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I Total Synthesis of (–)-Mitrephorone A

II Stereoselective Synthesis of Tetrasubstituted Olefins *via* 1,4-Semihydrogenation of 1,3-Dienes

III Synthesis of Primary Amines from Nitriles *via* a Radical Cyclization/Reduction Cascade

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presented by

MICHAEL SCHNEIDER

MSc ETH Chemistry
Born on 07.11.1992
Citizen of Germany and the United States of America

accepted on the recommendation of
Prof. Dr. Erick M. Carreira, examiner
Prof. Dr. Bill Morandi, co-examiner

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PUBLICATIONS

M. Schneider, M. J. R. Richter, E. M. Carreira, Total Synthesis of (–)-Mitrephorone A Enabled by Stereoselective Nitrile Oxide Cycloaddition and Tetrasubstituted Olefin Synthesis, *J. Am. Chem. Soc.* **2020**, *142*, 17802–17809.

M. Schneider, M. J. R. Richter, S. Krautwald, E. M. Carreira, Asymmetric Synthesis of the Tricyclooctane Core of Trachylobane Natural Products and Related Terpenoids, *Org. Lett.* **2019**, *21*, 8705–8707.

M. J. R. Richter, M. Schneider, M. Brandstätter, S. Krautwald, E. M. Carreira, Total Synthesis of (–)-Mitrephorone A, *J. Am. Chem. Soc.* **2018**, *140*, 16704–16710.

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.

POSTER PRESENTATIONS

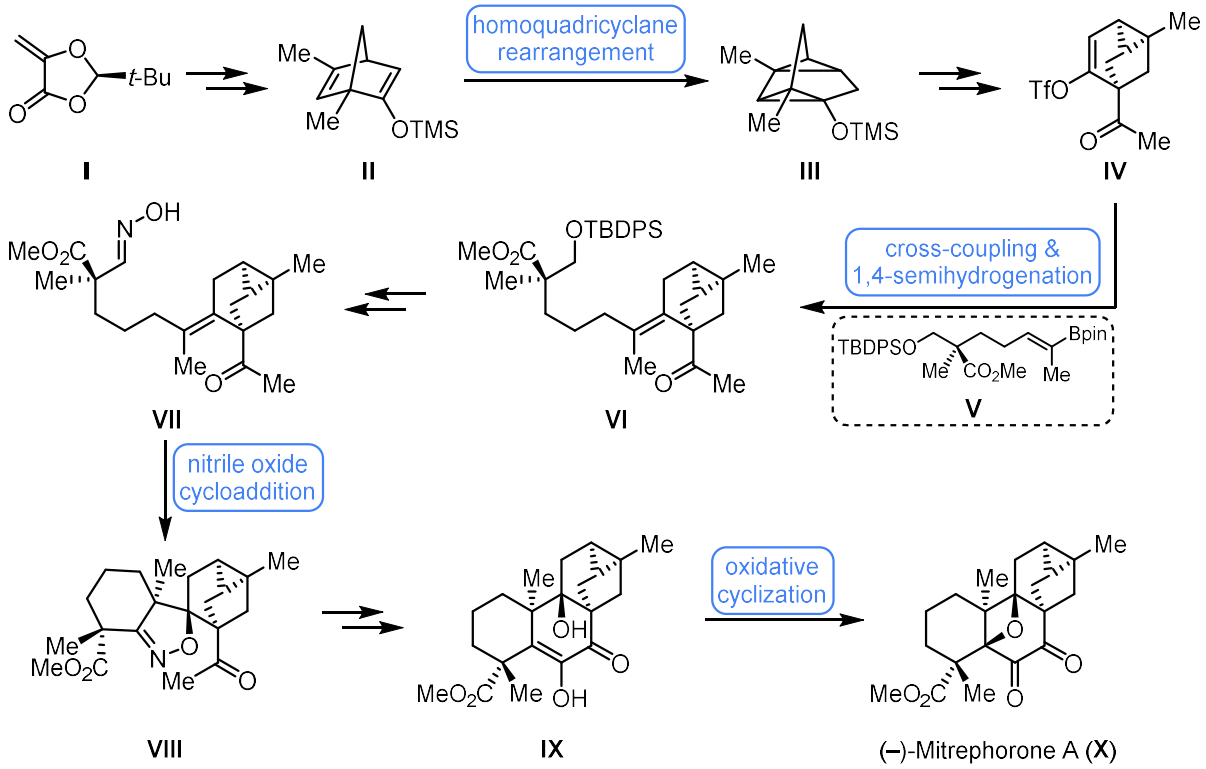
Poster Presentation at the 12th Symposium of the Scholarship Fund of the Swiss Chemical Industry 2020: “Total Synthesis of (–)-Mitrephorone A”

TABLE OF CONTENTS

ABSTRACT

The first chapter of this thesis describes the total synthesis of the trachylobane diterpenoid (–)-mitrephorone A (**X**), which was isolated from the bark of the Bornean shrub *Mitrephora Glabra* Scheff in 2005. The fully substituted oxetane at the center of the molecule is a unique structural feature amongst the trachylobane natural products. Throughout this chapter, different approaches towards the synthesis of this diterpenoid are discussed. These include methods for oxetane formation, such as a [2 + 2] cycloaddition reaction and an intramolecular oxa-MICHAEL reaction, as well as various approaches towards the stereoselective synthesis of tetrasubstituted olefins.

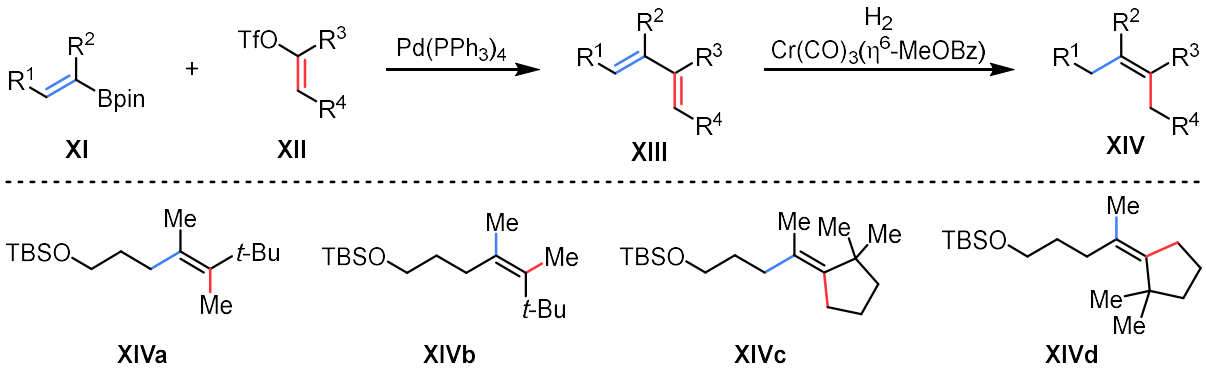
The final synthesis of (–)-mitrephorone A (**X**) commenced with the preparation of norbornadiene **II** from enantiopure olefin **I** *via* a diastereoselective DIELS–ALDER cycloaddition reaction (Scheme I). Cyclopropanation of **II** induced a homoquadricyclane rearrangement and led to the formation dicyclopropane **III**. Vinyl boronate **V** was synthesized *via* pig liver esterase-mediated malonate



Scheme I. Outline of the total synthesis of (–)-mitrephorone A (**X**).

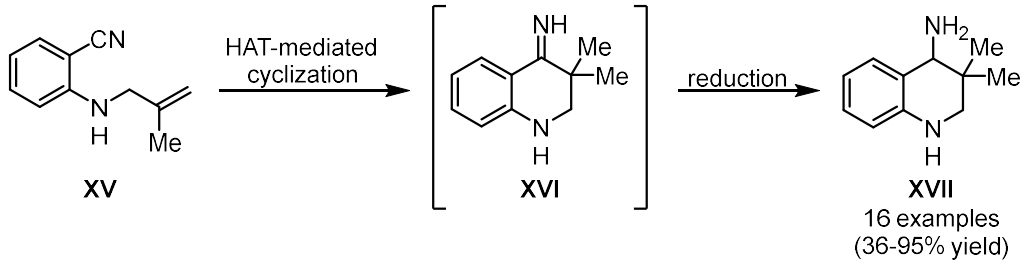
desymmetrization and was subjected to SUZUKI–MIYAURA cross-coupling with vinyl triflate **IV**. 1,4-Semihydrogenation of the resulting diene afforded tetrasubstituted olefin **VI** as a single olefin isomer. Highly diastereoselective nitrile oxide cycloaddition reaction of **VII** gave isoxazoline **VIII**, whereby the facial selectivity was fully controlled by the α-stereocenter of the nitrile oxide. Finally, (–)-mitrephorone A (**X**) was obtained *via* oxidative cyclization of δ-hydroxydiosphenol (**IX**).

The second chapter features the 1,4-semihydrogenation of 1,3-dienes. This reaction has been known since the 1960's, however, there was hardly any precedence for the synthesis of tetrasubstituted olefins using this approach. Moreover, no examples for the combination of sp^2–sp^2 cross-coupling and 1,4-semihydrogenation had been reported. After the successful implementation of this sequence in the total synthesis of (–)-mitrephorone A (**X**), the stereoselective synthesis of tetrasubstituted olefins **XIV** was further explored employing this approach. Most interestingly, both olefin geometric isomers could be prepared selectively from the same vinyl triflate **XII** by variation of vinyl boronate **XI** as shown for olefin isomers **XIVa** and **XIVb** as well as **XIVc** and **XIVd** (Scheme **II**).



Scheme II. Stereoselective synthesis of tetrasubstituted olefins *via* sequential sp^2–sp^2 cross-coupling and 1,4-semihydrogenation.

The final chapter of this thesis discusses the synthesis of primary amines from nitriles *via* a hydrogen atom transfer-mediated cyclization/reduction cascade. The combination of sodium borohydride and $Mn(dpm)_3$ showed the best results in optimization studies and allowed for the synthesis of 16 primary amines from aromatic or aliphatic nitriles (Scheme III). Substrates bearing a malonate in the connecting backbone could be transformed either into the corresponding primary amines or lactams depending on the reaction conditions.

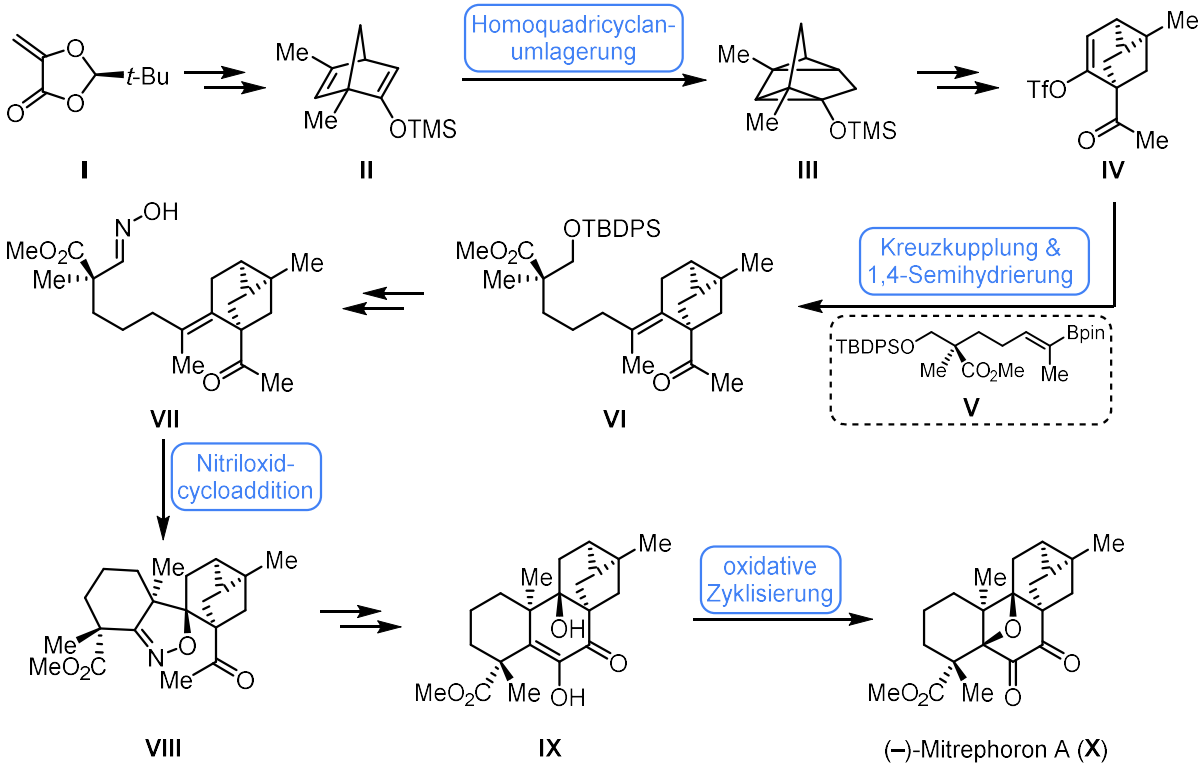


Scheme III. Synthesis of primary amines from nitriles *via* a HAT-mediated cyclization/reduction cascade.

ZUSAMMENFASSUNG

Das erste Kapitel dieser Dissertation befasst sich mit der Totalsynthese des Trachylobanditerpenoids (–)-Mitrephoron A (**X**), welches 2005 aus der Rinde des bornesischen Strauchs *Mitrephora Glabra* Scheff isoliert wurde. Das vollständig substituierte Oxetan im Zentrum des Moleküls ist ein einzigartiges Strukturelement unter den Trachylobannaturstoffen. Im Rahmen dieses Kapitels werden verschiedene Ansätze zur Synthese dieses Diterpenoids diskutiert. Dazu gehören Methoden zum Aufbau des Oxetans, wie eine [2 + 2] Cycloadditionsreaktion und eine intramolekulare oxa-MICHAEL Addition, sowie verschiedene Ansätze zur stereoselektiven Synthese von tetrasubstituierten Olefinen.

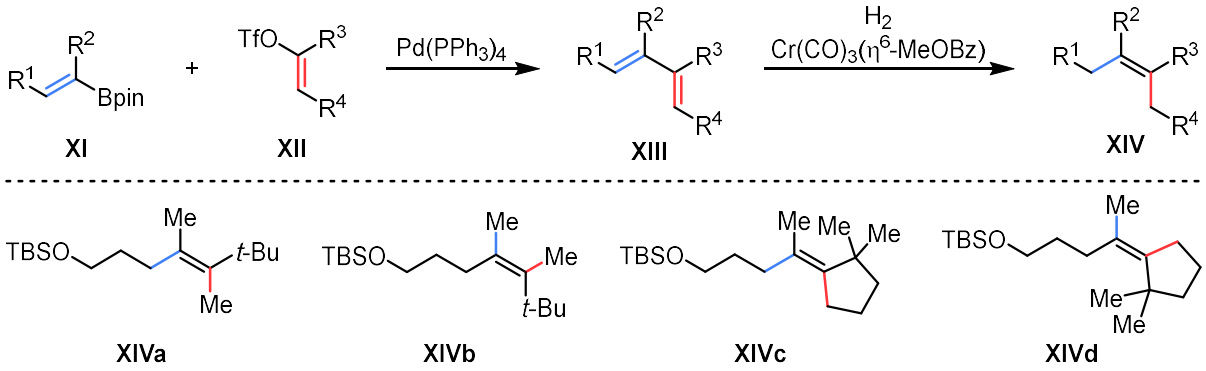
Die finale Synthese von (–)-Mitrephoron A (**X**) begann mit der Herstellung von Norbornadien **II** aus enantiomerenreinem Olefin **I** durch eine diastereoselektive DIELS–ALDER Cycloadditionsreaktion (Schema I). Cyclopropanierung von **II** löste eine Homoquadricyclanumlagerung aus und führte zur Bildung von Dicyclopropan **III**. Vinylboronat **V** wurde durch eine



Schema I. Übersicht der Totalsynthese von (–)-Mitrephorone A (**X**).

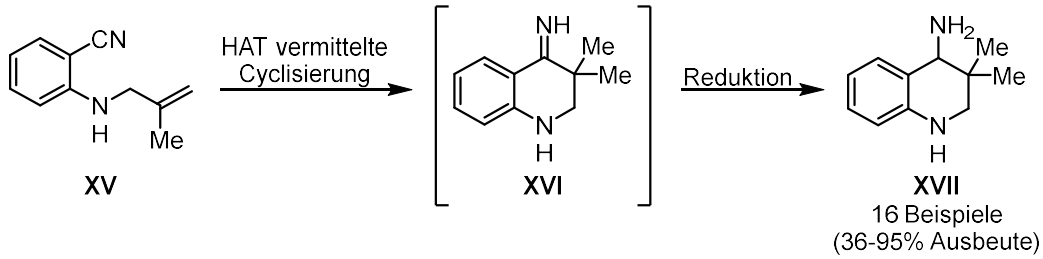
Schweineleberesterase-vermittelte Malonatdesymmetrisierung hergestellt und durch eine SUZUKI–MIYAURA Kreuzkupplung mit Vinyltriflat **IV** verbunden. 1,4-Semihydrierung des entstandenen Diens lieferte das tetrasubstituierte Olefin **VI** als einziges Olefinisomer. Hoch diastereoselektive Nitriloxidcycloadditions-reaktion von **VII** ergab Isoxazolin **VIII**, wobei die faciale Selektivität vollständig durch das α-Stereozentrum des Nitriloxids bestimmt wurde. Abschließend wurde (–)-Mitrephoron A (**X**) durch eine oxidative Zyklisierung von δ-Hydroxy-diosphenol (**IX**) erhalten.

Im zweiten Kapitel wird die 1,4-Semihydrierung von 1,3-Dienen behandelt. Diese Reaktion ist bereits seit den 1960er Jahren bekannt, es gab jedoch kaum eine Präzedenz für die Synthese von tetrasubstituierten Olefinen unter Verwendung dieses Ansatzes. Darüber hinaus gab es keine Beispiele für die Kombination von sp^2–sp^2 Kreuzkupplung und 1,4-Semihydrierung. Nach der erfolgreichen Anwendung dieser Sequenz in der Totalsynthese von (–)-Mitrephoron A (**X**) wurde die stereoselektive Synthese von tetrasubstituierten Olefinen **XIV** über diesen Ansatz genauer untersucht. Besonders interessant hierbei ist, dass beide geometrischen Olefinisomere aus demselben Vinyltrilfat **XII** durch Variation des Vinylboronats **XI** hergestellt werden konnten, wie für Isomere **XIVa** und **XIVb** sowie **XIVc** und **XIVd** gezeigt wurde (Schema II).



Schema II. Stereoselektive Synthese von tetrasubstituierten Olefinen durch sequenzielle sp^2–sp^2 Kreuzkupplung und 1,4-Semihydrierung.

Das letzte Kapitel dieser Arbeit diskutiert die Synthese von primären Aminen aus Nitrilen durch eine Kaskade aus einer von Wasserstoffatomtransfer herbeigeführter Zyclisierung und Reduktion. Die Kombination aus Natriumborhydrid und $Mn(dpm)_3$ zeigte die besten Resultate in der Reaktionsoptimierung und ermöglichte die Synthese von 16 primären Aminen aus aromatischen oder aliphatischen Nitrilen (Schema III). Substrate, die ein Malonat im verbindenden Backbone enthielten, konnten abhängig von den Reaktionsbedingungen entweder in die entsprechenden primären Amine oder Laktame umgewandelt werden.



Schema III. Synthese von primären Aminen aus Nitrilen über eine durch HAT herbeigeführte Zyklisierungs- und Reduktionskaskade.

LIST OF ABBREVIATIONS

Å	Ångstrom
Ac	acetyl
acac	acetylacetonato
AIBN	2,2‘-azobis(isobutyronitrile)
aq	aqueous
ATP	adenosine triphosphate
Bn	benzyl
br	broad
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
CAM	cerium ammonium molybdate
cat.	Catalytic
CIDNP	chemically induced dynamic nuclear polarization
cm^{-1}	reciprocal centimeters
CMP	cytidine monophosphate
CoA	coenzyme A
CSA	10-camphorsulfonic acid
CTP	cytidine triphosphate
d	day, doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethylallyl pyrophosphate
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	DESS–MARTIN periodinane
DMSO	dimethylsulfoxide

dpm	2,2,6,6,-tetramethyl-3,5-heptanedionato (dipivaloylmethanato)
d.r.	diastereomeric ratio
DFT	discrete Fourier transform
ee	enantiomeric excess
EI	electron ionization
ent	enantiomeric
equiv.	equivalents
ESI	electron spray ionization
Et	ethyl
FPP	farnesyl pyrophosphate
g	gram
GGPP	geranyl geranyl pyrophosphate
GPP	geranyl pyrophosphate
h	hour
hν	light
HAT	hydrogen atom transfer
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetrethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso* (prefix for alkyl groups)
IPP	isopentyl pyrophosphate
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
L	liter
LC/MS	Liquid chromatography/mass spectrometry

LDA	lithium diisopropylamide
M	molar, mega, metal
m	multiplet, milli
m-CPBA	3-chloroperbenzoic acid
Me	methyl
MEP pathway	deoxyxylulose pathway
min	minute
mol	mole
MoOPH	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
mol%	percentage by moles
MS	methanesulfonyl, molecular sieves
MVA pathway	mevalonic acid pathway
n	normal (prefix for alkyl groups)
n	nano
NADPH	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	*ortho*
P	phosphate
p	*para*
p	quintet
Ph	phenyl
pH	negative logarithm of H_3O^+ concentration in aqueous solutions
pin	pinacol
piv	pivaloyl
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr	pyridine

q	quartet
quant.	Quantitative
R	residue
rac	racemic
R_f	retardation factor
rmsd	root-mean-square deviation
r.t.	room temperature
s	singlet, second
sat.	saturated
Ser	serine
t	*tert* (prefix for alkyl groups)
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	triflormethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylene-1,2-diamine
TMS	trimethylsilyl
TPP	thiamine diphosphate
Ts	*p*-toluenesulfonyl
TS	transition state
UV	ultraviolet
W	watt
wt%	percentage by weight
Δ	reflux
δ	chemical shift

ε	molar attenuation coefficient
η	hapticity
λ	wavelength
μ	micro
μW	microwave
3D	three dimensional

1

Total Synthesis of (–)-Mitrephorone A

I TOTAL SYNTHESIS OF (–)-MITREPHORONE A

1. INTRODUCTION

1.1. Terpenoids

1.1.1. Properties, Classes and Functions of Terpenoids

Hydrocarbon natural products that are derived from 5-carbon isoprene units are referred to as terpenes.[1] They are classified by the number of C_5 isoprene units they are build up from: hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes (C_{5n}). Structurally related natural products that can differ from terpenes with respect to oxidation pattern and carbon connectivity are called terpenoids. A selection of terpenoids and the terpenes they are derived from is

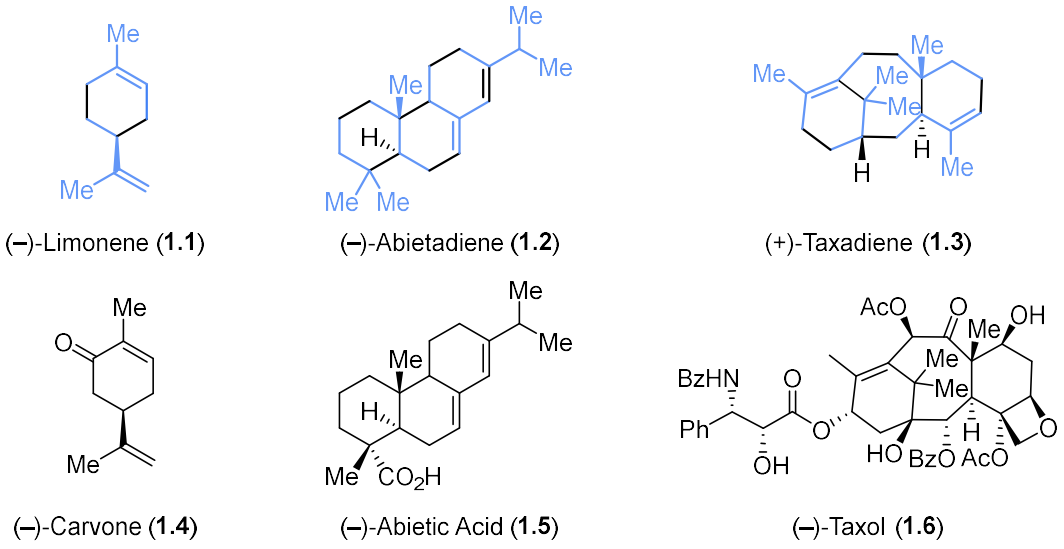


Figure 1.1. Structure of selected terpenes **1.1-1.3** and related terpenoids **1.4-1.6**. The isoprene units in the terpenes are highlighted in blue.

[1] *IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford, 1997, online version.*

depicted in Figure 1.1.[2,3] To date, more than 35'000 terpenoids have been isolated and characterized.

Terpenes and terpenoids are produced by plants, as well as by animals, and exhibit various biological functions.[4,5] Those range from the attraction of insects for pollination by low molecular weight terpenes to antifeedant properties and to signaling functions by steroid hormones. Since ancient times, terpene- and terpenoid-rich plants have been used as medicines,[6] and still today some of these natural products are applied as pharmaceuticals. For example, the diterpenoid Taxol (**1.6**) is a potent chemotherapeutic agent that displays activity against a broad spectrum of human cancer cell lines.[7]

1.1.2. Biosynthesis of Terpenoids

1.1.2.1. Biosynthesis of Acyclic Precursors

Nature utilizes isopentenyl pyrophosphate (IPP, **1.12**) and dimethylallyl pyrophosphate (DMAPP, **1.13**) as synthetic equivalents of isoprene.[2] Biosynthetically, these two key building blocks can be prepared *via* two pathways: the mevalonic acid pathway (MVA, Scheme 1.1A) and the deoxyxylulose pathway (MEP, Scheme 1.1B).

The MVA pathway starts with the enzyme-catalyzed CLAISEN condensation of two acetyl-CoA (**1.7**) to give acetoacetyl-CoA (**1.8**).[2] Aldol addition of an enzyme-bound thioester to the keto group followed by hydrolysis furnished 3-hydroxy-3-methylglutaryl-CoA (**1.9**). NADPH-mediated reduction of the

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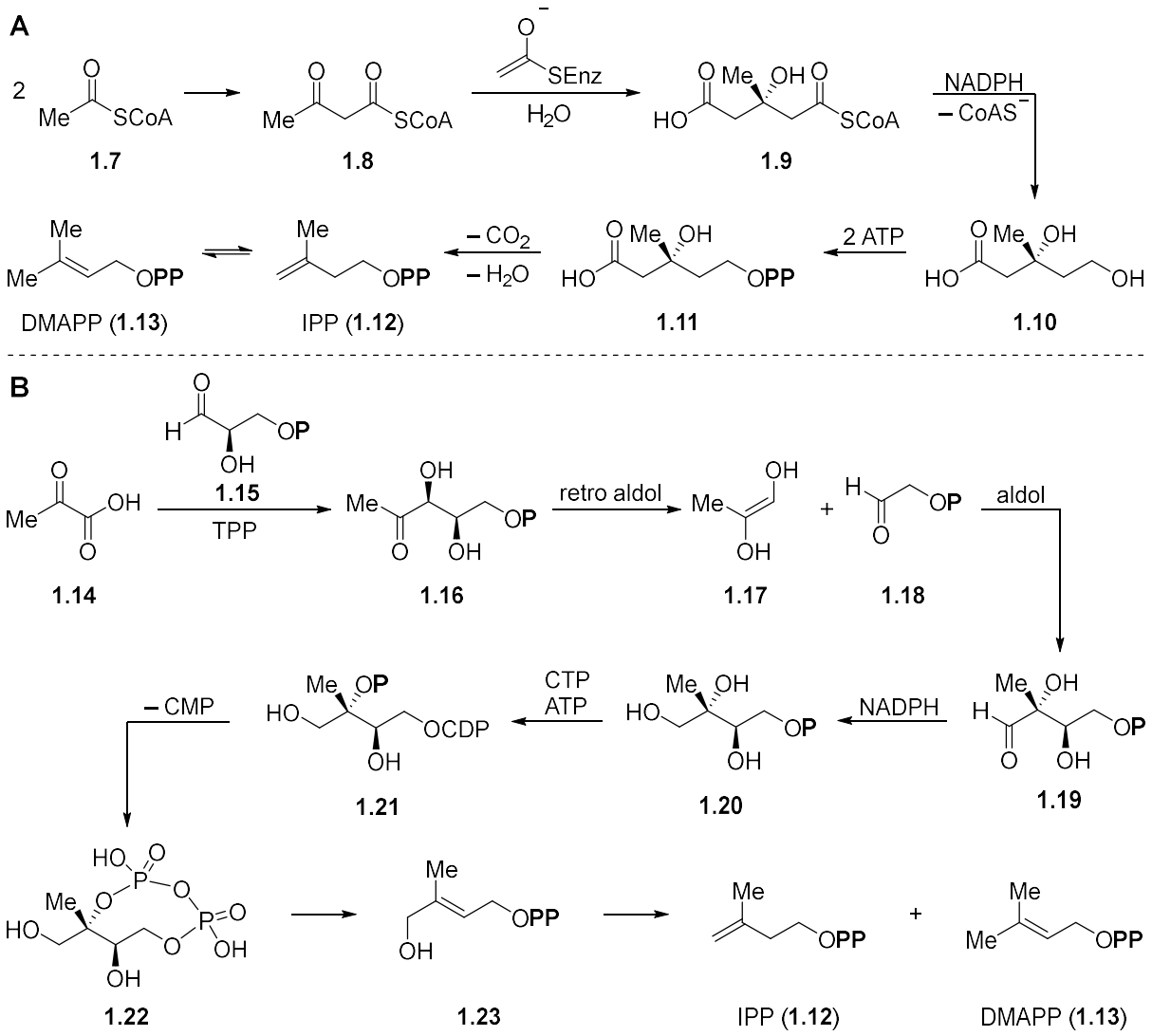
[2] Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach, 3rd Edition*, John Wiley & Sons Ltd., West Sussex, 2009.
[3] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.
[4] Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones,* Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2006.
[5] Bugg, T. D. H. *Introduction to Enzyme and Coenzyme Chemistry, 3rd edition*, John Wiley & Sons Ltd., West Sussex, 2012.
[6] Jaeger, R.; Cuny, E. *Nat. Prod. Commun.* **2016**, *11*, 1373–1390.
[7] Khanna, C.; Rosenberg, M.; Vail, D. M. *J. Vet. Intern. Med.* **2015**, *29*, 1006–1012.

thioester to mevalonic acid (**1.10**) and subsequent phosphorylation of the primary alcohol with ATP leads to intermediate **1.11**. Decarboxylative fragmentation of **1.11** gives IPP (**1.12**), which can be isomerized to DMAPP (**1.13**).

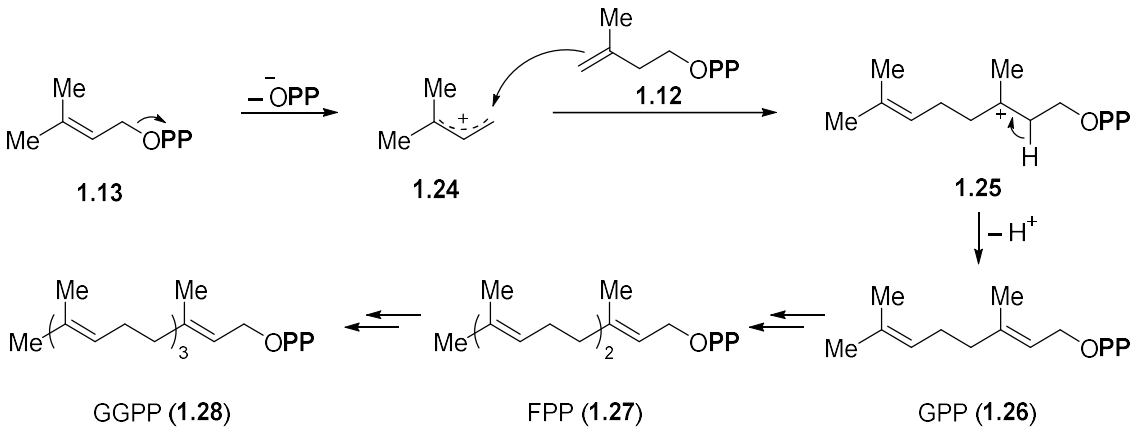
In the MEP pathway, pyruvic acid (**1.14**) is transformed into an acetaldehyde anion equivalent with thiamine diphosphate (TPP) and added to glyceraldehyde-3-phosphate (**1.15**) to form 1-deoxyxylulose-5-phosphate (**1.16**).[2] Retro-aldol addition and readdition with opposite regiochemistry furnishes aldehyde **1.19**, which is reduced to erythritol derivative **1.20** by NADPH. A series of phosphorylations and anhydride formation affords cyclic diphosphate **1.22**. The final reductions of **1.22** to IPP (**1.12**) and DMAPP (**1.13**) are not yet fully



Scheme 1.1. Synthesis of IPP (**1.12**) and DMAPP (**1.13**) *via* the mevalonic acid pathway (**A**) and the deoxyxylulose pathway (**B**).

understood but have been shown to proceed *via* allylic alcohol (**1.23**). Which pathway is operational can be determined for every terpenoid individually by feeding [1-^{13}C]-labeled glucose to the system, leading to differently labeled IPP (**1.12**) and DMAPP (**1.13**) depending on the pathway.[2]

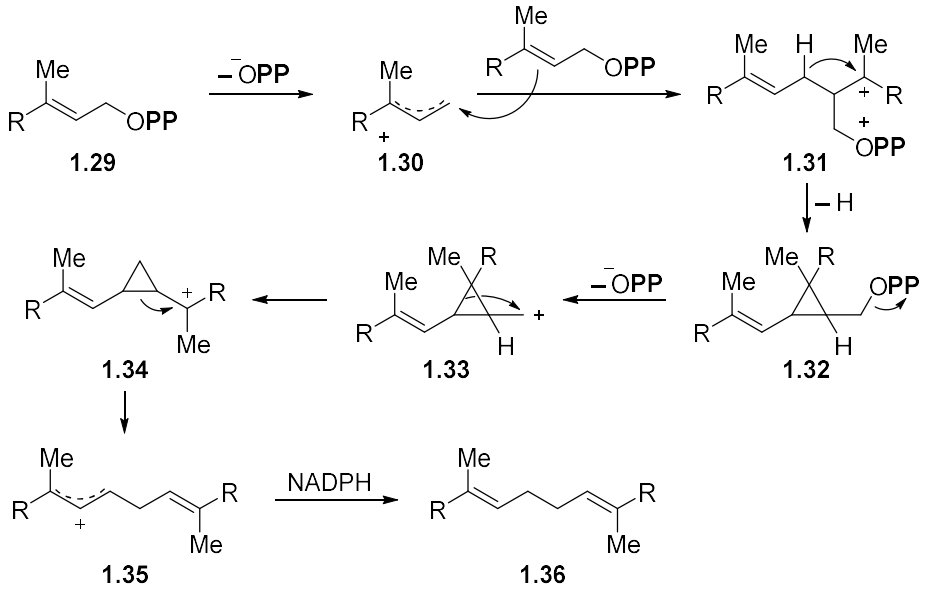
The two isomers IPP (**1.12**) and DMAPP (**1.13**) exhibit a different reactivity. DMAPP **1.13** can release the pyrophosphate to form allylic cation **1.24**, which renders it a good electrophile. For IPP, heterolytic *C*-*O* cleavage would lead to the formation of a non-stabilized primary cation. The most stable IPP-derived cation, namely a tertiary cation, can be formed *via* nucleophilic addition of the terminal olefin to an electrophile. This inverse reactivity is utilized in the so-called head-to-tail coupling (Scheme 1.2). Upon cleavage of the *C*-*O* bond in DMAPP (**1.13**), the resulting allylic cation **1.24** is trapped by IPP (**1.12**). Deprotonation of **1.25** leads to the formation of geranyl pyrophosphate (**1.26**), which itself is an allylic pyrophosphate and can undergo further reactions with IPP (**1.12**) to form farnesyl pyrophosphate (FPP, **1.27**) and geranylgeranyl pyrophosphate (GGPP, **1.28**).



Scheme 1.2. Head-to-tail coupling of DMAPP (**1.13**) and IPP (**1.12**).

Another way to join isoprene units is the tail-to-tail coupling of two allylic pyrphosphates.[2] The tail-to-tail dimerization of farnesyl pyrophosphate (**1.27**) is a key step in the synthesis of squalene, a biosynthetic precursor of steroids. In this transformation, allylic cation **1.30** formed from **1.29** is trapped by another molecule of **1.29**. Deprotonation of **1.31** leads to concomitant cyclopropane

formation. Heterolytic cleavage of the *C*-*O* bond in **1.32** provides primary cation **1.33**, which rearranges first to tertiary cation **1.34** and then to allylic cation **1.35**. Finally, reduction of the allylic cation with NADPH forms the coupling product **1.36**.



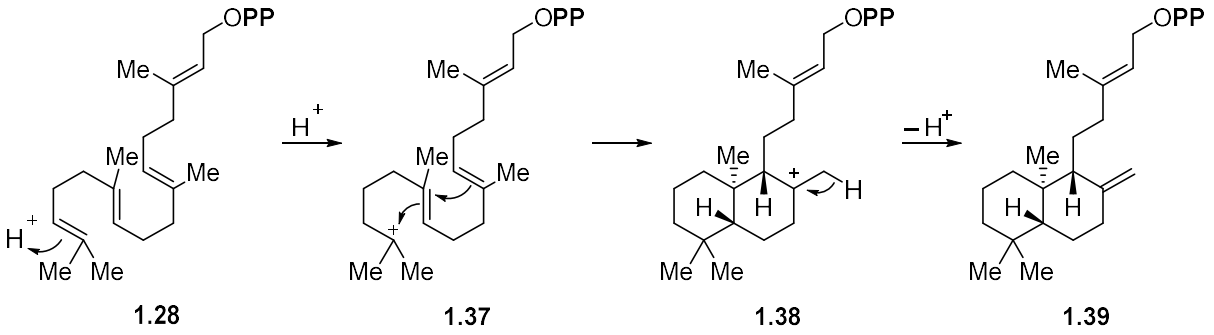
Scheme 1.3. Tail-to-tail coupling oft two allylic pyrophosphates.

1.1.2.2. Cyclization Mechanisms

Cyclic terpenes and terpenoids are formed *via* cation–π cyclizations from the acyclic precursors discussed in the previous section.[2] The cation can be generated by ionization of the allylic pyrophosphate analogous to the synthesis of the acyclic precursors, or *via* protonation or epoxidation and epoxide opening of one of the double bonds. Upon cation–π cyclization, the newly formed cation can undergo a variety of different transformations: further cation–π cyclizations, deprotonation, and alkyl or proton migrations. Scheme 1.4 shows the conversion of geranylgeranyl pyrophosphate (**1.28**) to *ent*-copalyl pyrophosphate (**1.39**), which is catalyzed by the enzyme *ent*-copalyl diphosphate synthase.[8] The process is initiated by protonation of one of the double bonds, and, after two cation-π

[8] Köksal, M.; Hu, H.; Coates, R. M.; Peters, R. J.; Christianson, D. W. *Nature Chemical Biology* **2011**, *7*, 431–433.

cyclizations, terminated by deprotonation. Terpene synthase-mediated cation–π cyclizations are generally enantioselective processes – they convert the achiral acyclic precursors to chiral, enantiopure intermediates. The enzyme catalyzing the formation of the enantiomer of **1.39** is abietadiene synthase.[9]



Scheme 1.4. *ent*-Copalyl diphosphate synthase-mediated transformation of geranylgeranyl pyrophosphate (**1.28**) to *ent*-copalyl pyrophosphate (**1.39**).

1.1.2.3. Post-Cyclization Modifications

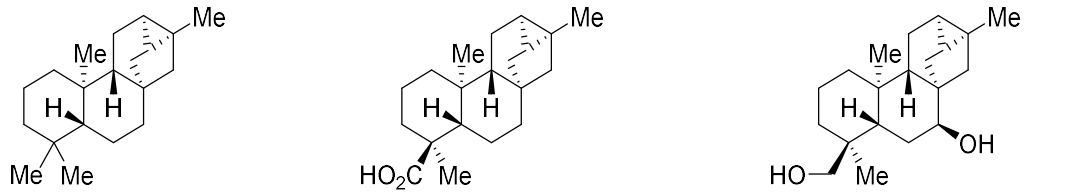
Some terpenoids, e.g. (–)-Taxol (**1.6**), are highly oxidized organic molecules (Figure 1.1). These cannot be obtained directly *via* cyclization of the acyclic precursors and their biosynthesis requires further modifications after cyclization. The most common of these post-cyclization modifications are oxidations. As an example, the monoterpene (–)-limonene (**1.1**, Figure 1.1) can be oxidized and isomerized to at least 16 different terpenoids.[2] This immense diversification of a single cyclization product is one of the main reasons for the vast number of terpenoids found in nature.

[9] Peters, R.; Ravn, M. M.; Coates, R. M.; Croteau, R. B. *J. Am. Chem. Soc.* **2001**, *123*, 8974–8978.

1.2. Trachylobane Diterpenoids

1.2.1. General

Trachylobane diterpenoids are characterized by a tricyclo[3.2.1.$0^{2,7}$]octane which is part of a pentacyclic carbon skeleton (Figure 1.2).[10] The first members of this family were isolated in 1963 from the resin of the Madagascan tree Hymenaea verrucosa.[11] To date, more than 100 members of this family have been isolated and characterized.[12a] All known trachylobanes are biosynthetically derived from *ent*-copalyl pyrophosphate (**1.39**) and have the absolute configuration shown for *ent*-trachylobane (**1.40**) in Figure 1.2. Interestingly, most trachylobane natural products differ only in the oxidation pattern on the decalin rings while the tricyclo[3.2.1.$0^{2,7}$]octane remains unaffected in post-cyclization modications.[12b]



ent-Trachylobane (**1.40**) *ent*-Trachyloban-18-oic acid (**1.41**) *ent*-Trachyloban-7β,18-diol (**1.42**)

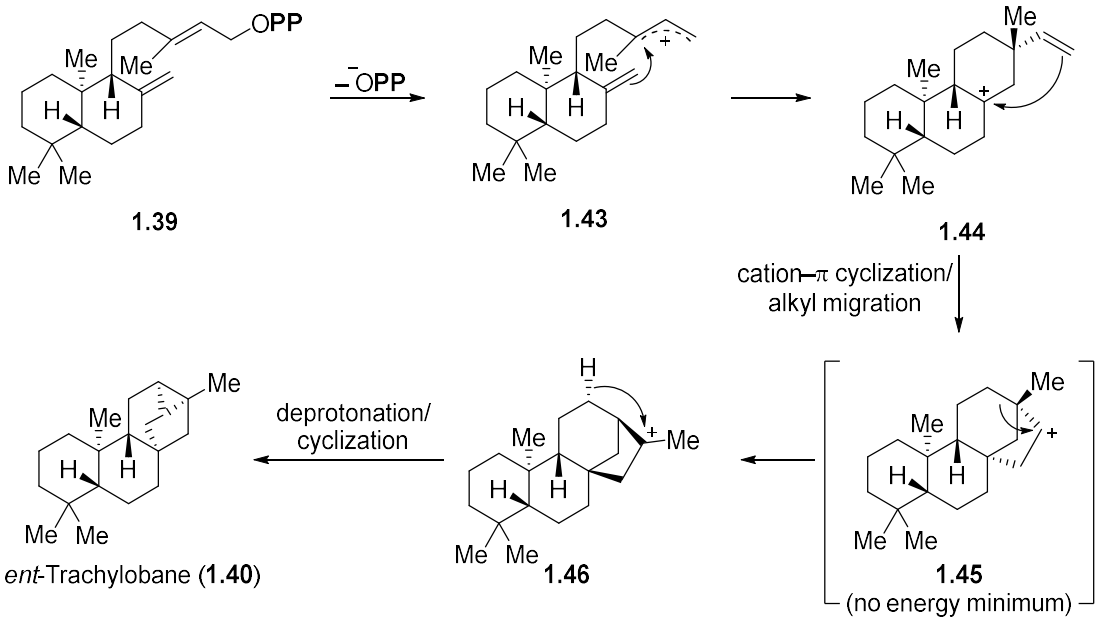
Figure 1.2. Structure of *ent*-trachylobane (**1.40**) and selected related terpenoids **1.41** and **1.42**.

1.2.2. Biosynthesis of *ent*-Trachylobane (1.40)

The biosynthetic transformation of *ent*-copalyl pyrophosphate (**1.39**) commences with the cleavage of the *C–O* bond to form allylic cation **1.43**, which is intramolecularly trapped by the 1,1-disubstituted olefin to form tertiary cation **1.44**. The next cation–π cyclization would form secondary cation **1.45**, but computational studies by HONG and TANTILLO suggest that the cyclization is

[10] Fraga, B. M. *Phytochem. Anal.* **1994**, *5*, 49-56.
[11] Hugel, G.; Lods, L.; Mellor, J. M.; Theobald, D. W.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1963**, 1974–1976.
[12] (a) Determined by searching for the trachylobane skeleton in Reaxys and limiting the results to "Isolated from Natural Sources". (b) In this search, the tricyclo[3.2.1.$0^{2,7}$]octane remained unchanged in 94 out of 123 trachylobanes.

accompanied by an alkyl migration to form tertiary cation **1.46** in a concerted asynchronous fashion.[13] *ent*-Trachylobane (**1.40**) is subsequently formed *via* concomitant deprotonation and ring closure.



Scheme 1.5. Proposed biosynthesis for the formation of *ent*-trachylobane (**1.40**) from *ent*-copalyl pyrophosphate (**1.39**).

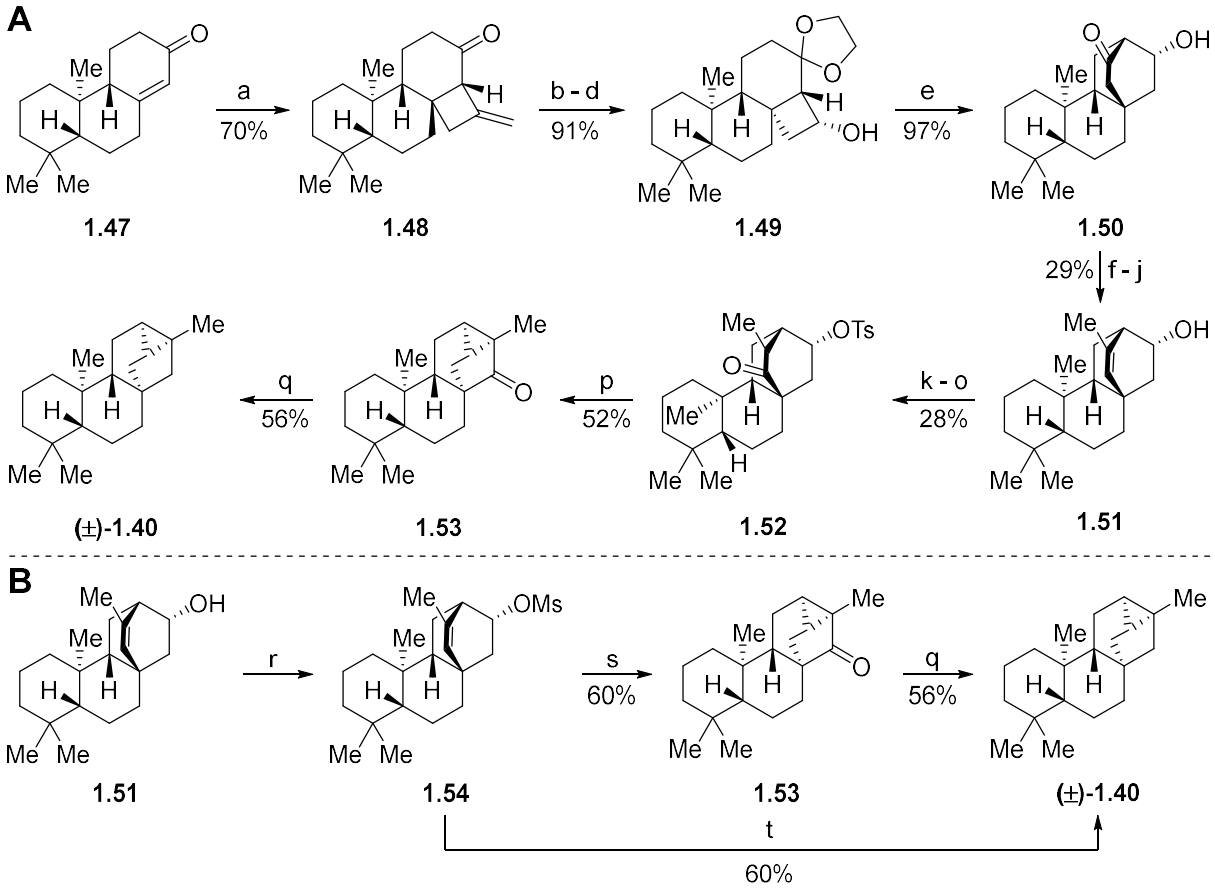
1.2.3. Previous Syntheses of the Trachylobane Skeleton

1.2.3.1. Kelly's Synthesis of (±)-Trachylobane ((±)-1.40)

The first synthesis of the trachylobane skeleton was reported by KELLY and co-workers in the 1970s.[14] During their studies on the synthesis of (±)-trachylobane (**(±)-1.40**), they disclosed three different methods for the synthesis of the tricyclo[3.2.1.$0^{2,7}$]octane scaffold. In their first approach, they converted known enone **1.47** into γ-tosyloxy ketone **1.52** in 15 steps (Scheme 1.6A). Key reactions are the photochemical [2+2]-cycloaddition of **1.47** with allene to give methylenecyclobutane **1.48** and the acetal cleavage of **1.49** with concomitant skeletal rearrangement *via* a retro-aldol/aldol cascade to form

[13] Hong, Y. J.; Tantillo, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 5375–5386.
[14] (a) Kelly, R. B.; Eber, J.; Hung, H. K. *Can. J. Chem.* **1973**, *51*, 2534–2541. (b) Kelly, R. B.; Eber, J.; Hung, H. K. *J. Chem. Soc. Chem. Commun.* **1973**, 689–690. (c) Kelly, R. B.; Beckett, B. A.; Eber, J.; Hung, H. K.; Zamecnik, J. *Can. J. Chem.* **1975**, *53*, 143–147.

1.50. Heating **1.52** in DMSO in the presence of methylsulfinyl carbanion led to enolate formation and nucleophilic displacement of the tosylate to afford cyclopropyl ketone **1.53** in 52% yield. Finally, **1.53** was reduced to (±)-trachylobane (**(±)-1.40**) *via* WOLFF–KISHNER reduction. In their second and third report, the authors presented more efficient transformations of **1.51** into the natural product in two and three steps, respectively, compared to seven steps in their first report (Scheme 1.6B). In both cases, the alcohol in **1.51** is transformed into the corresponding mesylate **1.54**. Upon heating, the mesylate is nucleophilically displaced by the olefin to form the cyclopropane and the resulting

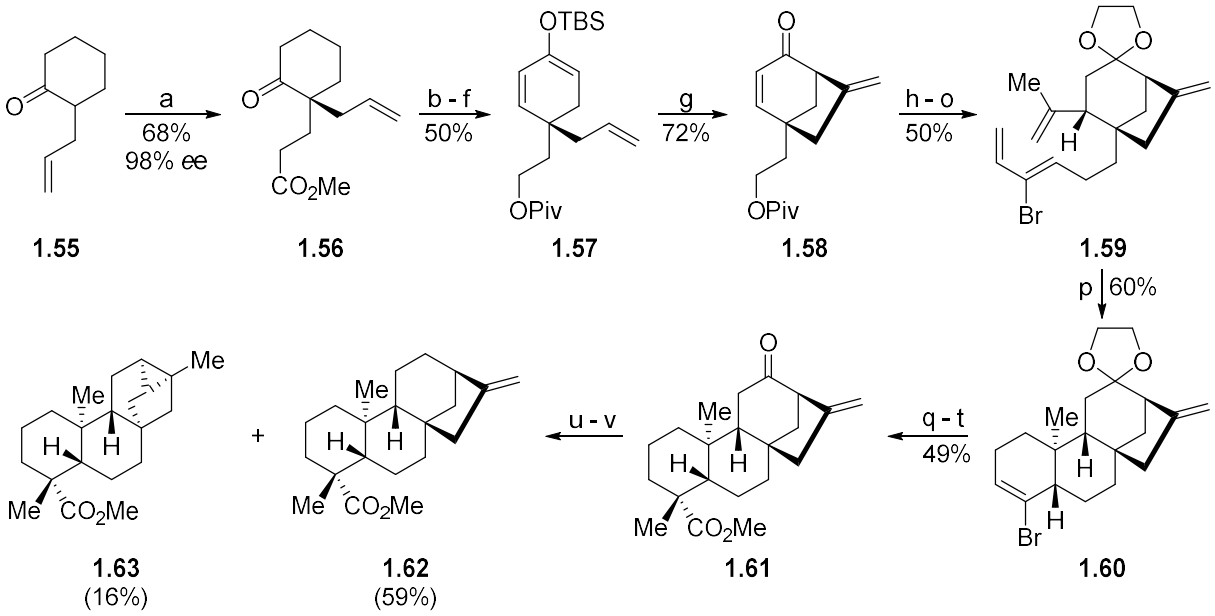


Scheme 1.6. Total synthesis of (±)-trachylobane (**(±)-1.40**) by KELLY. A) First report; B) Second and third report. Reagents and conditions: a) allene, hν, hexane, –70 °C, 70%; b) $(CH_2OH)_2$, *p*-TsOH·H_2O (7 mol%), PhH, reflux, 98%; c) OsO_4 (8 mol%), $NaIO_4$, pyr, dioxane–H_2O (12:1), 95%; d) $LiAlH_4$, Et_2O, r.t. to reflux, 98%; e) 1 M aq HCl–THF (4:5), 97%; f) Ac_2O, pyr, 92%; g) MeLi, THF–Et_2O, 0 °C to r.t., 85%; h) Jones' reagent, acetone, 86%; i) *p*-TsOH·H_2O, PhH, reflux, 78%; j) $LiAlH_4$, Et_2O, 55% + 42% of epimeric alcohol; k) BnCl, NaH, PhH, reflux, 80%; l) BH_3, THF, 0 °C, then aq NaOH, aq H_2O_2, 68%; m) CrO_3, pyr, 67%; n) H_2 (1 atm), Pd/C (50 wt%), MeOH, 76%; o) *p*-TsCl, pyr; p) $CH_3S(O)CH_2Na$, DMSO, 60 °C, 52% over two steps; q) Na, N_2H_4, diglycol, 180 °C, 56%; r) MsCl, pyr, –14 to 10 °C; s) DMSO, 60 °C, 60% over two steps; t) $LiAlH_4$, Et_2O, reflux, 60% over two steps.

cation is trapped by either DMSO to give ketone **1.53** or by $LiAlH_4$ to give the final product **(±)-1.40** directly. The ketone in **1.53** was transformed into the natural product as described above.

1.2.3.2. Ihara's Synthesis of (–)-Methyl Kaur-16-en-19-oate (1.62) and (–)-Methyl Trachyloban-19-oate (1.63)

IHARA and co-workers reported the total synthesis of (–)-methyl kaur-16-en-19-oate (**1.62**).[15] In the final step, they also obtained small quantities of (–)-methyl



Scheme 1.7. Total synthesis of (–)-methyl kaur-16-en-19-oate (**1.62**) and (–)-methyl trachyloban-19-oate (**1.63**) by IHARA. Reagents and conditions: (a) (*S*)-phenylethanamine, 5 Å MS, PhMe, reflux, then methyl acrylate, r.t., then H_2O–MeOH–AcOH (10:5:2), 68%, 98% *ee*; (b) $LiAlH_4$, THF, 0 °C; (c) PivCl, pyr, CH_2Cl_2, 0 °C to r.t., then MsCl, Et_3N, 0 °C; (d) DBU, 110 °C, 78% over 3 steps; (e) CrO_3 (20 mol%), aq TBHP, CH_2Cl_2, 0 to 10 °C, 64%; (f) LDA, TBSCl, HMPA, THF, –78 to 0 °C; (g) $Pd(OAc)_2$ (3 mol%), O_2 (1 atm), DMSO, r.t., 72% over two steps; (h) isopropenylmagnesium bromide, CuBr·SMe_2 (13 mol%), HMPA, TMSCl, THF, – 78 °C, 88%; (i) aq *n*-Bu_4NOH, THF, 79%; (j) $(CH_2OH)_2$, PPTS (1.3 mol%), PhH, reflux, 86%; (k) SO_3·pyr, DIPEA, CH_2Cl_2–DMSO (5:1), r.t.; (l) $Ph_3P{=}C(Br)CO_2Et$, PhMe, 80 °C, 76% over two steps; (m) DIBAL-H, PhMe, 0 °C, 76%; (n) MnO_2, PhMe, r.t.; (o) $MePPh_3Br$, *n*-BuLi, THF, r.t., 76% over two steps; (p) PhMe, 200 °C, 60%; (q) *t*-BuLi, THF, –78 °C, then $ClCO_2Me$, 82%; (r) Mg, MeOH, sonication, 63%; (s) LDA, MeI, HMPA, THF, –78 to 0 °C; (t) aq $HClO_4$, THF, r.t., 94% over two steps; (u) $N_2H_4·H_2O$, diglycol, 135 °C, then KOH, 200 °C; (v) CH_2N_2, Et_2O, r.t., 59% **1.62**, 16% **1.63**.

[15] (a) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916−4925. (b) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565−4570.

trachyloban-19-oate (**1.63**). The synthesis commenced with an enantioselective MICHAEL addition of 2-allylcyclohexanone (**1.55**) to methyl acrylate mediated by (*S*)-phenylethanamine (Scheme 1.7). Additional salient features of the approach are the palladium-catalyzed oxidative cycloalkenylation of silyl enol ether **1.57** to form bicycle **1.58** and an intramolecular DIELS–ALDER cycloaddition reaction of **1.59** to complete the ring system of (–)-methyl kaur-16-en-19-oate (**1.62**). Subjecting ketone **1.61** to WOLFF–KISHNER conditions followed by reesterification with diazomethane afforded deoxygenation product **1.62** in 59% along with 16% of (–)-methyl trachylobane-19-oate (**1.63**). The latter is formed presumably *via* a homologous diazene rearrangement.

1.3. (–)-Mitrephorone A

(–)-Mitrephorone A (**1.64**) was isolated from the bark of the Bornean shrub *Mitrephora Glabra* Scheff in 2005 along with closely related (–)-mitrephorones B and C (**1.65** and **1.66**) (Figure 1.3).[16] Its structure was elucidated based on extensive NMR studies, high resolution mass spectrometry and infrared spectroscopy. The oxidation of C_9, the presence of an oxetane and a 1,2-diketone are unique structural features amongst the trachylobane family of natural products.

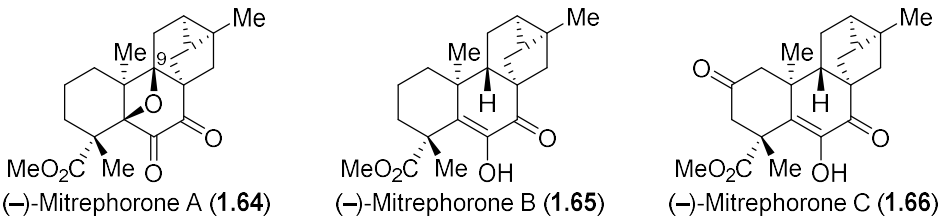
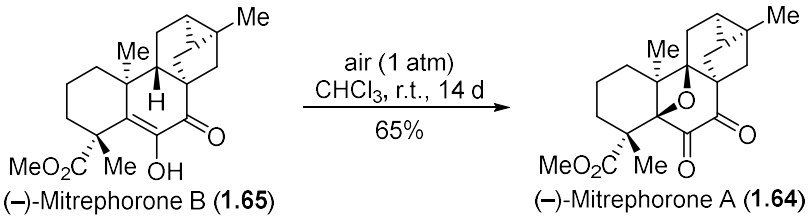


Figure 1.3. Structures of (–)-mitrephorones A–C (**1.64**–**1.66**).

Recently, KUTATELADZE reported the parametric/DFT hybrid computational method *DU8+* for the computation of ^{13}C NMR shifts, which extends known approaches for the structure elucidation of organic molecules.[17] For most of the evaluated structures, the calculated ^{13}C chemical shifts have a root-mean-square deviation (rmsd) of 1.0 to 1.6 ppm compared to the experimentally determined values. The rmsd value observed for (–)-mitrephorone A (**1.64**, rmsd(δ_C) = 1.13 ppm) strongly supports the structural assignment of **1.64** made by the isolation team.

[16] Li, C.; Lee, D.; Graf, T. N.; Phifer, S. S.; Nakanishi, Y.; Burgess, J. P.; Riswan, S.; Setyowati, F. M.; Saribi, A. M.; Soejarto, D. D.; Farnsworth, N. R.; Falkinham III, J. O.; Kroll, D. J.; Kinghorn, A. D.; Wani, M. C.; Oberlies, N. H. *Org. Lett.* **2005**, *7*, 5709–5712.
[17] Kutateladze, A. G.; Holt, T.; Reddy, D. S. *J. Org. Chem.* **2019**, *84*, 7575–7586.

After completion of this study, a semisynthetic approach to (–)-mitrephorone A (**1.64**) by RENATA revealed the autooxidation of (–)-mitrephorone B (**1.65**) to **1.64** (Scheme 1.8).[18] The oxidation of **1.65** can be considered as a possible biosynthetic pathway of **1.64**.



Scheme 1.8. Autooxidation of (–)-mitrephorone B (**1.65**) to (–)-mitrephorone A (**1.64**).

Similar to various other trachylobane natural products,[10,19] (–)-mitrephorones A–C (**1.64**–**1.66**) all showed comparable cytostatic activity against a number of bacterial and fungal pathogens (31-125 μg/mL) in an antimicrobial assay.[16] In a cell toxicity assay, only (–)-mitrephorone A (**1.64**) exhibited significant cytotoxicity against a series of cancer cell lines (MCF-7, H460, SF-268). This increased cell toxicity was attributed to the unique oxetane in **1.64**, which is the key structural difference between **1.64** and (–)-mitrephorone B (**1.65**).

[18] Zhang, X.; King-Smith, E.; Dong, L.-B.; Yang, L. C.; Rudolf, J. D.; Shen, B.; Renata, H. *Science* **2020**, *369*, 799–806.
[19] Zgoda-Pols, J. R.; Freyer, A. J.; Killmer, L. B.; Porter, J. R. *Fitoterapia* **2002**, *73*, 434–438.

1.4. Project Outline

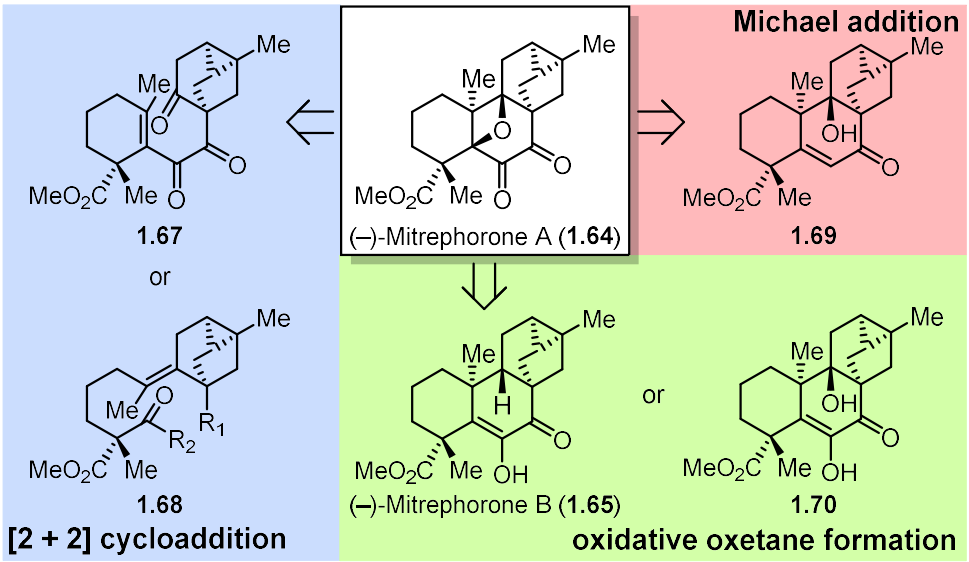
The unique hexacyclic skeleton of the *ent*-trachylobane diterpenoid (–)-mitrephorone A (**1.64**), which includes a fully substituted oxetane at the center of the molecule, along with a rare 1,2-diketone and five contiguous stereocenters, render this natural product an interesting target for total synthesis and inspired us to embark on synthetic endeavors towards this diterpenoid. Key to success will be the synthesis of the highly congested tricyclo[3.2.1.$0^{2,7}$]octane scaffold and the stereoselective introduction of the oxetane. As the tricyclo[3.2.1.$0^{2,7}$]octane remains unchanged in most of the trachylobane diterpenoids, commencing the synthesis with the preparation of this moiety might allow for the divergent synthesis of various members of this class of natural products.

2. Results and Discussion

2.1. Approaches to Oxetane Synthesis

The synthesis of the fully substituted oxetane was central to the retrosynthetic analysis of (–)-mitrephorone A (**1.64**). Strategically, there were various options for its disconnection. These included [2 + 2] cycloadditions, intramolecular oxa-Michael additions, and oxidative oxetane formations (Scheme 1.9). Other methods for oxetane formation, such as the Williamson ether synthesis, were not considered, because alkylative strategies at tertiary carbons had proven to be challenging.

Previous studies on the synthesis of (–)-mitrephorone A (**1.64**) by Simon Krautwald in the group of E. M. Carreira *via* the [2 + 2] cycloaddition of **1.67** and related structures had proven unfruitful. In our first approach, we focused on a regiochemically alternative disconnection of the oxetane *via* [2 + 2] cycloaddition of **1.68**. Other approaches to **1.64** *via* intramolecular oxa-Michael addition of δ-hydroxyenone **1.69** or oxidation of δ-hydroxydiosphenol **1.70** will be discussed in the course of this chapter.

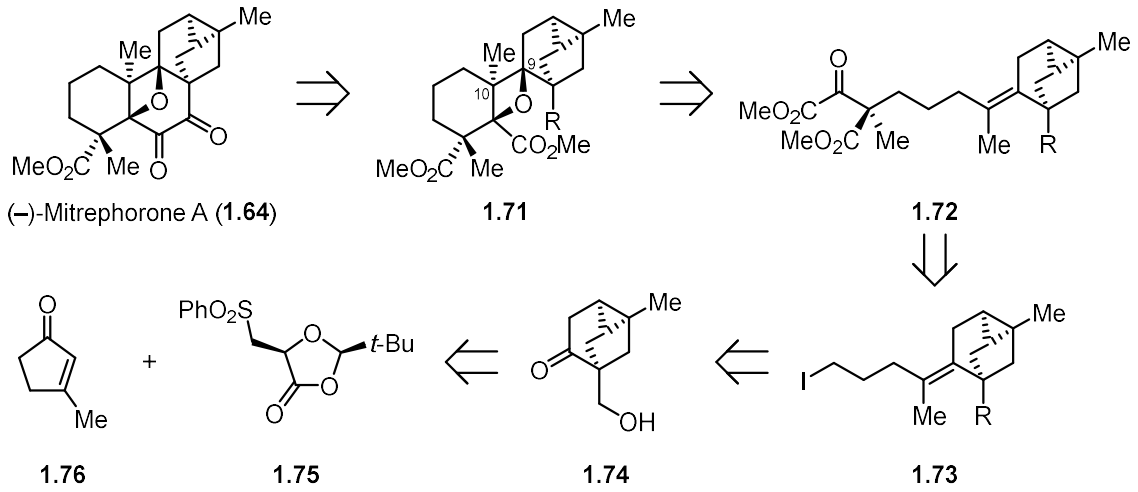


Scheme 1.9. Retrosynthetic analysis of the fully substituted oxetane in (–)-mitrephorone A (**1.64**).

2.2. The [2 + 2] Cycloaddition Approach

2.2.1. Retrosynthetic Analysis

Our retrosynthetic analysis of (–)-mitrephorone A (**1.64**) commenced with the disconnection of the 1,2-diketone to ester **1.71**, which would be formed by an intramolecular [2 + 2] cycloaddition reaction of α-ketoester **1.72** (Scheme 1.10). Aliphatic keto groups show high molar attenuation coefficients ε only for high energy light (≤ 220 nm).[20] However, α-ketoesters absorb light at higher wavelengths. For example, diethyl 2-oxosuccinate has an absorption maximum at 248 nm (ε = 3540),[21] which renders α-ketoesters suitable for photochemical [2 + 2] cycloaddition reactions.[22] The relative configuration of the stereogenic centers at C_9 and C_{10} will be controlled by the olefin geometry. Therefore, the stereoselective preparation of the tetrasubstituted olefin in **1.72** was thought to play a key role in the synthesis of **1.64**. We surmised that the absolute configuration of these two stereogenic centers would be controlled by the



Scheme 1.10. Retrosynthetic analysis of (–)-mitrephorone A (**1.64**) *via* [2 + 2] cycloaddition of α-ketoester **1.72**.

[20] Pretsch, E.; Bühlmann, P.; Badertscher, M. *Structure Determination of Organic Compounds*, 4th Edition, Springer, 2009, 402.
[21] Cantlon, I. J.; Cocker, W.; McMurry, T. B. H. *Tetrahedron* **1961**, *15*, 46–52.
[22] For examples of photochemical [2 + 2] cycloaddition reactions of α-ketoesters, see: (a) Hu, S.; Neckers, D. C. *J. Org. Chem.* **1997**, *62*, 564–567; (b) Hu, S.; Neckers, D. C. *J. Org. Chem.* **1997**, *62*, 6820–6826; (c) Koch, H.; Runsink, J.; Scharf, H.-D. *Tetrahedron Lett.* **1983**, *24*, 3217–3220.

α-stereogenic center of the ketone in **1.72**. α-Ketoester **1.72** was traced back to iodide **1.73** *via* an alkylation reaction. We envisioned preparing the tetrasubstituted olefin in **1.73** from ketone **1.74**, which has been previously synthesized from known sulfone **1.75** and commercially available 3-methyl-2-cyclopentenone (**1.76**) by SIMON KRAUTWALD albeit in low overall yield (8.2% on the enantioenriched route based on **1.75** and 4.3% on the racemic route based on **1.76**, respectively).[23] Our efforts towards the synthesis of **1.64** commenced with the optimization of the synthesis of **1.74**, followed by studies on the stereoselective olefination of the ketone in **1.74**.

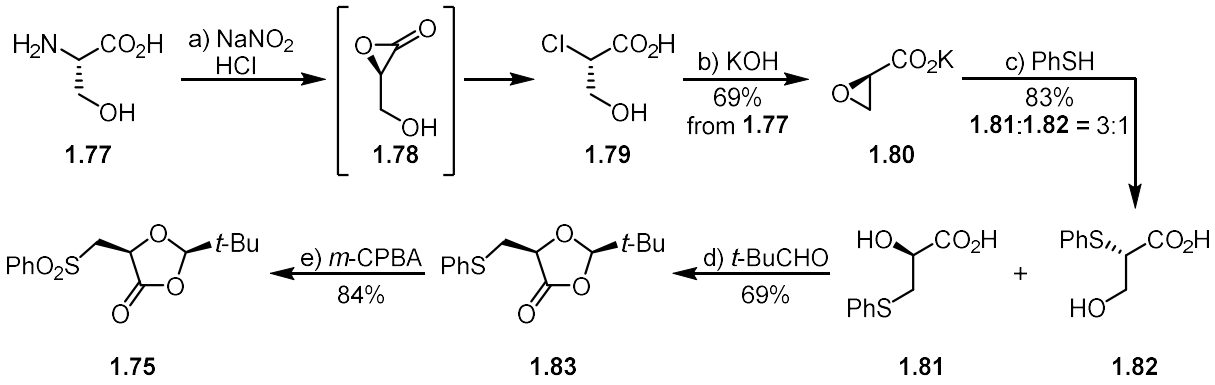
2.2.2. Optimization of the Synthesis of the [3.2.1.0^{2,7}]octane Core

We began our investigations on the synthesis of (–)-mitrephorone A (**1.64**) with the optimization of the synthesis of the tricyclo[3.2.1.0^{2,7}]octanone **1.74**, which had been previously developed by SIMON KRAUTWALD. The route commenced with the preparation of enantiopure sulfone **1.75**, which is the synthetic precursor of a known dienophile for diastereoselective DIELS–ALDER cycloaddition reactions.[24]

Starting from L-serine (**1.77**), sulfone **1.75** was prepared following a literature procedure (Scheme 1.11):[24a] Diazotization of **1.77** with sodium nitrite in 7.2 M aqueous HCl led to the formation of chlorohydrin **1.79** with retention of configuration. The reaction proceeds *via* α-lactone **1.78** and lactone opening with HCl. Treatment of **1.79** with potassium hydroxide in ethanol afforded epoxide **1.80** in 69% over two steps. In a first attempt, **1.80** was obtained in low yield (38%). Later, we found that most of the material was lost during the work-up of the second step. Upon completion of the etherification, the mixture was filtered to remove potassium chloride formed in the reaction. The filter cake had to be thoroughly washed with methanol to obtain good yield of **1.80** due to low

[23] For details, see: laboratory journal of Simon Krautwald.
[24] (a) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380–3387; (b) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327–330.

solubility of the product in methanol. Epoxide opening with thiophenol gave thioether **1.81** in 83% as a 3:1 mixture with its regioisomer **1.82**. Condensation of this mixture with pivaldehyde furnished dioxolone **1.83** as a single isomer in 69% yield. Traces of the *trans*-isomer of **1.83** were observed in the ^{1}H NMR spectrum of the unpurified product mixture and the diastereomers were separated by flash column chromatography. Regioisomer **1.82** did not form the corresponding dioxanone under the reaction conditions and **1.82** was removed from the product mixture by extraction. Oxidation of the thioether in **1.83** with *m*-CPBA afforded sulfone **1.75** in 84% yield. Following this procedure, 45 g of **1.75** were prepared in a single batch.

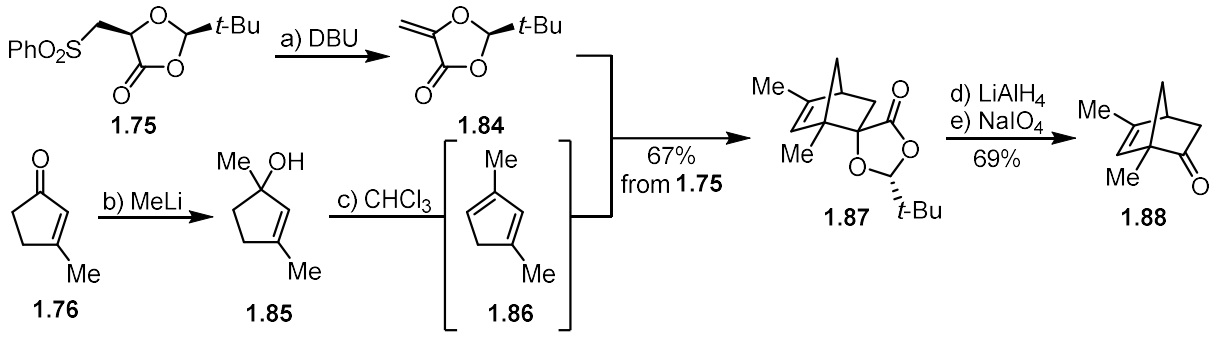


Scheme 1.11. Synthesis of sulfone **1.75** from *L*-serine (**1.77**). Reagents and conditions: (a) $NaNO_2$, aq HCl, 0 °C; (b) KOH, EtOH, 0 °C to r.t., 69% over two steps; (c) thiophenol, MeOH, 0 °C to r.t., 83%, **1.81**:**1.82** = 3:1; (d) pivaldehyde, $BF_3 \cdot OEt_2$, Et_2O, 0 °C, 69%, single isomer; (e) *m*-CPBA, CH_2Cl_2, 0 °C to r.t., 84%.

Treatment of sulfone **1.75** with DBU led to clean formation of enantiopure olefin **1.84** (Scheme 1.12).[25] For the preparation of diene **1.86**, addition of methyllithium to 3-methyl-2-cyclopentenone (**1.76**) gave tertiary alcohol **1.85** as a 10:1 mixture of product and starting material. In the initial route developed by SIMON KRAUTWALD, the hydroxy group in **1.85** had been eliminated using *p*-TsOH and hydroquinone, and 1,3-diene **1.86** had been collected by distillation.[26] We found that the hydroxy group also eliminated rapidly in chloroform at room

[25] For the first synthesis of **1.84**, see: Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104–1114.
[26] McLean, S.; Haynes, P. *Tetrahedron* **1965**, *21*, 2313–2327.

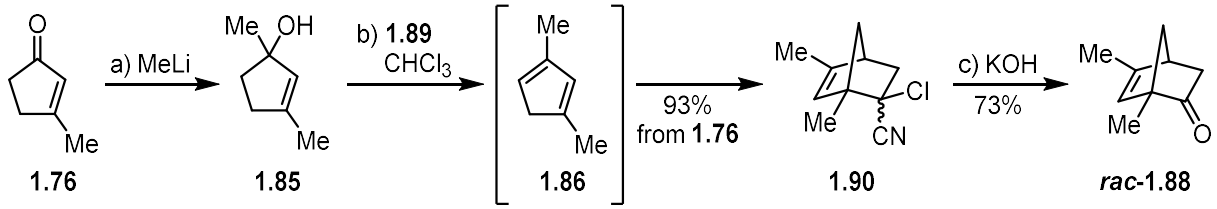
temperature. This observation was used to develop a one-pot procedure for elimination and cycloaddition: Stirring a mixture of unpurified dienophile **1.84** and alcohol **1.85** in chloroform in the presence of magnesium sulfate at room temperature first led to elimination of the hydroxy group and subsequently to exoselective DIELS–ALDER cycloaddition reaction of **1.84** and **1.86** to furnish bicycle **1.87** in 67% from sulfone **1.75** as an inseparable mixture of regio- and diastereoisomers (>90% desired isomer as determined by analysis of the ^{1}H NMR spectrum).[24a] Analysis of ^{1}H NMR spectra of aliquots of the reaction mixture indicated that the elimination was complete after a few hours and that full conversion of dienophile **1.84** was observed after several days. Reduction of dioxolone **1.87** to the corresponding diol with lithium aluminum hydride, followed by sodium periodate-mediated diol cleavage afforded norbornenone **1.88** in 69% yield over two steps as an inseparable 25:1 mixture with its regioisomeric ketone.



Scheme 1.12. Synthesis of norbornene **1.88** *via* Diels–Alder cycloaddition reaction of **1.84** and **1.86** and elaboration of the cycloadduct into norbornenone **1.88**. Reagents and conditions: (a) DBU, CH_2Cl_2, 0 °C; (b) MeLi, THF, –78 °C to r.t.; (c) $MgSO_4$, $CHCl_3$, r.t., 91 h, 67% from **1.75**, mixture of regio- and diastereoisomers, >90% shown isomer; (d) $LiAlH_4$, Et_2O–THF (8:1), 0 °C, 82%; (e) $NaIO_4$, NaH_2PO_4, H_2O, 0 °C to r.t., 84%, 25:1 mixture with regioisomeric ketone.

Racemic norbornenone ***rac*-1.88** was prepared following a similar route: Diels–Alder cycloaddition reaction of *in situ* generated diene **1.86** with achiral α-chloroacrylonitrile (**1.89**) in chloroform at 50 °C afforded cycloadduct **1.90** as an inconsequential 9:2 mixture of diastereomers in 93% from **1.76**

(Scheme 1.13).[27] Notably, the elimination of the tertiary hydroxy group in **1.85** even took place when the chloroform was filtered through basic alumina prior to the reaction. In contrast to the enantioenriched route, this DIELS–ALDER cycloaddition reaction furnished cycloadduct **1.90** as a single regioisomer, which can be attributed to the higher polarization of the olefin in **1.89** compared to **1.84**.[28] Treatment of chloronitrile **1.90** with potassium hydroxide in DMSO–H_2O gave norbornenone ***rac*-1.88** in 73% yield.[27]

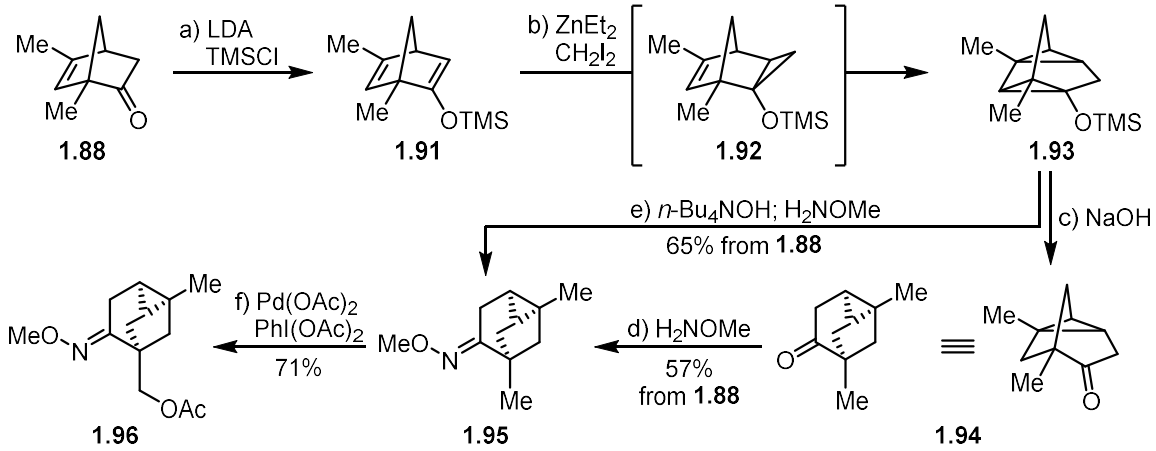


Scheme 1.13. Synthesis of ***rac*-1.88**. Reagents and conditions: (a) MeLi, THF, –78 °C to r.t.; (b) α-chloroacrylonitrile (**1.89**), $CHCl_3$, 50 °C, 93% from **1.76**, d.r. = 9:2; (c) KOH, DMSO–H_2O (6:1), r.t., 73%.

Inspired by the work of RAGAUSKAS and STOTHERS,[29] norbornenone **1.88** was converted into the tricyclo[3.2.1.$0^{2,7}$]octane scaffold *via* a homoquadricyclane rearrangement. To this end, ketone **1.88** was transformed into the corresponding trimethylsilyl enol ether **1.91** with LDA and TMSCl (Scheme 1.14). Subjecting crude **1.91** to FURUKAWA–SIMMONS–SMITH conditions ($ZnEt_2$, CH_2I_2)[30] led to cyclopropanation of the more electron-rich double bond and concomitant homoquadricyclane rearrangement forming dicyclopropane **1.93**. Full conversion of the reaction was ensured using excess diethyl zinc and methylene iodide (two equivalents each). No intermediate monocyclopropane **1.92** was observed by analysis of the ^{1}H NMR spectrum of the unpurified product mixture. Interestingly, the reaction was completely suppressed if one equivalent of THF from the previous reaction remained in the starting material. Therefore, silyl enol ether **1.91**

[27] For the use of α-chloroacrylonitrile **1.89** as a ketene equivalent in Diels–Alder cycloadditions, see: Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211–2214.
[28] For a review on regio- and stereoselectivity in DIELS–ALDER cycloadditions, see: Martin, J. G.; Hill, R. K. *Chem Rev.* **1961**, *61*, 537–562.
[29] Ragauskas, A.; Stothers, J. B. *Can. J. Chem.* **1983**, *61*, 2254–2256.
[30] Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *28*, 3353–3354.

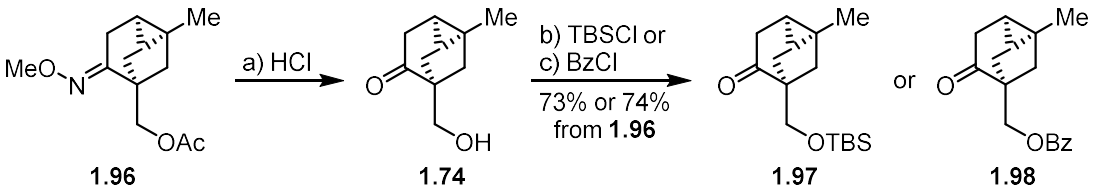
had to be thoroughly dried, which, at the same time, led to hydrolysis of a small amount of **1.91** back to norbornenone **1.88**. Cleavage of the silyl ether in **1.93** with methanolic sodium hydroxide afforded tricyclic ketone **1.94**. Functionalization of the α-methyl group was envisioned *via C–H* acetoxylation directed by *O*-methyloximes developed by SANFORD and co-workers.[31] Thus, ketone **1.94** was converted into the corresponding oxime **1.95** using *O*-methylhydroxylamine hydrochloride in pyridine. Later, a one-pot transformation of cyclopropyl silyl ether **1.93** into oxime **1.95** was developed: Treatment of **1.93** with methanolic tetra-*n*-butylammonium hydroxide, followed by addition of *O*-methyl-hydroxylamine hydrochloride afforded oxime **1.95** in 65% yield from norbornenone **1.88**.[32] The *C–H* acetoxylation of oxime **1.95** proceeded smoothly using slightly different conditions compared to those reported by SANFORD (15 mol% $Pd(OAc)_2$, two equivalents $PhI(OAc)_2$, AcOH–Ac_2O (1:1), 90 °C) to give acetate **1.96** in 71% yield.



Scheme 1.14. Synthesis of the tricyclo[3.2.1.$0^{2,7}$]octane **1.96** *via* homoquadricyclane rearrangement and C–H acetoxylation. Reagents and conditions: (a) LDA, TMSCl, THF, –78 °C to r.t.; (b) $ZnEt_2$, CH_2I_2, Et_2O, 0 °C to r.t., then pyr; (c) NaOH, MeOH, r.t.; d) *O*-methylhydroxylamine hydrochloride, pyr, r.t., 57% from **1.88**, (e) *n*-Bu_4NOH, MeOH, r.t., then *O*-methylhydroxylamine hydrochloride, r.t., 65% from **1.88**; (f) $Pd(OAc)_2$ (15 mol%), $PhI(OAc)_2$, AcOH–Ac_2O (1:1), 90 °C, 71%.

[31] Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543.
[32] This reaction was carried out for the first time by Matthieu Richter.

Initially, the ester and oxime in **1.96** were hydrolyzed concomitantly using paraformaldehyde and Amberlyst 15® in acetone–water at 80 °C.[33] This procedure proved inefficient, mostly due to depolymerization of paraformaldehyde, evaporation of the resulting formaldehyde and repolymerization in the reflux condenser. In an optimized procedure, **1.96** was treated with HCl in acetone–water at 60 °C to afford the corresponding hydroxyketone **1.74** (Scheme 1.15).[34] TBS-protection (TBSCl, imidazole, catalytic DMAP) gave silyl ether **1.97** in 73% over two steps. To determine the optical purity of **1.74**, benzoate **1.98** was prepared in 74% yield from **1.96** and the enantiomers were separable by chiral SFC (95% ee). Typically, silyl ether **1.97** and benzoate **1.98** were prepared without purification of the intermediate hydroxyketone **1.74**, but the latter could also be isolated in 80% yield from acetate **1.96**. The absolute configuration of the tricyclo[3.2.1.$0^{2,7}$]octane was assigned according to previous studies on the diastereoselective DIELS–ALDER cycloaddition reaction using chiral dienophile **1.84** (Scheme 1.12).[24a] Based on the route developed by SIMON KRAUTWALD, key intermediate **1.74** was prepared in 17.1% yield on the enantioenriched route based on sulfone **1.75** and in 25.1% yield on the racemic route based on cyclopentenone **1.76**, respectively, after optimization of reaction procedures.



Scheme 1.15. Synthesis of silyl ether **1.97** and benzoate **1.98**. Reagents and conditions: (a) HCl, acetone–H_2O (2.9:1), 60 °C, 80%; (b) TBSCl, imidazole, DMAP (10 mol%), CH_2Cl_2, r.t., 73% over two steps; (c) BzCl, Et_3N, DMAP (20 mol%), CH_2Cl_2, r.t., 74% over two steps.

[33] Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250–3263.
[34] Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702–4715.

2.2.3. Synthesis of the Tetrasubstituted Olefin

With a high yielding and well-scalable synthesis of tricyclo[3.2.1.$0^{2,7}$]octanone **1.74** in hand, we next turned our attention to the stereoselective preparation of the central tetrasubstituted olefin. The conversion of cyclic ketones to exocyclic olefins has been studied extensively. Methods for this transformation include one-step olefination methods, such as WITTIG[35] and HORNER–WADSWORTH–EMMONS[36] olefinations or MCMURRY couplings,[37] but also multi-step approaches involving sigmatropic rearrangements, such as CLAISEN rearrangements.[38]

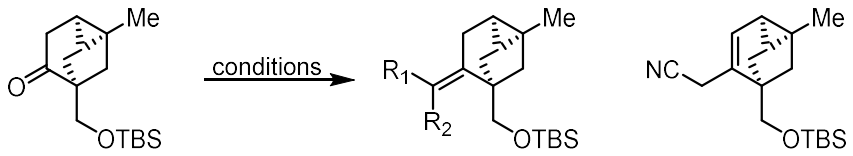
2.2.3.1. One-Step Ketone Olefinations

We began our investigations by testing different one-step olefination methods. This attempt could include the direct synthesis of a tetrasubstituted olefin or the synthesis of a 1,1-di- or trisubstituted olefin, which would subsequently be transformed into a tetrasubstituted alkene. WITTIG olefination of ketone **1.97** with isopropyltriphenylphosphonium iodide (**1.101**) or *n*-butyltriphenylphosphonium bromide (**1.102**) did not lead to any formation of tetra- or trisubstituted olefin **1.99a** or **1.99b**, respectively (Table 1.1, entries 1 and 2). The only successful WITTIG olefination was observed with methyltriphenylphosphonium bromide (**1.103**) to furnish 1,1-disubstituted olefin **1.99c** in 92% yield (entry 3). HORNER–WADSWORTH–EMMONS olefination using diethyl cyanomethyl-phosphonate (**1.104**) gave trisubstituted olefin **1.99d** as a mixture of *trans*- and *cis*-isomers (6:1) along with β,γ-unsaturated nitrile **1.100** in 53% combined yield (entry 4). Soluble lanthanum salt $LaCl_3 \cdot 2LiCl$ had been previously shown to activate ketones towards addition of organometal reagents and to suppress

[35] Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318–1330.
[36] Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
[37] McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709.
[38] For a review on CLAISEN rearrangements, see: Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.

enolization.[39,40] Addition of this LEWIS acid increased reaction rate and selectivity and afforded **1.99d** in 87% yield as a single isomer (entry 5).[41] Unfortunately, under the same conditions, the use of diethyl (1-cyanoethyl)phopsphonate (**1.105**) did not afford any tetrasubstituted olefin **1.88e** (entry 6). An attempt to form dibromoolefin **1.88f** in a RAMIREZ olefination (CBr_4, PPh_3) did not afford any desired product (entry 7).[42] Subjecting a mixture of ketone **1.97** and methyl

Table 1.1. Conditions for WITTIG, HORNER–WADSWORTH–EMMONS or RAMIREZ olefinations and MCMURRY coupling of ketone **1.97**.



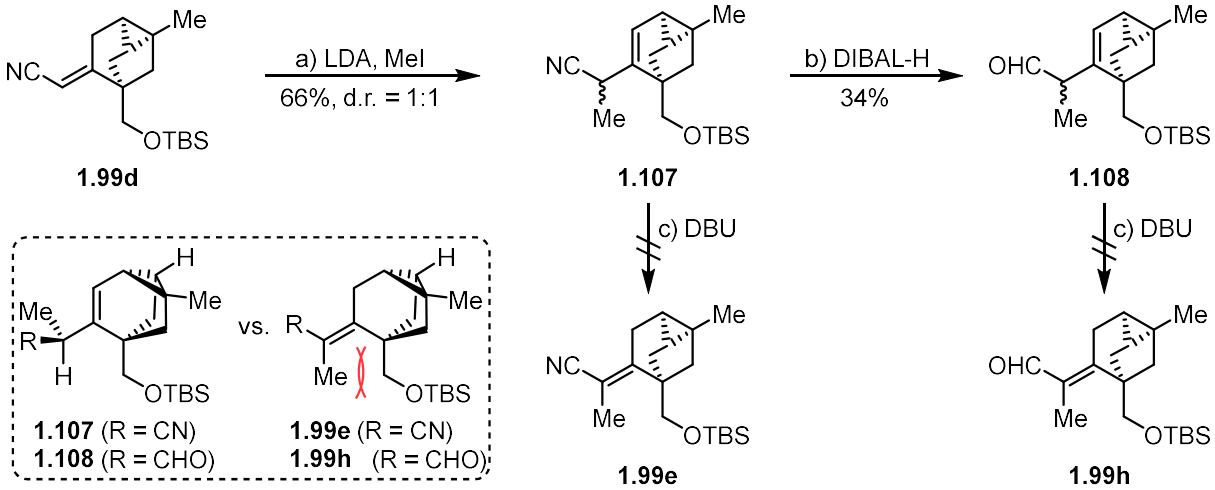
1.97 **1.99** **1.100**

Entry	Conditions	Product	Result
1	*i*-PrPPh$_3$I (**1.101**) *n*-BuLi, THF, 50 °C, or KO*t*-Bu, THF, r.t.	**1.99a** (R_1 = R_2 = Me)	0%
2	*n*-BuPPh$_3$Br (**1.102**) *n*-BuLi, THF, 50 °C, or KO*t*-Bu, THF, r.t.	**1.99b** (R_1 = *n*-Bu, R_2 = H)	0%
3	MePPh$_3$Br (**1.103**), KO*t*-Bu THF, r.t.	**1.99c** (R_1 = R_2 = H)	92%
4	(EtO)$_2$P(O)CH$_2$CN (**1.104**) KO*t*-Bu, THF, 65 °C	**1.99d** (R_1 = CN, R_2 = H)	53%, mixture of (***E*/*Z***)-**1.99d** and **1.100**
5	(EtO)$_2$P(O)CH$_2$CN (**1.104**), $LaCl_3$·2LiCl KO*t*-Bu, THF, 65 °C	**1.99d** (R_1 = CN, R_2 = H)	87%, single isomer
6	(EtO)$_2$P(O)CH(Me)CN (**1.105**), $LaCl_3$·2LiCl KO*t*-Bu, THF, 65 °C	**1.99e** (R_1 = CN, R_2 = Me)	0%
7	CBr_4, PPh_3 PhMe, 115 °C	**1.99f** (R_1 = R_2 = Br)	0%
8	methyl acetoacetate (**1.106**), Zn $TiCl_4$·2THF, THF, 65 °C	**1.99g** (R_1 = CH_2CO_2Me, R_2 = Me)	0%

[39] Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497–500.
[40] When the commercial solution of $LaCl_3$·2LiCl in THF was not available, a new procedure for its preparation was developed: Anhydrous $LaCl_3$ (1 eq.) and anhydrous LiCl (2 eq.) were mixed in a glove box. THF (0.5 M in $LaCl_3$) was added and the mixture was stirred at reflux until all solids dissolved (~24 h).
[41] The configuration of the olefin in **1.99d** was assigned *via* 2D NOESY NMR spectroscopy, which displayed a NOE interaction between the vinylic proton and C*H*$_2$OTBS.
[42] Sam, B.; Montgomery, T. P.; Krische, M. J. *Org. Lett.* **2013**, *15*, 3790–3793.

acetoacetate (**1.106**) to McMurry coupling conditions (Zn, $TiCl_4 \cdot 2THF$) did not give any olefin **1.99g** (entry 8).[43]

After no tetrasubstituted olefin was obtained from the one-step olefination methods, we envisioned alkylating trisubstituted olefin **1.99d**. To this end, **1.99d** was treated with LDA and methyl iodide, which led to formation of α-methyl-β,γ-unsaturated nitrile **1.107** in 66% yield and ~1:1 diastereomeric ratio (Scheme 1.16). In the hope that the double bond would migrate back into the exocyclic position, nitrile **1.107** was reduced with DIBAL-H but β,γ-unsaturated aldehyde **1.108** was obtained as the sole aldehydic product in 34% yield.[44] Treatment of β,γ-unsaturated nitrile **1.107** or aldehyde **1.108** with DBU did not induce double bond migration to α,β-unsaturated nitrile **1.99e** or aldehyde **1.99h**.[45]



Scheme 1.16. Synthesis of β,γ-unsaturated nitrile **1.07** and aldehyde **1.108** and attempted double bond migration. Reagents and conditions: (a) LDA, THF, –78 °C to r.t., 66%, d.r. = 1:1; (b) DIBAL-H, PhMe, –78 °C, 34%; (c) DBU, CH_2Cl_2, r.t.

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[43] Casimiro-Garcia, A.; Micklatcher, M.; Turpin, J. A.; Stup, T. L.; Watson, K.; Buckheit, R. W.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 4861–4874.

[44] Ochi, Y.; Yokoshima, S.; Fukuyama, T. *Synthesis* **2017**, *49*, 96–114.

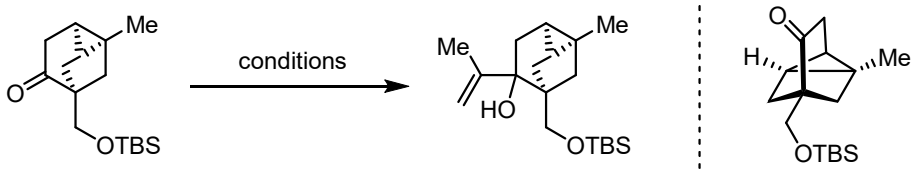
[45] Determined by analysis of the ^1H, ^{13}C and 2D HSQC NMR spectra of the unpurified product mixture and indicated by the absence of vinylic methyl groups (1.5 – 2.0 ppm in ^1H NMR) and β-carbons of trisubstituted acrylonitriles or acroleins (160 – 170 ppm in ^{13}C NMR) and comparison with NMR spectra predicted by MestReNova and with literature data for related compounds: For an α-methyl-β-disubstituted acrylonitrile, see: Stastna, E.; Krishnan, K.; Manion, B. D.; Taylor, A.; Rath, N. P.; Chen, Z.-W.; Evers, A. S.; Zorumski, C. F.; Mennerick, S.; Covey, D. F. *J. Med. Chem.* **2011**, *54*, 3926–3934. For an α-methyl-β-disubstituted acrolein, see: Sesenoglu, Ö.; Candela Lena, J. I.; Altinel, E.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Asymmetry* **2005**, *16*, 995–1015.

The preference of forming β,γ-unsaturated nitrile **1.107** or aldehyde **1.108** over their α,β-unsaturated analogues **1.99e** and **1.99h** can be rationalized using a 3D model of these four structures (Scheme 1.16, Box). **1.99e** and **1.99h** display an 1,3-allyic interaction between the vinylic methyl group and CH_2OTBS, which is not present in **1.107** and **1.108**.

2.2.3.2. Olefin Synthesis *via* CLAISEN Rearrangements

We next investigated CLAISEN rearrangements for the synthesis of the tetrasubstituted double bond, which required the transformation of ketone **1.97** into tertiary alcohol **1.109**. Treatment of **1.97** with isopropenylmagnesium bromide (**1.110**) did not afford any alcohol **1.109** (Table 1.2, entry 1). Also, addition of cerium(III) chloride as a LEWIS acidic additive did not lead to any product formation (entry 2).[46] Replacing the GRIGNARD reagent with

Table 1.2. Conditions for organometal addition to ketone **1.97**.



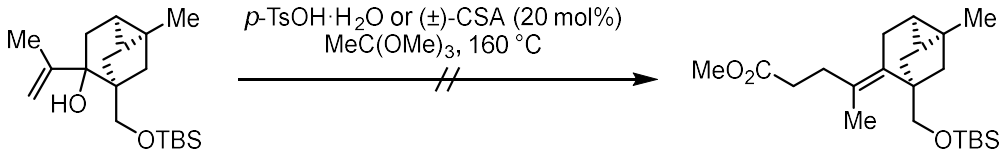
1.97 **1.109** **1.97**

Entry	Conditions	Result
1	**1.110** (1.5 equiv.) THF, 0 °C to r.t.	0% Recovery of **1.98**
2	**1.110** (1.5 equiv.) $CeCl_3$ (1.5 equiv.) THF, 0 °C to r.t.	0% Recovery of **1.98**
3	**1.111** (1.2 equiv.) THF, –78 °C to r.t.	13% d.r. = 1.2:1
4	**1.111** (1.5 equiv.) TMEDA (1.6 equiv.) THF, –78 °C to r.t.	0% Recovery of **1.98**
5	**1.110** (2.0 equiv.) $LaCl_3 \cdot 2LiCl$ (1.6 equiv.) THF, 0 °C to r.t.	86% d.r. = 1.2:1

[46] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

isopropenyllithium (**1.111**), which was generated *in situ* from isopropenyl bromide and *t*-BuLi, afforded allylic alcohol **1.109** in 13% yield as a 1.2:1 mixture of diastereomers (entry 3). No product was observed when using **1.111** and TMEDA as an additive (entry 4).[47] Subjecting ketone **1.97** to isopropenyl-magnesium bromide (**1.110**) in combination with soluble lanthanum salt $LaCl_3 \cdot 2LiCl$ afforded alcohol **1.119** in 86% yield and the same diastereomeric ratio as above (d.r. = 1.2:1, entry 5).[39] The low diastereoselectivity can be rationalized using the 3D representation of **1.97** (Table 1.2, top right), which shows that the two faces of the ketone are only differentiated by the distant methyl and hydrogen.

In the following, we first explored the JOHNSON–CLAISEN rearrangement of allylic alcohol **1.109**. Unfortunately, subjecting **1.109** to 20 mol% *p*-TsOH or (±)-CSA in trimethyl orthoacetate at 160 °C did not afford any tetrasubstituted olefin **1.112** (Scheme 1.17).



1.109 **1.112**

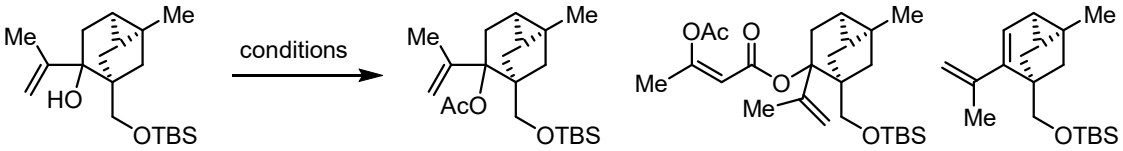
Scheme 1.17. Attempted JOHNSON–CLAISEN rearrangement.

We then shifted our attention to IRELAND–CLAISEN rearrangements. For the synthesis of allylic acetate **1.113**, alcohol **1.109** was treated with acetic anhydride and DMAP at 50 °C, which led to decomposition of **1.109** (Table 1.3, entry 1). Reducing the temperature to r.t. as well as running the reaction in the presence of triethylamine resulted in low conversion to 3-acetoxy-2-butenoate **1.114** but no acetate **1.113** was observed (entries 2 and 3).[48] The formation of **1.114** presumably proceeds *via* initial formation of acetate **1.113** followed by *C*-acylation to give the

[47] Hashimoto, S.; Katoh, S.; Kato, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2017**, *139*, 16420–16429.
[48] **1.114** was obtained as a single olefin isomer but the configuration was not determined.

corresponding β-ketoester and *O*-acylation to give **1.114**.[49] Using HBTU as a coupling reagent for the esterification of **1.109** with acetic acid did not lead to any reaction (entry 4). Treatment of alcohol **1.109** with acetic acid and catalytic amounts of cerium triflate at room temperature or scandium triflate at 120 °C led to decomposition of starting material (entries 5 and 6).[50,51] Heating **1.109** to 120 °C in acetic anhydride in the presence of sodium acetate resulted in elimination of the hydroxy group to give 1,3-diene **1.115** in 45% yield (entry 7).[52] No reaction was observed when using two equivalents of acetyl chloride and four equivalents of *N*,*N*-dimethylaniline in CH_2Cl_2 (entry 8).[53] Finally, acetate **1.113** was obtained

Table 1.3. Conditions for acetylation of allylic alcohol **1.109**.



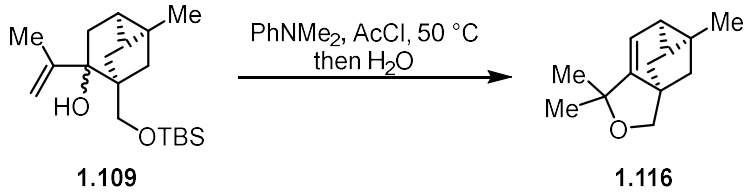
1.109 **1.113** **1.114** **1.115**

Entry	Conditions	Result
1	DMAP (20 mol%), Ac_2O (solvent), 50 °C	decomposition
2	DMAP (30 mol%), Ac_2O (solvent), r.t.	**1.114** (low conversion)
3	DMAP (30 mol%), Et_3N (eq.), Ac_2O, r.t.	**1.114** (low conversion)
4	AcOH (10 eq.), HBTU (1.5 eq.), DMAP (20 mol%), CH_2Cl_2, 50 °C	no reaction
5	$Ce(OTf)_4$ (20 mol%), AcOH (solvent), r.t.	decomposition
6	$Sc(OTf)_3$ (20 mol%), AcOH (solvent), 120 °C	decomposition
7	NaOAc (1.2 eq.), Ac_2O (solvent), 120 °C	**1.115** (45%)
8	$PhNMe_2$ (4 eq.), AcCl (2 eq.), CH_2Cl_2, r.t. to 50 °C	no reaction
9	$PhNMe_2$ (4 eq.), AcCl (solvent), 50 °C	**1.113** (64%)

[49] (a) Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294–7302; (b) Gampe, C. M.; Carreira, E. M. *Chem. Eur. J.* **2012**, *18*, 15761–15771.
[50] Iranpoor, N.; Shekarriz, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 455–458.
[51] Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351–352.
[52] Komsta, Z.; Mayes, B.; Moussa, A.; Shelbourne, M.; Stewart, A.; Tyrrell, A. J.; Wallis, L. L.; Weymouth-Wilson, A. C.; Yurek-George, A. *Tetrahedron Lett.* **2014**, *55*, 6216–6219.
[53] Gao, D.-W.; Vinogradova, E. V.; Nimmagadda, S. K.; Medina, J. M.; Xiao, Y.; Suciu, R. M.; Cravatt, B. F.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 8069–8073.

in 64% yield using four equivalents of *N*,*N*-dimethylaniline in neat acetyl chloride at 50 °C (entry 9).

During the scale-up of the successful acetylation reaction (Table 1.3, entry 9), rapid quenching with water led to decomposition of acetate **1.113** and remaining starting material **1.109**. The combination of acidic conditions and heat evolution led to the formation of cyclic ether **1.116** (Scheme 1.18). Its formation can be rationalized under acidic conditions *via* elimination of the allylic alcohol or acetate, silyl ether cleavage, and addition of the alcohol to the diene. To avoid this side reaction, the reaction mixture was added dropwise to ice-cooled saturated aqueous potassium carbonate solution followed by extraction with diethyl ether.



1.109 1.116

Scheme 1.18. Decomposition of alcohol **1.109** and acetate **1.113** in the work-up of the acetylation reaction.

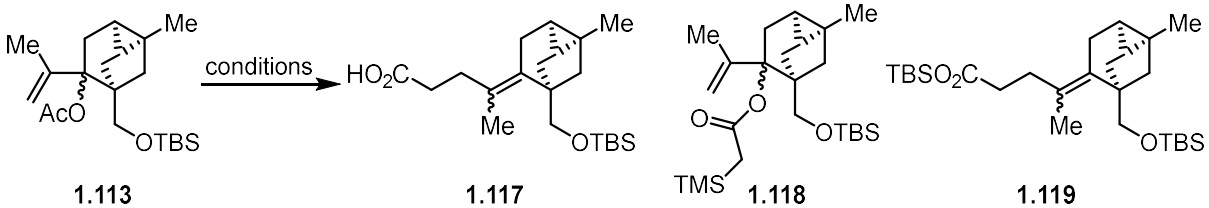
Next, we tested several conditions to induce the IRELAND–CLAISEN rearrangement. First, allylic acetate **1.113** was subjected to LDA and TMSCl or KHMDS and TMSOTf, which resulted in partial conversion to *C*-silylated product **1.118** (Table 1.4, entries 1 and 2).[54,55] Using TMSOTf in combination with either LDA or *n*-BuLi afforded the same product that was observed in the work-up of the acetylation (**1.116**) (entries 3 and 4). With KHMDS and TMSCl, acetate **1.113** was converted into **1.116** and alcohol **1.109** (entry 5). Changing the silyl source to TBSCl and the base to LiHMDS still resulted in the formation of **1.116** (entry 6). Finally, addition of HMPA was found to be crucial for the IRELAND–

[54] **1.118** was obtained as an inseparable mixture with acetate **1.113** and was assigned using 2D HSQC und HMBC NMR spectra: The TMS group (0.16 ppm) had an HMBC coupling to a methylene group, which in turn coupled to the ester carbon. The remaining ^{1}H NMR signals were very similar to acetate **1.113**.

[55] For an example of *C*-silylation in CLAISEN rearrangements, see: Beaudry, C. M.; Trauner, D. *Org. Lett.* **2005**, *7*, 4475–4477.

CLAISEN rearrangement and silyl ester **1.119**, which is the initial product of IRELAND–CLAISEN rearrangements, could be isolated.[56] Later, the reaction was quenched with 1 M aqueous HCl and stirred for 15 min at room temperature, which led to selective hydrolysis of the silyl ester over the silyl ether and carboxylic acid **1.117** was obtained in 72% yield and 2.3:1 diastereomeric ratio (entry 7).

Table 1.4. Conditions for IRELAND–CLAISEN rearrangement of allylic acetate **1.115**.



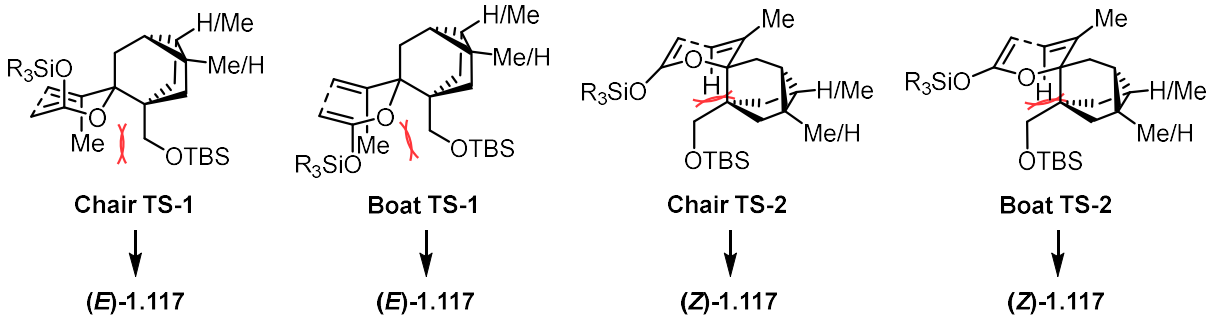
1.113 **1.117** **1.118** **1.119**

Entry	Conditions	Result
1	LDA, TMSCl, THF, –78 °C to r.t.	**1.118**
2	KHMDS, TMSOTf, THF, –78 °C to r.t.	**1.118**
3	LDA, TMSOTf, THF, –78 to 50 °C	**1.116**
4	*n*-BuLi, TMSOTf, THF, –78 °C to r.t.	**1.116**
5	KHMDS, TMSCl, THF, –78 °C to r.t.	**1.116**, **1.109**
6	LiHMDS, TBSCl, THF, –78 °C to r.t.	**1.116**
7	LiHMDS, TBSCl, HMPA, THF, –78 °C to r.t. then aq HCl	**1.117** (72%, d.r. = 2.3:1)

For the IRELAND–CLAISEN rearrangement, four transition states can be envisioned (Scheme 1.19). These include two chair-like and two boat-like transition states. With respect to steric interactions, the first two transition states, **Chair TS-1** and **Boat TS-1**, feature a *syn*-pentane interaction between the vinylic methyl group and the silyloxymethyl group while the other two transition states, **Chair TS-2** and **Boat TS-2**, include a 1,3-allylic interaction between the vinylic

[56] For an example of an IRELAND–CLAISEN rearrangement from which the silyl ester could be isolated, see: Durham, T. B.; Blanchard, N.; Savall, B. M.; Powell, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2004**, *126*, 9307–9317.

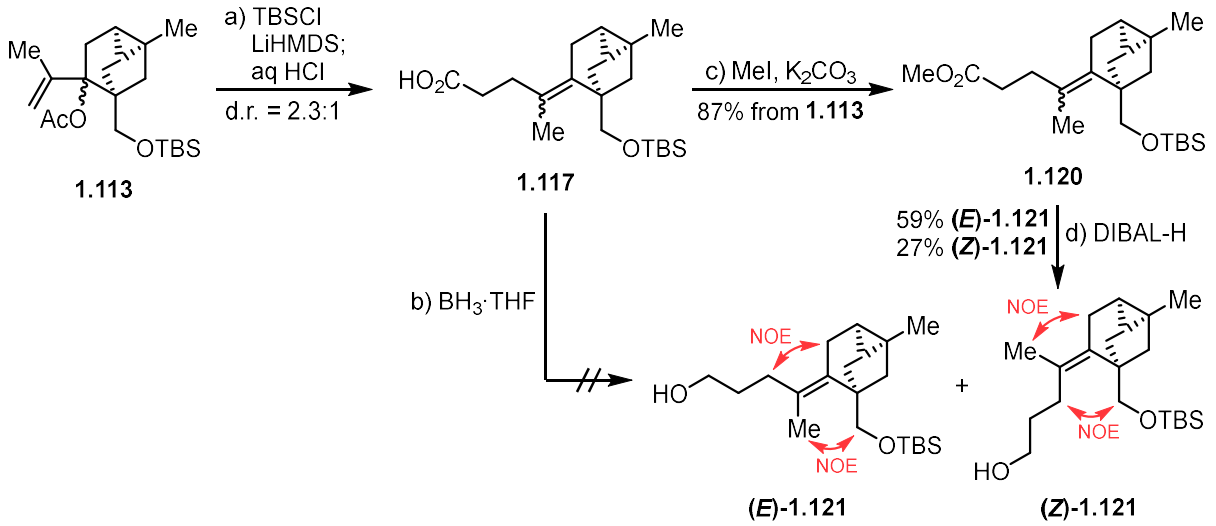
proton and the quaternary center in the tricyclo[3.2.1.$0^{2,7}$]octane.[57] None of these transition states appears highly favored, which explains the low selectivity observed in this sigmatropic rearrangement. The transition state models further indicate the same stereochemical outcome for the reaction of both diastereomers of allylic acetate **1.113**. All four transition states for both diastereomers vary only in the position of the distant methyl and hydrogen as indicated by H/Me and Me/H in the transition state structures.



Scheme 1.19. Possible transition states in the IRELAND–CLAISEN rearrangement of allylic acetate **1.113**.

After the successful IRELAND–CLAISEN rearrangement, we attempted to reduce carboxylic acid **1.117** to the corresponding alcohols **(*E*)-1.121** and **(*Z*)-1.121** using borane-THF, which resulted in a complex mixture (Scheme 1.20). This was attributed to the concurrent hydroboration of the tetrasubstituted olefin in **1.117**. At this point, the carboxylic acid was esterified using methyl iodide and potassium carbonate, which afforded methyl ester **1.120** in 87% yield from allylic acetate **1.113**. Reduction of the ester with DIBAL-H and separation of the diastereomers by flash column chromatography afforded alcohols **(*E*)-1.121** and **(*Z*)-1.121** in 59% and 27% yield, respectively. The configuration of the two olefin geometric isomers **1.121** was assigned *via* 2D NOESY NMR spectroscopy. The relevant NOE interactions are highlighted in Scheme 1.20.

[57] For a discussion on stereoselectivities in IRELAND–CLAISEN rearrangements as well as on steric interactions, see: Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2009.

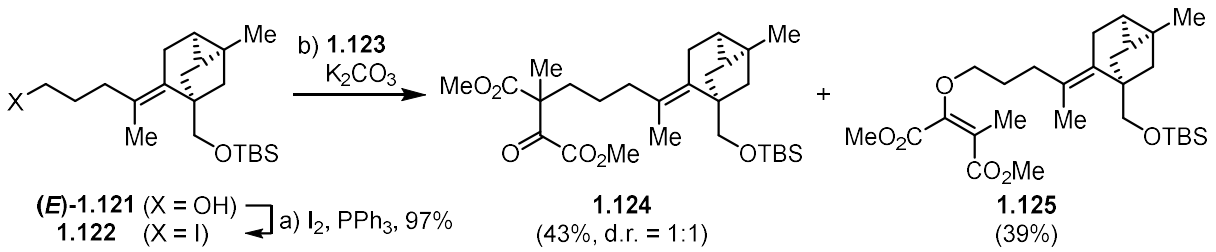


Scheme 1.20. Synthesis of alcohols **(*E*)-1.121** and **(*Z*)-1.121**. Reagents and conditions: (a) LiHMDS, TBSCl, HMPA, THF, –78 °C to r.t., then 1 M HCl, r.t., d.r. = 2.3:1; (b) BH_3·THF, THF, 0 °C to r.t.; (c) MeI, K_2CO_3, DMF, r.t., 87% over two steps; (d) DIBAL-H, PhMe, –78 °C to r.t., 59% **(*E*)-1.121**, 27% **(*Z*)-1.121**.

2.2.4. [2 + 2] Cycloaddition

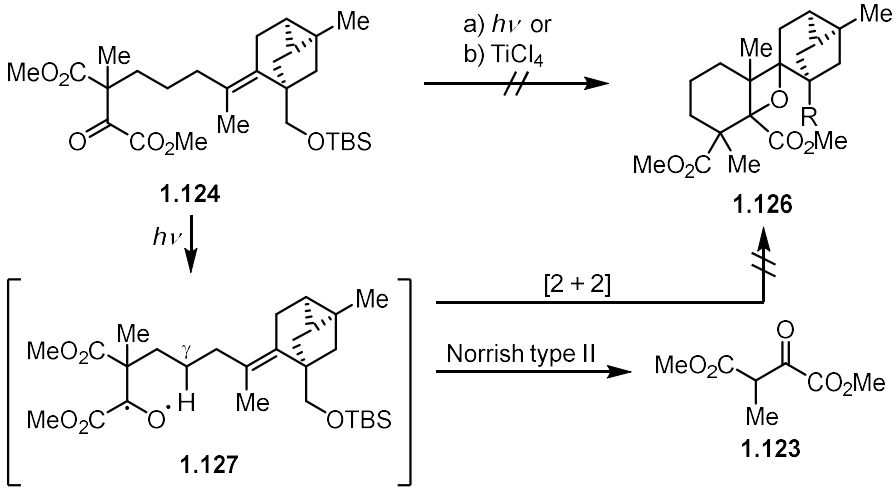
Alcohol **(*E*)-1.121** was transformed into the corresponding iodide **1.122** in an APPEL reaction (iodine, triphenylphosphine, imidazole) in 97% yield (Scheme 1.21).[58] The subsequent alkylation of dimethyl 2-oxo-3-methylsuccinate (**1.123**)[59] afforded α-ketoester **1.124** as an inseparable 1:1 mixture of diastereomers in 43% yield along with *O*-alkylation product **1.125** in 39% yield.[60,61] We envisioned testing the [2 + 2] cycloaddition using this mixture of diastereomers, and, in case of a successful reaction, focus on the diastereoselective synthesis of **1.124** at a later stage.

[58] Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740–1741.
[59] Akita, H.; Furuichi, Koshiji, H.; Korikoshi, K.; Oishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 4384–4390.
[60] Shimizu, I.; Makuta, T.; Oshima, M. *Chem. Lett.* **1989**, *18*, 1457–1460.
[61] *O*-alkylation product **1.125** was obtained as a single olefin isomer, however, its configuration was not assigned.



Scheme 1.21. Synthesis of α-ketoester **1.124**. Reagents and conditions: (a) I_2, PPh_3, imidazole, CH_2Cl_2, r.t., 97%; (b) dimethyl 2-oxo-3-methylsuccinate (**1.123**), K_2CO_3, DMF, r.t., 43% **1.124**, d.r. = 1:1, 39% **1.125**.

We commenced our efforts on [2 + 2] cycloadditions using photochemical conditions. Irradiation of **1.124** with a mercury vapor lamp (400 W) in deuterated benzene, acetonitrile or dichloromethane did not afford any oxetane **1.126**.[22] ^{1}H NMR spectra recorded after a few minutes of irradiation revealed the formation of 2-oxosuccinate **1.123** and olefinic signals. This is suggestive of a Norrish type II fragmentation, in which the irradiation of the ketone leads to biradical **1.127** followed by abstraction of a γ-proton and fragmentation.[62] Prolonged irradiation led to decomposition. In an attempt to thermally induce the



Scheme 1.22. Attempted [2 + 2] cycloaddition of α-ketoester **1.124**. Reagents and conditions: (a) *hv* (mercury vapor lamp, 400 W), C_6D_6 or D_3CCN or CD_2Cl_2; (b) $TiCl_4$, Et_3N, CH_2Cl_2, –78 °C to r.t.

[62] Norrish, R. G. W.; Bamford, C. H. *Nature* **1937**, *140*, 195–196.

[2 + 2] cycloaddition reaction, treatment of α-ketoester **1.124** with titanium tetrachloride and triethylamine only afforded a complex mixture.[63]

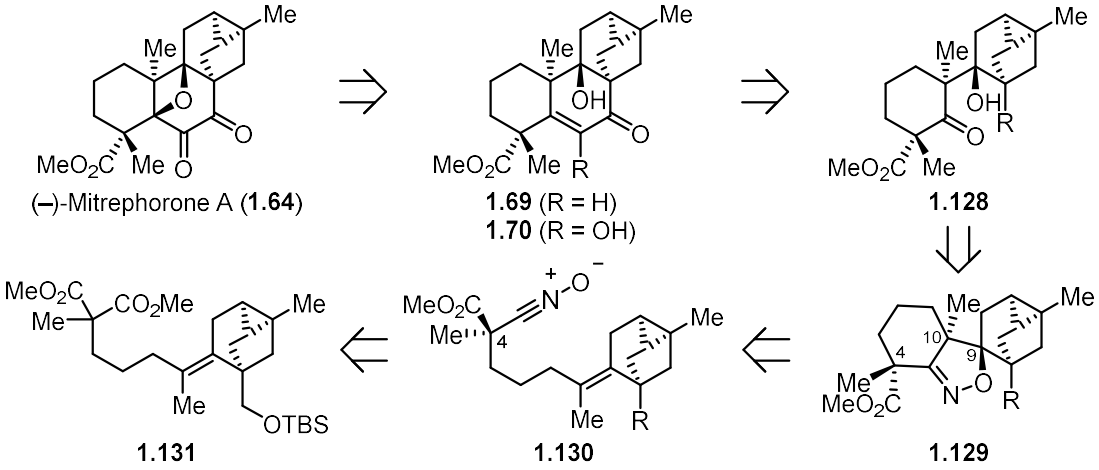
The results of our attempted [2 + 2] cycloadditions of α-ketoester **1.124**, especially the observed NORRISH type II fragmentation, prompted us to pursue an alternative approach for functionalization of the tetrasubstituted olefin. To this end, we identified nitrile oxide cycloaddition as a reaction that would form an isoxazoline, which would be a versatile intermediate for further elaboration. This approach will be discussed in detail in the following chapter.

[63] Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493–1501.

2.3. The Nitrile Oxide Cycloaddition Approach

2.3.1. Retrosynthetic Analysis

In an alternative approach, (–)-mitrephorone A (**1.64**) was disconnected to β-hydroxyketone **1.128** *via* δ-hydroxyenone **1.69** or δ-hydroxydiosphenol **1.70** (Scheme 1.23). After additions to tricyclo[3.2.1.$0^{2,7}$]octanones have proven challenging in the previous sections, the synthesis of highly sterically encumbered **1.128** *via* an aldol addition did not appear very promising to us. However, β-hydroxyketones are also a keying element for a nitrile oxide cycloaddition strategy.[64] Accordingly, **1.128** was traced back to isoxazoline **1.129** and nitrile oxide **1.130**. We envisioned preparing **1.130** *via* the desymmetrization of malonate **1.131**. Similar to the [2 + 2] cycloaddition strategy, the relative configuration at C_9 and C_{10} in **1.129** will be controlled by the olefin geometry in **1.130**. We conceived that the facial selectivity in the nitrile oxide cycloaddition reaction is controlled by the stereogenic center at C_4.



Scheme 1.23. Retrosynthetic analysis of (–)-mitrephorone A (**1.64**) *via* a nitrile oxide cycloaddition reaction.

[64] For a discussion on the sequence of nitrile oxide cycloaddition reaction followed by reductive *N–O* cleavage, see: (a) Bode, J. W., Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612; (b) Muri, D.; Carreira, E. M. *J. Org. Chem.* **2009**, *74*, 8695–8712; (c) Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857–3858.

2.3.2. Forward Synthesis

Malonate **1.131** was prepared *via* an alkylation reaction of dimethyl 2-methylmalonate (**1.132**) with alkyl iodide **1.122**, which was discussed in Section 2.2.4, in 98% yield (Scheme 1.24A). For rapid testing of the nitrile oxide cycloaddition reaction, we decided to commence our efforts *via* non-diastereoselective reduction of one of the two esters in malonate **1.131**. To this end, treatment of **1.131** with DIBAL-H at –78 °C led to the formation of the corresponding α-formylester **1.133** in 67% yield as a 1:1 mixture of diastereomers.[65] Although two equivalents of DIBAL-H were used, the reaction stops at the α-formylester because the stable tetrahedral intermediate formed in DIBAL-H reductions sterically blocks a nucleophilic attack to the other ester.[66] Treatment of **1.133** with hydroxylamine hydrochloride in ethanol–pyridine afforded oxime **1.134** in 82% yield.[64c] Oxidation of **1.134** to the corresponding nitrile oxide **1.130** was effected using aqueous sodium hypochlorite in CH_2Cl_2. No cycloaddition reaction took place under the oxidation conditions, but after isolation of **1.130**, it could be induced by heating it to 100 °C in toluene. The product was obtained as a 1:1 mixture of two diastereomeric isoxazolines **1.129** and **1.135**. The relative configuration of the two isomers was determined by single crystal X-ray crystallography (Scheme 1.24B). This revealed that the desired isomer was indeed formed and that both diastereomers had the same relative configuration at C_4, C_9, and C_{10}. The latter clearly showed that the facial selectivity in the nitrile oxide cycloaddition reaction was fully controlled by the α-stereocenter of the nitrile oxide. No other isomeric isoxazolines were observed. Later, the oxidation/cycloaddition protocol was optimized to oxidize oxime **1.134** with $PhI(OAc)_2$ in methanol at –10 °C,[67] followed by extraction with toluene and directly heating the extracts to 100 °C for one hour. This procedure afforded the mixture of **1.129** and **1.135** in 61% yield.

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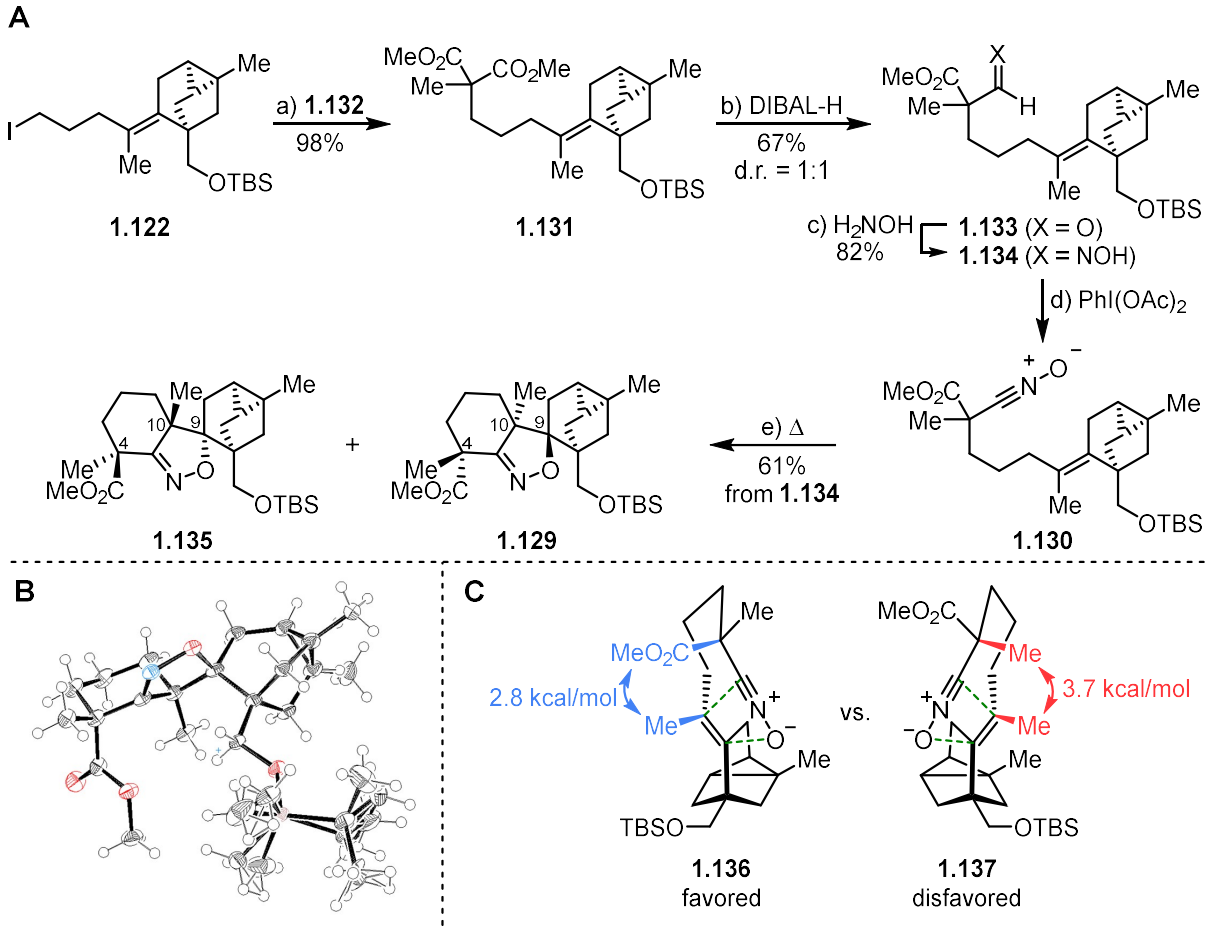
[65] Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469.
[66] Davis, C. R.; Swenson, D. C.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 6843–6850.
[67] Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F., Aulakh, V. S., Cuifolini, M. A. *Org. Lett.* **2009**, *11*, 1539–1542.

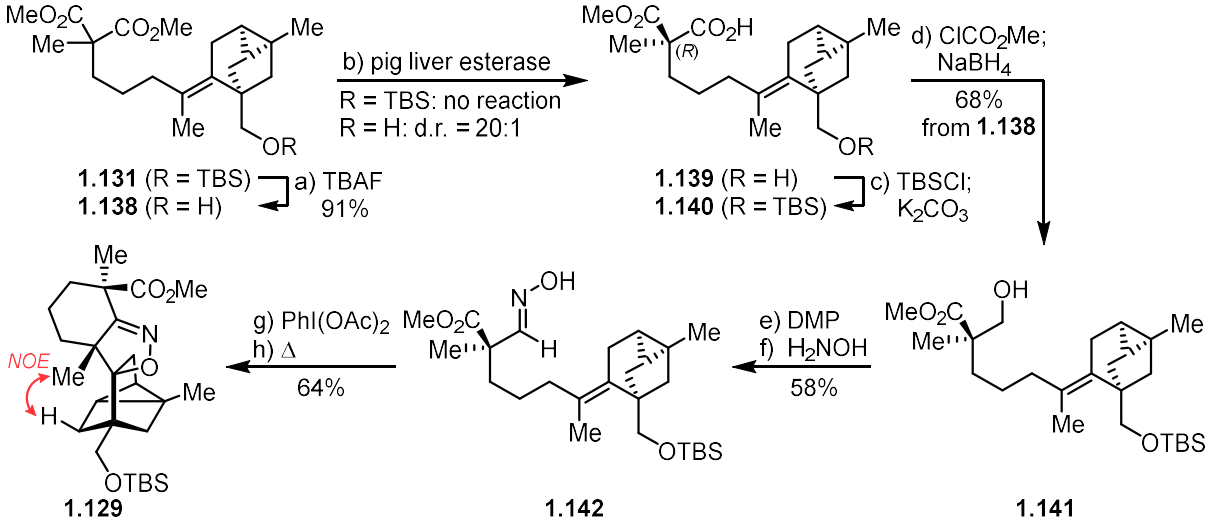


Scheme 1.24. A) Synthesis of isoxazolines **1.129** and **1.135** *via* nitrile oxide cycloaddition. B) Crystal structure of a mixture of **1.129** and **1.135**. C) Rational for the facial selectivity in the nitrile oxide cycloaddition. Reagents and conditions: (a) dimethyl 2-methylmalonate (**1.132**), NaH, 0 °C, then **1.122**, 80 °C, 98%; (b) DIBAL-H, CH_2Cl_2, –78 °C, 67%, d.r. = 1:1; (c) $H_2NOH{\cdot}HCl$, EtOH–pyr (8:1), r.t., 82%, d.r. = 1:1; (d) $PhI(OAc)_2$, MeOH, –10 °C; (e) PhMe, 100 °C, 1:1 mixture of **1.129** and **1.135**, 61% combined yield.

The facial selectivity in the nitrile oxide cycloaddition reaction can be rationalized using the two transition state models **1.136** and **1.137** (Scheme 1.24C). The key difference between these two transitions states is the 1,3-diaxial interaction between either a methyl and a methyl ester group in **1.136** or two methyl groups in **1.137**, which are expected to differ by ~0.9 kcal/mol.[68]

[68] Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765–780.

After the successful implementation of the nitrile oxide cycloaddition, we turned to the selective reduction of the pro-(*S*) ester in **1.131**. No influence of the distant stereocenters in **1.131** on the stereoselectivity of the reduction with DIBAL-H was observed and we expected the same result for the use of other achiral reagents. Therefore, we envisioned applying biocatalysis for the selective differentiation of the two esters in malonate **1.131**.[69] Subjecting **1.131** to pig liver esterase in aqueous phosphate buffer and DMSO did not lead to any hydrolysis of **1.131**. In contrast, after cleavage of the silyl ether in **1.131**, the enzymatic hydrolysis proceeded smoothly and gave malonic acid monoester **1.139** in 20:1 d.r. (Scheme 1.25). Based on literature data, the configuration of the newly formed stereocenter was assigned as (*R*).[70] Reprotection of the hydroxy group in **1.139** as its TBS ether, followed by chemoselective reduction of the carboxylic acid over the ester in **1.140** by first forming the anhydride with methyl chloroformate and



Scheme 1.25. Diastereoselective synthesis of isoxazoline **1.129** *via* enzymatic malonate desymmetrization and nitrile oxide cycloaddition. Reagents and conditions: (a) TBAF, THF, r.t., 91%; (b) pig liver esterase, NaOH, 0.1 M aq sodium phosphate buffer–DMSO (10:1), r.t., d.r. = 20:1; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, r.t.; K_2CO_3, MeOH–THF–H_2O (20:10:3), r.t.; (d) methyl chloroformate, Et_3N, THF, 0 °C to r.t.; $NaBH_4$, MeOH, 0 °C, 68% from **1.138** + 12% **1.131**; (e) DMP, *t*-BuOH, CH_2Cl_2, r.t., 71%; (f) $H_2NOH{\cdot}HCl$, EtOH–pyr (8:1), r.t., 82%; (g) $PhI(OAc)_2$, MeOH, 0 °C; (h) PhMe, 100 °C, 64% over two steps.

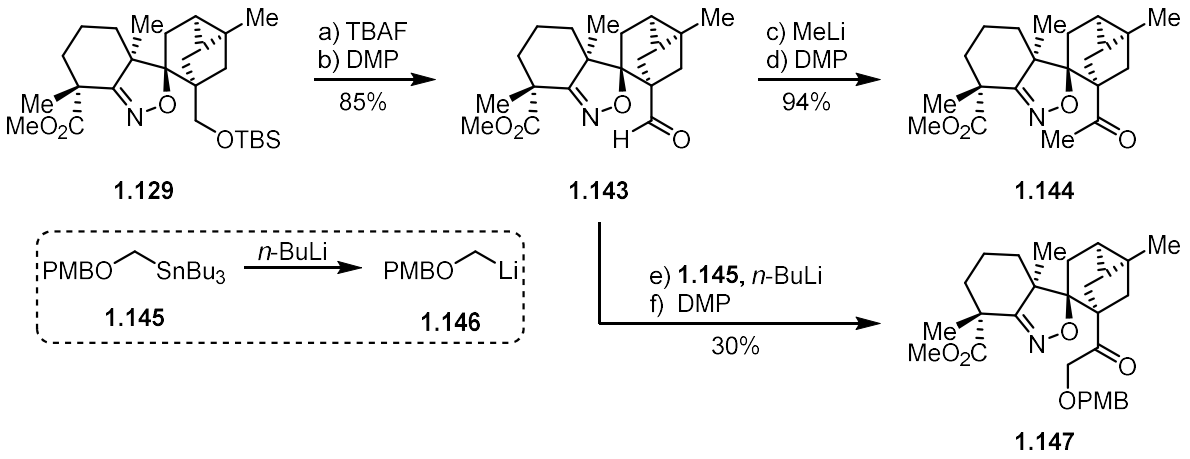
[69] For a review on enzymatic desymmetrization reactions in organic synthesis, see: García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110–PR180.

[70] (a) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347–1352; (b) Banerjee, S.; Wiggins, W. J.; Geoghegan, J. L.; Anthony, C. T.; Woltering, E. A.; Masterson, D. S. *Org. Biomol. Chem.* **2013**, *11*, 6307–6319.

subsequent reduction with sodium borohydride gave β-hydroxyester **1.141** in 68% yield from **1.138**.[71] Oxidation of the alcohol with DMP followed by treatment with hydroxylamine hydrochloride afforded oxime **1.142** in 58% yield over two steps. Subjecting **1.142** to nitrile oxide cycloaddition conditions led to the formation of isoxazoline **1.129** in 64% yield. The relative configuration of the cycloadduct was determined by 1D NOE NMR experiments.

After establishing the highly diastereoselective synthesis of isoxazoline **1.129**, we turned our attention to the completion of the carbon skeleton of (–)-mitrephorone A (**1.64**). We envisioned achieving this *via* intramolecular nucleophilic addition to the isoxazoline. To this end, silyl ether **1.129** was converted into the corresponding methyl ketone **1.144** in four steps (Scheme 1.26): Deprotection with TBAF was followed by oxidation with DMP to give aldehyde **1.143** in 85% over two steps. The subsequent methyllithium addition initially suffered from low conversion when the organometal reagent was added very carefully to a solution of aldehyde **1.143** in THF at –78 °C or from decomposition when the reagent was added too quickly. The latter presumably occurred due to addition to the other electrophilic functional groups in the molecule. In an optimized procedure, slow addition of 18 equivalents of methyllithium in six portions every ten minutes to **1.143** led to clean conversion to the corresponding secondary alcohol. Oxidation with DMP afforded methyl ketone **1.144** in 94% over two steps. Additionally, protected α-hydroxyketone **1.147** was prepared *via* addition of organolithium reagent **1.146**, which was generated from the corresponding organostannane **1.145** and *n*-butyllithium, followed by oxidation with DMP in 30% over two steps.[72]

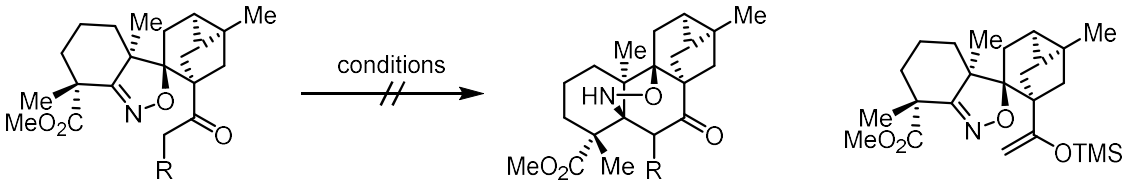
[71] Prantz, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5030–5033.
[72] Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2002**, 1736–1737.



Scheme 1.26. Conversion of cycloadduct **1.129** into ketones **1.144** and **1.147**. Reagents and conditions: (a) TBAF, THF, 60 °C, 99%; (b) DMP, *t*-BuOH, CH_2Cl_2, 86%; (c) MeLi, THF–Et_2O (3:1), –78 °C; (d) DMP, *t*-BuOH, CH_2Cl_2, 94% over two steps; (e) **1.145**, *n*-BuLi, THF, –78 °C; (f) DMP, *t*-BuOH, CH_2Cl_2, 30% over two steps.

We envisioned closing the last all-carbon ring *via* an intramolecular MANNICH-type addition of the ketone to the isoxazoline in **1.144** and **1.147**. To this end, methyl ketone **1.144** was treated with LDA and TMSCl, which led to the formation of silyl enol ether **1.150**, but no cyclization to give isoxazolidine **1.148** was observed (Table 1.5, entry 1). This showed that enolate formation occurs upon treatment of **1.144** with LDA, however, no cyclization product **1.148** formed neither from the intermediate enolate nor from silyl enol ether **1.150** under the reaction conditions. Treatment of **1.150** with boron trifluoride etherate did not induce cyclization and instead, hydrolysis to ketone **1.144** occurred (entry 2). Subjecting ketone **1.147** to either LDA or sodium methoxide did not lead to any formation of isoxazolidine **1.149** and starting material was recovered (entries 3 and 4). Also, inducing cyclization *via* formation of the enamine of ketone **1.147** with pyrrolidine proved unfruitful (entry 5). The failure of the MANNICH-type reactions was attributed to either lack of reactivity of the isoxazoline towards nucleophilic addition or reversibility of the addition.

Table 1.5. Unsuccessful intramolecular MANNICH-type addition.



1.144 (R = H)
1.147 (R = OPMB)

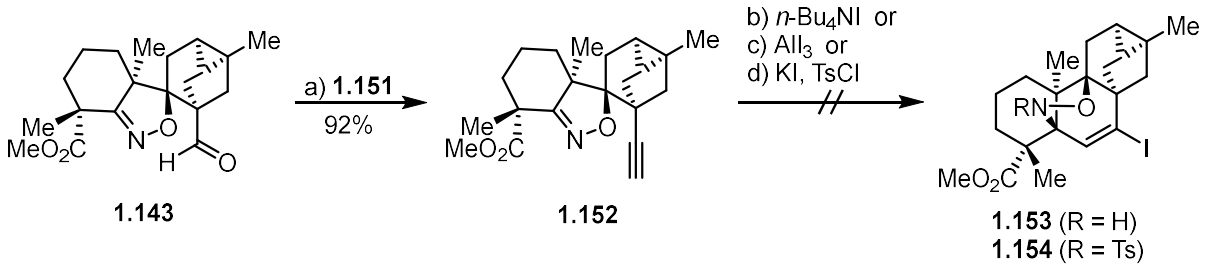
1.148 (R = H)
1.149 (R = OPMB)

1.150

Entry	Starting material	Conditions	Result
1	**1.144**	LDA, TMSCl, THF, –78 °C to r.t.	**1.150**
2	**1.150**	$BF_3 \cdot OEt_2$, CH_2Cl_2, –78 °C to r.t.	recovered **1.144**
3	**1.147**	LDA, THF, –78 to –10 °C	recovered **1.147**
4	**1.147**	NaOMe, MeOH, r.t. to 50 °C	recovered **1.147**
5	**1.147**	pyrrolidine, PhH, 80 °C	recovered **1.147**

Overman has reported the addition of alkynes to iminium ions in the presence of an iodide source.[73] To test a similar approach for addition to the isoxazoline, we transformed aldehyde **1.143** into alkyne **1.152** using OHIRA–BESTMANN reagent (**1.151**) and potassium carbonate in 92% yield (Scheme 1.27).[74] Large excess of both reagents (22 and 30 equivalents, respectively) had to be used to obtain high conversion of aldehyde **1.143**. Subjecting alkyne **1.152** to tetrabutylammonium iodide and camphorsulfonic acid in acetonitrile at 80 °C led to decomposition of the tricyclo[3.2.1.$0^{2,7}$]octane core as shown by the absence of the characteristic cyclopropane proton around 0.7 ppm in the ^{1}H NMR spectrum. Also, the use of aluminum iodide as the iodide source did not lead to any formation of isoxazolidine **1.153**.[75] An attempt to induce cyclization with potassium iodide with subsequent trapping of the resulting isoxazolidine **1.153** as the corresponding sulfohydroxamic acid **1.154** did not lead to any conversion of **1.152**.

[73] Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612–614.
[74] Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564.
[75] Li, H.; Chen, Q.; Lu, Z.; Li, A. *J. Am. Chem. Soc.* **2016**, *138*, 15555–15558.



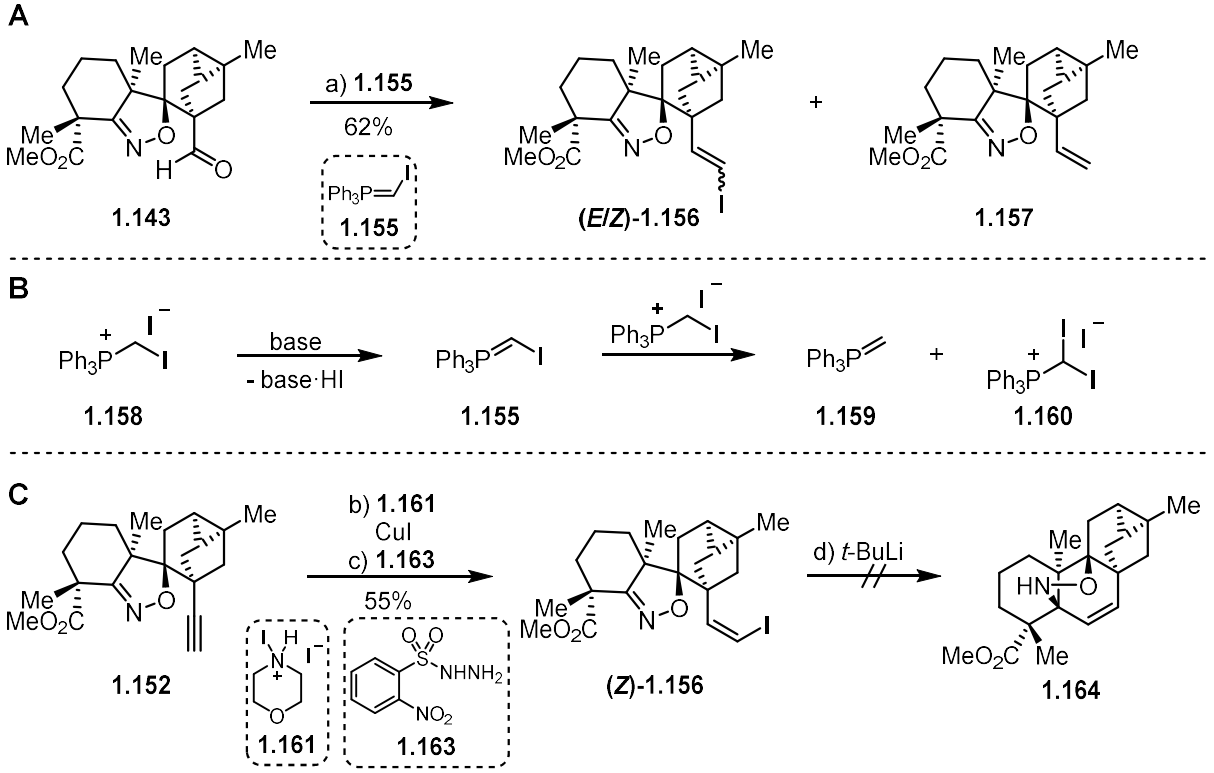
Scheme 1.27. Synthesis of alkyne **1.152** and unsuccessful cyclization to **1.153** and **1.154**. Reagents and conditions: (a) OHIRA–BESTMANN reagent (**1.151**), K_2CO_3, MeOH, r.t., 92%; (b) *n*-Bu_4NI, (±)-CSA, MeCN, 80 °C; (c) AlI_3, PhMe, –78 to –10 °C; (d) KI, TsCl, MeCN, r.t.

In an alternative approach, we envisioned transforming aldehyde **1.143** into (*Z*)-vinyl iodide **(*Z*)-1.156** and induce cyclization *via* lithium-halogen exchange. In contrast to the MANNICH-type addition discussed above, an organolithium addition to the isoxazoline would be irreversible. To this end, **1.143** was treated with ylide **1.155**, which was generated *in situ* from iodomethyltriphenylphosphonium iodide (**1.158**) and NaHMDS, for which high (*Z*)-selectivities had been reported.[76] This gave rise to an inseparable mixture of *cis*- and *trans*-isomers of **1.156** and desiodo analogue **1.157** in 56% combined yield in an approximately 4:2:3 ratio (Scheme 1.28A). The highest (*Z*)-selectivities had been reported when running the reaction at –78 °C. In our case, no reaction was observed at this temperature and the reaction was slowly warmed to room temperature overnight, which may be the reason for the low selectivity observed.

The formation of desiodo analogue **1.157** in the WITTIG olefination is rationalized in Scheme 1.28B: Deprotonation of iodomethyltriphenylphosphonium iodide (**1.158**) first leads to formation of ylide **1.155**, which reacts with another molecule of **1.158** to give a mixture of ylide **1.159** and diiodomethyltriphenylphosphonium iodide (**1.160**).[77] The WITTIG olefination of aldehyde **1.143** with ylide **1.159** gives rise to olefin **1.157**. Sterically and electronically, ylide **1.159** is expected to be the most reactive amongst all ylides present in the reaction mixture.

[76] Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174.
[77] Bestmann, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron* **1989**, *30*, 5261–5262.

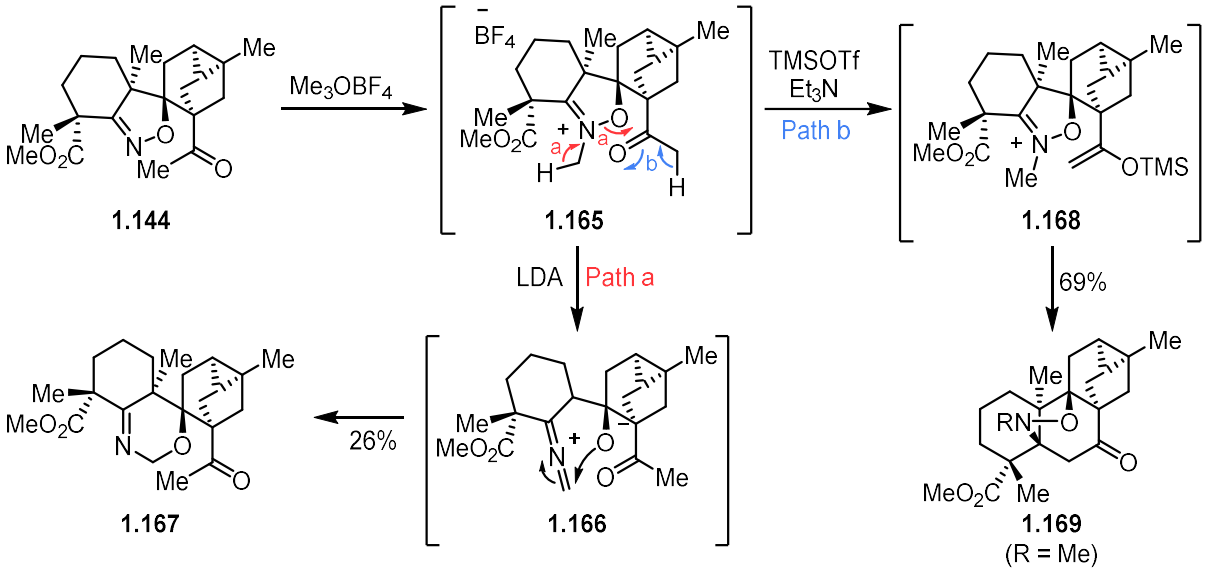
Alternatively, **(*Z*)-1.156** was prepared selectively by transforming alkyne **1.143** into the corresponding iodoalkyne **1.162** using *N*-iodomorpholin hydroiodide (**1.161**) followed by diimide reduction using 2-nitrobenzenesulfonohydrazide (**1.163**) in 55% over two steps (Scheme 1.28C).[78,79,80] Treatment of vinyl iodide **(*Z*)-1.156** with *t*-BuLi at –78 °C did not afford any isoxazolidine **1.164**. Analysis of the ^{1}H NMR spectrum of the unpurified product mixture indicated full protodeiodination.[81]



Scheme 1.28. (A) Synthesis of a mixture of vinyl iodides **(*E*/*Z*)-1.156** and olefin **1.157** *via* WITTIG olefination of aldehyde **1.143**. (B) Mechanistic rational for the formation of **1.157**. (C) Synthesis of vinyl iodide **(*Z*)-1.156** *via* alkyne semireduction and failed intramolecular addition to the isoxazoline. Reagents and conditions: (a) iodomethyltriphenylphosphonium iodide (**1.158**), NaHMDS, THF, r.t., then **1.143**, –78 °C to r.t., 62% combined yield; (b) **1.161**, CuI (5 mol%), THF, r.t., 70%; (c) **1.163**, Et_3N, THF–*i*-PrOH (1:1), r.t., 79%; (d) *t*-BuLi, Et_2O, –78 °C.

[78] Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8018–8021.
[79] Nguyen, K. D.; Herkommer, D.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 5238–5241.
[80] Myers, A. G.; Zheng, B.; Movassagi, M. *J. Org. Chem.* **1997**, *62*, 7507.
[81] All olefinic protons arose from vinyl groups (CH_2 at 4.85-5.05 ppm and CH at 6.18-6.55 ppm). The only methyl ester signal corresponds to **1.157**, which accounts for ~20% of the product mixture.

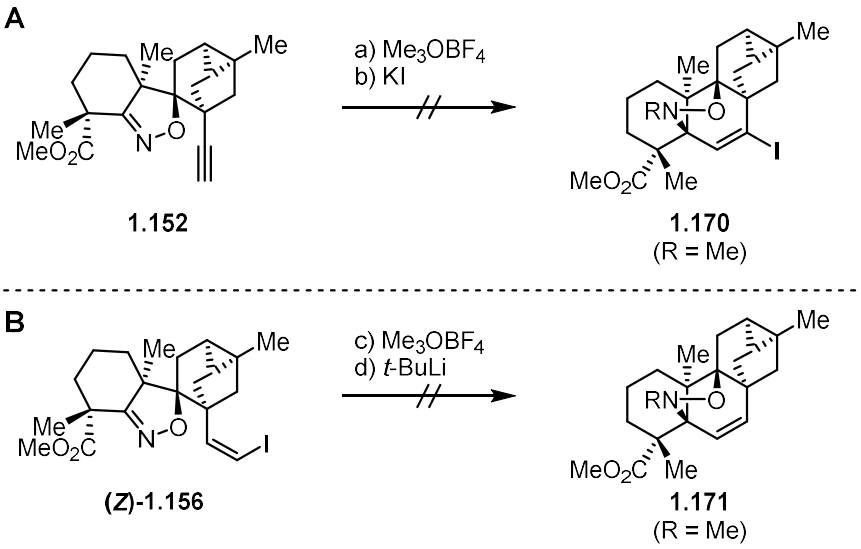
As an additional option to increase the reactivity of the isoxazoline and to reduce the reversibility of MANNICH-type reactions, we identified the transformation of the isoxazoline into the corresponding isoxazolinium salt *via* *N*-alkylation. To this end, isoxazoline **1.144** was treated with MEERWEIN's salt (Me_3OBF_4, Scheme 1.29). Subjecting the intermediate isoxazolinium tetrafluoroborate **1.165** to LDA in THF at –78 °C did not afford any desired isoxazolidine **1.169** but led to the formation of dihydro-1,3-oxazine **1.167** in 26% yield. Its formation presumably occurs *via* deprotonation of the *N*-methyl and *N–O* bond cleavage to give betaine **1.166** (path a). Nucleophilic addition of the alcoholate to the terminal carbon atom of the *N*-methyleneiminium moiety gives rise to **1.167**.[82] In contrast, treatment of isoxazolinium salt **1.165** *in situ* with trimethylsilyl triflate and triethylamine afforded isoxazolidine **1.169** in 69% yield *via* silyl enol ether **1.168** and completed the carbon skeleton of the natural product (path b).



Scheme 1.29. Methylation of isoxazoline **1.144** and conversion of isoxazolinium salt **1.165** into **1.167** or **1.169**. Reagents and conditions: (Path a) Me_3OBF_4, CH_2Cl_2, r.t.; LDA, THF, –78 °C, 26%; (Path b) Me_3OBF_4, CH_2Cl_2, r.t., then TMSOTf, Et_3N, r.t., 69%.

[82] For a similar rearrangement of a *N*-methyl benzo[*d*]isoxazolium salt, see: King, J. F.; Durst, T. *Can. J. Chem.* **1962**, *40*, 882–889.

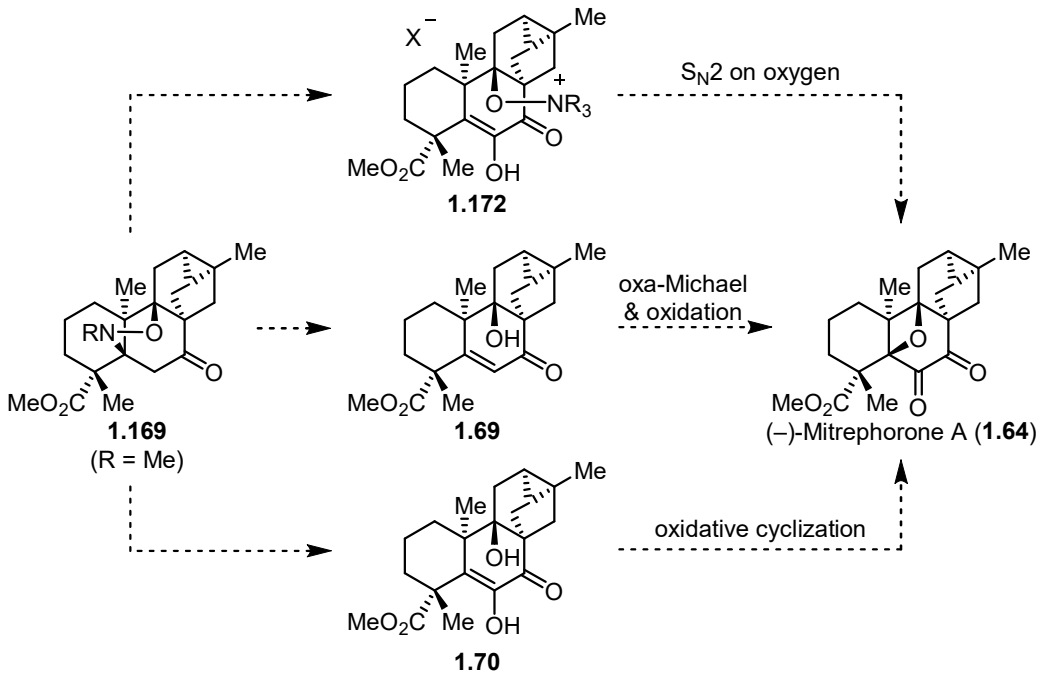
Following the same idea of activating the isoxazoline by methylation and subsequent nucleophilic addition to the isoxazolium carbon atom, we envisioned cyclizing also alkyne **1.152** and vinyl iodide **(*Z*)-1.156**. Accordingly, both **1.152** and **1.156** were treated first with MEERWEIN's salt and thereafter with either potassium iodide or *t*-BuLi, respectively, but no cyclization products **1.170** or **1.171** were observed (Scheme 1.30).



Scheme 1.30. Attempts to cyclize alkyne **1.152** and vinyl iodide **(*Z*)-1.156** *via N*-methylation of the isoxazoline. Reagents and conditions: (a) Me_3OBF_4, CH_2Cl_2, 50 °C; (b) KI, MeCN, 80 °C; (c) Me_3OBF_4, CH_2Cl_2, r.t.; (d) *t*-BuLi, THF, –78 °C.

2.3.3. Completion of the Synthesis

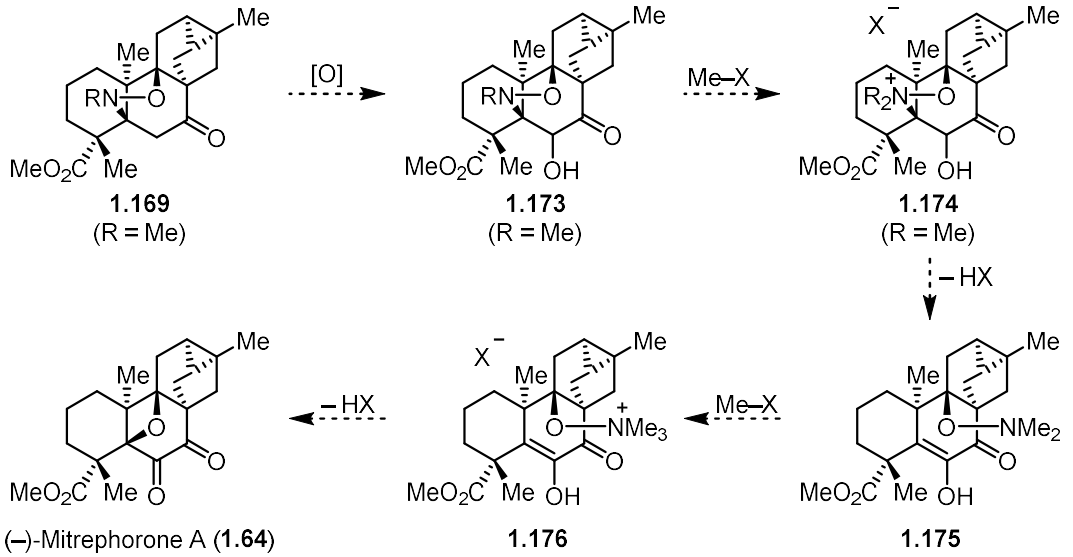
After completion of the carbon skeleton of (–)-mitrephorone A (**1.64**), all that remained for the completion of the total synthesis was nitrogen extrusion and oxidation. Continuing from isoxazolidine **1.169**, several modes for oxetane formation can be envisioned (Scheme 1.31). These include S_N2 displacement on the hydroxylammonium oxygen atom in **1.172**, intramolecular oxa-MICHAEL addition of δ-hydroxyenone **1.69** followed by oxidation, and oxidative cyclization of δ-hydroxydiosphenol **1.70**.



Scheme 1.31. Envisioned routes for oxetane formation from **1.169**.

We chose to start our investigations on oxetane synthesis *via* S_N2 displacements on the oxygen atom.[83] To this end, we envisioned transforming ketone **1.169** first into the corresponding α-hydroxyketone **1.173**, followed by treatment with a methylating agent (Scheme 1.32). This would lead to isoxazolidinium salt **1.174**, followed by elimination to give hydroxylamine **1.175**. A second *N*-methylation is planned to give rise to hydroxylammonium salt **1.176**, which would subsequently undergo S_N2 displacement to form the natural product (–)-mitrephorone A (**1.64**).

[83] For examples of nucleophilic displacement on oxygen atoms, see: (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M. *J. Org. Chem.* **1984**, *49*, 3243–3244; (b) Wu, B.; Yang, J.; Gao, M.; Hu, L. *Org. Lett.* **2020**, *22*, 5561–5566.



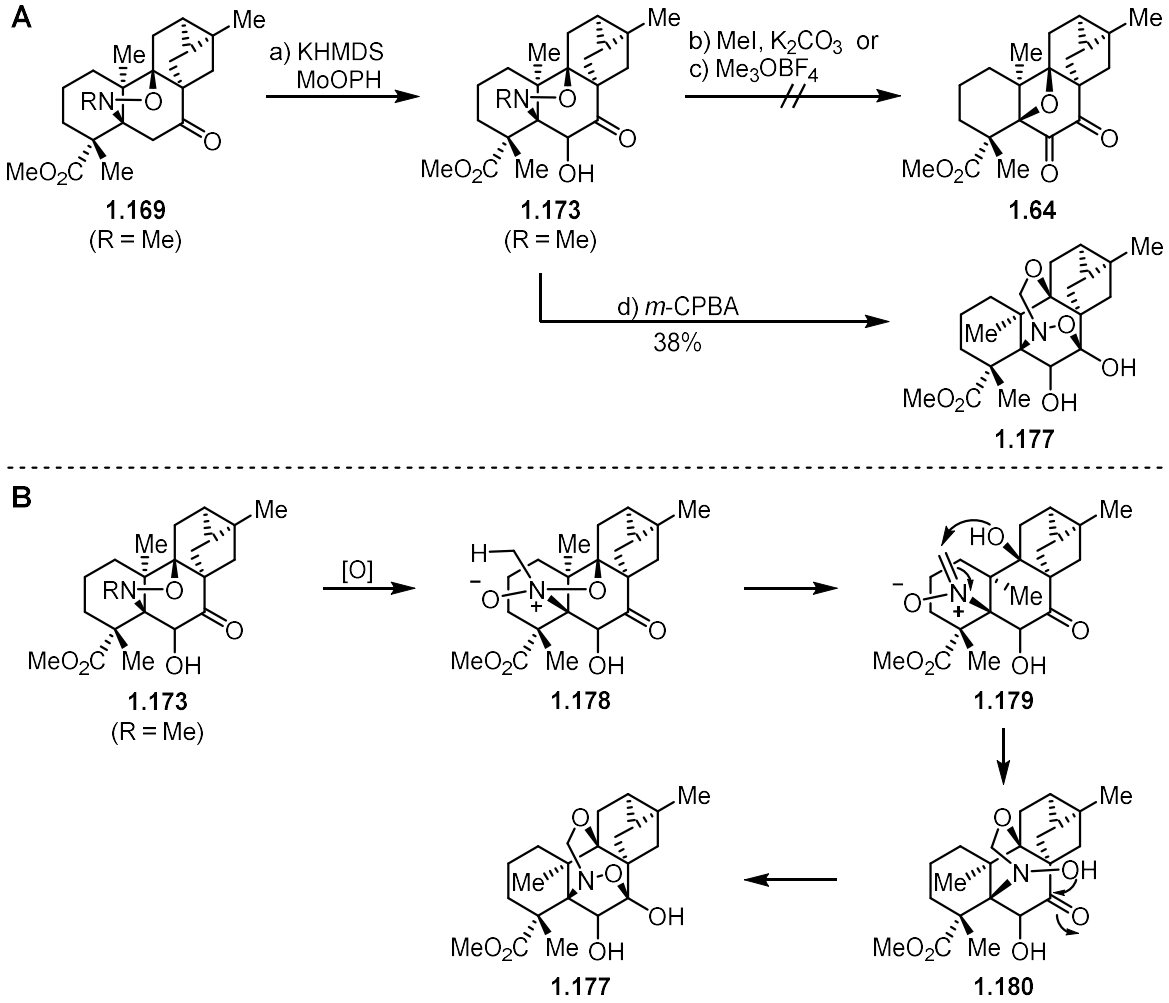
Scheme 1.32. Envisioned transformation of isoxazolidine **1.169** into (–)-mitrephorone A (**1.64**) *via* S_N2 displacement on oxygen.

Treatment of ketone **1.169** with KHMDS and VEDEJS' reagent MoOPH (MoO_5·pyr·HMPA) led to clean formation of α-hydroxyketone **1.173** (Scheme 1.33A).[84] Partial lactone formation with the ester was observed during purification on silica gel and therefore, **1.173** was used in the following reactions without chromatographic purification. Unfortunately, subjecting **1.173** to methyl iodide and potassium carbonate or to MEERWEIN's salt did not lead to *N*-methylation.

Alternatively, oxidation of **1.173** with *m*-CPBA to effect a COPE-type elimination also did not afford the natural product but gave rise to **1.177** in 38% yield, which is presumably formed *via* a mechanism similar to path a in Scheme 1.29: *N*-oxidation with *m*-CPBA is followed by fragmentation to give nitrone **1.179** (Scheme 1.33B). Nucleophilic addition of the hydroxy group to the nitrone carbon atom gives *N*-hydroxy-1,3-oxazinane **1.180**, which forms product **1.177** *via* hemiacetal formation of the hydroxylamine oxygen with the ketone.[85]

[84] (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944–5946; (b) Clive, D. L. J.; Sgarbi, P. W. M.; He, X.; Sun, S.; Zhang, J.; Ou, L. *Can. J. Chem.* **2003**, *81*, 811–824.

[85] For a *m*-CPBA-mediated oxidation/rearrangement cascade of isoxazolidines to 1,3-oxazinanes, see: Hashmi, S. M. A.; Ali, S. A.; Wazeer, M. I. M. *Tetrahedron* **1998**, *54*, 12959–12972.

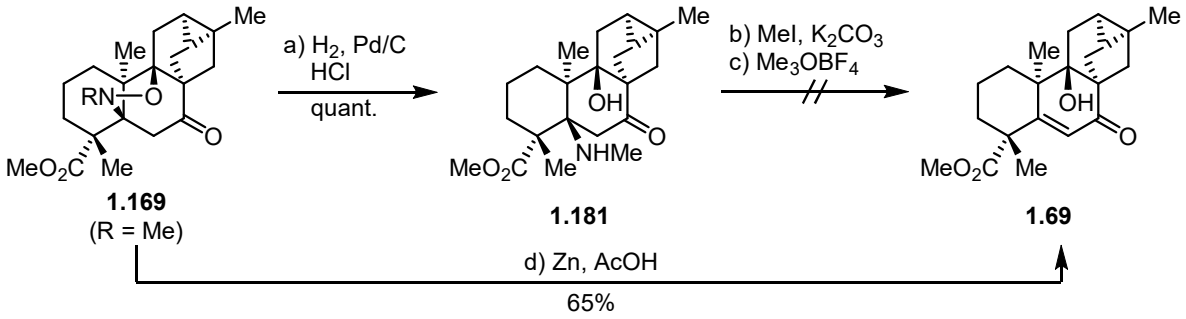


Scheme 1.33. (A) Synthesis of α-hydroxyketone **1.173** *via* oxidation of ketone **1.169** and attempted transformation of **1.173** into (–)-mitrephorone A (**1.64**) *via* S_N2 displacement on oxygen. (B) Mechanistic rational for the formation of **1.177**. Reagents and conditions: (a) KHMDS, THF, –78 to –15 °C, then MoOPH, –15 °C; (b1) MeI, K_2CO_3, MeOH, r.t.; (b2) MeI, K_2CO_3, MeOH–CH_2Cl_2 (6:5), 60 °C; (c) Me_3OBF_4, CH_2Cl_2; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 38% **1.177**.

Next, we concerned ourselves with intramolecular oxa-MICHAEL additions of enone **1.69** for oxetane synthesis (Scheme 1.31). To this end, hydrogenation of isoxazolidine **1.169** in the presence of HCl in methanol at 60 °C gave rise to aminoalcohol **1.181** in quantitative yield (Scheme 1.34).[86] However, no elimination of β-aminoketone **1.181** to the corresponding enone **1.69** could be induced with either methyl iodide or MEERWEIN's salt. Alternatively,

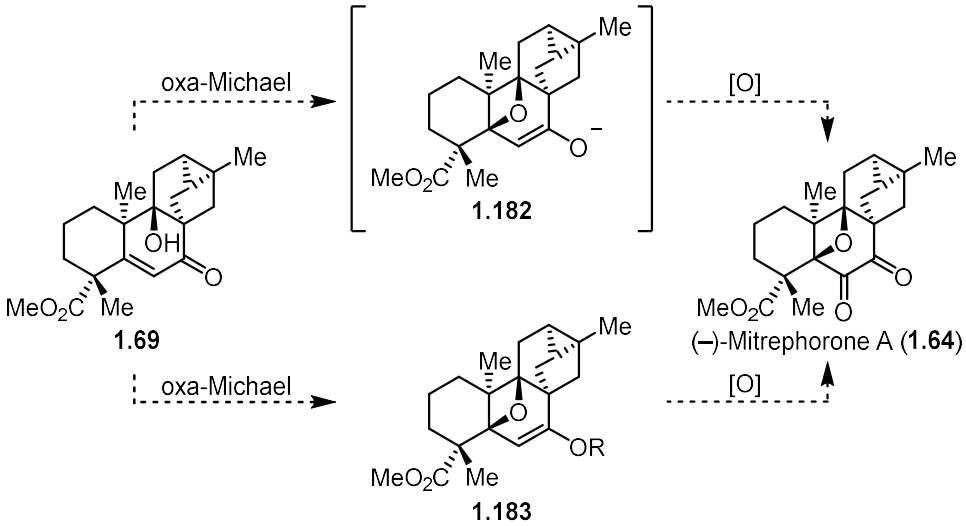
[86] The reaction was carried out using a 1:1 mixture of diastereomers of isoxazolidine **1.172**, which was obtained *via* the non-diastereoselective route (Scheme 1.24).

isoxazolidine **1.169** was treated with zinc in acetic acid at 50 °C.[87] This led to reductive *N–O* bond cleavage and concomitant methylamine elimination to afford enone **1.69** in 65% yield. Traces of the corresponding saturated ketone and intermediate aminoalcohol **1.181** were observed *via* ^{1}H NMR analysis of the unpurified product mixture.



Scheme 1.34. Reduction of isoxazolidine **1.169** to aminoalcohol **1.181** enone **1.69**. Reagents and conditions: (a) H_2 (1 atm), Pd/C (30 mol%), HCl, MeOH, 60 °C, quant.; (b) MeI, K_2CO_3, MeOH, r.t.; (c) Me_3OBF_4, MeOH, r.t.; (d) Zn, AcOH, 50 °C, 65%.

For the oxa-MICHAEL/oxidation sequence of enone **1.69**, we identified two possible approaches: (1) Oxa-MICHAEL addition in the presence of an oxidant may directly lead to (–)-mitrephorone A (**1.64**) *via* enolate **1.182**, or (2) oxa-MICHAEL



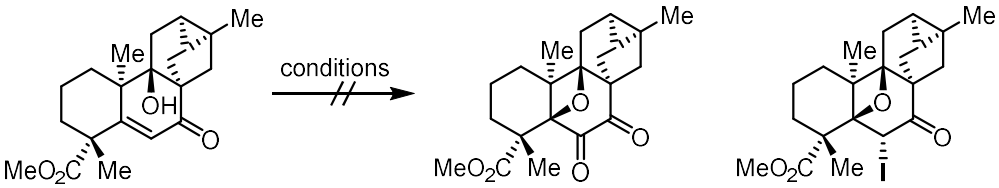
Scheme 1.35. Envisioned synthesis of (–)-mitrephorone A (**1.64**) *via* oxidation of enolate **1.182** or enol ether **1.183**.

[87] Gribble, G. W.; Barden, T. C. *J. Org. Chem.* **1985**, *50*, 5900–5902.

addition in the presence of an electrophile such as a silyl chloride would lead to enol ether **1.183**, which is oxidized in a second step (Scheme 1.35).

Ideally, the oxidation of enolate **1.182** would directly furnish the natural product in a single operation. Conditions for this transformation include enolate *C*-halogenation and subsequent KORNBLUM oxidation and oxidation with molecular oxygen.[88,89] In a first attempt, δ-hydroxyenone **1.69** was subjected to *N*-bromosuccinimide and sodium bicarbonate in DMSO, which did not induce any reaction of **1.69** and starting material was recovered (Table 1.6, entry 1). Treating **1.69** with iodine and triethylamine and gradually increasing the temperature did not lead to conversion of **1.69** up to 100 °C and to decomposition at 140 °C (entry 2). The use of phenyl iododiacetate or oxygen gas in combination with potassium *tert*-butoxide only returned enone **1.69** (entries 3 and 4). Also, an attempted two-step protocol of oxa-MICHAEL addition with concomitant α-hydroxylation of the resulting enolate using MoOPH and KHMDS followed by

Table 1.6. Attempted conditions for oxidation of enone **1.69**.



1.69 **(–)-Mitrephorone A (1.64)** **1.184**

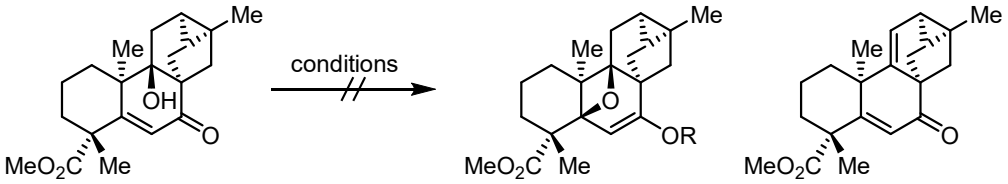
Entry	Conditions	Result
1	NBS, $NaHCO_3$, DMSO, r.t. to 80 °C	recovery of **1.69**
2	I_2, Et_3N, DMSO, r.t. to 140 °C	decomposition at 140 °C
3	$PhI(OAc)_2$, KO*t*-Bu, DMSO, r.t.	recovery of **1.69**
4	O_2 (1 atm), KO*t*-Bu, THF, r.t.	recovery of **1.69**
5	1. MoOPH, KHMDS, THF, 0 °C to r.t. 2. DMP, $NaHCO_3$, CH_2Cl_2, r.t.	recovery of **1.69**
6	Ipy_2BF_4, CH_2Cl_2, r.t.	decomposition

[88] Tatsugi, J.; Okumura, S.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3311–3313.
[89] Kreilein, M. M.; Hofferberth, J. E.; Hart, A. C.; Paquette, L. A. *J. Org. Chem.* **2006**, *71*, 7329–7336.

oxidation with DMP did not furnish any natural product **1.64** (entry 5). Subjecting enone **1.69** to BARLUENGA's reagent (Ipy_2BF_4) in an attempt to induce iodoetherification to give **1.184** led to decomposition of **1.69** (entry 6).[90]

To induce oxa-MICHAEL addition with concurrent enol ether formation, δ-hydroxyenone **1.69** was subjected to TBSOTf and 2,6-lutidine or proton sponge (Table 1.7, entries 1 and 2). The former led to elimination of the hydroxy group to give diene **1.187** and the latter predominantly returned starting material **1.69**.[91] Treatment of enone **1.69** with MEERWEIN's salt and sodium bicarbonate afforded a complex mixture, which included diene **1.187** (entry 3). In all cases, analysis of the ^{1}H NMR of the unpurified reaction mixtures revealed the absence of enol ether protons, which are expected between 4.0 and 5.0 ppm.[92]

Table 1.7. Attempted conditions for oxa-MICHAEL addition and enol ether formation.



1.69 | **1.185** (R = TBS), **1.186** (R = Me) | **1.187**

Entry	Conditions	Result
1	TBSOTf, 2,6-lutidine CH_2Cl_2, r.t.	**1.187**
2	TBSOTf, proton sponge CH_2Cl_2, –78 °C to r.t.	no reaction
3	Me_3OBF_4, $NaHCO_3$ CH_2Cl_2, r.t.	complex mixture

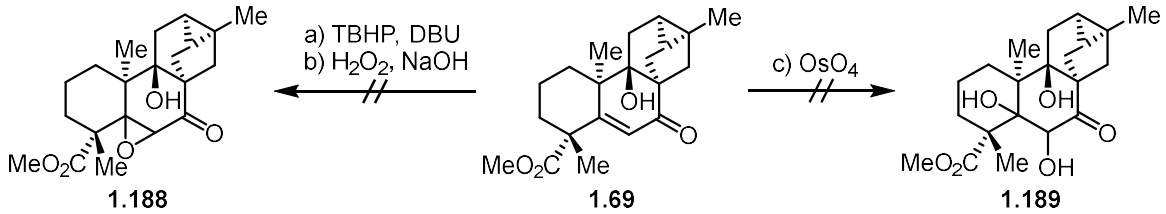
[a]Assigned by analysis of the ^{1}H NMR of the unpurified product mixture and by LC/MS.

[90] Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem. Int. Ed.* **1985**, *24*, 319–320.

[91] Diene **1.187** was assigned by analysis of the ^{1}H NMR of the unpurified product mixture and by LC/MS.

[92] For related structures which include a silyl 1-cyclohexenyl ether or methyl 1-cyclohexenyl ether, see: (a) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420–4423 (4.51 ppm, OTBS); (b) Schultz, A. G.; Plummer, M.; Taveras, A. G.; Kullnig, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 5547–5555 (4.85 ppm, OMe); (c) Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L.-Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244–3254 (4.26 ppm, OMe).

We next focused on oxidations of δ-hydroxydiosphenol **1.70** (Scheme 1.31). Methods for preparation of diosphenols from the corresponding enones include epoxidation of the double bond followed by rearrangement under acidic conditions and dihydroxylation and subsequent elimination of the β-hydroxy group.[93,94] To this end, we subjected enone **1.69** to *tert*-butylhydroperoxide (TBHP) and DBU, which only returned starting material (Scheme 1.36). The same result was observed under WEITZ–SCHEFFER conditions (H_2O_2, NaOH).[95] Also, treatment of enone **1.69** with osmium tetroxide and TMEDA did not afford triol **1.191**.

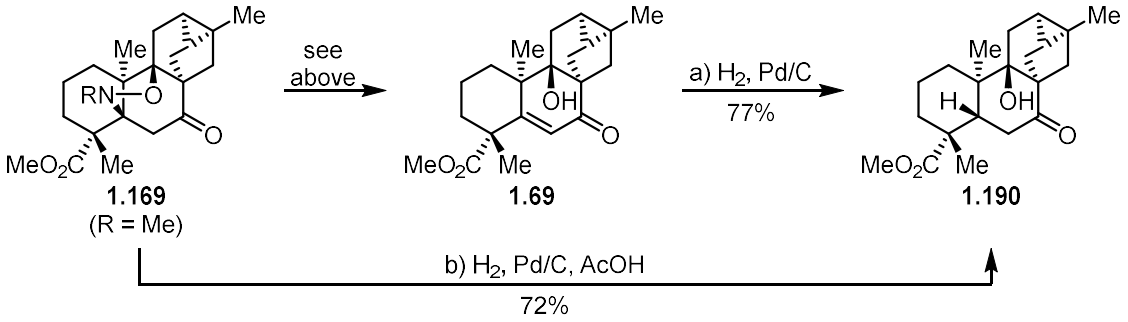


Scheme 1.36. Attempted oxidations of enone **1.69** *via* nucleophilic epoxidation or dihydroxylation. Reagents and conditions: (a) *tert*-butylhydroperoxide (TBHP), DBU, CH_2Cl_2, r.t.; (b1) aq H_2O_2, NaOH, THF, r.t.; (b2) aq H_2O_2, NaOH, THF–H_2O, 50 °C; (c) OsO_4, TMEDA, CH_2Cl_2, –78 °C to r.t.

After all oxidative functionalizations of enone **1.69** had failed to deliver the natural product, we decided to reduce the enone to the corresponding saturated ketone **1.190**, which would allow for alternative oxidation strategies. Hydrogenation of **1.69** in the presence of palladium on carbon afforded ketone **1.190** in 77% yield as a single diastereomer (Scheme 1.37). **1.190** could also be obtained from isoxazolidine **1.169** directly *via* hydrogenation in the presence of stoichiometric amounts of palladium on carbon in ethyl acetate and acetic acid at 80 °C *via* a cascade of reductive *N-O* cleavage, methylamine elimination and hydrogenation of the resulting enone. Both intermediates were observed when the reaction was not run to completion. The configuration of the newly formed

[93] Kravina, A. G.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2018**, *57*, 13159–13162.
[94] Ciattini, P.; Morera, E.; Ortar, G. *Synth. Commun.* **1992**, *22*, 1949–1952.
[95] Weitz, E.; Scheffer, A. *Ber. Dt. Chem. Ges.* **1921**, *54*, 2327–2344.

stereocenter in ketone **1.190** was assigned based on a computed structure of enone **1.69** and the directing effect of the nearby hydroxy group.[96,97]

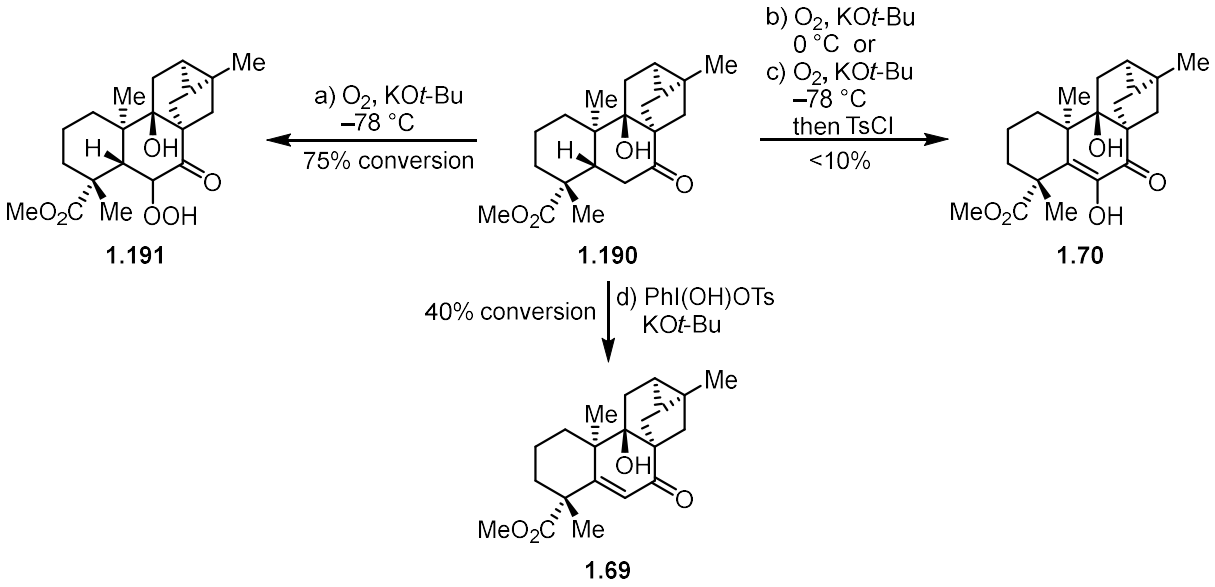


Scheme 1.37. (A) Synthesis of **1.190** *via* hydrogenation of isoxazolidine **1.169** or enone **1.69**. Reagents and conditions: (a) H_2 (1 atm), Pd/C (30 mol%), EtOAc, r.t., 77%; (b) H_2 (1 atm), Pd/C, EtOAc–AcOH (4:1), 80 °C, 72%.

As a first attempt for the oxidation of ketone **1.190** to diosphenol **1.70**, **1.190** was treated with potassium *tert*-butoxide in THF under an atmosphere of oxygen at –78 °C, which gave rise to hydroperoxide **1.191** (Scheme 1.38). After increasing the temperature to 0 °C, only traces of diosphenol **1.70** were observed in the ^{1}H NMR spectrum of the unpurified product mixture. Also, treatment of hydroperoxide **1.191** *in situ* with tosyl chloride at –78 °C only delivered traces of **1.70** in a complex mixture. An attempt to oxidize **1.190** using KOSER's reagent (PhI(OH)OTs) and potassium *tert*-butoxide led to 40% conversion to enone **1.69** but no other oxidation products were observed by analysis of the ^{1}H NMR spectrum of the unpurified product mixture. The reaction presumably proceeds *via* α-oxidation of ketone **1.190** followed by elimination to give enone **1.69**.

[96] The structure of enone **1.69** was calculated using Chem3D, which uses molecular mechanics (MM2) calculations for minimization of steric energy. In the calculated structure, the γ-methyl and γ'-methyl ester are positioned pseudo-axially and block hydrogenation from the bottom face of the olefin.

[97] For hydroxy-directed hydrogenations, see: Thompson, H. W. *J. Org. Chem.* **1971**, *36*, 2577–2581.

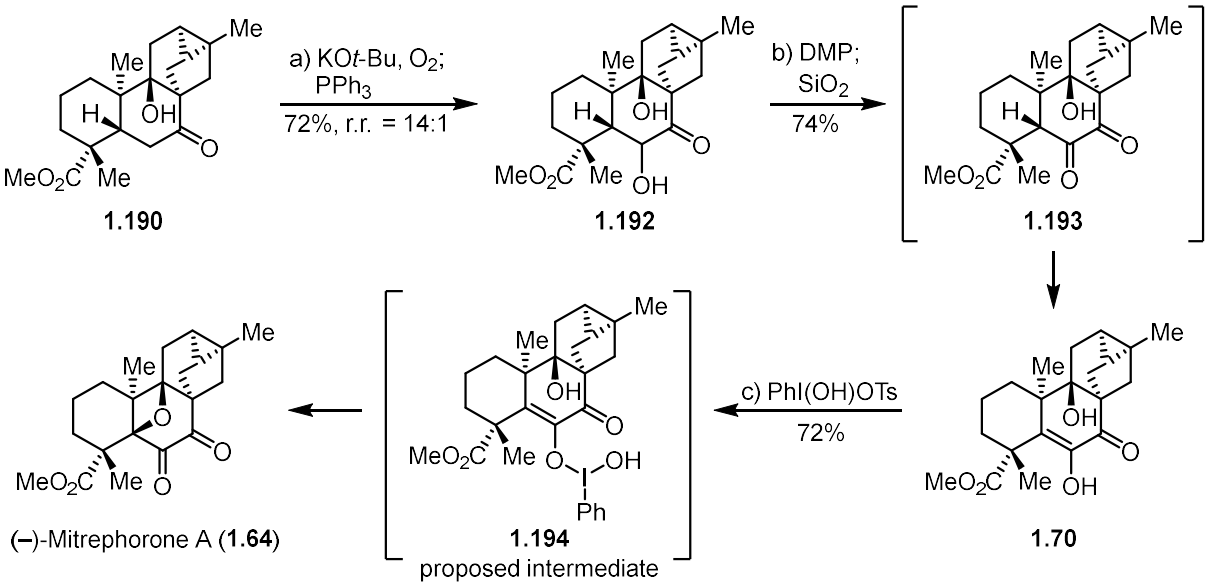


Scheme 1.38. Attempted oxidations of ketone **1.190** to diosphenol **1.70**. Reagents and conditions: (a) O_2 (1 atm), KO*t*-Bu, THF, –78 °C, 75% conversion; (b) O_2 (1 atm), KO*t*-Bu, THF, 0 °C, <5%; (c) O_2 (1 atm), KO*t*-Bu, THF, –78 °C, then TsCl, <10%; (d) PhI(OH)OTs, KO*t*-Bu, DMSO, r.t.

Next, we turned to the sequential oxidation of ketone **1.190** *via* α-hydroxyketone **1.192**. To this end, **1.190** was treated with KHMDS and MoOPH.[84] α-Hydroxyketone **1.192** was obtained as an inconsequential 14:1 mixture with its regioisomeric α-hydroxyketone but even with a large excess of both reagents, only ~50% conversion of **1.190** was observed.[98] Alternatively, forming hydroperoxide **1.191** with potassium *tert*-butoxide and oxygen and quenching with triphenylphosphine at –78 °C gave rise to **1.192** in 72% yield (Scheme 1.39).[99] Oxidation of **1.192** with DMP led to the formation of the corresponding 1,2-diketone **1.193**, which tautomerized to diosphenol **1.70** on silica gel.

[98] The regioisomer is formed by tautomerization of **1.192**.
[99] Paquette, L. A.; Hofferberth, J. E. *J. Org. Chem.* **2003**, *68*, 2266–2275.

Finally, diosphenol **1.70** was subjected to KOSER's reagent in the presence of sodium bicarbonate in CH_2Cl_2 at room temperature (Scheme 1.39).[100,101] The solution immediately turned from colorless to bright yellow, indicating the formation of a 1,2-diketone. After two minutes, the reaction was quenched with a mixture of aqueous sodium thiosulfate and sodium bicarbonate and the final product (–)-mitrephorone A (**1.64**) was isolated in 72% yield. We surmise that this oxidation proceeds *via* intermediate **1.194** and an S_N2' displacement of the iodine by the hydroxy group.



Scheme 1.39. Completion of the synthesis of (–)-mitrephorone A (**1.64**). Reagents and conditions: (a) KO*t*-Bu, O_2 (1 atm), THF, –78 °C, then PPh_3, –78 °C to r.t., 72%; (b) DMP, *t*-BuOH, CH_2Cl_2; SiO_2, hexane–EtOAc (3:1), 74%; (c) PhI(OH)OTs, $NaHCO_3$, CH_2Cl_2, 72%.

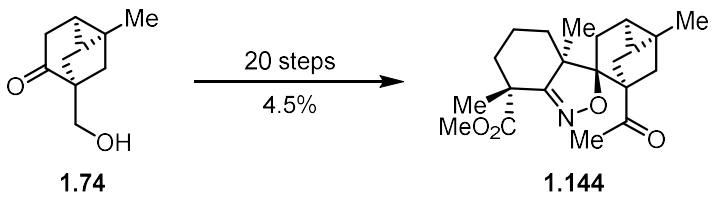
[100] For a discussion on hypervalent iodine-mediated oxidations of carbonyls, see: Arava, S.; Kumar, J. N.; Maksymenko, S.; Iron, M. A.; Parida, K. N.; Fristrup, P.; Szpilman, A. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 2599–2603.

[101] This reaction was carried out for the first time under base-free conditions by MATTHIEU RICHTER, who prepared diosphenol **1.70** *via* an alternative route.

2.4. Route Optimization

2.4.1. 1,4-Semihydrogenation of 1,3-Dienes

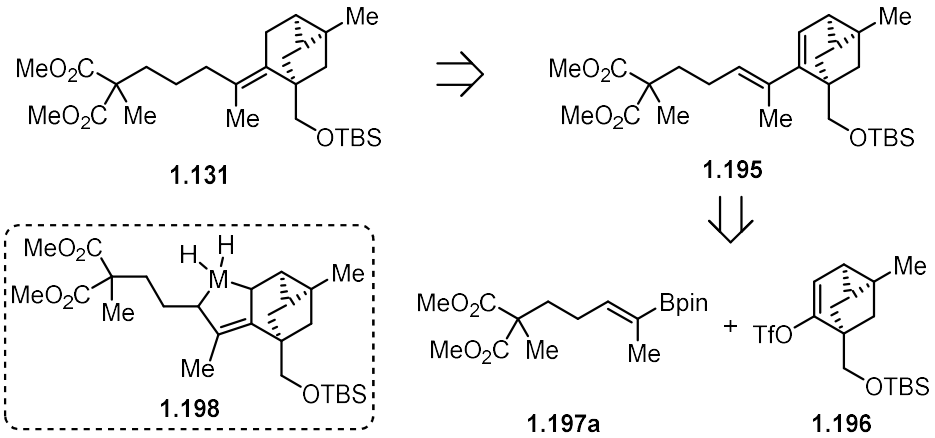
After the successful synthesis of (–)-mitrephorone A (**1.64**), we set out to optimize the route. We did not expect that we could significantly improve the first part of the synthesis, which is constructed around the enantioselective DIELS–ALDER cycloaddition reaction and homoquadricyclane rearrangement, and the end-game, for which we tested various conditions and only the final ones worked well. However, the middle part of the synthesis appeared lengthy. Here, the conversion of hydroxyketone **1.74** to isoxazoline **1.144** was achieved in a linear sequence of 20 steps and 4.5% overall yield (Scheme 1.40). Within this route, we identified three major aspects which we sought to optimize: (1) The CLAISEN rearrangement afforded the tetrasubstituted olefin in only 2.3:1 diastereomeric ratio (Section 2.2.3.2.). (2) The route included two protection and deprotection steps each of the primary alcohol in **1.74**. In particular, we wanted to avoid deprotection and reprotection before and after the enzymatic desymmetrization step (Section 2.3.2.). We surmised this may be achieved either by changing the protecting group or by transforming the primary alcohol to the corresponding methyl ketone at an earlier stage of the synthesis. (3) If we could identify an alternative approach to the synthesis of the tetrasubstituted double bond, it may be possible to couple hydroxyketone **1.74** with a chiral, enantioenriched building block so that the synthesis could be performed in a more convergent manner, in which the enzymatic desymmetrization would not be part of the longest linear sequence.



1.74 1.144

Scheme 1.40. Synthesis of isoxazoline **1.148** from β-hydroxyketone **1.74**.

As described in Section 2.2.3., we had already tested various approaches for the synthesis of the tetrasubstituted olefin. As an alternative, we identified the 1,4-semihydrogenation of 1,3-dienes as a reaction, which was reported to afford olefins with excellent stereoselectivity.[102] 1,3-Dienes are readily available *via* sp^2–sp^2 cross-coupling reactions. Accordingly, tetrasubstituted olefin **1.131**, which has been prepared in eight steps from hydroxyketone **1.74** *via* the first generation route, was disconnected to 1,3-diene **1.195** and further to vinyl triflate **1.196** and vinyl boronate **1.197a** (Scheme 1.41). The 1,4-semihydrogenation is thought to proceed *via* metallacyclopentene **1.198**, which provides a rational for the high stereoselectivities reported for this transformation.



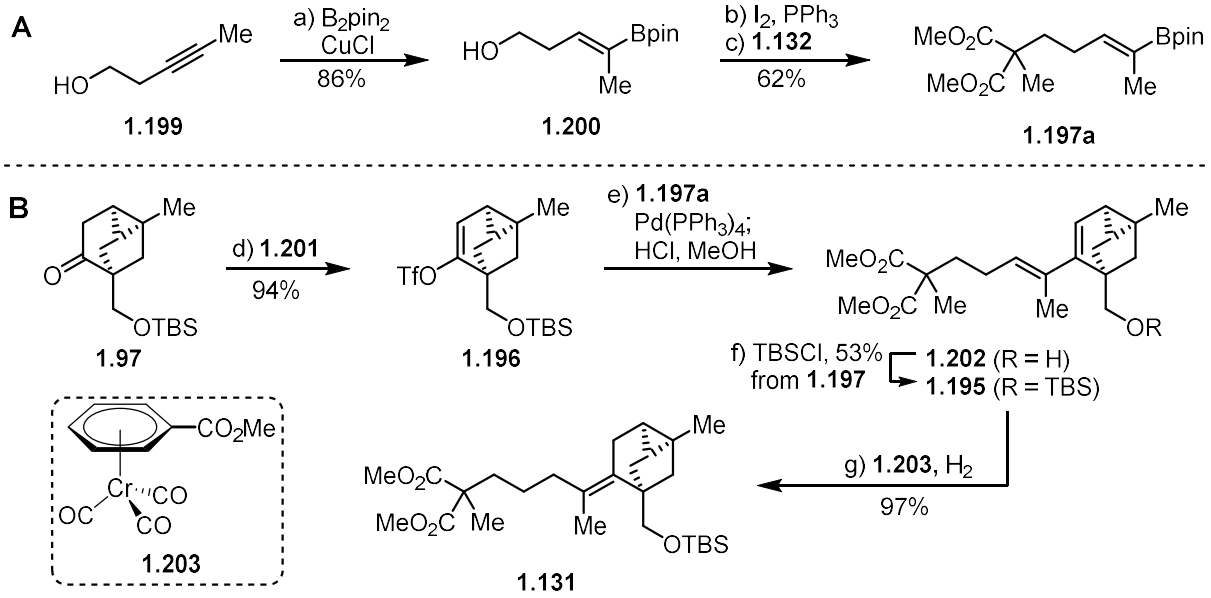
Scheme 1.41. Retrosynthetic analysis of malonate **1.131** *via* 1,4-semihydrogenation of 1,3-diene **1.195**. Box: Structure of metallacyclopentene **1.198**.

Vinyl boronate **1.197a** was prepared *via* copper-catalyzed and hydroxy-directed hydroboration of pent-3-yn-1-ol (**1.199**) (Scheme 1.42).[103] APPEL reaction of alcohol **1.200** followed by alkylation with dimethyl 2-methylmalonate (**1.132**) afforded vinyl boronate building block **1.197a** in 62% yield over two steps. Vinyl triflate **1.196** was prepared from ketone **1.97** using COMINS' reagent (**1.201**) and KHMDS.[104] These two building blocks were then subjected to

[102] Frankel, E. N.; Selke, E.; Glass, C. A. *J. Am. Chem. Soc.* **1968**, *90*, 2446–2448.
[103] Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12444–12448.
[104] Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740–1741.

catalytic amounts of $Pd(PPh_3)_4$ and aqueous sodium bicarbonate at 80 °C.[105] Cross-coupling product **1.195** was obtained as a 1:4 mixture with its TBS-deprotected analogue **1.202**. In order to obtain alcohol **1.202** as a single product, the cross-coupling reaction was quenched with HCl in methanol at 0 °C. TBS-reprotection of alcohol **1.202** afforded 1,3-diene **1.197** in 53% over two steps. Varying the palladium catalyst, e.g. employing BUCHWALD's precatalysts, or changing the base to potassium carbonate did not improve the yield of the reaction.[106]

Subjecting 1,3-diene **1.195** to 20 mol% of chromium catalyst **1.203** in acetone at 120 °C under 70 bar of hydrogen led to 37% conversion of **1.195** to desired tetrasubstituted olefin **1.131**. Increasing the catalyst loading to 50 mol% resulted in full conversion of **1.195**, and **1.131** was isolated in 97% yield as a single

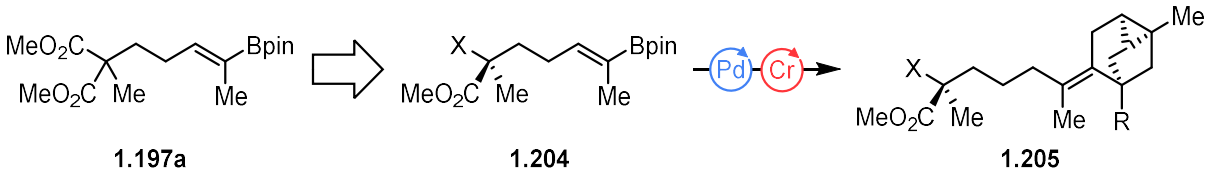


Scheme 1.42. (A) Synthesis of vinyl boronate **1.197a**. (B) Synthesis of malonate **1.131** *via* 1,4-semihydrogenation of 1,3-diene **1.195** mediated by chromium catalyst **1.203**. Reagents and conditions: (a) B_2pin_2, CuCl (10 mol%), PPh_3 (12 mol%), KO*t*-Bu (40 mol%), MeOH, THF, 0 °C to r.t., 86%; (b) I_2, PPh_3, imidazole, CH_2Cl_2, r.t., 91%; (c) dimethyl 2-methylmalonate (**1.132**), NaH, DMF, 0 °C to r.t., 68%; (d) COMINS' reagent (**1.203**), KHMDS, THF, –78 °C to r.t., 94%; (e) **1.197a**, $Pd(PPh_3)_4$ (5 mol%), aq $NaHCO_3$, DME, 80 °C, then 1 M HCl in MeOH, 0 °C; (f) TBSCl, imidazole, DMAP (10 mol%), CH_2Cl_2, 53% over two steps; (g) **1.203** (50 mol%), H_2 (70 bar), acetone, 120 °C, 97%.

[105] Su, N.; Theorell, J. A.; Wink, D. J.; Driver, T. G. *Angew. Chen. Int. Ed.* **2015**, *54*, 12942–12946.
[106] Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161–4166.

geometric isomer. No overreduction to the saturated analogue was observed. Following this new route, malonate **1.131** was prepared in five steps and 44% overall yield compared to eight steps and 24% yield in the initial route.

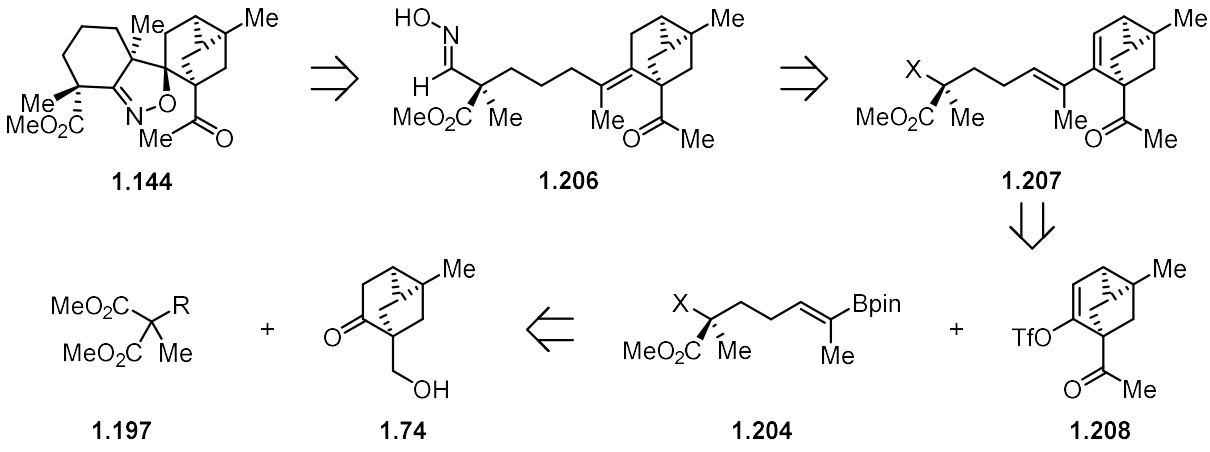
The highly efficient sequence of SUZUKI–MIYAURA cross-coupling and 1,4-semihydrogenation of the intermediate 1,3-diene using achiral vinyl boronate **1.197a** prompted us to further explore this approach using chiral, enantioenriched vinyl boronates **1.204** (Scheme 1.43). This would render the synthesis more convergent as the malonate desymmetrization would be carried out prior to cross-coupling.



Scheme 1.43. Envisioned convergent approach to tetrasubstituted olefins **1.205**.

2.4.2. Synthesis and Use of Chiral, Enantioenriched Vinyl Boronates

In this modified approach, isoxazoline **1.144** was derived from 1,3-diene **1.207** *via* oxime **1.206** (Scheme 1.44). Residue X in **1.207** would be a functional group which tolerates the SUZUKI–MIYAURA cross-coupling and 1,4-semihydrogenation conditions and could be transformed into the oxime



Scheme 1.44. Retrosynthetic analysis of **1.144** *via* chiral and enantioenriched vinyl boronates **1.204**.

thereafter. 1,3-Diene **1.207** was further disconnected to vinyl triflate **1.208** and vinyl boronate **1.204** as before. The coupling of two enantioenriched but not enantiopure building blocks gives rise to a mixture of diastereomers. The diastereomeric ratio depends on two factors: (1) The enantiomeric excess of the two coupling partners, and (2) the diastereoselectivity of the reaction, i.e. if one enantiomer of the first building block preferentially reacts with one enantiomer of the other building block. In the context of this synthesis, the distant stereocenter in vinyl boronates **1.204** was not expected to induce significant diastereoselectivity in the cross-coupling reaction. In any case, a high enantiomeric excess of **1.204** and **1.208** was essential to obtain diene **1.207** in a high diastereomeric ratio. Vinyl triflate **1.208** would be derived from hydroxyketone **1.74**, which was prepared in 95% ee in Section 2.2.2. We envisioned preparing vinyl boronate **1.204** *via* enzymatic desymmetrization of dimethyl malonates **1.197**. The substituent R in **1.197** will either already include the vinyl boronate or a synthetic precursor.

MASTERSON and BJÖRKLING have reported that the enantiomeric excess and absolute configuration of the resulting malonic acid monoesters **1.209** in the pig liver esterase-mediated monohydrolysis of 2-methyl-2-alkylmalonates **1.197** depend on the size of the substituent R in **1.197**.[70] This can be rationalized using a JONES active site model (Figure 1.4).[107] This model splits the active site of the pig liver esterase in five compartments – two polar ones, P_B and P_F, and three hydrophobic ones, H_S, H_L, and a third one which is not depicted in Figure 1.4 and is found out of plane towards the reader. When **1.197** is bound in the active pocket, the two esters are located in the two polar compartments and the methyl group is

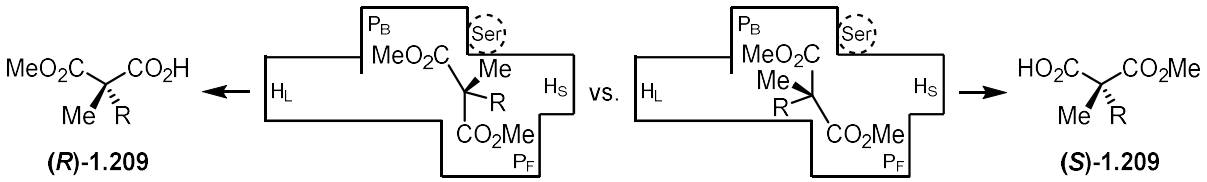
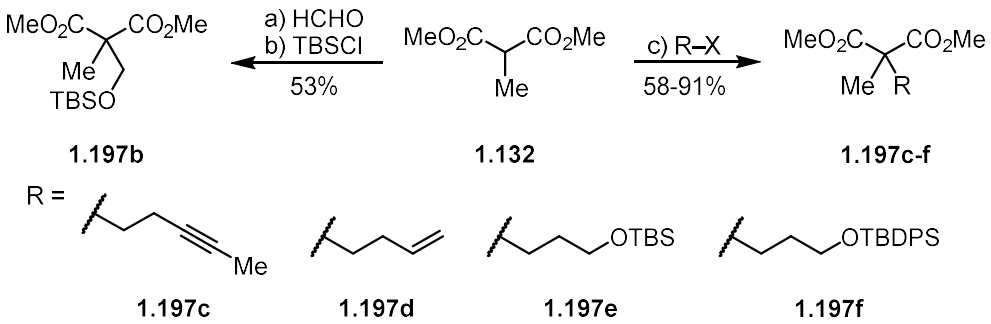


Figure 1.4. JONES active site model for pig liver esterase-mediated malonate hydrolysis and fit of two possible conformational arrangements of malonates **1.197** in the active pocket.

[107] Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946–4952.

placed in the fifth compartment. Depending on its size, the R group is located either in H_S or H_L. Small R groups are preferentially found in H_S while larger groups will be located in H_L. The ester located in P_B will be hydrolyzed, which is catalyzed by a nearby serine. As the two arrangements depicted in Figure 1.4 will lead to the formation of different enantiomers of malonic acid monoesters **1.209**, this model explains the observed switch in enantioselectivity.

With these observations in mind, we prepared a series of five dimethyl malonates **1.197b-f** in addition to vinyl boronate-containing malonate **1.197a**. All side chains in **1.197b-f** could potentially be transformed into the required vinyl boronate. In this context, alkynes and terminal olefins are transformed into vinyl boronates *via* hydroboration or cross-metathesis, respectively.[108,109] Protected alcohols generally are versatile intermediates in organic synthesis, despite their elaboration into vinyl boronates requiring a multi-step sequence. Silyloxymethyl substituted malonate **1.197b** was prepared according to literature precedent *via* hydroxymethylation of dimethyl 2-methylmalonate (**1.132**) with aqueous formaldehyde followed by TBS protection in 53% yield over two steps



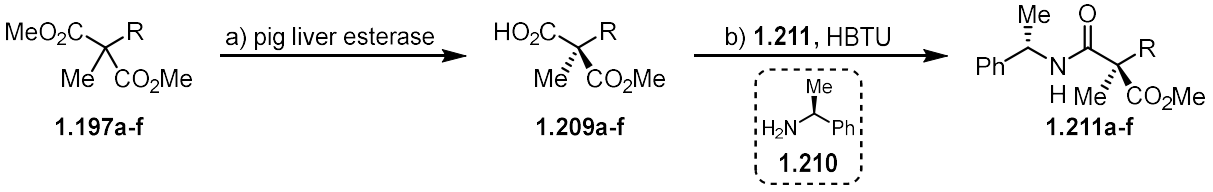
Scheme 1.45. Synthesis of α,α-disubstituted dimethylmalonates **1.197b-f**. Reagents and conditions: (a) 37% aq formaldehyde, Et_3N (5 mol%), DMF, 50 °C; (b) TBSCl, imidazole, DMAP (10 mol%), MeCN, 53% over two steps; (c) R–I or R–Br, KI (50 mol%) or R–OTs, KI (50 mol%), NaH, DMF, 4 °C or r.t. or 80 °C, 58-91%.

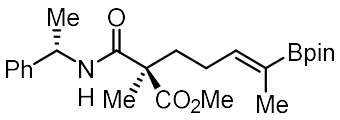
[108] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255.
[109] Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3172–3174.

(Scheme 1.45).[110] The other four malonates **1.197c-f** were prepared *via* alkylation of **1.132** with the respective alkyl iodides in 58-91% yield.[111,112]

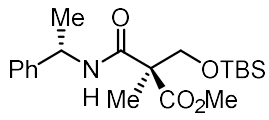
We commenced our study on malonate desymmetrization with silyloxymethyl-substituted malonate **1.197b**, which has been previously employed in pig liver esterase-mediated malonate monohydrolysis by KEESE.[110] Subjecting **1.197b** to pig liver esterase (PLE) in 0.1 M pH7 sodium phosphate buffer–DMSO (10:1) led to the formation of the corresponding malonic acid monoester **1.209b** (Table 1.8). For quick determination of enantioselectivity in this reaction, **1.209b** was subsequently coupled with enantiopure (*S*)-phenylethanamine (**1.210**) using HBTU as a coupling reagent. The diastereomeric ratio of the resulting amide **1.211b** was determined by analysis of the ^{1}H NMR spectrum (d.r. ~ 37:1). This ratio is equivalent to the enantiomeric

Table 1.8. Enzymatic desymmetrization of α,α-disubstituted malonates **1.197** and amide coupling with (*S*)-phenylethanamine **1.210**.

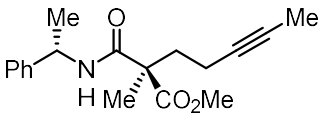




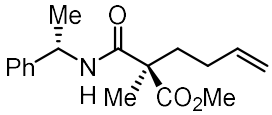
1.211a
(9%, d.r. = 7:1, 75% ee*)



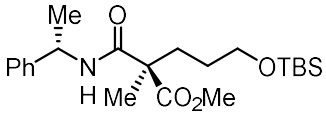
1.211b
(39%, d.r. ~ 37:1, 95% ee*)



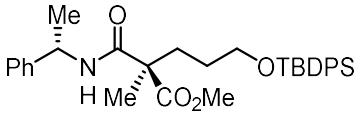
1.211c
(74%, d.r. = 3:2, 20% ee*)



1.211d
(97%,d.r. = 1.6:1, 23% ee*)



1.211e
(67%, d.r. > 50:1, >95% ee*)



1.211f
not formed

Reagents and conditions: (a) pig liver esterase, aq NaOH, 0.1 M pH 7 sodium phosphate buffer–DMSO (10:1), r.t.; (b) **1.210**, HBTU, DIPEA, DMF, r.t. *Enantiomeric excesses correspond to the intermediate malonic acid monoesters **1.209**.

[110] Luyten, M.; Müller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250–1254.
[111] Craig, D.; Funai, K.; Gore, S. J.; Kang, A.; Mayweg, A. V. W. *Org. Biomol. Chem.* **2011**, *9*, 8000–8002.
[112] Some of the alkyl iodides were generated *in situ* from the corresponding alkyl bromides or tosylates and potassium iodide.

ratio of the intermediate carboxylic acid **1.209b** and corresponds to 95% ee which is in full agreement with KEESE's result. To validate the coupling with **1.210** for the determination of the enantioselectivity of the desymmetrization reaction, **1.197b** was hydrolyzed racemically using sodium hydroxide followed by amide coupling to give **1.211b** as a 1:1 mixture of diastereomers.

Analogously, the other five malonates **1.197** were subjected to the desymmetrization/amide coupling sequence (Table 1.8). Vinyl boronate-containing amide **1.211a** was obtained in 7:1 d.r. but very low yield (9%) presumably due to instability of the vinyl boronate under the hydrolysis conditions. Amides **1.211c** and **1.211d** were isolated in 74% and 97% yield, respectively, but low diastereomeric ratio (d.r. = 3:2 and 1.6:1, respectively). The highest enantioselectivity was observed for the desymmetrization of **1.197e**. The corresponding amide **1.211e** was obtained in 67% yield and >50:1 d.r, which corresponds to >95% ee.[113] Interestingly, no conversion was observed for the analogous TBDPS-protected substrate **1.197f**. This lack of reactivity could be attributed to either insolubility of the substrate in the phosphate buffer–DMSO mixture or a poor fit of the substrate into the enzyme pocket. In fact, none of malonates **1.197** is well soluble in the reaction medium and complete dissolving of the substrates indicated high to full conversion. For all substrates **1.197**, racemic hydrolysis using sodium hydroxide followed by coupling with **1.210** afforded amides **1.211** in 1:1 d.r. for comparison purposes.

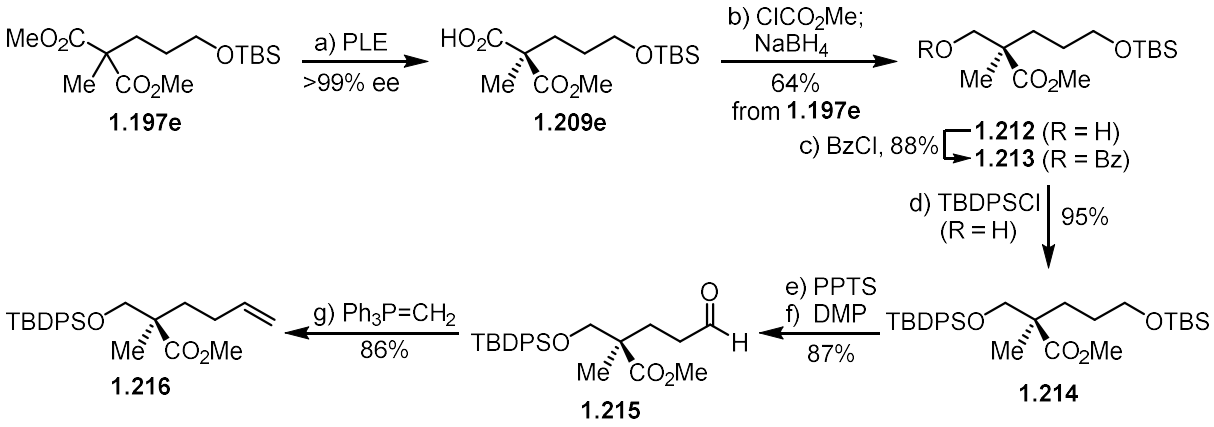
The high yield and enantioselectivity observed in the hydrolysis of malonate **1.197e** prompted us to use it as the starting point for our studies towards the synthesis of enantioenriched vinyl boronates. Following literature reports, the absolute configuration of the intermediate malonic acid monoester **1.209e** was tentatively assigned as (*R*).[70,110,114] Accordingly, the carboxylic acid in **1.209e**

[113] The used assay has its limitations for the precise determination of very high diastereomeric ratios.

[114] In the study by BJÖRKLING with 2-methyl-2-*n*-alkylmalonates,[70a] the major enantiomer was (*S*)-configured for ethyl to butyl substituents and (*R*)-configured for pentyl to heptyl. We did not determine the absolute configuration at this step but will assign it at a later stage by comparison with intermediates prepared on previous routes.

needed to be transformed into an oxime precursor X. To this end, the carboxylic acid was reduced chemoselectively to the corresponding alcohol **1.212** using methyl chloroformate and sodium borohydride as described in Section 2.3.2. (Scheme 1.46). For a more accurate determination of the enantiomeric excess of malonic acid monoester **1.209e**, alcohol **1.212** was converted into the corresponding benzoate **1.213** in 88% yield. The enantiomers were separable by chiral HPLC (>99% ee).

