DISSERTATION ZUR ERLANGUNG DES DOKTORGRADES
DER FAKULTÄT FÜR CHEMIE UND PHARMAZIE
DER LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Studies Toward the Total Synthesis of Mitrephorone A

von

Lara Weisheit

aus Bonn, Deutschland

2019

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Thomas Magauer betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfsmittel erarbeitet.

München, den 28. Januar 2019

_____

Lara Weisheit

Dissertation eingereicht am:	28. Januar 2019
1. Gutachter:	Prof. Dr. Thomas Magauer
2. Gutachter:	Prof. Dr. Oliver Trapp
Mündliche Prüfung am:	22. März 2019

Für meine Familie

“Lass dich nicht unterkriegen. Sei frech und wild und wunderbar!”

Astrid Lindgren

Parts of this thesis have been presented at scientific conferences:

"*Studies toward the total synthesis of mitrephorone A*" (oral presentation), L. Weisheit, T. Magauer. CMBI Meeting, Vils, Austria, September 2018.

Publication, which is not discussed in this thesis:

"Synthesis of Xenia Diterpenoids and Related Metabolites Isolated from Marine Organisms" – T. Huber,† L. Weisheit,† T. Magauer, *Beilstein J. Org. Chem.* **2015**, *11*, 2521−2539.

† Equal contributors.

Zusammenfassung

Diese Doktorarbeit beschreibt unsere Studien zu der Totalsynthese des *ent*-Trachyloban Diterpenoids Mitrephorone A.

Mitrephorone A wurde aus der Rinde von *Mitrephora glabra*, einem indonesischen Annonengewächs, isoliert. Der Naturstoff hat einen einzigartigen molekularen Aufbau mit einem hexazyklischen Ringsystem, acht Stereozentren, einem Diketon und einem Oxetanring. Mitrephorone A zeigt moderate zytotoxische Aktivität gegen Tumorzelllinien und ist somit ein potentielles Krebsmedikament.

Der erste Teil dieser Doktorarbeit beschreibt unsere Versuche, eine enantioselektive und konvergente Syntheseroute der Kernstruktur von Mitrephorone A zu entwickeln. Die ausgearbeitete Route beginnt mit der Herstellung von Enon **I** durch eine enantioselektive Diels–Alder Reaktion. Die Umwandlung zu Alkin **II** wurde in einer sechsschrittigen Sequenz realisiert, die eine intramolekulare Diels–Alder Reaktion beinhaltet und die Käfigstruktur des Naturstoffs aufbaut. Als nächstes wurden die Bausteine **II** und **III** in einer Sonogashira Kupplung miteinander verbunden. Eine asymmetrische dearomative Zyklisierung von **V** schließt den letzten Kohlenstoffring von Mitrephorone A und setzt an C10 die richtige Stereochemie. Des Weiteren werden Studien zu dem Versuch, die Vorstufe **VI** in den Naturstoff umzuwandeln, präsentiert.

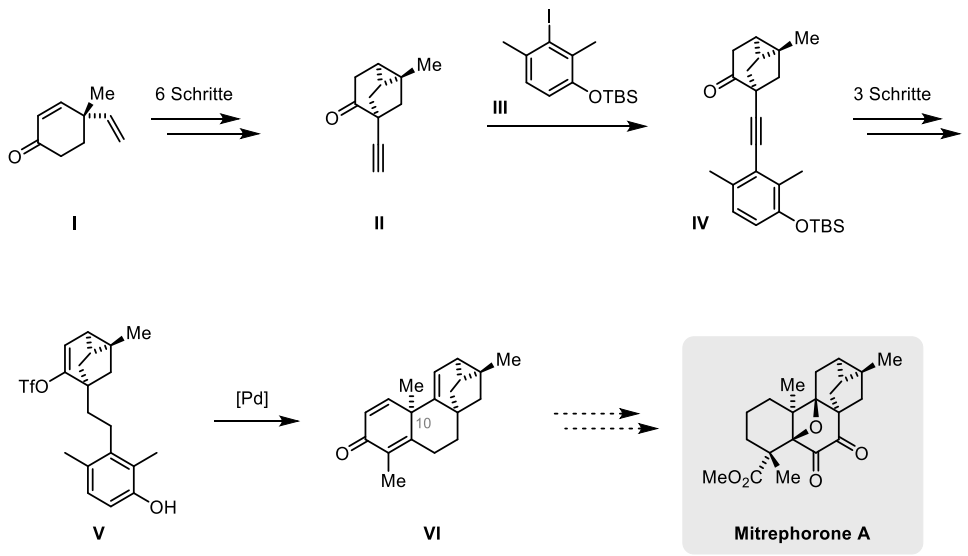


Abbildung A Konvergente und enantioselektive Syntheseroute für die Kernstruktur von Mitrephorone A.

In dem zweiten Teil dieser Doktorarbeit haben wir eine andere, robuste und enantioselektive Synthese des kompletten Kohlenstoffgerüsts von Mitrephorone A entwickelt. Die Synthesesequenz beginnt mit dem literaturbekannten Baustein **VII**. Eine Sharpless Dihydroxylierung und eine Robinson Annulierungssequenz ergeben Enon **VII**, das unter anderem durch eine α-Vinylierung und eine intramolekulare Diels–Alder Reaktion weiter zu **IX** umgesetzt wird. Die anspruchsvolle finale Entschützung von Carbonat **IX** ergibt Triol **X**. Zusammenfassend präsentieren wir eine vielseitige synthetische Strategie, mit der ein funktionalisiertes Gerüst der *ent*-Trachylobane unter vergleichbar milden Bedingungen herstellt werden konnte.

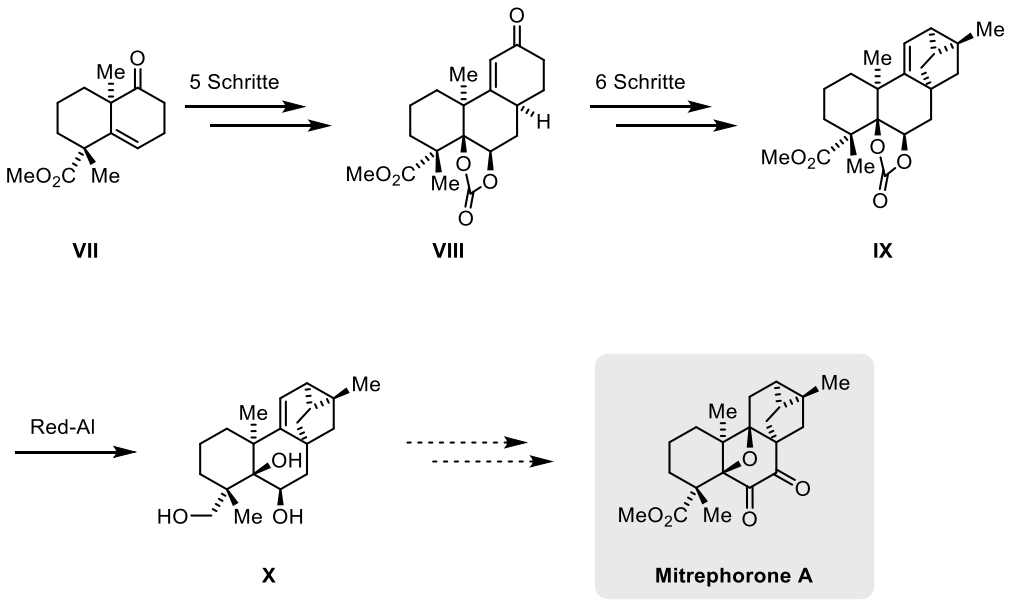


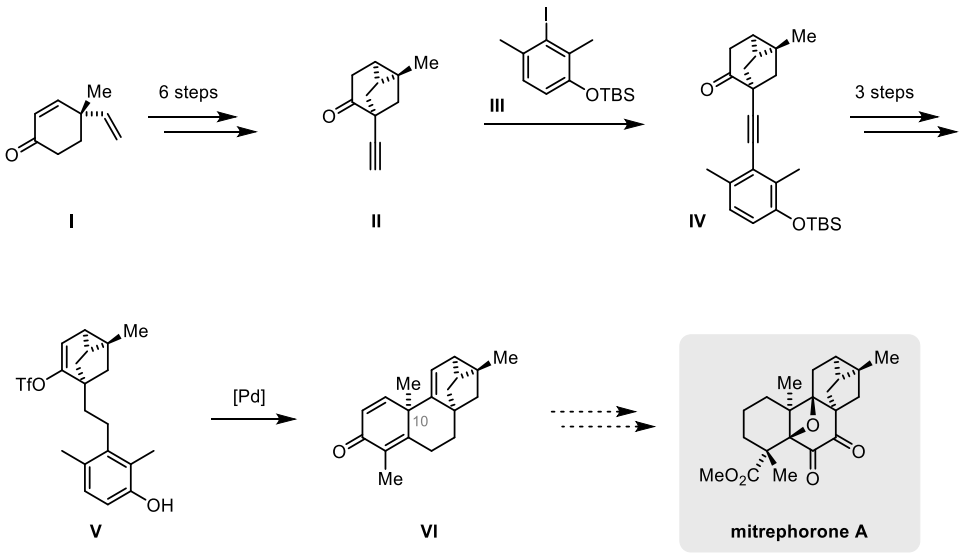
Abbildung B Enantioselektive Synthese des kompletten Kohlenstoffgerüsts von Mitrephorone A.

Abstract

This Ph.D. thesis describes progress toward the total syntheses of the *ent*-trachylobane diterpenoid mitrephorone A.

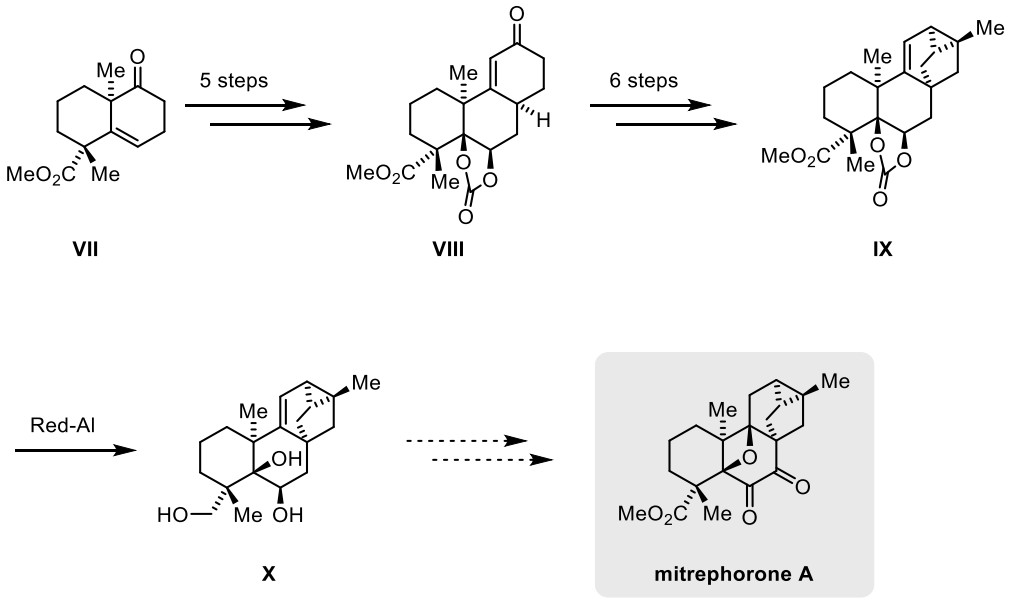
Mitrephorone A was isolated from the bark of *Mitrephora glabra*, an Indonesian custard apple tree. The natural product possesses an interesting molecular scaffold, comprising a hexacyclic ring system with eight stereocenters, an adjacent ketone moiety and an oxetane ring. Mitrephorone A shows moderate cytotoxic activities against tumour cell lines, which makes it a potential chemotherapeutic agent.

The first part of this thesis describes our efforts to develop an enantioselective and convergent synthetic route to the core structure of mitrephorone A. The elaborated route commences with the preparation of enone **I** via an enantioselective Diels–Alder reaction. Conversion to alkyne **II** is realized in a six-step sequence involving an intramolecular Diels–Alder reaction to build up the caged structure found in the natural product. Next, the two building blocks **II** and **III** are joined via a Sonogashira cross coupling. An asymmetric dearomative cyclization of **V** closes the last carbon ring of mitrephorone A and sets the right quaternary stereochemistry at C10. Moreover, studies to advance precursor **VI** to the natural product are presented.



Scheme A Convergent and enantioselective synthesis of the core of mitrephorone A.

In the second part of this thesis, we present an alternative enantioselective synthesis of the complete mitrephorone A carbon skeleton. This robust synthetic sequence starts with literature-known building block **VII**. A Sharpless dihydroxylation and a Robinson annulation sequence gave enone **VIII**, which is further converted to **IX** by α-vinylation and a late stage intramolecular Diels–Alder reaction. The challenging final deprotection of carbonate **IX** afforded triol **X**. In summary, a versatile synthetic strategy which yields a decorated scaffold of the ent-trachylobanes under comparably mild conditions is presented.



Scheme B Enantioselective synthesis of the complete carbon skeleton of mitrephorone A.

Danksagung

Zuallererst gilt mein Dank Prof. Dr. Thomas Magauer, der mir stets mit all seiner Erfahrung und seinem Wissen zur Seite stand. In zwei spannenden Projekten durfte ich vielseitige Themen der organischen Chemie kennenlernen. Dabei wurde ich durch intensive Betreuung und sein fortwährendes Interesse stets unterstützt.

Mein Dank gilt auch den Mitgliedern meiner Prüfungskommission: Prof. Bracher und Prof. Karaghiosoff. Insbesondere möchte ich mich bei Prof. Trapp für die freundliche Übernahme des Zweitgutachtens bedanken. Für das geduldige Korrekturlesen dieser Arbeit danke ich Giulio Volpin, Bryan Matsuura, Antonio Rizzo, Christa Gerlinger und Raphael Wildermuth.

Die ersten Jahre des Arbeitskreises in München habe ich in besonders guter Erinnerung. Wir waren ein eingeschworenes Team und ich danke der ganzen Gruppe für die schöne gemeinsame Zeit. Insbesondere danke ich Tatjana Huber, der besten Laborkollegin der Welt, für ihre ruhige, besonnene Art, ihr schier unerschöpfliches Wissen und die vielen inspirierenden Gespräche während langer Säulen. Ich danke Klaus Speck für seine Hilfsbereitschaft, seine Geduld und seine stets direkten, unverblümten Worte. Cedric Hugelshofers Leidenschaft für die Chemie war ansteckend und faszinierend. Ich danke ihm für die unvergessene gemeinsame Zeit. Des Weiteren danke ich Raphael Wildermuth, Johannes Feierfeil und Adriana Grossmann für die tolle Arbeitsatmosphäre in München.

Außerdem danke ich dem gesamten AK Trauner für ihre Unterstützung und die Zusammenarbeit mit unserem AK. Ein ganz besonderer Dank gilt den Kollegen aus denen Freunde wurden: Giulio Volpin, auf den immer Verlass ist; Antonio Rizzo, für unzählige lehrreiche und unterhaltsame Gespräche; Shushu Liu, für ihre aufbauenden und motivierenden Worte; Bryan Matsuura, für spannende Diskussionen; sowie Nina und Felix Hartrampf, die mir zwischenzeitlich ein Zuhause gaben.

Mit dem Umzug nach Innsbruck waren wir plötzlich eine ganz neue Gruppe. Auch hier gibt es Kollegen, denen ich besonders danken möchte: Ich danke meinem neuen Laborkollegen Raphael Wildermuth für viele unterhaltsame und lustige Gespräche. Matthias Schmid danke ich für hilfreiche Diskussionen über mein Projekt. Ohne Sofia Torres Venegas Organisationsgeschick und unermüdlichen Einsatz für die Gruppe wären wir untergegangen. Meinem letzten Laborpartner Lukáš Maier danke ich für lebhafte Diskussionen über die Chemie und das Leben. Ein besonderer Dank gilt Kevin Sokol, der mit beeindruckender Hingabe und unendlicher Geduld an Psammaplysin arbeitet. Franz-Lucas Haut und Gabriele Prina Cerai danke ich für gute Stimmung

und die musikalische Untermalung des Laboralltags. Außerdem danke ich allen Innsbrucker Kollegen der anderen Arbeitskreise. Besonderer Dank gilt hier Raphael Plangger, Kevin Erharter und Johannes Kremser, die mich immer wieder aufgebaut und zum Lachen gebracht haben. Des Weiteren danke ich Eva-Maria Schneeberger für ihre Freundschaft und die schönen Restaurant- und Cocktailabende.

Während meiner Doktorarbeit durfte ich die Projekte von drei talentierten und motivierten Studenten betreuen. Mein Dank gilt Katrin Möderl, Aylin Hirschvogel und Lukas Wein, die durch Fleiß und harte Arbeit zu dieser Doktorarbeit beigetragen haben. Lukas Wein danke ich hierbei ganz besonders, da er mein Projekt übernommen hat und hoffentlich noch zu einem erfolgreichen Ende führen wird.

Ich danke der Analytik Abteilung der LMU München: Dr. Manfred Spahl, Sonja Kosak und Carola Draxler für die Massenspektrometrie Messungen; Dr. David Stephenson, Claudia Dubler und Petra Keilholz für die NMR Daten und Dr. Peter Mayer für die Einkristallstrukturanalyse. An der Leopold-Franzens-Universität Innsbruck möchte ich assoz. Prof. Christoph Kreutz für die NMR Analytik und assoz. Prof. Thomas Müller für die Massenspektrometrie Messungen danken.

Ohne die Mitarbeiter, die unsere Arbeit im Hintergrund organisatorisch unterstützen, wäre keine Doktorarbeit denkbar. Dafür danke ich an der LMU München: Dr. Martin Sumser, Aleksandra Sarman Grilic und Heike Traub; sowie in Innsbruck: Gerhard Scherzer, Astrid Weber und Inge Gander. Ein sehr spezieller Dank gilt Dr. med. Christina Binder und ihrem Praxisteam für ihre Unterstützung.

Abschließend möchte ich mich bei meinen Freunden außerhalb des Labors bedanken. In dreieinhalb oft schwierigen Jahren standet ihr immer geduldig an meiner Seite. Ihr habt mich ermutigt, abgelenkt, aufgebaut, motiviert, mit mir gefeiert, geweint und gelacht: Caren Wanzke, Christa Gerlinger, Irene Savakis, Achim Keidel, Trixi von Schlippenbach und Katinka Günther. Außerdem danke ich Julian Rotter für eine unglaublich intensive Zeit mit vielen Höhen und Tiefen. Mein größter Dank gilt jedoch meiner Familie: meiner Schwester Isabel, meiner Mutter und meinem Vater. Ihr habt immer an mich geglaubt und mir die Kraft gegeben zu kämpfen.

List of Abbreviations

°C	degrees Celsius
δ	chemical shift in ppm downfield relative to a standard
Ac	acetyl
AIBN	1,1′-azobis(isobutyronitrile)
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
Bz	benzoyl
Calcd	calculated
CAM	ceric ammonium molybdate(IV)
cat.	catalytic
CCDC	Cambridge Crystallographic Data Centre
CBS	Corey−Bakshi−Shibata
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
CPP	copalyl diphosphate
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$(DHDQ)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIBAl-H	diisobutylaluminium hydride
DIPA	*N*,*N*-diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine (Hünig's base)
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DMP	Dess−Martin Periodinan
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dppf	1,1’-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent(s)

Et	ethyl
ESI	electrospray ionization
e.g.	*exempli gratia* (for example)
g	gram
GGPP	geranylgeranyl diphosphate
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HR-MS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i-	*iso*
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MIC	minimal inhibitory concentration
Min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl acetal
MsCl	mesylsulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
p	*para*
Pd/C	palladium on charcoal
PG	protecting group
Ph	phenyl

Ph.D.	Doctor of Philosophy
phen	phenanthroline
PIDA	phenyliodine(III) diacetate
PMB	*para*-methoxybenzyl
PMHS	polymethylhydrosiloxane
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
py	pyridine
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydrid
R*f*	retardation factor (TLC)
ROESY	Rotating frame Overhauser enhancement spectroscopy
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Super-Hydride®	Lithium triethylborohydride
T	temperature
T	time
t-	*tert*
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TADDOL	(4*S*-*trans*)-2,2-Dimethyl-*α,α,α′,α′*-tetra(1-naphthyl)-1,3-dioxolane-4,5-dimethanol
TCDI	1,1'-thiocarbonyldiimidazole
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
Ts	tosyl
UV	ultraviolet
wt%	weight percent

Table of Contents

1 Introduction

1.1 General Introduction

Since the synthesis of urea by F. Wöhler in 1828,[1] total synthesis of natural products has evolved into an important branch of organic chemistry with many opportunities for discoveries and innovation. The reasons for performing natural product synthesis are diverse, ranging from the development of useful synthetic methods or reagents to improve chemical processes.[2] One important aspect is that small molecules isolated from natural sources often possess medically relevant biological activity. Over the last decades, pharmacologically active compounds from plants and microbes have played an important role for drug discovery. From the 1940s to 2014, 49% of all approved anti-cancer agents worldwide were "either natural products or directly derived therefrom".[3]

1.2 Oxetane Natural Products

Paclitaxel (**2**) is probably one of the best known examples of a natural product successfully applied in cancer chemotherapy. Its potent biological activity is reliant on the oxetane ring present in the structure (Figure 1). The oxetane, as small polar heterocycle, serves as hydrogen-bond acceptor[4] and conformationally locks the entire structure.[5] Since the track record of paclitaxel as a highly potent pharmaceutical, oxetanes have emerged as potentially attractive structural motif in drug discovery.

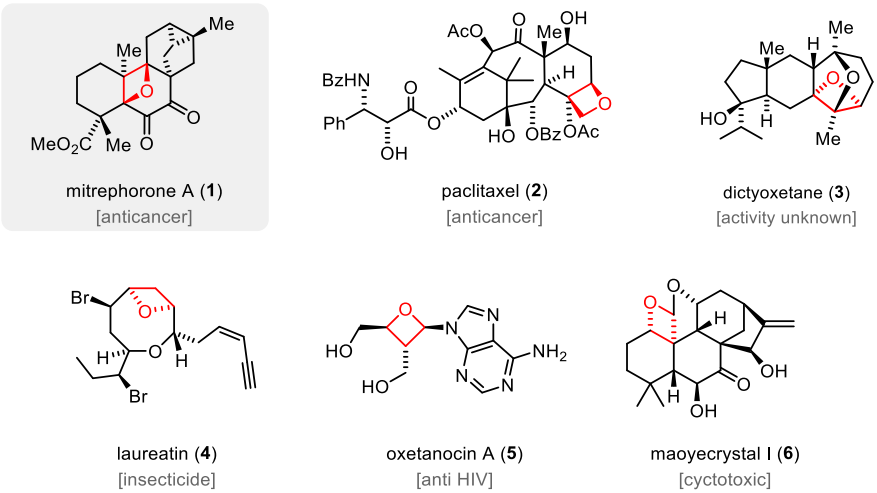


Figure 1 Examples of natural products containing an oxetane ring: mitrephorone A (**1**), taxol (**2**), dictyoxetane (**3**), laureatin (**4**), oxetanocin A (**5**), maoyecrystal I (**6**).

Studies have shown that the incorporation of oxetanes beneficially influences the "druglike" properties of a molecule like solubility and metabolic stability. As a result, oxetane rings have gained interest in medicinal chemistry as gem-dimethyl and carbonyl group isosteres.[6] Natural products containing oxetane rings are rare, but often show interesting biological activity. For example, marine oxocene laureatin (**4**) exhibits insecticidal activity,[7] oxetanocin A (**5**) inhibits the in vivo replication of human immunodeficiency virus[8] and maoyecrystal I (**6**) is cytotoxic (Figure 1).[9] A review of J. Bull et al. gives a detailed overview of recent advances in the synthesis, reactivity, and medicinal chemistry of oxetanes.[10]

1.3 *ent*-Trachylobane Diterpenoids

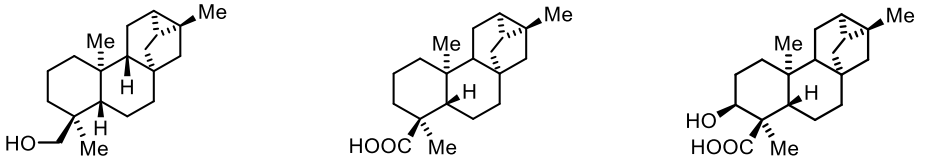
The first *ent*-trachylobane diterpenes were extracted from the resin of *Trachylobium verrucosum* (family *Leguminosae*) by Ourisson and coworkers in 1965.[11] The flowering plant *Trachylobium verrucosum* is a large tropical tree, originally native in East Africa now cultivated in many tropical regions of the world (Figure 2).

Figure 2 Image of the plant *Trachylobium verrucosum*.*

Three *ent*-trachylobanes shown in Figure 3 have been isolated: *ent*-trachyloban-18-ol (**7**), *ent*-trachyloban-18-oic acid (**8**) and *ent*-3α-hydroxy-trachyloban-18-oic acid (**9**). Until now, more than 60 different *ent*-trachylobanes have been isolated from natural sources and new compounds are still discovered today.[12] *ent*-Trachylobanes all share the same carbon skeleton but vary in their

* Photograph and copyright by John Elliott.

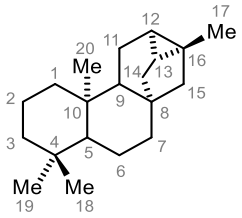
oxidation pattern. Most remarkable about their complex hexacyclic scaffold is the caged tricyclo-[3.2.1.$0^{2,7}$]oct-3-ene structure present in all *ent*-trachylobanes.



ent-trachyloban-18-ol (**7**) | *ent*-trachyloban-18-oic acid (**8**) | *ent*-3α-hydroxy-trachyloban-18-oic acid (**9**)

Figure 3 Structures of the first three isolated *ent*-trachylobanes: *ent*-trachyloban-18-ol (**7**), *ent*-trachyloban-18-oic acid (**8**) and 3α-hydroxy-trachyloban-18-oic acid (**9**).[11]

As depicted in Figure 3, most of the *ent*-trachylobane natural products have no trivial names and are consistently named and numbered according to the IUPAC nomenclature.[13] This common numbering of the carbon skeleton is also used throughout this thesis and shown in Figure 4.

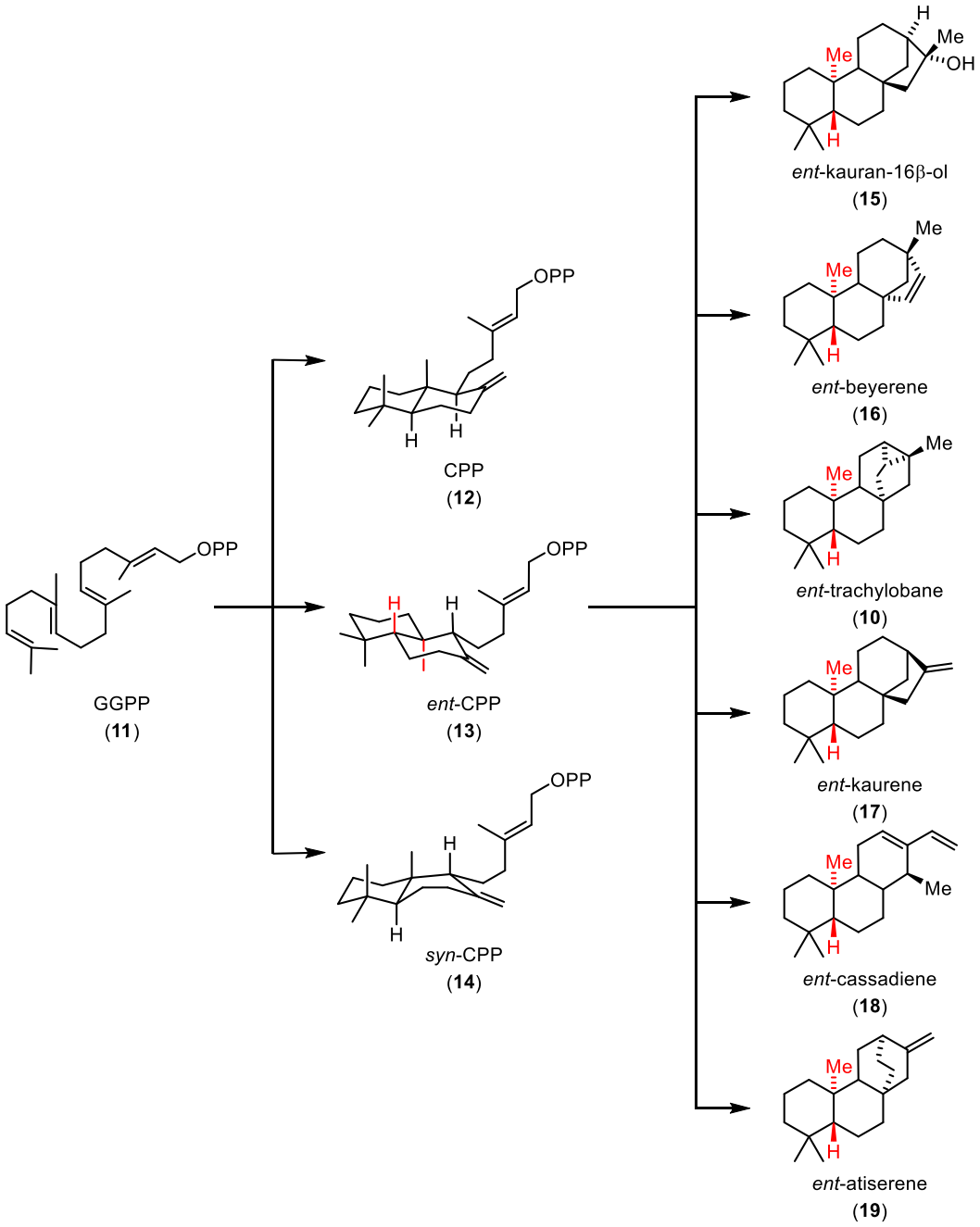


ent-trachylobane (**10**)

Figure 4 Common numbering of the *ent*-trachylobane carbon skeleton.[13]

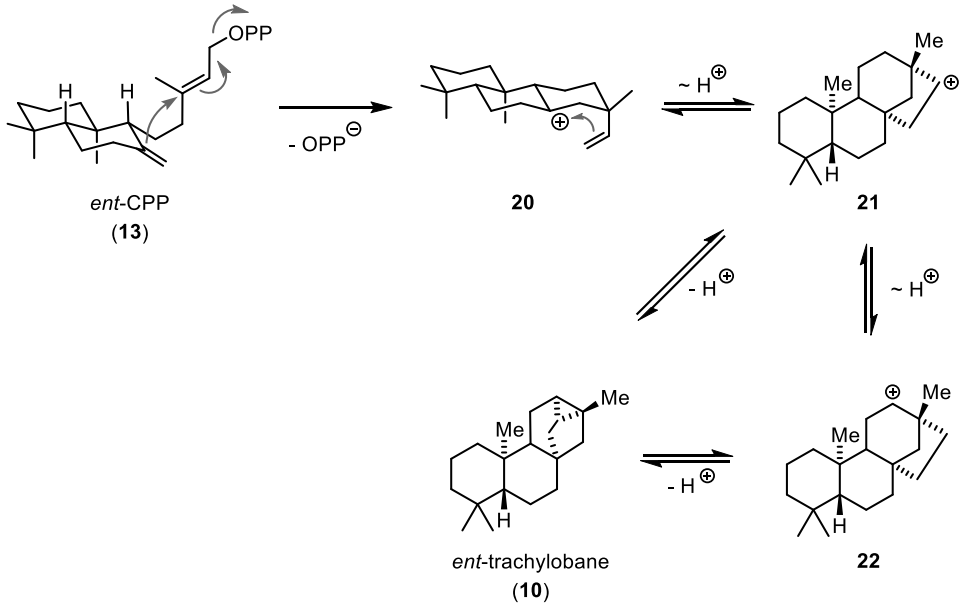
1.3.1 Biosynthesis of the *ent*-Trachyloane Skeleton

ent-Trachylobanes belong to the labdane-related diterpenoids and are biosynthetically derived from the general diterpenoid precursor (*E*,*E*,*E*)-geranylgeranyl diphosphate (**11**).[14] An initial double cyclization event leads to a copalyl diphosphate (CPP) intermediate which is mediated by a class II diterpene cyclases (Scheme 1). Three different cyclization modes are possible leading either to normal CPP (**12**), *ent*-CPP (**13**) or *syn*-CPP (**14**). From each CPP intermediate a variety of natural products can be formed. A few examples of *ent*-CPP derived natural products are shown in Scheme **1**.[15]



Scheme 1 Selected examples of labdane-related diterpenoids and the origin of their underlying stereochemistry.[15]

Starting from intermediate *ent*-CPP (**13**) different biosynthetic pathway towards *ent*-trachylobane (**10**) have been proposed over the years. In 2007, Coates and co-workers suggested the mechanism depicted in Scheme 2.[16] They propose that the biosynthesis of *ent*-trachylobane and other tetra- and pentacyclic diterpenes includes a secondary carbocation **21** as a key branch point. Their assumption is based on isotopic labelling studies with *ent*-kaurene synthase,[17][18][19] experiments with mutant kaurene synthases[20] and on related biosyntheses published previously.[21]

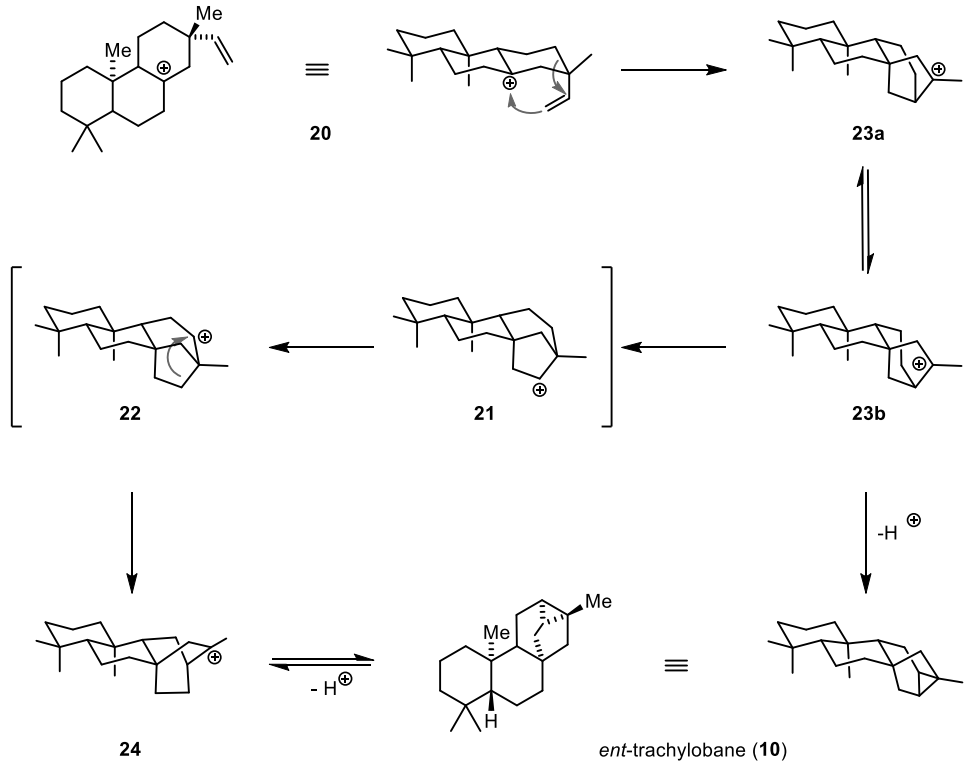


Scheme 2 Mechanism of the biosynthesis of *ent*-trachylobane (**10**) proposed by Roy et al.[16]

ent-CCP (**13**) undergoes an $S_N´$ ring closure with loss of pyrophosphate to generate carbocation **20**. A cation–alkene cyclization then results in a new carbocation **21**. Deprotonation of the secondary carbocation **21** gives *ent*-trachylobane (**10**).

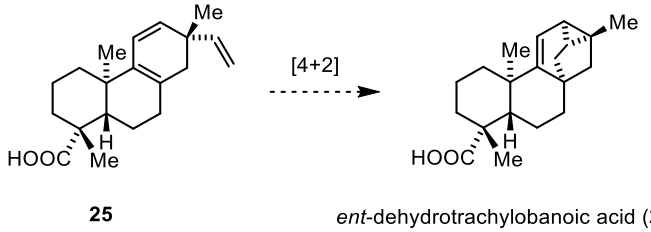
A more recent study from 2010 by Hong and Tantillo suggests a modified biosynthesis of the *ent*-trachylobane skeleton based on quantum chemical calculations.[22] Earlier computational studies have shown that biosynthetic pathways are often concerted processes and many formerly proposed secondary carbocations are actually transition state structures instead of reaction intermediates.[23][24]

Their reformed biosynthesis starts just like the pathway postulated by Roy et al. with the formation of carbocation **20** (Scheme 3). Instead of a cation–alkene cyclization to generate a secondary cation, **20** undergoes a cyclization and an alkyl shift in a concerted fashion. Hereby, tertiary carbocation **23a** is formed, which is then more stable in conformation **23b**. The authors' calculations predict that *ent*-trachylobane (**10**) can then be directly formed by ring closure and deprotonation from **23b** or from intermediate **24**. Tertiary carbocation **24** is another possible transition state found in their calculations, which is formed in a three-step process (concerted alkyl shift, 1,3-H shift, alkyl shift) and also serves as precursor for other diterpenes.[22]



Scheme 3 Proposed changes to the mechanism of the biosynthesis of *ent*-trachylobane (**10**) by Hong and Tantillo.[22]

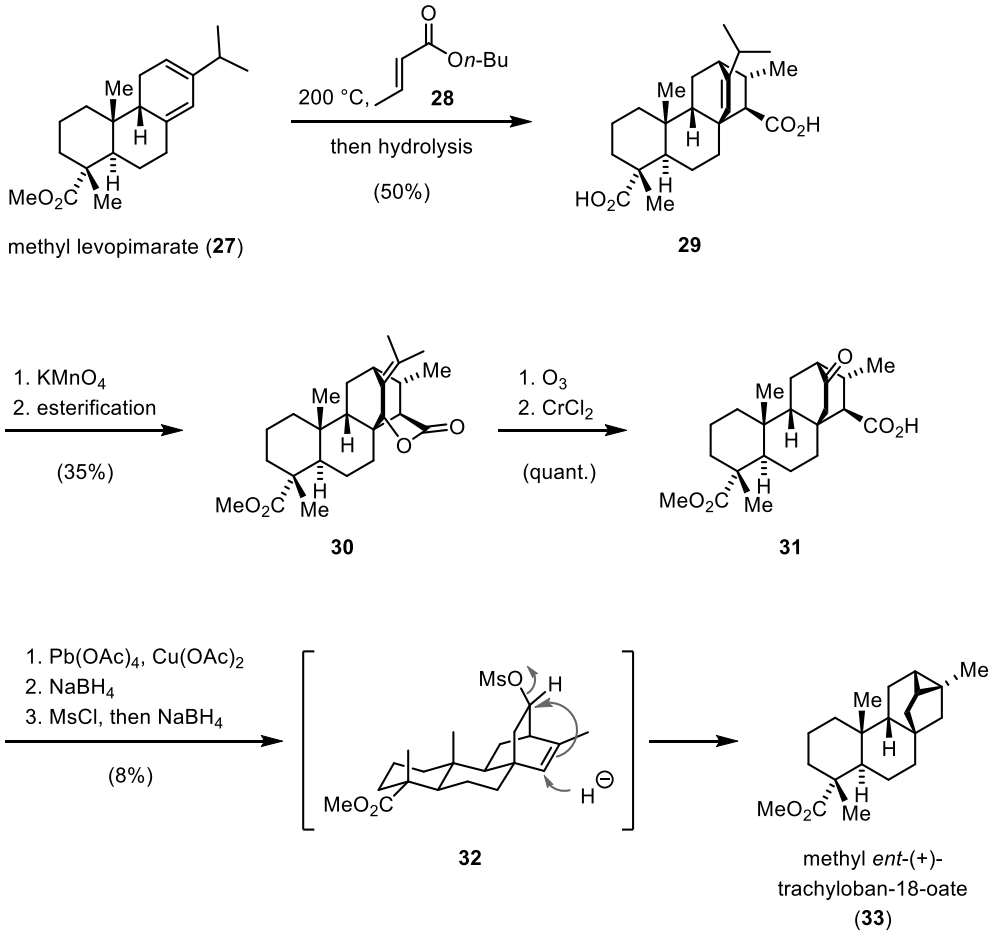
A completely different biosynthetic hypothesis was postulated by Trauner and co-workers.[25] They speculated whether the biosynthesis of *ent*-trachylobanes could involve an intramolecular Diels–Alder reaction of an *ent*-pimarane-type precursor **25** (Scheme 4). Their studies on intramolecular [4+2] cycloadditions of unactivated 5-vinyl-1,3-cyclohexadienes leading to the same caged structures and the fact that other Diels–Alder reactions are known in the biosyntheses of natural products,[26][27] nourishes this tantalizing notion.



Scheme 4 Speculative biosynthetic pathway via a [4+2] cycloaddition suggested by Trauner et al.[25]

1.3.2 Syntheses of *ent*-Trachylobane Natural Products

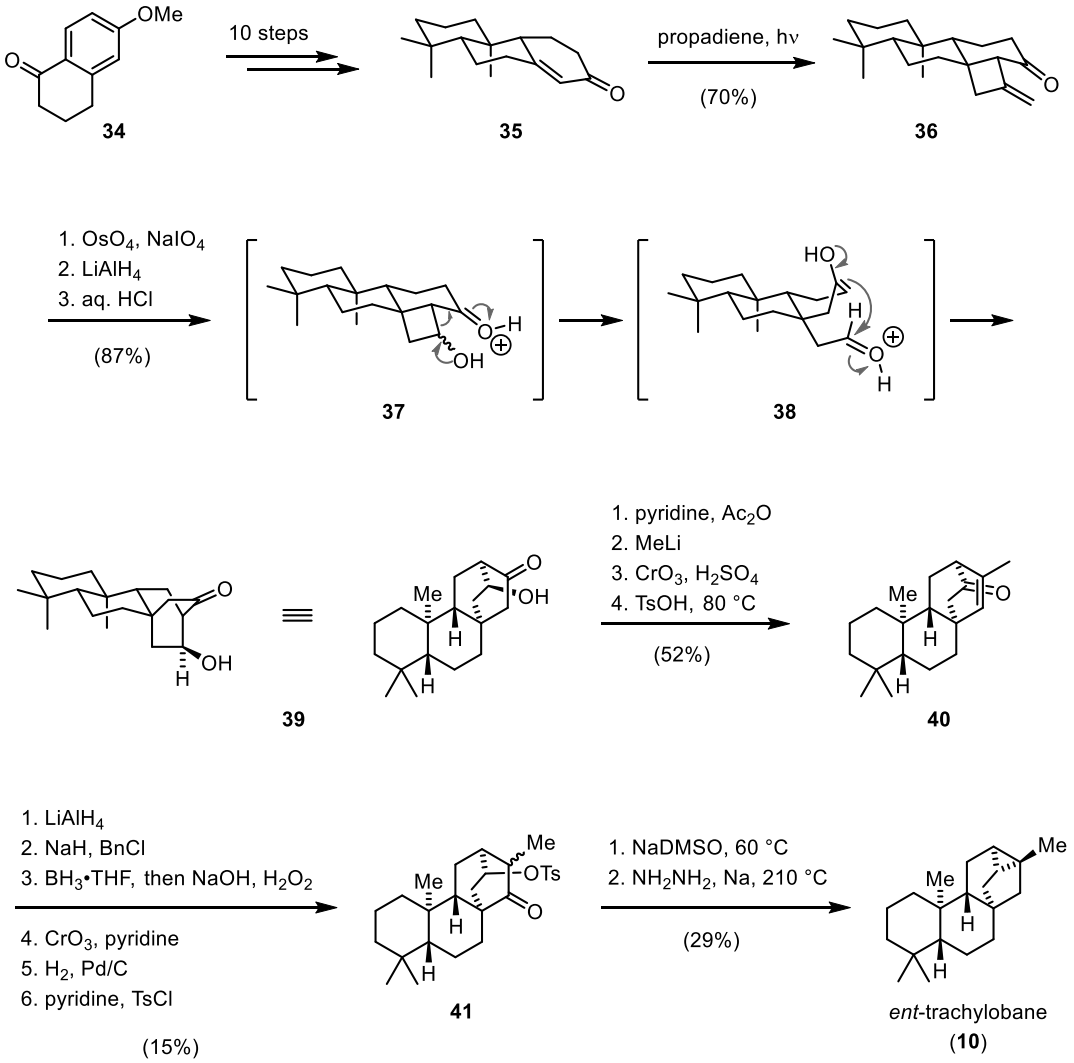
The remarkable molecular structures make the *ent*-trachylobane natural products attractive targets for synthetic chemists. However, only a few total syntheses have been reported since their first isolation in 1965.



Scheme 5 Semisynthesis of methyl *ent*-(+)-trachyloban-18-oate (**33**) by Herz.[28]

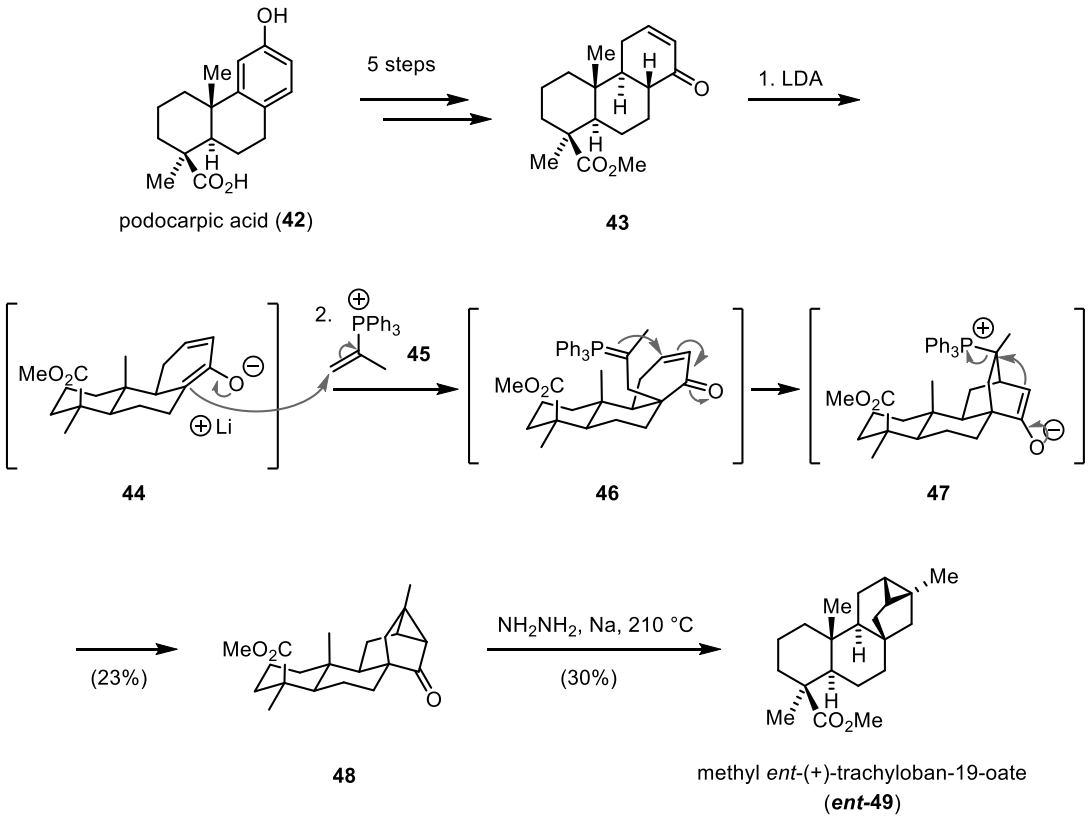
The first synthesis of the unusual caged ring system of the *ent*-trachylobane family was reported by Herz et al. in 1968 (Scheme 5).[28] Their semisynthetic approach starts with levopimaric acid, a commercially available natural product isolated from pine oleoresin. Methyl levopimarate (**27**) underwent a Diels–Alder reaction with *n*-butyl crotonate (**28**) and after hydrolysis of both esters, [2.2.2]bicyclooctene **29** was obtained. Oxidative lactonization and subsequent esterification yielded lactone **30**. Ozonolysis of **30** followed by reduction and opening of the lactone to acid **31** proceeded in quantitative yield. Oxidative decarboxylation of acid **31** introduced a double bond and subsequent reduction and mesylation of the ketone gave mesylate **32**. Treating **32** with sodium borohydride without intermediate aqueous work-up gave methyl *ent*-(+)-trachyloban-18-oate (**33**) via a cationic cyclization terminated by hydride attack. In a detailed full paper published shortly

after this communication, Herz and co-workers intensively discuss all their elaborated routes towards the successful semisynthesis shown in Scheme 5.[29]



Scheme 6 Kelly's *ent*-trachylobane synthesis.[30]

Kelly et. al. started their synthesis from literature known enone **35** (Scheme 6).[31] Stereo- and regiospecific photo-addition of propadiene to enone **35** gave cyclobutane **36** in good yield. Subsequent oxidative Lemieux–Johnson cleavage[32] followed by reduction of the resulting ketone gave **37**. Treatment with aqueous hydrochloric acid resulted in a retro-aldol reaction forming intermediate **38**, which underwent a skeletal rearrangement to give keto alcohol **39** in excellent yield. Following protection, methylation, oxidation and dehydration steps afforded ketone **40**. In further seven steps **40** is converted to tosylate **41**. Finally, an intramolecular attack of the generated enolate of **41** onto the tosylate formed the tricyclic trachylobane scaffold. The ketone was removed via a Wolff–Kishner reduction[33] under very harsh conditions to afford *ent*-trachylobane (**10**).

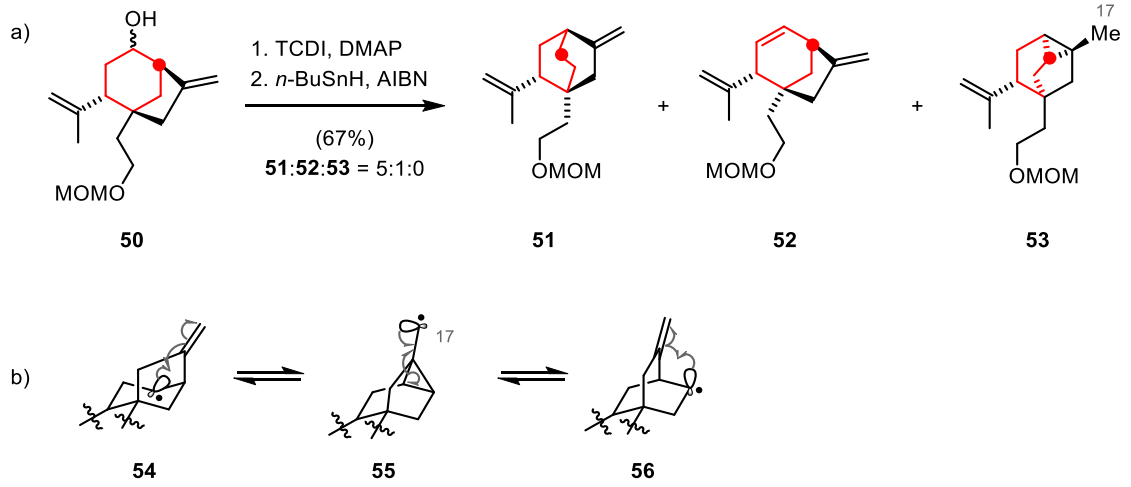


Scheme 7 Semisynthesis of methyl *ent*-trachyloban-19-oate (***ent*-49**) by Cory.[34]

In 1980, Cory et al. developed a novel strategy, they called "bicycloannulation", to access the caged trachylobane structure (Scheme 7).[34] Starting from readily available podocarpic acid (**42**), enone **43** was synthesized in five steps by a procedure of Cambie et al.[35] Treatment of **43** with lithium diisopropylamide (LDA) gave enolate **44**, which attacked the polarized double bond of vinylphosphonium salt **45** whereupon the Wittig ylide **46** underwent a 1,4-addition to the enone. The obtained enolate **47** underwent a S_N2' reaction eliminating triphenylphosphine. Obtained ketone **48** was reduced under Wolff–Kishner conditions to yield methyl *ent*-trachyloban-19-oate (***ent*-49**).

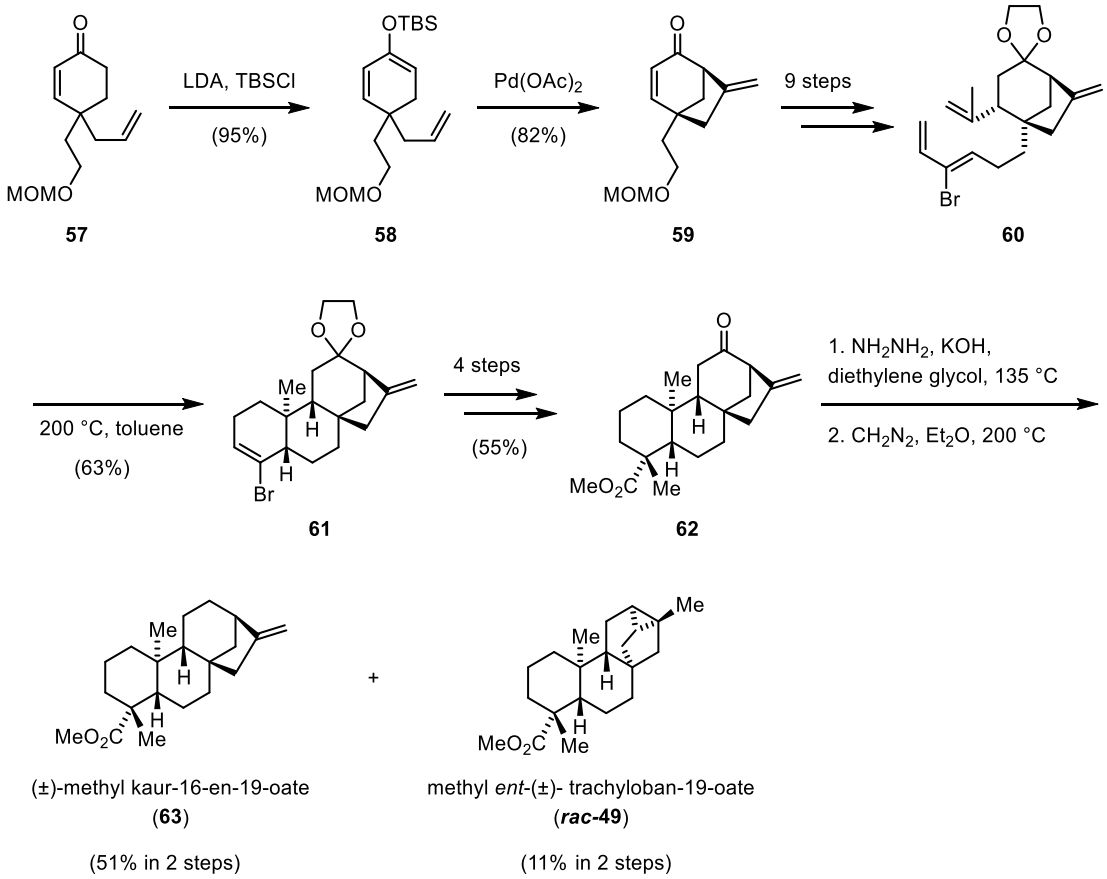
During their efforts to synthesize **63**, Toyota et al. wanted to mimic the originally proposed biosynthesis by Wenkert which suggested non-classical cations.[36] To achieve such a transformation under mild conditions with satisfactory selectivity, Toyota and co-workers designed cyclopropylcarbinyl radical precursor **50** which should rearrange to **51** and **52**, and furthermore, the introduction of hydrogen at C17, if possible, would afford **53 (**Scheme 8a).[37] However, the more stable secondary radical **56** is formed as soon as the cyclopropane ring in **55** is closed. Both alternative structures share a more stable secondary homoallyl radical. The equilibrium reaction

favored the more stable products **51** and **52** therefore cyclopropane **53** could not be isolated (Scheme 8b).



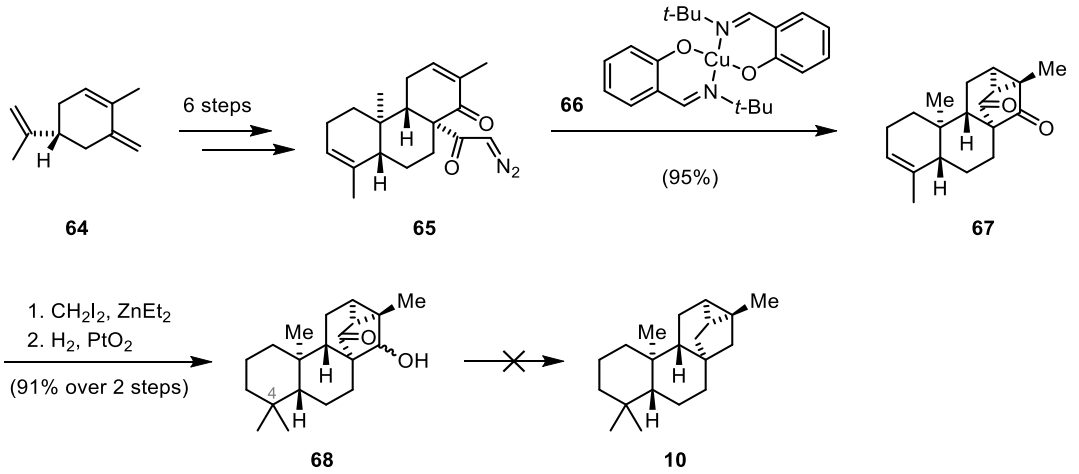
Scheme 8 a) Synthesis and **b)** mechanism of Toyota's radical cyclization.

Despite this setback Toyota et al. were able to synthesize a trachylobane natural product using a different cyclopropanation strategy (Scheme 9). Their total synthesis started with known enone **57**[38] which was transformed into the silyl enol ether **58**. A palladium(II)–catalyzed cyclization afforded *exo*-methylene **59**. Diels–Alder precursor **60** was obtained in nine further steps. The intramolecular Diels–Alder reaction built up the decalin system **61** and four further steps were required to afford intermediate **62**. During the final Wolff–Kishner reduction towards kaurene natural product **63**, methyl trachyloban-19-oate (***rac*-49**) was formed as a side product, presumably via an acyl radical.



Scheme 9 Racemic methyl trachyloban-19-oate (***rac*-49**) as a side product under Wollf–Kishner conditions.[38]

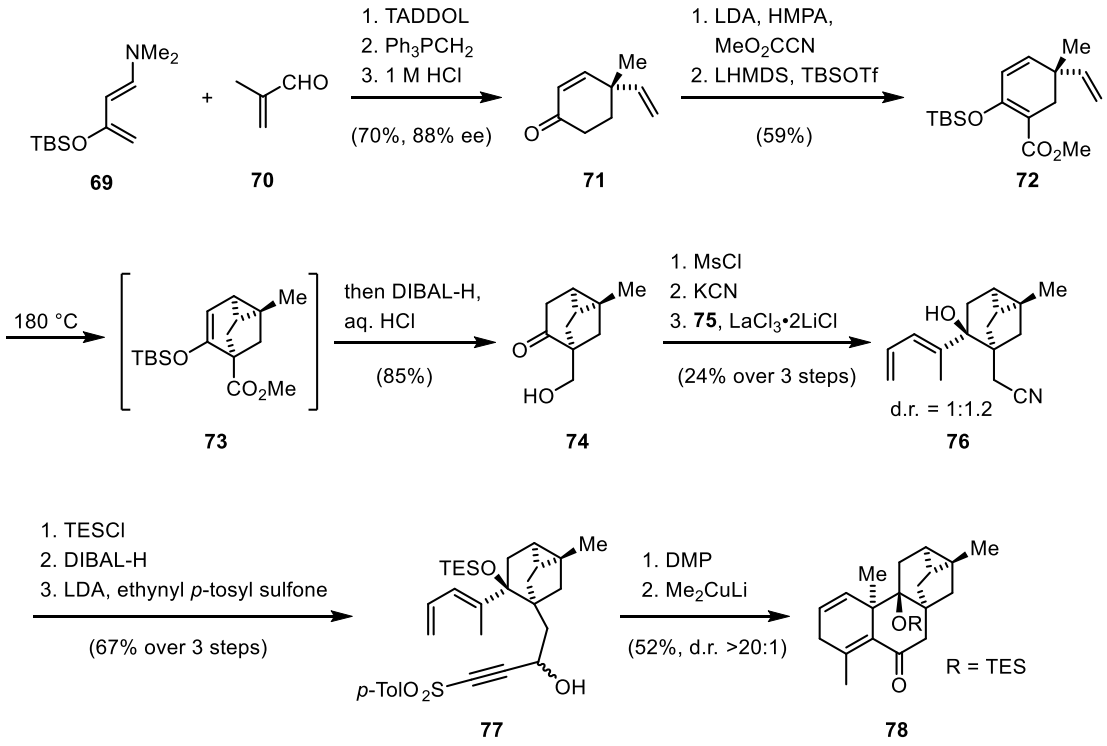
In 2006, Abad et al. came up with a new approach to the tricyclooctane structure of trachylobanes and related natural product families (Scheme 10).[39] Starting from chiral hydrocarbon **64** diazo-precursor **65** was prepared in six steps using a similar strategy as developed by Toyota.[37] α-Diazoketone **65** was activated by copper(II) complex **66** to form *in situ* a carbene, which reacted with the double bond of the enone. A stereoselective Simmons–Smith cyclopropanation sequence introduced the C19 methyl group to give the complete trachylobane skeleton. Noteworthy this reaction took place stereoselectively from the less hindered upper side of the double bond. The characteristic diterpene C4 gem-dimethyl group was introduced by opening the cyclopropane under reductive conditions to afford **68**. Unfortunately, intermediate **68** could not be successfully advanced to *ent*-trachylobane (**10**).



Scheme 10 Cyclopropanation of Abad et al.[39]

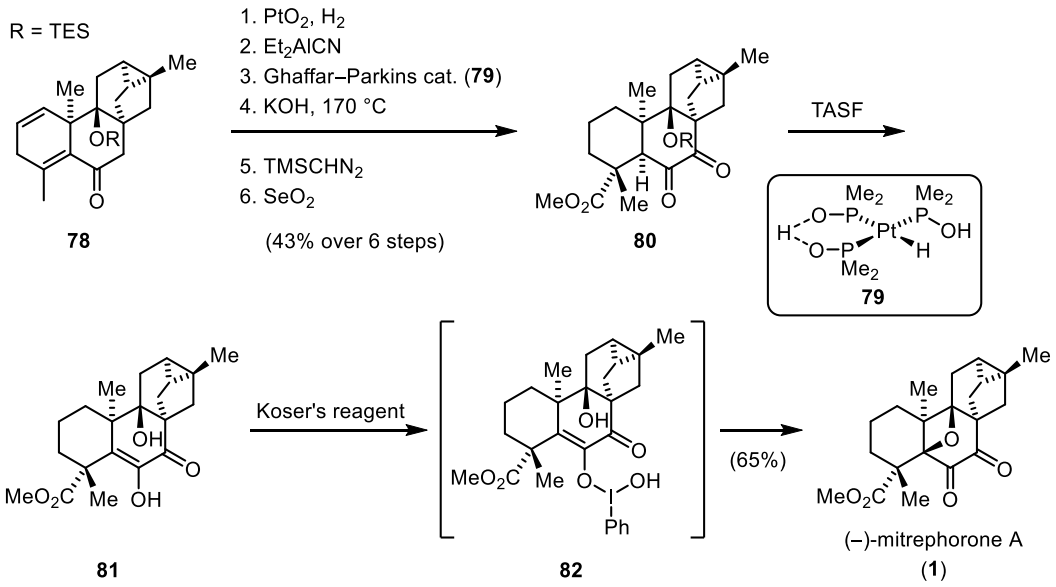
Concurrent with our efforts, the Carreira group published the first total synthesis of mitrephorone A (**1**) in late 2018 (Scheme 11).[40]†

† The total synthesis by Carreira was published after we finished our own synthetic studies towards mitrephorone A. Hence, none of the synthetic work presented in this PhD thesis was inspired or affected by their results.



Scheme 11 Synthesis of the core of mitrephorone A (**1**) by Carreira.[40]

Their synthesis commenced with a TADDOL-catalyzed Diels−Alder reaction[41] of Rawal's diene (**69**) with methacrolein (**70**), followed by Wittig methenylation and acidic hydrolysis to afford cyclohexenone **71** (Scheme 12).[42] Alkylation using Mander's reagent[43] and TBS protection gave triene **72**. The caged tricyclooctane structure in ring C was obtained by an intramolecular Diels−Alder reaction and subsequent *in situ* reduction of **73** yielded hydroxyketone **74**. Alcohol **74** was further converted to nitrile **76** in two steps. Introduction of the 1,3-diene was realized by addition of penta-2,4-dien-2-yllithium (**75**) in the presence of lanthanum(III) chloride bis(lithium chloride) complex.[44] Extensive investigations were undertaken to improve the diastereoselectivity (d.r. = 1:1.2) in the ketone addition reaction. However, only 28% of the correct diastereomer **76** could be isolated. Subsequent protection of the tertiary alcohol, reduction of the nitrile group and addition of lithiated ethynyl *p*-tosyl sulfone to the generated aldehyde gave secondary alcohol **77**. The following key Diels–Alder reaction of **77** proceeded spontaneously following DMP oxidation of the propargyl alcohol at room temperature. A challenging substitution of the sulfone with methyl cuprate furnished **78**, the pentacyclic core of the mitrephorone skeleton. The completion of the total synthesis is depicted in Scheme 12.

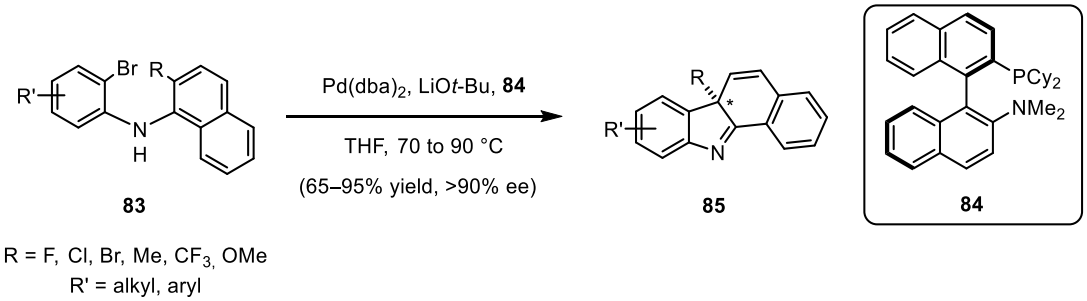


Scheme 12 Completion of the total synthesis of mitrephorone A (**1**).[40]

Diene **78** was chemoselectively reduced using Adams' catalyst. Installation of the quaternary center that incorporates an ester was realized by hydrocyanation with Nagata's reagent,[45] subsequent hydration with Ghaffar–Parkins catalyst (**79**),[46] basic hydrolysis and esterification with trimethylsilyldiazomethane. Riley oxidation[47] with selenium dioxide installed the 1,2-diketone and afforded **80** in high yield. Final one-pot deprotection of the tertiary silyl ether with tris-(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and subsequent reaction of **81** with Koser's reagent (PhI(OH)OTs) closed the oxetane ring and completed the total synthesis.

1.4 Asymmetric Dearomative Cyclizations of Phenols in Natural Product Synthesis

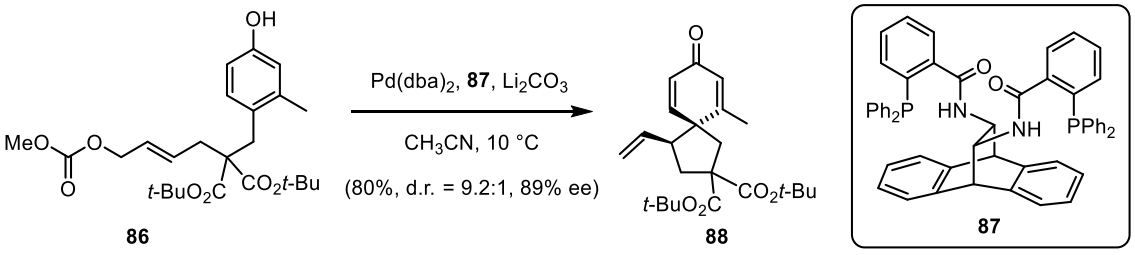
The dearomatization of aromatic compounds has been widely recognized as a powerful transformation for the generation of high levels of molecular complexity from simple planar starting materials. The following section outlines current developments in asymmetric dearomative cyclization reactions forming complex ring structures by using transition-metal catalysts.



Scheme 13 Palladium-catalyzed asymmetric dearomatization of naphthalene derivatives by Buchwald.[48]

In 2009, Buchwald and co-workers found that a palladium(0)complex bearing the chiral P,N-ligand **84** catalyzed asymmetric, intramolecular dearomatizations of naphthalene derivatives **83** to produce fused tetracyclic indolenines **85** which contains two contiguous nonaromatic rings proximal to a quaternary stereocenter (Scheme 13).[48]

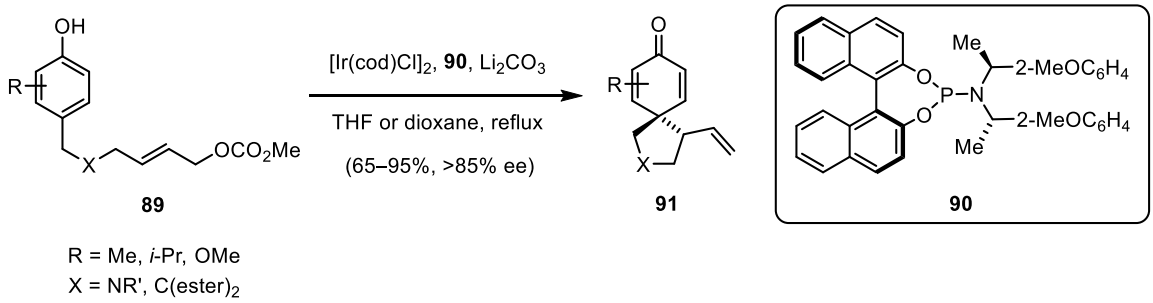
Since then, various asymmetric dearomative cyclizations have been investigated. Of particular interest is the dearomatization of phenols to cyclohexadienone derivatives. These are versatile intermediates for further functionalization towards more complex molecules or natural products.



Scheme 14 Palladium-catalyzed intramolecular *ipso*–Friedel–Crafts allylic alkylation of phenols by Hamada.[49]

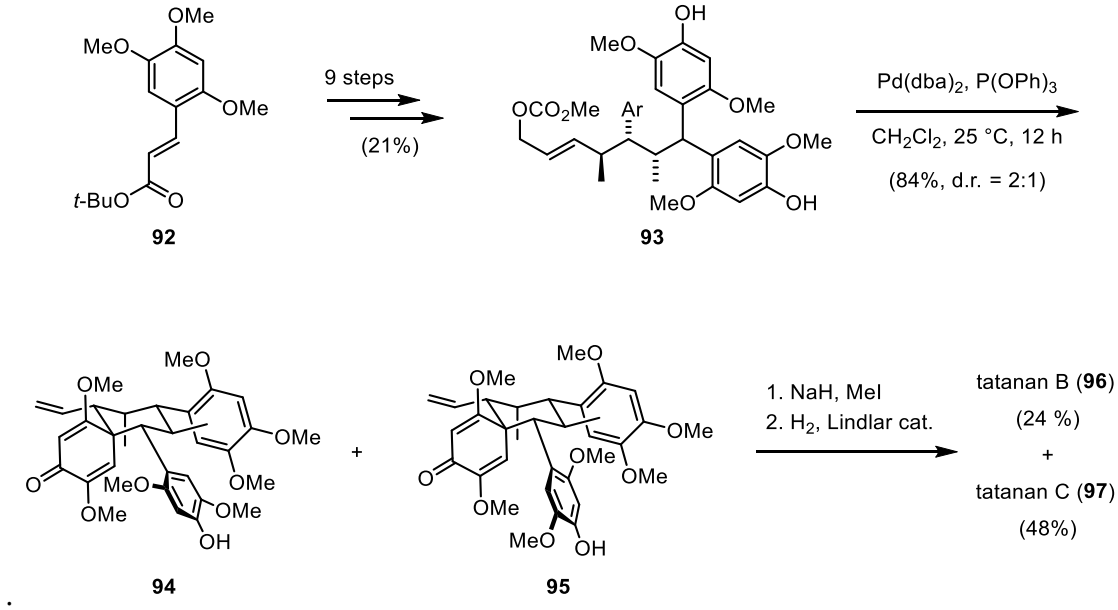
One year later, the Hamada group published the first Pd-catalyzed intramolecular *ipso*-Friedel–Crafts allylic alkylation of phenols (Scheme 14). This novel method provided new access to spiro[4.5]cyclohexadienones. In one example, the authors demonstrated the application of their method to the catalytic enantioselective construction of an all-carbon quaternary spirocenter in cyclohexadienone **88**. In the following years they further developed their methodology, but focused

on broadening the substrate scope rather than developing other enantioselective variants of this reaction.[50][51][52]



Scheme 15 Iridium-catalyzed intramolecular asymmetric allylic dearomatization of phenols by You.[53]

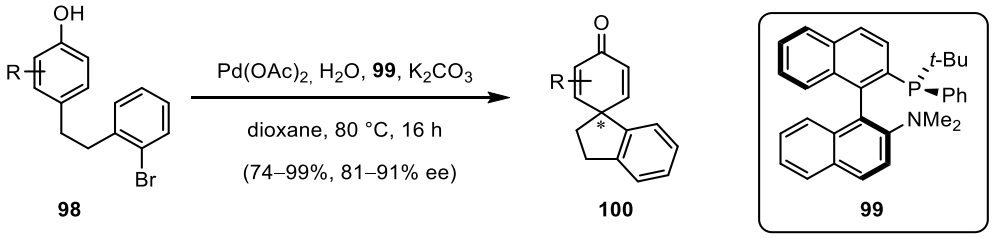
Similar substrates as Hamada et al. were also used in the methodology by You and co-workers.[53] Their iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols **89** is depicted in Scheme 15. The reaction provides facile access to enantioenriched, substituted spirocyclohexadienone derivatives **91** with up to 97% enantiomeric excess.



Scheme 16 Total synthesis of tatanan B (**96**) and C (**97**) by Zakarian.[54]

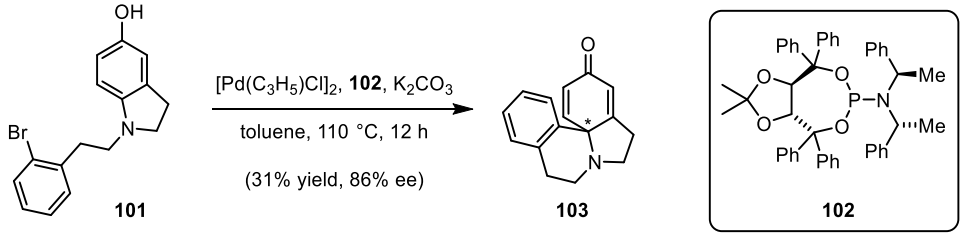
Based on the methodologies by Hamada and You, Zakarian and co-workers realized their enantioselective total synthesis of tatanans A–C, potential antidiabetic agents.[54] Starting from cinnamic ester **92**, enantiomeric pure phenol **93** was synthesized in nine steps (Scheme 16). For the key intramolecular allylic dearomatization several iridium and palladium catalyst / ligand systems were screened. Under optimized conditions, the desired cyclization could be achieved and afforded atropisomeric products **94** and **95** together with one undesired diastereomer. During this

challenging reaction, three of the six stereocenters of the target molecule, including the quaternary center at the core of the spirocyclic ring system, are set with a high degree of stereocontrol. Remarkably, only the formation of three out of sixteen possible stereoisomers has been observed. Methylation and chemoselective hydrogenation of the vinyl group finished the total synthesis of tatanan B (**96**) and C (**97**).



Scheme 17 Asymmetric dearomatization of phenols **98** to spirocyclohexadienones **100**.[55]

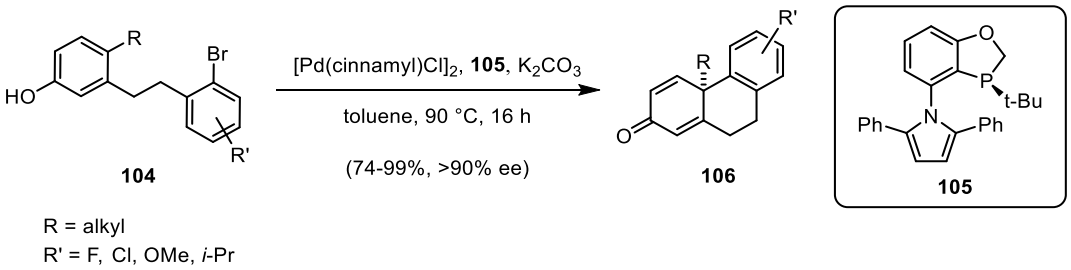
In 2011, Buchwald and co-workers published their studies on the palladium-catalyzed arylative dearomatization of phenols to give spirocyclohexadienones bearing all-carbon quaternary centers in good to excellent yields. Initial studies with two substrates **98** using ligand **99**, they demonstrated that the development of a highly enantioselective variant of this reaction is practical (Scheme 17).



Scheme 18 Asymmetric dearomatization of aminophenols **101** to spiroamines **103** by You.[56]

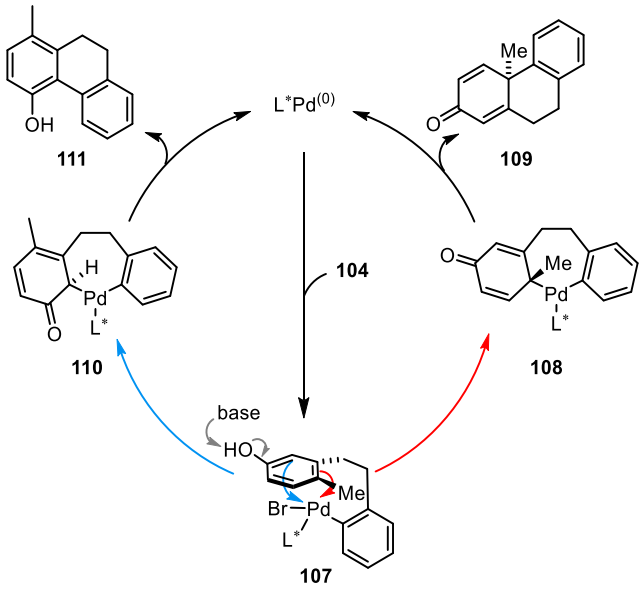
Three years later, You and co-workers reported a highly efficient intramolecular dearomative arylation method to convert 5-hydroxyl indolines to tetracyclic spiroamines.[56] In addition to a broad substrate scope resulting in racemic dearomatization products, the first asymmetric reactions were also performed. The successful asymmetric dearomative cyclization of phenol **101** to spiroamine **103** is depicted in Scheme 18. This methodology is a promising tool towards natural products containing an erythrinane skeleton.

Comprehensive studies with exclusive focus on asymmetric dearomatization reactions were published by Tang and co-workers in 2015.[57] Aim of their work was the development of an efficient enantioselective method to synthesize natural products (Scheme 19).



Scheme 19 Dearomative cyclization for the synthesis of terpenes and steroids by Tang.[57]

They developed a novel and efficient palladium-catalyzed dearomative cyclization, which enabled the synthesis of a series of chiral tricyclic phenanthrenone derivatives **106** bearing all-carbon quaternary centers in excellent enantioselectivities. Studies on diverse P-chiral ligands showed that dihydrobenzooxaphosphole ligand **105** gave the best results. Investigation of the substrate scope of the asymmetric cyclization revealed a reasonable tolerance for several functional groups. Furthermore substrates bearing alternate aromatic motifs, for example naphthalene, quinone or furan motifs were also found to be competent reaction partners. Moreover, the reaction is also suitable for vinyl triflates as well as of aromatic bromides **104**.



Scheme 20 Proposed mechanism of palladium-catalyzed asymmetric cyclization of phenol **104**.[57]

The proposed catalytic cycle is shown in Scheme 20 and it rationalizes all other mechanisms presented in this chapter. The authors assumed, that asymmetric dearomative cyclization reaction of bromine-substituted phenol **104** could either result in the desired spirocyclohexadienone **109** or the regioisomeric biaryl **111**. Both pathways start with oxidative addition of **104** to form palladium(II)-complex **107**. Base promoted nucleophilic substitution could lead to cyclization

products **109** and **111**, respectively. Reductive elimination of **110** provides achiral ortho-product **111** wheras chiral spirocyclohexadienone **109** could result from **108**. Formation of the dearomative cyclization product **109** is assumed to be the kinetically favored pathway.

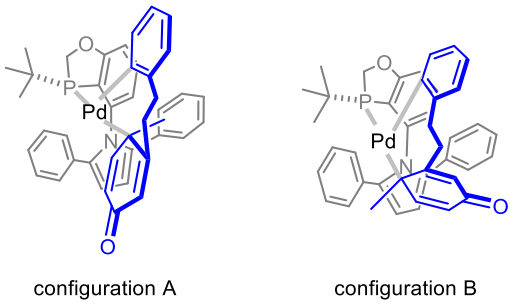
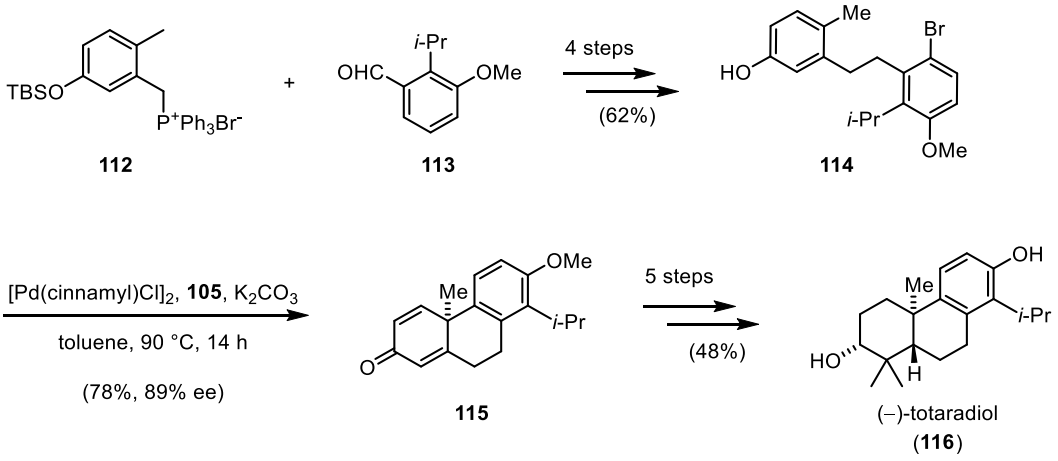


Figure 5 Proposed stereochemical model for the reductive elimination step of the cyclization of **104** with Pd/**105** as the catalyst.[57]

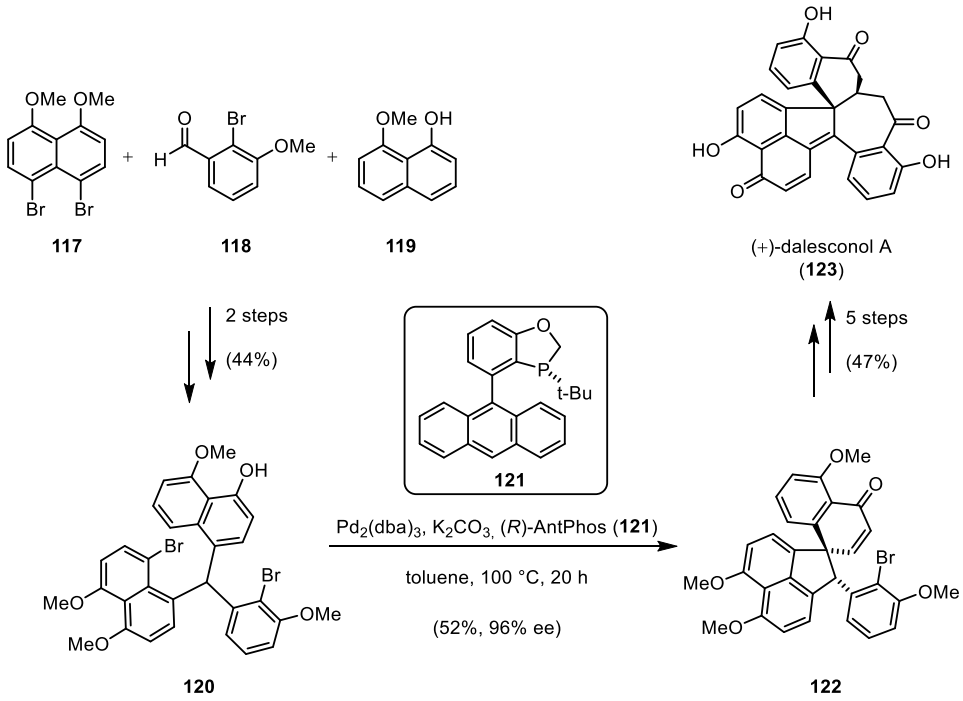
The authors suggested a stereochemical model for the cyclization which could rationalize the high enantioselectivity of the reaction. As shown in Figure 5, the 2,5-diphenylpyrrole moiety of rigid ligand **105** blocks the backside of the complex, and its bulky tert-butyl group can well dictate the orientation of substrate coordination. It is assumed, that after oxidative addition and nucleophilic substitution, the substrate could adopt two major conformers, A and B, when coordinated to the Pd/**105** complex. Conformer B appears to be more strained whereas the more favorable conformer A undergoes reductive elimination to provide the cyclization product **109** with the observed *R*-configuration.



Scheme 21 Total synthesis of (–)-totaradiol (**116**) by Tang.[57]

Tang and co-workers applied their new dearomatization strategy to the synthesis of a kaurane intermediate and the synthesis of the boldenone skeleton.[57] Furthermore (–)-totaradiol (**116**) was synthesized in ten steps (Scheme 21). Starting from known aldehyde **113**[58] and Wittig salt **112**,

key intermediate **114** was prepared in four steps. Asymmetric cyclization of **114** with Pd/**105** as the catalyst provided the desired product **115** in 78% yield and 89% enantiomeric excess. The total synthesis of (–)-totaradiol (**116**) was completed in five further steps.



Scheme 22 Total synthesis of (+)-dalesconol A (**123**) by Tang.[59]

Recently, W. Tang and co-workers published the first enantioselective synthesis of immunosuppressant (+)-dalesconol A (Scheme 22).[59] Starting from commercially available precursors **117**, **118** and **119**, key intermediate **120** was obtained in three steps. Asymmetric dearomative cyclization reaction of **120** resulted in product **122** in excellent enantioselectivity. The synthesis of (+)-dalesconol A (**123**) could be completed in five further steps.

In conclusion, asymmetric dearomative cyclizations of phenols can be an efficient strategy to synthesize complex natural products bearing all carbon quaternary centers.

2 Project Outline

2.1 Mitrephorone A – Isolation and Bioactivity

Figure 6 Images of the custard apple tree *Mitrephora glabra*.‡

Mitrephorone A (**1**) is an *ent*-trachylobane-type diterpenoid that was isolated in 2005 from the bark of *Mitrephora glabra* (family Annonaceae), an Indonesian flowering plant (Figure 6).[60] One kilogram of dried bark was extracted and concentrated to a tannin-free organic extract, which was separated by flash silica gel column chromatography and purified with reversed phase HPLC to give mitrephorone A (**1**) in 0.00021% yield (21 mg).

Together with mitrephorone A, mitrephorone B (**124**) and C (**125**) were isolated (Figure 7). They all share the *ent*-trachylobane skeleton, but only mitrephorone A features the intriguing oxetane ring. Mitrephorone A (**1**) has a complex hexacyclic scaffold that contains a caged tricyclooctane, the oxetane ring and an adjacent 1,2-diketone moiety. Furthermore it has eight stereogenic centers, four of which are quaternary.

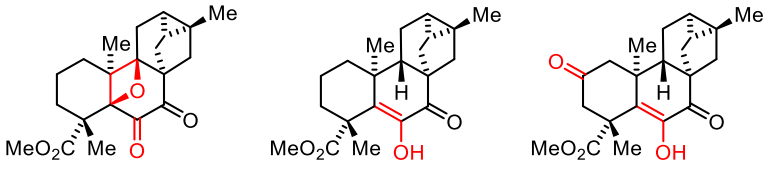


Figure 7 Three mitrephorones A, B and C isolated from *Mitrephora glabra*.

None of the three mitrephorones is crystalline, so no crystal structure is available. Oberlies and coworkers established the relative stereochemistry of mitrephorone A based on ROESY data

‡ Photograph and copyright by Prof. Dr. Kamarudin Mat Salleh.

analysis (Figure 8). The absolute stereochemistry for all three compounds was presumed to belong to their enantio-series, as determined by crystallographic analysis and chemical transformations of other known *ent*-trachylobane-type diterpenoids.[60]

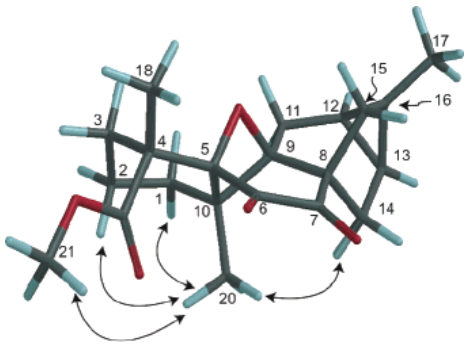


Figure 8 Energy minimized model of **1** illustrating the major ROESY correlations used to define the relative stereochemistry.[60]

With the limited material of mitrephorone A, Oberlies and co-workers conducted a first biological screen (Table 1). All three mitrephorones show moderate activity against bacteria (*Micrococcus luteus* and *Mycobacterium smegmatis*), a yeast (*Saccharomyces cerevisiae*), and a filamentous fungus (*Aspergillus niger*). Among them, mitrephorone C (**125**) exhibits the strongest antimicrobial activity and mitrephorone A (**1**) exhibits promising activity against human cancer cell lines.

Table 1 Antimicrobial activity and cytotoxicity of mitrephorone A–C.[60]

mitrephorone	**Antimicrobial Activity** MIC, [µg/mL][a]				**Anticancer Activity** IC_{50}, [µg/mL][b]			
	M. luteus	*M. smegmatis*	*S. cerevisiae*	*A. niger*	KB	MCF-7	H460	SF-268
A	125	63	63	63	8.0	15.7	23.3	30.9
B	88	88	88	88	7.0	inactive	inactive	inactive
C	63	31	31	63	inactive	inactive	inactive	inactive

[a] Antimicrobial activity results were recorded as minimal inhibitory concentration (MIC, [µg/mL]), which corresponds to the lowest concentration of compound that prevents visible growth of a microorganism. [b] Anticancer activity against human cancer cell panels was described in half maximal inhibitory concentration (IC_{50}, [µg/mL]), the concentration to inhibit growth by 50%. KB = oral epidermoid carcinoma, MCF-7 = mammary adenocarcinoma, H460 = large cell lung carcinoma, SF-268 = brain cancer.

The authors of the study conclude: *„The oxetane ring in mitrephorone A was not present in any of the known members of this class, making it the first representative of this novel hexacyclic ring system. On the basis of a limited set of human tumor cell cytotoxicity data, this unique structure seems to impart a greater degree of anticancer activity than in the other trachylobanes."*[60]

2.2 Aims of the Project

Mitrephorone A (**1**) represents a unique and challenging target for total synthesis. The primary challenge lies in the successful construction of the sterically demanding carbon skeleton. Additionally, the installation of its four quaternary stereocenters was expected to cause difficulties. The rare 1,2-diketone moiety and the adjacent oxetane ring render this natural product a veritable challenge in synthetic chemistry and these functionalities are planned to be introduced after the assembly of the highly congested carbon skeleton.

We planned to access mitrephorone A (**1**) by two different strategies (Figure 9). At first, we aimed to synthesize the core structure with a convergent dearomatization approach by disconnection of bond C9−C10 (Strategy A), relying on new methodologies for phenol dearomatization strategies. In addition, we set out to investigate the assembly of the carbon skeleton from literature known building block **129** by a Robinson annulation (Strategy B).

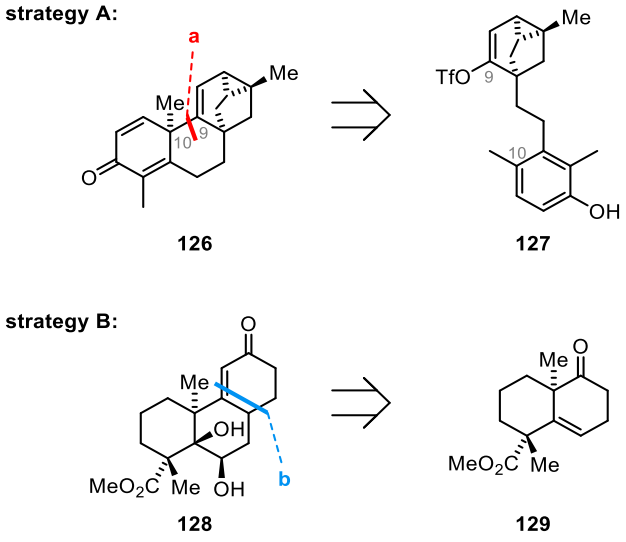


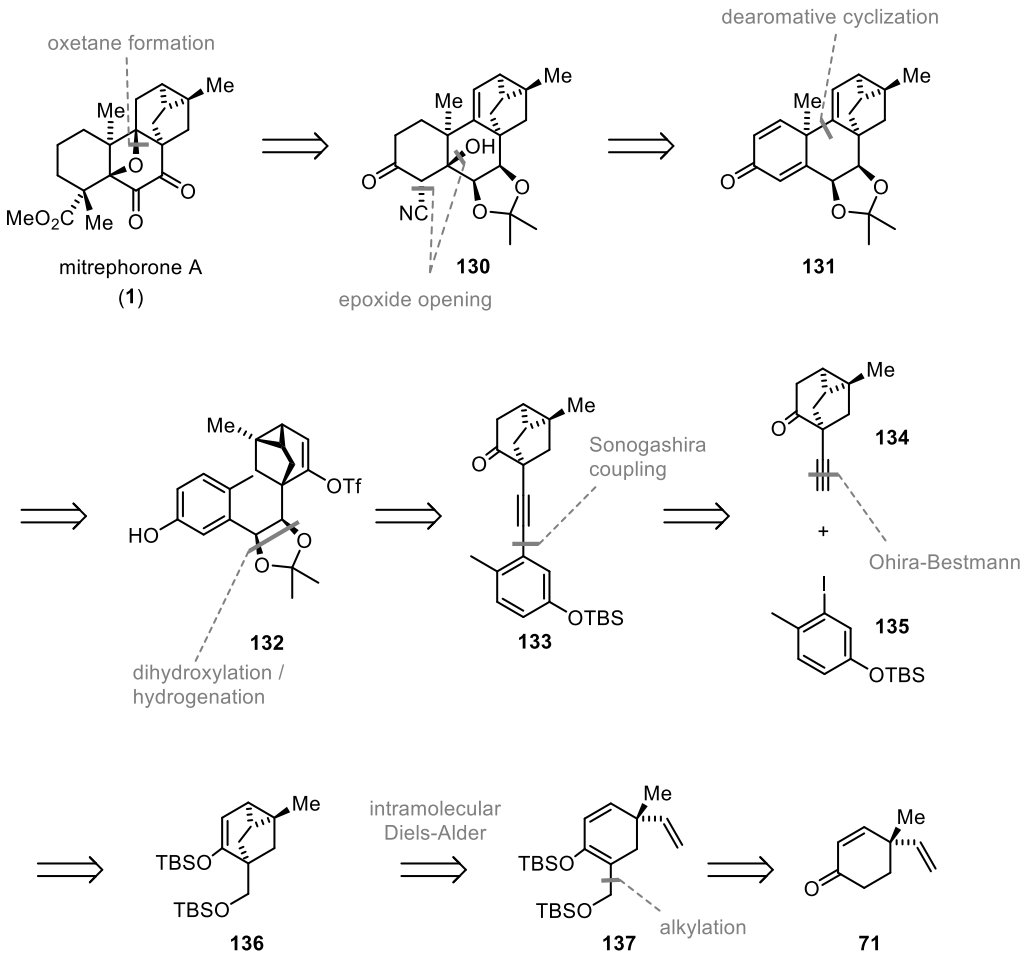
Figure 9 Retrosynthetic bond disconnections for the tricyclic core structure of mitrephorone A (**1**).

3 Results and Discussion

3.1 Strategy A: Dearomative Cyclization

3.1.1 First-generation Approach: Dihydroxylation and Dearomatization

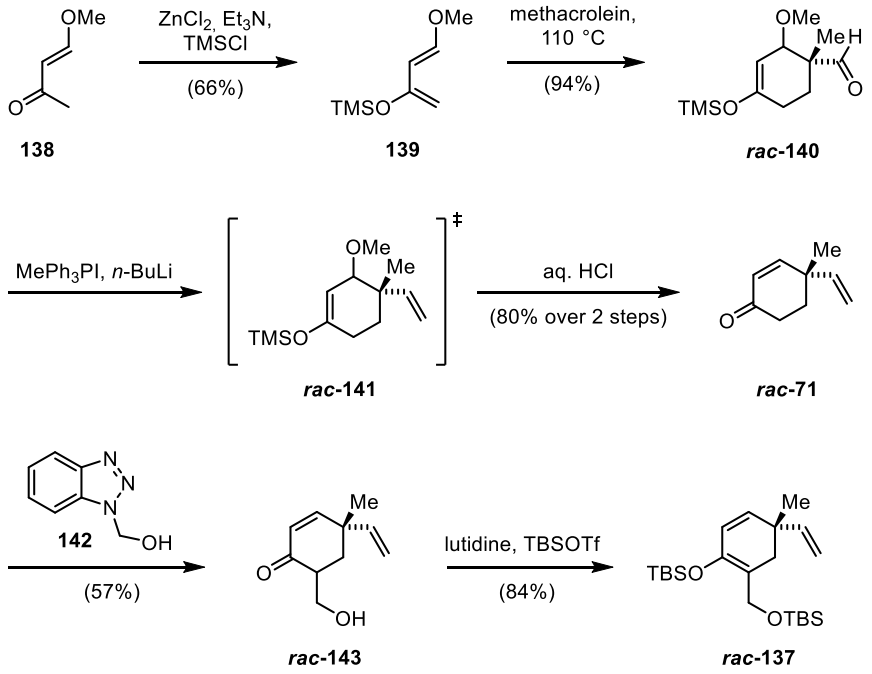
The earlier synthetic approaches towards trachylobane natural products (see chapter 1.3.2) struggled with the construction of the caged tricyclooctene structure in ring C. Harsh reaction conditions were needed to install these unique carbon-carbon bonds at the end of the syntheses. Thus, only very few functional groups were tolerated and only unfunctionalized trachylobanes have been synthetized. Since mitrephorone A is a highly functionalized natural product, a completely new synthetic strategy was necessary. Due to the literature known challenges in synthesizing the caged tricyclooctene at later stages, we envisioned to start our synthesis with the caged ring structure.



Scheme 23 Initial retrosynthetic analysis for mitrephorone A (**1**).

