and triethylamine (1.76 mL, 12.6 mmol, 16 equiv), trimethylsilyl chloride (0.81 mL, 6.3 mmol, 8.0 equiv) and DMAP (48 mg, 0.40 mmol, 50 mol%) were added sequentially. After stirring at 0 °C for 10 min, the reaction mixture was quenched with $NH_4Cl$ solution (10 mL, sat. aqueous) and the phases were separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 40 mL) and the combined organic phases were washed with $NH_4Cl$ solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded epoxide **76** (194 mg, 76%) as a colorless oil.

**TLC:** $R_f$ = 0.75 (EtOAc/hexane, 30:70; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.82 (q, $J$ = 1.4 Hz, 1H), 4.65 (dq, $J$ = 1.6, 0.8 Hz, 1H), 3.77 (dd, $J$ = 5.1, 2.4 Hz, 1H), 3.03 (ddd, $J$ = 5.1, 3.8, 2.6 Hz, 1H), 2.84 (dd, $J$ = 5.3, 3.8 Hz, 1H), 2.76–2.72 (m, 1H), 2.69 (ddd, $J$ = 5.3, 2.6 Hz, 0.4 Hz, 1H), 2.47 (dd, $J$ = 18.8, 7.9 Hz, 1H), 2.34–2.27 (m, 1H), 1.94–1.87 (m, 2H), 1.78 (app dt, $J$ = 1.3, 0.6 Hz, 3H), 1.73–1.65 (m, 1H), 1.62–1.56 (m, 2H), 1.51–1.40 (m, 1H), 1.03 (s, 3H), 0.05 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.5, 146.6, 109.9, 71.2, 56.4, 53.0, 49.5, 47.9, 45.6, 38.9, 38.7, 33.9, 23.3, 22.7, 16.3, 0.2; **IR** (thin film): 2941, 1738, 1643, 1451, 1406, 1374, 1251, 1146, 1124, 1047, 996, 887, 842 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{23}$ –23.8° (c = 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{18}H_{31}O_3Si$ [$(M+H)^+$] 323.2037, found 323.2039.



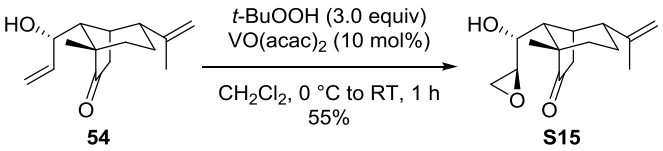

76 77

**(2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-2-(Hydroxymethyl)-4-methyl-7-(prop-1-en-2-yl)-3-((trimethyl-silyl)-oxy)octahydro-1*H*-1,4-methanoinden-8-one (77).** A 0.36 M solution of LDA in THF was prepared as follows: *n*-BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added dropwise to a

solution of diisopropylamine (0.14 mL, 1.0 mmol) in THF (2 mL) at 0 °C and the resulting slightly yellowish reaction mixture was stirred at this temperature for 15 min.

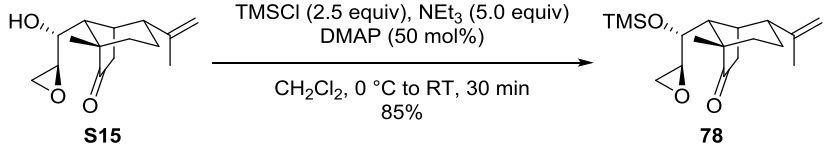
To a solution of epoxide **76** (33 mg, 0.10 mmol, 1.0 equiv) and HMPA (0.18 mL, 1.0 mmol, 10 equiv) in THF (6.4 mL) at 0 °C was added freshly prepared LDA (0.36 M in THF, 1.4 mL, 0.51 mmol, 5.0 equiv) dropwise over 1 min. The resulting clear yellow reaction mixture was stirred at ambient temperature for 1 h before it was quenched with $NH_4Cl$ solution (10 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with diethyl ether (3 x 40 mL) and the combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 15:85) afforded alcohol **77** (18 mg, 53%) as a yellowish oil together with unreacted starting material **76** (9 mg, 27%).

**TLC:** $R_f$ = 0.13 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.78 (app td, $J$ = 1.5, 0.8 Hz, 1H), 4.67–4.65 (m, 1H), 4.49 (dd, $J$ = 9.6, 4.1 Hz, 1H), 3.53 (dd, $J$ = 12.0, 7.8 Hz, 1H), 3.43 (dd, $J$ = 12.0, 7.6 Hz, 1H), 2.65–2.54 (m, 1H), 2.43–2.34 (m, 2H), 2.19–2.15 (m, 1H), 2.12 (app dt, $J$ = 3.6, 1.7 Hz, 1H), 1.74–1.72 (m, 3H), 1.66–1.51 (m, 3H), 1.50–1.38 (m, 1H), 1.25 (s, 3H), 0.13 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.7, 147.1, 110.2, 72.9, 61.2, 56.0, 55.0, 50.5, 46.1, 44.8, 42.5, 38.4, 24.4, 22.4, 19.1, –0.2; **IR** (thin film): 3448, 2928, 1732, 1644, 1374, 1251, 1170, 1121, 1044, 1019, 939, 927, 890, 841, 747 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{23}$ +132.1° (c = 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{18}H_{31}O_3Si$ $[(M+H)^+]$ 323.2037, found 323.2040.



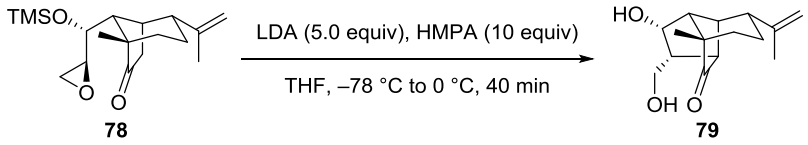

**(1*R*,2*R*,5*S*,8*R*)-8-((*R*)-Hydroxy((*S*)-oxiran-2-yl)methyl)-5-methyl-2-(prop-1-en-2-yl)bicyclo-[3.2.1]octan-6-one (S15).** To a solution of allylic alcohol **54** (60.0 mg, 0.256 mmol, 1.0 equiv) in $CH_2Cl_2$ (1.5 mL) at 0 °C was added vanadyl acetylacetonate (6.8 mg, 26 µmol, 10 mol%), followed by *tert*-butyl hydroperoxide (5.5 M in decane, 0.14 mL, 0.78 mmol, 3.0 equiv). The resulting deep red reaction mixture was stirred at ambient temperature for 1 h before it was quenched with $Na_2S_2O_3$ solution (1.5 mL, sat. aqueous) and stirred vigorously for 10 min. The mixture was then diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 25:75) afforded epoxide **S15** (35 mg, 55%) as a colorless oil.

**TLC:** $R_f$ = 0.25 (EtOAc/hexane, 30:70; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.83 (q, $J$ = 1.4 Hz, 1H), 4.68–4.63 (m, 1H), 3.73–3.64 (m, 1H), 3.04 (td, $J$ = 4.0, 2.8 Hz, 1H), 2.85–2.76 (m, 2H), 2.69–2.64 (m, 1H), 2.37–2.25 (m, 2H), 2.11–1.98 (m, 2H), 1.82–1.79 (m, 1H), 1.79–1.75 (m, 3H), 1.74–1.56 (m, 3H), 1.50–1.41 (m, 1H), 1.15 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 221.1, 146.3, 110.2, 71.6, 57.4, 53.4, 51.1, 47.5, 44.5, 39.1, 38.1, 36.2, 23.2, 22.8, 18.0; **IR** (thin film): 3446, 2933, 1731, 1643, 1453, 1377, 1053, 889, 854 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{15}H_{22}NaO_3$ [$(M+Na)^+$] 273.1461, found 273.1464.



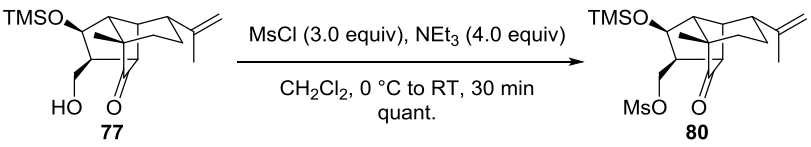

**(1*R*,2*R*,5*S*,8*R*)-5-Methyl-8-((*R*)-((*S*)-oxiran-2-yl)((trimethylsilyl)oxy)methyl)-2-(prop-1-en-2-yl)bicyclo[3.2.1]octan-6-one (78).** To a solution of alcohol **S15** (30 mg, 0.12 mmol, 1.0 equiv) in $CH_2Cl_2$ (1.5 mL) at 0 °C were sequentially added a solution of triethylamine (84 µL, 0.60 mmol, 5.0 equiv) in $CH_2Cl_2$ (0.3 mL), DMAP (7.3 mg, 60 µmol, 50 mol%) and a solution of trimethylsilyl chloride (38 µL, 0.30 mmol, 2.5 equiv) in $CH_2Cl_2$ (0.3 mL). The resulting clear colorless reaction mixture was stirred at ambient temperature for 30 min before it was quenched with $NH_4Cl$ solution (1.5 mL, sat. aqueous), diluted with water (5 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with $NH_4Cl$ solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded silyl ether **78** (33 mg, 85%) as a colorless oil.

**TLC:** $R_f$ = 0.72 (EtOAc/hexane, 30:70; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.82 (q, $J$ = 1.4 Hz, 1H), 4.64 (dq, $J$ = 1.6, 0.8 Hz, 1H), 3.52 (dd, $J$ = 6.5, 2.7 Hz, 1H), 2.95 (ddd, $J$ = 6.5, 3.7, 2.6 Hz, 1H), 2.80 (dd, $J$ = 5.2, 3.7 Hz, 1H), 2.63–2.59 (m, 1H), 2.52–2.46 (m, 1H), 2.37–2.26 (m, 2H), 2.05 (dd, $J$ = 5.0, 2.7 Hz, 1H), 2.00–1.92 (m, 1H), 1.77–1.75 (m, 3H), 1.71–1.54 (m, 3H), 1.45–1.37 (m, 1H), 1.18 (s, 3H), 0.09 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.6, 146.4, 110.0, 77.0, 57.4, 53.7, 50.4, 47.8, 47.5, 39.1, 38.6, 37.9, 23.1, 22.8, 18.5, 0.3; **IR** (thin film): 2933, 2856, 1737, 1642, 1451, 1375, 1251, 1114, 841 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{31}O_3Si$ [$(M+H)^+$] 323.2037, found 323.2039.




**(2*R*,3*R*,3a*R*,4*S*,7*R*,7a*R*)-3-Hydroxy-2-(hydroxymethyl)-4-methyl-7-(prop-1-en-2-yl)octahydro-1*H*-1,4-methanoinden-8-one (79).** To a solution of epoxide **78** (5.0 mg, 16 µmol, 1.0 equiv) and HMPA (27 µL, 0.16 mmol, 10 equiv) in THF (1 mL) at –78 °C was added dropwise freshly prepared LDA (0.36 M in THF, 0.22 mL, 79 µmol, 5.0 equiv). The resulting clear yellow reaction mixture was stirred at –78 °C for 10 min, then at 0 °C for 30 min before it was quenched with $NH_4Cl$ solution (2 mL, sat. aqueous). The mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90, then EtOAc) afforded alcohol **79** (yield not determined) as white needles.

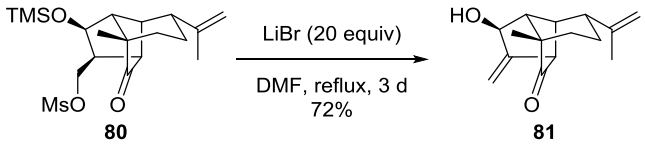
**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.79 (q, $J$ = 1.3 Hz, 1H), 4.67 (app dt, $J$ = 2.0, 1.1 Hz, 1H), 4.43 (dd, $J$ = 7.0, 2.1 Hz, 1H), 3.93–3.79 (m, 2H), 2.93 (d, $J$ = 2.2 Hz, 1H), 2.62 (d, $J$ = 2.8 Hz, 1H), 2.52 (app dt, $J$ = 12.5, 3.7 Hz, 1H), 2.28 (d, $J$ = 2.2 Hz, 1H), 2.26–2.16 (m, 1H), 2.13–2.02 (m, 2H), 1.78–1.73 (m, 3H), 1.72–1.64 (m, 2H), 1.63–1.52 (m, 1H), 1.51–1.37 (m, 1H), 1.03 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.9, 147.5, 110.0, 70.5, 62.5, 58.6, 54.1, 47.2, 45.4, 43.6, 41.8, 36.4, 24.6, 22.5, 17.1; **IR** (thin film): 3401, 2933, 1727, 1643, 1458, 1376, 1078, 1049, 1028, 1002, 890 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{15}H_{22}NaO_3$ [$(M+Na)^+$] 273.1461, found 273.1459.




**((2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-Methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)-octahydro-1H-1,4-methanoinden-2-yl)methyl methanesulfonate (80).** To a solution of alcohol **77** (18 mg, 56 µmol, 1.0 equiv) in $CH_2Cl_2$ at 0 °C was added triethylamine (31 µL, 0.22 mmol, 4.0 equiv), followed by a solution of methanesulfonyl chloride (13 µL, 0.17 mmol, 3.0 equiv) in $CH_2Cl_2$ (0.5 mL). The resulting clear yellowish reaction mixture was stirred at ambient temperature for 30 min before it was quenched with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by

column chromatography (EtOAc/hexane, 15:85) afforded mesylate **80** (23 mg, quant.) as a yellow oil.

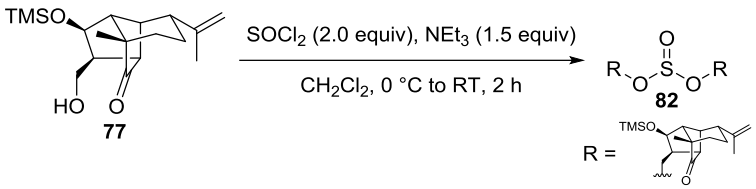
**TLC:** $R_f$ = 0.35 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 4.80 (q, $J$ = 1.3 Hz, 1H), 4.70–4.62 (m, 1H), 4.51 (dd, $J$ = 9.7, 4.2 Hz, 1H), 4.22–4.07 (m, 1H), 3.83 (dd, $J$ = 10.3, 9.4 Hz, 1H), 3.05 (s, 3H), 2.81–2.68 (m, 1H), 2.66 (dd, $J$ = 4.8, 1.9 Hz, 1H), 2.39 (d, $J$ = 11.8 Hz, 1H), 2.20–2.10 (m, 2H), 1.73 (s, 3H), 1.66–1.56 (m, 3H), 1.51–1.41 (m, 1H), 1.22 (s, 3H), 0.11 (s, 9H); **IR** (thin film): 2928, 2854, 1734, 1455, 1357, 1252, 1175, 1122, 958, 890, 843, 749 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{19}H_{33}O_5SSi$ [$(M+H)^+$] 401.1812, found 401.1812.



**80** **81**

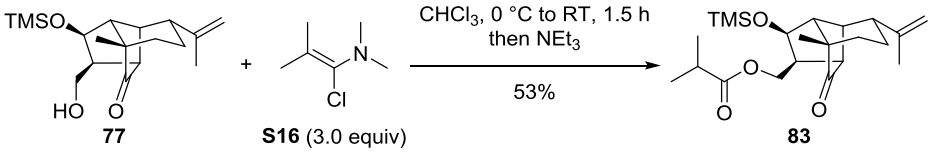
**(3*S*,3a*R*,4*S*,7*R*,7a*R*)-3-Hydroxy-4-methyl-2-methylene-7-(prop-1-en-2-yl)octahydro-1*H*-1,4-methanoinden-8-one (81).** Mesylate **80** (4.8 mg, 12 µmol, 1.0 equiv) and lithium bromide (21 mg, 0.24 mmol, 20 equiv) were dissolved in DMF (1 mL) and heated to reflux temperature. After 3 d, the orange reaction mixture was allowed to cool to ambient temperature, diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were sequentially washed with water (2 x 20 mL) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 25:75) afforded alkene **81** (2.0 mg, 72%) as a colorless oil.

**TLC:** $R_f$ = 0.23 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.28 (d, $J$ = 2.8 Hz, 1H), 5.18–5.15 (m, 1H), 4.80 (td, $J$ = 1.5, 0.8 Hz, 1H), 4.71 (s, 1H), 4.68 (td, $J$ = 1.4, 0.7 Hz, 1H), 3.23–3.18 (m, 1H), 2.47–2.40 (m, 1H), 2.30 (dt, $J$ = 4.4, 2.1 Hz, 1H), 2.29–2.26 (m, 1H), 1.75–1.82 (m, 3H), 1.70–1.62 (m, 3H), 1.53–1.39 (m, 1H), 1.30 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 215.4, 147.8, 146.8, 110.8, 110.3, 76.1, 62.3, 53.8, 48.8, 45.4, 42.5, 38.1, 24.1, 22.4, 19.7; **IR** (thin film): 3445, 2928, 2852, 1727, 1645, 1452, 1375, 1133, 1099, 1087, 1056, 891 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{15}H_{21}O_2$ [$(M+H)^+$] 233.1536, found 233.1540.



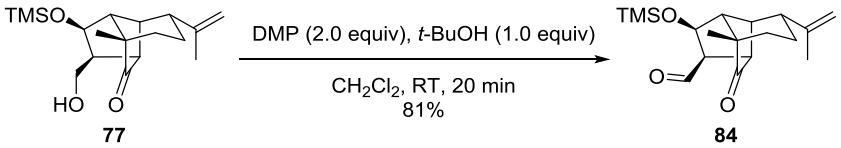

**Bis(((2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)octahydro-1*H*-1,4-methanoinden-2-yl)methyl) sulfite (82).** A solution of triethylamine (3.2 µL, 23 µmol, 1.5 equiv) in $CH_2Cl_2$ (0.1 mL) was added to a solution of alcohol **77** (5.0 mg, 16 µmol, 1.0 equiv) in $CH_2Cl_2$ (0.2 mL), and the resulting mixture was cooled to 0 °C. A solution of thionyl chloride (2.3 µL, 31 µmol, 2.0 equiv) in $CH_2Cl_2$ (0.1 mL) was then added dropwise, and the resulting clear colorless reaction mixture was stirred at ambient temperature for 2 h before it was quenched with $NaHCO_3$ solution (0.5 mL, sat. aqueous), diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 7:93 to 15:85) afforded dithiocarbonate **82** (ca. 1 mg), along with recovered alcohol **77** (2 mg, 40%).

**TLC:** $R_f$ = 0.62 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.79–4.77 (m, 2H), 4.69–4.63 (m, 2H), 4.49 (dt, *J* = 9.1, 4.4 Hz, 2H), 4.07 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.89–3.75 (m, 2H), 3.60 (dd, *J* = 10.9, 8.3 Hz, 1H), 2.71–2.58 (m, 4H), 2.42–2.33 (m, 2H), 2.21–2.14 (m, 2H), 2.14–2.08 (m, 2H), 1.76–1.70 (m, 6H), 1.66–1.57 (m, 6H), 1.50–1.38 (m, 4H), 1.23 (d, *J* = 6.0 Hz, 6H), 0.11 (d, *J* = 4.4 Hz, 18H).; **HRMS** (ESI): exact mass calculated for $C_{36}H_{62}NO_7SSi_2$ [$(M+NH_4)^+$] 708.3780, found 708.3775.



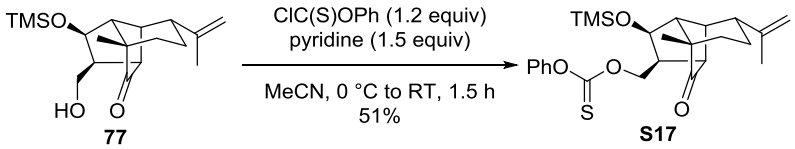

**((2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-Methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)octahydro-1*H*-1,4-methanoinden-2-yl)methyl isobutyrate (83).** A solution of GHOSEZ's reagent (**S16**) (6.5 µL, 47 µmol, 1.0 equiv) in $CHCl_3$ (50 µL) was added to a solution of alcohol **77** (5.0 mg, 16 µmol, 1.0 equiv) in $CHCl_3$ (0.3 mL) at 0 °C. The resulting clear colorless reaction mixture was stirred at ambient temperature for 1.5 h, before it was cooled to 0 °C and quenched with triethylamine (10 µL). It was then concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded isobutyrate **83** (3.2 mg, 53%) as a white solid.

**TLC:** $R_f$ = 0.65 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.78 (td, $J$ = 1.5, 0.8 Hz, 1H), 4.66 (dq, $J$ = 1.5, 0.7 Hz, 1H), 4.48 (dd, $J$ = 10.0, 4.2 Hz, 1H), 4.10 (dd, $J$ = 11.8, 6.1 Hz, 1H), 3.75 (dd, $J$ = 11.8, 8.5 Hz, 1H), 2.66–2.57 (m, 2H), 2.53 (app p, $J$ = 7.0 Hz, 1H), 2.32–2.33 (m, 1H), 2.16–2.13 (m, 1H), 2.12–2.09 (m, 1H), 1.76–1.70 (m, 3H), 1.66–1.38 (m, 4H), 1.23 (s, 3H), 1.16 (dd, $J$ = 7.0, 5.1 Hz, 6H), 0.10 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 219.5, 177.0, 147.2, 110.1, 71.9, 62.2, 55.8, 55.0, 50.4, 46.2, 42.6, 42.5, 38.5, 33.9, 24.4, 22.5, 19.3, 19.0, –0.3; **IR** (thin film): 2934, 1734, 1645, 1460, 1252, 1193, 1160, 1125, 890, 843 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{22}H_{37}O_4Si$ [$(M+H)^+$] 393.2456, found 393.2465.



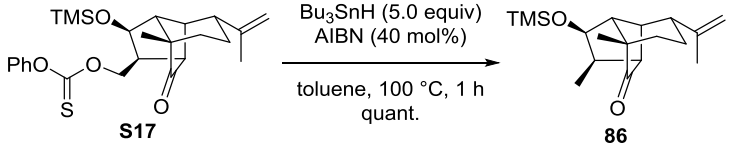

**(2*R*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-Methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)octahydro-1*H*-1,4-methanoindene-2-carbaldehyde (84).** DESS–MARTIN periodinane (26 mg, 62 μmol, 2.0 equiv) was added to a solution of alcohol **77** (10 mg, 31 μmol, 1.0 equiv) in $CH_2Cl_2$ (0.5 mL) at ambient temperature. After 5 min, *t*-BuOH (3.0 μL, 31 μmol, 1.0 equiv) was added, and the resulting orange reaction mixture was stirred at ambient temperature for 15 min before it was quenched with $Na_2S_2O_3$ solution (0.3 mL, sat. aqueous). The mixture was stirred for 5 min, poured on $NaHCO_3$ solution (1 mL, sat. aqueous), diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90, then EtOAc/hexane, 3:97) afforded aldehyde **84** (8.0 mg, 81%) as a yellowish oil.

**TLC:** $R_f$ = 0.62 (EtOAc/hexane, 40:60; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 9.73 (s, 1H), 4.77 (q, $J$ = 1.3 Hz, 1H), 4.68–4.63 (m, 2H), 2.81 (d, $J$ = 1.9 Hz, 1H), 2.49 (d, $J$ = 4.4 Hz, 1H), 2.42–2.33 (m, 1H), 2.17 (dt, $J$ = 4.1, 1.8 Hz, 1H), 2.11–2.07 (m, 1H), 1.70–1.68 (m, 3H), 1.68–1.61 (m, 2H), 1.58 (dd, $J$ = 12.7, 4.5 Hz, 1H), 1.50–1.40 (m, 1H), 1.31 (s, 3H), 0.10 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.1, 198.2, 146.6, 110.3, 71.7, 60.8, 55.1, 52.5, 50.2, 44.5, 41.9, 38.2, 24.2, 22.4, 19.1, –0.2; **IR** (thin film): 2932, 2871, 2852, 1744, 1721, 1644, 1452, 1375, 1251, 1147, 1101, 883, 842 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{28}NaO_3Si$ [$(M+Na)^+$] 343.1700, found 343.1705.




***O*-(((2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-Methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)octahydro-1*H*-1,4-methanoinden-2-yl)methyl) *O*-phenyl carbonothioate (S17).** A solution of pyridine (3.8 µL, 47 µmol, 1.5 equiv) in MeCN (50 µL) was added dropwise to a solution of alcohol **77** (10 mg, 31 µmol, 1.0 equiv) in MeCN (0.5 mL) at 0 °C, followed by a solution of phenyl chlorothionoformate (5.2 µL, 37 µmol, 1.2 equiv) in MeCN (50 µL). The resulting clear yellow reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 30 min before it was quenched with $NaHCO_3$ solution (0.5 mL, sat. aqueous) at 0 °C. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90, then 1:99) afforded carbonothioate **S17** (7.2 mg, 51%) as a white solid.

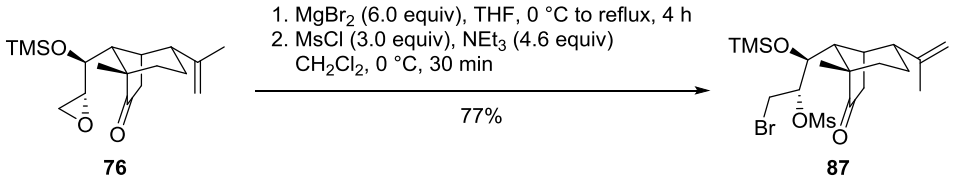
**TLC:** $R_f$ = 0.41 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 7.46–7.36 (m, 2H), 7.32–7.24 (m, 1H), 7.14–7.06 (m, 2H), 4.80 (q, *J* = 1.3 Hz, 1H), 4.69–4.66 (m, 1H), 4.58–4.47 (m, 2H), 4.24 (dd, *J* = 11.3, 7.4 Hz, 1H), 2.83 (dtd, *J* = 9.7, 7.5, 4.8 Hz, 1H), 2.67 (dd, *J* = 4.9, 1.8 Hz, 1H), 2.40 (d, *J* = 11.6 Hz, 1H), 2.22–2.18 (m, 1H), 2.16 (dt, *J* = 3.7, 1.8 Hz, 1H), 1.77–1.72 (m, 3H), 1.70–1.41 (m, 4H), 1.27 (s, 3H), 0.14 (s, 9H); **HRMS** (ESI): exact mass calculated for $C_{25}H_{35}O_4SSi$ [$(M+H)^+$] 459.2020, found 459.2017.




**(2*R*,3*R*,3a*R*,4*S*,7*R*,7a*R*)-2,4-Dimethyl-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)-octahydro-1*H*-1,4-methanoinden-8-one (86).** Tributylstannane (21 µL, 76 µmol, 5.0 equiv) and AIBN (1.0 mg, 6.1 µmol, 40 mol%) were sequentially added to a solution of carbonothioate **S17** (7.0 mg, 15 µmol, 1.0 equiv) in toluene (1.5 mL, degassed by sparging with nitrogen for 30 min). The resulting clear colorless reaction mixture was stirred at 100 °C for 1 h, before it was allowed to cool to ambient temperature and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:99) afforded ketone **86** (5 mg, quant.) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.78–4.74 (m, 1H), 4.67–4.62 (m, 1H), 4.36 (dd, *J* = 9.5, 4.1 Hz, 1H), 2.50–2.39 (m, 2H), 2.39–2.32 (m, 1H), 2.18–2.13 (m, 1H), 2.05 (dt, *J* = 3.6, 1.6 Hz, 1H), 1.75–1.70 (m, 3H), 1.66–1.56 (m, 3H), 1.53–1.42 (m, 1H), 1.21 (s, 3H), 0.77 (d, *J* = 7.1 Hz, 3H),

0.08 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.6, 147.6, 109.9, 72.4, 58.2, 56.0, 50.2, 46.3, 42.7, 38.6, 38.4, 24.5, 22.5, 19.2, 12.4, –0.3; **IR** (thin film): 2956, 2930, 2872, 1737, 1644, 1450, 1374, 1256, 1173, 1130, 1077, 890, 840 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{31}O_2Si$ [$(M+H)^+$] 307.2088, found 307.2090.




**76** **87**

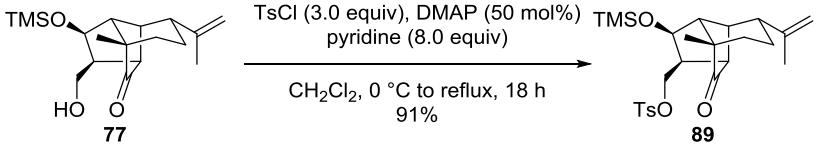
**(1*S*,2*S*)-3-Bromo-1-((1*S*,4*R*,5*R*,8*R*)-1-methyl-7-oxo-4-(prop-1-en-2-yl)bicyclo[3.2.1]octan-8-yl)-1-((trimethylsilyl)oxy)propan-2-yl methanesulfonate (87).** A solution of epoxide **76** (20 mg, 62 μmol, 1.0 equiv) in THF (0.3 mL) was added to a solution of $MgBr_2$ (34 mg, 0.19 mmol, 3.0 equiv) in THF (1 mL) at 0 °C. The resulting clear yellowish reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 90 min before another portion of $MgBr_2$ (34 mg, 0.19 mmol, 3.0 equiv) was added. The reaction mixture was then heated to reflux temperature and stirred for 2 h. It was allowed to cool to ambient temperature, quenched with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were sequentially washed with $NH_4Cl$ solution (20 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford the corresponding bromohydrin (25 mg) as a yellowish oil. The crude product was used in the following transformation without further purification.

**TLC:** $R_f$ = 0.33 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.81 (q, $J$ = 1.4 Hz, 1H), 4.63 (dq, $J$ = 1.5, 0.7 Hz, 1H), 3.97–3.86 (m, 2H), 3.64–3.56 (m, 1H), 3.56–3.43 (m, 1H), 2.90–2.84 (m, 1H), 2.47–2.41 (m, 1H), 2.37 (dd, $J$ = 18.7, 7.9 Hz, 1H), 2.31–2.23 (m, 1H), 1.98–1.96 (m, 1H), 1.95–1.88 (m, 1H), 1.78–1.75 (m, 3H), 1.72–1.64 (m, 1H), 1.64–1.55 (m, 2H), 1.49–1.36 (m, 1H), 1.04 (s, 3H), 0.12 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.9, 146.5, 109.8, 73.9, 73.2, 54.9, 50.0, 47.7, 39.3, 38.8, 36.4, 34.1, 23.2, 22.8, 16.7, 0.6; **IR** (thin film): 3442, 2932, 2855, 1725, 1643, 1441, 1404, 1253, 1096, 1049, 1013, 887, 840, 753 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{32}BrO_3Si$ [$(M+H)^+$] 403.1299, found 403.1296.

To a solution of the above product (25 mg, 62 μmol, 1.0 equiv) in $CH_2Cl_2$ (1.5 mL) at 0 °C was added triethylamine (40 μL, 0.29 mmol, 4.6 equiv), followed by a solution of methanesulfonyl chloride (14 μL, 0.19 mmol, 3.0 equiv) in $CH_2Cl_2$ (0.1 mL). The resulting clear yellowish reaction mixture was stirred at 0 °C for 30 min before it was quenched with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced

pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded mesylate **87** (23 mg, 77%) as a yellowish oil.

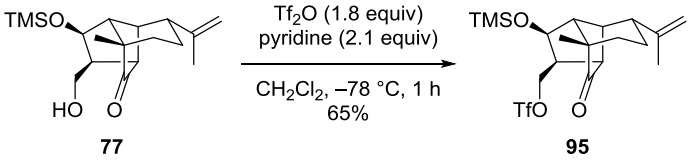
**TLC:** $R_f$ = 0.19 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.89 (dt, $J$ = 6.6, 3.9 Hz, 1H), 4.83 (q, $J$ = 1.4 Hz, 1H), 4.66–4.62 (m, 1H), 4.15 (t, $J$ = 3.8 Hz, 1H), 3.72 (dd, $J$ = 11.9, 3.9 Hz, 1H), 3.59 (dd, $J$ = 11.9, 6.6 Hz, 1H), 3.17 (s, 3H), 2.78–2.72 (m, 1H), 2.37–2.24 (m, 2H), 2.00–1.91 (m, 2H), 1.81–1.77 (m, 3H), 1.72–1.57 (m, 3H), 1.51–1.38 (m, 1H), 1.08 (s, 3H), 0.16 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 220.1, 146.4, 110.1, 83.9, 72.8, 55.1, 50.3, 47.3, 39.5, 39.2, 38.5, 34.0, 30.7, 23.1, 22.7, 16.8, 0.6; **IR** (thin film): 2937, 2856, 1735, 1643, 1451, 1409, 1360, 1254, 1176, 1118, 954, 893, 842, 525 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{19}H_{34}BrO_5SSi$ [$(M+H)^+$] 481.1074, found 481.1070.




**((2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-Methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)octahydro-1*H*-1,4-methanoinden-2-yl)methyl 4-methylbenzenesulfonate (89).** Pyridine (20 µL, 0.25 mmol, 4.0 equiv) and TsCl (18 mg, 93 µmol, 1.5 equiv) were sequentially added to a solution of alcohol **77** (20 mg, 62 µmol, 1.0 equiv) in $CH_2Cl_2$ (1 mL) at 0 °C. The resulting clear colorless reaction mixture was stirred at ambient temperature for 1 h. Then, another portion of pyridine (20 µL, 0.25 mmol, 4.0 equiv) and TsCl (18 mg, 93 µmol, 1.5 equiv) was added, followed by DMAP (3.8 mg, 31 µmol, 50 mol%). The resulting reaction mixture was stirred at ambient temperature for 2 h, then at reflux temperature for 15 h. The colorless solution was allowed to cool to ambient temperature, quenched with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 5:95) afforded tosylate **89** (27 mg, 91%) as a white solid.

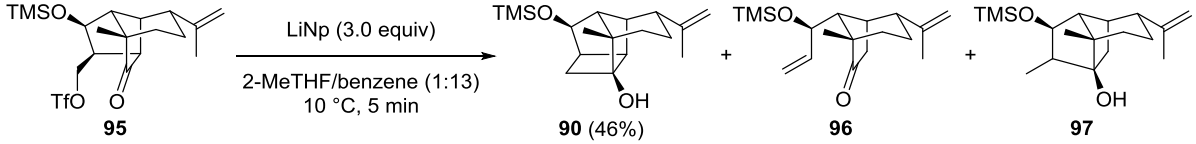
**TLC:** $R_f$ = 0.52 (EtOAc/hexane, 20:80; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 7.80–7.75 (m, 2H), 7.36–7.31 (m, 2H), 4.79–4.75 (m, 1H), 4.63–4.61 (m, 1H), 4.47 (dd, $J$ = 10.0, 4.2 Hz, 1H), 4.03 (dd, $J$ = 10.0, 7.6 Hz, 1H), 3.71 (dd, $J$ = 10.2, 6.8 Hz, 1H), 2.67 (dtd, $J$ = 9.6, 7.2, 4.8 Hz, 1H), 2.56–2.53 (m, 1H), 2.44 (s, 3H), 2.34 (dd, $J$ = 10.3, 6.0 Hz, 1H), 2.15–2.12 (m, 1H), 2.10 (dt, $J$ = 3.8, 1.8 Hz, 1H), 1.71 (dt, $J$ = 1.3, 0.6 Hz, 3H), 1.65–1.52 (m, 3H), 1.44–1.36 (m, 1H), 1.16 (s, 3H), 0.09 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 219.4, 146.9, 144.6, 133.1, 129.8, 127.9, 110.2, 71.5, 68.2, 55.5, 54.6, 50.5, 46.3, 43.0, 42.3, 38.5, 24.3, 22.4, 21.6, 19.3,

–0.4; **IR** (thin film): 2930, 2872, 1736, 1644, 1599, 1453, 1362, 1252, 1176, 1123, 964, 889, 843, 665, 554 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{25}H_{37}O_5SSi$ [$(M+H)^+$] 477.2125, found 477.2127.




**((2*S*,3*S*,3a*R*,4*S*,7*R*,7a*R*)-4-Methyl-8-oxo-7-(prop-1-en-2-yl)-3-((trimethylsilyl)oxy)octahydro-1*H*-1,4-methanoinden-2-yl)methyl trifluoromethanesulfonate (95).** To a solution of alcohol **77** (56 mg, 0.17 mmol, 1.0 equiv) in $CH_2Cl_2$ (4 mL) at –78 °C was added pyridine (0.030 mL, 0.37 mmol, 2.1 equiv) followed by a solution of trifluoromethanesulfonic anhydride (53 µL, 0.31 mmol, 1.8 equiv) in $CH_2Cl_2$ (0.5 mL). The resulting colorless reaction mixture was stirred at –78 °C for 1 h before it was quenched with $NH_4Cl$ solution (4 mL, sat. aqueous) and allowed to warm to ambient temperature. The mixture was diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 40 mL). The combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 3:97) afforded triflate **95** (51 mg, 65%) as white crystals.

**TLC:** $R_f$ = 0.83 (EtOAc/hexane, 30:70; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.81 (app td, $J$ = 1.4, 0.8 Hz, 1H), 4.66 (dq, $J$ = 1.3, 0.6 Hz, 1H), 4.52 (dd, $J$ = 9.6, 4.1 Hz, 1H), 4.45 (dd, $J$ = 10.3, 8.0 Hz, 1H), 4.30 (dd, $J$ = 10.3, 6.5 Hz, 1H), 2.75 (dddd, $J$ = 9.6, 8.0, 6.5, 4.8 Hz, 1H), 2.63 (dd, $J$ = 4.8, 1.9 Hz, 1H), 2.44–2.35 (m, 1H), 2.21–2.14 (m, 2H), 1.75–1.73 (m, 3H), 1.69–1.57 (m, 3H), 1.50–1.39 (m, 1H), 1.24 (s, 3H), 0.13 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 218.9, 146.7, 118.6 (app d, $J$ = 320 Hz, $CF_3$, very weak), 110.5, 74.8, 71.6, 55.4, 54.4, 50.7, 46.2, 42.9, 42.3, 38.4, 24.3, 22.5, 19.3, –0.5; **IR** (thin film): 2934, 1738, 1416, 1246, 1207, 1148, 1126, 944, 890, 877, 845, 612 $cm^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ +87.6° (c = 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{19}H_{30}F_3O_5SSi$ [$(M+H)^+$] 455.1530, found 455.1527.




**(1*R*,3*R*,4*R*,4a*R*,5*R*,6*R*,8a*S*,9*R*)-8a-Methyl-6-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)decahydro-1,3,5-(epimethanetriyl)naphthalen-1-ol (90).** A solution of naphthalene (140 mg, 1.1 mmol) in 2-methyltetrahydrofuran (2.2 mL) under an atmosphere of argon was placed in an

ultrasonic bath filled with ice and water. Lithium (6.9 mg, 1.0 mmol) was added, and the resulting mixture was sonicated for 1 h at 0 °C. The mixture turned dark green as soon as sonication was started.

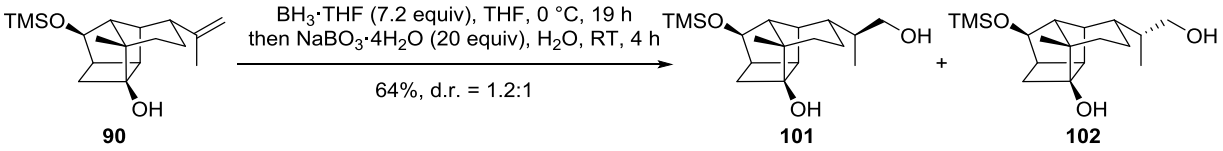
A solution of triflate **95** (0.070 g, 0.15 mmol, 1.0 equiv) in benzene (14 mL) under an atmosphere of argon was cooled to 10 °C. Freshly prepared lithium naphthalenide solution (0.45 M, 1.0 mL, 0.46 mmol, 3.0 equiv) was added dropwise, and the reaction mixture first decolored instantaneously after every drop. When the addition was complete, the color persisted. After 5 min, the now dark brown reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic phases were sequentially washed with $NH_4Cl$ solution (40 mL, sat. aqueous) and NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 5:95) afforded cyclobutanol **90** (22 mg, 46%). The analytical data for byproducts **96** and **97** were obtained from the test reactions described in Table 1.2.

Cyclobutanol **90**: **TLC:** $R_f$ = 0.51 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.75–4.72 (m, 1H), 4.70–4.68 (m, 1H), 4.01 (dd, $J$ = 7.2, 3.1 Hz, 1H), 2.60–2.54 (m, 1H), 2.47 (d, $J$ = 10.1 Hz, 1H), 2.28–2.19 (m, 1H), 2.19–2.12 (m, 1H), 1.82–1.68 (m, 1H), 1.78–1.64 (m, 7H), 1.56–1.49 (m, 2H), 1.37–1.30 (m, 1H), 1.18 (s, 3H), 0.10 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 148.8, 108.9, 78.3, 76.3, 54.8, 52.6, 45.7, 43.9, 43.1, 37.0, 34.5, 30.7, 24.9, 22.5, 18.4, 0.0; **IR** (thin film): 3421, 2929, 2855, 1729, 1643, 1453, 1373, 1262, 1250, 1194, 1158, 1120, 1097, 921, 897, 882, 840, 746 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ +29.2° (c = 0.50, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{18}H_{30}NaO_2Si$ [$(M+Na)^+$] 329.1907, found 329.1915.

Alkene **96**: $R_f$ = 0.71 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.98–5.88 (m, 1H), 5.23–5.16 (m, 2H), 4.80 (q, $J$ = 1.4 Hz, 1H), 4.63 (dq, $J$ = 1.5, 0.8 Hz, 1H), 4.36 (ddt, $J$ = 6.2, 2.6, 1.2 Hz, 1H), 2.68 (dd, $J$ = 7.7, 1.5 Hz, 1H), 2.48 (dd, $J$ = 18.6, 7.7 Hz, 1H), 2.18 (dd, $J$ = 12.3, 4.7 Hz, 1H), 1.86 (ddd, $J$ = 18.6, 1.8, 0.6 Hz, 1H), 1.76–1.73 (m, 3H), 1.69–1.61 (m, 2H), 1.61–1.52 (m, 2H), 1.52–1.38 (m, 1H), 1.07 (s, 3H), 0.04 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 221.0, 146.8, 140.2, 115.4, 109.7, 73.4, 59.5, 49.8, 48.0, 38.8, 33.2, 23.4, 22.7, 16.5, 0.4; **IR** (thin film): 3085, 2956, 2930, 2855, 1738, 1643, 1450, 1406, 1374, 1251, 1126, 1093, 1044, 102, 929, 886, 841, 750 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{30}NaO_2Si$ [$(M+Na)^+$] 329.1907, found 329.1909.

Alcohol **97**: $R_f$ = 0.38 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.72–4.68 (m, 1H), 4.61–4.58 (m, 1H), 3.21 (d, $J$ = 4.5 Hz, 1H), 2.15–2.01 (m, 2H), 1.82–1.73 (m, 2H), 1.71–1.68 (m, 3H), 1.66–1.56 (m, 3H), 1.52–1.41 (m, 1H), 1.33 (s, 1H), 1.24–1.19 (m, 1H);

1.07 (s, 3H), 1.04 (d, $J$ = 6.8 Hz, 3H), 0.09 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 148.5, 108.5, 84.0, 81.9, 55.0, 47.7, 46.9, 45.6, 37.3, 32.2, 27.3, 24.0, 22.2, 18.7, 11.3, 0.2; **IR** (thin film): 3369, 2956, 2928, 2875, 2854, 1718, 1643, 1455, 1374, 1300, 1286, 1250, 1083, 1067, 1020, 924, 875, 839, 747 cm$^{-1}$.

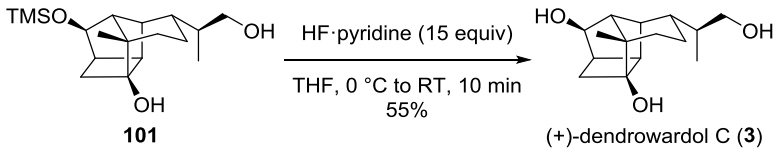



**(1*R*,3*R*,4*R*,4a*R*,5*R*,6*R*,8a*S*,9*R*)-6-((*S*)-1-Hydroxypropan-2-yl)-8a-methyl-4-((trimethylsilyl)-oxy)decahydro-1,3,5-(epimethanetriyl)naphthalen-1-ol (101).** Borane tetrahydrofuran complex (1.0 M in THF, 0.11 mL, 0.11 mmol, 5.2 equiv) was added to a solution of alkene **90** (6.5 mg, 21 µmol, 1.0 equiv) in THF (0.6 mL) at 0 °C. The resulting clear colorless reaction mixture was stirred at 0 °C for 15 h. Another portion of borane tetrahydrofuran complex (1.0 M in THF, 0.04 mL, 0.04 mmol, 2 equiv) was added, and stirring was continued at 0 °C for 4 h. Then, water/THF (1:1, 2 mL) was added, followed by sodium perborate tetrahydrate (65 mg, 0.42 mmol, 20 equiv), and the resulting white suspension was stirred at ambient temperature for 4 h before it was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with $NH_4Cl$ solution (20 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 30:70) afforded alcohol **101** (2.4 mg, 35%) as a yellow oil and minor diastereomer **102** (2.0 mg, 29%) as a colorless oil.

Major diastereomer **101**: **TLC:** $R_f$ = 0.34 (EtOAc/hexane, 40:60; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 3.99 (dd, $J$ = 7.2, 3.1 Hz, 1H), 3.63 (dd, $J$ = 10.6, 4.1 Hz, 1H), 3.51 (dd, $J$ = 10.6, 6.0 Hz, 1H), 2.58–2.53 (m, 1H), 2.46 (d, $J$ = 10.0 Hz, 1H), 2.19–2.11 (m, 1H), 1.79–1.72 (m, 2H), 1.67–1.51 (m, 5H), 1.48–1.37 (m, 1H), 1.32–1.27 (m, 1H), 1.17 (s, 3H), 0.94 (d, $J$ = 6.8 Hz, 3H), 0.09 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 78.4, 76.3, 66.4, 54.7, 52.5, 45.6, 43.2, 39.4, 37.6, 37.0, 34.4, 30.7, 24.6, 18.4, 14.8, 0.0; **IR** (thin film): 3374, 2932, 2876, 1718, 1455, 1372, 1308, 1251, 1192, 1115, 1032, 891, 841, 747 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ +20.6° (c = 0.10, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{18}H_{32}NaO_3Si$ [$(M+Na)^+$] 347.2013, found 347.2015.

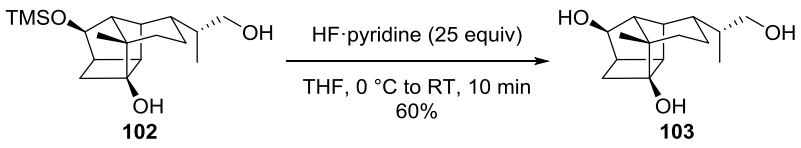
Minor diastereomer **102**: **TLC:** $R_f$ = 0.23 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 3.99 (dd, $J$ = 7.2, 3.1 Hz, 1H), 3.66 (dd, $J$ = 10.6, 4.0 Hz, 1H), 3.50 (dd, $J$ = 10.6, 6.2 Hz, 1H), 2.56–2.51 (m, 1H), 2.47 (d, $J$ = 10.1 Hz, 1H), 2.19–2.12 (m, 1H), 1.79–1.72 (m, 2H), 1.69–1.37 (m, 6H), 1.34–1.28 (m, 1H), 1.17 (s, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H), 0.09 (s, 9H);

**$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 78.4, 76.4, 66.1, 54.6, 52.2, 45.6, 42.3, 39.4, 37.8, 36.9, 34.4, 30.7, 25.4, 18.4, 15.3, 0.0; **IR** (thin film): 3377, 2930, 2874, 1722, 1456, 1372, 1308, 1251, 1190, 1117, 1032, 891, 840, 747 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{18}H_{32}NaO_3Si$ [$(M+Na)^+$] 347.2013, found 347.2013.




**(+)-Dendrowardol C (3).** To a solution of silyl ether **101** (4.9 mg, 15 µmol, 1.0 equiv) in THF (0.6 mL) in a 15 mL polypropylene tube at 0 °C was slowly added hydrogen fluoride pyridine (70 wt% HF, 0.03 mL, 0.23 mmol, 15 equiv). The resulting reaction mixture was stirred at ambient temperature for 10 min before it was cooled to 0 °C and carefully quenched with $KHCO_3$ solution (5 mL, sat. aqueous). The mixture was then extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 90:10) afforded (+)-dendrowardol C (**3**) (2.1 mg, 55%) as a white solid.

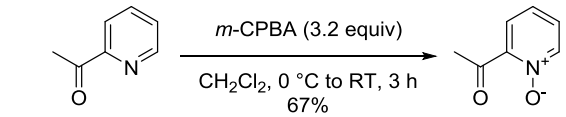
**TLC:** $R_f$ = 0.12 (EtOAc/hexane, 80:20; $KMnO_4$); **$^1$H NMR** (400 MHz, pyridine-$d_5$): $\delta$ 6.44–6.25 (m, br, 2H), 5.84 (s, br, 1H), 4.43 (dd, $J$ = 7.3, 3.0 Hz, 1H), 3.99 (dd, $J$ = 10.4, 4.2 Hz, 1H), 3.80 (dd, $J$ = 10.4, 6.5 Hz, 1H), 3.11 (d, $J$ = 9.7 Hz, 1H), 2.96–2.88 (m, 1H), 2.45 (app tdd, $J$ = 7.4, 5.4, 1.3 Hz, 1H), 2.33–2.13 (m, 4H), 1.99–1.87 (m, 2H), 1.85–1.69 (m, 5H), 1.52–1.39 (m, 1H), 1.22 (d, $J$ = 6.8 Hz, 3H); **$^{13}$C NMR** (101 MHz, pyridine-$d_5$): $\delta$ 78.5, 76.6, 66.2, 56.0, 54.3, 46.7, 45.0, 41.1, 38.9, 38.8, 35.6, 31.7, 25.5, 20.2, 16.1; **IR** (thin film): 3336, 2928, 2875, 1549, 1456, 1305, 1272, 1194, 1160, 1104, 1071, 1033, 993 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ +37.6° (c = 0.10, MeOH); **HRMS** (ESI): exact mass calculated for $C_{15}H_{24}NaO_3$ [$(M+Na)^+$] 275.1618, found 275.1622.




**12-*epi*-Dendrowardol C (103).** To a solution of silyl ether **102** (1.0 mg, 3.1 µmol, 1.0 equiv) in THF (0.3 mL) in a 15 mL polypropylene tube at 0 °C was slowly added hydrogen fluoride pyridine (70 wt% HF, 10 µL, 78 µmol, 25 equiv). The resulting reaction mixture was stirred at ambient temperature for 10 min before it was cooled to 0 °C and carefully quenched with

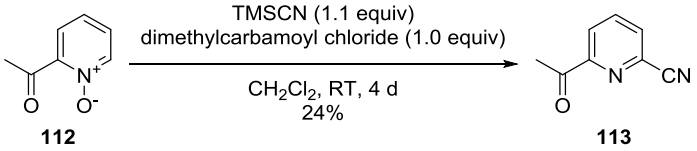
$KHCO_3$ solution (3 mL, sat. aqueous). The mixture was then extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 90:10) afforded 12-*epi*-dendrowardol C (**103**) (0.5 mg, 60%) as a white solid.

**TLC:** $R_f$ = 0.26 (EtOAc/hexane, 90:10; $KMnO_4$); **$^1$H NMR** (400 MHz, pyridine-$d_5$): $\delta$ 6.34–6.28 (m, 2H), 5.75 (t, $J$ = 5.2 Hz, 1H), 4.46 (app dt, $J$ = 6.7, 3.0 Hz, 1H), 3.98 (app dt, $J$ = 10.3, 4.4 Hz, 1H), 3.77 (ddd, $J$ = 10.3, 6.6, 5.1 Hz, 1H), 3.09 (d, $J$ = 9.7 Hz, 1H), 2.90–2.85 (m, 1H), 2.48–2.40 (m, 1H), 2.29–2.06 (m, 4H), 1.96–1.92 (m, 1H), 1.92–1.79 (m, 2H), 1.78–1.67 (m, 4H), 1.47–1.36 (m, 1H), 1.24 (d, $J$ = 6.7 Hz, 3H); **$^{13}$C NMR** (101 MHz, pyridine-$d_5$): $\delta$ 78.5, 76.7, 65.8, 56.0, 54.1, 46.7, 44.0, 41.1, 39.2, 38.8, 35.6, 31.7, 26.5, 20.2, 16.5; **IR** (thin film): 3349, 2928, 2875, 1549, 1457, 1305, 1272, 1194, 1160, 1103, 1071, 1029, 994 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{15}H_{24}NaO_3$ [$(M+Na)^+$] 275.1618, found 275.1618.




**2-Acetylpyridine 1-oxide (112).** Similar to a procedure reported by J. R. PEDRO and co-workers,[117] *m*-CPBA (70%, 35.2 g, 143 mmol, 3.2 equiv) was added to a solution of 2-acetylpyridine (**111**) (5.0 mL, 45 mmol, 1.0 equiv) in $CH_2Cl_2$ (450 mL) at 0 °C. The resulting clear yellowish reaction was first stirred at this temperature for 45 min, then at ambient temperature for 2 h. Concentration under reduced pressure and purification by column chromatography (EtOAc) afforded *N*-oxide **112** (4.1 g, 67%) as a yellow oil which solidified upon standing.

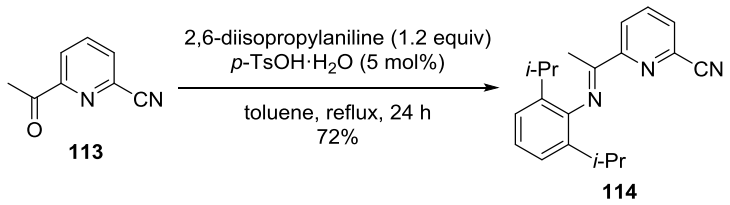
**TLC:** $R_f$ = 0.88 (EtOAc; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 8.22–8.17 (m, 1H), 7.69 (dd, $J$ = 7.7, 2.4 Hz, 1H), 7.40–7.27 (m, 2H), 2.81 (s, 3H). According to the spectral data reported in the literature.[117]




**6-Acetylpicolinonitrile (113).** To a solution of *N*-oxide **112** (2.00 g, 14.6 mmol, 1.0 equiv) in $CH_2Cl_2$ (30 mL) at ambient temperature was added trimethylsilyl cyanide (2.0 mL, 16 mmol, 1.1 equiv), and the resulting clear solution was stirred for 5 min. Then, dimethylcarbamoyl

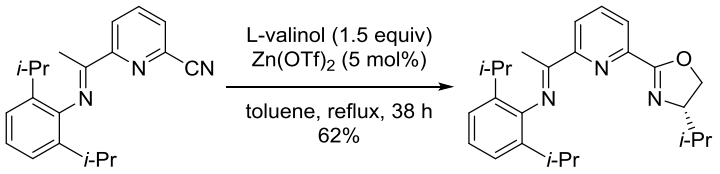
chloride (1.34 mL, 14.6 mmol, 1.0 equiv) was added and the resulting yellow reaction mixture was stirred for 4 d before it was quenched with 10% $K_2CO_3$ solution (30 mL) and stirred overnight. The resulting dark purple mixture was extracted with $CH_2Cl_2$ (2 x 50 mL), dried over $K_2CO_3$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 15:85) afforded nitrile **113** (518 mg, 24%) as off-white crystals.

**TLC:** $R_f$ = 0.58 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 8.23 (dd, $J$ = 8.0, 1.1 Hz, 1H), 8.01 (app t, $J$ = 7.8 Hz, 1H), 7.87 (dd, $J$ = 7.7, 1.2 Hz, 1H), 2.73 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 198.2, 154.4, 138.2, 133.2, 131.3, 124.5, 116.6, 25.6; **IR** (thin film): 3038, 3012, 2240, 1703, 1580, 1448, 1359, 1292, 1265, 1109, 1083, 991, 958, 850, 816, 734, 683, 606, 565 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_8H_6N_2O$ [$M^+$] 146.0475, found 146.0475.




**(*E*)-6-(1-((2,6-Diisopropylphenyl)imino)ethyl)picolinonitrile (114).** According to the procedure reported by Z. HUANG and co-workers,[116] 2,6-diisopropylaniline (0.76 mL, 4.0 mmol, 1.2 equiv) was added to a solution of nitrile **113** (492 mg, 3.37 mmol, 1.0 equiv) in toluene (8.6 mL) at ambient temperature, followed by the addition of *p*-toluenesulfonic acid monohydrate (32 mg, 0.17 mmol, 5 mol%). The resulting clear orange reaction mixture was set to reflux and the water generated in the course of the reaction was removed using a Dean–Stark apparatus. After 24 h, the mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 3:90) afforded a first portion of imine **114** (148 mg, 14%) along with mixed fractions containing the product and 2,6-diisopropylaniline. These were partially concentrated under reduced pressure, whereupon imine **114** (592 mg, 58%) crystallized and could be isolated as yellow crystals by decanting the mother liquor and washing with pentane.

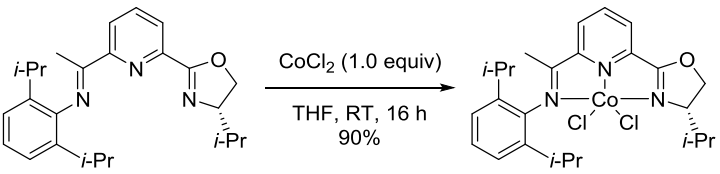
**TLC:** $R_f$ = 0.21 (EtOAc/hexane, 10:90; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 8.59 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.95 (app t, $J$ = 7.9 Hz, 1H), 7.83–7.77 (m, 1H), 7.21–7.06 (m, 3H), 2.66 (app p, $J$ = 6.9 Hz, 2H), 2.21 (s, 3H), 1.14 (dd, $J$ = 6.9, 2.9 Hz, 12H). According to the spectral data reported in the literature.[116]




**114** **115**

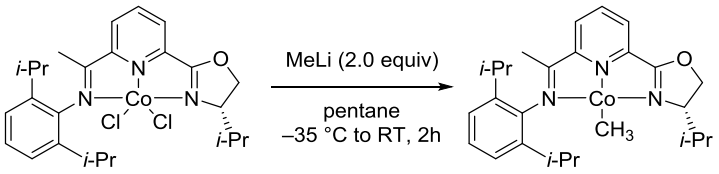
**(*S*,*E*)-2,6-Diisopropyl-*N*-(1-(6-(4-isopropyl-4,5-dihydrooxazol-2-yl)pyridin-2-yl)ethylidene)-aniline (115).** According to the procedure reported by Z. HUANG and co-workers, [116] zinc trifluoromethanesulfonate (8.9 mg, 25 µmol, 5 mol%) was added to a solution of nitrile **114** (150 mg, 0.49 mmol, 1.0 equiv) in toluene (2.6 mL) at ambient temperature. The resulting suspension was stirred for 5 min before a solution of l-valinol (76 mg, 0.74 mmol, 1.5 equiv) in toluene (1.8 mL) was added dropwise. The resulting yellow reaction mixture was stirred at reflux temperature for 38 h. It was then allowed to cool to ambient temperature and diluted with EtOAc (30 mL), sequentially washed with $NaHCO_3$ solution (3 x 10 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 5:95; then 10:90) afforded oxazoline **115** (120 mg, 62%) as a pale yellow solid.

**TLC:** $R_f$ = 0.39 (EtOAc/hexane, 20:80; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 8.50 (dd, $J$ = 8.0, 1.1 Hz, 1H), 8.19 (dd, $J$ = 7.8, 1.2 Hz, 1H), 7.89 (app t, $J$ = 7.9 Hz, 1H), 7.19–7.05 (m, 3H), 4.60–4.50 (m, 1H), 4.31–4.13 (m, 2H), 2.72 (app p, $J$ = 6.9 Hz, 2H), 2.28 (s, 3H), 1.99–1.85 (m, 1H), 1.17–1.05 (m, 15H), 0.97 (d, $J$ = 6.7 Hz, 3H). According to the spectral data reported in the literature.[116]



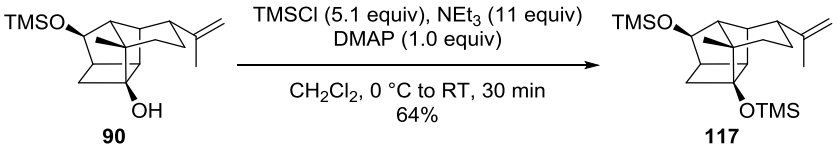

**115** **116**

**[(*S*)-*i*-Pr-IPO]$CoCl_2$ (116).** According to the procedure reported by Z. HUANG and co-workers,[116] $CoCl_2$ (0.040 g, 0.30 mmol, 1.0 equiv) was added to a solution of oxazoline **115** (119 mg, 0.304 mmol, 1.0 equiv) in THF (4.5 mL) at ambient temperature. The resulting greenish suspension was stirred for 16 h before it was concentrated under reduced pressure. The residue was then taken up in diethyl ether (10 mL), filtered and washed with diethyl ether (3 x 10 mL). Drying under high vacuum afforded [(*S*)-*i*-Pr-IPO]$CoCl_2$ **116** (142 mg, 90%) as a green-white solid which was used in the next transformation without further analysis.




116 106

**[(*S*)-*i*-Pr-IPO]CoCH$_3$ (106).** According to the procedure reported by Z. HUANG and co-workers,[116] methyl lithium (3.1 M in diethoxymethane, 0.030 mL, 93 µmol, 2.0 equiv) was added to a solution of Co(II) complex **116** (24 mg, 47 µmol, 1.0 equiv) in pentane (2.4 mL) at –35 °C. The resulting mixture was allowed to warm to ambient temperature, upon which it became dark red. Stirring was continued at ambient temperature for 2 h. Then, the reaction mixture was taken up in a syringe equipped with a syringe filter which had been flushed with nitrogen and washed with pentane. After filtration, the solution was transferred into a Schlenk tube and the solvent was evaporated under inert conditions. The resulting dark red Co(I) complex **106** was then immediately transferred to a nitrogen-filled glovebox and stored therein. It was used in the next transformation without further analysis.

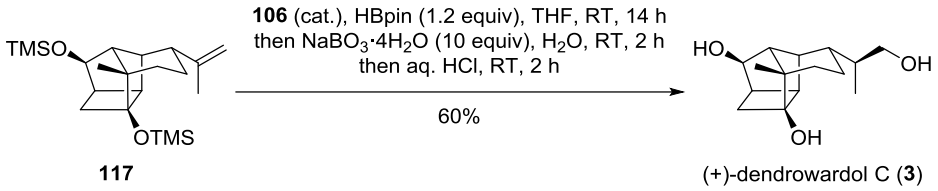



90 117

**(((3*R*,3a*R*,4*S*,7*R*,7a*R*,8*R*)-4-Methyl-7-(prop-1-en-2-yl)octahydro-1*H*-1,4,2-(epiethane[1,1,2]-triyl)indene-3,8-diyl)bis(oxy))bis(trimethylsilane) (117).** To a solution of alcohol **90** (14 mg, 46 µmol, 1.0 equiv) in $CH_2Cl_2$ (1.6 mL) at 0 °C were sequentially added triethylamine (0.070 mL, 0.50 mmol, 11 equiv), DMAP (5.6 mg, 46 µmol, 1.0 equiv) and trimethylsilyl chloride (0.030 mL, 0.24 mmol, 5.1 equiv). The resulting clear slightly orange reaction mixture was stirred at ambient temperature for 30 min before it was quenched with $NH_4Cl$ solution (2 mL, sat. aqueous), diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were washed with $NH_4Cl$ solution (20 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (pentane) afforded silyl ether **117** (11 mg, 64%) as a colorless oil.

**TLC:** $R_f$ = 0.33 (pentane; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 4.74–4.71 (m, 1H), 4.68–4.65 (m, 1H), 3.96 (dd, $J$ = 7.2, 3.1 Hz, 1H), 2.63–2.56 (m, 1H), 2.40 (d, $J$ = 10.1 Hz, 1H), 2.23–2.16 (m, 1H), 2.15–2.08 (m, 1H), 1.95 (dd, $J$ = 10.1, 8.1 Hz, 1H), 1.85–1.73 (m, 2H), 1.74–1.69 (m, 3H), 1.64–1.57 (m, 2H), 1.41 (app dtd, $J$ = 11.5, 5.1, 2.5 Hz, 1H), 1.18 (dd, $J$ = 13.0, 5.0 Hz, 1H), 1.12 (s, 3H), 0.11 (s, 9H), 0.09 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 149.4, 108.6, 79.5,

76.3, 54.5, 52.8, 46.6, 44.3, 43.2, 37.8, 34.0, 31.2, 24.6, 22.5, 18.6, 2.1, 0.1; **IR** (thin film): 2954, 2930, 1643, 1453, 1372, 1312, 1250, 1198, 1122, 1101, 1059, 920, 904, 882, 837, 749 $cm^{-1}$; **Optical rotation:** $[\alpha]_D^{23}$ +17.0° (c = 0.10, $CHCl_3$).

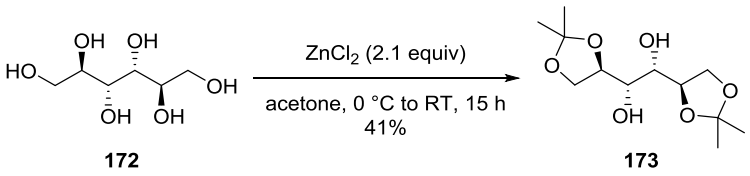



**117** (+)-dendrowardol C (**3**)

**(+)-Dendrowardol C (3).** In a nitrogen-filled glovebox, a solution of alkene **117** (10 mg, 26 µmol, 1.0 equiv) in degassed THF (0.4 mL) was added to one tip of a micro spatula of Co(I) complex **106** in a 5 mL vial. Then, a solution of freshly distilled pinacolborane (4.6 µL, 32 µmol, 1.2 equiv) in degassed THF (0.05 mL) was added to the pink solution, and the resulting dark brown-green reaction mixture was stirred at ambient temperature for 14 h. The now dark brown-red mixture was removed from the glovebox and water/THF (1:1, 2 mL) was added, followed by sodium perborate tetrahydrate (40 mg, 0.26 mmol, 10 equiv). The resulting greenish suspension was stirred at ambient temperature for 2 h. 6 M HCl (10 drops) was added, and the now clear colorless reaction mixture was stirred at ambient temperature for 2 h. It was then taken up in water (10 mL) and EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic phases were sequentially washed with $NaHCO_3$ solution (20 mL, sat. aqueous) and NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 85:15) afforded (+)-dendrowardol C (**3**) (4.0 mg, 60%) as a white powder.

# 3.3 Experimental Part for the Investigation of Anti-Inflammatory Epoxyisoprostanes and their Analogs

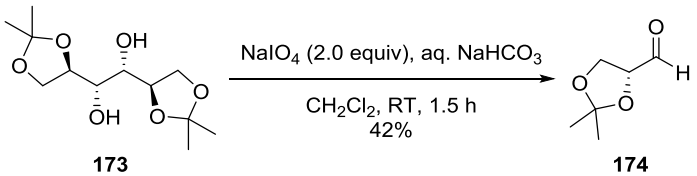
## 3.3.1 Experimental Procedures for the Structure–Activity Relationship Studies




172 173

**(1*S*,2*S*)-1,2-bis((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (173).** According to a procedure reported by Y. HIRAI and co-workers,[168] D-mannitol (**172**) (30 g, 170 mmol, 1.0 equiv) was added to a solution of zinc chloride (47 g, 350 mmol, 2.1 equiv) in acetone (300 mL) at 0 °C. The resulting first turbid, then clear colorless reaction mixture was stirred at ambient temperature for 15 h before it was cooled to 0 °C and quenched with a solution of $K_2CO_3$ (48 g) in water (60 mL). The resulting white suspension was stirred at ambient temperature for 1 h. It was then filtered and the precipitate was washed with EtOAc (3 x 50 mL). $NH_4OH$ solution (1 mL, sat. aqueous) was added and the mixture was concentrated under reduced pressure. Water (100 mL) was added and the resulting white slurry was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with water (100 mL), dried over $K_2CO_3$, filtered and concentrated under reduced pressure. Recrystallization from EtOAc afforded diol **173** (18 g, 41%) as a white powder.

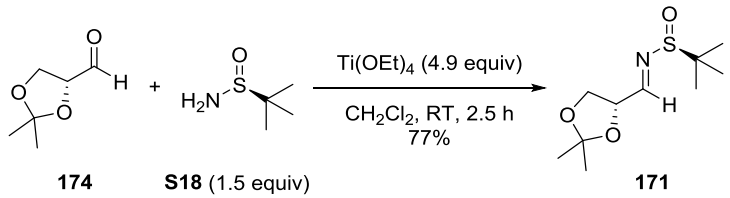
**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 4.25–4.03 (m, 4H), 4.01–3.93 (m, 2H), 3.79–3.70 (m, 2H), 2.57 (dd, $J$ = 6.7, 1.2 Hz, 2H), 1.42 (s, 6H), 1.36 (s, 6H). According to the spectral data reported in the literature.[168]




173 174

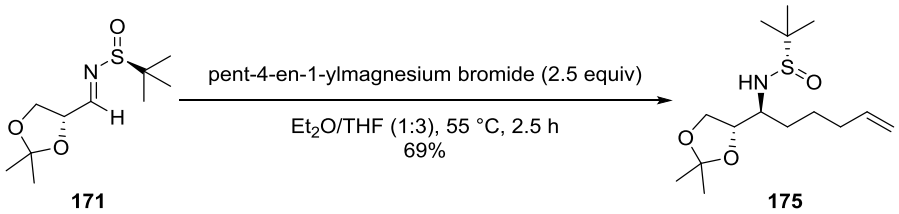
**(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (174).** Similar to a procedure reported by B. BALTAS and co-workers,[169] $NaHCO_3$ solution (2.7 mL, sat. aqueous) was added to a solution of diol **173** (6.7 g, 26 mmol, 1.0 equiv) in $CH_2Cl_2$ (60 mL) at ambient temperature. Sodium periodate (11 g, 51 mmol, 2.0 equiv) was then added, and the resulting suspension was stirred at ambient temperature for 1.5 h. $MgSO_4$ was added, and stirring was continued for 15 min before the mixture was filtered and concentrated under reduced pressure. Distillation (65 °C, 20 mbar) afforded aldehyde **174** (2.8 g, 42%) as a colorless oil.

**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 9.72 (d, $J$ = 1.9 Hz, 1H), 4.38 (ddd, $J$ = 7.4, 4.8, 1.9 Hz, 1H), 4.17 (dd, $J$ = 8.8, 7.4 Hz, 1H), 4.10 (dd, $J$ = 8.8, 4.8 Hz, 1H), 1.49 (d, $J$ = 0.7 Hz, 3H), 1.42 (d, $J$ = 0.7 Hz, 3H). According to the spectral data reported in the literature.[169]




**(*S*)-*N*-((*E*)-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide (171).** Similar to a procedure reported by J. A. ELLMAN and co-workers,[170] aldehyde **174** (505 mg, 3.88 mmol, 1.0 equiv) and (*S*)-(–)-2-methyl-2-propanesulfinamide (**S18**) (699 mg, 5.77 mmol, 1.5 equiv) were dissolved in $CH_2Cl_2$ (96 mL). Titanium ethoxide (4.0 mL, 19 mmol, 4.9 equiv) was added and the resulting clear yellowish reaction mixture was stirred at ambient temperature for 2.5 h. It was then cooled to 0 °C and cold water (4 mL) was added. The resulting white slurry was filtered through a short plug of celite eluting with EtOAc. The filtrate was washed with NaCl solution (50 mL, sat. aqueous), the phases were separated and the aqueous phase extracted with EtOAc (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded imine **171** (694 mg, 77%) as a yellowish oil.

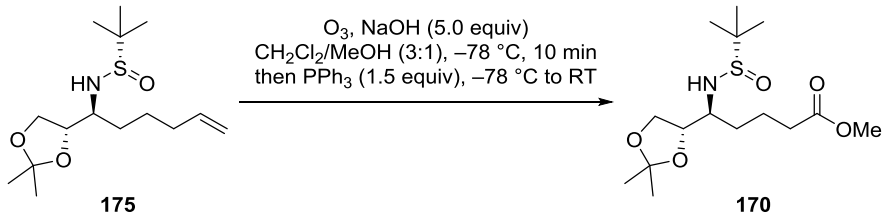
**TLC:** $R_f$ = 0.76 (EtOAc/hexane, 20:80; DNP); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 8.07 (d, $J$ = 4.1 Hz, 1H), 4.84 (ddd, $J$ = 6.8, 5.1, 4.1 Hz, 1H), 4.23 (dd, $J$ = 8.6, 6.8 Hz, 1H), 4.04 (dd, $J$ = 8.6, 5.1 Hz, 1H), 1.45 (d, $J$ = 0.7 Hz, 3H), 1.42 (d, $J$ = 0.7 Hz, 3H), 1.20 (s, 9H). According to the spectral data reported in the literature.[170]




**(*S*)-*N*-((*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)hex-5-en-1-yl)-2-methylpropane-2-sulfinamide (175).** 5-Bromopent-1-ene (3.37 mL, 28.5 mmol, 2.5 equiv) was added dropwise to a suspension of magnesium turnings (860 mg, 35 mmol, 3.1 equiv) in diethyl ether (72 mL) at ambient temperature. The resulting turbid yellowish mixture was stirred at reflux temperature for 30 min and then allowed to cool to ambient temperature. The supernatant was added dropwise to a solution of sulfinimine **171** (2.66 g, 11.4 mmol, 1.0 equiv) in THF (213 mL) at ambient

temperature. The resulting clear colorless reaction mixture was stirred at 55 °C for 2.5 h, before it was allowed to cool to ambient temperature and quenched with $NH_4Cl$ solution (200 mL, sat. aqueous). The resulting mixture was extracted with EtOAc (3 x 200 mL), and the combined organic phases were washed with NaCl solution (200 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 40:60 to 50:50) afforded sulfinamide **175** (2.4 g, 69%) as a yellow oil which solidified upon standing.

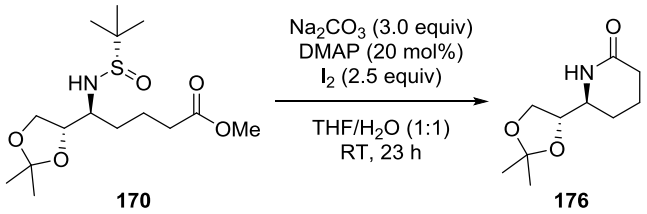
**TLC:** $R_f$ = 0.07 (EtOAc/hexane, 20:80; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.78 (ddt, $J$ = 17.0, 10.2, 6.7 Hz, 1H), 5.06–4.93 (m, 2H), 4.30 (td, $J$ = 6.5, 4.4 Hz, 1H), 4.04 (dd, $J$ = 8.5, 6.7 Hz, 1H), 3.84 (dd, $J$ = 8.5, 6.2 Hz, 1H), 3.51 (d, $J$ = 6.2 Hz, 1H), 3.42–3.33 (m, 1H), 2.11–2.05 (m, 2H), 1.67–1.37 (m, 7H), 1.33 (d, $J$ = 0.7 Hz, 3H), 1.22 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 138.2, 115.0, 109.3, 78.0, 65.6, 56.9, 56.1, 33.5, 30.3, 26.3, 25.0, 24.8, 22.7; **IR** (thin film): 3167, 2981, 2930, 2867, 1642, 1457, 1369, 1256, 1212, 1159, 1047, 908, 859 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{28}$ +18.5° (c = 0.32, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{15}H_{30}NO_3S$ [$(M+H)^+$] 304.1941, found 304.1947.




**Methyl (*S*)-5-(((*S*)-*tert*-butylsulfinyl)amino)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (170).** A solution of NaOH (670 mg, 16 mmol, 5.0 equiv) in MeOH (28 mL) was added to a solution of alkene **175** (1.0 g, 3.3 mmol, 1.0 equiv) in $CH_2Cl_2$ (84 mL), and the resulting mixture was cooled to –78 °C. Ozone was bubbled through the reaction mixture for 10 min, followed by purging with nitrogen for 10 min. Triphenylphosphine (1.3 g, 4.9 mmol, 1.5 equiv) was added and the reaction mixture was allowed to warm to ambient temperature. It was then diluted with water (40 mL) and diethyl ether (40 mL), and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 40 mL), and the combined organic phases were washed with NaCl solution (50 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc) afforded ester **170** (800 mg) still containing triphenylphosphine oxide.

**TLC:** $R_f$ = 0.31 (EtOAc; $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 4.29 (app td, $J$ = 6.4, 4.8 Hz, 1H), 4.06 (dd, $J$ = 8.6, 6.8 Hz, 1H), 3.84 (dd, $J$ = 8.6, 6.1 Hz, 1H), 3.67 (s, 3H), 3.52 (d, $J$ = 6.6 Hz, 1H), 3.34 (app ddt, $J$ = 7.5, 6.0, 4.9 Hz, 1H), 2.34 (t, $J$ = 7.1 Hz, 2H), 1.86–1.77 (m,

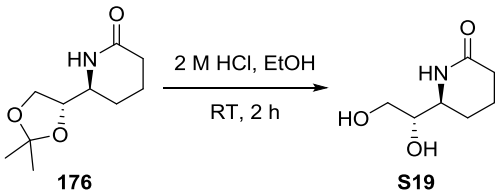
1H), 1.71–1.51 (m, 3H), 1.44–1.41 (m, 3H), 1.33 (d, $J$ = 0.7 Hz, 3H), 1.23 (s, 9H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 173.7, 109.4, 78.0, 65.9, 60.4, 57.3, 51.6, 33.7, 30.4, 26.3, 24.8, 22.7, 21.2; **IR** (thin film): 3222, 2984, 2953, 1738, 1457, 1438, 1370, 1247, 1213, 1162, 1062, 857 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{15}H_{30}NO_5S$ [$(M+H)^+$] 336.1839, found 336.1840.




**170** **176**

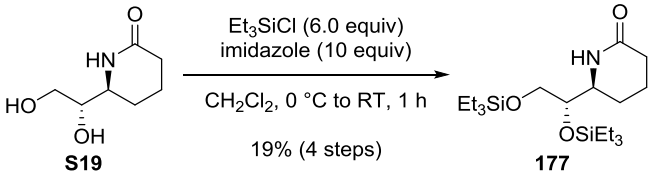
**(*S*)-6-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (176).** $Na_2CO_3$ (190 mg, 1.8 mmol, 3.0 equiv) and DMAP (15 mg, 0.12 mmol, 20 mol%) were added to a solution of ester **170** (0.20 g, 0.60 mmol, 1.0 equiv) in THF/$H_2O$ (1:1 v/v, 9.4 mL) at 0 °C. After 5 min, iodine (378 mg, 1.49 mmol, 2.5 equiv) was added, and the resulting dark red reaction mixture was stirred at ambient temperature for 23 h. It was then diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc) afforded lactam **176** (72 mg) still containing DMAP. An analytically pure sample was obtained *via* careful column chromatography.

**TLC:** $R_f$ = 0.10 (EtOAc; CAM); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 5.88 (s, 1H), 4.13 (ddd, $J$ = 7.2, 6.5, 4.0 Hz, 1H), 3.99 (dd, $J$ = 8.1, 6.5 Hz, 1H), 3.76 (dd, $J$ = 8.1, 7.2 Hz, 1H), 3.71 (ddd, $J$ = 10.7, 4.8, 3.7 Hz, 1H), 2.44 (dddd, $J$ = 17.7, 5.2, 3.2, 1.9 Hz, 1H), 2.29 (ddd, $J$ = 17.7, 11.4, 5.8 Hz, 1H), 1.98–1.87 (m, 2H), 1.80–1.68 (m, 1H), 1.44 (d, $J$ = 0.7 Hz, 3H), 1.35 (d, $J$ = 0.7 Hz, 3H), 1.32–1.20 (m, 1H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 172.2, 109.3, 77.2, 64.2, 53.2, 31.6, 26.3, 24.9, 24.7, 19.8; **IR** (thin film): 3203, 3089, 2961, 2878, 1659, 1486, 1452, 1403, 1372, 1259, 1213, 1165, 1073, 852 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ +8.4° (c = 0.10, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{10}H_{18}NO_3$ [$(M+H)^+$] 200.1281, found 200.1278.




**(*S*)-6-((*S*)-1,2-Dihydroxyethyl)piperidin-2-one (S19).** Similar to a procedure reported by P. Talukdar and co-workers,[173] 2 M HCl (1 mL) was added to a solution of acetonide **176** (70 mg, 0.35 mmol, 1.0 equiv) in EtOH (4 mL) at ambient temperature and the resulting clear reaction mixture was stirred for 2 h. It was then neutralized with solid $K_2CO_3$ and concentrated under reduced pressure. Purification by column chromatography ($MeOH/CH_2Cl_2$, 20:80) afforded diol **S19** (42 mg) still containing DMAP. An analytically pure sample was obtained by careful column chromatography.

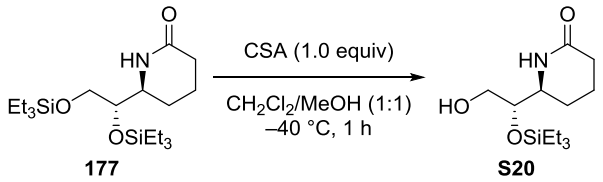
**TLC:** $R_f$ = 0.37 ($MeOH/CH_2Cl_2$, 20:80; CAM); **$^1$H NMR** (500 MHz, $CD_3OD$): $\delta$ 3.65–3.58 (m, 3H), 3.55–3.49 (m, 1H), 2.37–2.22 (m, 2H), 1.99–1.84 (m, 2H), 1.77–1.65 (m, 2H); **$^{13}$C NMR** (126 MHz, $CD_3OD$): $\delta$ 175.5, 74.0, 64.5, 56.7, 32.0, 23.6, 20.1; **IR** (thin film): 3280, 2932, 1728, 1623, 1477, 1408, 1329, 1306, 1092, 1037 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_7H_{14}NO_3$ [$(M+H)^+$] 160.0968, found 160.0969.




**(*S*)-6-((*S*)-3,3,8,8-Tetraethyl-4,7-dioxa-3,8-disiladecan-5-yl)piperidin-2-one (177).** To a solution of diol **S19** (40 mg, 0.25 mmol, 1.0 equiv) in $CH_2Cl_2$ (7 mL) at 0 °C was added imidazole (171 mg, 2.51 mmol, 10 equiv), followed by triethylchlorosilane (0.26 mL, 1.5 mmol, 6.0 equiv). The resulting white suspension was stirred at ambient temperature for 1 h before it was quenched with $NH_4Cl$ solution (6 mL, sat. aqueous), diluted with water (10 mL) and extracted with EtOAc (3 x 40 mL). The combined organic phases were washed with NaCl solution (40 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 40:60) afforded lactam **177** (57 mg, 19% over four steps) as a yellowish oil.

**TLC:** $R_f$ = 0.33 (EtOAc/hexane, 40:60; CAM); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 6.22 (s, 1H), 3.66–3.58 (m, 3H), 3.55–3.49 (m, 1H), 2.39 (dddd, $J$ = 17.7, 5.1, 3.1, 1.5 Hz, 1H), 2.26 (ddd, $J$ = 17.7, 11.3, 6.1 Hz, 1H), 1.95–1.84 (m, 2H), 1.70–1.54 (m, 2H), 0.96 (app td, $J$ = 8.0, 3.3 Hz, 18H), 0.64–0.57 (m, 12H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 172.2, 74.3, 64.8, 57.5, 31.7, 24.1, 20.0, 6.8, 6.7, 4.9, 4.2; **IR** (thin film): 3202, 3091, 2953, 2911, 2876, 1667, 1458, 1412, 1239,

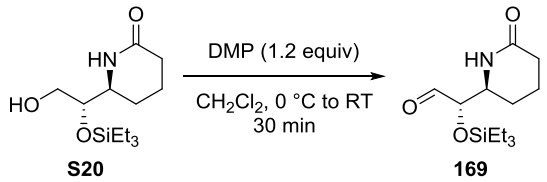
1126, 1079, 1004, 963, 815, 789, 726, 673 $cm^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ –18.3° (c = 0.40, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{19}H_{42}NO_3Si_2$ $[(M+H)^+]$ 388.2698, found 388.2696.




**177** **S20**

**(*S*)-6-((*S*)-2-Hydroxy-1-((triethylsilyl)oxy)ethyl)piperidin-2-one (S20).** CSA (111 mg, 0.477 mmol, 1.0 equiv) was added to a solution of lactam **177** (185 mg, 0.477 mmol, 1.0 equiv) in $CH_2Cl_2$/MeOH (1:1 v/v, 72 mL) at –40 °C. The resulting clear colorless reaction mixture was stirred at this temperature for 1 h. It was then quenched with triethylamine (0.13 mL, 0.95 mmol, 2.0 equiv) and allowed to warm to ambient temperature. Concentration under reduced pressure and purification by column chromatography (MeOH/$CH_2Cl_2$, 4:96) afforded alcohol **S20** (109 mg) as white crystals containing ca. 12% of the regioisomeric monoprotected diol.

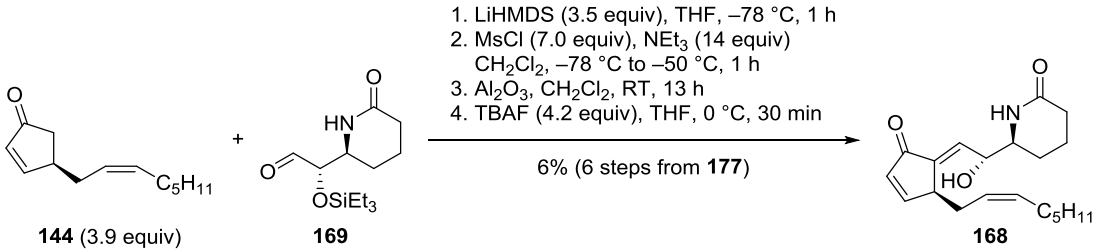
**TLC:** $R_f$ = 0.77 (MeOH/$CH_2Cl_2$, 10:90; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 6.12 (s, 1H), 3.80–3.51 (m, 4H), 2.47–2.35 (m, 1H), 2.34–2.22 (m, 1H), 1.99–1.82 (m, 2H), 1.78–1.62 (m, 1H), 1.61–1.46 (m, 2H), 1.01–0.93 (m, 9H), 0.70–0.56 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 172.4, 74.1, 63.5, 56.4, 31.5, 24.3, 19.7, 6.8, 4.9; **HRMS** (ESI): exact mass calculated for $C_{13}H_{27}NNaO_3Si$ $[(M+Na)^+]$ 296.1652, found 296.1659.




**S20** **169**

**(*S*)-2-((*S*)-6-Oxopiperidin-2-yl)-2-((triethylsilyl)oxy)acetaldehyde (169).** To a solution of alcohol **S20** (109 mg, 0.400 mmol, 1.0 equiv) in $CH_2Cl_2$ (15 mL) at 0 °C was added DESS–MARTIN periodinane (203 mg, 0.478 mmol, 1.2 equiv), and the resulting white suspension was stirred at ambient temperature for 30 min. It was then quenched with a mixture of $NaHCO_3$ solution (15 mL, sat. aqueous) and $Na_2S_2O_3 \cdot 5H_2O$ (3.5 g). Stirring was continued for 10 min. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with NaCl solution (2 x 50 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford aldehyde **169** (119 mg) as a colorless oil which was used in the following transformation without further purification.

**TLC:** $R_f$ = 0.37 (EtOAc; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 9.65 (dd, $J$ = 2.3, 0.7 Hz, 1H), 6.17 (s, 1H), 3.82 (dd, $J$ = 4.5, 2.3 Hz, 1H), 3.67 (dt, $J$ = 9.2, 4.5 Hz, 1H), 2.47–2.35 (m, 1H), 2.25 (ddd, $J$ = 17.6, 11.3, 6.0 Hz, 1H), 1.99–1.83 (m, 2H), 1.77–1.60 (m, 2H), 1.01–0.93 (m, 9H), 0.64 (qd, $J$ = 7.9, 0.7 Hz, 6H).

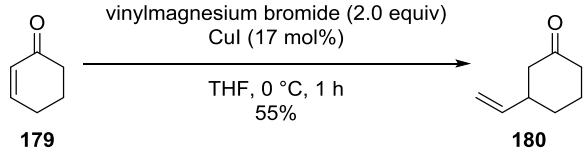



**(*S*)-6-((*R*,*E*)-1-Hydroxy-2-((*S*)-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)ethyl)-piperidin-2-one (168).**[175] A solution of enone **144**[153] (158 mg, 0.82 mmol, 3.9 equiv) in THF (2 mL) was added to a solution of LiHMDS (124 mg, 0.740 mmol, 3.5 equiv) in THF (5 mL) at –78 °C, and the resulting reaction mixture was stirred at this temperature for 30 min. Then, a solution of crude aldehyde **169** (58 mg, 0.21 mmol, 1.0 equiv) in THF (2 mL) was added dropwise, and stirring was continued at –78 °C for 1 h. The reaction mixture was quenched with $NH_4Cl$ solution (sat. aqueous) and allowed to warm to ambient temperature. It was then extracted with diethyl ether and the organic phase was washed with NaCl solution (sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc to EtOAc/MeOH, 98:2 to 95:5 to 90:10) afforded the aldol adduct (73 mg) as a yellow oil, which was directly used in the next step.

To a solution of the above product (36 mg) in $CH_2Cl_2$ (2 mL) at –78 °C was added triethylamine (0.15 mL, 1.1 mmol, 14 equiv), followed by methanesulfonyl chloride (42 µL, 0.54 mmol, 7.0 equiv). The resulting reaction mixture was allowed to warm to –50 °C over 1 h before it was filtered through a short plug of silica gel and separated into six fractions. $CH_2Cl_2$ (4 mL) and excess aluminum oxide (200 mg) were added to each fraction and they were stirred vigorously at ambient temperature for 13 h. All six fractions were filtered over a short plug of celite, combined and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 50:50 to EtOAc to EtOAc/MeOH, 90:10) afforded the elimination product (8.3 mg), which was directly used in the following transformation.

TBAF (1.0 M in THF, 79 µL, 79 µmol, 4.2 equiv) was added to a solution of the above product (8.3 mg) in THF (1.5 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 30 min before it was quenched with $NH_4Cl$ solution (sat. aqueous) and extracted with EtOAc. The organic phase was washed with NaCl solution (sat. aqueous), dried over $Na_2SO_4$, filtered and

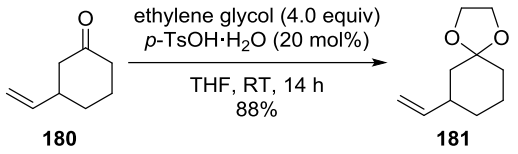
concentrated under reduced pressure. Purification by column chromatography (EtOAc to EtOAc/MeOH, 95:5 to 90:10) afforded alcohol **168** (2.3 mg, 6% over six steps) as a colorless oil. **TLC:** $R_f$ = 0.16 (EtOAc; UV, CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 7.57 (ddd, $J$ = 6.0, 2.6, 0.9 Hz, 1H), 6.55–6.43 (m, 2H), 6.36 (dd, $J$ = 6.0, 1.9 Hz, 1H), 5.58–5.45 (m, 1H), 5.38–5.25 (m, 1H), 4.58–4.46 (m, 1H), 3.76–3.61 (m, 2H), 2.62 (dt, $J$ = 12.0, 5.5 Hz, 1H), 2.46–2.32 (m, 1H), 2.33–2.16 (m, 2H), 2.04–1.78 (m, 4H), 1.78–1.65 (m, 1H), 1.42–1.20 (m, 7H), 0.93–0.82 (m, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 196.6, 173.6, 163.0, 141.0, 134.3, 133.3, 129.7, 124.4, 70.7, 57.5, 43.3, 31.5, 31.4, 31.3, 29.2, 27.4, 23.1, 22.5, 19.7, 14.0; **IR** (thin film): 3301, 2925, 2856, 1705, 1654, 1455, 1409, 1329, 1208, 1083, 809 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{26}$ +123.5° (c = 0.080, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{20}H_{30}NO_3$ [$(M+H)^+$] 332.2220, found 332.2223.



**179** **180**

**3-Vinylcyclohexan-1-one (180).** According to a procedure reported by F. A. J. KERDESKY and co-workers,[180] CuI (334 mg, 1.76 mmol, 17 mol%) was added to vinylmagnesium bromide (0.7 M in THF, 29.5 mL, 20.7 mmol, 2.0 equiv) at 0 °C and the resulting first greenish, then black mixture was stirred at 0 °C for 15 min. Then, a solution of cyclohex-2-enone (**179**) (1.0 mL, 10 mmol, 1.0 equiv) in THF (11.5 mL) was added dropwise over 25 min and the resulting black reaction mixture was stirred at 0 °C for 1 h. It was then poured on a mixture of $NH_4Cl$ solution (sat. aqueous) and $NH_4OH$ solution (25% aqueous) (9:1 v/v, 30 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with $NH_4Cl$ solution (100 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (diethyl ether/pentane, 10:90) afforded ketone **180** (700 mg, 55%) as a colorless oil.

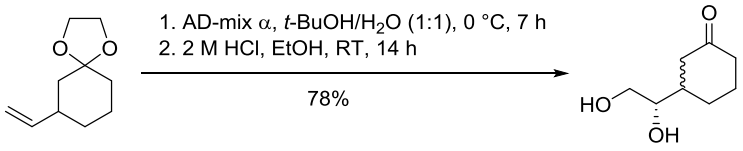
**TLC:** $R_f$ = 0.37 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.79 (ddd, $J$ = 17.3, 10.5, 6.1 Hz, 1H), 5.04 (dt, $J$ = 8.1, 1.3 Hz, 1H), 4.99 (d, $J$ = 1.4 Hz, 1H), 2.58–2.16 (m, 5H), 2.06 (ddtd, $J$ = 12.0, 5.6, 4.3, 3.4 Hz, 1H), 1.99–1.89 (m, 1H), 1.70 (dtdd, $J$ = 12.9, 11.2, 5.0, 3.2 Hz, 1H), 1.59–1.47 (m, 1H). According to the spectral data reported in the literature.[180]




180 181

**7-Vinyl-1,4-dioxaspiro[4.5]decane (181).** According to a procedure reported by F.-P. WANG and co-workers,[181] ethylene glycol (1.26 mL, 22.6 mmol, 4.0 equiv) was added to a solution of ketone **180** (0.700 g, 5.64 mmol, 1.0 equiv) in THF (12.5 mL) at ambient temperature, followed by *p*-toluenesulfonic acid monohydrate (214 mg, 1.13 mmol, 20 mol%). The resulting clear colorless reaction mixture was stirred at ambient temperature for 14 h before it was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (diethyl ether/pentane, 5:95) afforded dioxolane **181** (832 mg, 88%) as a colorless liquid.

**TLC:** $R_f$ = 0.61 (EtOAc/hexane, 10:90; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 5.77 (ddd, $J$ = 17.2, 10.4, 6.5 Hz, 1H), 4.98 (dt, $J$ = 17.2, 1.6 Hz, 1H), 4.91 (ddd, $J$ = 10.4, 1.7, 1.2 Hz, 1H), 3.97–3.93 (m, 4H), 2.37–2.20 (m, 1H), 1.85–1.68 (m, 4H), 1.64–1.23 (m, 3H), 1.12–0.94 (m, 1H). According to the spectral data reported in the literature.[181]

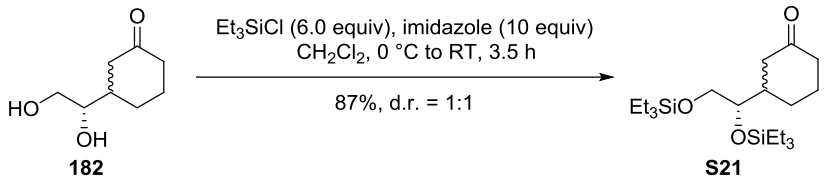



181 182

**3-((*S*)-1,2-Dihydroxyethyl)cyclohexan-1-one (182).** AD-mix α (6.0 g) was dissolved in *t*-BuOH/$H_2O$ (1:1 v/v, 44 mL) at ambient temperature. The mixture was then cooled to 0 °C, and dioxolane **181** (724 mg, 4.30 mmol, 1.0 equiv) was added (rinsed with 2 mL of *t*-BuOH). The resulting reaction mixture was stirred at 0 °C for 7 h before sodium sulfite (6.4 g) was added. Stirring was continued at ambient temperature for 1 h. Then, the mixture was diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude diol (969 mg) which was used in the next step without further purification.

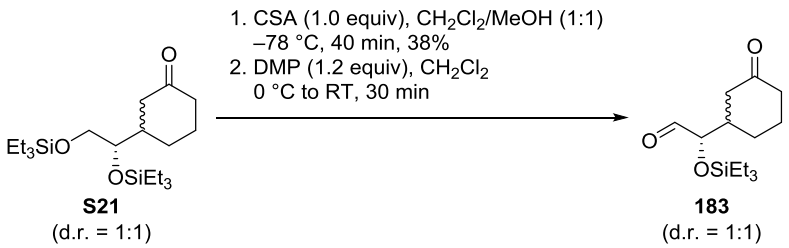
2 M HCl (13 mL) was added to a solution of the above product (0.43 mmol) in EtOH (50 mL) at ambient temperature and the resulting clear reaction mixture was stirred for 14 h. It was then neutralized with solid $K_2CO_3$ and concentrated under reduced pressure. Purification by column chromatography (EtOAc) afforded ketone **182** (533 mg, mixture of diastereomers, 78%) as a colorless oil.

**TLC:** $R_f$ = 0.42 (EtOAc/MeOH, 95:5; $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 3.77–3.48 (m, 3H), 2.51–2.20 (m, 4.5H), 2.17–2.07 (m, 1H), 2.07–2.00 (m, 0.5H), 1.98–1.88 (m, 1H), 1.86–1.49 (m, 4H); **$^{13}$C NMR** (126 MHz, $CDCl_3$; all peaks reported): $\delta$ 211.5, 211.1, 74.9, 74.9, 64.6, 64.6, 44.5, 42.9, 41.4, 41.4, 41.3, 41.3, 27.9, 26.3, 25.1, 25.0; **IR** (thin film): 3405, 2938, 2868, 1700, 1449, 1422, 1316, 1230, 1078, 1042, 870, 529 cm$^{-1}$; **HRMS** (ESI): exact mass calculated for $C_8H_{14}NaO_3$ [$(M+Na)^+$] 181.0835, found 181.0834.




**3-((*S*)-3,3,8,8-Tetraethyl-4,7-dioxa-3,8-disiladecan-5-yl)cyclohexan-1-one (S21).** To a solution of diol **182** as a mixture of diastereomers (533 mg, 3.37 mmol, 1.0 equiv) in $CH_2Cl_2$ (90 mL) at 0 °C was added imidazole (2.29 g, 33.7 mmol, 10 equiv), followed by triethylchlorosilane (3.42 mL, 20.2 mmol, 6.0 equiv). The resulting white suspension was stirred at ambient temperature for 3.5 h before it was quenched with $NH_4Cl$ solution (90 mL, sat. aqueous) and extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with NaCl solution (150 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 1:99) afforded silyl ether **S21**(1.14 g, 87%, d.r. = 1:1) as a colorless oil.

**TLC:** $R_f$ = 0.93 (EtOAc; $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 3.72–3.39 (m, 3H), 2.40–2.17 (m, 4H), 2.13–2.01 (m, 2H), 1.86–1.70 (m, 1H), 1.69–1.47 (m, 2H), 1.00–0.90 (m, 18H), 0.65–0.54 (m, 12H); **$^{13}$C NMR** (126 MHz, $CDCl_3$; all peaks reported): $\delta$ 212.7, 212.6, 75.6, 75.5, 64.5, 64.3, 45.4, 41.5, 41.5, 41.4, 41.3, 40.9, 28.6, 25.3, 25.2, 24.2, 6.9, 6.8, 6.8, 5.1, 5.1, 4.3, 4.3; **IR** (thin film): 2955, 2912, 2877, 1716, 1458, 1416, 1240, 1129, 1103, 1076, 1006, 963, 811, 772, 741 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ –12.5° (c = 1.0, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{20}H_{43}O_3Si_2$ [$(M+H)^+$] 387.2745, found 387.2736.



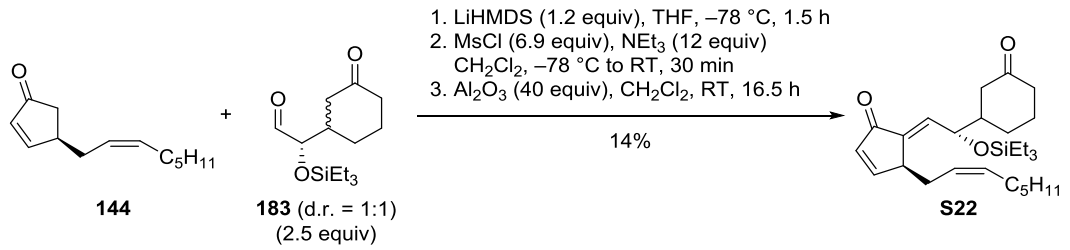

**(2*S*)-2-(3-Oxocyclohexyl)-2-((triethylsilyl)oxy)acetaldehyde (183).** CSA (0.300 g, 1.29 mmol, 1.0 equiv) was added to a solution of silyl ether **S21** as a mixture of diastereomers (0.500 g,

1.29 mmol, 1.0 equiv) in $CH_2Cl_2$/MeOH (1:1 v/v, 180 mL) at –78 °C. The resulting clear colorless reaction mixture was stirred at this temperature for 40 min. It was then quenched with triethylamine (0.36 mL, 2.59 mmol, 2.0 equiv) and allowed to warm to ambient temperature. The reaction was quenched before completion in order to avoid double deprotection. Concentration under reduced pressure and purification by column chromatography (EtOAc/hexane, 35:65) afforded the corresponding monoprotected diol (133 mg, mixture of diastereomers, 38%) as a colorless oil, along with recovered doubly protected diol **S21** (171 mg).

**TLC:** $R_f$ = 0.93 (EtOAc; $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 3.69–3.49 (m, 3H), 2.49–2.32 (m, 2H), 2.32–2.14 (m, 2H), 2.14–1.72 (m, 4H), 1.71–1.36 (m, 2H), 1.01–0.93 (m, 9H), 0.69–0.57 (m, 6H); **HRMS** (ESI): exact mass calculated for $C_{14}H_{28}NaO_3Si$ [$(M+Na)^+$] 295.1700, found 295.1698.

To a solution of the above product (130 mg, 0.477 mmol, 1.0 equiv) in $CH_2Cl_2$ (18 mL) at 0 °C was added DESS–MARTIN periodinane (243 mg, 0.573 mmol, 1.2 equiv), and the resulting white suspension was stirred at ambient temperature for 30 min. It was then quenched with a mixture of $NaHCO_3$ solution (18 mL, sat. aqueous) and $Na_2S_2O_3 \cdot 5H_2O$ (4.3 g). Stirring was continued for 10 min. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with NaCl solution (50 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford aldehyde **183** (139 mg, d.r. = 1:1) as a yellow oil which was used in the following transformation without further purification.

**TLC:** $R_f$ = 0.80 (EtOAc/hexane, 40:60; CAM); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 9.64 (d, $J$ = 1.6 Hz, 0.5H), 9.59 (d, $J$ = 1.8 Hz, 0.5H), 3.90 (dd, $J$ = 3.9, 1.8 Hz, 0.5H), 3.83 (dd, $J$ = 3.8, 1.6 Hz, 0.5H), 2.45–2.00 (m, 6H), 1.90–1.49 (m, 3H), 1.02–0.91 (m, 9H), 0.70–0.56 (m, 6H).



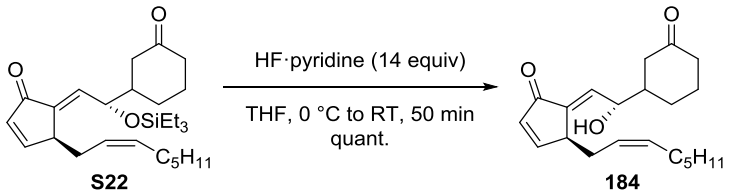

**3-((*S*,*E*)-2-((*S*)-2-((*Z*)-Oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)-1-((triethylsilyl)oxy)-ethyl)cyclohexan-1-one (S22).** A solution of enone **144** (37 mg, 0.19 mmol, 1.0 equiv) in THF (0.8 mL) was added dropwise to a solution of LiHMDS (39 mg, 0.23 mmol, 1.2 equiv) in THF (1.2 mL) at –78 °C, and the resulting clear yellowish reaction mixture was stirred at this temperature for 30 min. Then, a solution of crude aldehyde **183** as a mixture of diastereomers (0.48 mmol, 2.5 equiv) in THF (0.8 mL) was added dropwise, and stirring was continued at –

78 °C for 1.5 h. The reaction mixture was quenched with $NH_4Cl$ solution (5 mL, sat. aqueous) and water (3 mL) and allowed to warm to ambient temperature. It was then extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with NaCl solution (10 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 30:70) afforded the aldol adduct (44 mg, 95 µmol) as a yellowish oil.

**TLC:** $R_f$ = 0.11 (EtOAc/hexane, 20:80; UV, CAM); **HRMS** (ESI): exact mass calculated for $C_{27}H_{46}NaO_4Si$ [$(M+Na)^+$] 485.3058, found 485.3071.

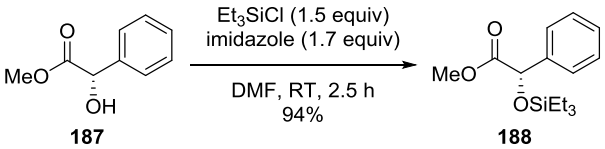
To a solution of the above product (43 mg, 93 µmol, 1.0 equiv) in $CH_2Cl_2$ (0.9 mL) at –78 °C was added triethylamine (0.15 mL, 1.1 mmol, 11 equiv), followed by methanesulfonyl chloride (50 µL, 0.64 mmol, 6.9 equiv). The resulting yellow reaction mixture was stirred at –78 °C for 30 min, then allowed to warm to ambient temperature. It was quenched with $NaHCO_3$ solution (3 mL, sat. aqueous) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and filtered over a short plug of silica gel eluting with EtOAc (50 mL). The resulting solution was concentrated under reduced pressure at ambient temperature to a volume of ca. 0.5 mL. $CH_2Cl_2$ (0.5 mL) and aluminum oxide (95 mg, 0.93 mmol, 10 equiv, activated by stirring under high vacuum at 180 °C for 3 h) were added, and the resulting yellow suspension was stirred at ambient temperature. Three portions of aluminum oxide (3 x 95 mg, 2.8 mmol, 30 equiv) were added after 14 h, 15.5 h and 16 h, respectively. After 16.5 h, the reaction mixture was filtered through a short plug of celite eluting with $CH_2Cl_2$ and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded enone **S22** (12 mg, 14% over two steps) as a single diastereomer as a yellowish oil.

**TLC:** $R_f$ = 0.80 (EtOAc/hexane, 40:60; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 7.52 (ddd, $J$ = 6.0, 2.6, 1.0 Hz, 1H), 6.46 (ddd, $J$ = 10.0, 1.6, 1.0 Hz, 1H), 6.36 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.59–5.48 (m, 1H), 5.32 (dddd, $J$ = 12.5, 6.0, 3.3, 1.6 Hz, 1H), 4.39 (dd, $J$ = 10.0, 4.0 Hz, 1H), 3.49 (ddd, $J$ = 8.9, 4.1, 2.2 Hz, 1H), 2.59–2.46 (m, 2H), 2.41–2.31 (m, 2H), 2.31–2.20 (m, 1H), 2.20–2.03 (m, 2H), 2.03–1.86 (m, 3H), 1.84–1.76 (m, 1H), 1.71–1.58 (m, 2H), 1.44–1.11 (m, 6H), 0.96–0.83 (m, 12H), 0.58–0.48 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 211.4, 196.4, 161.5, 137.1, 134.7, 134.6, 133.5, 124.2, 72.3, 45.5, 43.4, 42.5, 41.3, 32.3, 31.6, 29.1, 28.1, 27.5, 25.1, 22.5, 14.0, 6.8, 5.0; **IR** (thin film): 2956, 2932, 2876, 1710, 1660, 1582, 1459, 1227, 1081, 1005, 790, 745 $cm^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ +84.9° (c = 0.23, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{27}H_{44}NaO_3Si$ [$(M+Na)^+$] 467.2952, found 467.2946.




**3-((*S*,*E*)-1-Hydroxy-2-((*S*)-2-((*Z*)-oct-2-en-1-yl)-5-oxocyclopent-3-en-1-ylidene)ethyl)cyclohexan-1-one (184).** To a solution of silyl ether **S22** (2.5 mg, 5.6 µmol, 1.0 equiv) in THF (0.3 mL) in a 15 mL polypropylene tube at 0 °C was added hydrogen fluoride pyridine (70 wt% HF, 10 µL, 78 µmol, 14 equiv). The resulting clear colorless reaction mixture was stirred at 0 °C for 30 min, then at ambient temperature for 20 min before it was cooled again to 0 °C and carefully quenched with $KHCO_3$ solution (3 mL, sat. aqueous). The phases were separated, the aqueous phase was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 50:50) afforded alcohol **184** (1.8 mg, quant.) as a yellowish film.

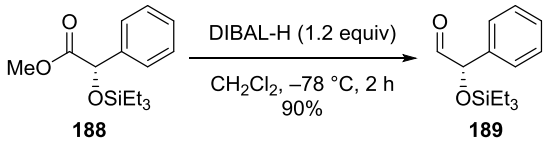
**TLC:** $R_f$ = 0.29 (EtOAc/hexane, 50:50; UV, $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.55 (ddd, $J$ = 6.0, 2.6, 0.9 Hz, 1H), 6.48 (ddd, $J$ = 8.4, 1.6, 0.9 Hz, 1H), 6.36 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.57–5.49 (m, 1H), 5.35–5.25 (m, 1H), 4.48–4.40 (m, 1H), 3.68–3.60 (m, 1H), 2.64–2.52 (m, 2H), 2.44–2.36 (m, 1H), 2.33–2.19 (m, 3H), 2.13 (ddt, $J$ = 12.5, 5.9, 3.1 Hz, 1H), 2.07–1.94 (m, 3H), 1.93–1.85 (m, 1H), 1.72–1.52 (m, 3H), 1.37–1.20 (m, 6H), 0.89 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 210.7, 196.6, 162.5, 139.6, 134.4, 133.5, 132.5, 124.3, 72.1, 44.8, 43.2, 42.7, 41.3, 31.7, 31.5, 29.1, 27.6, 27.4, 25.0, 22.5, 14.0; **IR** (thin film): 3419, 2927, 2857, 1705, 1654, 1580, 1450, 1210, 808 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ +89.5° (c = 0.066, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{30}NaO_3$ [$(M+Na)^+$] 353.2087, found 353.2093.




**Methyl (*S*)-2-phenyl-2-((triethylsilyl)oxy)acetate (188).** To a solution of alcohol **187** (0.10 g, 0.60 mmol, 1.0 equiv) in DMF (0.7 mL) at ambient temperature was added imidazole (70 mg, 1.0 mmol, 1.7 equiv), followed by triethylchlorosilane (0.15 mL, 0.90 mmol, 1.5 equiv). The resulting clear colorless reaction mixture was stirred at ambient temperature for 2.5 h before it was quenched with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were sequentially washed with water (2 x 20 mL) and NaCl solution (20 mL, sat.

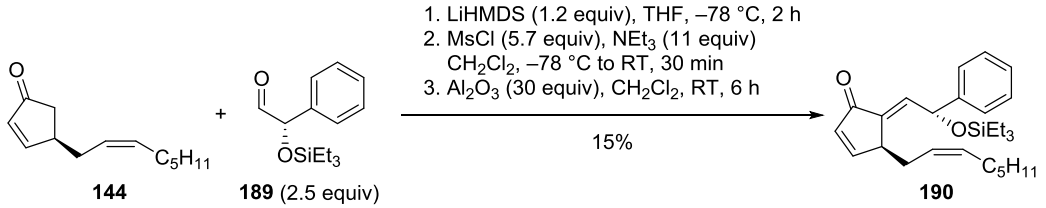
aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 4:96) afforded silyl ether **188** (160 mg, 94%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.51–7.44 (m, 2H), 7.37–7.27 (m, 3H), 5.24 (s, 1H), 3.69 (s, 3H), 0.93 (t, $J$ = 7.9 Hz, 9H), 0.66–0.58 (m, 6H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 172.6, 139.2, 128.4, 128.2, 126.4, 74.2, 52.2, 6.6, 4.6; **IR** (thin film): 2955, 2913, 2878, 1760, 1738, 1455, 1435, 1262, 1242, 1207, 1191, 1170, 1127, 1072, 1015, 838, 729, 697 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ +54.3° (c = 1.0, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{15}H_{24}NaO_3Si$ [$(M+Na)^+$] 303.1387, found 303.1387.




**(*S*)-2-Phenyl-2-((triethylsilyl)oxy)acetaldehyde (189).** Similar to a procedure reported by S. R. ANGLE and co-workers,[184] DIBAL-H (1 M in $CH_2Cl_2$, 0.34 mL, 0.34 mmol, 1.2 equiv) was added dropwise to a solution of ester **188** (80 mg, 0.29 mmol, 1.0 equiv) in $CH_2Cl_2$ (0.6 mL) at –78 °C. The resulting clear colorless reaction mixture was stirred at –78 °C for 2 h. It was then quenched with MeOH (0.4 mL) and allowed to warm to ambient temperature before it was filtered through a short plug of celite eluting with water (10 mL) and $CH_2Cl_2$ (10 mL). The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 5:95) afforded aldehyde **189** (64 mg, 90%) as a colorless oil.

**TLC:** $R_f$ = 0.21 (EtOAc/hexane, 5:95; UV, DNP); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 9.52 (d, $J$ = 2.2 Hz, 1H), 7.42–7.35 (m, 4H), 7.34–7.30 (m, 1H), 5.01–4.99 (m, 1H), 0.97–0.91 (m, 9H), 0.67–0.60 (m, 6H). According to the spectral data reported in the literature.[184]



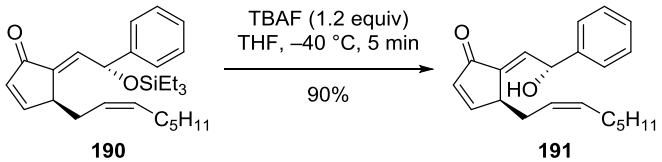

**(*S*,*E*)-4-((*Z*)-Oct-2-en-1-yl)-5-((*R*)-2-phenyl-2-((triethylsilyl)oxy)ethylidene)cyclopent-2-en-1-one (190).** A solution of enone **144** (20 mg, 0.10 mmol, 1.0 equiv) in THF (0.4 mL) was added dropwise to a solution of LiHMDS (21 mg, 0.13 mmol, 1.2 equiv) in THF (0.6 mL) at –78 °C,

and the resulting clear yellowish reaction mixture was stirred at this temperature for 30 min. Then, a solution of aldehyde **189** (65 mg, 0.26 mmol, 2.5 equiv) in THF (0.4 mL) was added dropwise, and stirring was continued at –78 °C for 2 h. The reaction mixture was quenched with $NH_4Cl$ solution (5 mL, sat. aqueous) and water (3 mL) and allowed to warm to ambient temperature. It was then extracted with EtOAc (3 x 10 mL), and the combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90) afforded the aldol adduct (32 mg, 72 µmol) as a yellowish oil.