Alcohol **1.212** was protected as its TBDPS-ether **1.214** in 95% yield (Scheme 1.46). The TBS-ether in **1.214** could be cleaved selectively using 20 mol% PPTS in ethanol.[115] Oxidation with DMP followed by WITTIG olefination afforded terminal olefin **1.216** in 75% yield over three steps.

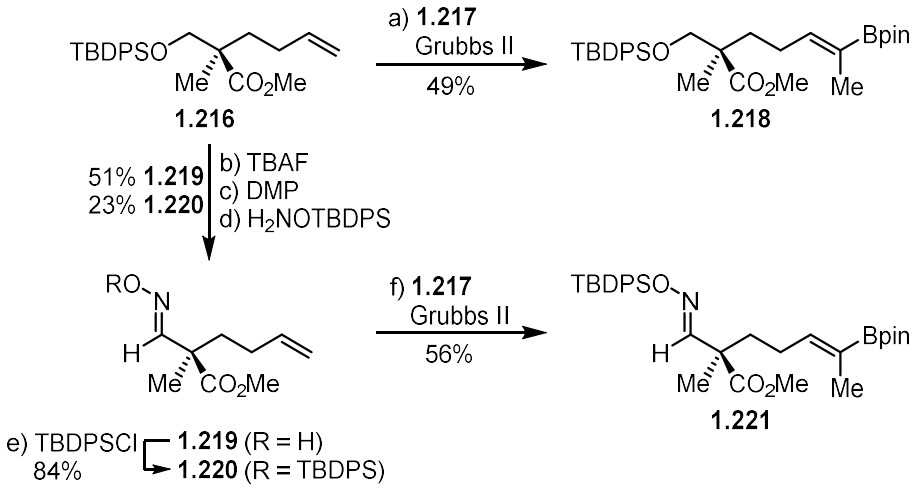


Scheme 1.46. Synthesis of terminal olefin **1.216**. Reagents and conditions: (a) pig liver esterase, aq NaOH, 0.1 M pH7 sodium phosphate buffer–DMSO (10:1), r.t., >99% ee; (b) $ClCO_2Me$, Et_3N, THF, 0 °C to r.t.; $NaBH_4$, MeOH, 0 °C, 64% over two steps; (c) BzCl, Et_3N, DMAP (20 mol%), CH_2Cl_2, r.t., 88%; (d) TBDPSCl, imidazole, DMAP (20 mol%), CH_2Cl_2, r.t., 95%; (e) PPTS (20 mol%), EtOH, r.t.; (f) DMP, *t*-BuOH, CH_2Cl_2, r.t., 87% over two steps; (g) $MePPh_3Br$, KO*t*-Bu, THF, r.t., 86%.

With a scalable and high yielding synthesis of terminal olefin **1.216** in hand, we subsequently focused on the preparation of vinyl boronates. Cross-metathesis of **1.216** with isopropenylboronic acid pinacol ester (**1.217**) in the presence of 10 mol% Grubbs 2nd generation catalyst afforded vinyl boronate **1.218** in 49% yield (Scheme 1.47). Additionally, the silyl ether in **1.216** was transformed into

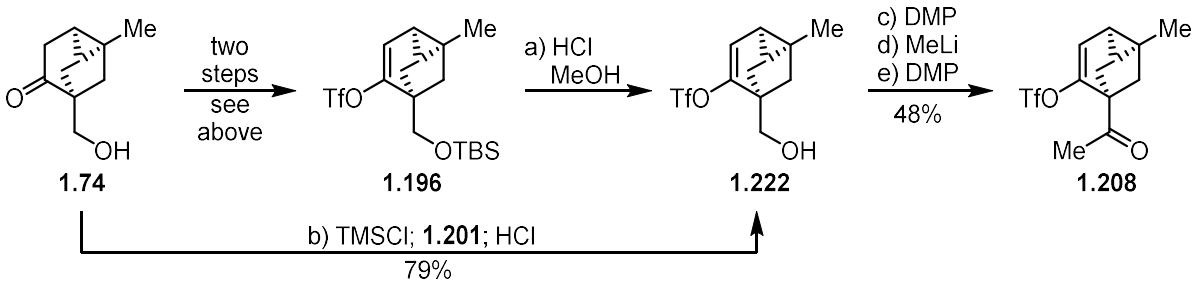
[115] Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19–22.

the corresponding TBDPS-protected oxime **1.219** *via* deprotection with TBAF, oxidation with DMP, and oxime formation with *O*-TBDPS hydroxylamine in 51% yield over three steps along with 23% yield of unprotected oxime **1.220**. The latter was converted into its silyl ether **1.219** in 84% yield. Cross-metathesis of **1.219** with **1.217** gave vinyl boronate **1.221** in 56% yield.



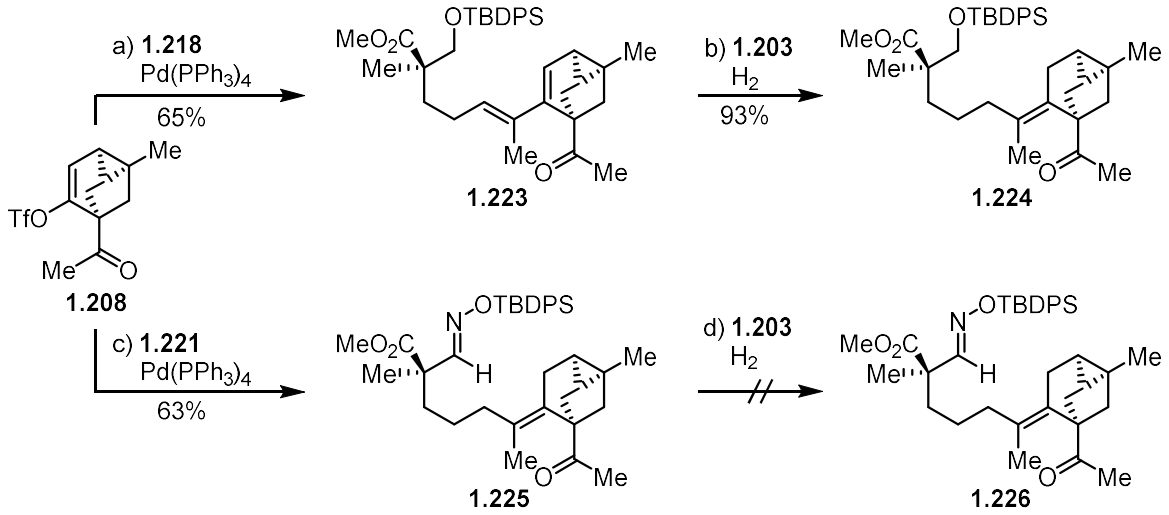
Scheme 1.47. Synthesis of vinyl boronates **1.218** and **1.221**. Reagents and conditions: (a) isopropenylboronic acid pinacol ester (**1.217**), Grubbs 2nd generation catalyst (10 mol%), CH_2Cl_2, 50 °C, 49%; (b) TBAF, THF, r.t., 85%; (c) DMP, *t*-BuOH, CH_2Cl_2, r.t.; (d) H_2NOTBDPS, EtOH–pyr (8:1), r.t., 60% **1.219**, 27% **1.220**; (e) TBDPSCl, imidazole, DMAP (20 mol%), CH_2Cl_2, r.t., 84%; (f) isopropenylboronic acid pinacol ester (**1.217**), Grubbs 2nd generation catalyst (10 mol%), CH_2Cl_2, 50 °C, 56%.

Next, we concerned ourselves with the synthesis of vinyl triflate **1.208**. In the cross-coupling reaction of silyl ether-containing vinyl triflate **1.196**, the silyl ether was cleaved and had to be reformed (Section 2.4.1.). Therefore, we envisioned transforming the hydroxy group in **1.74** to the corresponding methyl ketone prior to cross-coupling. Initially, the silyl ether in **1.196** was cleaved using methanolic HCl (Scheme 1.48). In an optimized procedure, vinyl triflate **1.222** was prepared from hydroxyketone **1.74** in a one-pot procedure including transient TMS-protection of the primary alcohol, vinyl triflate formation with KHMDS and COMINS' reagent (**1.201**) and silyl ether cleavage with aqueous HCl in 79%. The hydroxy group in **1.222** was converted into the corresponding methyl ketone **1.208** in three steps *via* oxidation with DMP, methyllithium addition and again oxidation with DMP in 48% overall yield.



Scheme 1.48. Synthesis of vinyl triflate **1.208**. Reagents and conditions: (a) HCl, MeOH, r.t., 64% combined with subsequent DMP oxidation; (b) TMSCl, imidazole, THF, r.t., then KHMDS, COMINS' reagent (**1.201**), –78 °C, then aq HCl, r.t., 79%; (c) DMP, *t*-BuOH, CH_2Cl_2, r.t., 92%; (d) MeLi, THF, –78 °C; (e) DMP, *t*-BuOH, CH_2Cl_2, r.t., 52% over two steps.

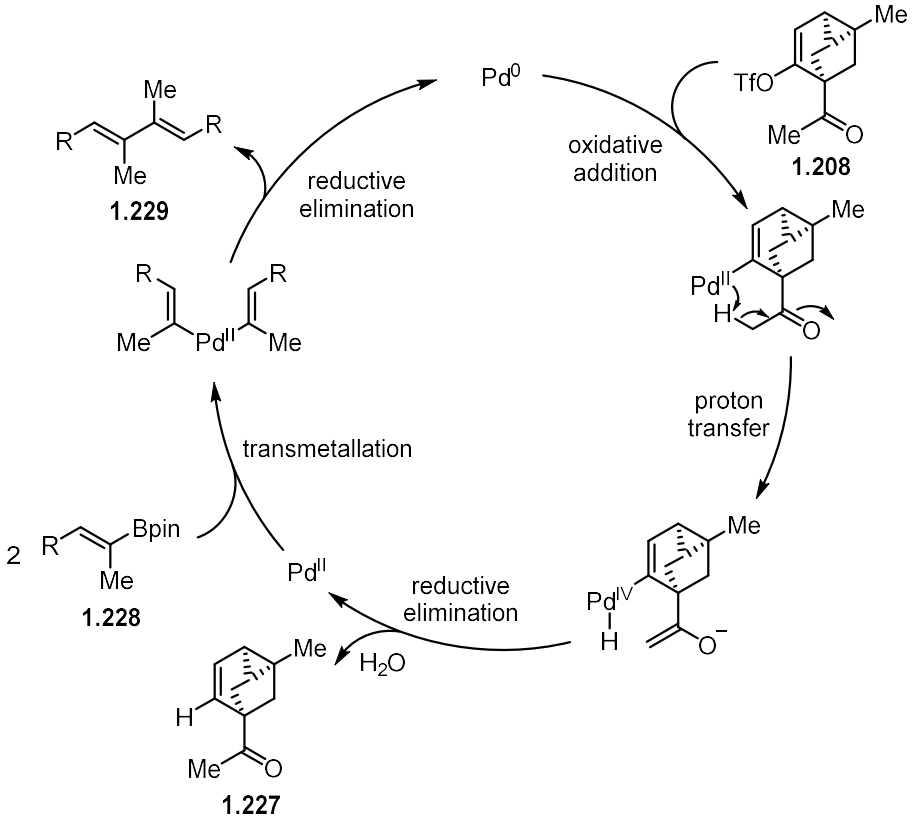
With vinyl triflate **1.208** and vinyl boronates **1.218** and **1.221** in hand, we turned our attention to the cross-coupling/1,4-semihydrogenation sequence. SUZUKI–MIYAURA cross-coupling of **1.208** and **1.218** under the same conditions as described in Section 2.4.1 ($Pd(PPh_3)_4$, aqueous $NaHCO_3$) afforded 1,3-diene **1.223** in 65% yield (Scheme 1.49). Subsequent 1,4-semihydrogenation gave tetrasubstituted olefin **1.224** in 93% as a single olefin isomer. Cross-coupling of **1.208** with oxime-containing vinyl boronate **1.221** delivered 1,3-diene **1.225** in 63% yield. Unfortunately, the 1,4-semihydrogenation did not afford any desired tetrasubstituted olefin **1.226**. A mixture of starting material and TBDPS-OH was



Scheme 1.49. Synthesis of tetrasubstituted olefin **1.224** and unsuccessful synthesis of **1.226**. Reagents and conditions: (a) **1.218**, $Pd(PPh_3)_4$ (2.5 mol%), aq $NaHCO_3$, DME, 85 °C, 65%; (b) $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (**1.203**, 50 mol%), H_2 (70 bar), acetone, 120 °C, 93%; (c) **1.221**, $Pd(PPh_3)_4$ (4 mol%), aq $NaHCO_3$, DME, 85 °C, 65%; (d) $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (**1.203**, 50 mol%), H_2 (70 bar), acetone, 120 °C.

isolated indicating instability of the protected oxime under the reaction conditions either *via* reductive *N–O* bond cleavage or hydrolytic *O–Si* cleavage.

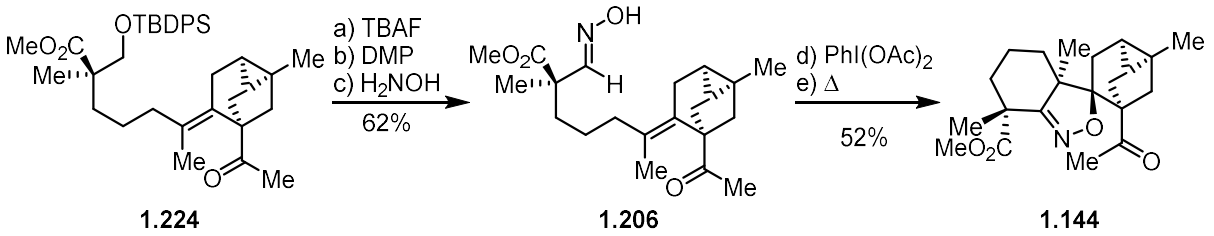
Interestingly, in the cross-couplings with vinyl triflate **1.208**, vinyl boronate homocoupling and vinyl triflate protodetriflation occured in a 1:1 ratio as side reactions.[116] This was not observed when silyl ether-containing vinyl triflate **1.196** was used. A plausible mechanism is depicted in Scheme 1.50. Oxidative addition of vinyl triflate **1.208** to Pd^0 is followed by deprotonation α to the ketone by palladium delivering a Pd^{IV} hydride *via* a six-membered ring transition state.[117] Reductive elimination gives protodetriflation product **1.227** and Pd^{II}. Transmetallation of two vinyl boronates **1.228** to the palladium and reductive elimination yields homocoupling product **1.229** and regenerates Pd^0.



Scheme 1.50. Proposed mechanistic cycle for the formation of **1.227** and **1.229**.

[116] The ratio was determined by analysis of the ^{1}H NMR of the unpurified product mixture.
[117] For a review on Pd^{IV} chemistry, see: Sehnal, P.; Taylor, J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824–889.

After the successful synthesis of tetrasubstituted olefin **1.224**, we set out to test the nitrile oxide cycloaddition on this new substrate. To this end, the silyl ether in **1.224** was transformed into the corresponding oxime **1.206** *via* deprotection with TBAF, oxidation with DMP and oxime formation with hydroxylamine hydrochloride in 62% overall yield (Scheme 1.51). Under the same conditions for oxidation of the oxime to the corresponding nitrile oxide and cycloaddition as described in Section 2.3.2 ($PhI(OAc)_2$; Δ), isoxazoline **1.144** was obtained in 52% yield.

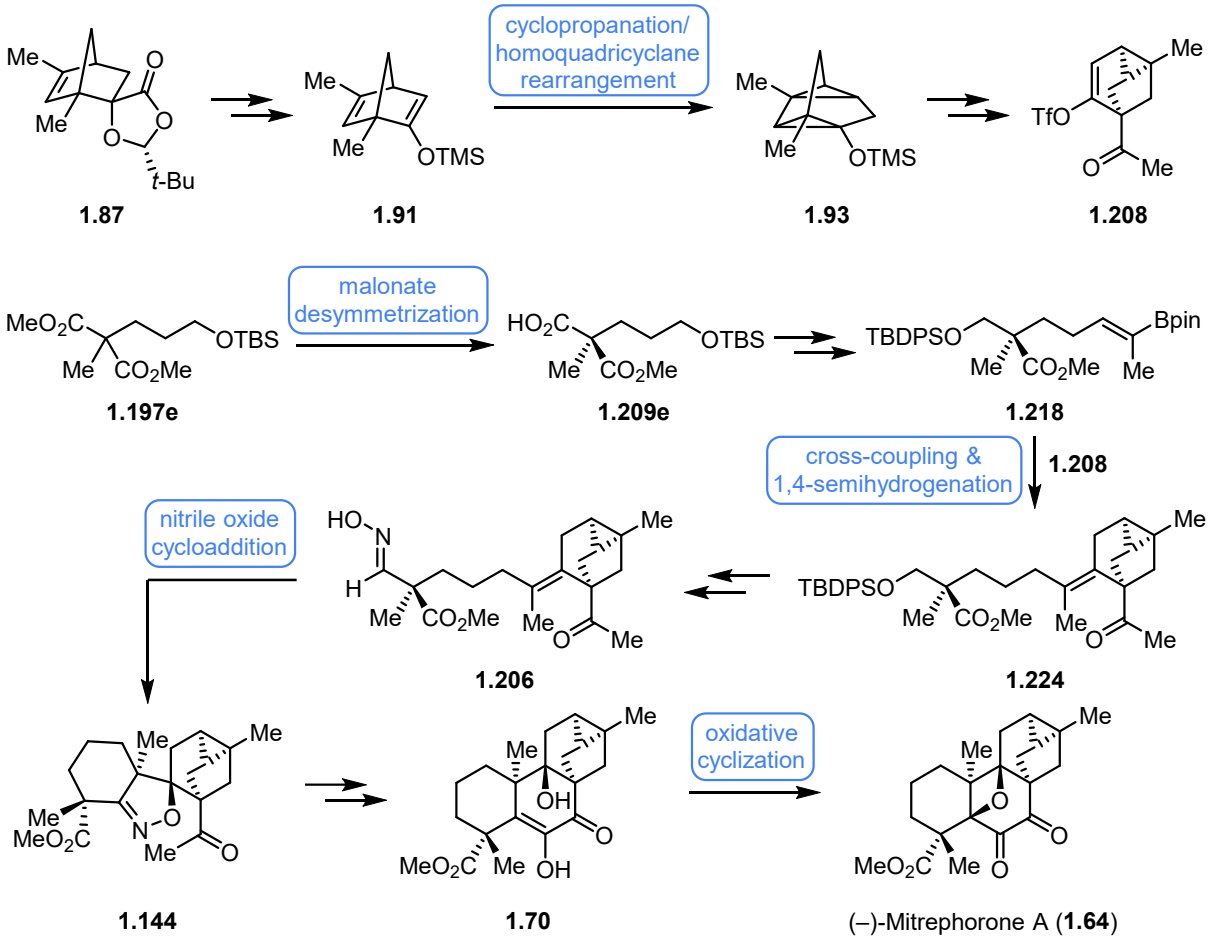


Scheme 1.51. Conversion of tetrasubstituted olefin **1.224** into isoxazoline **1.144**. Reagents and conditions: (a) TBAF, THF, r.t.; (b) DMP, *t*-BuOH, CH_2Cl_2, r.t., 73% over two steps; (c) $H_2NOH{\cdot}HCl$, EtOH–pyr (8:1), 85%; (d) $PhI(OAc)_2$, MeOH, 0 °C; (e) PhMe, reflux, 52% over two steps.

The successful implementation of chiral, enantioenriched vinyl boronate **1.218** in the cross-coupling/1,4-semihydrogenation sequence along with the conversion of the primary alcohol to the methyl ketone at an early stage of the synthesis completed our studies on the optimization of the total synthesis of (–)-mitrephorone A (**1.64**). Overall, these improvements have shortened the longest linear sequence from hydroxyketone **1.74** to isoxazoline **1.144** from 20 steps and 4.5% overall yield in the first generation route to eleven steps and 7.4% overall yield in the final route.

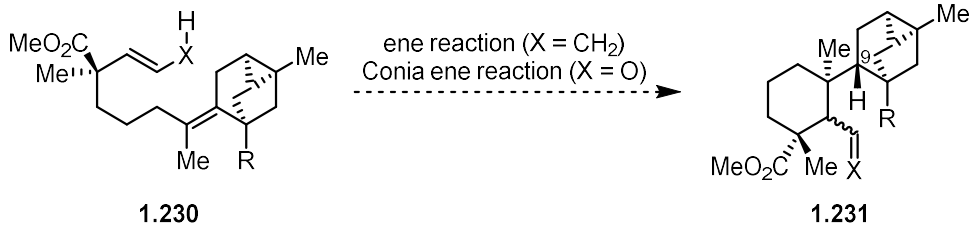
3. Conclusion and Outlook

In summary, we have developed a highly enantio- and diastereoselective synthesis of the *ent*-trachylobane diterpenoid (–)-mitrephorone A (**1.64**). Key features of the synthesis are a diastereoselective Diels–Alder cycloaddition to form **1.87**, a cyclopropanation/homoquadricyclane rearrangement cascade, a highly enantioselective pig liver esterase-mediated desymmetrization of malonate **1.197e**, a sequence of sp^2–sp^2 cross-coupling of vinyl triflate **1.208** and vinyl boronate **1.218** and 1,4-semihydrogenation of the resulting 1,3-diene for the highly stereoselective preparation of tetrasubstituted olefin **1.224**, a highly diastereoselective nitrile oxide cycloaddition, and a late-stage oxidative cyclization to form the oxetane.



Scheme 1.52. Summary of the total synthesis of (–)-mitrephorone A (**1.64**).

The synthesis commences with the preparation of the tricyclo[3.2.1.$0^{2,7}$]octane scaffold, which remains unchanged in most *ent*-trachylobane diterpenoids. Thus, our synthetic strategy allows for late-stage diversification towards the synthesis of other members of this family of natural products. While the nitrile oxide cycloaddition addresses the unique oxidation of (–)-mitrephorone A (**1.64**) at C_9, alternative functionalizations of the tetrasubstituted olefin, such as ene reactions of **1.230**, may provide access to other *ent*-trachylobanes. The same facial selectivity will be expected for these reactions as in the nitrile oxide cycloaddition reaction, in which the selectivity was fully controlled by the α stereocenter of the nitrile oxide.



1.230 **1.231**

Scheme 1.53. Possible entry to other *ent*-trachylobane diterpenoids *via* ene or CONIA-ene reaction of **1.232**.

The sequence of sp^2–sp^2 cross-coupling followed by 1,4-semihydrogenation of the resulting 1,3-diene represents a powerful method for the stereoselective synthesis of tetrasubstituted double bonds. After the successful implementation of this transformation in the total synthesis, it will be discussed in more detail in the following chapter.

2

Stereoselective Synthesis of Tetrasubstituted Olefins via 1,4-Semihydrogenation of 1,3-Dienes

II Stereoselective Synthesis of Tetrasubstituted Olefins via 1,4-Semihydrogenation of 1,3-Dienes

1. Introduction

1.1. Transformations of Olefins

Olefins are highly versatile intermediates in organic synthesis. Their reactions can be classified in three categories: oxidative, reductive and redox-neutral transformations. A selection of examples of each category is depicted in Scheme 2.1. Most prominently, reductive transformations of olefins include metal-catalyzed hydrogenation to the corresponding alkane **2.2** and hydroboration to alkylborane **2.3**.[118,119] Examples of oxidative transformations of olefins **2.1** are dihalogenations using elemental halogens (Cl_2, Br_2, I_2),[120] dihydroxylations,[121] and epoxidations.[122] Redox-neutral reactions include cyclopropanations,[123] hydrations,[124] and cycloadditions, such as the Diels–Alder cycloaddition.[125] Furthermore, for most transformations of olefins, asymmetric variants have been reported.[126]

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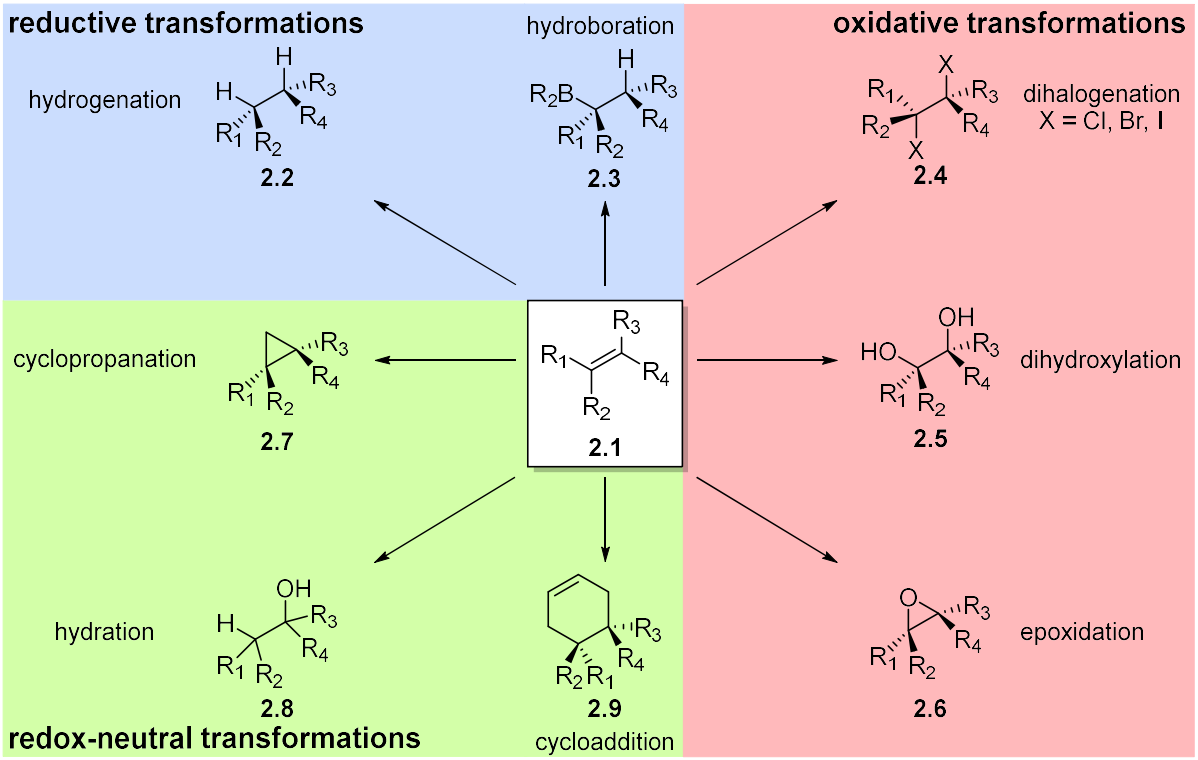
[118] For the first example of the hydrogenation of an olefin, see: Sabatier, P.; Senderens, J.-B. *Compt. rend.* **1897**, *124*, 616–618.
[119] Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695.
[120] For a review on stereoselective dihalogenations of olefins, see: Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. *Angew. Chem. Int. Ed.* **2015**, *54*, 15642–15682.
[121] (a) For *syn*-dihydroxylation, see: VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976; (b) For *trans*-dihydroxylation, see: Prévost, C. *Compt. rend.* **1933**, *196*, 1129–1131.
[122] (a) For electrophilic epoxidations using peroxycarboxylic acids, see: Prilezhaev, N. *Ber.* **1909**, *42*, 4811–4815; (b) For nucleophilic epoxidations using H_2O_2 and NaOH, see: Weitz, E.; Scheffer, A. *Ber.* **1921**, *54*, 2327–2344.
[123] For a review on nucleophilic and electrophilic cyclopropanations, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
[124] For an example of the hydration of olefins via hydrogen atom transfer, see: Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *18*, 1071–1074.
[125] Diels, O.; Alder, K. *Ann.* **1928**, *460*, 98–122.
[126] For reviews and book chapters on enantioselective variants of the different transformations,

In all reactions presented above, one or both olefinic carbons might be transformed into a stereogenic center depending on the substituents R_1 – R_4. The relative configuration of these newly formed stereocenters is determined by the olefin geometry and the reaction mechanism (*syn*- vs. *anti*-addition). Therefore, the stereoselective preparation of one geometric isomer (*E* or *Z*) of the olefin is of upmost importance for its efficient use in organic synthesis.

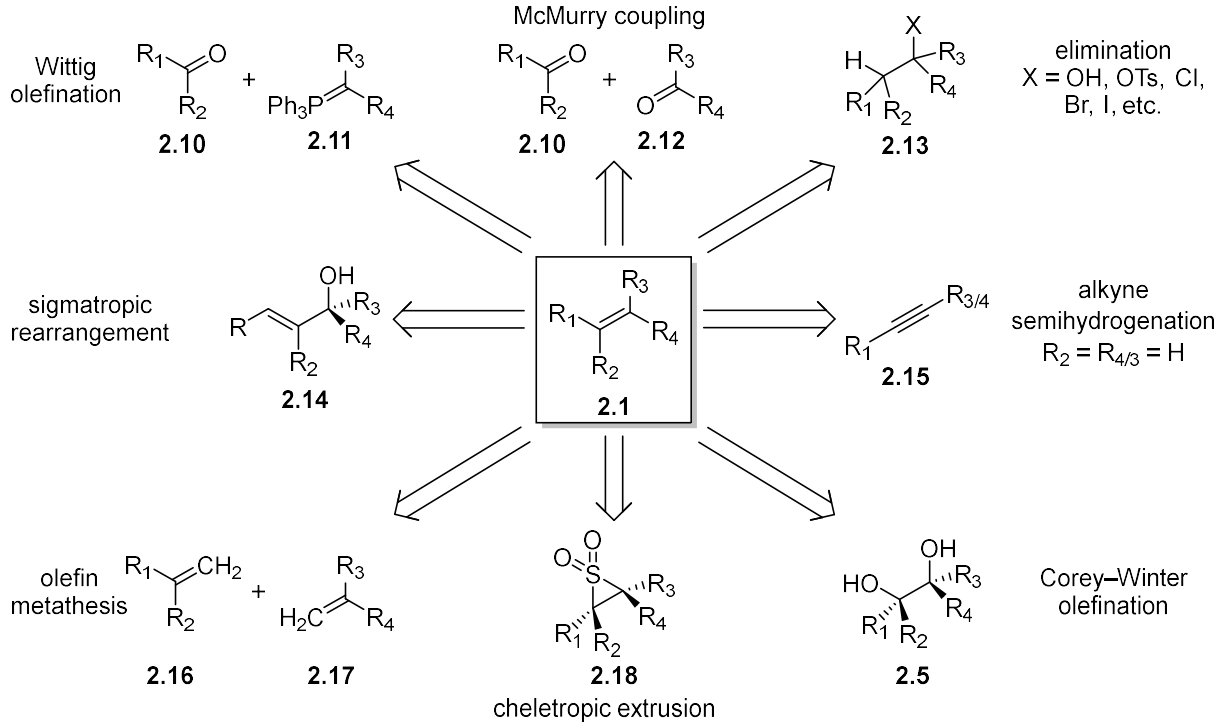


Scheme 2.1. Reductive, oxidative and redox-neutral transformations of olefins.

see: (a) Hydrogenation: Genet, J.-P. Reduction of Functionalized Alkenes in Modern Reduction Methods, Wiley-VCH GmbH & Co. KGaA, Weinheim, 2008; (b) Hydroboration: Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695–4712; (c) Dihalogenations: Castellanos, A.; Fletcher, S. P. *Chem. Eur. J.* **2011**, *17*, 5766–5776; (d) Dihydroxylations: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (e) Epoxidations: Xia, Q. H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-B.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603–1662; (f) Cyclopropanations: see ref 123; (g) Hydrations: Boersma, A. J.; Coquière, D.; Geerdink, D.; Rosati, F.; Feringa, B. L.; Roelfes, G. *Nat. Chem.* **2010**, *2*, 991–995 ; (h) DIELS–ALDER cycloadditions: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.

1.2. Synthesis of Olefins

The development of the vast variety of transformations of olefins depicted above has, at the same time, also led to advances in their preparation. A selection of examples for the preparation of olefins is shown in Scheme 2.2. These include the WITTIG olefination of a ketone or aldehyde **2.10** with phosphonium ylides **2.11**,[127] the MCMURRY coupling of two carbonyls **2.10** and **2.12**,[128] and elimination reactions.[129] A conceptually different approach for olefin synthesis is the rearrangement of molecules that already contain an olefin. Most prominently, this includes CLAISEN and 2,3-WITTIG rearrangements of allylic alcohols **2.14**.[130]1,2-Disubstituted olefins may be synthesized *via* the semihydrogenation of



Scheme 2.2. Various olefin syntheses.

[127] Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318–1330.
[128] McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709.
[129] Under most conditions, *syn*- and *anti*-elimination are possible, which can lead to a mixture of olefin isomers. For an example of a reagent-controlled *syn*-elimination, see: Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224–5226.
[130] (a) For the CLAISEN rearrangement, see: Claisen, L. *Ber.* **1913**, *45*, 3157–3166; (b) For the 2,3-WITTIG rearrangement, see: Wittig, G.; Döser, H.; Lorenz, I. *Liebigs Ann. Chem.* **1949**, *562*, 192–205.

alkynes **2.15**.[131] Other notable examples for the preparation of olefins are the cross-metathesis of two olefins **2.16** and **2.17**,[132] cheletropic extrusions, such as the extrusion of SO_2 from cyclic sulfone **2.18**, which is the last step of the RAMBERG–BÄCKLUND reaction,[133] and the COREY–WINTER olefination of diol **2.5**.[134]

Most of the presented methods are suited for the synthesis of mono-, di-, tri- and tetrasubstituted olefins. While the olefin geometry can often be predicted well in the synthesis of 1,2-di- and trisubstituted olefins and high selectivities may be observed, the synthesis of tetrasubstituted alkenes often suffers from poor stereoselectivity and low reactivity.[135] The method discussed in the following section provides an alternative approach to the stereoselective synthesis of olefins, in which the configuration of the newly formed doubled bond can be easily predicted.

[131] (a) For the hydrogenation of alkynes to *cis*-olefins, see: Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446–450; For the hydrogenation of alkynes to *trans*-olefins, see: (b) Pasto, D. J. Reductions of C=C and C≡C by Noncatalytic Chemical Methods in Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry, Trost, B. M.; Fleming, I. Pergamon Press, Oxford, 1991; (c) Radkowski, K.; Sundararaju, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 355–360.

[132] For reviews on olefin metathesis, see: Vougioukalakis, G. C.; Grubbs, R. H. *Chem Rev.* **2010**, *110*, 1746–1787; (b) Schrock, R. R. *Chem. Rev.* **2009**, *109*, 3211–3226.

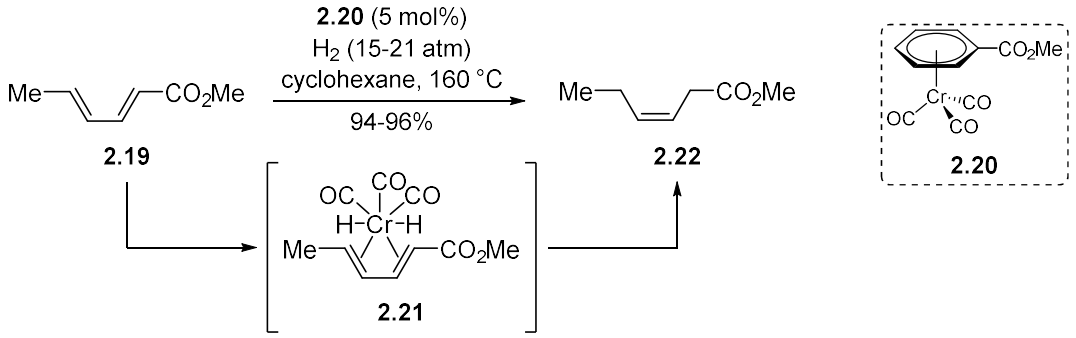
[133] For a review on the RAMBERG–BÄCKLUND reaction, see: Taylor, R. J. K. *Chem. Commun.* **1999**, 217–227.

[134] Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677–2678.

[135] (a) Wang, J.; Dong, Z.; Yang, C.; Dong, G. *Nat. Chem.* **2019**, *11*, 1106–1112; (b) For a review on the synthesis of tetrasubstituted olefins, see: Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745.

1.3. 1,4-Semihydrogenation of 1,3-Dienes

The first example of the 1,4-semihydrogenation of a 1,3-diene was reported by GLASS in 1968.[102] Subjecting methyl sorbate (**2.19**) to 5 mol% of [$Cr(CO)_3(\eta^6$-MeOBz)] (**2.20**) in cyclohexane under 15-21 atm of H_2 at 160 °C led to the formation of *cis*-methyl 3-hexenoate (**2.22**) with high stereo- and regioselectivity (Scheme 2.3). Mechanistically, the reaction is thought to proceed via η^4-complex **2.21**, which locks the substrate in the s-*cis* conformation and leads to the high stereoselectivity observed in this reduction.

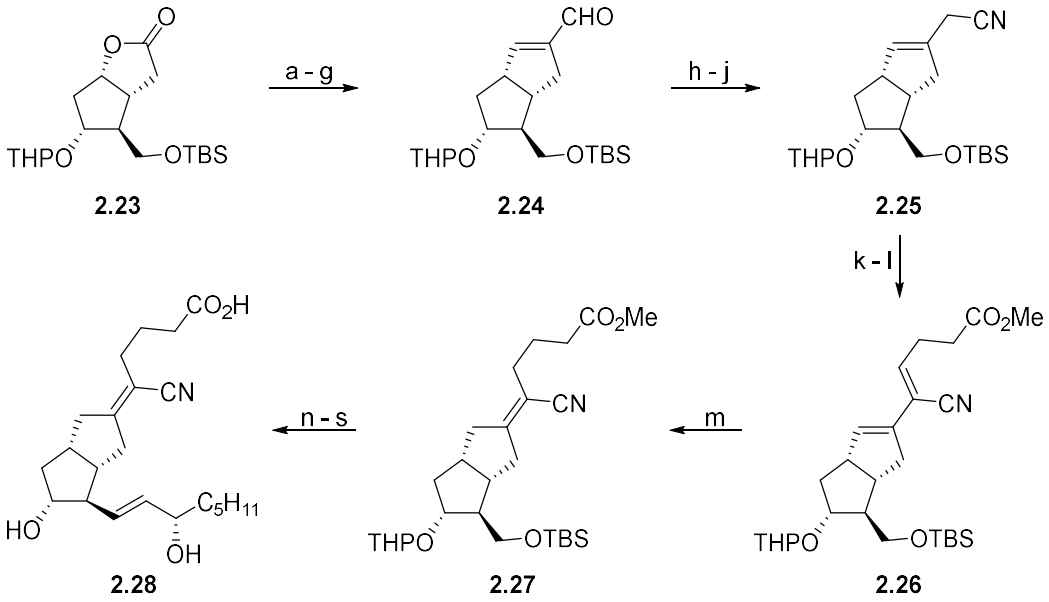


Scheme 2.3. 1,4-Semihydrogenation of methyl sorbate (**2.19**) to *cis*-methyl 3-hexenoate (**2.22**) in the presence of [$Cr(CO)_3(\eta^6$-MeOBz)] (**2.20**).

The first application of the 1,4-semihydrogenation of a 1,3-diene in a total synthesis was reported by SHIBASAKI in 1991 in the synthesis of carbacyclin and analogs thereof (Scheme 2.4).[136] Starting from protected COREY-lactone **2.23**, cyano-substituted 1,3-diene **2.26** was prepared in twelve steps.[137] The exocyclic, tetrasubstituted double bond was installed *via* the 1,4-semihydrogenation of diene **2.26**. In another six steps, the protecting groups were removed, the bottom right side chain was completed, and the ester was hydrolyzed to the corresponding carboxylic acid to afford cyanocarbacyclin (**2.28**). SHIBASAKI also observed that

[136] Sodeoka, M.; Ogawa, Y.; Kirio, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1991**, *39*, 309–322.
[137] The first five steps where reported in: Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, 579–582.

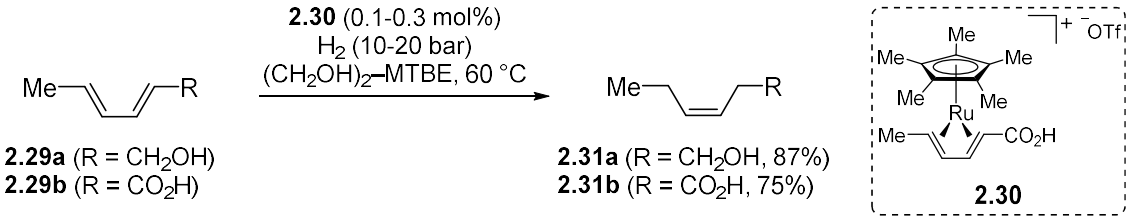
alkynes and acyclic enones are reduced to the corresponding (*Z*)-olefins and saturated ketones, respectively, under the same hydrogenation conditions.[138]



Scheme 2.4. Synthesis of cyanocarbacyclin (**2.28**) from protected Corey lactone **2.23**. Reagents and conditions: (a) DIBAL-H, PhMe; (b) $MePPh_3Br$, KO*t*-Bu, THF; (c) PCC, NaOAc, CH_2Cl_2, 94% over three steps; (d) Zn, $TiCl_4$, CH_2Br_2, 90%; (e) disiamylborane, THF, 0 °C, then NaOH, H_2O_2, H_2O, quant.; (f) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C, then Et_3N, –60 °C to r.t.; (g) $Bn_2NH\cdot TFA$, PhH, 70 °C, 76% over two steps; (h) DIBAL-H, PhMe, –70 °C, 98%; (i) CBr_4, PPh_3, CH_2Cl_2, –60 to –25 °C, 89%; (j) KCN, 18-crown-6, MeCN, r.t., 99%; (k) LDA, methyl 4-oxobutanoate, THF, –78 °C, 82%; (l) MsCl, Et_3N, CH_2Cl_2, 83%; (m) H_2 (70 bar), $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (**2.20**, 21 mol%), acetone, 120 °C, quant.; (n) TBAF, THF, r.t., 93%; (o) $SO_3\cdot pyr$, Et_3N, DMSO, r.t.; (p) NaH, $(MeO)_2(O)PCH_2C(O)C_5H_{11}$, THF, r.t., 82% over two steps; (q) $NaBH_4$, MeOH, –20 °C, (r) 65% aq. AcOH, THF, 50 °C, 51% over two steps; (s) 10% aq. NaOH, MeOH, –5 to 0 °C, 92%.

More recently, DRIEßEN-HÖLSCHER and co-workers reported that ruthenium-based catalysts can also catalyze the 1,4-semihydrogenation of 1,3-dienes.[139] In their studies, subjecting sorbic alcohol (**2.29a**) and sorbic acid (**2.29b**) to catalyst **2.30** under 10 – 20 bar of H_2 at 60 °C in ethylene glycol and MTBE led to the formation of semihydrogenation products **2.31a** and **2.31b** in high *Z*-selectivities (>98%).

[138] Sodeoka, M.; Shibasaki, M. *Synthesis* **1993**, *1993*, 643–658.
[139] Steines, S.; Englert, U.; Drießen-Hölscher, B. *Chem. Commun.* **2000**, 217–218.



Scheme 2.5. 1,4-Semihydrogenation of sorbic alcohol (**2.29a**) and sorbic acid (**2.29b**) in the presence of catalyst **2.30**. Yields do not corresponds to isolated yields but are calculated based on conversion and selectivity of the reaction.

In comparing the two catalysts **2.20** and **2.30**, it was shown that for ruthenium-based catalyst **2.30**, significantly lower catalyst loadings and slightly lower hydrogen pressures were needed to induce the 1,4-semihydrogenation. While chromium-based catalyst **2.20** is available in one step from cheap and commercially available starting materials, **2.30** requires are multi-step synthesis from more expensive starting materials *via* highly air and moisture sensitive intermediates.[140]

[140] Koelle, U.; Kossakowski, J. *J. Organomet. Chem.* **1989**, *362*, 383–398.

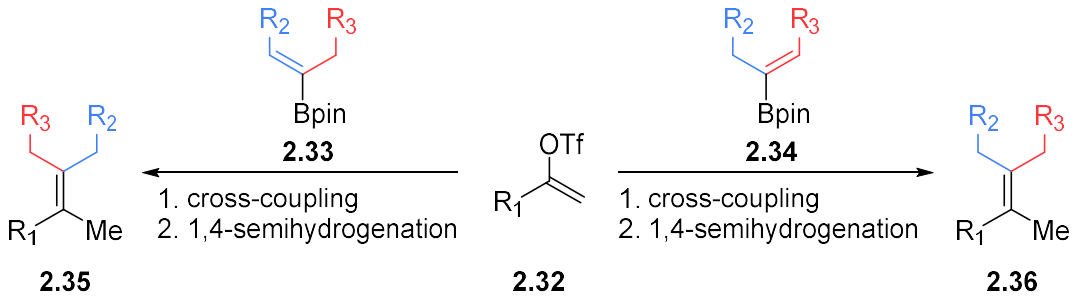
1.4. Project Outline

Stereoselective preparation of tetrasubstituted olefins still remains challenging in organic synthesis. Although high yields and stereoselectivities have been reported for the 1,4-semihydrogenation of 1,3-dienes, there is only a very limited numbers of reports on the use of this method and even less for the synthesis of tetrasubstituted olefins. While SHIBASAKI's synthesis of cyanocarbycyclin (**2.28**) required a multi-step synthesis of 1,3-diene **2.26**, modern palladium-catalyzed cross-coupling reactions would allow for a rapid preparation of various 1,3-dienes. The successful implementation of a cross-coupling/ 1,4-semihydrogenation sequence in Chapter 1 of this thesis and the scarcity of reports on the synthesis of tetrasubstituted olefins *via* this semihydrogenation strategy prompted us to embark on the development of a synthetic methodology that would allow for the stereoselective synthesis of tetrasubstituted olefins in two steps from readily available vinyl triflates and vinyl boronates.

2. Results and Discussion

2.1. Project Design

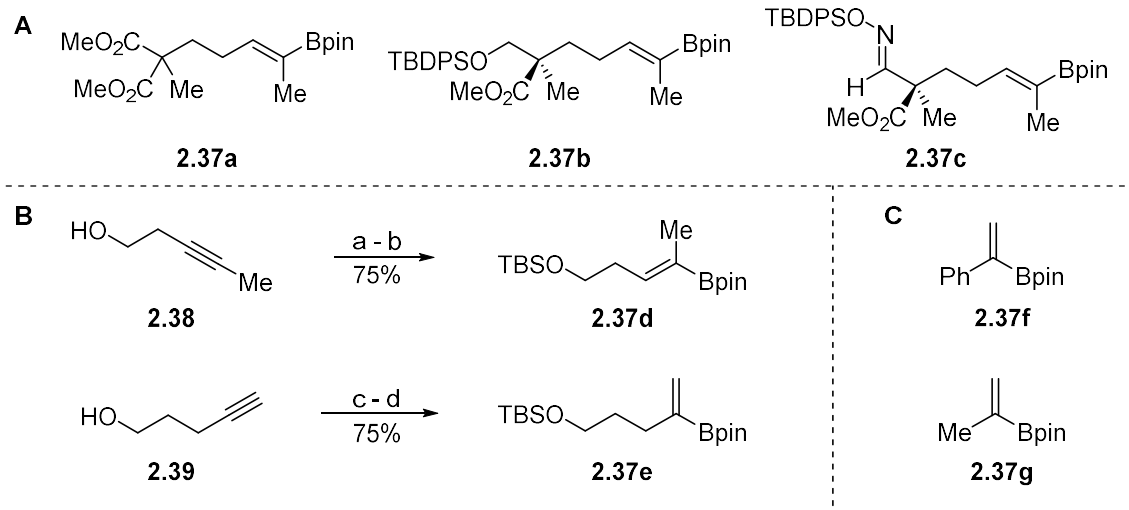
One of the key features of the 1,4-semihydrogenation of 1,3-dienes discussed in Section 1.3 is the high stereoselectivity that is observed because the substrate is locked in the s-*cis* conformation during the reaction. When the 1,3-diene is synthesized *via* an sp^2–sp^2 cross-coupling reaction, the olefin geometry of the hydrogenation product is fully determined by the structure of the two coupling partners. Variation of one of the two coupling partners may allow for the stereoselective synthesis of both olefin isomers (Scheme 2.6). We decided to primarily focus on the synthesis of tetrasubstituted olefins that have two structural features that render their stereoselective preparation challenging: (1) The products include an allylic quaternary center, which drastically reduces the reactivity in many of the methods for olefin synthesis discussed in Section 1.2, and (2) one of the olefinic carbons bears two substituents that do not greatly differ in size, predominantly one methyl and one linear alkyl substituent, which often leads to low stereoselectivity in the olefin formation using traditional methods.



Scheme 2.6. Synthesis of both olefin isomers **2.35** and **2.36** from the same vinyl triflate **2.32** by variation of the vinyl boronate.

2.2. Synthesis of Vinyl Boronates and Vinyl Triflates

Our studies commenced with the preparation of a series of vinyl boronates **2.37** and vinyl triflates **2.41**. Generally, vinyl boronates can be prepared *via* various reactions. These include the hydroboration of alkynes,[141] the cross-metathesis of other vinyl boronates,[109] and the MIYAURA boration of vinyl halides and triflates.[142] In Chapter 1 of this thesis, vinyl boronates **2.37a**, **2.37b** and **2.37c** have been prepared *via* hydroboration and cross-metathesis, respectively (Scheme 2.7A).[143] The two regioisomeric vinyl boronates **2.37d** and **2.37e** were prepared from the corresponding alkynes *via* hydroboration according to literature procedures (Scheme 2.7B): Copper-catalyzed and alcohol-directed hydroboration of pent-3-yn-1-ol (**2.38**) followed by TBS-protection afforded **2.37d**.[103] α-Vinyl boronate **2.37e** was prepared from pent-4-yn-1-ol (**2.39**) *via* TBS-protection followed by branched-selective hydroalumination and quenching with



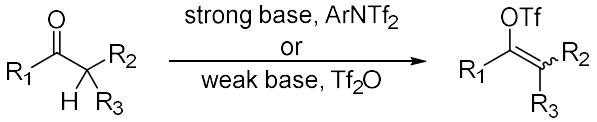
Scheme 2.7. A) Vinyl boronates prepared in Chapter 1 of this thesis; B) Preparation of vinyl boronates **2.37d** and **2.37e**; C) Commercially available vinyl boronates. Reagents and conditions: (a) B_2pin_2, CuCl (10 mol%), PPh_3 (12 mol%), KO*t*-Bu (40 mol%), MeOH, THF, 0 °C to r.t., 86%; (b) TBSCl, imidazole, DMAP (10 mol%), CH_2Cl_2, r.t., 87%; (c) TBSCl, imidazole, DMAP (20 mol%), CH_2Cl_2, r.t., 92%; (d) $Ni(dppp)_2$ (3 mol%), DIBAL-H, THF–PhMe (1.7:1), r.t., then starting material, 0 °C to r.t., then MeO–Bpin, 80 °C, 73%.

[141] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255.
[142] Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 126–127.
[143] Vinyl boronates **2.37a**, **2.37b** and **2.37c** were numbered as **1.199a**, **1.220** and **1.123** in the first chapter of this thesis and were renumbered here for clarity.

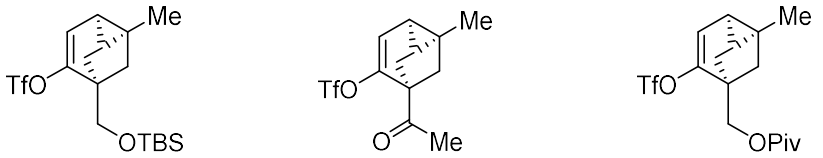
MeO–Bpin.[144] Vinyl boronates **2.37f** and **2.37g** are commercially available (Scheme 2.7C).

Vinyl triflates **2.41** are commonly prepared from the corresponding ketones **2.40**. Typical conditions for their preparation can be divided in two groups: (1) The combination of a strong base with a bistriflimide as the triflating agent, and (2) the use of a weak base and triflic anhydride as a more LEWIS acidic triflating agent (Table 2.1).[145] The two vinyl triflates that were discussed in Chapter 1 of this thesis, **2.41a** and **2.42b**,[146] as well as **2.41c** and **2.41f** were prepared under conditions classified under the first category (KHMDS, COMINS' reagent).[147] The syntheses of the other three vinyl triflates, **2.41d**, **2.41e** and **2.41g**, followed protocols of the second category (Na_2CO_3 or DTBMP, Tf_2O).[148,149]

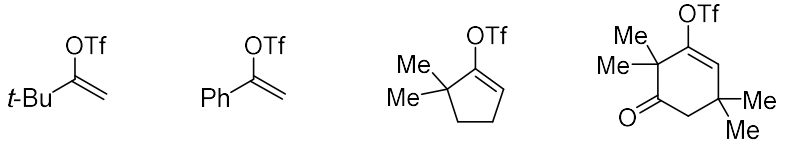
Table 2.1. Preparation of vinyl triflates **2.41**.



2.40 **2.41**



2.41a[a] **2.41b**[a] **2.41c**[a]



2.41d[b] **2.41e**[b] **2.41f**[a] **2.41g**[c]

Reagents and conditions: [a]KHMDS, COMINS' reagent, THF, –78 °C to r.t.; [b]Na_2CO_3, Tf_2O, CH_2Cl_2, r.t.; [c]2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), Tf_2O, DCE, 80 °C.

[144] Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.
[145] Ritter, K. *Synthesis* **1993**, *1993*, 735–762.
[146] Vinyl triflates **2.41a** and **2.42b** were numbered as **1.198** and **1.210** in the first chapter of this thesis and were renumbered here for clarity.
[147] Nicolaou, K. C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Follmann, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3637–3642.
[148] García Martínez, A.; Herrera, A.; Martínez, R.; Teso, E.; García, A.; Osío, J.; Pargada, L.; Unanue, R.; Subramanian, L. R.; Hanack, M. *J. Heterocycl. Chem.* **1988**, *25*, 1237–1241.
[149] Willis, M. C.; Claverie, C. K. *Tetrahedron Lett.* **2001**, *42*, 5105–5107.

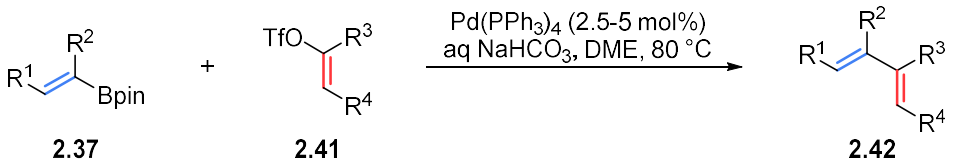
2.3. Cross-Coupling and 1,4-Semihydrogenation

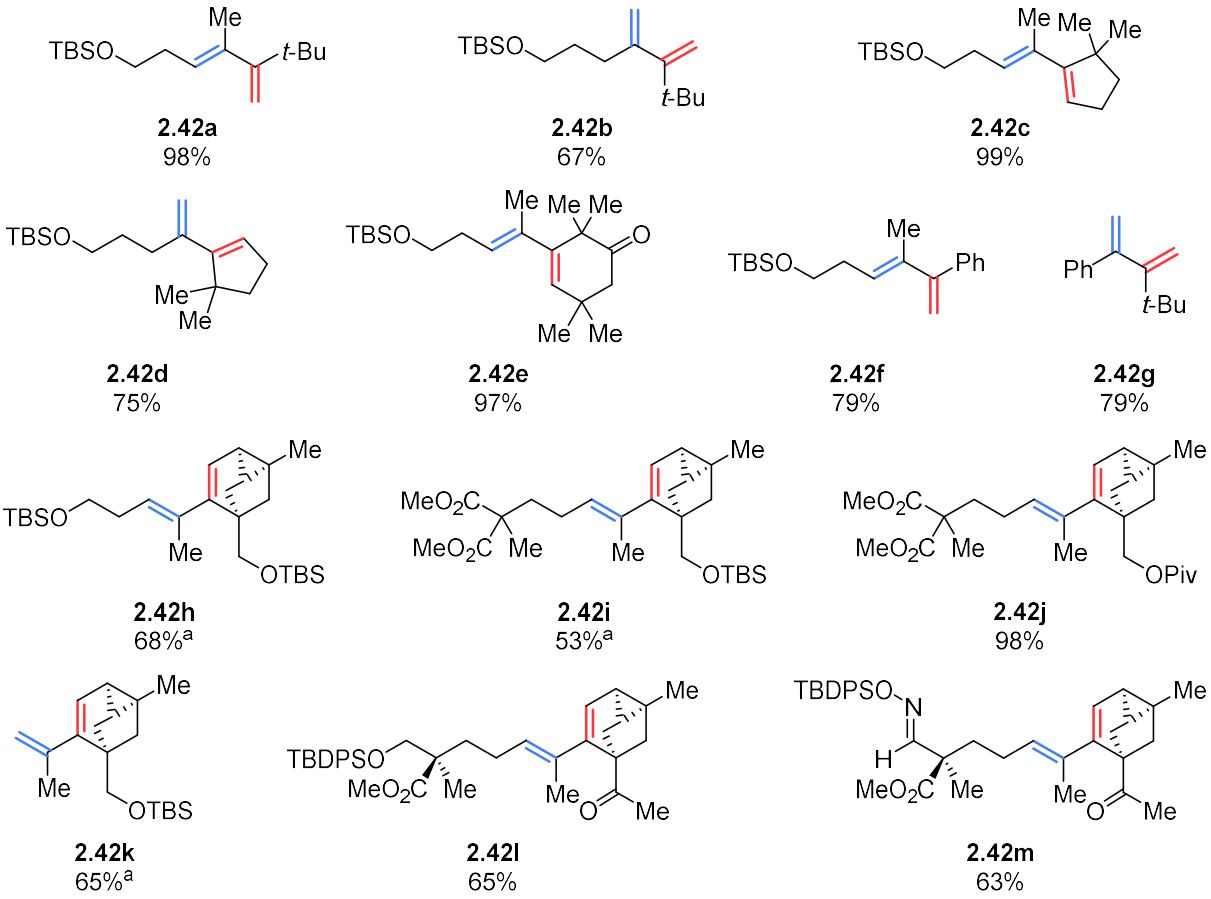
With seven vinyl boronates **2.37** and seven vinyl triflates **2.41** in hand, we set out to prepare a series of 1,3-dienes *via* SUZUKI–MIYAURA cross-coupling. A mixture of **2.37** and **2.41** in 1,2-dimethoxyethane (DME) was subjected to catalytic amounts of $Pd(PPh_3)_4$ (2.5-5 mol%) and aqueous sodium bicarbonate at 80 °C (Table 2.2).[105] Besides the three dienes, **2.42i**, **2.42l** and **2.42m**,[150] that were discussed in Chapter 1 of this thesis, another ten 1,3-dienes **2.42** were prepared following this protocol. For compounds **2.42h**, **2.42i** and **2.42k** bearing a silyloxymethyl substituent on the tricyclo[3.2.1.$0^{2,7}$]octane scaffold, approximately 80% of this silyl ether was cleaved during the cross-coupling reaction and was reformed using standard TBS-protection conditions. Variation of the reaction time had no influence on the extent of silyl ether cleavage indicating that this deprotection took place during the cross-coupling event. Changing the protecting group to TBDPS led to a 1:1 mixture of protected and deprotected product. A pivalate protecting group remained unaffected in the synthesis of 1,3-diene **2.42j**.

We next turned to the reduction of 1,3-dienes **2.42** to tetrasubstituted olefins **2.43** *via* 1,4-semihydrogenation. Subjecting regioisomeric dienes **2.42a** and **2.42b** to 20 mol% of catalyst **2.20** led to the selective formation of the two geometric isomers **2.43a** and **2.43b** in 94% and 87% yield, respectively (Table 2.3). Analogously, exocyclic olefins **2.43c** and **2.43d** were prepared in 90% and 87% yield, respectively.[151] The ketone in **2.42e** was well tolerated under the reduction conditions and also styrene **2.43f** could be prepared from the corresponding 2-phenylbutadiene **2.42f**. Remarkably, tetrasubstituted olefin **2.43g** bearing a phenyl and a *tert*-butyl substituent *cis* on the double bond could be prepared successfully in 84% yield highlighting the ability of this method for the preparation of highly sterically encumbered tetrasubstituted olefins. In Chapter 1

[150] Dienes **2.42i**, **2.42l** and **2.42m** were numbered as **1.197**, **1.225** and **1.227** in the first chapter of this thesis and were renumbered here for clarity.
[151] For olefins **2.43c** and **2.43d**, the configuration of the double bond was confirmed by 2D NOESY NMR spectroscopy.

Table 2.2. Synthesis of 1,3-dienes **2.42** via SUZUKI–MIYAURA cross-coupling of vinyl boronates **2.37** and vinyl triflates **2.41**.





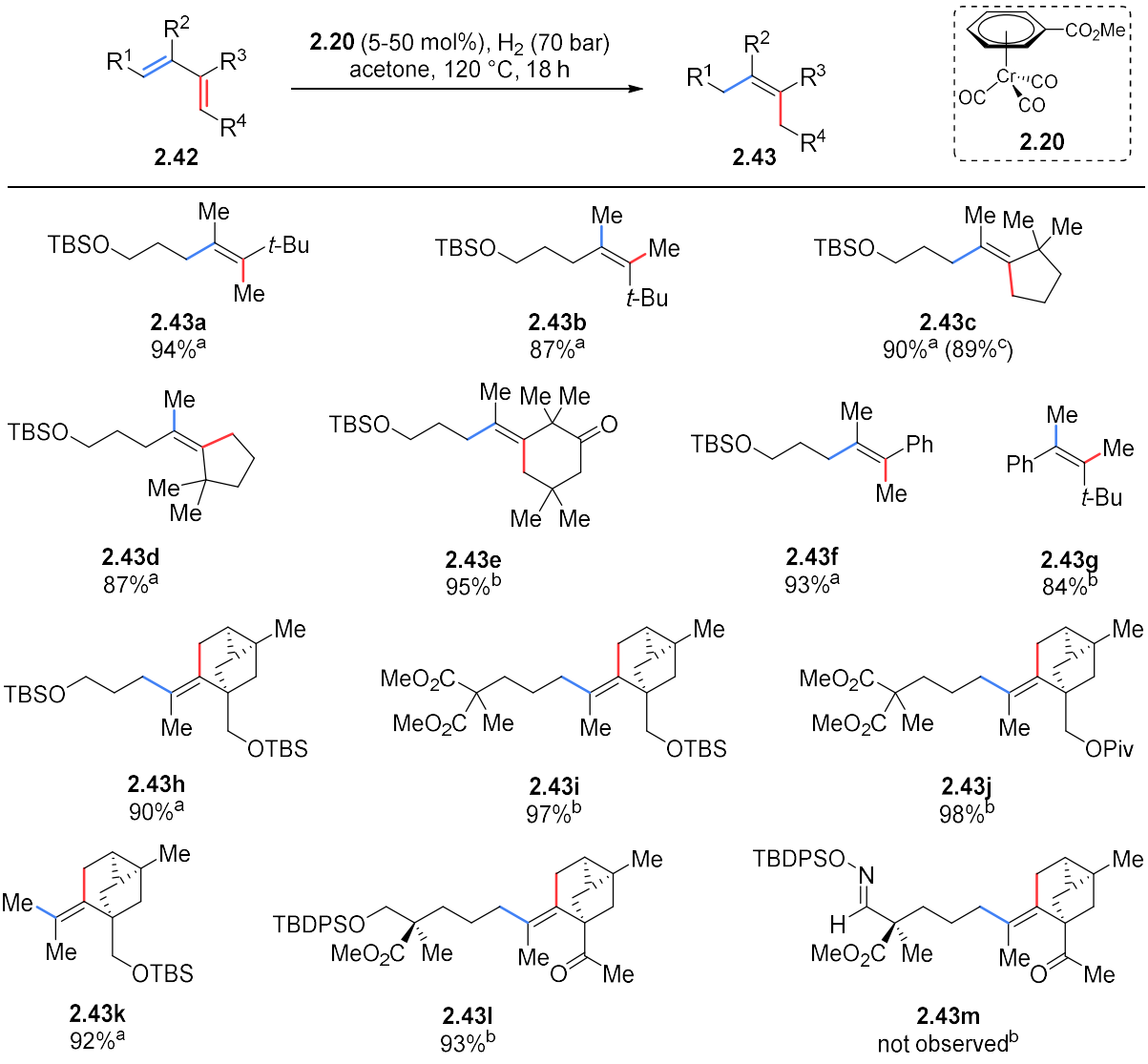
[a]During the reaction, most of the (right) silyl ether was cleaved and was resynthesized using TBSCl, imidazole and DMAP (10 mol%) in CH_2Cl_2 at r.t. The yields indicate the combined yield over cross-coupling and TBS-protection.

of this thesis, the syntheses of **2.43i**, **2.43l** and **2.43m** *via* 1,4-semihydrogenation was discussed in the context of the total synthesis of (–)-mitrephorone A showing that a malonate and a methyl ketone were well tolerated under the reaction conditions.[152] Additionally, olefins **2.43h**, **2.43j** and **243k** which include the tricyclo[3.2.1.$0^{2,7}$]octane scaffold of *ent*-trachylobane diterpenoids could be prepared in high yields. In the hydrogenation of **2.42e**, **2.42g** and **2.42i**,

[152] Olefins **2.43i**, **2.43l** and **2.43m** were numbered as **1.135**, **1.226** and **1.228** in the first chapter of this thesis and were renumbered here for clarity.

incomplete conversion was observed using 20 mol% of catalyst **2.20**. Increasing the catalyst loading to 50 mol% led to full conversion for these substrates. For **2.42l** and **2.42m**, 50 mol% of **2.20** was used directly to ensure full conversion. For diene **2.42c**, reducing the catalyst loading to 5 mol% led to incomplete conversion after the standard reaction time (18 h, 54% conversion). Increasing the reaction time to 42 h led to full conversion and **2.43c** was isolated in 89% yield, which clearly showed that the catalyst is still active after the standard reaction time. All olefins **2.43** were obtained in >20:1 diastereomeric ratio. In most cases, traces of regioisomeric olefins (<5%) were observed. For none of the reactions,

Table 2.3. Synthesis of tetrasubstituted olefins **2.43** *via* 1,4-semihydrogenation of 1,3-dienes **2.42** in the presence of chromium catalyst **2.20**.



[a]20 mol% of **2.20** was used; [b]50 mol% of **2.20** was used; [c]5 mol% of **2.20** was used.

any overreduction to the corresponding alkane was detected. For **2.43i**, reducing the hydrogen pressure to 55 bar completely shut down the reaction. Scaling-up the reaction to 2.3 mmol and variation of the concentration between 6.9 and 50 mM did not influence yield or selectivity of the reduction.

3. CONCLUSION AND OUTLOOK

In summary, we have developed a highly stereoselective and high yielding sequence of SUZUKI–MIYAURA sp^2–sp^2 cross-coupling and 1,4-semi-hydrogenation of the resulting 1,3-dienes for the synthesis of tetrasubstituted olefins. In this sequence, the olefin geometry is fully determined by the structure of the coupling partners and can be easily predicted. Accordingly, both olefin isomers **2.43a** and **2.43b** as well as **2.43c** and **2.43d** along with eight other examples **2.43e** – **2.43j** were successfully prepared in >20:1 diastereomeric ratio.

The ease of preparing vinyl boronates and vinyl triflates along with the highly selective formation of one olefin geometrical isomer over the other one render this method highly efficient in the stereoselective synthesis of tetrasubstituted double bonds, which would be challenging to access *via* conventional synthetic methods. We assume that this method will therefore find further application in the synthesis of complex organic molecules.

3

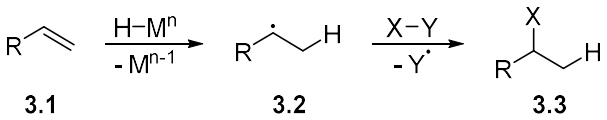
Synthesis of Primary Amines from Nitriles via a Radical Cyclization/ Reduction Cascade

III SYNTHESIS OF PRIMARY AMINES FROM NITRILES *VIA* A RADICAL CYCLIZATION/REDUCTION CASCADE

1. INTRODUCTION

1.1. Hydrogen Atom Transfer Reactions

As discussed in the previous chapter, olefins are highly versatile intermediates in organic synthesis. The hydrofunctionalization of olefins through hydrogen atom transfer (HAT) reactions proceeds *via* the addition of a hydrogen radical from a metal hydride to a double bond to form an alkyl radical, which can undergo quenching reactions with radical acceptors (Scheme 3.1).[153] The hydrogen atom transfer to the olefin generally leads to the more stabilized radical and, therefore, the hydrofunctionalization proceeds with MARKOVNIKOV selectivity.

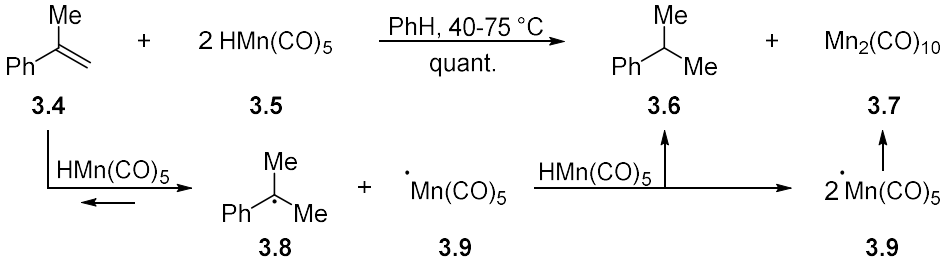


Scheme 3.1. Hydrofunctionalization of olefins *via* hydrogen atom transfer reactions.

First-row transition metal hydrides, such as Mn–H, Fe–H or Co–H, were first used for olefin functionalization in hydrogenation reactions.[154] In 1977, HALPERN and SWEANY proposed a mechanism for the hydrogenation of α-methylstyrene (**3.4**) using an excess of hydridopentacarbonylmanganese(I) (**3.5**), in which **3.4** reacts with the metal hydride to form benzylic radical **3.8** and manganese radical **3.9** (Scheme 3.2).[155] Hydrogenation product **3.6** is formed by another hydrogen atom transfer from a second molecule of **3.5** to radical **3.8**. Finally, two manganese radicals **3.9** recombine to form dimanganesedecacarbonyl **3.7**. The authors supported their mechanistic proposal using CIDNP NMR spectroscopy,

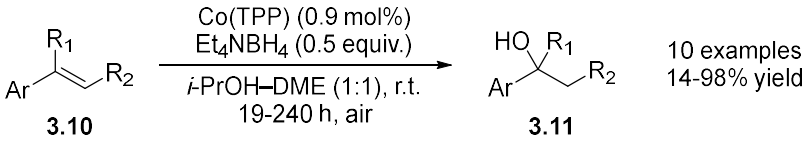
[153] Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. *Chem. Rev.* **2016**, *116*, 8912–9000.
[154] Kwiatek. J.; Mador, I. L.; Seyler, J. K. *J. Am. Chem. Soc.* **1962**, *84*, 304–305.
[155] Sweany, R. L.; Halpern, J. *J. Am. Chem. Soc.* **1977**, *99*, 8335–8337.

which indicated the formation of free radicals as intermediates and reversibility of the first step of the mechanism.



Scheme 3.2. Hydrogenation of α-methylstyrene (**3.4**) using manganese hydride **3.5**.

Over the following decades, the hydrofunctionalization of olefins *via* HAT reactions outlined in Scheme 3.1 has been studied using various carbon and heteroatom radicophiles in intra- and intermolecular reactions. Amongst these, the most prominent one is the hydration of olefins using molecular oxygen as the radical acceptor, which was initially reported by OKAMOTO and OKA,[156] and later studied extensively by MUKAIYAMA.[157] In contrast to HALPERN's work, the metal hydride is generated *in situ* by the reaction of a metal catalyst with a reducing agent. In OKAMOTO and OKA's work, cobalt(II) porphyrin catalyst Co(TPP) and tetraethylammonium borohydride were used for the synthesis of benzylic alcohols



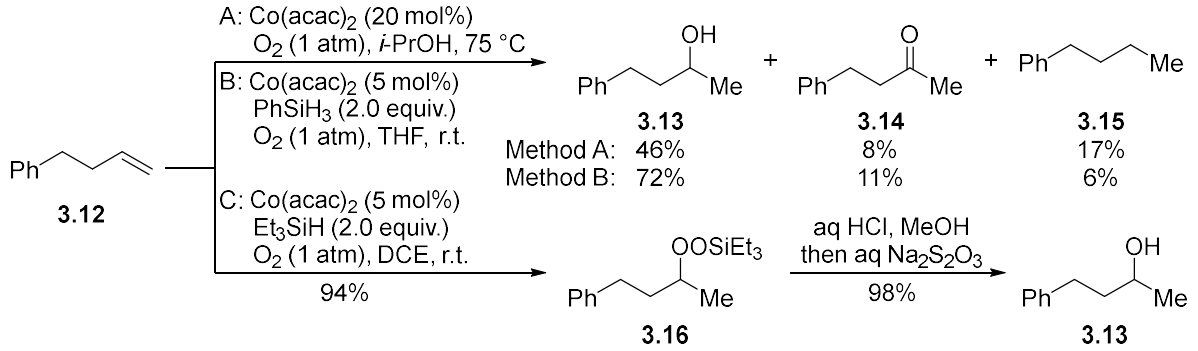
Scheme 3.3. Synthesis of benzylic alcohols **3.11** *via* hydration of styrenes **3.10** by OKAMOTO and OKA.

[156] (a) Okamoto, T.; Oka, S. *Tetrahedron Lett.* **1981**, *22*, 2191–2194; (b) Okamoto, T.; Oka, S. *J. Org. Chem.* **1984**, *49*, 1589–1594.

[157] (a) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449–452; (b) Inoki, S.; Kato, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 515–518; (c) Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 179–186; (d) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071–1074; (e) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 569–572; (f) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573–576; (g) Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305–1310; (h) Isayama, S.; Mukoyama, M. *Production of Hydroxyl Group-Containing Compound*, Patent JPH03206058A, 1991.

3.11 from the corresponding styrenes **3.10** (Scheme 3.3). Addition of the intermediate alkyl radical to molecular oxygen initially leads to peroxide formation, which is subsequently reduced to the corresponding alcohol by tetraethylammonium borohydride.

MUKAIYAMA and co-workers extended the substrate scope to aliphatic olefins. They reported three approaches for the hydration of olefins using cobalt catalysts. In the first one, isopropanol serves as the hydride source, which required elevated temperatures and afforded a mixture of alcohol **3.13** with the corresponding ketone **3.14** and alkane **3.15** (Scheme 3.4, method A). In their second approach, phenylsilane was used as the reducing agent, which allowed for a lower catalyst loading and temperature, and resulted in a more selective formation of alcohol **3.13** (method B). In method C, phenylsilane was replaced with triethylsilane, which led to the formation of stable triethylsilyl peroxide **3.16** in 94% yield. Desilylation followed by peroxide reduction gave alcohol **3.13** in 98% yield.

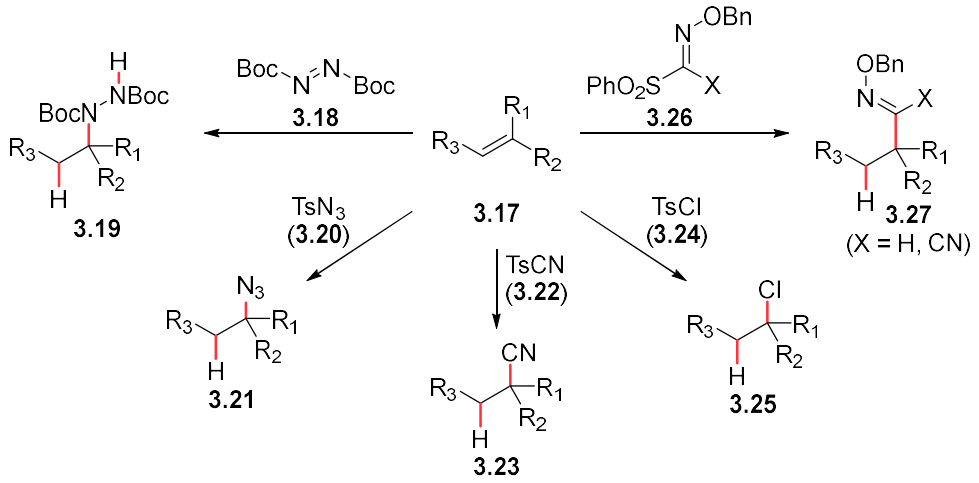


Scheme 3.4. Cobalt-catalyzed hydration of olefin **3.12** *via* three different methods by MUKAIYAMA.

Starting from 2004, CARREIRA and co-workers reported a series of olefin hydrofunctionalizations mediated by cobalt and manganese catalysts in combination with a silane reducing agent.[158] The authors commenced their studies

[158] (a) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676–5677; (b) Waser, J.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4099–4102; (c) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294–8295; (d) Gaspar, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4519–4522; (e) Gaspar, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 5758–5760; (f) Gaspar, B.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 13214–13215.

with the hydrohydrazination of olefins **3.17** using di-*tert*-butylazodicarboxylate **3.18** as the radical acceptor, which afforded *N*,*N*'-diprotected hydrazines **3.19**.[158a,b] In the following years, the study was extended to hydroazidation (**3.21**),[158c] hydrocyanation (**3.23**),[158d] and hydrochlorination (**3.25**)[158e] using tosyl azide (**3.20**), tosyl cyanide (**3.22**) or tosyl chloride (**3.24**), respectively, as the radicophile. Finally, oxime ethers **3.27** could be formed by employing phenyl sulfonyl oxime ethers **3.26** as radical acceptors.[158f]

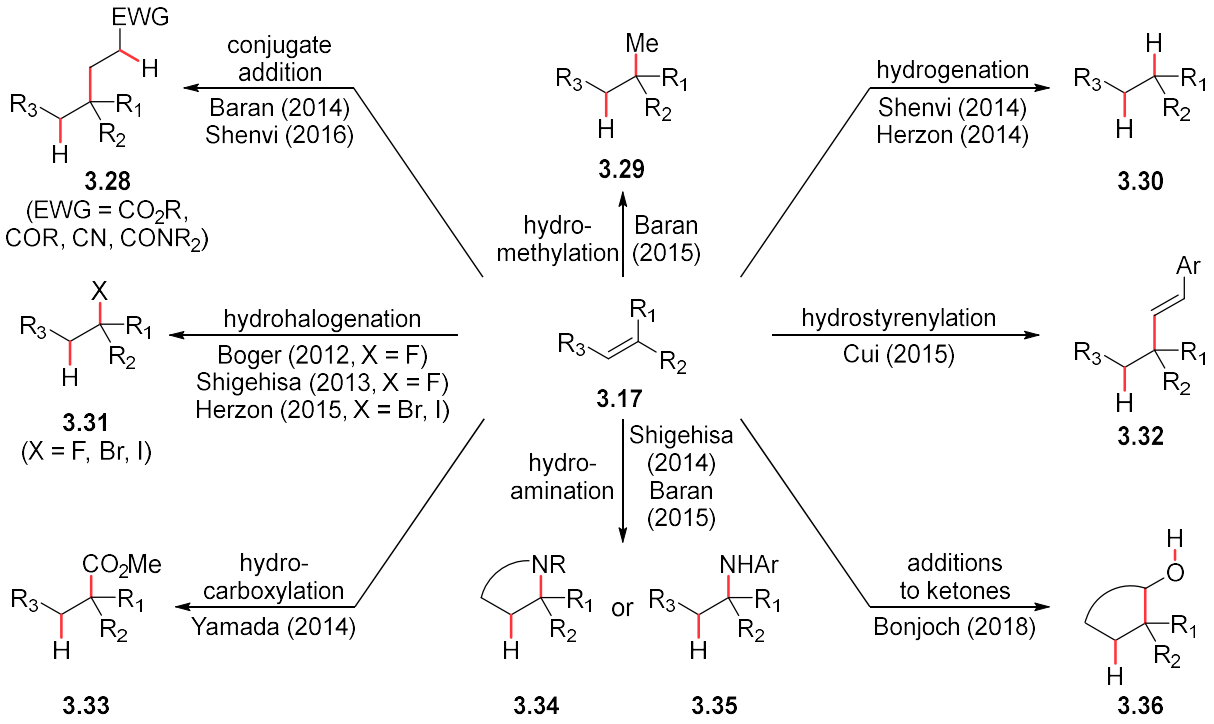


Scheme 3.5. Hydrofunctionalization of olefins reported by CARREIRA and co-workers. Red bonds indicate newly formed bonds.

More recently, various contributions to HAT-mediated olefin hydrofunctionalization using various radical acceptors have been made using iron, manganese, or cobalt catalysts, most prominently by the groups of BARAN and SHENVI.[159] These two groups reported the conjugate addition of the intermediate

[159] (a) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307; (b) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343–348; (c) Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962–4971; (d) Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 8046–8049; (e) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300–1303; (f) King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884–6887; (g) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13588–13591; (h) Shigehisa, H.; Nishi, E.; Fujisawa, M.; Hiroya, K. *Org. Lett.* **2013**, *15*, 5158–5161; (i) Ma, X.; Herzon, S. B. *Chem. Sci.* **2015**, *6*, 6250–6255; (j) Zheng, J.; Wang, D.; Cui, S. *Org. Lett.* **2015**, *17*, 4572–4575; (k) Hayashi, C.; Hayashi, T.; Kikuchi, S.; Yamada, T. *Chem. Lett.* **2014**, *43*, 565–567; (l) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K. *J. Am. Chem. Soc.* **2014**, *136*, 13534–13537; (m) Shigehisa, H.; Aoki, T.; Yamaguchi, S.;

alkyl radical to acrylates and related structures in 2014 and 2016, respectively (Scheme 3.6).[159a-c] The hydromethylation of olefins was achieved using a formaldehyde *N*-sulfonylhydrazone as the radicophile.[159d] SHENVI and HERZON have reported the HAT-mediated hydrogenation of olefins.[159e,f] In this context, HERZON was able to reduce vinyl chlorides to the corresponding alkyl chlorides, which is challenging using traditional hydrogenation methods. The hydrofluorination of olefins **3.17** was reported by BOGER, who used Selectfluor® as the fluorine source, and SHIGEHISA using an *N*-fluoropyridinium salt in 2012 and 2013, respectively.[159g,h] In analogy to the work by CARREIRA and co-workers, HERZON reported the hydrobromination and hydroiodination using tosyl bromide or methylene iodide, respectively.[159i] CUI employed β-nitrostyrenes for olefin hydrostyrenylation.[159j] In this reaction, radical addition to the styrene is followed by fragmentation under extrusion of nitrogen dioxide, which is subsequently



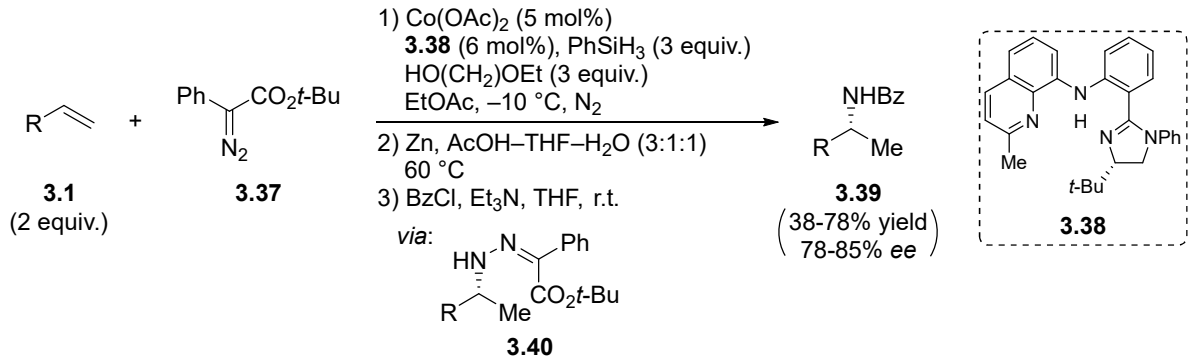
Scheme 3.6. Selected examples of recent advances in the hydrofunctionalization of olefins. Red bonds indicate newly formed bonds.

Shimizu, N.; Hiroya, K. *J. Am. Chem. Soc.* **2013**, *135*, 10306–10309; (n) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. *Science* **2015**, *348*, 886–892; (o) Saladrigas, M.; Bosch, C.; Saborit, G. V.; Bonjoch, J.; Bradshaw, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 182–186.

reduced to a nitrite anion under the reaction conditions. YAMADA and co-workers reported the synthesis of esters **3.33** *via* hydrocarboxylation of olefin **3.17** using carbon dioxide, followed by esterification with TMS-diazomethane.[159k] Under conditions very similar to their hydrofluorination reaction, SHIGEHISA and co-workers achieved an intramolecular hydroamination reaction.[159l] The reaction presumably proceeds *via* oxidation of the intermediate alkyl radical to the corresponding carbocation, followed by nucleophilic ring closure. The same group also reported the analogous intermolecular hydroalkoxylation.[159m] BARAN reported an alternative approach to olefin hydroamination employing nitroarenes.[159n] Control experiments indicated that the nitroarene is reduced to the corresponding nitrosoarene, which subsequently serves as the radical acceptor. In 2018, BONJOCH reported the HAT-mediated intramolecular addition of olefins to ketones to generate tertiary alcohols **3.36**.

Recently, LU and co-workers reported an enantioselective cobalt-catalyzed hydroamination of monosubstituted olefins **3.1** using α-diazoester **3.37** in the presence of cobalt(II) acetate and a chiral tridentate ligand **3.38** (Scheme 3.7).[160,161] The initial product of the hydrogen atom transfer reaction is alkylidene hydrazine **3.40**, which is formed by addition of the alkyl radical to the terminal nitrogen atom of diazo compound **3.37**. It is subsequently transformed to the protected amine **3.39** *via* reductive *N–O* cleavage and benzoyl protection.

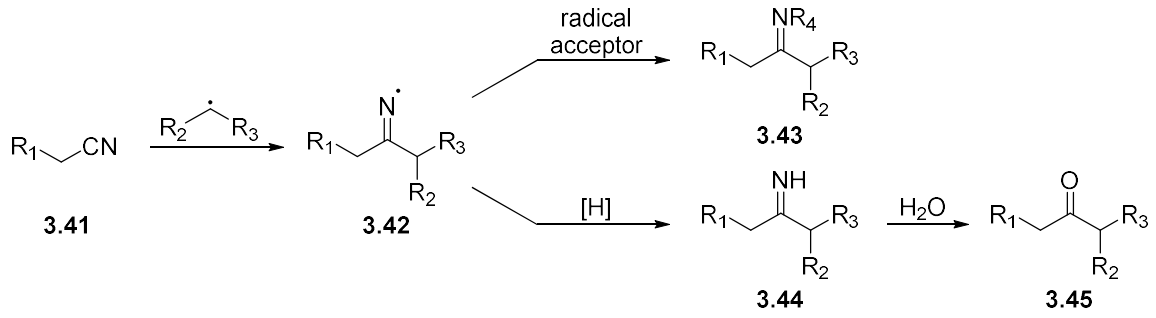
[160] Shen, X.; Chen, X.; Chen, J.; Sun, Y.; Cheng, Z.; Lu, Z. *Nat. Commun.* **2020**, *11*, 783–790.
[161] For other HAT-mediated enantioselective hydrofunctionalizations of olefins *via* a radical-polar crossover approach, see: (a) Discolo, C. A.; Touney, E. E.; Pronin, S. V. *J. Am. Chem. Soc.* **2019**, *141*, 17527–17532; (b) Ebisawa, K.; Izumi, K.; Ooka, Y.; Kato, H.; Kanazawa, S.; Komatsu, S.; Nishi, E.; Shigehisa, H. *J. Am. Chem. Soc.* **2020**, *142*, 13481–13490.



Scheme 3.7. Enantioselective hydroamination of monosubstituted olefins **3.1** by LU and co-workers.

1.2. Radical Additions to Nitriles

Nitriles are a class of organic compounds that are characterized by a *C–N* triple bond, of which the carbon atom is bound to the molecule. They can be introduced as nucleophiles by means of inorganic cyanide salts or *via* the α-anion of alkyl nitriles or as electrophiles using for example cyanogen bromide. Syntheses of nitriles by functional group interconversion include dehydration of primary amides or oximes,[162] the SCHMIDT reaction using aldehydes,[163] and oxidation of primary amines.[164] Common transformations of nitriles are reductions to the corresponding primary amines or aldehydes, organometal additions to form ketones, hydrolysis to the corresponding carboxylic acids or amides, and addition of radicals. The latter will give rise to iminyl radical **3.42**, which can subsequently either react with another radical acceptor to form secondary imine **3.43** or is reduced to the corresponding primary imine **3.44** (Scheme 3.8). Primary imines typically rapidly hydrolyze to the corresponding ketones **3.45**.[165]

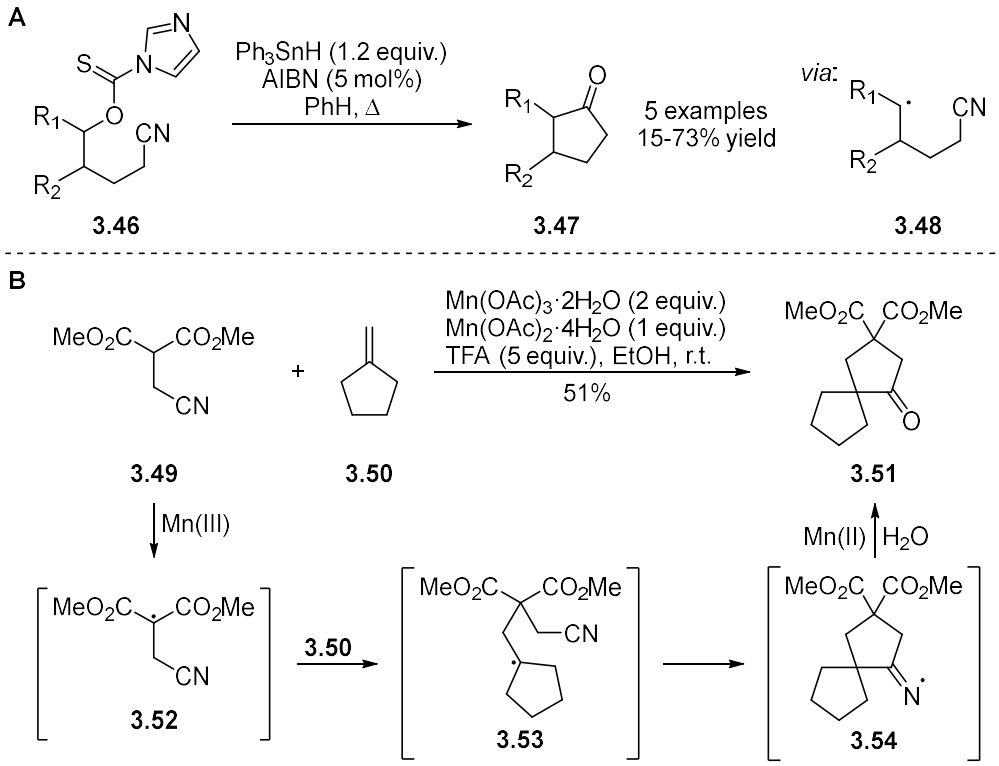


Scheme 3.8. Formation of iminyl radical **3.42** *via* radical addition to nitrile **3.41** and transformation into either secondary imine **3.43** or ketone **3.45**.

[162] (a) Claremon, D. A.; Phillips, B. T. *Tetrahedron Lett.* **1988**, *29*, 2155–2158; (b) Miller, C. P.; Kaufmann, D. H. *Synlett* **2000**, *2000*, 1169–1171; (c) Ding, R.; Liu, Y.; Han, M.; Jiao, W.; Li, J.; Tian, H.; Sun, B. *J. Org. Chem.* **2018**, *83*, 12939–12944.
[163] Rokade, B. V.; Prabhu, K. R. *J. Org. Chem.* **2012**, *77*, 5364–5370.
[164] Dutta, I.; Yadav, S.; Sarbajna, A.; De, S.; Hölscher, M.; Leitner, W.; Bera, J. K. *J. Am. Chem. Soc.* **2018**, *140*, 8662–8666.
[165] Smith, M. B. *March's Advanced Organic Chemistry*, 7th edition, John Wiley & Sons, Inc., Hoboken, New Jersey, 2013, p. 1077.

A radical addition to nitriles was reported by CLIVE and co-workers in the synthesis of cyclopentanones **3.47** from thionocarbamates **3.46**, which are readily accessible from the corresponding alcohols (Scheme 3.9A).[166] The reaction proceeds *via* generation of alkyl radical **3.48** by treatment of **3.46** with triphenyltin hydride and catalytic AIBN, followed by radical addition to the nitrile.

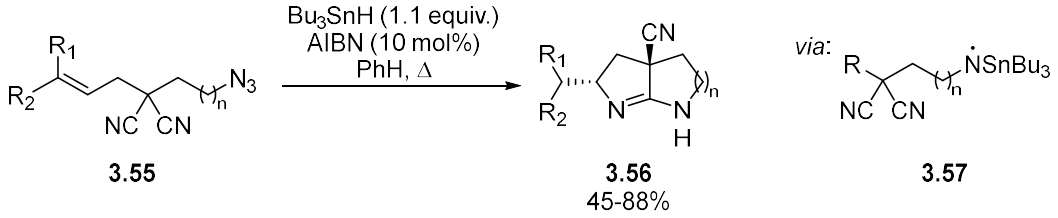
Following a different approach for radical generation, SNIDER and BUCKMAN reported the synthesis of cyclopentanone **3.51** *via* radical annulation of dimethyl 2-cyanomethyl malonate (**3.49**) and 1,1-disubstituted olefin **3.50** (Scheme 3.9B).[167] The reaction commences with the generation of malonate radical **3.52** using $Mn(OAc)_3$. Addition of the radical to olefin **3.50** generates tertiary radical **3.53**, which cyclizes onto the nitrile to form iminyl radical **3.54**. Eventually, **3.54** is reduced by Mn(II) and hydrolyzed to form ketone **3.51**.



Scheme 3.9. Synthesis of cyclic ketones **3.47** and **3.51** *via* intramolecular radical addition to nitriles.

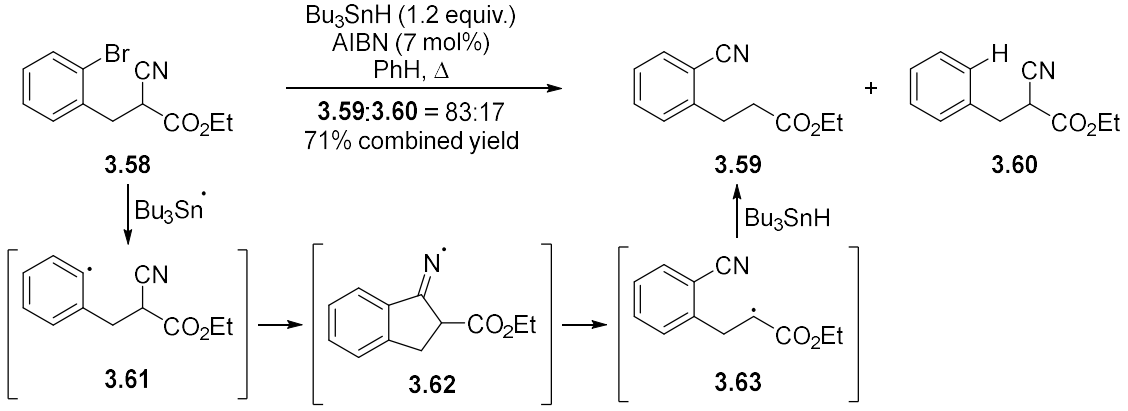
[166] Clive, D. L. J.; Beauliue, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313–1314.
[167] Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322–326.

In 2004, SPAGNOLO and co-workers reported the synthesis of bicyclic amidines **3.56** from malonitriles **3.55**, which contain an azide and an olefin, using tributyltin hydride and catalytic AIBN (Scheme 3.10).[168] Reduction of the azide in **3.55** to the corresponding aminyl radical **3.57** leads to a radical cascade, in which the aminyl radical intramolecularly adds to one of the two nitriles, whereupon the resulting iminyl radical cyclizes onto the olefin to form amidines **3.56**.



Scheme 3.10. Synthesis of bicyclic amidines **3.56** *via* a radical cascade from **3.55**.

However, in addition to the two reaction pathways shown in Scheme 3.8, radical additions to nitriles can also lead to cyano group migration. Treatment of bromobenzene **3.58** with tributyltin hydride and catalytic AIBN afforded a mixture of benzonitrile **3.59** and benzene derivative **3.60** (Scheme 3.11).[169] While the latter is formed by simple hydrogen atom abstraction by the intermediate aryl



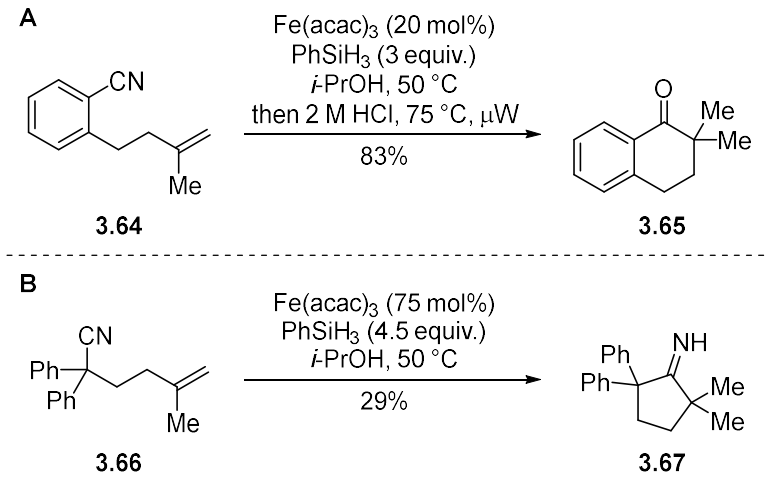
Scheme 3.11. Synthesis of benzonitrile **3.59** *via* radical cyano group migration.

[168] Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G.; Rizzoli, C. *Org. Lett.* **2004**, *6*, 417–420.
[169] Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565–2575.

radical **3.61**, the former arises from radical addition to the nitrile and fragmentation of the resulting iminyl radical **3.62** to alkyl radical **3.63**. It was shown later that changing the ester to less radical stabilizing functional groups,e.g. methyl, results in the formation of cyclic ketones *via* reduction and hydrolysis of iminyl radical **3.62**.[170]

1.2.1. Synthesis Ketones *via* HAT-Mediated Addition to Nitriles

Recently, MURPHY and co-workers reported the hydrogen atom transfer-mediated intramolecular addition of olefins to nitriles.[171] In their studies, a series of substrates containing either 1,1-di- or trisubstituted olefins were subjected to $Fe(acac)_3$ and phenyl silane followed by microwave-assisted acidic work-up (Scheme 3.12A). This gave rise to the corresponding cyclic ketones **3.65** in 61 – 94% yield. In one reaction, highly hindered imine **3.67** was isolated in 29% yield as the sole cyclization product (Scheme 3.12B).



Scheme 3.12. (A) Synthesis of ketones *via* HAT-mediated addition of olefins to nitriles. (B) Synthesis of highly hindered imine **3.67** *via* radical cyclization of **3.66**.

[170] Bowman, W. R.; Bridge, C. F.; Brookes, P. *Tetrahedron Lett.* **2000**, *41*, 8989–8994.
[171] Turner, O. J.; Murphy, J. A.; Hirst, D. J.; Talbot, E. P. A. *Chem. Eur. J.* **2018**, *24*, 18658–18662.

1.3. Project Outline

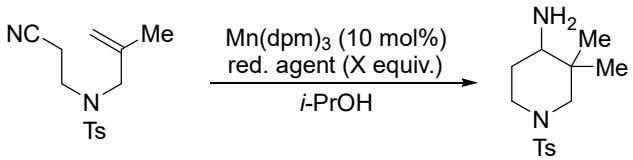
The vast majority of hydrogen atom transfer reactions discussed above in Sections 1.1 and 1.3 describe the simple hydrofunctionalization of an olefin without further modification of the product. We envisioned exploring an intramolecular hydrogen atom transfer-mediated addition of olefins to nitriles followed by reduction of the resulting imine to give primary amines. Key to this cascade reaction will be the choice of reducing agent, which needs to be capable of reducing imines without reducing nitriles. The study will commence with a screening of catalysts and reducing agents to identify suitable reaction conditions for the cyclization/reduction cascade followed by investigations on the scope of this reaction.

2. RESULTS AND DISCUSSION

2.1. Reaction Discovery and Development

We commenced our studies by testing various reducing agents for the transformation of nitrile **3.68a** into primary amine **3.69a**. We decided to focus on reducing agents that are commonly employed in imine reductions. These include formic acid, sodium cyanoborohydride and sodium borohydride. Hence, when **3.68a** was subjected to 10 mol% of $Mn(dpm)_3$ and sodium borohydride (5.0 equiv.) in isopropanol at room temperature, primary amine **3.69a** was obtained in 32% yield (Table 3.1, entry 1). In contrast, when the reductant was changed to sodium cyanoborohydride, only traces of **3.69a** were observed (entry 2). Furthermore, increasing the temperature to 70 °C did not lead to an improvement (entry 3). The use of formic acid as the reducing agent did not afford any product **3.69a** (entry 4). In all cases, the corresponding cyclic ketone was not observed.[172] At this point, we decided to use sodium borohydride to pursue our studies on the cyclization/reduction cascade. In an additional series of experiments, variation of the amount of sodium borohydride between two and five

Table 3.1. Screening of reducing agents for the cyclization/reduction cascade.



3.68a **3.69a**

Entry	Conditions	Yield
1	$NaBH_4$ (5 equiv.), r.t., 13 h	32%[a]
2	$NaBH_3CN$ (5 equiv.), r.t., 25 h	traces[b]
3	$NaBH_3CN$ (5 equiv.), 70 °C, 19 h	traces[c]
4	HCO_2H (16 equiv.), r.t., 17 h	0%[d]

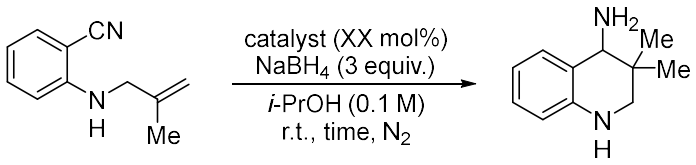
[a]Isolated yield after chromatographic purification. [b]Determined by ^1H NMR analysis after purification by acid/base extraction. [c]Determined by LC/MS analysis of the reaction mixture. [d]Determined by ^1H NMR analysis of the unpurified product mixture.

[172] For comparison, the ketone was prepared using phenylsilane as the reducing agent.

equivalents had no significant effect on the reaction. This was attributed to the low solubility of sodium borohydride in isopropanol.[173] Therefore, we continued our efforts using three equivalents of the reducing agent.

After the successful realization of the cyclization/reduction cascade, we focused on the optimization of reaction conditions using 2-aminobenzonitrile **3.68b**.[171] In the screening of reducing agents, the formation of primary amine **3.69a** had suffered from low conversion. Therefore, we increased the catalyst loading and subjected **3.68b** to 20 mol% of $Mn(dpm)_3$ and sodium borohydride (3.0 equiv.). This gave rise to tetrahydroquinoline **3.69b** in 68% yield along with 22% recovered starting material (Table 3.2, entry 1). When the reaction time was reduced to six hours, primary amine **3.69b** was observed in only slightly lower yield (62%, entry 2). Changing the catalyst to $Mn(acac)_3$ led to reduced conversion and **3.68b** was obtained in 40% yield (entry 3). Hardly any product formation was observed using either $Co(dpm)_3$ or $Fe(dpm)_3$ (entries 4 and 5).

Table 3.2. Optimization of the cyclization/reduction cascade with respect to catalyst and reaction time.



3.68b **3.69b**

Entry	Conditions	Yield[a]	Recovered 3.68b[a]
1	$Mn(dpm)_3$ (20 mol%), 17 h	68%	22%
2	$Mn(dpm)_3$ (20 mol%), 6 h	62%	33%
3	$Mn(acac)_3$ (20 mol%), 21 h	40%	53%
4	$Co(dpm)_3$ (20 mol%), 20 h	<5%	n.d.
5	$Fe(dpm)_3$ (20 mol%), 23 h	<5%	>95%
6	**$Mn(dpm)_3$ (50 mol%), 5 h**	**89%**	**5%**
7	$Mn(acac)_3$ (100 mol%), 6 h	89%	<5%

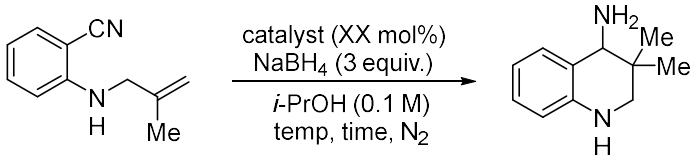
[a]NMR yield after purification by acid/base extraction relative to 1,1,2,2-tetrachloroethane as an internal standard, n.d.: not determined.

[173] The solubility of 3.7 mg/mL of $NaBH_4$ in *i*-PrOH corresponds to 0.98 equiv. at 0.1 M concentration in **3.68a**. Brown, H. C.; Mead, E. J.; Rao, B. C. S. *J. Am. Chem. Soc.* **1955**, *77*, 6209–6213.

After the catalyst loading was increased to 50 mol%, primary amine **3.69b** was obtained in 89% yield along with 5% recovered nitrile **3.68b** (entry 6). The same yield was observed when using one equivalent of $Mn(acac)_3$ (entry 7). However, analysis of ^1H NMR spectra indicated a less clean transformation of **3.68b** to **3.69b** compared to entry 6. For the following optimization studies, we chose to perform the reaction using 20 mol% catalyst and compare the results with entry 1.

Next, we investigated the effect of the reaction temperature on the cyclization/reduction cascade. Decreasing the temperature to 4 °C did not affect the yield of primary amine **3.69b** (Table 3.3, entry 2). However, only 8% of nitrile **3.68b** was recovered. When the temperature was increased to 50 °C, **3.69b** was obtained in 49% yield along with 45% recovered starting material after 73 minutes (entry 3). Increasing the reaction time to five hours under otherwise identical conditions afforded the product in only minimally higher yield (51%, entry 4). This indicated that either the catalyst rapidly decomposed or the reducing agent was fully consumed. However, strong gas evolution was observed for all reactions upon quenching with aqueous HCl, which indicated that some reducing agent had remained active. Hardly any product formation was observed using $Fe(dpm)_3$ at

Table 3.3. Optimization of the cyclization/reduction cascade with respect to catalyst and temperature.



3.68b **3.69b**

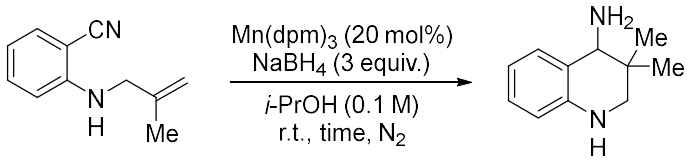
Entry	Conditions	Yield[a]	Recovered 3.68b[a]
1	$Mn(dpm)_3$ (20 mol%), 17 h	68%	22%
2	$Mn(dpm)_3$ (20 mol%), 4 °C, 22 h	69%	8%
3	$Mn(dpm)_3$ (20 mol%), 50 °C, 73 min	49%	45%
4	$Mn(dpm)_3$ (20 mol%), 50 °C, 5 h	51%	40%
5	$Fe(dpm)_3$ (20 mol%), 50 °C, 4.5 h	<5%	88%
6	$Fe(acac)_3$ (34 mol%), 50 °C, 4 h	15%	81%

[a]NMR yield after purification by acid/base extraction relative to 1,1,2,2-tetrachloroethane as an internal standard.

50 °C (entry 5). Changing the catalyst to $Fe(acac)_3$ afforded tetrahydroquinoline **3.69b** in 15% yield along with 81% recovered starting material (entry 6).

Two possible reasons for the high catalyst loadings required for this transformation are the reduction of the catalyst to Mn(II), which cannot be reoxidized to Mn(III) under the inert reaction conditions, and reduction of the dipivaloylmethane or acetylacetonate ligands, which may deactivate the catalyst. With respect to the latter, the diols formed by reduction of either dpm or acac ligands were observed in the analysis of the ^{1}H NMR spectra of the unpurified product mixture. When nitrile **3.68b** was subjected to $Mn(dpm)_3$ and sodium borohydride in the presence of one additional equivalent of dpm, no increase in yield of primary amine **3.69b** was observed (Table 3.4, entry 2). To account for a possible reduction of the catalyst to Mn(II), we performed the reaction open to air.[174] However, this led to reduced yield of **3.69b** as well as reduced amount of recovered **3.68b** (entry 3).

Table 3.4. Cyclization/reduction cascade with one additional equivalent of dpm or open to air.



3.68b 3.69b

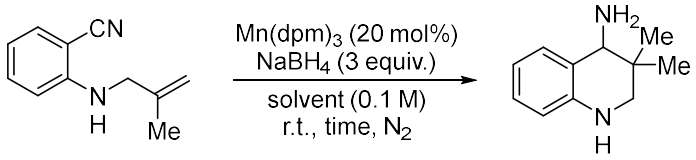
Entry	Deviation from Standard Conditions	Yield[a]	Recovered 3.68b[a]
1	-	68%	22%
2	+ 1 equiv. of dpm, 26 h	66%	5%
3	open to air, 6 h	49%	15%

[a]NMR yield after purification by acid/base extraction relative to 1,1,2,2-tetrachloroethane as an internal standard.

[174] Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacobini, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 2484–2503.

Finally, we investigated the effect of the solvent on the cyclization/reduction cascade. Replacing isopropanol with ethanol led to reduced conversion and primary amine **3.69b** was obtained in 55% yield along with 40% recovered nitrile **3.68b** (Table 3.5, entry 2). Mixtures of isopropanol with either CH_2Cl_2 or THF also led to diminished conversion of **3.68b** (entries 3 and 4). Running the reaction in CH_2Cl_2 or THF only afforded traces amounts of primary amine **3.69b** (entries 5 and 6).

Table 3.5. Screening of solvents for the cyclization/reduction cascade.



3.68b **3.69b**

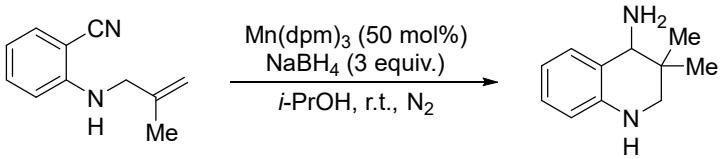
Entry	Conditions	Yield[a]	Recovered 3.68b[a]
1	*i*-PrOH, 17 h	68%	22%
2	EtOH, 23 h	55%	40%
3	*i*-PrOH–CH_2Cl_2 (1:1), 25 h	40%	54%
4	*i*-PrOH–THF (1:1), 25 h	52%	45%
5	CH_2Cl_2, 25 h	<5%	90%
6	THF, 23 h	10%	85%

[a]NMR yield after purification by acid/base extraction relative to 1,1,2,2-tetrachloroethane as an internal standard.

2.2. Control Experiments and Mechanistic Studies

To test if all reagents are required for inducing the cyclization/reduction cascade, we conducted a series of control experiments. First, subjecting nitrile **3.68b** to sodium borohydride in the absence of a manganese catalyst did not lead to any reaction and **3.68b** was recovered (Table 3.6). In the absence of sodium borohydride, $Mn(dpm)_3$ induced partial decomposition of **3.68b**.[175] Significantly more decomposition was observed when subjecting **3.68b** to 100 mol% $Mn(acac)_3$ instead of 50 mol% $Mn(dpm)_3$ in the absence of sodium borohydride.[176] This observation is in agreement with the results in our optimization studies, which indicated a cleaner transformation of nitrile **3.68b** into amine **3.69b** for $Mn(dpm)_3$ than for $Mn(acac)_3$ (Table 3.2).

Table 3.6. Control experiments in the absence of a manganese catalyst or sodium borohydride.



3.68b **3.69b**

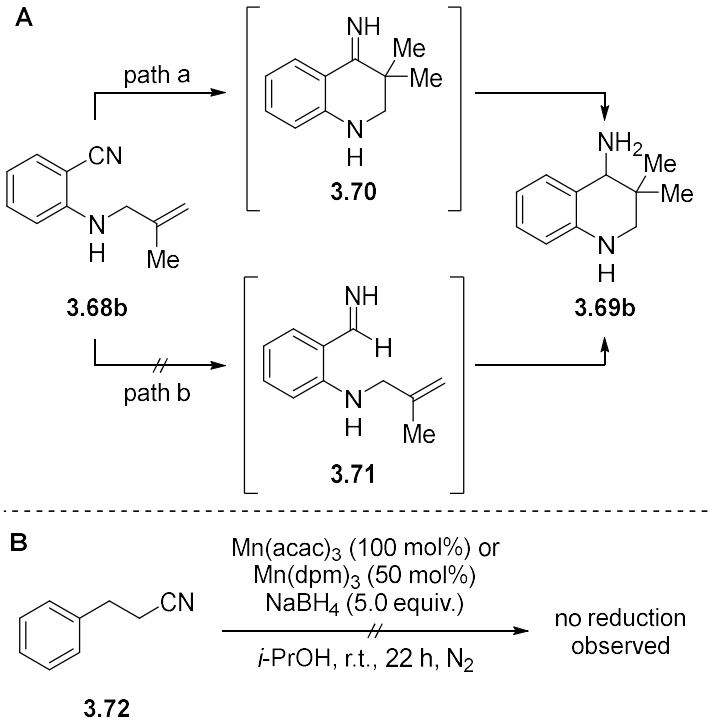
Entry	Deviation from Standard Conditions	Result
1	no $Mn(dpm)_3$	no reaction
2	no $NaBH_4$	no **3.69b** partial decomposition[a]
3	100 mol% $Mn(acac)_3$ instead of $Mn(dpm)_3$ no $NaBH_4$	no **3.69b** more decomposition than entry 2[a]

[a]Determined by ^{1}H NMR analysis of the unpurified product mixture by integration of olefinic and allylic protons of **3.68b** relative to all aromatic protons in the mixture.

Based on previous reports, we expected the reaction to proceed *via* a hydrogen atom transfer-mediated radical cyclization of **3.68b** to give ketimine **3.70**,

[175] Determined by analysis of the ^{1}H NMR spectrum of the unpurified product mixture.
[176] In the 1H NMR analysis of the unpurified product mixtures, 84% and 68% of all aromatic protons corresponded to nitrile **3.68** for entries 2 and 3, respectively.

followed by reduction to amine **3.69b** (Scheme 3.13A, path a). However, also the inverse order of events *via* aldimine **3.71** may be possible (path b). To test if nitriles can be reduced under the reaction conditions, we subjected 3-phenylpropionitrile (**3.72**) to sodium borohydride and either $Mn(dpm)_3$ or $Mn(acac)_3$ (Scheme 3.13B). No reduction products were observed and nitrile **3.72** was recovered, which excludes a reaction mechanism *via* path b.

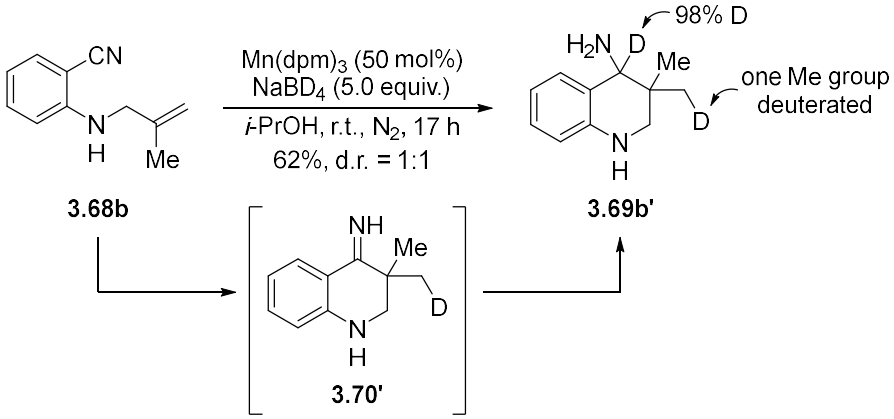


Scheme 3.13. (A) Possible reaction mechanisms. (B) Control experiment in the absence of an olefin.

To confirm whether sodium borohydride is the reducing agent for both reductions or whether isopropanol also reacts as a reductant, we replaced sodium borohydride with sodium borodeuteride.[177] Under these conditions, nitrile **3.68b** was transformed into primary amine **3.69b'** (Scheme 3.14). The product contained two deuterium atoms in the positions that are expected from the proposed reaction mechanism. The α-position of the amine was deuterated in 98% and one of the

[177] Sodium borodeuteride of 99% isotopic purity was used.

two methyl groups was mono-deuterated.[178] The product was obtained as a 1:1 mixture of diastereomers. This is in full agreement with the proposed reaction mechanism as there is no diastereoselectivity expected in the reduction of imine **3.70'**.

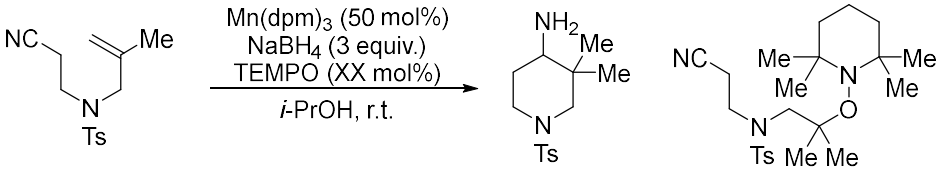


Scheme 3.14. Cyclization/reduction cascade using sodium borodeuteride instead sodium borohydride.

The hydrofunctionalization of olefins is commonly considered a radical reaction.[153] To test if the reaction is influenced by a radical scavenger, we performed the reaction in the presence of varying amounts of TEMPO.[159j] In both cases using either an equimolar amount of $Mn(dpm)_3$ and TEMPO or excess TEMPO, no primary amine **3.69a** was observed in the ^1H NMR spectrum or the LC/MS chromatogram of the unpurified product mixture (Table 3.7). Only traces of TEMPO adduct **3.73** were observed *via* LC/MS.[179] Nitrile **3.68a** was recovered in 85% and 80% yield, respectively.[180] These findings indicate that no hydrogen atom transfer to the olefin occurred, possibly due to hydrogen abstraction from the manganese hydride by TEMPO.

[178] The exact extent of deuteration of the methyl groups could not be determined by NMR spectroscopy due to overlapping signals of CH_3 and CH_2D but the ^1H NMR clearly indicated an almost full mono-deuteration of the *gem*-dimethyl group.
[179] The mass of TEMPO adduct **3.73** was observed (m/z = 436). However, the concentration of **3.73** was too low to be observed in the UV traces at 220 and 254 nm.
[180] Determined by ^1H NMR analysis relative to 1,1,2,2-tetrachloroethane after chromatographic removal of all paramagnetic impurities.

Table 3.7. Radical scavenging experiments using TEMPO.



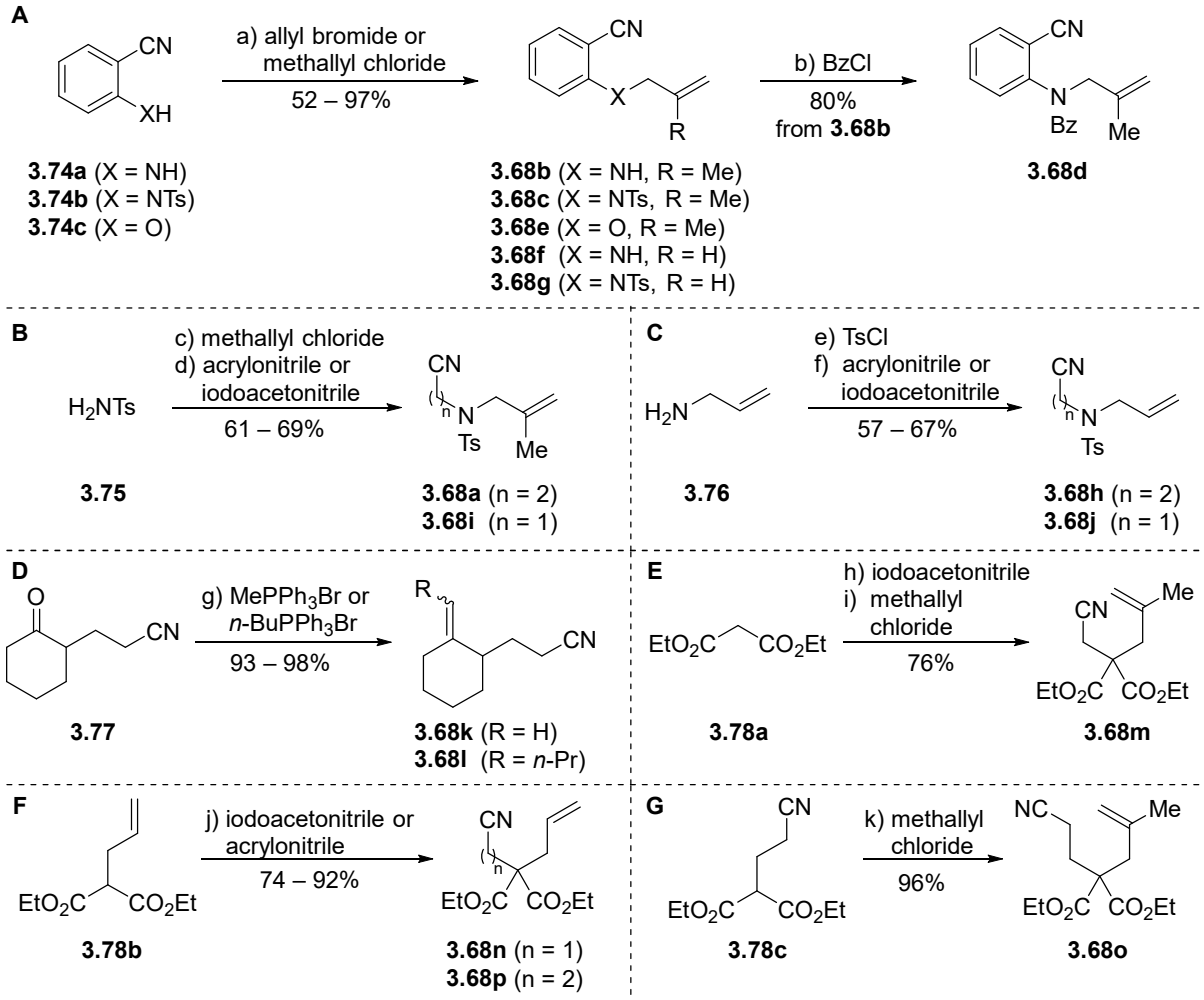
3.68a **3.69a** **3.73**

Entry	TEMPO	Result
1	-	58% **3.69a**
2	50 mol%	0% **3.69a**, 85% **3.68a** recovered[a] traces **3.73** by LC/MS
3	500 mol%	0% **3.69a**, 80% **3.68a** recovered[a] traces **3.73** by LC/MS

[a]Determined by ^{1}H NMR analysis after chromatographic removal of all paramagnetic impurities relative to 1,1,2,2-tetrachloroethane as an internal standard.

2.3. Substrate Scope

With the optimized reaction conditions in hand, we set out to explore the substrate scope of the radical cyclization/reduction cascade. To this end, we prepared a series of substrates **3.68** bearing an aromatic or aliphatic nitrile and a mono-, 1,1-di- or trisubstituted olefin. Substrates **3.68b-c,e-g** were prepared by allylation of the corresponding *ortho*-substituted benzonitriles **3.74**



Scheme 3.15. Synthesis of substrates. Reagents and conditions: (a1) allyl bromide or methallyl chloride, Na_2CO_3, KI, acetone, 55 °C, 52 – 93% for **3.68b**, **3.68e** and **3.68f**; (a2) allyl bromide or methallyl chloride, K_2CO_3, KI, DMF, r.t., 94 – 97% for **3.68c** and **3.68g**; (b) BzCl, Et_3N, DMAP (20 mol%), CH_2Cl_2, r.t., then K_2CO_3, 40 °C, 80%; (c) methallyl chloride, NaI, MeCN, 80 °C, 86%; (d1) acrylonitrile, K_2CO_3, DMF, r.t., 76%; (d2) iodoacetonitrile, NaH, DMF, r.t., 59%; (e) TsCl, Et_3N, DMAP (5 mol%), CH_2Cl_2, 0 °C to r.t.; 74%; (f1) acrylonitrile, K_2CO_2, DMF, r.t., 91%; (f2) iodoacetonitrile, NaH, DMF, r.t., 77%; (g) $MePPh_3Br$ or *n*-$BuPPh_3Br$, KO*t*-Bu, THF, r.t., 93 – 98%, d.r. = 3:1 for **3.68l**; (h) iodoacetonitrile, NaH, THF, 0 °C to r.t., 85%; (i) methallyl chloride, NaH, KI, DMF, r.t., 89%; (j1) iodoacetonitrile, NaH, DMF, r.t., 74%; (j2) acrylonitrile, KO*t*-Bu, *t*-BuOH, r.t., 92%; (k) methallyl chloride, NaH, KI, DMF, 95%.

(Scheme 3.15A).[181] Aniline **3.68b** was further benzoylated to give **3.68d**. Substrates **3.68a,h-j** bearing a tosylamide in the connecting backbone were prepared either by two consecutive alkylations of tosylamide **3.75** or by tosylation and alkylation of allylamine **3.76** (Scheme 3.15B-C).[182] Exocyclic olefins **3.68k-l** were obtained by WITTIG olefination of ketone **3.77** with either methyltriphenylphosphonium bromide or *n*-butyltriphenylphosphonium bromide (Scheme 3.15D).[183] Trisubstituted olefin **3.68l** was obtained as a 3:1 mixture of diastereomers. Malonate-containing substrates were synthesized *via* one or two alkylations of commercially available malonates **3.78a-c** (Scheme 3.15E-G).[111]

We then subjected benzonitrile derivatives **3.68b-g** to the optimized reaction conditions. As described above in the optimization studies, tetrahydroquinoline **3.69b** was obtained in 89% from 2-aminobenzonitrile **3.68b** (Table 3.8, entry 1). The corresponding tosyl and benzoyl protected anilines **3.68c** and **3.68d** also underwent the cascade reaction in 49% and 81% yield, respectively (entries 2 and 3). The analogous 4-aminochromane **3.69e** was obtained in 40% yield from phenol ether **3.68e** along with phenol **3.74c** in 38% yield (entry 4).[184] The formation of **3.74c** can be explained *via* radical fragmentation of tertiary radical **3.79** to a stabilized phenoxy radical (Scheme 3.16).[185] Monosubstituted olefins **3.68f** and **3.68g** were also suitable substrates for the radical cyclization/reduction cascade and 4-aminotetrahydroquinolines **3.69f** and **3.69g** were obtained in 58% and 42% yield as 1.5:1 and 1.7:1 mixtures of diastereomers, respectively (entries 5 and 6). Nitriles **3.68c**, **3.68d** and **3.68g** were insoluble in isopropanol

[181] (a) Anastasiou, D.; Campi, E. M.; Chaouk, H.; Fallon, G. D.; Jackson, W. R.; McCubbin, Q. J.; Trnacek, A. E. *Aust. J. Chem.* **1994**, *47*, 1043–1059; (b) Alp, C.; Özsoy, S.; Alp, N. A.; Erdem, D.; Gültekin, M. S.; Küfrevioğlu, Ö. I.; Şentürk, M.; Supuran, C. T. *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 818–824.

[182] (a) Hori, H.; Arai, S.; Nishida, A. *Org. Biomol. Chem.* **2019**, *17*, 4783–4788; (b) Hosseini, M. W.; Lehn, J.-M. *Helv. Chim. Acta* **1986**, *69*, 598–603; (c) Mukherjee, A.; Liue, R.-S. *Org. Lett.* **2011**, *13*, 660–663.

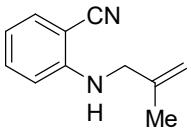
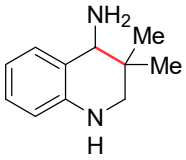
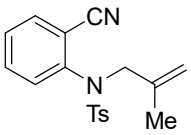
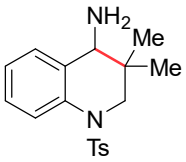
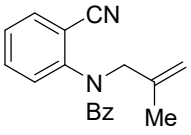
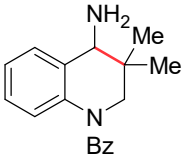
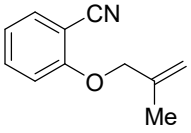
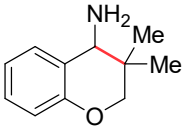
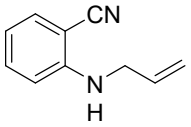
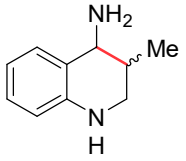
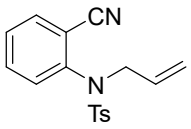
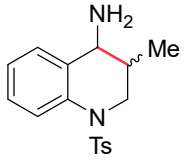
[183] Cren, S.; Schär, P.; Renaud, P.; Schenk, K. *J. Org. Chem.* **2009**, *74*, 2942–2946.

[184] The yield of phenol **3.74c** was determined by NMR spectroscopy after purification by acid/base extraction relative to 1,1,2,2-tetrachloroethane as an internal standard.

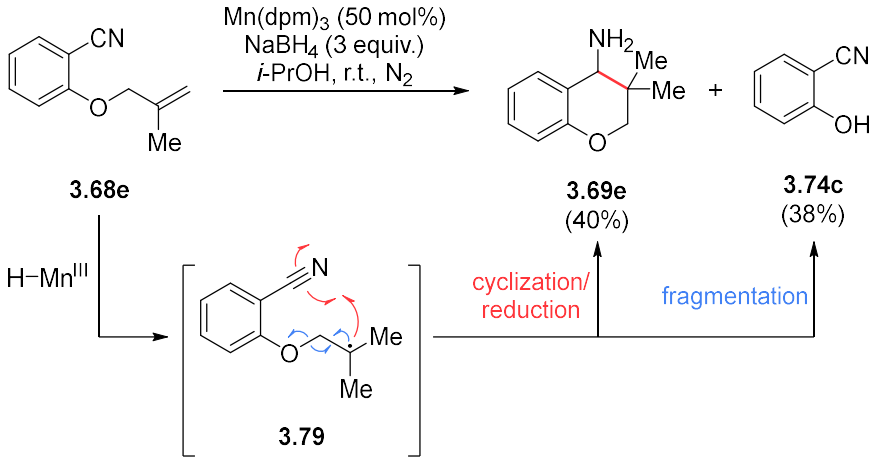
[185] For an example of a radical fragmentation to form a phenol, see: Roy, A.; Tuhina, K.; Biswas, B.; Venkateswaran, R. V. *Tetrahedron* **2012**, *68*, 6575–6580.

and the reactions were performed in a 3:1 mixture of isopropanol and methylene chloride.

Table 3.8. Scope of the radical cyclization/reduction cascade for benzonitriles **3.68b-g**.

Entry	Substrate	Product[a]	Yield[b]
1	 **3.68b**	 **3.69b**	89%
2	 **3.68c**	 **3.69c**	49%[c]
3	 **3.68d**	 **3.69d**	81%[c]
4	 **3.68e**	 **3.69e**	40%[d]
5	 **3.68f**	 **3.69f**	58% d.r. = 1.5:1
6	 **3.68g**	 **3.69g**	42%[c] d.r. = 1.7:1

[a]The red bonds indicate newly formed *C–C* bonds. [b]Conditions: Nitrile **3.68** (0.3 mmol), $Mn(dpm)_3$ (50 mol%), $NaBH_4$ (3.0 equiv.), *i*-PrOH (3 mL), r.t., N_2. Yields correspond to isolated yields after chromatographic purification. [c]1 mL CH_2Cl_2 was added to the reaction mixture to dissolve the substrate; [d]Phenol **3.74c** was isolated as a side-product in 38% yield.

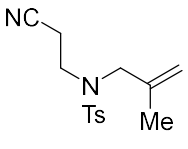
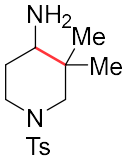
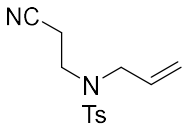
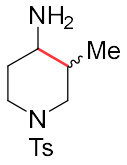
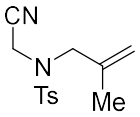
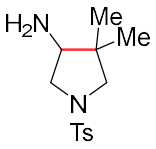
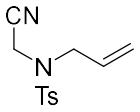
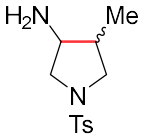
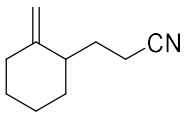
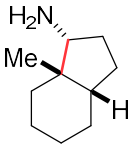
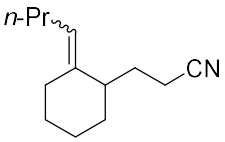
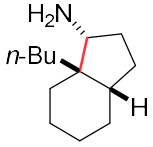


Scheme 3.16. Rational for the formation of phenol **3.74c** from phenol ether **3.68e** under the standard reaction conditions. The red bond indicates newly formed *C–C* bond.

Next, we shifted our attention to aliphatic nitriles **3.68a,h-l**. We first investigated a series of substrates bearing a tosyl amide in the connecting backbone. Under the optimized reaction conditions, 4-aminopiperidine **3.69a** was obtained in 58% yield from nitrile **3.68a** (Table 3.9, entry 1). Changing the methallyl substituent in the substrate to an allyl group gave rise to primary amine **3.69h** in 36% yield as a ~1:1 mixture of diastereomers (entry 2). 2-Aminoacetonitrile derivatives **3.68i** and **3.68j** underwent the cyclization/reduction cascade to form 3-aminopyrrolidines **3.69i** and **3.69j** in 68% and 61% yield, respectively (entries 3 and 4). The latter was obtained in a 2:1 diastereomeric ratio.

We then investigated the cyclization/reduction cascade of exocyclic olefins **3.68k** and **3.68l**, which would generate two new stereocenters in addition to the one present in the substrate. When we subjected **3.68k** and **3.68l** to the optimized reaction conditions, primary amines **3.69k** and **3.69l** were obtained in 81% and 72% yield, respectively. Both products were obtained in higher than 20:1 diastereomeric ratio. The relative configuration of the three stereogenic centers in **3.69k** and **3.69l** was assigned based on ball-and-stick models of the intermediate radical and imine. The radical cyclization is expected to form the *cis*-fused bicycle and the subsequent imine reduction is thought to proceed from the convex face of the bicycle.

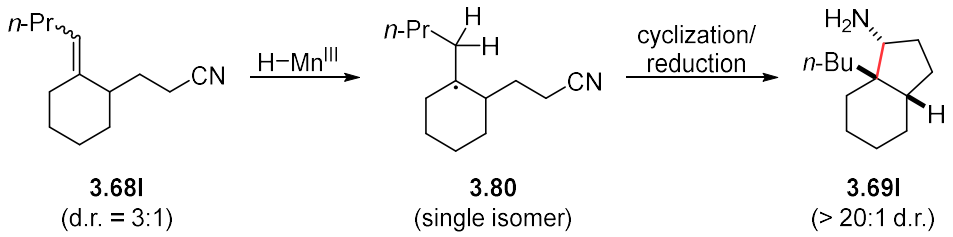
Table 3.9. Scope of the radical cyclization/reduction cascade for aliphatic nitriles **3.68a,h-l**.

Entry	Substrate	Product[a]	Yield[b]
1	 **3.68a**	 **3.69a**	58%
2	 **3.68h**	 **3.69h**	36% d.r. = 1:1
3	 **3.68i**	 **3.69i**	68%
4	 **3.68j**	 **3.69j**	61% d.r. = 2:1
5	 **3.68k**	 **3.69k**	81% d.r. > 20:1
6	 **3.68l** (d.r. = 3:1)	 **3.69l**	72% d.r. > 20:1

[a]The red bonds indicate newly formed *C–C* bonds. [b]Conditions: Nitrile **3.68** (0.3 mmol), $Mn(dpm)_3$ (50 mol%), $NaBH_4$ (3.0 equiv.), *i*-PrOH (3 mL), r.t., N_2. Yields correspond to isolated yields after chromatographic purification.

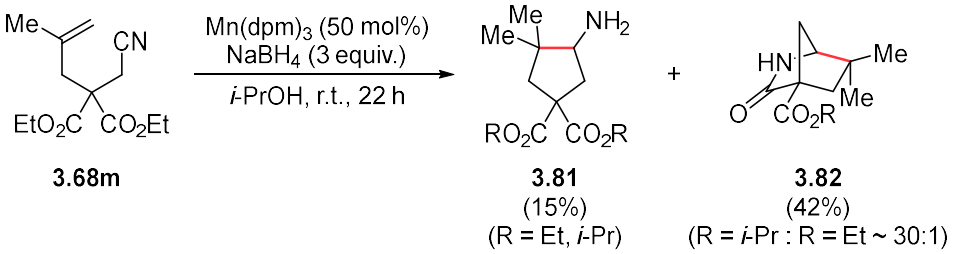
Trisubstituted olefin **3.68l** was used in the cyclization/reduction cascade as a 3:1 mixture of *cis* and *trans* isomers. However, the product was obtained in higher than 20:1 diastereomeric ratio. This can be rationalized by the initial HAT step,

in which both diastereomers of **3.68l** will be transformed into the same tertiary radical **3.80** (Scheme 3.17). Therefore, an identical stereochemical outcome for the cyclization/reduction cascade can be expected for both diastereomers of **3.68l**, which is in full agreement with the observed result.



Scheme 3.17. Rational for the formation of a single diastereomer of primary amine **3.69l** from a mixture of diastereomers of trisubstituted olefin **3.68l**. The red bond indicates the newly formed *C*–*C* bond.

Substrates bearing a malonate in the connecting backbone represent a special set of starting materials. After the cyclization/reduction cascade, the resulting primary amines can undergo lactamization with one of the two esters of the malonate to form bridged bicyclic structures. When we subjected nitrile **3.68m** to the standard reaction conditions, amines **3.81** were observed in 15% yield along with lactams **3.82** in 42% yield (Scheme 3.18).[186] Both products were observed as a mixture of ethyl and isopropyl esters.



Scheme 3.18. Synthesis of amines **3.81** and lactams **3.82** from malonate-containing substrate **3.69m**. The red bonds indicate newly formed *C*–*C* bonds.

[186] The yield of amines **3.81** was determined by analysis of the ^{1}H NMR spectrum of the unpurified product mixture relative to 1,1,2,2-tetrachloroethane as an internal standard. The ratio of the four possible amines **3.81** was not determined.

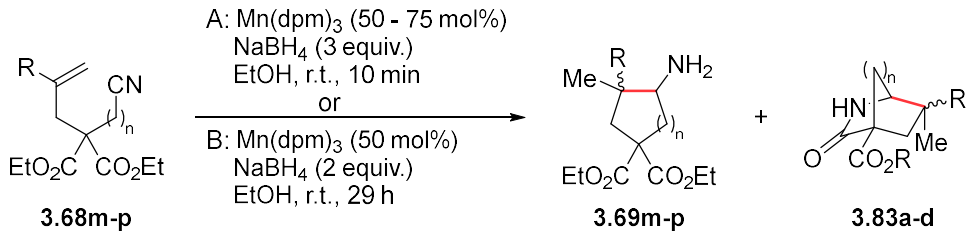
These preliminary results showed that full conversion of **3.68m** was observed after 22 hours but lactamization was incomplete. This indicates that amide formation proceeds at a lower rate than the cyclization/reduction cascade. Our optimization studies had shown that isopropanol as the solvent furnishes the corresponding amines in higher yields than ethanol. However, to avoid undesired transesterification, we decided to use ethanol for substrates bearing a diethyl malonate in the connecting backbone. Sodium borohydride has a significantly higher solubility in ethanol than in isopropanol and only partially dissolves under the standard reaction conditions.[187] As an additional effect besides avoiding transesterification, the solvent change may therefore also accelerate the cyclization/reduction cascade and allow for the selective synthesis of primary amines at short reaction times.

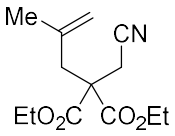
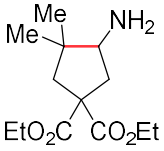
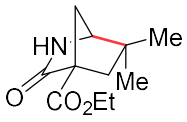
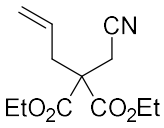
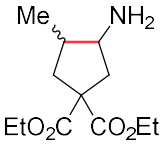
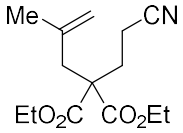
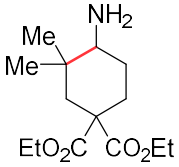
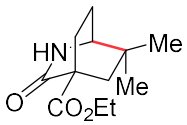
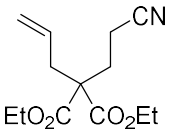
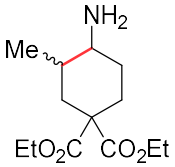
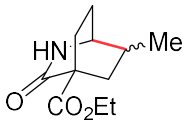
When subjecting nitrile **3.68m** to 50 mol% of $Mn(dpm)_3$ and three equivalents of sodium borohydride in ethanol, full conversion of **3.68m** was observed after ten minutes and amine **3.69m** was isolated in 95% yield (Table 3.10, method A). No lactam **3.83a** was observed in the analysis of the ^1H NMR spectrum of the unpurified product mixture. In contrast, when the reaction time was increased to 29 hours, complete lactamization of amine **3.69m** occurred. However, the ester in **3.83a** was partially reduced to the corresponding alcohol. Reducing the amount of sodium borohydride from three to two equivalents afforded lactam **3.83a** in 63% yield (method B). Monosubstituted olefin **3.68n** was transformed into the corresponding primary amine **3.69n** in 88% yield as a 7:1 mixture of diastereomers using method A. Method B afforded lactam **3.83b** in 52% yield and 5:1 diastereomeric ratio along with 27% yield of amine **3.69n** as a single diastereomer. Nitrile **3.68o** was transformed into the corresponding cyclohexylamine **3.69o** and lactam **3.83c** in 53% and 50% yield *via* method A and B, respectively. Subjecting monosubstituted olefin **3.68p** to method A afforded amine **3.69p** in 69% yield as a 3:1 mixture of diastereomers. Method B for the

[187] Solubility of $NaBH_4$: 31.6 mg/mL in ethanol, 3.7 mg/mL in isopropanol. Banfi, L.; Narisano, E.; Riva, R.; Stiasni, N.; Hiersemann, M.; Yamada, T.; Tsubo, T. Sodium Borohydride in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd., West Sussex, 2014.

same substrate gave a lactam **3.83d** in 29% yield as an equimolar mixture of diastereomers, along with amine **3.69d** in 31% yield and 15:1 diastereomeric ratio.

Table 3.10. Synthesis of amines **3.69** and lactams **3.83** from nitriles **3.68**.



Substrate	Products[a]		Result[b]
 **3.68m**	 **3.69m**	 **3.83a**	Method A: 95% **3.69m** <5% **3.83a**[c] Method B: <5% **3.69m**[c] 63% **3.83a**
 **3.68n**	 **3.69n**	 **3.83b**	Method A: 88% **3.69n**, d.r. = 7:1 <5% **3.83b**[c] Method B: 27% **3.69n**, d.r. > 20:1 52% **3.83b**, d.r. = 5:1
 **3.68o**	 **3.69o**	 **3.83c**	Method A: 53% **3.69o** <5% **3.83c**[c] Method B: <5% **3.69o**[c] 50% **3.83c**
 **3.68p**	 **3.69p**	 **3.83d**	Method A: 69% **3.69p**, d.r. = 3:1 <5% **3.83d**[c] Method B: 31% **3.69p**, d.r. = 15:1 29% **3.83d**, d.r. = 1:1

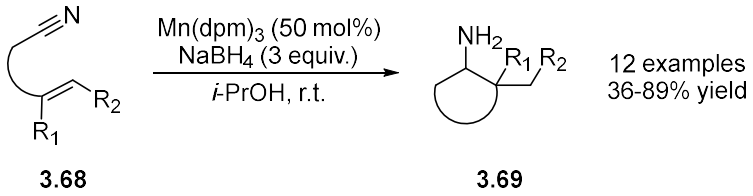
[a]The red bonds indicate newly formed *C–C* bonds. [b]Yields correspond to isolated yields after chromatographic purification. [c]Determined by analysis of the ^{1}H NMR of the unpurified product mixture relative to 1,1,2,2-tetrachloroethane as an internal standard.

The results for malonate-containing substrates **3.68m-p** demonstrated that aminocyclopentanes **3.69m** and **3.69n** were formed in higher yields than the corresponding aminocyclohexanes **3.69o** and **3.69p**. This was attributed to the general kinetic preference for the formation of five-membered over six-membered rings.[188] The lactamization of aminomalonates **3.69m-p** proceeded at a higher rate for *gem*-dimethyl substituted intermediates **3.69m** and **3.69o**, for which complete lactamization was observed. This can be explained with the THORPE–INGOLD effect, which describes the rate acceleration of cyclization reactions by substituting a methylene group with a quaternary center in the connecting backbone.[189] α-Monomethyl substituted amines **3.69n** and **3.69p** were formed as mixtures of diastereomers. However, the rate of lactamization of the two diastereomers differed. In both cases, the minor diastereomer of the amine cyclized faster giving rise to lactams **3.83b** and **3.83d** in a lower diastereomeric ratio than the corresponding amines **3.69n** and **3.69p** obtained *via* method A. Accordingly, unreacted amines **3.69n** and **3.69p** that were obtained *via* method B were isolated in an increased diastereomeric ratio.

[188] For a study on the kinetics of the lactonization of ω-bromo carboxylates, see: Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591–2597.
[189] (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080–1106; (b) For a review on the Thorpe–Ingold effect, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

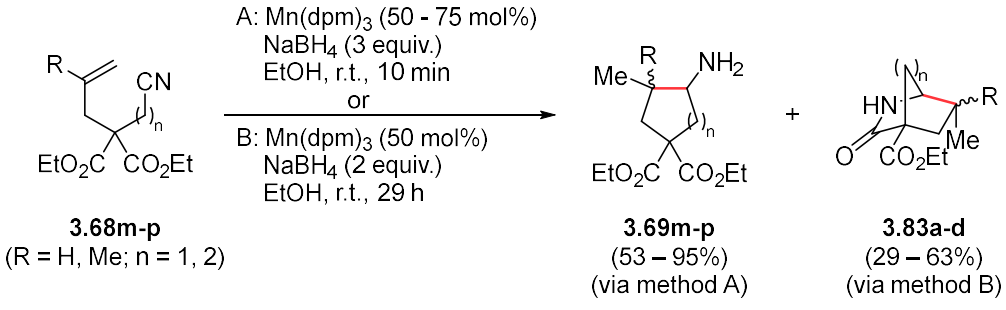
3. CONCLUSION AND OUTLOOK

We have reported a radical cyclization/reduction cascade for the synthesis of primary amines from nitriles using a manganese/sodium borohydride catalytic system. The radical cyclization was induced *via* hydrogen atom transfer-mediated activation of olefins. The reaction proceeds with aromatic and aliphatic nitriles in combination with mono-, 1,1-di- and trisubstituted olefins. Under the optimized reaction conditions, a series of twelve primary amines was prepared successfully in 36-89% yield (Scheme 3.19). However, products containing vicinal stereogenic centers were obtained in low diastereomeric ratios. Here, a greater difference in size of the two α-substituents of the intermediate cyclic imine may lead to higher diastereoselectivities in the reduction.



Scheme 3.19. Synthesis of primary amines **3.69** from nitriles **3.68** *via* a radical cyclization/reduction cascade.

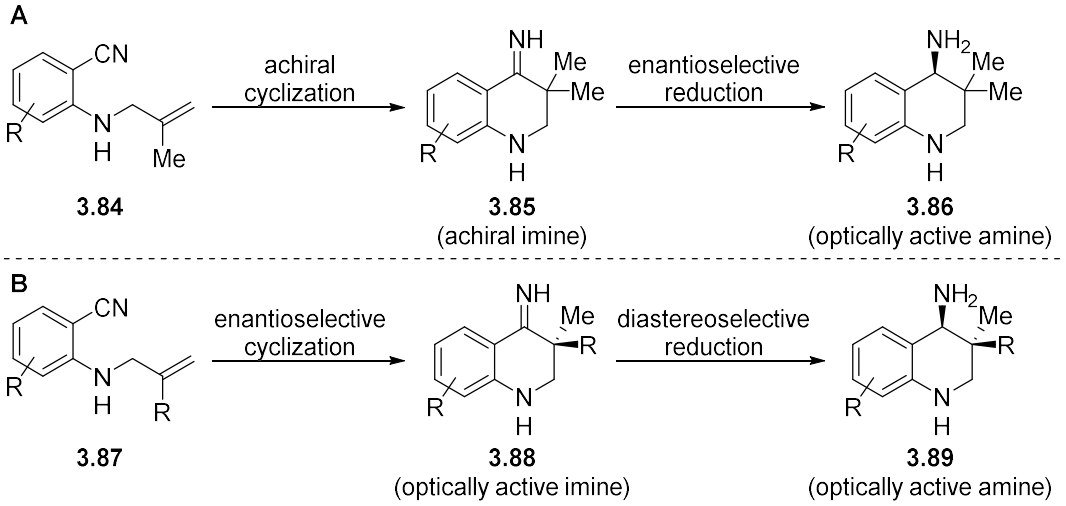
Substrates bearing a diethyl malonate in the connecting backbone could be transformed either into primary amines or lactams depending on the reaction conditions in 53-95% and 29-63% yield, respectively (Scheme 3.20). Significantly higher yields of amines **3.69** were observed for substrates forming



Scheme 3.20. Synthesis of primary amines **3.69m-p** and lactams **3.83a-d** from substrates bearing a diethyl malonate in the connecting backbone.

cyclopentane rings (n = 1) compared to cyclohexane rings (n = 2) and lactamization occurred at a higher rate for primary amines **3.69** bearing *gem*-dimethyl substituents (R = Me).

The presented study affords racemic products. However, this method may be extended to an enantioselective transformation in two possible ways. Substrates **3.84** bearing a methallyl substituent form achiral imines **3.85** as intermediates, which may be reduced enantioselectively to the corresponding optically active primary amines **3.86** (Scheme 3.21A). Alternatively, enantioselectivity may be induced in substrates that form chiral imines **3.88** as intermediates using chiral manganese catalysts, whereupon the subsequent reduction takes place under diastereocontrol (Scheme 3.21B).



Scheme 3.21. Possible approaches to optically active amines *via* the cyclization/reduction cascade.

4

Experimental Part

IV EXPERIMENTAL PART

1. General Methods and Materials

Solvents and reagents: All chemicals were purchased from ABCR, ACROS, Sigma Aldrich, Fluka, TCI, Strem, Alfa Aesar, Combi-Blocks, or Fluorochem, and were used without further purification unless otherwise mentioned. Anhydrous solvents were either purchased over molecular sieves or were obtained using an LC Technology Solutions SP-1 solvent purification system. Deuterated solvents were purchased from Armar Chemicals or Cambridge Isotope Laboratories. Pyridin and diisopropylamine were distilled from KOH under an atmosphere of dry nitrogen. Triethylamine was distilled from CaH_2 under an atmosphere of dry nitrogen.

Reaction handling: All non-aqueous reactions were performed in vacuum dried glassware sealed with rubber septa under a positive pressure of dry nitrogen. Reactions were monitored by thin layer chromatography and stirred magnetically. Thin layer chromatography was performed on MERCK silica gel F254 TLC glass plates and visualized with UV fluorescence quenching, $KMnO_4$ stain, Vanillin stain, or CAM stain. Concentrations under reduced pressure were performed by rotary evaporation at 40 °C at the appropriate pressure. Chromatographic purification was performed as flash column chromatography with 0.3–0.5 bar pressure using SILICYCLE SiliaFlash® Silica Gel P60. The yields given refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise.

NMR spectroscopy: Nuclear Magnetic Resonance spectra were recorded on BRUKER ASCEND, BRUKER AVIII, BRUKER DRX, or BRUKER NEO (400 MHz / 500 MHz for ^{1}H NMR and 126 / 101 MHz for ^{13}C NMR) spectrometers. Measurements were carried out at room temperature. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.16 ppm, acetone at 2.05 and 29.84 ppm, methanol at 3.31 and 49.00 ppm). The data is reported as (s = singlet, d = doublet, t = triplet, m = multiplet or

unresolved, coupling constant(s), integration). ^{13}C NMR spectra were recorded with complete ^{1}H decoupling.

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

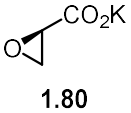
Mass spectrometry: Mass spectrometric analyses were performed as high resolution ESI and EI measurements by the mass spectrometry service of the Laboratorium für Organische Chemie at ETH Zürich by Mr. LOUIS BERTSCHI, Mr. MICHAEL MEIER, Mr. OSWALD GRETER and Mr. DANIEL WIRZ under supervision of Dr. BERTRAN GERRTIS.

Optical rotation: Optical rotations were measured on a Jasco P-2000 Polarimeter, 10 cm, 1.5 mL cell.

Chiral separation: Supercritical fluid chromatography (SFC) was performed on a Jasco 2080 Plus system with a diode array detector. High performance liquid chromatography (HPLC) was performed on a Waters Alliance e2695 HPLC.

2. Total Synthesis of (–)-Mitrephorone A

Potassium (*R*)-oxirane-2-carboxylate (1.80)



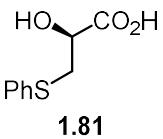
1.80

To a solution of L-serine (156 g, 1.48 mol, 1.0 equiv.) in 7.2 M aq. HCl (1.56 L) at 0 °C was added dropwise over 3 h sodium nitrite (153 g, 2.22 mol, 1.5 equiv.). The mixture was stirred at 0 °C for 4 h and extracted with Et_2O (12 x 0.9 L). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in EtOH (1.44 L) and cooled to 0 °C. KOH (183 g, 3.26 mol, 2.2 equiv.) was added in portions over 1 h. The mixture was stirred at r.t. for 11 h and filtered. The filter cake was washed with cold methanol (3 x 600 mL). To the combined filtrates was added Et_2O (2 L). The precipitate was collected by filtration and washed with Et_2O (2 x 200 mL). The combined filtrates were concentrated to ~400 mL. Et_2O (400 mL) was added and the precipitate was collected by filtration and washed with Et_2O (2 x 200 mL). The combined precipitates were dried *in vacuo* yielding the title compound (130 g, 1.03 mol, 69%) as an off-white solid.

NMR data is in full agreement with the reported values.[24a]

^{1}H NMR (400 MHz, D_2O): δ 3.35 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.92 (dd, *J* = 5.8, 4.8 Hz, 2H), 2.76 (dd, *J* = 5.8, 2.8 Hz, 2H); **^{13}C NMR** (101 MHz MHz, D_2O): δ 176.7, 49.3, 45.9.

(*S*)-2-Hydroxy-3-(phenylthio)propanoic acid (1.81)



1.81

To a solution of potassium (*R*)-oxirane-2-carboxylate (**1.80**) (110 g, 875 mmol, 1.0 equiv.) in methanol (1.44 L) at 0 °C was added dropwise thiophenol (100 mL, 971 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 91 h and concentrated to ~200 mL. EtOAc (400 mL) was added followed by conc. HCl–H_2O–brine (500 mL, 1:1:3). The phases were separated and the aqueous layer was extracted with EtOAc (3 x 350 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to ~200 mL. Hexane (500 mL) was added. The precipitate was collected by filtration and

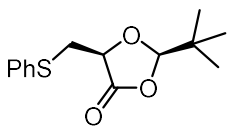
washed with hexane (2 x 100 mL) yielding the title compound (143 g, 721 mmol, 83%) as a white solid and a 3:1 mixture with its regioisomer **1.82**. The material was used for the next steps without further purification.

^{1}H NMR data is in full agreement with the reported values.[24a]

Note: *Analytical data represents a 3:1 mixture of regioisomers, signals of the minor isomer labeled with an asterisk.*

^{1}H NMR (400 MHz, Acetone-d6) δ 7.57 – 7.52 (m, 2H*), 7.48 – 7.43 (m, 2H), 7.40 – 7.30 (m, 2H, 3H*), 7.26 – 7.19 (m, 1H), 4.41 (dd, *J* = 6.8, 4.3 Hz, 1H), 3.96 – 3.81 (m, 3H*), 3.46 (dd, *J* = 13.6, 4.3 Hz, 1H), 3.25 (dd, *J* = 13.6, 6.8 Hz, 1H).

(2*R*,5*S*)-2-(*tert*-Butyl)-5-((phenylthio)methyl)-1,3-dioxolan-4-one (1.83)



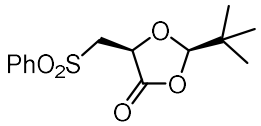
1.83

To a solution of (*S*)-2-hydroxy-3-(phenylthio)propanoic acid (**1.81**) (52.1 g, 263 mmol, 1.0 equiv., 3:1 mixture with regioisomer **1.82**) and pivaldehyde (31.9 mL, 289 mmol, 1.1 equiv.) in Et_2O at 0 °C was added dropwise $BF_3 \cdot OEt_2$ (100 mL, 789 mmol, 3.0 equiv.) over 45 min. The solution was stirred at 0 °C for 4 h. Sat. aq. K_2CO_3 (200 mL) was added dropwise at 0 °C followed by H_2O (1500 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 x 800 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 100:1 to 5:1 gradient) yielding the title compound (48.0 g, 180 mmol mmol, 69%) as a colorless oil that solidified upon standing.

NMR data is in full agreement with the reported values.[24a]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 4.49 (ddd, *J* = 7.1, 3.4, 1.2 Hz, 1H), 3.49 (dd, *J* = 14.5, 3.4 Hz, 1H), 3.20 (dd, *J* = 14.4, 7.1 Hz, 1H), 0.95 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.8, 135.4, 130.4, 129.2, 127.0, 109.9, 75.1, 35.3, 34.5, 23.6.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-((phenylsulfonyl)methyl)-1,3-dioxolan-4-one (1.75)

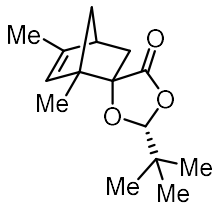

1.75

To a solution of (2*R*,5*S*)-2-(*tert*-butyl)-5-((phenylthio) methyl)-1,3-dioxolan-4-one (**1.83**) (48.0 g, 180 mmol, 1.0 equiv.) in CH_2Cl_2 (337 mL) at 0 °C was added dropwise a solution of 77% *m*-CPBA (89.0 g, 396 mmol, 2.2 equiv.) in CH_2Cl_2 (721 mL). The mixture was stirred at r.t. for 18 h. A mixture of sat. aq. $NaHCO_3$ (1000 mL), sat. aq. $Na_2S_2O_3$ (250 mL) and H_2O (600 mL) was added and the mixture was stirred until gas evolution ceased. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 800 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from hexane–EtOAc yielding the title compound (45.4 g, 152 mmol, 84%) as colorless crystals.

NMR data is in full agreement with the reported values.[24a]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.71 – 7.65 (m, 1H), 7.61 – 7.55 (m, 2H), 5.11 (d, *J* = 1.2 Hz, 1H), 4.82 (ddd, *J* = 10.2, 1.9, 1.2 Hz, 1H), 3.68 (dd, *J* = 15.0, 1.8 Hz, 1H), 3.41 (dd, *J* = 15.0, 10.2 Hz, 1H), 0.77 (s, 9H); **13C NMR** (101 MHz, $CDCl_3$) δ 170.4, 139.5, 134.2, 129.4, 128.5, 110.5, 70.4, 57.6, 34.2, 23.2.

(1*R*,2*S*,2'*R*,4*S*)-2'-(*tert*-Butyl)-1,5-dimethylspiro[bicyclo[2.2.1]heptane-2,4'-[1,3]dioxolan]-5-en-5'-one (1.87)


1.87

A: To a solution of 3-methylcyclopent-2-enone (**1.76**) (21.9 mL, 221 mmol, 3.0 equiv.) in THF (737 mL) at –78 °C was added dropwise methyllithium, 1.6 M in Et_2O (207 mL, 332 mmol, 4.5 equiv.). The mixture was stirred at –78 °C for 30 min and at r.t. for 2 h. H_2O (500 mL) was added carefully while stirring and the phases were separated. The aqueous layer was extracted with Et_2O (3 x 250 mL). The combined organic layers were washed with brine (700 mL), dried over

Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (295 mL).

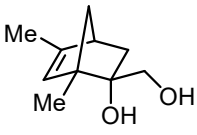
B: To a solution of (2*R*,5*S*)-2-(*tert*-butyl)-5-((phenylsulfonyl)methyl)-1,3-dioxolan-4-one (**1.75**) (22.0 g, 73.7 mmol, 1.0 equiv.) in CH_2Cl_2 (492 mL) at 0 °C was added dropwise DBU (14.5 mL, 96.0 mmol, 1.3 equiv.). The mixture was stirred at 0 °C for 3 h. H_2O (300 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with sat. aq. NH_4Cl (500 mL), sat. aq. $NaHCO_3$ (500 mL) and again sat. aq. NH_4Cl (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

Solution A was added to residue B followed by anhydrous $MgSO_4$ (26.6 g, 221 mmol, 3.0 equiv.). The suspension was stirred at r.t. for 91 h, filtered with $CHCl_3$ (3 x 50 mL) and concentrated under reduced pressure. The residue was purified by FC on silica (hex:Et_2O = 50:1) yielding the title compound (12.3 g, 49.1 mmol, 67%) as yellow oil and inseparable mixture of diastereo- and regioisomers (>93% major isomer).

Note: *NMR data represents the major isomer.*

TLC: R_f = 0.63 (hexane:EtOAc = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.44 – 5.41 (m, 1H), 5.23 (s, 1H), 2.58 – 2.55 (m, 1H), 2.37 (dd, *J* = 12.5, 3.7 Hz, 1H), 2.01 (dt, *J* = 8.9, 1.0 Hz, 1H), 1.83 (d, *J* = 1.7 Hz, 3H), 1.41 (dd, *J* = 12.4, 4.0 Hz, 1H), 1.33 – 1.30 (m, 1H), 1.29 (s, 3H), 0.89 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.5, 150.5, 130.4, 109.4, 89.7, 58.7, 51.9, 46.4, 43.4, 35.3, 23.3, 15.7, 15.0; **IR** (thin film): 2962, 2935, 2908, 2874, 1787, 1631, 1483, 1459, 1443, 1403, 1361, 1343, 1311, 1279, 1256, 1237, 1210, 1156, 1139, 1102, 1070, 1057, 1035, 984, 937, 907, 850, 795, 776, 704, 693, 641, 609, 585, 560, 502 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{28}$ –136.9° (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{15}H_{23}O_3$ $[(M+H)^+]$ 251.1642, found 251.1642.

(1*R*,2*S*,4*S*)-2-(Hydroxymethyl)-1,5-dimethylbicyclo[2.2.1]hept-5-en-2-ol (1.S1)



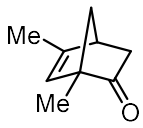
1.S1

To a solution of (1*R*,2*S*,2'*R*,4*S*)-2'-(tert-butyl)-1,5-dimethylspiro [bicyclo[2.2.1]heptane-2,4'-[1,3]dioxolan]-5-en-5'-one (**1.87**) (12.3 g, 49.1 mmol, 1.0 equiv.) in Et_2O (491 mL) at 0 °C was added dropwise $LiAlH_4$, 2.4 M in THF (61.4 mL, 147 mmol, 3.0 equiv.). The mixture was stirred at 0 °C for 15 min. H_2O (5.6 mL) was added dropwise followed by 15% aq. NaOH (5.6 mL) and H_2O (16.8 mL) and the mixture was stirred at r.t. for 15 min. Anhydrous $MgSO_4$ (112 g) was added and stirring was continued at r.t. for 15 min. The mixture was filtered and the filter cake was washed with Et_2O (3 x 100 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 1:1) yielding the title compound (6.74 g, 40.1 mmol, 82%) as yellowish oil and inseparable mixture of diastereo- and regioisomers (>90% major isomer).

Note: *NMR data represents the major isomer.*

TLC: R_f = 0.28 (hex:EtOAc = 2:3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.46 – 5.44 (m, 1H), 3.82 (dd, *J* = 11.1, 1.0 Hz, 1H), 3.58 (d, *J* = 11.0 Hz, 1H), 2.51 – 2.48 (m, 1H), 2.08 (dd, *J* = 12.9, 3.7 Hz, 1H), 2.06 (bs, 1H), 1.83 (d, *J* = 1.7 Hz, 3H), 1.66 (s, 1H), 1.48 (ddd, *J* = 8.8, 3.7, 2.0 Hz, 1H), 1.43 (dt, *J* = 8.8, 1.0 Hz, 1H), 1.17 (s, 3H), 1.14 (dd, *J* = 12.9, 3.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.7, 130.2, 83.3, 68.4, 55.7, 53.3, 46.2, 42.9, 15.7, 13.8; **IR** (thin film): 3392, 3046, 2954, 2870, 1633, 1443, 1374, 1321, 1279, 1239, 1154, 1124, 1102, 1066, 1027, 996, 973, 921, 853, 797, 740, 690, 611, 547 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{27}$ –84.6 (*c* 0.77, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{10}H_{16}O_2$ $[M^{\cdot+}]$ 168.1145, found 168.1165.

(1*R*,4*S*)-1,5-Dimethylbicyclo[2.2.1]hept-5-en-2-one (**1.88**)



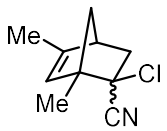
1.88

To a emulsion of (1*R*,2*S*,4*S*)-2-(hydroxymethyl)-1,5-dimethylbicyclo [2.2.1] hept-5-en-2-ol (**1.S1**) (6.74 g, 40.1 mmol, 1.0 equiv.) and H_2O (40 mL) at 0 °C was added sodium hydrogenphosphate dodecahydrate (2.87 g, 8.01 mmol, 0.2 equiv.) followed dropwise addition of a solution of sodium periodate (9.43 g, 44.1 mmol, 1.1 equiv.) in H_2O (160 mL). The mixture was stirred at r.t. for 65 min. Pentane (100 mL) was added and the mixture was filtered through Celite® with pentane (3 x 100 mL). The phases of the filtrate were separated and the aqueous layer was extracted with pentane (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 20:1) yielding the title compound (4.59 g, 33.7 mmol, 84%) as colorless oil and as mixture of regioisomers (25:1).

Note: *Analytical data represents a 25:1 mixture of regioisomers, signals of the minor isomer are labeled with an asterisk. Some ^{1}H NMR signals of the minor isomer were assigned using 2D NMR spectroscopy.*

TLC: R_f = 0.32 (hex:EtOAc = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.77 – 5.75 (m, 1H*), 5.21 – 5.17 (m, 1H), 2.78 – 2.76 (m, 1H*), 2.74 – 2.69 (m, 1H), 2.05 (ddd, *J* = 9.0, 4.5, 2.5 Hz, 1H), 1.97 (ddd, *J* = 17.0, 3.3, 0.6 Hz, 1H), 1.97 – 1.76 (m, 4H*), 1.85 (dd, *J* = 16.4, 4.5 Hz, 1H), 1.77 (d, *J* = 1.7 Hz, 3H), 1.74 – 1.73 (m, 3H*), 1.71 (d, *J* = 9.0 Hz, 1H), 1.31 (s, 3H*), 1.16 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 216.2, 216.1*, 154.0, 141.6*, 139.4*, 127.0, 62.4*, 59.9, 55.9*, 54.8, 47.8*, 44.4*, 43.2, 37.9, 19.2*, 16.3, 15.8*, 12.3; **IR** (thin film): 2963, 2927, 2871, 1738, 1627, 1442, 1419, 1378, 1323, 1308, 1263, 1234, 1195, 1176, 1146, 1126, 1109, 1082, 1040, 1026, 978, 936, 911, 853, 795, 728, 618, 605, 570, 522 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{28}$ –817.7 (*c* 1.00, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_9H_{12}O$ [$M^{\cdot+}$] 136.0883, found 136.0882.

(±)-2-Chloro-1,5-dimethylbicyclo[2.2.1]hept-5-ene-2-carbonitrile (1.90)



1.90

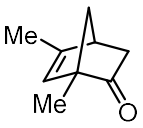
To a solution of 3-methylcyclopent-2-enone (**1.76**) (12.2 mL, 123 mmol, 1.0 equiv.) in THF (410 mL) at –78 °C was added dropwise methyllithium, 1.6 M in Et_2O (100 mL, 160 mmol, 1.3 equiv.). The mixture was stirred at –78 °C for 15 min and at r.t. for 120 min. After cooling to r.t., water (300 mL) was added slowly. The mixture was extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

The crude product was used for the next step without further purification. The crude material was dissolved in $CHCl_3$ (616 mL) before 2-chloroacrylonitrile (9.83 mL, 123 mmol, 1.0 eq.) was added. The mixture was stirred at 50 °C for 12 h followed by concentration under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 5:1) yielding the title compound (20.9 g, 115 mmol, 93%) as yellow oil and inconsequential mixture of diastereomers (9:2).

Note: *Analytical data represents a 9:2 mixture of diastereomers, signals of the minor isomer labeled with an asterisk. If a multiplet contains signals of both diastereomers, the number of protons for both diastereomers is indicated separately (m, xH, yH*).*

TLC: R_f = 0.62 (hexane:EtOAc = 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.47 – 5.45 (m, 1H*), 5.40 – 5.38 (m, 1H), 2.84 (dd, *J* = 13.3, 3.8 Hz, 1H), 2.73 – 2.69 (m, 1H), 2.68 – 2.65 (m, 1H*), 2.47 (ddd, *J* = 13.4, 3.6, 0.7 Hz, 1H*), 2.36 (ddd, *J* = 13.3, 2.7, 0.7 Hz, 1H*), 1.86 – 1.79 (m, 4H, 4H*), 1.71 – 1.64 (m, 2H, 1H*), 1.53 (s, 3H), 1.50 (s, 3H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.4*, 150.0, 129.1*, 129.0, 120.7, 120.3*, 63.7, 63.2*, 60.8, 60.6*, 52.2, 50.3*, 48.8*, 47.9, 46.9, 46.7*, 15.6*, 15.2, 14.6*, 14.4; **IR** (thin film): 3057, 2969, 2935, 2910, 2874, 2234, 1634, 1443, 1384, 1323, 1305, 1278, 1249, 1215, 1169, 1087, 1054, 1036, 1003, 986, 961, 929, 885, 866, 848, 827, 792, 629, 617, 600, 583, 505 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{10}H_{12}N$ [$(M-Cl)^+$] 146.0964, found 146.0969.

(±)-1,5-Dimethylbicyclo[2.2.1]hept-5-en-2-one (***rac*-1.88**)

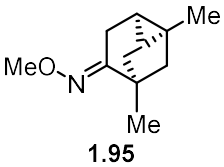


***rac*-15**

To a solution of (±)-2-chloro-1,5-dimethylbicyclo[2.2.1]hept-5-ene-2-carbonitrile (**1.90**) (20.9 g, 115 mmol, 1.0 equiv.) in DMSO (574 mL) was added 6 M aq. KOH (96.0 mL, 574 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 70 h. Brine (500 mL) was added and the mixture was extracted with pentane (4 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 30:1 to 7:1 gradient) yielding the title compounds (11.4 g, 84 mmol, 73%) as yellowish oil.

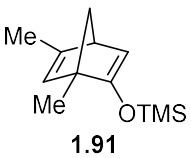
Analytical data is in full agreement with enantioenriched **1.88**.

(1*S*,2*R*,5*S*,7*S*,*E*)-1,5-Dimethyltricyclo[3.2.1.0^{2,7}]octan-4-one *O*-methyl oxime (**1.95**)



1.95

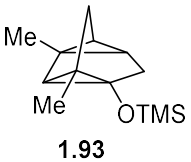
To a solution of diisopropylamine (4.81 mL, 33.8 mmol, 1.15 equiv.) in THF (132 mL) at –78 °C was added dropwise *n*-BuLi, 1.6 M in hexane (20.2 mL, 32.3 mmol, 1.10 equiv.). The mixture was stirred at –78 °C for 30 min. A solution of (1*R*,4*S*)-1,5-dimethylbicyclo[2.2.1]hept-5-en-2-one (**1.88**) (4.00 g, 29.4 mmol, 1.0 equiv.) in THF (15 mL) was added dropwise and stirring was continued at –78 °C for 30 min. TMSCl (5.26 mL, 41.1 mmol, 1.40 equiv.) was added dropwise and stirring was continued at –78 °C for 20 min and at r.t. for 140 min. The mixture as poured into sat. aq. $NaHCO_3$ (200 mL). The phases were separated and the aqueous layer was extracted with pentane (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude silyl enol ether **S3** (5.87 g). The product was found to be instable on silica gel (partial cleavage of silyl ether) and was used in the next step without further purification.



1.91

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (p, *J* = 1.7 Hz, 1H), 5.29 (d, *J* = 3.3 Hz, 1H), 2.94 – 2.91 (m, 1H), 2.03 (dd, *J* = 5.4, 2.0 Hz, 1H), 1.94 (dd, *J* = 5.4, 1.5 Hz, 1H), 1.81 (d, *J* = 1.8 Hz, 3H), 1.22 (s, 3H), 0.17 (s, 9H).

The residue was dissolved in Et_2O (188 mL) and cooled to 0 °C. Diethylzinc, 1 M in hexanes (56.3 mL, 56.3 mmol, 2.00 equiv.) was added dropwise. The mixture was stirred at 0 °C for 5 min. Diiodomethane (4.54 mL, 56.3 mmol, 2.00 equiv.) was added dropwise. Stirring was continued at 0 °C for 30 min and at r.t. for 2.5 h. Pyridine (18.2 mL, 225 mmol, 8.00 equiv.) was added dropwise. The mixture was stirred at r.t. for 30 min followed by filtration through a pad of silica gel with pentane (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was redissolved in pentane (50 mL) and filtered through a pad of Celite® with pentane (3 x 20 mL). The filtrate was concentrated under reduced pressure to give crude silyl cyclopropyl ether **19** (6.36 g). The product was found to be instable on silica gel (partial cleavage of silyl ether) and was used in the next step without further purification.



1.93

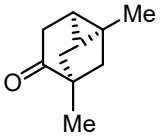
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (dd, *J* = 12.0, 4.6 Hz, 1H), 1.92 (d, *J* = 12.1 Hz, 1H), 1.72 (ddd, *J* = 12.5, 4.0, 1.2 Hz, 1H), 1.64 (d, *J* = 12.5 Hz, 1H), 1.34 (s, 3H), 1.15 (s, 3H), 1.12 (s, 1H), 1.00 – 0.92 (m, 2H), 0.14 (s, 9H).

The residue was dissolved in methanol (35 mL). Tetrabutylammonium hydroxide, 1 M in methanol (35.2 mL, 35.2 mmol, 1.3 equiv.) was added dropwise and the mixture was stirred at r.t. for 1 h. *O*-methylhydroxylamine hydrochloride (3.53 g, 42.3 mmol, 1.5 equiv.) was added and stirring was continued at r.t. for 2 h. The mixture was poured into brine–1 M HCl solution (1:1, 200 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 80:1 to 50:1 gradient) yielding the title compound (3.29 g, 18.4 mmol, 65%) as colorless oil and 20:1 mixture of trans- and cis-oximes.

Note: *NMR data represents the major isomer.*

TLC: R_f = 0.61 (hex:EtOAc = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 2.70 (ddd, *J* = 20.2, 2.7, 0.7 Hz, 1H), 2.63 (dd, *J* = 20.2, 2.7 Hz, 1H), 1.80 – 1.75 (m, 1H), 1.64 – 1.59 (m, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.02 (dd, *J* = 7.7, 3.4 Hz, 1H), 0.77 (dt, *J* = 7.6, 2.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.6, 61.3, 43.5, 43.4, 38.1, 23.4, 23.1, 21.7, 20.1 (2x), 18.0; **IR** (thin film): 3024, 2923, 2898, 2853, 2814, 1635, 1445, 1421, 1377, 1315, 1293, 1174, 1149, 1112, 1050, 996, 967, 886, 866, 847, 801, 603 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{28}$ –1.9 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{11}H_{18}NO$ $[(M+H)^+]$ 180.1383, found 180.1383.

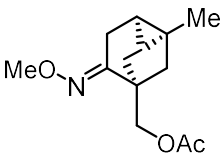
Characterization data for the intermediate dimethyltricyclo[3.2.1.$0^{2,7}$]octanone (**1.94**):



1.94

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 – 2.49 (m, 2H), 1.92 – 1.87 (m, 1H), 1.76 – 1.66 (m, 3H), 1.25 (s, 3H), 1.16 (dd, *J* = 7.6, 3.3 Hz, 1H), 1.03 (s, 3H), 0.91 – 0.86 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 213.2, 76.9, 51.7, 41.9, 36.6, 33.8, 23.2, 22.7, 19.5, 18.2, 17.7.

((1*S*,2*R*,5*R*,7*S*,*E*)-4-(Methoxyimino)-1-methyltricyclo[3.2.1.$0^{2,7}$]octan-5-yl) methyl acetate (1.96)



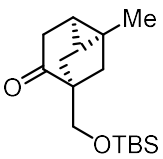
1.96

To a solution of (1*S*,2*R*,5*S*,7*S*,*E*)-1,5-dimethyltricyclo[3.2.1.$0^{2,7}$] octan-4-one *O*-methyl oxime (**1.95**) (7.63 g, 42.5 mmol, 1.0 equiv.) in acetic acid (142 mL) and acetic anhydride (142 mL) was added phenyliodo diacetate (27.4 g, 85.0 mmol, 2.0 equiv.) followed by palladium(II) acetate (1.43 g, 6.38 mmol, 15 mol%). The mixture was stirred at 90 °C for 90 min. After cooling to r.t., pentane (300 mL) was added followed by water (300 mL). Sat. aq. K_2CO_3 (200 mL) was added dropwise while stirring. The phases were separated and the aqueous layer was extracted with pentane (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and

concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 10:1 to 7:1 gradient) yielding the title compound (7.20 g, 30.3 mmol, 71%) as colorless oil.

TLC: R_f = 0.36 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26 (d, *J* = 11.7 Hz, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 3.77 (s, 3H), 2.72 (dd, *J* = 20.2, 2.7 Hz, 1H), 2.65 (dd, *J* = 20.2, 2.7 Hz, 1H), 2.07 (s, 3H), 2.01 (dd, *J* = 12.1, 3.5 Hz, 1H), 1.81 (d, *J* = 12.0 Hz, 1H), 1.55 (dd, *J* = 12.1, 7.0 Hz, 2H), 1.22 (s, 3H), 1.08 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.81 (dt, *J* = 7.6, 2.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2, 159.8, 64.5, 61.6, 46.5, 37.9, 32.7, 22.8, 22.4, 21.5, 21.1, 20.0, 17.5; **IR** (thin film): 2935, 2863, 2816, 1742, 1637, 1446, 1386, 1365, 1312, 1231, 1174, 1143, 1086, 1046, 977, 894, 870, 849, 804, 636, 603, 569, 537 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{27}$ –4.5 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{13}H_{20}NO_3$ $[(M+H)^+]$ 238.1438, found 238.1438.

(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyltricyclo-[3.2.1.0^{2,7}]octan-4-one (1.97)



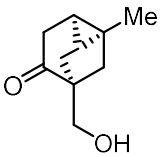
1.97

To a solution of ((1*S*,2*R*,5*R*,7*S*,*E*)-4-(methoxyimino)-1-methyl-tricyclo[3.2.1.0^{2,7}] octan-5-yl)methyl acetate (**1.96**) (2.05 g, 8.63 mmol, 1.0 equiv.) in acetone (173 mL) was added 1 M aq. HCl (60.4 mL, 60.4 mmol, 7.0 equiv.). The resulting mixture was stirred at 60 °C for 16 h. After cooling to r.t., the mixture was diluted with CH_2Cl_2 (250 mL). The phases were separated and the organic layer was washed with water (200 mL) and sat. aq. $NaHCO_3$ (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

To a solution of unpurified alcohol **1.74** in CH_2Cl_2 (173 mL) was added TBSCl (1.95 g, 13.0 mmol, 1.5 equiv.) followed by imidazole (1.18 g, 17.3 mmol, 2.0 equiv.) and DMAP (0.105 g, 0.863 mmol, 10 mol%). The mixture was stirred at r.t. for 17 h. Water (200 mL) was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The

residue was purified by FC on silica (pentane:Et_2O = 50:1) yielding the title compound (1.76 g, 6.27 mmol, 73% over 2 steps) as colorless oil.

TLC: R_f = 0.40 (pentane:Et_2O = 15:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (d, *J* = 10.7 Hz, 1H), 3.63 (d, *J* = 10.7 Hz, 1H), 2.59 (ddd, *J* = 20.4, 2.7, 0.8 Hz, 1H), 2.51 (dd, *J* = 20.4, 2.7 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.02 (d, *J* = 12.4 Hz, 1H), 1.54 – 1.49 (m, 2H), 1.28 (s, 3H), 1.18 (dd, *J* = 7.5, 3.4 Hz, 1H), 0.91 – 0.86 (m, 10H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.3, 60.8, 56.4, 35.5, 34.1, 30.4, 25.9, 22.5, 22.0, 19.5, 18.3, 17.5, –5.5; **IR** (thin film): 2927, 2856, 1716, 1471, 1387, 1360, 1250, 1195, 1169, 1108, 1064, 1000, 938, 884, 852, 835, 774, 735, 663, 580, 521 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{29}O_2Si$ [M+H$^+$] 281.1931, found 281.1930

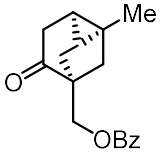


1.74

Occasionally, the intermediate alcohol **1.74** could be isolated in 80% yield by FC on silica (pent:Et_2O = 2:1) as a colorless oil.

TLC: R_f = 0.29 (pentane:Et_2O = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.63 (s, 2H), 2.66 (dd, *J* = 20.7, 2.6 Hz, 1H), 2.58 (dd, *J* = 20.7, 2.6 Hz, 1H), 2.35 (bs, 1H), 1.95 (dd, *J* = 12.8, 3.3 Hz, 1H), 1.89 – 1.80 (m, 2H), 1.74 (d, *J* = 12.8 Hz, 1H), 1.30 (s, 3H), 1.26 (dd, *J* = 7.6, 3.2 Hz, 1H), 0.98 – 0.92 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 214.7, 65.1, 56.8, 37.3, 34.1, 32.2, 22.8, 22.0, 19.4, 17.7; **IR** (thin film): 3423, 3027, 2924, 2865, 1708, 1447, 1401, 1349, 1308, 1187, 1158, 1079, 1055, 1034, 997, 980, 881, 863, 844, 811, 748, 545 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –8.3 (*c* 1.00, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{10}H_{14}O_2$ [M$^+$] 166.0988, found 166.0989.

(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyltricyclo-[3.2.1.0^{2,7}]octan-4-one (1.98)

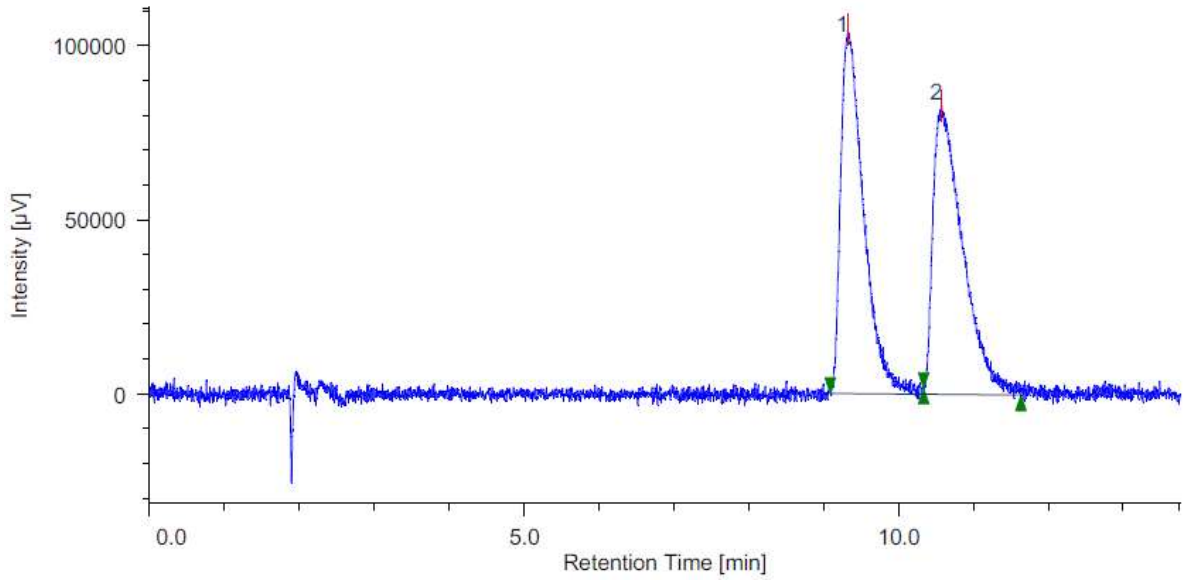


1.98

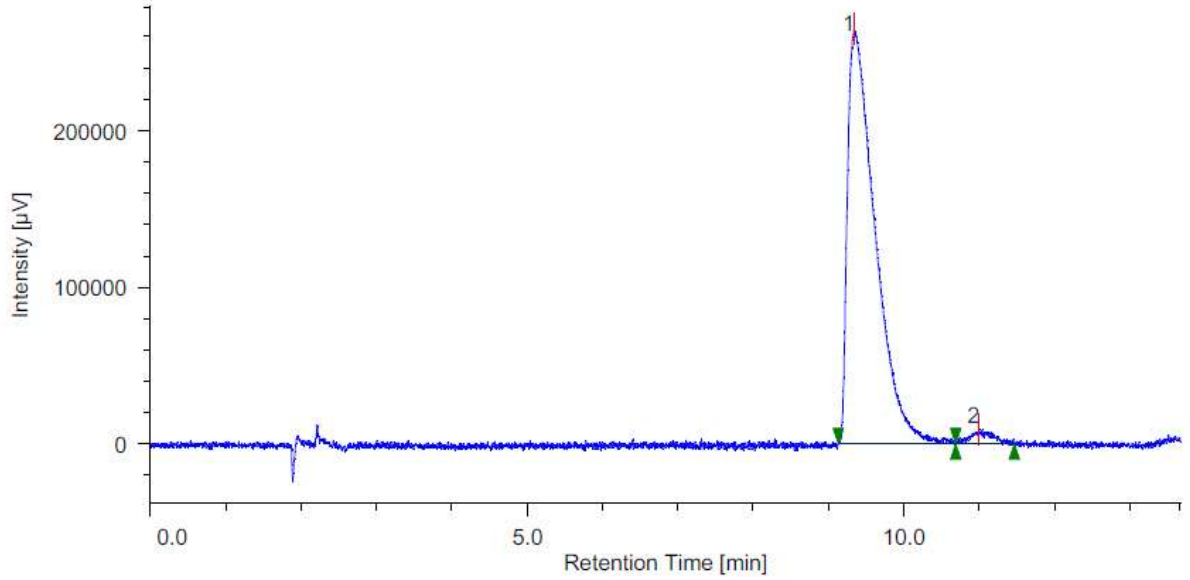
To a solution of (1*S*,2*R*,5*S*,7*S*)-5-(hydroxymethyl)-1-methyltricyclo[3.2.1.0^{2,7}] octan-4-one (**1.74**) (32.0 mg, 0.193 mmol, 1.0 equiv.) in CH_2Cl_2 (2.6 mL) was added Et_3N (54 µL, 0.385 mmol, 2.0 equiv.) followed by benzoyl chloride (27 µL, 0.231 mmol, 1.2

equiv.) and DMAP (4.7 mg, 0.039 mmol, 0.2 equiv.). The mixture was stirred at r.t. for 15 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 20:1) yielding the title compound (47.8 mg, 0.177 mmol, 92%) as yellowish oil.

TLC: R_f = 0.39 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.60 – 7.54 (m, 1H), 7.48 – 7.42 (m, 2H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 2.71 (ddd, *J* = 20.5, 2.7, 0.8 Hz, 1H), 2.63 (dd, *J* = 20.5, 2.7 Hz, 1H), 2.23 – 2.15 (m, 1H), 2.01 – 1.96 (m, 1H), 1.84 (dd, *J* = 12.7, 1.3 Hz, 2H), 1.32 (s, 3H), 1.29 (dd, *J* = 7.6, 3.4 Hz, 1H), 1.01 – 0.96 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.0, 166.5, 133.1, 130.3, 129.7, 128.4, 64.0, 54.8, 37.0, 33.9, 31.9, 22.8, 22.0, 19.4, 17.6; **IR** (thin film): 3062, 3032, 2923, 2863, 1715, 1601, 1584, 1491, 1466, 1450, 1423, 1402, 1383, 1354, 1341, 1313, 1269, 1200, 1174, 1161, 1109, 1079, 1069, 1048, 1026, 1010, 977,956, 937, 896, 875, 844, 812, 746, 709, 687, 657, 617, 595, 580, 563, 549, 483, 448, 421, 403 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –12.2 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{17}H_{19}O_3$ $[(M+H)^+]$ 271.1329, found 271.1330; Enantiomeric purity was determined by SFC analysis in comparison with racemic material T_R = 9.3 (major), T_R= 11.0 (minor) (95% ee shown); Chiracel AS-H column, 99% CO_2 to 1% MeOH 2.0 mL/min, 224 nm, 25 °C).

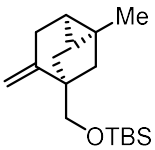


#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	9.320	2240244	104361	49.526	55.758	N/A	4711	1.996	2.069	
2	Unknown	9	10.573	2283084	82808	50.474	44.242	N/A	3492	N/A	2.509	



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	9.340	6763924	264677	97.412	96.640	N/A	3129	2.591	2.734	
2	Unknown	9	11.000	179690	9201	2.588	3.360	N/A	5084	N/A	1.236	

tert-Butyldimethyl(((1*R*,2*R*,5*R*,7*S*)-1-methyl-4-methylenetricyclo[3.2.1.0^{2,7}]octan-5-yl)methoxy)silane (1.99c)

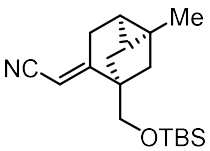


1.99c

To a suspension of methyltriphenylphosphonium bromide (424 mg, 1.19 mmol, 3.3 equiv.) in THF (3.60 mL) was added dropwise KO*t*-Bu, 1 M in THF (1.08 mL, 1.08 mmol, 3.0 equiv.) and the mixture was stirred at r.t. for 60 min. A solution of (1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo-[3.2.1.0^{2,7}]octan-4-one (**1.97**) (101 mg, 0.360 mmol, 1.0 equiv.) in THF (3.60 mL) was added and the mixture was stirred at r.t. for 16 h. Sat. aq. NH_4Cl (10 mL) was added and THF was removed under reduced pressure. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex) yielding the title compound (92 mg, 0.330 mmol, 92%) as a colorless oil.

TLC: R_f = 0.79 (hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.48 – 4.45 (m, 1H), 4.45 – 4.42 (m, 1H), 3.61 (s, 2H), 2.76 – 2.62 (m, 2H), 1.94 (dd, *J* = 11.5, 3.5 Hz, 1H), 1.76 (d, *J* = 11.4 Hz, 1H), 1.41 – 1.33 (m, 2H), 1.19 (s, 3H), 0.99 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.90 (s, 9H), 0.69 – 0.63 (m, 1H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.5, 101.2, 64.9, 48.2, 38.9, 27.1, 25.9, 23.3, 20.4, 19.3, 18.4, -5.5, -5.5; **IR** (thin film): 3025, 2952, 2927, 2894, 2857, 1638, 1471, 1462, 1386, 1361, 1309, 1254, 1192, 1170, 1140, 1079, 1006, 938, 872, 854, 836, 814, 773, 740, 666, 563, 471, 404 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{31}OSi$ $[M+H]^+$ 279.2139, found 279.2137.

(*E*)-2-((1*R*,2*R*,5*R*,7*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)acetonitrile (1.99d)



1.99d

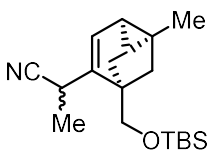
To a solution of (1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-one (**1.97**) (198 mg, 0.706 mmol, 1.0 equiv.) in THF (7.06 mL) was added diethyl cyanomethylphosphonate (0.482 mL, 2.96 mmol, 4.2 equiv.) followed by KO*t*-Bu, 1 M in THF (2.82 mL, 2.82 mmol, 4.0 equiv.) and $LaCl_3 \cdot 2LiCl$, 0.6 M in THF (3.53 mL, 2.12 mmol, 3.0 equiv.). The mixture was

stirred at 65 °C for 1 h. After cooling to r.t., sat. aq. NH_4Cl (10 mL) was added and THF was removed under reduced pressure. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex) yielding the title compound (186 mg, 0.613 mmol, 87%) as a colorless oil.

Note: *The olefin geometry was assigned via 2D NOESY NMR spectroscopy.*

TLC: R_f = 0.48 (hex:EtOAc = 15:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.05 (td, *J* = 2.7, 0.6 Hz, 1H), 3.57 (s, 2H), 3.00 – 2.83 (m, 2H), 1.82 (dd, *J* = 12.1, 3.4 Hz, 1H), 1.63 (d, *J* = 12.0 Hz, 1H), 1.52 – 1.45 (m, 2H), 1.21 (s, 3H), 1.10 (dd, *J* = 7.7, 3.3 Hz, 1H), 0.89 – 0.81 (m, 10H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 117.4, 88.3, 65.5, 50.0, 38.6, 33.4, 27.1, 25.8, 23.0, 22.5, 19.7, 18.4, 18.2, -5.6, -5.6; **IR** (thin film): 3028, 2952, 2928, 2885, 2857, 2214, 1619, 1471, 1463, 1419, 1388, 1361, 1312, 1284, 1252, 1186, 1163, 1107, 1074, 1029, 1006, 983, 939, 883, 835, 814, 774, 666, 616, 598, 539, 452, 433, 417 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{30}NOSi$ $[M+H]^+$ 304.2091, found 304.2092.

2-((1*S*,2*R*,5*R*,7*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)propanenitrile (1.107)



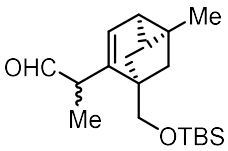
1.107

To a solution of diisopropylamine (39.4 µL, 0.277 mmol, 1.4 equiv.) in THF (2.20 mL) at 0 °C was added dropwise *n*-BuLi, 1.6 M in hexane (161 µL, 0.257 mmol, 1.3 equiv.). The mixture was stirred at 0 °C for 10 min and cooled to –78 °C. A solution of (*E*)-2-((1*R*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-ylidene)acetonitrile (**1.99d**) (60.0 mg, 0.198 mmol, 1.0 equiv.) in THF (1.10 mL) was added dropwise. The mixture was stirred at –78 °C for 30 min. Methyl iodide (30.9 µL, 0.494 mmol, 2.5 equiv.) was added and stirring was continued for 15 h gradually increasing the temperature to r.t. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pent:CH_2Cl_2 = 5:1 to 4:1

gradient) yielding the title compound (41.7 mg, 0.131 mmol, 66%) as a colorless oil and a 1:1 mixture of diastereomers.

TLC: R_f = 0.55 (hex:EtOAc = 15:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.13 – 6.10 (m, 1H), 3.99 (dd, *J* = 10.5, 7.3 Hz, 1H), 3.88 (qd, *J* = 7.1, 1.1 Hz, 1H), 3.66 (dd, *J* = 10.5, 3.0 Hz, 1H), 1.59 – 1.47 (m, 2H), 1.44 (dd, *J* = 7.1, 6.1 Hz, 3H), 1.31 – 1.18 (m, 5H), 0.89 (s, 11H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.2, 137.1, 123.0, 123.0, 122.1, 122.0, 67.0, 67.0, 48.1, 48.1, 39.8, 39.0, 34.0, 33.3, 26.0, 25.2, 25.0, 25.0, 24.8, 24.4, 24.4, 24.0, 23.8, 19.8, 19.6, 18.5, 18.4, 18.4, -5.4, -5.4, -5.4, -5.5; **IR** (thin film): 3036, 2927, 2856, 2236, 1635, 1471, 1462, 1412, 1387, 1361, 1286, 1253, 1194, 1159, 1143, 1075, 1006, 939, 911, 834, 814, 775, 735, 670, 498, 408 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{32}NOSi$ $[M+H]^+$ 318.2248, found 318.2244.

2-((1*S*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)propanal (1.108)



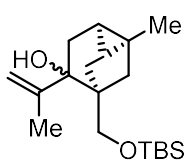
1.108

To a solution of 2-((1*S*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl) oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}] oct-3-en-4-yl)propane-nitrile (**1.107**) (36.0 mg, 0.113 mmol, 1.0 equiv.) in PhMe (2.23 mL) at –78 °C was added dropwise DIBAL-H, 1 M in PhMe (0.227 mL, 0.227 mmol, 2.0 equiv.). The mixture was stirred at –78 °C for 30 min. MeOH (0.2 mL) was added followed by sat. aq. potassium sodium tartrate (7 mL). The mixture was stirred at r.t. for 2.5 h and extracted with EtOAc (3 x 7 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 50:1) yielding the title compound (12.5 mg, 0.039 mmol, 34%) as a colorless oil and a 1:1 mixture of diastereomers.

TLC: R_f = 0.40 (hex:EtOAc = 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 1.5 Hz, 1H), 9.42 (d, *J* = 1.6 Hz, 1H), 5.72 – 5.68 (m, 1H), 3.80 – 3.69 (m, 2H), 3.50 (q, *J* = 7.7, 6.9 Hz, 1H), 1.59 – 1.53 (m, 1H), 1.53 – 1.48 (m, 1H), 1.31 – 1.22 (m, 5H), 1.19 (dd, *J* = 7.0, 5.1 Hz, 3H), 0.88 (s, 9H), 0.77 (dd, *J* = 15.5,

11.3 Hz, 2H), 0.05 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.4, 201.4, 139.0, 138.9, 122.3, 122.3, 66.9, 66.8, 48.4, 48.4, 47.3, 39.3, 38.8, 33.4, 32.9, 26.0, 24.9, 24.9, 24.4, 23.5, 23.4, 18.6, 18.5, 18.4, 15.3, 15.2, -5.4, -5.4, -5.4, -5.4; **IR** (thin film): 3035, 2952, 2928, 2887, 2857, 2708, 1721, 1626, 1471, 1462, 1412, 1386, 1361, 1285, 1252, 1194, 1159, 1143, 1076, 1028, 1006, 981, 939, 836, 814, 775, 670, 501, 405 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{33}O_2Si$ $[M+H]^+$ 321.2244, found 321.2250.

rac-(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-4-(prop-1-en-2-yl)tricyclo [3.2.1.0^{2,7}]octan-4-ol (**1.109**)



1.109

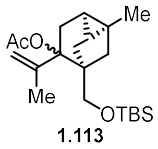
To a solution of *rac*-(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl) oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-one (**1.97**) (4.11 g, 14.7 mmol, 1.0 equiv.) in THF (49 mL) was added $LaCl_3$·2LiCl, 0.5 M in THF (46.9 mL, 23.5 mmol, 1.6 equiv.). The mixture was stirred at r.t. for 1 h and cooled to 0 °C. Isopropenylmagnesium bromide, 0.5 M in THF (58.6 mL, 29.3 mmol, 2.0 equiv.) was added dropwise. The mixture was stirred at r.t. for 30 min. Sat. aq. NH_4Cl (100 mL) and water (100 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 20:1) yielding the title compound (4.06 g, 12.6 mmol, 86%) as a colorless oil and inconsequential mixture of diastereomers (6:5).

Note: *Analytical data represents a 6:5 mixture of diastereomers, ^{1}H NMR signals that correspond to both diastereomers are labeled with an asterisk.*

TLC: R_f = 0.65 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.04 – 5.00 (m, 1H*), 5.00 – 4.95 (m, 1H*), 4.24 (t, *J* = 1.0 Hz, 1H), 4.22 (t, *J* = 0.9 Hz, 1H), 3.83 – 3.74 (m, 1H*), 3.21 – 3.15 (m, 1H*), 2.68 – 2.58 (m, 1H*), 2.32 (td, *J* = 15.2, 2.6 Hz, 1H*), 1.95 – 1.86 (m, 4H*), 1.81 – 1.72 (m, 1H*), 1.30 (dd, *J* = 11.9, 3.2 Hz, 1H), 1.22 – 1.10 (m, 4H*), 1.05 – 0.96 (m, 2H), 0.92 – 0.84 (m, 9H*, 1H), 0.69 – 0.62 (m, 1H*), 0.08 – 0.01 (m, 6H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ

151.3, 151.2, 113.3, 113.2, 78.0, 77.8, 70.8, 70.7, 49.2, 49.1, 37.8, 36.5, 35.6, 35.6, 32.1, 30.7, 25.8, 25.7, 22.7, 22.7, 22.1, 22.1, 21.0, 20.9, 20.3, 20.0, 18.5, 18.5, 18.0, -5.7, -5.8, -5.8; **IR** (thin film): 3498, 2953, 2929, 2859, 1631, 1471, 1361, 1253, 1149, 1102, 1059, 1004, 974, 937, 898, 835, 777, 667, 535, 432 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{34}O_2Si$ $[M+Na]^+$ 345.2220, found 345.2215.

rac-(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyl-4-(prop-1-en-2-yl)tri-cyclo[3.2.1.0^{2,7}]octan-4-yl acetate (1.113)



1.113

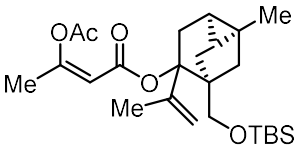
To a solution of *rac*-(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-1-methyl-4-(prop-1-en-2-yl)tricyclo [3.2.1.0^{2,7}]octan-4-ol (**1.109**) (1.06 g, 3.29 mmol, 1.0 equiv.) in freshly distilled acetyl chloride (32.9 mL) was added *N*,*N*-dimethylaniline (1.67 mL, 13.1 mmol, 4.0 equiv.). The mixture was stirred at 50 °C for 24 h. After cooling to r.t., the mixture was diluted with Et_2O (50 mL) and added dropwise to ice-cooled sat. aq. K_2CO_3 (150 mL). After the addition was complete, the mixture was stirred at r.t. for 10 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with sat. aq. K_2CO_3 (100 mL) and 1 M HCl (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:Et_2O = 100:1 to 40:1 gradient) yielding the title compound (0.771 g, 2.11 mmol, 64%) as a colorless oil.

Note: *Analytical data represents a 6:5 mixture of diastereomers, ^{1}H NMR signals that correspond to both diastereomers are labeled with an asterisk.*

TLC: R_f = 0.52 (pentane:Et_2O = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.11 – 5.07 (m, 1H*), 4.86 (s, 1H), 4.84 (s, 1H), 3.61 – 3.57 (m, 1H*), 3.41 – 3.36 (m, 1H*), 2.79 – 2.69 (m, 1H*), 2.32 – 2.21 (m, 1H*), 2.02 (s, 3H), 2.02 (s, 3H), 1.89 – 1.55 (m, 7H*), 1.17 (s, 3H), 1.15 (s, 3H), 0.90 – 0.83 (m, 10H*), 0.66 – 0.58 (m, 1H*), 0.04 – -0.01 (m, 6H*), **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 170.0, 146.5, 146.4, 114.3, 114.3, 86.9, 86.5, 62.5, 62.4, 51.1, 51.0, 34.3, 34.1, 33.7,

33.2, 28.2, 27.6, 25.9, 25.9, 21.8, 21.8, 21.8, 21.8, 21.6, 21.6, 21.2, 20.1, 20.0, 18.4, 18.3, 18.3, 18.2, -5.5, -5.5, -5.5, **IR** (thin film): 2952, 2929, 2858, 1738, 1634, 1471, 1462, 1365, 1251, 1224, 1199, 1176, 1109, 1090, 1062, 1047, 1002, 939, 902, 834, 815, 773, 719, 670, 646, 611, 556, 510 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{36}NaO_3Si$ $[M+Na]^+$ 387.2326, found 387.2327.

Analytical data for cyclic ether **1.114**:

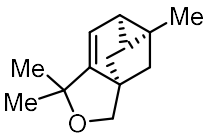


1.114

Note: *Analytical data represents a 6:5 mixture of diastereomers, ^1H NMR signals that correspond to both diastereomers are labeled with an asterisk.*

^{1}H NMR (400 MHz, CDCl3) δ 5.70 – 5.66 (m, 1H*), 5.14 – 5.08 (m, 1H*), 4.89 (s, 1H), 4.87 (s, 1H), 3.61 – 3.54 (m, 1H*), 3.43 – 3.34 (m, 1H*), 2.84 – 2.71 (m, 1H*), 2.39 – 2.25 (m, 4H*), 2.18 (s, 3H), 2.18 (s, 3H), 1.92 – 1.58 (m, 7H*), 1.17 (s, 3H), 1.15 (s, 3H), 0.94 – 0.83 (m, 10H*), 0.64 (ddd, *J* = 10.8, 6.8, 3.4 Hz, 1H*), 0.02 (s, 3H*), 0.00 (d, *J* = 0.9 Hz, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2, 168.1, 165.1, 165.0, 163.9, 146.5, 146.4, 114.4, 114.4, 110.7, 110.6, 87.3, 86.9, 62.4, 62.3, 51.2, 51.1, 34.4, 34.3, 34.1, 33.7, 33.1, 28.1, 27.5, 25.9, 21.9, 21.8, 21.6, 21.5, 21.2, 21.1, 20.0, 20.0, 18.4, 18.3, 18.3, 18.2, 18.0, -5.5, -5.5.

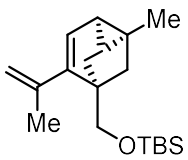
Analytical data for 3-acetoxy-2-butenoate **1.116**:



1.116

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (d, *J* = 5.6 Hz, 1H), 3.95 (s, 2H), 1.72 (dd, *J* = 11.0, 2.3 Hz, 1H), 1.46 – 1.39 (m, 2H), 1.29 (s, 3H), 1.28 (s, 3H), 1.28 (s, 3H), 1.13 (dd, *J* = 7.1, 1.7 Hz, 1H), 0.76 (d, *J* = 10.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 108.7, 81.2, 70.9, 50.1, 38.5, 32.8, 28.0, 27.9, 23.0, 22.6, 22.1, 18.7.

tert-Butyldimethyl(((1*S*,2*R*,5*R*,7*S*)-1-methyl-4-(prop-1-en-2-yl)tricyclo [3.2.1.0^{2,7}]oct-3-en-5-yl) methoxy)silane (1.115)

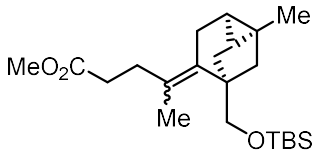


1.115

To a solution of (1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-1-methyl-4-(prop-1-en-2-yl)tricyclo [3.2.1.0^{2,7}]octan-4-ol (**1.109**) (107 mg, 0.332 mmol, 1.0 equiv.) in acetic anhydride (6.6 mL) was added sodium acetate (40.8 mg, 0.498 mmol, 1.5 equiv.). The mixture was stirred at 120 °C for 23 h. After cooling to r.t., the mixture was diluted with Et_2O (20 mL) and cooled to 0 °C. Sat. aq. K_2CO_3 (10 mL) was added dropwise and the mixture was stirred at r.t. for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 60:1) yielding the title compound (45 mg, 0.148 mmol, 45%) as a colorless oil.

TLC: R_f = 0.68 (hex:EtOAc = 200:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 5.9 Hz, 1H), 4.79 (dq, *J* = 2.9, 1.5 Hz, 1H), 4.66 – 4.63 (m, 1H), 3.78 (d, *J* = 10.0 Hz, 1H), 3.75 (d, *J* = 10.0 Hz, 1H), 1.87 – 1.85 (m, 3H), 1.81 (dd, *J* = 11.1, 2.4 Hz, 1H), 1.52 (d, *J* = 11.0 Hz, 1H), 1.46 – 1.42 (m, 1H), 1.31 (s, 3H), 1.22 (dd, *J* = 7.1, 2.4 Hz, 1H), 0.91 (s, 9H), 0.74 – 0.67 (m, 2H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.5, 144.5, 119.6, 112.2, 65.0, 48.0, 37.8, 31.9, 25.9, 25.5, 24.3, 24.0, 23.5, 18.7, 18.3, -5.5, -5.6; **IR** (thin film): 3077, 3034, 2952, 2927, 2857, 1616, 1471, 1462, 1411, 1387, 1361, 1251, 1221, 1193, 1143, 1119, 1082, 1006, 938, 886, 837, 814, 773, 666, 533, 405 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{33}OSi$ $[M+H]^+$ 305.2295, found 305.2297.

***rac*-(*E*)- and (*Z*)-methyl 4-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentanoate (1.120)**



1.120

To a solution of *rac*-(1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-4-(prop-1-en-2-yl)tricyclo[3.2.1.0^{2,7}]octan -4-yl acetate (**1.13**) (2.91 g, 7.98 mmol, 1.0 eqiuv.) in THF (107 mL) at –78 °C was added

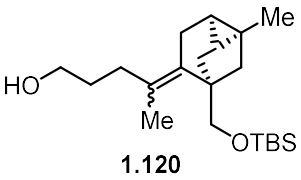
LiHMDS, 1 M in THF (12.8 mL, 12.8 mmol, 1.6 equiv.) followed by TBSCl (1.93 g, 12.8 mmol, 1.6 equiv.) in THF (21 mL) and HMPA (2.22 mL, 12.8 mmol, 1.6 equiv.). The mixture was stirred for 44 h gradually increasing the temperature to r.t. 1 M HCl (40 mL) was added and the mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

The residue was redissolved in DMF (71 mL). Methyl iodide (4.99 mL, 79.8 mmol, 10.0 equiv.) was added followed by K_2CO_3 (5.52 g, 39.9 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 2 h. The mixture was diluted with brine (200 mL) and Et_2O (200 mL). The phases were separated and the aqueous layer was extracted with Et2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 50:1) yielding the title compound (2.64 g, 6.97 mmol, 87%) as a colorless oil and mixture of diastereomers (*E*:*Z* = 2.3:1).

Note: *Analytical data represents a 2.3:1 mixture of diastereomers, ^{1}H NMR signals that correspond to both diastereomers are labeled with an asterisk.*

TLC: R_f = 0.42 (hex:EtOAc = 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 2H, 2H*), 3.67 (s, 3H), 3.64 (s, 3H*), 2.67 – 2.53 (m, 2H), 2.51 – 2.41 (m, 5H*), 2.36 – 2.28 (m, 2H, 1H*), 2.24 – 2.17 (m, 2H), 1.84 (m, 1H, 1H*), 1.72 (t, *J* = 1.9 Hz, 3H), 1.70 – 1.63 (m, 1H, 1H*), 1.54 – 1.45 (m, 2H, 5H*), 1.18 – 1.14 (m, 3H, 3H*), 0.99 – 0.94 (m, 1H, 1H*), 0.89 (s, 9H, 9H*), 0.76 – 0.67 (m, 1H, 1H*), 0.04 (s, 6H*), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.4, 174.1*, 135.0*, 134.7, 120.7*, 120.4, 68.1*, 67.9, 51.6, 51.5*, 51.3, 51.2*, 41.2*, 41.0, 35.8*, 35.6, 34.8*, 32.6, 32.1, 30.8*, 28.5*, 27.1, 26.1 (C,C*), 23.8, 23.8*, 23.8*, 23.8, 21.1*, 20.5*, 20.3, 20.2, 20.2*, 18.8, 18.5*, 18.5, -5.3, -5.3, -5.3*, -5.4*; **IR** (thin film): 2951, 2928, 2857, 1741, 1471, 1462, 1435, 1388, 1360, 1252, 1193, 1161, 1110, 1080, 1005, 939, 836, 774, 664, 568, 418 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{38}NaO_3Si$ $[M+Na]^+$ 401.2482, found 401.2478.

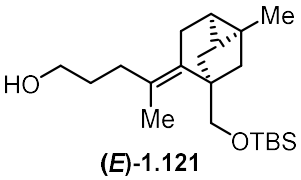
rac-(_E_)- and (_Z_)-4-((1_R_,2_R_,5_R_,7_R_)-5-(((_tert_-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-ylidene)pentan-1-ol (1.121)



1.120

To a solution of _rac_-(_E_)- and (_Z_)-methyl 4-((1_R_,2_R_,5_R_,7_R_)-5-(((_tert_-butyldi-methylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-ylidene) pentanoate (**1.120**) (1.40 g, 3.68 mmol, 1.0 equiv.) in toluene (74 mL) at –78 °C was added dropwise DIBAL-H, 1 M in toluene (9.21 mL, 9.21 mmol, 2.5 equiv.). The mixture was stirred at –78 °C for 30 min and at r.t. for 40 min. Sat. aq. potassium sodium tartrate (100 mL) was added and the mixture was stirred vigorously for 2 h. The phases were separated and the aqueous layer was extracted with EtOAc (3 x100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 12:1 to 5:1 gradient) yielding the (_E_)-isomer (0.76 g, 2.17 mmol, 59%) as a colorless oil and the (_Z_)-isomer (0.34 g, 0.98 mmol, 27%) as a colorless oil.

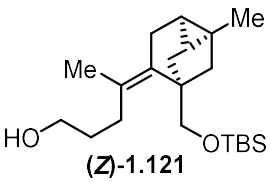
(_E_)-isomer:



(_E_)-1.121

TLC: R_f = 0.28 (pentane:Et_2O = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.74 (s, 2H), 3.64 (t, _J_ = 6.4 Hz, 2H), 2.71 – 2.55 (m, 2H), 2.00 – 1.93 (m, 2H), 1.85 (dd, _J_ = 11.6, 3.5 Hz, 1H), 1.74 (t, _J_ = 1.9 Hz, 3H), 1.70 – 1.58 (m, 3H), 1.55 – 1.48 (m, 2H), 1.40 (s, 1H), 1.17 (s, 3H), 0.96 (dd, _J_ = 7.7, 3.5 Hz, 1H), 0.89 (s, 9H), 0.73 – 0.67 (m, 1H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.7, 121.9, 68.1, 63.6, 51.3, 41.1, 35.7, 33.4, 30.5, 27.2, 26.1, 23.9, 23.8, 20.4, 20.2, 19.1, 18.5, -5.3, -5.3; **IR** (thin film): 3320, 2928, 2857, 1471, 1360, 1252, 1110, 1081, 1060, 1005, 938, 836, 773, 662, 496, 416 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{38}NaO_2Si$ $[M+Na]^+$ 373.2533, found 373.2536.

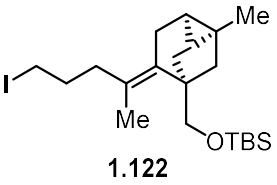
(*Z*)-isomer:



(*Z*)-1.121

TLC: R_f = 0.42 (pentane:Et_2O = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 (s, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.57 – 2.43 (m, 2H), 2.23 – 2.10 (m, 2H), 1.88 (dd, *J* = 11.6, 3.5 Hz, 1H), 1.70 (d, *J* = 11.5 Hz, 1H), 1.62 (ddt, *J* = 9.0, 7.8, 6.6 Hz, 2H), 1.54 – 1.52 (m, 3H), 1.51 – 1.44 (m, 2H), 1.17 (s, 3H), 0.97 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.90 (s, 9H), 0.76 – 0.70 (m, 1H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.2, 122.0, 68.0, 63.2, 51.2, 41.0, 35.6, 32.9, 31.2, 28.5, 26.1, 23.8, 23.8, 21.4, 20.5, 20.2, 18.6, -5.2, -5.2; **IR** (thin film): 3319, 3021, 2951, 2927, 2856, 1471, 1462, 1376, 1360, 1313, 1289, 1251, 1198, 1156, 1109, 1081, 1059, 1005, 939, 834, 815, 773, 664, 569, 501, 455, 429, 406 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{38}NaO_2Si$ $[M+Na]^+$ 373.2533, found 373.2535.

***rac-tert*-butyl(((1*R*,2*R*,5*R*,7*R*,*E*)-4-(5-iodopentan-2-ylidene)-1-methyltricyclo [3.2.1.0^{2,7}] octan-5-yl)methoxy)dimethylsilane (1.122)**



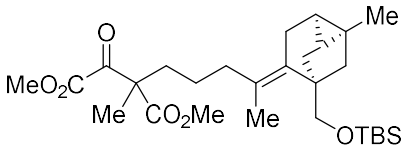
1.122

To a solution of triphenylphosphine (0.684 g, 2.61 mmol, 1.5 equiv.) in CH_2Cl_2 (8.7 mL) was added iodine (0.662 g, 2.61 mmol, 1.5 equiv.). The mixture was stirred at r.t. for 20 min. Imidazole (0.296 g, 4.35 mmol, 2.5 equiv.) and the mixture was stirred at r.t. for 10 min. (*E*)-4-((1*R*,2*R*, 5*R*,7*R*)-5-(((*tert*-butyl-dimethylsilyl)oxy) methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentan-1-ol (**(E)-1.121**) (0.610 g, 1.74 mmol, 1.0 equiv.) in CH_2Cl_2 (8.7 mL) was added. The mixture was stirred at r.t. for 90 min. Sat. aq. $Na_2S_2O_3$ (10 mL) and water (10 mL) were added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane) yielding the title compound (0.778 g, 1.69 mmol, 97%) as a colorless oil.

TLC: R_f = 0.53 (hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 2H), 3.18 (t, *J* = 6.9 Hz, 2H), 2.68 – 2.54 (m, 2H), 2.00 – 1.81 (m, 5H), 1.72 (t, *J* = 1.9 Hz, 3H),

1.69 – 1.65 (m, 1H), 1.50 (dd, *J* = 11.6, 6.9 Hz, 2H), 1.17 (s, 3H), 0.96 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.89 (s, 9H), 0.73 – 0.68 (m, 1H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.3, 120.5, 68.0, 51.3, 41.1, 38.1, 35.7, 31.7, 27.3, 26.1, 23.9, 23.8, 20.3, 20.2, 19.2, 18.5, 7.4, -5.3, -5.3; **IR** (thin film): 3021, 2952, 2927, 2856, 1471, 1462, 1387, 1360, 1252, 1229, 1164, 1111, 1081, 1005, 939, 836, 773, 663, 593 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{37}INaOSi$ $[M+Na]^+$ 483.1551, found 483.1548.

***rac*-Dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-1-methyl-tricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (1.124)**



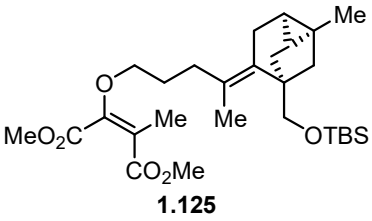
1.124

To a solution of *rac-tert*-butyl(((1*R*,2*R*,5*R*,7*R*,*E*)-4-(5-iodopentan-2-ylidene)-1-methyltricyclo[3.2.1.0^{2,7}] octan-5-yl)methoxy)dimethylsilane (**1.122**) (89.0 mg, 0.193 mmol, 1.0 equiv.) and dimethyl 2-methyl-3-oxosuccinate (**1.123**) (101 mg, 0.580 mmol, 3.0 equiv.) in DMF (5.52 mL) was added potassium carbonate (134 mg, 0.966 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 7 h. Brine (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pentane:Et_2O = 30:1 to 20:1 gradient) yielding the title compound (42.0 mg, 0.083 mmol, 43%) as a colorless oil and 1:1 mixture of diastereomers along with *O*-alkylation product **1.125** (38.0 mg, 0.075 mmol, 39%).