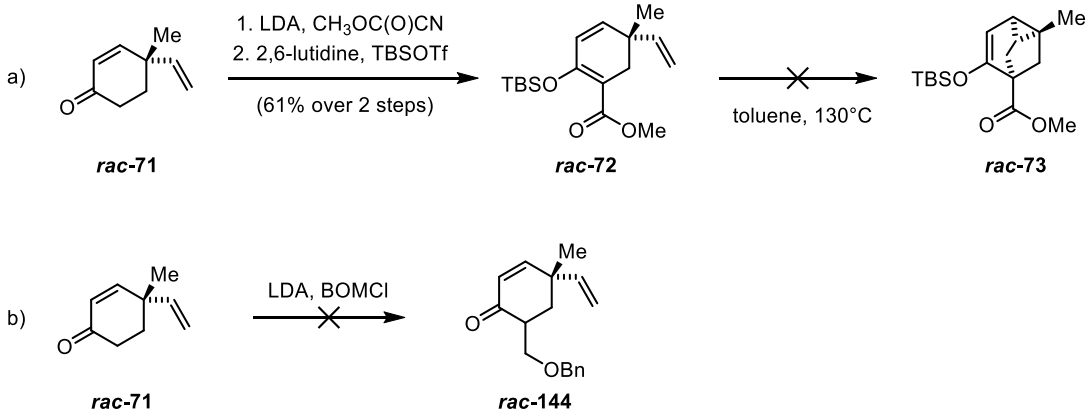
The retrosynthetic analysis for mitrephorone A (**1**) is depicted in Scheme 23. The oxetane ring should be introduced in a late stage of the synthesis via cyclization onto the activated double bond of **130**. This activation could be realized by epoxidation or halocyclization. As the key step of the synthesis we envisioned an intramolecular dearomative cyclization to assemble the sterically demanding ring structure of mitrephorone A. Key intermediate **132** could be prepared by dihydroxylation after *Z*-selective Lindlar reduction of alkyne **133**. To allow for a convergent assembly process, we disconnected the alkyne **133** by Sonogashira coupling, giving rise to aromatic building block **135** and tricycle **134**. To construct the caged tricyclo-[3.2.1.0]oct-3-ene structure of **134** we foresaw an intramolecular Diels-Alder reaction of precursor **137** which can be traced back to literature known enone **71**.[61]

Based on a literature known procedure, racemic enone ***rac*-71** was synthesized in four steps (Scheme 24). Starting from 4-methoxy-3-buten-2-one (**138**), Danishefsky's diene (**139**) was prepared followed by Diels–Alder reaction with methacrolein to obtain aldehyde ***rac*-140**. Wittig olefination and subsequent acidic work-up gave enone ***rac*-71**. Deprotonation of ***rac*-71** with LDA, followed by quenching the resulting enolate with 1*H*-benzothiazole-1-methanol (**142**) furnished the labile hydroxymethyl product ***rac*-143** which was immediately protected with *tert*-butyl-dimethylsilyl trifluoromethanesulfonate (TBSOTf) to afford compound ***rac*-137**.



Scheme 24 Racemic synthesis of Diels–Alder precursor **137**.

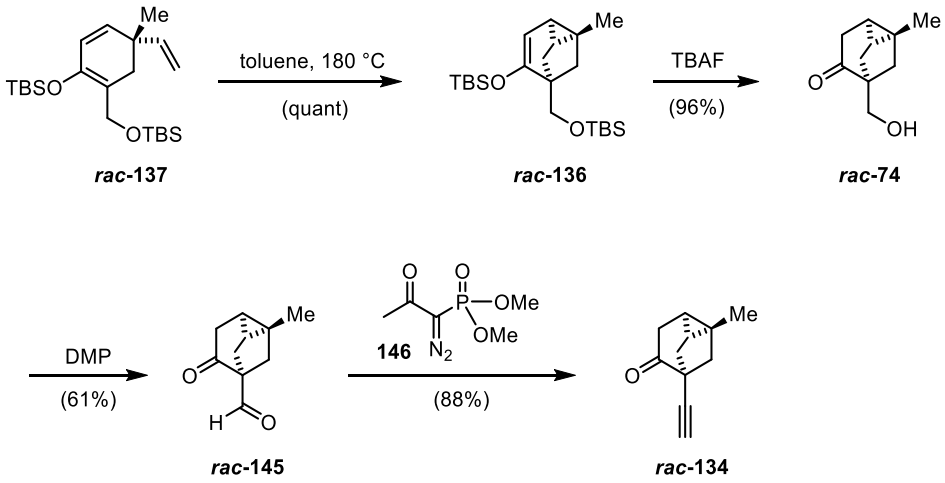
In order to achieve better yields for a Diels–Alder precursor and to diversify the possible substrates for the first key step, two alternative alkylations were tested (Scheme 25). With Mander's reagent a methylester ***rac*-72** was synthesized (Scheme 25a), but subsequent Diels–Alder reaction did only afford a complex mixture of products. Additionally, the corresponding benzyl chloromethyl ether did not lead to the desired enone ***rac*-144** (Scheme 25b).



Scheme 25 Alternative substrates for the intramolecular Diels–Alder reaction.

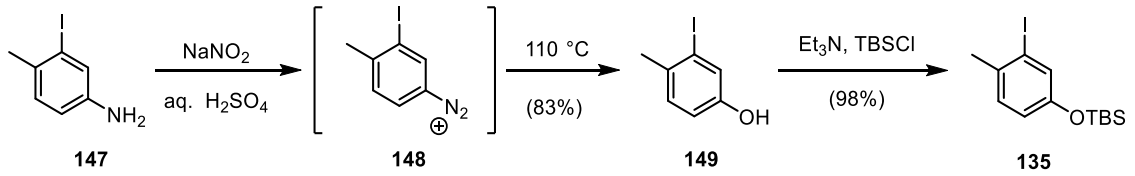
However, by heating the TBS-protected Diels–Alder precursor ***rac*-137** the intramolecular cycloaddition smoothly afforded the caged cyclooctene ***rac*-136** (Scheme 26). Following, the synthesis of alkyne ***rac*-134** required some optimization. Deprotection of ***rac*-136** gave primary alcohol ***rac*-74**, which was further oxidized to aldehyde ***rac*-145** with Dess–Martin periodinane

(DMP). In comparison, impurities from an alternative Swern oxidation of ***rac*-74** influenced the following Sonogashira coupling and dramatically decreased the yield. The oxidation attempt with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide led to incomplete conversion. Finally, Ohira-Bestmann homologation of aldehyde ***rac*-145** afforded alkyne ***rac*-134** in very good yield.



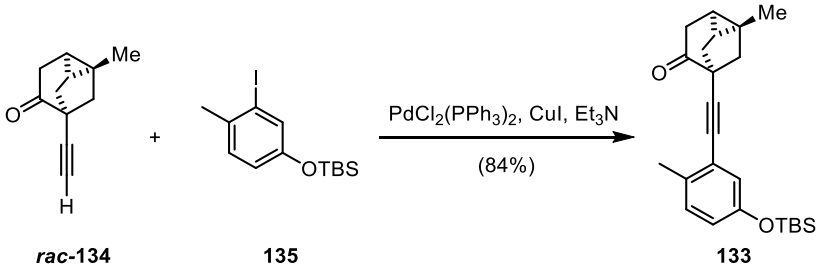
Scheme 26 Racemic synthesis of alkyne ***rac*-134**.

The coupling partner for alkyne ***rac*-134** was synthesized in two steps starting from commercially available aniline **147** (Scheme 27). Sandmeyer reaction of the aryldiazonium salt **148** yielded phenol **149**, which was subsequently TBS protected to give aryl iodide **135**.



Scheme 27 Synthesis of aryl iodide **135**.

With the two building blocks alkyne ***rac*-134** and aryl iodide **135** in hand, it was possible to carry out the following Sonogashira coupling (Scheme 28).

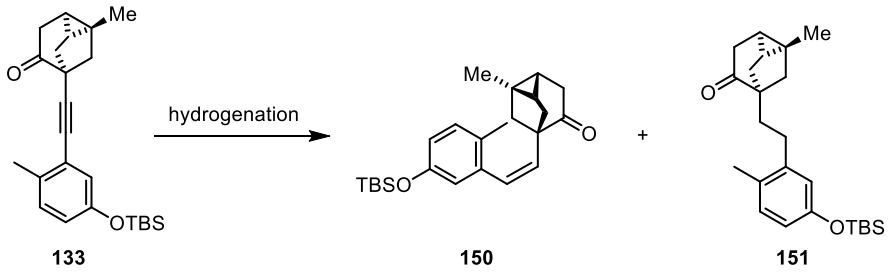


***rac*-134** **135** **133**

Scheme 28 Sonogashira coupling of alkyne ***rac*-134** and aryl iodide **135**.

The following hydrogenation had to be optimized. Screening different reaction conditions, *Z*-selective Lindlar hydrogenation of alkyne **133** was optimized to obtain alkene **150** in excellent yield with only traces of the alkane **151** (Table 2).

Table 2 Investigation of the hydrogenation of alkyne **133**.

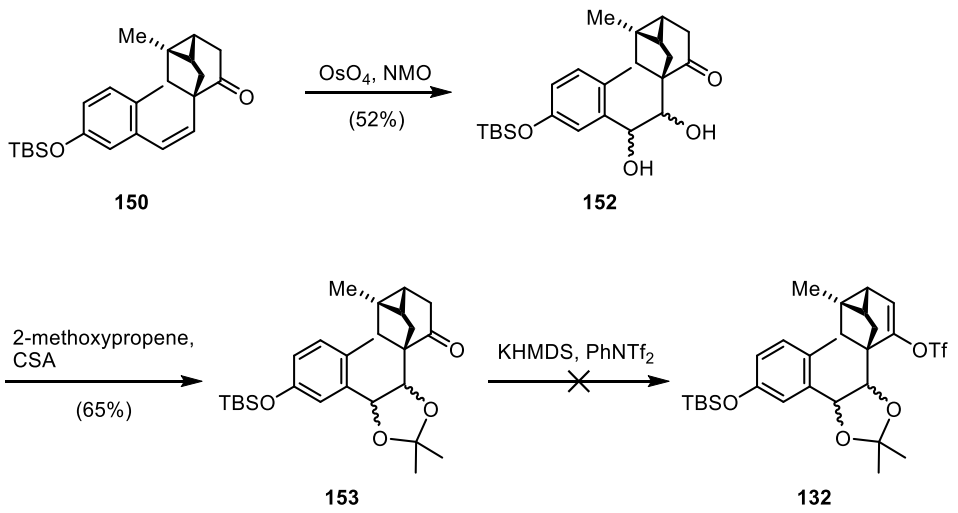


133 **150** **151**

Entry[a]	Catalyst	Solvent	t [min][b]	Observation
1	Rosenmund[c]	THF	5	no conversion
2	Lindlar[d]	THF	5	no conversion
3	Rosenmund	MeOH	2	**150** : **151** (1:2)
4	Lindlar	MeOH	2	**150** : **151** (1:1)
5	Lindlar	THF / MeOH	8	no conversion
6	Lindlar	MeOH	1	**150** (94% yield)

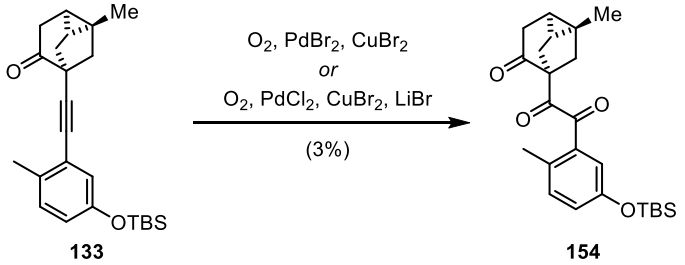
[a] all reactions were conducted on a 0.01 mmol scale. [b] purging the solution with H_2 gas. [c] 5% Pd on $BaSO_4$. [d] 5% Pd on $CaCO_3$ with 3.5% Pb.

Dihydroxylation of styrene **150** gave a diastereomeric mixture of diol **152** (d.r. = 3:7) that proved to be inseparable (Scheme 29). The moderate yield of this reaction was attributed to overoxidation of the alkene, leading to carbon–carbon bond cleavage. Asymmetric Sharpless dihydroxylation was tested, but no conversion was observed, probably due to the steric encumbrance of alkene **150**. Therefore, diol **152** was protected as an acetonide to yield **153**. A first attempt to convert a small amount of ketone **153** into the vinyl triflate **132** gave a mixture of products.



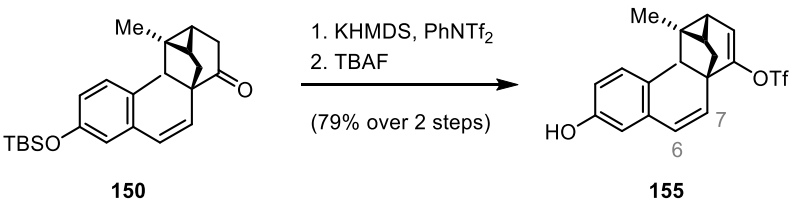
Scheme 29 Synthesis of acetonide **153**.

As dihydroxylation was not productive, we decided to modify the synthetic sequence. An alternative route towards the dearomatization precursor was to synthesize diketone **154** (Scheme 30). According to a publication of Zhao and co-workers a Wacker-type oxidation using molecular oxygen was applied.[62] Unfortunately only small amounts of diketone **154** could be isolated as most of the starting material decomposed.



Scheme 30 Wacker-type oxidation of alkyne **133**.

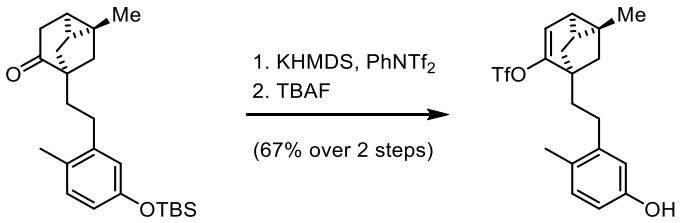
Given this result, we decided to introduce the diketone oxidation stage after the key dearomatization. Therefore, before putting additional effort into synthesizing acetonide **153**, we proceeded with the route to alkene **155** in order to investigate the key dearomative cyclization. Ketone **150** was converted to the corresponding vinyl triflate, which was subsequently treated with TBAF to obtain phenol **155** (Scheme 31).



150 **155**

Scheme 31 Synthesis of dearomatization precursor **155**.

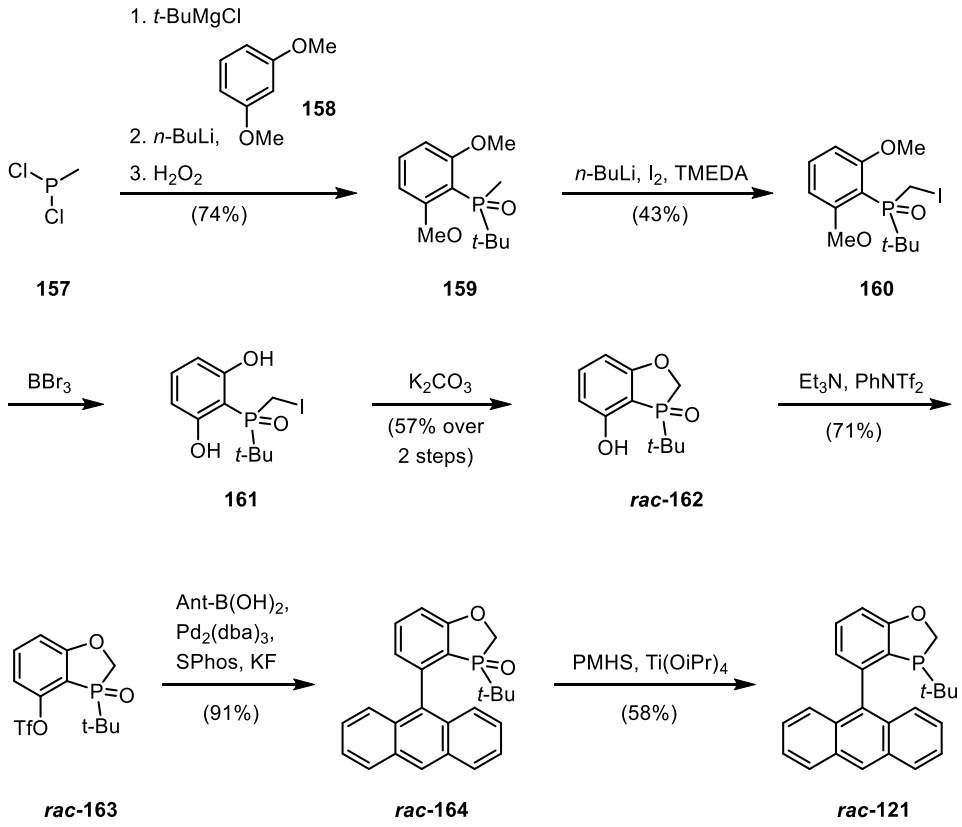
Additionally, as the intramolecular cyclization methodology is only known for substrates without substitution or unsaturation at the C6-C7 bridge,[57] we also synthesized alkane **156** (Scheme **32**) as a possible substrate for the dearomative cyclization. Ketone **151** was converted to the corresponding vinyl triflate, which was subsequently TBS-deprotected to obtain phenol **156**.



151 **156**

Scheme 32 Synthesis of dearomatization precursor **156**.

In parallel to the building block syntheses, the dihydrobenzooxaphosphole ligand AntPhos **121** for the dearomatization key step was synthesized according to a literature known procedure (Scheme **33**).[63] Commercially available dichloromethylphosphine (**157**) was alkylated with *tert*-butylmagnesium chloride and arylated with lithiated 1,3-dimethoxybenzene (**158**), followed by oxidation to give phosphine oxide **159** in good yield. Subsequent iodination gave iodide **160** in moderate yield, but unreacted starting material could be reisolated.

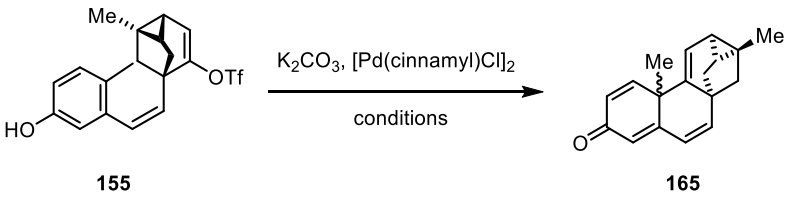


Scheme 33 Synthesis of racemic dihydrobenzooxaphosphole ligand AntPhos ***rac*-121**.

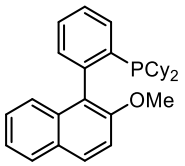
Dihydroxybenzene **161** was prepared using a modified procedure which involved an aqueous work up. Subsequently, it was cyclized to phenol ***rac*-162** in 57% yield over two steps. Starting from this intermediate ***rac*-162**, the enantiomerically pure ligands could be synthesized by chiral resolution of the corresponding menthyl carbonate. For the moment we proceeded to prepare the racemic ligand. Therefore, phenol ***rac*-162** was converted to triflate ***rac*-163** and subsequent Suzuki coupling with antracene boronic acid gave dihydrobenzooxaphosphole oxide ***rac*-164** in very good yield. Final reduction of ***rac*-164** using polymethylhydrosiloxane (PMHS) proved challenging. In solution dihydrobenzo-oxaphosphole ***rac*-121** is extremely sensitive to reoxidation. A quickly performed aqueous work-up with thoroughly degassed solvents was not sufficient to prevent reoxidation. However, addition of degassed water to the reaction mixture in a Schlenk tube under argon atmosphere and repeated decanting of the organic phase enabled reduction of ***rac*-164** to ligand ***rac*-121**. The concentrated and dried dihydrobenzooxaphosphole ***rac*-121** was stable under air.

The stage was set to investigate the dearomative cyclization with vinyl triflate ***rac*-155** (Table 3). The literature known conditions did not lead to the desired product **165** (Entry 1).

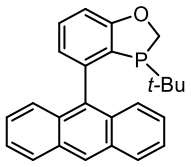
Table 3 Investigation of dearomative cyclization of alkene **155**.



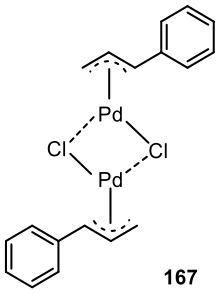
155 **165**



166



***rac*-121**

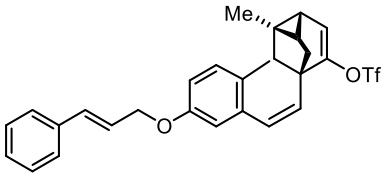


167

Entry[a]	Ligand	Solvent	T [°C]	Observation
1	*rac*-AntPhos (***rac*-121**)	toluene	90	traces of side product **168**
2	*rac*-AntPhos (***rac*-121**)	dioxane	90	no conversion
3	*rac*-AntPhos (***rac*-121**)	dioxane	120	decomposition
4	**166**	toluene	90	no conversion

[a] all reactions were conducted on a 0.03 mmol scale.

Instead we isolated small amounts of **168** which result from a Tsuji–Trost allylic alkylation of deprotonated phenol and the cinnamyl ligand. More polar solvent as dioxane (Entry 2) or higher temperatures were also ineffective (Entry 3). We also tested ligand **166**, which was used by Buchwald and co-workers for similar palladium-catalyzed arylative dearomatization,[55] but it also led to no conversion of the starting material (Entry 4).

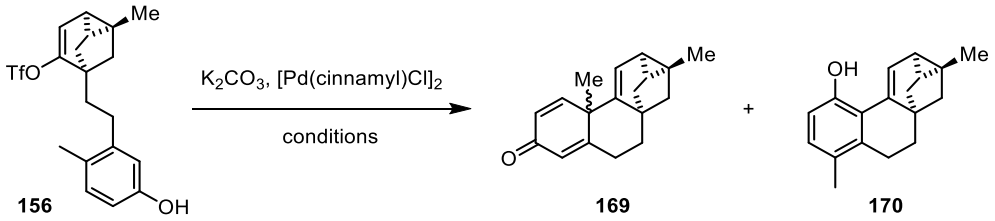


168

Figure 10 Isolated side product of the dearomatization attempts of alkene **155**.

Moreover, the cyclization was investigated for alkane **156** (Table 4). Instead of the desired dearomatization to dienone **169**, the reaction occurred at the free *ortho* position and gave rearomatized phenol **170** in 47% yield (d.r. = 1:1). Buchwald's ligand **166** led to no conversion, hence the dihydrobenzooxaphosphole ligand **121** seems crucial for the proceeding of the reaction.

Table 4 Investigation of dearomative cyclization of alkane **156**.



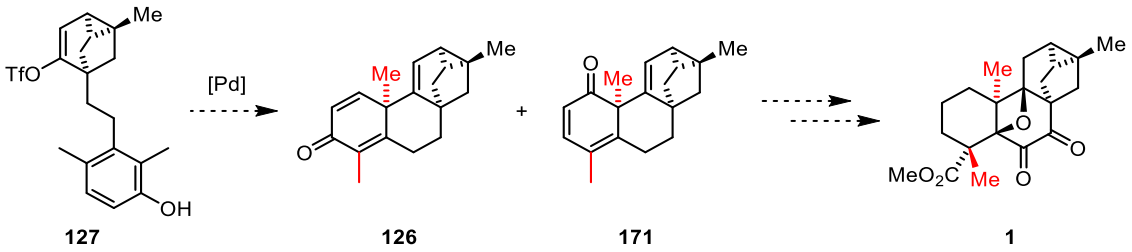
Entry[a]	Ligand	Solvent	T [°C]	Observation
1	*rac*-AntPhos (***rac*-121**)	toluene	90	**170** (47% yield)
2	*rac*-AntPhos (***rac*-121**)	dioxane	90	traces **170**
3	**166**	toluene	90	decomposition
4	**166**	dioxane	90	no conversion

[a] all reactions were conducted on a 0.03 mmol scale.

Although rearomatized compound **170** was useless for our purpose, these results showed, that palladium inserts into the triflate and a cyclization of system **156** is possible. As proposed by Tang, maybe steric effects inhibit the attack at the methyl substituted *para* position.[57]

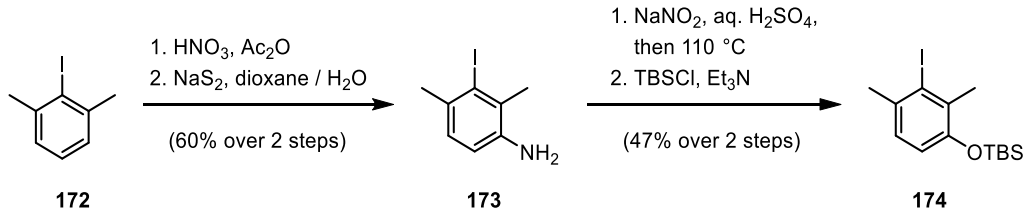
3.1.2 Second-generation Approach: Enantioselective Synthesis

As the dearomative cyclization of precursor **156** led to the *ortho* functionalization followed by rearomatization, we redesigned our retrosynthetic plan. Since methyl groups are needed in *ortho* and *para* position, we foresaw to introduce them both into the aromatic ring (Scheme 34). Intramolecular cyclization of **127** should then either give dienone **126** (*para* attack) or enone **171** (*ortho* attack). A rearomatization is not possible in either systems and both products could be further used in our total synthesis.



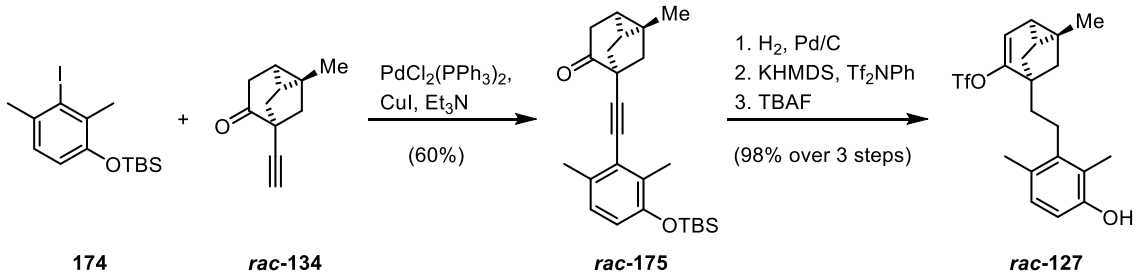
Scheme 34 Foreseen synthesis of an alternative key intermediate **127**.

In a four-step sequence, iodine **174** was prepared starting from 2-iodo-*m*-xylene (**172**) in good yield (Scheme 35).



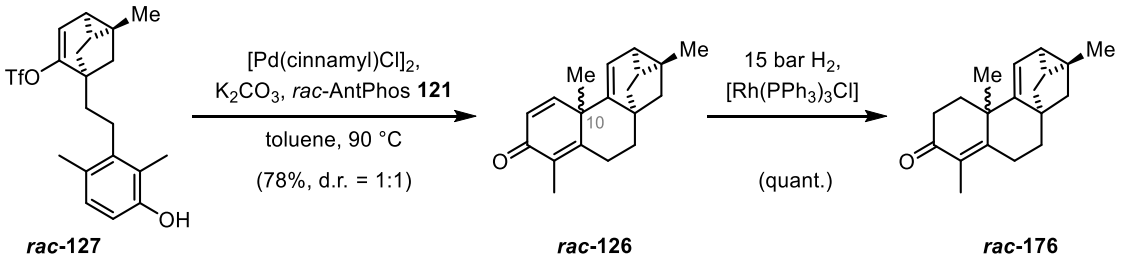
Scheme 35 Synthesis of aromatic building block **174**.

According to the already established route, building blocks **174** and ***rac*-134** were coupled by Sonogashira cross coupling to ***rac*-175**. Subsequent hydrogenation, triflation and deprotection gave phenol ***rac*-127** (Scheme 36).



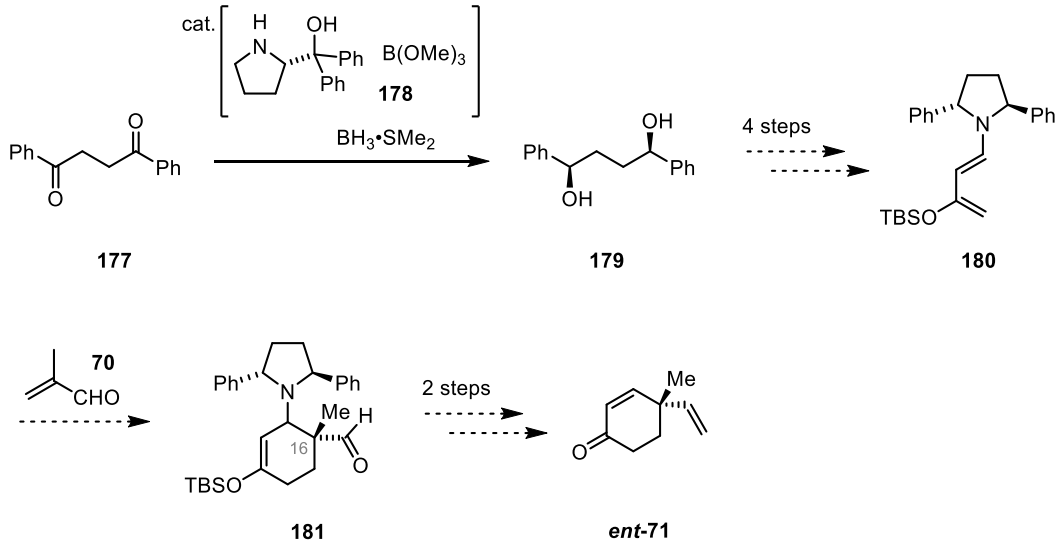
Scheme 36 Synthetic route towards vinyl triflate ***rac*-127**.

With vinyl triflate ***rac*-127** in hand, we investigated the palladium catalyzed cyclization (Scheme **37**). We were pleased to find that under the reported conditions[57] only *para* product ***rac*-126** was obtained as an inseparable mixture of diastereomers (d.r. = 1:1) at C10. The next steps of the synthesis were continued with the diastereomeric mixture of ***rac*-126**. Hydrogenation of the least hindered double bond gave enone ***rac*-176** in full conversion. However, high catalyst loading (0.5 eq) and 15 bar pressure were necessary for this hydrogenation. The diastereomers of enone ***rac*-176** were still not separable.



Scheme 37 Successful dearomatization of ***rac*-127** and subsequent hydrogenation to ***rac*-176**.

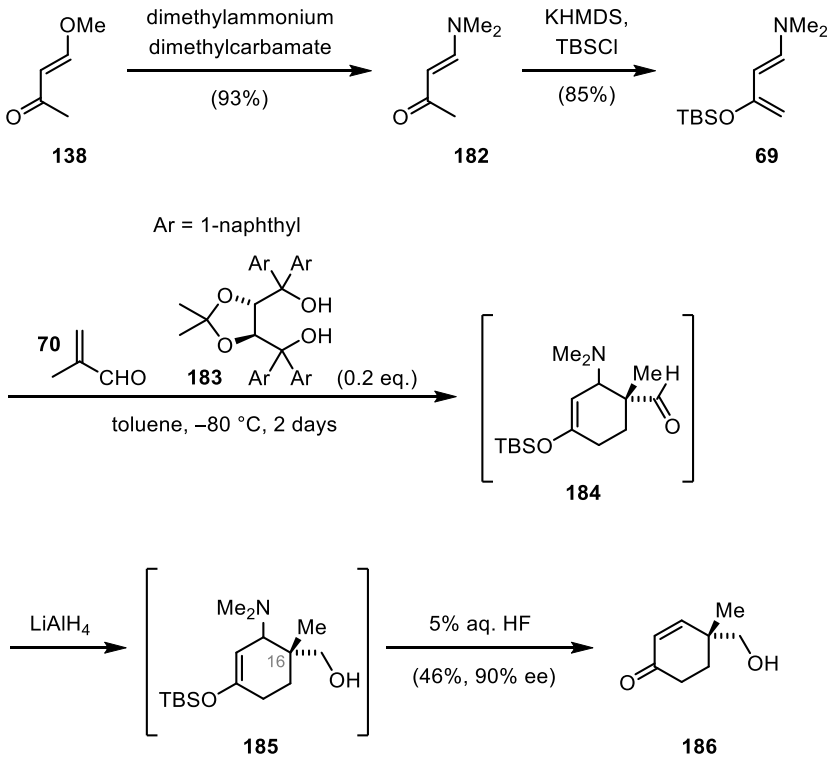
With these promising results we decided to tackle the enantioselective route. The first attempt towards enantiopure enone ***ent*-71** was performed according to Rawal via an auxiliary mediated asymmetric Diels–Alder reaction (Scheme 38).[64][65]



Scheme 38 Initially envisioned asymmetric Diels–Alder reaction towards enone ***ent*-71**.

The chiral amino siloxy diene **180** should react with methacrolein and thereby set the stereocenter at C16. This option was discarded as the synthesis proved to be not amenable due to the low solubility of 1,2-dibenzoylethane (**177**).

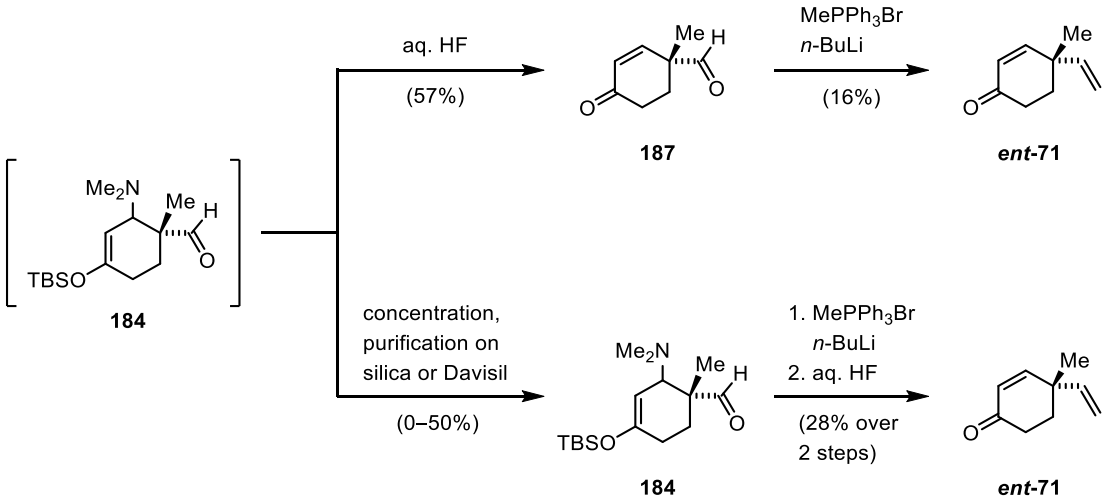
Therefore we turned to hydrogen bonding catalysis mediated Diels–Alder reaction (Scheme 5).[42] Hydrogen bonding of the dienophile to TADDOL (**183**) enables an asymmetric Diels-Alder reaction between Rawal's diene **69** and methacrolein (**70**). *"The dienophile is expected to complex with TADDOL through a two-point interaction. First, the free hydroxyl group on TADDOL is expected to form a strong intermolecular hydrogen bond to the carbonyl group of the dienophile, which provides the necessary lowering of the lowest unoccupied molecular orbital energy through a Lewis acid-like mechanism. Second, the complexed, electrondeficient carbonyl double bond is expected to be stabilized through a π–π donor-acceptor interaction with the electron-rich system of the proximal equatorial 1-napthyl ring, which would selectively shield one face of the dienophile."* [66]



Scheme 39 TADDOL controlled asymmetric Diels–Alder reaction of Rawal's diene (**69**).

In a two-step procedure twenty gram of Rawal's diene (**69**) were prepared (Scheme 39). Subsequent Diels–Alder reaction with methacrolein gave unstable aldehyde **184** which was *in situ* reduced to alcohol **185**. Crude intermediate **185** was then converted to enone **186**. The enantiomeric excess of alcohol **186** (90.4% ee) was determined by ^{1}H NMR analysis of the two diastereomeric Mosher's ester derivatives.[67] This synthetic sequence confirmed the reproducibility of the reaction and the reported enantiomeric excess.

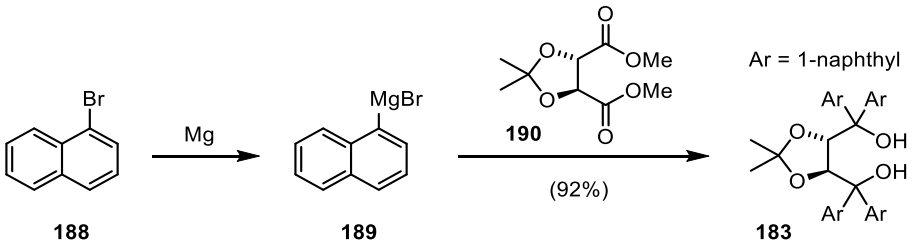
For our synthesis, we require a robust and scalable procedure of enone ***ent*-71**, which turned out to be more challenging to synthesize. Different procedures were tested as shown in Scheme 40. The main challenges were instability of the intermediates, evaporation of toluene from volatile products and separation of TADDOL after the Diels–Alder step. First, we tried to react intermediate aldehyde **184** with hydrofluoric acid and isolate enone **187**, which could then be subjected to further Wittig reaction. But aldehyde **187** is quite unstable and was always obtained in maximum 50–57% yield. Different olefination attempts never yielded more than 16% of enone ***ent*-71**.



Scheme 40 Synthetic approaches towards enone ***ent*-71**.

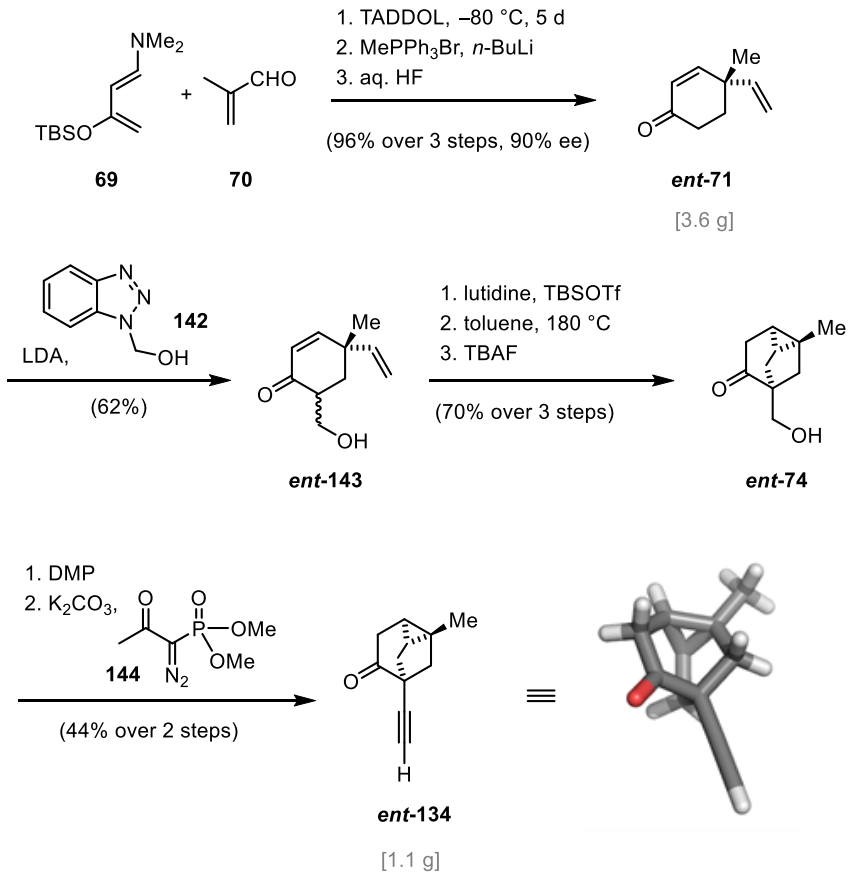
Therefore, we next tried to isolate and purify aldehyde **184**, but as suspected aldehyde **184** was even more unstable than aldehyde **187** and different purifications always led to low yield or complete decomposition. In addition, both routes suffered from severe yield dropping during scale up.

Given these results, we decided to try a one-pot procedure to avoid isolating the unstable intermediates **184** and **187** (Scheme 42). We assumed that TADDOL would not interfere the following Wittig reaction and the subsequent deprotection-elimination sequence. We were pleased to find, that adding the Diels–Alder reaction mixture to the deprotonated Wittig salt, and stirring overnight, followed by addition of aqueous hydrofluoric acid gave enone ***ent*-71** in 96% yield over three steps. The remaining toluene was removed from highly volatile ***ent*-71** by column chromatography and crude ***ent*-71** could then be purified by column chromatography using a mixture of diethyl ether and pentane.



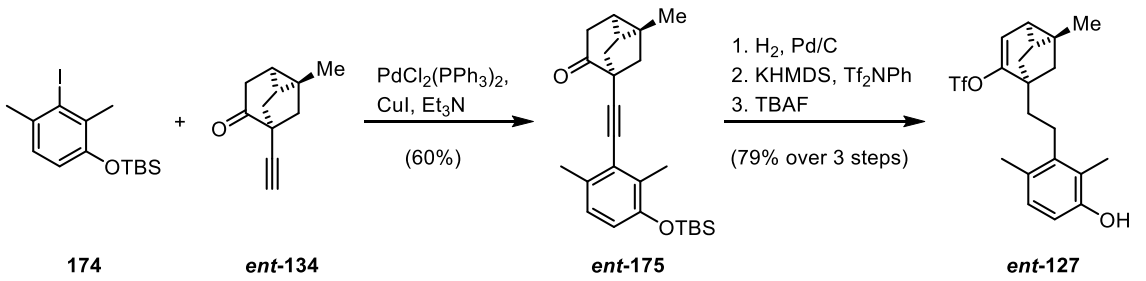
Scheme 41 Gram-scale synthesis of TADDOL **183**.

Since TADDOL **183** is commercially available but rather expensive, it was synthesized on 160 mmol scale (Scheme 41). Although purification was challenging, we were able to obtain twelve gram of clean TADDOL. With sufficient amount of TADDOL and the optimized one-pot procedure in hand the stage was set to scale the route up. Multigram quantities of enone ***ent*-71** were prepared in one-pot in excellent yield starting from Rawal's diene **69** (Scheme 42).



Scheme 42 Enantioselective scale up and molecular structure of alkyne ***ent*-134**.

Following the established racemic route (see Scheme 24 and Scheme 26), alkyne ***ent*-134** was synthesized in 29% yield over six steps. The structure of alkyne ***ent*-134** was further verified by single crystal X-ray analysis (Scheme 42).

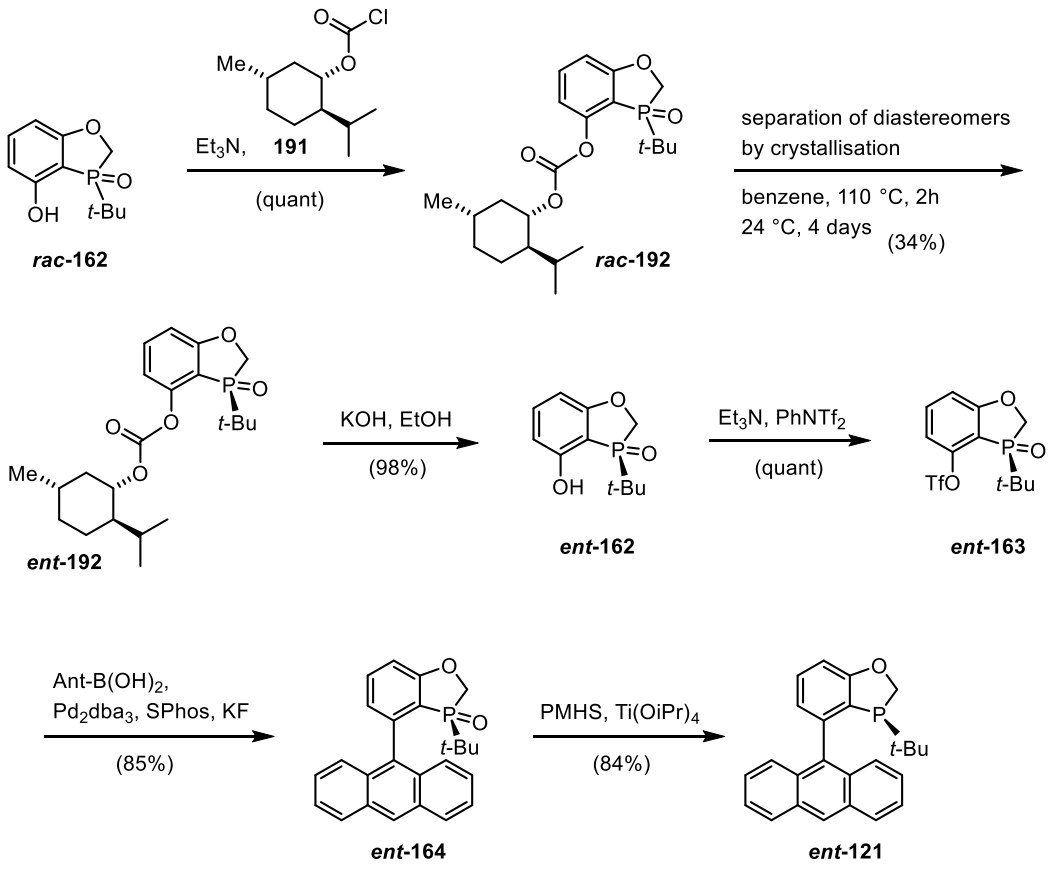


174 ***ent*-134** ***ent*-175** ***ent*-127**

Scheme 43 Synthesis of enantiopure vinyl triflate ***ent*-127**.

With alkyne ***ent*-134** in hand, cyclization precursor ***ent*-127** was prepared in further four steps (Scheme 43).

For the subsequent dearomative cyclization of enantiopure vinyl triflate ***ent*-127**, we prepared chiral AntPhos ligand ***ent*-121** in order to achieve the highest possible diastereoselectivity. Following the procedure by Tang and coworkers, chiral ***ent*-121** was prepared in five steps from intermediate ***rac*-162** (Scheme 44).[63]

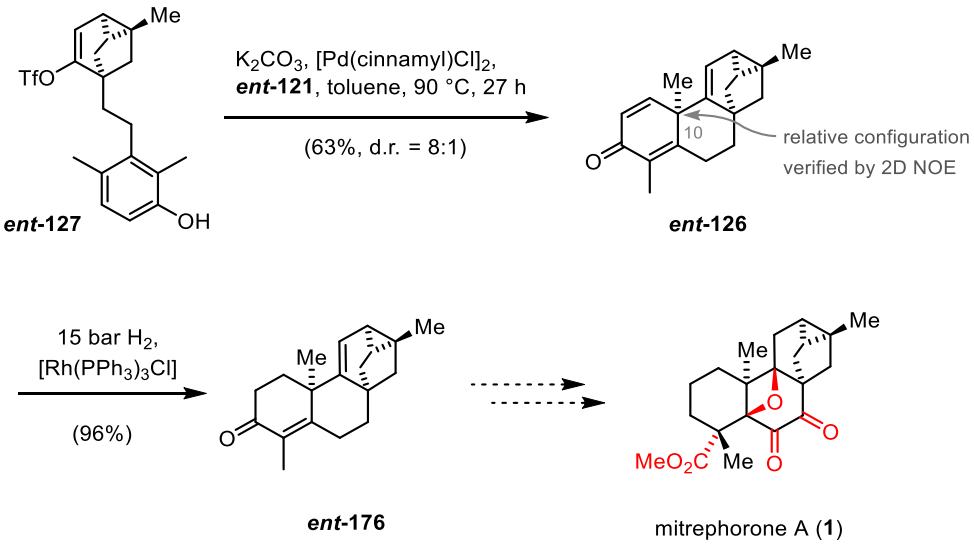


***rac*-162** **191** ***rac*-192** ***ent*-192** ***ent*-162** ***ent*-163** ***ent*-164** ***ent*-121**

Scheme 44 Completed synthesis of dihydrobenzooxaphosphole ligand (*S*)-AntPhos ***ent*-121**.

Resolution of ***rac*-162** was successfully accomplished by conversion to menthyl carbonate ***rac*-192**. After crystallization of the diastereomerically pure isomer ***ent*-192** was isolated in 34% yield. Basic hydrolysis of carbonate ***ent*-192** afforded enantiomerically pure compound ***ent*-162**. The following transformation to (*S*)-AntPhos ***ent*-121** was accomplished according to the synthesis of the racemic ligand shown in Scheme 44.[§]

Hence, the stage was set for the key cyclization. The first attempt to cyclize vinyl triflate ***ent*-127** gave tricycle ***ent*-126** in 63% yield as an 8:1 mixture of diastereomers. The relative configuration of the newly installed stereogenic center at C10 position was verified by NOESY experiments to be corresponding to the one of the natural product. Hydrogenation of the least hindered double bond gave enone ***ent*-176** in excellent yield.

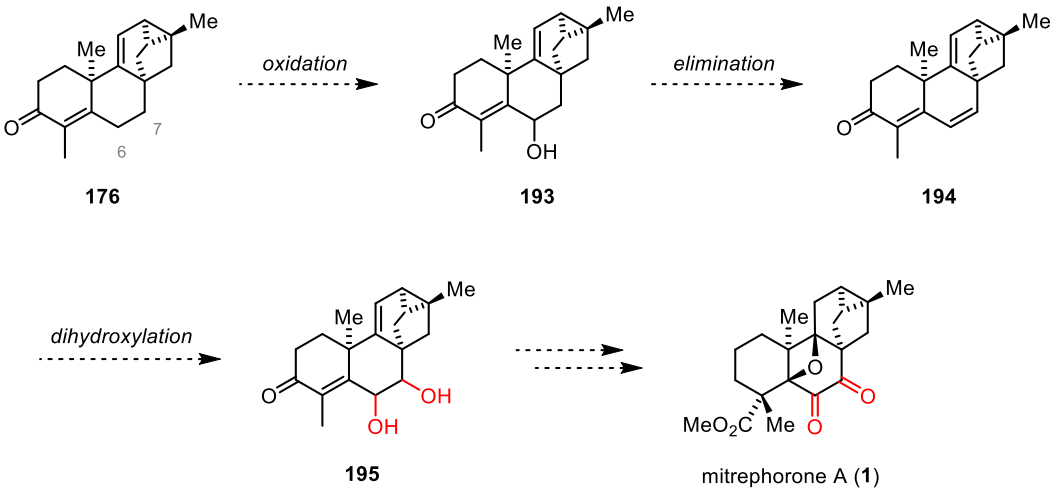


Scheme 45 Successful dearomative cyclization of vinyl triflate ***ent*-127**.

[§] Meanwhile an improved synthesis of intermediate ***ent*-162** was published[107] and (*S*)-AntPhos ligand **121** (CAS: 1807740-34-6) is now commercially available from Strem chemicals.

3.1.3 Functionalization Attempts of the Core Structure

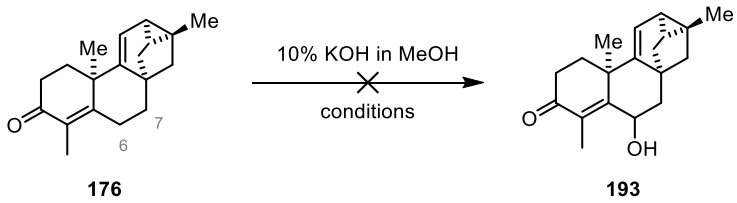
Starting from dienone **126** or enone **176** (see Scheme 45) various options to reach mitrephorone A can be pursued. For example, γ-hydroxylation of decalin enone **176**, elimination and dihydroxylation was planned to introduce the oxygens at C6 and C7 needed for the diketone moiety in mitrephorone A (**1**) (Scheme 46).



Scheme 46 Envisioned functionalization of enone **176**.

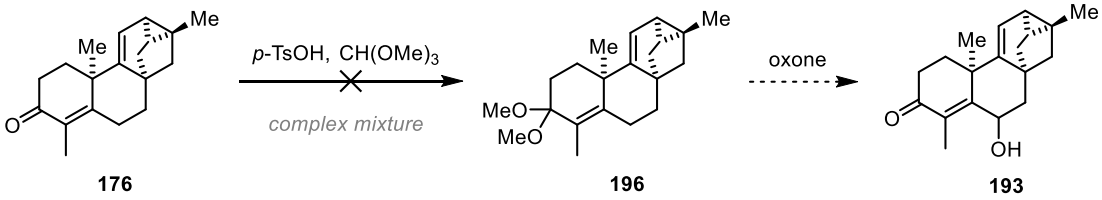
Oxidation under conditions reported by Baran and coworkers in their synthesis of thapsigargin[68] were tested (Table 5), but no alcohol **193** could be isolated. Entry 2 looked promising based on ^{1}H NMR analysis, however repeating the conditions with more material to isolate the main products revealed that the starting material decomposed (Entry 3).

Table 5 Investigation of γ-hydroxylation of enone **176**.



Entry	Oxygen source	Scale [mg]	Observation
1	air	0.5	no conversion
2	O_2 balloon	0.5	unidentified products
3	O_2 balloon	5	decomposition

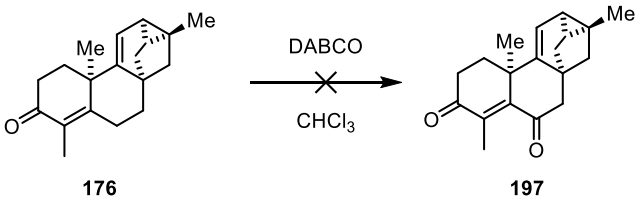
We then tested Ang Li's two-step protocol used in a synthesis of epoxyeujindole.[69] Unfortunately, the desired ketal **196** could not be obtained, and the subsequent oxidation step was therefore not attempted (Scheme 47).



Scheme 47 Oxidation attempt towards allylic alcohol **193**.

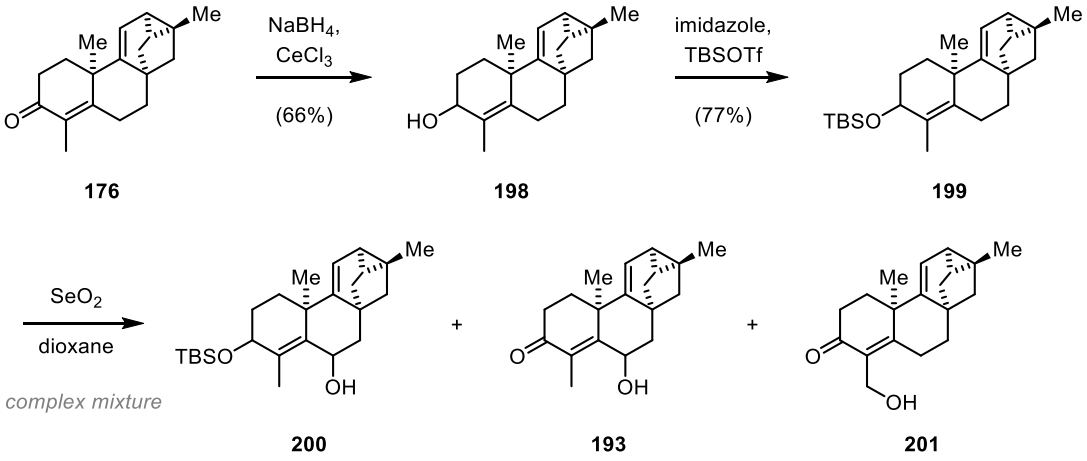
Next, oxidation under conditions reported in Ang Li's synthesis of longeracinphyllin A[70] were tested (Table 6), but no diketone **197** could be isolated.

Table 6 Investigation of oxidation of enone **176**.



Entry	Oxygen source	T [°C]	t [h]	Observation
1	air	24	3	no conversion
2	air	40	5	no conversion
3	O_2 balloon	40	22	no conversion

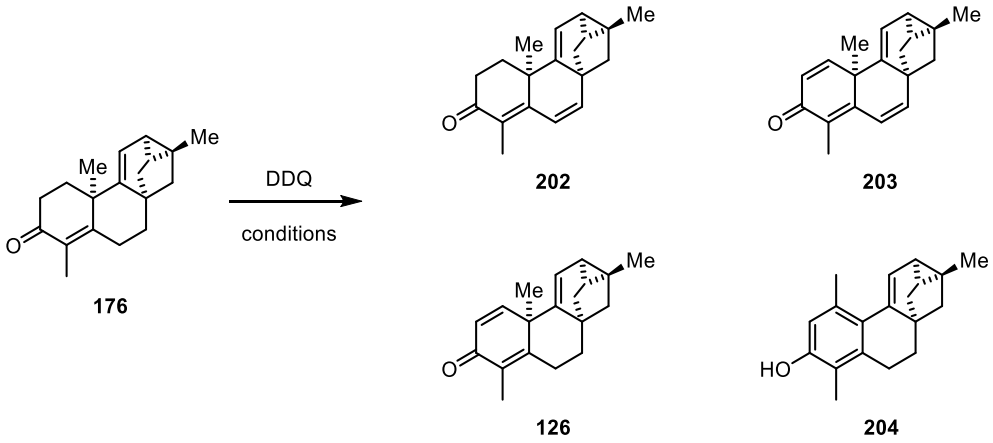
Since the abovementioned oxidation methods failed on our system **176**, we investigated the classical selenium dioxide-mediated allylic oxidation. Therefore, enone **176** was reduced to allylic alcohol **198** and TBS protected to obtain precursor **199** (Scheme 48). No conversion was observed in dioxane at 24 °C. Heating the reaction mixture to 80 °C gave a mixture of different products. Although, the ^{1}H NMR of the main isolated compound looked promising, alcohol **193** could not be prepared on reasonable scale and the reaction proved unreproducible, resulting in intractable product mixtures. The desired TBS-protected allylic alcohol **200** was never observed.



Scheme 48 Allylic oxidation attempts towards alcohol **200**.

Moreover, the introduction of a C6–C7 double bond was investigated starting from enone **176**. With the desired product **202** in hand dihydroxylation could directly introduce the two oxygen atoms required for the diketone moiety in mitrephorone A.

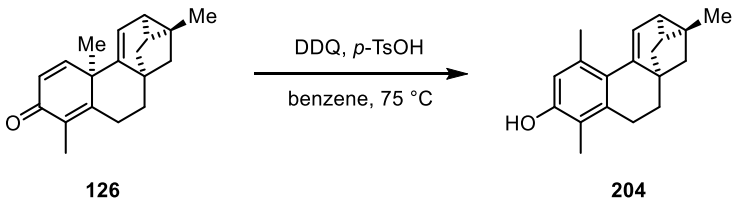
Table 7 Investigation of DDQ oxidation of enone **176**.



Entry	Solvent	T [°C]	Additive	Observation
1	benzene	24	-	no conversion
2	benzene	75	-	no conversion
3	benzene	75	*p*-TsOH	complex mixture, containing **203** and **204**
4	1,4-dioxane	24	-	no conversion
5	1,4-dioxane	75	-	no conversion

6	1,4-dioxane	75	*p*-TsOH	complex mixture, containing **176** and **126**

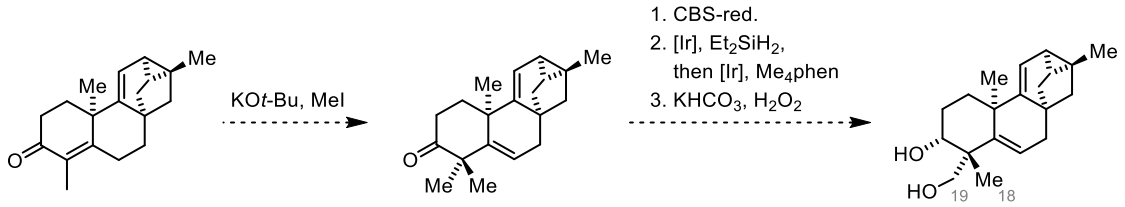
As shown in Table 7, oxidation of **176** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone **(**DDQ) was unselective and led to product mixtures. It was not possible to obtain one main product cleanly, in line with literature reports that often proceed in only moderate yield. Similarly, DDQ oxidation of dienone **126** afforded traces of rearranged aromatized phenol **204** (Scheme 49).



126 **204**

Scheme 49 DDQ oxidation attempt of dienone **126**.

Another idea for functionalizing decalin **176** towards the synthesis of **1**, is depicted in Scheme 50. Selective reduction and directed iridium-catalyzed oxidative functionalization, established by Simmons and Hartwig,[71] could introduce the C-19 oxidation.

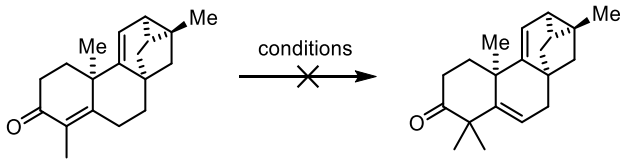


176 **205** **206**

Scheme 50 Foreseen synthesis of alcohol **206** towards mitrephorone A (**1**).

Methylation of similar decalin enones have been reported and are most commonly carried out using potassium *tert*-butoxide as base.[72][73][74] Table 8 shows different conditions that were investigated for this transformation. Unfortunately, all conditions tested only led to decomposition of starting enone **176** or resulted in its recovery.

Table 8 Investigation of methylation of enone **176**.

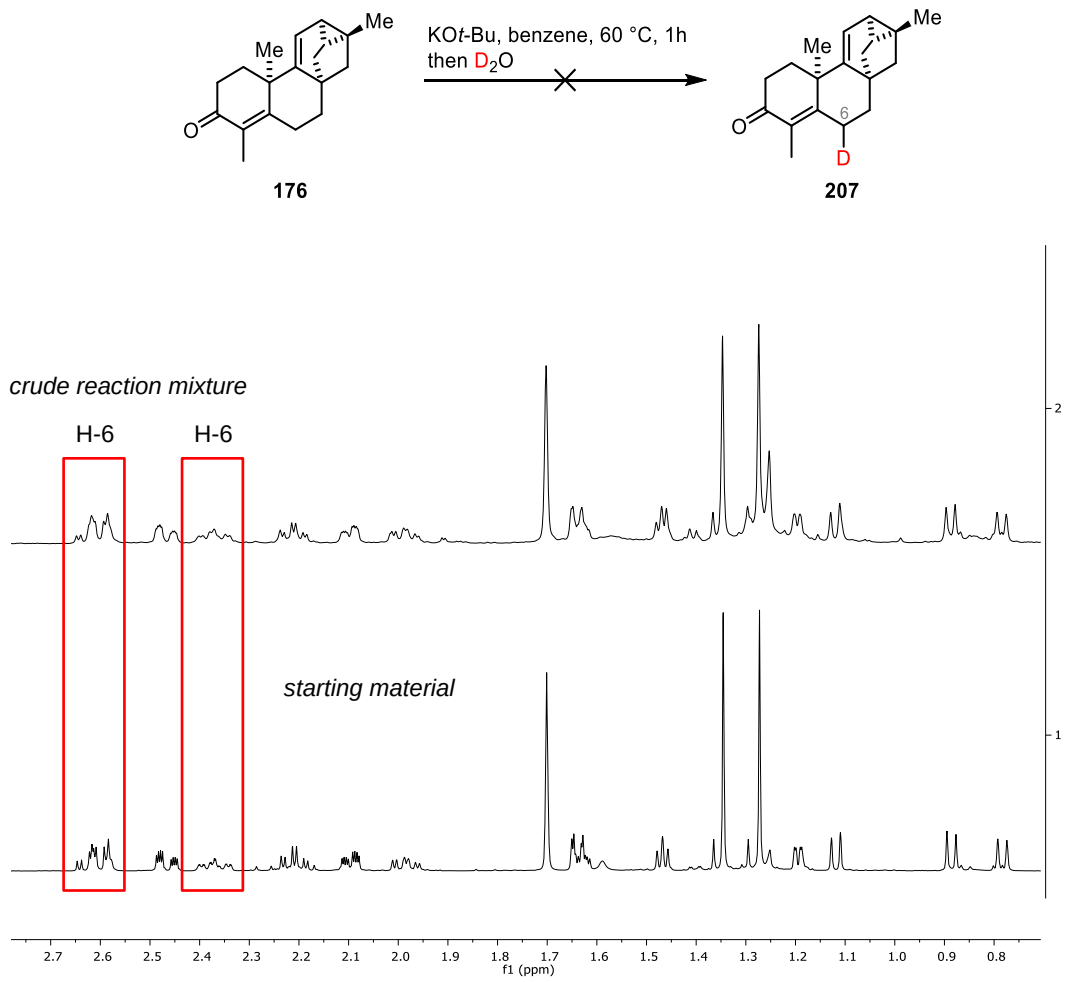


176 **205**

Entry[a]	Solvent	T [°C]	Base [equiv.]	Observation
1	benzene	60–70	KO*t*-Bu [1.0]	no conversion
2	*t*-BuOH	60–70	KO*t*-Bu [1.2]	no conversion
3	*t*-BuOH	60–70	KO*t*-Bu [excess]	decomposition
4	1,4-dioxane	85	NaH [1.1]	decomposition
5	THF, HMPA	0–25	LDA [1.1]	no conversion

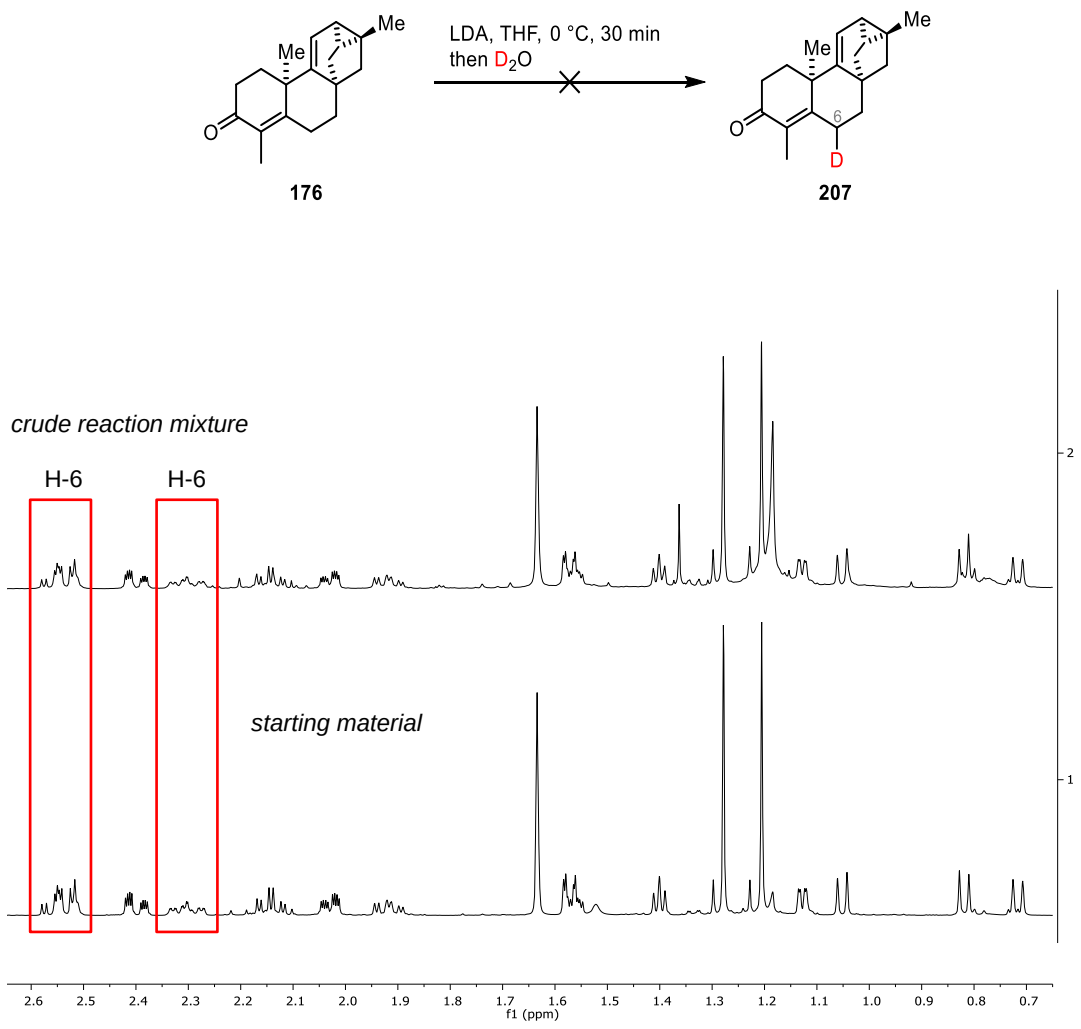
[a] all reactions were conducted on a 0.01 mmol scale with an excess of MeI.

Since alkylation of enone **176** with methyl iodide proved unsuccessful we examined whether the deprotonation at C6 occurs at all. Thus, a solution of **176** in benzene was treated with potassium *tert*-butoxide (1.5 equiv) at 60 °C for one hour before an excess of deuterium oxide was added. NMR studies revealed that no deuterium incorporation took place (Scheme 51).



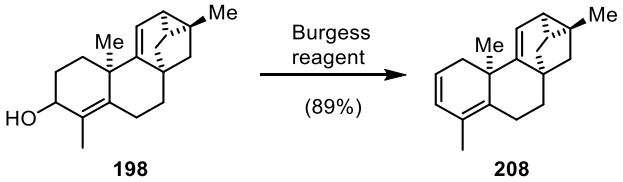
Scheme 51 Deuterium incorporation experiment with KO*t*-Bu as a base.

Considering that with potassium *tert*-butoxide only a small fraction of the starting material is deprotonated, we repeated the experiment with lithium diisopropylamide at 0 °C for 30 minutes (Scheme 52). Again, no deuterium incorporation was observed. We reasoned that the tetrasubstituted carbon center and the caged C ring create a sterically demanding periphery that complicates further functionalization of enone **176**.



Scheme 52 Deuterium incorporation experiment with LDA as a base.

Furthermore a different approach to functionalize enone **176** was tested. Allylic alcohol **198** was eliminated to diene **208** (Scheme 53). A Diels–Alder reaction of diene **208** with singlet oxygen would give intermediate endoperoxide **209**.

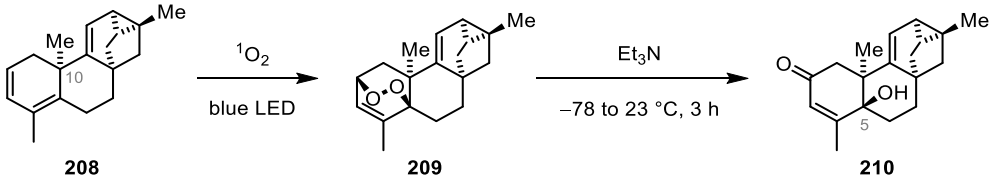


Scheme 53 Synthesis of diene **208**.

We hypothesized that the stereochemistry would be controlled by the methyl group at C10 and shielding the a-side of the molecule. Subsequent Kornblum–DeLaMare rearrangement[75] should

then introduce the tertiary alcohol at C5 and establish a new α,β-unsaturated ketone **210** that could undergo a 1,4-addition of methyl cuprate to complete the carbon skeleton. However, different reaction conditions led to no conversion and prolonged reaction times, led to decomposition of the starting material (Table 9).

Table 9 [4+2] attempts with diene **208** and singlet oxygen.

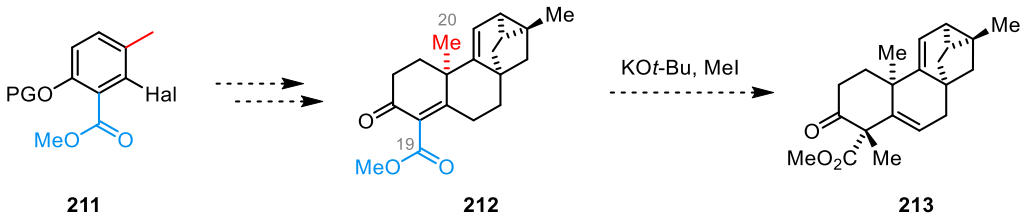


208 **209** **210**

Entry	T [°C]	Photosentizer	Solvent	Observation
1	–78 to 0	rose bengal	CH_2Cl_2	no conversion
2	–78 to 15	rose bengal	CH_2Cl_2	no conversion
3	–78	rose bengal	CH_2Cl_2 / MeOH	no conversion
4	–78	TPP	CH_2Cl_2	decomposition
5	–40	rose bengal	CH_2Cl_2 / MeOH	decomposition

3.1.4 Third-generation Approach: B-Alkyl Suzuki–Miyaura cross coupling

In parallel to the route presented in chapter 3.1.3, a modified alternative approach towards mitrephorone A (**1**) was investigated. A cyclization product such as **212**, which already contains the desired methyl ester at C19, might simplify the following functionalization towards the natural product significantly (Scheme 54). In only one methylation step the complete carbon skeleton of **1** would be generated with full control of the stereochemistry, since methylation would be controlled by the sterical hindrance imparted by the C20 methyl group. For this route, an aromatic building block such as **211** was required.



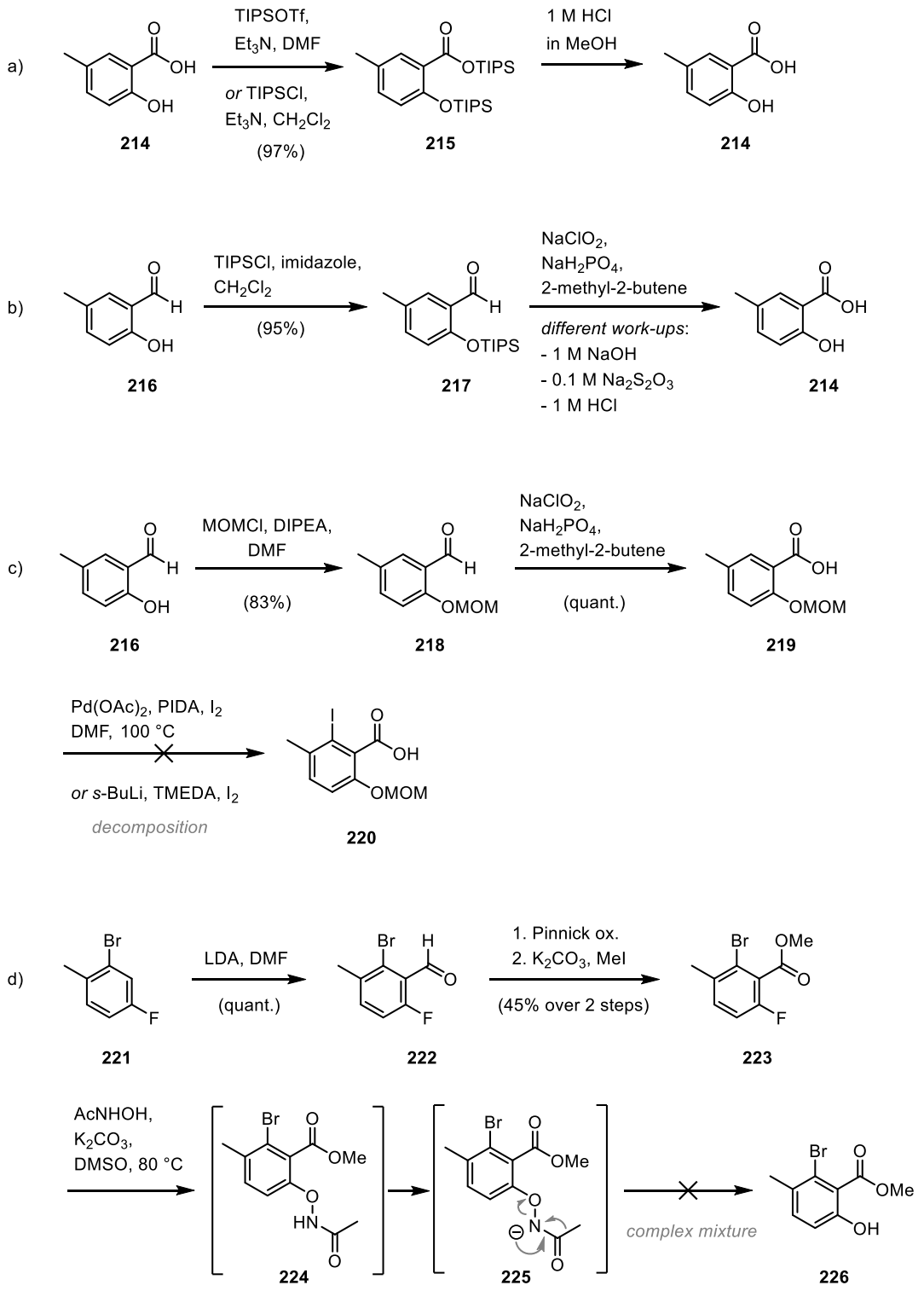
Scheme 54 Envisioned alternative synthesis towards mitrephorone carbon skeleton **213**.

Scheme 55 summarizes our efforts towards building blocks of type **211**. The first attempt failed, because methyl salicylic acid **214** could not be selectively TIPS protected or deprotected (Scheme **55**a).

The next approach started from methyl salicylic aldehyde **216**, which was protected as triisopropylsilyl (TIPS) ether to obtain **217** (Scheme 55b). Subsequent Pinnick oxidation cleaved the TIPS group regardless of the reaction or workup conditions, revealing an unexpected instability of the phenolic silyl group.

Therefore, the more stable methoxymethyl acetal (MOM) group was employed and mono-protected acid **218** could be prepared (Scheme 55c). Unfortunately, the direct iodination to give **220** was not successful, and led to decomposition.

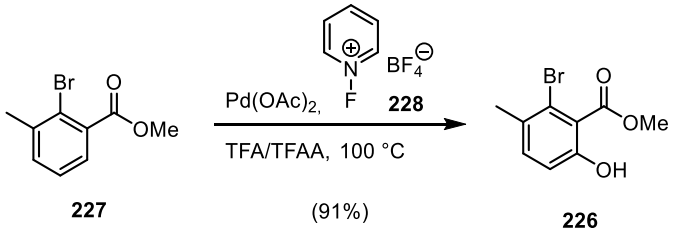
Another approach was based on a methodology by Merck to convert haloarenes to phenols by a S_NAr reaction / Lossen rearrangement sequence (Scheme 55d).[76] Intermediate **223** could be synthesized in three steps in 45% overall yield. However, several attempts to convert aryl fluoride **223** to phenol **226** via the depicted sequence were unsuccessful.



Scheme 55 Failed attempts to synthesize a methyl ester building block **211**.

Due to these results, a new approach towards aryl bromide **211** was investigated. Based on studies published by G. Shan et al., a one-step synthesis starting from the commercially available methyl 2-bromo-3-methylbenzoate (**227**) was envisioned.[77] Mechanistically chelation of palladium(II) to the carbonyl leads to a palladium-catalyzed C–H functionalization and oxidation with

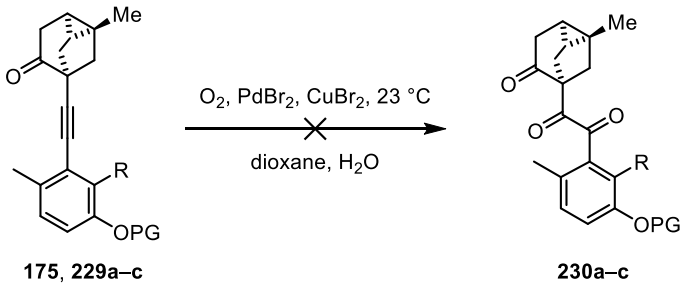
1-fluoropyridinium tetrafluoroborate (**228**) forms a trifluoroacetated product which is converted into the desired phenol **226** under aqueous work up. The reaction gives the building block **226** in excellent yield (Scheme 56).



Scheme 56 Palladium-catalyzed C–H oxygenation of benzoate **227**.

With the new aromatic building block **226** in hand, different alkynes **175** and **229a–c** have been prepared (according to Scheme 28). An alternative possibility to introduce the missing diketone moiety is the direct Wacker-type oxidation of alkynes (Table 10). This methodology was already investigated for the racemic system (see Scheme 30).[62] However, with four different substrates this methodology led to no conversion and prolonged reaction times led to decomposition. Only with alkyne **229b** traces of diketone **230b** could be isolated.

Table 10 Wacker oxidation attempts of alkynes.

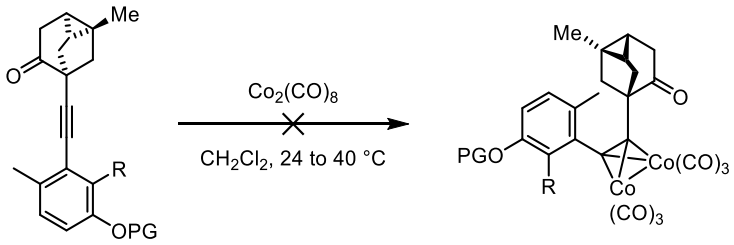


Entry	Substrate	R	PG	Observation
1	**175**	Me	TBS	no conversion, starts to decompose
2	**229a**	Me	Bn	no conversion, starts to decompose
3	**229b**	CO_2Me	TBS	complex mixture, traces **230b**
4	**229c**	CO_2Me	Bn	complex mixture

With the same alkyne substrates **229a–d**, we also investigated the formation of a cobalt complex to mask the alkyne for later functionalization.[78] Upon addition of dicobalt octacarbonyl, the

hexacarbonyldicobalt moiety of the bridged alkyne complexes reduces the bond order from triple to approximately that of a double bond, with corresponding change in bond angles. Hence, the substituents are in much more favorable locations for cyclization reactions. However, no reaction was observed and only starting material was isolated (Table 11). With a tetrasubstituted carbon as one substituent, and an *ortho,ortho*-disubstituted aromatic ring on the other, the internal the triple bond is probably not accessible enough for the cobalt complex.

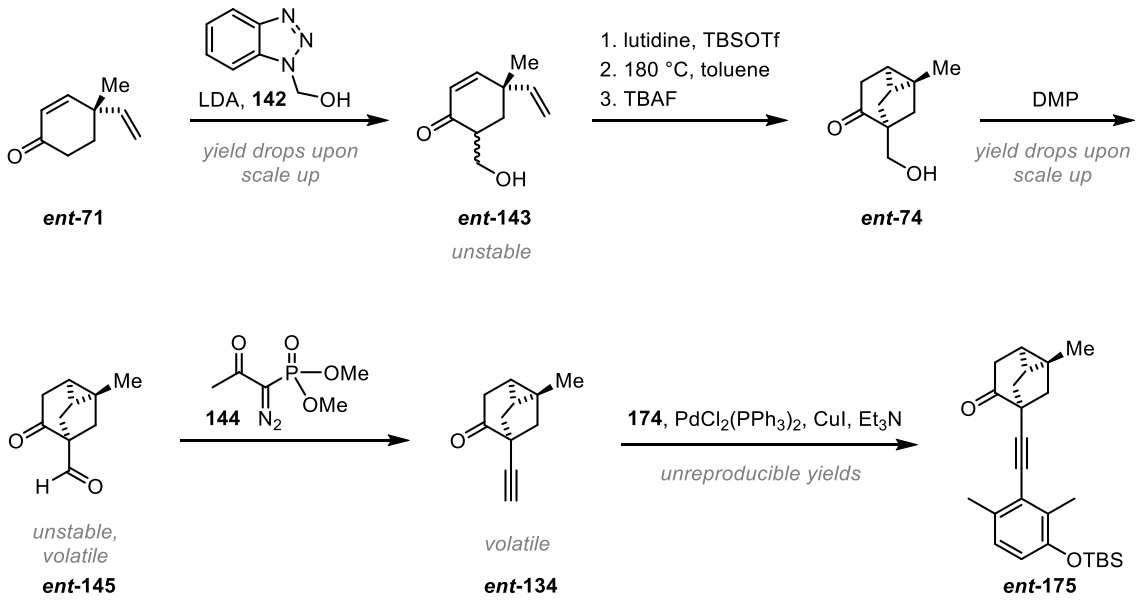
Table 11 Attempts to protect alkynes with dicobalt octacarbonyl.



175, **229a–c** **231a–d**

Entry	Substrate	R	PG	Observation
1	**175**	Me	TBS	no conversion, starts to decompose
2	**229a**	Me	Bn	no conversion
3	**229b**	CO_2Me	TBS	no conversion, starts to decompose
4	**229c**	CO_2Me	Bn	no conversion

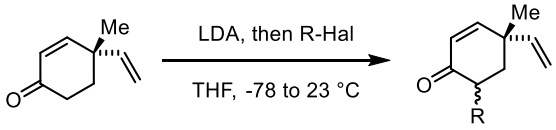
In order to find an opportunity to improve the synthesis of the cage and look for alternative C_2 spacers to connect the aromatic ring, we were working on the modification and improvement of the synthesis for the cage building block. Major challenges where the instability of β-hydroxy ketone **143** and aldehyde **145**, the volatility of alkyne **134** and aldehyde **145** as well as unreproducible yields in the Sonogashira coupling to alkyne **175** (Scheme 57). Furthermore the alkylation step to alcohol **143** and the DMP oxidation of alcohol **74** gave lower yields for large scale reactions.



Scheme 57 Summary of the drawbacks of the synthetic route presented in chapter 3.1.2.

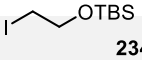
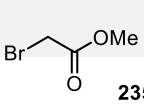
We planned to skip the preparation of an alkyne and prepare a C_2 alkyl chain instead in order to perform a sp^3-sp^2 coupling as an alternative to the current Sonogashira coupling. The first improvement would be a more efficient and reliable alkylation of enone ***ent*-71**. Table 12 summarizes alkylation attempts of enone ***ent*-71**. We were pleased to find that upon addition of three equivalents of hexamethylphosphoramide (HMPA), the stable methyl ester ***ent*-232** could be prepared in high yields.

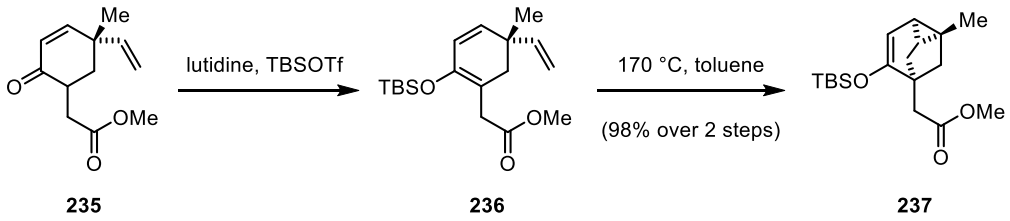
Table 12 Investigation of alternative alkylations of enone **71**.



***ent*-71**

232: R = **234**
233: R = **235**

Entry	R-Hal	Additive	Observation
1	 **234**	-	no conversion
2		HMPA (3 equiv.)	no conversion
3	 **235**	-	**233** (20% yield)
4		HMPA (3 equiv.)	**233** (84% yield)
5		HMPA (2 equiv.)	**233** (71% yield)
6		HMPA (1 equiv.)	**233** (43% yield)

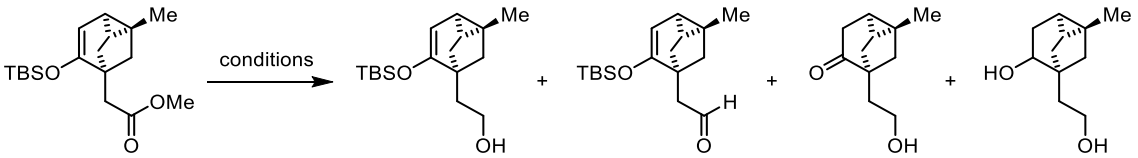


235 **236** **237**

Scheme 58 Synthesis of methyl ester **237**.

Ketone **235** was transformed into diene **236** and subsequent intramolecular Diels-Alder smoothly furnished **237** (Scheme 58). However, subsequent reduction of the methyl ester **237** was not successful (Table 13). TBS enol ether **237** is probably too unstable under reductive conditions.

Table 13 Investigation of reduction conditions towards primary alcohol **238**.

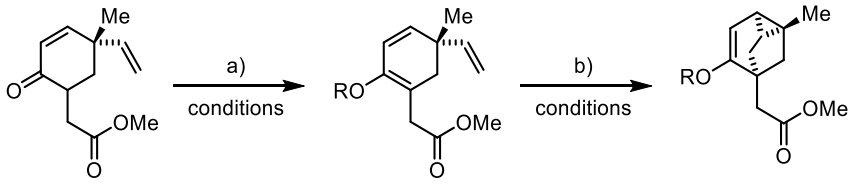


237 **238** **239** **240** **241**

Entry	Reagent	T [°C]	Observation
1	$LiAlH_4$	0	complex mixture, containing **240**, **241**
2	DIBAL-H	–78	complex mixture, containing **239**, **240**
3	DIBAL-H	0	complex mixture, containing **239**, **240**, **241**
4	DIBAL-H	24	complex mixture, containing **240**, **241**

Next we investigated alternative enol ethers (triflate, TIPS and TBDPS). Vinyl triflate **243** and TIPS enol ether **242** were prepared (Table 14). The TBDPS protecting group was too bulky and no conversion took place. While with TIPS enol ether **242** the intramolecular Diels-Alder was performed successfully, for vinyl triflate **243** no conversion was observed.

Table 14 Investigation of alternative Diels-Alder precursors.



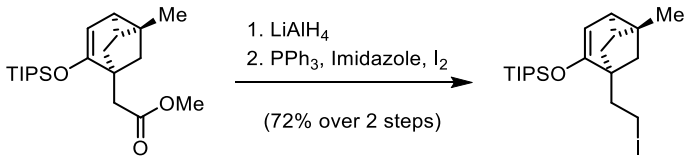
233

242 (R = TIPS)
243 (R = Tf)

244 (R = TIPS)
245 (R = Tf)

	Entry	R	Conditions	Observation
a)	1	Tf	KHMDS, $PhNTf_2$	**243** (20% yield)
	2	TIPS	lutidine, TIPSOTf, 24 °C	**242** (84% yield)
	3	TBDPS	lutidine, TIPSOTf, 50 °C	no conversion
	4	TBDPS	imidazole, TIPSOTf, 50 °C	no conversion
b)	5	Tf	130 to 180°C	no conversion
	6	TIPS	170 °C	**244** (quant. yield)

Reduction of TIPS enol ether **244** gave a primary alcohol which was sensitive to silica gel and was therefore used without further purification for the subsequent iodation under Appel's conditions. The desired iodide **246** was formed in good yield over two steps and proved amendable to storage over prolonged periods of time (Scheme 59).[**]

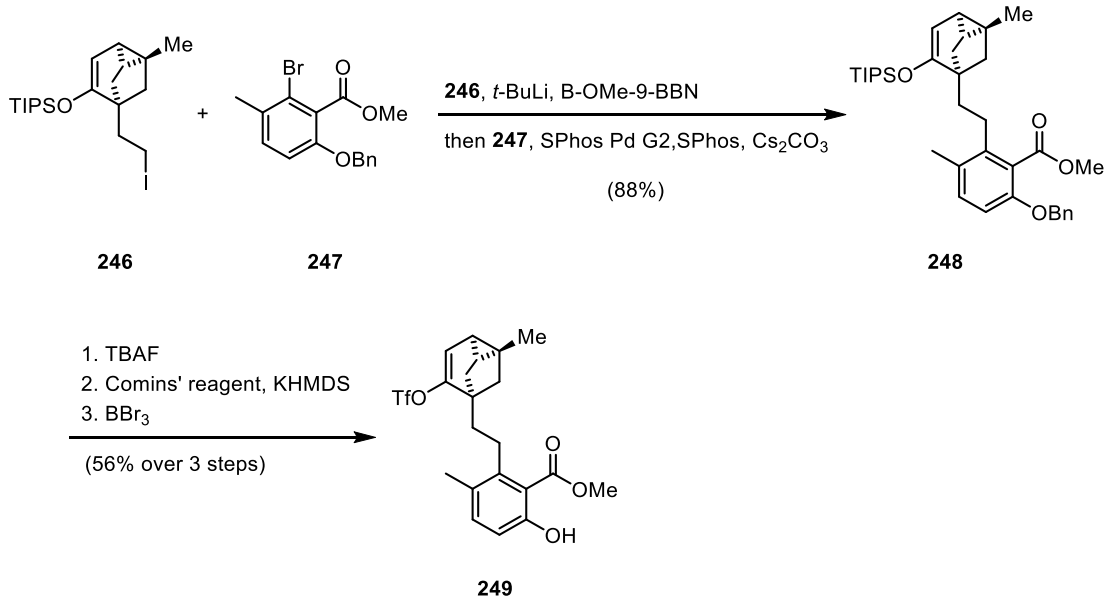


244 **246**

Scheme 59 Conversion of ester **244** to iodine **246**.

Suzuki–Miyaura cross coupling between the boronate derived from iodide **246** and aryl bromide **247** using Buchwald's SPhos ligand and SPhos second generation precatalyst gave **248** in very good yield (Scheme 60).[79] TIPS deprotection, triflation and benzyl deprotection gave vinyl triflate **249**.

[**] Optimization of the synthetic steps shown in Scheme 59 and Scheme 60 was carried out by Aylin Hirschvogel.



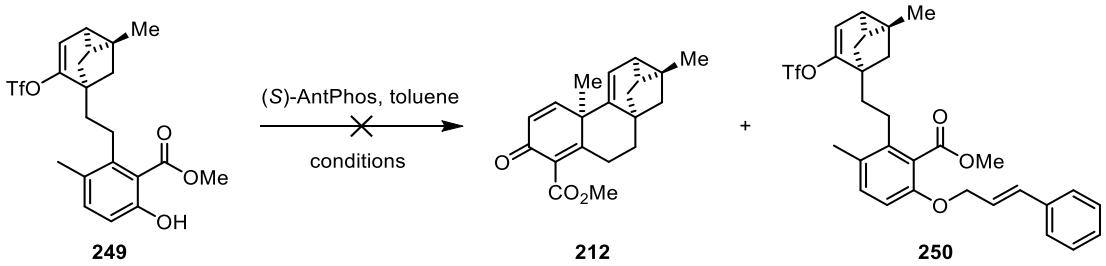
Scheme 60 Suzuki–Miyaura cross coupling between iodide **246** and aryl bromide **247**.

With cyclization precursor **249** in hand, studies on the asymmetric dearomatization were performed (Table 15).[††] Unfortunately, reaction of **249** under our standard conditions (see Scheme 45) mainly resulted in decomposition. Only an undesired Tsuji–Trost allylation between **249** and the cinnamyl ligand was observed (Entry 1). To avoid competing Tsuji–Trost reaction of key intermediate **249**, other palladium sources were investigated. However, $Pd(OAc)_2$, $Pd_2(dba)_3$ or $[Pd_2(dppf)Cl]_2$ resulted in either no reaction or the recovery of starting material **249** (Entries 2–4). Using potassium acetate or silver carbonate while maintaining the original palladium-source ($[Pd(cinnamyl)Cl]_2$) also did not led to product **212** (Entry 5 and 6).

Cesium carbonate as base resulted in decomposition, but traces of the desired cyclization product **212** could be isolated (Entry 7). However, repeating the experiment on a larger scale (0.08 mmol) impaired the reaction and even less product was isolated than on small scale (0.02 mmol). Lowering the reaction temperature led to no conversion (Entry 8). Screening other palladium source with cesium carbonate also did not afford conversion to **212** either (Entries 9–11).

[††] Experiments of entry 1-7 in Table 15 were carried out by Aylin Hirschvogel.

Table 15 Attempts of the dearomative cyclization of vinyl triflate **249**.

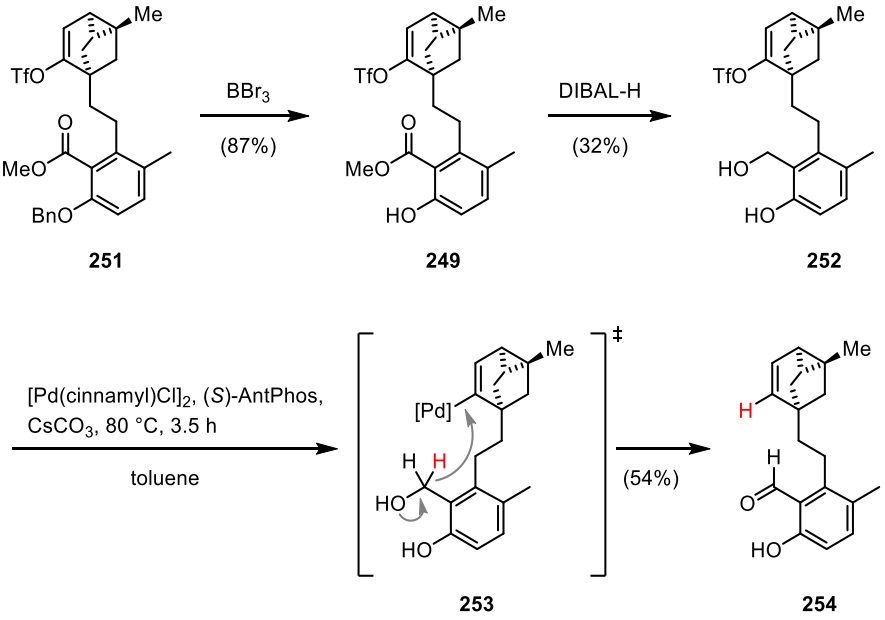


249 **212** **250**

Entry[a]	Catalyst	Base	Observation
1	$Pd(cinnamyl)Cl]_2$	K_2CO_3	**250** (traces)
2	$Pd(OAc)_2$	K_2CO_3	no conversion, starts to decompose
3	$Pd_2(dba)_3$	K_2CO_3	no conversion, starts to decompose
4	$[Pd_2(dppf)Cl]_2$	K_2CO_3	no conversion, starts to decompose
5	$Pd[(cinnamyl)Cl]_2$	KOAc	**250** (traces)
6	$Pd[(cinnamyl)Cl]_2$	Ag_2CO_3	decomposition
7	$Pd[(cinnamyl)Cl]_2$	Cs_2CO_3	**212** (traces), decomposition
8[b]	$Pd[(cinnamyl)Cl]_2$	Cs_2CO_3	no conversion
9	$Pd(OAc)_2$	Cs_2CO_3	no conversion, starts to decompose
10	$Pd_2(dba)_3$	Cs_2CO_3	**212** (traces), decomposition
11	$[Pd_2(dppf)Cl]_2$	Cs_2CO_3	no conversion, starts to decompose

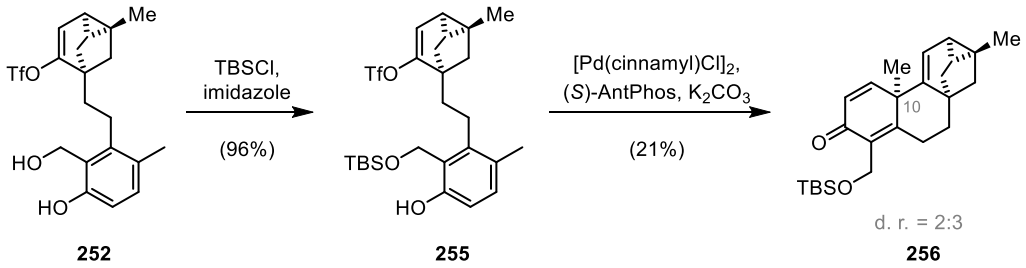
[a] all reactions were conducted on a 0.02 to 0.03 mmol scale, with a 0.05 M concentration, reaction temperature of 90 °C and a reaction time of 15–18 h. [b] reaction temperature: 70 °C.

Therefore, we decided to reduce ester **249** to benzyl alcohol **252** (Scheme 61). The unprotected alcohol was subjected to the dearomative cyclization conditions. A new product was isolated, but NMR analysis revealed the formation of benzaldehyde **254**, probably formed via the suggested mechanism.



Scheme 61 Cyclization attempt of unprotected benzyl alcohol **252**.

Protection of benzyl alcohol **252** with TBSCl smoothly gave monoprotected **255**. The standard dearomatization conditions gave a mixture of products (Scheme 62). Out of this mixture, dienone **256** could be isolated in 21% yield as an inseparable mixture of diastereomers at C10 (d.r. = 2:3).