**TLC:** $R_f$ = 0.16 (EtOAc/hexane, 10:90; UV, CAM); **HRMS** (EI): exact mass calculated for $C_{25}H_{37}O_3Si$ [$(M–C_2H_5)^+$] 413.2507, found 413.2515.

To a solution of the above product (30 mg, 68 µmol, 1.0 equiv) in $CH_2Cl_2$ (0.6 mL) at –78 °C was added triethylamine (0.10 mL, 0.72 mmol, 11 equiv), followed by methanesulfonyl chloride (30 µL, 0.39 mmol, 5.7 equiv). The resulting reaction mixture was stirred at –78 °C for 30 min, then allowed to warm to ambient temperature. It was quenched with $NaHCO_3$ solution (2 mL, sat. aqueous) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and filtered over a short plug of silica gel eluting with EtOAc (50 mL). The resulting solution was concentrated under reduced pressure at ambient temperature to a volume of 0.5 mL. $CH_2Cl_2$ (0.5 mL) and aluminum oxide (69 mg, 0.68 mmol, 10 equiv, activated by stirring under high vacuum at 180 °C for 3 h) were added, and the resulting yellow suspension was stirred at ambient temperature. Two portions of aluminum oxide (2 x 69 mg, 1.4 mmol, 20 equiv) were added after 30 min and 2 h, respectively. After 6 h, the reaction mixture was directly loaded on a column. Purification by column chromatography (EtOAc/hexane, 4:96) afforded enone **190** (6.3 mg, 15%) as yellowish oil.

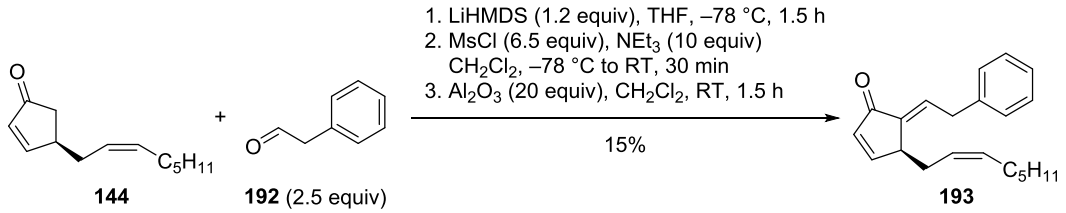
**TLC:** $R_f$ = 0.79 (EtOAc/hexane, 20:80; UV, CAM); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.55 (ddd, $J$ = 6.0, 2.7, 1.0 Hz, 1H), 7.41–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.29–7.26 (m, 1H), 6.65 (ddd, $J$ = 8.6, 1.6, 1.0 Hz, 1H), 6.35 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.52–5.45 (m, 2H), 5.32–5.25 (m, 1H), 3.64 (dtd, $J$ = 8.6, 2.7, 1.2 Hz, 1H), 2.65 (dddd, $J$ = 16.0, 6.4, 4.3, 1.5 Hz, 1H), 2.17 (dddd, $J$ = 14.4, 9.3, 7.7, 1.3 Hz, 1H), 1.93 (app qd, $J$ = 7.3, 1.6 Hz, 2H), 1.36–1.17 (m, 6H), 0.92–0.85 (m, 12H), 0.56 (app qd, $J$ = 7.9, 1.3 Hz, 6H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 197.1, 161.9, 142.1, 135.8, 135.6, 134.6, 133.2, 128.5, 127.9, 126.6, 124.4, 71.8, 43.5, 32.0, 31.5, 29.2, 27.4, 22.5, 14.0, 6.7, 4.9; **IR** (thin film): 2955, 2931, 2876, 1707, 1659, 1583, 1456, 1201, 1098, 1062, 1004, 794, 745, 728, 698 $cm^{-1}$; **HRMS** (EI): exact mass calculated for $C_{27}H_{40}O_2Si$ [$M^+$] 424.2792, found 424.2790.




**190** **191**

**(*S*,*E*)-5-((*R*)-2-Hydroxy-2-phenylethylidene)-4-((*Z*)-oct-2-en-1-yl)cyclopent-2-en-1-one (191).** TBAF (1.0 M in THF, 16 µL, 16 µmol, 1.2 equiv) was added to a solution of silyl ether **190** (5.6 mg, 13 µmol, 1.0 equiv) in THF (0.6 mL) at –40 °C. The resulting clear yellowish reaction mixture was stirred at this temperature for 5 min, then quenched with $NH_4Cl$ solution (2 mL, sat. aqueous) and allowed to warm to ambient temperature. It was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded alcohol **191** (3.7 mg, 90%) as a colorless oil.

**TLC:** $R_f$ = 0.29 (EtOAc/hexane, 30:70; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 7.57 (ddd, $J$ = 6.1, 2.6, 1.0 Hz, 1H), 7.46–7.29 (m, 5H), 6.71 (ddd, $J$ = 8.2, 1.7, 1.0 Hz, 1H), 6.36 (dd, $J$ = 6.1, 1.8 Hz, 1H), 5.60–5.54 (m, 1H), 5.51–5.42 (m, 1H), 5.27 (dddd, $J$ = 11.0, 8.3, 5.1, 1.6 Hz, 1H), 3.77 (app ddq, $J$ = 8.7, 4.3, 2.0 Hz, 1H), 2.62 (dddd, $J$ = 13.0, 6.3, 4.3, 1.5 Hz, 1H), 2.20 (dddd, $J$ = 14.4, 9.3, 7.8, 1.3 Hz, 1H), 2.05 (s, br, 1H), 1.96–1.85 (m, 2H), 1.34–1.15 (m, 6H), 0.87 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 196.9, 162.5, 141.6, 138.0, 134.4, 133.7, 133.3, 128.9, 128.5, 126.6, 124.4, 71.7, 43.4, 31.5, 31.5, 29.1, 27.3, 22.5, 14.0; **IR** (thin film): 3403, 3009, 2956, 2927, 2856, 1698, 1653, 1579, 1454, 1206, 1028, 763, 699 $cm^{-1}$; **Optical rotation:** $[\alpha]_D^{27}$ +142.8° (c = 0.11, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{21}H_{26}O_2$ [$M^+$] 310.1928, found 310.1931.




**144** **192** (2.5 equiv) **193**

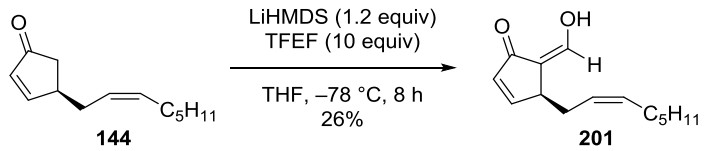
**(*S*,*E*)-4-((*Z*)-Oct-2-en-1-yl)-5-(2-phenylethylidene)cyclopent-2-en-1-one (193).** A solution of enone **144** (20 mg, 0.10 mmol, 1.0 equiv) in THF (0.4 mL) was added dropwise to a solution of LiHMDS (21 mg, 0.13 mmol, 1.2 equiv) in THF (0.6 mL) at –78 °C, and the resulting clear yellowish reaction mixture was stirred at this temperature for 30 min. Then, a solution of aldehyde **192** (29 µL, 0.26 mmol, 2.5 equiv) in THF (0.4 mL) was added dropwise, and stirring was continued at –78 °C for 1.5 h. The reaction mixture was quenched with $NH_4Cl$ solution (5 mL, sat. aqueous) and water (3 mL) and allowed to warm to ambient temperature. It was then

extracted with EtOAc (3 x 10 mL), and the combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded the aldol adduct as a mixture of diastereomers, which was directly used in the following transformation.

**TLC:** $R_f$ = 0.35 (EtOAc/hexane, 20:80; UV, CAM).

To a solution of the above product in $CH_2Cl_2$ (1 mL) at –78 °C was added triethylamine (0.14 mL, 1.0 mmol, 10 equiv), followed by methanesulfonyl chloride (50 µL, 0.64 mmol, 6.5 equiv). The resulting reaction mixture was stirred at –78 °C for 30 min, then allowed to warm to ambient temperature. It was quenched with $NaHCO_3$ solution (2 mL, sat. aqueous) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and filtered over a short plug of silica gel eluting with EtOAc (50 mL). The resulting solution was concentrated under reduced pressure at ambient temperature to a volume of 0.5 mL. $CH_2Cl_2$ (0.5 mL) and aluminum oxide (102 mg, 1.00 mmol, 10 equiv, activated by stirring under high vacuum at 180 °C for 3 h) were added, and the resulting yellow suspension was stirred at ambient temperature for 30 min. Another portion of aluminum oxide (102 mg, 1.00 mmol, 10 equiv) was added, and stirring was continued for 1 h. The reaction mixture was then directly loaded on a column. Purification by column chromatography (EtOAc/hexane, 5:95) afforded enone **193** (4.0 mg, 15%) as colorless oil, along with the corresponding mesylate (15 mg).

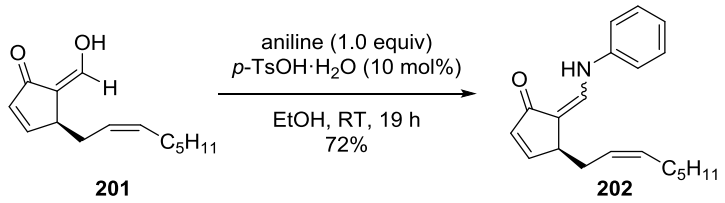
**TLC:** $R_f$ = 0.59 (EtOAc/hexane, 20:80; UV, CAM); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.54 (ddd, $J$ = 6.0, 2.6, 1.0 Hz, 1H), 7.34–7.28 (m, 2H), 7.25–7.18 (m, 3H), 6.75 (tdd, $J$ = 7.8, 1.6, 1.0 Hz, 1H), 6.36 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.51 (app dtt, $J$ = 10.4, 7.3, 1.5 Hz, 1H), 5.35 (app dddt, $J$ = 11.1, 8.4, 6.8, 1.6 Hz, 1H), 3.64 (d, $J$ = 7.8 Hz, 2H), 3.60 (ddd, $J$ = 8.9, 4.2, 2.2 Hz, 1H), 2.71–2.62 (m, 1H), 2.29 (dddd, $J$ = 14.4, 9.3, 8.1, 1.3 Hz, 1H), 1.98 (app qd, $J$ = 7.3, 1.6 Hz, 2H), 1.38–1.19 (m, 6H), 0.88 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 196.6, 161.8, 138.3, 138.1, 134.9, 133.5, 133.1, 128.7, 128.4, 126.6, 124.6, 43.4, 35.2, 31.5, 30.6, 29.2, 27.4, 22.5, 14.0; **IR** (thin film): 3028, 2956, 2926, 2856, 1704, 1655, 1582, 1496, 1454, 1218, 1179, 827, 787, 747, 698 cm$^{-1}$; **HRMS** (EI): exact mass calculated for $C_{21}H_{26}O$ [$M^+$] 294.1979, found 294.1979.




**(*S*,*Z*)-5-(Hydroxymethylene)-4-((*Z*)-oct-2-en-1-yl)cyclopent-2-en-1-one (201).** A solution of enone **144** (10 mg, 52 µmol, 1.0 equiv) in THF (0.3 mL) was added dropwise to a solution of

LiHMDS (10 mg, 62 µmol, 1.2 equiv) in THF (0.4 mL) at –78 °C, and the resulting clear yellowish reaction mixture was stirred at this temperature for 30 min. Then, 2,2,2-trifluoroethyl formate (50 µL, 0.52 mmol, 10 equiv) was added in one shot, and stirring was continued at –78 °C for 8 h. The reaction mixture was quenched with $NH_4Cl$ solution (3 mL, sat. aqueous) and allowed to warm to ambient temperature. It was then extracted with EtOAc (3 x 10 mL). After the first extraction, the aqueous phase was acidified with conc. HCl (1 drop). The combined organic phases were sequentially washed with $NH_4Cl$ solution (10 mL, sat. aqueous) and NaCl solution (10 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 20:80) afforded enol **201** (3 mg, 26%) as a red oil along with recovered starting material (2 mg). The product was not very stable and was used in the following transformation as quickly as possible.

**TLC:** $R_f$ = 0.19 (EtOAc/hexane, 30:70; UV, $KMnO_4$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 7.33 (dd, $J$ = 5.8, 2.3 Hz, 1H), 7.31–7.29 (m, 1H), 6.31 (dd, $J$ = 5.8, 1.9 Hz, 1H), 5.57–5.46 (m, 1H), 5.43–5.31 (m, 1H), 3.39 (ddd, $J$ = 7.2, 5.1, 2.2 Hz, 1H), 2.34–2.26 (m, 2H), 1.99 (q, $J$ = 7.1 Hz, 2H), 1.41–1.15 (m, 7H), 0.94–0.83 (m, 3H); **HRMS** (ESI): exact mass calculated for $C_{14}H_{21}O_2$ $[(M+H)^+]$ 221.1536, found 221.1532.



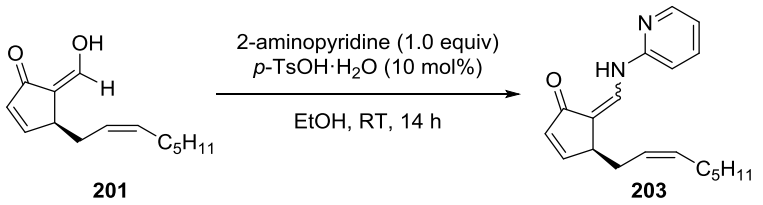

**201** **202**

**(*S*)-4-((*Z*)-Oct-2-en-1-yl)-5-((phenylamino)methylene)cyclopent-2-en-1-one (202).** To a solution of enol **201** (3.0 mg, 14 µmol, 1.0 equiv) in EtOH (0.3 mL) at ambient temperature was added *p*-toluenesulfonic acid monohydrate (0.3 mg, 1 µmol, 10 mol%), followed by aniline (1.2 µL, 14 µmol, 1.0 equiv). The resulting clear yellow reaction mixture was stirred at ambient temperature for 19 h before it was concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 7:93) afforded enaminone **202** (2.9 mg, 72%) as a yellow oil.

**TLC:** $R_f$ = 0.30 (EtOAc/hexane, 10:90; CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 10.83 (d, $J$ = 12.1 Hz, 1H), 7.39–7.28 (m, 3H), 7.23 (dd, $J$ = 5.8, 2.2 Hz, 1H), 7.01 (dd, $J$ = 8.3, 7.2 Hz, 3H), 6.32 (dd, $J$ = 5.7, 1.9 Hz, 1H), 5.59–5.49 (m, 1H), 5.49–5.39 (m, 1H), 3.41 (app tt, $J$ = 7.1, 2.1 Hz, 1H), 2.41–2.26 (m, 2H), 2.05–1.93 (m, 2H), 1.38–1.18 (m, 6H), 0.86–0.79 (m, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$): $\delta$ 197.4, 157.2, 140.7, 135.9, 135.4, 132.6, 129.6, 126.3, 122.6, 115.4, 111.6, 44.5, 31.5, 31.3, 29.2, 27.4, 22.5, 14.0; **IR** (thin film): 2927, 2856, 1668, 1601,

1581, 1509, 1273, 1226, 1181, 750 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{20}H_{26}NO$ $[(M+H)^+]$ 296.2009, found 296.2008.

When enaminone **202** was subjected to $^1H$ NMR analysis in DMSO-$d_6$, a 3:1 mixture of (*Z*) and (*E*) enaminone was observed at ambient temperature. At 80 °C, this ratio changed to 1.5:1.

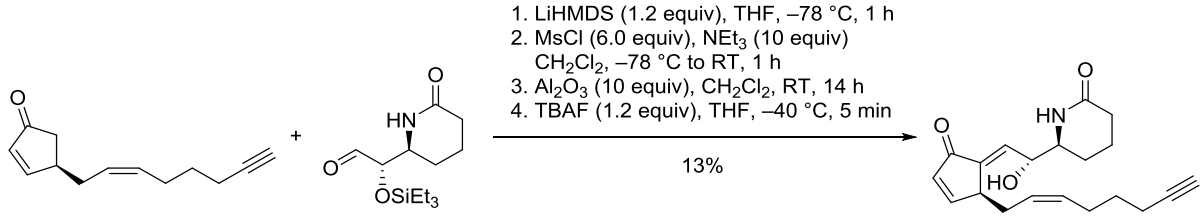



**201** **203**

**(*S*)-4-((*Z*)-Oct-2-en-1-yl)-5-((pyridin-2-ylamino)methylene)cyclopent-2-en-1-one (203).** To a solution of enol **201** (5.0 mg, 23 µmol, 1.0 equiv) in EtOH (0.5 mL) at ambient temperature was added *p*-toluenesulfonic acid monohydrate (0.4 mg, 2 µmol, 10 mol%), followed by 2-aminopyridine (2.1 µL, 23 µmol, 1.0 equiv). The resulting clear red reaction mixture was stirred at ambient temperature for 14 h before it was concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane, 10:90 to 20:80) afforded enaminone **203** (>1 mg) as a yellow oil.

**TLC:** $R_f$ = 0.19 (EtOAc/hexane, 10:90; UV, CAM); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 11.01 (d, *J* = 11.2 Hz, 1H), 8.26 (ddd, *J* = 5.0, 1.9, 0.8 Hz, 1H), 8.05 (d, *J* = 11.2 Hz, 1H), 7.57 (ddd, *J* = 8.2, 7.2, 1.9 Hz, 1H), 7.31 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.88 (ddd, *J* = 7.3, 5.0, 0.9 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.36–6.29 (m, 1H), 5.56–5.47 (m, 1H), 5.46–5.37 (m, 1H), 3.49–3.39 (m, 1H), 2.54–2.43 (m, 1H), 2.37–2.26 (m, 1H), 2.05–1.95 (m, 2H), 1.40–1.14 (m, 6H), 0.93–0.78 (m, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$, estimated from HSQC): $\delta$ 158, 148, 138, 135, 133, 133, 126, 117, 111, 45, 32, 31, 29, 27, 23, 14; **HRMS** (ESI): exact mass calculated for $C_{19}H_{25}N_2O$ $[(M+H)^+]$ 297.1954, found 297.1961.

### 3.3.2 Experimental Procedures for the Synthesis of Biotinylated EC Derivatives




**207** **169** (2.3 equiv) **208**

**(*S*)-6-((*R*,*E*)-1-Hydroxy-2-((*S*)-2-((*Z*)-oct-2-en-7-yn-1-yl)-5-oxocyclopent-3-en-1-ylidene)-ethyl)piperidin-2-one (208).** A solution of enone **207**[182] (20 mg, 0.11 mmol, 1.0 equiv) in THF (0.4 mL) was added to a solution of LiHMDS (21 mg, 0.13 mmol, 1.2 equiv) in THF (0.6 mL) at –78 °C, and the resulting clear yellowish reaction mixture was stirred at this temperature for 30 min. Then, a solution of crude aldehyde **169** (0.25 mmol, 2.3 equiv) in THF (0.4 mL) was added dropwise, and stirring was continued at –78 °C for 1 h. The reaction mixture was quenched with $NH_4Cl$ solution (5 mL, sat. aqueous) and water (3 mL) and allowed to warm to ambient temperature. It was then extracted with EtOAc (3 x 10 mL), and the combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc) afforded the aldol adduct as a colorless oil, which was directly used in the next step.

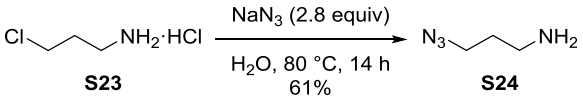
To a solution of the above product in $CH_2Cl_2$ (0.6 mL) at –78 °C was added triethylamine (0.15 mL, 1.1 mmol, 10 equiv), followed by methanesulfonyl chloride (50 µL, 0.64 mmol, 6.0 equiv). The resulting reaction mixture was stirred at –78 °C for 1 h, then allowed to warm to ambient temperature. It was quenched with $NaHCO_3$ solution (2 mL, sat. aqueous) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried over $Na_2SO_4$ and filtered over a short plug of silica gel eluting with EtOAc (50 mL). The resulting solution was concentrated under reduced pressure at ambient temperature to a volume of 0.5 mL. $CH_2Cl_2$ (0.5 mL) and aluminum oxide (108 mg, 1.06 mmol, 10 equiv, activated by stirring under high vacuum at 180 °C for 3 h) were added, and the resulting yellow suspension was stirred at ambient temperature for 14 h. It was then directly loaded on a column. Purification by column chromatography (EtOAc/hexane, 50:50) afforded the elimination product (12 mg) containing impurities.

**TLC:** $R_f$ = 0.72 (EtOAc; UV, CAM); **HRMS** (ESI): exact mass calculated for $C_{26}H_{40}NO_3Si$ $[(M+H)^+]$ 442.2772, found 442.2764.

TBAF (1.0 M in THF, 30 µL, 30 µmol, 1.2 equiv) was added to a solution of the above product (11 mg, 25 µmol, 1.0 equiv) in THF (1.2 mL) at –40 °C. The resulting clear yellowish reaction mixture was stirred at this temperature for 5 min, then quenched with $NH_4Cl$ solution (2 mL, sat.

aqueous) and allowed to warm to ambient temperature. It was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with NaCl solution (20 mL, sat. aqueous), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc, then MeOH/EtOAc, 5:95) afforded alcohol **208** (4.3 mg, 13% over four steps) as a colorless film.

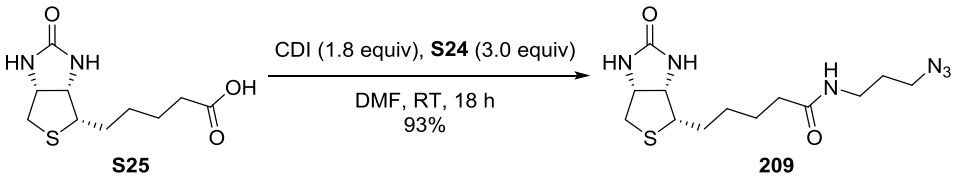
**TLC:** $R_f$ = 0.25 (EtOAc; UV, $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta$ 7.58 (ddd, $J$ = 6.0, 2.6, 0.9 Hz, 1H), 6.70 (s, 1H), 6.50 (ddd, $J$ = 7.6, 1.6, 1.0 Hz, 1H), 6.36 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.52–5.45 (m, 1H), 5.41–5.33 (m, 1H), 4.55 (dt, $J$ = 8.0, 4.2 Hz, 1H), 3.74 (ddt, $J$ = 8.7, 4.1, 2.0 Hz, 1H), 3.69 (dt, $J$ = 9.3, 4.2 Hz, 1H), 3.13 (d, $J$ = 5.0 Hz, 1H), 2.68 (dt, $J$ = 12.3, 5.5 Hz, 1H), 2.43–2.34 (m, 1H), 2.33–2.21 (m, 2H), 2.19 (td, $J$ = 6.9, 2.6 Hz, 2H), 2.16–2.09 (m, 2H), 1.99 (t, $J$ = 2.6 Hz, 1H), 1.96–1.90 (m, 1H), 1.90–1.82 (m, 1H), 1.75–1.64 (m, 1H), 1.62–1.51 (m, 3H); **$^{13}$C NMR** (126 MHz, $CDCl_3$): $\delta$ 196.5, 173.5, 162.8, 141.0, 134.4, 131.9, 129.6, 125.7, 84.3, 70.9, 68.7, 57.5, 43.3, 31.4, 31.3, 28.0, 26.2, 23.1, 19.7, 17.8; **IR** (thin film): 3288, 2937, 1702, 1651, 1409, 1330, 1210, 1083, 810 cm$^{-1}$; **Optical rotation:** $[\alpha]_D^{22}$ +142.6° (c = 0.20, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{20}H_{25}NNaO_3$ [$(M+Na)^+$] 350.1727, found 350.1732.




**3-Azidopropan-1-amine (S24).** According to a procedure reported by A. N. HULME and co-workers,[211] sodium azide (784 mg, 12.1 mmol, 2.8 equiv) was added to a solution of 3-chloropropan-1-amine hydrochloride (**S23**) (560 mg, 4.31 mmol, 1.0 equiv) in water (5 mL). The resulting clear yellowish reaction mixture was stirred at 80 °C for 14 h. It was then allowed to cool to ambient temperature and KOH pellets were added to basify the solution. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford amine **S24** (264 mg, 61%) as a yellow oil.

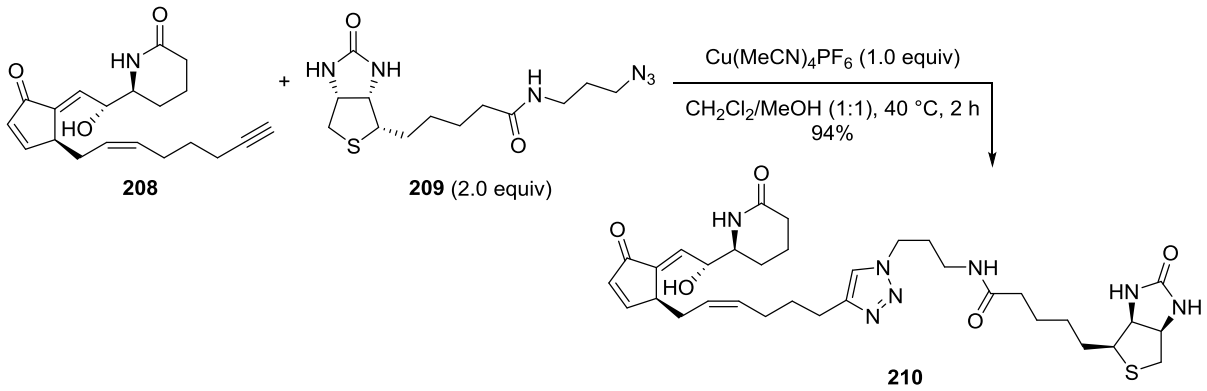
**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 3.37 (t, $J$ = 6.7 Hz, 2H), 2.81 (t, $J$ = 6.8 Hz, 2H), 1.73 (app p, $J$ = 6.8 Hz, 2H), 1.25 (s, 2H). According to the spectral data reported in the literature.[211]

[211] F. Landi, C. M. Johansson, D. J. Campopiano, A. N. Hulme, *Org. Biomol. Chem.* **2010**, *8*, 56–59.




***N*-(3-Azidopropyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (209).** According to a procedure reported by S. LIU and co-workers,[195] a solution of CDI (119 mg, 0.737 mmol, 1.8 equiv) in DMF (0.5 mL) was added dropwise to a suspension of D-biotin (**S25**) (100 mg, 0.409 mmol, 1.0 equiv) in DMF (3.1 mL) at ambient temperature. The resulting mixture was stirred for 3 h before a solution of amine **S24** (123 mg, 1.23 mmol, 3.0 equiv) in DMF (1.0 mL) was added dropwise over 30 min. The resulting clear yellowish reaction mixture was stirred at ambient temperature for 18 h. The solvent was evaporated under reduced pressure and the resulting white solid was recrystallized from *n*-butanol/AcOH/water (70:7:10 v/v/v, 1.5 mL) to afford azide **209** (124 mg, 93%) as a fluffy white solid.

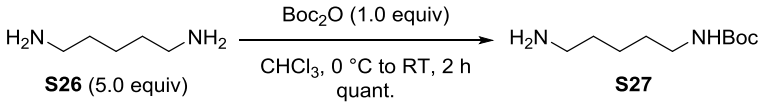
**$^1$H NMR** (400 MHz, $CD_3OD$): $\delta$ 4.49 (ddd, $J$ = 7.9, 5.0, 1.0 Hz, 1H), 4.30 (dd, $J$ = 7.9, 4.4 Hz, 1H), 3.35 (t, $J$ = 6.7 Hz, 2H), 3.29–3.16 (m, 3H), 2.93 (dd, $J$ = 12.8, 5.0 Hz, 1H), 2.71 (d, $J$ = 12.8 Hz, 1H), 2.24–2.16 (m, 2H), 1.83–1.54 (m, 6H), 1.45 (app q, $J$ = 7.3 Hz, 2H). According to the spectral data reported in the literature.[195]




***N*-(3-(4-((*Z*)-6-((*S*,*E*)-5-((*R*)-2-Hydroxy-2-((*S*)-6-oxopiperidin-2-yl)ethylidene)-4-oxocyclopent-2-en-1-yl)hex-4-en-1-yl)-1*H*-1,2,3-triazol-1-yl)propyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (210).** $Cu(MeCN)_4PF_6$ (4.6 mg, 12 µmol, 1.0 equiv) was added to a flask charged with alkyne **208** (4.0 mg, 12 µmol, 1.0 equiv) and azide **209** (8.0 mg, 24 µmol, 2.0 equiv). Methanol (0.3 mL, sparged with nitrogen for 5 min) and $CH_2Cl_2$ (0.3 mL, sparged with nitrogen for 5 min) were added at ambient temperature, and the resulting slightly blue reaction mixture was stirred in a sealed flask at 40 °C for 2 h. It was then directly purified by column chromatography ($MeOH/CH_2Cl_2$, 10:90 to 40:60) to afford a milky

oil. This was azeotroped with benzene and then with acetonitrile to afford triazole **210** (7.5 mg, 94%) as a yellowish solid.

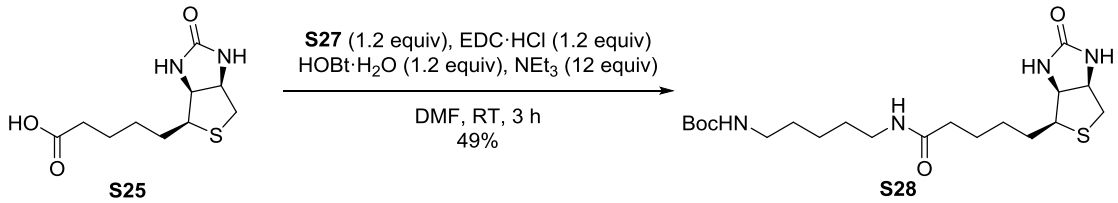
**TLC:** $R_f$ = 0.16 ($MeOH/CH_2Cl_2$, 10:90; UV, $KMnO_4$); **$^1$H NMR** (400 MHz, $CD_3OD$): $\delta$ 7.77 (s, 1H), 7.72 (ddd, $J$ = 6.0, 2.6, 1.0 Hz, 1H), 6.43 (ddd, $J$ = 8.1, 1.6, 0.9 Hz, 1H), 6.34 (dd, $J$ = 6.0, 1.8 Hz, 1H), 5.56–5.49 (m, 1H), 5.40–5.32 (m, 1H), 4.56 (dd, $J$ = 8.1, 4.3 Hz, 1H), 4.49 (ddd, $J$ = 7.9, 5.0, 1.0 Hz, 1H), 4.40 (t, $J$ = 7.0 Hz, 2H), 4.31 (dd, $J$ = 7.9, 4.4 Hz, 1H), 3.79 (ddd, $J$ = 8.6, 4.2, 2.3 Hz, 1H), 3.63–3.56 (m, 1H), 3.25–3.17 (m, 3H), 2.92 (dd, $J$ = 12.8, 5.0 Hz, 1H), 2.73–2.63 (m, 4H), 2.37–2.24 (m, 3H), 2.24–2.19 (m, 2H), 2.13–2.04 (m, 4H), 2.02–1.91 (m, 1H), 1.89–1.82 (m, 1H), 1.79–1.55 (m, 8H), 1.49–1.40 (m, 2H); **$^{13}$C NMR** (126 MHz, $CD_3OD$): $\delta$ 199.1, 176.3, 175.6, 166.1, 165.8, 149.0, 141.5, 134.9, 133.1, 132.9, 126.5, 123.5, 71.0, 63.4, 61.7, 58.2, 57.0, 49.0, 44.6, 41.0, 37.4, 36.8, 32.2, 32.2, 31.1, 30.3, 29.8, 29.5, 27.8, 26.8, 25.8, 23.7, 20.2; **IR** (thin film): 3374, 2933, 2862, 1634, 1464, 1214, 843 $cm^{-1}$; **Optical rotation:** $[\alpha]_D^{21}$ +73.9° (c = 0.10, MeOH); **HRMS** (ESI): exact mass calculated for $C_{33}H_{47}N_7NaO_5S$ [$(M+Na)^+$] 676.3252, found 676.3247.




***tert*-Butyl (5-aminopentyl)carbamate (S27).** According to a procedure reported by R. LAZARO and co-workers,[212] a solution of $Boc_2O$ (0.43 mL, 1.8 mmol, 1.0 equiv) in $CHCl_3$ (20 mL) was added dropwise to a solution of pentane-1,5-diamine (**S26**) (1.07 mL, 9.16 mmol, 5.0 equiv) in $CHCl_3$ (40 mL) at 0 °C. The resulting white suspension was stirred at ambient temperature for 2 h before it was filtered and concentrated under reduced pressure. The residue was taken up in EtOAc (40 mL) and washed with NaCl solution (40 mL, sat. aqueous). The aqueous phase was extracted with EtOAc (2 x 40 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford amine **S27** (395 mg, quant.) as a colorless oil.

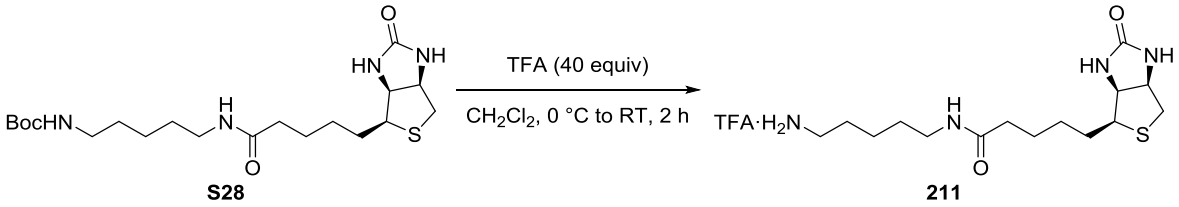
**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta$ 4.52 (s, br, 1H), 3.11 (app q, $J$ = 6.6 Hz, 2H), 2.69 (t, $J$ = 6.8 Hz, 2H), 1.53–1.28 (m, 17H). According to the spectral data reported in the literature.[213]

[212] J.-F. Pons, J.-L. Fauchère, F. Lamaty, A. Molla, R. Lazaro, *Eur. J. Org. Chem.* **1998**, 853–859.
[213] T. Jong, M. Bradley, *Org. Lett.* **2015**, *17*, 422–425.




***tert*-Butyl (5-(5-((3*aS*,4*R*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamido)pentyl)carbamate (S28).** Similar to a procedure reported by K. TACHIBANA and co-workers,[197] D-biotin (**S25**) (150 mg, 0.61 mmol, 1.0 equiv), HOBt·$H_2O$ (113 mg, 0.737 mmol, 1.2 equiv), EDC·HCl (141 mg, 0.737 mmol, 1.2 equiv) and triethylamine (1.0 mL, 7.2 mmol, 12 equiv) were added sequentially to a solution of amine **S27** (150 mg, 0.74 mmol, 1.2 equiv) in DMF (2.5 mL) at ambient temperature. The resulting yellowish suspension was stirred at ambient temperature for 3 h before it was concentrated under reduced pressure. The residue was dissolved in a mixture of EtOAc and $CH_2Cl_2$ (ca. 200 mL), washed with NaCl solution (2 x 20 mL, sat. aqueous), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (MeOH/$CHCl_3$, 5:95) afforded amide **S28** (138 mg, 93% pure, 49%) as an off-white solid, containing HOBt·$H_2O$ as an impurity.

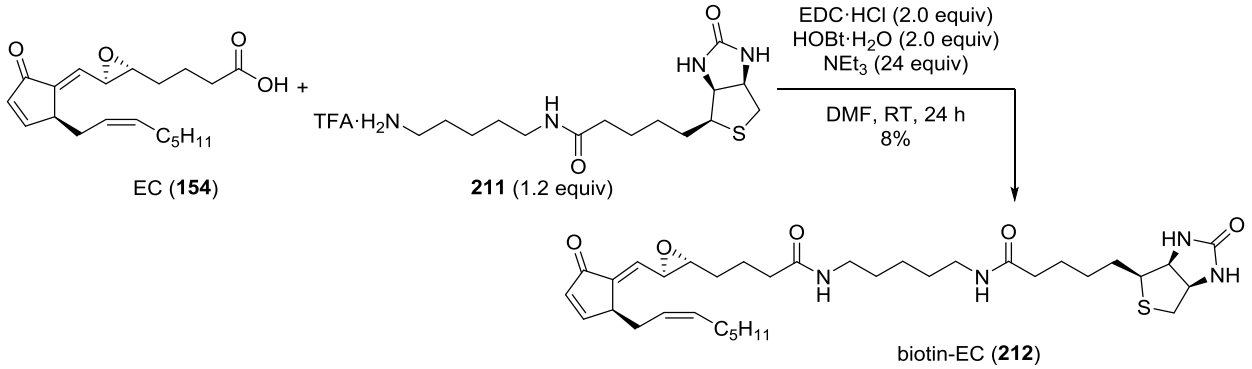
**TLC:** $R_f$ = 0.20 (MeOH/$CHCl_3$, 5:95; $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 5.98 (s, br, 1H), 5.72 (s, br, 1H), 5.01 (s, br, 1H), 4.64 (s, br, 1H), 4.53 (dd, $J$ = 7.7, 5.0 Hz, 1H), 4.38–4.30 (m, 1H), 3.23 (app qd, $J$ = 6.9, 2.6 Hz, 2H), 3.16 (td, $J$ = 7.4, 4.6 Hz, 1H), 3.10 (app q, $J$ = 6.7 Hz, 2H), 2.93 (dd, $J$ = 12.9, 5.0 Hz, 1H), 2.74 (d, $J$ = 12.9 Hz, 1H), 2.21 (td, $J$ = 7.2, 2.1 Hz, 2H), 1.79–1.58 (m, 4H), 1.55–1.41 (m, 15H), 1.38–1.30 (m, 2H). According to the spectral data reported in the literature.[197]




***N*-(5-Aminopentyl)-5-((3*aS*,4*R*,6*aR*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide trifluoroacetate (211).** TFA (1.0 mL, 13 mmol, 40 equiv) was added dropwise to a solution of amide **S28** (136 mg, 93% pure, 0.295 mmol, 1.0 equiv) in $CH_2Cl_2$ (2 mL) at 0 °C. The resulting clear yellowish reaction mixture was stirred at ambient temperature for 2 h. It was then concentrated under reduced pressure to afford amine **211** as its trifluoroacetic salt (255 mg) as a brownish oil which was used in the next step without further purification.

**$^1$H NMR** (400 MHz, $CD_3OD$): $\delta$ 4.49 (ddd, $J$ = 7.9, 5.0, 0.9 Hz, 1H), 4.29 (dd, $J$ = 7.9, 4.5 Hz, 1H), 3.23–3.15 (m, 3H), 2.95–2.88 (m, 3H), 2.70 (d, $J$ = 12.7 Hz, 1H), 2.20 (t, $J$ = 7.3 Hz, 2H),

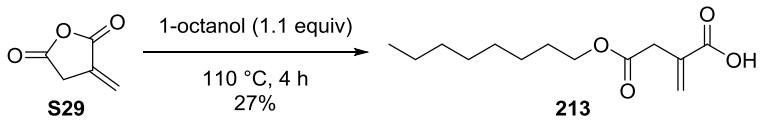
1.77–1.49 (m, 8H), 1.48–1.36 (m, 4H). According to the spectral data reported in the literature.[197]




**Biotin-EC (212).** To a solution of EC (**154**)[153] (34 mg, 0.10 mmol, 1.0 equiv) and amide **211** (54 mg, 0.12 mmol, 1.2 equiv) in DMF (1.1 mL) at ambient temperature were sequentially added HOBt·$H_2O$ (19 mg, 0.12 mmol, 1.2 equiv), EDC·HCl (23 mg, 0.12 mmol, 1.2 equiv) and triethylamine (0.17 mL, 1.2 mmol, 12 equiv). The resulting turbid yellow reaction mixture was stirred at ambient temperature for 6 h. Another portion of HOBt·$H_2O$ (12 mg, 81 µmol, 0.8 equiv), EDC·HCl (15 mg, 81 µmol, 0.8 equiv) and triethylamine (0.17 mL, 1.2 mmol, 12 equiv) was added and stirring was continued at ambient temperature. After a total stirring time of 24 h, the reaction mixture was concentrated under reduced pressure. Purification by column chromatography (MeOH/EtOAc, 20:80) afforded the product still containing impurities. It was taken up in EtOAc (10 mL) and water (10 mL), the phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. This procedure was repeated with $NaHCO_3$ solution (10 mL, sat. aqueous) instead of water. Then, purification by preparative TLC (MeOH/EtOAc, 25:75) followed by purification by column chromatography (MeOH/EtOAc, 20:80) afforded biotin-EC (**212**) (5.5 mg, 8%) as a white solid.

**TLC:** $R_f$ = 0.27 (MeOH/EtOAc, 20:80; UV, $KMnO_4$); **$^1$H NMR** (500 MHz, $CD_3OD$): $\delta$ 7.71 (ddd, $J$ = 6.0, 2.6, 1.0 Hz, 1H), 6.33 (dd, $J$ = 6.0, 1.9 Hz, 1H), 6.12 (ddd, $J$ = 8.2, 1.6, 1.0 Hz, 1H), 5.53–5.47 (m, 1H), 5.36–5.29 (m, 1H), 4.49 (ddd, $J$ = 7.9, 5.0, 1.0 Hz, 1H), 4.30 (dd, $J$ = 7.9, 4.5 Hz, 1H), 3.82 (ddt, $J$ = 5.9, 4.8, 2.2 Hz, 1H), 3.54 (dd, $J$ = 8.2, 2.1 Hz, 1H), 3.23–3.19 (m, 1H), 3.19–3.14 (m, 2H), 3.05 (ddd, $J$ = 6.4, 3.9, 2.1 Hz, 1H), 2.93 (dd, $J$ = 12.8, 5.0 Hz, 1H), 2.70 (d, $J$ = 12.8 Hz, 1H), 2.59 (dt, $J$ = 12.9, 6.1 Hz, 1H), 2.46–2.38 (m, 1H), 2.28–2.23 (m, 2H), 2.22–2.17 (m, 2H), 2.01 (app q, $J$ = 7.4 Hz, 2H), 1.83–1.24 (m, 24H), 0.93–0.88 (m, 3H); **$^{13}$C NMR** (126 MHz, $CD_3OD$): $\delta$ 198.1, 176.0, 175.4, 166.1, 165.1, 142.4, 134.8, 134.1, 132.9, 125.6, 63.4, 61.6, 61.1, 57.0, 56.0, 44.6, 41.0, 40.3, 40.2, 36.8, 36.6, 32.7, 32.5, 32.4, 30.4, 30.1

(2C), 29.8, 29.5, 28.3, 26.9, 25.3, 23.6, 23.5, 14.4; **IR** (thin film): 3285, 2928, 2858, 2407, 1684, 1635, 1461, 1208, 865 $cm^{-1}$; **HRMS** (ESI): exact mass calculated for $C_{35}H_{55}N_4O_5S$ $[(M+H)^+]$ 643.3888, found 643.3884.




**4-Octyl itaconate (213).** Similar to a procedure reported by L. A. O'NEILL and co-workers,[204] a mixture of itaconic anhydride (**S29**) (2.0 g, 18 mmol, 1.0 equiv) and 1-octanol (3.0 mL, 19 mmol, 1.1 equiv) was stirred at 110 °C for 4 h. The resulting clear colorless liquid was then allowed to cool to ambient temperature, upon which it solidified. Hexane (60 mL) was added, the mixture was filtered and the residue was washed with cold hexane (40 mL). The filtrate was partially concentrated under reduced pressure, then cooled to 0 °C and filtered again. The solids were combined and dried under high vacuum to afford 4-octyl itaconate (**213**) (1.2 g, 27%) as a white powder.

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta$ 10.83 (s, br, 1H), 6.45 (d, $J$ = 0.9 Hz, 1H), 5.83 (d, $J$ = 1.1 Hz, 1H), 4.10 (t, $J$ = 6.7 Hz, 2H), 3.34 (d, $J$ = 1.0 Hz, 2H), 1.68–1.56 (m, 2H), 1.39–1.18 (m, 10H), 0.92–0.83 (m, 3H). According to the spectral data reported in the literature.[204]

### 3.3.3 Details for Biological Testing

**Cell culture and stimulation.** Bone marrow cells from femur and tibur of 6–12 week old mice of strain C57BL/6 were differentiated into BMDCs in RPMI-1640 medium (Gibco) supplemented with granulocyte macrophage-colony stimulating factor (GM-CSF; supernatant from X63-GMCSF cell line), 2 mM L-glutamine (GE Healthcare), 10 mM HEPES (Lonza), 100 U/mL penicillin, 100 µg/mL streptomycin (Gibco), 10% FCS (Gibco). Fresh medium was added on day 3 and day 6, and non-adherent cells were harvested for experiments on day 7 of culture. Cells were subsequently plated in a 96-well plate at a density of $10^5$ cells/well and treated for 60 minutes with the synthetized compounds at the indicated concentrations in supplemented RPMI-1640 medium. After the incubation with the compounds, cells were washed with medium and stimulated with 5 µg/mL Toll-like receptor 7 ligand R837 to induce secretion of proinflammatory cytokines. After 20 hours of stimulation with R837, supernatants were collected for analysis.

**ELISA.** IL-6 in supernatants was quantified by sandwich enzyme-linked immunosorbent assay (ELISA) using the following antibody pair: MP5-20F3 & MP5-32C11 (eBioscience). Data were normalized and depicted as percentage (%) decrease of cytokine secretion relative to the control (untreated) group. Normalization was performed to allow comparison between different experiments.

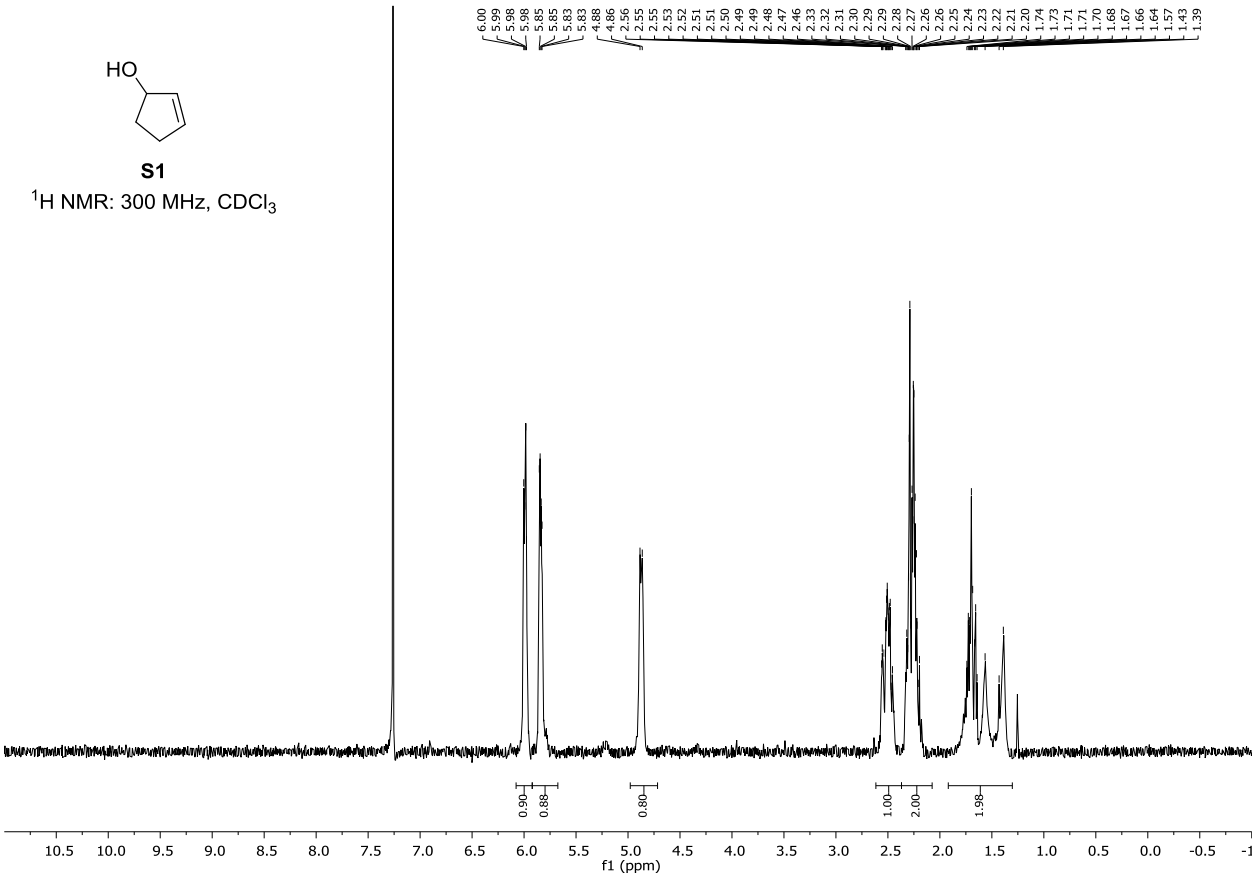
**Cytotoxicity.** Compound cytotoxicity at the different concentrations was tested by the Fixable viability dye eFluor® 780 (eBioscience). For the staining, the dye was diluted 1:4000 in pure PBS (phosphate buffered saline), and cells were incubated for 10 minutes on ice. Cells were finally acquired on a FACSCanto II (BD Bioscience) and data was analyzed in FlowJo software (Tree Star). Compounds were considered cytotoxic at a concentration where the reduction of the percentage of living cells compared to the control group was statistically significant (as determined by one-way ANOVA adjusted by Dunnett's multiple comparison test). Statistical tests were performed with GraphPad Prism Version 7.0c for Mac OS X.

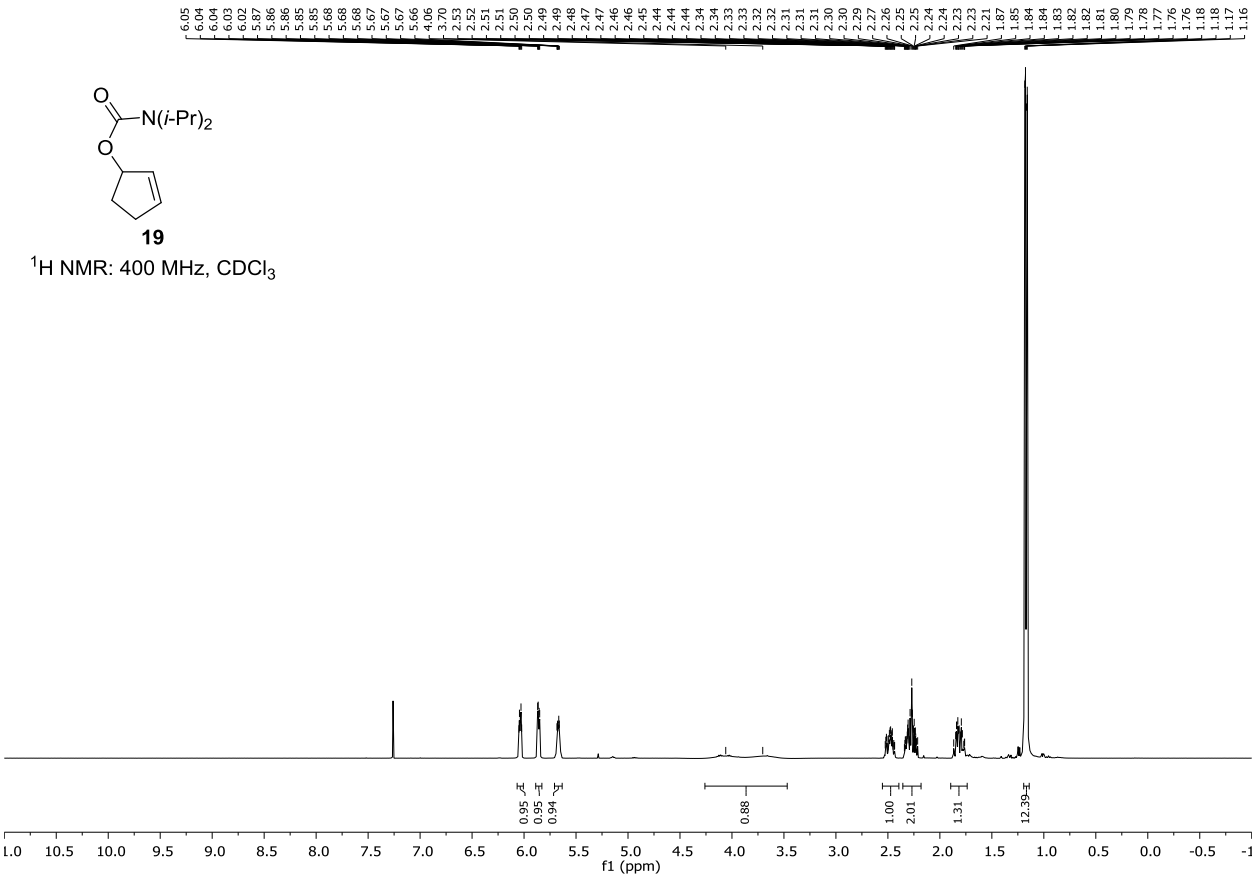
# 4

# *Appendix*

# 4. Appendix

## 4.1 NMR Spectra

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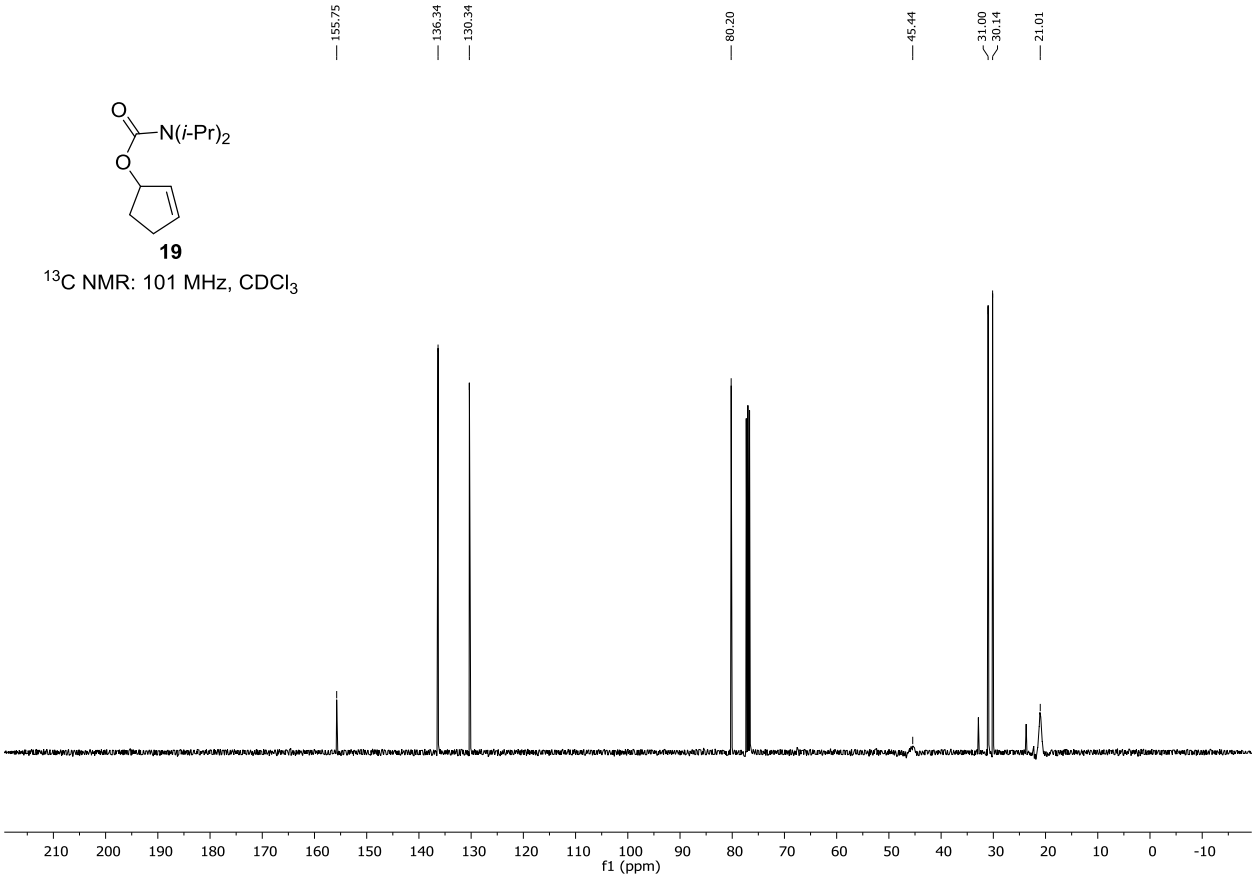
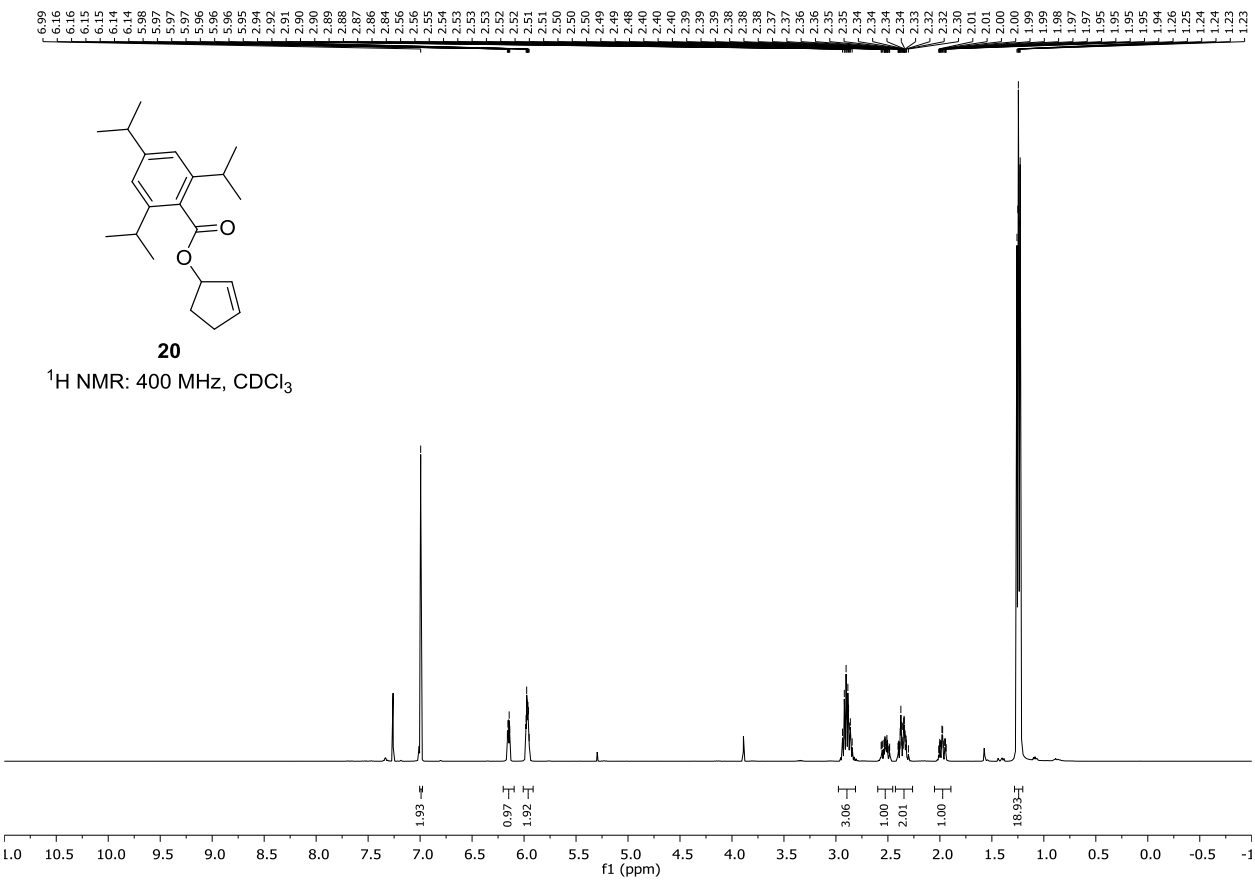
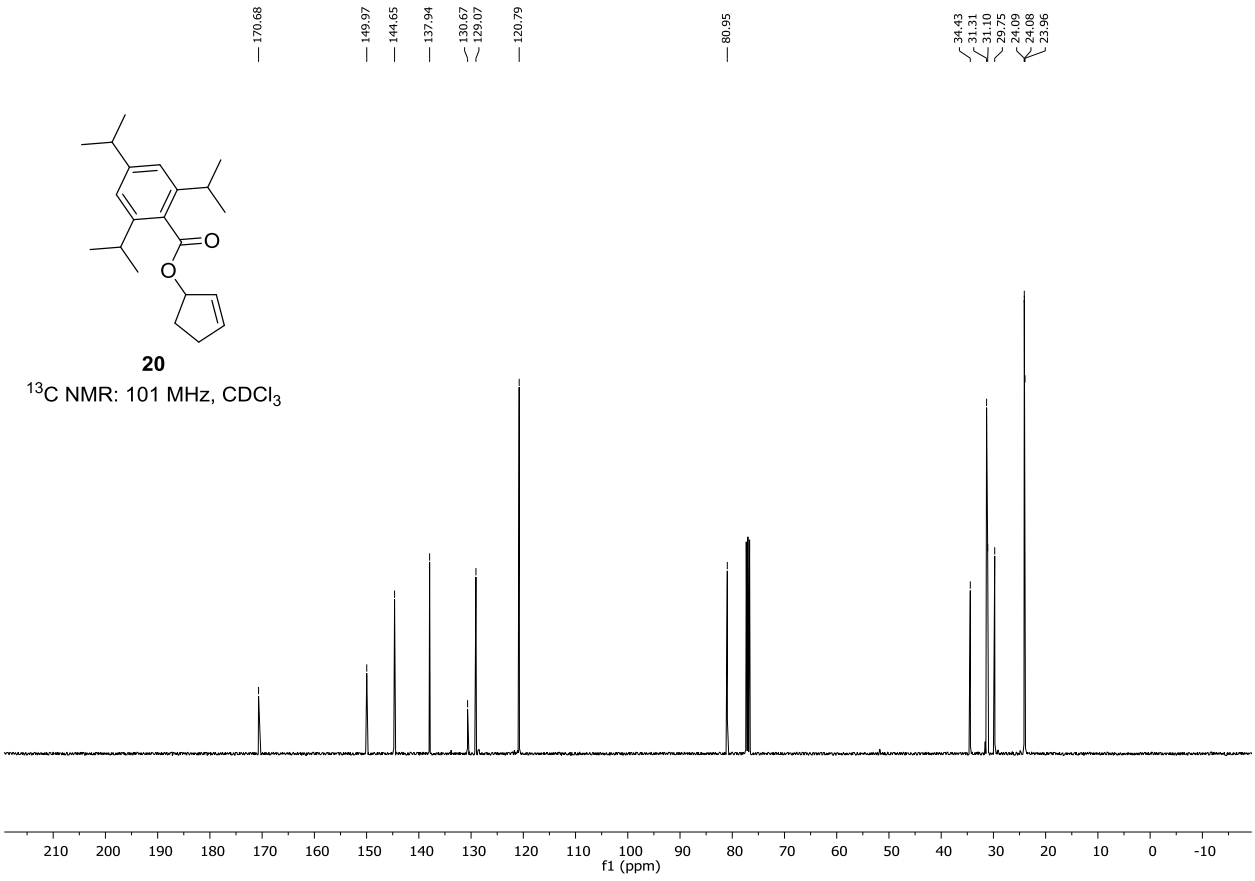
N(i-Pr)2
O
19
1H NMR: 400 MHz, CDCl3
f1 (ppm)


O
N(i-Pr)2
O
19
13C NMR: 101 MHz, CDCl3
155.75
136.34
130.34
80.20
45.44
31.00
30.14
21.01
f1 (ppm)



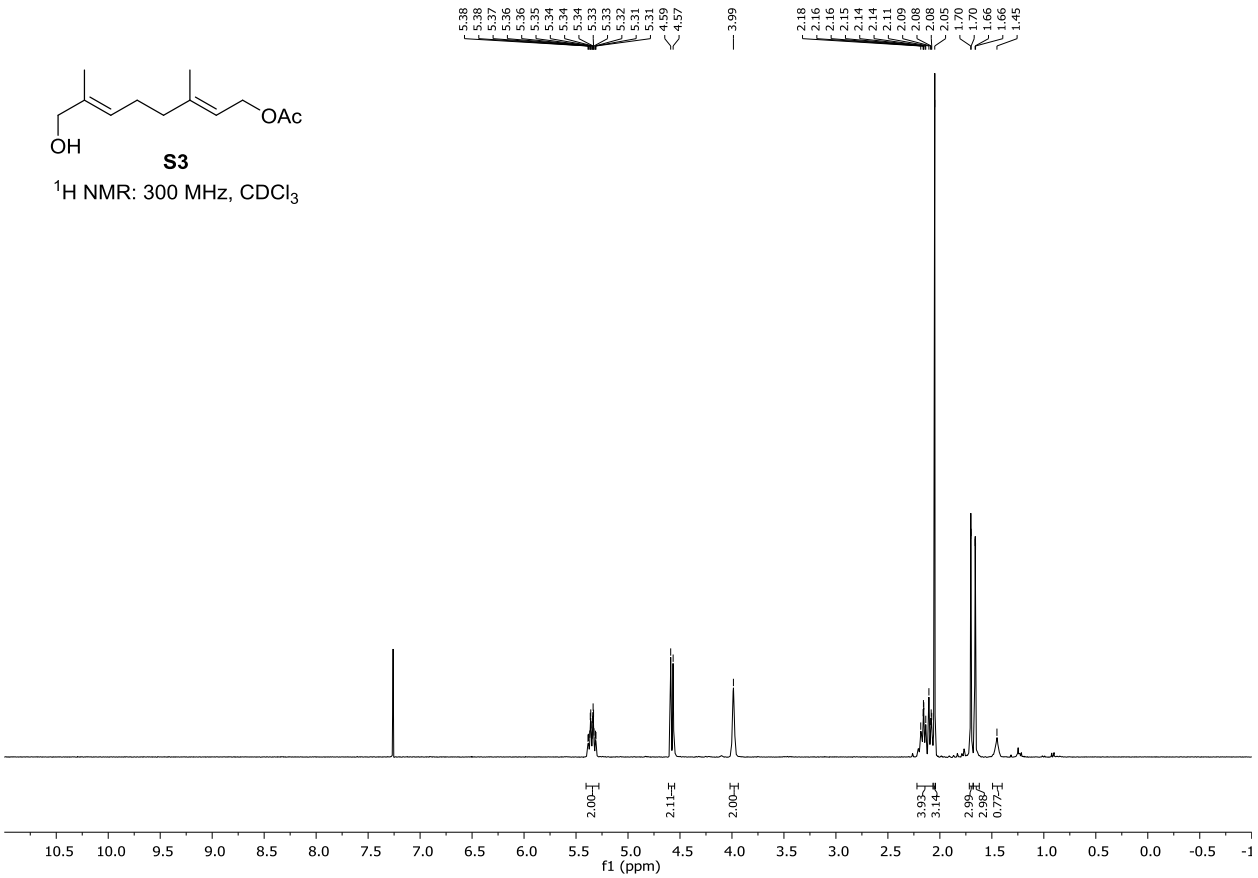
**20**

$^{1}$H NMR: 400 MHz, $CDCl_3$



**20**

$^{13}$C NMR: 101 MHz, $CDCl_3$


OAc
OH
S3
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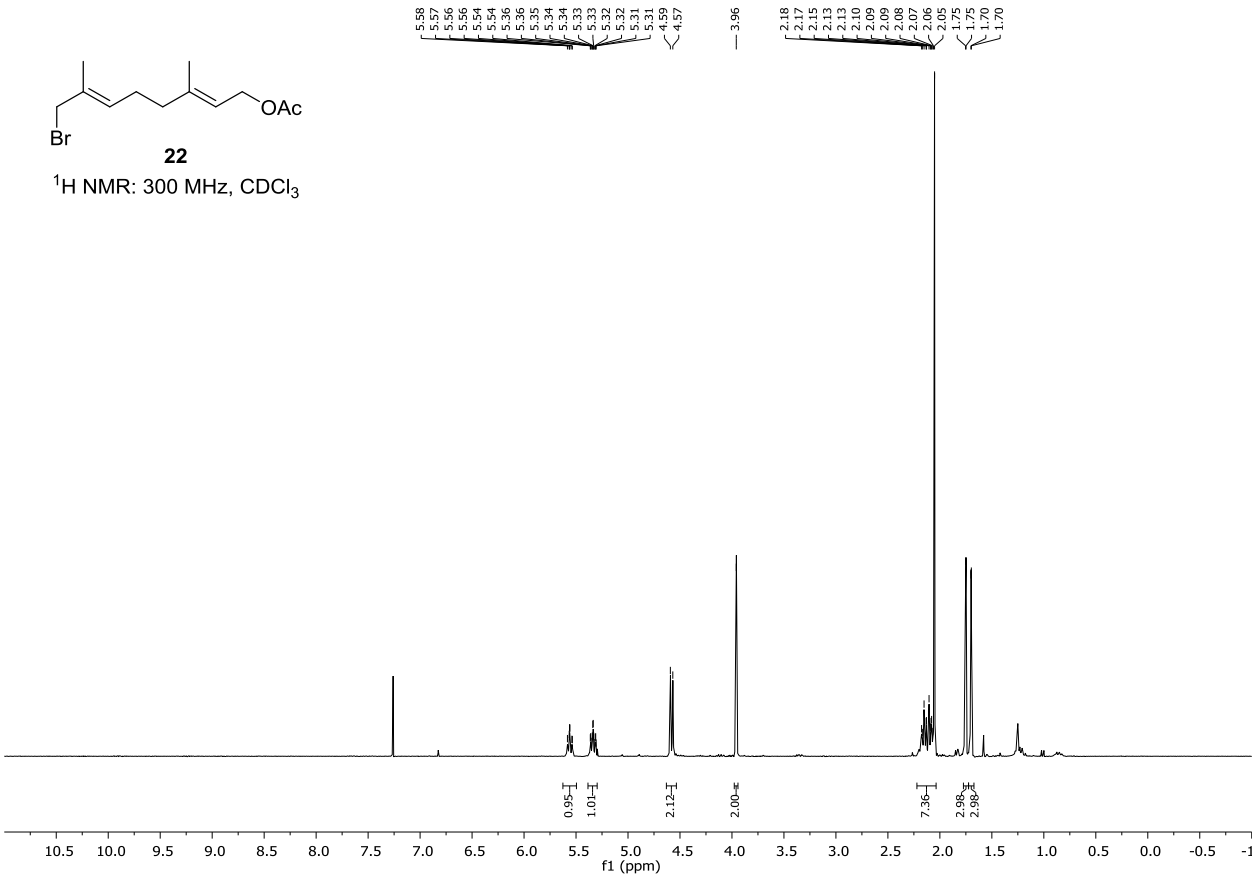
f1 (ppm)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Br
22
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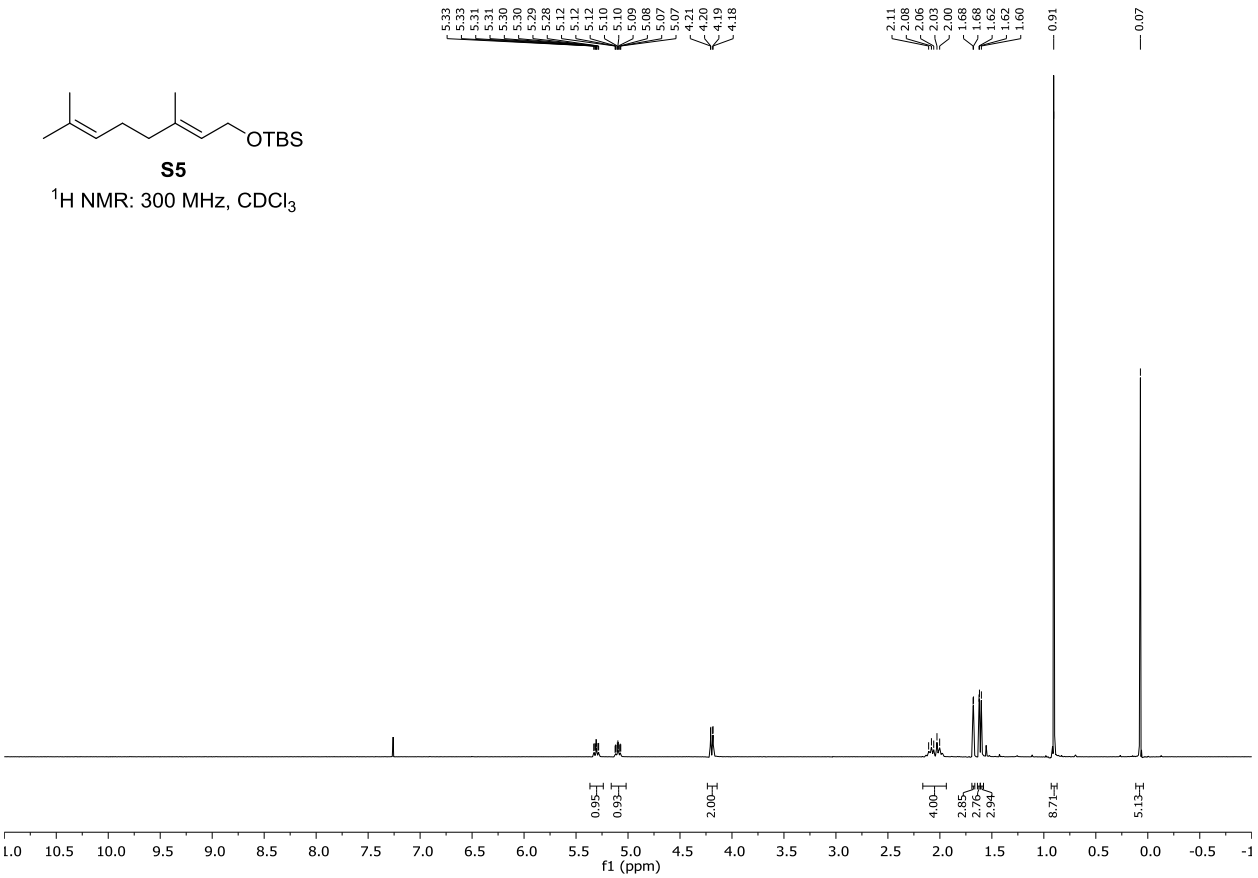
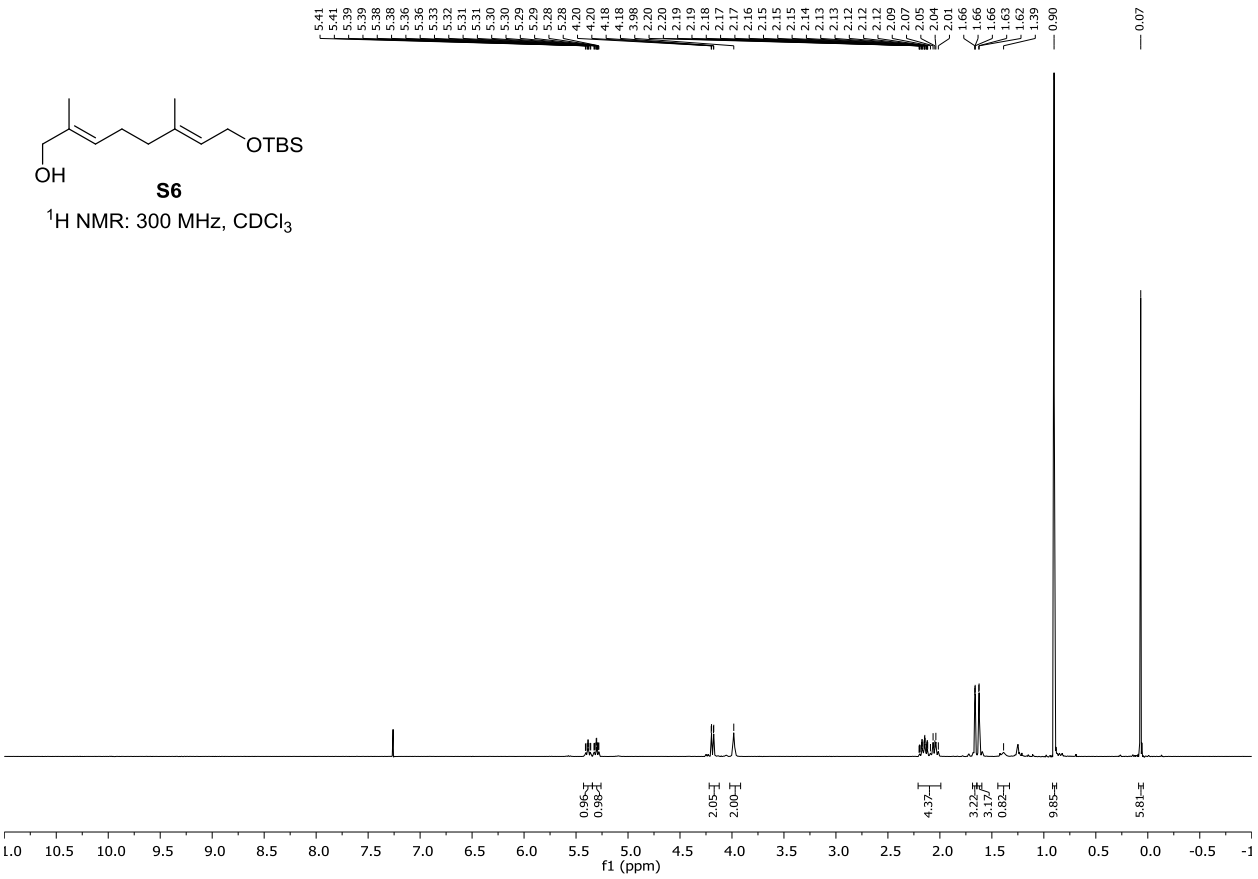
f1 (ppm)



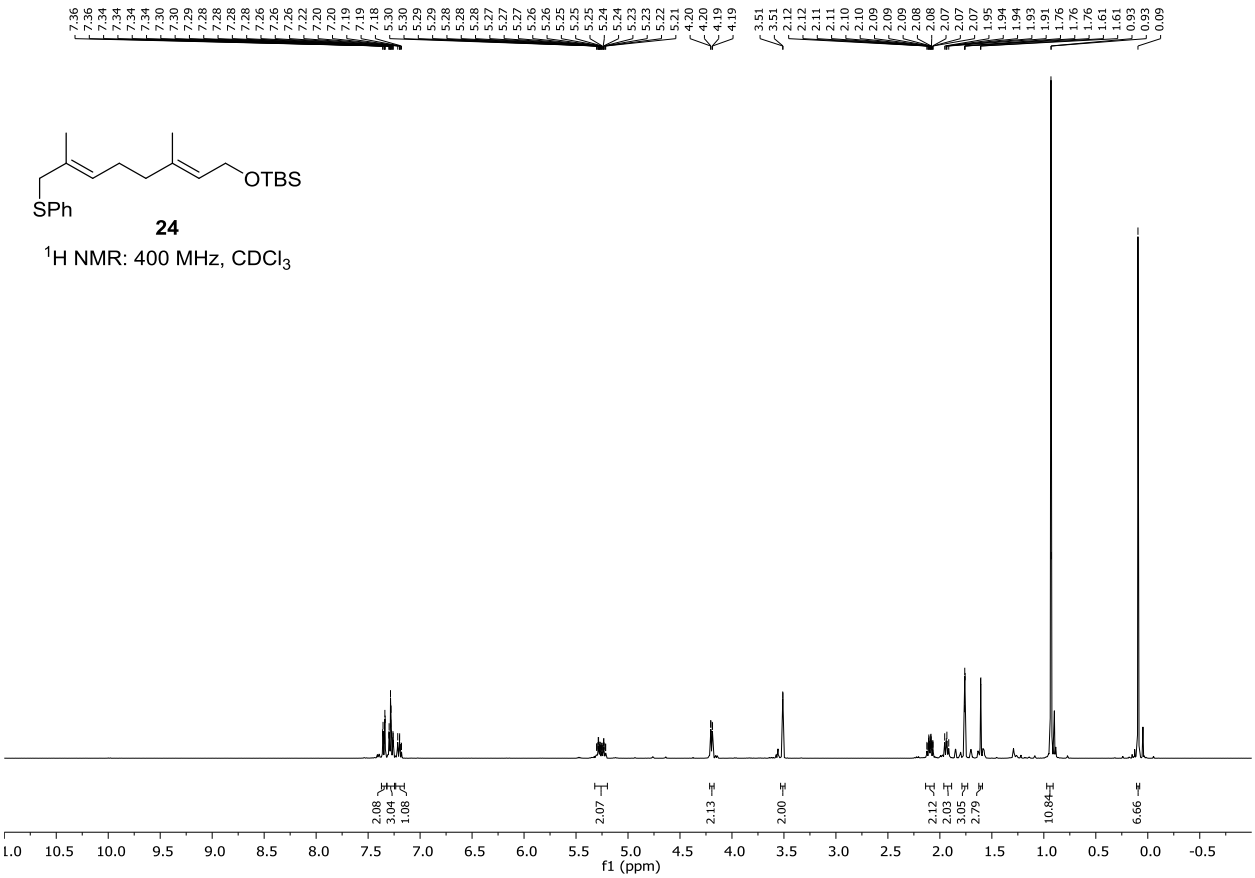

**S5**

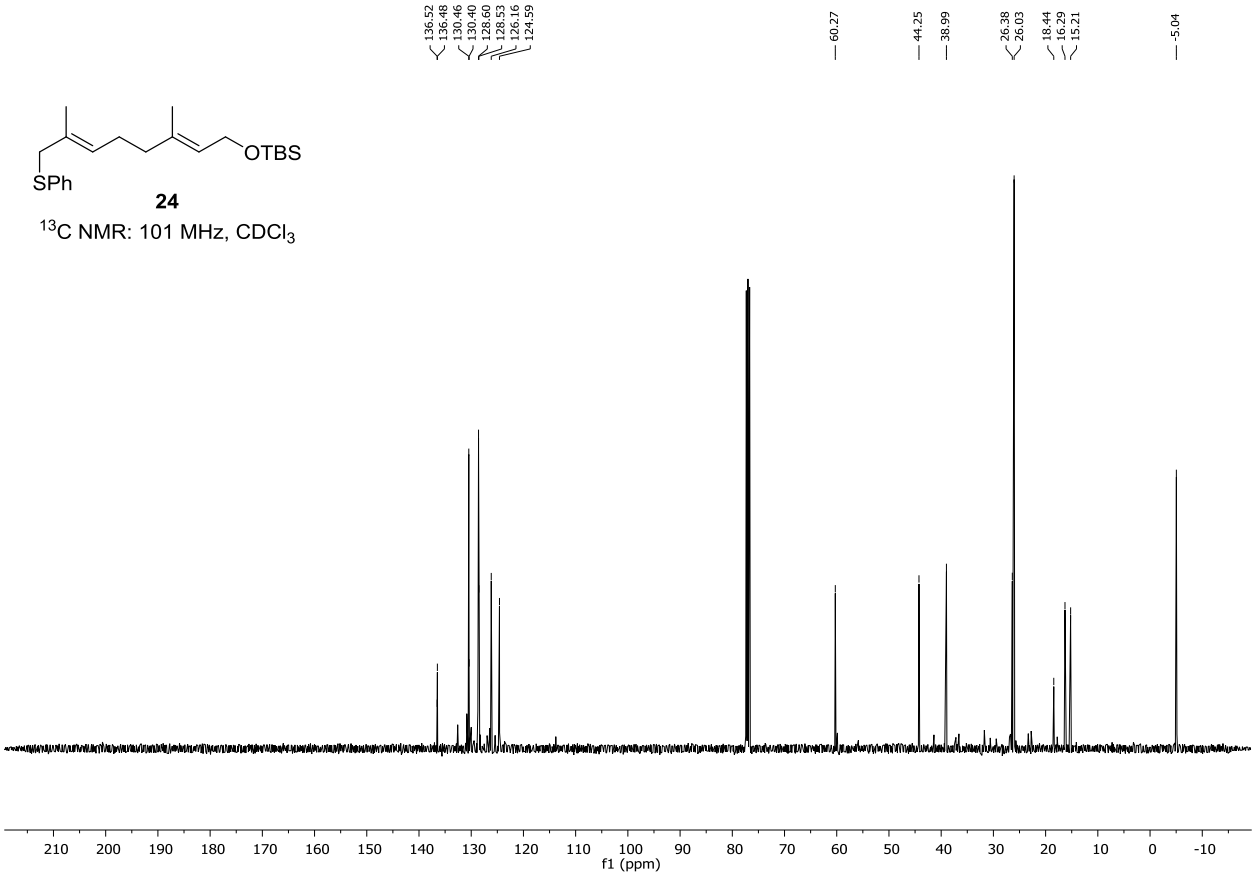
$^1$H NMR: 300 MHz, $CDCl_3$




**S6**

$^1$H NMR: 300 MHz, $CDCl_3$


OTBS
SPh
24
1H NMR: 400 MHz, CDCl3
f1 (ppm)


OTBS
SPh
24
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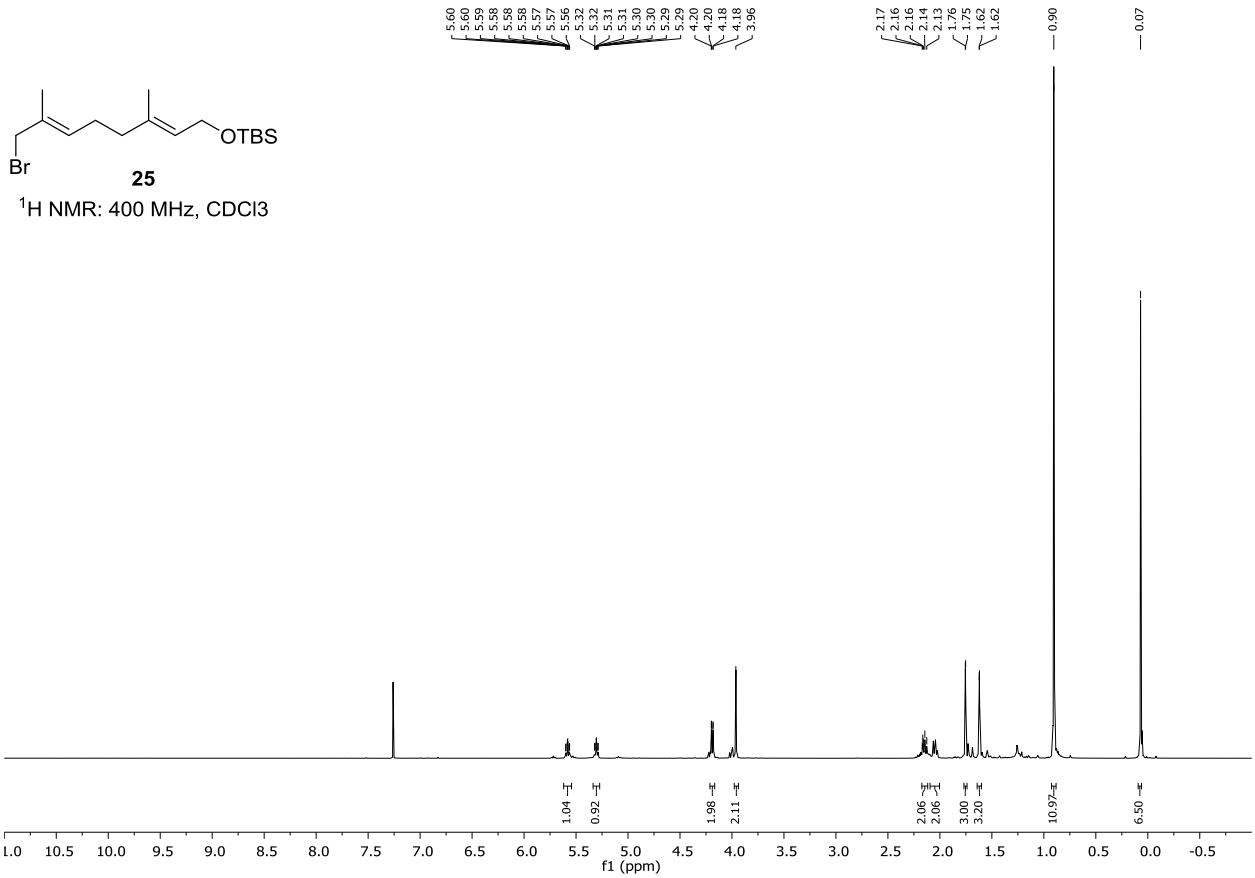
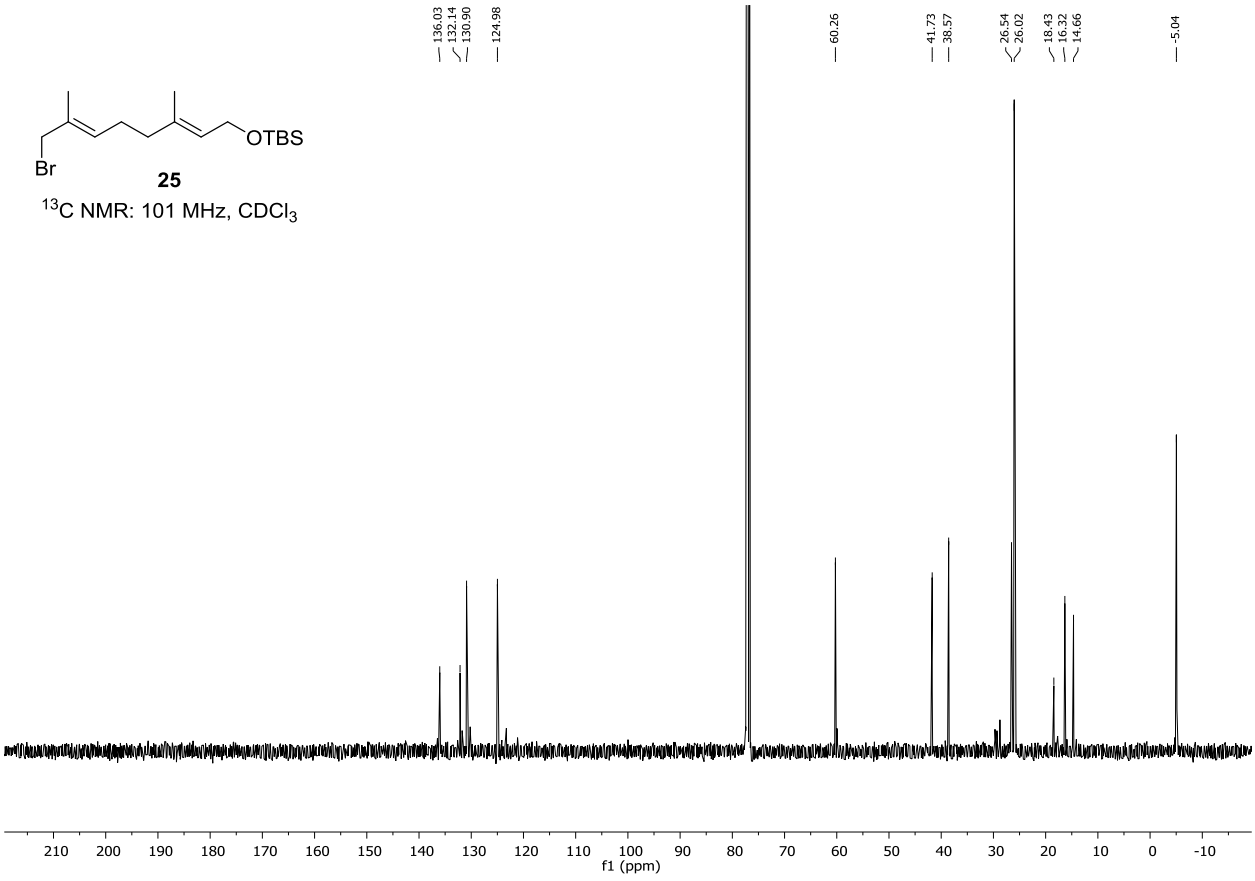
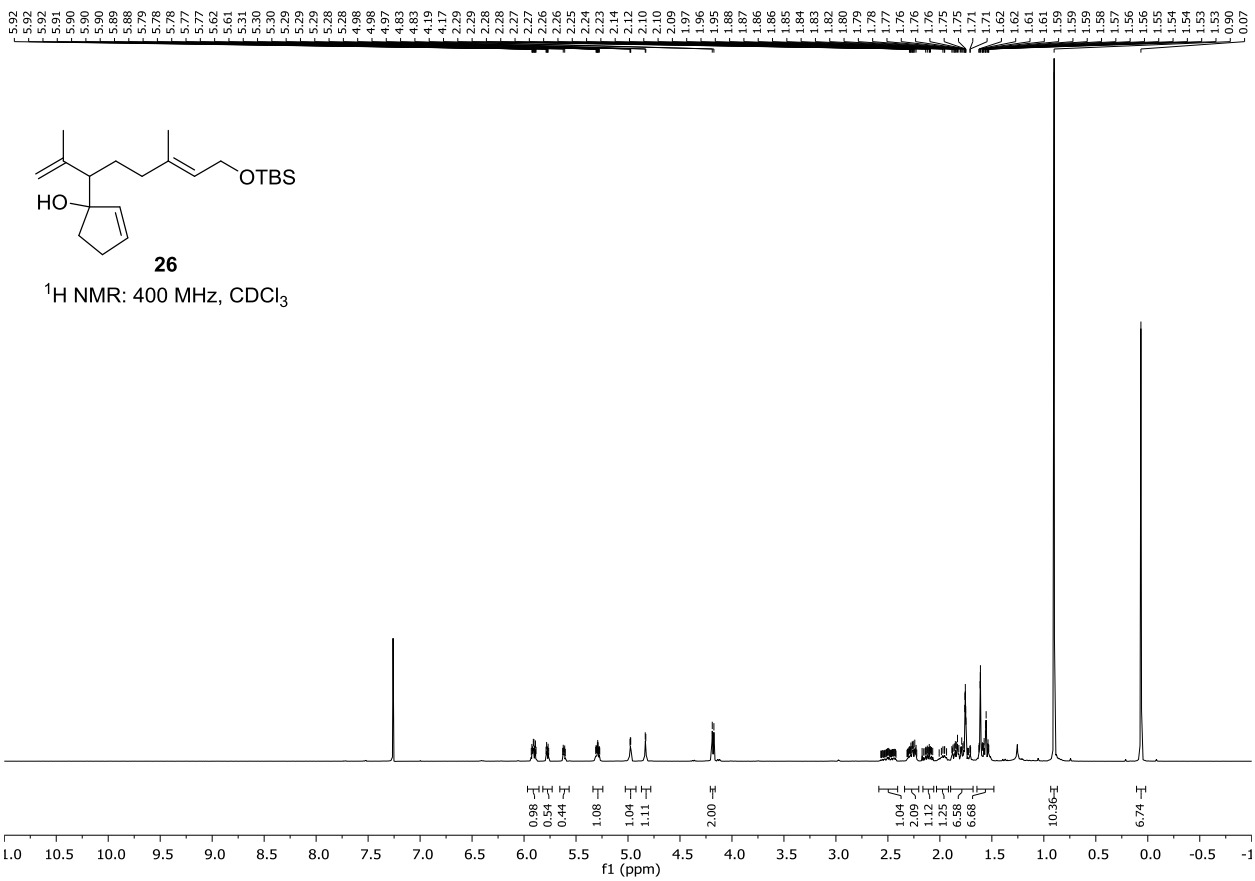
f1 (ppm)

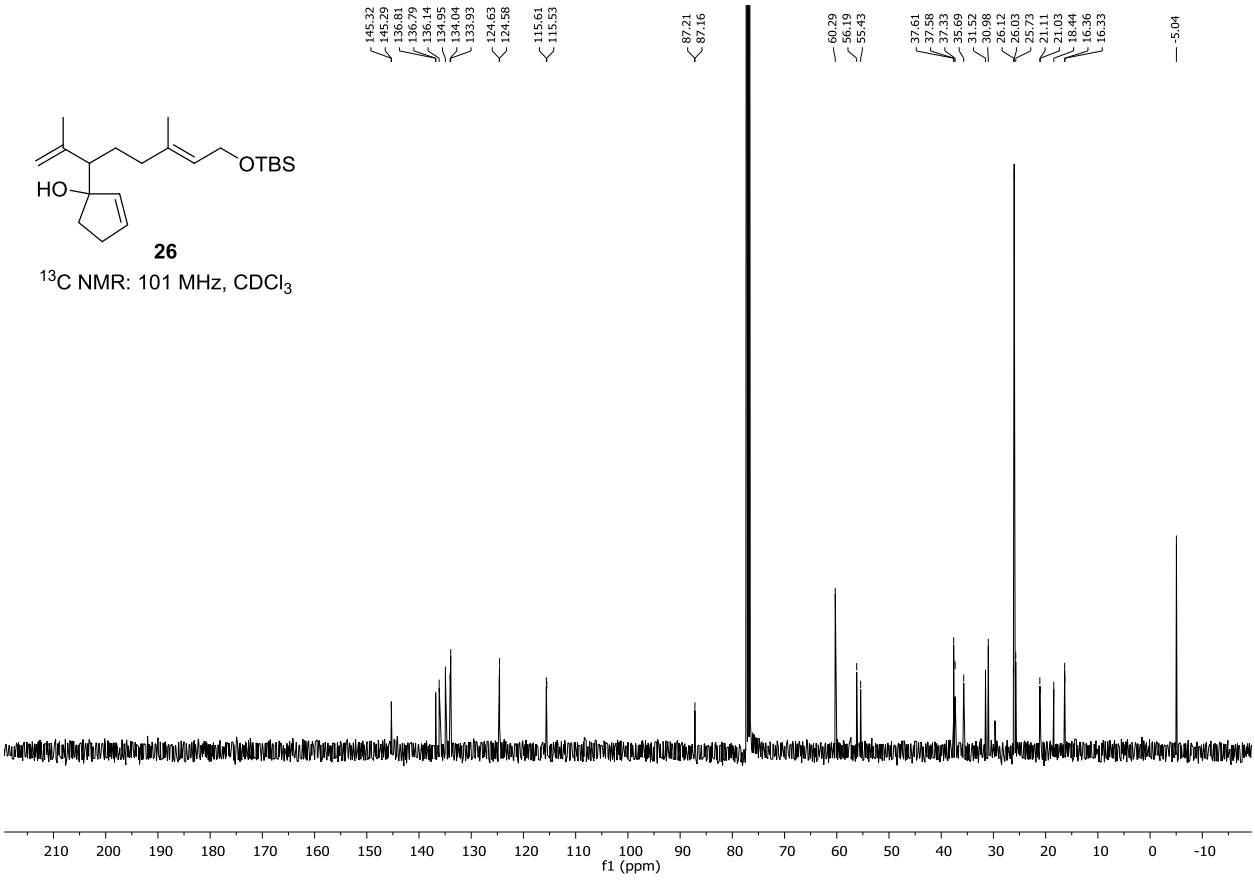

OTBS
Br
25
1H NMR: 400 MHz, CDCl3
f1 (ppm)


OTBS
Br
25
13C NMR: 101 MHz, CDCl3
f1 (ppm)



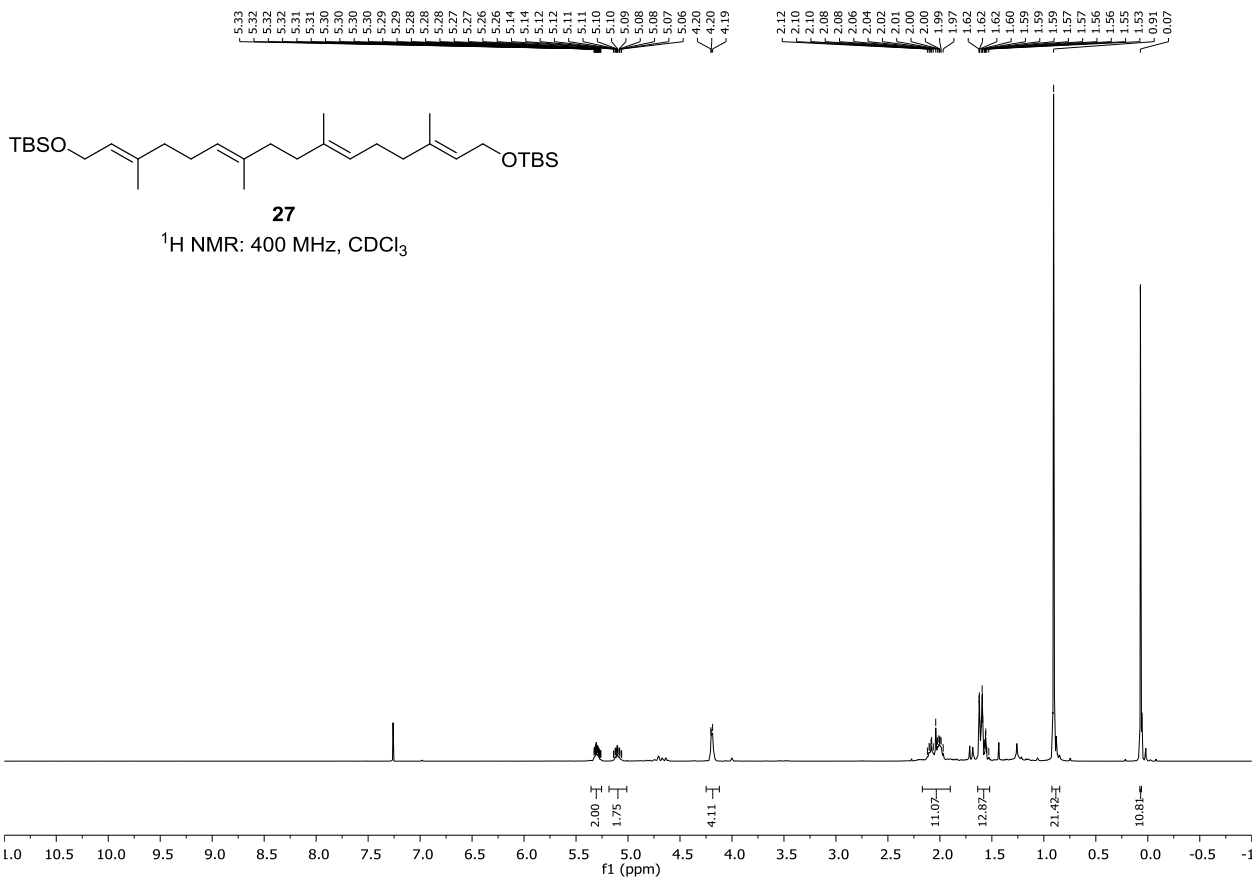

**26**

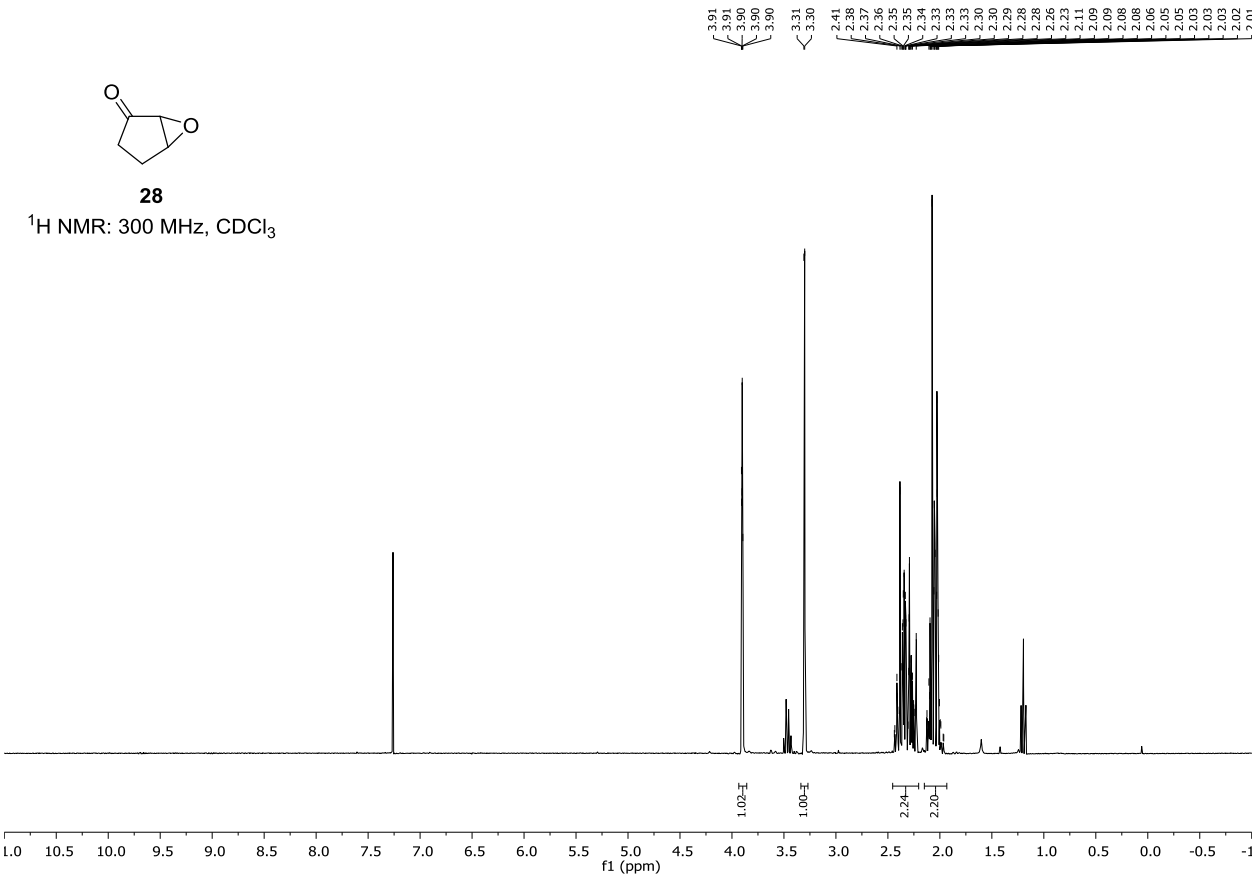
$^{1}$H NMR: 400 MHz, $CDCl_3$




**26**

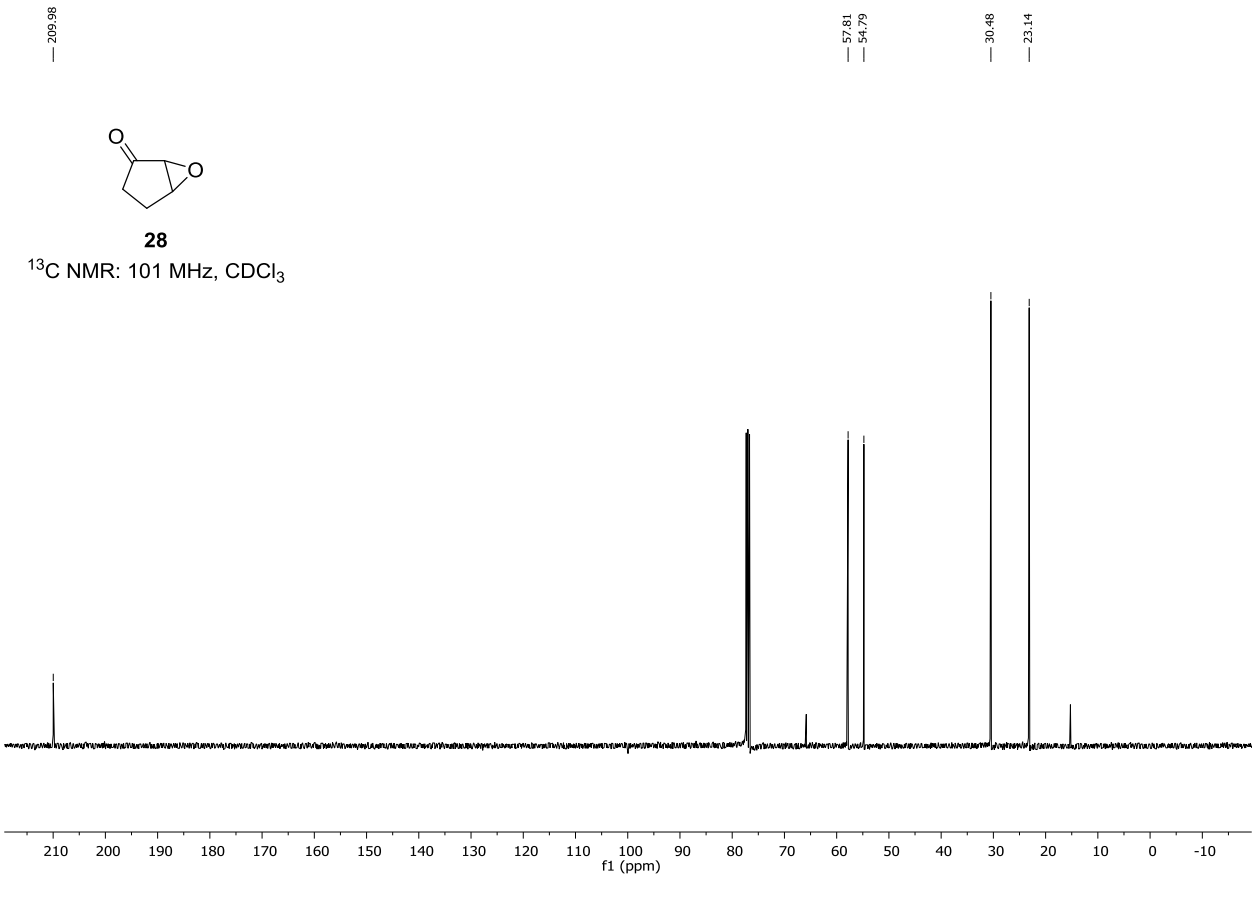
$^{13}$C NMR: 101 MHz, $CDCl_3$


TBSO
OTBS
27
1H NMR: 400 MHz, CDCl3
f1 (ppm)