TLC: R_f = 0.52 (pentane:Et_2O = 8:1); **^{1}H NMR** (400 MHz, CDCl3) δ 3.86 (s, 3H), 3.72 (s, 2H), 3.72 (s, 3H), 2.62 – 2.46 (m, 2H), 1.96 – 1.80 (m, 5H), 1.71 – 1.65 (m, 4H), 1.51 – 1.43 (m, 5H), 1.29 – 1.09 (m, 5H), 0.95 (dd, *J* = 7.7, 3.4 Hz, 1H), 0.88 (s, 9H), 0.70 – 0.65 (m, 1H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.7, 172.7, 161.0, 133.8, 121.4, 67.9, 56.6, 53.2, 52.6, 51.3, 41.0, 37.1, 35.6, 35.0, 27.2, 26.1, 23.9, 23.8, 21.7, 20.4, 20.3, 19.7, 19.6, 19.1, 18.5, -5.3, -5.3; **IR**

(thin film): 2952, 2928, 2857, 1759, 1731, 1462, 1435, 1377, 1360, 1297, 1251, 1150, 1111, 1080, 1062, 1028, 939, 836, 814, 774, 664 cm^{-1}; **HRMS** (ESI): exact mass calculated for C28H46NaO6Si $[M+Na]^+$ 529.2956, found 529.2955.

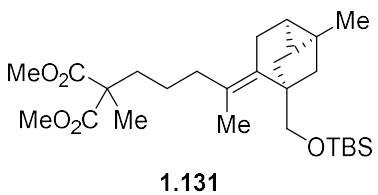
Characterization data for *O*-alkylation product **1.125**:



1.125

TLC: R_f = 0.39 (pentane:Et_2O = 8:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.86 (d, *J* = 6.4 Hz, 5H), 3.73 (s, 2H), 3.71 (s, 3H), 2.67 – 2.49 (m, 2H), 1.99 – 1.93 (m, 2H), 1.89 – 1.82 (m, 4H), 1.76 – 1.64 (m, 6H), 1.53 – 1.46 (m, 2H), 1.17 (s, 3H), 0.96 (dd, *J* = 7.7, 3.4 Hz, 1H), 0.89 (s, 9H), 0.71 – 0.65 (m, 1H), 0.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 164.9, 155.0, 134.1, 120.9, 109.8, 70.6, 67.9, 52.7, 51.9, 51.3, 41.0, 35.7, 33.0, 27.4, 27.1, 26.1, 23.9, 23.8, 20.3, 20.2, 19.1, 18.5, 10.9, -5.3, -5.3.

Dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (1.131)



1.131

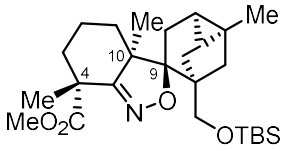
From dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyl-dimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (**1.122**): To a suspension of sodium hydride, 60% in mineral oil (202 mg, 5.05 mmol, 3.0 equiv.) in DMF (11 mL) at 0 °C was added dropwise dimethyl 2-methylmalonate (738 mg, 5.05 mmol, 3.0 equiv.) in DMF (11 mL). The mixture was stirred at 0 °C for 20 min. *tert*-Butyl(((1*R*,2*R*,5*R*,7*R*,*E*)-4-(5-iodopentan-2-ylidene)-1-methyltricyclo[3.2.1.0^{2,7}]octan-5-yl)methoxy)di-methylsilane (**1.122**) (775 mg, 1.68 mmol, 1.0 equiv.) in DMF (11 mL) was added. The mixture was stirred at 80 °C for 2 h. After cooling to r.t., sat. aq. NH_4Cl (30 mL) and water (30 mL) were added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was

purified by FC on silica (hexane:EtOAc = 35:1) yielding the title compound (787 mg, 1.64 mmol, 98%) as a colorless oil.

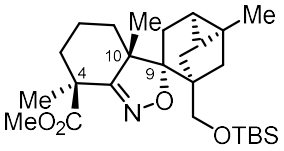
TLC: R_f = 0.38 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 2H), 3.72 (s, 6H), 2.64 – 2.48 (m, 2H), 1.90 – 1.81 (m, 5H), 1.68 (t, *J* = 1.8 Hz, 4H), 1.50 (d, *J* = 6.1 Hz, 1H), 1.47 (d, *J* = 6.1 Hz, 1H), 1.42 (s, 3H), 1.30 – 1.19 (m, 2H), 1.16 (s, 3H), 0.95 (dd, *J* = 7.8, 3.3 Hz, 1H), 0.89 (s, 9H), 0.71 – 0.65 (m, 1H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1, 133.5, 121.7, 67.9, 53.9, 52.6, 51.3, 41.0, 37.1, 35.8, 35.6, 27.2, 26.1, 23.9, 23.8, 22.0, 20.4, 20.3, 20.2, 19.1, 18.5, -5.3, -5.3; **IR** (thin film): 2997, 2951, 2928, 2857, 1735, 1462, 1433, 1378, 1360, 1314, 1251, 1228, 1195, 1167, 1153, 1111, 1080, 1063, 1027, 1004, 985, 939, 835, 815, 773, 680, 664, 561, 497, 471, 408 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –4.8 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{27}H_{46}NaO_5Si$ $[M+Na]^+$ 501.3007, found 501.3006.

***rac*-(1'S,2'R,3R,3aR,5'S,7R,7'S)-Methyl-5'-(((tert-butyldimethylsilyl)oxy) methyl)-1',3a,7-tri-methyl-3a,4,6,7-tetrahydro-5H-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.02,7]octane]-7-carboxylate** (**1.129**) and

***rac*-(1'S,2'R,3S,3aS,5'S,7S,7'S)-Methyl-5'-(((tert-butyldimethylsilyl)oxy) methyl)-1',3a,7-tri-methyl-3a,4,6,7-tetrahydro-5H-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.02,7]octane]-7-carboxylate** (**1.135**)



1.129



1.135

To a solution of *rac-d*imethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.$0^{2,7}$]octan-4-ylidene)pentyl) -2-methylmalonate (**1.131**) (105 mg, 0.219 mmol, 1.0 equiv.) in CH_2Cl_2 (4.39 mL) at –78 °C was added dropwise DIBAL-H, 1 M in PhMe (0.439 mL, 0.439 mmol, 2.0 equiv.). The mixture was stirred at –78 °C for 23 min. Sat. aq. potassium sodium tartrate (5 mL) was added and the mixture was stirred vigorously for 95 min and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was

purified by FC on silica (hex:EtOAc = 35:1) yielding the corresponding formylester **1.133** (66.2 mg, 0.148 mmol, 67%, d.r. = 1:1) as a colorless oil.

To the intermediate aldehyde **1.133** (64.0 mg, 0.143 mmol, 1.0 equiv.) in EtOH (2.53 mL) and pyridine (0.317 mL) was added hydroxylamine hydrochloride (14.9 mg, 0.214 mmol, 1.5 equiv.). The mixture was stirred at r.t. for 11.5 h and concentrated under reduced pressure. To the residue was added H_2O (20 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 20:1) yielding oxime **1.134** (54.0 mg, 0.116 mg, 82%, d.r. = 1:1) as a colorless oil.

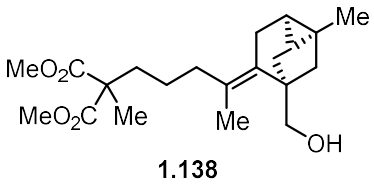
To a solution of the intermediate oxime **1.134** (30.5 mg, 65.7 µmol, 1.0 equiv.) in MeOH (3.29 mL) at –10 °C was added $PhI(OAc)_2$ (29.7 mg, 92.1 µmol, 1.4 equiv.). The mixture was stirred at –10 °C for 55 min. $Na_2S_2O_3$/$NaHCO_3$ solution (0.75 g $Na_2S_2O_3$ in 9 mL sat. aq. $NaHCO_3$ and 10 mL H_2O) was added and the mixture was extracted with PhMe (3 x 10 mL). The combined organic layers were dried over Na_2SO_4. The filtrate was stirred at 100 °C for 60 min and concentrated under reduced pressure. The residue was purified by FC on silica (hex:PhMe = 2:3 then hex:EtOAc = 50:1 to 40:1 gradient) yielding the title compounds (18.4 mg, 39.9 µmol, 61%) as colorless crystals and a 1:1 mixture.

Note: Signals corresponding to undesired diastereomer ***rac*-S3** are labeled with an asterisk. The relative configurations of the diastereomers were assigned by X-ray crystallography.

TLC: R_f = 0.56 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 3H*), 3.72 (s, 3H), 3.68 – 3.60 (m, 1H, 1H*), 3.44 – 3.38 (m, 1H, 1H*), 2.54 – 2.45 (m, 1H, 1H*), 2.28 – 2.17 (m, 1H, 1H*), 2.11 – 1.92 (m, 3H, 3H*), 1.88 – 1.71 (m, 2H, 2H*), 1.67 – 1.54 (m, 3H, 3H*), 1.54 – 1.44 (m, 4H, 4H*), 1.25 – 1.13 (m, 7H, 7H*), 0.89 (d, *J* = 0.5 Hz, 9H, 10H*), 0.82 (dd, *J* = 7.5, 3.2 Hz, 1H), 0.64 – 0.56 (m, 1H, 1H*), 0.03 (s, 3H), 0.03 (s, 3H*), 0.02 (s, 3H, 3H*); **^{13}C NMR** (101 MHz, CDCl3) δ 174.6*, 174.6, 165.1*, 165.1, 91.0*, 90.7, 61.6*, 61.5, 56.4*, 56.4, 52.3*, 52.3, 51.6, 51.3*, 46.6, 46.6*, 39.6, 39.4*, 36.4, 36.1*, 35.2,

32.1*, 29.8*, 27.0, 26.9*, 26.2, 26.1 (C, C*), 23.9*, 23.9, 22.3*, 22.1, 21.6*, 21.2, 20.1, 19.6, 19.6*, 18.8*, 18.6, 18.5*, 18.4, 17.8*, 17.7, -5.3*, -5.3, -5.3; **X-ray**: The crystal structure shows a mixture of ***rac*-32** and ***rac*-S3**. Both diastereomers show the same relative configuration at C_4, C_9 and C_{10}.

Dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(hydroxymethyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (1.138)

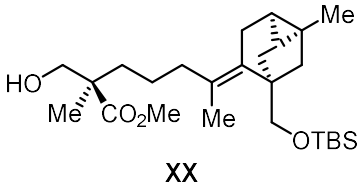


1.138

To a solution of dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (**1.131**) (563 mg, 1.18 mmol, 1.0 equiv.) in THF (11.8 mL) was added TBAF, 1 M in THF (11.8 mL, 11.8 mmol, 10 equiv.). The mixture was stirred at r.t. for 130 min. H_2O (50 mL) was added and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 7:1 to 4:1 gradient) yielding the title compound (389 mg, 1.07 mmol, 91%) as yellowish oil.

TLC: R_f = 0.42 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.78 (d, *J* = 11.1 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.70 (s, 6H), 2.65 – 2.48 (m, 2H), 1.91 – 1.80 (m, 4H), 1.79 – 1.72 (m, 4H), 1.66 – 1.55 (m, 4H), 1.40 (s, 3H), 1.31 – 1.20 (m, 2H), 1.17 (s, 3H), 1.00 (dd, *J* = 7.7, 3.3 Hz, 1H), 0.73 – 0.68 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.0, 132.9, 122.4, 68.8, 53.9, 52.5, 50.9, 41.8, 37.2, 36.4, 35.8, 27.0, 23.9, 23.8, 22.1, 20.3, 20.2, 20.0, 18.8; **IR** (thin film): 3552, 2996, 2950, 2862, 1732, 1433, 1378, 1261, 1196, 1169, 1115, 1038, 983, 881, 842, 816, 694, 507, 406 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –0.5 (*c* 1.00, $CDCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{32}NaO_5$ $[M+Na]^+$ 387.2142, found 387.2139.

(*R*,*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-(hydroxymethyl)-2-methylheptanoate (1.141)



XX

To a solution of dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(hydroxymethyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene) pentyl)-2-methylmalonate (**1.138**) (0.347 g, 0.952 mmol, 1.0 equiv.) in DMSO (3.80 mL) and 0.1 M pH7 sodium phosphate buffer (38 mL) was added pig liver esterase (79 mg, 1428 U) followed by 1 M aq. NaOH (0.952 mL, 0.952 mmol, 1.0 equiv.). The mixture was stirred at r.t. for 21.5 h. More pig liver esterase (79 mg, 1428 U) was added and stirring was continued for 18 h. 1 M pH2 sodium phosphate buffer (30 mL) was added. The mixture was extracted with EtOAc (5 x 45 mL) (phase separation was achieved by centrifugation). The combined organic layers were washed with 1 M HCl–brine (1:4, 150 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

The residue was redissolved in CH_2Cl_2 (19 mL). TBSCl (0.717 g, 4.76 mmol, 5.0 equiv.) was added followed by imidazole (0.648 g, 9.52 mmol, 10 equiv.) and DMAP (0.116 g, 0.952 mmol, 1.0 equiv.). The mixture was stirred at r.t. for 19 h and concentrated under reduced pressure. The residue was redissolved in MeOH–THF–H_2O (20:10:3, 9.9 mL). K_2CO_3 (0.263 mg, 1.90 mmol, 2.0 equiv.) was added and the mixture was stirred at r.t. for 60 min. 1 M HCl–brine (1:4, 40 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with 1 M HCl–brine (1:4, 40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was azeotroped with PhMe (3 x 5 mL).

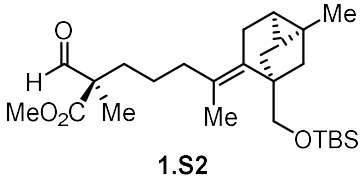
The residue was redissolved in THF (10.6 mL) and cooled to 0 °C. Et_3N (0.199 mL, 0.143 mmol, 1.5 equiv.) was added followed by methyl chloroformate (0.110 mL, 0.143 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 10 min and at r.t. for 90 min, filtered through cotton with Et_2O (10 mL) and concentrated under reduced pressure. The residue was cooled to 0 °C and redissolved in methanol

(10.6 mL). $NaBH_4$ (0.094 g, 2.47 mmol, 2.6 equiv.) was added and the mixture was stirred at 0 °C for 60 min. Sat. aq. NH_4Cl (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = :) yielding the title compound (0.293 g, 0.650 mmol, 68%) as colorless oil and mixture of diastereomers (~20:1) along with malonate (**1.131**) (55 mg, 0.115 mmol, 12%).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.26 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 – 3.69 (m, 6H), 3.47 (d, *J* = 11.2 Hz, 1H), 2.63 – 2.48 (m, 2H), 2.29 (bs, 1H), 1.89 – 1.79 (m, 3H), 1.71 – 1.65 (m, 4H), 1.60 – 1.45 (m, 4H), 1.34 – 1.21 (m, 2H), 1.18 (s, 3H), 1.16 (s, 3H), 0.95 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.88 (s, 9H), 0.70 – 0.65 (m, 1H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.7, 133.3, 121.6, 68.3, 67.8, 51.8, 51.1, 47.9, 40.9, 37.2, 35.9, 35.5, 27.0, 26.0, 23.8, 23.7, 21.8, 20.2, 20.1, 19.7, 18.9, 18.4, -5.4, -5.4; **IR** (thin film): 3449, 3020, 2949, 2928, 2857, 2736, 1729, 1470, 1462, 1433, 1387, 1360, 1328, 1251, 1212, 1196, 1149, 1111, 1079, 1055, 1004, 939, 835, 814, 773, 664, 497, 409 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –2.3 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{26}H_{46}NaO_4Si$ $[M+Na]^+$ 473.3058, found 473.3060.

(*R*,*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-formyl-2-methylheptanoate (1.S2)



1.S2

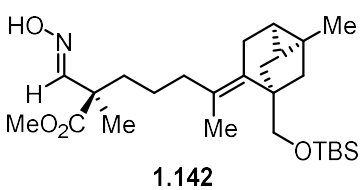
To a solution of (*R*,*E*)-methyl 6-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]oc-tan-4-ylidene)-2-(hydroxymethyl)-2-methylheptanoate (**1.141**) (0.293 g, 0.650 mmol, 1.0 equiv.) in CH_2Cl_2 (8.6 mL) was added *t*-BuOH (0.068 mL, 0.715 mmol, 1.1 equiv.) followed by DMP (0.331 g, 0.780 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 20 min. Et_2O (30 mL) was added followed by sat.

$Na_2S_2O_3$/$NaHCO_3$ solution (2.50 g $Na_2S_2O_3$ in 30 mL sat. aq. $NaHCO_3$ and the mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 40:1) yielding the title compound (0.206 g, 0.459 mmol, 71%) as colorless oil and mixture of diastereomers (~20:1).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.59 (hex:EtOAc = 7.1); **^{1}H NMR** (400 MHz, acetone-d6) δ 9.68 (s, 1H), 3.82 (s, 2H), 3.73 (s, 3H), 2.69 – 2.53 (m, 2H), 1.97 – 1.82 (m, 4H), 1.78 – 1.68 (m, 5H), 1.54 – 1.48 (m, 2H), 1.38 – 1.22 (m, 5H), 1.17 (s, 3H), 0.98 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.91 (s, 9H), 0.74 (dd, *J* = 7.4, 3.3 Hz, 1H), 0.07 (s, 6H); **^{13}C NMR** (101 MHz, acetone-d6) δ 199.2, 172.3, 133.2, 121.5, 67.6, 57.5, 51.7, 51.1, 40.7, 36.7, 35.3, 33.8, 26.7, 25.4, 23.6, 23.5, 21.6, 20.1, 19.4, 18.4, 18.0, 16.1, -6.2, -6.2; **IR** (thin film): 2951, 2928, 2857, 2736, 1751, 1723, 1471, 1461, 1433, 1389, 1374, 1360, 1314, 1251, 1194, 1151, 1112, 1080, 1005, 939, 905, 836, 814, 774, 664, 525, 466, 411, 404 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –8.8 (*c* 1.00, acetone); **HRMS** (ESI): exact mass calculated for $C_{26}H_{44}NaO_4Si$ $[M+Na]^+$ 471.2091, found 471.2090.

(*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-ylidene)-2-((*E*)-(hydroxyimino)methyl)-2-methylheptanoate (1.142)



1.142

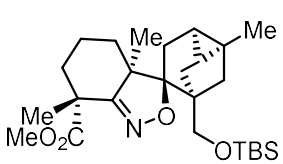
To a solution of (*R*,*E*)-methyl 6-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-bu-tyldimethylsilyl)oxy)methyl)-1-methyltri-cyclo[3.2.1.0^{2,7}]oct-an-4-yli-dene)-2-formyl-2-methyl-heptanoate (**1.S2**) (0.593 g, 1.32 mmol, 1.0 equiv.) in ethanol (23 mL) and pyridine (3 mL) was added hydroxylamine hydrochloride (0.119 g, 1.72 mmol, 1.3 equiv.). The mixture was stirred at r.t. for 13 h followed by concentration under reduced pressure. Et_2O (20 mL) and water (20 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O

(3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 15:1) yielding the title compound (500 mg, 1.08 mmol, 82%) as colorless oil and mixture of diastereomers (~20:1).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.38 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.59 (s, 1H), 3.73 (s, 2H), 3.72 (s, 3H), 2.64 – 2.48 (m, 2H), 1.91 – 1.62 (m, 9H), 1.49 (dd, *J* = 11.5, 5.8 Hz, 2H), 1.36 (s, 3H), 1.34 – 1.24 (m, 2H), 1.17 (s, 3H), 0.95 (dd, *J* = 7.7, 3.4 Hz, 1H), 0.89 (s, 9H), 0.71 – 0.65 (m, 1H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.5, 153.8, 133.5, 121.4, 67.8, 52.3, 51.1, 48.3, 40.8, 37.8, 36.9, 35.5, 27.1, 26.0, 23.8, 23.7, 21.9, 20.2, 20.1, 20.1, 18.9, 18.4, -5.4, -5.4; **IR** (thin film): 3341, 2950, 2928, 2857, 1738, 1471, 1461, 1433, 1377, 1360, 1252, 1194, 1149, 1111, 1080, 1004, 944, 836, 814, 774, 664, 576, 475, 406 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –6.1 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{26}H_{46}NO_4Si$ $[M+H]^+$ 464.3191, found 464.3186.

(1'*S*,2'*R*,3*R*,3a*R*,5'*S*,7*R*,7'*R*)-Methyl 5'-(((*tert*-butyldimethylsilyl)oxy)methyl)-1',3a,7-tri-methyl-4,5,6,7-tetrahydro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (1.129)



1.129

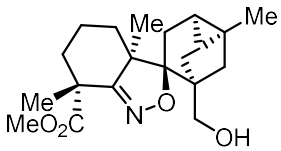
To a solution of (*E*)-methyl 6-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethyl-silyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-((*E*)-(hy-droxy-imino)methyl)-2-methyl-heptanoate (**1.142**) (0.219 g, 0.472 mmol, 1.0 equiv.) in methanol (16.4 mL) at 0 °C was added $PhI(OAc)_2$ (0.228 g, 0.708 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 30 min. PhMe (50 mL) was added followed by sat. aq. $Na_2S_2O_3$–sat. aq. $NaHCO_3$–H_2O (1:1:2, 80 mL). The phases were separated and the aqueous layer was extracted with PhMe (2 x 50 mL). The combined organic layers were washed with brine–sat. aq. $NaHCO_3$ (1:1, 100 mL) and dried over Na_2SO_4. The filtrate was heated to 100 °C for 90 min and concentrated under reduced pressure. The residue was purified by FC on silica

(hex:EtOAc = 25:1) yielding the title compound (0.088 g, 0.191 mmol, 64%) as colorless crystals and mixture of diastereomers (~20:1).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.56 (hex:EtOAc = 5:1); **Melting point:** 162 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.62 (d, *J* = 10.5 Hz, 1H), 3.41 (d, *J* = 10.5 Hz, 1H), 2.52 – 2.45 (m, 1H), 2.20 (dd, *J* = 15.8, 2.8 Hz, 1H), 2.07 – 1.99 (m, 2H), 1.95 (ttd, *J* = 12.4, 12.4, 3.3, 3.1, 0.7 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.63 – 1.52 (m, 3H), 1.50 (d, *J* = 12.4 Hz, 1H), 1.46 (s, 3H), 1.20 (td, *J* = 13.4, 4.2 Hz, 1H), 1.16 (s, 3H), 1.13 (d, *J* = 0.7 Hz, 3H), 0.89 (s, 9H), 0.81 (dd, *J* = 7.5, 3.2 Hz, 1H), 0.62 – 0.58 (m, 1H), 0.02 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 165.0, 90.7, 61.5, 56.4, 52.2, 51.6, 46.6, 39.6, 36.4, 35.2, 26.9, 26.2, 26.1, 23.9, 22.1, 21.2, 20.1, 19.6, 18.6, 18.4, 17.7, -5.3, -5.3; **IR** (thin film): 3020, 2950, 2932, 2884, 2856, 1738, 1602, 1471, 1459, 1433, 1376, 1360, 1300, 1251, 1220, 1206, 1193, 1145, 1110, 1090, 1076, 1039, 1023, 1006, 989, 969, 933, 918, 871, 836, 774, 728, 704, 685, 671, 605, 561, 497, 483, 460, 428 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –161.4 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{26}H_{44}NO_4Si$ [M+H$^+$] 462.3034, found 462.3036.

(1'*S*,2'*R*,3*R*,3a*R*,5'*S*,7*R*,7'*R*)-Methyl 5'-(hydroxymethyl)-1',3a,7-trimethyl-4,5,6,7-tetrahy-dro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}] octane]-7-carboxylate (**1.S3**)



1.S3

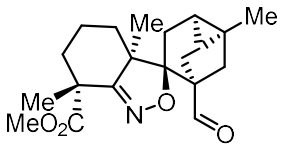
To a solution of (1'*S*,2'*R*,3*R*,3a*R*,5'*S*,7*R*,7'*R*)-methyl 5'-(((*tert*-butyl-dimethylsilyl)oxy)methyl)-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3aH-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxy-late (**1.129**) (55.0 mg, 0.119 mmol mmol, 1.0 equiv.) in THF (2.3 mL) was added TBAF, 1 M in THF (0.596 mL, 0.596 mmol, 5.0 equiv.). The mixture was stirred at 60 °C for 1 h. After cooling to r.t., water (20 mL) was added and the mixture was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica

(hex:EtOAc = 4:1) yielding the title compound (41.0 mg, 0.118 mmol, 99%) as colorless oil and mixture of diastereomers (~20:1).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.52 (hex:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.98 (d, *J* = 11.9 Hz, 1H), 3.70 (s, 3H), 3.30 (d, *J* = 11.9 Hz, 1H), 2.46 (d, *J* = 13.4 Hz, 2H), 2.41 (d, *J* = 12.6 Hz, 1H), 2.29 (dd, *J* = 15.5, 3.7 Hz, 1H), 1.97 (dd, *J* = 15.5, 2.1 Hz, 1H), 1.87 – 1.54 (m, 6H), 1.50 (d, *J* = 12.6 Hz, 1H), 1.46 (s, 3H), 1.27 – 1.20 (m, 1H), 1.17 (s, 3H), 1.16 (s, 3H), 0.90 (dd, *J* = 7.4, 2.8 Hz, 1H), 0.63 – 0.57 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1, 166.9, 92.2, 67.4, 56.4, 52.3, 49.8, 46.1, 38.7, 37.5, 34.9, 30.5, 28.3, 24.1, 22.6, 21.5, 19.5, 19.3, 19.2, 17.3; **IR** (thin film): 3440, 2948, 2874, 1736, 1458, 1435, 1376, 1348, 1301, 1253, 1221, 1146, 1101, 1074, 1052, 1024, 987, 917, 889, 852, 836, 809, 792, 754, 728, 704, 687, 668, 606, 585, 548, 531, 484, 461, 429, 415 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –66.0 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{20}H_{30}NO_4$ $[M+H^+]$ 348.2169, found 348.2171.

(1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-Methyl 5'-formyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro [benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (**1.143**)



1.143

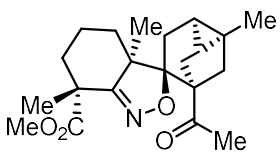
To a solution of (1'*S*,2'*R*,3*R*,3a*R*,5'*S*,7*R*,7'*R*)-methyl 5'-(hydroxymethyl) -1',3a,7-trimethyl-4,5,6,7-tetrahydro-3aH-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (**1.S3**) (41.0 mg, 0.118 mmol, 1.0 equiv.) and *t*-BuOH (12.4 µL, 0.130 mmol, 1.1 equiv.) in CH_2Cl_2 (2.4 mL) was added DMP (60.1 mg, 0.142 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 16 min. Et_2O (16 mL) was added followed by sat. $Na_2S_2O_3$/$NaHCO_3$ solution (0.75 g $Na_2S_2O_3$ in 9 mL sat. aq. $NaHCO_3$). The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 12:1)

yielding the title compound (35.1 mg, 0.102 mmol, 86%) as colorless oil and mixture of diastereomers (~20:1).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.36 (hex:EtOAc = 5:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.82 (d, *J* = 1.1 Hz, 1H), 3.66 (s, 3H), 2.66 (d, *J* = 11.8 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.36 (dd, *J* = 15.7, 2.9 Hz, 1H), 2.24 (ddd, *J* = 13.2, 3.4, 0.8 Hz, 1H), 2.12 (dd, *J* = 15.7, 2.9 Hz, 1H), 1.80 – 1.55 (m, 5H), 1.48 (s, 3H), 1.29 (dd, *J* = 11.6, 1.0 Hz, 1H), 1.27 – 1.18 (m, 4H), 1.02 – 0.99 (m, 1H), 0.94 (d, *J* = 0.7 Hz, 3H), 0.75 – 0.71 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.0, 174.0, 165.6, 90.0, 59.8, 56.3, 52.1, 45.9, 37.4, 37.4, 35.1, 27.1, 26.7, 24.0, 21.6, 21.3, 19.4, 19.4, 17.9, 16.9; **IR** (thin film): 3029, 2988, 2947, 2874, 2737, 1738, 1711, 1621, 1458, 1436, 1389, 1376, 1346, 1298, 1250, 1223, 1211, 1184, 1147, 1094, 1074, 1041, 1025, 985, 922, 904, 887, 854, 838, 808, 795, 770, 723, 708, 695, 667, 609, 550, 530, 483, 452, 426, 408 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –106.9 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{20}H_{28}NO_4$ $[M+H^+]$ 346.2013, found 346.2016.

(1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-acetyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro [benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (1.144)



1.144

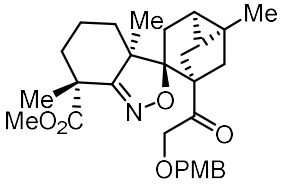
From (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-Methyl 5'-formyl-1', 3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro [benzo[*c*]is-oxazole-3,4'-tricyclo [3.2.1.0^{2,7}]octane]-7-carboxylate (**1.143**): To a solution of (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-formyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (**1.143**) (0.108 g, 0.313 mmol, 1.0 equiv.) in THF (10.4 mL) at –78 °C was added methyllithium, 1.6 M in Et_2O (3.52 mL, 5.63 mmol, 18 equiv.) in six portions every 10 min. After the final addition, the mixture was stirred at –78 °C for another 2 min. Methanol (3 mL) was added and the mixture was poured into sat. aq. NH_4Cl (40 mL). The mixture was extracted with

Et_2O (4 x 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

The residue was redissolved in CH_2Cl_2 (6.26 mL). *t*-BuOH (0.033 mL, 0.344 mmol, 1.1 equiv.) was added followed by DMP (0.159 g, 0.376 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 13 min. Et_2O (20 mL) was added followed by sat. aq. $NaHCO_3$ (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL). The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (0.106 g, 0.295 mmol, 94%) as colorless crystals and mixture of diastereomers (~20:1).

TLC: R_f = 0.52 (hex:EtOAc = 3:1); **Melting Point:** 143 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.62 (d, *J* = 12.0 Hz, 1H), 2.51 – 2.41 (m, 2H), 2.13 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.08 (dd, *J* = 15.4, 2.4 Hz, 1H), 1.87 – 1.58 (m, 5H), 1.46 (s, 3H), 1.43 (d, *J* = 12.2 Hz, 1H), 1.24 – 1.14 (m, 4H), 0.98 – 0.93 (m, 4H), 0.70 – 0.65 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.4, 174.1, 166.1, 91.5, 60.8, 56.6, 52.4, 45.8, 39.2, 36.7, 35.0, 29.8, 29.4, 29.3, 24.4, 22.2, 21.7, 19.6, 19.6, 18.8, 17.4; **IR** (thin film): 2947, 2876, 1736, 1694, 1457, 1434, 1376, 1355, 1300, 1249, 1229, 1183, 1143, 1075, 1025, 986, 975, 916, 885, 860, 837, 803, 771, 724, 701, 670, 588, 543, 496, 447, 427, 406cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ – 43.1 (*c* 0.60, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{30}NO_4$ $[M+H]^+$ 360.2169, found 360.2171.

Methyl (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*S*)-5'-(2-((4-methoxybenzyl)oxy)acetyl)-1', 3a,7-trimethyl-3a,4,6,7-tetrahydro-5*H*-spiro[benzo[c]isoxazole-3,4'-tricyclo [3.2.1.0^{2,7}]octane]-7-carboxylate (1.147)



1.147

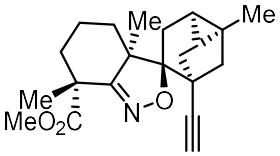
To a solution of tributyl(((4-methoxybenzyl)oxy)methyl) stannane (**1.145**) (47 mg, 0.107 mmol, 2.8 equiv.) in THF (0.94 mL) at –78 °C was added dropwise *n*-BuLi, 1.6 M in hexane (64 µL, 0.102 mmol, 2.7 equiv.) and the mixture was

stirred at –78 °C for 30 min. A solution of (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-for-myl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro [benzo [*c*]isoxazole-3,4'-tricyclo[3.2.1.$0^{2,7}$]octane]-7-carboxylate (**1.143**) (13 mg, 0.038 mmol, 1.0 equiv.) in THF (0.94 mL) was added dropwise and the mixture was stirred at –78 °C for 7 min. Sat. aq. NH_4Cl (5 mL) was added and the mixture was extracted with Et_2O (3 x 8 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAcc = 7:1 to 5:1 gradient) yielding the intermediate secondary alcohol (12 mg). The residue was redissolved in CH_2Cl_2 (0.96 mL). *t*-BuOH (2.5 µL, 0.027 mmol, 1.1 equiv.) was added followed by DMP (12.3 mg, 0.029 mmol, 1.2 equiv.) and the mixture was stirred at r.t. for 110 min. More DMP (12.3 mg, 0.029 mmol, 1.2 equiv.) was added and stirring was continued for another 84 min. Et_2O (2 mL) was added followed by sat. aq. $NaHCO_3$/$Na_2S_2O_3$ solution (4 mL) and the mixture was stirred vigorously for 15 min and diluted with Et_2O (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (hex:EtOAc = 2:1) yielding the title compound (5.7 mg, 0.011 mmol, 30% over two steps) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H), 6.90 – 6.83 (m, 4H), 4.61 (dd, *J* = 18.1, 1.7 Hz, 2H), 4.55 – 4.44 (m, 4H), 4.39 (dd, *J* = 18.0, 6.4 Hz, 2H), 3.80 (s, 6H), 3.64 (d, *J* = 1.1 Hz, 6H), 2.54 (ddd, *J* = 15.3, 8.4, 4.2 Hz, 2H), 2.47 – 2.39 (m, 4H), 2.31 (ddd, *J* = 13.3, 3.3, 0.8 Hz, 1H), 2.18 (dd, *J* = 13.4, 1.2 Hz, 1H), 2.07 – 1.86 (m, 4H), 1.79 – 1.59 (m, 9H), 1.46 (s, 6H), 1.42 (dd, *J* = 12.0, 1.0 Hz, 1H), 1.22 – 1.12 (m, 8H), 1.05 (dd, *J* = 7.8, 3.5 Hz, 1H), 0.98 (dd, *J* = 7.4, 3.1 Hz, 1H), 0.91 – 0.89 (m, 6H), 0.67 (td, *J* = 7.9, 2.7 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.6, 208.5, 173.8, 173.8, 166.6, 166.6, 159.3, 130.0, 129.9, 129.6, 113.8, 91.6, 91.1, 74.1, 74.0, 72.7, 72.7, 58.7, 58.2, 56.0, 56.0, 55.3, 52.4, 52.4, 45.5, 45.5, 39.4, 35.7, 35.5, 34.8, 34.2, 33.9, 33.5, 29.8, 29.7, 29.3, 24.5, 24.5, 22.7, 21.7, 21.6, 21.6, 20.0, 19.8, 19.4, 19.4, 19.2, 17.4, 17.1.

Methyl (1'*S*,2'*R*,3*S*,3a*R*,5'*S*,7*R*,7'*S*)-5'-ethynyl-1',3a,7-trimethyl-3a,4,6,7-tetrahydro-5*H*-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (1.152)



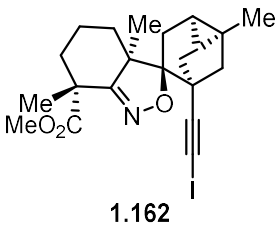
1.152

To (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-formyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (**1.143**) (44 mg, 0.127 mmol, 1.0 equiv.) was added a solution of OHIRA–BESTMANN reagent (538 mg, 2.80 mmol, 22 equiv.) in MeOH (5.1 mL) followed by potassium carbonate (528 mg, 3.82 mmol, 30 equiv.). The mixture was stirred at r.t. for 15 h. CH_2Cl_2 (20 mL) was added followed by sat. aq. $NaHCO_3$ (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 12:1) yielding the title compound (40 mg, 0.117 mmol, 92%) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.66 (s, 3H), 2.85 (d, *J* = 12.4 Hz, 1H), 2.80 (d, *J* = 12.3 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.22 (td, *J* = 15.5, 2.4 Hz, 2H), 2.16 (s, 2H), 2.11 – 1.79 (m, 7H), 1.78 – 1.69 (m, 2H), 1.66 – 1.53 (m, 7H), 1.48 (s, 6H), 1.39 (s, 3H), 1.38 (s, 3H), 1.23 – 1.14 (m, 8H), 1.01 (dd, *J* = 7.7, 3.2 Hz, 1H), 0.89 (dd, *J* = 7.6, 3.2 Hz, 1H), 0.69 – 0.59 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.6, 174.5, 164.7, 164.7, 89.7, 89.7, 87.4, 87.4, 71.6, 71.6, 57.1, 57.0, 51.7, 51.7, 46.2, 46.2, 42.6, 42.5, 42.4, 40.4, 39.2, 39.1, 37.4, 36.3, 36.1, 34.9, 26.2, 26.0, 23.8, 21.9, 21.6, 21.2, 20.9, 19.6, 19.6, 19.4, 19.2, 17.2, 17.2, 16.6, 16.6.

Methyl (1'*S*,2'*R*,3*S*,3a*R*,5'*S*,7*R*,7'*S*)-5'-(iodoethynyl)-1',3a,7-trimethyl-3a,4,6,7-tetrahydro-5*H*-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (1.162)



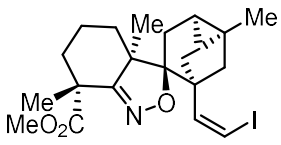
1.162

To a solution of methyl (1'*S*,2'*R*,3*S*,3a*R*,5'*S*,7*R*,7'*S*)-5'-ethynyl-1',3a,7-trimethyl-3a,4,6,7-tetrahydro-5*H*-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-car-boxylate (**1.152**) (5.0 mg, 0.015 mmol, 1.0 equiv.) in THF (0.59 mL) was added CuI (0.1 mg, 0.7 µmol, 5 mol%) followed by *N*-iodomorpholine hydroiodide (10.0 mg, 0.029 mmol, 2.0 equiv.). The mixture was stirred at r.t. for 20 h, filtered through basic alumina with CH_2Cl_2 (3 x 10 mL) and concentrated. The residue was redissolved in CH_2Cl_2 (10 mL) and washed with sat. aq. $Na_2S_2O_3$ (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 12:1) yielding the title compound (4.8 mg, 0.010 mmol, 70%) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H), 2.84 (d, *J* = 12.5 Hz, 1H), 2.78 (d, *J* = 12.3 Hz, 1H), 2.55 – 2.47 (m, 2H), 2.26 – 2.15 (m, 2H), 2.08 – 1.71 (m, 9H), 1.64 – 1.46 (m, 13H), 1.33 (s, 3H), 1.33 (s, 3H), 1.16 (d, *J* = 12.8 Hz, 8H), 1.01 (d, *J* = 7.7 Hz, 1H), 0.89 (dd, *J* = 7.7, 3.2 Hz, 1H), 0.63 (d, *J* = 19.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8, 174.8, 165.0, 165.0, 97.3, 97.3, 90.0, 90.0, 57.3, 57.2, 52.6, 52.6, 46.6, 46.6, 44.9, 44.9, 43.2, 40.3, 40.0, 39.9, 38.1, 36.4, 36.2, 34.8, 26.3, 26.1, 23.7, 23.7, 22.0, 21.7, 21.4, 21.0, 19.8, 19.7, 19.6, 19.4, 17.4, 17.3, 16.8, 16.7, -2.2, -2.3; **HRMS** (ESI): exact mass calculated for $C_{21}H_{27}INO_3$ [M+H$^+$] 468.1030, found 468.1025.

Methyl (1'*S*,2'*R*,3*S*,3a*R*,5'*S*,7*R*,7'*S*)-5'-((*Z*)-iodovinyl)-1',3a,7-trimethyl-3a,4,6,7-tetrahydro-5*H*-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate ((*Z*)-1.156)



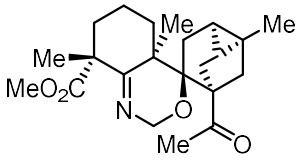
(*Z*)-1.156

To a solution of methyl (1'*S*,2'*R*,3*S*,3a*R*,5'*S*,7*R*,7'*S*)-5'-(iodoethynyl)-1',3a,7-trimethyl-3a,4,6,7-tetrahydro-5*H*-spiro[benzo[c]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (**1.162**) (4.8 mg, 0.010 mmol, 1.0 equiv.) in THF (0.21 mL) and *i*-PrOH (0.21 mL) at 0 °C was added 2-nitrobenzenesulfonylhydrazide (**1.163**) (8.0 mg, 0.037 mmol, 3.6 equiv.) followed by triethylamine (10.0 μL, 0.072 mmol, 10 equiv.). The mixture was stirred at r.t. for 22 h and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 12:1) yielding the title compound (3.8 mg, 0.008 mmol, 79%) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 – 6.66 (m, 2H), 6.03 – 5.96 (m, 2H), 3.67 (s, 3H), 3.67 (s, 3H), 2.84 (dd, *J* = 12.9, 3.4 Hz, 1H), 2.68 (d, *J* = 12.7 Hz, 1H), 2.61 – 2.44 (m, 4H), 2.35 – 2.23 (m, 2H), 2.01 (t, *J* = 15.2 Hz, 2H), 1.86 – 1.71 (m, 4H), 1.66 – 1.51 (m, 8H), 1.46 (s, 6H), 1.23 – 1.11 (m, 14H), 0.98 (d, *J* = 4.8 Hz, 2H), 0.70 – 0.61 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3, 174.3, 164.9, 164.9, 141.6, 141.6, 91.0, 90.9, 73.1, 56.6, 56.6, 52.6, 52.4, 52.3, 52.2, 45.9, 45.9, 40.7, 38.2, 38.1, 36.4, 36.1, 35.5, 34.6, 28.8, 27.2, 27.1, 24.0, 23.9, 21.9, 21.4, 20.6, 20.6, 19.9, 19.5, 19.5, 19.5, 17.5, 17.4, 16.8, 16.7.

Methyl (1'*S*,2'*R*,4*R*,4a*R*,5'*R*,7'*S*,8*R*)-5'-acetyl-1',4a,8-trimethyl-2,4a,5,6,7,8-hexahydrospiro[benzo[d][1,3]oxazine-4,4'-tricyclo[3.2.1.0^{2,7}]octane]-8-carboxylate (1.167)



1.167

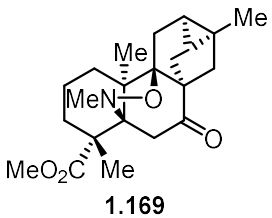
To a solution of (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-acetyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricy-clo[3.2.1.0^{2,7}]octane]-7-carboxylate

(**1.144**) (5.5 mg, 0.015 mmol, 1.0 equiv.) in CH_2Cl_2 (0.46 mL) was added trimethyloxonium tetrafluoroborate (4.5 mg, 0.031 mmol, 2.0 equiv.). The mixture was stirred at r.t. for 7.5 h and concentrated under reduced pressure. The residue was redissolved in THF (0.25 mL) and cooled to –78 °C. LDA, 0.24 M in THF (0.25 mL, 0.060 mmol, 4.0 equiv.) was added dropwise and the mixture was stirred at –78 °C for 70 min. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 x 8 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (1.5 mg, 0.004 mmol, 26%) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers. The structure was assigned based on ^1H and 2D NMR spetra and HRMS.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.49 (m, 2H), 5.35 (d, *J* = 17.7 Hz, 2H), 3.66 (s, 3H), 3.66 (s, 3H), 2.72 (d, *J* = 11.4 Hz, 1H), 2.68 (d, *J* = 11.6 Hz, 1H), 2.44 – 2.35 (m, 2H), 2.27 (s, 3H), 2.26 (s, 3H), 2.16 (d, *J* = 13.6 Hz, 4H), 1.92 – 1.80 (m, 5H), 1.78 – 1.60 (m, 7H), 1.48 – 1.41 (m, 1H), 1.36 (s, 6H), 1.34 – 1.27 (m, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.01 (s, 6H), 0.97 – 0.88 (m, 2H), 0.70 – 0.62 (m, 2H); **HRMS** (ESI): exact mass calculated for $C_{22}H_{32}NO_4$ [M+H$^+$] 374.2326, found 374.2324.

(4*R*,4a*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-Methyl 4,7a,9b,11-tetramethyl-6-oxodo-decahydro-9a,4a-(epoxyimino)-6a,8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (**1.169**)



1.169

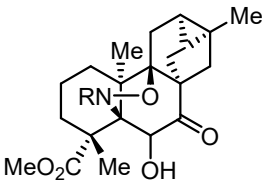
To a solution of (1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-acetyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricy-clo [3.2.1.0^{2,7}]octane]-7-carboxylate (**1.144**) (69.0 mg, 0.192 mmol, 1.0 equiv.) in CH_2Cl_2 (5.8 mL) was added trimethyloxonium tetrafluoroborate (71.0 mg, 0.480 mmol, 2.5 equiv.). The mixture was stirred at r.t. for 9.5 h. Triethylamine (0.214 mL, 0.1.54 mmol, 8.00 equiv.) was added followed by trimethylsilyl

trifluoromethanesulfonate (0.174 mL, 0.960 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 8.3 h. Sat. aq. $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine–1 M HCl (1:1, 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 12:1) yielding the title compound (49.7 mg, 0.133 mmol, 69%) as colorless crystals and mixture of diastereomers (~20:1).

Note: *NMR data represents the major diastereoisomer.*

TLC: R_f = 0.34 (hex:EtOAc = 5:1); **Melting point:** 212 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.30 (d, *J* = 20.2 Hz, 1H), 2.97 (d, *J* = 20.1 Hz, 1H), 2.72 (s, 3H), 2.47 (d, *J* = 11.4 Hz, 1H), 2.10 – 1.73 (m, 9H), 1.63 – 1.52 (m, 1H), 1.40 – 1.32 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 0.91 (dd, *J* = 7.7, 3.0 Hz, 1H), 0.67 (dd, *J* = 7.6, 3.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 214.9, 176.0, 83.6, 68.0, 58.1, 51.8, 51.6, 47.2, 43.3, 41.9, 39.6, 35.7, 32.9, 29.3, 25.1, 24.4, 22.9, 20.3, 19.6, 18.7, 18.4, 17.5; **IR** (thin film): 3028, 2953, 2933, 2869, 1720, 1689, 1457, 1447, 1427, 1416, 1403, 1385, 1350, 1338, 1315, 1301, 1275, 1241, 1212, 1184, 1151, 1137, 1098, 1087, 1076, 1062, 1036, 1011, 979, 966, 914, 886, 874, 853, 821, 803, 757, 711, 685, 653, 634, 604, 584, 559, 521, 478 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –44.2 (*c* 0.60, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{22}H_{32}NO_4$ $[M+H^+]$ 374.2326, found 374.2323.

Methyl (4*R*,4a*R*,6a*R*,7a*S*,8*S*,8a*R*,9a*R*,9b*R*)-5-hydroxy-4,7a,9b,11-tetramethyl-6-oxodecahydro-2*H*,7*H*-9a,4a-(epoxyimino)-6a,8-methanocyclopropa[b]phenanthrene-4-carboxylate (1.176)



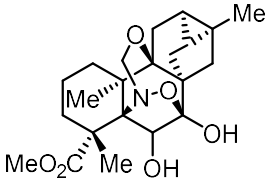
1.176
(R = Me)

To a solution of (4*R*,4a*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 4,7a,9b,11-tetramethyl-6-oxododecahydro-9a,4a-(epoxyimino)-6a,8-methanocy-clopropa[*b*]phenanthrene-4-carboxylate (**1.169**) (10.0 mg, 0.027 mmol, 1.0 equiv.) in THF (0.54 mL) at –78 °C was added KHMDS, 1 M in THF (0134 mL, 0.134 mmol, 5 equiv.) and the mixture was stirred at –78 °C for 30 min. MoOPH (116 mg, 0.268 mmol, 10 equiv.) was added and the mixture was stirred at –15 °C for 45 min. Sat. aq. $Na_2S_2O_3$ (1 mL) was added. The mixture was stirred vigorously for 15 min and diluted with Et_2O (5 mL) and sat. aq. $Na_2S_2O_3$ (5 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was used for the next steps without further purification.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

HRMS (ESI): exact mass calculated for $C_{22}H_{32}NO_5$ [M+H$^+$] 390.2275, found 390.2273.

Methyl (4*R*,4a*R*,7*R*,7a*R*,8a*S*,9*S*,9a*R*,10a*R*,10b*R*)-7,14-dihydroxy-4,8a,10b-trimethyloctahydro-2*H*,7*H*,8*H*-10a,5-(epoxymethano)-4a,7:7a,9-dimethanobenzo[c]cyclopropa[4,5]benzo[1,2-e][1,2]oxazepine-4-carboxylate (1.177)



1.177

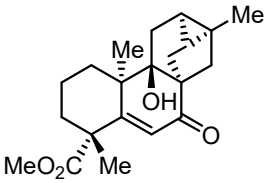
To a solution of crude methyl (4*R*,4a*R*,6a*R*,7a*S*,8*S*,8a*R*,9a*R*,9b*R*)-5-hydroxy-4,7a,9b,11-tetramethyl-6-oxodecahydro -2*H*,7*H*-9a,4a-(epoxyimino)-6a,8-methanocyclopropa[b] phenanthrene-4-carboxylate (**1.173**) (2.5 mg, 6.4 µmol, 1.0 equiv.) in CH_2Cl_2 (0.43 mL) at 0 °C was added *m*-CPBA (2.2 mg, 13 µmol, 2.0 equiv.). The mixture was stirred at 0 °C for 2 h. CH_2Cl_2 (5 mL) was added followed by

sat. aq. $NaHCO_3$ (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 3:1) yielding the title compound (1.0 mg, 2.5 μmol, 38%) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers. The structure was assigned based on ^1H and 2D NMR spetra and HRMS.*

^{1}H NMR (400 MHz, acetone-d6) δ 5.27 (s, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 4.74 – 4.71 (m, 1H), 4.63 (dd, *J* = 11.7, 4.2 Hz, 1H), 4.39 – 4.36 (m, 1H), 3.79 (s, 3H), 2.42 – 1.21 (m, 18H), 1.15 (d, *J* = 5.5 Hz, 3H), 0.82 (dd, *J* = 8.0, 3.4 Hz, 1H), 0.61 – 0.50 (m, 1H); **HRMS** (ESI): exact mass calculated for $C_{22}H_{32}NO_6$ [M+H$^+$] 406.2224, found 406.2221.

(4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-Methyl 9a-hydroxy-4,7a,9b-trimethyl-6-oxo-1,2,3,4,6,7,7a,8, 8a,9,9a,9b-dodecahydro-6a,8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (1.69)



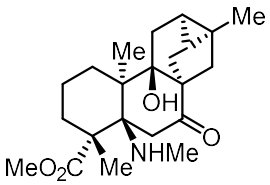
1.69

To a solution of (4*R*,4a*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 4,7a,9b,11-tetramethyl-6-oxododecahydro-9a,4a-(epoxyimino)-6a,8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (**1.169**) (22.2 mg, 0.059 mmol, 1.0 equiv.) in acetic acid (1.5 mL) was added zinc powder (78.0 mg, 1.2 mmol, 20 equiv.). The mixture was stirred at 50 °C for 14 h. After cooling to r.t., the mixture was filtered through Celite® with EtOAc (15 mL). The mixture was washed with brine–sat. aq. $NaHCO_3$ (1:1, 15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 5:1) yielding the title compound (13.4 mg, 0.039 mmol, 65%) as colorless oil and recovered starting material (4.1 mg, 0.011 mmol, 18%).

TLC: R_f = 0.36 (hex:EtOAc = 2:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.19 (s, 1H), 3.65 (s, 3H), 2.35 – 2.27 (m, 2H), 2.23 (d, *J* = 15.3 Hz, 1H), 2.18 (d, *J* = 12.4

Hz, 1H), 2.13 (td, *J* = 13.5, 4.4 Hz, 1H), 2.01 – 1.93 (m, 2H), 1.82 (qt, *J* = 13.7, 3.6 Hz, 1H), 1.71 (dd, *J* = 15.3, 3.8 Hz, 1H), 1.66 – 1.59 (m, 2H), 1.52 – 1.46 (m, 1H), 1.39 (s, 3H), 1.30 – 1.21 (m, 7H), 0.95 (dd, *J* = 7.6, 3.0 Hz, 1H), 0.74 – 0.70 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.6, 175.1, 167.2, 127.6, 75.5, 55.7, 52.6, 47.7, 47.1, 38.4, 35.7, 35.4, 30.6, 27.6, 27.1, 26.5, 22.0, 20.0, 19.9, 18.0, 17.7; **IR** (thin film): 3508, 2946, 2872, 1730, 1655, 1610, 1466, 1376, 1355, 1314, 1269, 1239, 1206, 1177, 1161, 1145, 1115, 1071, 987, 917, 884, 849, 830, 799, 754, 710, 665, 598, 564, 495, 412 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{29}O_4$ [M+H$^+$] 345.2060, found 345.2063.

Methyl (4*R*,4a*R*,6a*R*,7a*S*,8*S*,8a*R*,9a*R*,9b*R*)-9a-hydroxy-4,7a,9b-trimethyl-4a-(methylamino)-6-oxotetradecahydro-6a,8-methanocyclopropa[b]phenanthrene-4-carboxylate (1.181)



1.181

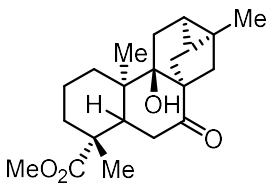
To a solution of (4*R*,4a*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 4,7a,9b,11-tetramethyl-6-oxododecahydro-9a,4a-(epoxyimino)-6a,8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (**1.169**) (5.0 mg, 0.013 mmol, 1.0 equiv.) in MeOH (1.34 mL) was added 1 M HCl in MeOH (27µL, 0.027 mmol, 2.0 equiv.) followed by Pd/C, 10 wt% (4.3 mg, 0.004 mmol, 30 mol%). The flask was evacuated and back-filled with H_2 (3x) and the mixture was stirred under an atmosphere at 60 °C for 30 min. After cooling to r.t., the flask was evacuated and back-filled with N_2 (3x). The mixture was filtered through a pad of Celite® with EtOAc, washed with brine–sat. aq. $NaHCO_3$ and concentrated under reduced pressure yielding the title compound (5.0 mg, 0.013 mmol, quant.) as a colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

TLC: R_f = 0.22 (hex:EtOAc = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 2H), 3.69 (s, 3H), 3.69 (s, 3H), 3.51 – 3.42 (m, 2H), 3.06 – 2.97 (m, 2H), 2.54 – 2.43 (m, 8H), 2.35 – 1.88 (m, 11H), 1.75 – 1.48 (m, 6H), 1.46 – 1.30 (m, 5H), 1.24 (s, 6H), 1.19 (s, 3H), 1.14 (s, 9H), 0.97 (dd, *J* = 7.5, 3.0 Hz, 1H), 0.83 (dd, *J* = 7.6, 3.1 Hz, 1H), 0.67 – 0.57 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 213.8,

213.8, 176.3, 78.3, 78.3, 66.5, 66.4, 61.1, 61.0, 52.2, 51.3, 51.3, 46.4, 46.4, 42.1, 42.0, 41.7, 36.2, 34.5, 31.8, 31.7, 31.6, 31.2, 29.1, 25.5, 25.5, 25.2, 25.1, 21.9, 21.8, 20.3, 19.7, 19.7, 19.6, 19.4, 19.3, 18.2, 18.1, 17.5; **IR** (thin film): 3377, 2937, 2862, 1720, 1697, 1465, 1431, 1417, 1378, 1299, 1248, 1232, 1197, 1148, 1120, 1098, 1075, 1012, 993, 966, 915, 888, 868, 847, 793, 731, 646, 602, 561, 540, 411 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{34}NO_4$ $[M+H^+]$ 376.2482, found 276.2484.

(4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-Methyl 9a-hydroxy-4,7a,9b-trimethyl-6-oxotetradecahydro-6a,8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (1.190)



1.190

From (4*R*,4a*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-Methyl 4,7a,9b, 11-tetra-methyl-6-oxododecahydro-9a,4a-(epoxyimino)-6a, 8-methanocyclo-propa[*b*]phenanthrene-4-carboxylate (**1.169**): To a solution of (4*R*,4a*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 4,7a,9b,11-tetramethyl-6-oxododecahy-dro-9a,4a-(epoxy-imino)-6a,8-methano-cyclopropa[*b*]phenanthrene-4-carboxy-late (**1.169**) (20.1 mg, 0.054 mmol, 1.0 equiv.) in EtOAc (8.97 mL) and AcOH (1.79 mL) was added 10% palladium on carbon (28.6 mg, 0.027 mmol, 0.5 equiv.). The flask was evacuated and back-filled with H_2 (3x). The mixture was stirred at 80 °C for 10.5 h. After 5.5 and 9.5 h, more 10% palladium on carbon (57.2 mg, 0.054 mmol, 1.0 equiv.) was added and stirring was continued at 80 °C. After cooling to r.t., the flask was evacuated and back-filled with N_2 (3x). The mixture was filtered through Celite® with EtOAc, washed with sat. aq. K_2CO_3–H_2O (50 mL, 1:3), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 6:1) yielding the title compound (13.2 mg, 0.038 mmol, 72%) as a colorless oil.

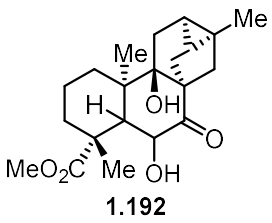
From (4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-Methyl 9a-hydroxy-4,7a,9b-trimethyl-6-oxo-1,2,3,4,6,7,7a,8,8a,9,9a,9b-dodecahydro-6a,8-methanocyclopropa[*b*] phenanthrene-4-carboxylate (**1.69**):

To a solution of (4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 9a-hydroxy-4,7a,9b-trimethyl-6-oxo-1,2,3,4,6,7,7a,8,8a,9,9a,9b-dodeca-hydro-6a,8-methano-cyclopropa[*b*]phenan-threne-4-carboxylate (**1.69**) (15.7 mg, 0.046 mmol, 1.0 equiv.) in EtOAc (3.0 mL) was added 10% palladium on carbon (14.6 mg, 0.014 mmol, 0.3 equiv). The flash was evacuated and backfilled with H_2 (3x) and stirred under an atmosphere of H_2 for 15 min. The flask was evacuated and backfilled with N_2 (3x). The mixture was filtered through Celite® with EtOAc followed by concentration under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 6:1) yielding the title compound (12.2 mg, 0.035 mmol, 77%) as colorless oil.

Note: *The configuration of the newly formed stereogenic center was not assigned.*

TLC: R_f = 0.55 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.95 (dd, *J* = 15.9, 13.9 Hz, 1H), 2.63 (dd, *J* = 15.9, 3.5 Hz, 1H), 2.43 (dd, *J* = 15.8, 2.2 Hz, 1H), 2.29 (d, *J* = 12.4 Hz, 1H), 2.21 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.15 (dtd, *J* = 13.5, 3.2, 1.5 Hz, 1H), 2.04 (dd, *J* = 12.9, 0.6 Hz, 1H), 1.98 (d, *J* = 12.8 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.77 – 1.67 (m, 1H), 1.61 – 1.48 (m, 4H), 1.44 – 1.38 (m, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 1.10 – 0.99 (m, 4H), 0.89 (dd, *J* = 7.5, 2.9 Hz, 1H), 0.70 – 0.64 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 213.7, 177.7, 77.1, 58.9, 51.6, 46.1, 44.0, 43.4, 39.3, 37.4, 35.1, 34.0, 31.0, 30.7, 28.4, 21.0, 20.1, 19.8, 18.6, 17.8, 16.3; **IR** (thin film): 3529, 2937, 2866, 1723, 1694, 1467, 1445, 1382, 1344, 1308, 1231, 1189, 1154, 1120, 1100, 1058, 1016, 1003, 988, 931, 914, 880, 847, 795, 753, 694, 666, 656, 597, 566, 504, 455 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –49.1 (*c* 0.60, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found 369.2036.

Methyl (4*R*,6a*R*,7a*S*,8*S*,8a*R*,9a*R*,9b*R*)-5,9a-dihydroxy-4,7a,9b-trimethyl-6-oxotetradeca-hydro-6a,8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (1.192)



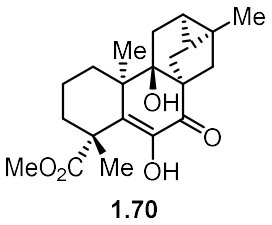
1.192

To a solution of (4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 9a-hydroxy-4,7a,9b-trimethyl-6-oxotetradecahydro-6a,8-methanocyclopropa[*b*] phenanthrene-4-carboxylate (**1.190**) (7.2 mg, 0.021 mmol, 1.0 equiv.) in THF (2.1 mL) at –78 °C was added potassium *tert*-butoxide, 1 M in THF (0.42 mL, 0.42 mmol, 20 equiv.). Oxygen was bubbled through the mixture for 5 min and the mixture was stirred at –78 °C for 90 min. Triphenylphosphine (27 mg, 0.10 mmol, 5.0 equiv.) was added. The mixture was stirred at –78 °C for 8 min and at r.t. for 150 sec. Sat. aq. NH_4Cl (8 mL) was added and the mixture was extracted with Et_2O (3 x 6 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 5:1) yielding the title compound (5.4 mg, 0.015 mmol, 72% as a colorless oil)

Note: *The configuration of the newly formed stereogenic center was not assigned. The product was obtained as a 14:1 mixture with its regioisomeric α-hydroxyketone. NMR data represents the major regioisomer.*

TLC: R_f = 0.52 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.91 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.92 (d, *J* = 3.6 Hz, 1H), 3.73 (s, 3H), 2.46 (dd, *J* = 15.8, 2.2 Hz, 1H), 2.36 (d, *J* = 12.2 Hz, 1H), 2.20 – 2.09 (m, 2H), 2.05 (d, *J* = 12.9 Hz, 1H), 2.00 (d, *J* = 11.7 Hz, 1H), 1.85 – 1.57 (m, 5H), 1.54 – 1.46 (m, 1H), 1.45 (s, 3H), 1.41 – 1.35 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H), 1.07 (td, *J* = 13.4, 4.0 Hz, 1H), 0.95 (dd, *J* = 7.6, 2.9 Hz, 1H), 0.71 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 213.6, 178.0, 77.5, 75.2, 57.8, 52.5, 51.8, 45.3, 44.8, 39.2, 35.3, 33.1, 31.6, 31.5, 31.4, 20.5, 19.9, 19.8, 18.6, 17.9, 17.7; **IR** (thin film): 3452, 2927, 2866, 1724, 1701, 1462, 1380, 1343, 1300, 1229, 1205, 1148, 1093, 1067, 1044, 989, 936, 910, 880, 838, 789, 551, 504, 437, 419, 407 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –59.9 (*c* 0.30, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{31}O_5$ $[M+H]^+$ 363.2166, found 363.2165.

(4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-Methyl 5,9a-dihydroxy-4,7a,9b-trimethyl-6-oxo-1,2,3,4,6,7,7a,8,8a,9,9a,9b-dodecahydro-6a,8-methanocyclopropa[*b*] phenanthrene-4-carboxylate (1.70)

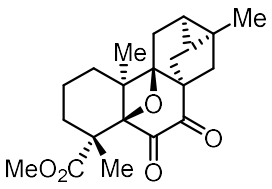


1.70

To a solution of methyl (4*R*,6a*R*,7a*S*,8*S*,8a*R*,9a*R*,9b*R*)-5,9a-dihydroxy-4,7a,9b-trimethyl-6-oxotetradecahydro-6a,8-methanocyclopropa [*b*]phen-anthrene-4-carboxylate (**1.192**) (6.9 mg, 0.019 mmol, 1.0 equiv.) in CH_2Cl_2 (mL) was added *t*-BuOH (5.5 µL, 0.057 mmol, 3.0 equiv.) followed by DMP (24 mg, 0.057 mmol, 3.0 equiv.). The mixture was stirred at r.t. for 20 min. Et_2O (3 mL) was added followed by sat. aq $Na_2S_2O_3$ (2 mL) and sat. aq. $NaHCO_3$ (2 mL). The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 4 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was redissolved in hexane–EtOAc (3:1, 5 mL). Silica gel (500 mg) was added and the mixture was stirred at r.t. for 15 h, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane:EtOAc = 2:1) yielding the title compound (5.1 mg, 0.014 mmol, 74%) as colorless oil.

TLC: R_f = 0.49 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.66 (s, 3H), 2.39 – 2.27 (m, 3H), 2.16 – 2.05 (m, 2H), 2.03 – 1.95 (m, 2H), 1.81 – 1.63 (m, 4H), 1.57 – 1.45 (m, 8H), 1.23 (s, 3H), 1.00 (dd, *J* = 7.6, 3.1 Hz, 1H), 0.78 – 0.72 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.6, 176.9, 143.0, 137.2, 75.2, 54.9, 52.4, 45.9, 45.0, 38.7, 36.6, 32.5, 29.4, 27.8, 26.3, 22.7, 22.2, 20.1, 19.9, 17.5, 15.9; **IR** (thin film): 3519, 3417, 2979, 2946, 2870, 1727, 1655, 1629, 1459, 1382, 1367, 1345, 1282, 1252, 1231, 1206, 1142, 1127, 1051, 984, 949, 903, 882, 866, 851, 803, 756, 699, 540, 506, 497, 488, 480, 453, 417, 405 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ +31.2 (*c* 0.30, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{28}NaO_5$ $[M+Na]^+$ 383.1829, found 383.1830.

(–)-Mitrephorone A (1.64)

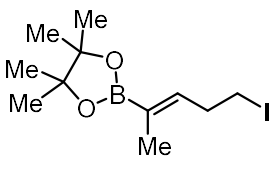


1.64

To a solution of (4*R*,6a*R*,7a*S*,8*R*,8a*R*,9a*R*,9b*R*)-methyl 5,9a-dihydro-xy-4,7a,9b-trimethyl-6-oxo-1,2,3,4,6,7,7a,8,8a,9,9a,9b-dodecahydro-6a, 8-methanocyclopropa[*b*]phenanthrene-4-carboxylate (**1.70**) (5.0 mg, 0.015 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was added sodium bicarbonate (12 mg, 0.14 mmol, 10 equiv) followed by PhI(OH)OTs (54 mg, 0.14 mmol, 10.0 equiv.). The mixture was stirred at r.t. for 2 min, poured into sat. aq. $Na_2S_2O_3$–sat. aq. $NaHCO_3$ (1:1, 6 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (hex:EtOAc = 4:1) yielding the title compound (3.6 mg, 0.010 mmol, 72%) as yellow oil.

TLC: R_f = 0.48 (hex:EtOAc = 3:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.48 (dd, *J* = 12.6, 3.3 Hz, 1H), 2.31 (d, *J* = 11.9 Hz, 1H), 2.26 (dd, *J* = 16.8, 2.4 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.09 (dd, *J* = 16.7, 3.1 Hz, 1H), 1.80 – 1.75 (m, 1H), 1.73 (d, *J* = 12.6 Hz, 1H), 1.66 – 1.52 (m, 5H), 1.19 (s, 3H), 1.11 (s, 3H), 1.08 (d, *J* = 0.6 Hz, 3H), 1.06 (dd, *J* = 7.7, 3.4 Hz, 1H), 0.74 – 0.71 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.8, 190.2, 175.0, 89.2, 87.5, 59.1, 51.9, 48.7, 43.2, 40.2, 35.2, 32.5, 30.3, 26.6, 21.7, 21.1, 19.3, 18.6, 18.5, 17.9, 17.7; **IR** (thin film): 2946, 2868, 1745, 1724, 1458, 1384, 1347, 1312, 1295, 1260, 1244, 1193, 1164, 1115, 1082, 1066, 1026, 986, 954, 918, 895, 865, 852, 818, 803, 761, 721, 691, 646, 602, 566,509, 493, 477, 436cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –86.2 (*c* 0.25, CH_2Cl_2); **HRMS** (ESI): exact mass calculated for $C_{21}H_{26}NaO_5$ $[M+Na]^+$ 381.1672, found 381.1675.

(*Z*)-2-(5-Iodopent-2-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.S4)



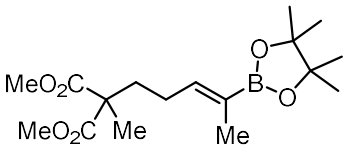
1.S4

To a solution of iodine (1.32 g, 5.21 mmol, 1.6 equiv.) in CH_2Cl_2 (24.8 mL) was added triphenylphosphine (1.37 g, 5.21 mmol, 1.6 equiv.). The mixture was stirred at r.t. for 20 min. Imidazole (0.562 g, 8.25 mmol, 2.5 equiv.) was added

and stirring was continued at r.t. for 10 min. (*Z*)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-ol (**1.200**)[103] (0.700 g, 3.30 mmol, 1.0 equiv.) in CH_2Cl_2 (8.25 mL) was added and stirring was continued at r.t. for 75 min. Sat. aq. $Na_2S_2O_3$ (25 mL) was added followed by water (25 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 40:1) yielding the title compound (0.97 g, 3.02 mmol, 91%) as colorless oil.

TLC: R_f = 0.22 (hex:EtOAc = 40:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.26 – 6.14 (m, 1H), 3.16 (t, *J* = 7.6 Hz, 2H), 2.79 – 2.71 (m, 2H), 1.69 – 1.67 (m, 3H), 1.26 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3, 83.5, 33.3, 25.0, 14.3, 3.7; **IR** (thin film): 2977, 2929, 1630, 1445, 1409, 1368, 1342, 1304, 1271, 1241, 1213, 1165, 1141, 1111, 1094, 1046, 974, 953, 856, 833, 763, 736, 688, 666, 578, 520, 502, 468, 425, 417 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{10}H_{17}O_2BI$ $[M–CH_3]^+$ 307.0361, found 307.0359.

Dimethyl (*Z*)-2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl) malonate (1.197a)

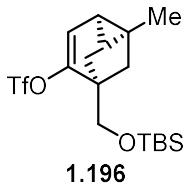


1.197a

To a solution of dimethyl 2-methylmalonate (1.45 g, 9.89 mmol, 1.5 equiv.) in DMF (16.5 mL) at 0 °C was added sodium hydride, 60% in mineral oil (0.395 g, 9.89 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 15 min. (*Z*)-2-(5-iodopent-2-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1.S4**) (2.12 g, 6.59 mmol, 1.0 equiv.) in DMF (16.5 mL) was added dropwise. The mixture was stirred at r.t. for 1.5 h. Sat. aq. NH_4Cl (100 mL) was added followed by water (100 mL) and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hexane:EtOAc = 25:1 to 8:1 gradient) yielding the title compound (1.54 g, 4.52 mmol, 68%) as white solid.

TLC: R_f = 0.46 (hex:EtOAc = 5:1); **Melting point:** 46 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.26 (tq, *J* = 6.9, 1.8 Hz, 1H), 3.71 (s, 6H), 2.11 – 2.02 (m, 2H), 2.01 – 1.93 (m, 2H), 1.68 – 1.64 (m, 3H), 1.43 (s, 3H), 1.25 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 144.6, 83.3, 53.7, 52.6, 34.8, 24.9, 23.7, 20.1, 13.9; **IR** (thin film): 2978, 2953, 1733, 1632, 1448, 1434, 1410, 1370, 1335, 1303, 1267, 1233, 1214, 1198, 1164, 1137, 1111, 1091, 1060, 1004, 971, 991, 858, 834, 816, 750, 689, 668, 578, 520, 499, 470, 421, 407 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{29}BNaO_6$ $[M+Na]^+$ 363.1953, found 363.1952.

(1*S*,2*S*,5*S*,7*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (**1.196**)



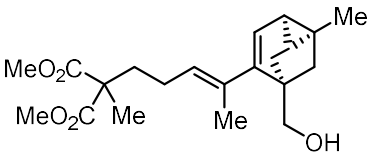
1.196

To a solution of (1*S*,2*R*,5*S*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-1-me-thyltricyclo[3.2.1.0^{2,7}]octan-4-one (**1.97**) (1.29 g, 4.60 mmol, 1.0 equiv.) in THF (46 mL) at –78 °C was added dropwise KHMDS, 20wt% in THF (7.84 mL, 6.89 mmol, 1.5 equiv.). The mixture was stirred at –78 °C for 45 min. Comin's reagent (2.71 g, 6.89 mmol, 1.5 equiv.) was added and stirring was continued for 20 h gradually increasing the temperature to r.t. Sat. aq. NH_4Cl (50 mL) was added and THF was removed under reduced pressure. The residue was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 40:1) yielding the title compound (1.78 g, 4.31 mmol, 94%) as colorless oil.

TLC: R_f = 0.60 (hex:EtOAc = 40:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.95 (d, *J* = 6.7 Hz, 1H), 3.81 (d, *J* = 10.3 Hz, 1H), 3.78 (d, *J* = 10.3 Hz, 1H), 1.85 (ddd, *J* = 11.6, 2.3, 0.9 Hz, 1H), 1.57 – 1.48 (m, 2H), 1.37 – 1.33 (m, 1H), 1.31 (s, 3H), 0.98 (d, *J* = 11.3 Hz, 1H), 0.97 (d, *J* = 11.5 Hz, 1H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.6, 118.7 (q, *J* = 320 Hz), 113.2, 62.5, 48.1, 37.9, 32.3, 26.0, 25.0, 23.7, 22.1, 18.5, 18.1, -5.5; **IR** (thin film): 2953, 2929, 2896, 2858, 1648, 1472, 1463, 1418, 1361, 1247, 1205, 1169, 1141, 1093, 1062, 1006, 960, 936, 881, 837, 776, 722, 705, 668, 648, 614, 599, 515, 493, 411 cm^{-1}

Optical Rotation: $[\alpha]_D^{24}$ –30.1 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{17}H_{27}F_3NaO_4SSi$ $[M+Na]^+$ 435.1244, found 435.1247.

Dimethyl 2-((*E*)-4-((1*S*,2*R*,5*R*,7*S*)-5-(hydroxymethyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)-2-methylmalonate (1.202)

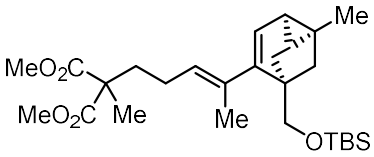


1.202

To a solution of (1*S*,2*S*,5*S*,7*S*)-5-(((*tert*-butyldimethyl-silyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (**1.196**) (0.310 g, 0.751 mmol, 1.00 equiv.) and (*Z*)-2-(5-iodopent-2-en-2-yl)-4,4,5,5-tetrame-thyl-1,3,2-dioxaborolane (**1.197a**) (0.320 g, 0.939 mmol, 1.25 equiv.) in dimethoxyethane (10.0 mL) was added $[Pd(PPh_3)_4]$ (0.026 g, 0.023 mmol, 0.03 equiv.) followed by sat. aq. $NaHCO_3$ (1.63 mL). The mixture was stirred at 85 °C for 52 min and cooled to 0 °C. 1 M HCl in methanol (7.51 mL, 7.51 mmol, 10.0 equiv.) was added and the mixture was stirred at 0 °C for 10 min. Sat. aq. NH_4Cl (50 mL) and H_2O (20 mL) were added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 4:1) yielding the title compound (0.158 g, 0.436 mmol, 58%) as yellow oil.

TLC: R_f = 0.39 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, acetone-d6) δ 5.61 (d, *J* = 5.8 Hz, 1H), 5.10 (td, *J* = 7.0, 1.4 Hz, 1H), 3.69 (s, 8H), 3.34 (t, *J* = 5.5 Hz, 1H), 1.99 – 1.84 (m, 5H), 1.70 (s, 3H), 1.58 (d, *J* = 11.0 Hz, 1H), 1.43 – 1.36 (m, 4H), 1.27 (s, 3H), 1.19 (dd, *J* = 7.1, 2.2 Hz, 1H), 0.64 (t, *J* = 10.4 Hz, 2H); **^{13}C NMR** (101 MHz, acetone-d6) δ 173.0, 148.4, 136.9, 126.8, 119.7, 64.3, 54.2, 52.6, 49.0, 38.3, 36.2, 32.3, 24.7, 24.5, 24.0, 23.9, 20.3, 18.9, 18.9; **IR** (thin film): 3555, 3456, 2038, 2993, 2949, 2921, 2862, 1732, 1619, 1458, 1434, 1378, 1315, 1255, 1234, 1198, 1171, 1113, 1077, 1054, 1029, 995, 979, 935, 878, 840, 804, 753, 692, 665, 613, 577, 530, 507, 497, 478, 462, 449, 438, 430, 424, 411 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –20.0 (*c* 1.00, acetone); **HRMS** (ESI): exact mass calculated for $C_{21}H_{30}NaO_5$ $[M+Na]^+$ 385.1985, found 385.1984.

Dimethyl 2-((E)-4-((1S,2R,5R,7S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)-2-methylmalonate (1.195)

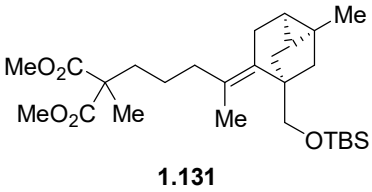


1.195

To a solution of dimethyl 2-((*E*)-4-((1*S*,2*R*,5*R*,7*S*)-5-(hydroxymethyl)-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl) pent-3-en-1-yl)-2-methylmalonate (**1.202**) (0.162 g, 0.447 mmol, 1.0 equiv.) in CH_2Cl_2 (8.9 mL) was added TBSCl (0.101 g, 0.670 mmol, 1.5 equiv.) followed by imidazole (0.076 g, 1.12 mmol, 2.5 equiv.) and DMAP (10.9 mg, 0.089 mmol, 20 mol%). The mixture was stirred at r.t. for 22 h. Sat. aq. NH_4Cl (10 mL) and H_2O (5 mL) were added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 35:1) yielding the title compound (0.200 g, 0.420 mmol, 94%) as colorless oil.

TLC: R_f = 0.22 (hex:EtOAc = 20:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.63 (d, *J* = 5.8 Hz, 1H), 5.08 – 5.04 (m, 1H), 3.74 (s, 6H), 3.70 (d, *J* = 10.0 Hz, 1H), 3.68 (d, *J* = 10.0 Hz, 1H), 1.98 – 1.89 (m, 4H), 1.79 (dd, *J* = 11.1, 2.4 Hz, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.49 (d, *J* = 11.1 Hz, 1H), 1.46 (s, 3H), 1.39 (dd, *J* = 7.0, 5.9 Hz, 1H), 1.29 (s, 3H), 1.19 (dd, *J* = 7.1, 2.2 Hz, 1H), 0.90 (s, 9H), 0.67 (dd, *J* = 13.2, 11.1 Hz, 2H), 0.04 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.9, 147.5, 136.1, 125.6, 119.0, 65.0, 53.8, 52.6, 48.3, 38.0, 35.7, 32.1, 26.1, 24.2, 23.9, 23.5, 23.3, 20.1, 19.0, 18.8, 18.5, -5.4, -5.4; **IR** (thin film): 3029, 2951, 2928, 2857, 1736, 1461, 1434, 1378, 1360, 1251, 1231, 1197, 1164, 1112, 1079, 1005, 938, 877, 836, 814, 774, 667, 528, 403 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –25.7 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{27}H_{45}O_5Si$ $[M+H]^+$ 477.3031, found 477.3030.

Dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (1.131)

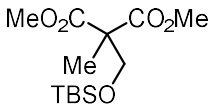


1.131

From dimethyl 2-((E)-4-((1S,2R,5R,7S)-5-(((tert-butyl-dimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)-2-methylmalonate (**1.195**): A solution of dimethyl 2-((E)-4-((1S,2R,5R,7S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)-2-methylmalonate (**1.195**) (0.400 g, 0.839 mmol, 1.0 equiv.) and [Cr(CO)$_3$(η^6-methyl benzoate)] (0.114 g, 0.420 mmol, 0.5 equiv.) in degassed acetone (34 mL) was placed in a 100 mL autoclave. The autoclave was purged with nitrogen (3x) and with hydrogen (3x). The mixture was stirred at 120 °C under hydrogen pressure (74 bar) for 19 h. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 35:1) yielding the title compound (379 mg, 0.792 mmol, 94%) as colorless oil.

Analytical data is in full agreement with **1.131** prepared *via* alkylation of malonate **1.131**.

Dimethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylmalonate (1.197b)



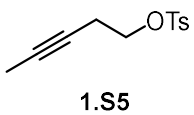
1.197b

To a solution of formaldehyde, 37% in H_2O (1.28 mL, 17.2 mmol, 2.50 equiv.) and Et_3N (48.0 µL, 0.344 mmol, 0.05 equiv.) in DMF (2.46 mL) at 50 °C was added a solution of dimethyl 2-methylmalonate (**1.132**) (1.01 g, 6.88 mmol, 1.00 equiv.) in DMF (14.8 mL) dropwise over 25 min. The mixture was stirred at 50 °C for 2 h. After cooling to r.t., the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

The residue was redissolved in acetonitrile (27.5 mL). TBSCl (1.24 g, 8.25 mmol, 1.20 equiv.) was added followed by imidazole (0.936 g, 13.8 mmol, 2.00 equiv.) and DMAP (0.084 g, 0.687 mmol, 0.10 equiv.). The mixture was stirred at r.t. for 80 min. Sat. aq. NH_4Cl (80 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 18:1) yielding the title compound (1.05 g, 3.62 mmol, 53%) as a colorless oil.

TLC: R_f = 0.48 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.95 (s, 2H), 3.71 (s, 6H), 1.48 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 66.3, 56.2, 52.5, 18.3, 18.2, -5.5; **IR** (thin film): 2953, 2931, 2885, 2857, 1735, 1450, 1434, 1387, 1362, 1302, 1254, 1221, 1143, 1094, 1005, 969, 939, 888, 836, 816, 776, 741, 683, 663, 558, 479 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{13}H_{26}NaO_5Si$ $[M+Na]^+$ 313.1442, found 313.1438.

Pent-3-yn-1-yl 4-methylbenzenesulfonate (1.S5)



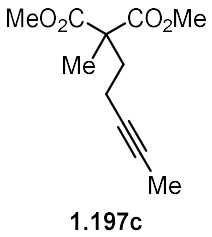
1.S5

To a solution of pent-3-yn-1-ol (0.250 mL, 2.71 mmol, 1.0 equiv.) in CH_2Cl_2 (13.6 mL) was added tosyl chloride (0.620 g, 3.25 mmol, 1.2 equiv.) followed by Et_3N (0.453 mL, 3.25 mmol, 1.2 equiv.) and DMAP (0.033 g, 0.271 mmol, 0.1 equiv.). The mixture was stirred at r.t. for 14 h. Sat. aq. NH_4Cl (20 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1) yielding the title compound (0.621 g, 2.61 mmol, 96%) as a colorless oil.

TLC: R_f = 0.22 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.40 – 7.31 (m, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 2.52 – 2.43 (m, 5H), 1.71 (t, *J* = 2.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 133.2, 130.0, 128.1, 78.4, 73.3, 68.4, 21.8, 19.9, 3.5; **IR** (thin film): 2921, 1597, 1495, 1445, 1358, 1307, 1291, 1220, 1188, 1175, 1120, 1096, 1072, 1019, 971, 899, 843, 814,

767, 705, 687, 662, 582, 571, 553, 533 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{12}H_{14}NaO_3S$ $[M+Na]^+$ 261.0556, found 261.0559.

Dimethyl 2-methyl-2-(pent-3-yn-1-yl)malonate (1.197c)

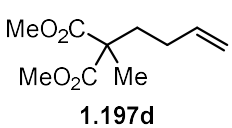


1.197c

To a solution of dimethyl 2-methylmalonate (**1.132**) (0.172 mL, 1.30 mmol, 1.0 equiv.) in DMF (5.75 mL) at 0 °C was added sodium hydride, 60% in mineral oil (0.078 g, 1.94 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 15 min. Pent-3-yn-1-yl 4-methylbenzenesulfonate (**1.S5**) (0.617 g, 2.59 mmol, 2.0 equiv.) in DMF (2.88 mL) was added followed by potassium iodide (0.107 g, 0.647 mmol, 0.5 equiv.) and stirring was continued at 80 °C for 13.5 h. After cooling to r.t., sat. aq. NH_4Cl (30 mL) was added followed by H_2O (15 mL) and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 20:1) yielding the title compound (0.158 g, 0.744 mmol, 58%) as a colorless oil.

TLC: R_f = 0.34 (hex:EtOAc = 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 6H), 2.20 – 2.05 (m, 4H), 1.75 (t, *J* = 2.3 Hz, 3H), 1.42 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 78.0, 76.3, 53.3, 52.7, 35.2, 20.0, 14.5, 3.6; **IR** (thin film): 2953, 2921, 1732, 1434, 1380, 1237, 1199, 1111, 983, 876, 820, 746, 690, 569, 492, 408 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{11}H_{16}NaO_4$ $[M+Na]^+$ 235.0941, found 235.0942.

Dimethyl 2-(but-3-en-1-yl)-2-methylmalonate (1.197d)



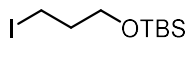
1.197d

To a suspension of sodium hydride, 60% in mineral oil (2.40 g, 60.1 mmol, 2.0 equiv.) in DMF (200 mL) at 0 °C was added dropwise dimethyl 2-methylmalonate (**1.132**) (4.00 mL, 30.1 mmol, 1.0 equiv.). The mixture was stirred at 0 °C for 15 min. 4-Bromobut-1-ene (6.10 mL, 60.1 mmol, 2.0 equiv.) was added dropwise followed by potassium

iodide (2.49 g, 15.0 mmol, 0.5 equiv.). The mixture was stirred at 4 °C for 24 h. Sat. aq. NH_4Cl (400 mL) was added followed by H_2O (200 mL) and the mixture was extracted with (3 x 200 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 12:1) yielding the title compound (4.99 g, 24.9 mmol, 83%) as a colorless oil.

TLC: R_f = 0.51 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.69 (m, 1H), 5.10 – 4.92 (m, 2H), 3.72 (s, 6H), 2.07 – 1.91 (m, 4H), 1.43 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 137.7, 115.2, 53.6, 52.6, 35.0, 28.8, 20.1; **IR** (thin film): 2954, 1731, 1642, 1434, 1379, 1266, 1237, 1203, 1153, 1112, 1036, 995, 913, 874, 817, 751, 638, 555 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{10}H_{16}NaO_4$ $[M+Na]^+$ 223.0941, found 223.0937.

tert-Butyl(3-iodopropoxy)dimethylsilane (1.S6)



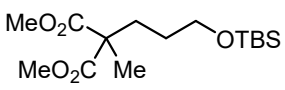
1.S6

To a solution of TBSCl (10.0 g, 66.3 mol, 1.0 equiv.) in DMF (166 mL) was added dropwise propane-1,3-diol (47.9 mL, 663 mmol, 10 equiv.) followed by imidazole (5.42 g, 80.0 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 12 h. Brine–H_2O (1:1, 500 mL) was added and the mixture was extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with H_2O (2 x 250 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

To a solution of iodine (25.3 g, 100 mmol, 1.5 equiv.) in CH_2Cl_2 (241 mL) was added triphenylphosphine (26.1 g, 100 mmol, 1.5 equiv.). The mixture was stirred at r.t. for 20 min. Imidazole (11.3 g, 166 mmol, 2.5 equiv.) was added and stirring was continued at r.t. for 10 min. The intermediate mono-protected diol in CH_2Cl_2 (24.1 mL) was added dropwise and the mixture was stirred at r.t. for 110 min. Sat. aq. $Na_2S_2O_3$–H_2O (1:1, 500 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 50:1) yielding the title compound (13.2 g, 43.9 mmol, 66%) as a colorless oil.

TLC: R_f = 0.53 (hex:EtOAc = 40:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (t, *J* = 5.7 Hz, 2H), 3.28 (t, *J* = 6.7 Hz, 2H), 1.99 (tt, *J* = 6.7, 5.7 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 62.5, 36.3, 26.1, 18.5, 3.9, -5.2; **IR** (thin film): 2952, 2928, 2894, 2856, 1470, 1424, 1383, 1360, 1283, 1253, 1180, 1136, 1096, 1051, 1005, 928, 831, 812, 774, 713, 661, 605, 518, 446, 416 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_9H_{21}OSi$ $[M-I]^+$ 173.1356, found 173.1356.

Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylmalonate (**1.197e**)

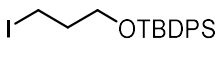


1.197e

To a suspension of dimethyl 2-methylmalonate (**1.132**) (3.00 mL, 22.5 mmol, 2.0 equiv.) in DMF (47.0 mL) at 0 °C was added sodium hydride, 60wt% in mineral oil (0.992 g, 24.8 mmol, 2.2 equiv.). The mixture was stirred at 0 °C for 15 min. *tert*-Butyl(3-iodopropoxy)dimethylsilane (1.**S6**) (3.38 , 11.3 mmol, 1.0 equiv.) in DMF (9.39 mL) was added dropwise. The mixture was stirred at r.t. for 16 h. Sat. aq. NH_4Cl (150 mL) was added followed by H_2O (50 mL). The mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1) yielding the title compound (3.26 g, 10.3 mmol, 91%) as a colorless oil.

TLC: R_f = 0.62 (hex:EtOAc= 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.71 (s, 6H), 3.60 (t, *J* = 6.4 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.49 – 1.39 (m, 5H), 0.88 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, CDCl3) δ 172.8, 63.0, 53.5, 52.4, 32.1, 27.8, 25.9, 20.0, 18.3, -5.3; **IR** (thin film): 2953, 2930, 2886, 2857, 1734, 1462, 1434, 1380, 1361, 1315, 1254, 1234, 1200, 1117, 1096, 1055, 1037, 1005, 984, 938, 834, 814, 774, 713, 661, 569, 486 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{30}NaO_5Si$ $[M+Na]^+$ 341.1755, found 341.1765.

***tert*-Butyl(3-iodopropoxy)diphenylsilane (1.S7)**



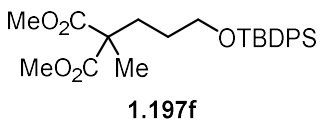
1.S7

To a solution of TBDPSCl (0.500 mL, 1.95 mol, 1.0 equiv.) in DMF (4.87 mL) was added dropwise propane-1,3-diol (1.41 mL, 19.5 mmol, 10 equiv.) followed by imidazole (0.159 g, 2.34 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 15 h. Brine–H_2O (1:1, 30 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 40 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

To a solution of iodine (0.741 g, 2.92 mmol, 1.5 equiv.) in CH_2Cl_2 (7.08 mL) was added triphenylphosphine (0.766 g, 2.92 mmol, 1.5 equiv.). The mixture was stirred at r.t. for 20 min. Imidazole (0.331 g, 4.86 mmol, 2.5 equiv.) was added and stirring was continued at r.t. for 10 min. The intermediate mono-protected diol in CH_2Cl_2 (0.71 mL) was added dropwise and the mixture was stirred at r.t. for 120 min. Sat. aq. $Na_2S_2O_3$–H_2O (1:1, 10 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 100:1) yielding the title compound (0.724 g, 1.71 mmol, 88%) as a colorless oil.

TLC: R_f = 0.54 (hex:EtOAc = 40:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.48 – 7.35 (m, 6H), 3.71 (t, *J* = 5.7 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.07 – 2.00 (m, 2H), 1.05 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 133.7, 129.8, 127.8, 63.3, 36.3, 27.0, 19.4, 3.6; **IR** (thin film): 3070, 2929, 2856, 1589, 1471, 1427, 1389, 1360, 1242, 1181, 1134, 1106, 1050, 1006, 930, 822, 786, 739, 700, 687, 613, 504, 418 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{26}IOSi$ [M+H] 425.0792, found 425.0795.

Dimethyl 2-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-2-methylmalonate (1.197f)



1.197f

To a solution of dimethyl 2-methylmalonate (**1.132**) (0.231 mL, 1.73 mmol, 2.0 equiv.) in DMF (2.90 mL) at 0 °C was added sodium hydride, 60% in mineral oil (77.0 mg, 1.91 mmol, 2.2 equiv.). The mixture was stirred at 0 °C for 15 min. *tert*-Butyl(3-iodopropoxy)diphenylsilane (**1.S7**) (0.369 g, 0.869 mmol, 1.0 equiv.) in DMF (1.45 mL) was added and stirring was continued at r.t. for 15 h. Sat. aq. NH_4Cl (20 mL) was added followed by H_2O (10 mL). The mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1) yielding the title compound (0.724 g, 1.71 mmol, 88%) as a colorless oil.

TLC: R_f = 0.42 (hex:EtOAc = 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 4H), 7.46 – 7.35 (m, 6H), 3.70 (s, 6H), 3.65 (t, *J* = 6.3 Hz, 2H), 1.98 – 1.90 (m, 2H), 1.52 – 1.42 (m, 2H), 1.40 (s, 3H), 1.04 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.9, 135.7, 134.0, 129.7, 127.8, 63.8, 53.6, 52.6, 32.2, 27.7, 27.0, 20.2, 19.3; **IR** (thin film): 3071, 2998, 2952, 2894, 2858, 1733, 1589, 1461, 1428, 1380, 1361, 1314, 1263, 1234, 1200, 1110, 1036, 997, 984, 938, 870, 822, 784, 762, 741, 725, 702, 687, 613, 505, 419 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{25}H_{34}NaO_5Si$ $[M+Na]^+$ 465.2068, found 465.2066.

General Procedure A: Enzymatic Hydrolysis

To a solution of dimethyl malonate (**1.197**) (1.0 equiv.) in DMSO (0.286 M) was added 0.1 M pH 7 sodium phosphate buffer (0.029 M) followed by 0.1 M aq. NaOH (1.0 equiv.) and pig liver esterase (1447 U/mmol **1.197**). The mixture was stirred at r.t. for the indicated time. EtOAc was added followed by 1 M pH 2 phosphate buffer. The mixture was filtered through a pad of Celite® with EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc (2).

The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

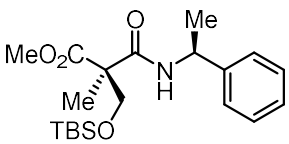
General Procedure B: Racemic Hydrolysis

To a solution of dimethyl malonate (**1.197**) (1.0 equiv.) in THF (0.15 M) at 0 °C was added 0.5 M aq. NaOH (1.5 equiv.). The mixture was stirred at the indicated temperature and for the indicated time. EtOAc was added followed by 1 M pH2 sodium phosphate buffer. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

General Procedure C: Amide Coupling

The unpurified malonic acid monoester **1.209** obtained from general procedure C or D was dissolved in DMF (0.05 M). HBTU (1.5 equiv.) was added followed by DIPEA (2.5 equiv.) and (*S*)-1-phenylethanmine (1.5 equiv.). The mixture was stirred at r.t. for 2.5 h. Sat. aq. NH_4Cl (40 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica.

(*R*)-Methyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-3-oxo-3-(((*S*)-1-phenylethyl) amino)propanoate (1.211a)



1.211a

Enzymatic hydrolysis:

Following general procedures A and B using dimethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylmalonate (**1.197a**) (103 mg, 0.355 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 10:1. Yield: 52.0 mg, 0.137 mmol, 39% as a colorless oil and ~37:1 mixture of diastereomers.

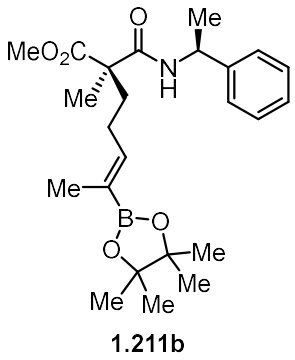
Racemic hydrolysis:

Following general procedures B and C using dimethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylmalonate (**1.197a**) (100 mg, 0.344 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 8:1. Yield: 95.8 mg, 0.252 mmol, 73% as a colorless oil and 1:1 mixture of diastereomers.

Note: *Two sets of NMR data are provided. One for diastereomerically enriched* ***1.211a*** *obtained via enzymatic hydrolysis (d.r. = 37:1) and one for* ***1.211a*** *containing equimolar amounts of both diastereomers obtained via racemic hydrolysis. In the NMR data, signals of the minor diastereoisomer obtained from enzymatic hydrolysis are labeled with an asterisk.*

TLC: R_f = 0.55 (hex:EtOAc = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H*), 7.58 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.20 (m, 5H, 5H*), 5.18 – 5.08 (m, 1H, 1H*), 3.96 (m, 1H, 1H*), 3.83 (d, *J* = 9.9 Hz, 1H*), 3.79 (d, *J* = 9.8 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H*), 1.49 (d, *J* = 7.0 Hz, 3H), 1.46 (d, *J* = 6.9 Hz, 3H*), 1.38 (s, 3H, 3H*), 0.83 (s, 9H*), 0.82 (s, 9H), 0.06 (s, 3H*), 0.04 (s, 3H, 3H*), 0.00 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4, 173.4*, 170.2, 170.2*, 143.5, 143.5*, 128.7, 128.6*, 127.3, 127.2*, 126.2*, 126.2, 67.7*, 67.6, 55.6, 55.6*, 52.5, 52.4*, 48.9, 48.8*, 25.7, 25.7*, 22.2*, 21.9, 18.4, 18.3*, 18.1, 18.1*, -5.6*, -5.6, -5.6*, -5.7; **IR** (thin film): 3353, 2928, 2856, 1737, 1664, 1527, 1461, 1254, 1093, 836, 778, 698, 505, 462, 429, 415, 404 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –1.7 (*c* 0.70, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{20}H_{33}NNaO_4Si$ $[M+Na]^+$ 402.2071, found 402.2073.

(*R*,*Z*)-methyl 2-methyl-2-(((*S*)-1-phenylethyl)carbamoyl)-6-(4,4,5,5-tetramethyl-1,3,2-dio-xaborolan-2-yl)hept-5-enoate (**1.211b**)



1.211b

Enzymatic hydrolysis:

Following general procedures A and B using (*Z*)-dimethyl 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pent-3-en-1-yl) malonate (**1.197b**) (28.0 mg, 0.082 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 4:1. Yield: 3.0 mg, 0.007 mmol, 9% as a colorless oil and 7:1 mixture of diastereomers.

Racemic hydrolysis:

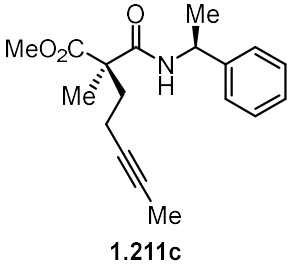
Following general procedures B and C using (*Z*)-dimethyl 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl) malonate (**1.197b**) (30.0 mg, 0.088 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 4:1. Yield: 6.8 mg, 0.016 mmol, 28% as a colorless oil and 1:1 mixture of diastereomers.

Note: *Two sets of NMR data are provided. One for diastereomerically enriched* ***1.211b*** *obtained via enzymatic hydrolysis (d.r. = 7:1) and one for* ***1.211b*** *containing equimolar amounts of both diastereomers obtained via racemic hydrolysis. In the NMR data, signals of the minor diastereoisomer obtained from enzymatic hydrolysis are labeled with an asterisk.*

TLC: R_f = 0.29 (hex:EtOAc = 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 6H, 6H*), 6.31 – 6.24 (m, 1H*), 6.24 – 6.17 (m, 1H), 5.19 – 5.07 (m, 1H, 1H*), 3.75 (s, 3H), 3.73 (s, 3H*), 2.22 – 1.83 (m, 4H, 4H*), 1.70 – 1.66 (m, 3H*), 1.59 – 1.55 (m, 3H), 1.53 – 1.43 (m, 6H, 6H*), 1.28 (s, 12H*), 1.26 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8, 175.7*, 170.2, 170.1*, 144.4*, 144.4, 143.5, 143.4*, 128.8 (C,C*), 127.4 (C,C*), 126.2, 126.1*, 83.3*, 83.3, 53.6, 53.6*, 52.7, 52.6*, 49.2, 49.2*, 37.4, 37.3*, 25.0*, 24.9, 24.5*, 24.4, 22.2*, 22.1, 21.1, 21.0*, 13.9*, 13.9; **IR** (thin film): 3343, 2977, 2930, 1736, 1718, 1643, 1524, 1495, 1451, 1410, 1370, 1334, 1303, 1272, 1237, 1212, 1141, 1112, 1061, 1020, 970, 895, 858, 760, 699, 668, 578, 541, 406 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$

–34.5 (*c* 0.15, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{24}H_{37}BNO_5$ $[M+H]^+$ 430.2764, found 430.2764.

(*R*)-Methyl 2-methyl-2-(((*S*)-1-phenylethyl)carbamoyl)hept-5-ynoate (1.211c)



1.211c

Enzymatic hydrolysis:

Following general procedures A and B using dimethyl 2-methyl-2-(pent-3-yn-1-yl)malonate (**1.197c**) (30.0 mg, 0.141 mmol, 1.0 equiv.). Purified by preparative TLC: hex:EtOAc = 3:1. Yield: 31.4 mg, 0.104 mmol, 74% as a colorless oil and 3:2 mixture of diastereomers.

Racemic hydrolysis:

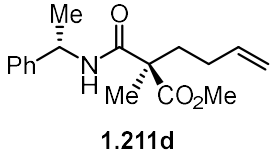
Following general procedures B and C using dimethyl 2-methyl-2-(pent-3-yn-1-yl)malonate (**1.197c**) (48.0 mg mg, 0.226 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 8:1. Yield: 47.7 mg, 0.158 mmol, 70% as a colorless oil and 1:1 mixture of diastereomers.

Note: *Two sets of NMR data are provided. One for diastereomerically enriched* ***1.211c*** *obtained via enzymatic hydrolysis (d.r. = 3:2) and one for* ***1.211c*** *containing equimolar amounts of both diastereomers obtained via racemic hydrolysis. In the NMR data, signals of the minor diastereoisomer obtained from enzymatic hydrolysis are labeled with an asterisk.*

TLC: R_f = 0.42 (hex:EtOAc = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.15 (m, 6H, 6H*), 5.14 – 5.03 (m, 1H, 1H*), 3.73 (s, 3H), 3.72 (s, 3H*), 2.27 – 1.97 (m, 4H, 4H*), 1.75 (t, *J* = 2.4 Hz, 3H*), 1.71 (t, *J* = 2.3 Hz, 3H), 1.49 – 1.46 (m, 3H*), 1.45 (s, 3H), 1.42 (s, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6, 175.5*, 169.9, 169.7*, 143.5, 143.4*, 128.8*, 128.7, 127.4*, 127.3, 126.0, 126.0*, 77.9*, 77.8, 76.5, 76.5*, 53.1*, 53.0, 52.7*, 52.7, 49.2, 49.2*, 37.1*, 37.0, 22.2*, 22.2, 21.5, 21.4*, 15.1*, 15.0, 3.6*, 3.6; **IR** (thin film): 3335, 3029, 2976, 2950, 2920, 1733, 1645, 1522, 1495, 1449, 1377, 1283, 1238, 1204, 1117, 1020, 992,

943, 896, 837, 761, 699, 606, 540, 497, 418, 406 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –22.3 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{18}H_{23}NNaO_3$ $[M+Na]^+$ 324.1570, found 324.1566.

(*R*)-Methyl 2-methyl-2-(((*S*)-1-phenylethyl)carbamoyl)hex-5-enoate (1.211d)



1.211d

Enzymatic hydrolysis:

Following general procedures A and B using dimethyl 2-(but-3-en-1-yl)-2-methylmalonate (**1.197d**) (103 mg, 0.514 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 8:1. Yield: 145 mg, 0.501 mmol, 97% as a colorless oil and 1.6:1 mixture of diastereomers.

Racemic hydrolysis:

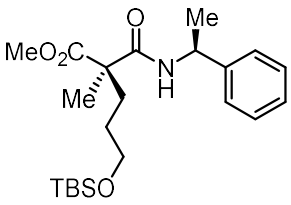
Following general procedures B and C using dimethyl 2-(but-3-en-1-yl)-2-methylmalonate (**1.197d**) (104 mg, 0.519 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 8:1. Yield: 89 mg, 0.309 mmol, 59% as a colorless oil and 1:1 mixture of diastereomers.

Note: *Two sets of NMR data are provided. One for diastereomerically enriched* ***1.211d*** *obtained via enzymatic hydrolysis (d.r. = 1.6:1) and one for* ***1.211d*** *containing equimolar amounts of both diastereomers obtained via racemic hydrolysis. In the NMR data, signals of the minor diastereoisomer obtained from enzymatic hydrolysis are labeled with an asterisk.*

TLC: R_f = 0.43 (hex:EtOAc = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 6H, 6H*), 5.84 – 5.63 (m, 1H, 1H*), 5.16 – 4.88 (m, 3H, 3H*), 3.74 (s, 3H*), 3.72 (s, 3H), 2.13 – 1.80 (m, 4H, 4H*), 1.49 (d, *J* = 6.9 Hz, 3H), 1.47 (d, *J* = 6.7 Hz, 3H*), 1.45 (s, 3H*), 1.43 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8*, 175.8, 170.2*, 170.1, 143.5*, 143.4, 137.6, 137.5*, 128.8, 128.8*, 127.4, 127.4*, 126.1*, 126.1, 115.3, 115.2*, 53.4, 53.4*, 52.7*, 52.7, 49.2*, 49.2, 37.5*, 37.4, 29.6, 29.4*, 22.2, 22.1*, 21.3, 21.1*; **IR** (thin film): 3343, 3063, 3029, 2977, 2951, 1733, 1641, 1521, 1495, 1450, 1377, 1239, 1208, 1147, 1124, 994, 910, 838, 760, 699, 624, 609, 540, 497 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –40.4 (*c* 2.00,

$CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1751, found 290.1751.

(*R*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-methyl-2-(((*S*)-1-phenylethyl) carbamoyl)pentanoate (1.211e)



1.211e

Enzymatic hydrolysis:

Following general procedures A and B using dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy) propyl)-2-methylmalonate (**1.197e**) (104 mg, 0.327 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 10:1. Yield: 88.3 mg, 0.217 mmol, 67% as a colorless oil and >50:1 mixture of diastereomers.

Racemic hydrolysis:

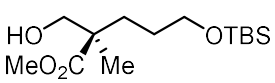
Following general procedures B and C using dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy) propyl)-2-methylmalonate (**1.197e**) (29 mg, 0.091 mmol, 1.0 equiv.). FC conditions: hex:EtOAc = 12:1. Yield: 13 mg, 0.032 mmol, 39% as a colorless oil and 1:1 mixture of diastereomers.

Note: *Two sets of NMR data are provided. One for diastereomerically enriched* ***1.211e*** *obtained via enzymatic hydrolysis (d.r. > 50:1) and one for* ***1.211e*** *containing equimolar amounts of both diastereomers obtained via racemic hydrolysis. In the NMR data, signals of the minor diastereoisomer obtained from enzymatic hydrolysis are labeled with an asterisk.*

TLC: R_f = 0.44 (hex:EtOAc = 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 6H, 6H*), 5.17 – 5.06 (m, 1H, 1H*), 3.76 (s, 3H), 3.74 (s, 3H*), 3.68 – 3.50 (m, 2H, 2H*), 2.04 – 1.80 (m, 2H, 2H*), 1.54 – 1.32 (m, 8H, 8H*), 0.91 (s, 9H*), 0.89 (s, 9H), 0.06 (s, 6H*), 0.03 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8, 175.8*, 170.4, 170.3*, 143.5, 143.4*, 128.8*, 128.8, 127.4*, 127.3, 126.1, 126.1*, 63.0*, 63.0, 53.5, 53.5*, 52.7, 52.7*, 49.2, 49.1*, 34.8, 34.7*, 28.6*, 28.5, 26.1*, 26.1, 22.2*, 22.1, 21.0*, 20.9, 18.5*, 18.4, -5.1*, -5.2, -5.2; **IR** (thin film): 3345, 3030, 2953, 2929, 2857, 1735, 1648, 1523, 1495, 1461,

1379, 1360, 1253, 1205, 1097, 1031, 940, 835, 775, 699, 661, 542 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –26.5 (*c* 0.30, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{22}H_{37}NNaO_4Si$ $[M+Na]^+$ 430.2384, found 430.2390.

(*R*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-2-methylpentanoate (1.212)



1.212

Enantioenriched:

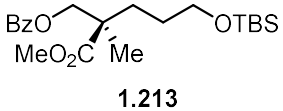
To a solution of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylmalonate (**1.197e**) (1.43 g, 4.48 mmol, 1.0 equiv.) in DMSO (10.9 mL) was added 0.1 M aq. pH7 sodium phosphate buffer (109 mL) followed by pig liver esterase (0.249 g, 4480 U) and 1 M aq. NaOH (4.48 mL, 4.48 mmol, 1.0 equiv.). The mixture was stirred at r.t. for 49 h. More pig liver esterase (0.249 g, 4480 U) was added and stirring was continued for 45 h. 1 M aq. pH2 sodium phosphate buffer–brine (1:3, 320 mL) was added followed by EtOAc (250 mL). The biphasic mixture was filtered, the phases were separated and the aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Crude intermediate **17e** was redissolved in THF (49.8 mL) and cooled to 0 °C. Et_3N (0.937 mL, 6.72 mmol, 1.5 equiv.) was added followed by methyl chloroformate (0.519 mL, 6.72 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 10 min and at r.t. for 90 min, filtered through cotton and concentrated under reduced pressure. The residue was redissolved in methanol (49.8 mL) and cooled to 0 °C. $NaBH_4$ (0.441 , 11.7 mmol, 2.6 equiv.) was added and the mixture was stirred at 0 °C for 65 min. Sat. aq. NH_4Cl (200 mL) was added followed by H_2O (100 mL) and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine–1 M HCl (4:1, 200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 4:1) yielding the title compound (0.831 g, 2.86 mmol, 64%) as a colorless oil.

Racemic:

To a solution of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylmalonate (**1.197e**) (107 mg, 0.336 mmol, 1.0 equiv.) in THF (3.36 mL) was added lithium tri(*tert*-butoxy)aluminum hydride, 1.0 M in THF (1.68 mL, 1.68 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 22 h. 10% aq. $KHSO_4$ (5 mL) was added slowly followed by H_2O (10 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 3:1) yielding the title compound (72.0 g, 0.248 mmol, 74%) as a colorless oil.

TLC: R_f = 0.56 (hex:EtOAc = 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.70 (d, *J* = 3.2 Hz, 4H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.51 (d, *J* = 11.3 Hz, 1H), 2.22 (b s, 1H), 1.68 – 1.42 (m, 4H), 1.18 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.5, 68.1, 63.3, 51.9, 47.5, 32.0, 27.6, 25.9, 19.8, 18.3, -5.3; **IR** (thin film): 3457, 2952, 2930, 2857, 1729, 1471, 1388, 1361, 1253, 1204, 1099, 1038, 937, 835, 775, 660, 497, 423 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ +0.6 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{14}H_{30}NaO_4Si$ $[M+Na]^+$ 313.1806, found 313.1806.

(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxycarbonyl)-2-methylpentyl benzoate (1.213)

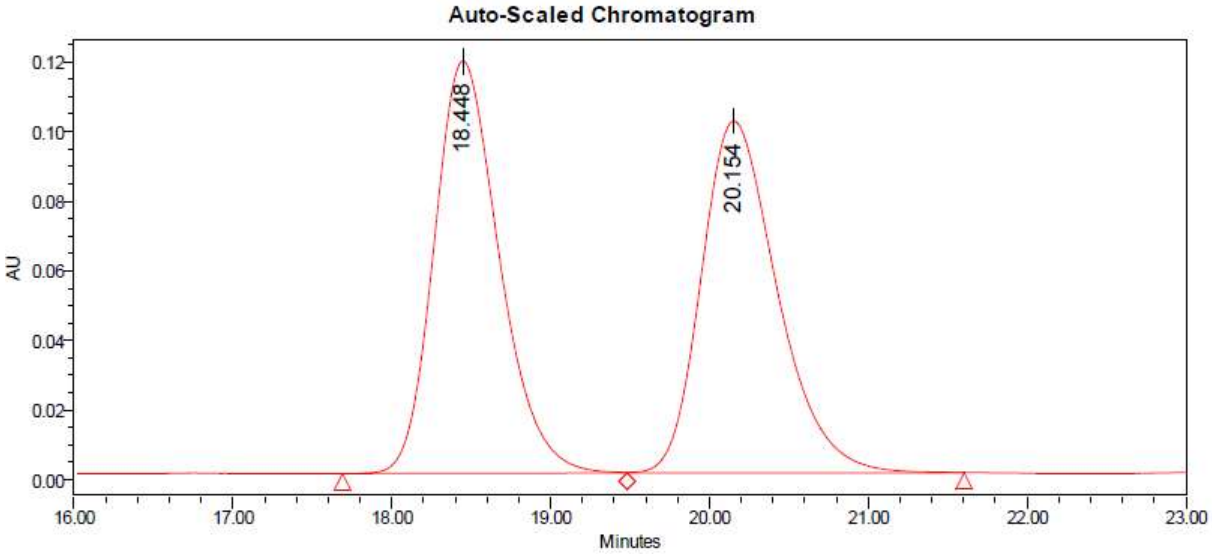


1.213

To a solution of (*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-2-methylpentanoate (**1.212**) (38.7 mg, 0.133 mmol, 1.0 equiv.) in CH_2Cl_2 (1.78 mL) was added Et_3N (37.1 µL, 0.266 mmol, 2.0 equiv.) followed by DMAP (3.26 mg, 0.027 mmol, 0.2 equiv.) and benzoyl chloride (18.6 µL, 0.160 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 12 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 1 M HCl (10 mL), dried over Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 20:1) yielding the title compound (46.4 mg, 0.118 mmol, 88%) as a colorless oil.

TLC: R_f = 0.31 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 2H), 7.60 – 7.52 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 3.71 (s, 3H), 3.60 (t, *J* = 6.2 Hz, 2H), 1.85 – 1.74 (m, 1H), 1.69 – 1.41 (m, 3H), 1.31 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6, 166.3, 133.2, 130.1, 129.7, 128.5, 69.6, 63.2, 52.2, 46.4, 32.4, 27.8, 26.1, 20.0, 18.4, -5.2; **IR** (thin film): 2952, 2929, 2886, 2856, 1770, 1724, 1602, 1584, 1470, 1451, 1387, 1314, 1270, 1250, 1199, 1176, 1142, 1097, 1069, 1026, 985, 938, 901, 834, 775, 709, 686, 677, 661, 420 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –5.0 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{35}O_5Si$ $[M+H]^+$ 395.2248, found 395.2250.



Peak Results

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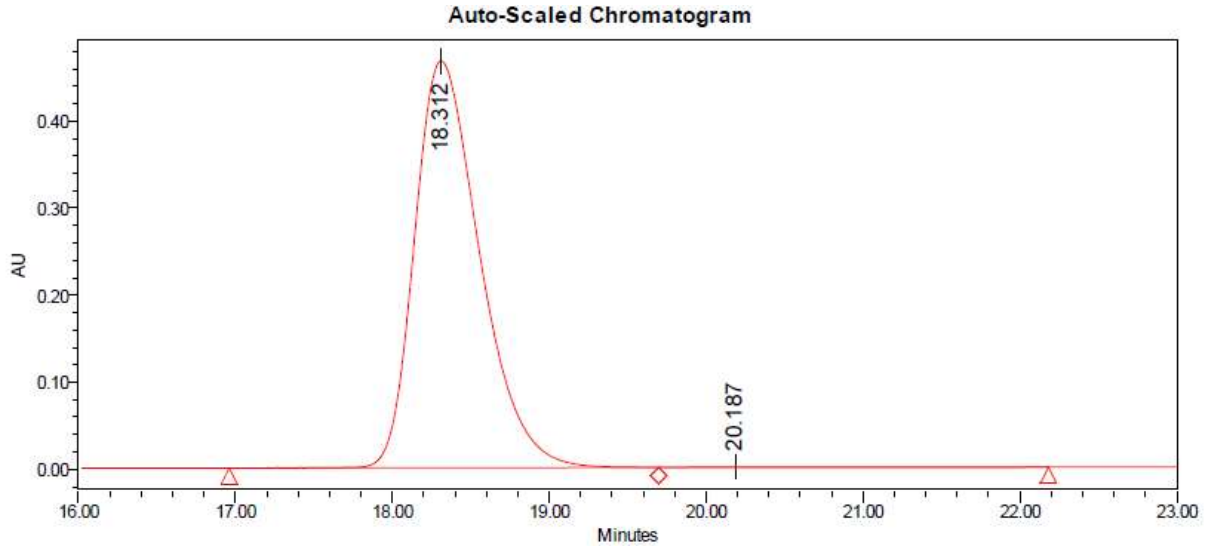
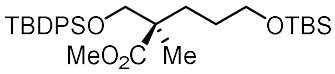


Peak Results

	Name	RT	Area	% Area	Height	Units
1		18.312	13475919	99.71	467470	
2		20.187	39236	0.29	674	

(*R*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(((tert-butyldiphenylsilyl)oxy) methyl)-2-methylpentanoate (1.214)



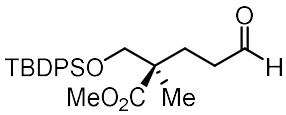
1.214

To a solution of (*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-2-methylpentanoate (**1.212**) (0.831 g, 2.86 mmol, 1.0 equiv.) in CH_2Cl_2 (28.6 mL) was added TBDPSCl (1.10 mL, 4.29 mmol, 1.5 equiv.) followed by imidazole (0.487 g, 7.14 mmol, 2.5 equiv.) and DMAP (0.070 g, 0.572 mmol, 0.2 equiv.). The mixture was stirred at r.t. for 9 h. Sat. aq. NH_4Cl (30 mL) was added followed by H_2O (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with sat. aq. NH_4Cl (60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 40:1) yielding the title compound (1.432 g, 2.71 mmol, 95%) as a colorless oil.

TLC: R_f = 0.29 (hex:EtOAc = 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 4H), 7.48 – 7.35 (m, 6H), 3.77 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.61 – 3.50 (m, 3H), 1.72 – 1.61 (m, 1H), 1.54 – 1.31 (m, 3H), 1.24 (s, 3H), 1.03 (s, 9H),

0.88 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 135.6, 135.6, 133.5, 133.4, 129.6, 127.6, 127.6, 69.5, 63.4, 51.6, 48.5, 31.6, 27.8, 26.7, 26.0, 19.4, 19.3, 18.4, -5.3; **IR** (thin film): 2952, 2930, 2857, 1736, 1472, 1428, 1389, 1361, 1252, 1195, 1102, 1006, 938, 834, 775, 739, 701, 612, 504 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ +1.3 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{30}H_{48}NaO_4Si_2$ $[M+Na]^+$ 551.2983, found 551.2978.

(*R*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-5-oxopentanoate (1.215)



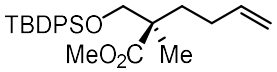
1.215

To a solution of (*R*)-methyl 5-((*tert*-butyldimethylsilyl) oxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methylpentanoate (**1.214**) (0.651 g, 1.23 mmol, 1.0 equiv.) in EtOH (16.4 mL) was added PPTS (0.062 g, 0.246 mmol, 0.2 equiv.). The mixture was stirred at r.t. for 20 h and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (15 mL) and washed with sat. aq. $NaHCO_3$ (15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was azeotroped with PhMe (2 mL). The crude intermediate was dissolved in CH_2Cl_2 (16.4 mL). *t*-BuOH (0.141 mL, 1.48 mmol, 1.2 equiv.) was added followed by DMP (0.626 g, 1.48 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 15 min and poured into a mixture of Et_2O (70 mL), sat. aq. $Na_2S_2O_3$ (70 mL) and sat. aq. $NaHCO_3$ (70 mL). The biphasic mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (0.510 g, 1.07 mmol, 87%) as a colorless oil.

Note: *The intermediate alcohol was not stable on silica gel (lactone formation) and was therefore not characterized and used for the next step without further purification.*

TLC: R_f = 0.47 (hex:EtOAc = 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.4 Hz, 1H), 7.68 – 7.62 (m, 4H), 7.49 – 7.38 (m, 6H), 3.74 (d, *J* = 9.7 Hz, 1H), 3.68 (s, 3H), 3.66 (d, *J* = 9.7 Hz, 1H), 2.48 – 2.31 (m, 2H), 2.06 (ddd, *J* = 14.1, 9.6, 6.3 Hz, 1H), 1.80 (ddd, *J* = 14.0, 9.4, 6.6 Hz, 1H), 1.23 (s, 3H), 1.06 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.7, 175.9, 135.8, 133.3, 133.3, 129.9, 127.8, 69.2, 51.9, 47.9, 39.5, 27.2, 26.9, 19.7, 19.5; **IR** (thin film): 2932, 2858, 1728, 1589, 1472, 1428, 1390, 1361, 1238, 1190, 1111, 998, 937, 823, 762, 740, 702, 612, 504, 489 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ ±0 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{24}H_{32}NaO_4Si$ $[M+Na]^+$ 435.1962, found 435.1968.

(*R*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhex-5-enoate (**1.216**)



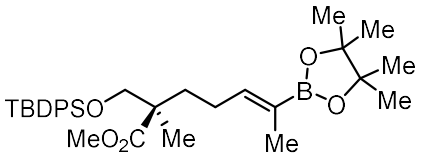
1.216

To a suspension of methyltriphenylphosphonium bromide (1.72 g, 4.81 mmol, 4.5 equiv.) in THF (10.7 mL) was added dropwise KO-*t*-Bu, 1 M in THF (4.28 mL, 4.28 mmol, 4.0 equiv.). The mixture was stirred at r.t. for 70 min. (*R*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy) methyl)-2-methyl-5-oxopentanoate (**1.215**) (0.441 g, 1.07 mmol, 1.0 equiv.) in THF (10.7 mL) was added dropwise and stirring was continued at r.t. for 15 min. Sat. aq. NH_4Cl (50 mL) was added followed by H_2O (20 mL) and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 35:1) yielding the title compound (0.379 g, 0.92 mmol, 86%) as a colorless oil.

TLC: R_f = 0.44 (hex:EtOAc = 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H), 7.40 (d, *J* = 12.5 Hz, 6H), 5.76 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.03 – 4.87 (m, 2H), 3.77 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.57 (d, *J* = 9.5 Hz, 1H), 2.08 – 1.85 (m, 2H), 1.81 – 1.71 (m, 1H), 1.55 – 1.45 (m, 1H), 1.25 (s, 3H), 1.03 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 138.3, 135.6, 135.6, 133.4, 133.4, 129.7, 127.7, 127.6, 114.5, 69.3, 51.6, 48.5, 34.4, 28.7, 26.7, 19.4, 19.3; **IR** (thin film): 2931, 2857, 1734, 1640, 1472, 1428, 1389, 1191, 1111, 997, 910, 822, 739,

701, 613, 504 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ +2-2 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{25}H_{34}NaO_3Si$ $[M+Na]^+$ 433.2169, found 433.2172.

(*R*,*Z*)-Methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-enoate (1.218)

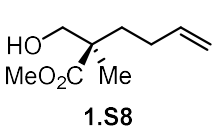


1.218

To a solution of (*R*)-methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhex-5-enoate (**1.216**) (0.166 g, 0.404 mmol, 1.0 equiv.) in CH_2Cl_2 (4.04 mL, purged with argon for 20 min) was added isopropenylboronoic acid pinacol ester (**1.217**) (0.380 mL, 2.02 mmol, 5.0 equiv.) followed by Grubbs 2nd generation catalyst (0.034 g, 0.040 mmol, 0.1 equiv.). The mixture was stirred at 50 °C for 3 h. The mixture was concentrated under reduced pressure. The residue was purified by FC on silica (a: hex:EtOAc = 25:1, b: PhMe:CH_2Cl_2 = 1:1) yielding the title compound (0.109 g, 0.198 mmol, 49%) as a colorless oil.

TLC: R_f = 0.62 (hex:EtOAc = 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H), 7.47 – 7.32 (m, 6H), 6.31 – 6.21 (m, 1H), 3.78 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.58 (d, *J* = 9.6 Hz, 1H), 2.17 – 1.93 (m, 2H), 1.76 (ddd, *J* = 13.5, 11.5, 5.3 Hz, 1H), 1.67 – 1.61 (m, 3H), 1.51 (ddd, *J* = 13.5, 11.4, 5.4 Hz, 1H), 1.26 (s, 3H), 1.25 (s, 12H), 1.04 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 145.4, 135.6, 135.6, 133.4, 133.4, 129.6, 127.6, 127.6, 83.1, 69.3, 51.5, 48.6, 34.3, 26.8, 24.8, 23.7, 19.4, 19.3, 13.8; **IR** (thin film): 3071, 2976, 2931, 2858, 1735, 1631, 1589, 1471, 1428, 1410, 1370, 1335, 1303, 1271, 1239, 1214, 1190, 1143, 1111, 998, 972, 858, 822, 773, 740, 701, 690, 669, 613, 504, 490, 437, 419 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ +3.0 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{32}H_{47}BNaO_5Si$ $[M+Na]^+$ 573.3178, found 573.3176.

(*R*)-Methyl 2-(hydroxymethyl)-2-methylhex-5-enoate (1.S8)

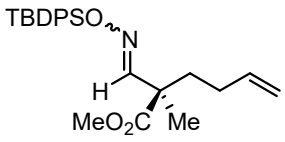


1.S8

To a solution of (*R*)-methyl 2-(((*tert*-butyldiphenylsilyl)oxy) methyl)-2-methylhex-5-enoate (**1.216**) (1.74 g, 4.24 mmol, 1.0 equiv.) in THF (42.4 mL) was added dropwise TBAF, 1 M in THF (21.2 mL, 21.2 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 5.25 h. H_2O (150 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pent:Et_2O = 2:1 to 1:1 gradient) yielding the title compound (0.622 g, 3.61 mmol, 85%) as a colorless oil.

TLC: R_f = 0.49 (hex:EtOAc = 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.92 (ddt, *J* = 10.2, 1.9, 1.3 Hz, 1H), 3.72 – 3.66 (m, 4H), 3.48 (dd, *J* = 11.2, 5.7 Hz, 1H), 2.53 (t, *J* = 6.3 Hz, 1H), 2.08 – 1.91 (m, 2H), 1.72 – 1.53 (m, 2H), 1.17 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4, 138.1, 114.9, 68.2, 52.0, 47.7, 35.1, 28.7, 19.6; **IR** (thin film): 3449, 3077, 2977, 2949, 1720, 1641, 1451, 1434, 1388, 1285, 1208, 1145, 1045, 995, 910, 809, 497, 444, 417 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ +1.4 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_9H_{16}NaO_3$ $[M+Na]^+$ 195.0992, found 195.0997.

(*R*,*E*)-Methyl 2-((((*tert*-butyldiphenylsilyl)oxy)imino)methyl)-2-methylhex-5-enoate (1.220)

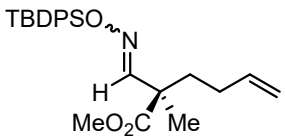


1.220

To a solution of (*R*)-methyl 2-(hydroxymethyl)-2-methylhex-5-enoate (**1.S8**) (622 mg, 3.61 mmol, 1.0 equiv.) in CH_2Cl_2 (36.1 mL) was added DMP (1.83 g, 4.33 mmol, 1.2 equiv.) followed by *t*-BuOH (0.415 mL, 4.33 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 15 min and poured into a mixture of sat. aq. $Na_2S_2O_3$ (250 mL), sat. aq. $NaHCO_3$ (250 mL), and Et_2O (200 mL). The biphasic mixture was stirred vigorously for 10 min. The phases were separated

and the aqueous layer was extracted with Et_2O (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

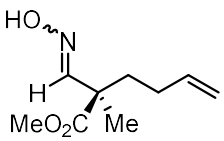
The residue was redissolved in EtOH (23.1 mL) and pyridine (2.88 mL). *O*-(*tert*-butyldiphenylsilyl)hydroxylamine (1.37 g, 5.06 mmol, 1.3 equiv.) was added. The mixture was stirred at r.t. for 8 h and concentrated under reduced pressure. H_2O (30 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 35:1) yielding the title compound (992 mg, 2.34 mmol, 60%) as a colorless oil and 6:1 mixture of trans- and cis-oximes and unprotected oxime **XX** (194 mg, 1.05 mmol, 27%) as a yellow oil and 25:1 mixture of trans- and cis-oximes.



1.220

Note: *Analytical data represents a 6:1 mixture of trans- and cis-oximes, signals of the cis-oxime are labeled with an asterisk.*

TLC: R_f = 0.62 (hex:EtOAc = 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.73 – 7.64 (m, 4H, 4H*), 7.45 – 7.32 (m, 6H, 6H*), 6.91 (s, 1H*), 5.87 – 5.64 (m, 1H, 1H*), 5.11 – 4.89 (m, 2H, 2H*), 3.69 (s, 3H), 3.63 (s, 3H*), 2.16 – 1.75 (m, 4H, 4H*), 1.53 (s, 3H*), 1.33 (s, 3H), 1.12 (s, 9H), 1.07 (s, 9H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7, 174.2*, 157.6, 156.9*, 143.3, 137.8, 137.8*, 135.6, 135.6, 135.4*, 135.4*, 133.7, 133.7, 133.2*, 129.9*, 129.9*, 129.7, 127.8*, 127.8*, 127.6, 115.3*, 115.0, 52.4, 52.1*, 48.4, 46.7*, 36.9*, 36.9, 28.9, 28.7*, 27.3, 27.0*, 21.0, 20.3*, 19.6, 19.3*; **IR** (thin film): 3072, 2951, 2858, 1770, 1758, 1740, 1641, 1460, 1428, 1377, 1241, 1114, 1057, 923, 852, 821, 740, 699, 605, 505, 505, 438 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ +11.5 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{25}H_{33}NNaO_3Si$ $[M+Na]^+$ 446.2122, found 446.2119.



1.219

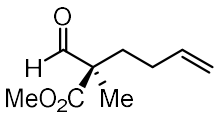
Note: *Analytical data represents a 25:1 mixture of trans- and cis-oximes, ^{1}H NMR signals of the cis-oxime are labeled with an asterisk.*

TLC: R_f = 0.24 (hex:EtOAc = 5:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.59 (s, 1H), 6.73 (s, 1H*), 5.83 – 5.70 (m, 1H, 1H*), 5.06 – 4.94 (m, 2H, 2H*), 3.72 (s, 3H), 3.70 (s, 3H*), 2.10 – 1.95 (m, 2H, 2H*), 1.93 – 1.78 (m, 2H, 2H*), 1.43 (s, 3H*), 1.37 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 153.4, 137.5, 115.1, 52.4, 48.0, 36.8, 28.7, 20.2; **IR** (thin film): 3423, 3078, 2981, 2951, 1729, 1641, 1434, 1377, 1232, 1145, 1119, 943, 914, 821, 788, 764, 701, 557, 497, 463, 415 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –1.8 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_9H_{15}NNaO_3$ $[M+Na]^+$ 208.0944, found 208.0941.

Reprotection of oxime:

To a solution of free oxime **1.219** (49.0 mg, 0.265 mmol, 1.0 equiv.) in CH_2Cl_2 (5.29 mL) was added TBDPSCl (0.102 mL, 0.397 mmol, 1.5 equiv.) followed by imidazole (45.0 mg, 0.661 mmol, 2.5 equiv.) and DMAP (6.5 mg, 0.053 mmol, 0.2 equiv.). The mixture was stirred at r.t. for 16 h. Sat. aq. NH_4Cl (10 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtIAc = 20:1) yielding the title compound (94.0 mg, 0.222 mmol, 84%) as a colorless oil and 6:1 mixture of trans- and cis-oximes.

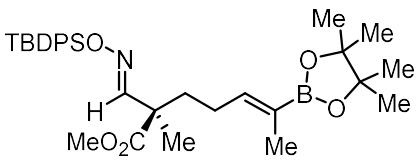
For characterization, a small amount of the intermediate aldehyde **1.S9** was purified by FC on silica (hex:EtOAc = 12:1).



1.S9

TLC: R_f = 0.45 (hex:EtOAc = 5:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 5.81 – 5.71 (m, 1H), 5.08 – 4.94 (m, 2H), 3.76 (s, 3H), 2.09 – 1.95 (m, 3H), 1.87 – 1.77 (m, 1H), 1.32 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.5, 172.7, 137.3, 115.6, 57.6, 52.6, 33.7, 28.7, 17.1; **IR** (thin film): 3079, 2980, 2953, 2846, 2726, 1719, 1642, 1452, 1434, 1393, 1375, 1316, 1257, 1208, 1149, 1121, 1077, 995, 912, 882, 867, 811, 776, 702, 632, 553, 489, 468, 449 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ +2.1 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_9H_{14}NaO_3$ $[M+Na]^+$ 193.0835, found 193.0832.

(*R*,*Z*)-Methyl 2-((*E*)-(((*tert*-butyldiphenylsilyl)oxy)imino)methyl)-2-methyl-6-(4,4,5,5-tetra-methyl-1,3,2-dioxaborolan-2-yl)hept-5-enoate (1.221)

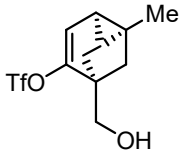


1.221

To a solution of (*R*,*E*)-methyl 2-((((*tert*-butyldiphenyl-silyl)oxy)imino)methyl)-2-methyl-hex-5-enoate (**1.220**) (192 mg, 0.453 mmol, 1.0 equiv.) in CH_2Cl_2 (4.53 mL, degassed by freeze-pump-thaw technique) under argon atmosphere was added isopropenylboronic acid pinacol ester (**1.217**) (0.426 mL, 2.27 mmol, 5.0 equiv.) followed by Grubbs 2nd generation catalyst (38.5 mg, 0.045 mmol, 0.1 equiv.). The flask was sealed and the mixture was stirred at 50 °C for 5 h. The solvent was removed under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 25:1) yielding the title compound (142 mg, 0.252 mmol, 56%) as a colorless oil.

TLC: R_f = 0.37 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.75 – 7.67 (m, 4H), 7.46 – 7.34 (m, 6H), 6.23 (tq, *J* = 6.8, 1.6 Hz, 1H), 3.71 (s, 3H), 2.17 – 1.99 (m, 2H), 1.95 – 1.77 (m, 2H), 1.64 – 1.61 (m, 3H), 1.36 (s, 3H), 1.28 (s, 12H), 1.14 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.4, 157.5, 144.7, 135.5, 135.5, 133.6, 133.6, 129.6, 127.5, 127.5, 83.2, 52.2, 48.5, 36.7, 27.2, 24.8, 23.8, 20.6, 19.4, 13.8; **IR** (thin film): 3072, 2976, 2932, 2858, 1737, 1632, 1590, 1472, 1460, 1428, 1410, 1370, 1335, 1303, 1271, 1215, 1194, 1165, 1139, 1113, 1063, 1030, 998, 926, 858, 821, 792, 740, 709, 699, 668, 613, 606, 578, 504, 489, 408 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ +16.9 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{32}H_{47}BNO_5Si$ $[M+H]^+$ 564.3311, found 564.3117.

(1*S*,2*S*,5*S*,7*S*)-5-(Hydroxymethyl)-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoro-methanesulfonate (1.222)



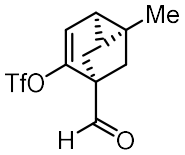
1.222

To a solution of (1*S*,2*R*,5*S*,7*R*)-5-(hydroxymethyl)-1-methyltricyclo [3.2.1.0^{2,7}]octan-4-one (**1.74**) (0.627 g, 3.77 mmol, 1.0 equiv.) in THF (37.7 mL) was added TMSCl (0.530 mL, 4.15 mmol, 1.1 equiv.) followed by imidazole (0.334 g, 4.90 mmol, 1.3

equiv.). The mixture was stirred at r.t. for 6 min and cooled to –78 °C. KHMDS, 1 M in THF (9.43 mL, 9.32 mmol, 2.5 equiv.) and the mixture was stirred at –78 °C for 20 min. Comins' reagent (**1.201**) (3.70 g, 9.43 mmol, 2.5 equiv.) was added and stirring was continued at –78 °C for 70 min. 1 M aq. HCl (25.3 mL, 25.4 mmol, 6.7 equiv.) was added and the mixture was stirred at r.t. (water bath) for 10 min. Sat. aq. NH_4Cl (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (0.893 g, 2.99 mmol, 79%) as a yellowish oil.

TLC: R_f = 0.63 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.98 (d, *J* = 6.8 Hz, 1H), 3.86 (s, 2H), 1.87 (s, 1H), 1.79 (dd, *J* = 11.1, 2.2 Hz, 1H), 1.56 – 1.51 (m, 1H), 1.50 – 1.45 (m, 1H), 1.39 (dd, *J* = 7.0, 2.0 Hz, 1H), 1.31 (s, 3H), 1.11 – 1.05 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.2, 118.5 (q, *J* = 320 Hz), 113.7, 63.4, 48.0, 38.1, 32.6, 25.1, 23.6, 22.0, 17.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –73.8; **IR** (thin film): 3374, 3043, 2929, 2868, 1648, 1460, 1415, 1246, 1203, 1138, 1098, 1081, 1062, 1009, 955, 929, 894, 879, 856, 841, 803, 769, 723, 702, 680, 650, 599, 515, 493, 414, 406 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{24}$ –34.5 (*c* 1.00, $CHCl_3$); **HRMS** (EI): exact mass calculated for $C_{11}H_{13}O_4F_3S$ $[M]^+$ 298.04812, found 298.04826.

(1*S*,2*S*,5*R*,7*S*)-5-Formyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (1.S10)



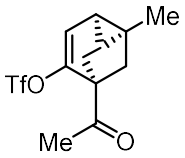
1.S10

To a solution of (1*S*,2*S*,5*S*,7*S*)-5-(hydroxymethyl)-1-methyltricyclo[3.2.1.0^{2,7}] oct-3-en-4-yl trifluoromethanesulfonate (**1.222**) (0.768 g, 2.57 mmol, 1.0 equiv.) in CH_2Cl_2 (34.3 mL) was added *t*-BuOH (0.271 µL, 2.83 mmol, 1.1 equiv.) followed by DMP (1.20 g, 2.83 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 15 min, poured into a mixture of Et_2O (150 mL), sat. aq. $Na_2S_2O_3$ (150 mL), and sat. aq. $NaHCO_3$ (150 mL), and stirred vigorously for 10 min. The phases were separated and the

aqueous layer was extracted with Et_2O (2 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (0.700 g, 2.36 mmol, 92%) as a yellowish oil.

TLC: R_f = 0.37 (hex:EtOAc = 6:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 6.08 (d, *J* = 6.9 Hz, 1H), 2.09 (ddd, *J* = 11.7, 2.3, 0.8 Hz, 1H), 1.79 (dd, *J* = 11.6, 0.9 Hz, 1H), 1.62 (tt, *J* = 6.9, 0.9 Hz, 1H), 1.52 (dd, *J* = 6.9, 2.1 Hz, 1H), 1.35 (s, 3H), 1.29 – 1.23 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.5, 143.3, 118.7 (q, *J* = 321 Hz), 115.5, 55.7, 37.4, 32.4, 25.0, 23.1, 21.9, 17.3; **^{19}F NMR** (471 MHz, $CDCl_3$) δ –73.0; **IR** (thin film): 2928, 2867, 1712, 1448, 1400, 1336, 1306, 1158, 1080, 1001, 847, 810, 714, 564, 427 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{25}$ –36.6 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{11}H_{11}F_3NaO_4S$ $[M+Na]^+$ 319.0222, found 319.0227.

(1*S*,2*S*,5*R*,7*S*)-5-Acetyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (1.208)



1.208

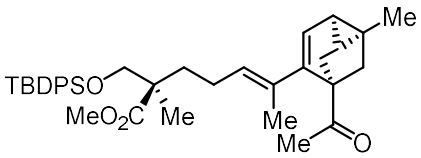
To a solution of (1*S*,2*S*,5*R*,7*S*)-5-formyl-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (**1.222**) (212 mg, 0.716 mmol, 1.0 equiv.) in THF (14.3 mL) at –78 °C was added dropwise methyllithium, 1.6 M in Et_2O (1.79 mL, 2.86 mmol, 4.0 equiv.). The mixture was stirred at –78 °C for 20 min. Methanol (1 mL) was added at –78 °C followed by sat. aq. NH_4Cl (30 mL) and H_2O (20 mL). The mixture was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

The residue was redissolved in CH_2Cl_2 (7.14 mL). DMP (333 mg, 0.785 mmol, 1.1 equiv.) was added followed by *t*-BuOH (75.0 µL, 0.785 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 15 min and poured into a mixture of sat. aq. $Na_2S_2O_3$ (30 mL), sat. aq. $NaHCO_3$ (30 mL), and Et_2O (25 mL). The biphasic mixture was stirred vigorously for 10 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers

were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:PhMe:CH_2Cl_2 = 2:1:1) yielding the title compound (116 mg, 0.374 mmol, 52%) as a colorless oil.

TLC: R_f = 0.37 (hex:EtOAc = 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.06 (d, *J* = 6.9 Hz, 1H), 2.26 (s, 3H), 2.06 (dd, *J* = 11.3, 2.2 Hz, 1H), 1.75 (d, *J* = 11.7 Hz, 1H), 1.59 (t, *J* = 6.9 Hz, 1H), 1.44 (dd, *J* = 6.9, 2.0 Hz, 1H), 1.36 – 1.29 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.4, 143.5, 123.3, 120.1, 117.0, 114.4, 113.8, 58.5, 38.4, 33.1, 28.7, 24.7, 23.1, 21.9, 17.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –73.3; **IR** (thin film): 2932, 2869, 1715, 1645, 1419, 1360, 1246, 1208, 1139, 1099, 1063, 889, 839, 769, 721, 606, 496, 408 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ –39.1 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{12}H_{13}F_3NaO_4S$ $[M+Na]^+$ 333.0379, found 333.0381.

(*R*,*E*)-Methyl 6-((1*S*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhept-5-enoate (1.223)

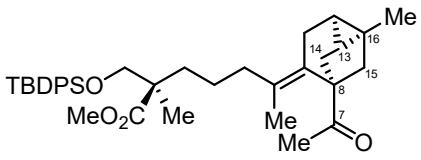


1.223

To a solution of (1*S*,2*S*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (**1.208**) (86.0 mg, 0.277 mmol, 1.0 equiv.) and (*R*,*Z*)-methyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-enoate (**1.218**) (251 mg, 0.456 mmol, 1.6 equiv.) in 1,2-dimethoxyethane (5.54 mL, purged with argon for 30 min) was added $Pd(PPh_3)_4$ (8.0 mg, 6.93 µmol, 2.5 mol%) followed by sat. aq. $NaHCO_3$ (0.603 mL). The mixture was stirred at 85 °C for 60 min. After cooling to r.t., sat. aq. NH_4Cl (25 mL) was added followed by H_2O (25 mL). The mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1) yielding the title compound (106 mg, 0.181 mmol, 65%) as a yellowish oil.

TLC: R_f = 0.55 (hex:EtOAc = 6:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 4H), 7.46 – 7.35 (m, 6H), 5.84 (d, *J* = 6.0 Hz, 1H), 5.14 (tq, *J* = 7.3, 1.4 Hz, 1H), 3.76 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.55 (d, *J* = 9.5 Hz, 1H), 2.07 (s, 3H), 1.99 – 1.79 (m, 3H), 1.70 – 1.62 (m, 2H), 1.61 – 1.58 (m, 3H), 1.52 – 1.47 (m, 1H), 1.40 (ddd, *J* = 13.4, 12.0, 5.1 Hz, 1H), 1.29 (s, 4H), 1.24 (s, 3H), 1.03 (s, 11H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.0, 176.4, 143.5, 135.8, 135.8, 134.8, 133.6, 133.5, 129.8, 129.8, 127.8, 127.8, 126.0, 120.9, 69.5, 60.3, 51.7, 48.8, 38.3, 35.0, 32.5, 28.5, 26.9, 24.3, 24.1, 23.4, 23.3, 19.5, 19.5, 18.3, 16.6; **IR** (thin film): 3034, 2929, 2858, 1733, 1704, 1589, 1472, 1459, 1428, 1388, 1353, 1234, 1189, 1168, 1106, 1007, 998, 937, 823, 778, 740, 702, 613, 503, 489, 435 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ –22.2 (*c* 0.60, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{37}H_{48}NaO_4Si$ [M+Na] 607.3214, found 607.3209.

(*R*,*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylheptanoate (1.224)



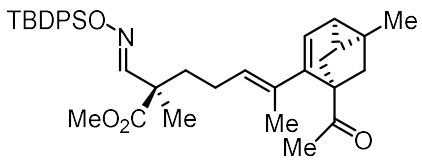
1.224

A solution of (*R*,*E*)-methyl 6-((1*S*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl)-2-(((*tert*-butyl-diphenylsilyl)oxy)methyl)-2-methyl-hept-5-enoate (**1.223**) (0.430 g, 0.735 mmol, 1.0 equiv.) and [$Cr(CO)_3$(η^6-methyl benzoate)] (**1.203**) (0.100 g, 0.368 mmol, 0.5 equiv.) in acetone (30 mL, degassed by freeze-pump-thaw technique) was placed in a 100 mL autoclave. The autoclave was purged with nitrogen (3x) and with hydrogen (3x). The mixture was stirred at 120 °C under hydrogen pressure (74 bar) for 19 h. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1) yielding the title compound (0.401 g, 0.683 mmol, 93%) as colorless oil.

Note: *The NMR spectra show a mixture of rotamers, presumably around C_7 and C_8. The ^{1}H and ^{13}C NMR signals of C_{13}, C_{14}, C_{15} and C_{16} are broadened or not visible.*

TLC: R_f = 0.55 (hex:EtOAc = 6:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 4H), 7.47 – 7.36 (m, 6H), 3.74 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.57 (d, *J* = 9.6 Hz, 1H), 2.69 – 2.58 (m, 2H), 2.13 (s, 3H), 1.86 (t, *J* = 7.7 Hz, 2H), 1.63 (td, *J* = 12.6, 4.6 Hz, 1H), 1.44 – 1.36 (m, 4H), 1.32 – 1.14 (m, 9H), 1.08 – 1.01 (m, 10H), 0.74 – 0.70 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.2, 176.6, 135.8, 135.7, 133.6, 133.5, 132.7, 129.8, 127.8, 127.8, 125.2, 69.5, 60.8, 51.7, 48.8, 40.5, 35.7, 35.5, 35.3, 27.9, 26.9, 25.8, 22.2, 19.9, 19.7, 19.5, 19.0; **IR** (thin film): 3071, 3920, 2858, 1734, 1702, 1589, 1471, 1461, 1427, 1389, 1352, 1292, 1235, 1188, 1167, 1135, 1106, 998, 936, 822, 760, 740, 701, 613, 568, 504, 488, 434 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ –14.5 (*c* 0.65, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{37}H_{50}NaO_4Si$ $[M+Na]^+$ 609.3371, found 609.3363.

(*R*,*E*)-Methyl 6-((1*S*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl)-2-((*E*)-(((*tert*-butyldiphenylsilyl)oxy)imino)methyl)-2-methylhept-5-enoate (1.225)

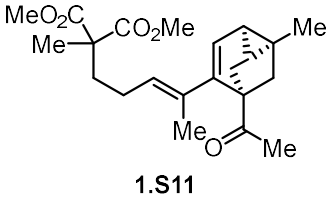


1.225

To a solution of (1*S*,2*S*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoro-methanesulfonate (**1.208**) (0.170 g, 0.548 mmol, 1.0 equiv.) and (*R*,*Z*)-methyl 2-((*E*)-(((*tert*-butyldiphenylsilyl)oxy)imino)methyl)-2-methyl-6-(4,4,5,5-tetra-methyl-1,3,2-dioxa-borolan-2-yl)hept-5-enoate (**1.221**) (0.550 g, 0.976 mmol. 1.8 equiv.) in 1,2-dimethoxyethane (11.0 mL, purged with argon for 45 min) was added $Pd(PPh_3)_4$ (0.025 g, 0.022 mmol, 4 mol%) followed by sat. aq. $NaHCO_3$ (1.19 mL). The mixture was stirred at 85 °C for 75 min. After cooling to r.t., sat. aq. NH_4Cl (50 mL) was added followed by H_2O (50 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (a: PhMe:CH_2Cl_2 = 1:1 then pentane:Et_2O = 5:1, b: pentane:Et_2O = 7:1) yielding the title compound (0.207 g, 0.348 mmol, 63%) as a colorless oil.

TLC: R_f = 0.42 (pentane:Et_2O = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.75 – 7.67 (m, 4H), 7.46 – 7.33 (m, 6H), 5.87 (d, *J* = 6.0 Hz, 1H), 5.16 – 5.10 (m, 1H), 3.71 (s, 3H), 2.08 (s, 3H), 2.03 – 1.70 (m, 5H), 1.67 (d, *J* = 11.3 Hz, 1H), 1.56 – 1.49 (m, 4H), 1.37 – 1.30 (m, 7H), 1.14 (s, 9H), 1.07 – 1.00 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 210.8, 174.6, 157.6, 143.4, 135.6, 135.6, 135.2, 133.7, 133.7, 129.7, 127.6, 125.4, 121.0, 60.2, 52.4, 48.6, 38.3, 37.2, 32.5, 28.5, 27.3, 24.3, 24.1, 23.6, 23.3, 20.9, 19.6, 18.3, 16.6; **IR** (thin film): 3071, 3033, 3920, 2858, 1736, 1704, 1616, 1590, 1472, 1458, 1428, 1378, 1353, 1232, 1192, 1168, 1114, 1085, 1054, 998, 928, 841, 822, 800, 741, 709, 699, 661, 606, 505, 489, 439, 407 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ –5.0 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{37}H_{48}NO_4Si$ $[M+H]^+$ 598.3347, found 598.3342.

Dimethyl 2-((*E*)-4-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentyl)-2-methylmalonate (1.S11)



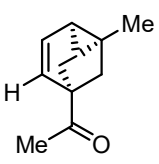
1.S11

To a solution of (1*S*,2*S*,5*R*,7*S*)-5-acetyl-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yltrifluoromethanesulfonate (**1.208**) (0.081 g, 0.261 mmol, 1.0 equiv.) and dimethyl (*Z*)-2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl) malonate (**1.197b**) (0.148 g, 0.435 mmol. 1.7 equiv.) in 1,2-dimethoxyethane (2.61 mL, purged with argon for 30 min) was added $Pd(PPh_3)_4$ (7.5 g, 0.006 mmol, 2.5 mol%) followed by sat. aq. $NaHCO_3$ (0.57 mL). The mixture was stirred at 85 °C for 12 min. After cooling to r.t., sat. aq. NH_4Cl (20 mL) was added followed by H_2O (5 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 8:1) yielding the title compound (0.074 g, 0.198 mmol, 76%) as a colorless oil.

TLC: R_f = 0.22 (hex:EtOAc = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (d, *J* = 6.0 Hz, 1H), 5.20 – 5.13 (m, 1H), 3.70 (s, 6H), 2.08 (s, 3H), 1.98 – 1.82 (m,

5H), 1.69 – 1.59 (m, 4H), 1.49 (t, *J* = 6.5 Hz, 1H), 1.41 (s, 3H), 1.33 – 1.26 (m, 4H), 1.05 – 0.97 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8, 172.6, 143.2, 135.2, 125.0, 121.0, 60.1, 53.5, 52.5, 38.2, 35.2, 32.4, 28.4, 24.2, 23.9, 23.3, 23.2, 20.0, 18.1, 16.5; **IR** (thin film): 3032, 2950, 2863, 1733, 1704, 1616, 1458, 1434, 1379, 1354, 1258, 1233, 1197, 1165, 1113, 1085, 1020, 983, 924, 878, 841, 804, 690, 661, 590, 537, 487, 419 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{22}H_{31}O_5$ $[M+H]^+$ 375.2166, found 375.2160.

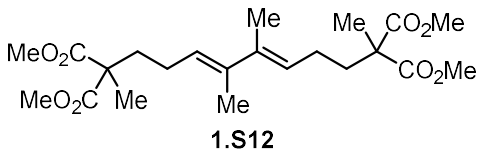
Analytical data for alkene **1.227**:



1.227

Appearance: colorless oil; **TLC**: R_f = 0.31 (hex:EtOAc = 15:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.08 (dd, *J* = 8.4, 5.6 Hz, 1H), 6.02 (dd, *J* = 8.4, 2.1 Hz, 1H), 2.21 (s, 3H), 2.00 (dd, *J* = 11.2, 2.5 Hz, 1H), 1.71 (d, *J* = 11.1 Hz, 1H), 1.54 – 1.51 (m, 1H), 1.33 – 1.29 (m, 4H), 0.89 – 0.85 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.3, 126.4, 124.7, 56.6, 37.7, 32.2, 26.7, 24.3, 23.5, 22.3, 18.3; **IR** (thin film): 3042, 2925, 2865, 1706, 1614, 1457, 1354, 1283, 1225, 1173, 1072, 843, 784, 730, 671, 581, 409 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{11}H_{14}O$ $[M]^+$ 162.1039, found 162.1037.

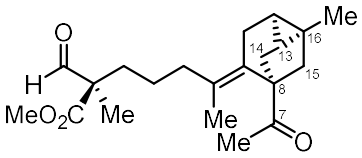
Analytical data for diene **1.S12**:



1.S12

Appearance: colorless oil; **TLC**: R_f = 0.13 (hex:EtOAc = 8:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.45 (t, *J* = 6.7 Hz, 2H), 3.72 (s, 12H), 2.11 – 2.02 (m, 4H), 1.97 – 1.90 (m, 4H), 1.73 (d, *J* = 1.1 Hz, 6H), 1.45 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 137.1, 124.6, 53.7, 52.6, 35.8, 23.8, 20.2, 14.0; **IR** (thin film): 2991, 2952, 2926, 2855, 1731, 1451, 1434, 1378, 1314, 1259, 1233, 1198, 1140, 1112, 1054, 984, 935, 878, 836, 817, 752, 694, 497, 407 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{22}H_{35}O_8$ $[M+H]^+$ 427.2326, found 427.2325.

(*R*,*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-formyl-2-methylheptanoate (1.S14)



1.S14

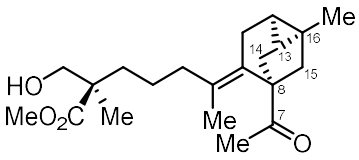
To a solution of (*R*,*E*)-methyl 6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-(((*tert*-butyldi-phenylsilyl)oxy)methyl)-2-methylheptanoate (**1.224**) (401 mg, 0.683 mmol, 1.0 equiv.) in THF (6.83 mL) was added TBAF, 1 M in THF (3.42 mL, 3.42 mmol, 5.0 equiv.). The mixture was stirred at r.t. for 5 h. H_2O (25 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

The residue was redissolved in CH_2Cl_2 (6.83 mL). DMP (319 mg, 0.751 mmol, 1.1 equiv.) was added followed by ^{t}BuOH (71.9 µL, 0.751 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 17 min and poured into a mixture of Et_2O (25 mL), sat. aq. $NaHCO_3$ (25 mL) and sat. aq. $Na_2S_2O_3$ (25 mL). The resulting biphasic mixture was stirred at r.t. for 10 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The

residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (172 mg, 0.496 mmol, 73% over 2 steps) as a yellowish oil.

Note: *The NMR spectra show a mixture of rotamers, presumably around C_7 and C_8. The ^1H and ^{13}C NMR signals of C_{13}, C_{14}, C_{15} and C_{16} are broadened or not visible.*

TLC: R_f = 0.43 (hex:EtOAc = 4:1); **^{1}H NMR** (400 MHz, acetone-d_6) δ 9.68 (s, 1H), 3.73 (s, 3H), 2.77 – 2.63 (m, 2H), 2.11 (s, 3H), 1.99 – 1.93 (m, 2H), 1.92 – 1.82 (m, 1H), 1.77 – 1.67 (m, 1H), 1.42 (t, *J* = 1.8 Hz, 3H), 1.39 – 1.29 (m, 2H), 1.27 (s, 3H), 1.18 (s, 3H), 1.05 (dd, *J* = 7.6, 3.7 Hz, 1H), 0.82 – 0.76 (m, 1H); **^{13}C NMR** (101 MHz, acetone-d_6) δ 210.6, 200.1, 173.1, 134.1, 125.3, 61.4, 58.3, 52.6, 41.1, 35.9, 35.7, 34.4, 27.8, 26.3, 22.6, 20.3, 20.0, 18.9, 17.1; **IR** (thin film): 2930, 2863, 1747, 1720, 1702, 1457, 1433, 1378, 1353, 1313, 1236, 1214, 1168, 1122, 1059, 971, 921, 862, 841, 795, 744, 701, 652, 613, 569, 504, 471 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ –6.6 (*c* 0.80, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found 369.2033.



1.S13

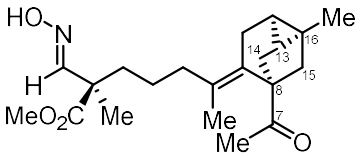
A small amount of the intermediate alcohol **1.S13** was purified by preparative TLC (PhMe:^{i}PrOH = 15:1):

Note: *The NMR spectra show a mixture of rotamers, presumably around C_7 and C_8. The ^1H and ^{13}C NMR signals of C_{13}, C_{14}, C_{15} and C_{16} are broadened or not visible.*

TLC: R_f = 0.50 (hex:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 – 3.64 (m, 4H), 3.53 – 3.45 (m, 1H), 2.72 – 2.58 (m, 2H), 2.33 (t, *J* = 6.5 Hz, 1H), 2.14 (s, 3H), 1.87 (t, *J* = 7.7 Hz, 2H), 1.64 – 1.43 (m, 3H), 1.39 (t, *J* = 1.9 Hz, 3H), 1.27 (dtd, *J* = 15.2, 7.9, 7.3, 5.4 Hz, 2H), 1.18 (s, 3H), 1.17 (s, 3H), 1.04 (dd, *J* = 7.6, 3.4 Hz, 1H), 0.77 – 0.70 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.1, 177.7, 133.0, 125.0, 68.3, 60.8, 52.0, 47.9, 40.6, 35.7, 35.6, 35.4, 27.9, 25.8, 22.0, 19.9, 19.8, 19.6, 19.0; **IR** (thin film): 3455, 2932, 2863, 1727, 1702, 1432, 1380, 1353, 1213, 1166, 1133, 1045, 926, 840, 802, 701, 568, 506 cm^{-1}; **Optical**

Rotation: $[\alpha]_D^{24}$ –6.9 (*c* 1.00, $CHCl_3$); **HRMS** (ESI): exact mass calculated for $C_{21}H_{33}O_4$ $[M+H]^+$ 349.2373, found 349.2369.

(*R*,*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-((*E*)-(hydroxyimino)methyl)-2-methylheptanoate (1.206)



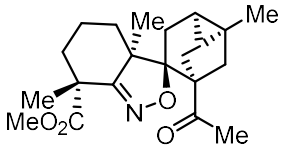
1.206

To a solution of (*R*,*E*)-Methyl 6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-formyl-2-methyl-heptanoate (**1.S14**) (172 mg, 0.496 mmol, 1.0 equiv.) in EtOH (7.36 mL) was added hydroxylamine hydrochloride (41.4 mg, 0.596 mmol, 1.2 equiv.) followed by pyridine (0.919 mL). The mixture was stirred at r.t. for 12 h and concentrated under reduced pressure. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 5:1) yielding the title compound (152 mg, 0.420 mmol, 85%) as a yellowish oil.

Note: *The NMR spectra show a mixture of rotamers, presumably around C_7 and C_8. The ^1H and ^{13}C NMR signals of C_{13}, C_{14}, C_{15} and C_{16} are broadened or not visible.*

TLC: R_f = 0.25 (hex:EtOAc = 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.58 (s, 1H), 3.72 (s, 3H), 2.71 – 2.58 (m, 2H), 2.15 (s, 3H), 1.89 (t, *J* = 7.7 Hz, 2H), 1.81 – 1.58 (m, 4H), 1.40 (t, *J* = 1.8 Hz, 3H), 1.35 (s, 3H), 1.34 – 1.24 (m, 2H), 1.19 (s, 3H), 1.05 (dd, *J* = 7.6, 3.1 Hz, 1H), 0.77 – 0.73 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.1, 174.6, 153.8, 133.1, 124.8, 60.9, 52.5, 48.3, 40.6, 37.6, 35.4, 35.4, 27.9, 25.8, 22.2, 20.5, 19.9, 19.7, 19.0; **IR** (thin film): 3386, 2933, 2864, 1735, 1702, 1433, 1378, 1354, 1246, 1169, 1119, 1058, 949, 840, 572, 425, 405 cm^{-1}; **Optical Rotation**: $[\alpha]_D^{23}$ –6.2 (*c* 0.50, CH_2Cl_2); **HRMS** (ESI): exact mass calculated for $C_{21}H_{32}NO_4$ $[M+H]^+$ 362.2326, found 362.2327.

(1'*S*,2'*R*,3*R*,3a*R*,5'*R*,7*R*,7'*R*)-methyl 5'-acetyl-1',3a,7-trimethyl-4,5,6,7-tetrahydro-3a*H*-spiro[benzo[*c*]isoxazole-3,4'-tricyclo[3.2.1.0^{2,7}]octane]-7-carboxylate (1.144)



1.144

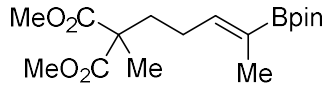
From (*R*,*E*)-methyl 6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-((*E*)-(hydroxyimino)methyl)-2-methylheptanoate (**1.206**): To a solution of (*R*,*E*)-methyl6-((1*R*,2*R*,5*R*,7*S*)-5-acetyl-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)-2-((*E*)-(hydroxyimino)methyl)-2-methylheptanoate (**1.206**) (102 mg, 0.282 mmol, 1.0 equiv.) in methanol (5.64 mL) at 0 °C was added $PhI(OAc)_2$ (136 mg, 0.423 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 34 min. Toluene (20 mL) was added followed by sat. aq. $Na_2S_2O_3$ (8 mL), sat. aq. $NaHCO_3$ (8 mL) and H_2O (16 mL). The phases were separated and the aqueous layer was extracted with toluene (2 x 20 mL). The combined organic layers were washed with brine–H_2O (50 mL, 1:1) and dried over Na_2SO_4. The filtrate was heated to 120 °C for 1 h and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1 to 3:1 gradient) yielding the title compound (52 mg, 0.147 mmol, 52%) as colorless solid and recovered starting material (10 mg, 0.028 mmol, 10%) as colorless oil.

Analytical data is in full agreement with **1.144** prepared from aldehyde **1.143**.

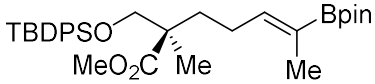
3. Stereoselective Synthesis of Tetrasubstituted Olefins via 1,4-Semihydrogenation of 1,3-Dienes

Preparation of vinyl boronates:

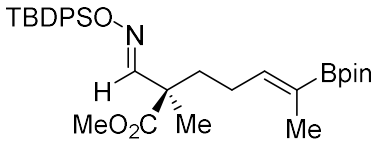
The syntheses of vinyl boronates **2.37a**, **2.37b** and **2.37c** was described in Section 2. Known vinyl triflates were prepared according to literature procedures (**2.37d**[103] and **2.37e**[144]) or purchased from commercial sources (**2.47f** and **2.37g**).



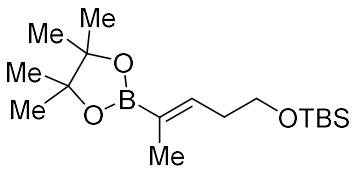
1.199a/2.37a



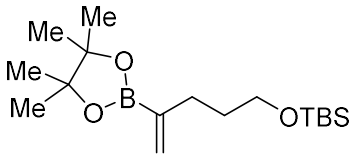
1.220/2.37b



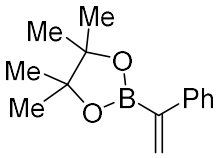
1.123/2.37c



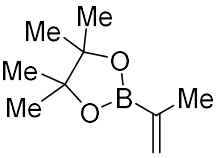
2.37d



2.37e



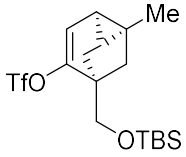
2.37f



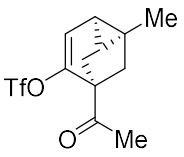
2.37g

Preparation of vinyl triflates:

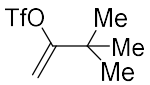
The syntheses of vinyl triflates **2.41a** and **2.42b** was described in Section 2. Known vinyl triflates **2.41d**, **2.41e** and **2.41f** were prepared according to literature procedures.[149,190]



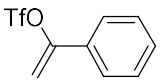
1.198/2.41a



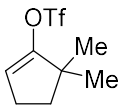
1.210/2.41b



2.41d



2.41e

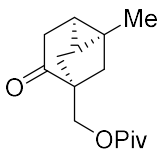


2.41f

Other vinyl triflates were prepared as described below:

[190] Caille, S.; Crockett, R.; Ranganathan, K.; Wang, X.; Woo, J. C. S.; Walker, S. D. Catalytic Asymmetric Synthesis of a Tertiary Benzylic Carbon Center via Phenol-Directed Alkene Hydrogenation, *J. Org. Chem.* **2011**, *76*, 5198–5206.

rac-((1*S*,2*R*,5*S*,7*R*)-1-Methyl-4-oxotricyclo[3.2.1.02,7]octan-5-yl)methyl pivalate (2.S1)

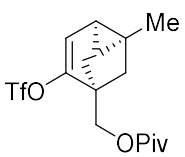


2.S1

To a solution of *rac*-(1S,2R,5S,7R)-5-(hydroxymethyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-one (**1.74**) (0.115 g, 0.692 mmol, 1.0 equiv.), Et_3N (0.386 mL, 2.77 mmol, 4.0 equiv.) and DMAP (8.5 mg, 0.069 mmol, 0.1 equiv.) in CH_2Cl_2 (9.23 mL) at 0 °C was added pivaloyl chloride (0.255 mL, 2.08 mmol, 3.0 equiv.). The mixture was stirred for 16 h gradually increasing the temperature to r.t. Sat. aq. $NaHCO_3$ (10 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1) yielding the title compound (0.132 g, 0.527 mmol, 76%) as a colorless oil.

TLC: R_f = 0.22 (hex:EtOAc = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.14 (d, *J* = 11.5 Hz, 1H), 4.10 (d, *J* = 11.4 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.05 (ddt, *J* = 12.8, 3.6, 1.0 Hz, 1H), 1.86 – 1.81 (m, 1H), 1.75 – 1.70 (m, 2H), 1.28 (s, 3H), 1.23 (dd, *J* = 7.6, 3.4 Hz, 1H), 1.17 (s, 9H), 0.95 – 0.91 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.8, 178.3, 63.4, 54.7, 39.0, 36.9, 33.8, 31.7, 27.3, 22.8, 22.0, 19.4, 17.7; **IR** (thin film): 2958, 2929, 2867, 1727, 1480, 1459, 1397, 1364, 1339, 1283, 1157, 1125, 1079, 1062, 1034, 986, 940, 901, 845, 799, 769, 745, 668, 578, 547, 496, 483, 447, 422 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1640.

rac-((1*S*,2*S*,5*S*,7*R*)-1-Methyl-4-(((trifluoromethyl)sulfonyl)oxy)tricyclo [3.2.1.0^{2,7}]oct-3-en-5-yl)methyl pivalate (2.41c)



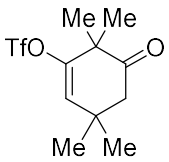
2.41c

To a solution of *rac*-((1*S*,2*R*,5*S*,7*R*)-1-Methyl-4-oxotricyclo[3.2.1.02,7]octan-5-yl)methyl pivalate (**2.S1**) (0.102 g, 0.407 mmol, 1.0 equiv.) in THF (3.40 mL) at –78 °C was added KHMDS, 1 M in THF (0.611 mL, 0.611 mmol, 1.5 equiv.). The mixture was stirred at –78 °C for 30 min. Comins' reagent (0.240 g, 0.611 mmol,

1.5 equiv.) was added and stirring was continued for 24 h gradually increasing the temperature to r.t. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 40:1) yielding the title compound (0.138 g, 0.361 mmol, 89%) as a colorless oil.

TLC: R_f = 0.38 (hex:EtOAc = 15:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 6.8 Hz, 1H), 4.27 (s, 2H), 1.77 (ddd, *J* = 11.7, 2.3, 0.9 Hz, 1H), 1.59 – 1.54 (m, 1H), 1.46 (d, *J* = 11.5 Hz, 1H), 1.42 (dd, *J* = 7.2, 2.3 Hz, 1H), 1.33 (s, 3H), 1.20 (s, 9H), 1.17 – 1.10 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.3, 146.2, 118.7 (q, *J* = 321 Hz) 113.7, 64.5, 46.1, 39.0, 38.8, 33.3, 27.2, 25.2, 23.6, 22.0, 17.8; **IR** (thin film): 2959, 2871, 1732, 1648, 1481, 1460, 1417, 1399, 1365, 1280, 1247, 1206, 1140, 1105, 1080, 1064, 1035, 1007, 980, 961, 939, 882, 855, 842, 799, 769, 722, 681, 652, 621, 515, 494 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{21}F_3NaO_5S$ $[M+Na]^+$ 405.0954, found 405.0951.

3,3,6,6-Tetramethyl-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (**2.41h**)



2.41g

To a solution of 2,2,5,5-tetramethylcyclohexane-1,3-dione[191] (0.696 g, 4.14 mmol, 1.00 equiv.) and 2,6-di-*tert*-butyl-4-methylpyridine (1.83 g, 8.89 mmol, 2.15 equiv.) in DCE (20.7 mL) was added dropwise triflic anhydride (1.47 mL, 8.69 mmol, 2.10 equiv.). The mixture was stirred at 80 °C for 15 h. After cooling to r.t., the mixture was poured into Et_2 (80 mL) and filtered. The filtercake was washed with Et_2O (20 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 20:1) yielding the title compound (0.811 g, 2.70 mmol, 65%) as an orange oil.

[191] Krief, A.; Surleraux, D.; Frauenrath, H. Novel Stereoselective Route to Cis-Chrysanthemic Acid, *Tetrahedron Letters* **1988**, *29*, 6157–6160.

TLC: R_f = 0.45 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 (s, 1H), 2.48 (s, 2H), 1.29 (s, 6H), 1.14 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.9, 150.7, 118.5 (q, *J* = 319 hZ), 113.8, 50.1, 47.8, 33.2, 29.4, 23.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -74.3; **IR** (thin film): 2966, 2940, 2876, 1725, 1672, 1466, 1369, 1341, 1293, 1269, 1244, 1205, 1177, 1138, 1086, 1022, 999, 974, 954, 945, 916, 878, 863, 820, 785, 759, 716, 673, 602, 547, 513, 475, 450, 425 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{10}H_{12}F_3O_4S$ $[M\text{-}CH_3]^+$ 285.0403, found 285.0399.

Cross-coupling and 1,4-semihydrogenation:

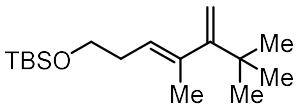
General Procedure D:

To a solution of the vinyl boronate **2.37** (1.0 – 1.4 equiv.) and vinyl triflate **2.41** (1.0 – 1.4 equiv.) in 1,2-dimethoxyethane (0.075 M, sparged with argon for 30 min) was added $Pd(PPh_3)_4$ (2.5 – 5 mol%) followed by sat. aq. $NaHCO_3$ (2.18 mL/mmol starting material). The mixture was stirred at 80 °C for the indicated time. After cooling to r.t., sat. aq. NH_4Cl–H_2O (2:1) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica using the indicated conditions.

General Procedure E:

To a solution of the appropriate diene **2.42** (1.0 equiv.) in acetone (6.9 – 50 mM, degassed by three cycles of freeze-pump-thaw) was added $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (20 – 50 mol%). The mixture was stirred at 120 °C under 70 bar of H_2 for 18 h, concentrated under reduced pressure and purified by FC on silica using the indicated conditions.

(*E*)-*tert*-Butyldimethyl((4,6,6-trimethyl-5-methylenehept-3-en-1-yl)oxy) silane (2.42a)

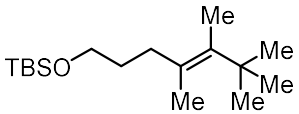


2.42a

Following General Procedure A using (Z)-*tert*-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl)oxy) silane (**2.37d**) (0.207 g, 0.634 mmol, 1.0 equiv.) and 3,3-dimethylbut-1-en-2-yl trifluoromethanesulfonate (**2.41d**) (0.206 g, 0.888 mmol, 1.4 equiv.). FC conditions: hex:EtOAc = 100:1. Yield: 0.175 g, 0.619 mmol, 98% as a colorless oil.

TLC: R_f = 0.35 (hex:EtOAc = 100:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.09 (tq, *J* = 7.2, 1.4 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.63 (d, *J* = 2.0 Hz, 1H), 3.62 (t, *J* = 7.1 Hz, 2H), 2.26 (qd, *J* = 7.1, 0.9 Hz, 2H), 1.79 – 1.74 (m, 3H), 1.07 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6, 139.5, 123.7, 108.8, 63.0, 35.9, 32.1, 30.3, 26.1, 19.4, 18.5, -5.1; **IR** (thin film): 3086, 2954, 2929, 2899, 2858, 1618, 1471, 1462, 1383, 1360, 1253, 1214, 1199, 1097, 1050, 1029, 1005, 937, 899, 833, 810, 773, 731, 679, 660, 575, 457 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{34}NaOSi$ $[M+Na]^+$ 305.2271, found 305.2272.

(*E*)-*tert*-Butyldimethyl((4,5,6,6-tetramethylhept-4-en-1-yl)oxy)silane (2.43a)



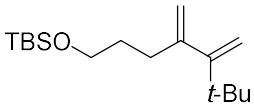
2.43a

Following General Procedure B using (*E*)-*tert*-butyldimethyl((4,6,6-trimethyl-5-methylenehept-3-en-1-yl) oxy)silane (**2.42a**) (0.169 g, 0.598 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (0.033 g, 0.120 mmol, 20 mol%). FC conditions: hex:EtOAc = 70:1. Yield: 0.160 g, 0.562 mmol, 94% as a colorless oil.

TLC: R_f = 0.55 (pent:Et_2O = 80:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.59 (t, *J* = 6.6 Hz, 2H), 2.04 – 1.98 (m, 2H), 1.78 (q, *J* = 1.4 Hz, 3H), 1.64 – 1.61 (m, 3H), 1.60 – 1.53 (m, 2H), 1.14 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.9, 128.4, 63.3, 36.0, 34.2, 31.7, 30.9, 26.1, 21.6, 18.5, 16.9, -5.1;

IR (thin film): 2951, 2929, 2858, 1471, 1463, 1376, 1361, 1254, 1204, 1173, 1094, 1039, 1006, 939, 894, 833, 813, 773, 714, 661, 608, 502 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{36}NaOSi$ $[M+Na]^+$ 307.2428, found 207.2424.

tert-Butyl((6,6-dimethyl-4,5-dimethyleneheptyl)oxy)dimethylsilane (2.42b)

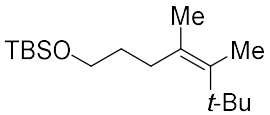


2.42b

Following General Procedure A using *tert*-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-1-yl)oxy)silane (**2.37e**) (0.320 g, 0.981 mmol, 1.0 equiv.) and 3,3-dimethylbut-1-en-2-yl trifluoromethanesulfonate (**2.41d**) (0.319 g, 1.37 mmol, 1.4 equiv.). FC conditions: hex:EtOAc = 150:1. Yield: 0.185 g, 0.655 mmol, 67% as a colorless oil.

TLC: R_f = 0.59 (hex:EtOAc = 50:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.93 (d, *J* = 1.9 Hz, 1H), 4.85 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.70 – 4.68 (m, 1H), 4.67 (d, *J* = 1.8 Hz, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 2.23 – 2.17 (m, 2H), 1.69 – 1.60 (m, 2H), 1.10 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6, 151.8, 112.3, 110.1, 62.9, 35.6, 34.3, 31.4, 30.3, 26.1, 18.5, -5.1; **IR** (thin film): 3087, 2954, 2929, 2858, 1617, 1471, 1463, 1384, 1360, 1254, 1212, 1099, 1006, 976, 955, 939, 899, 866, 834, 812, 773, 717, 679, 660, 608, 497, 475 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{35}OSi$ $[M+H]^+$ 283.2452, found 283.2455.

(*Z*)-*tert*-Butyldimethyl((4,5,6,6-tetramethylhept-4-en-1-yl)oxy)silane (2.43b)



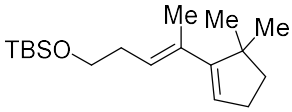
2.43b

Following General Procedure B using *tert*-butyl((6,6-dimethyl-4,5-dimethyleneheptyl)oxy)dimethylsilane (**2.42b**) (0.179 g, 0.634 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6$-MeOBz)] (0.034 g, 0.127 mmol, 20 mol%). FC conditions: pent:Et_2O = 80:1. Yield: 0.157 g, 0.552 mmol, 87% as a colorless oil.

TLC: R_f = 0.57 (hex:EtOAc = 50:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.62 (t, *J* = 6.4 Hz, 2H), 2.26 – 2.17 (m, 2H), 1.67 – 1.57 (m, 8H), 1.15 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8, 128.6, 63.7, 36.2, 32.9,

32.2, 31.5, 26.1, 21.8, 18.5, 17.6, -5.1; **IR** (thin film): 2951, 2929, 2894, 2857, 1471, 1463, 1382, 1361, 1254, 1179, 1096, 1034, 1006, 949, 834, 813, 773, 717, 659, 509, 452 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{13}H_{27}OSi$ $[M-^tBu]^+$ 227.1826, found 227.1826.

(*E*)-*tert*-Butyl((4-(5,5-dimethylcyclopent-1-en-1-yl)pent-3-en-1-yl)oxy)dimethylsilane (2.42c)

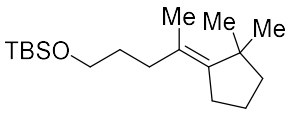


2.42c

Following General Procedure A using (Z)-tert-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl)oxy) silane (**2.37d**) (0.300 g, 0.0.919 mmol, 1.0 equiv.) and 5,5-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate (**2.41f**) (0.314 g, 0.1.29 mmol, 1.4 equiv.). FC conditions: hex:EtOAc = 100:1 to 30:1 gradient. Yield: 0.268 g, 0.910 mmol, 99% as a colorless oil.

TLC: R_f = 0.46 (hex:EtOAc = 50:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54 (s, 2H), 3.63 (t, *J* = 7.0 Hz, 2H), 2.34 (q, *J* = 7.1 Hz, 2H), 2.23 (td, *J* = 7.0, 2.4 Hz, 2H), 1.77 (s, 3H), 1.72 (t, *J* = 7.1 Hz, 2H), 1.18 (s, 6H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.6, 132.5, 125.7, 122.9, 63.0, 45.9, 43.6, 32.4, 28.9, 27.7, 26.1, 18.5, 16.4, -5.1; **IR** (thin film): 2952, 2929, 2857, 1462, 1378, 1361, 1253, 1099, 1005, 936, 834, 773, 662, 410 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{35}OSi$ $[M+H]^+$ 295.2452, found 295.2451.

(*E*)-*tert*-Butyl((4-(2,2-dimethylcyclopentylidene)pentyl)oxy)dimethylsilane (2.43c)

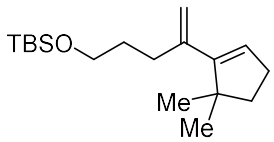


2.43c

Following General Procedure B using (*E*)-*tert*-Butyl((4-(5,5-dimethylcyclopent-1-en-1-yl)pent-3-en-1-yl)oxy)dimethylsilane (**2.43c**) (0.263 g, 0.893 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (0.049 g, 0.179 mmol, 20 mol%). FC conditions: hex:EtOAc = 100:1. Yield: 0.239 g, 0.806 mmol, 90% as a colorless oil.

TLC: R_f = 0.48 (hex:EtOAc = 50:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.58 (t, *J* = 6.7 Hz, 2H), 2.31 (t, *J* = 6.1 Hz, 2H), 2.01 – 1.93 (m, 2H), 1.71 (t, *J* = 1.9 Hz, 3H), 1.64 – 1.50 (m, 6H), 1.16 (s, 6H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 125.4, 63.3, 46.1, 41.5, 33.5, 33.0, 31.2, 27.8, 26.1, 23.1, 18.5, 18.1, -5.1; **IR** (thin film): 2951, 2929, 2857, 1770, 1471, 1462, 1383, 1361, 1253, 1178, 1097, 1005, 940, 833, 813, 773, 715, 661 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{36}NaOSi$ $[M+Na]^+$ 319.2428, found 319.2428.

tert-Butyl((4-(5,5-dimethylcyclopent-1-en-1-yl)pent-4-en-1-yl)oxy)dimethylsilane (2.42d)

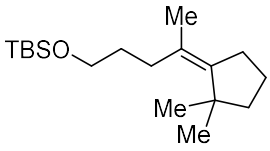


2.42d

Following General Procedure A using *tert*-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-1-yl)oxy)silane (**2.37e**) (0.333 g, 1.02 mmol, 1.0 equiv.) and 5,5-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate (**2.41f**) (0.299 g, 1.22 mmol, 1.2 equiv.). FC conditions: hex:EtOAc = 100:1 to 50:1 gradient. Yield: 0.225 g, 0.764 mmol, 75% as a colorless oil.

TLC: R_f = 0.26 (hex:EtOAc = 100:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.65 (t, *J* = 2.6 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.92 – 4.87 (m, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.29 – 2.21 (m, 4H), 1.77 – 1.62 (m, 4H), 1.18 (s, 6H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0, 143.8, 127.5, 111.1, 63.0, 46.1, 43.2, 33.0, 32.1, 29.1, 27.5, 26.1, 18.5, -5.1; **IR** (thin film): 2952, 2929, 2895, 2857, 1622, 1586, 1471, 1462, 1386, 1361, 1254, 1203, 1100, 1036, 1006, 972, 939, 888, 833, 814, 774, 726, 661, 532, 497, 450 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{35}OSi$ $[M+H]^+$ 295.2452, found 295.2451.

(*Z*)-*tert*-Butyl((4-(2,2-dimethylcyclopentylidene)pentyl)oxy)dimethylsilane (2.43d)

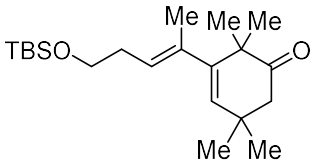


2.43d

Following General Procedure B using *tert*-butyl((4-(5,5-dimethylcyclopent-1-en-1-yl)pent-4-en-1-yl)oxy)dimethylsilane (**2.42d**) (0.179 g, 0.634 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (0.034 g, 0.127 mmol, 20 mol%). FC conditions: pent:Et_2O = 100:1. Yield: 0.117 g, 0.395 mmol, 87% as a colorless oil.

TLC: R_f = 0.29 (hex:EtOAc = 100:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.62 (t, *J* = 6.5 Hz, 2H), 2.29 – 2.24 (m, 2H), 2.17 – 2.12 (m, 2H), 1.64 – 1.50 (m, 9H), 1.17 (s, 6H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.4, 125.8, 63.7, 46.2, 41.6, 33.8, 32.2, 30.7, 28.6, 26.1, 23.0, 20.4, 18.5, -5.1; **IR** (thin film): 2951, 2930, 2857, 1471, 1463, 1383, 1361, 1254, 1187, 1153, 1098, 1005, 939, 834, 813, 774, 718, 660, 446 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{36}NaOSi$ $[M+Na]^+$ 319.2428, found 319.2419.

(*E*)-3-(5-((*tert*-Butyldimethylsilyl)oxy)pent-2-en-2-yl)-2,2,5,5-tetramethylcyclohex-3-enone (2.42e)



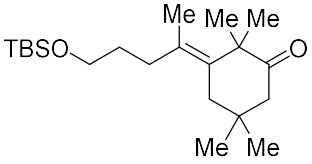
2.42e

Following General Procedure A using (Z)-tert-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl)oxy) silane (**2.37d**) (0.296 g, 0.907 mmol, 1.0 equiv.) and 3,3,6,6-tetramethyl-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (**2.41g**) (0.381 g, 1.27 mmol, 1.4 equiv.). FC conditions: PhMe:hex = 2:1 then PhMe. Yield: 0.309 g, 0.881 mmol, 97% as a colorless oil.

TLC: R_f = 0.32 (hex:EtOAc = 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 5.18 (tq, *J* = 7.2, 1.4 Hz, 1H), 3.64 (t, *J* = 6.9 Hz, 2H), 2.42 (s, 2H), 2.27 (q, *J* = 7.0 Hz, 2H), 1.80 – 1.75 (m, 3H), 1.17 (s, 6H), 1.03 (s, 6H), 0.89 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 215.0, 146.9, 136.8, 133.5, 126.2, 62.9,

50.2, 47.1, 36.3, 32.1, 29.9, 26.1, 25.4, 19.4, 18.5, -5.1; **IR** (thin film): 2956, 2929, 2888, 2857, 1714, 1463, 1383, 1363, 1291, 1254, 1185, 1092, 1040, 1005, 966, 935, 834, 811, 774, 720, 675, 661, 634, 599, 507, 452 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{38}NaO_2Si$ $[M+Na]^+$ 373.2533, found 373.2527.

(*E*)-3-(5-((*tert*-Butyldimethylsilyl)oxy)pentan-2-ylidene)-2,2,5,5-tetramethyl-cyclohexanone (2.43e)

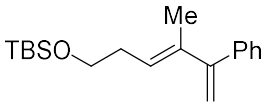


2.42e

Following General Procedure B using (*E*)-3-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-en-2-yl)-2,2,5,5-tetramethyl-cyclohex-3-enone (**2.42e**) (0.304 g, 0.867 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (0.118 g, 0.434 mmol, 50 mol%). FC conditions: hex:PhMe = 1:1 then hex:EtOAc = 30:1. Yield: 0.291 g, 0.825 mmol, 95% as a colorless oil.

TLC: R_f = 0.34 (hex:EtOAc = 15:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.59 (t, *J* = 6.2 Hz, 2H), 2.22 (s, 2H), 2.11 – 2.05 (m, 2H), 1.99 – 1.94 (m, 2H), 1.80 (s, 3H), 1.62 – 1.52 (m, 2H), 1.29 (s, 6H), 1.02 (s, 6H), 0.90 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 217.4, 135.5, 131.4, 63.0, 51.4, 50.2, 42.1, 33.7, 33.2, 31.8, 30.4, 26.1, 23.9, 19.8, 18.5, -5.1; **IR** (thin film): 2954, 2929, 2858, 1718, 1463, 1432, 1384, 1364, 1301, 1253, 1214, 1163, 1148, 1130, 1098, 1027, 1005, 950, 833, 813, 774, 713, 660, 613, 468 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{40}NaO_2Si$ $[M+Na]^+$ 375.2690, found 375.2688.

(*E*)-*tert*-Butyldimethyl((4-methyl-5-phenylhexa-3,5-dien-1-yl)oxy)silane (2.42f)



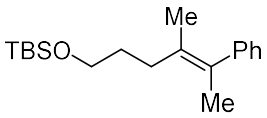
2.42f

Following General Procedure A using (Z)-tert-butyl-dimethyl ((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl)oxy) silane (**2.37d**) (0.203 g, 0.622 mmol, 1.0 equiv.) and 1-phenylvinyl trifluoromethanesulfonate (**2.41e**) (0.220 g, 0.871 mmol,

1.4 equiv.). FC conditions: hex:EtOAc = 100:1. Yield: 0.149 g, 0.619 mmol, 79% as a yellowish oil.

TLC: R_f = 0.64 (hex:EtOAc = 80:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 5.41 (t, *J* = 7.7 Hz, 1H), 5.22 (d, *J* = 1.4 Hz, 1H), 5.06 (d, *J* = 1.4 Hz, 1H), 3.62 (t, *J* = 6.9 Hz, 2H), 2.37 (q, *J* = 7.0 Hz, 2H), 1.87 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.9, 142.0, 137.0, 128.7, 128.3, 128.0, 127.2, 112.2, 62.7, 32.6, 26.1, 18.5, 15.1, -5.2; **IR** (thin film): 3023, 2952, 2928, 2895, 2856, 1594, 1574, 1493, 1471, 1462, 1443, 1382, 1360, 1327, 1253, 1220, 1097, 1050, 1027, 1005, 937, 889, 831, 812, 773, 700, 661, 593, 572, 505, 453 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{30}NaOSi$ $[M+Na]^+$ 325.1958, found 325.1960.

(*E*)-*ter*t-Butyldimethyl((4-methyl-5-phenylhex-4-en-1-yl)oxy)silane (2.43f)

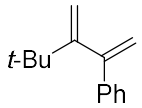


2.43f

Following General Procedure B using (*E*)-*ter*t-butyldimethyl((4-methyl-5-phenylhexa-3,5-dien-1-yl)oxy)silane (**2.42f**) (0.214 g, 0.707 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (0.039 g, 0.141 mmol, 20 mol%). FC conditions: pent:Et_2O = 80:1. Yield: 0.200 g, 0.657 mmol, 93% as a yellowish oil.

TLC: R_f = 0.39 (hex:EtOAc = 100:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.22 – 7.16 (m, 1H), 7.14 – 7.10 (m, 2H), 3.68 (t, *J* = 6.5 Hz, 2H), 2.26 – 2.20 (m, 2H), 1.98 – 1.94 (m, 3H), 1.75 – 1.65 (m, 2H), 1.57 (q, *J* = 1.4 Hz, 3H), 0.93 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.7, 131.1, 130.9, 128.5, 128.1, 125.9, 63.2, 31.5, 30.8, 26.1, 20.7, 20.1, 18.5, -5.1; **IR** (thin film): 3056, 3021, 2952, 2928, 2856, 1600, 1491, 1471, 1462, 1440, 1386, 1360, 1253, 1187, 1096, 1073, 1026, 1006, 978, 940, 909, 832, 812, 773, 764, 700, 660, 598, 571, 542 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{15}H_{23}OSi$ $[M-^tBu]^+$ 247.1513, found 247.1512.

(4,4-Dimethyl-3-methylenepent-1-en-2-yl)benzene (2.42g)

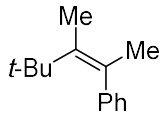


2.42g

Following General Procedure A using 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (**2.37f**) (0.272 g, 1.18 mmol, 1.0 equiv.) and 3,3-dimethylbut-1-en-2-yl trifluoromethanesulfonate (**2.41d**) (0.384 g, 1.66 mmol, 1.4 equiv.). FC conditionspentane. Yield: 0.175 g, 0.939 mmol, 79% as a yellowish oil.

TLC: R_f = 0.70 (hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.34 – 7.22 (m, 3H), 5.36 (d, *J* = 2.1 Hz, 1H), 5.23 (d, *J* = 1.9 Hz, 1H), 5.03 (d, *J* = 2.1 Hz, 1H), 4.95 (d, *J* = 1.9 Hz, 1H), 0.99 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9, 151.6, 141.4, 128.2, 127.5, 126.7, 114.8, 112.8, 30.5; **IR** (thin film): 3084, 2964, 2903, 2868, 1599, 1573, 1492, 1478, 1460, 1444, 1383, 1360, 1303, 1244, 1201, 1150, 1071, 1028, 901, 850, 781, 765, 752, 699, 678, 624, 543, 482, 410 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{14}H_{18}$ $[M]^+$ 186.1403, found 186.1402.

(*Z*)-(3,4,4-trimethylpent-2-en-2-yl)benzene (2.43g)

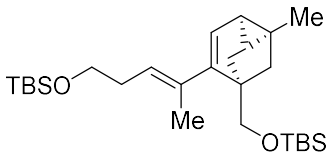


2.43g

Following General Procedure B using (4,4-Dimethyl-3-methylenepent-1-en-2-yl)benzene (**2.42g**) (0.168 g, 0.902 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6\text{-MeOBz})]$ (0.123 g, 0.451 mmol, 50 mol%). FC conditions: pentane. Yield: 0.142 g, 0.754 mmol, 84% as a yellowish oil containg 10 mol% of isomeric olefins.

TLC: R_f = 0.81 (hex); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 7.20 – 7.15 (m, 1H), 7.11 – 7.06 (m, 2H), 1.91 (d, *J* = 0.9 Hz, 3H), 1.82 – 1.78 (m, 3H), 0.89 (d, *J* = 0.9 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.3, 137.6, 130.1, 128.7, 127.7, 125.6, 37.7, 31.5, 25.8, 17.7; **IR** (thin film): 3075, 2057, 2955, 2906, 2867, 1597, 1574, 1489, 1477, 1440, 1393, 1378, 1360, 1285, 1237, 1196, 1130, 1072, 1051, 1027, 908, 847, 770, 760, 700, 658, 631, 578, 488, 471 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{14}H_{20}$ $[M]^+$ 188.1560, found 188.1558.

***rac-tert*-Butyl(((*E*)-4-((1*S*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)oxy)dimethylsilane (2.42h)**

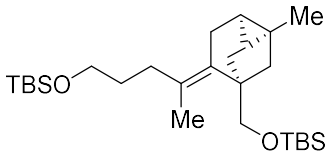


2.42h

Following General Procedure A using (Z)-tert-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl) oxy)silane (**2.37d**) (60.5 mg, 0.185 mmol, 1.5 equiv.) and *rac*-(1*S*,2*S*,5*S*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-tricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (**2.41a**) (51.0 mg, 0.124 mmol, 1.0 equiv.). During the cross-coupling reaction, most of the silyl ether was cleaved and was reprotected using TBSCl (27.9 mg, 0.185 mmol, 1.5 equiv.), imidazole (21.0 mg, 0.309 mmol, 2.5 equiv.) and DMAP (3.0 mg, 0.025 mmol, 10 mol%) in CH_2Cl_2 (2.5 mL). FC conditions: hex:Et_2O = 200:1. Yield: 39.0 mg, 0.084 mmol, 68% as a colorless oil.

TLC: R_f = 0.39 (hex:EtOAc = 30:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 (d, *J* = 5.8 Hz, 1H), 5.04 (tq, *J* = 7.2, 1.4 Hz, 1H), 3.69 (d, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.58 (t, *J* = 7.4 Hz, 2H), 2.23 (q, *J* = 7.9, 7.5 Hz, 2H), 1.78 (dd, *J* = 11.0, 2.3 Hz, 1H), 1.71 – 1.69 (m, 3H), 1.49 (d, *J* = 11.0 Hz, 1H), 1.40 – 1.36 (m, 1H), 1.28 (s, 3H), 1.17 (dd, *J* = 7.1, 2.1 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.69 – 0.60 (m, 2H), 0.06 (s, 6H), 0.02 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7, 137.0, 122.8, 118.9, 64.9, 63.1, 48.2, 37.9, 32.3, 32.0, 26.1, 26.1, 24.2, 23.9, 23.5, 19.2, 18.9, 18.6, 18.5, -5.1, -5.4, -5.4; **IR** (thin film): 3032, 2952, 2927, 2857, 1471, 1462, 1408, 1386, 1360, 1251, 1220, 1186, 1143, 1082, 1005, 936, 834, 813, 773, 664, 526, 472, 414 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{51}O_2Si_2$ $[M+H]^+$ 463.3422, found 463.3420.

***rac-tert*-Butyl(((*E*)-4-((1*R*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo[3.2.1.0^{2,7}]octan-4-ylidene)pentyl)oxy)dimethylsilane (2.43h)**

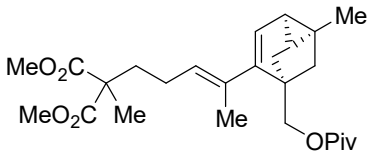


2.43h

Following General Procedure B using *tert*-butyl(((*E*)-4-((1*S*,2*R*,5*R*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyltricyclo [3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)oxy) dimethylsilane (**2.42h**) (0.089 g, 0.192 mmol, 1.0 equiv.) and [Cr(CO)$_3$(η^6-MeOBz)] (0.010 g, 0.038 mmol, 20 mol%). FC conditions: hex:EtOAc = 200:1. Yield: 0.081 g, 0.173 mmol, 90% as a colorless oil.

TLC: R_f = 0.39 (hex:EtOAc = 30:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 (s, 2H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.68 – 2.53 (m, 2H), 1.89 (td, *J* = 10.8, 5.5 Hz, 3H), 1.73 – 1.65 (m, 4H), 1.61 – 1.45 (m, 4H), 1.17 (s, 3H), 0.95 (dd, *J* = 7.7, 3.4 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.71 – 0.66 (m, 1H), 0.05 (s, 6H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.3, 121.8, 67.9, 63.3, 51.3, 41.0, 35.6, 33.3, 30.7, 27.1, 26.1, 23.9, 23.8, 20.4, 20.3, 19.2, 18.5, 18.5, -5.1, -5.3, -5.3; **IR** (thin film): 2951, 2928, 2885, 2856, 1471, 1462, 1387, 1360, 1287, 1252, 1089, 1005, 938, 834, 813, 773, 663 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{53}O_2Si_2$ $[M+H]^+$ 465.3579, found 463.3578.

***rac*-Dimethyl 2-methyl-2-((*E*)-4-((1*S*,2*R*,5*R*,7*S*)-1-methyl-5-((pivaloyloxy)methyl)tricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl)malonate (2.42j)**

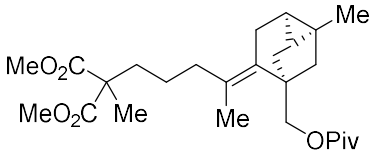


2.42j

Following General Procedure A using dimethyl (*Z*)-2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl) malonate (**2.37a**) (0.106 g, 0.312 mmol, 1.0 equiv.) and ((1*S*,2*S*,5*S*,7*R*)-1-methyl-4-(((trifluoromethyl)sulfonyl) oxy)tricyclo[3.2.1.0^{2,7}]oct-3-en-5-yl)methyl pivalate (**2.41c**) (0.143 g, 0.374 mmol, 1.2 equiv.). FC conditions: hex:EtOAc = 20:1. Yield: 0.137 g, 0.307 mmol, 98% as a colorless oil.

TLC: R_f = 0.26 (hex:EtOAc = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 5.9 Hz, 1H), 5.12 – 5.07 (m, 1H), 4.20 (d, *J* = 11.3 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 1H), 3.71 (s, 6H), 1.94 – 1.86 (m, 4H), 1.70 – 1.66 (m, 4H), 1.44 – 1.40 (m, 4H), 1.39 (d, *J* = 11.5 Hz, 1H), 1.28 (s, 3H), 1.23 – 1.21 (m, 1H), 1.17 (s, 9H), 0.84 – 0.77 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.6, 172.8, 146.2, 135.5, 126.4, 119.7, 66.9, 53.7, 52.6, 46.1, 39.0, 38.8, 35.5, 32.9, 27.3, 24.3, 23.8, 23.4, 23.4, 20.1, 18.7, 18.6; **IR** (thin film): 3030, 2953, 2865, 1729, 1480, 1459, 1434, 1397, 1377, 1280, 1254, 1231, 1197, 1157, 1113, 1080, 1033, 984, 938, 878, 841, 800, 769, 691, 666, 578, 525, 496, 417 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{38}NaO_6$ $[M+Na]^+$ 469.2561, found 469.2557.

rac-Dimethyl 2-methyl-2-((*E*)-4-((1*R*,2*R*,5*R*,7*S*)-1-methyl-5-((pivaloyloxy) methyl)tricyclo [3.2.1.0^{2,7}]octan-4-ylidene)pentyl)malonate (2.43j)

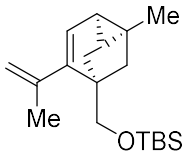


2.43j

Following General Procedure B using *rac*-dimethyl 2-methyl-2-((*E*)-4-((1*S*,2*R*,5*R*,7*S*)-1-methyl-5-((pivaloyloxy) methyl) tricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl)pent-3-en-1-yl) malonate (**2.42j**) (0.122 g, 0.273 mmol, 1.0 equiv.) and $[Cr(CO)_3(\eta^6$-MeOBz)] (0.037 g, 0.268 mmol, 50 mol%). FC conditions: hex:EtOAc = 12:1. Yield: 0.120 g, 0.268 mmol, 98% as a colorless oil.

TLC: R_f = 0.26 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.24 (d, *J* = 11.2 Hz, 1H), 4.20 (d, *J* = 11.2 Hz, 1H), 3.72 (s, 6H), 2.67 – 2.51 (m, 2H), 1.92 – 1.77 (m, 5H), 1.67 – 1.58 (m, 6H), 1.42 (s, 3H), 1.30 – 1.22 (m, 2H), 1.20 (s, 9H), 1.17 (s, 3H), 1.01 (dd, *J* = 7.8, 3.3 Hz, 1H), 0.76 – 0.71 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.6, 173.0, 132.6, 122.3, 69.6, 53.9, 52.6, 48.9, 41.7, 39.0, 37.1, 36.4, 35.8, 27.3, 26.9, 23.9, 23.8, 22.0, 20.3, 20.2, 20.0, 18.9; **IR** (thin film): 2953, 2926, 2863, 1729, 1479, 1458, 1433, 1397, 1378, 1264, 1228, 1195, 1155, 1113, 1063, 1034, 979, 939, 881, 841, 815, 799, 769, 694, 579, 486, 469, 413 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{40}NaO_6$ $[M+Na]^+$ 471.2717, found 471.2715.

***rac-tert*-Butyldimethyl(((1*S*,2*R*,5*R*,7*S*)-1-methyl-4-(prop-1-en-2-yl)tricyclo [3.2.1.0^{2,7}]oct-3-en-5-yl) methoxy)silane (2.42k)**



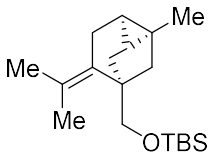
2.42k

Following General Procedure A using isopropenylboronic acid pinacol ester (**2.37g**) (0.136 g, 0.723 mmol, 1.4 equiv.) and *rac*-(1*S*,2*S*,5*S*,7*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-tricyclo[3.2.1.0^{2,7}]oct-3-en-4-yl trifluoromethanesulfonate (**2.41a**) (0.213 g, 0.516 mmol, 1.0 equiv.). During the cross-coupling reaction, most of the silyl ether was cleaved and was reprotected using TBSCl (0.117 g, 0.774 mmol, 1.5 equiv.), imidazole (0.088 g, 1.291 mmol, 2.5 equiv.) and DMAP (6.3 mg, 0.052 mmol, 10 mol%) in CH_2Cl_2 (6.5 mL). FC conditions: hex. Yield: 0.102 g, 0.335 mmol, 65% as a colorless oil.

Note: *Analytical data is identical to material prepared in chapter 1 via a different route.*

TLC: R_f = 0.68 (hex:EtOAc = 200:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 5.9 Hz, 1H), 4.79 (dq, *J* = 2.9, 1.5 Hz, 1H), 4.66 – 4.63 (m, 1H), 3.78 (d, *J* = 10.0 Hz, 1H), 3.75 (d, *J* = 10.0 Hz, 1H), 1.87 – 1.85 (m, 3H), 1.81 (dd, *J* = 11.1, 2.4 Hz, 1H), 1.52 (d, *J* = 11.0 Hz, 1H), 1.46 – 1.42 (m, 1H), 1.31 (s, 3H), 1.22 (dd, *J* = 7.1, 2.4 Hz, 1H), 0.91 (s, 9H), 0.74 – 0.67 (m, 2H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.5, 144.5, 119.6, 112.2, 65.0, 48.0, 37.8, 31.9, 25.9, 25.5, 24.3, 24.0, 23.5, 18.7, 18.3, -5.5, -5.6; **IR** (thin film): 3077, 3034, 2952, 2927, 2857, 1616, 1471, 1462, 1411, 1387, 1361, 1251, 1221, 1193, 1143, 1119, 1082, 1006, 938, 886, 837, 814, 773, 666, 533, 405 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{33}OSi$ $[M+H]^+$ 305.2295, found 305.2297.

***rac-tert*-Butyldimethyl(((1*R*,2*R*,5*R*,7*S*)-1-methyl-4-(propan-2-ylidene) tricyclo[3.2.1.0^{2,7}] octan-5-yl)methoxy)silane (2.43k)**



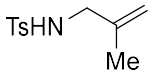
2.43k

Following General Procedure B using *rac-tert*-butyldimethyl (((1*S*,2*R*,5*R*,7*S*)-1-methyl-4-(prop-1-en-2-yl)tricyclo [3.2.1.0^{2,7}] oct-3-en-5-yl) methoxy)silane (**2.42k**) (0.063 g, 0.207 mmol, 1.0 equiv.) and [$Cr(CO)_3(\eta^6$-MeOBz)] (0.011 g, 0.041 mmol, 20 mol%). FC conditions: hex. Yield: 0.058 g, 0.191 mmol, 92% as a colorless oil.

TLC: R_f = 0.70 (hex:EtOAc = 200:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.76 (s, 2H), 2.61 – 2.43 (m, 2H), 1.87 (dd, *J* = 11.5, 3.5 Hz, 1H), 1.74 (t, *J* = 1.9 Hz, 3H), 1.69 (d, *J* = 11.5 Hz, 1H), 1.56 – 1.45 (m, 5H), 1.17 (s, 3H), 0.96 (dd, *J* = 7.7, 3.5 Hz, 1H), 0.90 (s, 9H), 0.74 – 0.69 (m, 1H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.9, 117.8, 68.0, 51.2, 40.9, 35.5, 28.3, 26.1, 23.9, 23.8, 23.6, 21.6, 20.6, 20.3, 18.6, -5.2, -5.3; **IR** (thin film): 3021, 2951, 2927, 2857, 1471, 1462, 1388, 1360, 1313, 1287, 1252, 1216, 1187, 1149, 1111, 1083, 1061, 1027, 1005, 985, 939, 919, 905, 849, 835, 814, 773, 679, 663, 568, 422 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{19}H_{35}OSi$ $[M+H]^+$ 307.2452, found 307.2427.

4. Synthesis of Primary Amines from Nitriles *via* a Radical Cyclization/Reduction Cascade

4-Methyl-*N*-(2-methylallyl)benzenesulfonamide (3.S1)



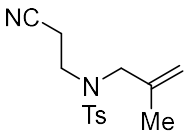
3.S1

A mixture of methallyl chloride (1.5 mL, 15.3 mmol, 1.0 equiv.), tosyl amide (5.22 g, 30.5 mmol, 2.0 equiv.), soidum iodide (2.29 g, 15.3 mmol, 1.0 equiv.) and potassium carbonate (8.43 g, 61.0 mmol, 4.0 equiv.) in MeCN (76 mL) was stirred at 80 °C for 16.5 g. After cooling to r.t., H_2O (200 mL) was added and the mixture was extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 2:1) yielding the title compound (2.55 g, 11.3 mmol, 74%) as an off-white solid.

Note: *Analytical data is in full agreement with literature data.*[192]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 2H), 7.34 – 7.29 (m, 2H), 4.85 (qd, *J* = 1.4, 0.7 Hz, 1H), 4.83 (ddd, *J* = 2.5, 1.5, 1.0 Hz, 1H), 4.43 (t, *J* = 6.4 Hz, 1H), 3.52 – 3.47 (m, 2H), 2.43 (s, 3H), 1.72 – 1.67 (m, 3H).

N-(2-Cyanoethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (3.68a)



3.68a

To a suspension of 4-Methyl-*N*-(2-methylallyl)benzenesulfonamide (**3.S1**) (5.91 g, 26.2 mmol, 1.0 equiv.) and potassium carbonate (6.66 g, 48.2 mmol, 1.8 equiv.) in DMF (65.5 mL) was added dropwise acrylonitrile (2.38 mL, 36.2 mmol, 1.4 equiv.). The mixture was stirred at r.t. for 16 h. H_2O (300 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 4:1 to 2:1 gradient) yielding the title compound (5.56 g, 20.0 mmol, 76%) as a colorless solid.

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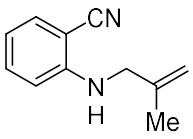
[192] Prier, C. K.; Hyster, T. K.; Farwell, C. C.; Huang, A.; Arnold, F. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4711–4715.

TLC: R_f = 0.17 (hex:EtOAc = 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 2H), 7.38 – 7.30 (m, 1H), 5.00 – 4.95 (m, 1H), 4.92 – 4.89 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2, 140.2, 135.8, 130.1, 127.4, 117.5, 116.1, 55.9, 43.8, 21.7, 19.9, 18.3; **IR** (thin film): 2923, 2251, 1655, 1597, 1494, 1449, 1378, 1335, 1306, 1235, 1185, 1159, 1104, 1018, 986, 963, 918, 873, 815, 748, 708, 692, 654, 586, 566, 547, 428, 408 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{14}H_{18}N_2NaO_2S$ $[M+Na]^+$ 301.0981, found 301.0979; **Melting Point:** 73 °C.

2-((2-Methylallyl)amino)benzonitrile (3.68b)

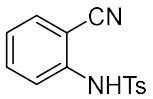


3.68b

To a solution of methallyl chloride (4.00 mL, 40.7 mmol, 1.0 equiv.) in acetone (40.7 mL) was added potassium iodide (6.75 g, 40.7 mmol, 1.0 equiv.) and the mixture was stirred at r.t. for 65 min. 2-Aminobenzonitrile (**3.74a**) (7.21 g, 61.0 mmol, 1.5 equiv.) was added and the mixture was stirred at 55 °C in a sealed flask for 15 h. After cooling to r.t., the mixture was diluted with EtOAc (300 mL), washed with half-saturated $Na_2S_2O_3$ (200 mL) and brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 15:1 to 10:1 gradient) yielding the title compound (4.48 g, 26.0 mmol, 64%) as a colorless solid.

TLC: R_f = 0.38 (hex:EtOAc = 10:1)**; ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H), 6.67 (t, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 4.97 – 4.94 (m, 1H), 4.94 – 4.90 (m, 1H), 4.82 (s, 1H), 3.77 (s, 2H), 1.79 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 141.2, 134.3, 132.8, 118.1, 116.8, 111.8, 111.2, 95.8, 49.3, 20.3; **IR** (thin film): 3383, 3085, 2974, 2915, 2852, 2212, 1655, 1606, 1576, 1516, 1464, 1375, 1328, 1314, 1303, 1288, 1272, 1237, 1166, 1125, 1076, 1052, 1039, 946, 895, 817, 748, 568, 496, 471, 420 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{11}H_{12}N_2$ $[M]^+$ 172.0885, found 172.0995; **Melting Point:** 49 °C.

_N_-(2-Cyanophenyl)-4-methylbenzenesulfonamide (3.74b)



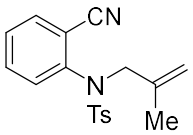
3.74b

To a solution of 2-aminobenzonitrile (**3.74a**) (1.00 g, 8.46 mmol, 1.0 equiv.) and pyridine (8.22 mL, 102 mmol, 12 equiv.) in CH_2Cl_2 (42.3 mL) at 0 °C was slowly added tosyl chloride (1.94 g, 10.2 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 24 h, washed with 2 M aq HCl (2 x 100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 4:1 and pent:Et_2O = 1:1) yielding the title compound (1.78 g, 6.55 mmol, 77%) as an off-white solid.

Note: *Analytical data is in full agreement with literature data.*[181b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 3H), 7.55 (ddd, *J* = 8.7, 7.7, 1.6 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.17 (td, *J* = 7.6, 1.1 Hz, 1H), 7.00 (s, 1H), 2.39 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 139.5, 135.6, 134.3, 132.8, 130.1, 127.5, 125.3, 121.7, 115.8, 104.3, 21.8.

_N_-(2-Cyanophenyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (3.68c)



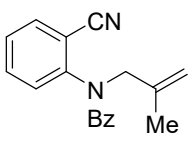
3.68c

To a solution of *N*-(2-cyanophenyl)-4-methylbenzenesulfonamide (**3.74b**) (0.498 g, 1.83 mmol, 1.0 equiv.) in DMF (7.31 mL) was added potassium carbonate (0.632 g, 4.57 mmol, 2.5 equiv.) followed by methallyl chloride (0.269 mL, 2.74 mmol, 1.5 equiv.) and potassium iodide (0.455 g, 2.74 mmol, 1.5 equiv.). The mixture was stirred at r.t. for 25 h. Sat. aq. NH_4Cl (40 mL) was added followed by H_2O (10 mL) and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 4:1 to 3:1 gradient) yielding the title compound (561 mg, 1.72 mmol, 94%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 3H), 7.56 (td, *J* = 7.9, 1.6 Hz, 1H), 7.40 (td, *J* = 7.6, 1.1 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.23 (d, *J* = 8.9 Hz, 1H),

4.78 – 4.73 (m, 1H), 4.71 – 4.66 (m, 1H), 4.17 (s, 2H), 2.45 (s, 3H), 1.80 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.5, 141.5, 139.4, 134.9, 134.1, 133.2, 130.8, 129.9, 128.6, 128.2, 116.7, 116.5, 115.1, 57.3, 21.8, 20.2; **IR** (thin film): 3075, 2923, 2232, 1654, 1596, 1489, 1448, 1352, 1301, 1220, 1162, 1091, 1025, 982, 908, 864, 815, 744, 684, 654, 575, 545, 508 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{18}H_{19}N_2O_2S$ $[M+H]^+$ 327.1162, found 327.1160.

N-(2-Cyanophenyl)-N-(2-methylallyl)benzamide (3.68d)



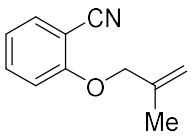
3.68d

To a solution of 2-((2-methylallyl)amino)benzonitrile (**3.68b**) in CH_2Cl_2 (8.59 mL) was added benzoyl chloride (0.399 mL, 3.44 mmol, 2.0 equiv.) followed by triethylamine (0.958 mL, 6.87 mmol, 4.0 equiv.) and DMAP (42 mg, 0.344 mmol, 20 mol%). The mixture was stirred at r.t. for 18 h. More benzoyl chloride (0.399 mL, 3.44 mmol, 2.0 equiv.) was added followed by potassium carbonate (0.950 g, 6.87 mmol, 4.0 equiv.) and the mixture was stirred at 40 °C for 26 h. Brine–1 M aq HCl (10 mL, 1:1) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 4:1) yielding the title compound (0.379 g, 1.37 mmol, 80%) as an off-white solid.

Note: *The NMR spectra show a mixture of rotamers.*

TLC: R_f = 0.41 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.08 (m, 9H), 4.88 (s, 1H), 4.81 (s, 1H), 4.30 (s, 2H), 1.85 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 135.4, 133.7, 133.4, 130.1, 129.6, 128.4, 127.9, 127.5, 116.5, 114.7, 112.7, 55.5, 20.6; **IR** (thin film): 3074, 2922, 2228, 1656, 1595, 1578, 1488, 1450, 1374, 1289, 1179, 1149, 1110, 1075, 1053, 1027, 954, 905, 790, 766, 721, 699, 649, 614, 558, 515, 491, 470, 440, 412 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1335, found 277.1338; **Melting Point:** 126 °C.

2-((2-Methylallyl)oxy)benzonitrile (3.68e)

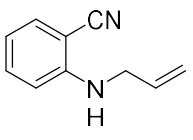


3.68e

To a suspension of 2-hydroxybenzonitrile (**3.74c**) (2.50 g, 21.0 mmol, 1.0 equiv.), potassium iodide (3.48 g, 21.0 mmol, 1.0 equiv.) and sodium carbonate (4.45 g, 42.0 mmol, 2.0 equiv.) in acetone (21.0 mL) was added methallyl chloride (3.10 mL, 31.5 mmol, 1.5 equiv.). The mixture was stirred at 55 °C in a sealed flask for 23 h. After cooling to r.t., the mixture was diluted with EtOAc (150 mL), washed with half-saturated $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (3.40 g, 19.6 mmol, 93%) as a colorless oil.

TLC: R_f = 0.48 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.03 – 6.97 (m, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 5.16 – 5.13 (m, 1H), 5.05 – 5.01 (m, 1H), 4.55 (s, 2H), 1.85 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.5, 139.7, 134.3, 133.9, 121.0, 116.5, 113.6, 112.8, 102.4, 72.5, 19.4; **IR** (thin film): 3081, 2977, 2918, 2227, 1659, 1598, 1579, 1490, 1449, 1377, 1291, 1256, 1230, 1165, 1111, 1048, 1005, 966, 905, 854, 832, 754, 605, 589, 566, 497, 425, 416 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{11}H_{10}NO$ $[M-H]^+$ 172.0757, found 172.0756.

2-(Allylamino)benzonitrile (3.68f)

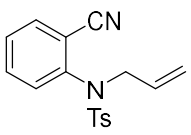


3.68f

To a solution of allyl bromide (2.00 mL, 23.1 mmol, 1.0 equiv.) in acetone (23.1 mL) was added potassium iodide (3.84 g, 23.1 mmol, 1.0 equiv.) and the mixture was stirred at r.t. for 20 min. 2-Aminobenzonitrile (**3.74a**) (4.10 g, 34.7 mmol, 1.5 equiv.) was added and the mixture was stirred at 55 °C in a sealed flask for 18 h. After cooling to r.t., the mixture was diluted with EtOAc (150 mL), washed with half-saturated $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 20:1) yielding the title compound (1.91 g, 12.1 mmol, 52%) as a yellowish oil.

TLC: R_f = 0.34 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 6.74 – 6.60 (m, 2H), 5.92 (ddd, *J* = 22.4, 10.4, 5.2 Hz, 1H), 5.37 – 5.19 (m, 2H), 4.75 (s, 1H), 3.87 (tt, *J* = 5.5, 1.6 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 134.3, 133.9, 132.8, 118.0, 117.2, 116.8, 111.1, 96.0, 45.8; **IR** (thin film): 3381, 3085, 3013, 2983, 2916, 2852, 2211, 1644, 1605, 1576, 1514, 1463, 1418, 1323, 1302, 1289, 1267, 1246, 1166, 1140, 1090, 1066, 1043, 1022, 993, 920, 845, 816, 747, 649, 498, 429, 416 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{10}H_{10}N_2$ $[M]^+$ 158.0838, found 158.0831.

N-Allyl-*N*-(2-cyanophenyl)-4-methylbenzenesulfonamide (3.68g)

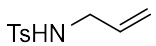


3.68g

To a solution of *N*-(2-cyanophenyl)-4-methylbenzenesulfonamide (**3.74b**) (0.540 g, 1.98 mmol, 1.0 equiv.) in DMF (7.93 mL) was added potassium carbonate (0.685 g, 4.96 mmol, 2.5 equiv.) followed by allyl bromide (0.257 mL, 2.97 mmol, 1.5 equiv.) and potassium iodide (0.494 g, 2.97 mmol, 1.5 equiv.). The mixture was stirred at r.t. for 26 h. Sat. aq. NH_4Cl (40 mL) was added followed by H_2O (10 mL) and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 3:1) yielding the title compound (602 mg, 1.93 mmol, 97%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 6.74 – 6.60 (m, 2H), 5.92 (ddd, *J* = 22.4, 10.4, 5.2 Hz, 1H), 5.37 – 5.19 (m, 2H), 4.75 (s, 1H), 3.87 (tt, *J* = 5.5, 1.6 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 134.3, 133.9, 132.8, 118.0, 117.2, 116.8, 111.1, 96.0, 45.8; **IR** (thin film): 3069, 2921, 2851, 2232, 1739, 1644, 1596, 1488, 1448, 1420, 1352, 1305, 1290, 1230, 1185, 1161, 1109, 1090, 1059, 1018, 998, 932, 863, 815, 800, 785, 762, 742, 710, 663, 589, 573, 542, 497 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{17}H_{17}N_2O_2S$ $[M+H]^+$ 313.1005, found 313.1014.

N-Allyl-4-methylbenzenesulfonamide (3.S2)



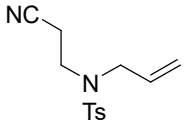
3.S2

To a solution of allylamine (**3.76**) (1.00 mL, 13.4 mmol, 1.0 equiv.), triethylamine (5.59 mL,40.1 mmol, 3.0 equiv.) and DMAP (82 mg, 0.668 mmol, 5 mol%) in CH_2Cl_2 (66.8 mL) at 0 °C was added tosyl chloride (2.80 g, 14.7 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 3.5 h. Brine–1 M aq HCl (100 mL, 1:1) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was used for the next steps without further purification.