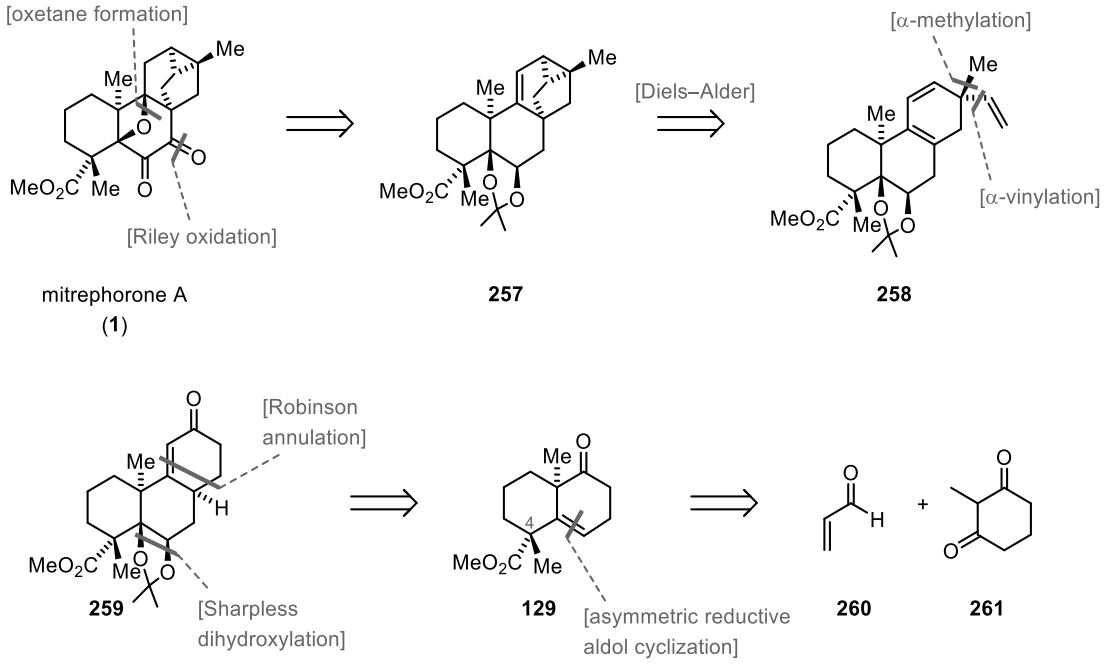


Scheme 62 Cyclization attempt of TBS-protected **255**.

The low yield and diastereoselectivity in the dearomatization reaction forced us to revise our approach and a new route was pursued as shown in chapter 3.2.

3.2 Strategy B: Robinson Annulation and late-stage Diels–Alder Reaction

Since further functionalization of decalin enone **176** proved difficult, a different alternative route was investigated in parallel to the synthetic studies presented in chapter 3.1. The general idea was to combine already established decalin chemistry for building the substitution pattern of ring A and B with our intramolecular Diels–Alder reaction to form the C-ring cage. The new retrosynthetic analysis is depicted in Scheme 63.

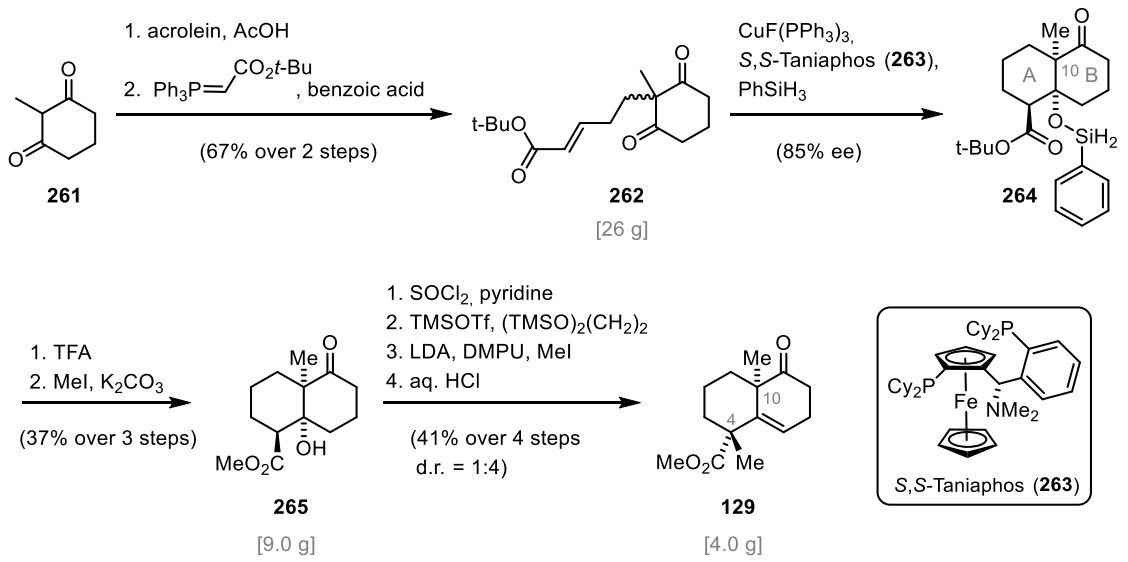


Scheme 63 Second-generation retrosynthetic analysis of mitrephorone A (**1**).

For the second-generation strategy, we envisioned to trace mitrephorone A (**1**) back to literature known intermediate **129**,[80] which already contains two of the three rings and the quaternary center at C4. As in our first strategy, the oxetane ring should be closed at last after the Riley oxidation to introduce the 1,2-diketone moiety. Disconnecting the caged ring by an intramolecular Diels-Alder reaction would lead to intermediate **258**, which could be traced back to enone **259** after methylation and vinylation in alpha position. A Robinson annulation would build up enone **259** and the diol motif should be introduced by a Sharpless asymmetric dihydroxylation of **129**, which can be build up from acrolein (**260**) and diketone **261** via an eight-step sequence.[80]

3.2.1 Synthesis of the Carbon Skeleton of Mitrephorone A

The literature known synthesis[80] of building block **129** is depicted in Scheme 64.‡‡ The sequence commenced with a Michael addition of 2-methyl-1,3-cyclohexadione (**261**) to acrolein[81] followed by Wittig reaction to access ester **262**. Subsequent enantioselective reductive aldol cyclization of **262** under copper(I)-catalysis, builds up ring A and B ring and sets the stereocenter at C10. The enantiomeric excess of intermediate **264** (85% ee) was determined by chiral gas chromatography.



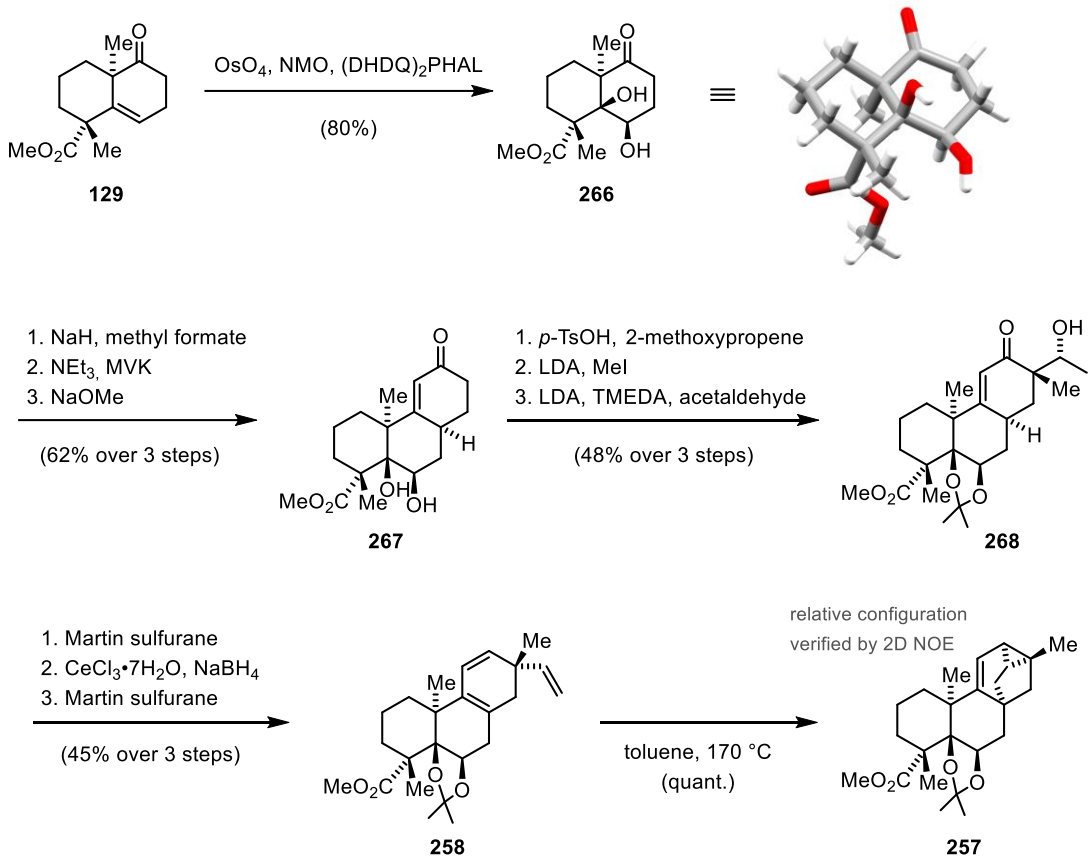
Scheme 64 Synthesis of literature known builig block **129**.

Treatment of silyl ether **264** with trifluoroacetic acid and subsequent esterification with methyl iodide gave methyl ester **265** in good yield over four steps. Subsequent elimination of the tertiary alcohol followed by carbonyl protection, α-methylation of the ester and deprotection afforded multigram amount of 5,6-dehydro decalin **129** (d.r. = 4:1). The diastereomers were separated by flash column chromatography. With methyl ester **129** in hand two stereocenters at C4 and C10 of mitrephorone A are already set.

The following dihydroxylation of sterically demanding alkene **129** proved to be challenging. This was solved by adding hydroquinidine-1,4-phthalazinediyl diether ligand [$(DHDQ)_2PHAL$] to the classical oxidation reagents osmium tetroxide and *N*-methylmorpholine *N*-oxide and heating the reaction mixture for three days to 80 °C in a sealed tube. Single crystal X-ray analysis of diol **266** verified the putative carbon skeleton and confirmed that the dihydroxylation occurred from the

‡‡ Optimization of the synthetic steps shown in Scheme 64 and Scheme 65 was carried out by Lukas Wein.

upper side of the molecule (Scheme 65). Diol **266** was subjected to a three-step Robinson annulation sequence[82][83] and enone **267** was obtained in good yield.



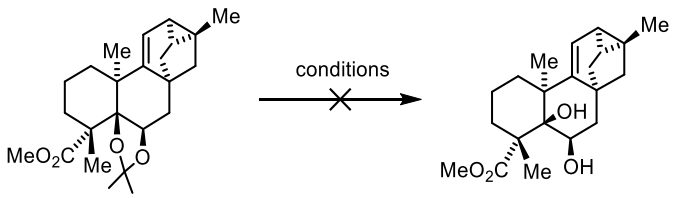
Scheme 65 Synthesis of the mitrephorone carbon skeleton **257**.

The next task was the installation of the triene motive needed for the intramolecular Diels–Alder reaction. Therefore diol **267** was protected as acetonide and the enone was methylated in alpha position. Following direct vinylation was not possible, therefore an aldol condensation of acetaldehyde was conducted to yield alcohol **268**. Elimination of the secondary alcohol using Martin sulfurane, Luche reduction of the enone and following dehydration of the resulting allylic alcohol gave the corresponding triene **258**.

With the corresponding [4+2]-cycloaddition-precursor **258** in hand the intramolecular Diels–Alder reaction was carried out in toluene to yield tricyclooctane **257** in quantitative yield. At this stage the full carbon skeleton of mitrephorone A was installed. The relative configuration of the carbon skeleton was verified by NOESY experiments.

For the envisioned endgame of the total synthesis, acetonide **257** needed to be deprotected. Unfortunately, an extensive screening of reaction conditions for the acetonide cleavage was unsuccessful and either no conversion or decomposition of the starting material was observed (Table 16).

Table 16 Deprotection attempts of acetonide **257**.



257 **269**

Entry	Reagent	Solvent	T [°C]	Observation
1	4 M aq. HCl	dioxane	24 to 110	decomposition
2	H_2SO_4	dioxane	80	no conversion
3	AcOH (80%)	AcOH	110	no conversion, starts to decompose
4	$BF_3{\cdot}OEt_2$	MeOH	–78 to 24	no conversion
5	$BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$	MeOH	0 to 24	no conversion
6	diluted $HClO_4$	THF	–20 to 24	no conversion
7	$HClO_4$ (70%)	THF	–20 to 24	no conversion, starts to decompose

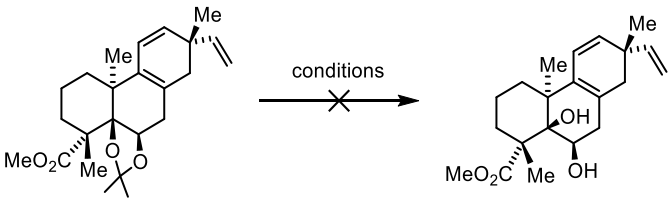
We investigated several standard conditions such as Brønsted-acid catalyzed deacetalizations (hydrochloric acid,[84] sulfuric acid[85], acetic acid[86] and perchloric acid[87]) as well as boron trifluride as strong Lewis-acid.[88] However, the acetonide proved to be surprisingly stable even under harsh reaction conditions.

Since attempts to deprotect acetonide **257** were unsuccessful, deprotection was investigated with acetonide **258**. The conformation of **258** before the Diels–Alder step is quite different to **257**. The formation of the caged ring structure changes the steric demand of the molecule and the acetonide should be more accessible in structure **258**.

In addition to the conditions already tested with acetonide **257**, we investigated further possible deprotection conditions for acetonide **258** (Table 17). Several Bronsted acids were screened including: Amberlyst,[89] para-toluene sulfonic acid[90] and trifluroacetic acid.[91] With iodine[92] and

magnesium bromide[93] even more uncommon conditions were used, but no product formation was observed.

Table 17 Attempts to deprotect acetonide **258**.



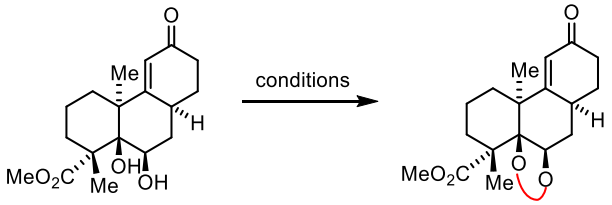
258 **270**

Entry	Reagent	Solvent	T [°C]	Observation
1	4 M aq. HCl	MeOH	80	no conversion
2	H_2SO_4	dioxane	80	no conversion
3	TsOH	MeOH	80	no conversion
4	TFA	CH_2Cl_2	60	no conversion
5	TFA	THF/H_2O	80	no conversion
6	Amberlyst	$CHCl_3$	60	no conversion
7	I_2	MeOH	24	no conversion, starts to decompose
8	$MgBr_2$	benzene	80	no conversion
9	BCl_3	CH_2Cl_2	24	decomposition
10	$BF_3{\cdot}OEt_2$	MeOH	–78 to 0	no conversion
11	$BF_3{\cdot}OAc$	MeOH	–78 to 0	no conversion
12	$BF_3{\cdot}OEt_2$	MeOH	0 to 24	no conversion, starts to decompose
13	$BF_3{\cdot}AcOH$	MeOH	0 to 24	no conversion, starts to decompose

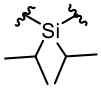
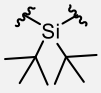
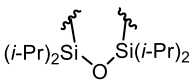
3.2.2 Protecting Group Studies

Since neither acetonide **257** nor **258** could be deprotected, we decided to put a different protecting group on diol **267**. Eight different diol protecting groups were investigated (Table 18). Successful protection of diol **267** could be realized with Bn or PMP acetal or a carbonate. Methyl orthoformate (entry 3) and di-silylether (entry 7) only protected the secondary alcohol and the tertiary alcohol remained unprotected. These results additionally confirmed that the diol functionality is sterically extremely hindered already in less hindered structure of enone **267** and even before the bulky cage in ring C is introduced.

Table 18 Protection attempts of diol **267**.

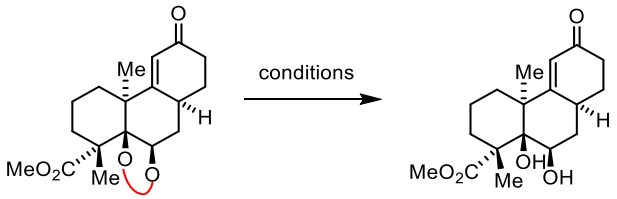


267 **271a–h**

Entry	Protecting group	Reagents	Observation
1		*p*-TsOH, benzaldehyde	product formation
2		*p*-TsOH, anisaldehyde	product formation
3		*p*-TsOH, $HC(OMe)_3$	undesired side product
4		pyridine, Me_2SiCl_2	product formation, but extremely unstable
5		lutidine, *i*-$Pr_2Si(OTf)_2$	complex mixture
6		lutidine, (*t*-$Bu)_2Si(OTf)_2$	no conversion
7		imidazol, Cl-Si(*i*-$Pr)_2OSi$(*i*-$Pr)_2$-Cl	undesired side product
8		pyridine, triphosgene	product formation

With the three protected diols in hand, we investigated different deprotection conditions starting with standard condition as shown in Table 19. Hydrogenation of the acetals did not lead to product formation, instead new compounds were detected. With 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), the PMP acetal decomposed and the carbonate deprotection led to new spots monitored by thin layer chromatography. Formation of diol **267** was not observed. Although no diol **267** formation was observed, these results did not indicate, that the protecting groups cannot be cleaved later on in the synthesis. However, it seemed not trivial to find a feasible diol protecting group for this molecule.

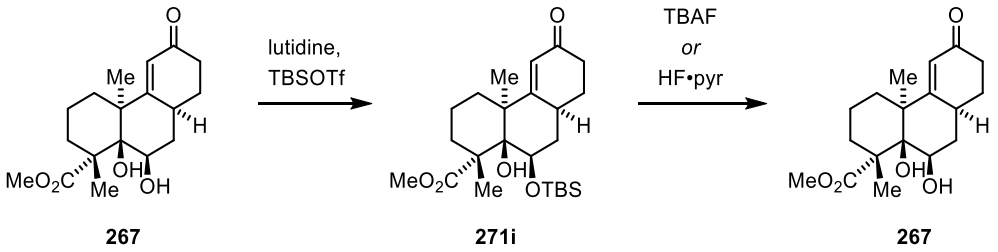
Table 19 Attempts to directly cleave the diol protecting group.



271a, **271b**, **271h** **267**

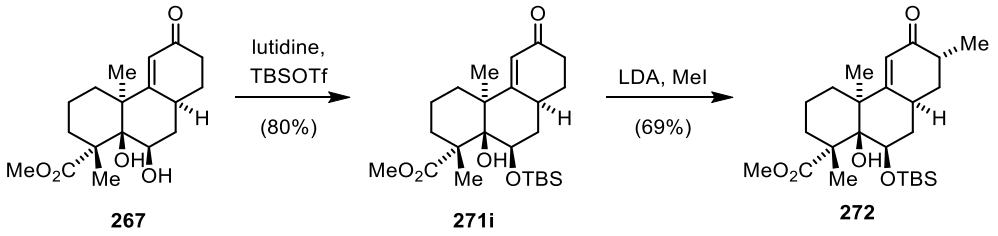
Entry	Protecting group	Reagents	Observation
1		H_2, $Pd(OH)_2$	complex mixture, no product formation
2		H_2, $Pd(OH)_2$	complex mixture, no product formation
3		DDQ	decomposition
4		KOH, MeOH / H_2O	complex mixture, no product formation

Since diol protecting groups proved to be challenging, we changed the strategy to a mono protected system. Since we assumed that the unprotected sterically extremely hindered tertiary alcohol will not interfere with the next steps.



Scheme 66 TBS protection and direct deprotection attempts of diol **267**.

The secondary alcohol of diol **267** could be mono protected with TBSOTf and subsequent deprotection was realized with both hydrofluoric acid in pyridine or tetrabutylammonium fluoride (TBAF) (Scheme 66).

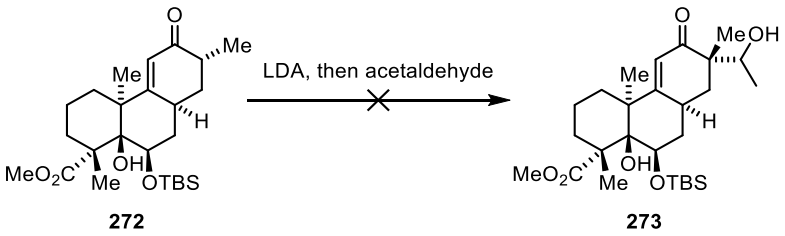


Scheme 67 Methylation of TBS protected alcohol **271**.

When performing the reaction on larger scale we found that also the silyl enol ether is formed under these conditions (Scheme 67). But since the enol ether is unstable on silica gel, after a second column chromatography, enone **271i** was afforded in good yield. Subsequent methylation of enone **271i** gave **272** in moderate yield.

The following alkylation with acetaldehyde to alcohol **273** was first performed with the optimized reaction conditions from the acetonide route (see Scheme 65): LDA and *N*,*N*,*N*′,*N*′-tetramethylethylendiamin (TMEDA) as additive. Under these conditions no conversion was observed and 70% of the starting material could be reisolated (Table 20). Also *N*,*N*′-dimethylpropyleneurea (DMPU) or without the addition of an additive no conversion of the starting material was observed. With HMPA a complex mixture of products and remaining starting material was obtained. Also the intermediate protection of the free tertiary alcohol with trimethylsilyl chloride and methyl lithium could not enable the reaction (entry 5). The intermediate TMS species was not isolated and analyzed, so maybe the tertiary alcohol was not protected but instead the enone was converted to the TMS enol ether.

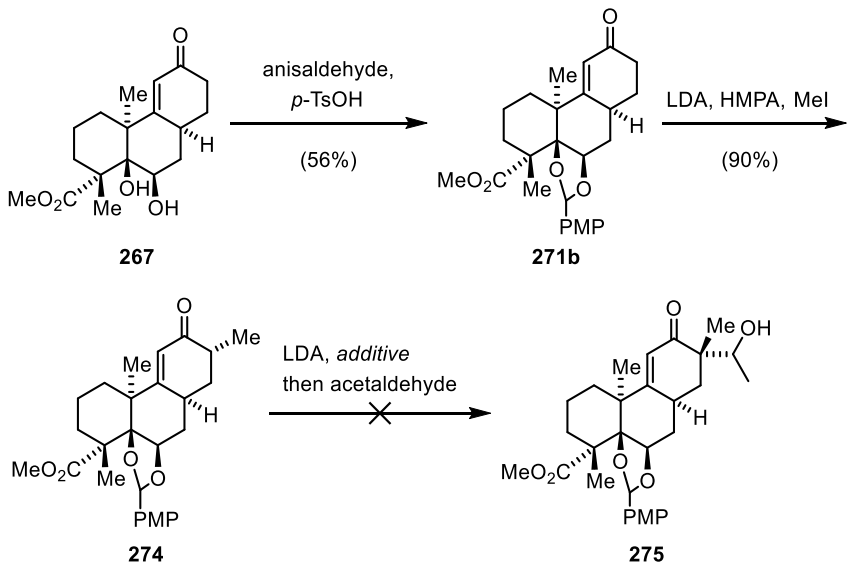
Table 20 Attempts to alkylate enone **272** with acetaldehyde.



272 **273**

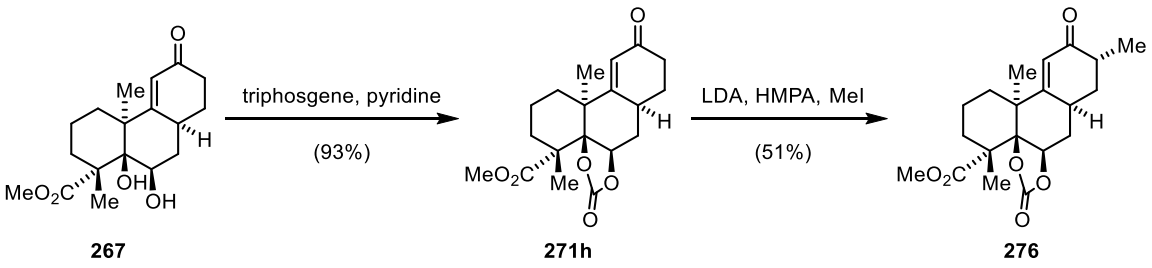
Entry	Additive	Observation
1	-	no conversion
2	DMPU	no conversion
3	TMEDA	no conversion
4	HMPA	decomposition
5	MeLi, TMSCl, then LDA, TMEDA, acetaldehyde	no conversion

Therefore we investigated the synthetic sequence with the PMP acetal protecting group (Scheme **68**). Protection of diol **267** gave only moderate yield of PMP acetal **271b**, but subsequent methylation worked smoothly under the addition of HMPA. Without the addition of HMPA, no conversion could be observed. The following alkylation of enone **271b** with acetaldehyde gave, similar to the TBS-protected version **272**, no product. The same conditions as for TBS protected alcohol **272** were tested (no additive, TMEDA, HMPA, DMPU). The aldol reaction with acetaldehyde seems to be the challenging "bottle neck" reaction of the sequence for which the protecting group is required.



Scheme 68 Investigation of the alkylation steps with PMP acetal protection.

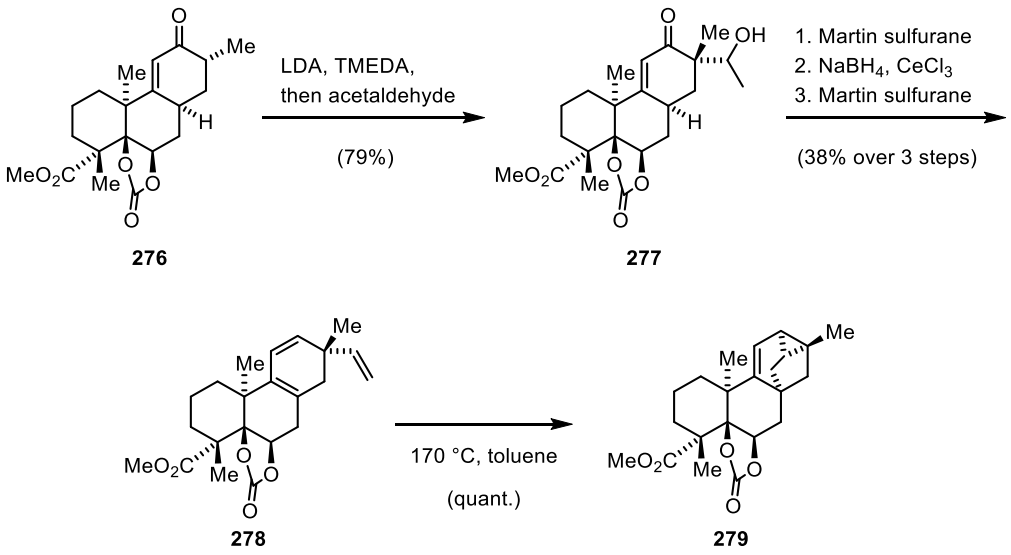
In parallel to the PMP acetal, carbonate protection was investigated (Scheme 69). Carbonate **271h** was obtained in excellent yield and subsequent methylation of **271h** gave enone **276** in acceptable yield. As with PMP acetal **274** no conversion for the methylation was observed without the addition of HMPA. The aldol reaction of enone **276** with acetaldehyde without additive led to no conversion and decomposition was observed when HMPA was added.



Scheme 69 Investigation of the alkylation steps with carbonate protected diol **271h**.

The addition of TMEDA gave alcohol **277** in good yield (Scheme 70). The subsequent elimination - reduction - elimination sequence gave diene **278** in moderate yield. We tried to improve the elimination reaction of alcohol **277** to vinyl **278** by using less expensive Burgess reagent (benzene, 25 to 80 °C) instead of Martin sulfurane, but no conversion to **278** was observed.

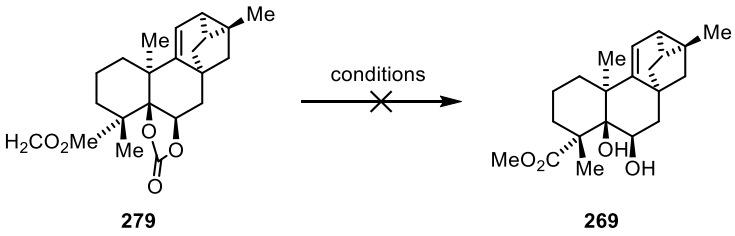
Intramolecular Diels−Alder reaction of **278** gave **279** in quantitative yield and built up the complete carbon skeleton of the natural product.



Scheme 70 Synthesis of the complete mitrephorone carbon skeleton.

With carbonate **279** in hand, we tested various deprotection methods. The efforts to deprotect carbonate **279** are summarized in Table 21. Basic, aqueous, as well as inert and water free conditions were tested.[94][95] Furthermore reducing reagents were investigated.[96] However, like the acetonides **258** and **257**, carbonate **279** proved to be surprisingly stable even under harsh reaction conditions.

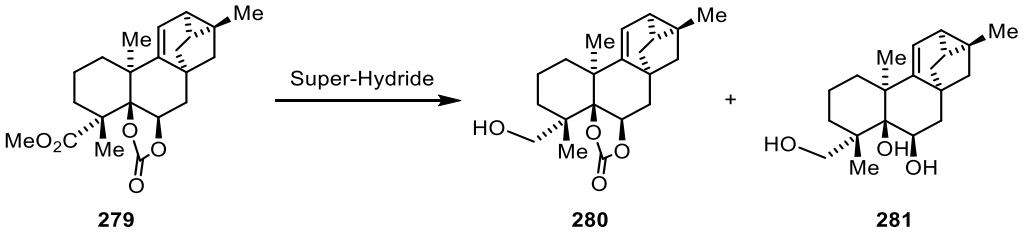
Table 21 Attempts to deprotect carbonate **279**.



Entry	Reagent	Solvent	T [°C]	Observation
1	K_2CO_3	MeOH	65	no conversion
2	NaOMe	MeOH	65	no conversion
3	K_2CO_3	MeOH / ethylene glycol	65	no conversion
4	NaOMe	MeOH / ethylene glycol	65	no conversion
5	$Ba(OH)_2$	H_2O	70	no conversion
6	$Ba(OH)_2$	H_2O / DMF	100	no conversion
7	LAH	THF	65	no conversion

8	LAH	toluene	100	no conversion
9	NaH	toluene	120	decomposition
10	KOH	ethylene glycol	150	no conversion
11	LiOH, H_2O_2	THF	60	no conversion

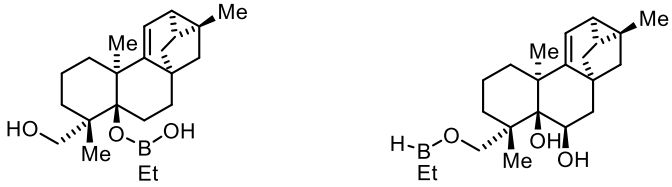
Treating carbonate **279** with lithium triethylborohydride (Super-Hydride®) finally resulted in conversion of the starting material. The product turned out to be an inseparable mixture of two products: alcohol **280** still being carbonate protected and completely reduced triol **281**.



279 **280** **281**

Scheme 71 First successful deprotection of carbonate **279**.

Repeating the same reaction conditions as shown in Scheme 71, this time under prolonged reaction time (60 h instead of 30 h) to get full conversion to triol **281**, unfortunately did not resulted in formation of the desired triol **281**. An unidentified new product was isolated, again as an inseparable mixture of two products. High resolution mass spectrometry revealed that a boron was incorporated into the molecule. Two hypothetical structures **282** and **283** that would fit to the found mass are depicted in Figure 11.

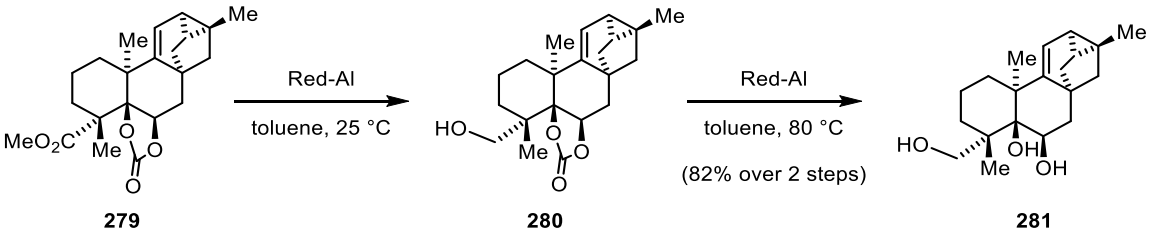


282 **283**

Figure 11 Hypothetical undesired reaction products after prolonged reaction time of carbonate **279** with Super-Hydride®.

In order to hydrolyze the putative boron species, the isolated material was subjected to aqueous acidic conditions. Unfortunately, only decomposition took place. Also with aqueous sodium hydroxide and hydrogen peroxide triol **281** could not be isolated.

The reduction of carbonate **279** to triol **281** was therefore tested with sodium bis(2-methoxyethoxy)aluminium hydrid (Red-Al), another strong reducing agent, without containing any boron. Indeed, reacting carbonate **279** with Red-Al at low temperatures first reduced the ester to alcohol **280** and in a second reduction step triol **281** could be obtained in very good yield.



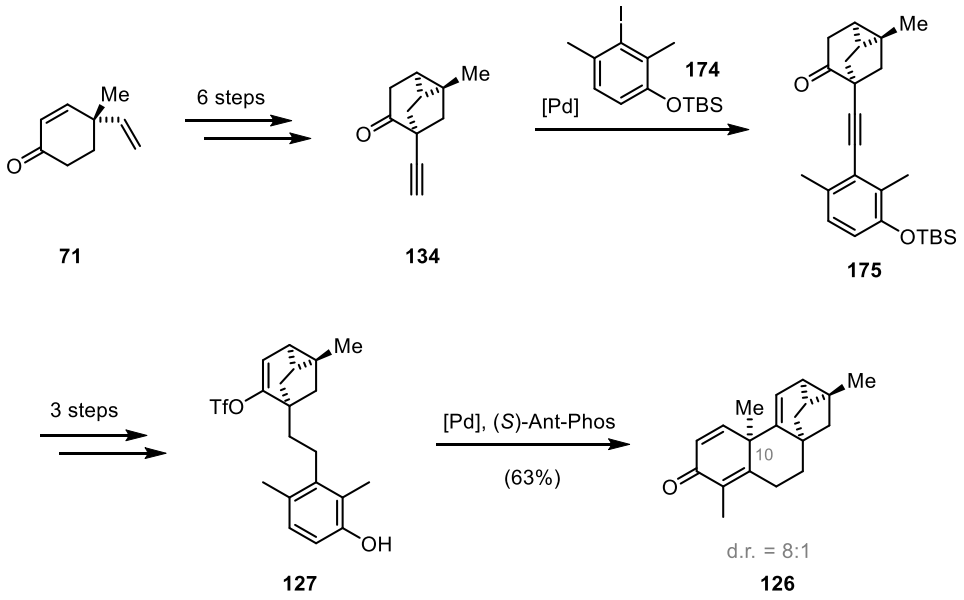
Scheme 72 Reduction and deprotection of carbonate **279** to triol **281**.

Although triol **281** is not ideal the methyl ester has to be rebuild, we were finally able to deprotect the diol, which represents a huge progress towards the total synthesis of mitrephorone A (**1**).

4 Summary and Outlook

Progress toward the total synthesis of the diterpenoid mitrephorone A (**1**) was discussed in this thesis.

At first, the challenging carbon core structure was constructed by employing a dearomatization strategy (Scheme 73). The elaborated route commences with the preparation of enone **71** via an enantioselective Diels–Alder reaction. Conversion towards alkyne **134** was realized in a six-step sequence involving an intramolecular Diels–Alder reaction to build up the caged structure found in the natural product. Next, the two building blocks **134** and **174** were coupled via a Sonogashira cross coupling reaction. Asymmetric dearomative cyclization of **127** closed the last carbon ring of mitrephorone A and set the right quaternary stereocenter at C10.

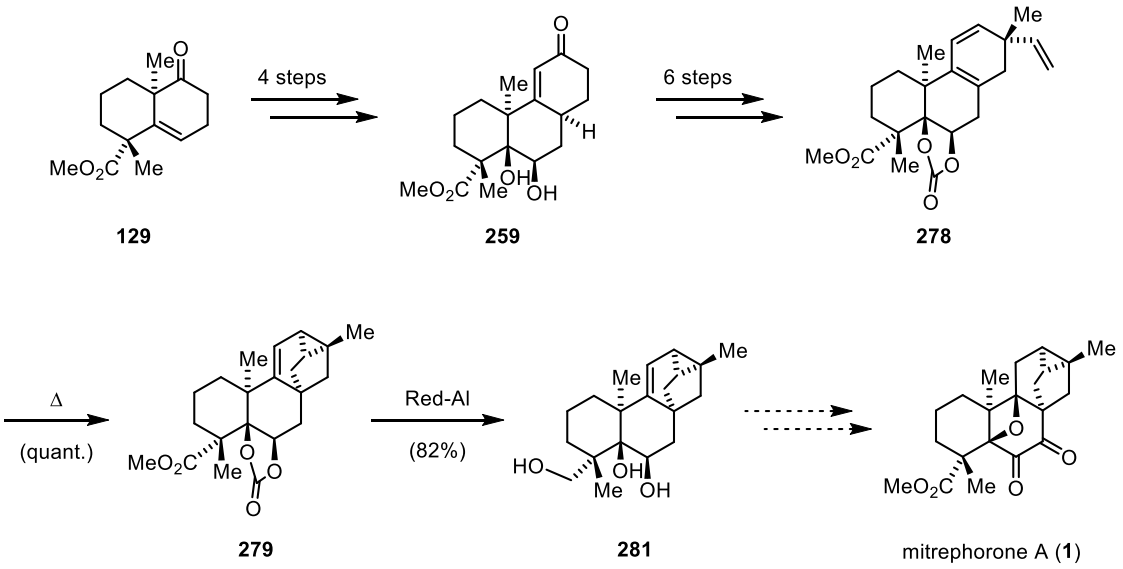


Scheme 73 Convergent asymmetric synthesis of the core structure of mitrephorone A (**1**).

With the established route toward the core structure of the natural product in hand, we extensively investigated various synthetic strategies toward the natural product. The convergent synthesis enabled the preparation of different coupling partners and thus diverse cyclization precursors. However, with this synthetic approach the further functionalization of the sterically demanding scaffold was found to be challenging.

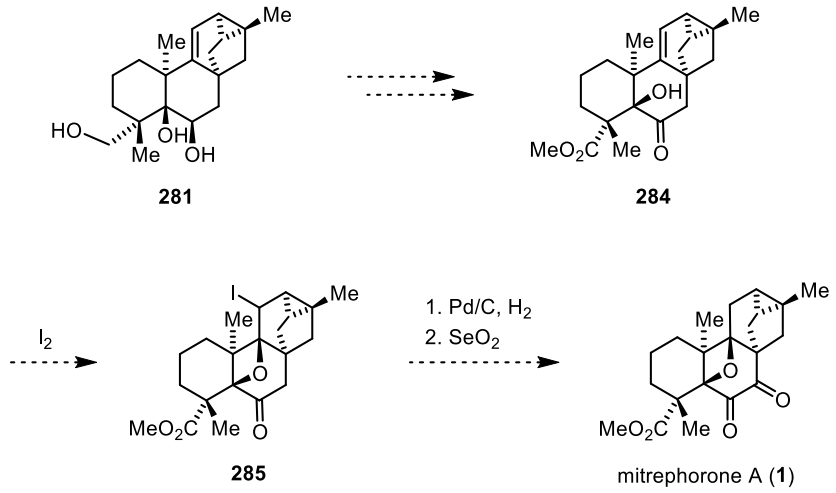
An alternative approach commenced with literature known building block **129** which was prepared in eight steps (Scheme 74). A Sharpless dihydroxylation and Robinson annulation sequence led to enone **259**. In six further steps enone **259** was converted to triene **278**. An intramolecular Diels–Alder reaction of **278** built up the complete carbon skeleton of the natural product. Subsequent

deprotection of carbonate **279** proved to be challenging and was realized using the strong reducing agent bis(2-methoxyethoxy)aluminium and resulted in the formation of triol **281**.



Scheme 74 Asymmetric synthesis of the mitrephorone carbon skeleton **281**.

In future, the substrate should be further transformed to ketone **284** via oxidation and esterification. With tertiary alcohol **284** in hand, the stage is set for the last key step of our synthesis.



Scheme 75 Envisioned synthesis of oxetane **285** and completion of the total synthesis of mitrephorone A.

We envision to activate the double bond of **284** with iodine to enable a 4-*exo*-trig cyclisation which should form oxetane **285**. Other reagents are conceivable for this transformation like *N*-bromosuccinimide, which was used for the oxetane cyclisation in cisclerodane diterpenes syntheses[97] or bis(sym-collidine)iodine perchlorate [$I(coll)_2ClO_4$] another reagent already successfully applied in oxetane formations.[98] Also for the following dehalogenation of **285** various

reducing protocols are possible: hydrogen gas and palladium,[99] a radical version with azobisisobutyronitrile (AIBN) and tributyltin hydride,[100] or a mild version using samarium iodide as applied in the total synthesis of (–)-huperzine Q.[101] A Riley oxidation with selenium dioxide should complete our total synthesis of mitrephorone A (**1**).

Overall, the pursued strategies presented in this thesis constitute significant progress toward the total synthesis of mitrephorone A (**1**). The developed robust and asymmetric route of the complete carbon skeleton of mitrephorone A provides a basis for further efforts toward this structurally unique natural product. Further studies on the completion of the total synthesis of mitrephorone A are currently under investigation in the Magauer laboratories.

5 Experimental Part

5.1 General Experimental Details

5.1.1 General Working Methods

All reactions were performed in glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. All glassware was dried in an oven at 130 °C prior to use. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas or were dissolved in appropriate solvents. High pressure reactions were conducted in a miniclave steel apparatus from *BÜCHI AG*. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (−78 °C), H_2O/ice (0 °C). Reaction temperatures above 24 °C were conducted in a heated oil bath. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using glass plates precoated with silica gel (0.25 mm, 60 Å pore size, *Merck*) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous basic potassium permanganate solution ($KMnO_4$), aqueous acidic ceric ammonium molybdate solution (CAM), or an aqueous acidic *p*-anisaldehyde solution and were developed by heating with a heat gun. Flash-column chromatography on silica gel was performed as described by Still *et al.*,[102] employing silica gel (60 Å, 40–63 µm, *Merck KGaA*). Flash column chromatography on silica gel using triethylamine pretreated silica gel was performed by preparing the silica gel slurry with triethylamine (7.5% v/v in corresponding eluent mixture) and flushing the column with the eluent prior to loading the compound on the column. The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

5.1.2 Solvents and Reagents

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine (DIPA) and *N*,*N*-diisopropylethylamine (DIPEA) were distilled under nitrogen atmosphere from calcium hydride prior to use. Benzene, toluene, 1,4-dioxane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (MeCN), ethanol (EtOH) and methanol (MeOH) were purchased from *Acros Organics* as 'extra dry' reagents and used as received. All other reagents and solvents were purchased from chemical suppliers (*Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals,*

TCI Europe, carbolution, ABCR) and were used as received. Solvents for extraction, crystallization and flash column chromatography on silica gel were purchased in technical grade and distilled under reduced pressure prior to use. Lithium chloride and lithium bromide were dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 130 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. 4 Å molecular sieves were washed (methanol, acetone, dichloromethane) and then dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 130 °C (760 mmHg); the molecular sieves were flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[103]

5.1.3 NMR Spectroscopy

NMR spectra were measured on a *Bruker* Avance III HD 800 MHz spectrometer equipped with a CryoProbeTM, *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbeTM, *Bruker* AXR300, *Varian* VXR400 S, *Bruker* AMX600, Bruker Avance Neo 400 MHz, an Agilent 500 DD2 or a Bruker Avance II 600 MHz spectrometer. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: 7.16). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, C_6D_6: 128.06). ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants *J* (Hz), integration intensity, assigned proton) (e.g. "5.21 (t, *J* = 7.3 Hz, 1H, H-9)"). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), se (sextet), h (heptet) and m (multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals, as well for centrosymmetric multiplets, is reported as the center of the resonance range. Protons of diastereotopic methylene groups are reported as H-Xa and H-Xb, where H-Xa is the more downfield shifted proton. The nomenclature is arbitrarily and does not correspond to the spin system. Furthermore, the numbering of the proton and carbon atoms does not correspond to the IUPAC nomenclature. ^{13}C NMR spectroscopic data are reported as follows: Chemical shift in ppm (assigned carbon) (e.g. "159.22 (C-21)"). In cases were resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g. the ^{13}C NMR assignment "18.29 (C-16, C-17), 17.84 (C-16, C-17)" indicates that the resonance at 18.29 is either C-16 or C-17). In addition to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence

(HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. All raw FID files were processed and the spectra analyzed using the program *MestReNova 9.0.1* from *Mestrelab Research S. L.*

5.1.4 Mass Spectrometry

Mass spectra were recorded on a MAT 95 (EI) and MAT 90 (ESI) from *Thermo Finnigan GmbH* at the Department of Chemistry, Ludwig-Maximilians-University Munich or a Thermo Scientific™ LTQ Orbitrap XL™ Hybrid Ion Trap-Orbitrap Mass Spectrometer at the Institute of Organic Chemistry and Center for Molecular Biosciences, University of Innsbruck. Mass spectra were recorded in high-resolution. The method used is reported at the relevant section of the experimental section.

5.1.5 IR Spectroscopy

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system or on a Bruker™ ALPHA FT-IR Spectrometer from Bruker. Data are represented in frequency of absorption (cm^{-1}). Samples were prepared as a neat film or a film by evaporation of a solution.

5.1.6 Optical Rotation

Optical rotation values were recorded on a *PerkinElmer 241* or *Anton Paar MCP 200* or a Schmidt+Haensch UniPol L1000 Peltier polarimeter. The specific rotation is calculated as follows:

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

α: recorded optical rotation

β: concentration of the analyte in 10 mg/mL

d: length of the cuvette in dm

φ: measuring temperature in °C

λ: wave length in nm

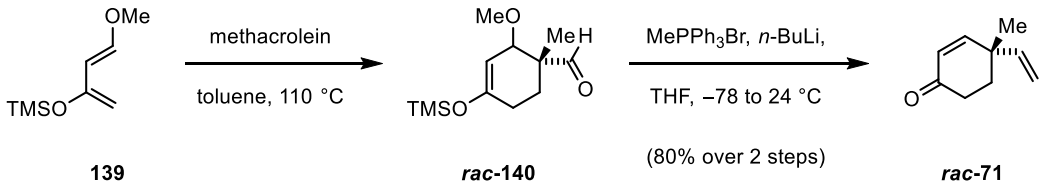
The respective concentration and the solvent are denoted in the analytical part of the experimental description.

5.1.7 Optical Rotation

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

5.2 Experimental Procedures

4-Methyl-4-vinylcyclohex-2-enone (*rac*-71)

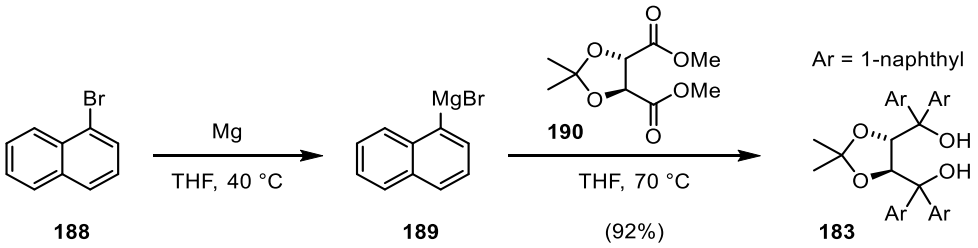


139 ***rac*-140** ***rac*-71**

In a pressure flask, a solution of the Danishefsky's diene[104] **139** (24.3 g, 141 mmol, 1 equiv) in toluene (260 mL) was sparged with argon for 5 min. Methacrolein (23.3 mL, 282 mmol, 2.00 equiv) was added. The reaction mixture was heated to 110 °C for 20 h. The mixture was allowed to cool to 24 °C and concentrated. The residue was used without further purification for the next step.

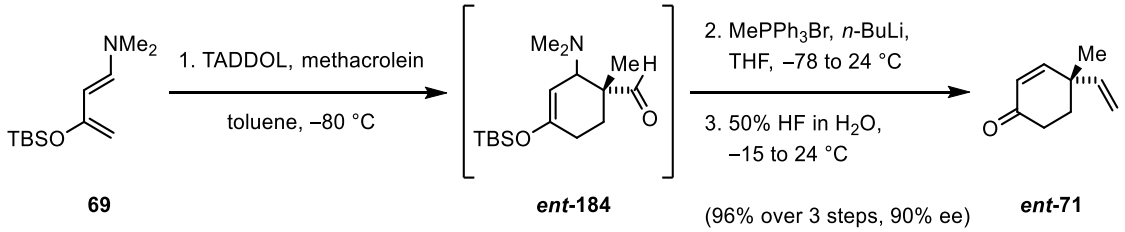
A suspension of methyltriphenylphosphonium bromide (60.4 g, 169 mmol, 1.20 equiv) in tetrahydrofuran (360 mL) was treated with *n*-butyl lithium (2.50 M in *n*-hexane, 67.7 mL, 1.20 equiv) at –20 °C and the orange suspension was warmed to 24 °C. After 30 min, the suspension was cooled to –40 °C. A solution of crude aldehyde ***rac*-140** in tetrahydrofuran (200 mL) was added via cannula over a period of 10 min. After 20 min, the orange cloudy mixture was allowed to warm to 24 °C and stirred for 1 h. The dark red mixture was cooled to 0 °C. Saturated aqueous ammonium chloride solution (400 mL), water (200 mL) and aqueous hydrochloric acid (1 M, 100 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated (Caution, the compound is volatile! Vacuum >300 mbar, 30 °C water bath). The residue was purified by flash column chromatography on silica gel (20–30% diethyl ether in pentane) to yield ***rac*-71** (15.4 g, 80% over two steps) as a yellow oil. The analytical data matched those previously described in the literature.[61]

(4S-*trans*)-2,2-Dimethyl-*α,α,α′,α′*-tetra(1-naphthyl)-1,3-dioxolane-4,5-dimethanol (183)



To preheated magnesium turnings (4.1 g, 168 mmol, 8.40 equiv), a grain of iodine and tetrahydrofuran (50 mL) was added. A solution of 1-bromonaphthalene (**188**) (22.3 mL, 160 mmol, 8.00 equiv) in tetrahydrofuran (100 mL) was added dropwise via a dropping funnel. After 10 min, 20 mL of the 1-bromonaphthalene solution were added and gentle refluxing of the tetrahydrofuran started. The remaining solution was added dropwise over 1 h. The reaction mixture was stirred at 24 °C for 1 h. A gray solid precipitated. More tetrahydrofuran (60 mL) was added and the mixture was warmed to 40 °C for 30 min. The resulting suspension was cooled to 24 °C. A solution of (+)-dimethyl 2,3-O-isopropylidene-D-tartrate (**190**) (4.4 g, 20 mmol, 1 equiv) in tetrahydrofuran (100 mL) was dropwise added via the dropping funnel over 1.5 h. The reaction mixture was heated to 70 °C and stirred for 3 h. The reaction mixture was cooled to 24 °C. Saturated aqueous ammonium chloride solution (200 mL) was added carefully. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 200 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to yield **183** (12.3 g, 92%) as light yellow solid. The analytical data matched those previously described in the literature.[105]

(*S*)-4-Methyl-4-vinylcyclohex-2-enone (*ent*-71)



The first reaction step was carried out in parallel in two separate flasks. The following procedure describes the synthesis for one batch of 13.8 mmol: (4S-*trans*)-2,2-Dimethyl-*α,α,α′,α′*-tetra(1-naphthyl)-1,3-dioxolane-4,5-dimethanol (**183**) (1.86 g, 2.76 mmol, 0.18 equiv) was added to a Schlenk tube. The tube was pumped and back-filled with argon three times. Toluene (15.5 mL) and

methacrolein (1.15 mL, 13.8 mmol, 1 equiv) were added dropwise. The orange solution was cooled to –80 °C using a cryostat and *trans*-3-(*tert*-butyldimethylsilyloxy)-*N*,*N*-dimethyl-1,3-butadien-1-amine **69**[106] (3.98 mL, 15.4 mmol, 1.10 equiv) was added dropwise. During the addition, the solution turned green and immediately afterwards the color changed to brown. The reaction mixture was stirred at –80 °C for five days.

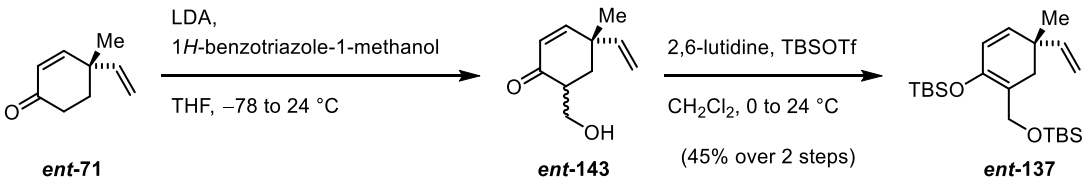
A phosphonium ylide suspension was prepared: Methyltriphenylphosphonium bromide (35.2 g, 96.6 mmol, 3.50 equiv) was added in a 3-necked round bottom flask. The flask was pumped and back-filled with argon for three times. Tetrahydrofuran (230 mL) was added and the suspension was cooled to –78 °C. A solution of *n*-butyl lithium (2.44 M in *n*-hexane, 39 mL, 3.45 equiv) was added dropwise and the orange suspension was warmed to 0 °C. After 30 min, the suspension was cooled to –78 °C. Both bathes of the crude Diels–Alder product ***ent*-184** were added dropwise to the prepared phosphonium ylide suspension. During the addition, a green foam occurred, which dissolved after 20 min and an orange suspension remained. The reaction mixture was allowed to warm to 24 °C.

After stirring for 15 h, the suspension was cooled to –15 °C and hydrofluoric acid (51% in water, 18.8 mL, 552 mmol, 20.0 equiv) was added dropwise into the open flask. The reaction mixture was allowed to warm to 24 °C. After 8 h, saturated aqueous sodium bicarbonate solution (600 mL) and solid sodium bicarbonate was added slowly over 12 h until the gas evolution stopped. Diethyl ether (300 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (5 × 150 mL) and the combined organic layers were washed with water (2 × 200 mL) and saturated aqueous sodium chloride solution (300 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated (Caution, the compound is volatile! Vacuum >300 mbar, 30 °C water bath). The residue was purified by flash column chromatography on silica gel (20% diethyl ether in pentanes) to remove high boiling toluene. A second flash column chromatography on silica gel (2–10% diethyl ether in pentane) provided ***ent*-71** (3.6 g, 96%, 90% ee as determined by Mosher[67] analysis using ^{1}H spectroscopy) as a yellow oil.

TLC (20 % diethyl ether in pentane): R_f = 0.37 (UV, CAM).

$[\alpha]_D^{20}$ = +110 (c = 1.20, CH_2Cl_2).

Triene *ent*-137



***ent*-71** **ent-143** ***ent*-137**

n-Butyllithium (2.40 M, 33.2 mL, 79.8 mmol, 3.00 equiv) was added dropwise at −78 °C to a solution of diisopropylamine (11.3 mL, 79.8 mmol, 3.00 equiv) in tetrahydrofuran (200 mL) and was stirred for 5 min at the same temperature. The reaction mixture was allowed to warm to 24 °C and stirred for 15 min. The reaction mixture was cooled to −78 °C. A solution of ***ent*-71** (4.00 g, 26.6 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added dropwise to the lithium diisopropylamide solution and was stirred for 30 min at the same temperature. 1*H*-Benzotriazole-1-methanol (8.10 g, 53.2 mmol, 2.00 equiv) was added and the reaction mixture was stirred for at −78 °C. After 3 h, water (100 mL) was added and the mixture was allowed to warm to 24 °C. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified by fast flash column chromatography on silica gel (40% ethyl acetate in hexanes) with deactivated silica (10% triethylamine) to yield the hydroxyl ketone ***ent*-143**.

2,6-Lutidine (6.41 mL, 53.9 mmol, 4.00 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.2 mL, 27.0 mmol, 2.00 equiv) were added at 0 °C to a solution of crude hydroxyl ketone ***ent*-143** (3.09 g, 18.6 mmol, 1 equiv) in dichloromethane (160 mL). The reaction mixture was stirred for 16 h at 24 °C. Saturated aqueous ammonium chloride solution (100 mL) was added to the reaction mixture. The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The dried solution filtrated and concentrated. The residue was purified by flash column chromatography on silica gel (1% ethyl acetate in hexanes) to yield ***ent*-137** (4.71 g, 45% over two steps) as a yellow oil.

TLC (20 % ethyl acetate in hexanes): R_f = 0.81 (UV, CAM).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2956, 2929, 2886, 2857, 1660, 1472, 1463, 1394, 1361, 1253, 1192, 1090, 1049 cm^{-1}.

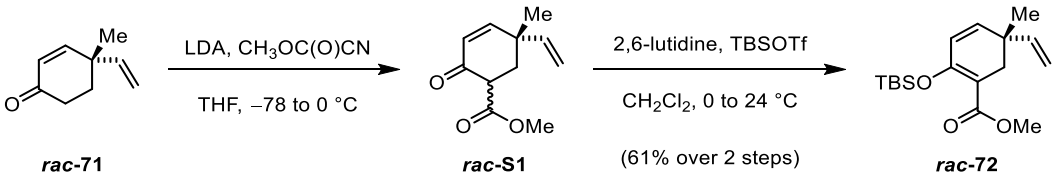
1H NMR (400 MHz, C_6D_6) δ = 5.85 (dd, J = 17.4, 10.6 Hz, 1H), 5.78 (d, J = 9.8 Hz, 1H), 5.47 (d, J = 9.8 Hz, 1H), 5.14 (dd, J = 17.4, 1.4 Hz, 1H), 4.96 (dd, J = 10.6, 1.4 Hz, 1H), 4.38 (s, 2H), 2.55 (d, J = 16.4 Hz, 1H), 2.39 (d, J = 16.4 Hz, 1H), 1.11 (s, 3H), 1.02 (s, 9H), 1.01 (s, 9H), 0.14 (s, 6H), 0.13 (s, 6H).

13C NMR (100 MHz, C_6D_6) δ = 145.1, 142.4, 135.8, 125.6, 114.2, 111.2, 60.1, 38.1, 37.2, 26.2, 26.0, 25.9, 18.6, 18.3, −4.0, −4.1, −5.1.

HRMS (ESI): calcd for $(C_{22}H_{43}O_2Si_2)^+$ $[M+H]^+$: 395.2796 , found: 395.2800.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +64.7 (c = 0.69, CH_2Cl_2).

Triene *rac*-72



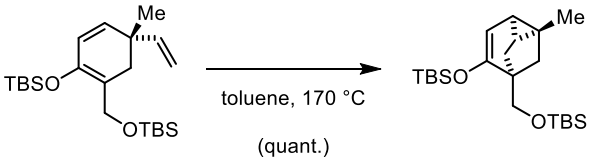
***rac*-71** ***rac*-S1** ***rac*-72**

A solution of diisopropylamine (0.13 mL, 0.92 mmol, 1.25 equiv) in tetrahydrofuran (7 mL) was treated with *n*-butyllithium solution (2.23 M in *n*-hexane, 0.40 mL, 0.88 mmol, 1.20 equiv) at –78 °C. After 5 min, the cooling bath was removed for 20 min, and then the mixture was cooled to –78 °C. A solution of the ***rac*-71** (100 mg, 0.73 mmol, 1 equiv) in THF (1 mL) was added and the solution was stirred for 30 min at –78 °C. Methyl cyanoformate (0.99 mL, 1.25 mmol, 1.70 equiv) was added. After 1 h, the reaction mixture was warmed to 0 °C and the color changed from yellow to dark red. After 1 h, ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (20 mL) was added. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (2 × 15 mL) and saturated sodium chloride solution (2 × 15 mL), dried over sodium sulfate. The dried solution filtrated and concentrated. The residue was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford ***rac*-S1** (95 mg, 67%) as inconsequential mixture of diastereomers.

To a solution of ***rac*-S1** (95 mg, 0.49 mmol, 1 equiv) in dichloromethane (2.5 mL) was added 2,6-lutidine (0.17 mL, 1.47 mmol, 3.00 equiv) at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.17 mL, 0.73 mmol, 1.50 equiv) was added. After 18 h, saturated aqueous ammonium

chloride solution (20 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (hexanes) to afford ***rac*-72** (139 mg, 92%) as a colorless oil. The analytical data matched those previously described in the literature.[40]

Tricyclo[3.2.1.0^{2,7}]octene *ent*-136



***ent*-137** ***ent*-136**

A solution of ***ent*-137** (4.71 g, 11.9 mmol) in toluene (100 mL) was sealed in a pressure tube and the solution was heated to 170 °C. After 13 h, the solution was cooled to 24 °C and concentrated to yield ***ent*-136** (4.71 g, 100%) as a yellow oil.

TLC (2% ethyl acetate in hexanes): $R_f = 0.57$ (UV, CAM).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3852, 3745, 3675, 3649, 3031, 2953, 2928, 2857, 1733, 1717, 1699, 1684, 1637, 1558, 1540, 1506, 1472, 1463 1388, 1363, 1343, 1307, 1244, 1209, 1177, 1162, 1076, 1005 cm^{-1}.

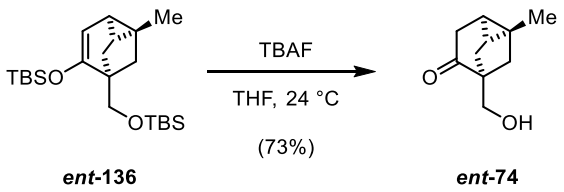
^{1}H NMR (600 MHz, C_6D_6) δ = 5.09 (d, *J* = 6.4 Hz, 1H), 4.05 (d, *J* = 2.8 Hz, 2H), 2.20 (dd, *J* = 10.9, 2.4 Hz, 1H), 1.89 (d, *J* = 10.7 Hz, 1H), 1.31 (t, *J* = 6.6 Hz, 1H), 1.23 (s, 3H), 1.09 (dd, *J* = 7.1, 2.4 Hz, 1H), 1.01 (s, 9H), 0.98 (s, 9H), 0.96 (d, *J* = 3.7 Hz, 1H), 0.94 (d, *J* = 3.6 Hz, 1H), 0.14 (s, 3H), 0.13 (s, 3H), 0.12 (s, 6H).

^{13}C NMR (150 MHz, C_6D_6) δ = 154.4, 96.4, 62.8, 48.4, 37.3, 31.6, 26.3, 26.0, 23.1, 22.7, 21.9, 18.8, 18.8, 18.4, −4.4, −4.5, −5.2.

HRMS (ESI): calcd for $(C_{22}H_{43}O_2Si_2)^+$ $[M+H]^+$: 395.2796, found: 395.2796.

$[\alpha]_D^{20}$ = –21.2 (c = 1.78, CH_2Cl_2).

Alcohol *ent*-74



***ent*-136** ***ent*-74**

To a solution of ***ent*-136** (4.71 g, 11.9 mmol, 1 equiv) in tetrahydrofuran (50 mL) at 0 °C was slowly added a solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 25.0 mL, 25.0 mmol, 2.10 equiv). The reaction mixture was stirred for 5 min at 0 °C and was then allowed to warm to 24 °C. The reaction mixture was stirred for 3 h. Saturated aqueous sodium hydrogen carbonate solution (150 mL) was added. The layers were separated. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (50–80% diethyl ether in pentane) to yield alcohol ***ent*-74** (1.7 g, 86%) as a yellow oil.

TLC (70% ethyl acetate in hexanes): $R_f = 0.34$ (UV, CAM).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3412, 3028, 2924, 2864, 2360, 1703, 1447, 1401, 1382, 1350, 1306, 1242, 1187, 1160, 1110, 1080, 1036 cm^{-1}.

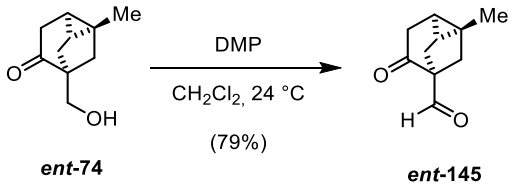
^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 3.61$ (d, $J = 6.6$ Hz, 2H), 2.60 (qd, $J = 20.9$, 2.4 Hz, 2H), 2.49 (t, $J = 6.9$ Hz, 1H), 1.93 (dd, $J = 12.8$, 3.3 Hz, 1H), 1.84 (s, 1H), 1.80 (s, 1H), 1.72 (d, $J = 12.7$ Hz, 1H), 1.28 (s, 3H), 1.24 (dd, $J = 7.6$, 3.2 Hz, 1H), 0.93 (ddd, $J = 7.6$, 2.7, 1.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 214.8$, 65.2, 56.8, 37.3, 34.1, 32.2, 22.8, 22.0, 19.4, 17.7.

HRMS (ESI): calcd for $(C_{10}H_{15}O_2)^+$ $[M+H]^+$: 167.1067, found: 167.1068.

$[\alpha]_D^{20} = -2.9$ (c = 0.90, CH_2Cl_2).

Aldehyde *ent*-145



***ent*-74** ***ent*-145**

Dess–Martin Periodinane (5.21 g, 12.3 mmol, 1.2 equiv) was added at 0 °C to a solution of alcohol ***ent*-74** (1.7 g, 10.2 mmol, 1 equiv) in dichlormethane (80 mL) and was stirred for 10 min. The reaction mixture was stirred for 2 h at 24 °C. Saturated aqueous sodium hydrogen carbonate solution (100 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 120 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtrated and concentrated (Caution, the compound is volatile! Vacuum >300 mbar, 30 °C water bath). The residue was purified by flash column chromatography on silica gel (30% diethyl ether in pentane) with deactivated silica gel (10% triethylamine) to yield aldehyde ***ent*-145**(1.57 g, 94%) as a light yellow oil.

TLC (50%ethyl acetate in hexanes): $R_f = 0.53$ (CAM).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3413, 3032, 2928, 2867, 2742, 1713, 1469, 1448, 1401, 1336, 1306, 1269, 1159, 1129, 1081, 1004 cm^{-1}.

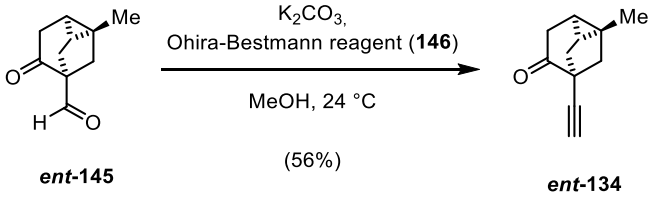
^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 10.01$ (s, 1H), 2.68 (qd, $J = 20.8$, 20.5, 2.7 Hz, 2H), 2.26 (dd, $J = 12.8$, 3.5 Hz, 1H), 2.10–1.91 (m, 3H), 1.32 (d, $J = 4.3$ Hz, 1H), 1.31 (s, 3H), 0.98 (ddt, $J = 7.2$, 2.6, 1.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 209.0$, 200.6, 64.1, 35.4, 34.1, 30.6, 22.4, 21.4, 19.1, 17.1.

HRMS (EI): calcd for $(C_{10}H_{12}O_2)^+$ $[M+H]^+$: 164.0832, found: 164.0833.

$[\alpha]_D^{20} = -8.4$ (c = 0.80, CH_2Cl_2).

Alkyne *ent*-134



***ent*-145** ***ent*-134**

Potassium carbonate (1.9 g, 13.7 mmol, 1.50 equiv) was added to a solution of aldehyde ***ent*-145** (1.5 g, 9.13 mmol, 1 equiv) in methanol (8 mL) at 24 °C. To this suspension was added dimethyl (1-diazo-2-oxopropyl)phosphonate (2.63 g, 13.7 mmol, 1.50 equiv) in methanol (5 mL). The reaction mixture was stirred for 2 h at 24 °C. The mixture was diluted with saturated aqueous sodium hydrogen carbonate solution (20 mL) and diethyl ether (5 mL). The layers were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated (Caution, the compound is volatile! Vacuum >300 mbar, 30 °C water bath). The residue was purified by flash column chromatography on silica gel (10% diethyl ether in pentane) to yield ***ent*-134** (1.05 g, 72%) as a white solid.

TLC (20% ethyl acetate in hexanes): $R_f = 0.35$ (Anis, CAM).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3275, 3031, 2927, 2866, 2119, 1728, 1446, 1424, 1403, 1336, 1306, 1289, 1261, 1249, 1156, 1095, 1081, 1068, 1036 cm^{-1}.

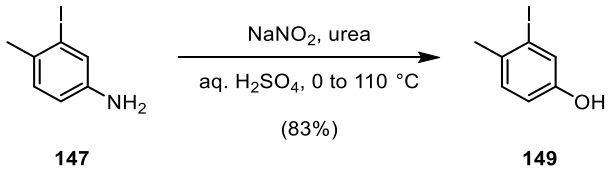
^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.72–2.60 (m, 2H), 2.39 (m, 1H), 2.37 (ddt, *J* = 12.9, 3.4, 1.0 Hz, 1H), 2.20 – 2.07 (m, 3H), 1.29 (s, 3H), 1.26 (dd, *J* = 7.6, 3.4 Hz, 1H), 0.93 (dtt, *J* = 7.8, 2.7, 1.2 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 205.6, 81.5, 73.6, 51.0, 41.7, 36.8, 33.3, 22.7, 21.8, 19.0, 17.3.

HRMS (EI): calcd for $(C_{11}H_{12}O)^+$: 160.0883, found: 160.0885.

$[\alpha]_D^{20}$ = –6.0 (c = 0.91, CH_2Cl_2).

Phenol 149



A suspension of aniline **147** (4.00 g, 17.2 mmol, 1 equiv) in water (25 mL) and aqueous sulfuric acid (0.5 M, 25 mL) was heated to 80 °C until the solid dissolved. The yellowish solution was cooled to 0 °C and a finely dispersed suspension was formed. Sodium nitrite (1.78 g, 25.8 mmol, 1.50 equiv) was added. The reaction mixture was stirred at 0 °C for 2 h. Urea (0.52 g, 8.6 mmol, 0.50 equiv) was added. The reaction mixture was allowed to warm to 24 °C. More aqueous sulfuric acid (0.5 M, 25 mL) was added and the reaction mixture was heated to 110 °C and refluxed for 30 min. After cooling down to 24 °C, ethyl acetate (150 mL) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried over sodium sulfate, filtrated and concentrated to yield a dark red oil. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield phenol **149** (3.36 g, 84%) as a yellow solid.

TLC (10% ethyl acetate in hexanes): $R_f = 0.22$ (UV, CAM).

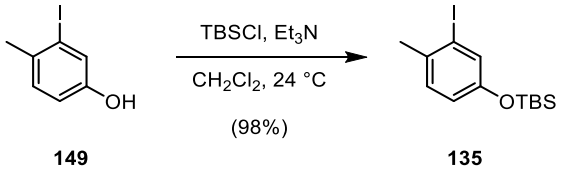
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3345, 2918, 1704, 1600, 1580, 1486, 1451, 1414, 1379, 1277, 1228, 1024 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 2.6 Hz, 1H), 7.10 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.61 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.6, 133.6, 129.9, 125.5, 115.3, 100.6, 26.8.

HRMS (EI): calcd for $(C_7H_7O_1{}^{127}I)^+$: 233.9536, found: 233.9538.

Silyl ether 135



To a orange solution of phenol **149** (3.30 g, 14.1 mmol, 1 equiv) in dichloromethane (7 mL) was added trimethylamine (2.35 mL, 16.9 mmol, 1.2 equiv). *tert*-Butyldimethylchlorosilane (2.55 g, 16.9 mmol, 1.2 equiv) was added and after a few minutes the solution turned into a yellow suspension which was stirred at 24 °C for five hours. Water (50 mL) and dichloromethane (50 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (80 mL), dried over sodium sulfate, filtrated and concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **135** (4.80 g, 98%) as a yellow oil.

TLC (10% ethyl acetate in hexanes): $R_f = 0.66$ (UV, CAM).

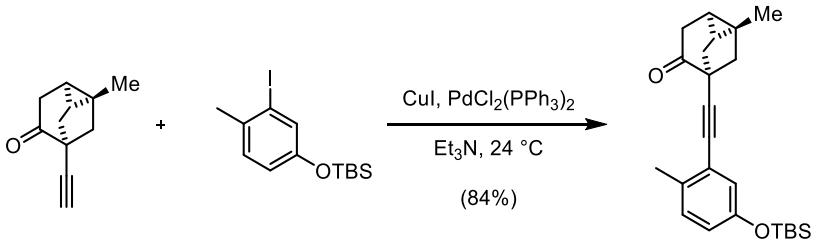
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2954, 2928, 2885, 2857, 1592, 1552, 1481, 1444, 1389, 1361, 1279, 1245, 1197, 1023, 1006 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 2.5 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.5 Hz, 1H), 2.35 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.8, 134.0, 130.3, 129.6, 119.8, 100.5, 27.0, 25.7, 18.19, –4.5.

HRMS (EI): calcd for $(C_{13}H_{21}O_1{}^{127}I_1{}^{28}Si_1)^+$: 348.0406, found: 348.0405.

Alkyne 133



***rac*-134** **135** **133**

To a stirring suspension of bis(triphenylphosphine)palladium(II) dichloride (7.0 mg, 0.01 mmol, 0.01 equiv) and copper(I) iodide (0.9 mg, 0.005 mmol, 0.005 equiv) in triethylamine (8 mL) was added a mixture of alkyne ***rac*-134** (160 mg, 1.00 mmol, 1 equiv) and iodide **135** (383 mg, 1.10 mmol, 1.1 equiv). The reaction mixture was stirred for 16 h at 24 °C. The mixture was diluted with water (100 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified

by flash column chromatography on silica gel (2% ethyl acetate in hexanes) to yield alkyne **133** (0.32 g, 84%) as a light yellow oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.50$ (Anis, CAM, UV).

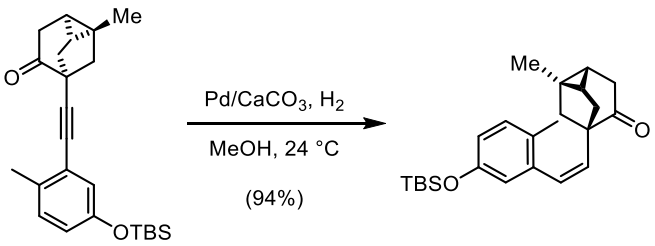
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3028, 2953, 2929, 2896, 2859, 1730, 1603, 1568, 1488, 1472, 1447, 1407, 1390, 1361, 1342, 1314, 1290, 1273, 1258, 1210, 1179, 1143, 1119, 1078, 1066, 1035 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.00 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 6.67 (dd, J = 8.3, 2.7 Hz, 1H), 2.78 – 2.61 (m, 2H), 2.45 (ddt, J = 12.9, 3.5, 1.1 Hz, 1H), 2.34 (s, 3H), 2.28 – 2.14 (m, 3H), 1.31 (s, 3H), 1.28 (dd, J = 7.7, 3.3 Hz, 1H), 0.96 (s, 9H), 0.96 – 0.94 (m, 1H), 0.16 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 205.7, 153.2, 133.4, 130.2, 123.8, 123.2, 120.4, 90.6, 84.5, 51.9, 42.1, 37.2, 33.5, 25.8, 22.8, 22.0, 19.9, 19.1, 18.3, 17.4, −4.3.

HRMS (EI): calcd for $(C_{24}H_{32}O_2Si)^+$: 380.2166, found: 380.2163.

Alkene 150



133 **150**

To a solution of **133** (200 mg, 0.53 mmol, 1 equiv) in methanol (20 mL) was added palladium on calcium carbonate (224 mg, 0.11 mmol, 0.2 equiv). The reaction mixture was stirred under a positive pressure of hydrogen and the gas was passed through the mixture. The reaction was monitored by TLC. After a hydrogen gas flow of altogether 3 min, the reduction was finished. The mixture was filtrated through celite. The filtrate was washed with dichloromethane. The washed solution was concentrated to yield alkene **150** (251 mg, 94%) as a light yellow oil.

TLC (10% ethyl acetate in hexanes): $R_f = 0.42$ (CAM, UV).

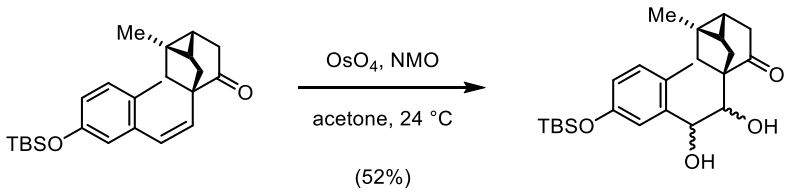
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2929, 2858, 1719, 1605, 1572, 1491, 1464, 1416, 1288, 1256, 1199, 1166, 1074 cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 6.96 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 9.2 Hz, 1H), 6.58 (s, 1H), 6.51 (d, J = 11.9 Hz, 1H), 5.70 (d, J = 13.0 Hz, 1H), 2.61 (d, J = 20.3 Hz, 1H), 2.55 (d, J = 20.5 Hz, 1H), 2.13 (s, 3H), 1.86 (d, J = 13.0 Hz, 1H), 1.77–1.70 (m, 2H), 1.66 (d, J = 12.9 Hz, 1H), 1.15 (s, 3H), 1.05 (d, J = 7.4 Hz, 1H), 0.96 (s, 9H), 0.81 (d, J = 5.7 Hz, 1H), 0.16 (s, 6H).

^{13}C NMR (200 MHz, $CDCl_3$) δ = 210.7, 153.2, 138.9, 131.0, 130.2, 129.8, 128.7, 120.3, 119.0, 57.8, 40.4, 35.2, 34.1, 25.9, 22.3, 21.9, 19.4, 19.3, 18.4, 17.6, −4.2.

HRMS (EI): calcd for $(C_{24}H_{34}O_2Si)^+$ $[M–CH_3]^+$: 382.2323, found: 382.2325.

Diol 152



150 **152**

To a solution of **150** (46 mg, 0.12 mmol, 1 equiv) in acetone (0.5 mL) was added 4-methylmorpholine N-Oxide (50% in water, 19.0 µL, 0.18 mmol, 1.50 equiv) and osmium tetroxide (73.0 µL, 0.01 mmol, 0.10 equiv). The reaction mixture was stirred at 24 °C for 14 h. Saturated aqueous sodium thiosulfate solution (10 mL) was added and the mixture was stirred for 15 min. Water (10 mL) and ethyl acetate (10 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5–20% ethyl acetate in hexanes) to yield **152** as mixture of diastereomers (26 mg, 52%) as a yellow oil.

TLC (40% ethyl acetate in hexanes): R_f = 0.23 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3448, 2929, 2859, 1698, 1608, 1495, 1472, 1287, 1254, 1160, 1004 cm^{-1}.

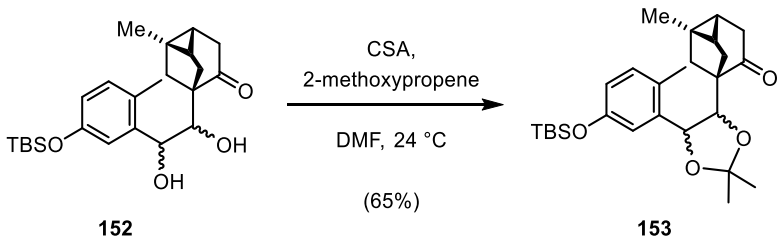
Peaks of the minor diastereomers are also visible in the NMR spectra, but only chemical shifts of the major diastereomer are reported:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.03 – 6.90 (m, 2H), 6.66 (d, 1H), 5.00 – 4.88 (m, 1H), 3.94 – 3.82 (m, 1H), 2.64 (dd, 2H), 2.28 (s, 3H), 2.18 – 1.97 (m, 2H), 2.04 (s, 1H), 1.64 (m, 1H), 1.43 (dd, , 1H), 1.27 (s, 3H), 0.98 (s, 9H), 0.88 (m, 1H), 0.18 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 215.9, 154.1, 141.2, 131.3, 128.4, 119.2, 117.7, 75.1, 72.2, 60.2, 36.9, 35.0, 31.8, 25.7, 22.9, 21.9, 19.1, 18.8, 18.2, 17.1, –4.3.

HRMS (EI): calcd for $(C_{24}H_{36}O_4Si)^+$: 416.2377, found: 416.2374.

Acetonide 153



152 **153**

To a solution of **152** (15 mg, 0.04 mmol, 1 equiv) in dimethylformamide (0.8 mL) was added camphorsulfonic acid (0.4 mg, 1.80 μmol, 0.05 equiv) and 2-methoxypropene (7.0 μL, 0.07 mmol, 2.00 equiv). The reaction mixture was stirred at 24 °C for 2 h. Saturated aqueous sodium bicarbonate solution (2 mL) and ethyl acetate (5 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **153** as mixture of diastereomers (11 mg, 65%) as a yellow oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.29 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2961, 2929, 2858, 2360, 1678, 1609, 1496, 1412, 1258, 1018 cm^{-1}.

Peaks of the minor diastereomers are also visible in the NMR spectra, but only chemical shifts of the major diastereomer are reported:

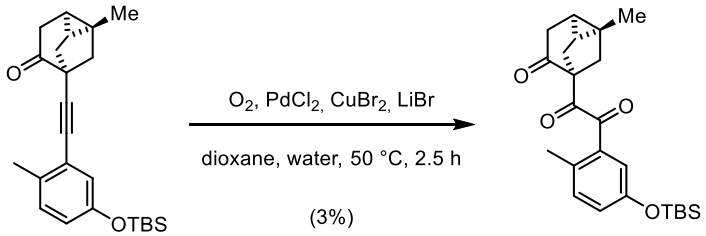
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.02 – 6.98 (m, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.7 Hz, 1H), 5.20 (d, *J* = 4.5 Hz, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 2.30 (s, 3H), 1.81 – 1.75 (m, 2H),

1.40 (t, *J* = 6.6 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 6H), 1.12 (dd, *J* = 7.0, 2.3 Hz, 1H), 1.07 (d, *J* = 10.7 Hz, 1H), 0.96 (s, 9H), 0.90 – 0.83 (m, 3H), 0.15 (d, *J* = 3.5 Hz, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 211.8, 175.0, 160.0, 151.8, 131.4, 119.2, 116.8, 114.0, 87.7, 85.7, 80.5, 45.1, 41.2, 34.5, 33.6, 29.7, 25.7, 21.7, 20.4, 18.5, 18.4, 18.2, –4.4.

HRMS (ESI): calcd for $(C_{27}H_{41}O_4Si)^+$ $[M+H]^+$: 457.2769, found: 457.2781.

Diketone 154



133 **154**

To a solution of **133** (25 mg, 65.7 μmol, 1 equiv) in dioxane (1.5 mL) and water (0.3 mL) was added palladium(II) chloride (2.3 mg, 13.1 μmol, 0.20 equiv), cupric bromide (6.0 mg, 26.3 μmol, 0.40 equiv) and lithium bromide (2.3 mg, 26.3 μmol, 0.4 equiv). The dark orange mixture was sparged with oxygen gas for 2 min, and stirring was then continued under an oxygen atmosphere (1 atm, balloon) at 50 °C for 2.5 h. The reaction mixture was cooled to 24 °C, diluted with water (5 mL) and diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (7% ethyl acetate in hexanes) to yield **154** (0.8 mg, 3%) as a yellow oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.39 (CAM, UV).

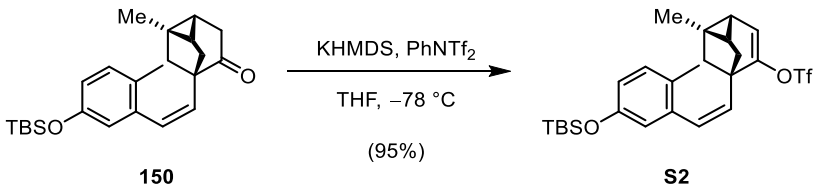
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2953, 2929, 2848, 1716, 1676, 1603, 1565, 1496, 1469, 1298, 1255 cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 2.7 Hz, 1H), 7.10 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.6 Hz, 1H), 2.75 – 2.65 (m, 2H), 2.59 – 2.55 (m, 1H), 2.42 (s, 3H), 2.39 – 2.27 (m, 4H), 1.35 (m, 1H), 1.34 (s, 3H), 0.96 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (200 MHz, $CDCl_3$) δ = 208.6, 201.7, 194.0, 153.2, 133.4, 133.0, 132.4, 125.0, 123.8, 65.2, 38.6, 34.2, 33.7, 25.9, 22.5, 21.5, 20.7, 19.0, 18.4, 17.3, –4.3.

HRMS (EI): calcd for $(C_{24}H_{32}O_4Si)^+$: 412.2064, found: 412.2065.

Vinyl-triflate S2



150 **S2**

To a solution of **150** (101 mg, 263 μmol, 1 equiv) in tetrahydrofuran (2 mL) at −78 °C was added dropwise a solution of potassium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 368 mL, 368 μmol, 1.4 equiv). The reaction mixture was stirred for 50 min at −78 °C. *N*-phenyl bis(trifluoromethanesulfonimide) (132 mg, 368 μmol, 1.4 equiv) was added. The mixture was stirred for 60 min at −78 °C. The reaction mixture was allowed to warm to 24 °C. The mixture was diluted with water (100 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was diluted with aqueous sodium chloride solution (20 mL) and was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **S2** (128 mg, 95%) as a light yellow oil.

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

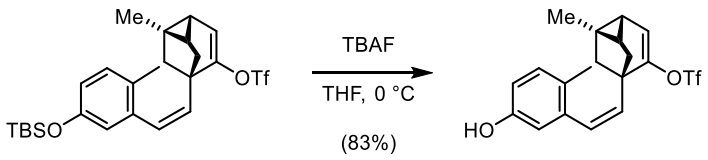
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 2930, 2860, 1605, 1572, 1492, 1473, 1420, 1288, 1248, 1208, 1142, 1119, 1098, 1058 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.97 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.61 (d, *J* = 12.1 Hz, 1H), 5.93 (d, *J* = 6.9 Hz, 1H), 5.84 (d, *J* = 12.1 Hz, 1H), 2.16 (s, 3H), 1.59 (dd, *J* = 11.8, 1.4 Hz, 1H), 1.46–1.40 (m, 1H), 1.28 (dd, *J* = 11.8, 1.2 Hz, 1H), 1.23 (dd, *J* = 6.8, 2.0 Hz, 1H), 1.19 (s, 3H), 1.05 (d, *J* = 11.8 Hz, 1H), 1.01 (d, *J* = 11.8 Hz, 1H), 0.96 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 153.4, 146.9, 138.6, 132.6, 130.3, 128.6, 128.3, 120.0, 119.3, 118.8 (q, *J* = 360.6 Hz), 113.4, 47.8, 41.3, 35.8, 25.8, 24.8, 23.6, 21.9, 19.3, 18.3, 17.8, −4.5.

HRMS (EI): calcd for $(C_{25}H_{33}F_3O_4SSi)^+$: 514.1815, found: 514.1809.

Phenol 155



S2 **155**

A solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran, 0.30 mL, 0.30 mmol, 1.2 equiv) was added dropwise to a solution of **S2** (128 mg, 0.25 mmol, 1 equiv) in tetrahydrofuran (2 mL) at 0 °C. The mixture was allowed to warm to 24 °C. The reaction mixture was diluted with aqueous ammonium chloride (20 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (20 mL). The washed solution was dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **155** (83 mg, 83%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.55$ (CAM, UV).

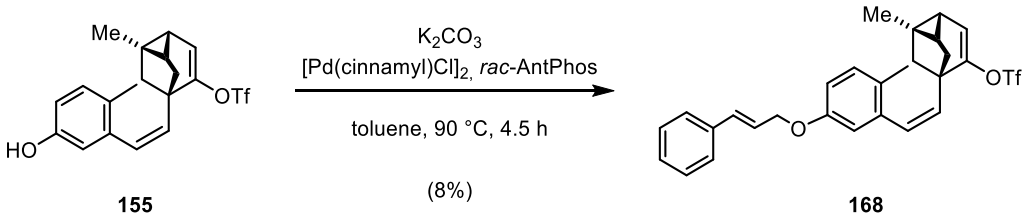
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3034, 2929, 2867, 2741, 1710, 1469, 1449, 1401, 1336, 1306, 1288, 1269, 1159, 1129, 1080, 1004 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00 (d, *J* = 9.0 Hz 1H), 6.66 (m, 2H), 6.60 (d, *J* = 12.2 Hz, 1H), 5.95 (d, *J* = 6.9 Hz, 1H), 5.86 (d, *J* = 12.1 Hz, 1H), 4.53 (s, 1H), 2.16 (s, 3H), 1.58 (d, *J* = 1.6 Hz, 1H), 1.44 (t, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 11.6 Hz 1H), 1.25–1.21 (m, 1H), 1.19 (s, 3H), 1.04 (d, *J* = 11.7 Hz, 1H), 0.99 (d, *J* = 11.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.2, 147.0, 138.8, 132.0, 130.6, 128.5, 128.2, 120.4, 115.5, 114.2, 113.2, 47.9, 41.4, 35.8, 24.7, 23.6, 21.8, 19.2, 17.8.

HRMS (EI): calcd for $(C_{19}H_{19}F_3O_4S)^+$: 400.0951, found: 400.0947.

Cinnamyl ether 168



In a Schlenk-tube a solution of **155** (10.0 mg, 25 µmol, 1 equiv) in degassed toluene (1 mL) was added to a mixture of potassium carbonate (5.18 mg, 37.5 µmol, 1.5 equiv), ligand *rac*-AntPhos (0.215 mg, 0.5 µmol, 0.02 equiv) and palladium(π-cinnamyl) chloride dimer (0.13 mg, 0.25 µmol, 0.01 equiv). The reaction vessel was heated in a preheated oil bath to 90 °C for 4.5 h. The reaction mixture was allowed to cool to 24 °C. Ethyl acetate (5 mL) was added. The reaction mixture was filtrated through celite. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **168** (1 mg, 8%).

TLC (10% ethyl acetate in hexanes): $R_f = 0.31$ (CAM, UV).

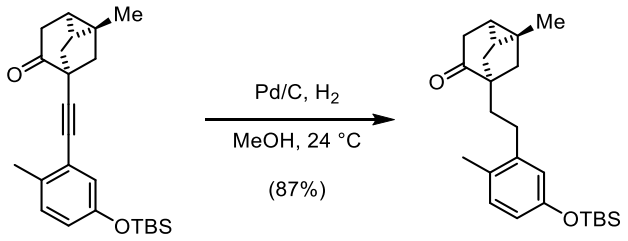
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2926, 1604, 1573, 1495, 1449, 1417, 1300, 1246, 1207, 1140, 1118, 1097, 1056, 1021 cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.24 (tt, *J* = 7.3, 1.1 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.64 (d, *J* = 12.1 Hz, 1H), 6.38 (dt, *J* = 15.9, 5.6 Hz, 1H), 5.85 (d, *J* = 12.1 Hz, 1H), 5.82 (d, *J* = 6.9 Hz, 1H), 4.65 (dd, *J* = 5.6, 1.6 Hz, 2H), 2.17 (s, 3H), 1.57–1.55 (m, 1H), 1.35 (t, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 11.8 Hz 1H), 1.18 (m, 1H), 1.16 (s, 3H), 1.02 (d, *J* = 11.8 Hz, 1H), 0.97 (d, *J* = 11.8 Hz, 1H).

^{13}C NMR (200 MHz, $CDCl_3$) δ = 156.3, 146.9, 138.6, 136.7, 132.7, 132.5, 130.4, 128.7, 128.5, 128.2, 127.9, 126.7, 124.8, 118.8 (d, *J* = 321.3 Hz), 114.9, 114.2, 113.3, 68.5, 47.9, 41.5, 35.8, 24.7, 23.6, 21.9, 19.2, 17.8.

HRMS (EI): calcd for $(C_{28}H_{27}F_3O_4S)^+$: 516.1577, found: 516.1568.

Alkane 151



133 **151**

To a solution of **133** (100 mg, 0.263 mmol, 1 equiv) in methanol (15 mL) was added palladium on carbon (29.5 mg, 27.7 µmol, 0.1 equiv) was added. Hydrogen was passed through the reaction mixture for 15 min. The mixture was filtrated through celite. The filtrate was washed with diethyl ether. The washed solution was concentrated to yield alkane **151** (88.3 mg, 87%) as a light yellow oil.

TLC (100% toluene): $R_f = 0.41$ (CAM, UV).

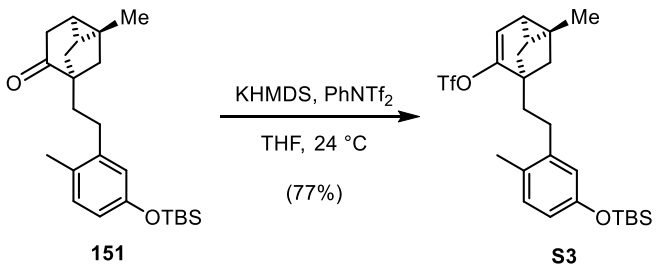
IR (Diamond-ATR, neat) $\tilde{\upsilon}_{max}$: 3026, 2953, 2928, 2858, 1717, 1607, 1576, 1498, 1271, 1463, 1406, 1361, 1289, 1260, 1207, 1161, 1116, 1099, 1077, 1054, 1000 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.95 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 6.56 (dd, *J* = 8.1, 2.6 Hz, 1H), 2.69–2.52 (m, 2H), 2.53–2.43 (m, 2H), 2.25 (s, 3H), 1.99 (dd, *J* = 12.7, 3.4 Hz, 1H), 1.83 (d, *J* = 3.4 Hz, 1H), 1.83–1.76 (m, 2H), 1.70–1.60 (m, 2H), 1.29 (s, 3H), 1.21 (dd, *J* = 7.6, 3.3 Hz, 1H), 0.97 (s, 9H), 0.93 (dd, *J* = 7.5, 2.6 Hz, 1H), 0.17 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.5, 153.8, 142.4, 130.9, 128.7, 120.6, 117.3, 55.1, 40.0, 34.9, 34.4, 33.8, 29.8, 25.9, 23.0, 22.4, 19.6, 18.5, 18.4, 18.1, −4.2.

HRMS (EI): calcd for ($C_{24}H_{36}O_2Si$): 384.2479, found: 384.2477.

Vinyl triflate S3



151 **S3**

To a solution of **151** (88.3 mg, 0.23 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added dropwise a solution of potassium bis(trimethylsilyl)amide (1 mol/L in tetrahydrofuran, 320 µL, 0.32 mmol, 1.4 equiv) at −78 °C. The reaction mixture was stirred at for 40 min at −78 °C. *N*-phenyl bis(trifluoromethanesulfonimide) (115 mg, 0.32 mmol, 1.4 equiv) was added. The mixture was stirred for 35 min at the same temperature. The reaction mixture was allowed to warm to 0 °C and was stirred for 45 min. The reaction mixture was allowed to warm to 24 °C and was stirred for 16 h. The mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was diluted with aqueous sodium chloride solution (5 mL) and was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **S3** (91 mg, 77%) as light yellow oil.

TLC (5% ethyl acetate in hexanes): $R_f = 0.55$ (CAM, UV).

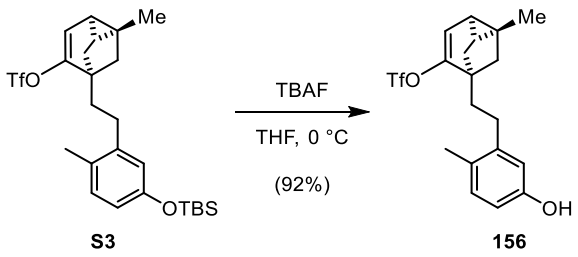
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3056, 2958, 2926, 2854, 1737, 1610, 1499, 1465, 1417, 1378, 1330, 1265, 1214, 1162, 1142, 1105, 1059 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 2.63 (dd, *J* = 10.5, 6.9 Hz, 2H), 2.23 (s, 3H), 1.91–1.81 (m, 2H), 1.77 (dd, *J* = 11.5, 2.2 Hz, 1H), 1.53 (t, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 11.5 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 1H), 1.33 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 1H), 1.12 (d, *J* = 6.5 Hz, 1H), 0.98 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0, 148.8, 141.5, 131.0, 128.3, 120.5, 118.7 (d, *J* = 320.5 Hz), 117.7, 113.0, 46.1, 41.0, 35.5, 33.4, 29.8, 25.9, 25.3, 23.9, 22.2, 18.5, 18.4, 18.0, −4.4.

HRMS (EI): calcd for ($C_{25}H_{35}F_3O_4SSi$): 516.1972, found: 516.1969.

Phenol 156



S3 **156**

To a solution of **S3** (85.0 mg, 165 μmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise tetrabutylammonium fluoride (1 M in tetrahydrofuran, 0.247 mL, 247 μmol, 1.5 equiv) at 0 °C. The reaction mixture was allowed to warm to 24 °C. The mixture was diluted with aqueous ammonium chloride (20 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with water (30 mL). The washed solution was dried over sodium sulfate. The dried solution was filtrated and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield phenol **156** (61 mg, 92%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): $R_f = 0.43$ (CAM, UV).

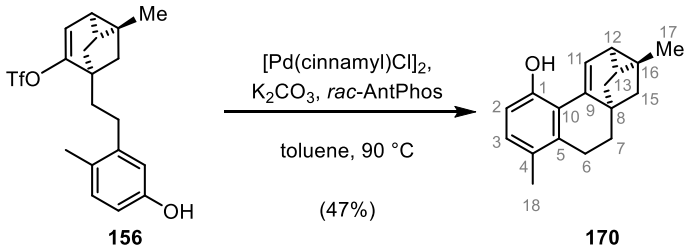
IR (Diamond-ATR, neat) $\tilde{\nu}$max: 3374, 3039, 2929, 2867, 1646, 1610, 1589, 1502, 1462, 1414, 1360, 1293, 1245, 1205, 1139, 1121, 1101, 1059, 1008 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 2.7 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.8 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 4.58 (s, 1H), 2.65 (dd, *J* = 10.7, 6.7 Hz, 2H), 2.23 (s, 3H), 1.92–1.83 (m, 2H), 1.77 (dd, *J* = 11.5, 1.3 Hz, 1H), 1.54 (t, *J* = 6.8 Hz, 1H), 1.46 (dd, *J* = 11.5, 1.2 Hz, 1H), 1.39 (dd, *J* = 7.1, 2.1 Hz, 1H), 1.33 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.9, 148.9, 141.9, 131.3, 127.8, 118.8 (q, *J* = 320.6 Hz), 115.76, 113.1, 112.9, 46.2, 41.1, 35.6, 33.6, 29.8, 25.3, 23.9, 22.2, 18.4, 18.0.

HRMS (EI): calcd for $(C_{19}H_{21}F_3O_4S)^+$: 402.1107, found: 402.1111.

Phenol 170



In a Schlenk-tube potassium carbonate (5.18 mg, 37.5 µmol, 1.5 equiv) was added to a solution of phenol **156** (10.1 mg, 25 µmol, 1 equiv) in degassed toluene (1 mL). To the mixture was added stock solution of ligand *rac*-AntPhos (***rac*-121**) (0.185 mg, 0.5 µmol, 0.02 equiv) and palladium(π-cinnamyl) chloride dimer (0.13 mg, 0.25 µmol, 0.01 equiv) in degassed toluene (0.1 mL). The reaction vessel was heated in a preheated oil bath to 90 °C for 16 h. The reaction mixture was cooled to 24 °C. Ethyl acetate (5 mL) was added. The mixture was filtrated through celite. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield ortho-cyclised product **170** (3.0 mg, 47%).