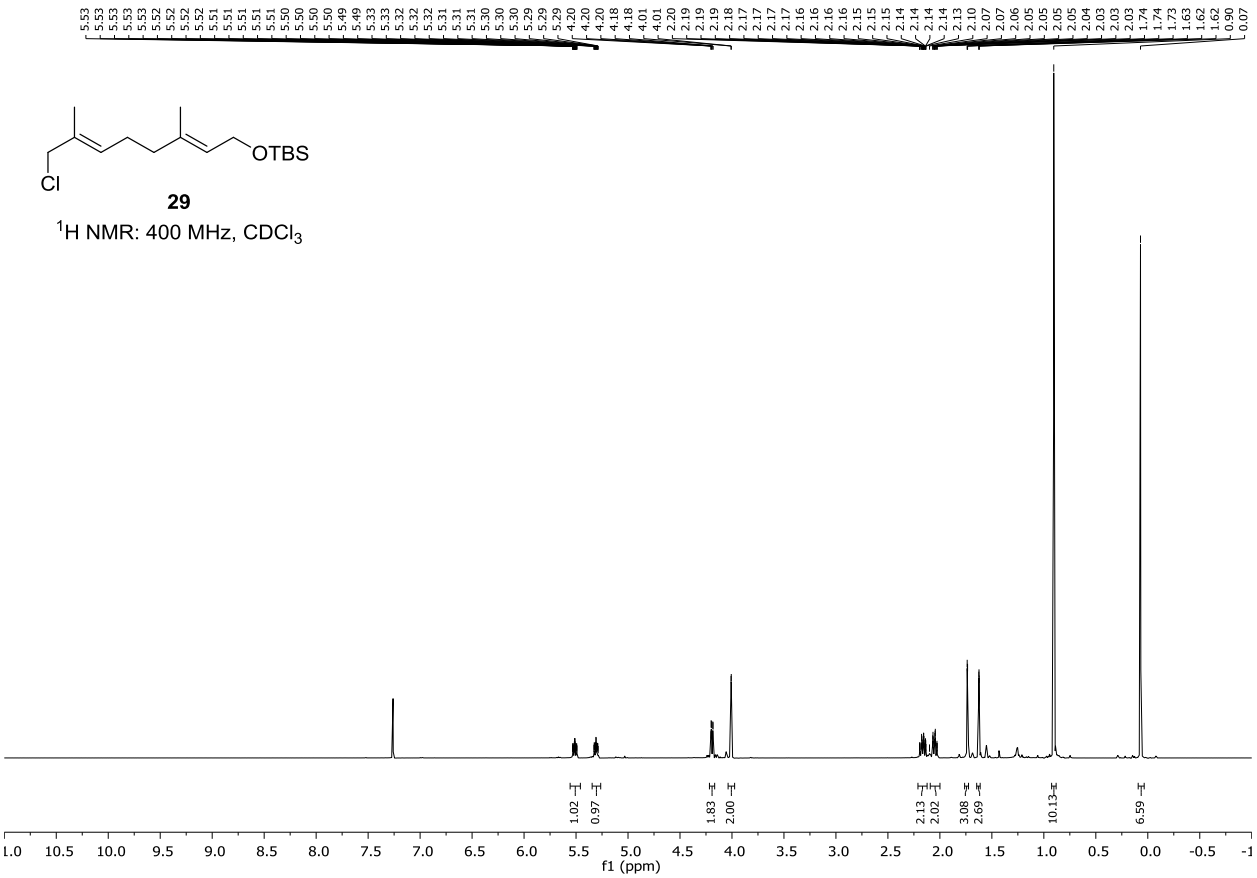

**28**

$^{1}$H NMR: 300 MHz, $CDCl_3$



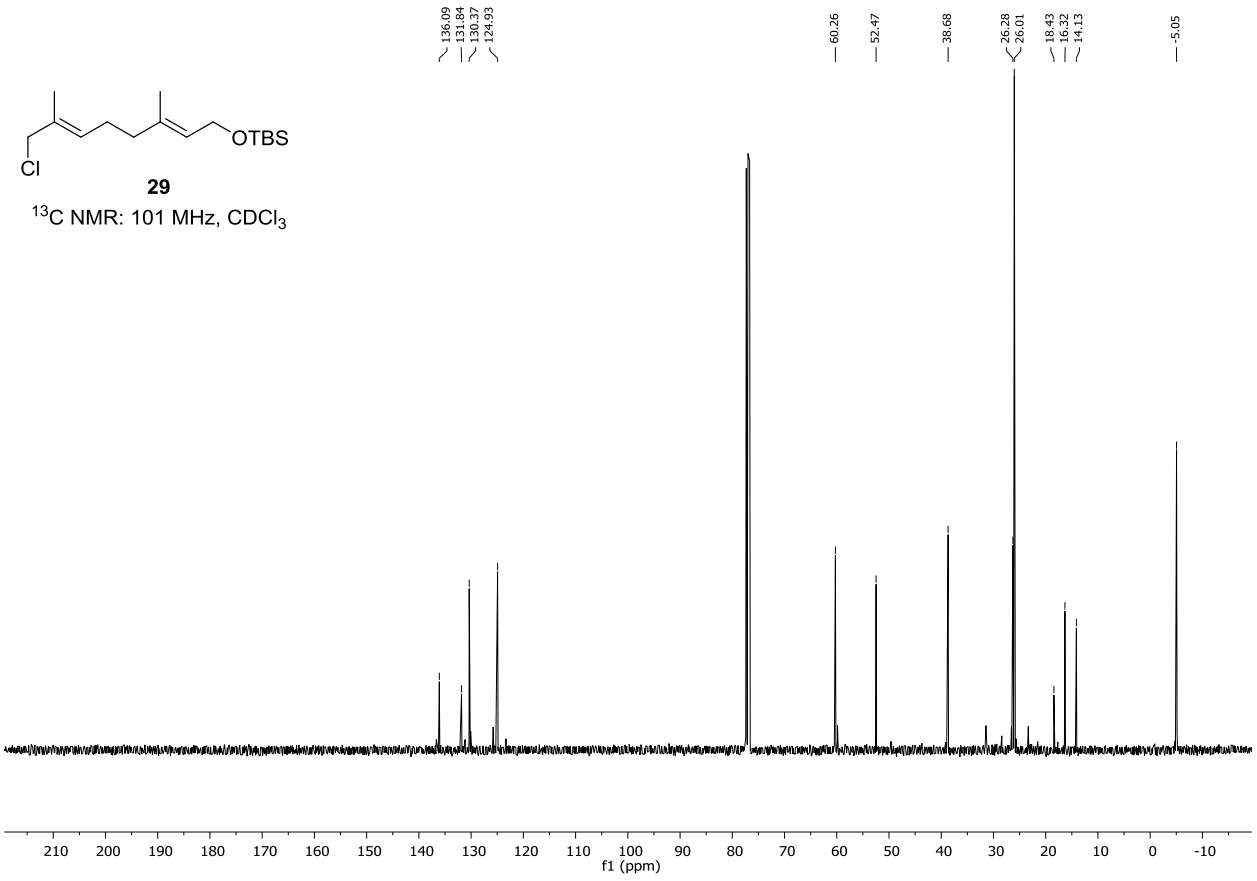

**28**

$^{13}$C NMR: 101 MHz, $CDCl_3$



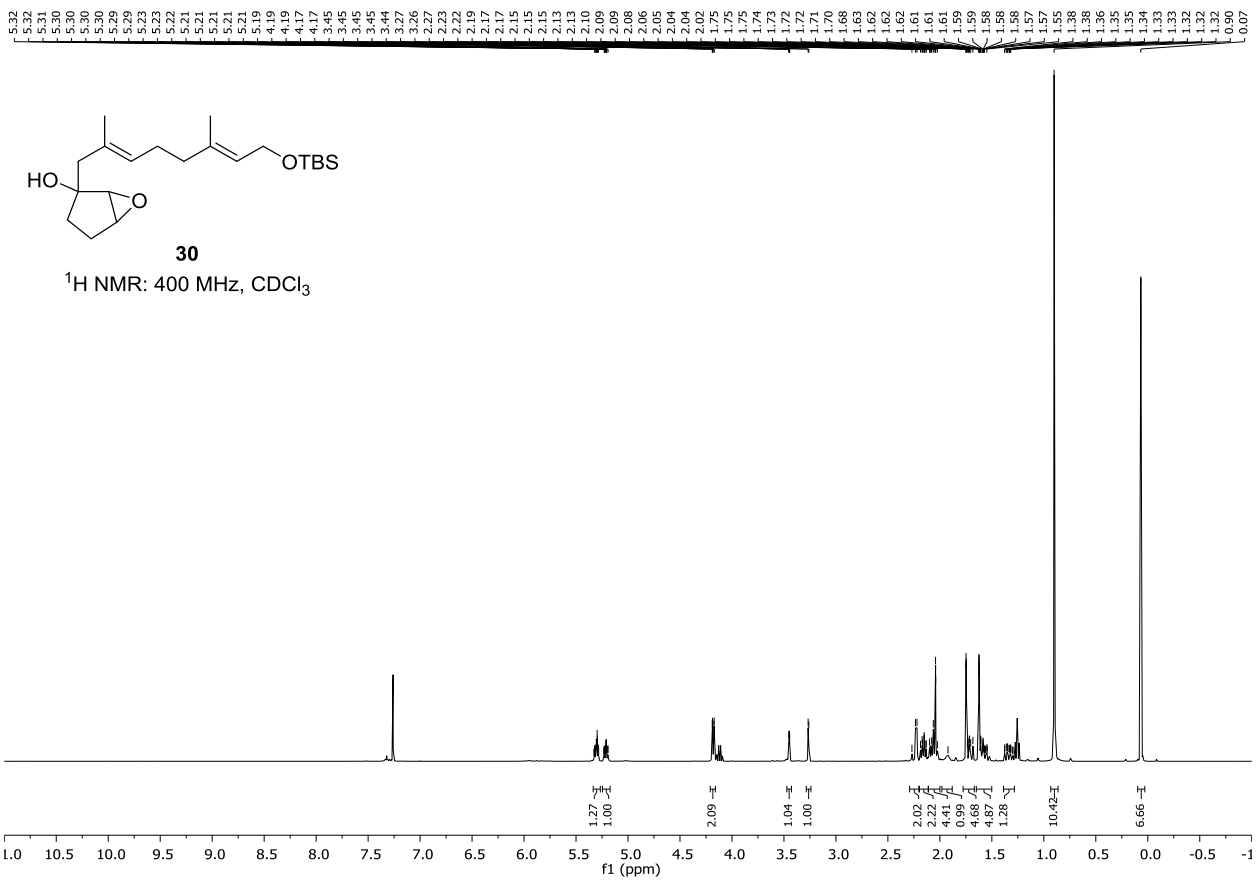

**29**

$^{1}$H NMR: 400 MHz, $CDCl_3$



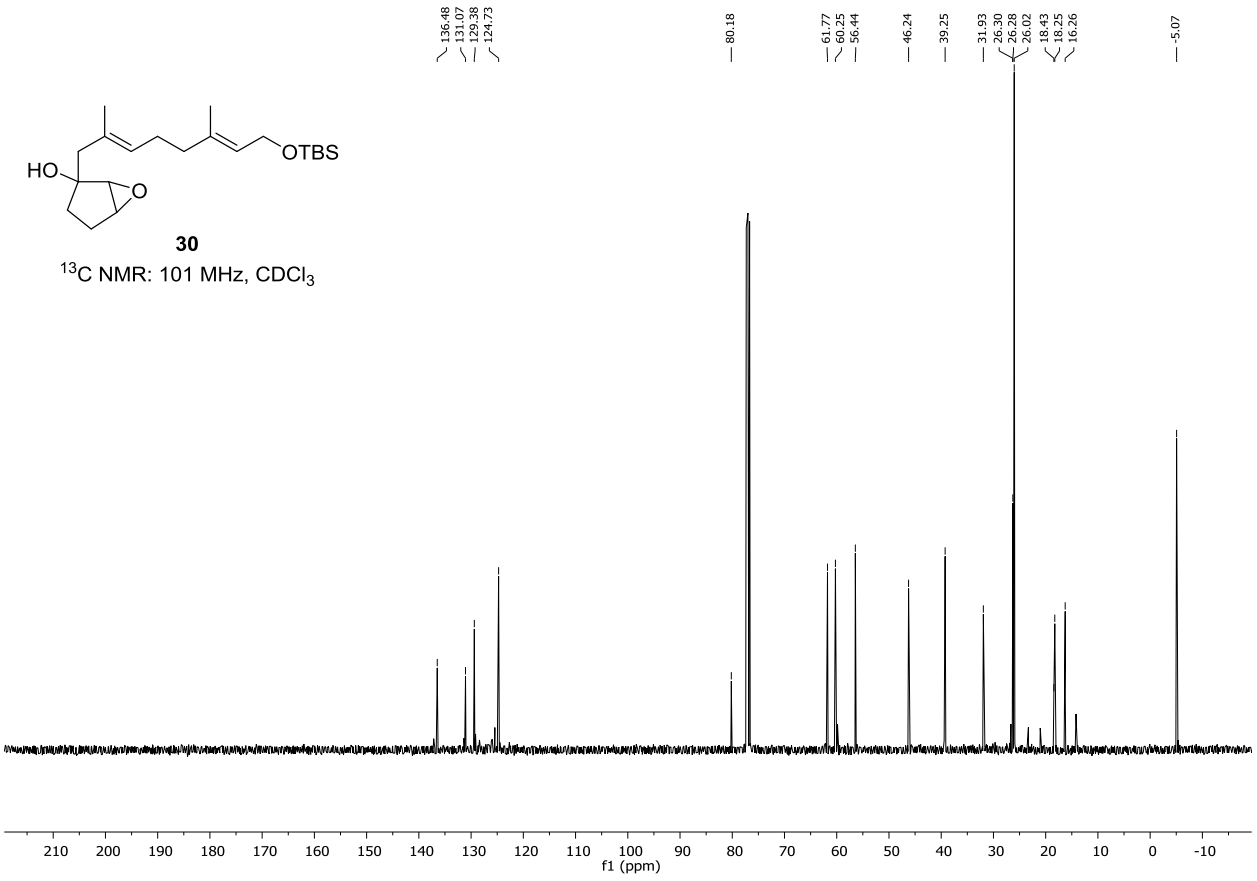

**29**

$^{13}$C NMR: 101 MHz, $CDCl_3$



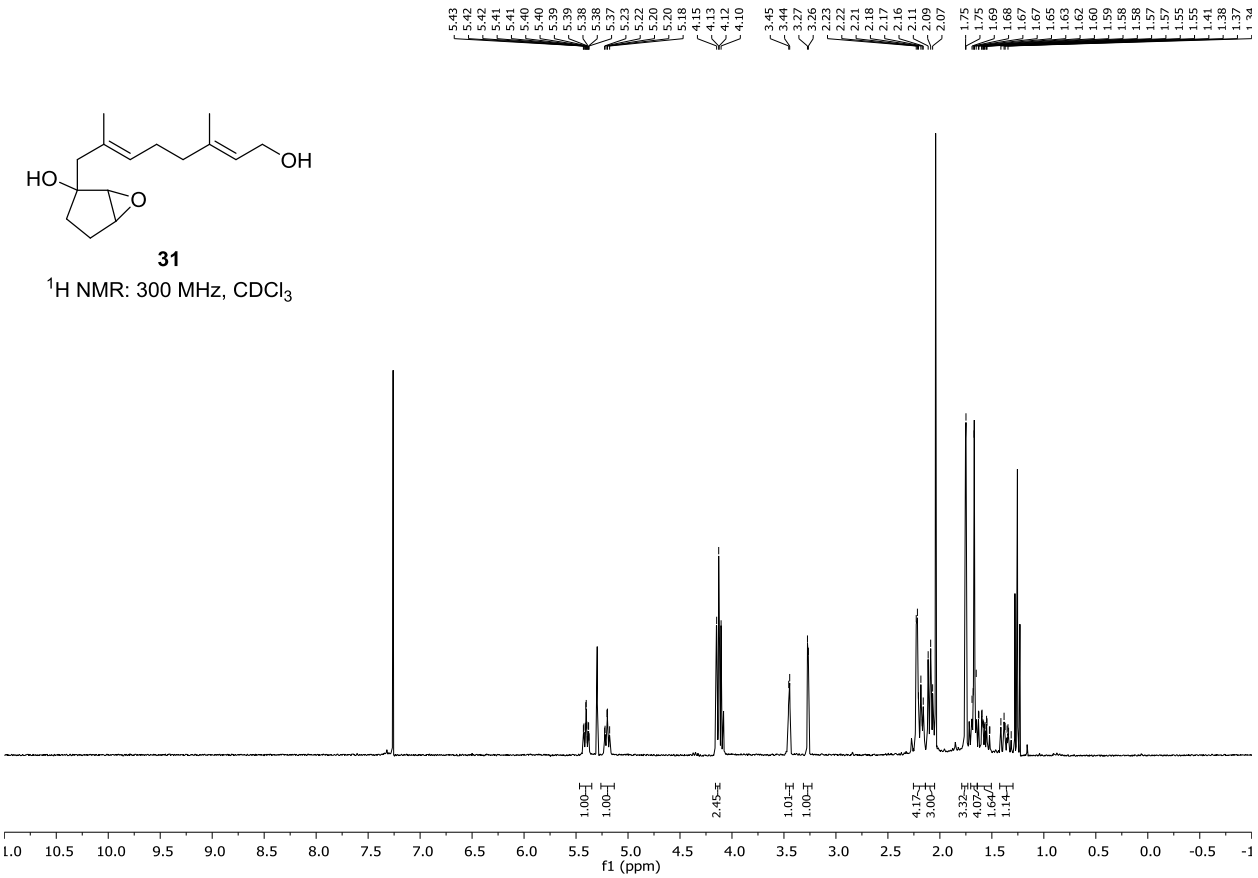

**30**

$^{1}$H NMR: 400 MHz, $CDCl_3$



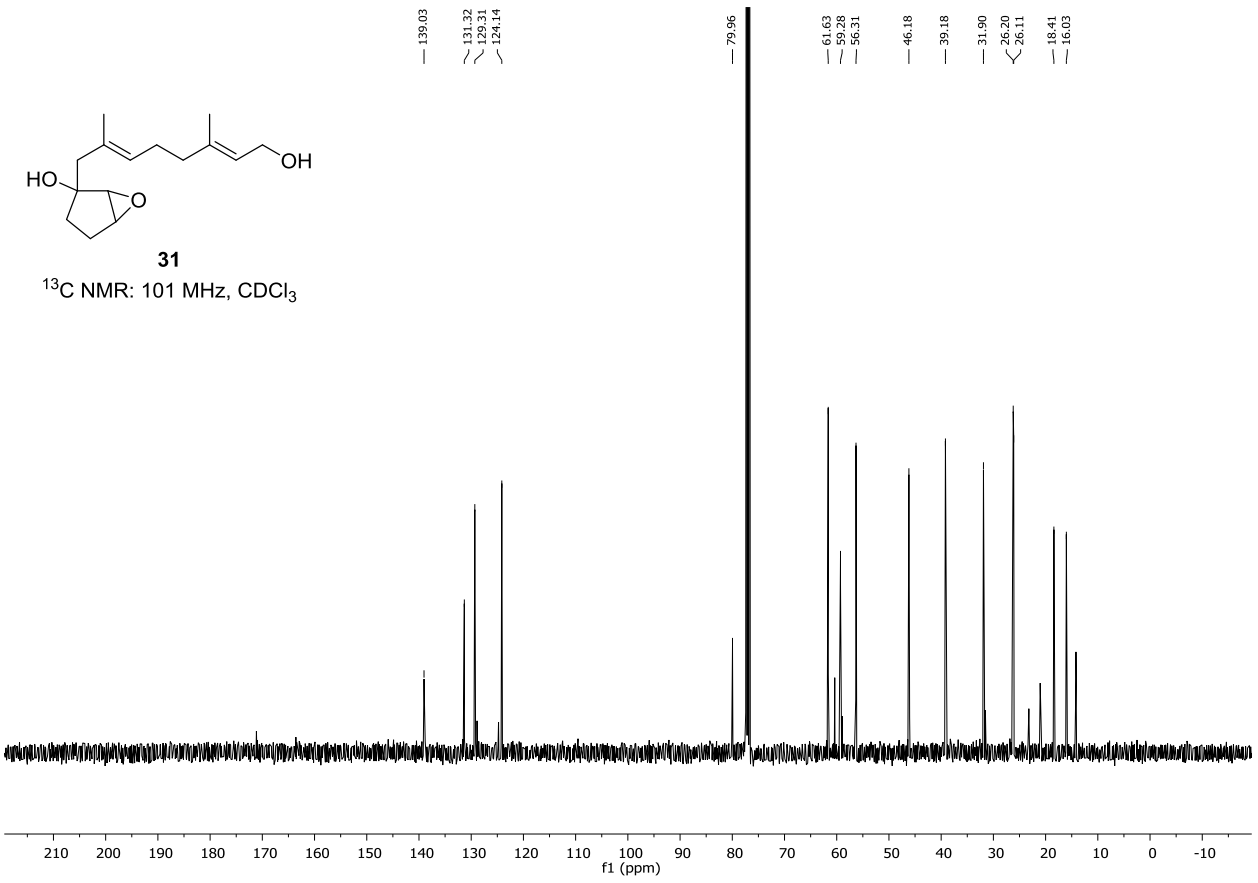

**30**

$^{13}$C NMR: 101 MHz, $CDCl_3$



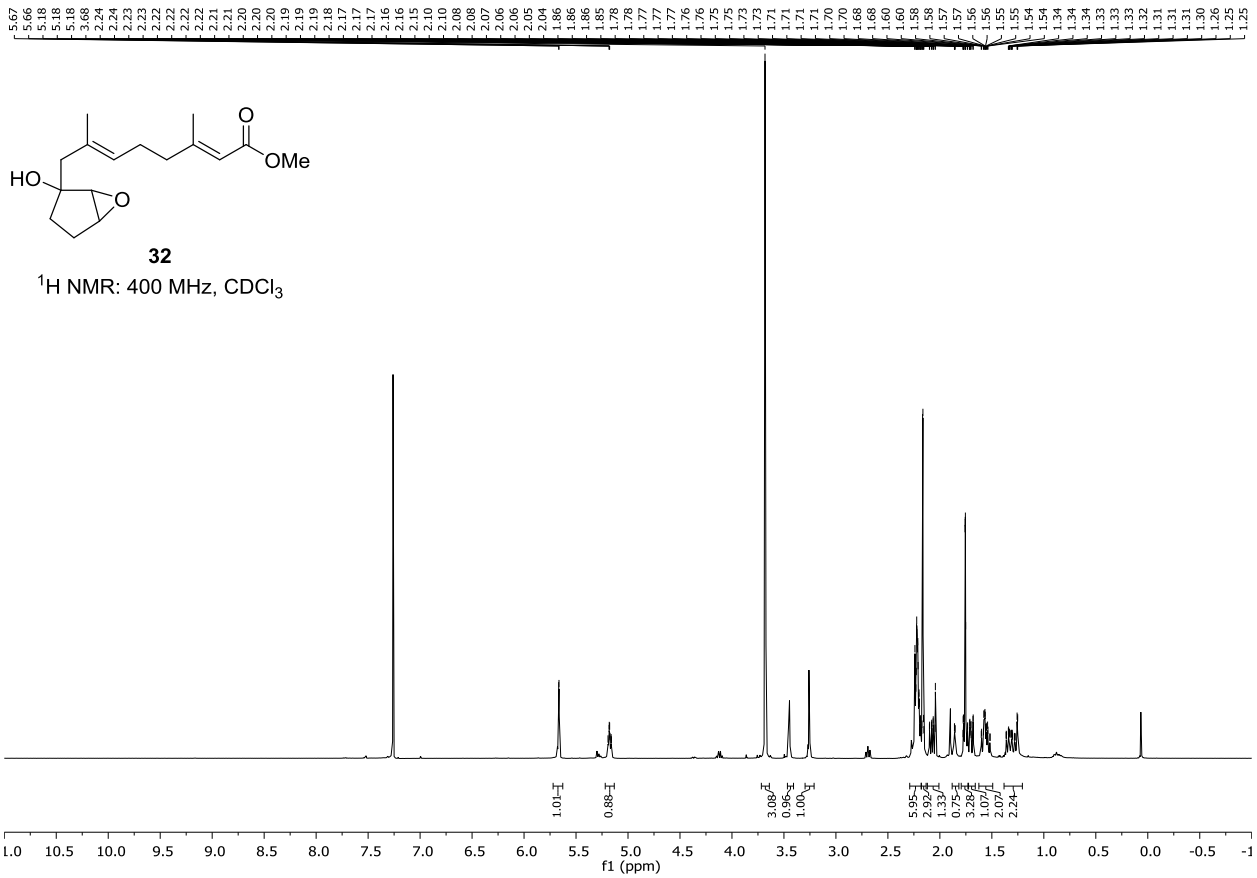

**31**

$^{1}$H NMR: 300 MHz, $CDCl_3$



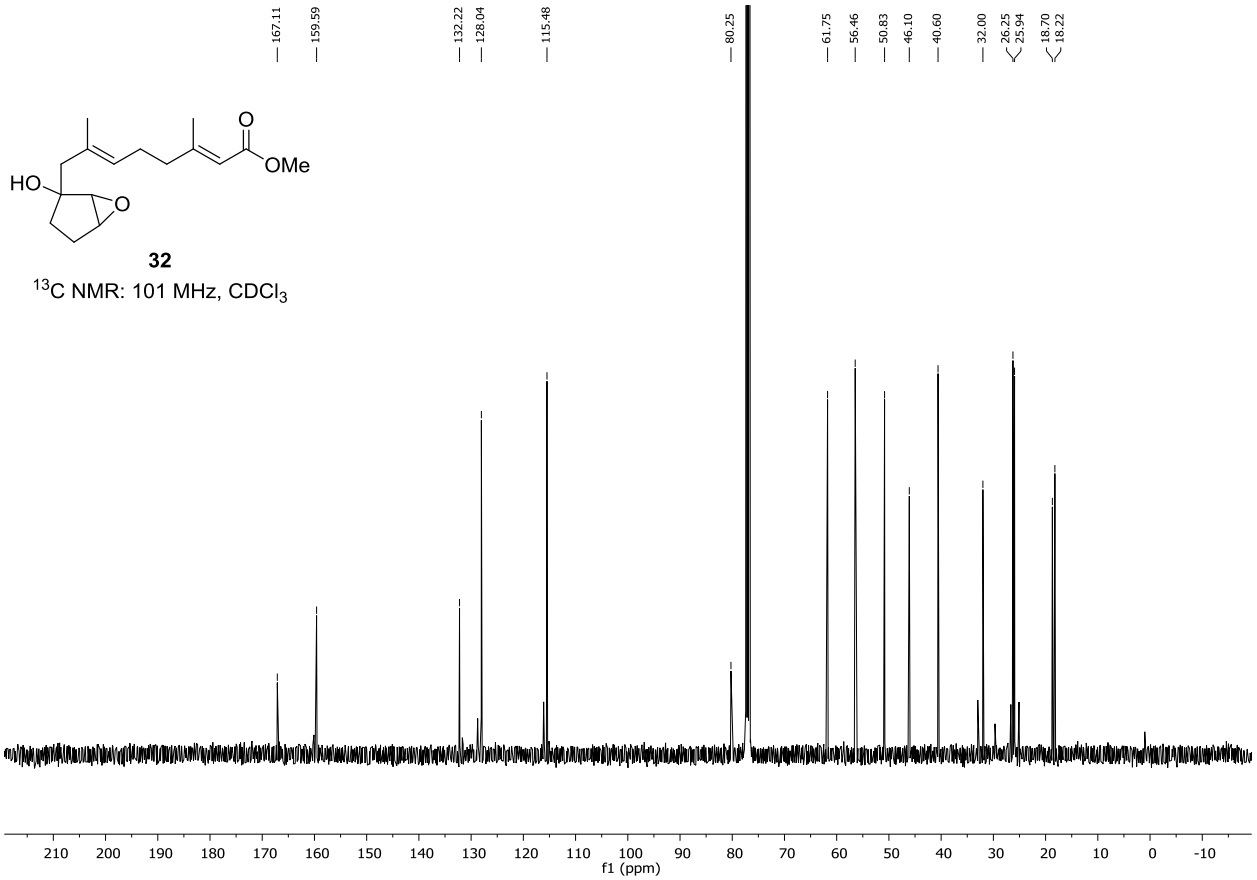

**31**

$^{13}$C NMR: 101 MHz, $CDCl_3$



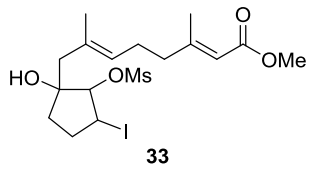

**32**

$^{1}$H NMR: 400 MHz, $CDCl_3$




**32**

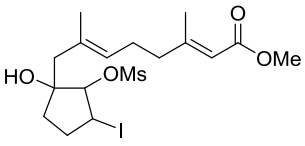
$^{13}$C NMR: 101 MHz, $CDCl_3$




**33**

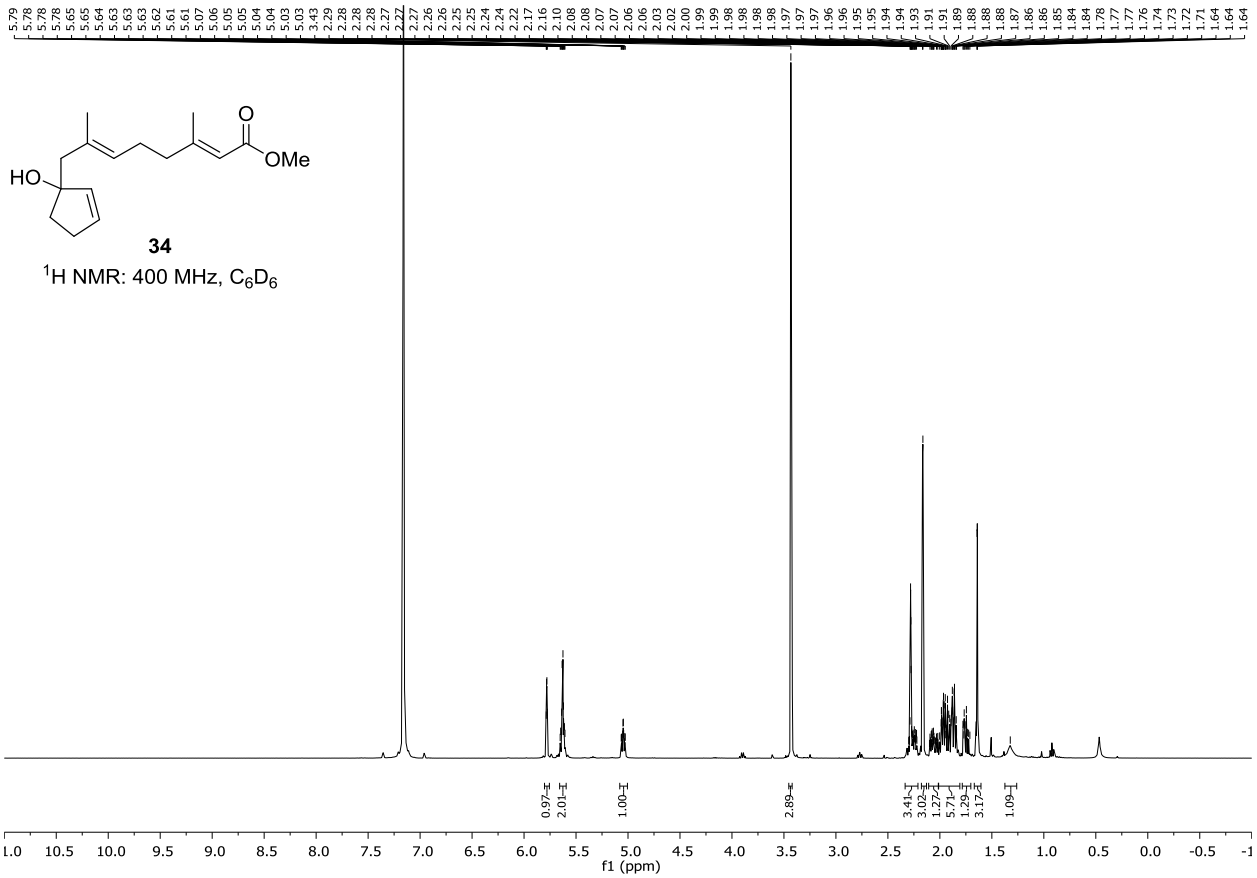
$^{1}$H NMR: 400 MHz, $CDCl_3$



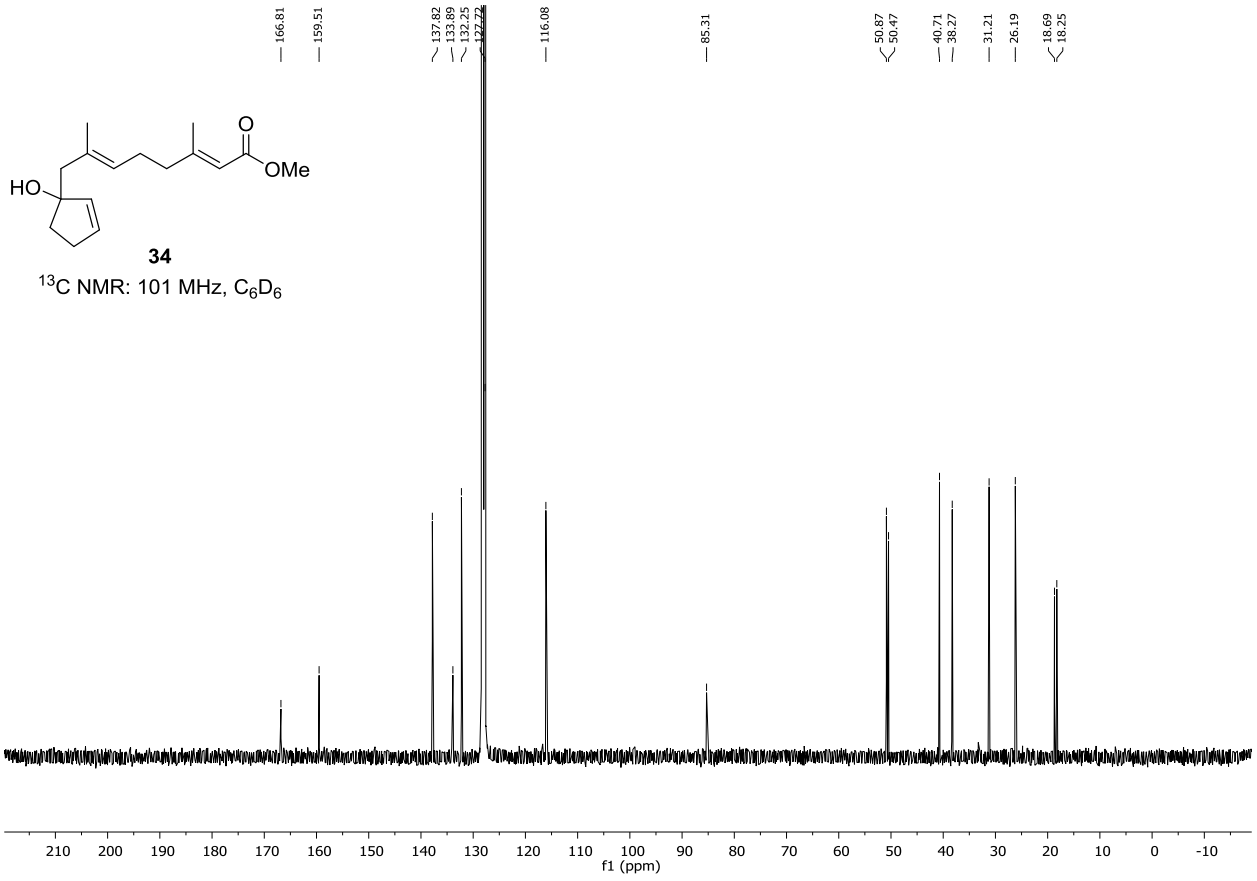

**33**

$^{13}$C NMR: 101 MHz, $CDCl_3$



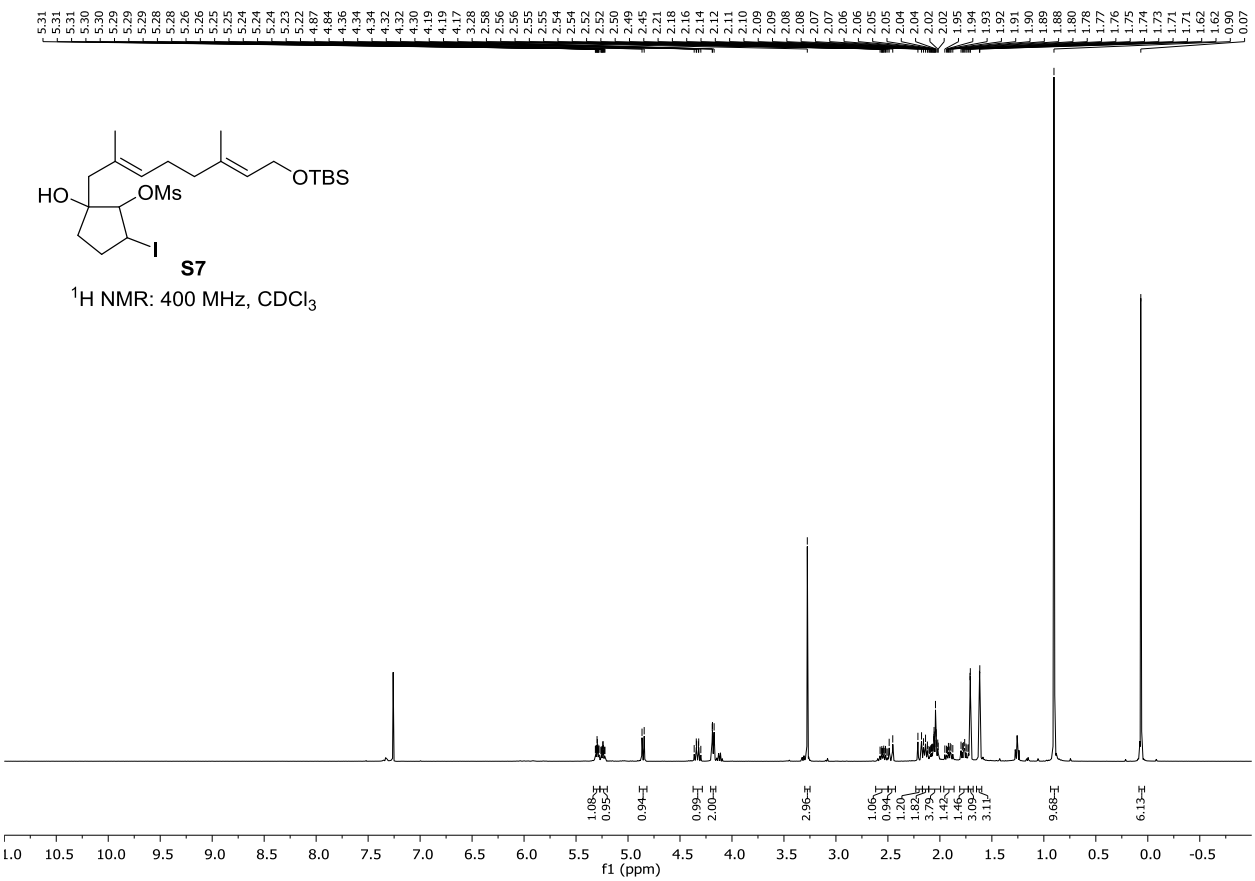

**34**

$^{1}$H NMR: 400 MHz, $C_6D_6$



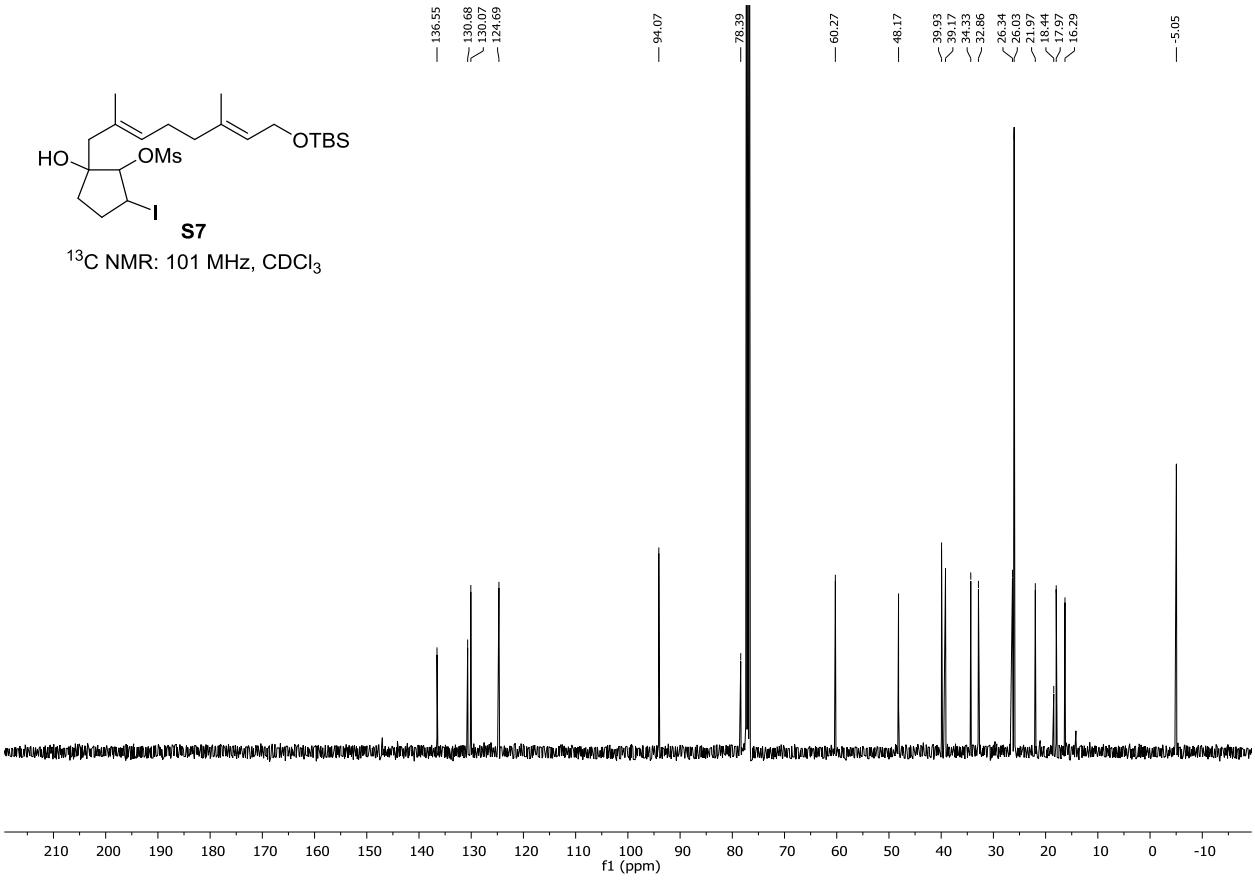

**34**

$^{13}$C NMR: 101 MHz, $C_6D_6$



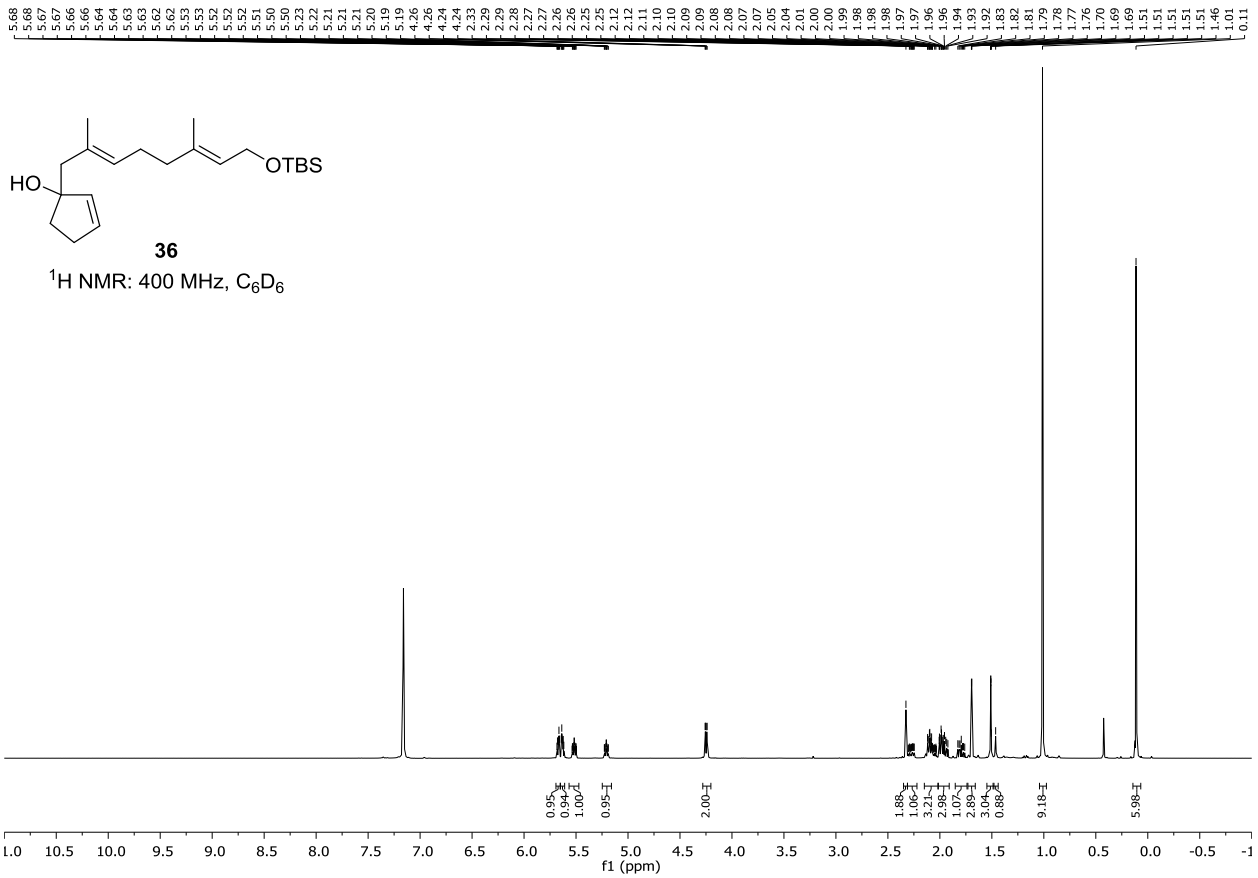

**S7**

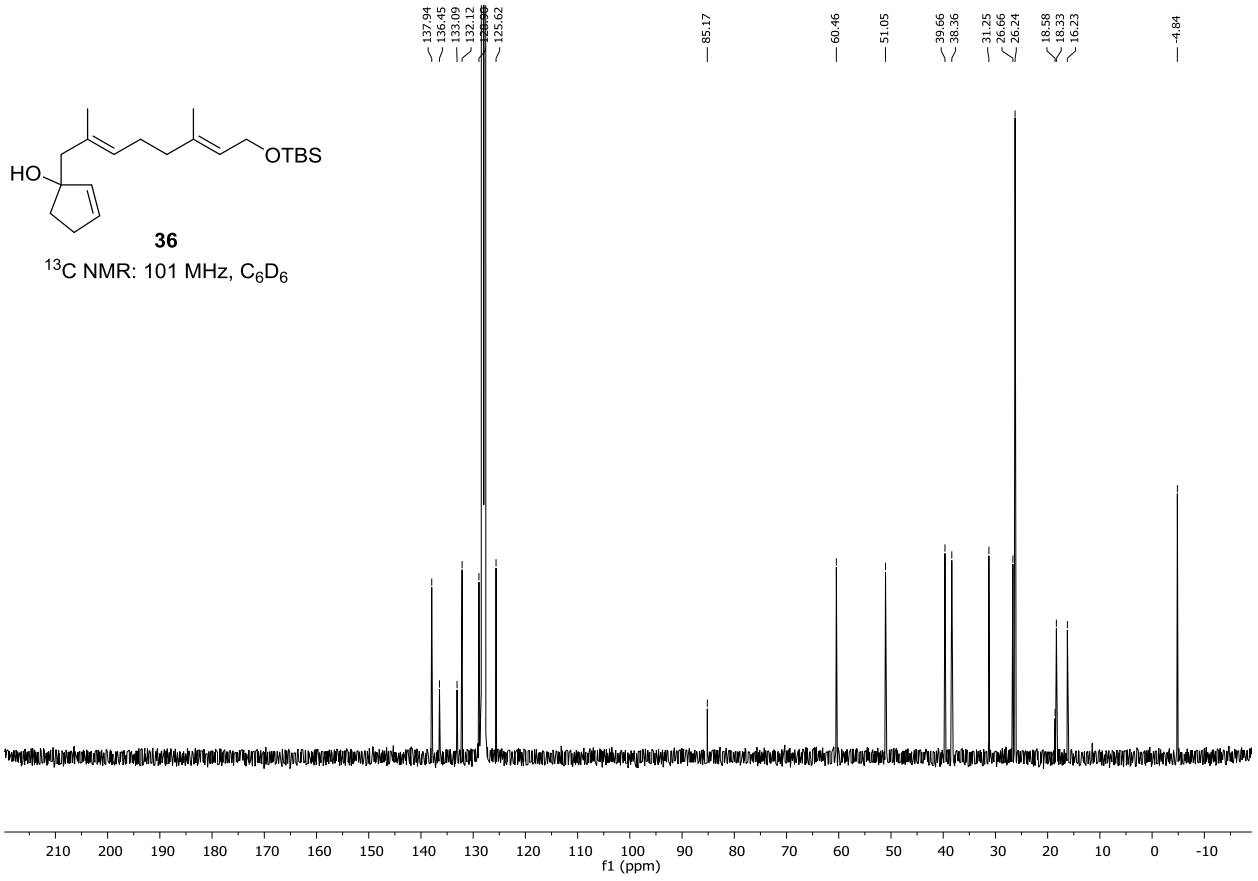
$^{1}$H NMR: 400 MHz, $CDCl_3$

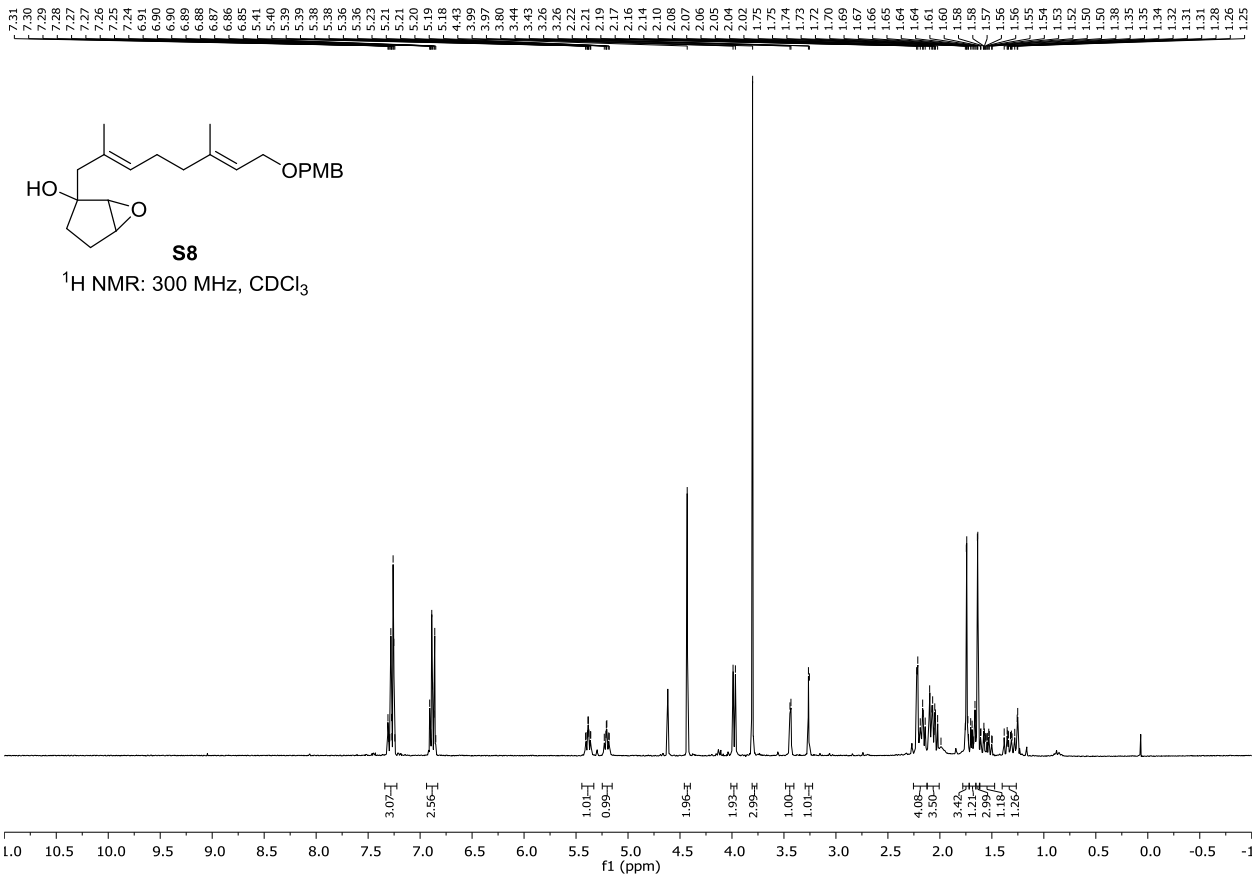



**S7**

$^{13}$C NMR: 101 MHz, $CDCl_3$

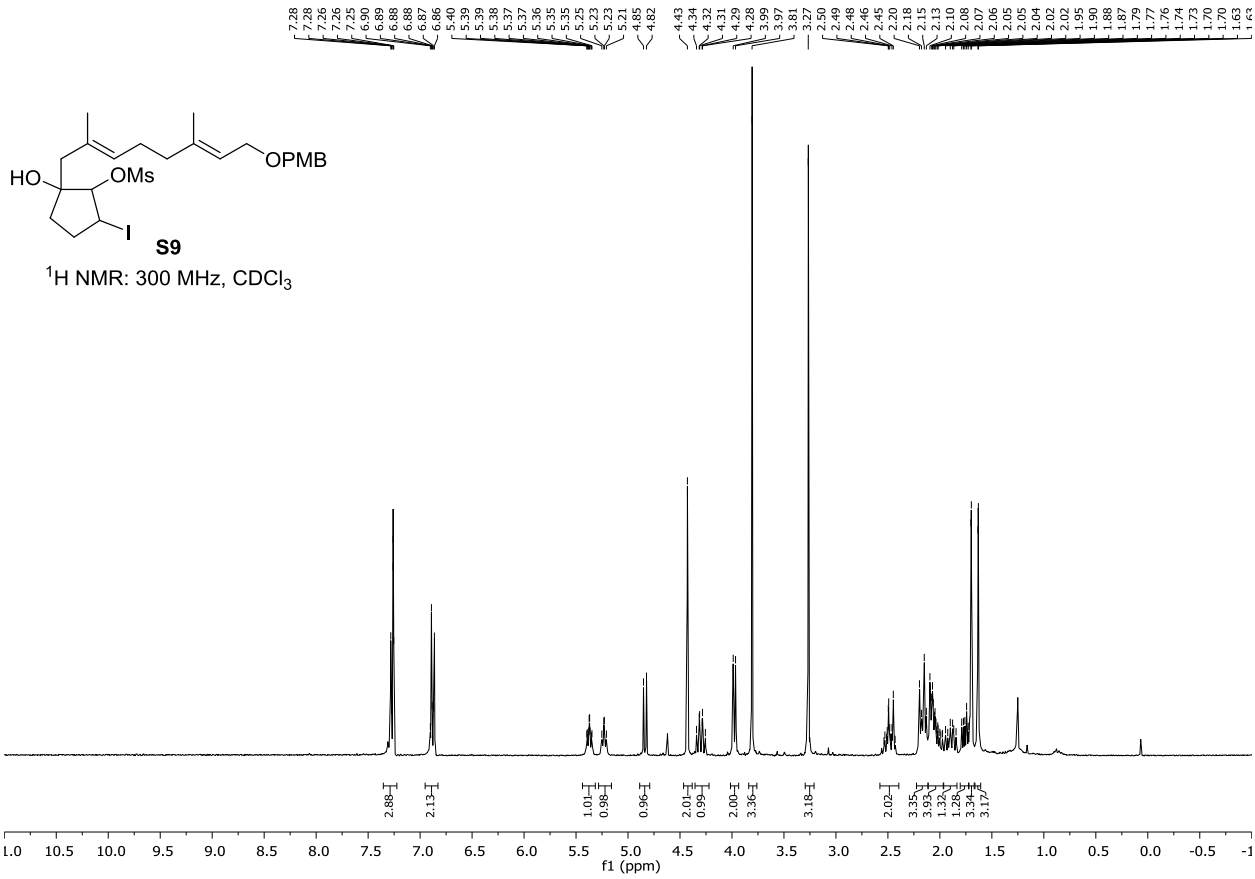

HO
OTBS
36
$^{1}$H NMR: 400 MHz, $C_6D_6$
f1 (ppm)


HO
OTBS
36
$^{13}$C NMR: 101 MHz, $C_6D_6$
f1 (ppm)



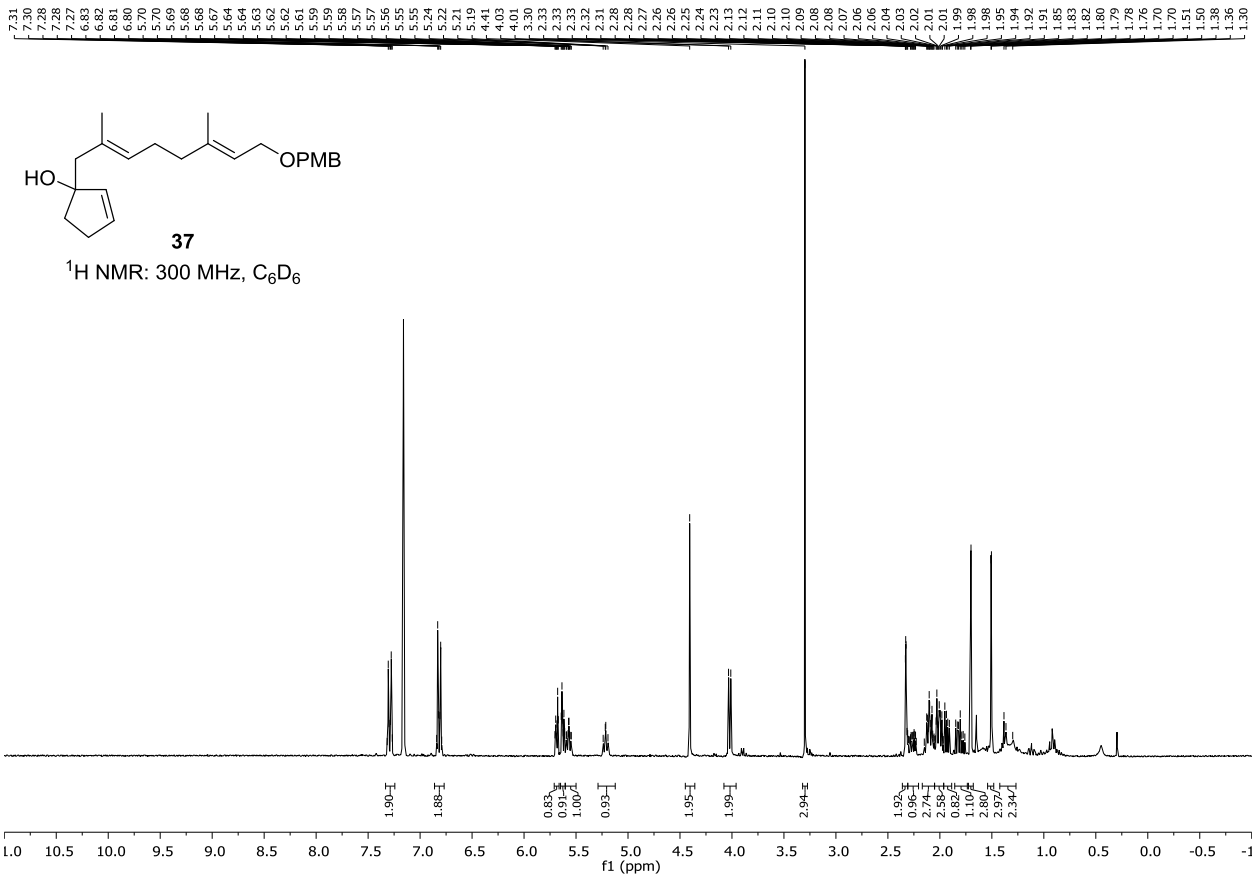

**S8**

$^1$H NMR: 300 MHz, $CDCl_3$



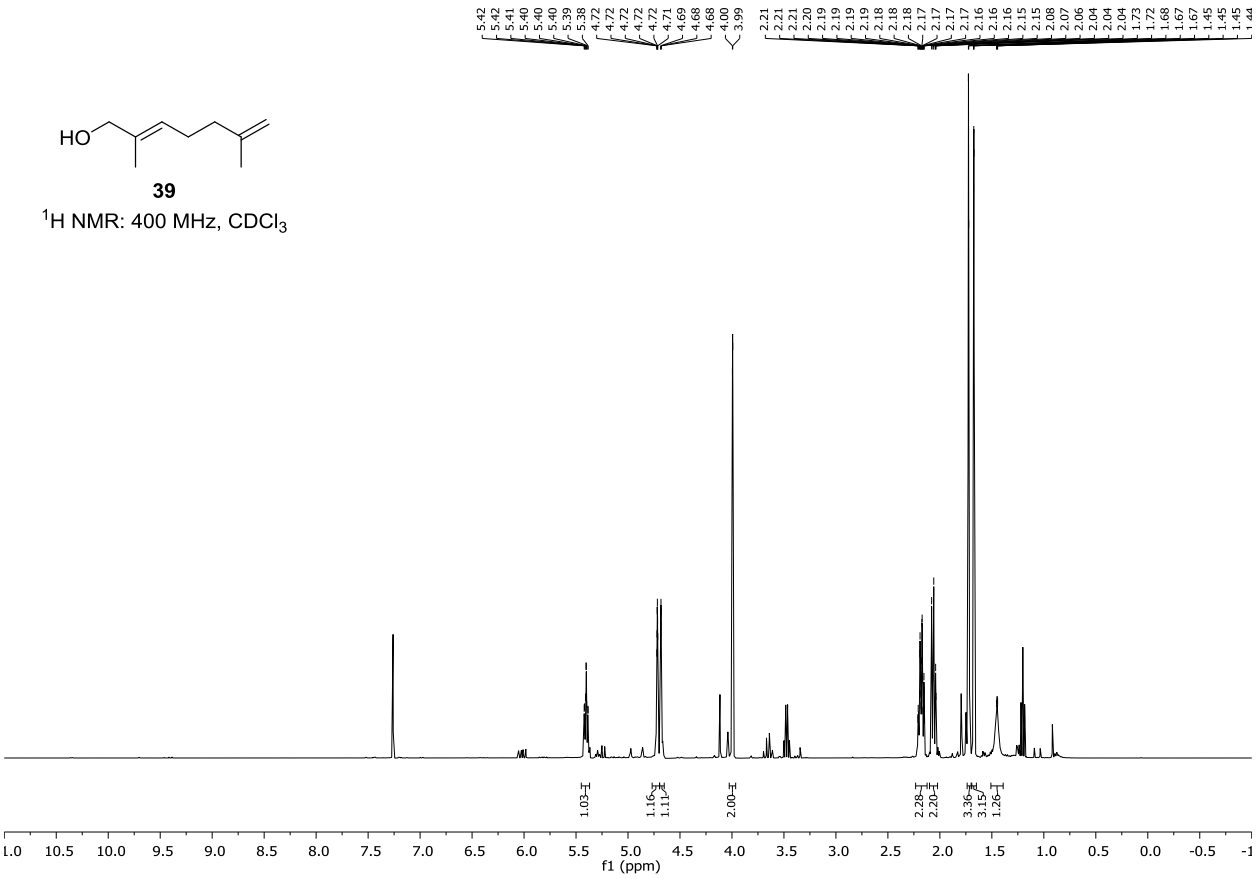

**S9**

$^1$H NMR: 300 MHz, $CDCl_3$



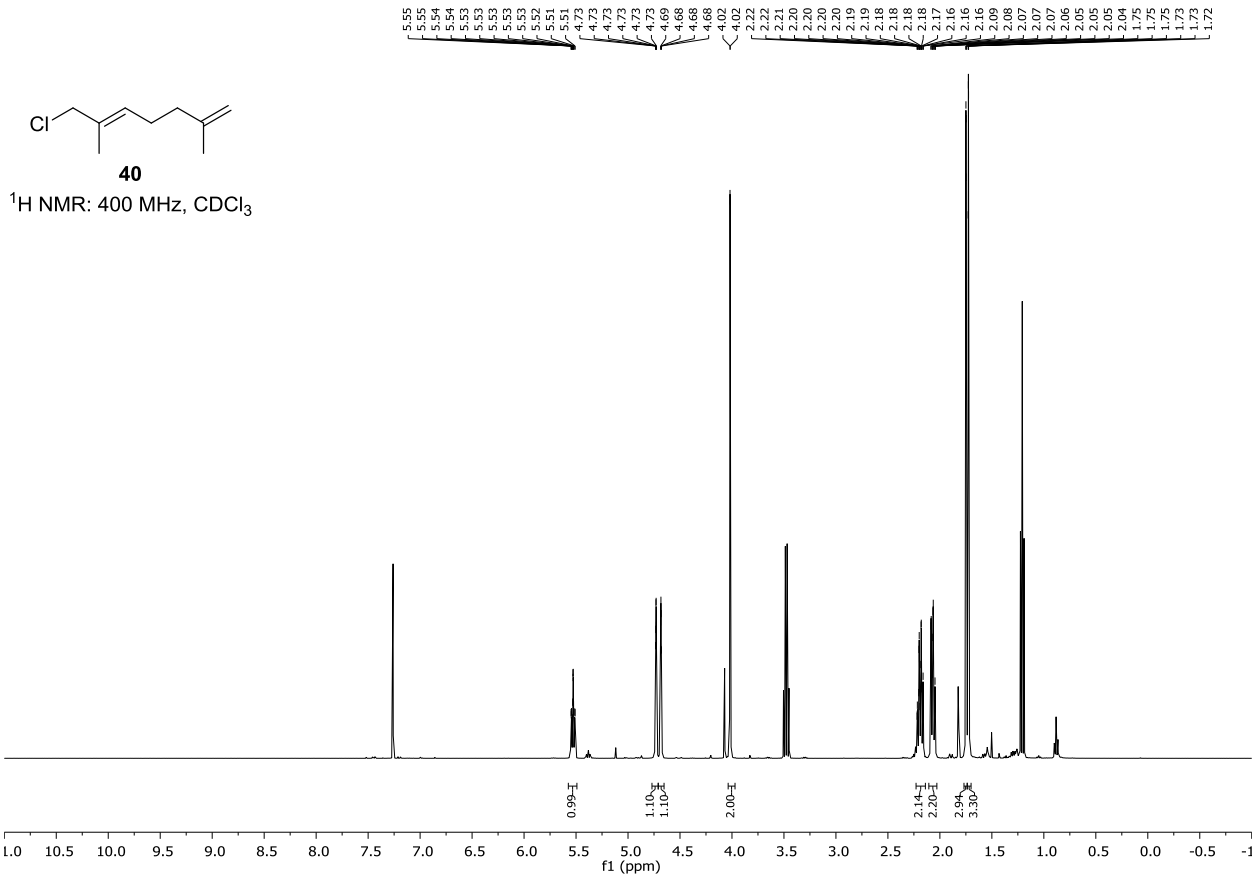

**37**

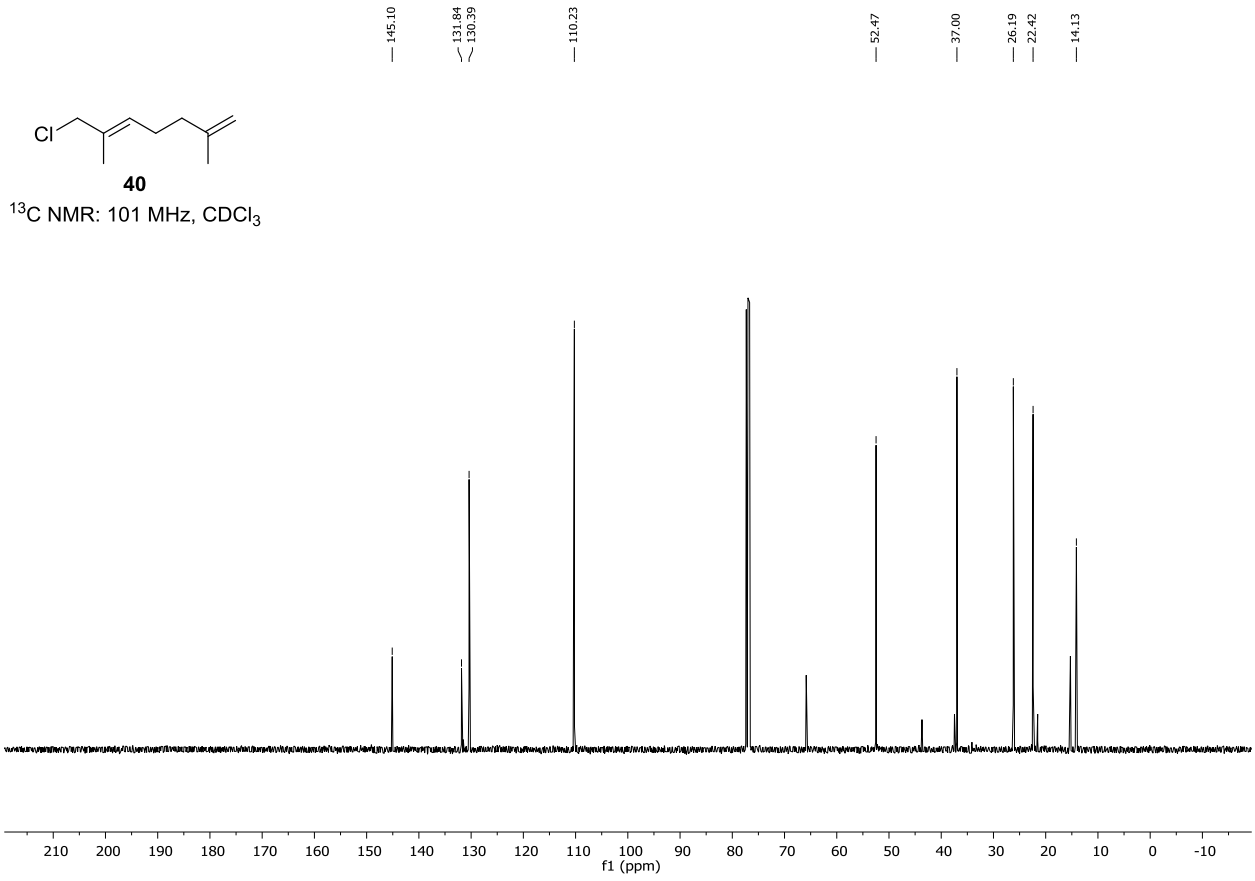
$^1$H NMR: 300 MHz, $C_6D_6$

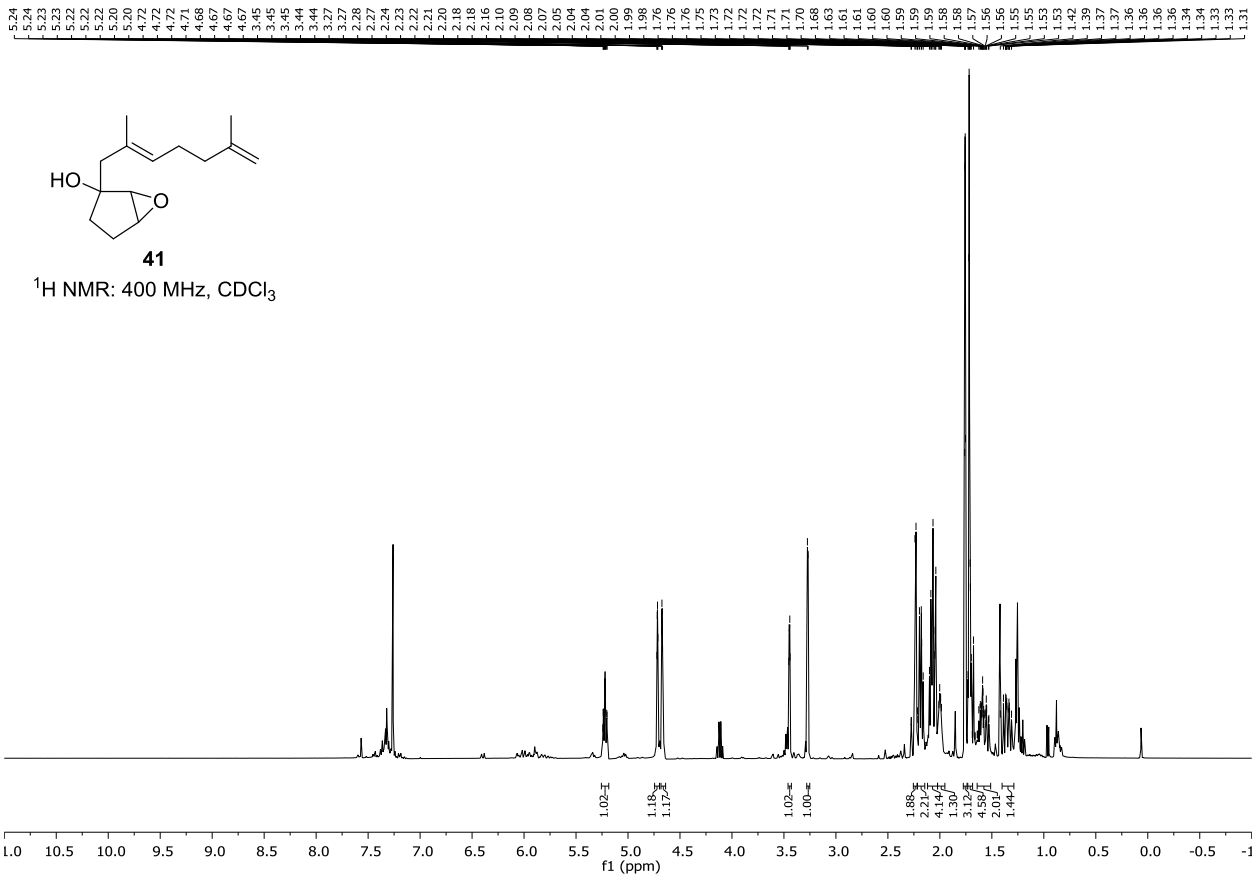



**39**

$^1$H NMR: 400 MHz, $CDCl_3$

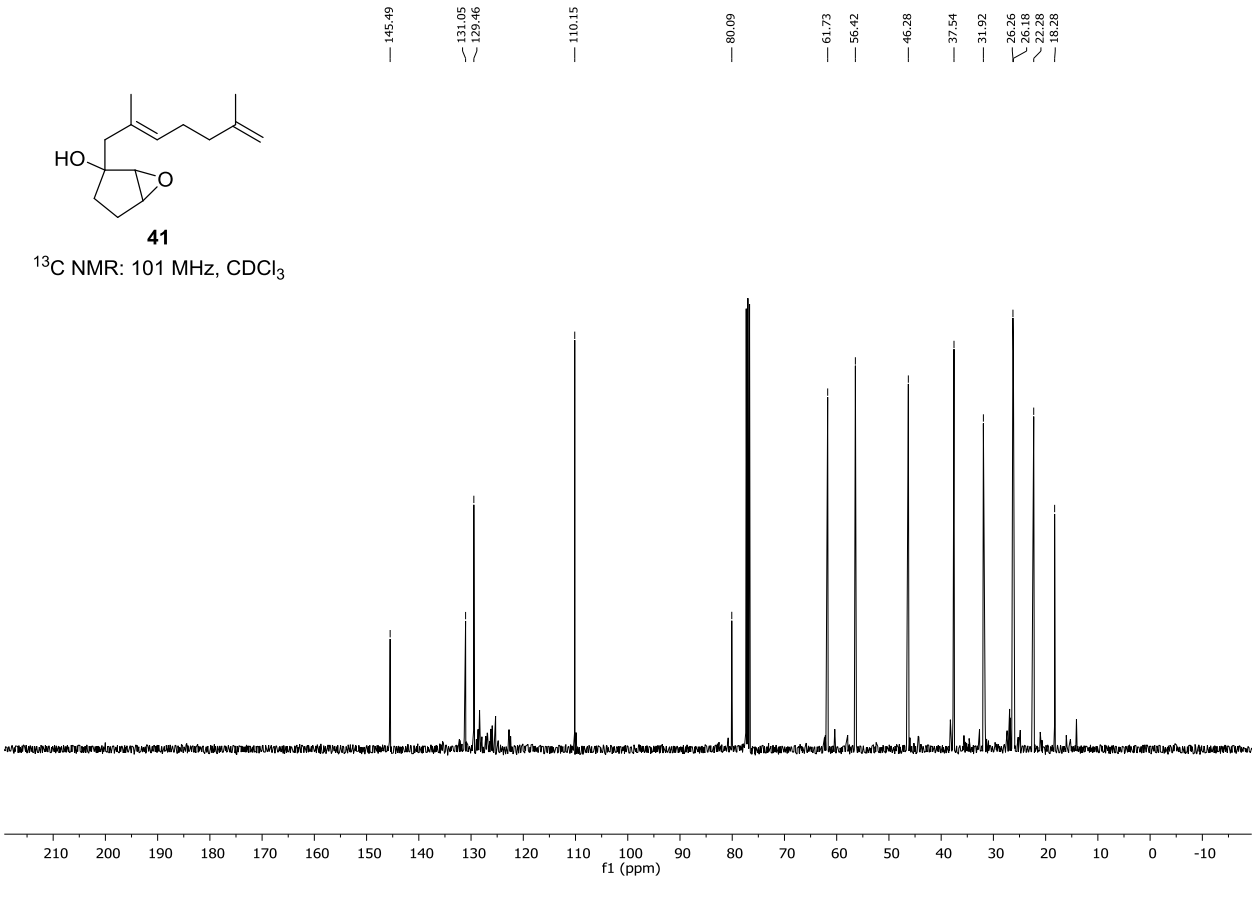

Cl
40
1H NMR: 400 MHz, CDCl3
f1 (ppm)


Cl
40
13C NMR: 101 MHz, CDCl3
f1 (ppm)



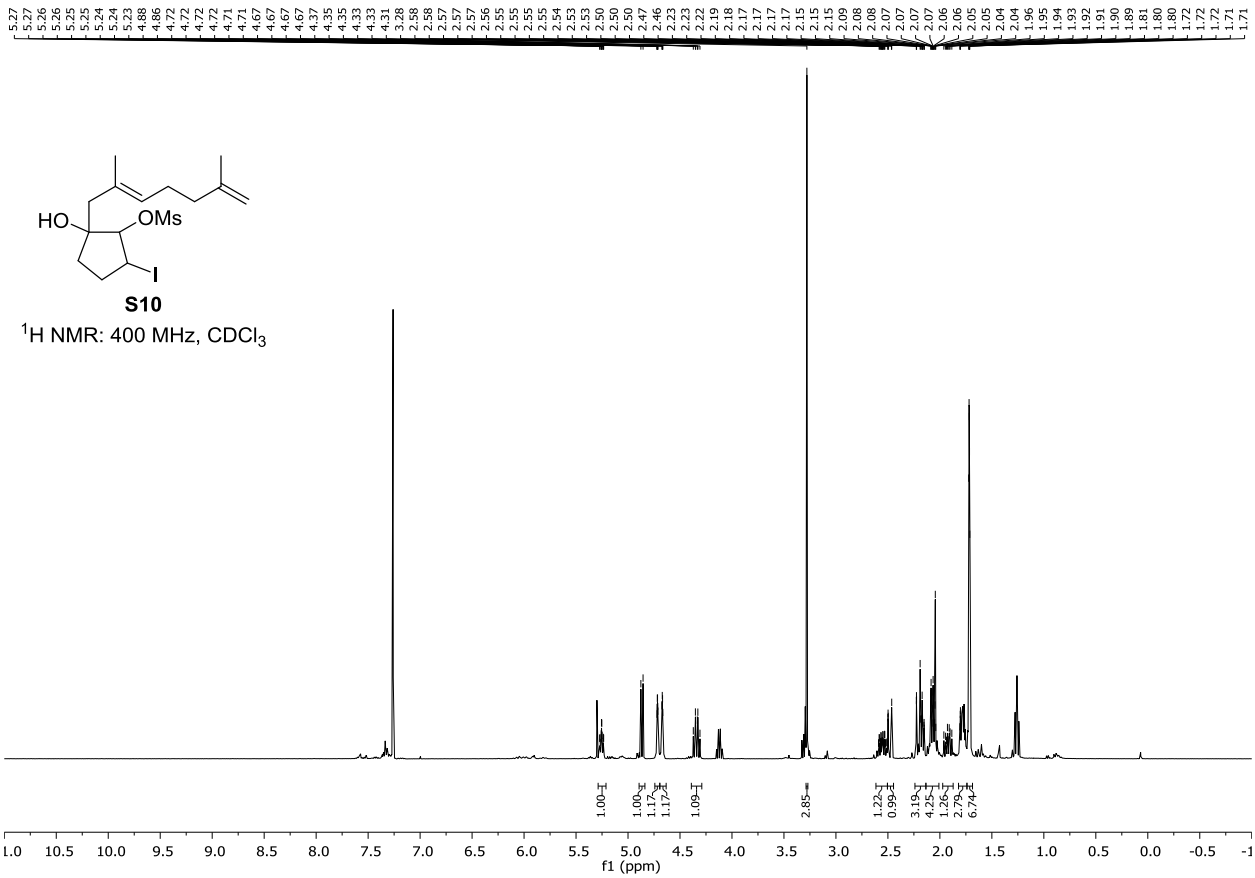

**41**

$^{1}$H NMR: 400 MHz, $CDCl_3$



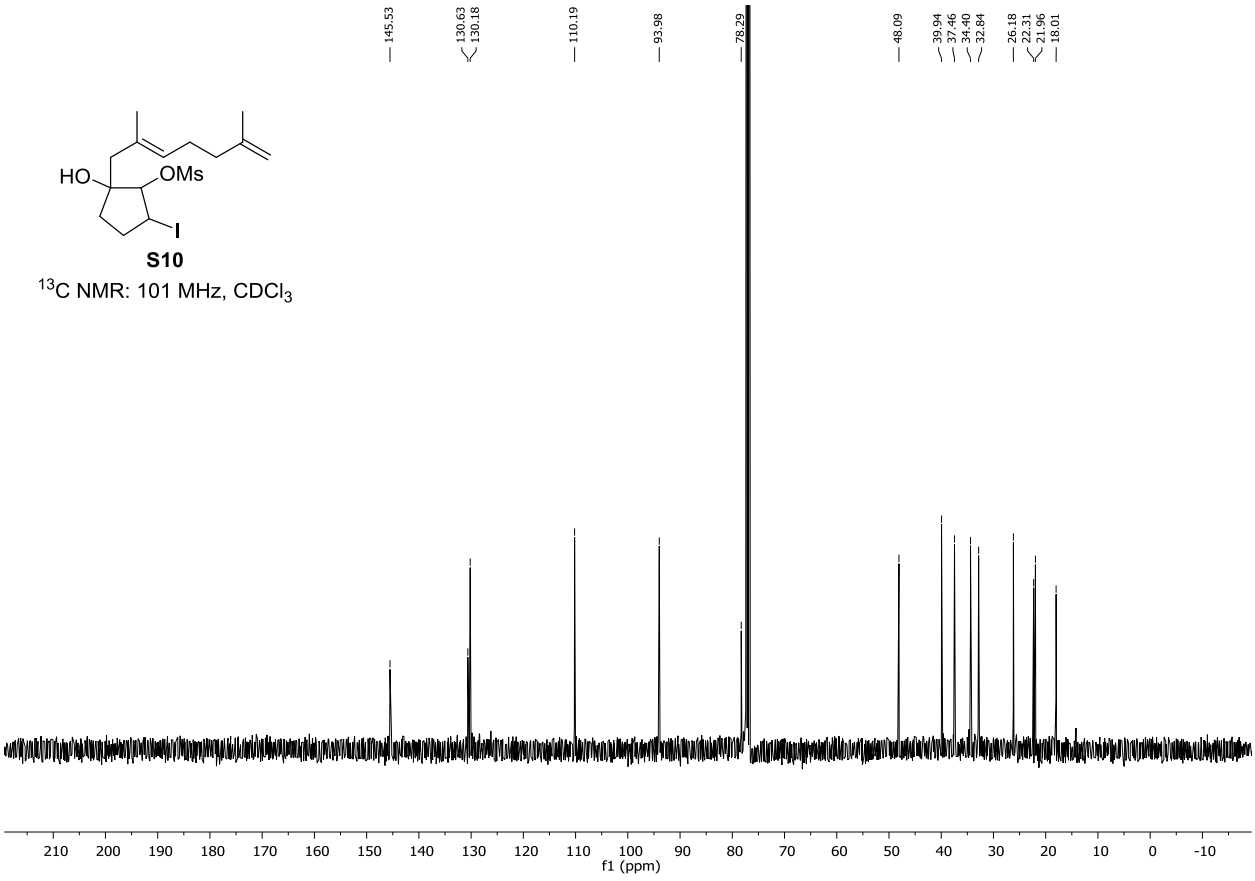

**41**

$^{13}$C NMR: 101 MHz, $CDCl_3$



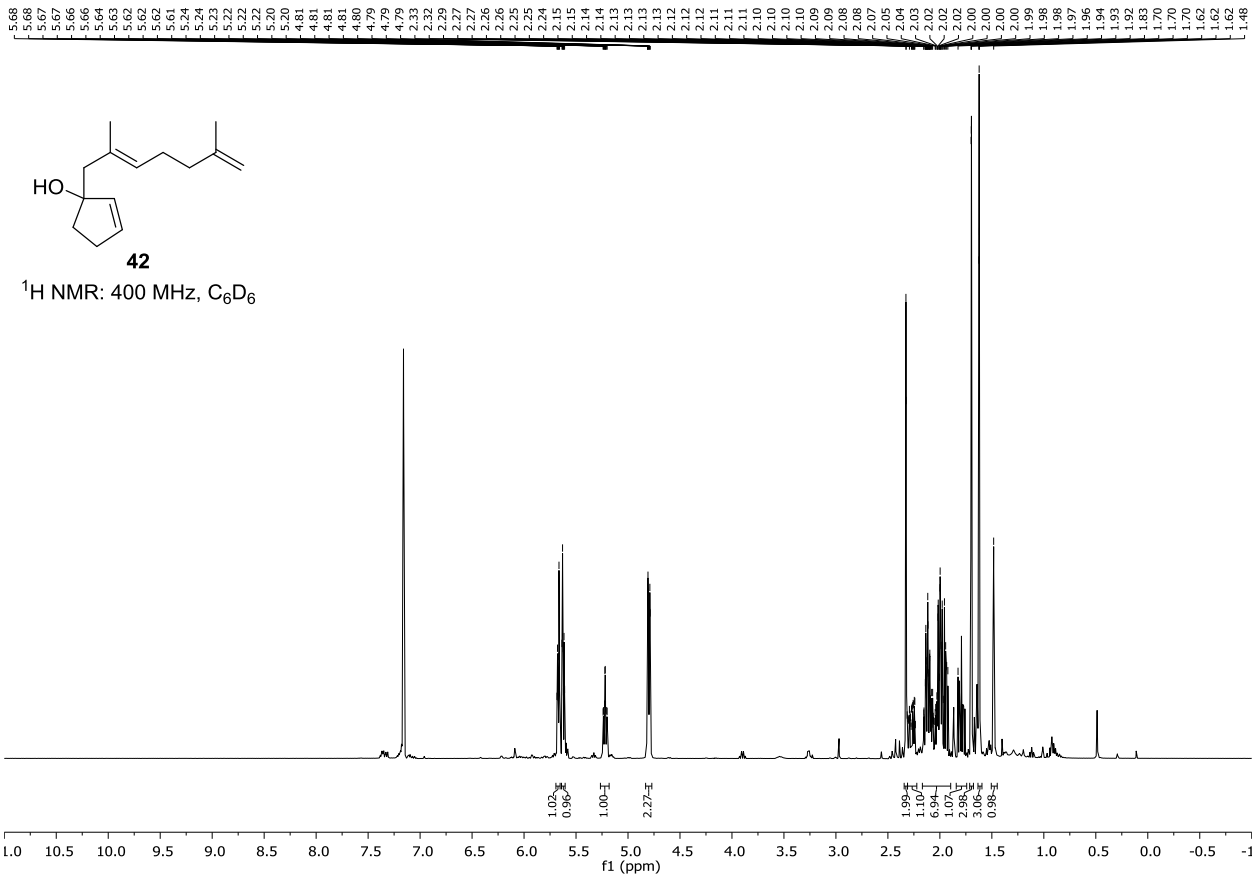

**S10**

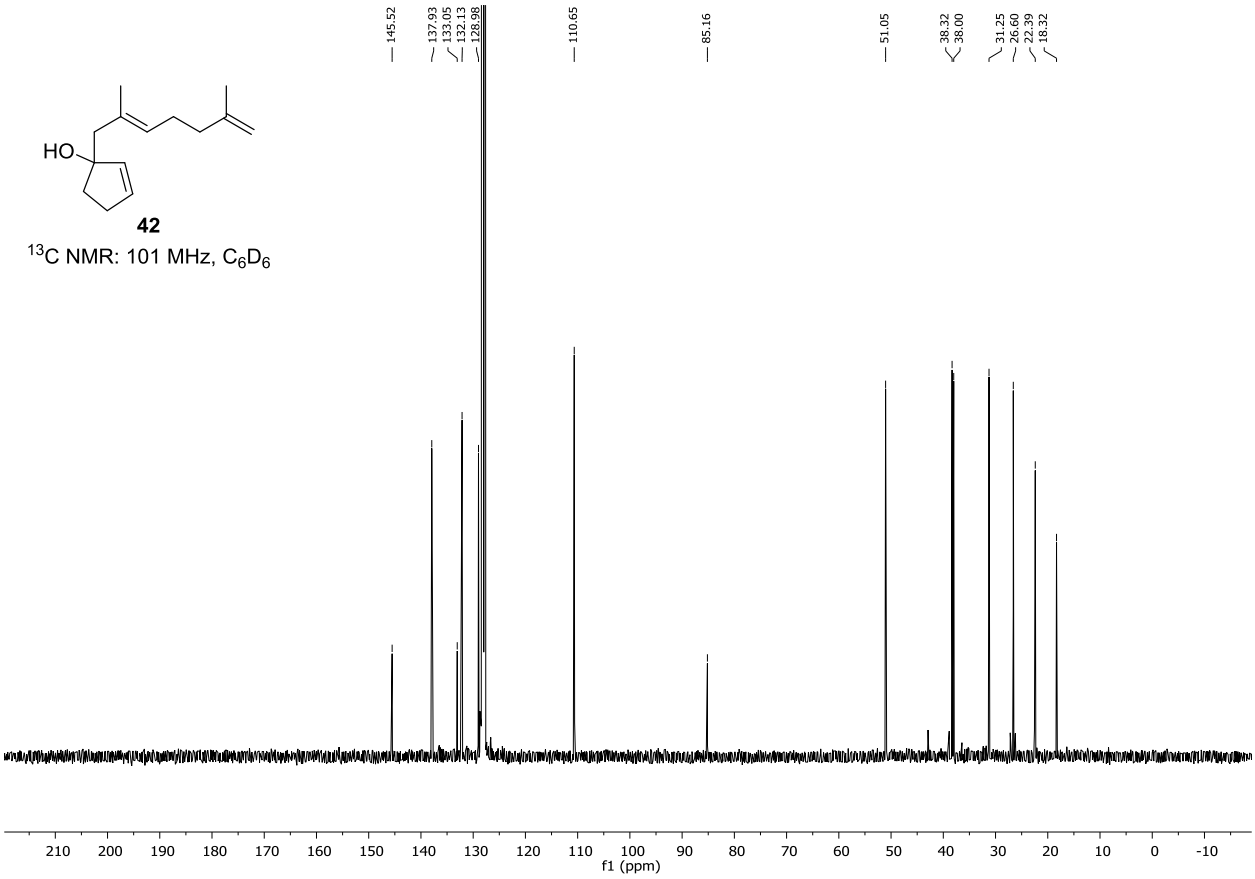
$^{1}$H NMR: 400 MHz, $CDCl_3$

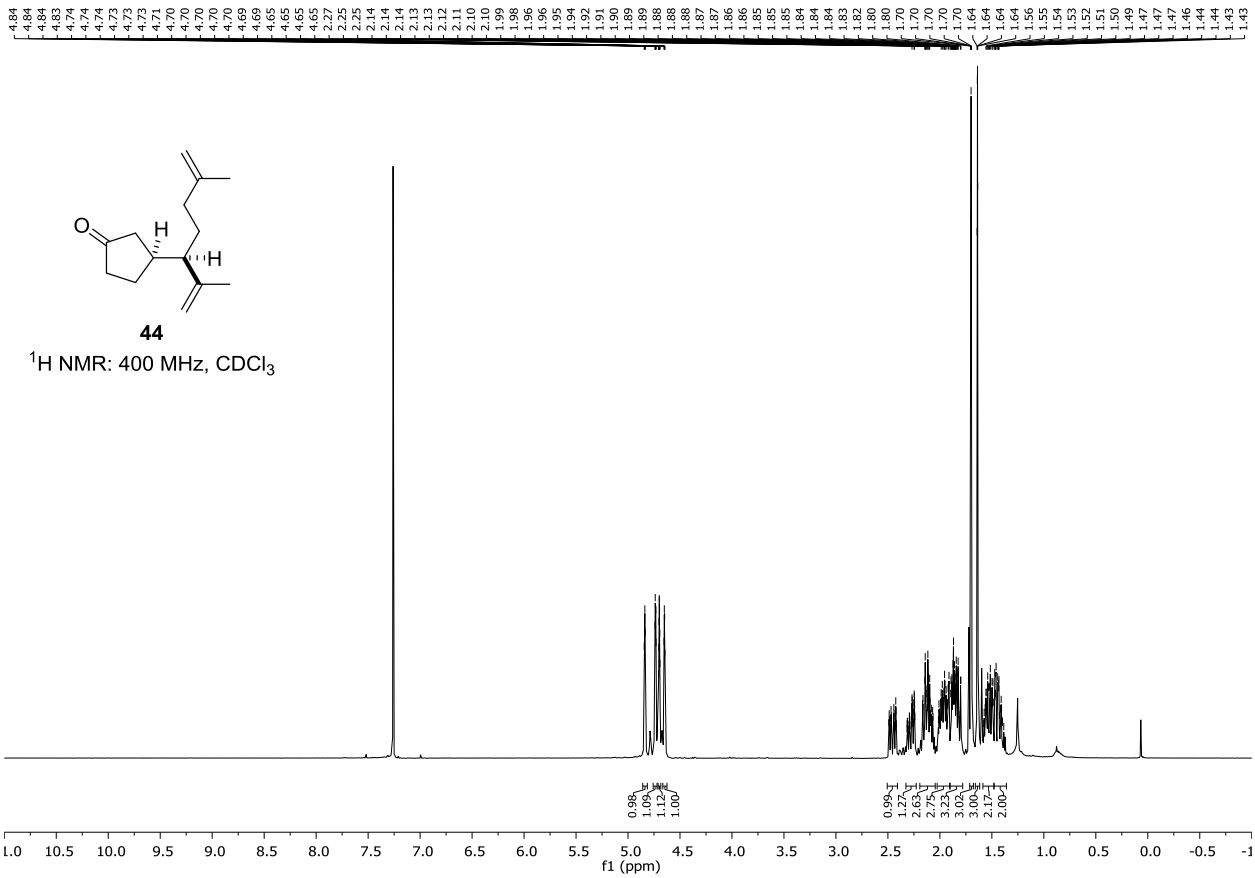



**S10**

$^{13}$C NMR: 101 MHz, $CDCl_3$

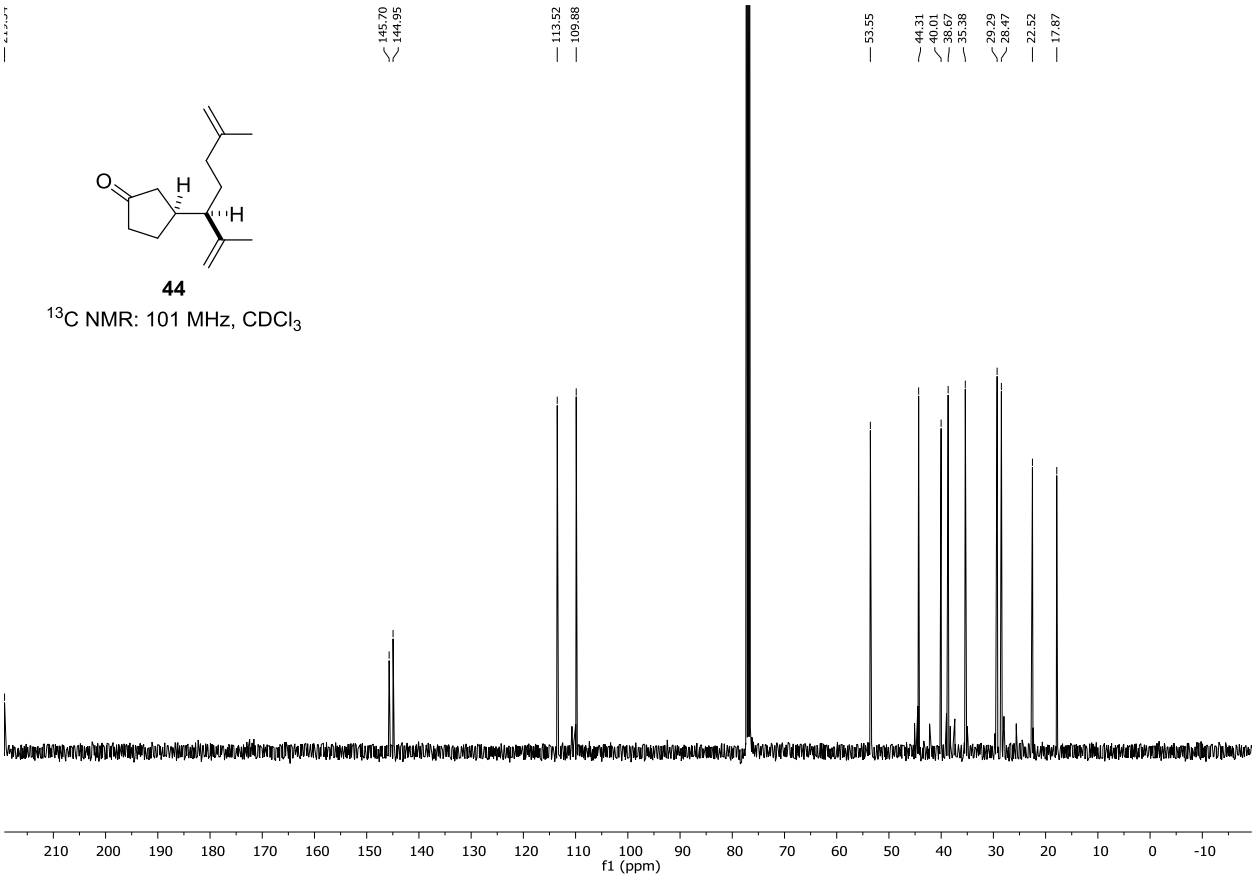

HO
42
1H NMR: 400 MHz, C6D6
f1 (ppm)


HO
42
13C NMR: 101 MHz, C6D6
145.52
137.93
133.05
132.13
128.98
110.65
85.16
51.05
38.32
38.00
31.25
26.60
22.39
18.32
f1 (ppm)



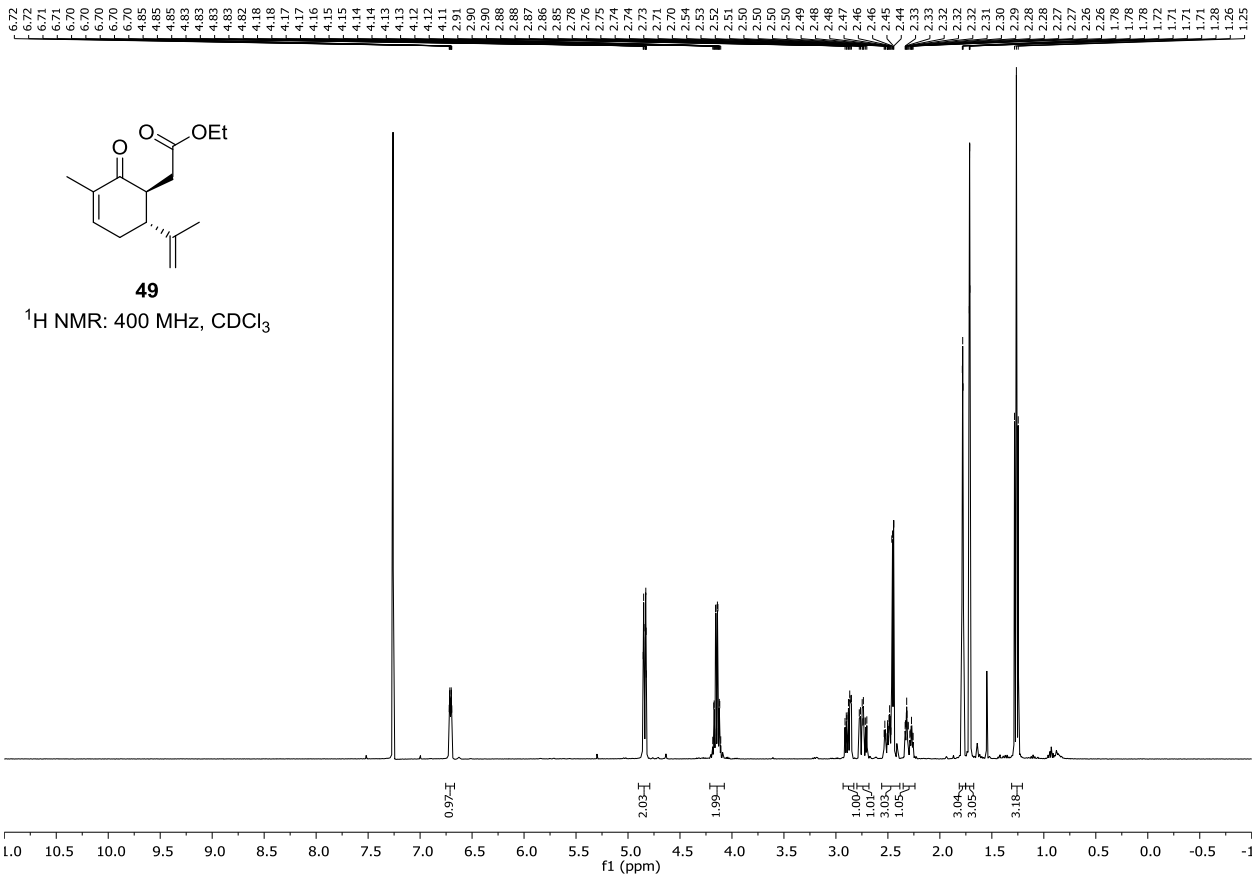

**44**

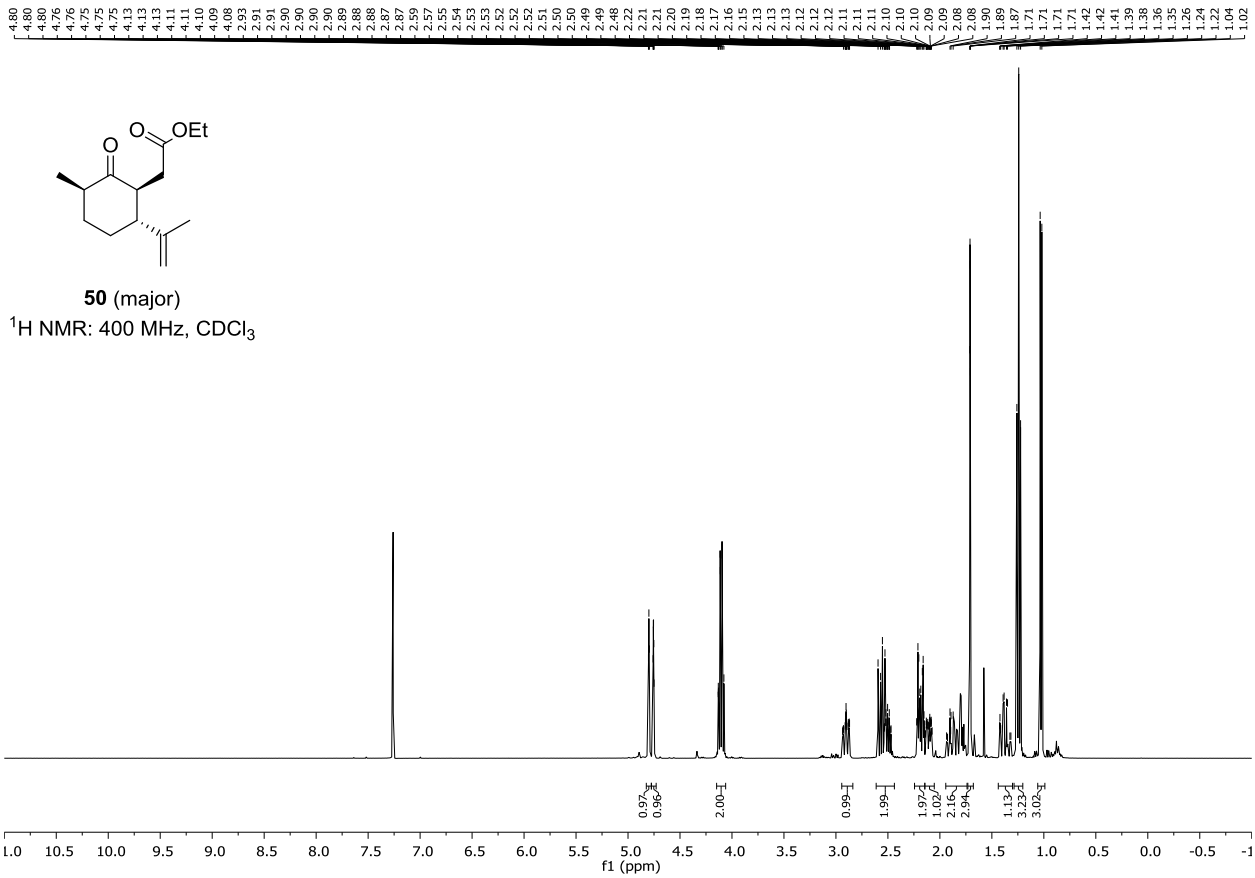
$^{1}$H NMR: 400 MHz, $CDCl_3$



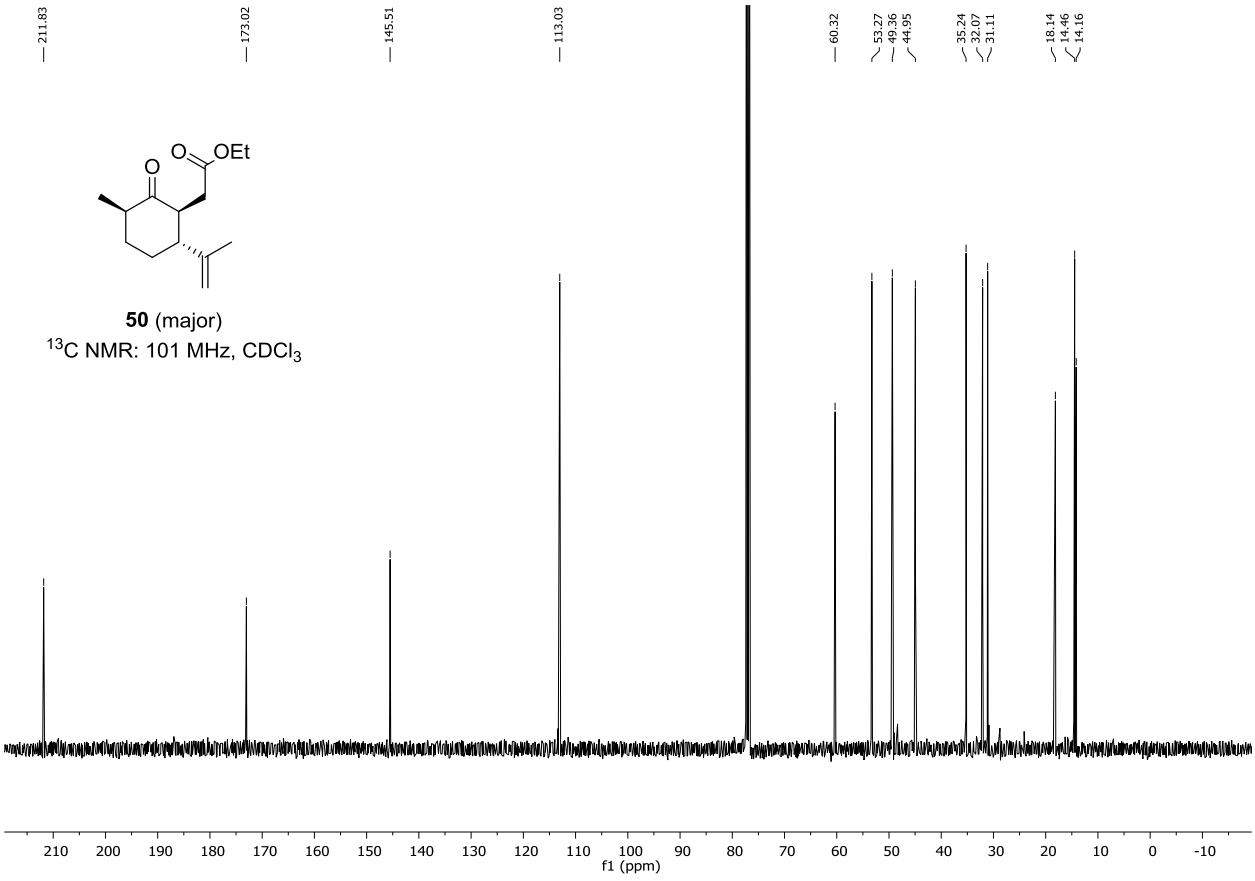

**44**

$^{13}$C NMR: 101 MHz, $CDCl_3$

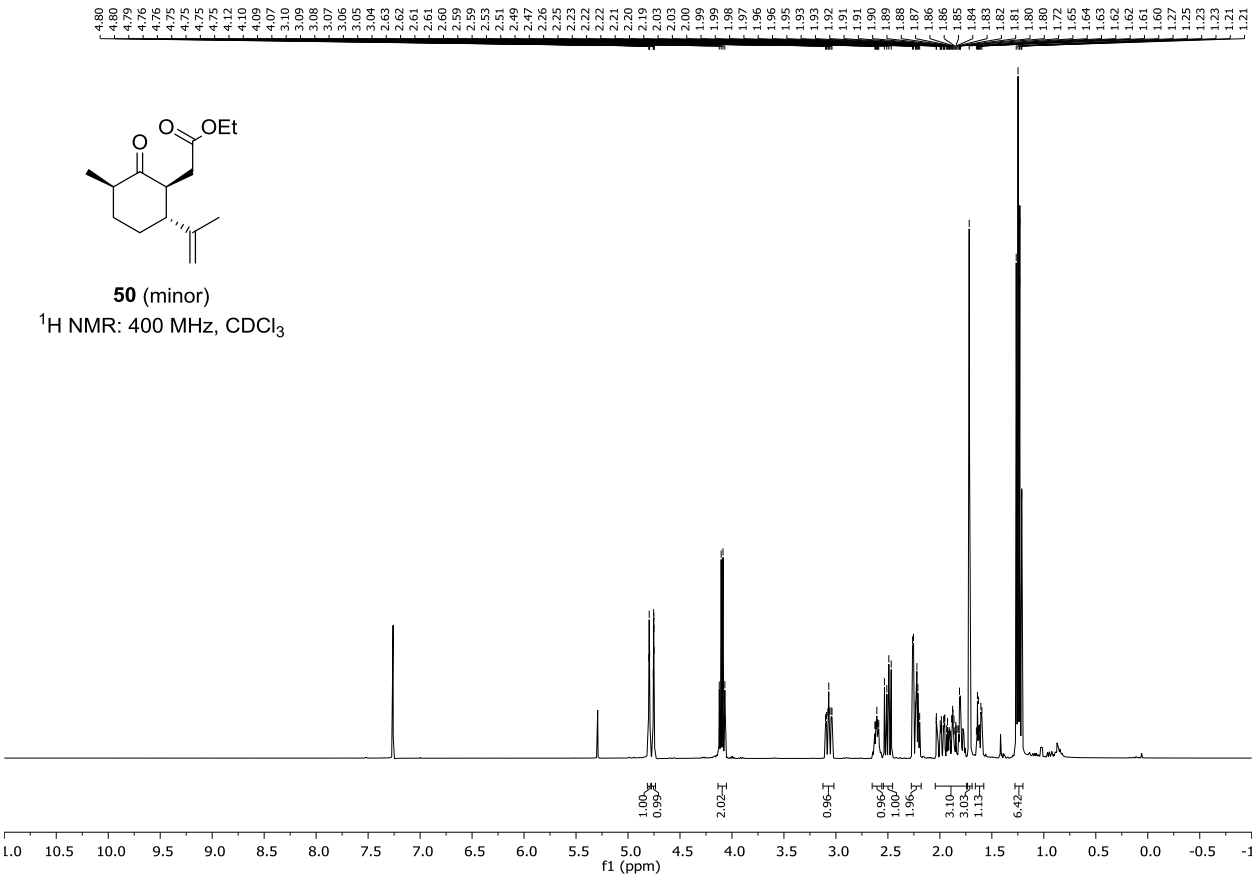

O
O
OEt
49
1H NMR: 400 MHz, CDCl3
0.97
2.03
1.99
1.00
1.01
3.03
1.05
3.04
3.05
3.18
f1 (ppm)