Note: *Analytical data is in full agreement with literature data.*[192]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 2H), 7.36 – 7.28 (m, 2H), 5.72 (ddt, *J* = 16.9, 10.1, 5.8 Hz, 1H), 5.22 – 5.06 (m, 2H), 4.46 (t, *J* = 6.3 Hz, 1H), 3.59 (tt, *J* = 6.1, 1.5 Hz, 2H), 2.43 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 137.1, 133.1, 129.9, 127.3, 117.9, 45.9, 21.7.

N-Allyl-*N*-(2-cyanoethyl)-4-methylbenzenesulfonamide (3.68h)



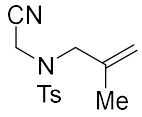
3.68h

To a suspension of *N*-allyl-4-methylbenzenesulfonamide (**3.S2**) (2.82 g, 13.4 mmol, 1.0 equiv.) and potassium carbonate (3.69 g, 26.7 mmol, 2.0 equiv.) in DMF (33.4 mL) was added dropwise acrylonitrile (1.23 mL, 18.7 mmol, 1.4 equiv.). The mixture was stirred at r.t. for 27 h. H_2O (100 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 3:1) yielding the title compound (3.23 g, 12.2 mmol, 91% over two steps) as a colorless solid.

TLC: R_f = 0.41 (hex:EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H), 7.40 – 7.30 (m, 2H), 5.74 – 5.61 (m, 1H), 5.26 – 5.23 (m, 1H), 5.21 (dq, *J* = 6.1, 1.2 Hz, 1H), 3.83 (dd, *J* = 6.6, 1.1 Hz, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 2.71 – 2.65 (m, 2H), 2.44 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2, 135.9,

132.5, 130.1, 127.4, 120.5, 117.6, 52.2, 43.2, 21.7, 18.8; **IR** (thin film): 2926, 2251, 1643, 1597, 1494, 1450, 1420, 1380, 1343, 1306, 1288, 1232, 1156, 1091, 1017, 982, 935, 872, 815, 778, 737, 706, 663, 620, 568, 547 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{17}N_2O_2S$ $[M+H]^+$ 265.1005, found 265.1004; **Melting Point:** 50 °C.

N-(Cyanomethyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (3.68i)

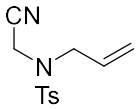


3.68i

To a solution of 4-methyl-*N*-(2-methylallyl)benzenesulfonamide (**3.S1**) (0.637 g, 2.83 mmol, 1.0 equiv.) in DMF (9.42 mL) at 0 °C was added NaH, 60% in mineral oil (0.170 g, 4.24 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 15 min. 2-Iodoacetonitrile (0.307 mL, 4.24 mmol, 1.5 equiv.) was added dropwise and the mixture was stirred at r.t. for 20 h. Sat. aq. NH_4Cl–H_2O (60 mL, 2:1) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pent:Et_2O = 5:1 to 2:1 gradient) yielding the title compound (0.443 g, 1.68 mmol, 59%) as a colorless oil.

TLC: R_f = 0.29 (pent:Et_2O = 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 5.07 – 5.05 (m, 1H), 5.04 – 5.01 (m, 1H), 4.16 (s, 2H), 3.72 (s, 2H), 2.45 (s, 3H), 1.77 (dd, *J* = 1.4, 0.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 138.2, 134.3, 130.2, 127.7, 117.4, 113.3, 53.8, 34.3, 21.8, 19.6; **IR** (thin film): 2984, 2921, 1656, 1597, 1494, 1445, 1417, 1378, 1352, 1307, 1289, 1247, 1214, 1186, 1162, 1121, 1096, 1019, 908, 887, 815, 802, 766, 709, 698, 658, 635, 573, 544, 496 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{16}N_2NaO_2S$ $[M+Na]^+$ 287.0825, found 287.0833.

N-Allyl-*N*-(cyanomethyl)-4-methylbenzenesulfonamide (3.68j)

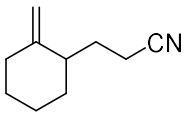


3.68j

To a solution of *N*-allyl-4-methylbenzenesulfonamide (**3.S2**) (0.622 g, 2.94 mmol, 1.0 equiv.) in DMF (9.81 mL) at 0 °C was added NaH, 60% in mineral oil (0.177 g, 4.42 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 15 min. 2-Iodoacetonitrile (0.320 mL, 4.42 mmol, 1.5 equiv.) was added dropwise and the mixture was stirred at r.t. for 20 h. Sat. aq. NH_4Cl–H_2O (60 mL, 2:1) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (pent:Et_2O = 3:1) yielding the title compound (0.564 g, 2.25 mmol, 77%) as a yellowish solid.

TLC: R_f = 0.38 (pent:Et_2O = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 2H), 7.42 – 7.34 (m, 2H), 5.73 (ddt, *J* = 17.1, 10.0, 6.6 Hz, 1H), 5.39 – 5.32 (m, 2H), 4.21 (s, 2H), 3.82 (dt, *J* = 6.6, 1.2 Hz, 2H), 2.45 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 134.4, 130.8, 130.3, 127.7, 121.9, 113.5, 50.4, 34.6, 21.8; **IR** (thin film): 2987, 2924, 1644, 1597, 1494, 1448, 1420, 1352, 1307, 1291, 1260, 1162, 1121, 1092, 1065, 1017, 992, 935, 883, 815, 802, 757, 705, 665, 582, 546 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{12}H_{14}N_2NaO_2S$ $[M+Na]^+$ 273.0668, found 273.0671; **Melting Point:** 33 °C.

3-(2-Methylenecyclohexyl)propanenitrile (3.68k)



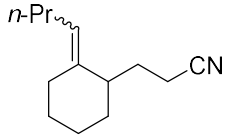
3.68k

To a suspension of methyltriphenylphosphonium bromide (3.15 gm 8.80 mmol, 1.3 equiv.) in THF (33.9 mL) was added dropwise KO*t*-Bu, 1 M in THF (8.80 mL, 8.80 mmol, 1.3 equiv.). The mixture was stirred at r.t. for 100 min. 3-(2-Oxocyclohexyl)propanenitrile (**3.77**) (1.00 mL, 6.77 mmol, 1.0 equiv.) was added dropwise and stirring was continued for 2 h. Sat. aq. NH_4Cl (30 mL) was added followed by H_2O (10 mL) and THF was removed under reduced pressure. The mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated

under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 25:1) yielding the title compound (0.94 g, 6.31 mmol, 93%) as a colorless oil.

TLC: R_f = 0.40 (hex:EtOAc = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.60 (s, 1H), 2.42 – 2.13 (m, 4H), 2.10 – 1.93 (m, 2H), 1.81 – 1.72 (m, 1H), 1.71 – 1.46 (m, 5H), 1.39 – 1.30 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 120.2, 107.6, 42.3, 34.1, 33.5, 28.7, 27.8, 23.8, 15.5; **IR** (thin film): 3072, 2929, 2855, 2245, 1644, 1446, 1425, 1339, 1252, 1156, 1087, 1008, 951, 891, 844, 777, 640, 599, 470, 440 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{10}H_{14}N$ $[M-H]^+$ 148.1121, found 148.1121.

(*E*/*Z*)-3-(2-Butylidenecyclohexyl)propanenitrile (3.68l)



3.68l

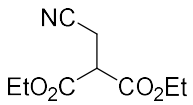
To a suspension of *n*-butyltriphenylphosphonium bromide (3.52 gm 8.80 mmol, 1.3 equiv.) in THF (33.9 mL) was added dropwise KO*t*-Bu, 1 M in THF (8.80 mL, 8.80 mmol, 1.3 equiv.). The mixture was stirred at r.t. for 100 min. 3-(2-Oxocyclohexyl)propanenitrile (**3.77**) (1.00 mL, 6.77 mmol, 1.0 equiv.) was added dropwise and stirring was continued for 21 h. Sat. aq. NH_4Cl (30 mL) was added followed by H_2O (10 mL) and THF was removed under reduced pressure. The mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 30:1) yielding the title compound (1.27 g, 6.65 mmol, 98%, d.r. = 3:1) as a colorless oil.

Note: *Analytical data represents a 3:1 mixture of diastereomers. ^{1}H and ^{13}C NMR signals of the minor isomer are labeled with an asterisk.*

TLC: R_f = 0.49 (hex:EtOAc = 10:1) ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.23 (t, *J* = 7.9 Hz, 1H*), 5.12 (t, *J* = 7.2 Hz, 1H), 2.85 – 2.76 (m, 1H*), 2.36 – 1.28 (m, 17H, 16H*), 0.94 – 0.85 (m, 3H, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.3, 138.8*, 125.5*, 123.3, 120.4*, 120.3, 43.7, 35.1*, 33.4, 32.8*, 31.9*, 29.3*, 29.3, 28.7*, 28.0, 27.6, 25.8, 23.4*, 23.4, 23.1, 21.4*, 15.5, 15.4*, 13.9, 13.9*; **IR** (thin

film): 2957, 2927, 2857, 2245, 1455, 1377, 1336, 1051, 898, 843, 596, 497, 465, 454, 432, 417, 406 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{13}H_{20}N$ $[M-H]^+$ 190.1590, found 190.1588.

Diethyl 2-(cyanomethyl)malonate (3.S3)



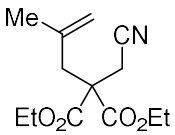
3.S3

To a susprnsion of NaH, 60% in mineral oil (1.16 g, 29.0 mmol, 2.1 equiv.) in THF (46.1 mL) at 0 °C was added dropwise diethyl malonate (**3.78a**) (4.20 mL, 27.6 mmol, 2.0 equiv.). The mixture was stirred at 0 °C for 40 min. 2-Iodoacetonitrile (1.00 mL, 13.8 mmol, 1.0 equiv.) was added dropwise and the mixture was stirred at r.t. for 24 h. Sat. aq. NH_4CL (70 mL) was added followed by H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 8:1 to 3:1 gradient) yielding the title compound (2.34 g, 11.7 mmol, 85%) as a colorless oil.

Note: *Analytical data is in full agreement with literature data.*[193]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 – 4.22 (m, 4H), 3.70 (t, *J* = 7.4 Hz, 1H), 2.92 (d, *J* = 7.4 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.6, 116.9, 62.8, 48.2, 17.1, 14.1.

Diethyl 2-(cyanomethyl)-2-(2-methylallyl)malonate (3.68m)



3.68m

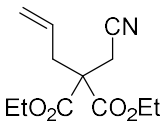
To a solution of diethyl 2-(cyanomethyl)malonate (**3.S3**) (0.995 g, 4.99 mmol, 1.0 equiv.) in DMF (16.7 mL) at 0 °C was added NaH, 60% in mineral oil (0.240 g, 5.99 mmol, 1.2 equiv.). The mixture was stirred at 0 °C for 15 min. Methallyl chloride (0.587 mL, 5.99 mmol, 1.2 equiv.) was added dropwise followed by potassium iodide (0.995 g,

[193] Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, *2*, 58–68.

5.99 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 15 h. Sat. aq. NH_4Cl (80 mL) was added followed by H_2O (20 mL). The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 10:1) yielding the title compound (1.13 g, 4.45 mmol, 89%) as a colorless oil.

TLC: R_f = 0.45 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.00 – 4.96 (m, 1H), 4.93 – 4.90 (m, 1H), 4.34 – 4.17 (m, 4H), 2.95 (s, 2H), 2.89 (d, *J* = 0.8 Hz, 2H), 1.66 – 1.65 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 139.0, 117.7, 116.7, 62.7, 54.7, 40.6, 23.0, 21.8, 14.1; **IR** (thin film): 3080, 2983, 2941, 2249, 1732, 1645, 1446, 1413, 1368, 1323, 1295, 1275, 1238, 1186, 1130, 1095, 1076, 1059, 1035, 1015, 940, 906, 860, 791, 759, 711, 676, 624, 595, 553, 478, 418 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{13}H_{19}NO_4$ $[M]^+$ 253.1309, found 253.1308.

Diethyl 2-allyl-2-(cyanomethyl)malonate (3.68n)



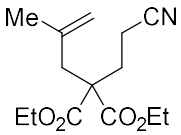
3.68n

To a suspension of NaH; 60% in mineral oil (0.242 g, 6.05 mmol, 1.2 equiv.) in DMF (16.8 mL) at 0 °C was added dropwise diethyl 2-allylmalonate (**3.78b**) (1.00 mL, 5.04 mmol, 1.0 equiv.). The mixture was stirred at 0 °C for 15 min. 2-Iodoacetonitrile (0.438 mL, 6.05 mmol, 1.2 equiv.) was added dropwise and the mixture was stirred at r.t. for 20 h. Sat. aq. NH_4Cl (100 mL) was added followed by H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_2 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EOAc = 10:1 to 5:1 gradient) yielding the title compound (0.891 g, 3.72 mmol, 74%) as a yellow oil.

TLC: R_f = 0.23 (hex:EtOAc = 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.61 (ddt, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.33 – 5.19 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 4H), 2.91 (s, 2H), 2.84 (dd, *J* = 7.5, 0.9 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5, 130.7, 121.4, 116.4, 62.7, 55.1, 37.4, 21.8, 14.1; **IR** (thin film):

3083, 2984, 2940, 2247, 1731, 1642, 1466, 1444, 1416, 1391, 1368, 1324, 1287, 1217, 1194, 1146, 1113, 1095, 1070, 1033, 1001, 933, 856, 802, 659, 597, 508, 427, 412 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{12}H_{17}NNaO_4$ $[M+Na]^+$ 262.1050, found 262.1048.

Diethyl 2-(2-cyanoethyl)-2-(2-methylallyl)malonate (3.68o)

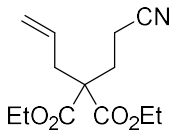


3.68o

To a suspension of NaH; 60% in mineral oil (0.243 g, 6.07 mmol, 1.2 equiv.) in DMF (16.9 mL) at 0 °C was added dropwise diethyl 2-(2-cyanoethyl)malonate (**3.78c**) (1.00 mL, 5.06 mmol, 1.0 equiv.). The mixture was stirred at 0 °C for 15 min. Methallylchloride (0.594 mL, 6.07 mmol, 1.2 equiv.) was added dropwise followed by potassium iodide (1.01 g, 6.07 mmol, 1.2 equiv.) and the mixture was stirred at r.t. for 15 h. Sat. aq. NH_4Cl (100 mL) was added followed by H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_2 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EOAc = 6:1) yielding the title compound (1.29 g, 4.84 mmol, 96%) as a colorless oil.

TLC: R_f = 0.35 (hex:EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.93 – 4.88 (m, 1H), 4.77 – 4.74 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 4H), 2.73 (s, 2H), 2.45 – 2.36 (m, 2H), 2.27 – 2.19 (m, 2H), 1.65 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.6, 139.9, 119.2, 116.6, 62.0, 55.8, 41.4, 28.9, 23.0, 14.1, 13.2; **IR** (thin film): 3078, 2982, 2940, 2249, 1725, 1645, 1446, 1368, 1298, 1264, 1234, 1200, 1183, 1090, 1070, 1021, 904, 862, 779, 741, 681, 606, 564, 499, 475, 459, 455, 448, 442, 434, 418, 406 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{14}H_{21}NNaO_4$ $[M+Na]^+$ 290.1363, found 290.1363.

Diethyl 2-allyl-2-(2-cyanoethyl)malonate (3.68p)



3.68p

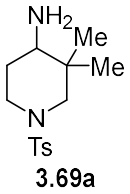
To a solution of KO*t*-Bu, 1 M in THF (0.504 mL, 0.504 mmol, 5 mol%) in *t*-BuOH (10.1 mL) was added dropwise diethyl 2-allylmalonate (**3.78b**) (2.00 mL, 10.1 mmol, 1.0 equiv.) followed by acrylonitrile (0.797 mL, 12.1 mmol, 1.2 equiv.). The mixture was stirred at r.t. for 19 h. Brine–1 M aq HCl (100 mL, 9:1) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EtOAc = 7:1) yielding the title compound (2.34 g, 9.24 mmol, 92%) as a colorless solid.

TLC: R_f = 0.31 (hex:EtOAc = 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.61 (ddt, *J* = 17.1, 9.7, 7.3 Hz, 1H), 5.18 – 5.15 (m, 1H), 5.15 – 5.12 (m, 1H), 4.28 – 4.16 (m, 4H), 2.66 (dt, *J* = 7.4, 1.2 Hz, 2H), 2.46 – 2.39 (m, 2H), 2.25 – 2.18 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 131.5, 120.2, 119.2, 62.0, 56.4, 38.0, 28.9, 14.2, 13.0; **IR** (thin film): 2983, 2249, 1725, 1641, 1546, 1445, 1368, 1296, 1273, 1241, 1210, 1190, 1144, 1086, 1019, 926, 858, 779, 744, 653, 581, 408 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{19}NNaO_4$ $[M+Na]^+$ 276.1206, found 276.1207; **Melting Point:** 38 °C.

General Procedure 3.1:

To a solution of nitrile **3.68** (0.300 mmol) in *i*-PrOH (3 mL) in a Schlenk tube was added $Mn(dpm)_3$ (91.0 mg, 0.150 mmol, 50 mol%) followed by $NaBH_4$ (34.0 mg, 0.900 mmol, 3.0 equiv.). The tube was evacuated and back-filled with N_2 (5x) and the mixture was stirred at r.t. for 17-24 h. $Na_2EDTA \cdot H_2O$ (300 mg) was added followed by 1 M aq HCl (6 mL). The mixture was stirred at r.t. for 2 min, poured into 2 M aq K_2CO_2 (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica.

3,3-Dimethyl-1-tosylpiperidin-4-amine (3.69a)

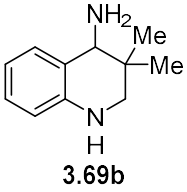


3.69a

Following general procedure 3.1 using *N*-(2-cyanoethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (**3.68a**). Yield: 33.2 mg, 0.186 mmol, 62%. Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 7.33 – 7.28 (m, 2H), 3.66 – 3.58 (m, 1H), 3.25 (dd, *J* = 11.5, 2.1 Hz, 1H), 2.44 – 2.34 (m, 4H), 2.30 (dd, *J* = 10.6, 4.2 Hz, 1H), 2.06 (d, *J* = 11.5 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.62 – 1.50 (m, 1H), 1.15 (s, 2H), 0.96 (s, 3H), 0.91 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 133.5, 129.7, 127.7, 56.6, 56.0, 45.8, 35.5, 30.7, 25.5, 21.6, 18.0; **IR** (thin film): 3379, 2926, 2856, 1597, 1494, 1463, 1393, 1335, 1305, 1286, 1214, 1183, 1158, 1120, 1089, 1066, 1041, 1023, 989, 968, 957, 941, 911, 887, 844, 815, 802, 761, 707, 677, 635, 611, 573, 558, 548, 516, 498, 475, 431, 419, 405 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{14}H_{23}N_2O_2S$ $[M+H]^+$ 283.1475, found 283.1477.

3,3-Dimethyl-1,2,3,4-tetrahydroquinolin-4-amine (3.69b)

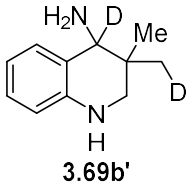


3.69b

Following general procedure 3.1 using 2-((2-methylallyl)amino) benzonitrile (**3.68b**). Yield: 48.0 mg, 0.272 mmol, 89%. Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 7.6 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.65 (td, *J* = 7.4, 1.2 Hz, 1H), 6.48 (dd, *J* = 8.0, 1.1 Hz, 1H), 3.96 (s, 1H), 3.49 (s, 1H), 3.17 (d, *J* = 11.3 Hz, 1H), 2.85 (d, *J* = 10.9 Hz, 1H), 1.42 (s, 2H), 0.98 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 129.4, 127.9, 124.6, 116.9, 113.7, 57.2, 49.3, 32.3, 25.1, 21.8; **IR** (thin film): 3407, 3302, 3019, 2953, 2925, 2866, 1607, 1583, 1499, 1460, 1386, 1360, 1349, 1324, 1303, 1265, 1181, 1154, 1113, 1083, 1033, 1011, 920, 847, 743, 707, 632, 532, 494, 464, 410 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{11}H_{16}N_2$ $[M]^+$ 176.1308, found 176.1305.

3-Methyl-3-(methyl-d)-1,2,3,4-tetrahydroquinolin-4-d-4-amine (3.69b')

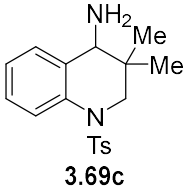


3.69b'

Following general procedure 3.1 using 2-((2-methylallyl)amino) benzonitrile (**3.68b**) and $NaBD_4$ (5 equiv.) instead of $NaBH_4$. Yield: 48.7 mg, 0.172 mmol, 58%. Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 6.65 (td, *J* = 7.4, 1.2 Hz, 1H), 6.48 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.95 (s, 1H), 3.49 (s, 0.02H), 3.17 (d, *J* = 11.4 Hz, 1H), 2.85 (d, *J* = 11.3 Hz, 1H), 1.56 – 1.35 (m, 2H), 1.00 – 0.91 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2, 129.4, 127.9, 124.5, 116.9, 113.7, 56.7 (t, *J* = 20.7 Hz), 49.3, 32.1, 25.0, 24.8 (t, *J* = 19.2 Hz), 21.8, 21.5 (t, *J* = 19.2 Hz); **IR** (thin film): 3407, 3303, 3051, 3019, 2952, 2924, 2853, 2164, 2105, 1607, 1582, 1499, 1458, 1336, 1376, 1349, 1314, 1271, 1211, 1154, 1135, 1110, 1079, 1018, 988, 928, 847, 745, 719, 699, 529, 496, 429, 412 cm^{-1}; **HRMS** (EI): exact mass calculated for sum $C_{11}H_{14}D_2N_2$ $[M]^+$ 178.1434, found 178.1432.

3,3-Dimethyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-amine (3.69c)

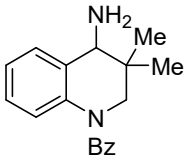


3.69c

Following general procedure 3.1 using *N*-(2-cyanophenyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (**3.68c**), the reaction mixture was diluted with CH_2Cl_2 (1 mL). Yield: 48.5 mg, 0.147 mmol, 49%. Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 8.4 Hz, 3H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.10 (m, 1H), 7.01 (dd, *J* = 7.4, 1.2 Hz, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.62 (dd, *J* = 12.0, 0.7 Hz, 1H), 3.37 (s, 1H), 2.37 (s, 3H), 1.30 (s, 2H), 0.95 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8, 136.8, 135.6, 131.0, 129.8, 129.1, 127.7, 127.0, 123.5, 120.0, 57.4, 53.8, 34.1, 25.0, 21.6, 21.3; **IR** (thin film): 3390, 3032, 2962, 2927, 2871, 1599, 1578, 1487, 1452, 1395, 1342, 1306, 1237, 1185, 1159, 1120, 1089, 1044, 1018, 1002, 943, 888, 811, 753, 729, 705, 657, 635, 609, 573 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{18}H_{22}N_2NaO_2S$ $[M+Na]^+$ 353.1294, found 353.1292.

(4-Amino-3,3-dimethyl-3,4-dihydroquinolin-1(2*H*)-yl)(phenyl)methanone (3.69d)

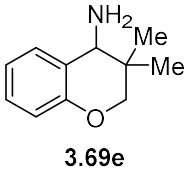


3.69d

Following general procedure 3.1 using *N*-(2-cyanophenyl)-N-(2-methylallyl)benzamide (**3.68d**), the reaction mixture was diluted with CH_2Cl_2 (1 mL). Yield: 68.0 mg, 0.243 mmol, 81%. Appearance: yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 3H), 7.42 – 7.37 (m, 1H), 7.36 – 7.30 (m, 2H), 7.11 – 6.96 (m, 3H), 3.74 (d, *J* = 12.8 Hz, 1H), 3.67 (s, 1H), 3.59 (d, *J* = 12.8 Hz, 1H), 1.49 (s, 2H), 1.01 (s, 3H), 0.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 137.3, 136.5, 132.7, 130.5, 128.6, 128.4, 128.4, 126.6, 124.7, 124.5, 57.7, 54.7, 35.7, 25.4, 21.0; **IR** (thin film): 3383, 3316, 3061, 2960, 2870, 1639, 1600, 1576, 1488, 1447, 1374, 1325, 1288, 1216, 1178, 1146, 1115, 1071, 1026, 1012, 984, 920, 852, 792, 760, 727, 700, 659, 602, 564, 497 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{18}H_{20}N_2NaO$ $[M+Na]^+$ 303.1468, found 303.1467.

3,3-Dimethylchroman-4-amine (3.69e)

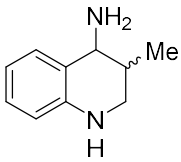


3.69e

Following general procedure 3.1 using 2-((2-methylallyl)oxy) benzonitrile (**3.68e**). Yield: 21.2 mg, 0.120 mmol, 40%. Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 1H), 7.18 – 7.11 (m, 1H), 6.91 (td, *J* = 7.4, 1.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.74 (dd, *J* = 10.8, 0.7 Hz, 1H), 3.60 (s, 1H), 1.49 (s, 2H), 0.98 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 129.2, 128.4, 126.1, 120.7, 116.4, 72.9, 55.4, 33.0, 23.6, 19.2; **IR** (thin film): 3388. 3036, 2957, 2869, 1608, 1582, 1485, 1465, 1450, 1394, 1365, 1347, 1323, 1307, 1288, 1264, 1228, 1183, 1150, 1111, 1046, 1024, 990, 926, 916, 828, 751, 708, 656, 628, 563, 547, 531, 508, 492, 469 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{11}H_{16}NO$ $[M+H]^+$ 178.1226, found 178.1224.

cis/*trans*-3-Methyl-1,2,3,4-tetrahydroquinolin-4-amine (3.69f)



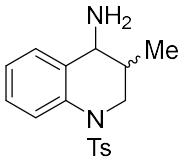
3.69f

Following general procedure 3.1 using 2-(allylamino)benzonitrile (**3.68f**). Yield: 28.0 mg, 0.173 mmol, 58%, d.r. = 1.5:1. Appearance: colorless oil.

Note: *Analytical data represents a 1.5:1 mixture of diastereomers. ^{1}H and ^{13}C NMR signals of the minor isomer are labeled with an asterisk.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.24 (m, 1H*), 7.15 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.06 – 6.98 (m, 1H, 1H*), 6.70 – 6.61 (m, 1H, 1H*), 6.52 – 6.45 (m, 1H, 1H*), 3.84 (d, *J* = 3.7 Hz, 1H), 3.56 (d, *J* = 5.3 Hz, 1H*), 3.40 (dd, *J* = 11.5, 3.5 Hz, 1H*), 3.21 – 3.07 (m, 2H), 2.99 (dd, *J* = 11.5, 6.0 Hz, 1H*), 2.11 – 1.98 (m, 1H), 1.89 – 1.78 (m, 1H*), 1.68 (s, 2H, 2H*), 1.05 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7*, 143.7, 129.5, 129.4*, 128.1, 127.9*, 125.2, 124.1*, 117.2*, 116.9, 114.1*, 114.1, 53.8*, 51.5, 44.1*, 43.2, 34.9*, 32.2, 16.7*, 14.4; **IR** (thin film): 3294, 3019, 2957, 2906, 2871, 1608, 1582, 1498, 1456, 1373, 1353, 1321, 1272, 1154, 1123, 1084, 1065, 1032, 1007, 927, 902, 849, 745, 627, 524, 507, 496, 486, 452, 433, 420, 415, 408, 403 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{10}H_{14}N_2Na$ $[M+Na]^+$ 185.1049, found 185.1044.

cis/*trans*-3-Methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-amine (3.69g)



3.69g

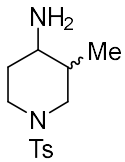
Following general procedure 3.1 using *N*-allyl-*N*-(2-cyanophenyl)-4-methylbenzenesulfonamide (**3.68g**), the reaction mixture was diluted with CH_2Cl_2 (1 mL). Yield: 40.0 mg, 0.126 mmol, 42%, d.r. = 1.7:1. Appearance: colorless oil.

Note: *Analytical data represents a 1.7:1 mixture of diastereomers. ^{1}H and ^{13}C NMR signals of the minor isomer are labeled with an asterisk.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.88 (m, 1H*), 7.76 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.58 – 7.53 (m, 2H, 2H*), 7.42 – 7.38 (m, 1H), 7.27 – 7.19 (m, 3H, 4H*), 7.15 (td, *J* = 7.5, 1.3 Hz, 1H), 7.12 – 7.07 (m, 1H*), 4.07 (dd, *J* = 13.3, 4.2 Hz,

1H), 3.95 (ddd, *J* = 12.6, 4.3, 1.0 Hz, 1H*), 3.63 (d, *J* = 3.6 Hz, 1H*), 3.49 – 3.34 (m, 1H, 1H*), 3.24 (d, *J* = 8.0 Hz, 1H), 2.40 (d, *J* = 0.8 Hz, 3H), 2.38 (d, *J* = 0.8 Hz, 3H*), 1.94 – 1.79 (m, 1H*), 1.60 – 1.45 (m, 1H), 1.13 (s, 2H, 2H*), 1.01 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7*, 143.7, 136.7, 136.0, 135.9*, 135.5*, 133.8, 133.2*, 129.6 (C, C*), 129.0,* 128.0, 127.9*, 127.4, 127.1, 127.1*, 124.9, 124.3*, 123.4, 122.8*, 54.5, 51.5*, 51.0, 47.5*, 36.2, 32.4*, 21.6, 21.6*, 16.7, 14.2*; **IR** (thin film): 3382, 3065, 2961, 2927, 2874, 1598, 1578, 1485, 1450, 1343, 1305, 1290, 1227, 1185, 1158, 1120, 1089, 1066, 1039, 1017, 969, 909, 886, 813, 757, 733, 711, 672, 660, 628, 574, 543, 495 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{17}H_{20}N_2NaO_2S$ $[M+Na]^+$ 339.1138, found 339.1138.

cis/*trans*-3-Methyl-1-tosylpiperidin-4-amine (3.69h)



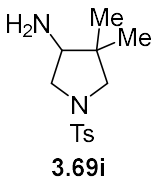
3.69h

Following general procedure 3.1 using *N*-allyl-*N*-(2-cyanoethyl)-4-methylbenzenesulfonamide (**3.68h**). Yield: 28.7 mg, 0.107 mmol, 36%, d.r. = 1:1. Appearance: colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 4H), 7.34 – 7.27 (m, 4H), 3.79 – 3.71 (m, 1H), 3.68 – 3.61 (m, 1H), 3.10 – 2.79 (m, 5H), 2.42 (s, 6H), 2.29 (td, *J* = 12.0, 2.8 Hz, 1H), 2.13 (ddd, *J* = 11.0, 9.6, 4.1 Hz, 1H), 1.98 – 1.72 (m, 4H), 1.62 (dtd, *J* = 13.4, 6.6, 3.7 Hz, 1H), 1.53 – 1.41 (m, 2H), 1.28 – 1.17 (m, 4H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 143.5, 133.4, 133.2, 129.7, 129.7, 127.8, 127.7, 54.5, 51.7, 48.7, 48.6, 45.9, 42.6, 39.1, 34.7, 34.5, 31.6, 21.7, 21.6, 15.7, 13.2; **IR** (thin film): 3373, 2923, 2852, 1597, 1494, 1464, 1335, 1304, 1289, 1252, 1215, 1184, 1157, 1102, 1088, 1055, 1018, 990, 956, 918, 881, 815, 802, 784, 747, 727, 708, 678, 656, 635, 605, 580, 548, 513, 494, 475, 435, 411, 406 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{21}N_2O_2S$ $[M+H]^+$ 269.1318, found 269.1317.

4,4-Dimethyl-1-tosylpyrrolidin-3-amine (3.69i)

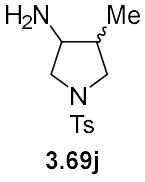


3.69i

Following general procedure 3.1 using *N*-(cyanomethyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (**3.68i**). Yield: 54.5 mg, 0.203 mmol, 68%. Appearance: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2H), 7.33 – 7.28 (m, 2H), 3.55 (dd, *J* = 9.4, 6.4 Hz, 1H), 3.18 (d, *J* = 9.7 Hz, 1H), 2.97 (d, *J* = 9.7 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.41 (s, 3H), 1.03 (s, 2H), 0.88 (s, 3H), 0.76 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 134.1, 129.7, 127.5, 59.5, 59.2, 53.9, 41.1, 24.5, 21.7, 19.2; **IR** (thin film): 3383, 2960, 2875, 1597, 1493, 1465, 1390, 1370, 1337, 1305, 1289, 1156, 1094, 1063, 1016, 932, 811, 708, 663, 634 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{20}N_2NaO_2S$ $[M+Na]^+$ 291.1138, found 291.1140.

4-Methyl-1-tosylpyrrolidin-3-amine (3.69j)



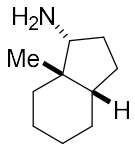
3.69j

Following general procedure 3.1 using *N*-allyl-*N*-(cyanomethyl)-4-methylbenzenesulfonamide (**3.68j**). Yield: 46.3 mg, 0.182 mmol, 61%, d.r. = 2:1. Appearance: colorless crystals.

Note: *Analytical data represents a 2:1 mixture of diastereomers. ^{1}H and ^{13}C NMR signals of the minor isomer are labeled with an asterisk.*

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H, 2H*), 7.31 (ddt, *J* = 7.8, 1.2, 0.7 Hz, 2H, 2H*), 3.58 – 3.50 (m, 2H), 3.45 – 3.36 (m, 2H*), 3.30 (td, *J* = 5.3, 3.4 Hz, 1H*), 3.08 (dd, *J* = 10.3, 3.4 Hz, 1H*), 2.96 (dd, *J* = 9.8, 8.4 Hz, 1H*), 2.88 (d, *J* = 7.1 Hz, 1H), 2.87 – 2.80 (m, 2H), 2.42 (s, 3H), 2.42 (s, 3H*), 2.14 – 2.03 (m, 1H*), 1.77 – 1.66 (m, 1H), 1.20 (s, 2H, 2H*), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.5, 143.4*, 134.0*, 133.8, 129.7, 129.7*, 127.5, 127.5*, 57.8, 55.7*, 55.3, 53.8*, 53.6, 52.3*, 41.9, 37.5*, 21.6 (C, C*), 15.6; 11.6*; **IR** (thin film): 3375, 2960, 2876, 1597, 1494, 1454, 1398, 1380, 1335, 1304, 1289, 1154, 1091, 1040, 1016, 994, 913, 864, 812, 784, 729, 708, 661 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{12}H_{19}N_2O_2S$ $[M+H]^+$ 255.1162, found 255.1158.

rac-(1*R*,3a*S*,7a*S*)-7a-Methyloctahydro-1H-inden-1-amine (3.69k)

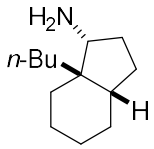


3.69k

Following general procedure 3.1 using 3-(2-methylenecyclohexyl) propanenitrile (**3.68k**). Yield: 37.1 mg, 0.242 mmol, 81%. Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 – 2.72 (m, 3H), 2.07 – 1.94 (m, 1H), 1.69 – 1.22 (m, 10H), 1.18 – 1.07 (m, 2H), 0.99 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 64.1, 43.2, 41.5, 29.9, 25.9, 24.6, 23.7, 22.3, 21.6, 20.7; **IR** (thin film): 3372, 2923, 2859, 1611, 1555, 1461, 1381, 1369, 1357, 1333, 1297, 1226, 1176, 1153, 1114, 1061, 1024, 1003, 974, 961, 935, 895, 871, 846, 813, 792, 733, 693, 658, 594, 511, 497, 476, 459, 407 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{10}H_{20}N$ $[M+H]^+$ 154.1590, found 154.1588.

rac-(1*R*,3a*S*,7a*S*)-7a-Butyloctahydro-1H-inden-1-amine (3.69l)



3.69l

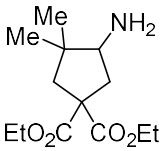
Following general procedure 3.1 using (*E*/*Z*)-3-(2-Butylidenecyclo-hexyl)propanenitrile (**3.68l**). Yield: 42.2 mg, 0.216 mmol, 72%. Appearance: colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (t, *J* = 9.1 Hz, 1H), 2.73 (s, 2H), 2.06 – 1.93 (m, 1H), 1.81 – 1.72 (m, 1H), 1.70 – 1.59 (m, 1H), 1.56 – 1.10 (m, 16H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.6, 43.5, 39.8, 33.3, 30.2, 25.8, 25.4, 24.4, 23.9, 23.7, 21.3, 20.5, 14.3; **IR** (thin film): 2924, 2857, 1571, 1456, 1377, 1360, 1288, 1265, 1171, 1151, 1066, 1026, 947, 909, 815, 794, 725, 694, 583, 518, 493, 418 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{26}N$ $[M+H]^+$ 196.2060, found 196.2055.

General Procedure 3.2:

To a solution of nitrile **3.68** (0.300 mmol) in EtOH (3 mL) in a Schlenk tube was added $Mn(dpm)_3$ (91.0 or 136 mg, 0.150 or 0.225 mmol, 50 or 75 mol%) followed by $NaBH_4$ (34.0 mg, 0.900 mmol, 3.0 equiv.). The tube was evacuated and back-filled with N_2 (5x) and the mixture was stirred at r.t. for 10 min. $Na_2EDTA \cdot H_2O$ (300 mg) was added followed by 1 M aq HCl (6 mL). The mixture was stirred at r.t. for 2 min, poured into 2 M aq K_2CO_2 (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica.

Diethyl 4-amino-3,3-dimethylcyclopentane-1,1-dicarboxylate (3.69m)

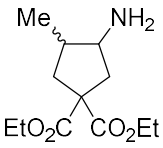


3.69m

Following general procedure 3.3 using diethyl 2-(cyanomethyl)-2-(2-methylallyl)malonate (**3.68m**) and 50 mol% $Mn(dpm)_3$. Yield: 73.3 mg, 0.285 mmol, 95%. Appearance: yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 – 4.13 (m, 4H), 2.90 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.56 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.30 (d, *J* = 14.0 Hz, 1H), 2.10 – 2.01 (m, 2H), 1.27 – 1.19 (m, 8H), 0.99 (s, 3H), 0.83 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.0, 172.7, 61.5, 61.5, 61.0, 55.9, 46.2, 41.5, 41.3, 27.0, 20.8, 14.0; **IR** (thin film): 3382, 2960, 2872, 1725, 1612, 1465, 1446, 1388, 1366, 1296, 1251, 1217, 1176, 1155, 1132, 1095, 1065, 1017, 861, 802, 704, 664, 557, 514, 444, 437, 419, 408 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{24}NO_4$ $[M+H]^+$ 258.1700, found 258.1697.

***cis*/*trans*-Diethyl 3-amino-4-methylcyclopentane-1,1-dicarboxylate (3.69n)**



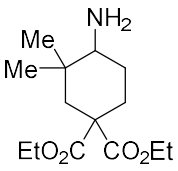
3.69n

Following general procedure 3.3 using diethyl 2-allyl-2-(cyanomethyl)malonate (**3.68n**) and 50 mol% $Mn(dpm)_3$. Yield: 64.3 mg, 0.264 mmol, 88%, d.r. = 7:1. Appearance: colorless oil.

Note: *Analytical data represents a 7:1 mixture of diastereomers.* ^{1}*H NMR signals of the minor isomer are labeled with an asterisk.* ^{13}*C NMR data corresponds to the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 – 4.10 (m, 4H, 4H*), 3.35 – 3.27 (m, 1H*), 2.75 (td, *J* = 9.2, 7.2 Hz, 1H), 2.62 (dd, *J* = 13.5, 7.3 Hz, 1H), 2.53 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.46 (dd, *J* = 14.2, 5.9 Hz, 1H*), 2.38 – 2.28 (m, 1H*), 2.15 (dd, *J* = 14.1, 3.5 Hz, 1H*), 2.10 – 2.00 (m, 2H*), 1.87 (dd, *J* = 13.5, 9.3 Hz, 1H), 1.72 (dd, *J* = 13.5, 11.1 Hz, 1H), 1.65 – 1.52 (m, 1H), 1.34 (s, 2H, 2H*), 1.26 – 1.19 (m, 6H, 6H*), 1.02 (d, *J* = 6.5 Hz, 3H), 0.99 – 0.95 (m, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 172.7, 61.6, 61.5, 59.5, 56.9, 43.3, 43.0, 40.6, 17.0, 14.2; **IR** (thin film): 3373, 2979, 2873, 1723, 1595, 1446, 1388, 1366, 1296, 1251, 1181, 1147, 1114, 1096, 1069, 1050, 1025, 909, 859, 707, 543, 499 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{12}H_{22}NO_4$ $[M+H]^+$ 244.1543, found 244.1543.

Diethyl 4-amino-3,3-dimethylcyclohexane-1,1-dicarboxylate (3.69o)

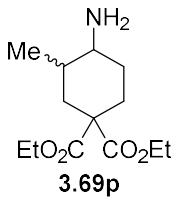


3.69o

Following general procedure 3.3 using diethyl 2-(2-cyanoethyl)-2-(2-methylallyl)malonate (**3.68o**). Yield: 43.4 mg, 0.160 mmol, 53%. Appearance: yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.01 (m, 4H), 2.48 – 2.42 (m, 1H), 2.38 – 2.29 (m, 1H), 2.15 (dd, *J* = 14.3, 2.4 Hz, 1H), 1.83 (d, *J* = 14.3 Hz, 1H), 1.70 – 1.48 (m, 3H), 1.40 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 3H), 0.71 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 172.0, 61.5, 61.2, 57.5, 53.2, 42.5, 34.8, 30.5, 29.6, 28.5, 19.2, 14.1, 14.0; **IR** (thin film): 3381, 2978, 2950, 2871, 1725, 1591, 1447, 1389, 1366, 1280, 1224, 1178, 1146, 1094, 1064, 1028, 966, 952, 862, 849, 690, 613, 567, 498, 486 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{14}H_{26}NO_4$ $[M+H]^+$ 272.1856, found 272.1856.

***cis*/*trans*-diethyl 4-amino-3-methylcyclohexane-1,1-dicarboxylate (3.69p)**



3.69p

Following general procedure 3.3 using diethyl 2-allyl-2-(2-cyanoethyl)malonate (**3.68p**). Yield: 53.4 mg, 0.208 mmol, 69%, d.r. = 3:1. Appearance: colorless oil.

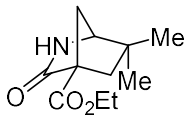
Note: *Analytical data represents a 3:1 mixture of diastereomers.* ^{1}H *and* ^{13}C *NMR signals of the minor isomer are labeled with an asterisk.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.04 (m, 4H, 4H*), 2.90 (q, *J* = 2.8 Hz, 1H*), 2.34 (dq, *J* = 13.5, 3.3 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.11 – 1.84 (m, 3H*), 1.82 – 1.61 (m, 2H, 4H*), 1.53 (s, 2H, 2H*), 1.38 (dd, *J* = 13.3, 12.4 Hz, 1H), 1.31 – 1.16 (m, 8H, 6H*), 0.97 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3*, 172.3, 171.3*, 171.0, 61.4, 61.4*, 61.2, 61.2*, 55.8, 55.2, 55.0*, 49.2*, 38.5, 37.0, 32.4, 32.2*, 32.1*, 30.6, 30.3*, 24.5*, 18.8, 18.4*, 14.1, 14.1*, 14.1; **IR** (thin film): 3376, 2957, 2871, 1725, 1583, 1448, 1388, 1367, 1299, 1239, 1176, 1130, 1096, 1061, 1028, 945, 860, 703, 635, 604, 554, 516 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{13}H_{24}NO_4$ $[M+H]^+$ 258.1700, found 258.1700.

General Procedure 3.3:

To a solution of nitrile **3.68** (0.300 mmol) in EtOH (3 mL) in a Schlenk tube was added $Mn(dpm)_3$ (91.0 mg, 0.150 mmol, 50 mol%) followed by $NaBH_4$ (22.7 mg, 0.600 mmol, 2.0 equiv.). The tube was evacuated and back-filled with N_2 (5x) and the mixture was stirred at r.t. for 29 h. $Na_2EDTA{\cdot}H_2O$ (300 mg) was added followed by 1 M aq HCl (6 mL). The mixture was stirred at r.t. for 2 min, poured into 2 M aq K_2CO_2 (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica.

rac-Ethyl (1*S*,4*S*)-6,6-dimethyl-3-oxo-2-azabicyclo[2.2.1]heptane-4-carboxylate (3.83a)

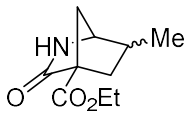


3.83a

Following general procedure 3.3 using diethyl 2-(cyanomethyl)-2-(2-methylallyl)malonate (**3.68m**). Yield: 40.0 mg, 0.189 mmol, 63%. Appearance: colorless solid.

TLC: R_f = 0.46 (hex:EtOAc = 1:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.26 – 4.19 (m, 2H), 3.27 (q, *J* = 1.6 Hz, 1H), 2.26 (dt, *J* = 9.7, 2.0 Hz, 1H), 2.15 (dt, *J* = 9.7, 1.5 Hz, 1H), 1.93 (d, *J* = 12.8 Hz, 1H), 1.64 (dd, *J* = 12.8, 2.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 3H), 1.06 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 169.8, 63.1, 61.3, 60.0, 43.4, 42.2, 41.7, 28.6, 25.8, 14.3; **IR** (thin film): 3243, 2969, 2874, 1733, 1702, 1699, 1473, 1452, 1390, 1369, 1321, 1289, 1263, 1230, 1196, 1165, 1118, 1089, 1073, 1035, 1011, 957, 938, 903, 858, 833, 771, 712, 558, 527, 459, 428, 418, 409, 403 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{11}H_{17}NNaO_3$ $[M+Na]^+$ 234.1101, found 234.1102.

rac-Ethyl (1*S*,4*S*)-6-methyl-3-oxo-2-azabicyclo[2.2.1]heptane-4-carboxylate (3.83b)



3.83b

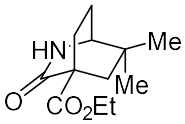
Following general procedure 3.3 using diethyl 2-allyl-2-(cyanomethyl)malonate (**3.68n**). Yield: 16.9 mg, 0.081 mmol, 27%, d.r. = 5:1 along with amine **3.69n** (30.7 mg, 0.156 mmol, 52%, d.r. > 20:1). Appearance: colorless oil.

Note: *Analytical data represents a 5:1 mixture of diastereomers. ^{1}H and ^{13}C NMR signals of the minor isomer are labeled with an asterisk.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H*), 7.15 (s, 1H), 4.29 – 4.16 (m, 2H, 2H*), 3.61 – 3.57 (m, 1H*), 3.49 – 3.44 (m, 1H), 2.39 – 2.31 (m, 2H*), 2.28 (dt, *J* = 9.4, 2.2 Hz, 1H*), 2.19 (dq, *J* = 9.6, 2.0 Hz, 1H), 2.15 – 2.08 (m, 2H), 2.03 – 1.94 (m, 1H*), 1.90 (dt, *J* = 9.7, 1.6 Hz, 1H), 1.83 (dt, *J* = 9.3, 1.4 Hz, 1H*), 1.63 – 1.52 (m, 1H), 1.33 – 1.23 (m, 3H, 3H*), 1.08 – 1.04 (m, 3H), 1.00 – 0.96 (m, 3H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2, 177.1, 170.0, 169.9, 61.3, 61.2, 59.9,

59.2, 59.1, 58.4, 45.6, 40.9, 39.0, 37.1, 35.1, 34.8, 19.8, 16.8, 14.3; **IR** (thin film): 3280, 2964, 2875, 1733, 1698, 1469, 1453, 1395, 1369, 1311, 1273, 1243, 1205, 1185, 1161, 1094, 1077, 1033, 1018, 1001, 942, 926, 901, 887, 859, 841, 780, 766, 741, 707, 530, 480 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{10}H_{15}NNaO_3$ $[M+Na]^+$ 220.0955, found 220.0945.

rac-Ethyl (1*S*,4*S*)-6,6-dimethyl-3-oxo-2-azabicyclo[2.2.2]octane-4-carboxylate (3.83c)

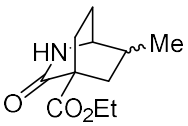


3.83c

Following general procedure 3.3 using diethyl 2-(2-cyanoethyl)-2-(2-methylallyl)malonate (**3.68o**). Yield: 33.8 mg, 0.150 mmol, 50%. Appearance: colorless oil.

TLC: R_f = 0.30 (hex:EtOAc = 1:1); **^{1}H NMR** (400 MHz, CDCl3) δ 7.24 (d, *J* = 3.8 Hz, 1H), 4.26 – 4.17 (m, 2H), 3.09 – 3.03 (m, 1H), 2.28 – 2.17 (m, 1H), 2.09 – 1.99 (m, 2H), 1.80 – 1.66 (m, 2H), 1.57 (d, *J* = 13.5 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6, 171.3, 61.2, 57.9, 51.7, 42.7, 35.0, 29.6, 28.6, 25.2, 24.0, 14.2; **IR** (thin film): 3249, 2961, 2872, 1732, 1674, 1478, 1455, 1433, 1389, 1367, 1344, 1328, 1293, 1253, 1228, 1194, 1176, 1168, 1081, 1056, 1019, 991, 950, 932, 907, 872, 858, 769, 752, 712, 584, 518, 496, 429, 404 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{12}H_{19}NNaO_3$ $[M+Na]^+$ 248.1257, found 248.1256.

rac-Ethyl (1*S*,4*S*)-6-methyl-3-oxo-2-azabicyclo[2.2.2]octane-4-carboxylate (3.83d)



3.83d

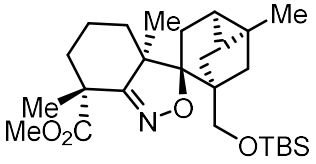
Following general procedure 3.3 using diethyl 2-allyl-2-(2-cyanoethyl)malonate (**3.68p**). Yield: 18.1 mg, 0.086 mmol, 29%, d.r. = 1:1 along with primary amine **3.69p** (23.8 mg, 0.092 mmol, 31%, d.r. = 15:1). Appearance: colorless oil.

Note: *Analytical data represents a 1:1 mixture of diastereomers.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.5 Hz, 1H), 6.86 (d, *J* = 4.5 Hz, 1H), 4.29 – 4.18 (m, 4H), 3.36 – 3.28 (m, 2H), 2.54 (ddd, *J* = 13.4, 11.0, 3.4 Hz, 1H), 2.30 – 2.03 (m, 4H), 1.97 – 1.63 (m, 9H), 1.32 – 1.24 (m, 6H), 1.03 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3, 174.3, 171.4, 171.3, 61.3, 53.6, 52.8, 50.9, 50.9, 36.0, 35.3, 33.5, 32.2, 28.2, 27.2, 25.7, 21.4, 20.6, 19.3, 14.3; **IR** (thin film): 3253, 2959, 2873, 1732, 1673, 1532, 1474, 1452, 1389, 1367, 1348, 1277, 1248, 1227, 1194, 1172, 1157, 1140, 1128, 1089, 1045, 1023, 991, 976, 943, 906, 888, 858, 768, 731 cm^{-1}; **HRMS** (ESI): exact mass calculated for sum $C_{11}H_{17}NNaO_3$ $[M+Na]^+$ 234.1101, found 234.1095.

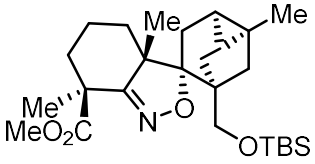
Crystallographic Data

X-Ray Crystallographic Data for a mixture of Compounds **25** and **S6**.

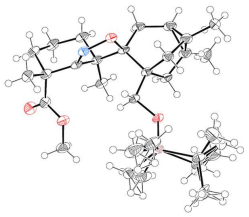


25

+



S6



Identification code	ca020218_1_1
Empirical formula	$C_{26}H_{43}NO_4Si$
Formula weight	461.70
Temperature/K	100.0(1)
Crystal system	triclinic
Space group	P-1
a/Å	6.45095(5)
b/Å	13.03858(10)
c/Å	15.35810(11)
α/°	84.7760(6)
β/°	89.1052(6)
γ/°	84.8033(6)
Volume/Å^3	1281.099(16)
Z	2
ρ_{calc}g/cm^3	1.197
μ/mm^{-1}	1.050
F(000)	504.0
Crystal size/mm^3	0.208 × 0.179 × 0.055
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.836 to 159.174
Index ranges	-8 ≤ h ≤ 8, -16 ≤ k ≤ 16, -19 ≤ l ≤ 19
Reflections collected	48931
Independent reflections	5471 [R_{int} = 0.0381, R_{sigma} = 0.0188]
Data/restraints/parameters	5471/219/369
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.1012
Final R indexes [all data]	R_1 = 0.0407, wR_2 = 0.1029
Largest diff. peak/hole / e Å^{-3}	0.34/-0.29

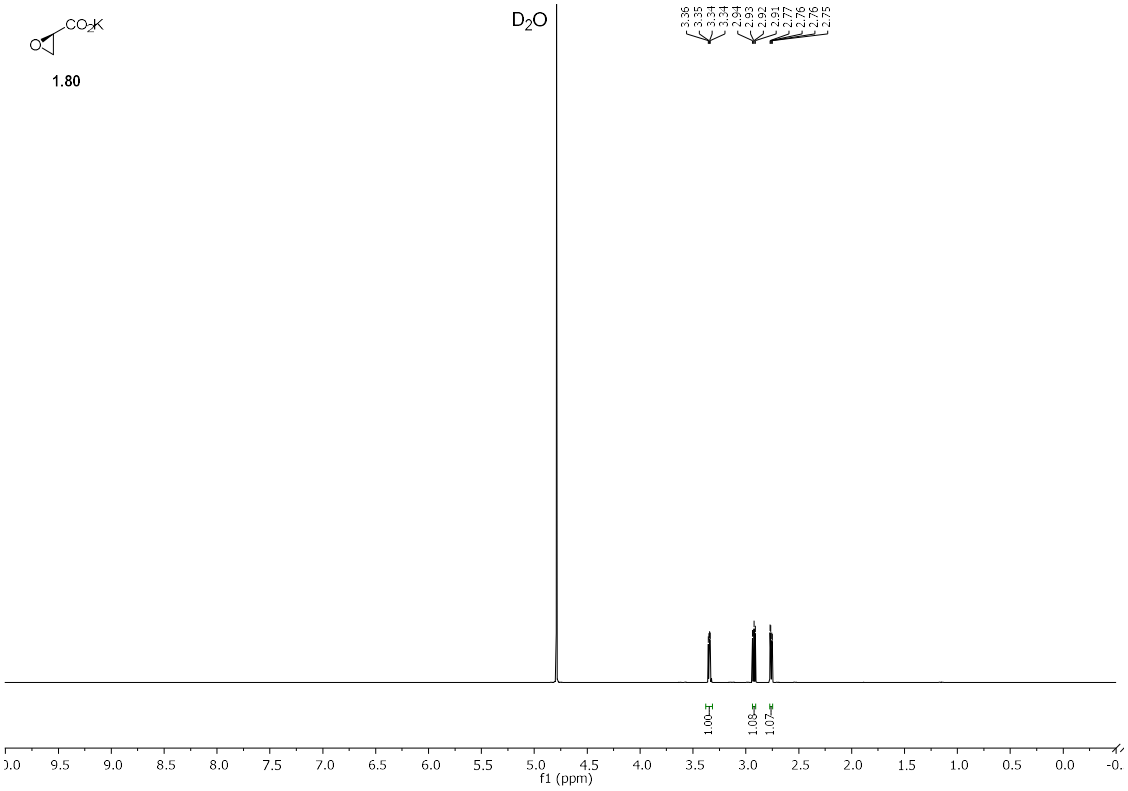
5

NMR Spectra

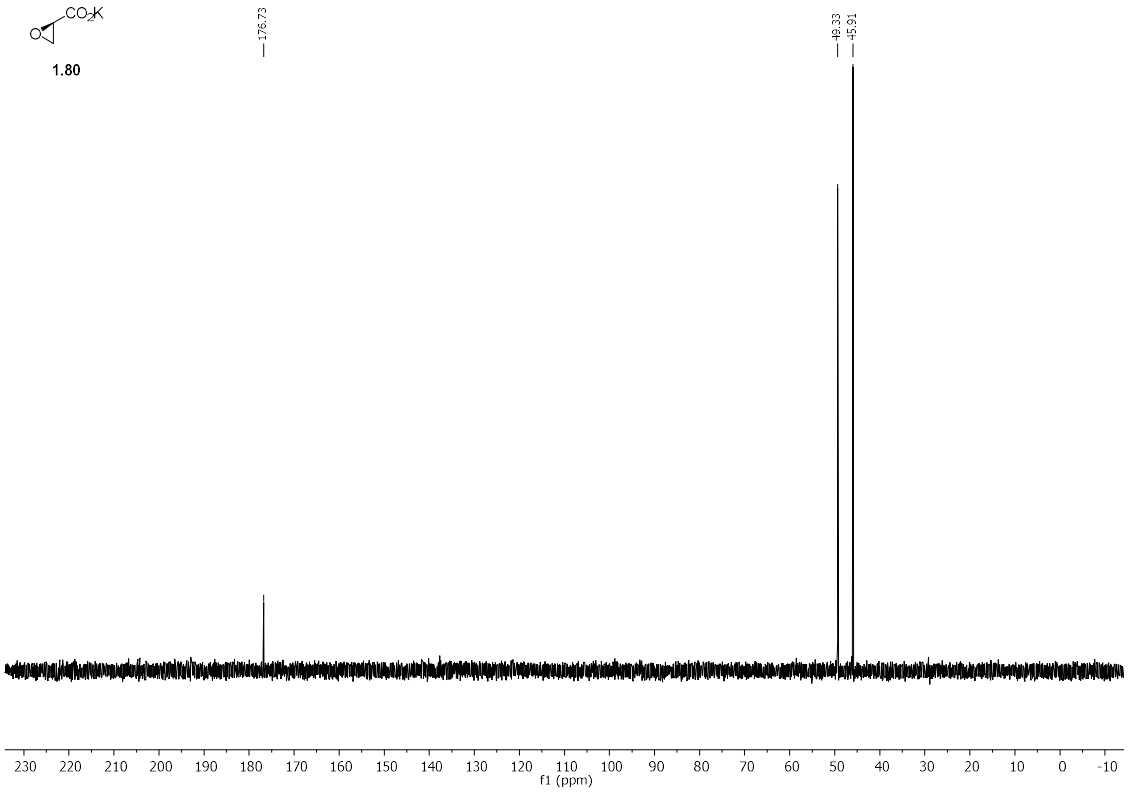
V NMR SPECTRA

1. Total Synthesis of (–)-Mitrephorone A

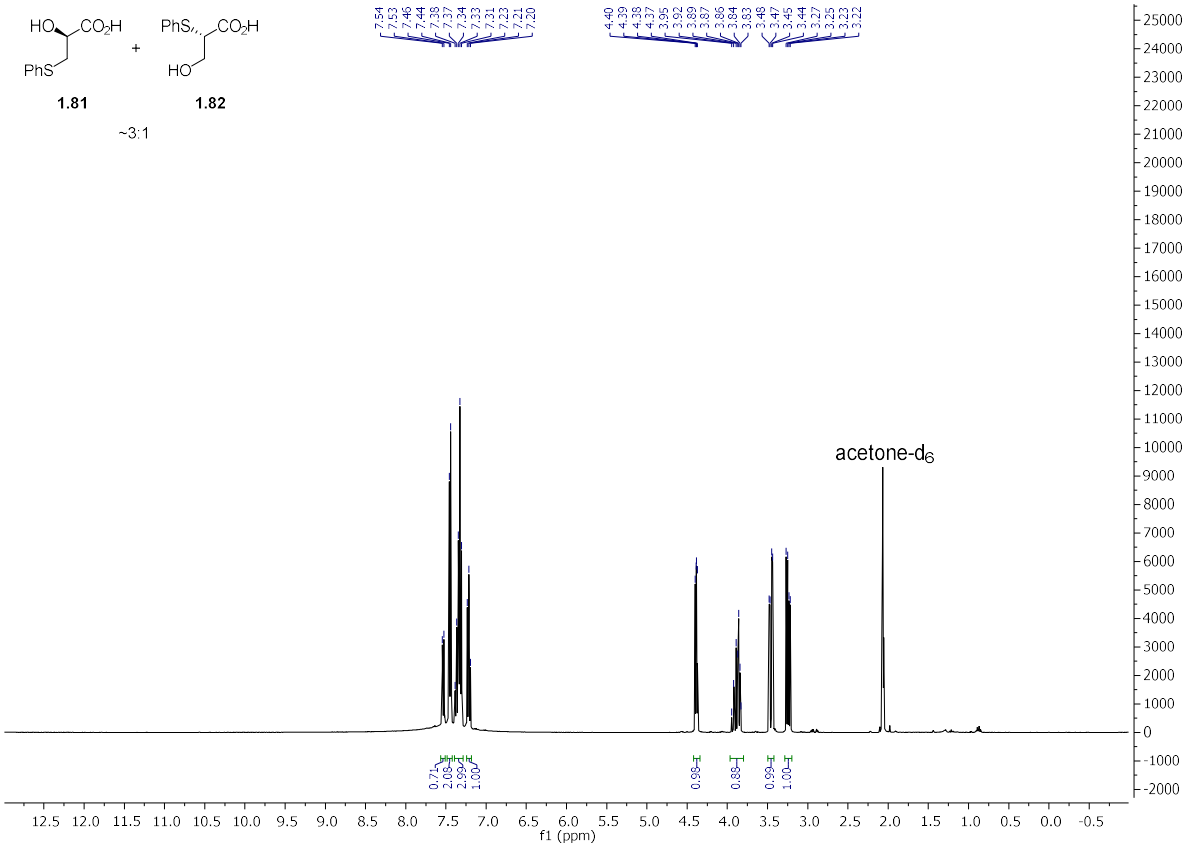
^{1}H NMR (400 MHz, D_2O) of **1.80**



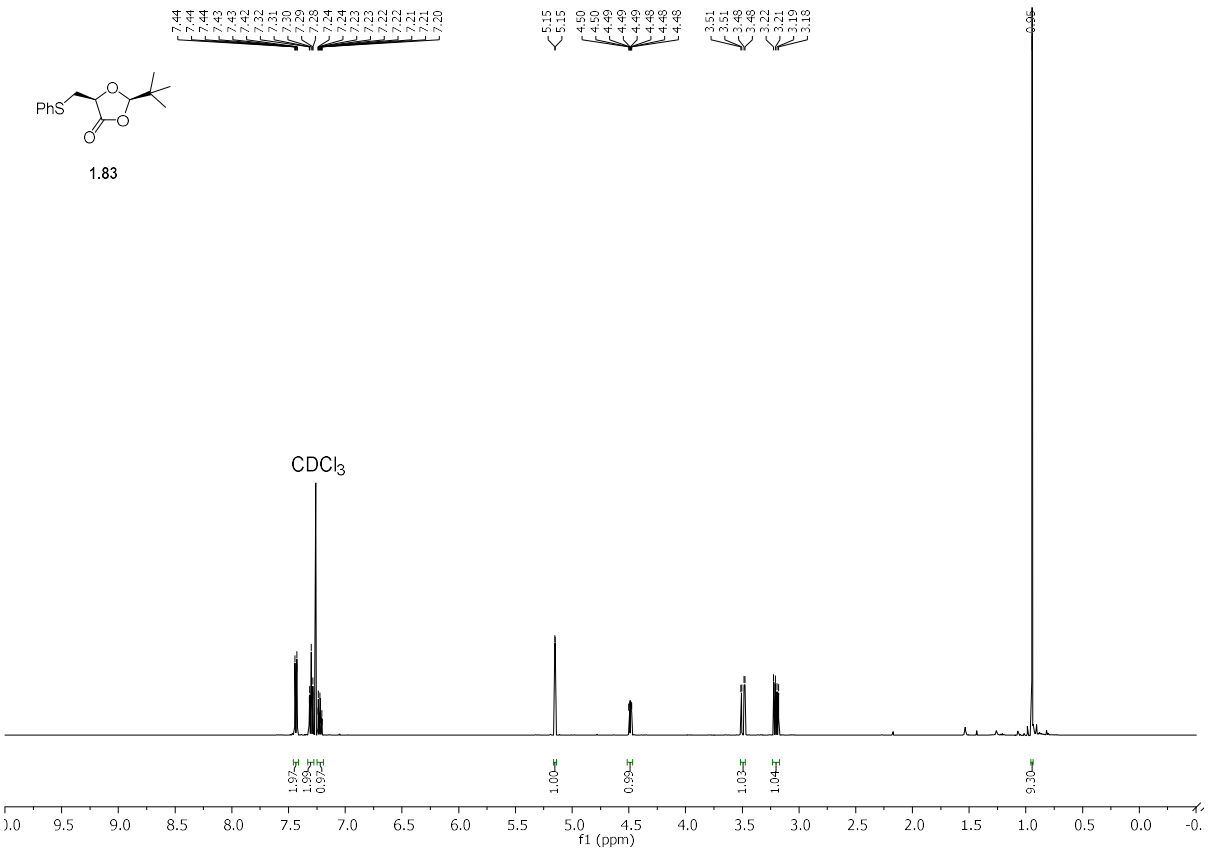
^{13}C NMR (101 MHz, D_2O) of **1.80**



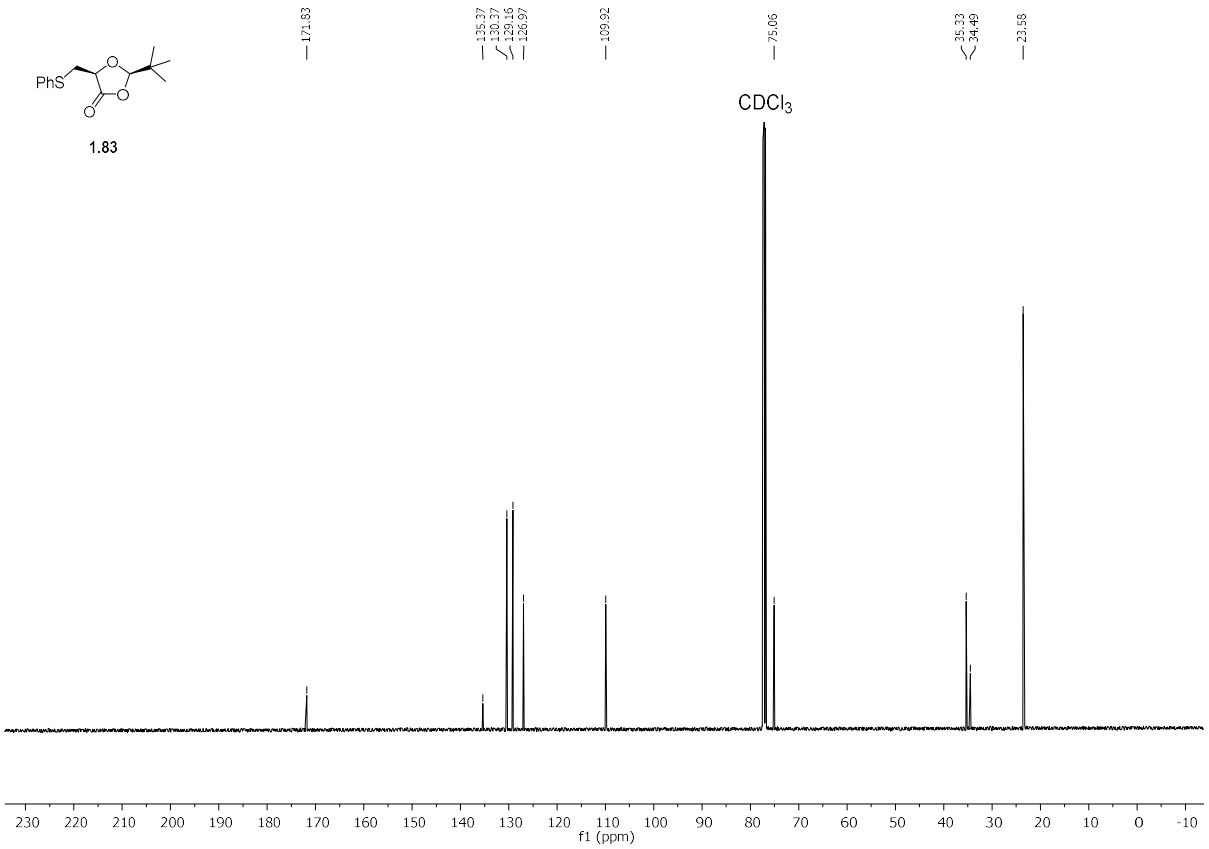
^{1}H NMR (400 MHz, acetone-d_6) of **1.81** and **1.82**



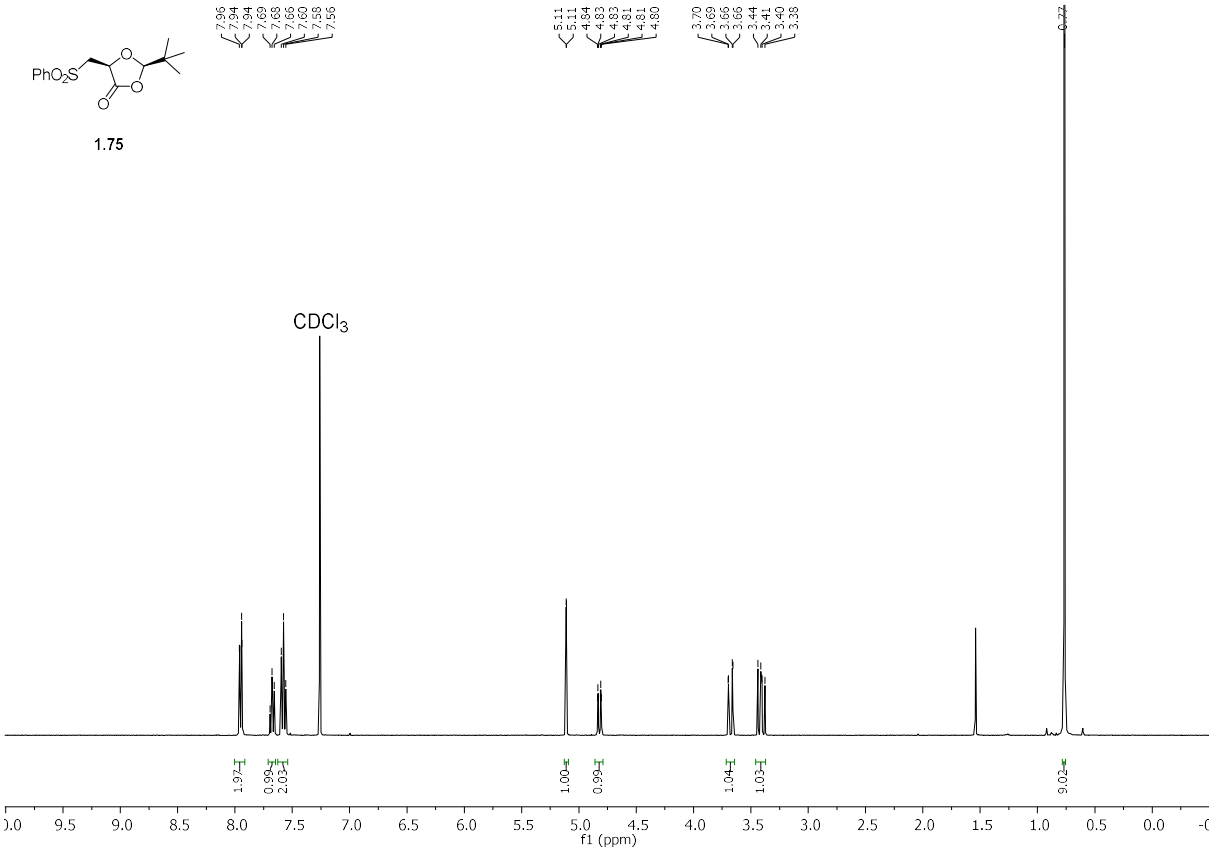
^{1}H NMR (500 MHz, $CDCl_3$) of **1.83**



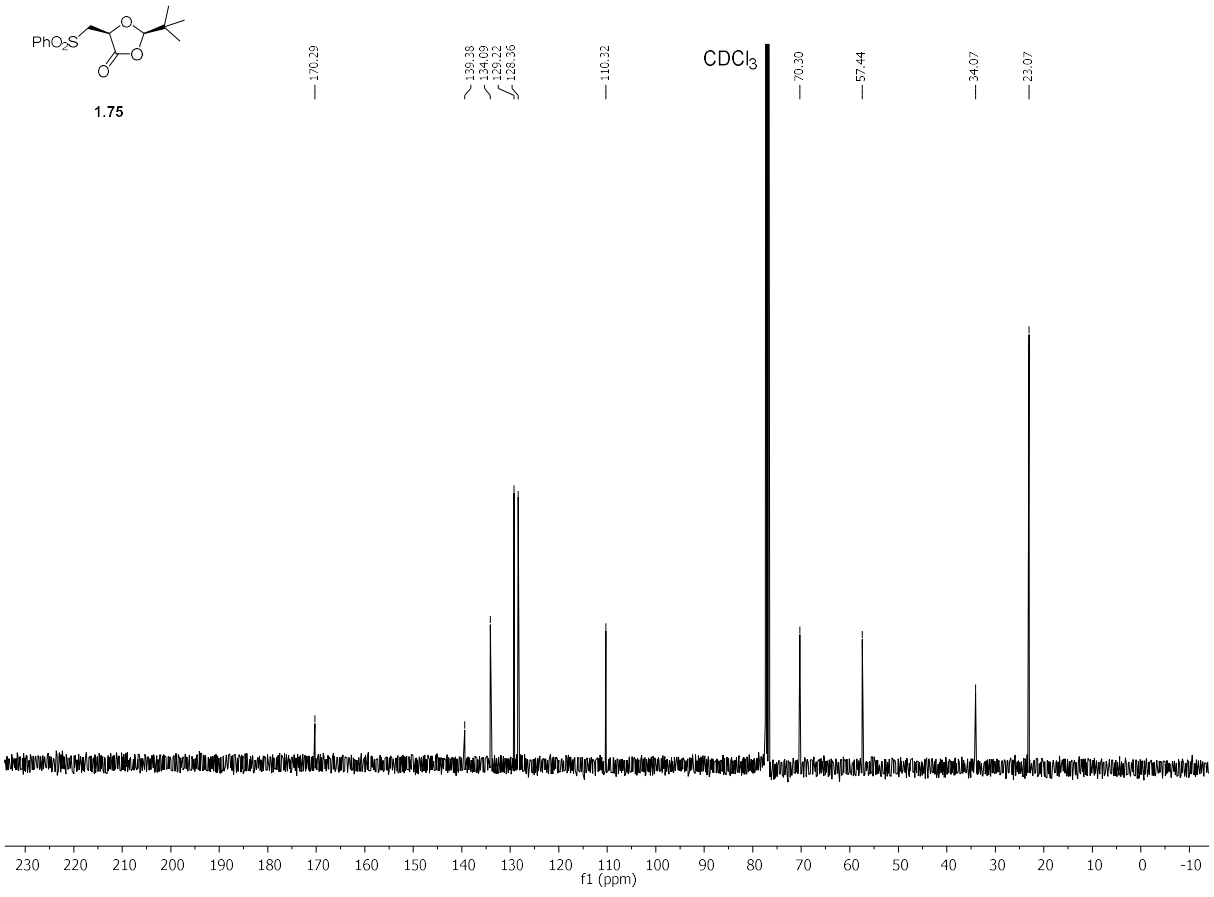
^{13}C NMR (126 MHz, $CDCl_3$) of **1.83**



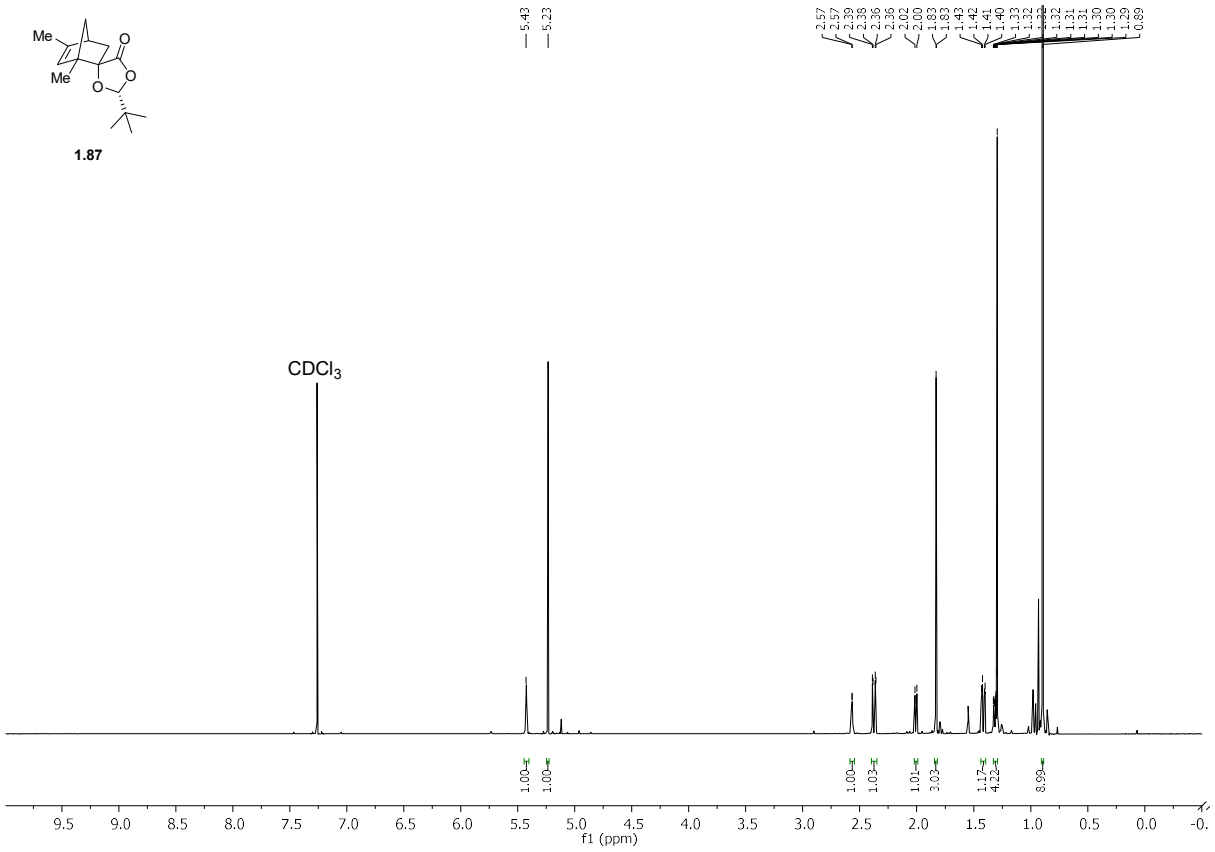
^{1}H NMR (400 MHz, $CDCl_3$) of **1.75**



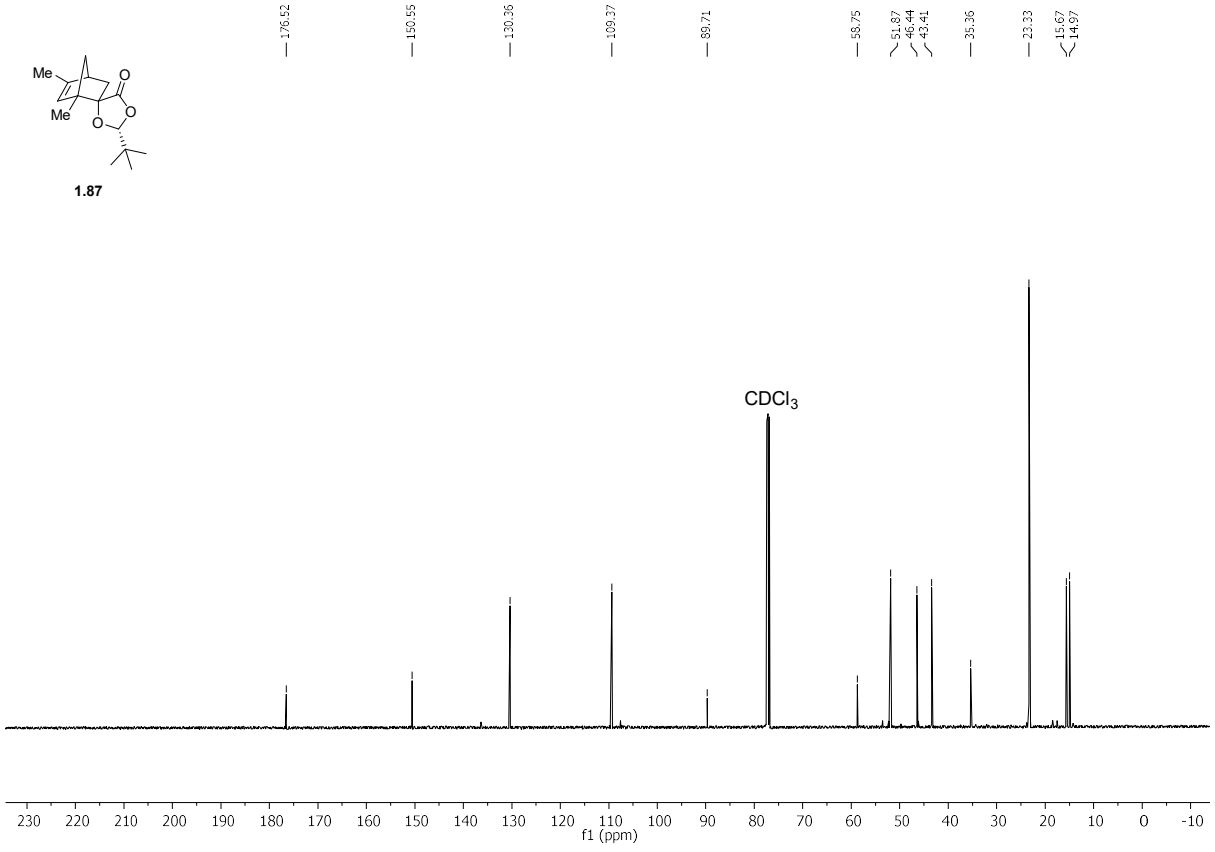
^{13}C NMR (101 MHz, $CDCl_3$) of **1.75**



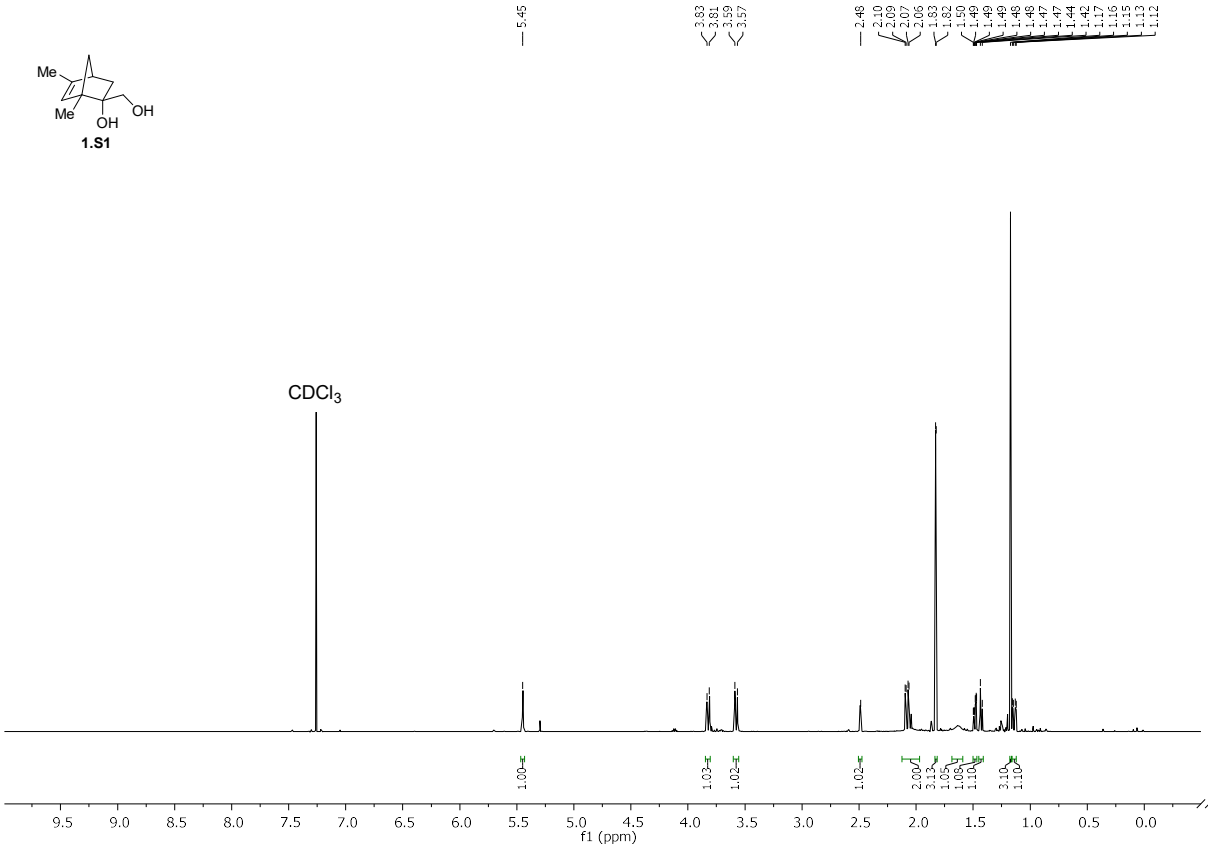
^{1}H NMR (500 MHz, $CDCl_3$) of **1.87**



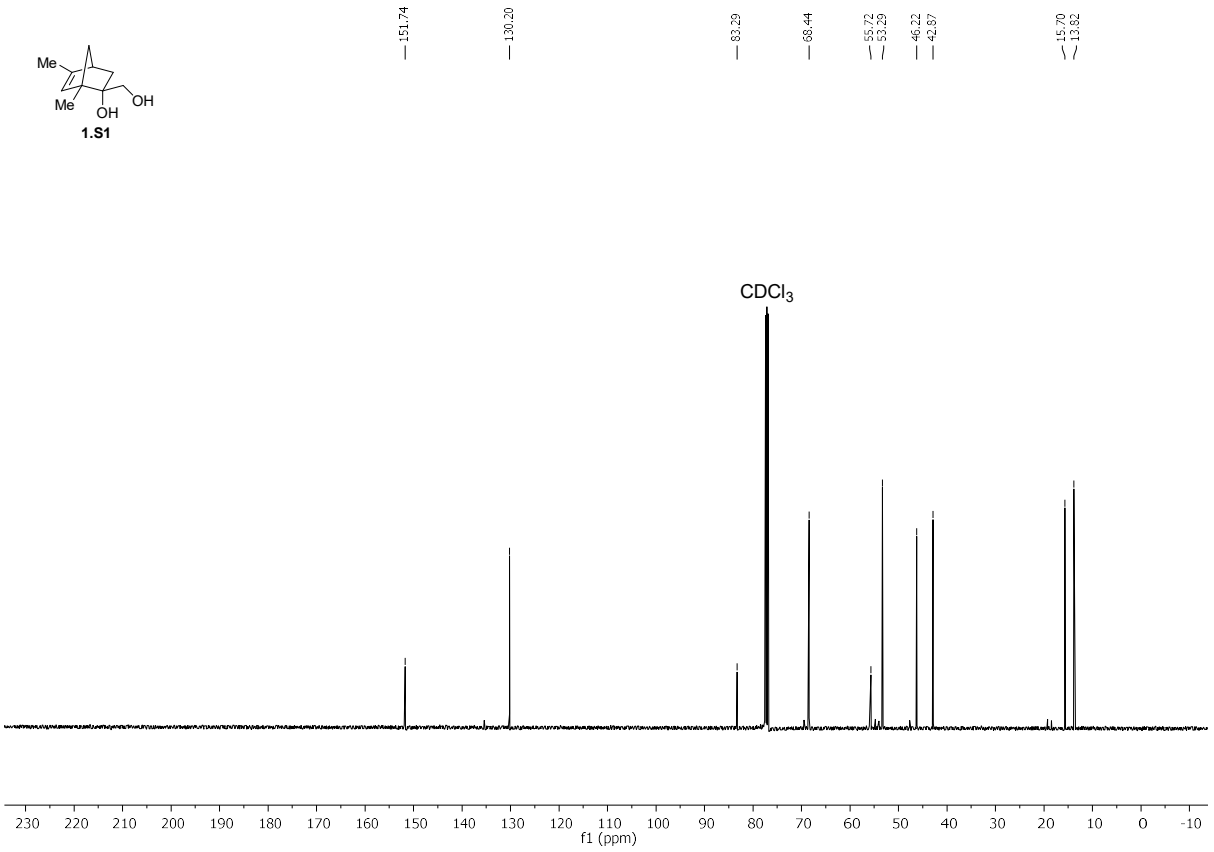
^{13}C NMR (126 MHz, $CDCl_3$) of **1.87**



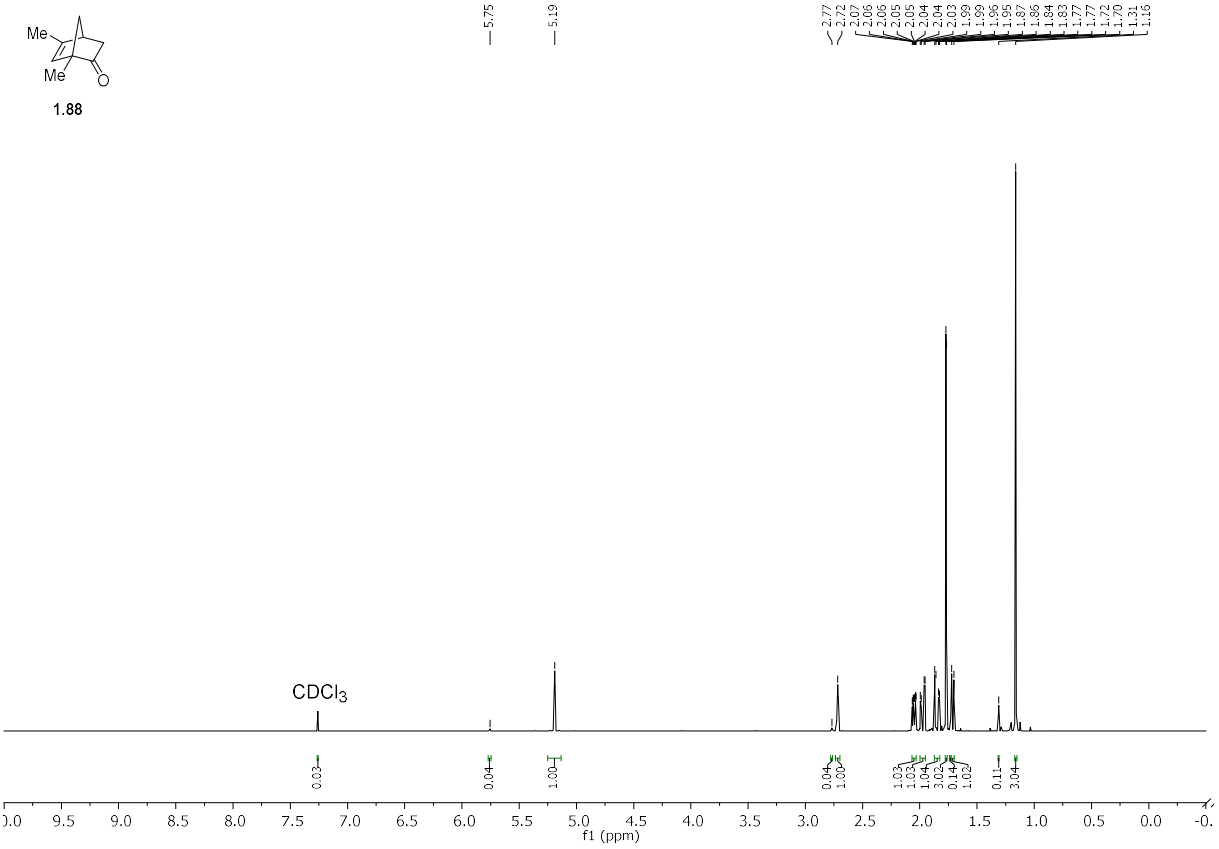
^{1}H NMR (500 MHz, $CDCl_3$) of **1.S1**



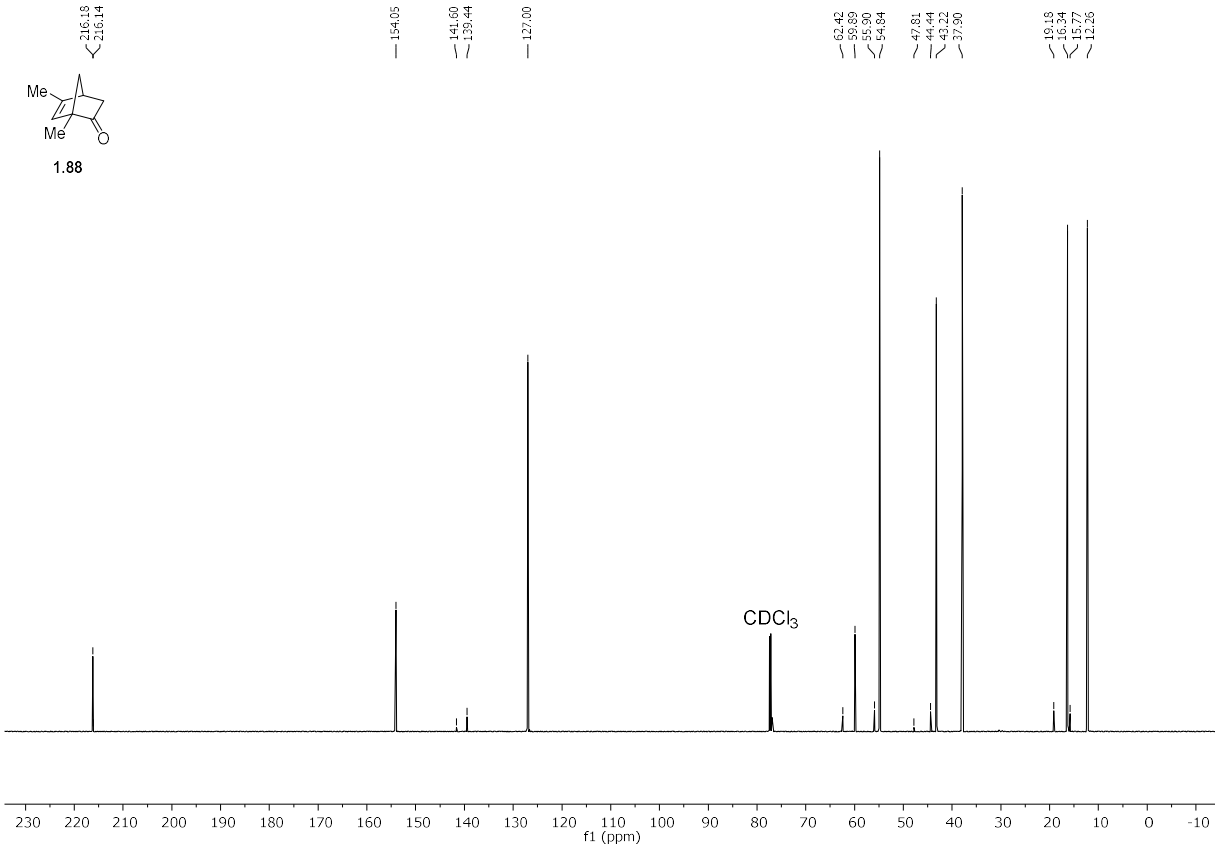
^{13}C NMR (126 MHz, $CDCl_3$) of **1.S1**



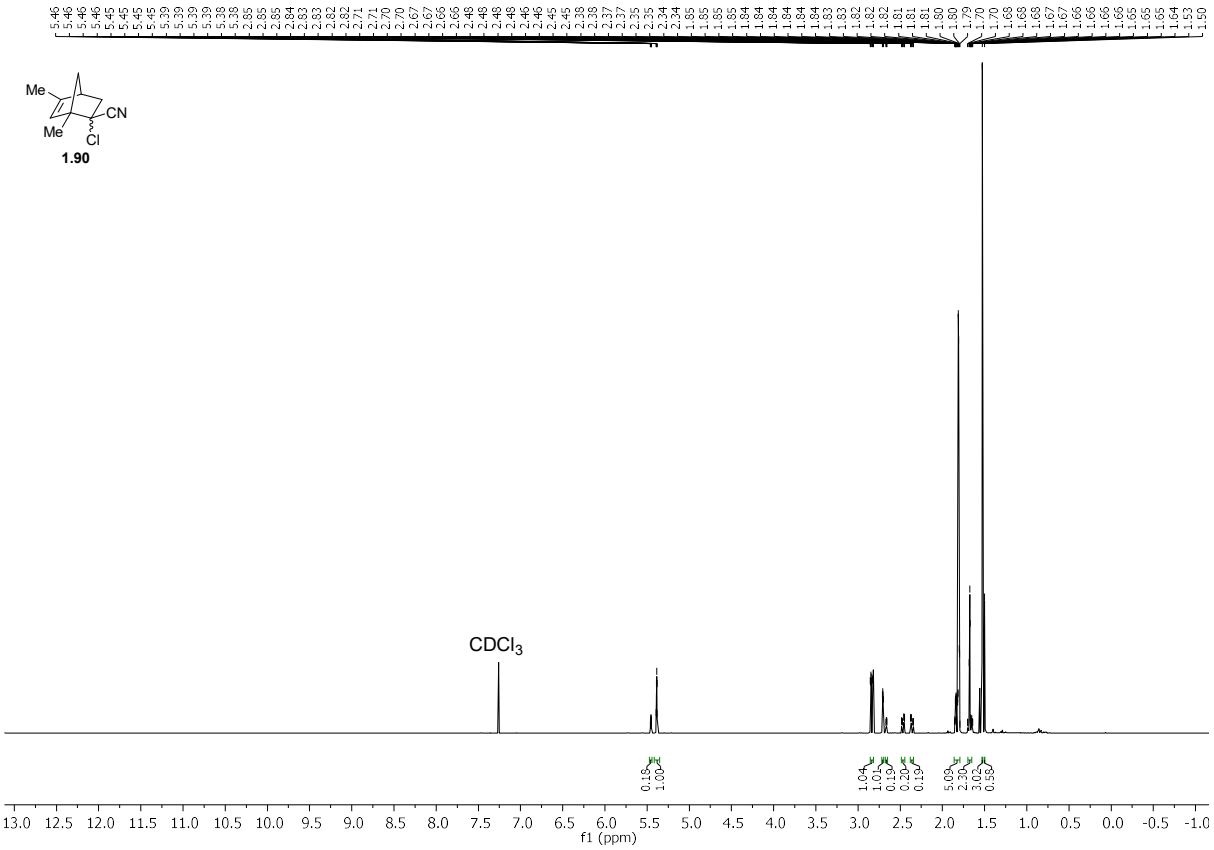
^{1}H NMR (500 MHz, $CDCl_3$) of **1.88**



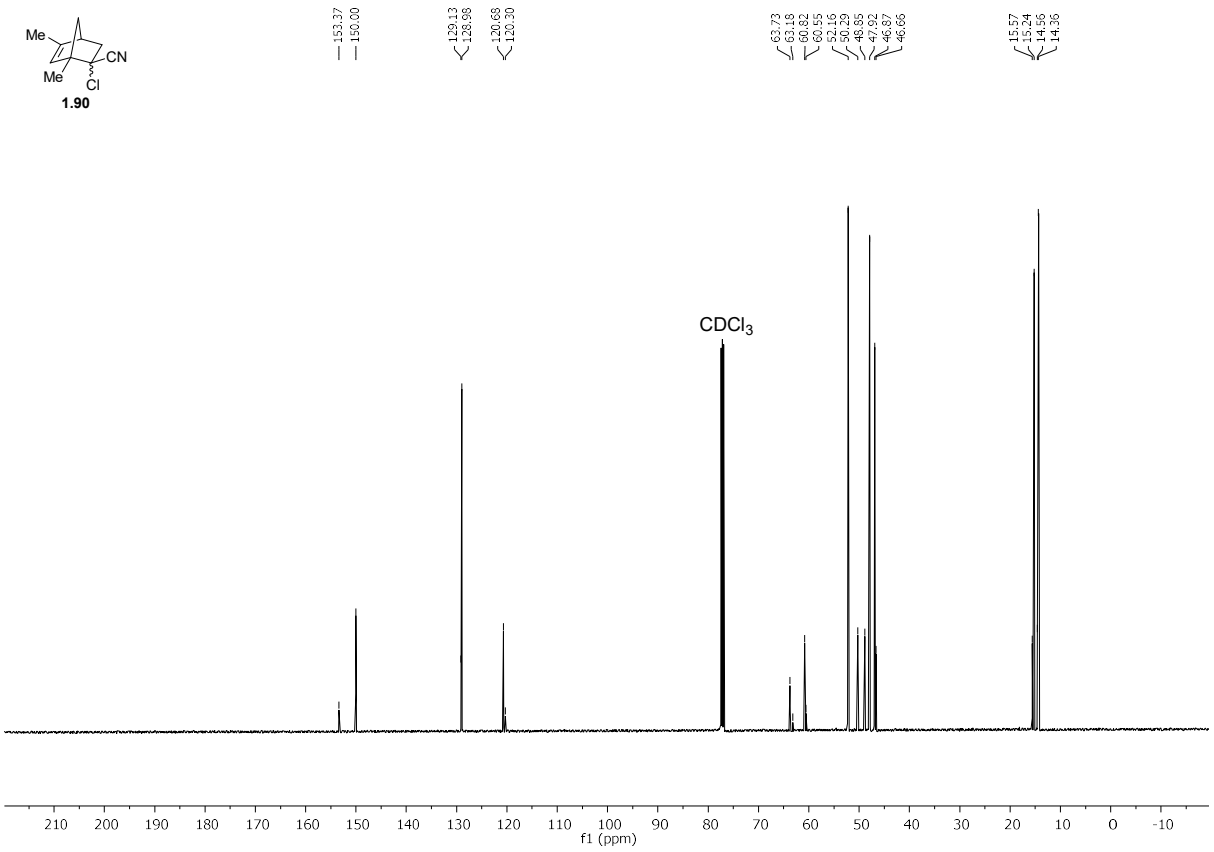
^{13}C NMR (126 MHz, $CDCl_3$) of **1.88**



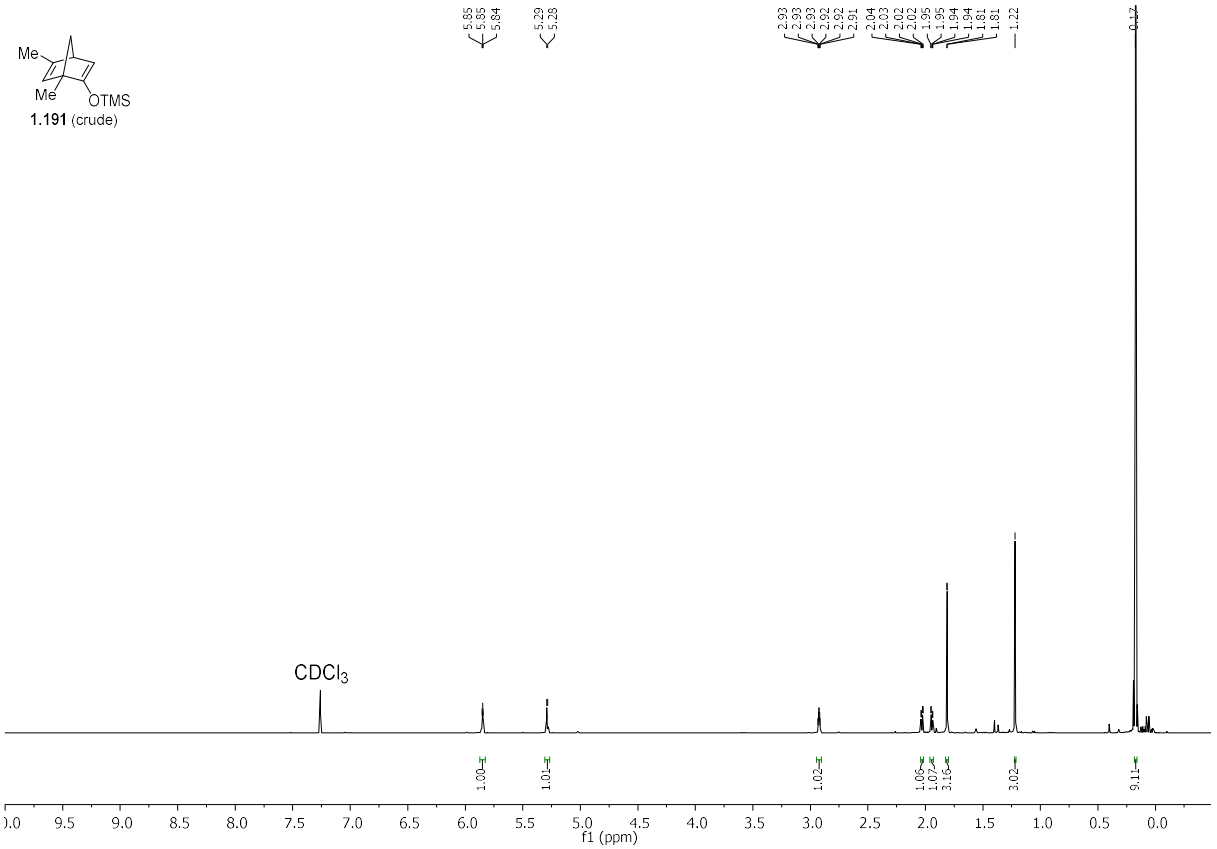
^{1}H NMR (500 MHz, $CDCl_3$) of **1.90**



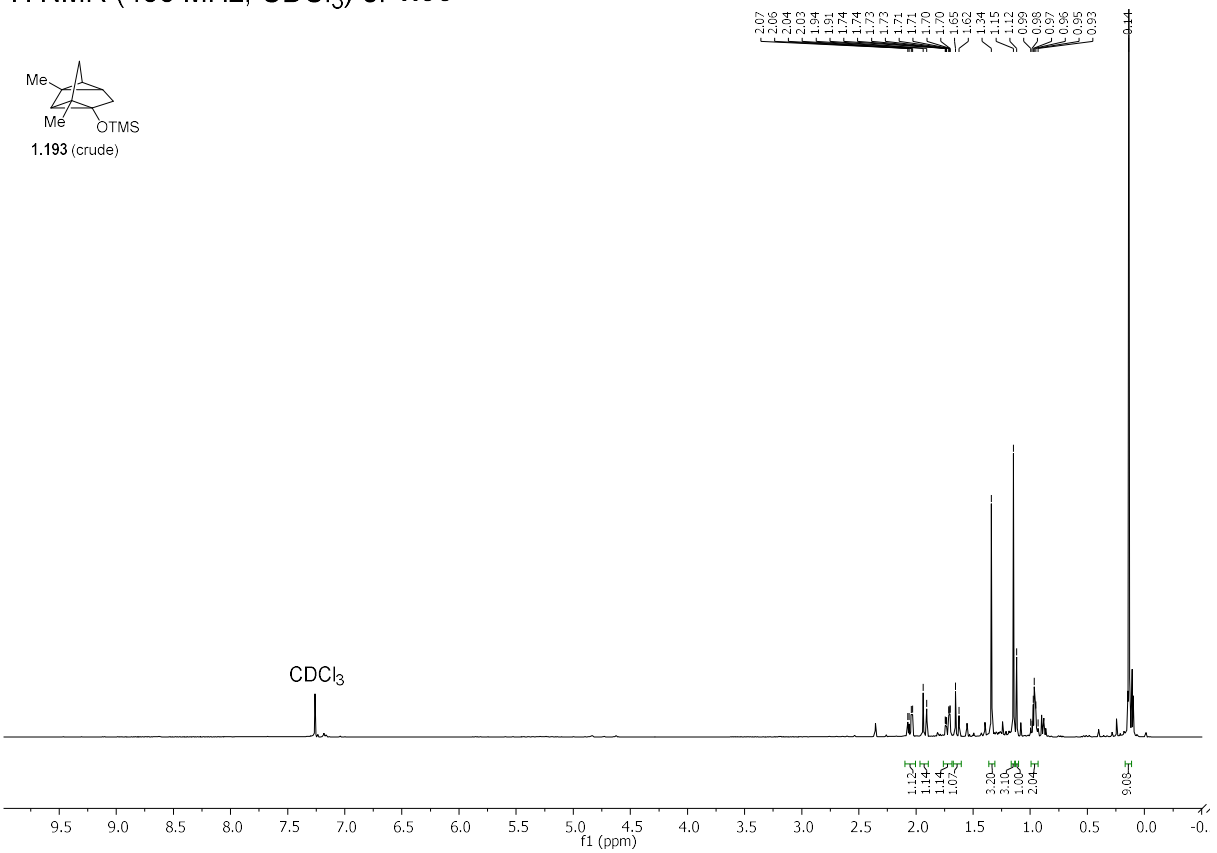
^{13}C NMR (126 MHz, $CDCl_3$) of **1.90**



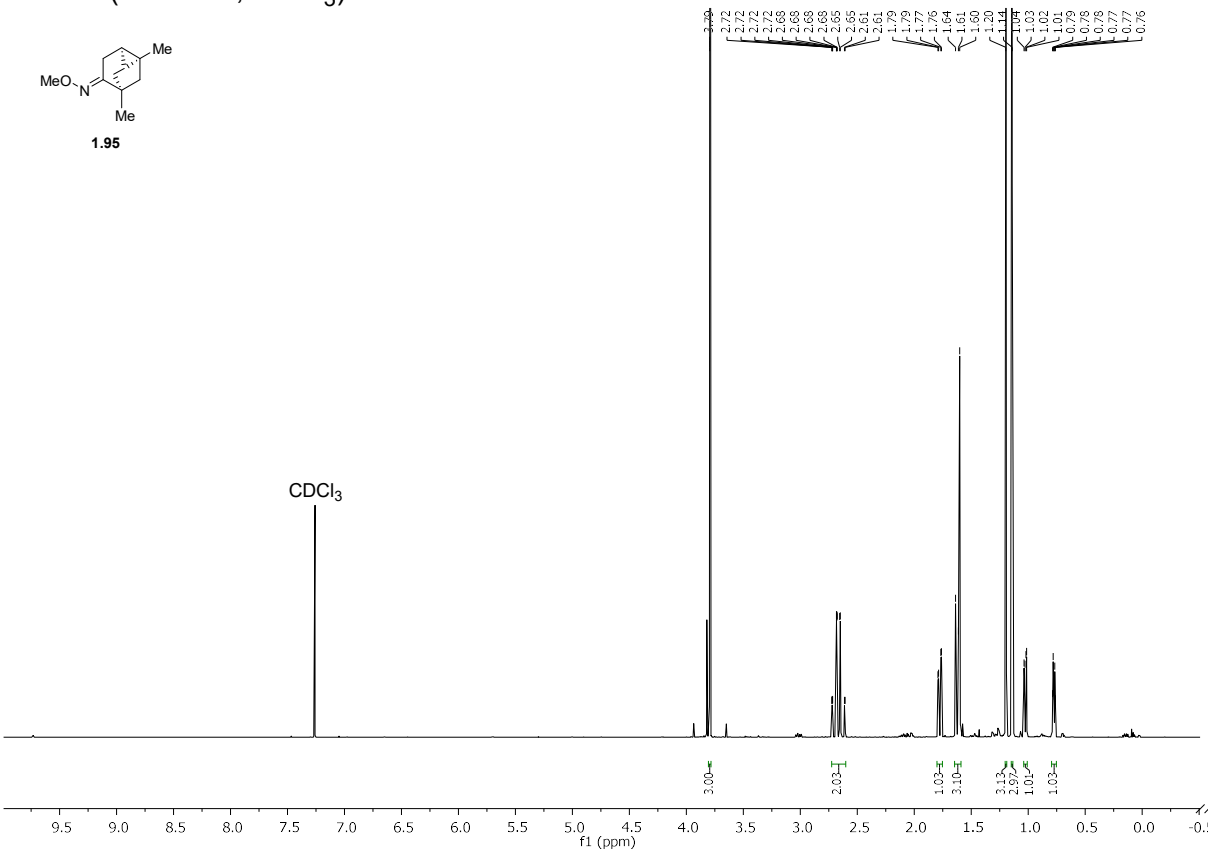
^{1}H NMR (400 MHz, $CDCl_3$) of **1.91**



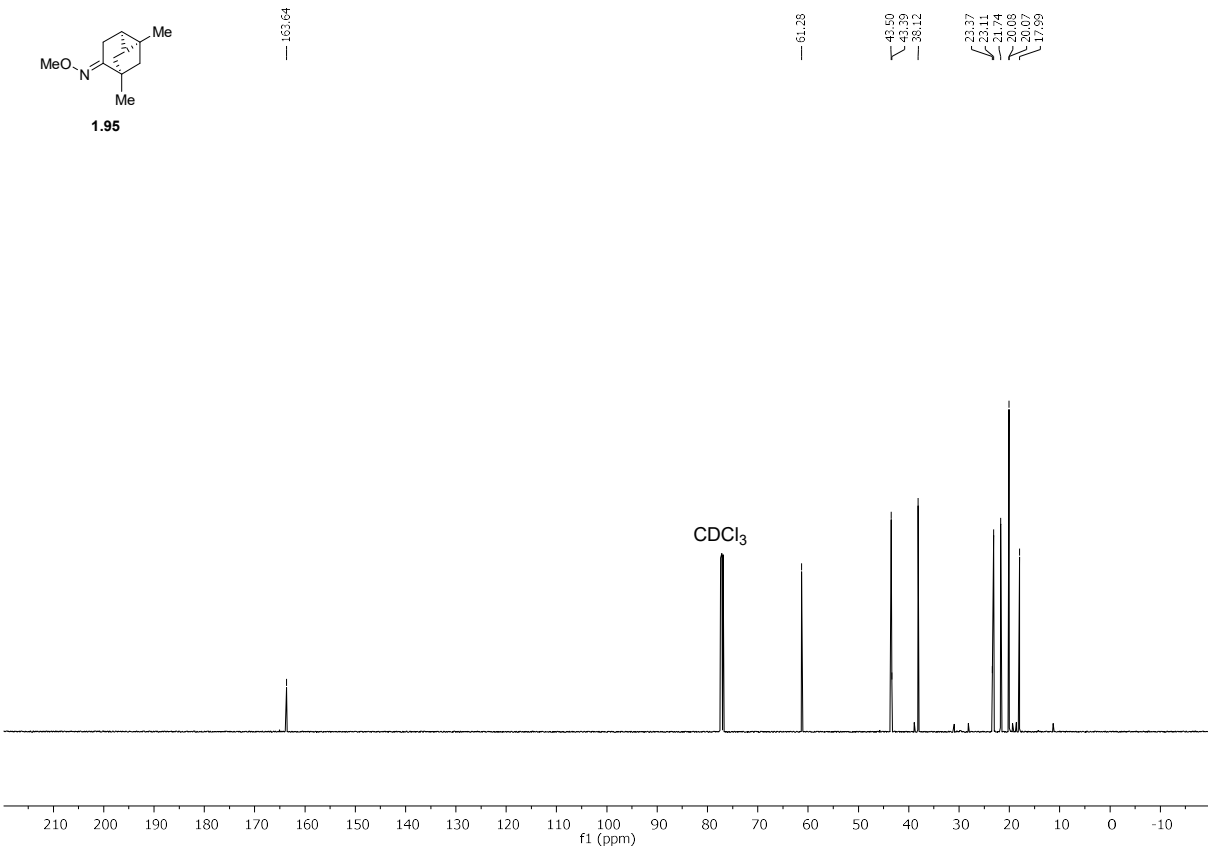
^{1}H NMR (400 MHz, $CDCl_3$) of **1.93**



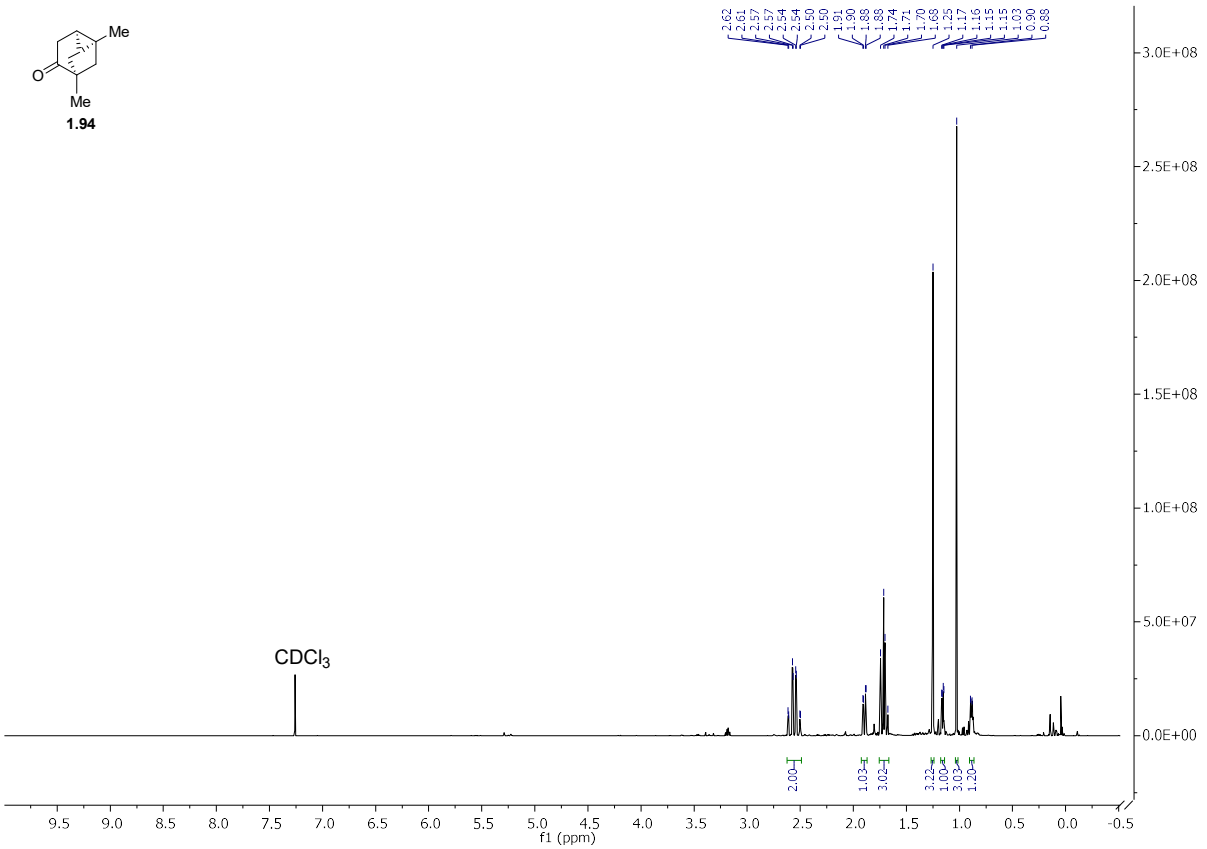
^{1}H NMR (500 MHz, $CDCl_3$) of **1.95**



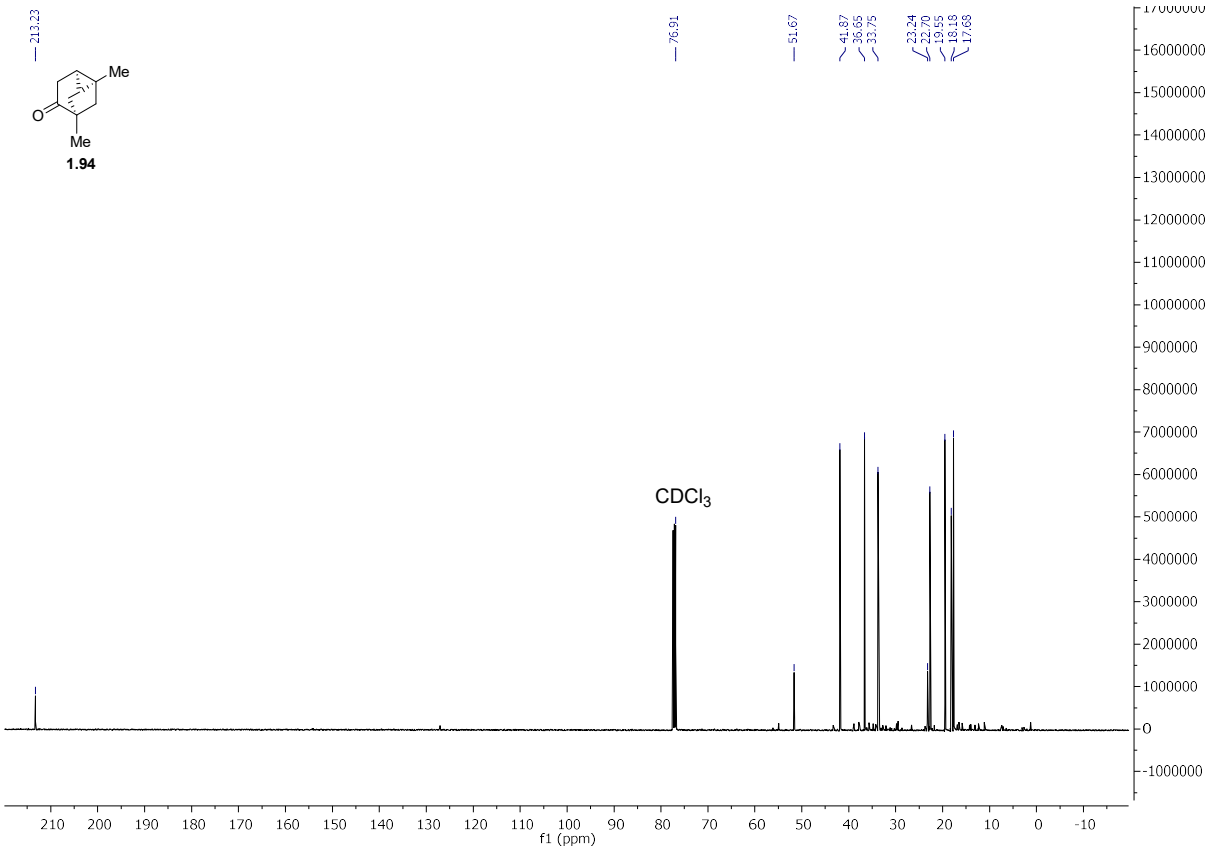
^{13}C NMR (126 MHz, $CDCl_3$) of **1.95**



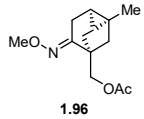
^{1}H NMR (500 MHz, $CDCl_3$) of **1.94**



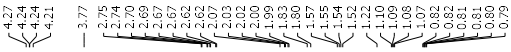
^{13}C NMR (126 MHz, $CDCl_3$) of **1.94**

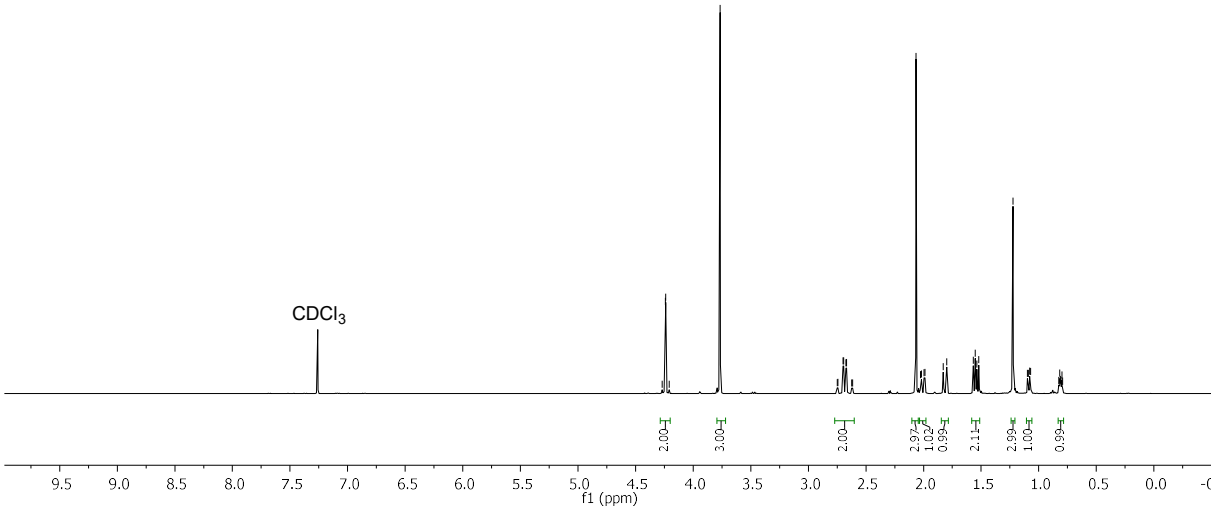


^{1}H NMR (400 MHz, $CDCl_3$) of **1.96**

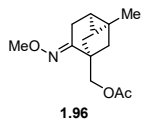


1.96

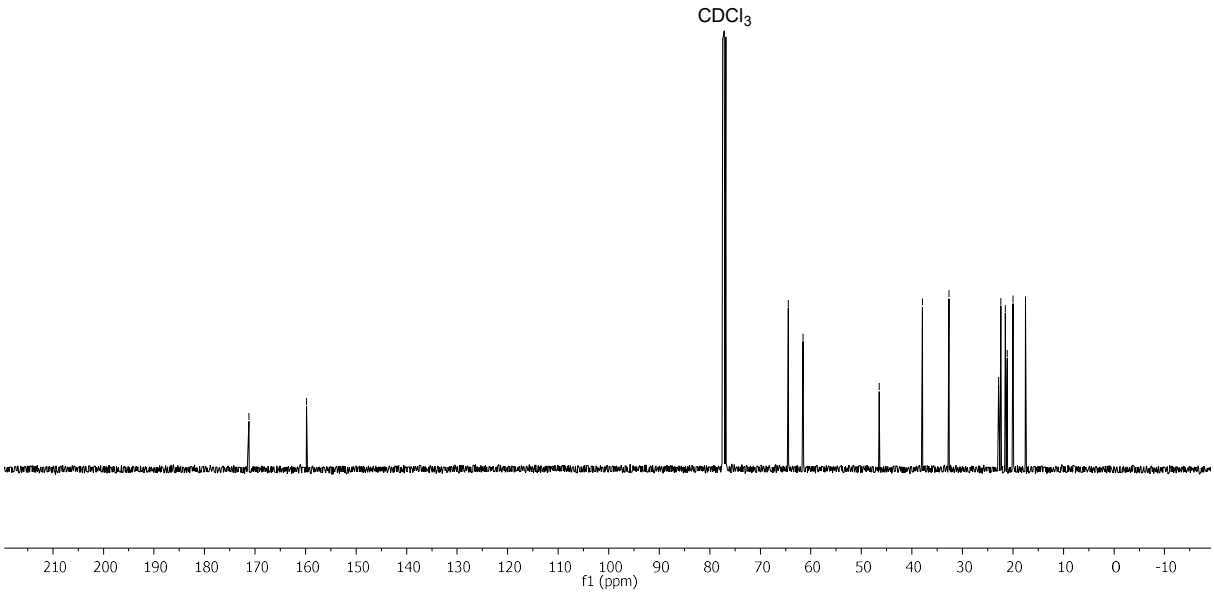




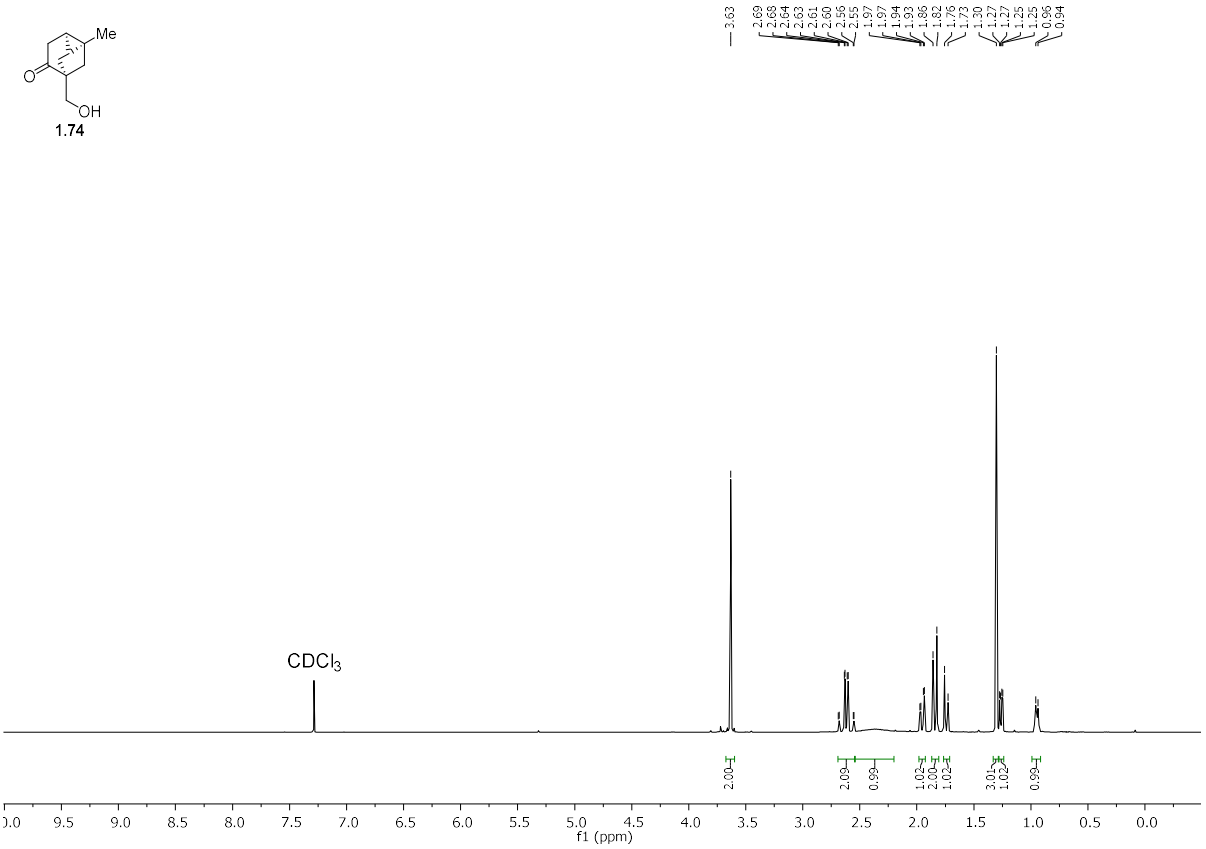
^{13}C NMR (101 MHz, $CDCl_3$) of **1.96**



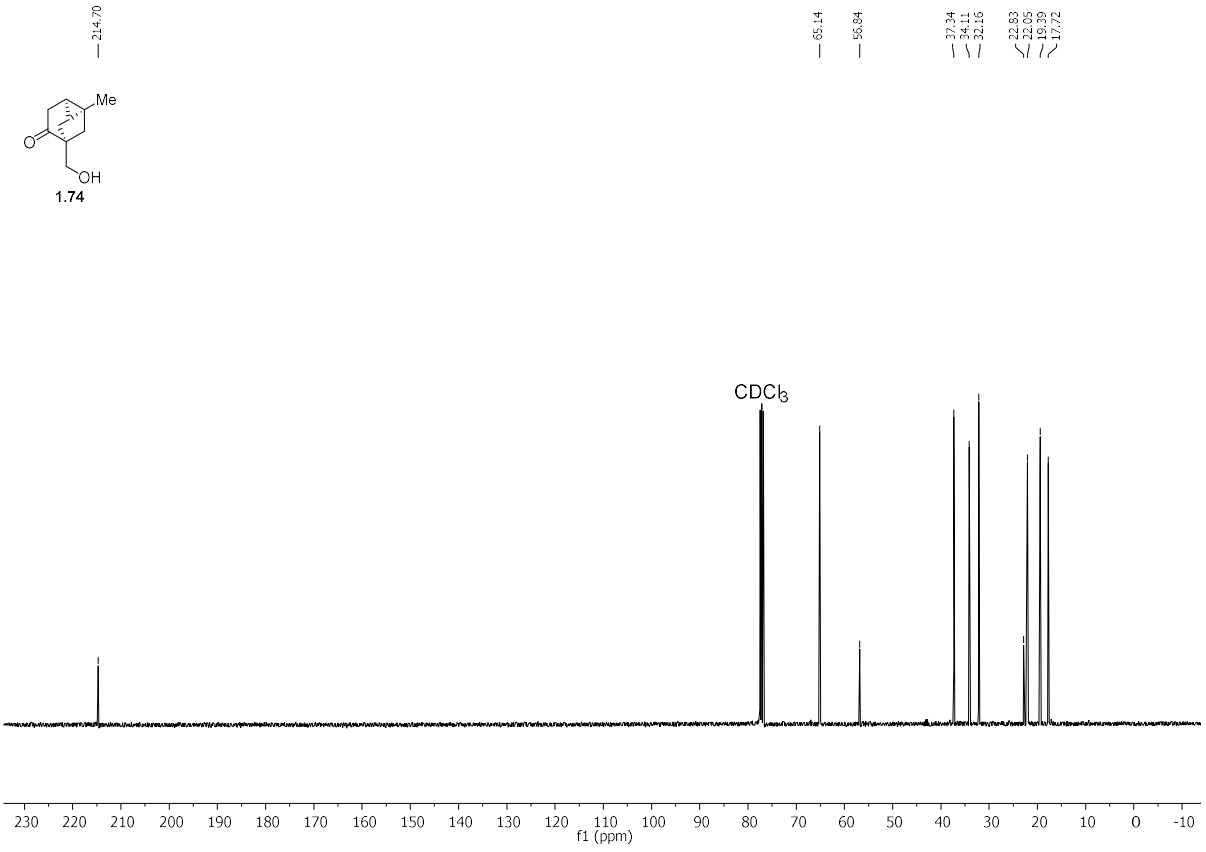
1.96



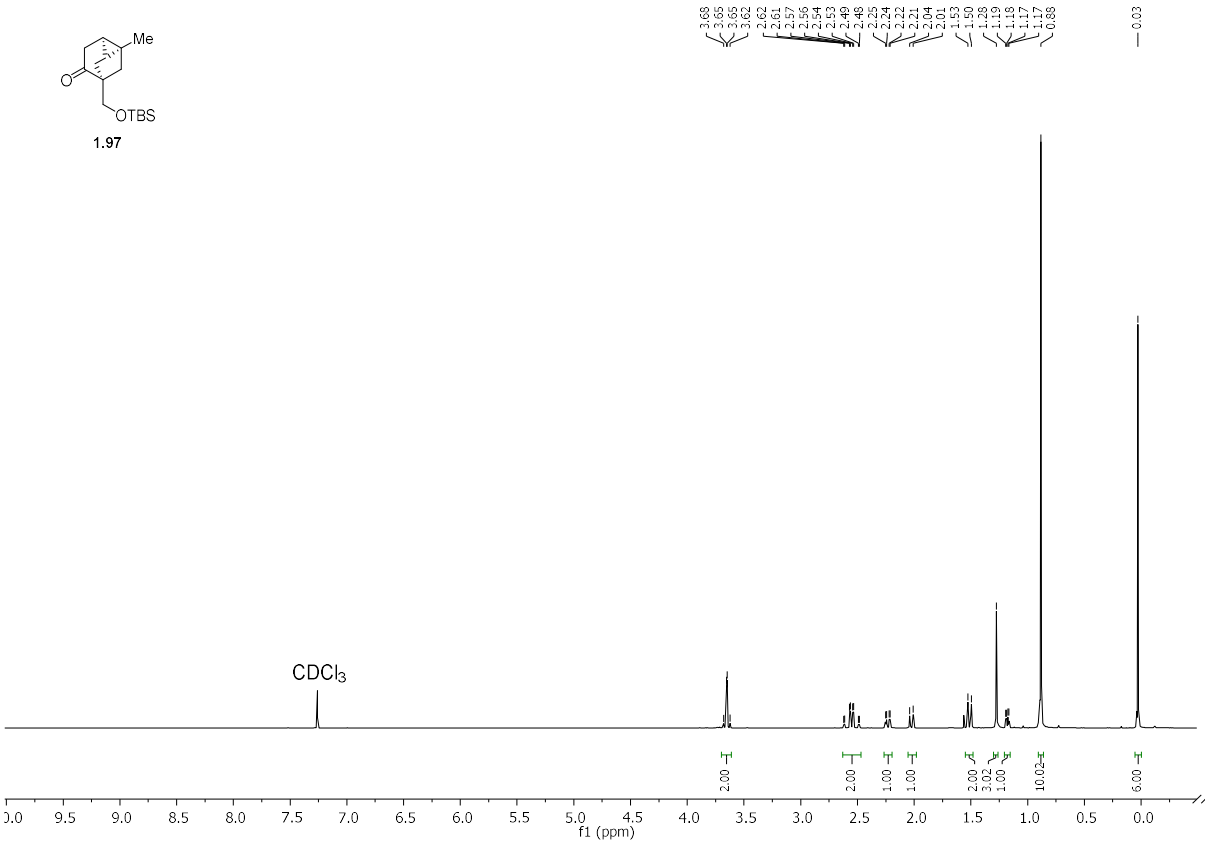
^{1}H NMR (400 MHz, $CDCl_3$) of **1.74**



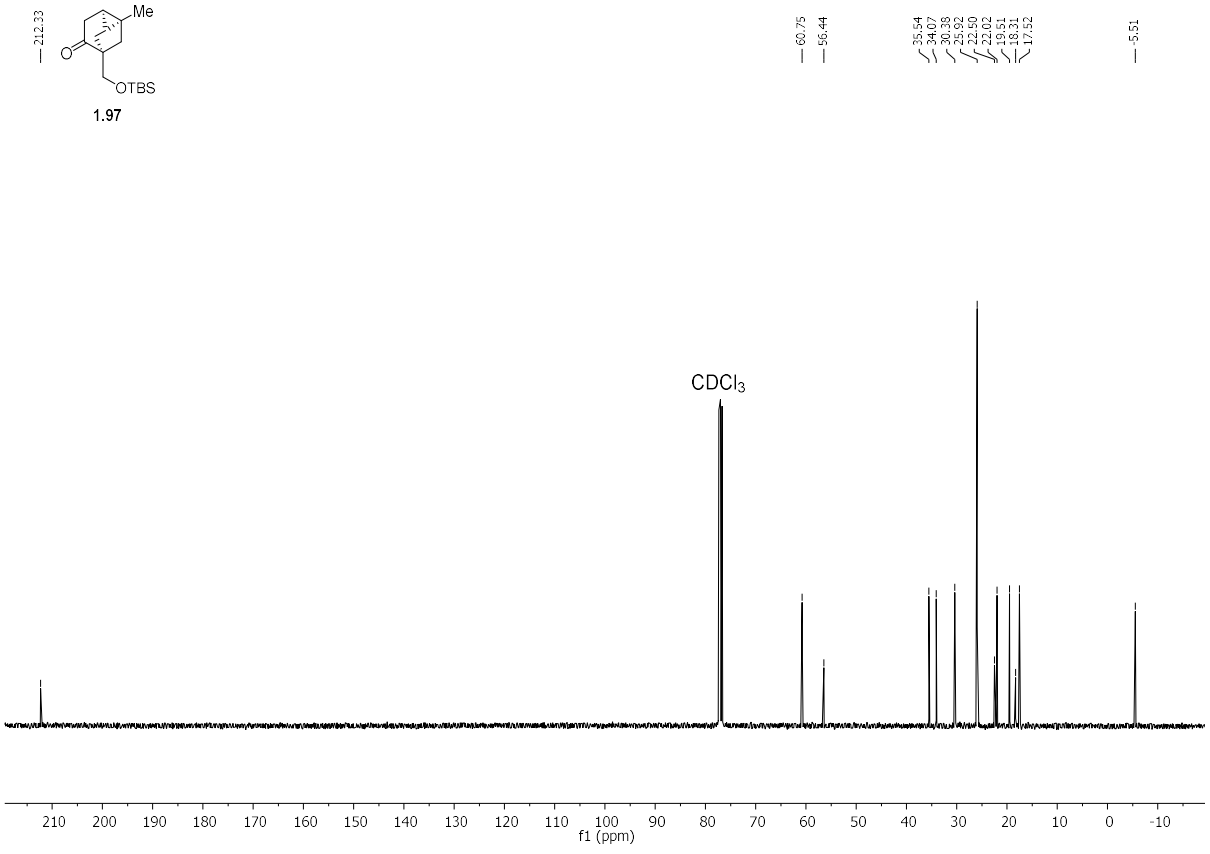
^{13}C NMR (101 MHz, $CDCl_3$) of **1.74**



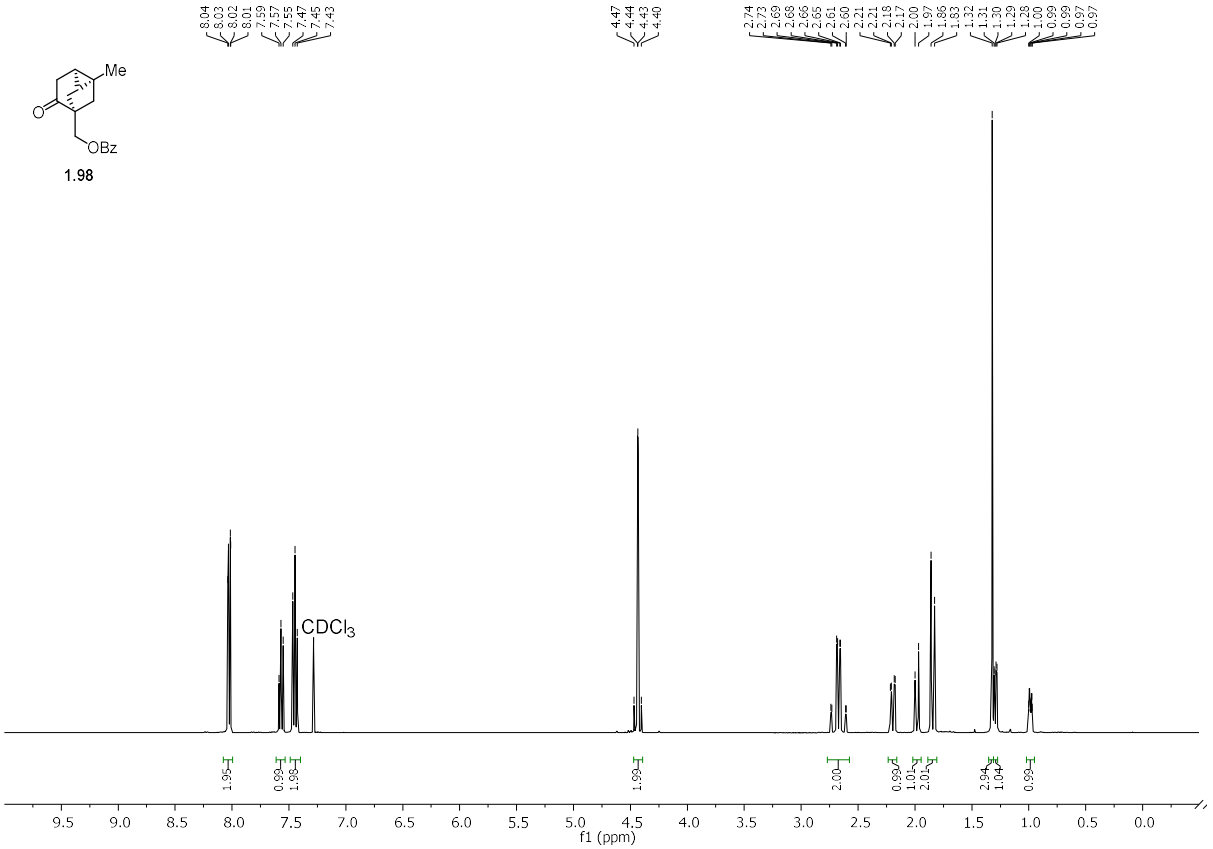
^{1}H NMR (400 MHz, $CDCl_3$) of **1.97**



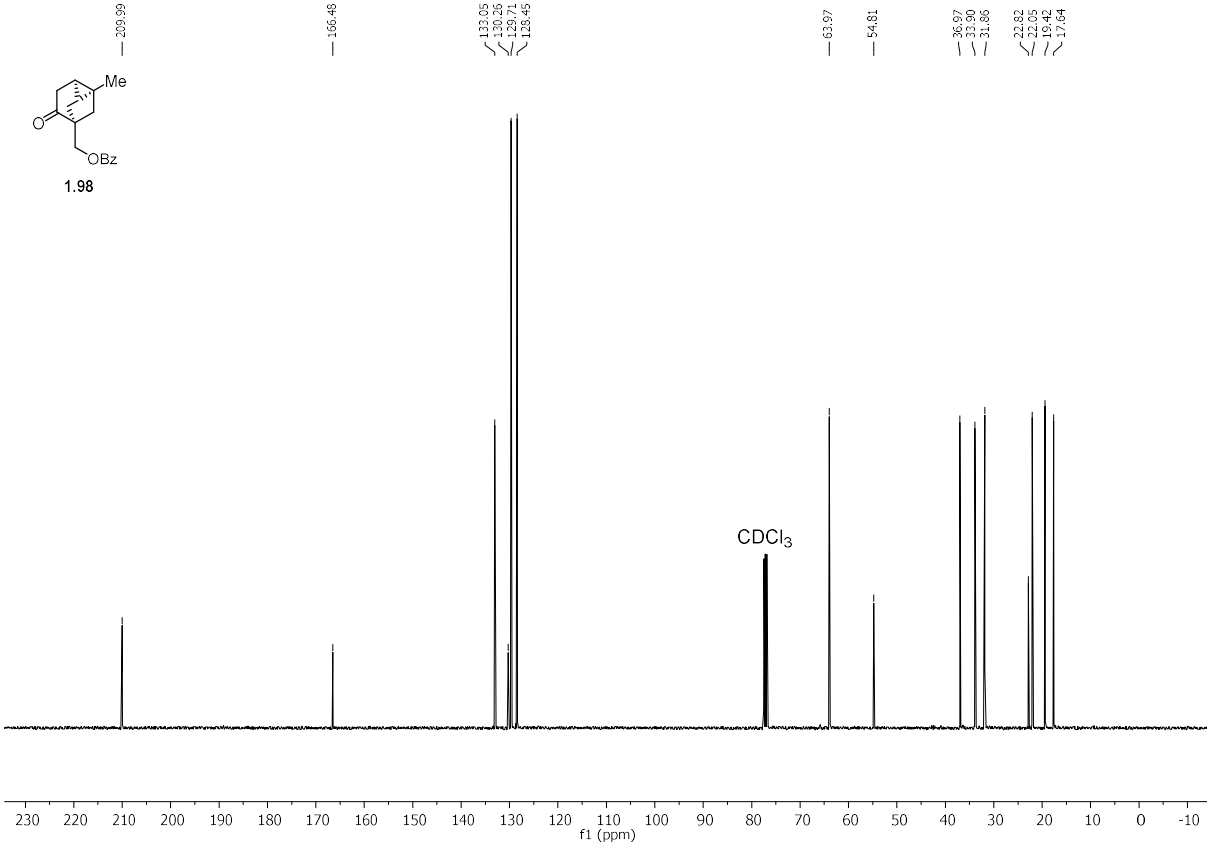
^{13}C NMR (101 MHz, $CDCl_3$) of **1.97**



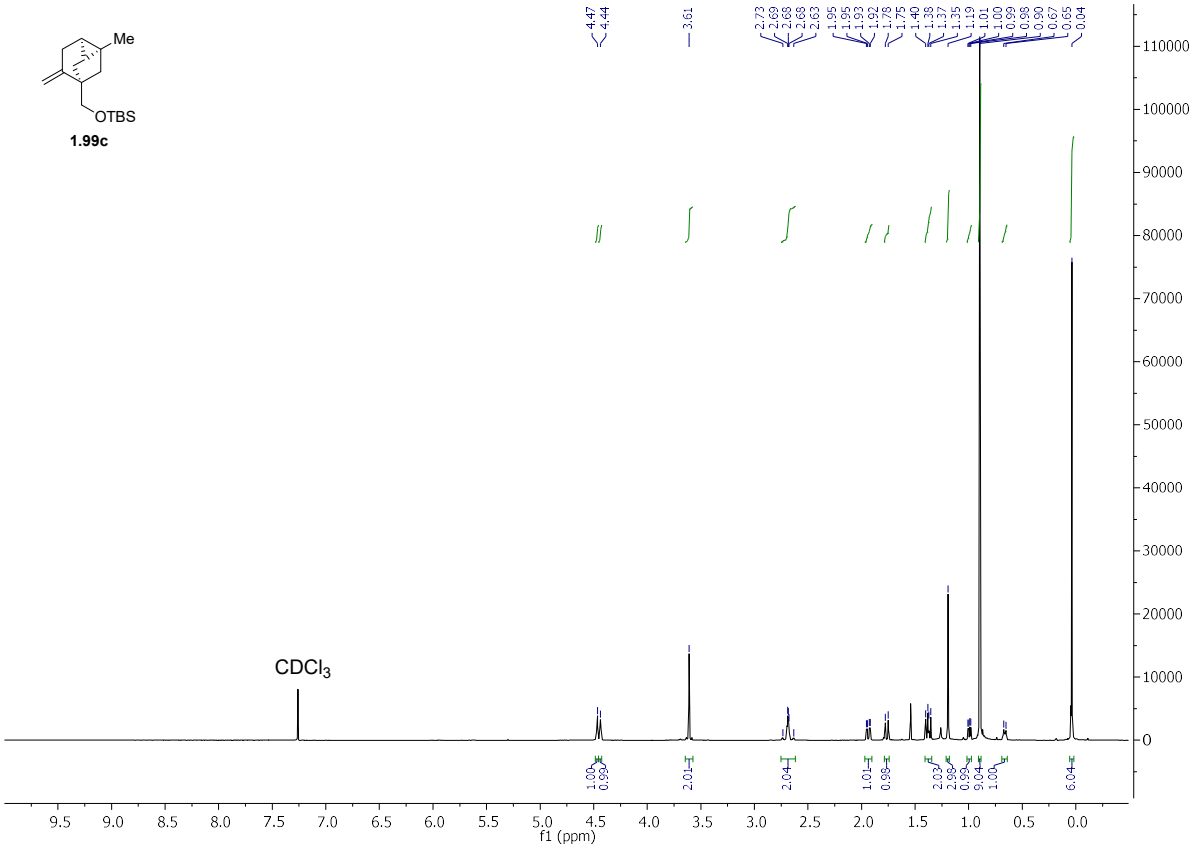
^{1}H NMR (400 MHz, $CDCl_3$) of **1.98**



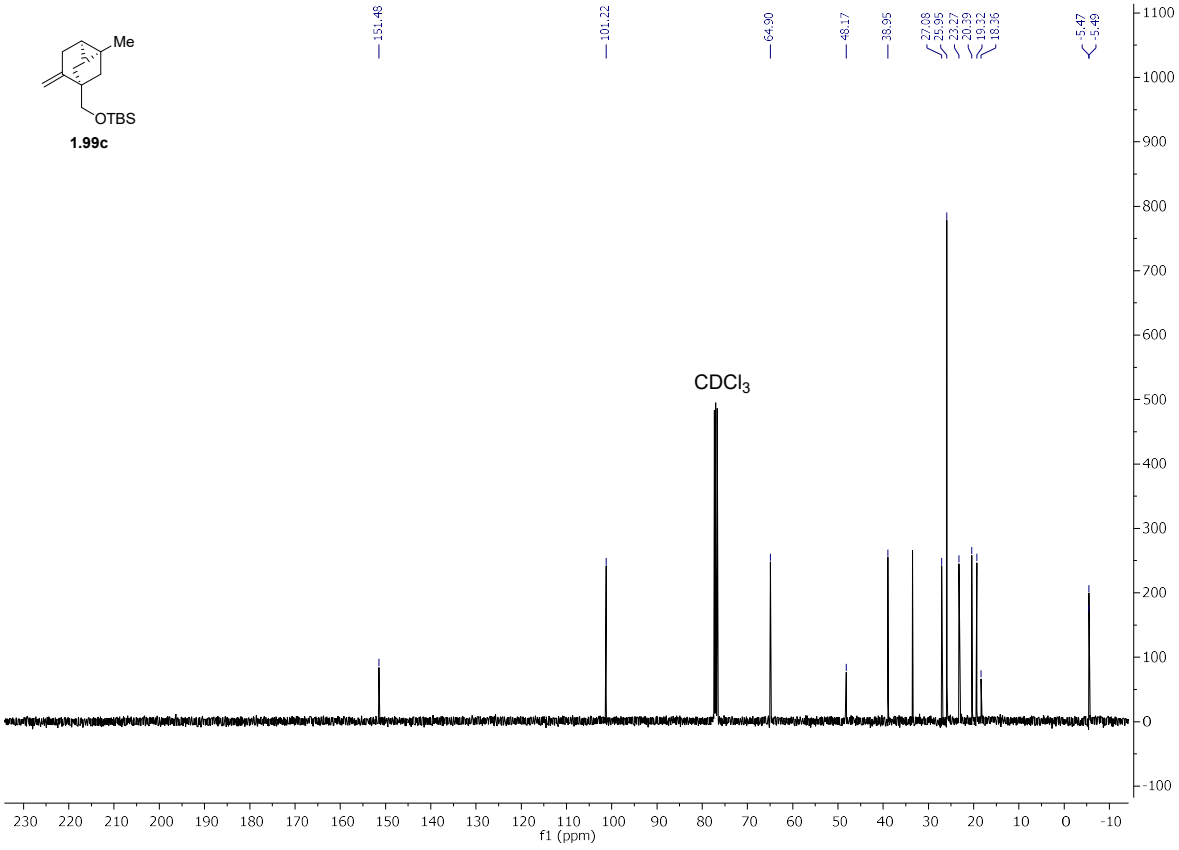
^{13}C NMR (101 MHz, $CDCl_3$) of **1.98**



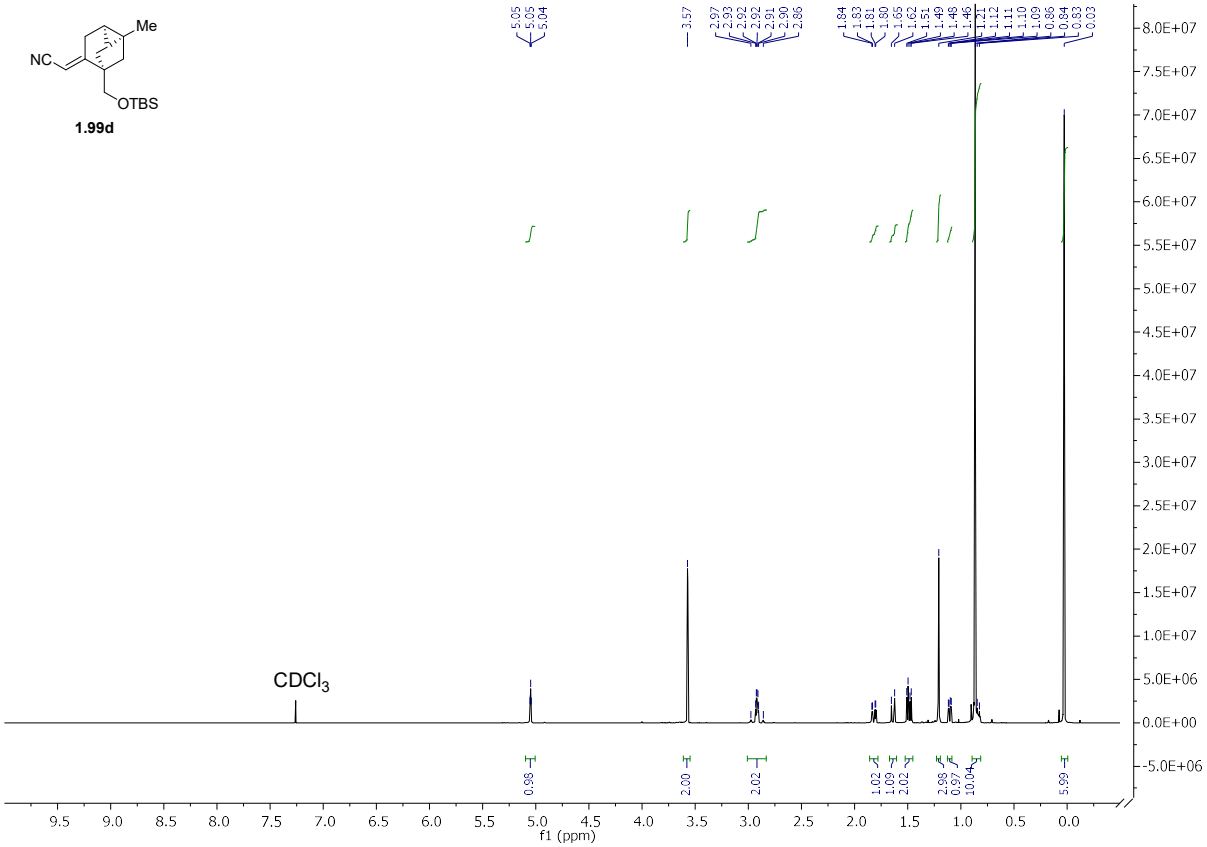
^{1}H NMR (400 MHz, $CDCl_3$) of **1.99c**



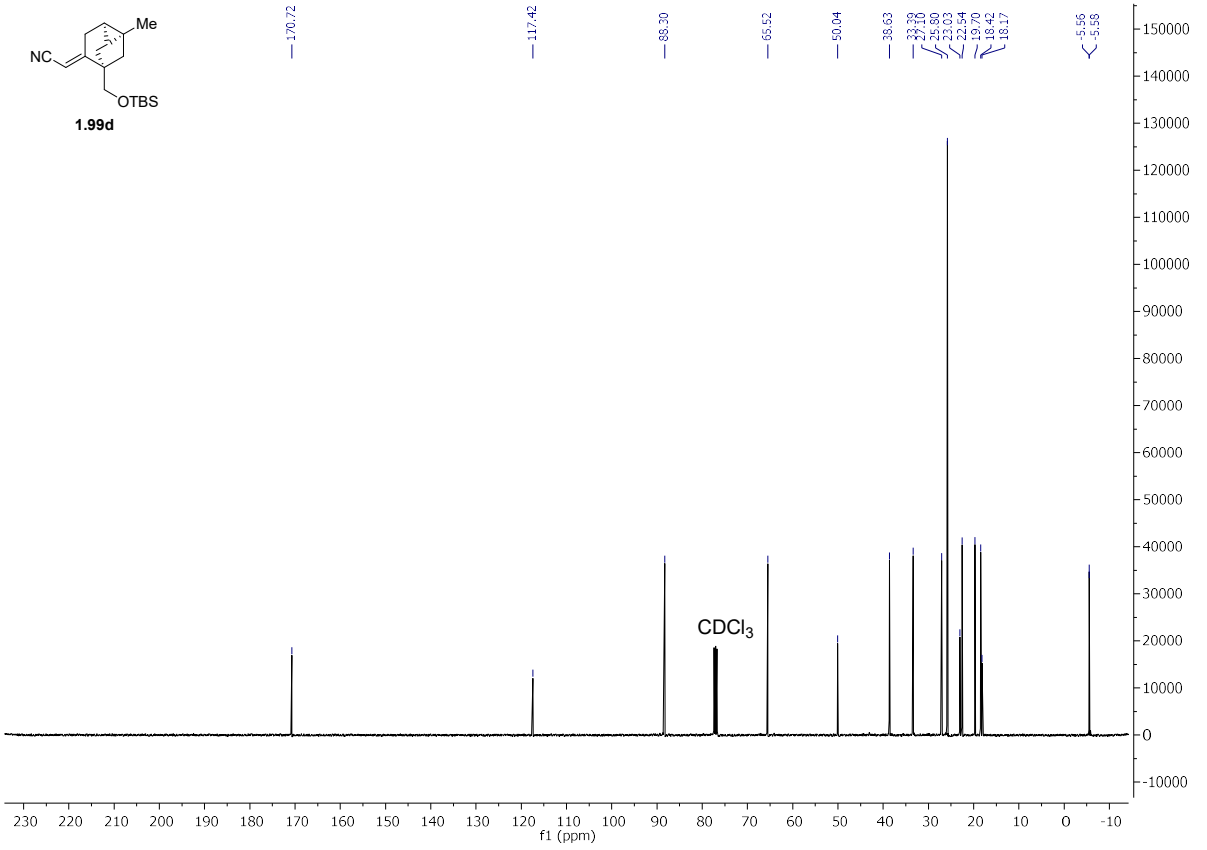
^{13}C NMR (101 MHz, $CDCl_3$) of **1.99c**



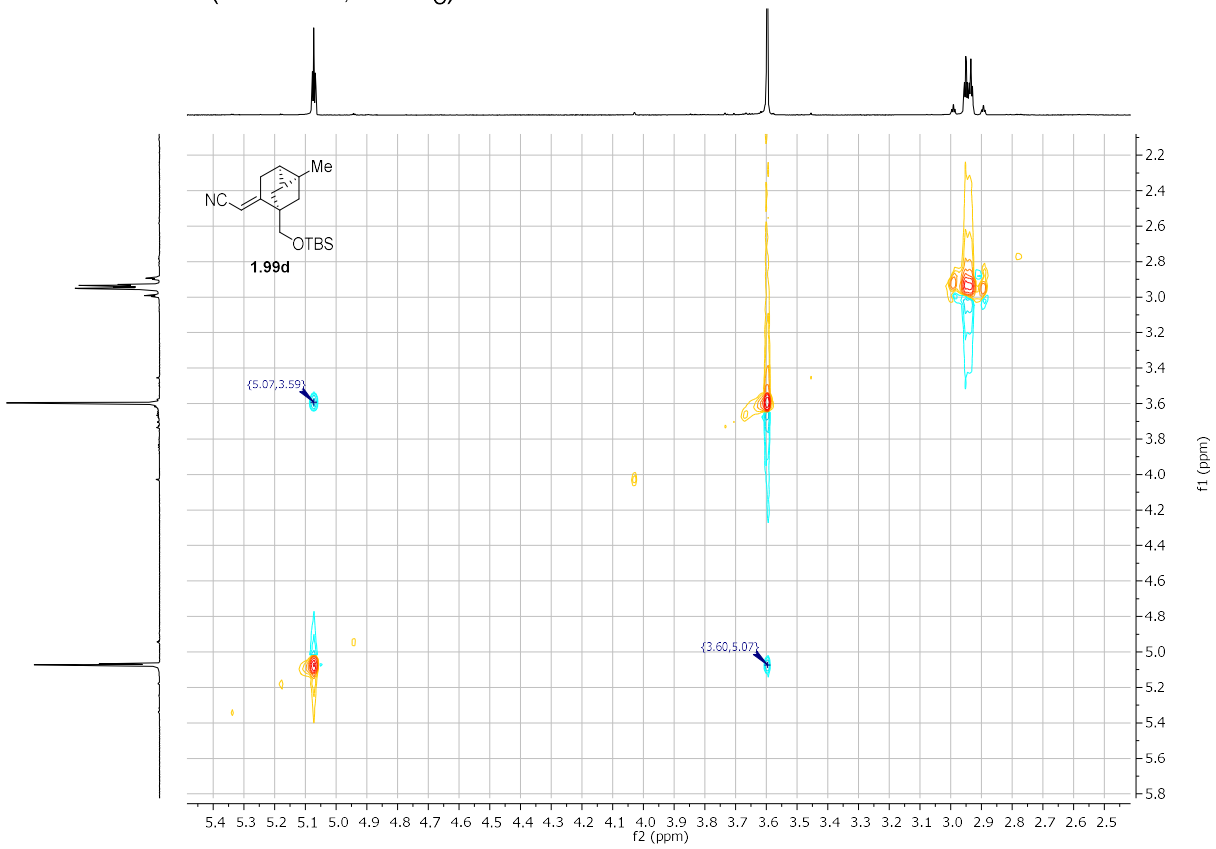
^{1}H NMR (400 MHz, $CDCl_3$) of **1.99d**



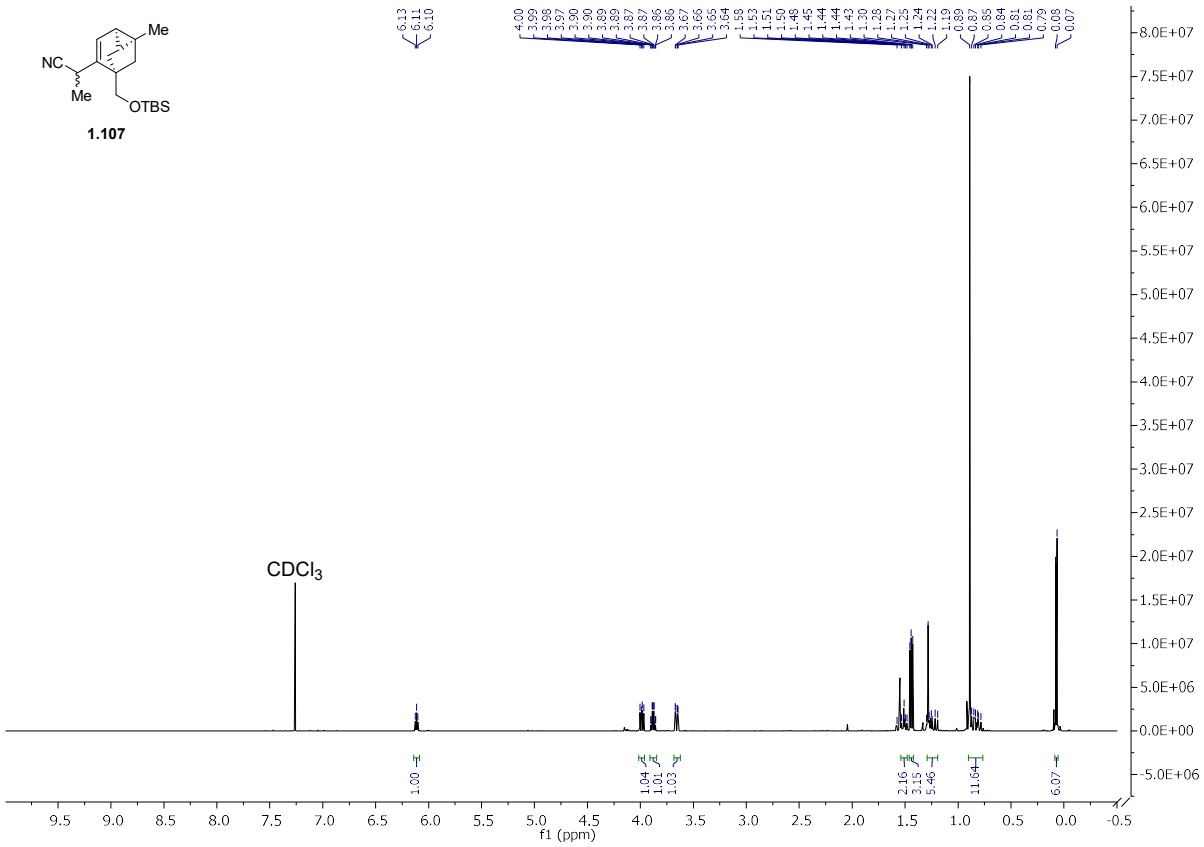
^{13}C NMR (101 MHz, $CDCl_3$) of **1.99d**



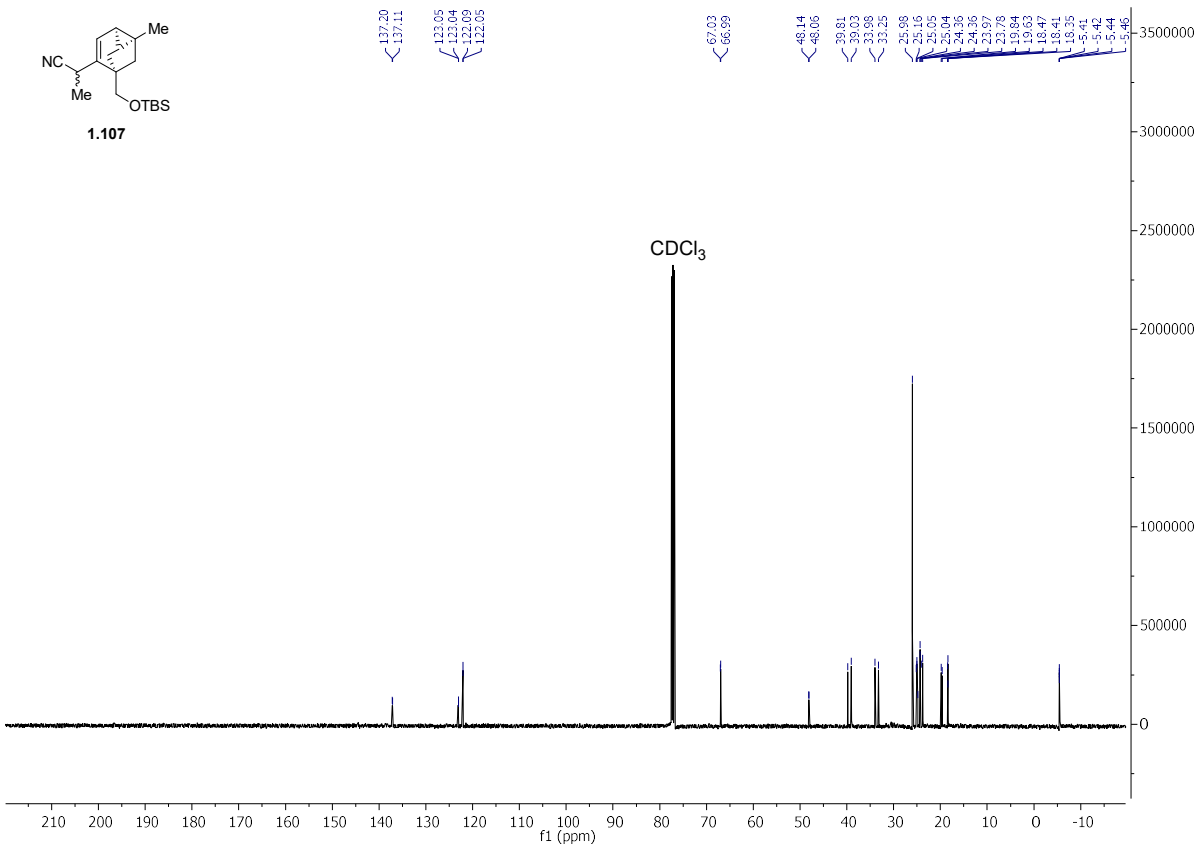
NOESY NMR (500 MHz, $CDCl_3$) of **1.99d**



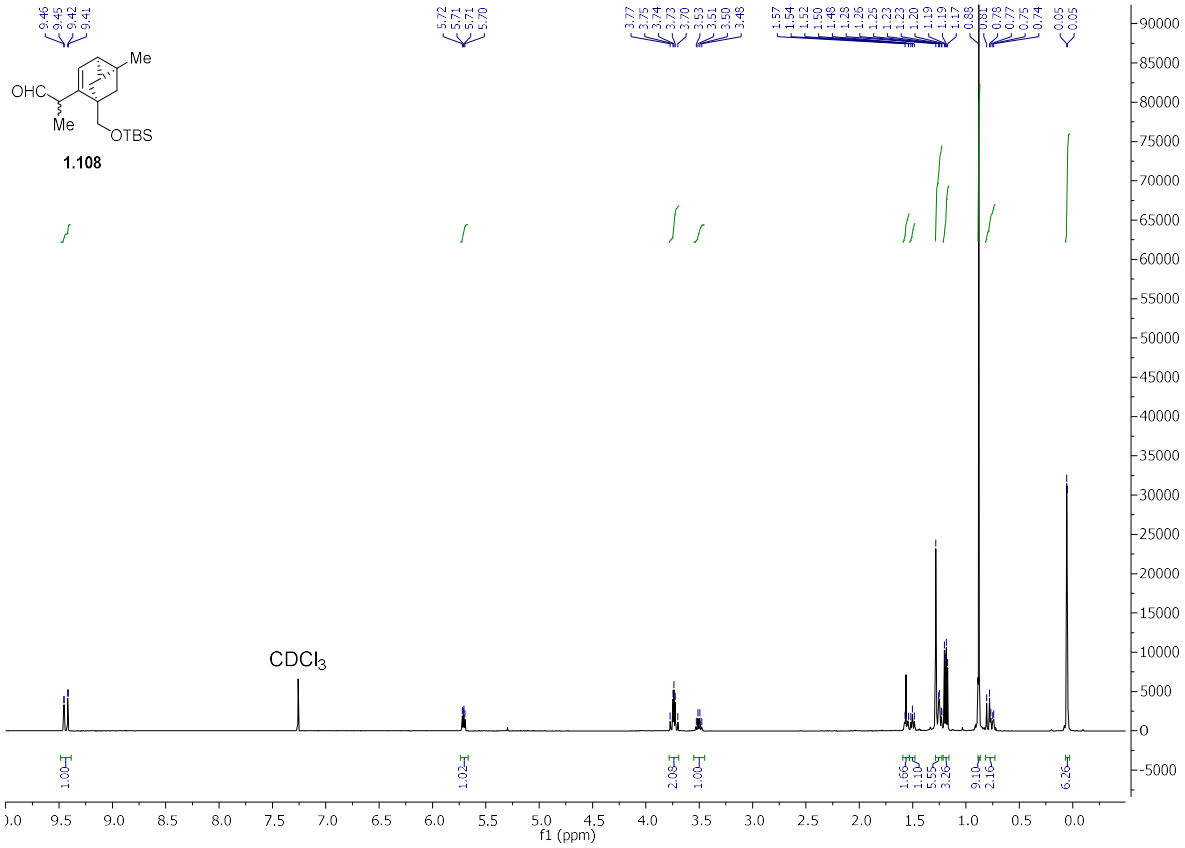
^{1}H NMR (500 MHz, $CDCl_3$) of **1.107**



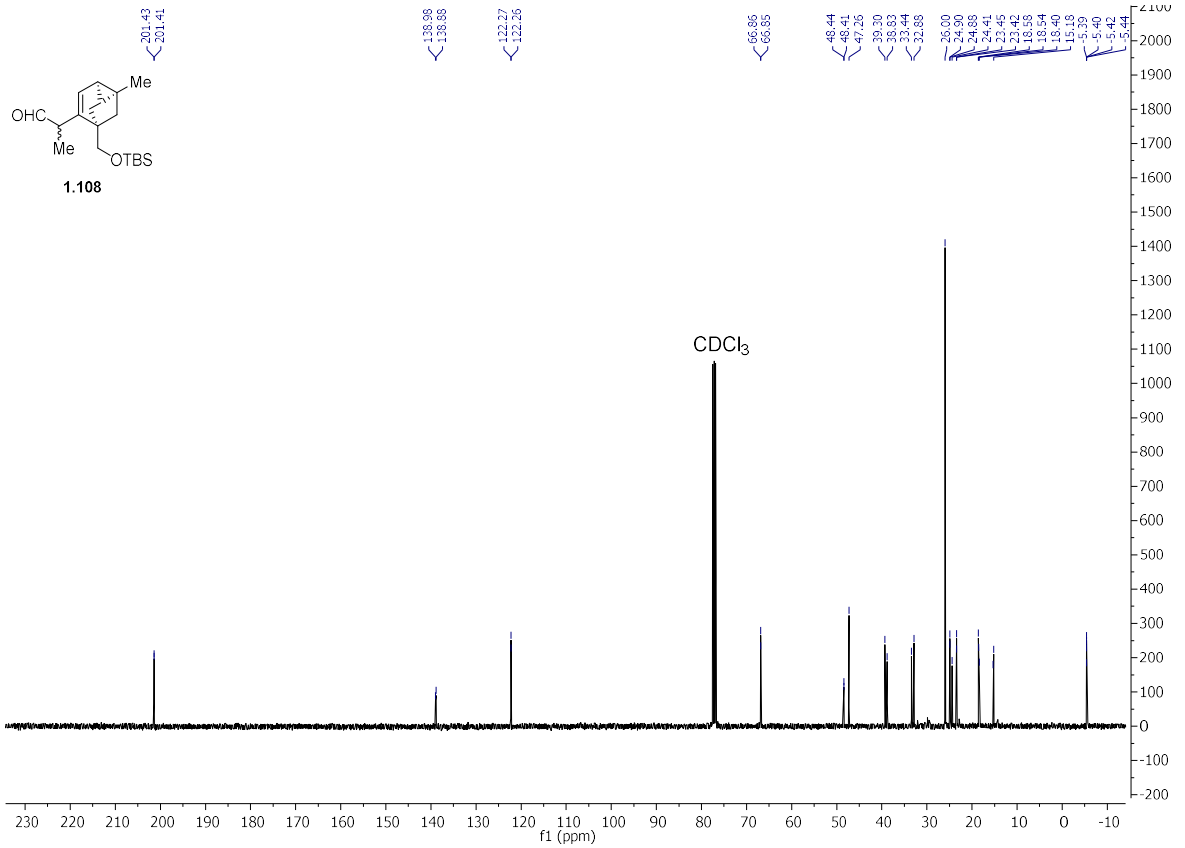
^{13}C NMR (126 MHz, $CDCl_3$) of **1.107**



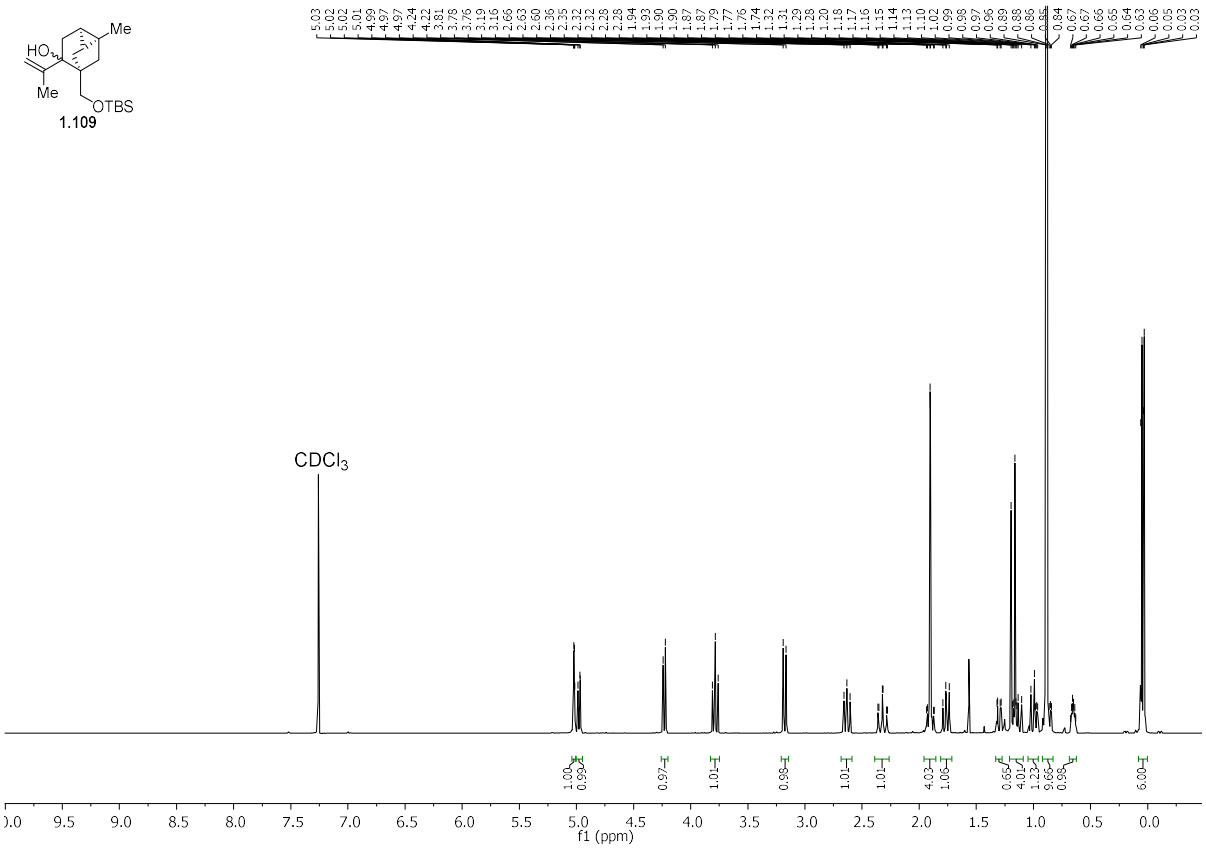
^{1}H NMR (400 MHz, $CDCl_3$) of **1.108**



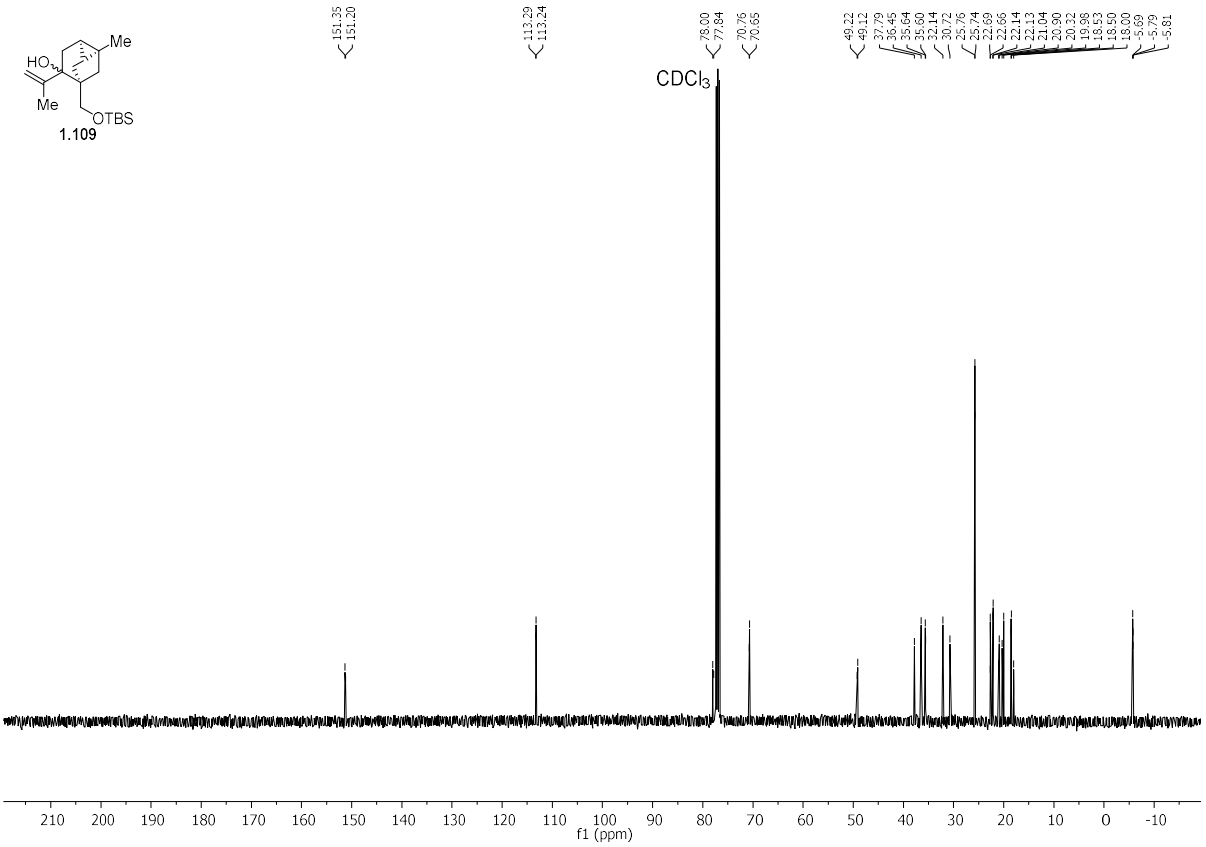
^{13}C NMR (101 MHz, $CDCl_3$) of **1.108**



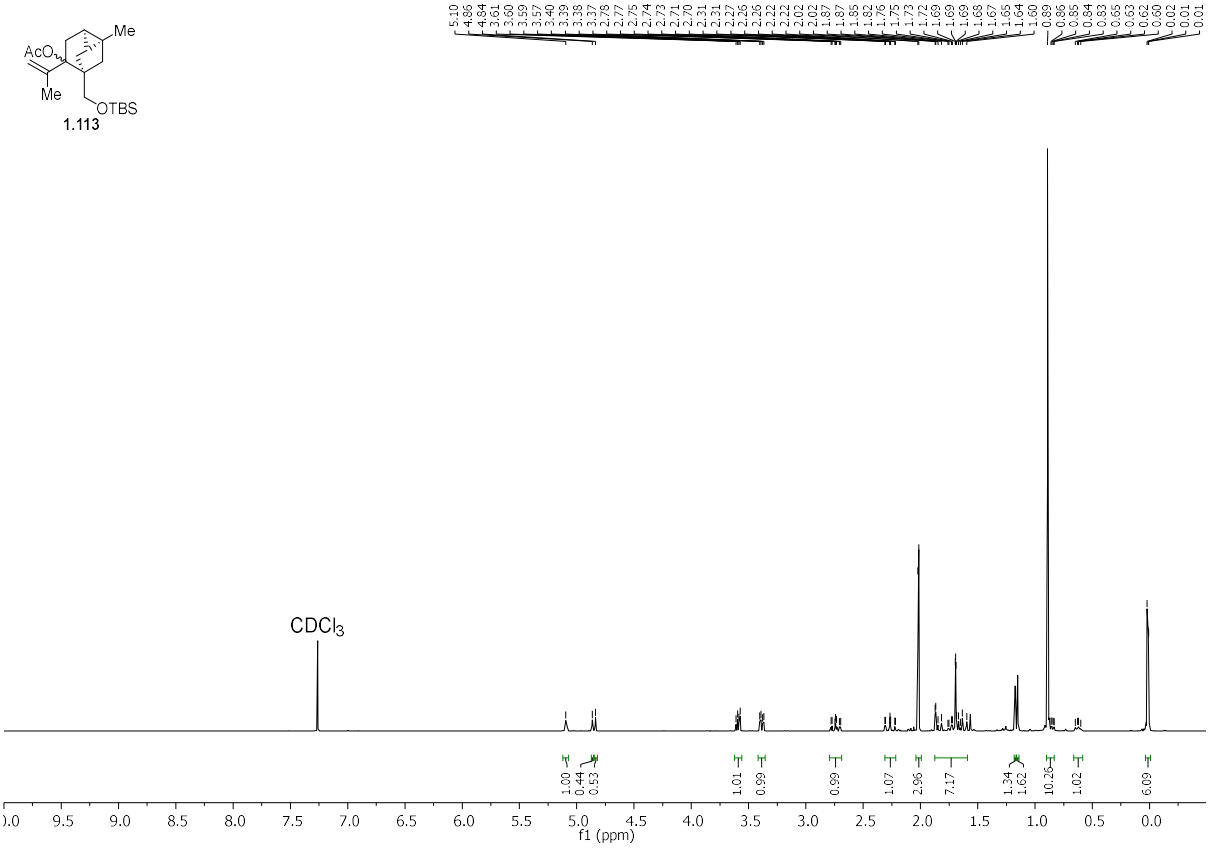
^{1}H NMR (400 MHz, $CDCl_3$) of **1.109**



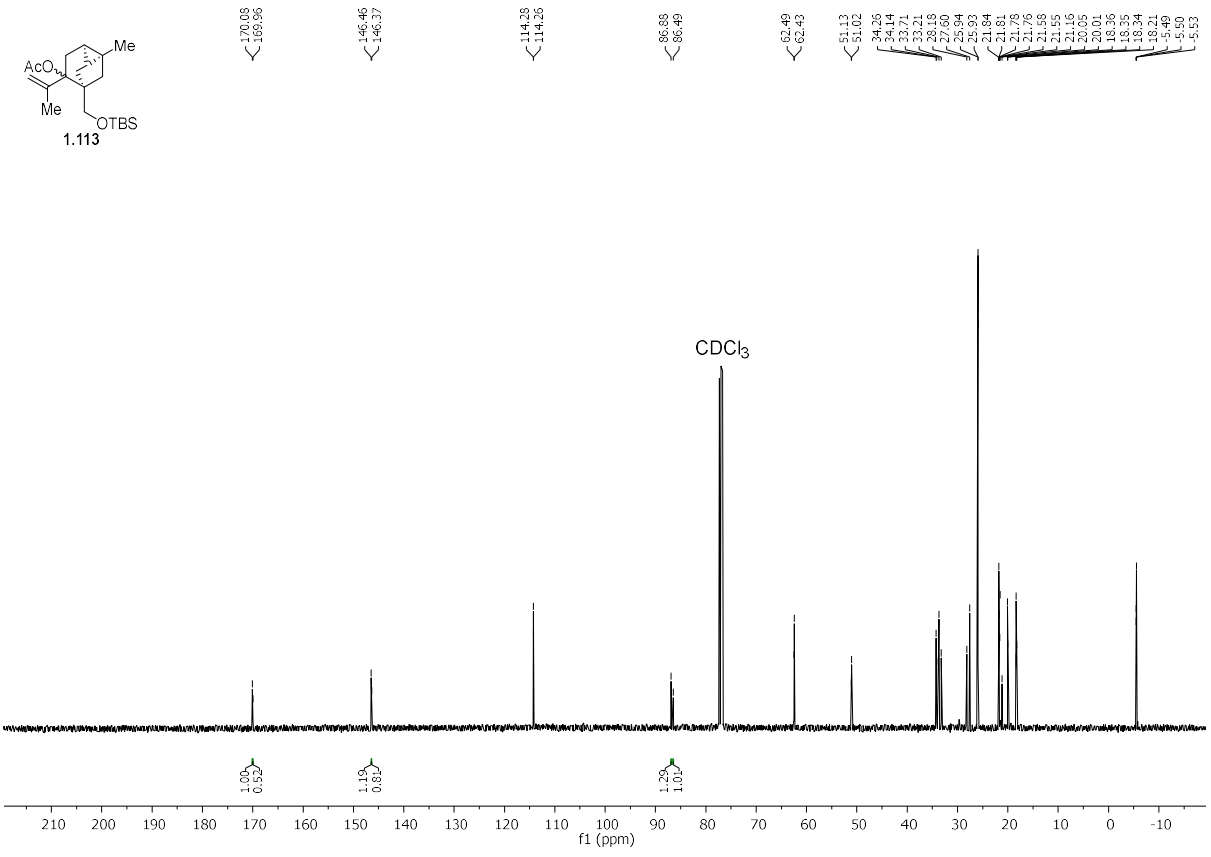
^{13}C NMR (101 MHz, $CDCl_3$) of **1.109**



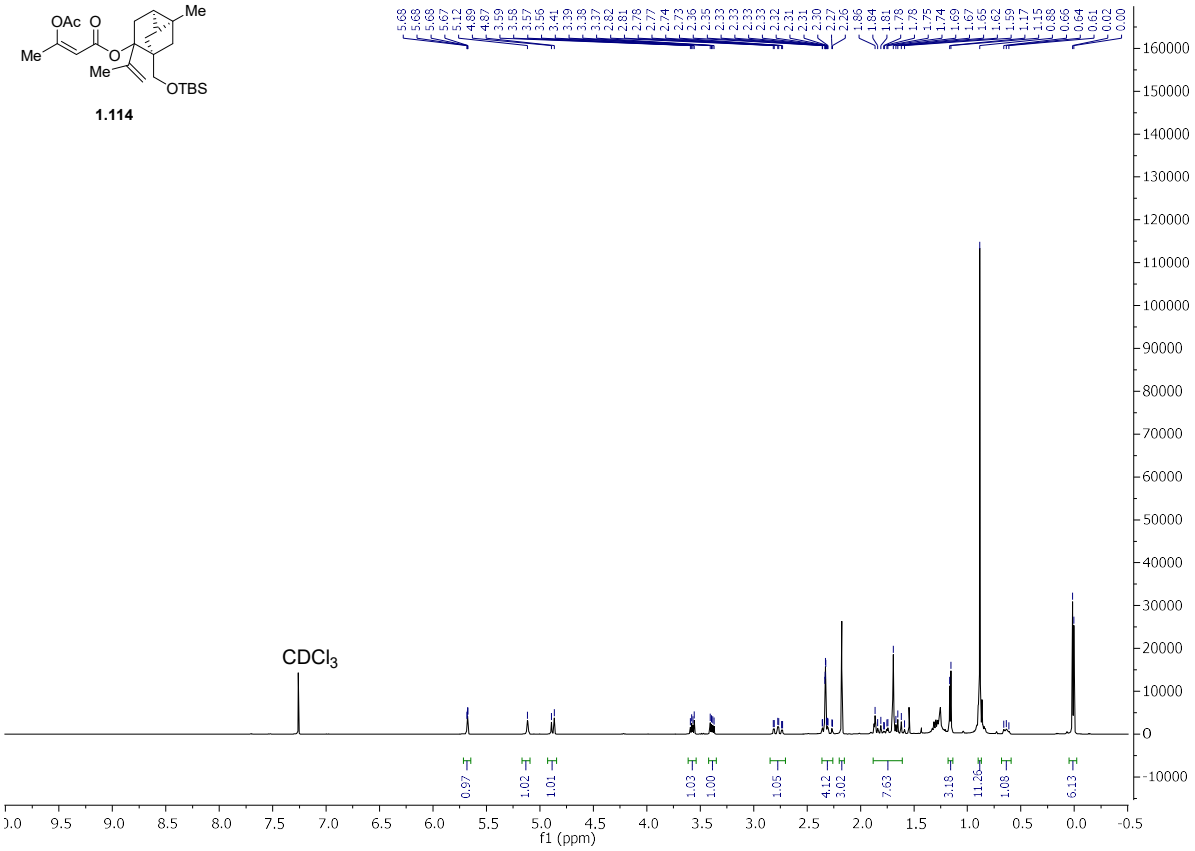
^{1}H NMR (400 MHz, $CDCl_3$) of **1.113**



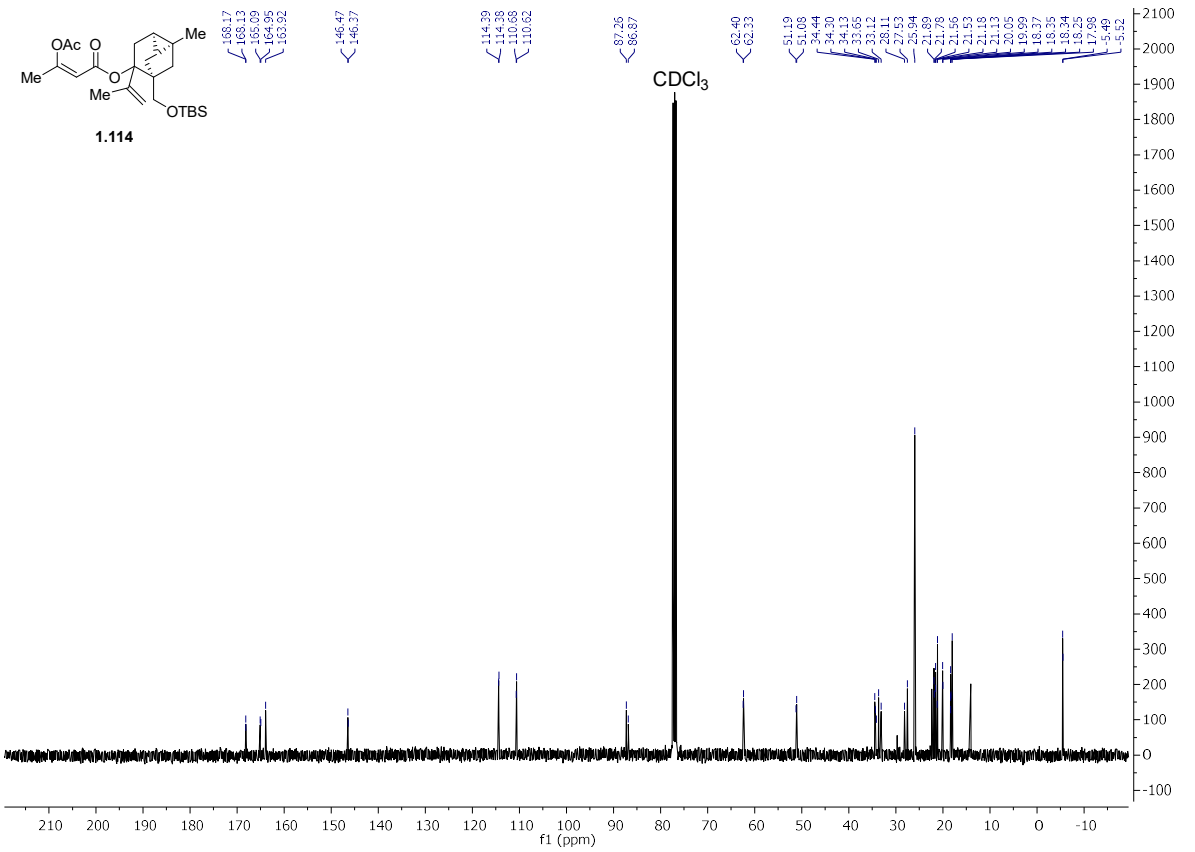
^{13}C NMR (101 MHz, $CDCl_3$) of **1.113**



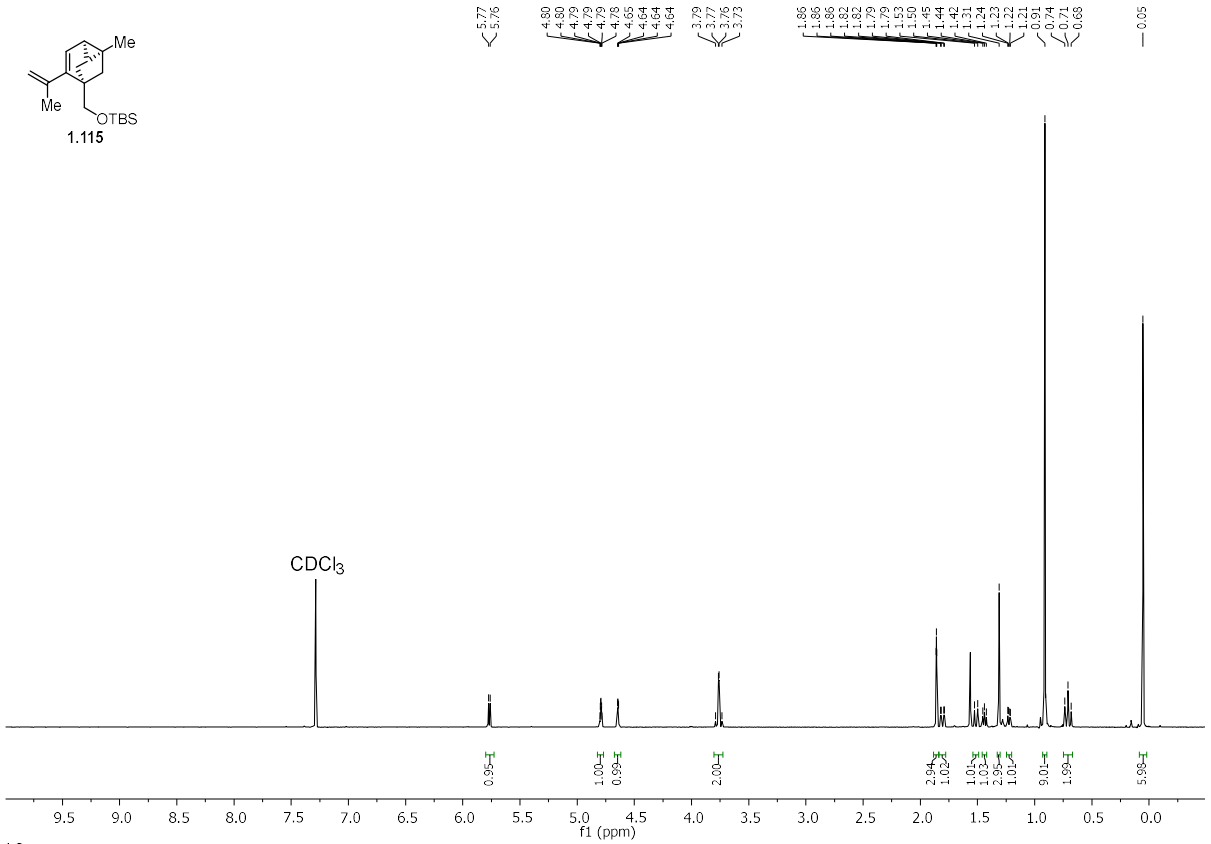
^{1}H NMR (400 MHz, $CDCl_3$) of **1.114**



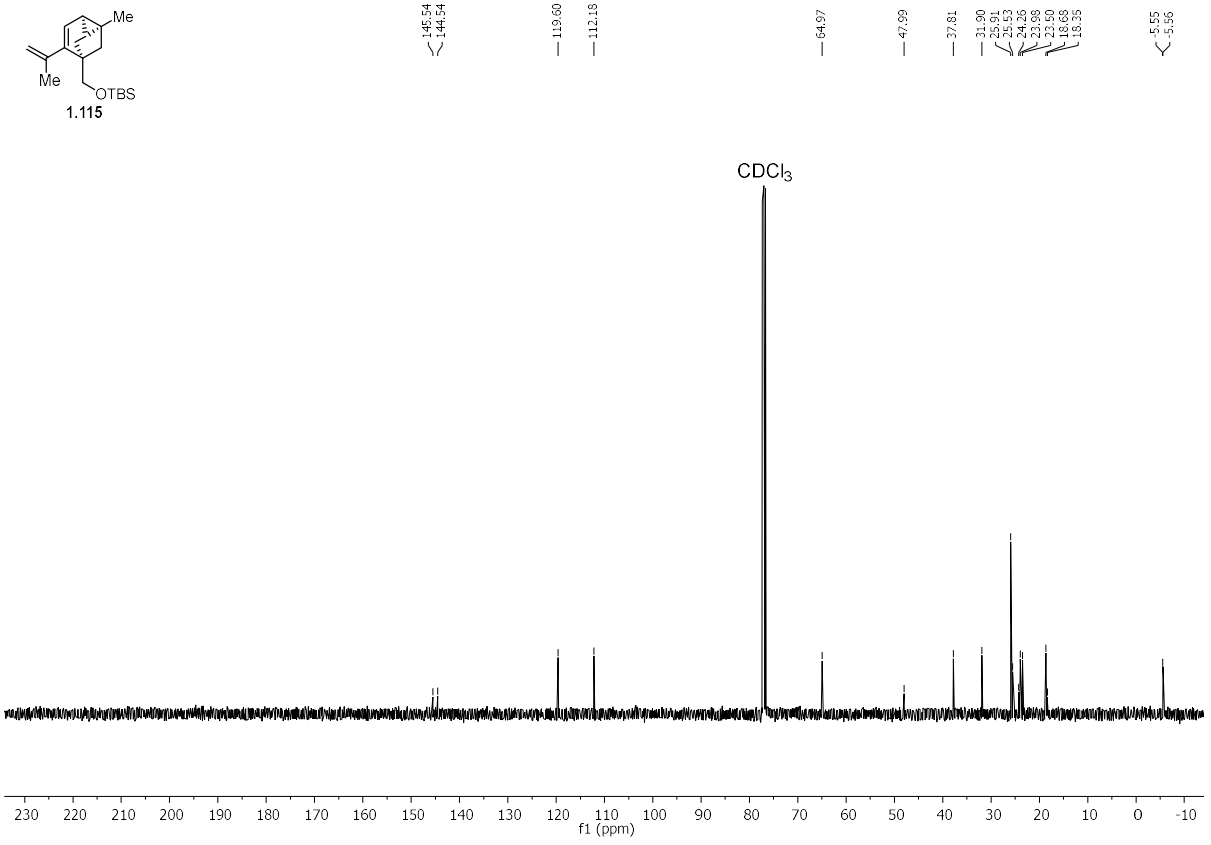
^{13}C NMR (101 MHz, $CDCl_3$) of **1.114**



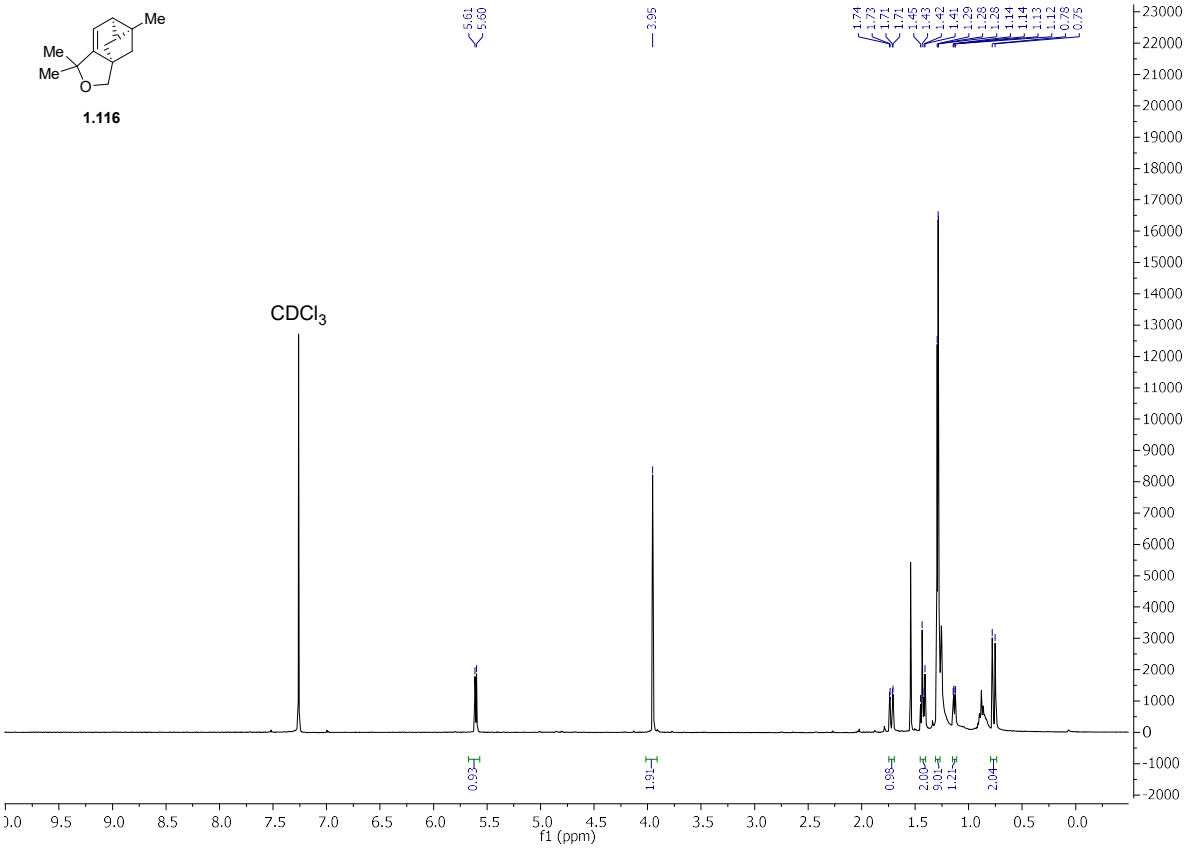
^{1}H NMR (400 MHz, $CDCl_3$) of **1.115**



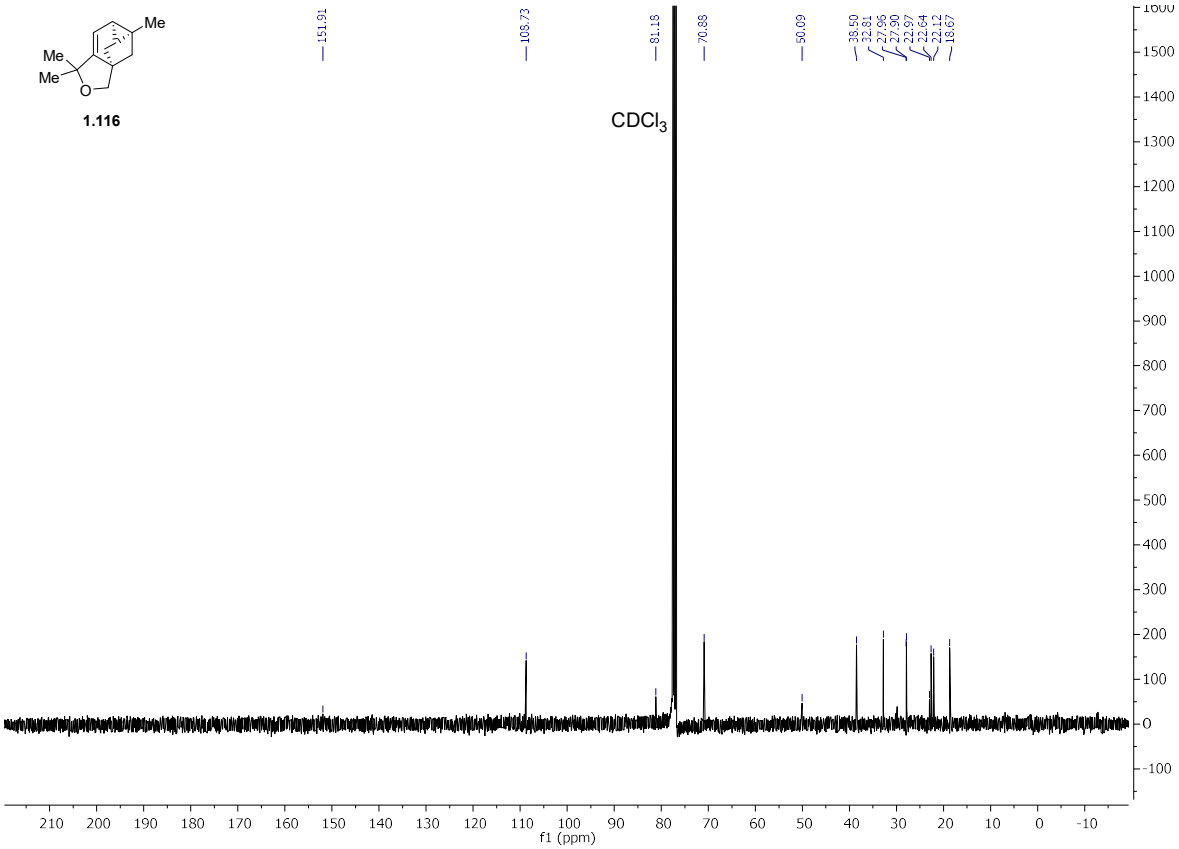
^{13}C NMR (101 MHz, $CDCl_3$) of **1.115**



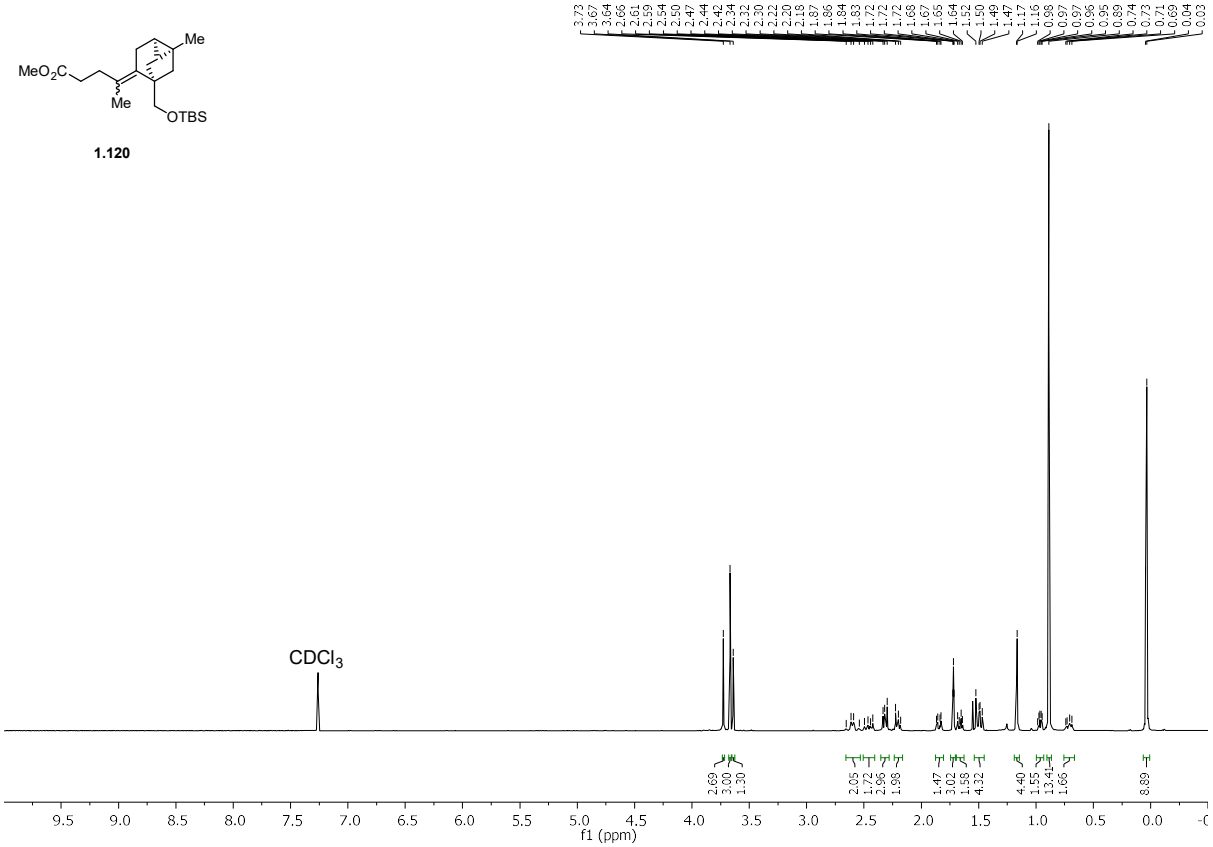
^{1}H NMR (400 MHz, $CDCl_3$) of **1.116**



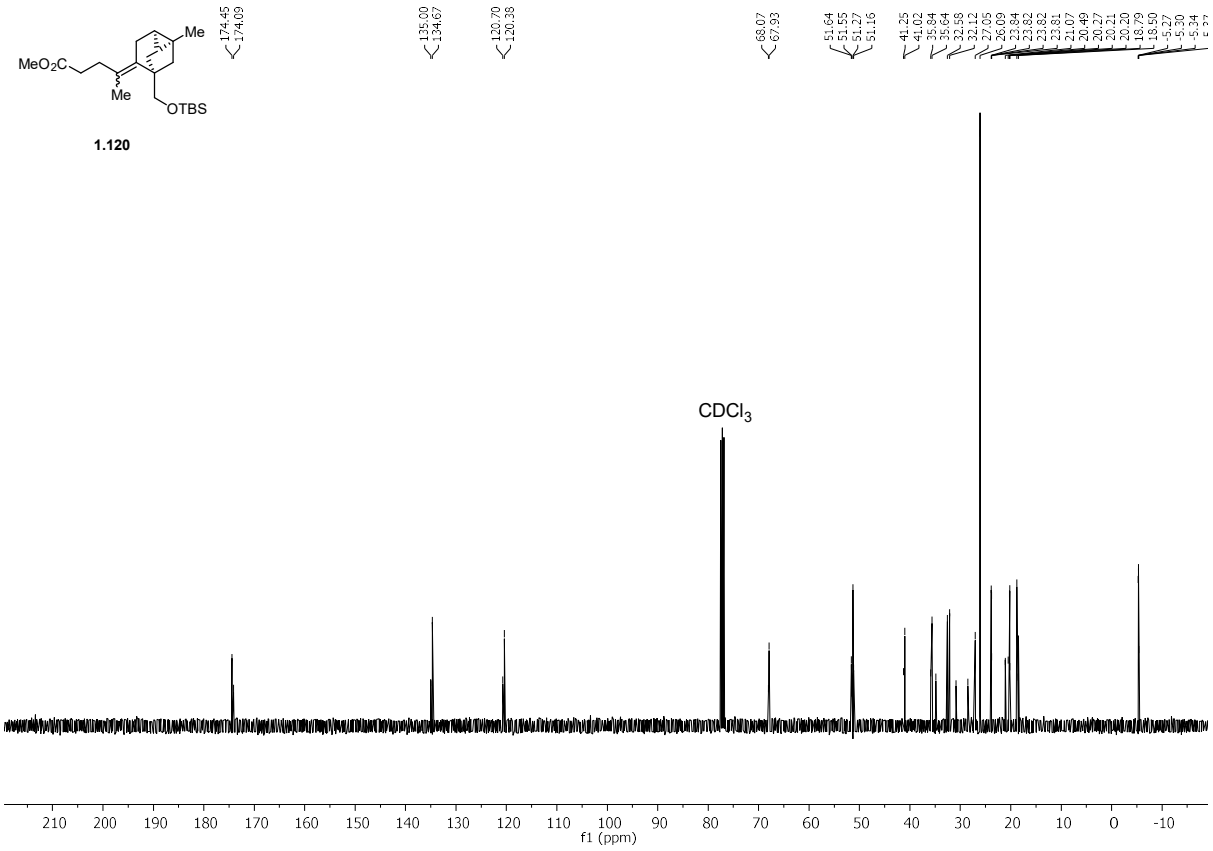
^{13}C NMR (101 MHz, $CDCl_3$) of **1.116**



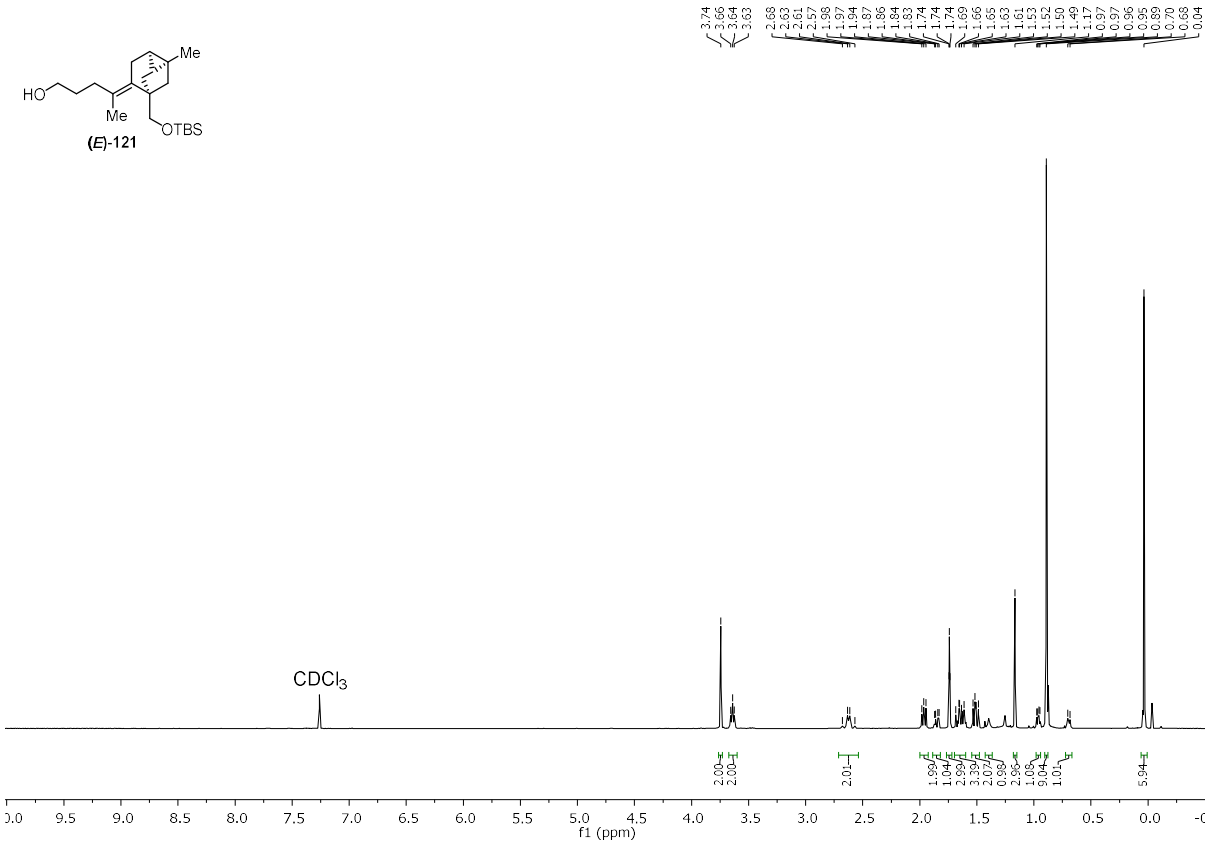
^{1}H NMR (400 MHz, $CDCl_3$) of **1.120**