TLC (20% ethyl acetate in hexanes): $R_f = 0.45$ (CAM, UV).

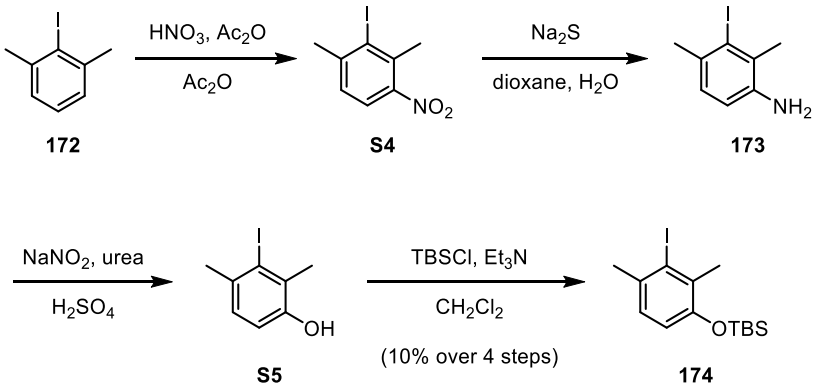
IR (Diamond-ATR, neat) $\tilde{\nu}$max: 3518, 3030, 2920, 2857, 1710, 1603, 1585, 1476, 1460, 1436, 1418, 1380, 1320, 1260, 1244, 1207, 1172, 1140, 1095, 1018 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (d, *J* = 8.2 Hz, 1H, H-3), 6.67 (d, *J* = 8.1 Hz, 1H, H-2), 6.60 (d, *J* = 5.9 Hz, 1H, H-11), 5.59 (s, 1H, OH), 2.59 (t, *J* = 5.8 Hz, 2H, H-6), 2.19 (s, 3H, H-18), 1.69 (t, *J* = 5.9 Hz, 2H, H-7), 1.66–1.61 (m, 2H, H-12, H-14a), 1.37 (s, 1H, H-13), 1.34 (s, 3H, H-17), 1.34 (m, 1H, H-15a), 1.06 (s, 1H, H-14b), 1.04 (s, 1H, H-15b).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.8 (C-1), 138.9 (C-5), 137.3 (C-9), 128.1 (C-3), 126.7 (C-4), 120.5 (C-10), 119.5 (C-11), 113.3 (C-2), 44.0 (C-8), 41.1 (C-15), 35.3 (C-14), 32.4 (C-7), 25.6 (C-6), 25.4 (C12), 24.7 (C-16), 23.8 (C-13), 19.4 (C-18), 18.7 (C-17).

HRMS (EI): calcd for $(C_{18}H_{20}O)^+$: 252.1509, found: 252.1505.

Silyl ether 174



Fuming nitric acid (100%, 1.1 mL, 25.9 mmol, 2.40 equiv) was added dropwise to acetic anhydride (24 mL) at 0 °C. 2-Iodo-1,3-dimethylbenzene (**172**) (1.55 mL, 10.8 mmol, 1 equiv) was added dropwise and the reaction mixture was stirred 30 min at 0 °C. The reaction mixture was heated to 50 °C and stirred for 2 h. The reaction mixture was cooled to 24 °C and then added to ice water (100 mL) and stirred for 1 h. Dichloromethane (100 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with aqueous sodium hydroxide solution (2 M, 2 × 100 mL) and water (100 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford **S4** as a red oil which was used without further purification for the next step.

To a solution of crude **S4** in dioxane (150 mL) and water (150 mL) was added sodium sulfide (4.21 g, 32.4 mmol, 3.00 equiv) and the mixture was heated to 60 °C. After16 h, dichloromethane (200 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with water (200 mL) saturated aqueous sodium chloride solution (200 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford **173** as a yellow oil which was used without further purification for the next step.

To a solution of crude **173** in sulfuric acid (0.25 M, 60 mL) was added sodium nitrite (0.45 g, 6.56 mmol, 1.50 equiv) at 0 °C. After 2 h, urea (0.13 g, 2.19 mmol, 0.50 equiv) was added and the reaction mixture was allowed to warm to 24 °C. After 1.5 h, more sulfuric acid (0.5 M, 60 mL) was added and the mixture was heated to 110 °C. After 1 h, ethyl acetate (200 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water (200 mL) saturated aqueous sodium chloride solution (200 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated the dark red solution was filtered through a plug of silica.

The filtrate was concentrated to yield **S5** as a red solid that was directly used in the following step without further purification.

To a solution of crude **S5** (assumed: 0.65 g, 2.62 mmol, 1 equiv) in dichloromethane (5 mL) was added triethylamine (0.44 mL, 3.14 mmol, 1.20 equiv) and *tert*-butyldimethylsilyl chloride (474 mg, 3.14 mmol, 1.20 equiv). The reaction mixture was stirred for 6.5 h at 24 °C. Water (20 mL) and dichloromethane (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (20 mL) saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **174** (949 mg, 10% over 4 steps) as a yellow amorphous solid.

TLC (10% ethyl acetate in hexanes): $R_f = 0.66$ (CAM, UV).

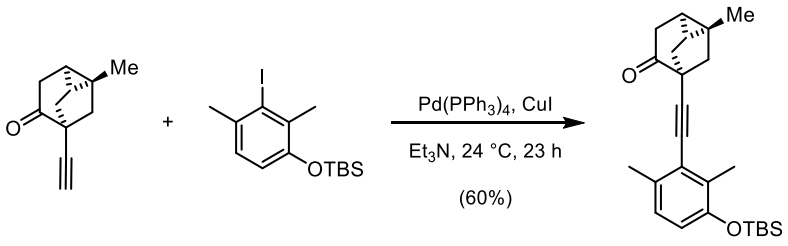
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2929, 2857, 1585, 1562, 1464, 1393, 1272, 1253, 1174, 1137 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.96 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 2.40 (s, 3H), 2.40 (s, 3H) 1.01 (s, 9H), 0.20 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 150.6, 134.5, 132.8, 126.7, 118.0, 109.5, 29.2, 25.8, 23.3, 18.2, –4.2.

HRMS (EI): calcd for $(C_{14}H_{23}O^{127}I^{28}Si)^+$: 362.0557, found: 362.0559.

Alkyne *ent*-175



***ent*-134** **174** ***ent*-175**

To a suspension of tetrakis(triphenylphosphine)palladium (16 mg, 23.1 μmol, 0.01 equiv) and cuprous iodide (2.0 mg, 11.5 μmol, 0.005 equiv) in triethylamine (degassed, 16 mL) in a Schlenk tube was added a solution of **174** (1.0 g, 2.77 mmol, 1.20 equiv) and alkyne ***ent*-134** (370 mg,

2.31 mmol, 1 equiv) in triethylamine (degassed, 4 mL). The reaction mixture was stirred at 24 °C for 23 h. Ethyl acetate (30 mL) and water (20 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5–10% ethyl acetate in hexanes) to yield ***ent*-175** (544 mg, 60%) as a yellow oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.37 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2929, 2858, 1731, 1474, 1278, 1254, 1170, 1114, 1072 cm^{-1}.

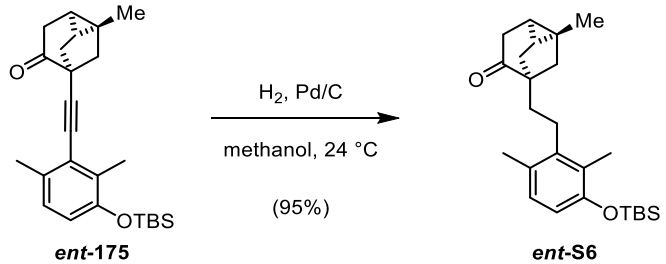
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.85 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 2.78 – 2.59 (m, 2H), 2.46 (dd, *J* = 12.9, 3.4 Hz, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 2.26 – 2.15 (m, 3H), 1.32 (s, 3H), 1.29 (dd, *J* = 7.7, 3.4 Hz, 1H), 1.00 (s, 9H), 0.98 – 0.94 (m, 1H), 0.16 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.7, 151.5, 133.2, 131.2, 126.8, 124.3, 118.1, 95.0, 83.5, 52.2, 42.3, 37.4, 33.5, 26.0, 22.8, 22.1, 20.7, 19.2, 18.4, 17.5, 15.2, –4.1.

HRMS (EI): calcd for $(C_{25}H_{34}O_2Si)^+$: 394.2323; found: 394.2322.

$[\alpha]_D^{20}$ = –4.3 (c = 0.23, CH_2Cl_2).

Alkane *ent*-S6



***ent*-175** ***ent*-S6**

To a solution of ***ent*-175** (544 mg, 1.38 mmol, 1 equiv) in methanol (12 mL) was added palladium on carbon (587 mg, 0.28 mmol, 0.2 equiv). Hydrogen was passed through the reaction mixture for 15 min. The mixture was filtrated through celite. The filtrate was washed with diethyl ether. The washed solution was concentrated to yield ***ent*-S6** (524 mg, 95%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.34 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955, 2928, 2857, 1718, 1594, 1474, 1268, 1253, 1076 cm^{-1}.

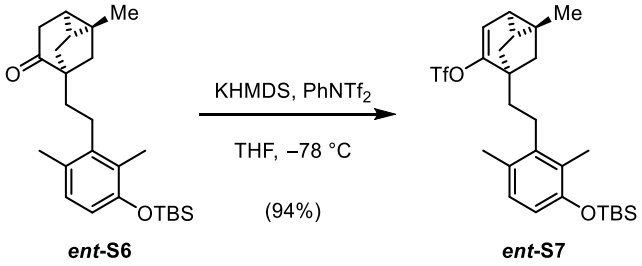
^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.82 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 2.67 – 2.54 (m, 4H), 2.28 (s, 3H), 2.23 (s, 3H), 2.01 (dd, *J* = 12.7, 3.4 Hz, 1H), 1.87 – 1.76 (m, 3H), 1.58 – 1.51 (m, 2H), 1.30 (s, 3H), 1.22 (dd, *J* = 7.5, 3.3 Hz, 1H), 1.01 (s, 9H), 0.95 – 0.91 (m, 1H), 0.19 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 212.4, 151.9, 140.6, 128.5, 127.4, 127.0, 115.8, 55.0, 39.8, 34.7, 34.2, 32.1, 26.4, 25.8, 22.8, 22.2, 19.4, 19.3, 18.3, 17.9, 12.4, –4.2.

HRMS (EI): calcd for $(C_{25}H_{38}O_2Si)^+$: 398.2636; found: 398.2633.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +8.5 (c = 1.08, CH_2Cl_2).

Vinyl triflate *ent*-S7



***ent*-S6** ***ent*-S7**

To a solution of ***ent*-S6** (440 mg, 1.10 mmol, 1 equiv) in tetrahydrofuran (12 mL) was added dropwise a solution of potassium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.43 mL, 1.43 mmol, 1.30 equiv) at –78 °C. After 1 h, *N*-phenylbis(trifluoromethanesulfonimide) (443 mg, 1.21 mmol, 1.10 equiv) was added. After 2 h, the reaction mixture was warmed to 0°C and stirred for 1.5 h. Water (100 mL) and diethyl ether (40 mL) and saturated aqueous sodium chloride solution (40 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 80 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield ***ent*-S7** (550 mg, 94%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.42 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2927, 2859, 1629, 1594, 1475, 1418, 1273, 1248, 1208, 1141, 1083 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.84 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 2.75 – 2.66 (m, 2H), 2.26 (s, 3H), 2.19 (s, 3H), 1.86 (dd, *J* = 11.5, 2.2 Hz, 1H), 1.82 – 1.70 (m, 2H), 1.52 – 1.55 (m, 2H), 1.39 (dd, *J* = 6.9, 2.0 Hz, 1H), 1.34 (s, 3H), 1.12 (m, 2H), 1.01 (s, 9H), 0.20 (s, 6H).

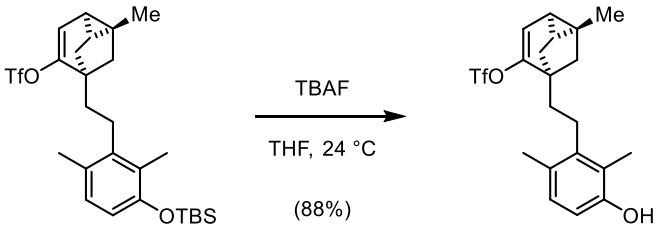
^{13}C NMR (150 MHz, $CDCl_3$) δ = 152.1, 149.2, 143.5, 140.2, 128.5, 127.8, 127.1, 116.3, 112.2, 46.3, 40.5, 35.0, 31.0, 26.5, 26.0, 25.2, 23.9, 22.1, 19.6, 18.4, 18.0, 12.6, –4.1 (signals for CF_3 group not visible).

^{19}F NMR (565 MHz, $CDCl_3$) δ = –72.9.

HRMS (ESI): calcd for $(C_{26}H_{38}O_4SSi)^+$ $[M+H]^+$: 531.221; found: 531.221.

$[\alpha]_D^{20}$ = +3.6 (c = 0.60, CH_2Cl_2).

Phenol *ent*-127



***ent*-S7** ***ent*-127**

To a solution of ***ent*-S7** (550 mg, 1.04 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added dropwise tetrabutylammonium fluoride solution (1 M in tetrahydrofuran, 1.55 mL, 1.55 mmol, 1.50 equiv) at 24 °C and the reaction mixture was stirred for 19 h. Saturated aqueous sodium bicarbonate solution (20 mL) and diethyl ether (20 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (100 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The

residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield ***ent*-127** (380 mg, 88%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.43 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 3552, 3282, 2928, 1596, 1498, 1414, 1201, 1137, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.02 (d, *J* = 6.8 Hz, 1H), 4.48 (s, 1H), 2.73 (dd, *J* = 10.5, 7.0 Hz, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 1.86 (dd, *J* = 11.3, 2.2 Hz, 1H), 1.77 (dt, *J* = 9.3, 6.7 Hz, 2H), 1.54 (m, 2H), 1.39 (dd, *J* = 7.2, 2.0 Hz, 1H), 1.34 (s, 3H), 1.13 (m, 2H).

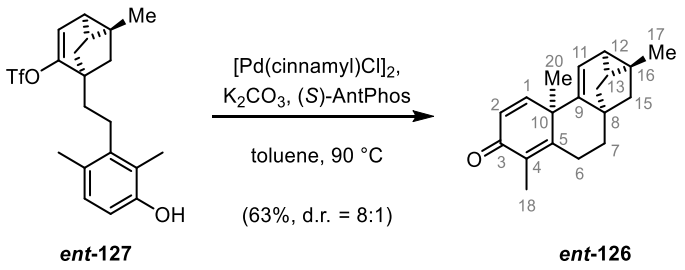
^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.1, 149.1, 140.2, 128.3, 128.2, 122.2, 112.6, 112.3, 46.2, 40.5, 35.1, 31.2, 26.3, 25.2, 23.9, 22.0, 19.6, 18.0, 11.6 (signals for CF_3 group not visible).

^{19}F NMR (377 MHz, $CDCl_3$) δ = –73.2.

HRMS (EI): calcd for $(C_{20}H_{23}O_4F_3SNa)^+$ $[M+Na]^+$: 439.116; found: 439,116.

$[\alpha]_D^{20}$ = +10.7 (c = 0.70, CH_2Cl_2).

Dienone *ent*-126



***ent*-127** ***ent*-126**

Potassium carbonate (119 mg, 0.86 mmol, 1.50 equiv), palladium(π-cinnamyl) chloride dimer (75 mg, 0.14 mmol, 0.25 equiv) and (*S*)-AntPhos (26 mg, 0.07 mmol, 0.12 equiv) were added to a dry Schlenk flask and the flask was evacuated and back-filled with argon three times. A solution of ***ent*-127** (240 mg, 0.58 mmol, 1 equiv) in degassed toluene (15 mL) was added. The orange suspension was heated to 90 °C. After 18 h, heating was ceased and the green suspension was allowed to cool to 24 °C. Dichloromethane (5 mL) was added and the mixture was filtered through a short pad of celite. The filter cake was rinsed with dichloromethane (30 mL) and the filtrate was

concentrated. The crude product was purified by flash column chromatography on silica gel (0–5% ethyl acetate in hexanes) to yield ***ent*-126** (97 mg, 63%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.50 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ 2954, 2918, 2850, 1738, 1658, 1614, 1459, 1377, 1260, 1182, 1088 cm^{-1}.

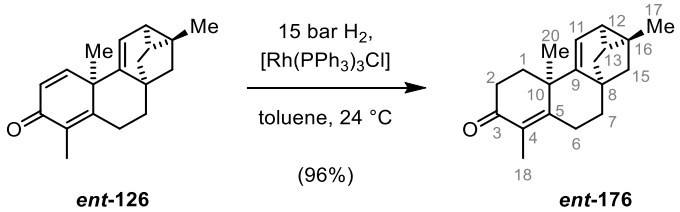
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 10.0 Hz, 1H, H-1), 6.22 (d, *J* = 10.0 Hz, 1H, H-2), 5.86 (d, *J* = 5.9 Hz, 1H, H-11), 2.73 – 2.56 (m, 1H, H-6), 2.40 (m, 1H, H-7a), 1.83 (s, 3H, H-18), 1.74 – 1.65 (m, 2H, H-7b, H-14a), 1.46 – 1.38 (m, 4H, H-12, H-20), 1.31 – 1.17 (m, 4H, H-17, H-13), 1.10 (d, *J* = 11.0 Hz, 1H, H-15a), 0.85 (d, *J* = 11.1 Hz, 1H, H-14b), 0.74 (d, *J* = 11.0 Hz, 1H, H-15a).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 185.2 (C-3), 159.0 (C-5), 153.9 (C-1), 142.4 (C-9), 130.1 (C-4), 125.5 (C-2), 117.2 (C-11), 43.8 (C-10), 42.5 (C-8), 41.6 (C-15), 36.8 (C-14), 29.8 (C-7), 29.7 (C-20), 27.1 (C-6), 24.5 (C-16), 24.1 (C-12), 22.9 (C-13), 18.4 (C-17), 10.7 (C-18).

HRMS (EI): calcd for $(C_{19}H_{22}O)^+$: 266.1665; found: 266.1666.

$[\alpha]_D^{20}$ = +228.9 (c = 0.43, CH_2Cl_2).

Enone *ent*-176



***ent*-126** **ent-176**

To a solution of ***ent*-126** (70 mg, 0.26 mmol, 1 equiv) in toluene (20 mL) was added tris(triphenylphosphine)rhodium(I) chloride (49 mg, 0.05 mmol, 0.20 equiv). The open flask was placed in a miniclave under argon atmosphere. The miniclave was closed and flushed with hydrogen three times. Hydrogen pressure (15 bar) was applied. The reaction mixture was stirred under hydrogen atmosphere at 24 °C. After 14 h, the hydrogen pressure was released, the miniclave was opened and the flask was removed. The solution was concentrated. The crude product was

purified by flash column chromatography on silica gel (5–10% ethyl acetate in hexanes) to yield ***ent*-176** (68 mg, 96%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.43 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ 2923, 2851, 1717, 1664, 1458, 1180 cm^{-1}.

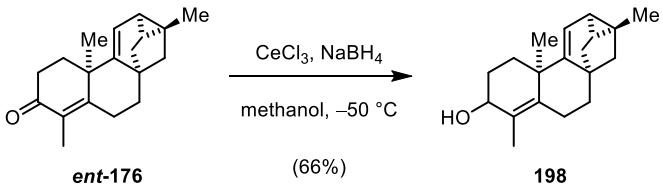
^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.78 (d, *J* = 6.0 Hz, 1H, H-11), 2.62 (m, 2H, H-6a, H-2a), 2.47 (ddd, *J* = 17.7, 4.9, 2.5 Hz, 1H, H-2b), 2.41 – 2.33 (m, 1H, H-6b), 2.21 (td, *J* = 13.6, 4.6 Hz, 1H, H-7a), 2.10 (ddd, *J* = 12.9, 5.2, 2.5 Hz, 1H, H-1a), 1.98 (dddd, *J* = 14.8, 13.0, 4.9, 0.9 Hz, 1H, H-1b), 1.70 (t, *J* = 1.3 Hz, 3H, H-18), 1.66 – 1.61 (m, 2H, H-7b, H-14a), 1.49 – 1.44 (m, 1H, H-12), 1.35 (s, 3H, H-20), 1.27 (s, 3H, H-17), 1.19 (dd, *J* = 7.0, 2.2 Hz, 1H, H-13), 1.12 (dd, *J* = 10.9, 0.9 Hz, 1H, H-15a), 0.89 (d, *J* = 10.8 Hz, 1H, H-15b), 0.78 (d, *J* = 11.1 Hz, 1H, H-14b).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 198.2 (C-3), 162.8 (C-5), 146.9 (C-9), 129.2 (C-4), 115.4 (C-11), 42.6 (C-16), 41.7 (C-15), 40.0 (C-10), 36.9 (C-14), 35.0 (C-1), 33.8 (C-2), 29.2 (C-7), 28.6 (C-20), 28.1 (C-6), 24.2 (C-12), 24.1 (C-8), 22.8 (C-13), 18.7 (C-17), 10.9 (C-18).

HRMS (EI): calcd for $(C_{19}H_{24}O)^+$: 268.1822; found: 268.1817.

$[\alpha]_D^{20}$ = +22.1 (c = 0.41, CH_2Cl_2).

Allyl alcohol *ent*-176



***ent*-176** **198**

To a solution of ***ent*-176** (15 mg, 0.06 mmol, 1 equiv) in methanol (1 mL) was added cerium(III) chloride (28 mg, 0.11 mmol, 2.00 equiv). The mixture was cooled to –50 °C and sodium borohydride (4.3 mg, 0.11 mmol, 2.00 equiv) was added. After 15 min, water (10 mL) and ethyl acetate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium

sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to yield **198** (10 mg, 66%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.19 (CAM).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ 3395, 2923, 2853, 2361, 1631, 1452, 1414, 1357, 1110 cm^{-1}.

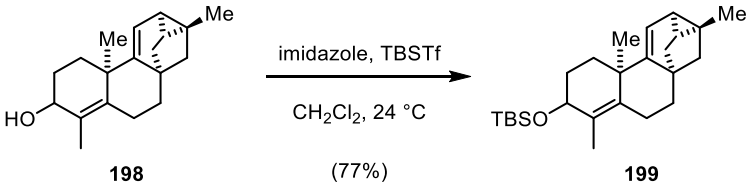
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.63 (d, *J* = 5.9 Hz, 1H), 3.99 (br s, 1H), 2.40 – 2.25 (m, 1H), 2.20 (d, *J* = 10.3 Hz, 1H), 2.07 (m, 1H), 1.81 – 1.46 (m, 5H), 1.62 (s, 3H) 1.41 (m, 2H), 1.25 (s, 6H), 1.12 (m, 1H), 1.05 (d, *J* = 10.9 Hz, 1H), 0.83 (d, *J* = 10.9 Hz, 1H), 0.75 (d, *J* = 11.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.7, 137.6, 127.7, 113.3, 71.4, 42.8, 41.7, 38.2, 37.0, 34.3, 31.1, 29.9, 29.6, 25.8, 24.0, 24.0, 22.7, 18.8, 14.7.

HRMS (ESI): not found

$[\alpha]_D^{20}$ = +16.7 (c = 0.41, CH_2Cl_2).

Silyl ether 199



198 **199**

To a solution of **198** (10 mg, 0.04 mmol, 1 equiv) in dichloromethane (0.5 mL) was added imidazole (3.1 mg, 0.04 mmol, 1.20 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (11 µL, 0.04 mmol, 1.20 equiv). After 5 h, water (10 mL) and dichloromethane (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to yield **199** (11 mg, 77%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.61 (CAM).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ 2925, 2856, 1462, 1410, 1361, 1295, 1257, 1073, 1048, 1009 cm^{-1}.

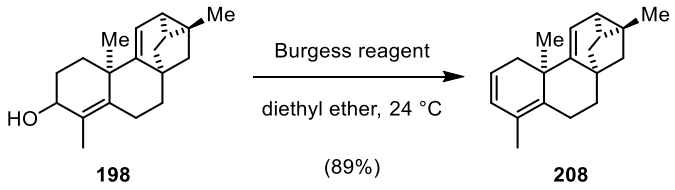
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.62 (d, *J* = 5.9 Hz, 1H), 4.04 (t, *J* = 8.0 Hz, 1H), 2.35 (m, 1H), 2.25 – 2.15 (m, 2H), 2.00 – 1.88 (m, 1H), 1.82 – 1.67 (m, 2H), 1.62 – 1.56 (m, 2H), 1.54 (s, 3H), 1.52 – 1.46 (m, 1H), 1.40 (t, *J* = 6.5 Hz, 1H), 1.25 (s, 6H), 1.12 (dd, *J* = 7.1, 2.2 Hz, 1H), 1.05 (d, *J* = 10.8 Hz, 1H), 0.91 (s, 9H), 0.83 (d, *J* = 10.9 Hz, 1H), 0.74 (d, *J* = 11.1 Hz, 1H), 0.08 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.3, 136.2, 128.8, 113.0, 72.2, 42.8, 41.7, 38.1, 37.0, 34.6, 31.1, 30.0, 26.2, 26.0, 24.0, 23.9, 22.7, 18.8, 18.4, 15.0, –3.9, –4.5.

HRMS (EI): calcd for $(C_{25}H_{40}OSi)^+$: 384.2843; found: 384.2840.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +7.5 (c = 0.08, CH_2Cl_2).

Diene 208



To a solution of **198** (3.0 mg, 0.01 mmol, 1 equiv) in diethyl ether (0.5 mL) was added (methoxycarbonylsulfamoyl)triethylammonium hydroxide (6.8 mg, 0.03 mmol, 2.50 equiv). After 3 h, the solvent was removed and the crude product was purified by flash column chromatography on silica gel (1% ethyl acetate in cyclohexane) to yield **208** (2.5 mg, 89%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.66 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ 2921, 2851, 1733, 1671, 1458, 13761179, 1080 cm^{-1}.

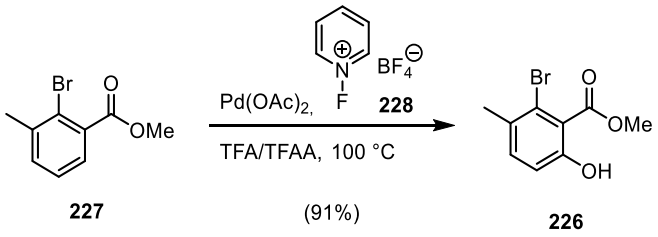
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 (dd, *J* = 7.6, 2.1 Hz, 1H), 5.72 (d, *J* = 5.9 Hz, 1H), 5.59 (d, *J* = 6.0 Hz, 1H), 2.60 (d, *J* = 16.6 Hz, 1H), 2.27 – 2.11 (m, 3H), 1.95 – 1.87 (m, 1H), 1.78 (s, 3H), 1.69 – 1.63 (m, 2H), 1.41 (t, *J* = 6.5 Hz, 1H), 1.25 (s, 6H), 1.13 – 1.07 (m, 1H), 0.90 – 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 141.3, 131.2, 125.0, 119.9, 112.3, 43.6, 43.4, 37.4, 36.7, 33.4, 32.8, 25.3, 23.8, 23.7, 22.5, 22.4, 20.1, 18.7, 1.2.

HRMS (EI): calcd for $(C_{20}H_{29}O)^+$ $[M+MeOH+H]^+$: 285.221; found: 285.129.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +95.5 (c = 0.12, CH_2Cl_2).

Phenol 226



227 **226**

A suspension of **227** (2.01 g, 8.77 mmol, 1 equiv), 1-fluoropyridinium tetrafluoroborate (**228**) (3.34 g, 17.5 mmol, 2.00 equiv) and palladium(II) acetate (296 mg, 1.32 mmol, 0.150 equiv) in a mixture of trifluoroacetic acid and trifluoroacetic anhydride (9:1, 90 mL) was heated to 100 °C in a pressure flask. After 16 h, the reaction mixture was diluted in dichloromethane (300 mL) and saturated aqueous sodium bicarbonate solution was added slowly over 7 h (1.5 L). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to give **226** (1.95 g, 91%) as a yellow solid.

TLC (20% ethyl acetate in hexanes): R_f = 0.29 (CAM, UV).

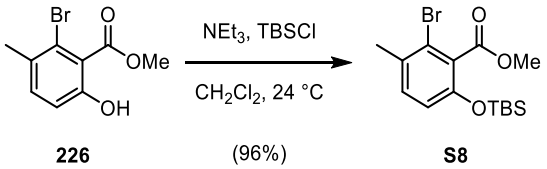
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3397, 2953, 1666, 1583, 1459, 1438, 1281, 1213, 1018 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 3.98 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 170.1, 159.9, 135.7, 131.2, 123.9, 116.8, 115.4, 52.5, 24.0.

HRMS (ESI): calcd for $(C_9H_9BrO_3K)^+$ $[M+K]^+$: 282.9367; found: 281.2753.

Silyl ether S8



226 **S8**

To a solution of **226** (133 mg, 0.543 mmol, 1 equiv) in dichloromethane (3 mL) was added triethylamine (0.226 mL, 1.63 mmol, 3.00 equiv) and *tert*-butyldimethylchlorosilane (100 mg,

0.651 mmol, 1.20 equiv) at 24 °C. After 15 h, the reaction mixture was diluted with dichloromethane (5 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (30 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **S8** (187 mg, 96%) as a yellow oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.35 (CAM, UV).

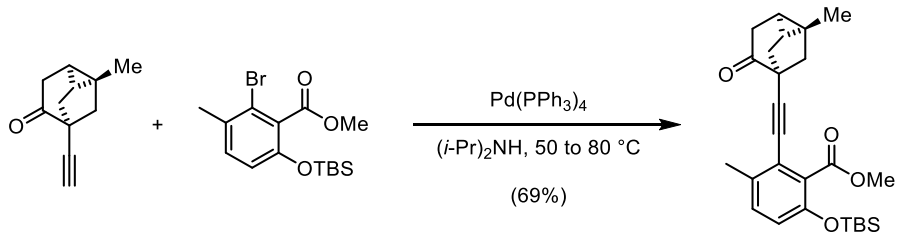
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 2952, 2859, 1739, 1598, 1469, 1280, 1224, 936, 781, 691.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.33 (s, 3H), 0.95 (s, 9H), 0.21 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.3, 151.1, 131.4, 130.9, 129.3, 121.5, 117.9, 52.6, 25.6, 22.3, 18.1, 4.3.

HRMS (ESI): calcd for $(C_{15}H_{23}BrO_3SiNa)^+$ $[M+Na]^+$: 381.0492; found: 381.0450.

Alkyne 229b



***rac*-134** **226** ***rac*-229b**

Tetrakis(triphenylphosphine)palladium (13.5 mg, 0.012, 0.050 equiv) was added to a Schlenk tube. A solution of **226** (100 mg, 0.278 mmol, 1.20 equiv) in degassed diisopropylamine (0.5 mL) was transferred to the Schlenk tube. The reaction mixture was heated to 50 °C. After 30 min, a solution of ***rac*-134** (37.2 mg, 0.232 mmol, 1 equiv) in diisopropylamine (0.5 mL) was added slowly and the reaction mixture was heated to 80 °C. After 20 h, the solution was allowed to cool to 24 °C and ethyl acetate (10 mL) and water (20 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (25 mL) and saturated aqueous sodium chloride solution (25 mL) and dried over sodium

sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **229b** (70.2 mg, 69%) as a yellow oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.15 (CAM, UV).

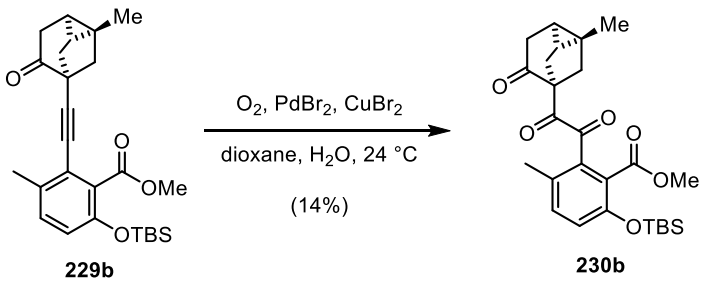
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2929, 2859, 1731, 1575, 1473, 1286, 1249, 1204, 1102, 839, cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.04 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 2.66 (qd, *J* = 2.7, 20.4 Hz, 2H), 2.44 (dd, *J* = 3.5, 12.9 Hz, 1H), 2.35 (s, 3H), 2.16 (m, 3H), 1.29 (s, 3H), 1.27 (dd, *J* = 3.5, 7.6 Hz, 1H), 0.95 (s, 10H), 0.17 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 204.9, 168.0, 150.0, 133.4, 131.0, 129.3, 121.5, 119.5, 94.6, 81.6, 52.3, 51.9, 42.0, 37.0, 33.4, 25.7, 22.8, 21.9, 20.0, 19.1, 18.2, 17.3, –4.3.

HRMS (ESI): calcd for $(C_{26}H_{34}O_4SiNa)^+$ $[M+Na]^+$: 461.2118; found: 461.2069.

Diketone 230b



229b **230b**

To a solution of **229b** (10.0 mg, 0.02 mmol, 1 equiv) in dioxane (0.75 mL) and water (0.1 mL) was added palladium(II) bromide (0.6 mg, 2.28 μmol, 0.10 equiv) and cupric bromide (1.0 mg, 4.56 μmol, 0.20 equiv). The dark orange mixture was sparged with oxygen gas for 2 min, and stirring was then continued under oxygen atmosphere (1 atm, balloon) at 24 °C. After 22 h, the reaction mixture diluted with water (5 mL) and diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **230b** (1.5 mg, 14%) as a yellow oil.

TLC (10% ethyl acetate in cyclohexan): R_f = 0.41 (CAM).

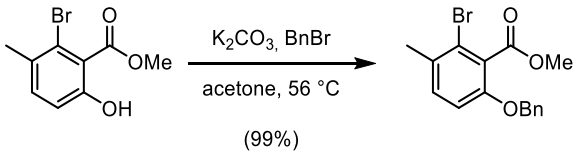
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2926, 2858, 1837, 1736, 1504, 1464, 1246, 1200, 1026 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.78 (s, 3H), 2.83 – 2.70 (m, 2H), 2.52 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.43 (m, 2H), 2.30 (d, *J* = 13.2 Hz, 1H), 2.21 (s, 3H), 1.34 (s, 3H), 1.04 (m, 1H), 0.99 (s, 9H), 0.96 (m, 1H), 0.20 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.2, 196.0, 191.0, 168.5, 153.0, 140.0, 135.8, 129.5, 122.5, 121.2, 64.8, 52.5, 36.7, 34.2, 31.7, 25.7, 22.0, 21.2, 19.3, 18.7, 18.4, 17.6, –4.2.

HRMS (ESI): calcd for $(C_{26}H_{34}O_6SiNa)^+$ $[M+Na]^+$: 493.202; found: 493.201.

Benzyl phenyl ether 247



226 **247**

To a solution of phenol **226** (287 mg, 1.17 mmol, 1 equiv) in acetone (12 mL) was added potassium carbonate (194 mg, 1.41 mmol, 1.20 equiv) and benzyl bromide (0.172 mL, 1.41 mmol, 1.20 equiv). The reaction mixture was stirred at 56 °C for 1.5 h, and then concentrated under reduced pressure to remove most acetone. The residue was diluted in ethyl acetate (15 mL) and aqueous hydrochloric acid solution (1 M, 20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to give **247** (388 mg, 99%) as a white solid.

TLC (5% ethyl acetate in hexanes): R_f = 0.16 (CAM, UV).

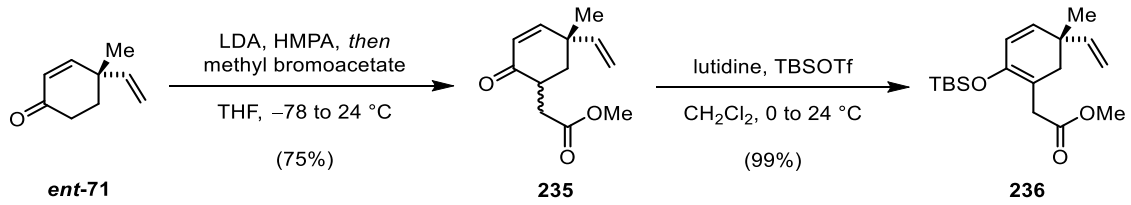
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950, 1735, 1596, 1452, 1381, 1225, 1107, 1013 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (m, 5H), 7.16 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.10 (s, 2H) 3.94 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 154.2, 136.5, 131.6, 130.9, 128.7, 128.1, 127.3, 127.1, 121.8, 112.1, 71.0, 52.8, 22.3.

HRMS (ESI): calcd for $(C_{16}H_{15}BrO_3Na)^+$ $[M + Na]^+$: 357.0097; found: 357.0046.

Triene 236



***ent*-71** **235** **236**

n-Butyllithium (2.51 M in *n*-hexane, 2.11 mL, 5.29 mmol, 1.20 equiv) was added dropwise to a solution of diisopropylamine (0.810 mL, 5.73 mmol, 1.30 equiv) in tetrahydrofuran (40 mL) at –78 °C. After 5 min, the cooling bath was removed, and the reaction mixture was allowed to warm to 24 °C. After 20 min, the solution was cooled to –78 °C and a solution of enone ***ent*-71** (600 mg, 4.41 mmol, 1 equiv) in tetrahydrofuran (6 mL) was added slowly. After 1 h, hexamethylphosphoric triamide (2.35 mL, 13.2 mmol, 3.00 equiv) was added and the solution was stirred for another hour at –78 °C. Methyl bromoacetate (2.14 mL, 22.0 mmol, 5.00 equiv) was added and the reaction mixture was allowed to warm to 24 °C and was stirred for 14 h. The solution was diluted with water (40 mL), aqueous hydrochloric acid solution (1 M, 30 mL) and ethyl acetate (60 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (2 × 20 mL) and saturated aqueous sodium chloride solution (2 × 15 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to yield **235** (688 mg, 75%) as a yellow oil.

A solution of enone **235** (120 mg, 0.58 mmol, 1 equiv) in dichloromethane (6 mL) was cooled to 0 °C. 2,6-Lutidine (0.20 mL, 1.73 mmol, 3.00 equiv) and triisopropylsilyl trifluoromethanesulfonate (0.20 mL, 0.86 mmol, 1.50 equiv) were added in sequence. The reaction mixture was allowed to warm to 24 °C and was stirred for 22 h. The solution was diluted with water (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (100% cyclohexane) to yield **236** (183 mg, 99%) as a yellow oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.57 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952, 2929, 2858, 1712, 1687, 1637, 1577, 1435, 1293, 1252, 1205 1055 cm^{-1}.

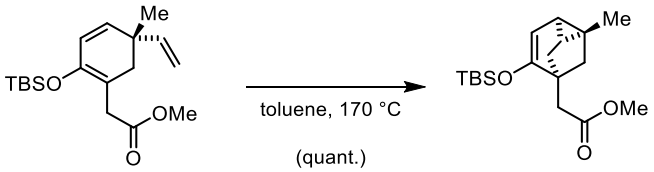
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.71 (d, *J* = 9.8 Hz, 1H), 5.52 (d, *J* = 9.8 Hz, 1H), 5.06 – 4.86 (m, 2H), 3.66 (s, 3H), 3.28 – 2.99 (m, 2H), 2.23 (q, *J* = 16.4 Hz, 2H), 1.11 (s, 3H), 0.94 (s, 9H), 0.11 (d, *J* = 3.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 145.1, 143.8, 135.6, 124.6, 111.3, 107.0, 51.7, 39.7, 38.1, 35.3, 25.9, 25.2, 18.2, –4.0.

HRMS (ESI): calcd for $(C_{18}H_{30}O_3Si)^+$: 322.1959; found: 322.1960.

$[\alpha]_D^{20}$ = +55.0 (c = 1.21, CH_2Cl_2).

Tricyclo-[3.2.1.0]oct-3-ene 237



236 **237**

A solution of **236** (170 mg, 0.53 mmol, 1 equiv) in toluene (11 mL) was sealed in a pressure tube and the solution was heated to 170 °C. After 13 h, the solution was cooled to 24 °C and concentrated to yield **237** (170 mg, quant.) as a yellow oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.58 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2947, 2930, 2853, 1741, 1722, 1689, 1637, 1462, 1280, 1217, 1160, 1050 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.90 (d, *J* = 6.4 Hz, 1H), 3.64 (s, 3H), 2.62 – 2.42 (m, 2H), 1.66 (ddd, *J* = 11.3, 2.5, 0.8 Hz, 1H), 1.35 (dd, *J* = 11.2, 1.1 Hz, 1H), 1.30 – 1.23 (m, 4H), 1.19 (d, *J* =

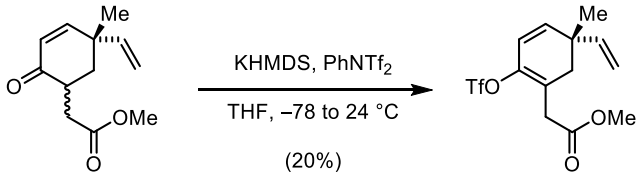
11.3 Hz, 1H), 1.12 (d, *J* = 11.3 Hz, 1H), 1.07 (dd, *J* = 7.1, 2.3 Hz, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 172.9, 153.8, 95.0, 51.2, 44.5, 41.1, 37.5, 35.5, 25.9, 23.3, 22.3, 21.5, 18.5, 18.3, –4.4, –4.6.

HRMS (ESI): calcd for $(C_{18}H_{30}O_3Si)^+$: 322.1959; found: 322.1957.

$[\alpha]_D^{20}$ = –8.9 (c = 0.30, CH_2Cl_2).

Vinyl triflate 243



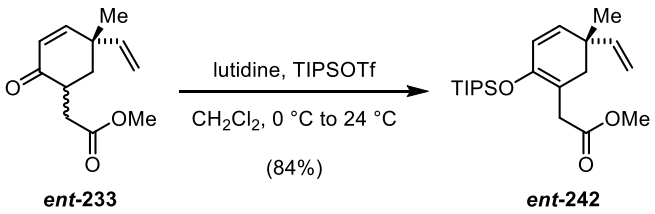
***rac*-233** ***rac*-243**

To a solution of ***rac*-233** (21 mg, 0.10 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise a solution of potassium bis(trimethylsilyl)amide (1 M, 141 µL, 0.14 mmol, 1.40 equiv) at –78°C. After 1 h, *N*-phenylbis(trifluoromethanesulfonimide) (50.4 mg, 0.14 mmol, 1.40 equiv) was added. The reaction mixture was allowed to warm to 24 °C and stirred for 14 h. Water (10 mL) and ethyl acetate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to yield **243** (7 mg, 20%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.36 (CAM, UV).

HRMS (ESI): calcd for $(C_{13}H_{14}O_5F_3S)^+$ $[M–H]^+$: 339.0509; found: 339.0504.

Triene 242



***ent*-233** ***ent*-242**

A solution of enone ***ent*-233** (688 mg, 3.30 mmol, 1 equiv) in dichloromethane (20 mL) was cooled to 0 °C. Dimethylpyridine (1.96 mL, 16.5 mmol, 5.00 equiv) and triisopropylsilyl trifluoromethane-sulfonate (2.75 mL, 9.91 mmol, 3.00 equiv) were added in sequence. The reaction mixture was allowed to warm to 24 °C and was stirred for 18 h. The solution was diluted with water (30 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate in cyclohexane) to yield **242** (688 mg, 84%) as a yellow oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.40 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2945, 2866, 1739, 1660, 1463, 1210, 997 cm^{-1}.

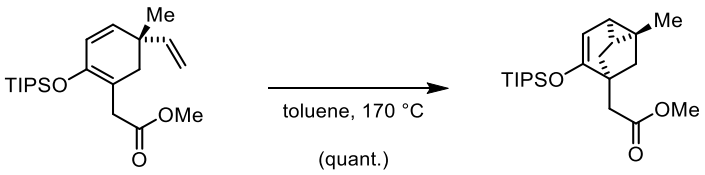
^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.86 (dd, *J* = 10.6, 17.5 Hz, 1H), 5.74 (d, *J* = 9.86 Hz, 1H), 5.52 (d, *J* = 9.87 Hz, 1H), 4.96 (m, 2H), 3.65 (s, 3H), 3.20 (m, 2H), 2.24 (m, 2H), 1.14 (m, 3H), 1.10 (s, 3H), 1.08 (d, *J* = 7.47 Hz, 18H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 172.1, 145.3, 143.9, 135.7, 124.2, 111.2, 105.4, 51.6, 39.8, 38.0, 35.4, 25.2, 18.2, 13.2.

HRMS (ESI): calcd for $(C_{21}H_{36}O_3SiNa)^+$ $[M+Na]^+$: 387.2136; found: 387.2271.

$[\alpha]_D^{20}$ = +21.5 (c = 0.55, CH_2Cl_2).

Tricyclo-[3.2.1.0]oct-3-ene 244



242 **244**

A solution of **242** (1.01 g, 2.76 mmol, 1 equiv) in toluene (20 mL) was sealed in a pressure tube and the solution was heated to 170 °C. After 15 h, the solution was cooled to 24 °C and concentrated to yield **244** (1.01 g, quant.) as a yellow oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.40 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2944, 2866, 1741, 1637, 1462, 1223, 1161 cm^{-1}.

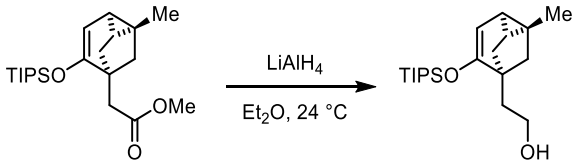
^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.85 (d, *J* = 6.4 Hz, 1H), 3.63 (s, 3H), 2.59 (q, *J* = 10.2, 15.8 Hz, 2H), 1.68 (dd, *J* = 2.5, 11.3 Hz, 1H), 1.36 (m, 1H), 1.25 (s, 3H), 1.18 (m, 6H), 1.06 (m, 19H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 173.0, 153.9, 93.7, 51.2, 44.7, 41.2, 37.5, 35.6, 23.2, 22.4, 21.5, 18.6, 18.2, 12.9.

HRMS (ESI): calcd for $(C_{21}H_{36}O_3SiNa)^+$ $[M+Na]^+$: 387.2136; found: 387.2270.

$[\alpha]_D^{20}$ = –6.4 (c = 0.10, CH_2Cl_2).

Alcohol S9



244 **S9**

To a solution of **244** (10.0 g, 27.4 mmol, 1 equiv) in diethyl ether (400 mL) was added lithium aluminum hydride (2.60 g, 68.6 mmol, 2.50 equiv) in small portions at 24 °C. After 4 h, the reaction mixture was diluted in diethyl ether (250 mL) and cooled to 0 °C. Excess lithium aluminum hydride was quenched by addition of water (10 mL), 15% aqueous sodium hydroxide solution (10 mL) and again water (30 mL) again. The suspension was allowed to warm to 24 °C.

After 30 min, anhydrous sodium sulfate was added. After 15 min, the suspension was filtered through a plug of sodium sulfate and the filtrate was concentrated. The remaining colorless oil **S9** was used in the next step without further purification. The product is sensitive to silica and could not be purified any further using flash column chromatography.

TLC (10% ethyl acetate in hexanes): R_f = 0.18 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3345, 2942, 2865, 1635, 1463, 1218, 1012 cm^{-1}.

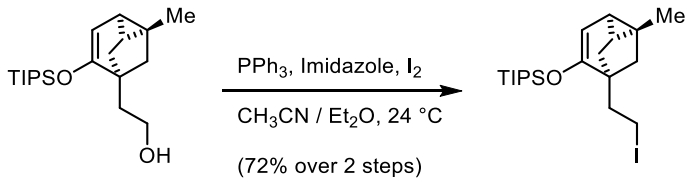
^{1}H NMR (600 MHz, C_6D_6) δ = 5.00 (d, *J* = 6.4 Hz, 1H), 3.75 (ddd, *J* = 3.7, 6.4, 7.6 Hz, 2H), 1.91 (m, 2H), 1.51 (dd, *J* = 2.4, 11.2 Hz, 1H), 1.26 (t, *J* = 6.8 Hz, 1H), 1.16 (m, 9H), 1.11 (dd, *J* = 3.4, 6.8 Hz, 18H), 1.00 (dd, *J* = 2.4, 7.1 Hz, 1H).

^{13}C NMR (150 MHz, C_6D_6) δ = 155.0, 95.0, 61.2, 45.5, 41.8, 36.8, 36.4, 23.3, 22.7, 22.0, 18.6, 18.4, 13.2.

HRMS (ESI): calcd for $(C_{20}H_{37}O_2Si)^+$ $[M+H]^+$: 337.2558; found: 337.2554.

$[\alpha]_D^{20}$ = –2.5 (c = 0.74, CH_2Cl_2).

Iodide 246



S9 **246**

To a solution of triphenylphosphine (10.9 g, 41.1 mmol, 1.50 equiv) in a mixture of diethyl ether (200 mL) and acetonitrile (100 mL) was added imidazole (5.65 g, 82.2 mmol, 3.00 equiv) and iodine (10.5 g, 41.1 mmol, 1.50 equiv) at 24 °C. A solution of **S9** (9.22 g, 27.4 mmol, 1 equiv) in diethyl ether (50 mL) was added slowly. After 5 h, the reaction mixture was diluted with diethyl ether (100 mL). The suspension was washed with aqueous sodium thiosulfate solution (2 × 150 mL) and water (150 mL). The combined aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (150 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate

was concentrated. The residue was purified by flash column chromatography on silica gel (2% ethyl acetate in cyclohexane) to yield **246** (8.81 g, 72% over two steps) as a yellow oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.19 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 2942, 2865, 1634, 1461, 1359, 1249, 1164, 1073 cm^{-1}.

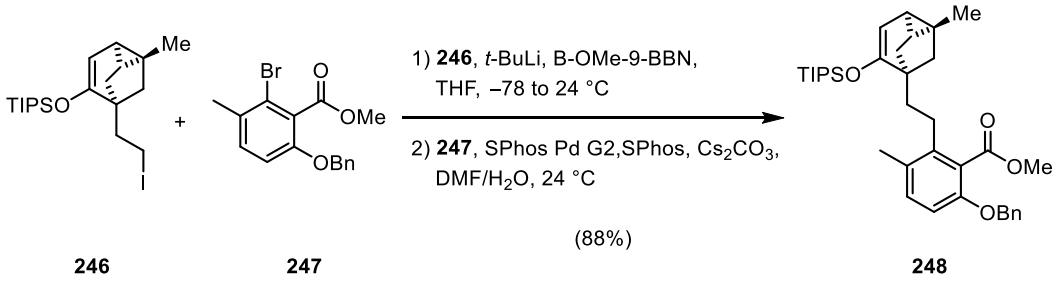
^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.85 (d, *J* = 6.3 Hz, 1H), 3.30 (dddd, *J* = 18.7, 11.8, 8.8, 5.4 Hz, 2H), 2.26 (m, 2H), 1.52 (m, 1H), 1.23 (m, 9H), 1.09 (dd, *J* = 2.8, 7.5 Hz, 18H), 0.97 (dd, *J* = 11.0, 6.2 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 154.2, 94.5, 48.6, 41.2, 40.2, 35.6, 23.2, 22.3, 21.7, 18.5, 18.3, 13.0, 3.7.

HRMS (ESI): calcd for $(C_{20}H_{36}IO_3Si)^+$ $[M + H]^+$: 447.1575; found: 447.2881.

$[\alpha]_D^{20}$ = –42.2 (c = 0.43, CH_2Cl_2).

Coupling product 248



246 **247** **248**

To a solution of **246** (153 mg, 0.343 mmol, 1.30 equiv) and *B*-methoxy-9-BBN (1 M in hexanes, 0.791 mL, 0.791 mmol, 3.00 equiv) in tetrahydrofuran (1.4 mL) was added *t*-butyllithium (1.72 M in hexanes, 0.598 mL, 1.03 mmol, 3.90 equiv) dropwise at –78 °C. After 5 min the reaction mixture was allowed to warm to 24 °C. After 30 min, the solution was transferred to a suspension of **247** (88.0 mg, 0.264 mmol, 1 equiv), caesium carbonate (174 mg, 0.527 mmol, 2.00 equiv), SPhos (5.6 mg, 0.013 mmol, 0.05 equiv) and SPhos Pd G2 (9.5 mg, 0.013 mmol, 0.05 equiv) in a mixture of dimethylformamide and water (9:1, 2.6 mL) at 24 °C. After 30 min, the reaction mixture was diluted in ethyl acetate (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution (25 mL) and dried over sodium sulfate. The dried

solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (3% ethyl acetate in cyclohexane) to yield **248** (133 mg, 88%) as a colorless oil.

TLC (5% ethyl acetate in hexanes): R_f = 0.27 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 2944, 2865, 1732, 1634, 1454, 1242, 1065, 882, 799, 694.

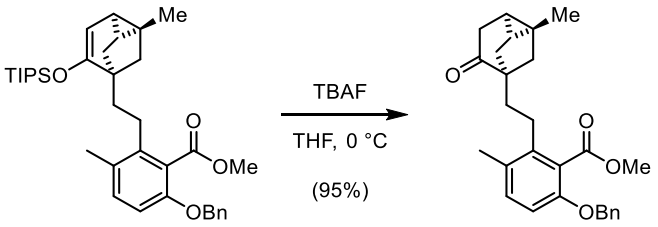
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (m, 5H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.70 (d, , *J* = 8.4 Hz, 1H), 5.08 (s, 2H), 4.87 (d, *J* = 6.4 Hz, 1H), 3.87 (s, 3H), 2.63 (t, *J* = 8.7 Hz, 2H), 2.27 (s, 3H), 1.86 (m, 2H1.73 (dd, *J* = 2.4, 11.1 Hz, 1H), 1.40 (d, *J* = 11.0 Hz, 1H), 1.27 (s, 3H), 1.22 (m, 4H), 1.06 (dd, *J* = 1.7, 7.4 Hz, 19H), 0.87 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5, 155.7, 153.7, 139.9, 137.3, 131,8, 129.2, 128.6, 127.8, 127.0, 125.0, 110.4, 94.1, 70.6, 52.1, 46.7, 39.9, 34.1, 31.7, 27.4, 23.3, 22.6, 21.6, 18.9, 18.8, 18.3, 13.1.

HRMS (ESI): calcd for $(C_{36}H_{50}O_4SiNa)^+$ $[M + Na]^+$: 597.3370; found: 597.3309.

$[\alpha]_D^{20}$ = –3.6 (c = 0.95, CH_2Cl_2).

Ketone S10



248 **S10**

To a solution of TIPS enol ether **248** (388 mg, 0.675 mmol, 1 equiv) in tetrahydrofuran (7 mL) was added tetrabutylammonium fluoride (1 M in *n*-hexanes, 0.810 mL, 0.810 mmol, 1.20 equiv) at 0 °C. After 1 h, the reaction mixture was added ethyl acetate (15 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL) and dried over sodium sulfate. The dried

solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to yield **S10** (269 mg, 95%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.23 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 3030, 2921, 2862, 1714, 1587, 1479, 1382, 1265, 1064, 733, 484.

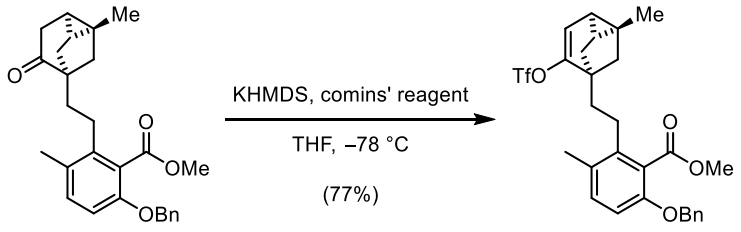
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (m, 5H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.07 (s, 2H), 3.93 (s, 3H), 2.55 (m, 4H), 2.33 (s, 3H), 1.73 (dd, *J* = 3.4, 12.7 Hz, 1H), 1.78 (m, 3H), 1.65 (m, 2H), 1.28 (s, 3H), 1.20 (dd, *J* = 3.3, 7.6 Hz, 1H), 0.92 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 212.2, 169.4, 153.6, 139.0, 137.3, 132.0, 129.5, 128.6, 127.8, 127.0, 124.9, 110.5, 70.6, 55.0, 52.3, 40.0, 34.8, 34.3, 33.5, 27.5, 23.0, 22.4, 19.6, 18.6, 18.1.

HRMS (ESI): calcd for $(C_{27}H_{30}O_4K)^+$ $[M+K]^+$: 457.1776; found: 457.1710.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –3.5 (c = 0.75, CH_2Cl_2).

Vinyl triflate S10



S10 **S11**

S10 (150 mg, 0.358 mmol, 1 equiv) and *N*-(5-chloro-2 pyridyl)-bis(trifluoromethanesulfonimide) (176 mg, 0.430 mmol, 1.20 equiv) were dissolved in tetrahydrofuran (0.1 M, 3.6 mL) and cooled to −78 °C. A potassium bis(trimethylsilyl)amide solution (1 M in tetrahydrofuran, 0.434 mL, 0.434 mmol, 1,21 equiv) was added dropwise. After 3 h, the reaction mixture was allowed to warm to 24 °C. Saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride

solution (20 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to yield **S11** (152 mg, 77%) as a colorless oil.

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

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 2947, 2867, 1730, 1588, 1415, 1207, 1139, 1061, 843, 611, 496.

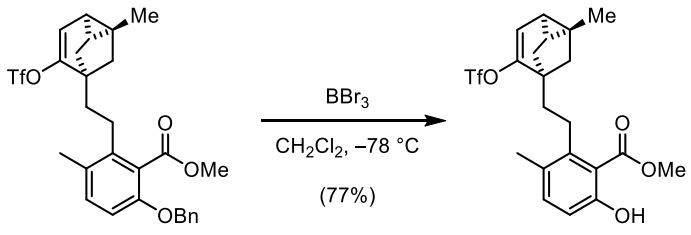
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 (m, 4H), 7.30 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 5.08 (s, 2H), 3.89 (s, 3H), 2.66 (dd, *J* = 7.5, 10.0 Hz, 2H), 2.28 (s, 3H), 1.90 (m, 2H), 1.83 (dd, *J* = 2.3, 11.4 Hz, 1H), 1.52 (m, 2H), 1.38 (m, 1H), 1.33 (s, 3H), 1.05 (dd, *J* = 7.6, 11.4 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.42, 153.80, 148.97, 138.30, 137.18), 132.15, 129.20, 128.59, 127.85, 127.02, 124.91, 118.78 (q, *J* = 321 Hz), 112.4, 110.8, 70.6, 52.3, 46.0, 40.2, 34.7, 31.7, 27.2, 25.2, 24.0, 22.0, 18.7, 18.0.

HRMS (ESI): calcd for $(C_{28}H_{29}F_3O_6SNa)^+$ $[M+Na]^+$: 589.1268; found: 589.1214.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –7.8 (c = 0.12, CH_2Cl_2).

Phenol 249



S11 **249**

To a solution of **S11** (61.0 mg, 0.111 mmol, 1 equiv) in dichloromethane (5.55 mL) was added dropwise boron tribromide (1 M in dichloromethane, 0.332 mL, 0.332 mmol, 3.00 equiv) at –78 °C. After 30 min, excess boron tribromide was quenched with methanol (1.5 mL) at –78 °C. Then, the solution was poured into a saturated sodium bicarbonate solution (10 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The

combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to yield **249** (39.3 mg, 77%) as a white solid.

TLC (10% ethyl acetate in hexanes): R_f = 0.22 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$ cm^{-1}: 2955, 1663, 1596, 1463, 1412, 1201, 1138, 841, 720, 610, 495.

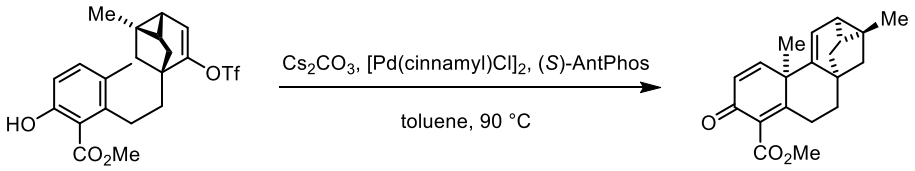
^{1}H NMR (600 MHz, $CDCl_3$) δ = 10.54 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 3.96 (s, 3H), 2.96 (m, 2H), 2.27 (s, 3H), 1.97 (dd, *J* = 2.3, 11.5 Hz, 1H), 1.87 (m, 2H), 1.64 (d, *J* = 11.4, 1H), 1.55 (m, 1H), 1.40 (m, 1H), 1.35 (s, 3H), 1.02 (dd, *J* = 7.7, 11.4 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 171.8, 160.3, 149.1, 142.0, 137.0, 128.2, 118.8 (q, *J* = 321 Hz), 115.7, 113.1, 112.7, 52.4, 46.0, 39.2, 33.7, 30.0, 27.2, 25.2, 23.9, 21.9, 19.7, 18.1.

HRMS (ESI): calcd for $(C_{21}H_{23}F_3O_6SK)^+$ $[M+K]^+$: 499.0798; found: 499.0734.

$[\alpha]_D^{20}$= –14.9 (c = 0.12, CH_2Cl_2).

Dienone 212



249 **212**

Cesium carbonate (9.9 mg, 0.030 mmol, 1.50 equiv), (*S*)-AntPhos (1.9 mg, 0.005 mmol, 0.25 equiv) and palladium (π-cinnamyl) chloride dimer (1.6 mg, 0.003 mmol, 0.15 equiv) were added to a Schlenk tube and the mixture was pumped and back-filled with argon for three times. A solution of **249** (9.2 mg, 0.020 mmol, 1 equiv) in toluene (0.5 mL) was added. The reaction mixture was placed in a preheated oil bath at 90 °C. After 13 h, heating was ceased and ethyl acetate (5 mL) was added. The suspension was filtered through a plug of celite and the filtrate was concentrated.

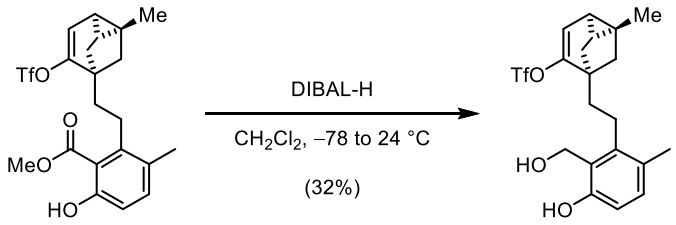
The residue was purified by flash column chromatography on silica gel (2% ethyl acetate in cyclohexane) to yield traces of **212** as a yellow oil.

*Only small amounts of **212** were isolated, which could be analyzed by ^{1}H-NMR spectroscopy and mass spectroscopy. Unfortunately, repeating the experiment on a larger scale mainly resulted in decomposition.*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 10.3 Hz, 1H), 6.24 (d, *J* = 10.2 Hz, 1H), 5.92 (d, *J* = 6.1 Hz, 1H), 3.86 (s, 3H), 2.69 (m, 2H), 2.31 (m, 1H), 1.70 (m, 2H), 1.48 (s, 3H), 1.25 (s, 4H), 1.13 (d, *J* = 11.2 Hz, 1H), 0.80 (m, 3H).

HRMS (ESI): calcd for $(C_{20}H_{22}O_3Na)^+$ $[M + Na]^+$: 333.1461; found: 333.1416.

Diol 252



249 **252**

To a solution of **249** (70 mg, 0.15 mmol, 1 equiv) in dichloromethane (2 mL) was added di-*iso*-butylaluminum hydride solution (1 M in tetrahydrofuran, 334 µL, 0.33 mmol, 2.20 equiv) at –78°C. The reaction mixture was allowed to warm to 24 °C. After 3 h, saturated aqueous Rochelle salt solution (10 mL) was added and the mixture was stirred for 30 min. Dichloromethane (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10–20% ethyl acetate in cyclohexane) to yield **252** (21 mg, 32%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.22 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3296, 2925, 2861, 1718, 1644, 1595, 1464, 14161218, 1246, 1208, 1140, 1119, 1061 cm^{-1}

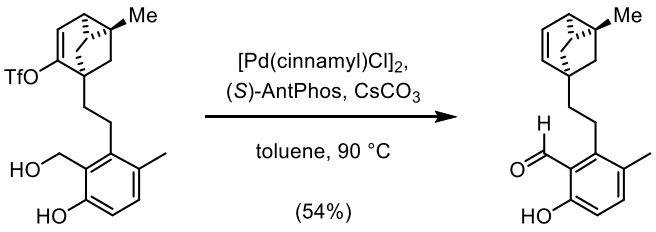
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 4.98 (d, *J* = 5.3 Hz, 2H), 2.70 (ddd, *J* = 10.6, 6.3, 2.3 Hz, 2H), 2.26 (s, 3H), 2.18 (t, *J* = 5.4 Hz, 1H), 1.83 – 1.69 (m, 3H), 1.57 – 1.53 (m, 1H), 1.52 – 1.48 (d, 11.3 Hz, 1H), 1.40 (dd, *J* = 7.0, 2.1 Hz, 1H), 1.34 (s, 3H), 1.16 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 155.2, 148.9, 138.2, 131.1, 127.7, 123.1, 114.6, 112.7, 112.7, 60.6, 46.2, 40.9, 35.5, 33.1, 25.9, 25.2, 23.9, 22.1, 19.4, 18.0.

HRMS (ESI): calcd for $(C_{20}H_{23}F_3O_5SNa)^+$ $[M+Na]^+$: 455.111; found: 455.111.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –8.5 (c = 0.80, CH_2Cl_2).

Aldehyde 254



252 **254**

Cesium carbonate (11.4 mg, 0.03 mmol, 1.50 equiv), palladium(π-cinnamyl) chloride dimer (1.2 mg, 2.31 µmol, 0.10 equiv) and AntPhos (1.7 mg, 4.62 µmol, 0.2 equiv) were added to a dry Schlenk flask and the flask was evacuated and back-filled with argon three times. A solution of **252** (10 mg, 0.02 mmol, 1 equiv) in degassed toluene (1.5 mL) was added. The yellow suspension was heated to 90 °C. After 17 h, heating was ceased and the mixture was allowed to cool to 24 °C. Dichloromethane (5 mL) was added and the mixture was filtered through a short pad of celite. The filter cake was rinsed with dichloromethane (30 mL) and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to yield **254** (3.5 mg, 54%) as a colorless oil.

TLC (10% ethyl acetate in hexanes): R_f = 0.57 (CAM, UV).

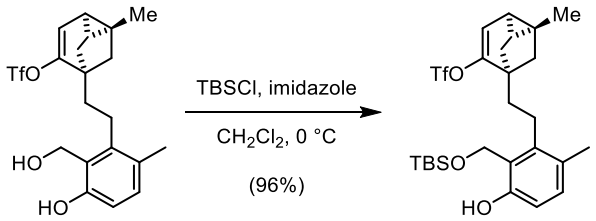
IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3035, 2921, 2863, 1642, 1611, 1465, 1285, 1233, 1203, 1157, 1101, 729 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 11.92 (s, 1H), 10.36 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.04 (dd, *J* = 8.3, 5.6 Hz, 1H), 5.84 (dd, *J* = 8.4, 1.9 Hz, 1H), 3.00 – 2.92 (m, 2H), 2.28 (s, 3H), 1.75 – 1.68 (m, 2H), 1.56 (dd, *J* = 10.9, 2.3 Hz, 1H), 1.52 – 1.47 (m, 1H), 1.31 (s, 3H), 1.26 (m, 2H), 0.81 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.7, 161.9, 144.9, 140.2, 131.0, 126.9, 124.3, 117.9, 115.6, 44.0, 40.5, 39.9, 34.7, 24.6, 24.2, 24.1, 23.2, 18.8, 18.7.

HRMS (ESI): calcd for $(C_{19}H_{23}O_2)^+$ $[M+H]^+$: 283.169; found: 283.264.

Silyl ether 255



252 **255**

To a solution of **252** (60 mg, 0.14 mmol, 1 equiv) in dichloromethane (5 mL) was added imidazole (21 mg, 0.31 mmol, 2.20 equiv) and *tert*-butyldimethylchlorosilane (26 mg, 0.17 mmol, 1.20 equiv) at 0 °C. After 2.5 h, water (10 mL) and dichloromethane (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to yield **255** (73 mg, 96%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.57 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3367, 2927, 2857, 1597, 1464, 1418, 1248, 1210, 1142, 1063 cm^{-1}.

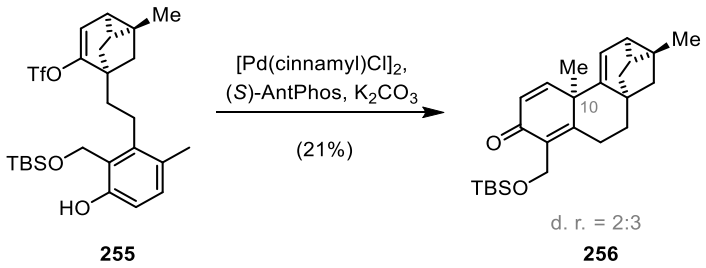
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 5.03 (s, 2H), 2.65 (m, 2H), 2.25 (s, 3H), 1.83 (dd, *J* = 11.4, 2.2 Hz, 1H), 1.72 (m, 2H), 1.59 – 1.47 (m, 2H), 1.41 (m, 1H), 1.35 (s, 3H), 1.14 (m, 2H), 0.94 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9, 148.8, 137.1, 130.8, 127.1, 122.2, 120.4, 114.8, 112.8, 62.6, 46.2, 40.6, 35.1, 32.1, 25.9, 25.6, 25.2, 23.9, 22.1, 19.44, 18.2, 18.0, –5.4.

HRMS (ESI): not found

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$= –7.5 (c = 0.08, CH_2Cl_2).

Dienone 256



255 **256**

Potassium carbonate (7.6 mg, 0.05 mmol, 1.50 equiv), palladium(π-cinnamyl) chloride dimer (1.9 mg, 3.66 μmol, 0.10 equiv) and (*S*)-AntPhos (2.7 mg, 7.32 μmol, 0.20 equiv) were added to a dry Schlenk flask and the flask was evacuated and back-filled with argon three times. A solution of **255** (20 mg, 0.04 mmol, 1 equiv) in degassed toluene (1.5 mL) was added. The yellow suspension was heated to 90 °C. After 13 h, heating was ceased and the mixture was allowed to cool to 24 °C. Dichloromethane (5 mL) was added and the mixture was filtered through a short pad of celite. The filter cake was rinsed with dichloromethane (30 mL) and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (0–5% ethyl acetate in hexanes) to yield **256** (3.0 mg, 21%) as a colorless oil.

TLC (20% ethyl acetate in hexanes): R_f = 0.48 (CAM, UV).

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954, 2926, 2855, 1732, 1661, 1628, 1461, 1406, 1253, 1211, 1141, 1072 cm^{-1}.

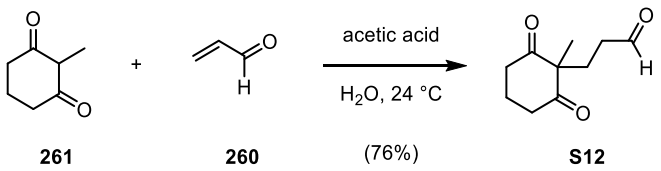
Peaks of the minor diastereomer are also visible in the NMR spectra, but only chemical shifts of the major diastereomer are reported:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (d, 1H), 6.21 (d, 1H), 5.88 (d, 1H), 4.53 (s, 2H), 3.02 (ddd, 1H), 2.83 (dd, 1H), 2.34 (dd, 1H), 1.76 – 1.63 (m, 2H), 1.43 (s, 3H), 1.37 (m, 1H), 1.29 (s, 2H), 1.24 (s, 3H), 1.11 (d, 1H), 0.96 – 0.92 (m, 1H), 0.86 (s, 9H), 0.72 (d, 1H), 0.05 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 183.9, 164.9, 153.9, 142.6, 132.8, 125.8, 118.0, 55.1, 44.0, 42.5, 41.9, 36.9, 30.5, 30.0, 29.9, 26.1, 25.8, 24.3, 23.1, 18.4, 1.2, –5.0.

HRMS (ESI): calcd for $(C_{25}H_{36}O_2SiNa)^+$ $[M + Na]^+$: 419.237; found: 419.470.

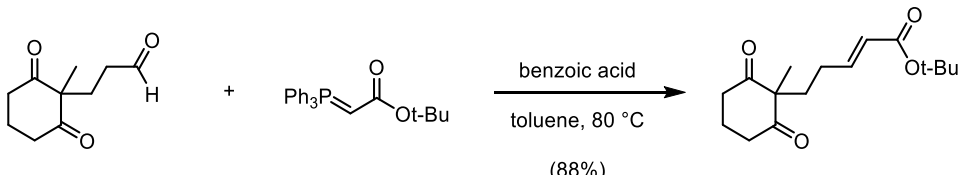
Aldehyde S12



261 **260** **S12**

To a suspension of 2-methyl-1,3-cyclohexanedione (**261**) (27.5 g, 211 mmol, 1 equiv) in water (250 mL) was added acrolein **260** (21.2 mL, 317 mmol, 1.50 equiv) and dropwise acetic acid (0.60 mL, 10.6 mmol, 0.05 equiv) at 24 °C. The mixture was vigorously stirred under exclusion of light. After 28 h, saturated aqueous sodium chloride soluetion (150 mL) was added the aqueous mixture was extracted with ethyl acetate (4 × 150 mL). The combined organic layers were washed with saturated sodium chloride solution (120 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrated was concentrated. The concentrated oil was filtered over a short plug of celite, to remove a white solid that precipitated, to yield **S12** (29.4 g, 76%) as a yellow oil, which was used without further purification. The analytical data were in full agreement with the literature.[80]

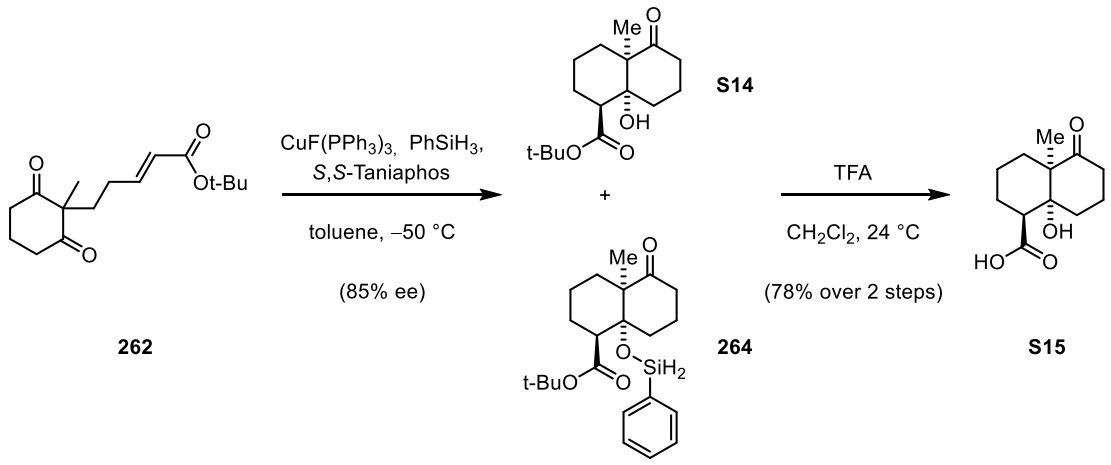
α,β-Unsaturated ester 262



S12 **S13** **262**

A solution of **S12** (19.3 g, 106 mmol, 1 equiv), phosphonium ylide **S13** (47.9 g, 127 mmol, 1.20 equiv) and benzoic acid (13 g, 106 mmol, 1.00 equiv) in toluene (300 mL) was heated to 80 °C. After 21 h, heating was ceased and aqueous saturated sodium bicarbonate solution (400 mL) was added and the layers were separated. The aqueous layer was diluted with saturated aqueous sodium chloride solution (200 mL) and extracted with ethyl acetate (5 × 200 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexane) to yield **262** (26.0 g, 88%) as a pale-yellow oil. The analytical data were in full agreement with the literature.[80]

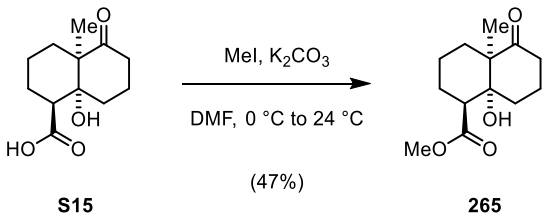
Acid S15



A solution of fluorotris(triphenylphosphine)copper (703 mg, 0.768 mmol, 0.0075 equiv) and *S,S*-Taniaphos (528 mg, 0.768 mmol, 0.0075 equiv) in toluene (1 L) was stirred at 24 °C for 30 min. Phenylsilane (17.1 mL, 133 mmol, 1.30 equiv) was added dropwise. The mixture was cooled to –50 °C and a solution of **262** (28.7 g, 102 mmol, 1 equiv) in toluene (150 mL) was added via a dropping funnel over the course of 2 h. The mixture was stirred at –50 °C for 6 h and then allowed to slowly warm up to 10 °C over 17 h. Then aqueous hydrogen chloride solution (2 M, 500 mL) was added and the biphasic mixture was left stirring for 2 h at 24 °C. The layers were separated and the aqueous layer was extracted with diethyl ether (4 × 300 mL). The combined organic layers were washed with saturated sodium chloride solution (400 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield a mixture of crude products **S14** and **264** (85% ee as determined by chiral GC analysis).

To a solution of **S14** and **264** in dichloromethane (1 L) was dropwise added trifluoracetic acid (76.5 mL, 1020 mmol, 10.0 equiv) at 24 °C. After 4 h, water (600 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 300 mL). The combined organic layers were concentrated to a volume of 200 mL and cooled to 0 °C. Aqueous sodium hydroxide solution (3 M, 800 mL) was added until pH 9. The layers were separated and the aqueous layer was washed with dichloromethane (3 × 400 mL). Concentrated aqueous hydrochloric acid was added to acidify the solution to pH 2. The aqueous layer was extracted with dichloromethane (5 × 300 mL) and diethyl ether (2 × 300 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield **S15** (18 g, 78% over 2 steps) as a white solid, which was used without further purification. The analytical data were in full agreement with the literature.[80]

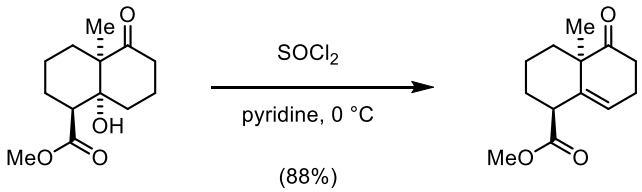
Methylester 265



S15 **265**

To a solution of **S15** (18.0 g, 79.6 mmol, 1 equiv) in *N*,*N*-dimethyl formamide (450 mL) were added potassium carbonate (13.6 g, 239 mmol, 3.00 equiv) and iodomethane (5.25 mL, 83.5 mmol, 1.05 equiv) successively at 0 °C. The mixture allowed to warm to 24 °C. After 22 h, the mixture was cooled to 0 °C and aqueous hydrochloric acid (2 M, 200 mL) was added carefully. The mixture was diluted with water (500 mL) and the aqueous layer was extracted with ethyl acetate (4 × 250 mL). The combined organic layers were washed with aqueous lithium chloride solution (10 wt%, 2 × 300 mL), aqueous hydrochloric acid (2 M, 300 mL) and saturated aqueous sodium chloride solution (300 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20–30% ethyl acetate in cyclohexane) to yield **265** (9.0 g, 47%) as a white solid. The analytical data were in full agreement with the literature.[80]

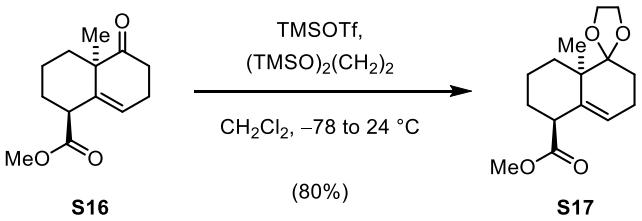
Olefin S16



265 **S16**

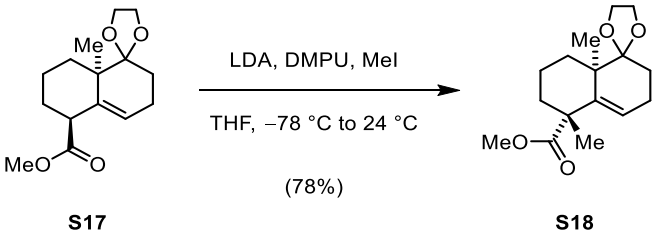
To a solution of **265** (4.58 g, 19.1 mmol, 1 equiv) in pyridine (150 mL) was added dropwise thionyl chloride (2.79 mL, 38.1 mmol. 2.00 equiv) over 10 min at 0 °C. After stirring for 5 min at 0 °C the mixture was diluted with water (150 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with saturated aqueous cupper sulfate solution (6 × 300 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexan) to yield **S16** (3.74 g, 88%) as a colorless oil. The analytical data were in full agreement with the literature.[80]

Acetal S17



To a solution of **S16** (6.82 g, 30.7 mmol, 1 equiv) in dichloromethane (300 mL) was dropwise added freshly distilled trimethylsilyl trifluoromethylsulfonate (285 µL, 1.53 mmol, 0.05 equiv) and ethylenedioxybis(trimethylsilane) (15.4 mL, 61.4 mmol, 2.00 equiv) at –78 °C. After 1 h, the mixture was warmed to 24 °C. After 21 h, pyridine (2 mL) was added dropwise. Aqueous saturated sodium bicarbonate solution (200 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL) and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrated was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in cyclohexan) to yield **S17** (6.6 g, 80%) as a white solid. The analytical data were in full agreement with the literature.[80]

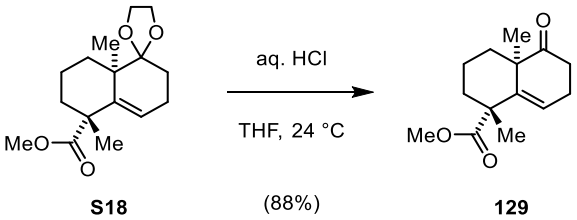
***α*-Tertiary methyl ester S18**



To a solution of diisopropylamine (15.8 mL, 111 mmol, 4.50 equiv) in tetrahydrofuran (300 mL) was added *n*-butyl lithium (2.5 M in hexanes, 39 mL, 4.00 equiv) at –78 °C. The mixture was warmed to 0 °C. *N*,*N*'-dimethylpropylene urea (29.9 mL, 246 mmol, 10.0 equiv) was added dropwise and the solution was stirred for 30 min at 0 °C. A solution of **S17** (6.55 g, 24.6 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added dropwise at 0 °C. The dark red solution returned pale yellow. After 3 h, the mixture was cooled to –78 °C and iodomethane (15.5 mL, 246 mmol, 10.00 equiv) was added dropwise. The reaction mixture was warmed to 24 °C. After 4 h, the excess of iodomethane was distilled off from the reaction mixture. Then, aqueous saturated ammonium chloride solution (200 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with saturated sodium chloride solution (200 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrated was concentrated. The residue was purified by flash column

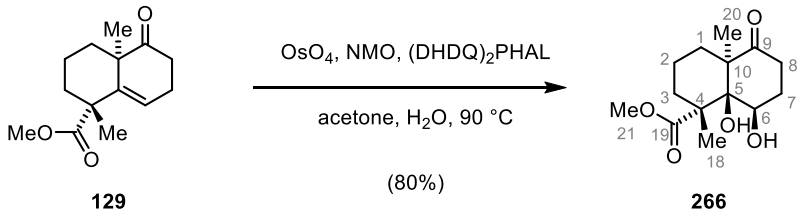
chromatography on silica gel (10% ethyl acetate in cyclohexane) to yield **S18** (5.35 g, 78%) as a white solid. The analytical data were in full agreement with the literature.[80]

Ketone 129



To a solution of **S18** (5.35 g, 19.1 mmol, 1 equiv) in tetrahydrofuran (100 mL) was added aqueous hydrogen chloride solution (2 M, 100 mL) and the solution was stirred at 24 °C. After 7 h, the reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL) and dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to yield **129** (3.97 g, 88%) as a white solid, which was used without further purification. The analytical data were in full agreement with the literature.[80]

Diol 266



To a solution of **129** (3.97 g, 16.8 mmol, 1 equiv) in a mixture of acetone (160 mL) and water (30 mL) in a pressure tube was added *N*-methylmorpholine oxide in water (50 wt%, 10.4 mL, 50.4 mmol, 3.00 equiv), hydroquinine 1,4-phthalazinediyldiether (276 mg, 0.34 mmol, 0.02 equiv) and osmium tetroxide in water (4 wt%, 10.4 mL, 50.4 mmol, 0.10 equiv). The mixture was heated to 90 °C in a pressure tube. After 72 h, heating was ceased and saturated aqueous saturated sodium thiosulfate solution (200 mL) and water (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with ethyl acetate (6 × 150 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20–70% ethyl acetate in cyclohexane) to yield **266** (3.66 g, 81%) as a white solid and recover **129** (0.58 g, 15%).

TLC (50% ethyl acetate in *n*-pentane): R_f = 0.50 (CAM).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.03 (dt, *J* = 10.5, 5.3 Hz, 1H, H-6), 3.76 (s, 3H, H-21), 2.76 (d, *J* = 5.0 Hz, 1H, sec. OH), 2.69 – 2.55 (m, 2H, tert OH, H-8a), 2.33 (ddd, *J* = 15.5, 6.0, 3.2 Hz, 1H, H-8b), 2.09 – 1.97 (m, 2H, H-7), 1.95 – 1.81 (m, 2H, H-3), 1.78 – 1.68 (m, 1H, H-2), 1.62 – 1.48 (m, 2H, H-2, H-1a), 1.42 (ddd, *J* = 14.2, 3.1, 1.7 Hz, 1H, H-1b), 1.33 (s, 3H, H-18), 1.03 (s, 3H, H-20).

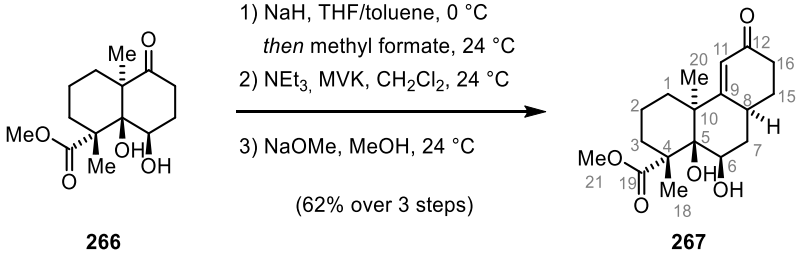
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 213.0 (C-9), 177.9 (C-19), 79.5 (C-5), 70.1 (C-6), 52.6 (C-10), 52.4 (C-21), 49.6 (C-4), 34.6 (C-8), 33.9 (C-3), 28.3 (C-7), 28.0 (C-1), 26.8 (C-18), 19.4 (C-20), 18.3 (C-2).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3484, 2948, 2878, 1711, 1459, 1433, 1308, 1211, 1149, 1093, 1070, 1052, 1038 cm^{-1}.

HRMS (ESI): calcd for $(C_{14}H_{23}O_5)^+$ $[M+H]^+$: 271.154; found: 271.153.

$[\alpha]_D^{20}$ = –7.95 (c = 0.67 in CH_2Cl_2).

Enone 267



To a solution of **266** (1.58 g, 5.84 mmol, 1 equiv) in toluene (15 mL) and tetrahydrofuran (25 mL) was added sodium hydride suspended in mineral oil (60 wt%, 935 mg, 23.4 mmol, 4.00 equiv) in one portion at 0 °C. After 40 min, methyl formate (5 mL, 80.8 mmol, 13.8 equiv) was added dropwise to the suspension. The reaction mixture was allowed to warm to 24 °C. After 90 min, aqueous saturated ammonium chloride solution (40 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated.

To a solution of the crude product in dichloromethane (10 mL) were dropwise added freshly distilled methyl vinyl ketone (2.43 mL, 29.2 mmol, 5.00 equiv) and triethyl amine (3.22 mL,

23.4 mmol, 4.00 equiv) at 24 °C. The mixture was left stirring at 24 °C under exclusion of light. After 40 h, the solvent was evaporated.

To a solution of the yellow residue in methanol (20 mL) was added sodium methoxide (995 mg, 17.5 mmol, 3.00 equiv) in one portion and the mixture was stirred at 24 °C. After 20 h, aqueous saturated ammonium chloride solution (20 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (9% acetone in dichloromethane) to yield **267** (1.16 g, 62%) as a pale yellow solid.

TLC (17% ethyl acetate in *n*-pentane): R_f = 0.50 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.95 (d, *J* = 2.2 Hz, 1H, H-11), 4.82 (dt, *J* = 11.9, 5.2 Hz, 1H, H-6), 3.77 (s, 3H, H-21), 2.77 – 2.66 (m, 1H, H-8), 2.64 (d, *J* = 5.3 Hz, 1H, sec OH), 2.42 (dt, *J* = 16.2, 4.0 Hz, 1H, H-16a), 2.25 (ddd, *J* = 16.3, 14.1, 5.0 Hz, 1H, H-16b), 2.13 (s, 1H, tert OH), 2.13 – 2.08 (m, 1H, H-15a), 2.03 – 1.97 (m, 1H, H-7a), 1.94 – 1.85 (m, 3H, H-1, H-2, H-3), 1.74 – 1.58 (m, 4H, H-2, H-3, H-7b, H-15b), 1.48 – 1.43 (m, 1H, H-1), 1.39 (s, 3H, H-18), 1.03 (s, 3H, H-20).

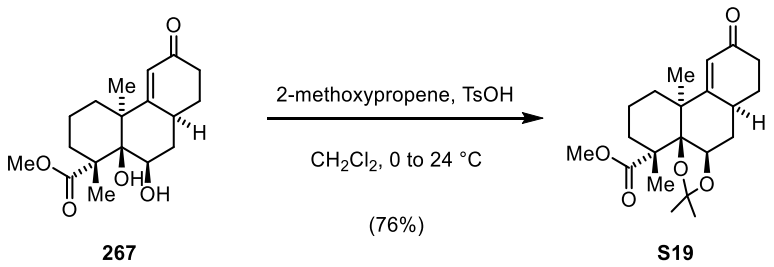
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.4 (C-12), 178.0 (C-19), 171.8 (C-9), 123.8 (C-11), 79.0 (C-5), 70.3 (C-6), 52.4 (C-21), 49.7 (C-4), 46.7 (C-10), 37.5 (C-7), 36.4 (C-16), 34.1 (C-3), 32.8 (C-8), 31.3 (C-1), 29.7 (C-15), 28.0 (C-18), 22.1 (C-20), 18.9 (C-2).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3463, 2944, 2877, 1719, 1660, 1606, 1458, 1379, 1353, 1263, 1210, 1188, 1155, 1108, 1009 cm^{-1}.

HRMS (ESI): calcd for $(C_{18}H_{26}NaO_5)^+$ $[M+Na]^+$: 345.1672; found: 345.1707.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +30.4 (c = 0.70 in CH_2Cl_2).

Acetonide S19



To a solution of **267** (967 mg, 3.00 mmol, 1 equiv) in dichloromethane (30 mL) was dropwise added 2-methoxypropene (888 µL, 9.00 mmol, 3.00 equiv) and *para*-toluene sulfonic acid (6.0 mg, 0.03 mmol, 0.01 equiv) at 0 °C. The mixture was warmed to 24 °C. After 25 min, pyridine (300 µL) and aqueous saturated ammonium chloride solution (30 mL) was added to the mixture. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated sodium chloride solution (30 mL) and dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (17–33% ethyl acetate in *n*-pentane) to yield **S19** (823 mg, 76%) as an amorphous white solid.

TLC (50% ethyl acetate in *n*-pentane): R_f = 0.64 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.80 (dd, *J* = 2.7, 0.9 Hz, 1H), 4.81 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.69 (s, 3H), 2.72 (dddd, *J* = 11.5, 9.6, 4.1, 2.5 Hz, 1H), 2.60 (ddd, *J* = 15.3, 9.6, 1.9 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.40 – 2.23 (m, 2H), 2.22 – 2.12 (m, 1H), 2.10 – 2.04 (m, 1H), 2.02 – 1.95 (m, 1H), 1.91 – 1.79 (m, 2H), 1.65 – 1.55 (m, 2H), 1.32 – 1.28 (m, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.16 – 1.11 (m, 1H), 1.10 (d, *J* = 1.1 Hz, 3H).

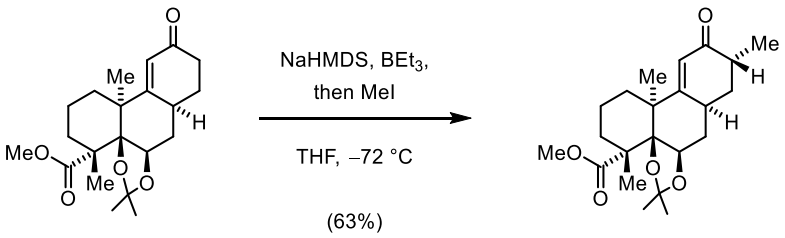
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 200.5, 176.9, 173.6, 123.5, 106.2, 89.0, 75.9, 51.8, 48.7, 46.2, 39.0, 33.2, 33.1, 32.4, 30.5, 29.8, 28.2, 27.8, 26.6, 21.5, 18.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3005, 2936, 2879, 1723, 1666, 1615, 1454, 1377, 1347, 1317, 1254, 1207, 1178, 1154, 1141, 1118 (m), 1045, 1018 cm^{-1}.

HRMS (ESI): calcd for $(C_{21}H_{30}NaO_5)^+$ $[M+Na]^+$: 385.1985; found: 385.2021.

$[\alpha]_D^{20}$ = +22.1 (c = 4.13 in CH_2Cl_2).

α-Methyl enone S20



A solution of **S19** (800 mg, 2.21 mmol, 1 equiv) in tetrahydrofuran (11 mL) was dropwise added to a sodium bis(trimethylsilyl)amide solution (1 M in tetrahydrofuran, 2.43 mL, 2.43 mmol, 1.10 equiv) at –78 °C. After stirring for 1 h the mixture was slowly heated to 0 °C. After 1 h, it was cooled to –72 °C and a triethylborane solution (1 M in *n*-hexane, 1.77 mL, 1.77 mmol, 0.800 equiv) was added dropwise at this temperature. After 30 min, iodomethane (555 µL, 8.83 mmol, 4.00 equiv) was added dropwise to the reaction mixture. The reaction mixture was warmed to 24 °C. After 17 h, the mixture was cooled to 0 °C and water (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with saturated sodium chloride solution (25 mL) and dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (17–33% ethyl acetate in *n*-pentane) to yield **S20** (522 mg, 63%) as an amorphous, white solid.

TLC (50% ethyl acetate in *n*-pentane): R_f = 0.67 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.71 (d, *J* = 2.6 Hz, 1H), 4.81 (dd, *J* = 3.5, 1.9 Hz, 1H), 3.68 (s, 3H), 2.87 (dddd, *J* = 12.0, 9.5, 4.5, 2.7 Hz, 1H), 2.59 (ddd, *J* = 15.3, 9.6, 1.9 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.16 (td, *J* = 12.7, 4.2 Hz, 1H), 2.09 – 2.02 (m, 1H), 1.89 – 1.79 (m, 2H), 1.75 (ddd, *J* = 12.5, 4.3, 1.5 Hz, 1H), 1.64 – 1.58 (m, 1H), 1.57 (dd, *J* = 6.7, 4.7 Hz, 1H), 1.33 – 1.27 (m, 3H), 1.25 (s, 3H), 1.25 (s, 3H), 1.18 – 1.13 (m, 1H), 1.11 (d, *J* = 7.4 Hz, 3H), 1.10 (d, *J* = 1.0 Hz, 3H).

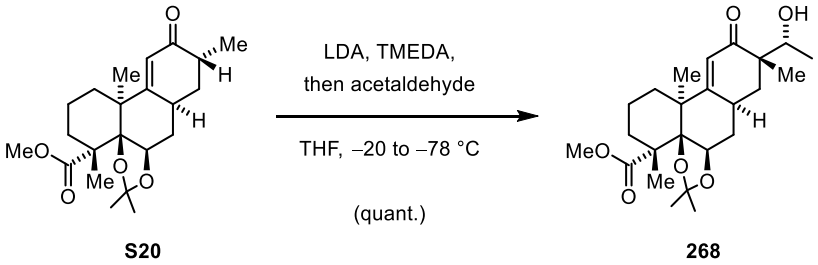
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 203.7, 176.8, 172.4, 122.1, 106.2, 89.1, 76.0, 51.7, 48.7, 46.1, 40.8, 39.2, 32.4, 30.2, 29.6, 28.2, 27.7, 27.3, 26.6, 21.4, 18.4, 15.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3006, 1724, 1663, 1616, 1456, 1436, 1377, 1315, 1256, 1231, 1207, 1179, 1149, 1133, 1034, 1017 cm^{-1}.

HRMS (ESI): calcd for $(C_{22}H_{32}NaO_5)^+$ $[M+Na]^+$: 399.2145; found: 399.2179.

$[\alpha]_D^{20}$ = +3.71 (c = 6.96 in CH_2Cl_2).

Secondary alcohol 268



To a solution of diisopropyl amine (144 µL, 1.01 mmol, 4.00 equiv) in tetrahydrofuran (1.2 mL) was added *n*-butyl lithium (2.45 M in hexanes, 303 µL, 757 µmol, 3.00 equiv) at –78 °C. Tetramethyl ethylene diamine (462 µL, 3.03 mmol, 12.0 equiv) was added dropwise to the reaction mixture. **S20** (95 mg, 252 µmol, 1 equiv) in tetrahydrofuran (1.8 mL) was added dropwise to solution at –78 °C. After 1 h, the reaction mixture was heated to –20 °C and stirred for 1 h. The mixture was cooled to –78 °C and acetaldehyde (285 µL, 5.05 mmol, 20.0 equiv) was added dropwise to the solution. After 80 min, water (3 mL) containing aqueous saturated ammonium chloride solution (3 drops) was added and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (33–38% ethyl acetate in *n*–pentane) to yield **268** (105 mg, quant.) as a white solid.

TLC (25% ethyl acetate in *n*-pentane): R_f = 0.13 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.79 (d, *J* = 2.5 Hz, 1H), 4.82 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.98 (qd, *J* = 6.3, 1.8 Hz, 1H), 3.69 (s, 3H), 2.80 (dddd, *J* = 12.2, 9.4, 4.4, 2.6 Hz, 1H), 2.58 (ddd, *J* = 15.3, 9.6, 1.9 Hz, 1H), 2.38 (dd, *J* = 13.8, 12.4 Hz, 1H), 2.25 – 2.14 (m, 2H), 2.12 – 2.04 (m, 1H), 1.93 – 1.79 (m, 3H), 1.66 – 1.57 (m, 2H), 1.33 – 1.29 (m, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.17 – 1.12 (m, 1H), 1.11 (d, *J* = 1.0 Hz, 3H), 1.02 (s, 3H).