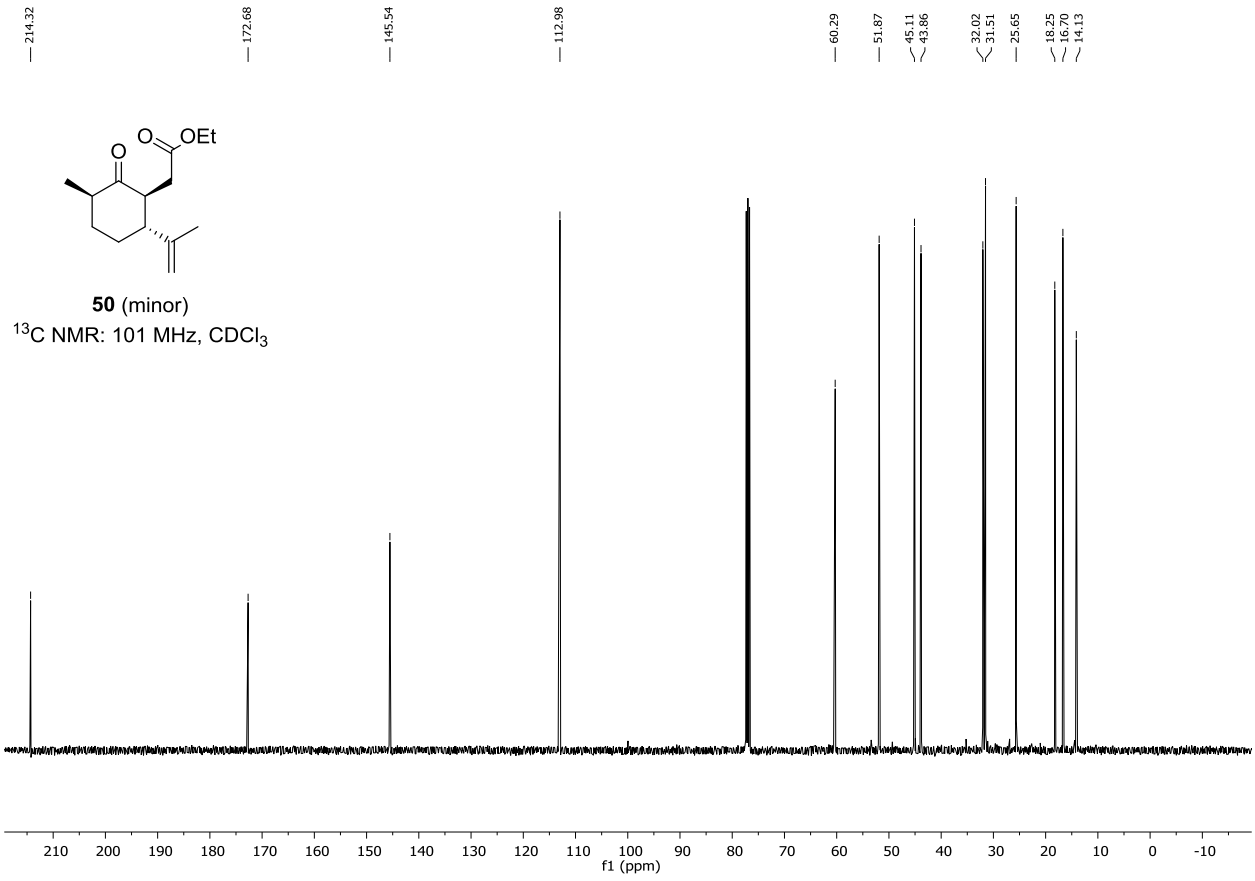

**50** (major)
$^{1}$H NMR: 400 MHz, $CDCl_3$



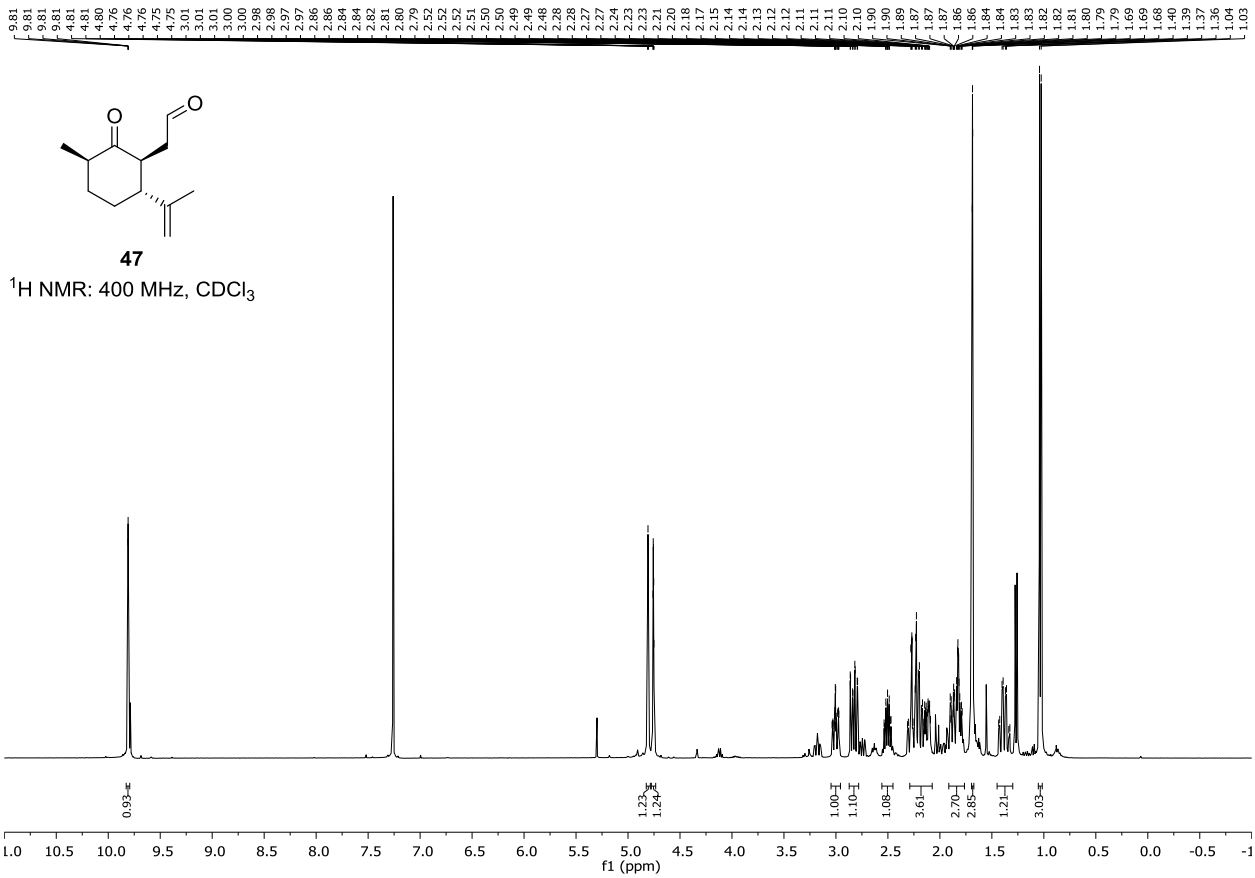

**50** (major)
$^{13}$C NMR: 101 MHz, $CDCl_3$




**50** (minor)
$^{1}$H NMR: 400 MHz, $CDCl_3$

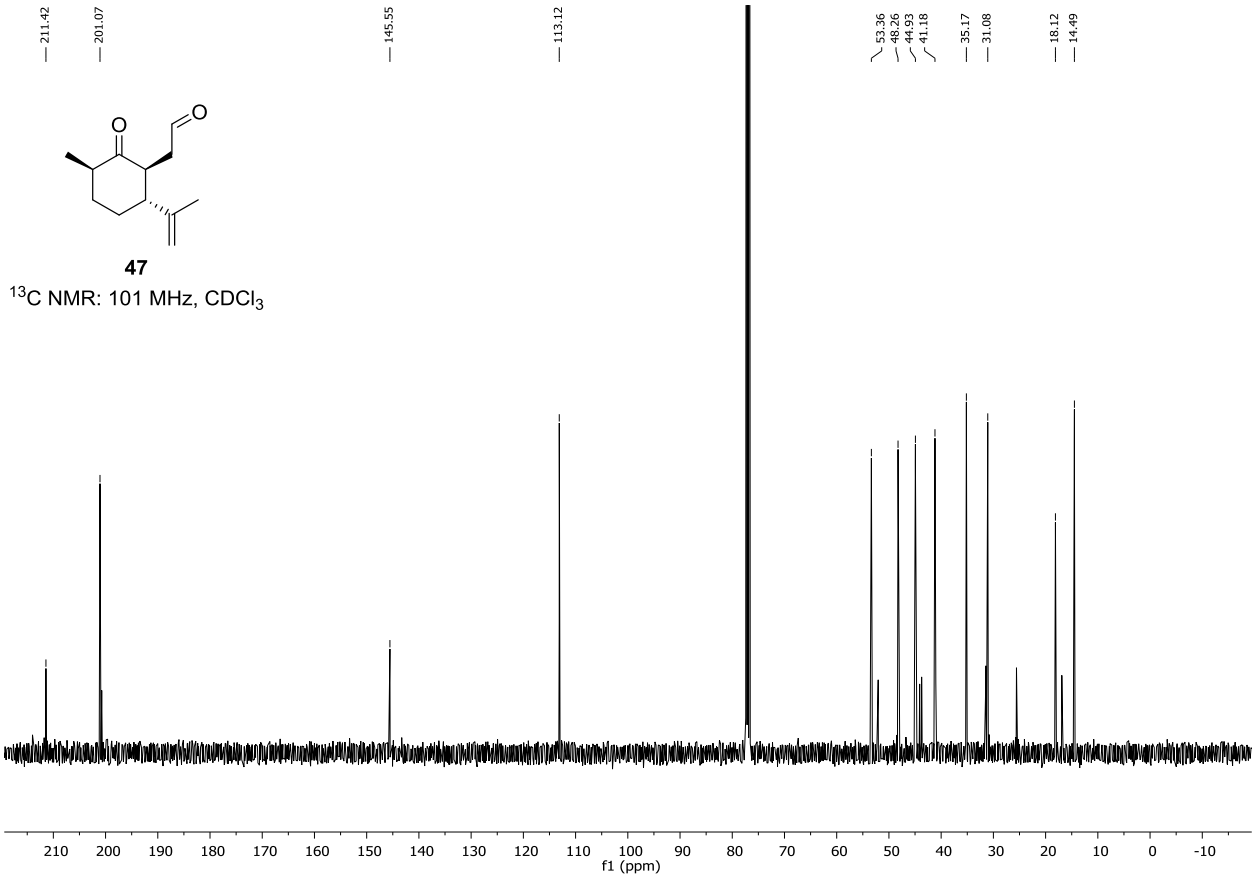



**50** (minor)
$^{13}$C NMR: 101 MHz, $CDCl_3$



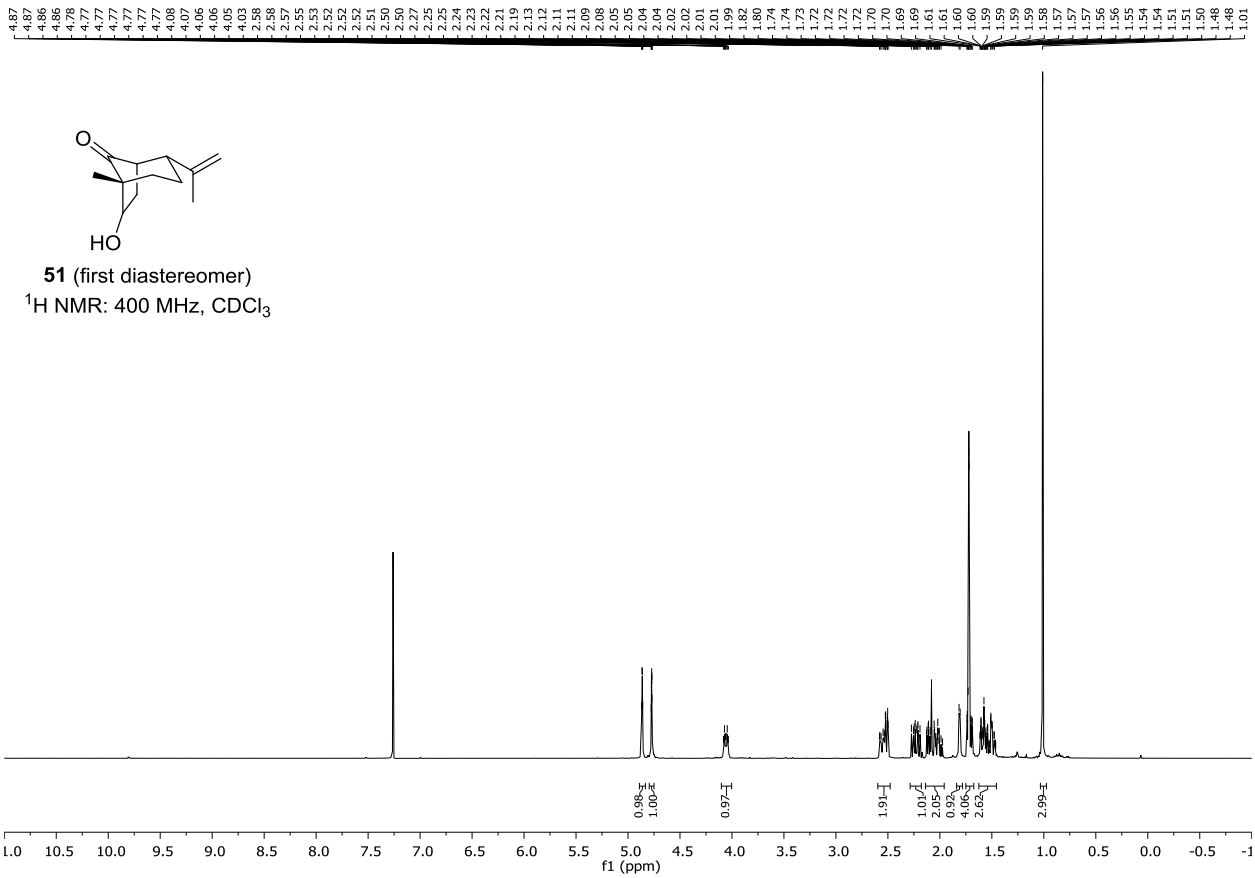
**47**

$^{1}$H NMR: 400 MHz, $CDCl_3$

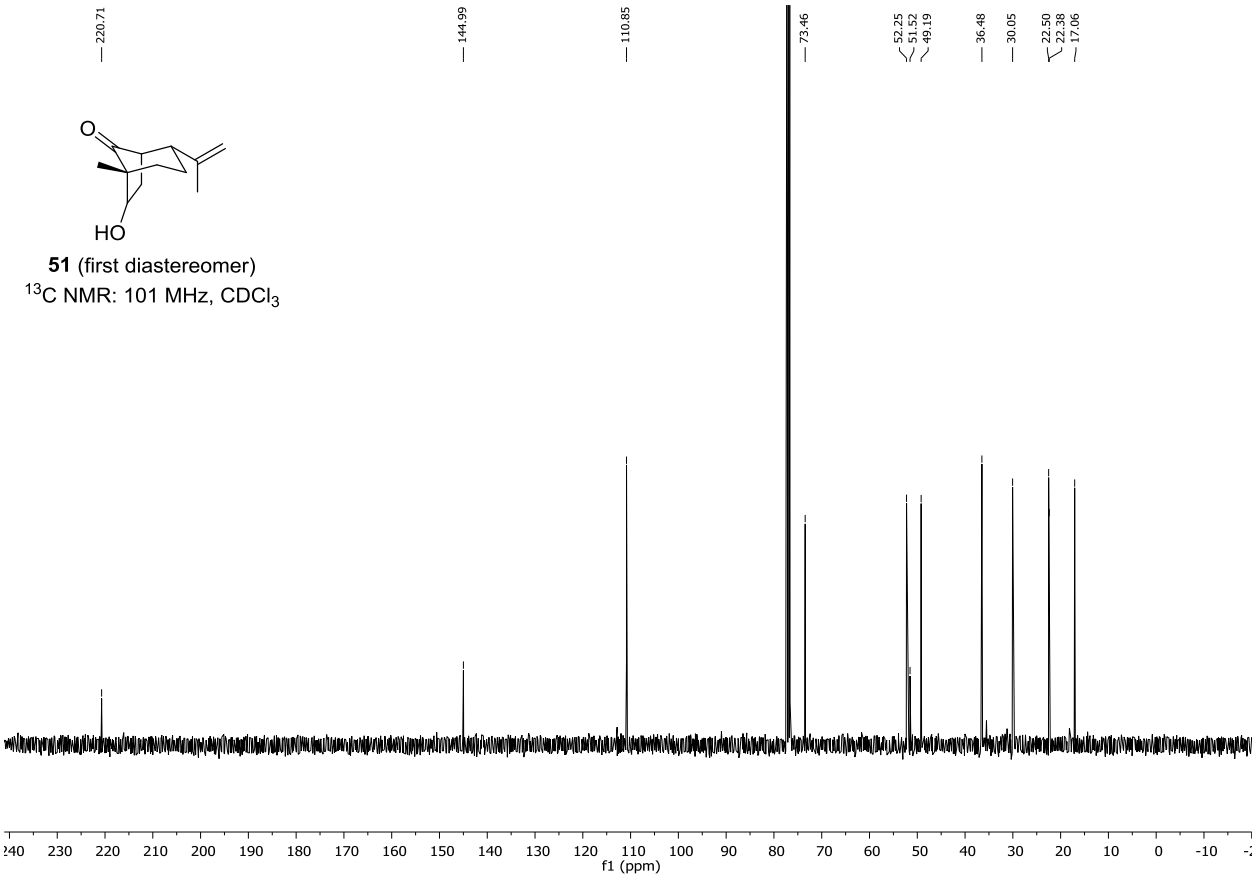


**47**

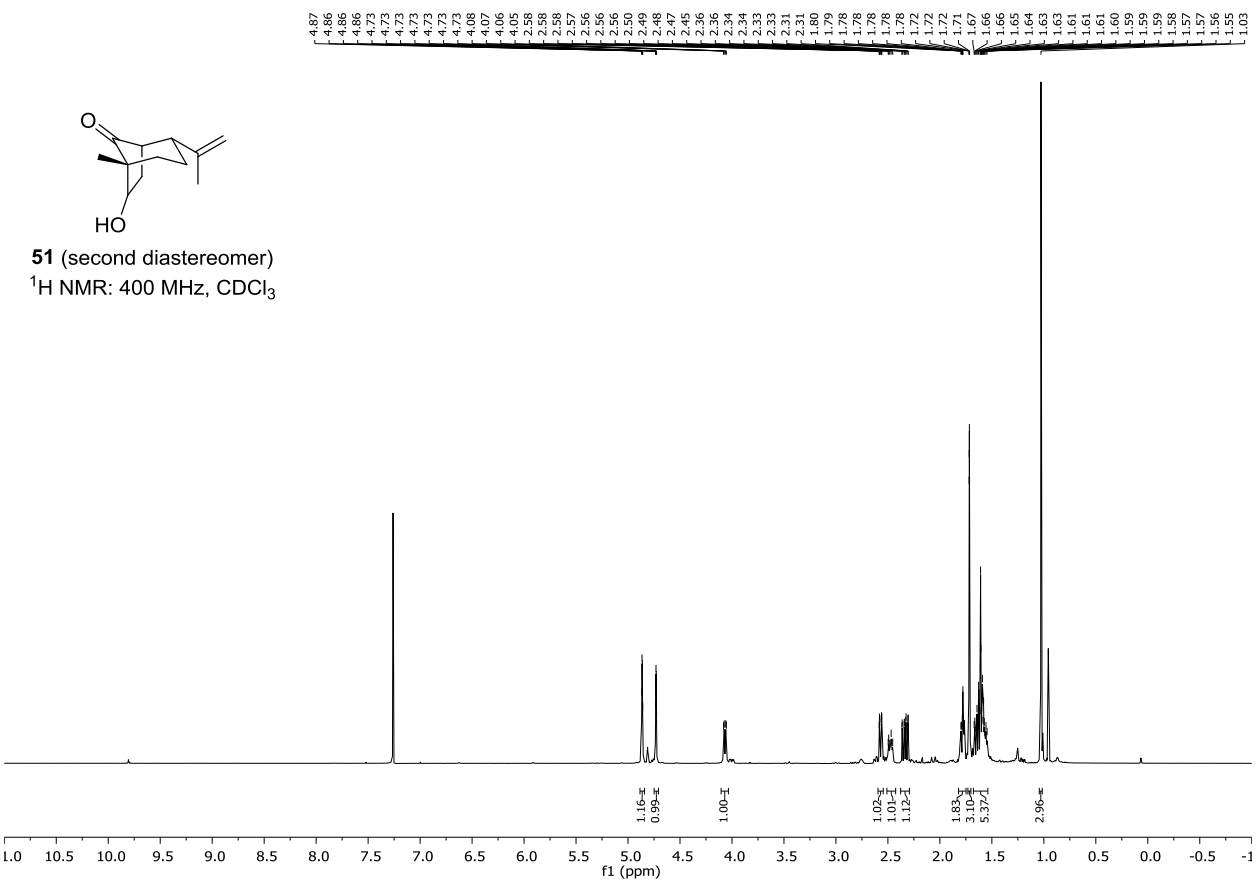
$^{13}$C NMR: 101 MHz, $CDCl_3$



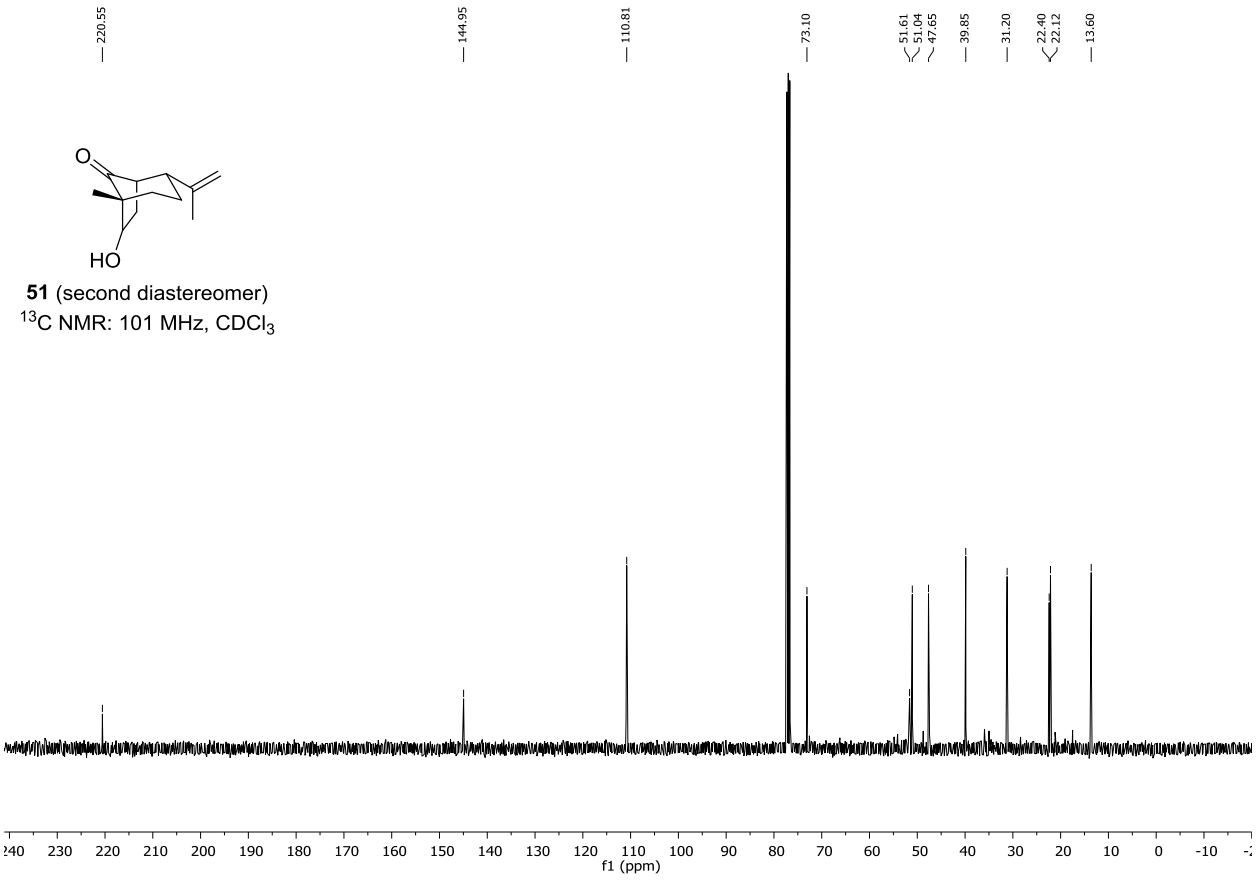

**51** (first diastereomer)
$^{1}$H NMR: 400 MHz, $CDCl_3$



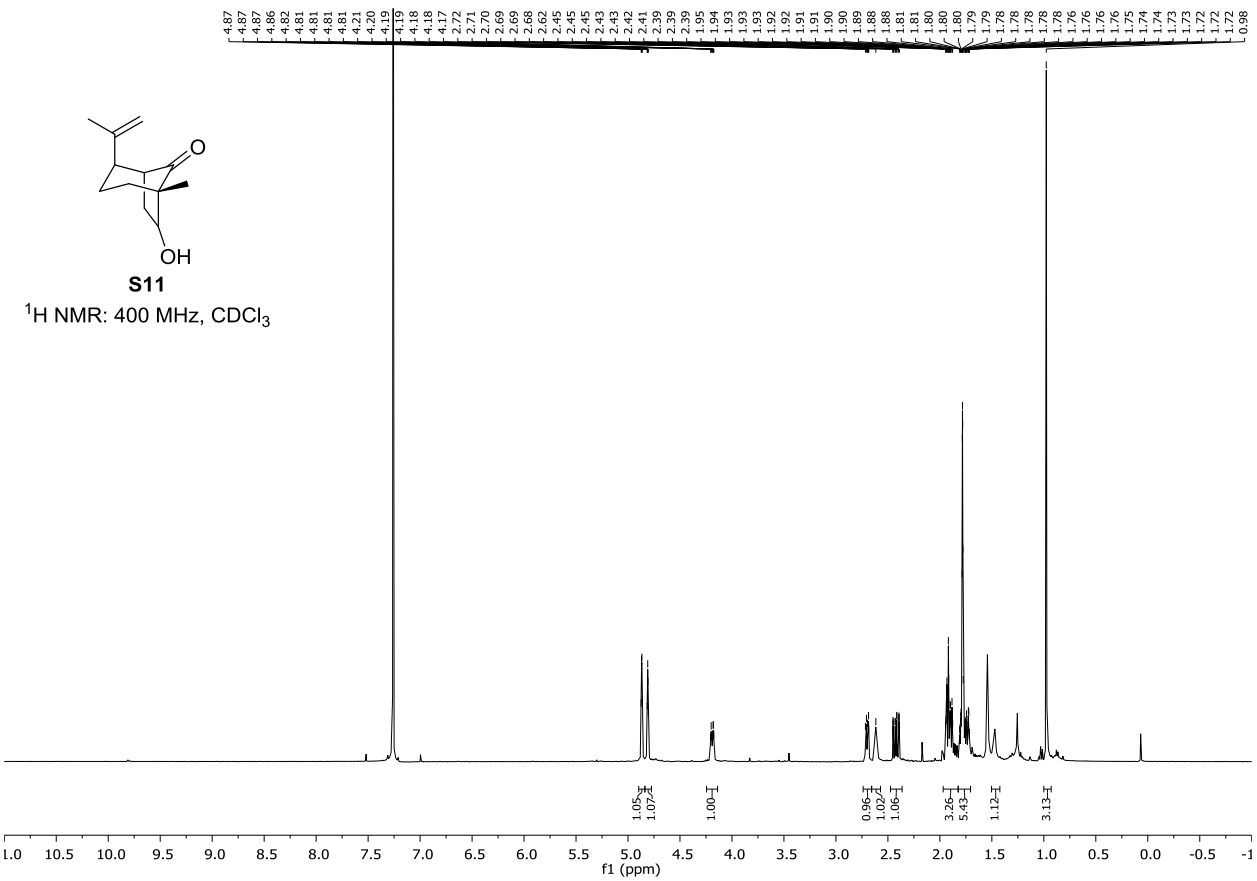

**51** (first diastereomer)
$^{13}$C NMR: 101 MHz, $CDCl_3$




**51** (second diastereomer)
$^{1}$H NMR: 400 MHz, $CDCl_3$

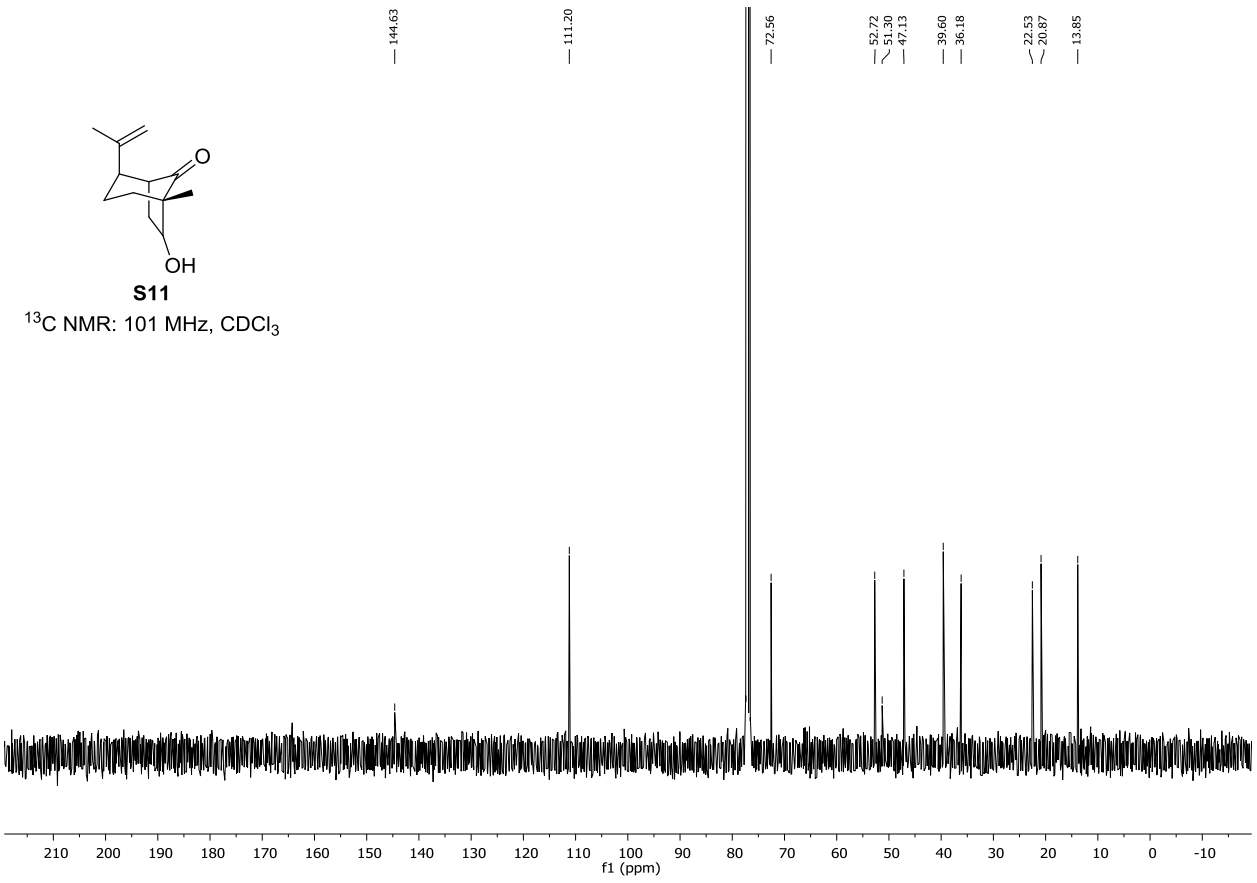



**51** (second diastereomer)
$^{13}$C NMR: 101 MHz, $CDCl_3$



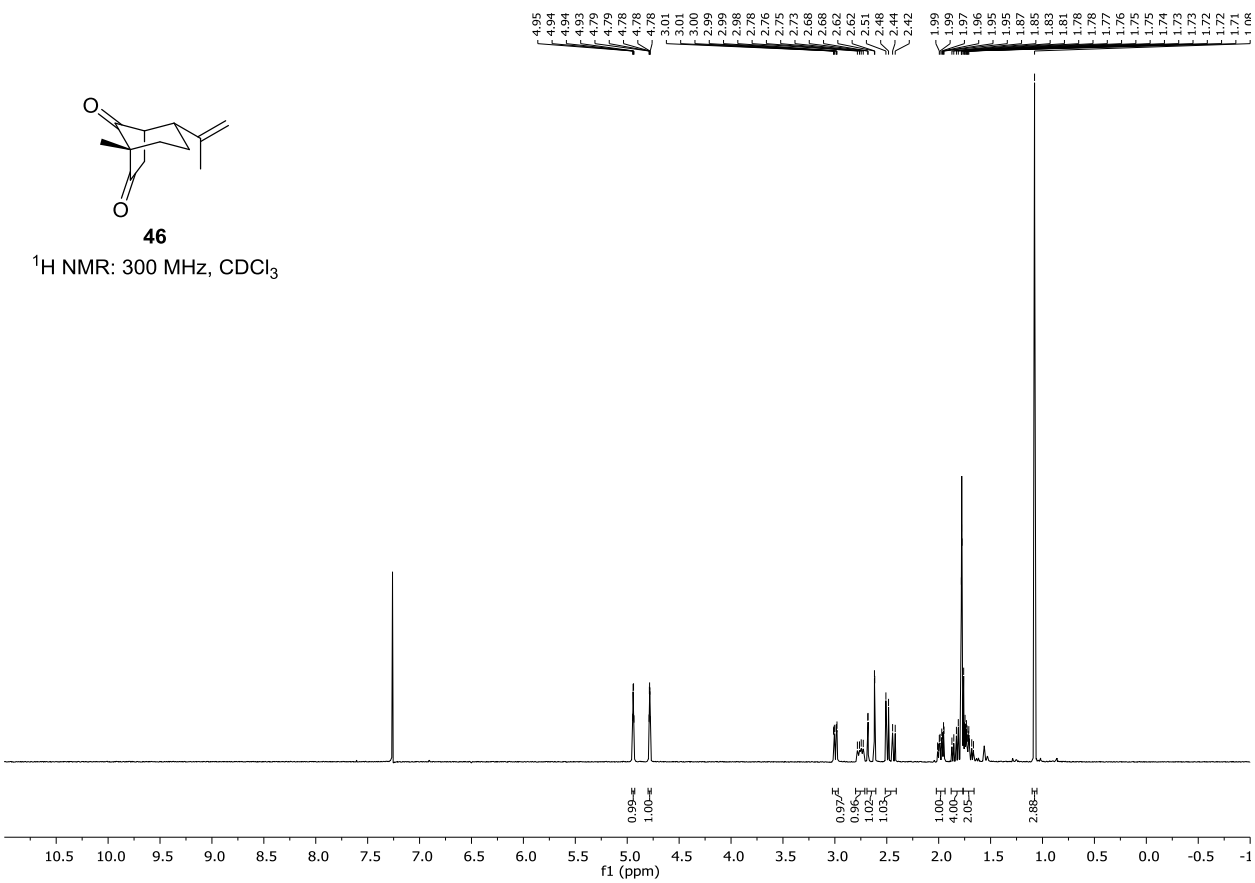

**S11**

$^{1}$H NMR: 400 MHz, $CDCl_3$



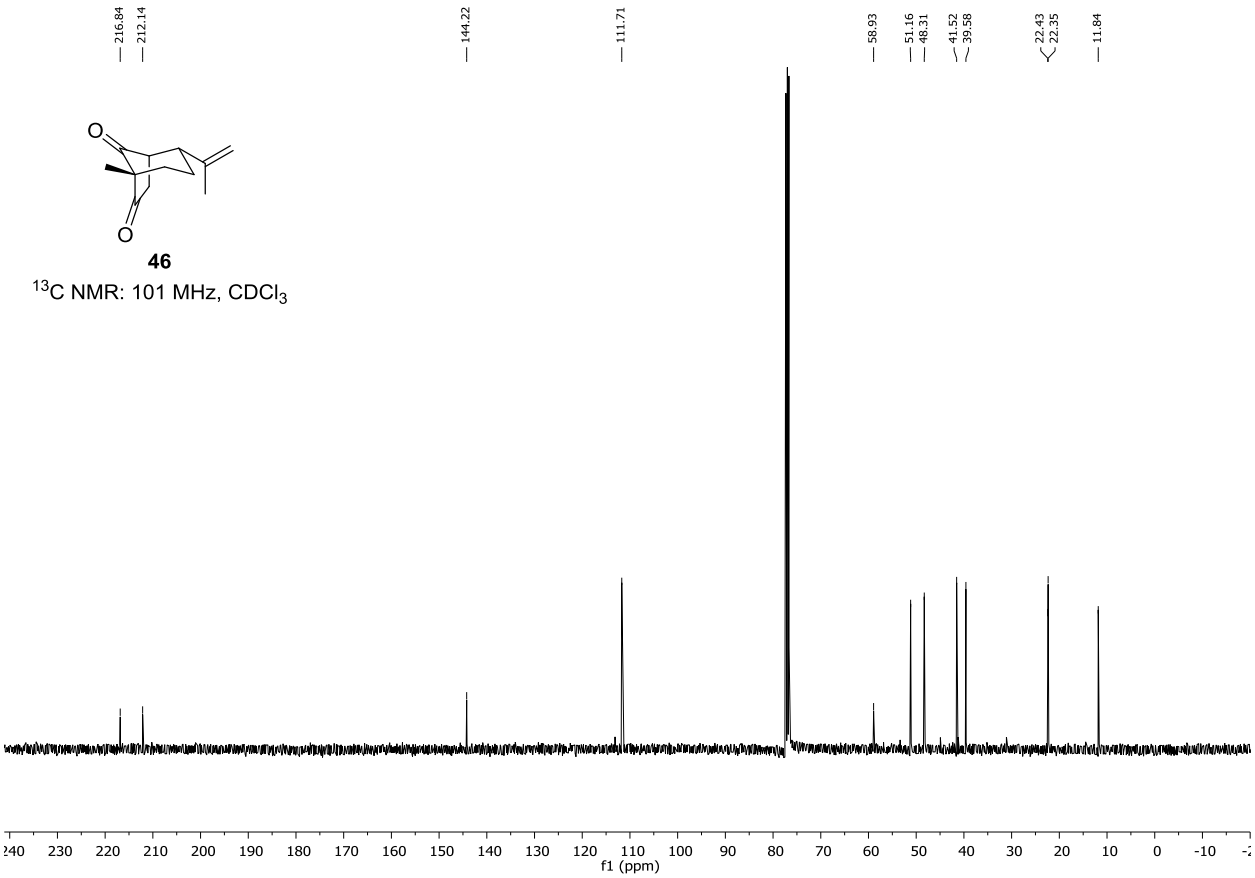

**S11**

$^{13}$C NMR: 101 MHz, $CDCl_3$



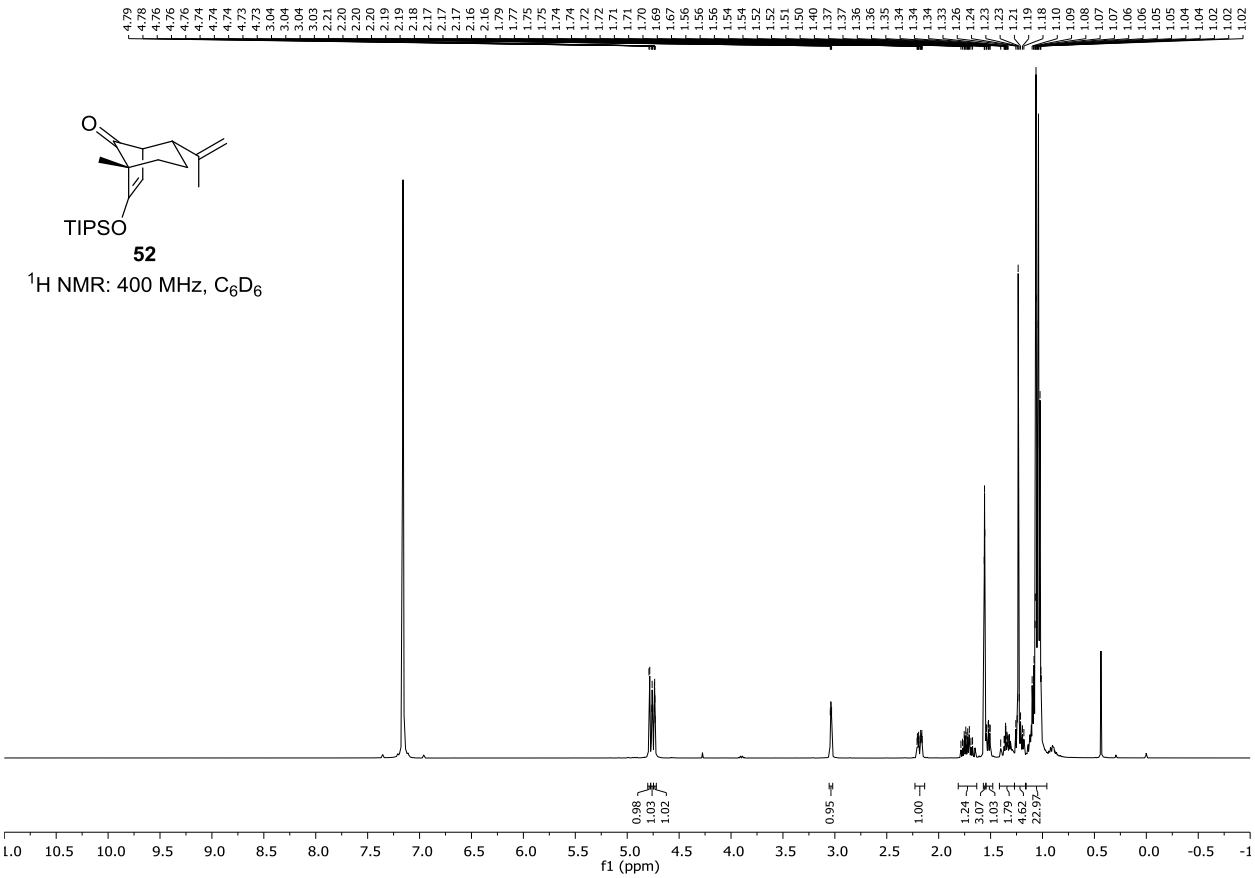

**46**

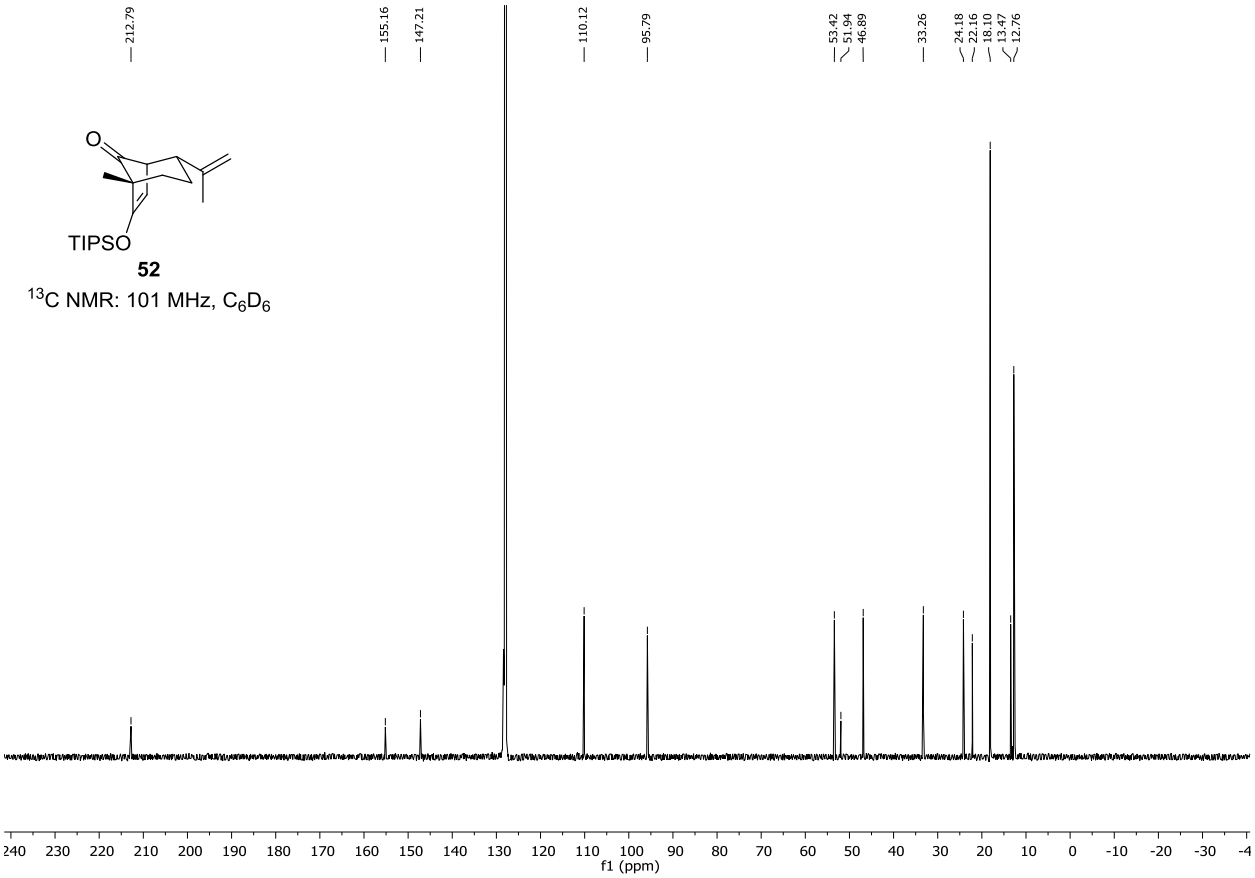
$^{1}$H NMR: 300 MHz, $CDCl_3$

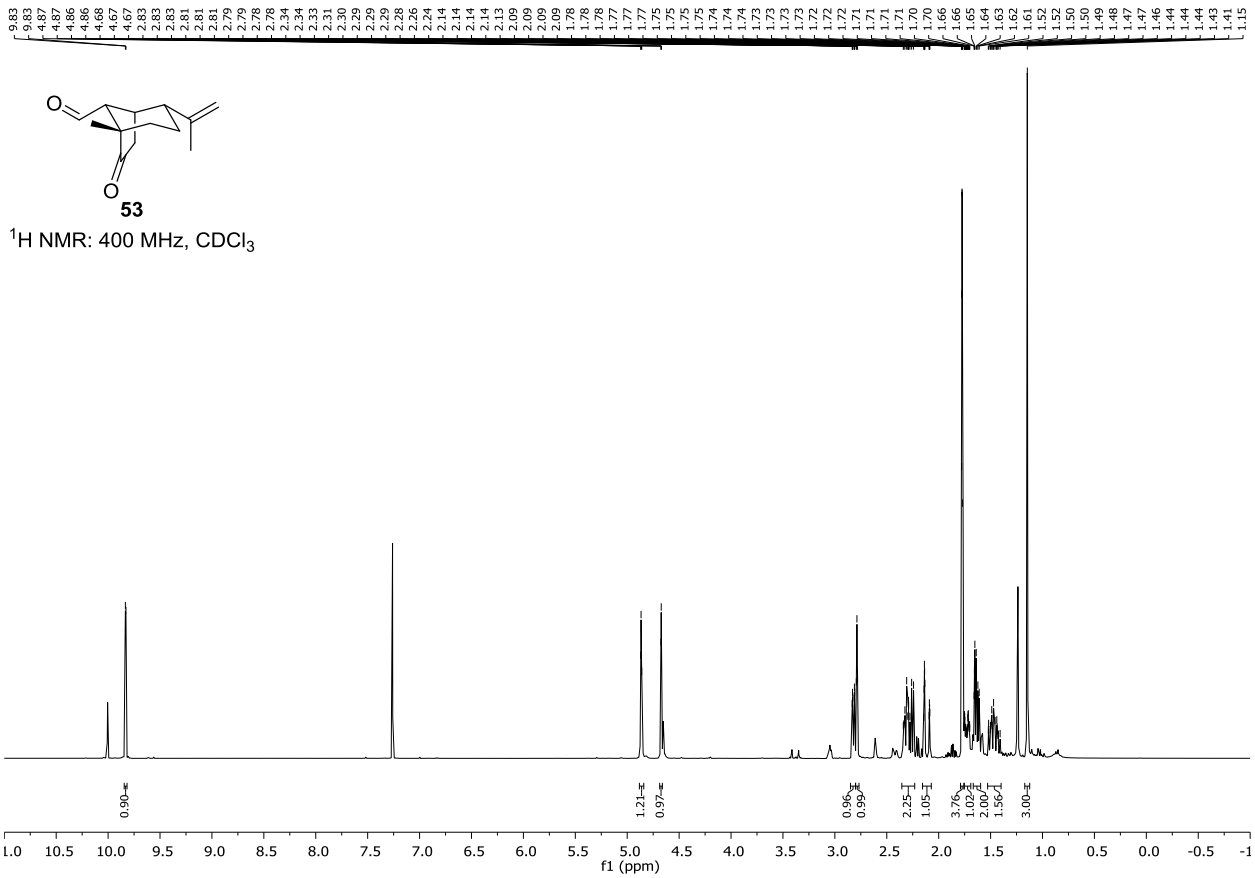



**46**

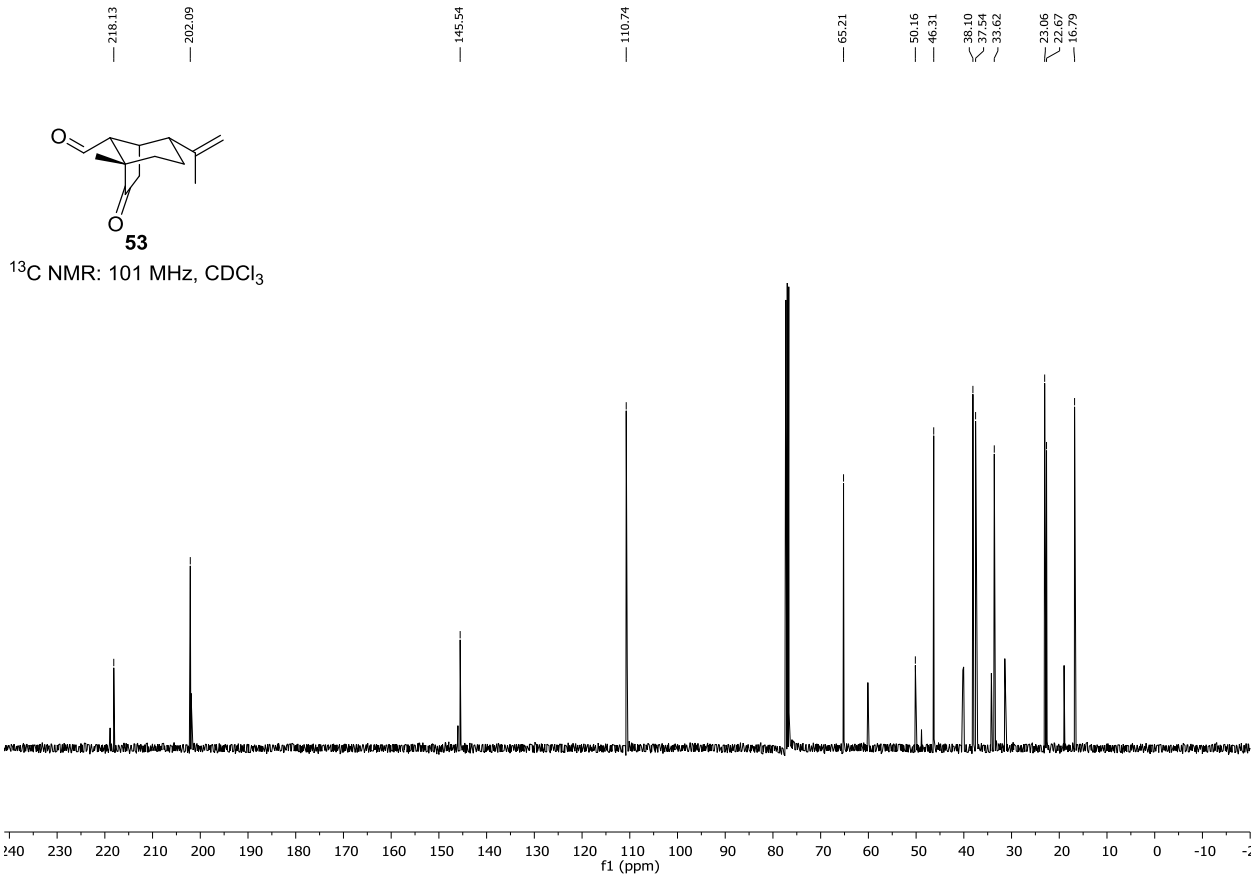
$^{13}$C NMR: 101 MHz, $CDCl_3$


TIPSO
52
$^{1}$H NMR: 400 MHz, $C_6D_6$
f1 (ppm)

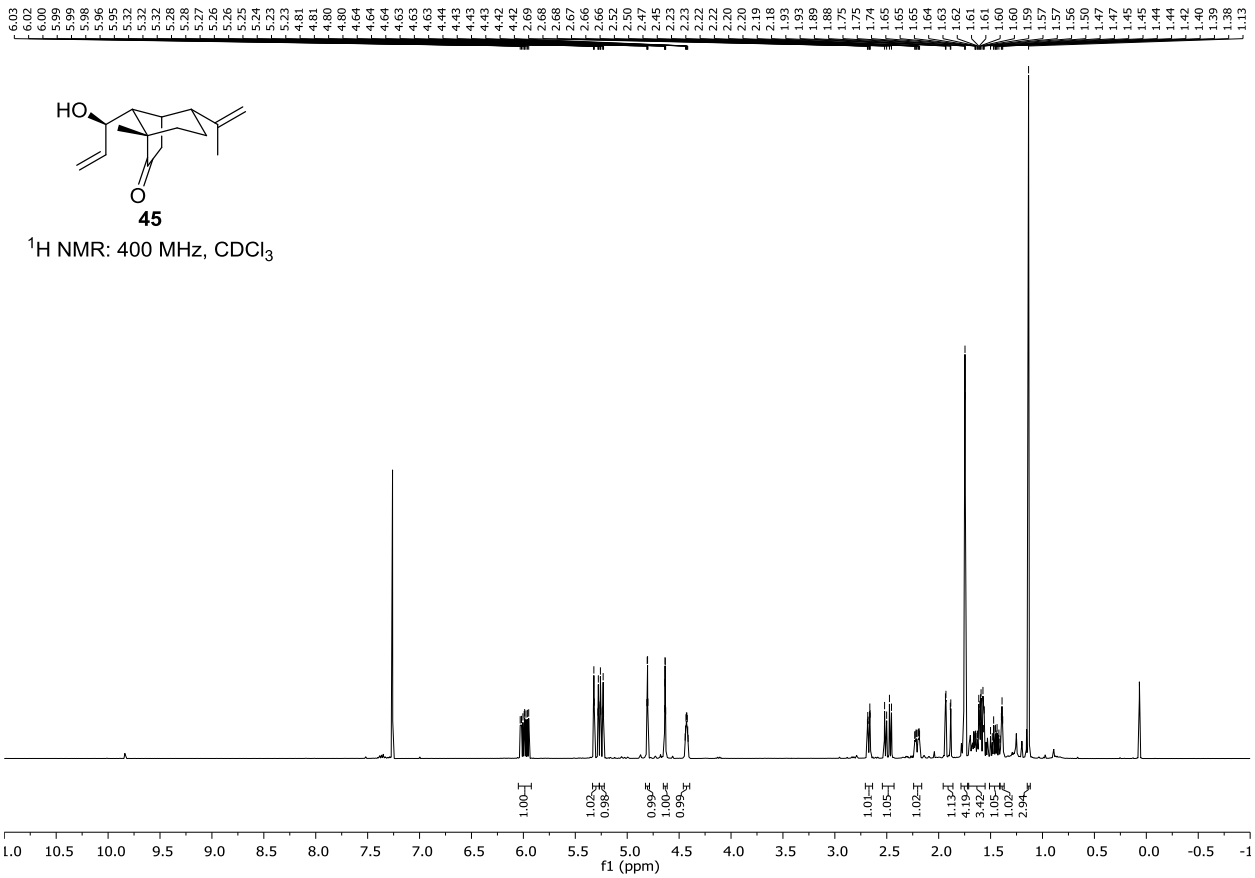

TIPSO
52
$^{13}$C NMR: 101 MHz, $C_6D_6$
f1 (ppm)

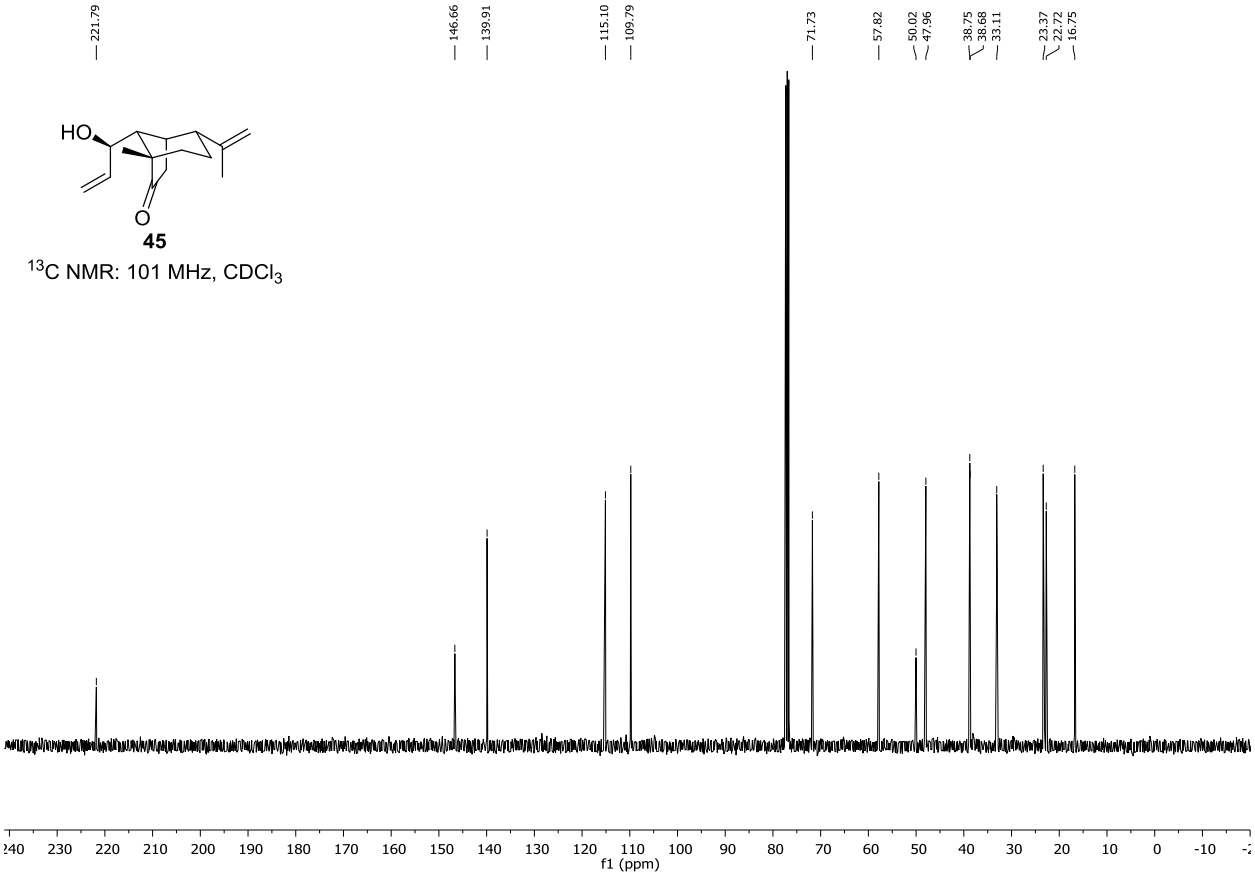


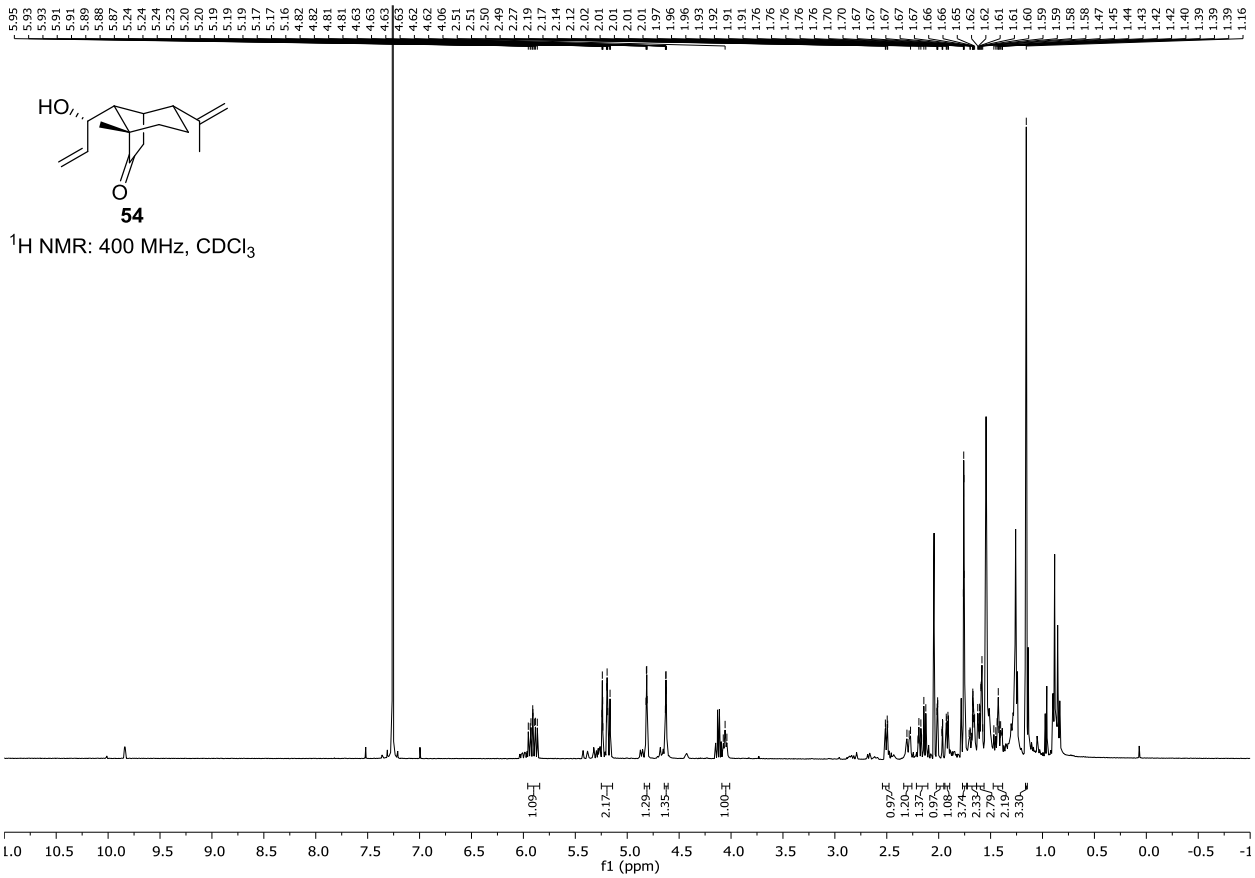

$^{1}$H NMR: 400 MHz, $CDCl_3$




$^{13}$C NMR: 101 MHz, $CDCl_3$

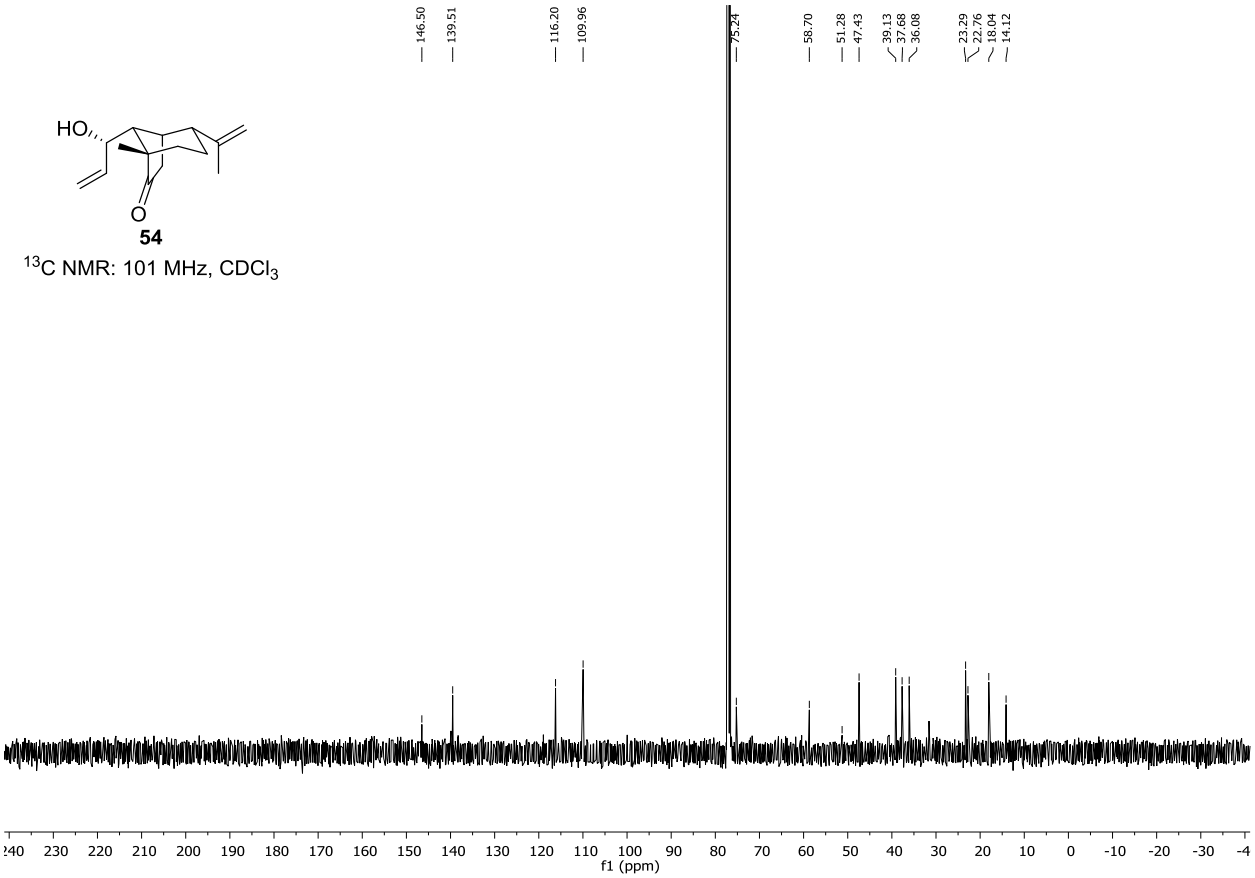

HO
O
45
1H NMR: 400 MHz, CDCl3
f1 (ppm)


HO
O
45
13C NMR: 101 MHz, CDCl3
f1 (ppm)



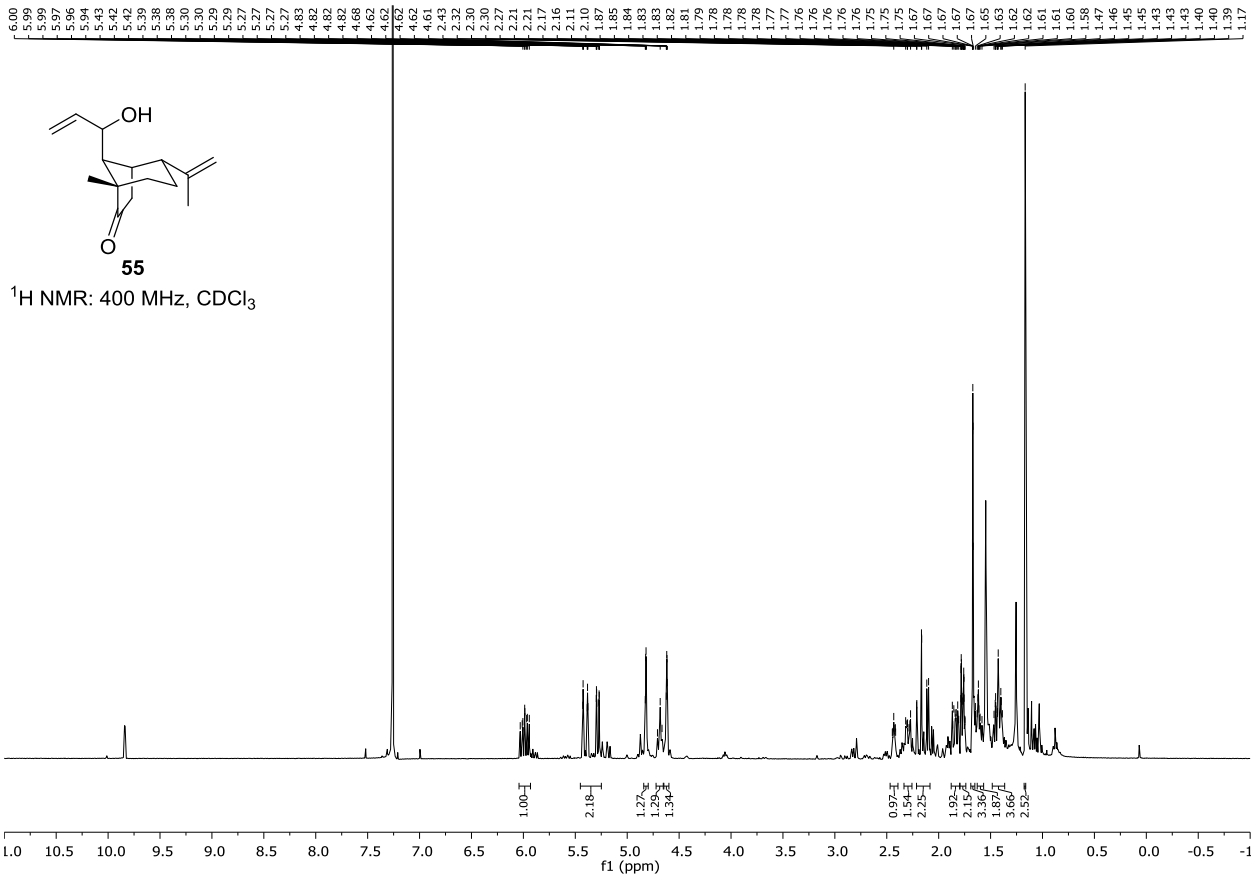

**54**

$^{1}$H NMR: 400 MHz, $CDCl_3$



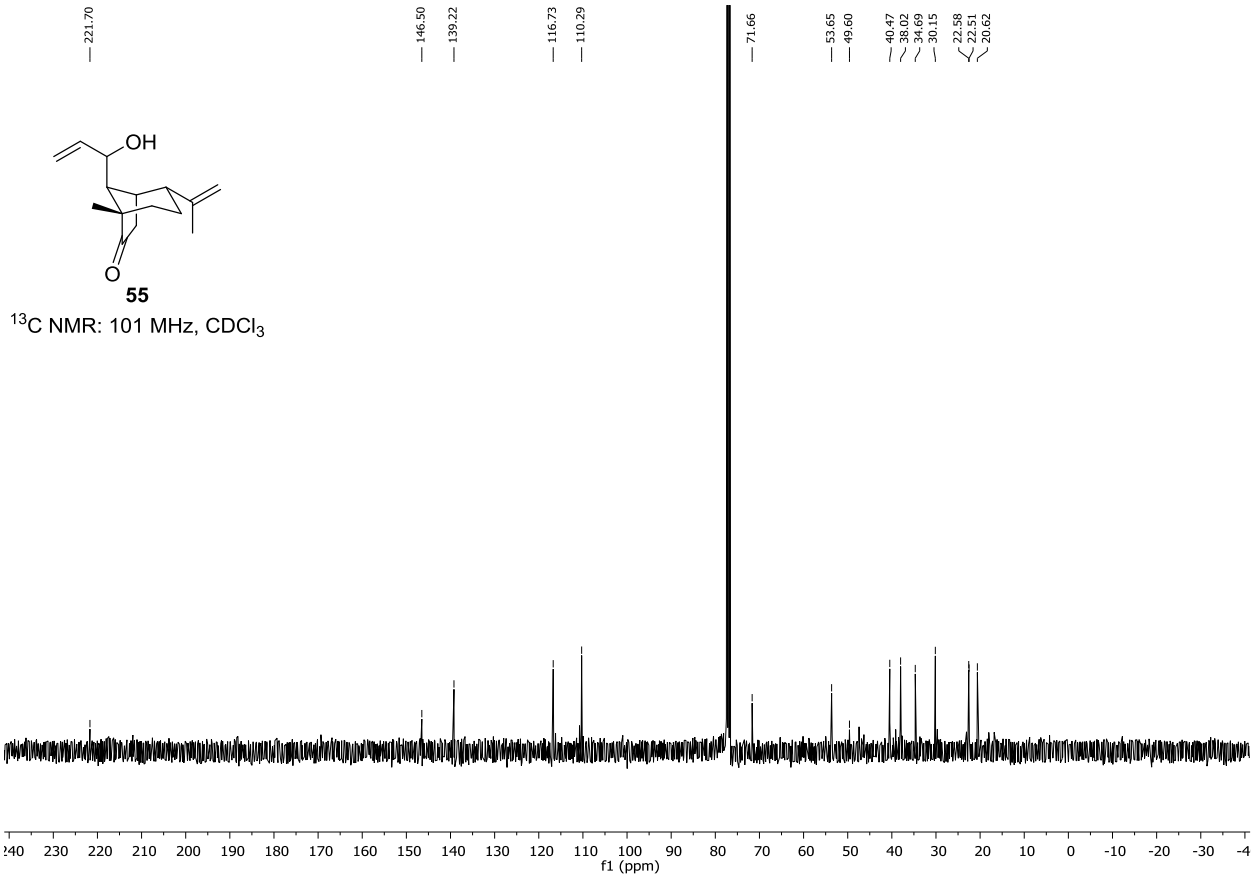

**54**

$^{13}$C NMR: 101 MHz, $CDCl_3$



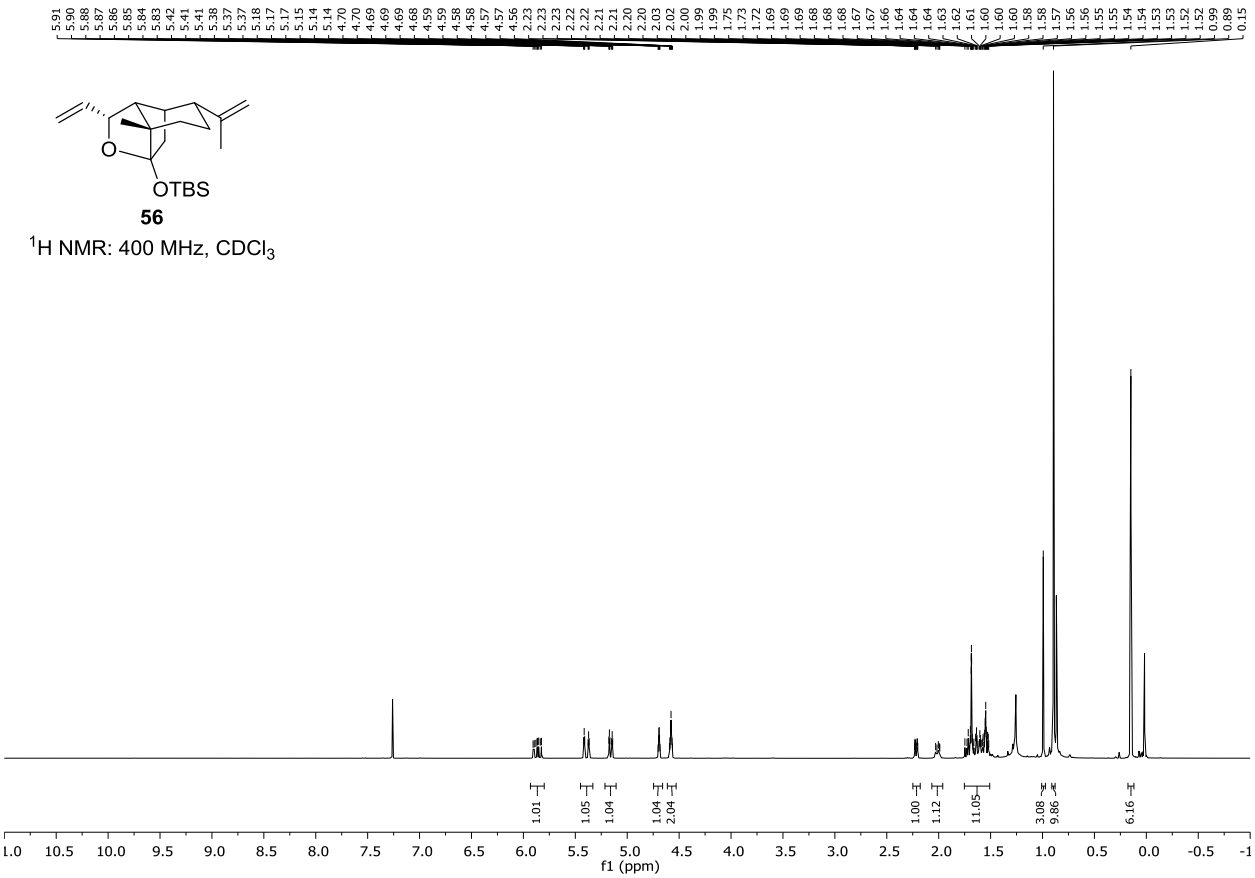

**55**

$^{1}$H NMR: 400 MHz, $CDCl_3$



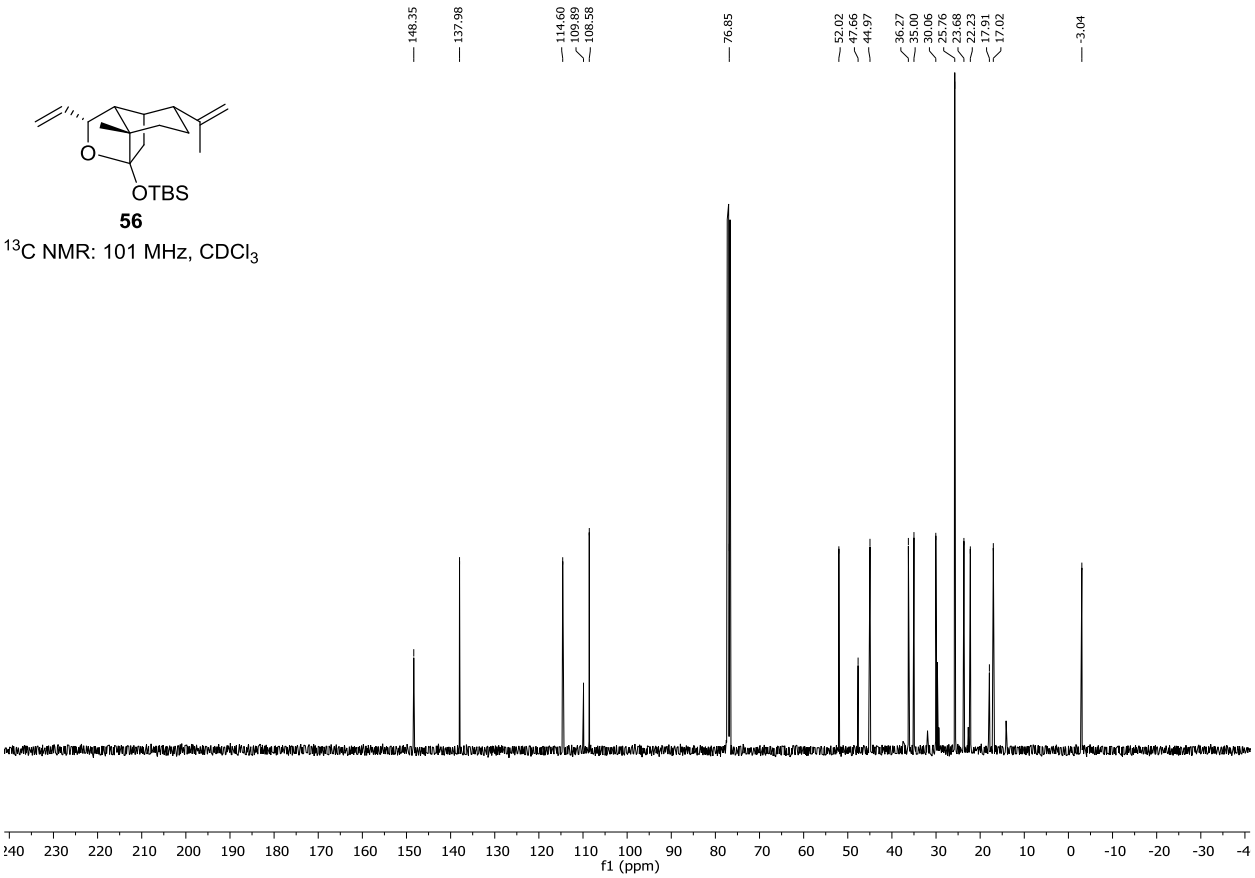

**55**

$^{13}$C NMR: 101 MHz, $CDCl_3$



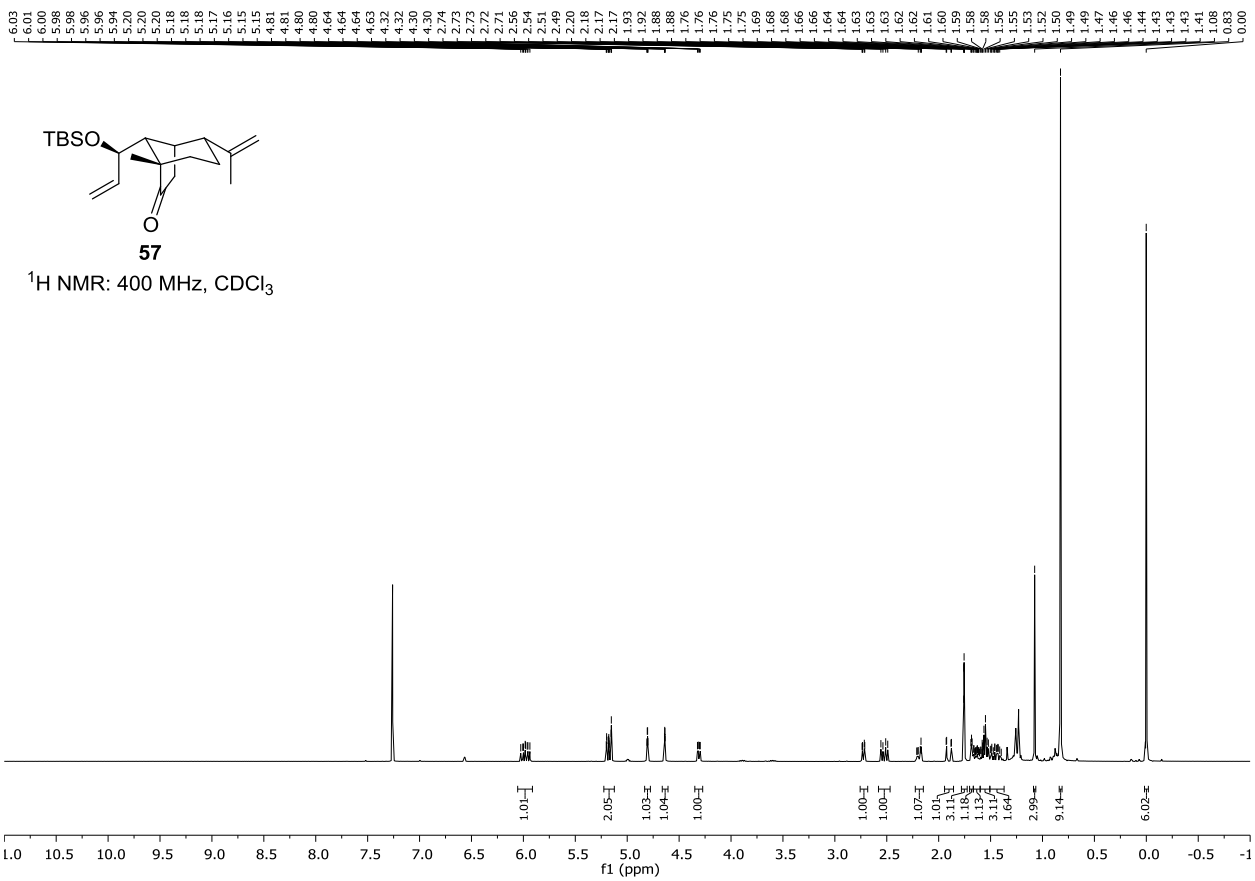

**56**

$^{1}$H NMR: 400 MHz, $CDCl_3$



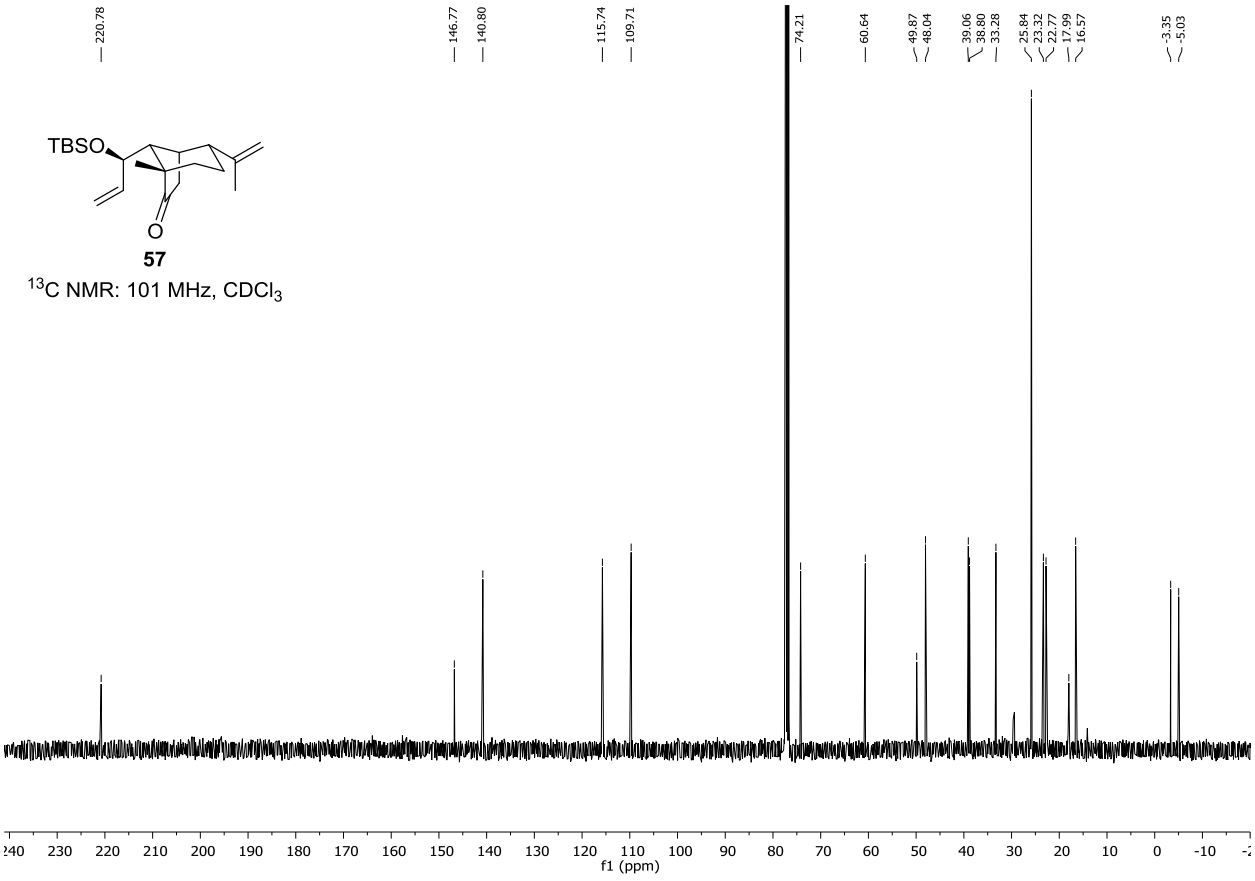

**56**

$^{13}$C NMR: 101 MHz, $CDCl_3$



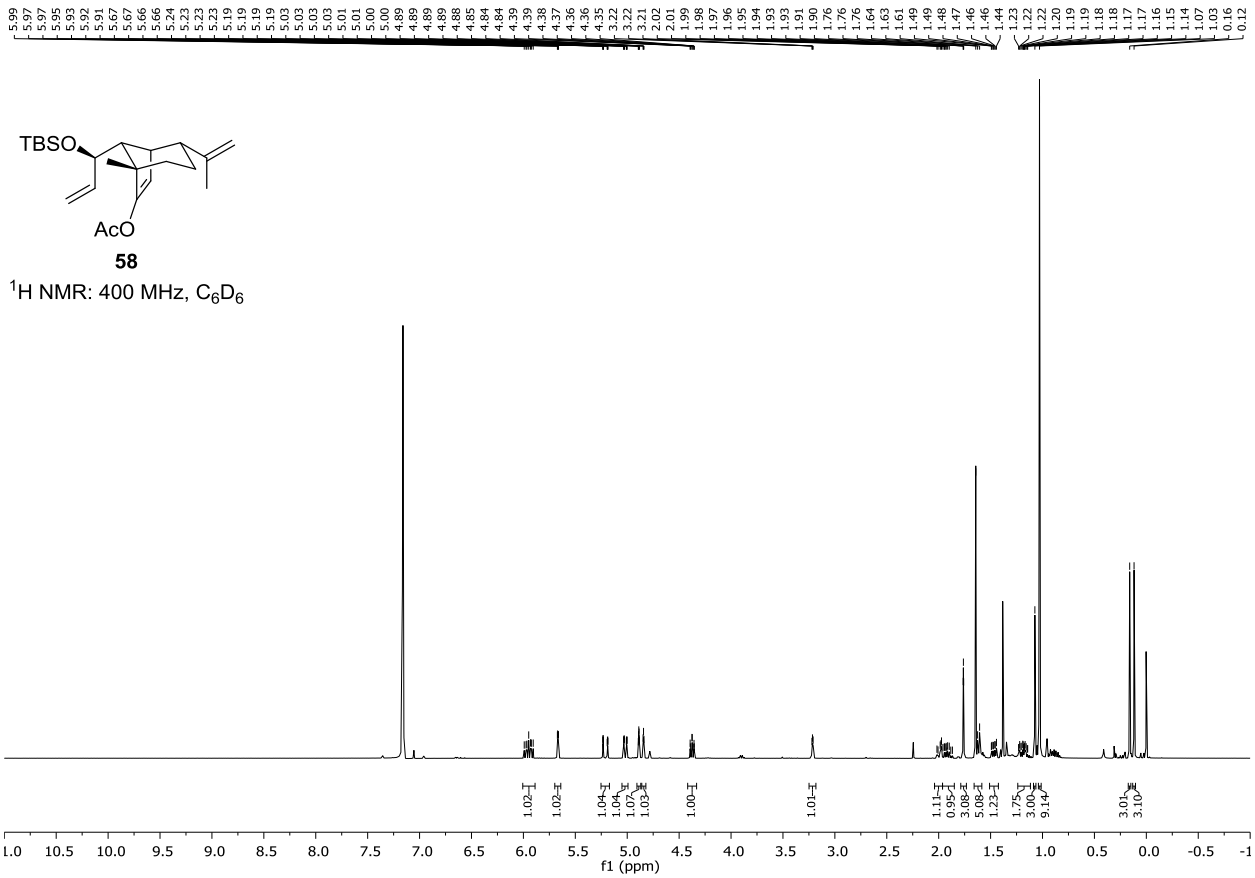

**57**

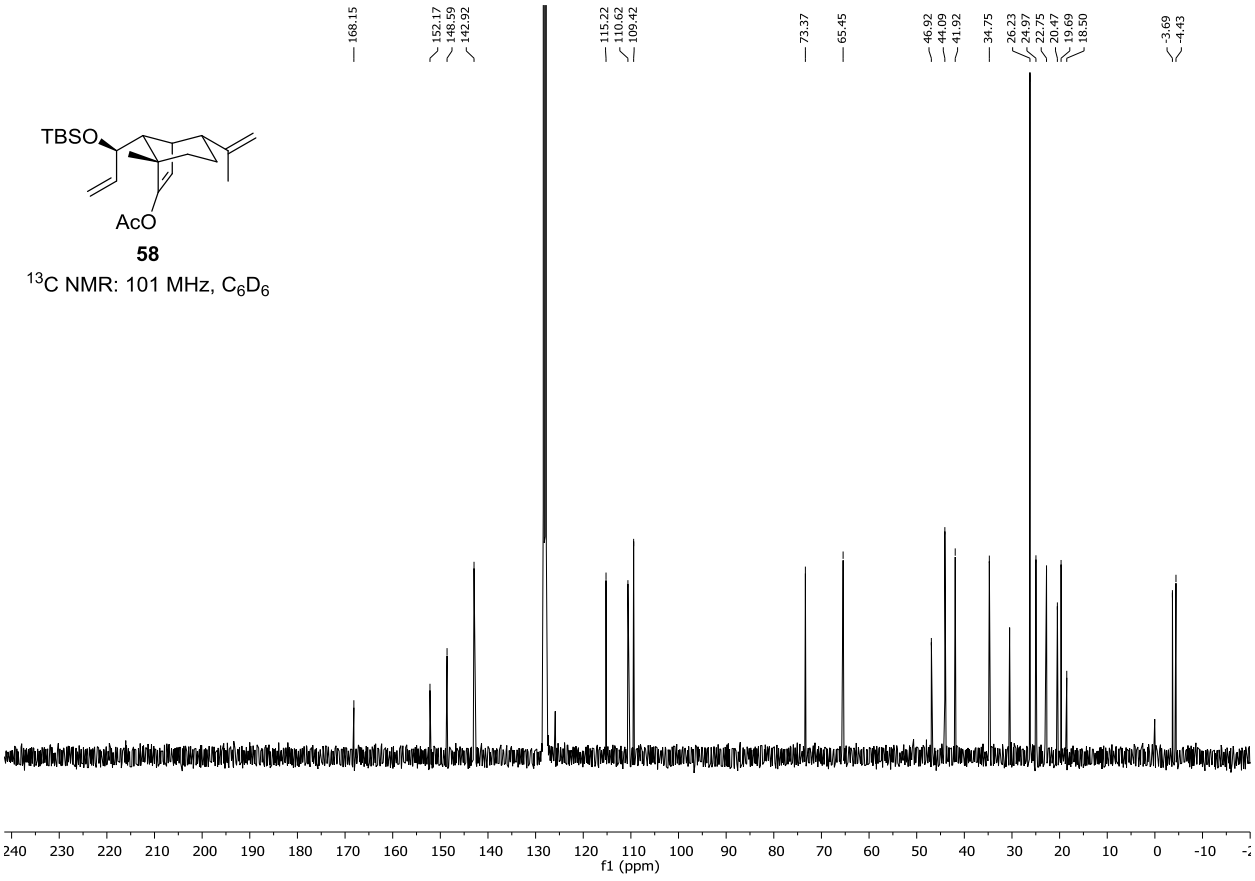
$^{1}$H NMR: 400 MHz, $CDCl_3$

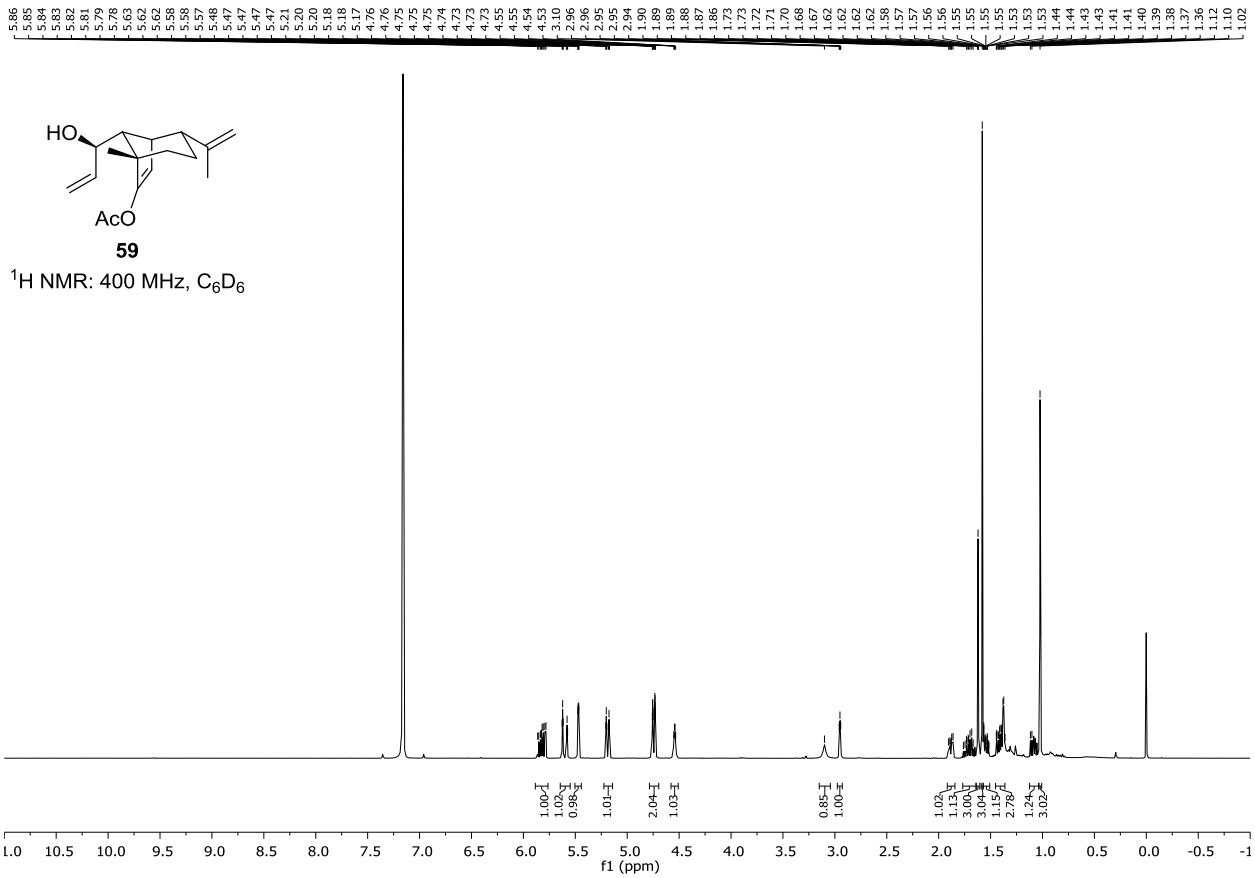


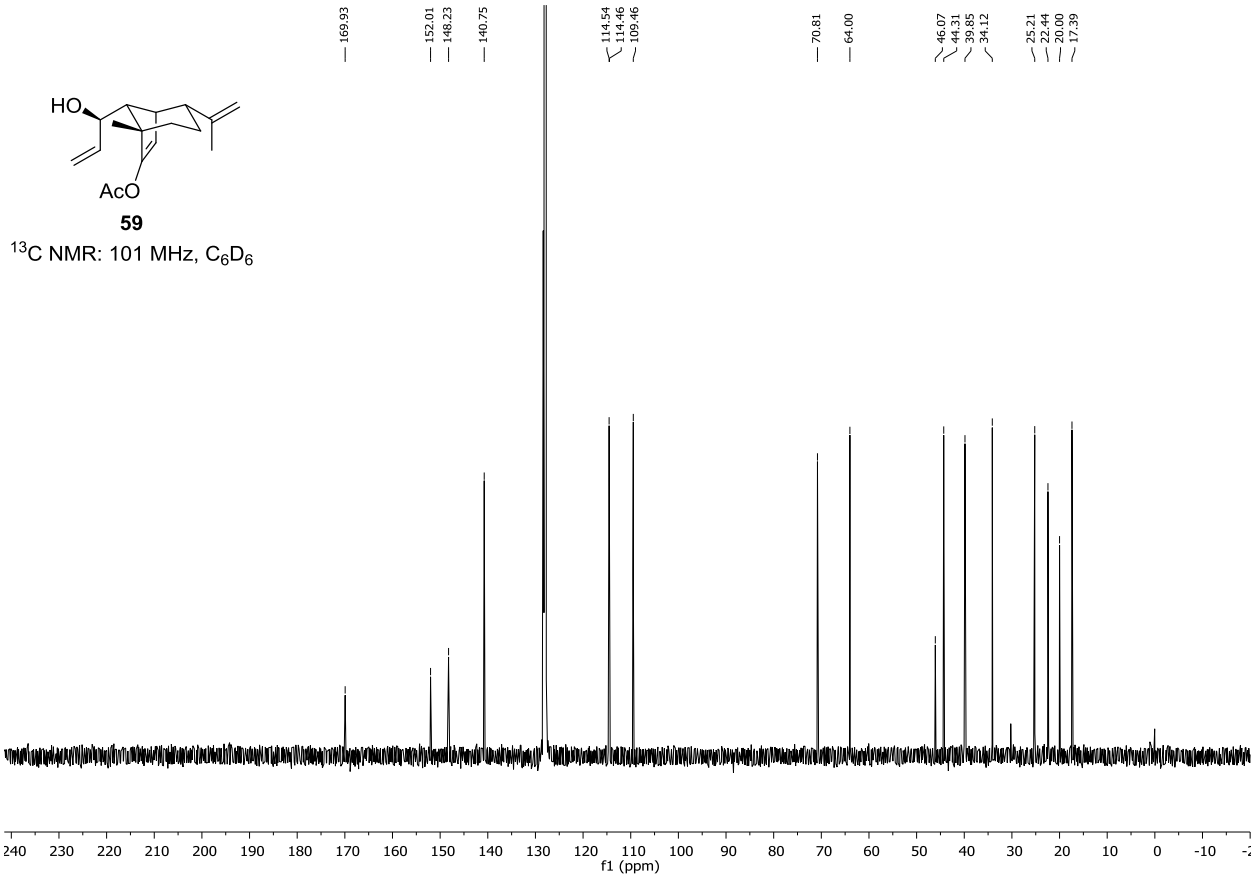

**57**

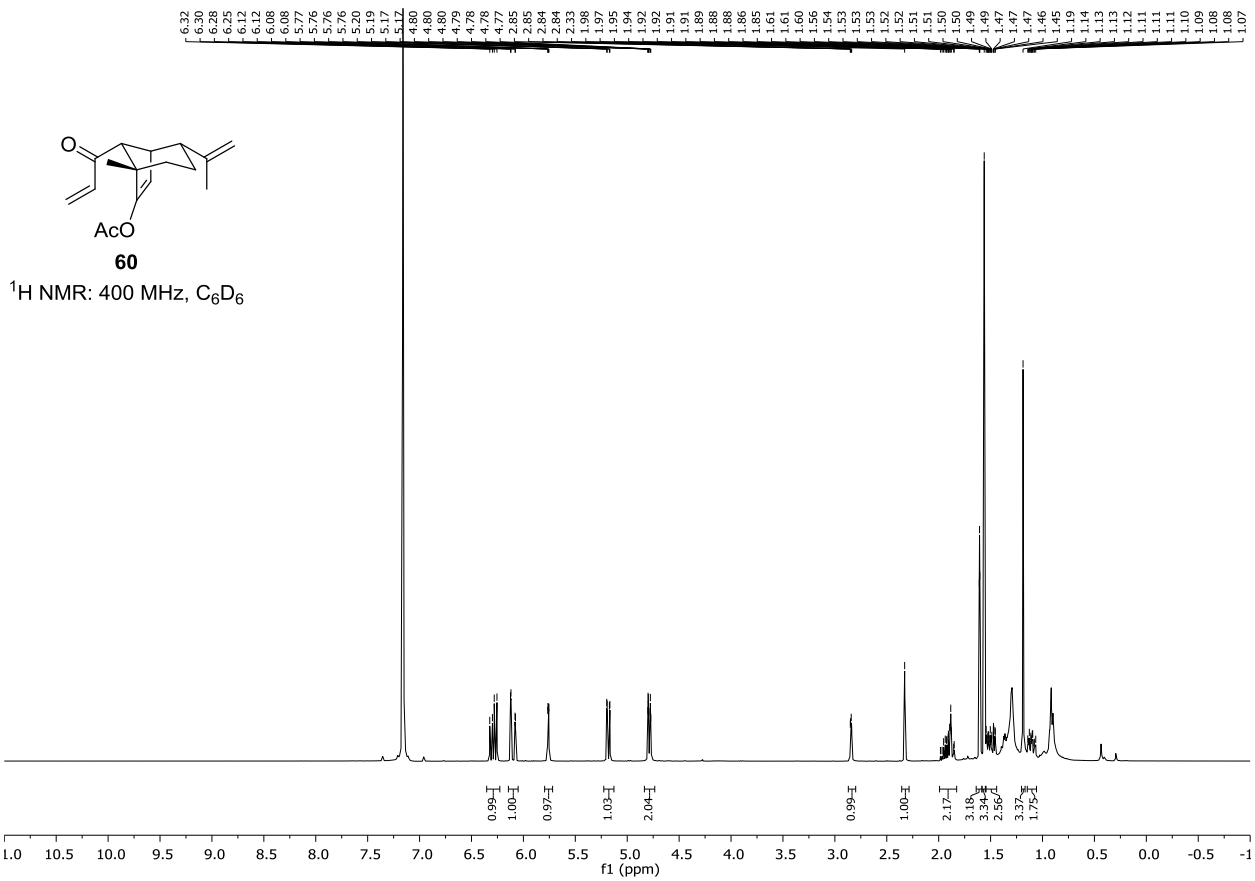
$^{13}$C NMR: 101 MHz, $CDCl_3$


TBSO
AcO
58
1H NMR: 400 MHz, C6D6
f1 (ppm)


TBSO
AcO
58
13C NMR: 101 MHz, C6D6
f1 (ppm)

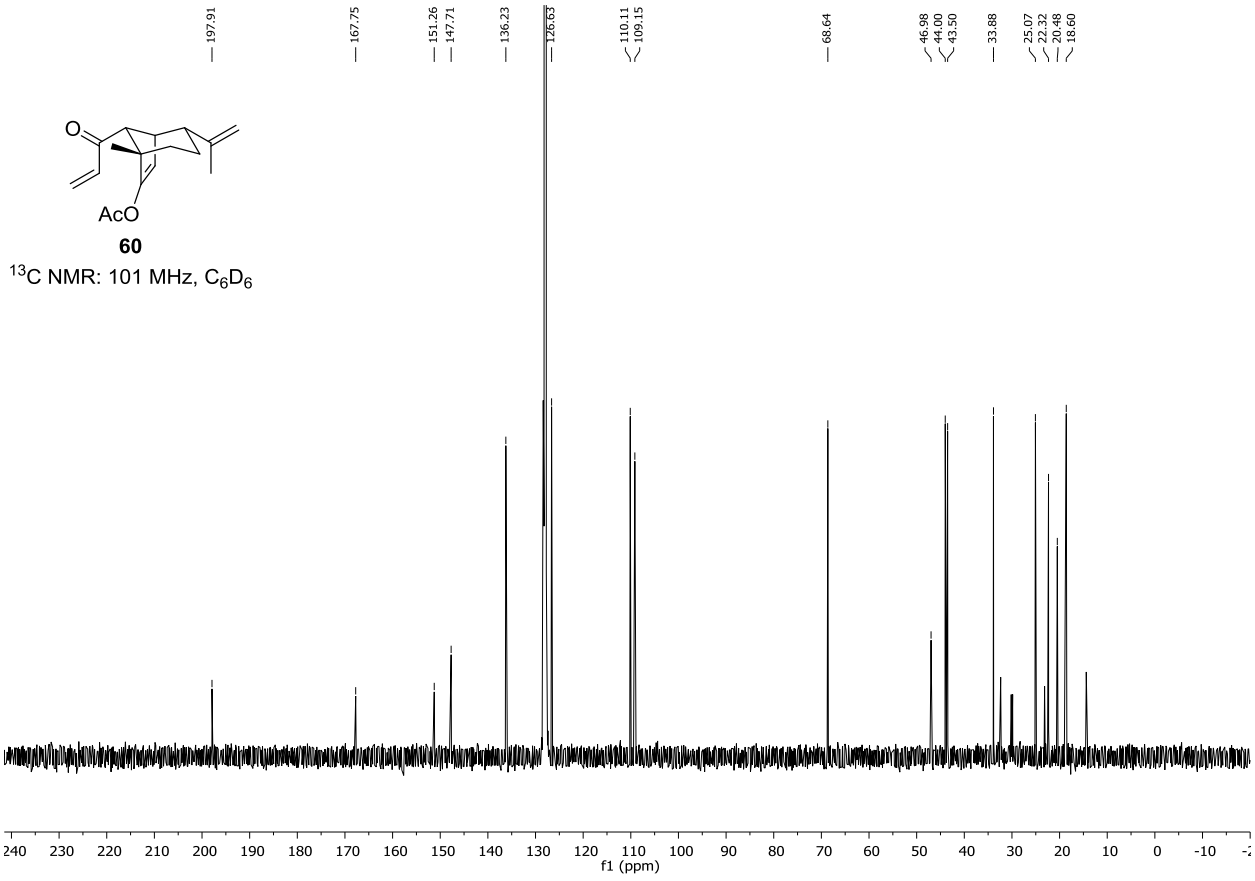

HO
AcO
59
1H NMR: 400 MHz, C6D6
f1 (ppm)


HO
AcO
59
13C NMR: 101 MHz, C6D6
169.93
152.01
148.23
140.75
114.54
114.46
109.46
70.81
64.00
46.07
44.31
39.85
34.12
25.21
22.44
20.00
17.39
f1 (ppm)



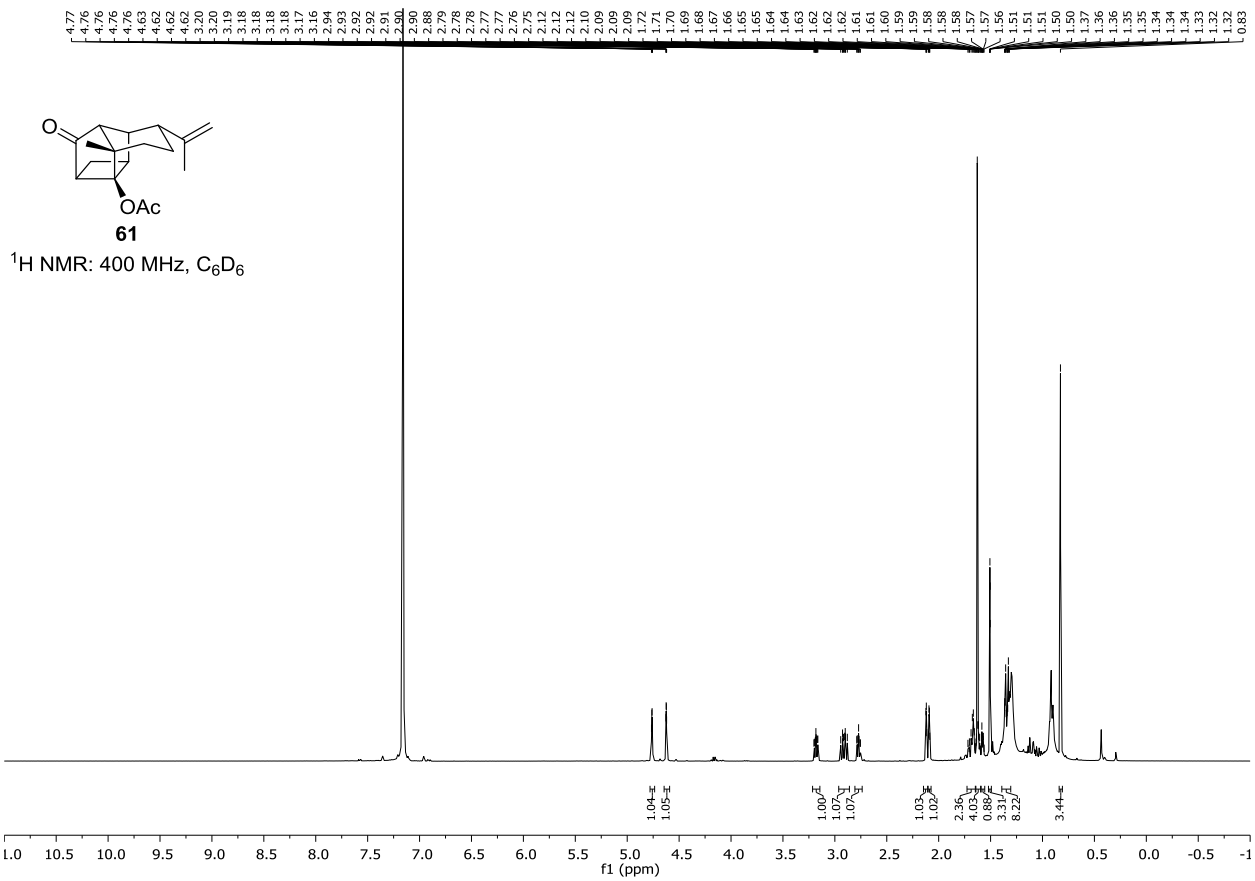

**60**

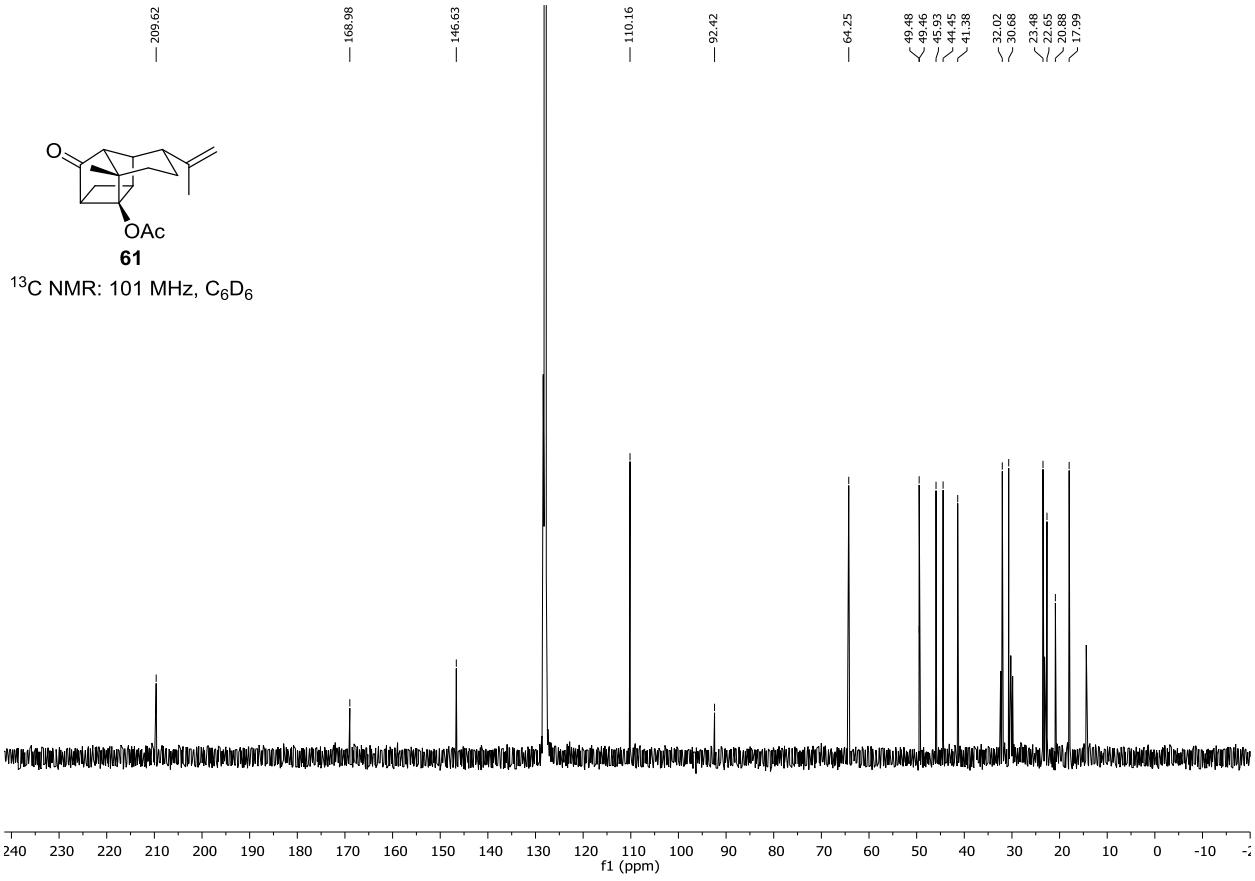
$^{1}$H NMR: 400 MHz, $C_6D_6$

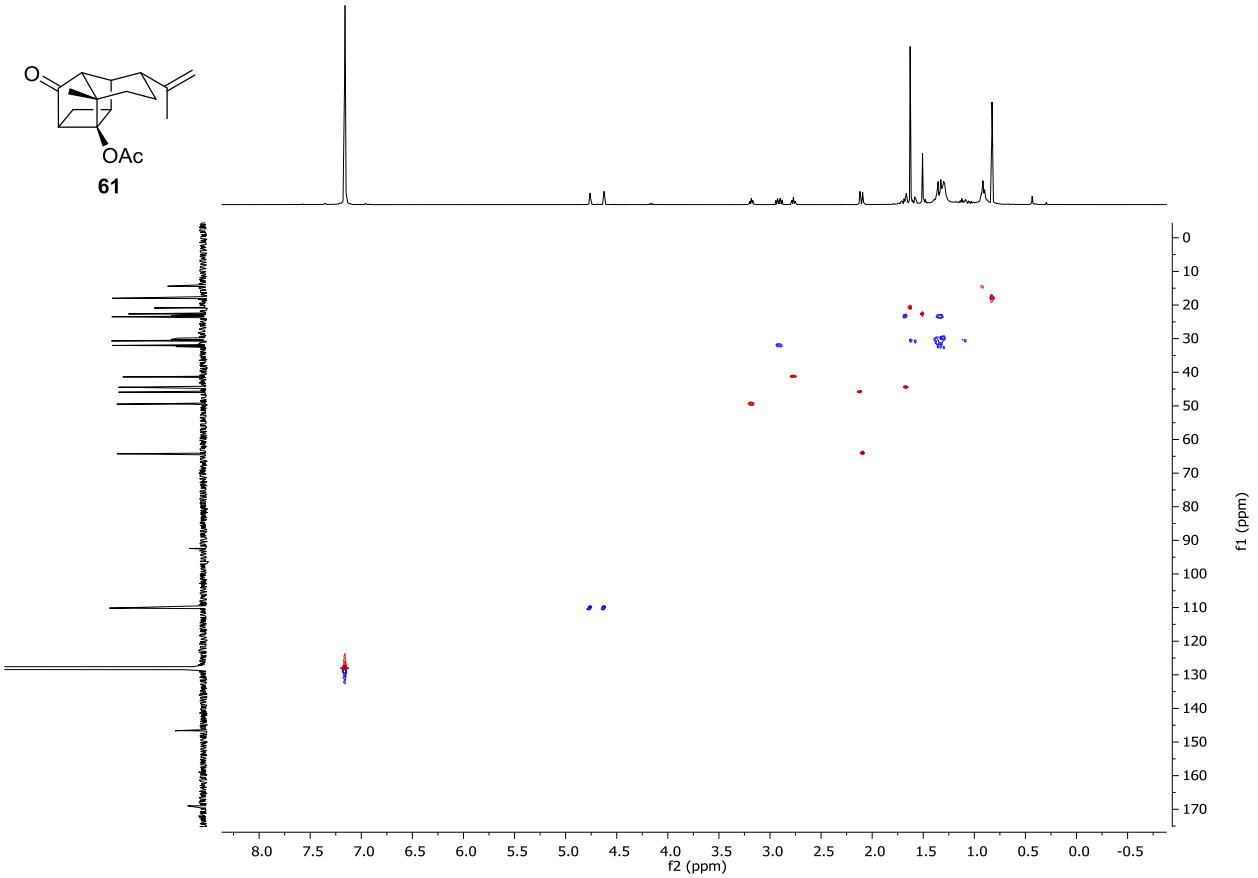


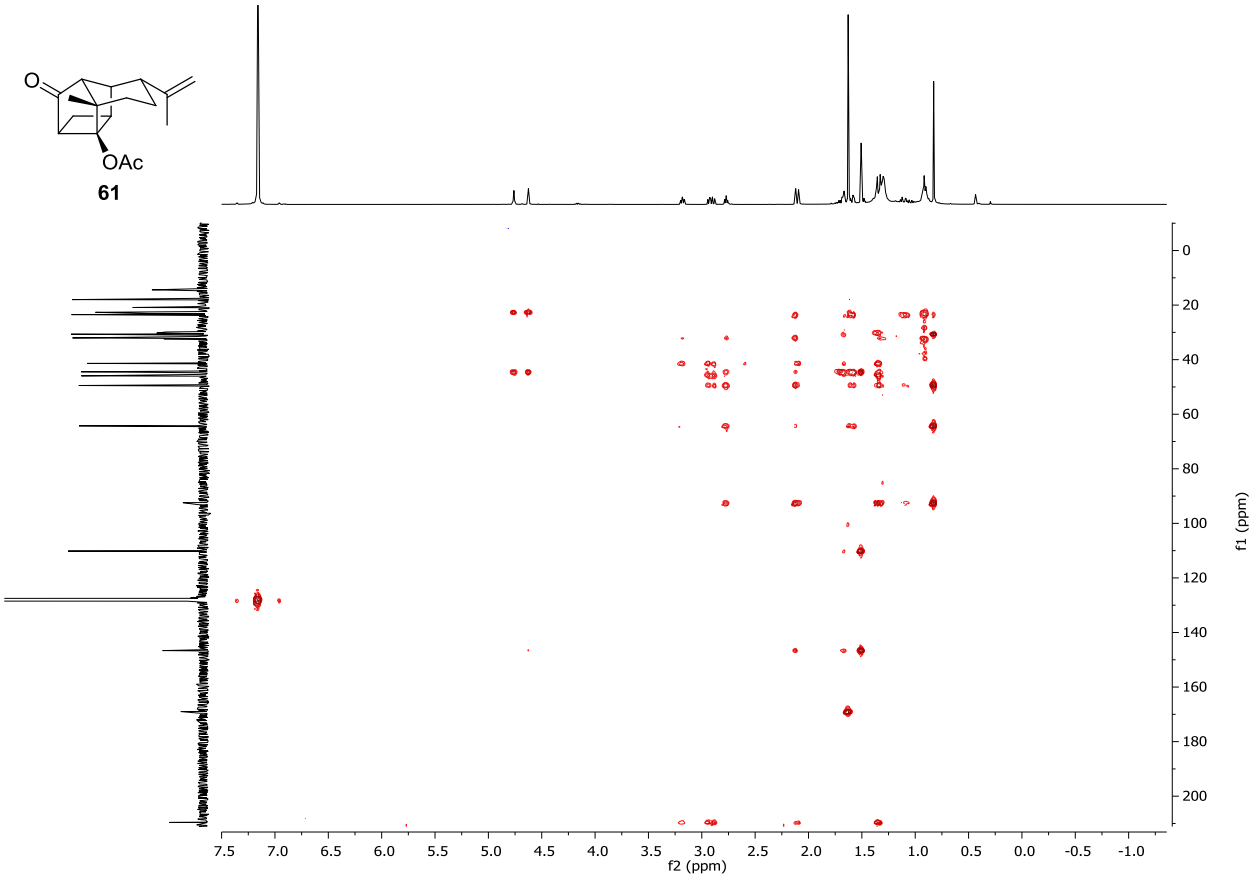

**60**

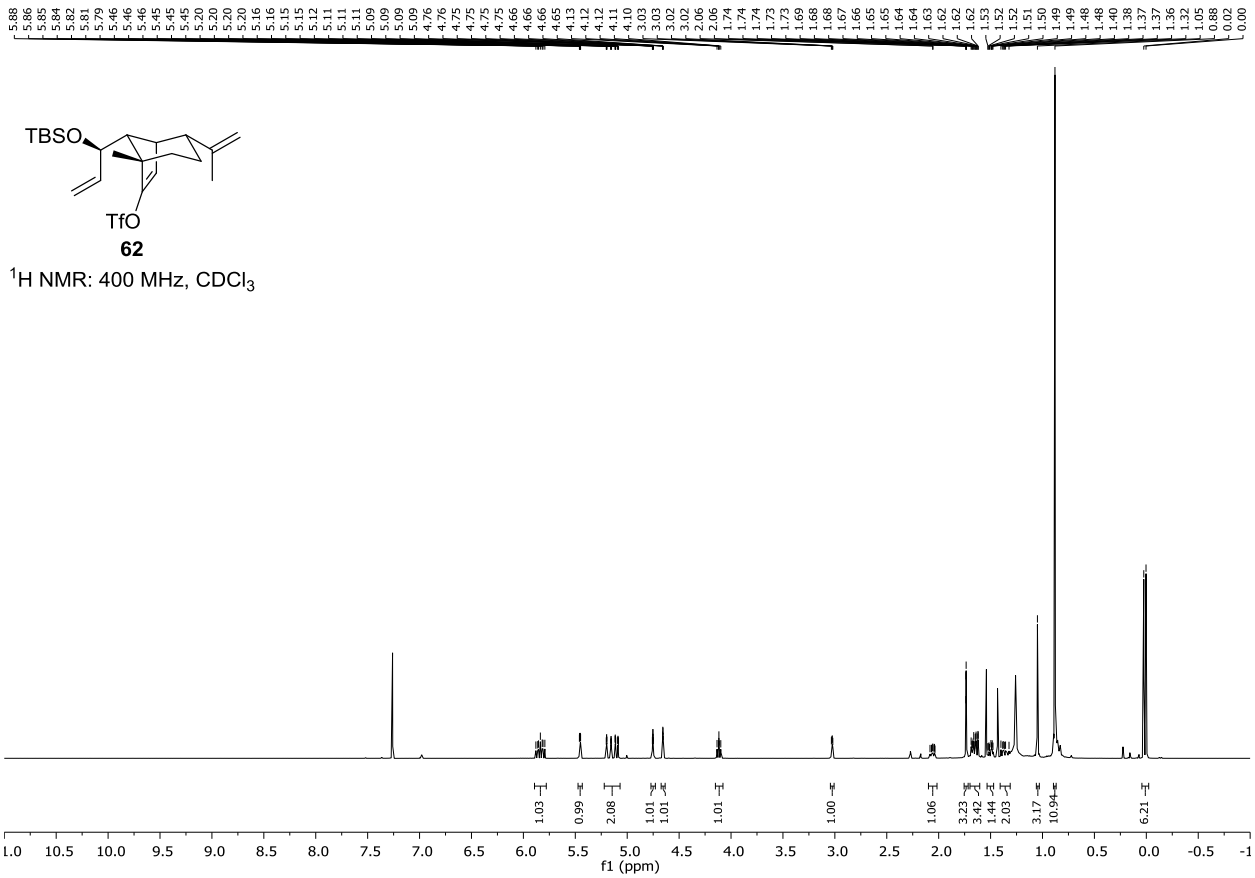
$^{13}$C NMR: 101 MHz, $C_6D_6$


OAc
61
1H NMR: 400 MHz, C6D6
f1 (ppm)