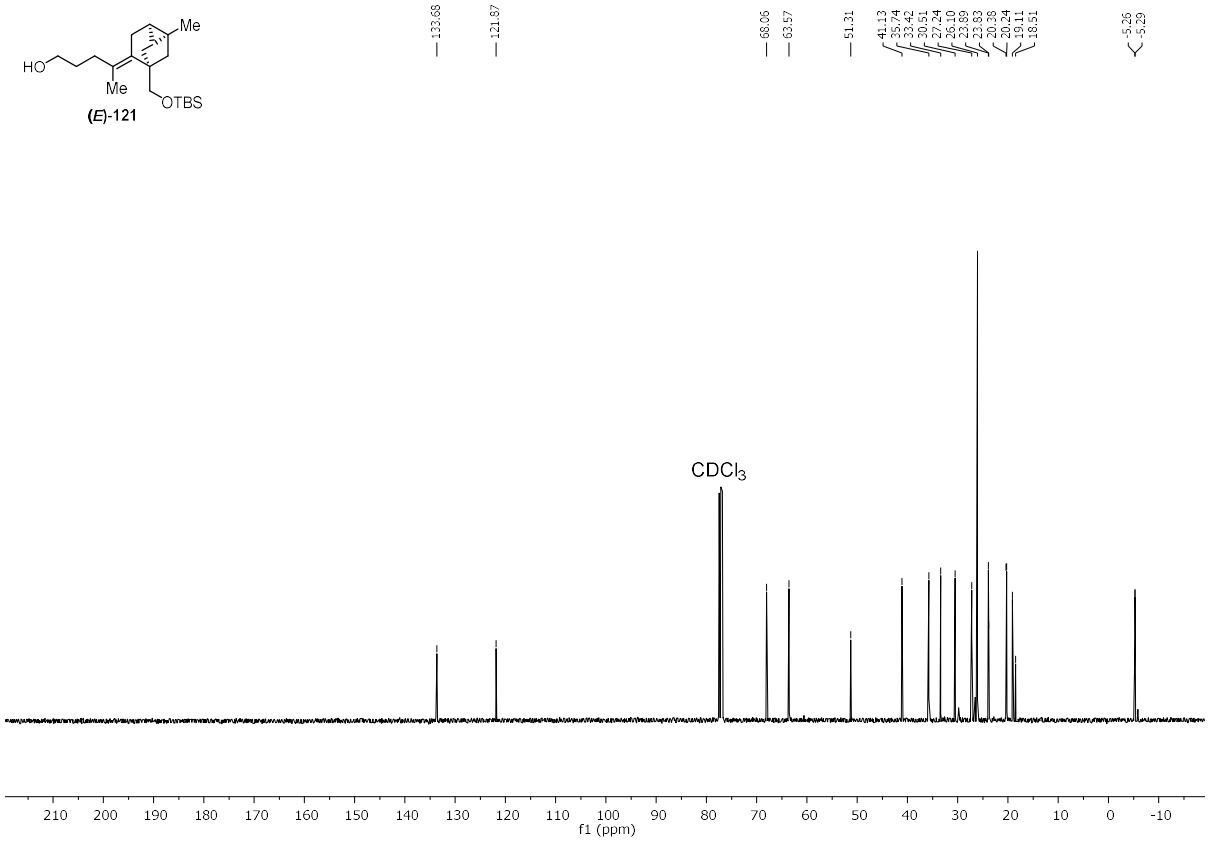
^{13}C NMR (101 MHz, $CDCl_3$) of **1.120**



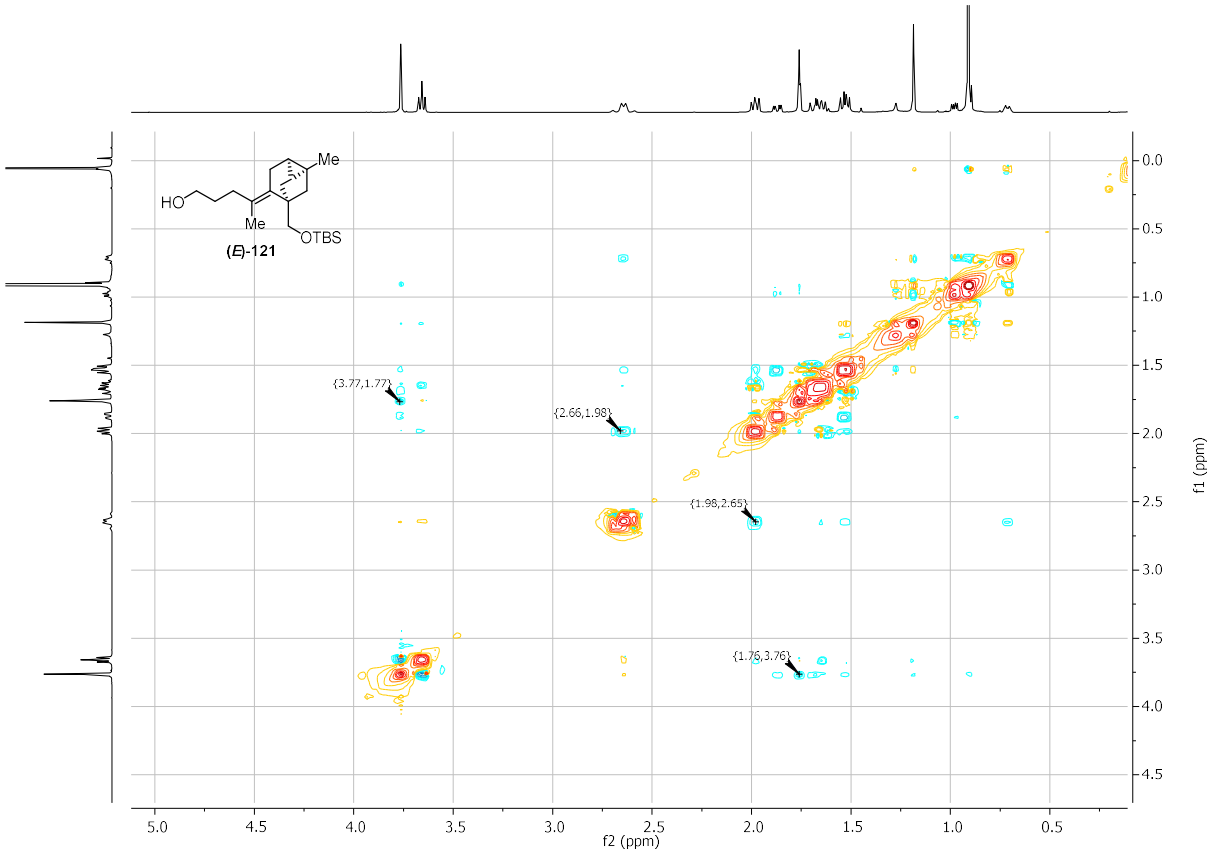
^{1}H NMR (400 MHz, $CDCl_3$) of **(*E*)-121**



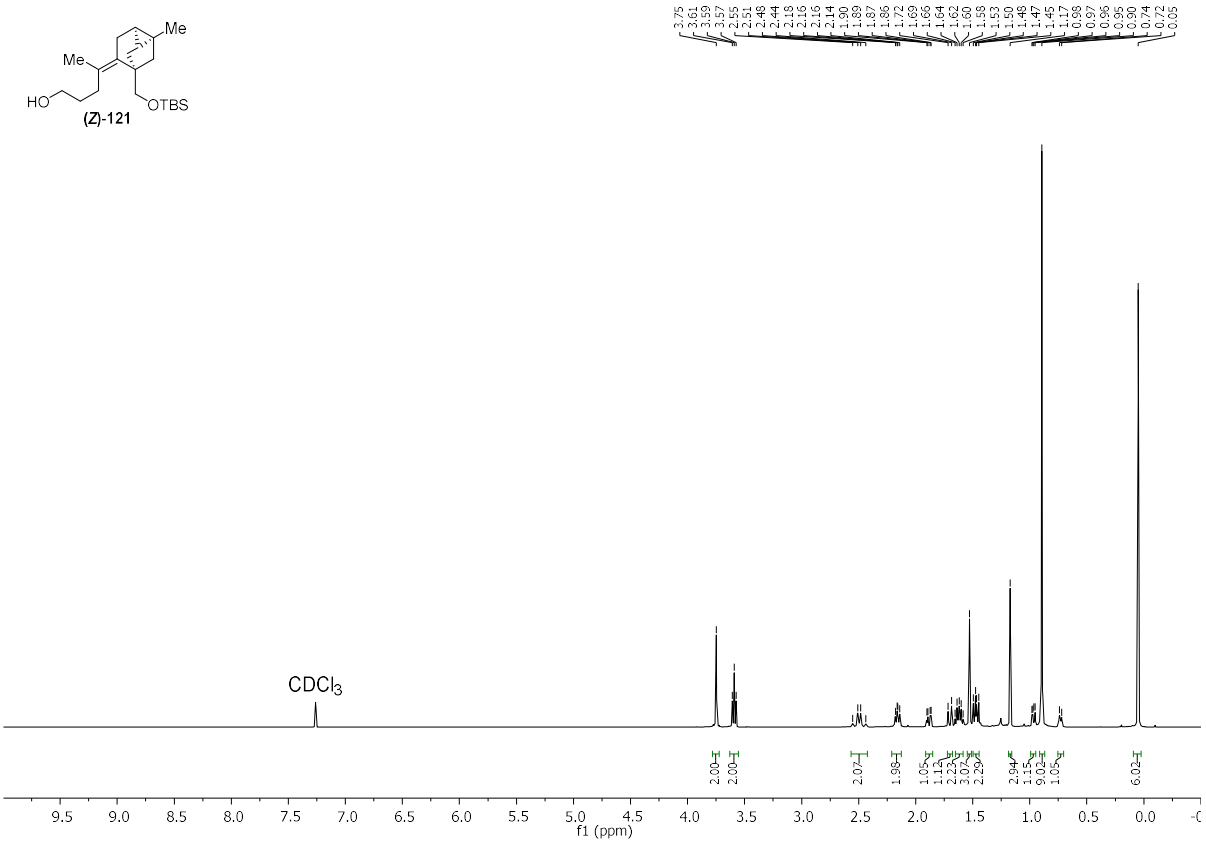
^{13}C NMR (101 MHz, $CDCl_3$) of **(*E*)-121**



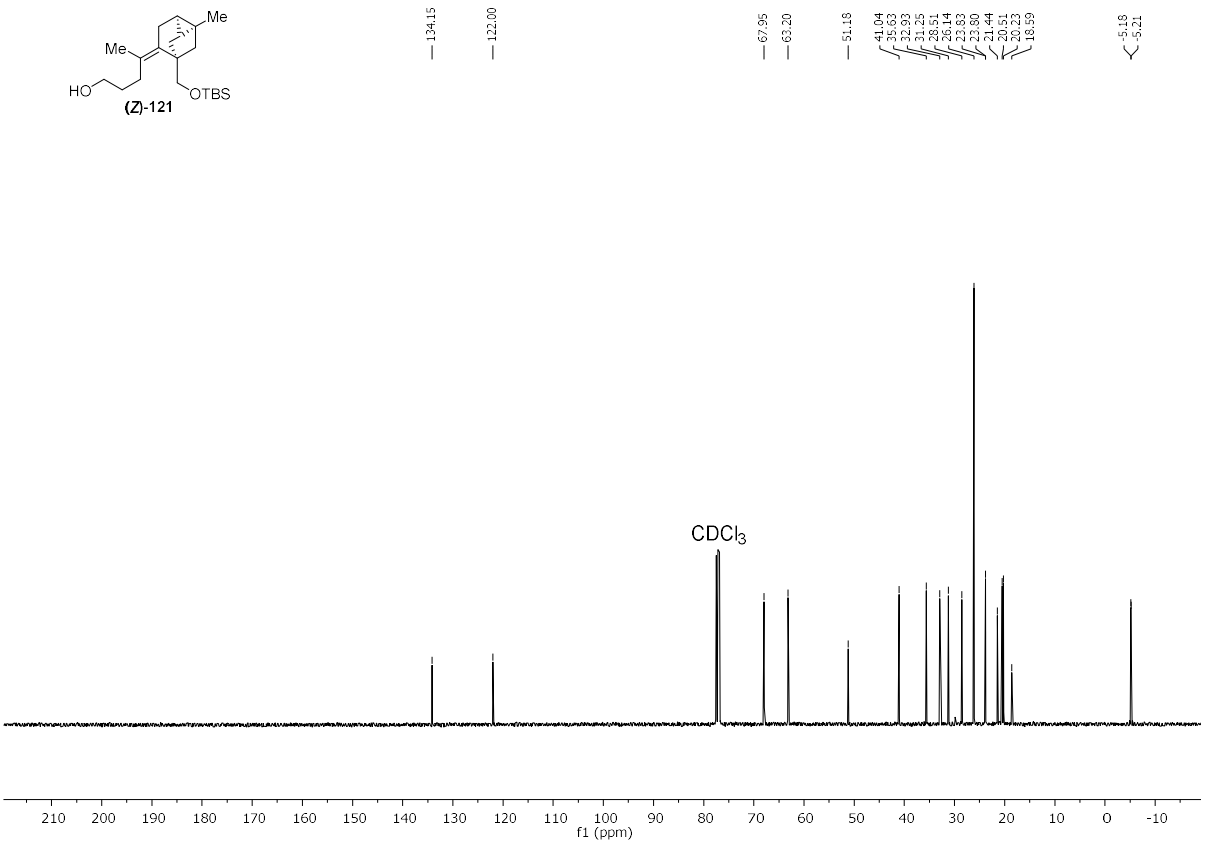
NOESY NMR (400 MHz, $CDCl_3$) of **(*E*)-121**



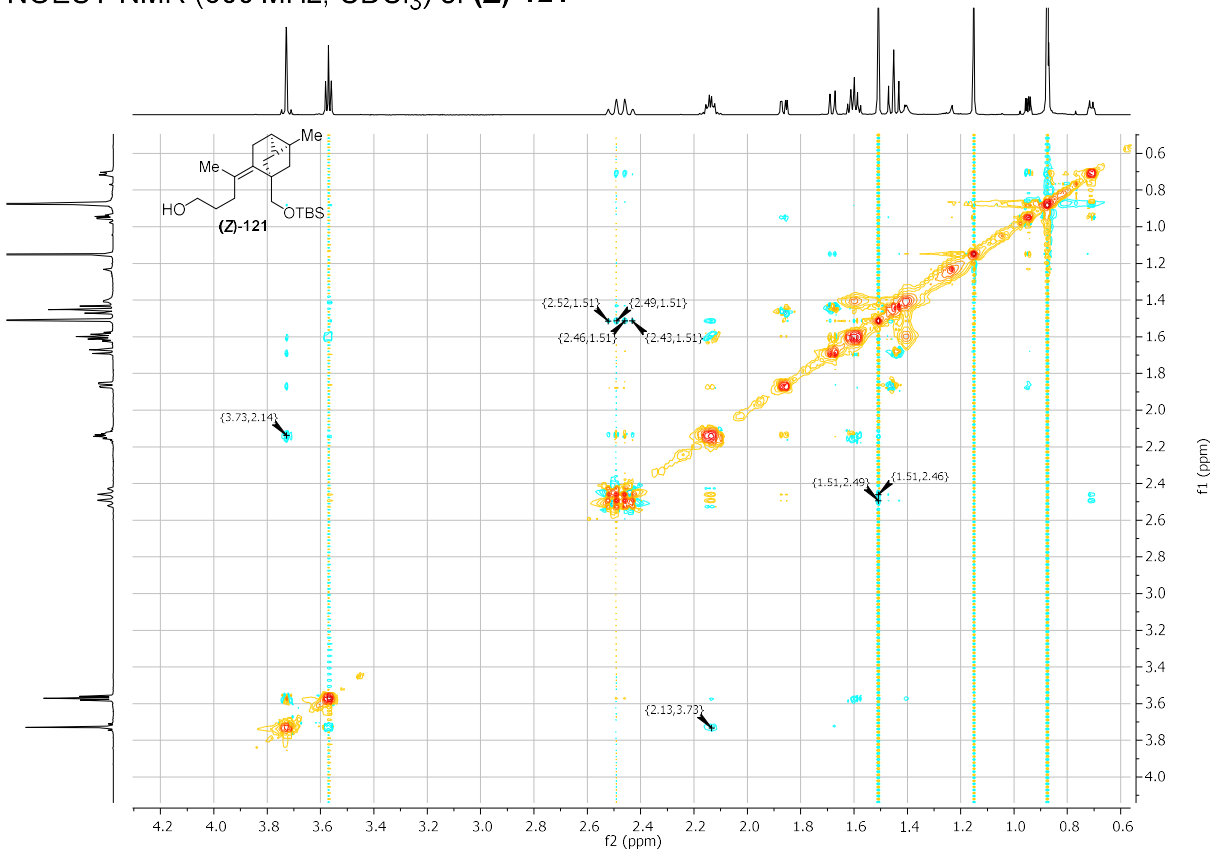
^{1}H NMR (400 MHz, $CDCl_3$) of **(*Z*)-121**



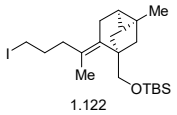
^{13}C NMR (101 MHz, $CDCl_3$) of **(*Z*)-121**



NOESY NMR (600 MHz, $CDCl_3$) of **(*Z*)-121**

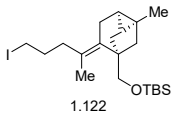


^{1}H NMR (400 MHz, $CDCl_3$) of **1.122**



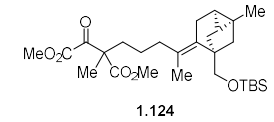
1.122

^{13}C NMR (101 MHz, $CDCl_3$) of **1.122**



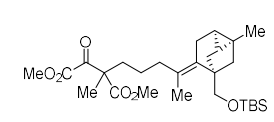
1.122

^{1}H NMR (400 MHz, $CDCl_3$) of **1.124**



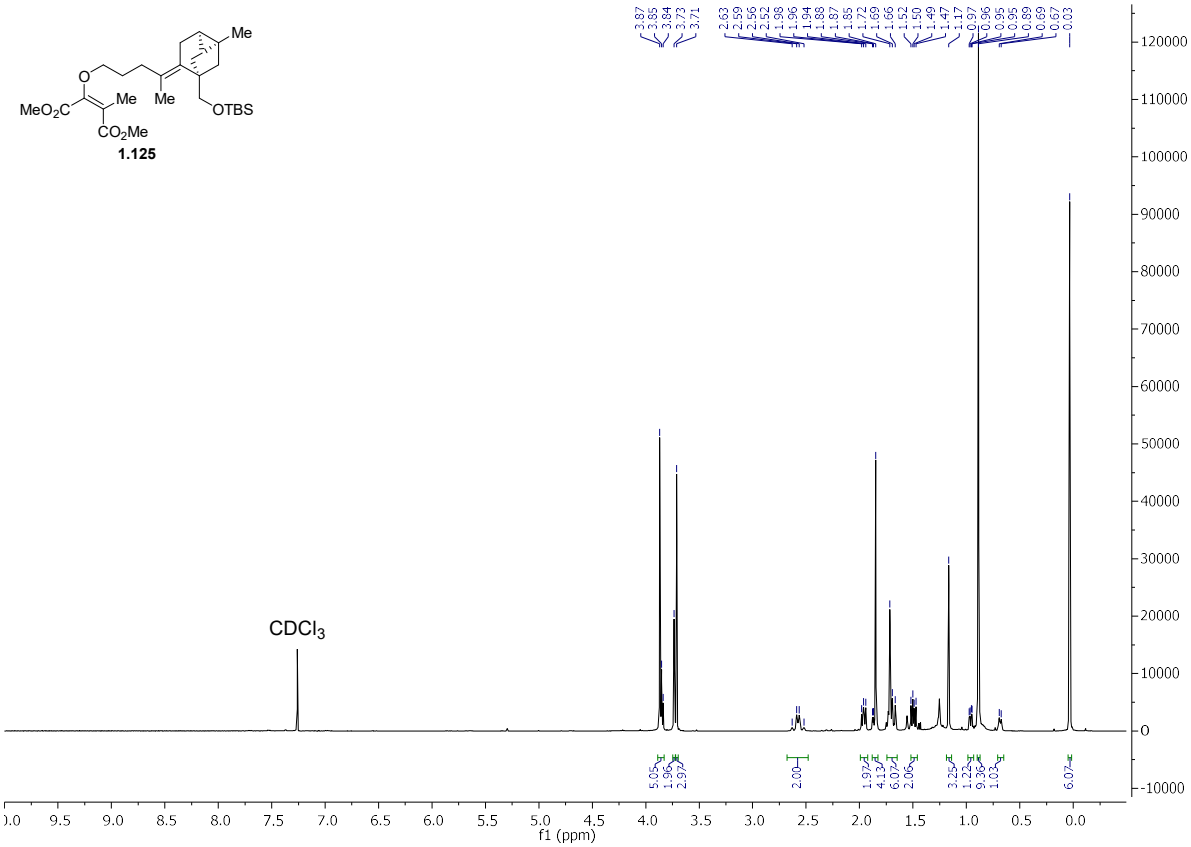
1.124

^{13}C NMR (101 MHz, $CDCl_3$) of **1.124**

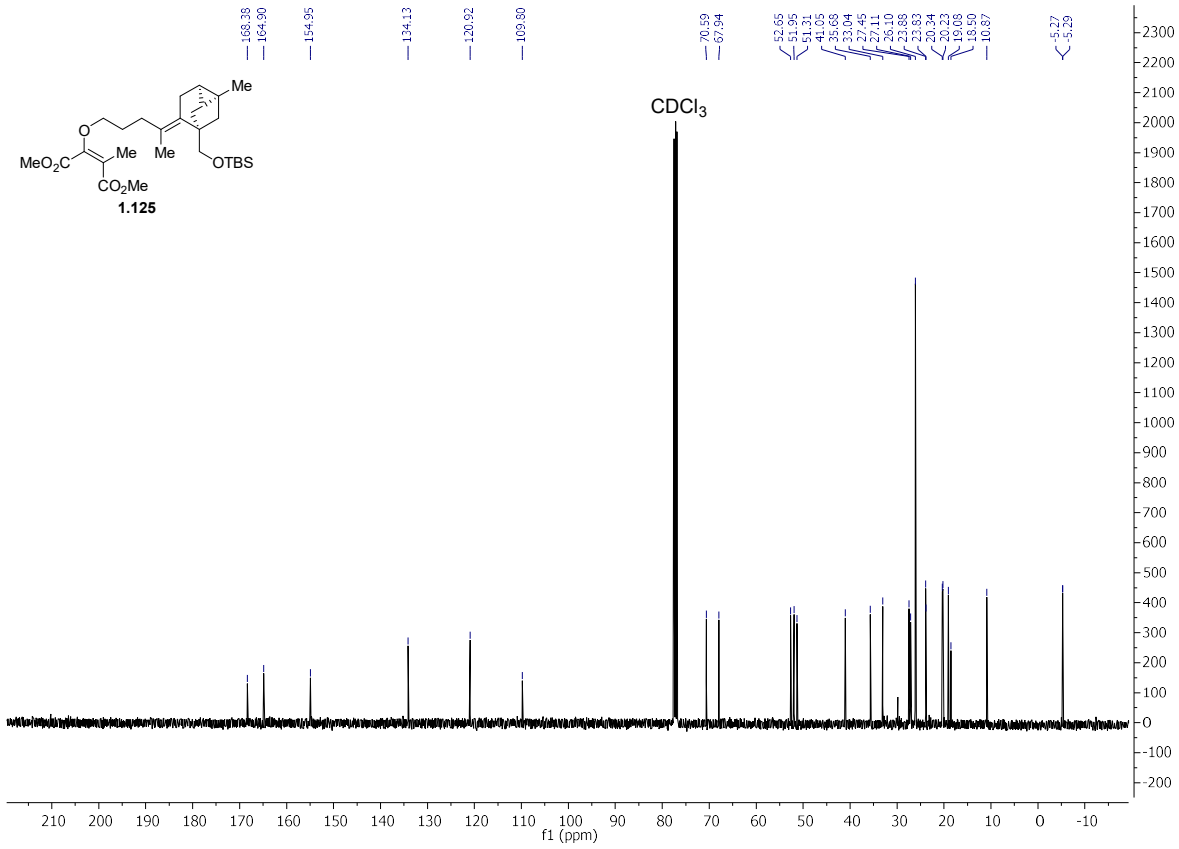


1.124

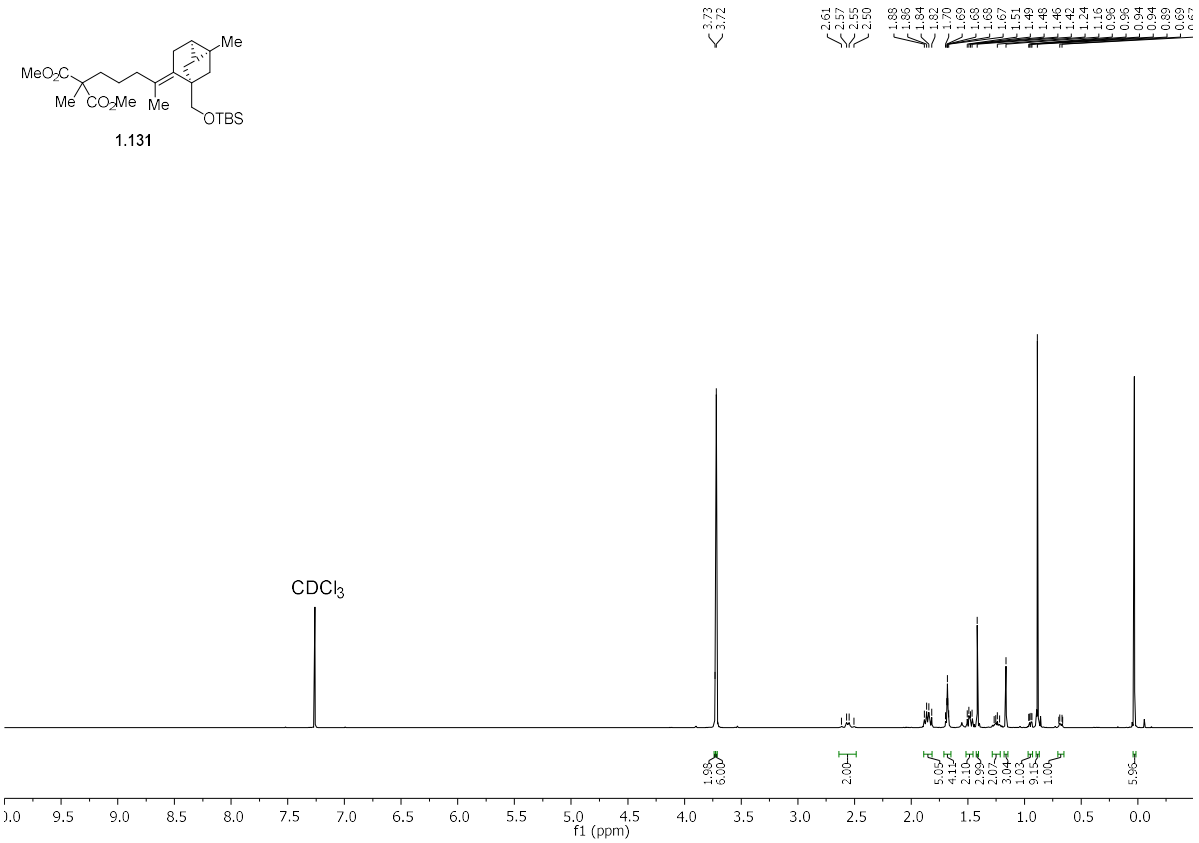
^{1}H NMR (400 MHz, $CDCl_3$) of **1.125**



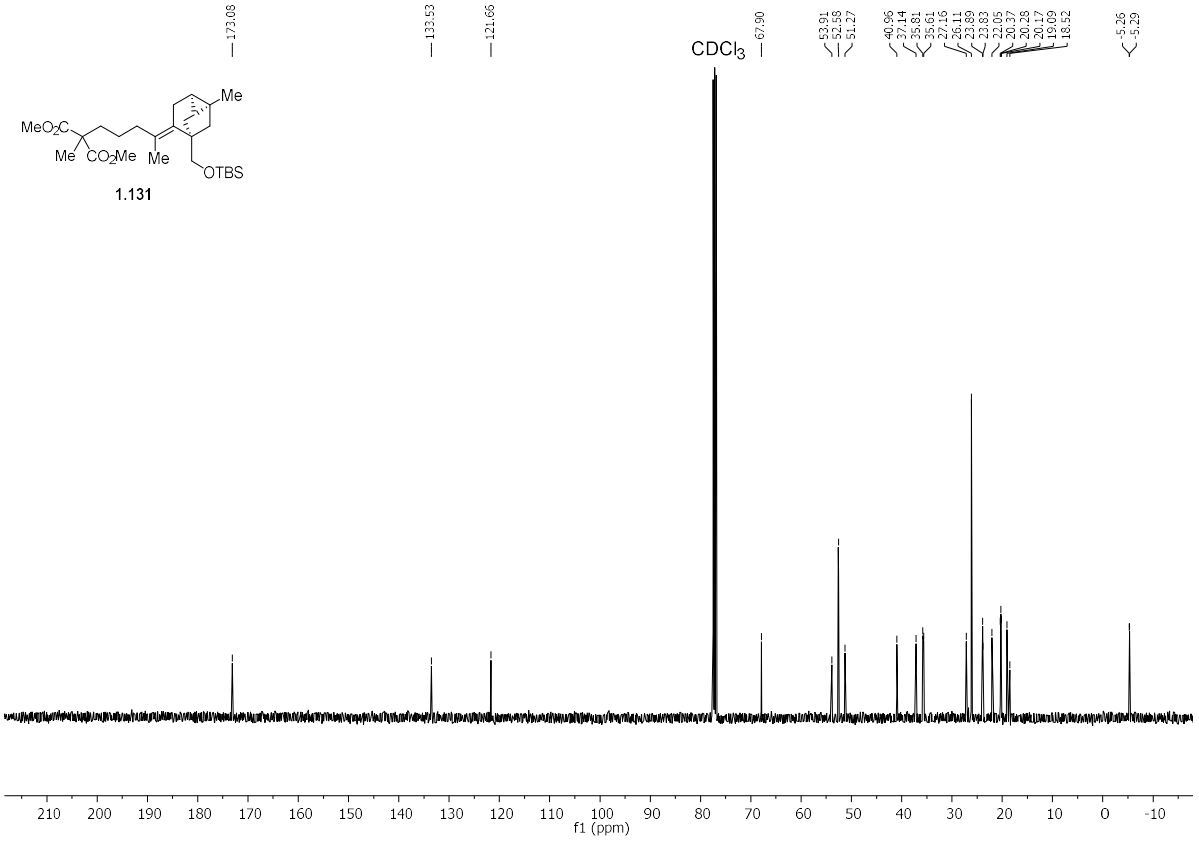
^{13}C NMR (101 MHz, $CDCl_3$) of **1.125**



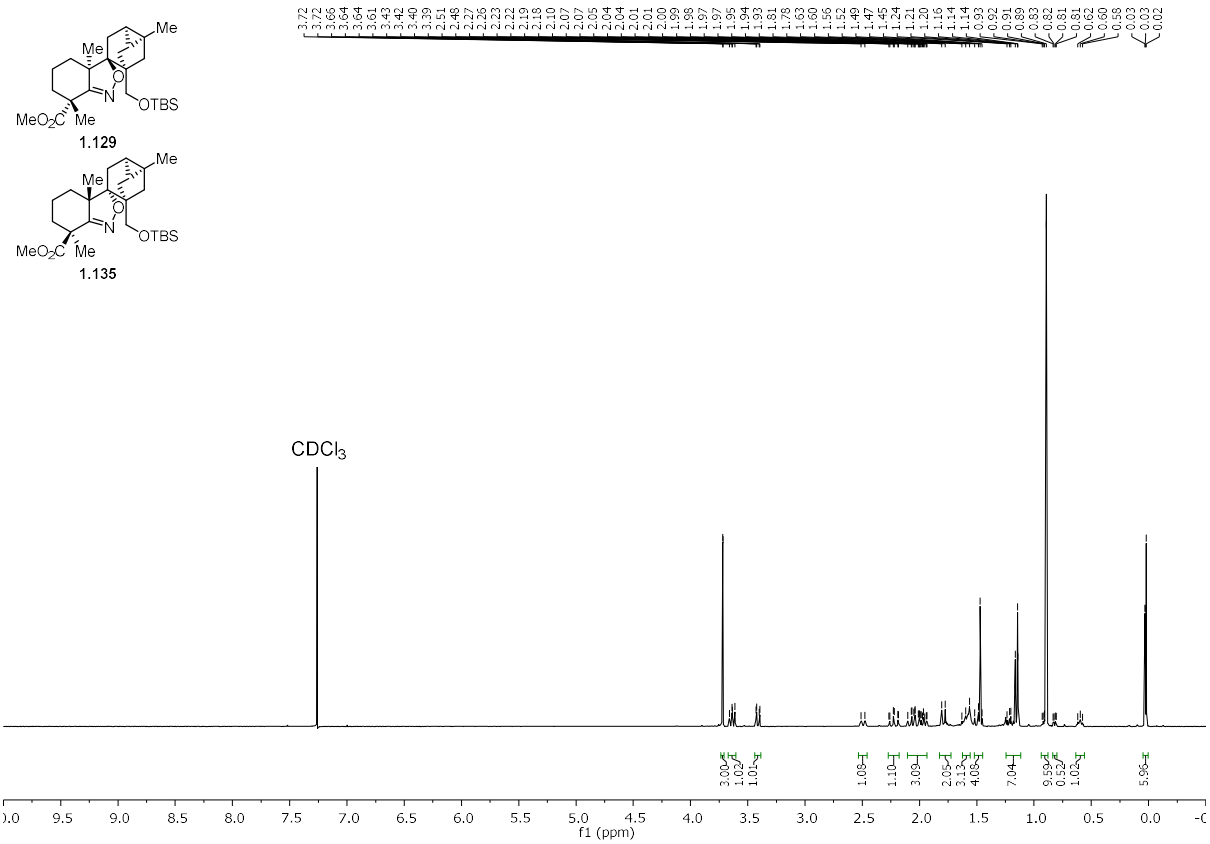
^{1}H NMR (400 MHz, $CDCl_3$) of **1.13**



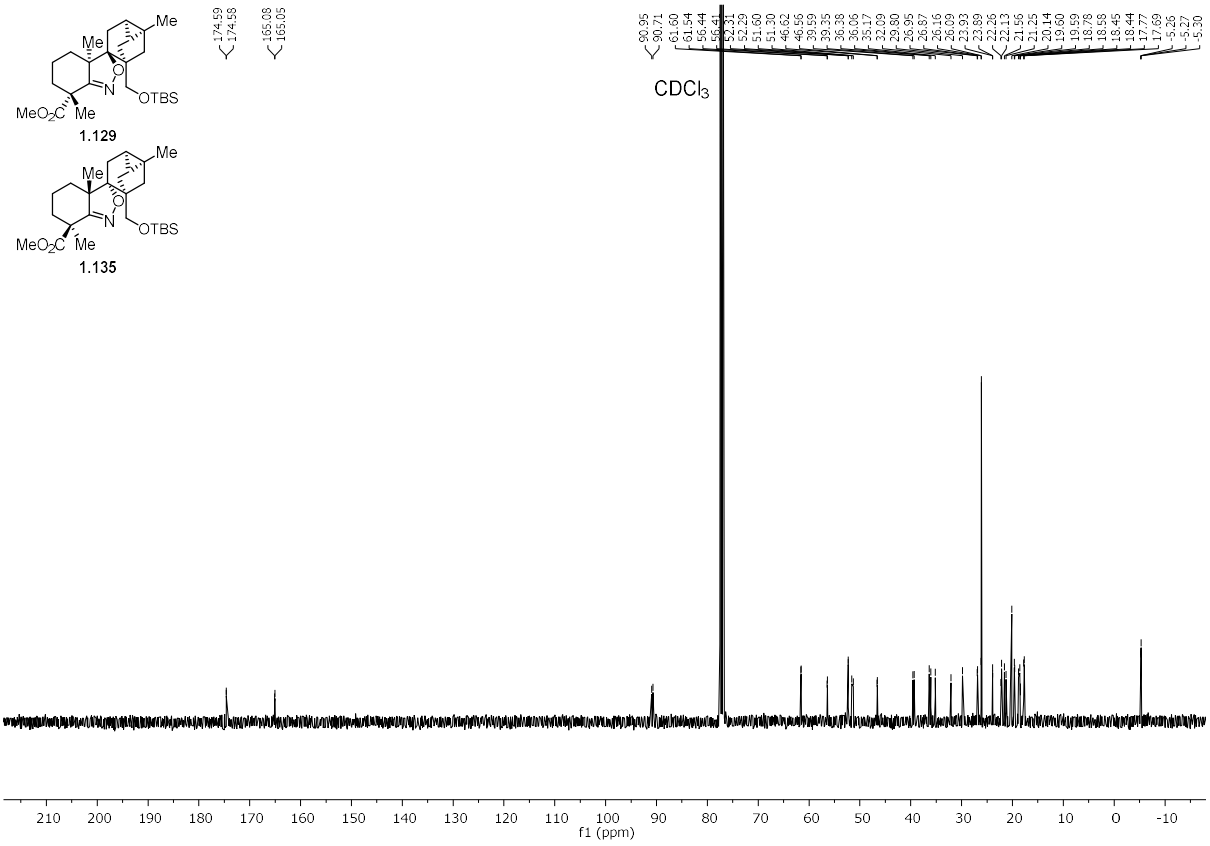
^{13}C NMR (101 MHz, $CDCl_3$) of **1.131**



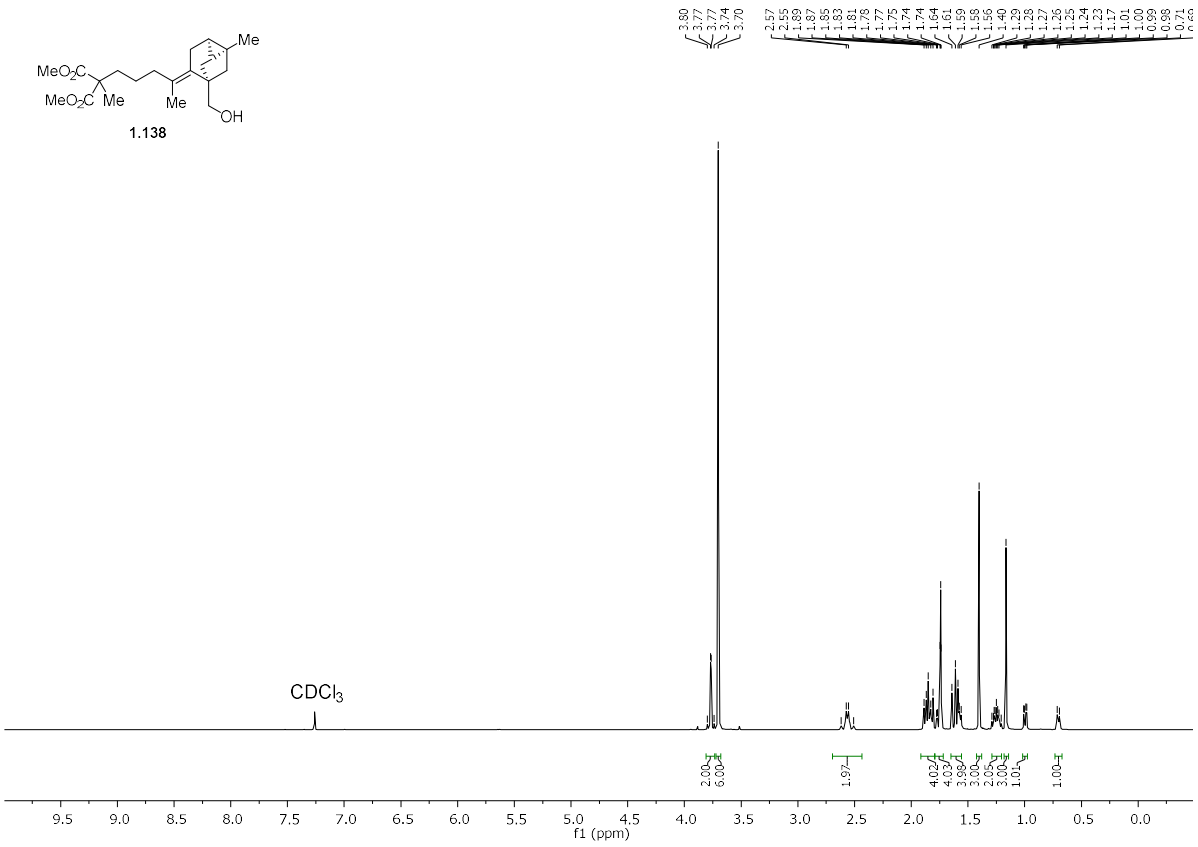
^{1}H NMR (400 MHz, $CDCl_3$) of **1.129** and **1.135** (1:1)



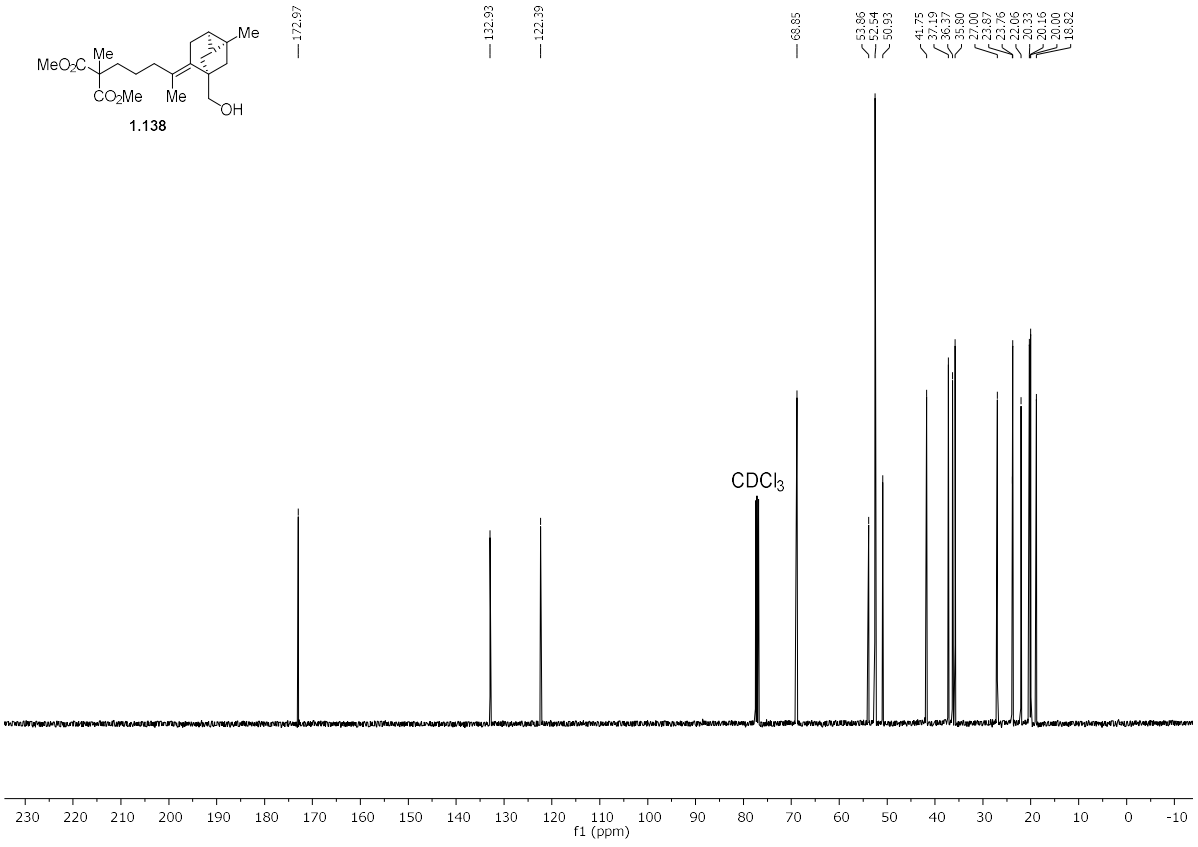
^{13}C NMR (101 MHz, $CDCl_3$) of **1.129** and **1.135** (1:1)



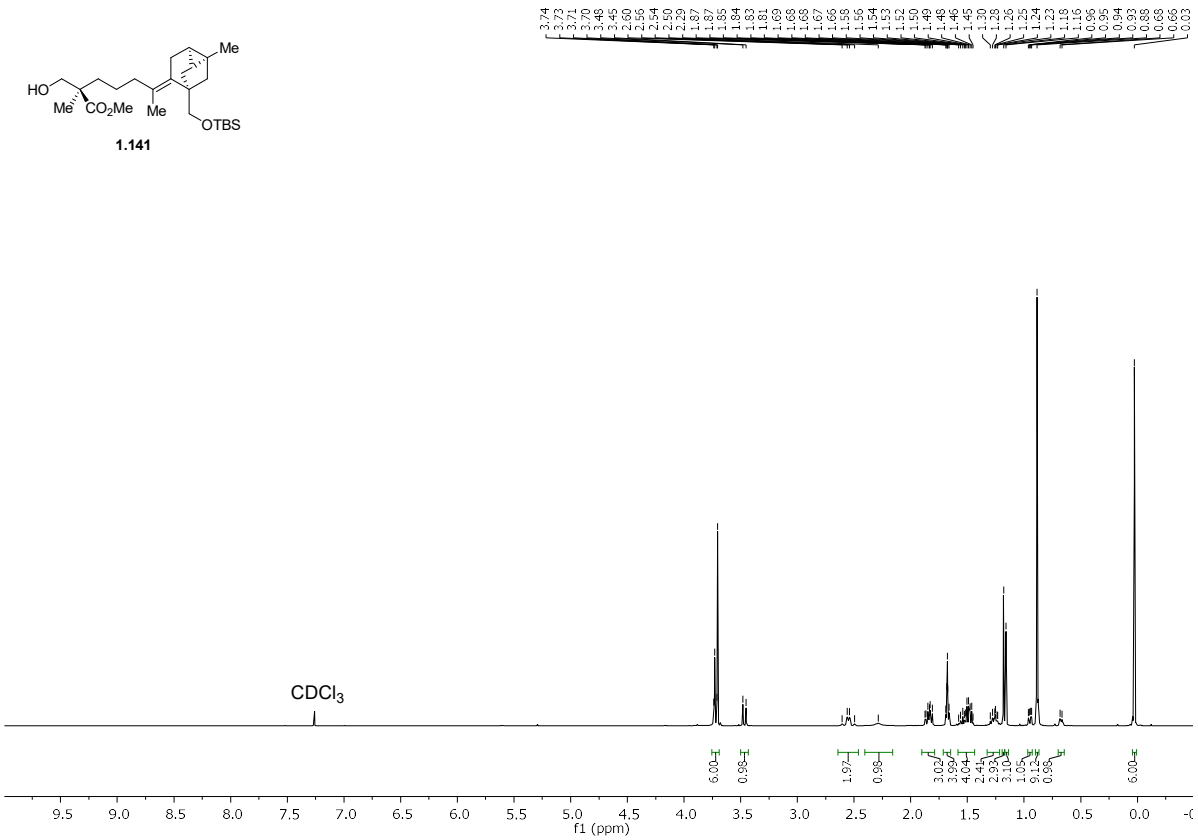
^{1}H NMR (400 MHz, $CDCl_3$) of **1.138**



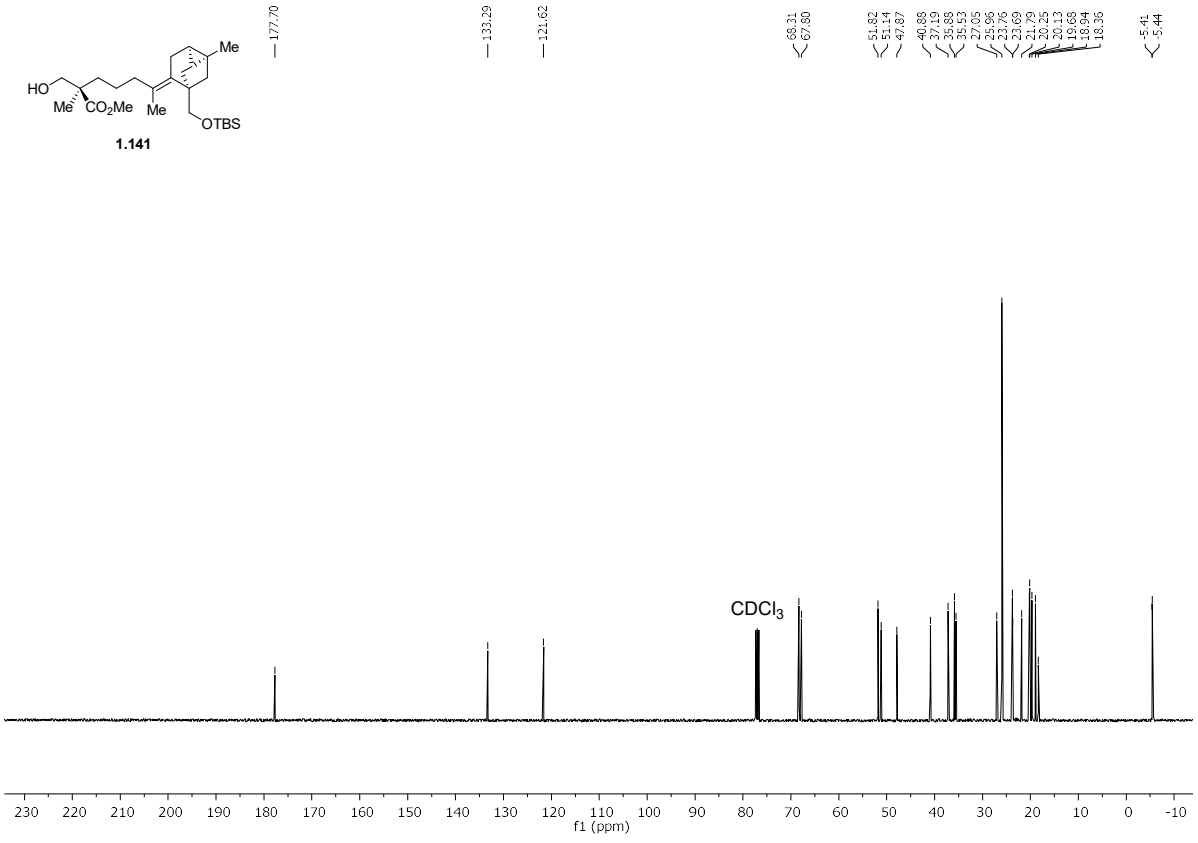
^{13}C NMR (101 MHz, $CDCl_3$) of **1.138**



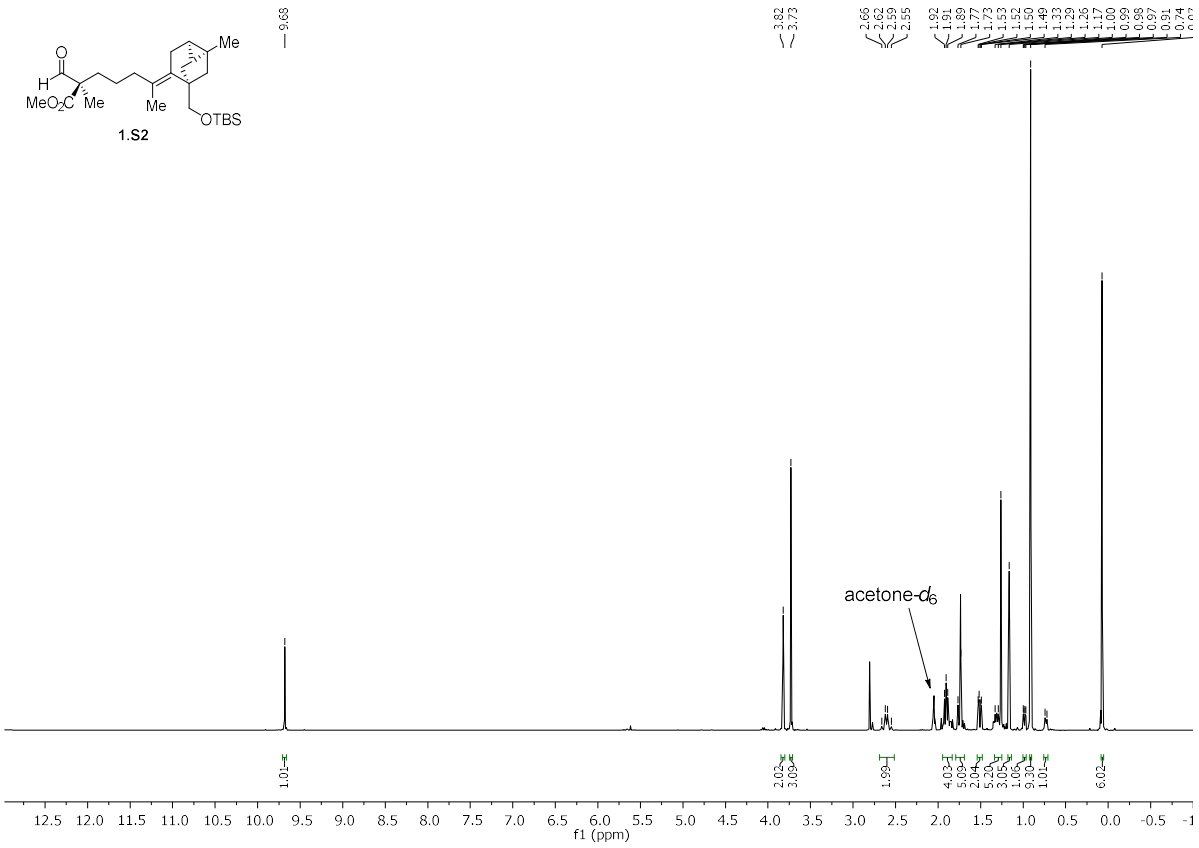
^{1}H NMR (400 MHz, $CDCl_3$) of **1.141**



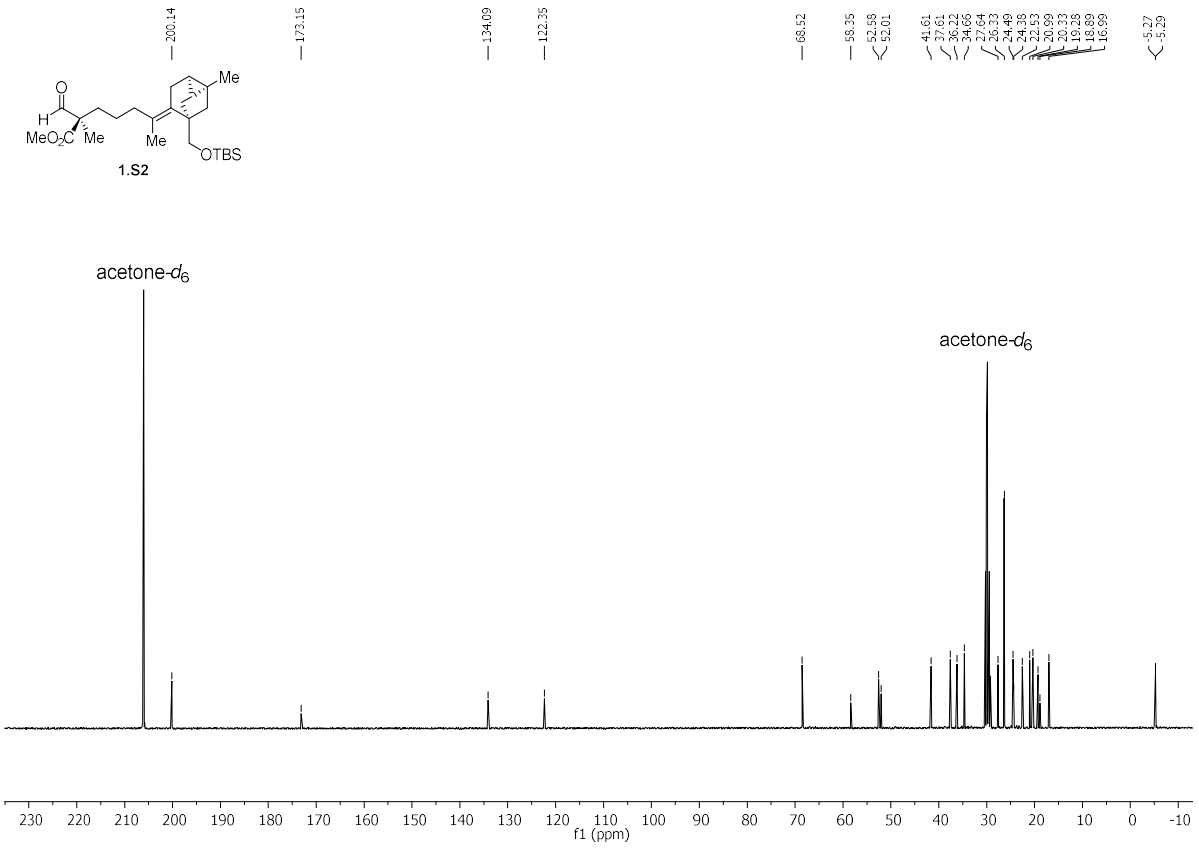
^{13}C NMR (101 MHz, $CDCl_3$) of **1.141**



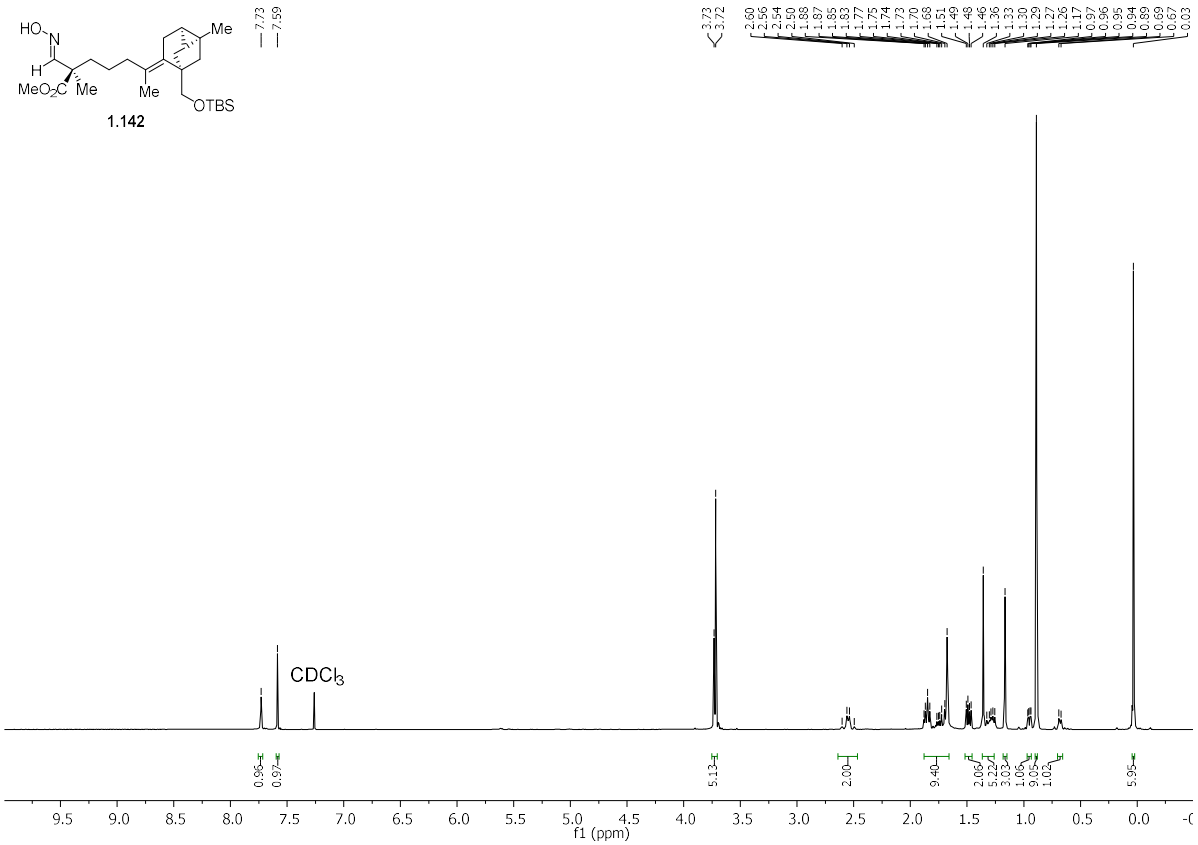
^{1}H NMR (400 MHz, acetone-d_6) of **1.S2**



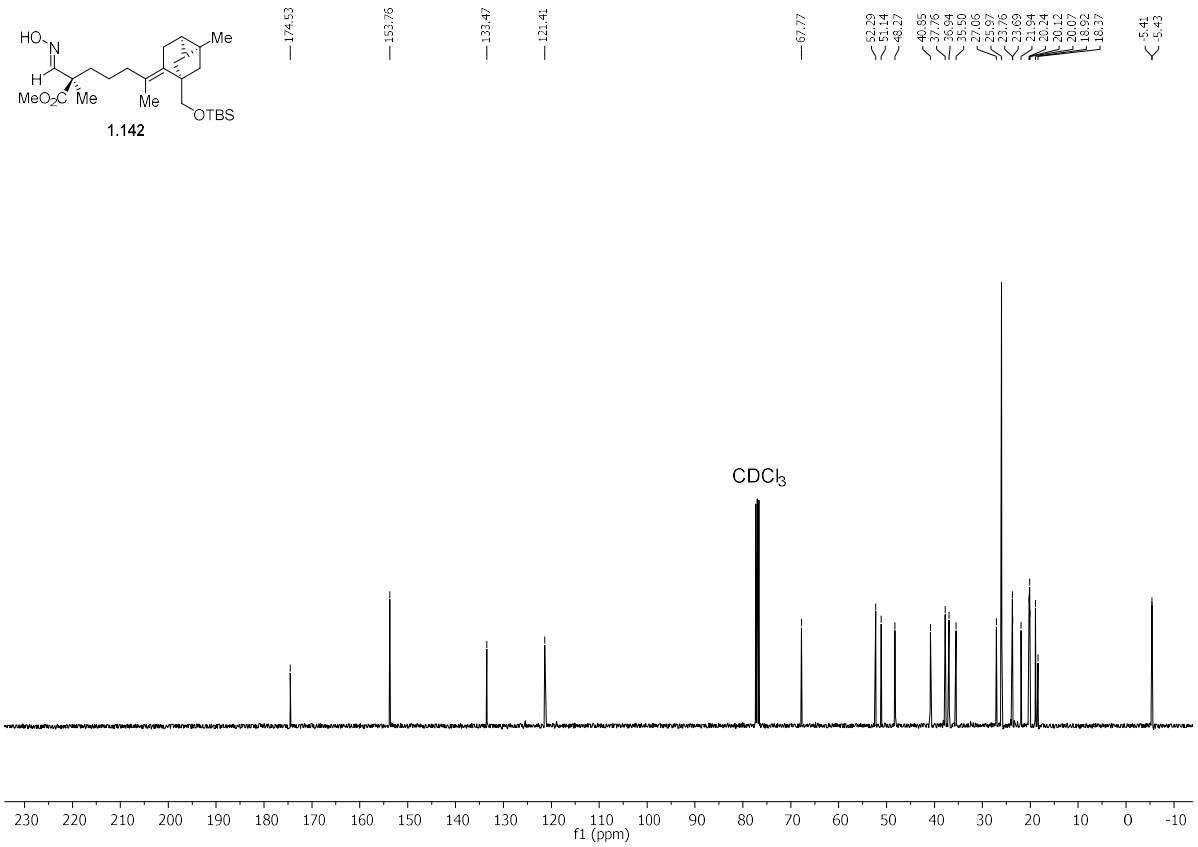
^{13}C NMR (101 MHz, acetone-d_6) of **1.S2**



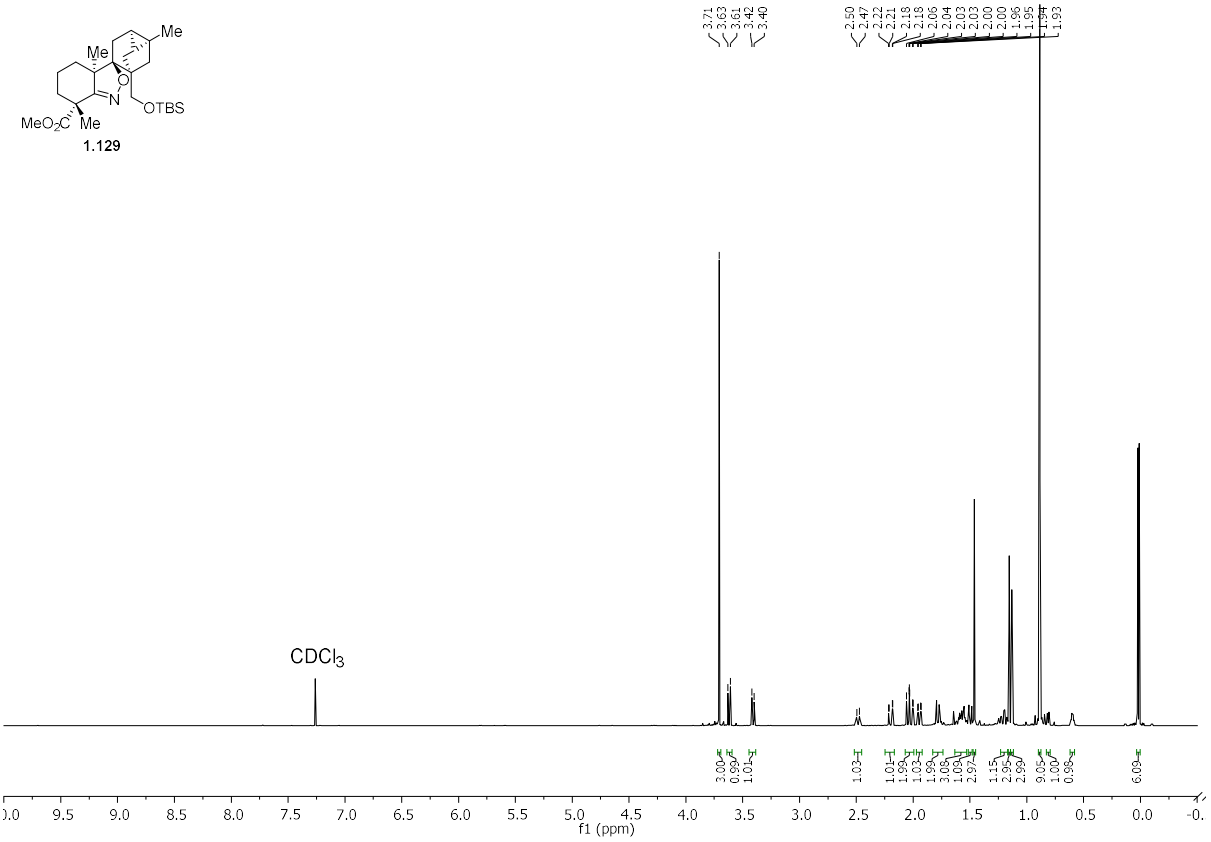
^{1}H NMR (400 MHz, $CDCl_3$) of **1.142**



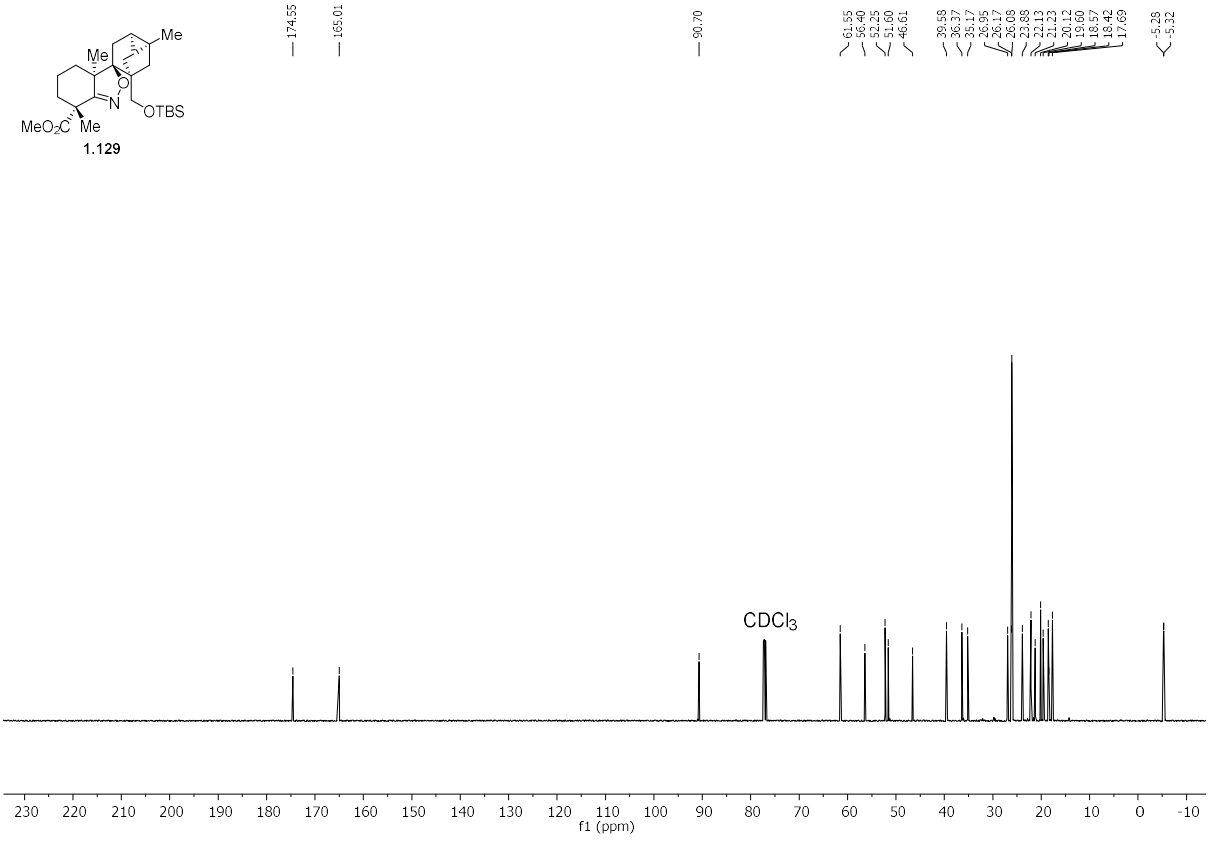
^{13}C NMR (101 MHz, $CDCl_3$) of **1.142**



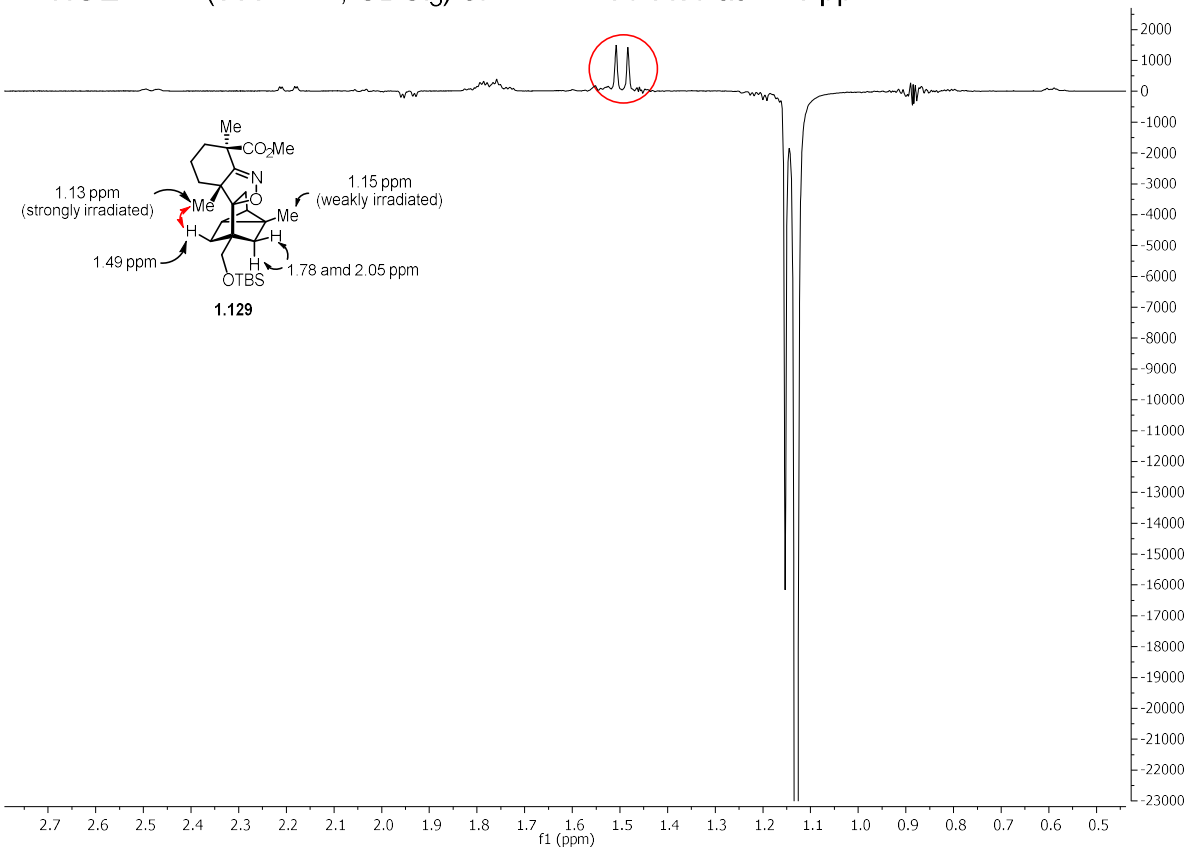
^{1}H NMR (500 MHz, $CDCl_3$) of **1.129**



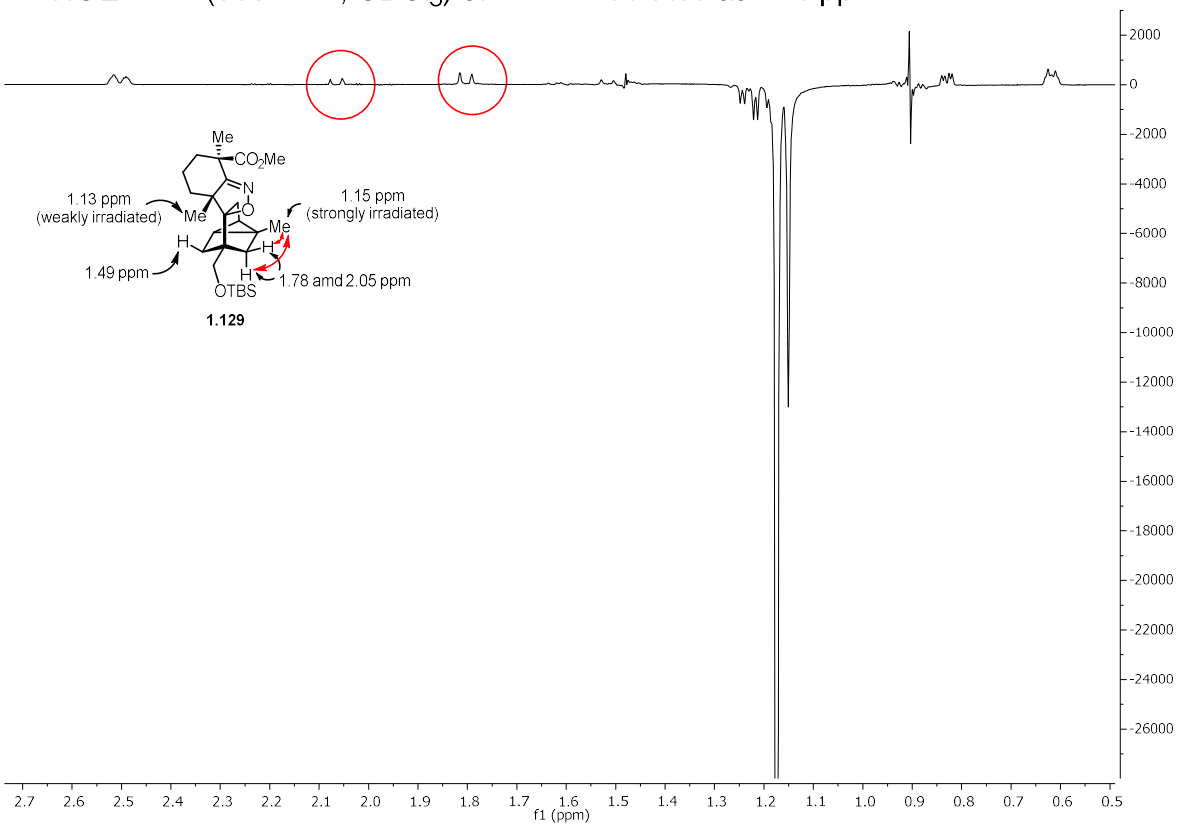
^{13}C NMR (126 MHz, $CDCl_3$) of **1.129**



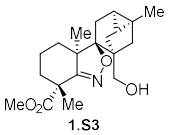
1D NOE NMR (500 MHz, $CDCl_3$) of **1.129** irradiated at 1.13 ppm



1D NOE NMR (500 MHz, $CDCl_3$) of **1.129** irradiated at 1.15 ppm

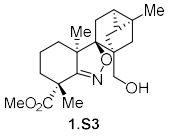


^{1}H NMR (400 MHz, $CDCl_3$) of **1.S3**



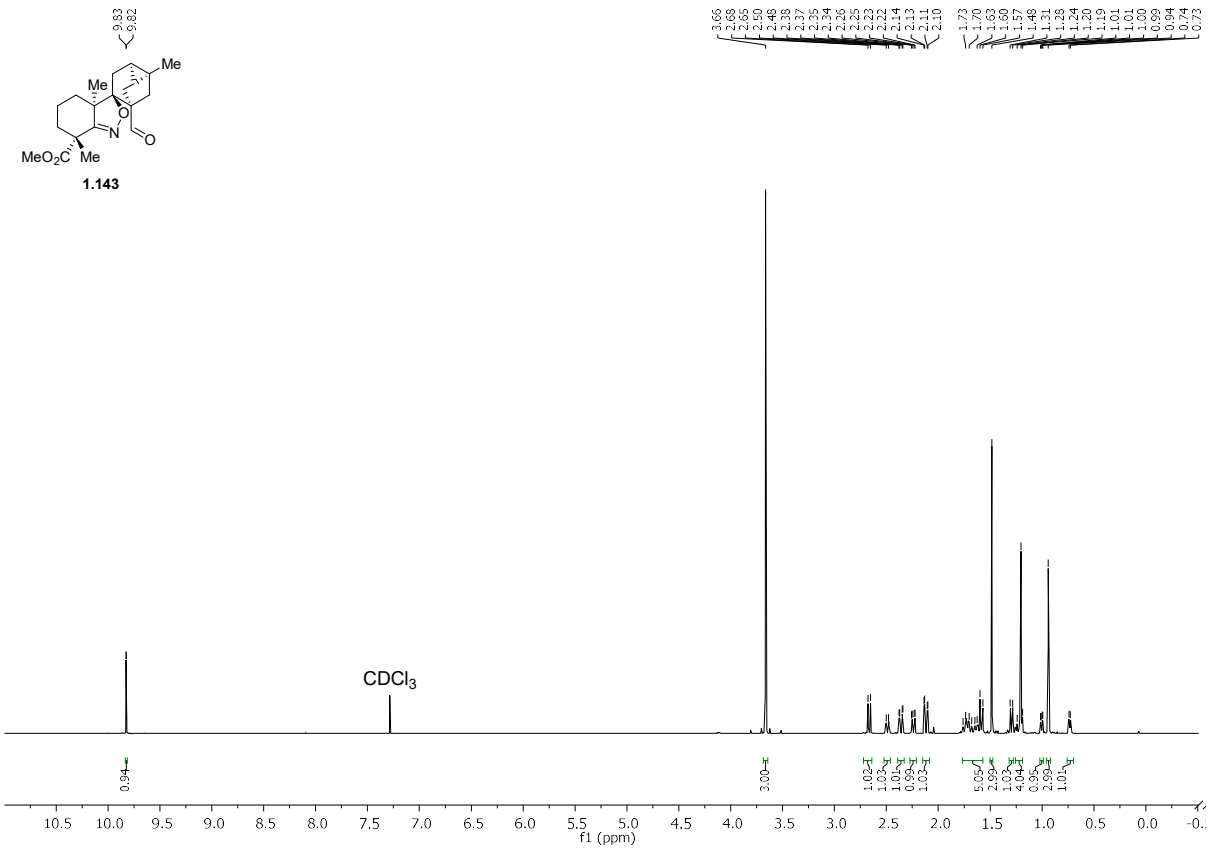
1.S3

^{13}C NMR (101 MHz, $CDCl_3$) of **1.S3**

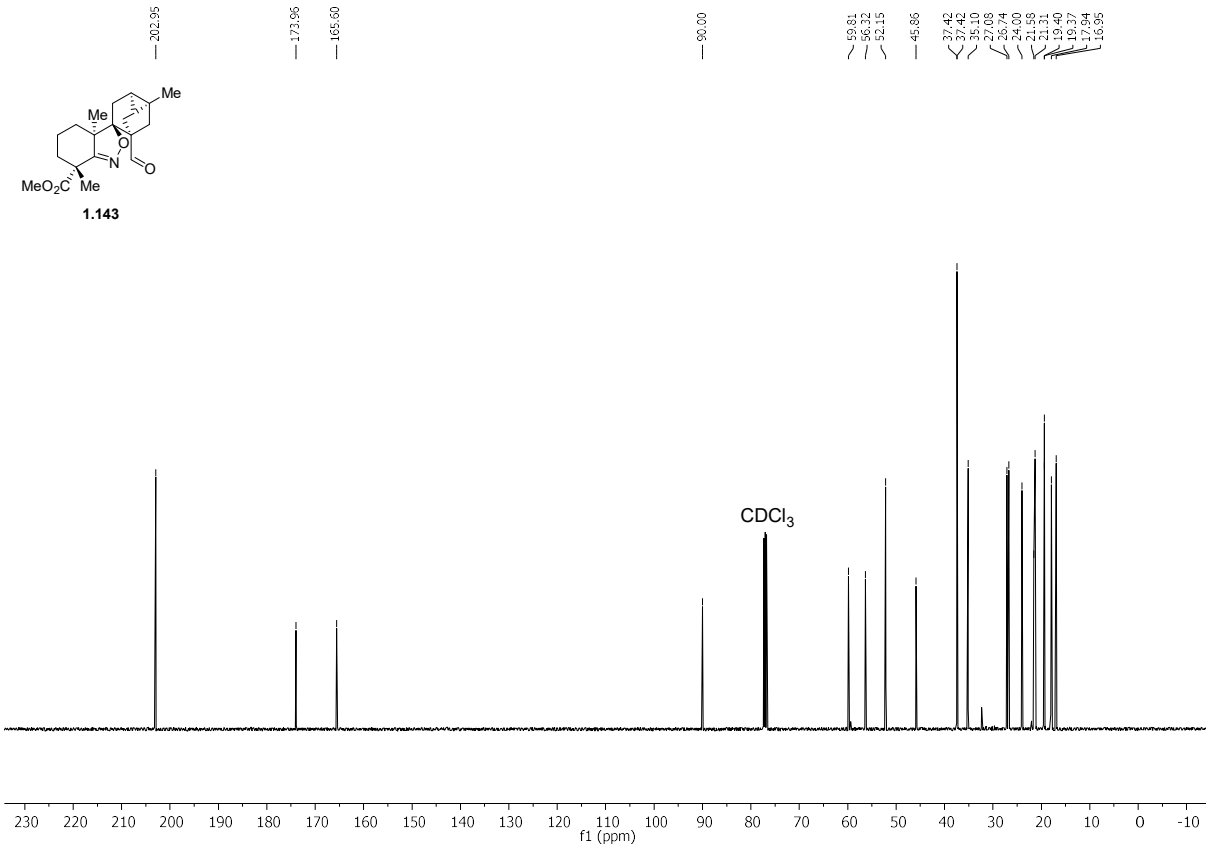


1.S3

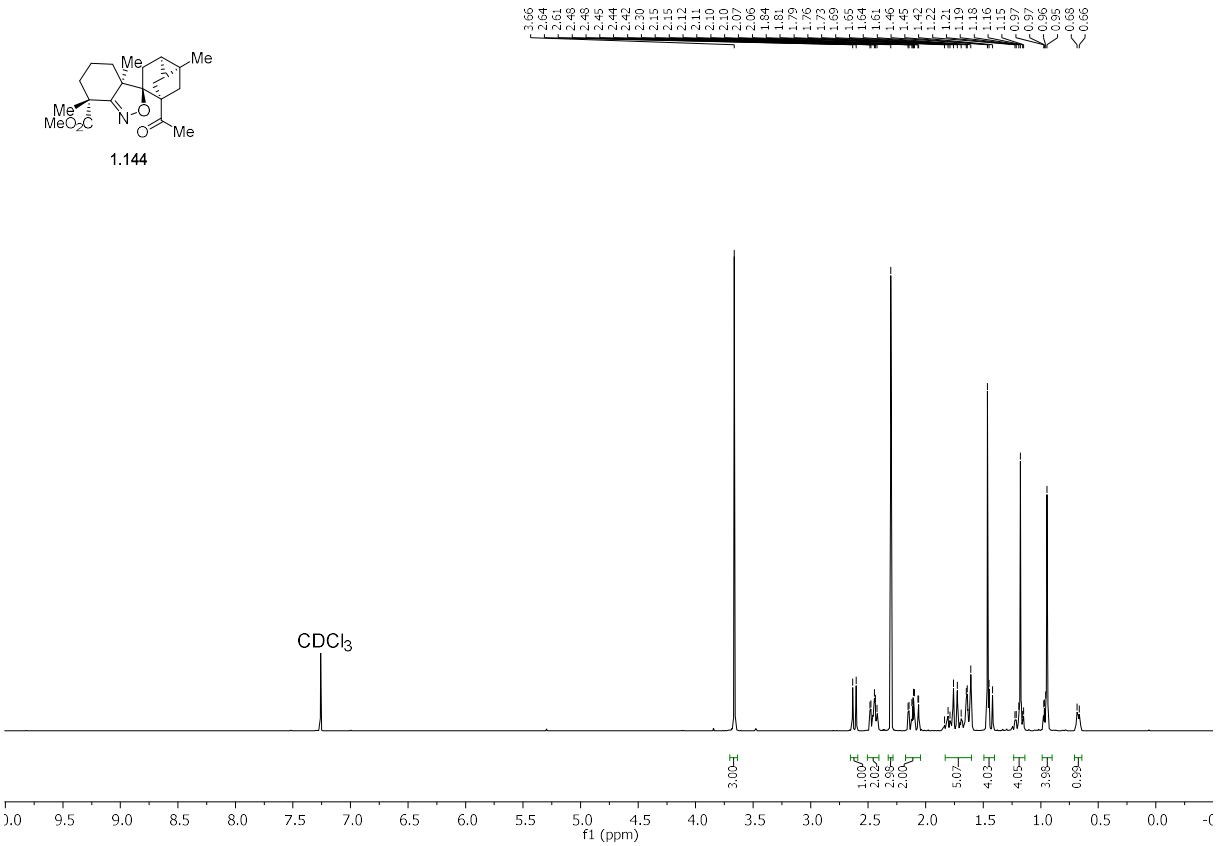
^{1}H NMR (500 MHz, $CDCl_3$) of **1.143**



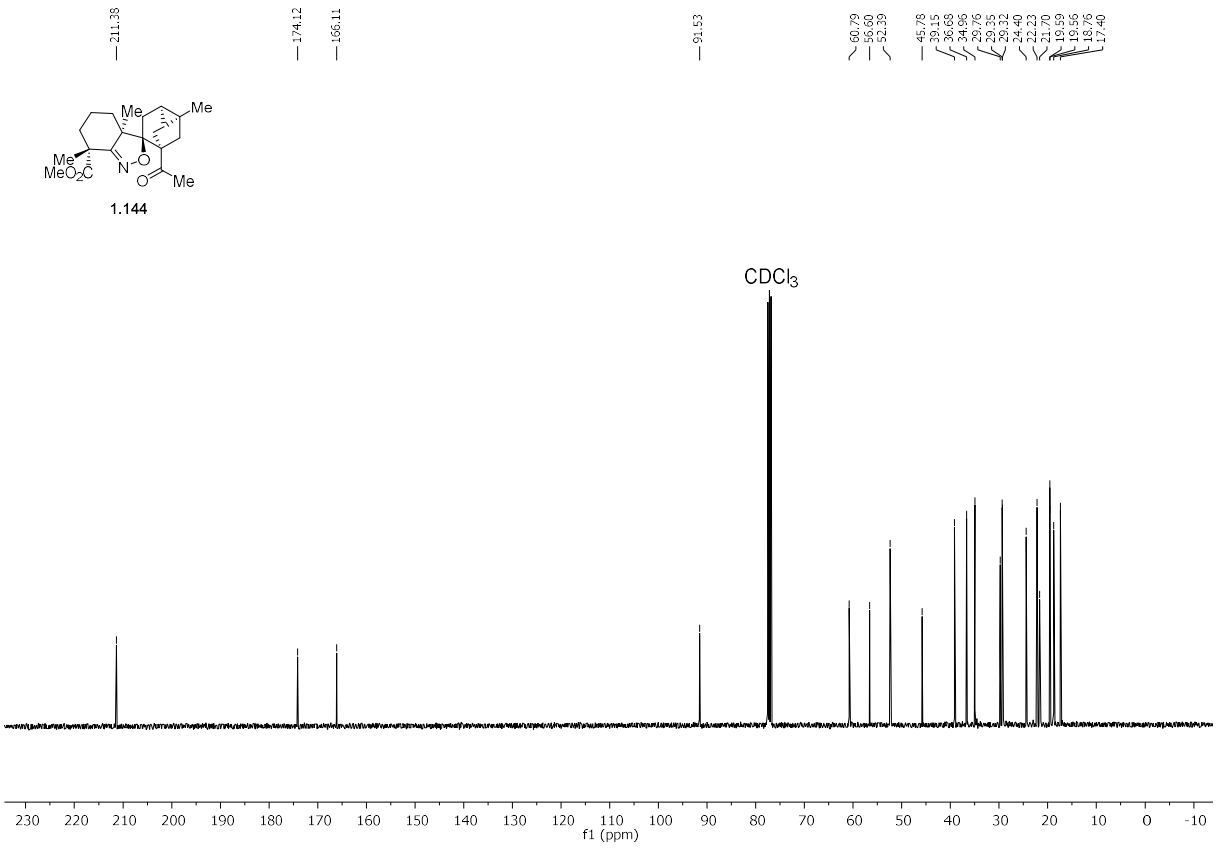
^{13}C NMR (126 MHz, $CDCl_3$) of **1.143**



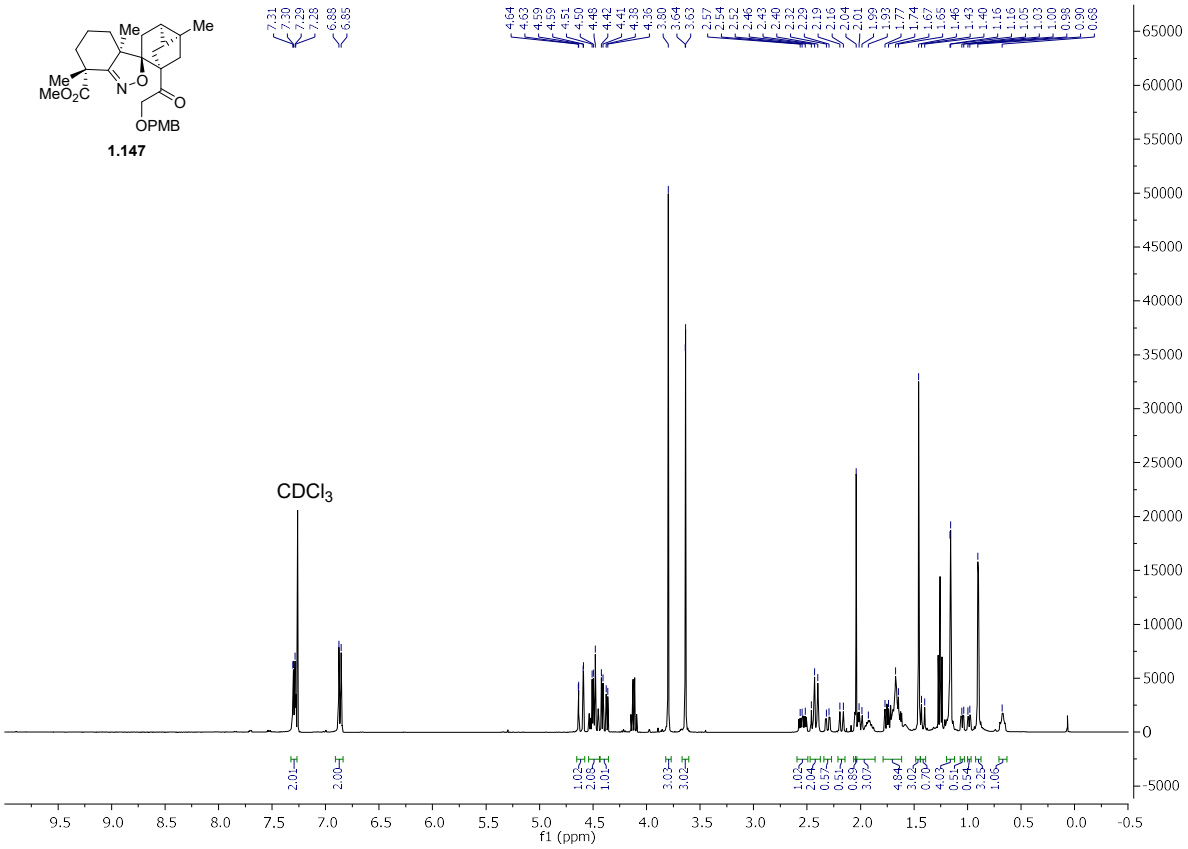
^{1}H NMR (400 MHz, $CDCl_3$) of **1.144**



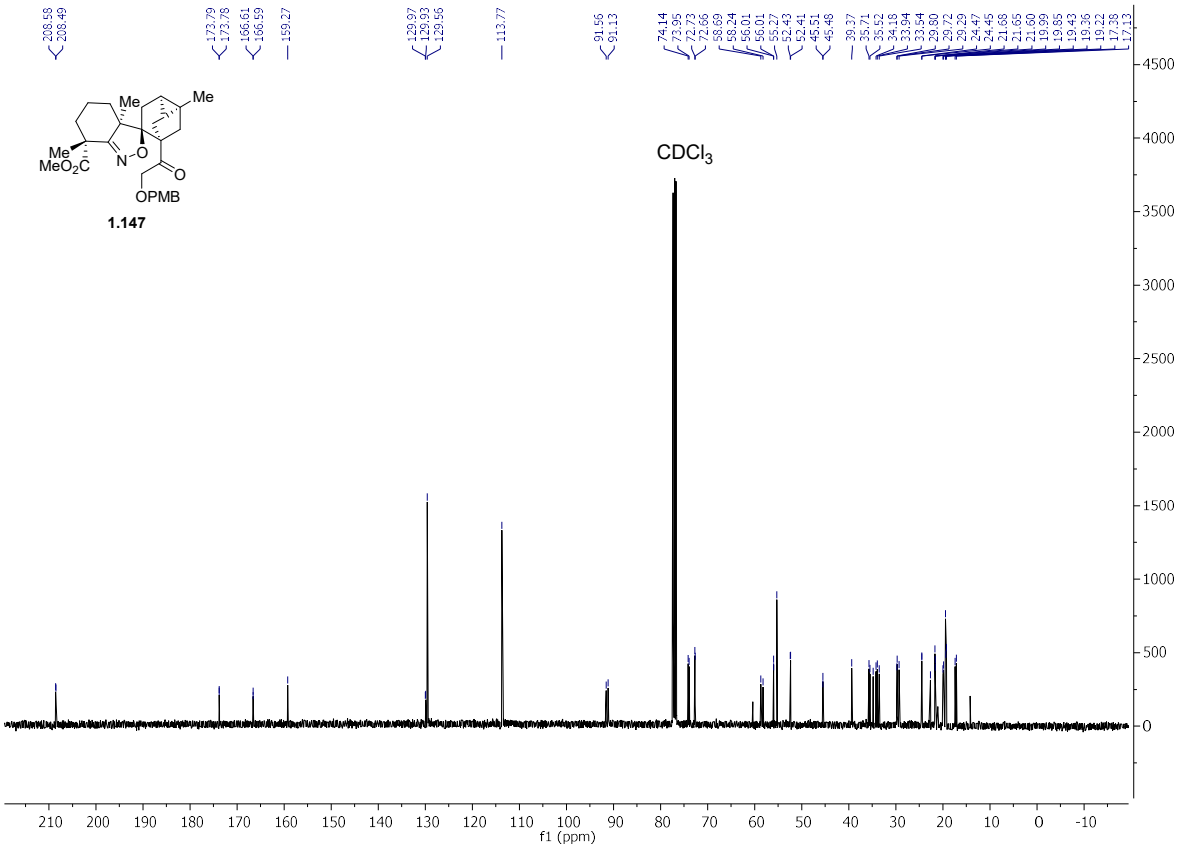
^{13}C NMR (101 MHz, $CDCl_3$) of **1.144**



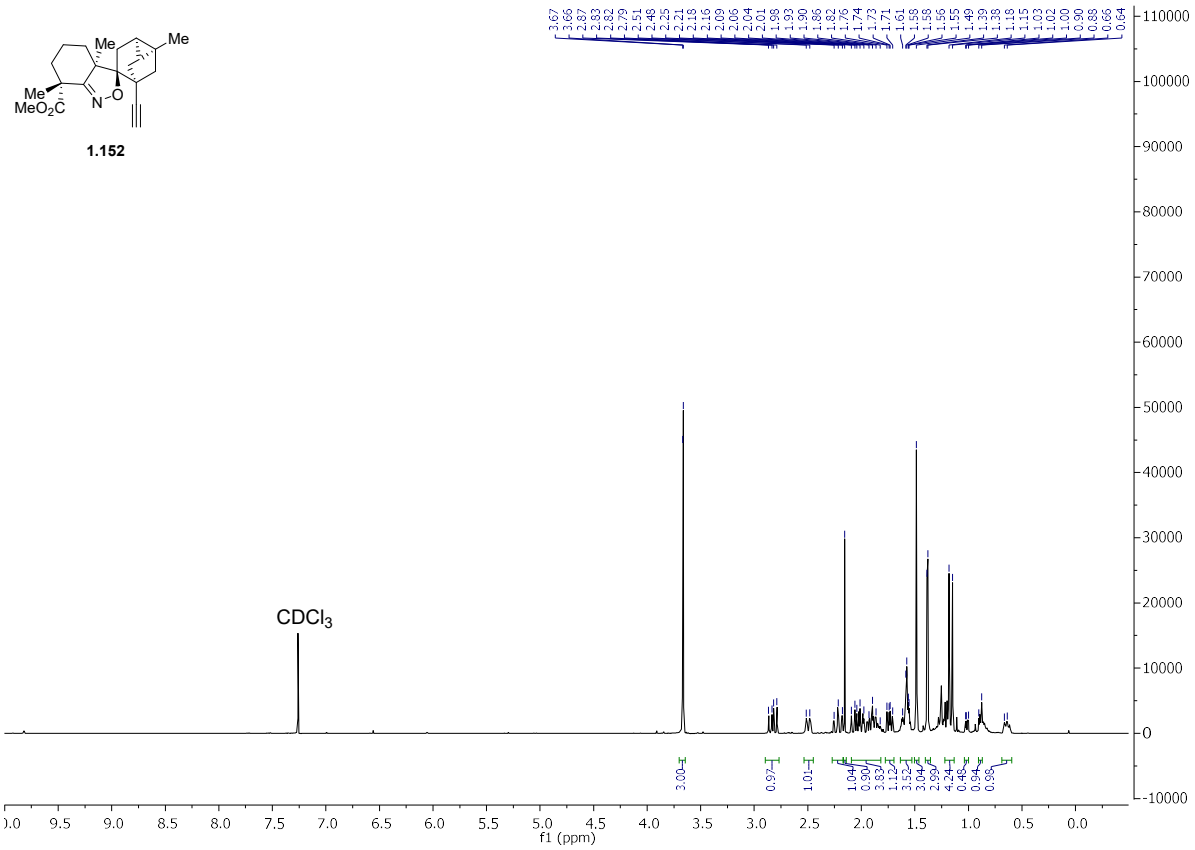
^{1}H NMR (400 MHz, $CDCl_3$) of **1.147**



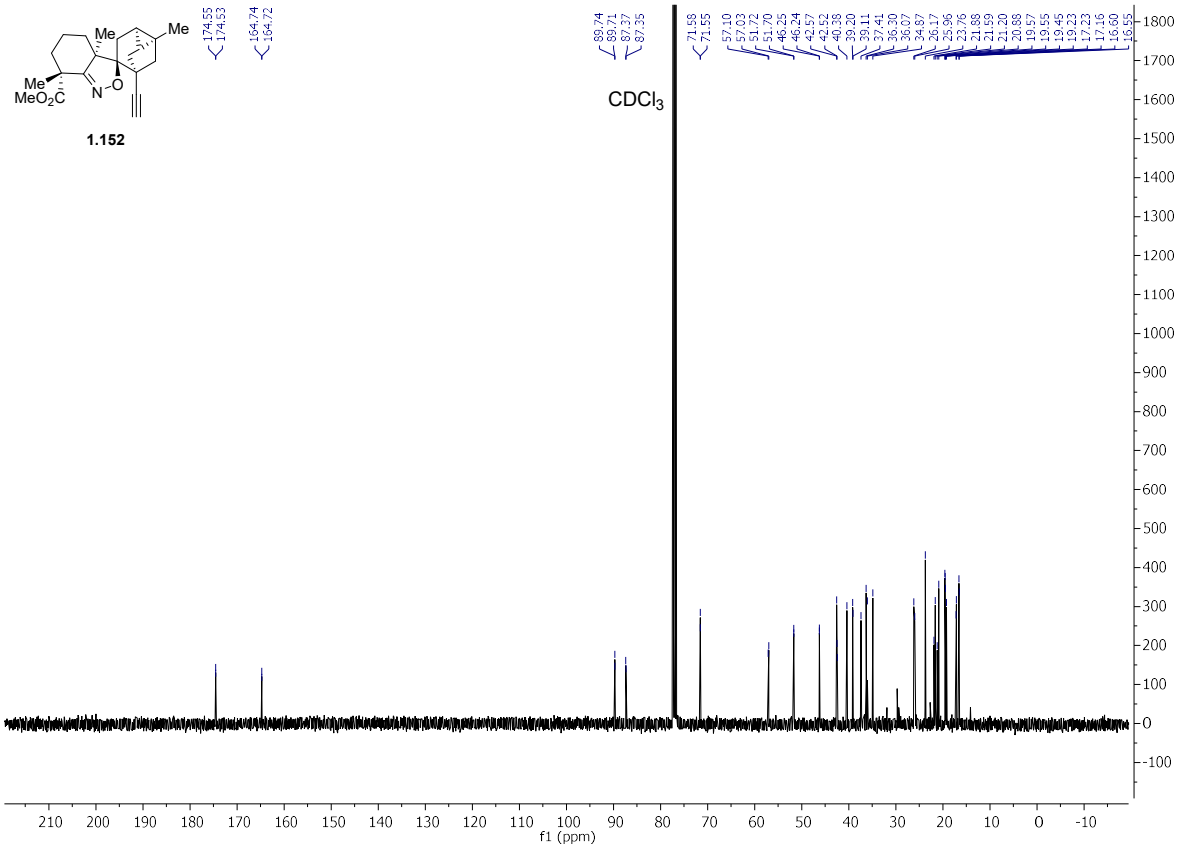
^{13}C NMR (101 MHz, $CDCl_3$) of **1.147**



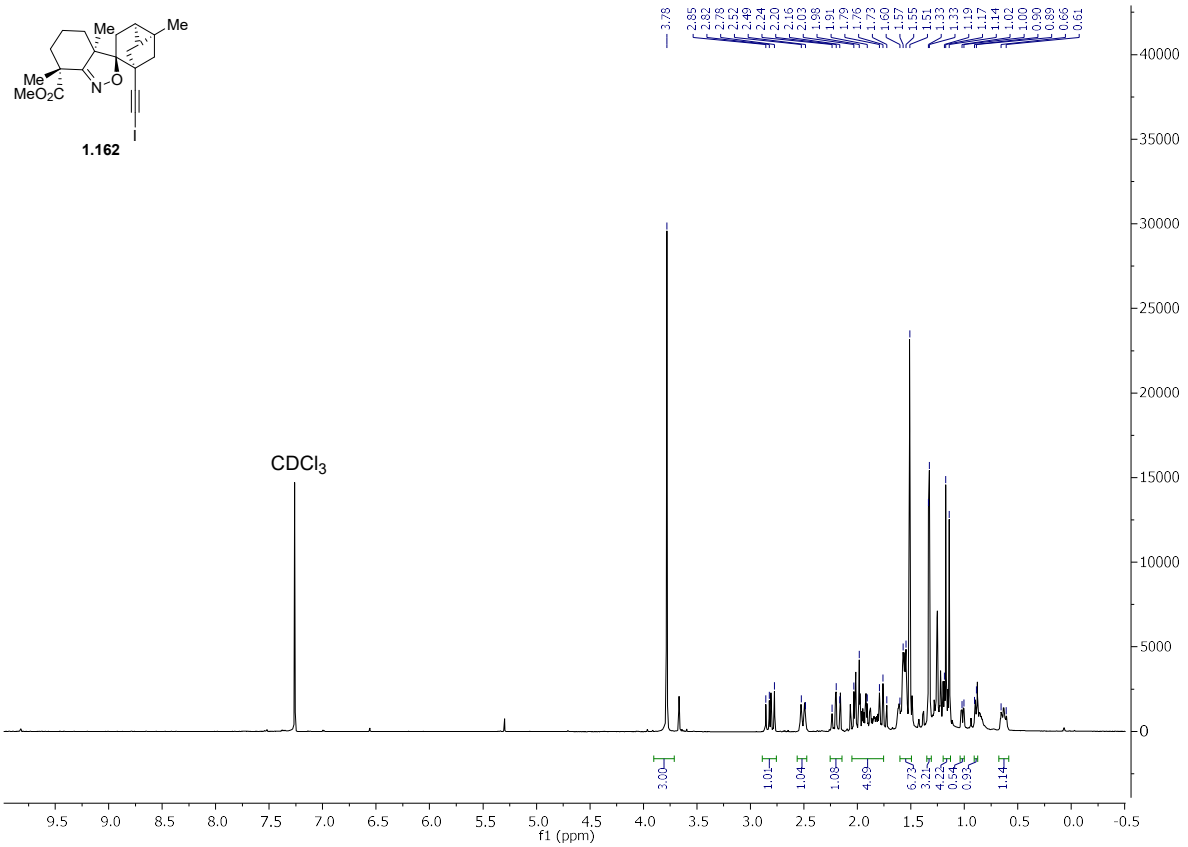
^{1}H NMR (400 MHz, $CDCl_3$) of **1.152**



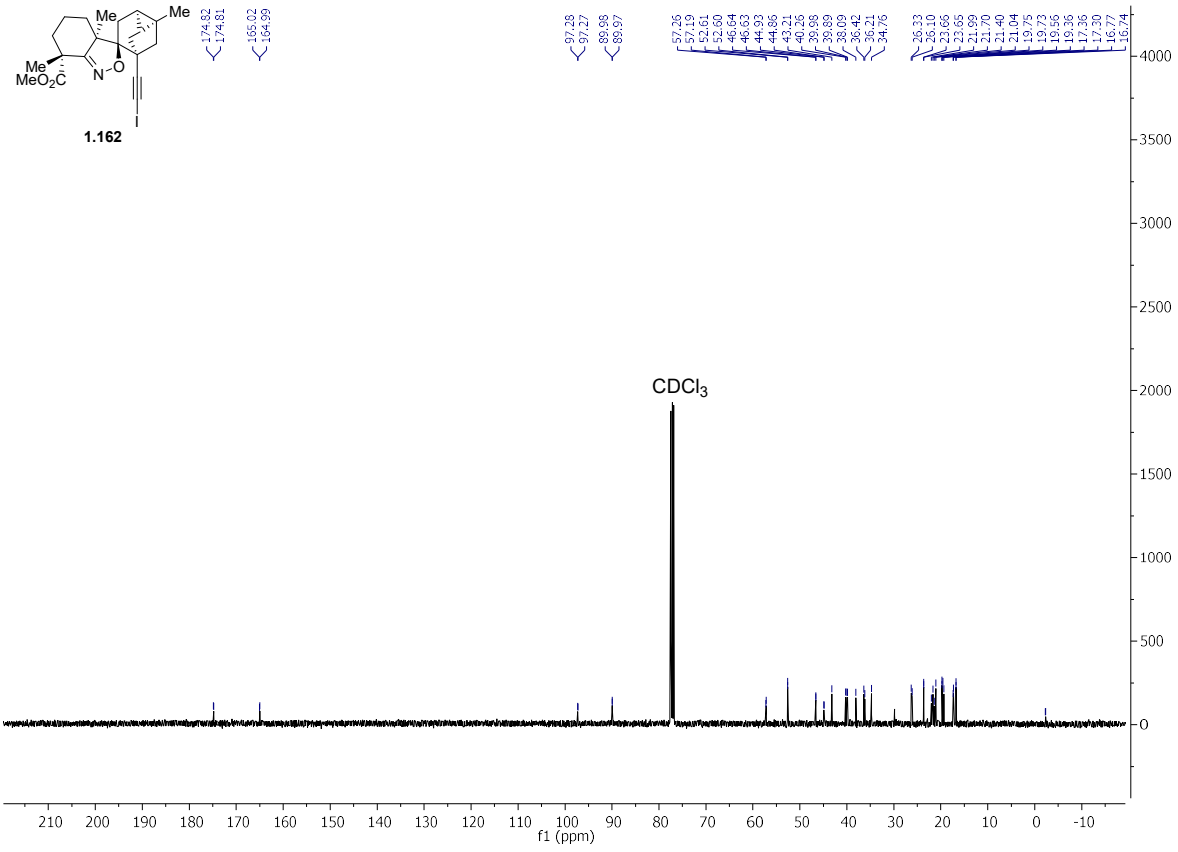
^{13}C NMR (101 MHz, $CDCl_3$) of **1.152**



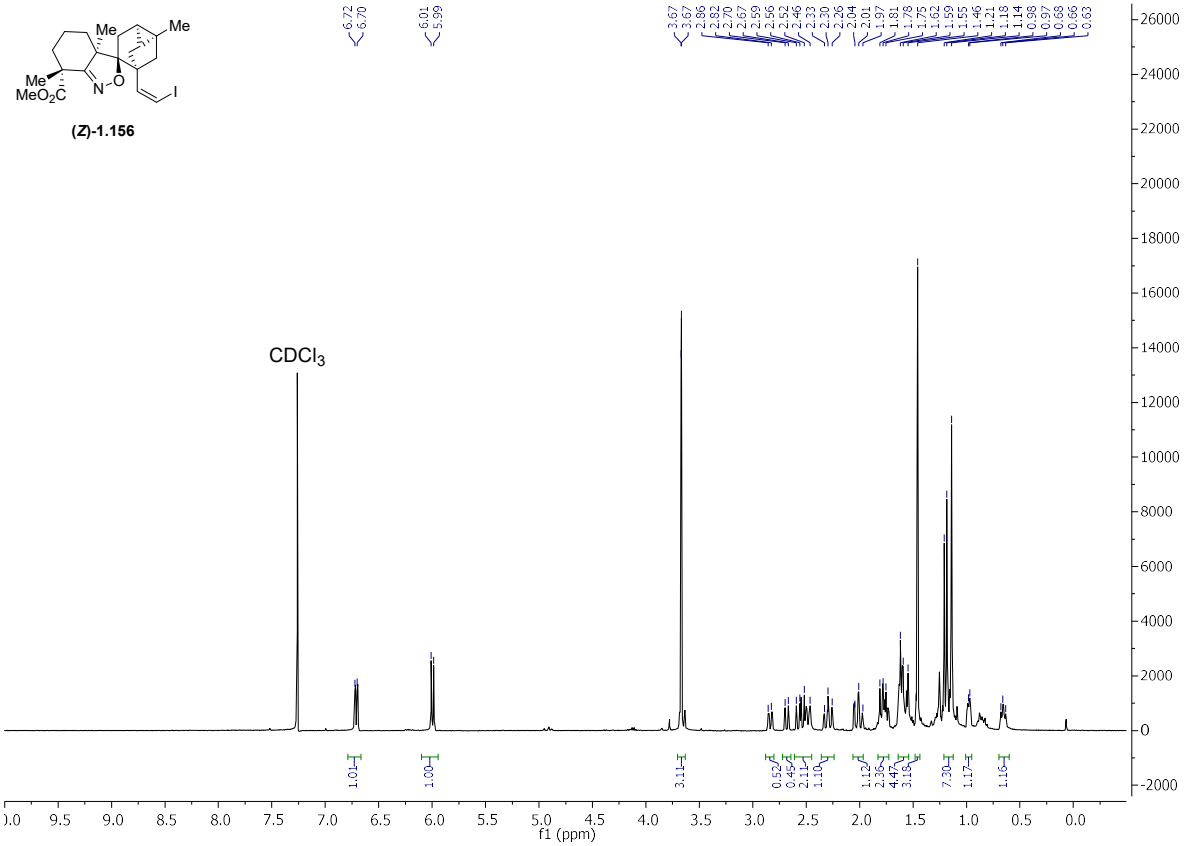
^{1}H NMR (400 MHz, $CDCl_3$) of **1.162**



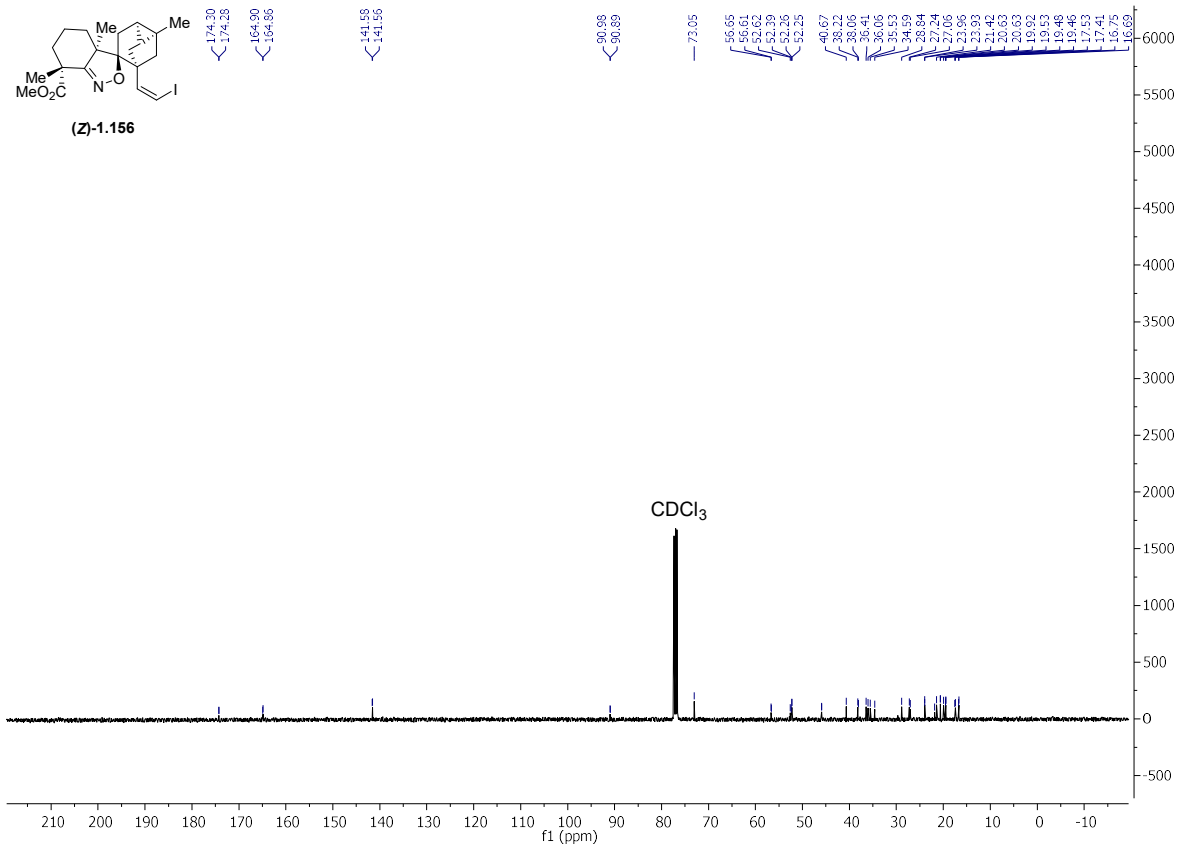
^{13}C NMR (101 MHz, $CDCl_3$) of **1.162**



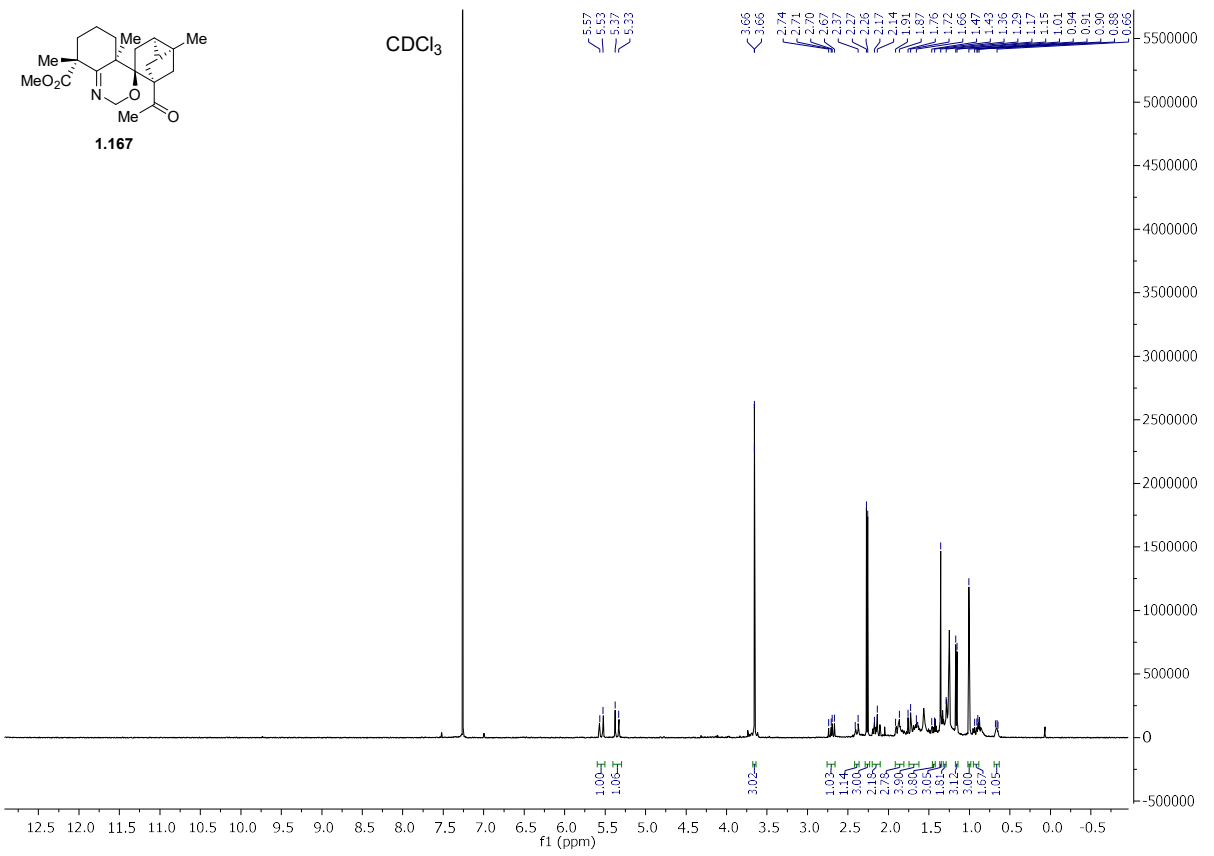
^{1}H NMR (400 MHz, $CDCl_3$) of **(*Z*)-1.156**



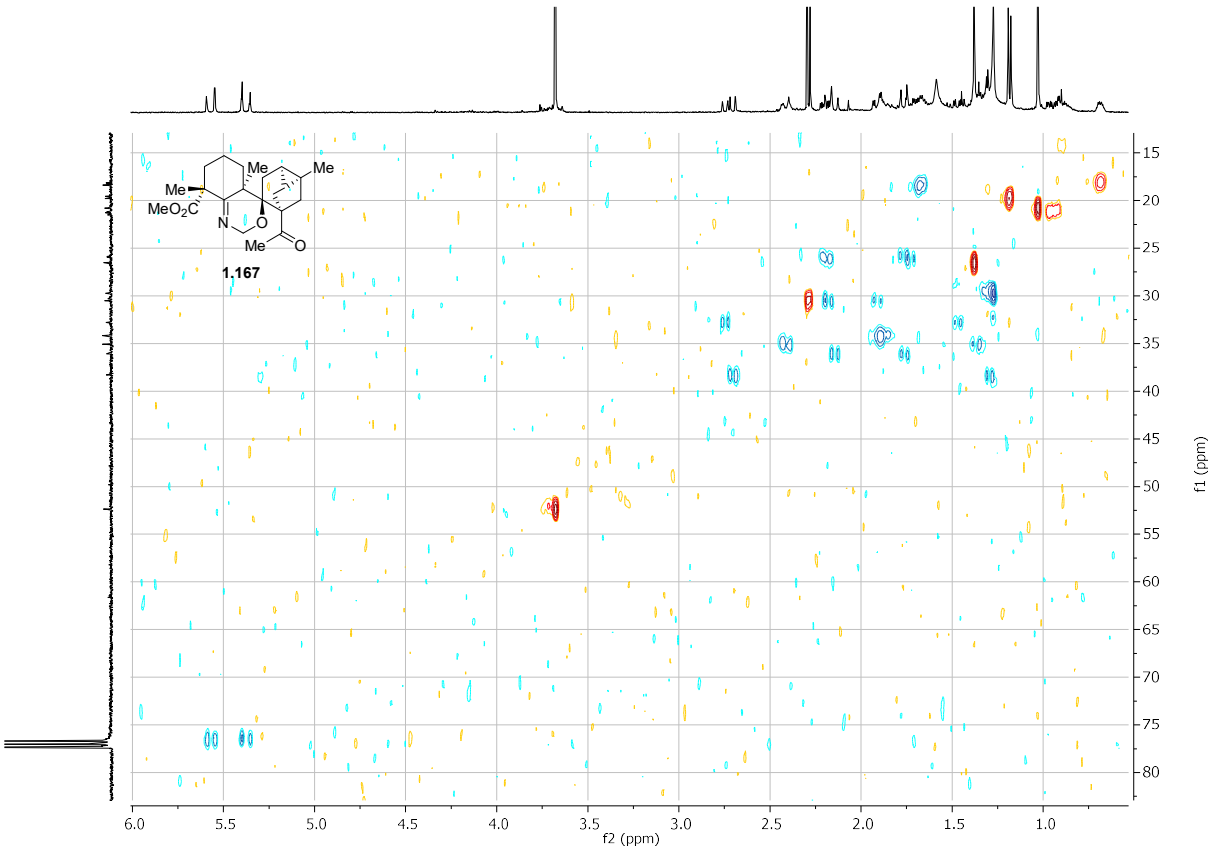
^{13}C NMR (101 MHz, $CDCl_3$) of **(*Z*)-1.156**



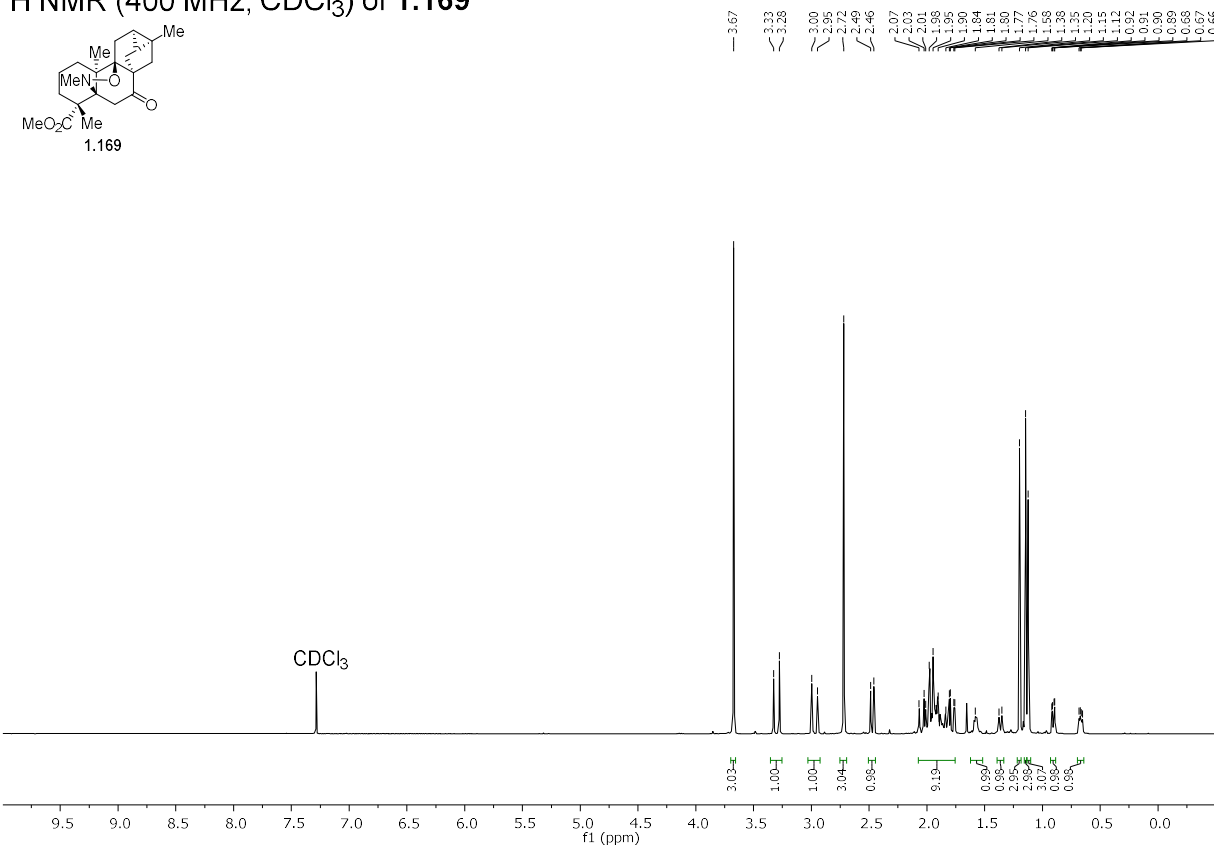
^{1}H NMR (400 MHz, $CDCl_3$) of **1.167**



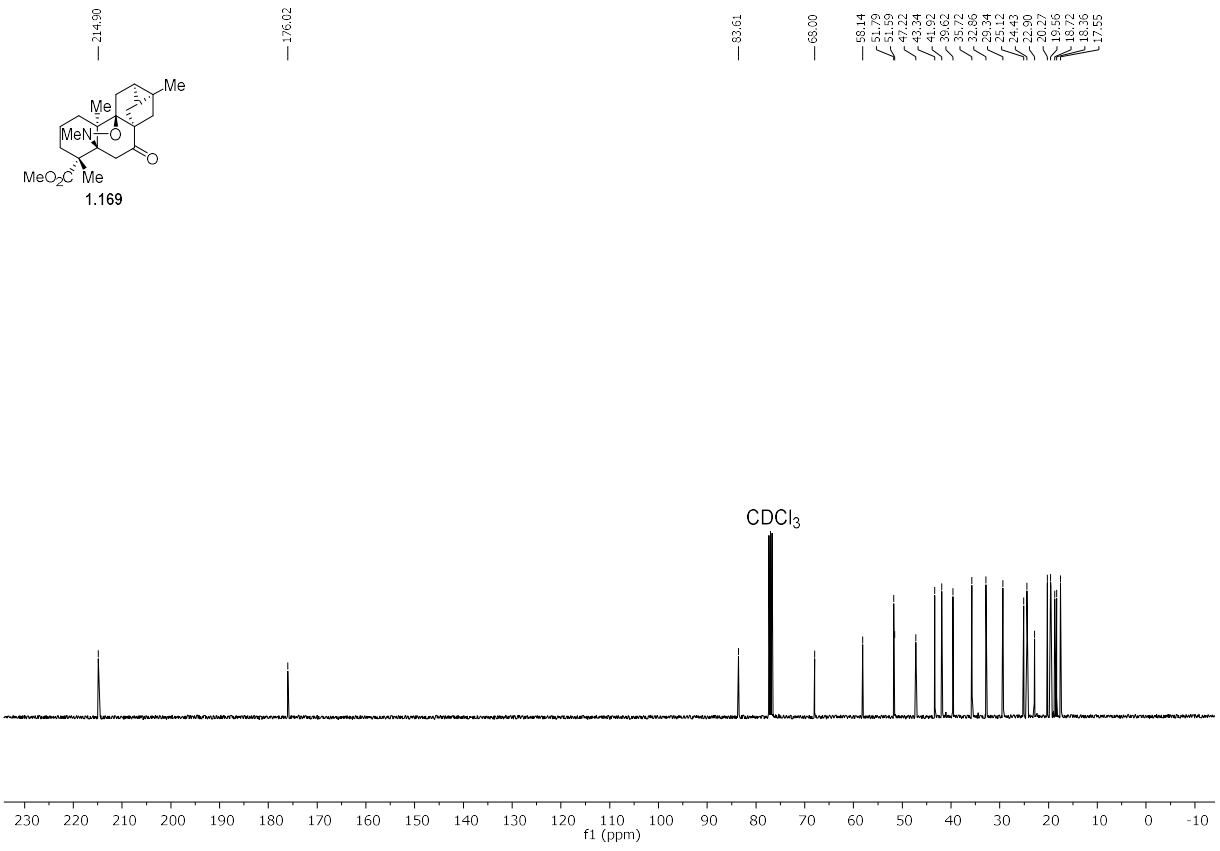
HSQC NMR ($CDCl_3$) of **1.167**



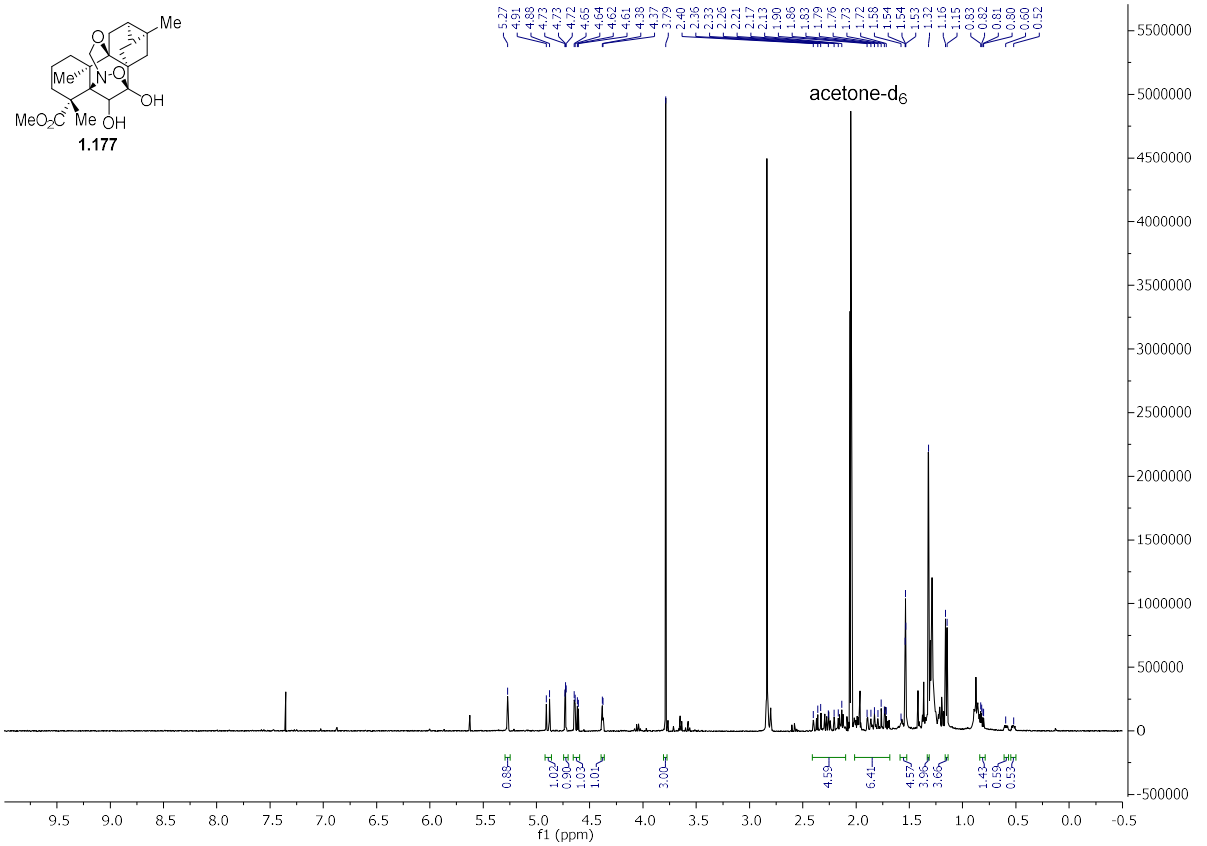
^{1}H NMR (400 MHz, $CDCl_3$) of **1.169**



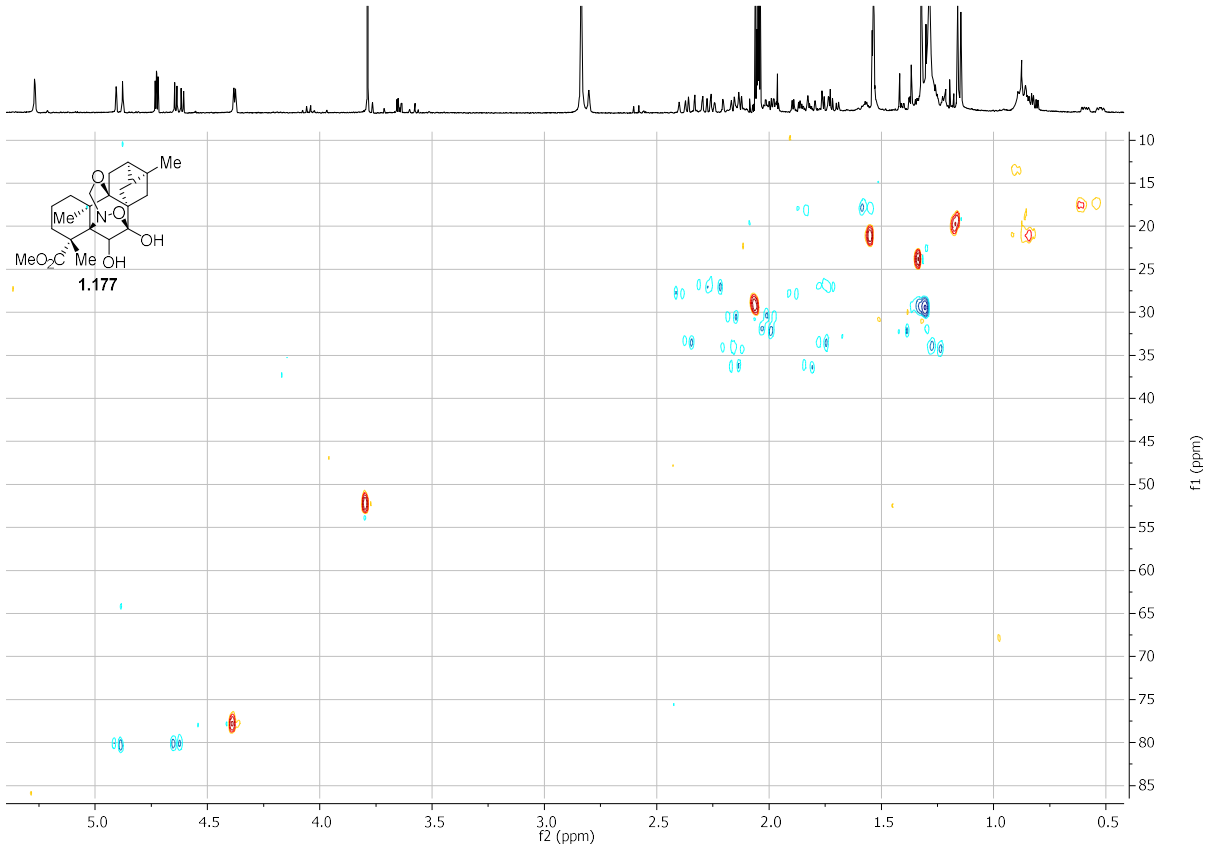
^{13}C NMR (101 MHz, $CDCl_3$) of **1.169**



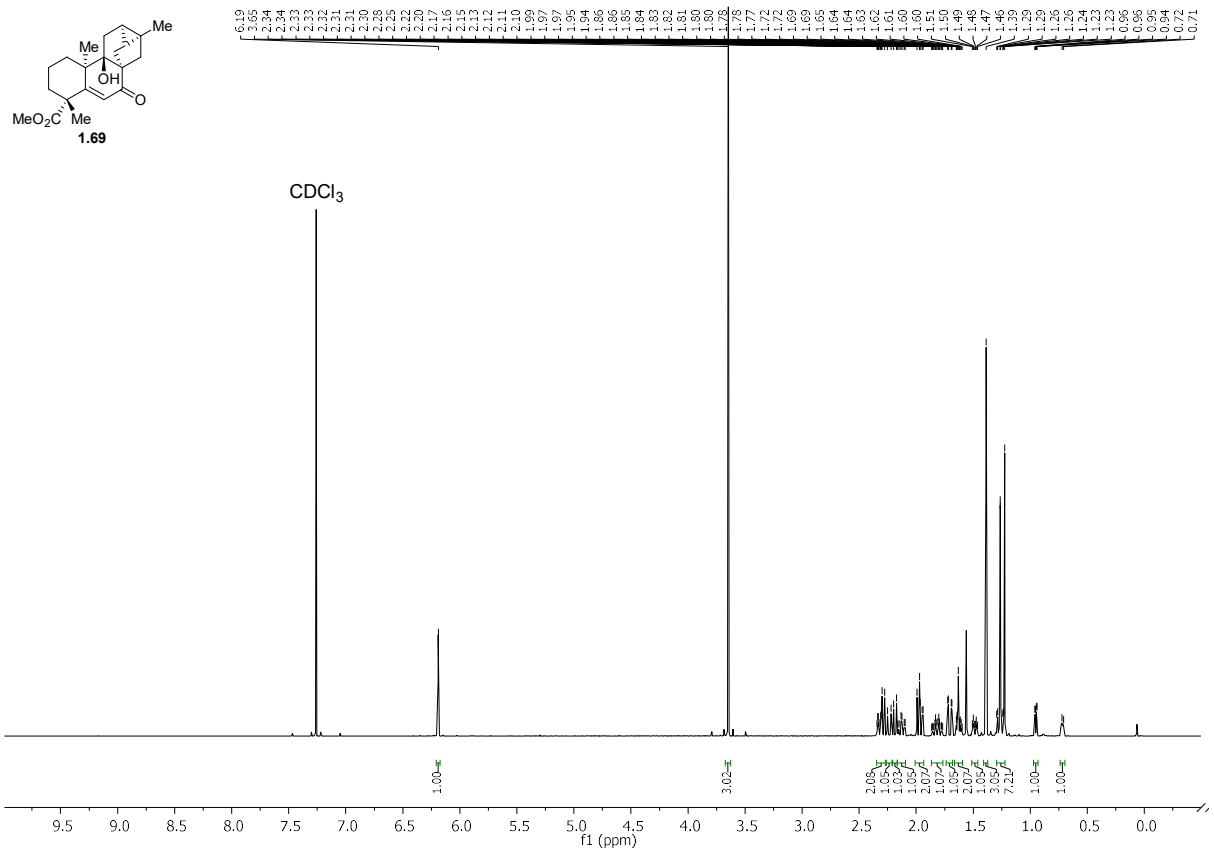
^{1}H NMR (400 MHz,acetone-d_6) of **1.177**



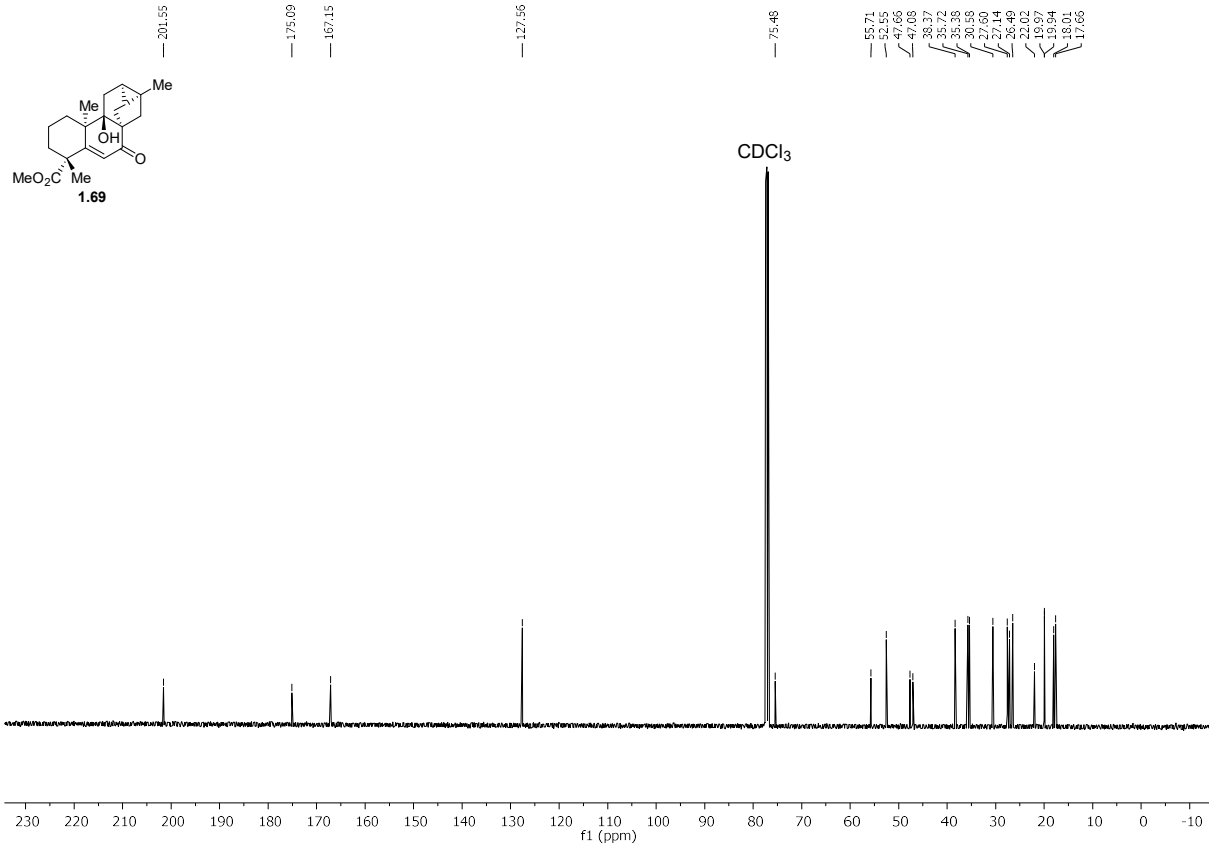
HSQC NMR (acetone-d_6) of **1.177**



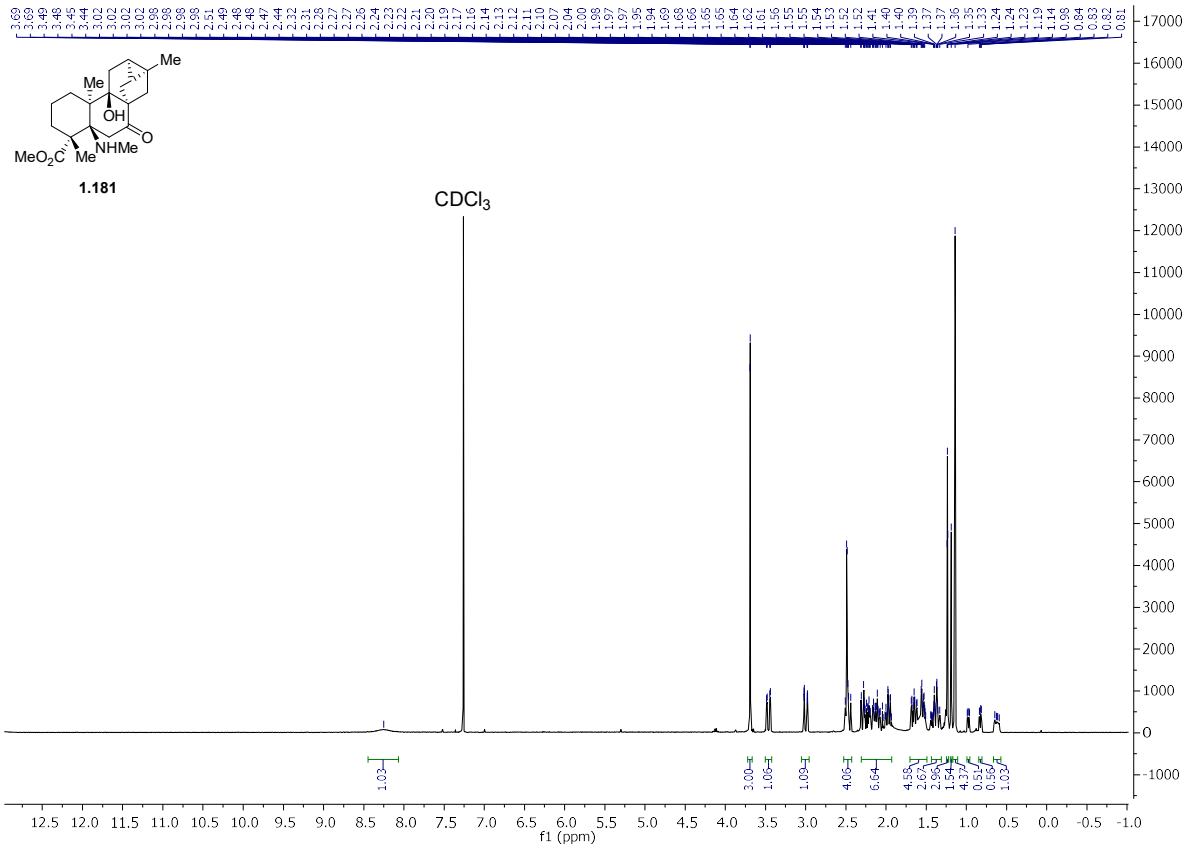
^{1}H NMR (500 MHz, $CDCl_3$) of **1.69**



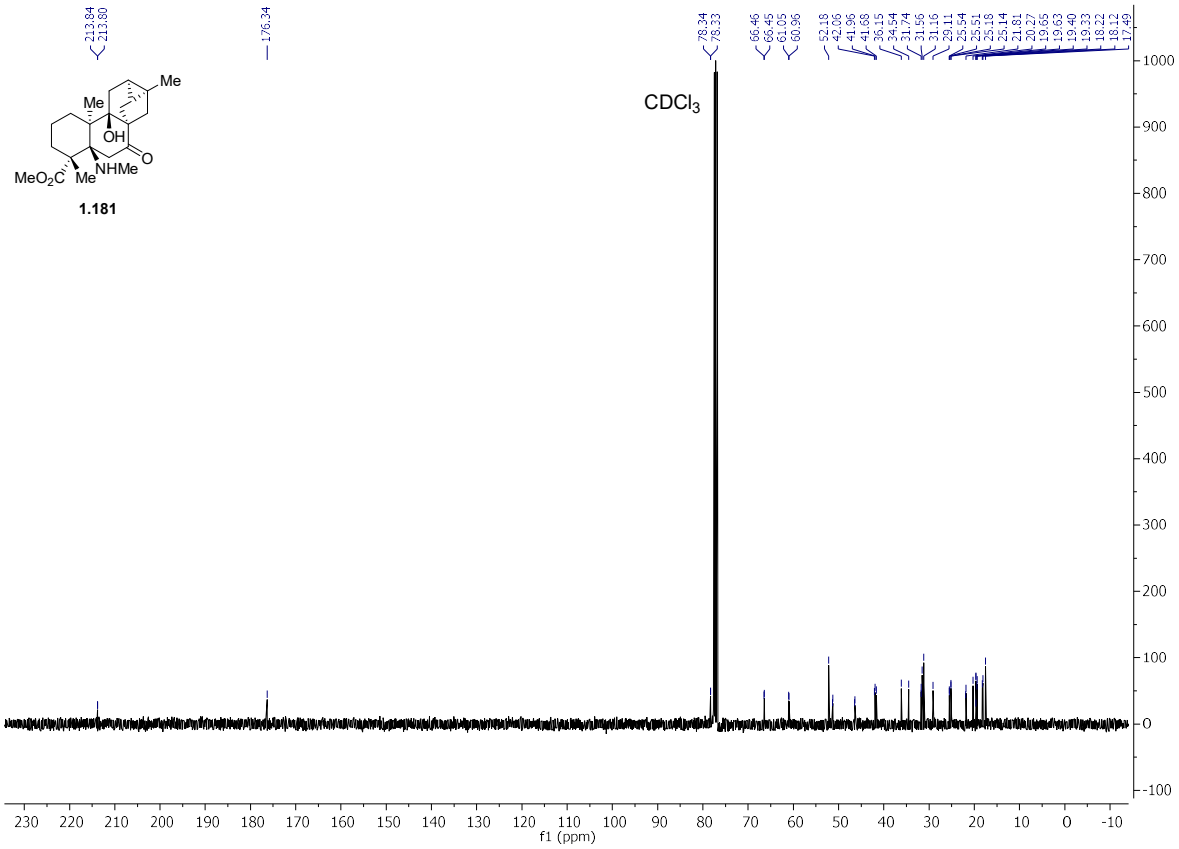
^{13}C NMR (126 MHz, $CDCl_3$) of **1.69**



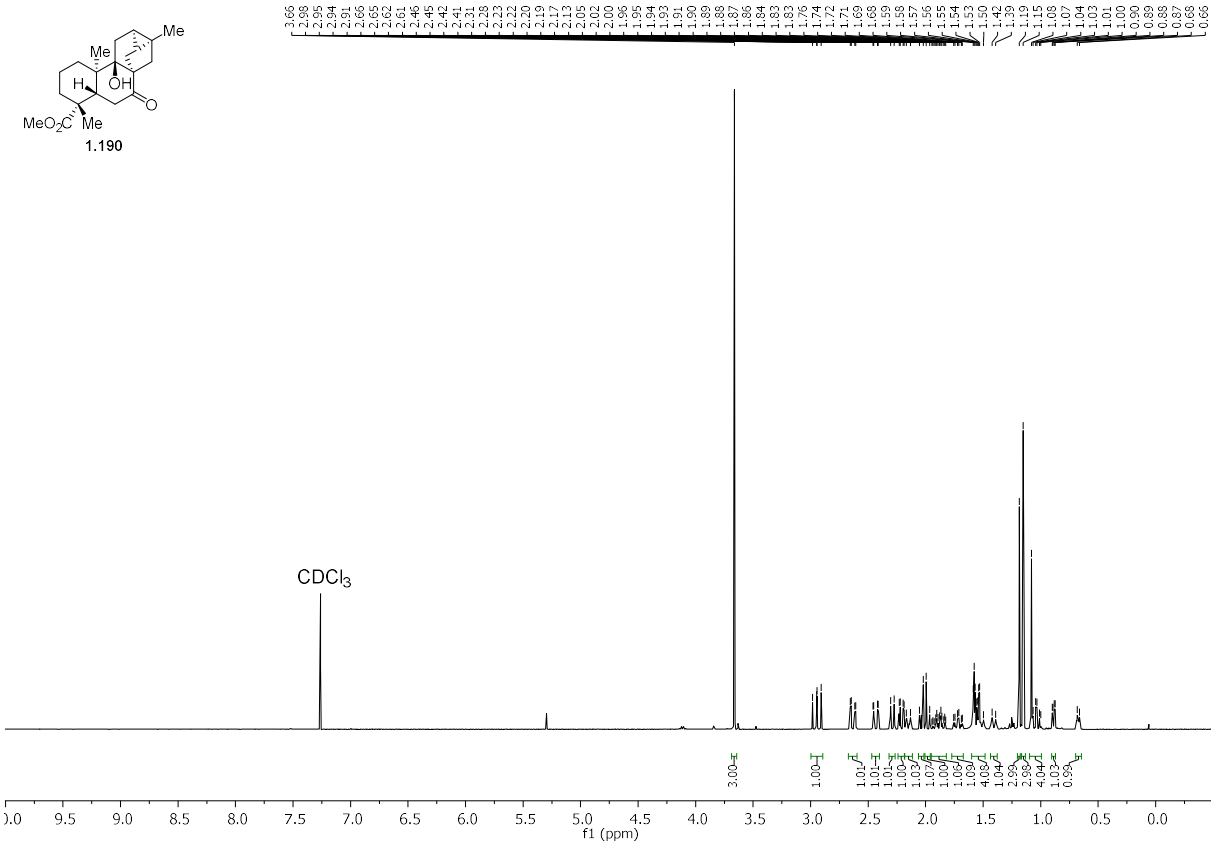
^{1}H NMR (400 MHz, $CDCl_3$) of **1.181**



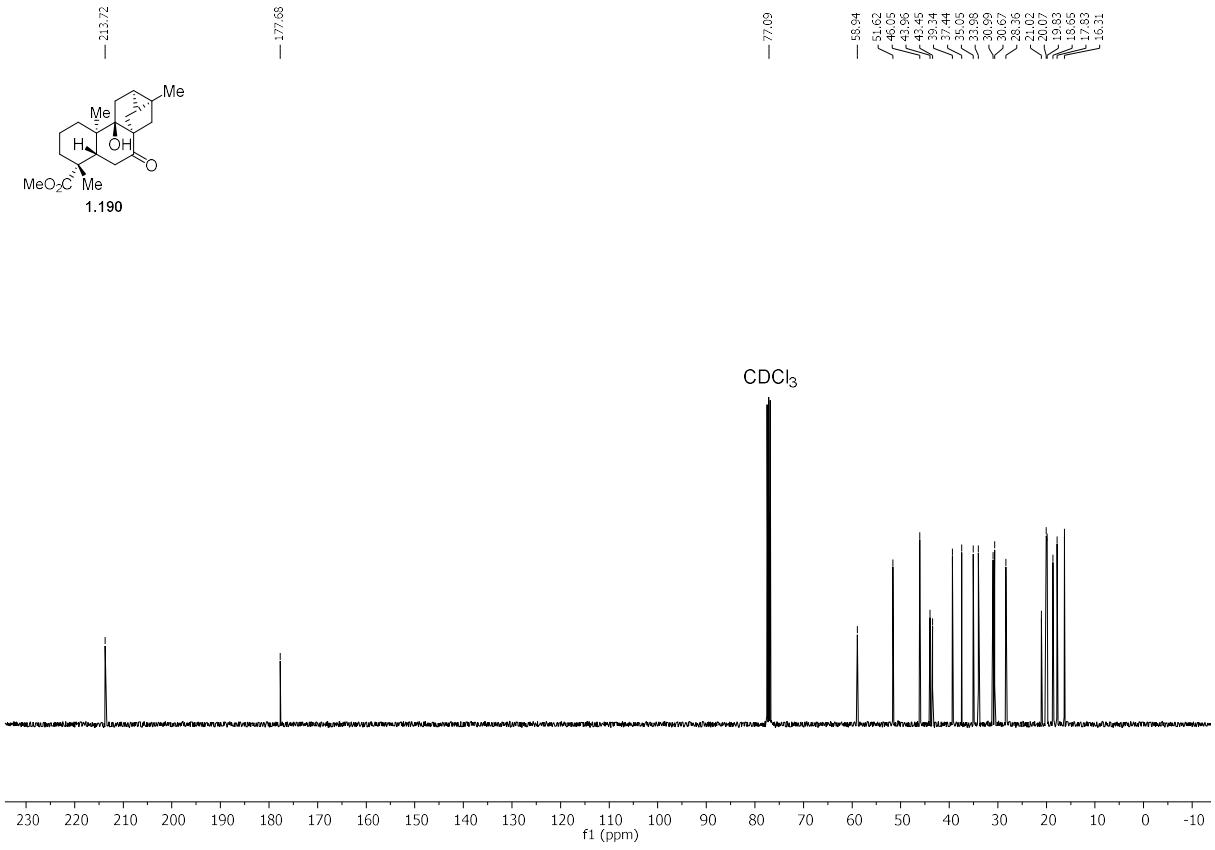
^{13}C NMR (101 MHz, $CDCl_3$) of **1.181**



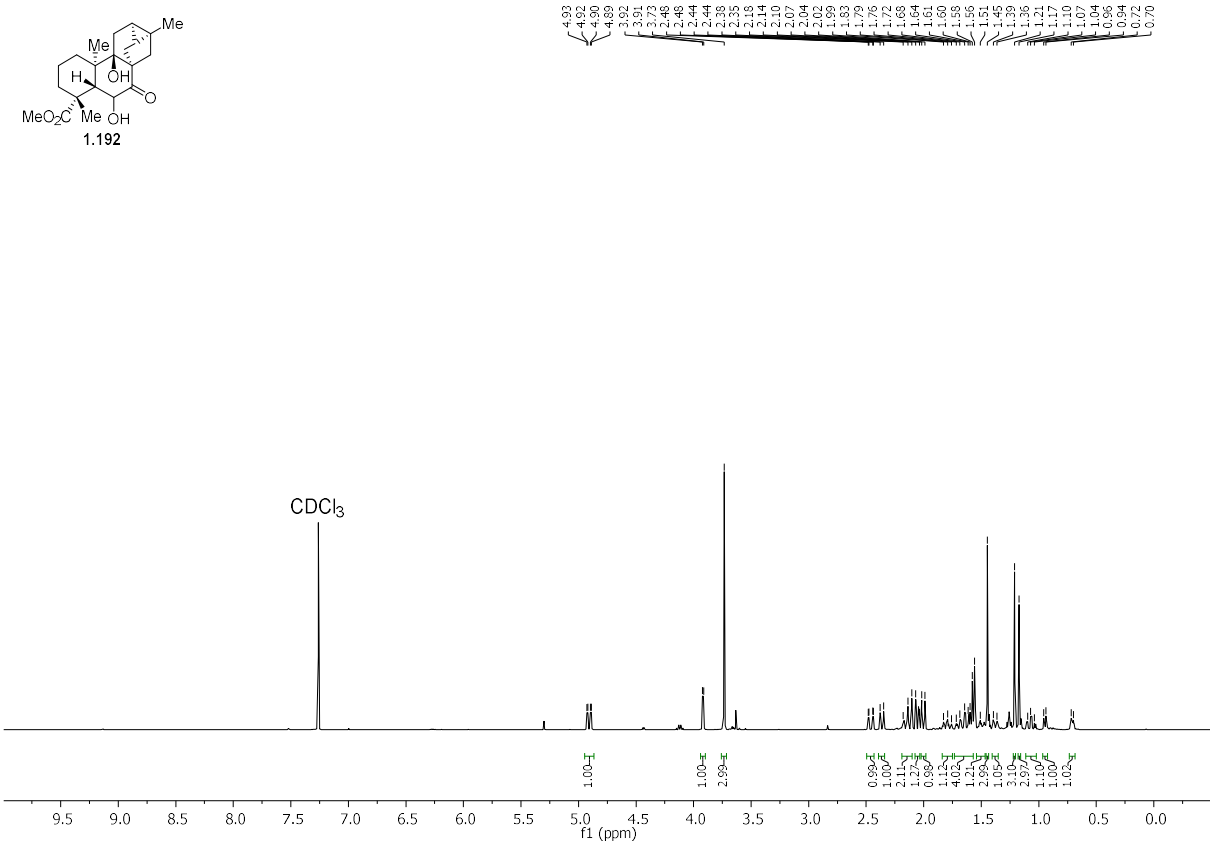
^{1}H NMR (400 MHz, $CDCl_3$) of **1.190**



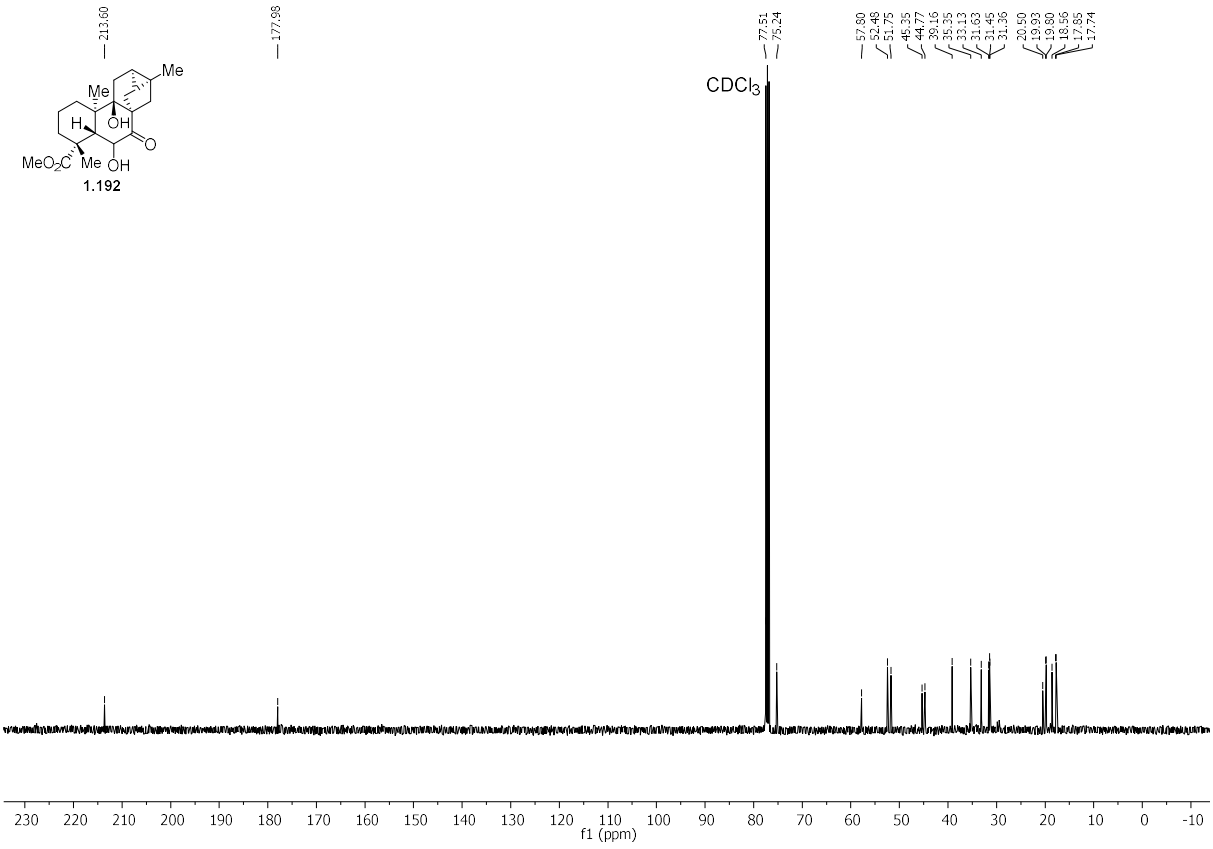
^{13}C NMR (101 MHz, $CDCl_3$) of **1.190**



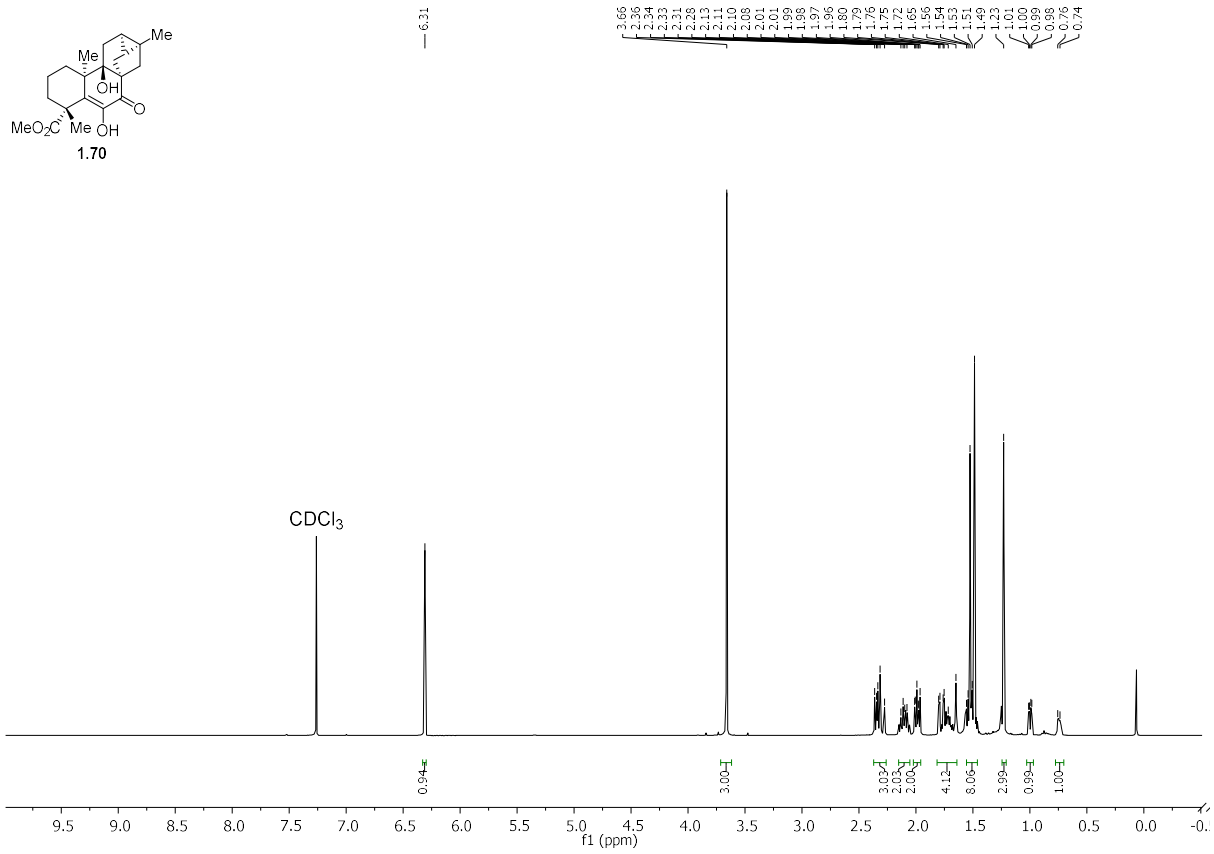
^{1}H NMR (400 MHz, $CDCl_3$) of **1.192**



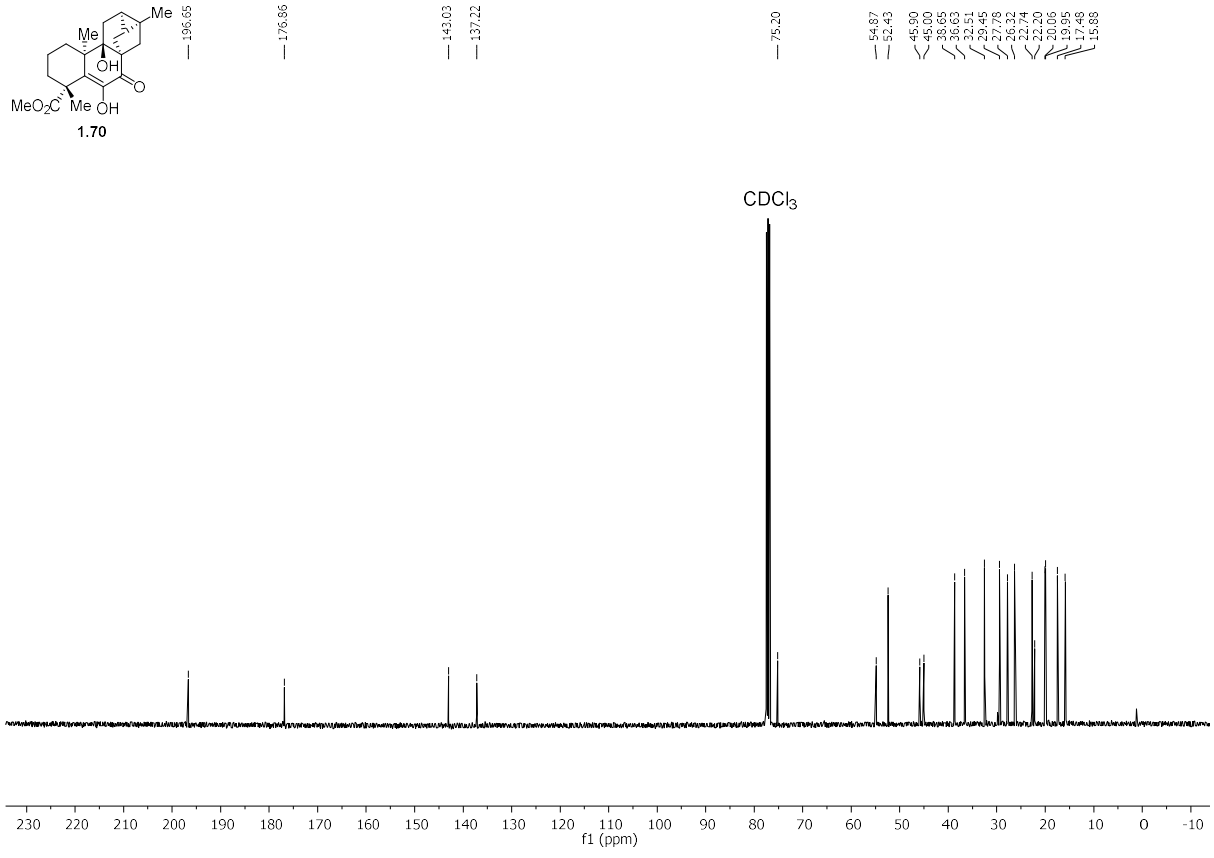
^{13}C NMR (101 MHz, $CDCl_3$) of **1.192**



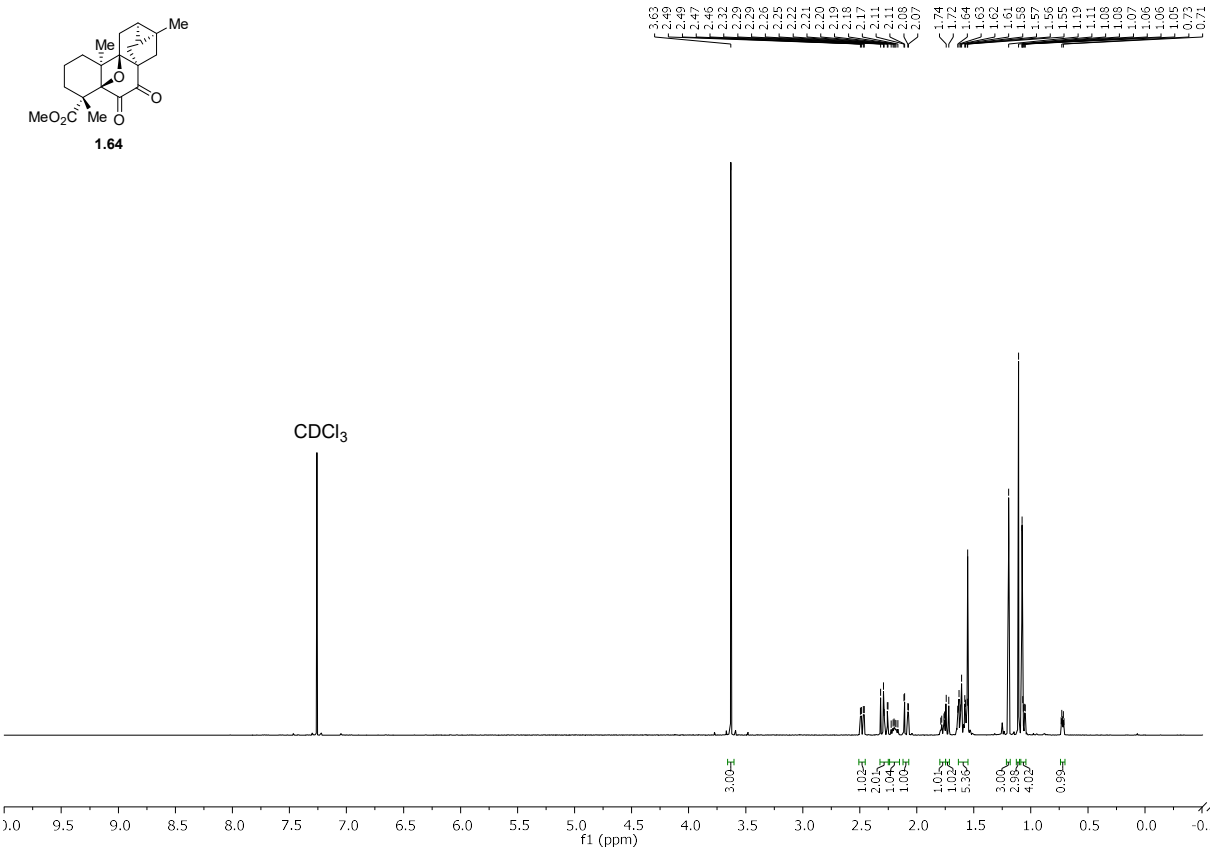
^{1}H NMR (400 MHz, $CDCl_3$) of **1.70**



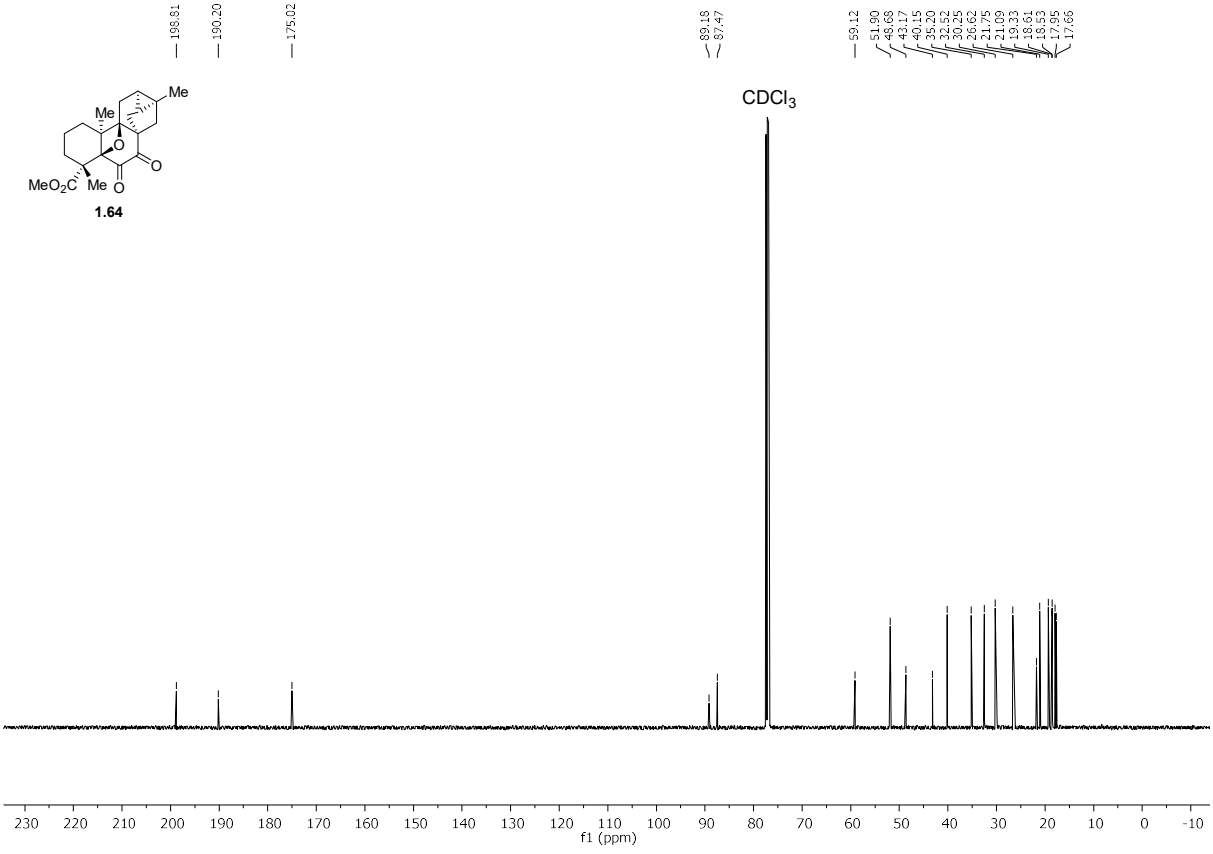
^{13}C NMR (101 MHz, $CDCl_3$) of **1.70**



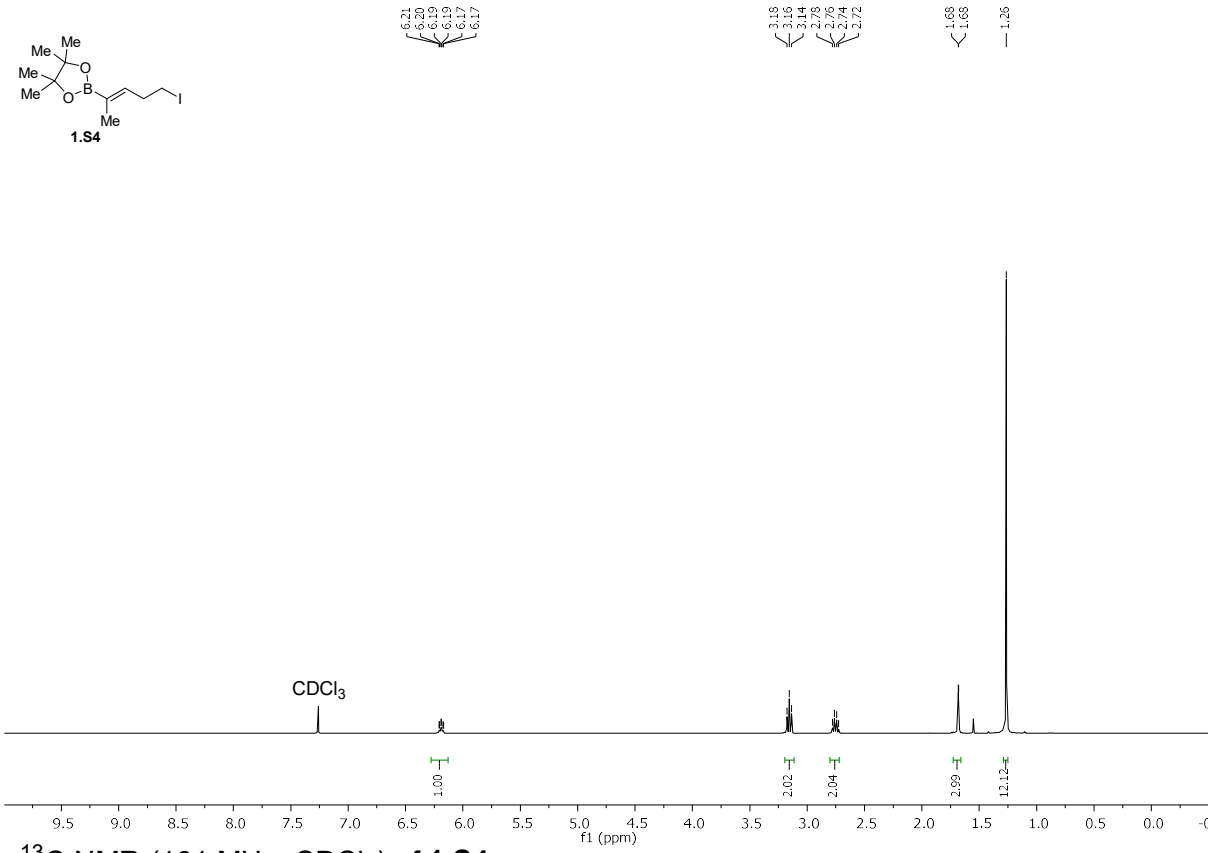
^{1}H NMR (500 MHz, $CDCl_3$) of **1.64**



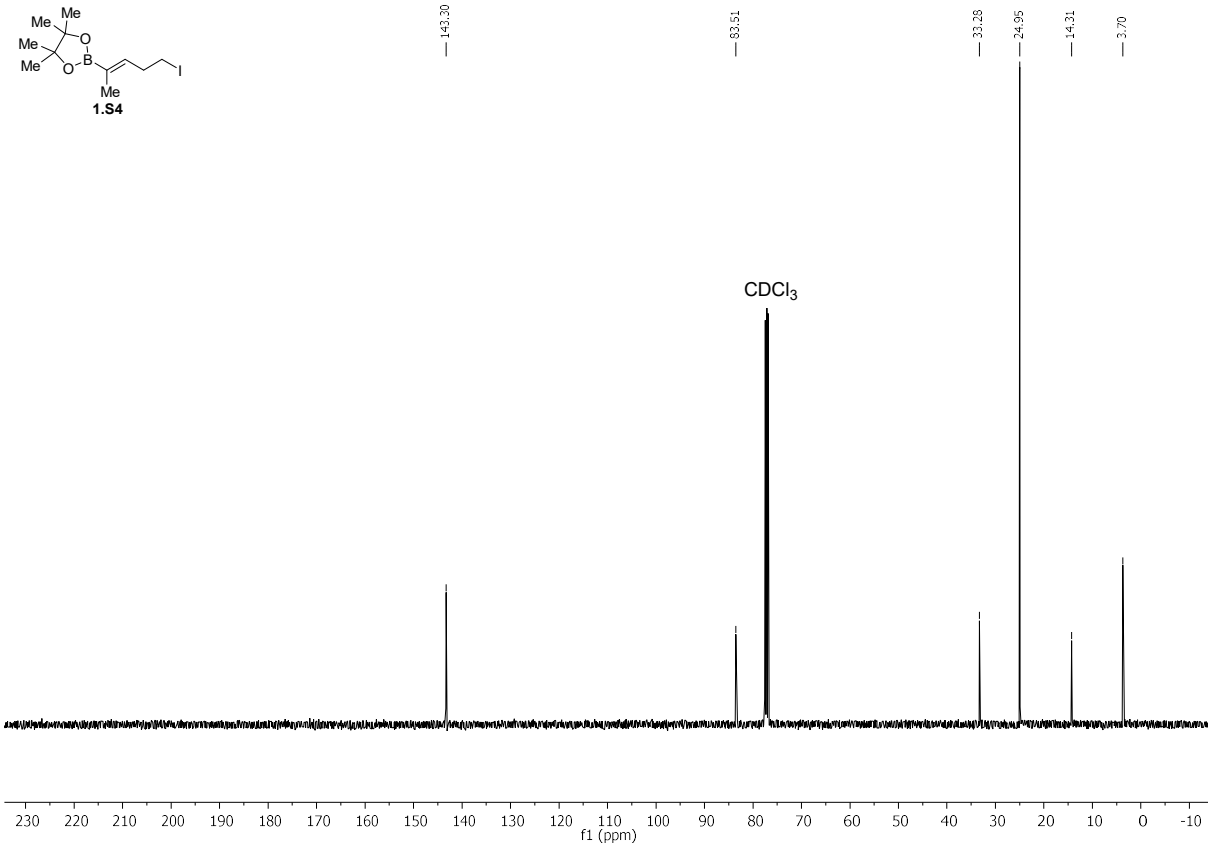
^{13}C NMR (126 MHz, $CDCl_3$) of **1.64**



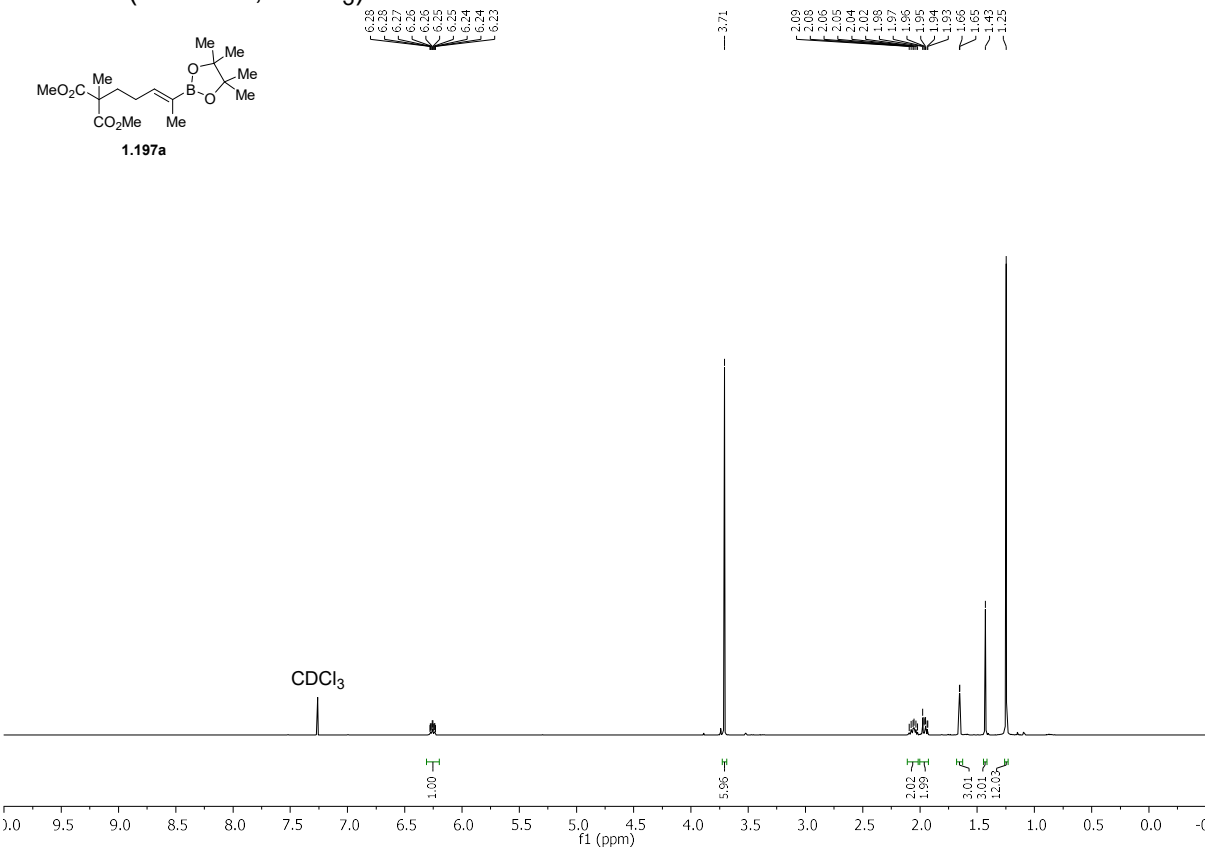
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S4**



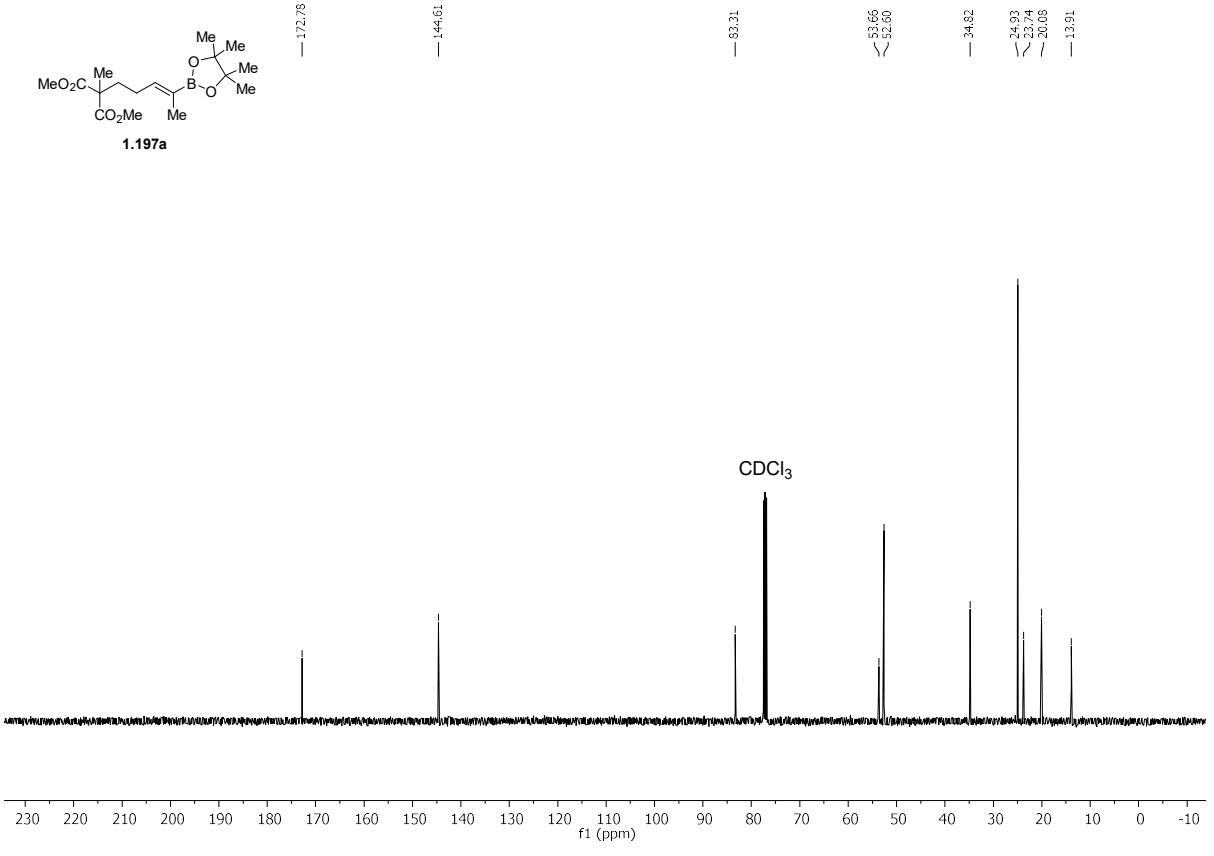
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S4**



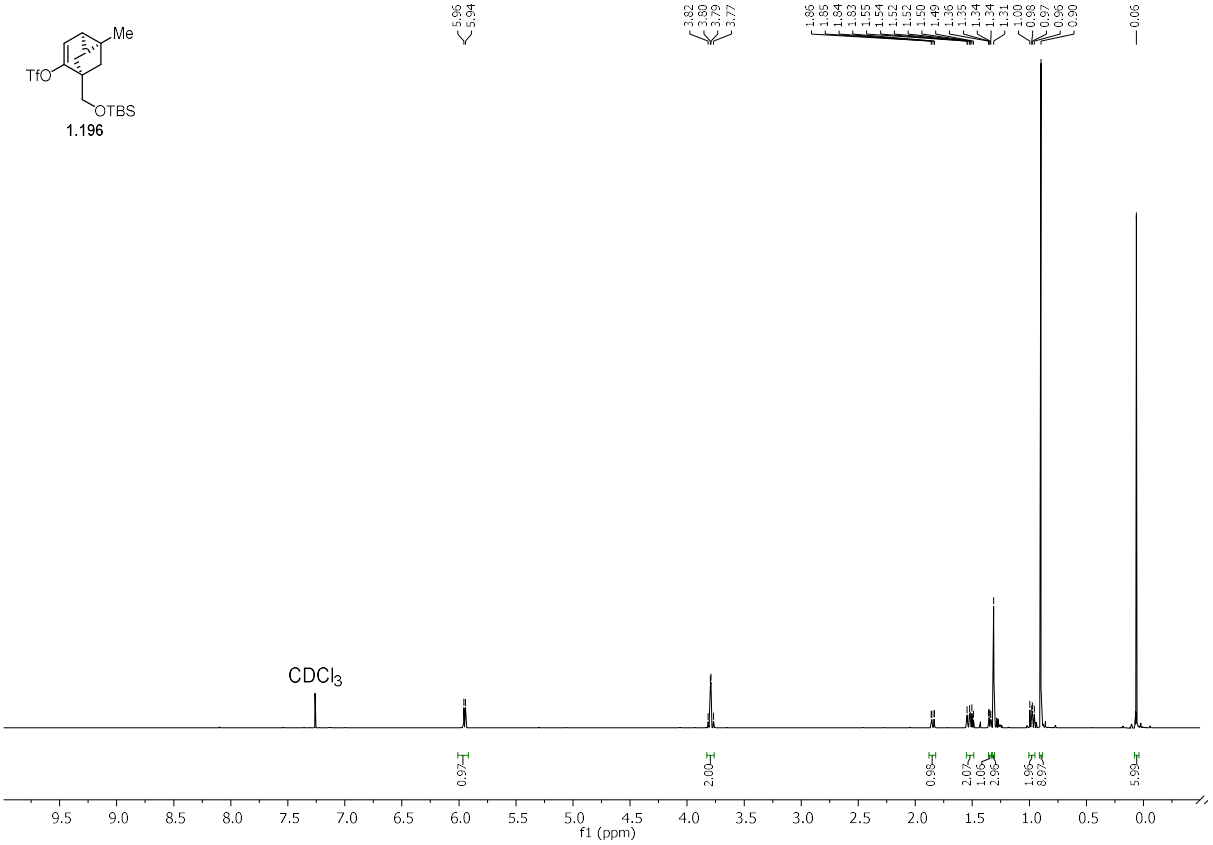
^{1}H NMR (400 MHz, $CDCl_3$) of **1.197a**



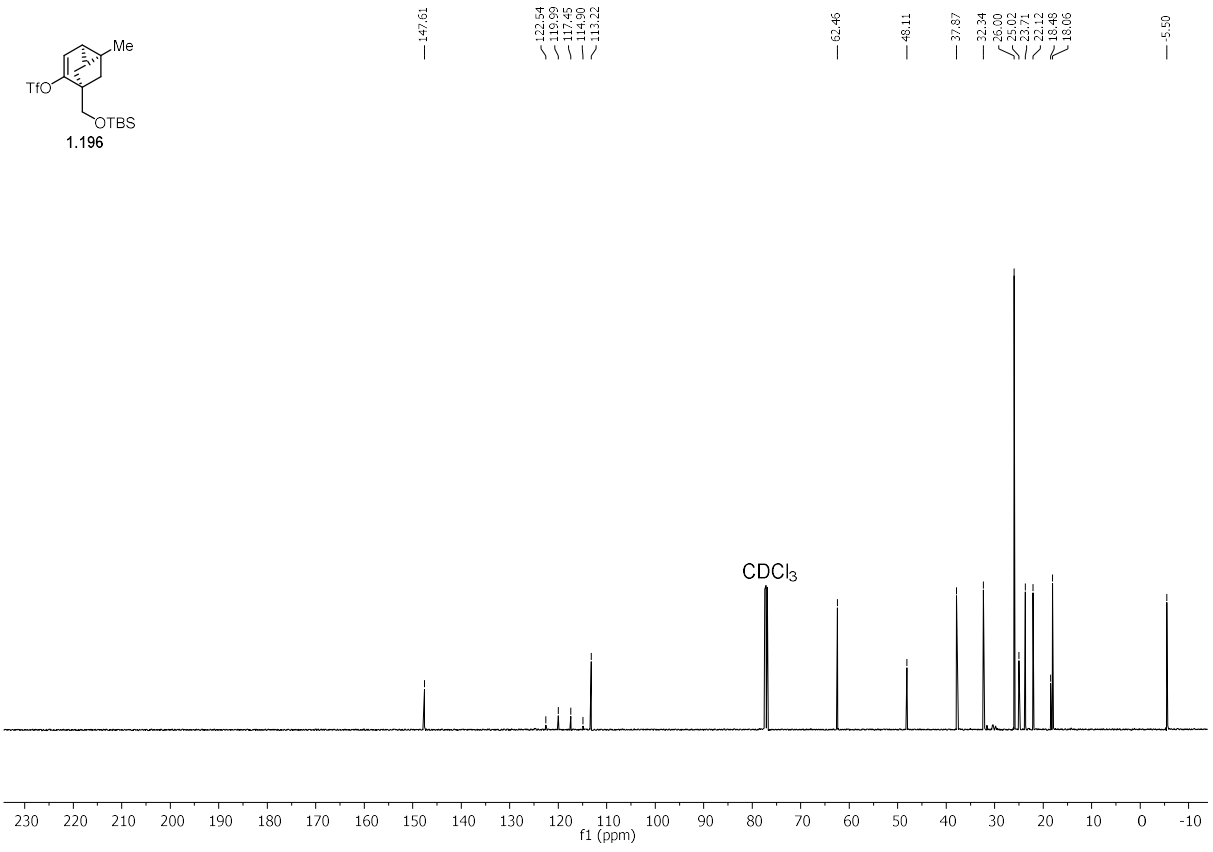
^{13}C NMR (101 MHz, $CDCl_3$) of **1.197a**



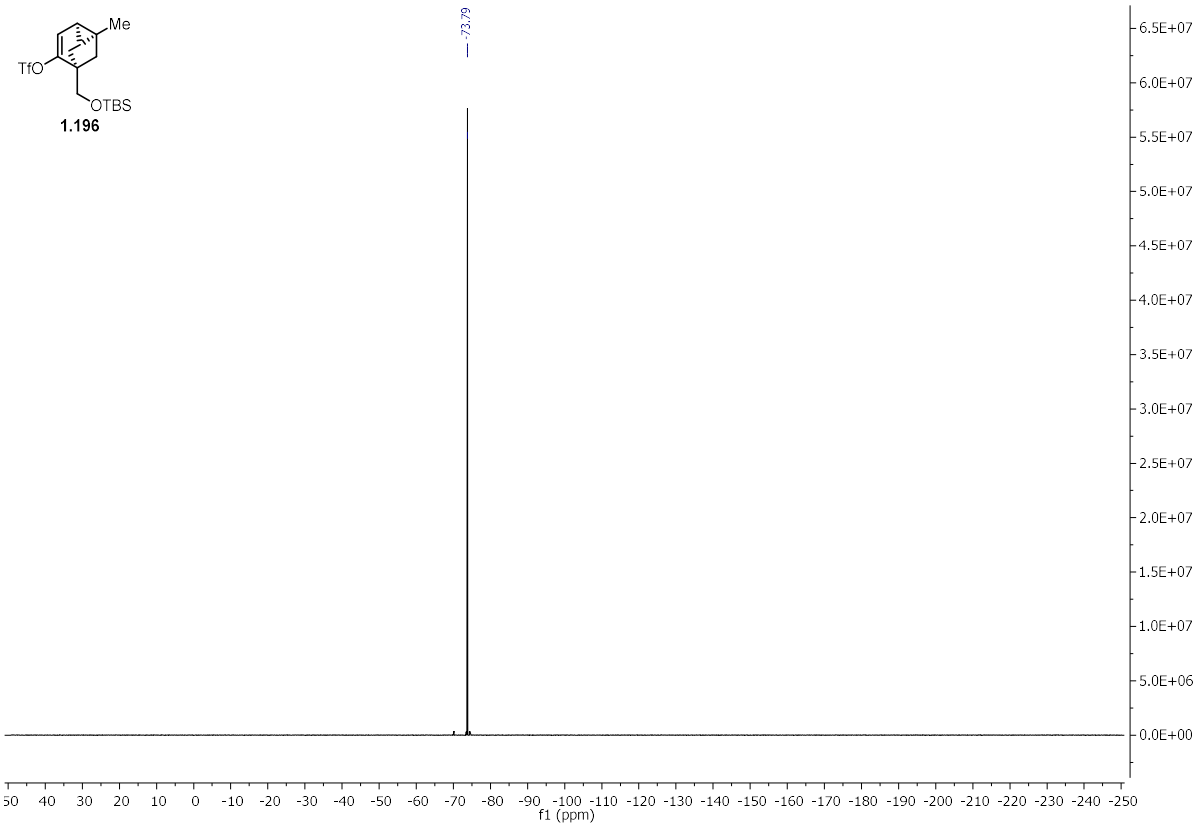
^{1}H NMR (500 MHz, $CDCl_3$) of **1.196**



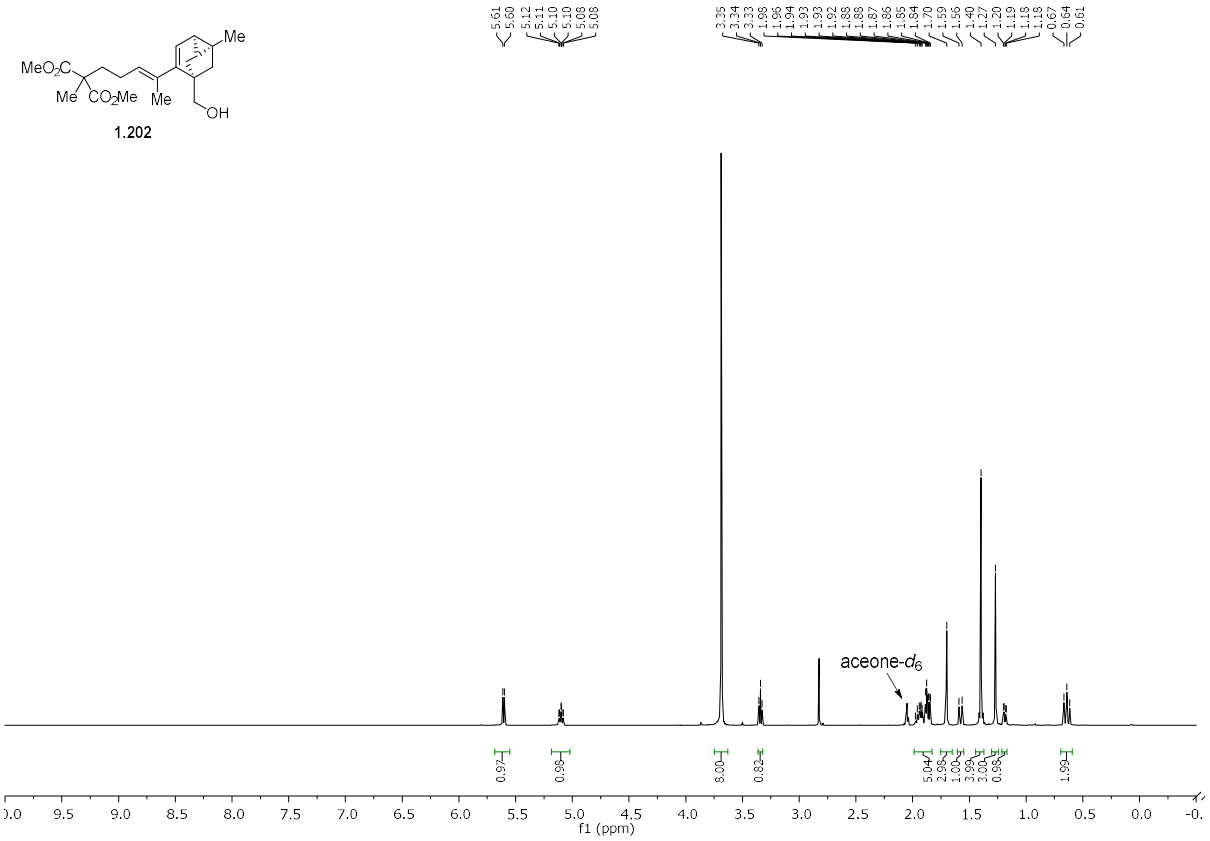
^{13}C NMR (126 MHz, $CDCl_3$) of **1.196**



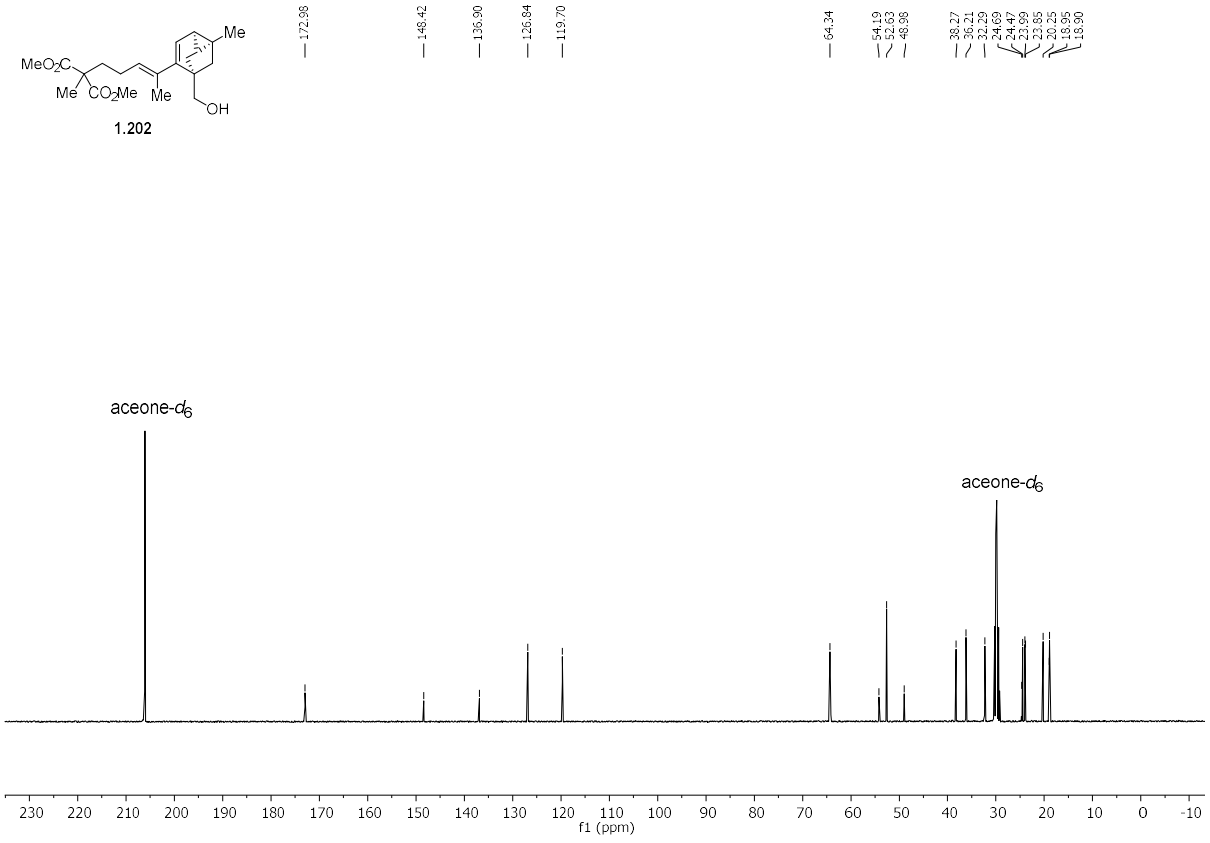
^{19}F NMR (377 MHz, $CDCl_3$) of **1.196**



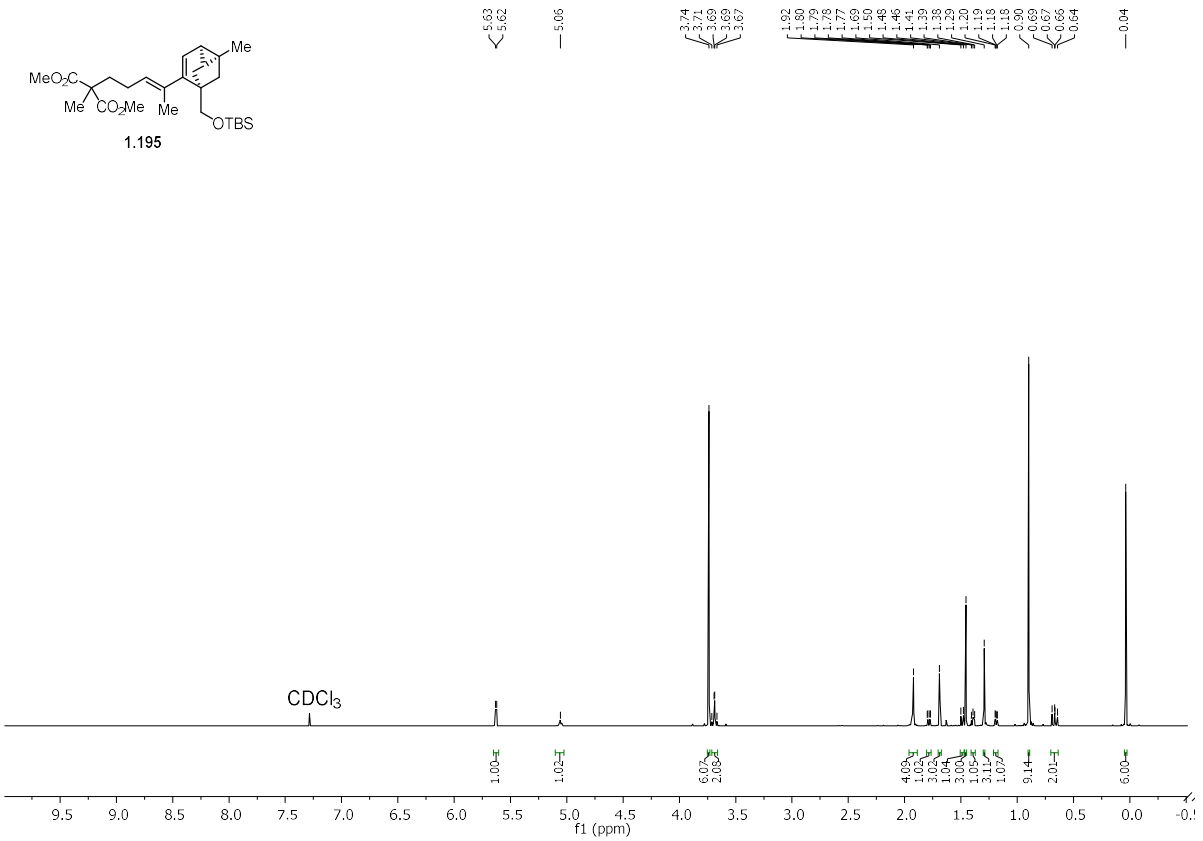
^{1}H NMR (400 MHz, acetone-d_6) of **1.202**



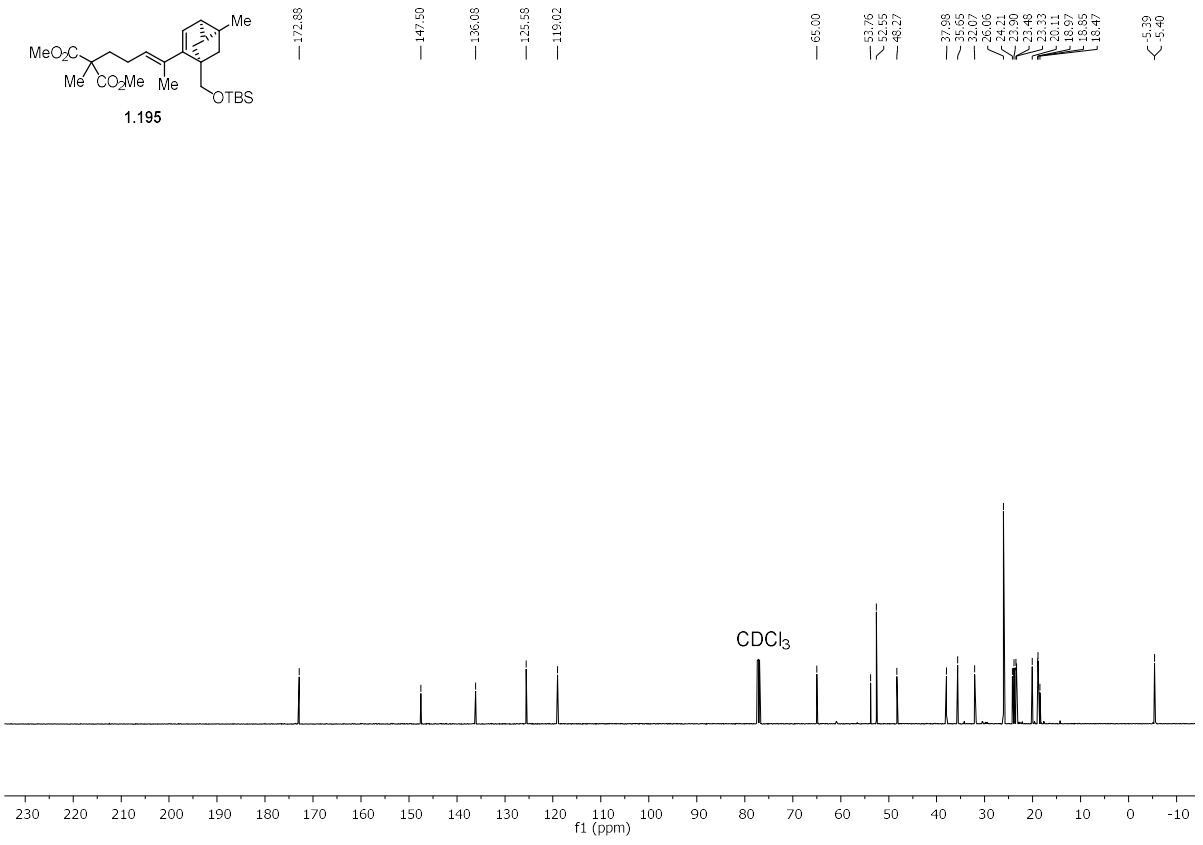
^{13}C NMR (101 MHz, aceton-d_6) of **1.202**



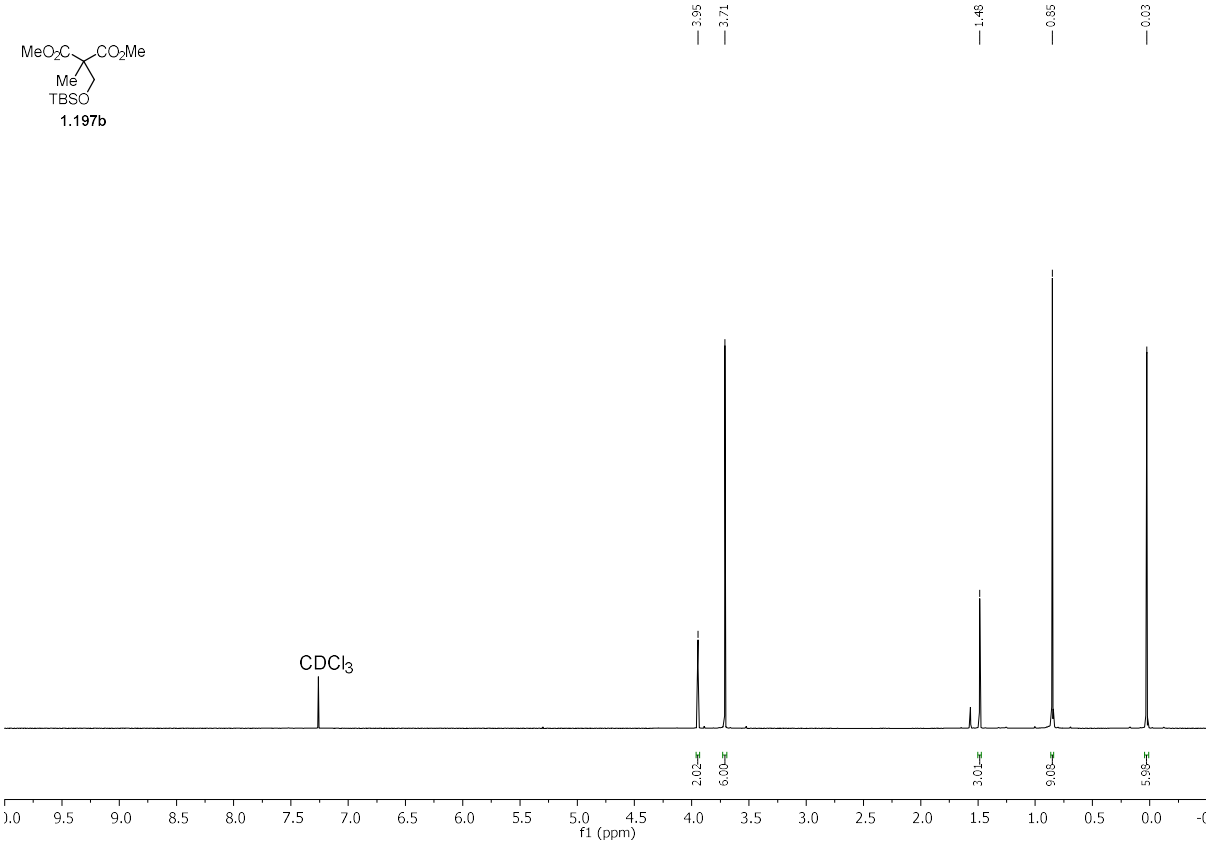
^{1}H NMR (500 MHz, $CDCl_3$) of **1.195**