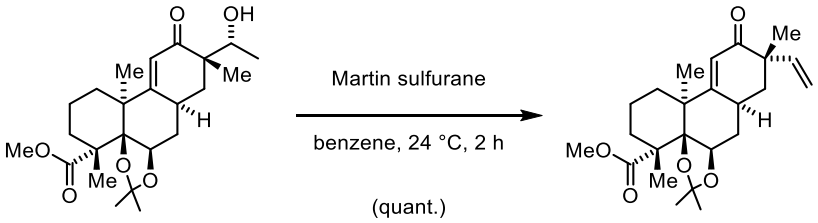
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 205.1, 176.8, 173.2, 122.5, 106.2, 89.3, 76.0, 67.7, 51.8, 49.2, 48.7, 46.1, 43.5, 32.4, 30.4, 29.7, 28.7, 28.2, 27.7, 26.6, 21.3, 18.4, 17.4, 16.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3481, 1725, 1651, 1552, 1456, 1312, 1259, 1237, 1209, 1179, 1103, 1084 cm^{-1}.

HRMS (ESI): calcd for $(C_{24}H_{36}NaO_6)^+$ $[M+Na]^+$: 443.2404; found: 443.2442.

$[\alpha]_D^{20}$ = +2.10 (c = 1.48 in CH_2Cl_2).

α-Vinyl enone S21



268 **S21**

To a solution of **268** (65.0 mg, 155 µmol, 1 equiv) in benzene (1 mL) was added dropwise a solution of Martin sulfurane (114 mg, 170 µmol, 1.10 equiv) in benzene (2 mL) at 24 °C. After 1 h, further Martin sulfurane (60 mg, 89.2 µmol, 0.570 equiv) in benzene (1 mL) was added. After 1 h, aqueous saturated sodium bicarbonate solution (5 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (17% ethyl acetate in *n*-pentane) to yield **S21** (62 mg, quant.) as an amorphous, white solid.

TLC (25% ethyl acetate in *n*-pentane): R_f = 0.69 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.81 – 5.71 (m, 2H), 5.02 (dd, *J* = 10.6, 0.9 Hz, 1H), 4.90 (dd, *J* = 17.6, 0.9 Hz, 1H), 4.83 (dd, *J* = 3.5, 1.9 Hz, 1H), 3.69 (s, 3H), 2.79 (dddd, *J* = 12.1, 9.5, 4.3, 2.8 Hz, 1H), 2.58 (ddd, *J* = 15.3, 9.7, 1.9 Hz, 1H), 2.38 (dd, *J* = 13.1, 11.9 Hz, 1H), 2.18 (td, *J* = 12.8, 4.4 Hz, 1H), 2.10 – 2.05 (m, 1H), 1.90 – 1.79 (m, 3H, H-2), 1.67 – 1.57 (m, 2H), 1.32 – 1.29 (m, 3H), 1.29 – 1.28 (m, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 1.15 – 1.09 (m, 1H), 1.06 (d, *J* = 1.1 Hz, 3H).

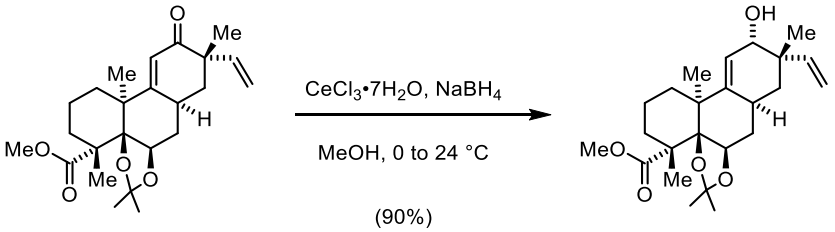
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.1, 176.9, 172.2, 140.8, 122.8, 114.5, 106.3, 89.2, 76.0, 51.8, 49.4, 48.7, 46.2, 46.0, 32.4, 30.2, 29.8, 29.8, 28.3, 27.7, 26.6, 24.2, 21.3, 18.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ =3319, 2931, 1726, 1651, 1630, 1454, 1379, 1314, 1264, 1230, 1210, 1192, 1176, 1079 cm^{-1}.

HRMS (ESI): calcd for $(C_{24}H_{34}NaO_5)^+$ $[M+Na]^+$: 425.2298; found: 425.2283.

$[\alpha]_D^{20}$ = +11.1 (c = 1.43 in CH_2Cl_2).

Allylic alcohol S22



S21 **S22**

To a solution of **S21** (62.0 mg, 154 µmol, 1 equiv) in methanol (3 mL) were added cerium(III)chloride heptahydride (63.1 mg, 169 µmol, 1.10 equiv) and sodium borohydride (11.9 mg, 308 µmol, 2.00 equiv) successively in one portion at 0 °C. The reaction mixture was slowly warmed to 24 °C. After 1 h, further sodium borohydride (11.9 mg, 308 µmol, 2.00 equiv) was added. After 1.5 h, the reaction mixture was diluted with water (5 mL) and aqueous saturated ammonium chloride solution (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate in *n*-pentane) to yield **S22** (55.8 mg, 90%) as a white solid.

TLC (10% ethyl acetate in *n*-pentane): R_f = 0.33 (CAM).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.17 – 5.90 (m, 1H), 5.23 (t, *J* = 1.3 Hz, 1H), 5.22 – 5.12 (m, 2H), 4.74 (dd, *J* = 3.3, 2.0 Hz, 1H), 4.01 (dd, *J* = 3.8, 2.0 Hz, 1H), 3.67 (s, 3H), 2.63 (ddt, *J* = 11.4, 7.7, 4.1 Hz, 1H), 2.39 (ddd, *J* = 15.3, 10.2, 2.1 Hz, 1H), 2.16 (td, *J* = 12.8, 4.4 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.98 – 1.80 (m, 2H), 1.67 (dd, *J* = 15.3, 3.2 Hz, 1H), 1.64 – 1.46 (m, 4H), 1.42 – 1.35 (m, 3H), 1.34 – 1.30 (m, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.09 – 1.05 (m, 1H), 1.03 (d, *J* = 1.0 Hz, 3H).

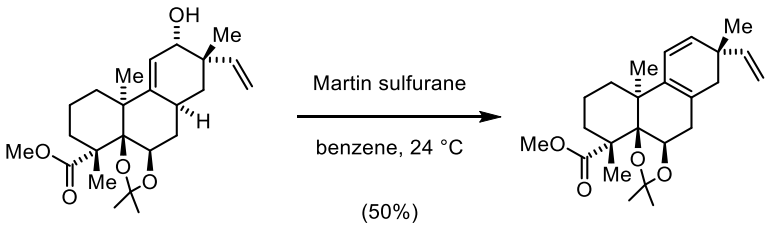
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 177.2, 146.4, 140.5, 122.3, 116.4, 105.8, 89.5, 76.3, 76.2, 51.6, 48.6, 46.2, 44.2, 42.0, 32.7, 30.0, 29.8, 28.5, 28.1, 27.5, 26.7, 24.4, 24.4, 18.6.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3498, 3005, 2931, 1727, 1413, 1312, 1234, 1205, 1180, 1122, 1103, 1056, 1021 cm^{-1}.

HRMS (ESI): calcd for $(C_{24}H_{36}NaO_5)^+$ $[M+Na]^+$: 427.2455; found: 427.2472.

$[\alpha]_D^{20}$ = –44.05 (c = 0.70 in CH_2Cl_2).

Triene 258



S22 **258**

To a solution of **S22** (20.9 mg, 51.7 µmol, 1 equiv) in benzene (1 mL) was added a solution of Martin sulfurane (52.1 mg, 77.5 µmol, 1.50 equiv) in benzene (0.5 mL) and the mixture was stirred at 24 °C. After 2 h, aqueous saturated sodium bicarbonate solution (3 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1–2% ethyl acetate in *n*-pentane) to yield **258** (10.0 mg, 50%) as an amorphous white solid.

TLC (5% ethyl acetate in *n*-pentane): R_f = 0.57 (CAM, UV).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.01 (d, *J* = 9.7 Hz, 1H), 5.68 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.41 (dd, *J* = 9.7, 1.4 Hz, 1H), 5.35 (dd, *J* = 4.8, 1.3 Hz, 1H), 4.87 (dd, *J* = 17.3, 1.5 Hz, 1H), 4.80 (dd, *J* = 10.5, 1.6 Hz, 1H), 3.66 (s, 3H), 2.69 (dt, *J* = 17.6, 4.2 Hz, 1H), 2.20 (dd, *J* = 17.3, 3.3 Hz, 1H), 2.12 – 1.99 (m, 4H), 1.83 (tdd, *J* = 13.8, 9.2, 4.6 Hz, 1H), 1.65 (td, *J* = 13.6, 5.1 Hz, 1H), 1.52 (td, *J* = 4.7, 2.3 Hz, 1H), 1.47 – 1.43 (m, 1H), 1.42 – 1.38 (m, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.11 (s, 3H), 0.84 (s, 3H).

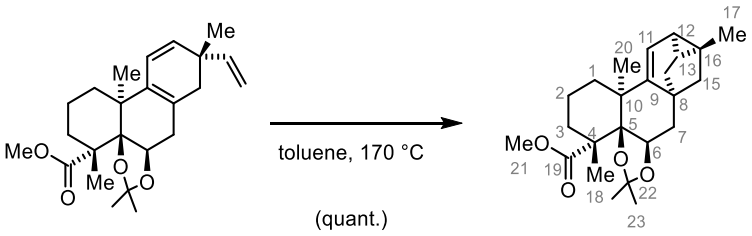
^{13}C-NMR (151 MHz, $CDCl_3$): δ = 177.2, 143.7, 137.0, 133.2, 127.8, 122.7, 110.3, 109.2, 91.8, 78.1, 51.7, 48.5, 42.5, 42.3, 37.3, 36.6, 32.3, 32.0, 29.2, 29.1, 27.3, 26.0, 20.9, 18.6.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2923, 2802, 1727, 1456, 1376, 1244, 1222, 1201, 1168, 1040, 1000 cm^{-1}.

HRMS (ESI): not found

$[\alpha]_D^{20}$ = –135.0 (c = 0.22 in CH_2Cl_2).

Tricyclo[3.2.1.0^{2,7}]octene 257



258 **257**

A solution of **258** (4.00 mg, 10.3 µmol, 1 equiv) in toluene (2 mL) was sealed in a pressure tube and the solution was heated to 170 °C. After 3 h, the solution was cooled to 24 °C and concentrated to yield **257** (4 mg, quant.) as amorphous, white solid.

TLC (100% toluene): R_f = 0.17 (CAM, UV).

^{1}H-NMR (600 MHz, C_6D_6): δ = 5.79 (d, *J* = 5.7 Hz, 1H, H-11), 5.12 – 5.01 (m, 1H, H-6), 3.24 (s, 3H, H-21), 2.52 (d, *J* = 14.9 Hz, 1H, H-7a), 2.29 (dd, *J* = 13.5, 5.3 Hz, 1H, H-3a), 2.24 (td, *J* = 12.9, 5.1 Hz, 1H, H-1a), 2.10 (d, *J* = 12.2 Hz, 1H, H-14a), 2.05 (dd, *J* = 14.9, 3.7 Hz, 1H, H-7b), 1.98 (dddd, *J* = 18.9, 13.5, 9.3, 5.2 Hz, 1H, H-2a), 1.81 (td, *J* = 13.5, 5.9 Hz, 1H, H-3b), 1.61 – 1.55 (m, 2H, H-2b, H-15a), 1.46 (s, 3H, H-23), 1.43 (d, *J* = 4.8 Hz, 1H, H-1b), 1.39 (d, *J* = 6.4 Hz, 1H, H-12), 1.30 (s, 3H, H-23), 1.26 (s, 3H, H-17), 1.25 (s, 3H, H-18),1.22 (d, *J* = 11.7 Hz, 1H, H-14b), 1.09 (s, 3H, H-20), 1.05 (dd, *J* = 6.8, 1.8 Hz, 1H, H-13), 0.80 (d, *J* = 10.8 Hz, 1H, H-15b).

^{13}C-NMR (151 MHz, C_6D_6): δ = 175.6 (C-19), 146.1 (C-9), 113.9 (C-11), 105.7 (C-22), 86.9 (C-5), 75.5 (C-6), 49.7 (C-21), 47.7 (C-4), 44.4 (C-14), 43.3 (C-10), 40.1 (C-8), 36.1 (C-15), 33.0 (C-

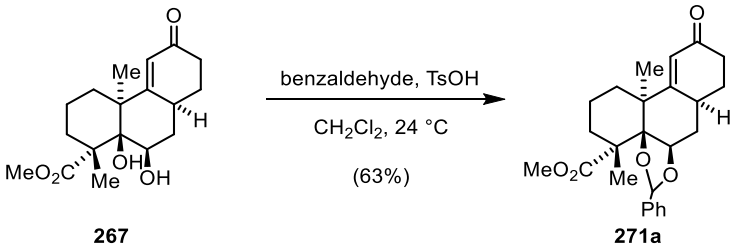
7), 31.7 (C-3), 29.0 (C-12), 28.5 (C-1), 28.2 (C-23), 28.1 (C-23), 26.5 (C-20), 25.5 (C-18), 23.3 (C-16), 22.1 (C-13), 18.1 (C-17), 17.6 (C-2).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3001 (w), 2929 (s), 2850 (w), 1728 (s), 1457 (m), 1376 (m), 1310 (m), 1260 (w), 1226 (s), 1204 (s), 1179 (m), 1150 (m), 1140 (m), 1055 (m), 1041 (s), 1030 (s), 988 (w), 872 (w), 776 (w) cm^{-1}.

HRMS (ESI): calcd for $(C_{24}H_{35}O_4)^+$ $[M+H]^+$: 387.2530; found: 387.2521.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +53.60 (c = 0.25 in CH_2Cl_2).

Benzylidene 271a



267 **271a**

To a solution of **267** (65 mg, 0.20 mmol, 1 equiv) in dichloromethane (4 mL) was added benzaldehyde (31 µL, 0.30 mmol, 1.50 equiv) and *para*-toluenesulfonic acid (0.4 mg, 2.02 µmol, 0.01 equiv) at 24 °C. After 2 h, the mixture was concentrated and the crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in cyclohexane) to yield **271a** (52 mg, 63%) as a colorless oil.

TLC (20% ethyl acetate in cyclohexan): R_f = 0.32 (CAM, UV).

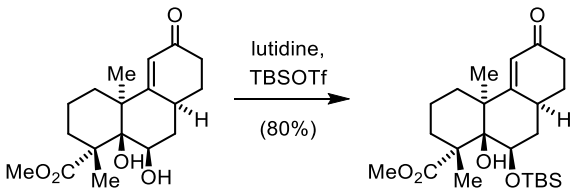
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.29 (m, 5H), 5.99 (d, *J* = 2.6 Hz, 1H), 5.80 (s, 1H), 5.33 (dd, *J* = 4.3, 2.0 Hz, 1H), 3.72 (s, 3H), 2.89 (m, 1H), 2.77 (ddd, *J* = 16.0, 10.4, 4.3 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.44 – 2.26 (m, 2H), 2.18 – 2.08 (m, 1H), 2.07 – 1.98 (m, 1H), 1.89 – 1.78 (m, 1H), 1.65 – 1.55 (m, 2H), 1.34 – 1.24 (m, 2H), 1.13 (d, *J* = 0.9 Hz, 3H), 1.10 (s, 3H), 0.92 – 0.81 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 199.8, 176.4, 172.9, 138.0, 128.8, 128.2, 126.1, 123.8, 102.1, 88.8, 75.9, 51.9, 48.6, 45.5, 38.6, 33.0, 33.0, 32.2, 31.6, 31.3, 23.9, 21.5, 18.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2930, 1724, 1669, 1613, 1515, 1462, 1306, 1031 cm^{-1}.

HRMS (ESI): calcd for $(C_{25}H_{30}NaO_5)^+$ $[M+Na]^+$: 433.199; found: 433.197.

Silyl ether 271i



267 **271i**

To a solution of **267** (130 mg, 0.40 mmol, 1 equiv) in dichloromethane (4 mL) was added 2,6-lutidine (480 µL, 4.03 mmol, 10.00 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (190 µL, 0.81 mmol, 2.00 equiv) at 0 °C. After 4 h, water (20 mL) and dichloromethane (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate. The dried solution was filtered. and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5–10% ethyl acetate in cyclohexane) to yield **271i** (140 mg, 80%) as a colorless oil.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.33 (CAM, UV).

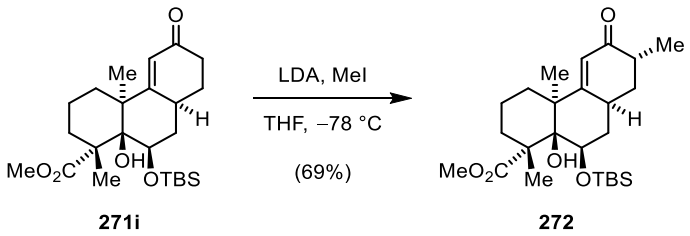
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.93 (d, *J* = 1.9 Hz, 1H), 5.22 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.72 (s, 3H), 2.71 – 2.61 (m, 1H), 2.56 (s, 1H), 2.40 (dt, *J* = 16.2, 4.6 Hz, 1H), 2.23 (m 1H), 2.10 (m, 1H), 2.01 – 1.92 (m, 2H), 1.87 – 1.79 (m, 2H), 1.74 – 1.60 (m, 3H), 1.40 (m, 1H), 1.29 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 200.5, 177.0, 172.3, 122.9, 79.2, 71.3, 51.8, 50.0, 46.5, 40.3, 36.0, 34.1, 32.2, 31.1, 29.3, 27.0, 26.2, 22.1, 18.9, 18.3, –3.4, –3.6.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3545, 2928, 2856, 1723, 1670, 1609, 1461, 1257, 1155, 1060 cm^{-1}.

HRMS (ESI): calcd for $(C_{24}H_{40}NaO_5Si)^+$ $[M+Na]^+$: 459.254; found: 459.252.

α-Methyl enone 272



271i **272**

A solution of *n*-butyl lithium (2.16 M in hexanes, 0.292 mL, 0.63 mmol, 2.50 equiv) was added dropwise to a solution of diisopropyl amine (0.108 mL, 0.76 mmol, 3.00 equiv) in tetrahydrofuran (3 mL) at −78 °C. After 10 min, the solution was allowed to warm to 0 °C. After 20 min at 0 °C, the solution was cooled to –78 °C and a solution of **271i** (110 mg, 0.25 mmol, 1 equiv) in tetrahydrofuran (1.5 mL) was added dropwise. After 35 min, iodomethane (0.127 mL, 2.02 mmol, 8.00 equiv) was added. After 6 h, water (20 mL) and ethyl acetate (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5–10% ethyl acetate in cyclohexane) to yield **272** (78 mg, 69%) as white amorphous solid.

TLC (30% ethyl acetate in cyclohexane): R_f = 0.47 (CAM, UV).

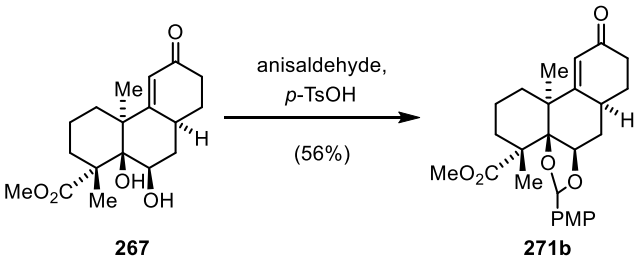
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.83 (d, *J* = 1.5 Hz, 1H), 5.22 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.71 (s, 3H), 2.79 – 2.68 (m, 1H), 2.59 (s, 1H), 2.45 (td, *J* = 7.3, 5.0 Hz, 1H), 2.01 (td, *J* = 12.9, 4.5 Hz, 1H), 1.94 – 1.62 (m, 6H), 1.59 – 1.50 (m, 1H), 1.37 – 1.30 (m, 1H), 1.27 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.01 – 0.99 (s, 3H), 0.89 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.4, 177.1, 170.4, 121.3, 79.5, 71.8, 51.8, 50.0, 46.1, 39.8, 38.1, 35.9, 34.1, 30.9, 29.5, 27.1, 26.3, 21.3, 18.9, 18.3, 15.8, –3.3, –3.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2954, 2926, 2855, 1725, 1673, 1461, 1378, 1257, 1154, 1081, 1058 cm^{-1}.

HRMS (ESI): calcd for $(C_{25}H_{43}O_5Si)^+$ $[M+H]^+$: 451.287; found: 451.285.

PMP acetal 271b



267 **271b**

To a solution of **267** (445 mg, 1.38 mmol, 1 equiv) in dichloromethane (15 mL) was added *para*-anisaldehyde (428 µL, 3.45 mmol, 2.50 equiv) and *para*-toluenesulfonic acid (13 mg, 0.07 mmol, 0.05 equiv) at 0 °C. After 10 min, the reaction mixture was warmed to 24 °C and stirred for 15 h. Water (20 mL) and dichloromethane (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10–20% ethyl acetate in cyclohexane) to yield **271b** (340 mg, 56%) as a white foam.

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

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.99 (d, *J* = 2.6 Hz, 1H), 5.78 (s, 1H), 5.35 – 5.30 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.91 (m, 1H), 2.78 (ddd, *J* = 15.2, 10.4, 4.3 Hz, 1H), 2.57 (dt, *J* = 17.1, 3.3 Hz, 1H), 2.36 (m, 2H), 2.19 – 2.08 (m, 2H), 2.08 – 2.00 (m, 2H), 1.95 – 1.78 (m, 1H), 1.68 – 1.54 (m, 2H), 1.34 – 1.28 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H).

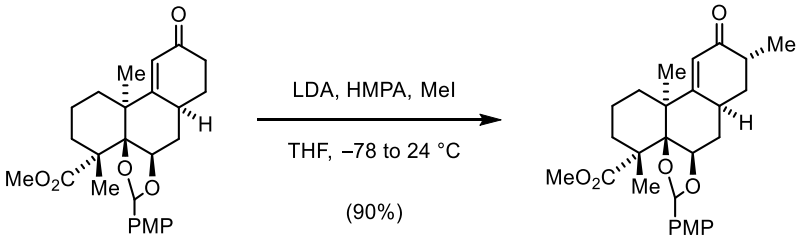
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 199.9, 176.4, 173.1, 160.1, 130.2, 127.2, 123.8, 113.6, 102.1, 88.7, 75.8, 55.3, 51.9, 48.6, 45.6, 38.7, 33.1, 32.3, 31.6, 31.3, 27.0, 24.0, 21.5, 18.5.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2930, 1724, 1669, 1613, 1515, 1462, 1306, 1031 cm^{-1}.

HRMS (ESI): calcd for $(C_{26}H_{33}O_6)^+$ $[M+H]^+$: 441.227; found: 441.225.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = –95.5 (c = 0.07 in CH_2Cl_2).

α-Methyl enone 274



A solution of *n*-butyl lithium (2.3 M in hexanes, 395 µL, 0.91 mmol, 2.00 equiv) was added dropwise to a solution of diisopropyl amine (149 µL, 1.04 mmol, 2.30 equiv) in tetrahydrofuran (4.5 mL) at –78 °C. After 10 min, the solution was allowed to warm to 0 °C. After 20 min at 0 °C, the solution was cooled to –78 °C and a solution of **271b** (200 mg, 0.45 mmol, 1 equiv) in tetrahydrofuran (4.5 mL) was added dropwise. After 10 min, hexamethylphosphoric triamide (403 µL, 2.27 mmol, 5.00 equiv) was added. After 30 min, iodomethane (228 µL, 3.63 mmol, 8.00 equiv) was added. After 4 h, the reaction mixture was allowed to warm to 24 °C. After 14 h, aqueous hydrochloric acid (1 M, 20 mL) and ethyl acetate (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5–10% ethyl acetate in cyclohexane) to yield **274** (185 mg, 90%) as a yellow oil.

TLC (40% ethyl acetate in cyclohexane): R_f = 0.42 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.92 (d, *J* = 2.7 Hz, 1H), 5.73 (s, 1H), 5.33 (dd, *J* = 4.5, 1.9 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.04 (t, *J* = 11.7 Hz, 1H), 2.78 (ddd, *J* = 15.5, 10.5, 4.4 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.29 (m, 2H), 2.07 – 1.80 (m, 4H), 1.65 – 1.52 (m, 2H), 1.31 – 1.24 (m, 1H), 1.19 (d, *J* = 7.5 Hz, 3H), 1.13 (s, 3H), 1.12 (s, 3H).

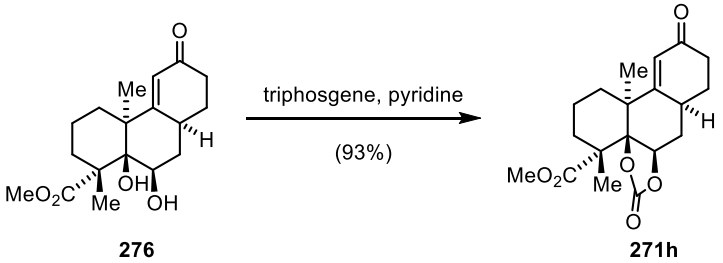
^{13}C-NMR (101 MHz, $CDCl_3$) δ 203.3, 176.6, 172.1, 160.2, 130.3, 127.7, 122.7, 113.7, 102.3, 88.9, 76.0, 55.4, 52.0, 48.7, 45.6, 40.6, 39.2, 33.1, 31.7, 31.3, 26.7, 24.1, 21.6, 18.7, 15.7.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2927, 1725, 1667, 1516, 1462, 1376, 1315, 12511172, 1077, 1045 cm^{-1}.

HRMS (ESI): calcd for $(C_{27}H_{35}O_6)^+$ $[M+H]^+$: 455.243; found: 455.241.

$[\alpha]_D^{20}$ = –9.5 (c = 0.05 in CH_2Cl_2).

Carbonate 271h



276 **271h**

To a solution of **276** (500 mg, 1.55 mmol, 1 equiv) in dichloromethane (15 mL) was added pyridine (0.63 mL, 7.75 mmol, 5.00 equiv) at 0 °C. A solution of triphosgene (388 mg, 2.33 mmol, 1.50 equiv) in dichloromethane (4 mL) was added dropwise. The reaction mixture was allowed to warm to 24 °C. After 14 h, saturated aqueous sodium bicarbonate (20 mL) and dichloromethane (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to yield **271h** (501 mg, 93%) as a yellow oil.

TLC (60% ethyl acetate in cyclohexane): R_f = 0.23 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.94 (d, *J* = 2.7 Hz, 1H), 5.57 (dd, *J* = 3.6, 2.2 Hz, 1H), 3.76 (s, 3H), 2.89 – 2.80 (m, 1H), 2.71 (ddd, *J* = 16.4, 9.8, 3.6 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.37 – 2.24 (m, 1H), 2.22 – 2.17 (m, 1H), 2.07 (m, 4H), 1.89 – 1.62 (m, 3H), 1.38 – 1.31 (m, 1H), 1.28 (s, 3H), 1.16 (s, 3H).

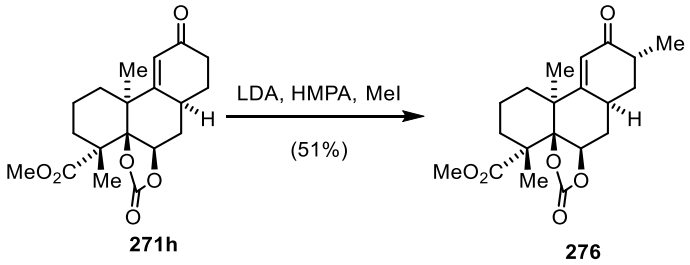
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 199.1, 174.9, 167.1, 152.6, 125.9, 89.1, 76.7, 52.6, 48.3, 44.6, 38.8, 33.2, 31.6, 31.1, 30.9, 30.5, 22.7, 21.4, 18.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2950, 1799, 1722, 1672, 1464, 1356, 1268, 1221, 1186, 1159, 1091, 1040 cm^{-1}.

HRMS (ESI): calcd for $(C_{19}H_{24}O_6Na)^+$ $[M+Na]^+$: 371.146; found: 371.144.

$[\alpha]_D^{20}$ = –12.0 (c = 0.13 in CH_2Cl_2).

α-Methyl enone 276



A solution of *n*-butyl lithium (2.5 M in hexanes, 1.10 mL, 2.76 mmol, 2.00 equiv) was added dropwise to a solution of diisopropyl amine (0.45 mL, 3.17 mmol, 2.30 equiv) in tetrahydrofuran (50 mL) at –78 °C. After 10 min, the solution was allowed to warm to 0 °C. After 20 min at 0 °C, the solution was cooled to –78 °C and a solution of **271h** (480 mg, 1.38 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added dropwise. After 10 min, hexamethylphosphoric triamide (1.47 mL, 8.27 mmol, 6.00 equiv) was added and the yellow solution turned dark orange. After 30 min, iodomethane (0.69 mL, 11.0 mmol, 8.00 equiv) was added and the solution turned yellow again. The reaction mixture was allowed to warm to –10 °C. After 7 h, aqueous phosphate buffer solution (pH = 7) (50 mL) and ethyl acetate (50 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride solution (50 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20–50% ethyl acetate in cyclohexane) to yield **276** (253 mg, 51%) as amorphous white solid.

TLC (60% ethyl acetate in cyclohexane): R_f = 0.23 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.88 (d, *J* = 2.7 Hz, 1H), 5.57 (dd, *J* = 3.7, 2.3 Hz, 1H), 3.76 (s, 3H), 3.00 (ddt, *J* = 13.0, 9.8, 3.7 Hz, 1H), 2.72 (ddd, *J* = 16.5, 9.9, 3.7 Hz, 1H), 2.55 (ddd, *J* = 7.5, 5.4, 2.0 Hz, 1H), 2.29 – 2.06 (m, 3H), 2.00 (dd, *J* = 16.5, 2.2 Hz, 1H), 1.89 – 1.61 (m, 4H), 1.37 – 1.30 (m, 1H), 1.27 (s, 3H), 1.16 – 1.14 (m, 6H).

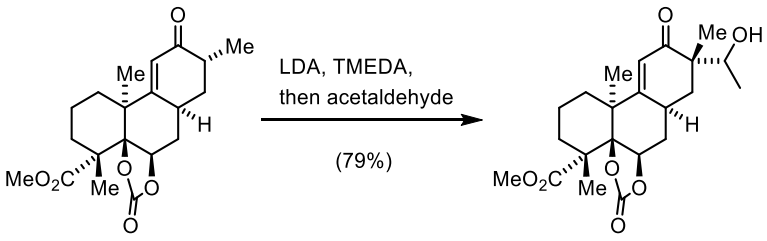
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 202.3, 174.9, 166.1, 152.6, 124.9, 89.2, 77.4, 52.6, 48.2, 44.6, 40.2, 39.3, 31.1, 30.7, 30.4, 26.0, 22.8, 21.4, 18.3, 15.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2932, 1797, 1734, 1670, 1616, 1464, 1358, 1317, 1268, 1221, 1185, 1160, 1049 cm^{-1}.

HRMS (ESI): calcd for $(C_{20}H_{27}O_6)^+$ $[M+H]^+$: 363.180; found: 363.178.

$[\alpha]_D^{20}$ = +27.0 (c = 0.07 in CH_2Cl_2).

Secondary alcohol 277



A solution of *n*-butyl lithium (2.4 M in hexanes, 0.20 mL, 0.47 mmol, 2.00 equiv) was added dropwise to a solution of diisopropyl amine (77.0 µL, 0.54 mmol, 2.30 equiv) in tetrahydrofuran (20 mL) at –78 °C. After 10 min, the solution was allowed to warm to 0 °C. After 20 min at 0 °C, the solution was cooled to –78 °C and a solution of **276** (85 mg, 0.23 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added dropwise. After 10 min, *N*,*N*,*N*',*N*'-tetramethylethylenediamine (0.29 mL, 1.88 mmol, 8.00 equiv) was added. After 30 min, acetaldehyde (0.66 mL, 11.7 mmol, 50.00 equiv) was added. The reaction mixture was allowed to warm to 10 °C. After 2 h, aqueous phosphate buffer solution (pH = 7, 30 mL) and ethyl acetate (30 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (30 mL) and saturated aqueous sodium chloride solution (30 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (20–50% ethyl acetate in cyclohexane) to yield **277** (75 mg, 79%) as amorphous white solid.

TLC (70% ethyl acetate in cyclohexane): R_f = 0.22 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.92 (d, *J* = 2.7 Hz, 1H), 5.54 (dd, *J* = 3.6, 2.2 Hz, 1H), 3.98 (q, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 3.03 – 2.94 (m, 1H), 2.68 (ddd, *J* = 16.5, 10.0, 3.6 Hz, 1H), 2.24 – 2.07 (m, 2H), 2.05 – 1.94 (m, 3H), 1.88 – 1.65 (m, 3H), 1.38 – 1.31 (m, 1H), 1.27 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.16 (s, 3H), 1.06 (s, 3H).

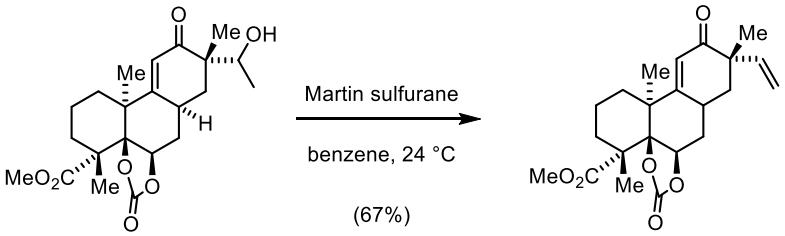
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 204.1, 174.8, 166.9, 152.44, 125.0, 89.3, 67.6, 53.6, 52.6, 49.1, 48.2, 44.6, 43.6, 31.1, 30.6, 30.6, 27.5, 22.8, 21.2, 18.3, 17.6, 16.9.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3501, 2938, 1794, 1724, 1658, 1459, 1361, 1313, 1268, 1222, 1161, 1049, 1032 cm^{-1}.

HRMS (ESI): calcd for $(C_{22}H_{31}O_7)^+$ $[M+H]^+$: 407.206; found: 407.204.

$[\alpha]_D^{20}$ = +17.6 (c = 0.11 in CH_2Cl_2).

α-Vinyl enone S23



277 **S23**

To a solution of **277** (70 mg, 0.17 mmol, 1 equiv) in benzene (10 mL) was added bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur (232 mg, 0.34 mmol, 2.00 equiv) at 24 °C. After 7.5 h, water (10 mL) and ethyl acetate (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5–20% ethyl acetate in cyclohexane) to yield **S23** (43 mg, 67%) as amorphous white solid.

TLC (40% ethyl acetate in cyclohexane): R_f = 0.30 (CAM, UV).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.88 (d, *J* = 2.8 Hz, 1H), 5.70 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.53 (t, *J* = 2.8 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.87 (d, *J* = 17.6 Hz, 1H), 3.73 (s, 3H), 2.90 (ddt, *J* = 12.3, 9.8, 3.6 Hz, 1H), 2.66 (ddd, *J* = 16.5, 10.0, 3.6 Hz, 1H), 2.21 – 2.14 (m, 1H), 2.06 (dd, *J* = 13.3, 4.5 Hz, 1H), 2.01 – 1.53 (m, 6H), 1.34 – 1.28 (m, 1H), 1.25 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H).

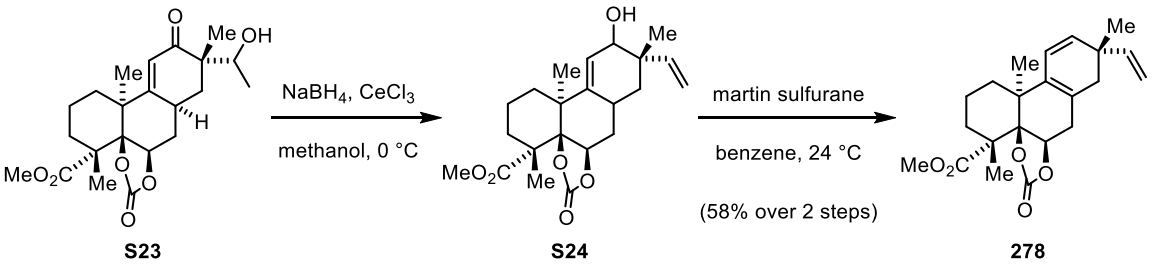
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 200.9, 174.7, 166.0, 152.5, 139.8, 124.9, 115.3, 89.3, 52.5, 49.6, 48.1, 45.9, 44.4, 31.0, 30.6, 30.3, 28.3, 24.1, 22.7, 21.1, 18.2.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2923, 2852, 1802, 1731, 1671, 1462, 1355, 1266, 1221, 1184, 1160, 1050 cm^{-1}.

HRMS (ESI): calcd for $(C_{22}H_{28}O_6Na)^+$ $[M+Na]^+$: 411.178; found: 411.177.

$[\alpha]_D^{20}$ = +42.0 (c = 0.07 in CH_2Cl_2).

Triene 278



To a solution of **S23** (45 mg, 0.12 mmol, 1 equiv) in methanol (2 mL) was added cerium(III) chloride (43 mg, 0.17 mmol, 1.50 equiv) and sodium borohydride (8.9 mg, 0.23 mmol, 2.00 equiv) at 0 °C. The reaction mixture was warmed to 24 °C and stirred for 3.5 h. Water (0.5 mL) and sodium sulfate was added. The mixture was filtered through a short plug of celite covered with silica gel and the filter cake was rinsed with dichloromethane (10 mL). The filtrate was concentrated and the crude product **S24** was used in the next step without further purification.

To a solution of **S24** (45 mg, 0.12 mmol, 1 equiv) in benzene (1 mL) was added bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur (194 mg, 0.29 mmol, 2.50 equiv) at 24 °C. After 9 h, water (10 mL) and ethyl acetate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5–20% ethyl acetate in cyclohexane) to yield **278** (25 mg, 58% over 2 steps) as amorphous white solid.

TLC (40% ethyl acetate in cyclohexane): R_f = 0.55 (CAM, UV).

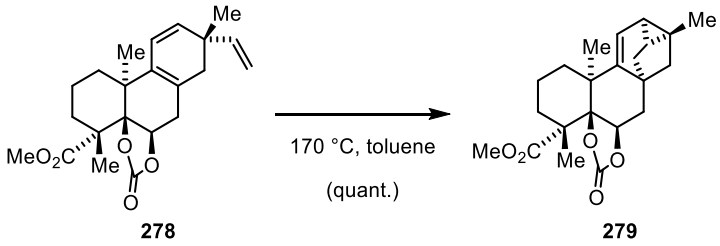
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.94 (d, *J* = 9.8 Hz, 1H), 5.80 (dd, *J* = 4.6, 1.3 Hz, 1H), 5.73 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.51 (dd, *J* = 9.8, 1.3 Hz, 1H), 4.95 – 4.85 (m, 2H), 3.73 (s, 3H), 2.78 (dq, *J* = 17.6, 1.9 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.22 (m, 3H), 1.98 (td, *J* = 13.1, 12.5, 4.3 Hz, 1H), 1.89 – 1.73 (m, 1H), 1.71 – 1.58 (m, 3H), 1.28 (s, 3H), 1.09 (s, 3H), 0.91 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 175.0, 154.4, 144.8, 135.1, 134.9, 124.6, 120.9, 111.0, 90.7, 77.9, 52.4, 48.1, 42.1, 41.1, 37.4, 34.0, 31.8, 31.0, 25.4, 23.2, 19.6, 18.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2926, 1790, 1732, 1457, 1355, 1269, 1217, 1155, 1055 cm^{-1}.

HRMS (ESI): calcd for $(C_{22}H_{28}O_5Na)^+$ $[M+Na]^+$: 395.183; found: 395.183.

Tricyclo[3.2.1.0^{2,7}]octene 279



278 279

A solution of **278** (8.0 mg, 0.02 mmol) in toluene (0.5 mL) was sealed in a pressure tube and the solution was heated to 170 °C. After 13 h, the solution was cooled to 24 °C and concentrated to yield **279** (8 mg, 100%) as a colorless oil.

TLC (50% ethyl acetate in cyclohexane): R_f = 0.64 (CAM).

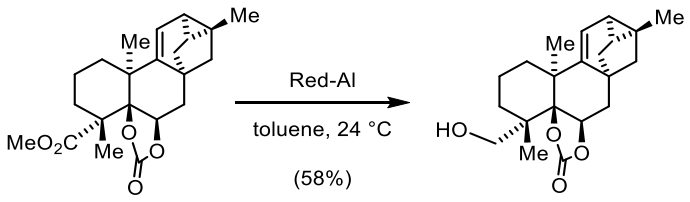
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.81 (dd, *J* = 4.2, 1.8 Hz, 1H), 5.72 (d, *J* = 6.0 Hz, 1H), 3.71 (s, 3H), 2.43 (dd, *J* = 16.1, 4.2 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.94 (dd, *J* = 16.1, 1.8 Hz, 1H), 1.87 – 1.71 (m, 2H), 1.68 – 1.55 (m, 5H), 1.44 (t, *J* = 6.5 Hz, 1H), 1.25 (s, 6H), 1.14 (dd, *J* = 7.0, 2.1 Hz, 1H), 0.98 (s, 3H), 0.88 (d, *J* = 11.3 Hz, 1H), 0.68 (d, *J* = 11.0 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 175.1, 154.4, 144.53, 116.4, 89.2, 77.4, 52.3, 48.3, 42.9, 41.4, 38.8, 37.9, 33.6, 31.9, 31.2, 25.3, 25.2, 24.0, 22.7, 21.8, 18.5, 18.4.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 2924, 1799, 1722, 1458, 1352, 1311, 1268, 1219, 1179, 1153, 1091, 1043, 1026 cm^{-1}.

HRMS (ESI): calcd for $(C_{22}H_{28}O_5Na)^+$ $[M+Na]^+$: 395.183; found: 395.183.

Alcohol 280



279 **280**

To a solution of **279** (3.0 mg, 8.05 µmol, 1 equiv) in toluene (0.3 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride solution (60 wt% in toluene, 26 µL, 0.08 mmol, 10.0 equiv) at –20 °C. The reaction mixture was allowed to warm to 24 °C. After 8 h, water (10 mL) and ethyl acetate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10–50% ethyl acetate in cyclohexane) to yield **280** (2.5 mg, 58%) as amorphous white solid.

TLC (50% ethyl acetate in cyclohexane): R_f = 0.29 (CAM).

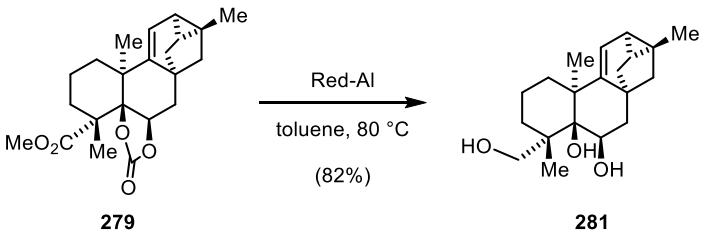
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.68 (d, *J* = 6.0 Hz, 1H), 5.50 (dd, *J* = 4.2, 1.7 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 1H), 3.55 (d, *J* = 11.1 Hz, 1H), 2.38 (dd, *J* = 16.0, 4.2 Hz, 1H), 1.88 – 1.82 (m, 1H), 1.71 – 1.63 (m, 2H), 1.44 – 1.40 (m, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.28 – 1.25 (m, 6H), 1.14 (s, 3H), 0.91 – 0.85 (m, 2H), 0.72 (d, *J* = 10.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 146.7, 114.7, 68.7, 45.5, 43.0, 42.8, 40.5, 38.3, 33.8, 32.1, 31.9, 29.9, 27.8, 25.4, 25.1, 23.8, 22.0, 21.7, 18.6, 17.7 (quaternary C of the Carbonate is not visible).

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3466, 2949, 2922, 2868, 1789, 1765, 1459, 1377, 1360, 1250, 1218, 1168, 1080, 1043, 1022 cm^{-1}.

HRMS (ESI): calcd for $(C_{21}H_{29}O_4)^+$ $[M+H]^+$: 345.206; found: 345.206.

Triol 281



279 **281**

To a solution of **279** (10.0 mg, 0.03 mmol, 1 equiv) in toluene (1 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride solution (60 wt% in toluene, 105 µL, 0.53 mmol, 20.0 equiv) at –20 °C. The reaction mixture was allowed to warm to 24 °C. After 3 h, the reaction mixture was heated to 70 °C. After 3.5 h, heating was ceased and water (10 mL) and ethyl acetate (10 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL) and saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate and the dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (10–50% ethyl acetate in cyclohexane) to yield **281** (7 mg, 82%) as amorphous white solid.

TLC (60% ethyl acetate in cyclohexane): R_f = 0.28 (CAM).

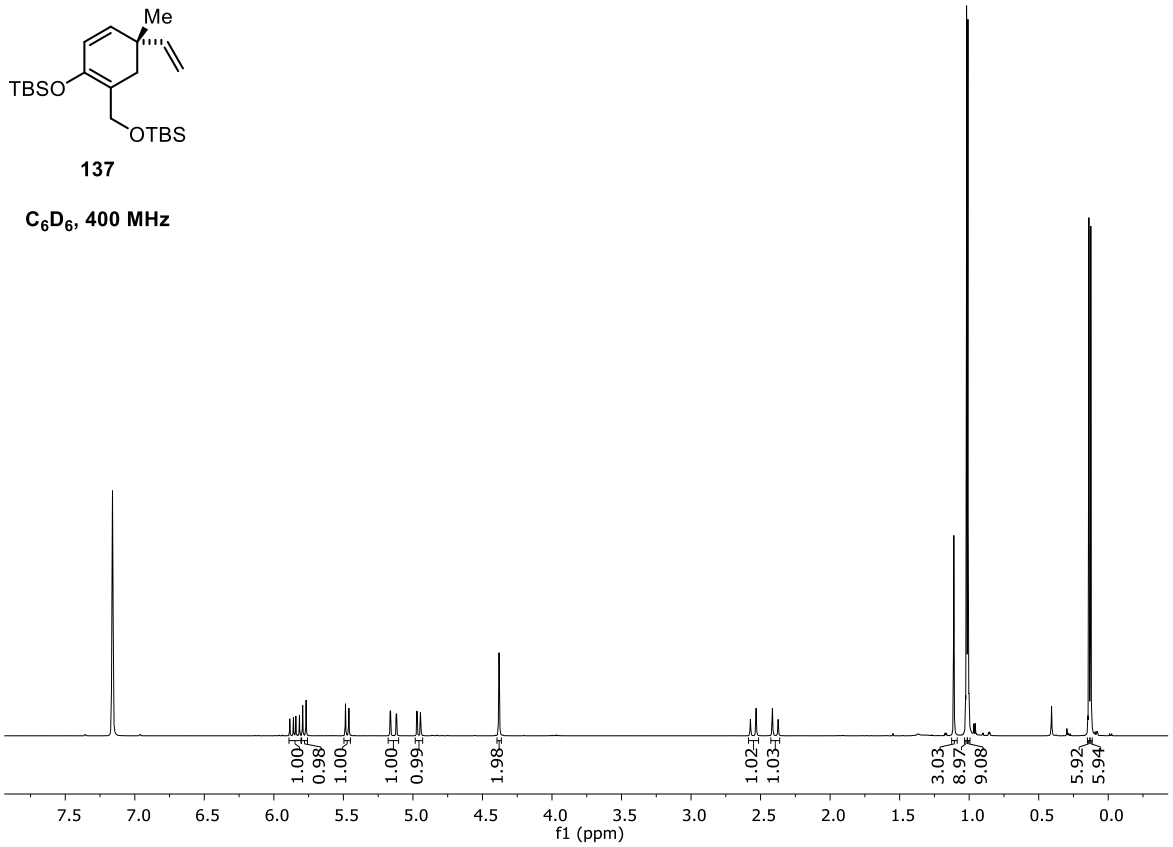
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.82 (d, *J* = 6.0 Hz, 1H), 4.28 (t, *J* = 6.5 Hz, 1H), 3.80 (t, *J* = 7.9 Hz, 2H), 3.25 (d, *J* = 7.3 Hz, 1H), 2.40 (dd, *J* = 15.5, 6.6 Hz, 1H), 1.97 (s, 1H), 1.61 (m, 2H), 1.41 (m, 2H), 1.30 (s, 1H), 1.28 – 1.22 (m, 6H) 1.19 (s, 3H), 1.14 (dd, *J* = 7.1, 2.3 Hz, 1H), 1.07 (s, 3H), 0.96 (d, *J* = 11.5 Hz, 1H), 0.90 – 0.83 (m, 2H), 0.65 (d, *J* = 11.1 Hz, 1H).

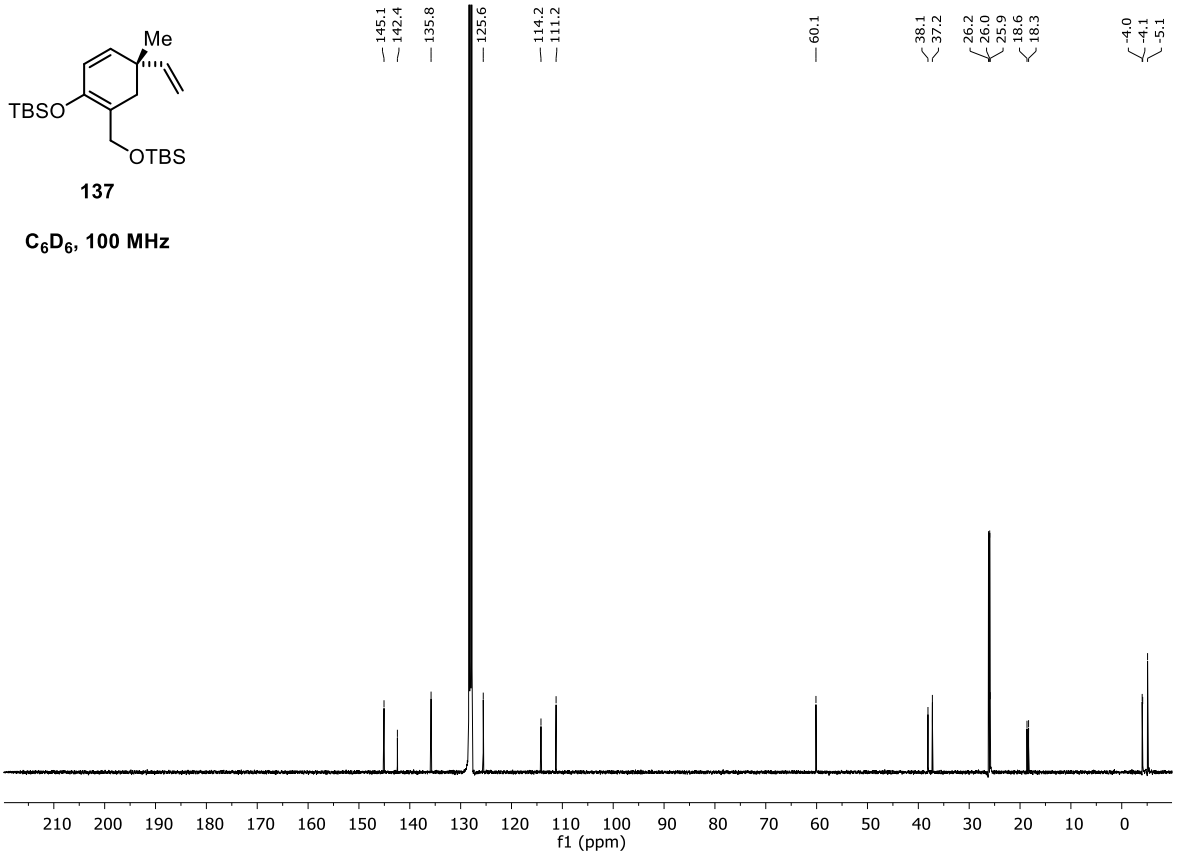
^{13}C-NMR (150 MHz, $CDCl_3$) δ = 148.6, 144.2, 117.4, 66.5, 66.2, 43.9, 42.6, 40.1, 38.9, 38.1, 32.8, 31.1, 29.7, 25.6, 24.9, 23.7, 22.6, 21.1, 18.5, 17.8.

IR (Diamond-ATR, neat): $\tilde{\nu}_{max}$ = 3418, 2923, 2855, 1731, 1458, 1377, 1261, 1012 cm^{-1}.

HRMS (ESI): calcd for $(C_{20}H_{30}O_3Na)^+$ $[M+Na]^+$: 341.209; found: 341.208.

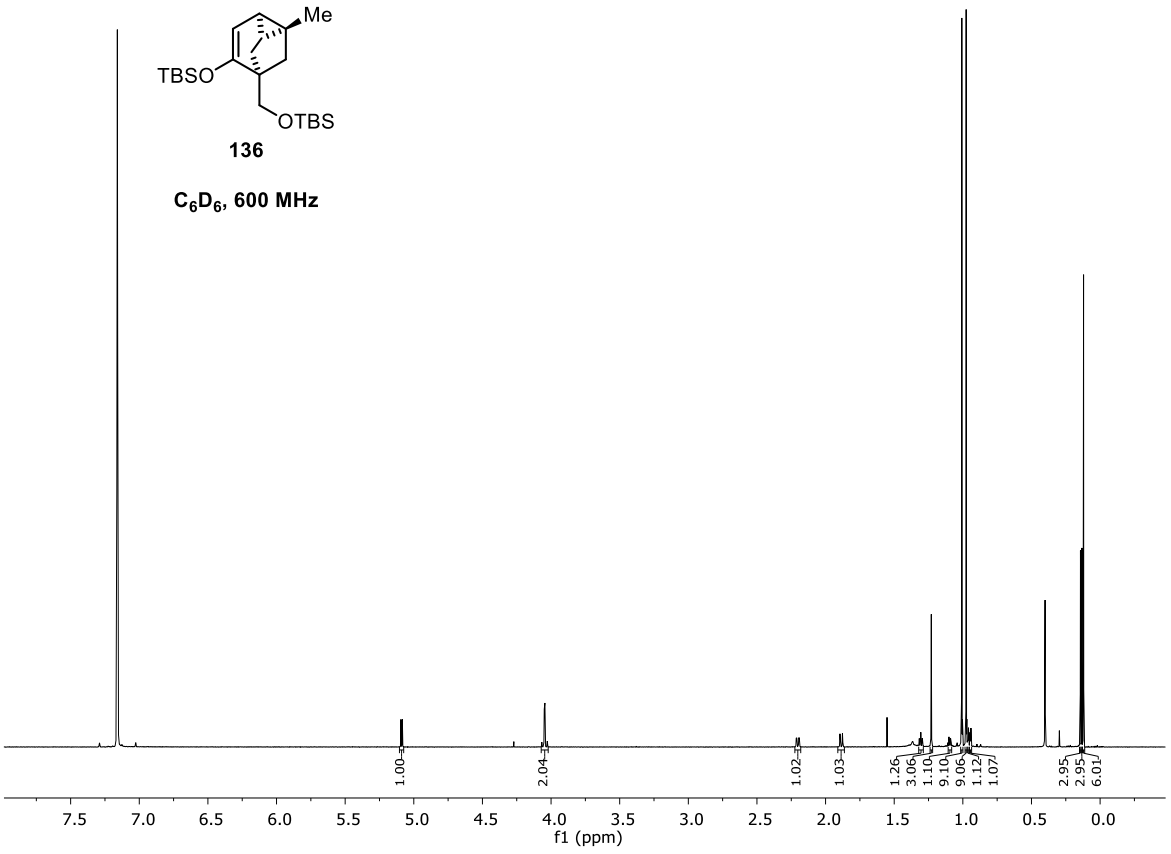
5.3 ^{1}H and ^{13}C NMR Spectra





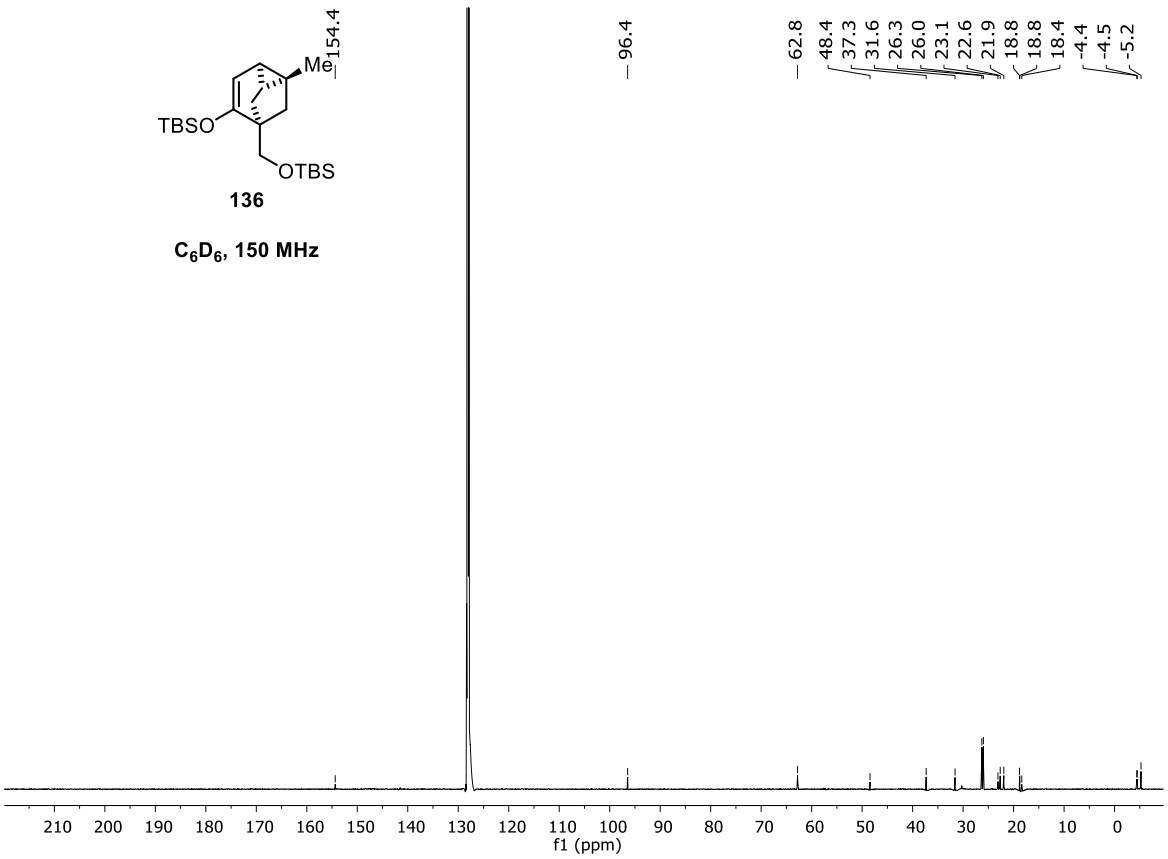
137

C_6D_6, 100 MHz



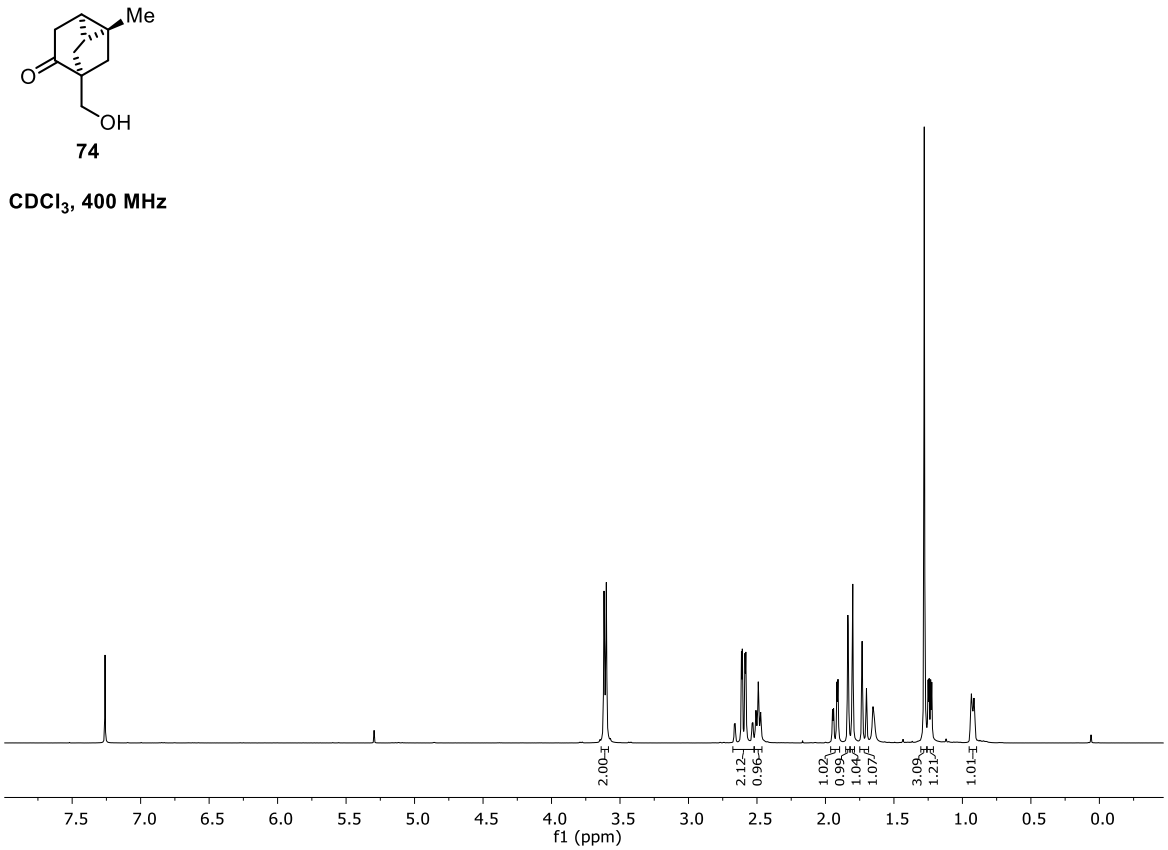
136

C_6D_6, 600 MHz



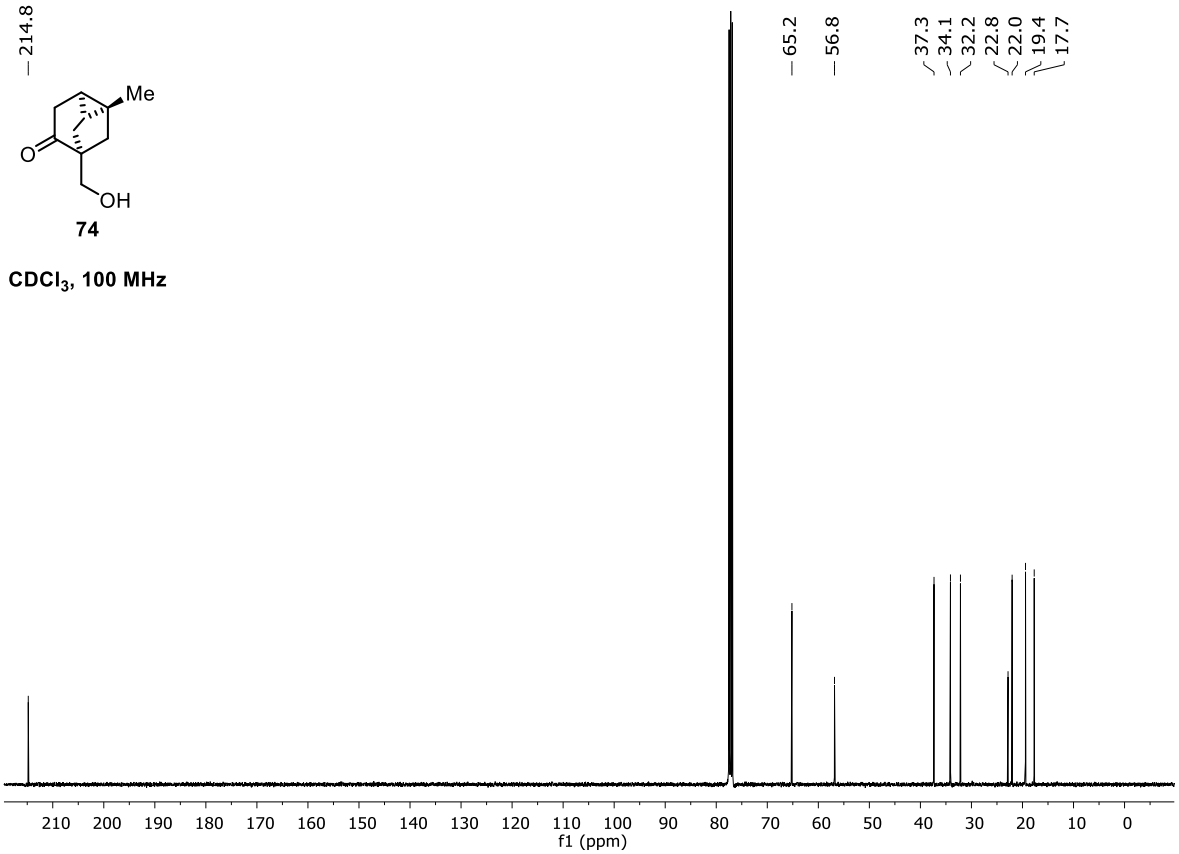
136

C_6D_6, 150 MHz



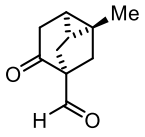
74

$CDCl_3$, 400 MHz



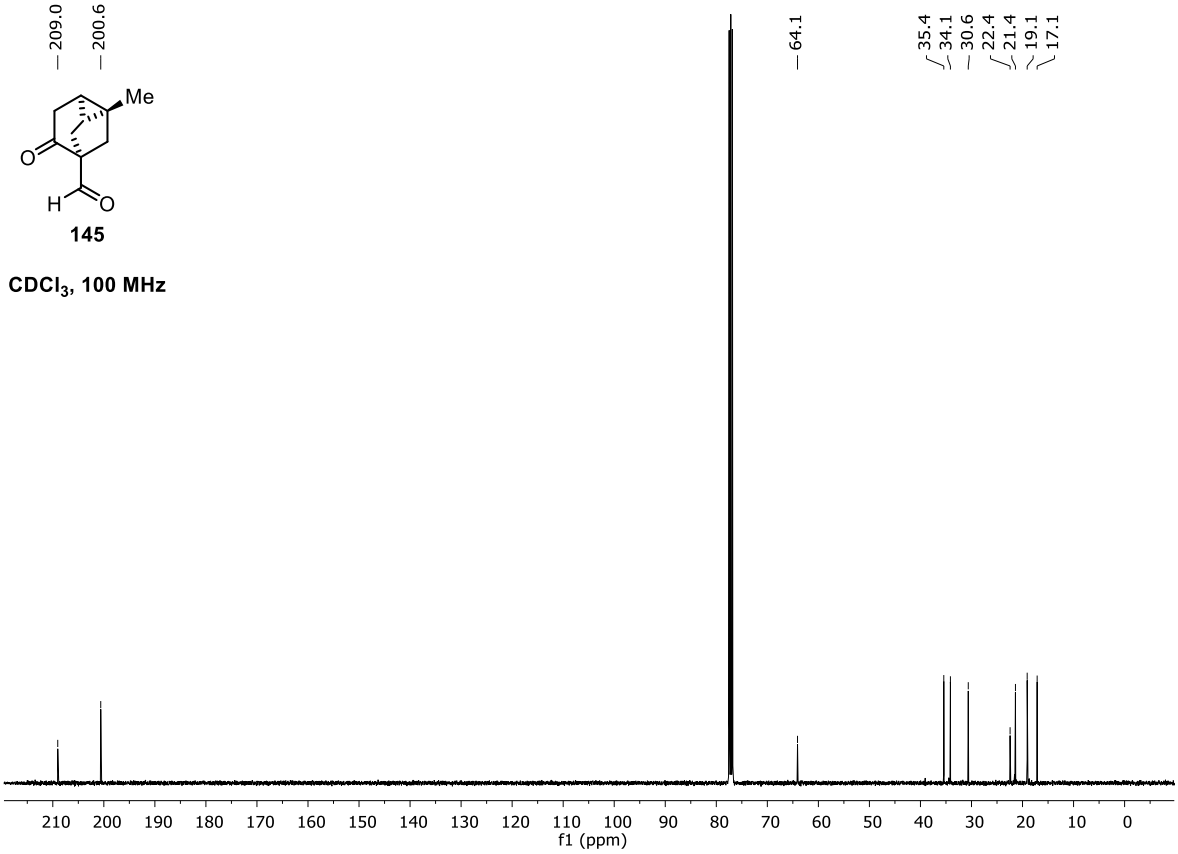
74

$CDCl_3$, 100 MHz



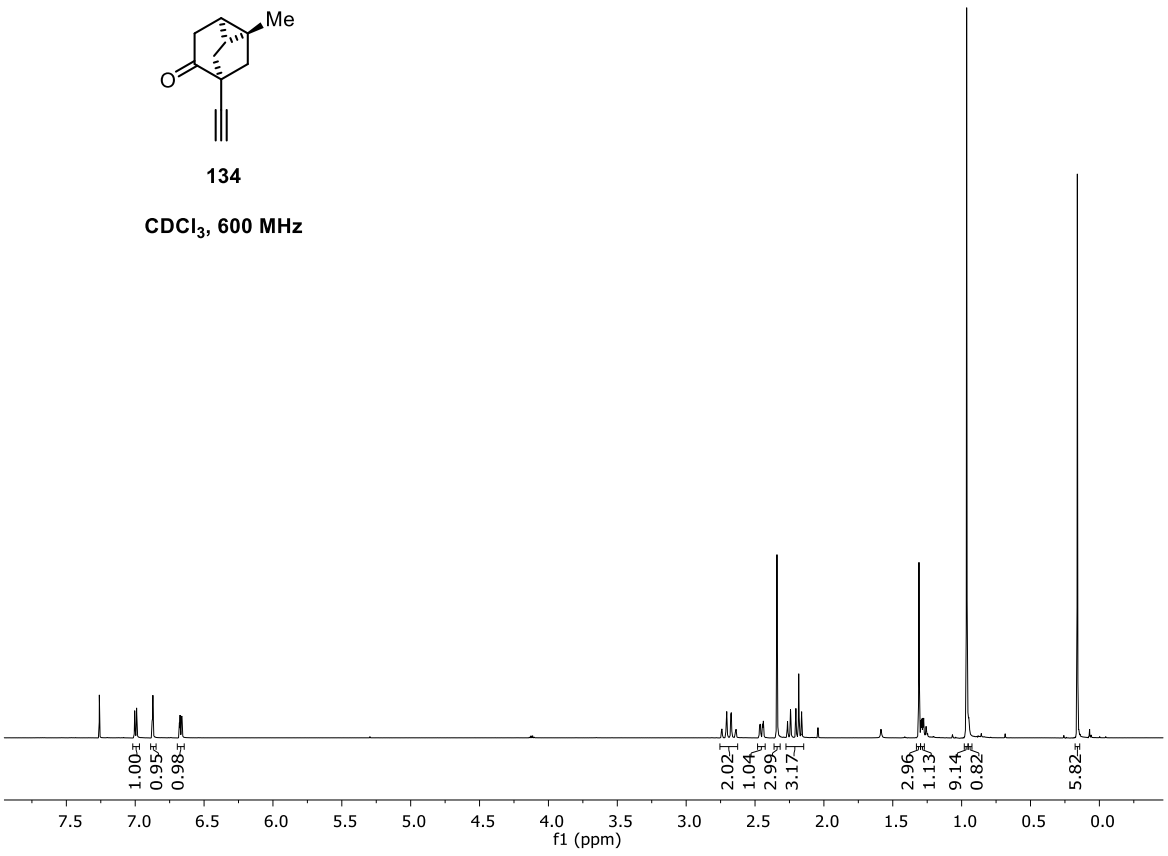
145

$CDCl_3$, 400 MHz



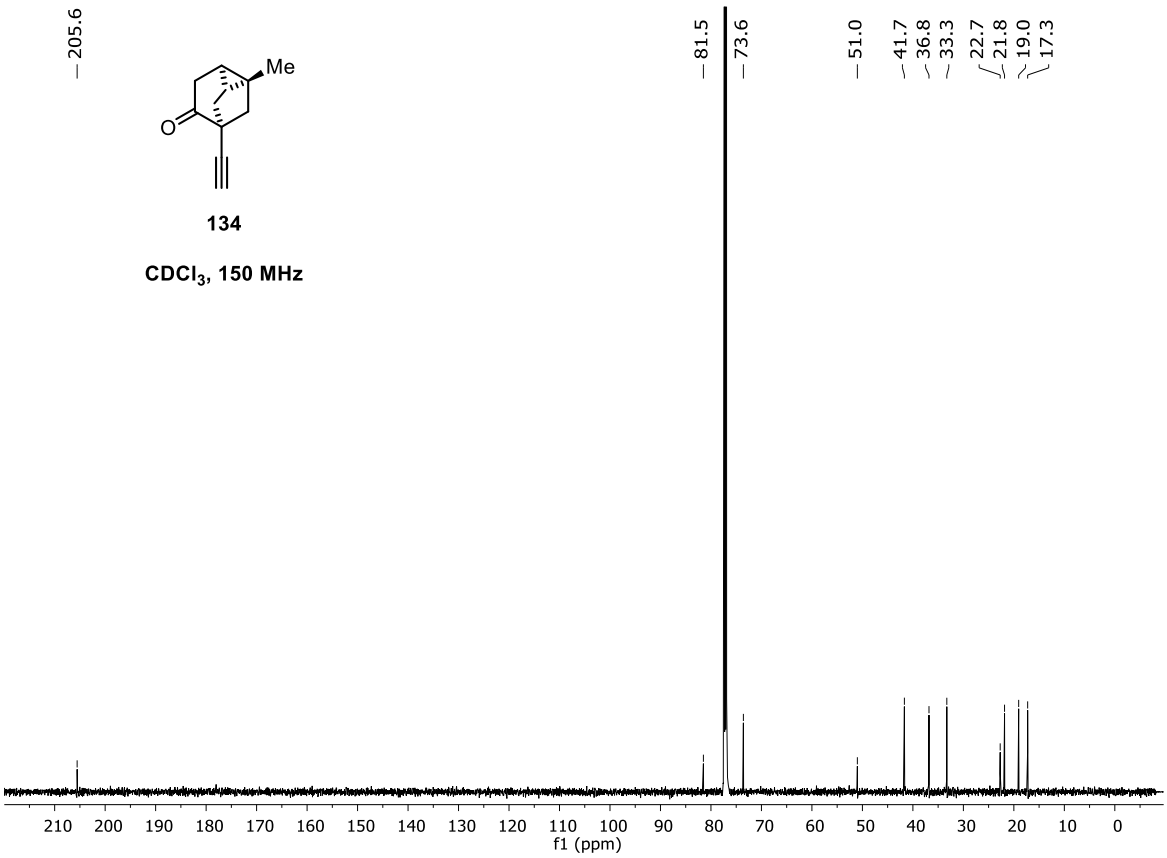
145

$CDCl_3$, 100 MHz



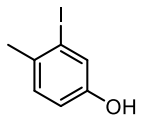
134

$CDCl_3$, 600 MHz



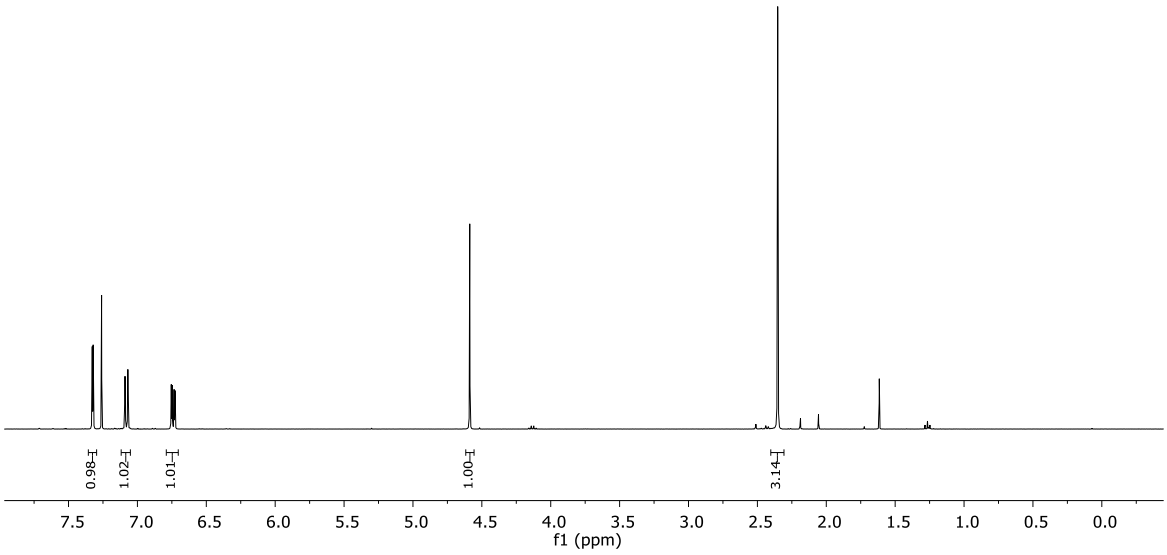
134

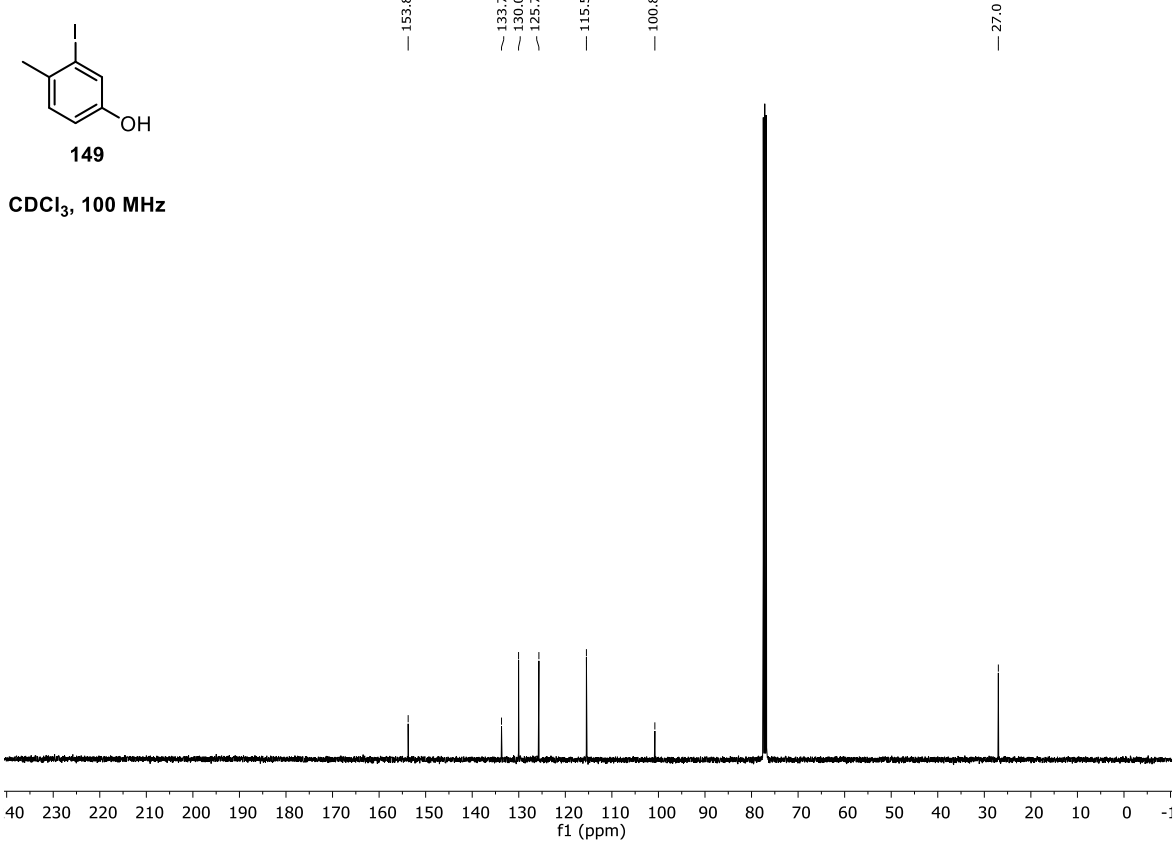
$CDCl_3$, 150 MHz

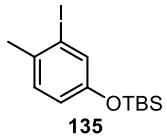


149

$CDCl_3$, 400 MHz

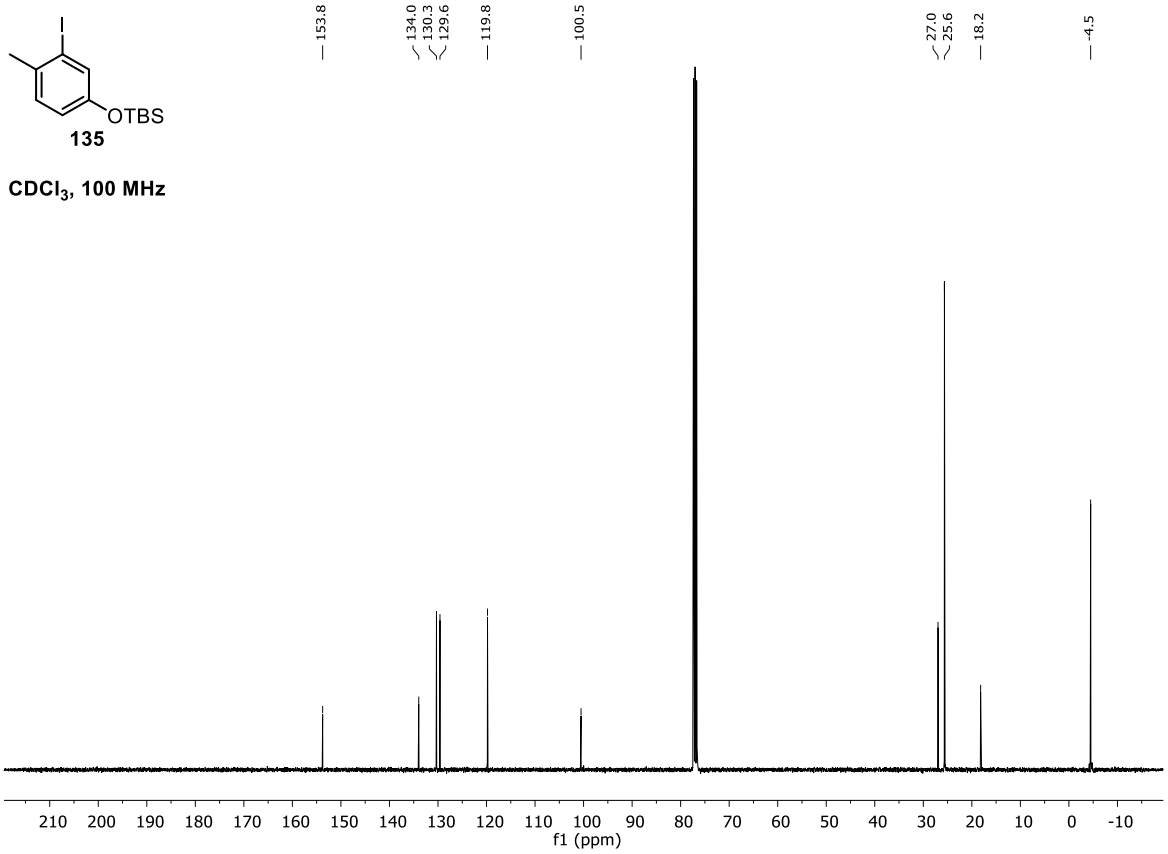


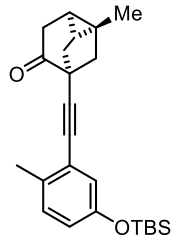

I
OH
149
CDCl3, 100 MHz
153.8
133.7
130.0
125.7
115.5
100.8
27.0
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



135

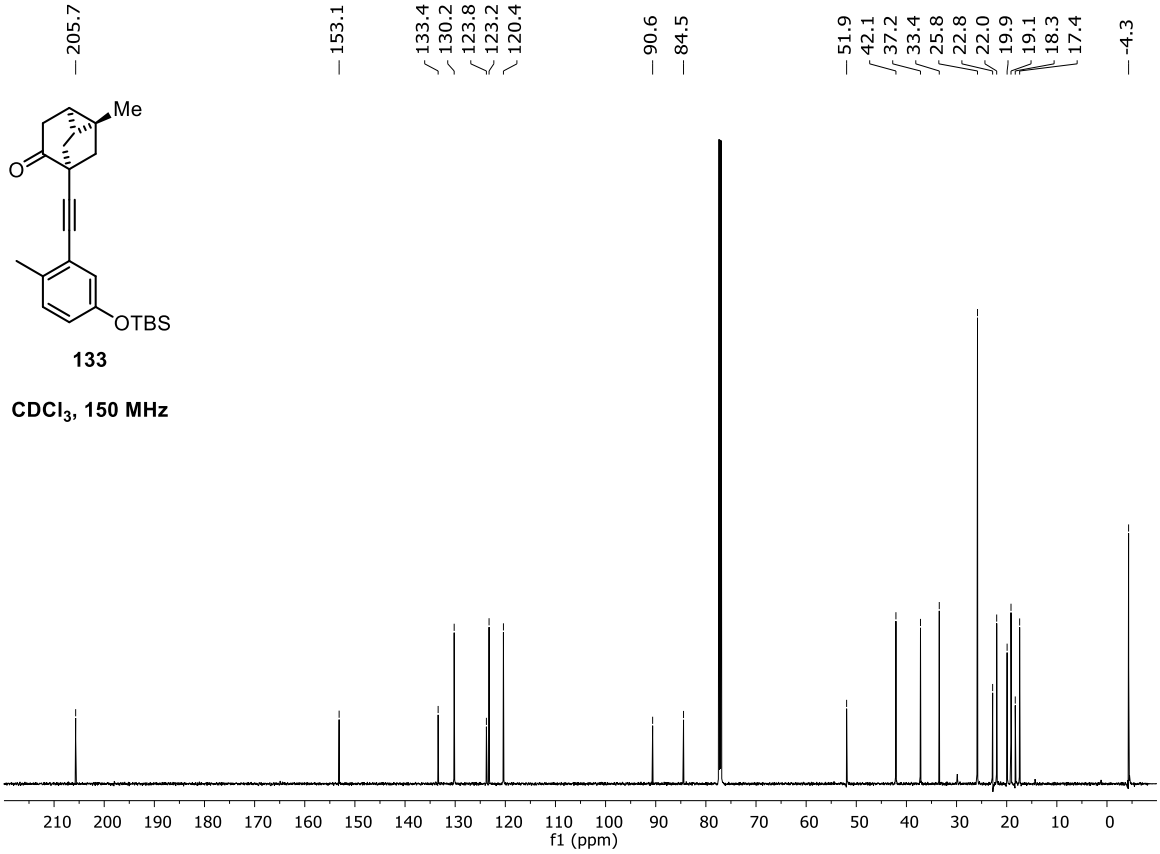
$CDCl_3$, 400 MHz


I
OTBS
135
CDCl3, 100 MHz
153.8
134.0
130.3
129.6
119.8
100.5
27.0
25.6
18.2
-4.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



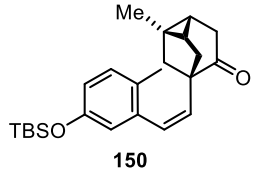
133

$CDCl_3$, 600 MHz



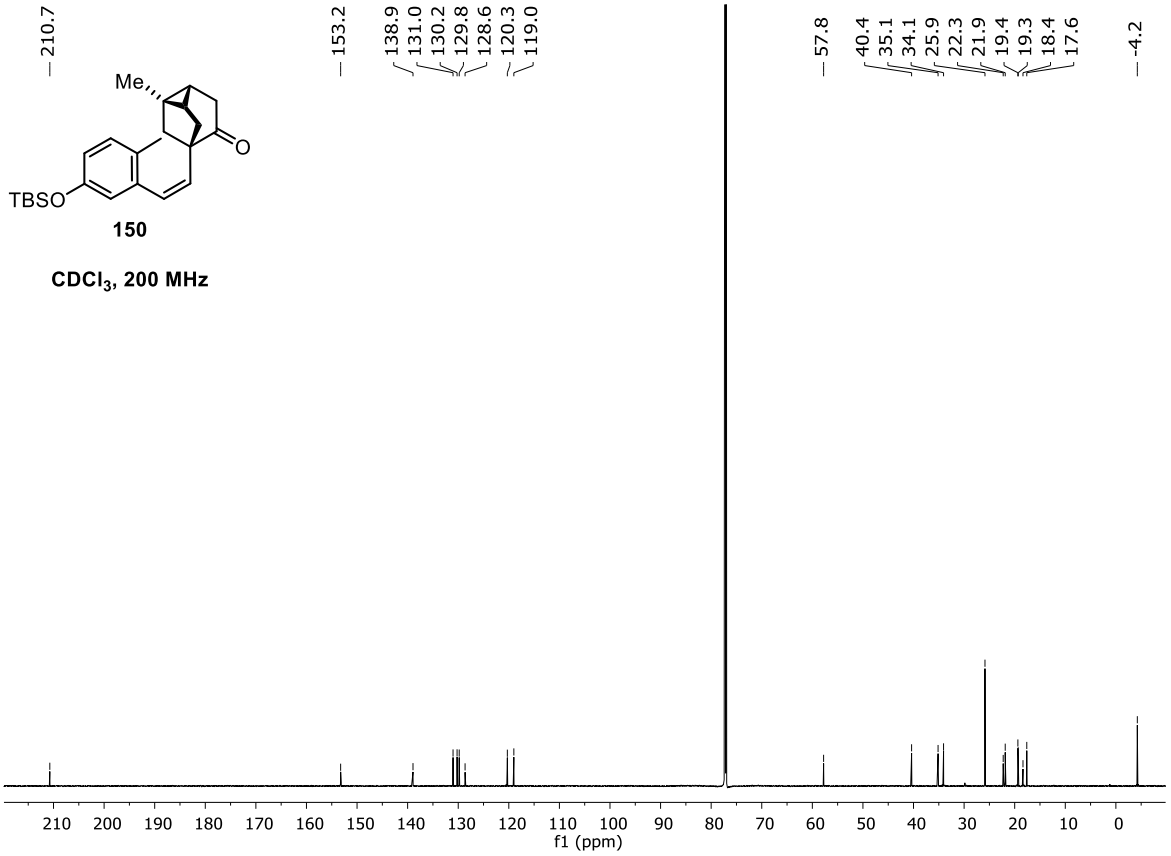
133

$CDCl_3$, 150 MHz



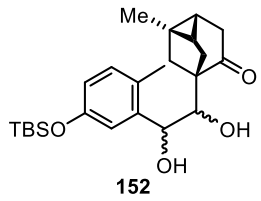
150

$CDCl_3$, 800 MHz



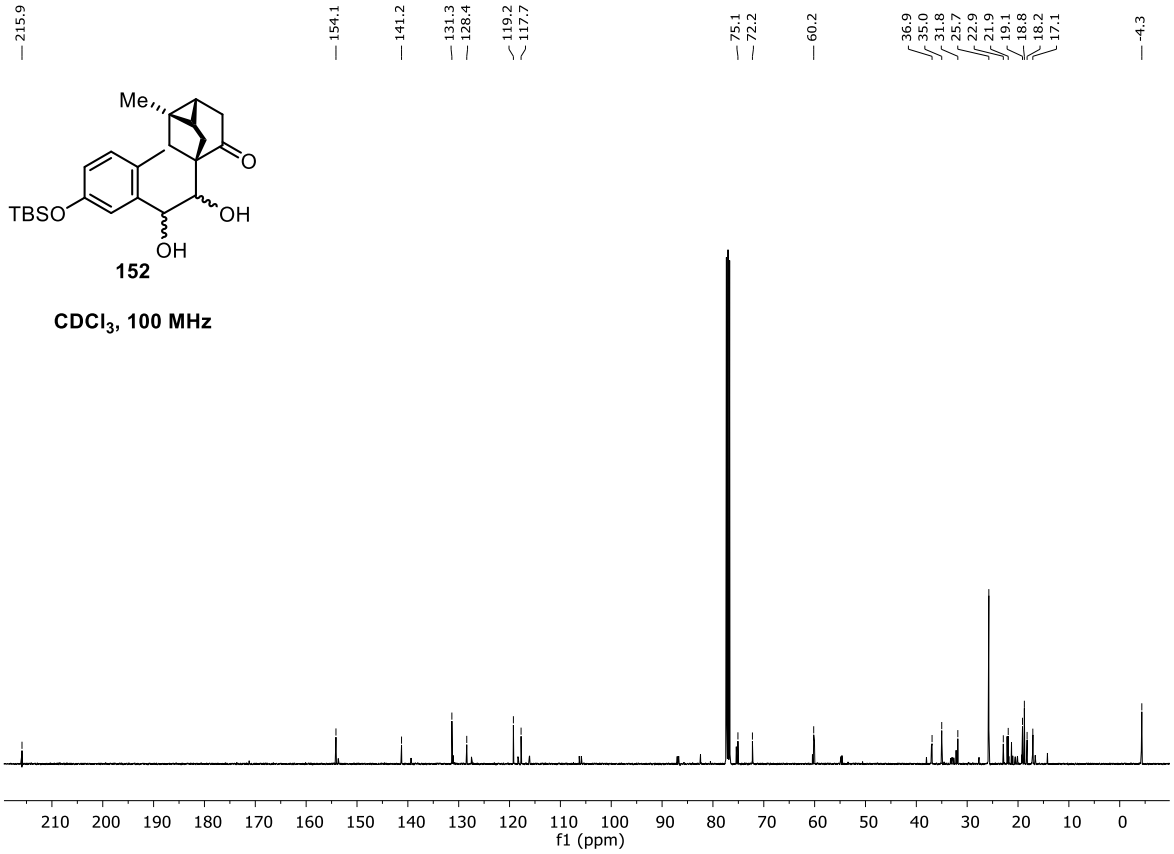
150

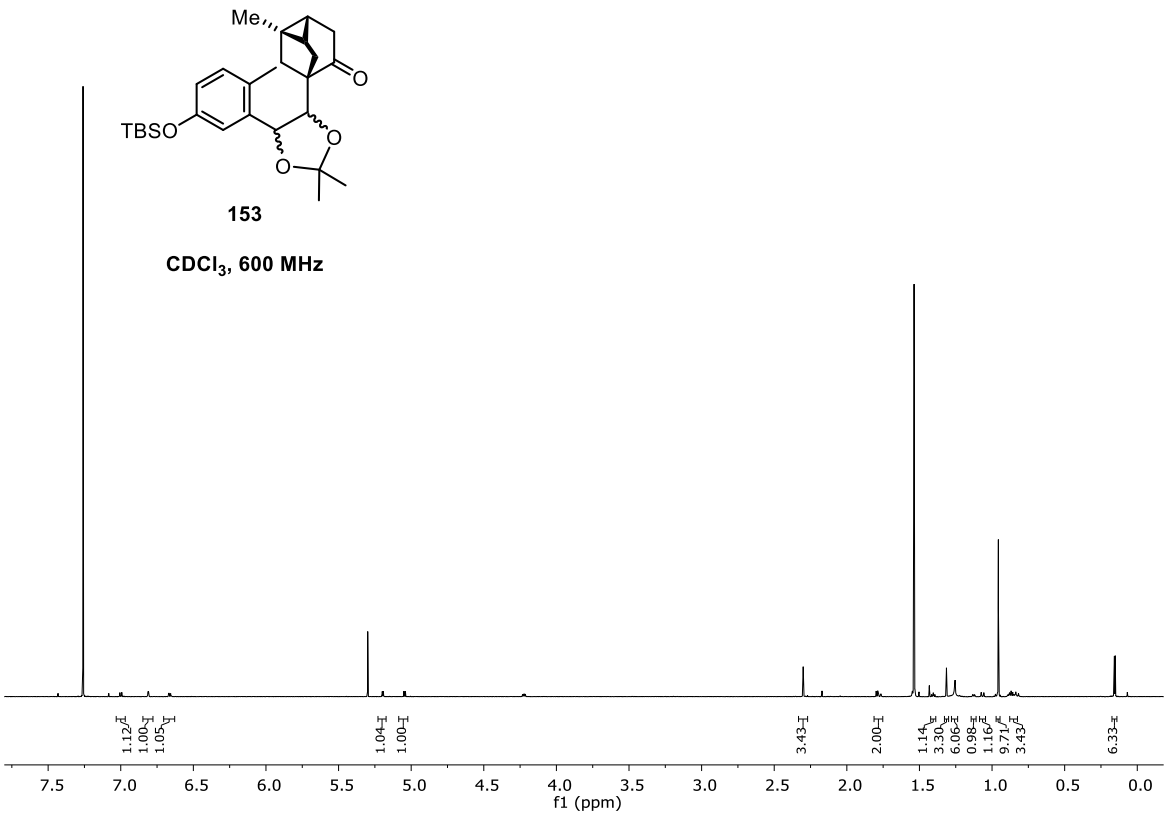
$CDCl_3$, 200 MHz



152

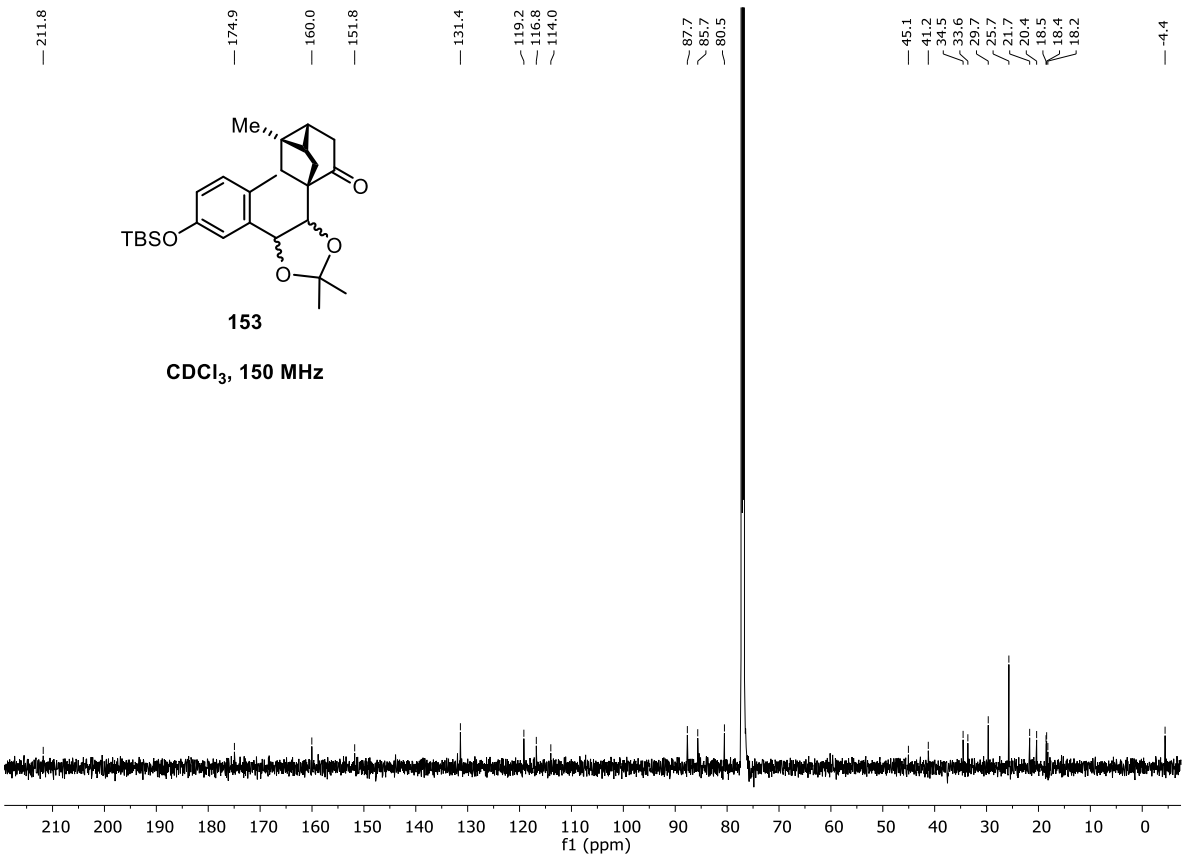
$CDCl_3$, 400 MHz


215.9
154.1
141.2
131.3
128.4
119.2
117.7
75.1
72.2
60.2
36.9
35.0
31.8
25.7
22.9
21.9
19.1
18.8
18.2
17.1
-4.3
Me
O
TBSO
OH
OH
152
CDCl3, 100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