OAc
61
13C NMR: 101 MHz, C6D6
f1 (ppm)

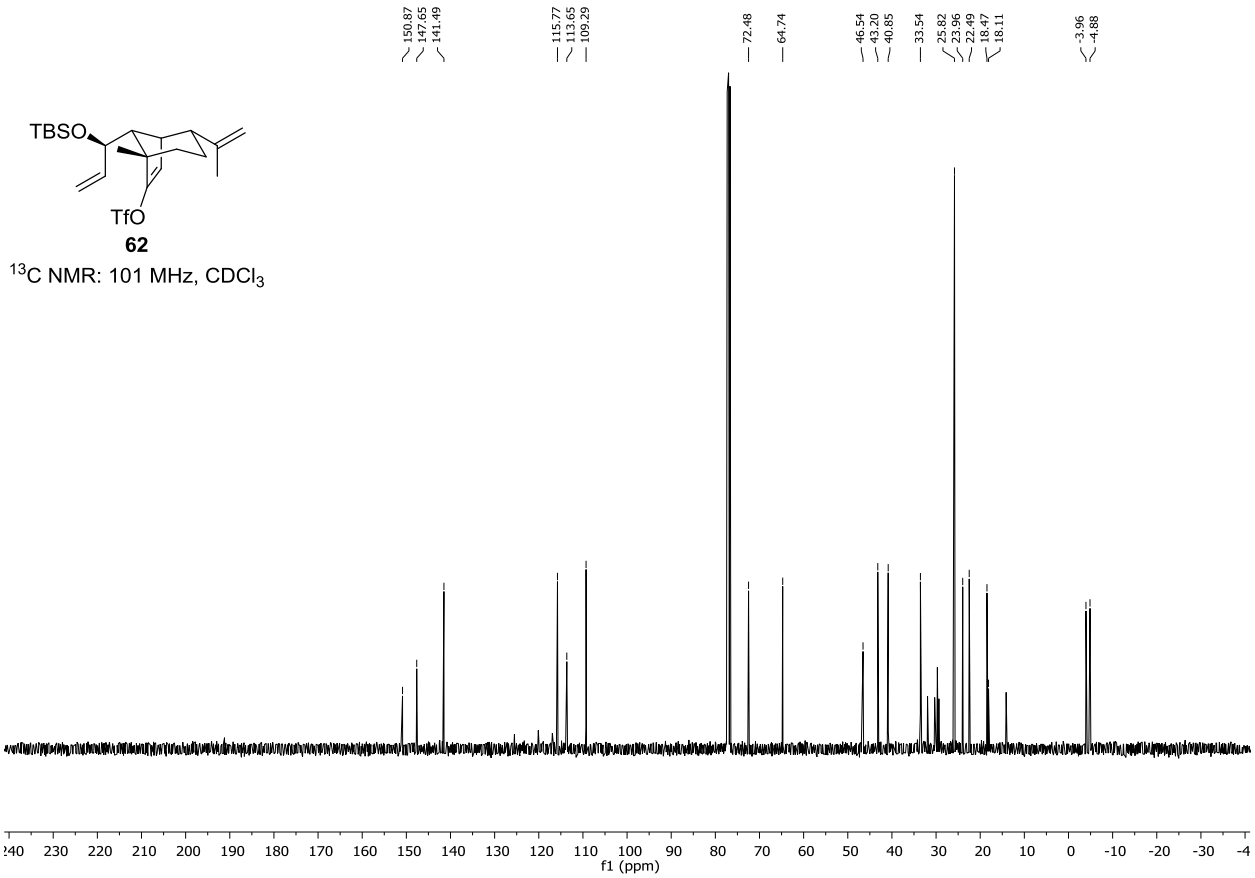

O
OAc
61
f2 (ppm)
f1 (ppm)


O
OAc
61
f2 (ppm)
f1 (ppm)



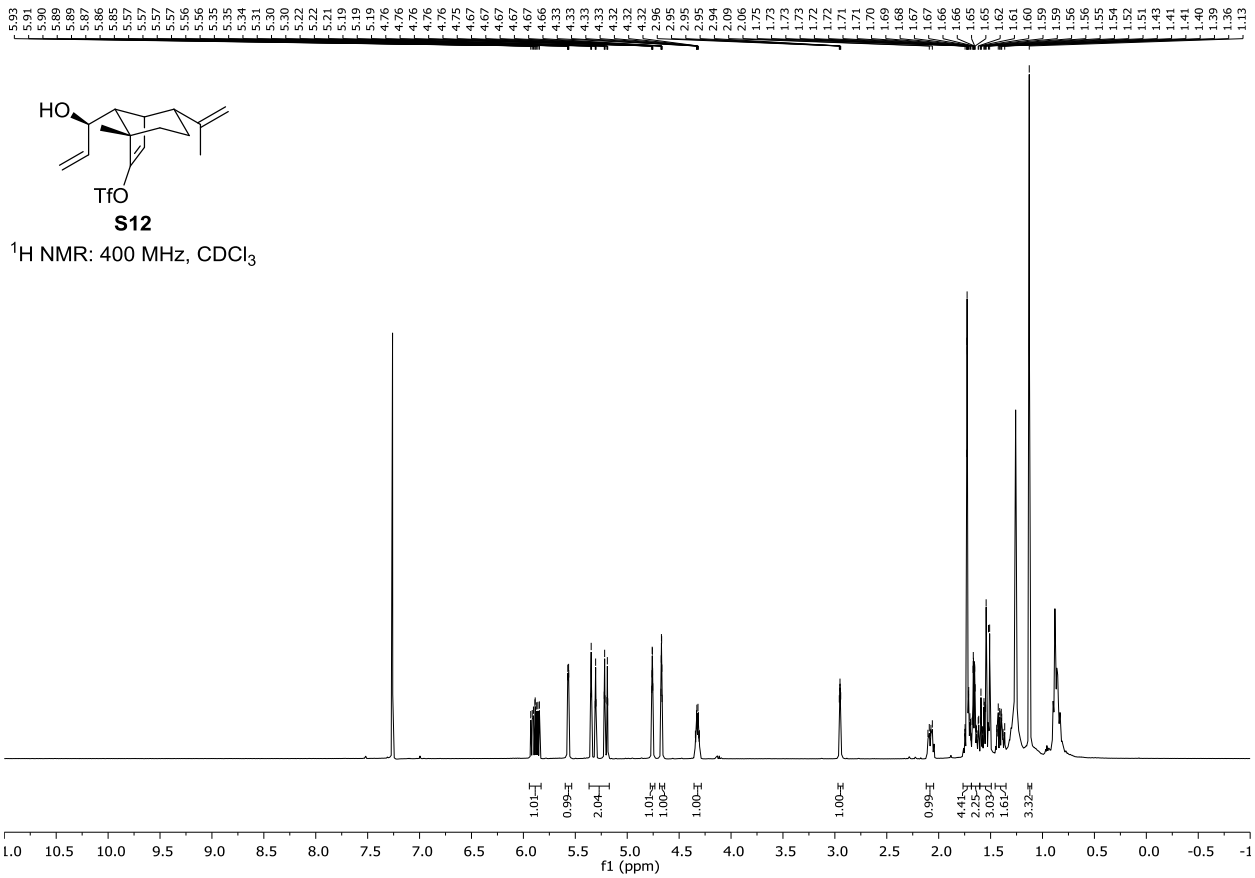

**62**

$^{1}$H NMR: 400 MHz, $CDCl_3$



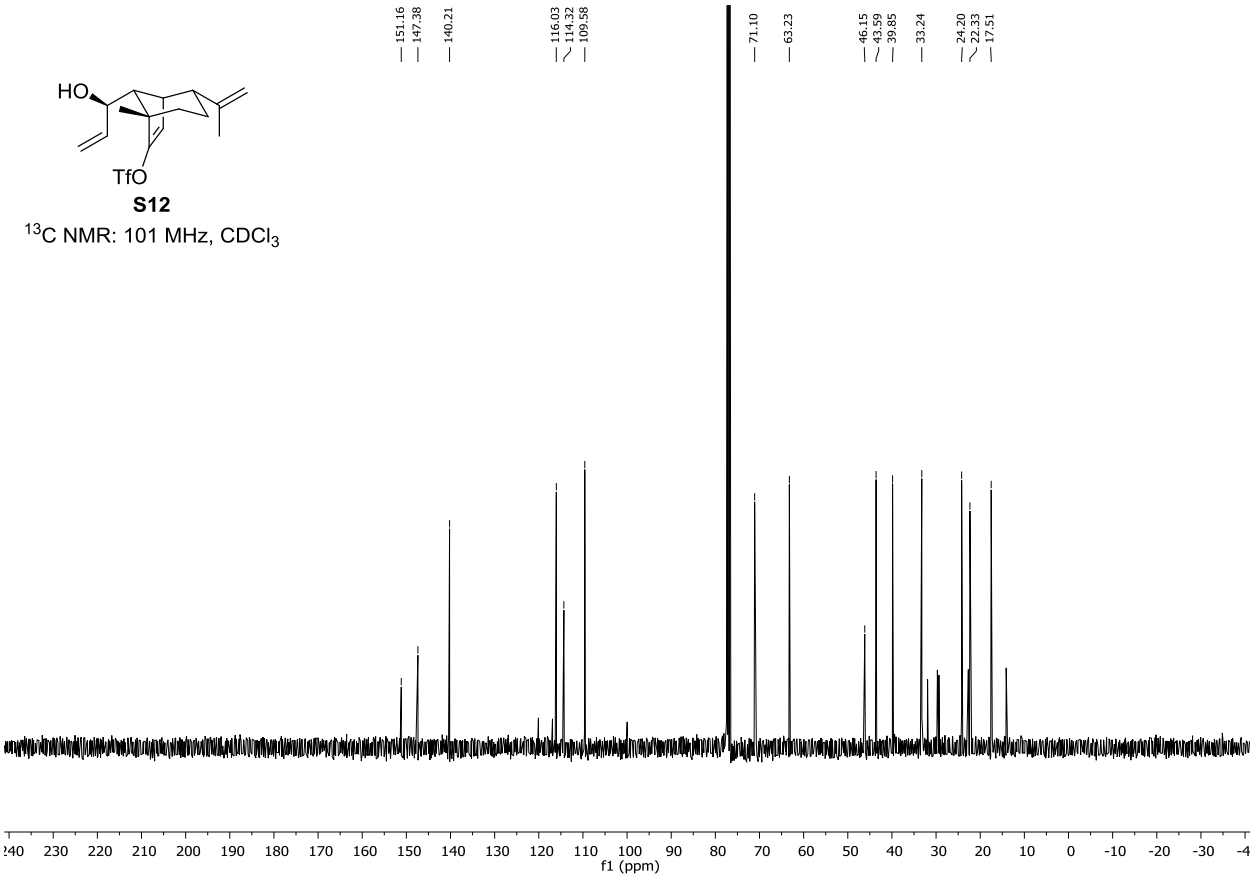

**62**

$^{13}$C NMR: 101 MHz, $CDCl_3$



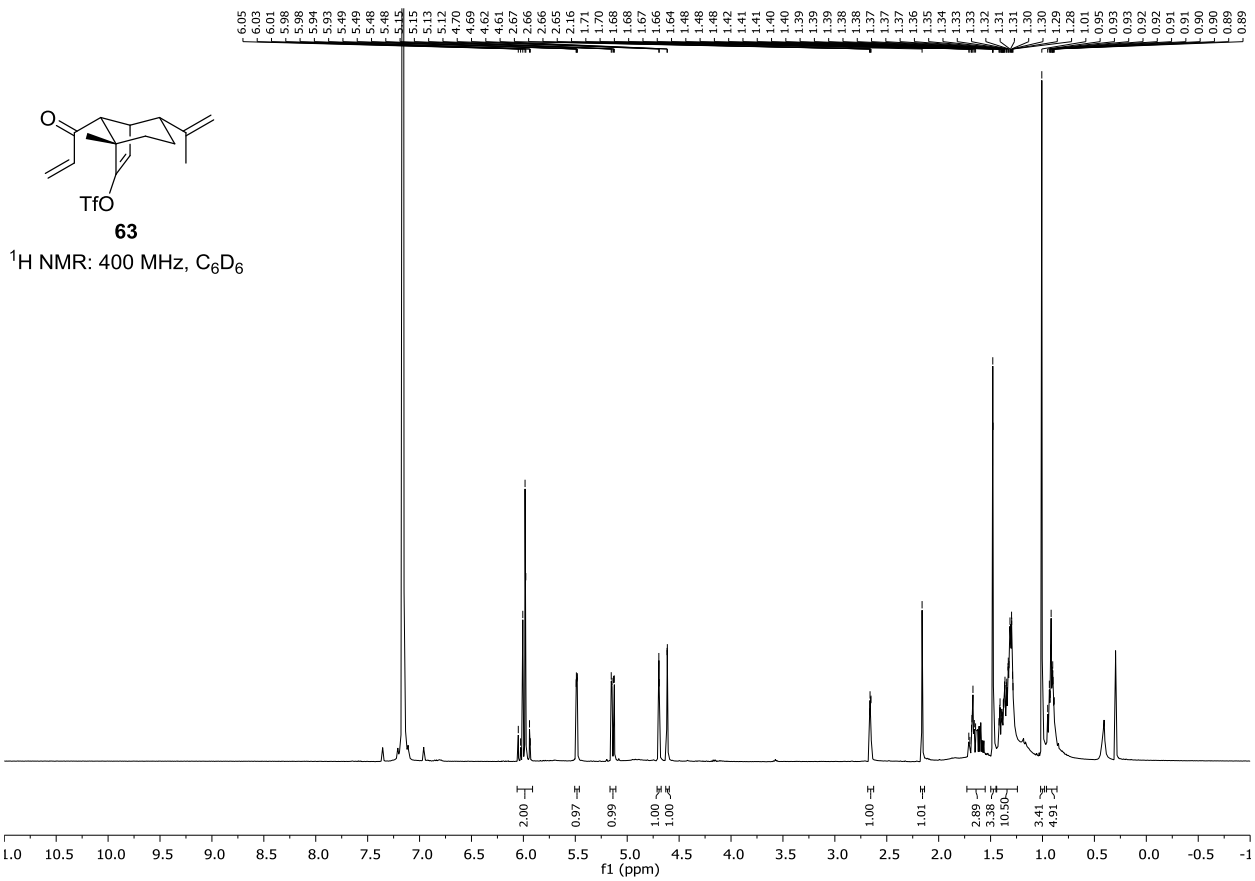

**S12**

$^{1}$H NMR: 400 MHz, $CDCl_3$



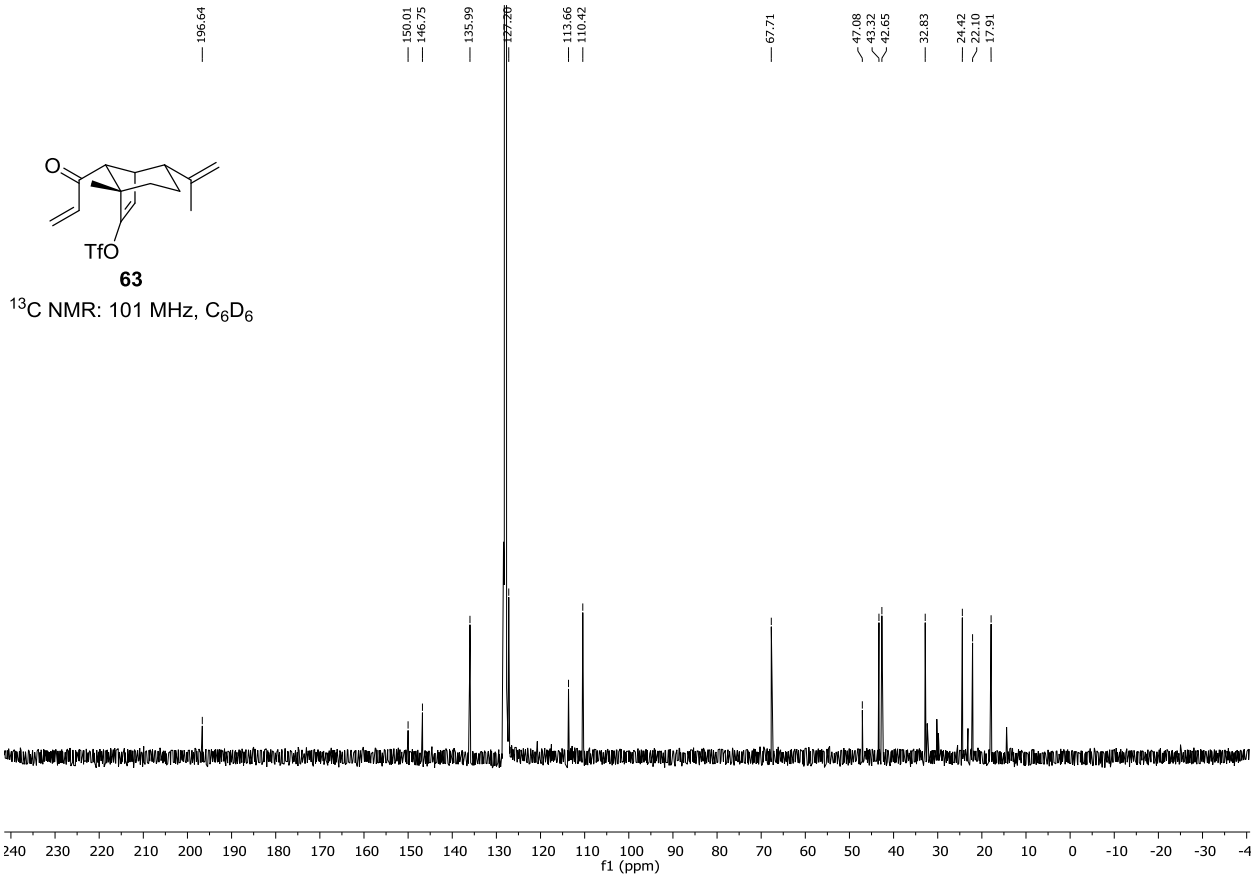

**S12**

$^{13}$C NMR: 101 MHz, $CDCl_3$



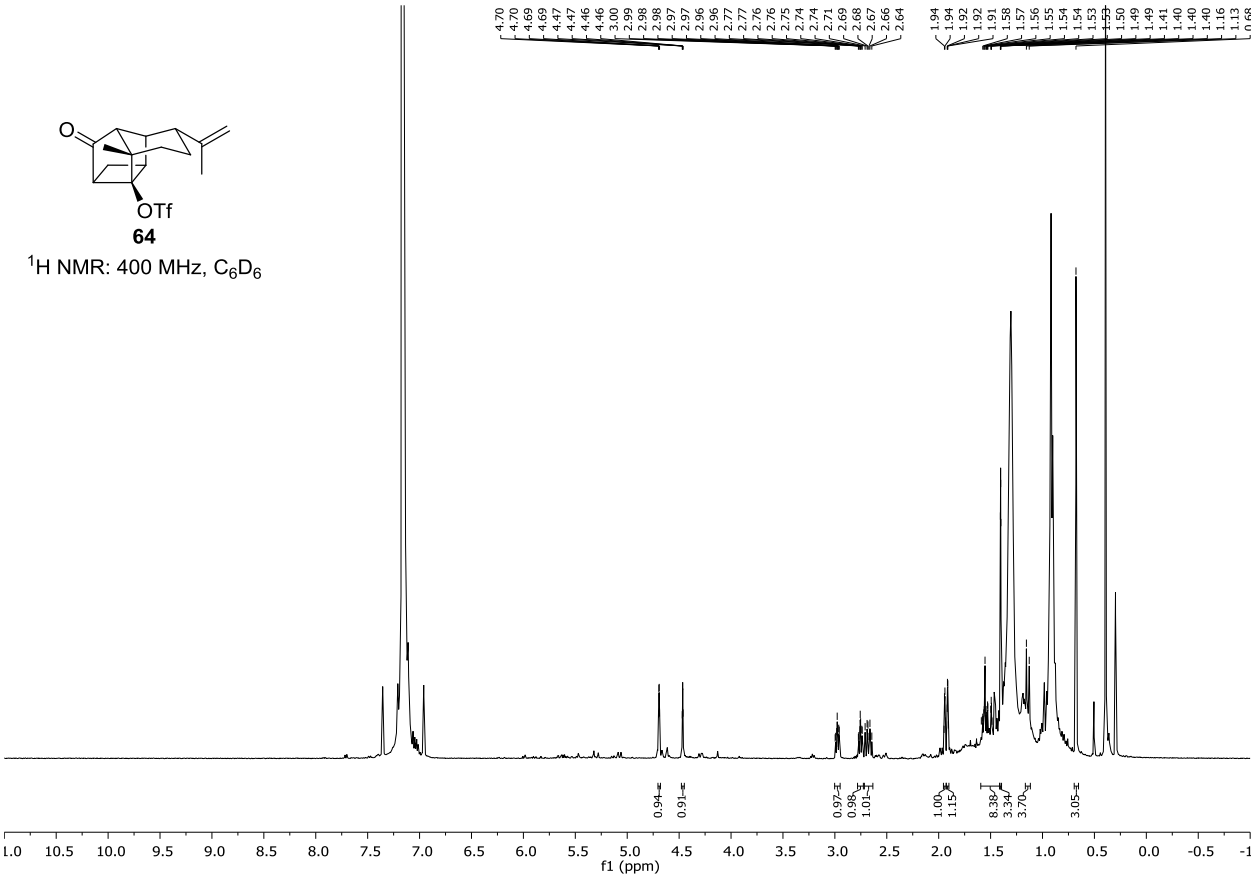

**63**

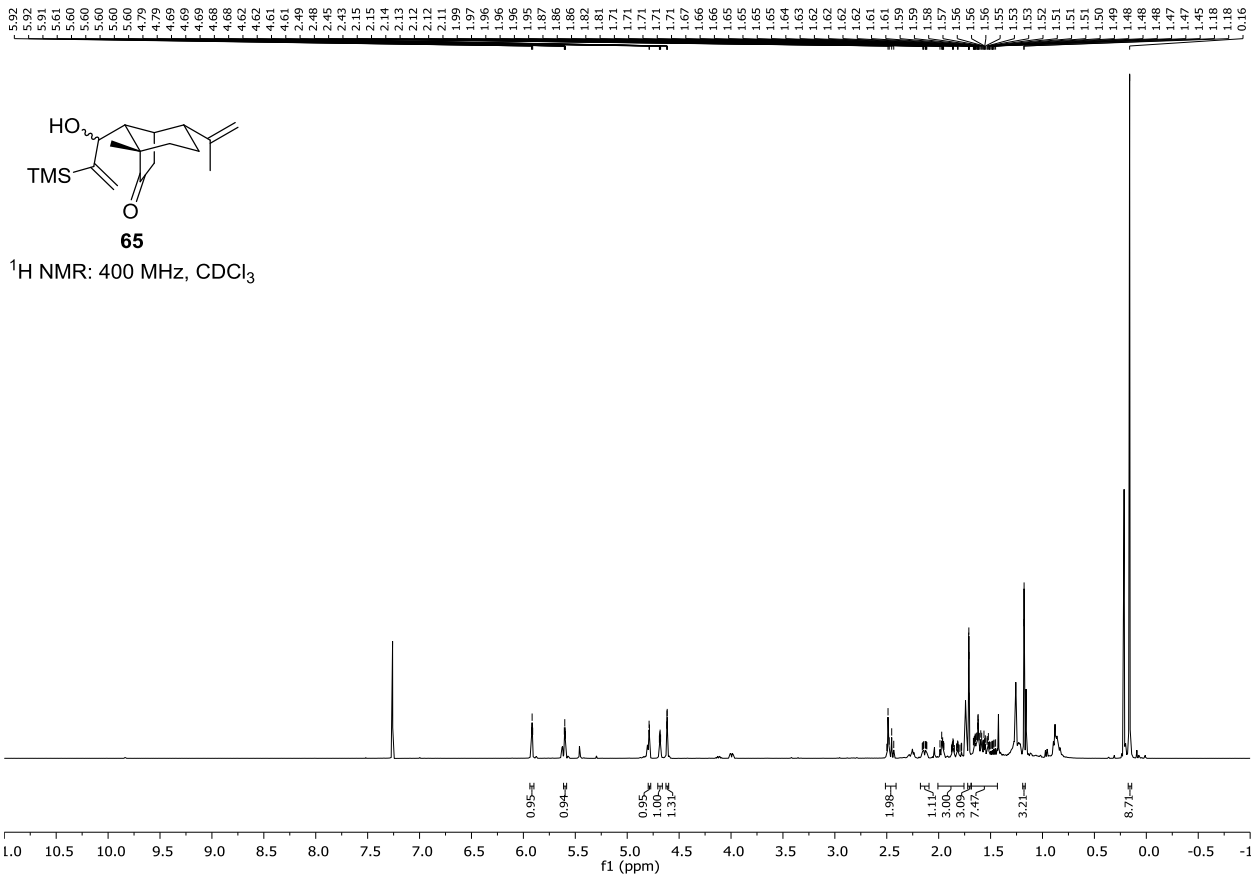
$^{1}$H NMR: 400 MHz, $C_6D_6$

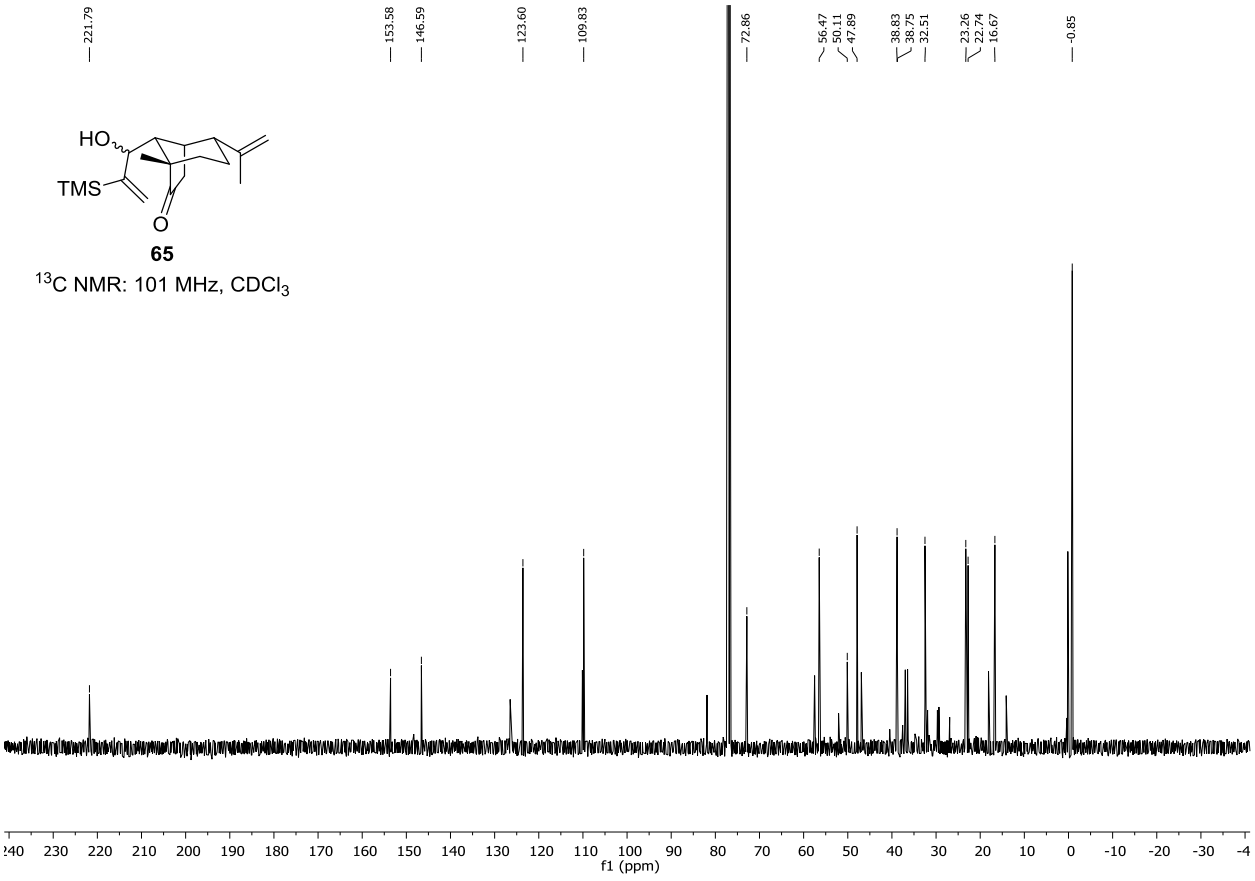


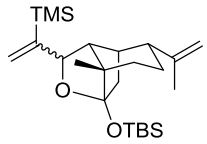

**63**

$^{13}$C NMR: 101 MHz, $C_6D_6$


O
OTf
64
1H NMR: 400 MHz, C6D6
f1 (ppm)


HO
TMS
O
65
1H NMR: 400 MHz, CDCl3
f1 (ppm)

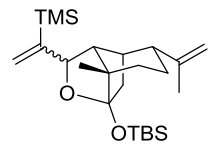

HO
TMS
O
65
13C NMR: 101 MHz, CDCl3
f1 (ppm)




**66**

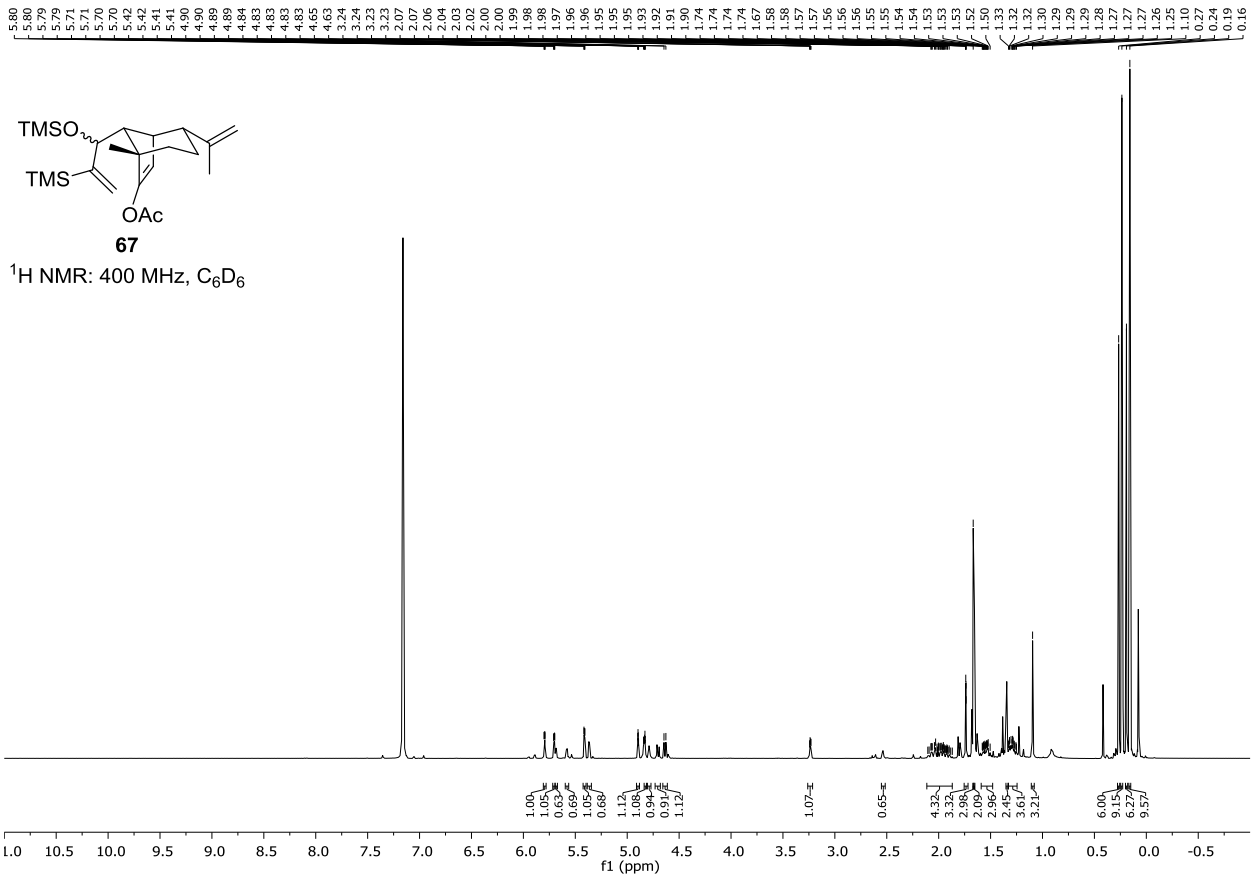
$^{1}$H NMR: 400 MHz, $CDCl_3$

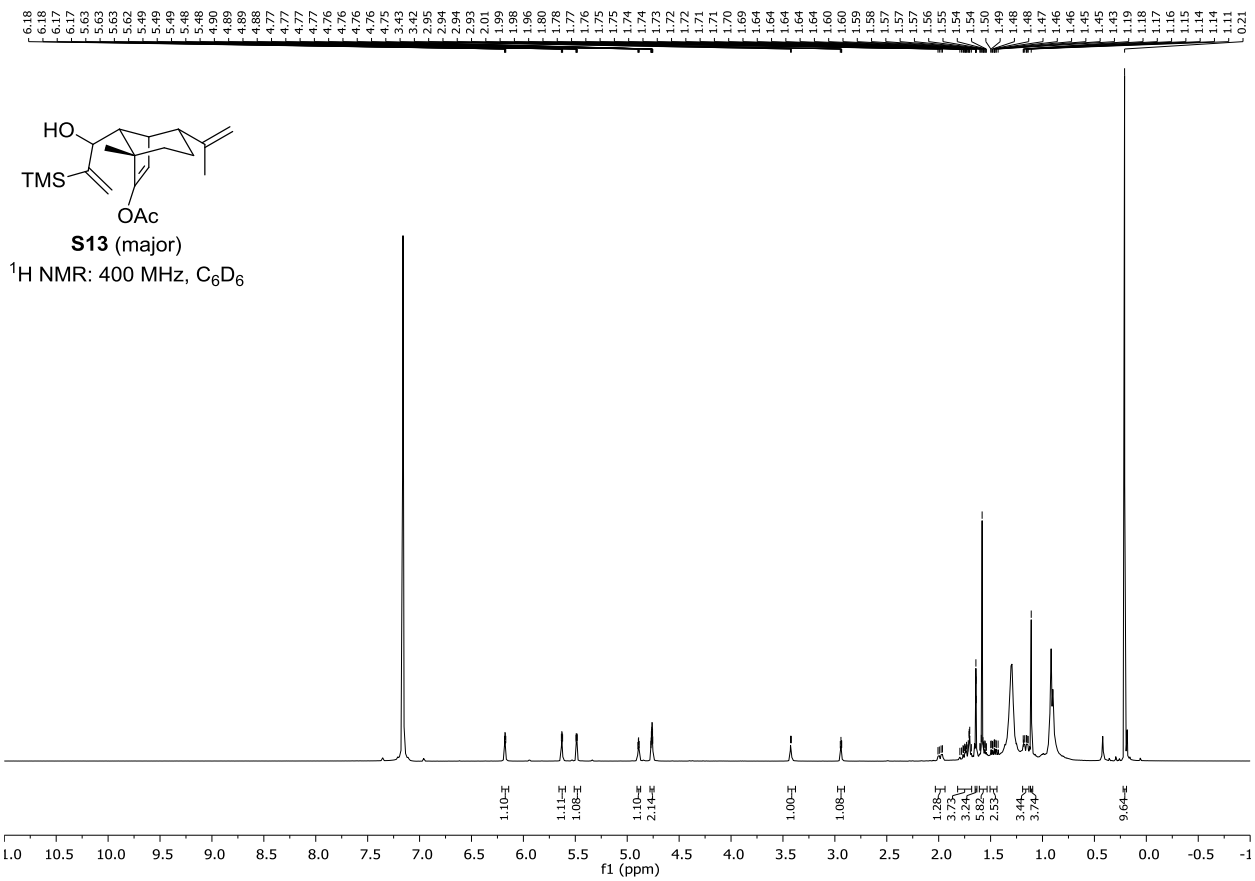


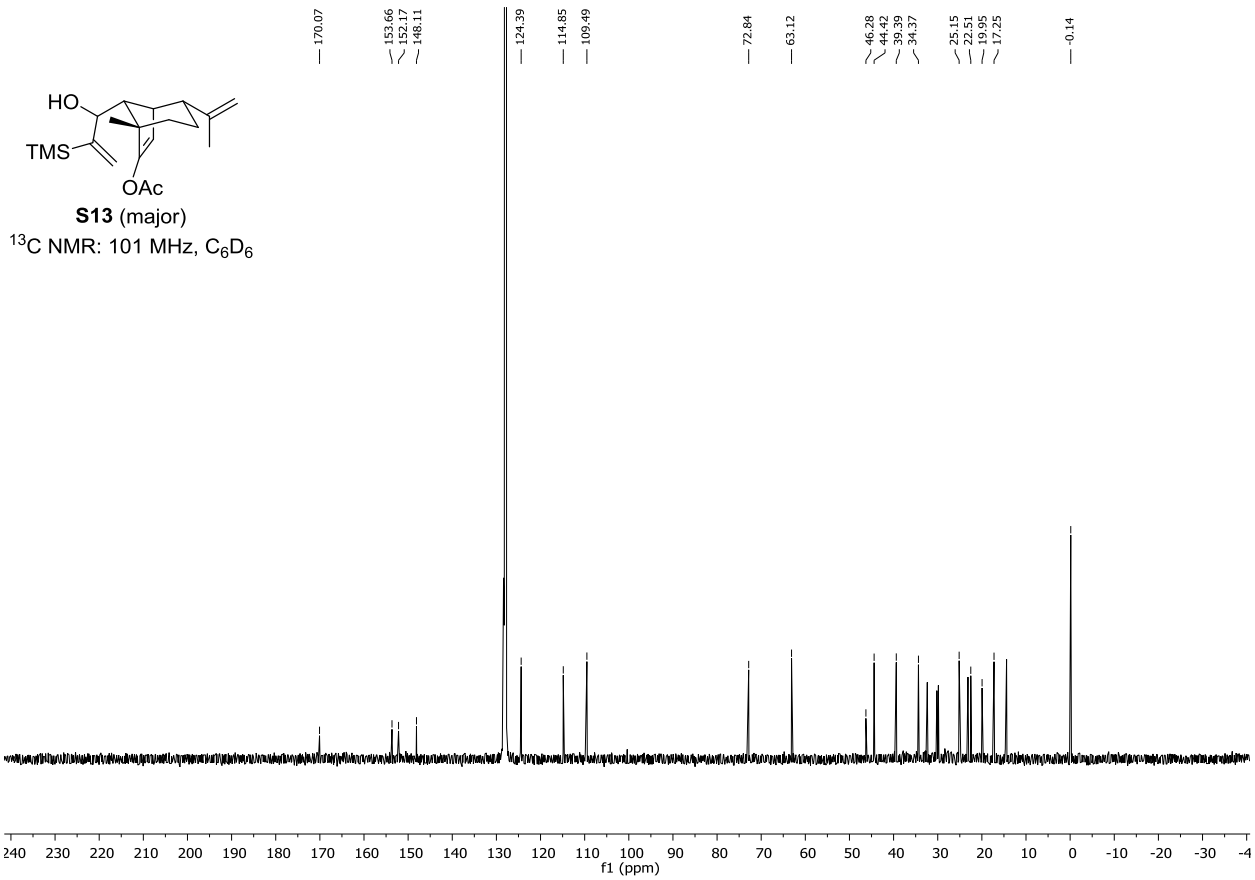

**66**

$^{13}$C NMR: 101 MHz, $CDCl_3$

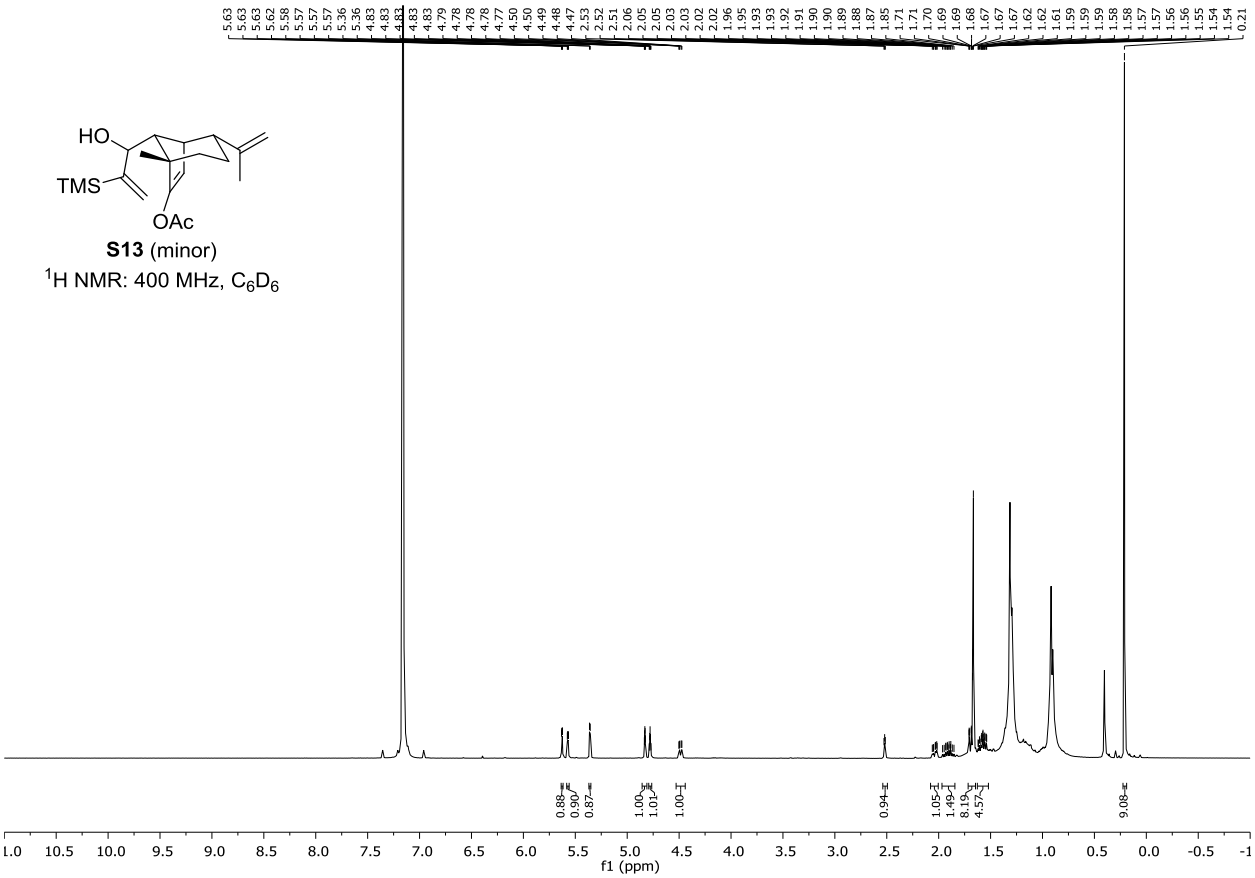

TMSO
TMS
OAc
67
1H NMR: 400 MHz, C6D6
f1 (ppm)




**S13** (major)
$^{1}$H NMR: 400 MHz, $C_6D_6$

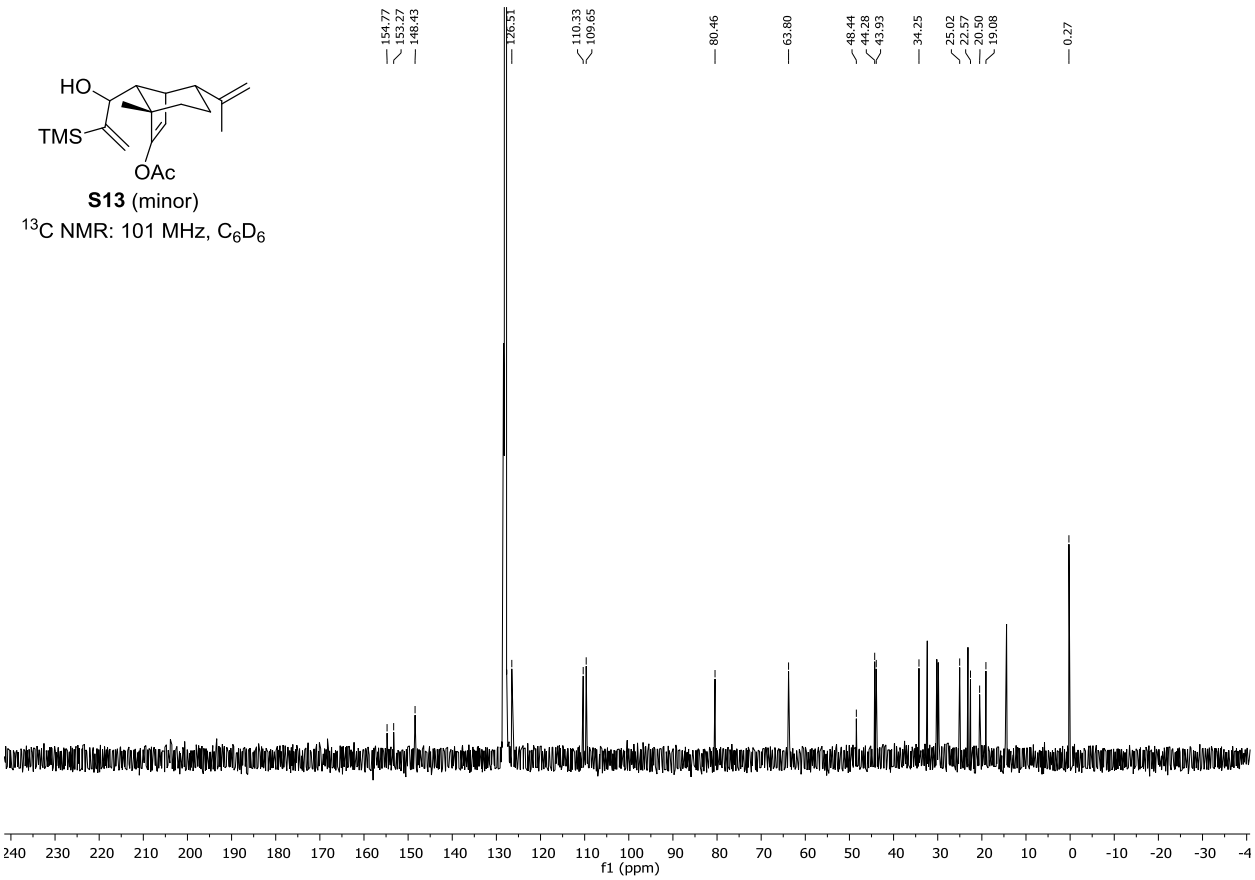



**S13** (major)
$^{13}$C NMR: 101 MHz, $C_6D_6$



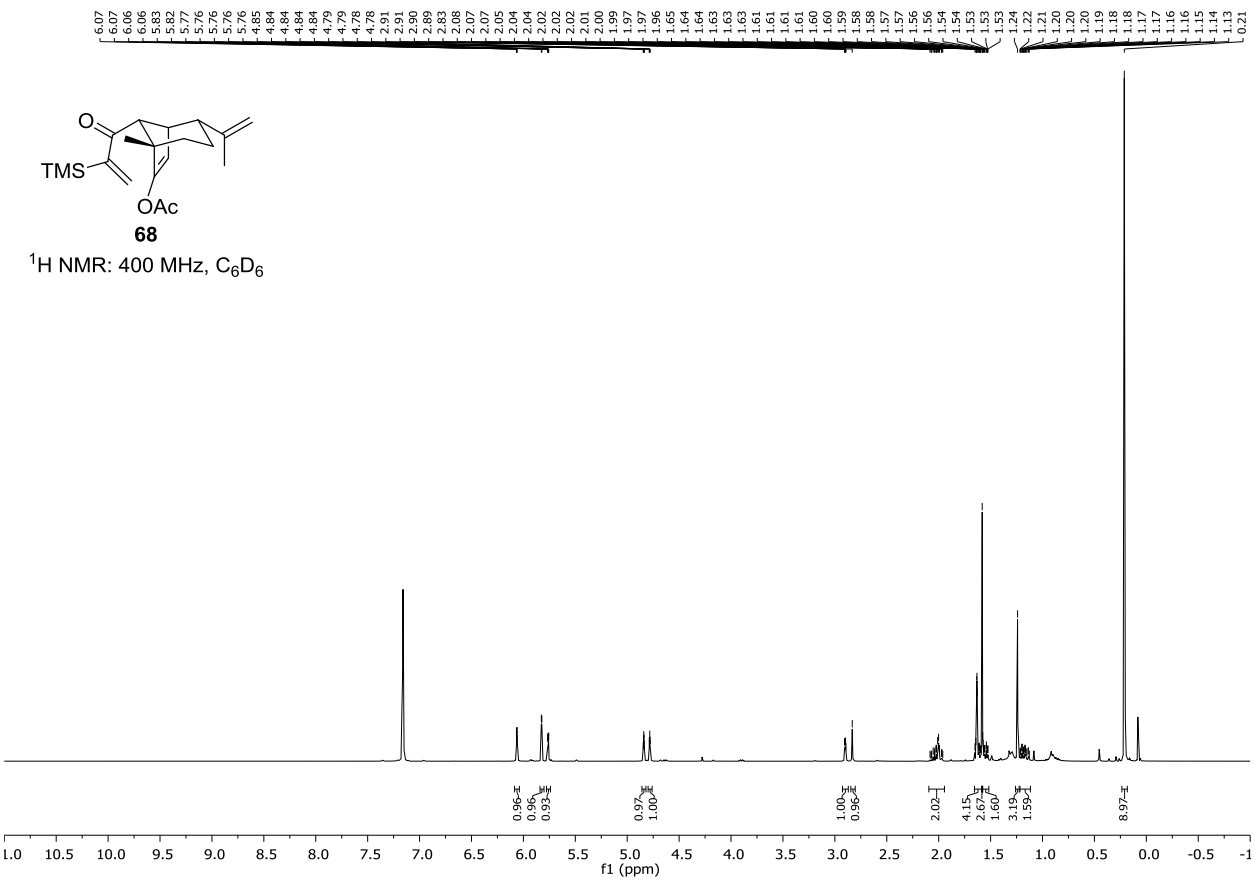

**S13** (minor)

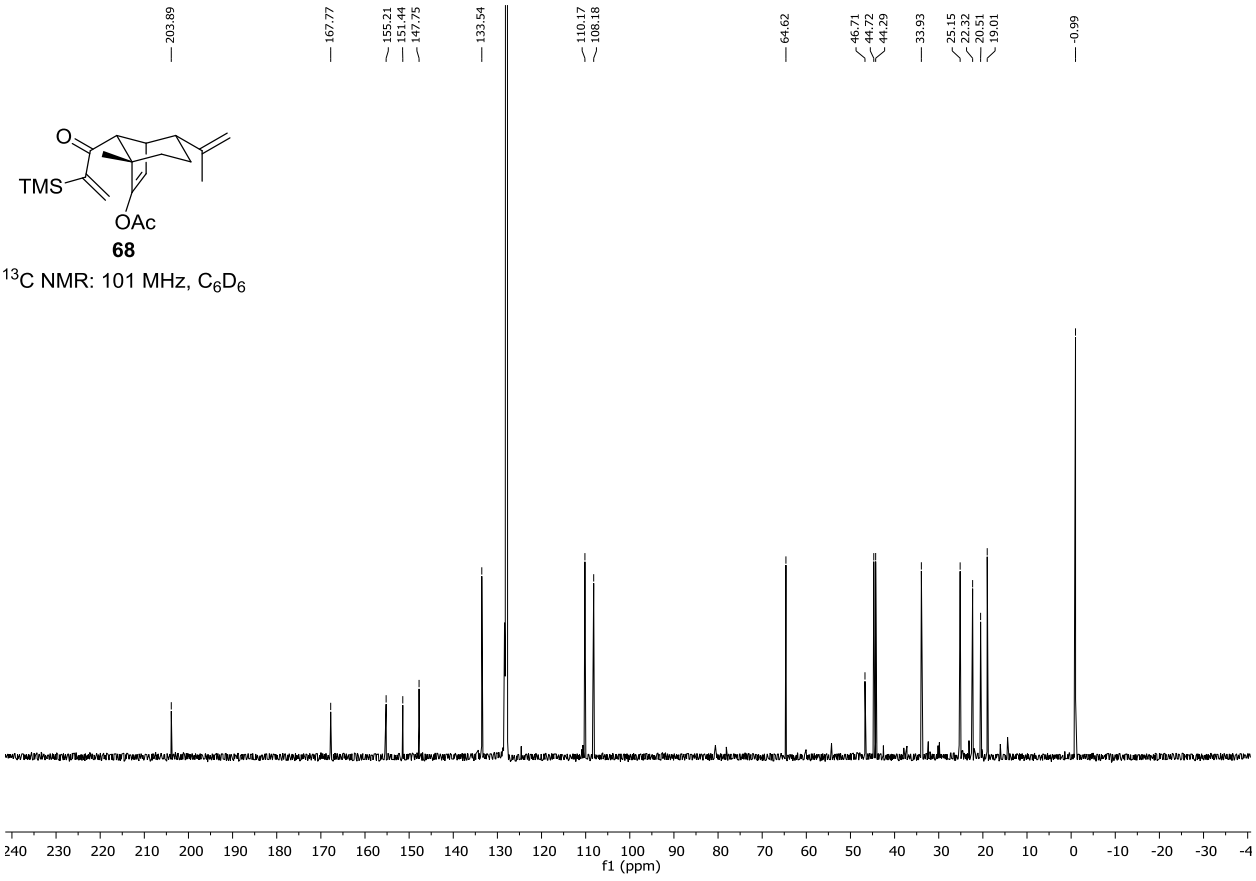
$^{1}$H NMR: 400 MHz, $C_6D_6$

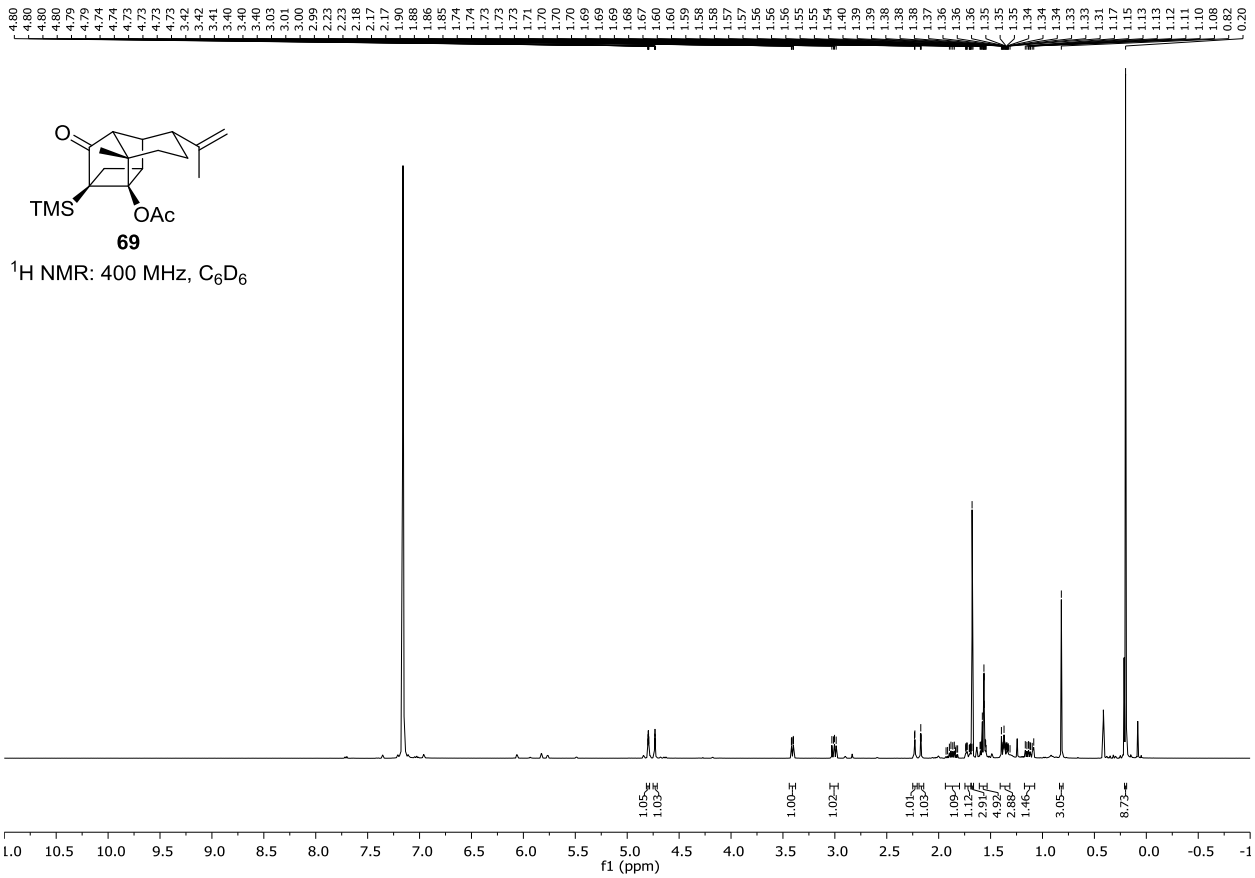


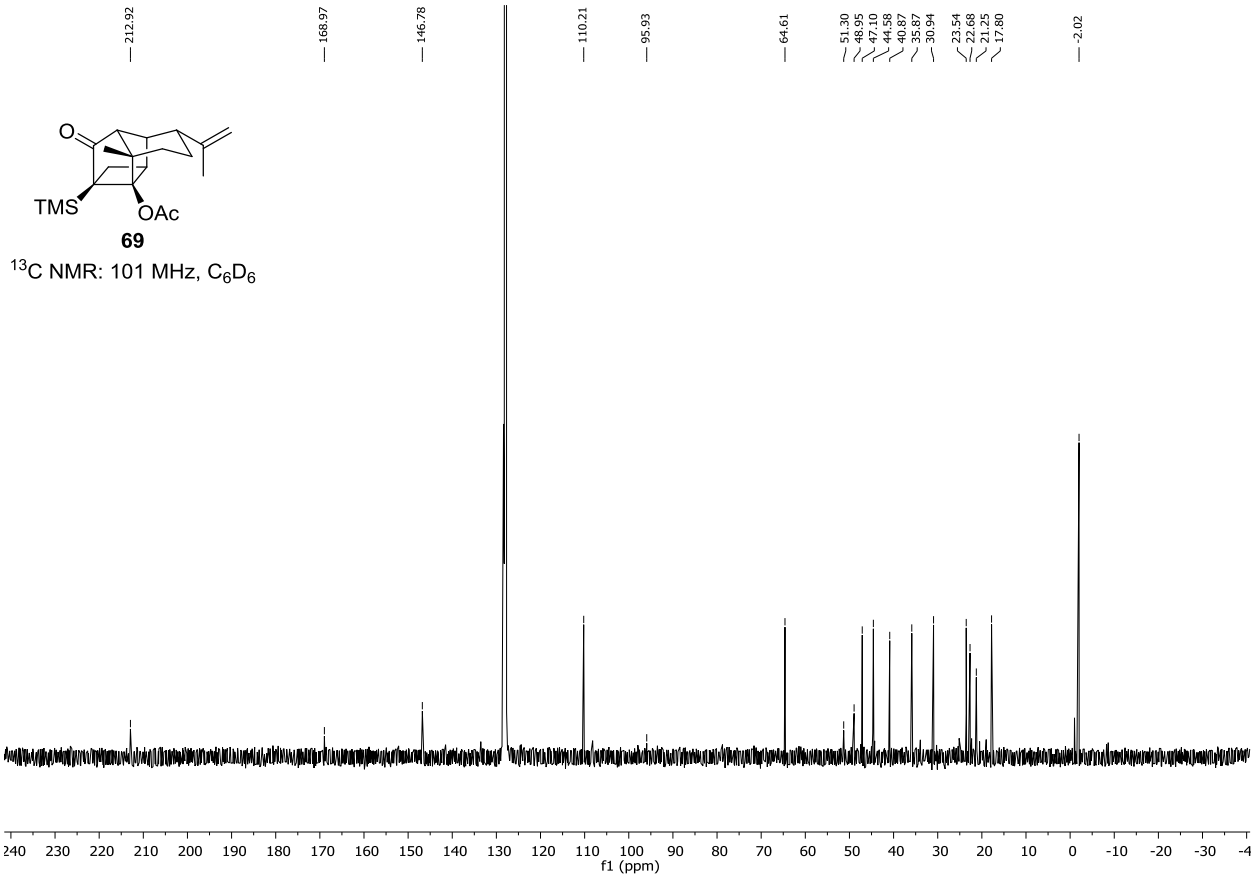

**S13** (minor)

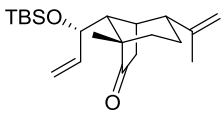
$^{13}$C NMR: 101 MHz, $C_6D_6$


TMS
OAc
68
1H NMR: 400 MHz, C6D6
f1 (ppm)


TMS
OAc
68
13C NMR: 101 MHz, C6D6
f1 (ppm)


TMS
OAc
69
1H NMR: 400 MHz, C6D6
f1 (ppm)

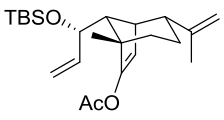

TMS
OAc
69
13C NMR: 101 MHz, C6D6
f1 (ppm)




**S14**

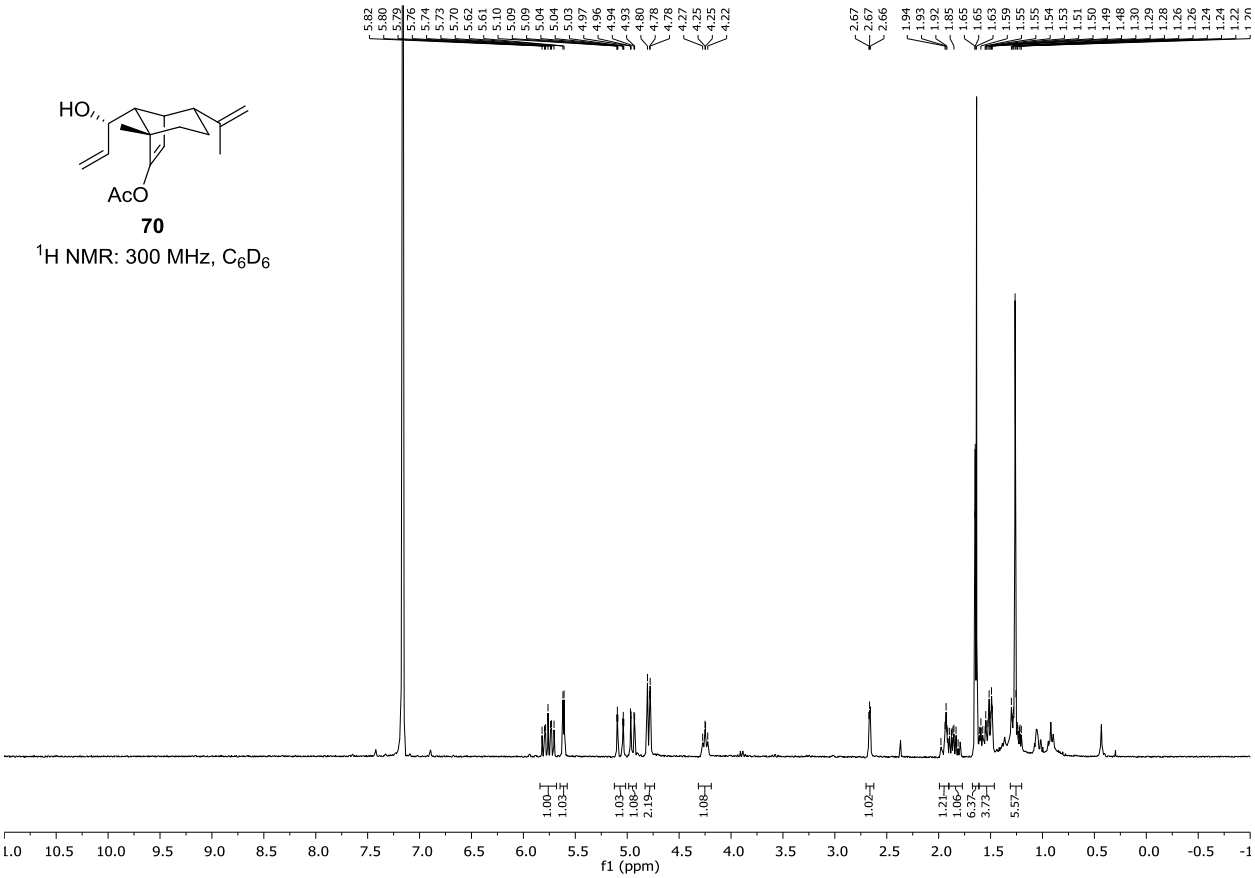
$^1$H NMR: 300 MHz, $CDCl_3$

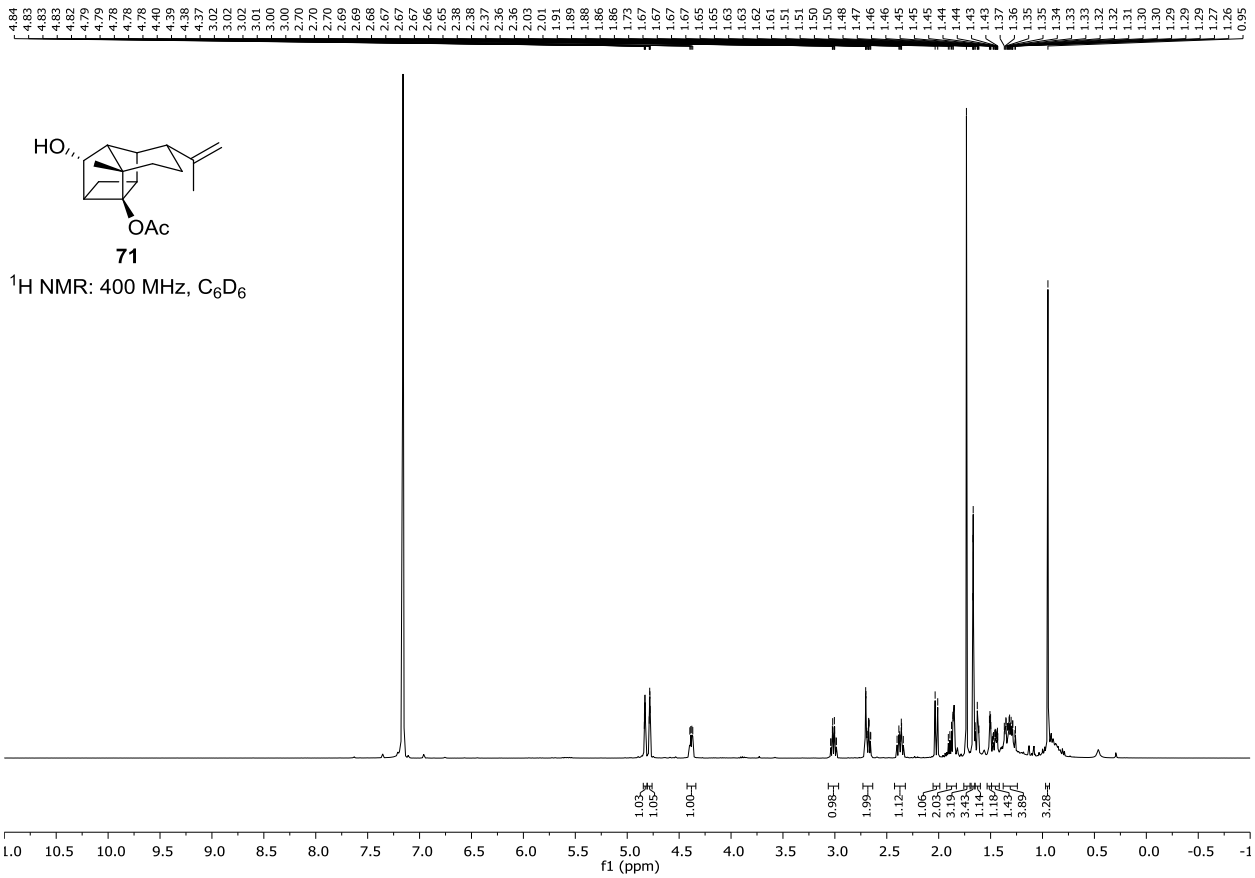



**73**

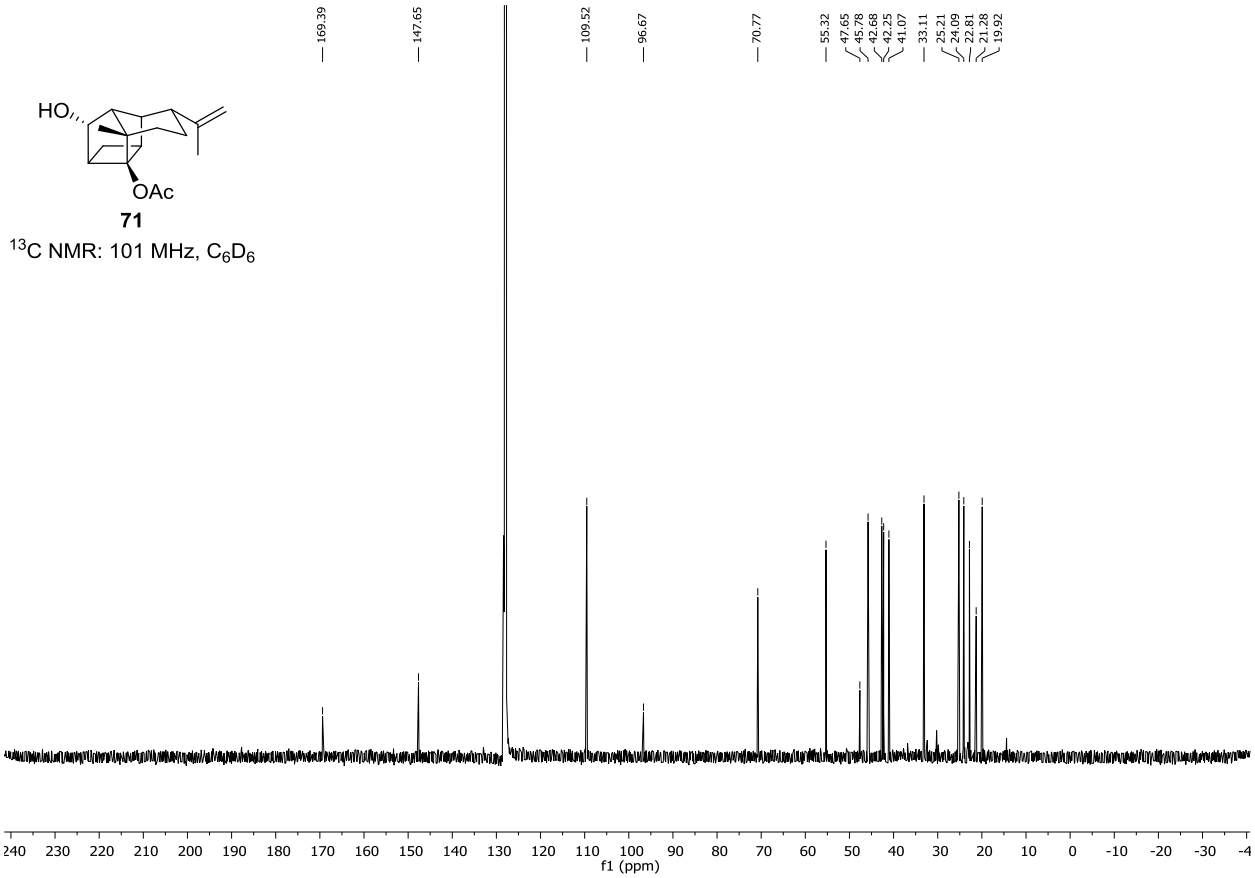
$^1$H NMR: 300 MHz, $C_6D_6$


HO
AcO
70
$^1$H NMR: 300 MHz, $C_6D_6$
f1 (ppm)



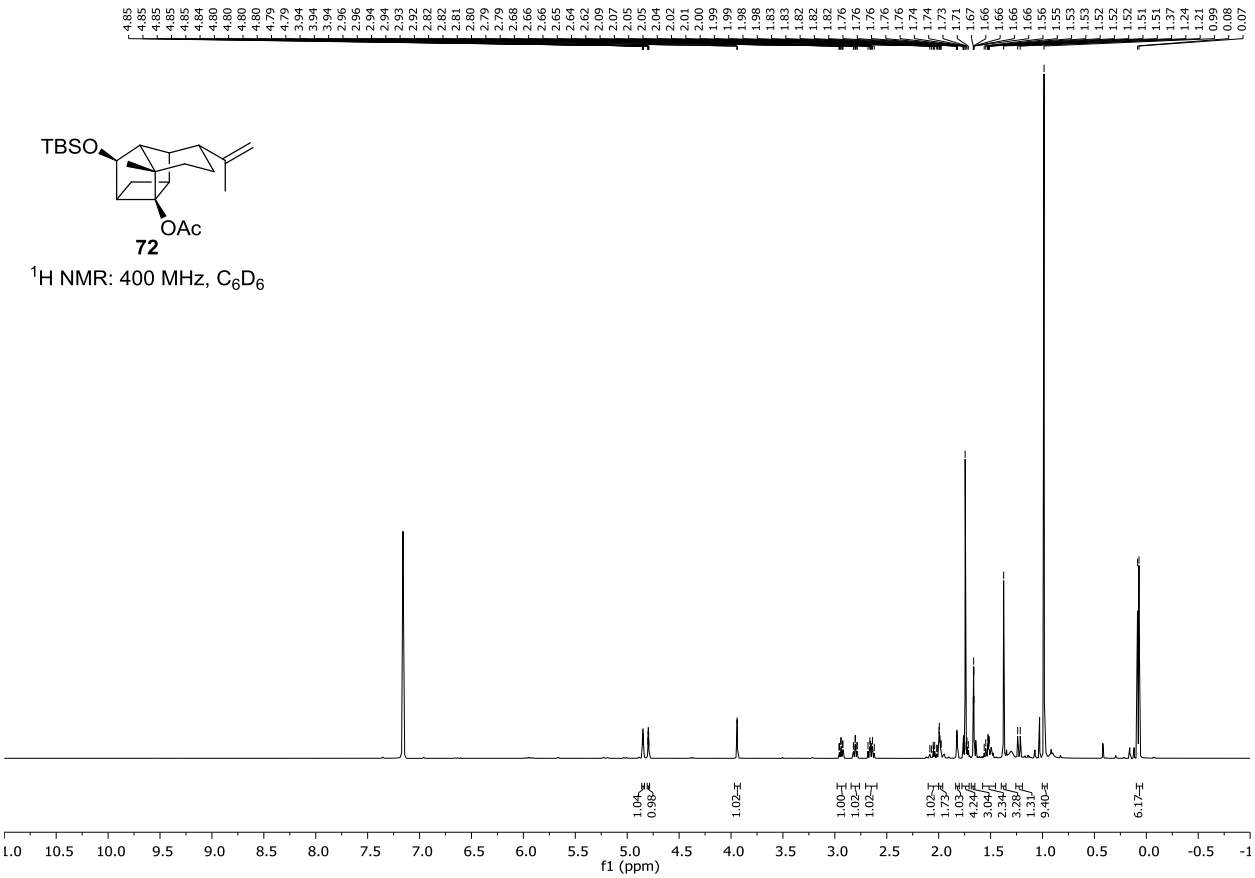

**71**

$^{1}$H NMR: 400 MHz, $C_6D_6$

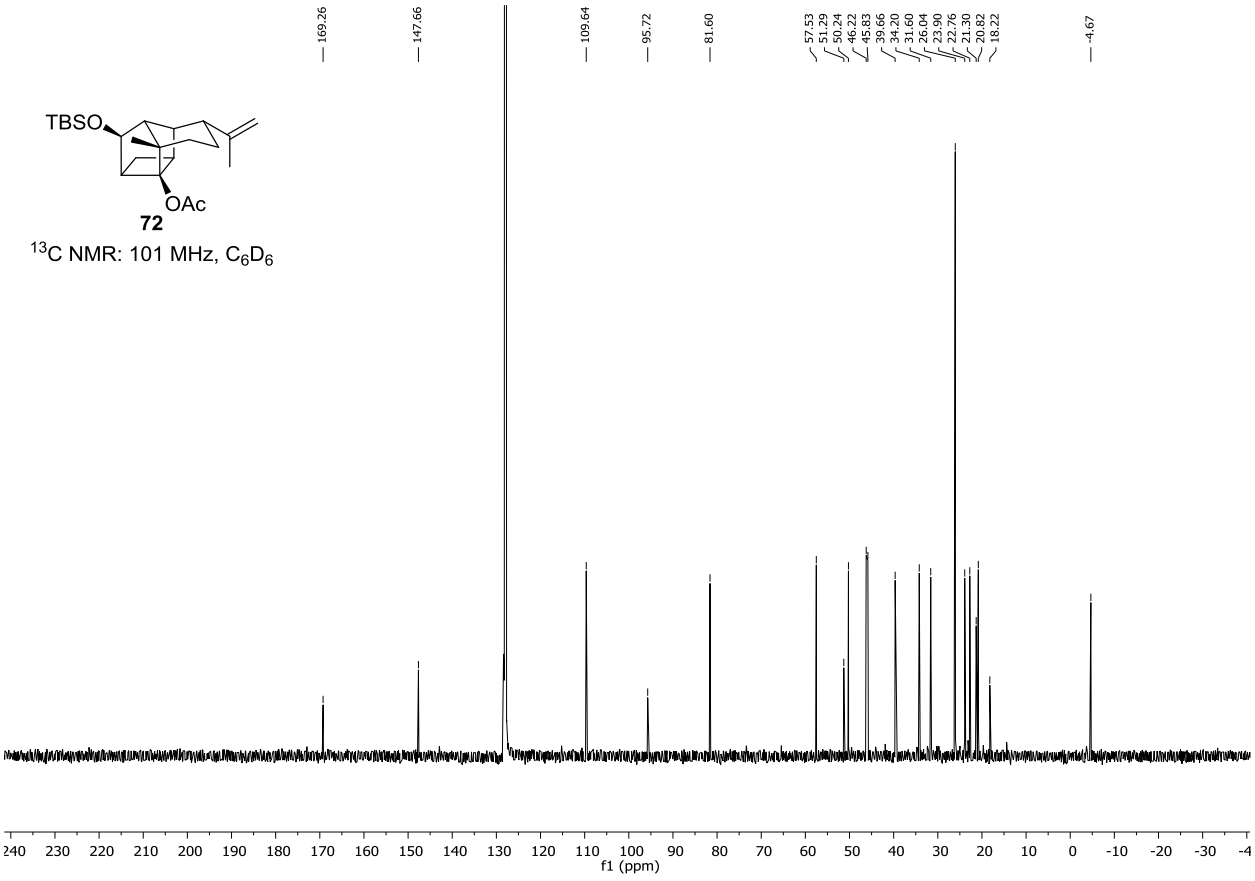



**71**

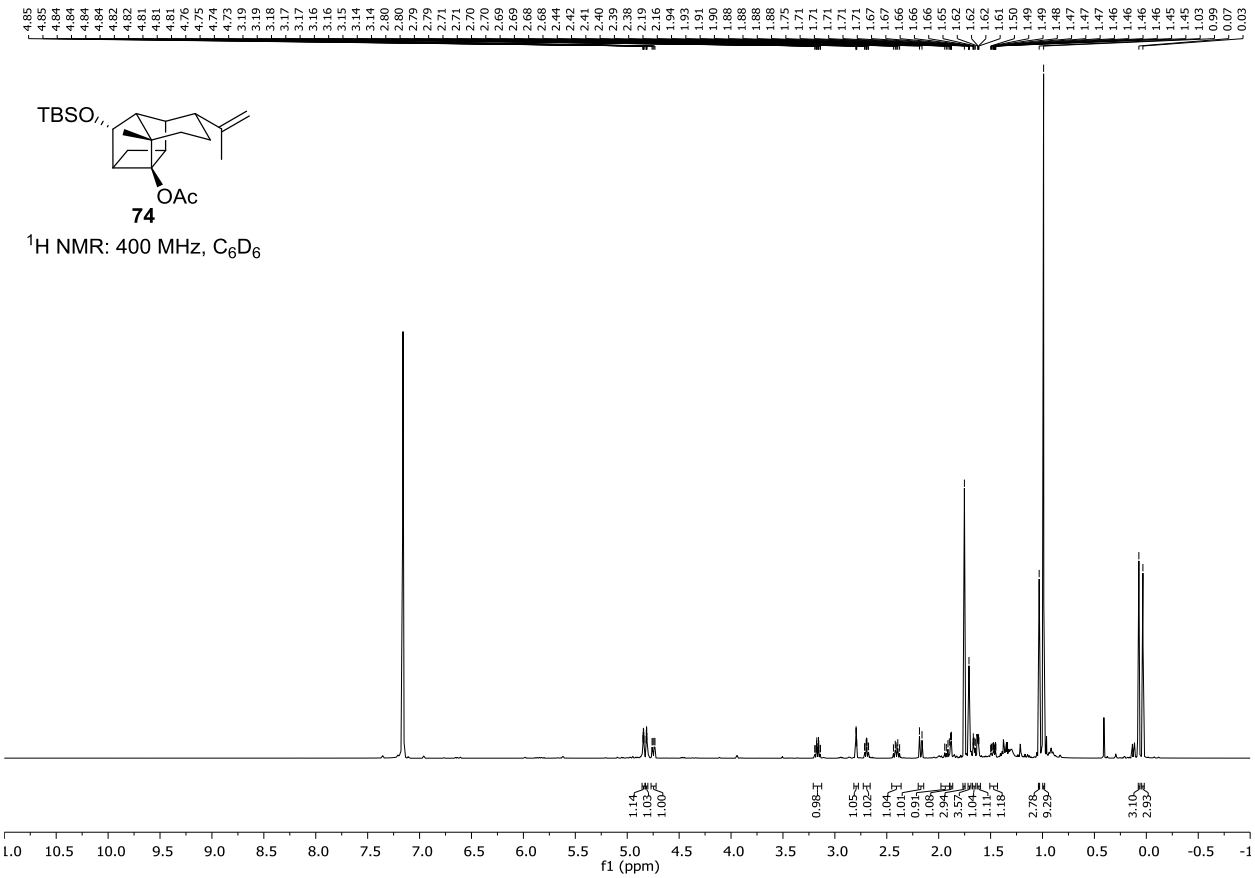
$^{13}$C NMR: 101 MHz, $C_6D_6$



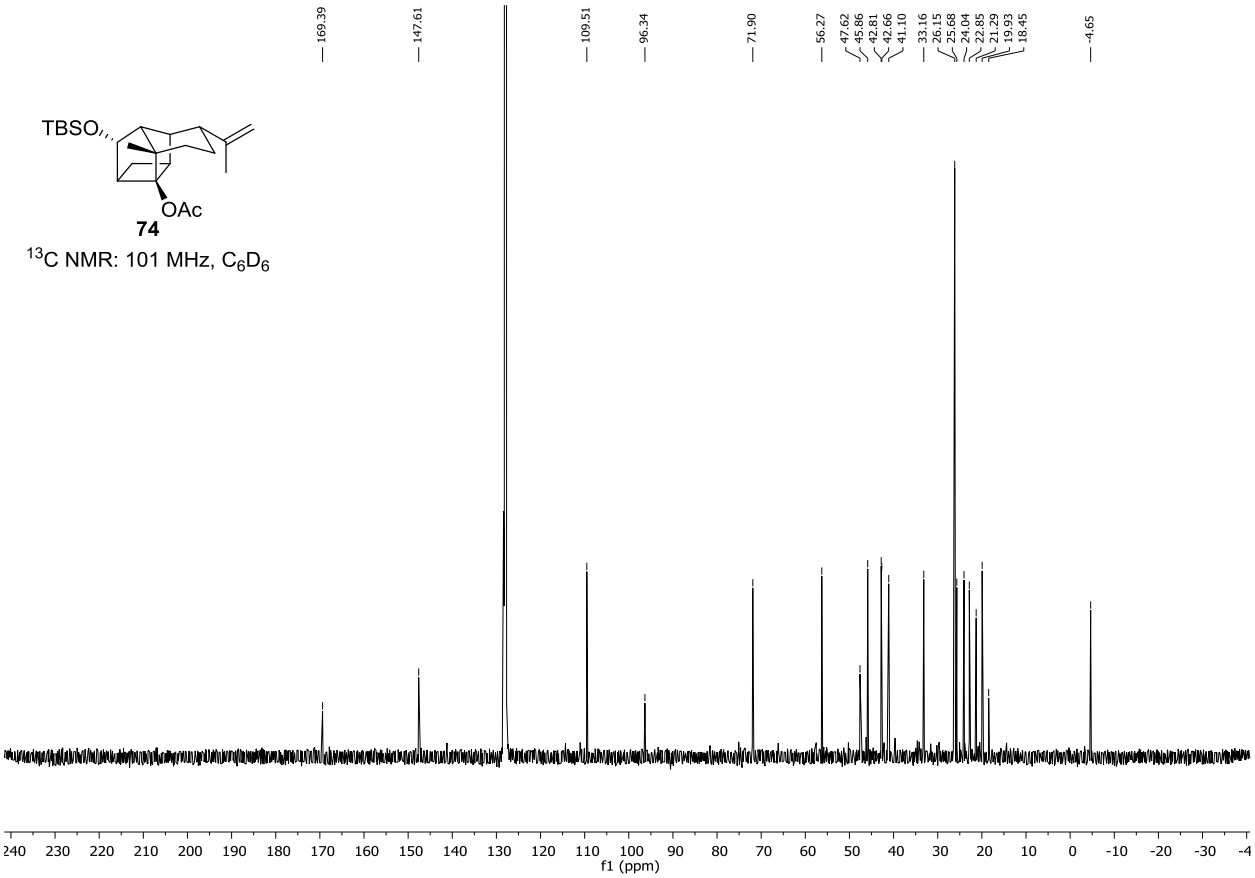

$^{1}$H NMR: 400 MHz, $C_6D_6$



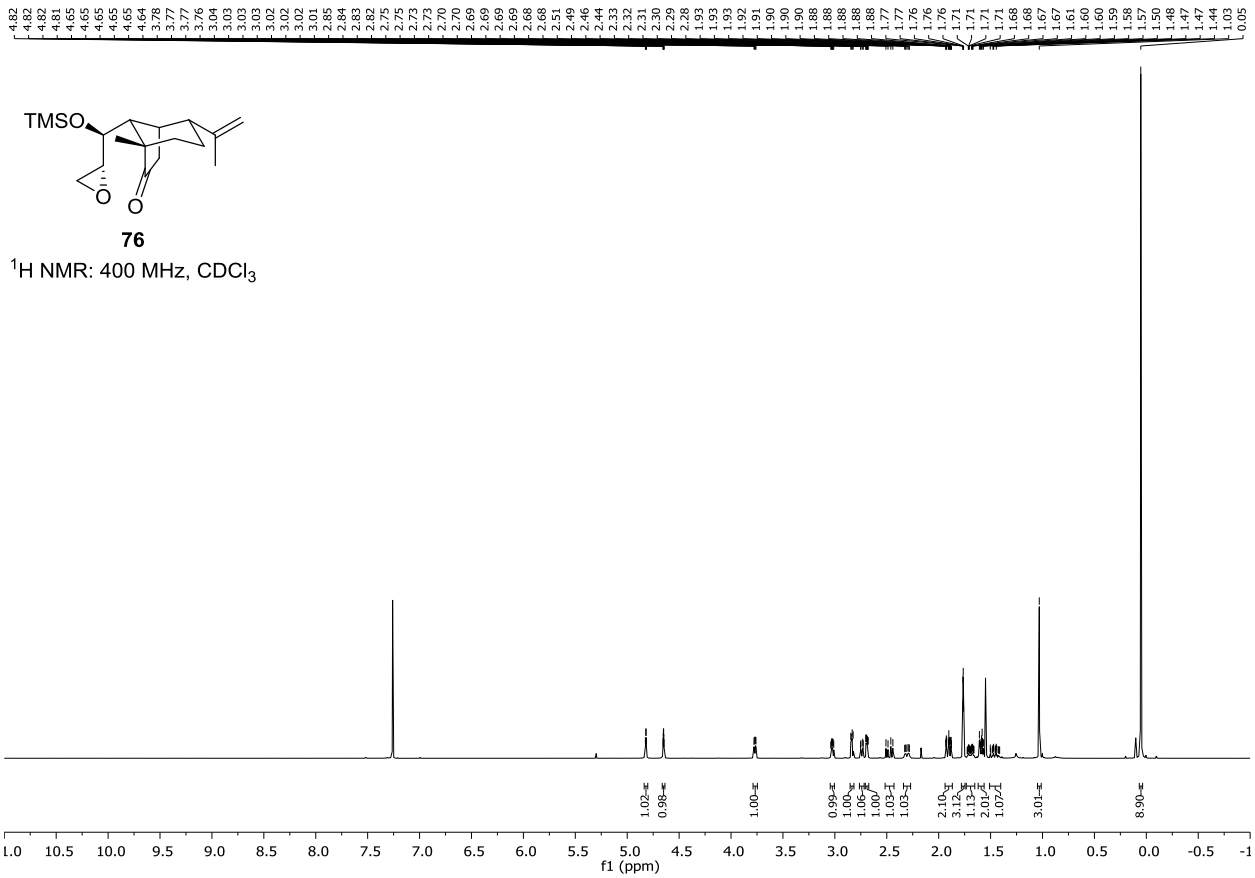

$^{13}$C NMR: 101 MHz, $C_6D_6$




$^{1}$H NMR: 400 MHz, $C_6D_6$

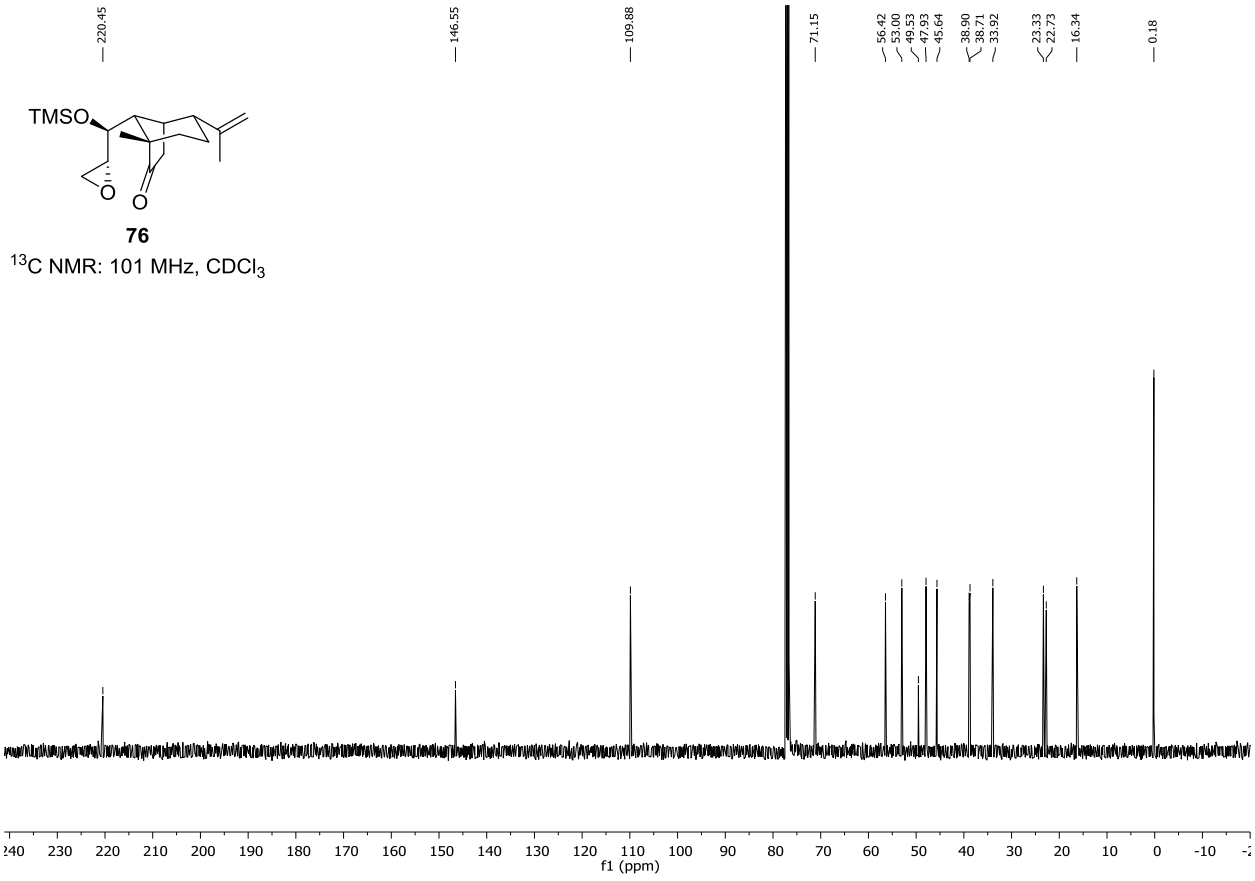



$^{13}$C NMR: 101 MHz, $C_6D_6$



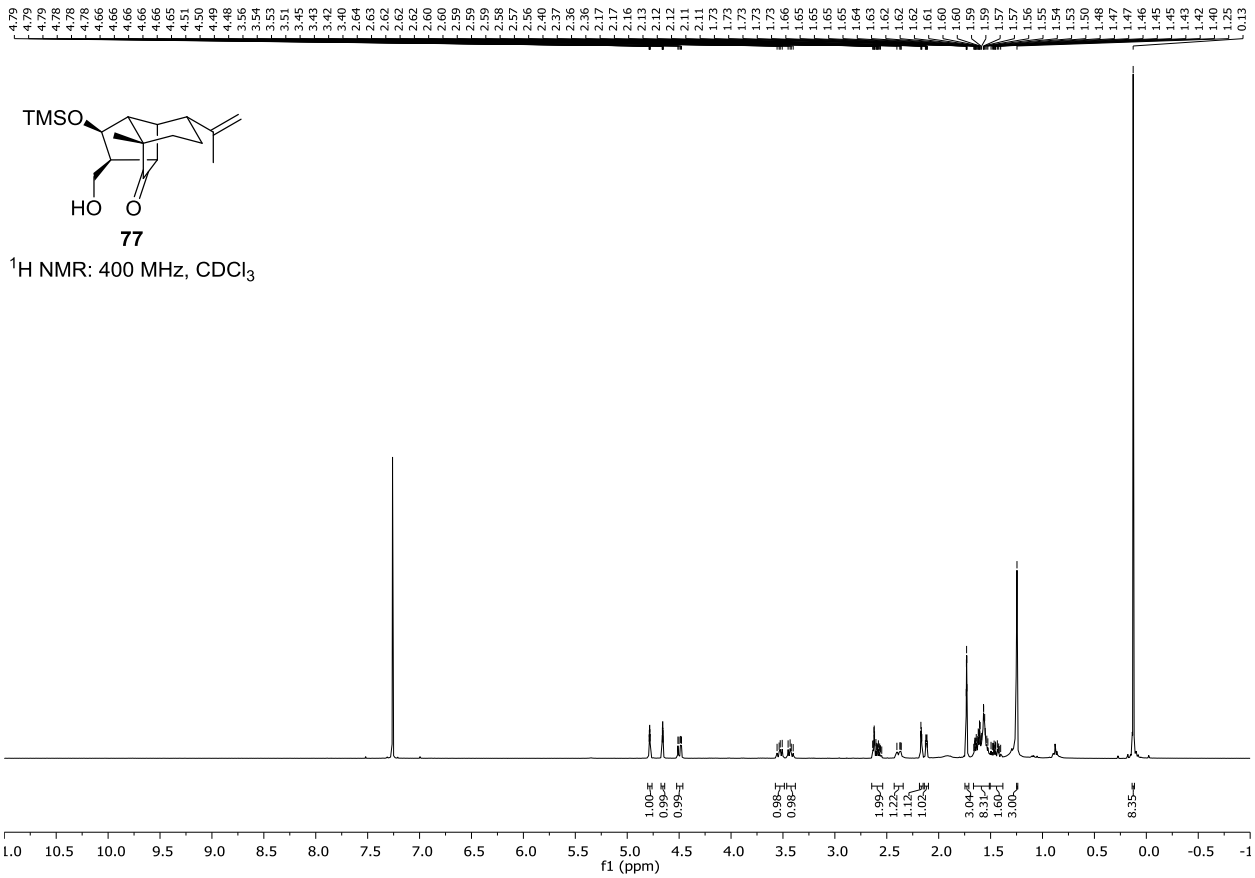

**76**

$^{1}$H NMR: 400 MHz, $CDCl_3$



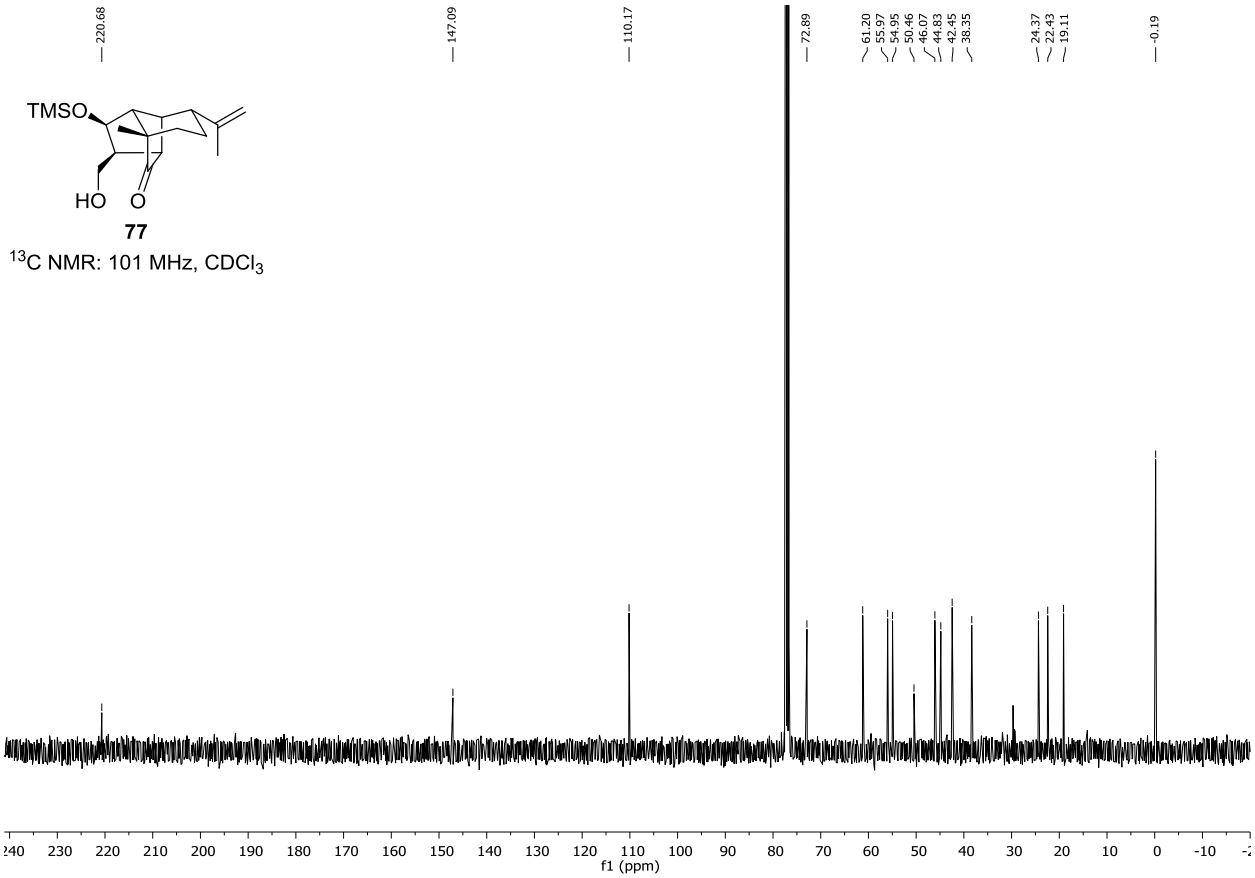

**76**

$^{13}$C NMR: 101 MHz, $CDCl_3$



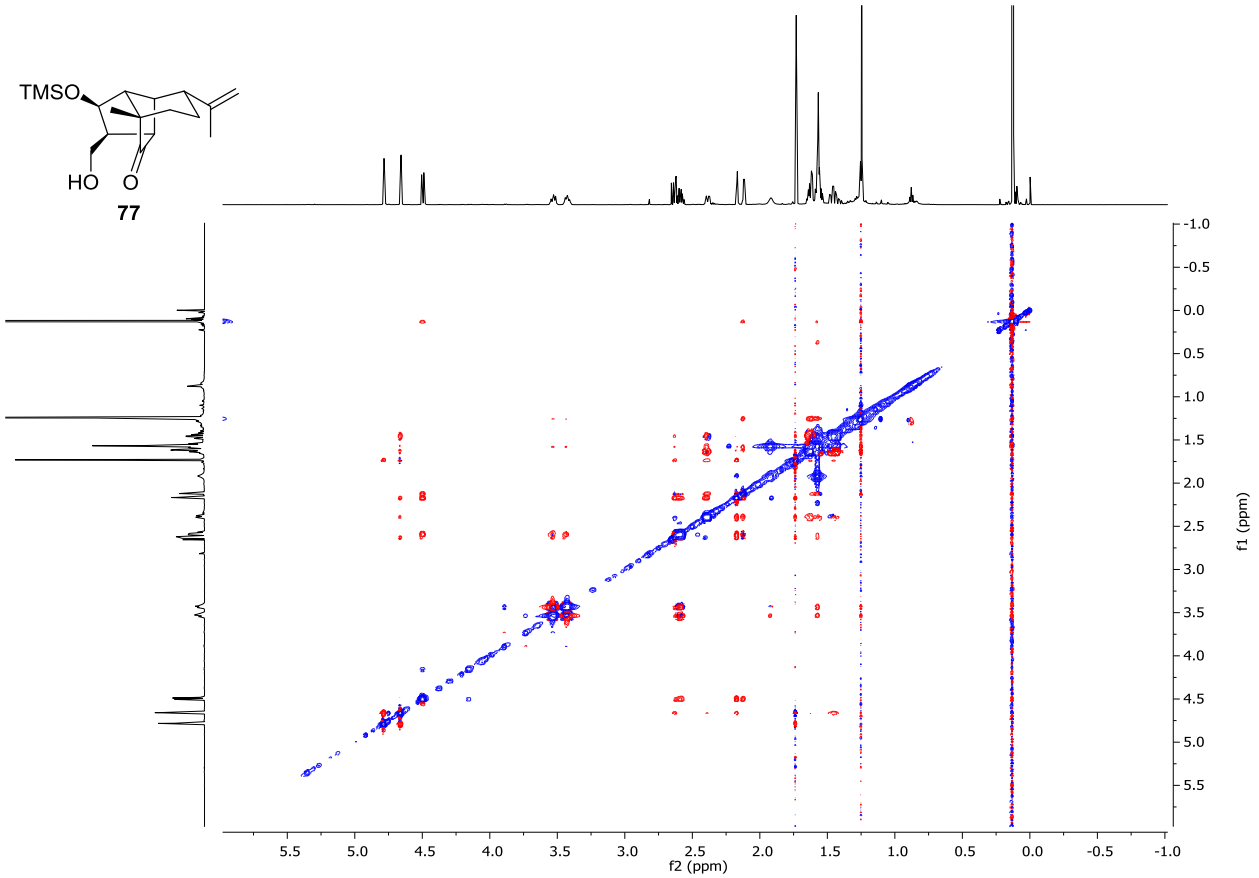

**77**

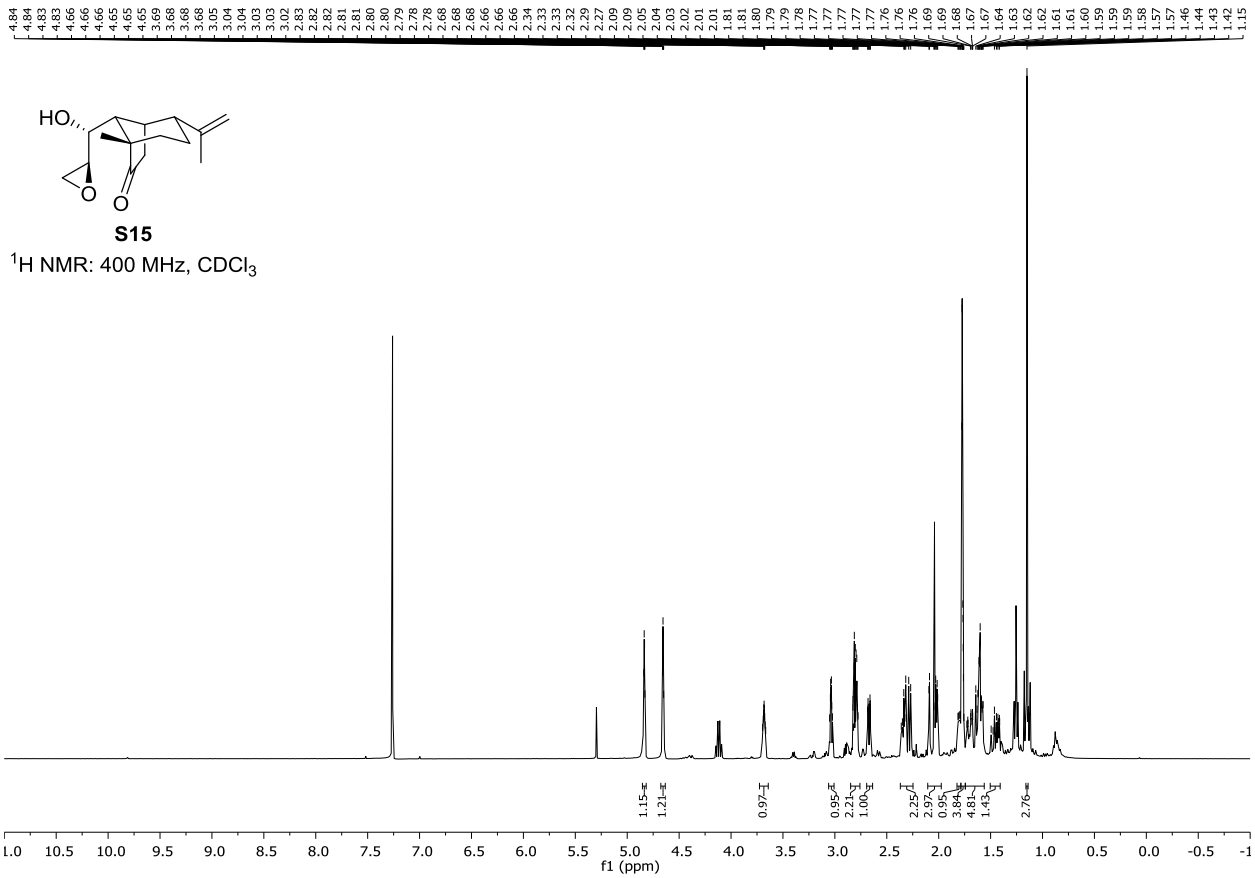
$^{1}$H NMR: 400 MHz, $CDCl_3$




**77**

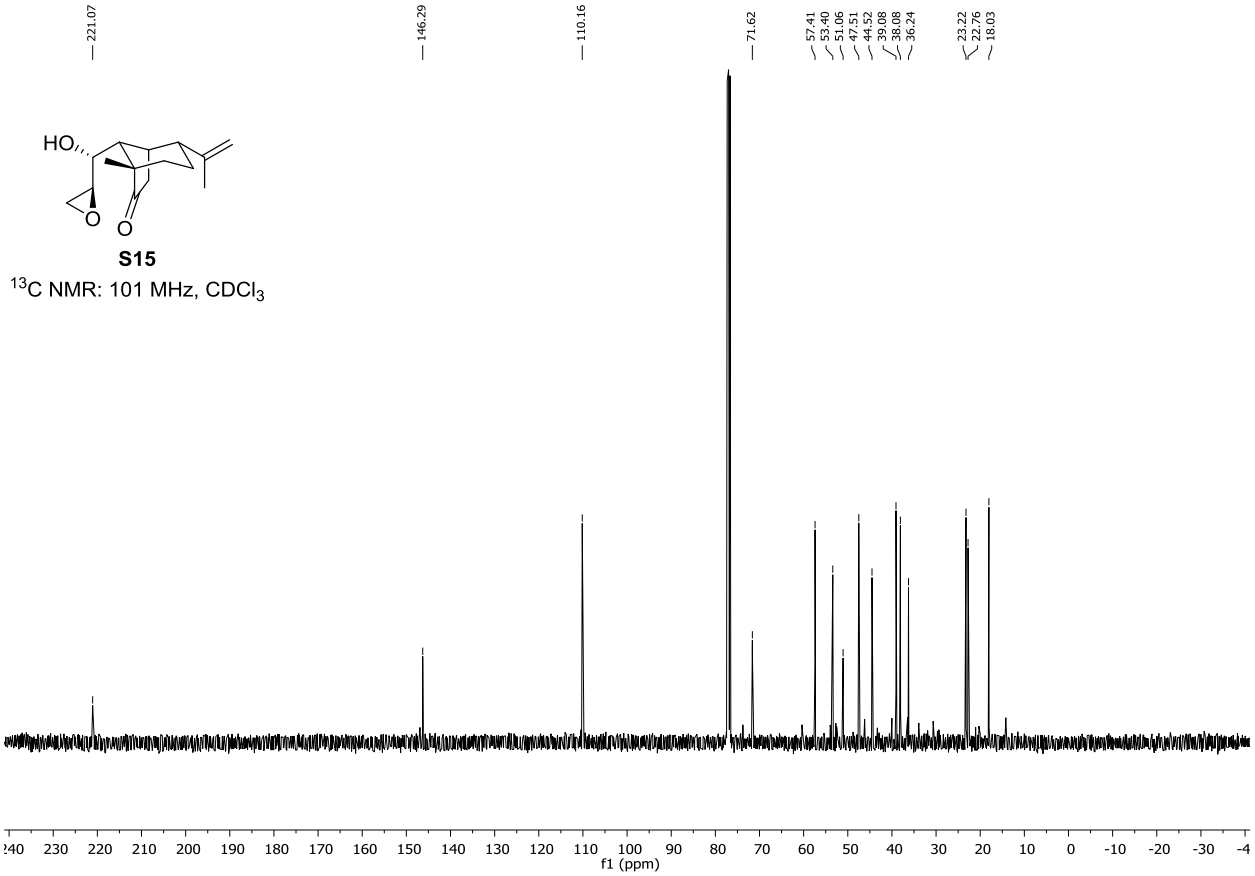
$^{13}$C NMR: 101 MHz, $CDCl_3$


TMSO
HO
O
77
f2 (ppm)
f1 (ppm)