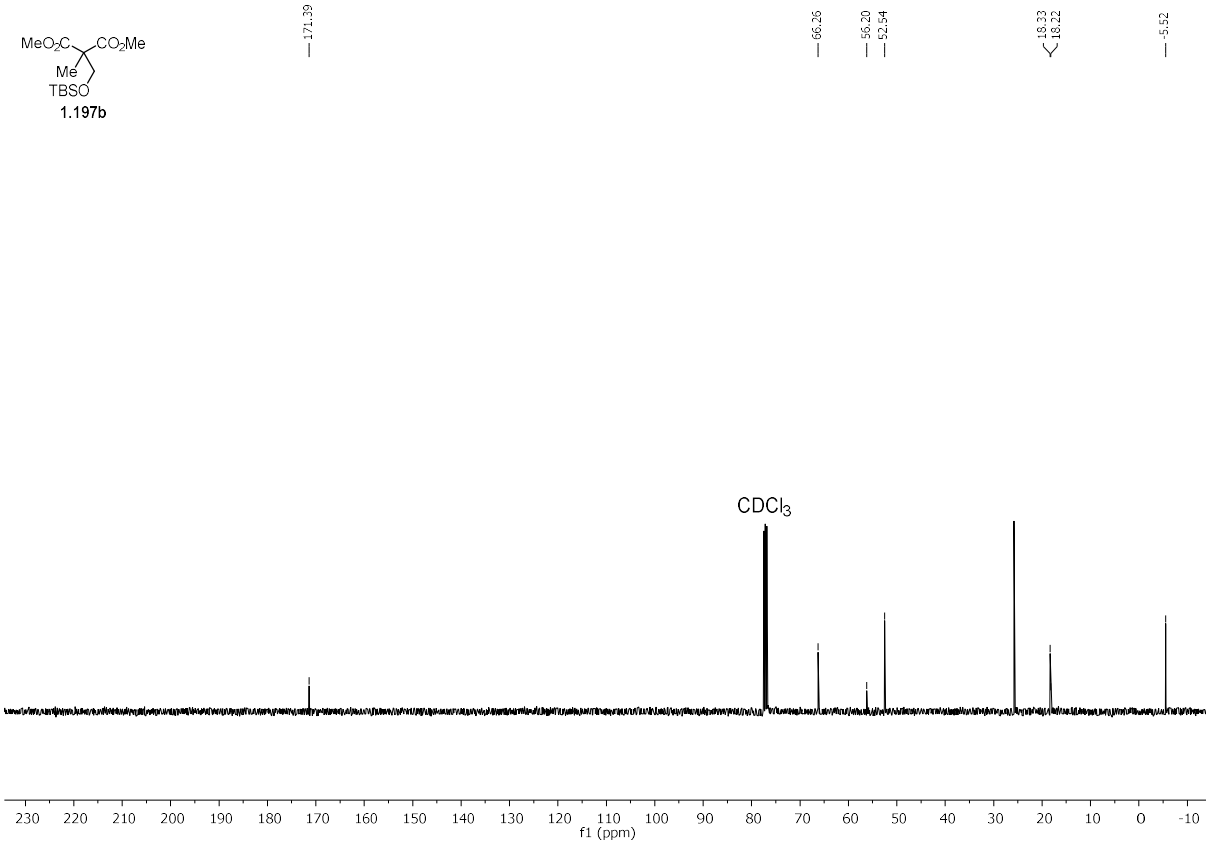
^{13}C NMR (126 MHz, $CDCl_3$) of **1.195**



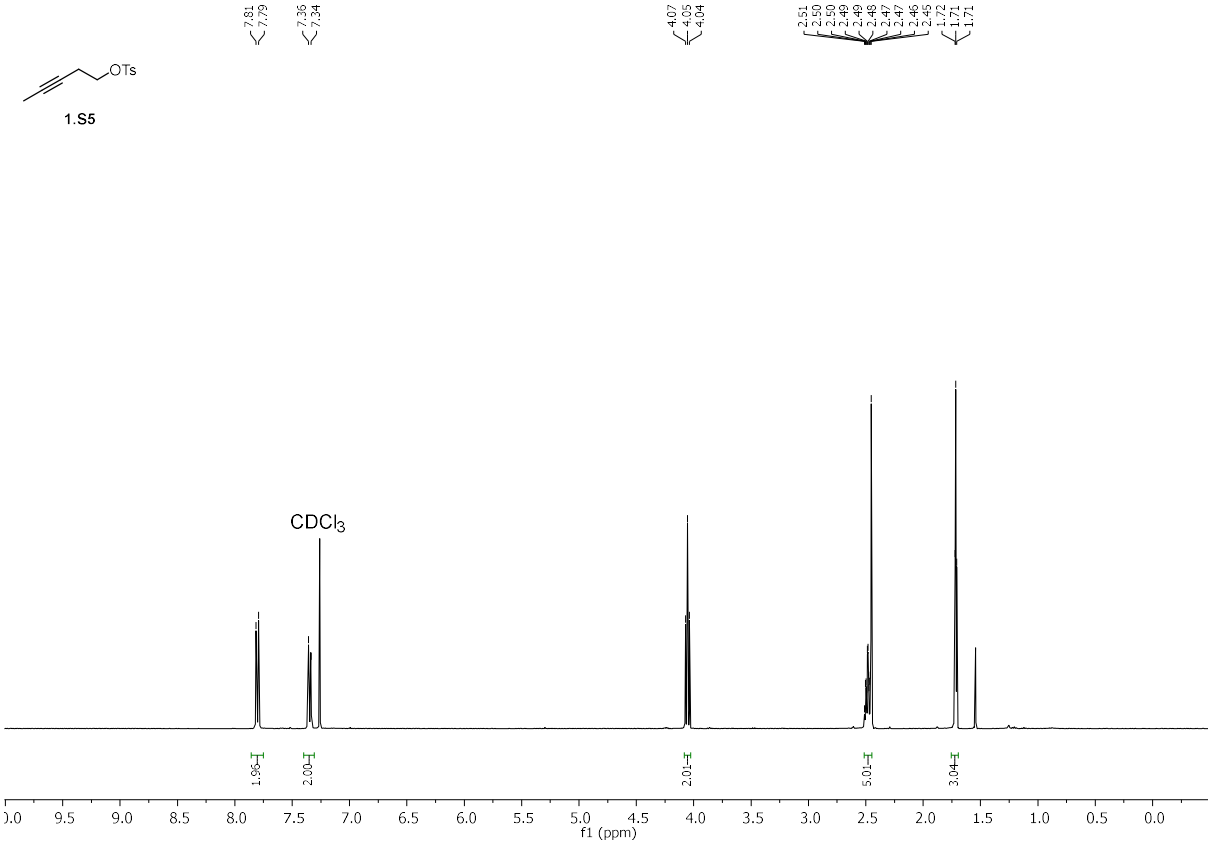
^{1}H NMR (400 MHz, $CDCl_3$) of **1.197b**



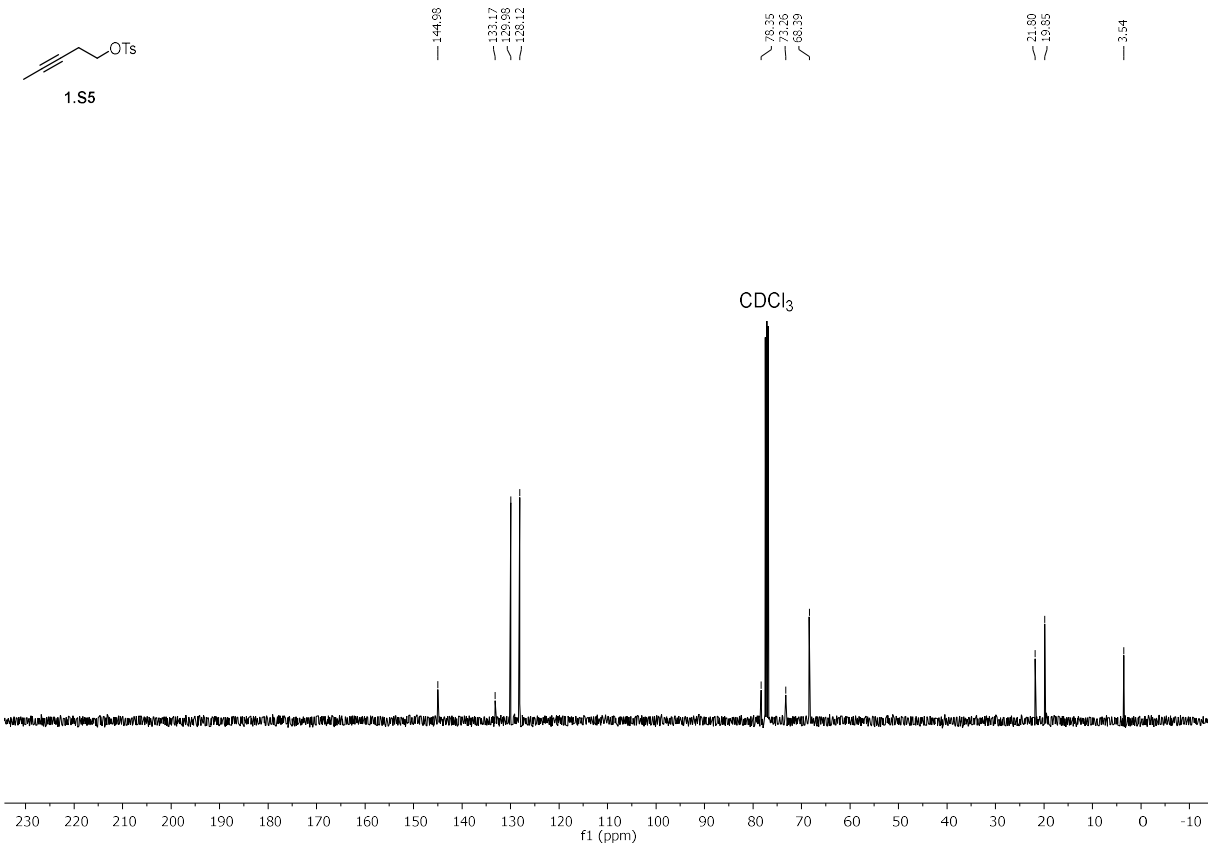
^{13}C NMR (101 MHz, $CDCl_3$) of **1.197b**



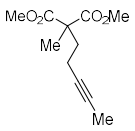
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S5**



^{13}C NMR (101 MHz, $CDCl_3$) of **1.S5**

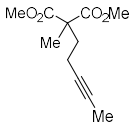


^{1}H NMR (400 MHz, $CDCl_3$) of **1.197c**



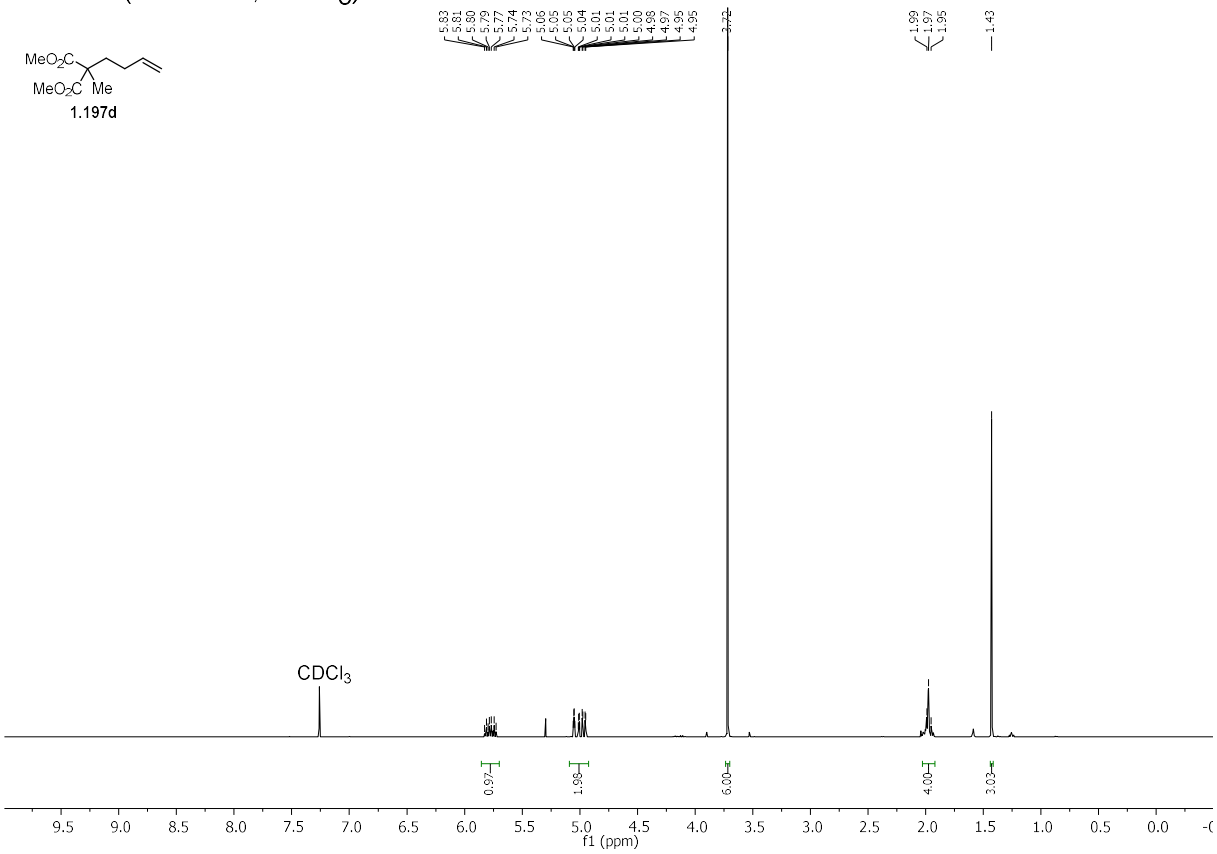
1.197c

^{13}C NMR (101 MHz, $CDCl_3$) of **1.197c**

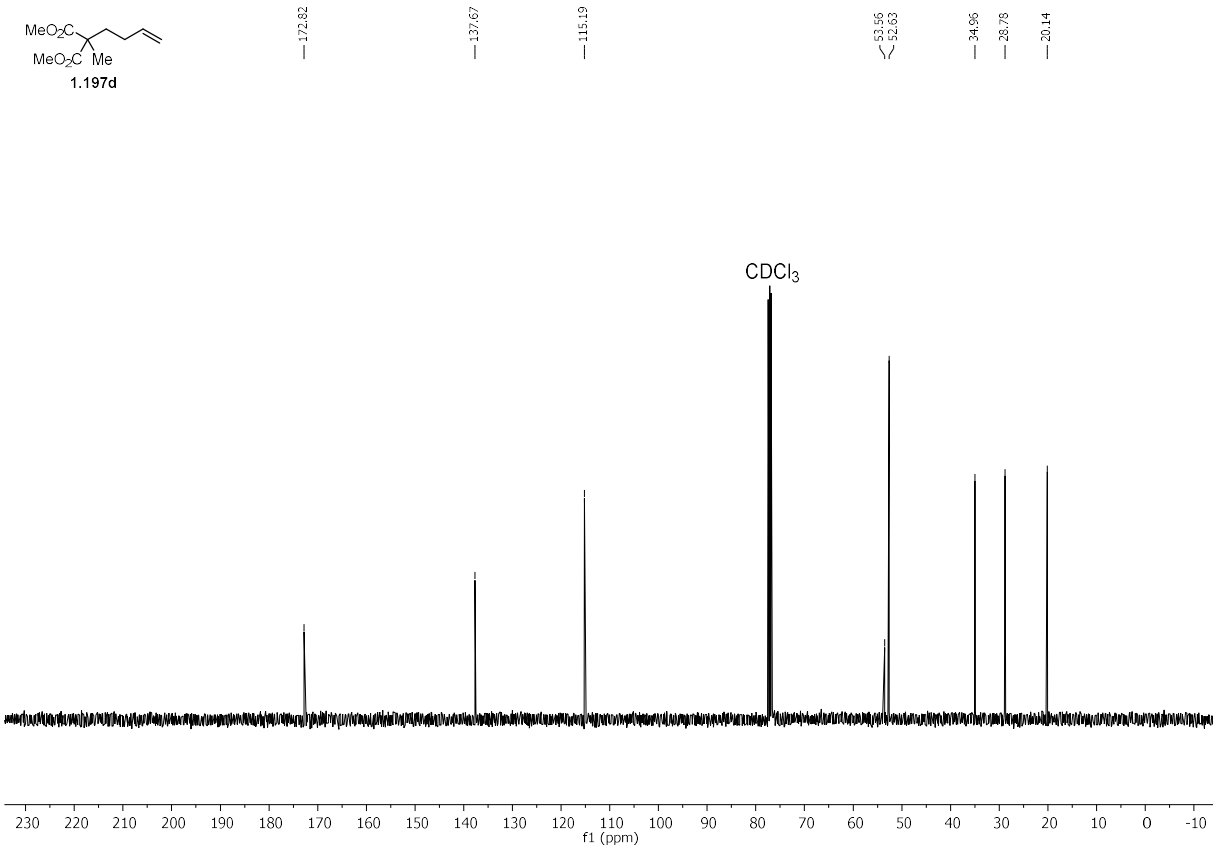


1.197c

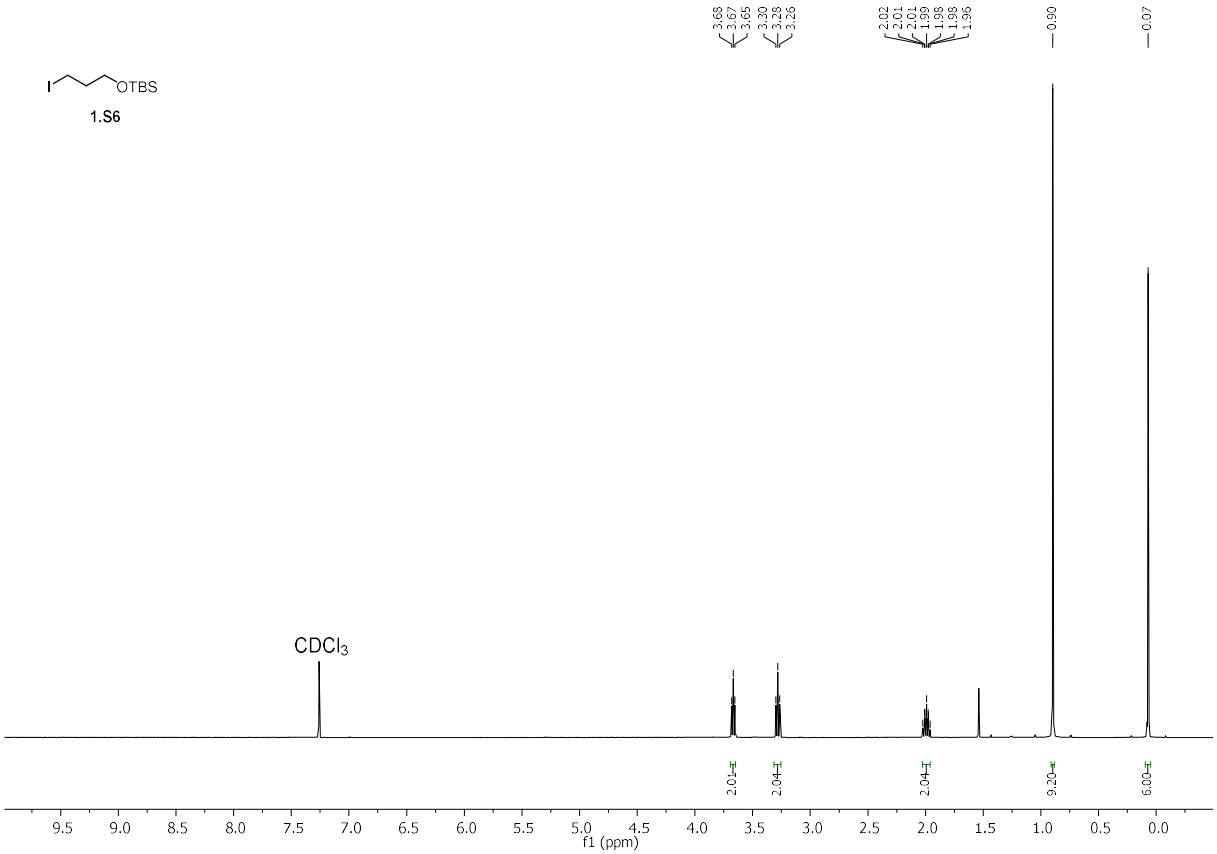
^{1}H NMR (400 MHz, $CDCl_3$) of **1.197d**



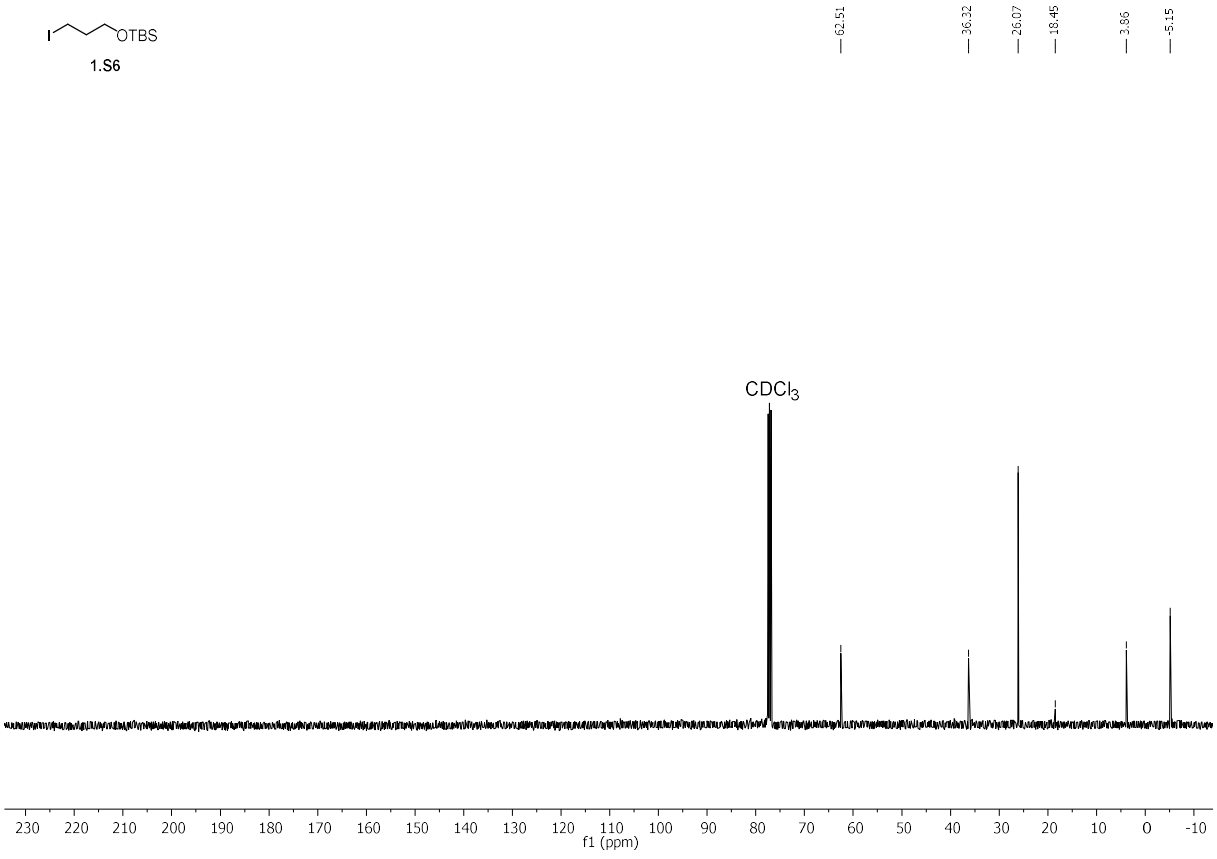
^{13}C NMR (101 MHz, $CDCl_3$) of **1.197d**



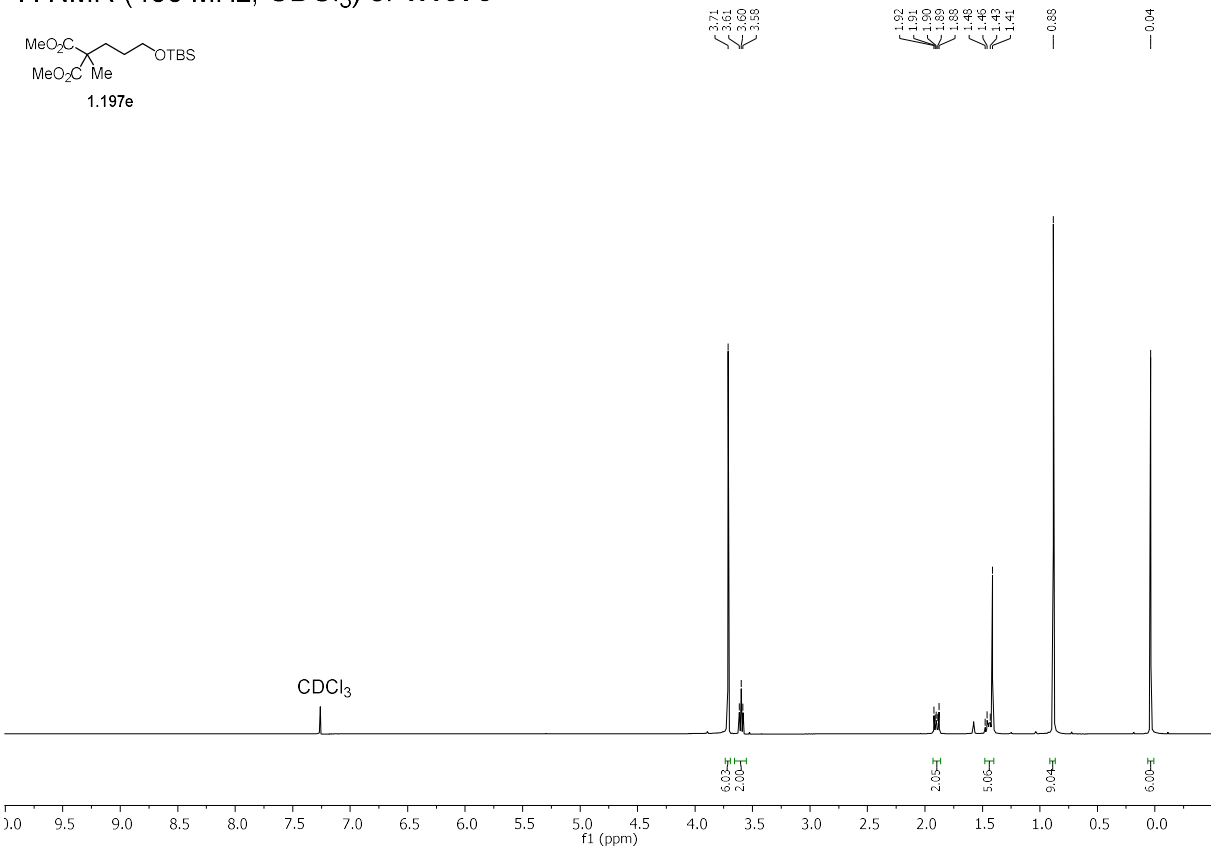
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S6**



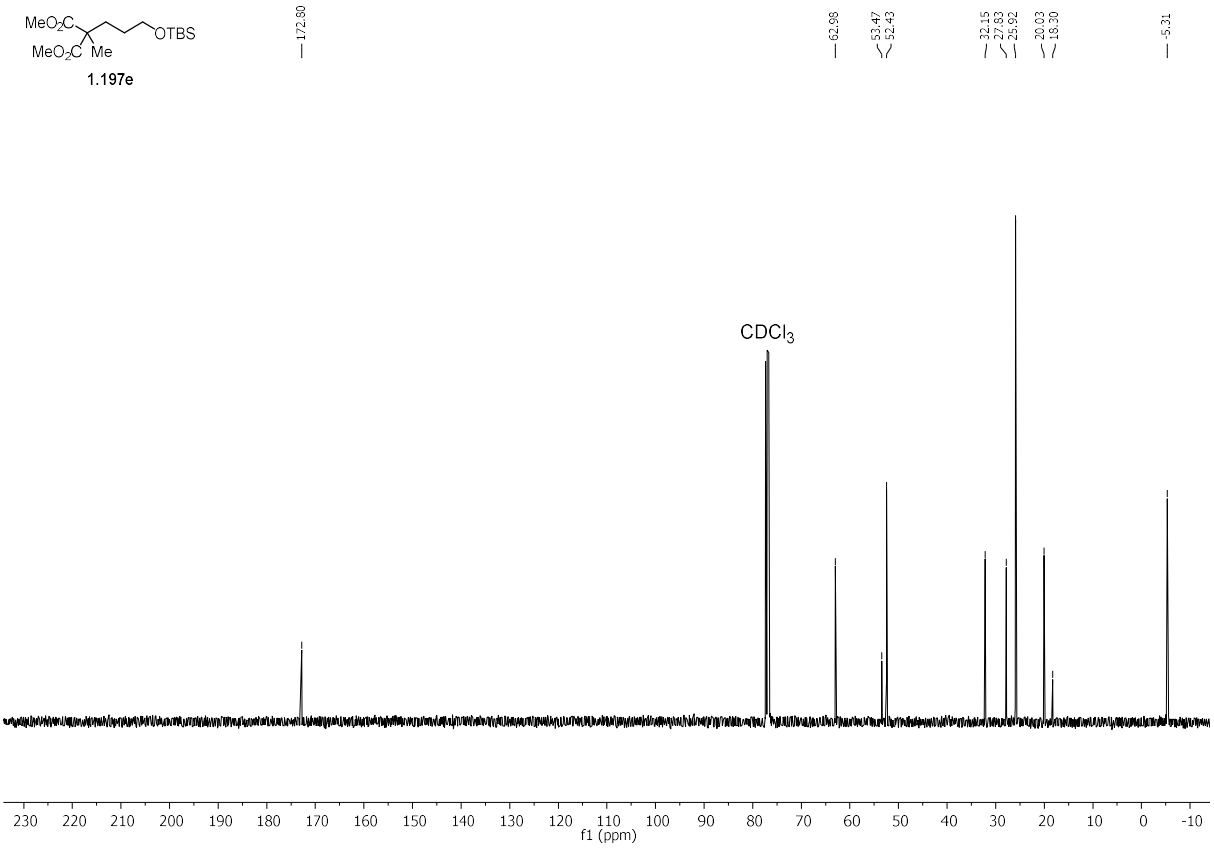
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S6**



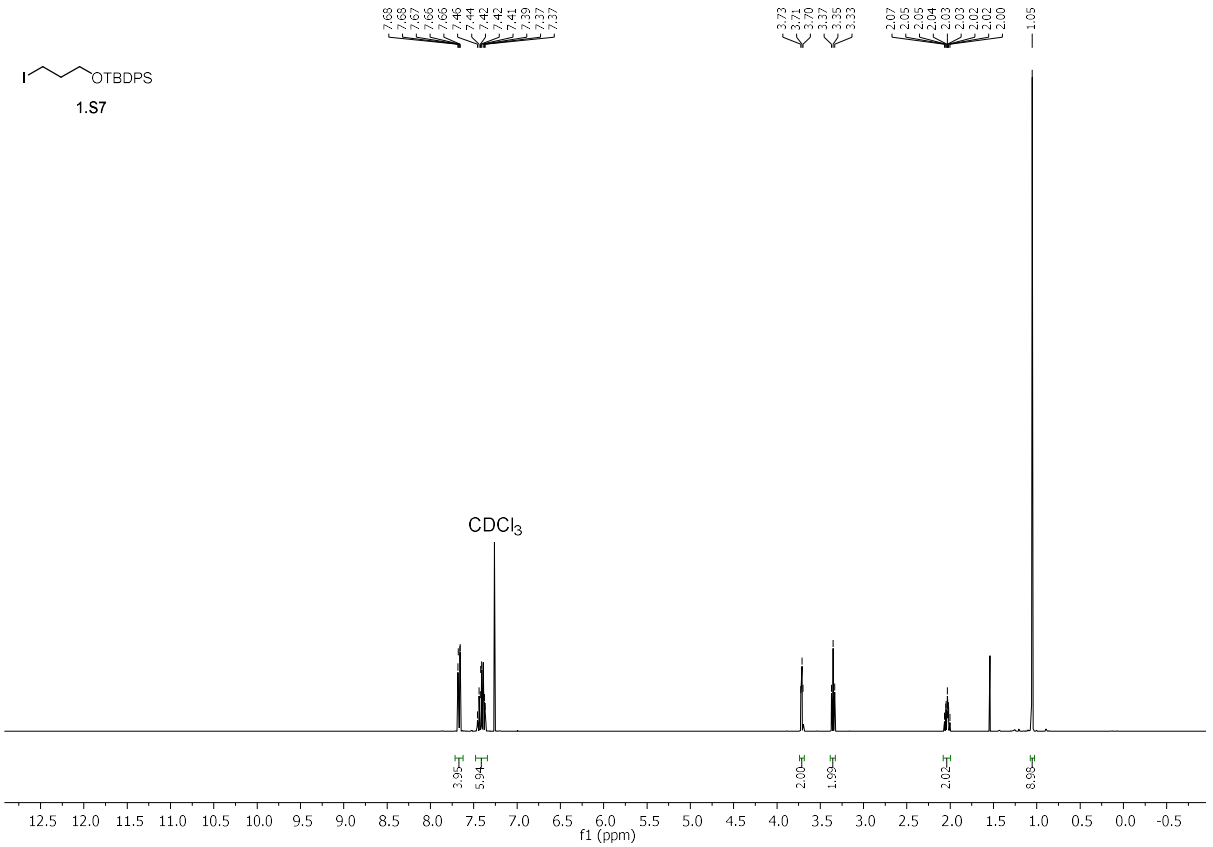
^{1}H NMR (400 MHz, $CDCl_3$) of **1.197e**



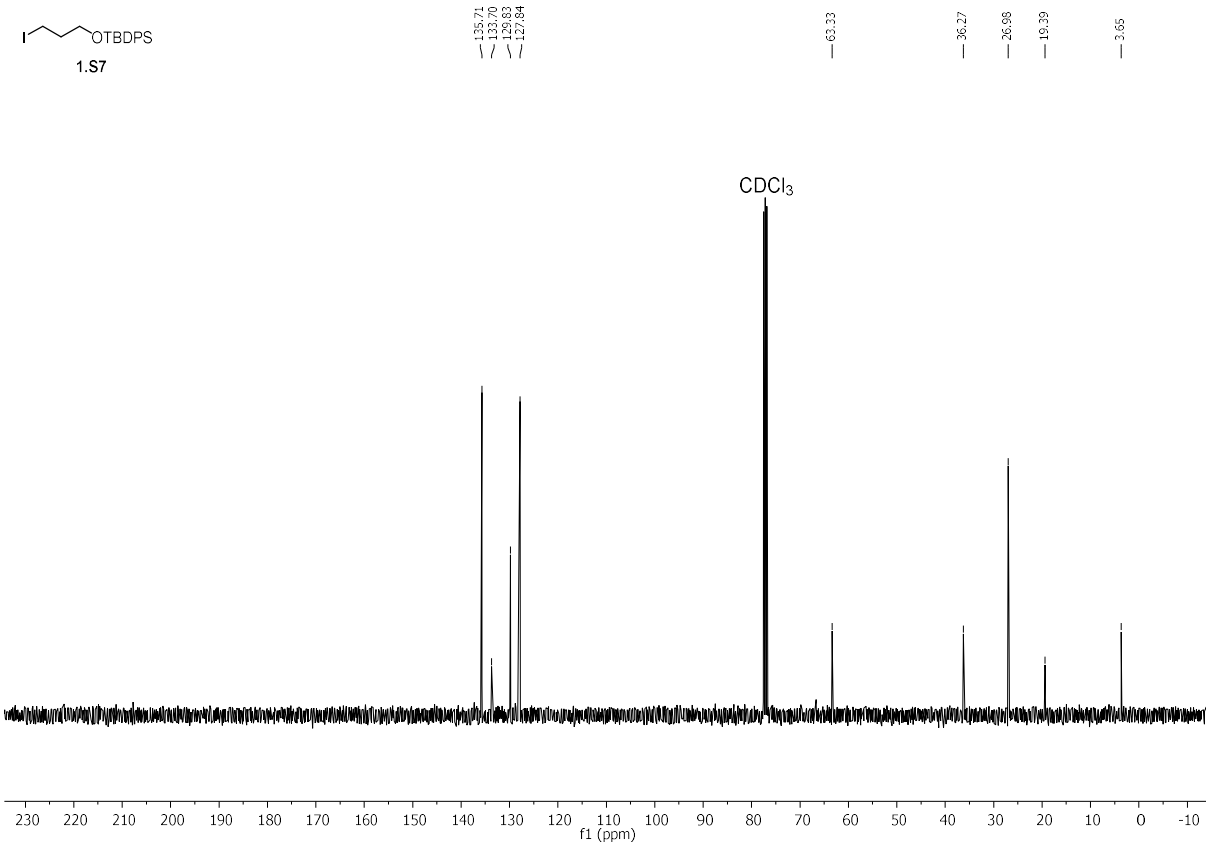
^{13}C NMR (101 MHz, $CDCl_3$) of **1.197e**



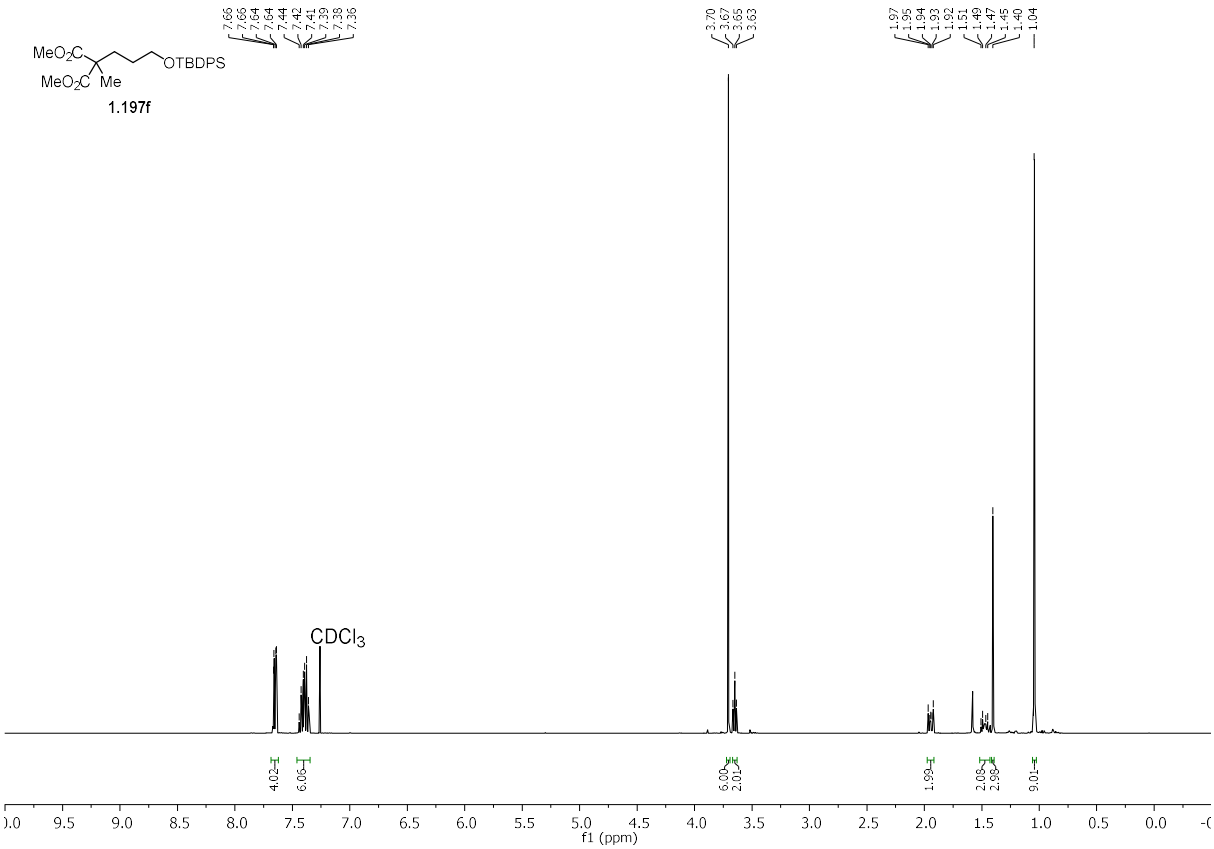
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S7**



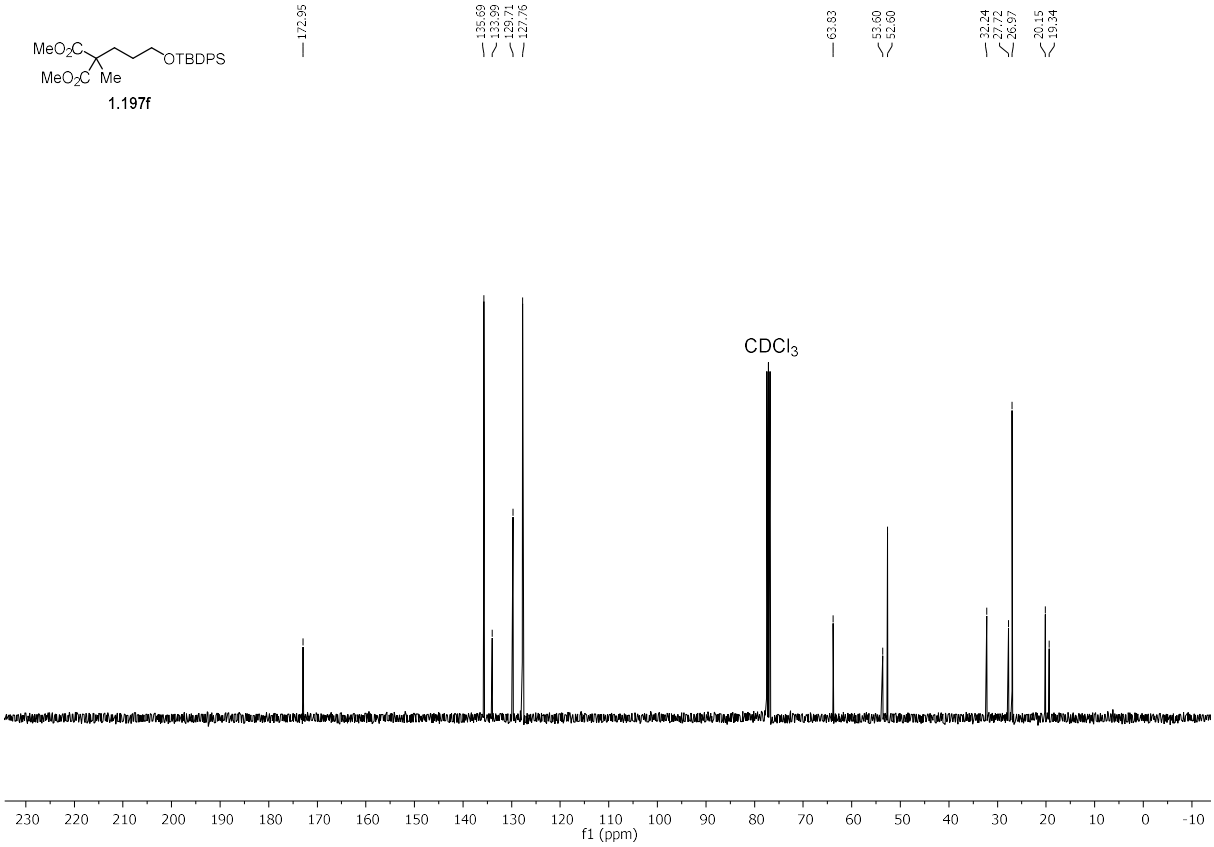
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S7**



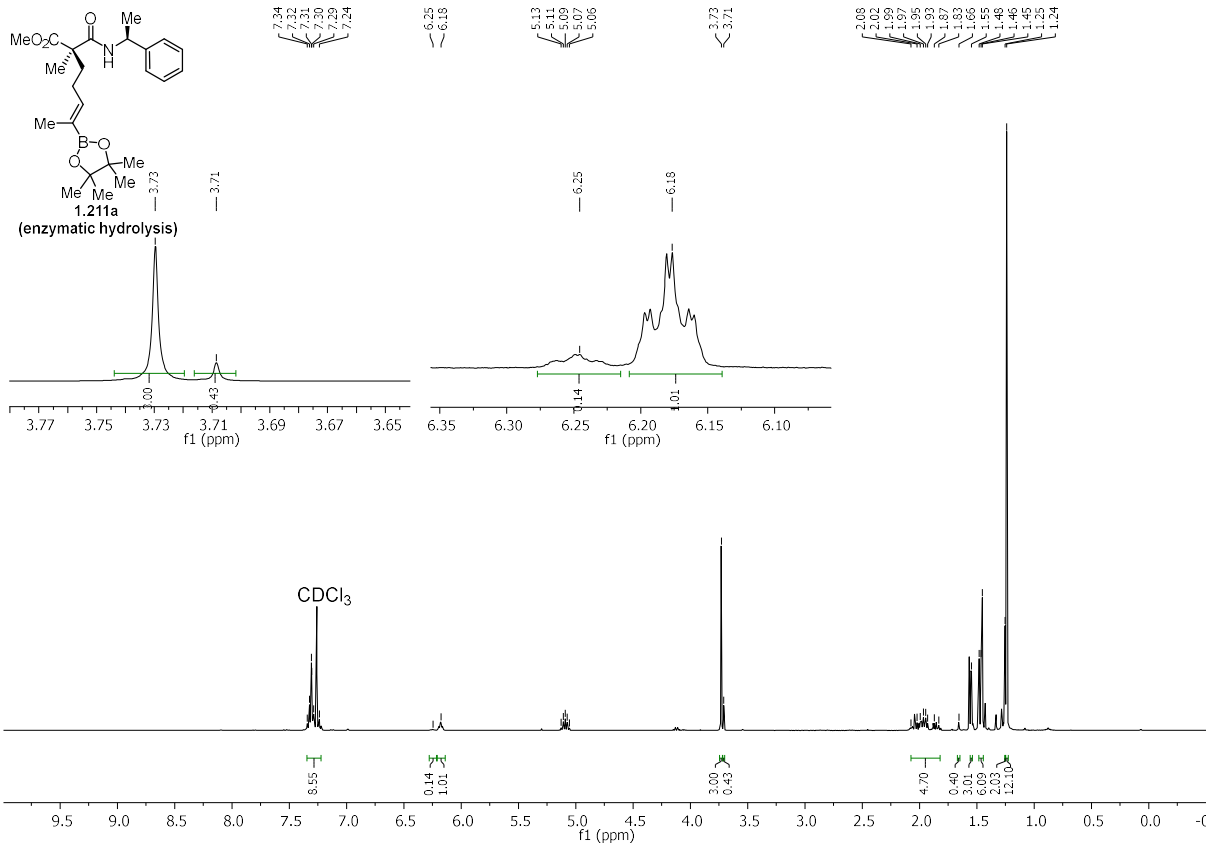
^{1}H NMR (400 MHz, $CDCl_3$) of **1.197f**



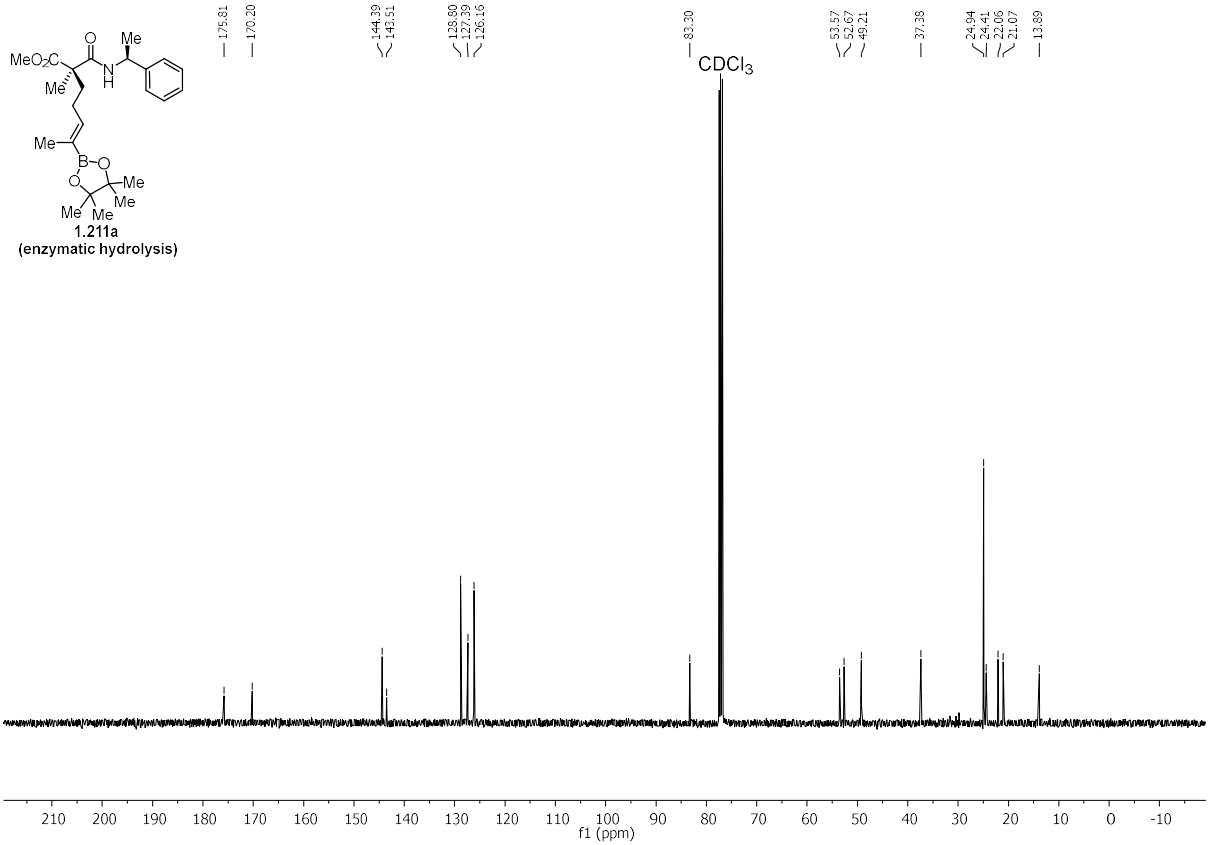
^{13}C NMR (101 MHz, $CDCl_3$) of **1.197f**



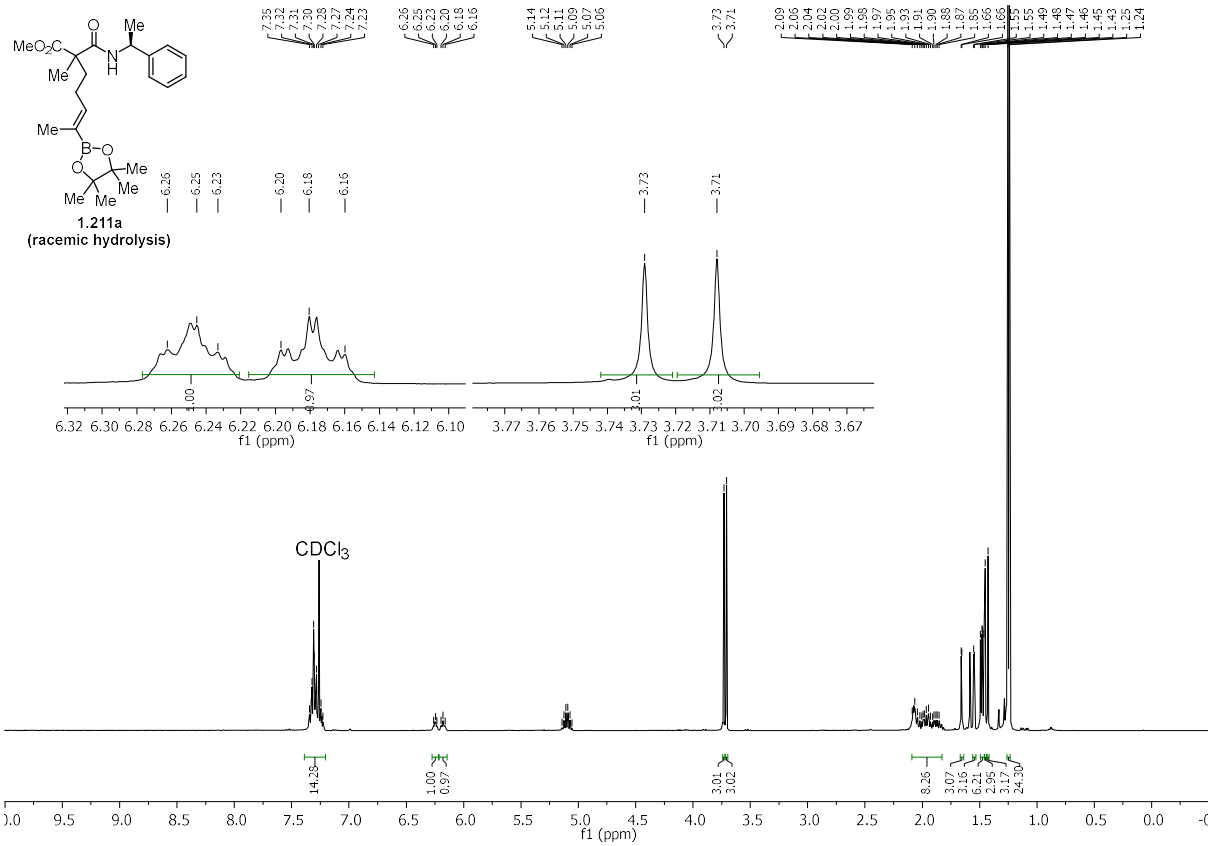
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211a**



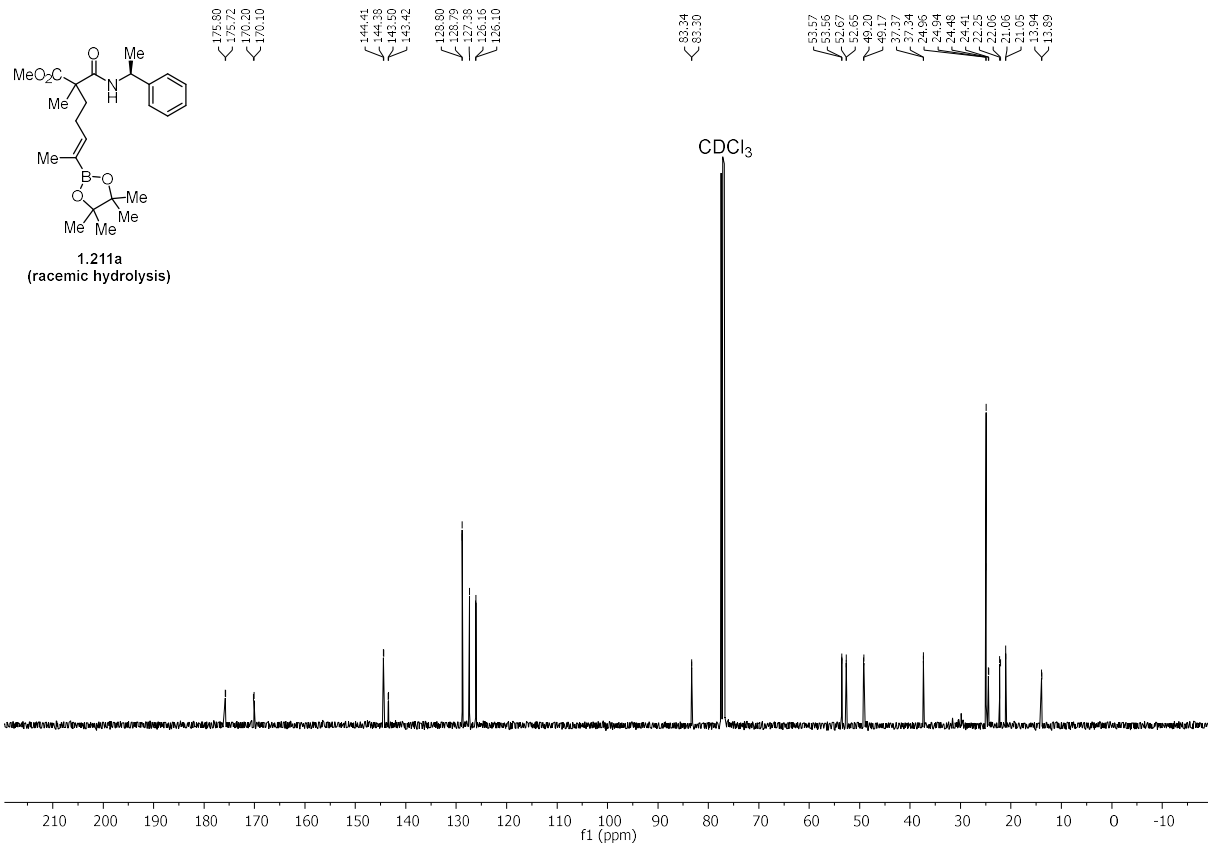
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211a**



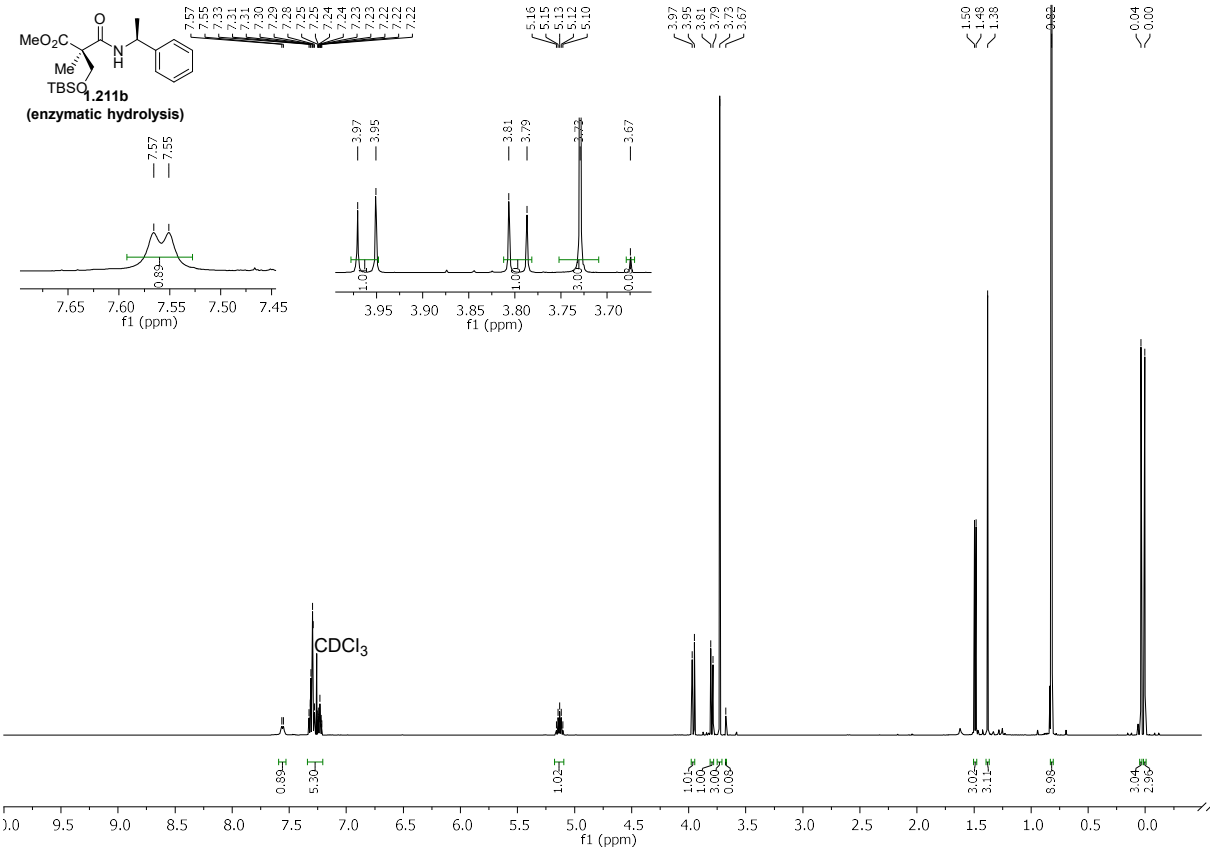
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211a**



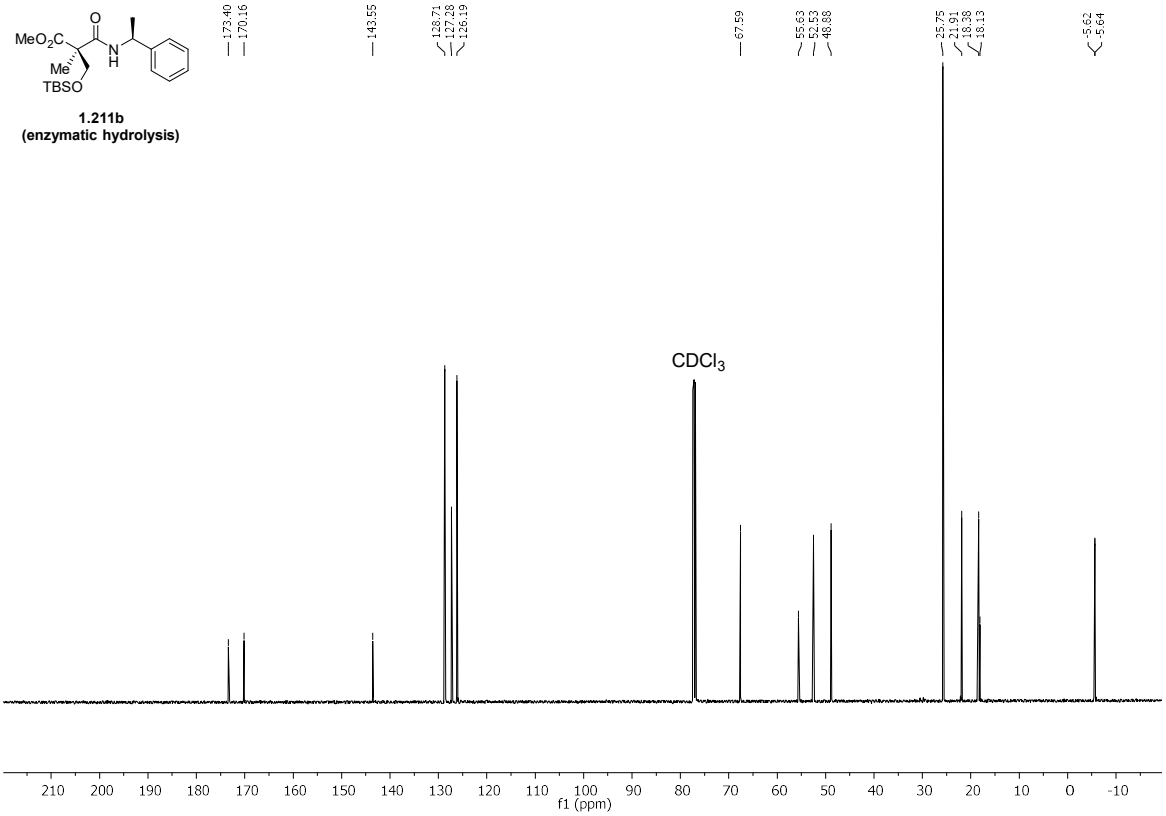
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211a**



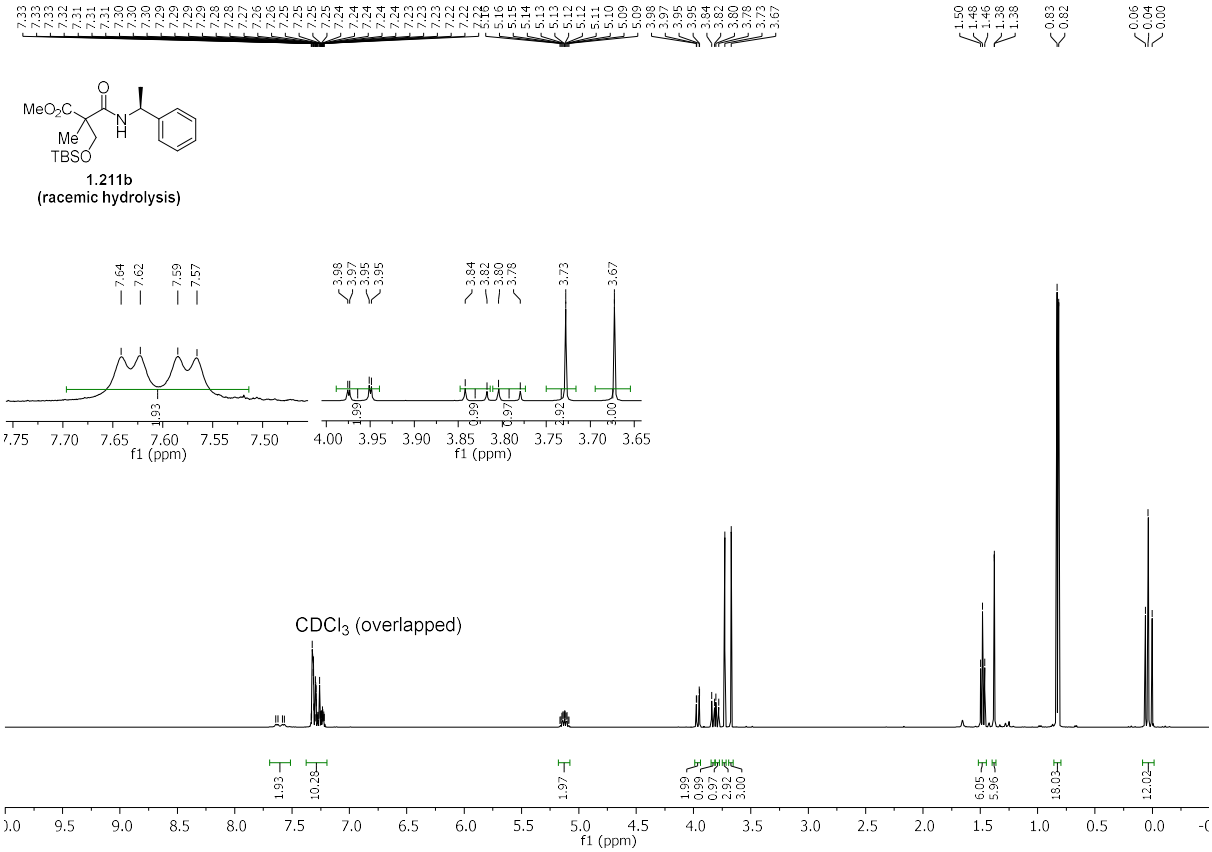
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211b**



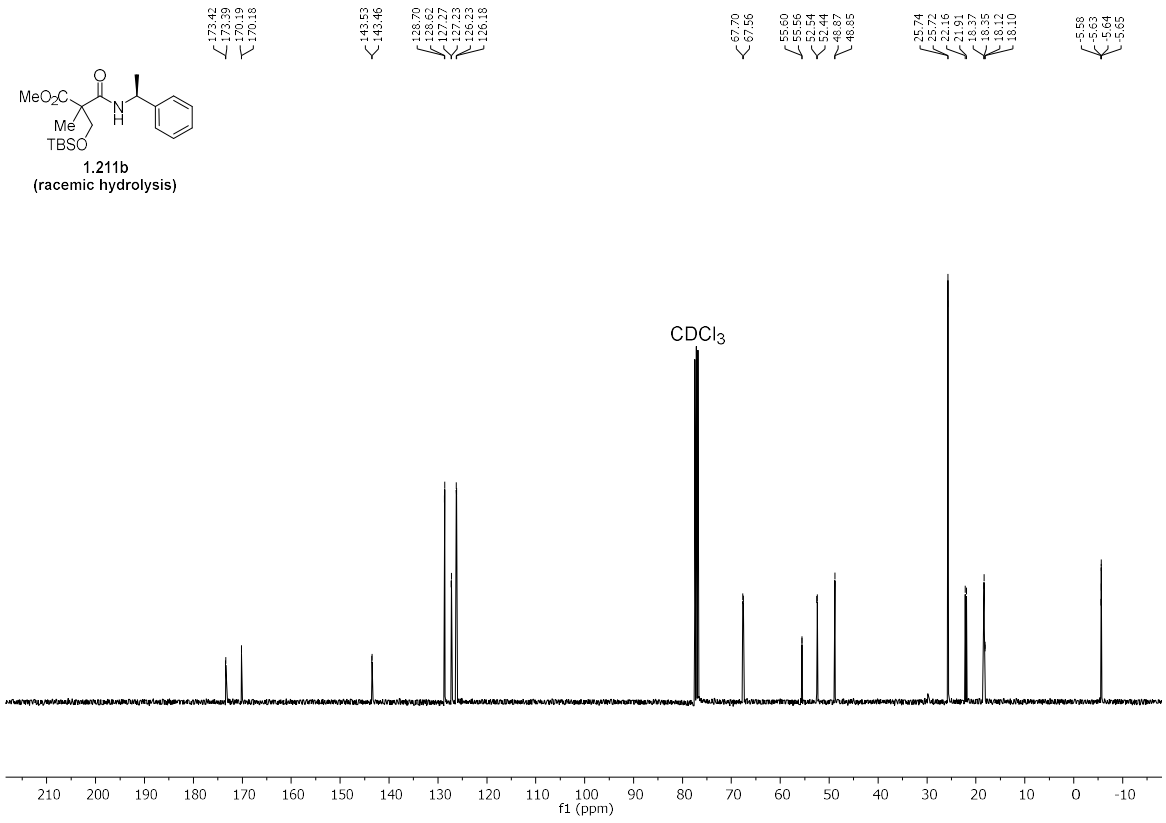
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211b**



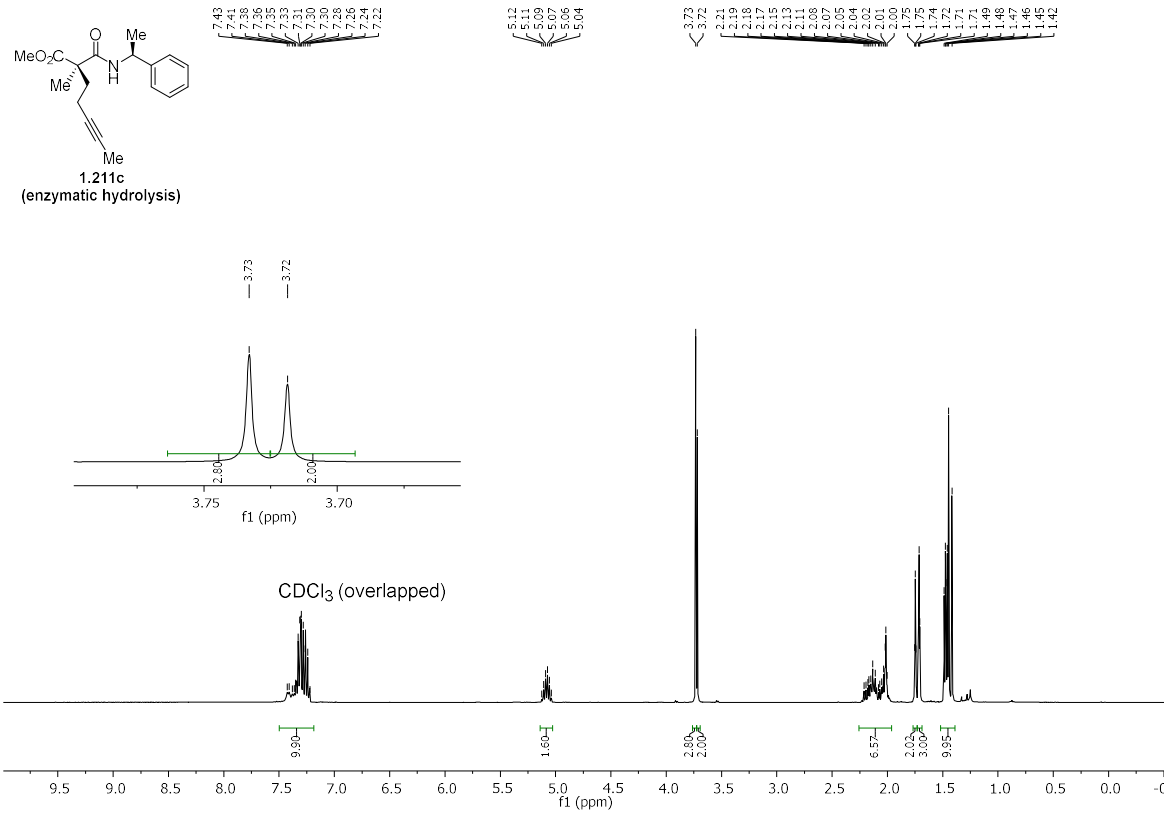
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211b**



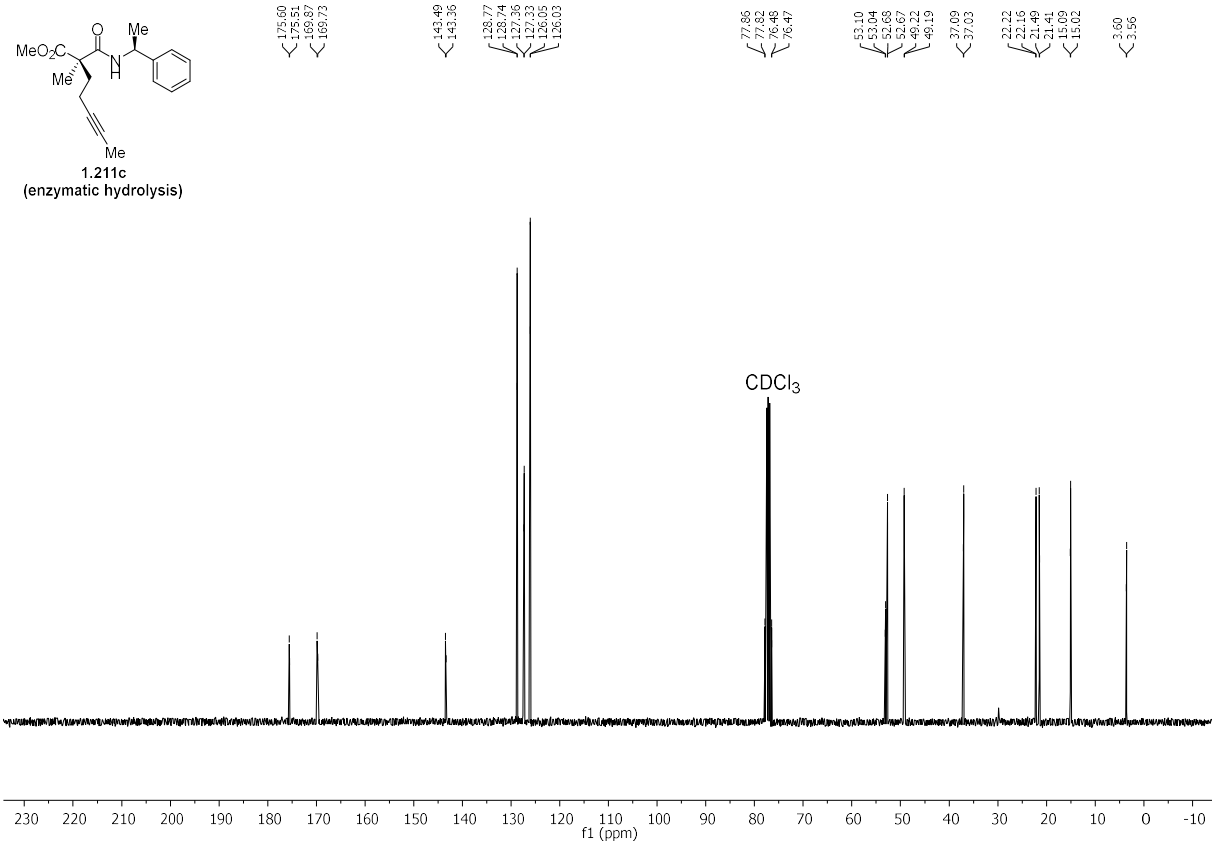
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211b**



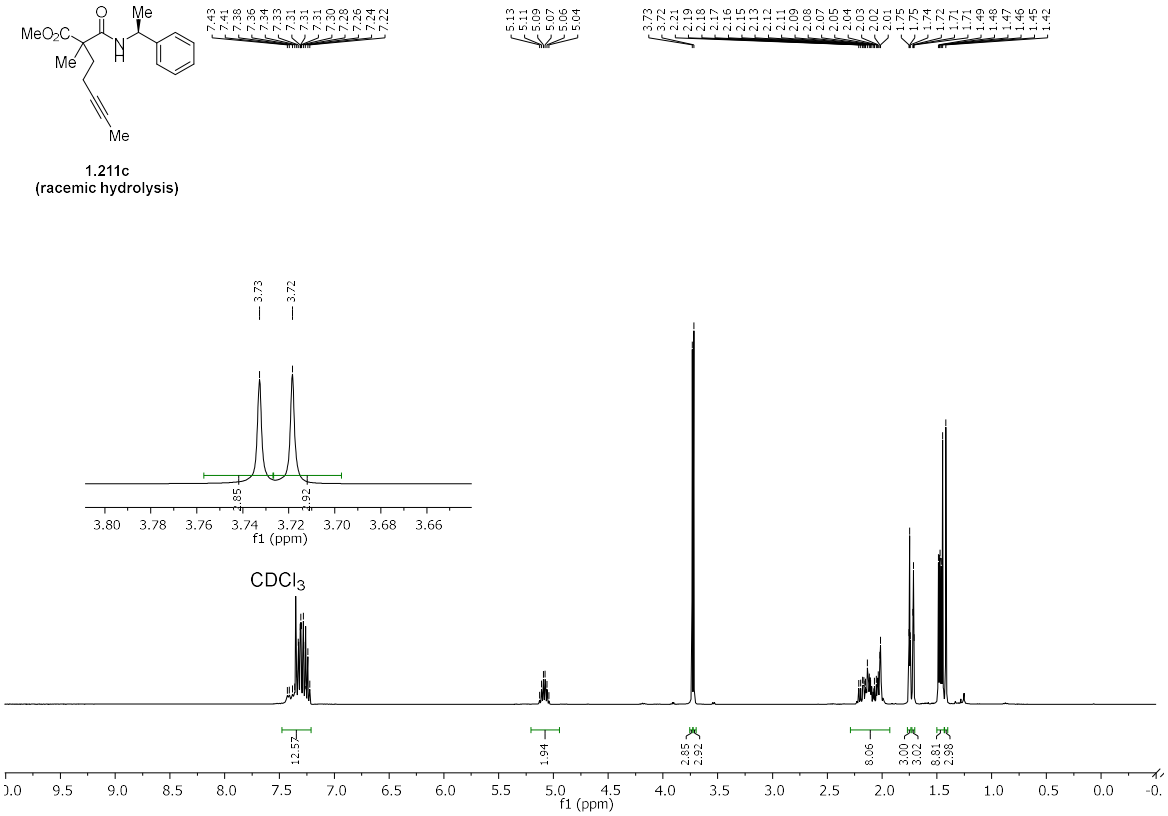
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211c**



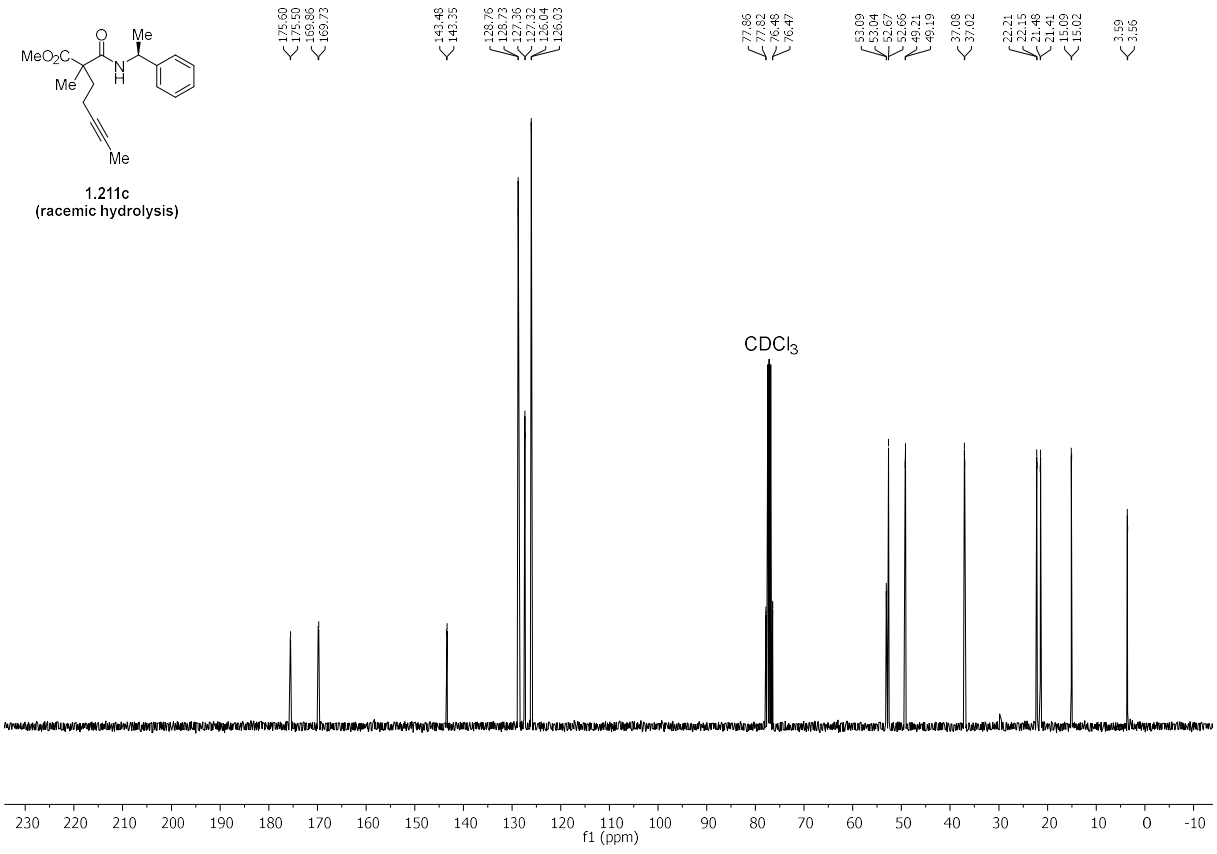
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211c**



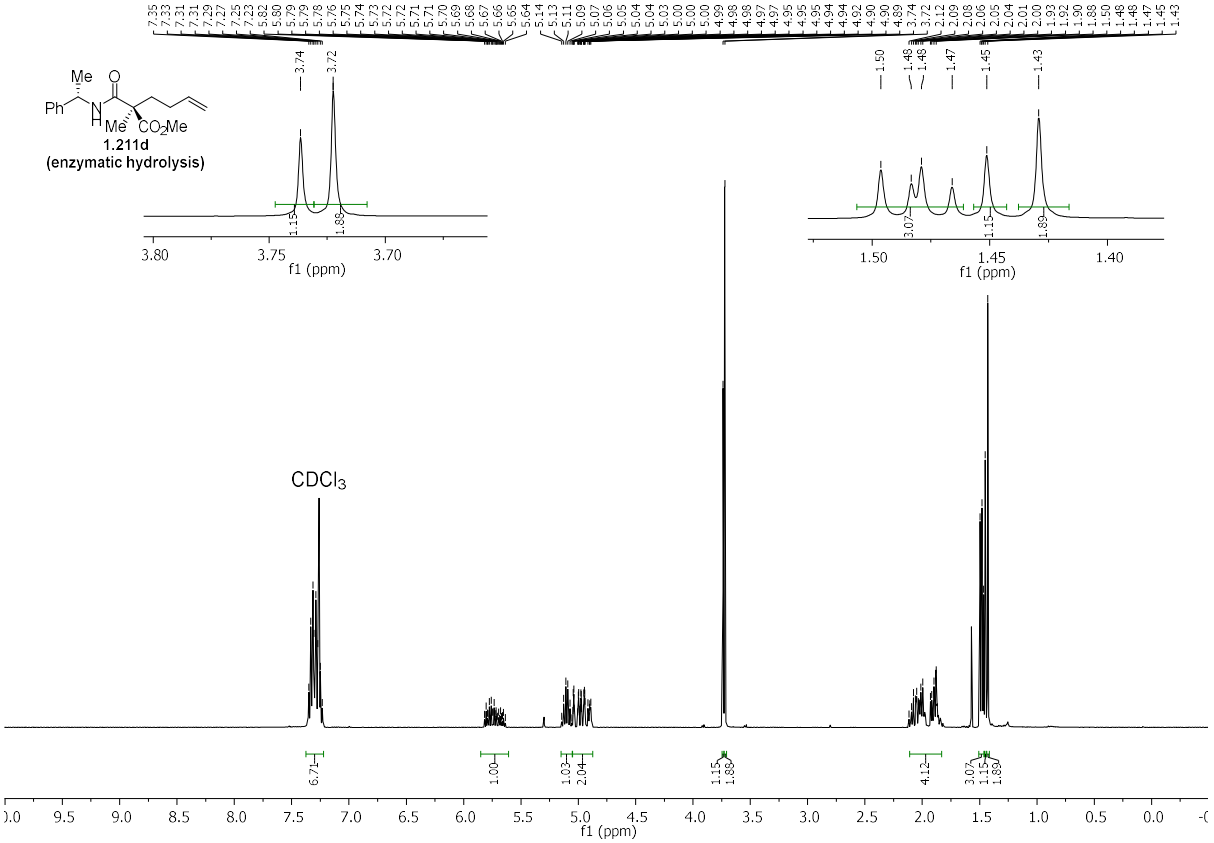
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211c**



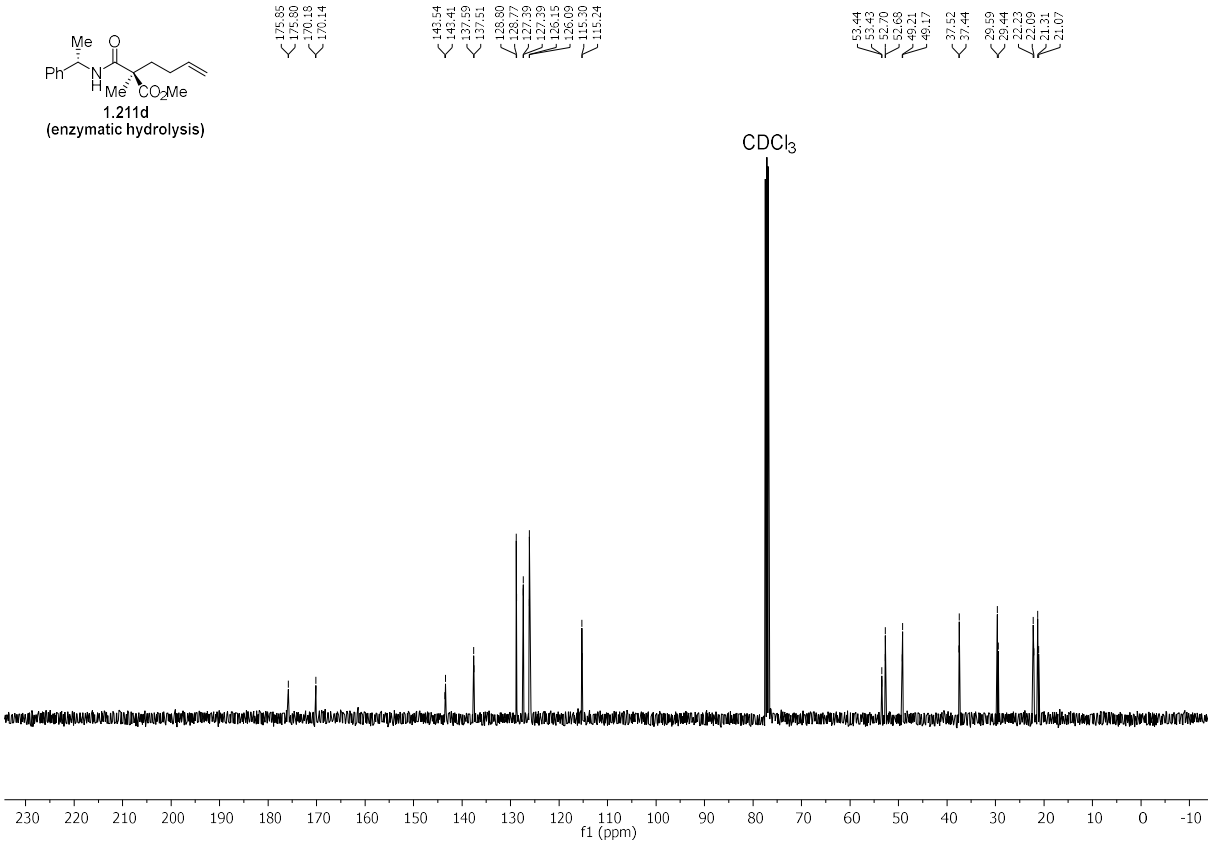
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211c**



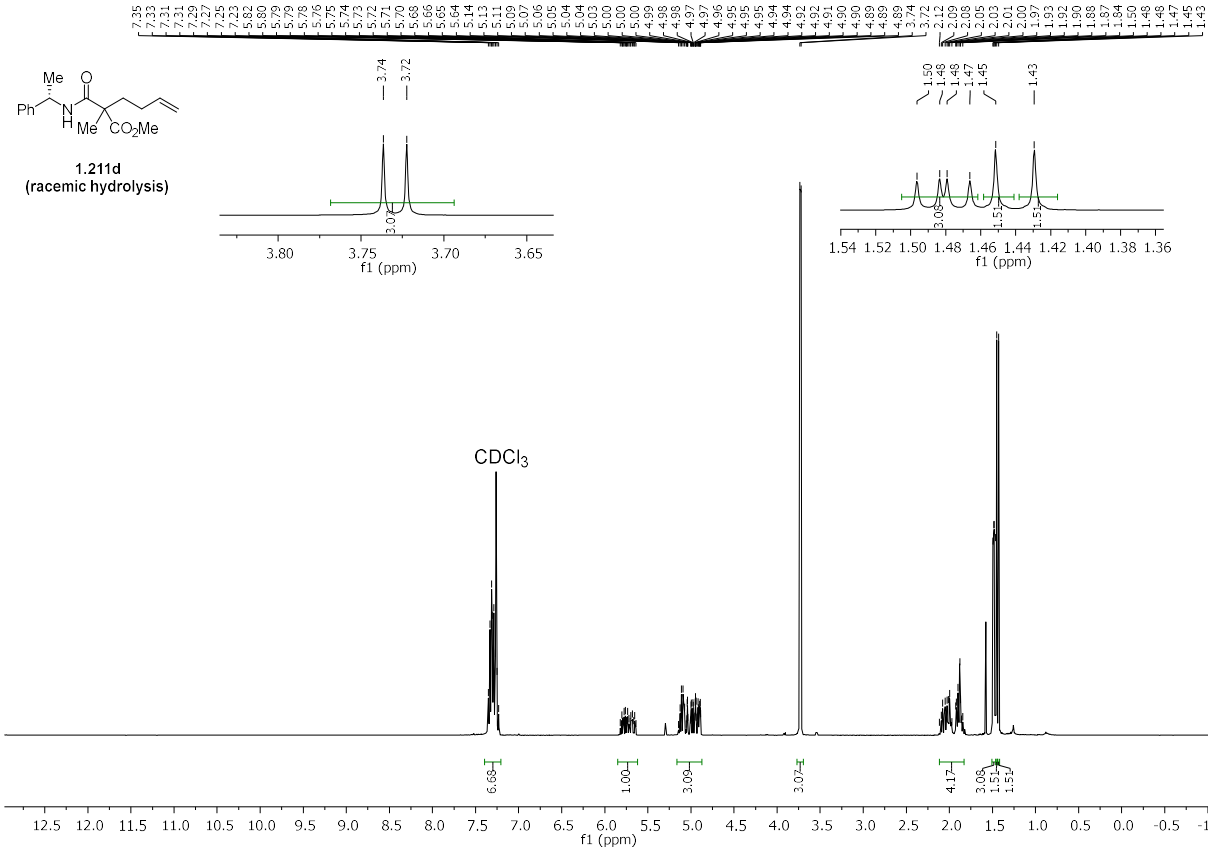
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211d**



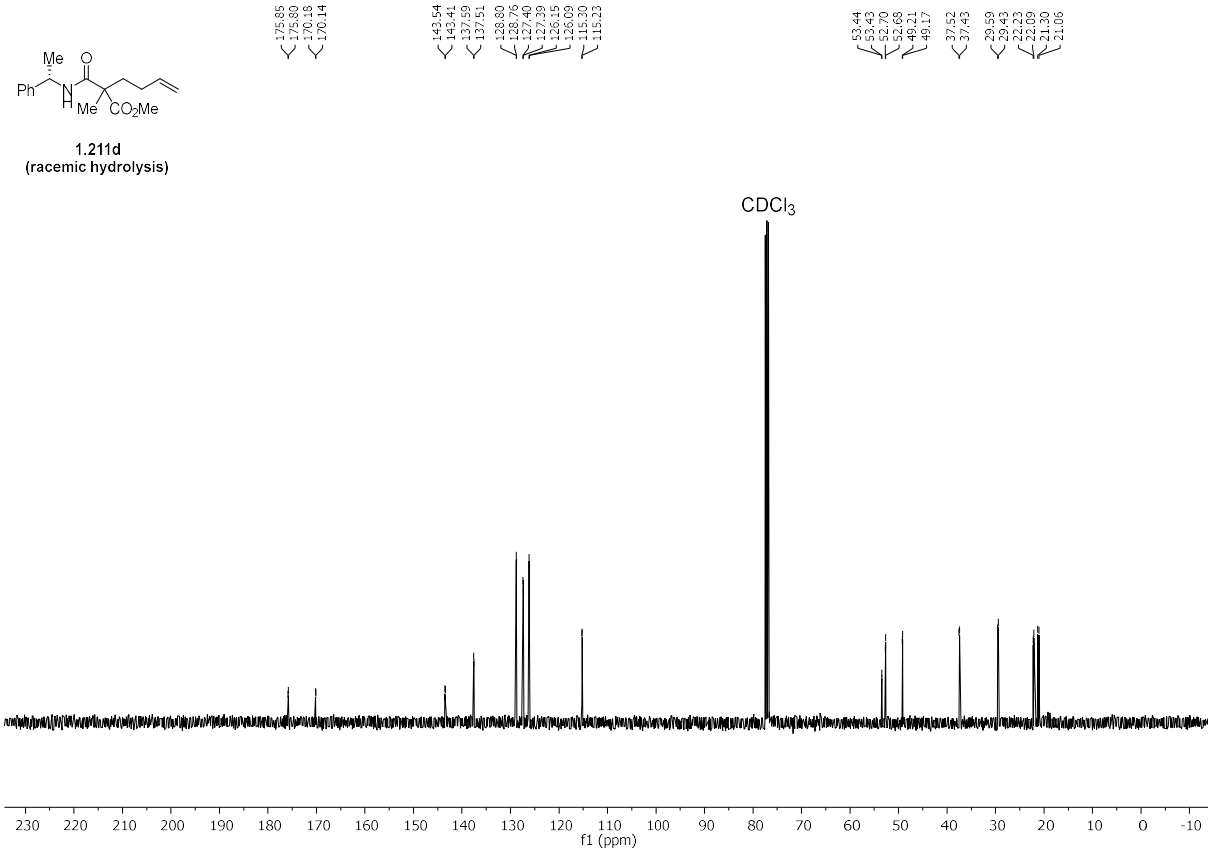
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211d**



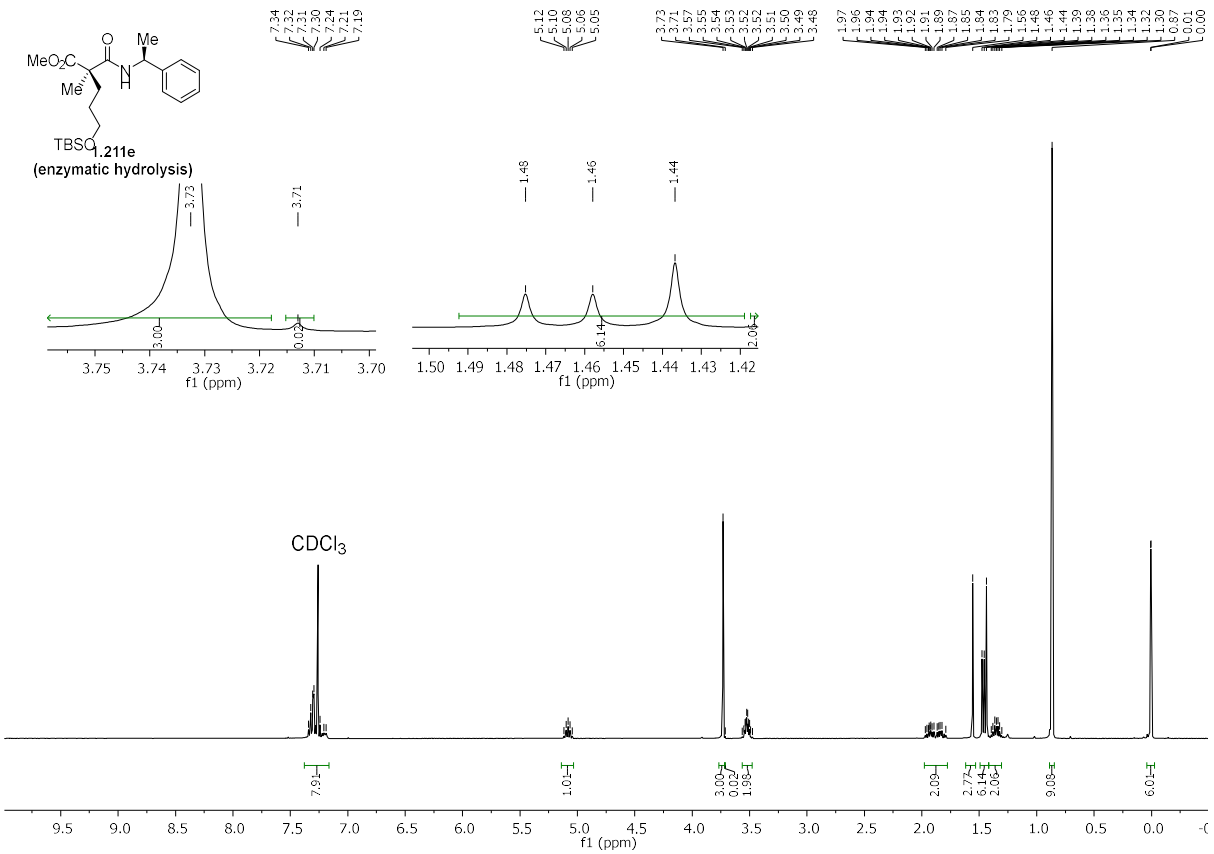
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211d**



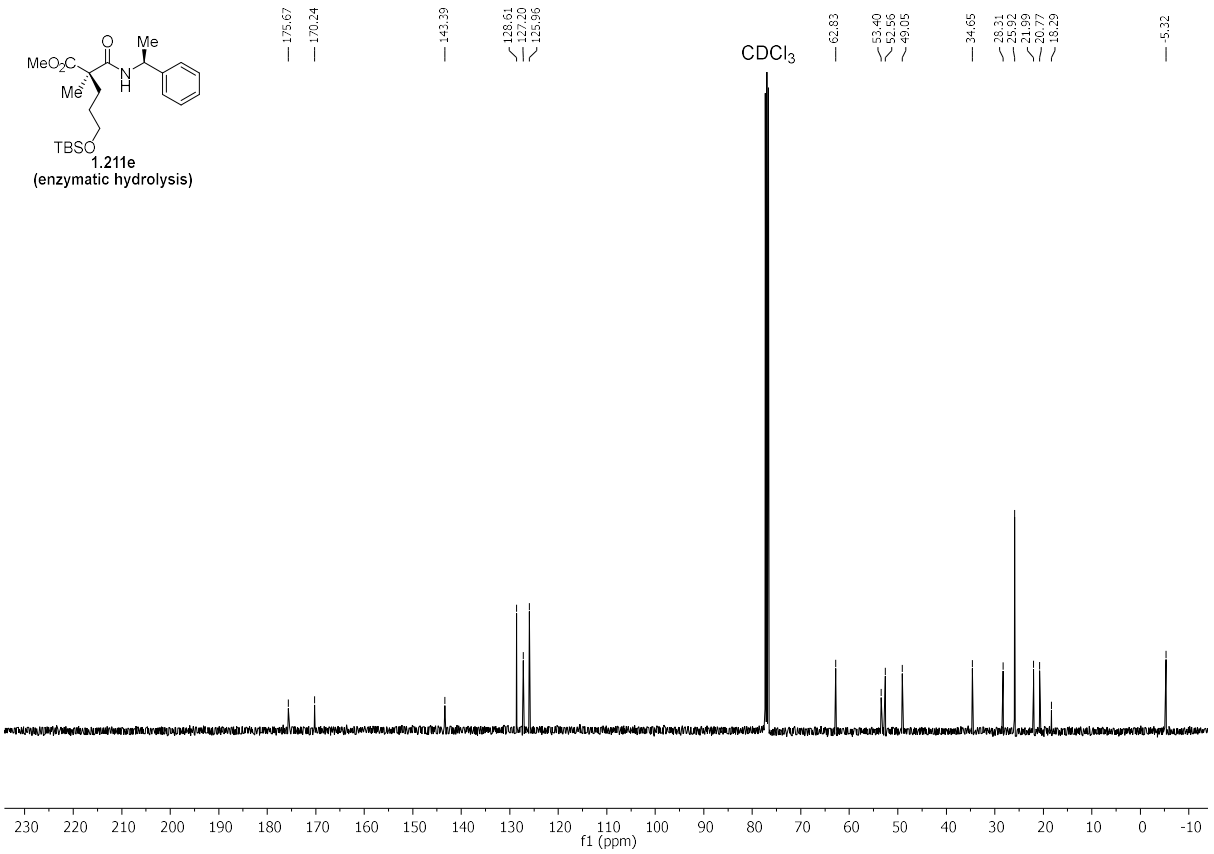
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211d**



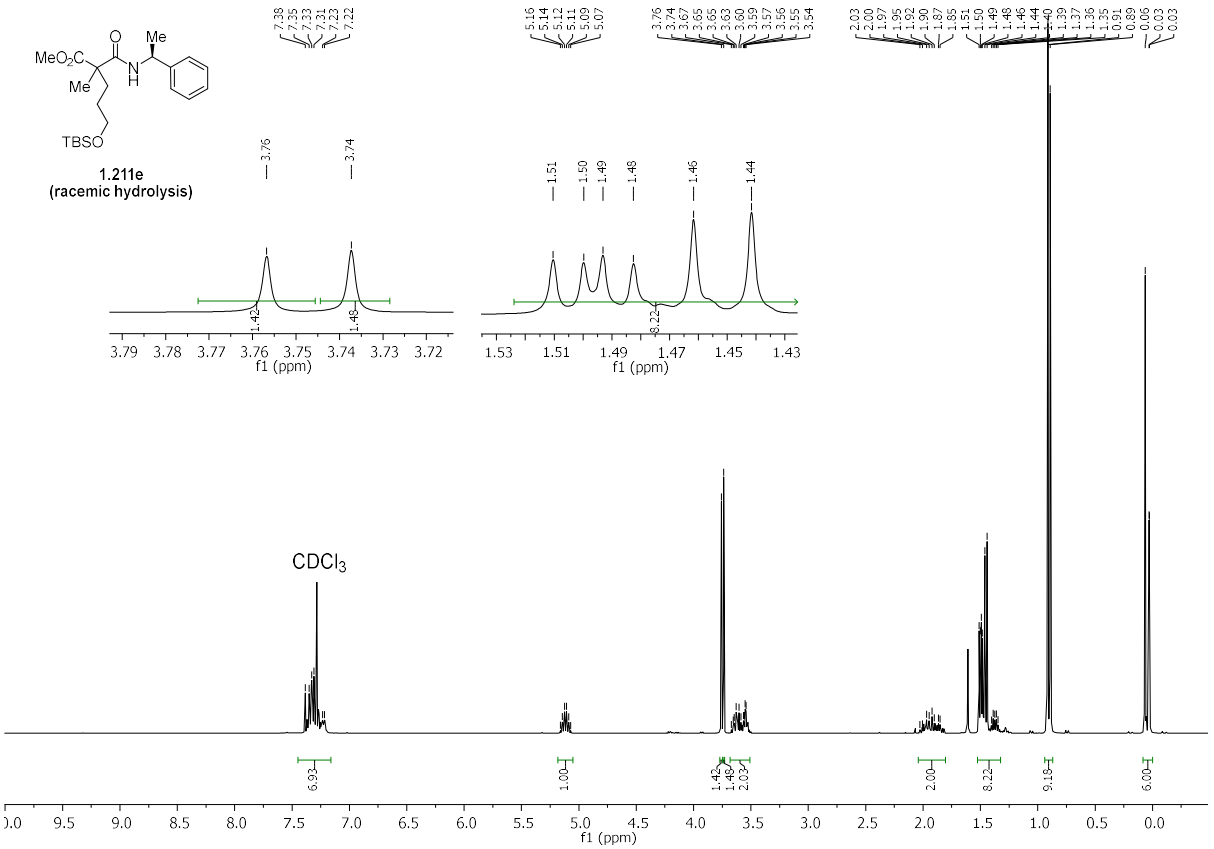
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211e**



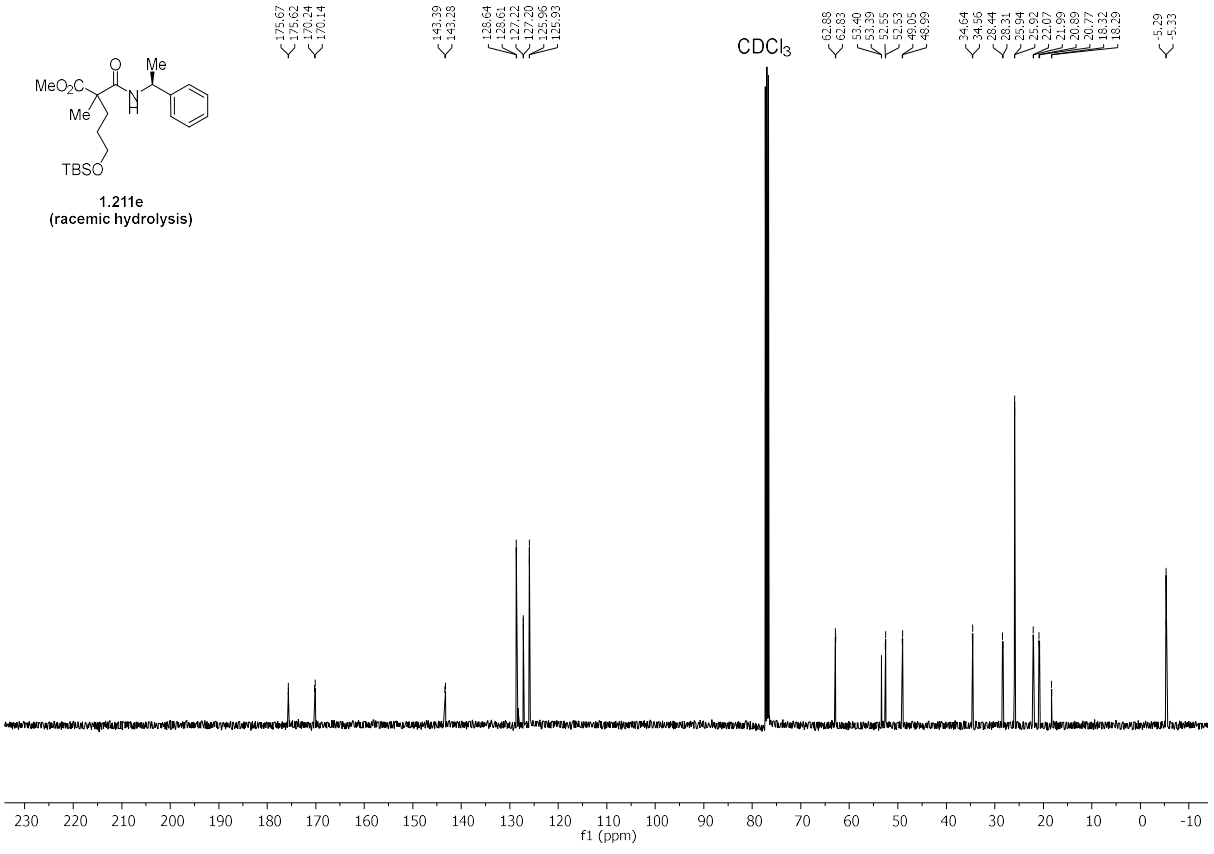
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211e**



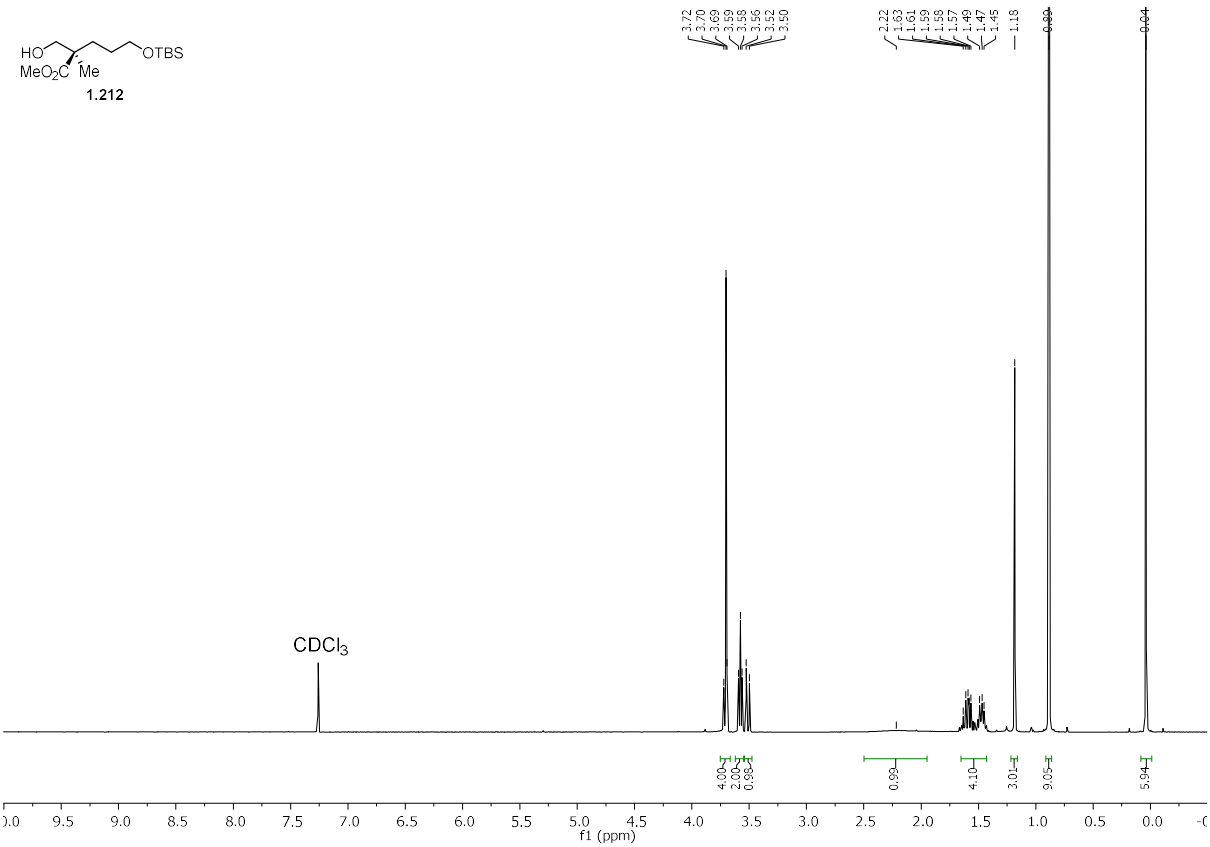
^{1}H NMR (400 MHz, $CDCl_3$) of **1.211e**



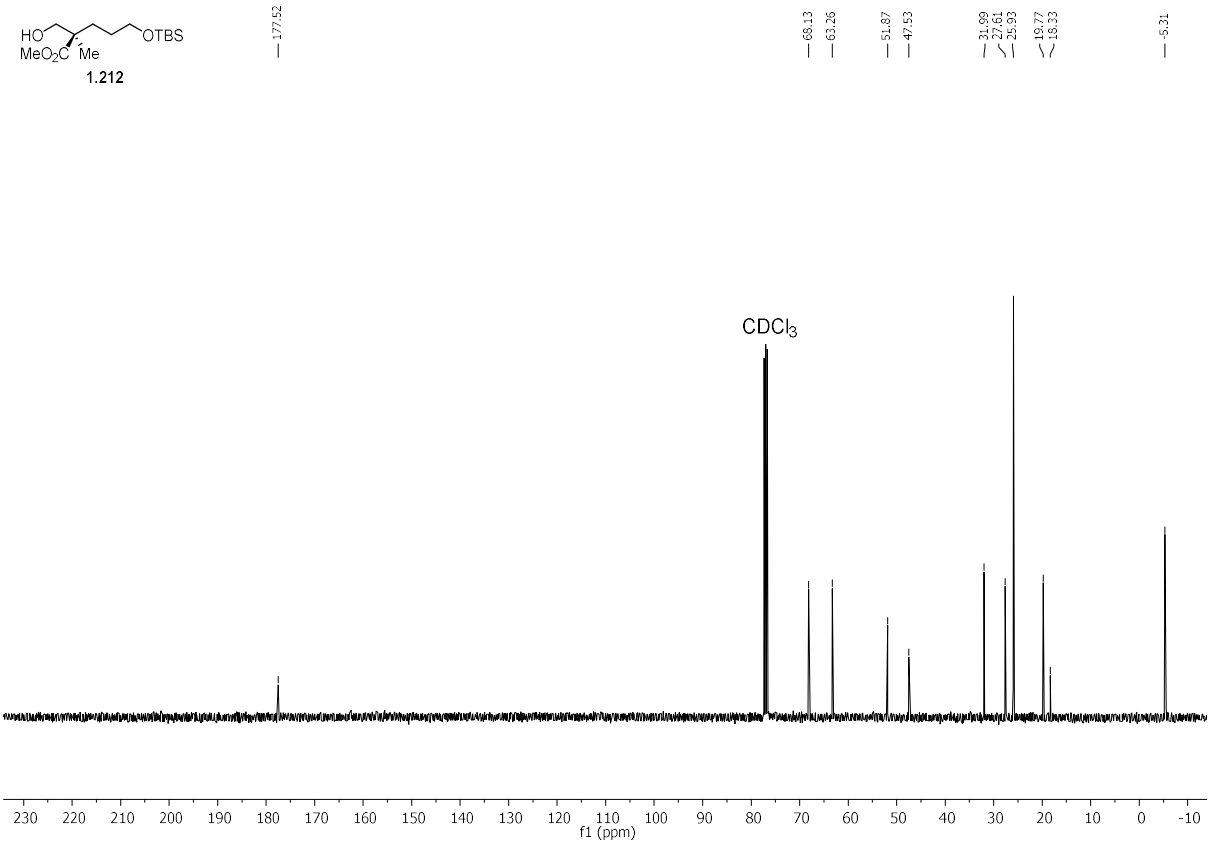
^{13}C NMR (101 MHz, $CDCl_3$) of **1.211e**



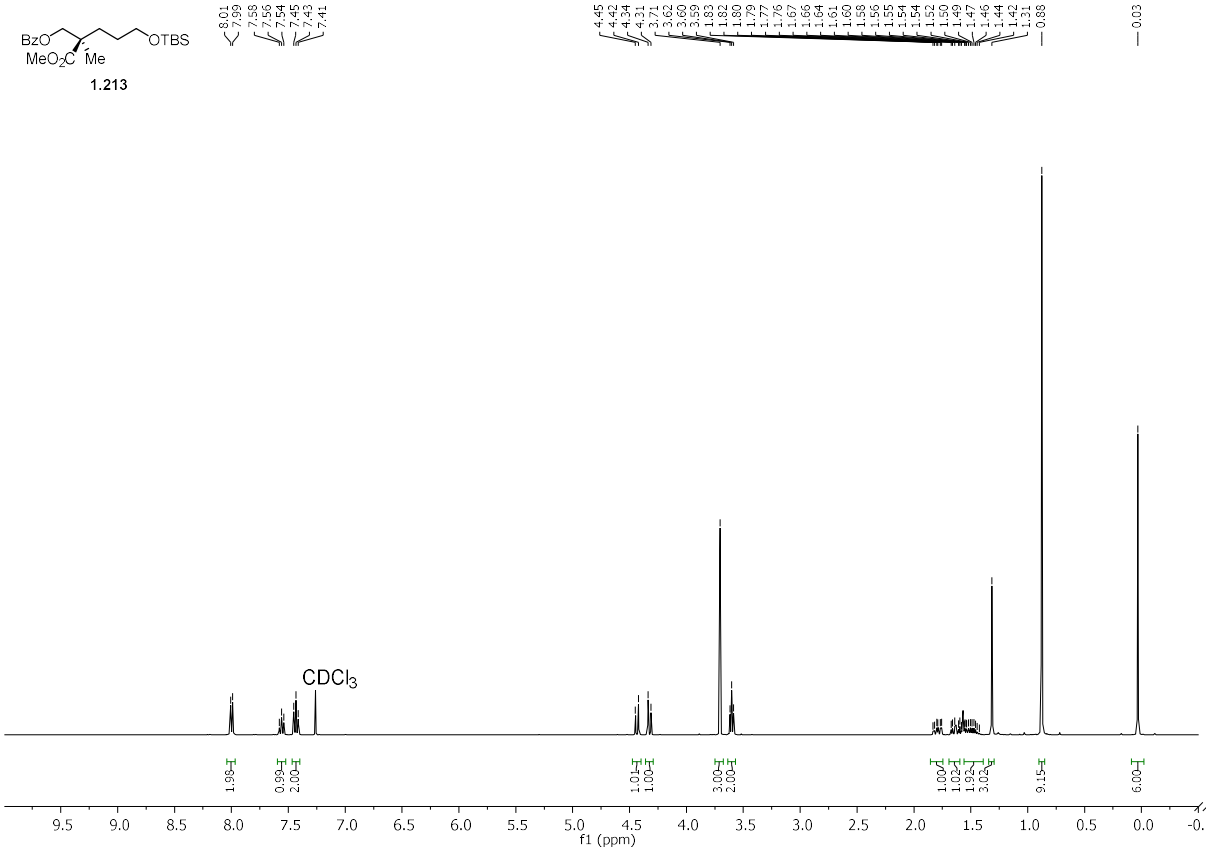
^{1}H NMR (400 MHz, $CDCl_3$) of **1.212**



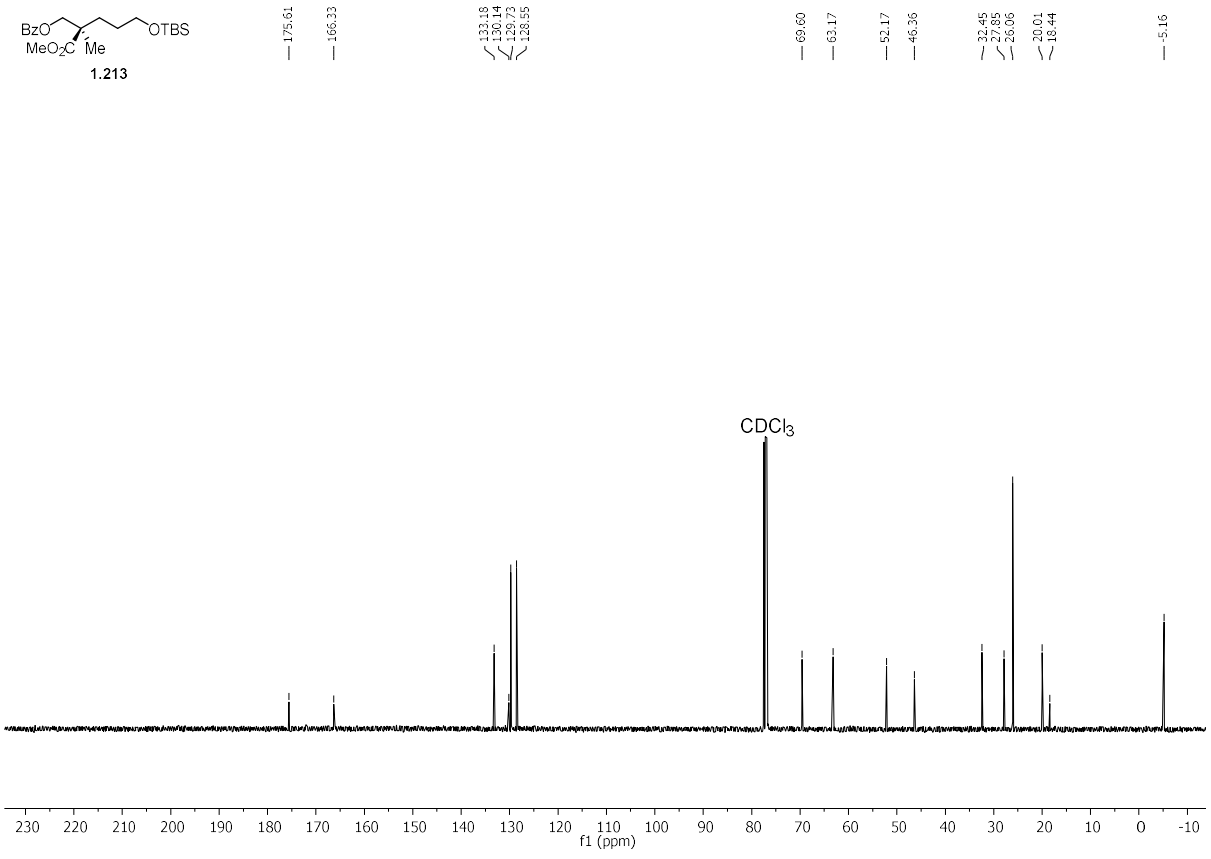
^{13}C NMR (101 MHz, $CDCl_3$) of **1.212**



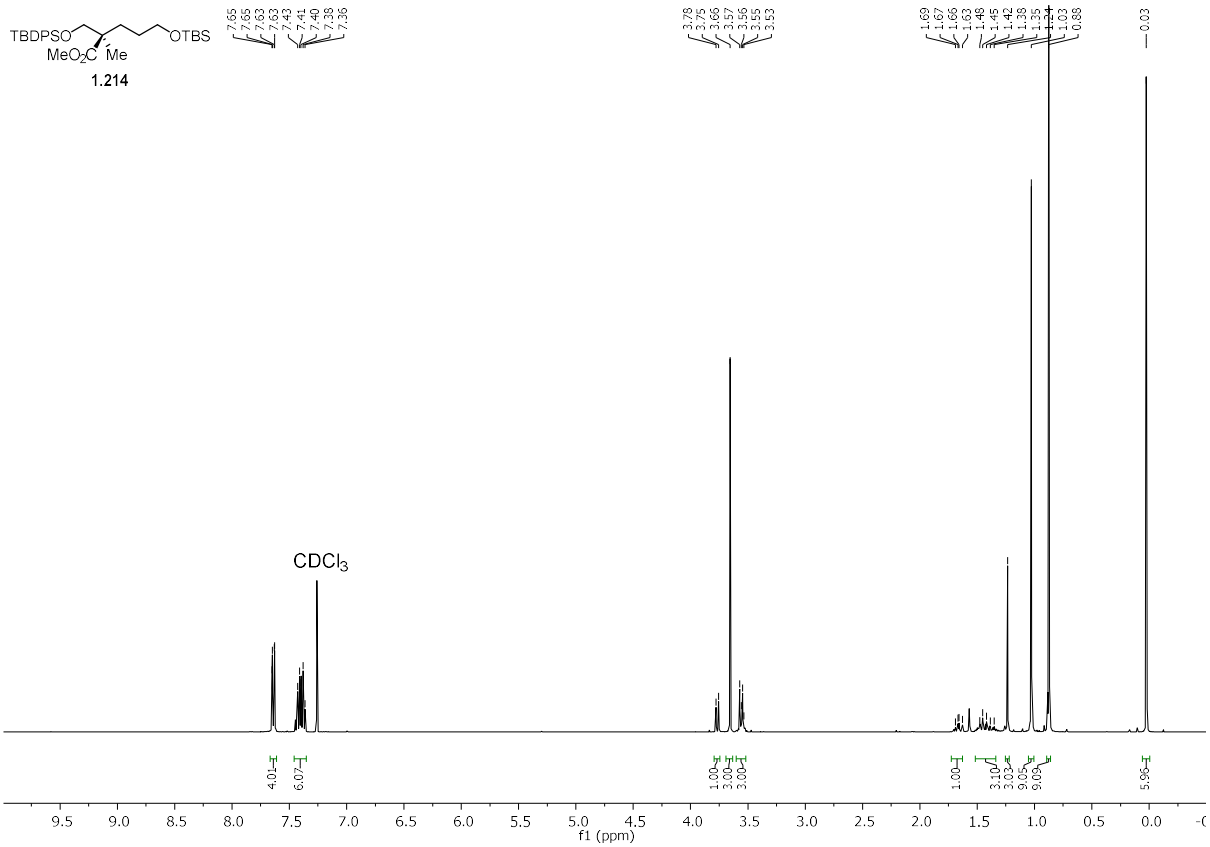
^{1}H NMR (400 MHz, $CDCl_3$) of **1.213**



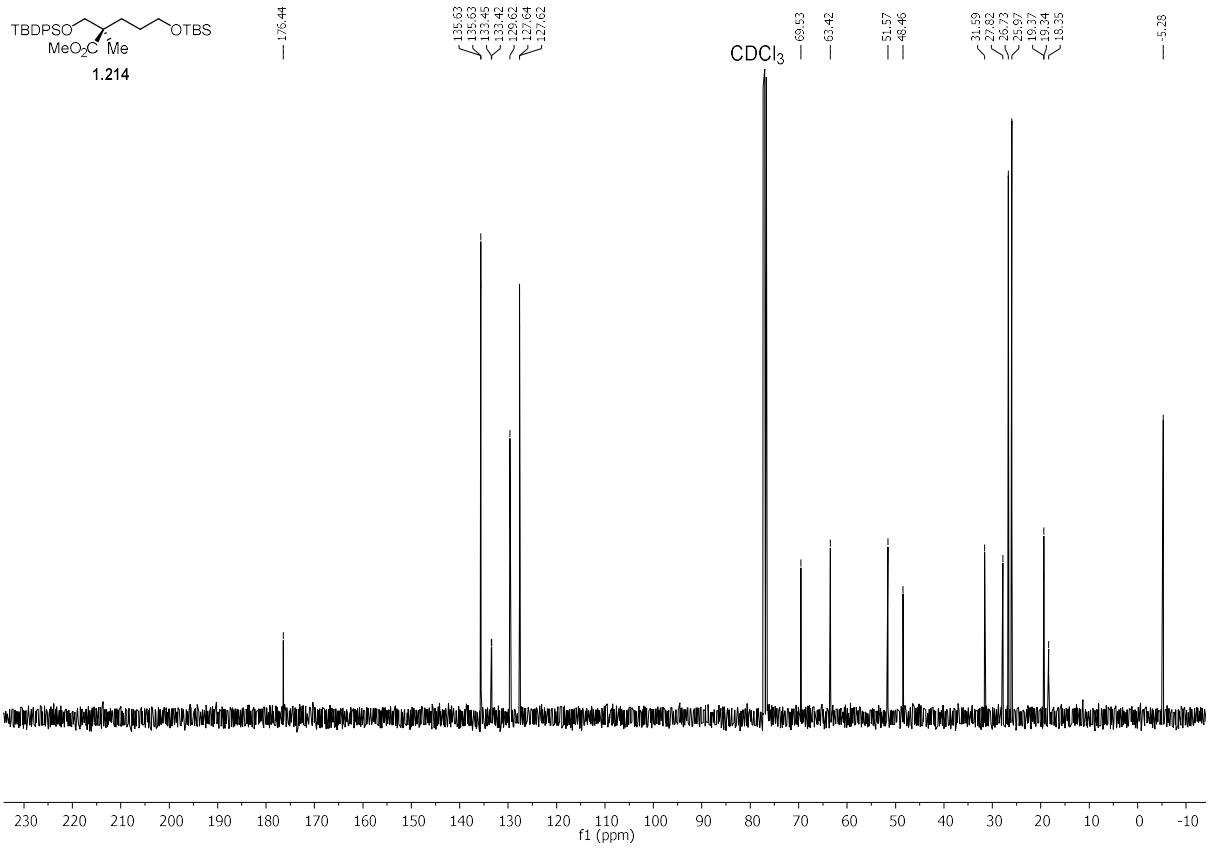
^{13}C NMR (101 MHz, $CDCl_3$) of **1.213**



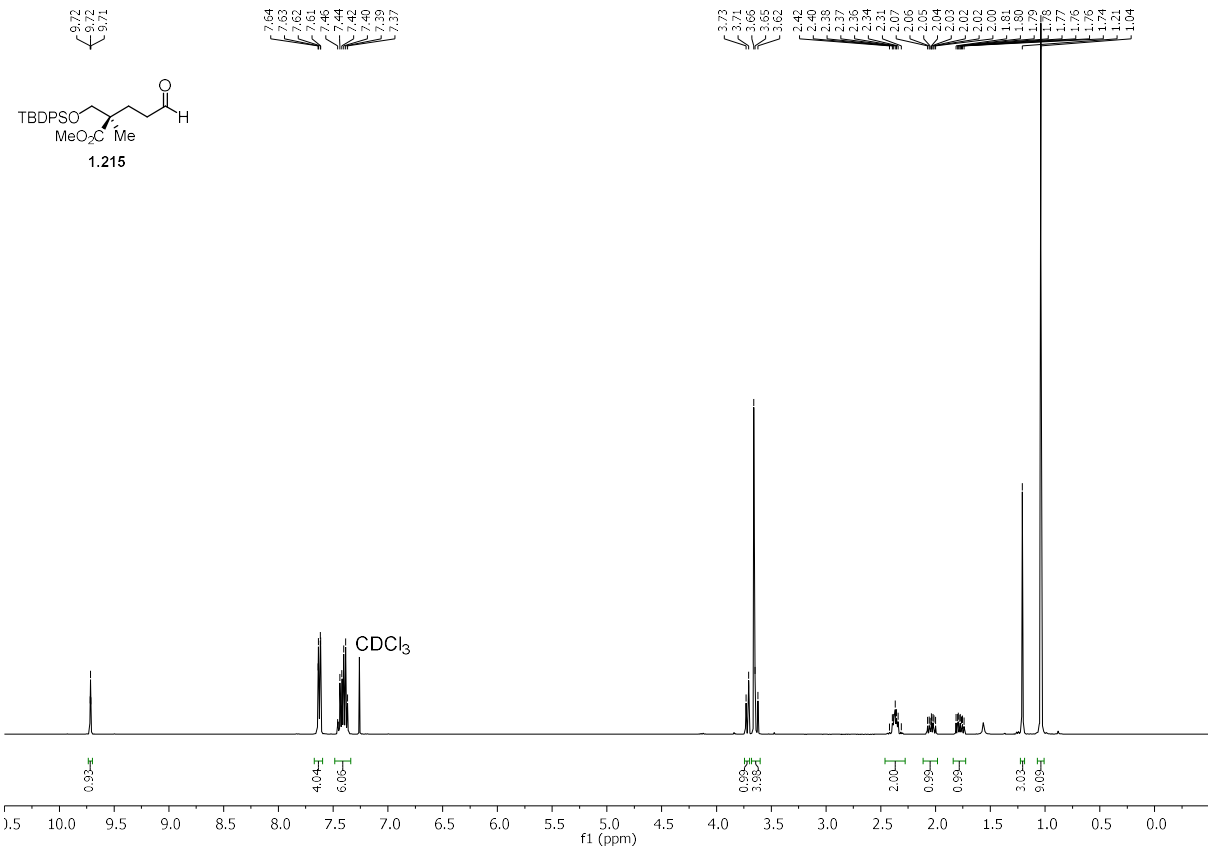
^{1}H NMR (400 MHz, $CDCl_3$) of **1.214**



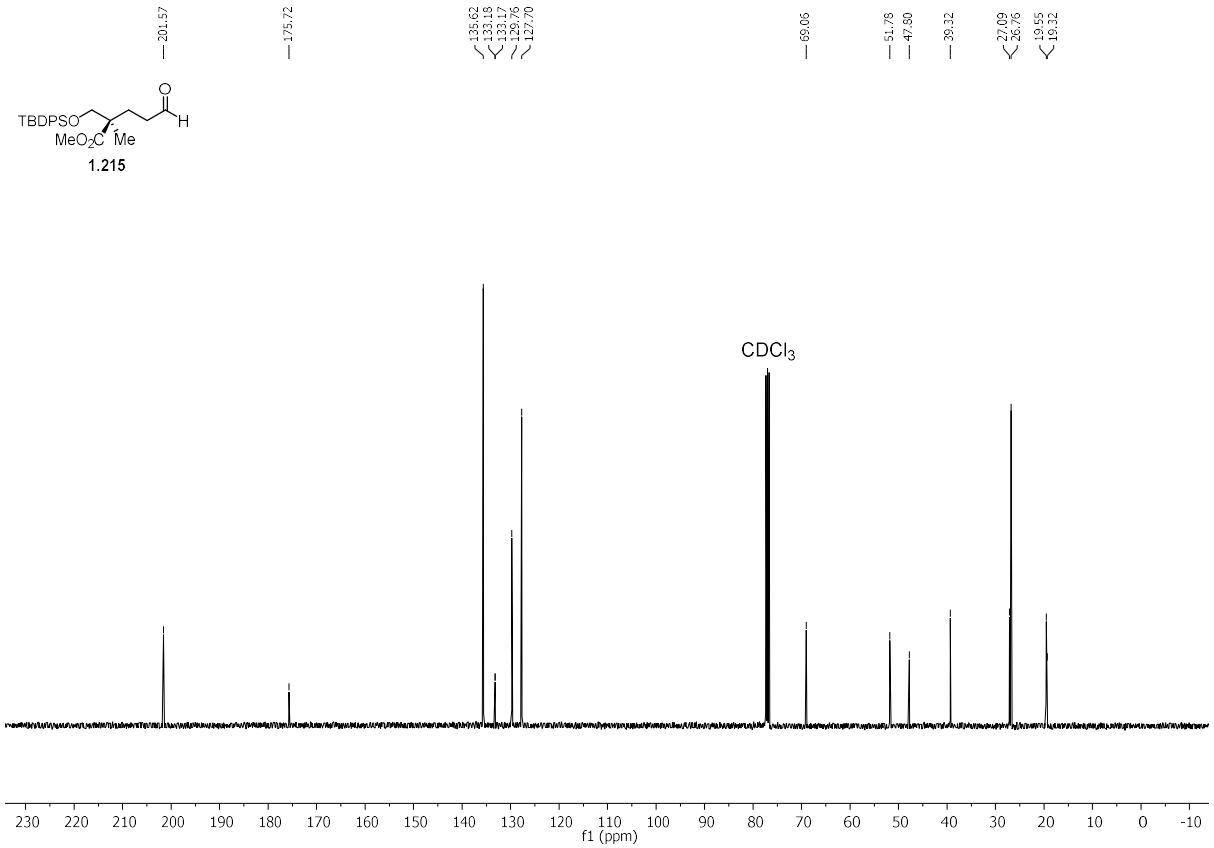
^{13}C NMR (101 MHz, $CDCl_3$) of **1.214**



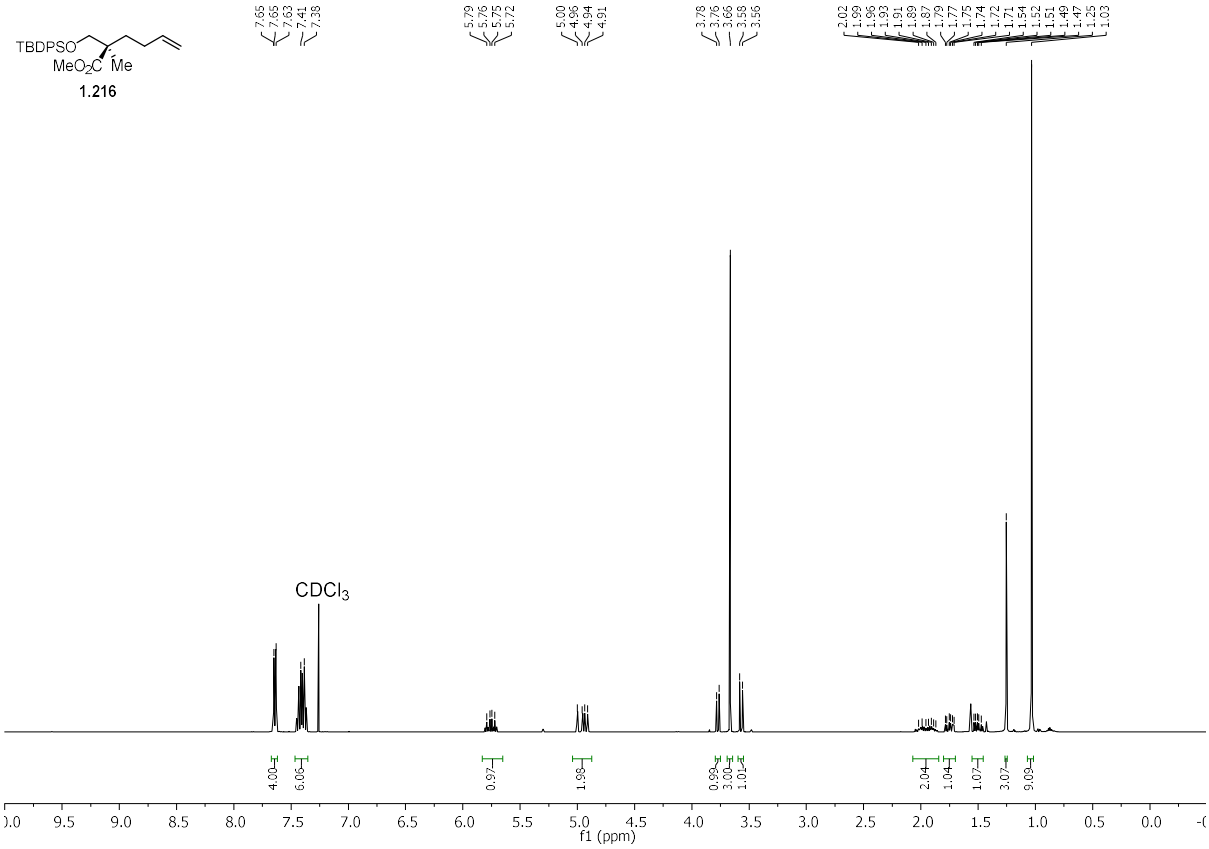
^{1}H NMR (400 MHz, $CDCl_3$) of **1.215**



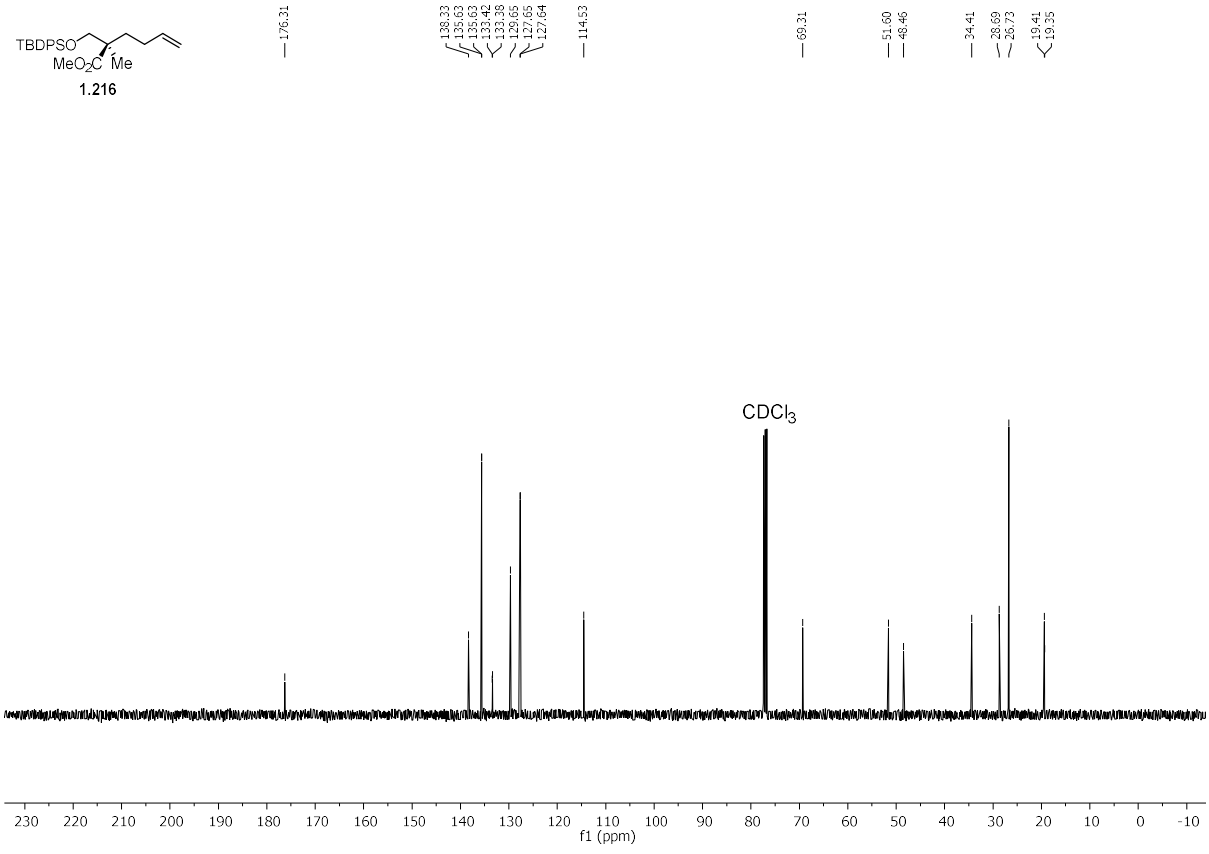
^{13}C NMR (101 MHz, $CDCl_3$) of **1.215**



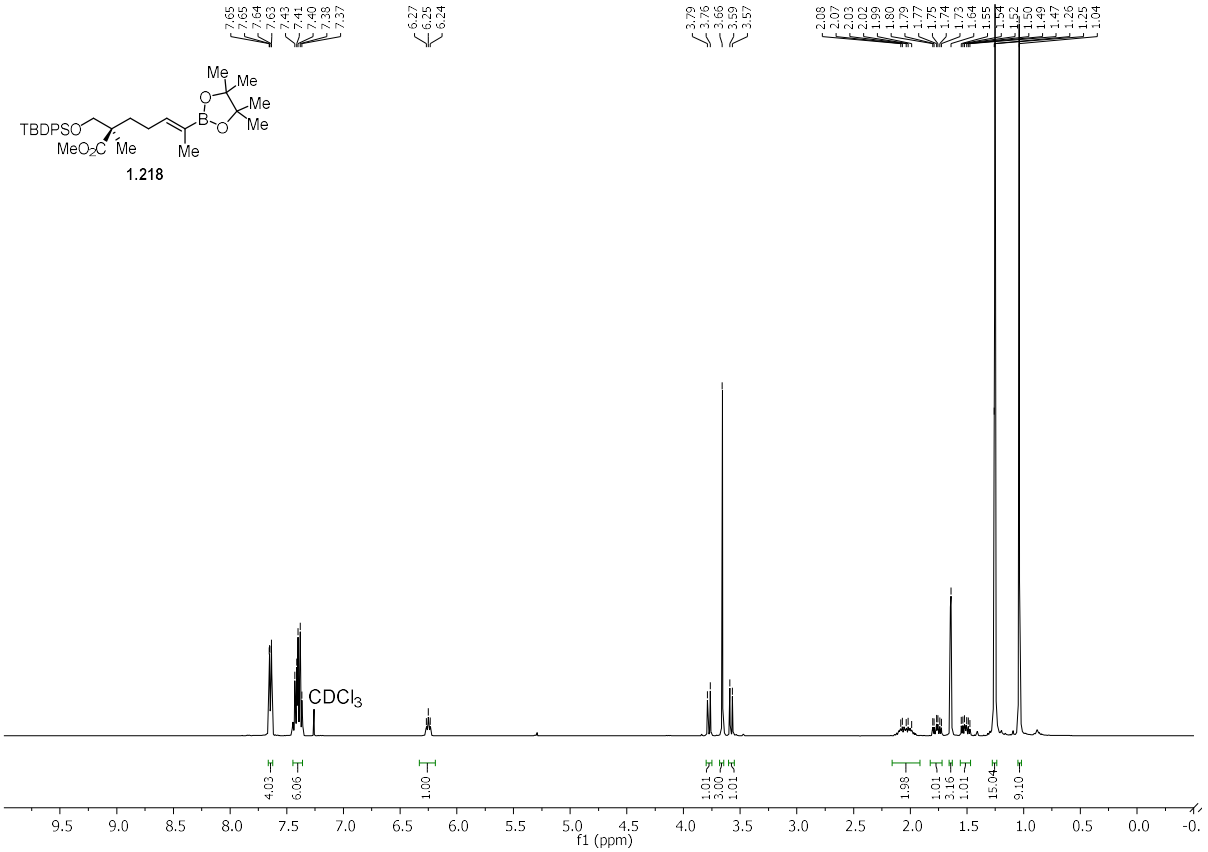
^{1}H NMR (400 MHz, $CDCl_3$) of **1.216**



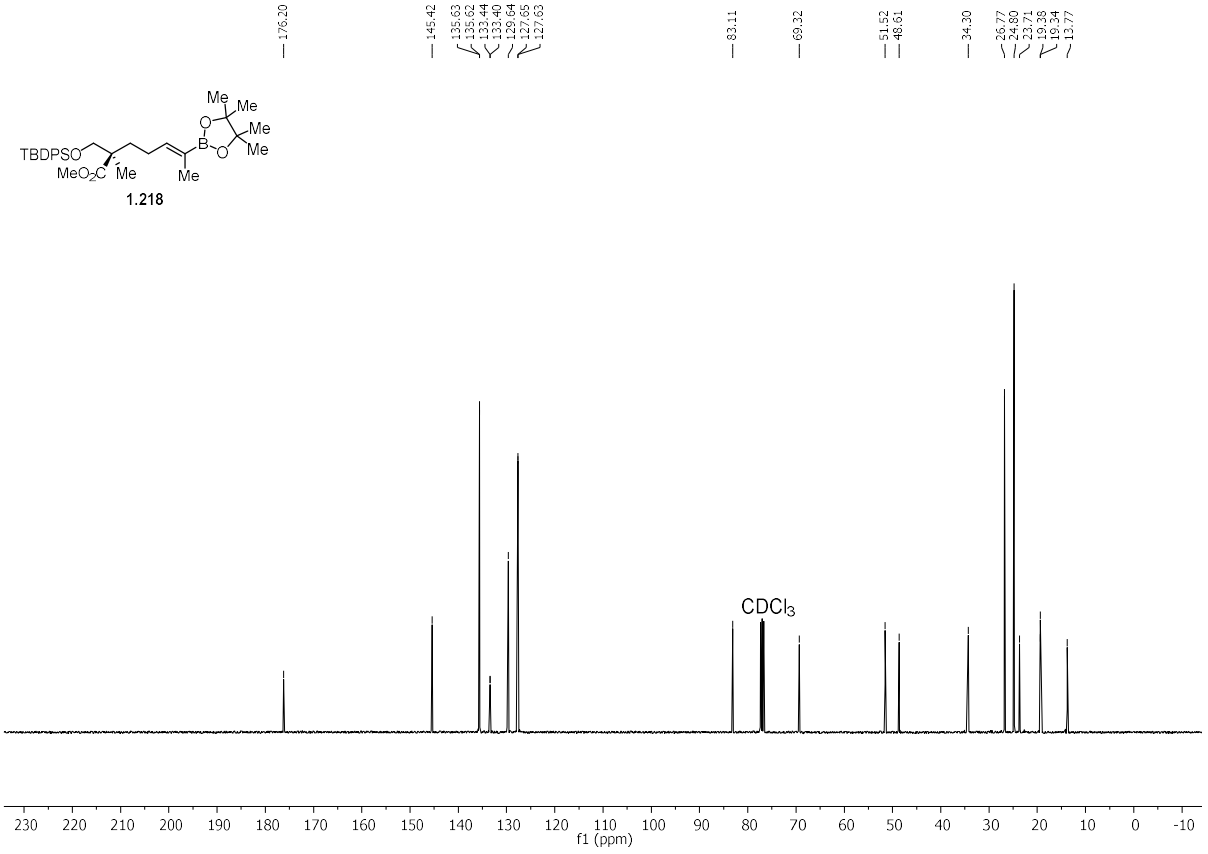
^{13}C NMR (101 MHz, $CDCl_3$) of **1.216**



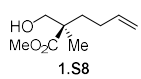
^{1}H NMR (400 MHz, $CDCl_3$) of **1.218**



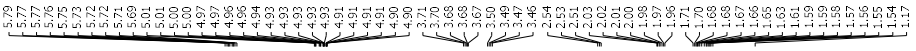
^{13}C NMR (101 MHz, $CDCl_3$) of **1.218**

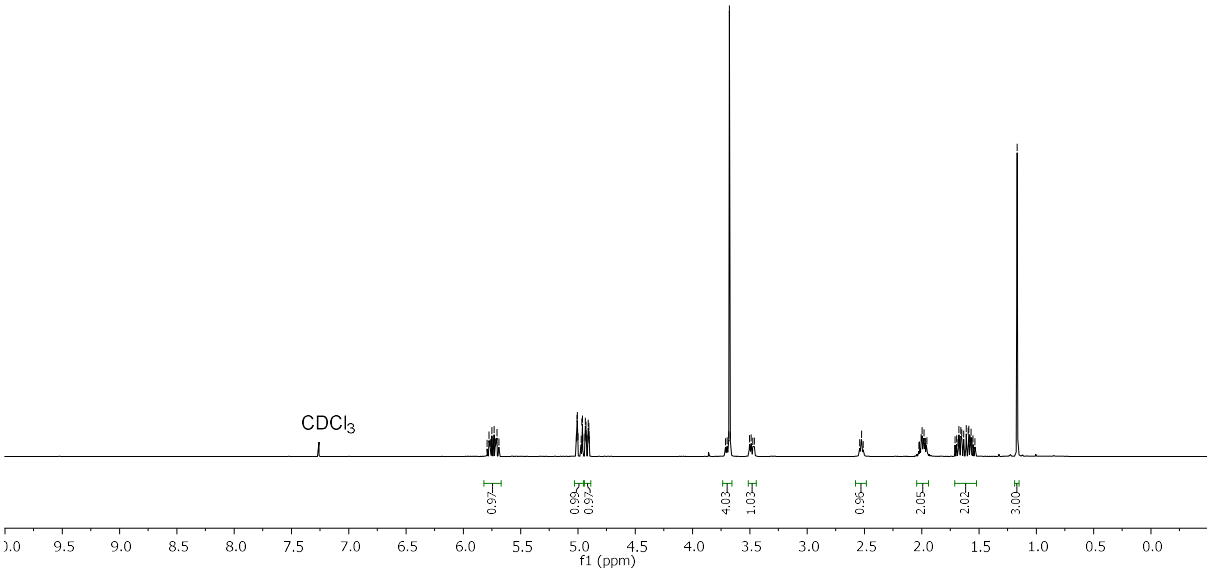


^{1}H NMR (400 MHz, $CDCl_3$) of **1.S8**

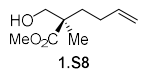


1.S8

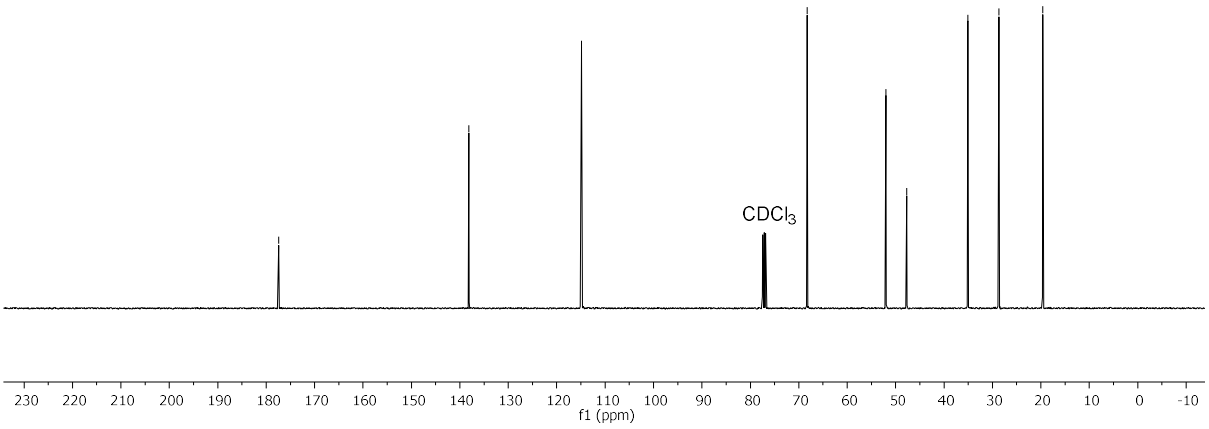




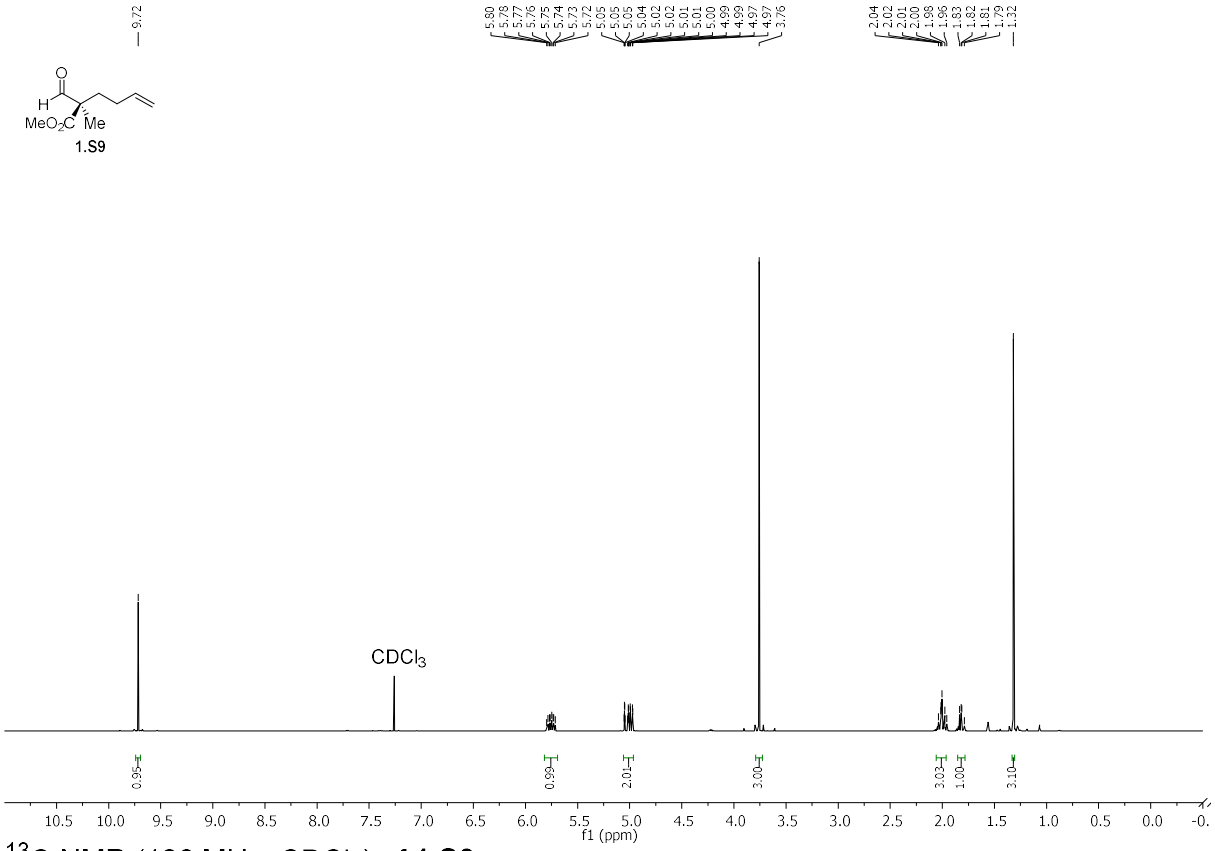
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S8**



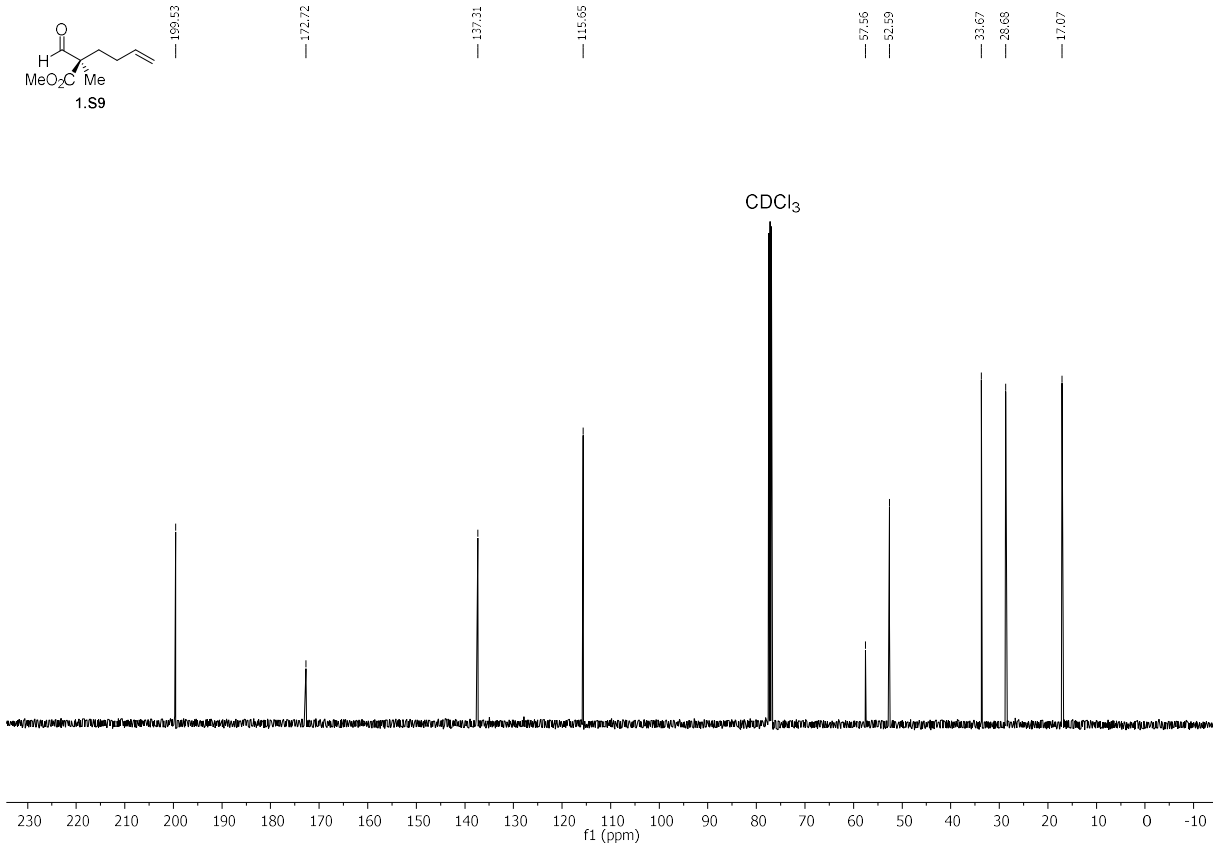
1.S8



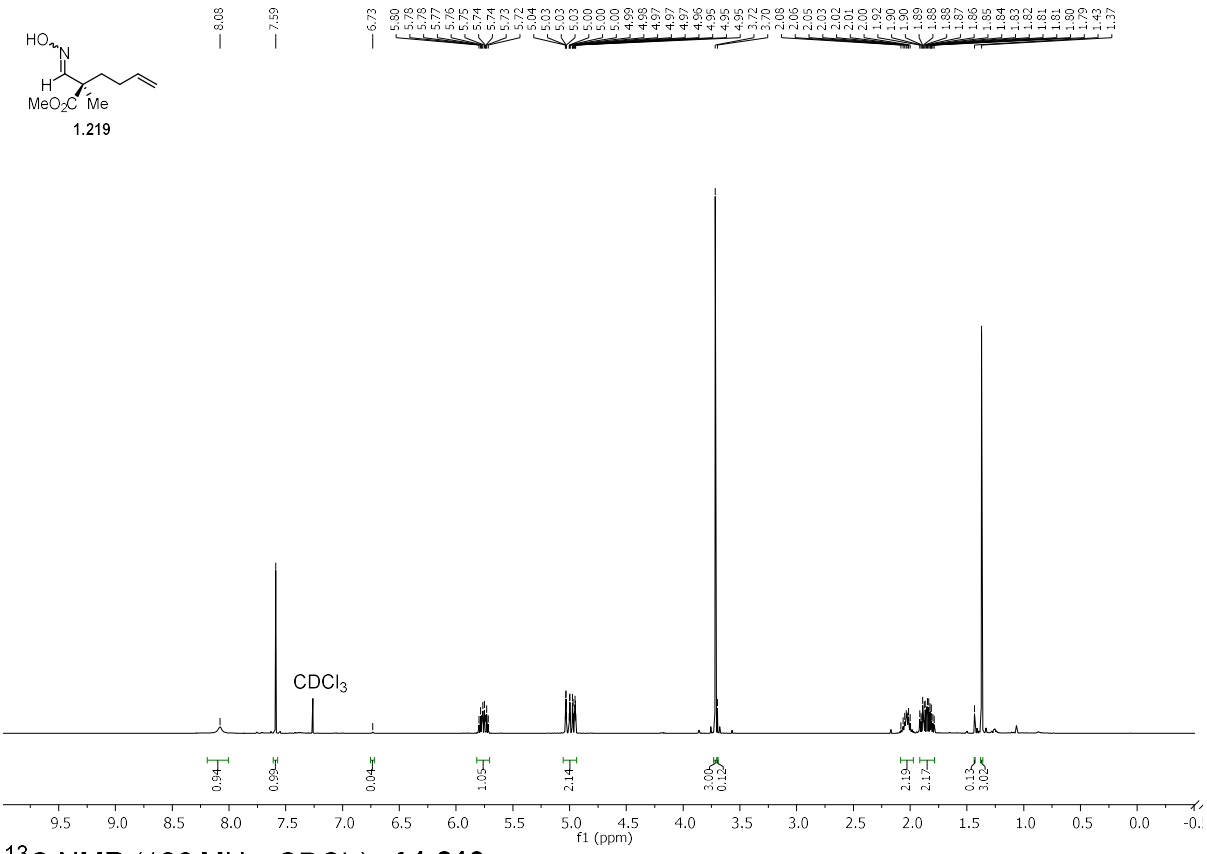
^{1}H NMR (500 MHz, $CDCl_3$) of **1.S9**



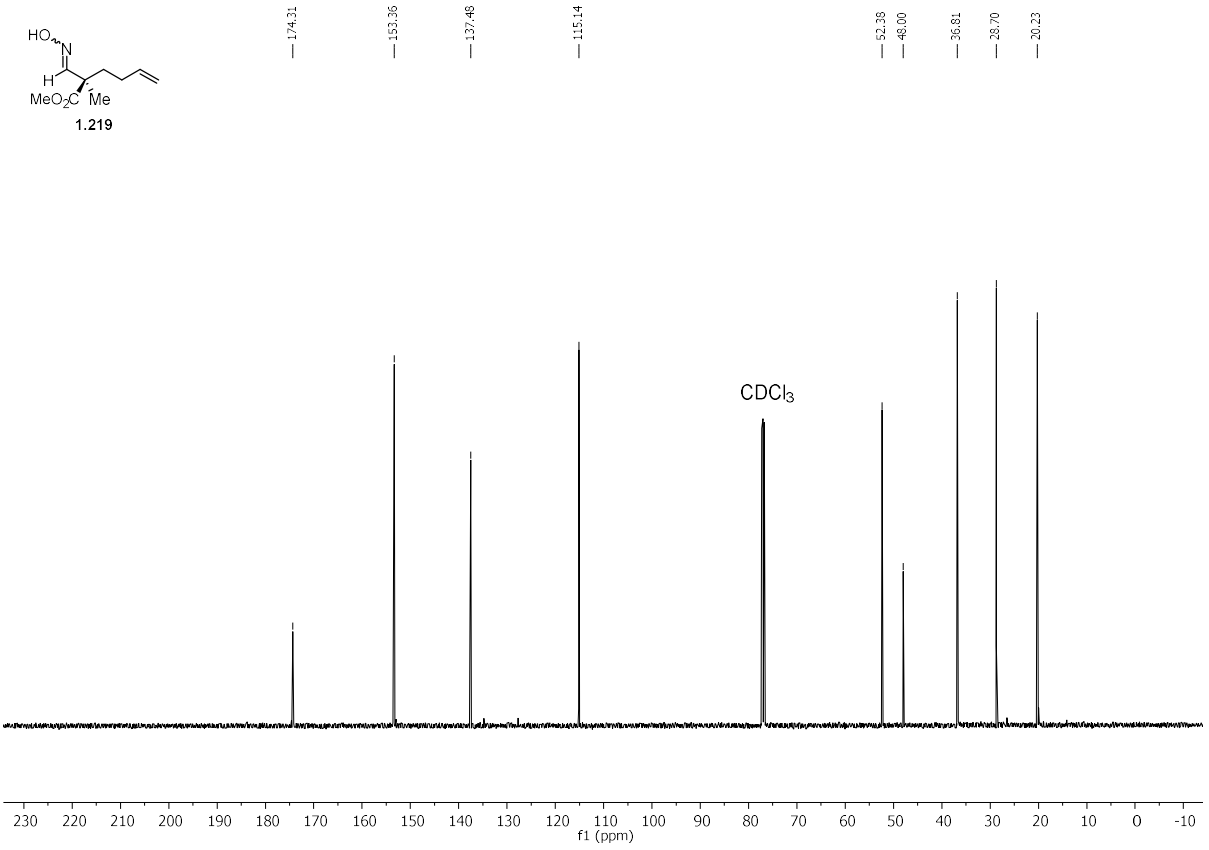
^{13}C NMR (126 MHz, $CDCl_3$) of **1.S9**



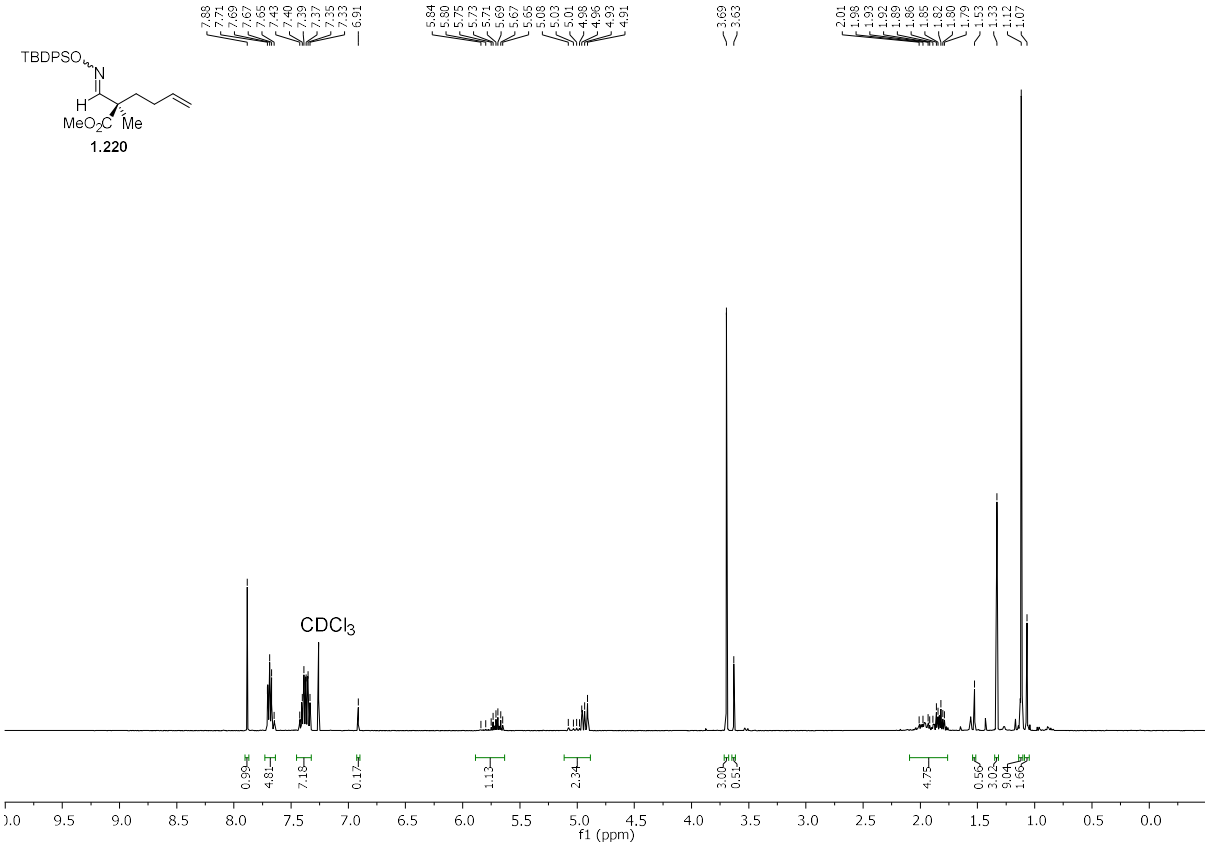
^{1}H NMR (500 MHz, $CDCl_3$) of **1.219**



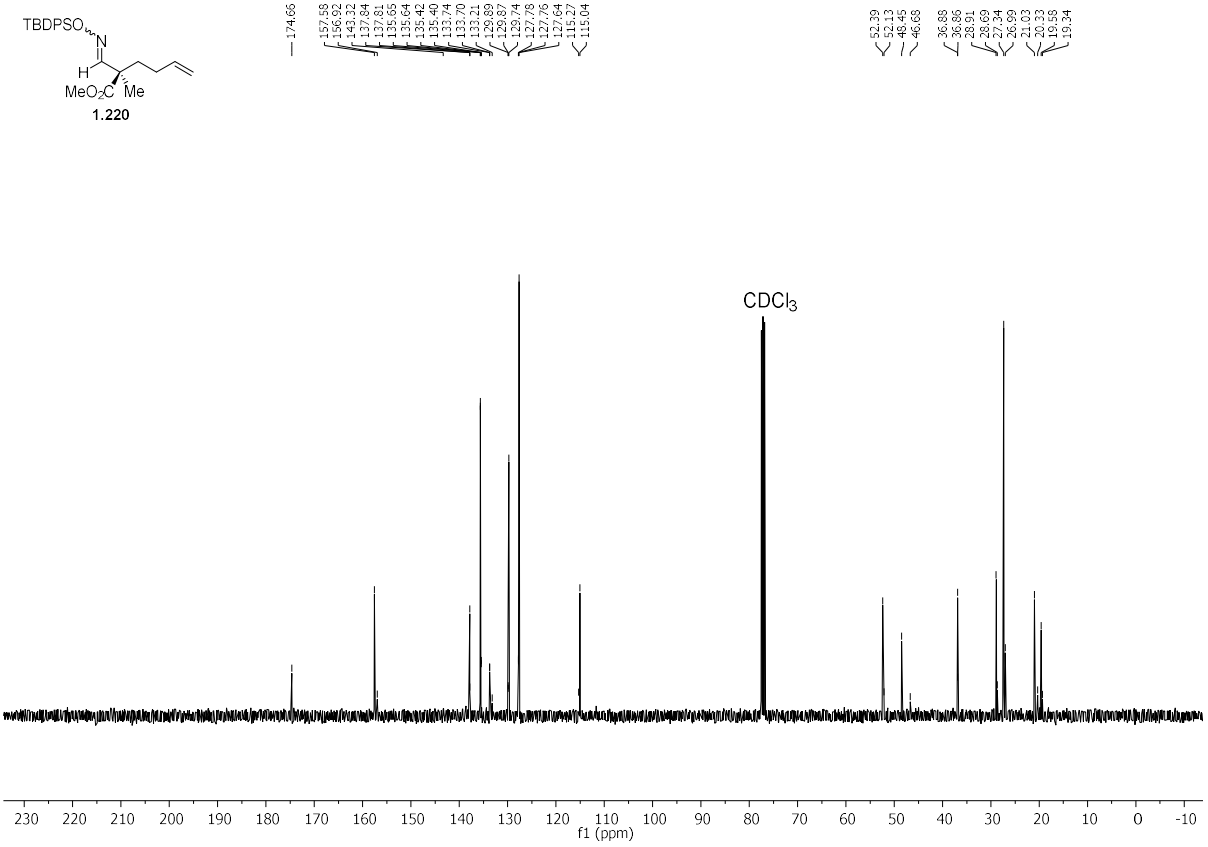
^{13}C NMR (126 MHz, $CDCl_3$) of **1.219**



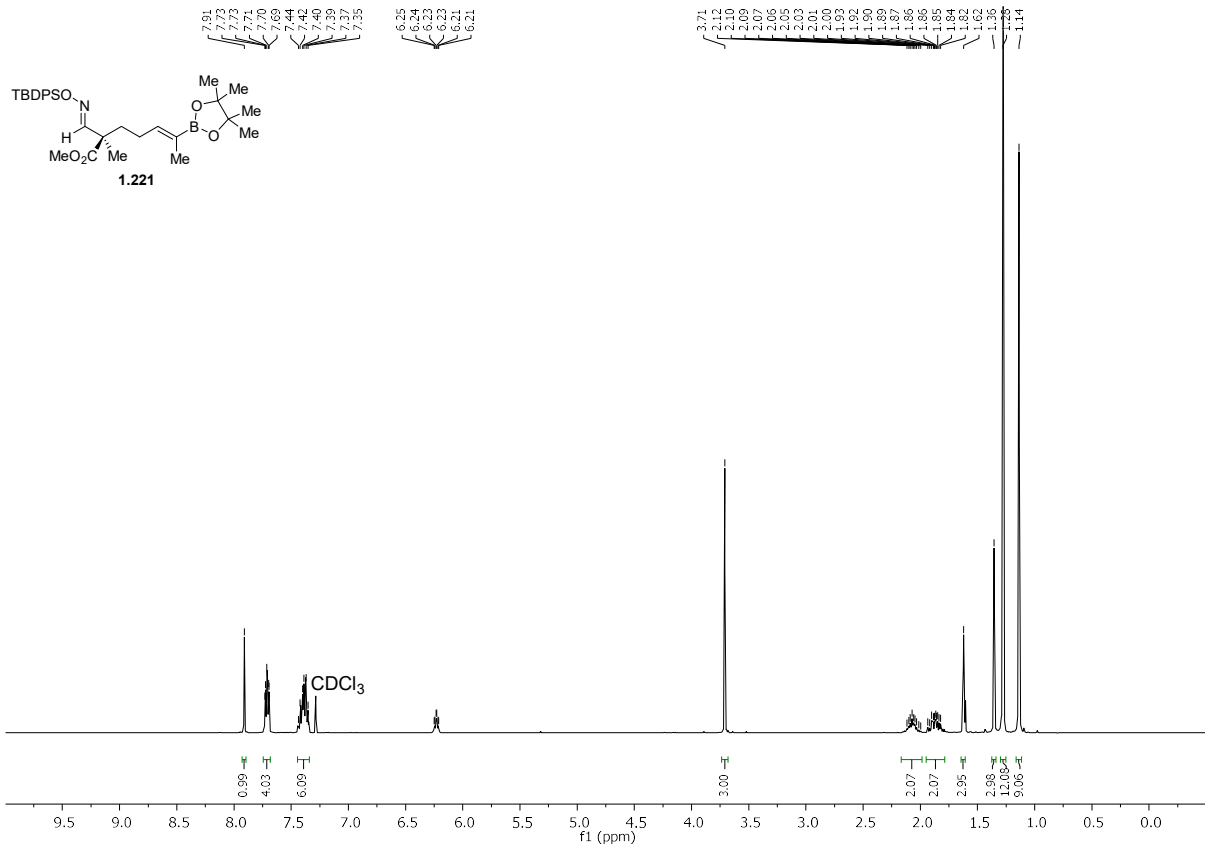
^{1}H NMR (500 MHz, $CDCl_3$) of **1.220**



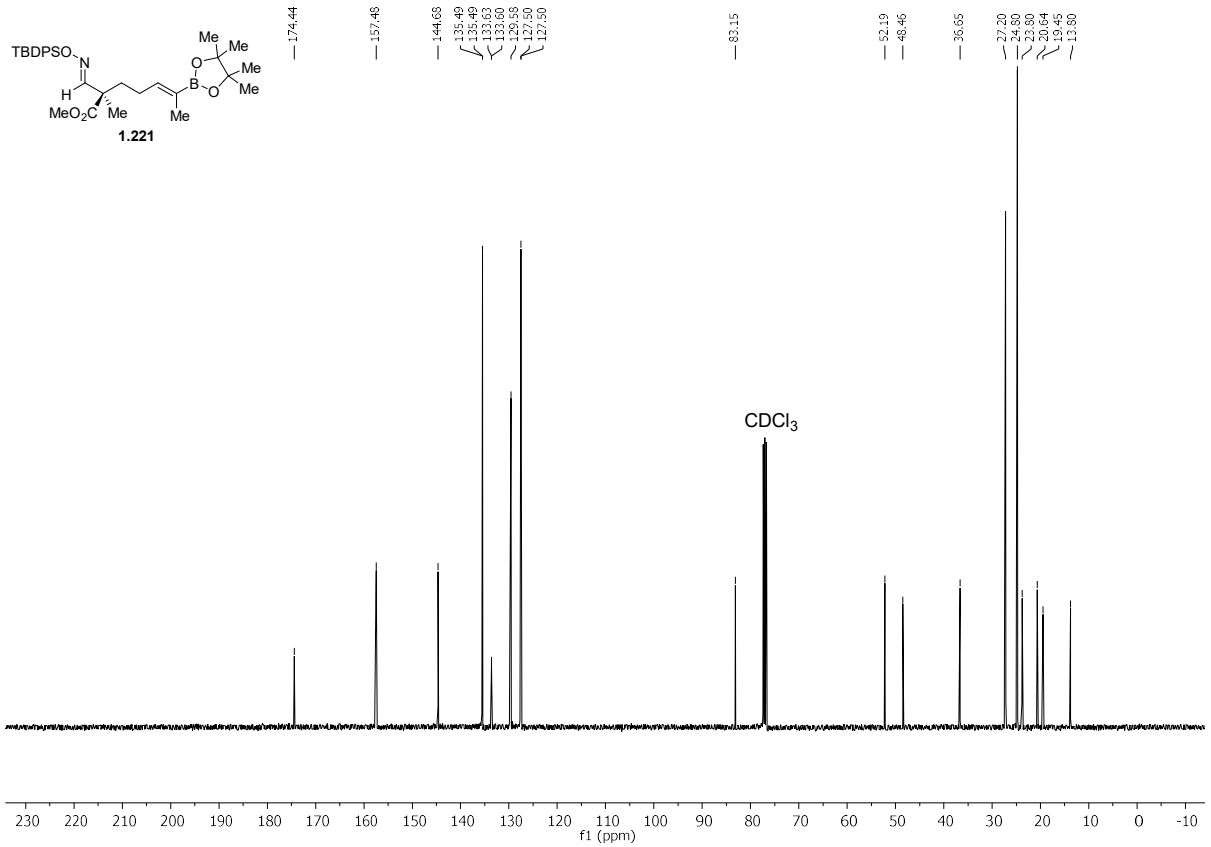
^{13}C NMR (126 MHz, $CDCl_3$) of **1.220**



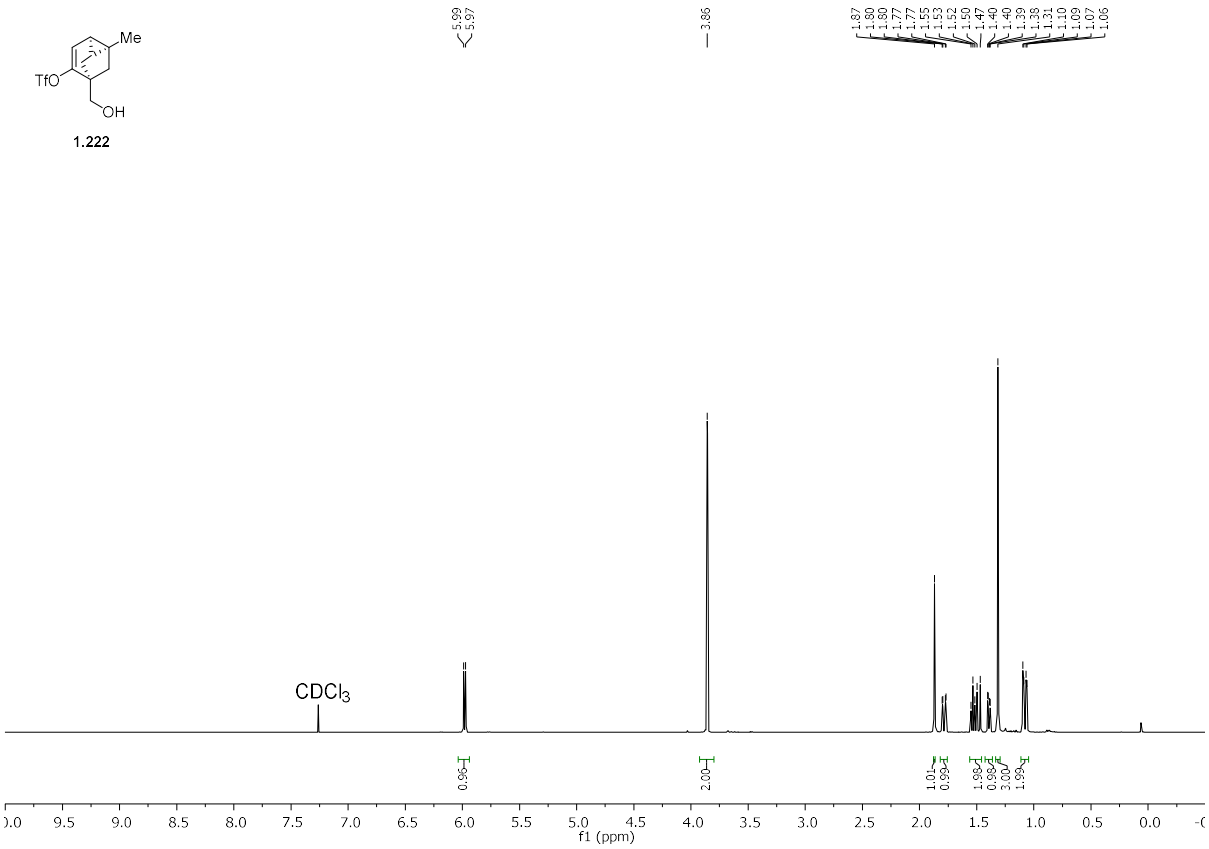
^{1}H NMR (400 MHz, $CDCl_3$) of **1.221**



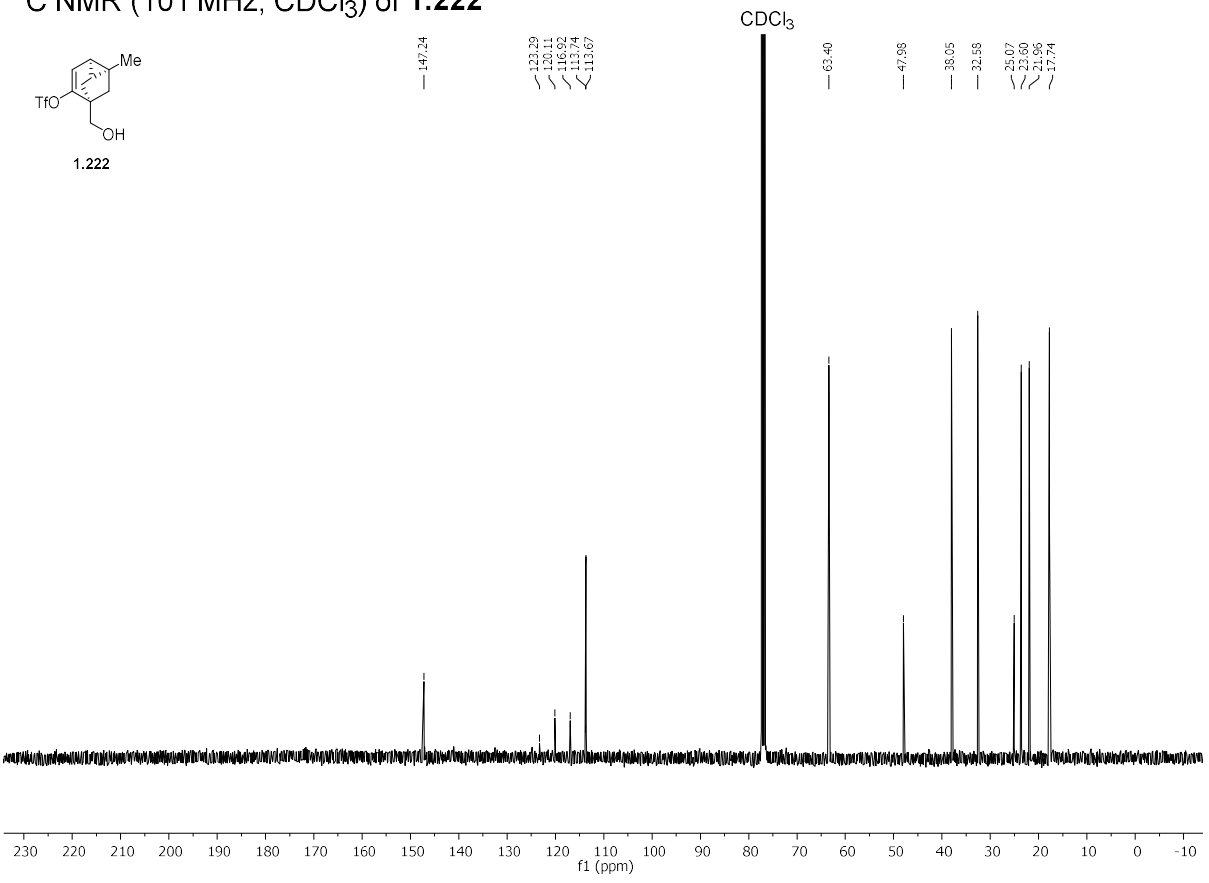
^{13}C NMR (101 MHz, $CDCl_3$) of **1.221**



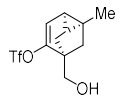
^{1}H NMR (400 MHz, $CDCl_3$) of **1.222**



^{13}C NMR (101 MHz, $CDCl_3$) of **1.222**

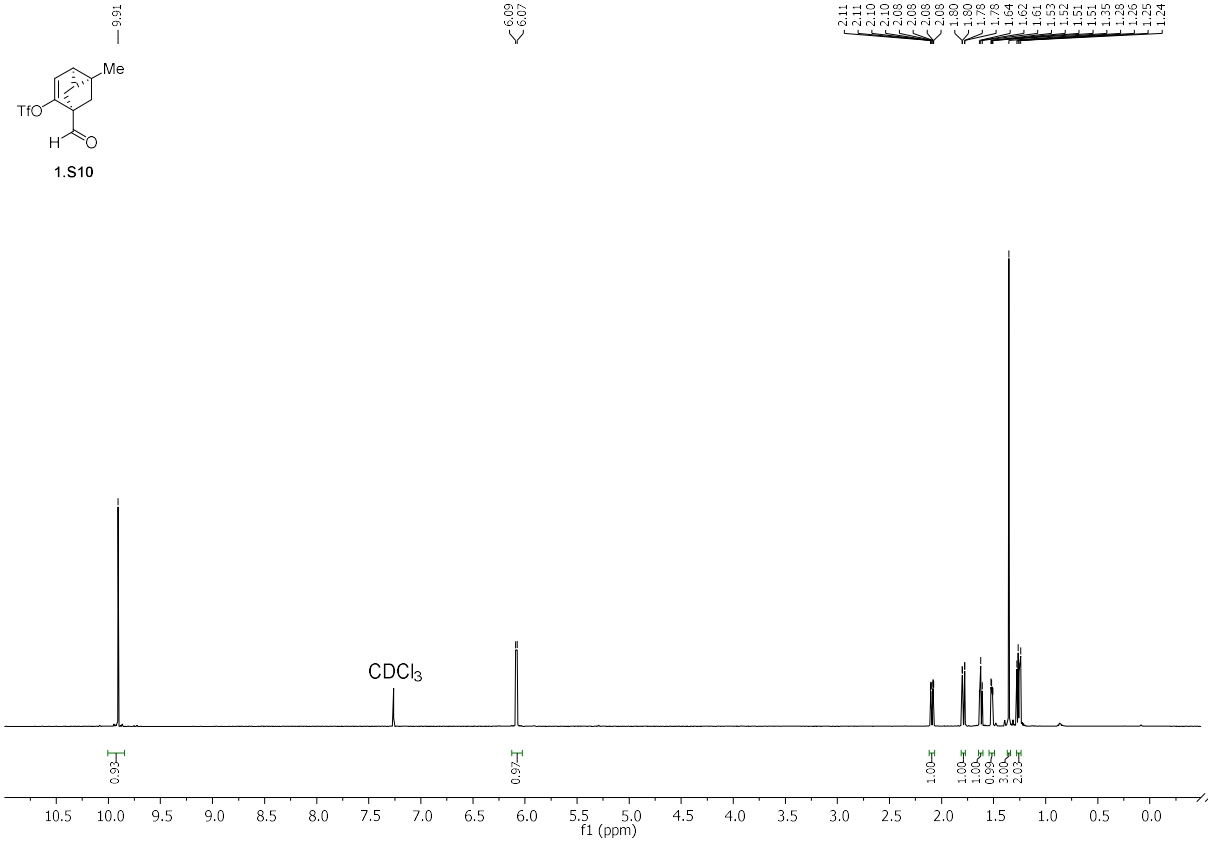


^{19}F NMR (376 MHz, $CDCl_3$) of **1.222**

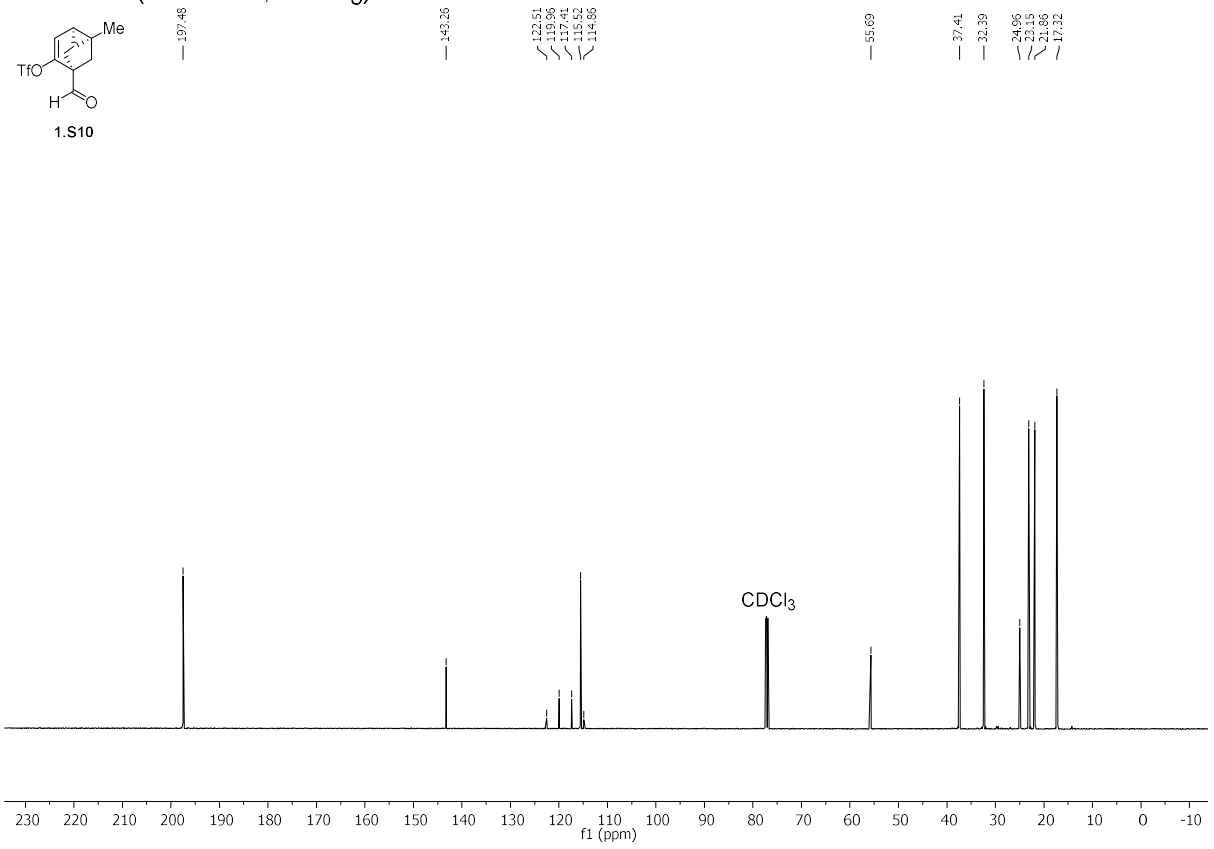


1.222

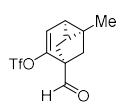
^{1}H NMR (500 MHz, $CDCl_3$) of **1.S10**



^{13}C NMR (126 MHz, $CDCl_3$) of **1.S10**

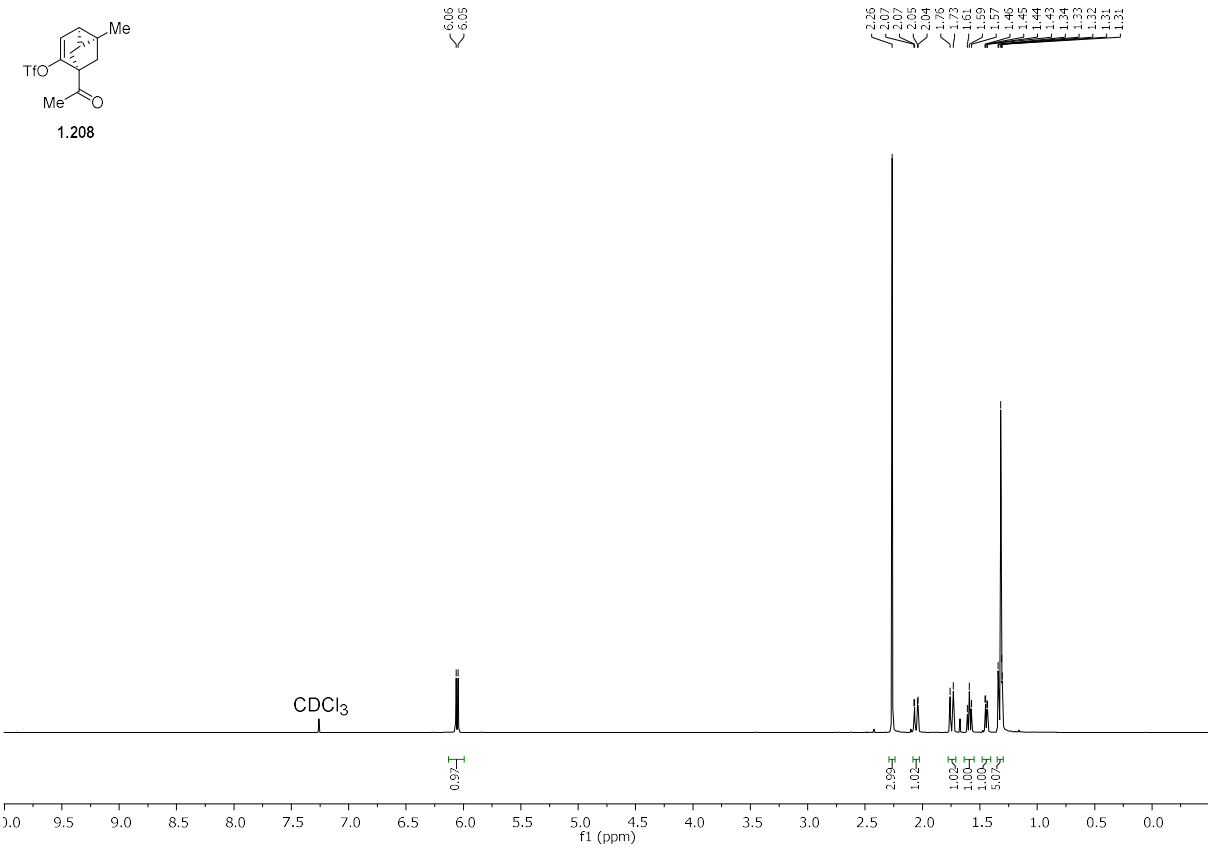


^{19}F NMR (471 MHz, $CDCl_3$) of **1.S10**

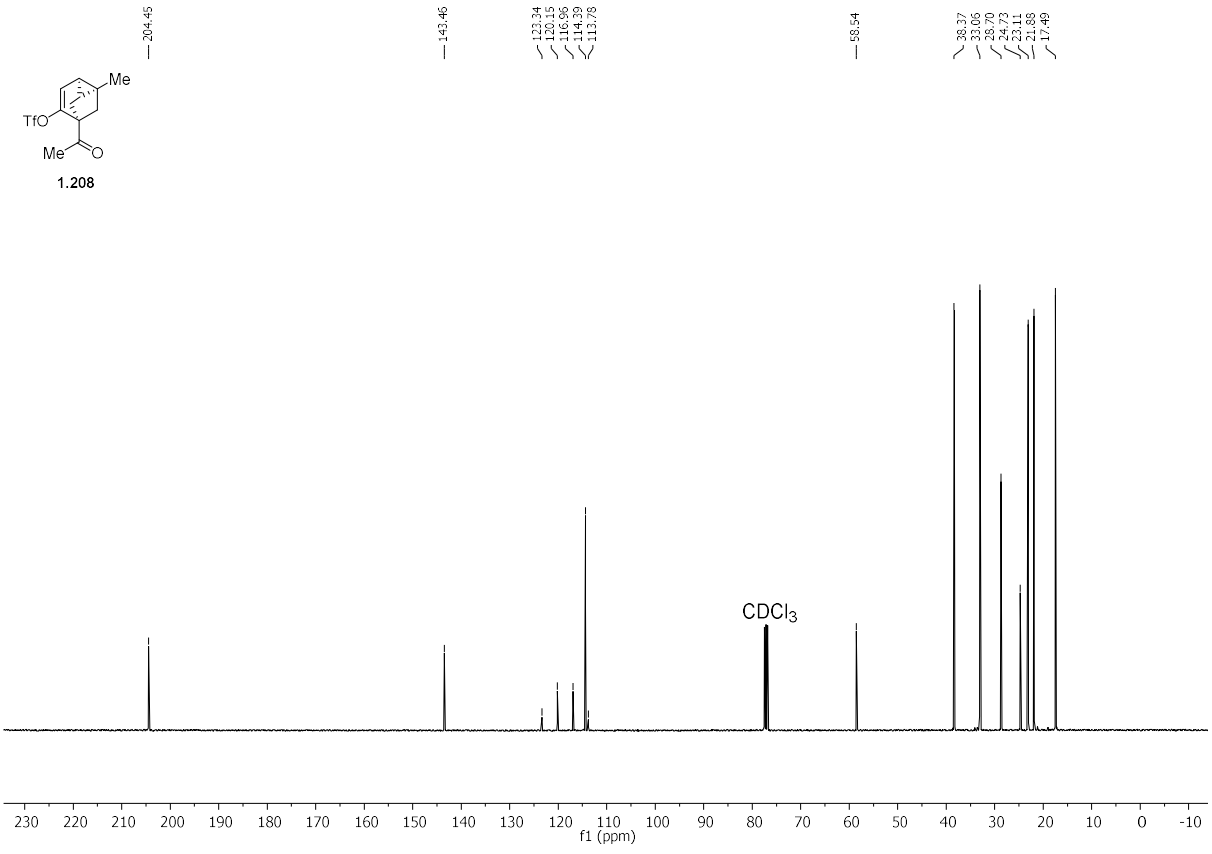


1.S10

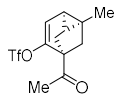
^{1}H NMR (400 MHz, $CDCl_3$) of **1.208**



^{13}C NMR (101 MHz, $CDCl_3$) of **1.208**

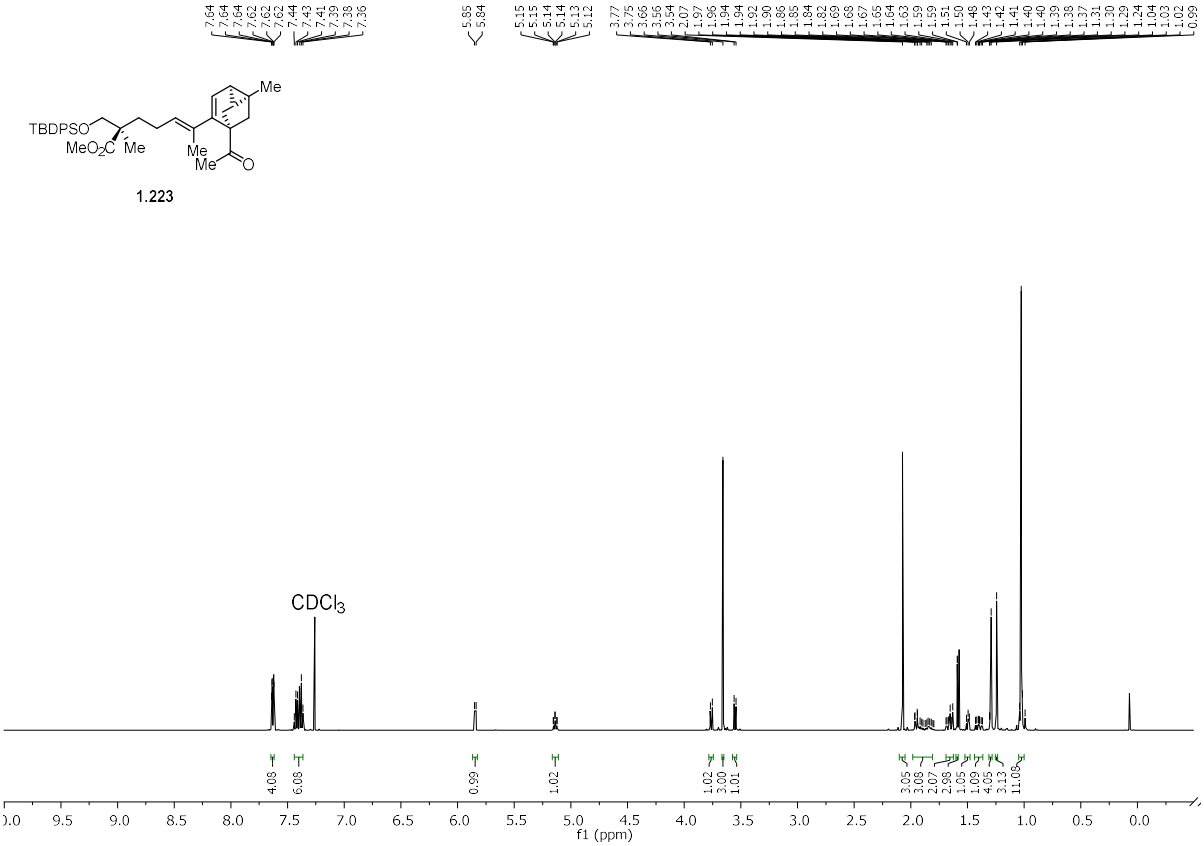


^{19}F NMR (377 MHz, $CDCl_3$) of **1.208**

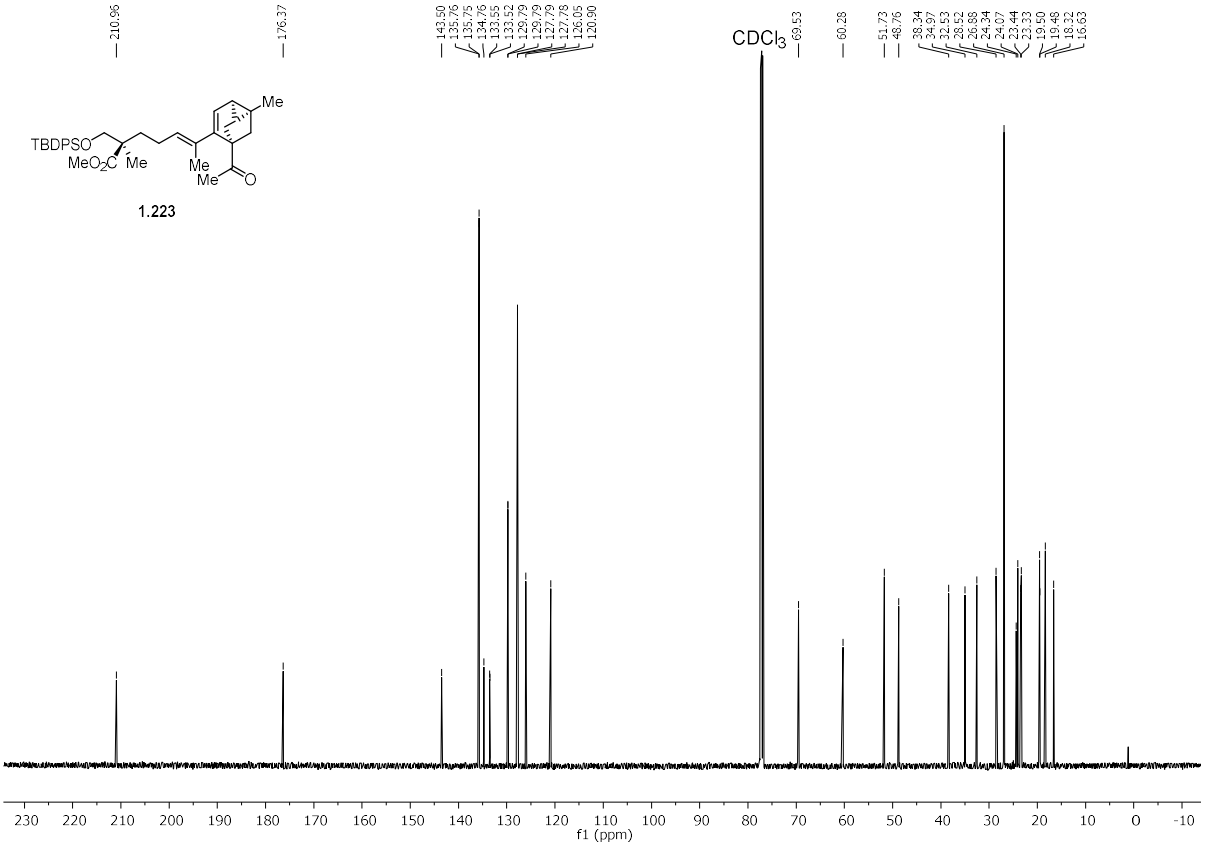


1.208

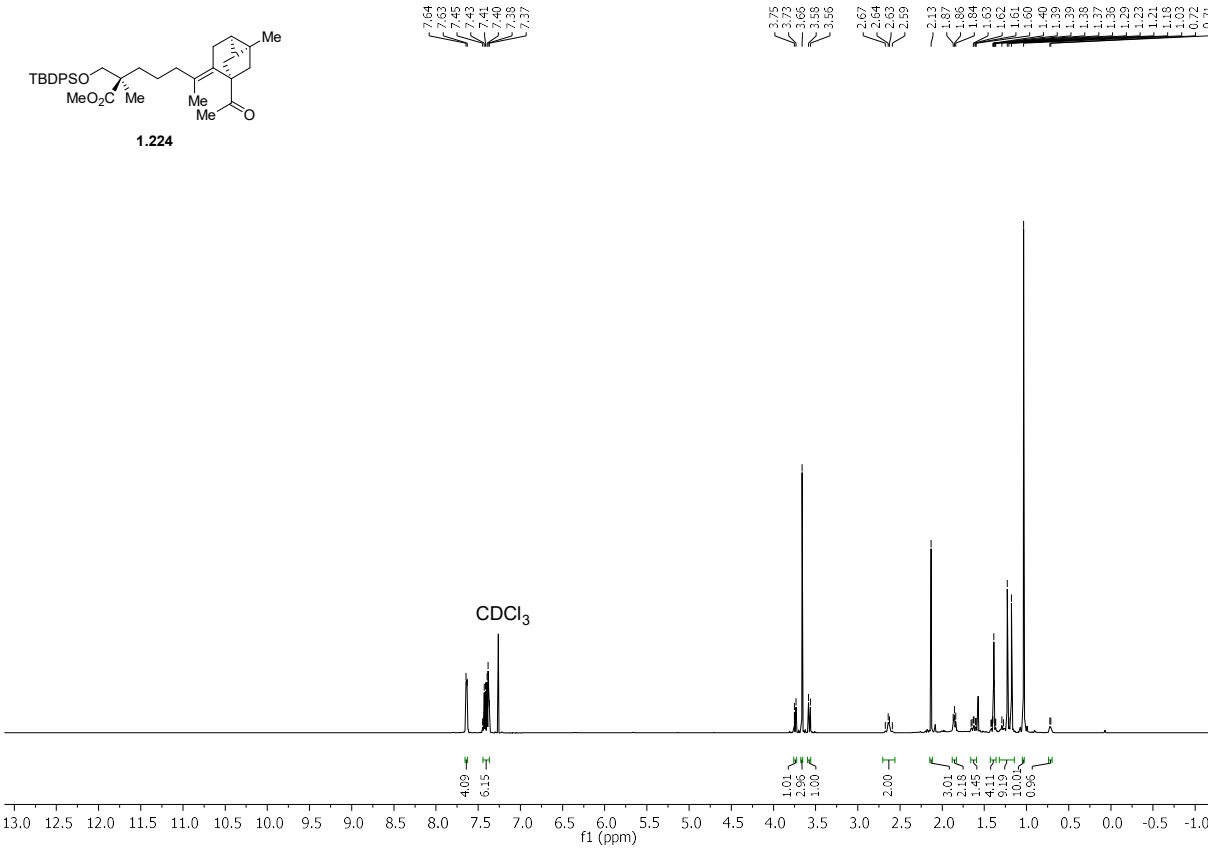
^{1}H NMR (500 MHz, $CDCl_3$) of **1.223**



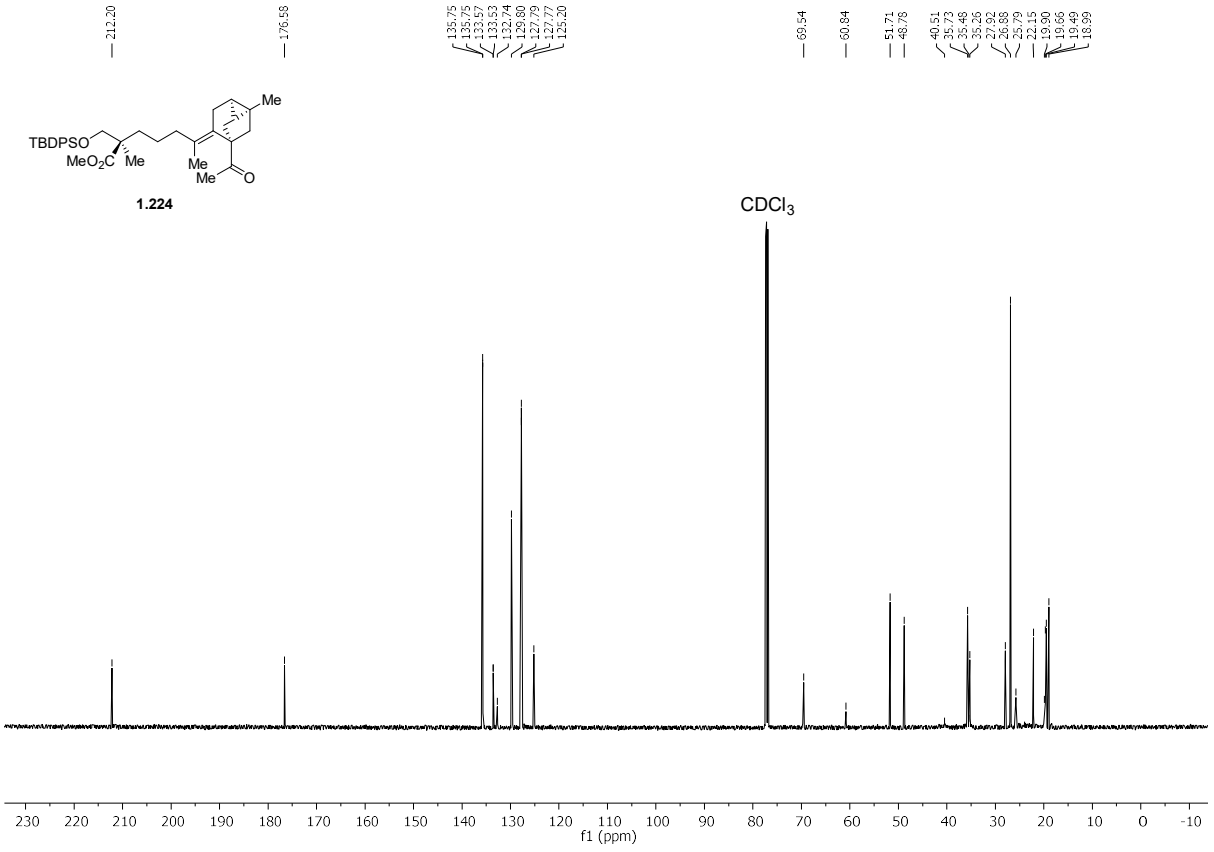
^{13}C NMR (126 MHz, $CDCl_3$) of **1.223**



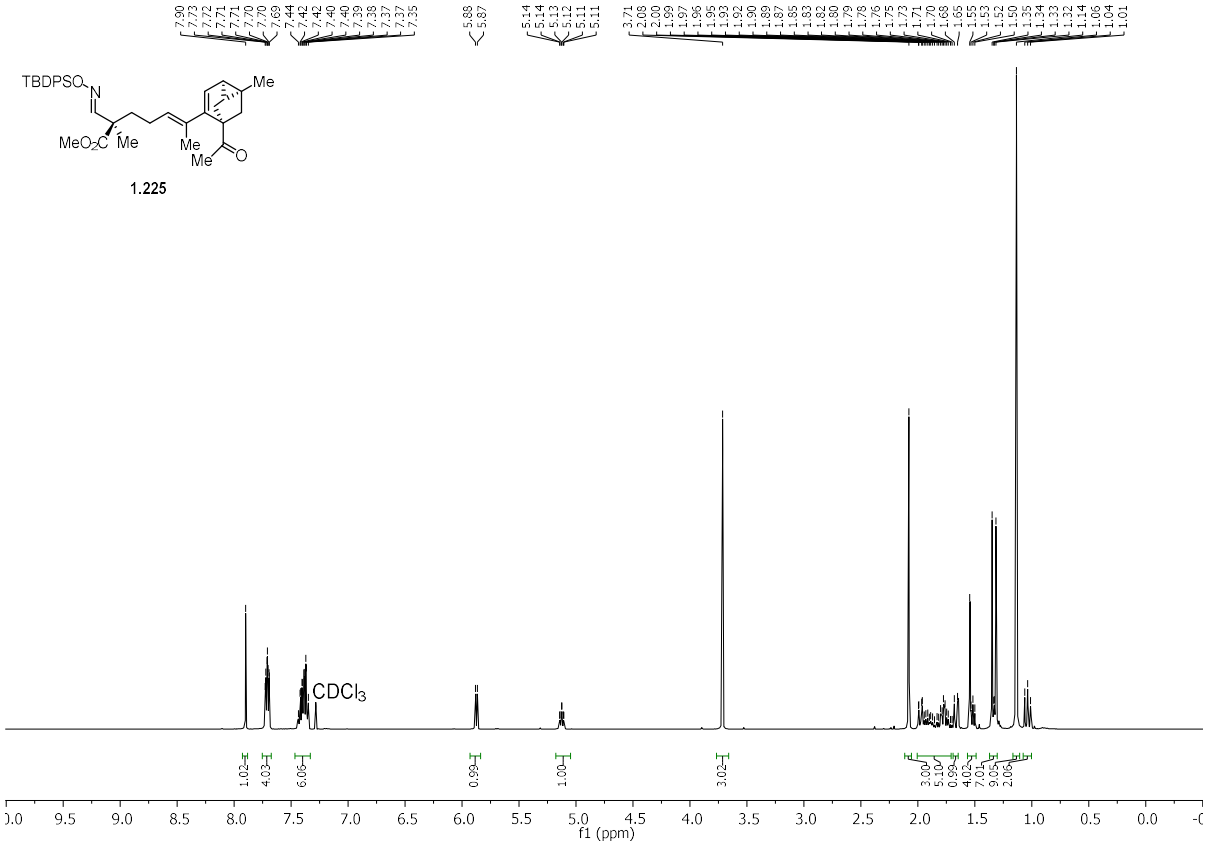
^{1}H NMR (500 MHz, $CDCl_3$) of **1.224**



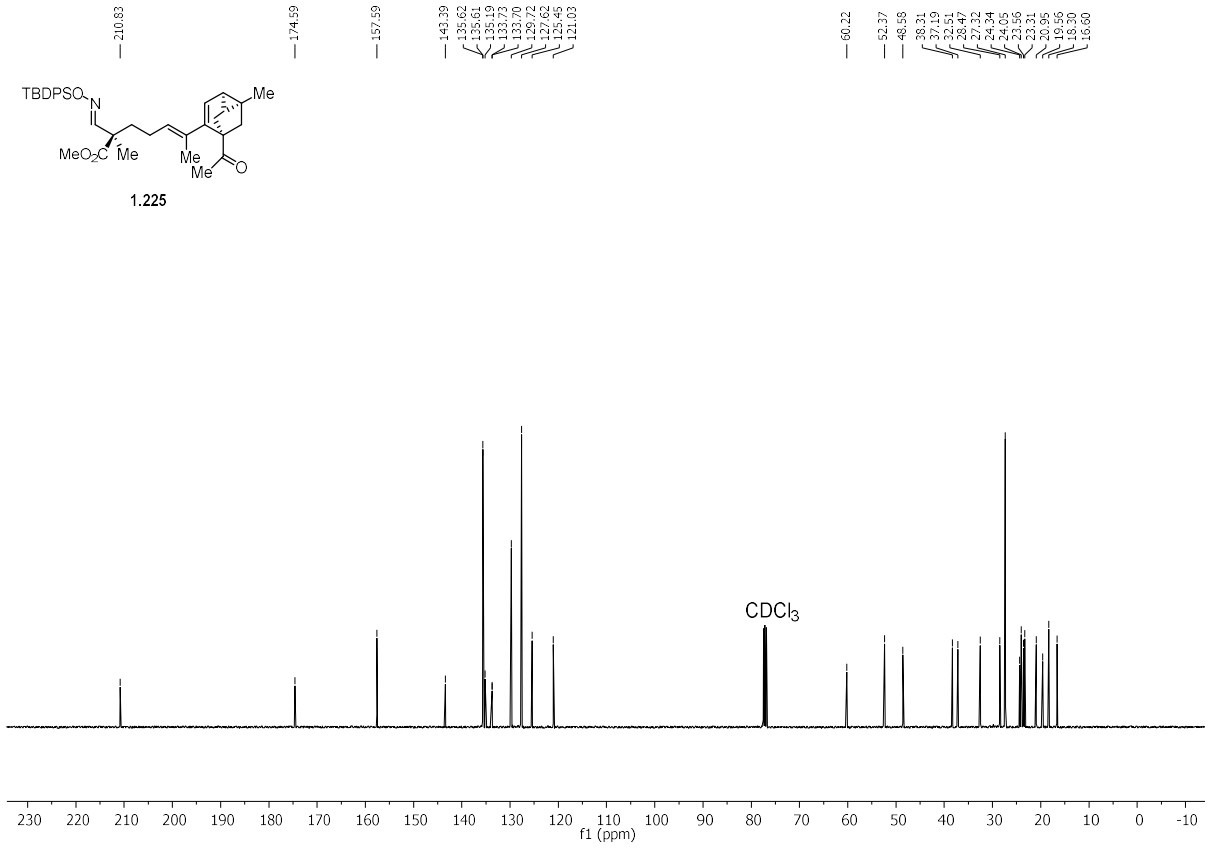
^{13}C NMR (126 MHz, $CDCl_3$) of **1.224**