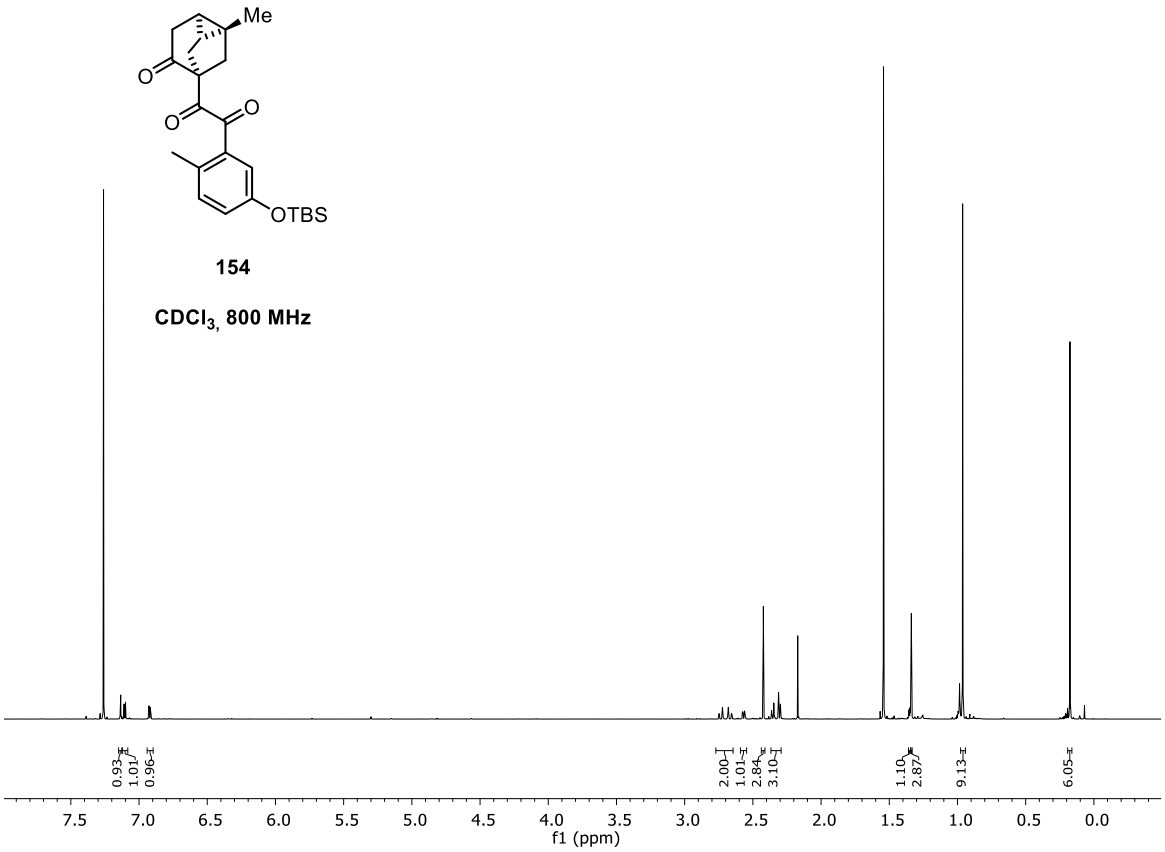
153

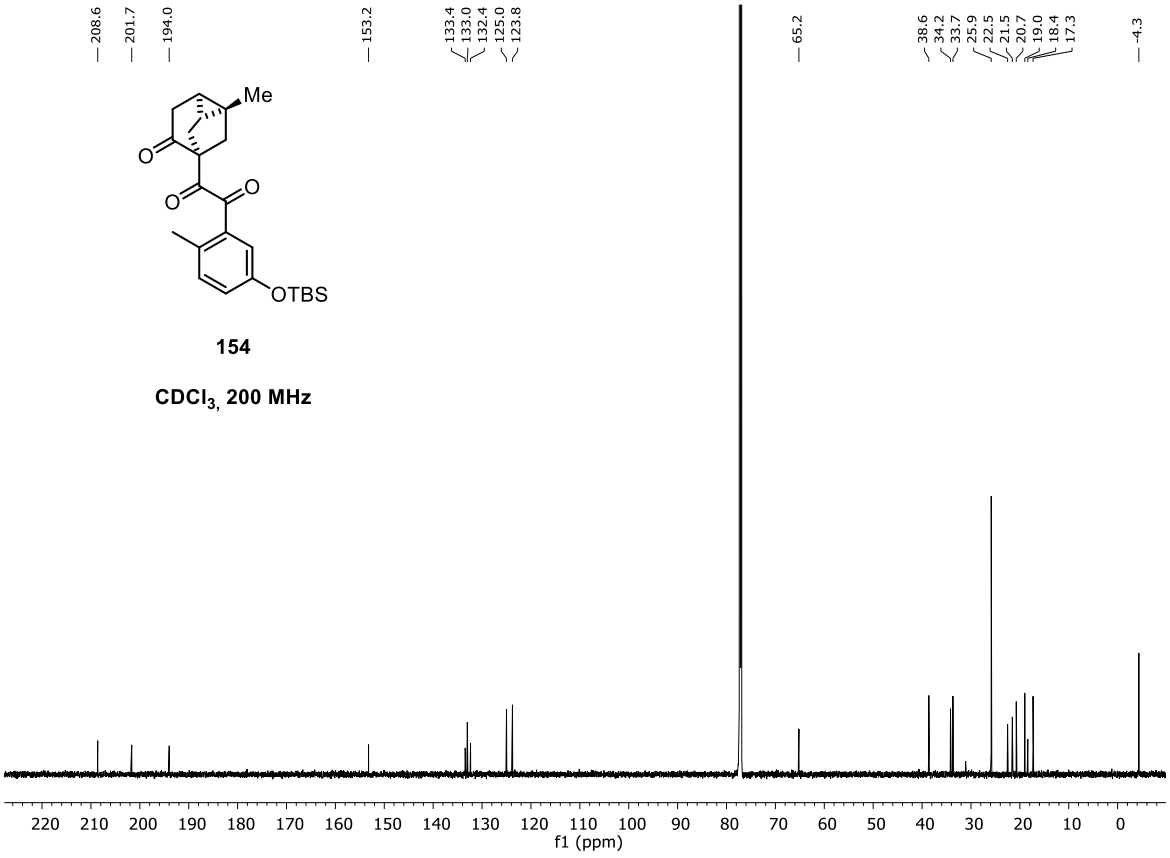
$CDCl_3$, 600 MHz



153

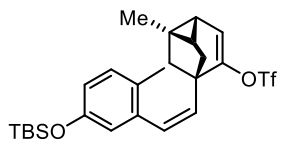
$CDCl_3$, 150 MHz


Me
O
O
O
OTBS
154
CDCl3, 800 MHz
0.93
1.01
0.96
2.00
1.01
2.84
3.10
1.10
2.87
9.13
6.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



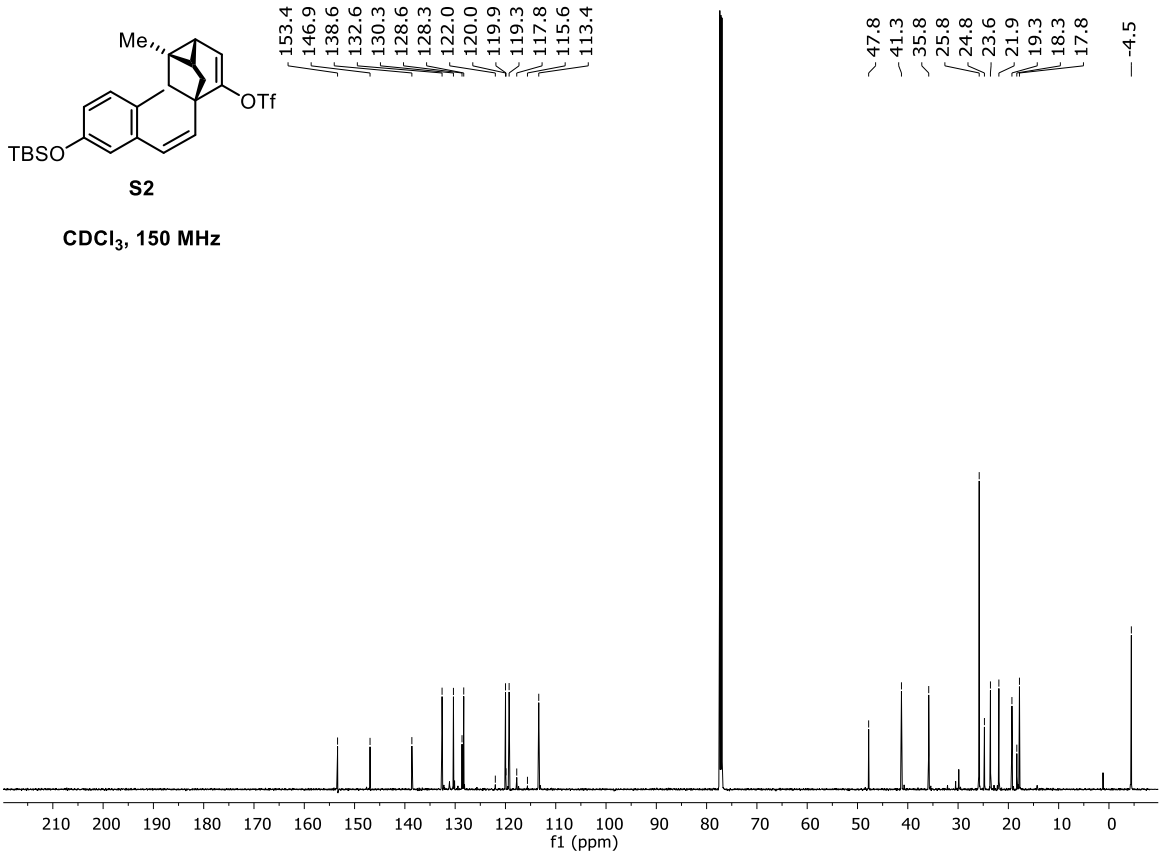
154

$CDCl_3$, 200 MHz



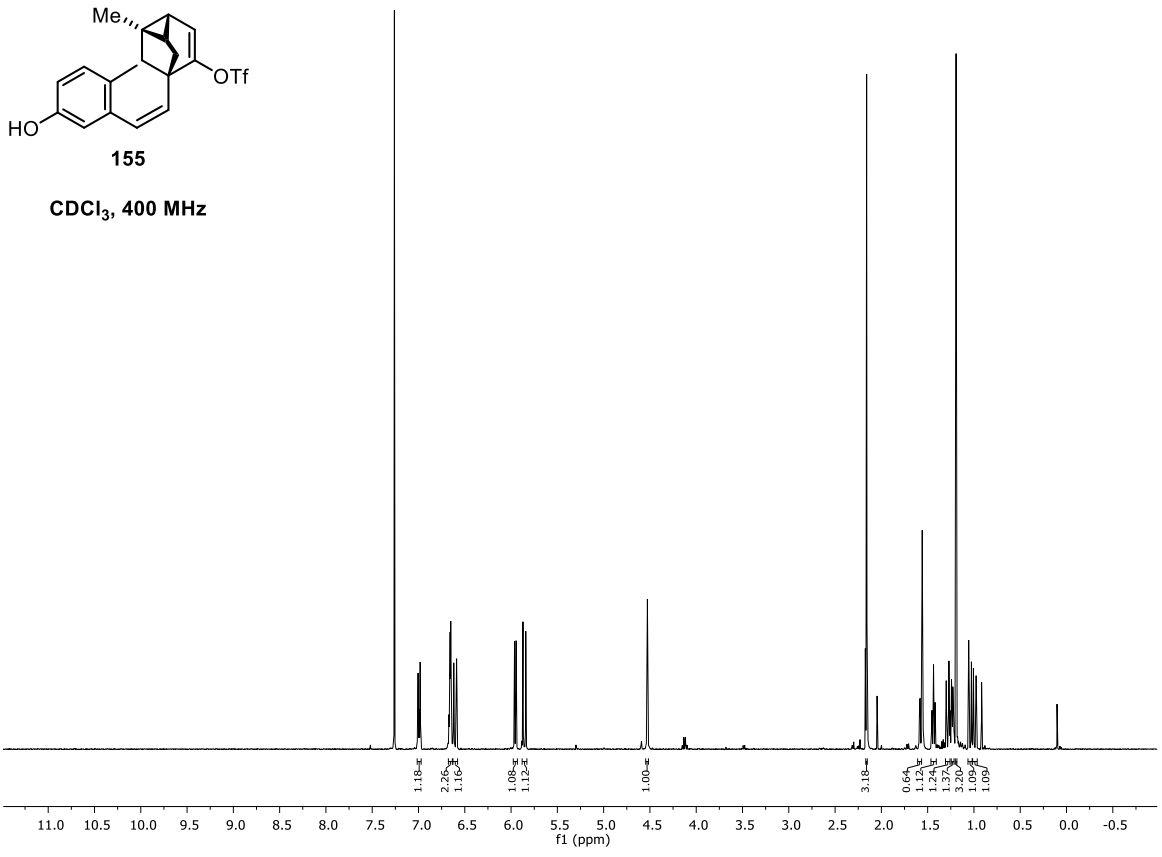
S2

$CDCl_3$, 600 MHz



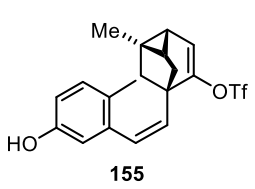
S2

$CDCl_3$, 150 MHz



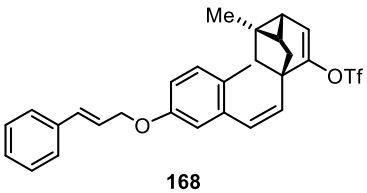
155

$CDCl_3$, 400 MHz



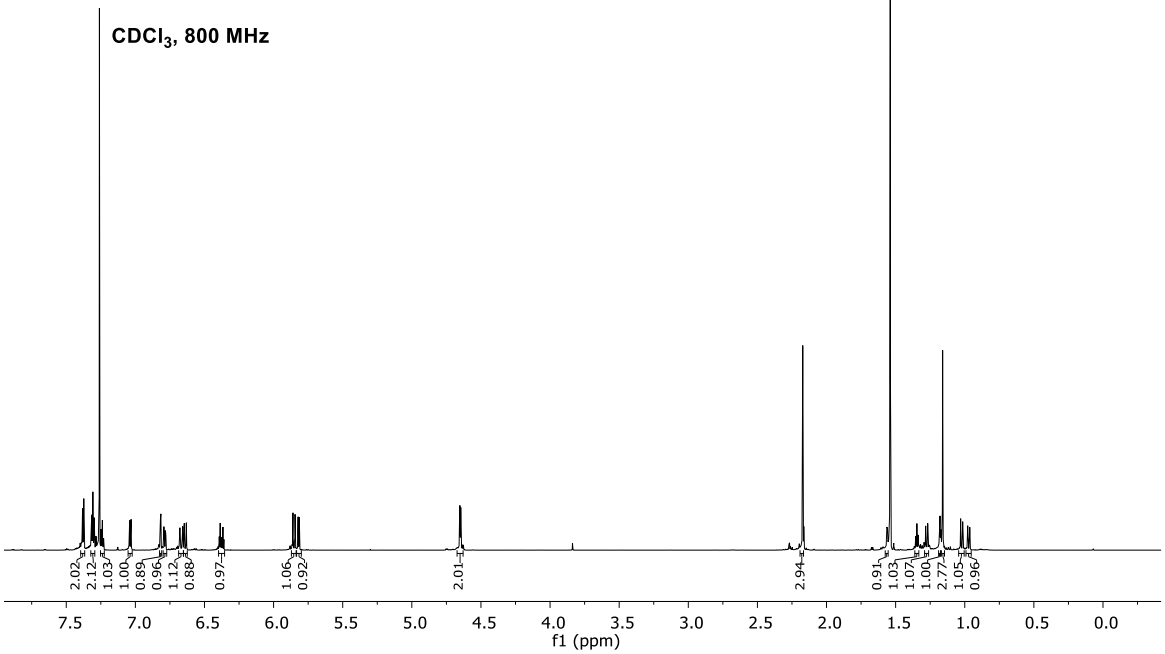
155

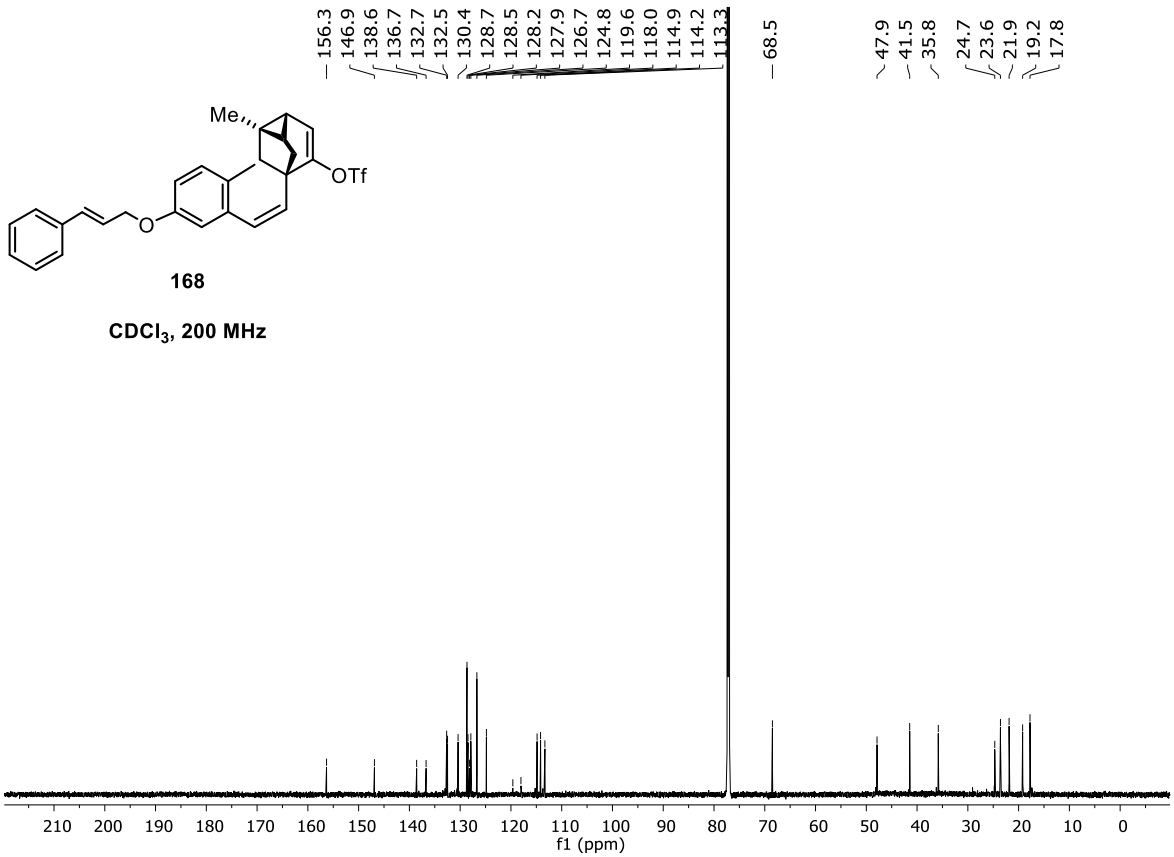
$CDCl_3$, 100 MHz



168

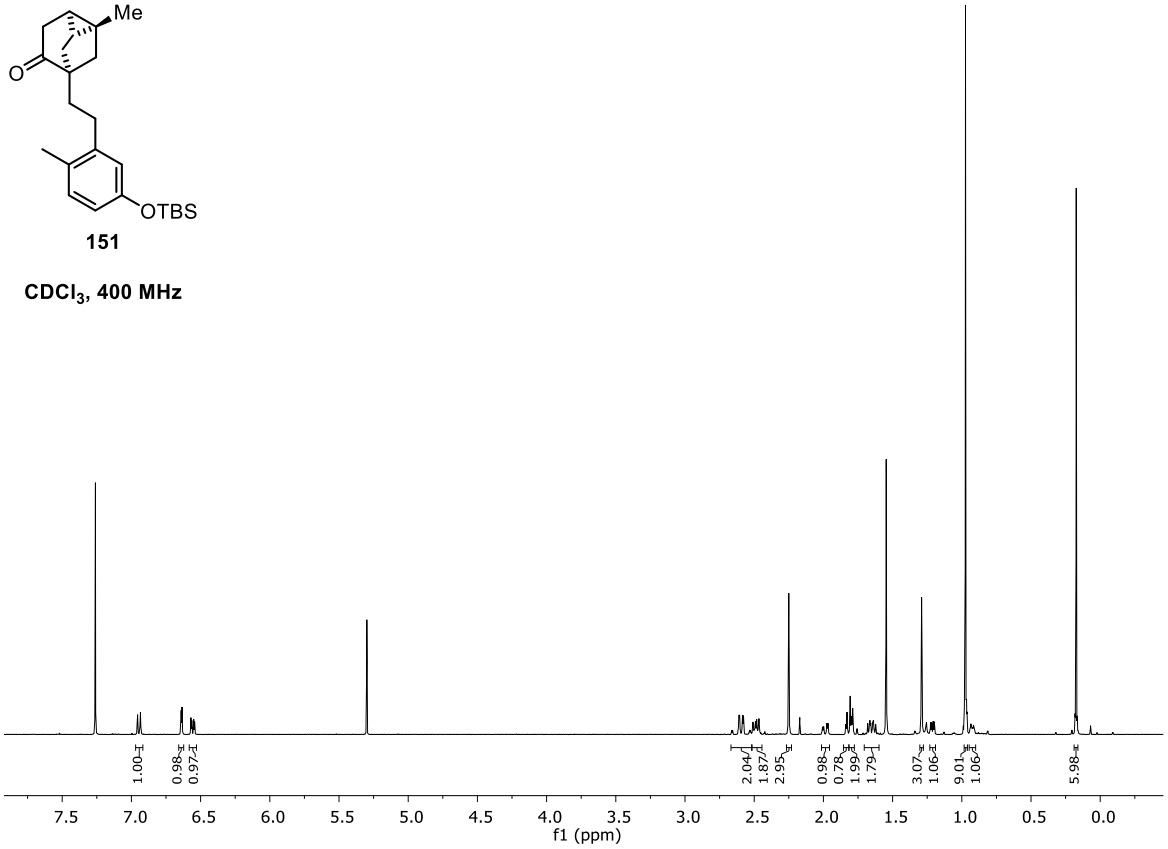
$CDCl_3$, 800 MHz

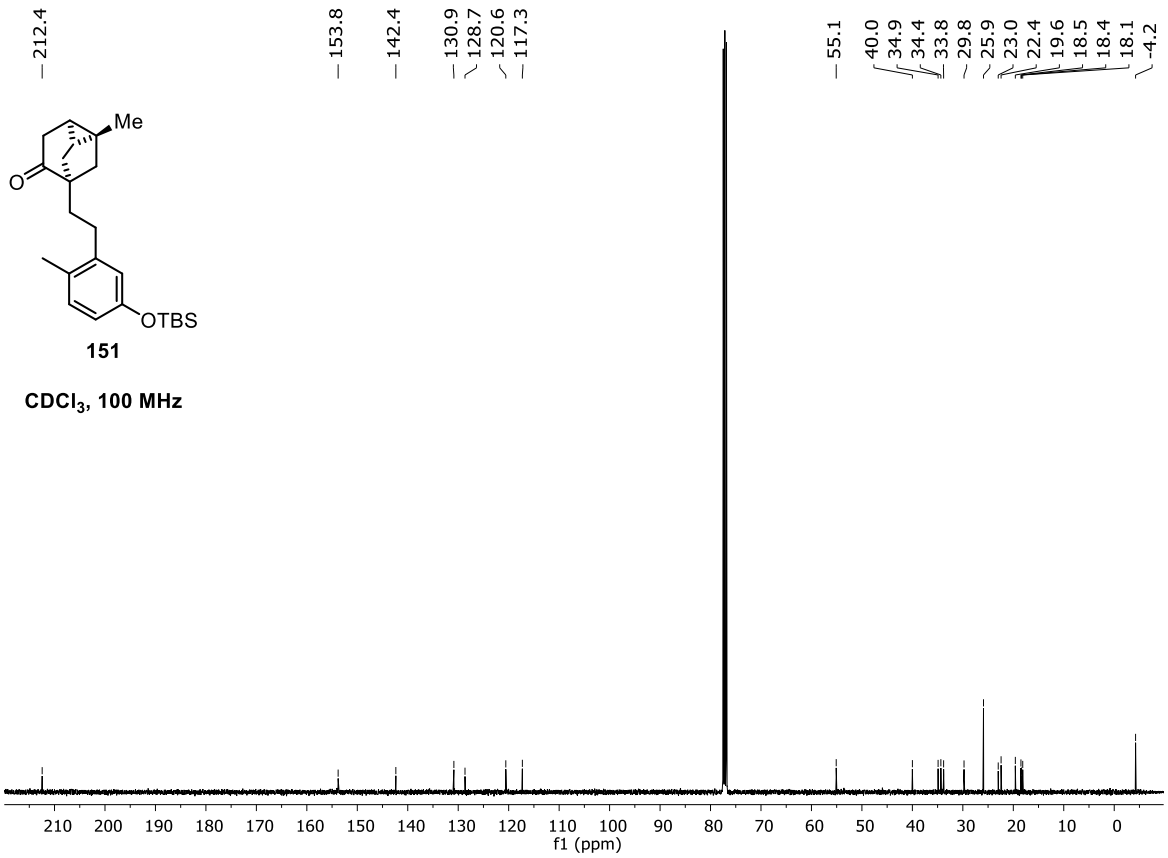




168

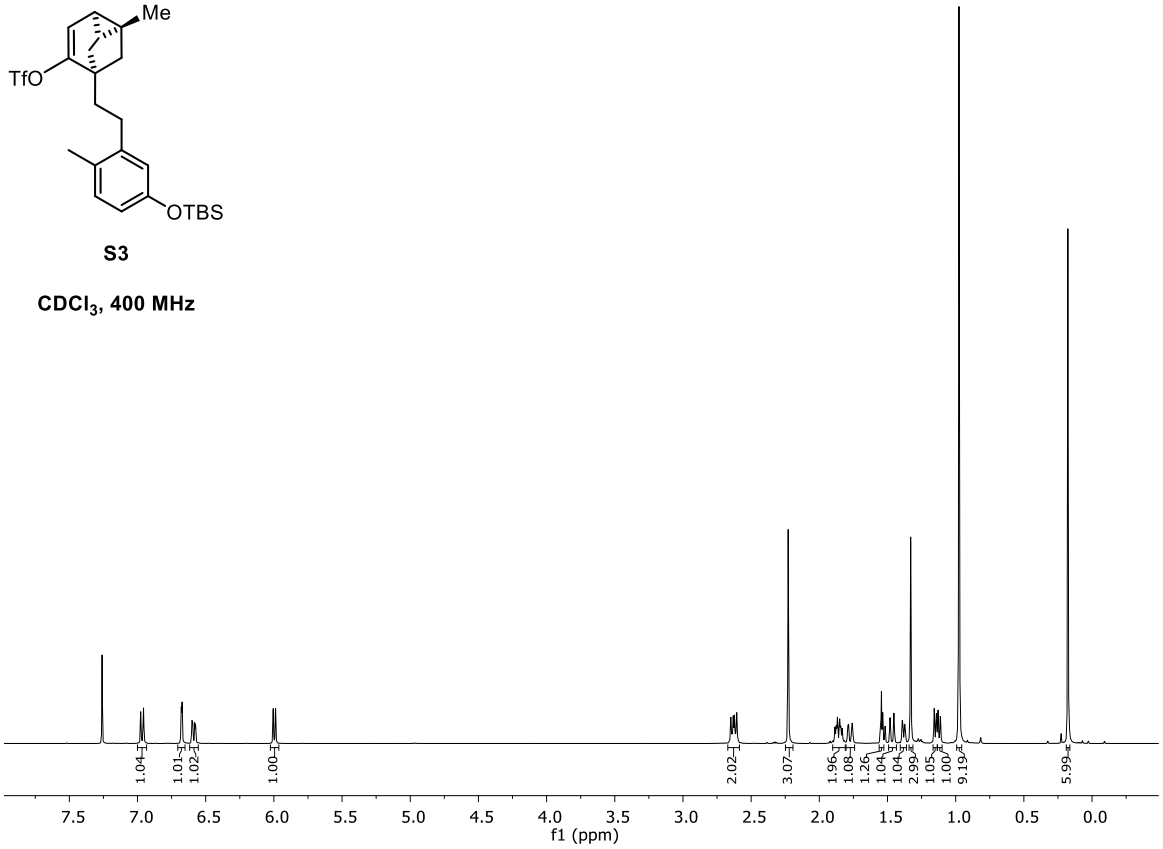
$CDCl_3$, 200 MHz


Me
O
OTBS
151
CDCl3, 400 MHz
1.00
0.98
0.97
2.04
1.87
2.95
0.98
0.78
1.99
1.79
3.07
1.06
9.01
1.06
5.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



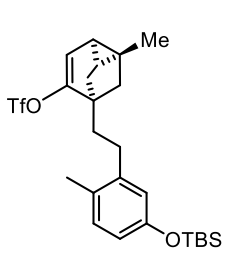
151

$CDCl_3$, 100 MHz



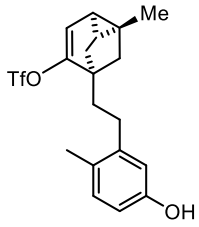
S3

$CDCl_3$, 400 MHz



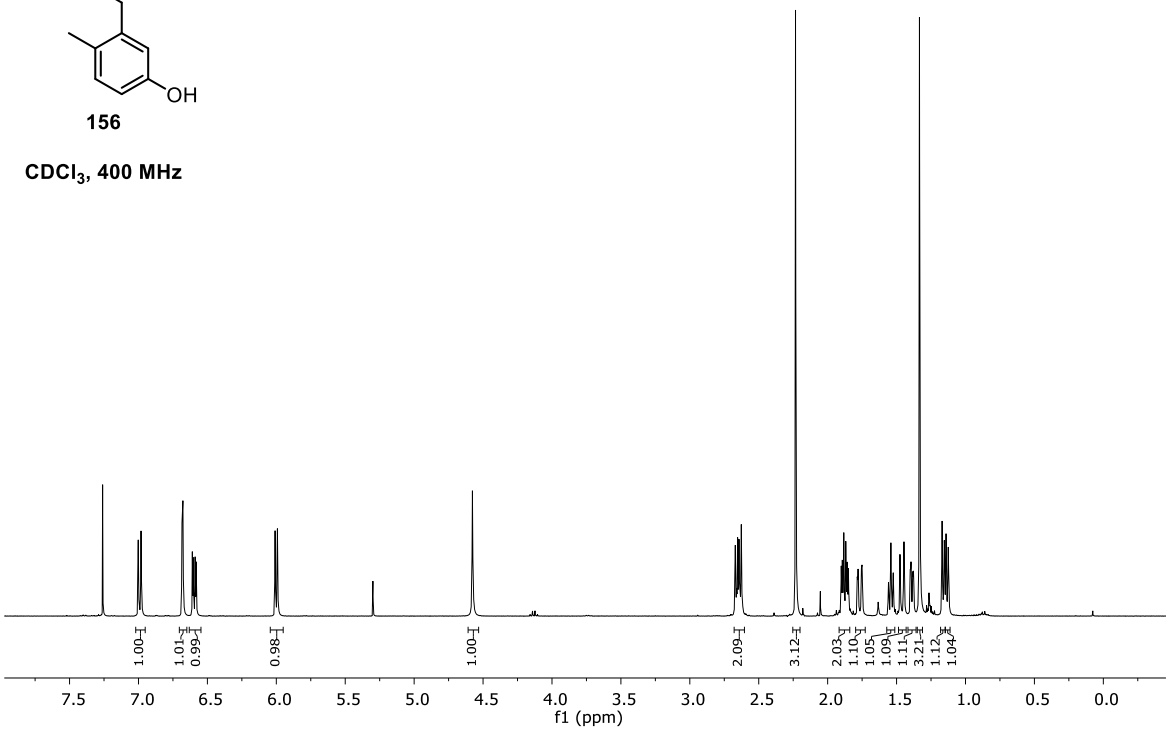
S3

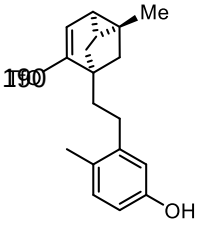
$CDCl_3$, 100 MHz



156

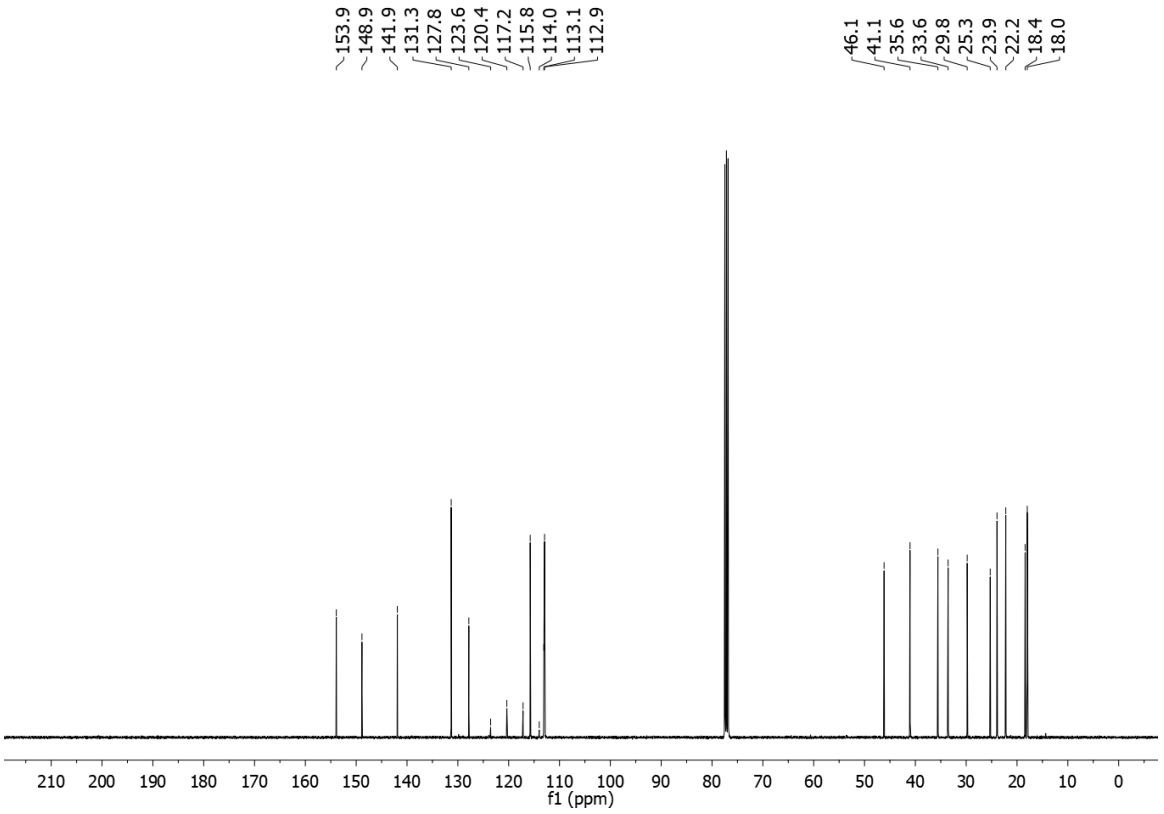
$CDCl_3$, 400 MHz

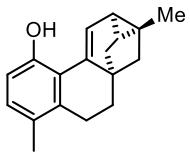




190

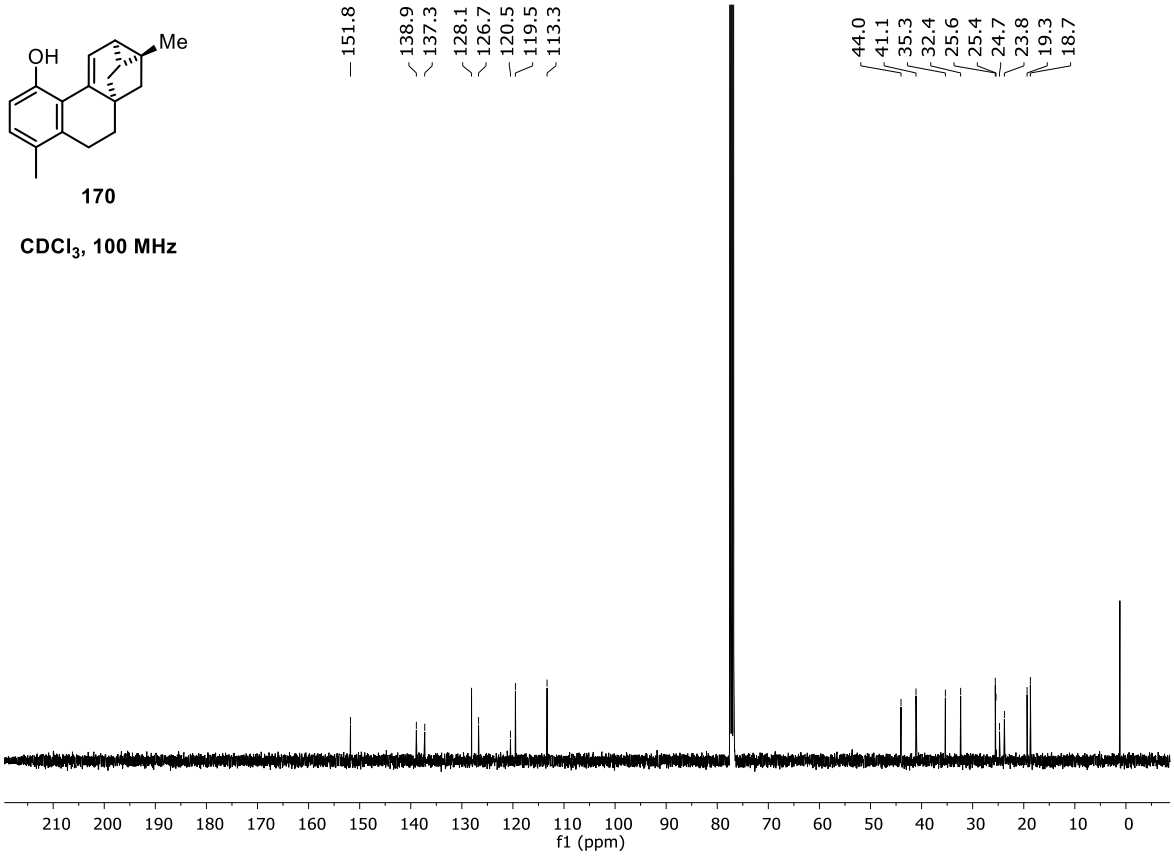
156





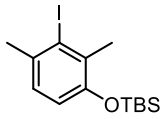
170

$CDCl_3$, 400 MHz



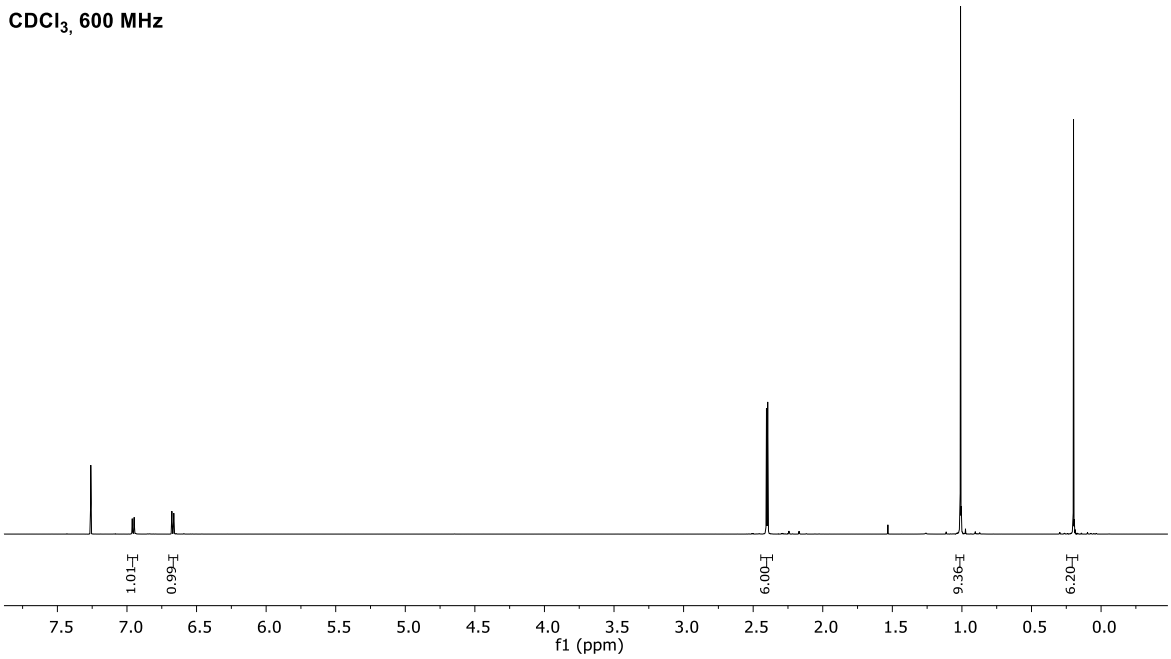
170

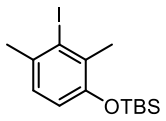
$CDCl_3$, 100 MHz



174

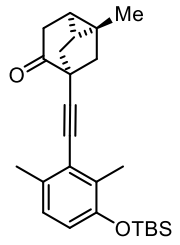
$CDCl_3$, 600 MHz





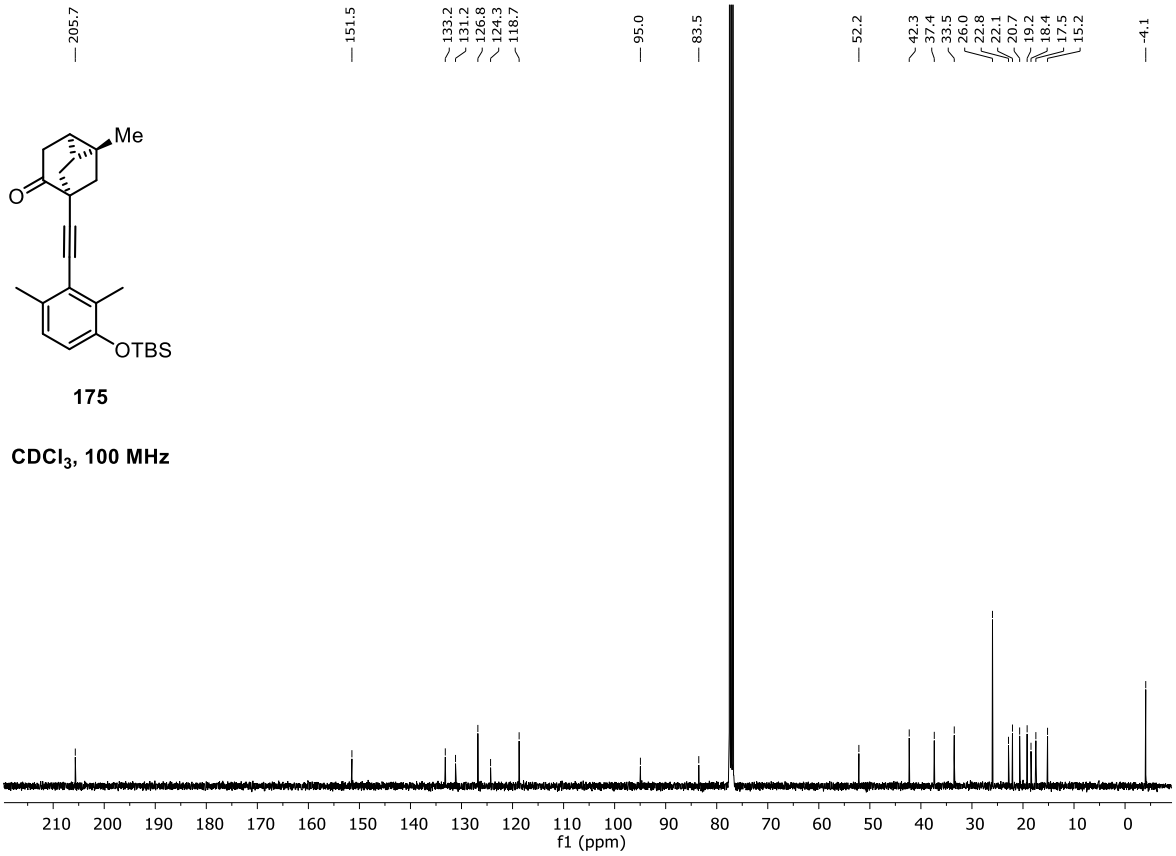
174

$CDCl_3$, 150 MHz



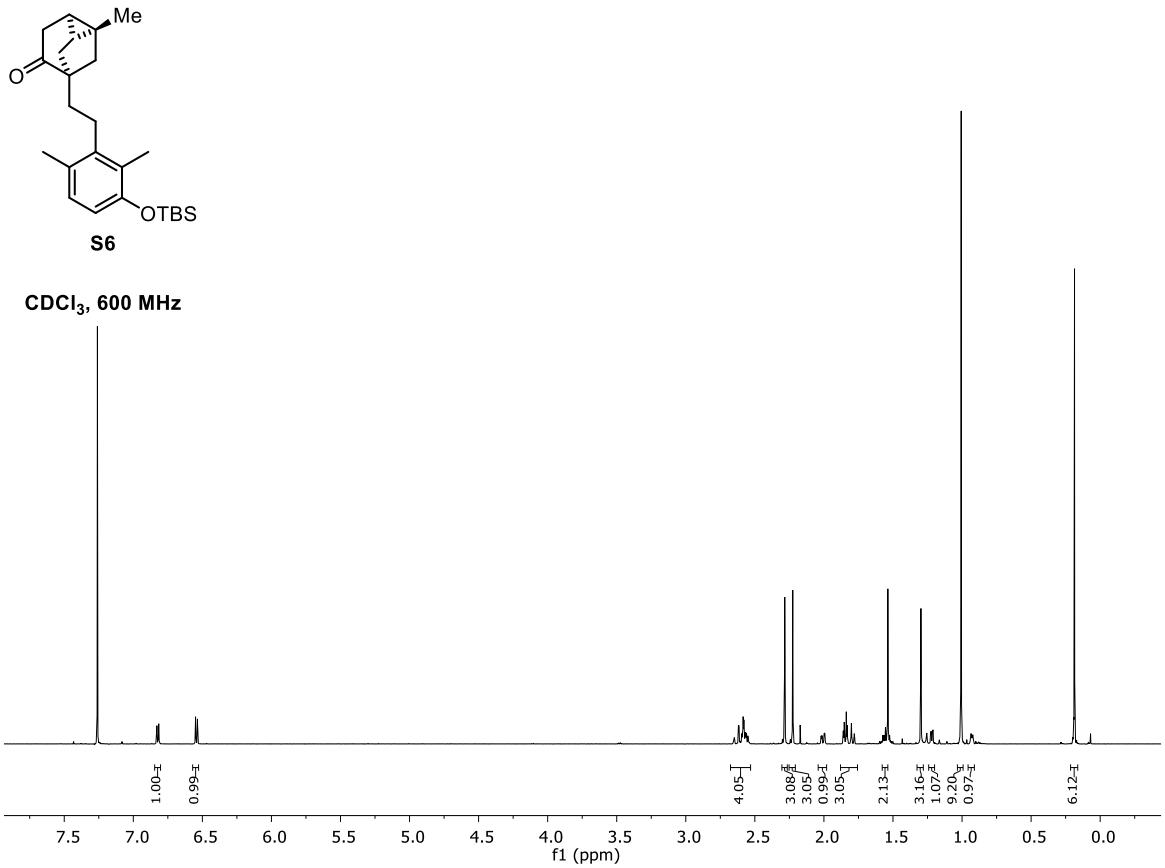
175

$CDCl_3$, 400 MHz



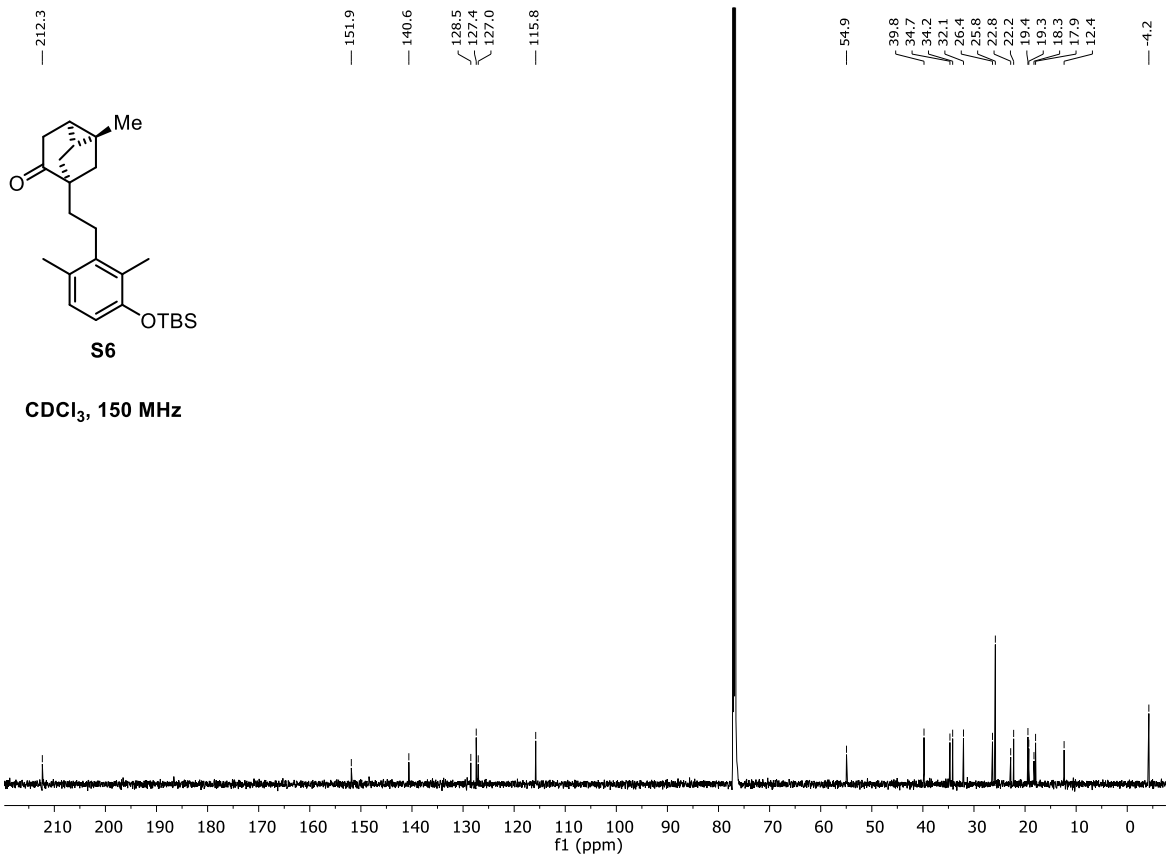
175

$CDCl_3$, 100 MHz



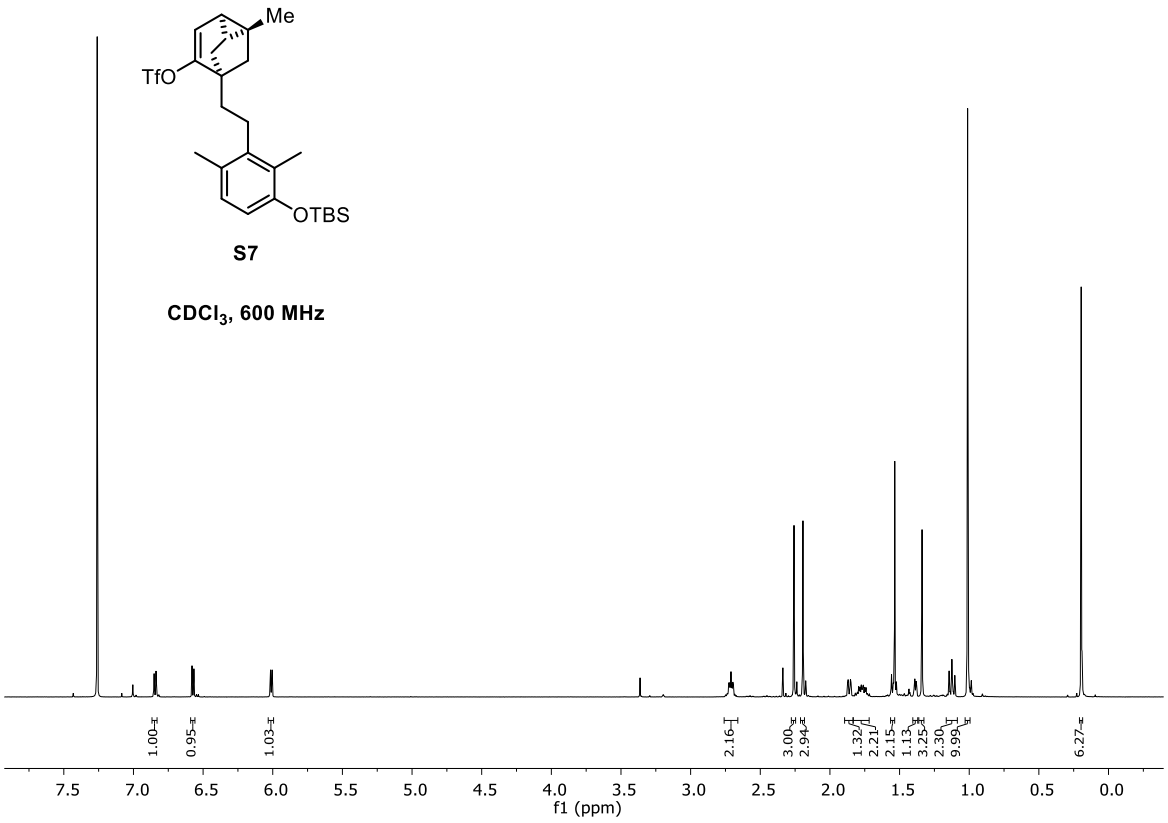
S6

$CDCl_3$, 600 MHz



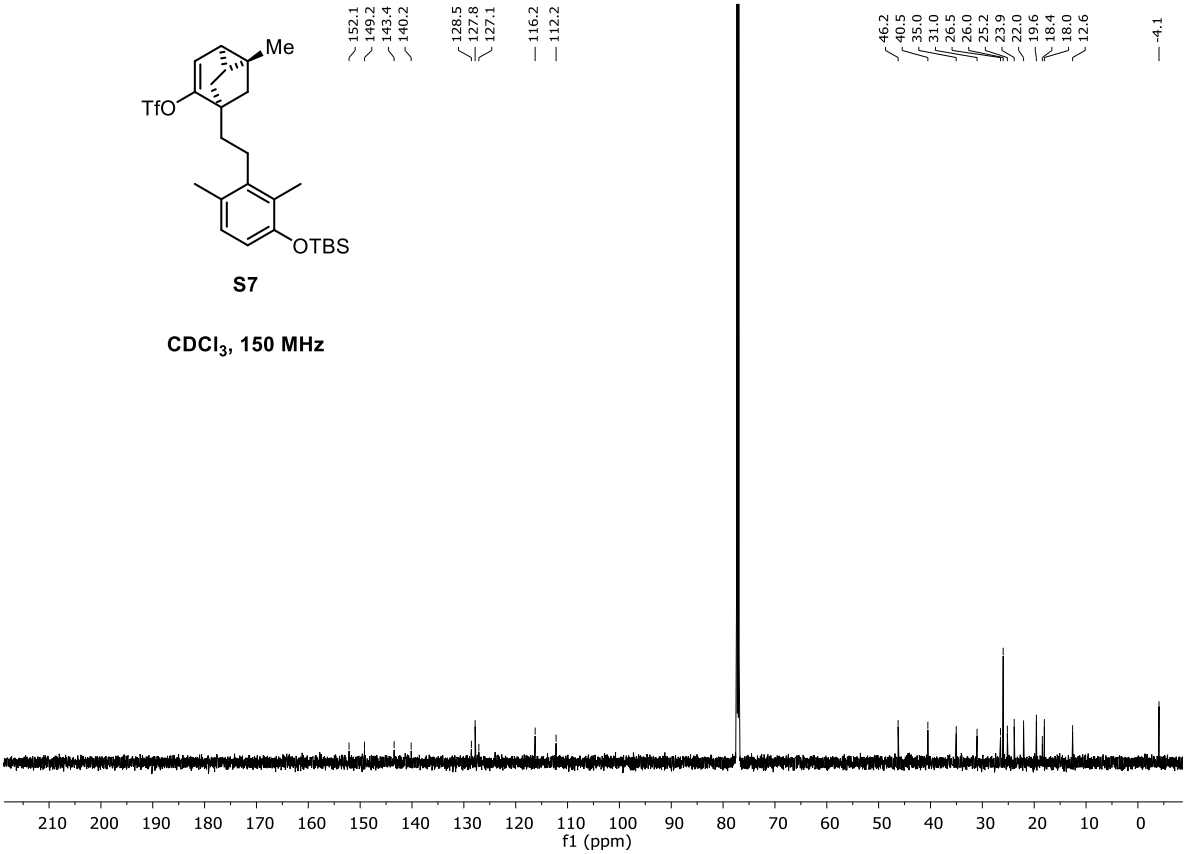
S6

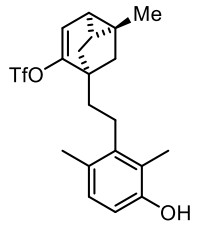
$CDCl_3$, 150 MHz



S7

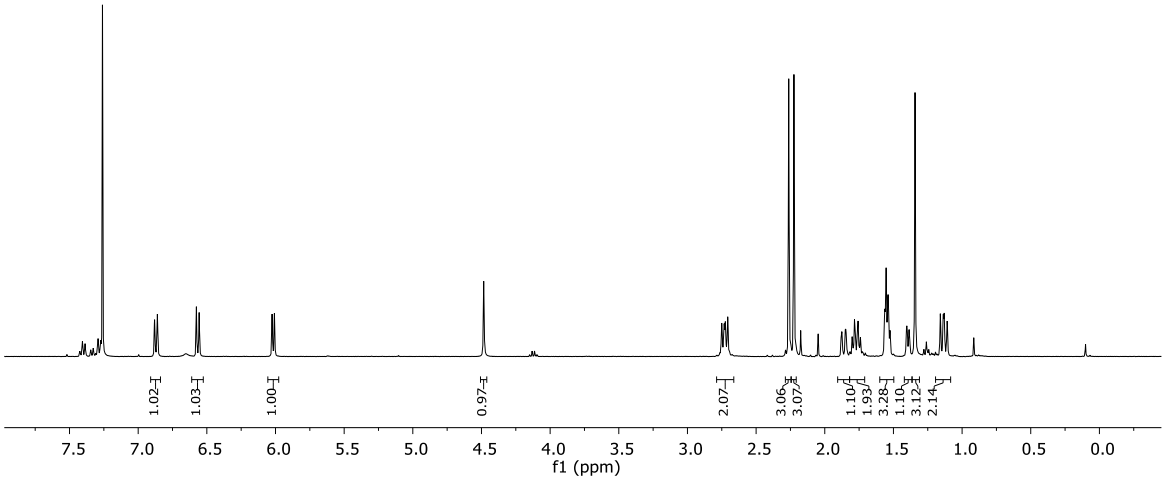
$CDCl_3$, 600 MHz

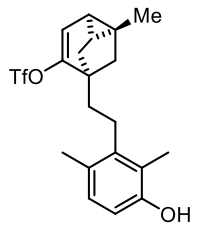

Me
TfO
OTBS
S7
CDCl3, 150 MHz
152.1
149.2
143.4
140.2
128.5
127.8
127.1
116.2
112.2
46.2
40.5
35.0
31.0
26.5
26.0
25.2
23.9
22.0
19.6
18.4
18.0
12.6
-4.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



127

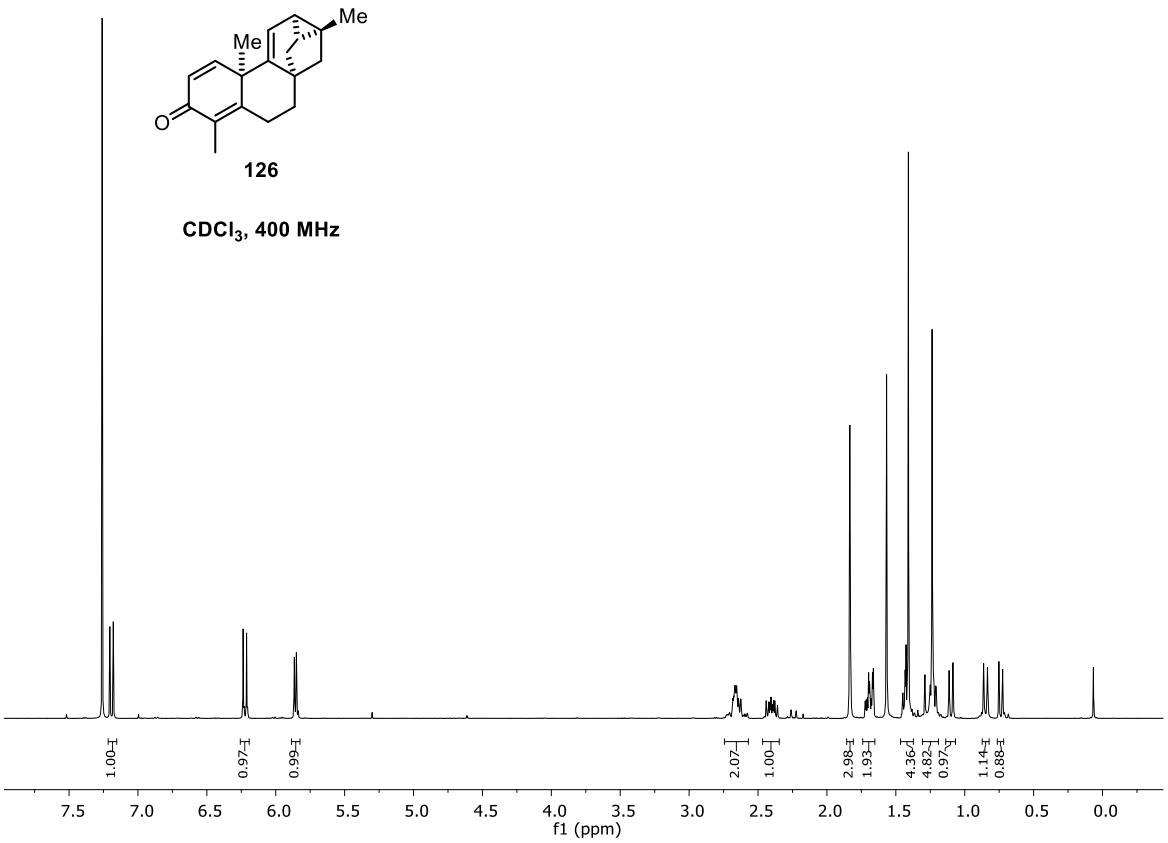
$CDCl_3$, 400 MHz

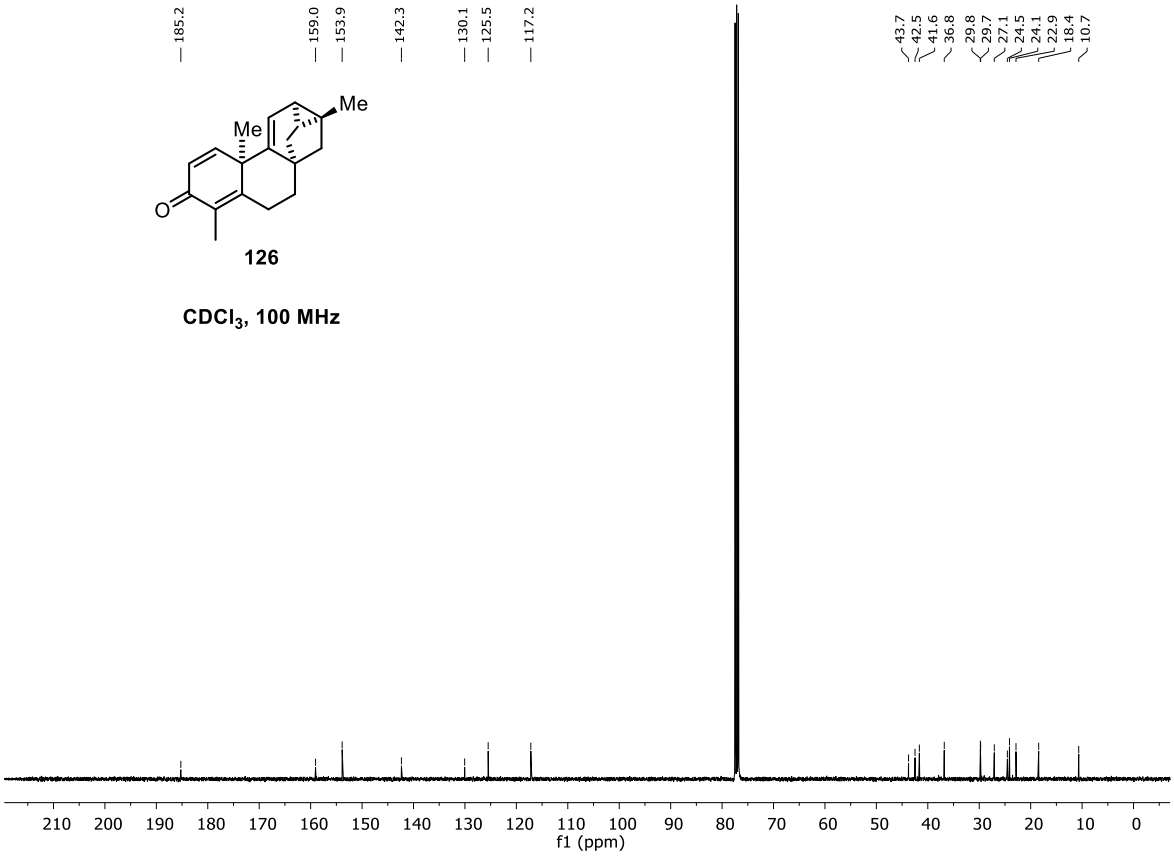


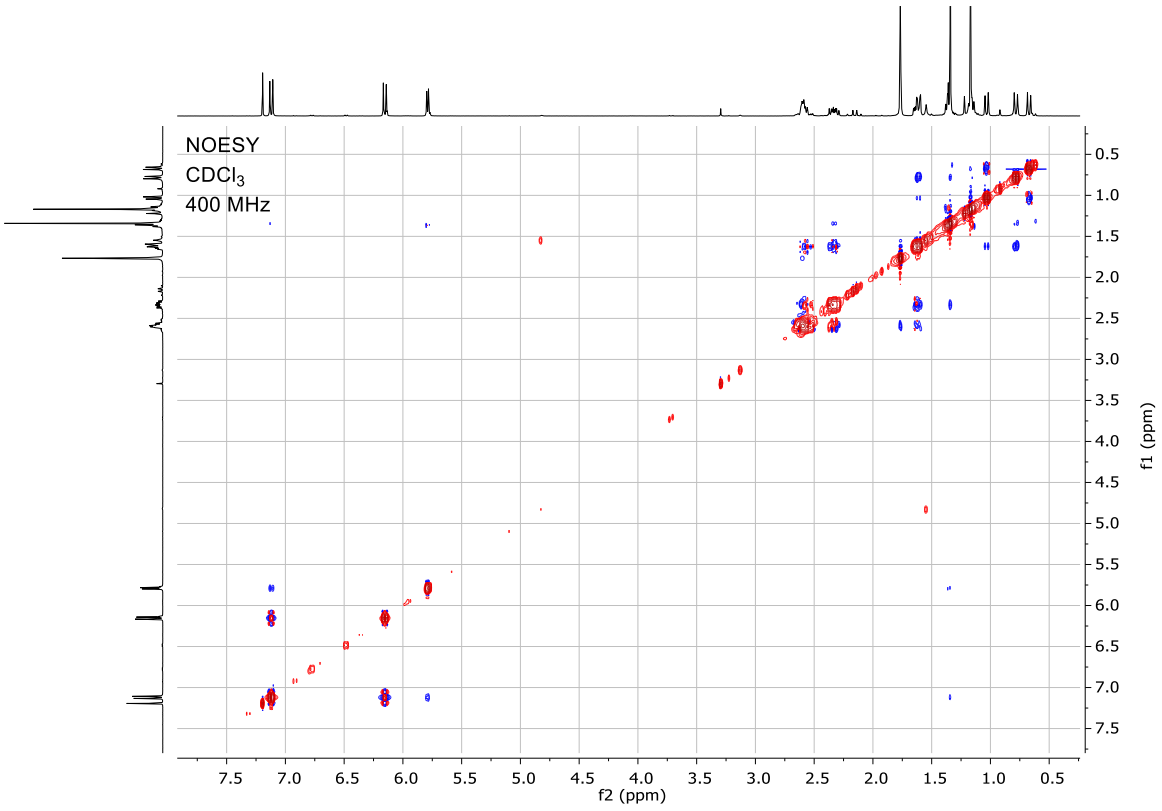


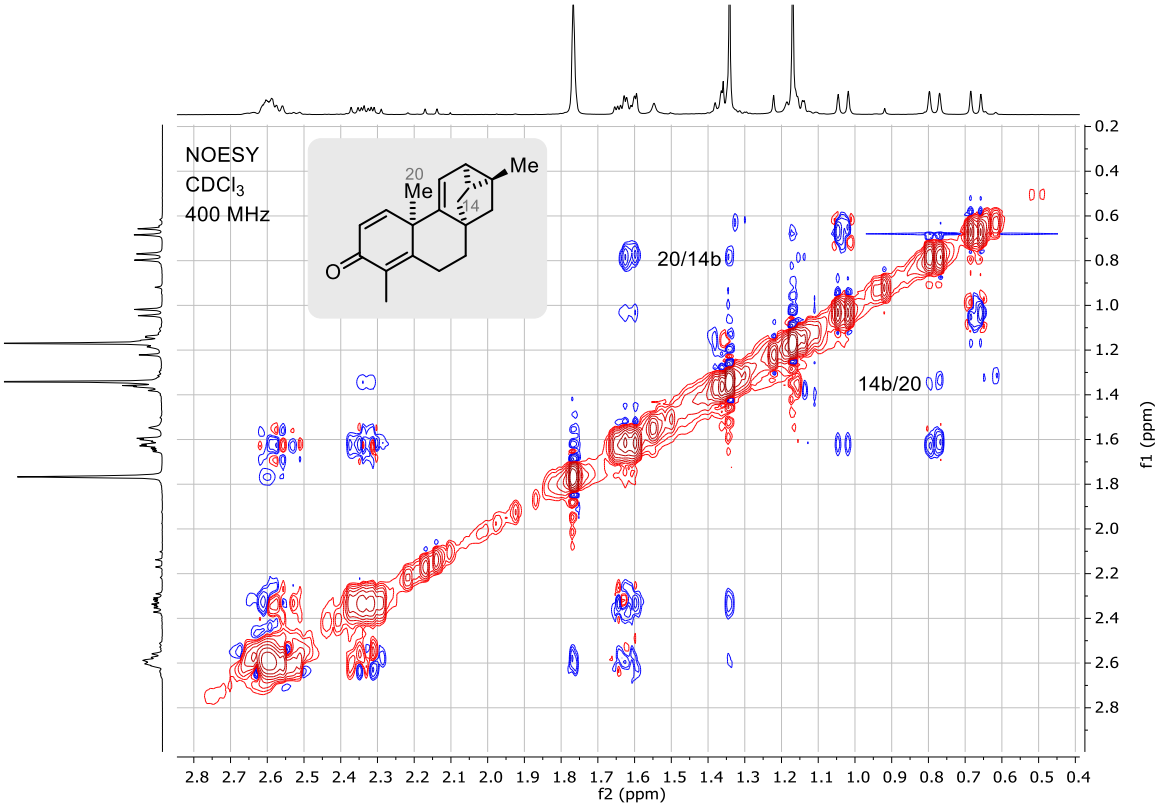
127

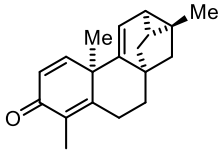
$CDCl_3$, 100 MHz


Me
Me
O
126
CDCl3, 400 MHz
1.00
0.97
0.99
2.07
1.00
2.98
1.93
4.36
4.82
0.97
1.14
0.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


185.2
159.0
153.9
142.3
130.1
125.5
117.2
43.7
42.5
41.6
36.8
29.8
29.7
27.1
24.5
24.1
22.9
18.4
10.7
Me
Me
O
126
CDCl3, 100 MHz
f1 (ppm)

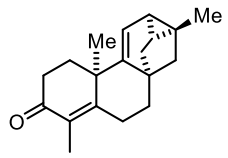

NOESY
CDCl3
400 MHz
f2 (ppm)
f1 (ppm)





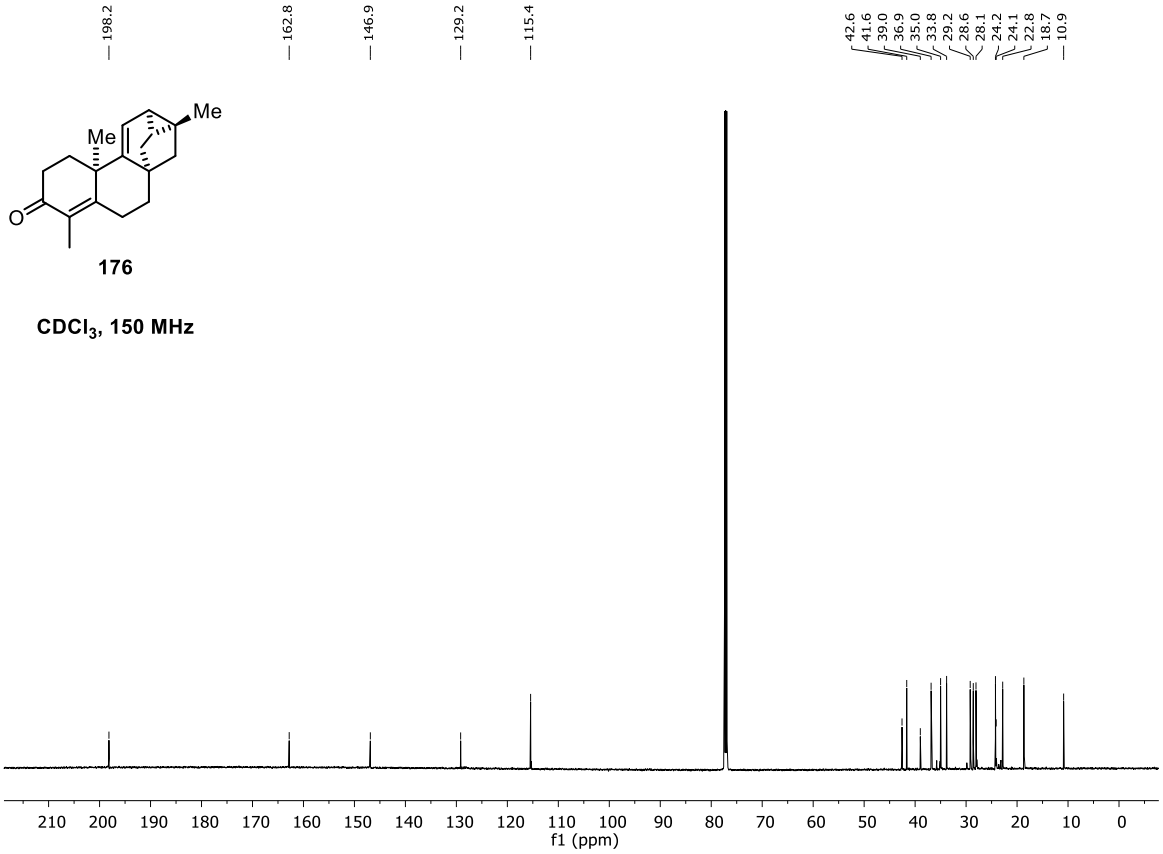
XX

$CDCl_3$, 100 MHz



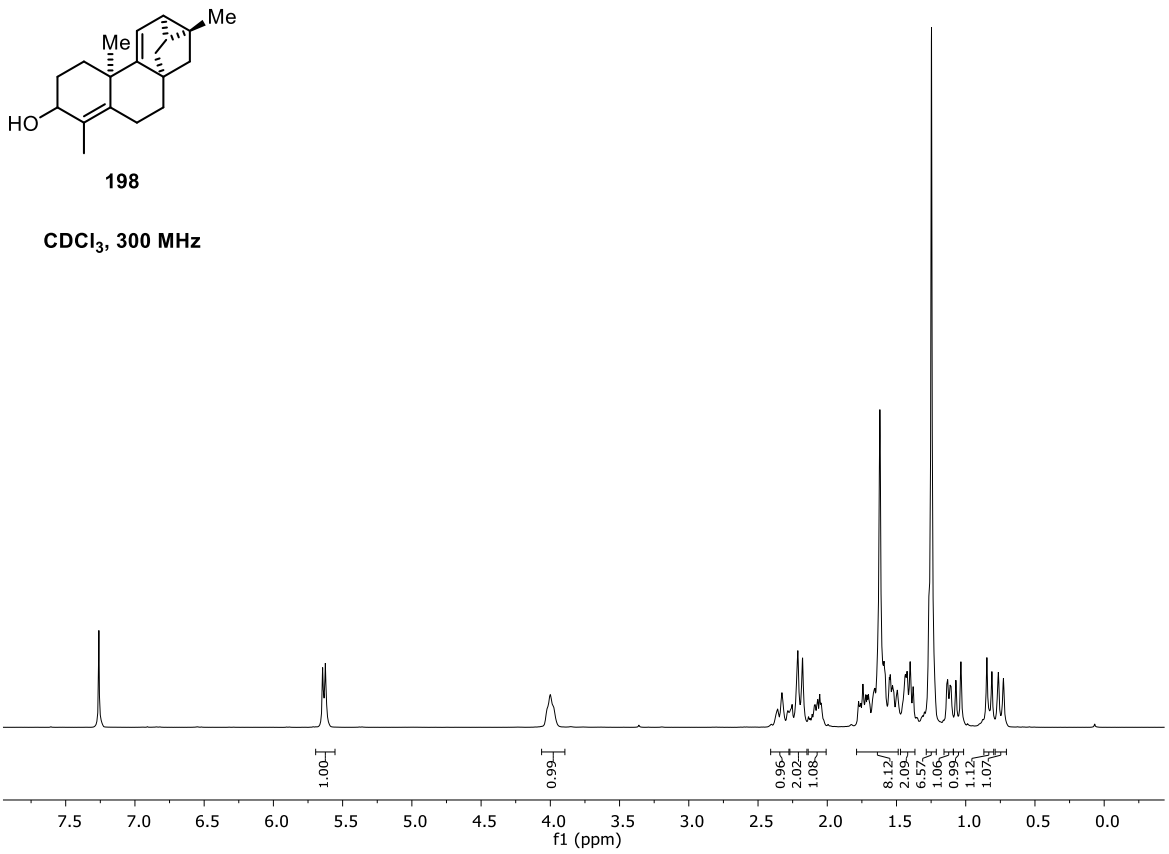
176

$CDCl_3$, 600 MHz



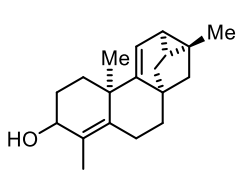
176

$CDCl_3$, 150 MHz



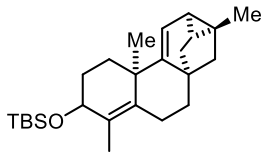
198

$CDCl_3$, 300 MHz



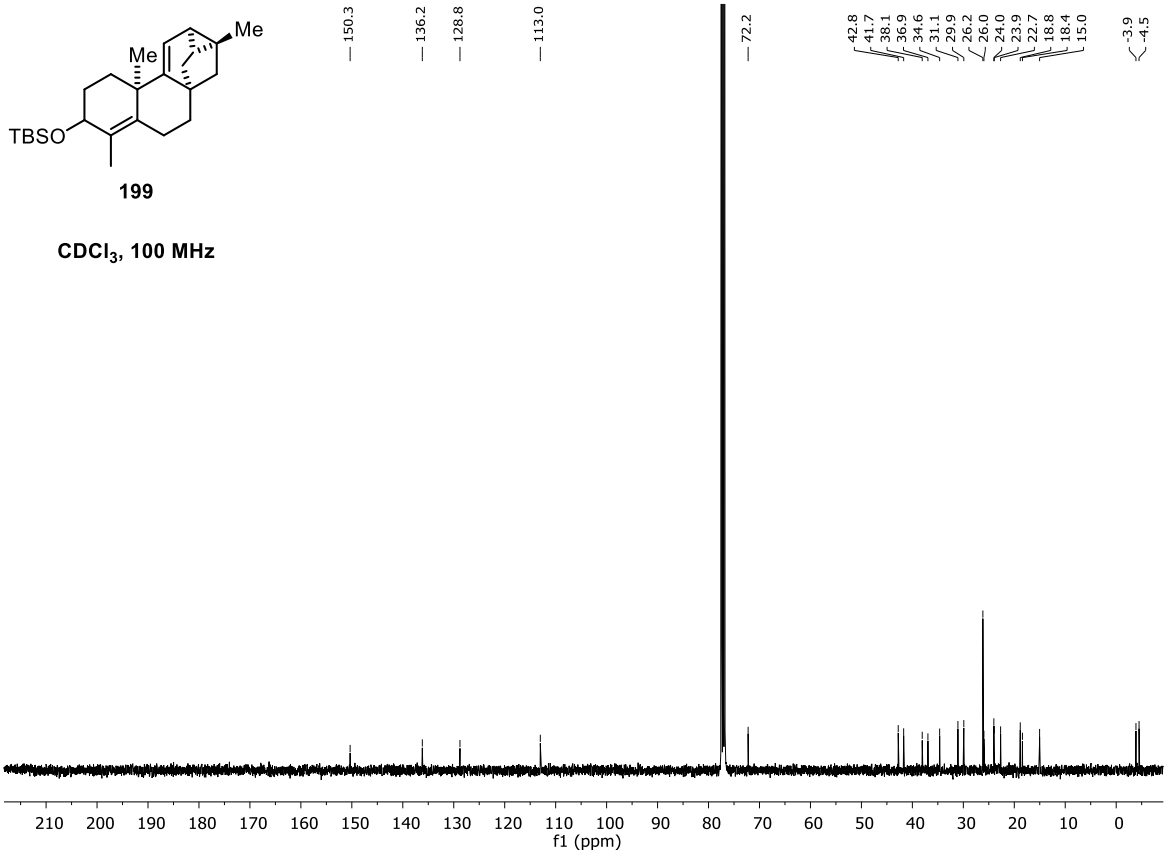
198

$CDCl_3$, 75 MHz



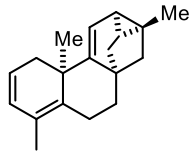
199

$CDCl_3$, 400 MHz

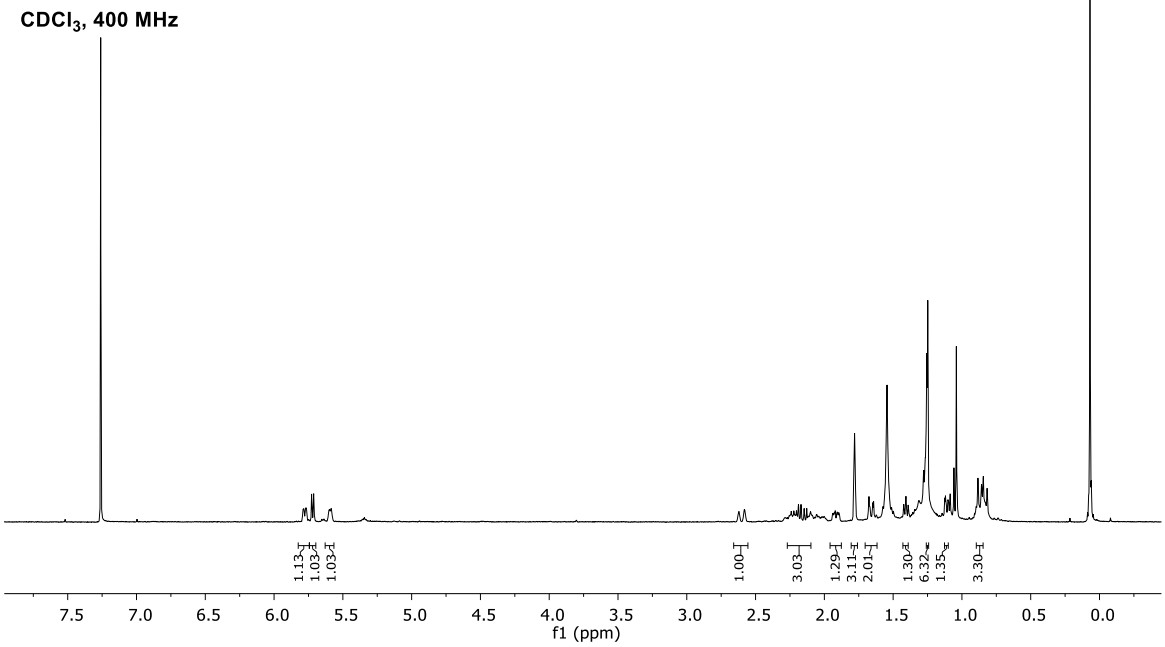


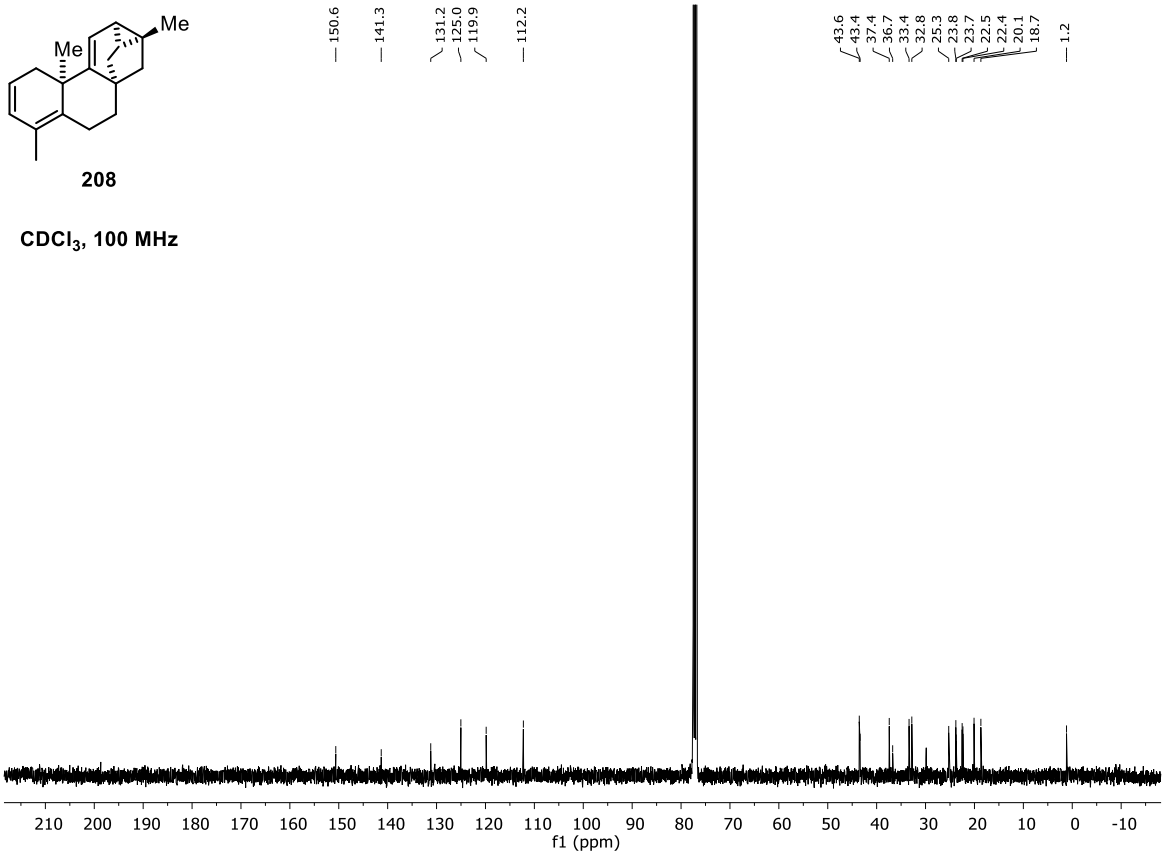
199

$CDCl_3$, 100 MHz


Me
Me

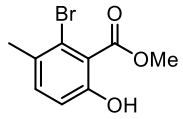
208


CDCl3, 400 MHz
1.13
1.03
1.03
1.00
3.03
1.29
3.11
2.01
1.30
6.32
1.35
3.30
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



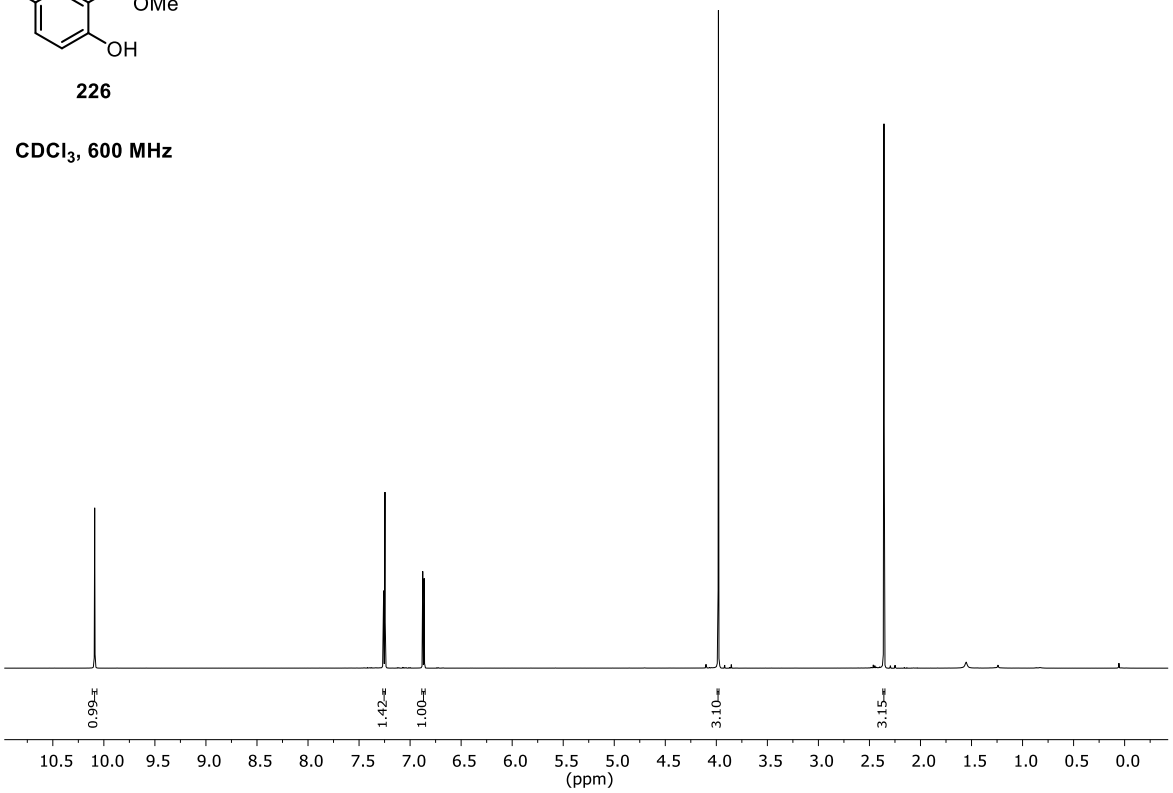
208

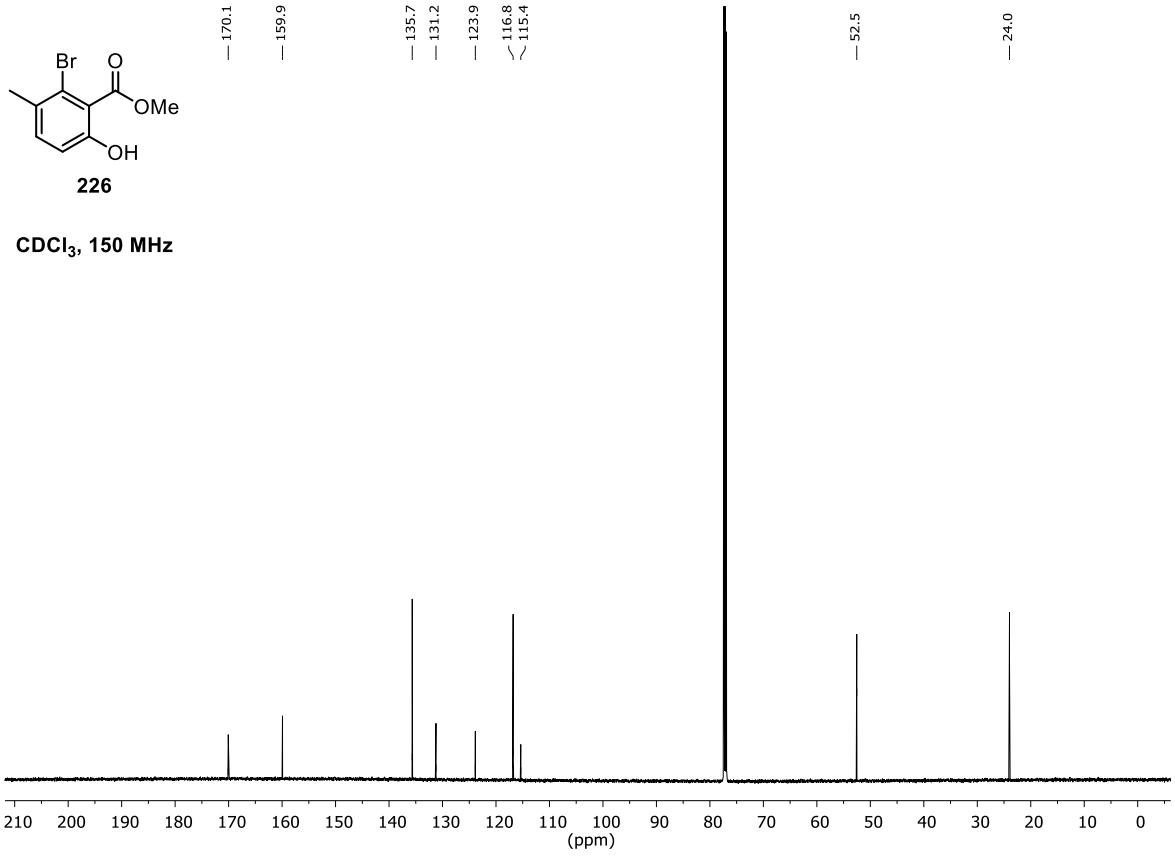
$CDCl_3$, 100 MHz

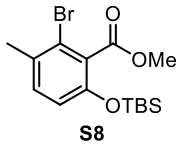


226

$CDCl_3$, 600 MHz

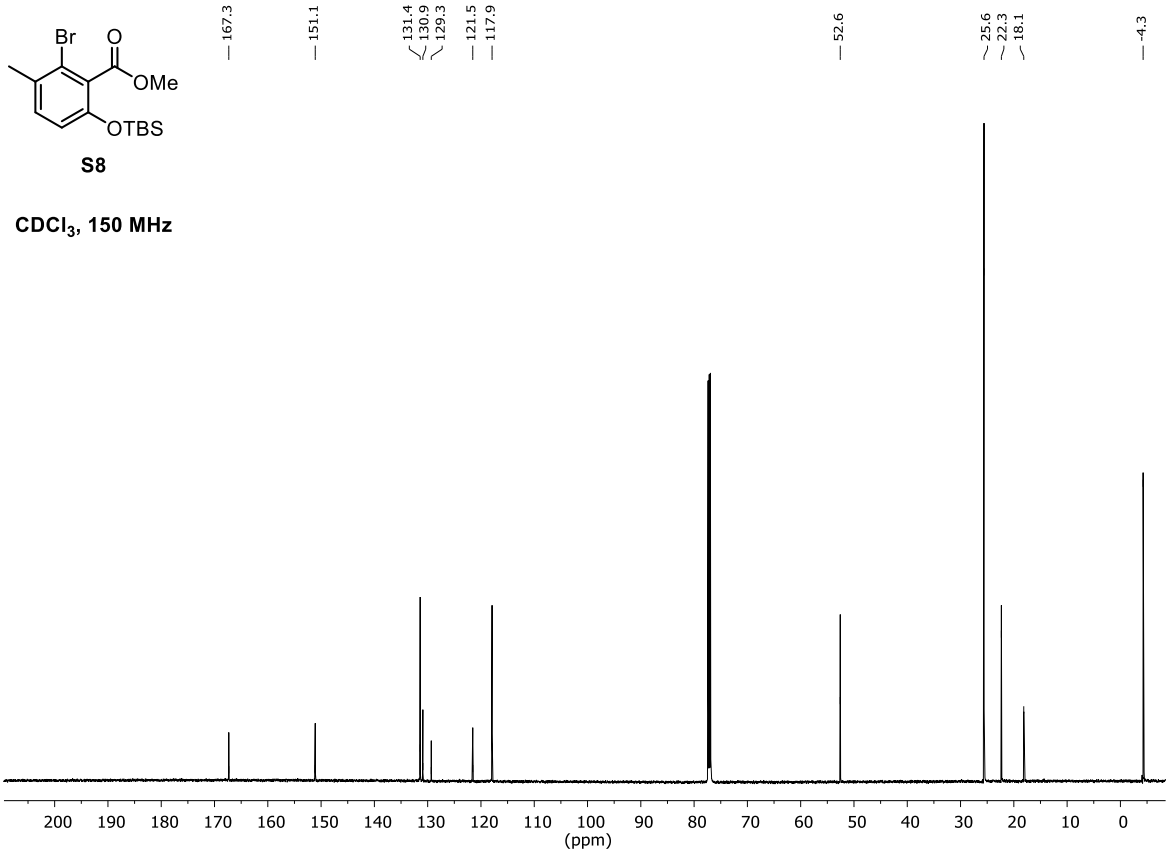



Br
O
OMe
OH
226
CDCl3, 150 MHz
170.1
159.9
135.7
131.2
123.9
116.8
115.4
52.5
24.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)