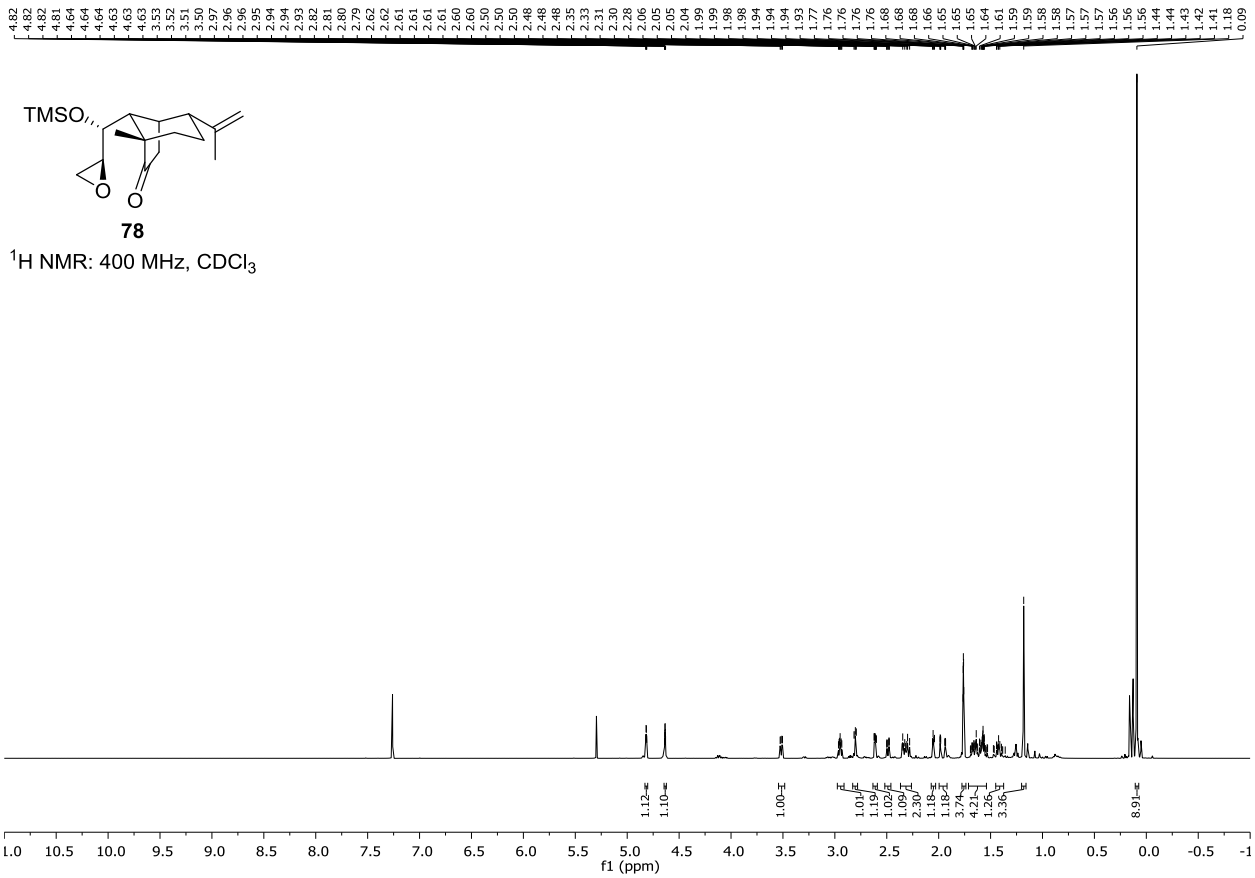

**S15**

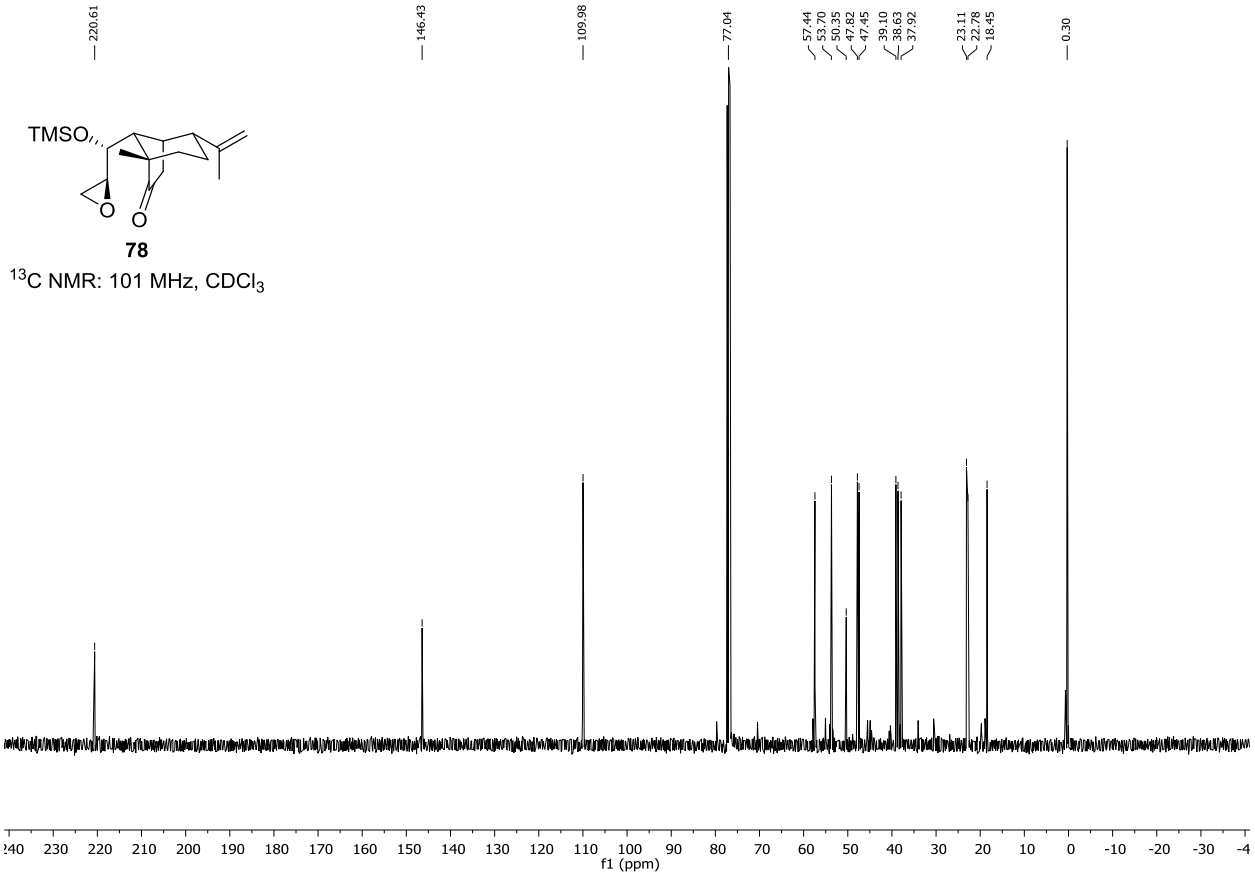
$^{1}$H NMR: 400 MHz, $CDCl_3$

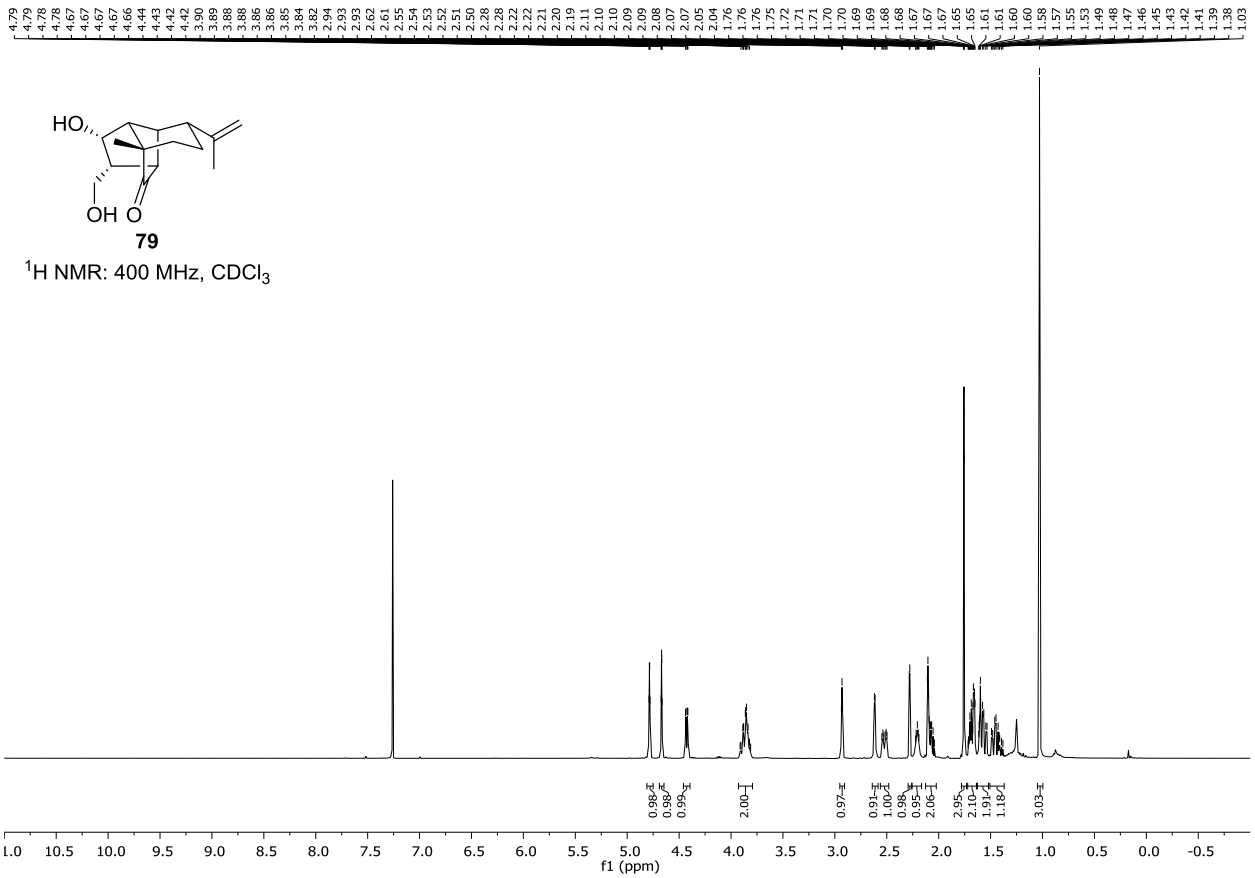


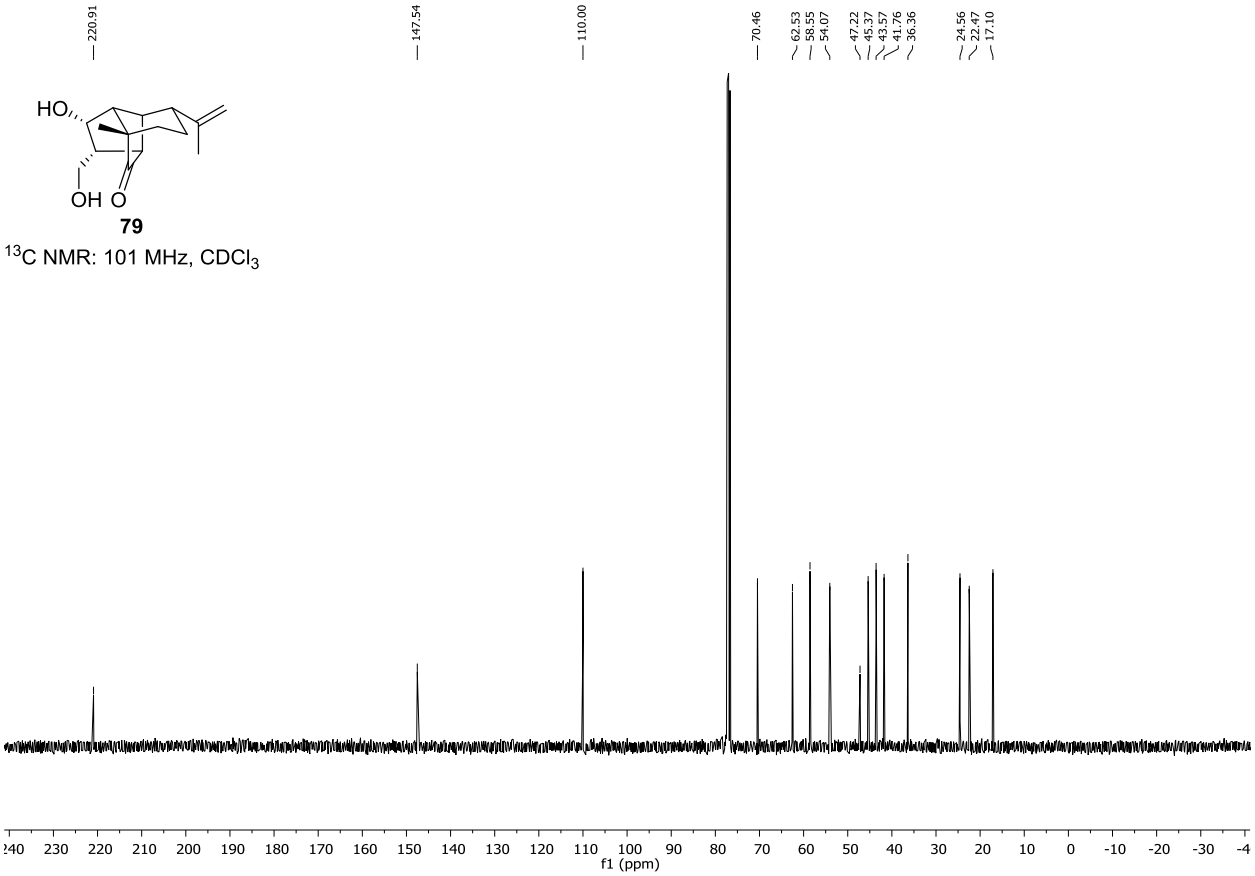

**S15**

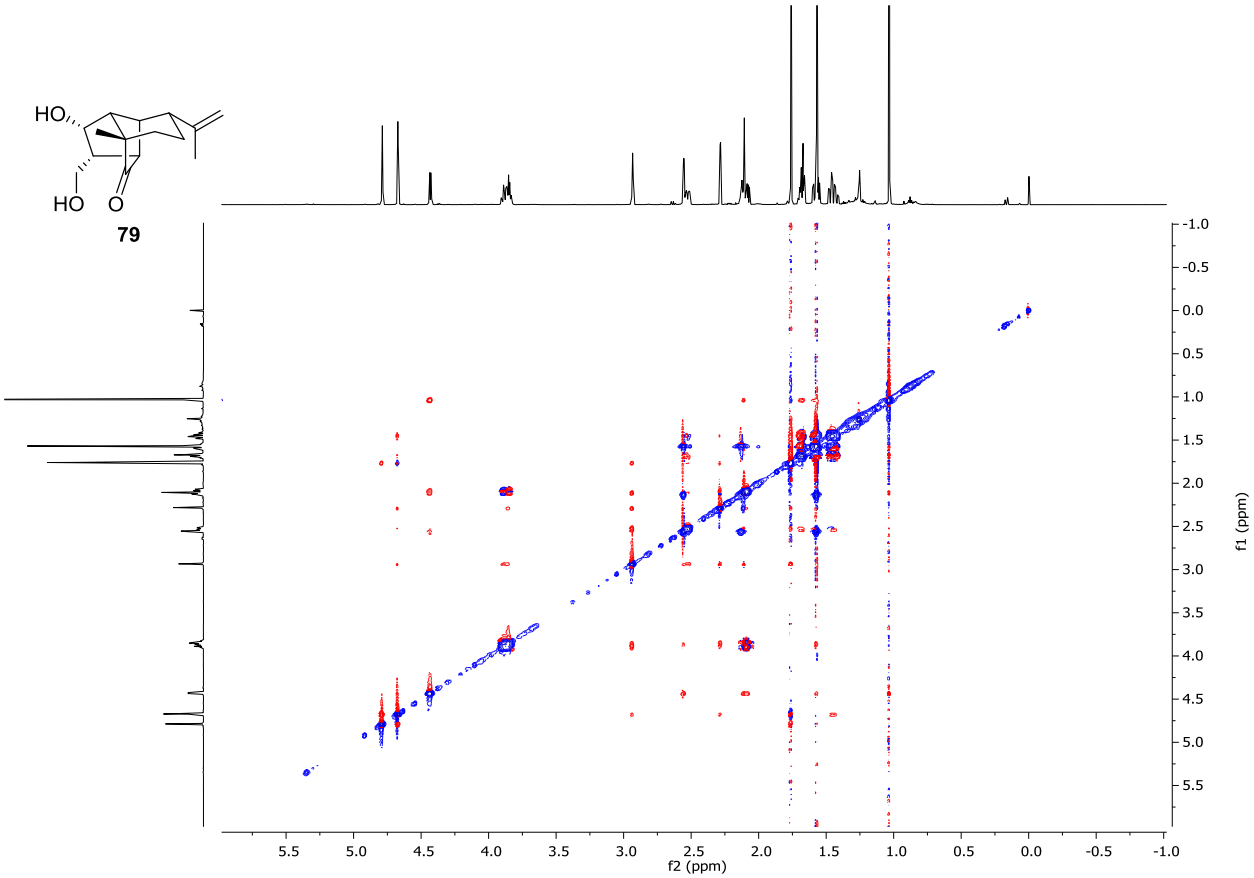
$^{13}$C NMR: 101 MHz, $CDCl_3$

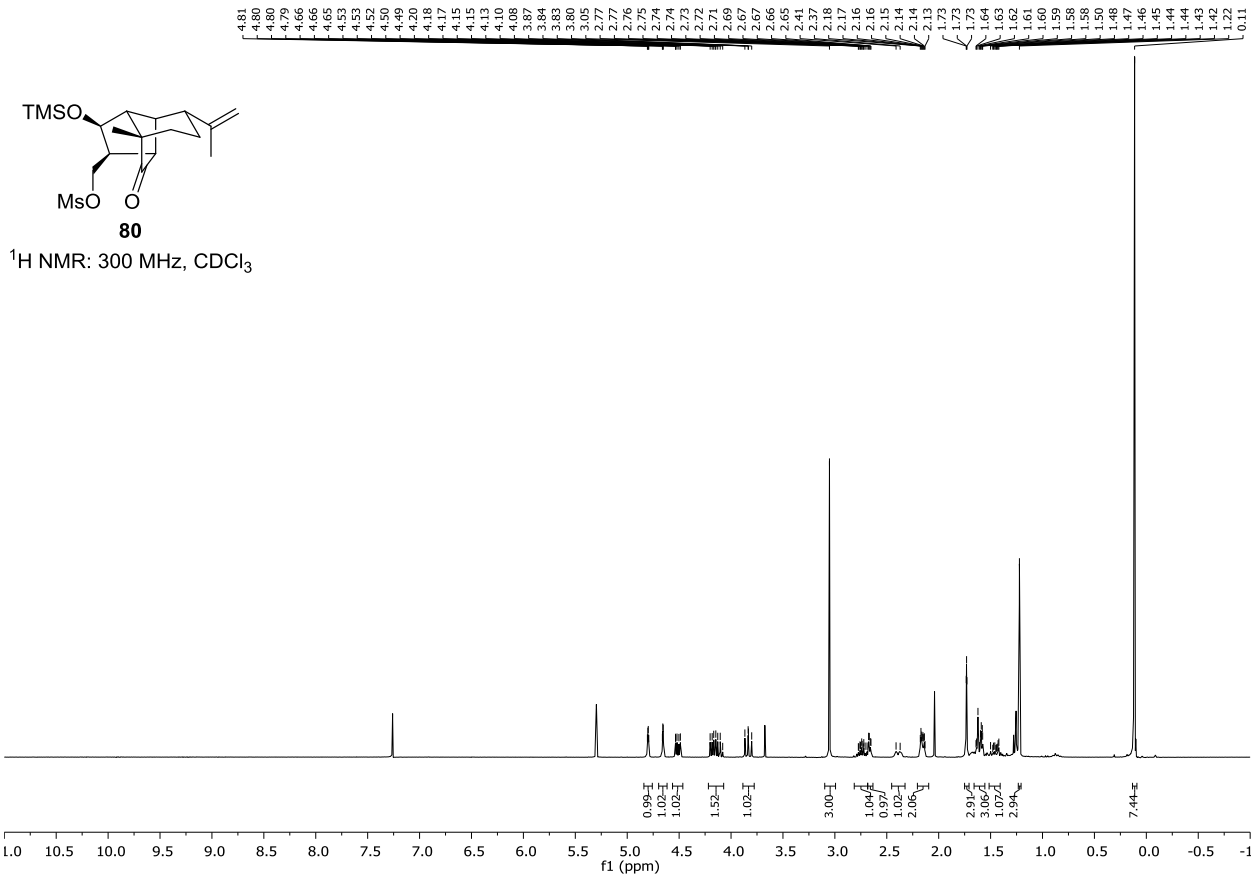

TMSO
O
O
78
1H NMR: 400 MHz, CDCl3
f1 (ppm)


TMSO
O
O
78
13C NMR: 101 MHz, CDCl3
f1 (ppm)


HO
OH O
79
1H NMR: 400 MHz, CDCl3
f1 (ppm)

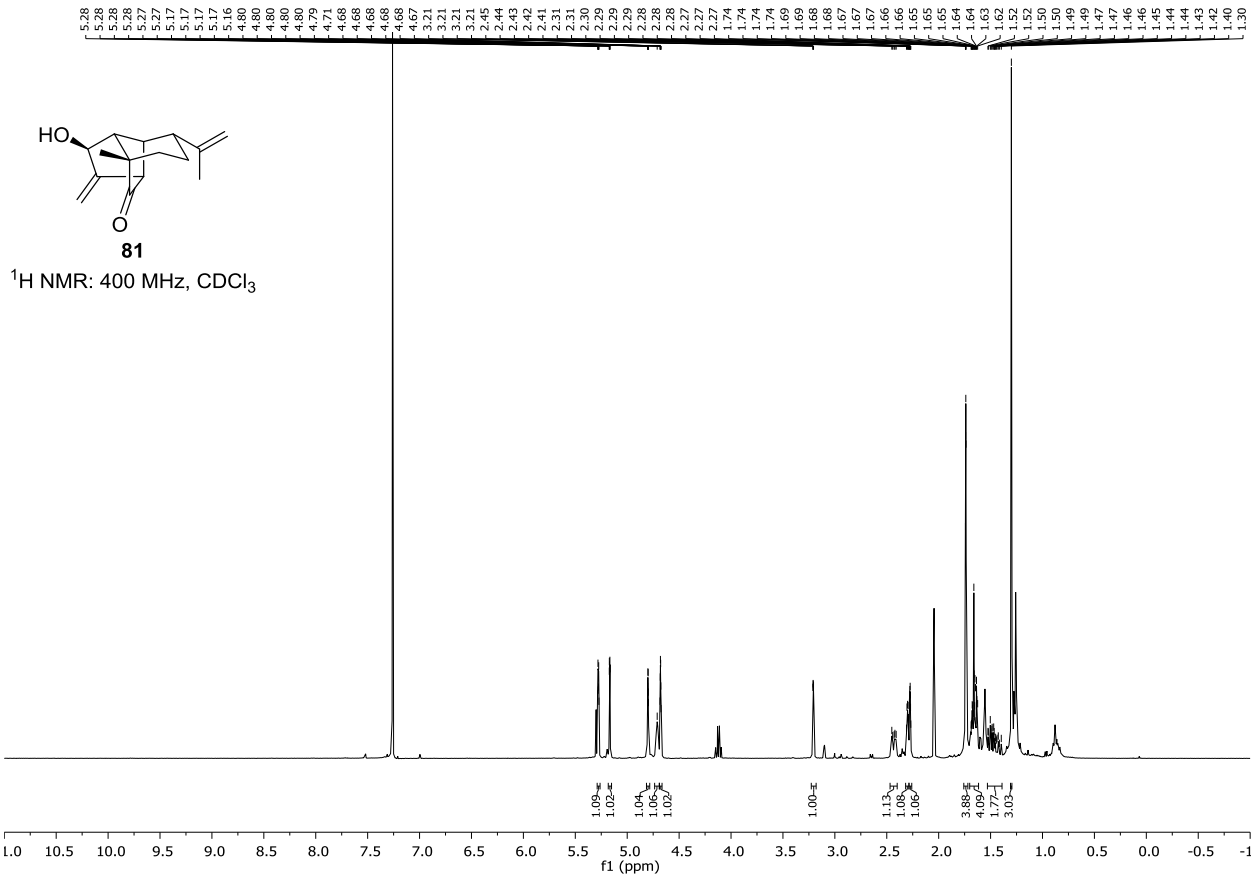

HO
OH O
79
13C NMR: 101 MHz, CDCl3
f1 (ppm)

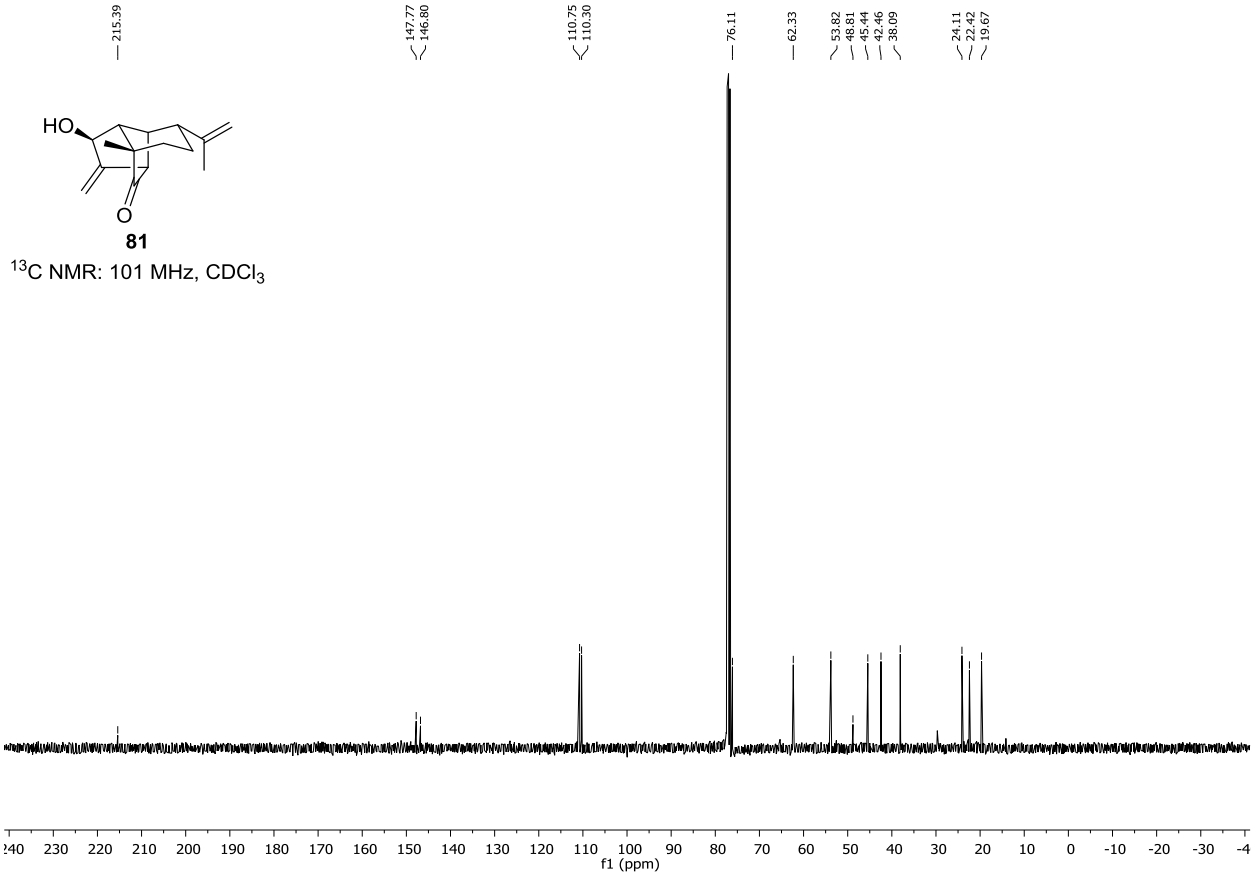

HO
HO
O
79
f2 (ppm)
f1 (ppm)

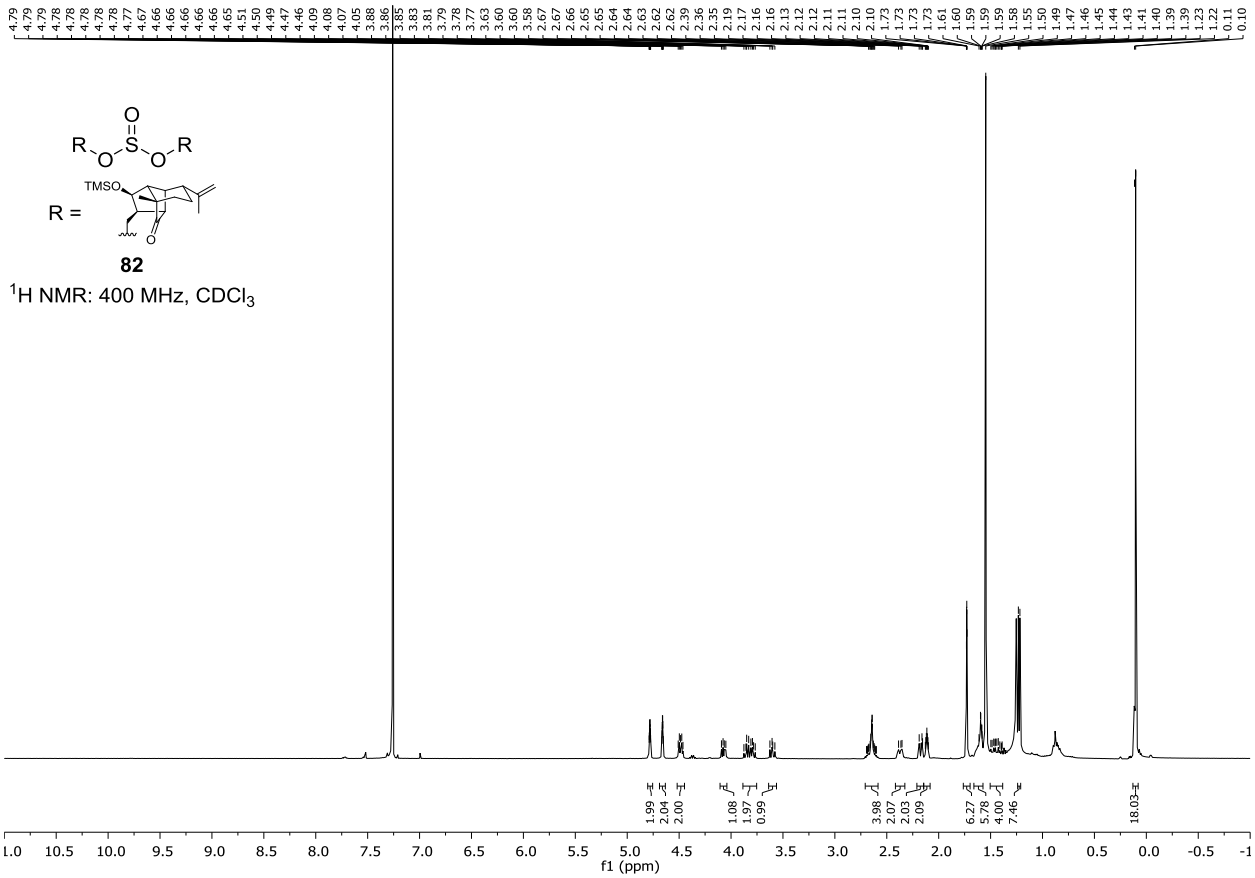


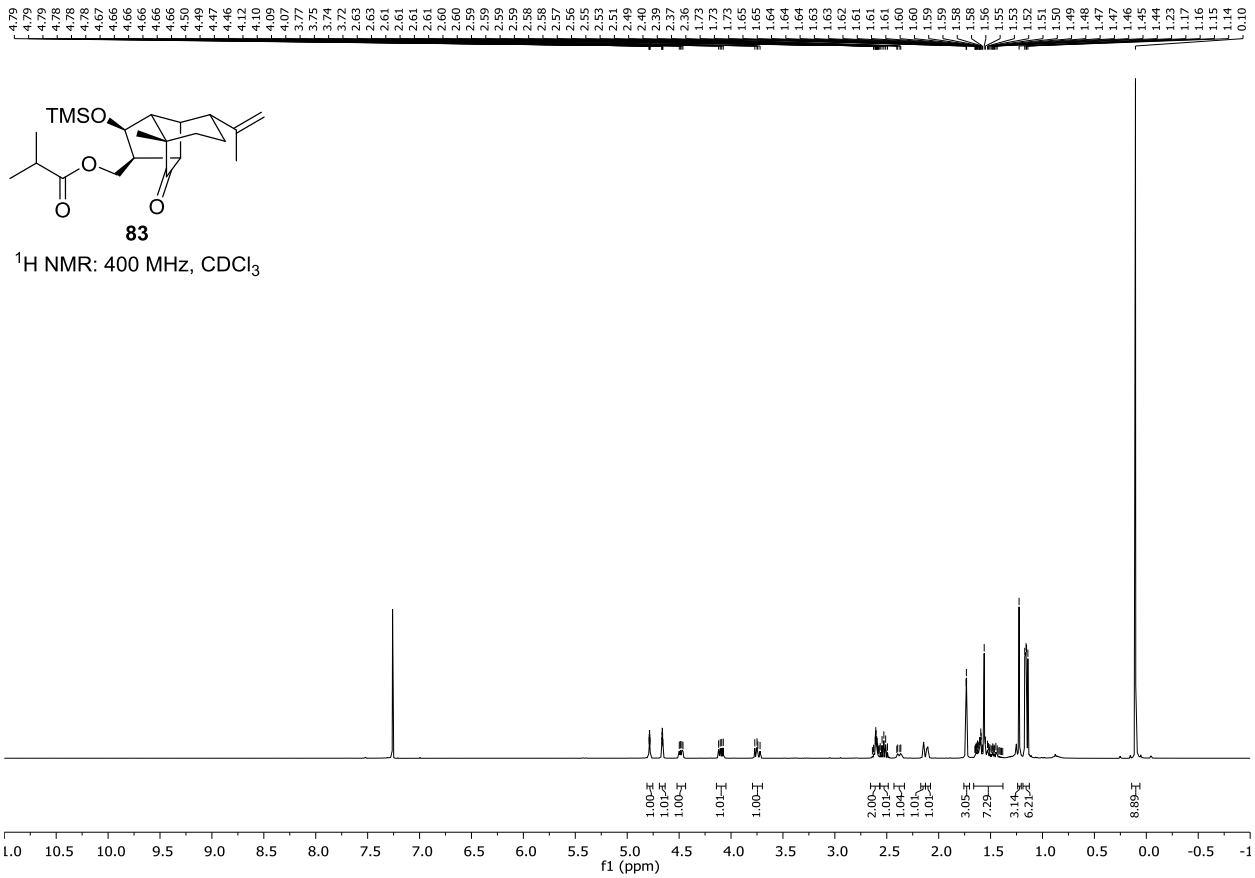

**80**

$^1$H NMR: 300 MHz, $CDCl_3$


HO
O
81
1H NMR: 400 MHz, CDCl3
f1 (ppm)

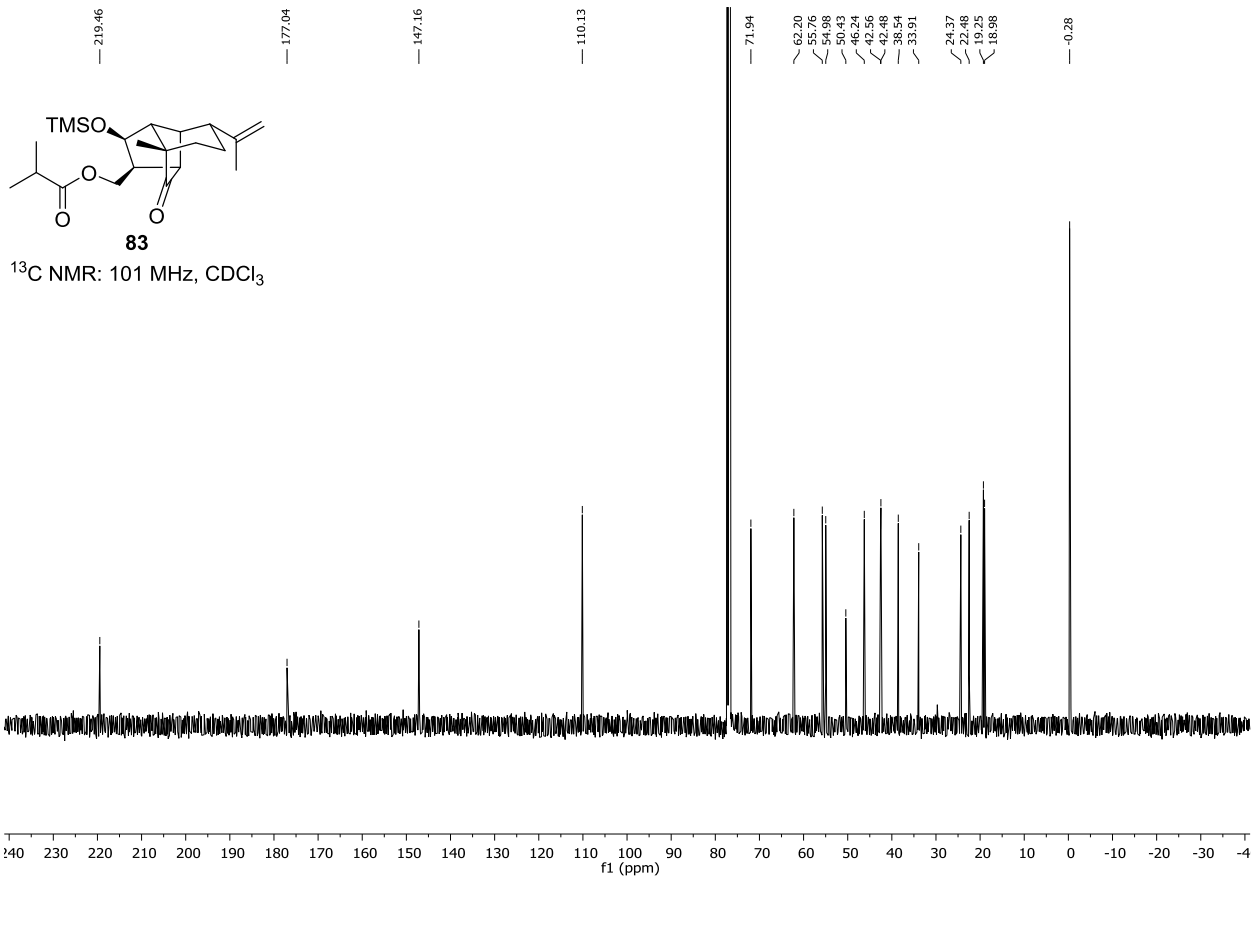

HO
O
81
13C NMR: 101 MHz, CDCl3
f1 (ppm)


R =
TMSO
O
O
S
O
R
O
R
82
$^1$H NMR: 400 MHz, CDCl$_3$
f1 (ppm)



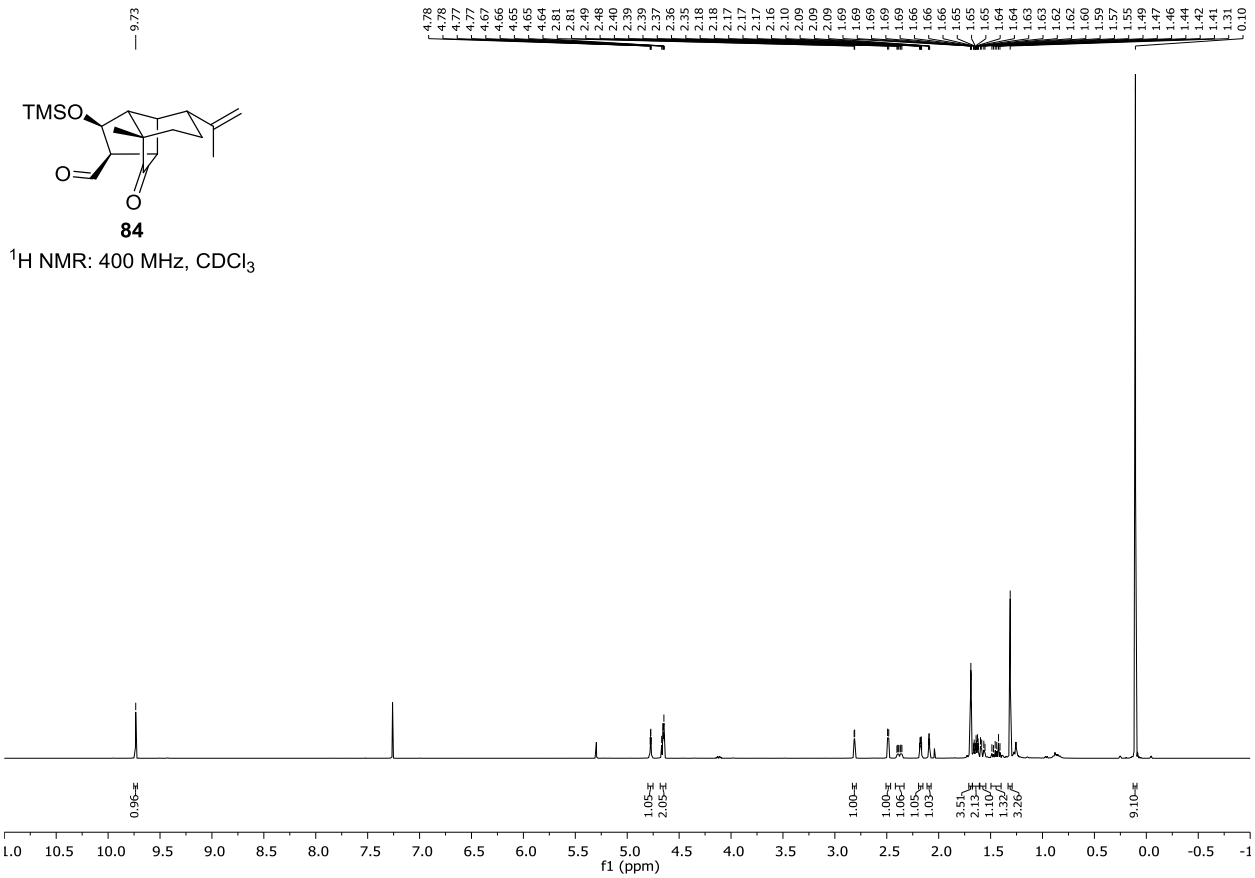

**83**

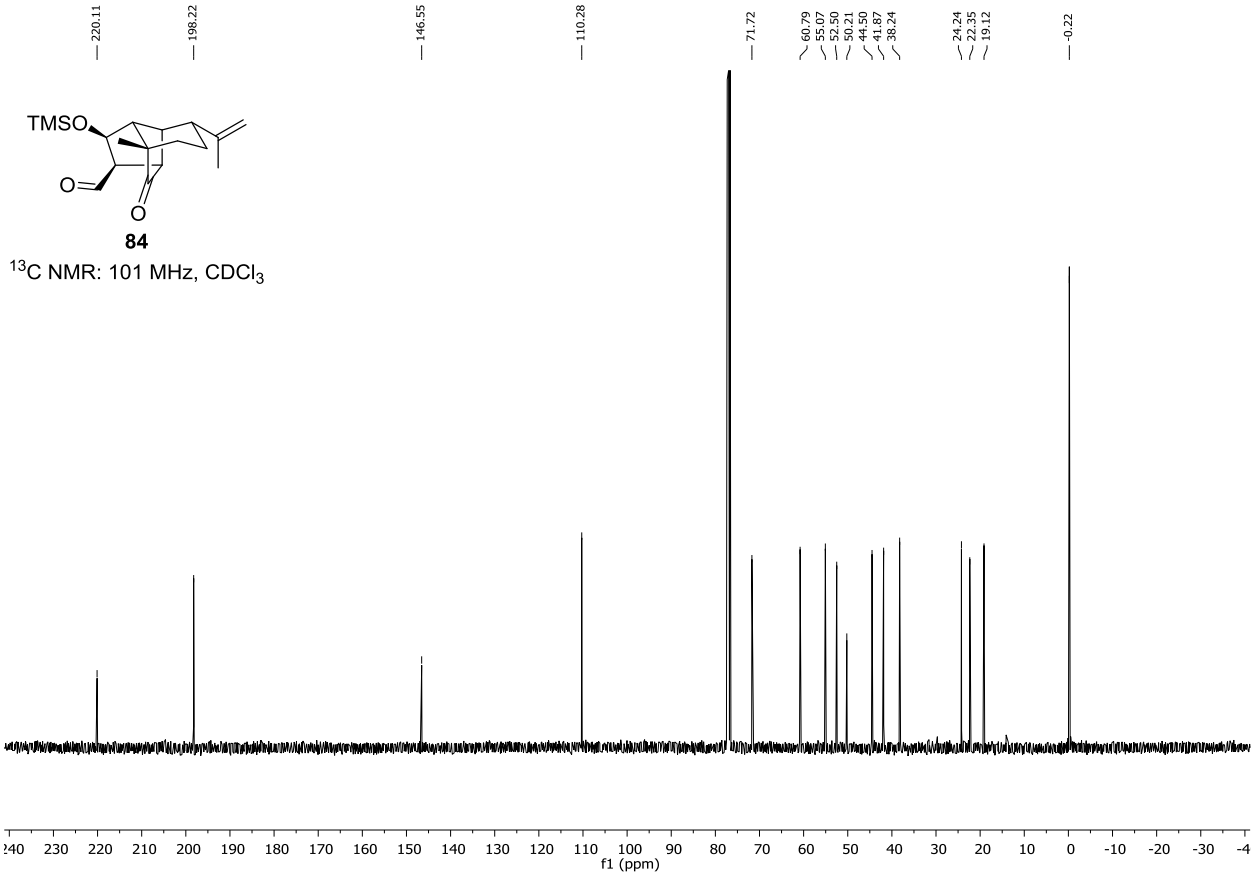
$^{1}$H NMR: 400 MHz, $CDCl_3$

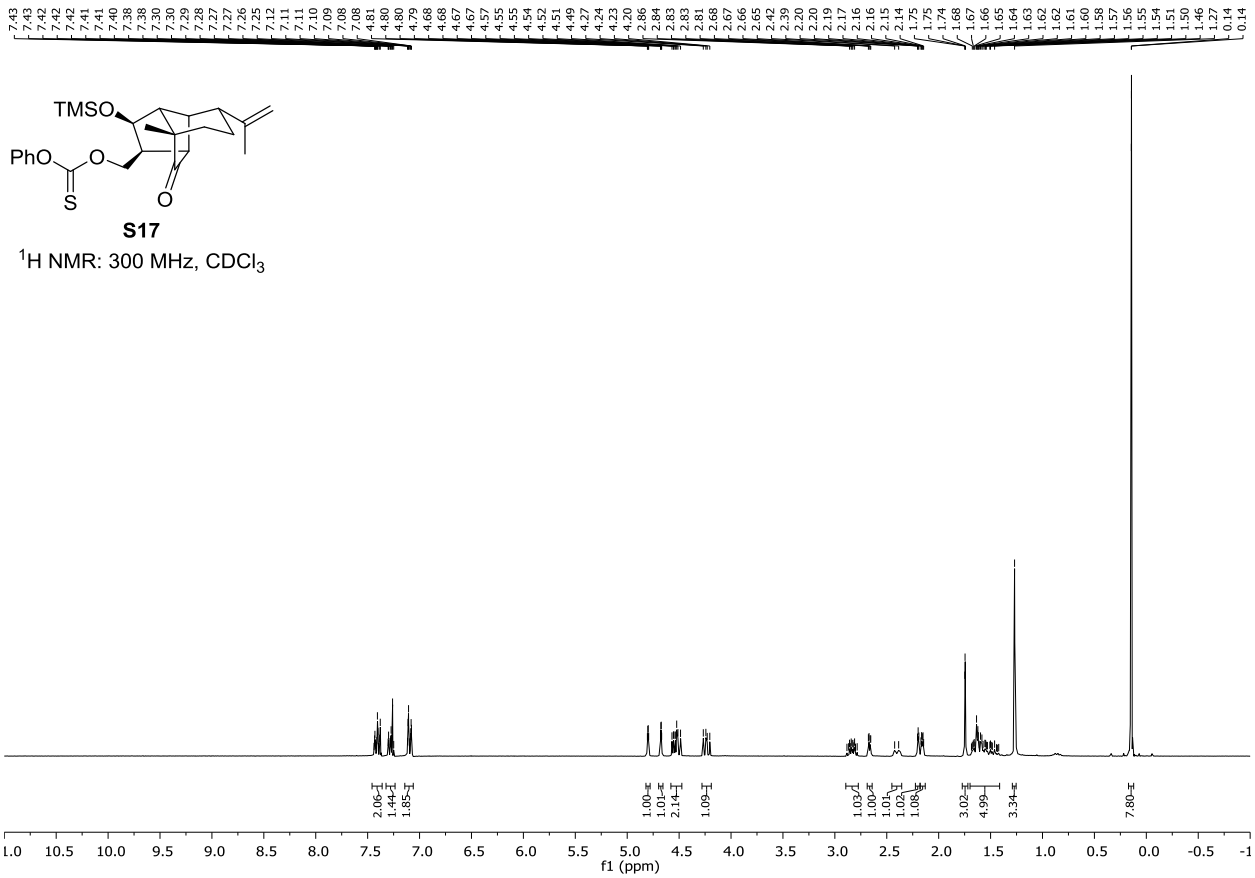



**83**

$^{13}$C NMR: 101 MHz, $CDCl_3$

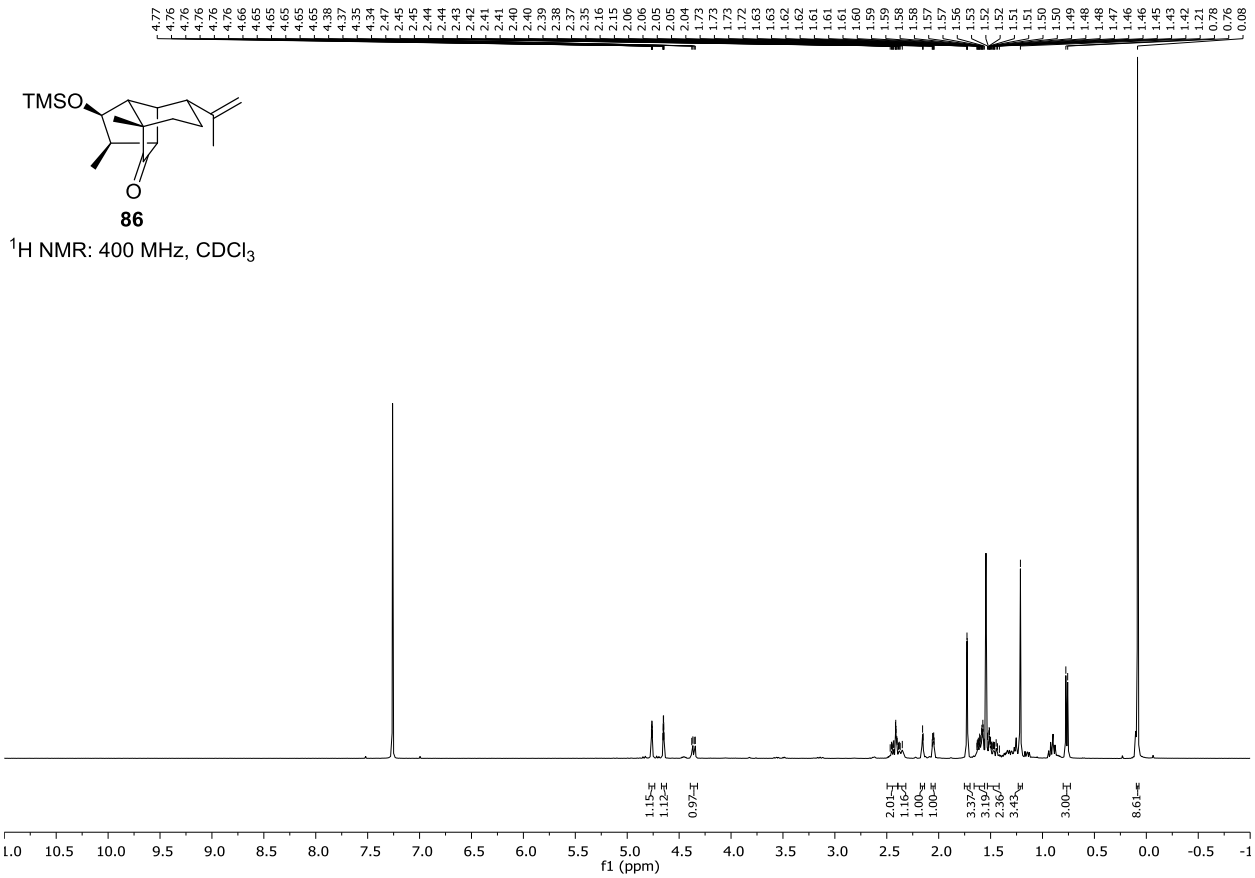

TMSO
O
O
84
$^1$H NMR: 400 MHz, $CDCl_3$
f1 (ppm)


TMSO
O
O
84
$^{13}$C NMR: 101 MHz, $CDCl_3$
f1 (ppm)



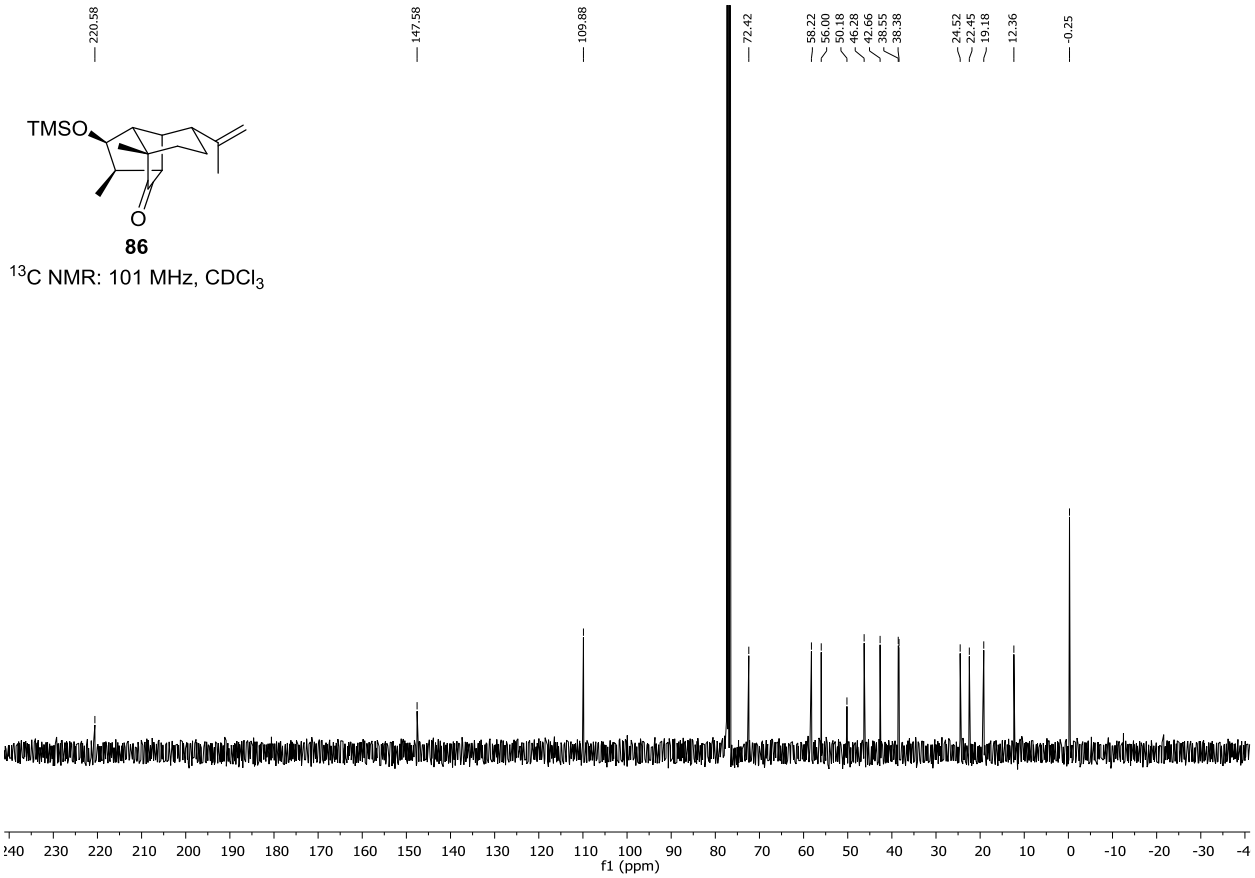

**S17**

$^1$H NMR: 300 MHz, $CDCl_3$



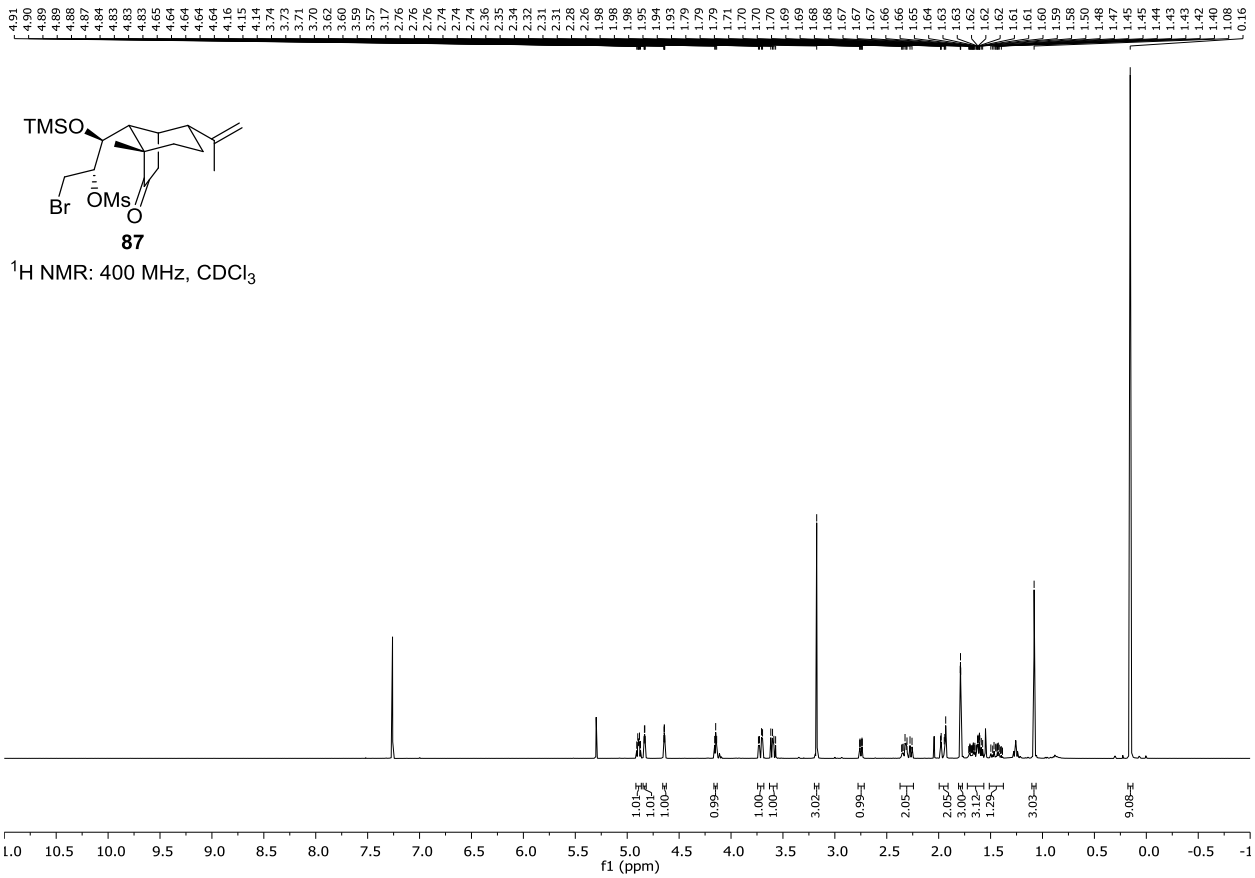

**86**

$^{1}$H NMR: 400 MHz, $CDCl_3$



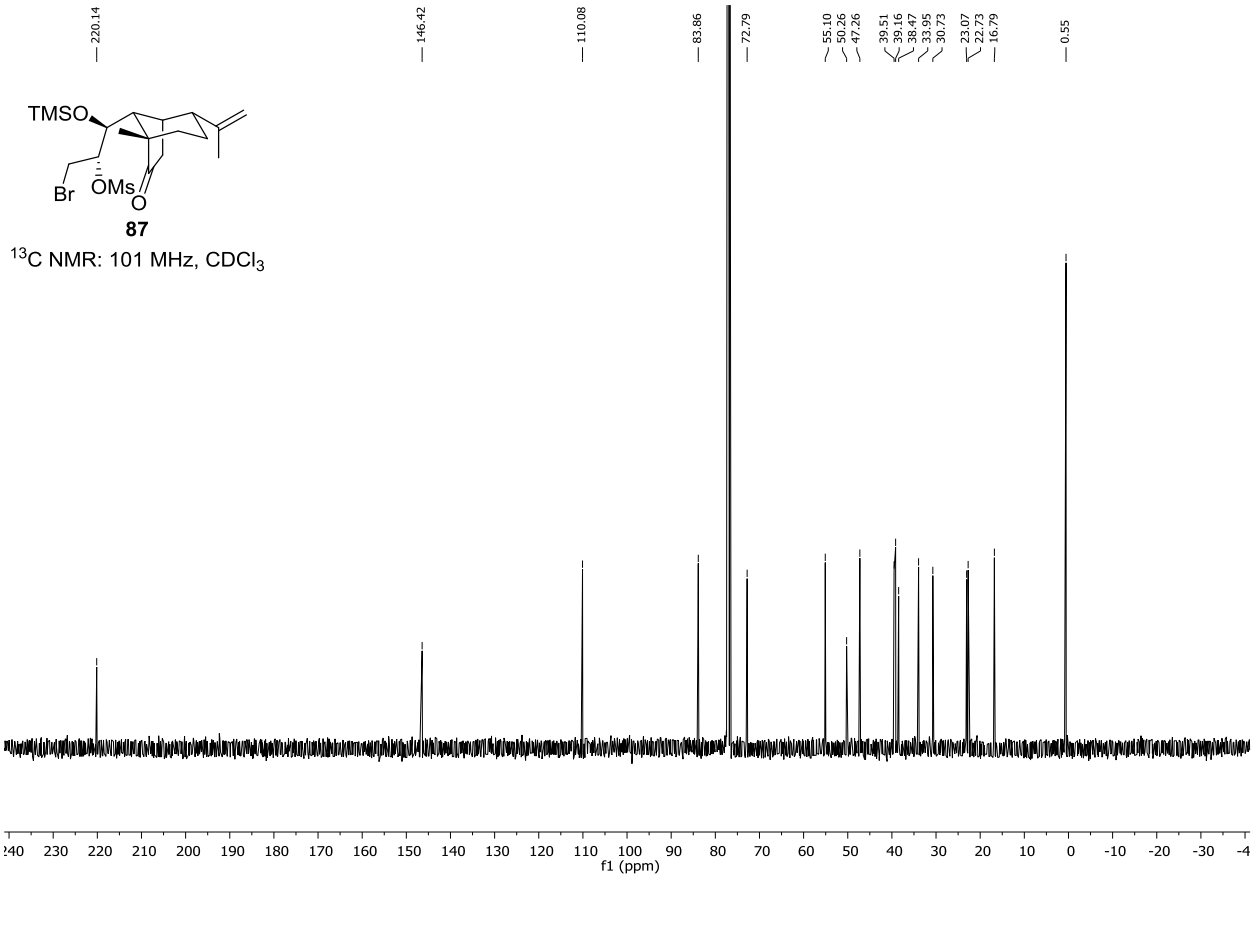

**86**

$^{13}$C NMR: 101 MHz, $CDCl_3$



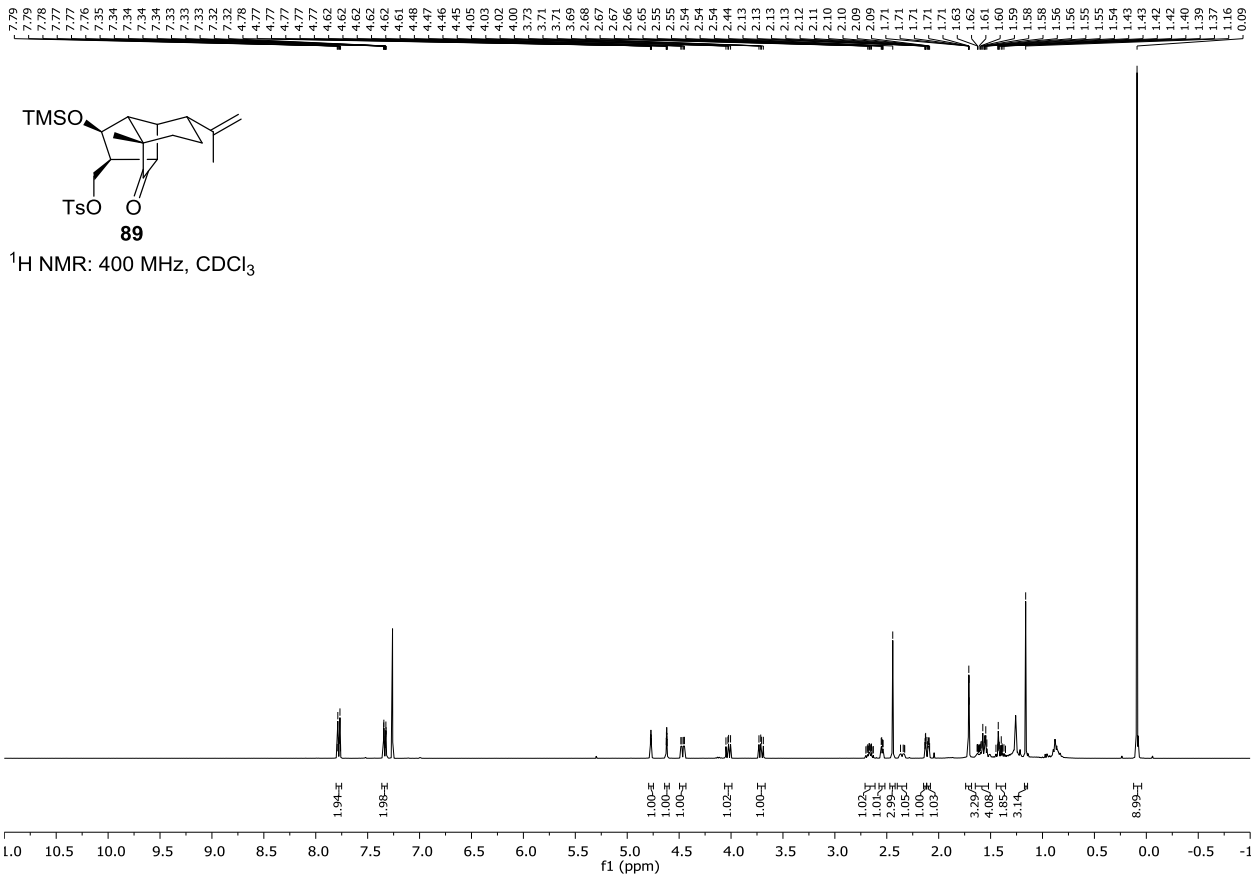

**87**

$^{1}$H NMR: 400 MHz, $CDCl_3$



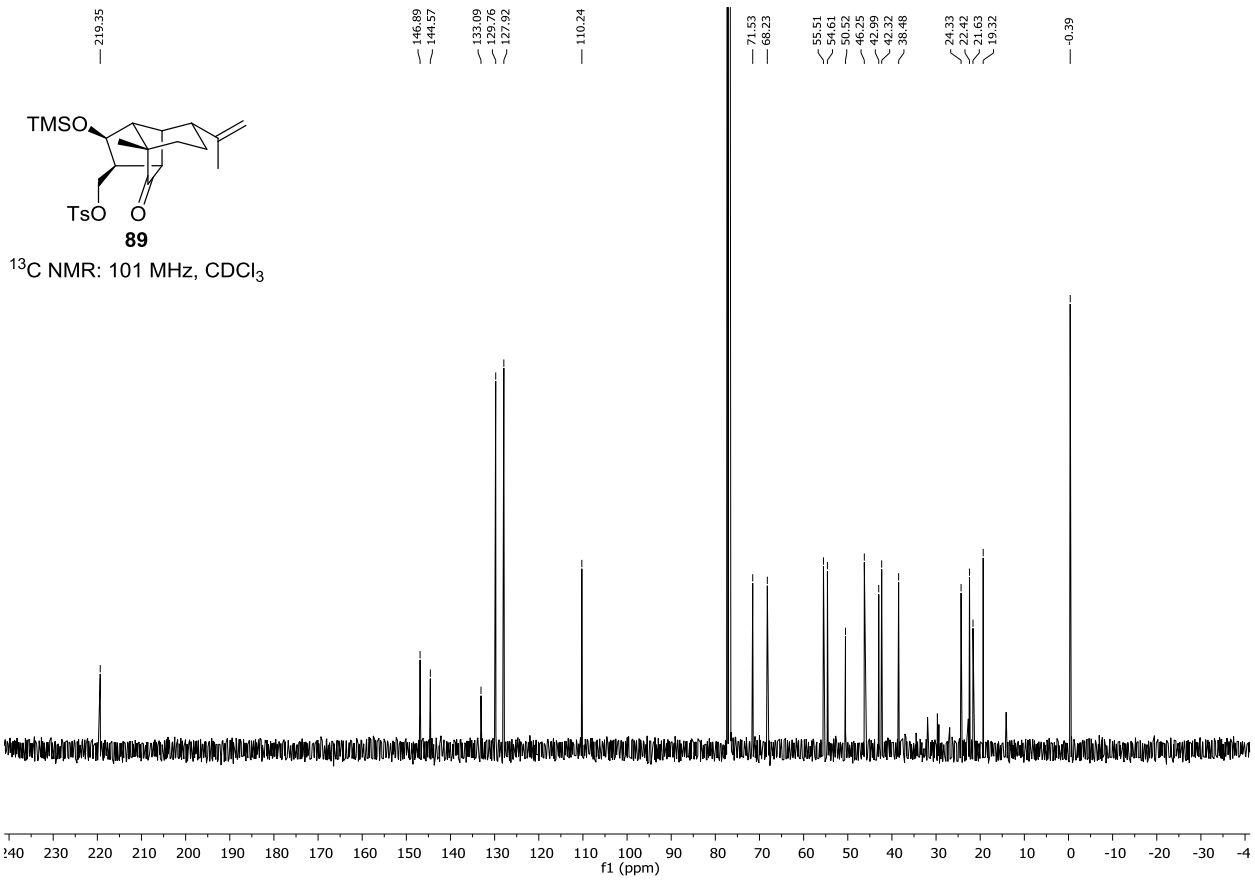

**87**

$^{13}$C NMR: 101 MHz, $CDCl_3$



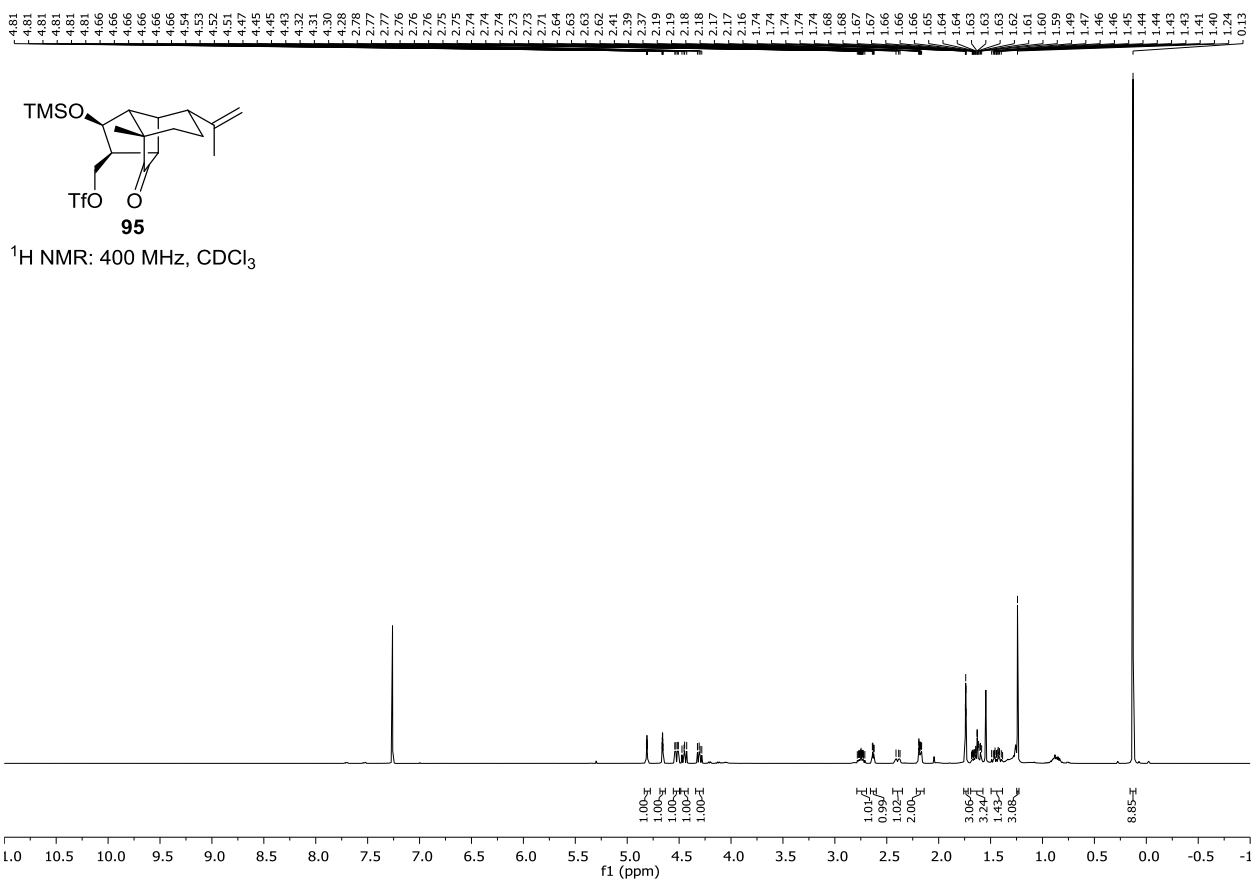

**89**

$^{1}$H NMR: 400 MHz, $CDCl_3$

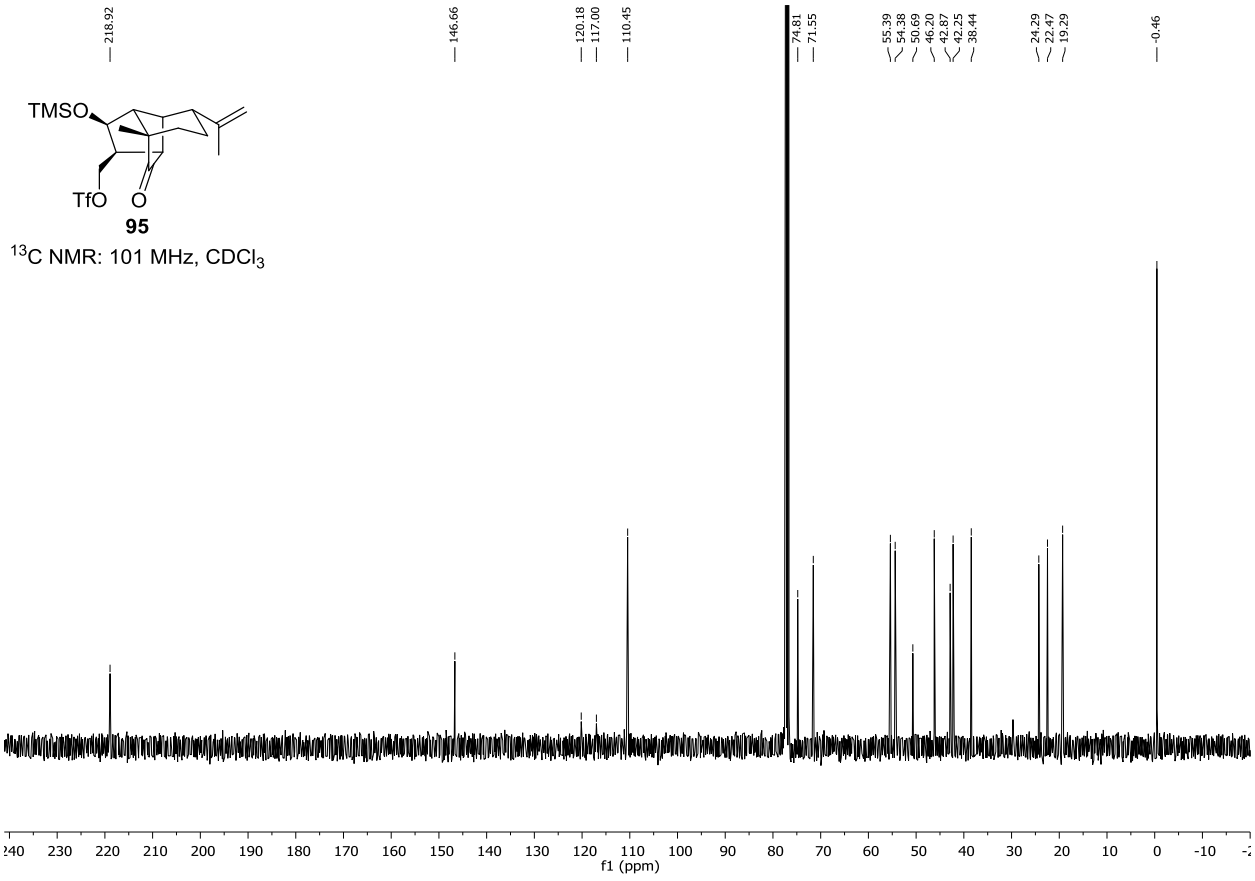



**89**

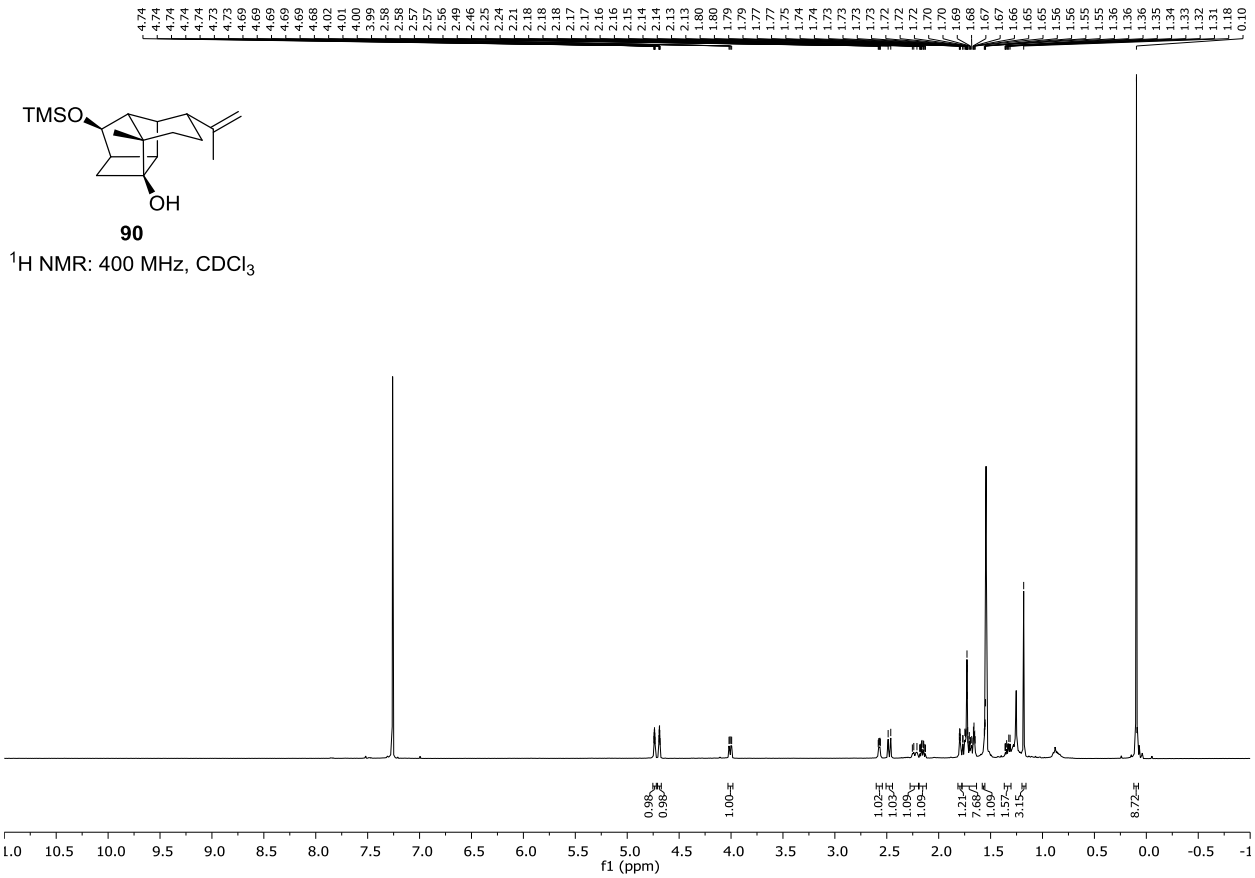
$^{13}$C NMR: 101 MHz, $CDCl_3$




$^{1}$H NMR: 400 MHz, $CDCl_3$



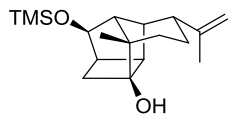

$^{13}$C NMR: 101 MHz, $CDCl_3$




**90**

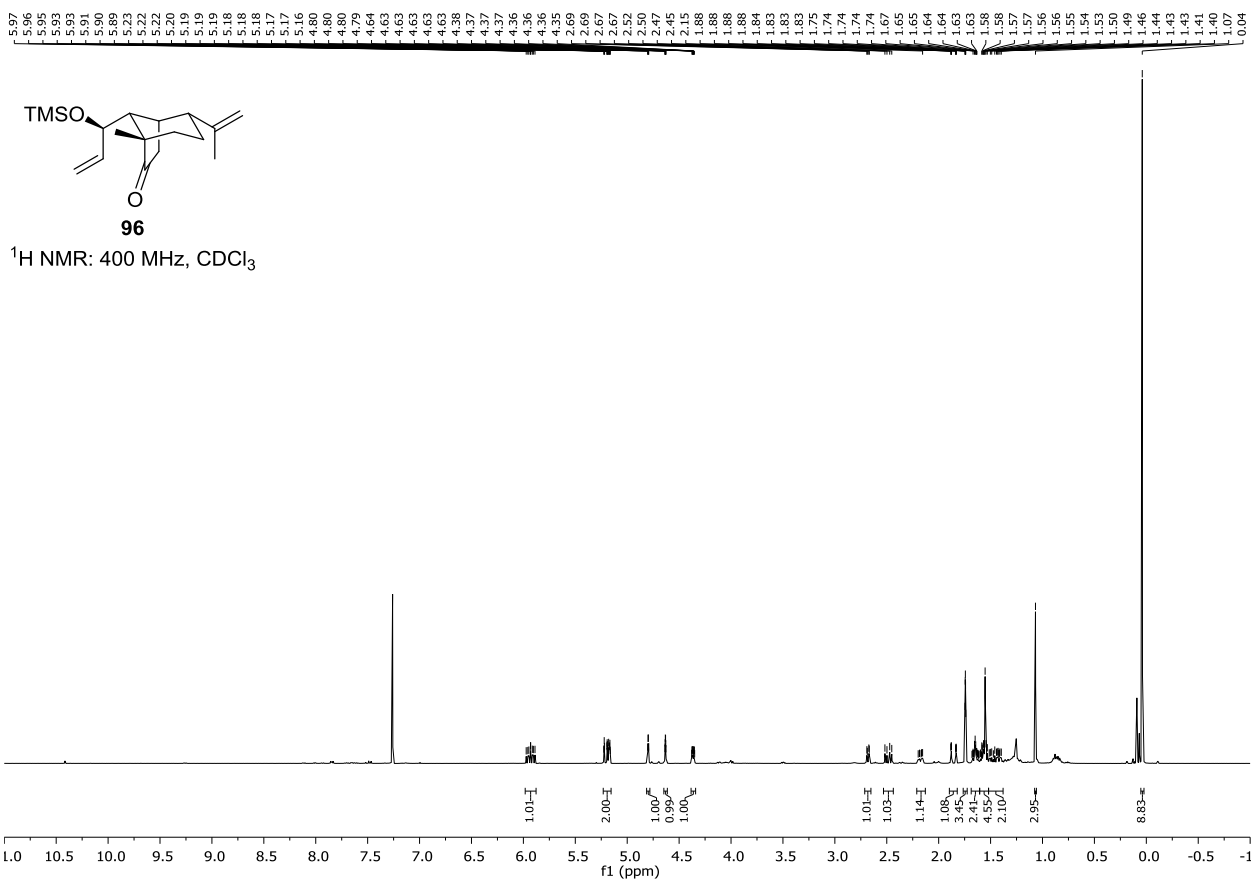
$^{1}$H NMR: 400 MHz, $CDCl_3$

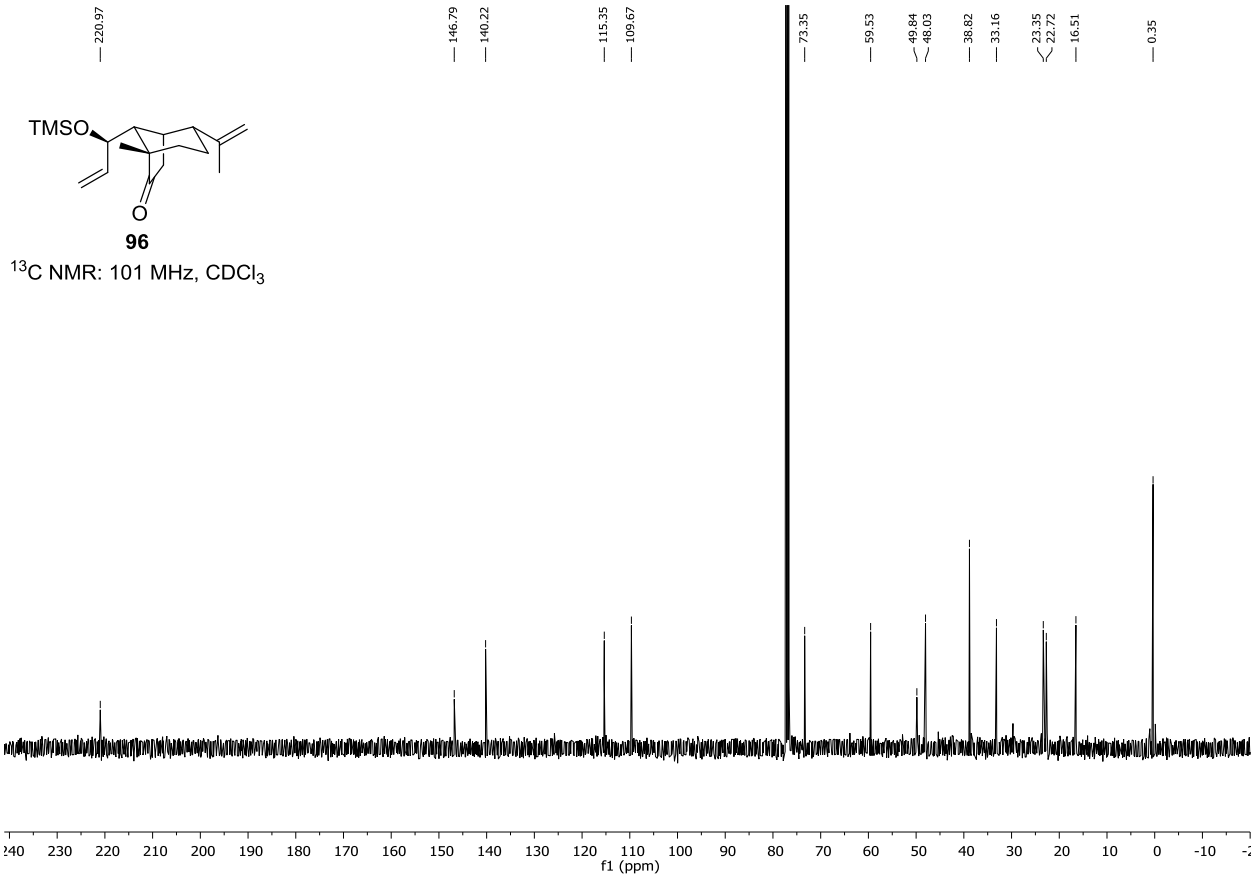


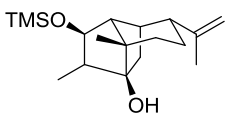




**90**

$^{13}$C NMR: 101 MHz, $CDCl_3$


TMSO
O
96
1H NMR: 400 MHz, CDCl3
f1 (ppm)

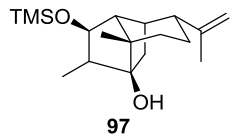

TMSO
O
96
13C NMR: 101 MHz, CDCl3
f1 (ppm)




**97**

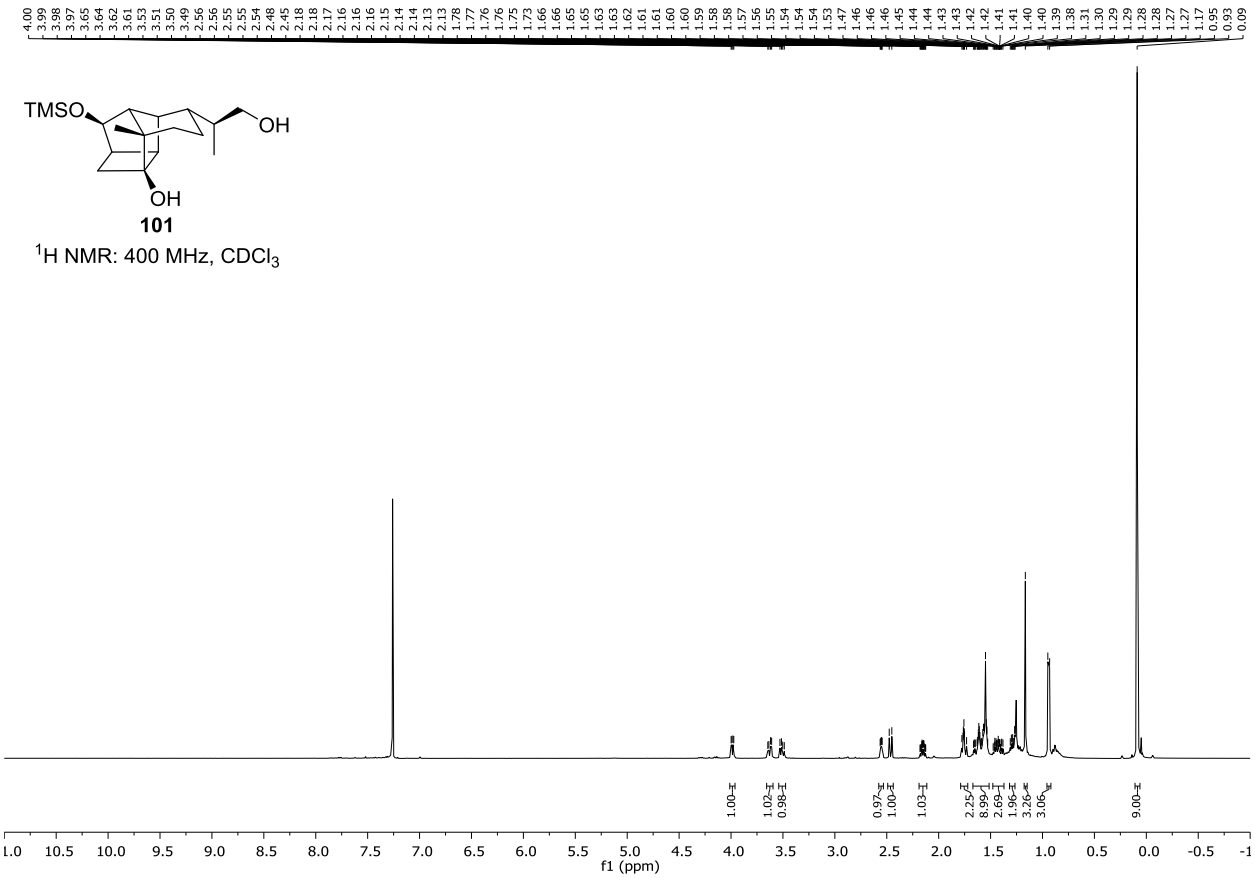
$^{1}$H NMR: 400 MHz, $CDCl_3$

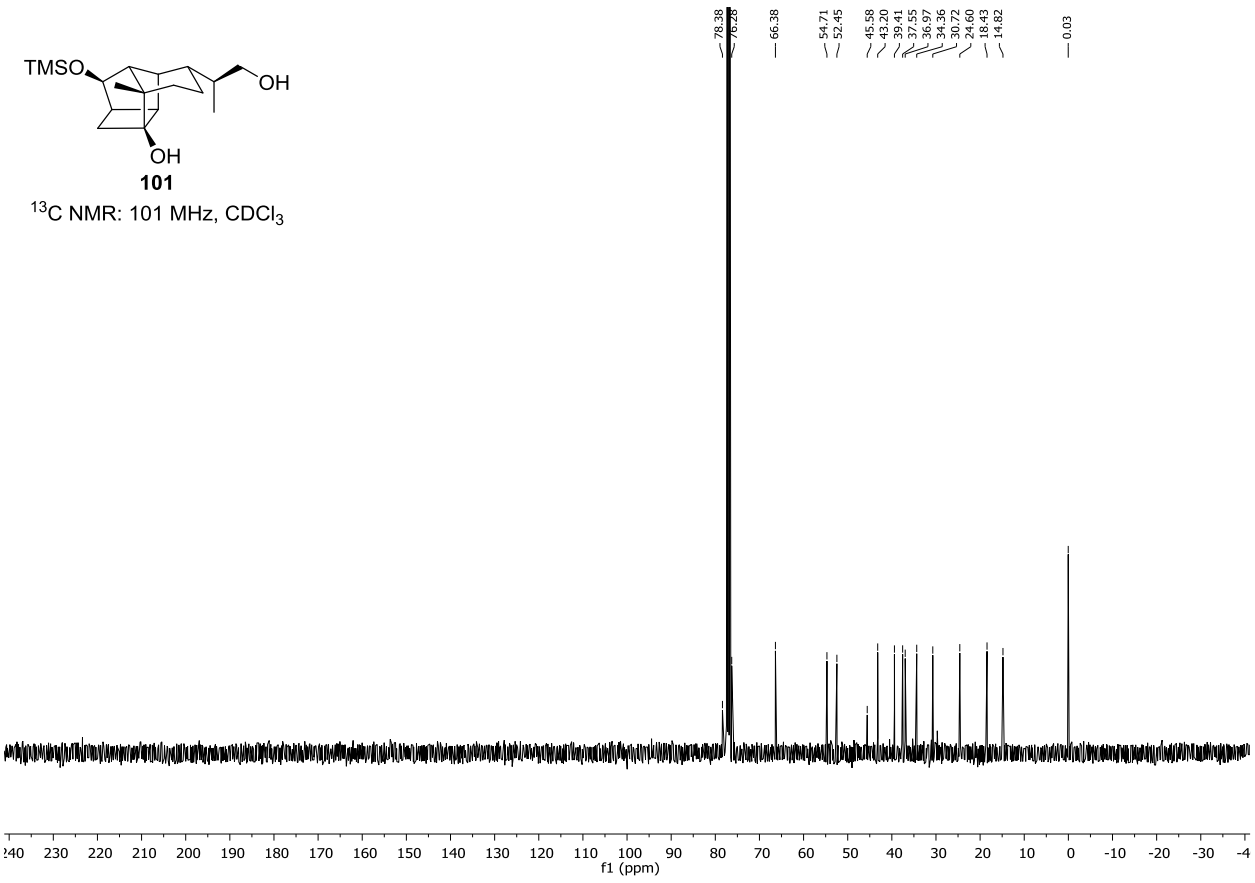


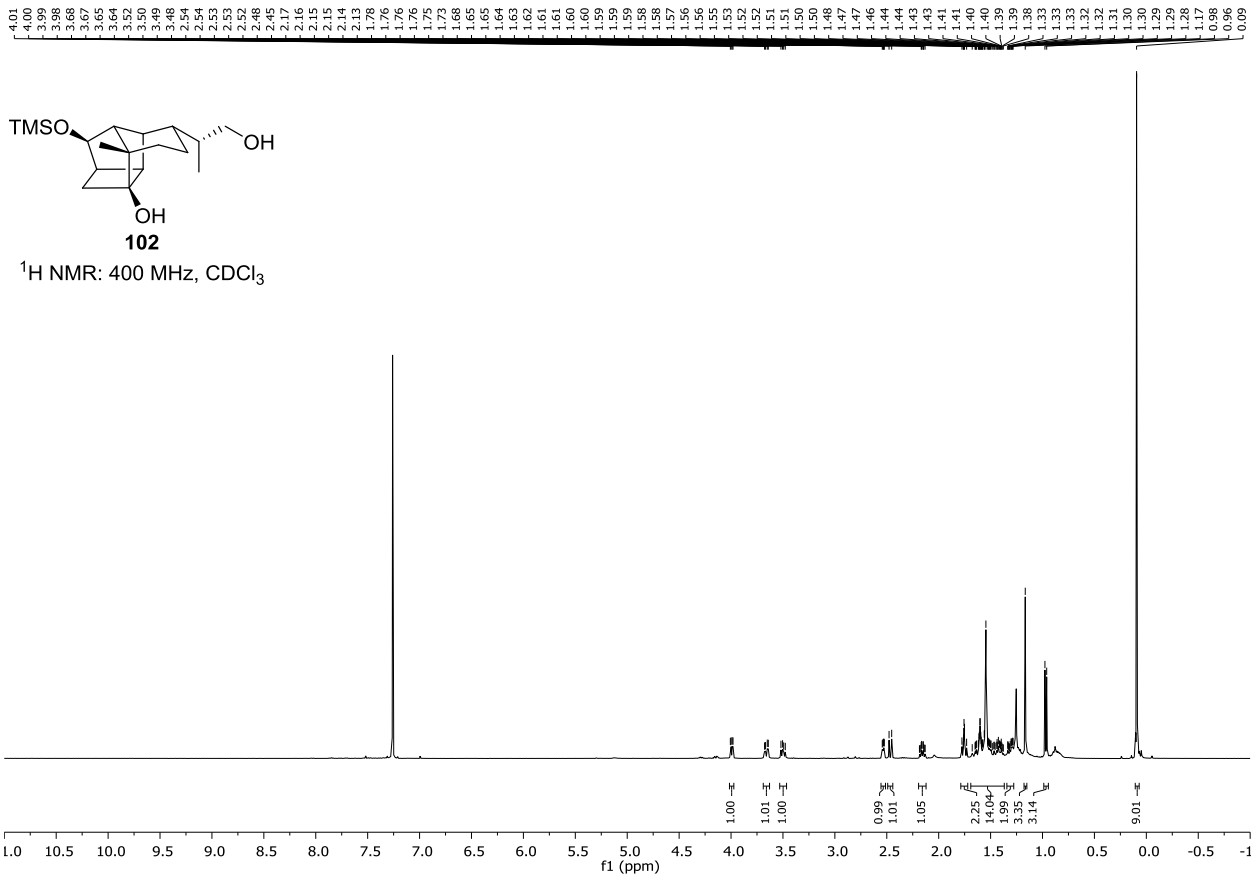




**97**

$^{13}$C NMR: 101 MHz, $CDCl_3$

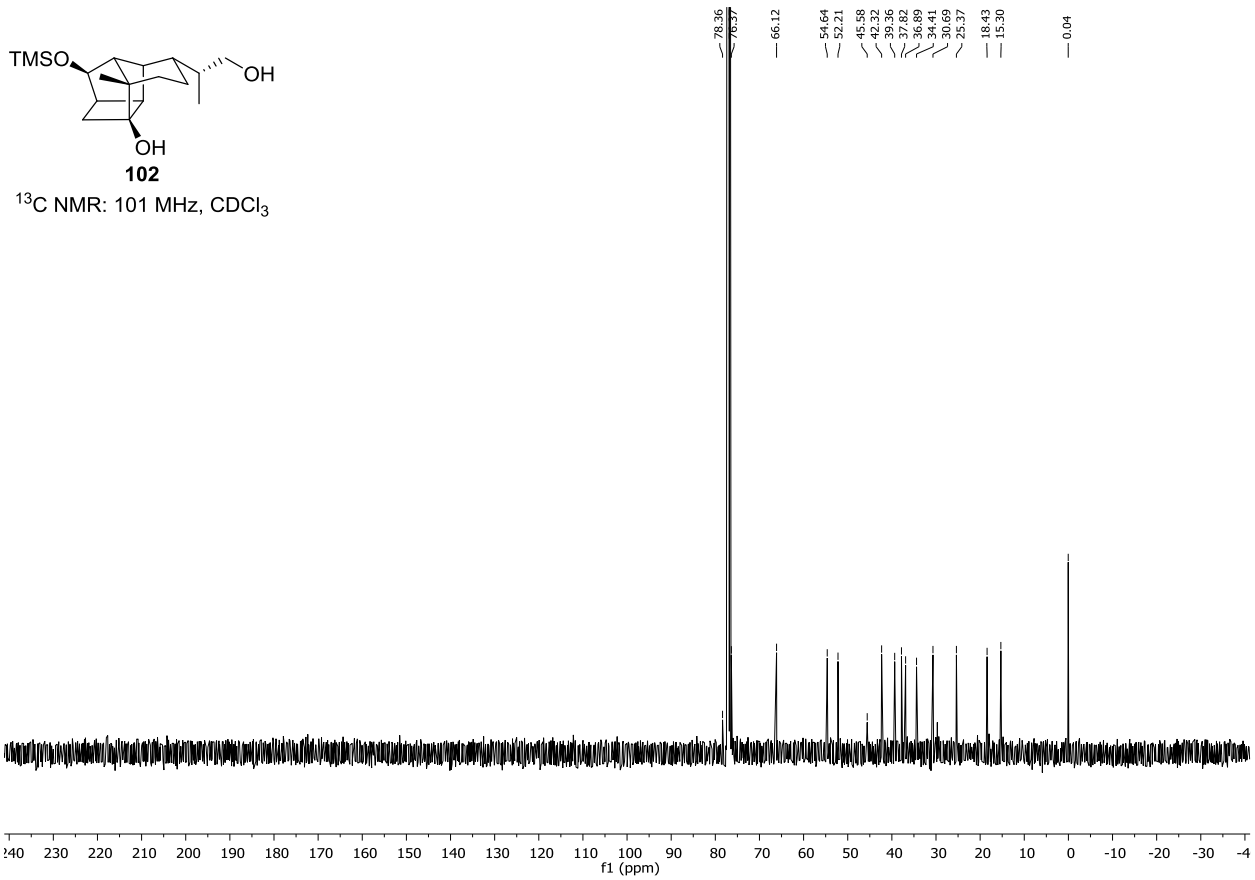

TMSO
OH
OH
101
1H NMR: 400 MHz, CDCl3
f1 (ppm)


TMSO
OH
OH
101
13C NMR: 101 MHz, CDCl3
f1 (ppm)