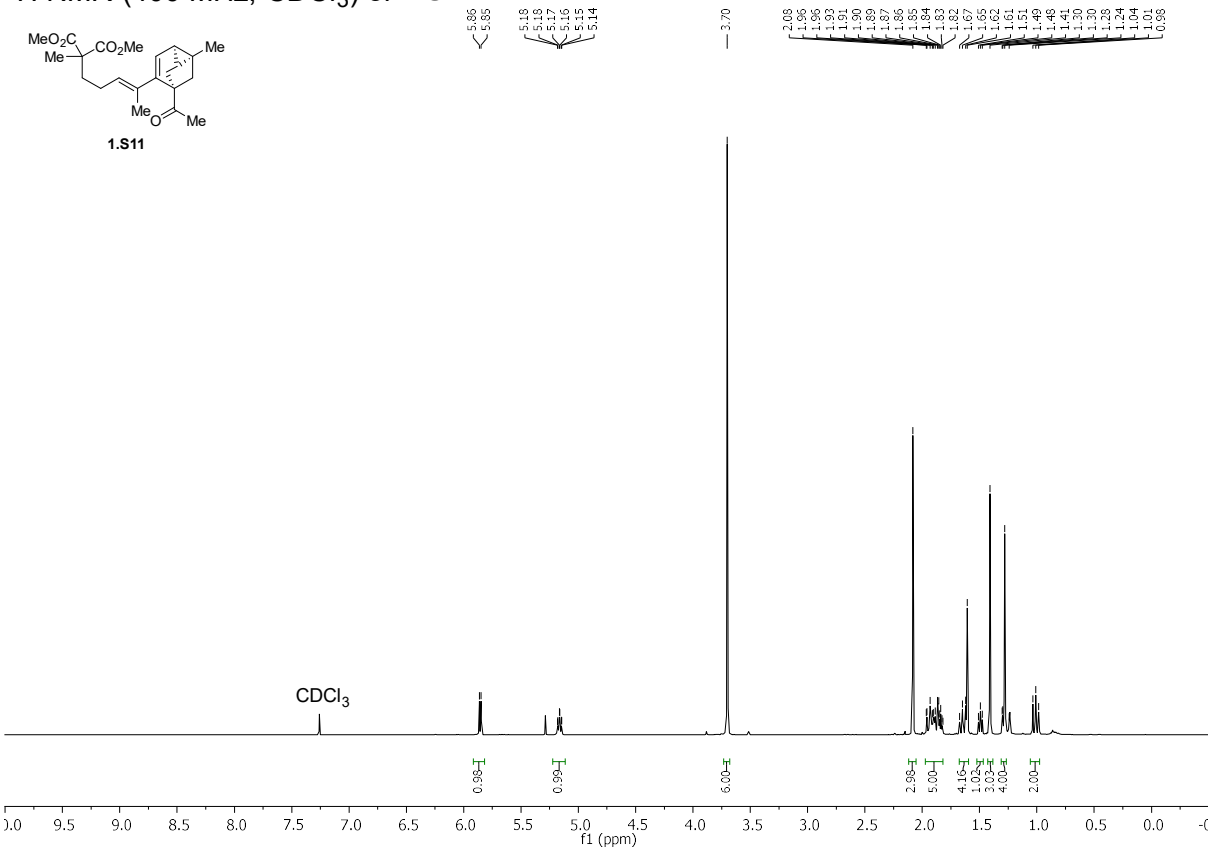
^{1}H NMR (400 MHz, $CDCl_3$) of **1.225**



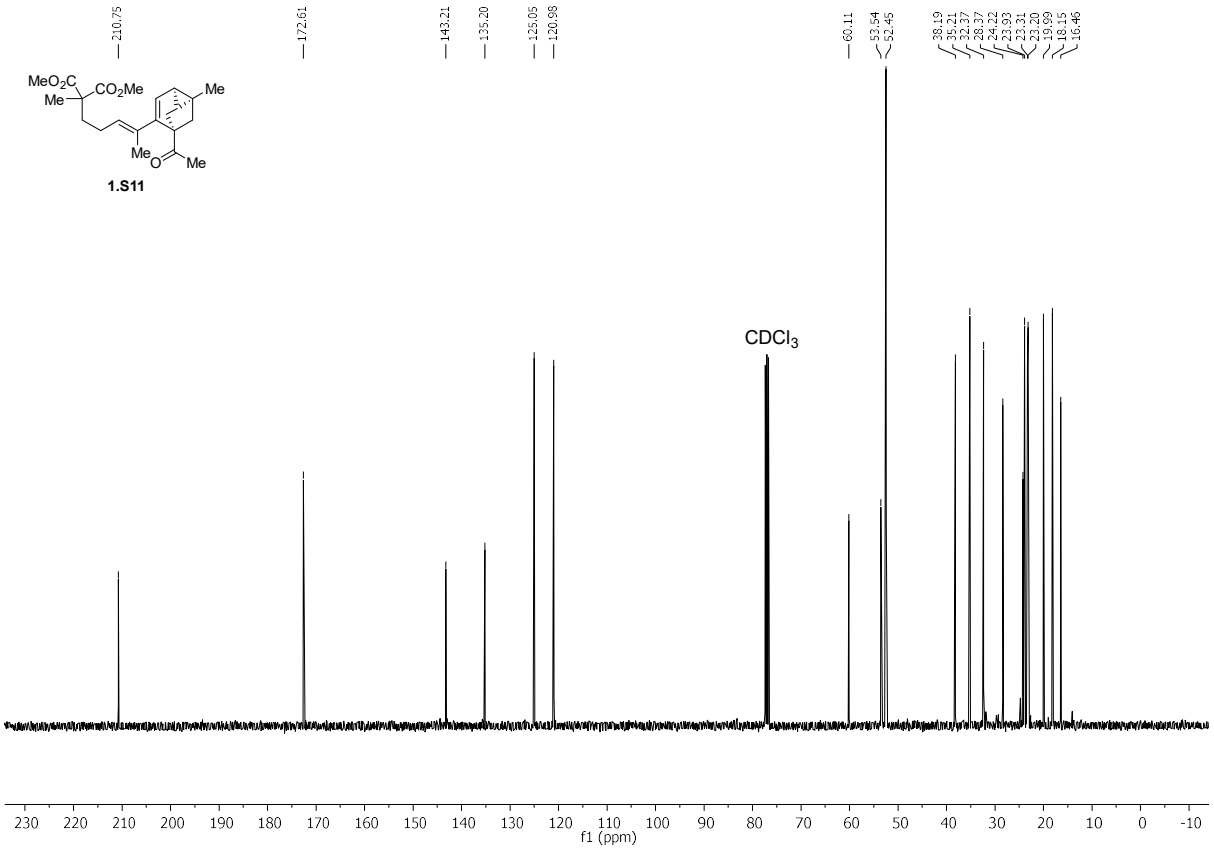
^{13}C NMR (101 MHz, $CDCl_3$) of **1.225**



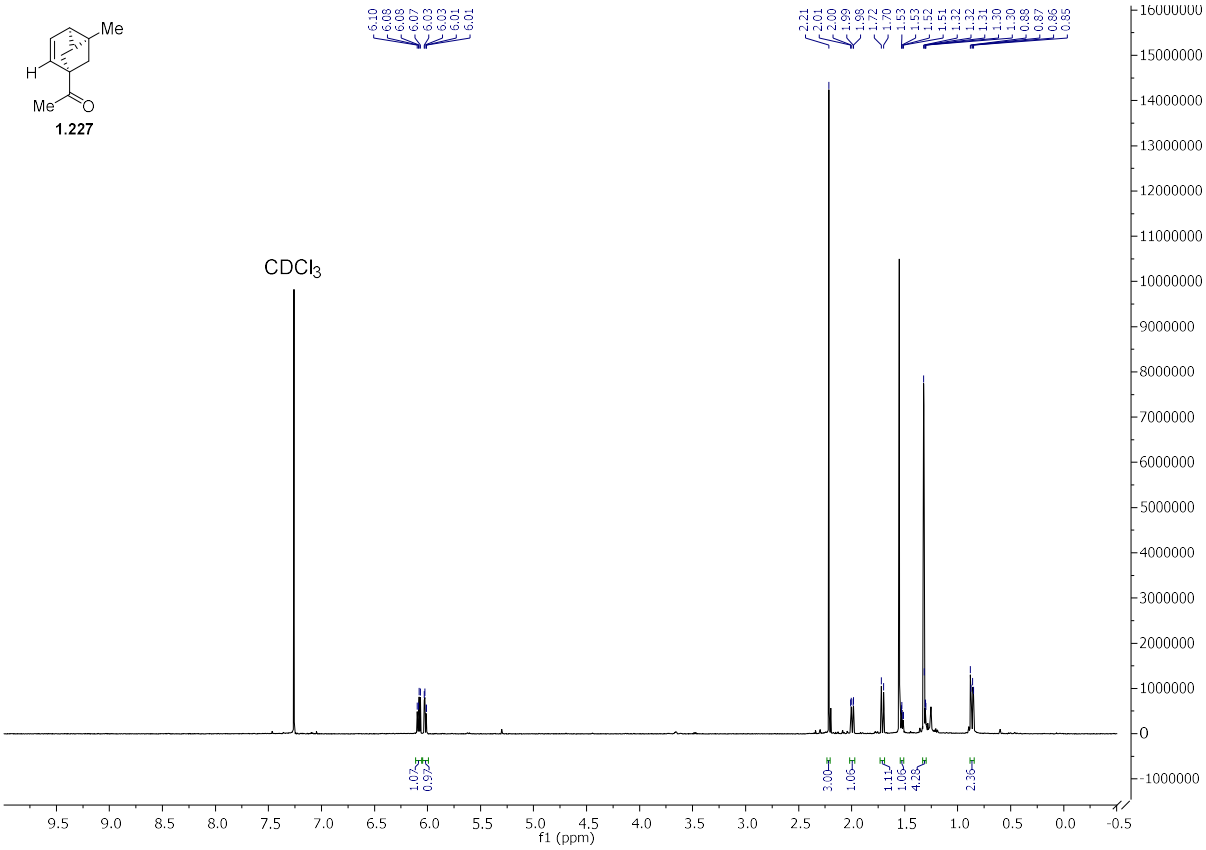
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S11**



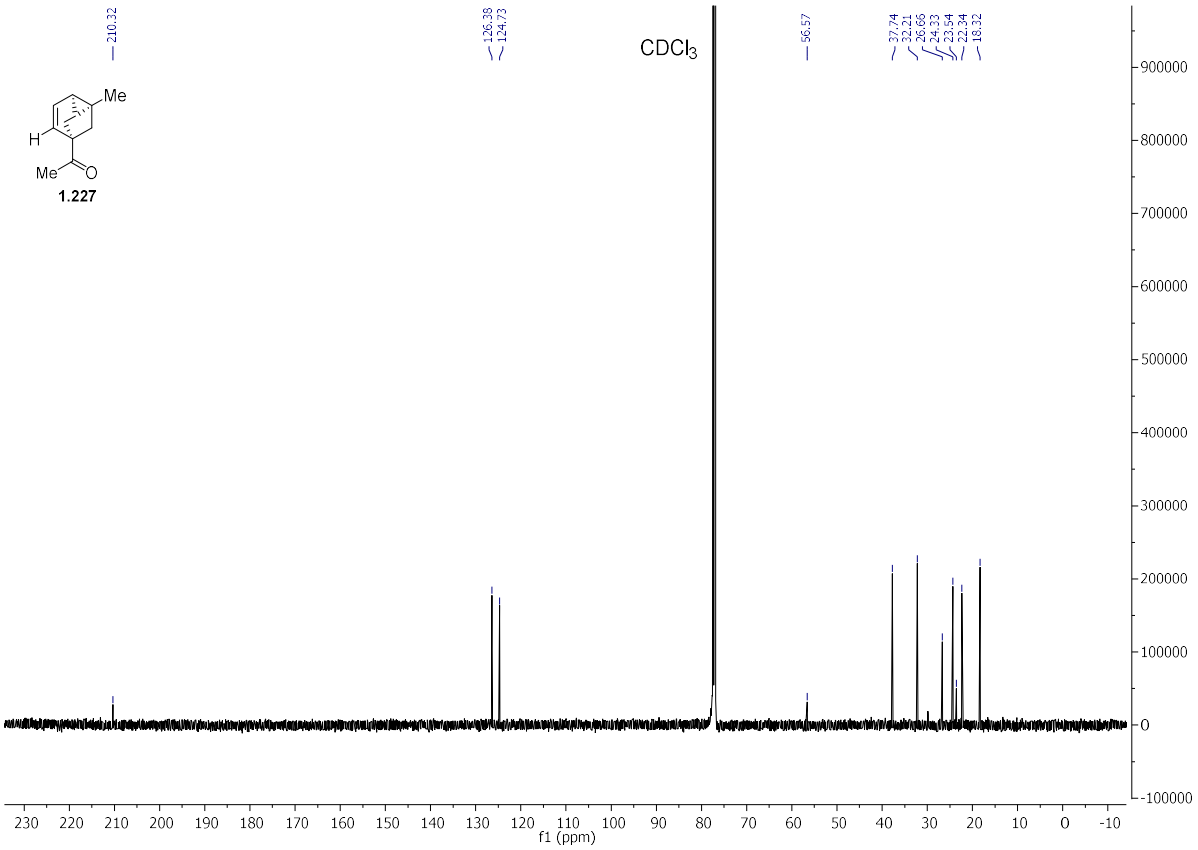
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S11**



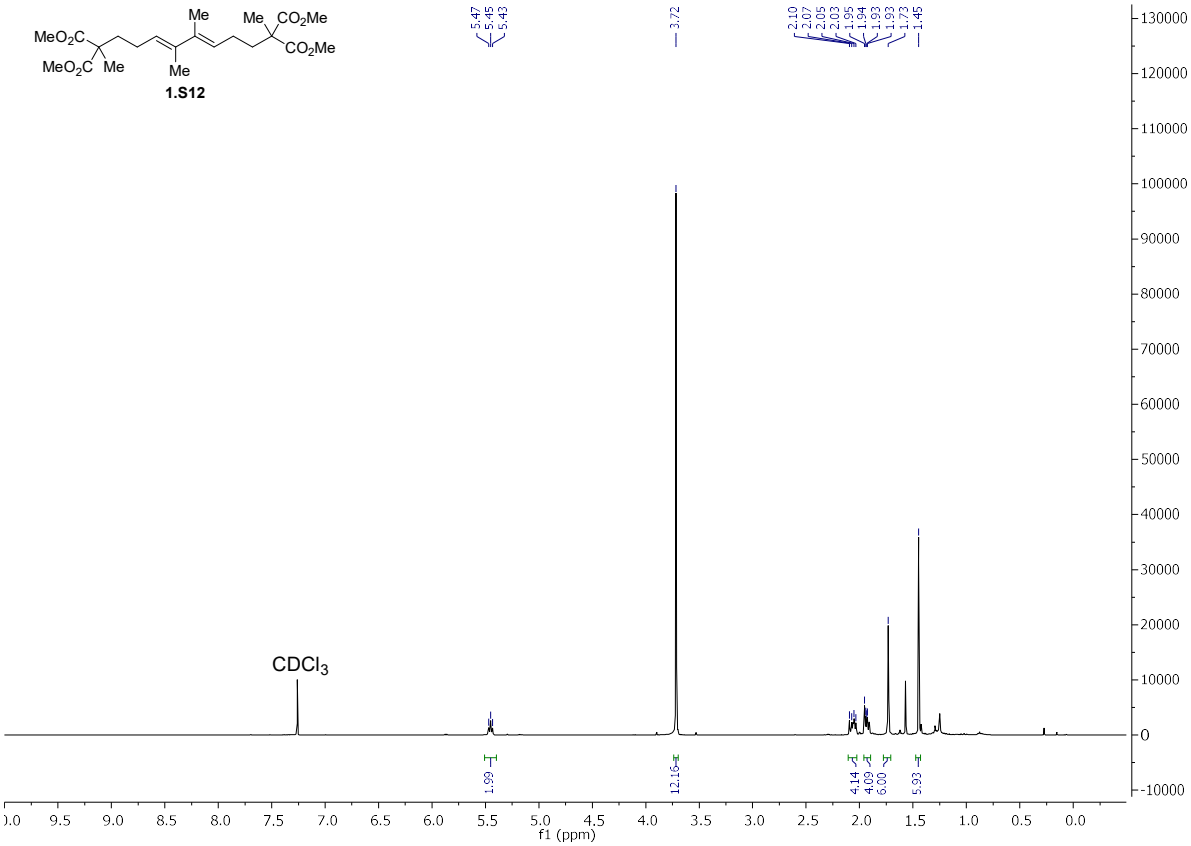
^{1}H NMR (400 MHz, $CDCl_3$) of **1.227**



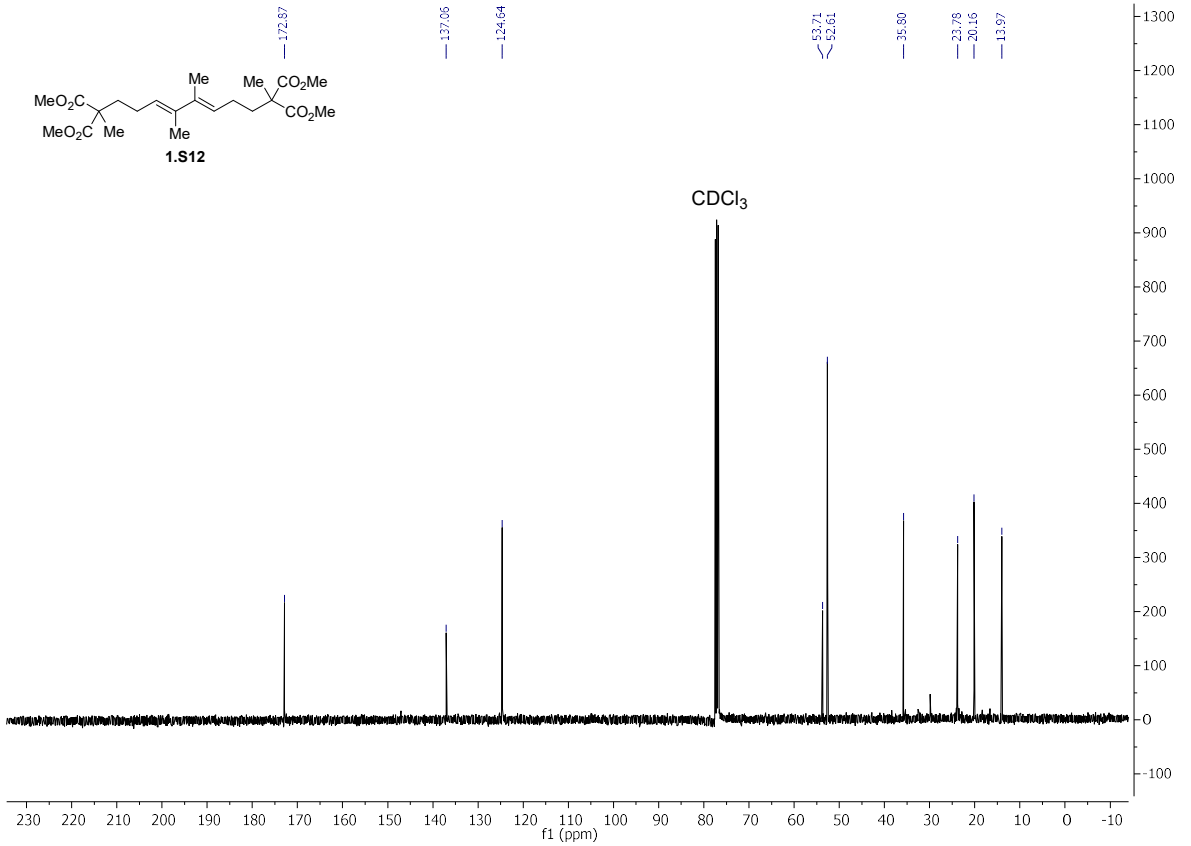
^{13}C NMR (101 MHz, $CDCl_3$) of **1.227**



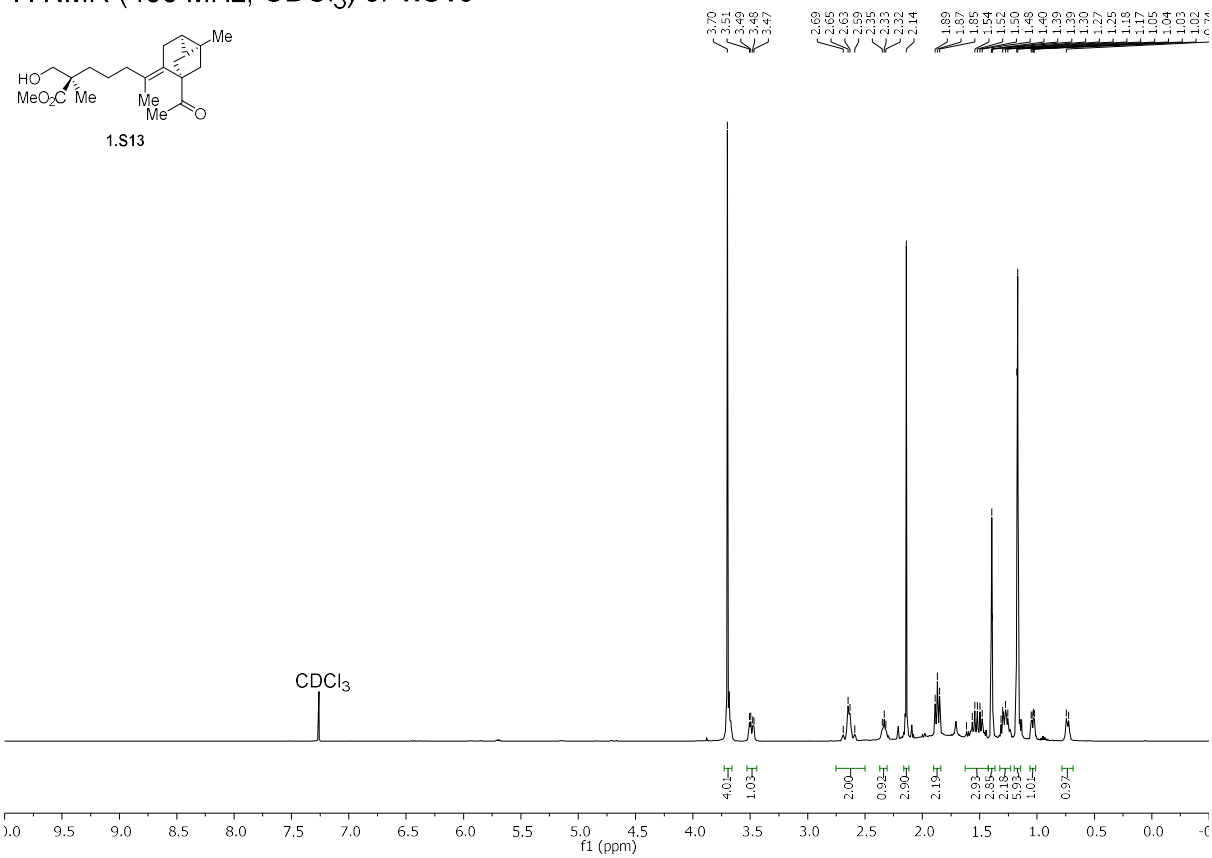
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S12**



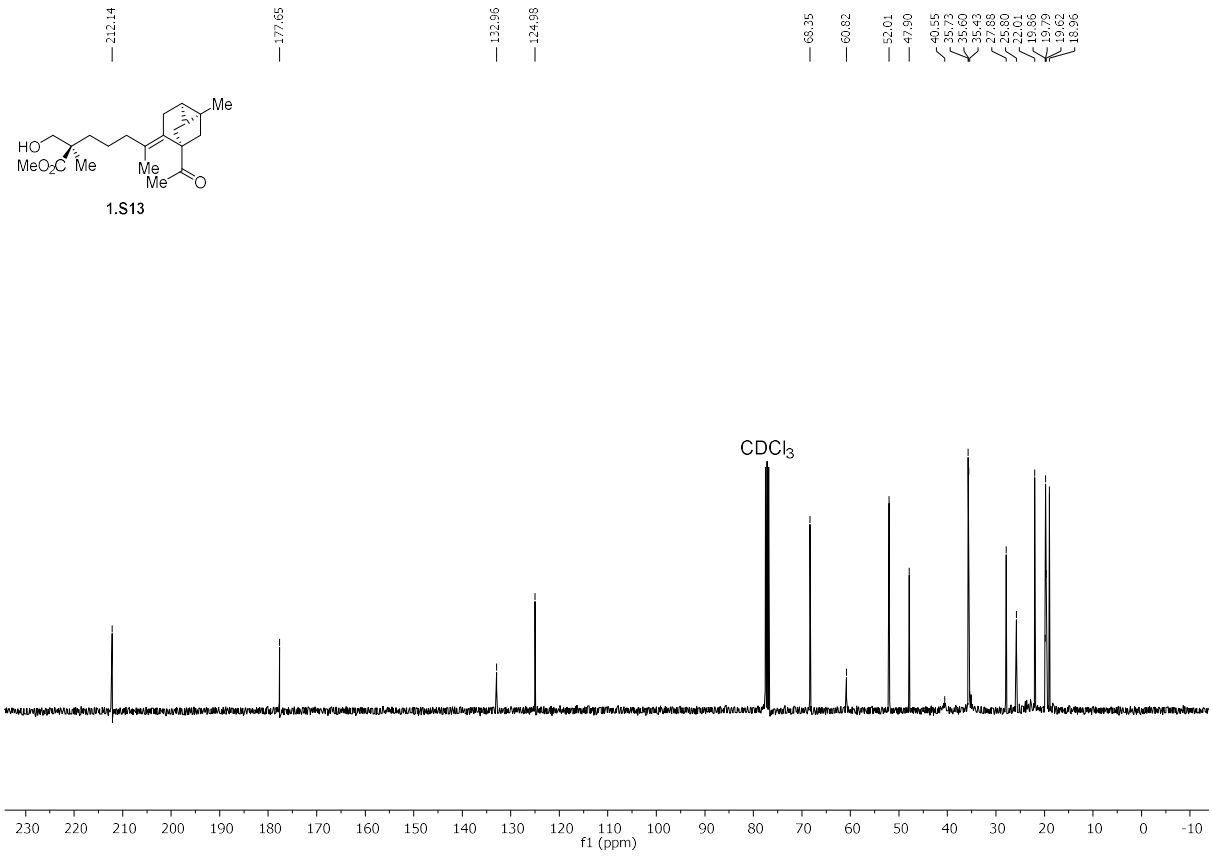
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S12**



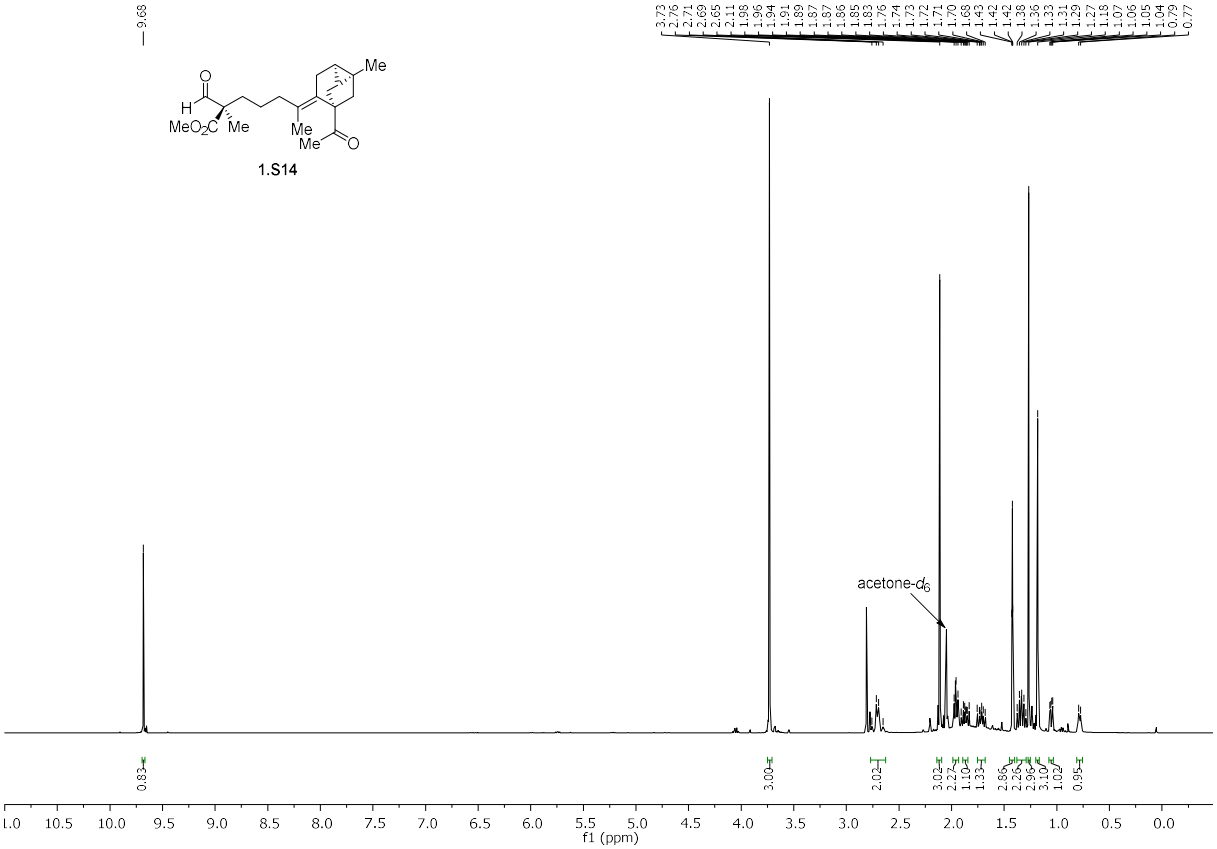
^{1}H NMR (400 MHz, $CDCl_3$) of **1.S13**



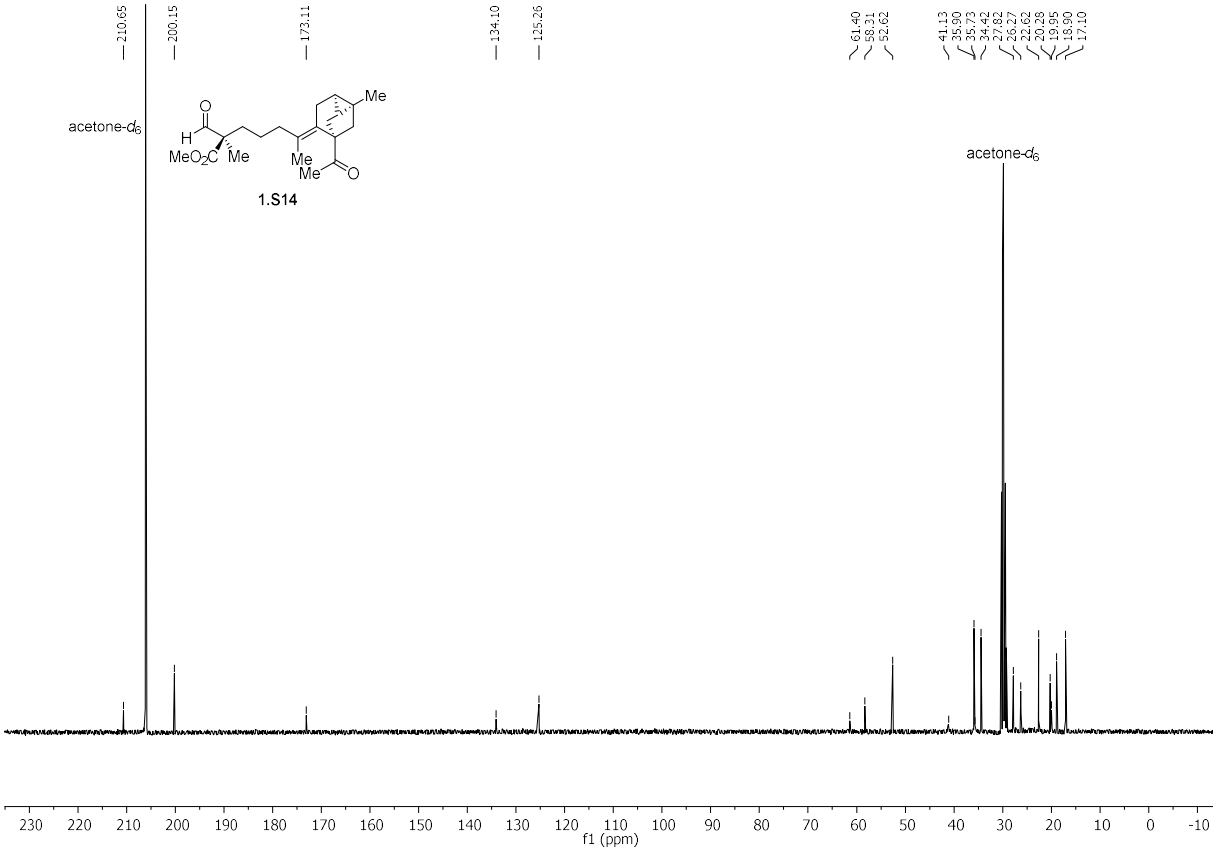
^{13}C NMR (101 MHz, $CDCl_3$) of **1.S13**



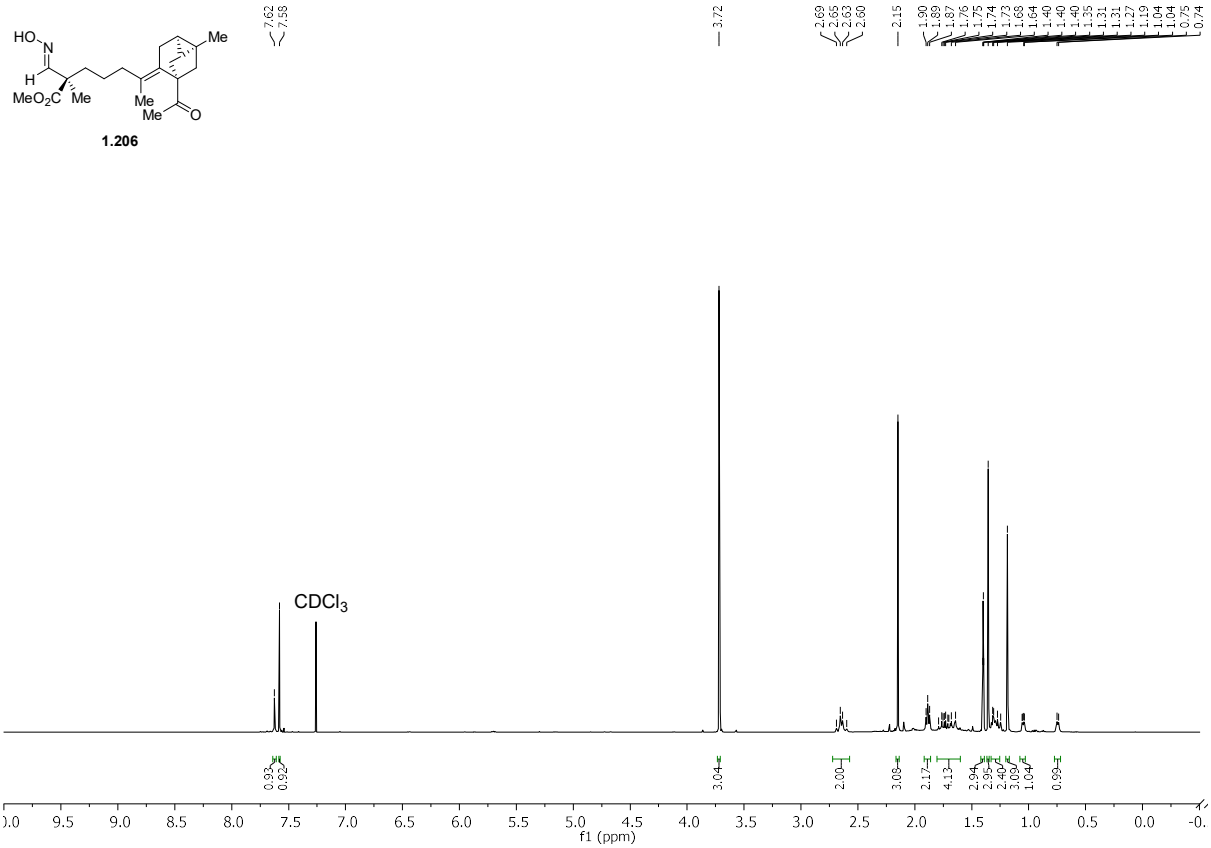
^{1}H NMR (400 MHz, acetone-d_6) of **1.S14**



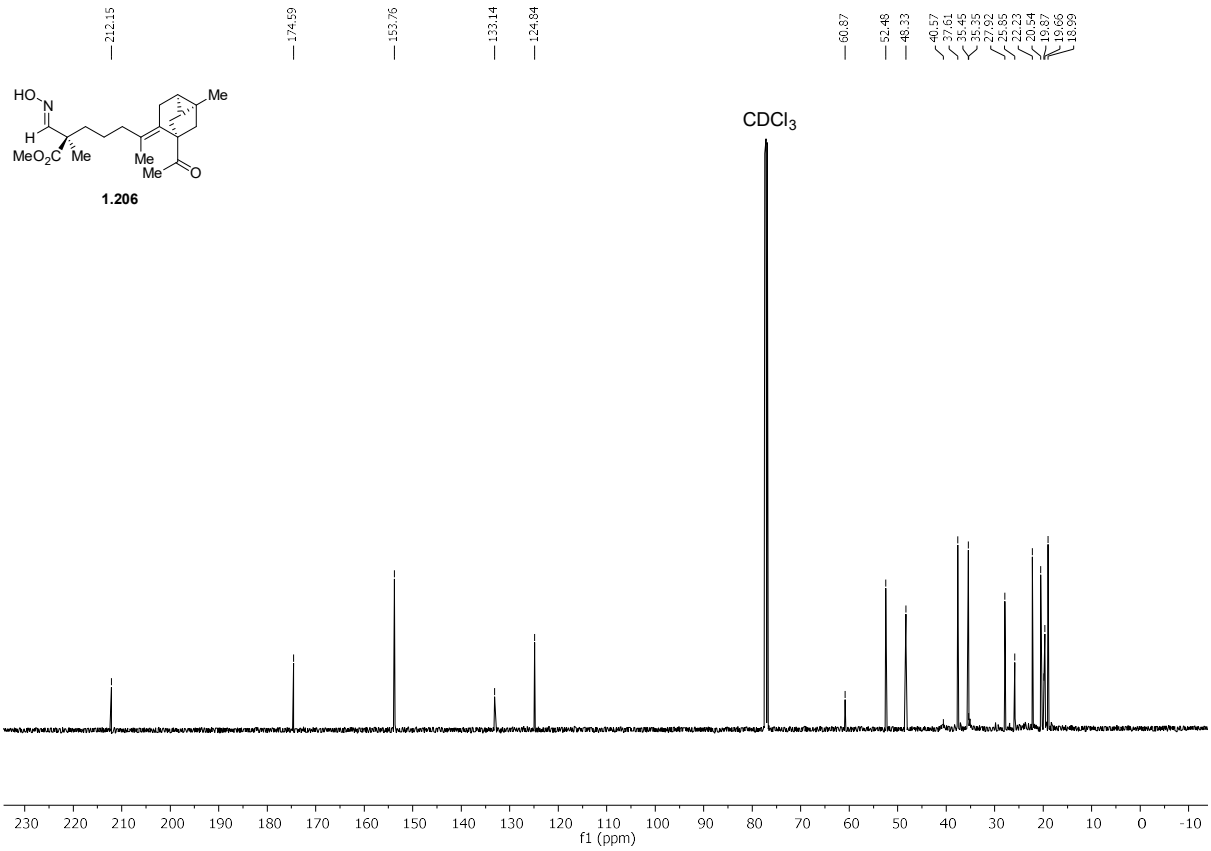
^{13}C NMR (101 MHz, acetone-d_6) of **1.S14**



^{1}H NMR (500 MHz, $CDCl_3$) of **1.206**

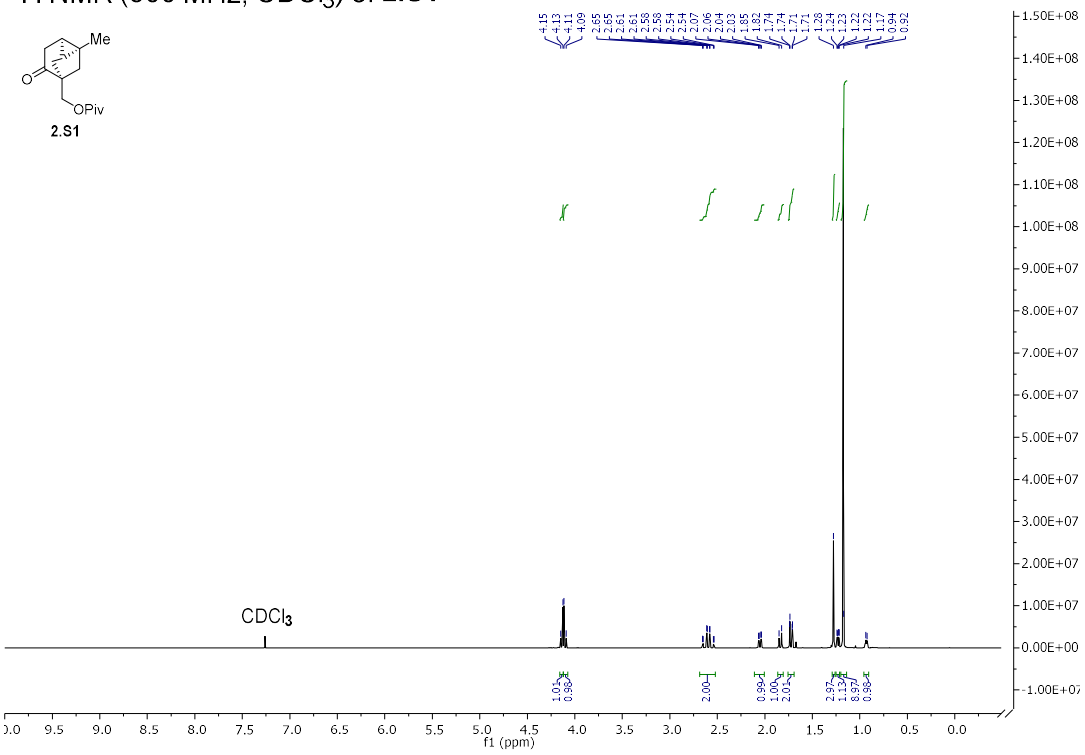


^{13}C NMR (126 MHz, $CDCl_3$) of **1.206**

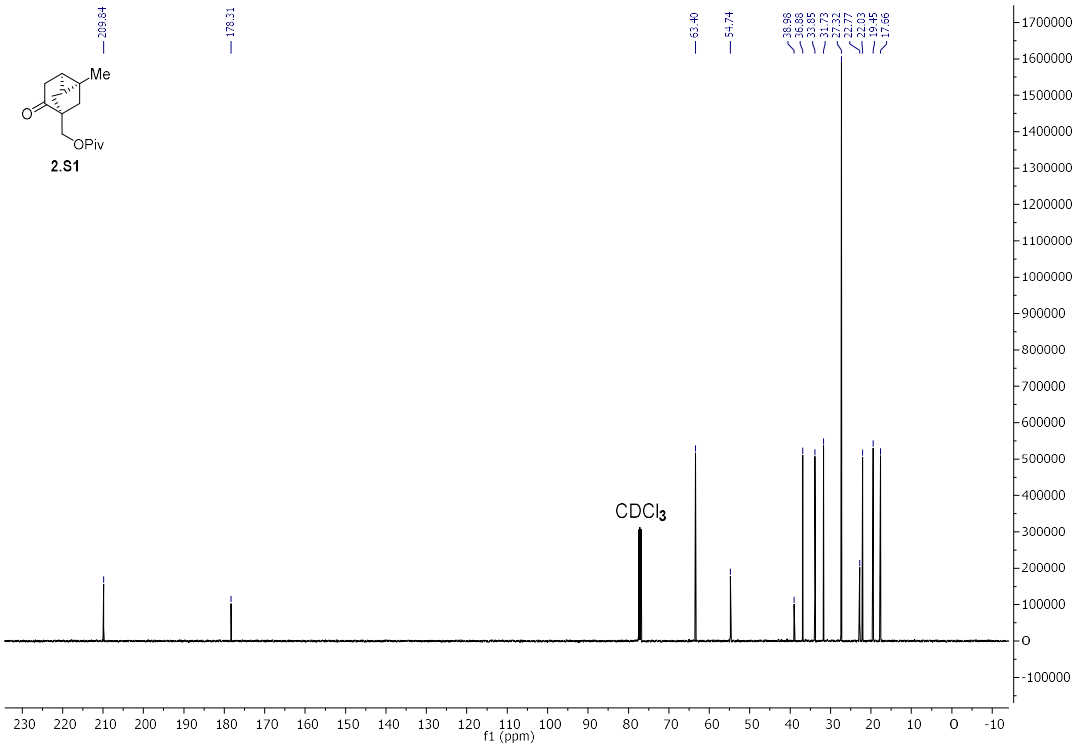


2. Stereoselective Synthesis of Tetrasubstituted Olefins via 1,4-Semihydrogenation of 1,3-Dienes

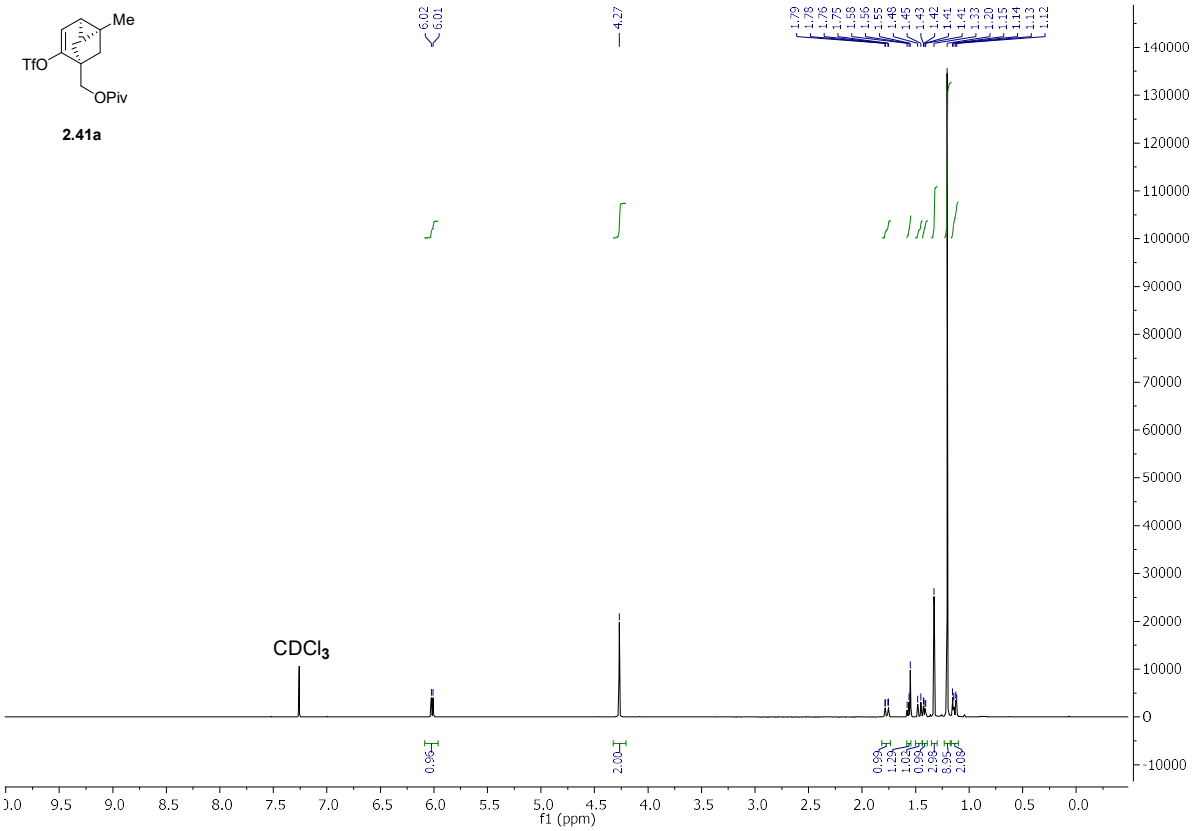
^{1}H NMR (500 MHz, $CDCl_3$) of **2.S1**



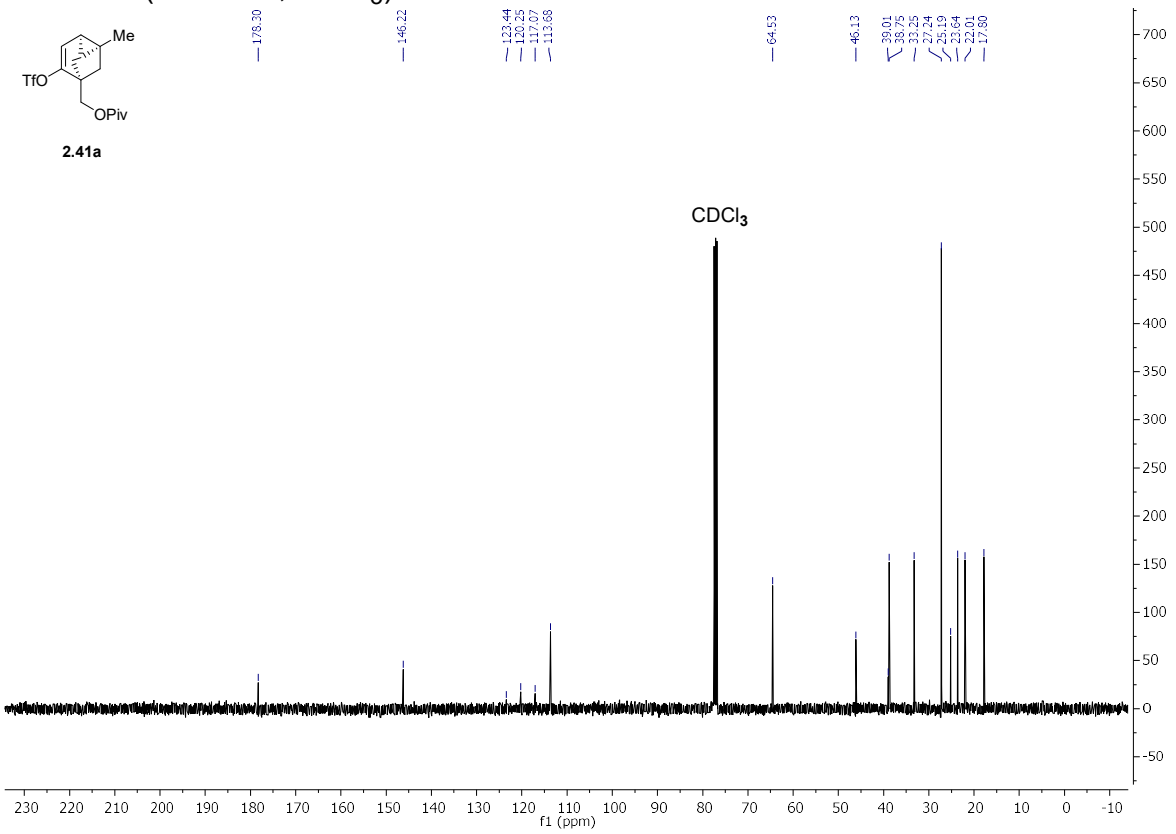
^{13}C NMR (126 MHz, $CDCl_3$) of **2.S1**



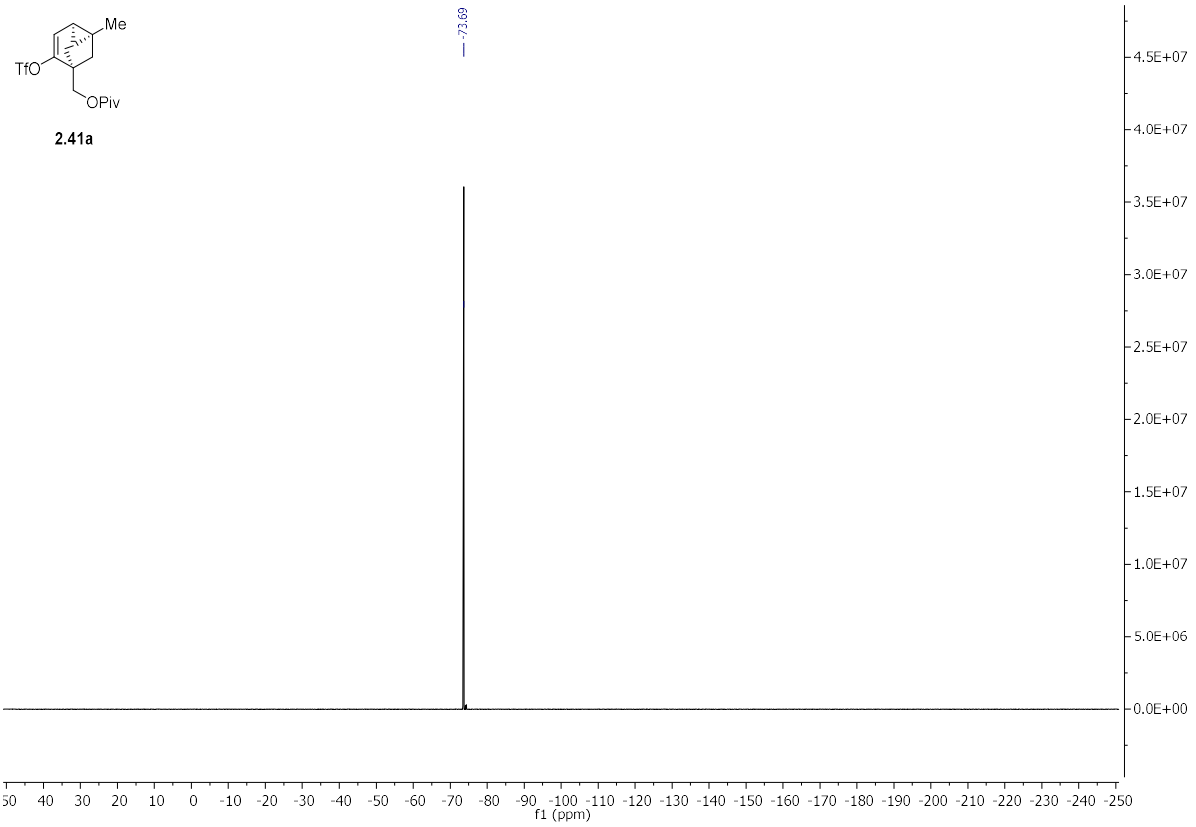
^{1}H NMR (400 MHz, $CDCl_3$) of **2.41a**



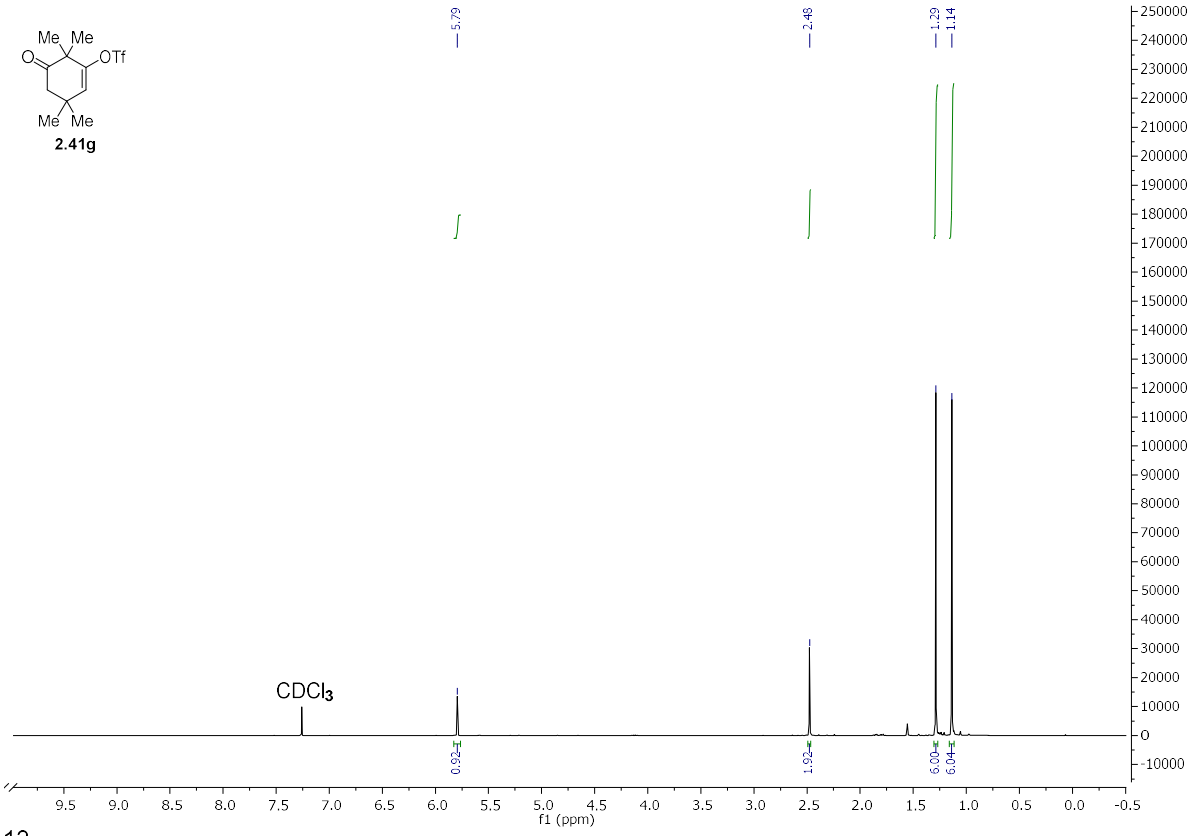
^{13}C NMR (101 MHz, $CDCl_3$) of **2.41a**



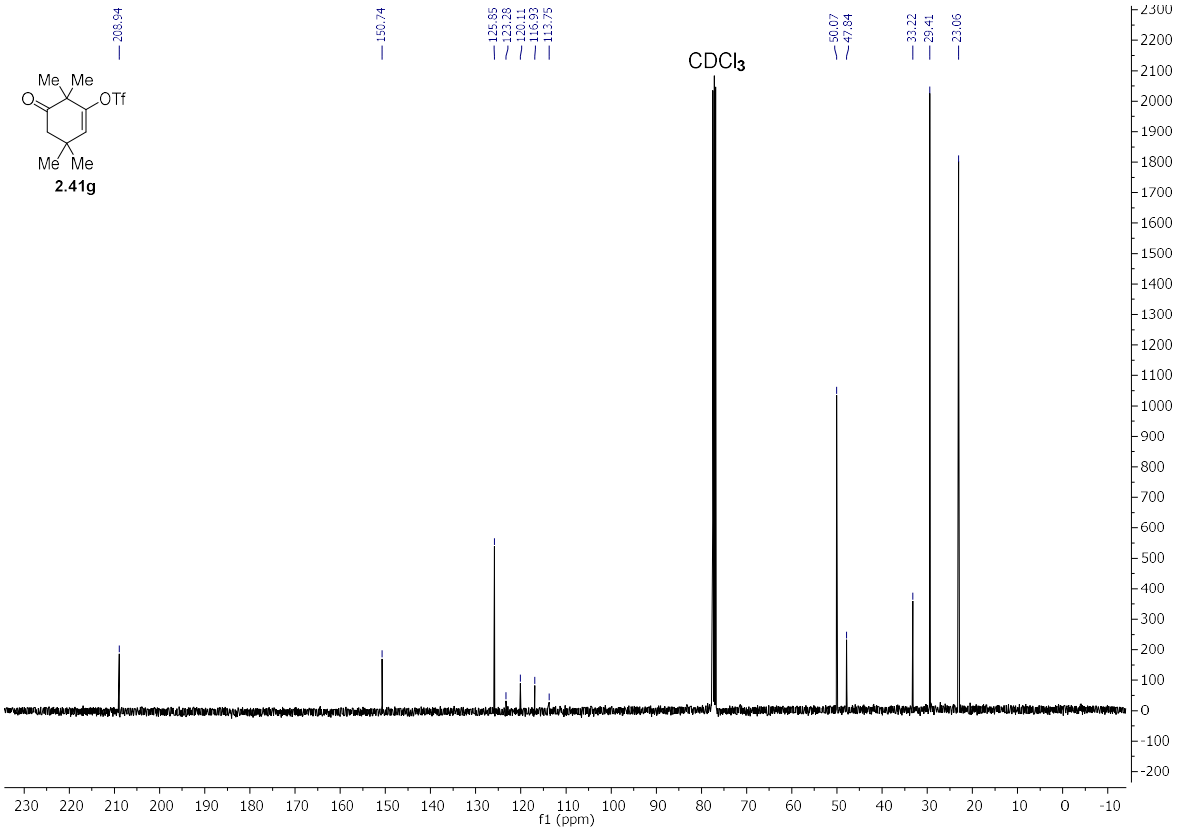
^{19}F NMR (400 MHz, $CDCl_3$) of **2.41a**



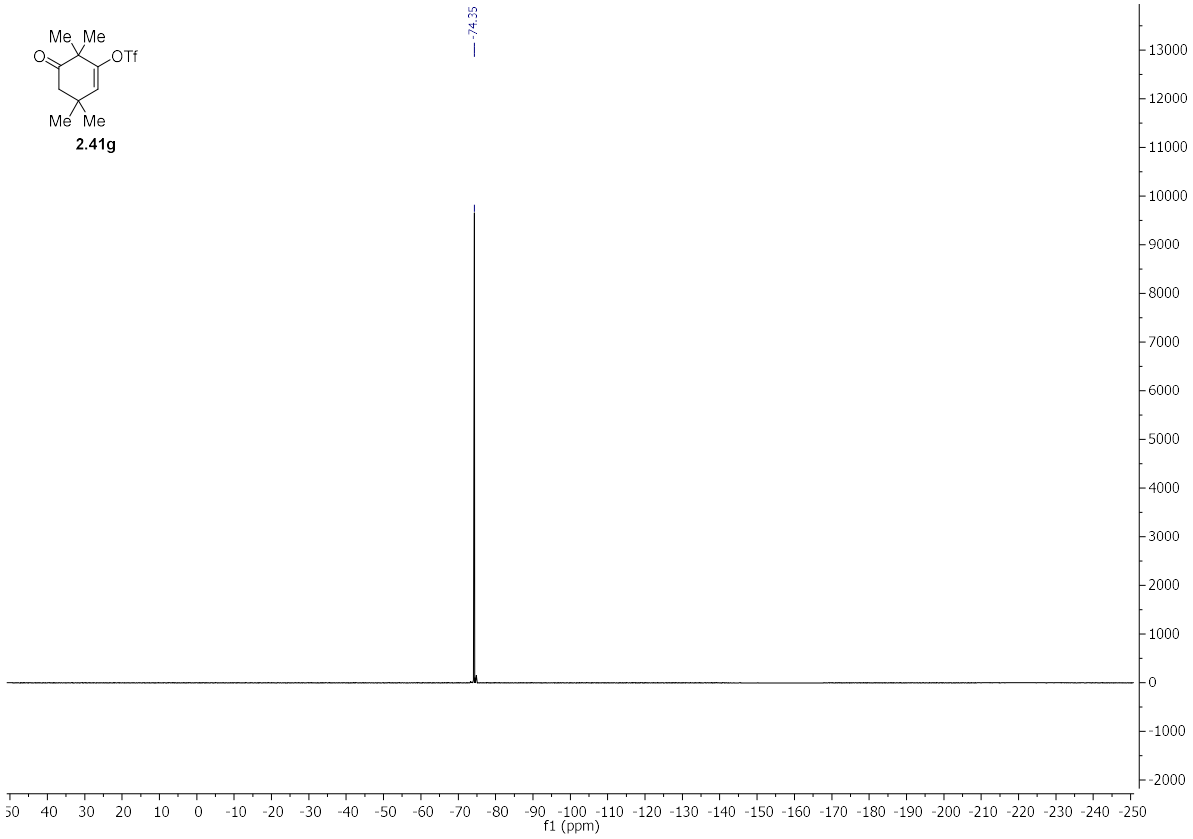
^{1}H NMR (400 MHz, $CDCl_3$) of **2.41g**



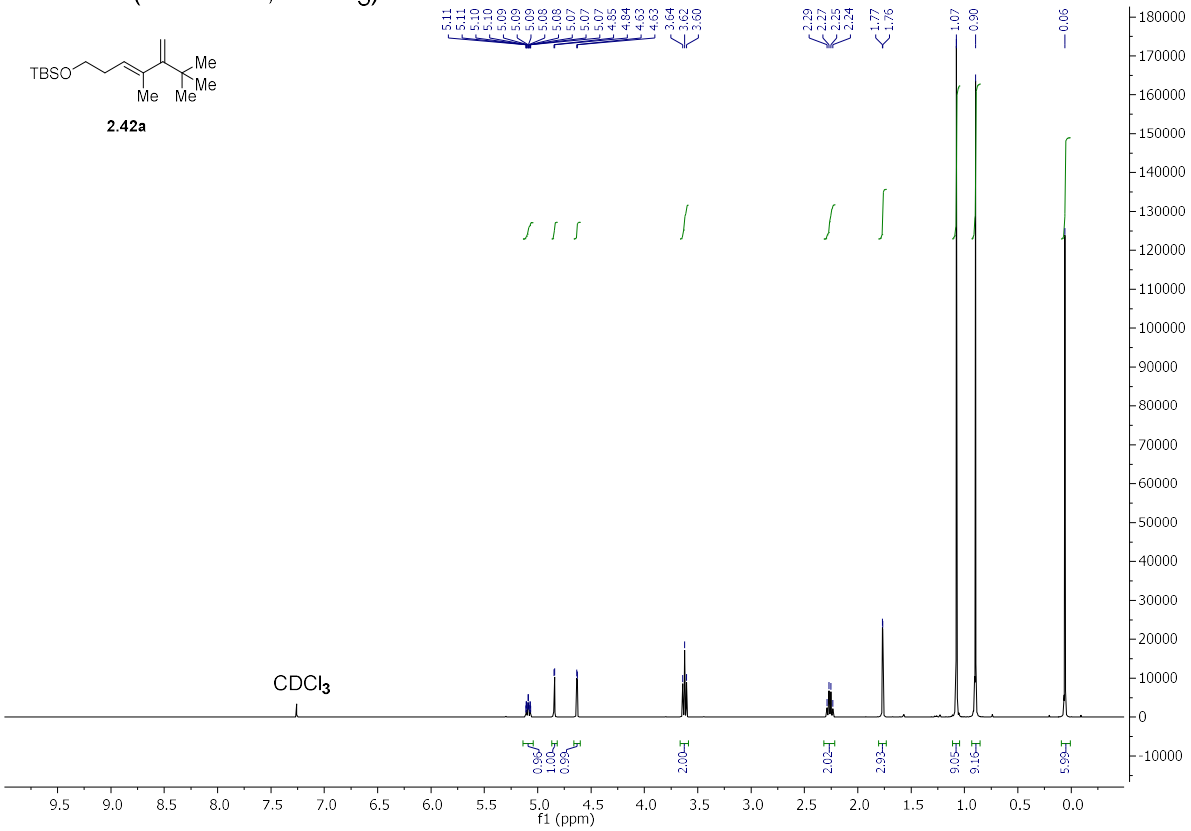
^{13}C NMR (101 MHz, $CDCl_3$) of **2.41g**



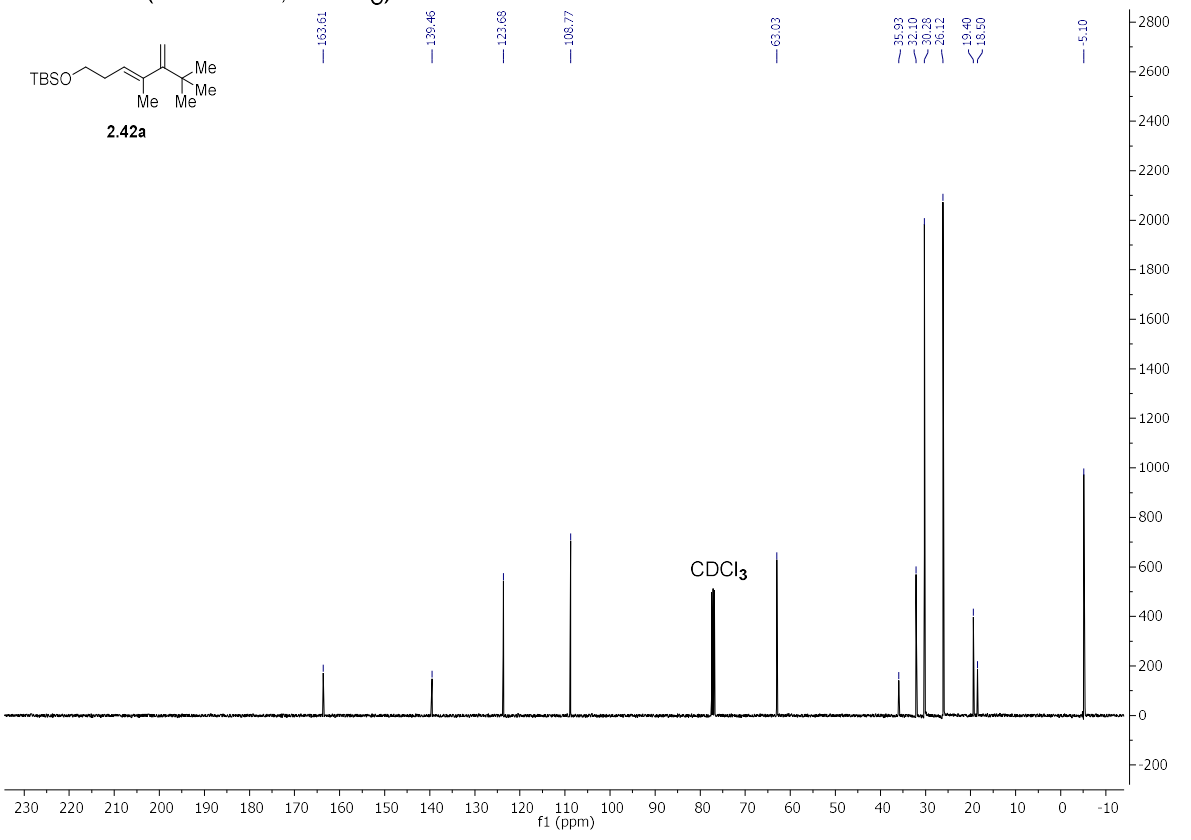
^{19}F NMR (377 MHz, $CDCl_3$) of **2.41g**



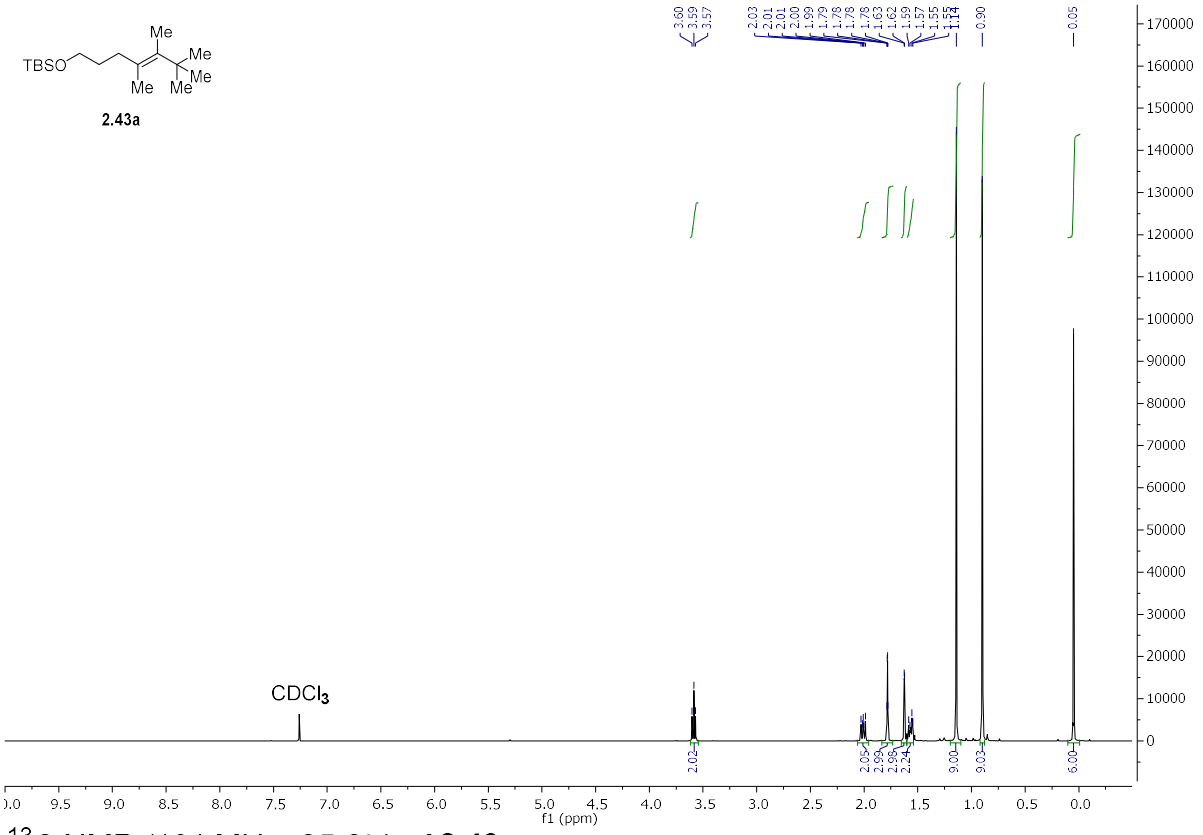
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42a**



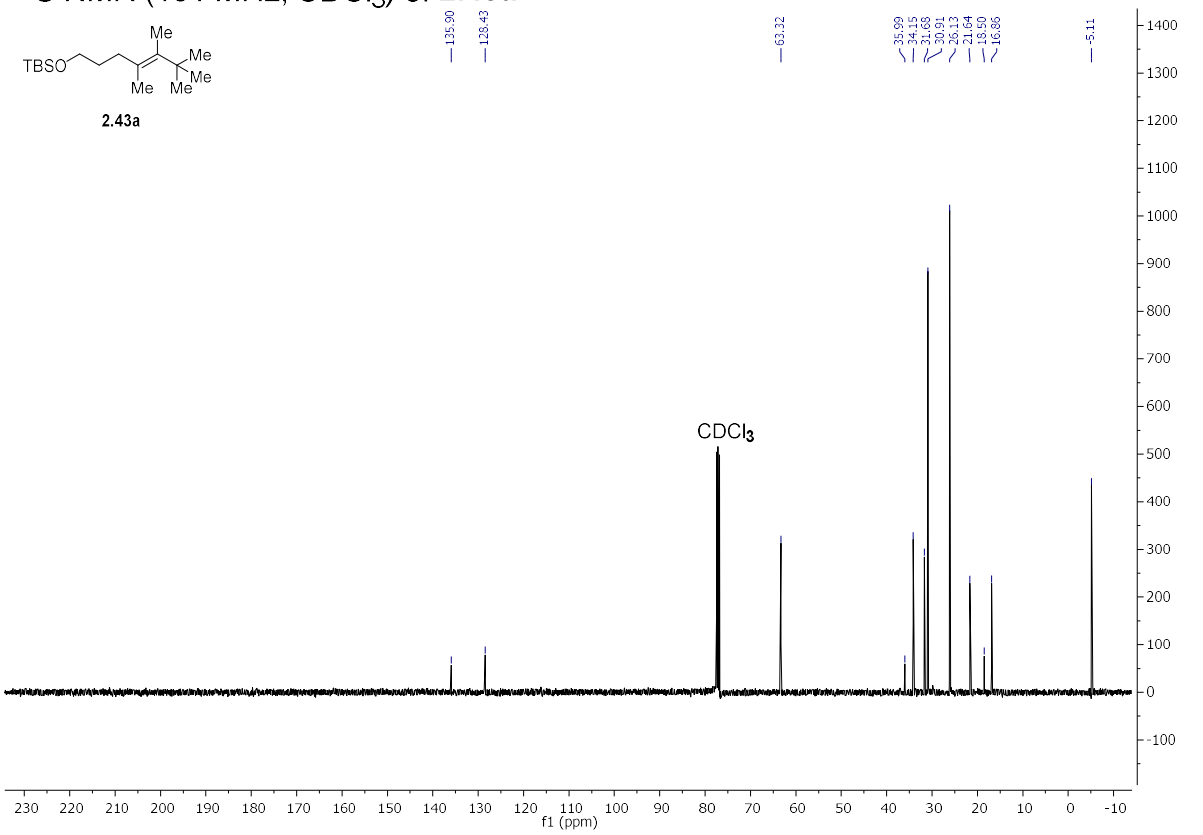
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42a**



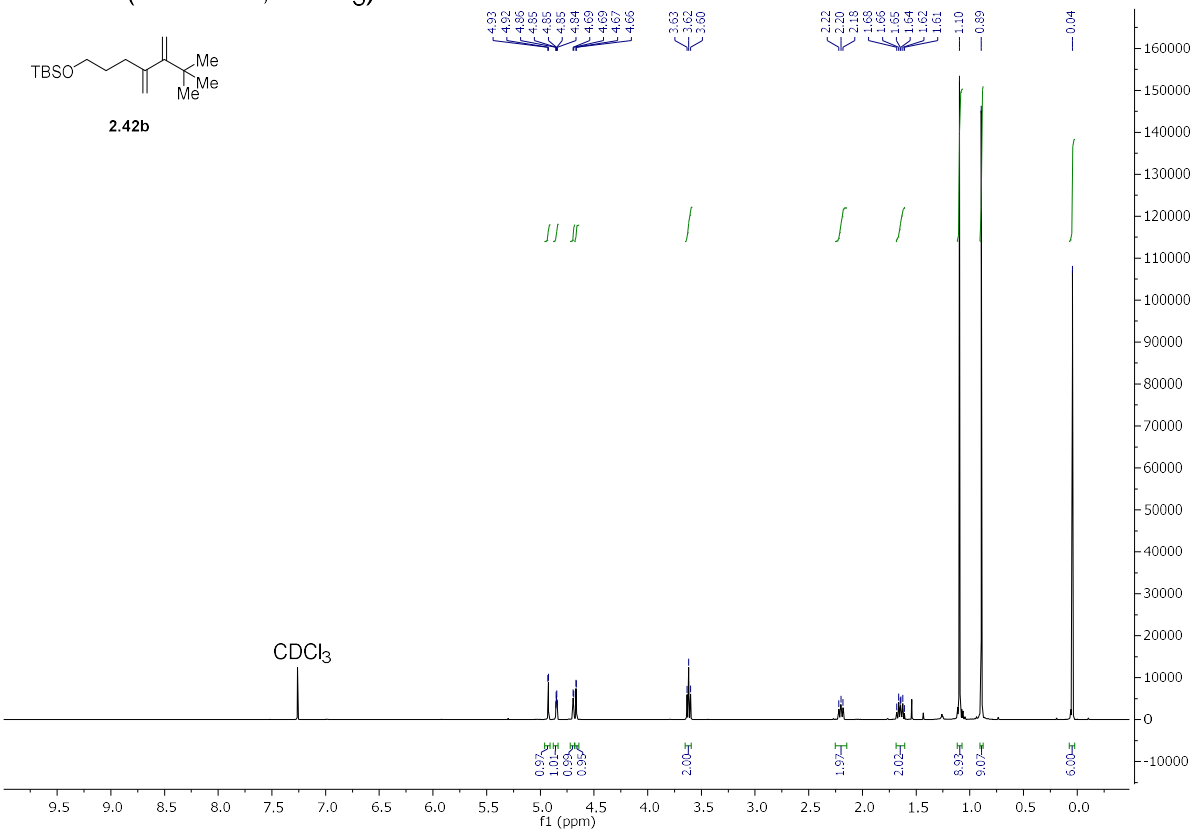
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43a**



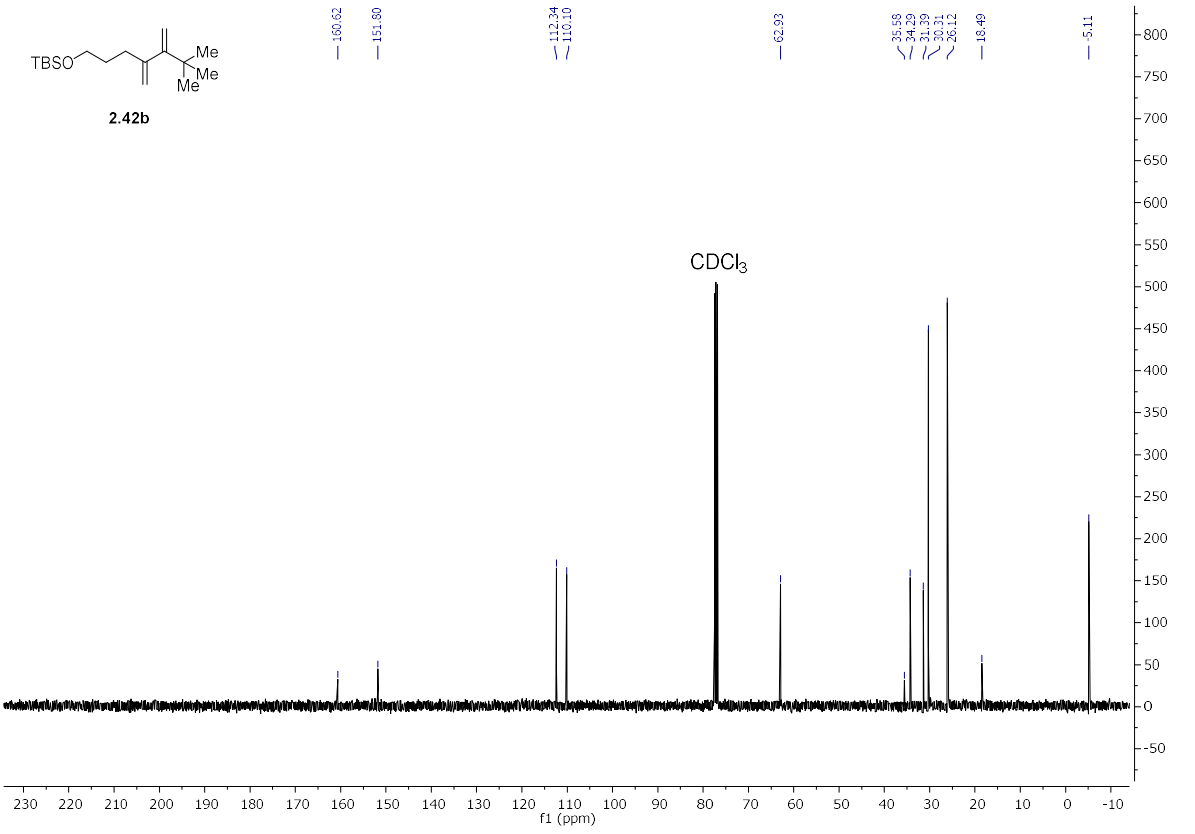
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43a**



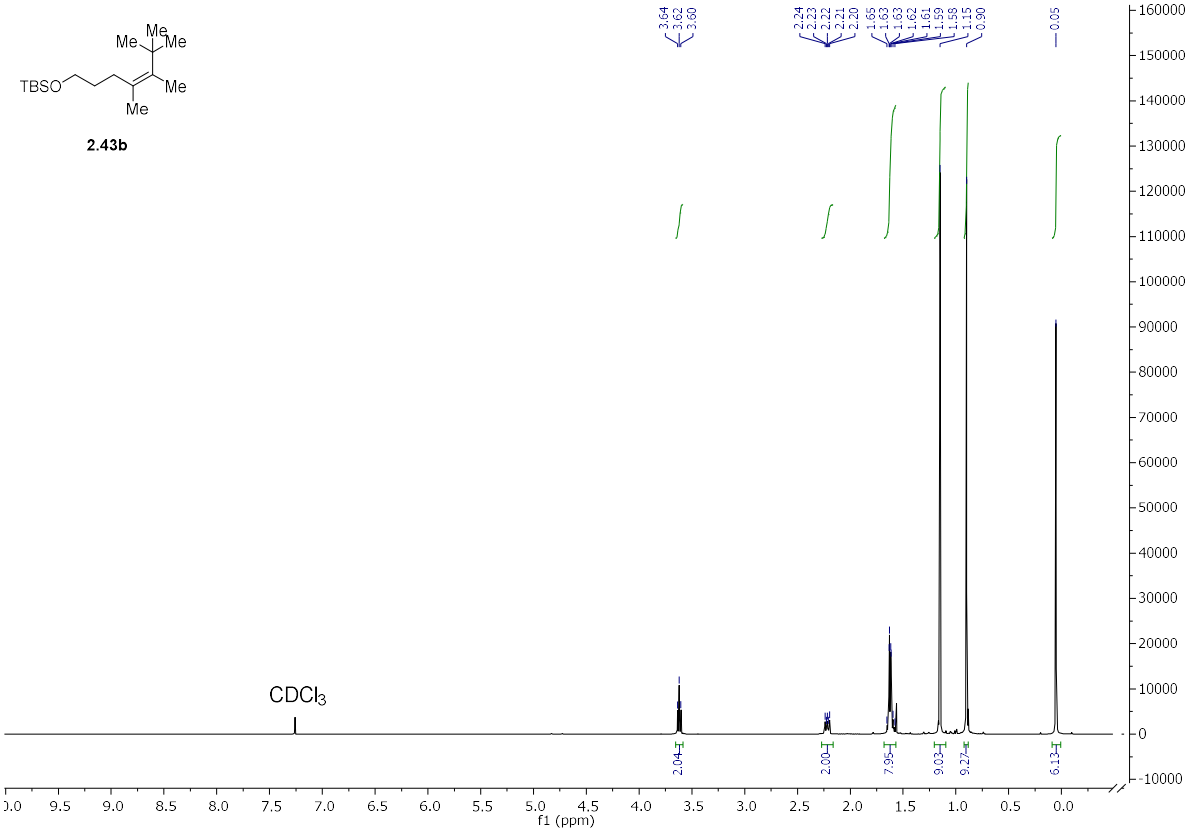
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42b**



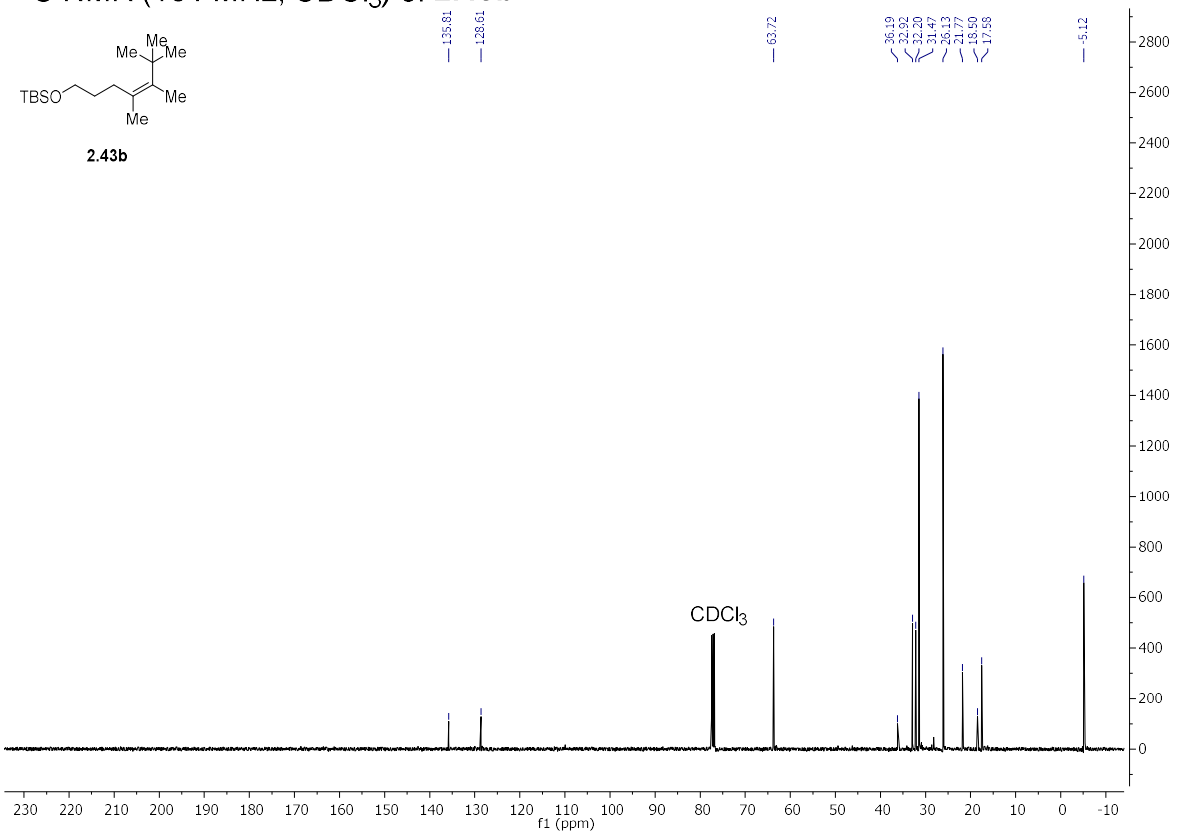
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42b**



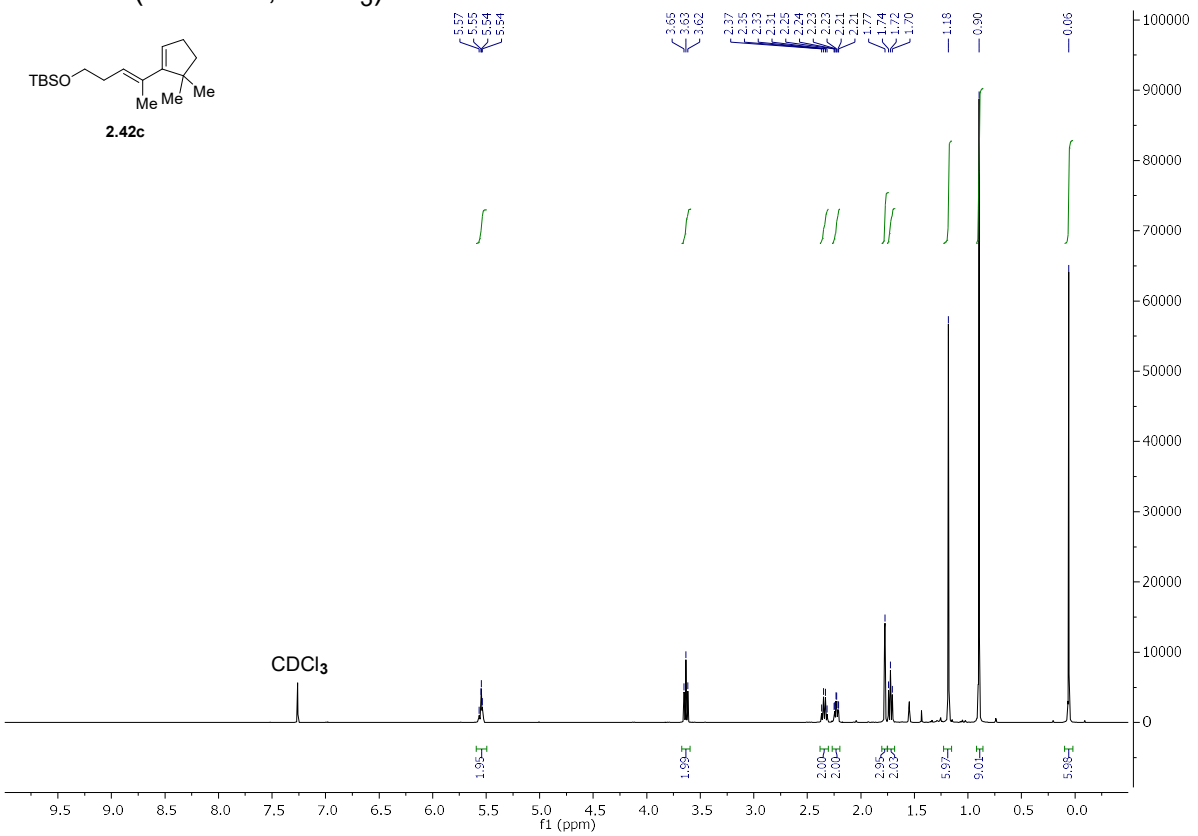
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43b**



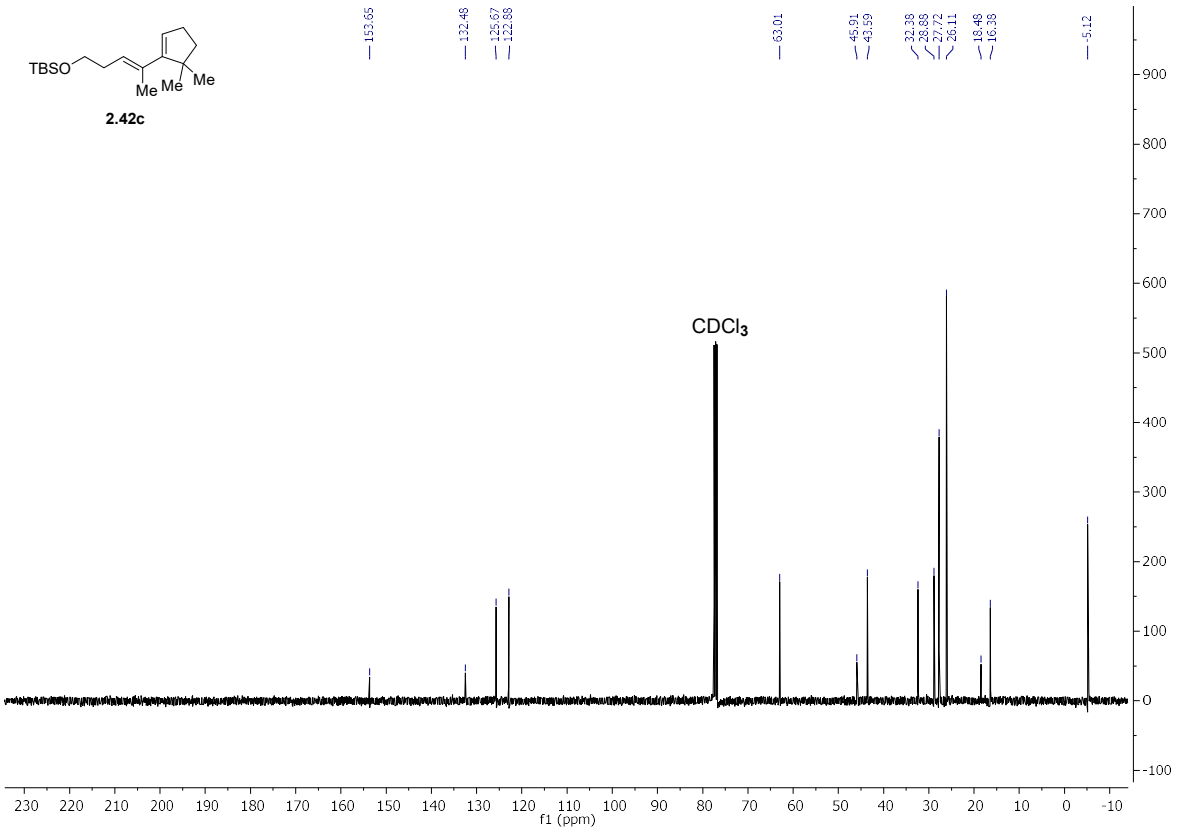
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43b**



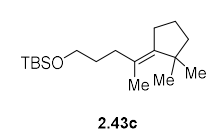
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42c**



^{13}C NMR (101 MHz, $CDCl_3$) of **2.42c**

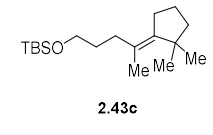


^{1}H NMR (400 MHz, $CDCl_3$) of **2.43c**



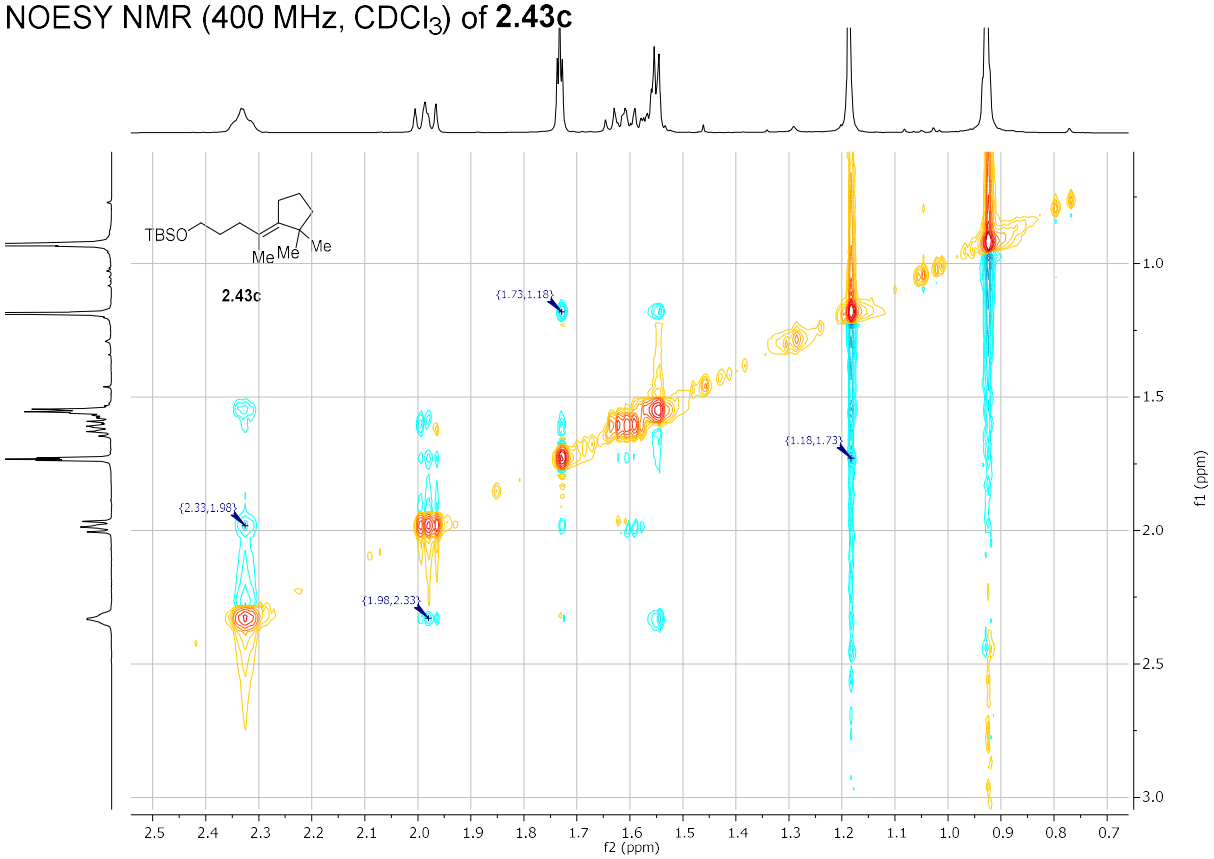
2.43c

^{13}C NMR (101 MHz, $CDCl_3$) of **2.43c**

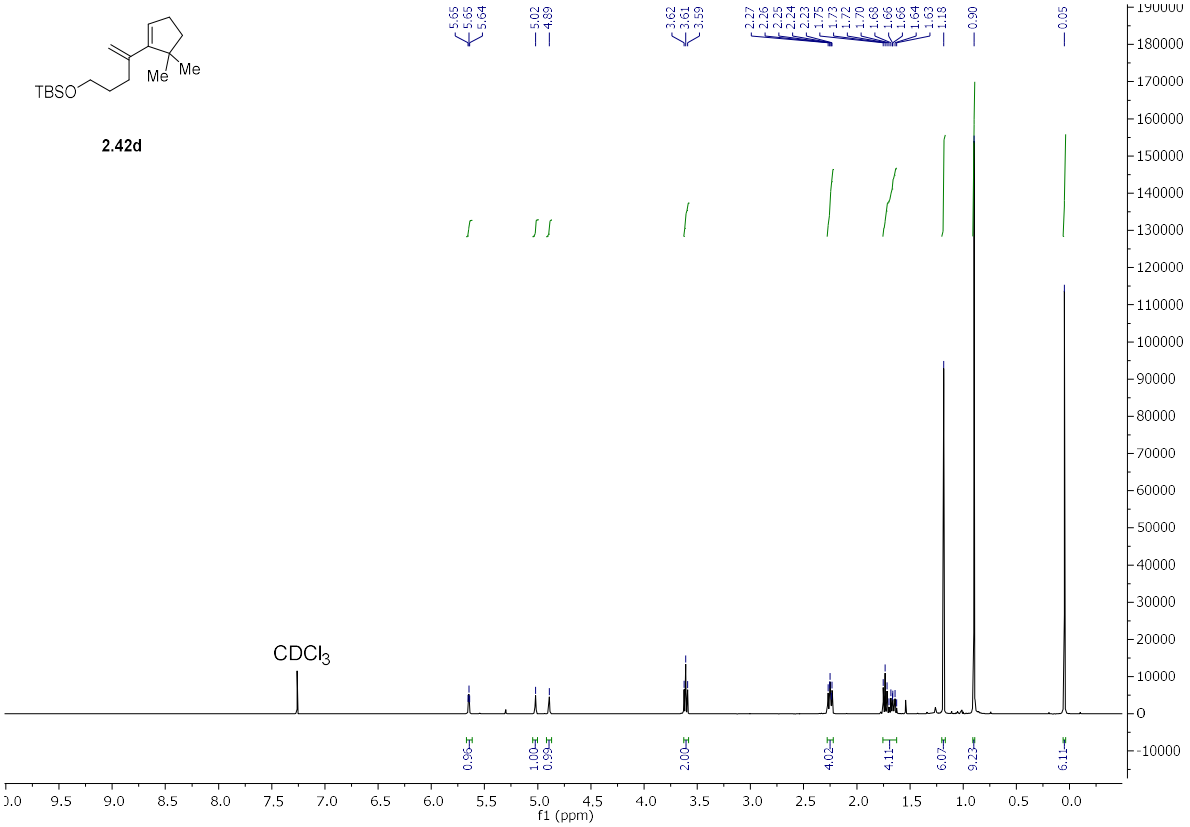


2.43c

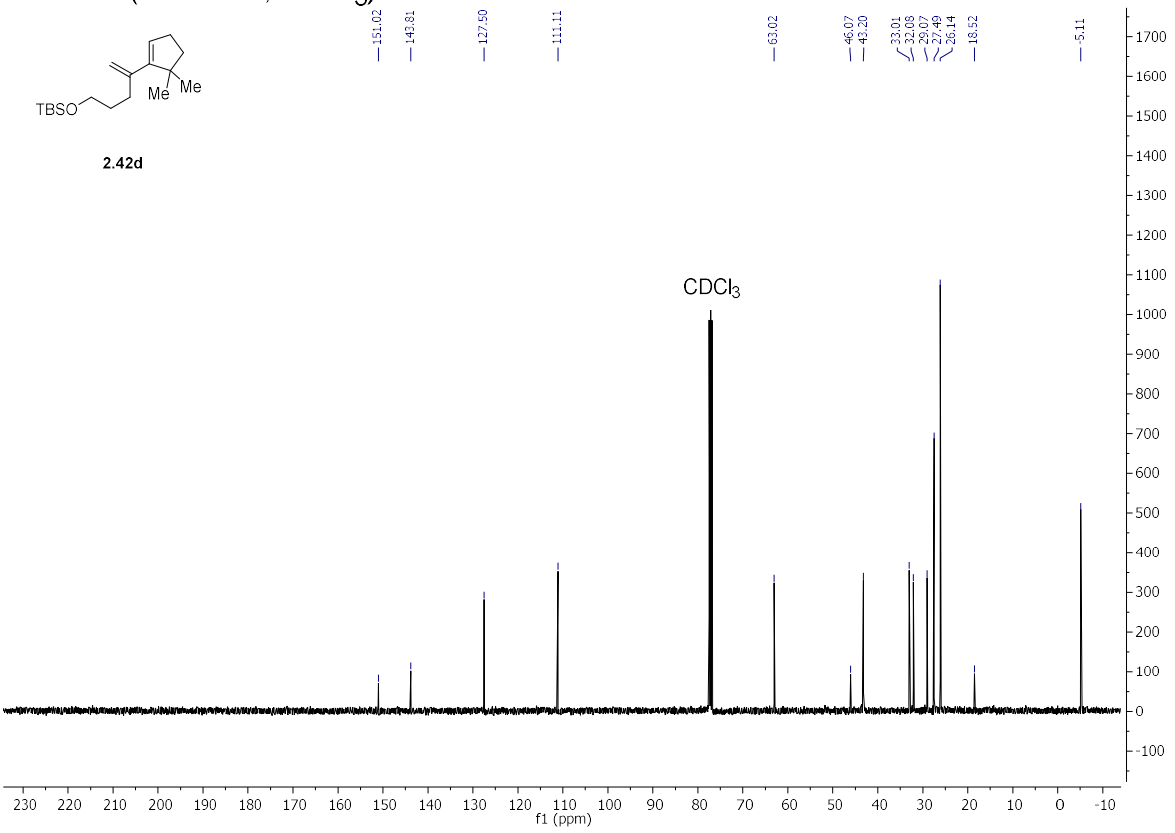
NOESY NMR (400 MHz, $CDCl_3$) of **2.43c**



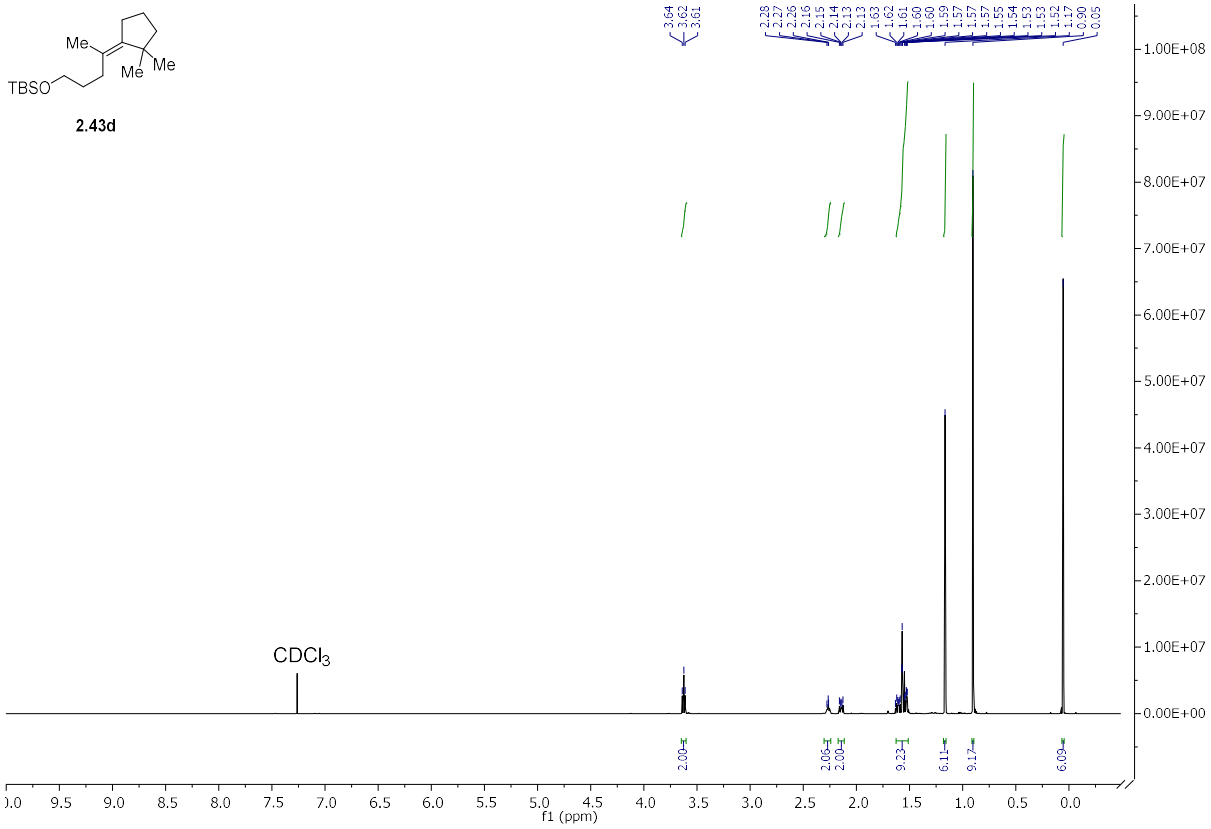
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42d**



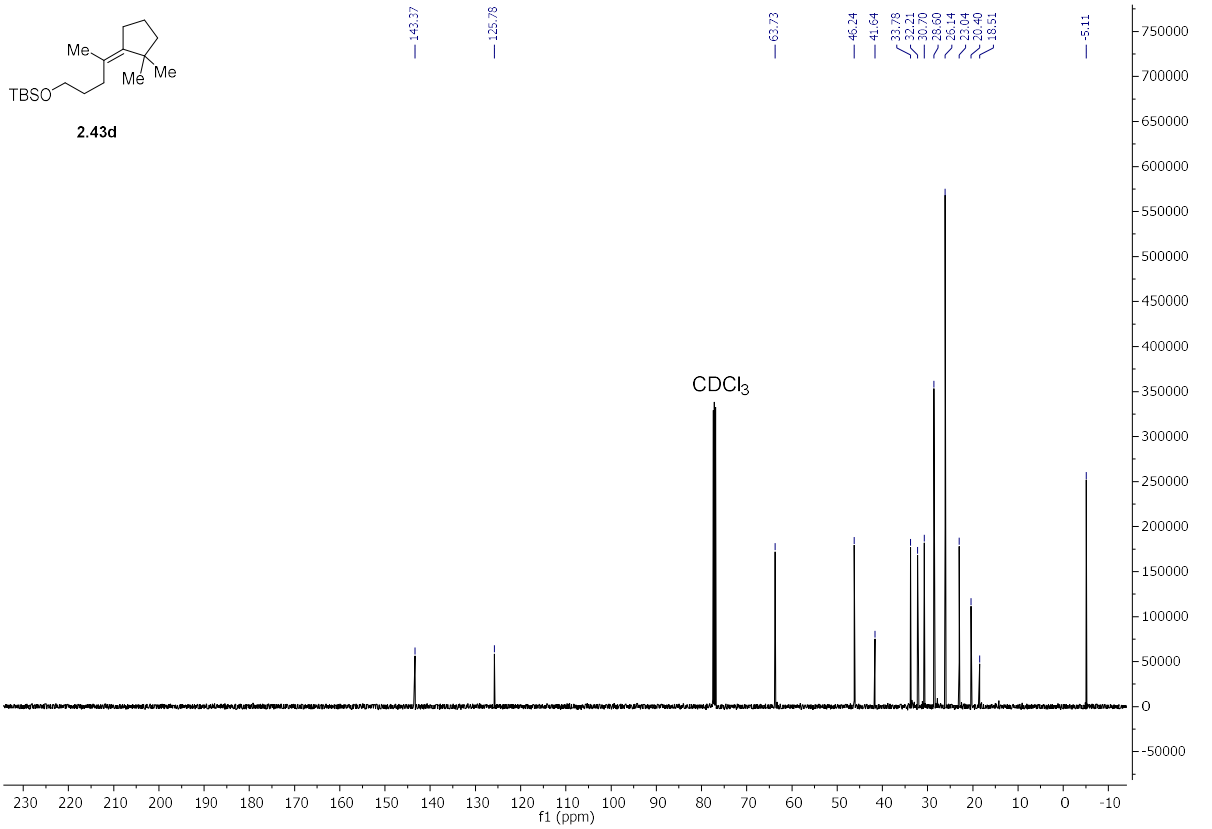
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42d**

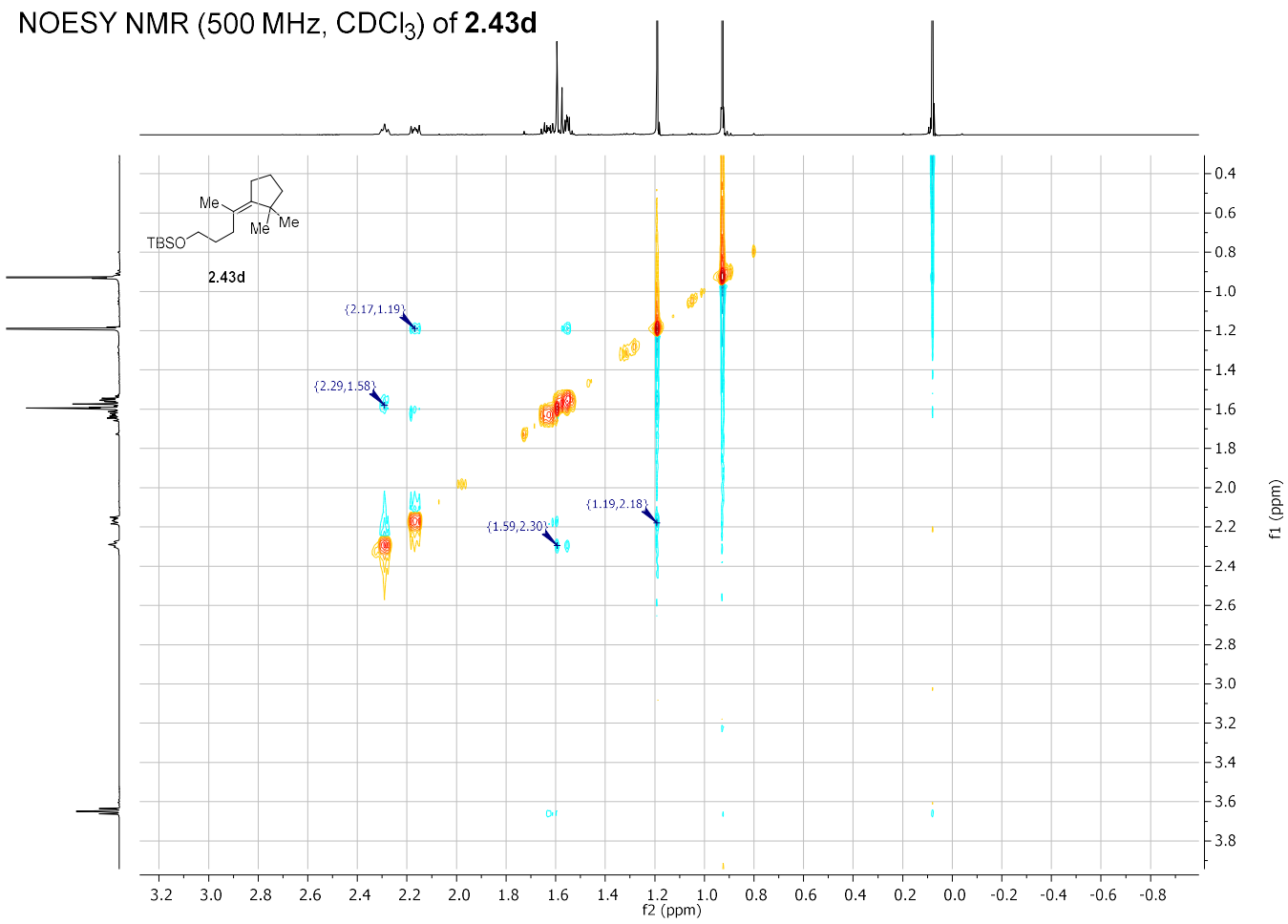


^{1}H NMR (500 MHz, $CDCl_3$) of **2.43d**

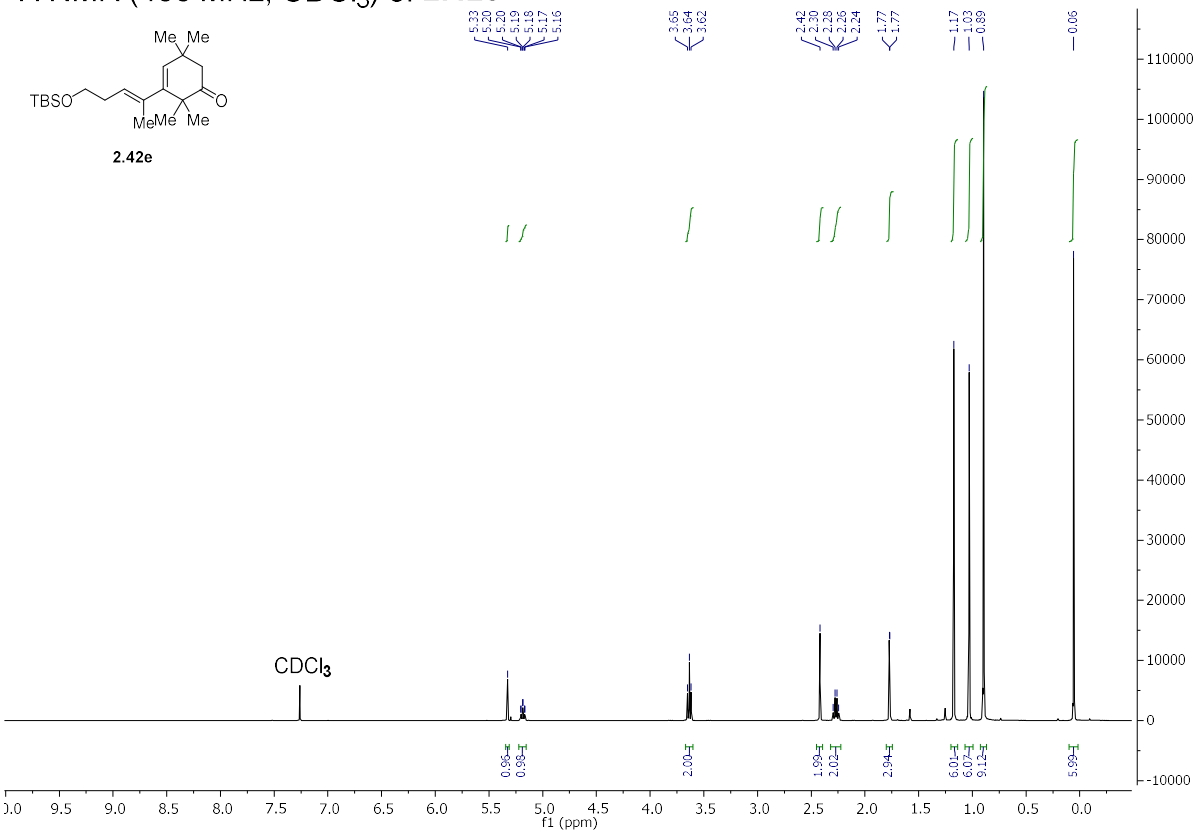


^{13}C NMR (126 MHz, $CDCl_3$) of **2.43d**

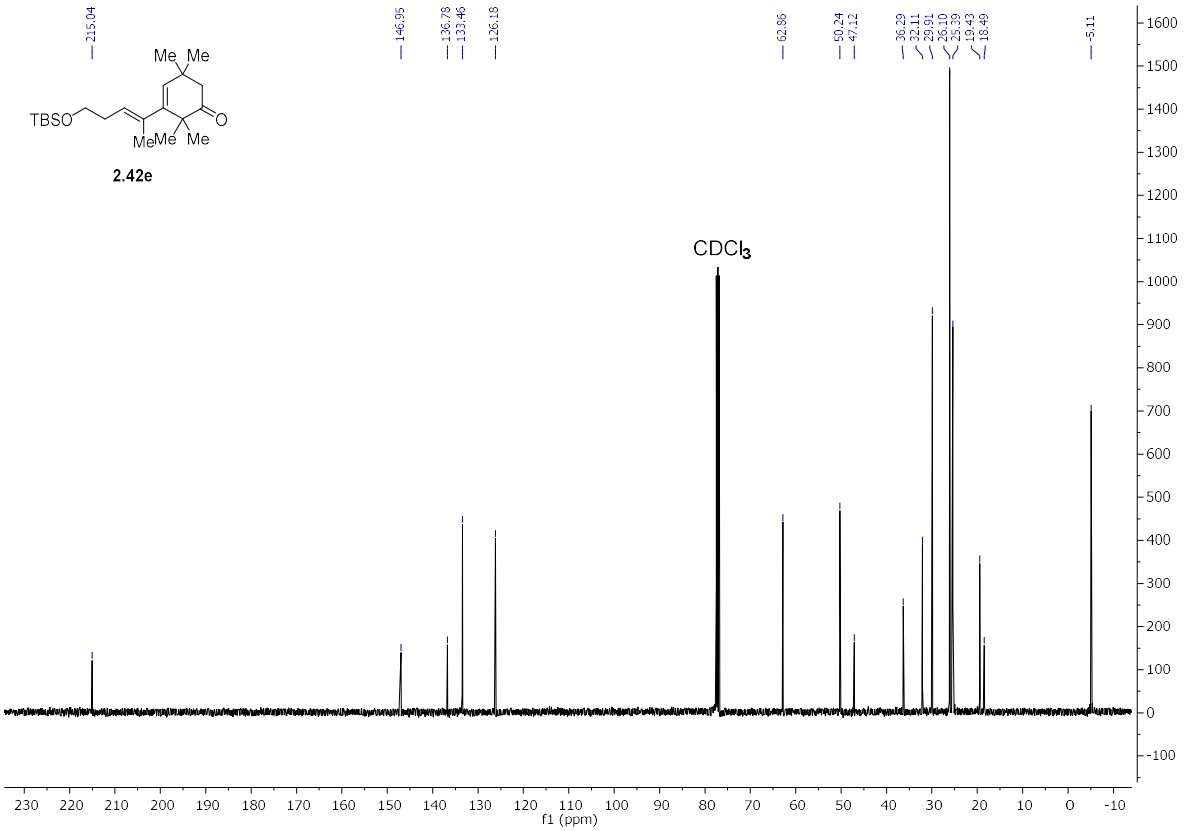



NOESY NMR (500 MHz, CDCl3) of 2.43d
Me
Me
Me
TBSO
2.43d
{2.17,1.19}
{2.29,1.58}
{1.19,2.18}
{1.59,2.30}
f2 (ppm)
f1 (ppm)

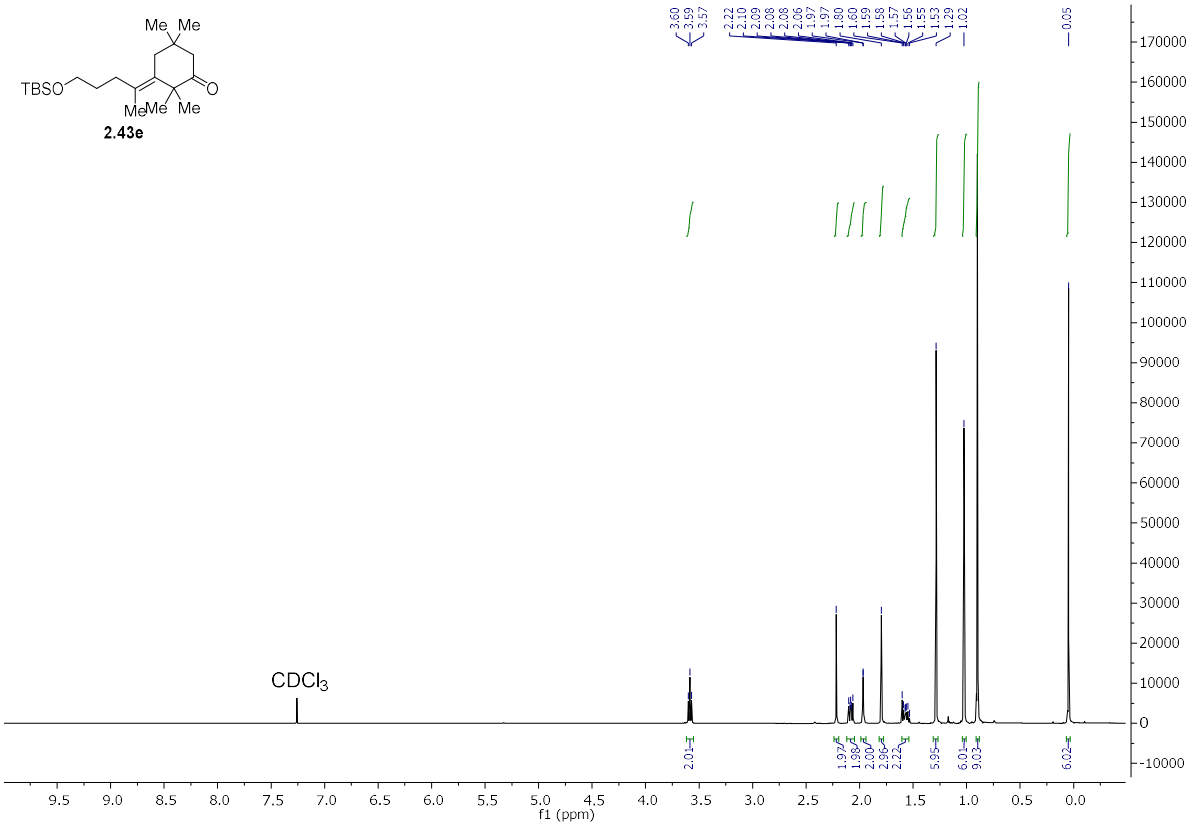
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42e**



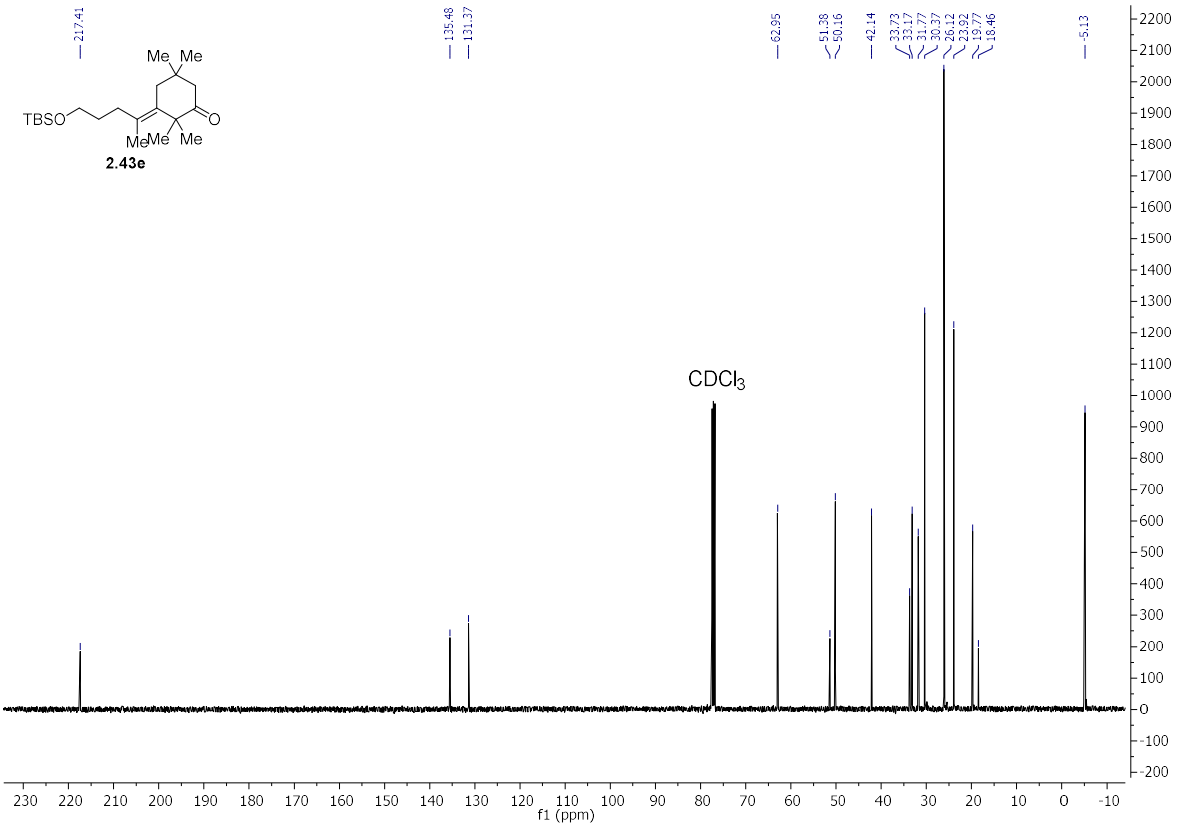
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42e**



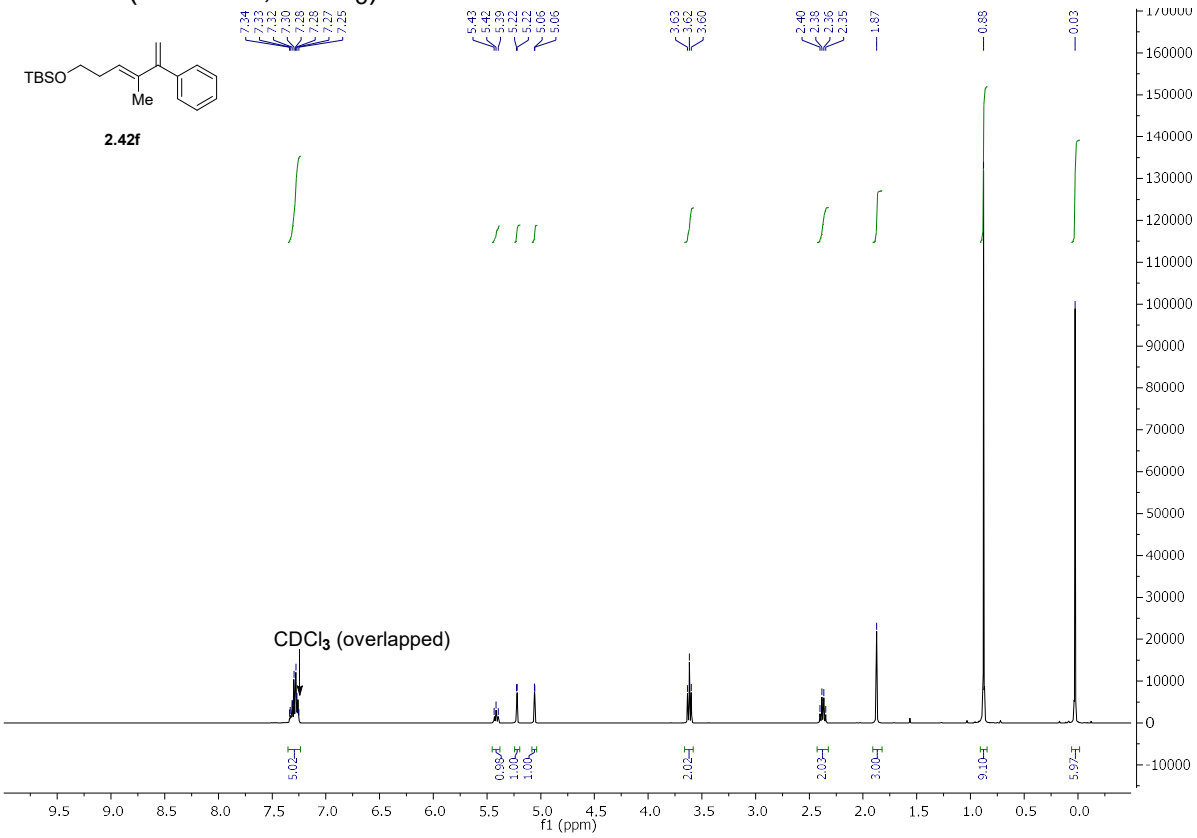
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43e**



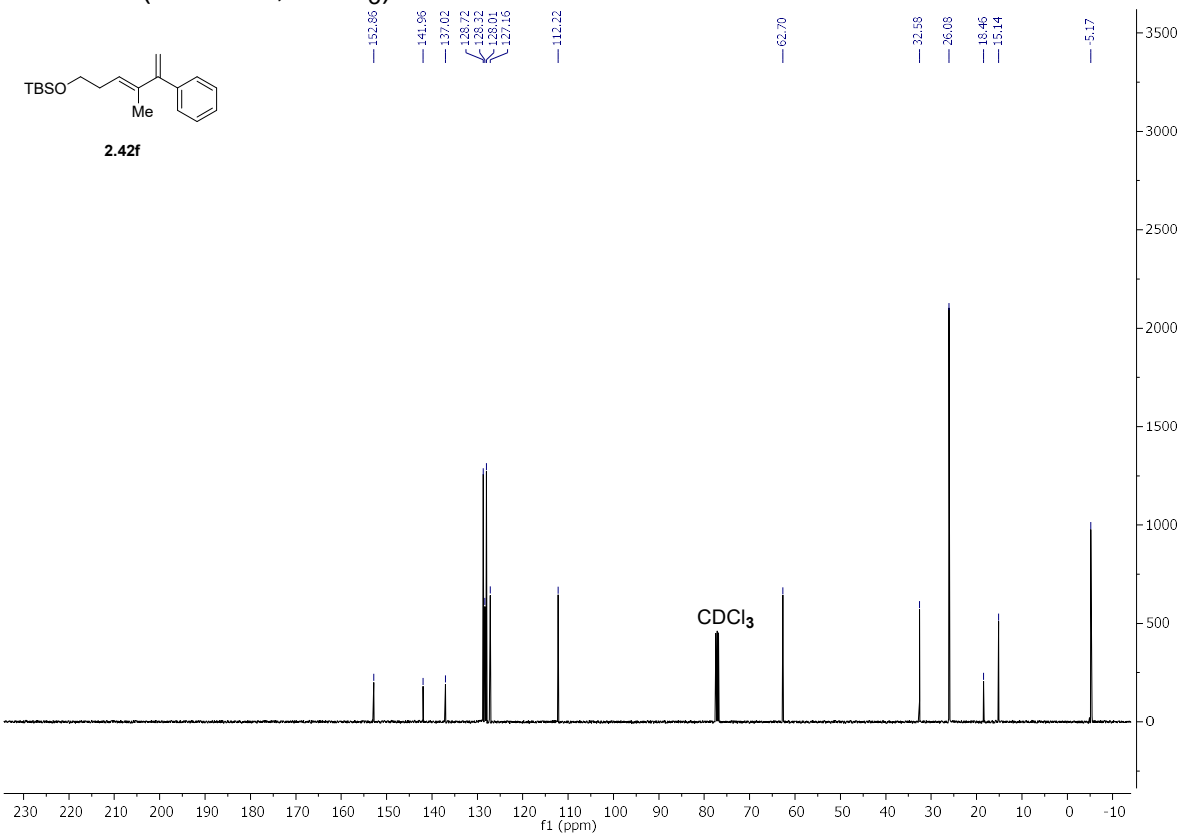
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43e**



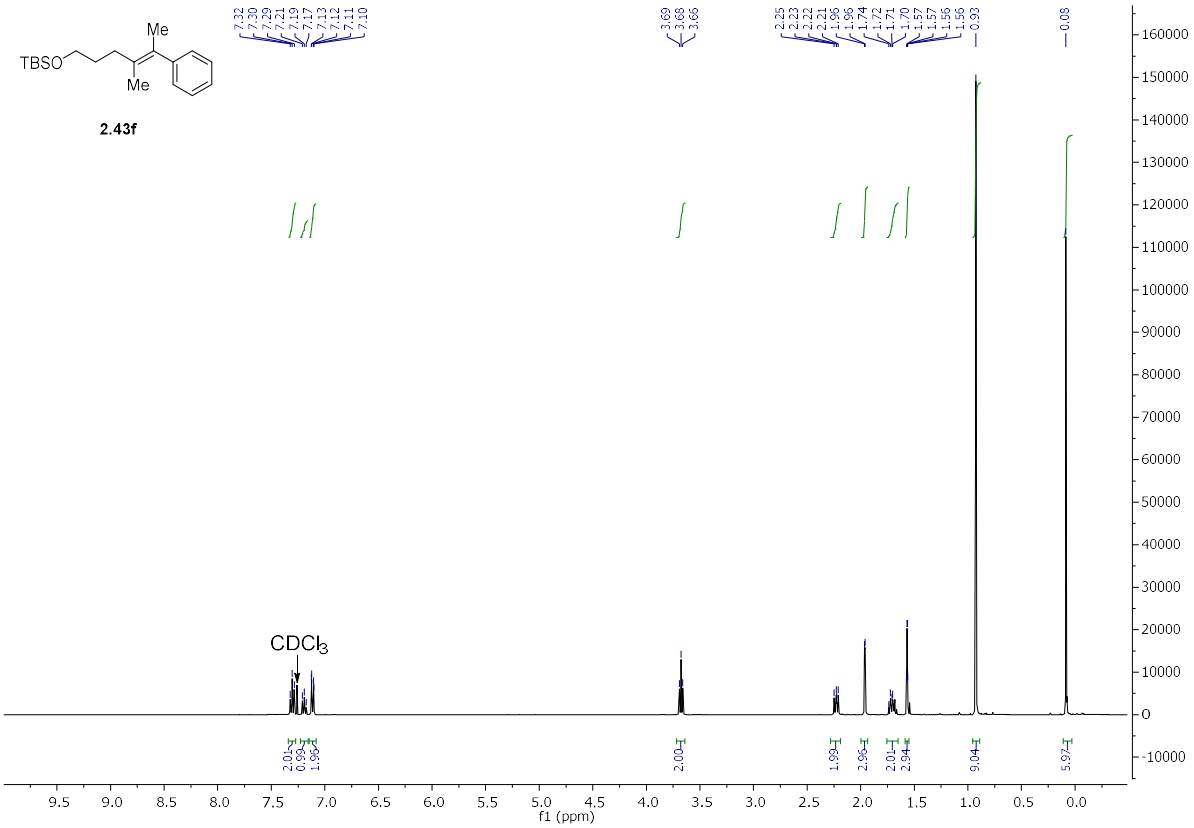
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42f**



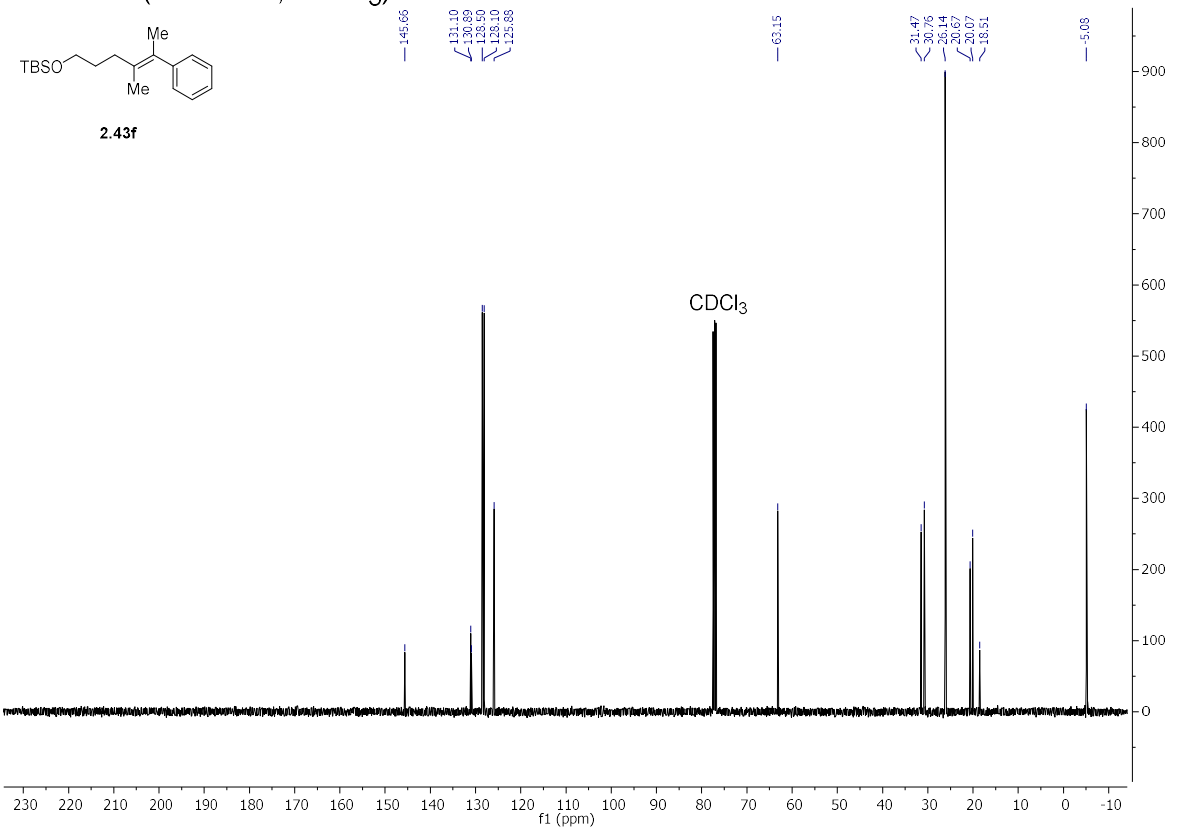
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42f**



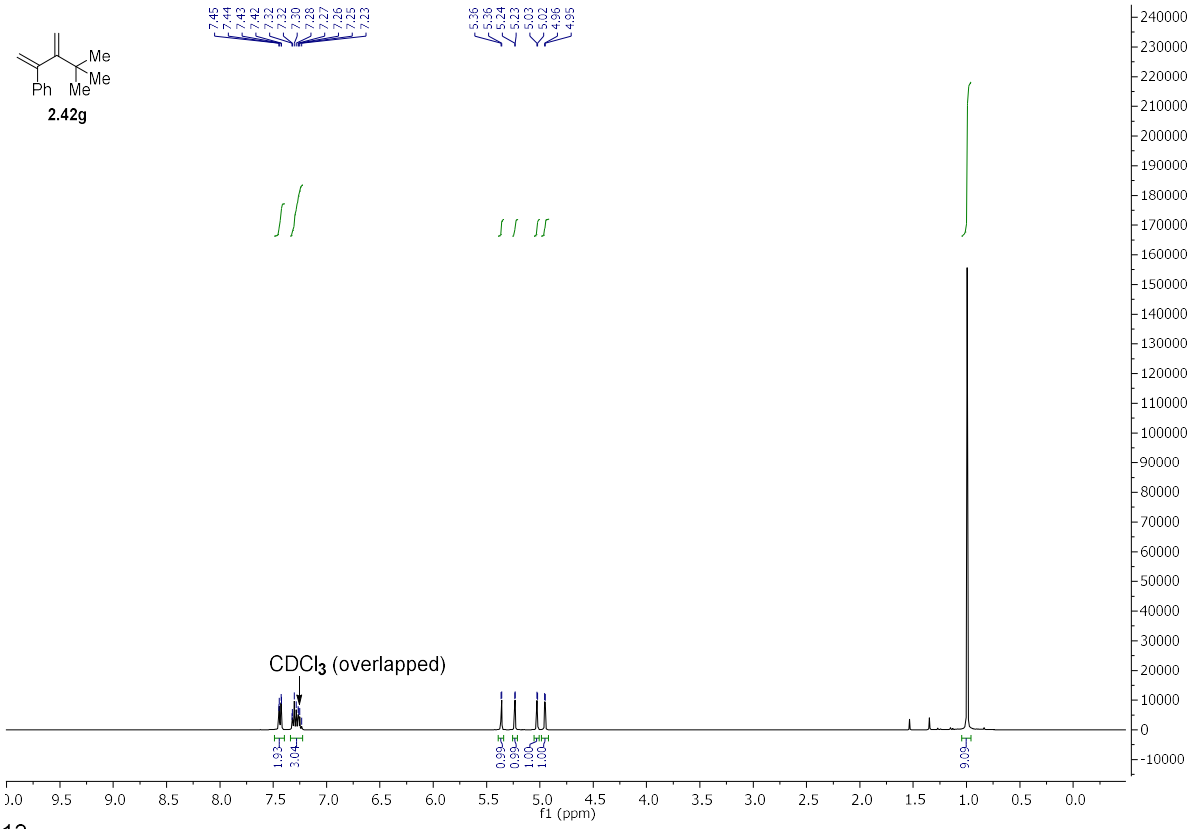
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43f**



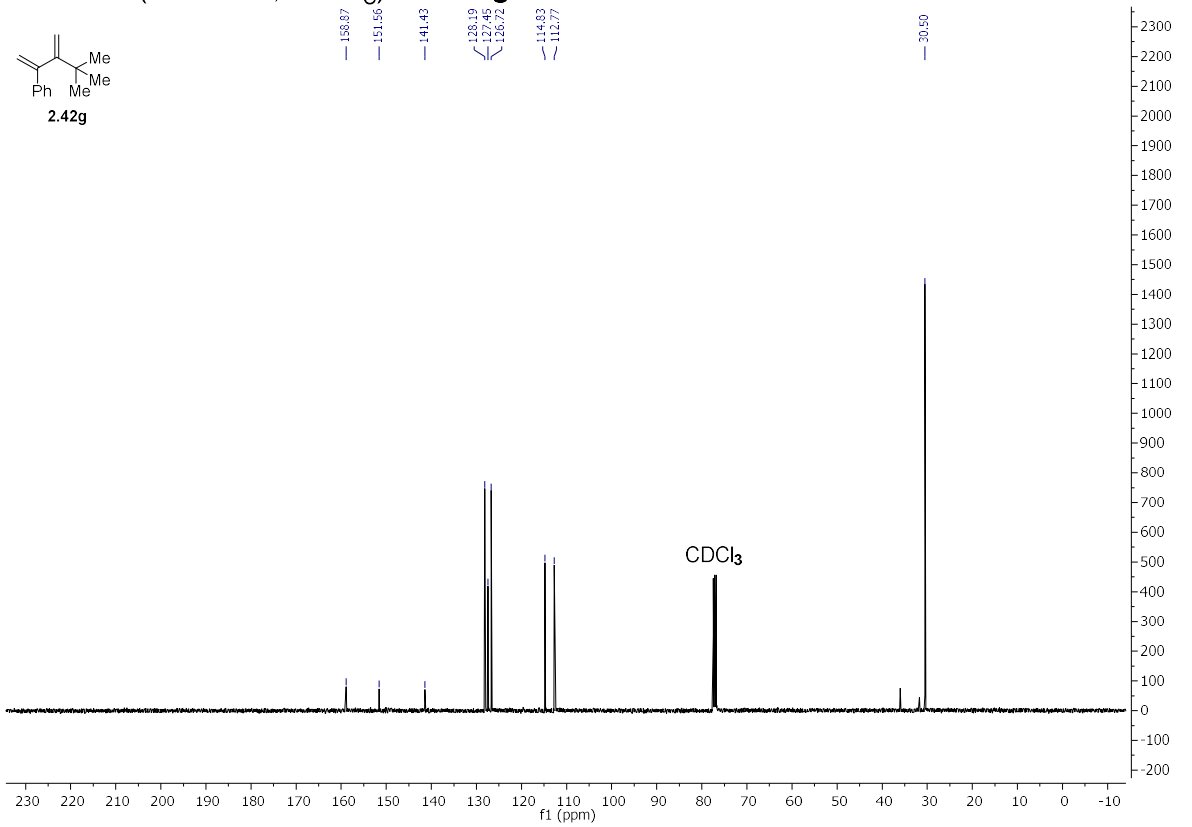
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43f**



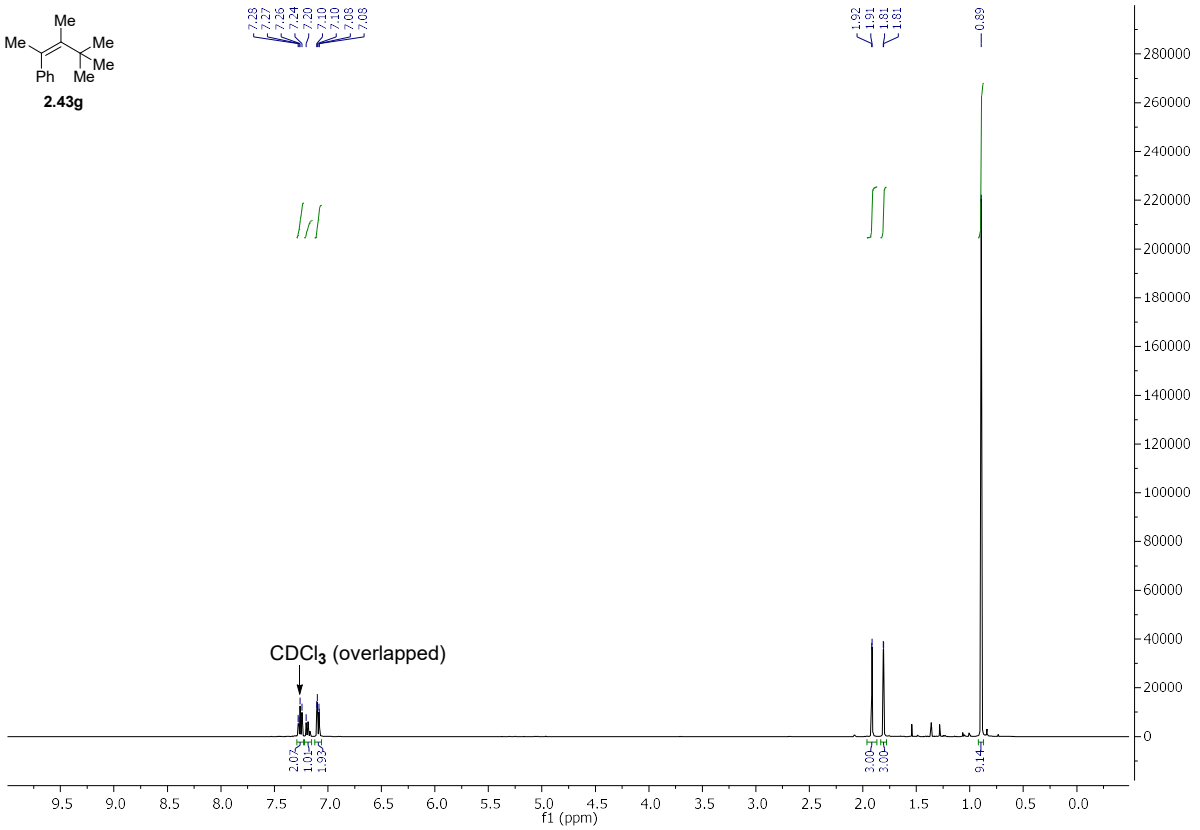
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42g**



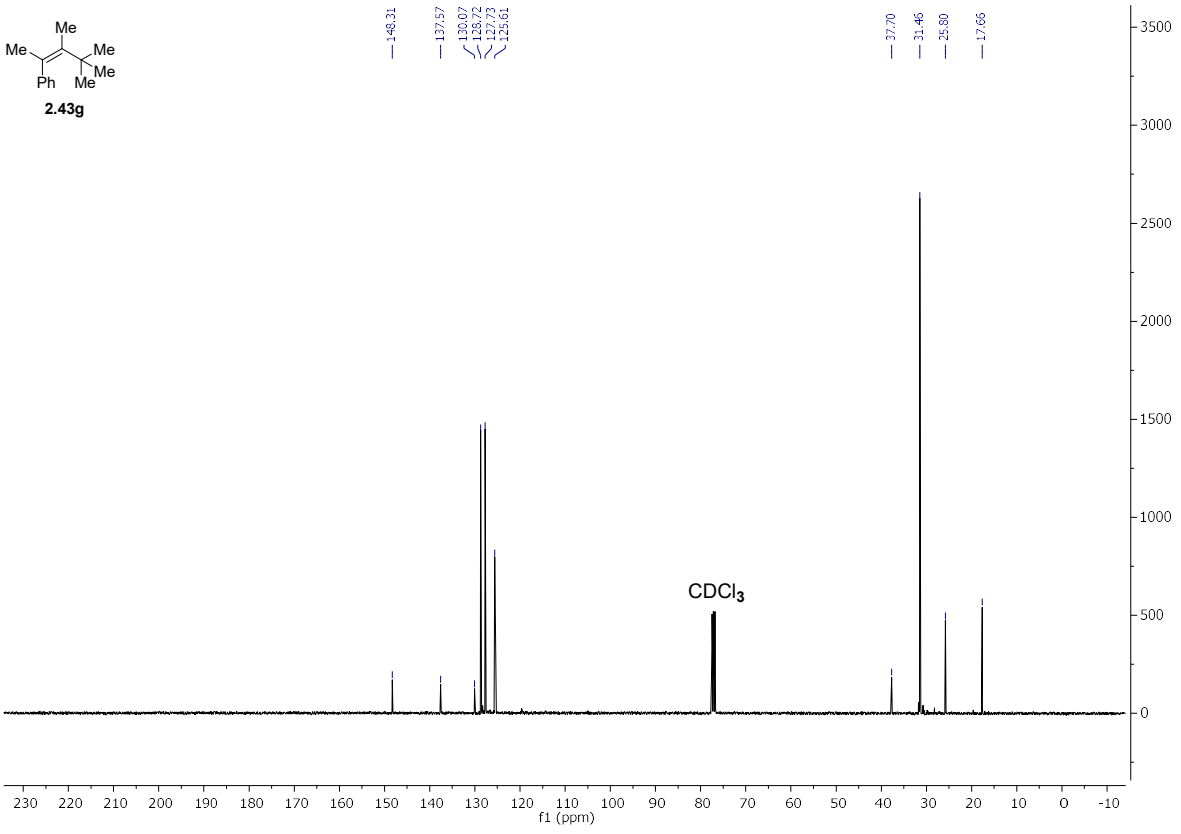
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42g**



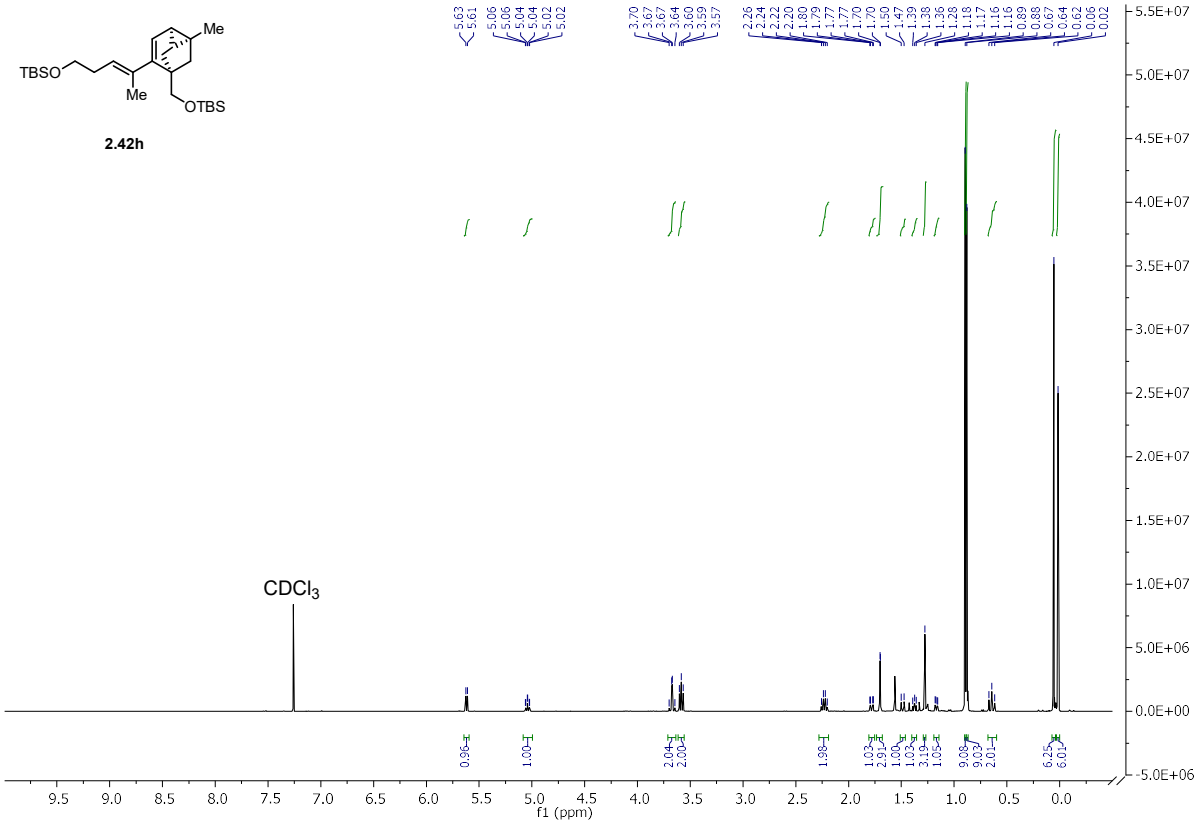
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43g**



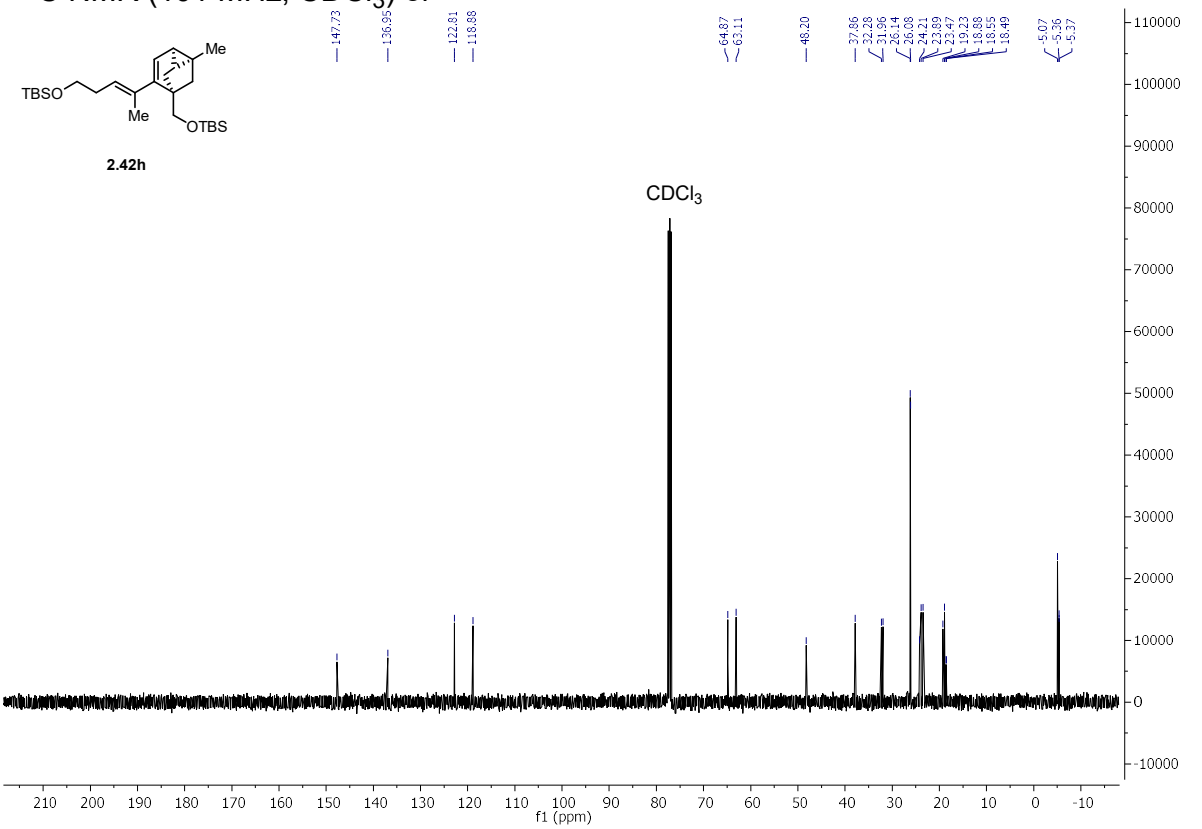
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43g**



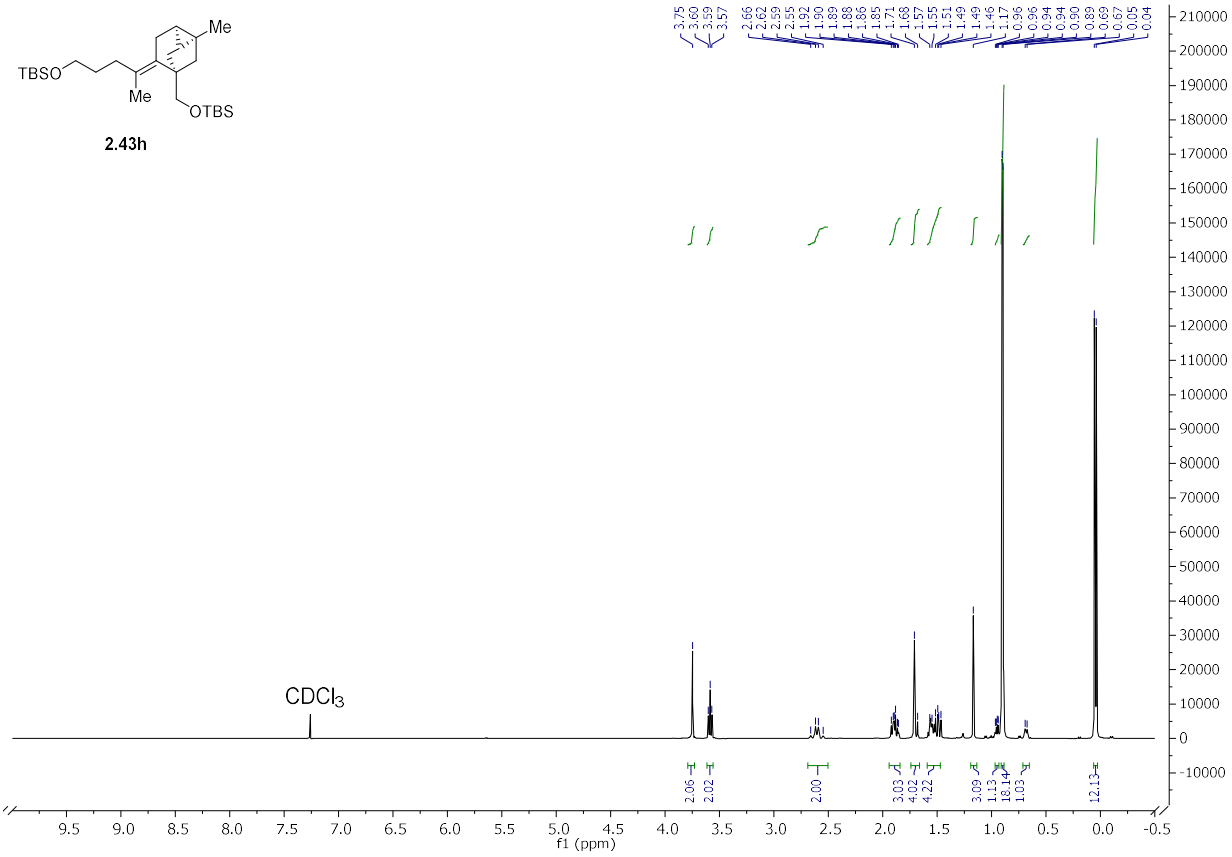
^{1}H NMR (400 MHz, $CDCl_3$) of **2.42h**



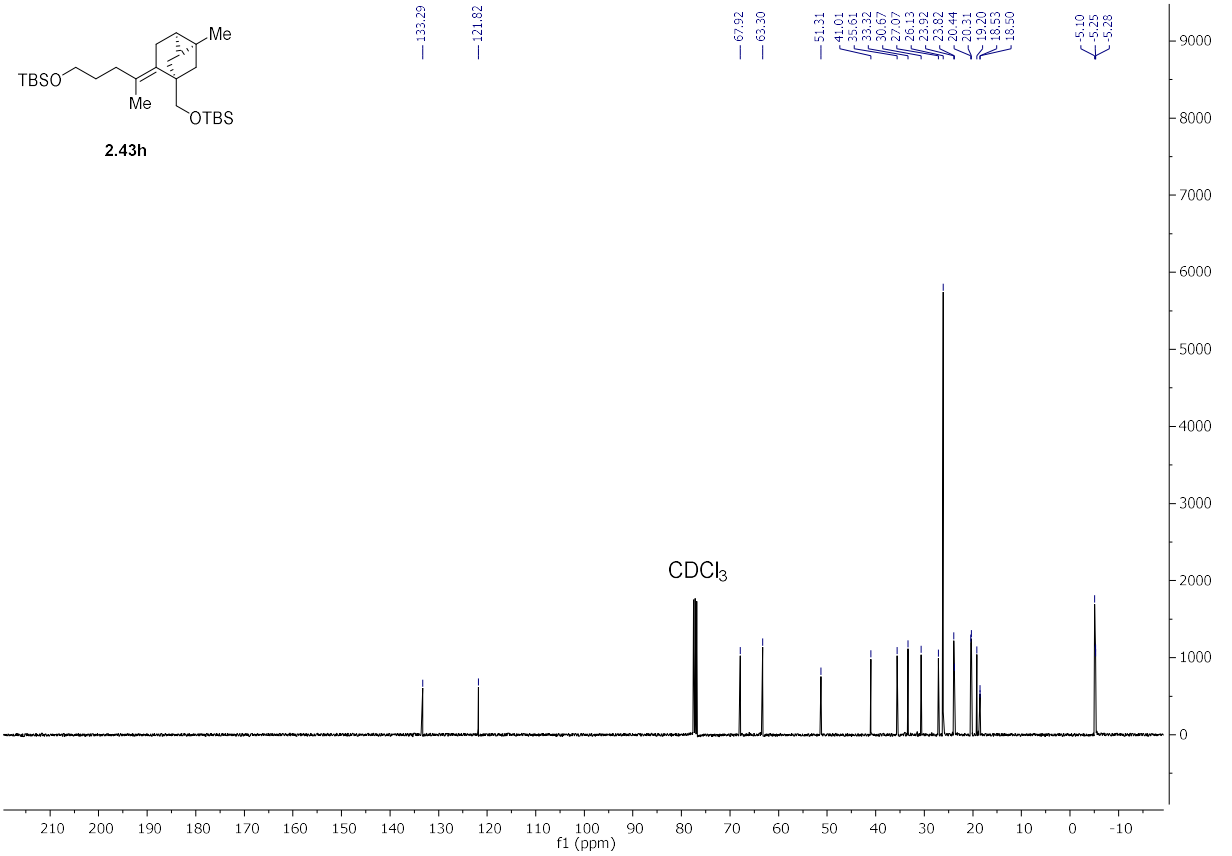
^{13}C NMR (101 MHz, $CDCl_3$) of **2.42h**



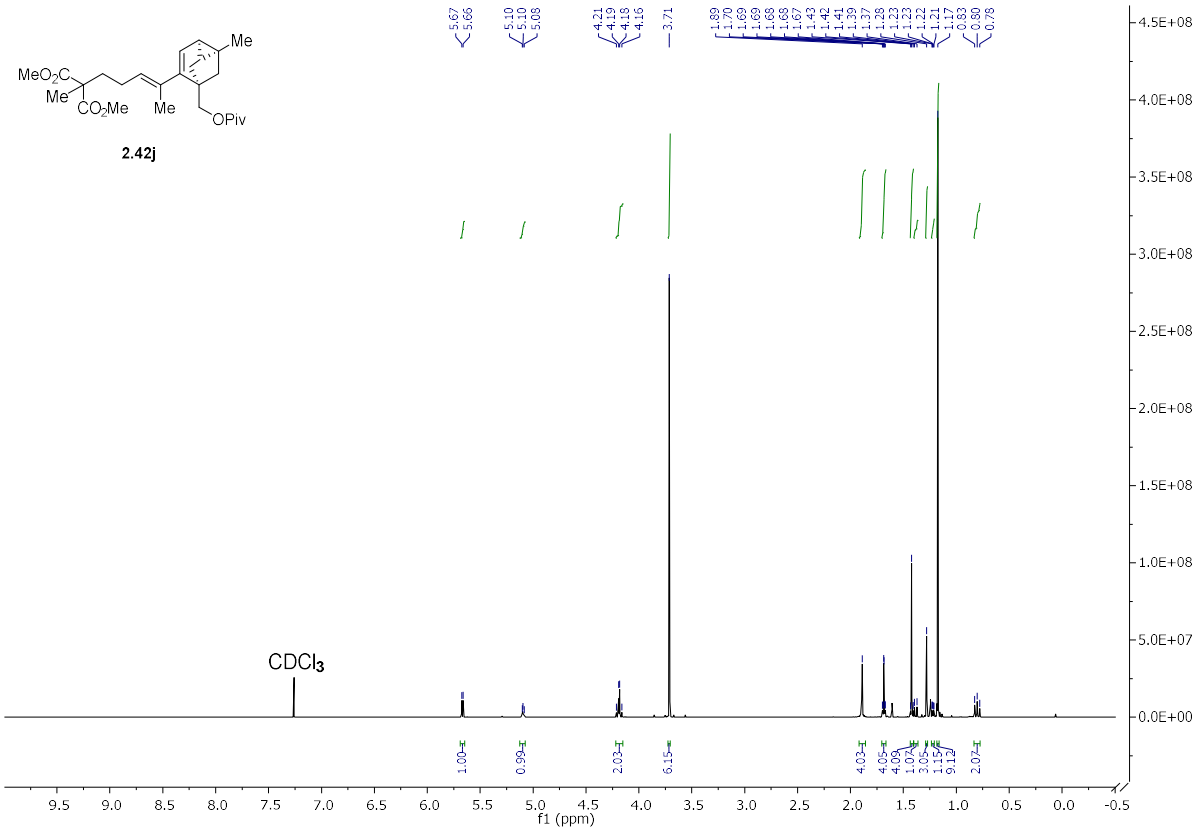
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43h**



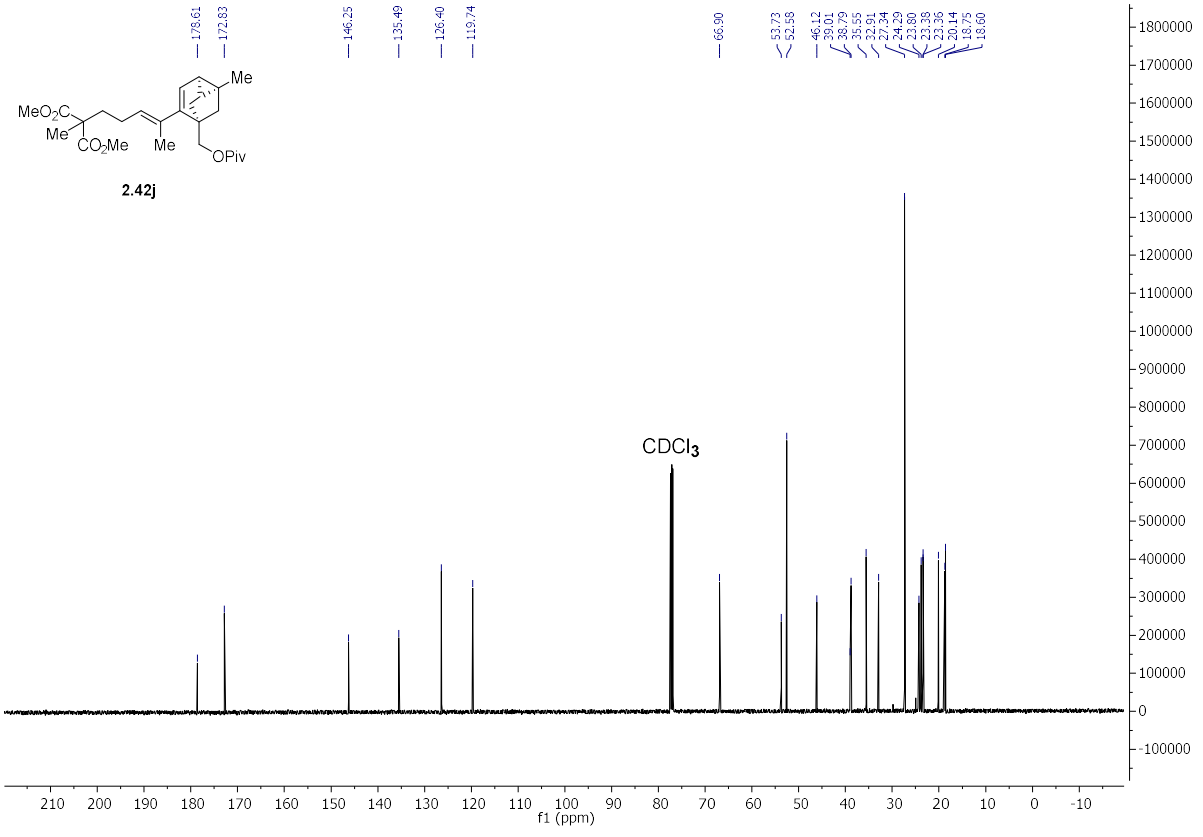
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43h**



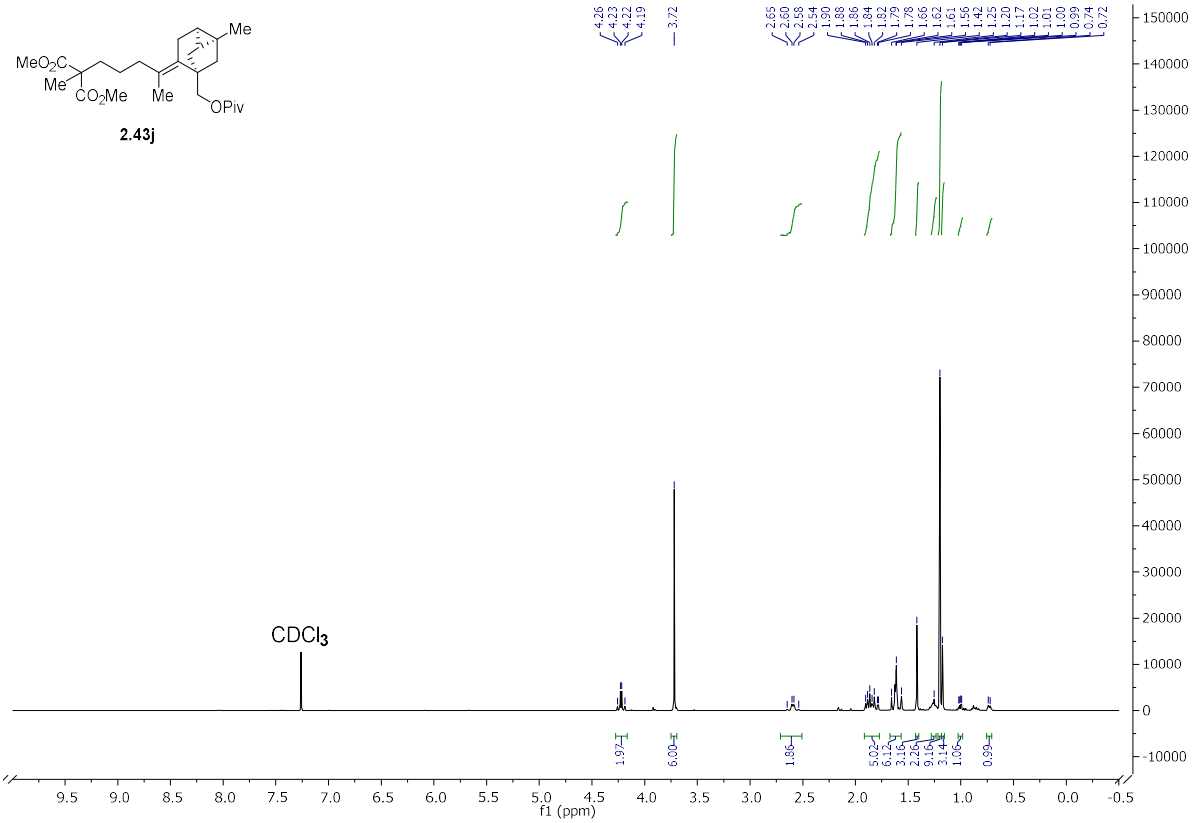
^{1}H NMR (500 MHz, $CDCl_3$) of **2.42j**



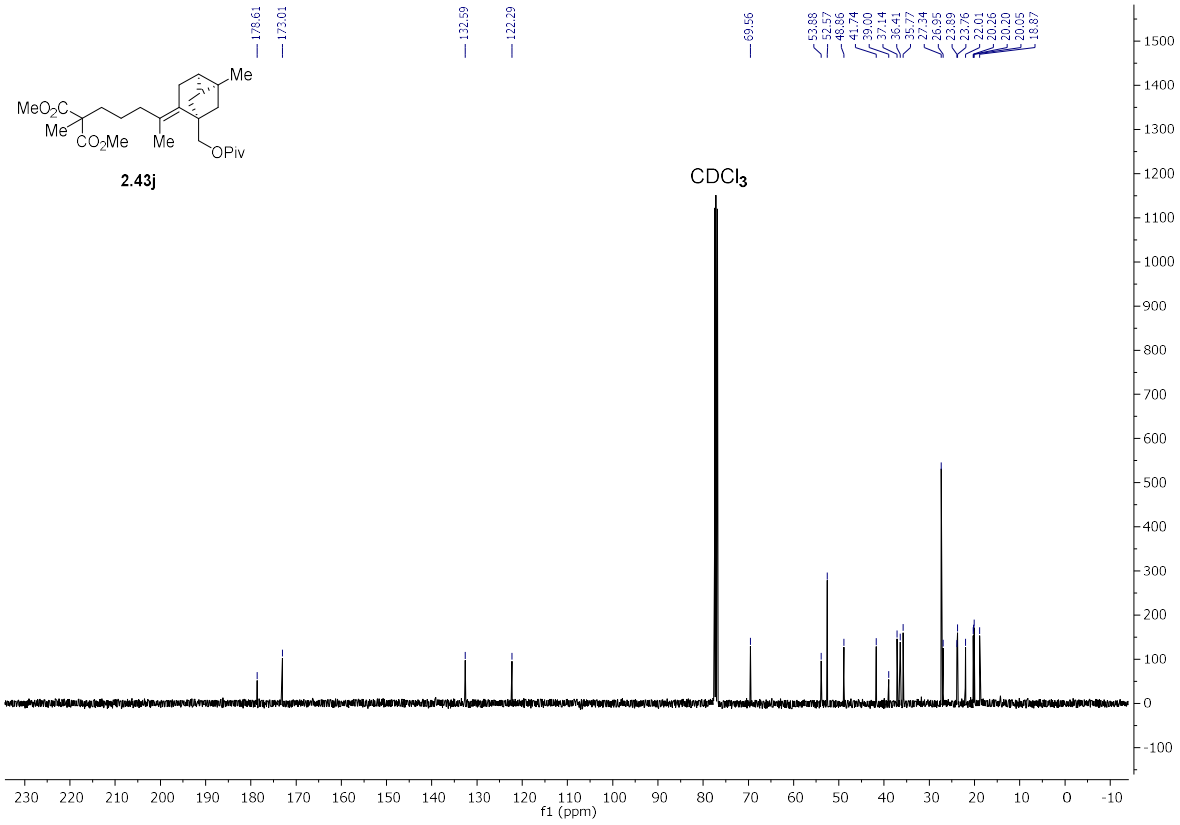
^{13}C NMR (126 MHz, $CDCl_3$) of **2.42j**



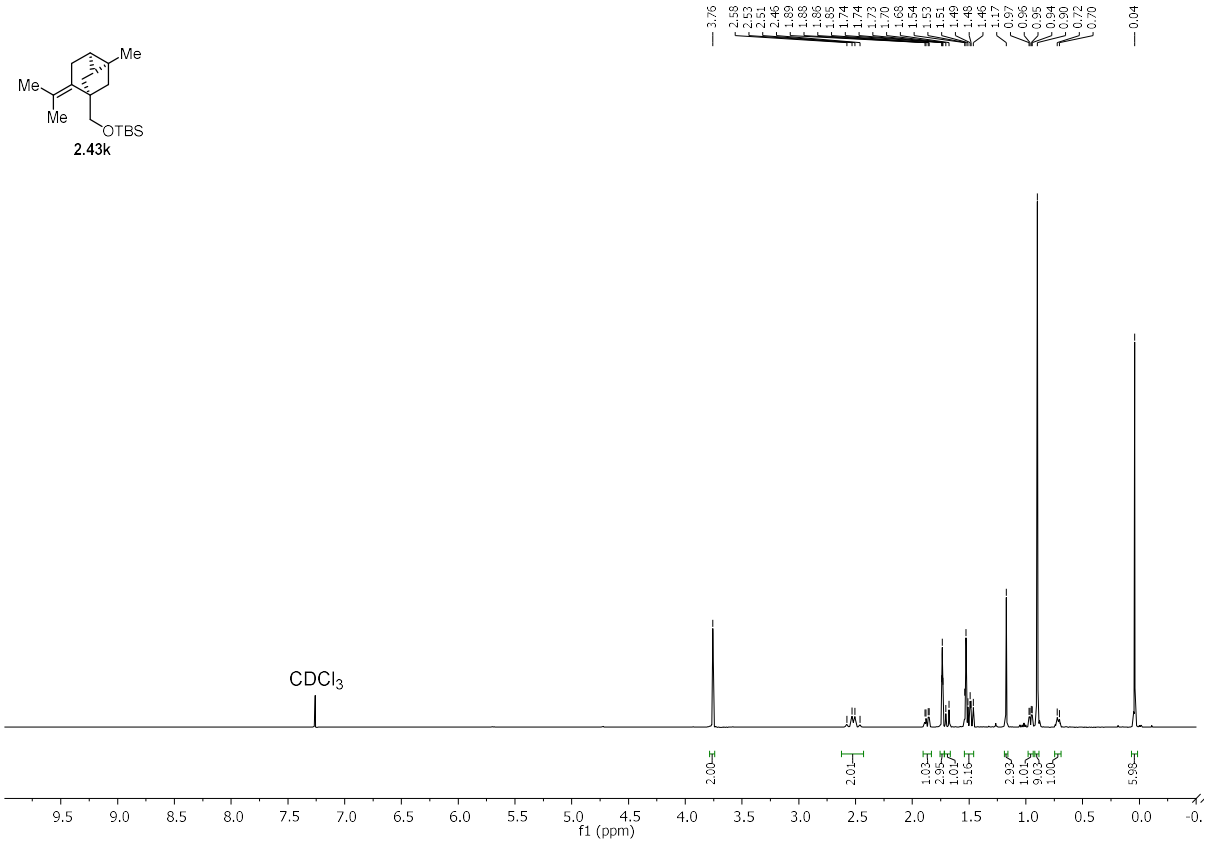
^{1}H NMR (400 MHz, $CDCl_3$) of **2.43j**



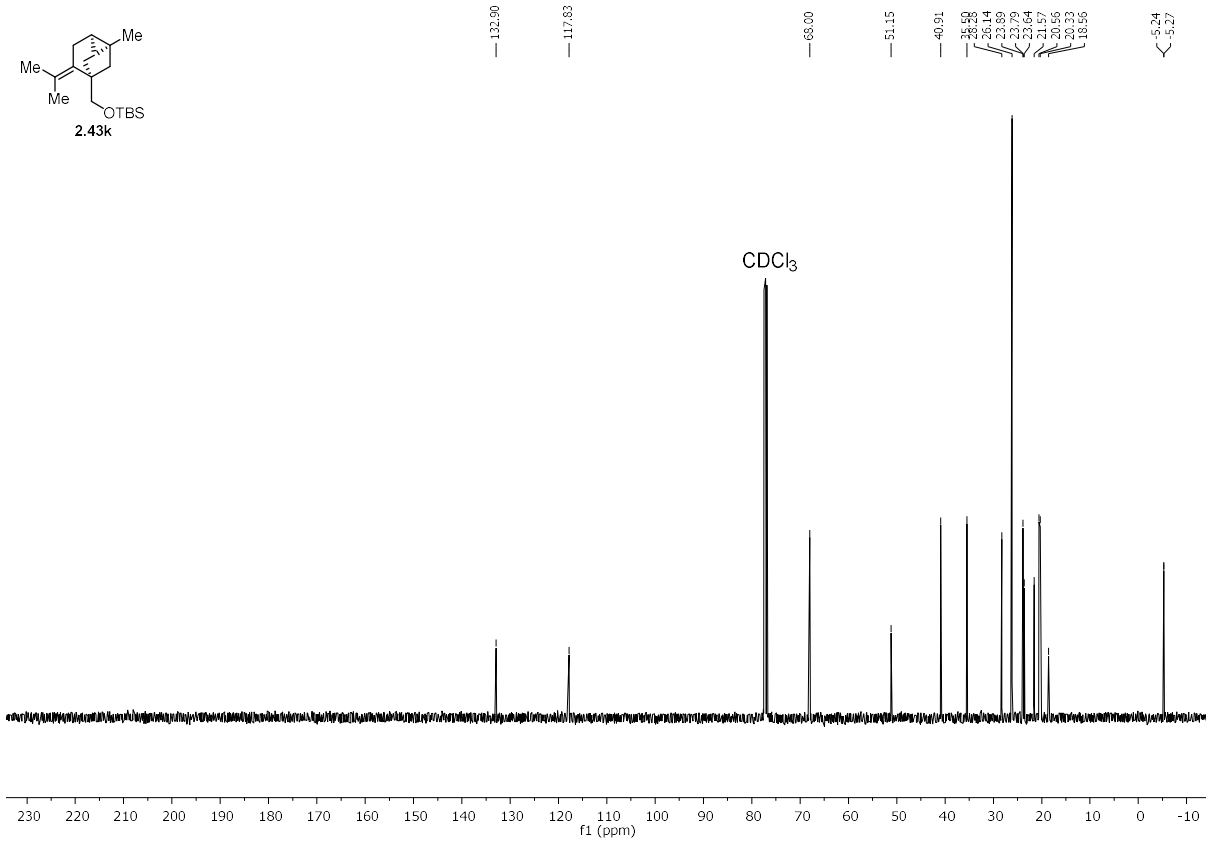
^{13}C NMR (101 MHz, $CDCl_3$) of **2.43j**



^{1}H NMR (400 MHz, $CDCl_3$) of **2.43k**

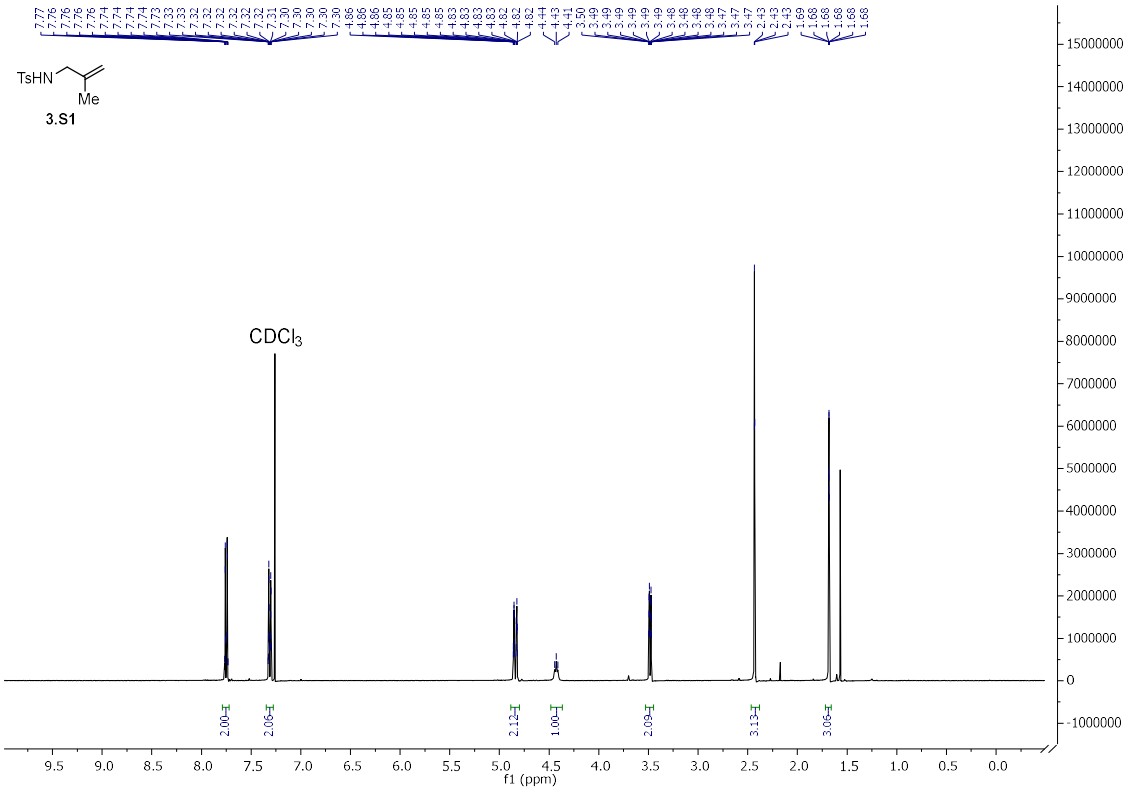


^{13}C NMR (101 MHz, $CDCl_3$) of **2.43k**

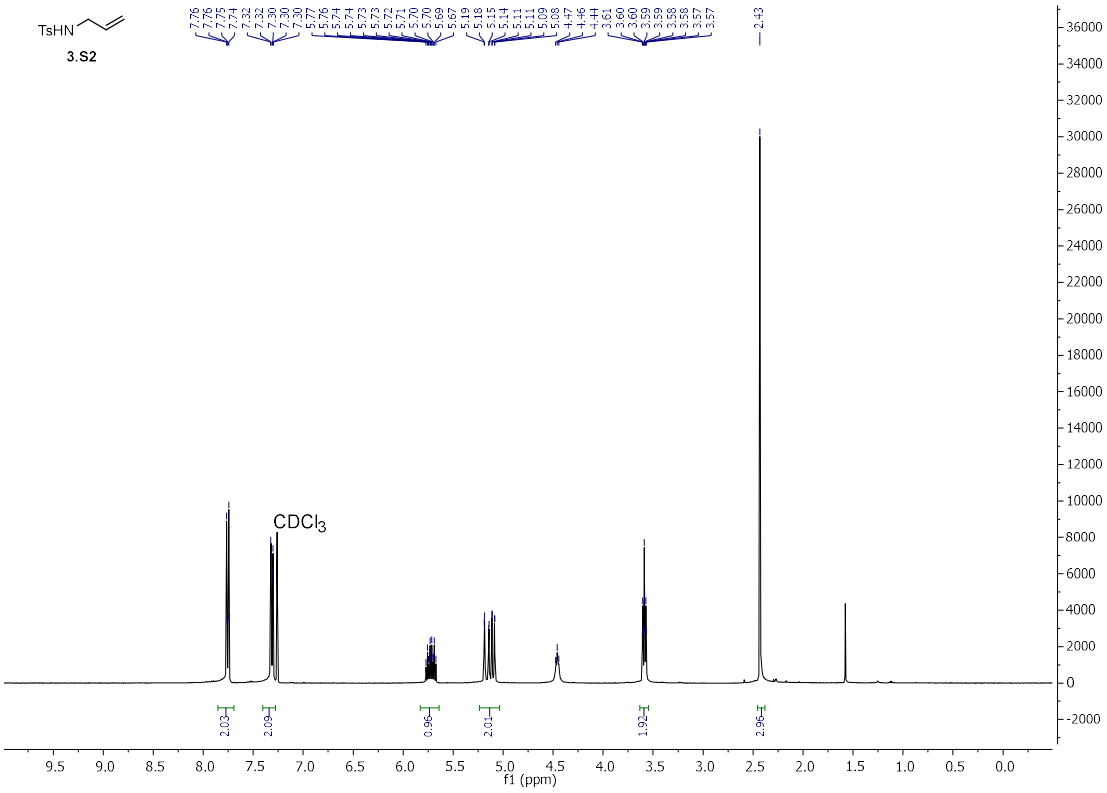


3. Synthesis of Primary Amines from Nitriles *via* a Radical Cyclization/Reduction Cascade

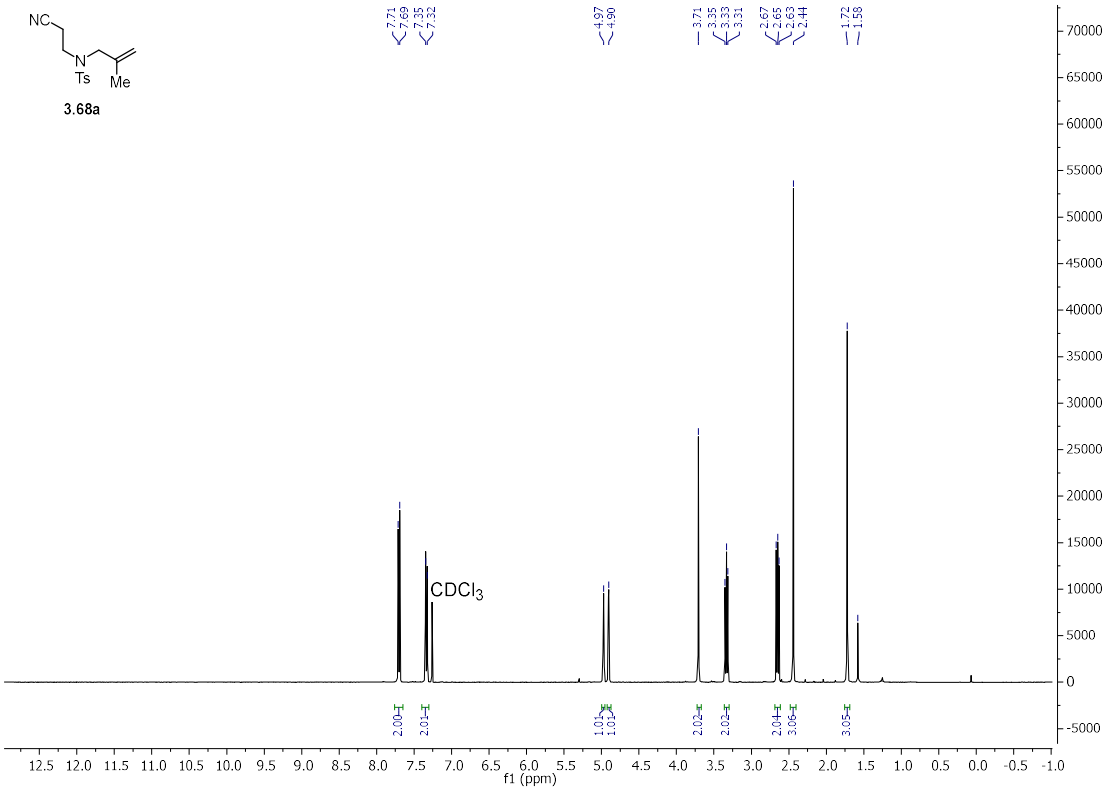
^{1}H NMR (400 MHz, $CDCl_3$) of **3.S1**



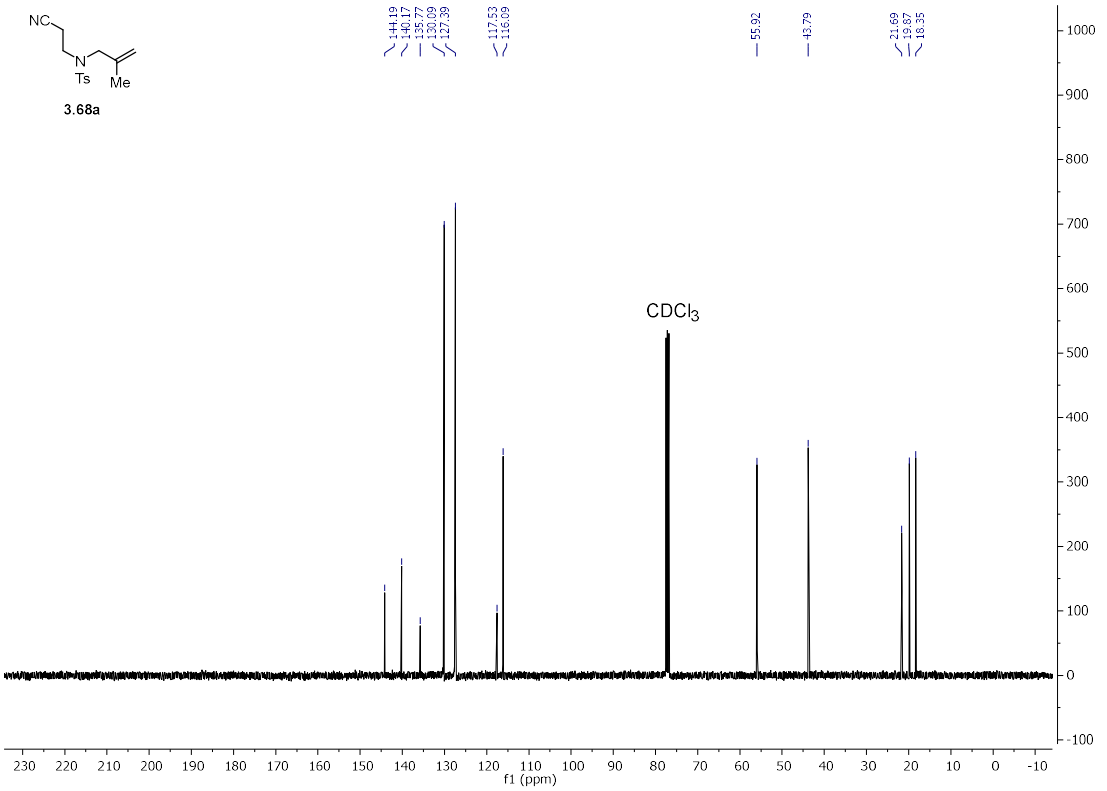
^{1}H NMR (400 MHz, $CDCl_3$) of **3.S2**



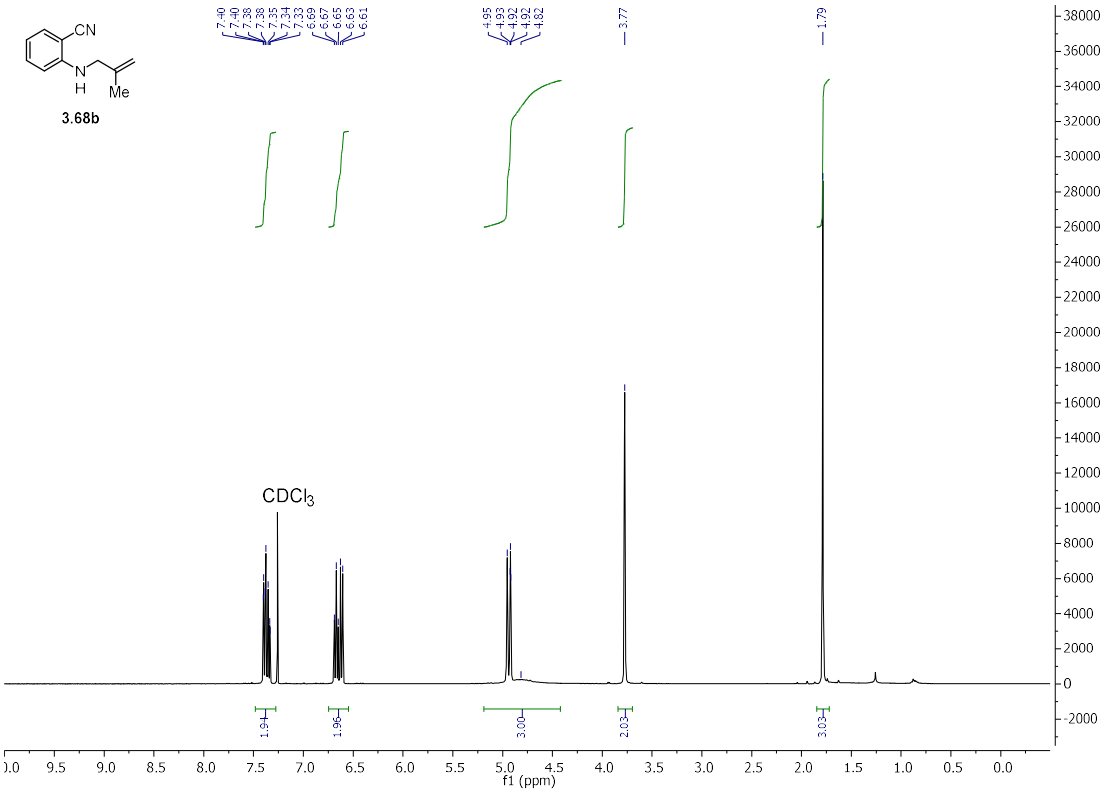
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68a**



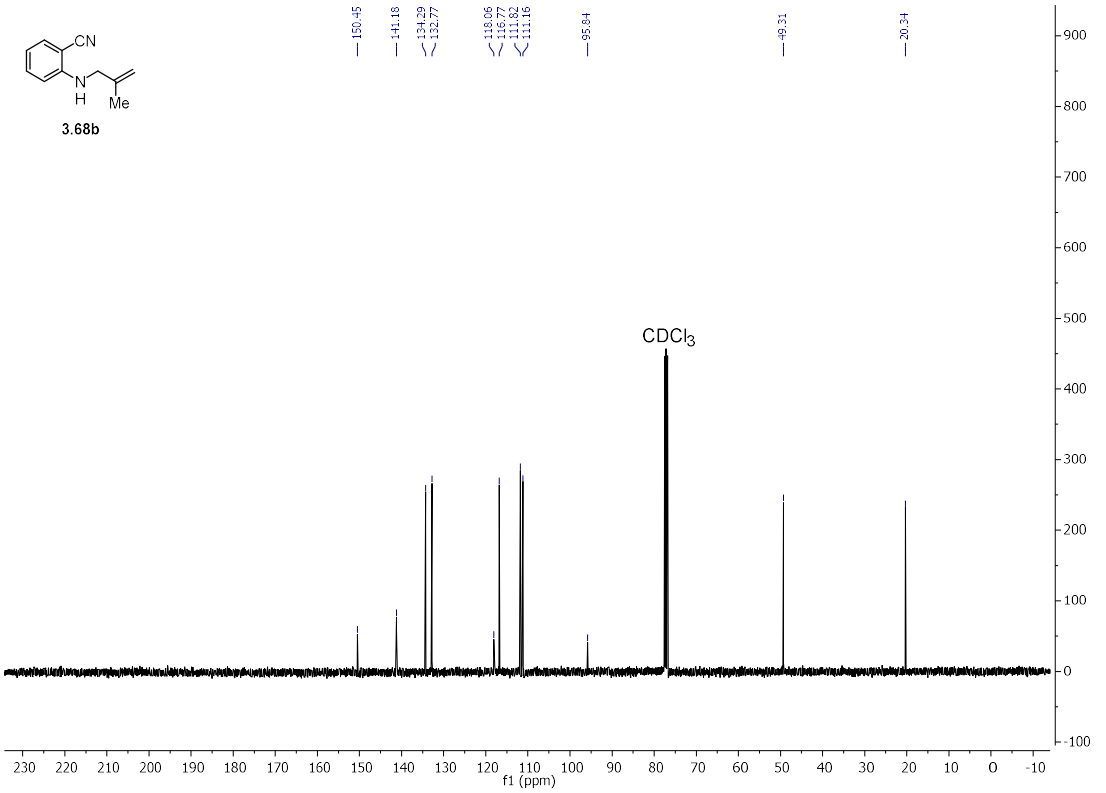
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68a**



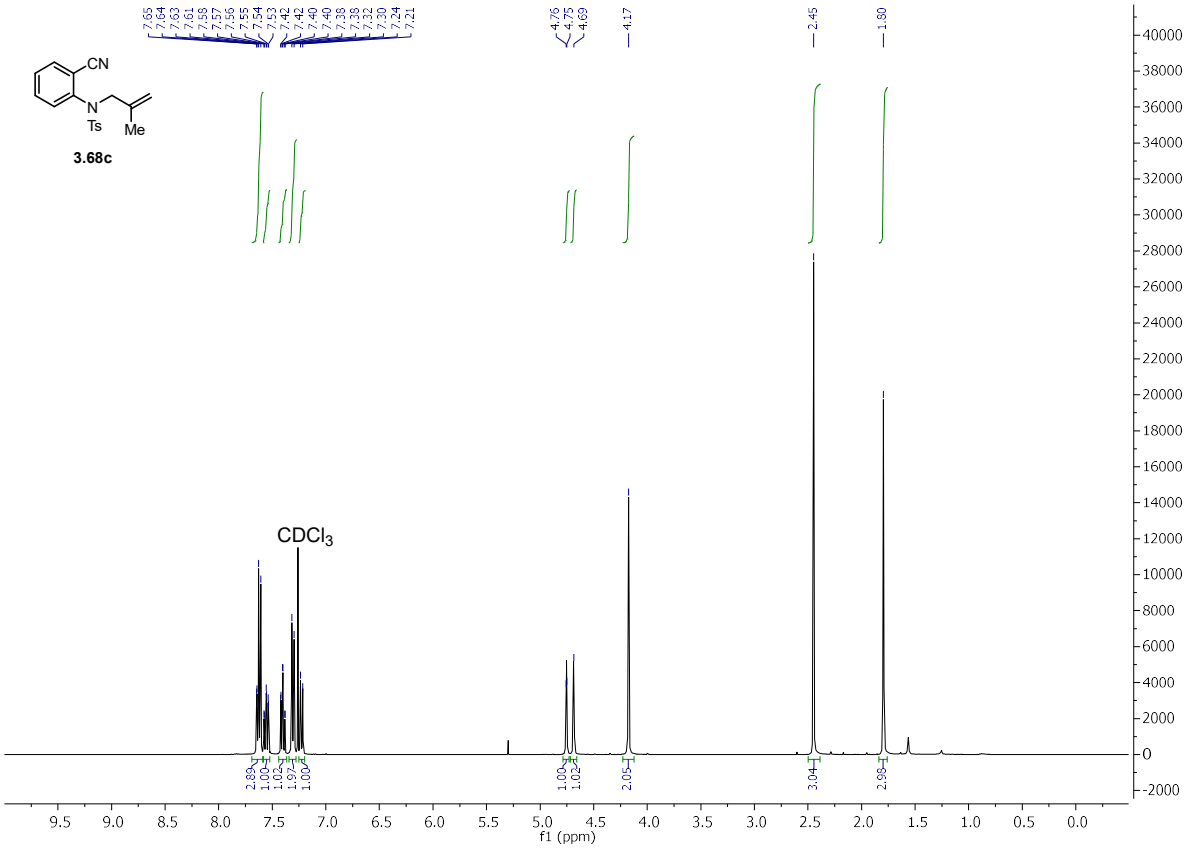
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68b**



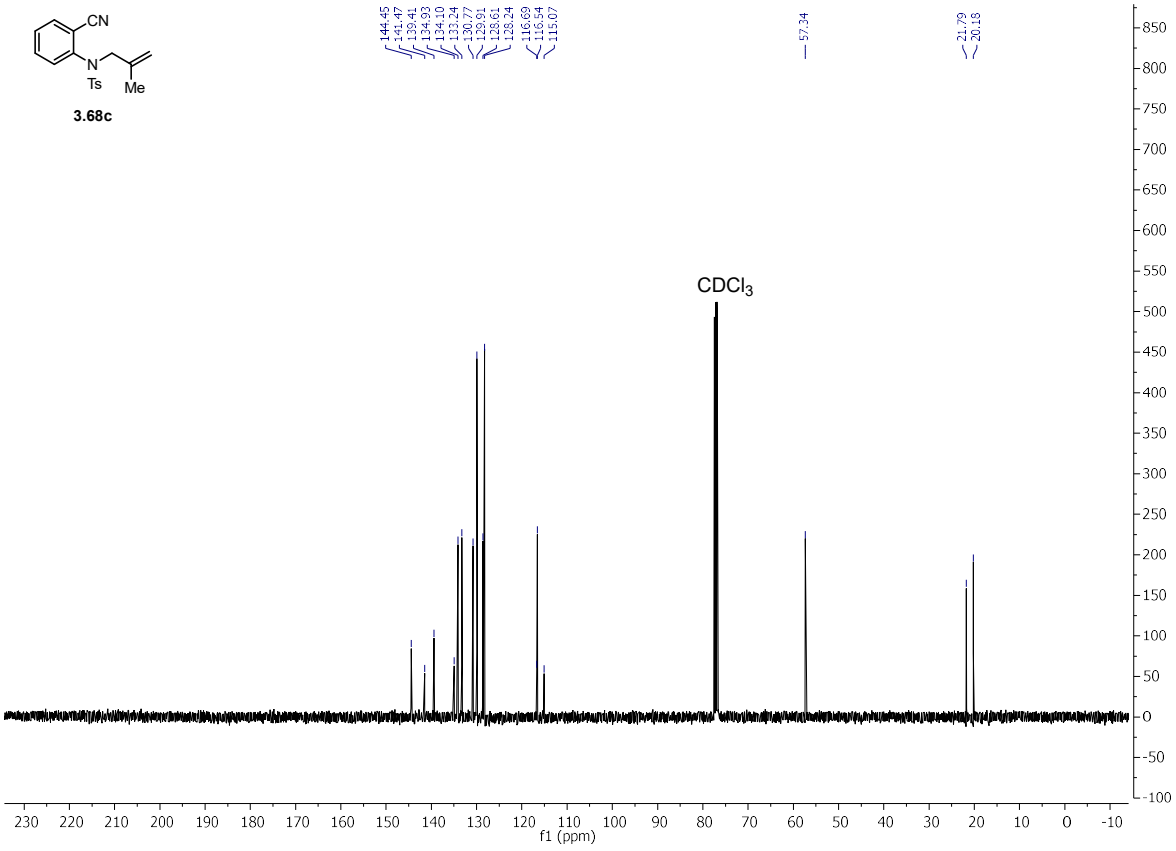
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68b**



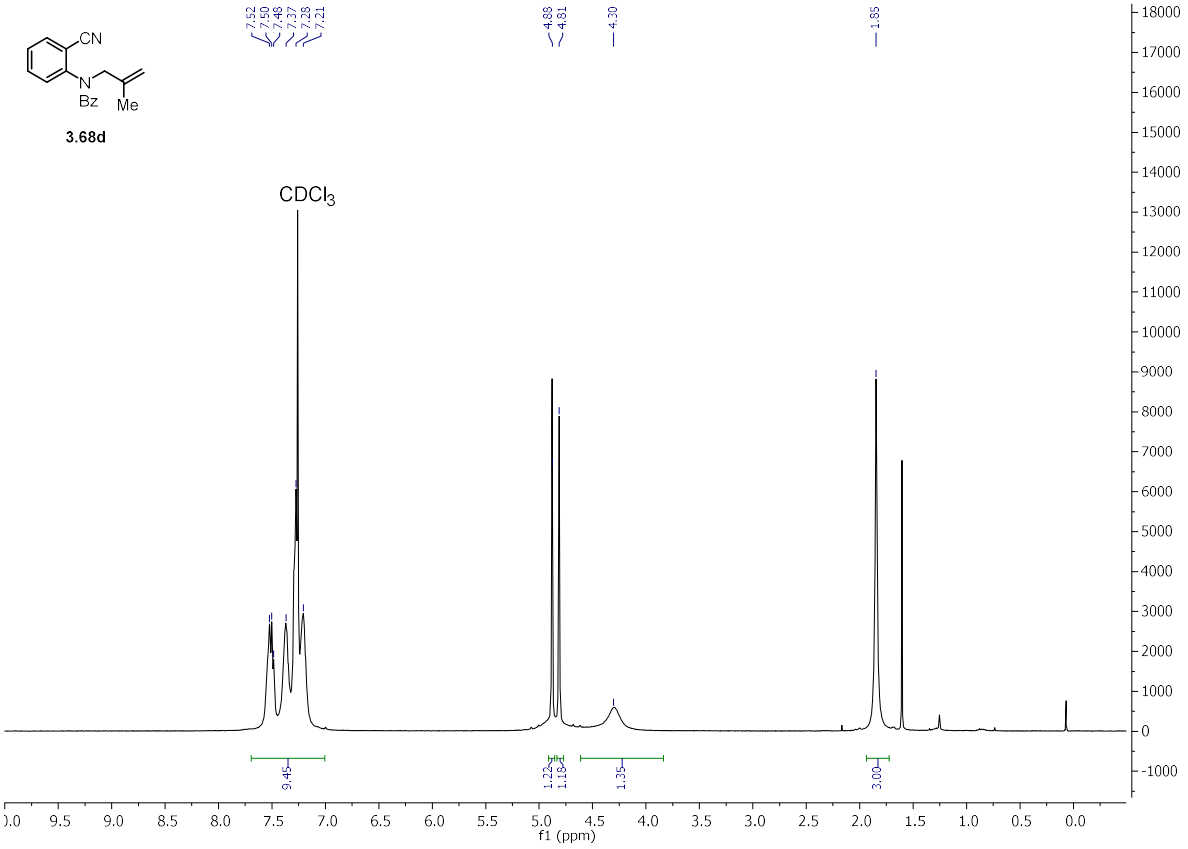
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68c**



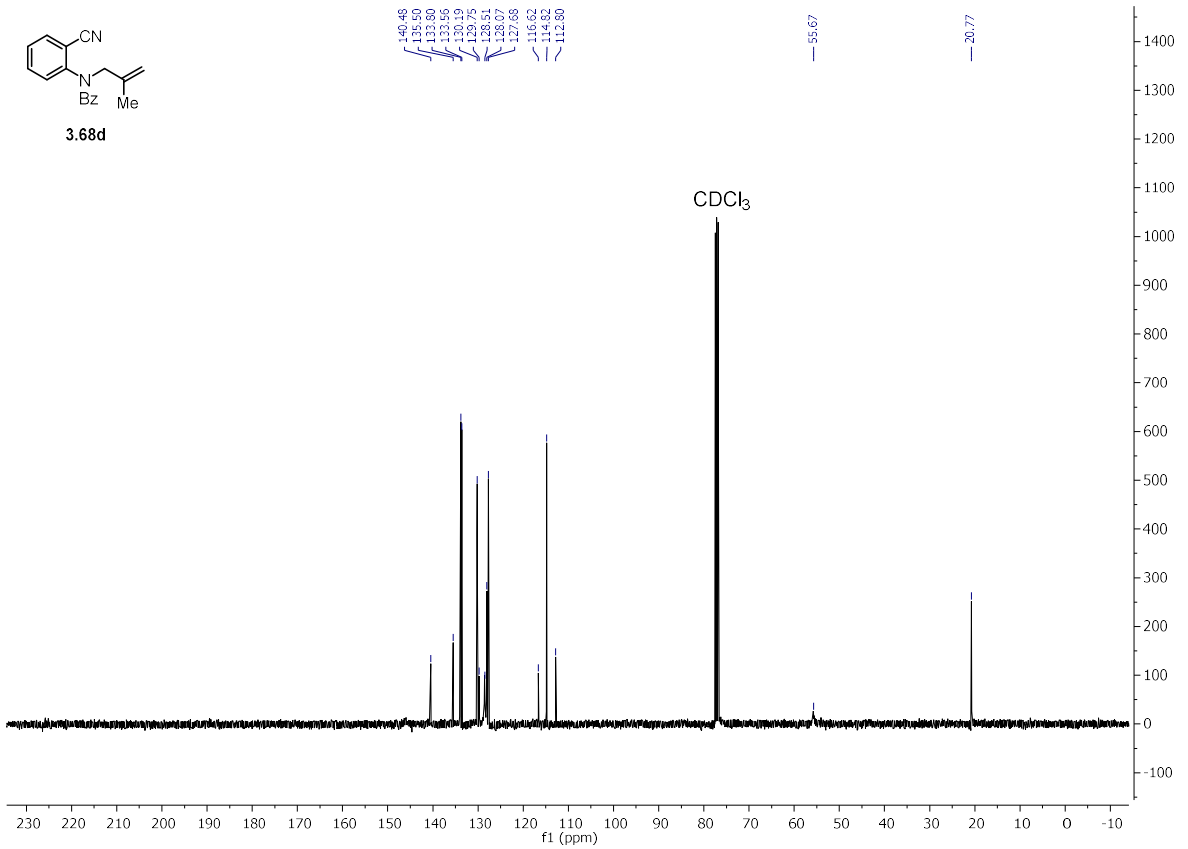
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68c**



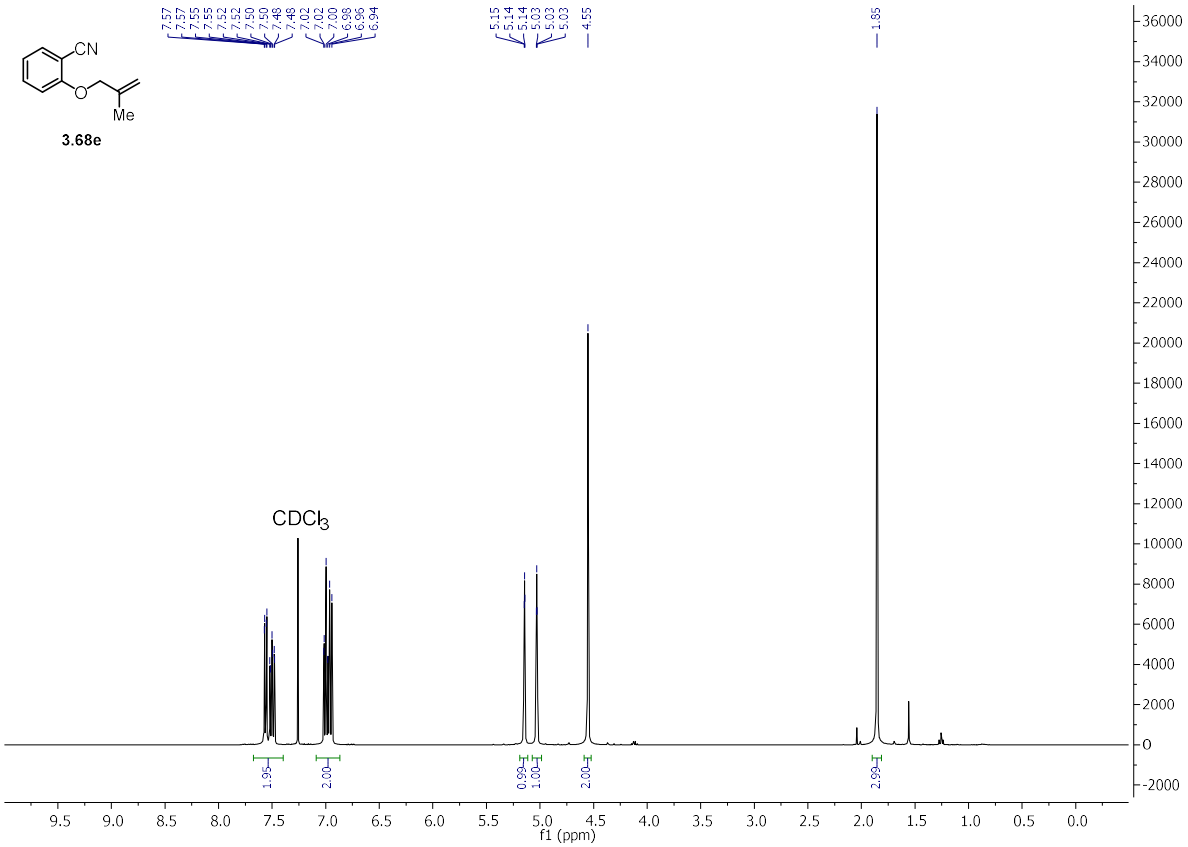
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68d**