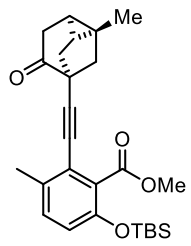
S8

$CDCl_3$, 600 MHz



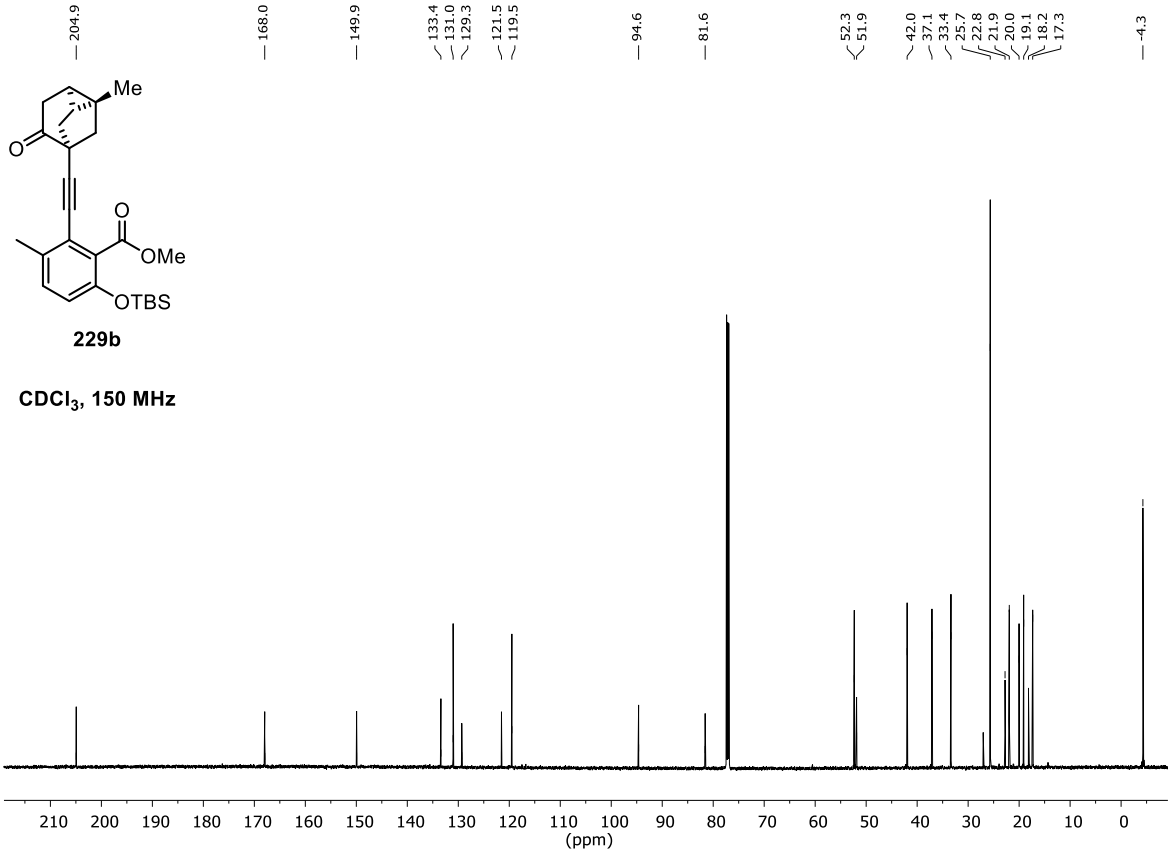
S8

$CDCl_3$, 150 MHz



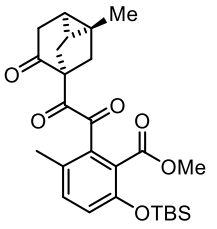
229b

$CDCl_3$, 600 MHz



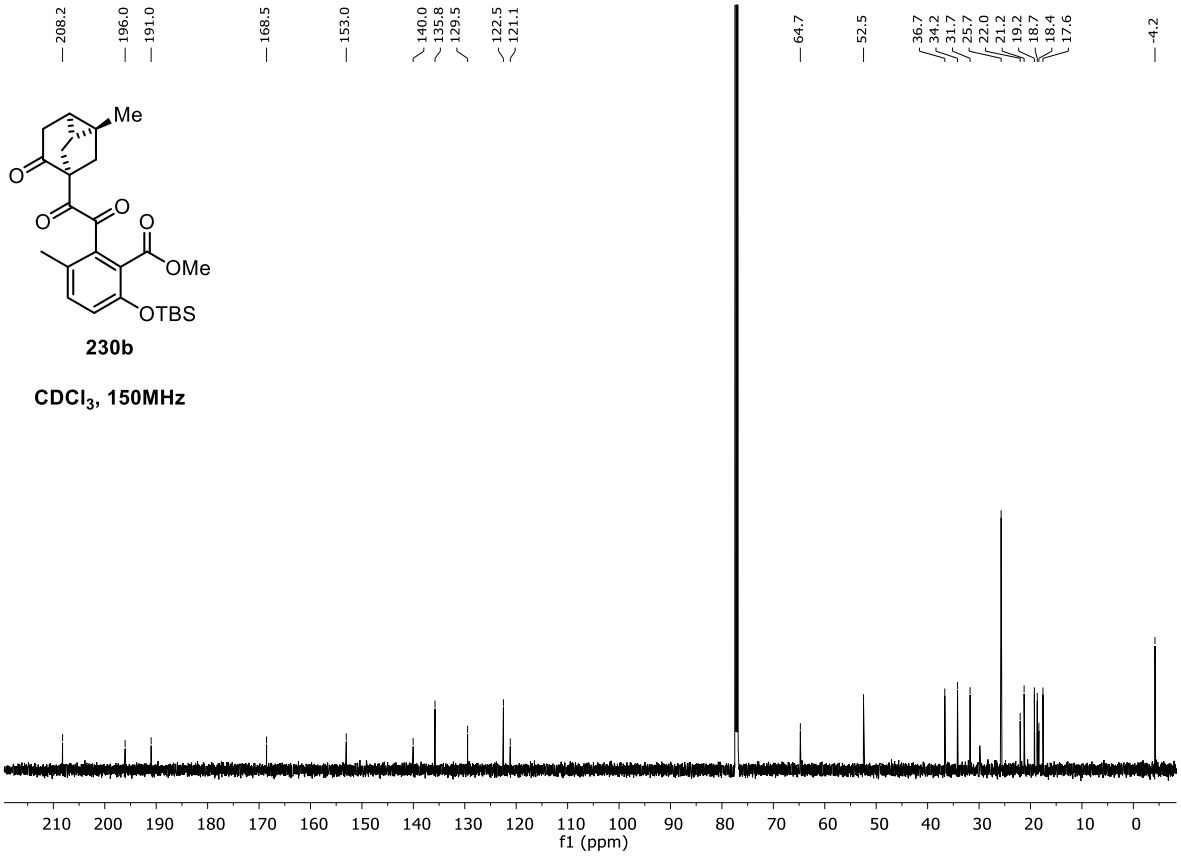
229b

$CDCl_3$, 150 MHz



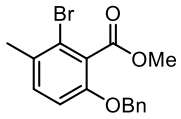
230b

$CDCl_3$, 600MHz



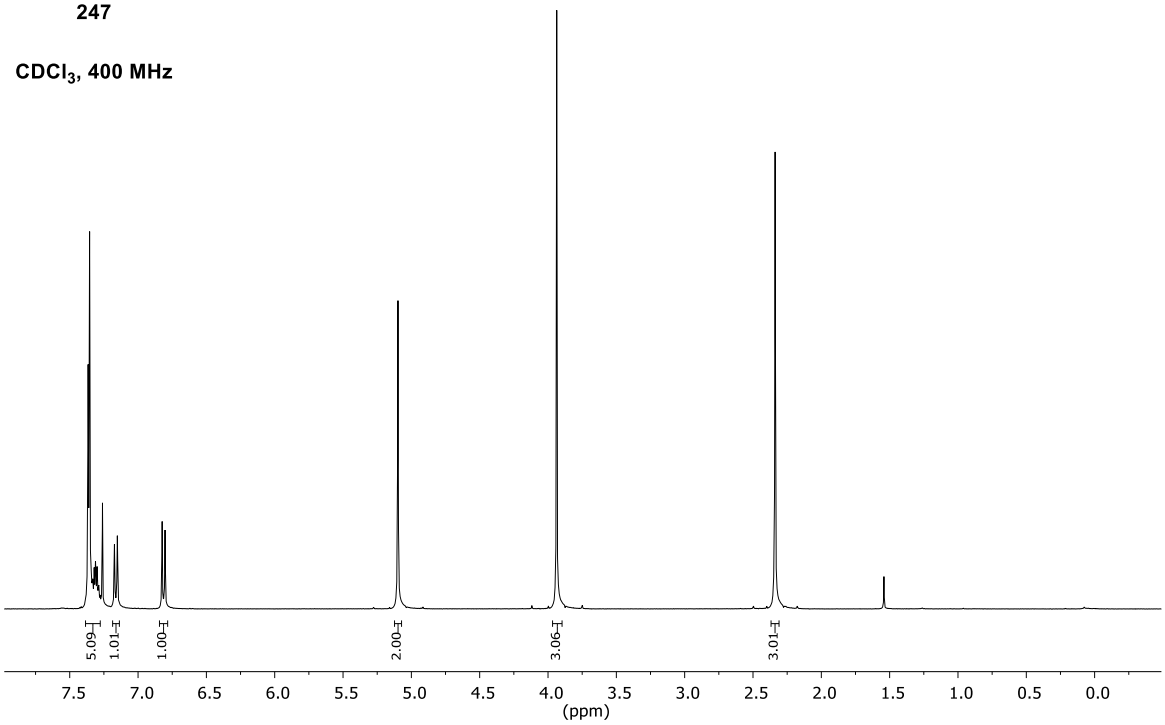
230b

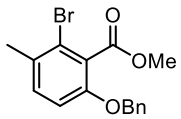
$CDCl_3$, 150MHz



247

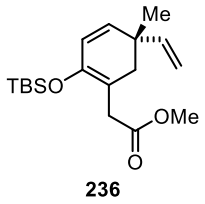
$CDCl_3$, 400 MHz





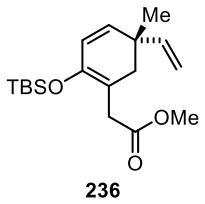
247

$CDCl_3$, 100 MHz



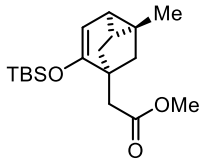
236

$CDCl_3$, 400 MHz



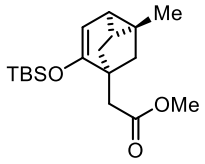
236

$CDCl_3$, 100 MHz



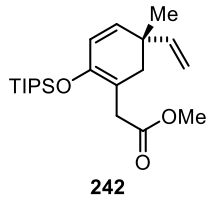
237

$CDCl_3$, 600 MHz



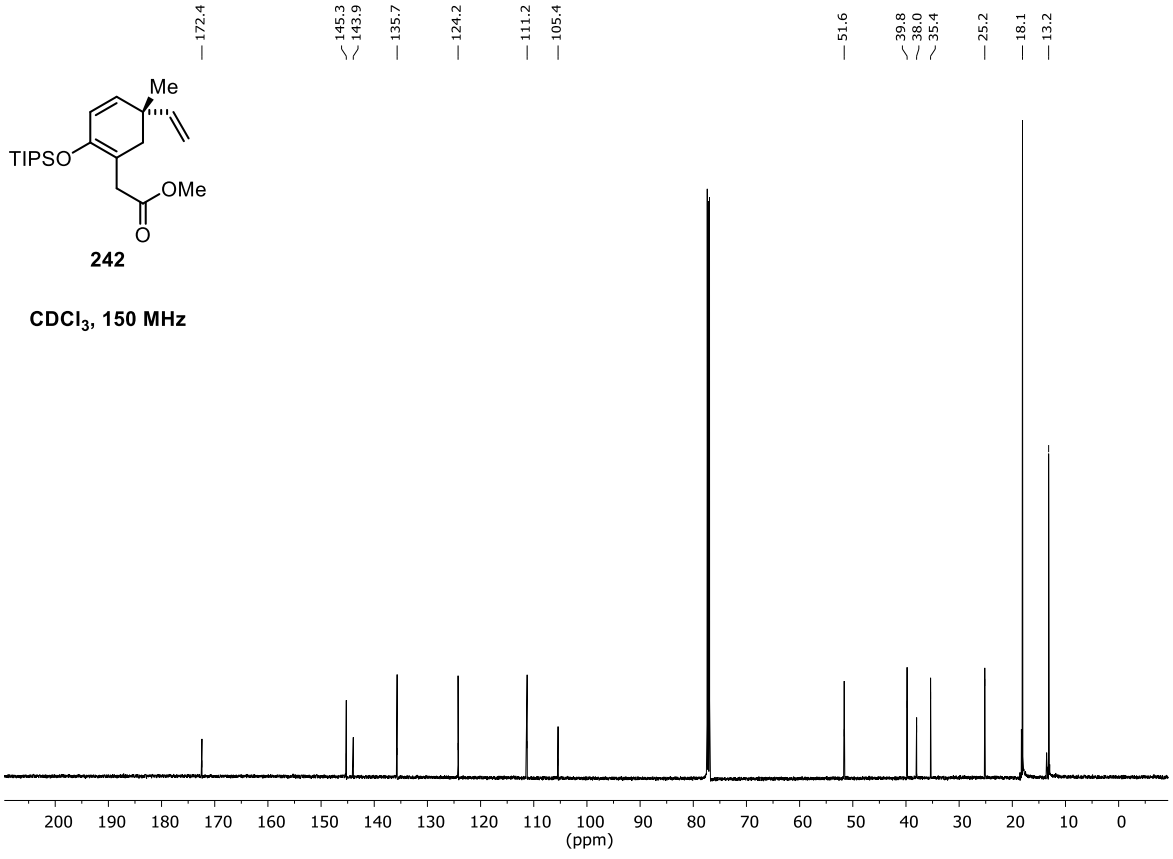
237

$CDCl_3$, 150 MHz



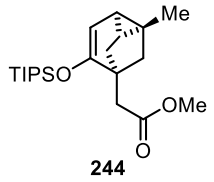
242

$CDCl_3$, 600 MHz



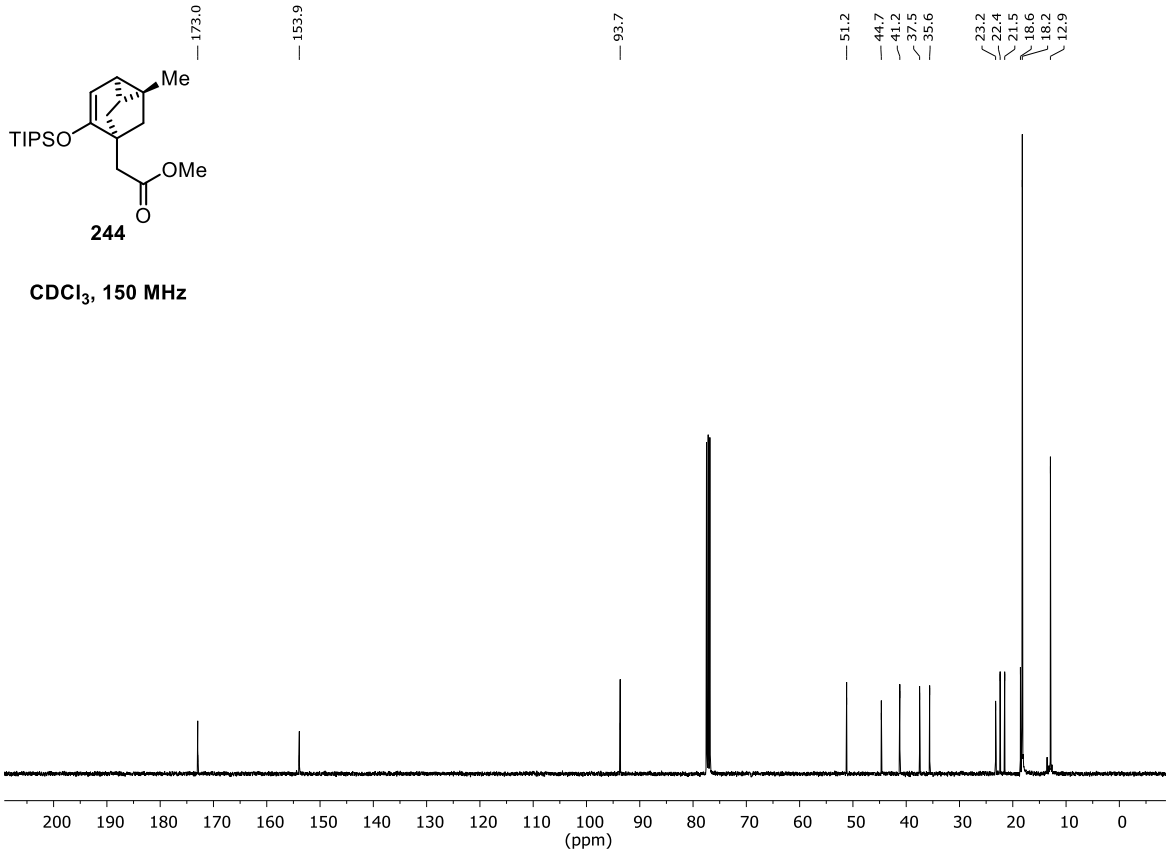
242

$CDCl_3$, 150 MHz



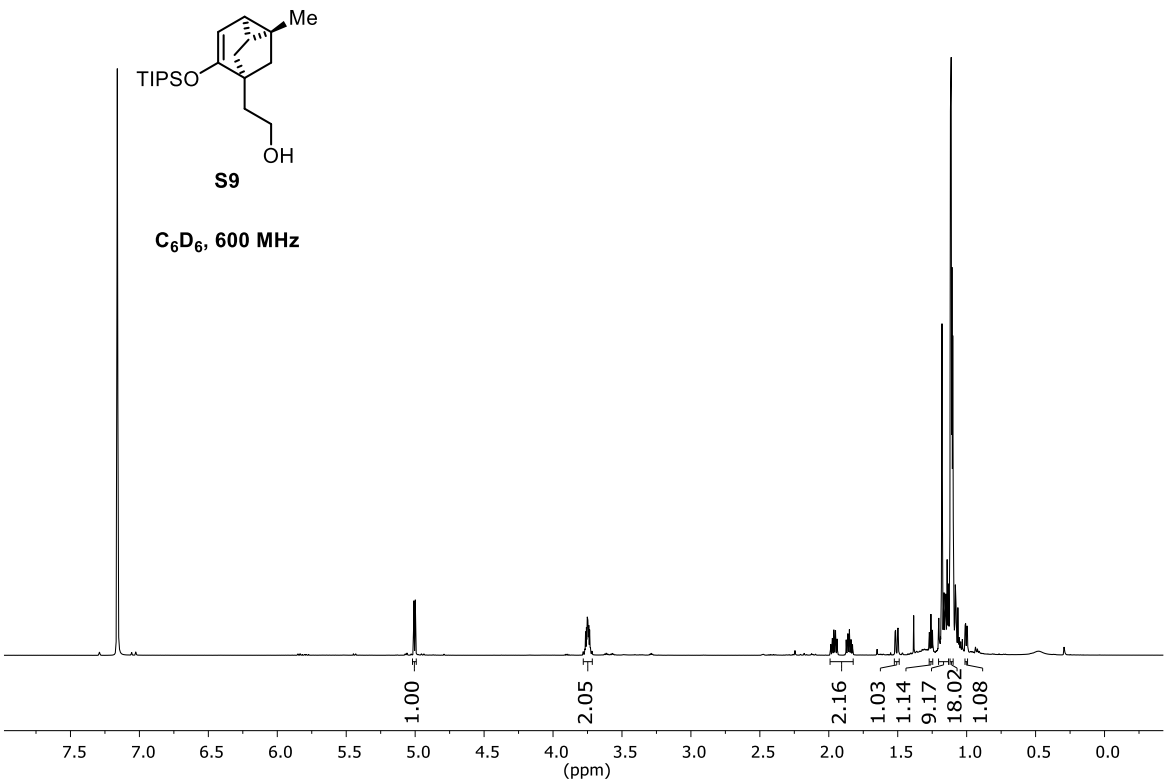
244

$CDCl_3$, 600 MHz



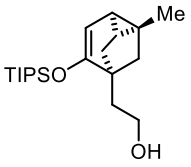
244

$CDCl_3$, 150 MHz



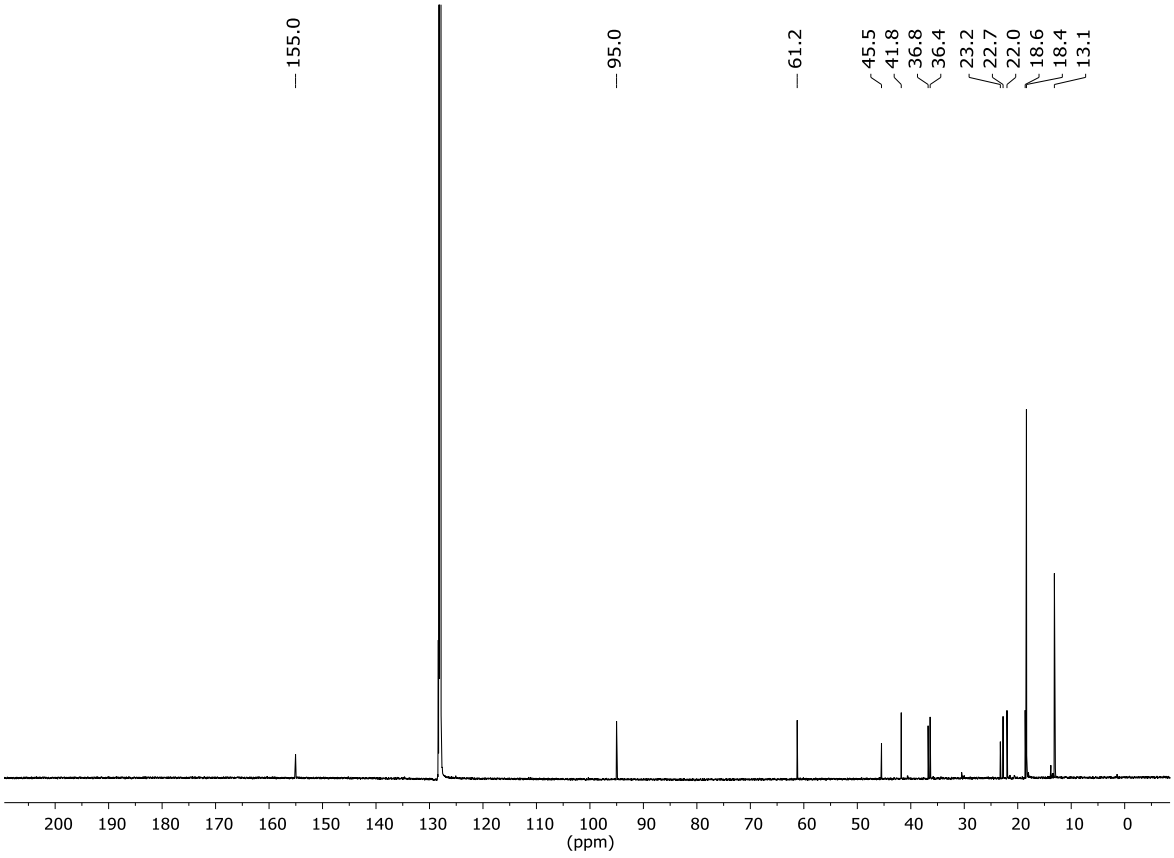
S9

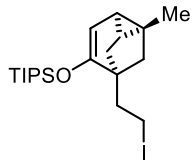
C_6D_6, 600 MHz



S9

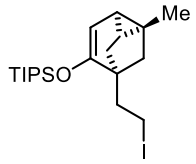
C_6D_6, 150 MHz


155.0
95.0
61.2
45.5
41.8
36.8
36.4
23.2
22.7
22.0
18.6
18.4
13.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)



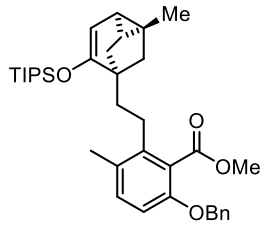
246

$CDCl_3$, 600 MHz



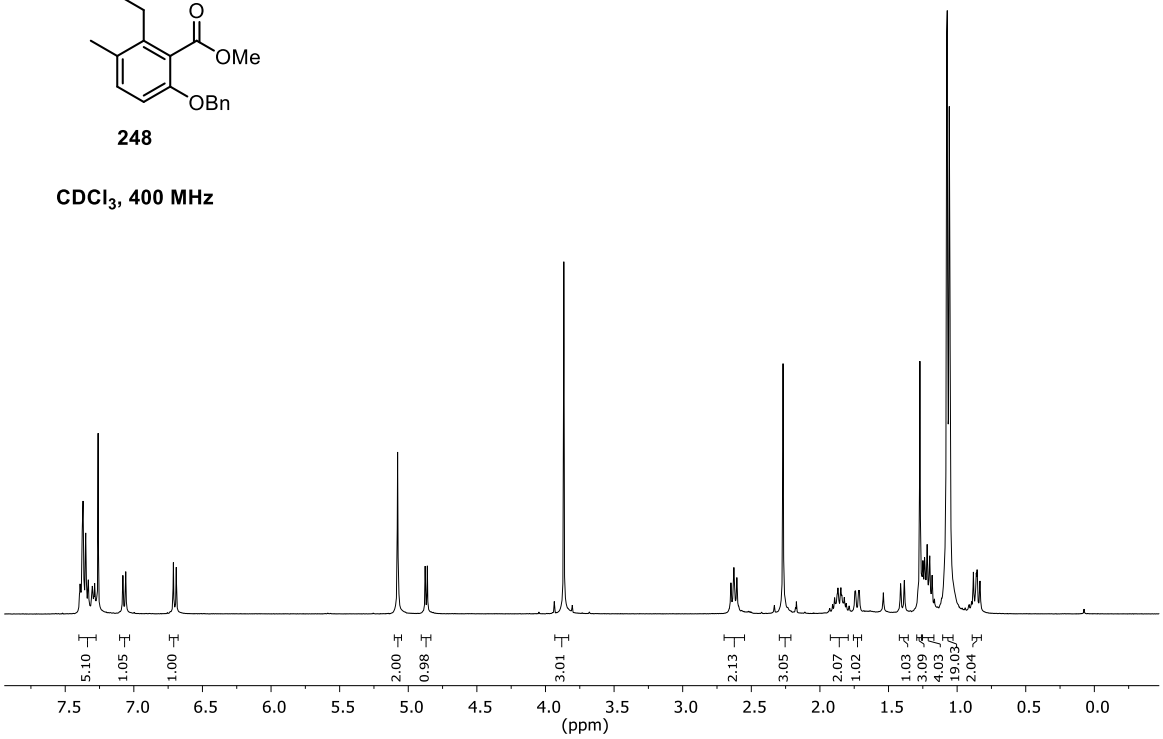
246

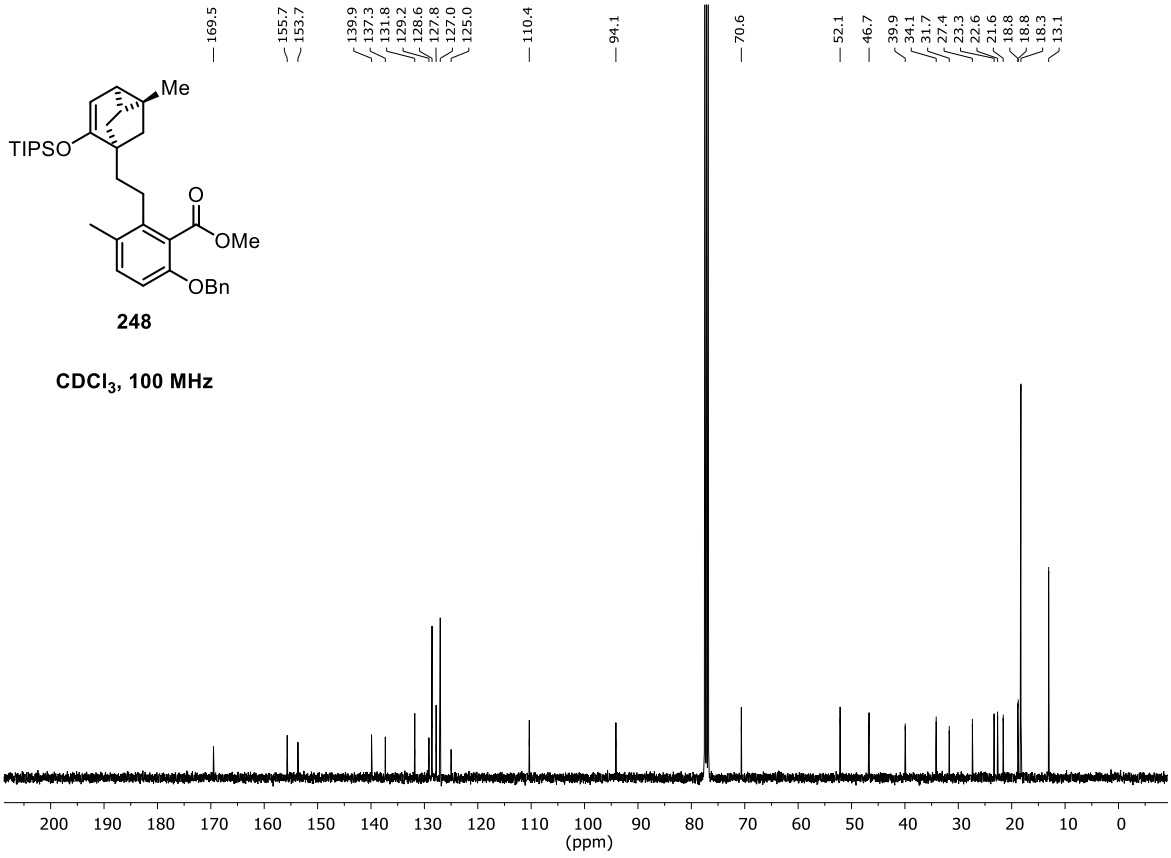
$CDCl_3$, 150 MHz

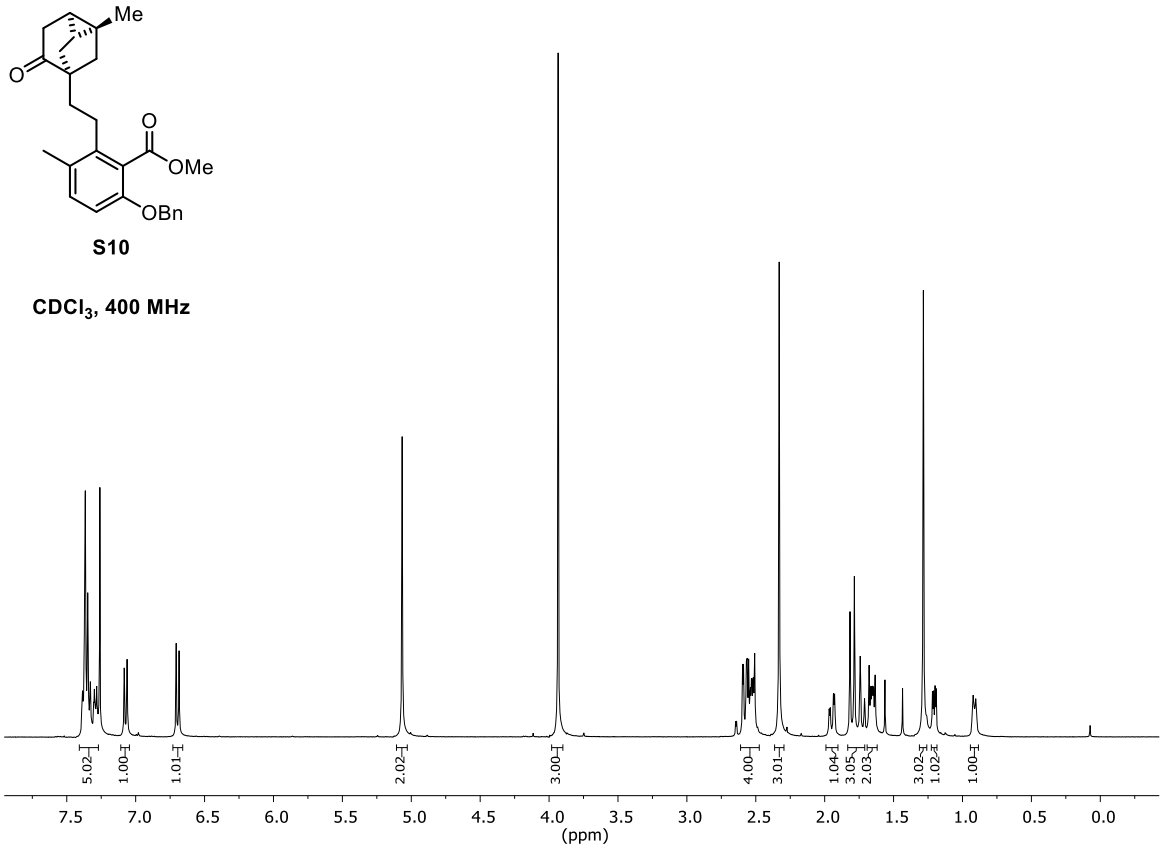


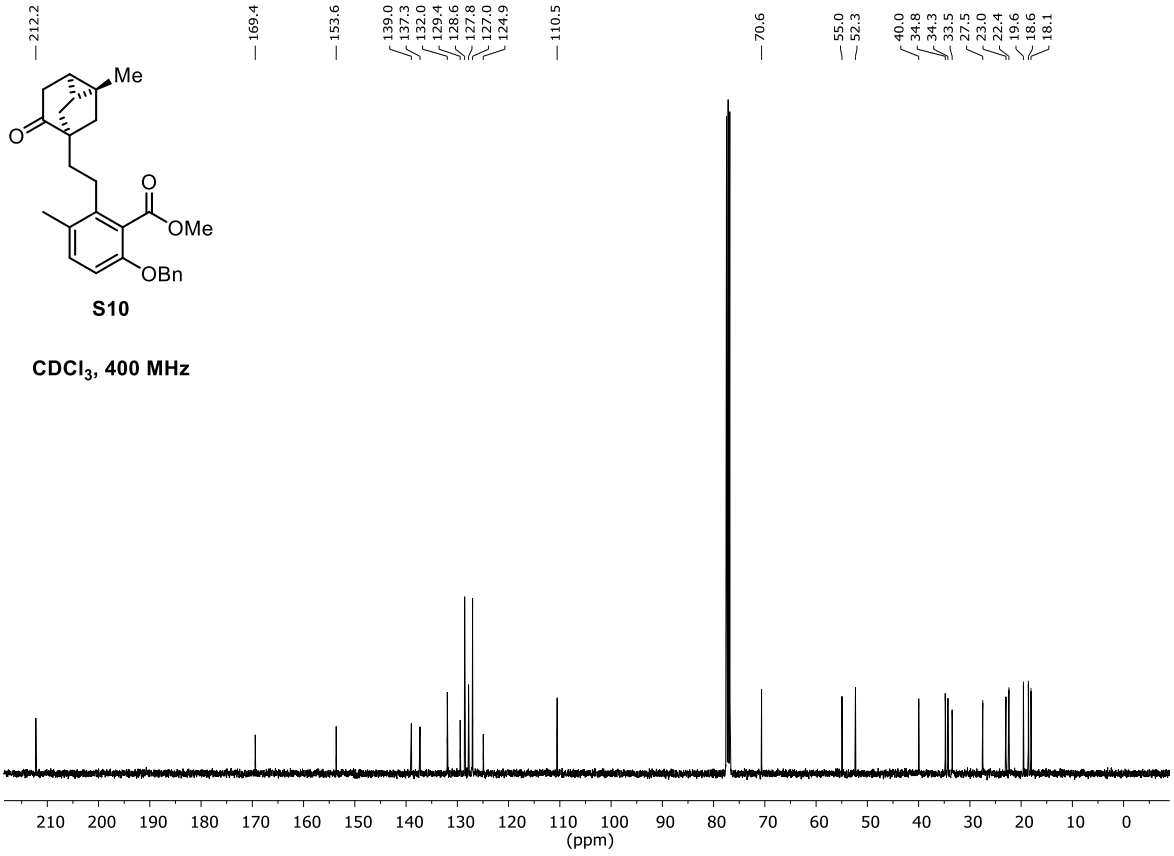
248

$CDCl_3$, 400 MHz



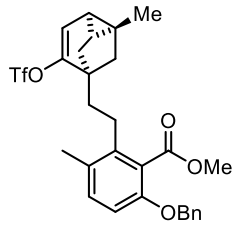

169.5
155.7
153.7
139.9
137.3
131.8
129.2
128.6
127.8
127.0
125.0
110.4
94.1
70.6
52.1
46.7
39.9
34.1
31.7
27.4
23.3
22.6
21.6
18.8
18.8
18.3
13.1
Me
TIPSO
O
OMe
OBn
248
CDCl3, 100 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


Me
O
O
OMe
OBn
S10
CDCl3, 400 MHz
5.02
1.00
1.01
2.02
3.00
4.00
3.01
1.04
3.05
2.03
3.02
1.02
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)



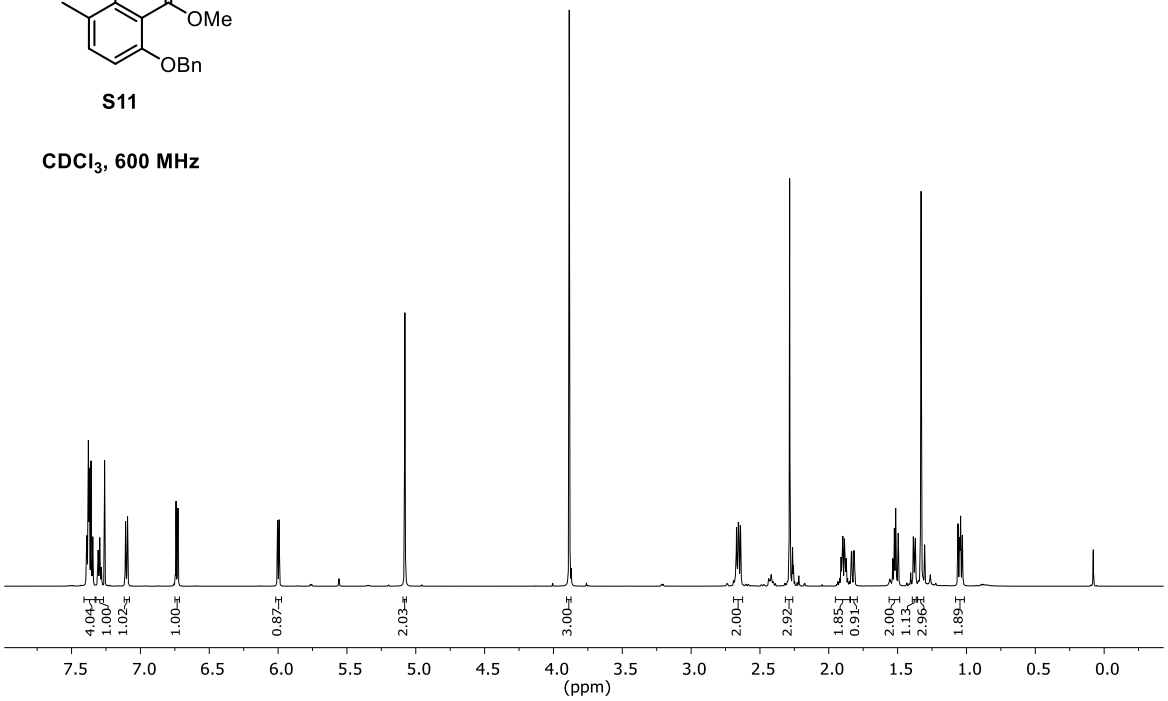
S10

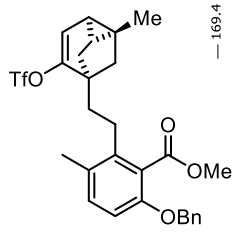
$CDCl_3$, 400 MHz



S11

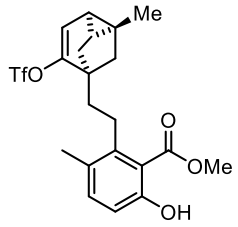
$CDCl_3$, 600 MHz





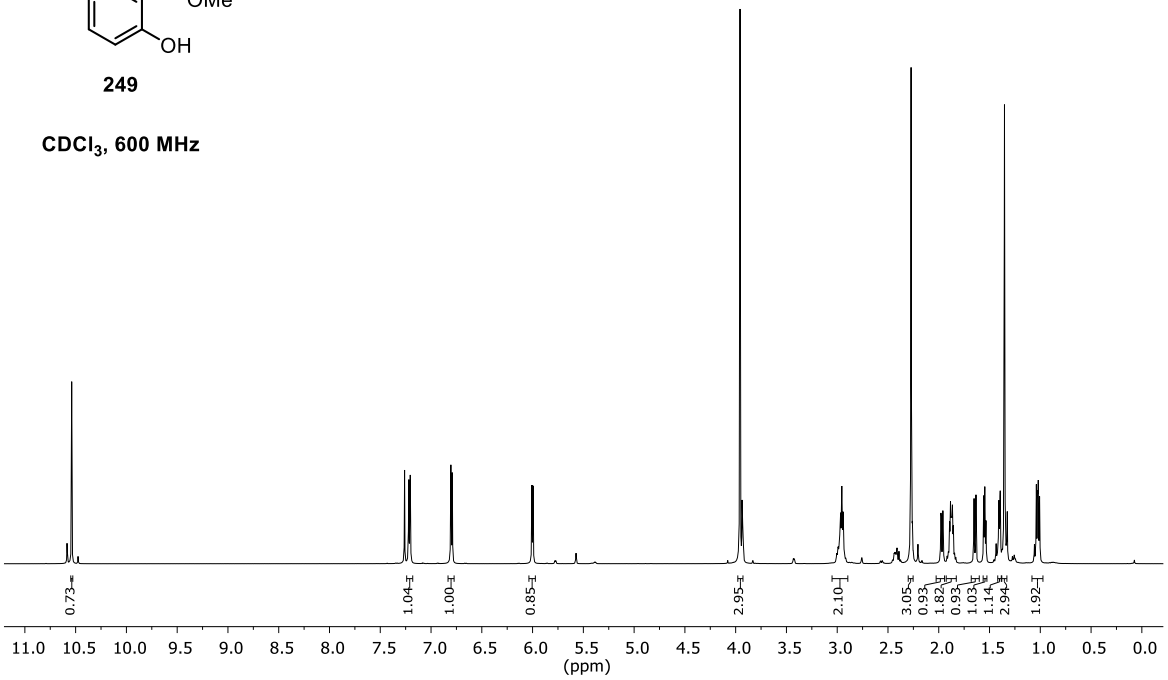
S11

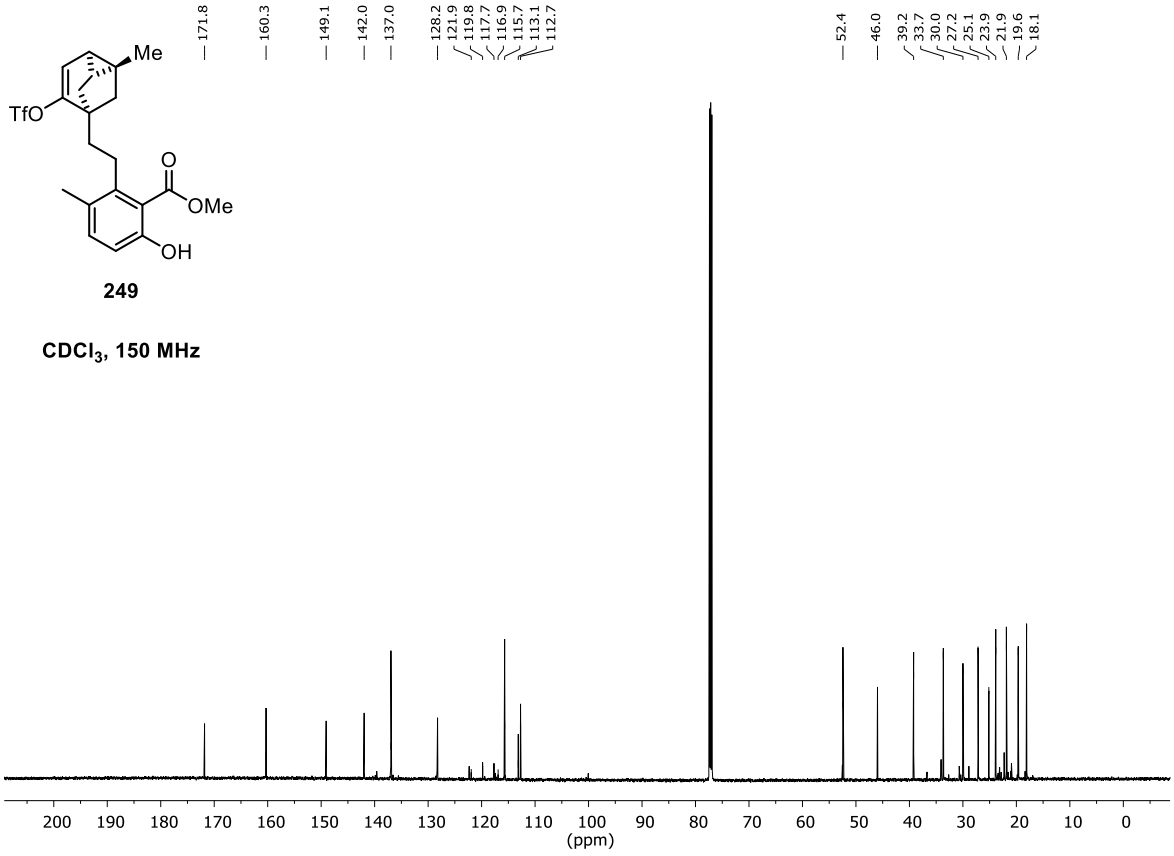
$CDCl_3$, 150 MHz



249

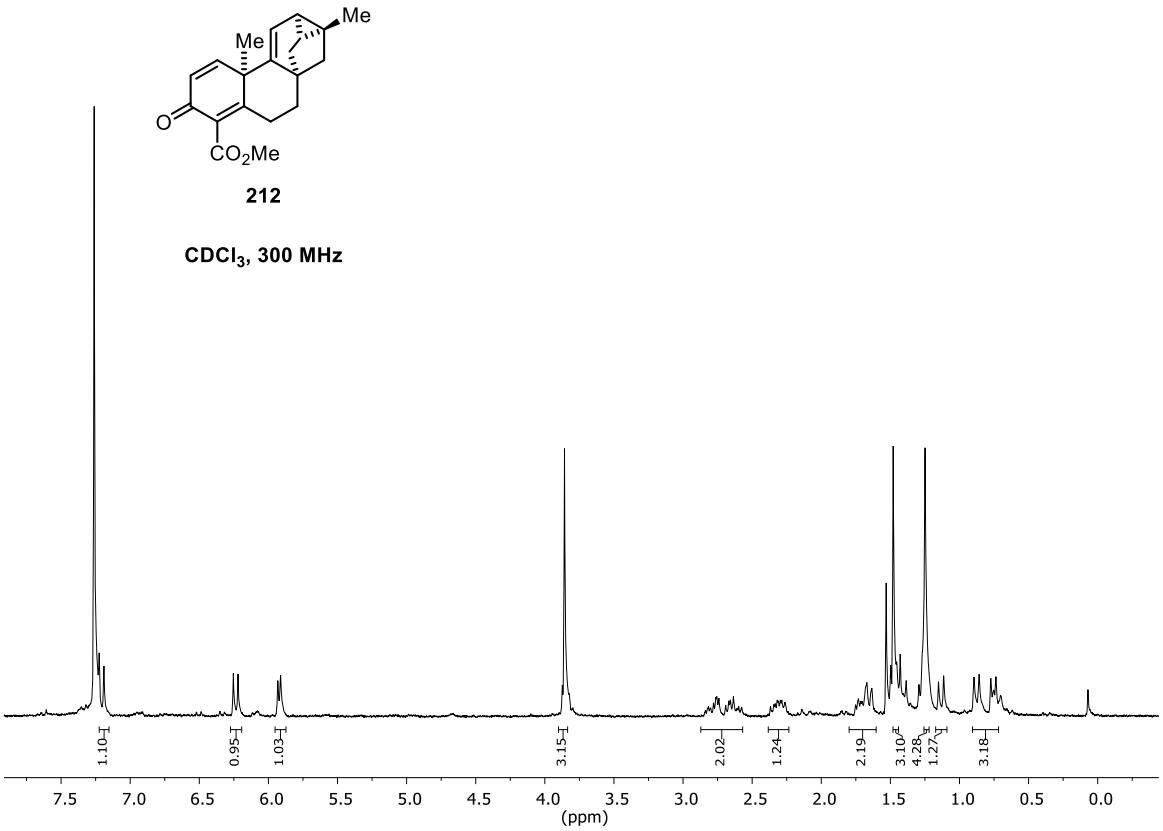
$CDCl_3$, 600 MHz

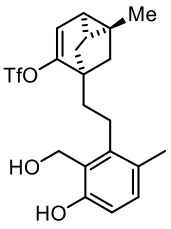




249

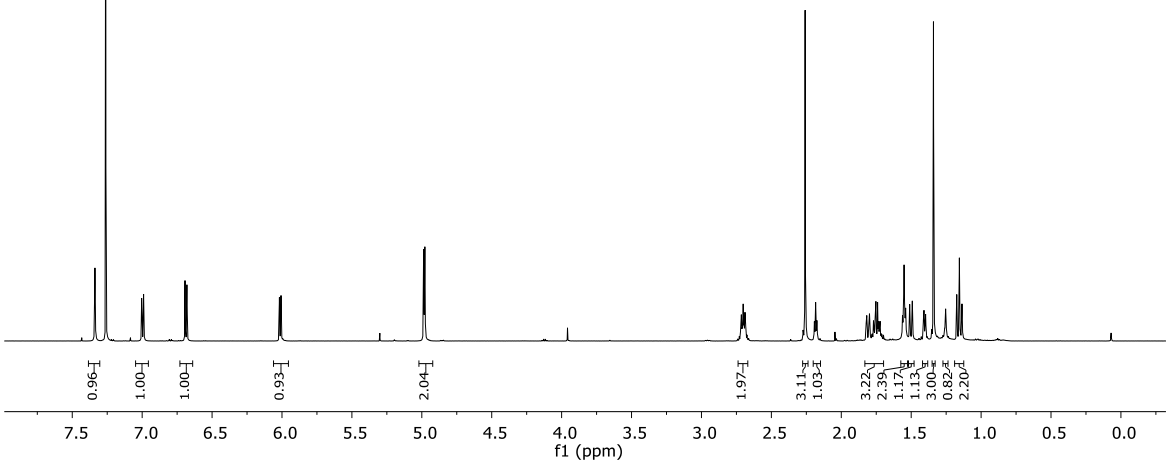
$CDCl_3$, 150 MHz

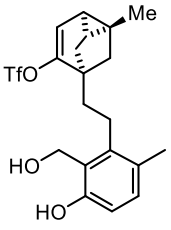

Me
Me
O
CO2Me
212
CDCl3, 300 MHz
1.10
0.95
1.03
3.15
2.02
1.24
2.19
3.10
4.28
1.27
3.18
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)



252

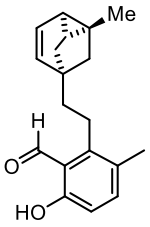
$CDCl_3$, 600 MHz





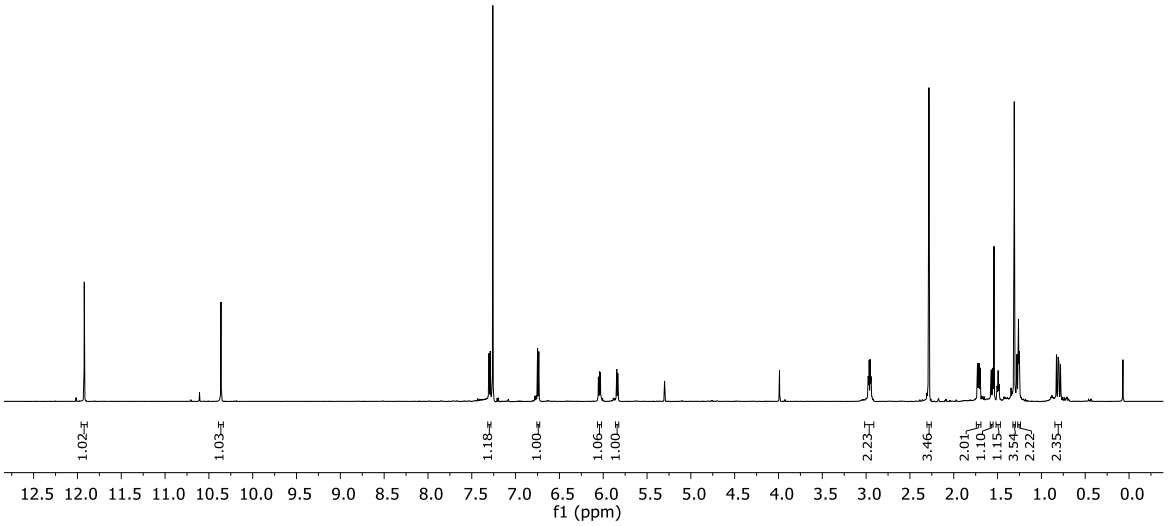
252

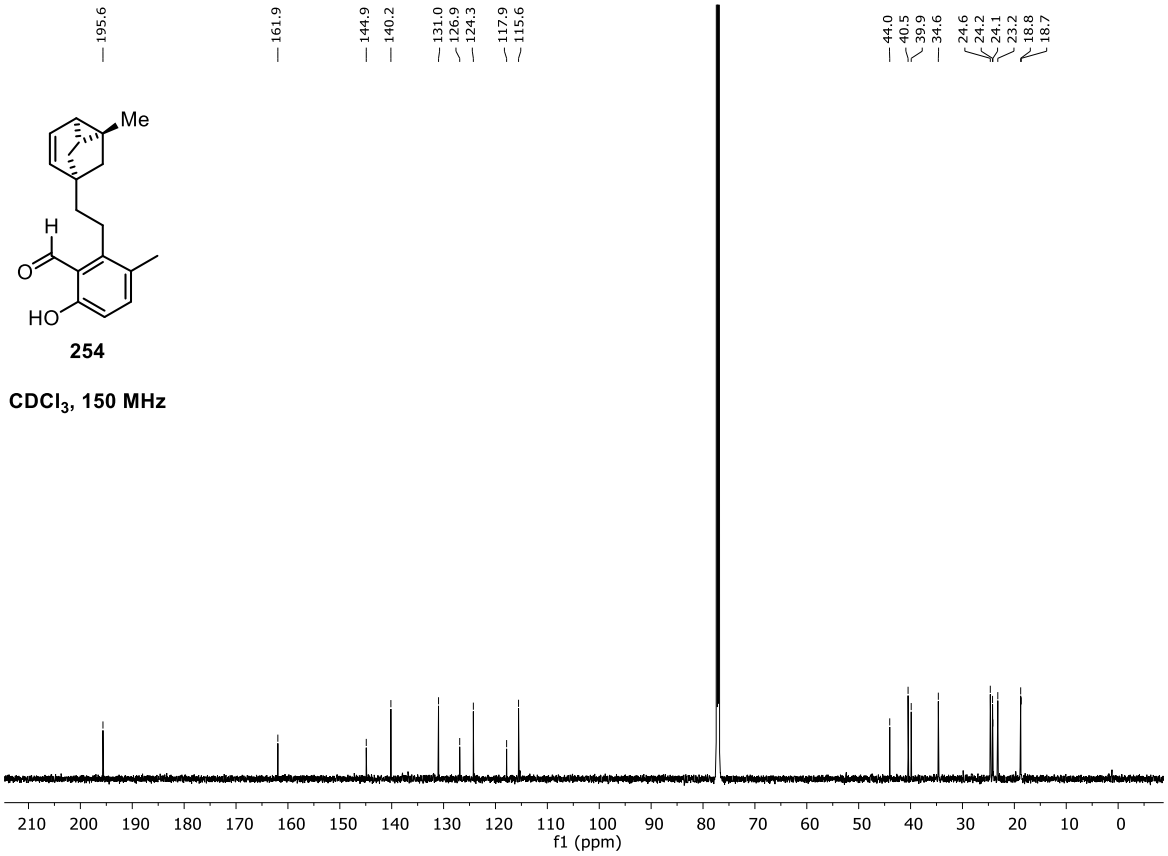
$CDCl_3$, 150 MHz



254

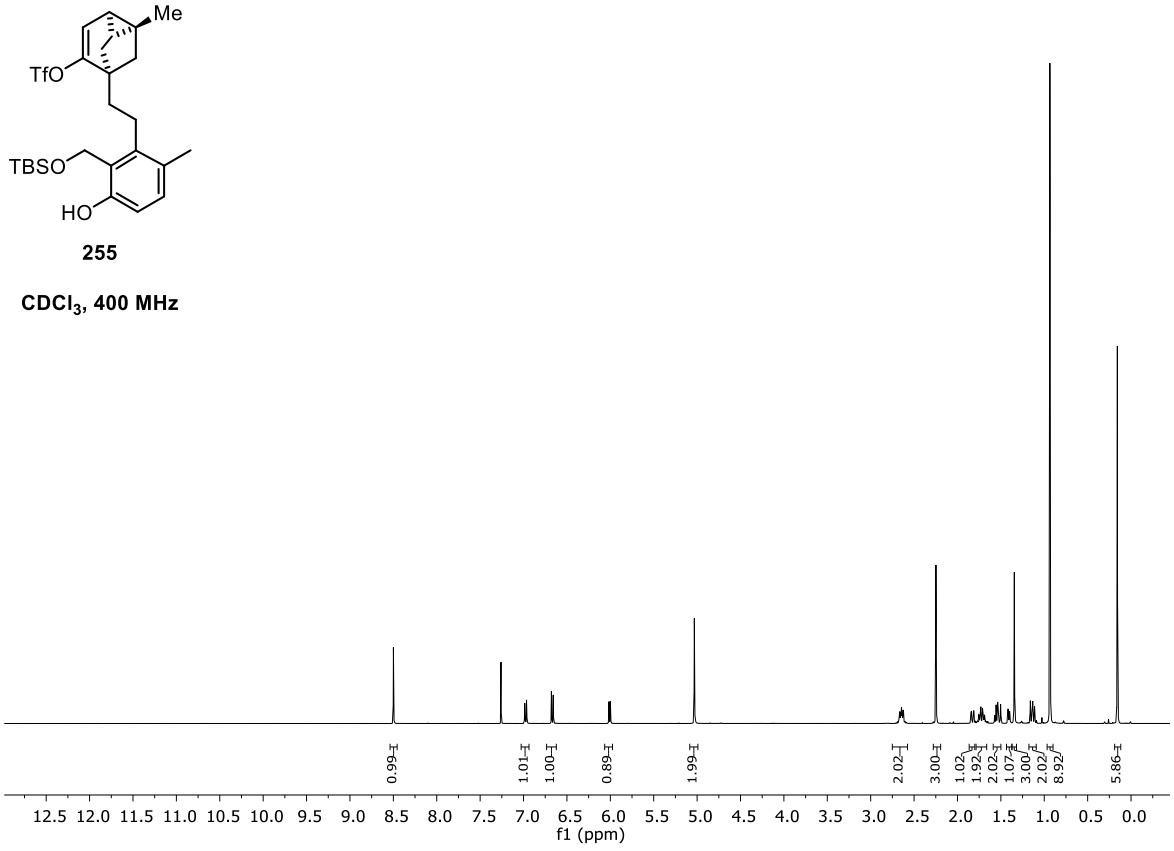
$CDCl_3$, 600 MHz





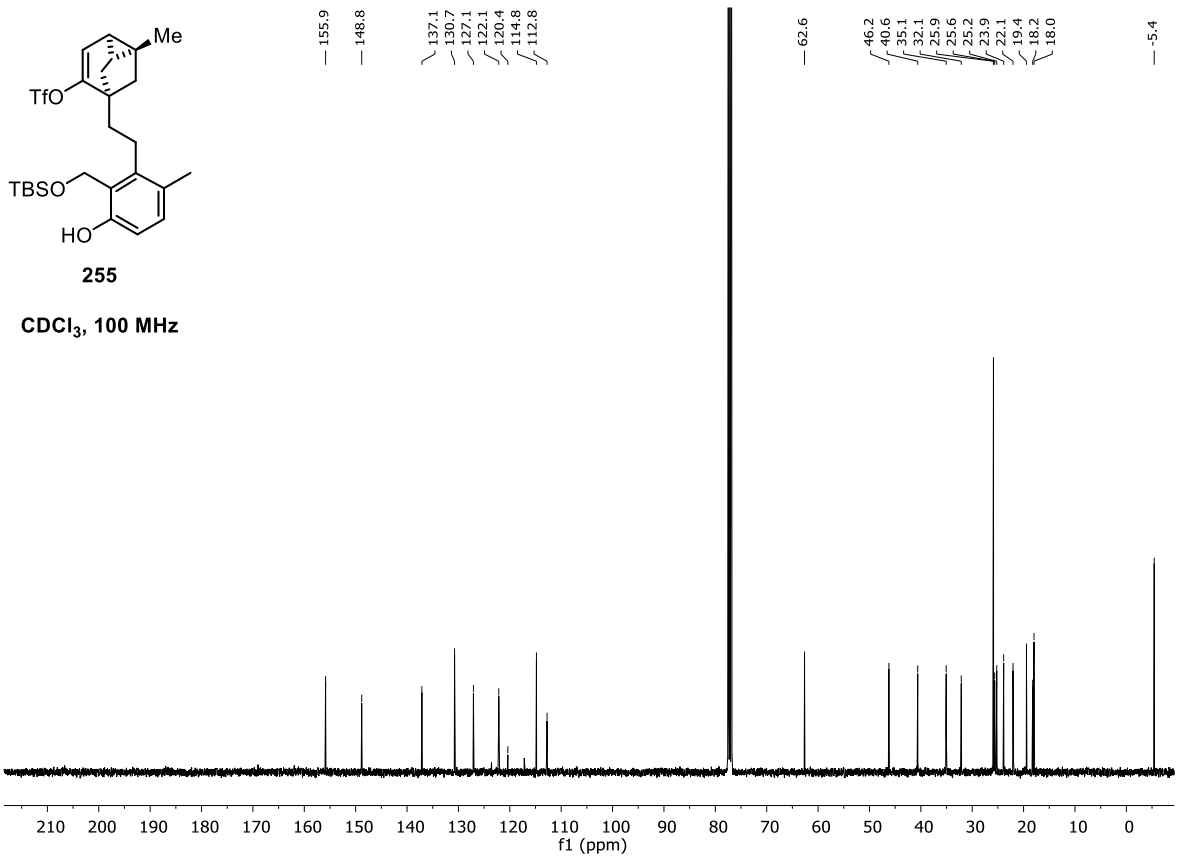
254

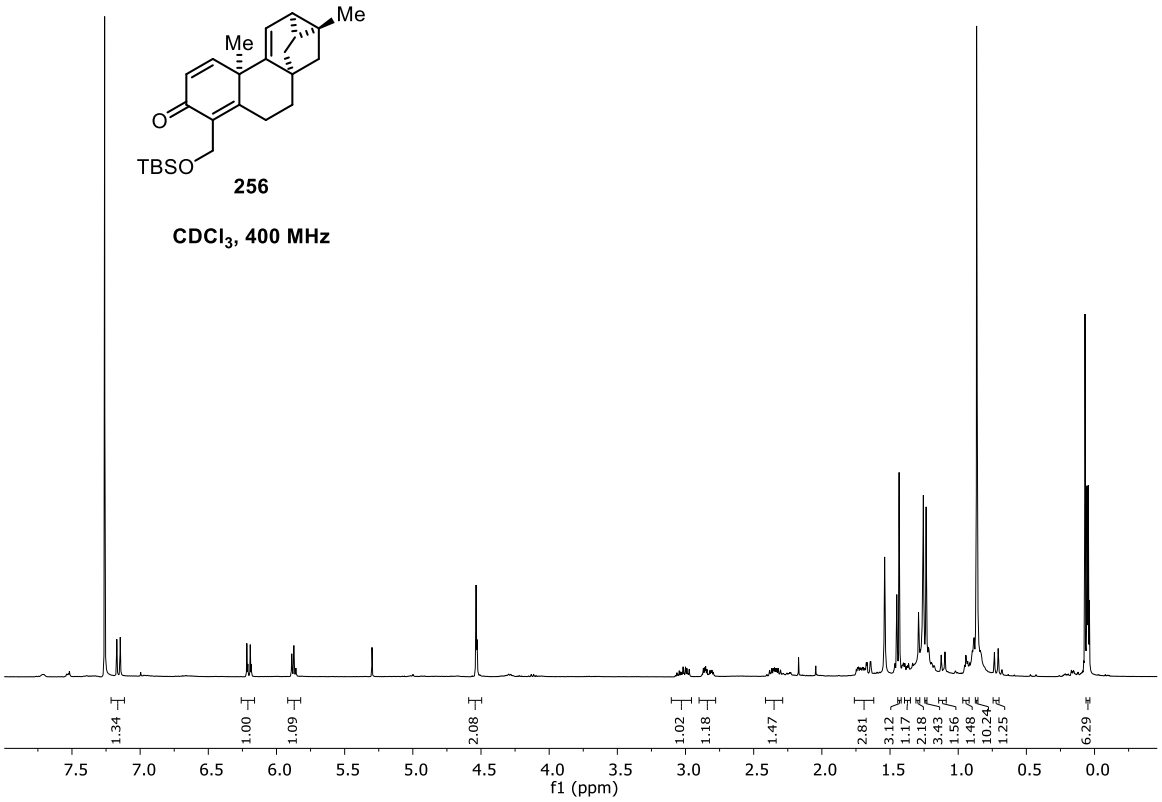
$CDCl_3$, 150 MHz

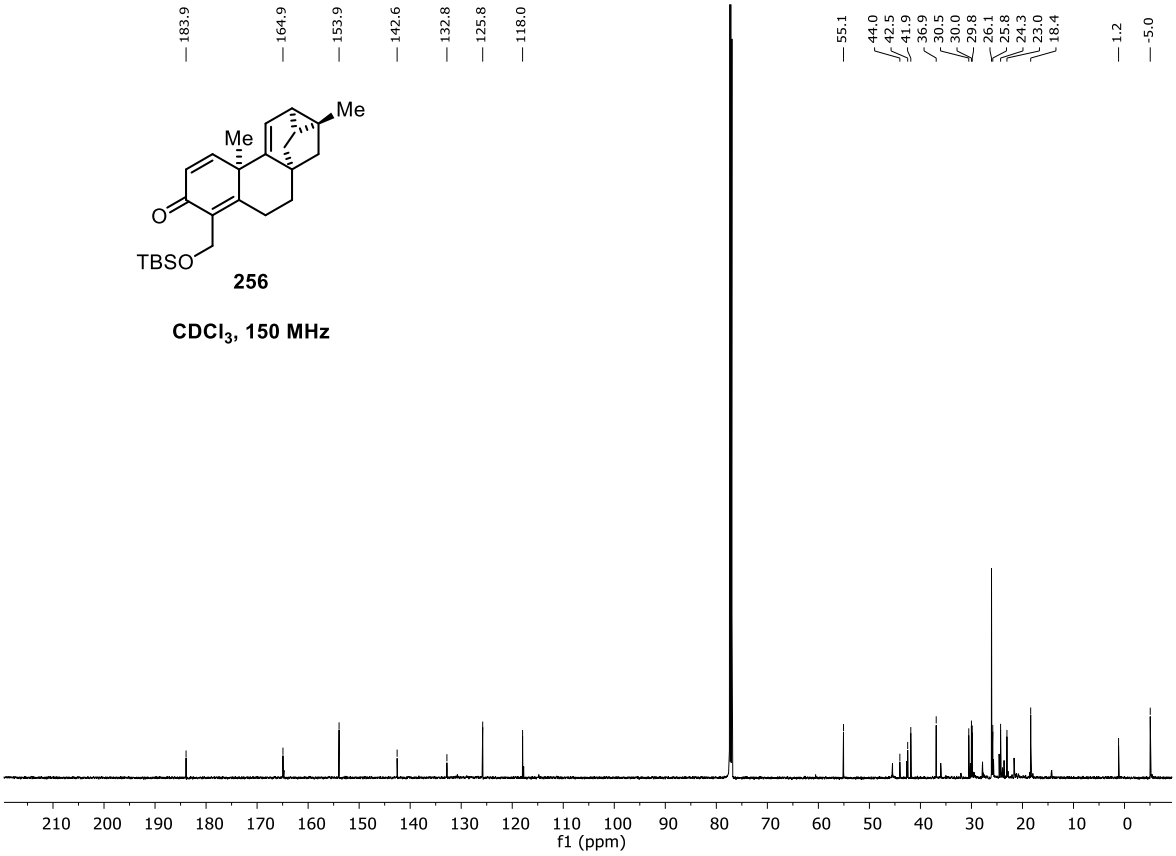


255

$CDCl_3$, 400 MHz

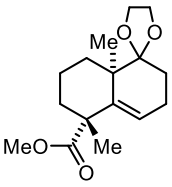

Me
TfO
TBSO
HO
255
CDCl3, 100 MHz
155.9
148.8
137.1
130.7
127.1
122.1
120.4
114.8
112.8
62.6
46.2
40.6
35.1
32.1
25.9
25.6
25.2
23.9
22.1
19.4
18.2
18.0
-5.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
O
TBSO
256
CDCl3, 400 MHz
1.34
1.00
1.09
2.08
1.02
1.18
1.47
2.81
3.12
1.17
2.18
3.43
1.56
1.48
10.24
1.25
6.29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



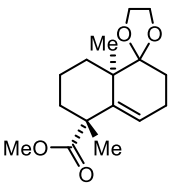
256

$CDCl_3$, 150 MHz



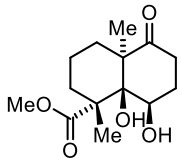
S18

$CDCl_3$, 600 MHz



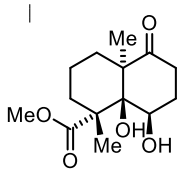
S18

$CDCl_3$, 150 MHz



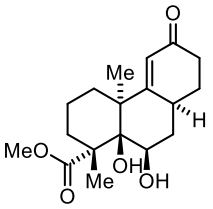
266

$CDCl_3$, 400 MHz



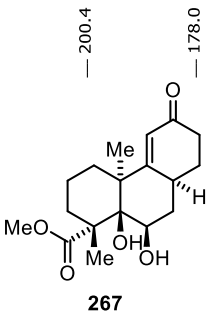
266

$CDCl_3$, 100 MHz



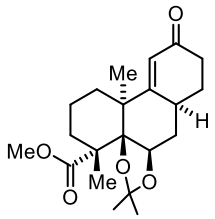
267

$CDCl_3$, 400 MHz



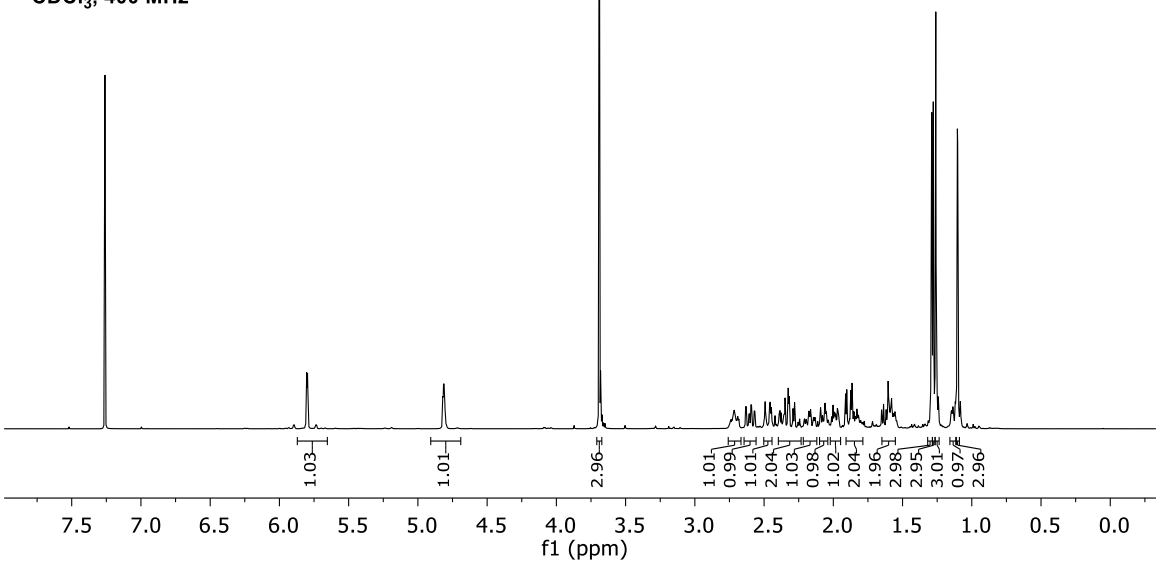
267

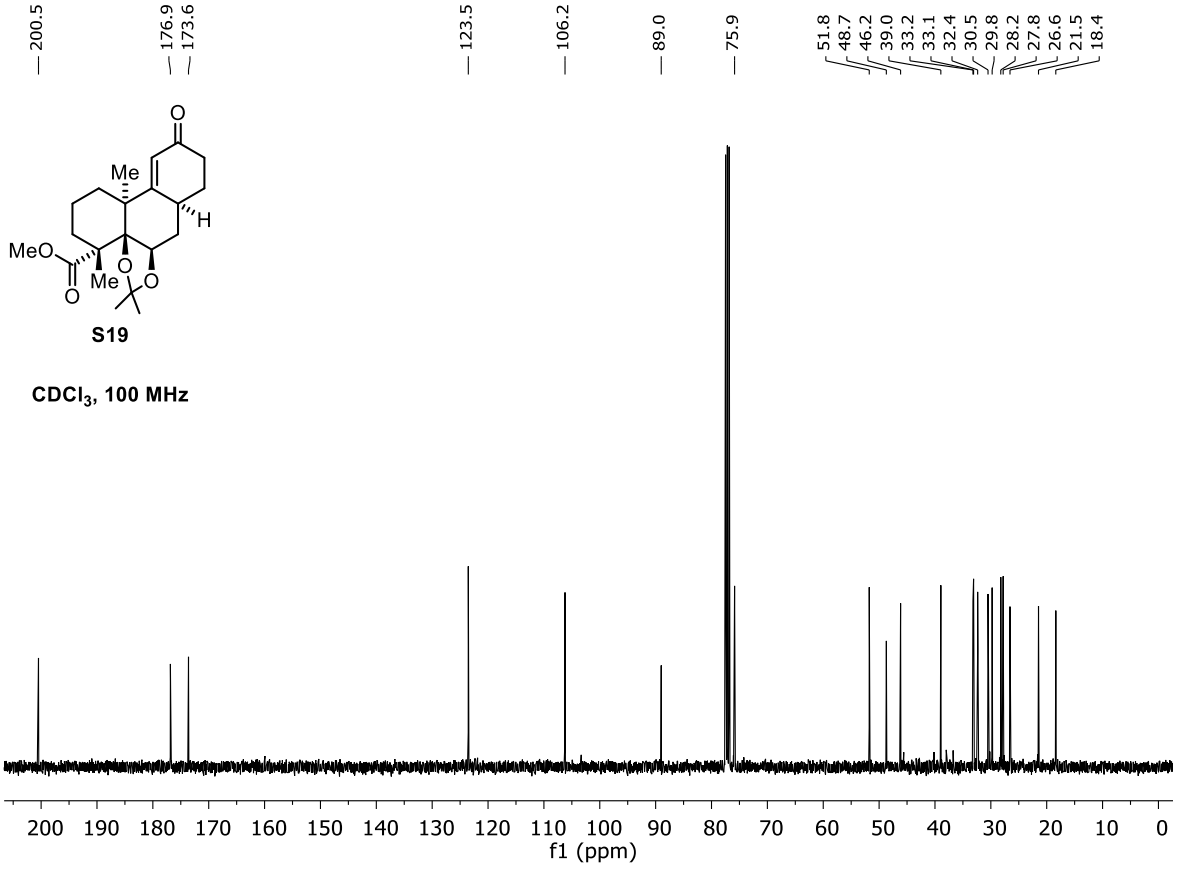
$CDCl_3$, 100 MHz



S19

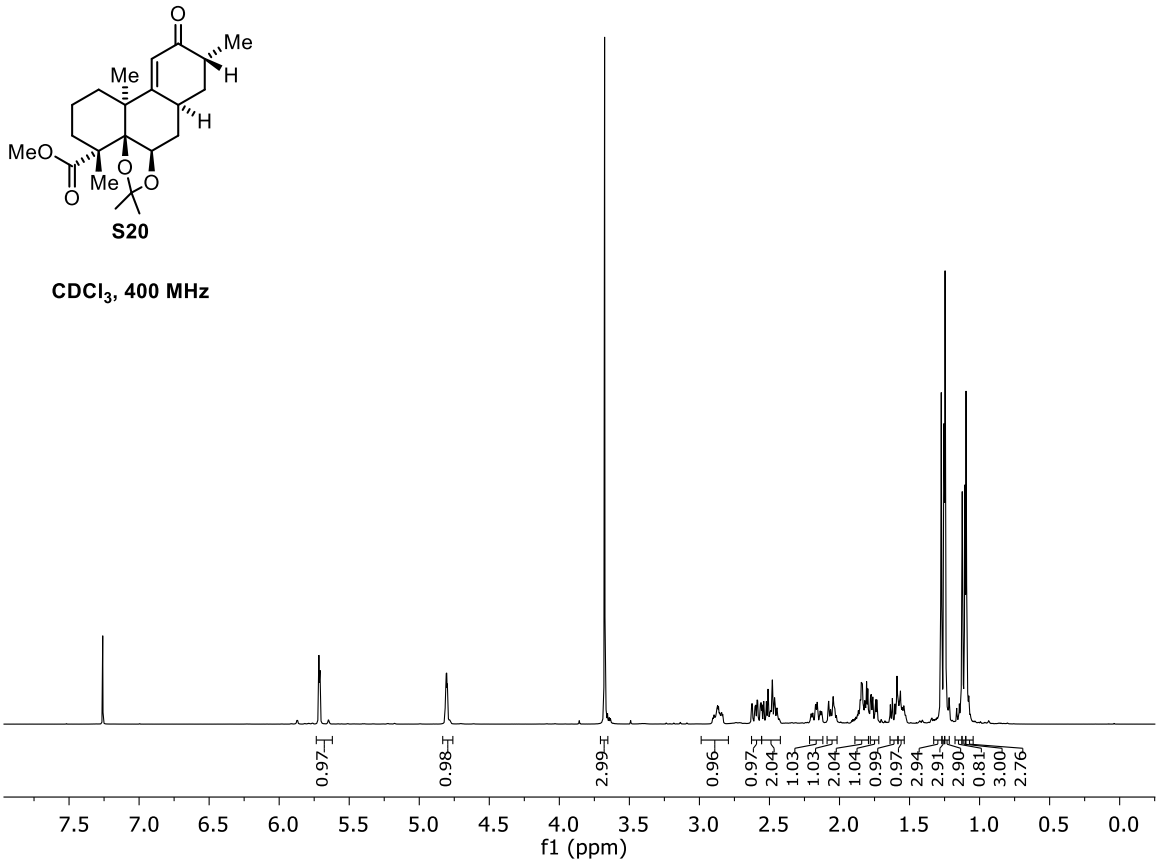
$CDCl_3$, 400 MHz

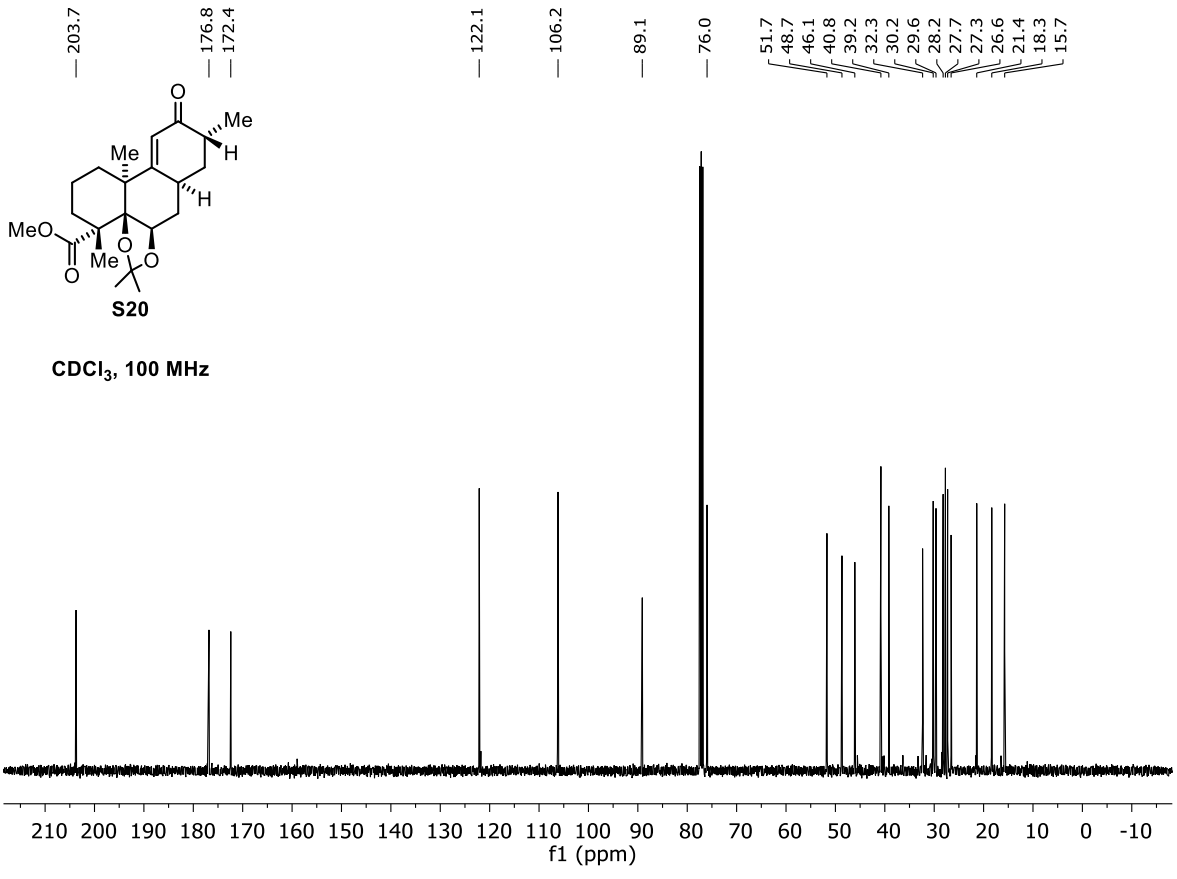


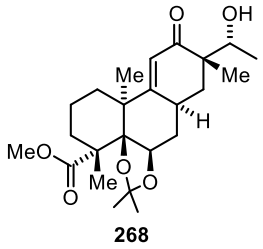


S19

$CDCl_3$, 100 MHz

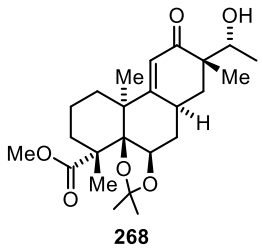

S20
CDCl3, 400 MHz
0.97
0.98
2.99
0.96
0.97
2.04
1.03
1.03
2.04
1.04
0.99
0.97
2.94
2.91
2.90
0.81
3.00
2.76
f1 (ppm)


203.7
176.8
172.4
122.1
106.2
89.1
76.0
51.7
48.7
46.1
40.8
39.2
32.3
30.2
29.6
28.2
27.7
27.3
26.6
21.4
18.3
15.7
S20
CDCl3, 100 MHz
f1 (ppm)



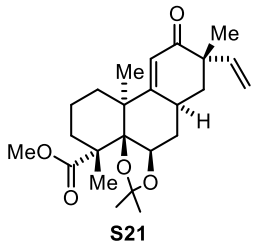
268

$CDCl_3$, 400 MHz



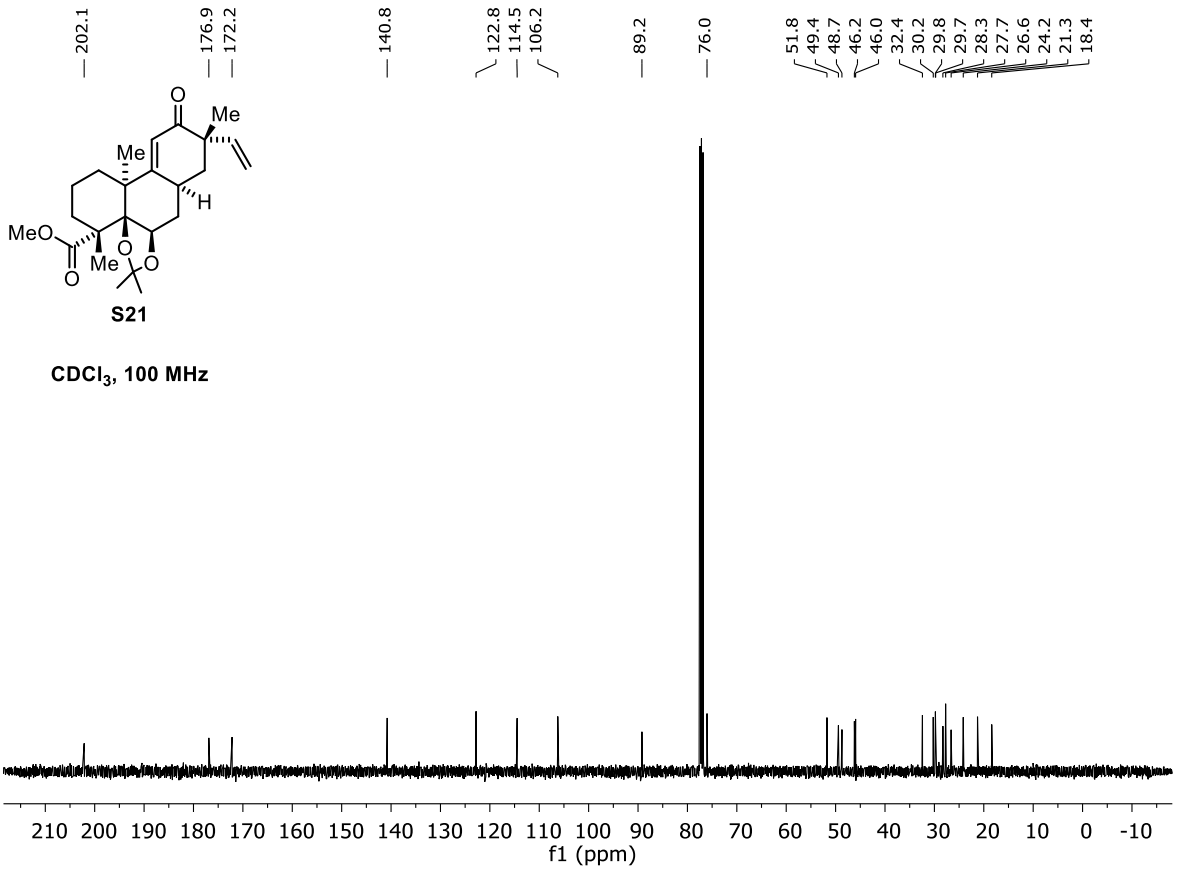
268

$CDCl_3$, 100 MHz



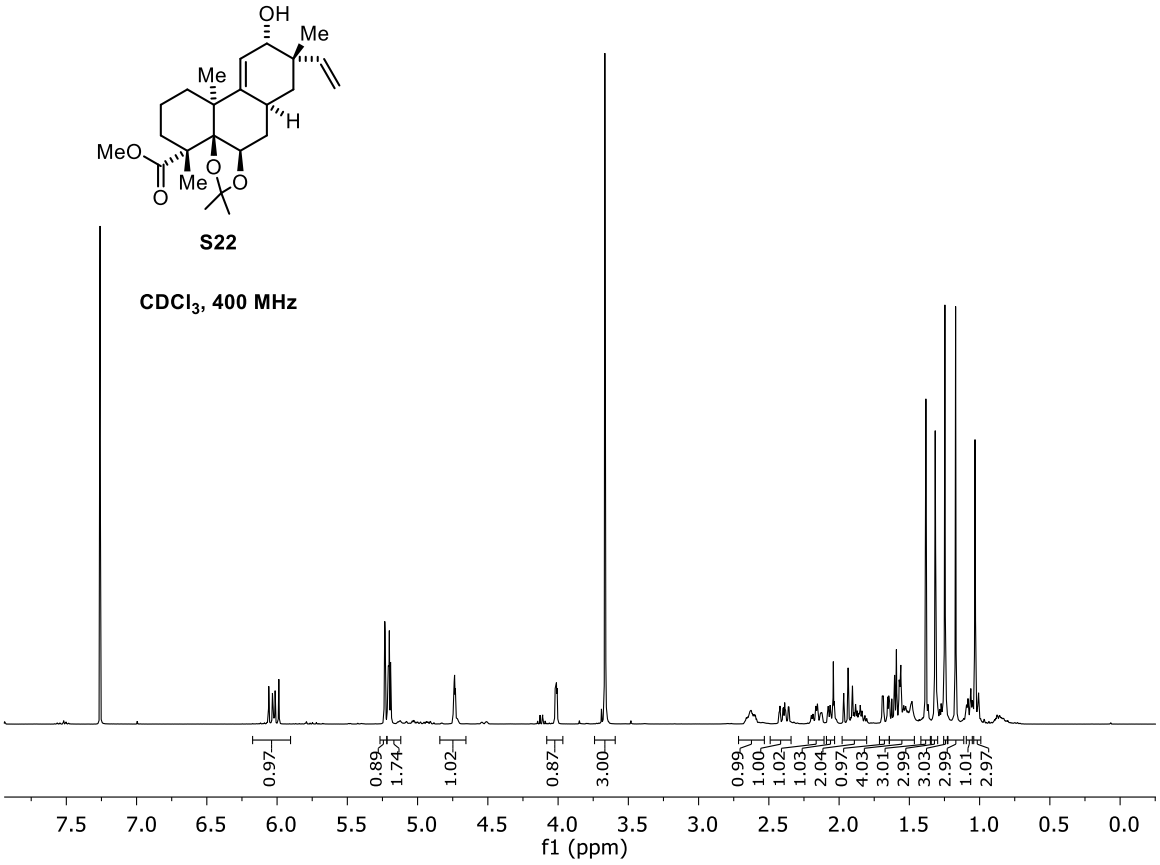
S21

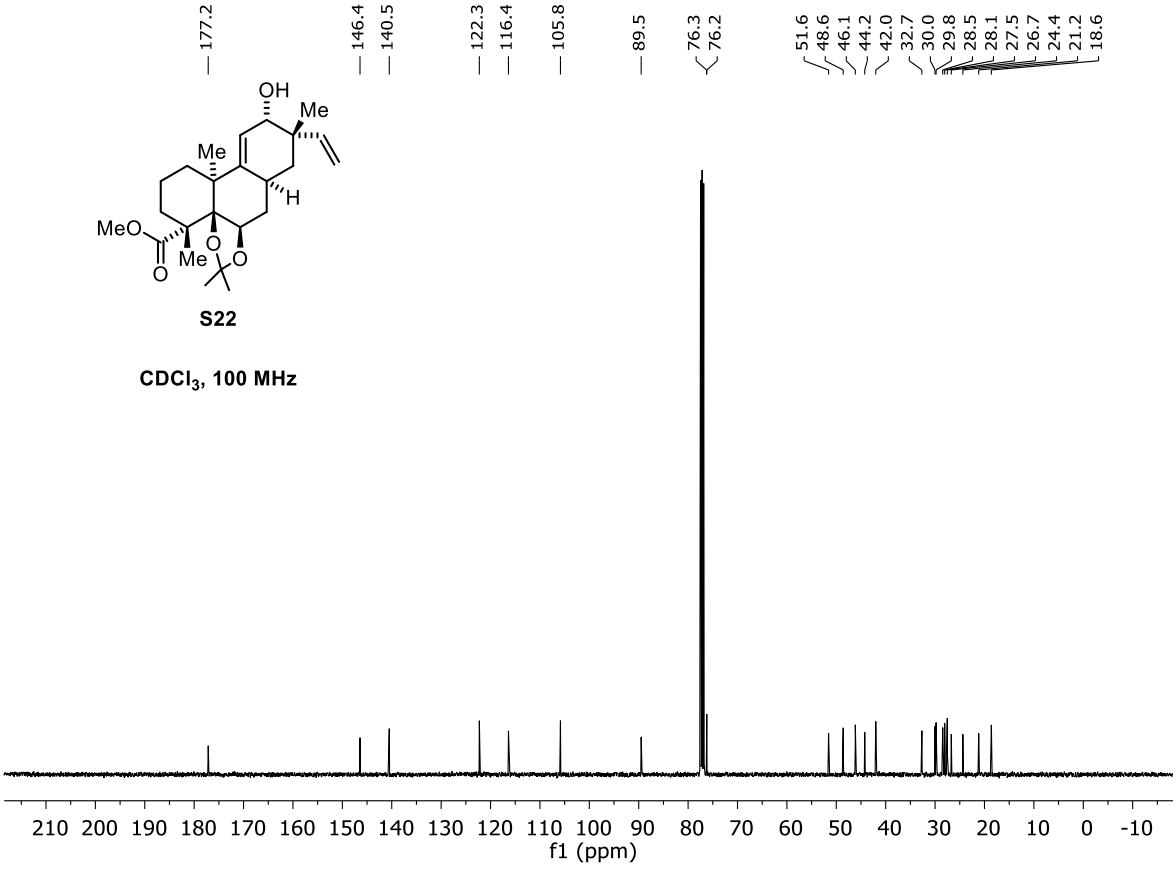
$CDCl_3$, 400 MHz

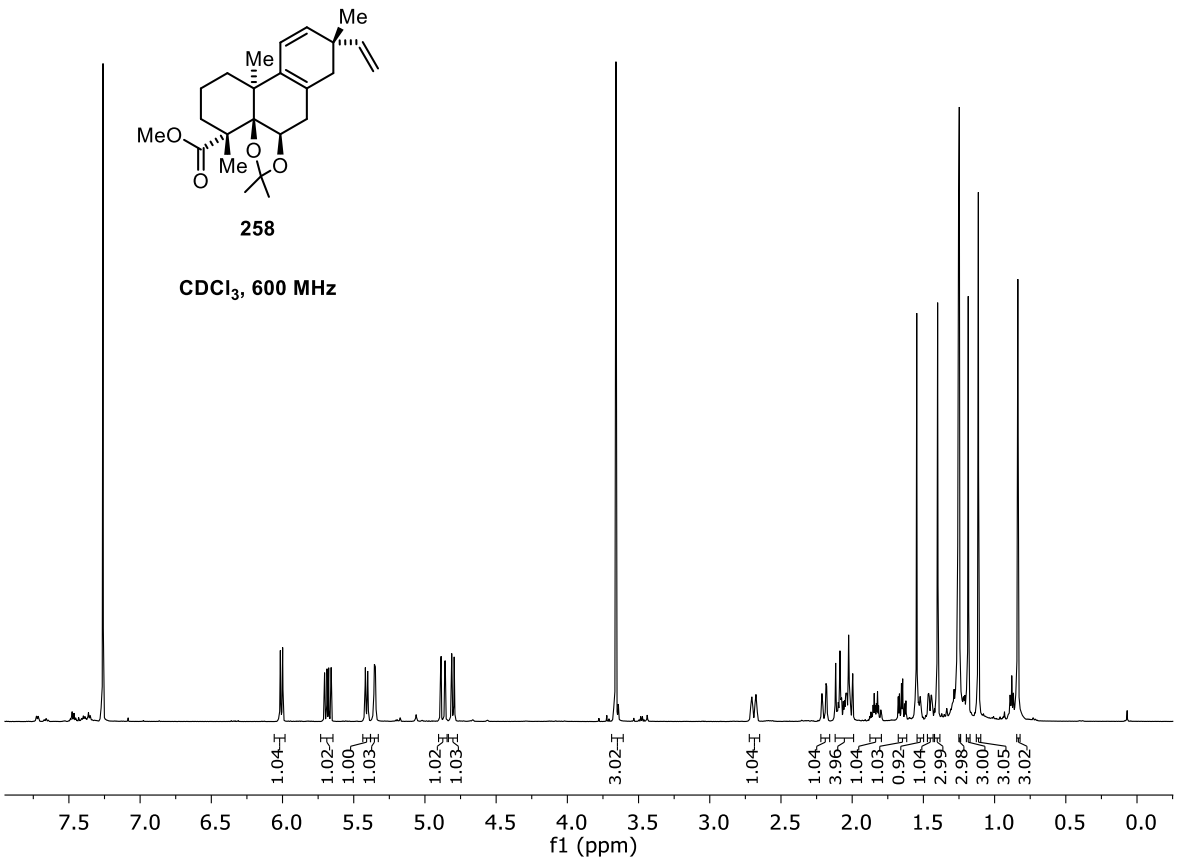


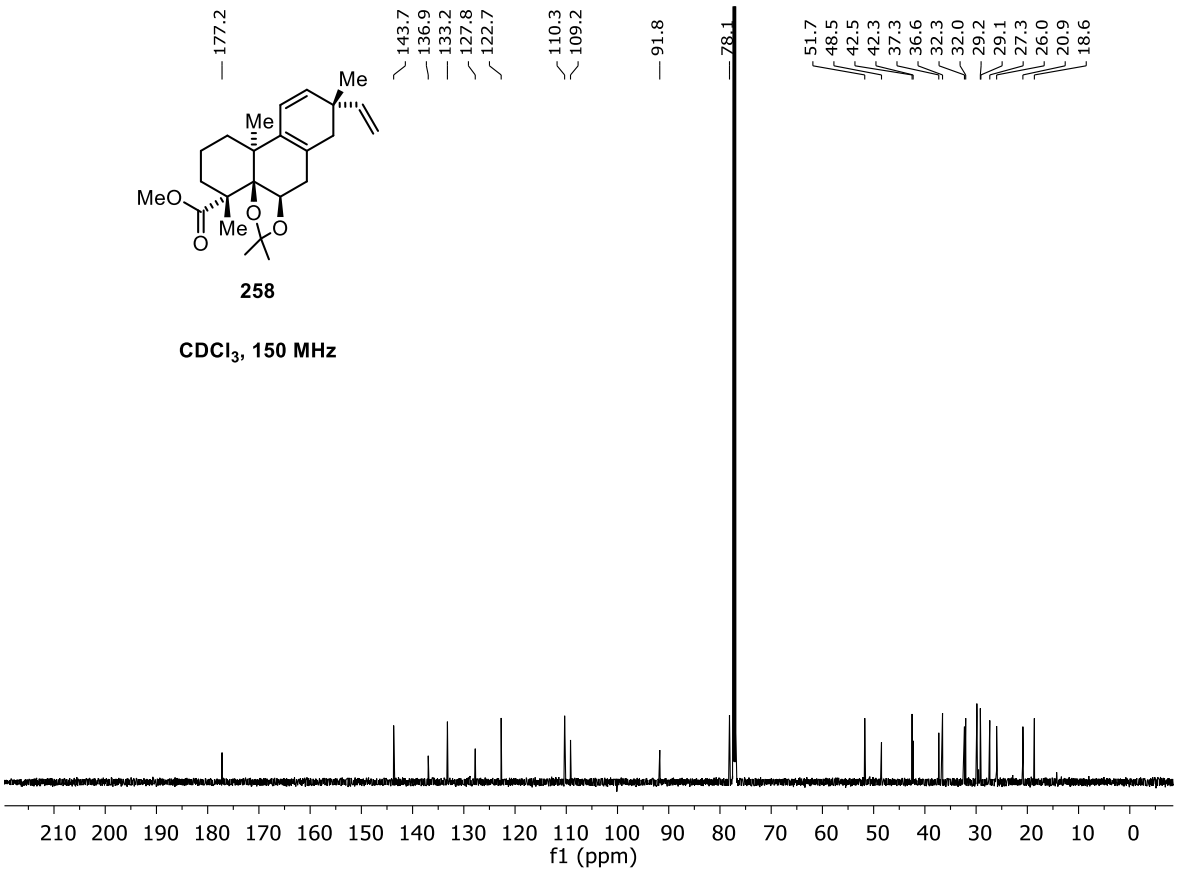
S21

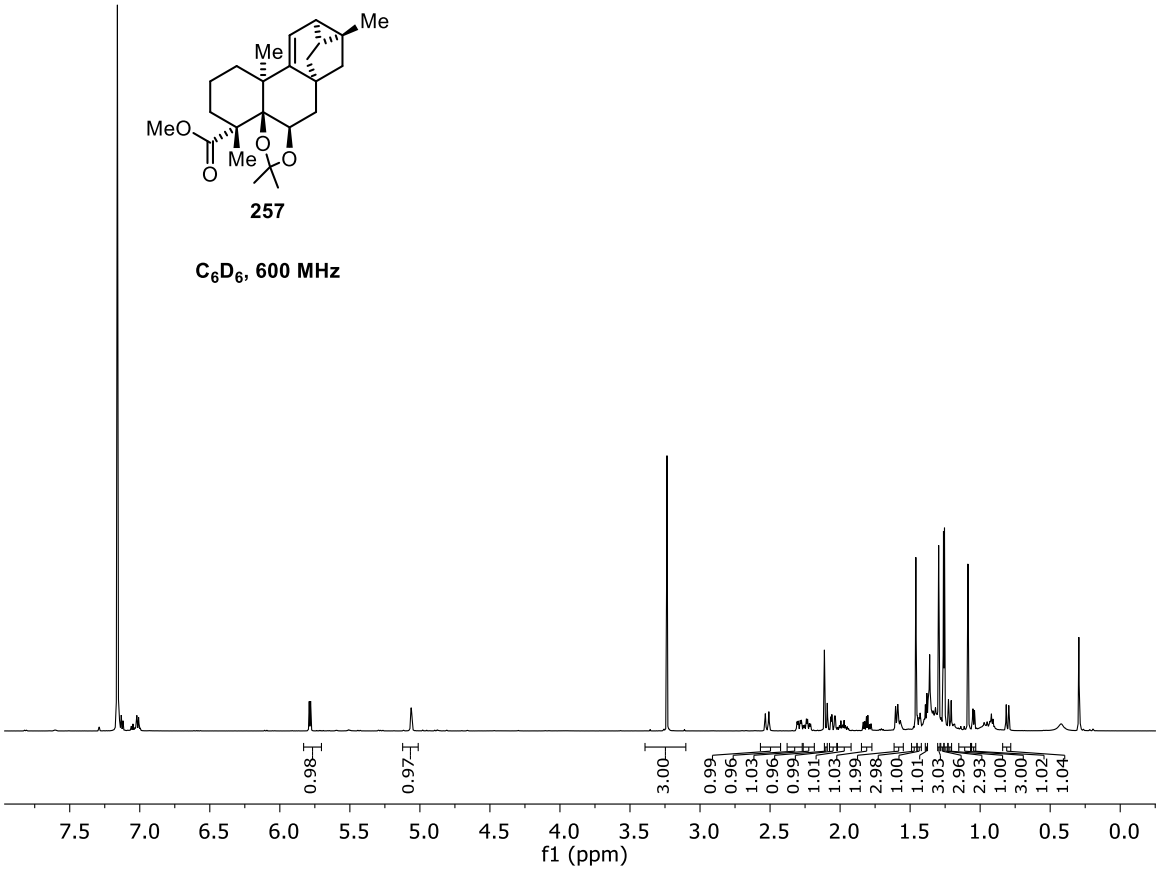
$CDCl_3$, 100 MHz

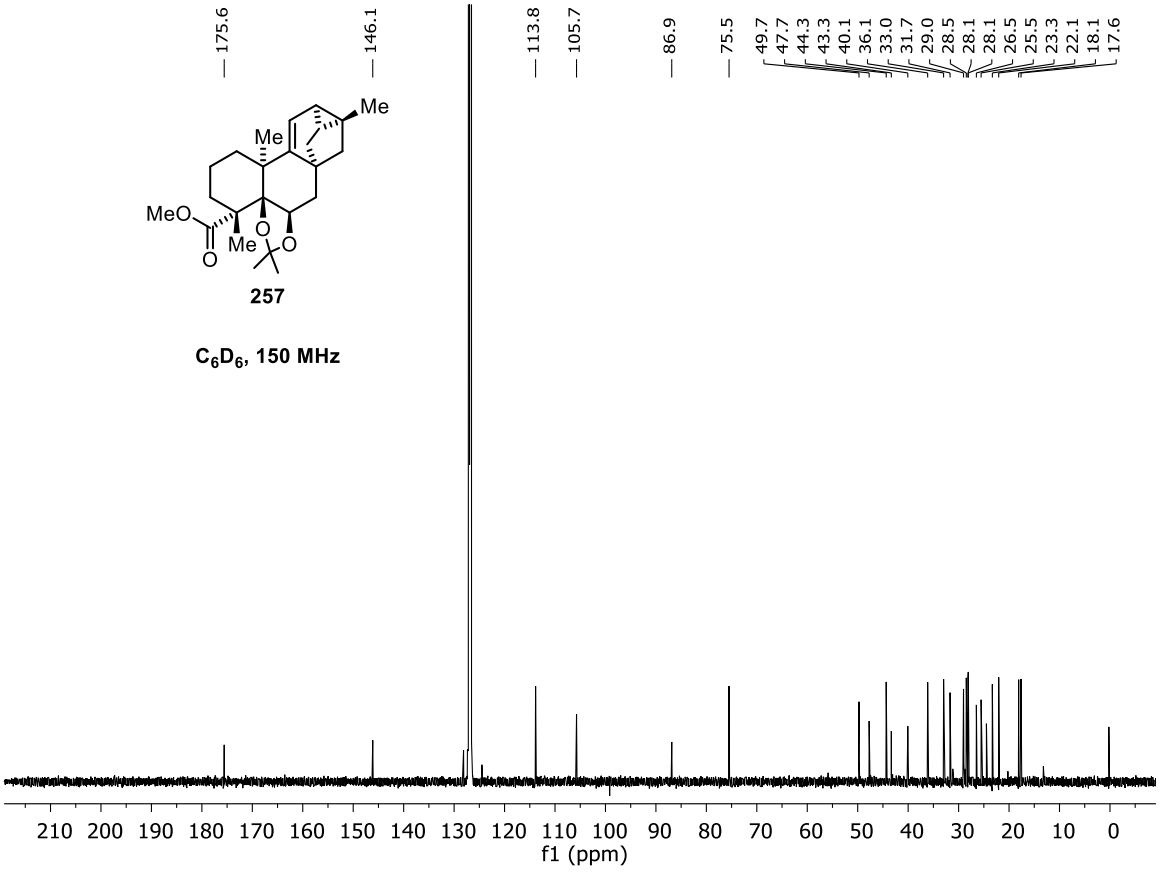

OH
Me
Me
H
MeO
O
Me
O
O
S22
CDCl3, 400 MHz
0.97
0.89
1.74
1.02
0.87
3.00
0.99
1.00
1.02
1.03
2.04
0.97
4.03
3.01
2.99
3.03
2.99
1.01
2.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