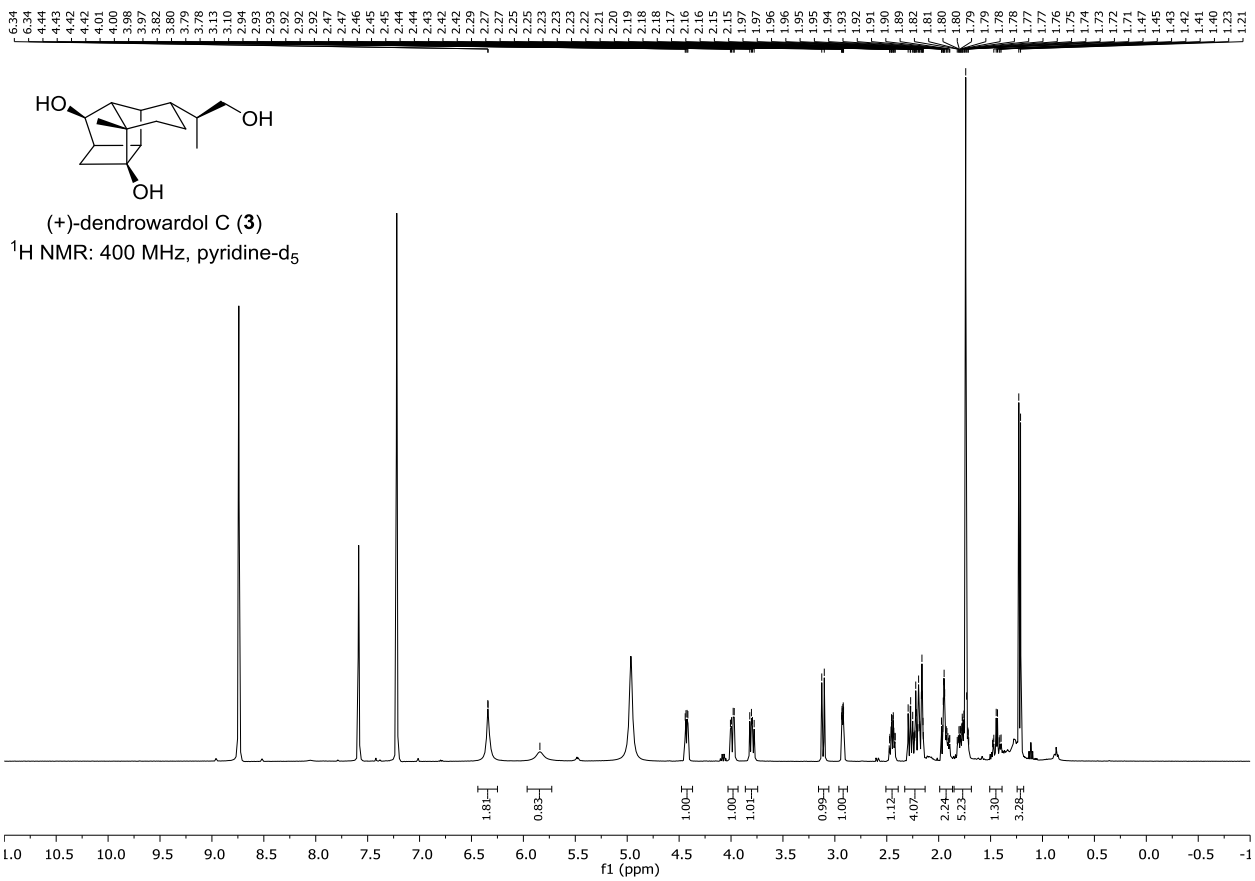

**102**

$^{1}$H NMR: 400 MHz, $CDCl_3$

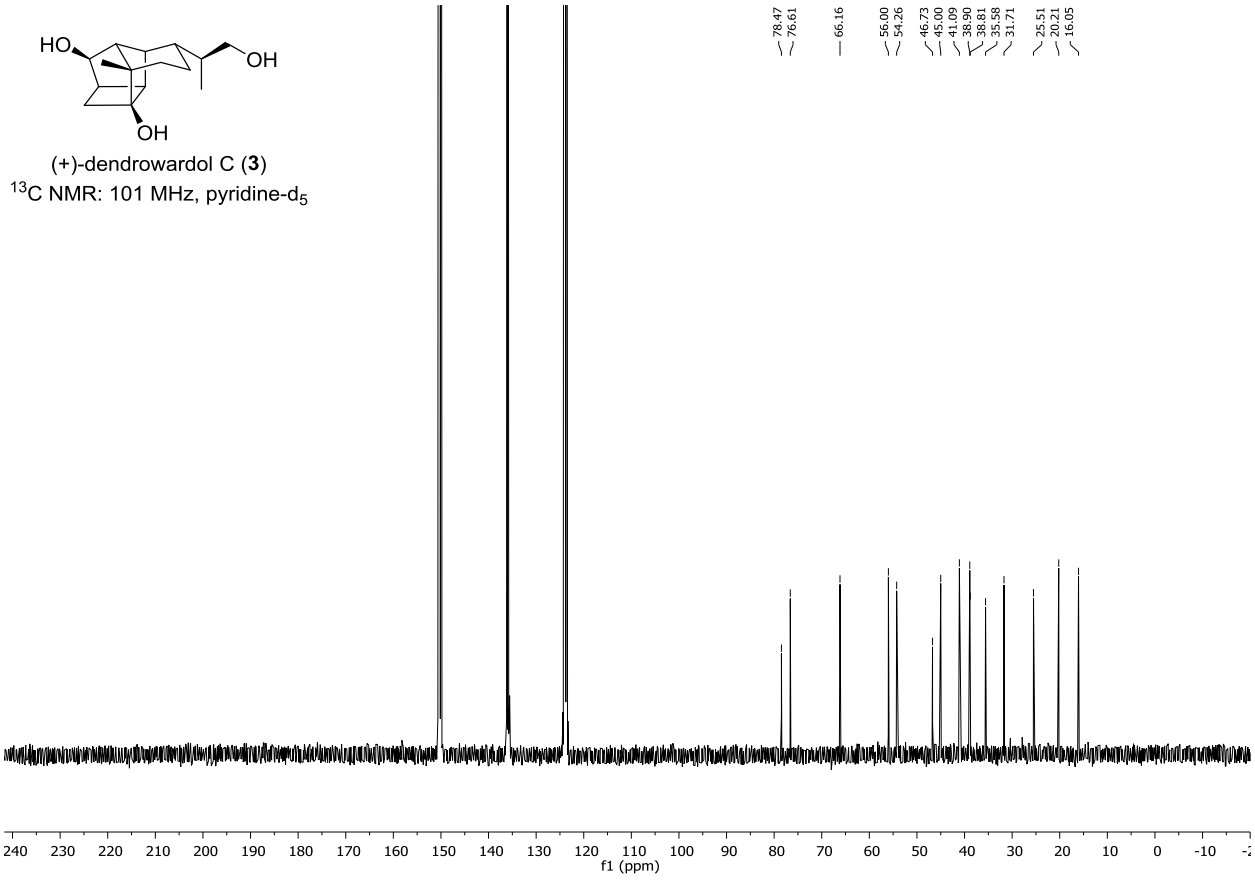



**102**

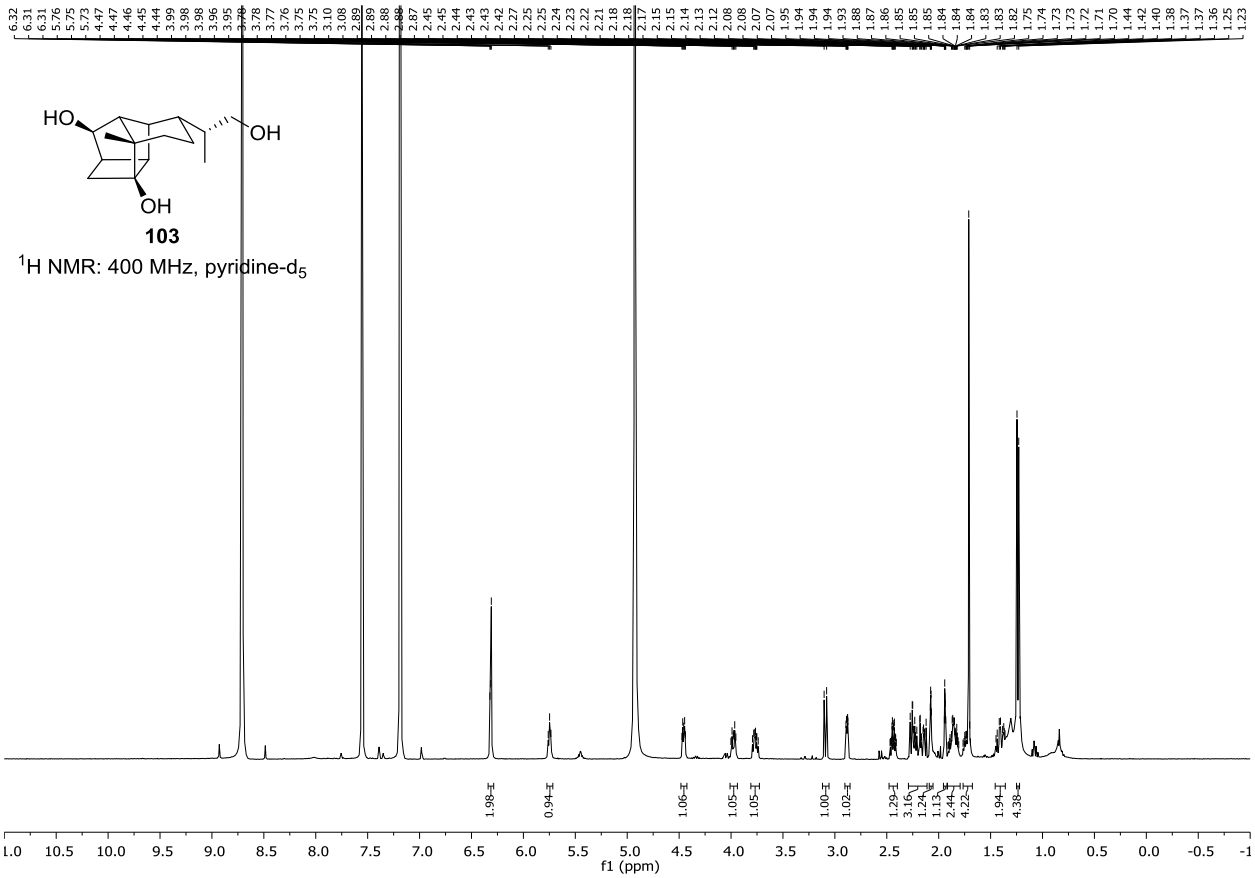
$^{13}$C NMR: 101 MHz, $CDCl_3$




(+)-dendrowardol C (**3**)
$^{1}$H NMR: 400 MHz, pyridine-$d_5$

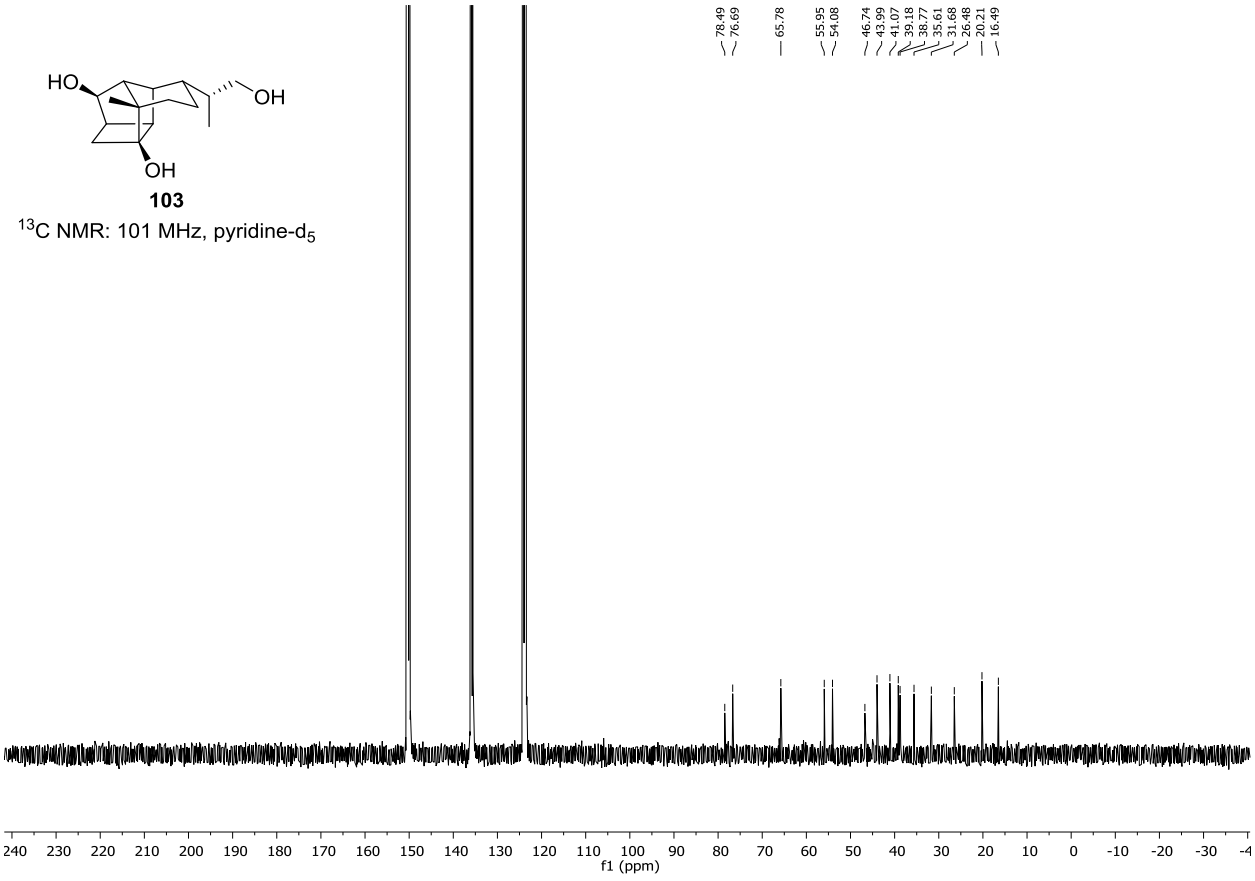



(+)-dendrowardol C (**3**)
$^{13}$C NMR: 101 MHz, pyridine-$d_5$



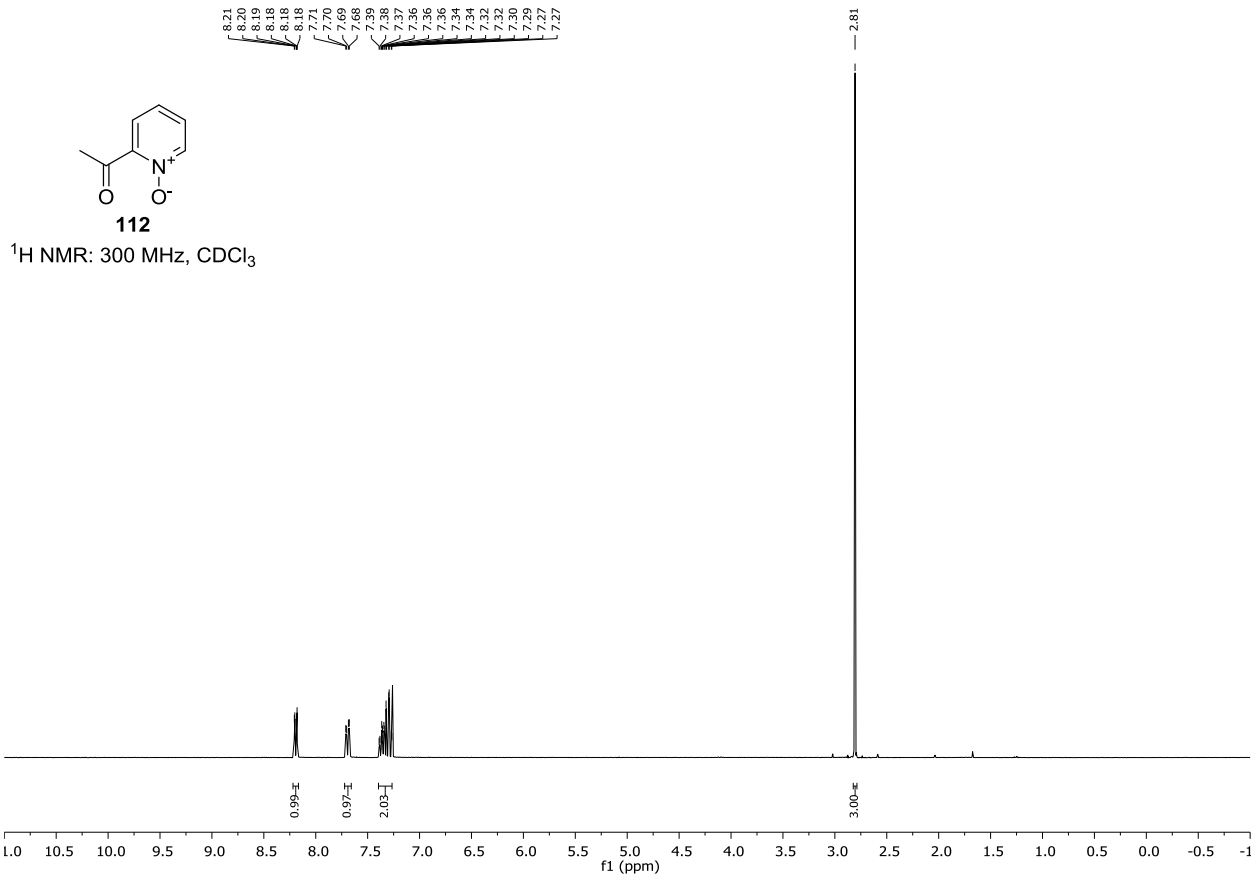

**103**

$^{1}$H NMR: 400 MHz, pyridine-$d_5$



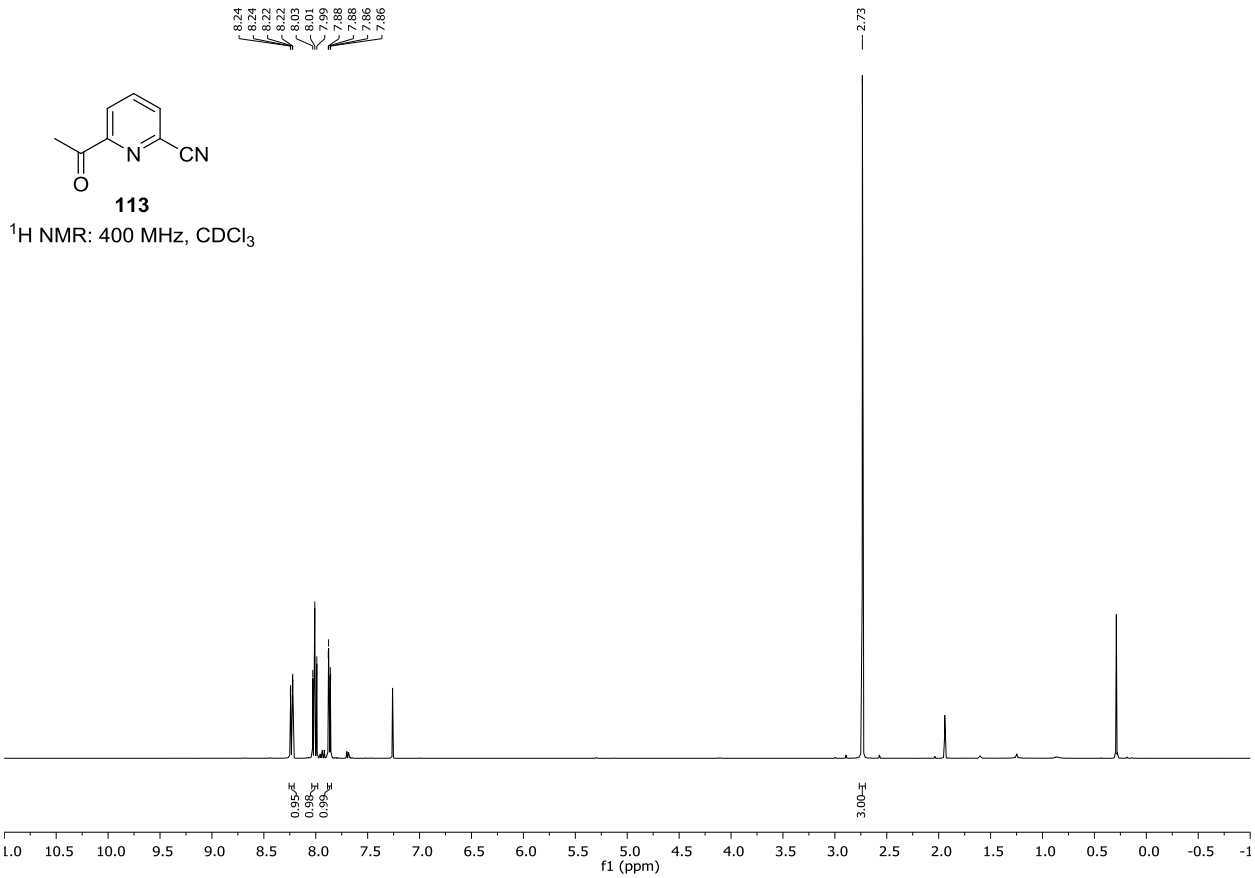

**103**

$^{13}$C NMR: 101 MHz, pyridine-$d_5$



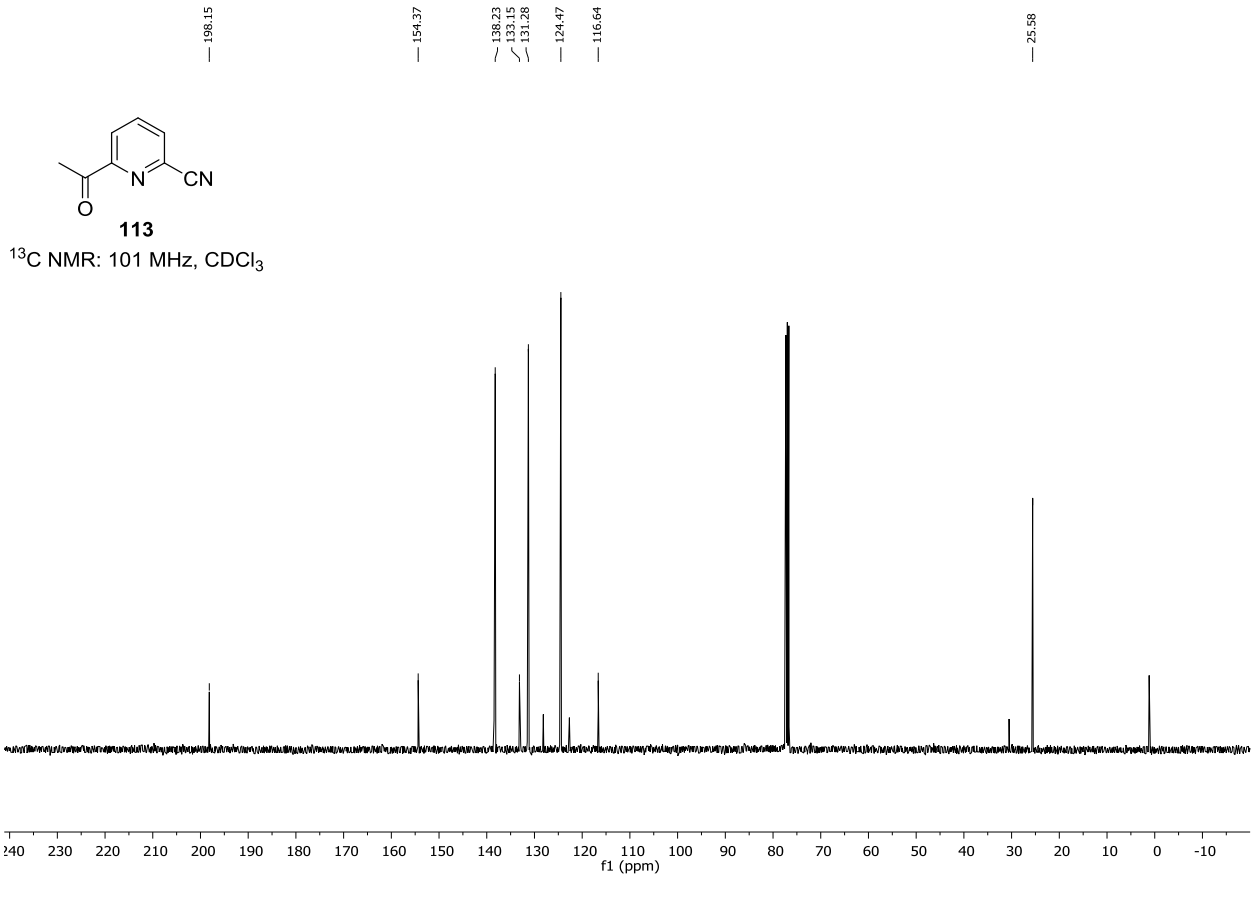

**112**

$^1$H NMR: 300 MHz, $CDCl_3$



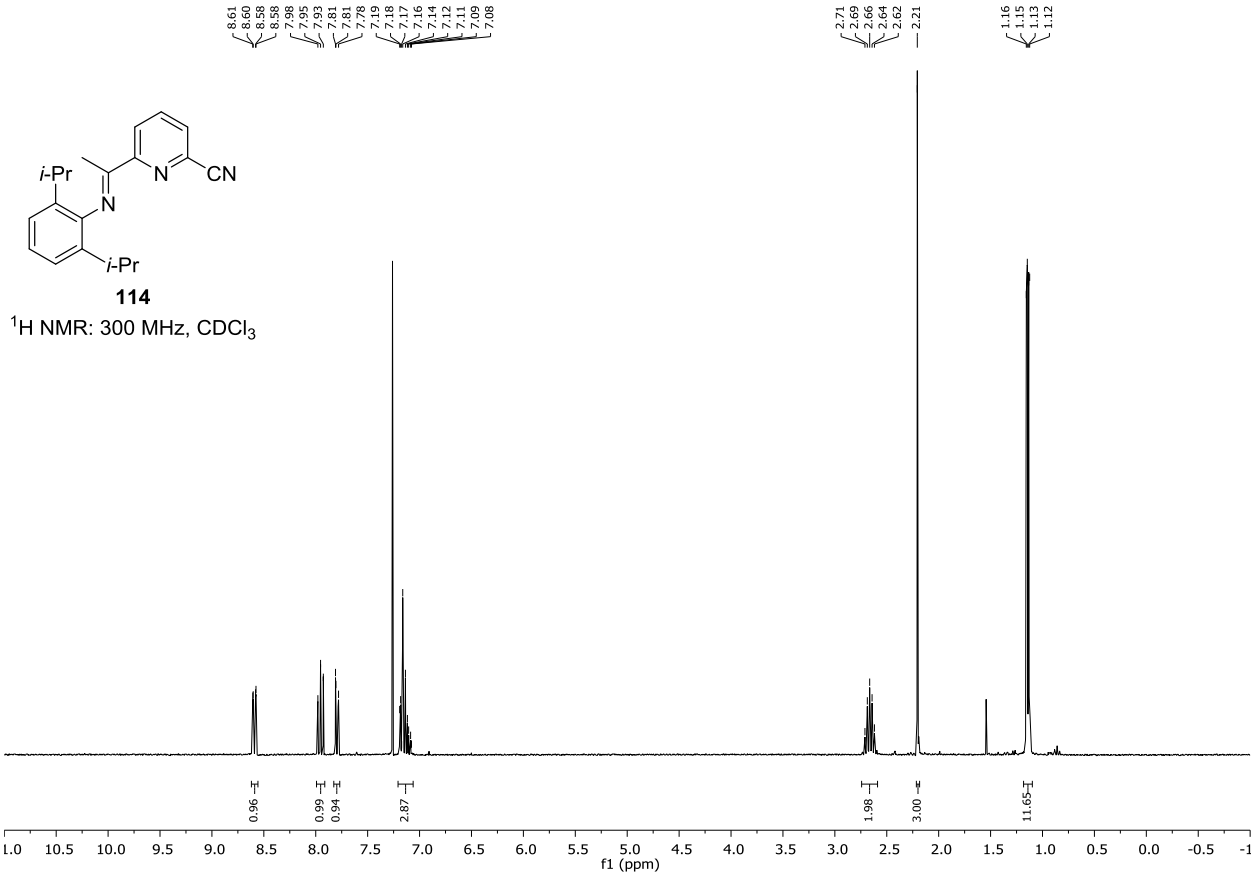

**113**

$^{1}$H NMR: 400 MHz, $CDCl_3$



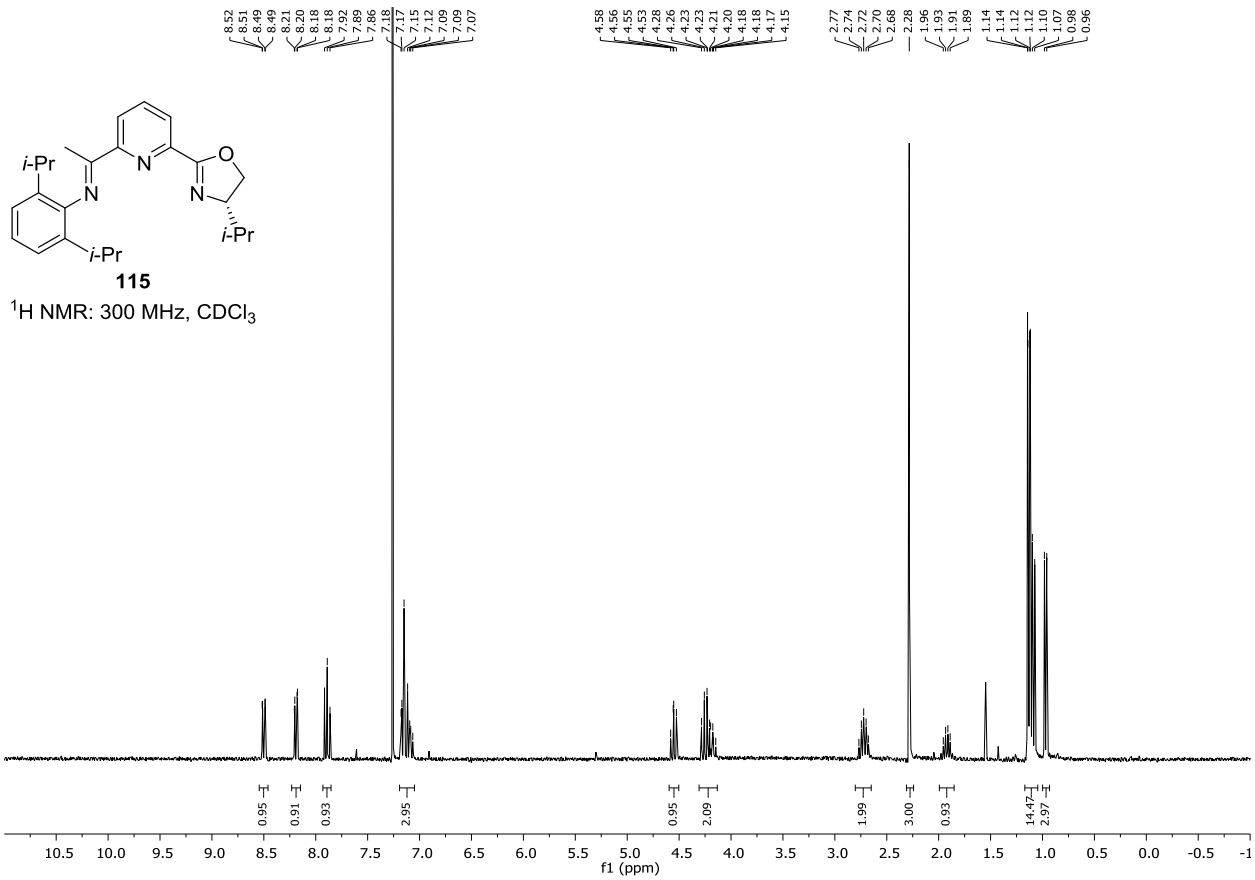

**113**

$^{13}$C NMR: 101 MHz, $CDCl_3$



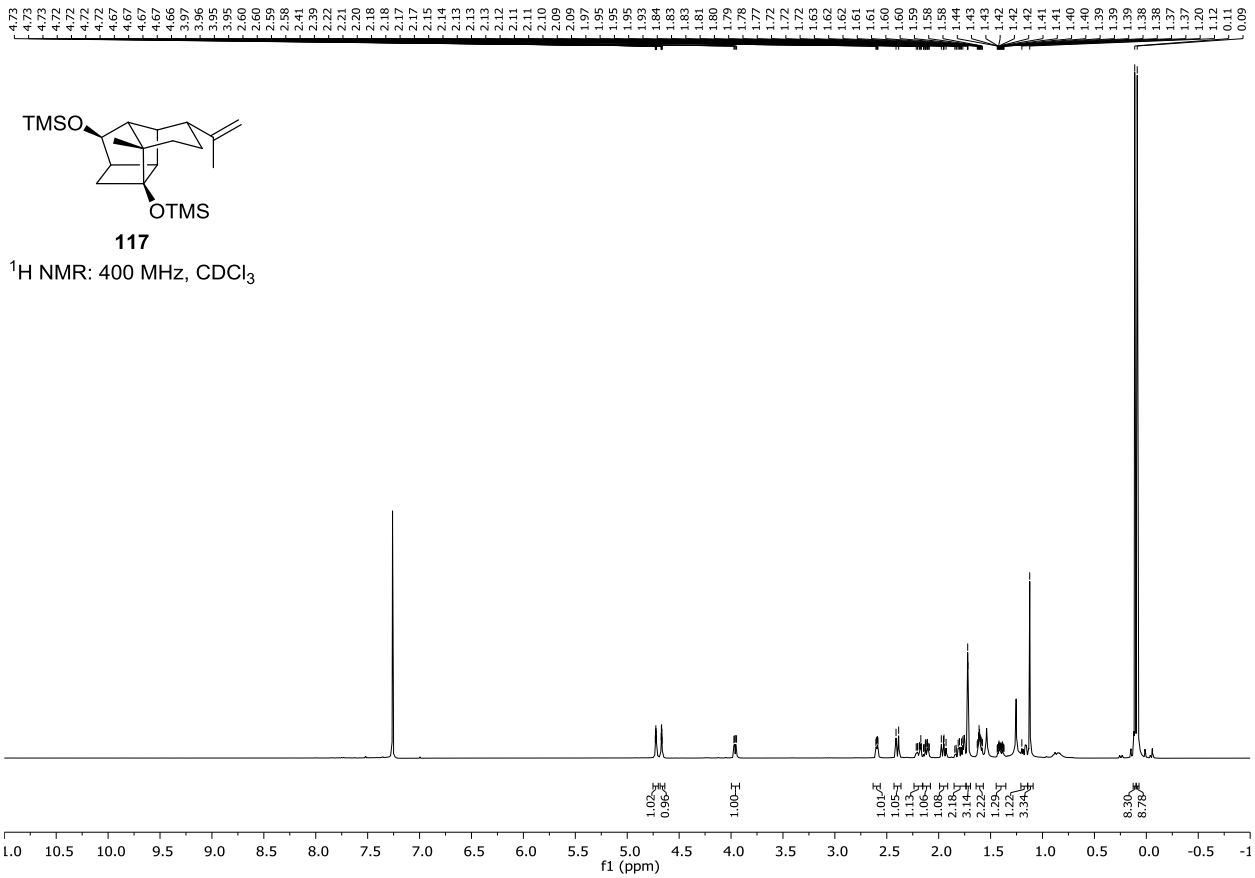

**114**

$^1$H NMR: 300 MHz, $CDCl_3$



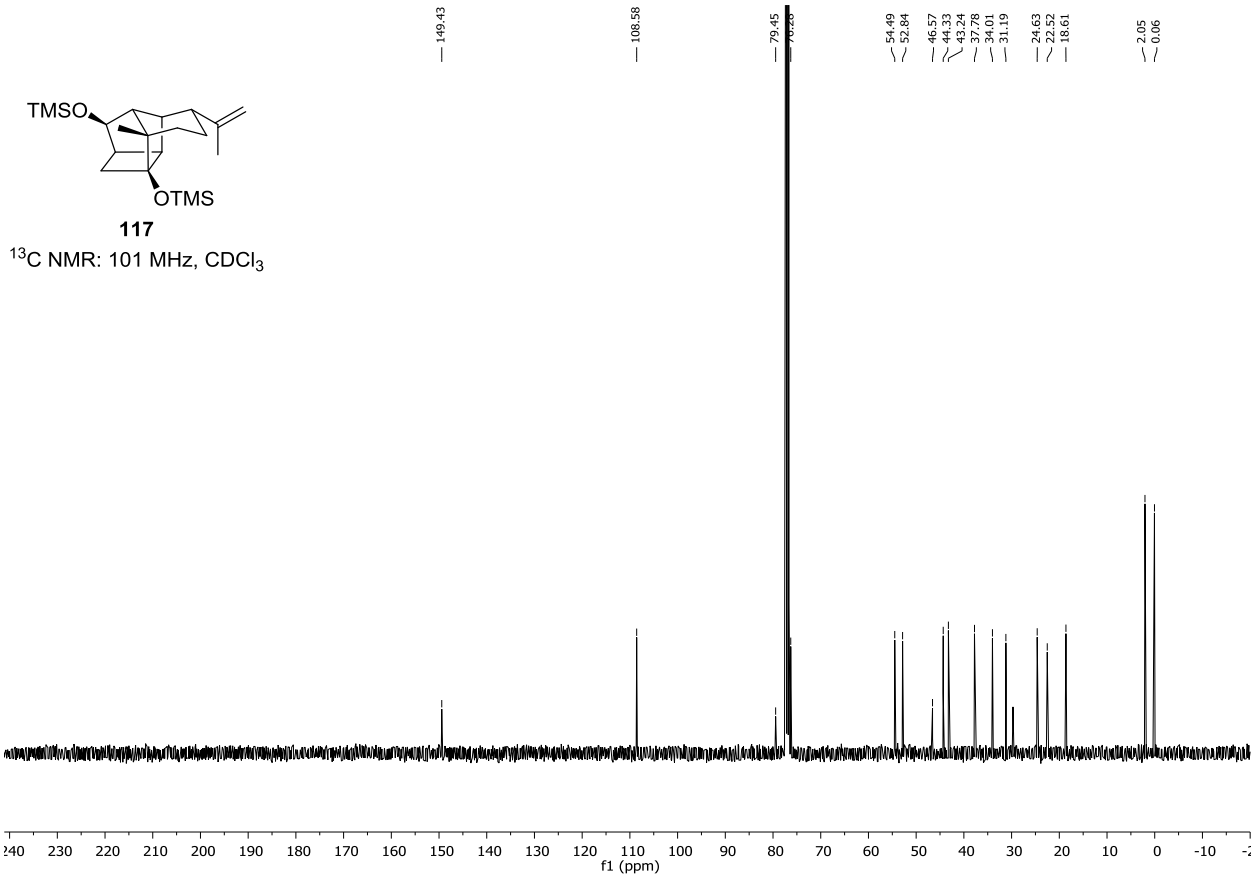

**115**

$^1$H NMR: 300 MHz, $CDCl_3$



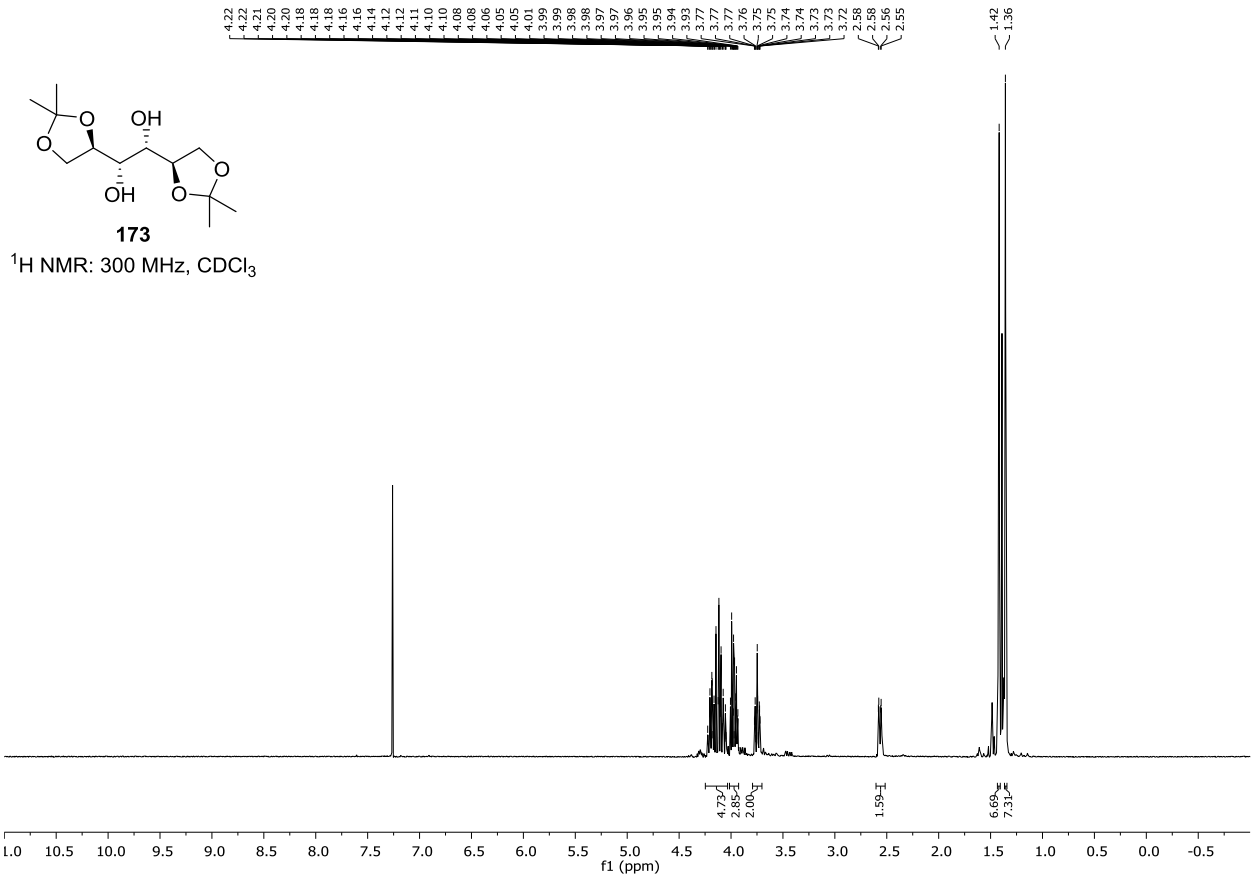

**117**

$^{1}$H NMR: 400 MHz, $CDCl_3$



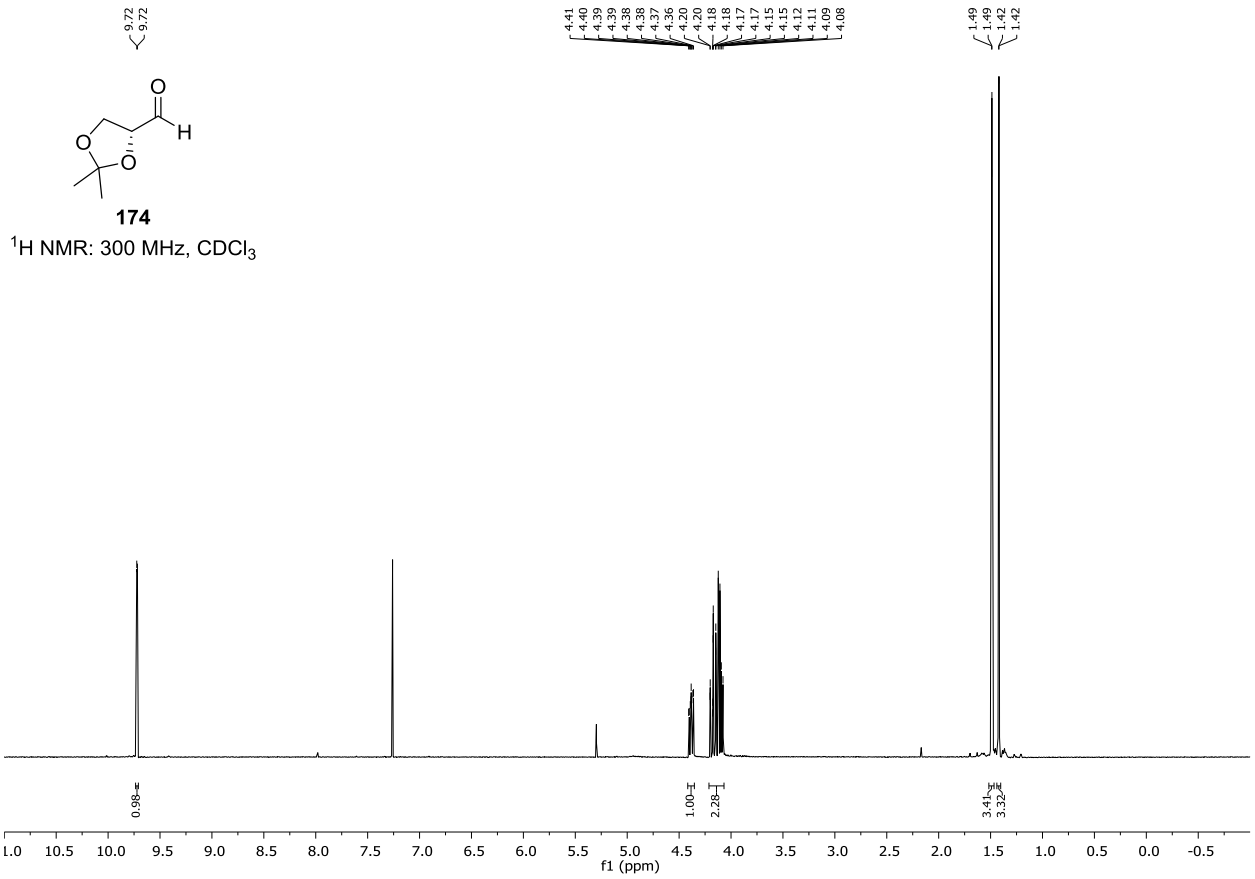

**117**

$^{13}$C NMR: 101 MHz, $CDCl_3$



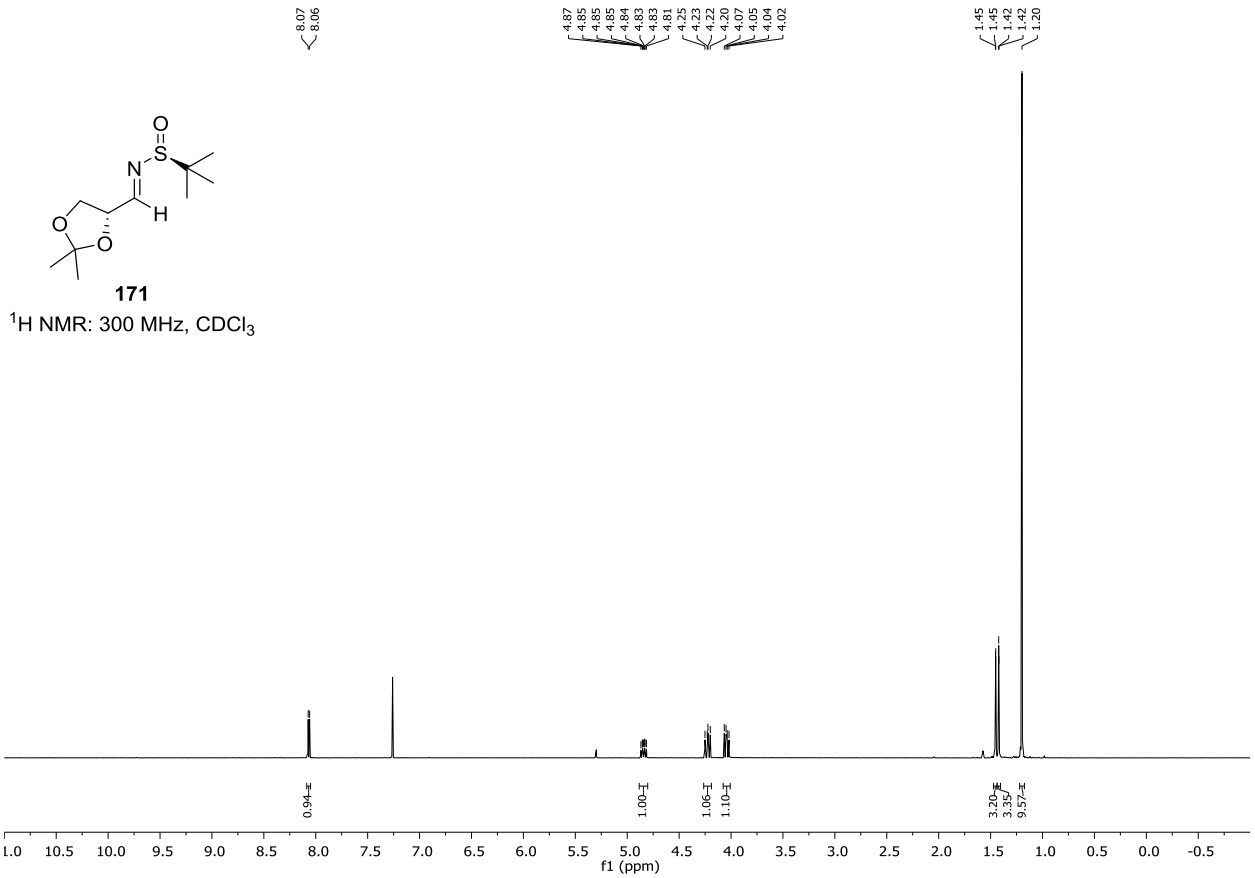

**173**

$^1$H NMR: 300 MHz, $CDCl_3$



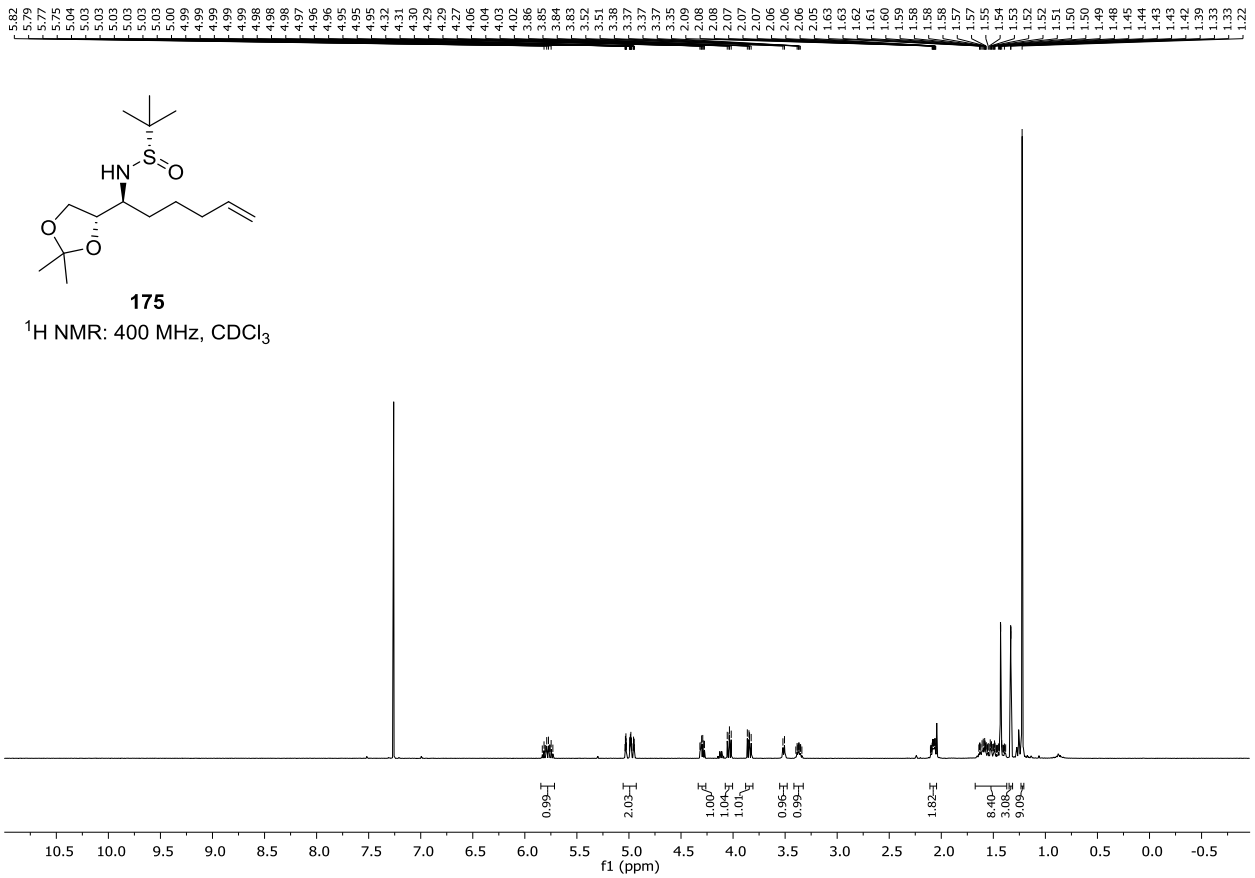

**174**

$^1$H NMR: 300 MHz, $CDCl_3$



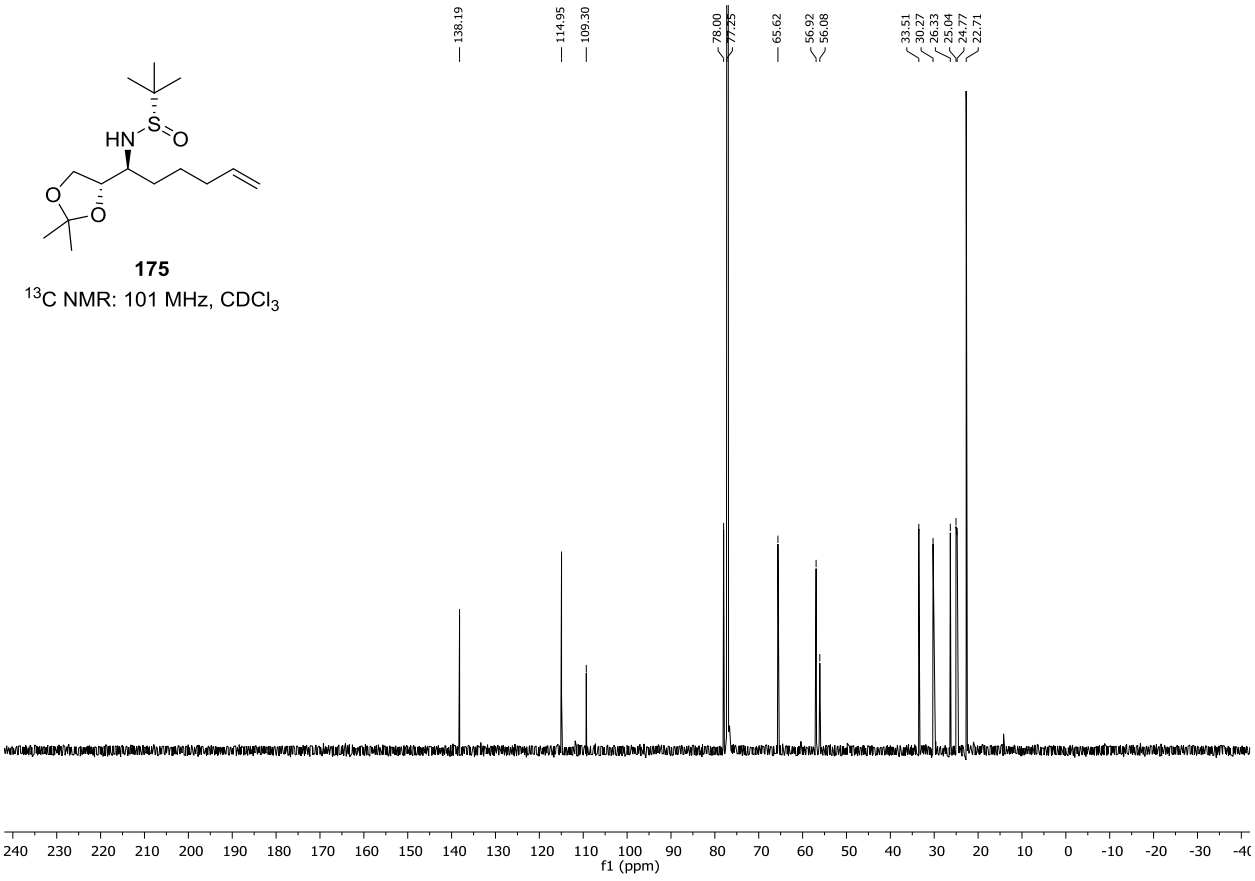

**171**

$^1$H NMR: 300 MHz, $CDCl_3$



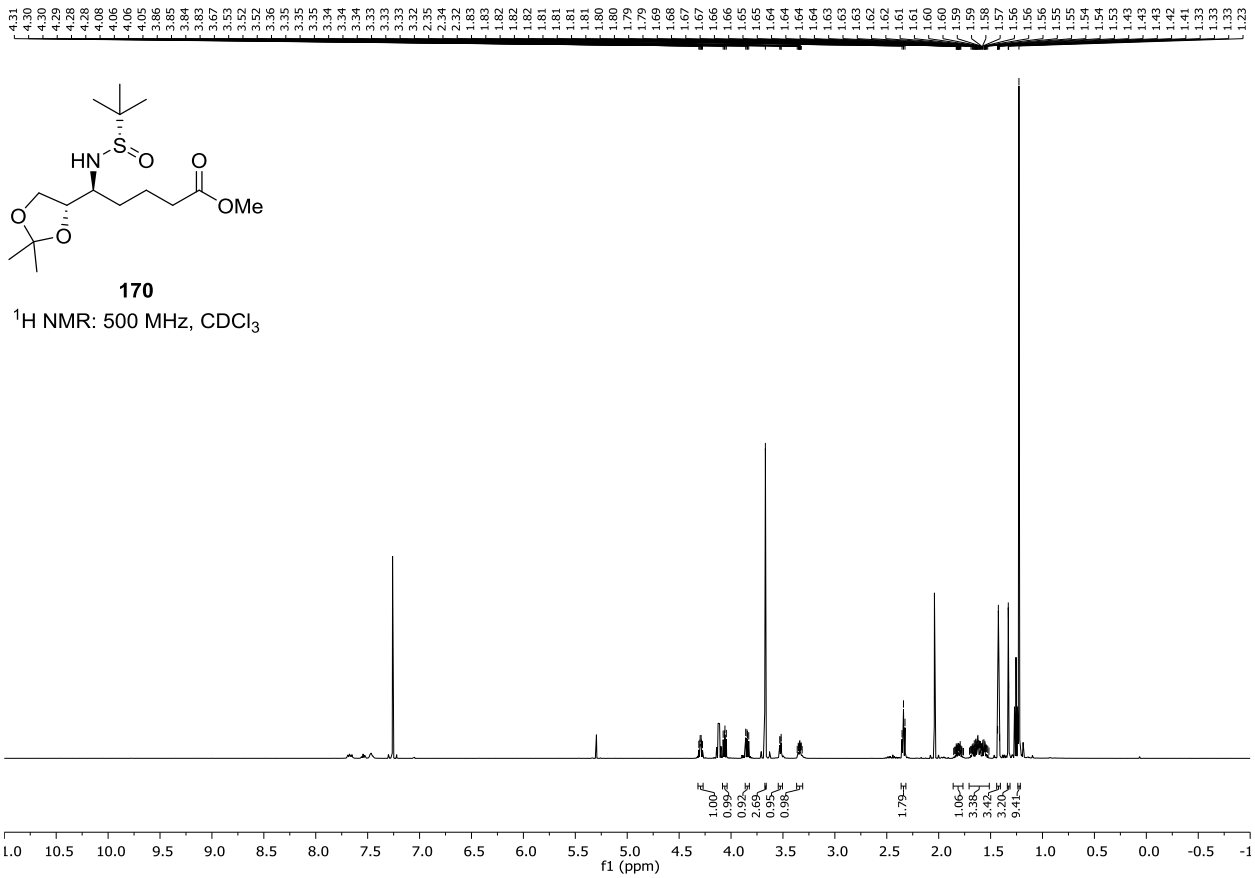
**175**

$^{1}$H NMR: 400 MHz, $CDCl_3$



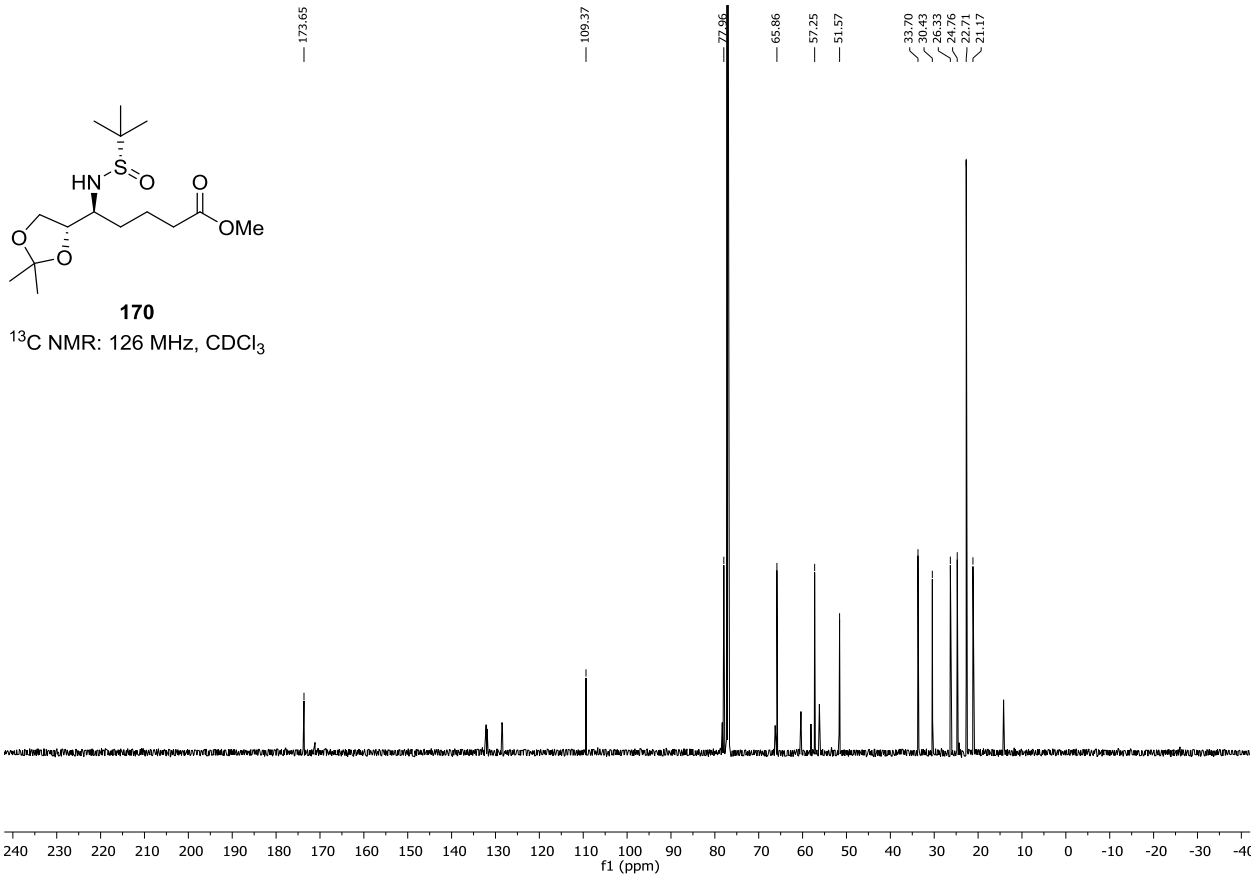
**175**

$^{13}$C NMR: 101 MHz, $CDCl_3$



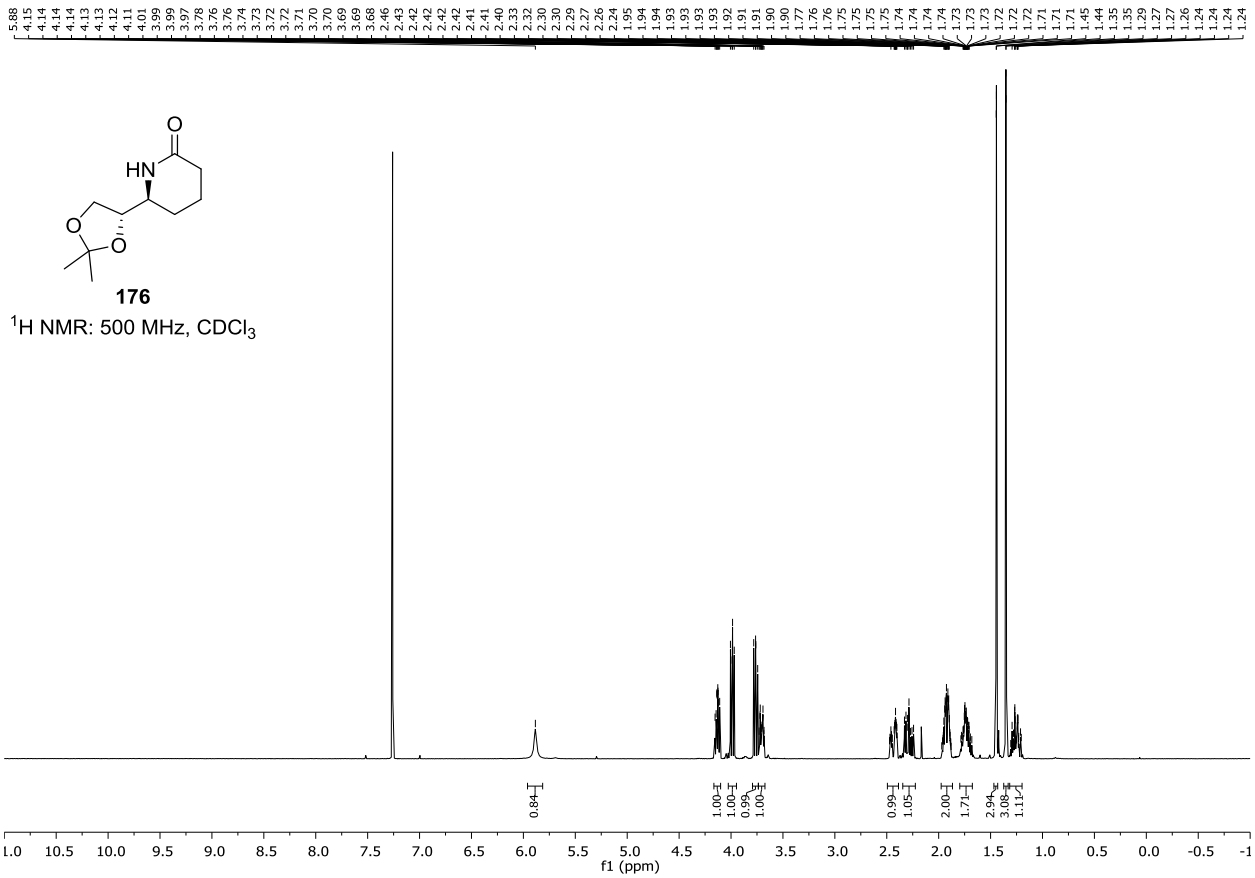

**170**

$^{1}$H NMR: 500 MHz, $CDCl_3$



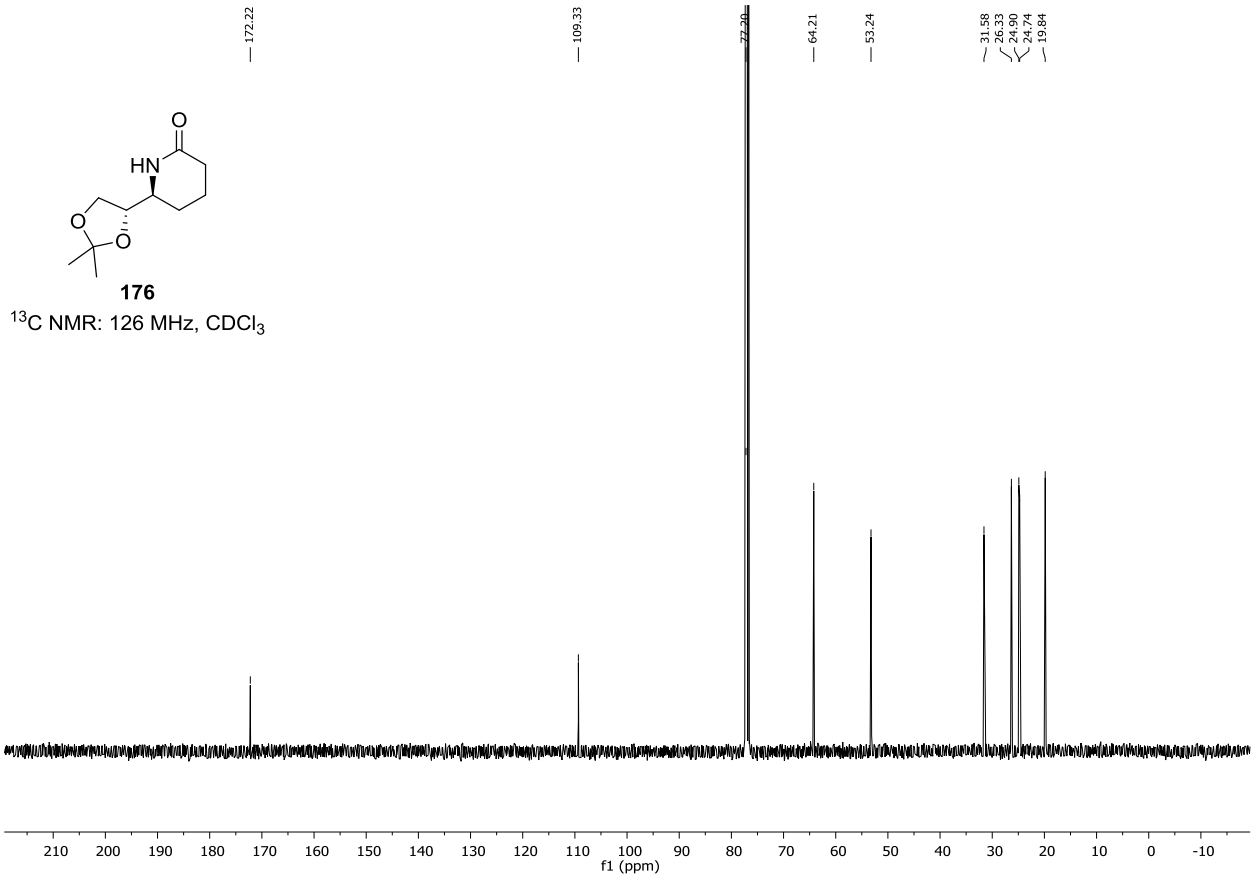

**170**

$^{13}$C NMR: 126 MHz, $CDCl_3$



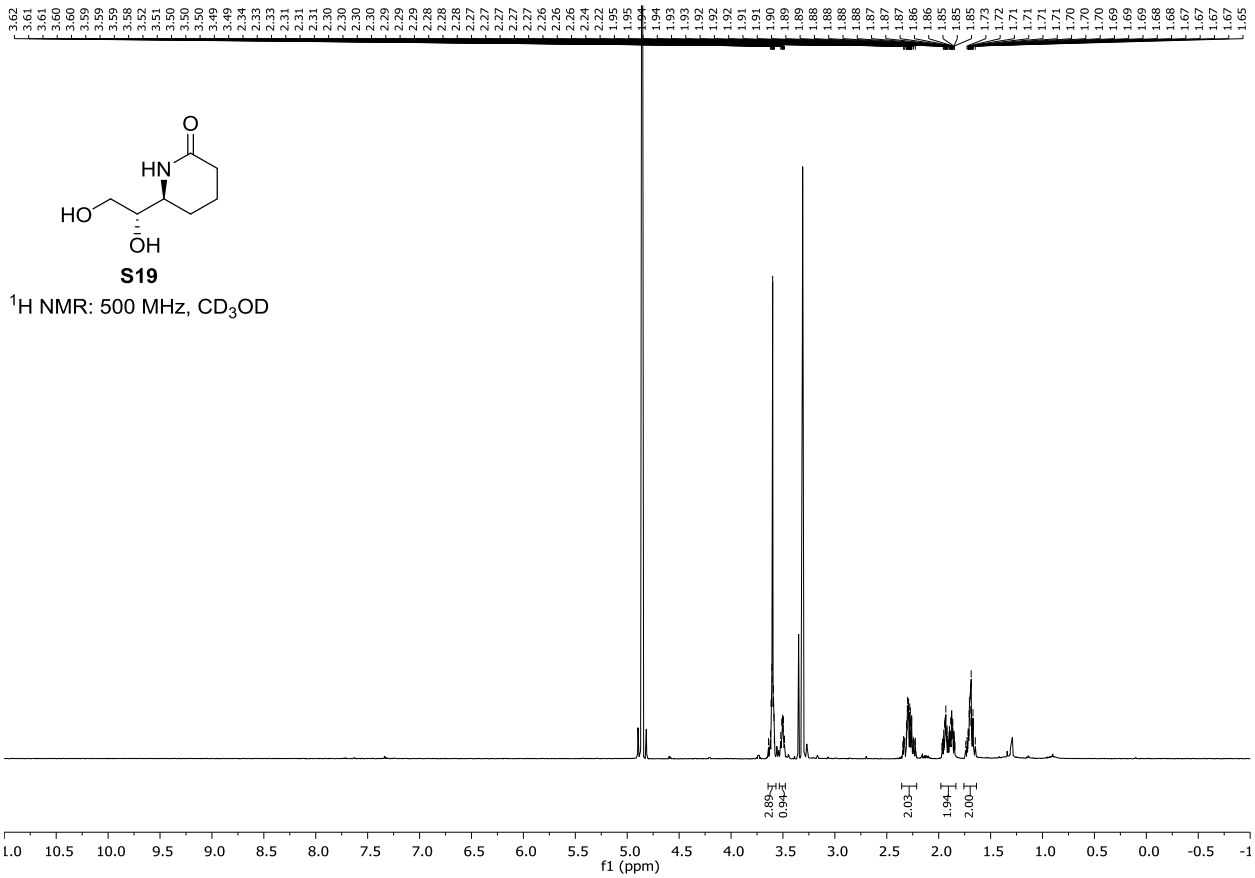

**176**

$^{1}$H NMR: 500 MHz, $CDCl_3$



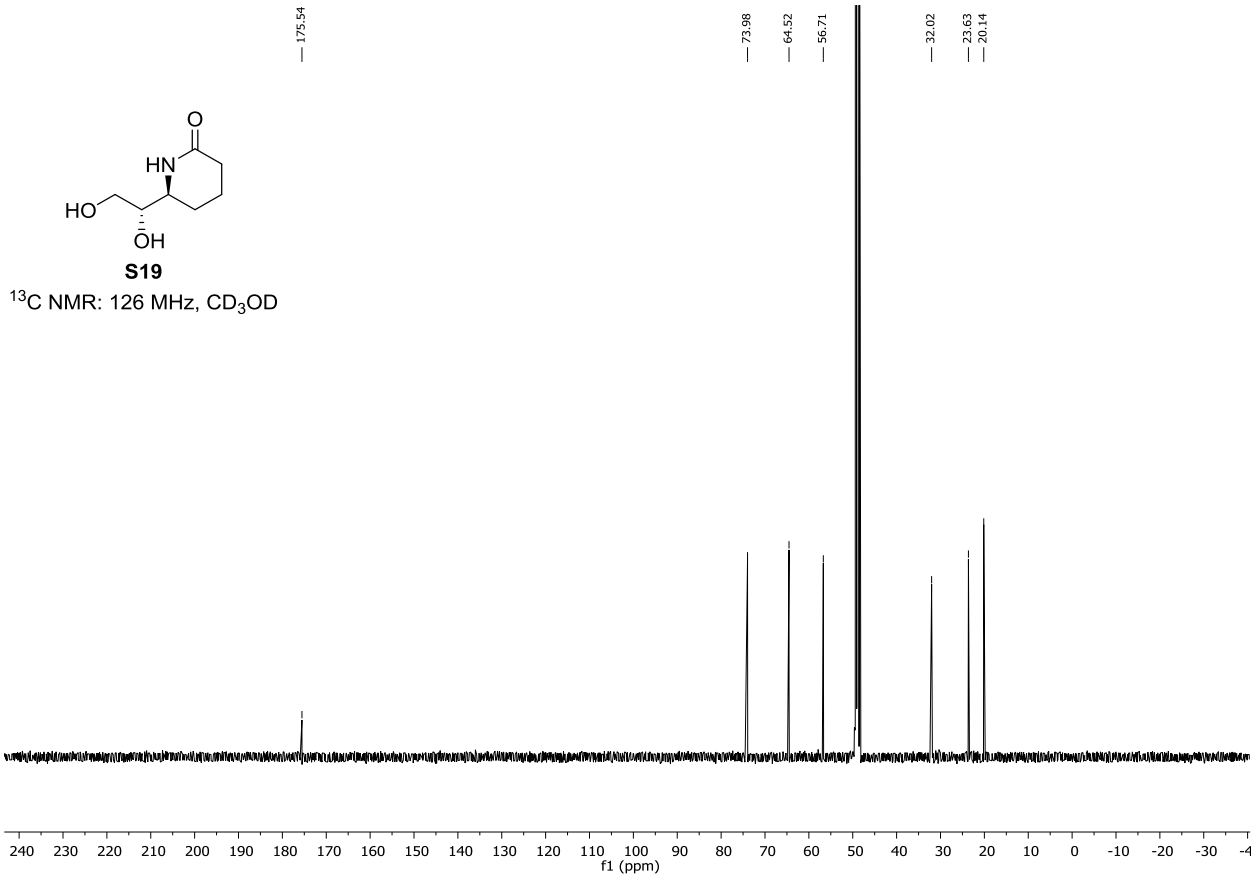

**176**

$^{13}$C NMR: 126 MHz, $CDCl_3$



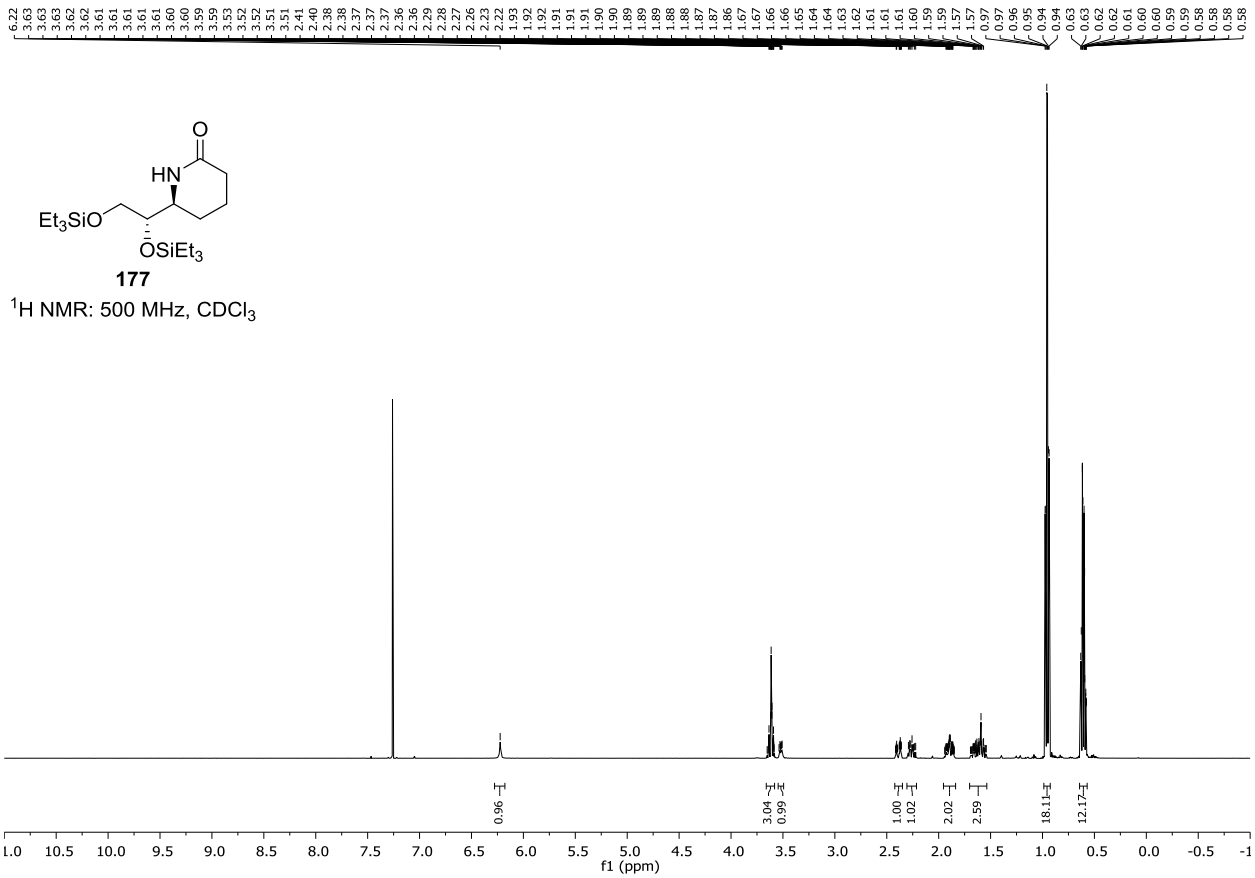

**S19**

$^{1}$H NMR: 500 MHz, $CD_3OD$



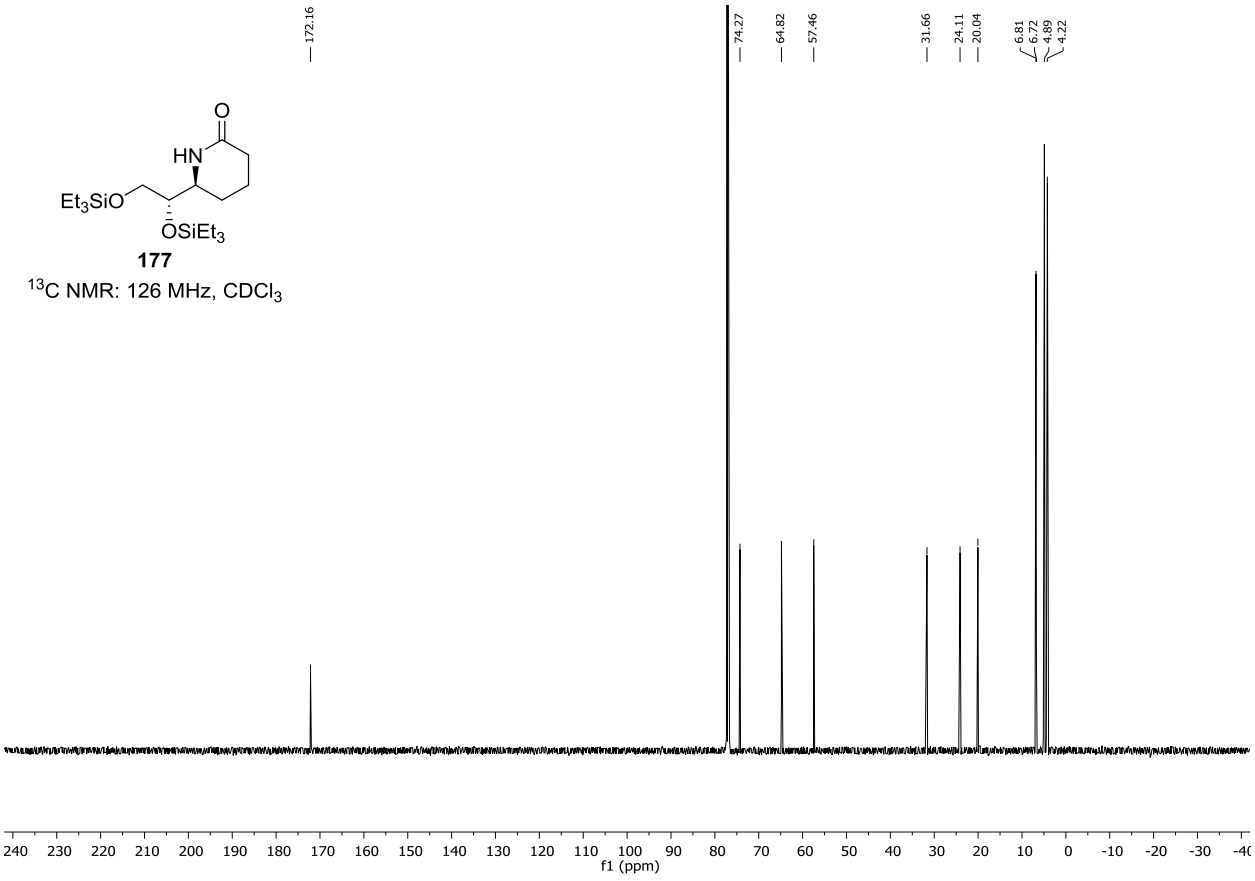

**S19**

$^{13}$C NMR: 126 MHz, $CD_3OD$



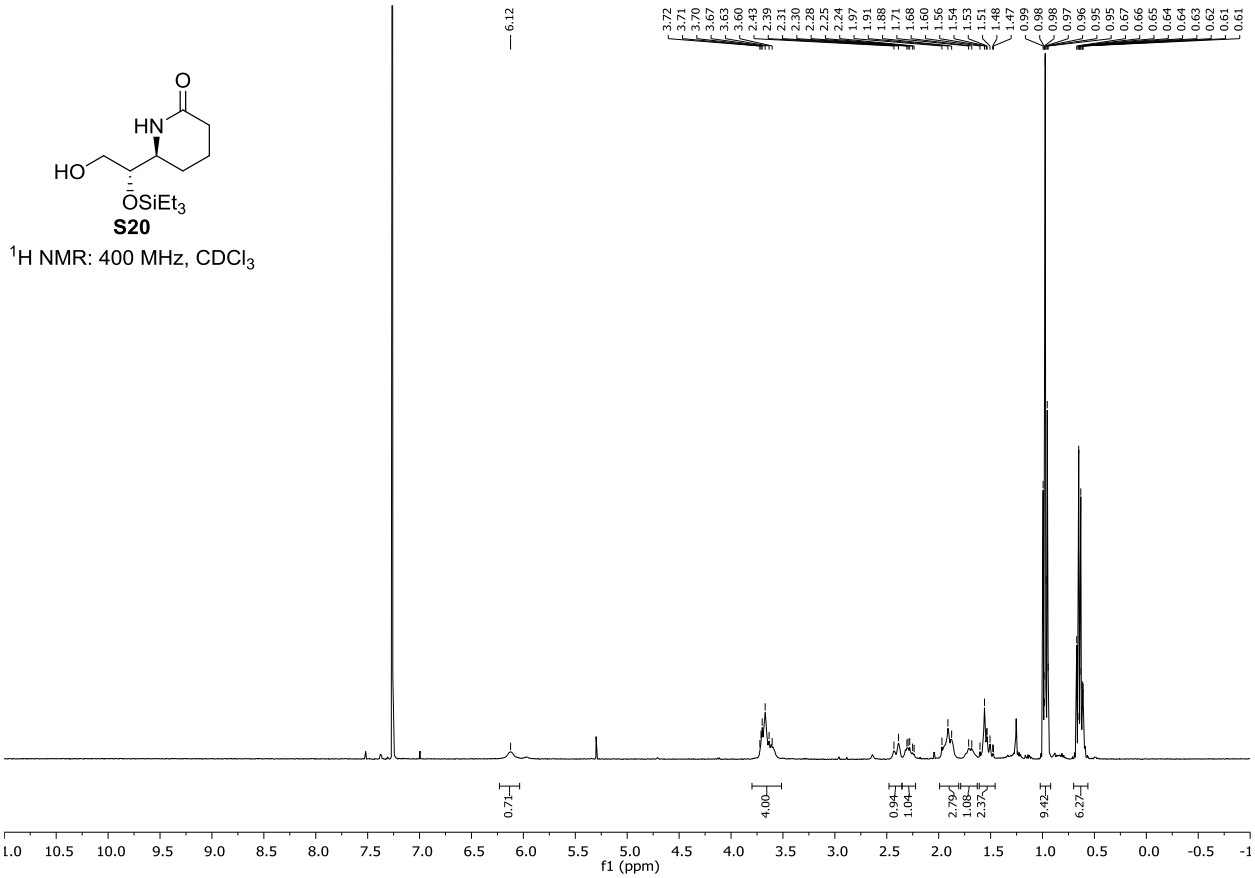

**177**

$^{1}$H NMR: 500 MHz, $CDCl_3$



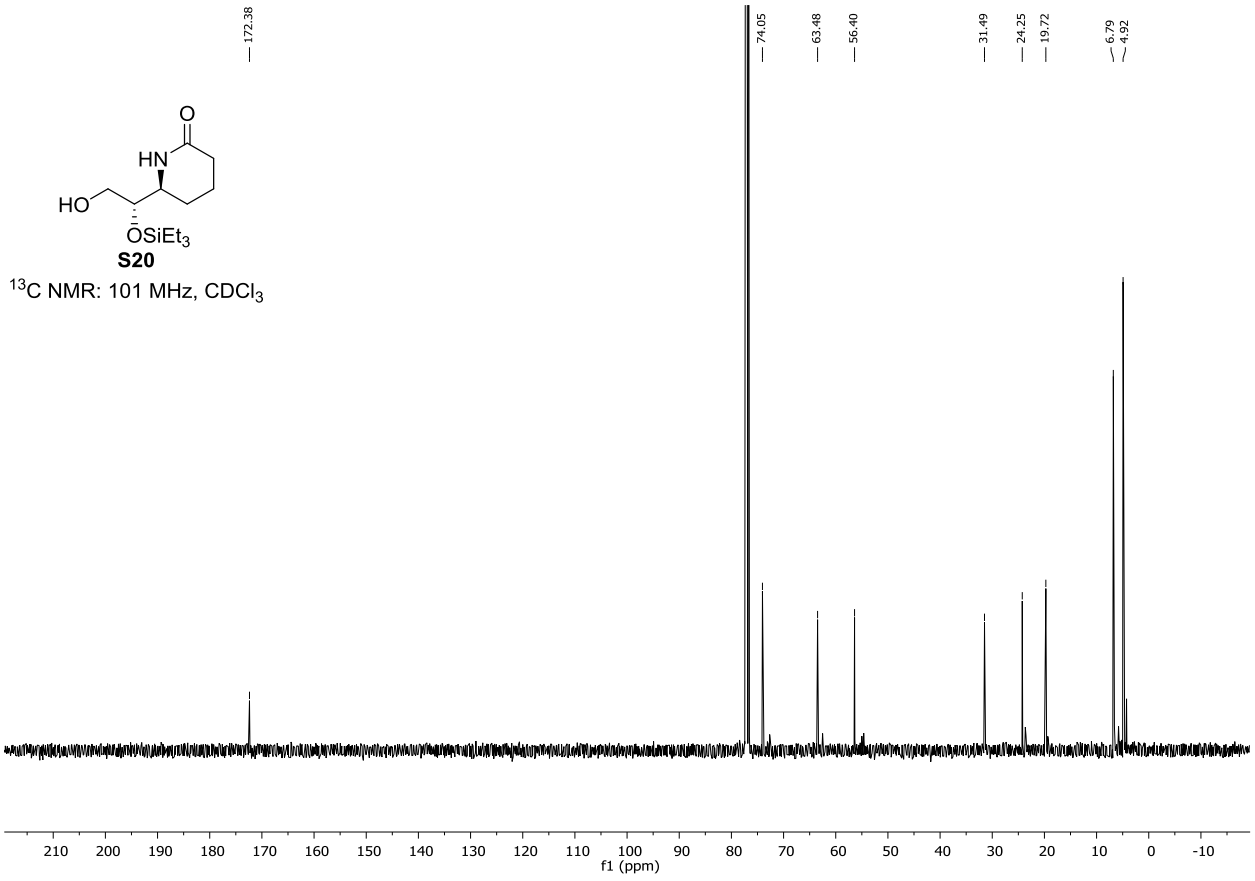

**177**

$^{13}$C NMR: 126 MHz, $CDCl_3$



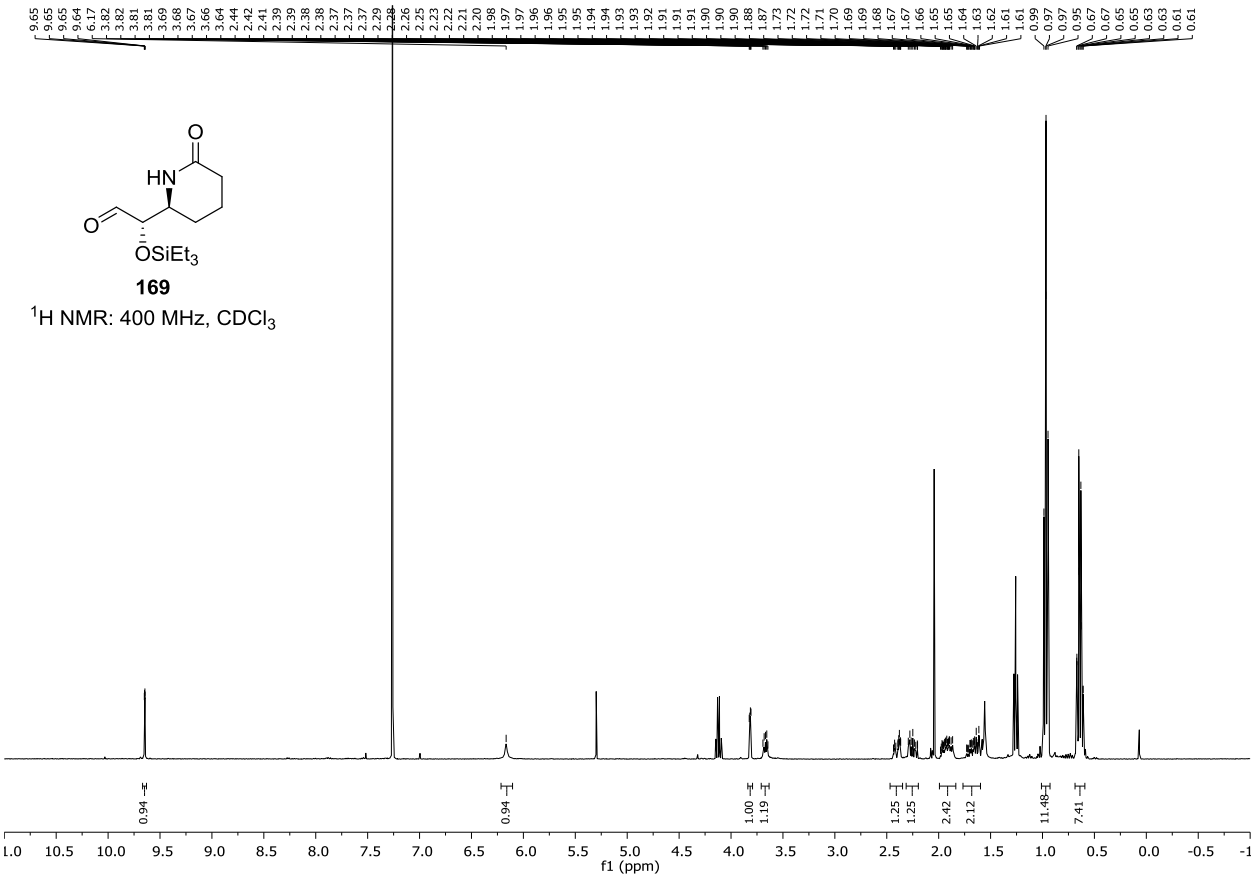

**S20**

$^{1}$H NMR: 400 MHz, $CDCl_3$



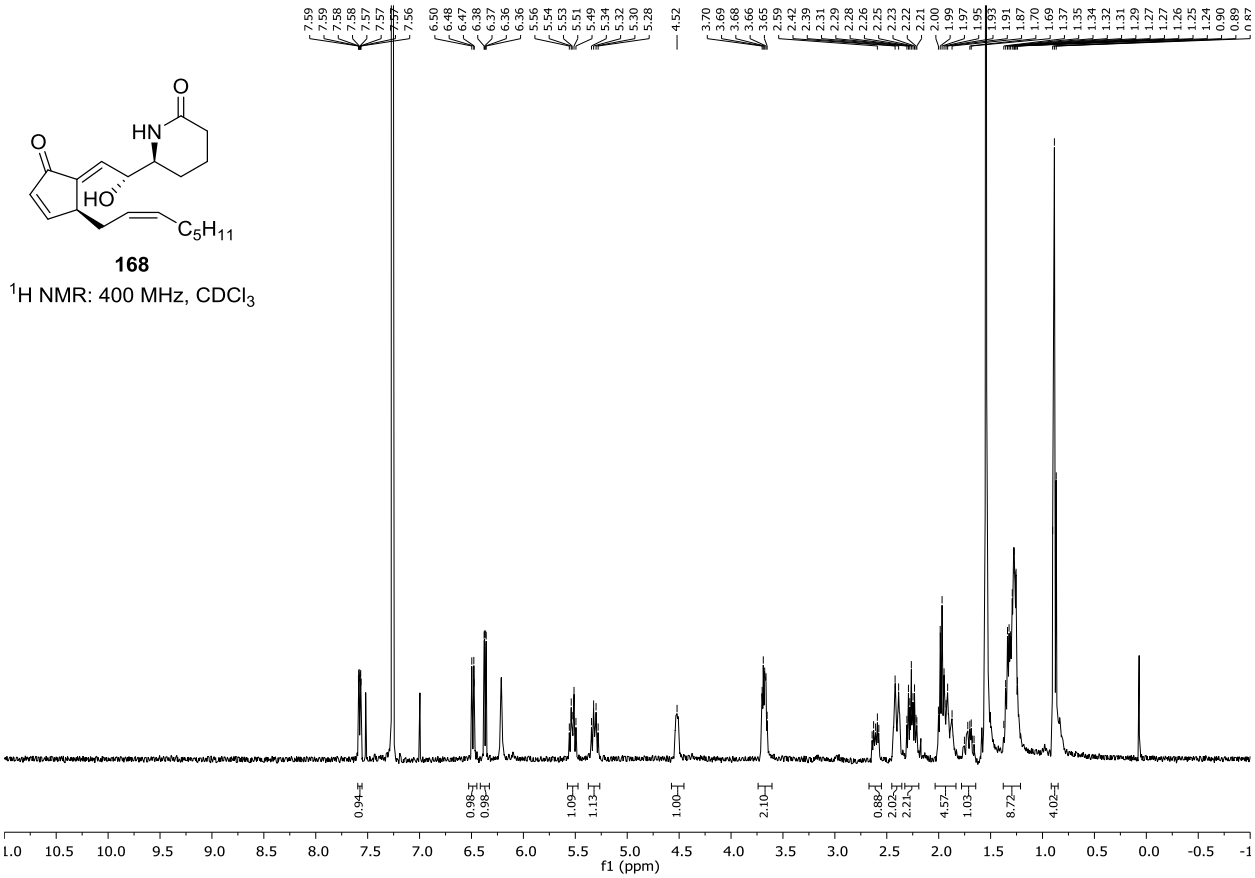

**S20**

$^{13}$C NMR: 101 MHz, $CDCl_3$



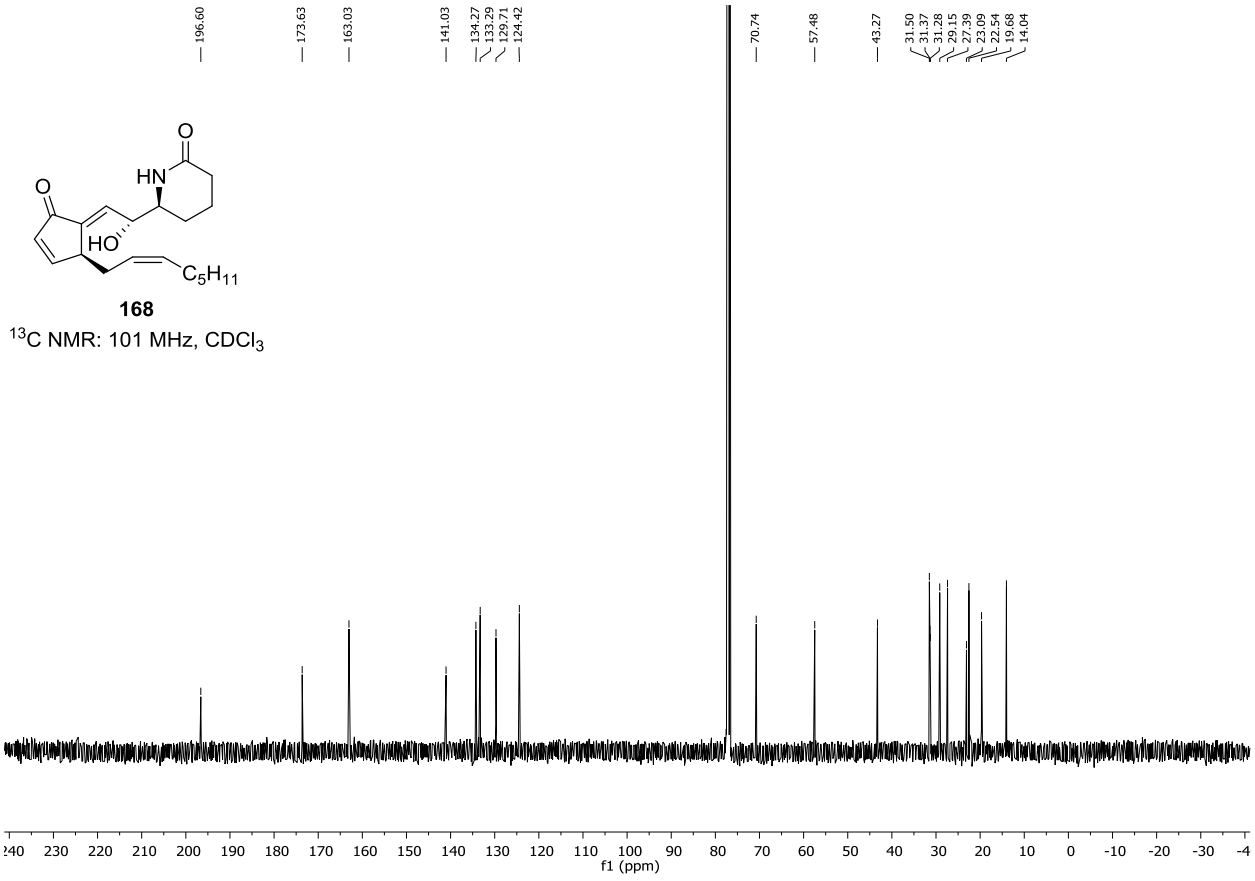

**169**

$^1$H NMR: 400 MHz, $CDCl_3$



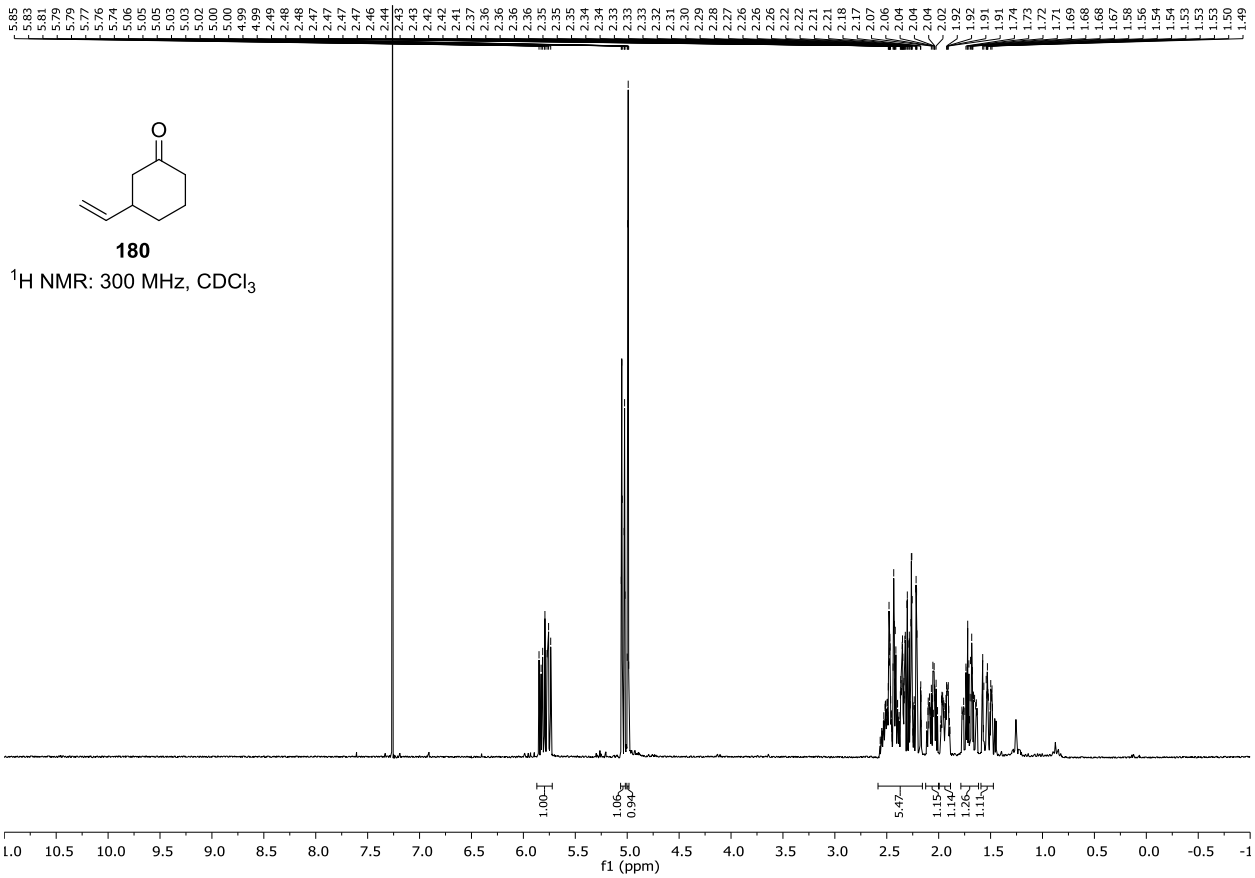

**168**

$^{1}$H NMR: 400 MHz, $CDCl_3$



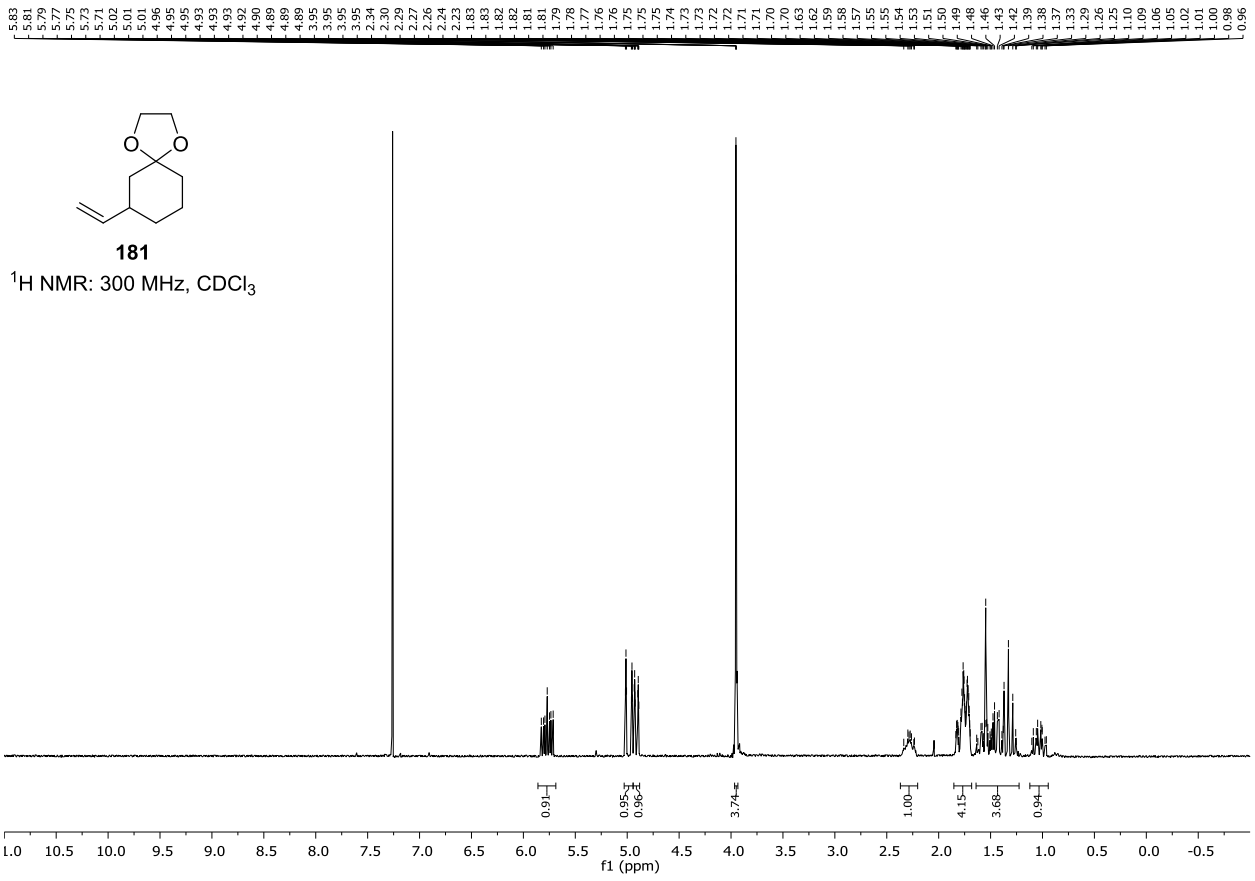

**168**

$^{13}$C NMR: 101 MHz, $CDCl_3$



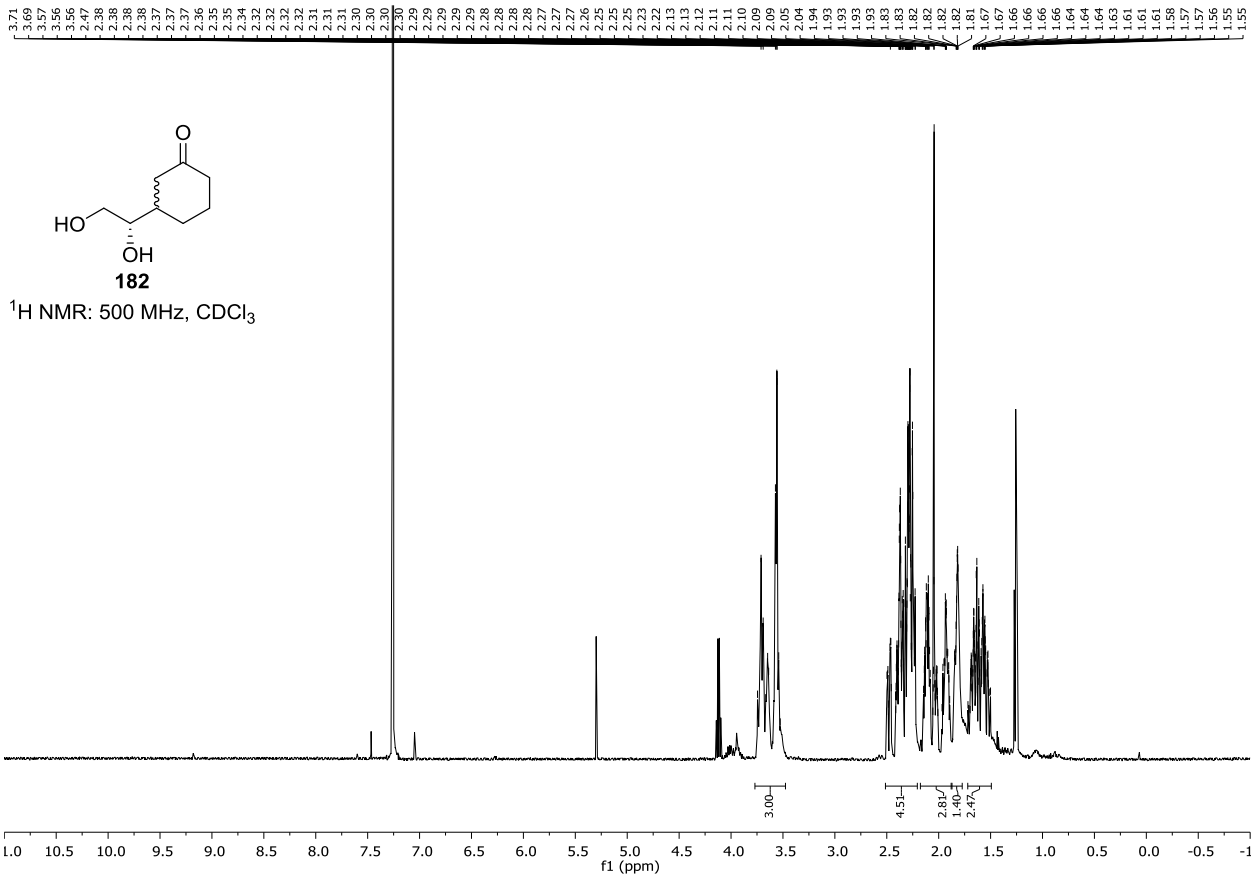

**180**

$^1$H NMR: 300 MHz, $CDCl_3$



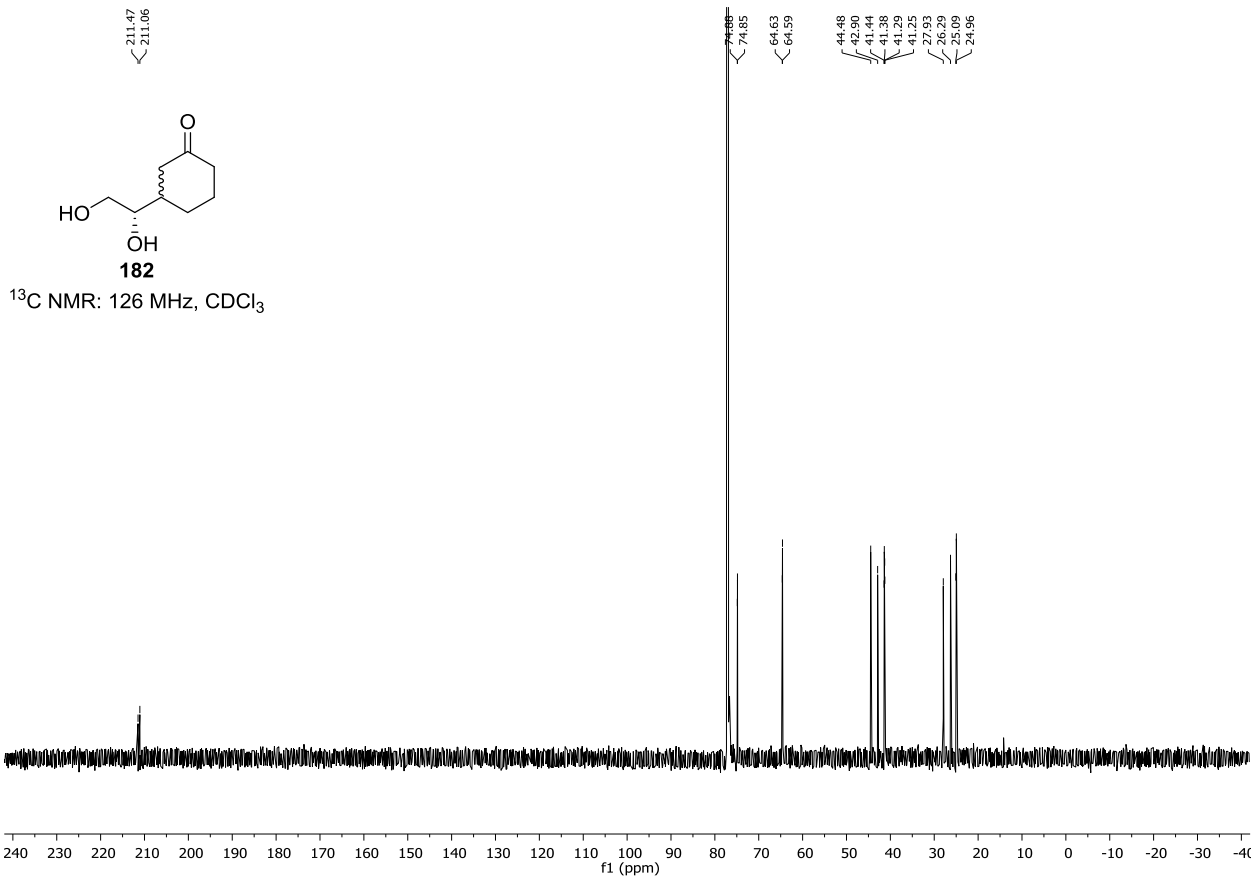

**181**

$^1$H NMR: 300 MHz, $CDCl_3$



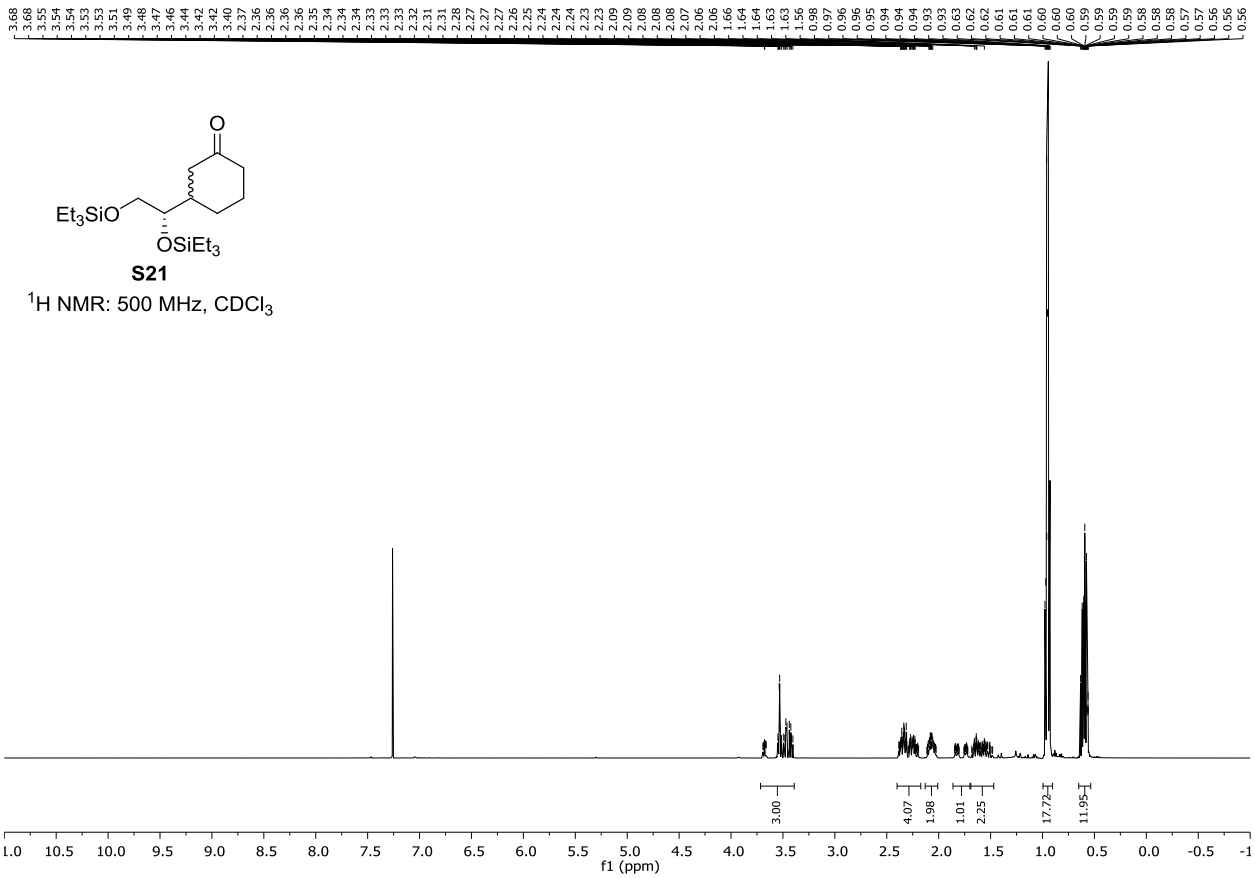

**182**

$^{1}$H NMR: 500 MHz, $CDCl_3$



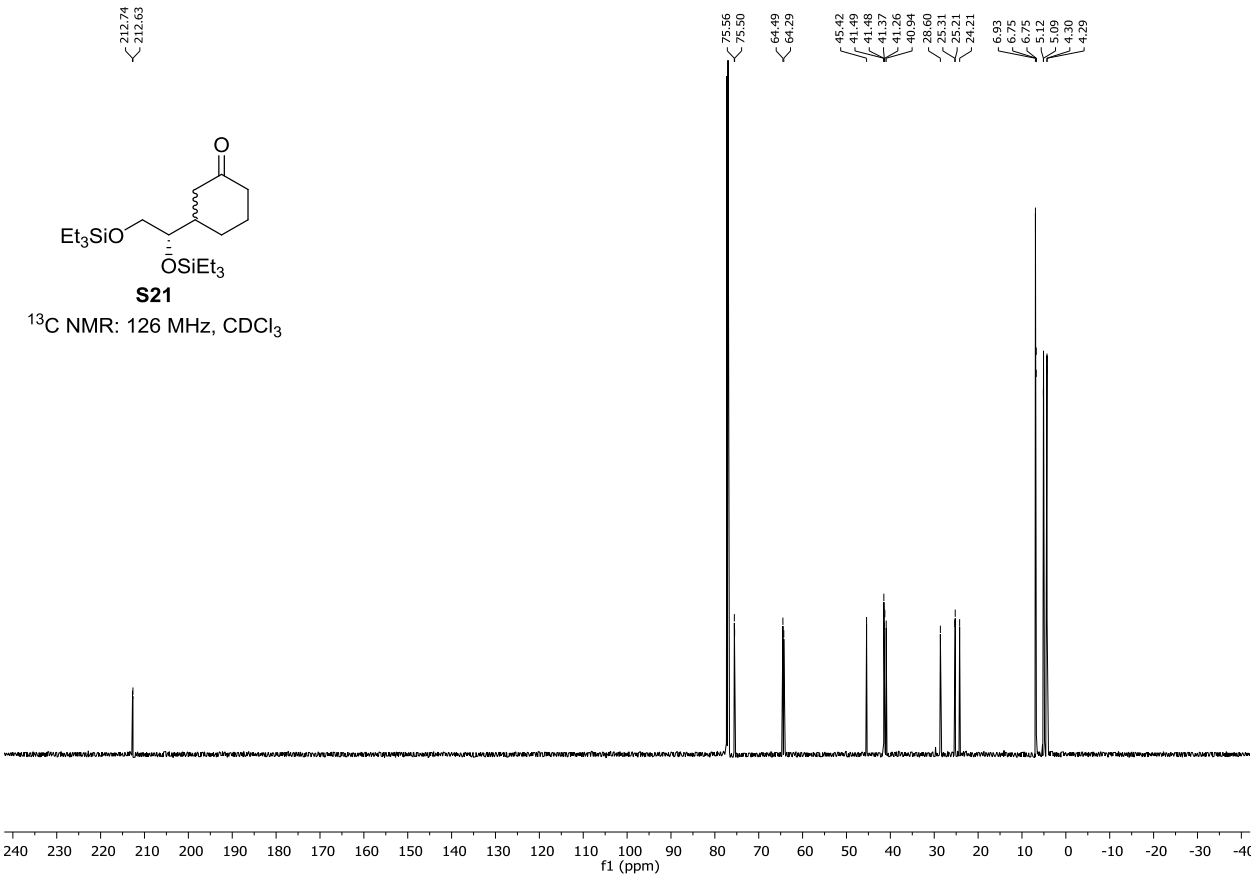

**182**

$^{13}$C NMR: 126 MHz, $CDCl_3$



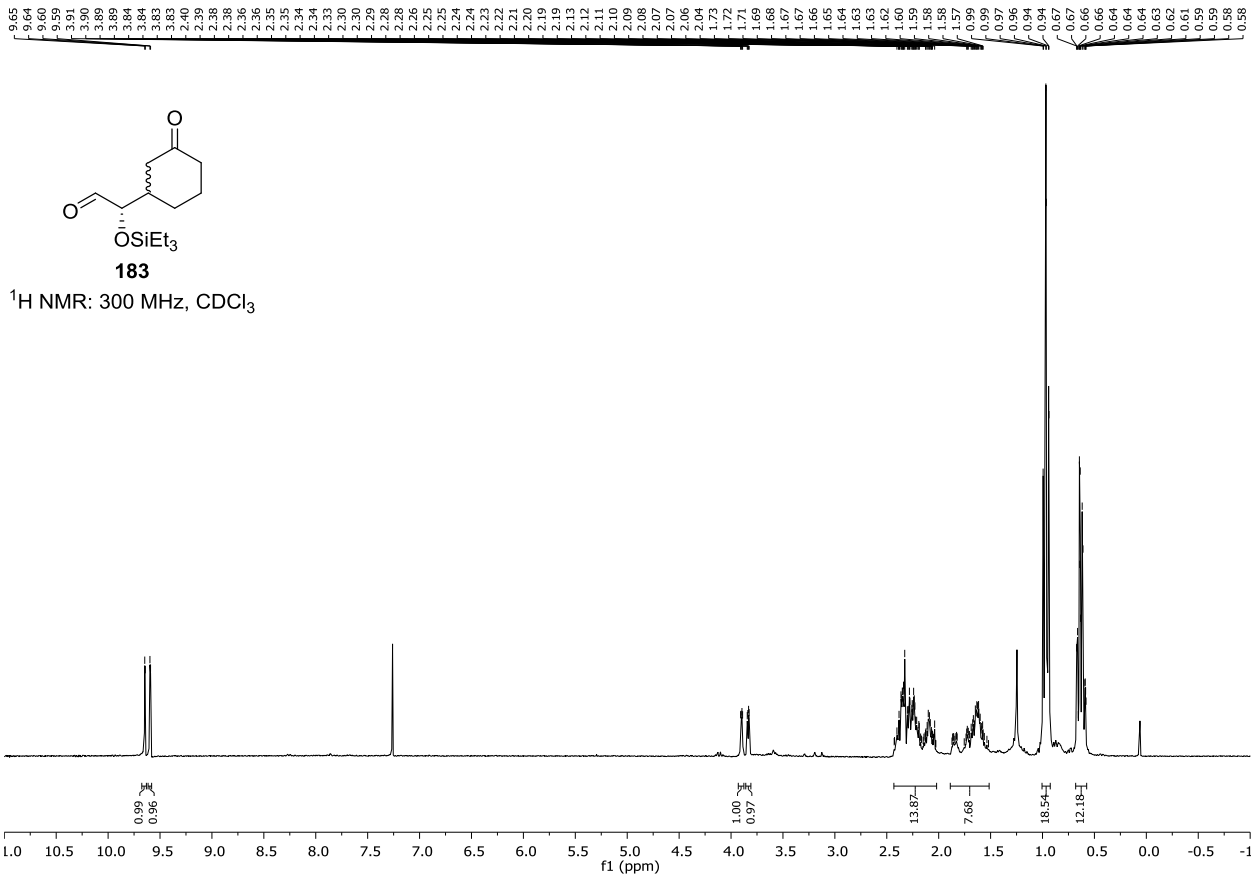

**S21**

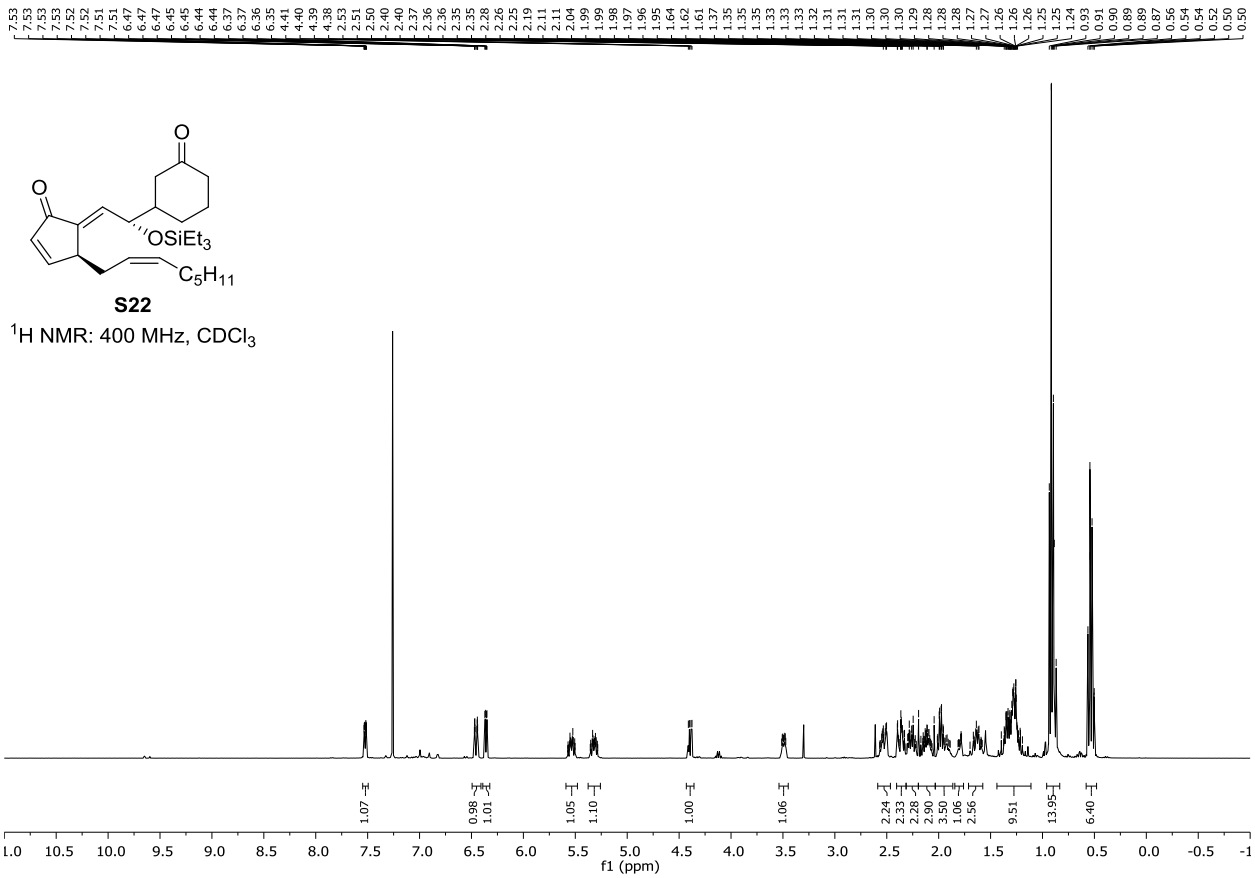
$^{1}$H NMR: 500 MHz, $CDCl_3$




**S21**

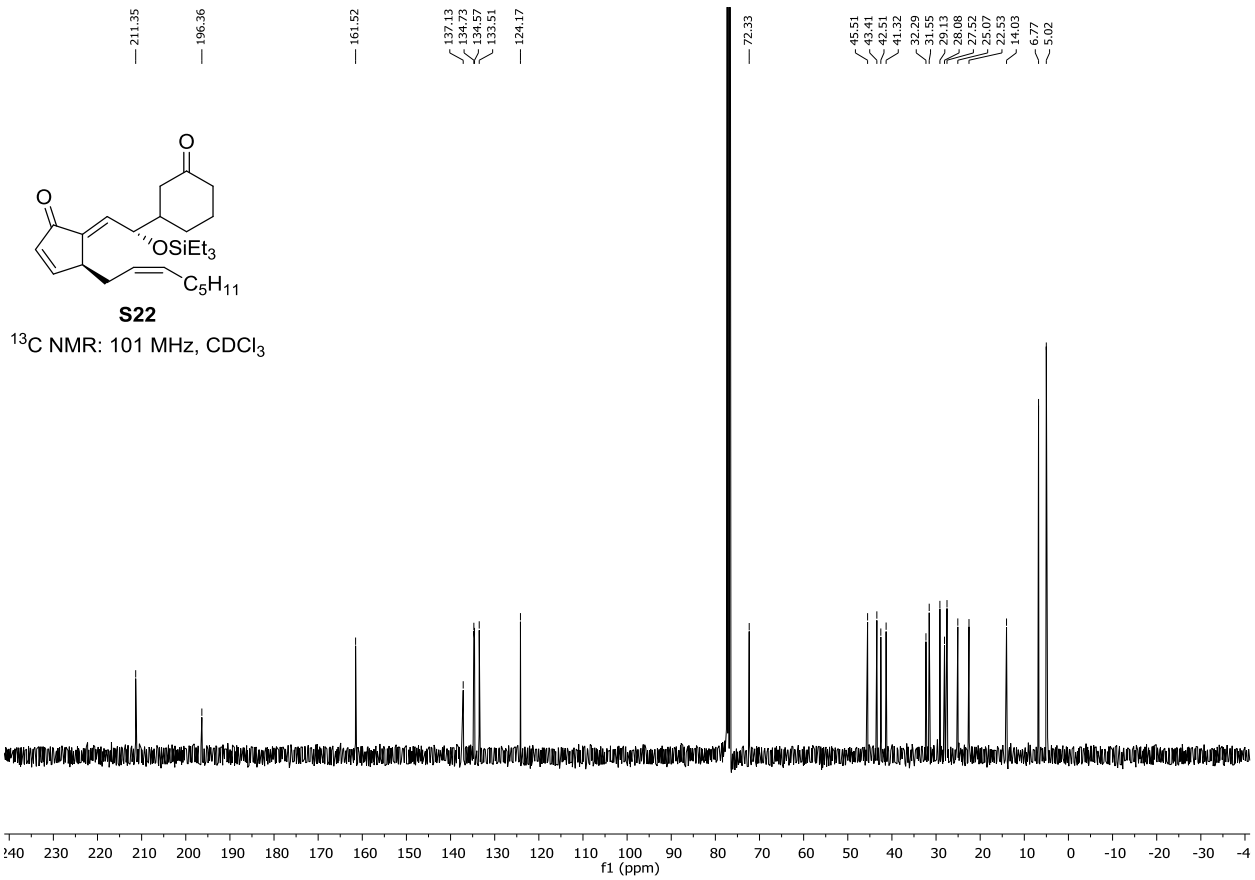
$^{13}$C NMR: 126 MHz, $CDCl_3$


OSiEt3
183
1H NMR: 300 MHz, CDCl3
0.99
0.96
1.00
0.97
13.87
7.68
18.54
12.18
f1 (ppm)