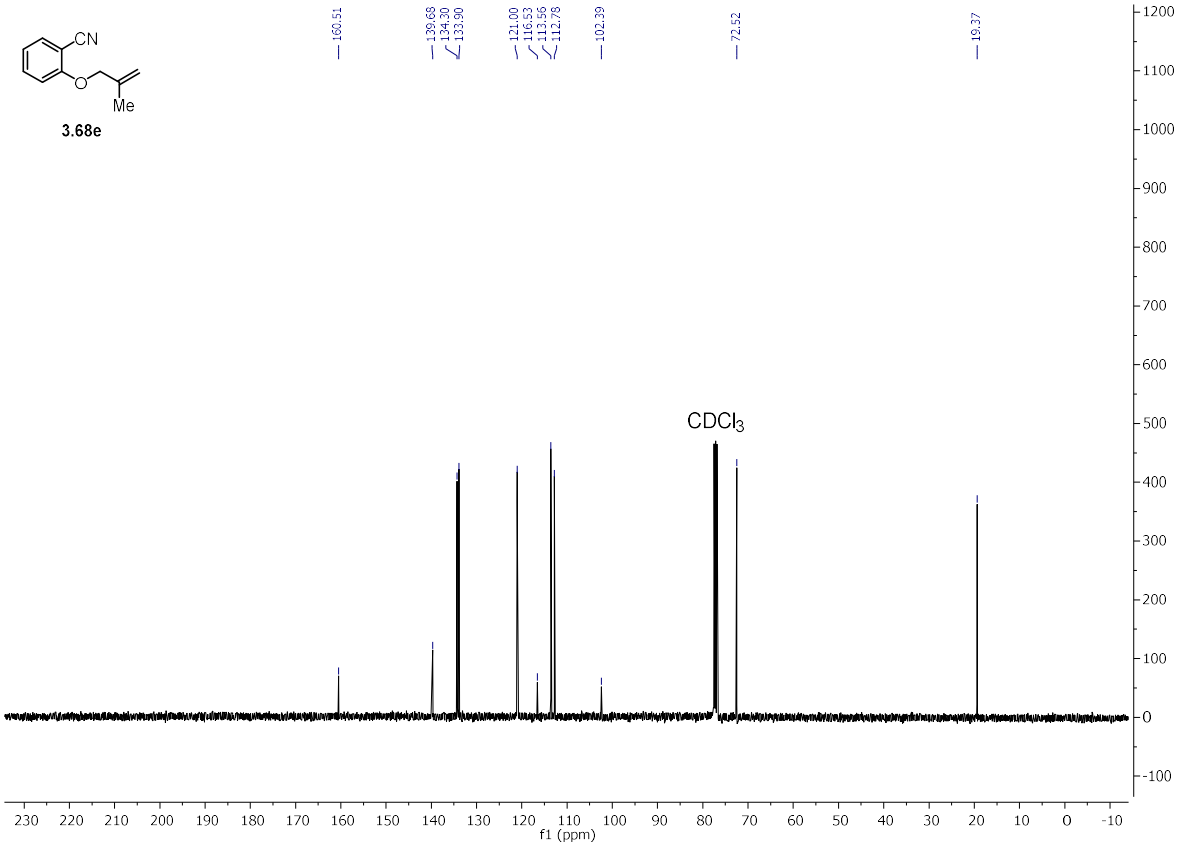
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68d**



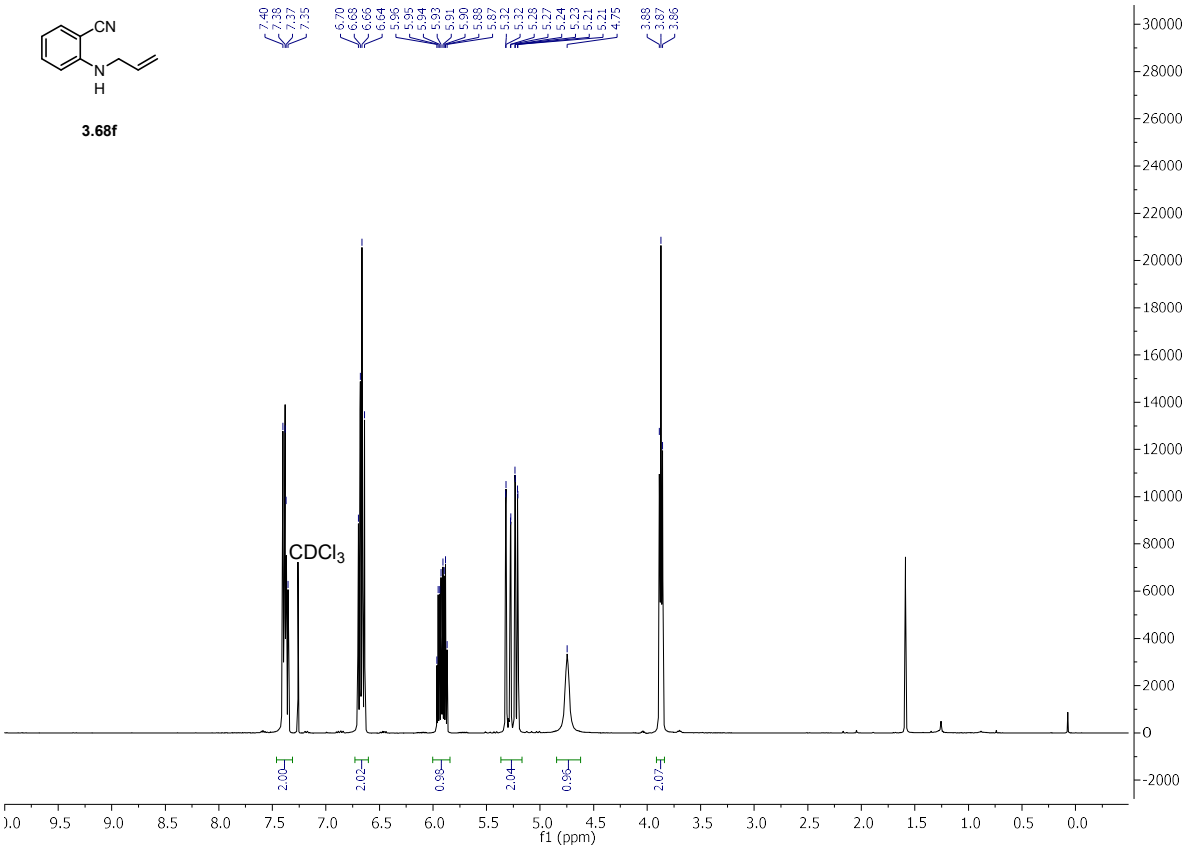
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68e**



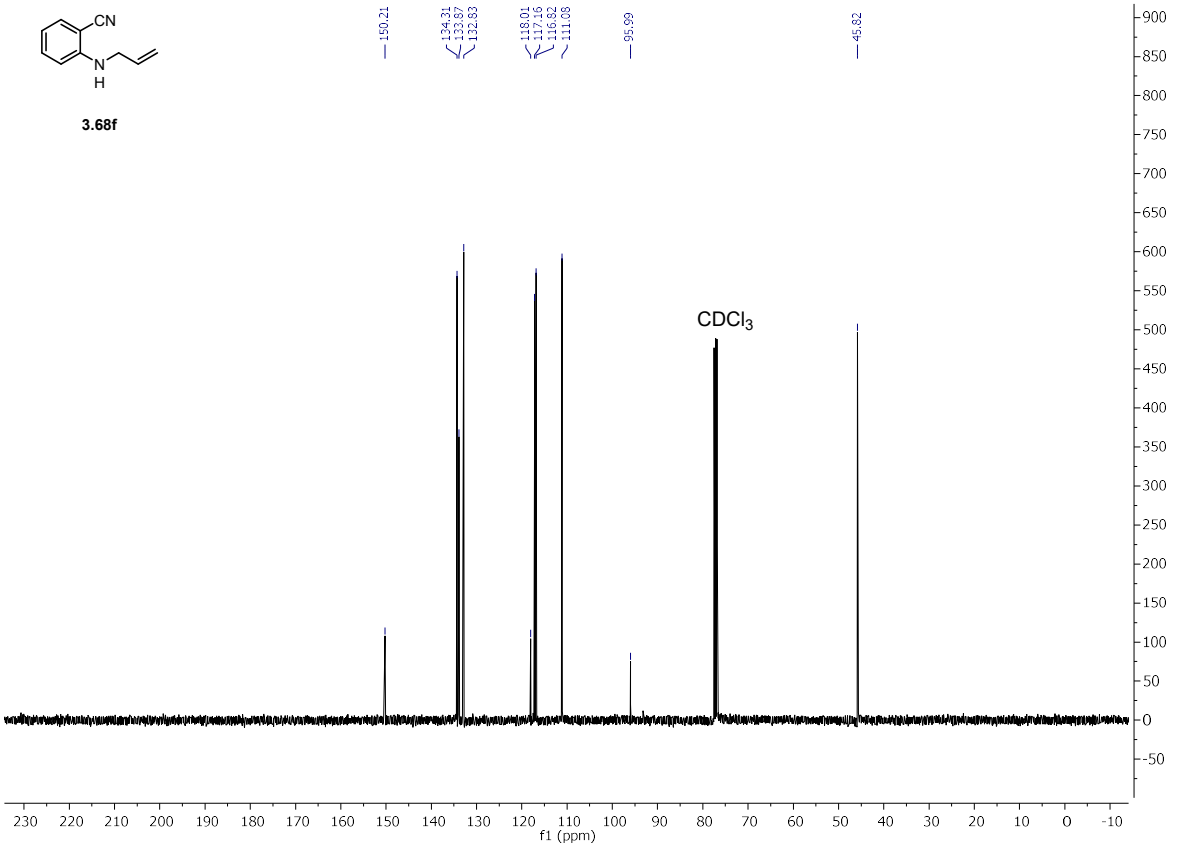
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68e**



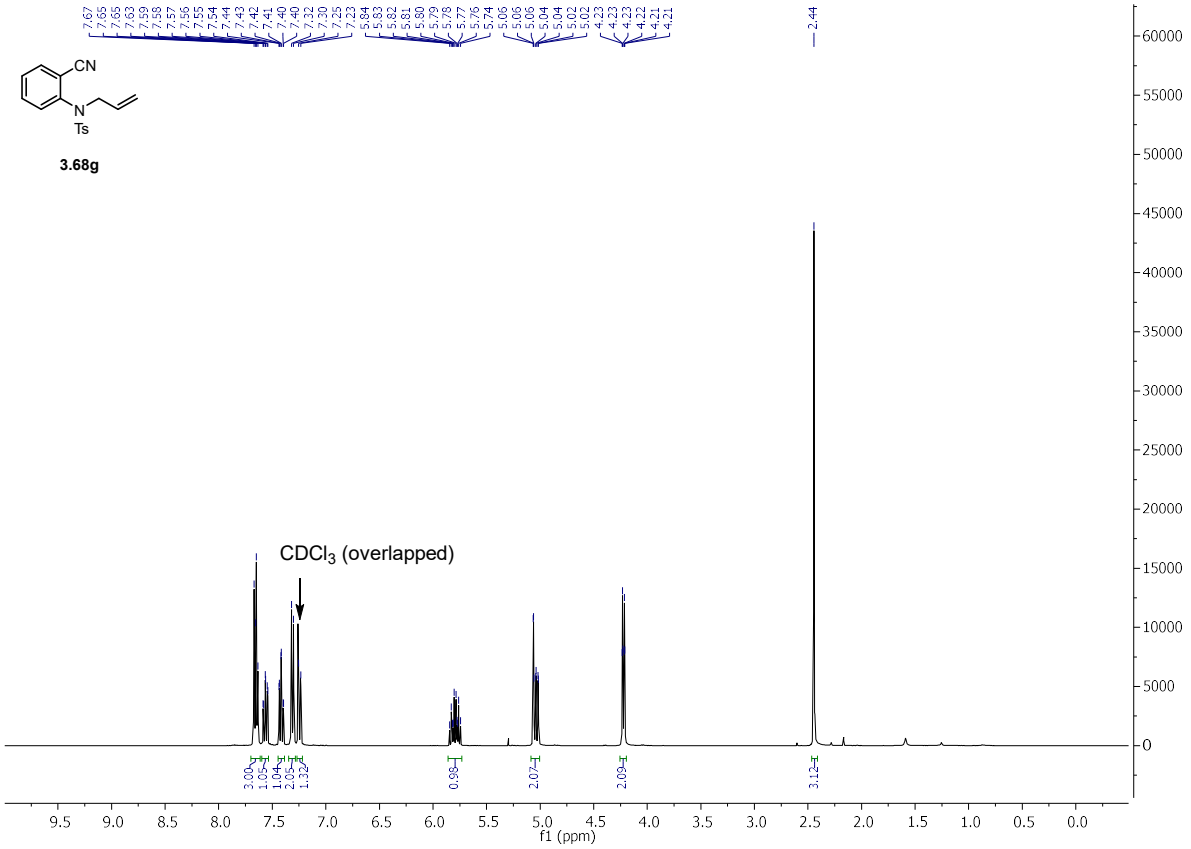
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68f**



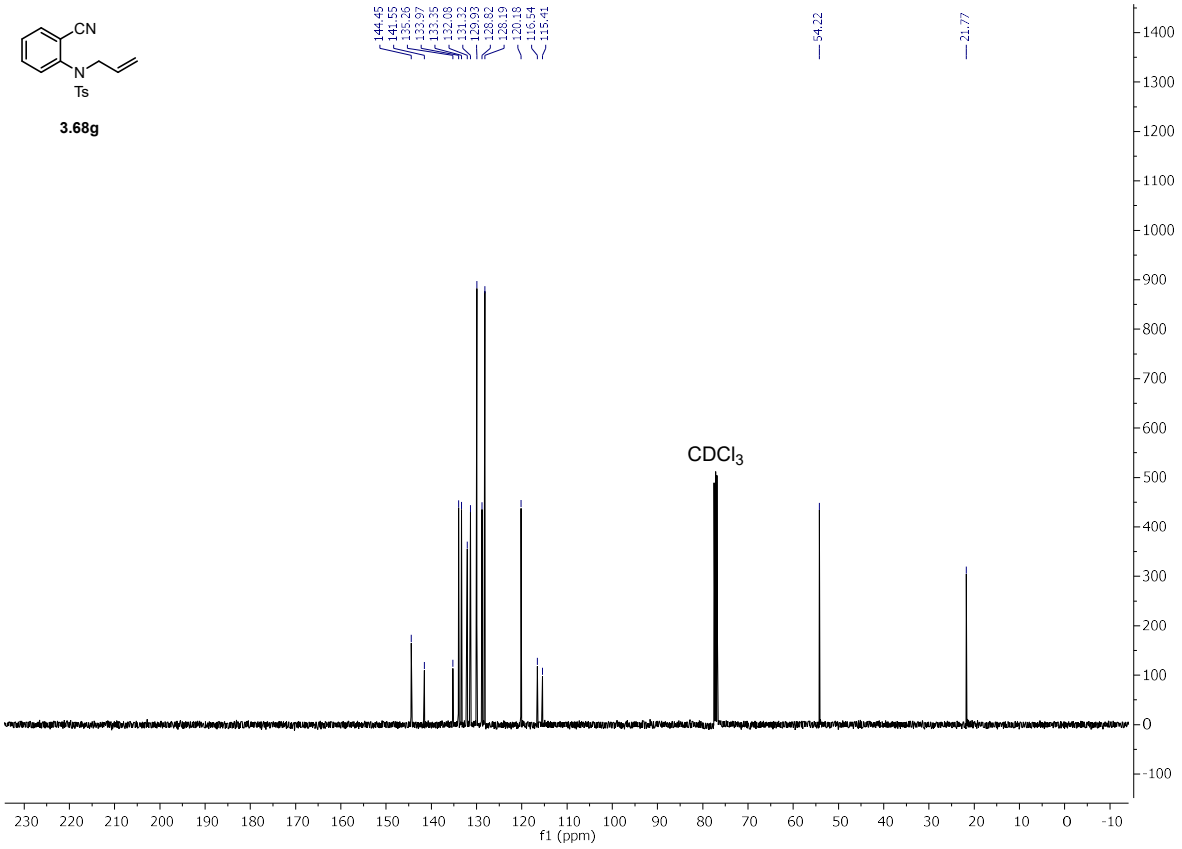
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68f**



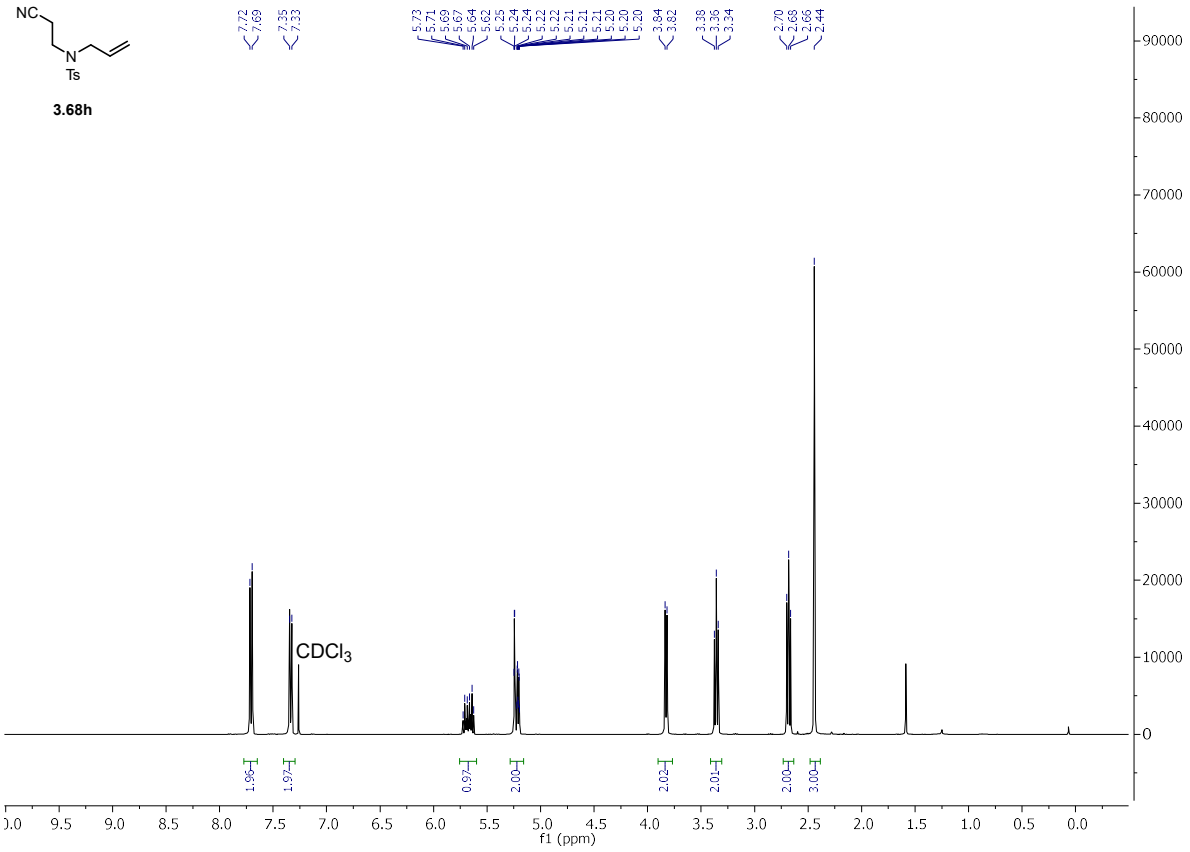
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68g**



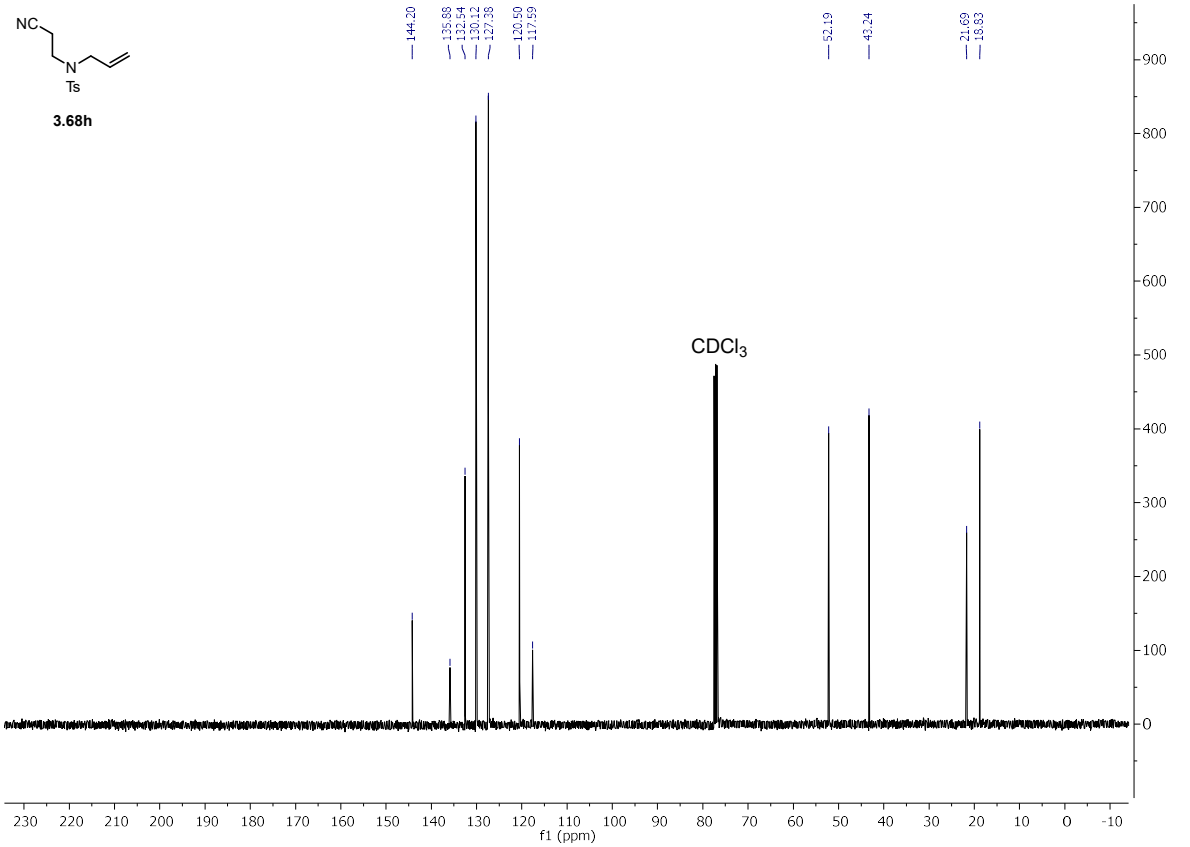
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68g**



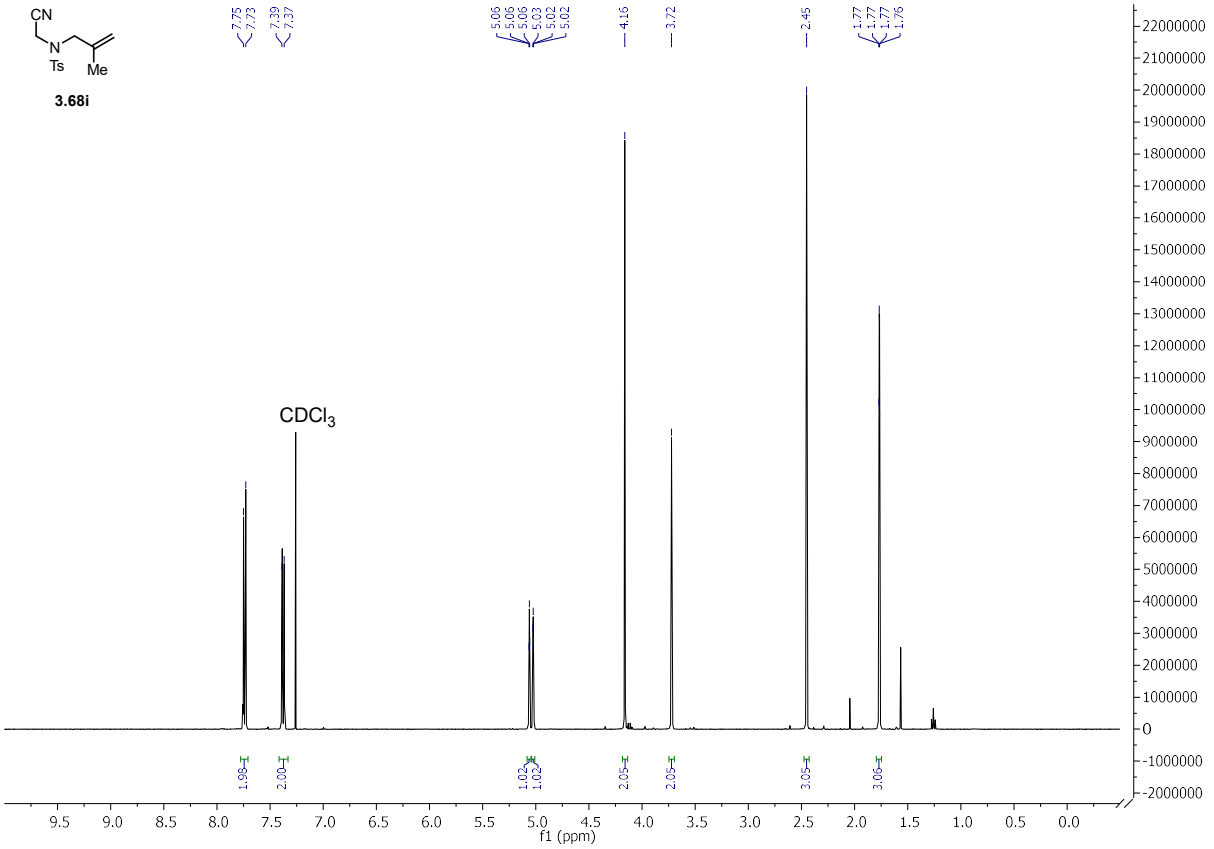
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68h**



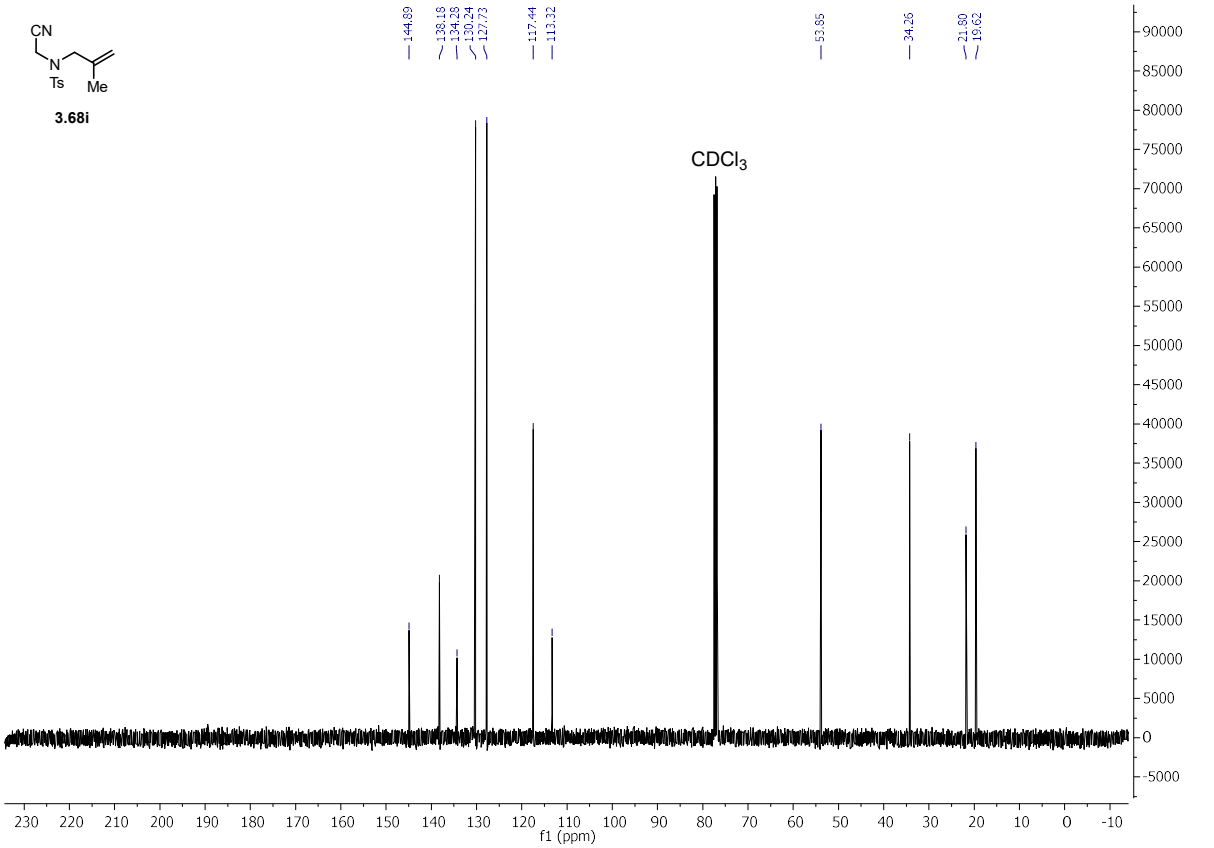
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68h**



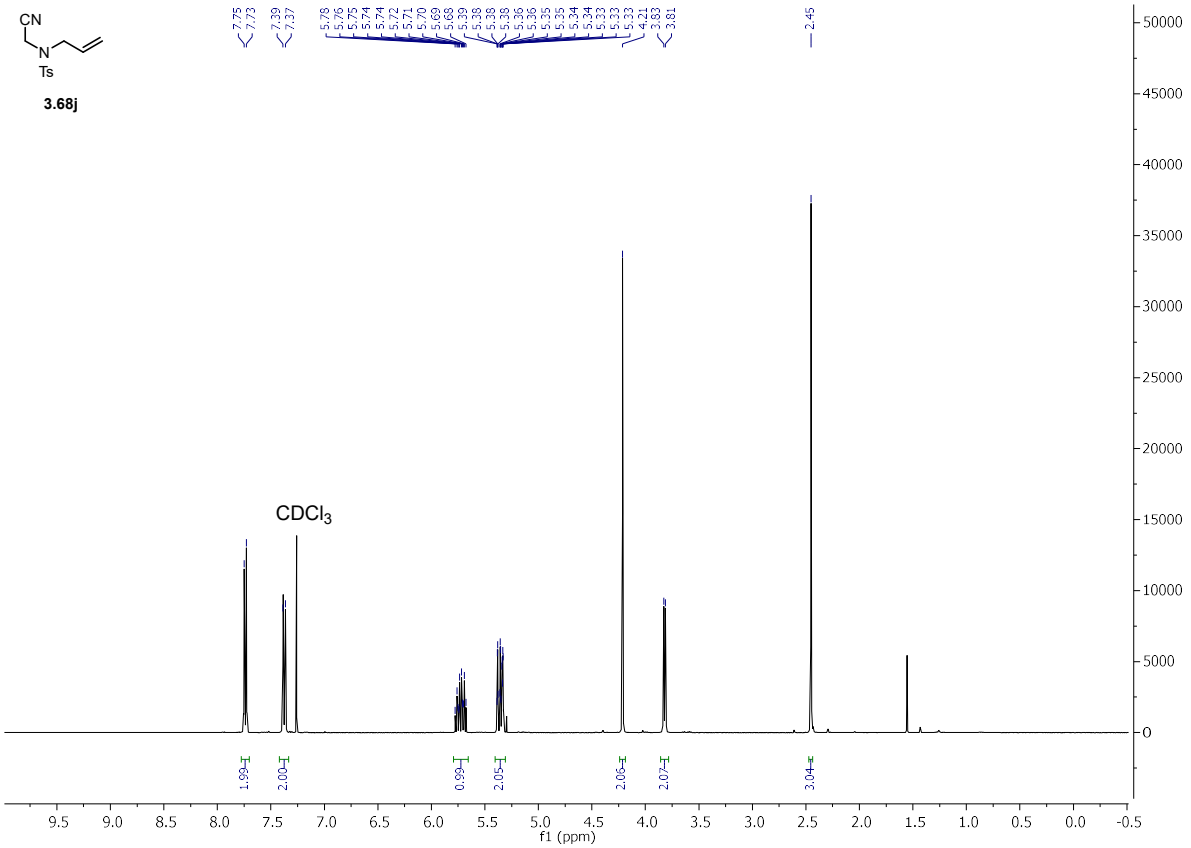
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68i**



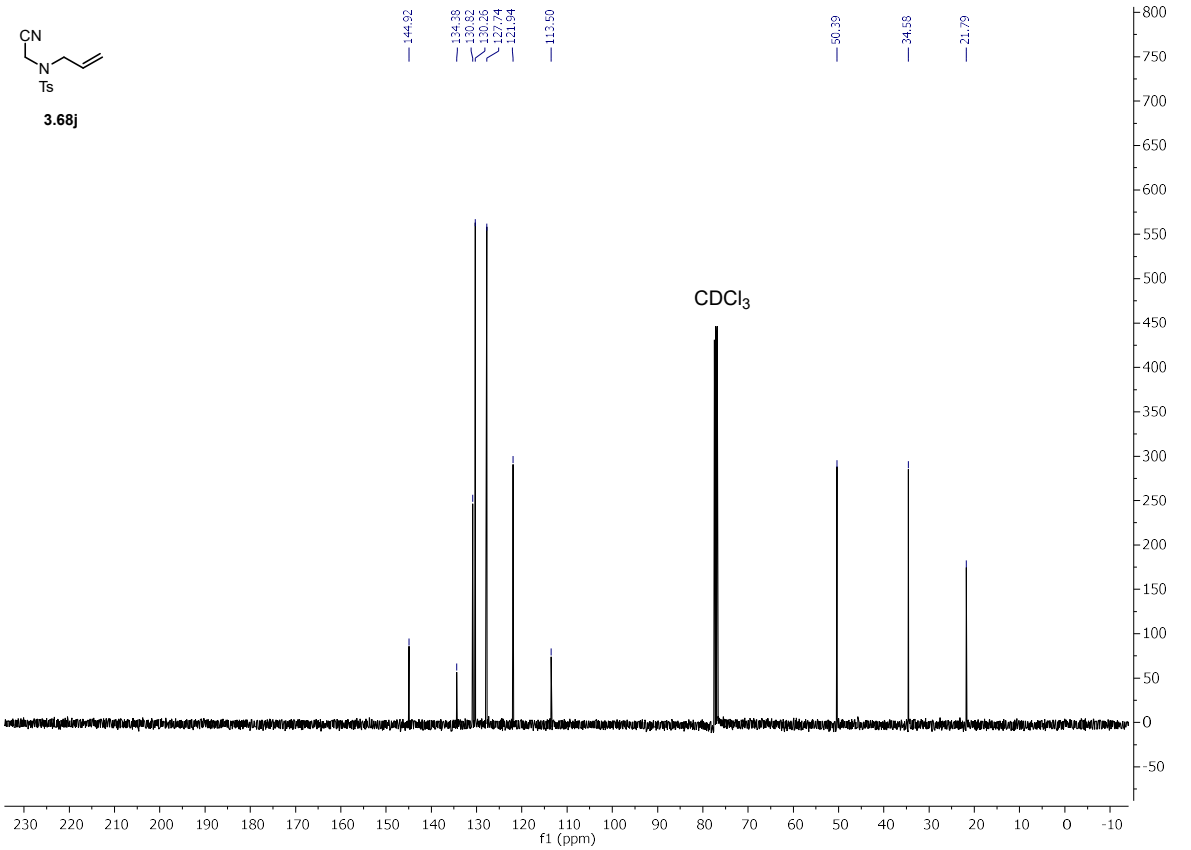
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68i**



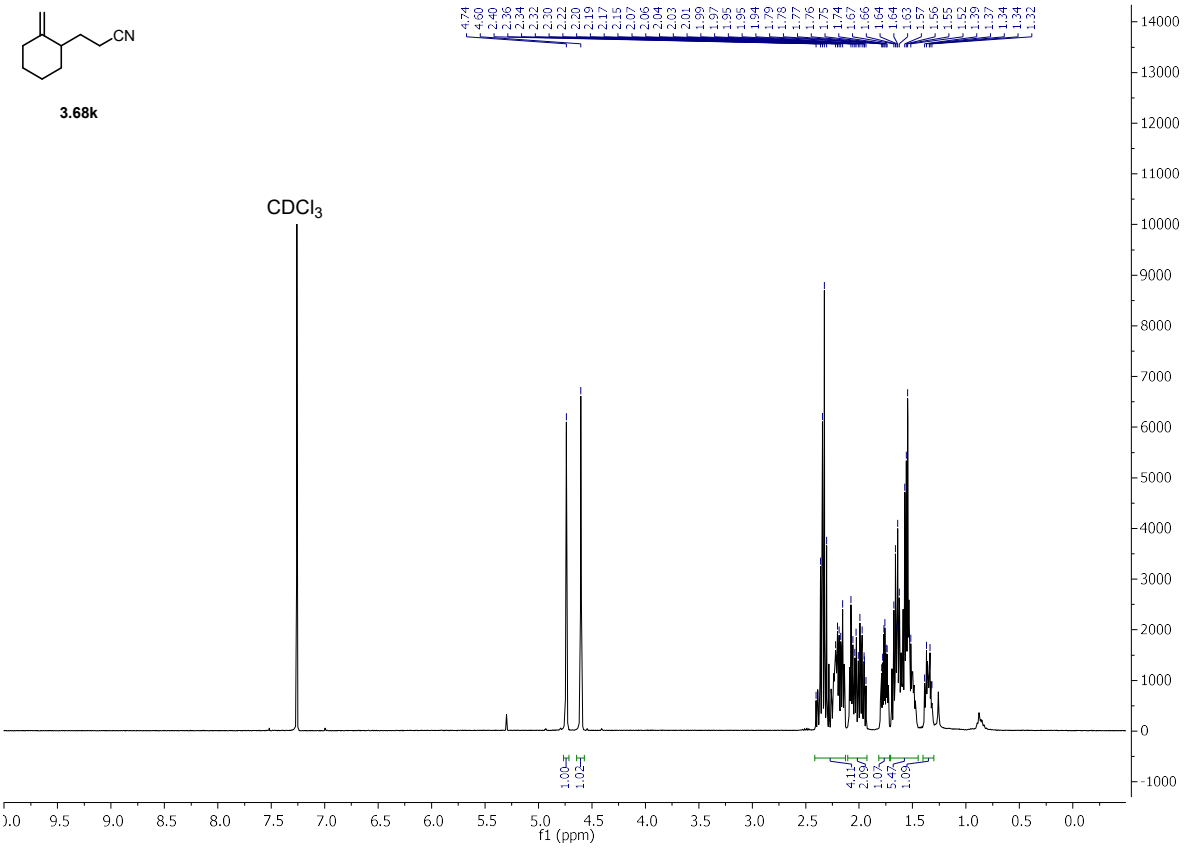
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68j**



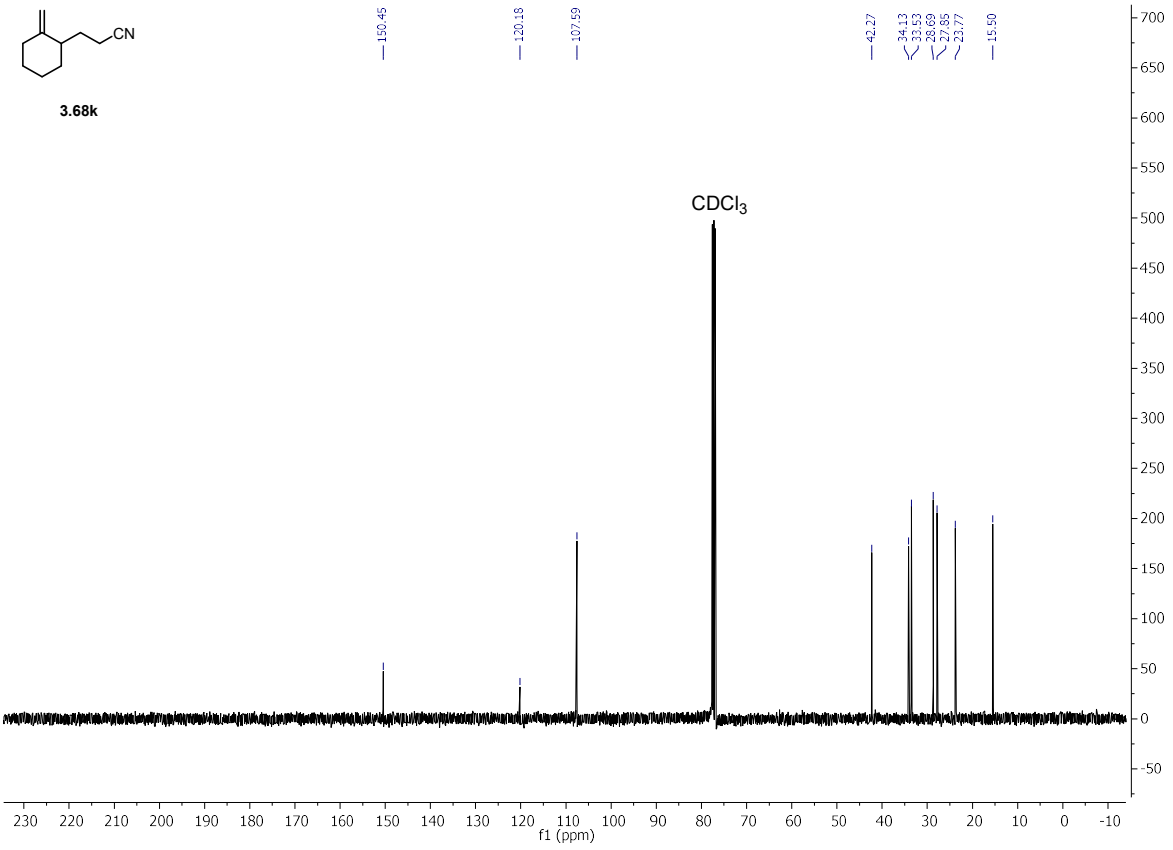
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68j**



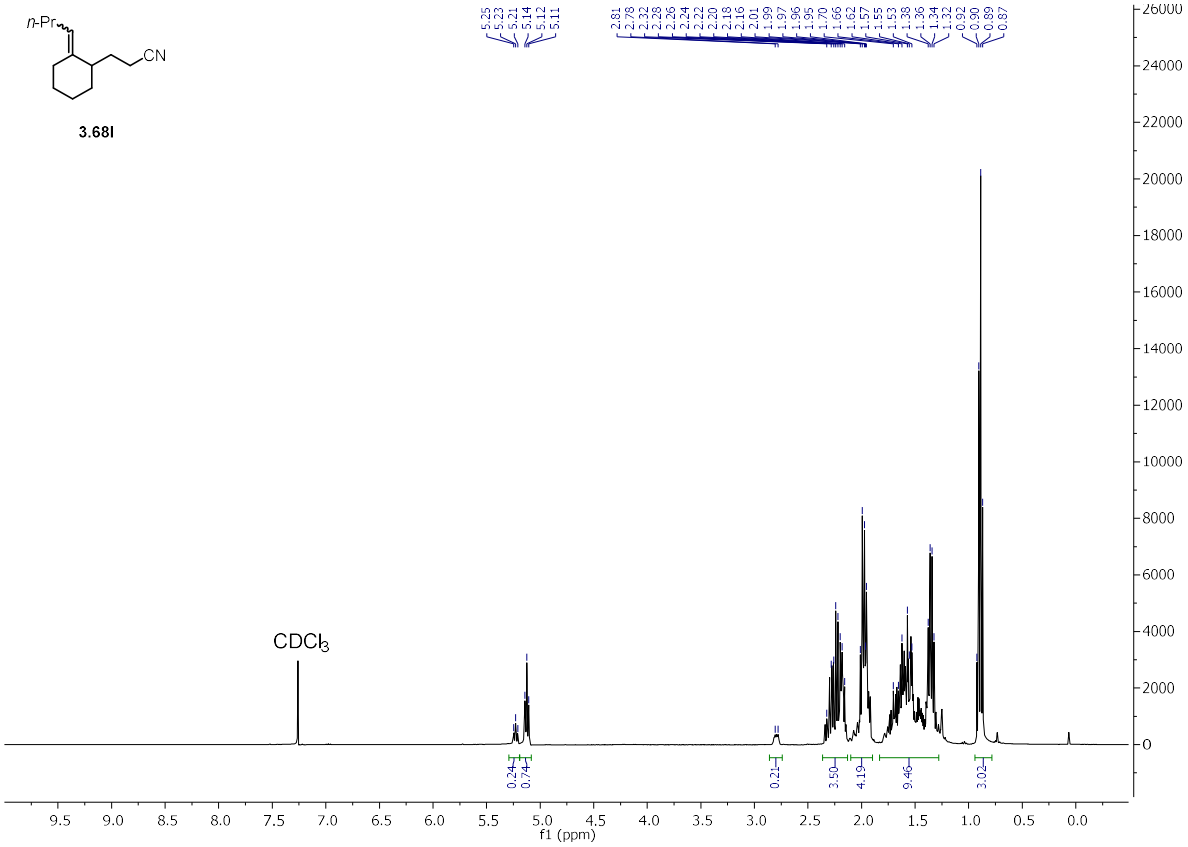
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68k**



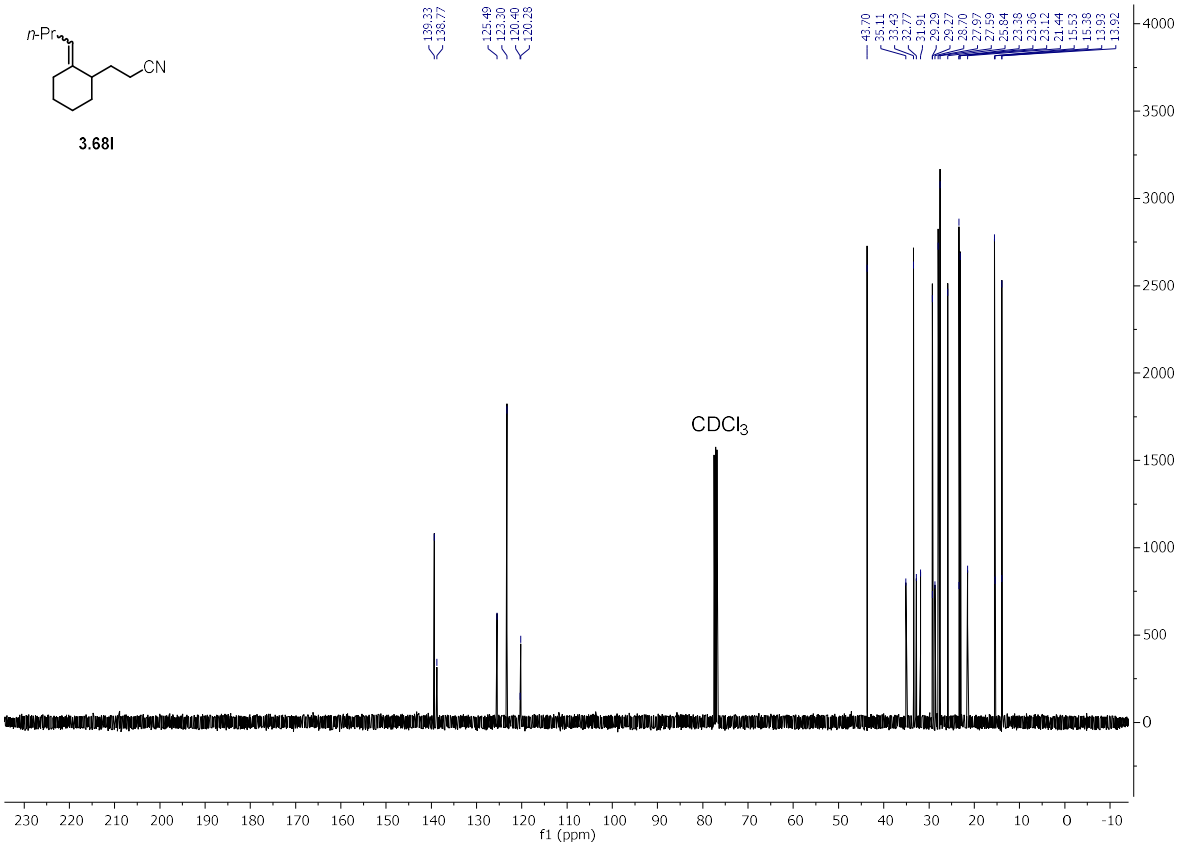
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68k**



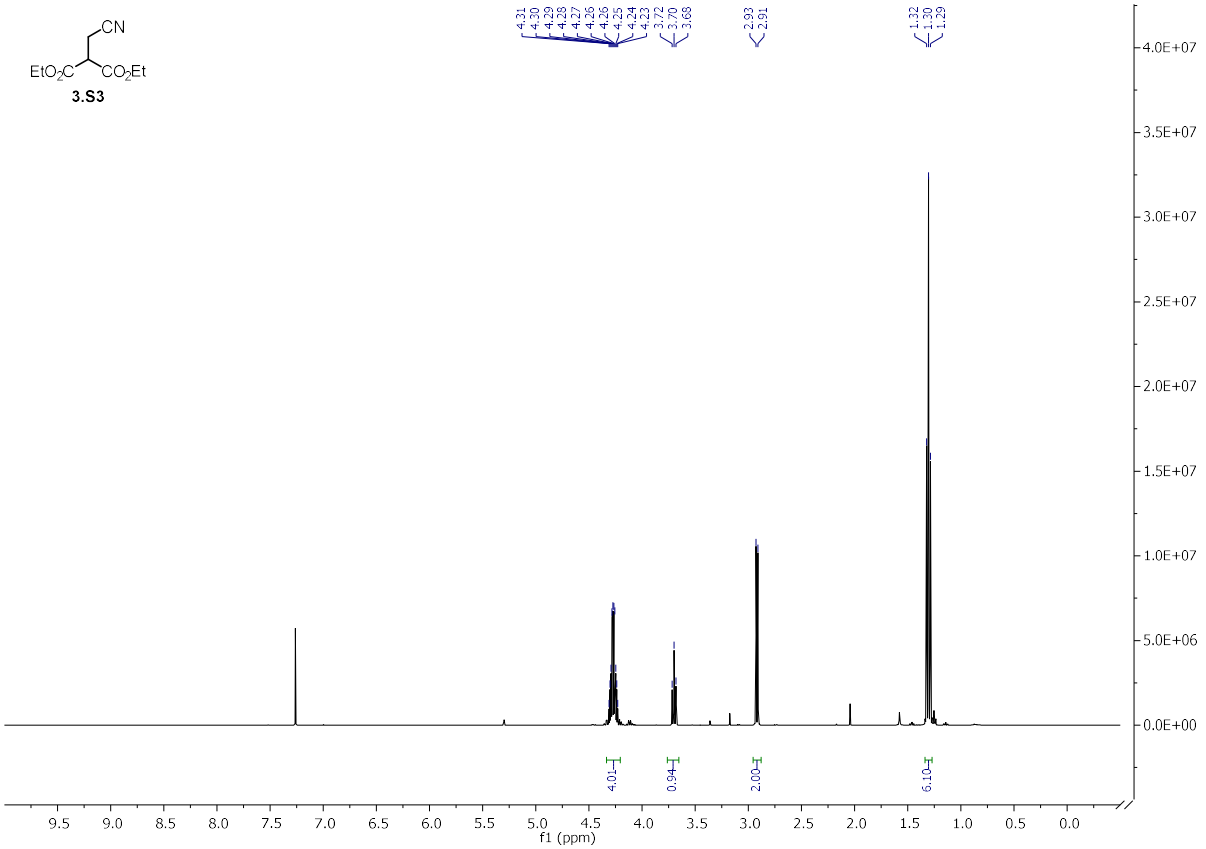
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68l**



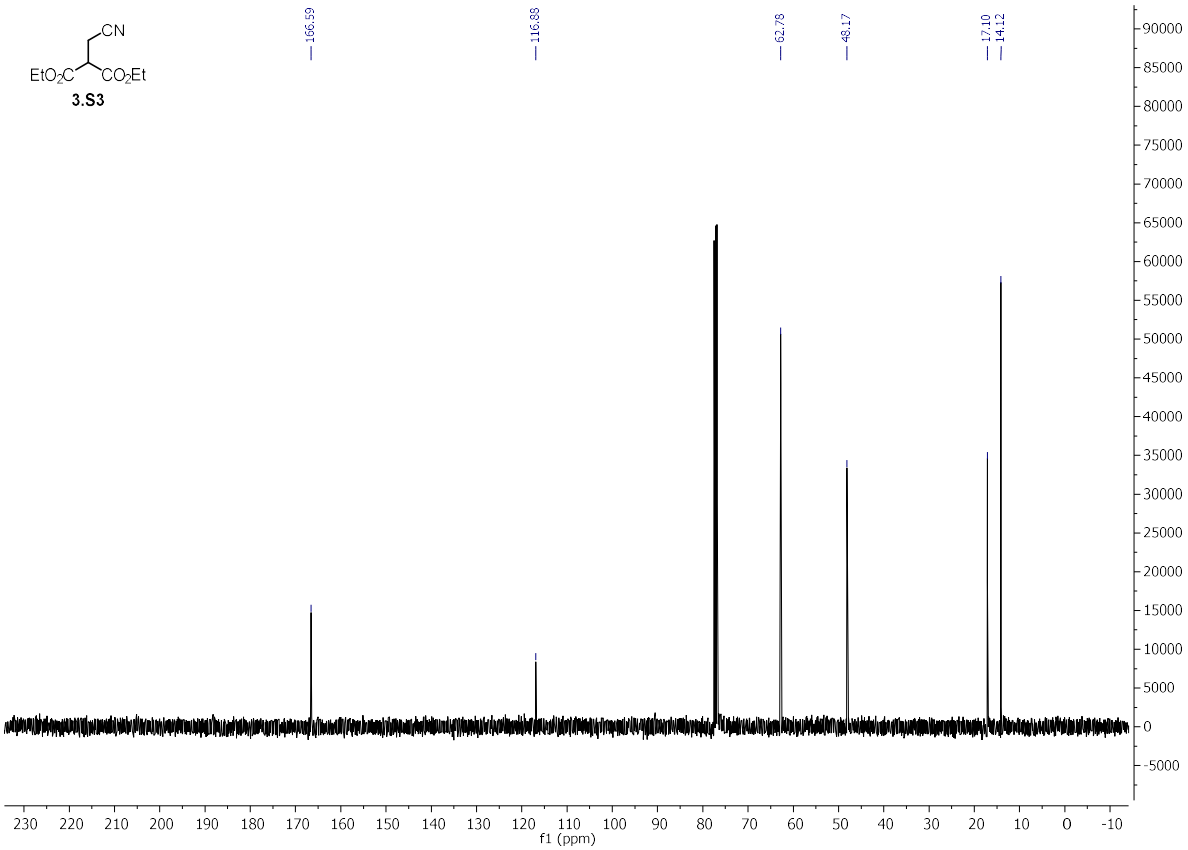
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68l**



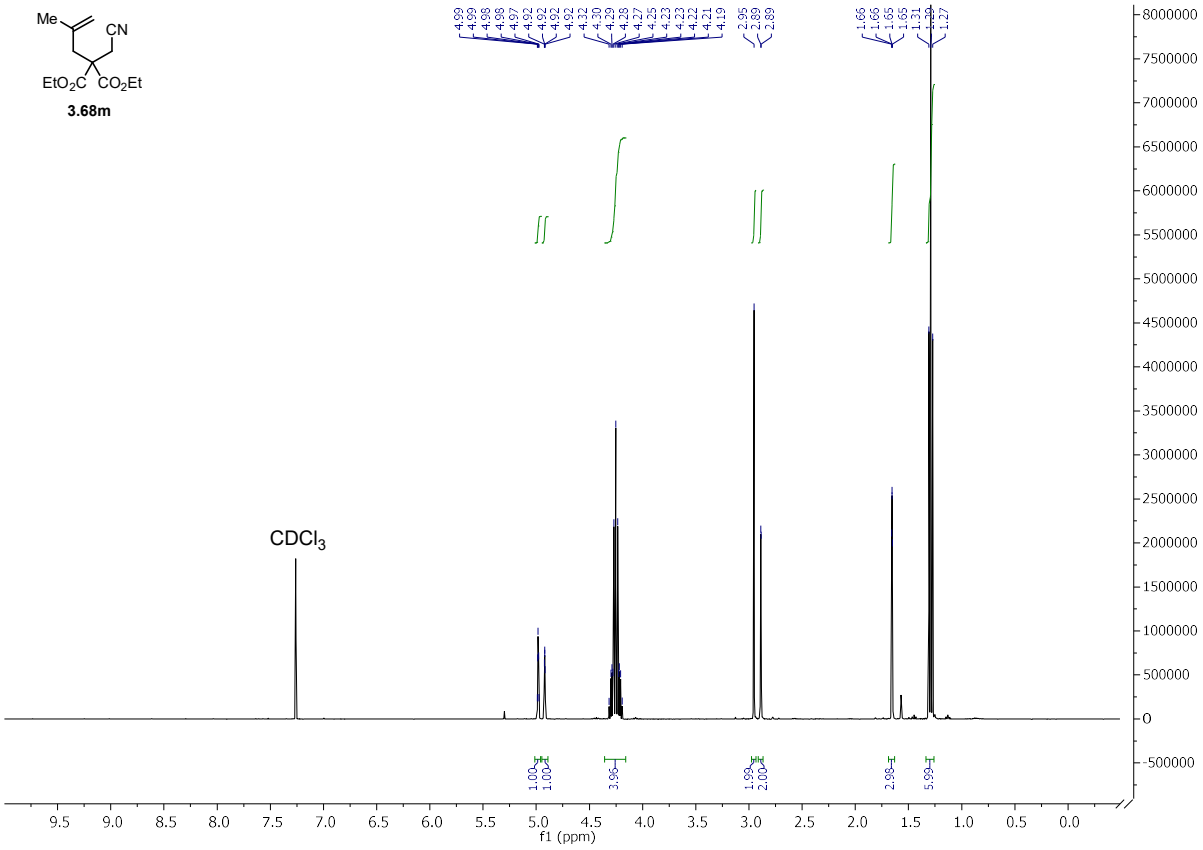
^{1}H NMR (400 MHz, $CDCl_3$) of **3.S3**



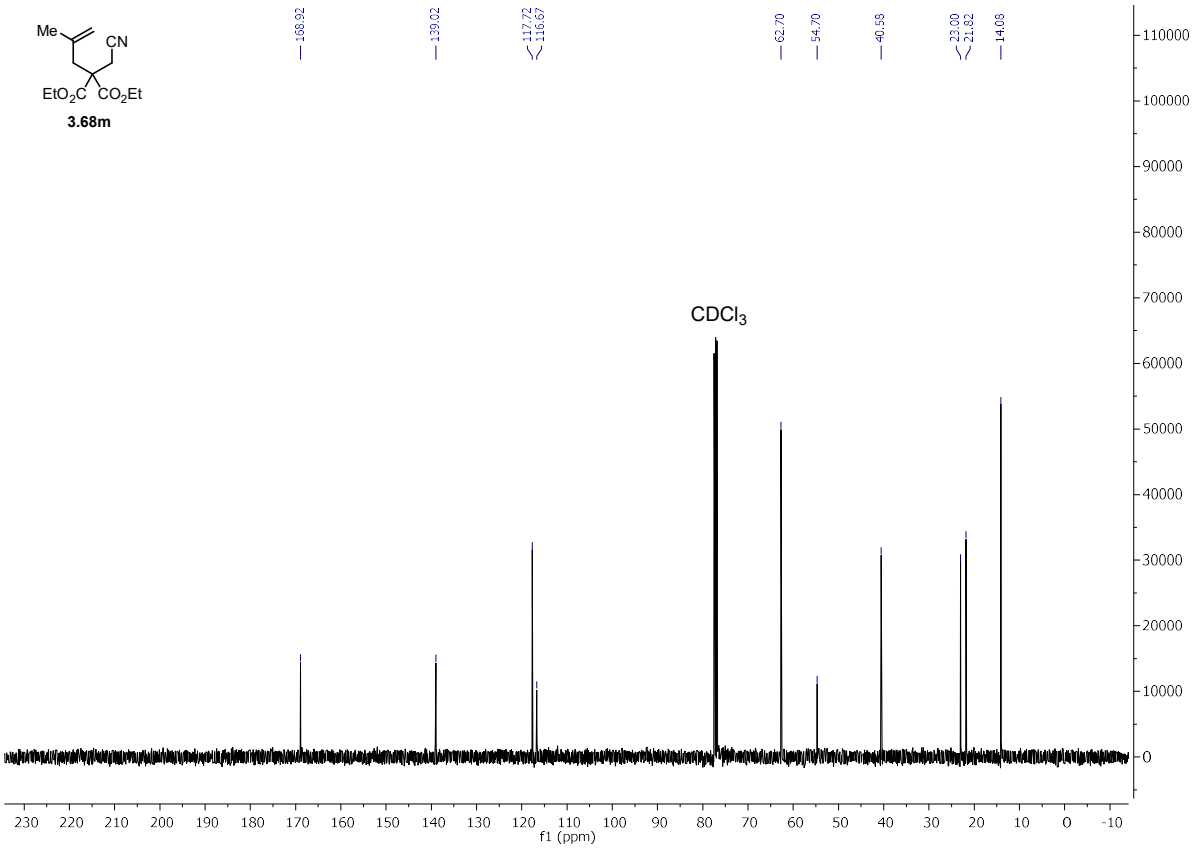
^{13}C NMR (400 MHz, $CDCl_3$) of **3.S3**



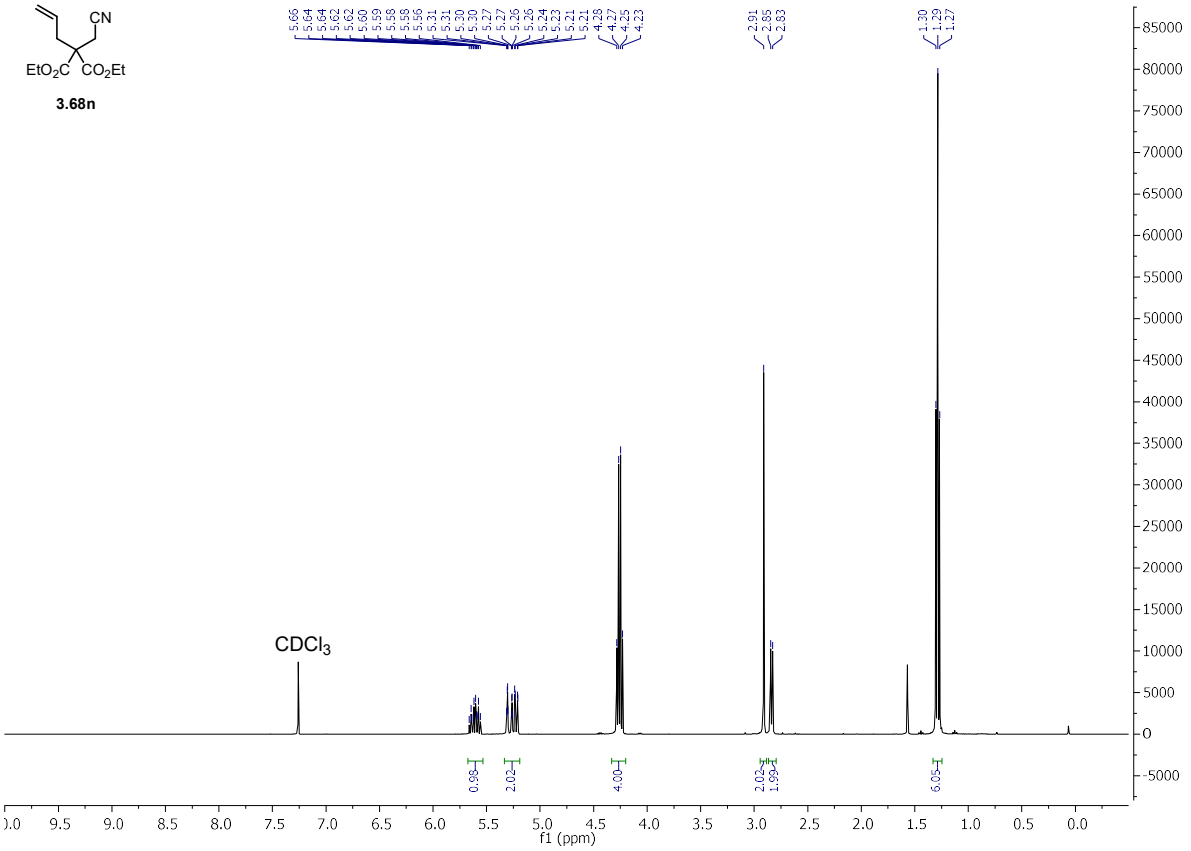
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68m**



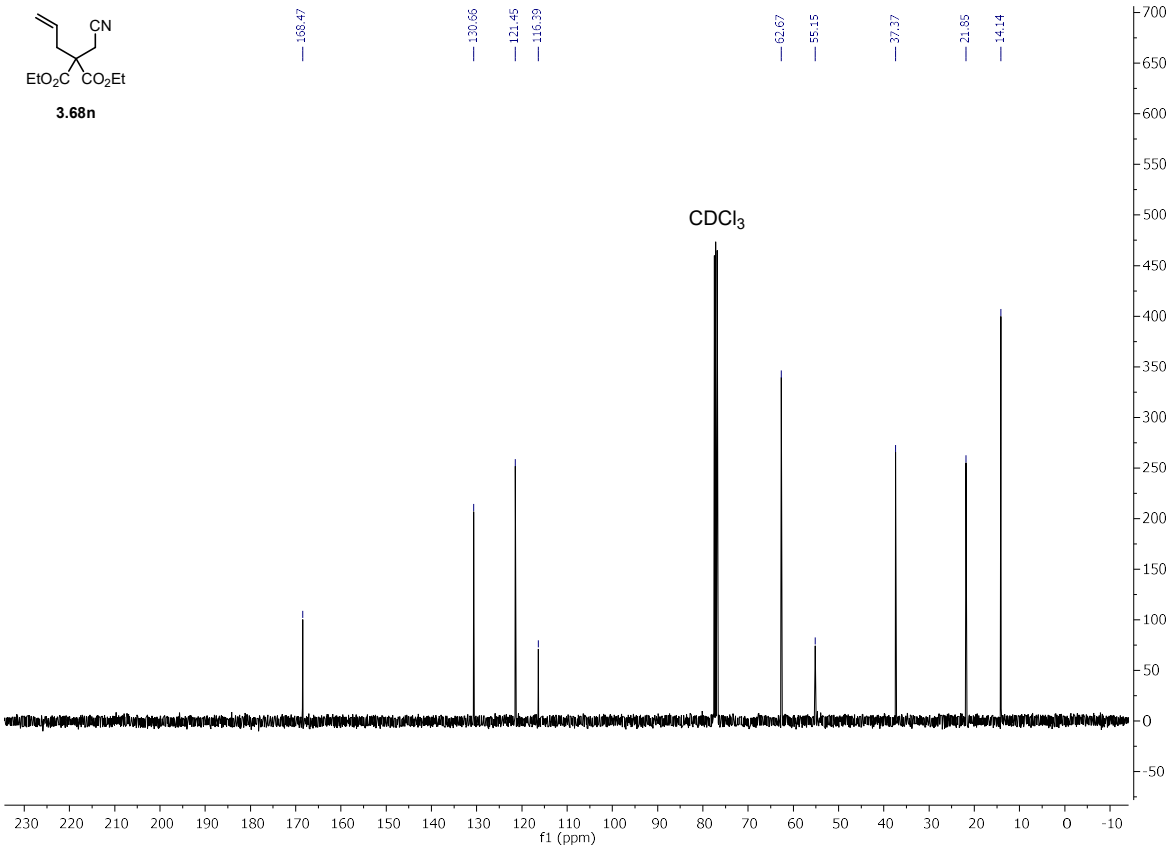
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68m**



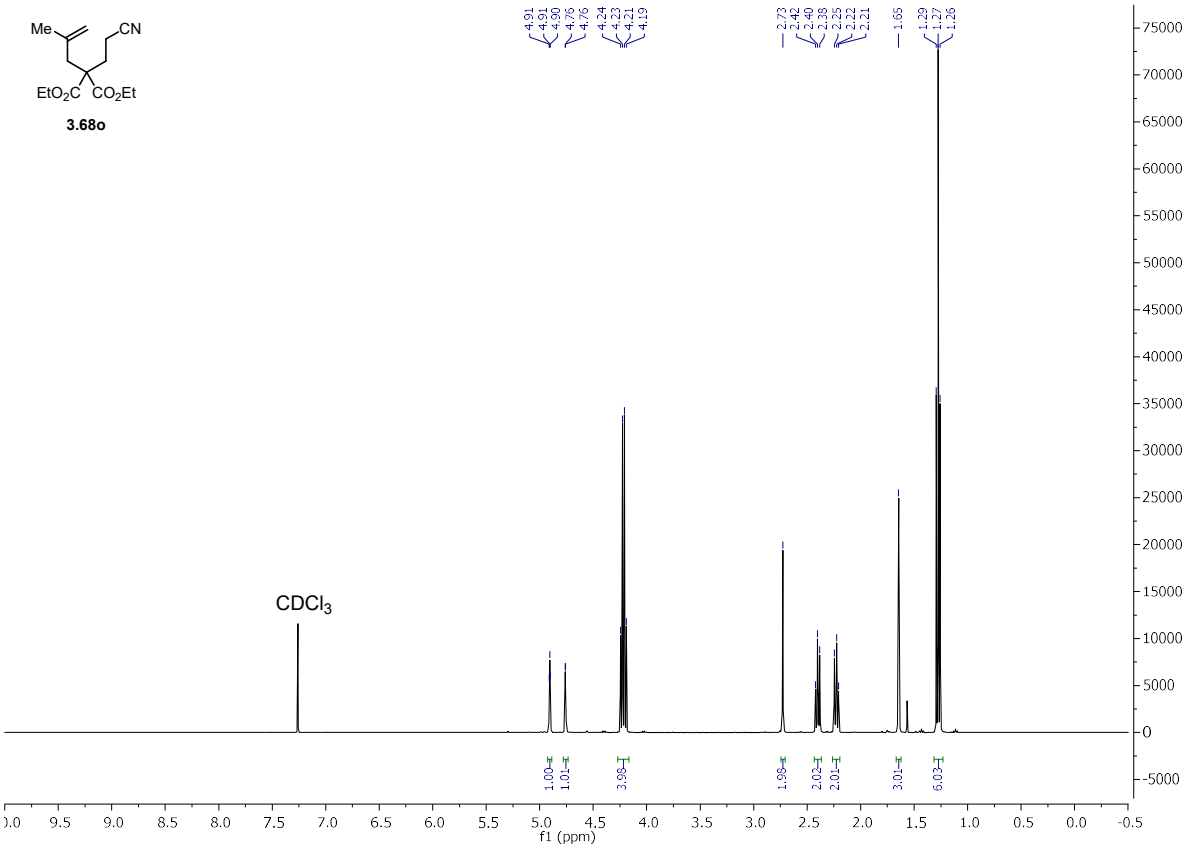
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68n**



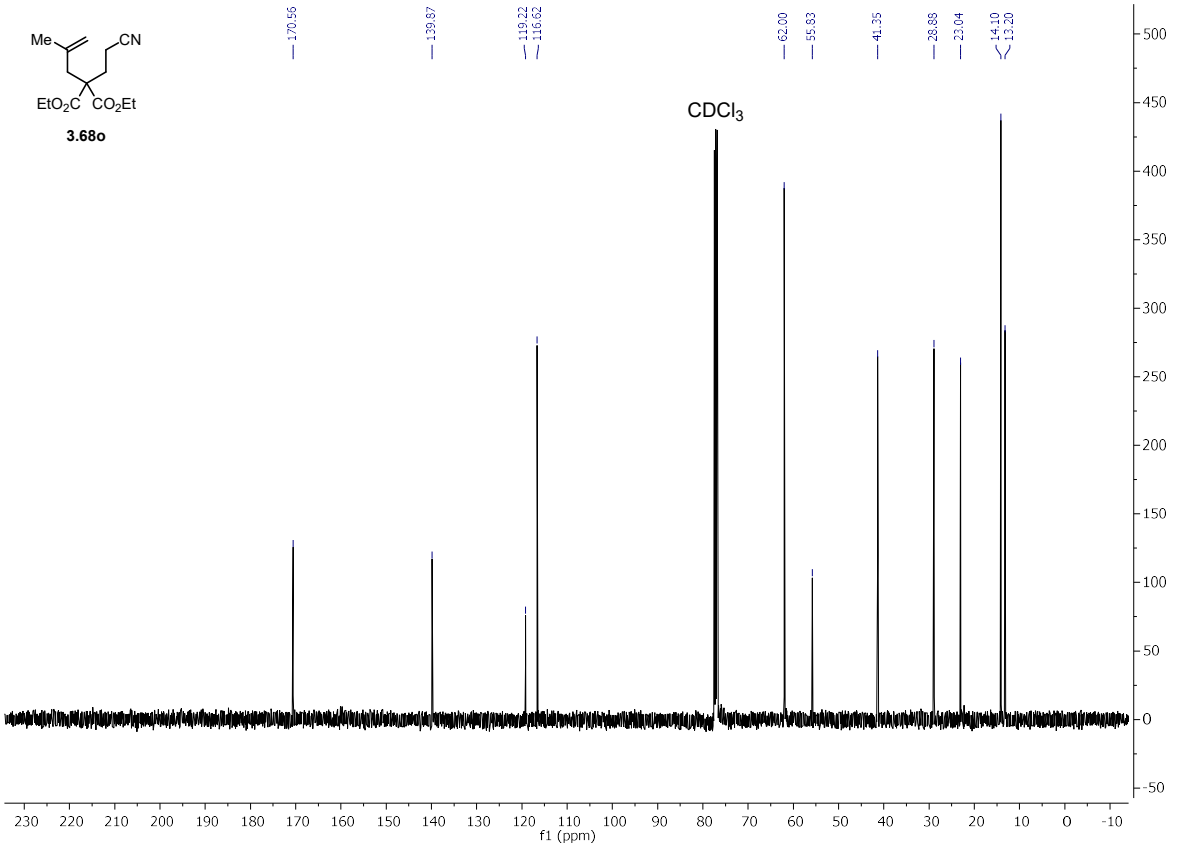
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68n**



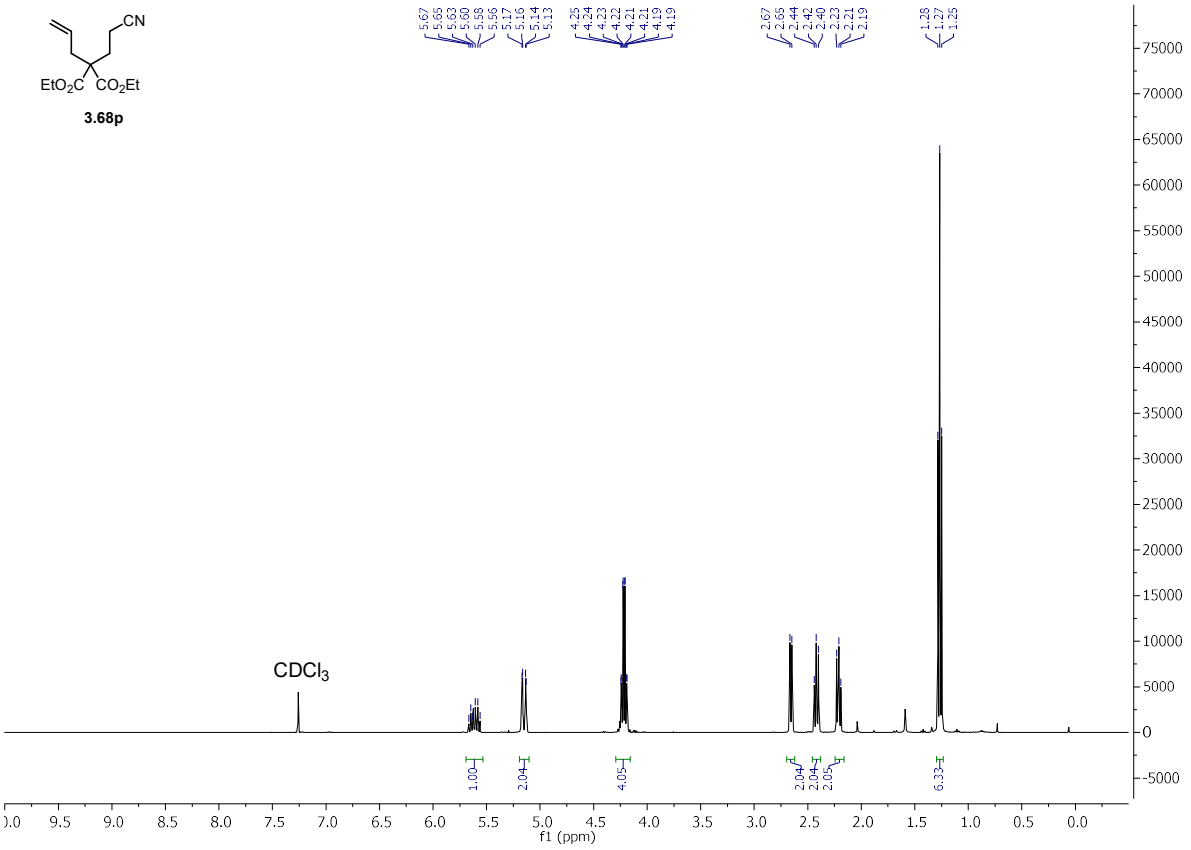
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68o**



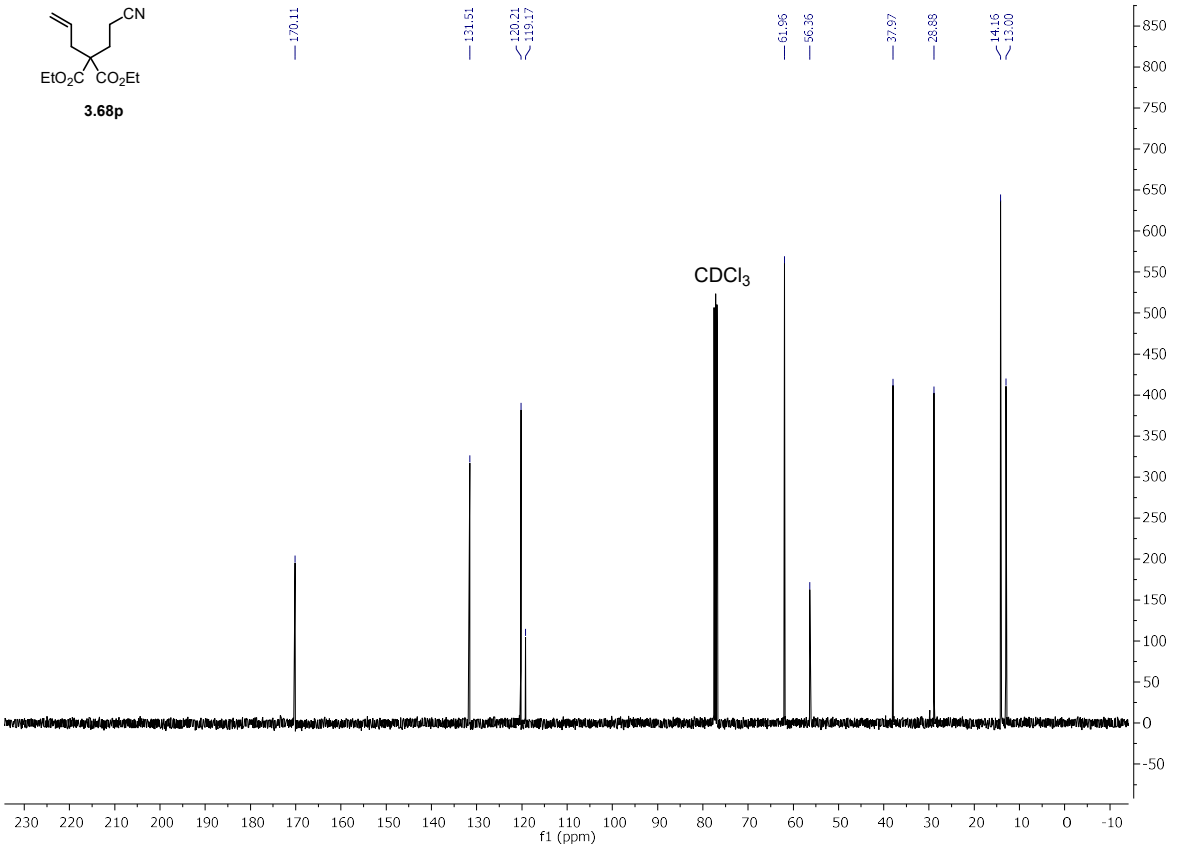
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68o**



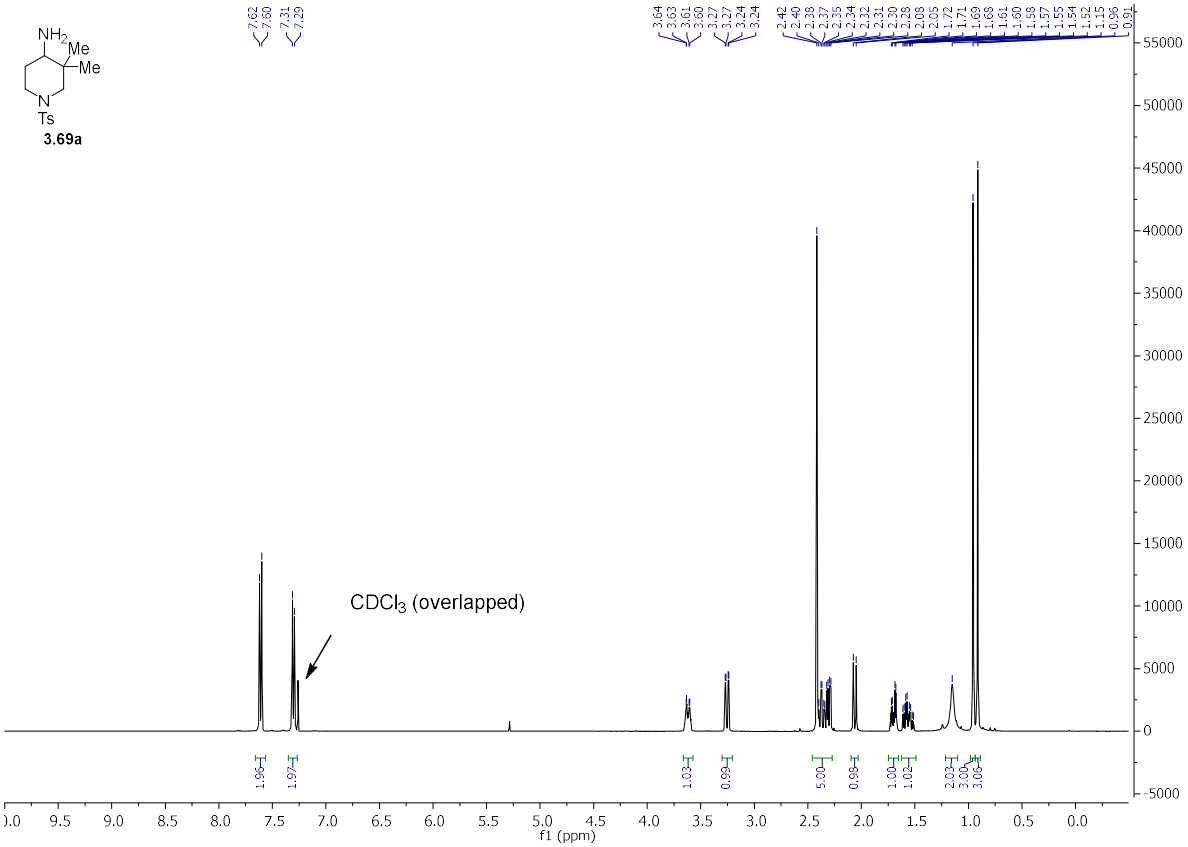
^{1}H NMR (400 MHz, $CDCl_3$) of **3.68p**



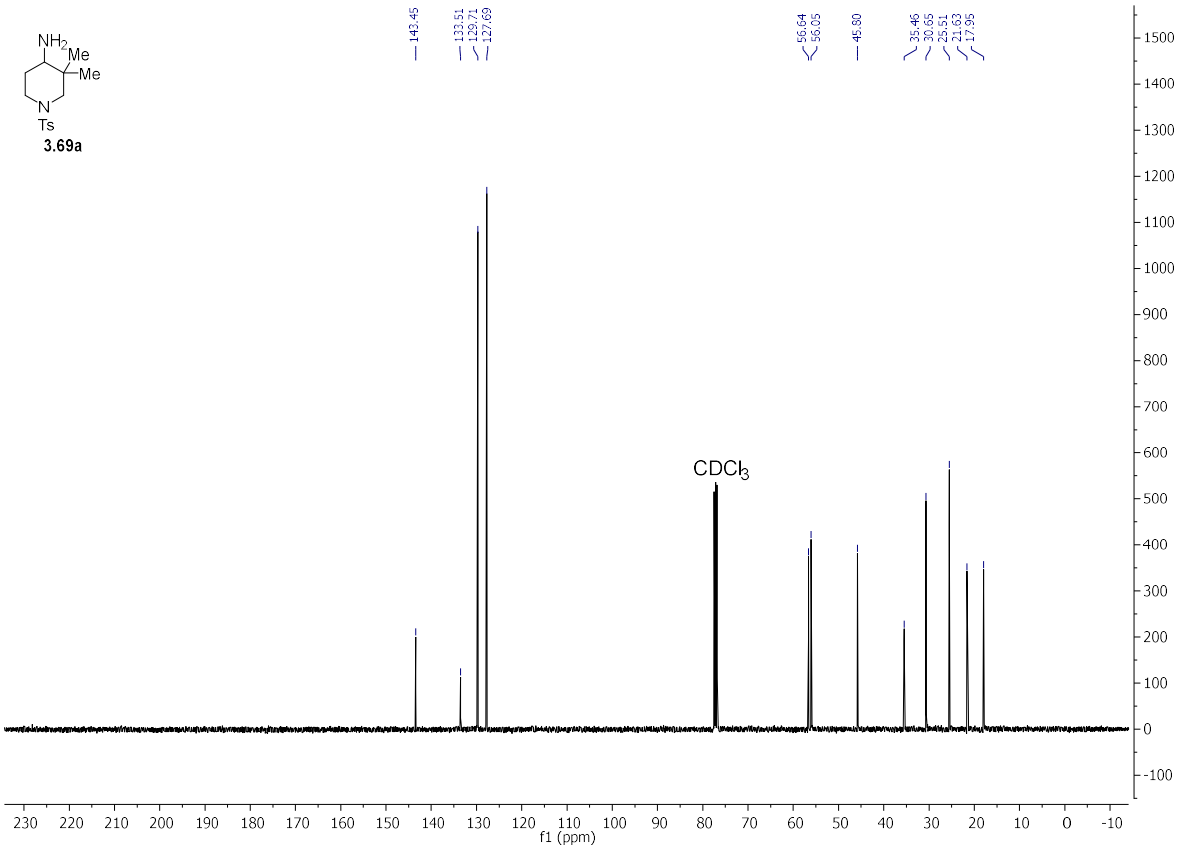
^{13}C NMR (101 MHz, $CDCl_3$) of **3.68p**



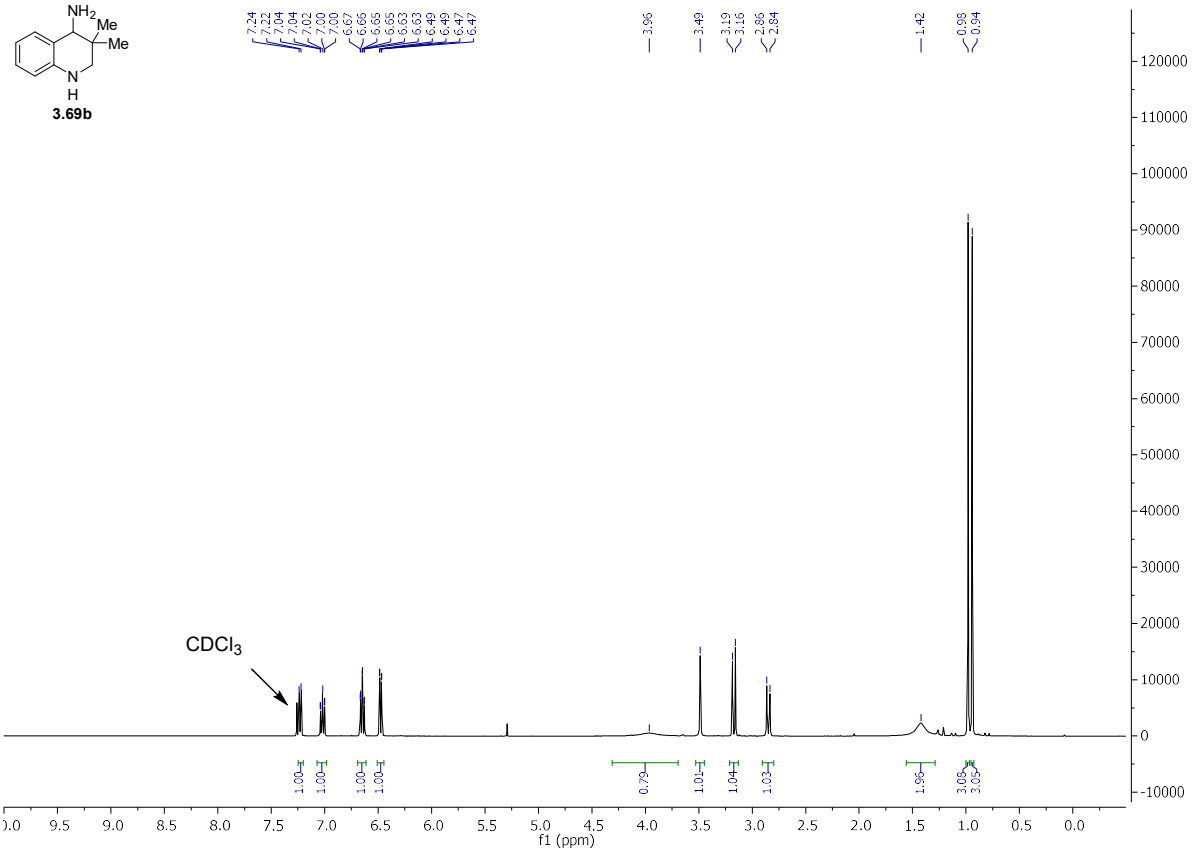
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69a**



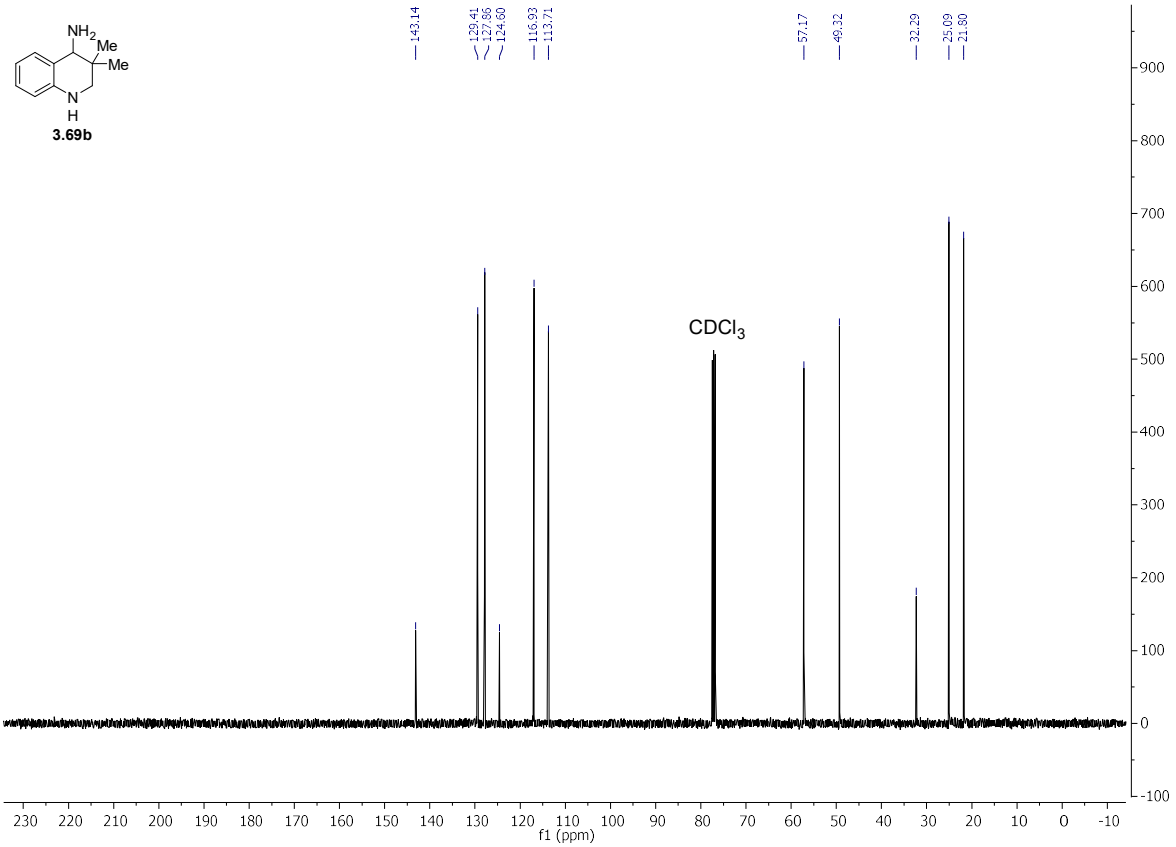
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69a**



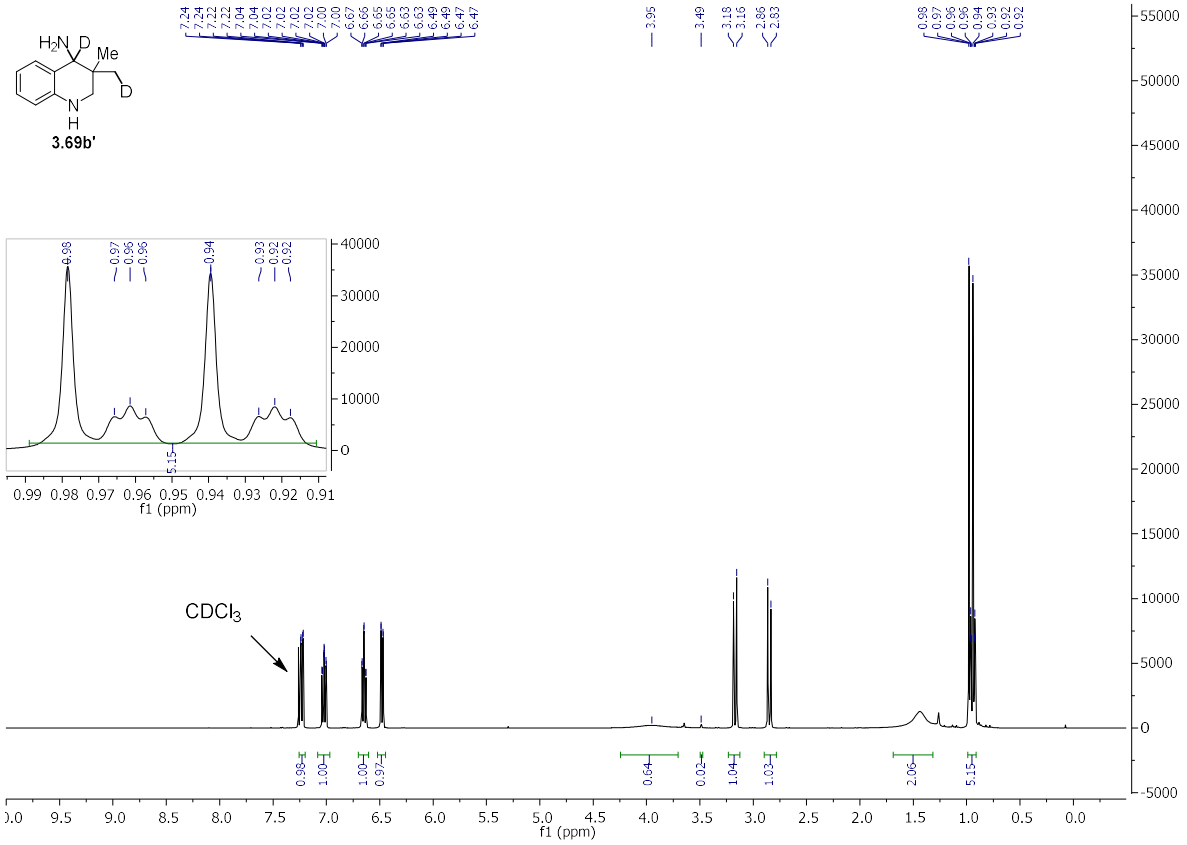
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69b**



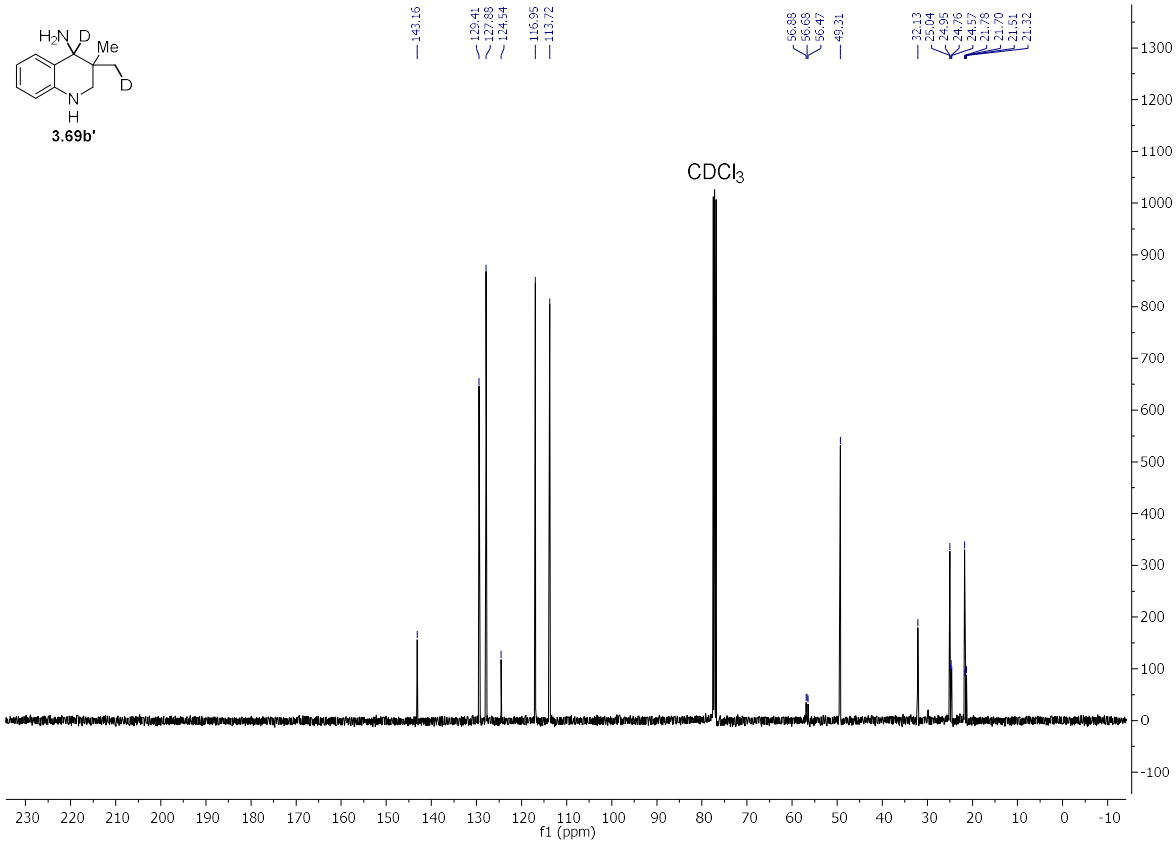
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69b**



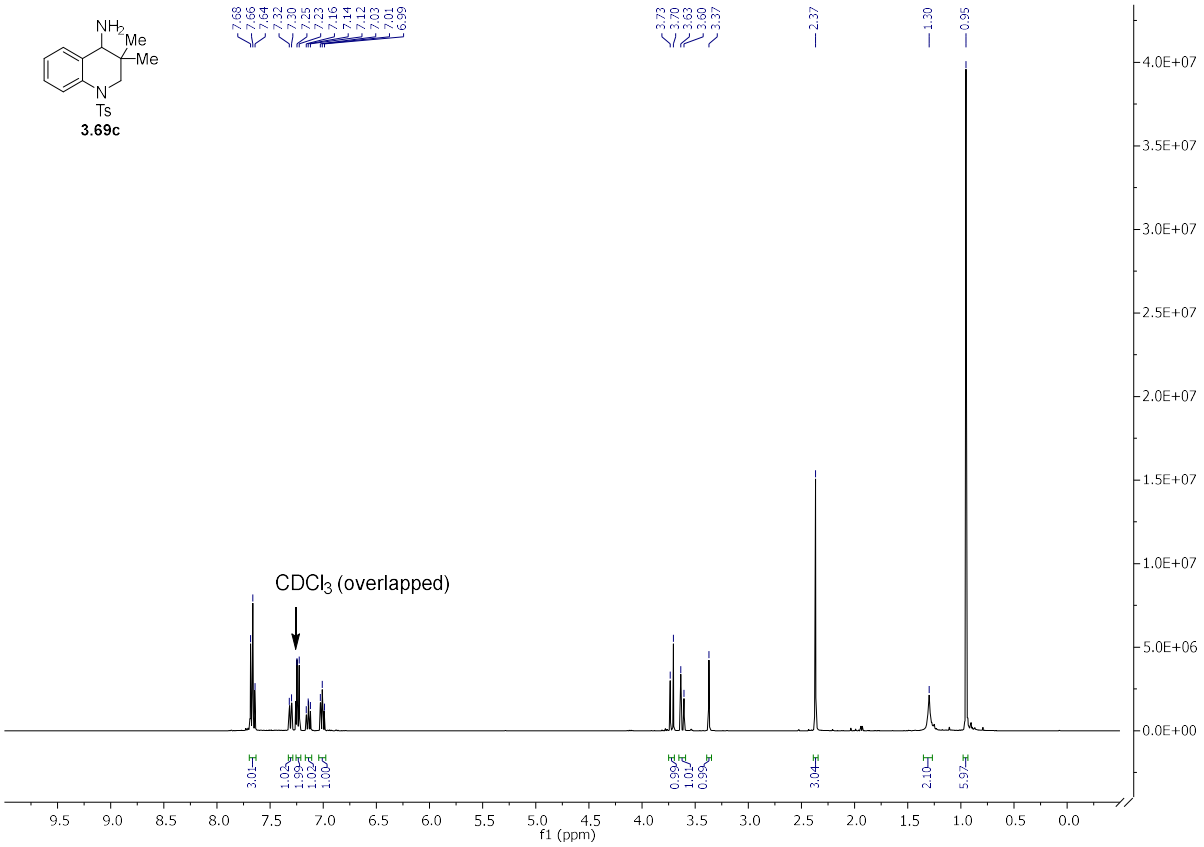
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69b'**



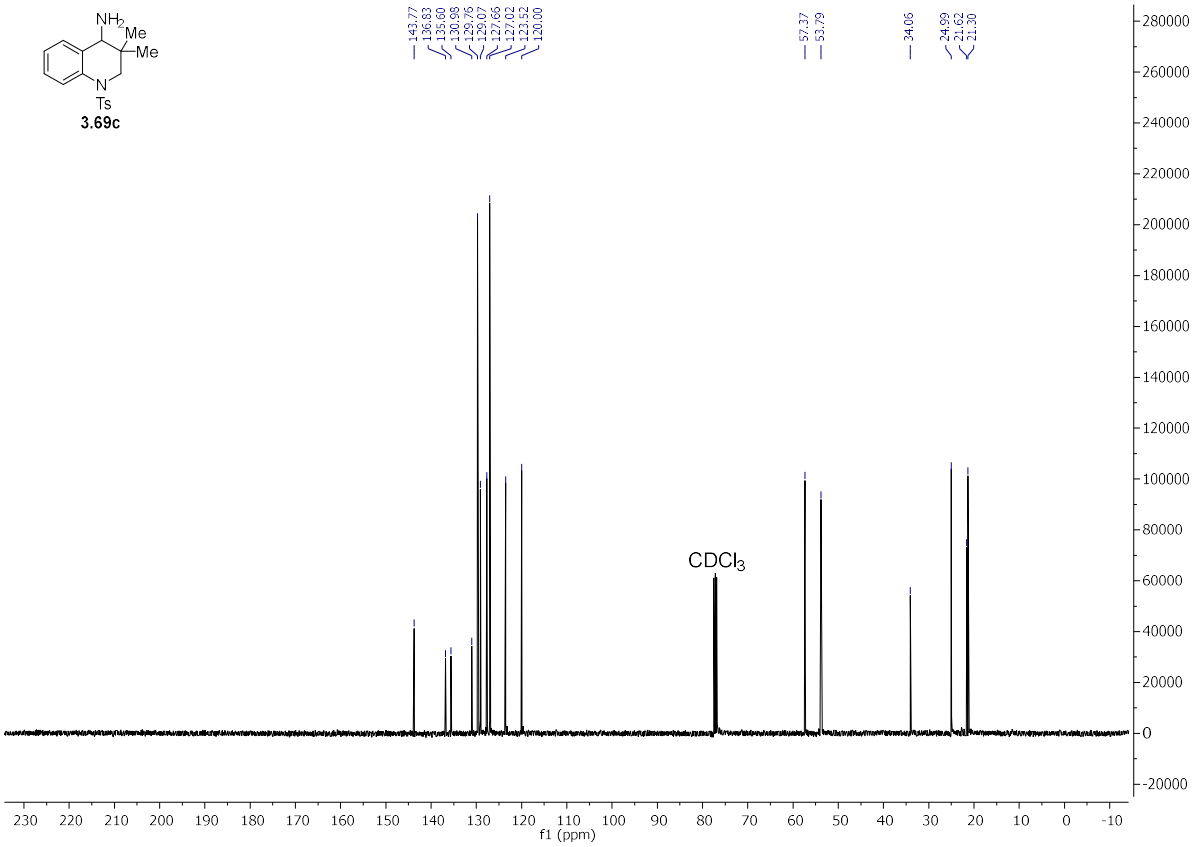
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69b'**



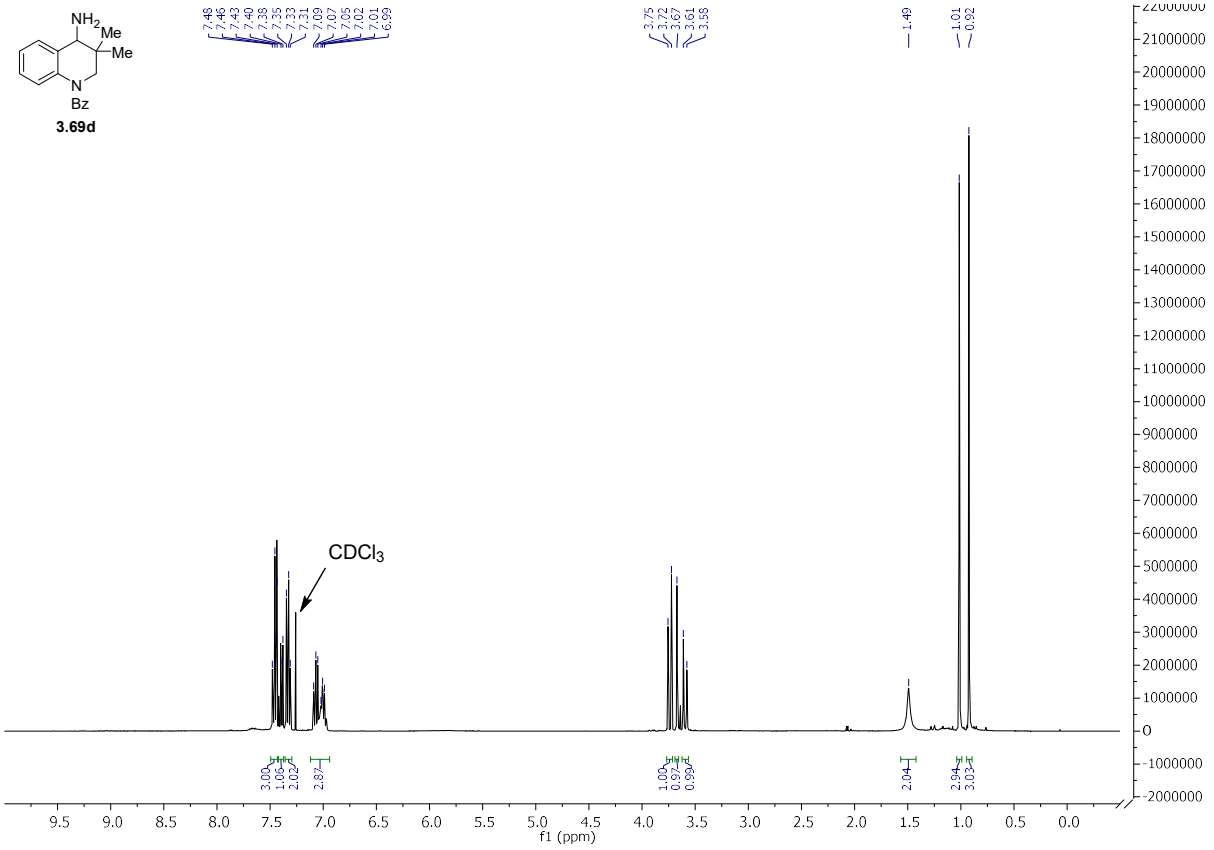
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69c**



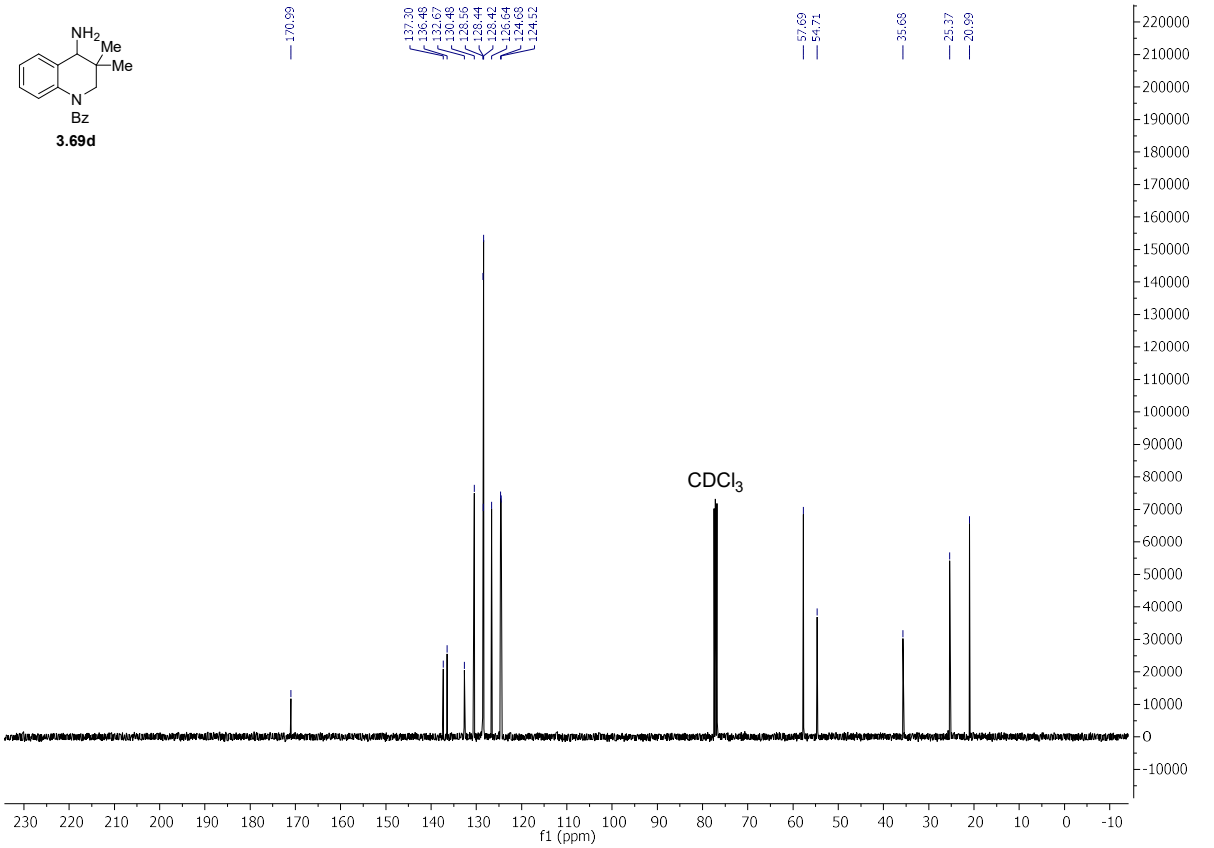
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69c**



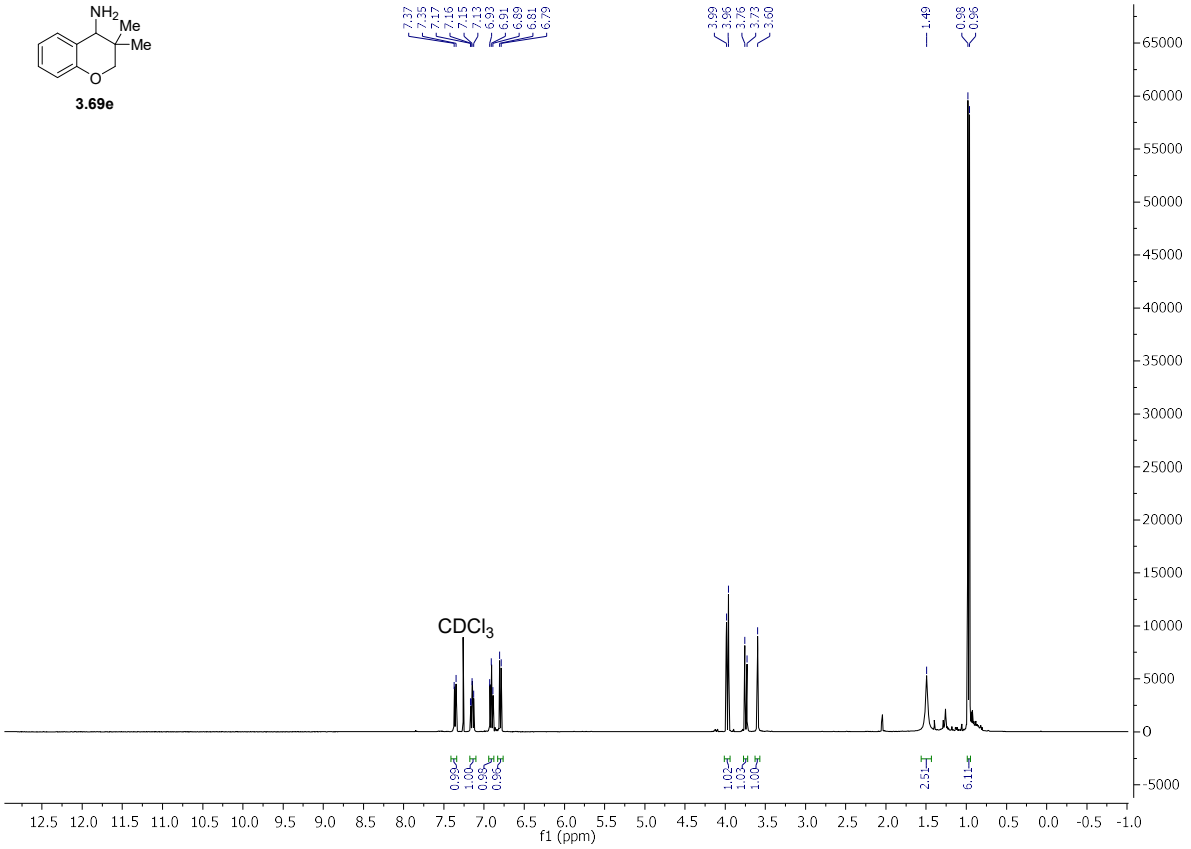
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69d**



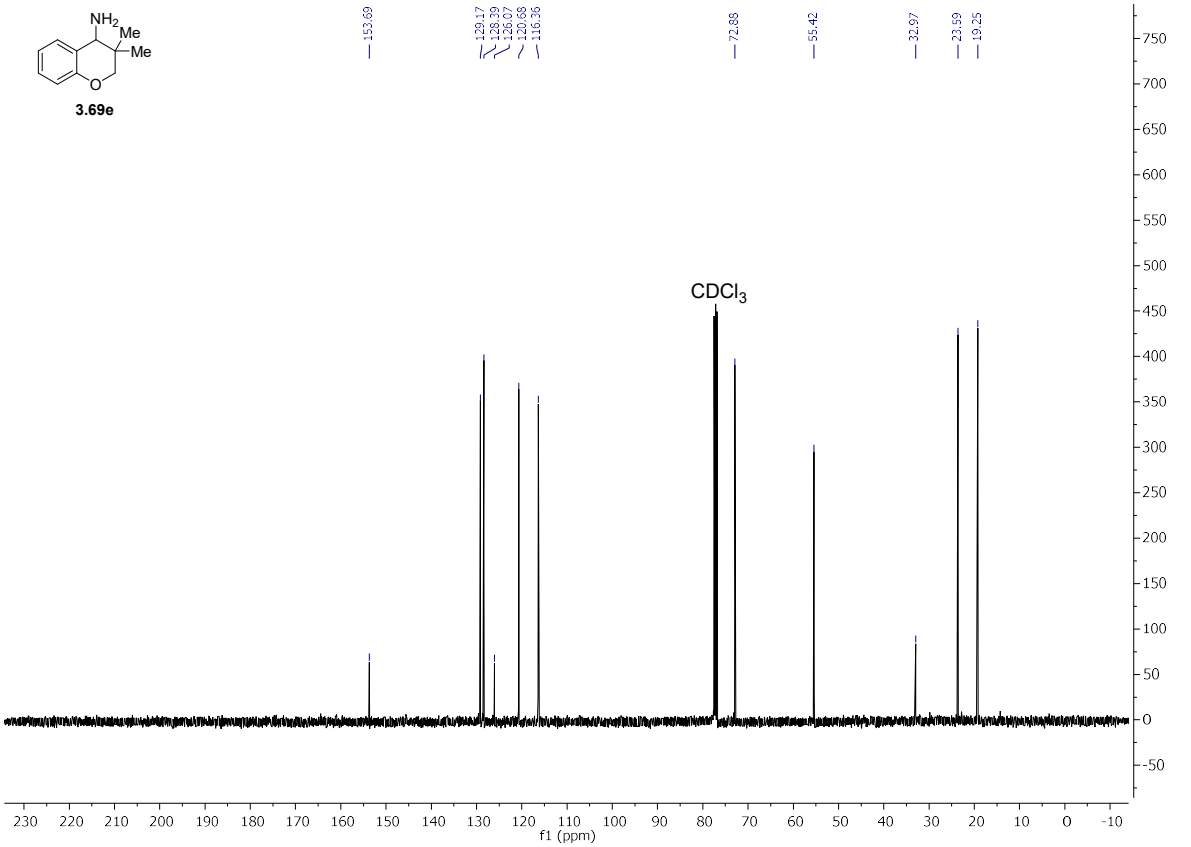
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69d**



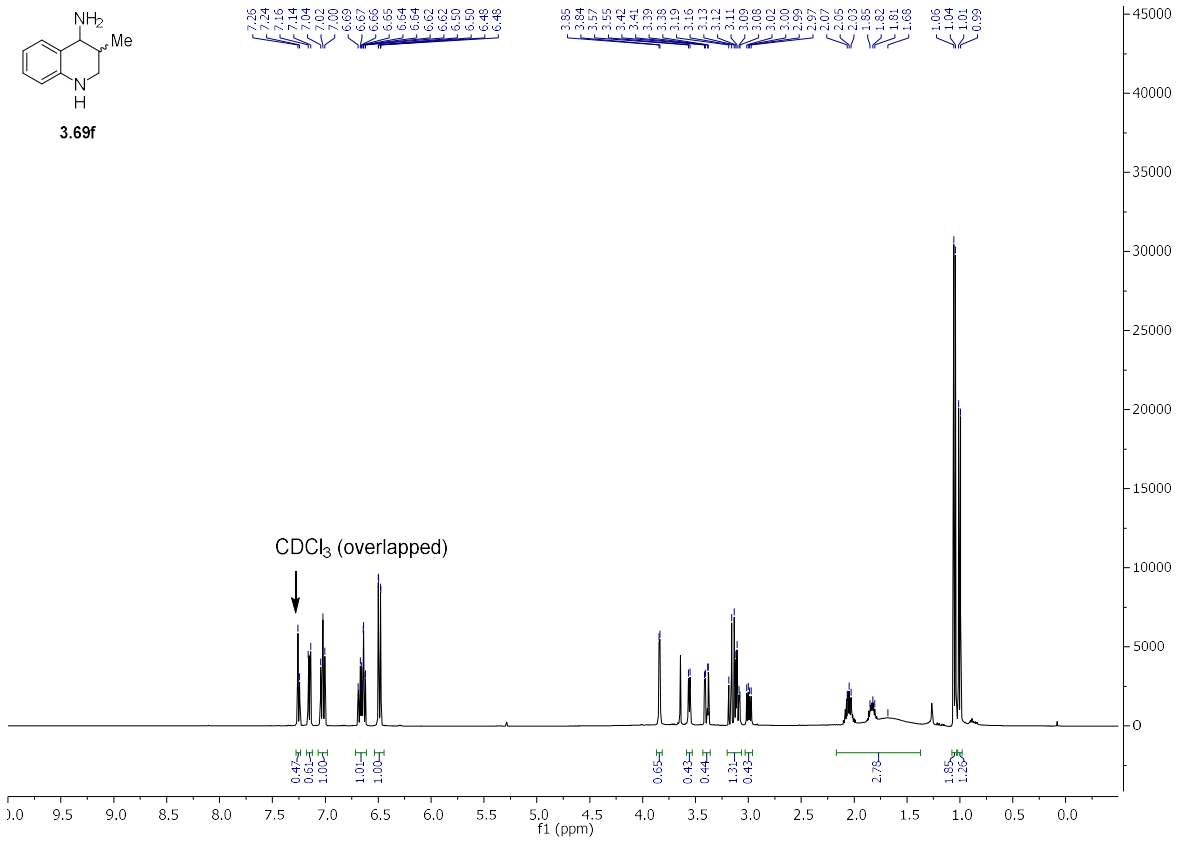
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69e**



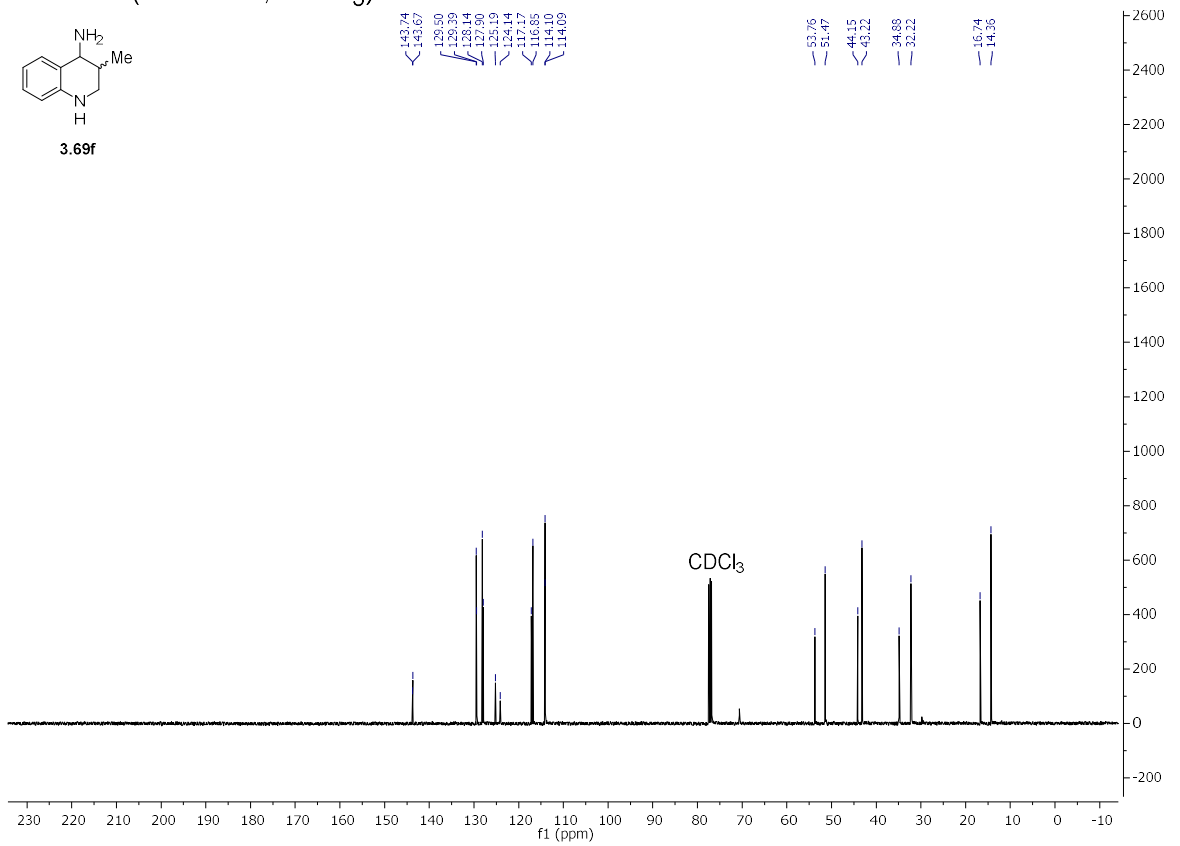
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69e**



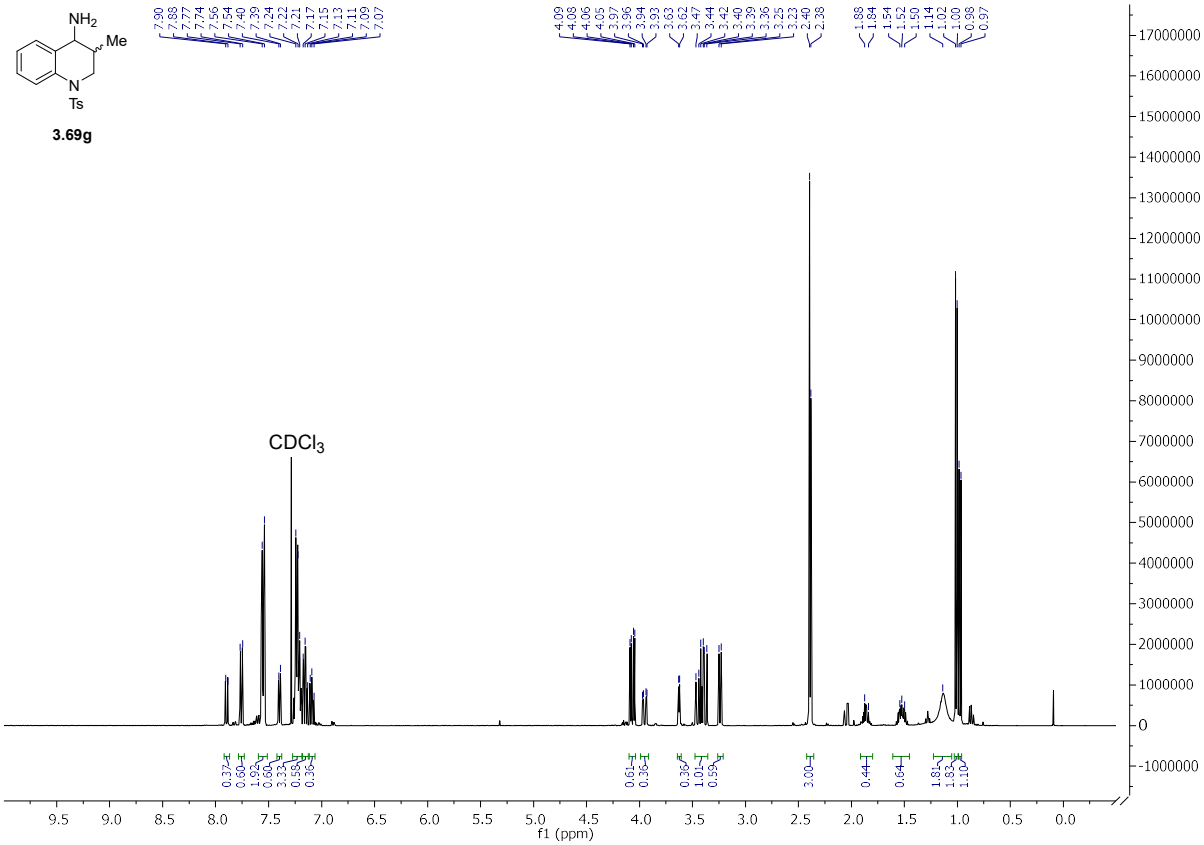
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69f**



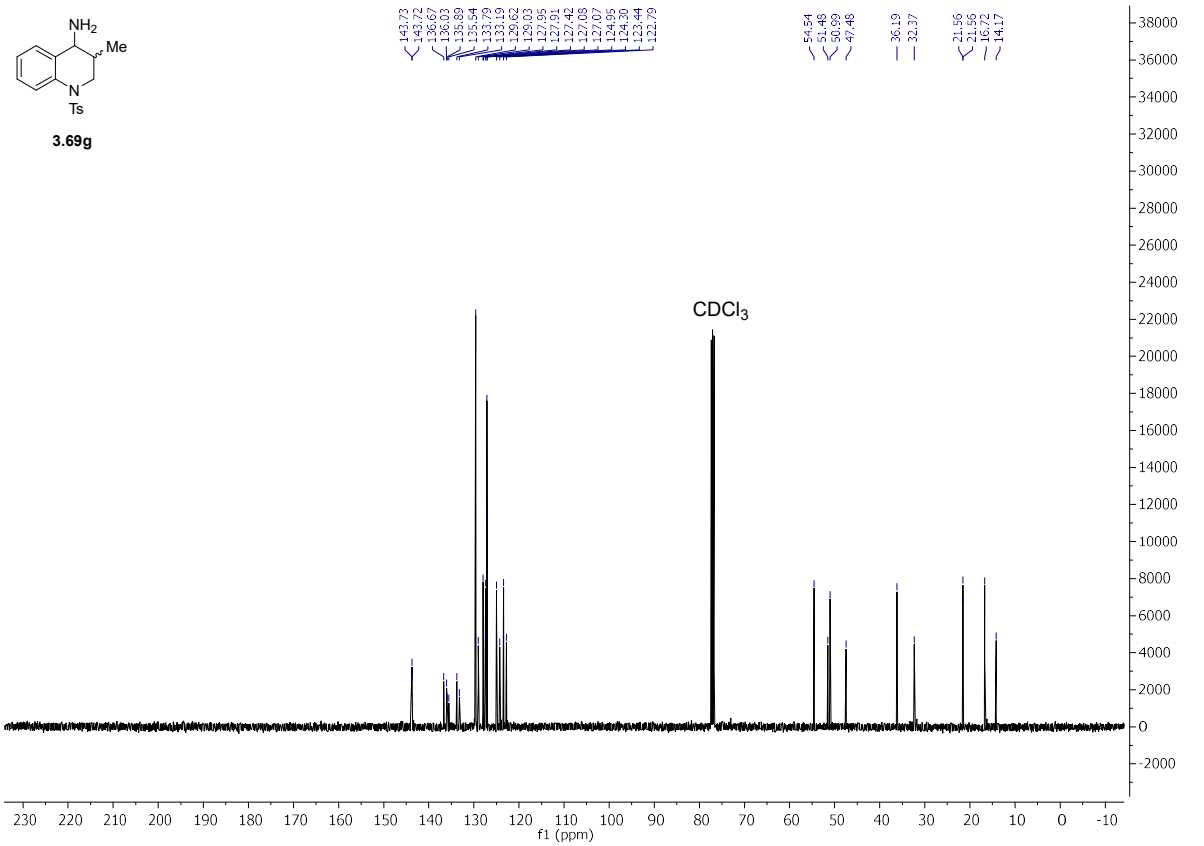
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69f**



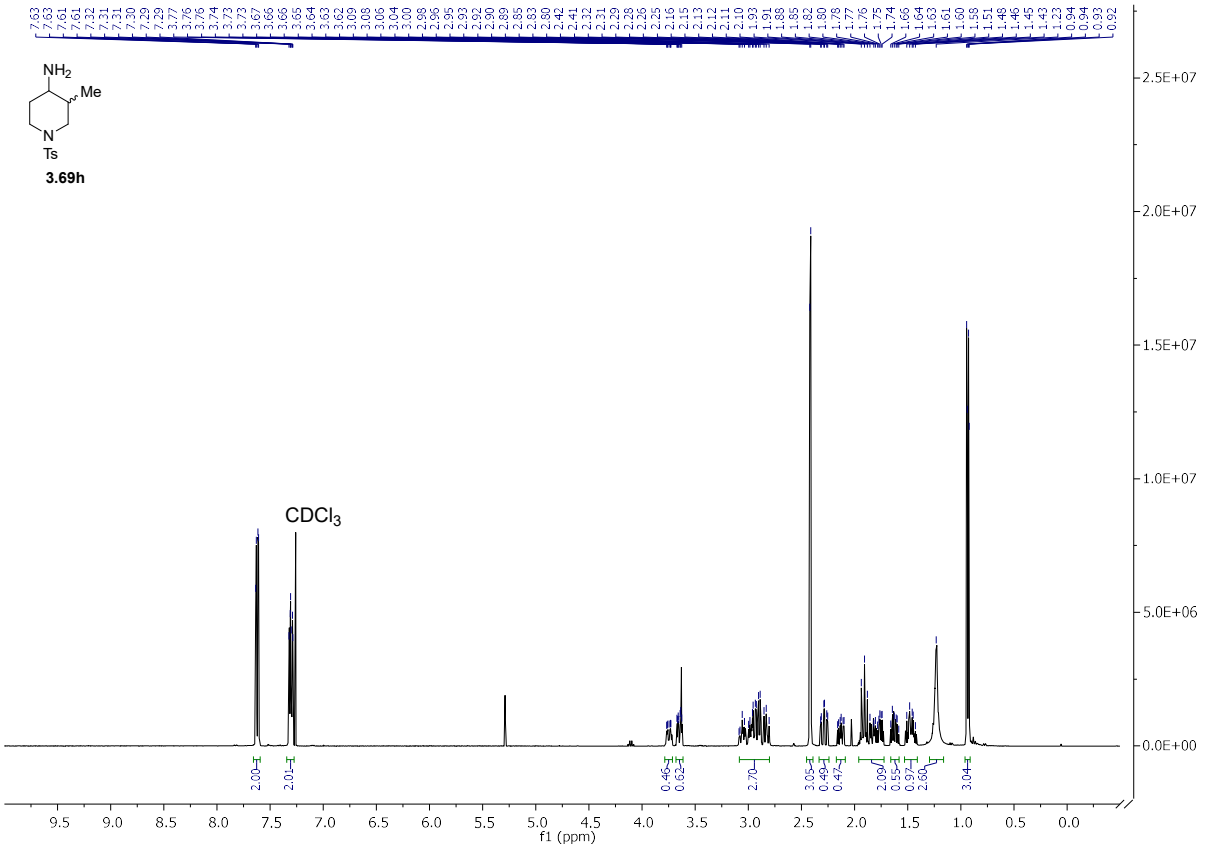
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69g**



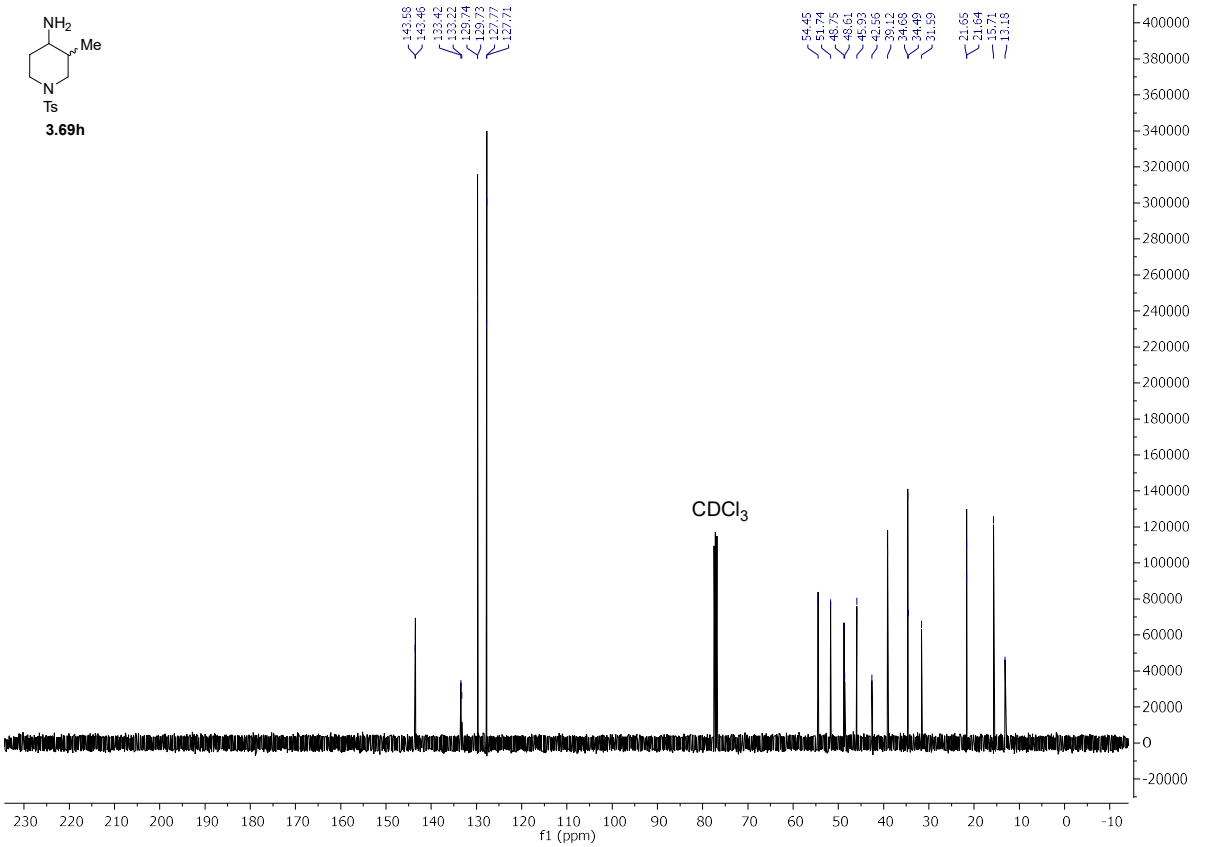
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69g**



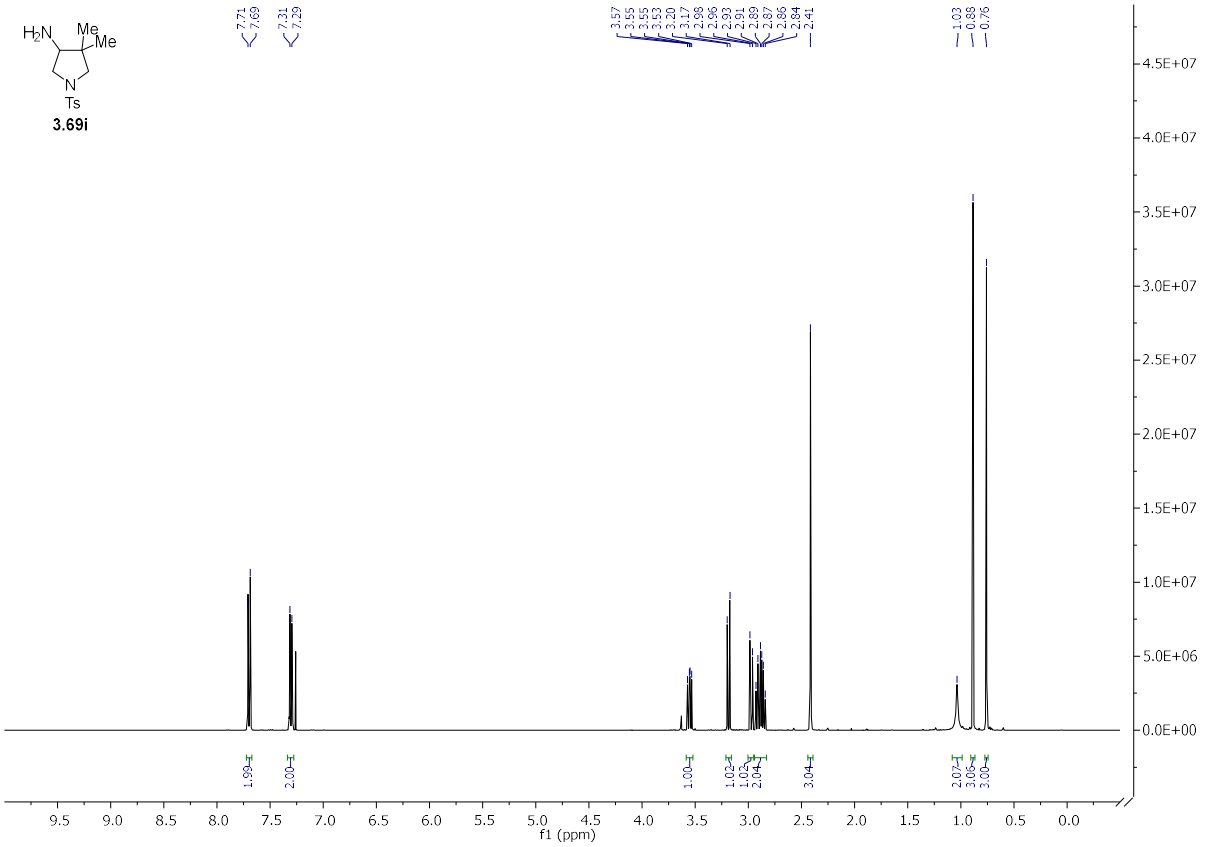
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69h**



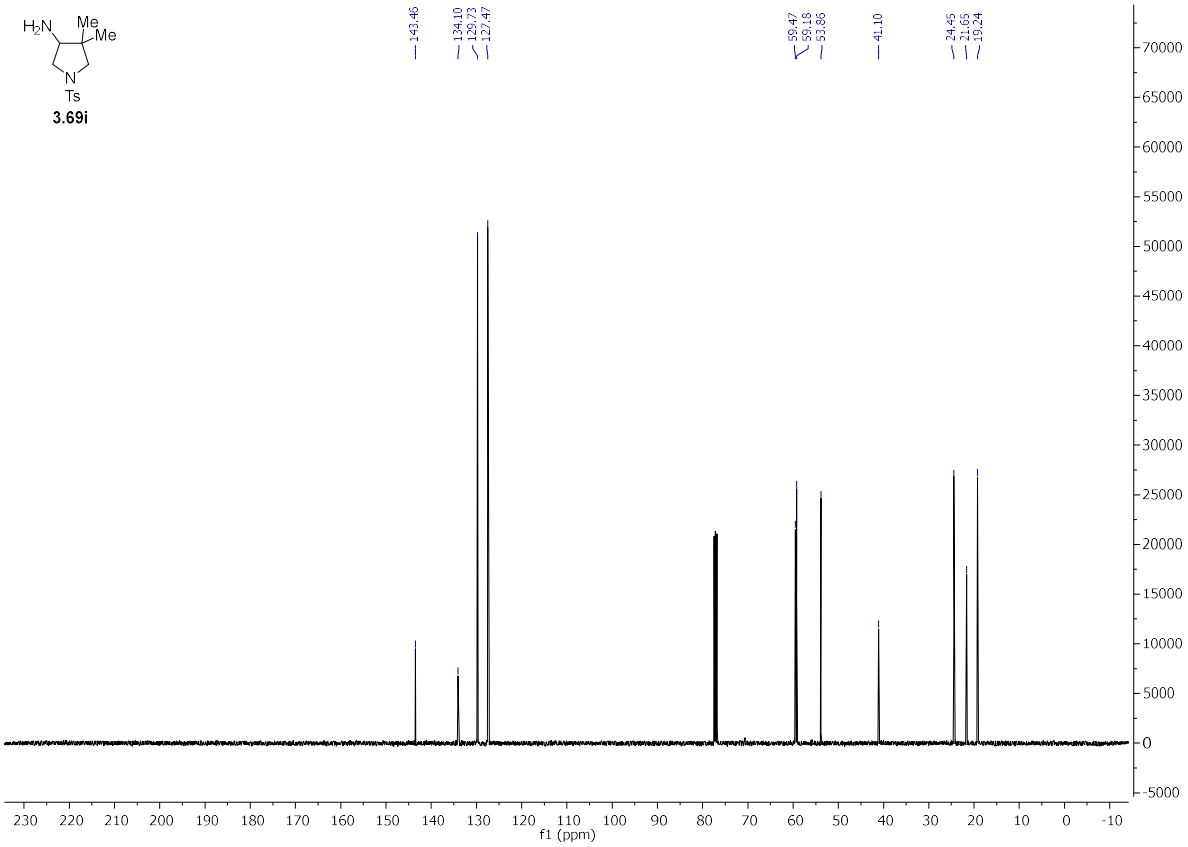
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69h**



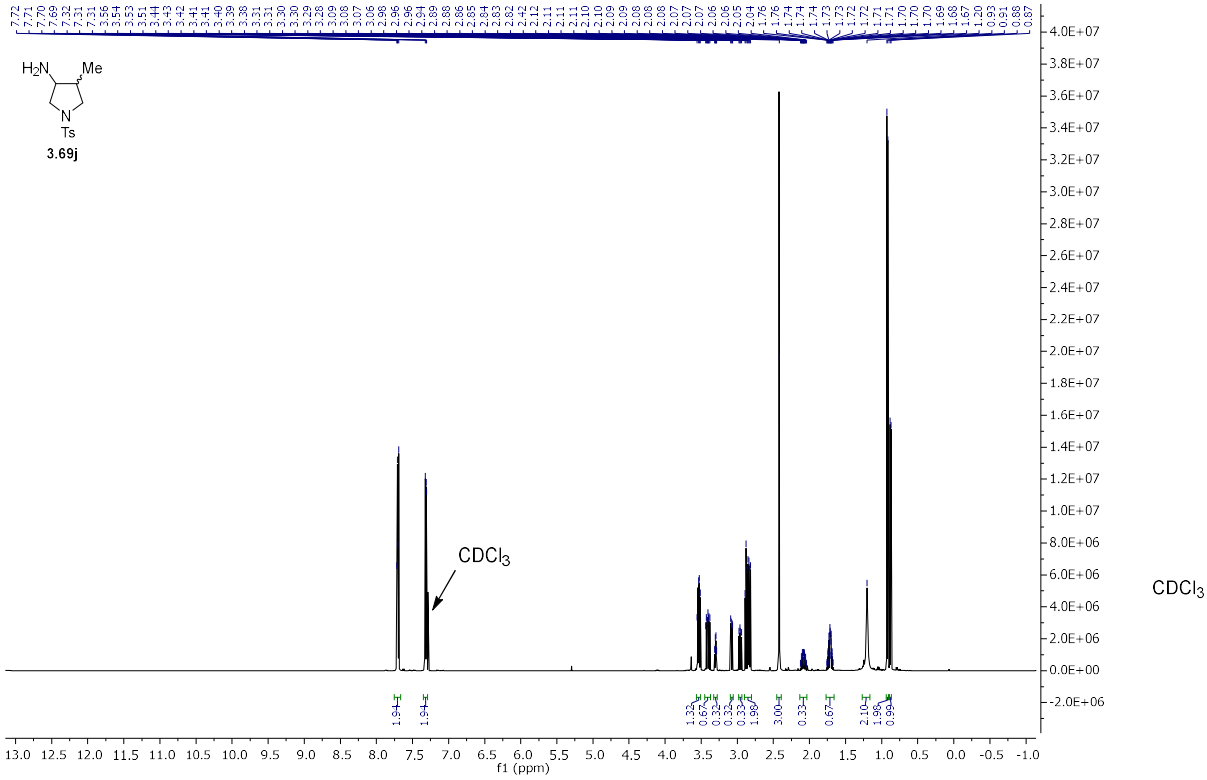
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69i**



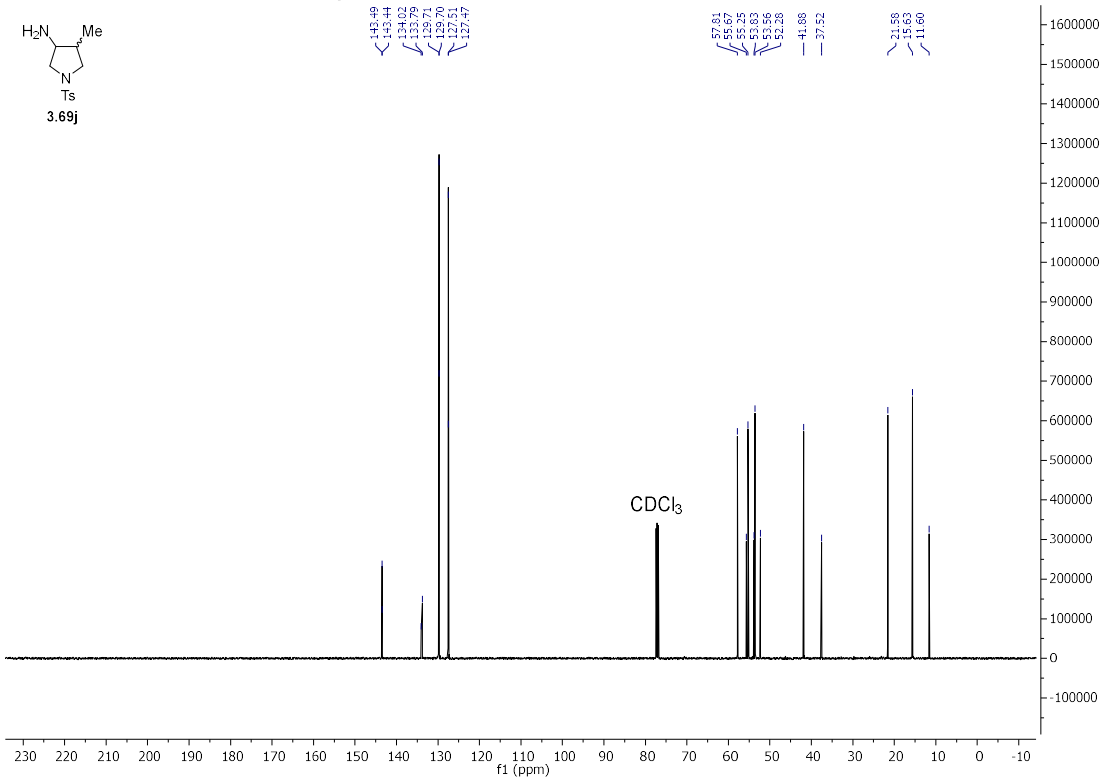
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69i**



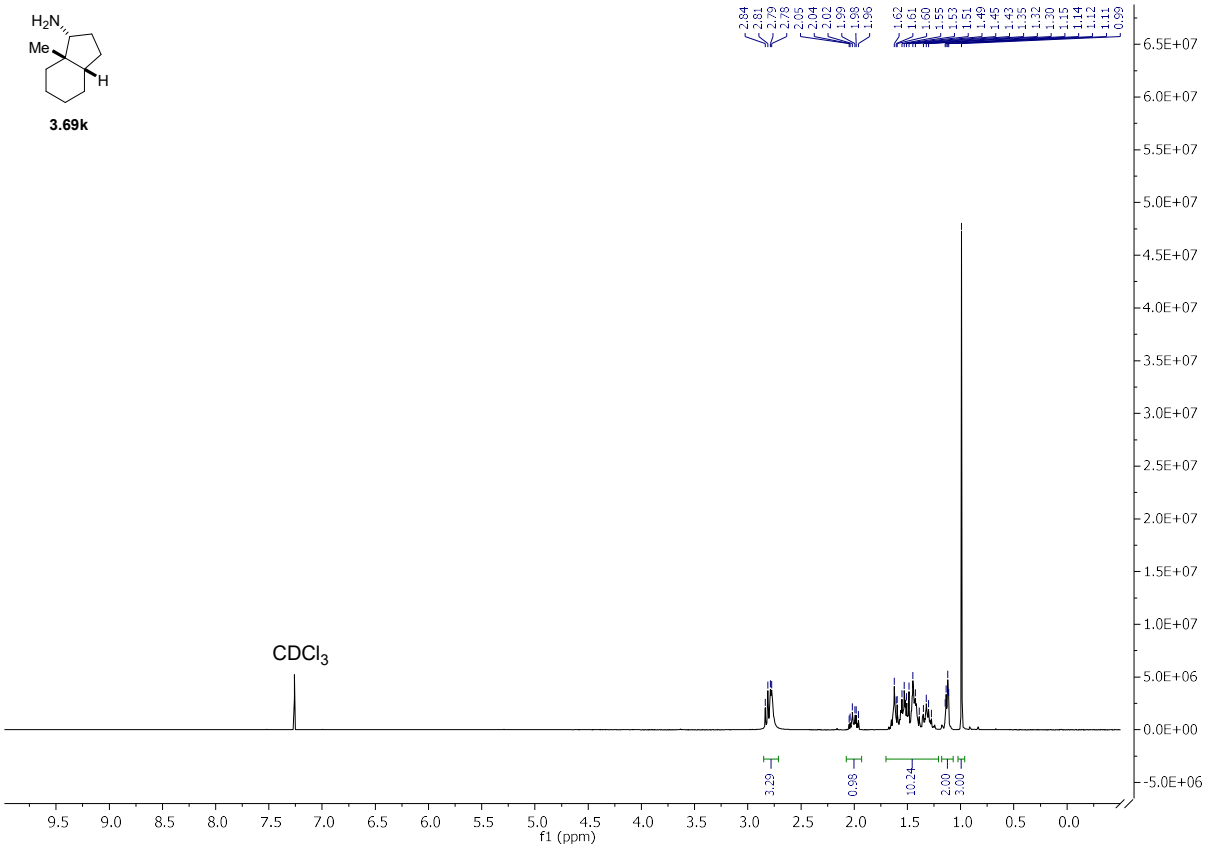
^{1}H NMR (500 MHz, $CDCl_3$) of **3.69j**



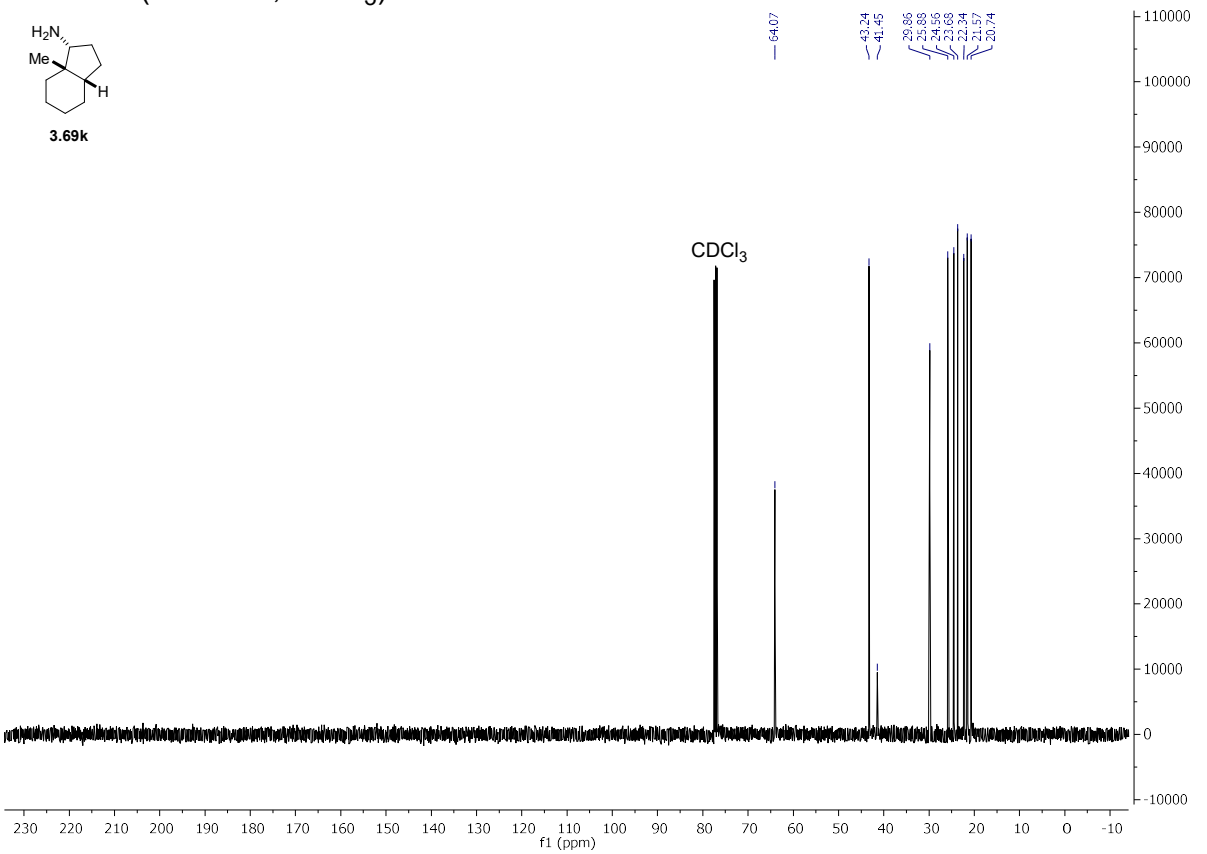
^{13}C NMR (126 MHz, $CDCl_3$) of **3.69j**



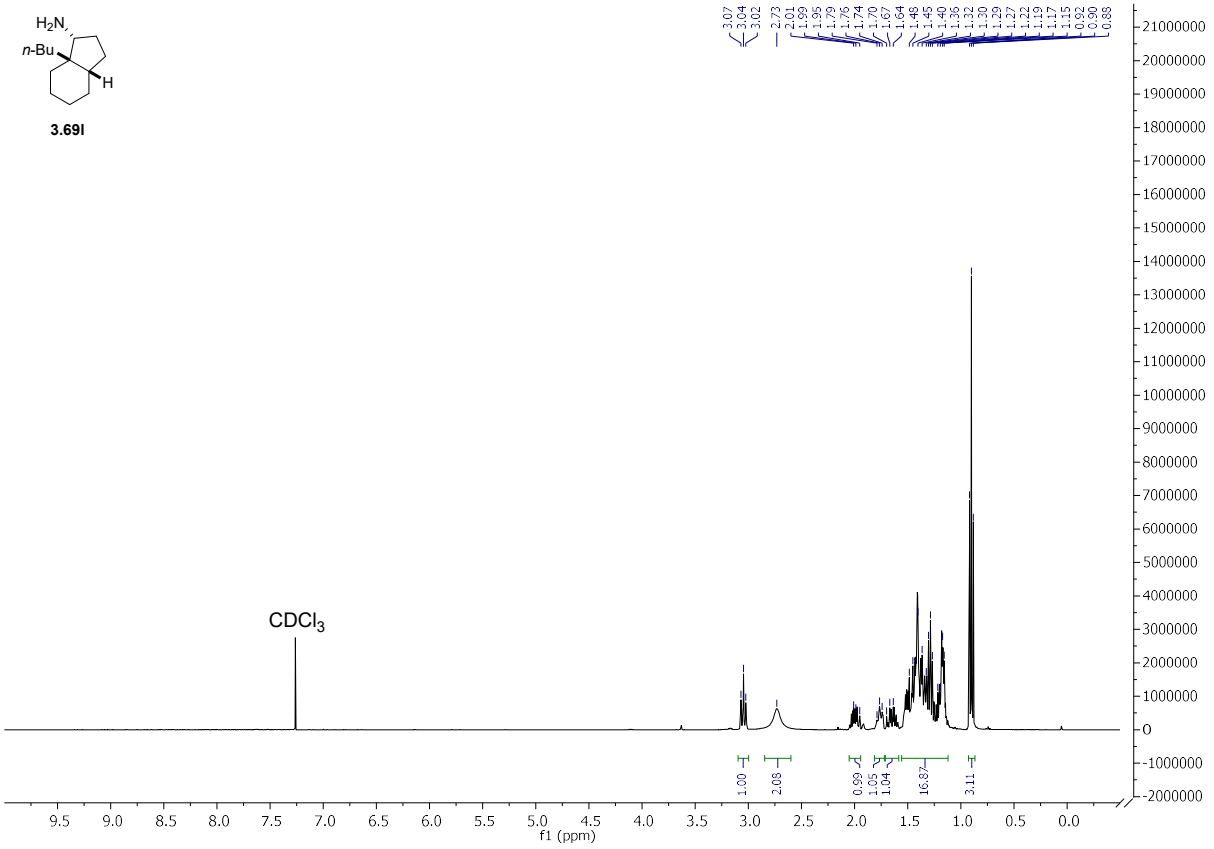
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69k**



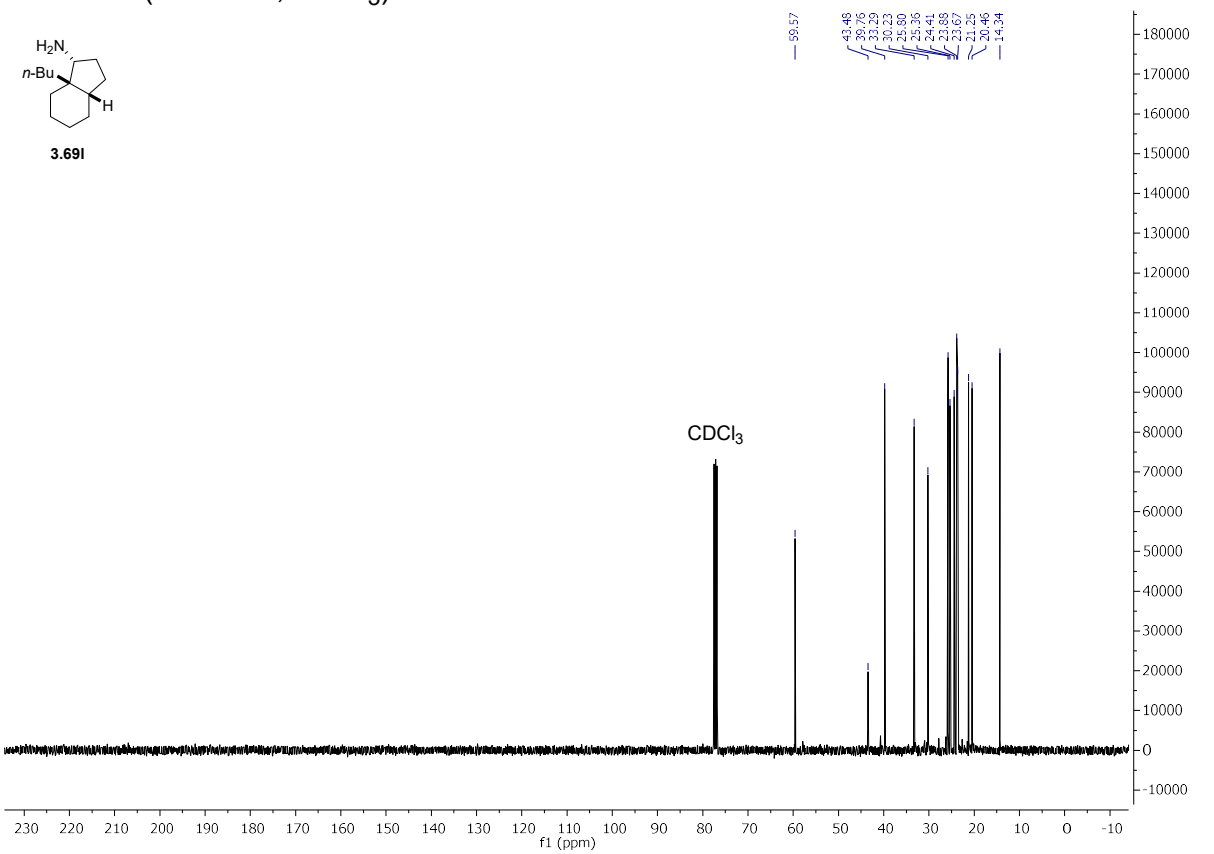
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69k**



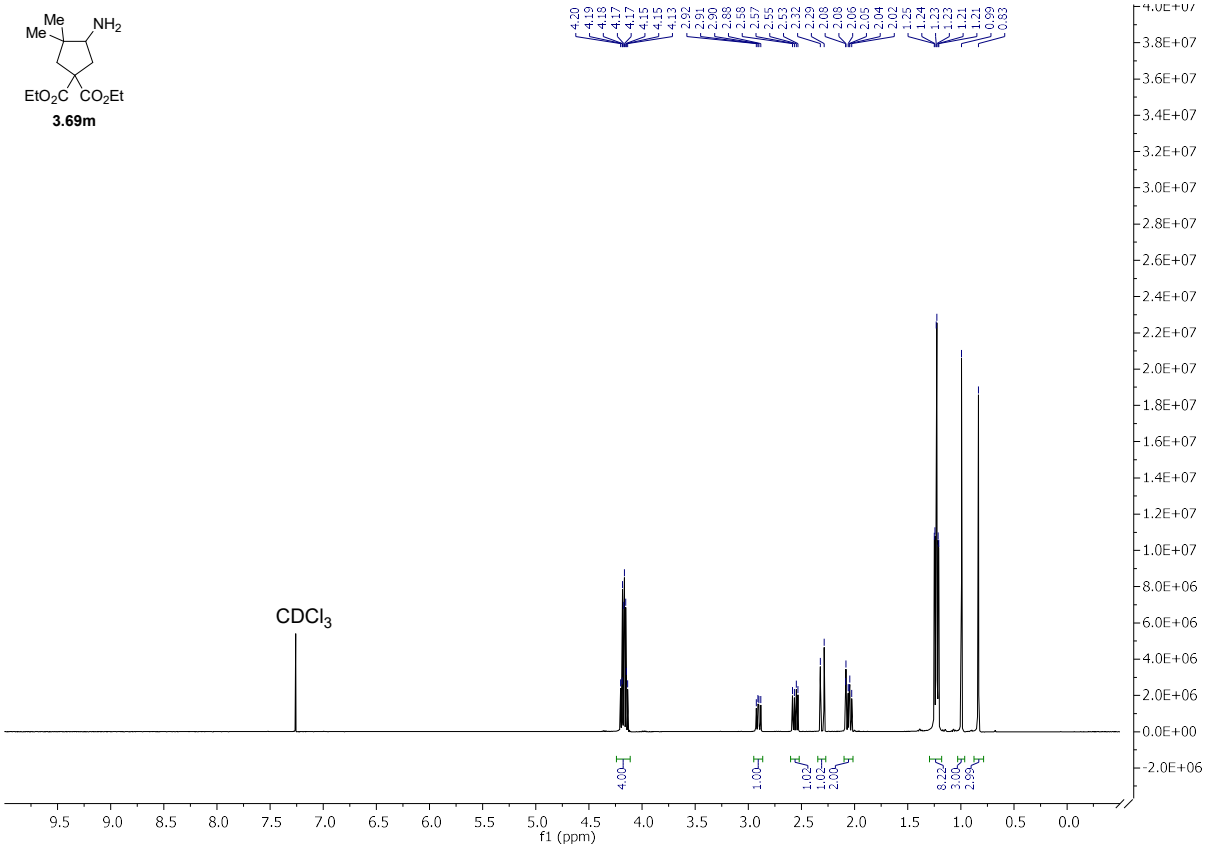
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69l**



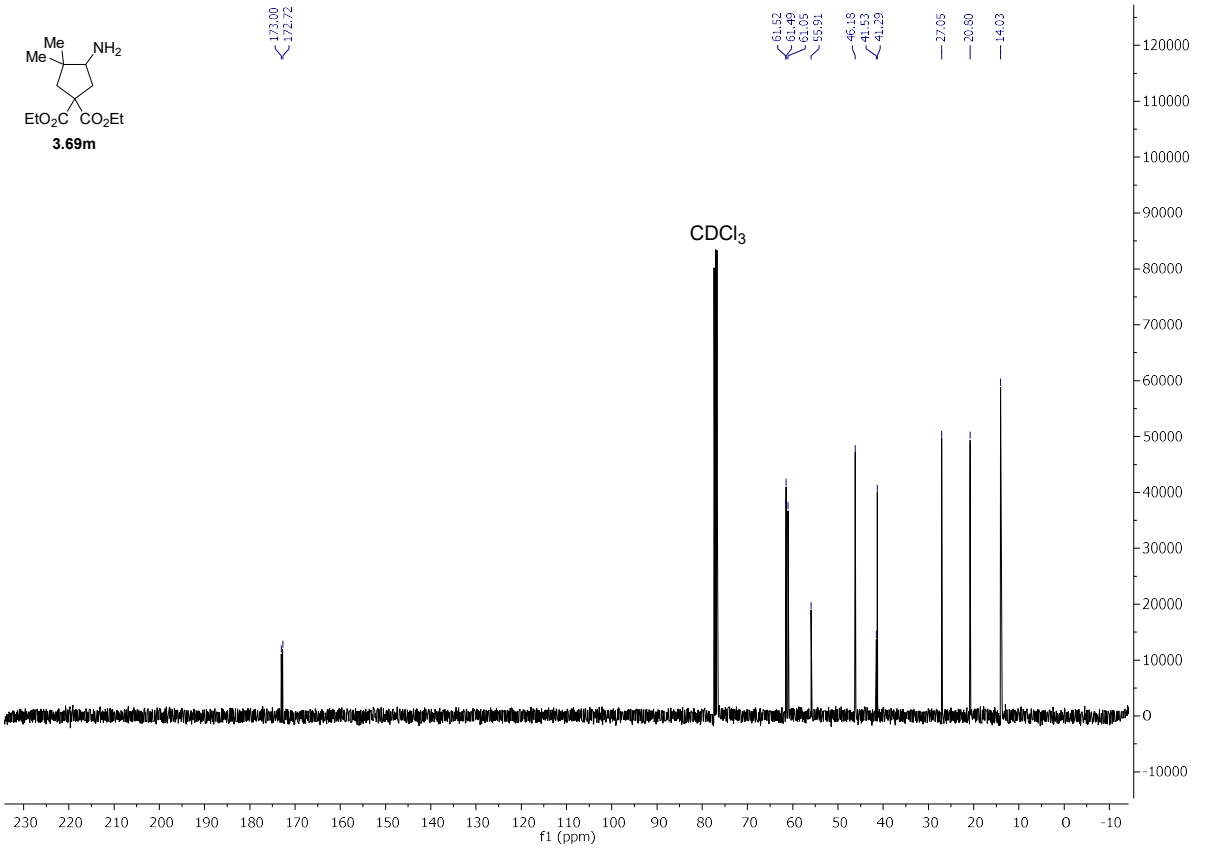
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69l**



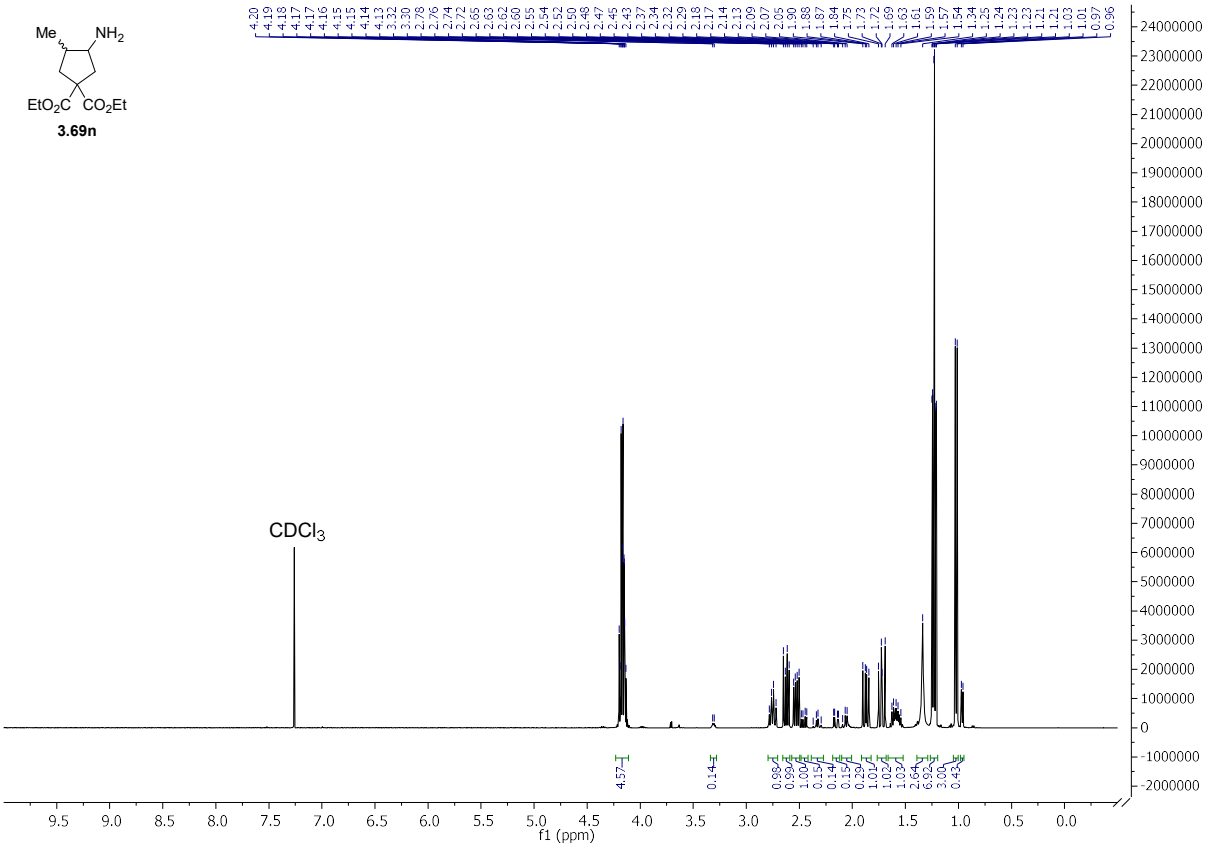
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69m**



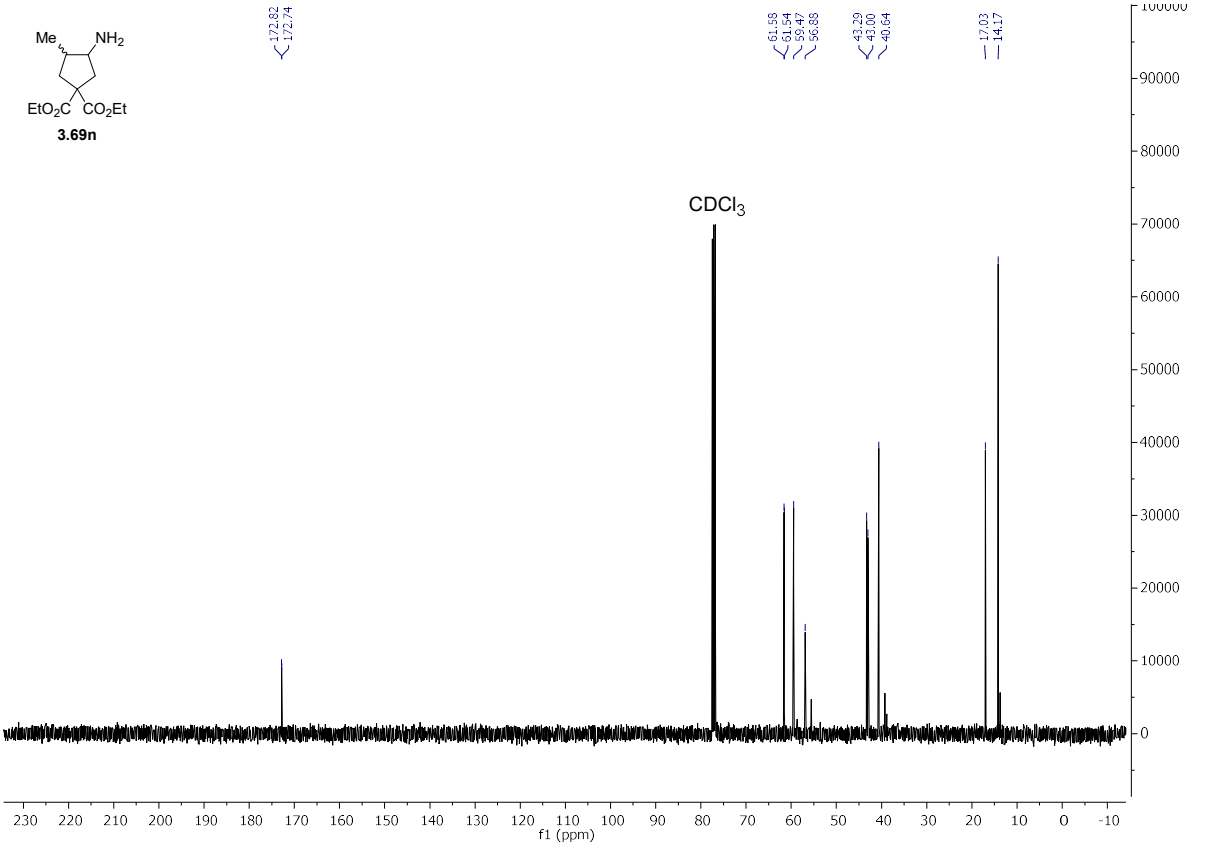
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69m**



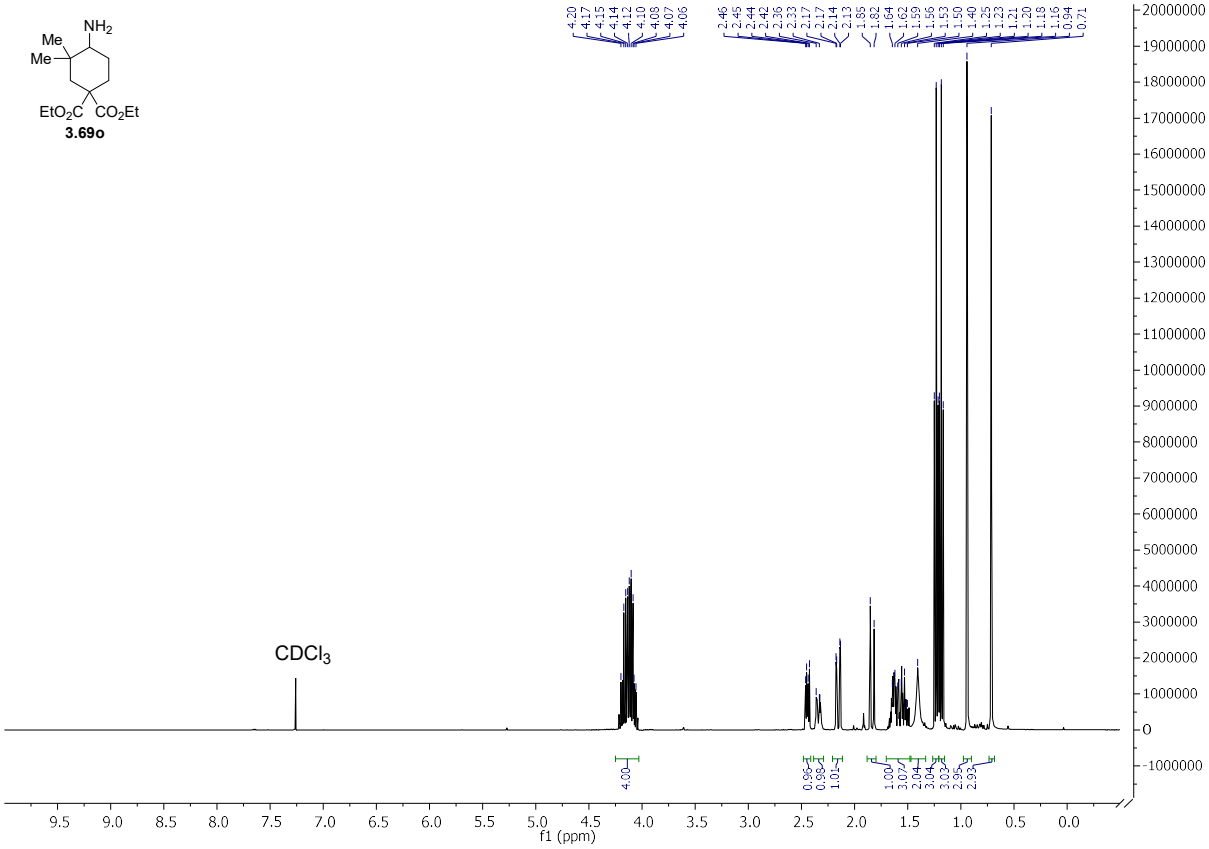
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69n**



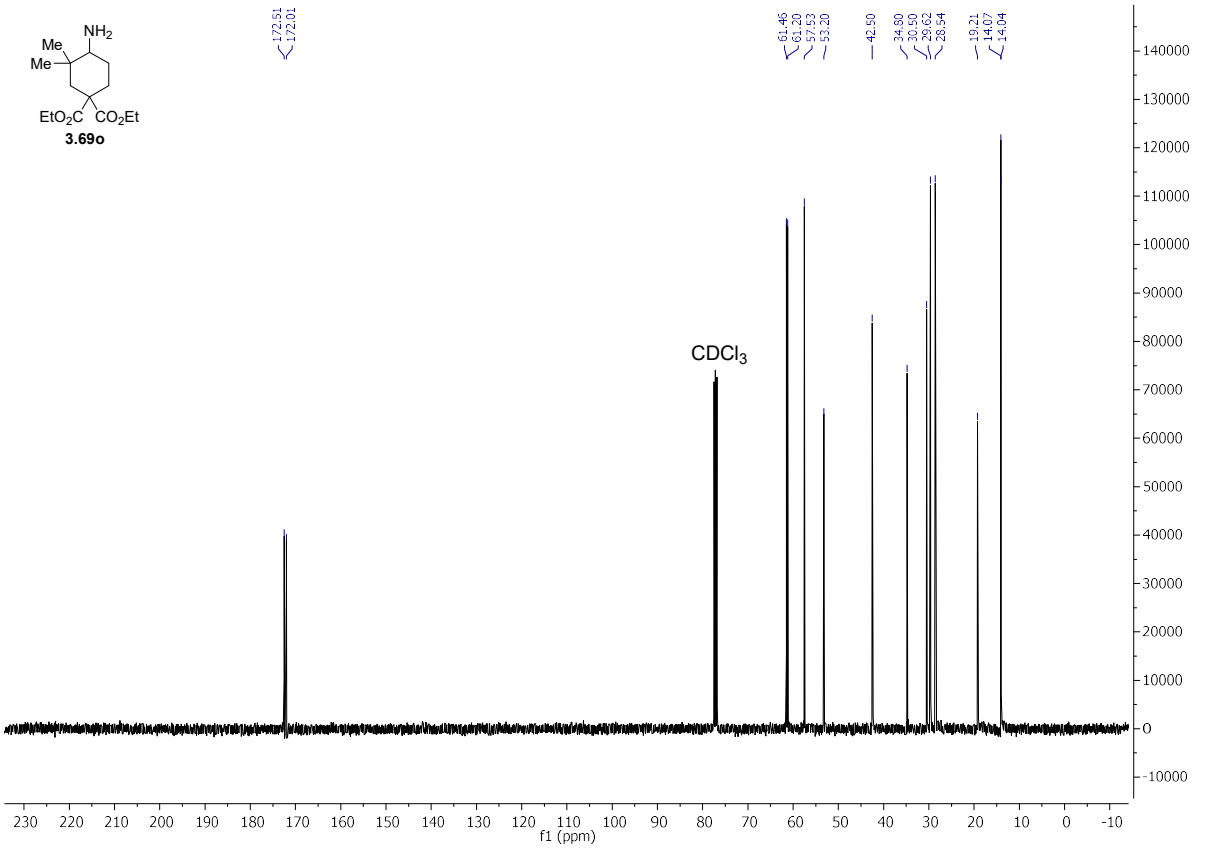
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69n**



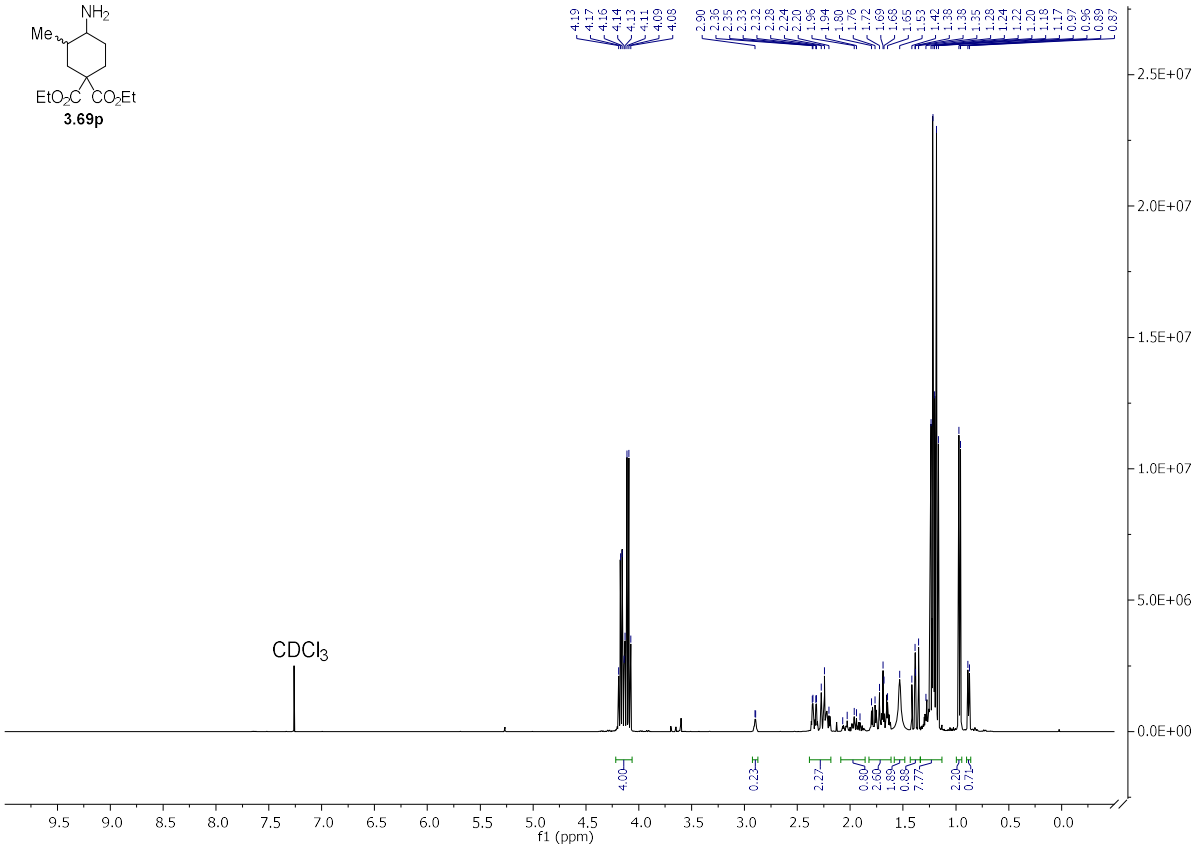
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69o**



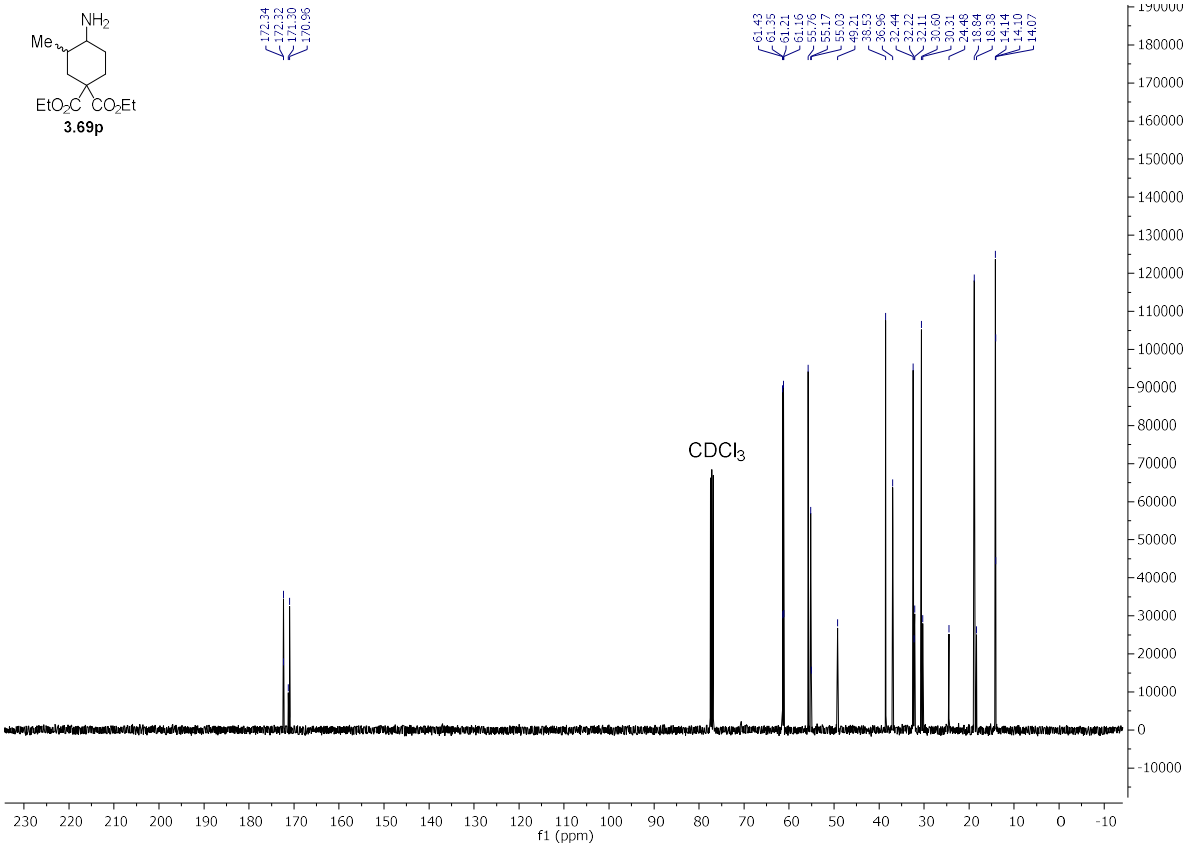
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69o**



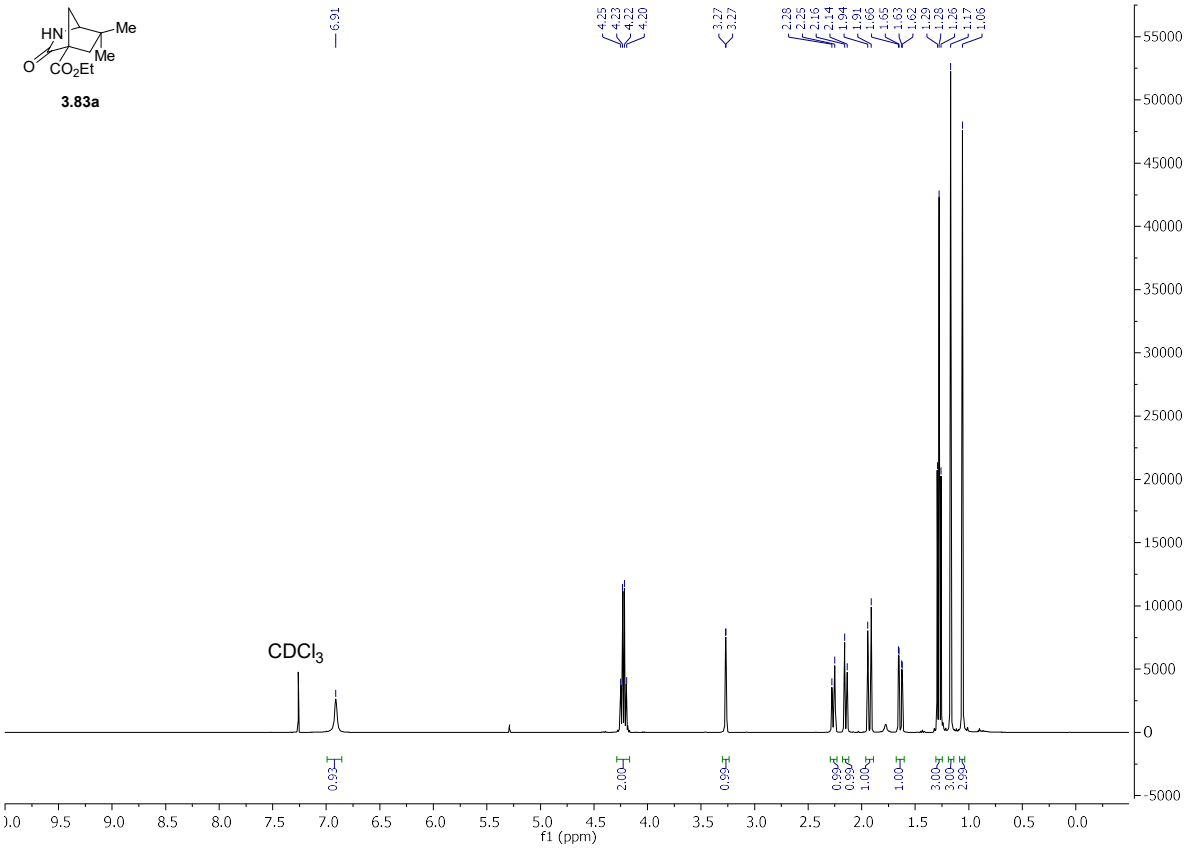
^{1}H NMR (400 MHz, $CDCl_3$) of **3.69p**



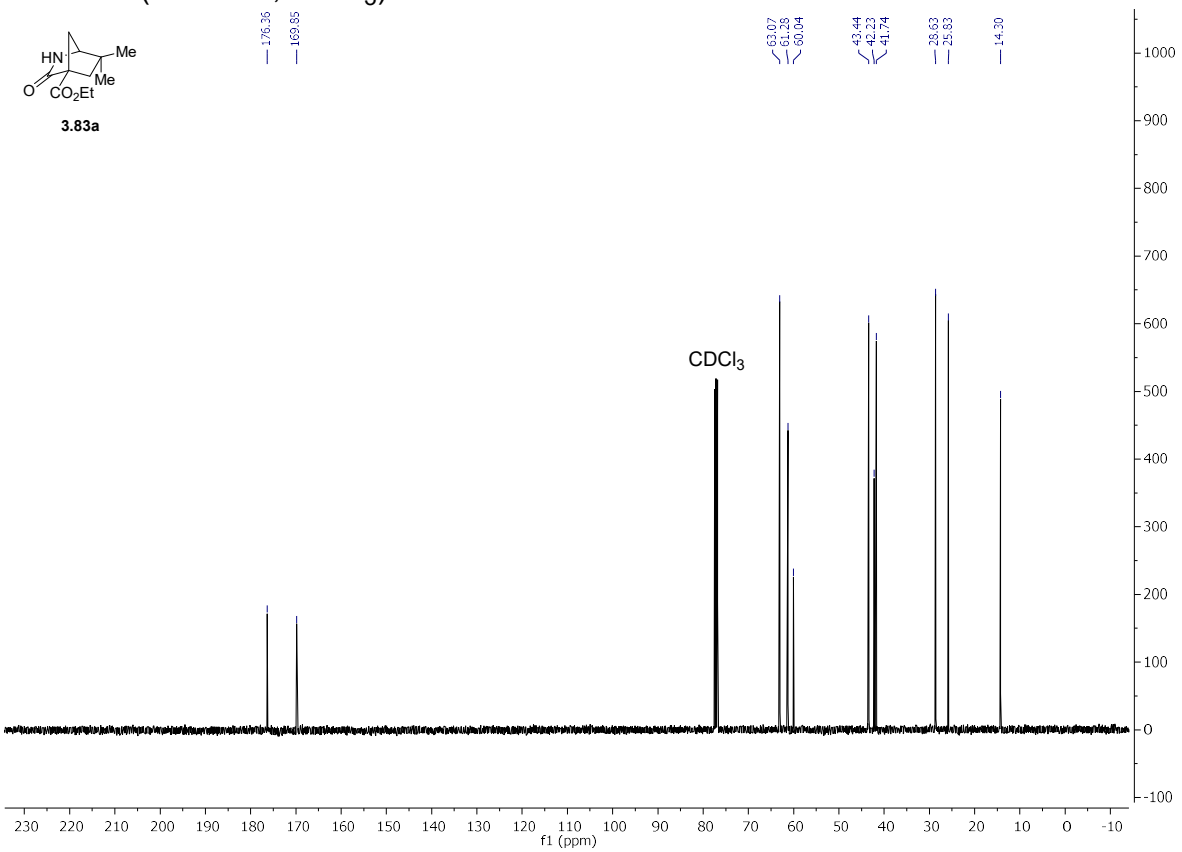
^{13}C NMR (101 MHz, $CDCl_3$) of **3.69p**



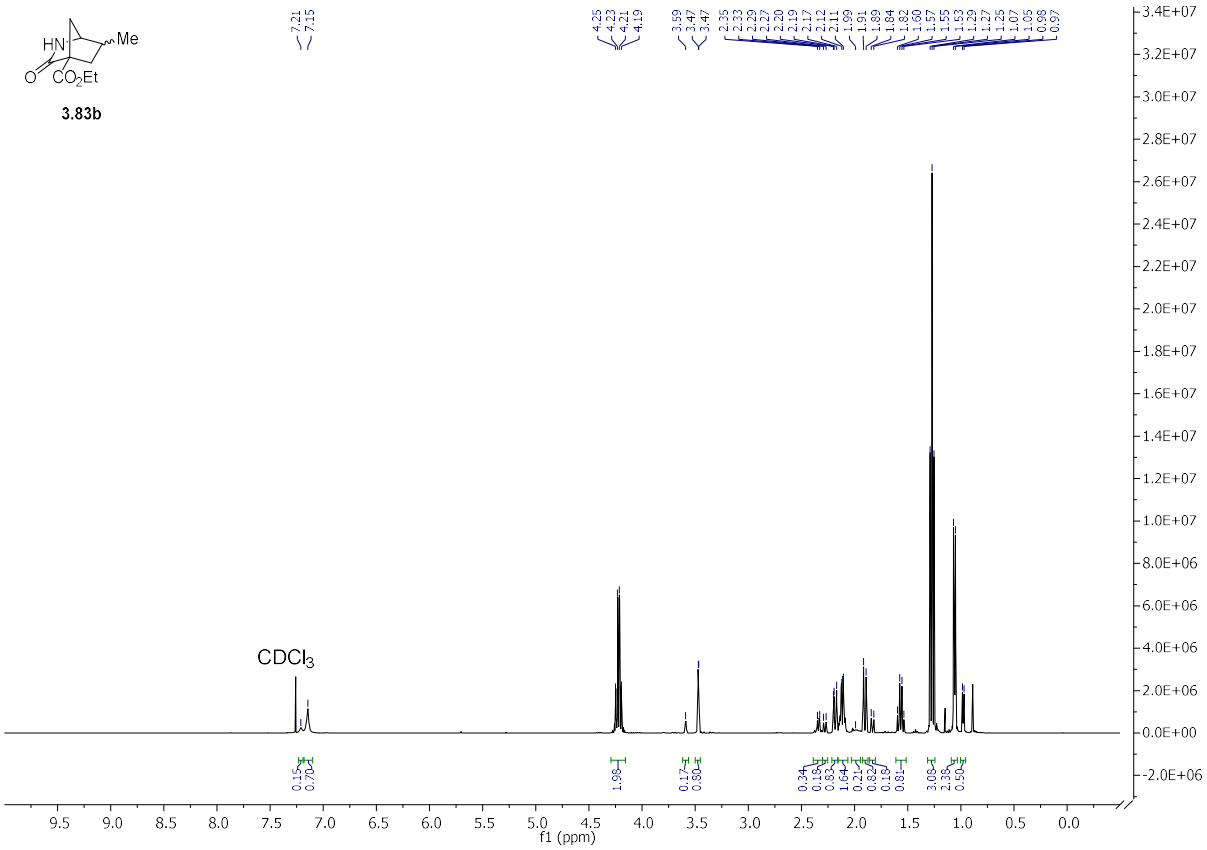
^{1}H NMR (400 MHz, $CDCl_3$) of **3.83a**



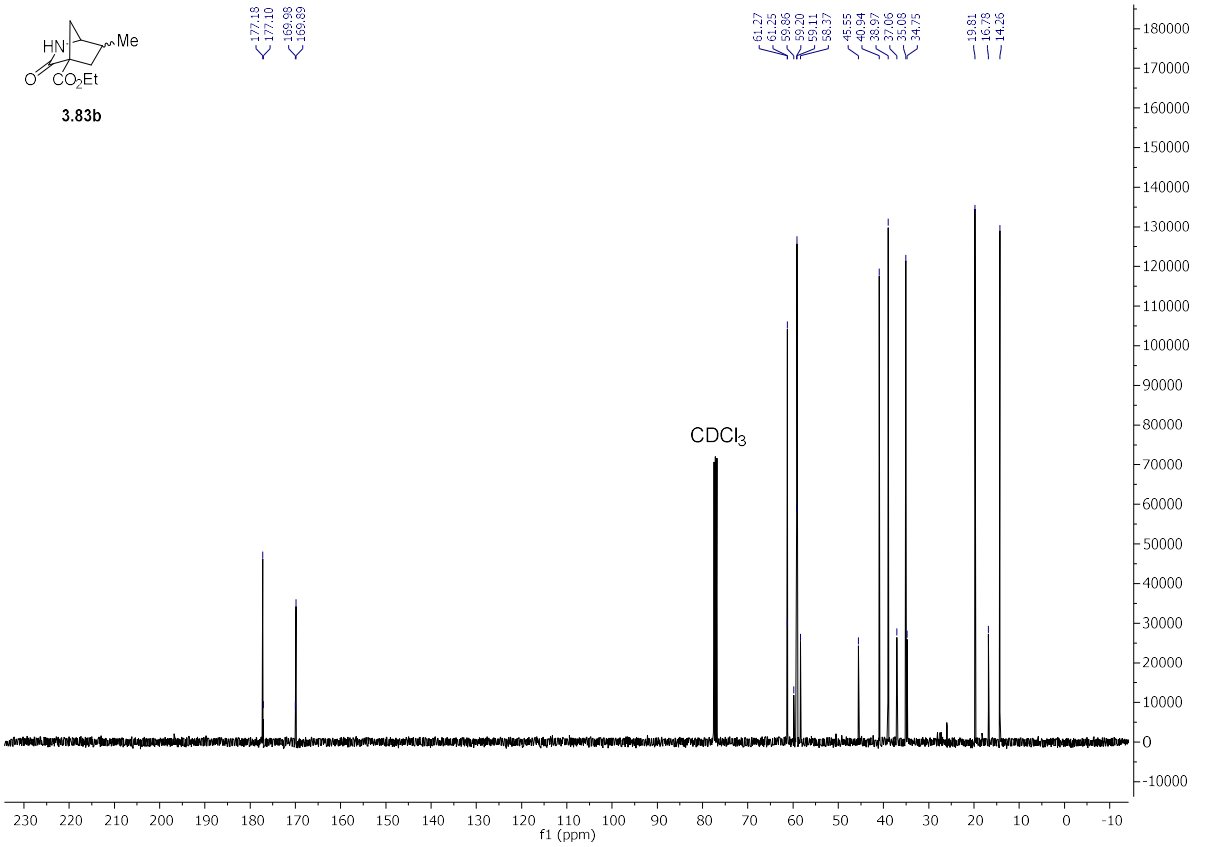
^{13}C NMR (101 MHz, $CDCl_3$) of **3.83a**



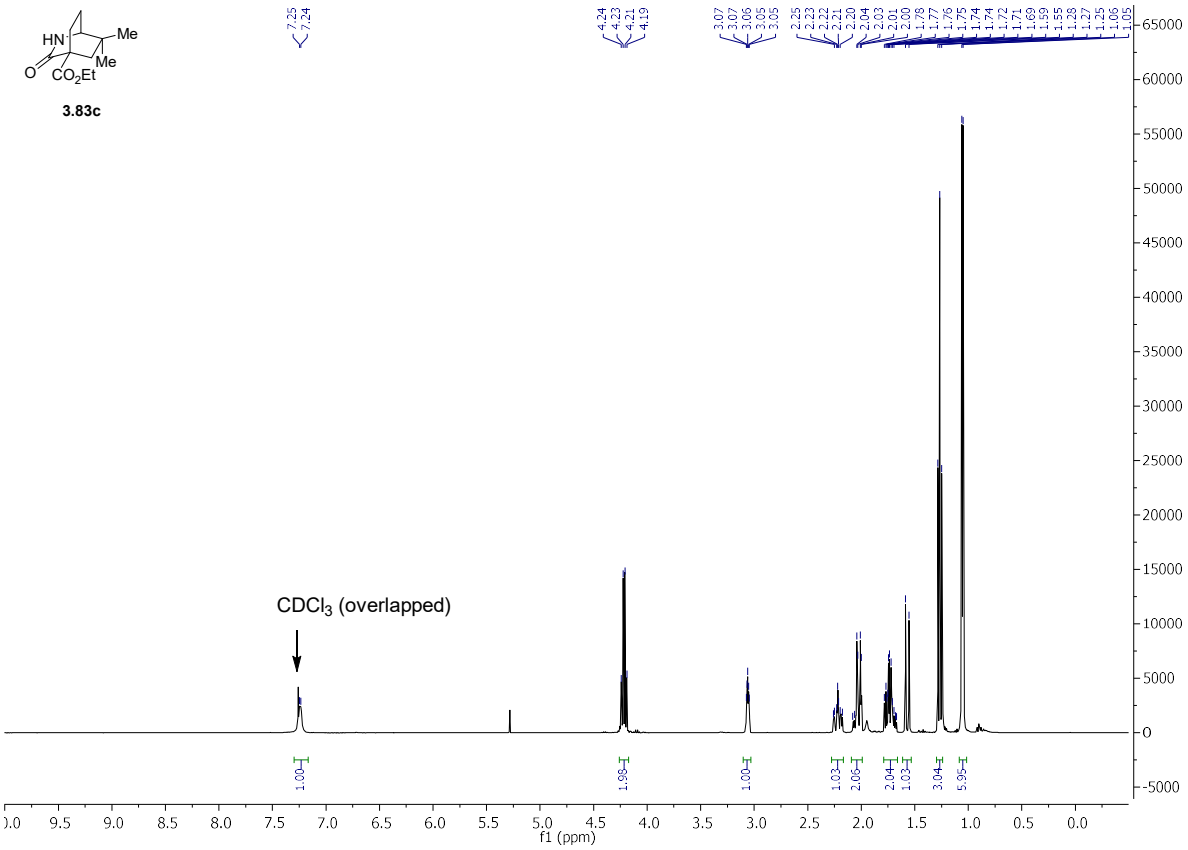
^{1}H NMR (400 MHz, $CDCl_3$) of **3.83b**



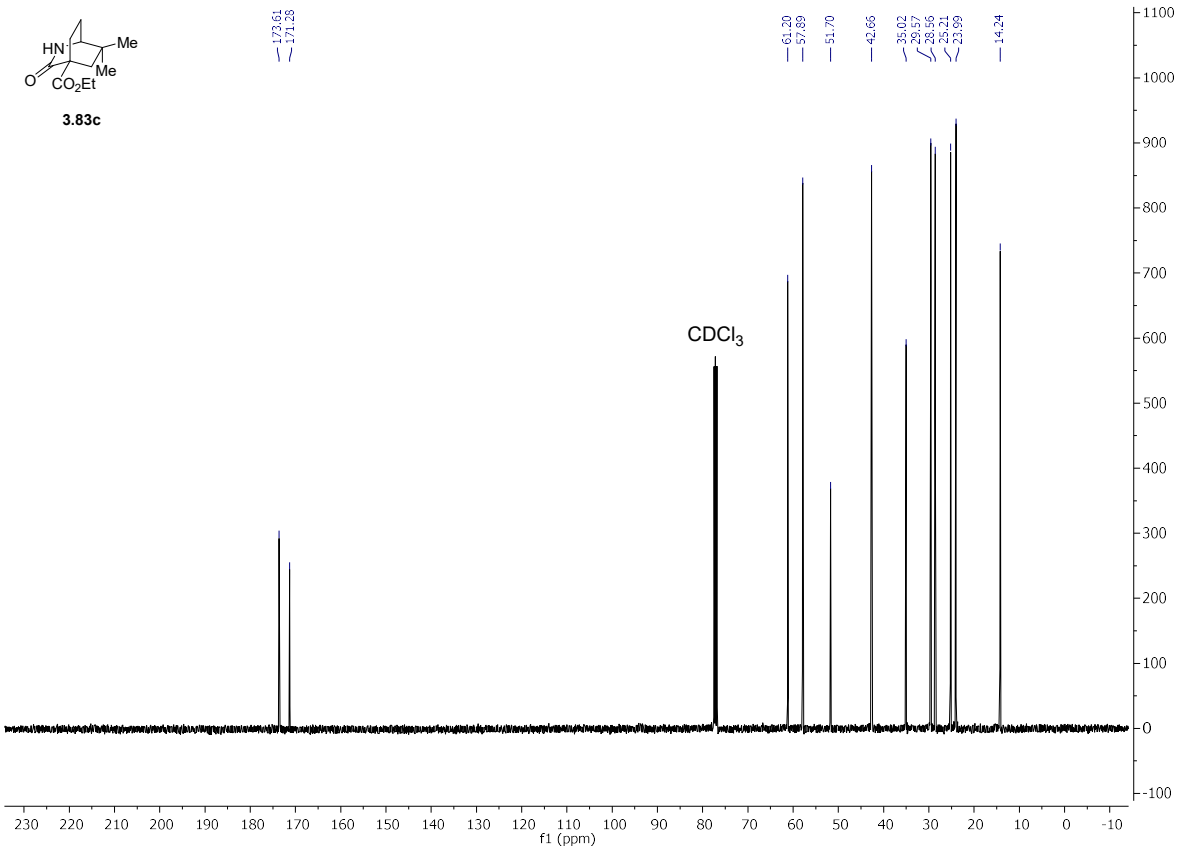
^{13}C NMR (101 MHz, $CDCl_3$) of **3.83b**



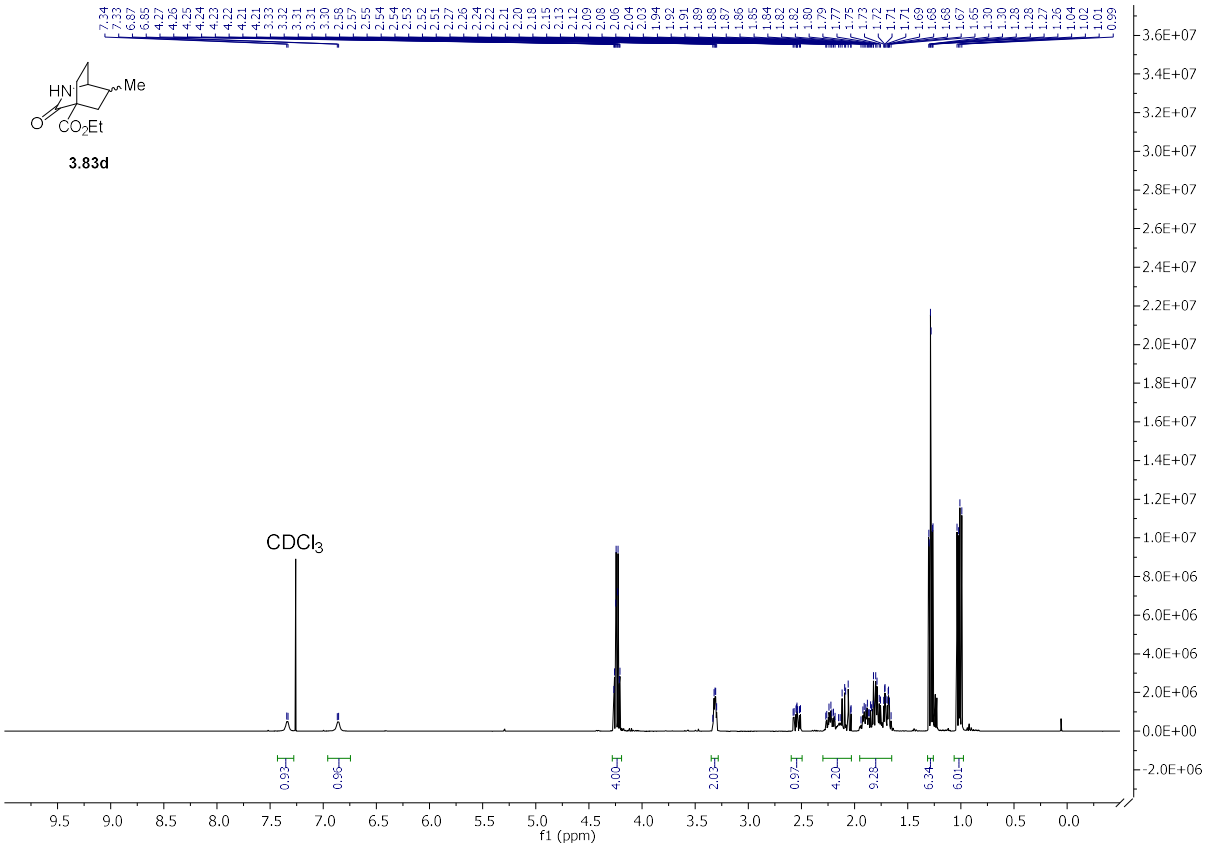
^{1}H NMR (400 MHz, $CDCl_3$) of **3.83c**



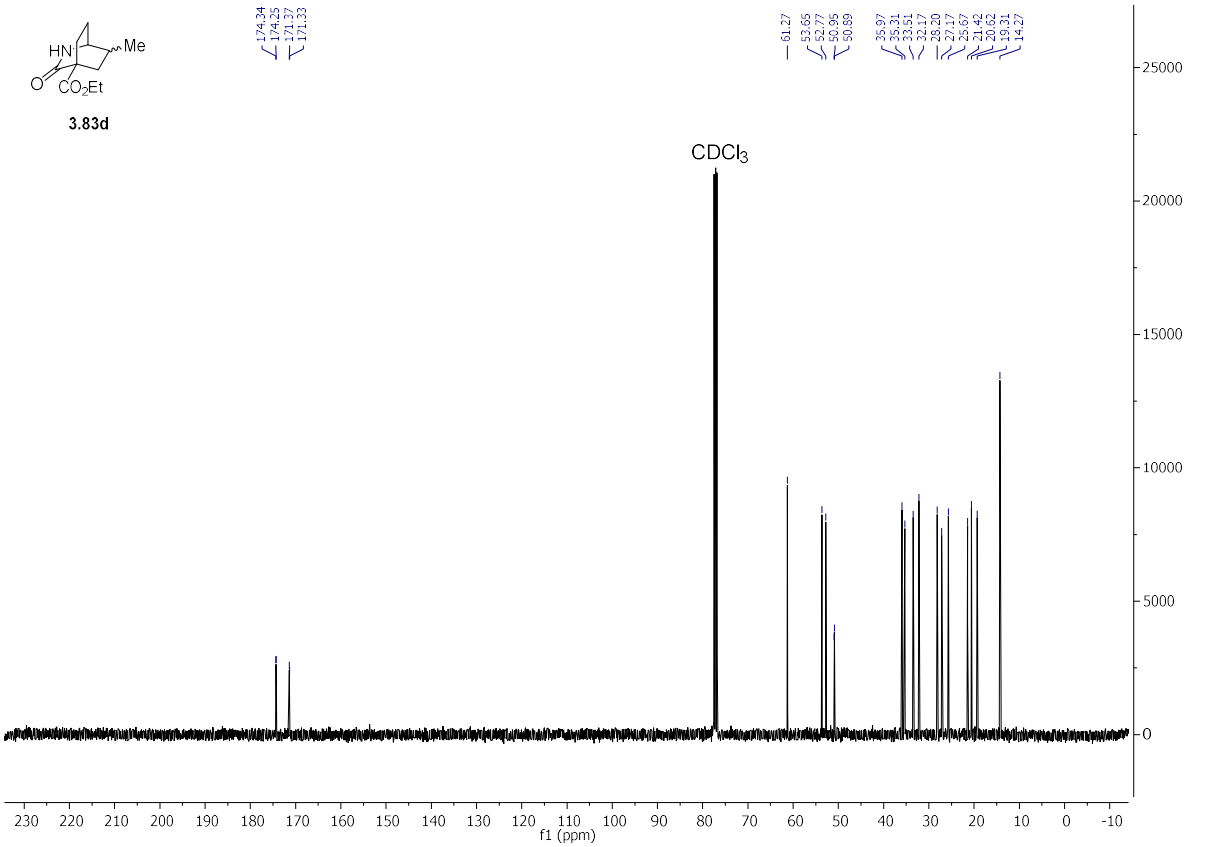
^{13}C NMR (101 MHz, $CDCl_3$) of **3.83c**



^{1}H NMR (400 MHz, $CDCl_3$) of **3.83d**



^{13}C NMR (101 MHz, $CDCl_3$) of **3.83d**



Curriculum Vitae

PERSONAL INFORMATION

Name:	Michael Schneider
Date of birth:	11/7/1992
Place of birth:	New Haven, CT, United States of America
Nationality:	Germany, United States of America

EDUCATION

2016 – Present	**Doctor of Sciences ETH Zurich** under the supervision of Prof. E. M. Carreira on natural product synthesis and synthetic methodology
2014 – 2016	**Master of Science ETH in Chemistry**, ETH Zurich Master thesis with Prof. E. M. Carreira on natural product synthesis Research projects with Prof. A. Togni on asymmetric catalysis and with Prof. E. M. Carreira on medicinal chemistry
2011 – 2014	**Bachelor of Science ETH in Chemistry**, ETH Zurich
2002 – 2011	**Abitur**, Staedtisches Gymnasium Wuelfrath, Germany
1998 – 2002	Grundschule Radenberg, Wuppertal, Germany

WORK EXPERIENCE AND OTHER ACTIVITIES

2018 – 2020	**Peer reviewer** for publications submitted to *J. Am. Chem. Soc.* and *Org. Lett.*
2018 – 2020	**Scientific writer** for the THIEME journal *Synfacts*. Selection and writing of highlight articles on state-of-the-art natural product syntheses
2015 – 2016	**Internship** at F. Hoffmann-LaRoche AG, Basel, Switzerland on medicinal chemistry
2013 – 2014	**Class representative** for 5th semester chemistry students, ETH Zurich

2007 – 2011 **Judo coach**, TSV Einigkeit Dornap (trained and successfully prepared more than 100 children for Kyu exam)

TEACHING EXPERIENCE

2019 – 2020 **Head teaching assistant** for the advanced-level lecture "Organic Synthesis: Methods and Strategies" by Prof. E. M. Carreira

2014 – 2019 **Teaching assistant** for five different introductory- and advanced-level organic and inorganic chemistry lectures

2017 **Teaching assistant** for an introductory-level organic chemistry laboratory course

PUBLICATIONS

M. Schneider, M. J. R. Richter, E. M. Carreira, Total Synthesis of (–)-Mitrephorone A Enabled by Stereoselective Nitrile Oxide Cycloaddition and Tetrasubstituted Olefin Synthesis, *J. Am. Chem. Soc.* **2020**, *141*, 17802–17809.

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PRESENTATIONS

Poster presentation at the 12th Symposium of the Scholarship Fund of the Swiss Chemical Industry, 2020, "Total Synthesis of (–)-Mitrephorone A"