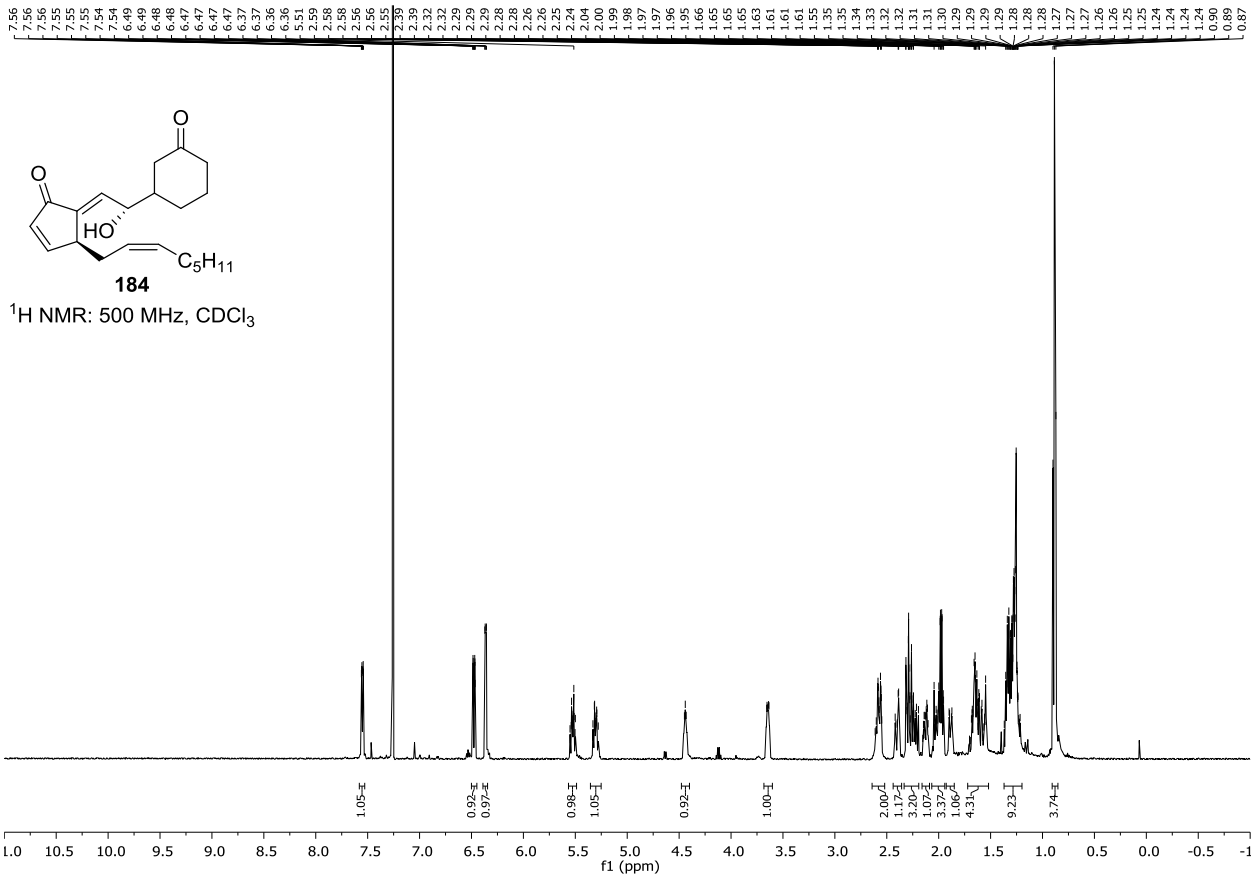

**S22**

$^{1}$H NMR: 400 MHz, $CDCl_3$



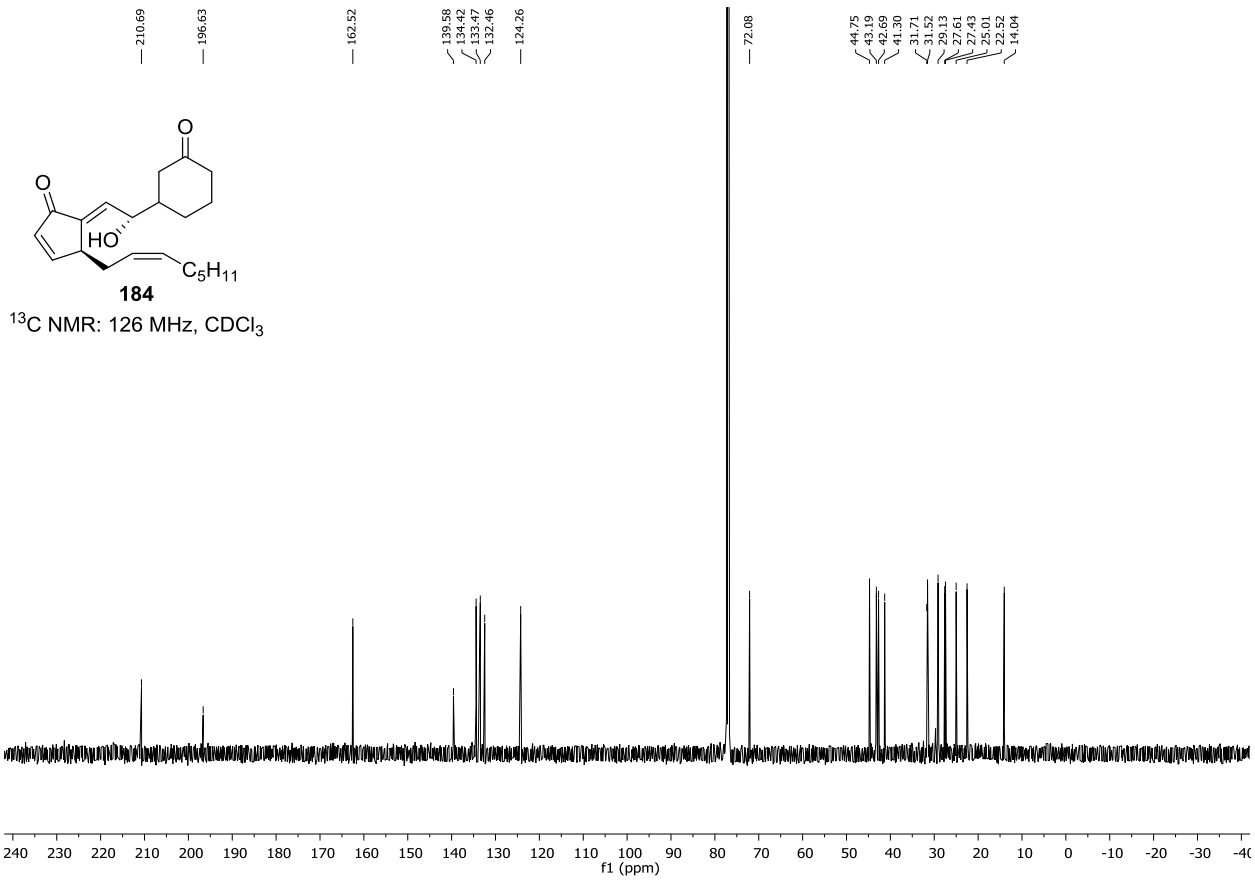

**S22**

$^{13}$C NMR: 101 MHz, $CDCl_3$



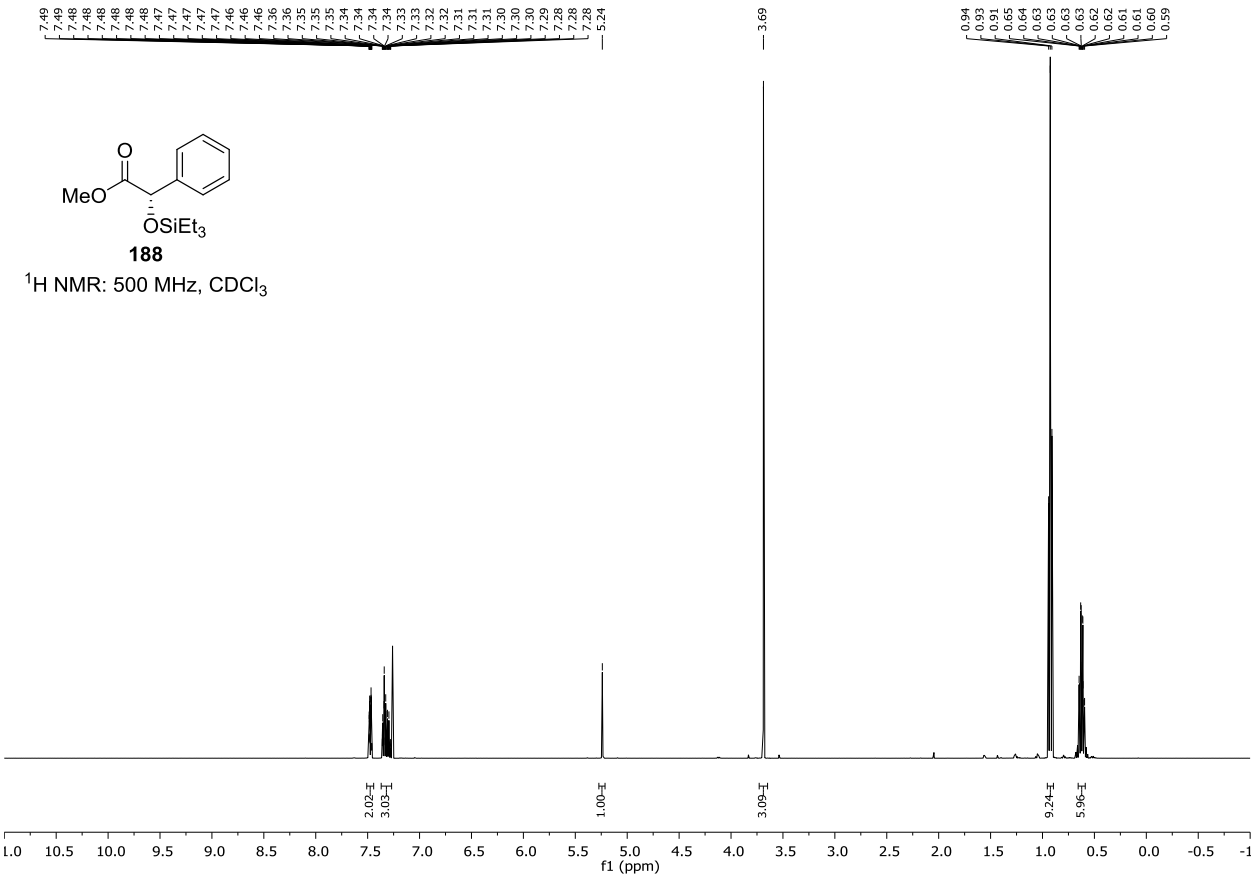

**184**

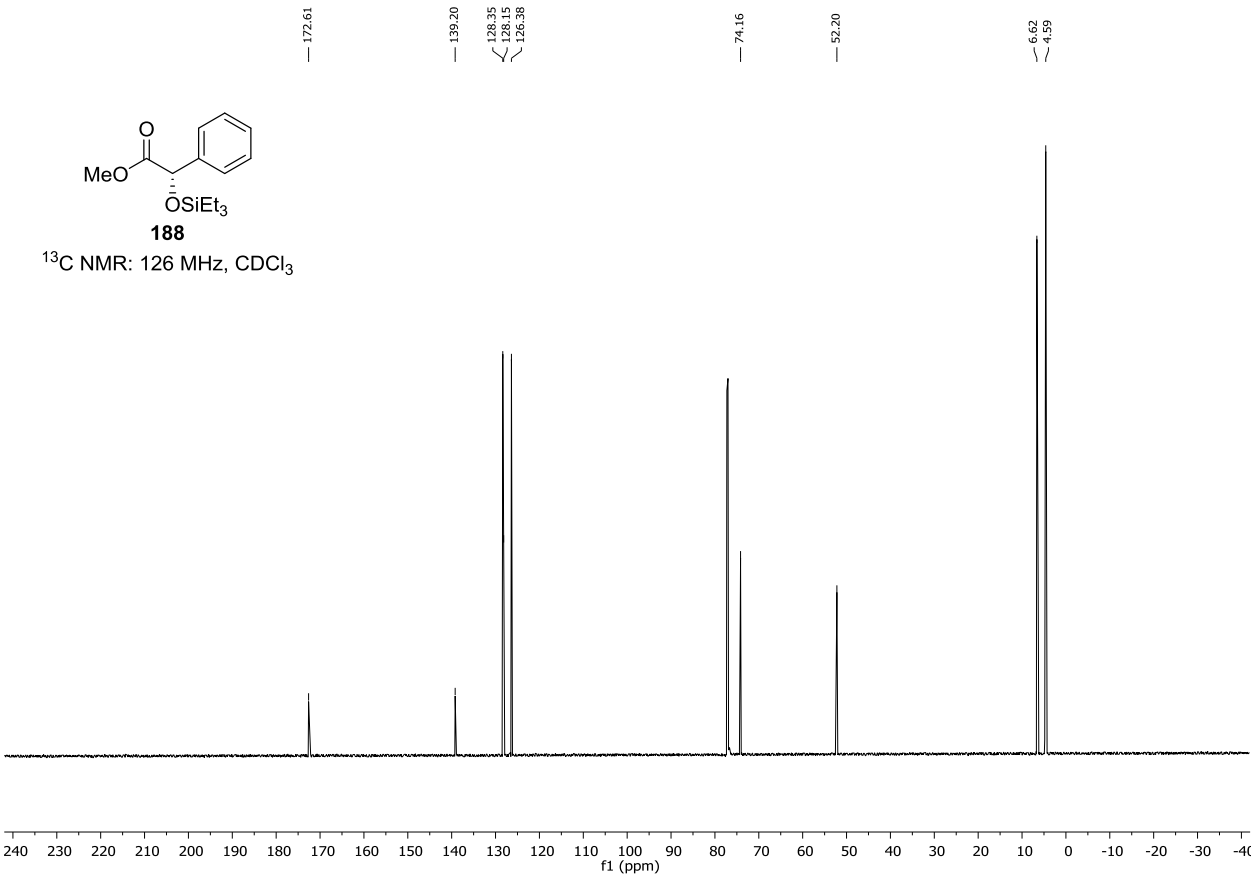
$^1$H NMR: 500 MHz, $CDCl_3$

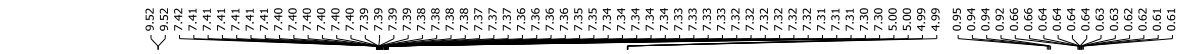


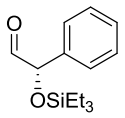

**184**

$^{13}$C NMR: 126 MHz, $CDCl_3$


MeO
OSiEt3
188
1H NMR: 500 MHz, CDCl3
f1 (ppm)

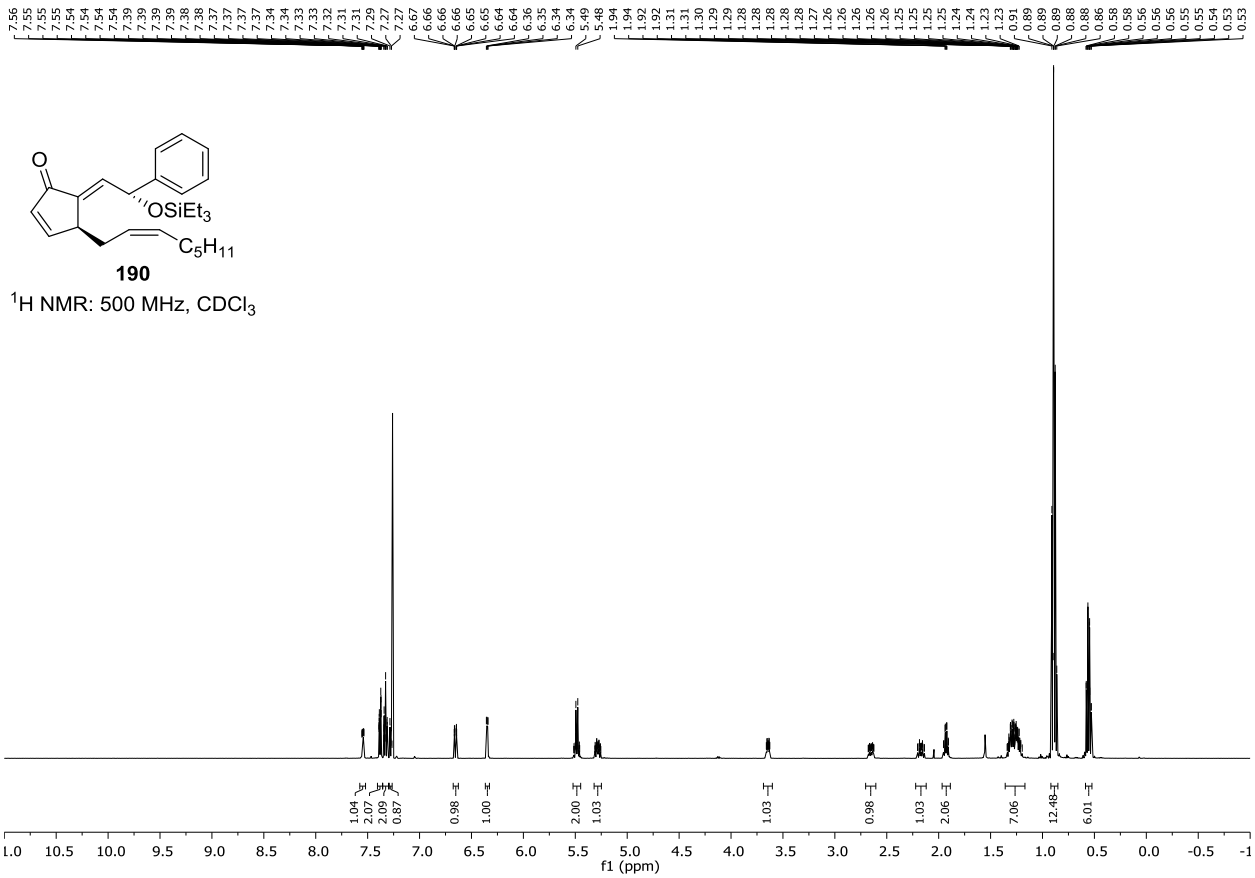

MeO
OSiEt3
188
13C NMR: 126 MHz, CDCl3
f1 (ppm)

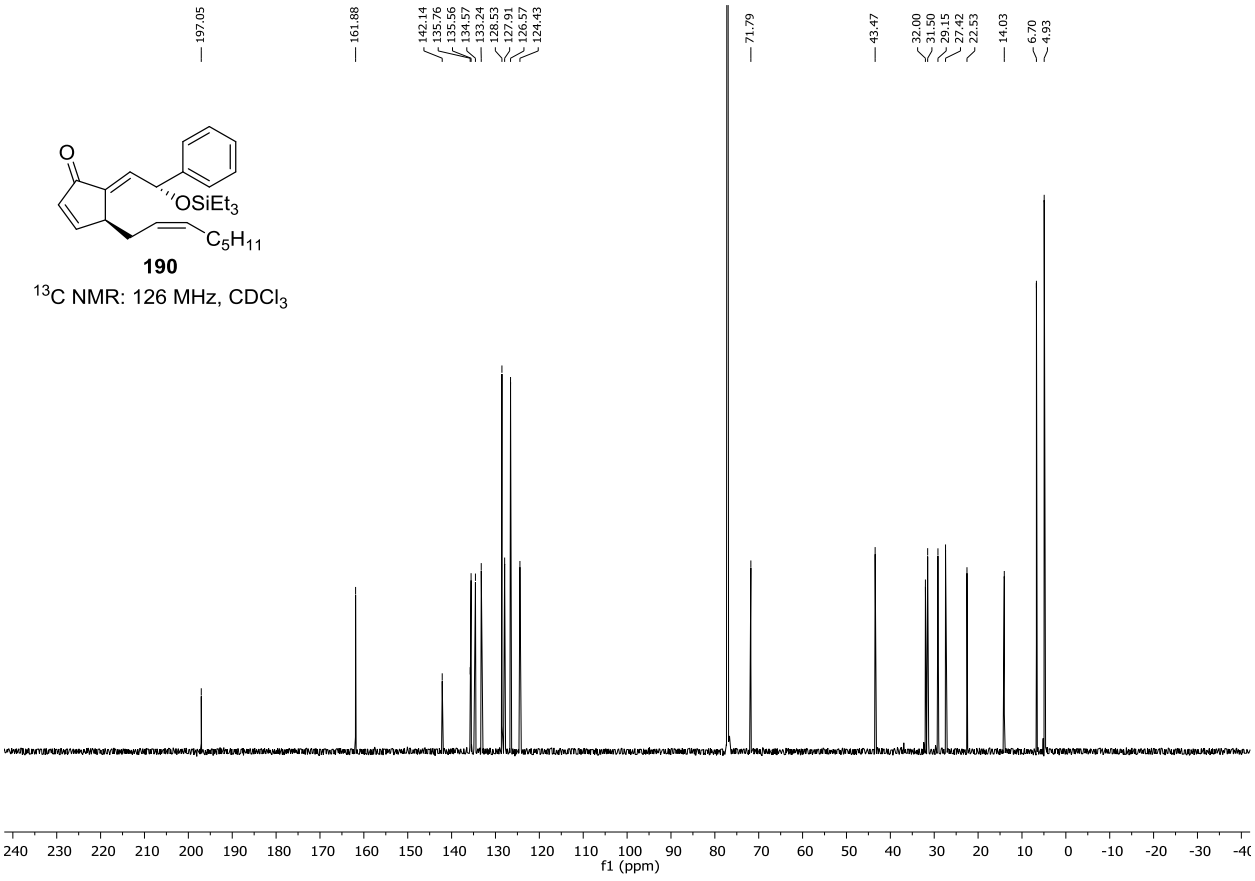


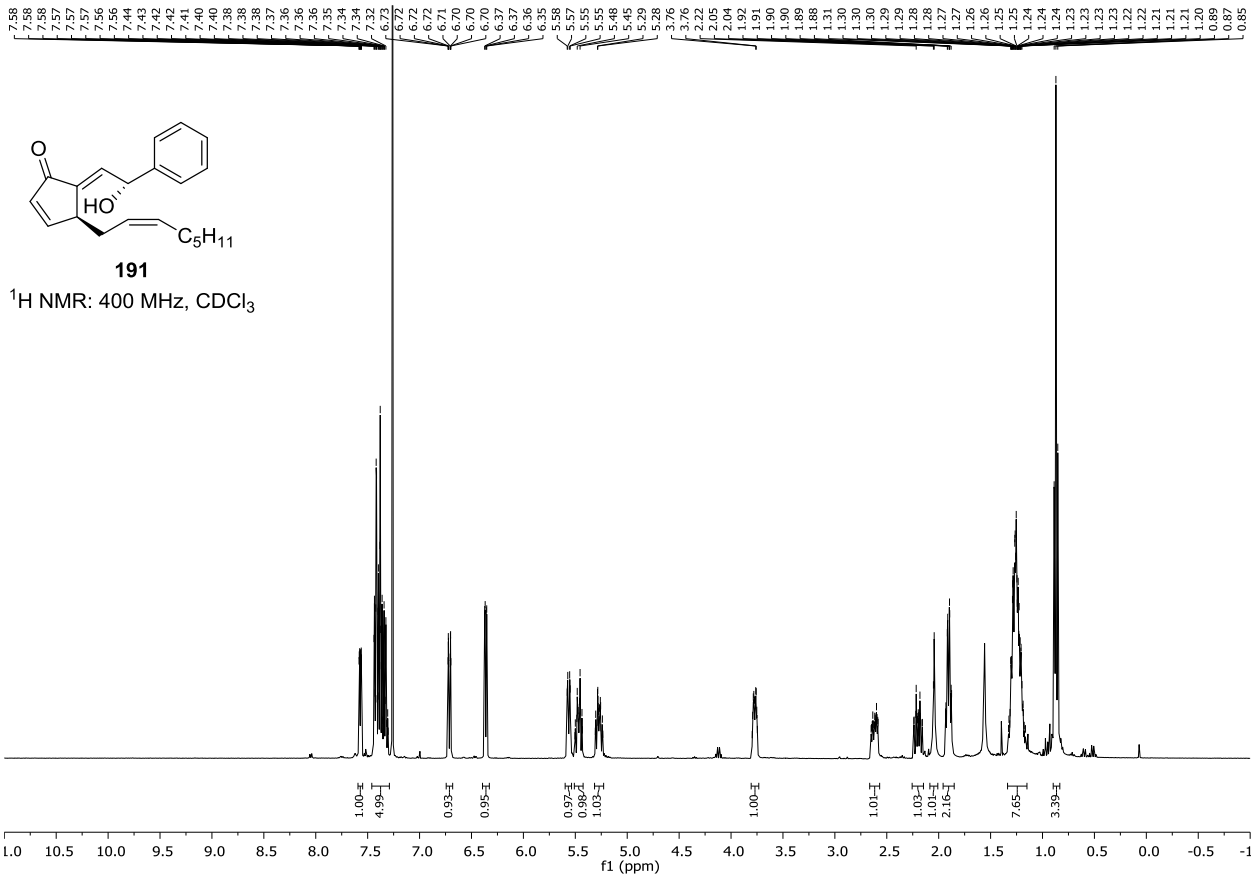


**189**

$^1$H NMR: 500 MHz, $CDCl_3$

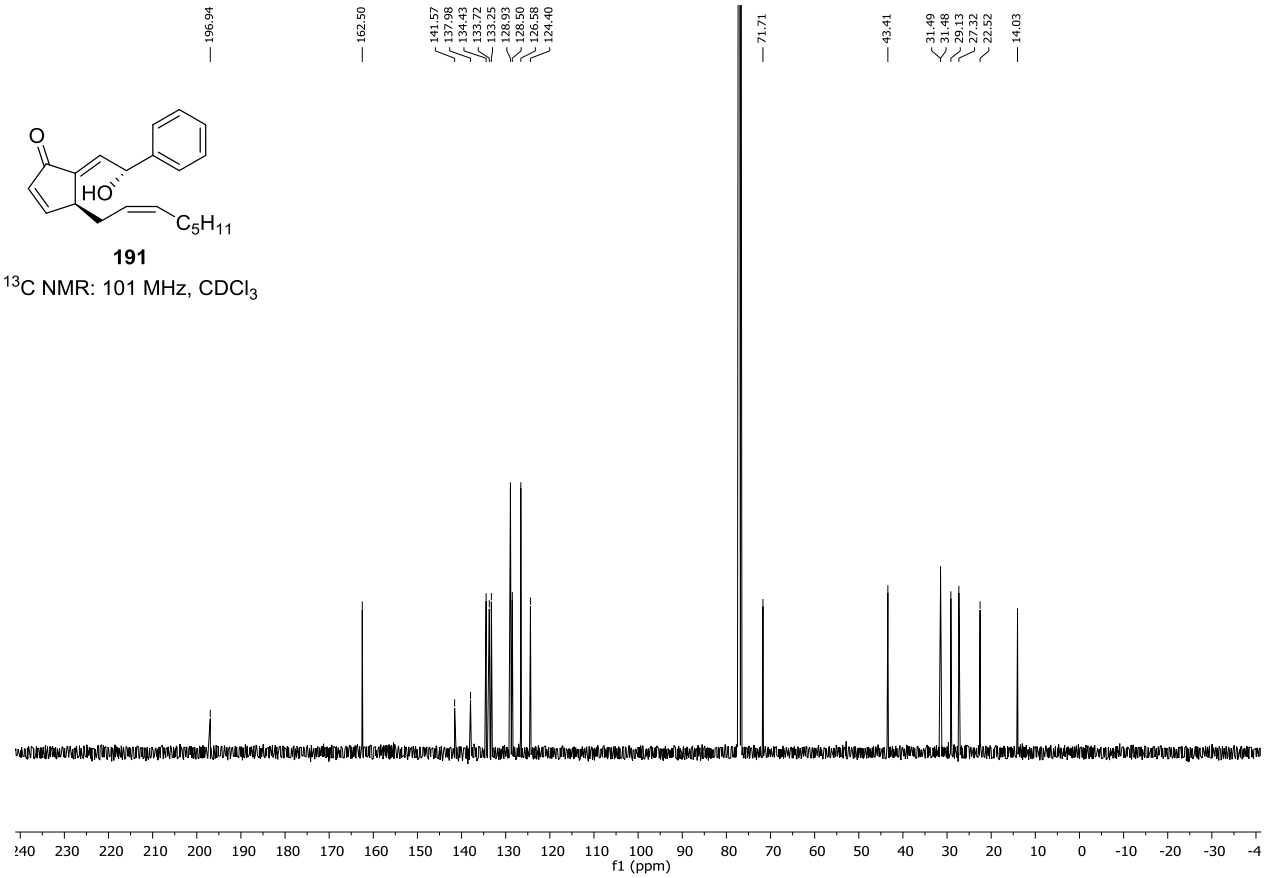

OSiEt3
C5H11
190
1H NMR: 500 MHz, CDCl3
f1 (ppm)


OSiEt3
C5H11
190
13C NMR: 126 MHz, CDCl3
f1 (ppm)



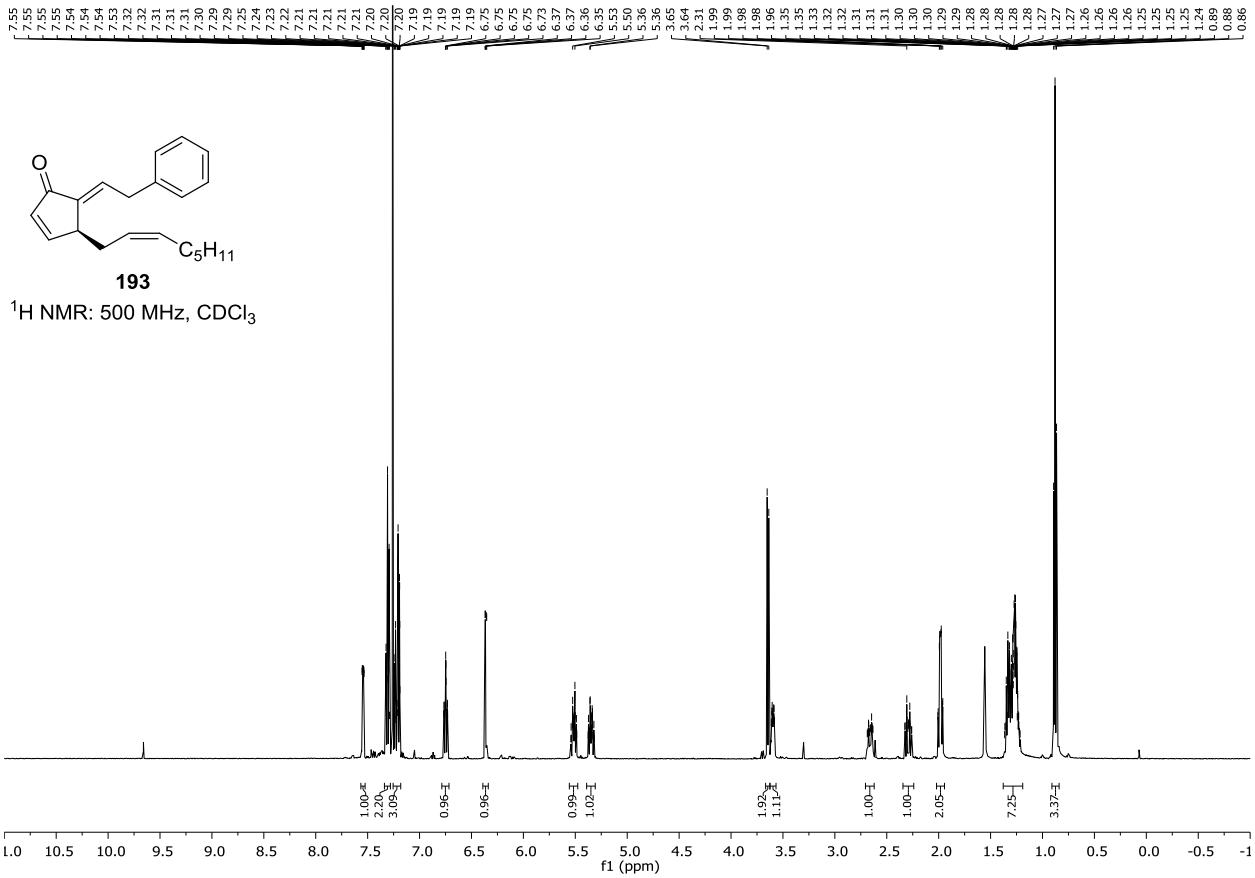

**191**

$^{1}$H NMR: 400 MHz, $CDCl_3$



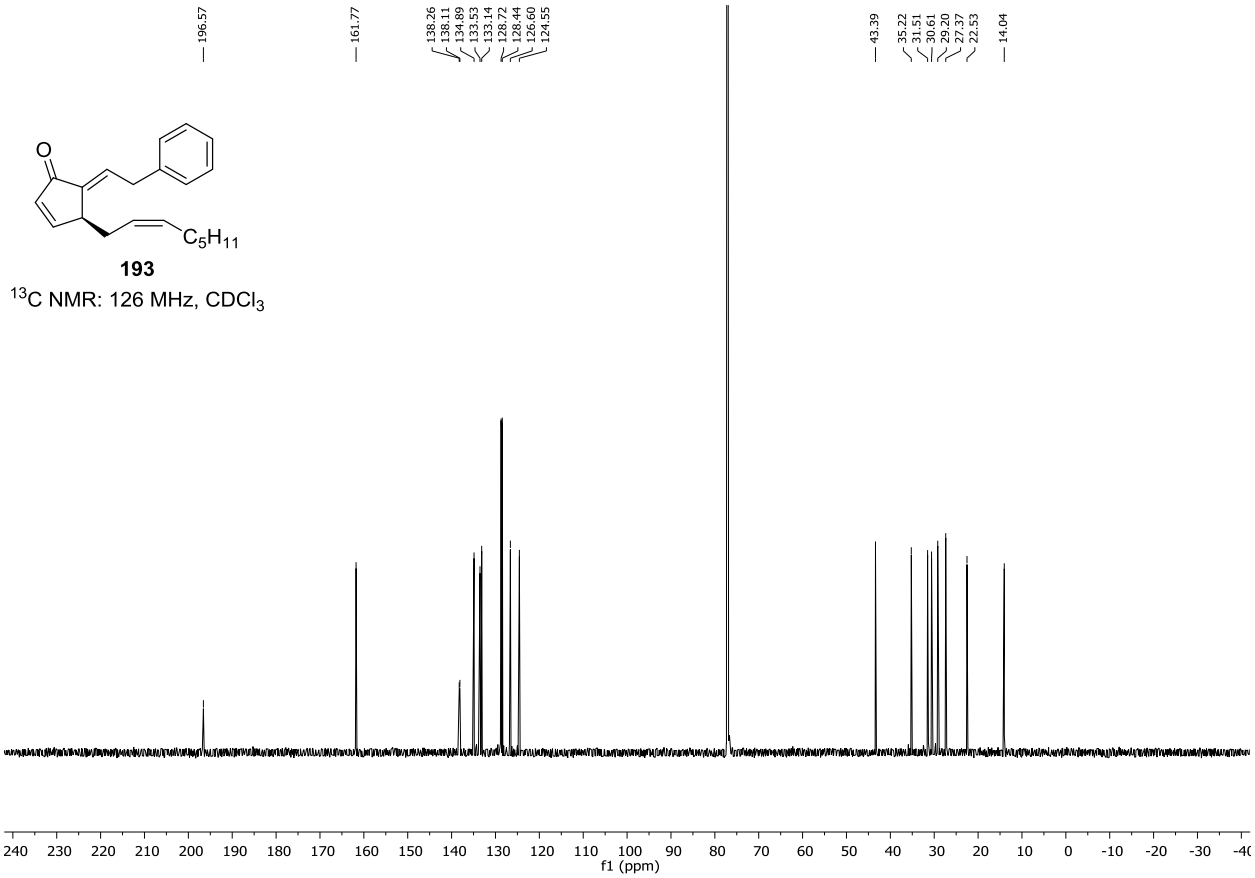

**191**

$^{13}$C NMR: 101 MHz, $CDCl_3$



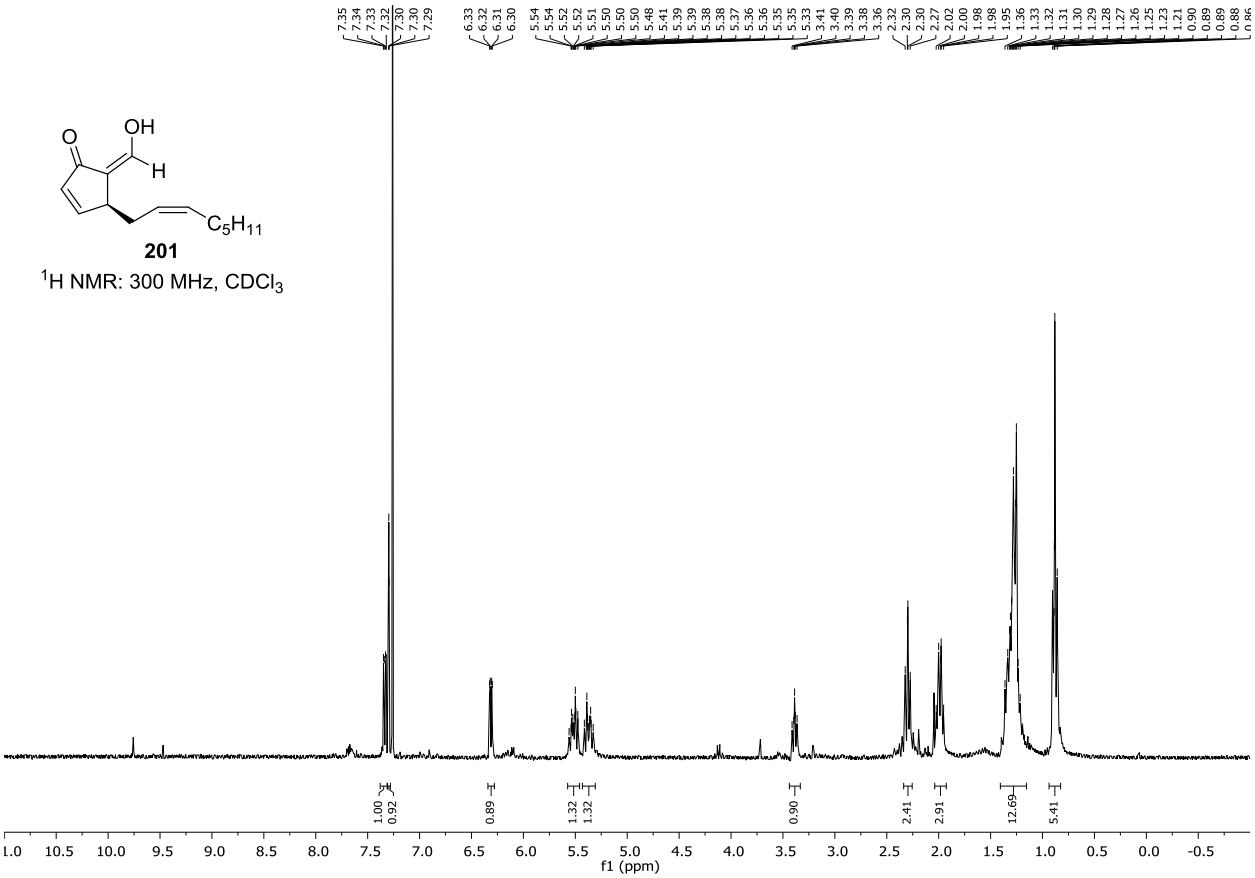

**193**

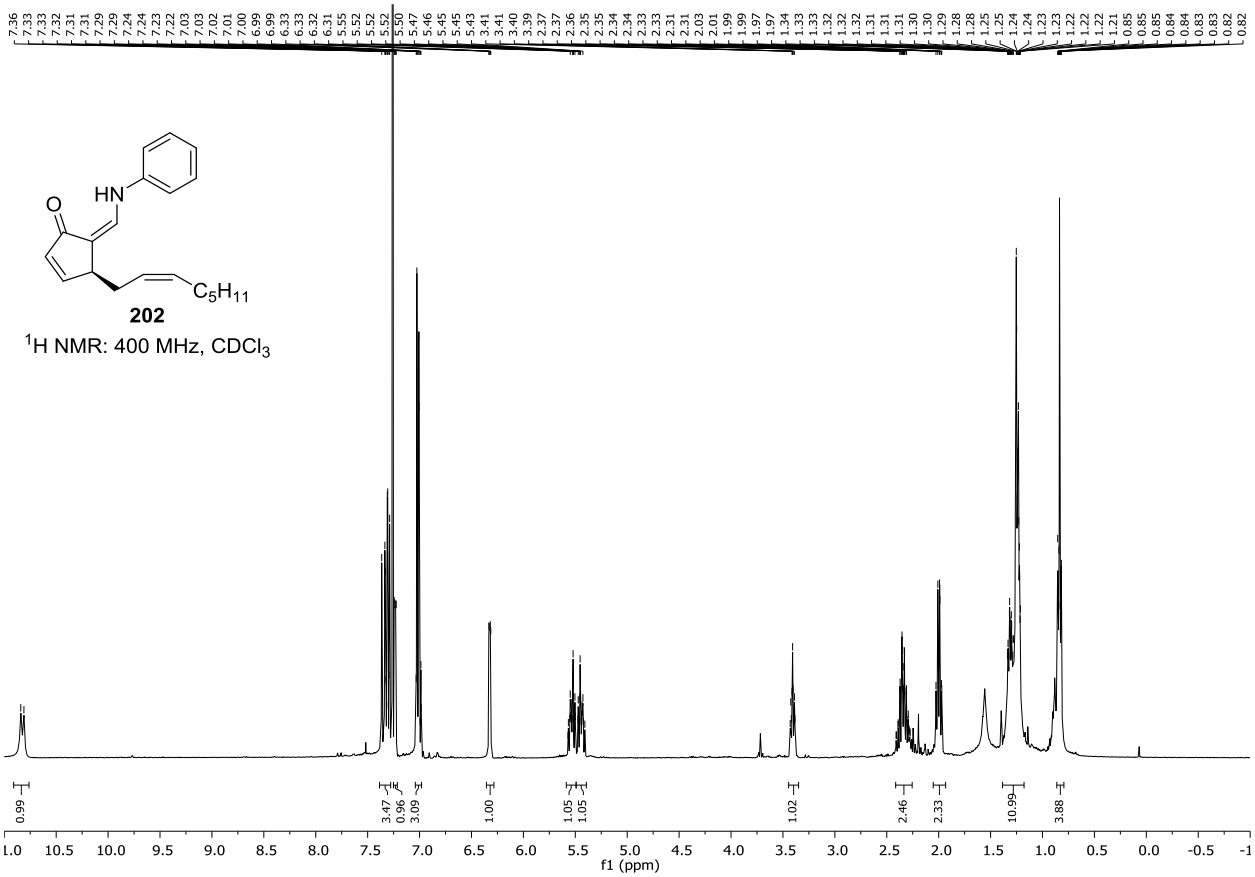
$^1$H NMR: 500 MHz, $CDCl_3$




**193**

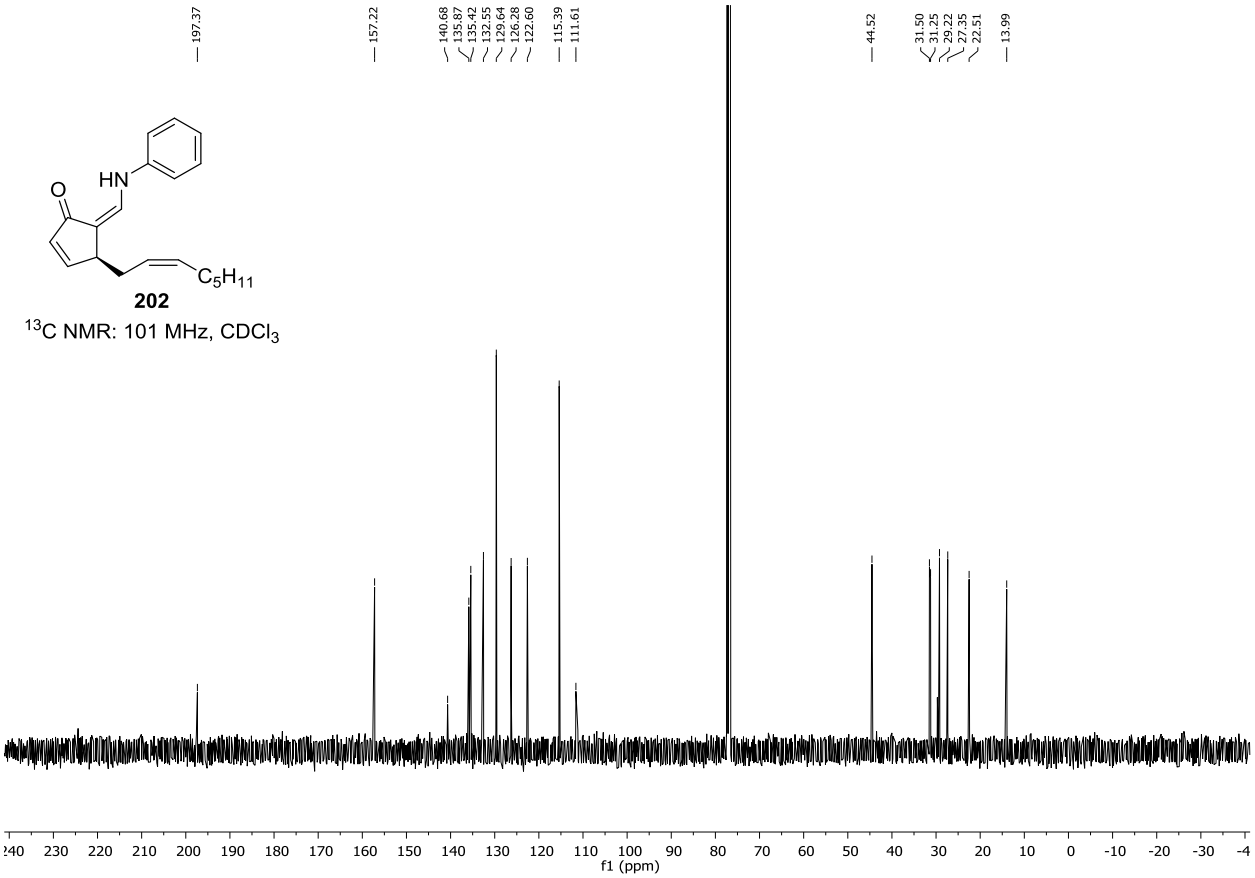
$^{13}$C NMR: 126 MHz, $CDCl_3$


OH
O
H
$C_5H_{11}$
201
$^1$H NMR: 300 MHz, $CDCl_3$
f1 (ppm)



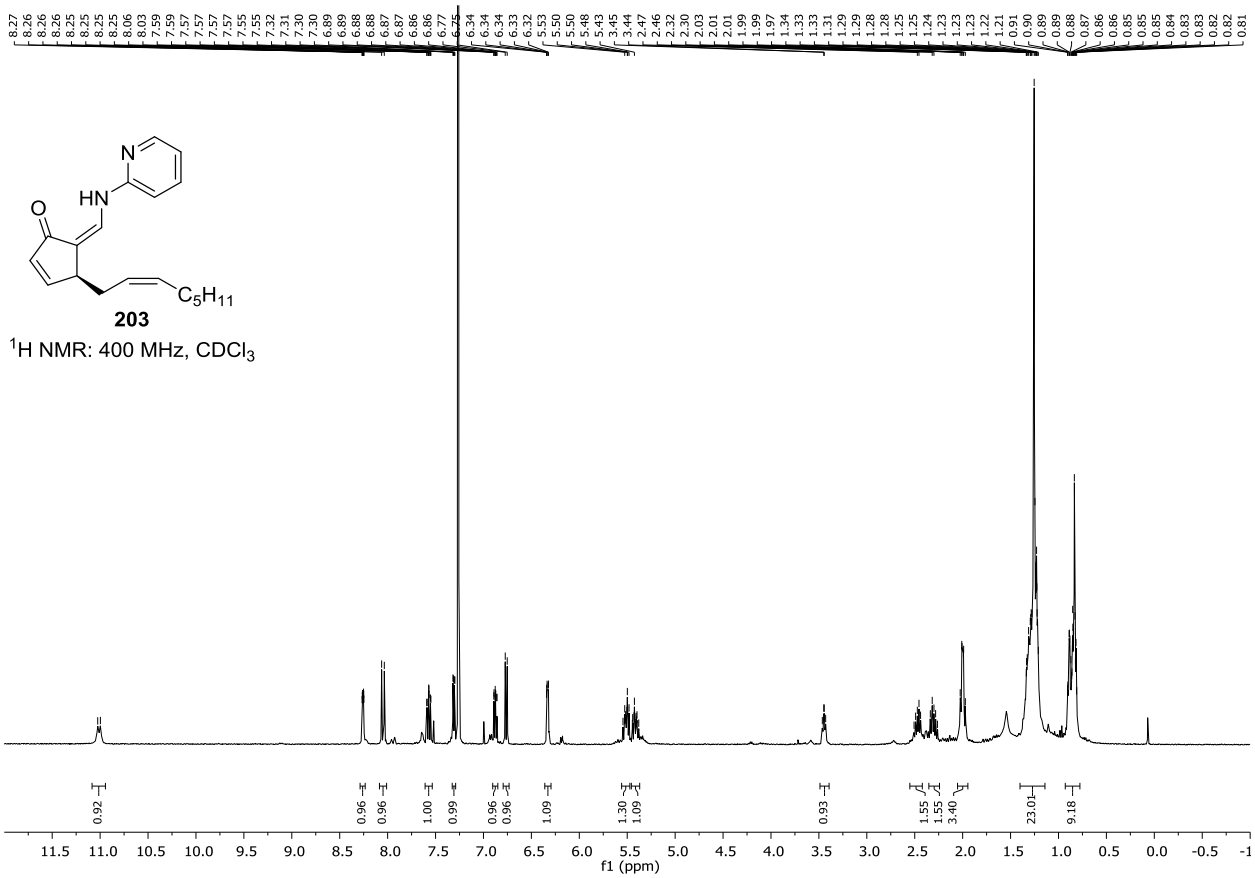

**202**

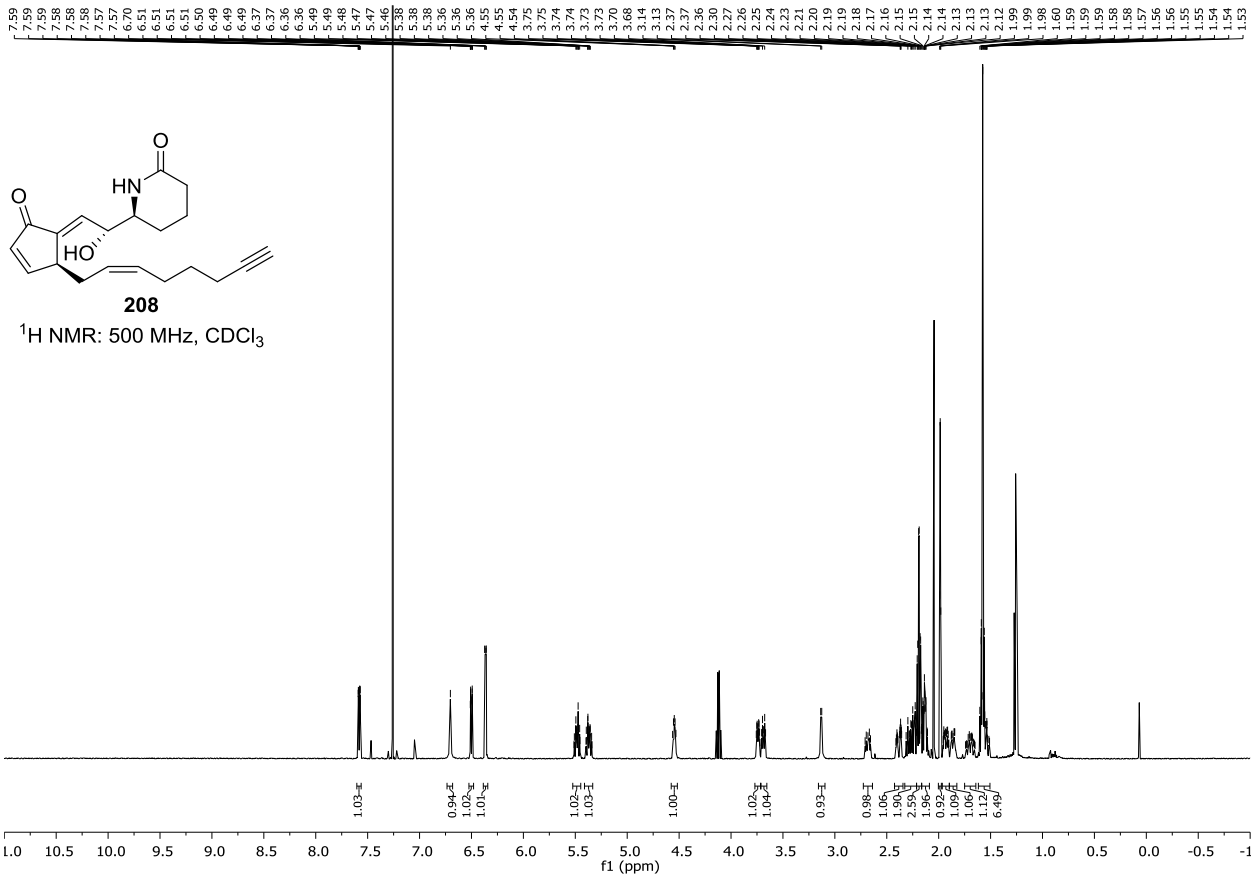
$^{1}$H NMR: 400 MHz, $CDCl_3$

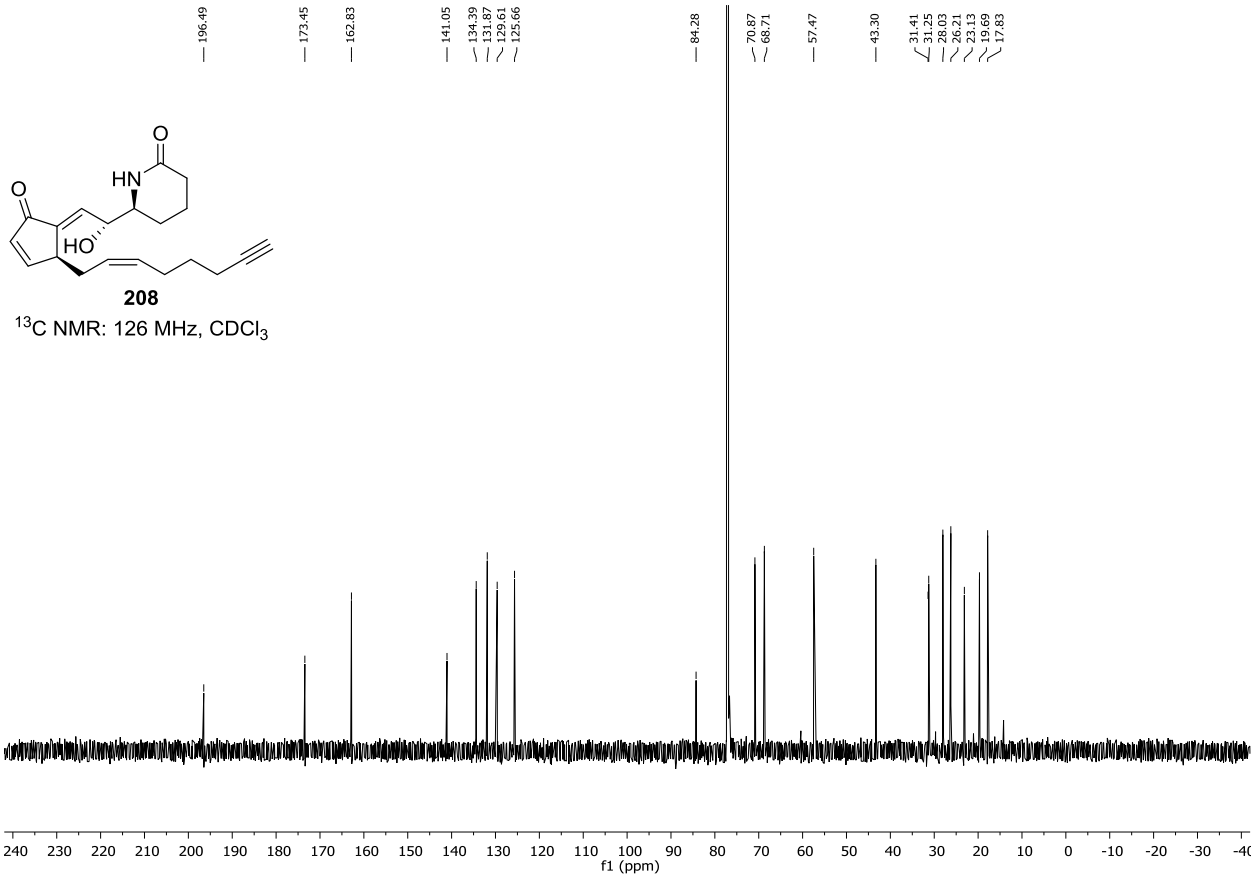


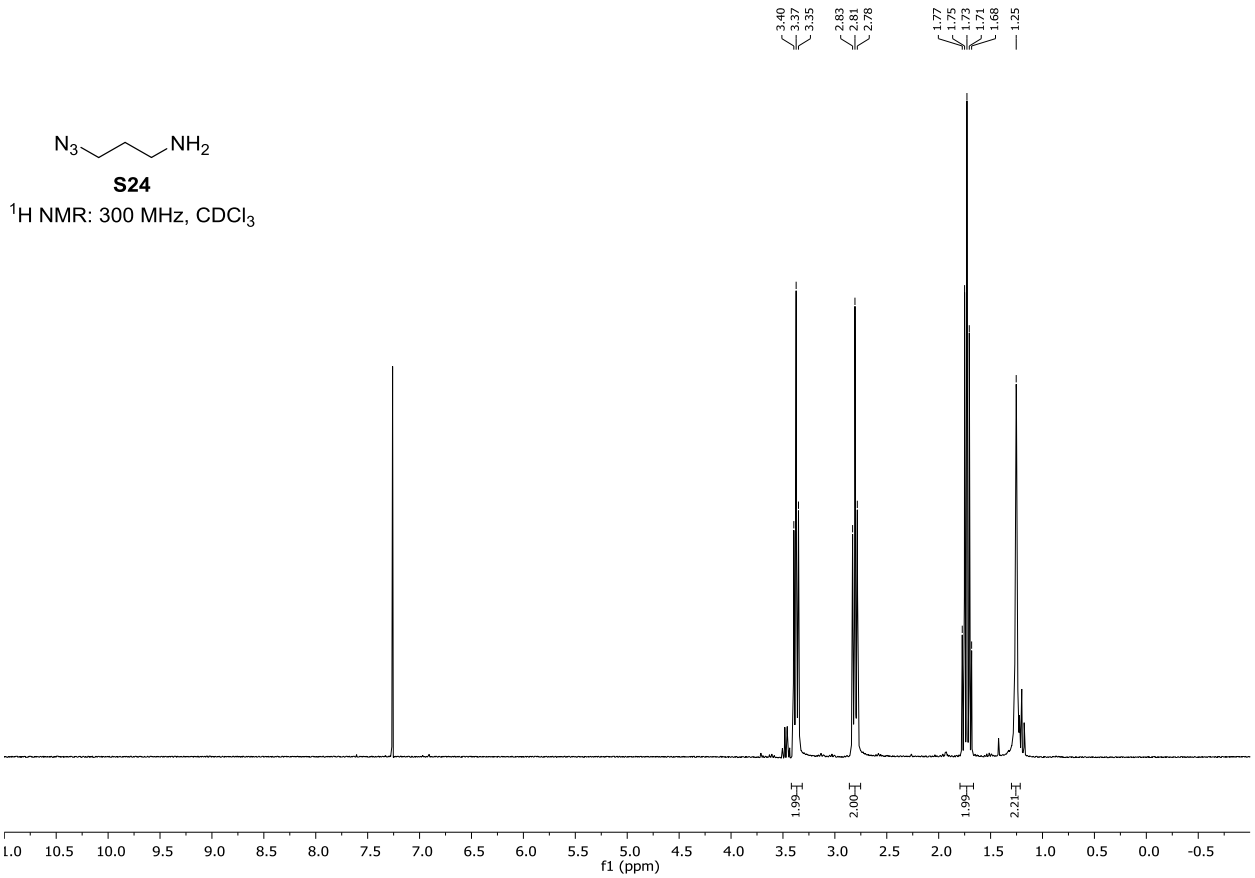

**202**

$^{13}$C NMR: 101 MHz, $CDCl_3$


N
HN
O
$C_5H_{11}$
203
$^1$H NMR: 400 MHz, $CDCl_3$
f1 (ppm)


HN
O
O
HO
208
1H NMR: 500 MHz, CDCl3
f1 (ppm)

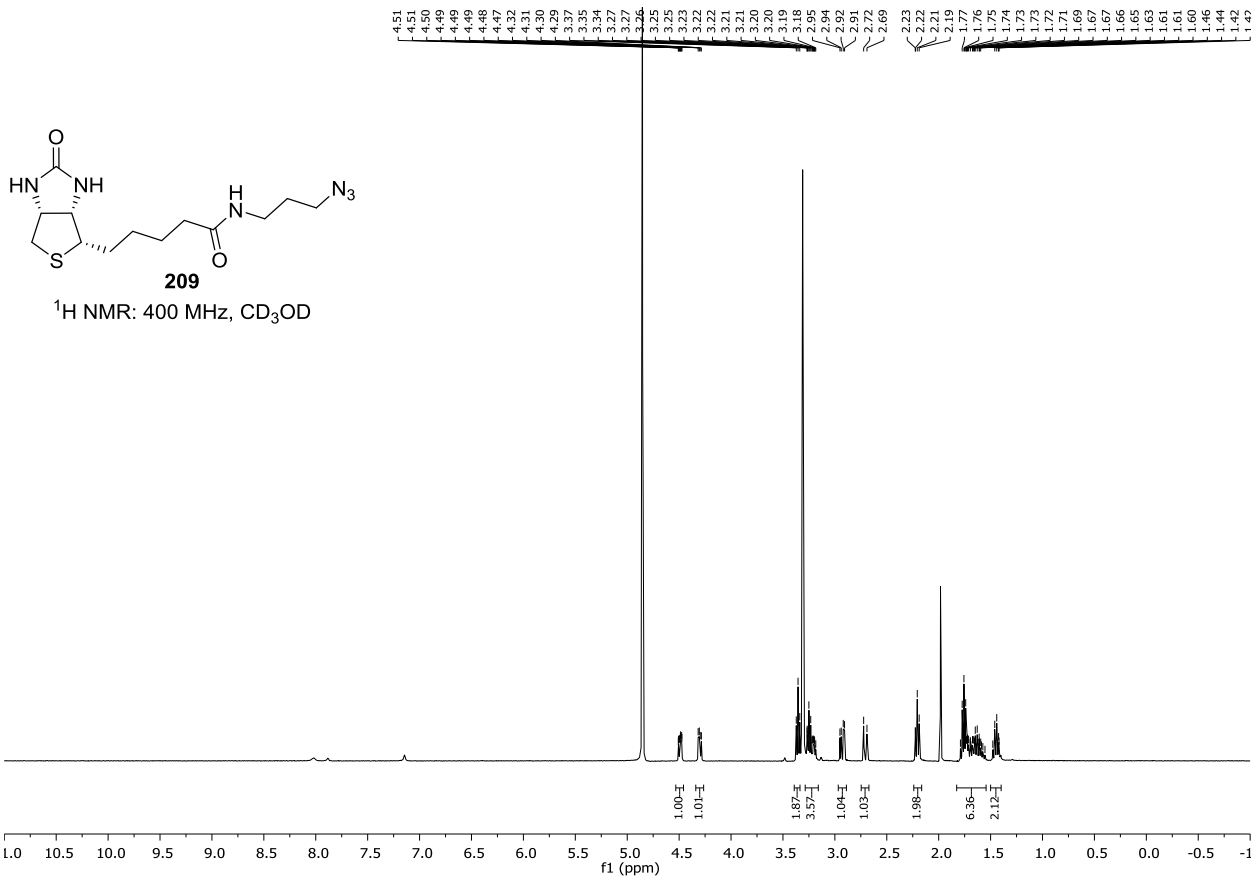

196.49
173.45
162.83
141.05
134.39
131.87
129.61
125.66
84.28
70.87
68.71
57.47
43.30
31.41
31.25
28.03
26.21
23.13
19.69
17.83
HN
O
O
HO
208
13C NMR: 126 MHz, CDCl3
f1 (ppm)




$N_3$—$NH_2$

**S24**

$^1$H NMR: 300 MHz, $CDCl_3$

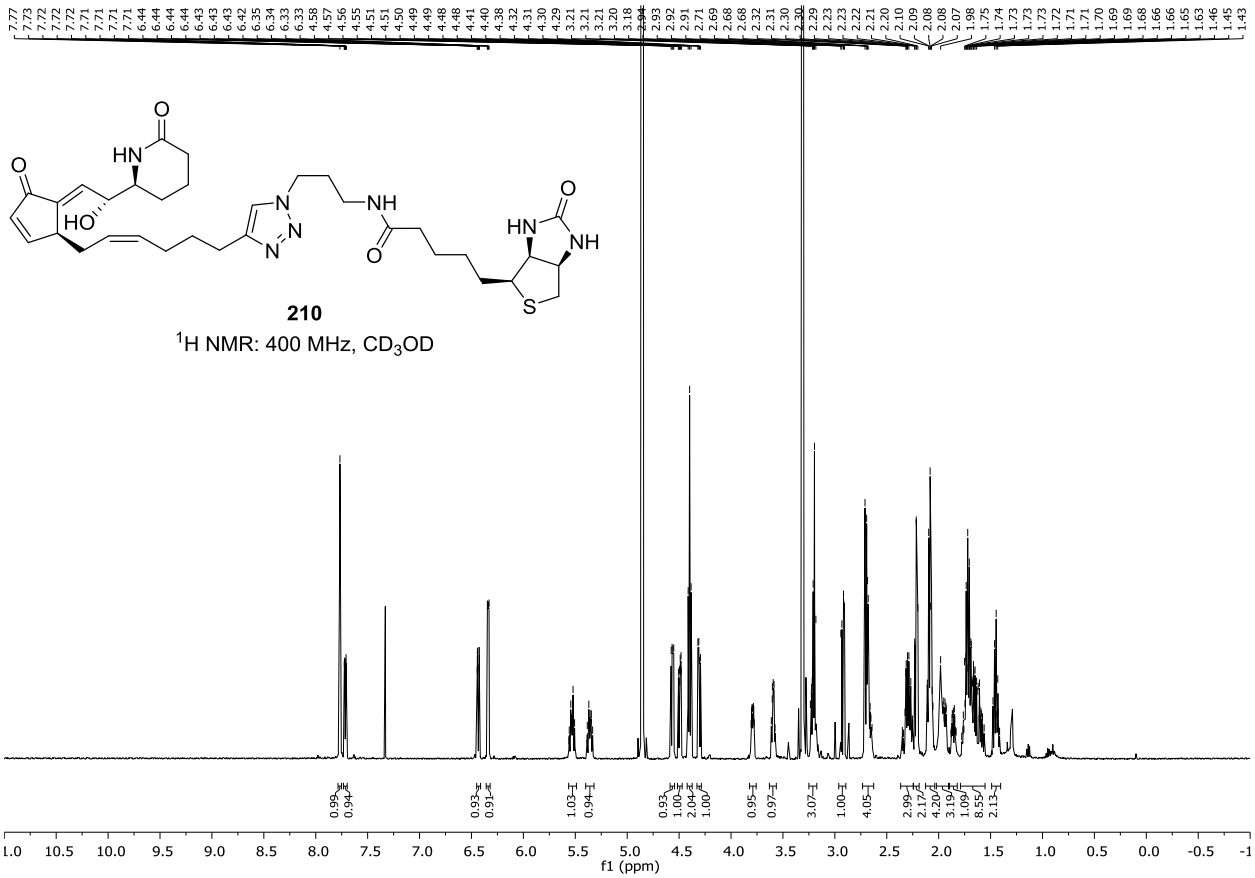






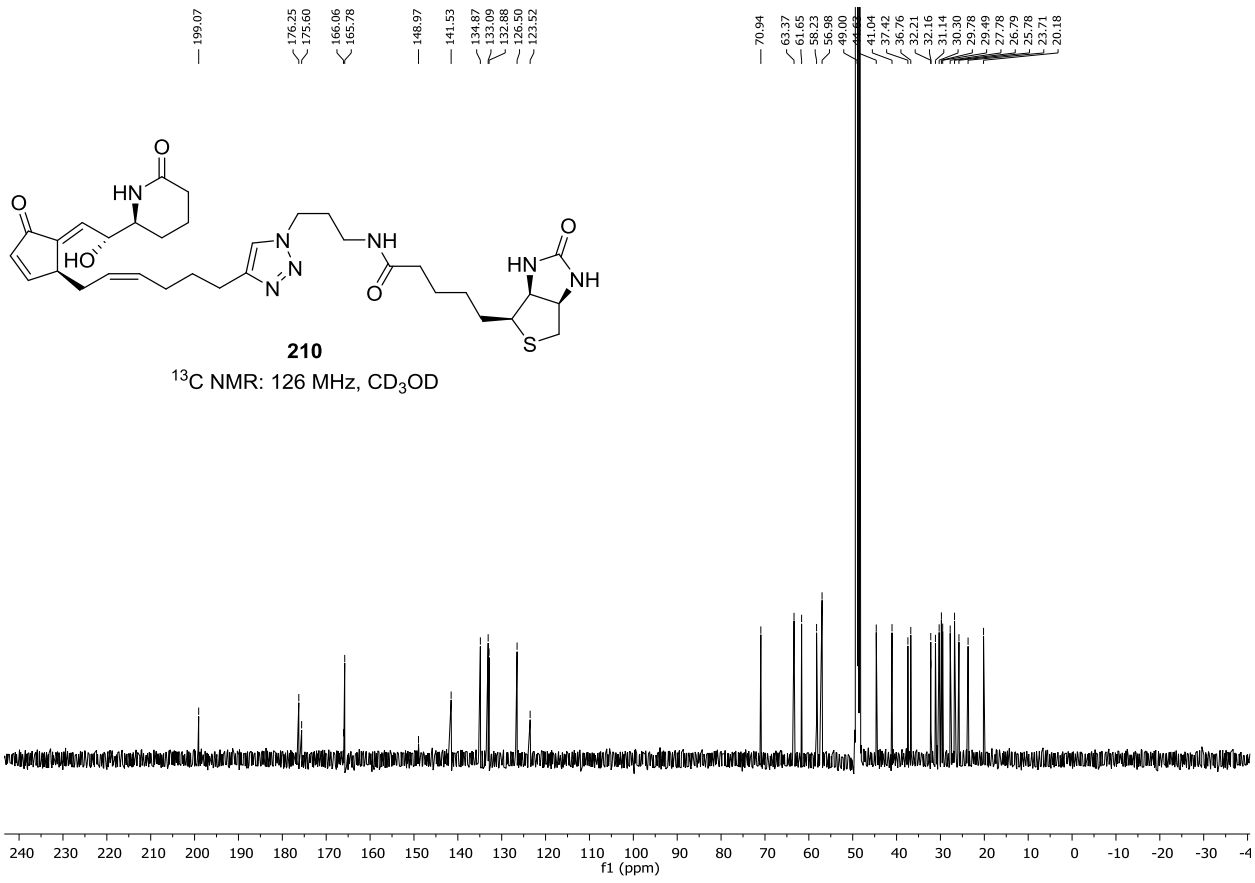
**209**

$^1$H NMR: 400 MHz, $CD_3OD$



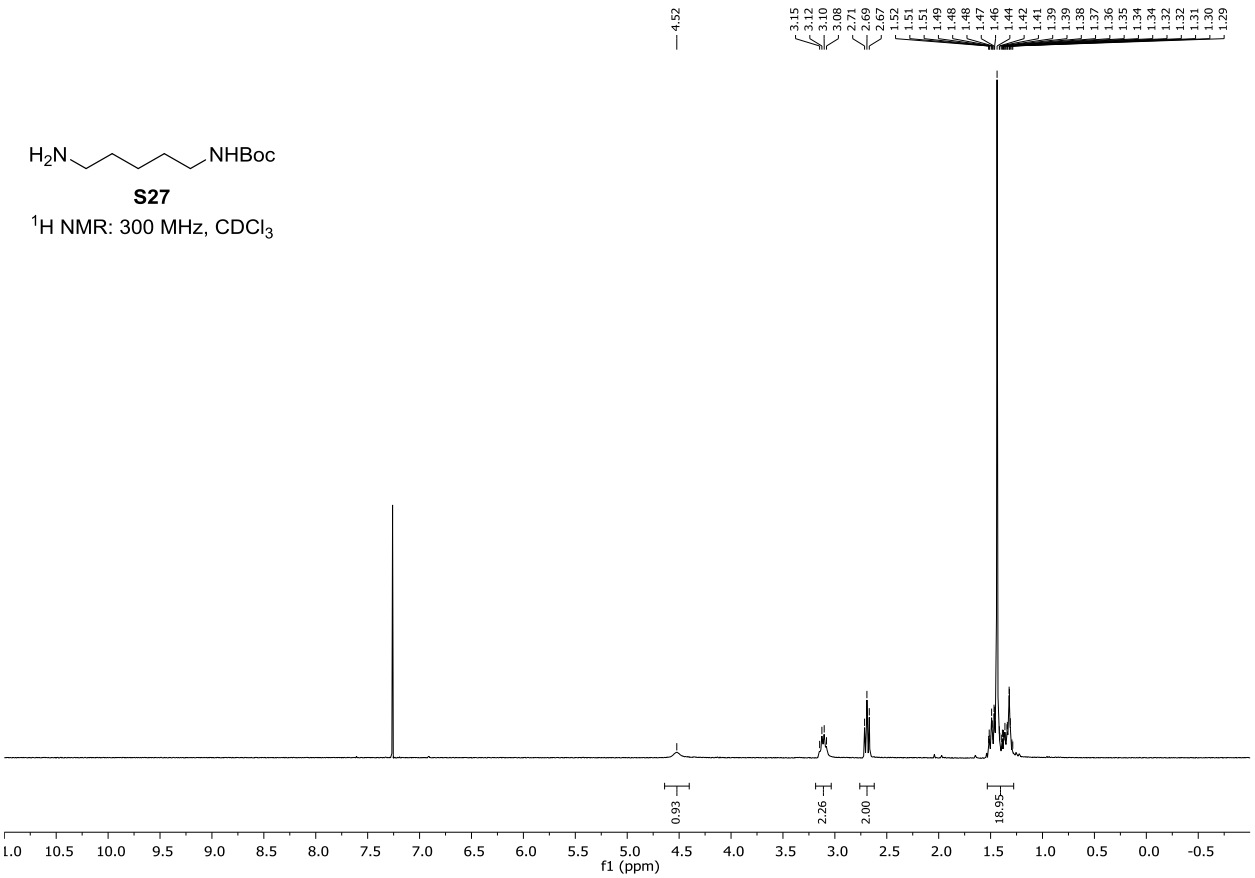
**210**

$^{1}$H NMR: 400 MHz, $CD_3OD$



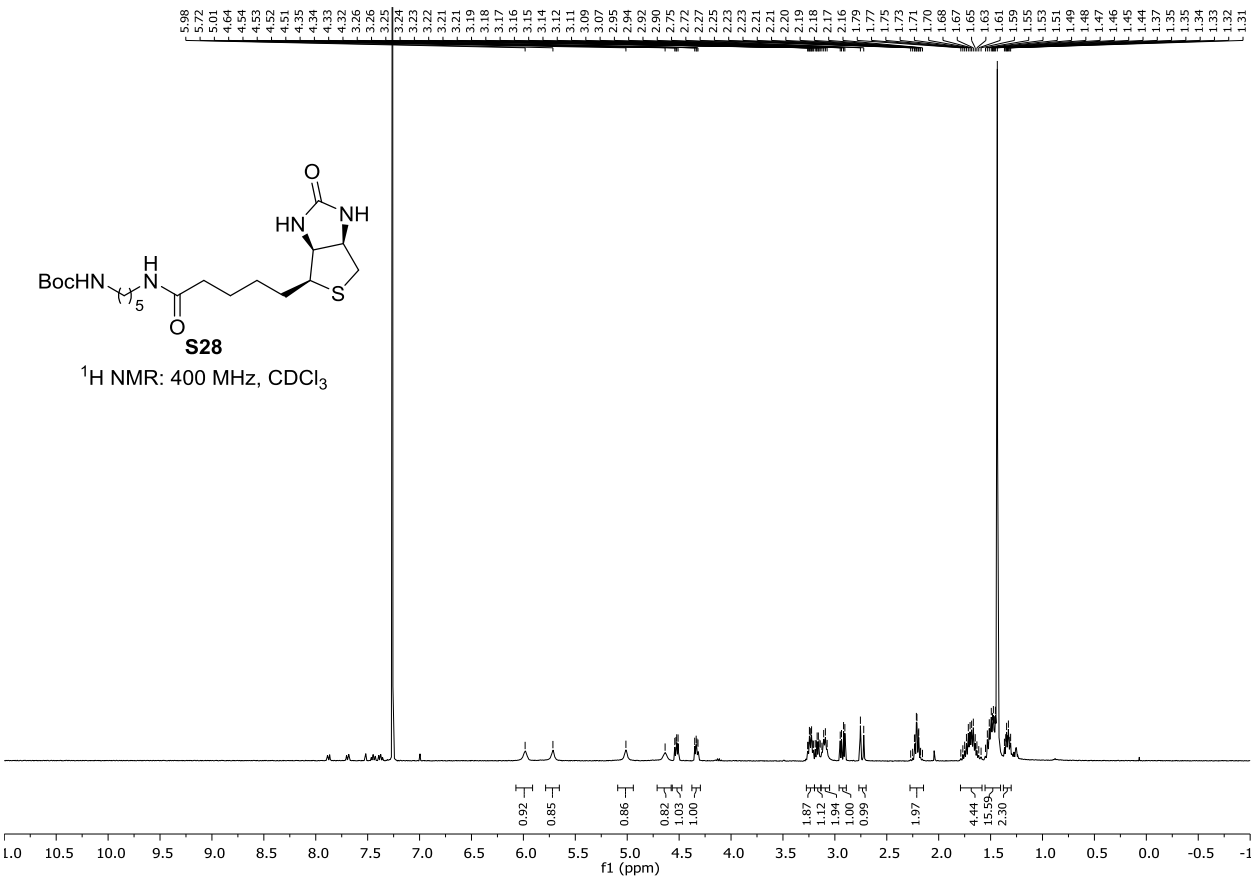
**210**

$^{13}$C NMR: 126 MHz, $CD_3OD$



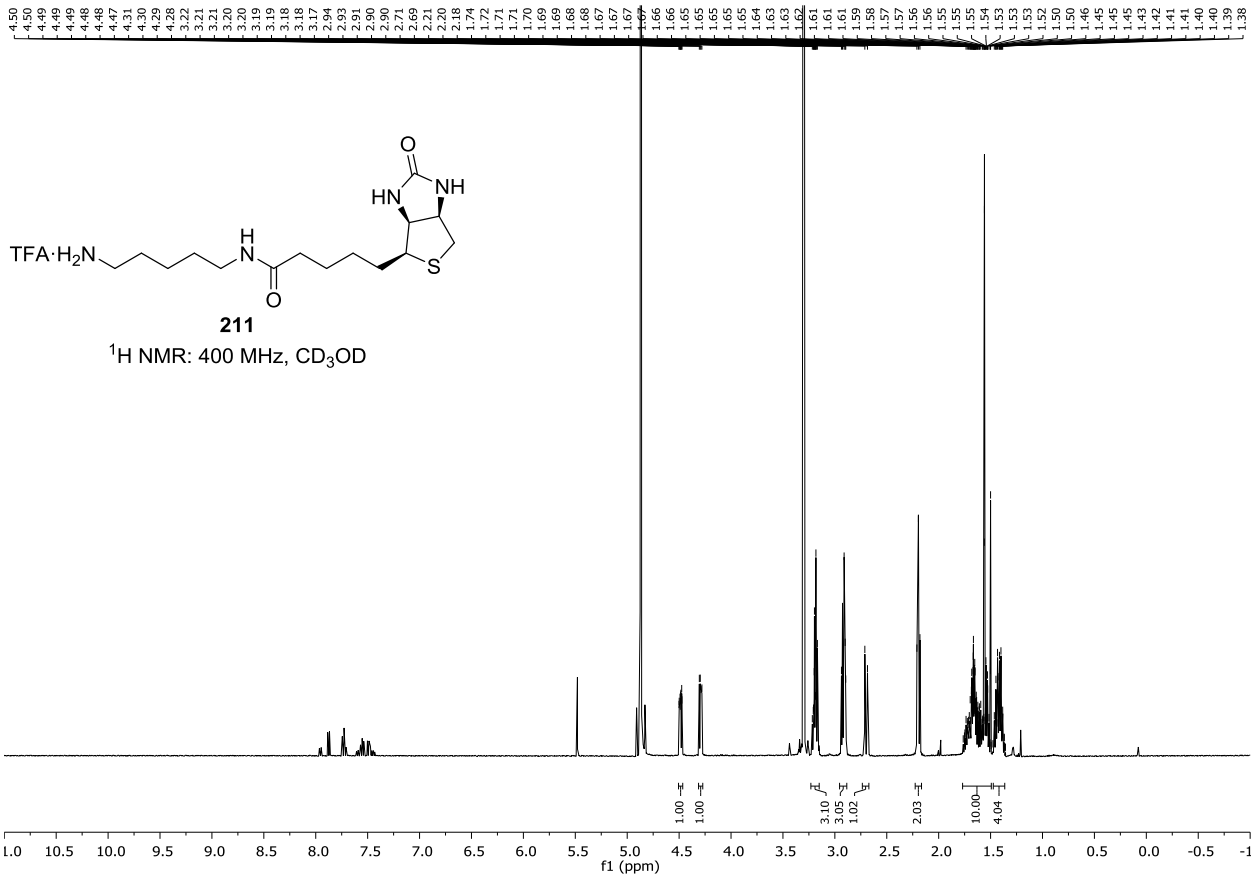

**S27**

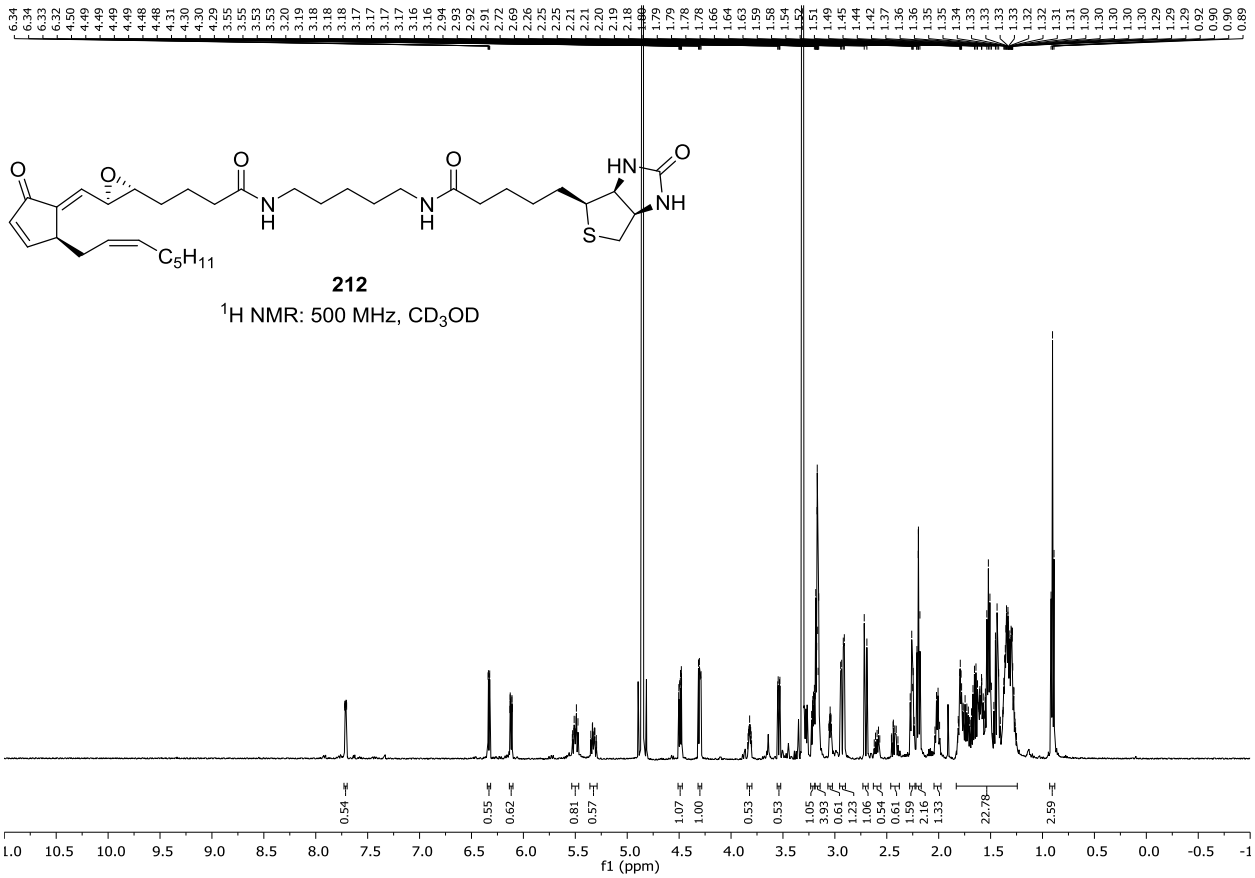
$^1$H NMR: 300 MHz, $CDCl_3$

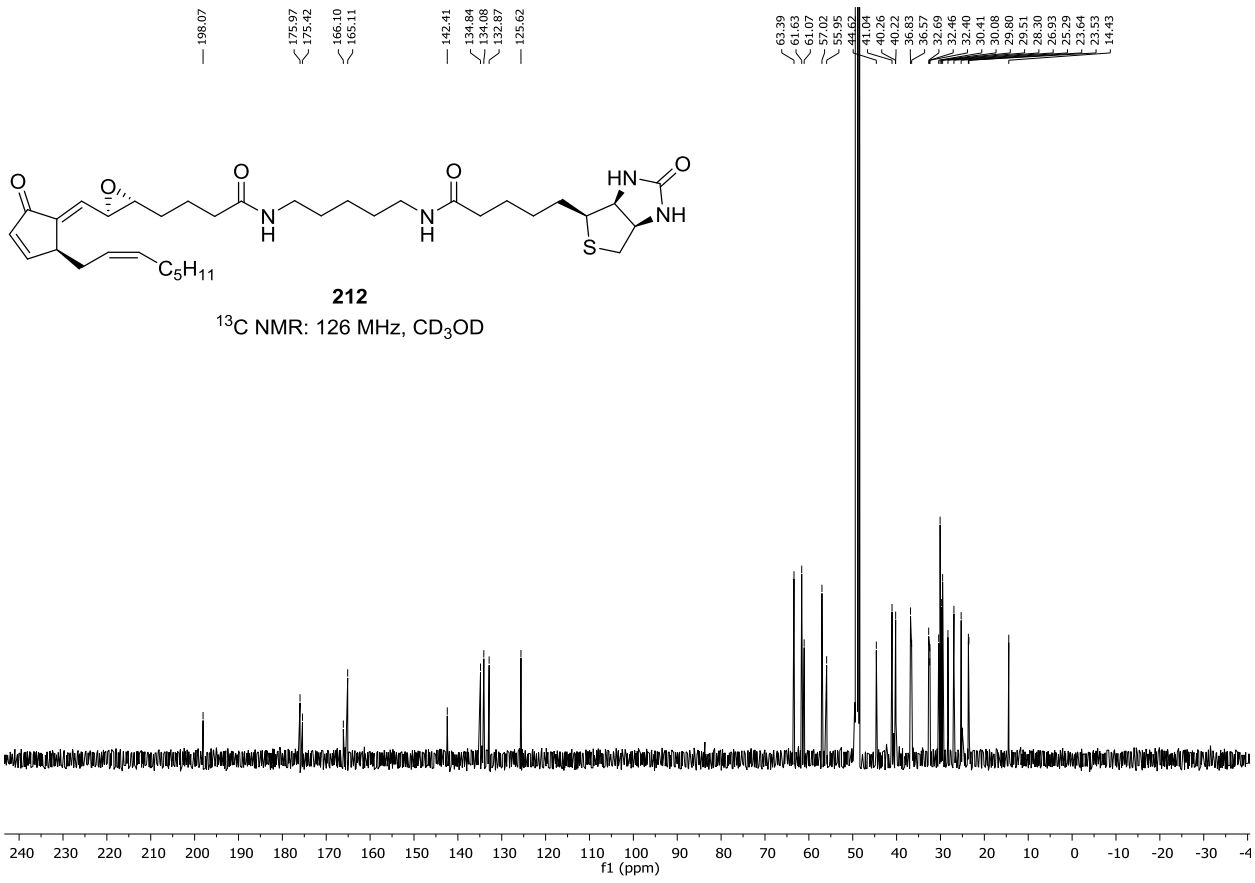


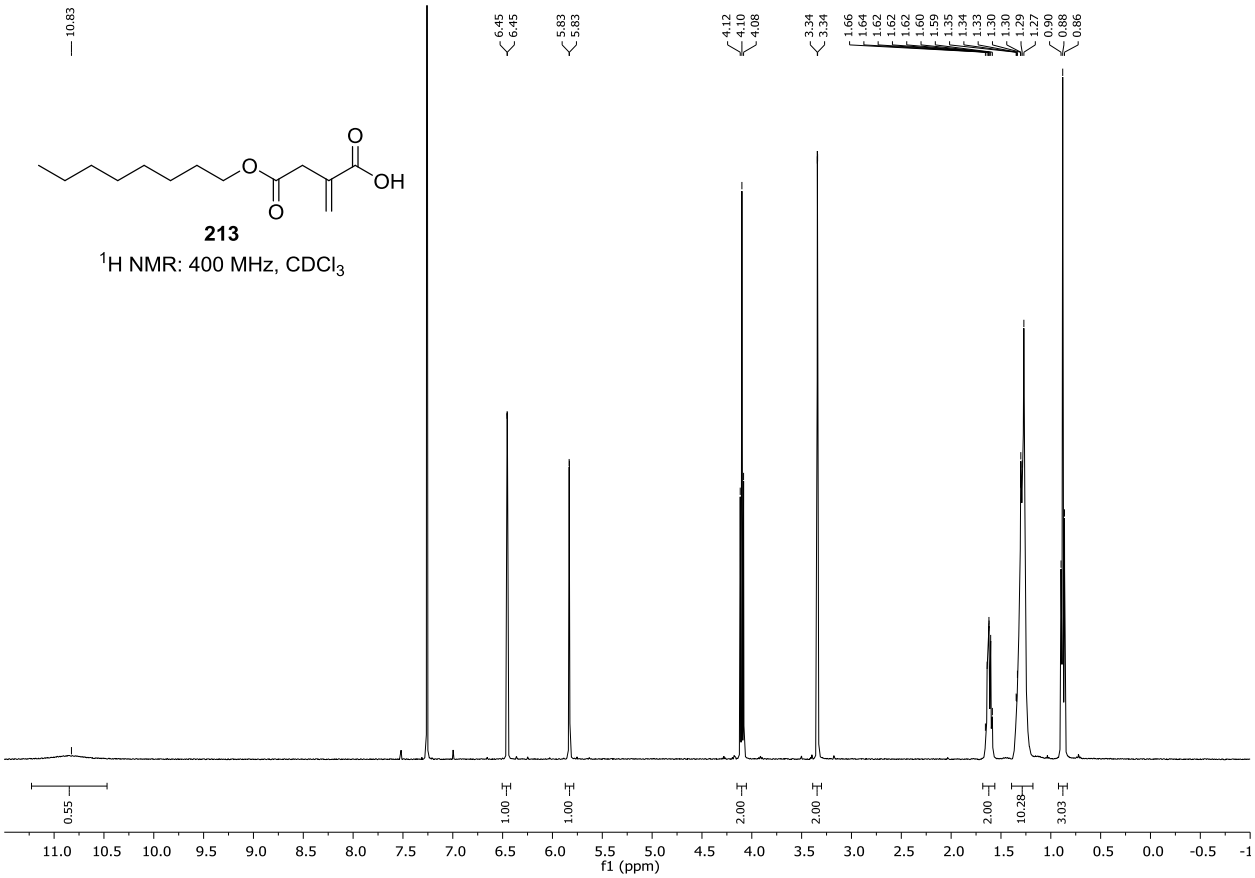

**S28**

$^1$H NMR: 400 MHz, $CDCl_3$


TFA·H2N
H
N
O
HN
NH
O
S
211
1H NMR: 400 MHz, CD3OD
1.00
1.00
3.10
3.05
1.02
2.03
10.00
4.04
f1 (ppm)

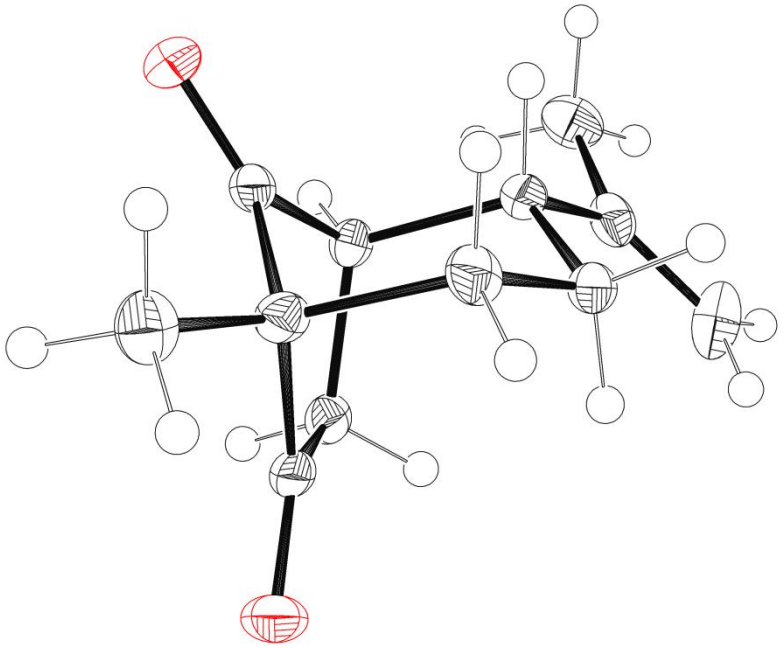

6.34 6.34 6.33 6.32 4.50 4.49 4.49 4.49 4.48 4.48 4.31 4.30 4.30 4.29 3.55 3.53 3.53 3.20 3.19 3.18 3.18 3.18 3.17 3.17 3.17 3.16 3.16 2.94 2.93 2.92 2.91 2.72 2.69 2.26 2.25 2.21 2.21 2.20 2.19 2.18 1.79 1.79 1.78 1.78 1.66 1.64 1.63 1.59 1.58 1.54 1.52 1.51 1.49 1.45 1.44 1.42 1.37 1.36 1.36 1.35 1.35 1.34 1.33 1.33 1.33 1.32 1.32 1.31 1.31 1.30 1.30 1.30 1.30 1.29 1.29 1.29 0.92 0.90 0.90 0.89
O
O
O
N
H
N
H
O
HN
O
NH
S
$C_5H_{11}$
212
$^1$H NMR: 500 MHz, $CD_3OD$
0.54 0.55 0.62 0.81 0.57 1.07 1.00 0.53 0.53 1.05 3.93 0.61 1.23 1.06 0.54 0.61 1.59 2.16 1.33 22.78 2.59
f1 (ppm)


198.07
175.97 175.42 166.10 165.11 142.41 134.84 134.08 132.87 125.62
63.39 61.63 61.07 57.02 55.95 44.62 41.04 40.26 40.22 36.83 36.57 32.69 32.46 32.40 30.41 30.08 29.80 29.51 28.30 26.93 25.29 23.64 23.53 14.43
O
O
O
N
H
N
H
O
HN
O
NH
S
$C_5H_{11}$
212
$^{13}$C NMR: 126 MHz, $CD_3OD$
f1 (ppm)


10.83
6.45
6.45
5.83
5.83
4.12
4.10
4.08
3.34
3.34
1.66
1.64
1.62
1.62
1.62
1.60
1.59
1.35
1.34
1.33
1.30
1.30
1.29
1.27
0.90
0.88
0.86
O
O
O
OH
213
$^1$H NMR: 400 MHz, $CDCl_3$
0.55
1.00
1.00
2.00
2.00
2.00
10.28
3.03
11.0 10.5 10.0 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 0.0 -0.5 -1
f1 (ppm)

## 4.2 X-Ray Crystallographic Data

### X-Ray Crystallographic Data for Diketone 46



Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1551440).

**Experimental:** A small sample of white amorphous solid was dissolved in diethyl ether (ca. 1 mL). The vial was sealed and the cap pierced with a needle. Slow evaporation afforded a colorless specimen of $C_{12}H_{16}O_2$, approximate dimensions 0.19 mm x 0.12 mm x 0.01 mm. The X-ray intensity data were measured on a BRUKER APEX2 DUO (Cu) diffractometer.

| | |
|---|---|
| CCDC identification code | CCDC 1551440 |
| Empirical formula | $C_{12}H_{16}O_2$ |
| Formula weight | 192.25 |
| Temperature/K | 100.0(2) |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| a/Å | 8.0662(5) |
| b/Å | 6.7104(4) |
| c/Å | 9.8648(6) |
| α/° | 90 |
| β/° | 100.240(4) |
| γ/° | 90 |
| Volume/Å$^3$ | 525.45(6) |
| Z | 2 |

| | |
|---|---|
| $\rho_{calc}$g/cm$^3$ | 1.215 |
| $\mu$/mm$^{-1}$ | 0.646 |
| F(000) | 208.0 |
| Crystal size/mm$^3$ | 0.19 × 0.12 × 0.01 |
| Radiation | CuK$\alpha$ ($\lambda$ = 1.54178) |
| 2$\Theta$ range for data collection/° | 9.11 to 133.148 |
| Index ranges | $-9 \leq h \leq 9$, $-7 \leq k \leq 7$, $-11 \leq l \leq 10$ |
| Reflections collected | 6565 |
| Independent reflections | 1522 [$R_{int}$ = 0.0273, $R_{sigma}$ = 0.0216] |
| Data/restraints/parameters | 1522/1/129 |
| Goodness-of-fit on F$^2$ | 1.125 |
| Final R indexes [I>=2$\sigma$ (I)] | $R_1$ = 0.0337, $wR_2$ = 0.0914 |
| Final R indexes [all data] | $R_1$ = 0.0351, $wR_2$ = 0.0924 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.16/-0.17 |
| Flack parameter | 0.33(14) |

# Curriculum Vitae

Born September 13th, 1990 in Berne, Switzerland

## Education

| | |
|---|---|
| **06/2015 – present** | Doctoral candidate in the group of Prof. Dr. Erick M. Carreira<br>ETH Zurich, Switzerland |
| **09/2013 – 01/2015** | Master of Science ETH in Chemistry, ETH Zurich, Switzerland<br>degree awarded with distinction (average grade 5.91 out of 6) |
| **09/2010 – 09/2013** | Bachelor of Science ETH in Chemistry, ETH Zurich, Switzerland<br>degree awarded with distinction (average grade 5.75 out of 6) |
| **12/2009** | Matura, Regionales Gymnasium Laufental-Thierstein, Switzerland<br>degree awarded with distinction (average grade 5.9 out of 6) |

## Research Experience

| | |
|---|---|
| **06/2015 – present** | Doctoral studies in the group of Prof. Dr. Erick M. Carreira<br>ETH Zurich, Switzerland |
| **02 – 04/2015** | Internship at Bayer HealthCare AG in the department of medicinal chemistry, Wuppertal, Germany |
| **09/2014 – 01/2015** | Master thesis in the group of Prof. Dr. Antonio Togni<br>ETH Zurich, Switzerland |
| **02 – 06/2014** | Research project in the group of Prof. Dr. Erick M. Carreira<br>ETH Zurich, Switzerland |
| **10/2012 –02/2013** | Research project in the group of Prof. Dr. Steven V. Ley<br>University of Cambridge, UK (as part of an Erasmus exchange) |

During my doctoral studies, I was a teaching assistant for two introductory-level organic chemistry laboratory courses and an advanced organic chemistry lecture. Also, I was responsible for the education of an apprentice (Laborantin EFZ Fachrichtung Chemie).