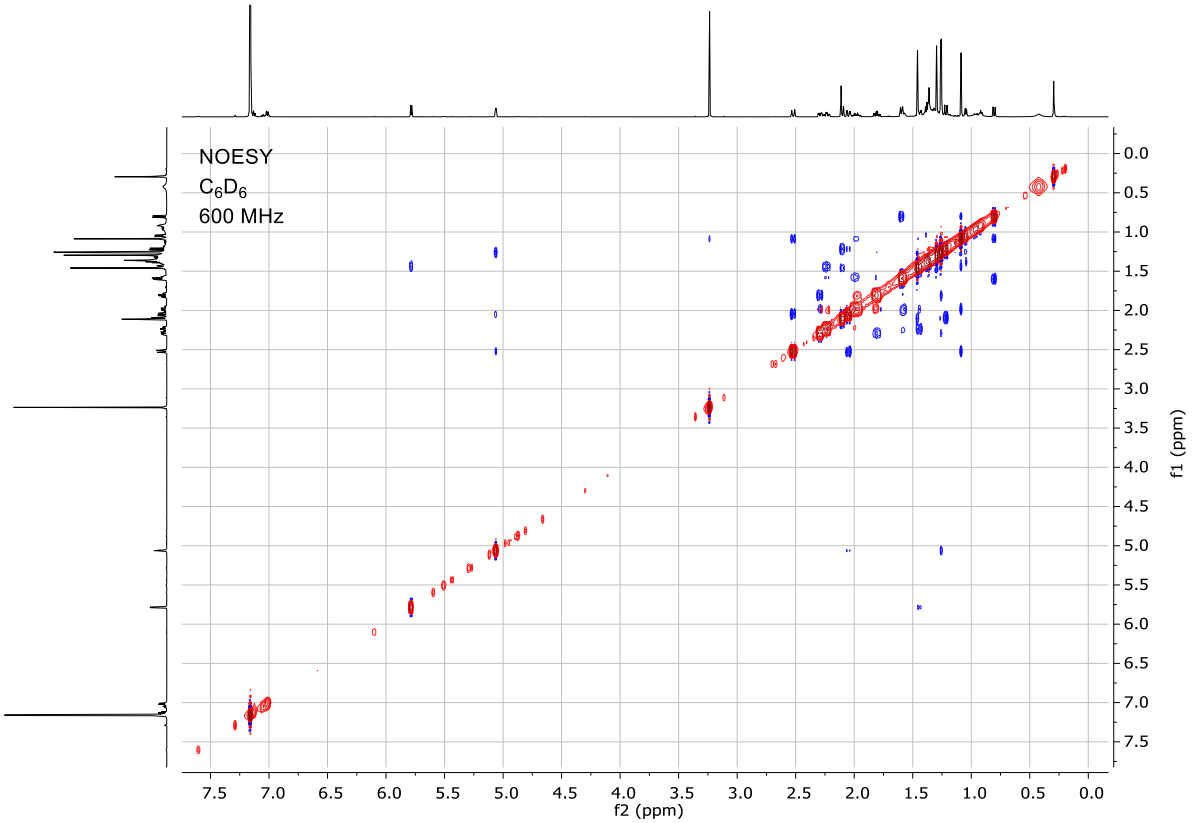

177.2
146.4
140.5
122.3
116.4
105.8
89.5
76.3
76.2
51.6
48.6
46.1
44.2
42.0
32.7
30.0
29.8
28.5
28.1
27.5
26.7
24.4
21.2
18.6
OH
Me
Me
H
MeO
O
Me
O
O
S22
CDCl3, 100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

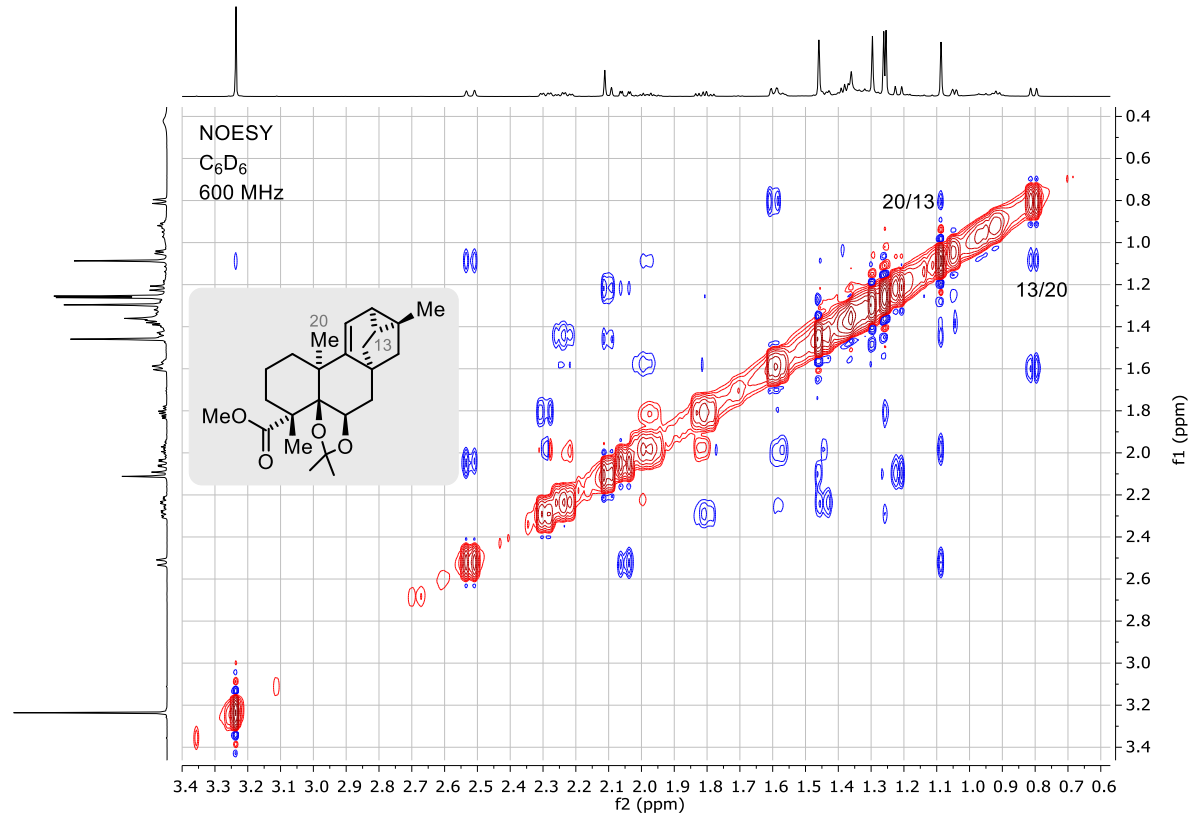

Me
Me
MeO
O
Me
O
O
258
CDCl3, 600 MHz
1.04
1.02
1.00
1.03
1.02
1.03
3.02
1.04
1.04
3.96
1.04
1.03
0.92
1.04
2.99
2.98
3.00
3.05
3.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

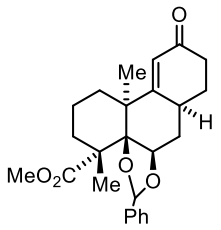

177.2
143.7
136.9
133.2
127.8
122.7
110.3
109.2
91.8
78.1
51.7
48.5
42.5
42.3
37.3
36.6
32.3
32.0
29.2
29.1
27.3
26.0
20.9
18.6
Me
Me
MeO
O
Me
O
O
258
CDCl3, 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
MeO
O
Me
O
O
257
C6D6, 600 MHz
0.98
0.97
3.00
0.99
0.96
1.03
0.96
0.99
1.01
1.03
1.99
2.98
1.00
1.01
3.03
2.96
2.93
1.00
3.00
1.02
1.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


175.6
146.1
113.8
105.7
86.9
75.5
49.7
47.7
44.3
43.3
40.1
36.1
33.0
31.7
29.0
28.5
28.1
28.1
26.5
25.5
23.3
22.1
18.1
17.6
Me
Me
MeO
O
Me
O
O
257
C6D6, 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

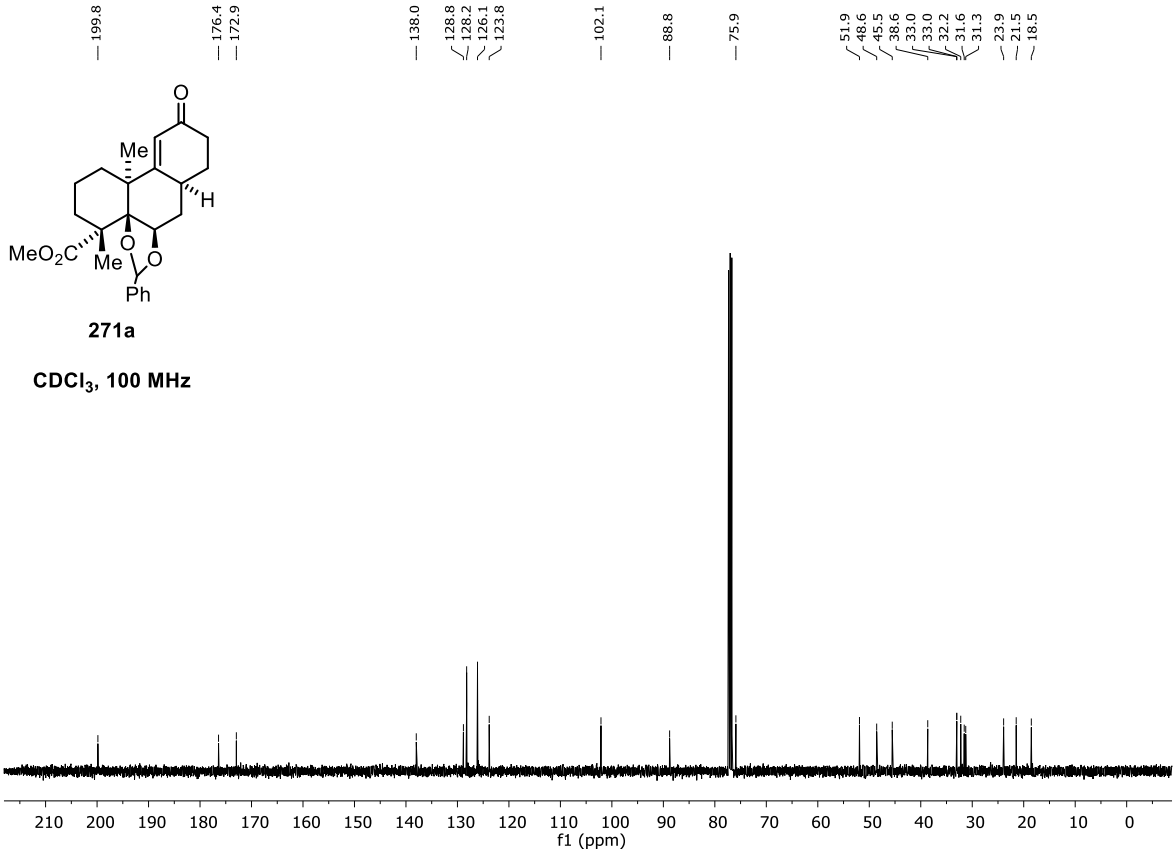

NOESY
C6D6
600 MHz
f2 (ppm)
f1 (ppm)


NOESY
C6D6
600 MHz
20/13
13/20
Me
20
Me
13
MeO
O
Me
O
O
f2 (ppm)
f1 (ppm)



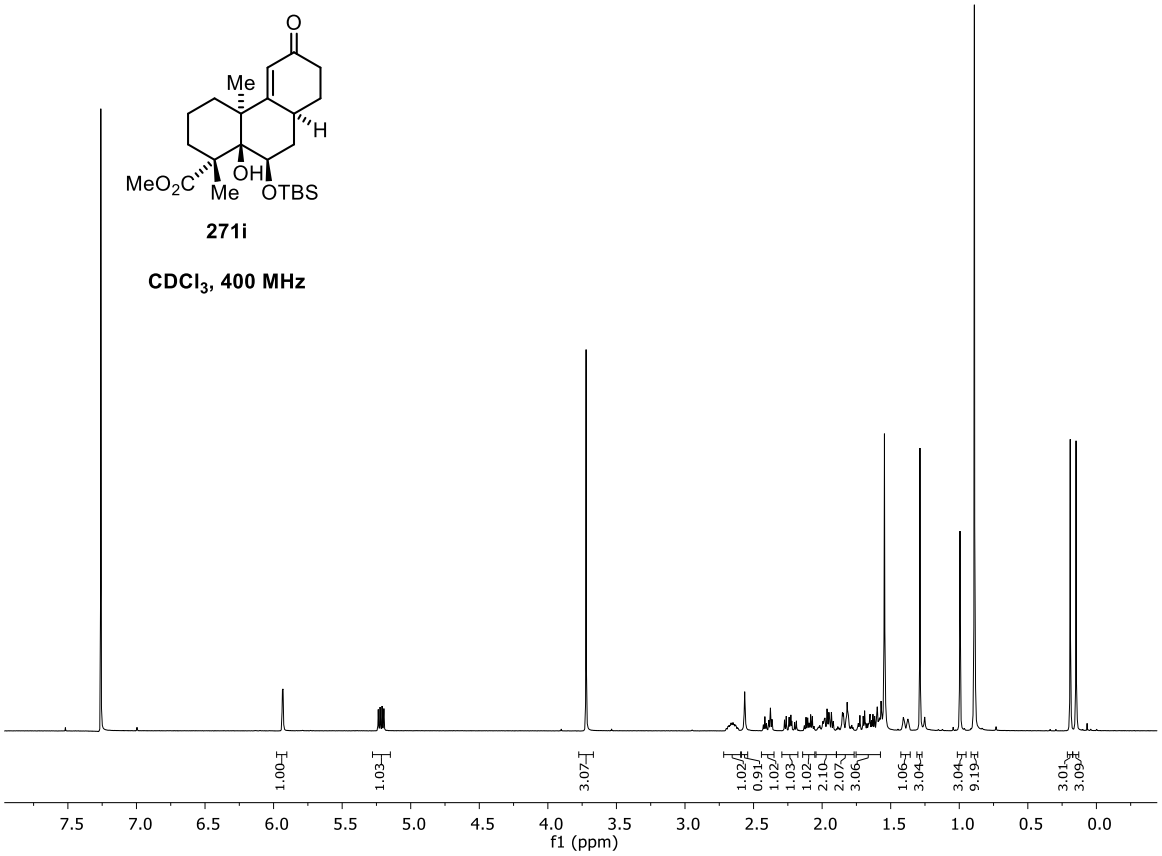
271a

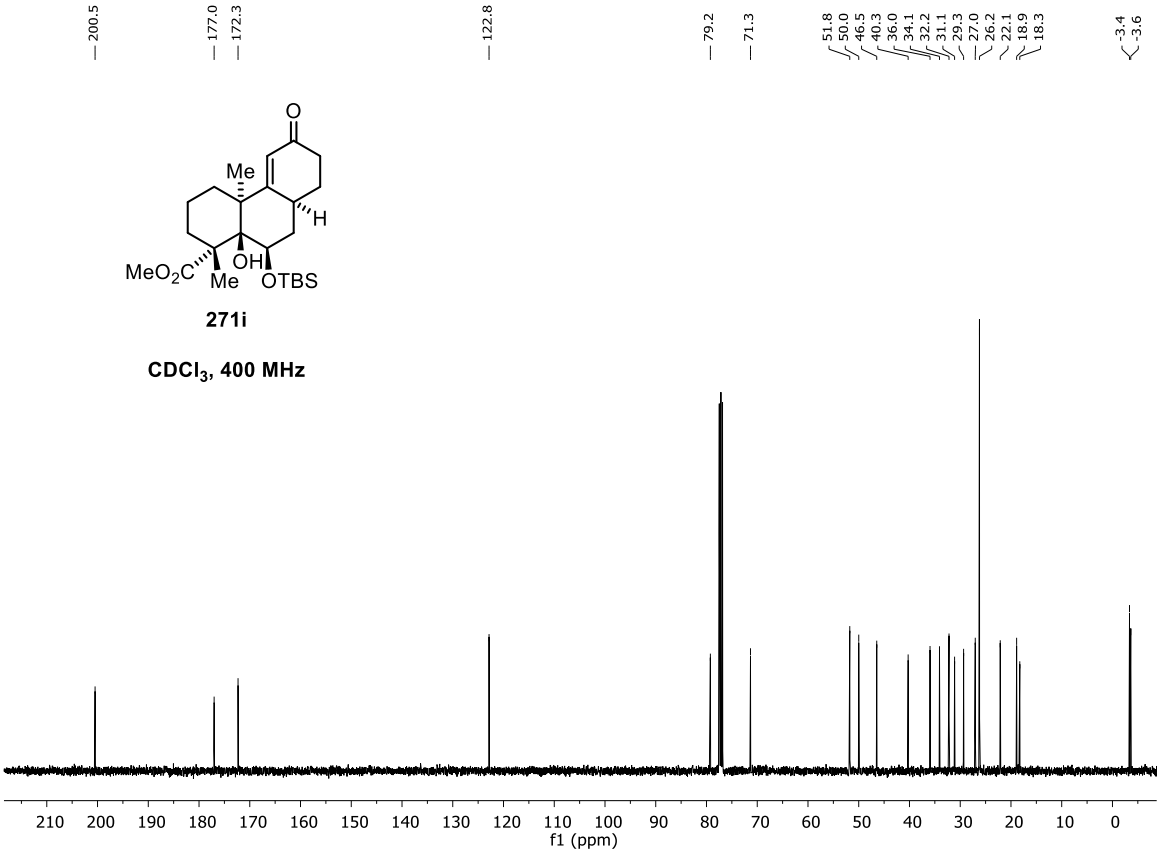
$CDCl_3$, 400 MHz



271a

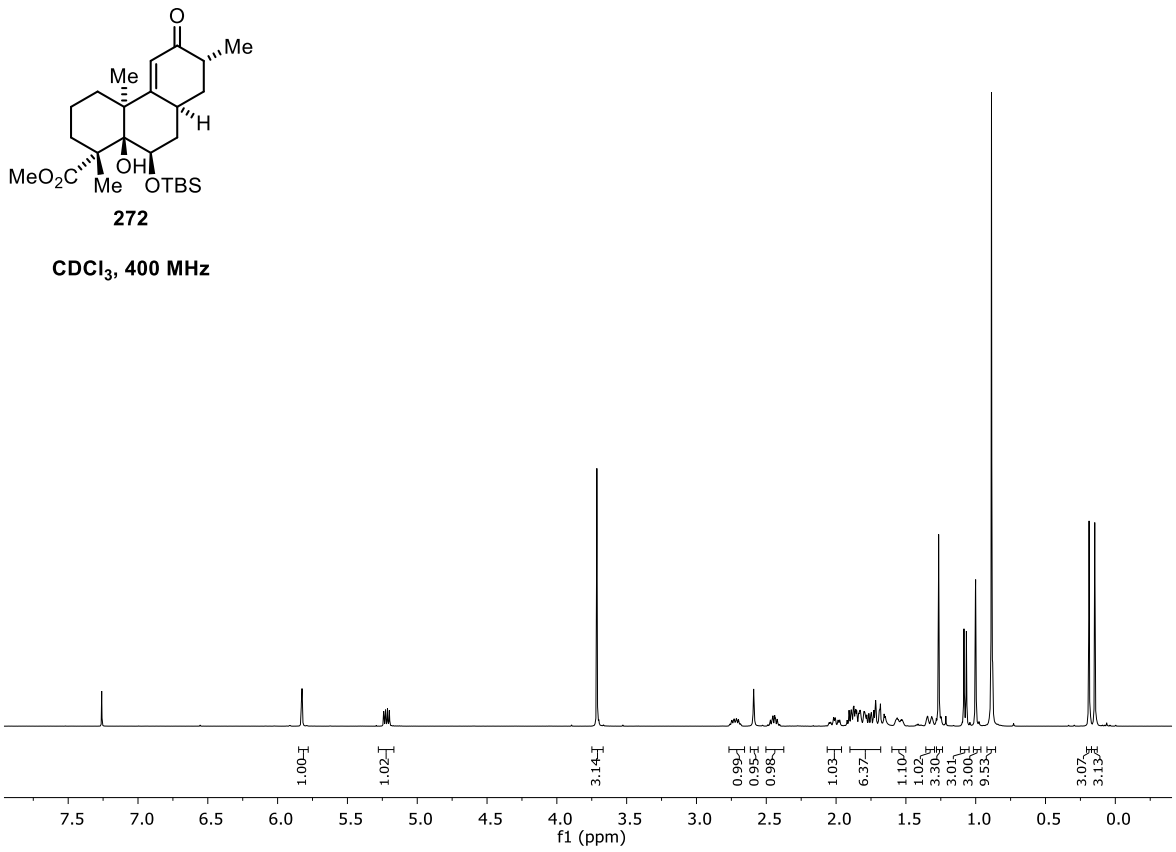
$CDCl_3$, 100 MHz


O
Me
H
MeO2C
OH
Me
OTBS
271i
CDCl3, 400 MHz
1.00
1.03
3.07
1.02
0.91
1.02
1.03
1.02
2.10
2.07
3.06
1.06
3.04
3.04
9.19
3.01
3.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



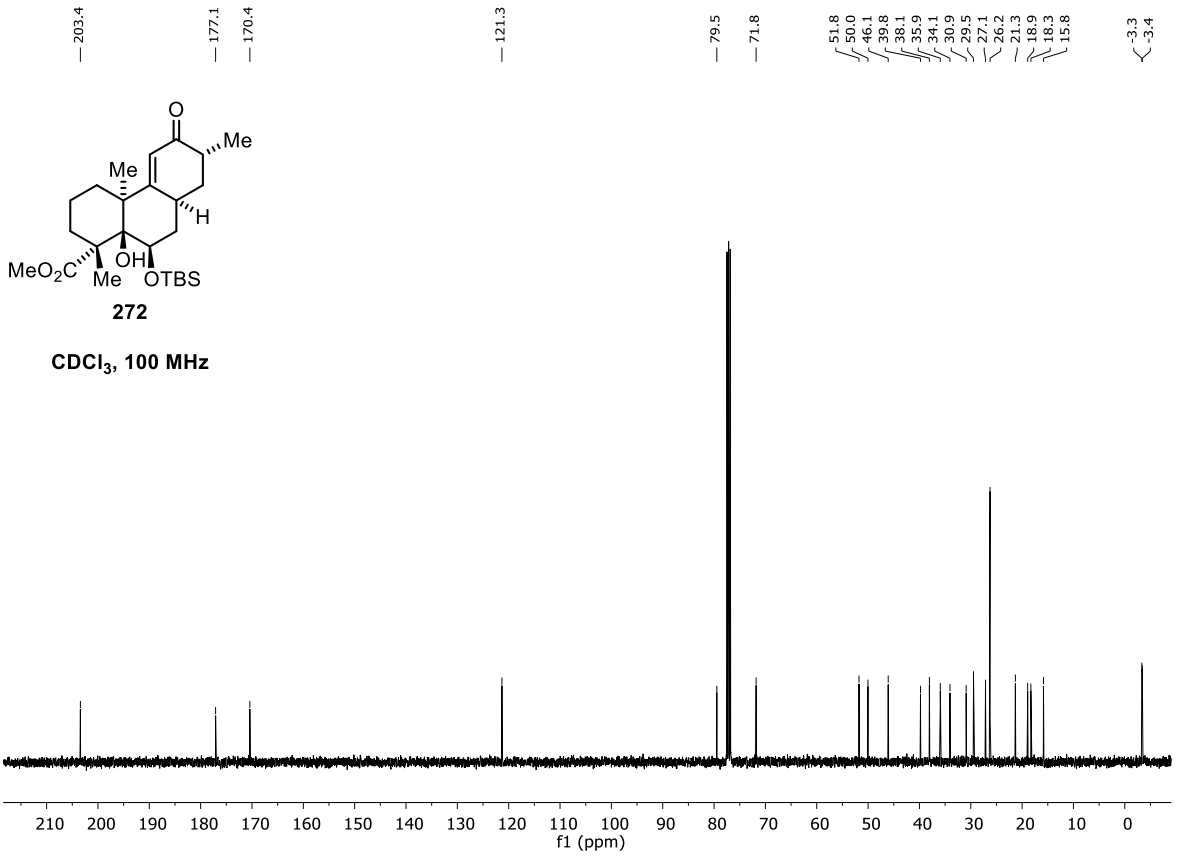
271i

$CDCl_3$, 400 MHz



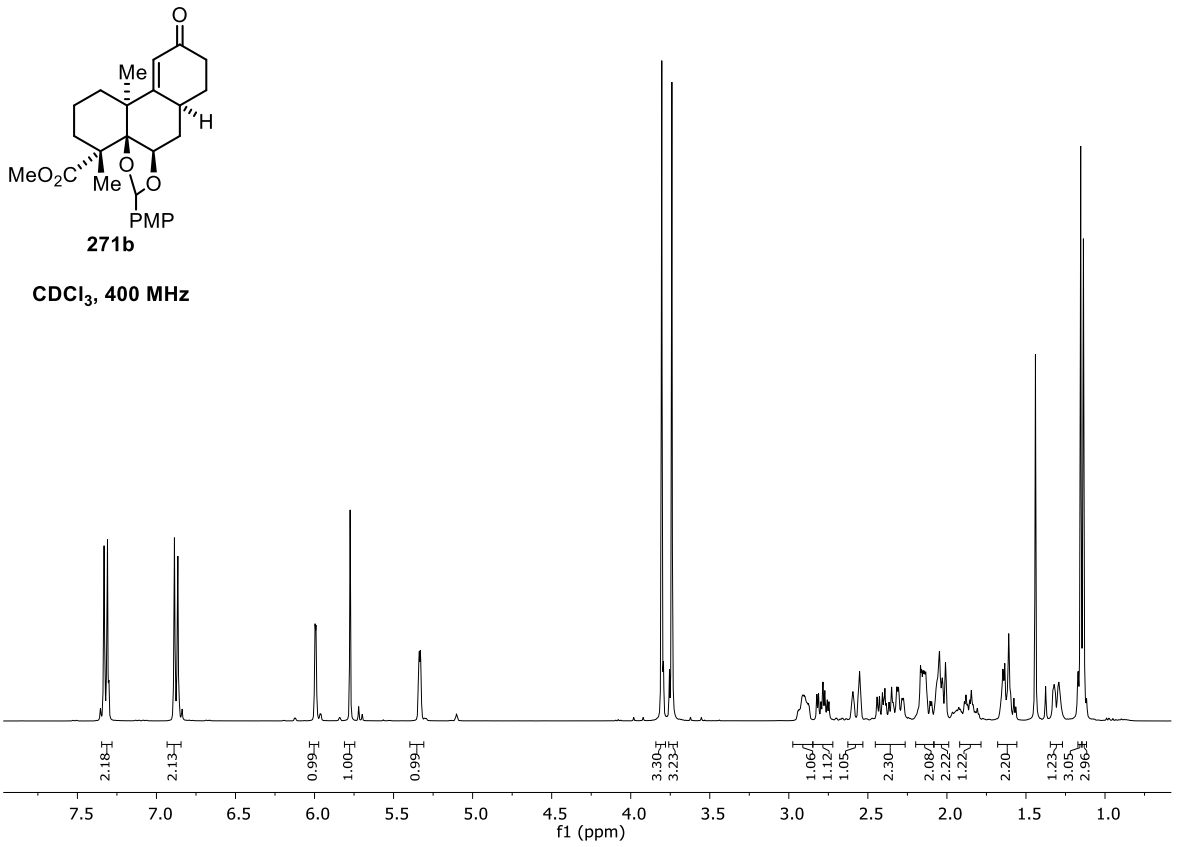
272

$CDCl_3$, 400 MHz



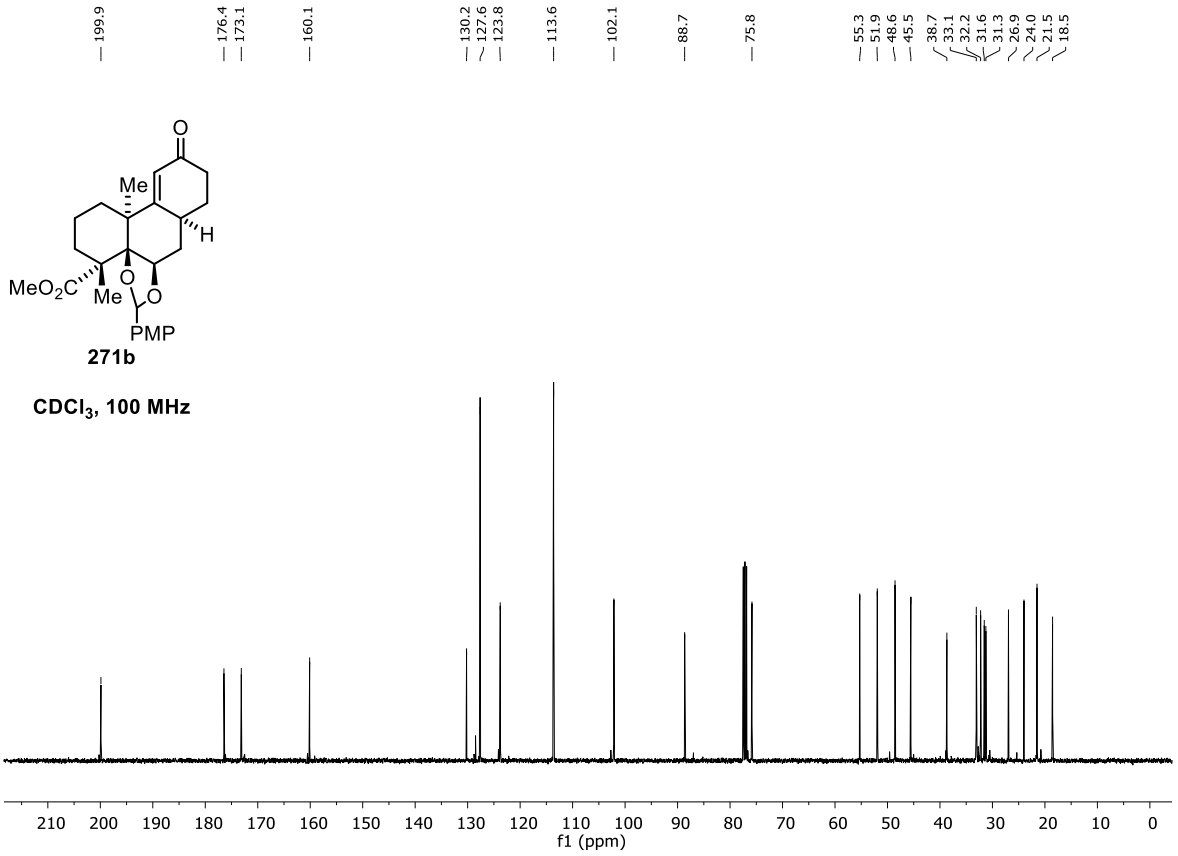
272

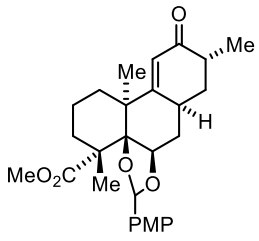
$CDCl_3$, 100 MHz



271b

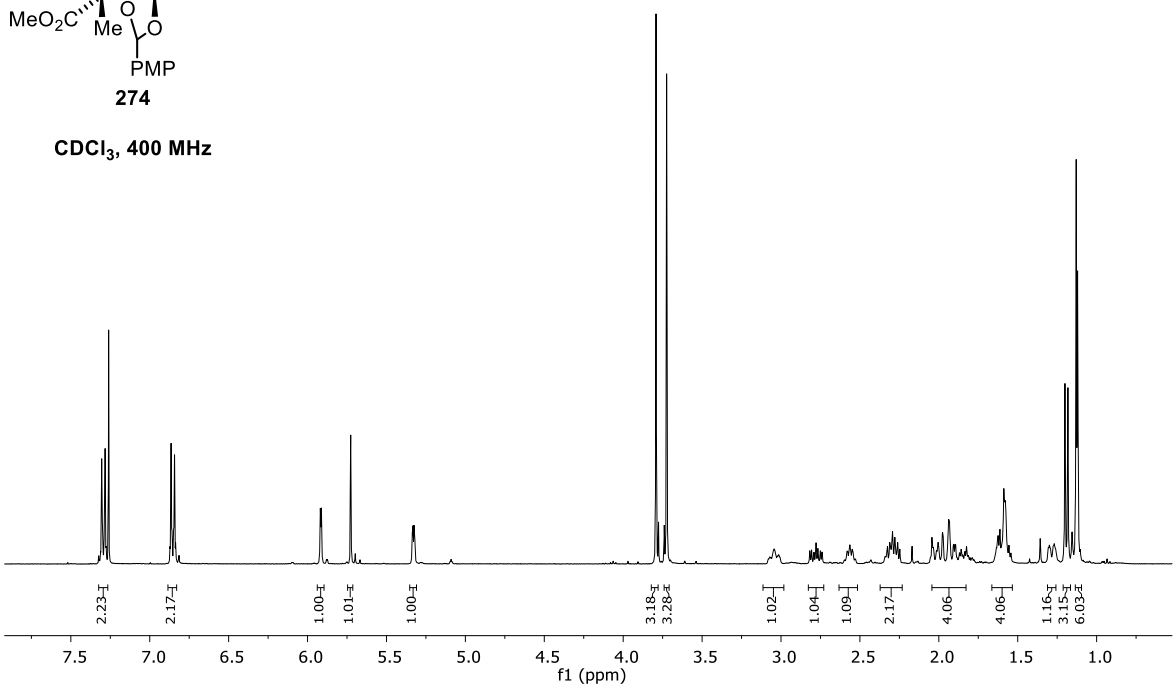
$CDCl_3$, 400 MHz

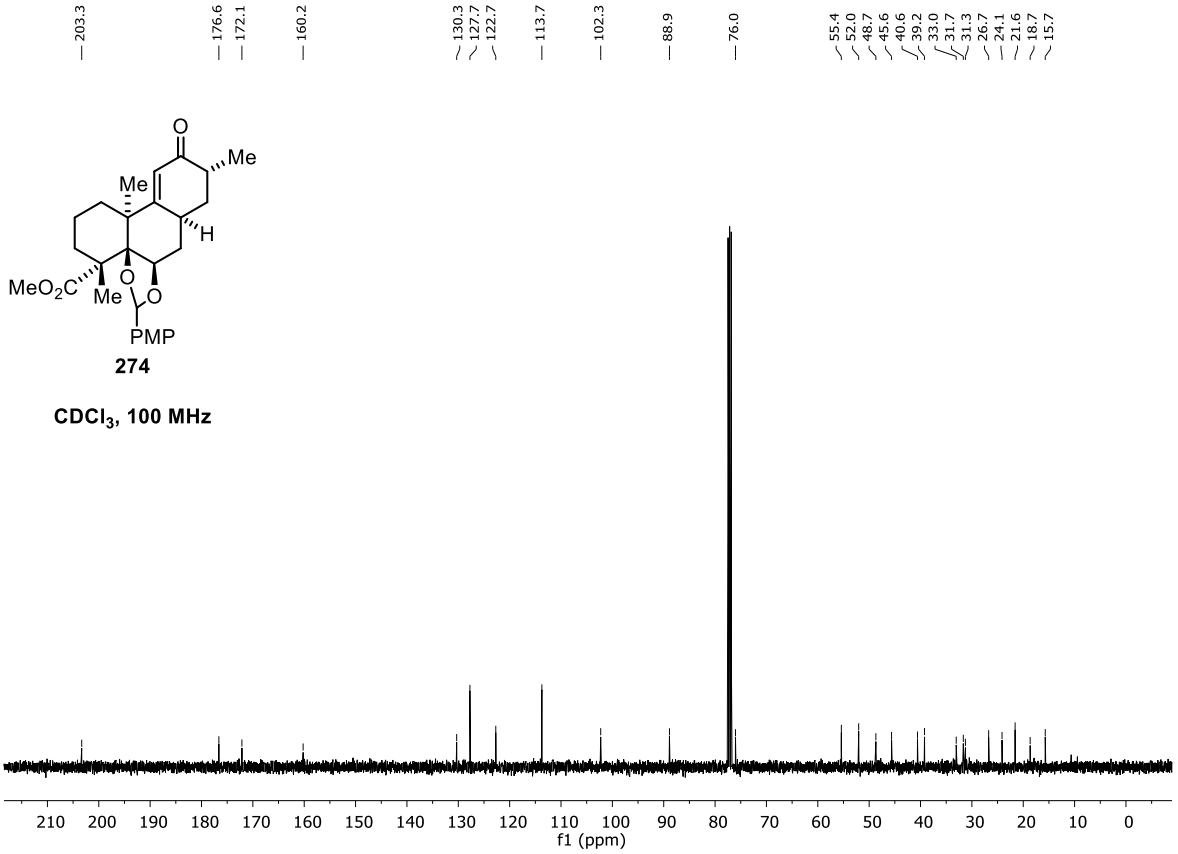

199.9
176.4
173.1
160.1
130.2
127.6
123.8
113.6
102.1
88.7
75.8
55.3
51.9
48.6
45.5
38.7
33.1
32.2
31.6
31.3
26.9
24.0
21.5
18.5
Me
H
MeO2C
Me
O
O
PMP
271b
CDCl3, 100 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



274

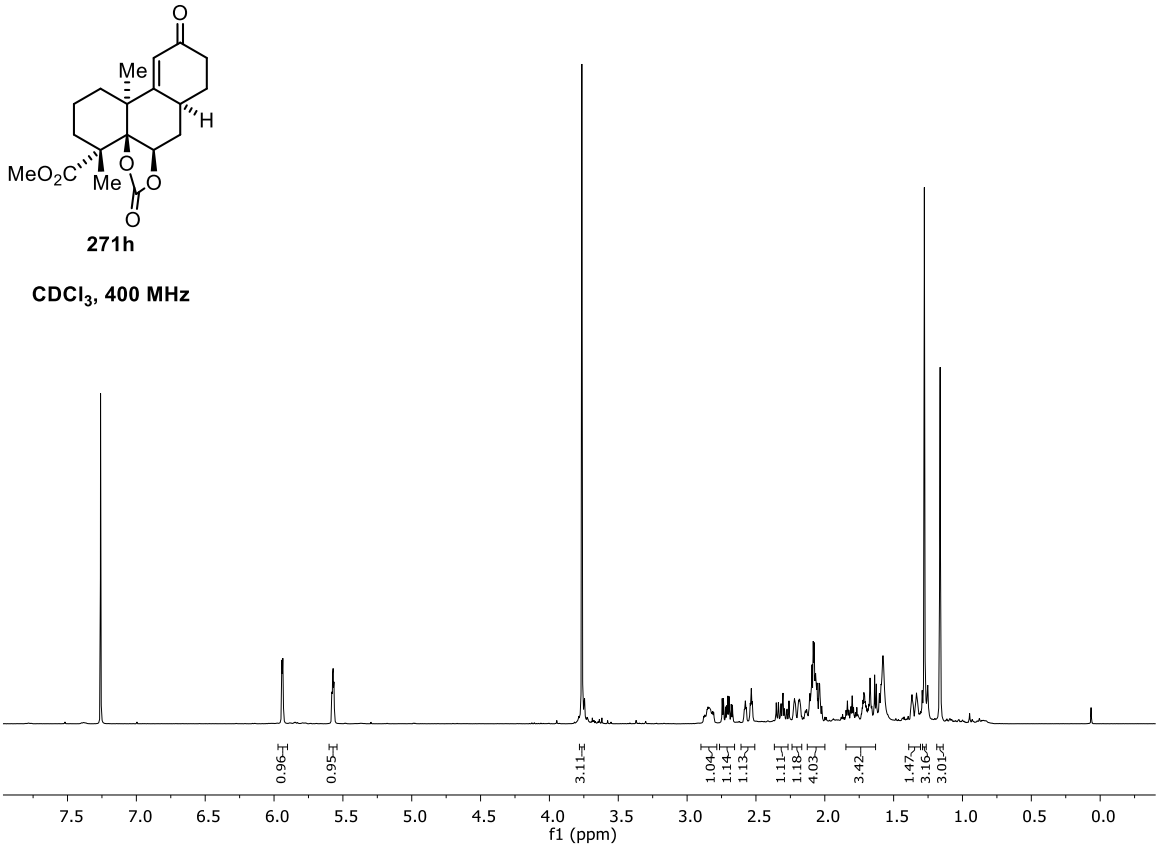
$CDCl_3$, 400 MHz





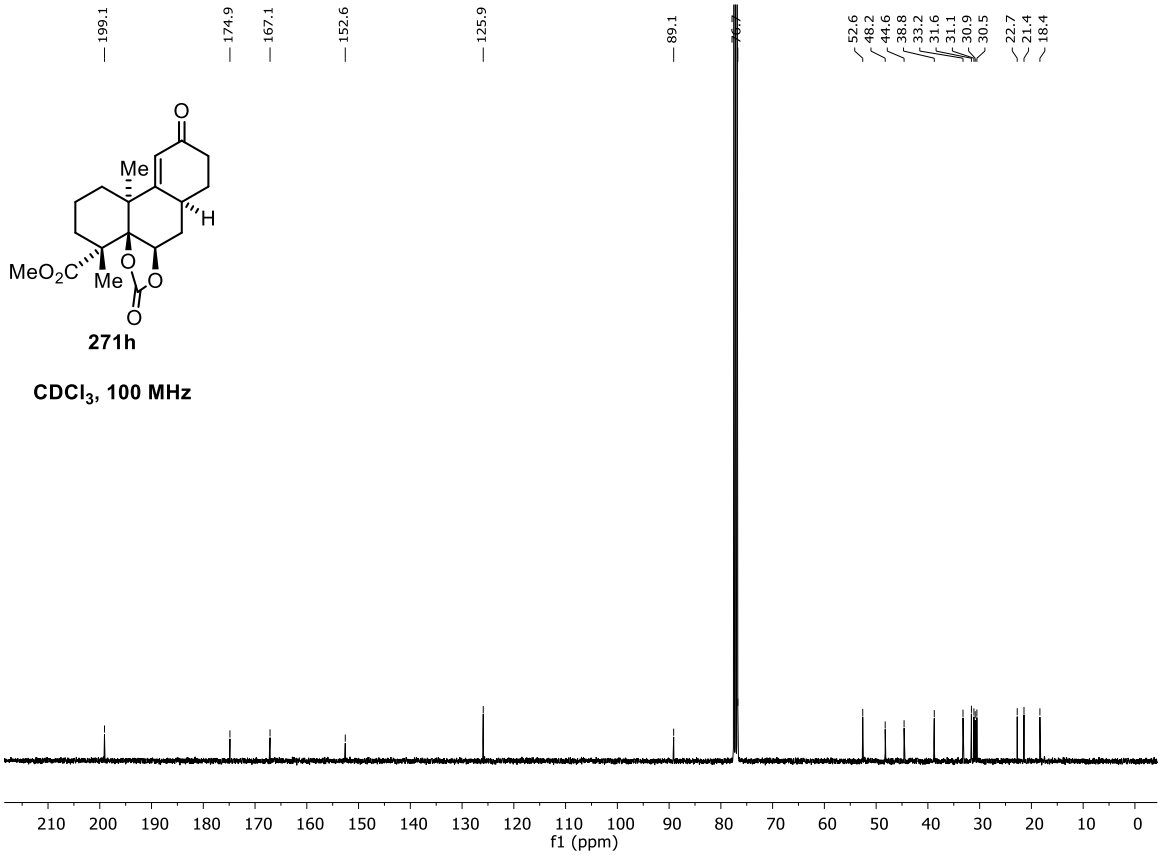
274

$CDCl_3$, 100 MHz



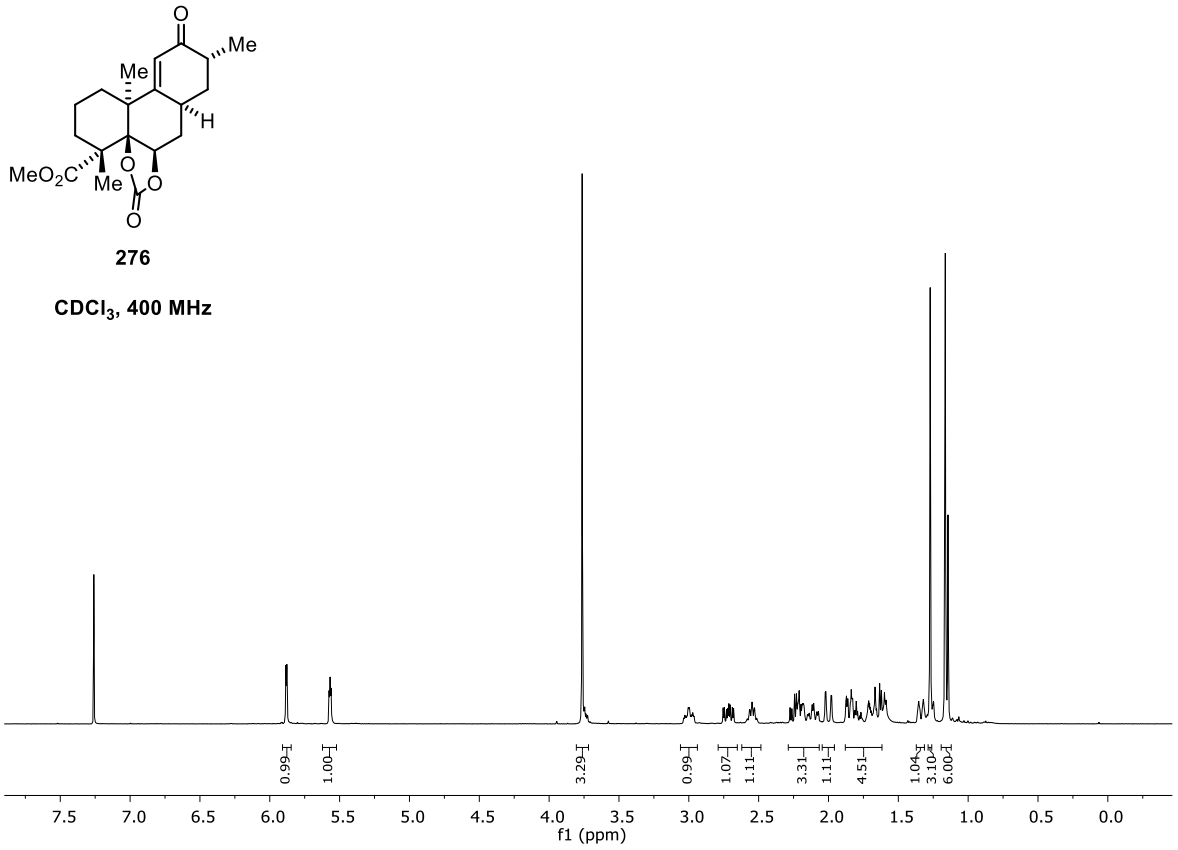
271h

$CDCl_3$, 400 MHz



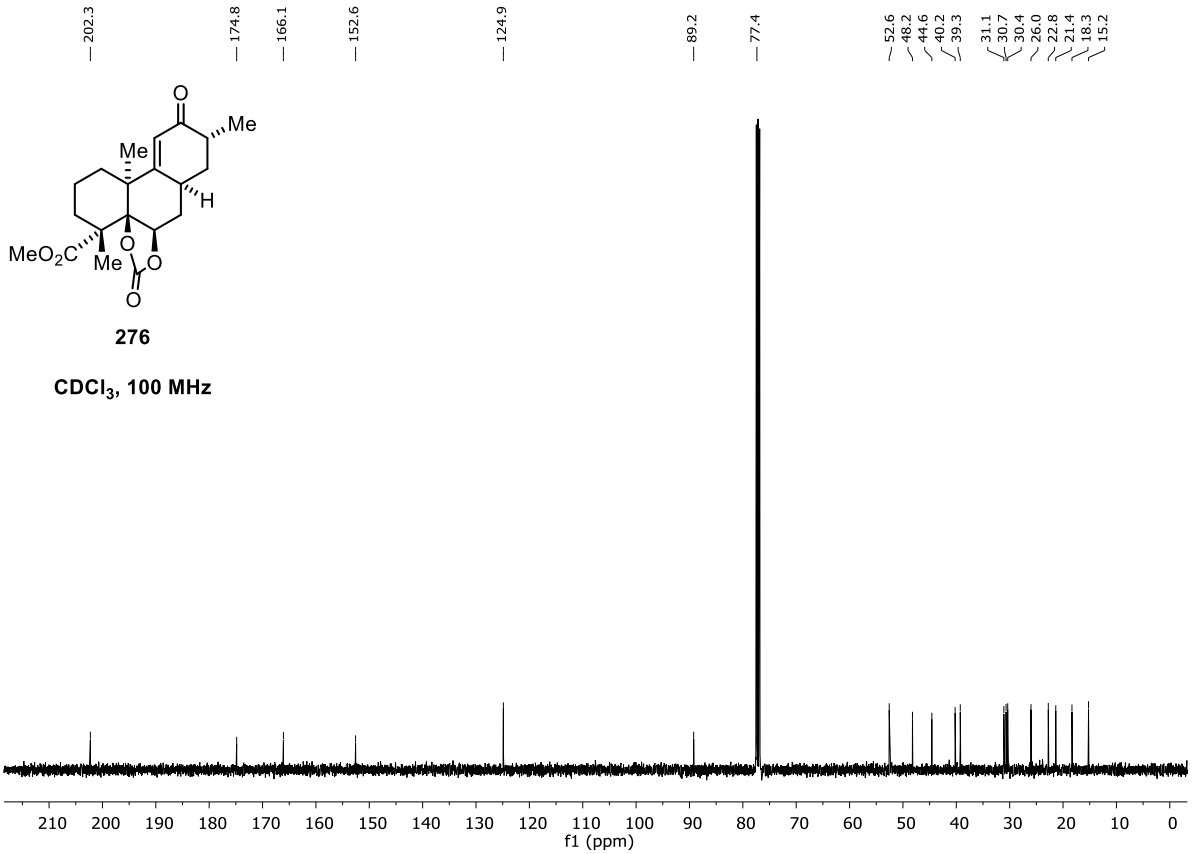
271h

$CDCl_3$, 100 MHz



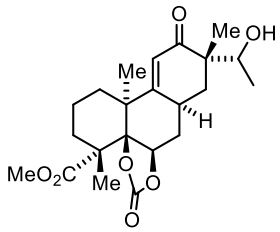
276

$CDCl_3$, 400 MHz



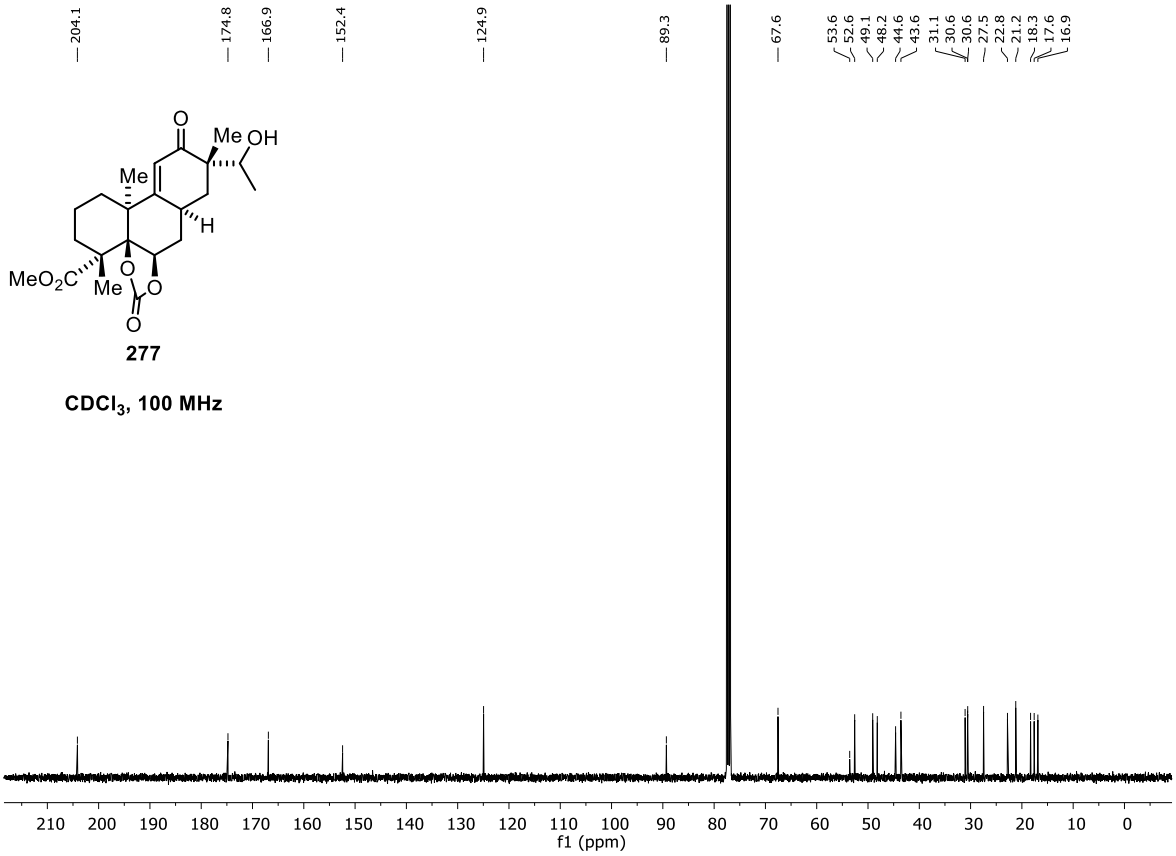
276

$CDCl_3$, 100 MHz



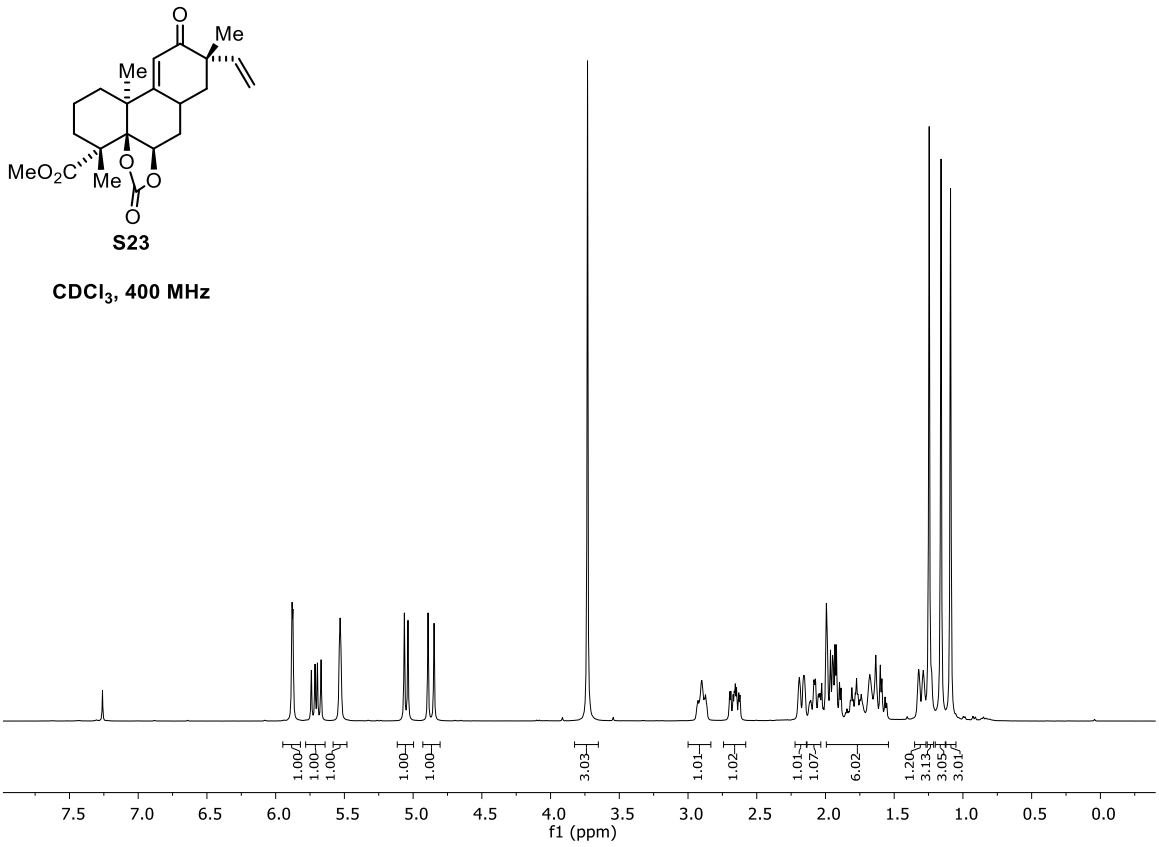
277

$CDCl_3$, 400 MHz



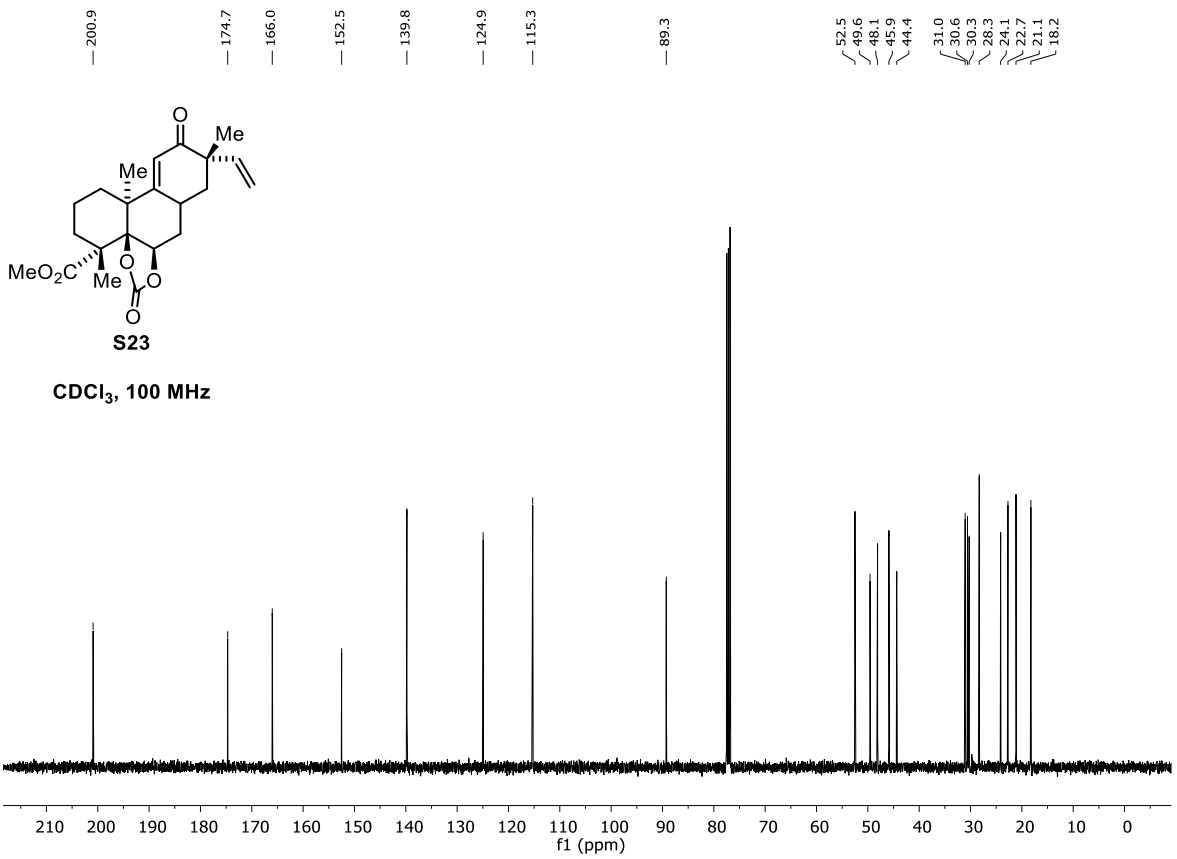
277

$CDCl_3$, 100 MHz



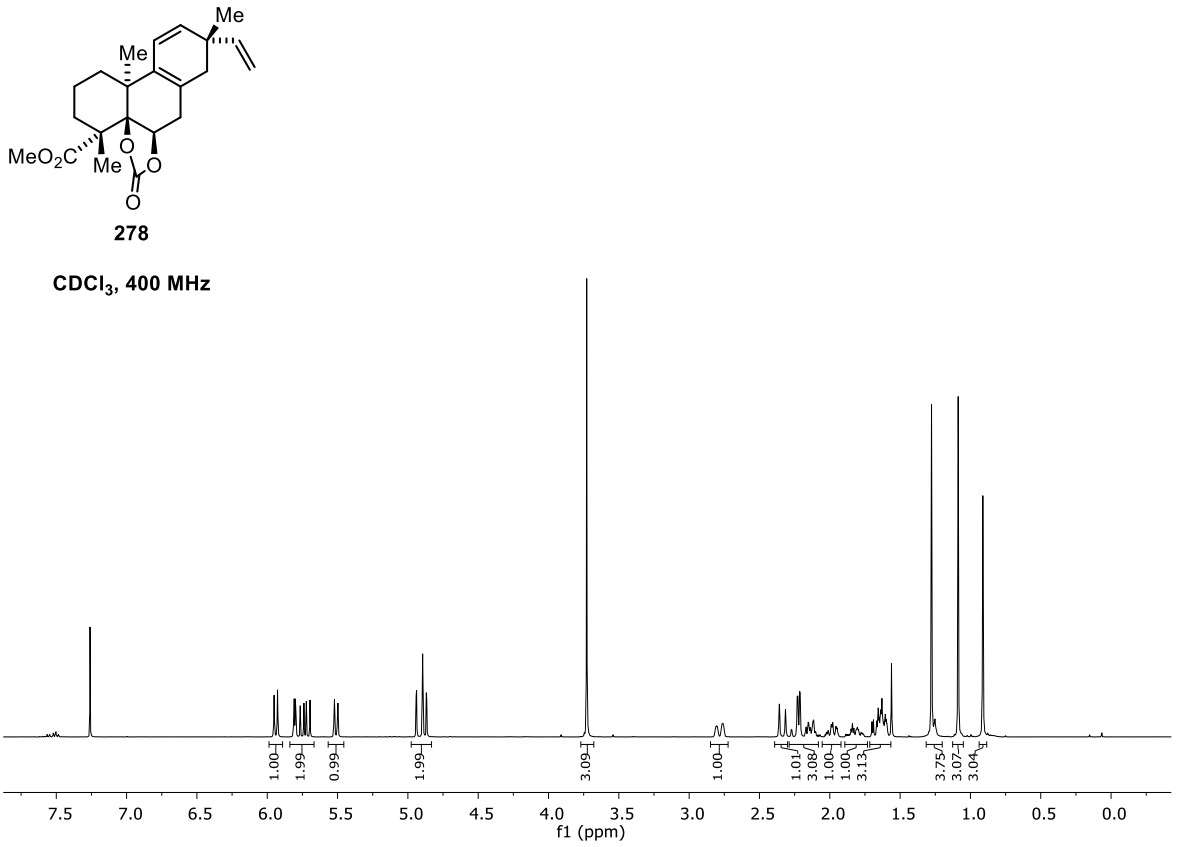
S23

$CDCl_3$, 400 MHz



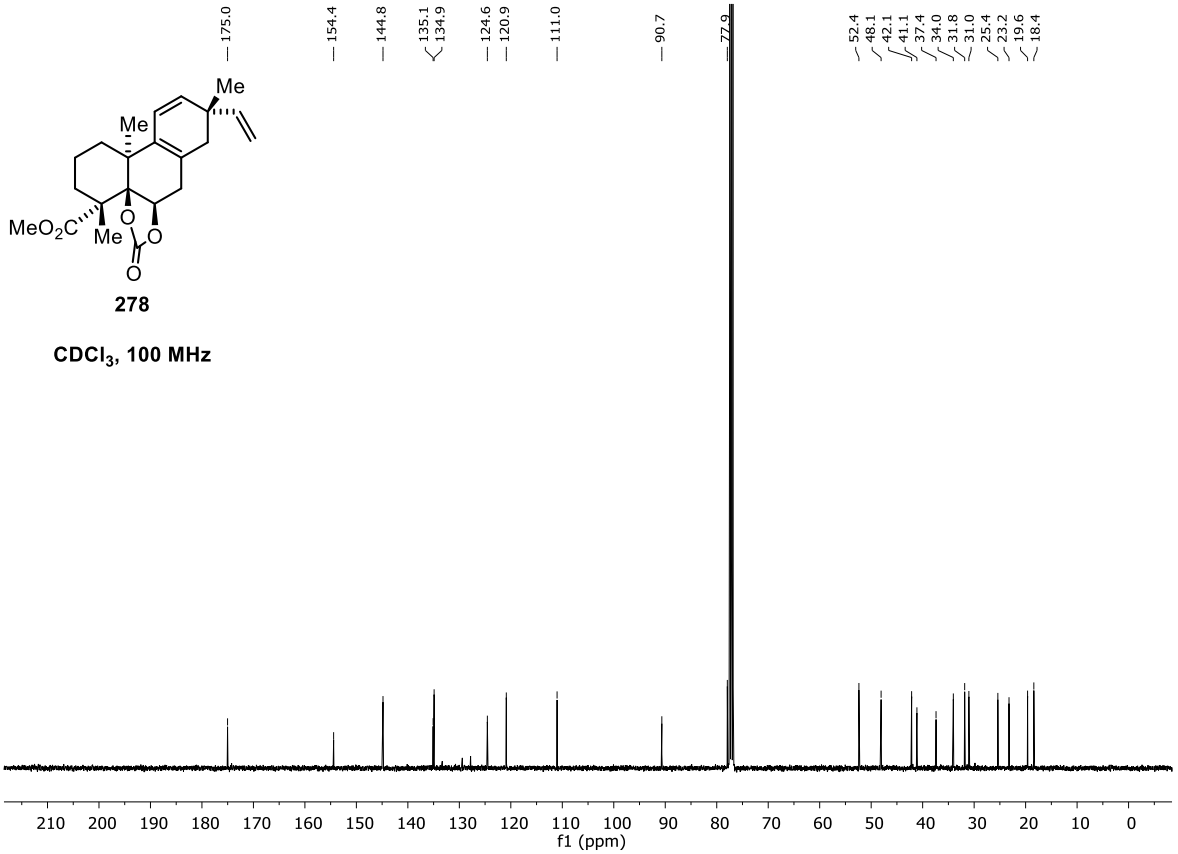
S23

$CDCl_3$, 100 MHz



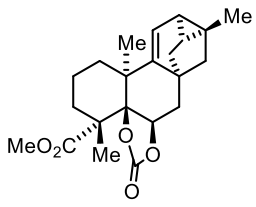
278

$CDCl_3$, 400 MHz



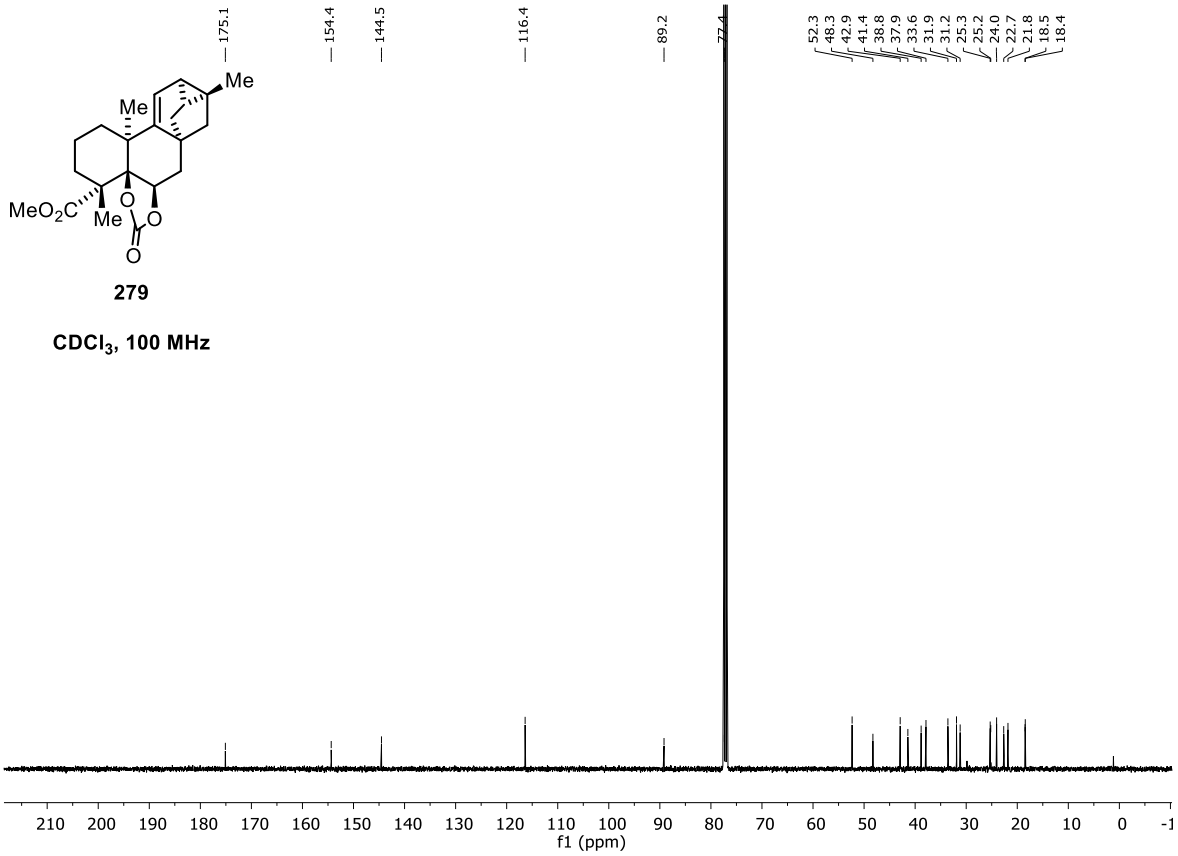
278

$CDCl_3$, 100 MHz



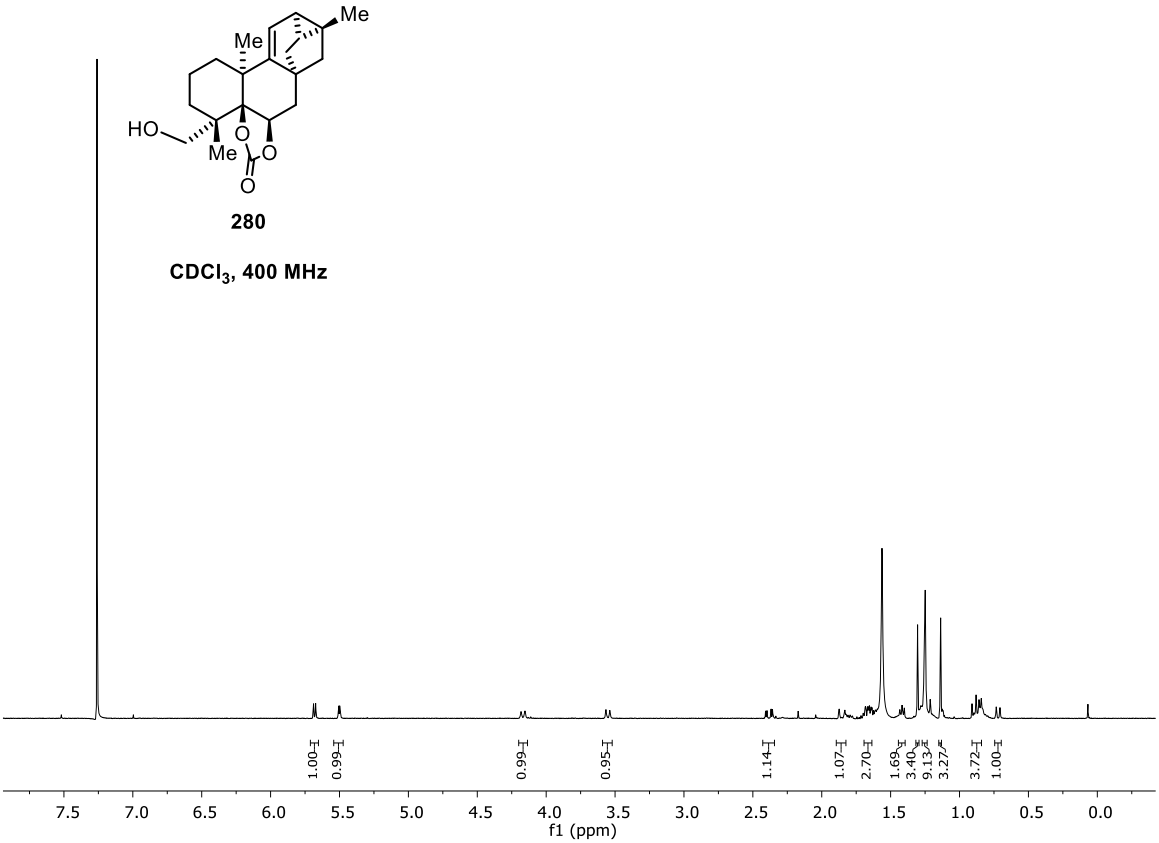
279

$CDCl_3$, 400 MHz



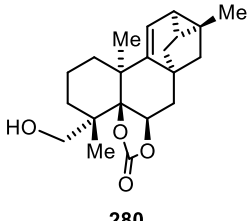
279

$CDCl_3$, 100 MHz

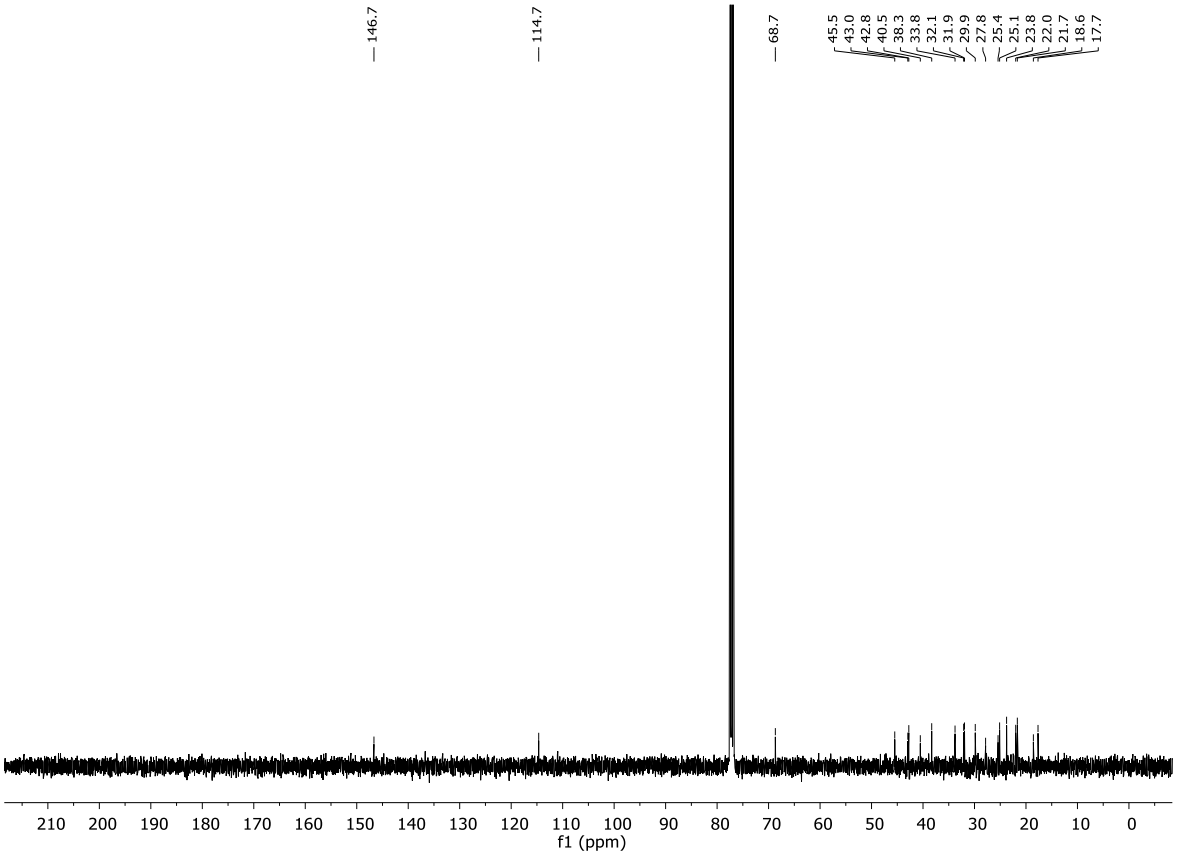


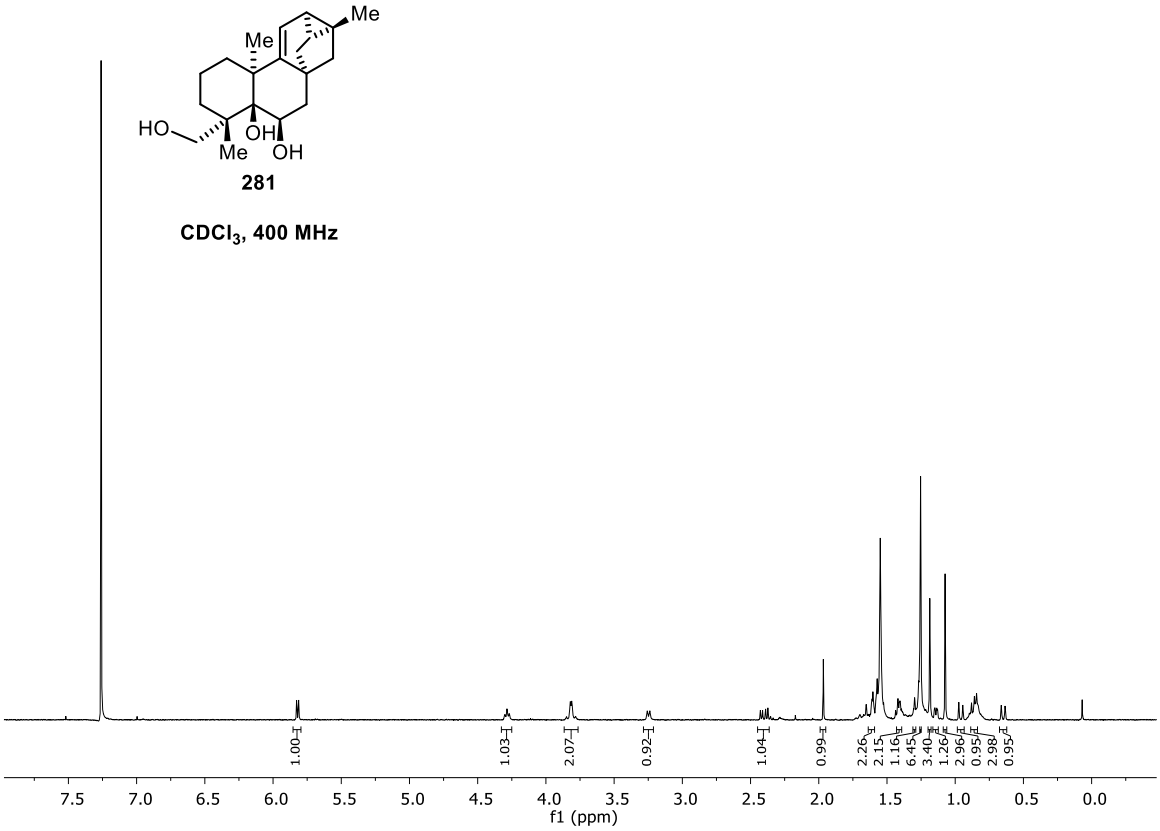
280

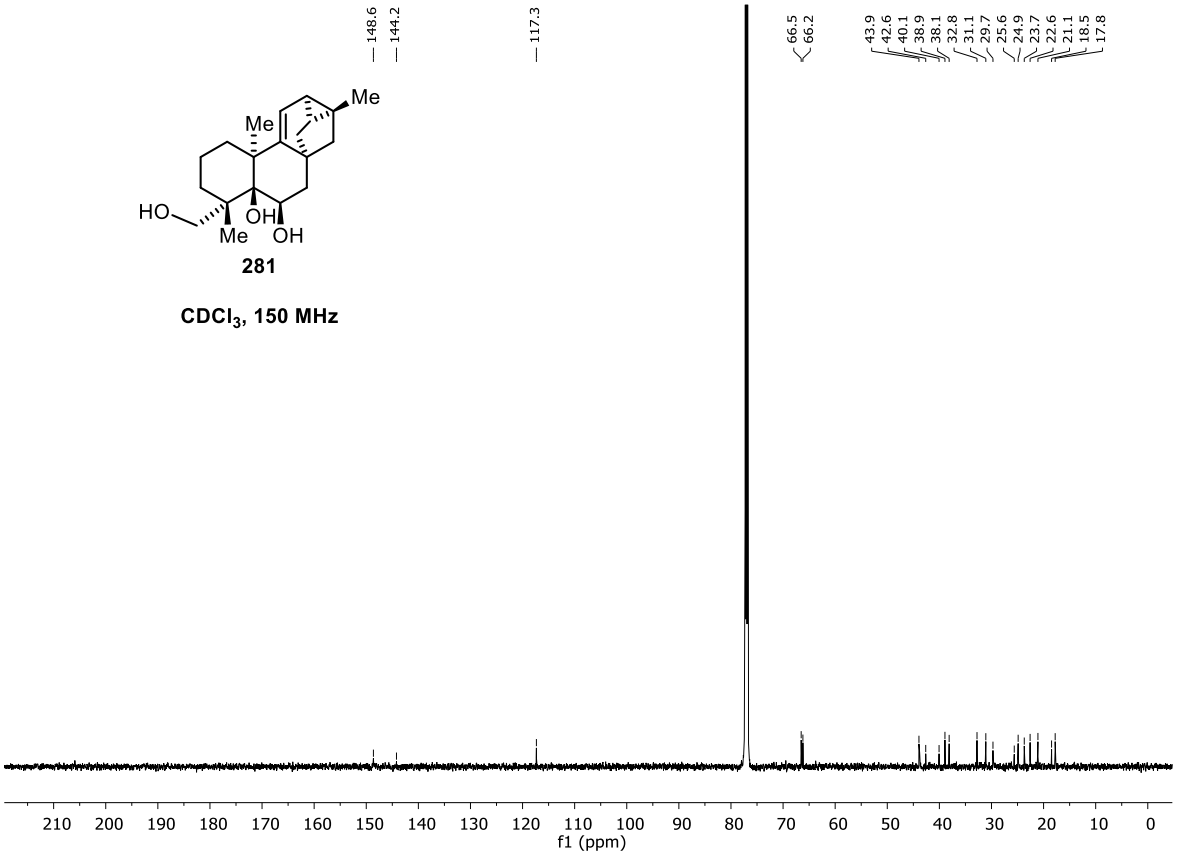
$CDCl_3$, 400 MHz



280


146.7
114.7
68.7
45.5
43.0
42.8
40.5
38.3
33.8
32.1
31.9
29.9
27.8
25.4
25.1
23.8
22.0
21.7
18.6
17.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
HO
OH
Me
OH
281
CDCl3, 400 MHz
1.00
1.03
2.07
0.92
1.04
0.99
2.26
2.15
1.16
6.45
3.40
1.26
2.96
0.95
2.98
0.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


148.6
144.2
117.3
66.5
66.2
43.9
42.6
40.1
38.9
38.1
32.8
31.1
29.7
25.6
24.9
23.7
22.6
21.1
18.5
17.8
Me
Me
HO
OH
Me
OH
281
CDCl3, 150 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5.4 Single Crystal X-ray Analysis

Alkyne *ent*-134.

Table 22 Crystallographic data for alkyne ***ent*-134**.

net formula	$C_{11}H_{12}O$
M_r/g mol^{-1}	160.21
crystal size/mm	0.100 × 0.090 × 0.050
T/K	100.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
a/Å	6.4826(2)
b/Å	21.1847(7)
c/Å	6.8691(2)
α/°	90
β/°	108.6300(10)
γ/°	90
V/Å^3	893.92(5)
Z	4
calc. density/g cm^{-3}	1.190
μ/mm^{-1}	0.074
absorption correction	Multi-Scan
transmission factor range	0.8924–0.9705
refls. measured	7806
R_{int}	0.0314
mean σ(I)/I	0.0456
θ range	3.274–26.372
observed refls.	3276
x, y (weighting scheme)	0.0477, 0.3148
hydrogen refinement	constr
refls in refinement	−0.3(7)
parameters	3466

restraints	219
$R(F_{obs})$	1
$R_w(F^2)$	0.0415
S	0.1090
$shift/error_{max}$	1.081
max electron density/e Å^{-3}	0.001
min electron density/e Å^{-3}	0.246

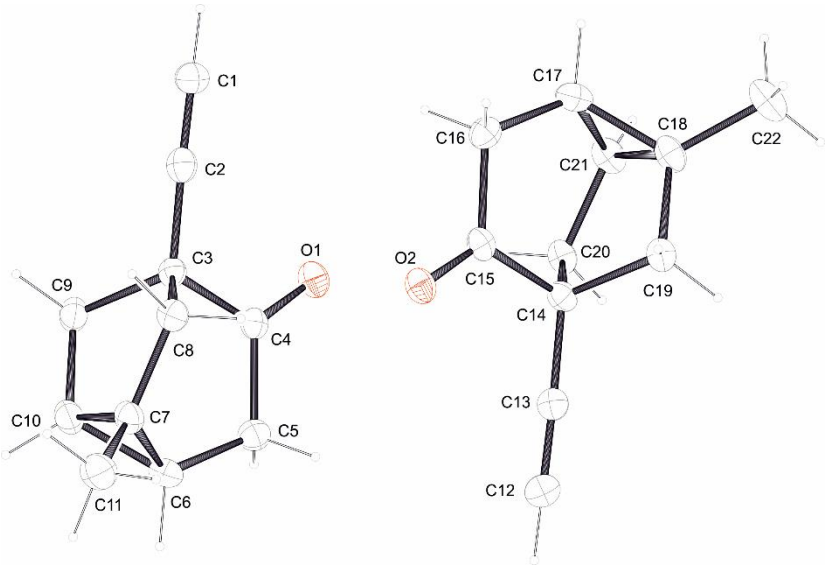


Figure 12 Molecular structure of alkyne ***ent*-134**. Ellipsoids are drawn at 50% probability level.

Diol 266.

Table 23 Crystallographic data for diol **266**.

Empirical formula	$C_{14}H_{22}O_5$
Formula weight	270.31
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$ (no. 14)
Unit cell dimensions	a = 12.8786(5) Å
	b = 6.9825(3) Å
	c = 15.1052(6) Å
Volume	1316.55(9) $Å^3$
Z	4
Density (calculated)	1.364 Mg/m^3
Absorption coefficient	0.102 mm^{-1}
F(000)	584
Crystal size	0.180 x 0.160 x 0.080 mm^3
Theta range for data collection	2.783 to 25.250°.
Index ranges	–15<=h<=14, -8<=k<=8, -18<=l<=18
Reflections collected	17524
Independent reflections	2388 [R(int) = 0.0282]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.971 and 0.957
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2388 / 2 / 182
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0923
R indices (all data)	R1 = 0.0405, wR2 = 0.0957
Extinction coefficient	0.022(2)
Largest diff. peak and hole	0.335 and -0.275 $e.Å^{-3}$
Empirical formula	C14 H22 O5

Formula weight	270.31
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$ (no. 14)
Unit cell dimensions	a = 12.8786(5) Å

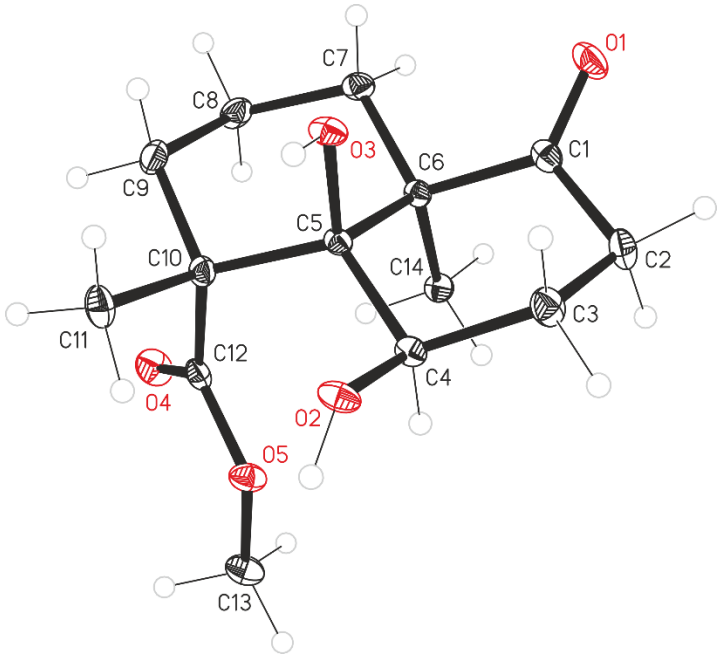


Figure 13 Molecular structure of diol **266**. Ellipsoids are drawn at 50% probability level.

Reference

[1] F. Wöhler, *Ann. der Phys. und Chemie* **1828**, *88*, 253–256.

[2] C. A. Kuttruff, M. D. Eastgate, P. S. Baran, *Nat. Prod. Rep.* **2014**, *31*, 419–432.

[3] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629–661.

[4] A. A. L. Gunatilaka, F. D. Ramdayal, M. H. Sarragiotto, D. G. I. Kingston, D. L. Sackett, E. Hamel, *J. Org. Chem.* **1999**, *64*, 2694–2703.

[5] T. C. Boge, M. Hepperle, D. G. Vander Velde, C. W. Gunn, G. L. Grunewald, G. I. Georg, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3041–3046.

[6] J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chemie Int. Ed.* **2010**, *49*, 9052–9067.

[7] K. Watanabe, K. Umeda, M. Miyakado, *Agric. Biol. Chem.* **1989**, *53*, 2513–2515.

[8] J. Seki, N. Shimada, K. Takahashi, T. Takita, T. Takeuchi, H. Hoshino, *Antimicrob. Agents Chemother.* **1989**, *33*, 773–775.

[9] Q. Han, J. Zhang, Y. Lu, Y. Wu, Q. Zheng, H. Sun, *Planta Med.* **2004**, *70*, 581–584.

[10] J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, *Chem. Rev.* **2016**, *116*, 12150–12233.

[11] G. Hugl, L. Lods, J. Mellor, D. Theobald, G. Ourisson, *Bull. Soc. Chim. Fr.* **1965**, 2888–2894.

[12] F. Dal Piaz, A. Bader, N. Malafronte, M. D'Ambola, A. M. Petrone, A. Porta, T. Ben Hadda, N. De Tommasi, A. Bisio, L. Severino, *Phytochemistry* **2018**, *155*, 191–202.

[13] P. M. Giles, *Pure Appl. Chem.* **1999**, *71*, 587–643.

[14] R. J. Peters, *Nat. Prod. Rep.* **2010**, *27*, 1521.

[15] S. Mafu, M. Jia, J. Zi, D. Morrone, Y. Wu, M. Xu, M. L. Hillwig, R. J. Peters, *Proc. Natl. Acad. Sci.* **2016**, *113*, 2526–2531.

[16] A. Roy, F. G. Roberts, P. R. Wilderman, K. Zhou, R. J. Peters, R. M. Coates, *J. Am. Chem. Soc.* **2007**, *129*, 12453–12460.

[17] R. M. Coates, P. L. Cavender, *J. Am. Chem. Soc.* **1980**, *102*, 6358–6359.

[18] K. A. Drengler, R. M. Coates, *J. Chem. Soc. Chem. Commun.* **1980**, 856.

[19] R. M. Coates, S. C. Koch, S. Hegde, *J. Am. Chem. Soc.* **1986**, *108*, 2762–2764.

[20] M. Xu, P. R. Wilderman, R. J. Peters, *Proc. Natl. Acad. Sci.* **2007**, *104*, 7397–7401.

[21] R. M. Coates, H.-Y. Kang, *J. Chem. Soc. Chem. Commun.* **1987**, 232.

[22] Y. J. Hong, D. J. Tantillo, *J. Am. Chem. Soc.* **2010**, *132*, 5375–5386.

[23] R. Rajamani, J. Gao, *J. Am. Chem. Soc.* **2003**, *125*, 12768–12781.

[24] B. A. Hess, *J. Am. Chem. Soc.* **2002**, *124*, 10286–10287.

[25] S. M. Ng, C. M. Beaudry, D. Trauner, **2003**, 10–13.

[26] T. Ose, K. Watanabe, T. Mie, M. Honma, H. Watanabe, M. Yao, H. Oikawa, I. Tanaka, *Nature* **2003**, *422*, 185–189.

[27] H. Oikawa, K. Katayama, Y. Suzuki, A. Ichihara, *J. Chem. Soc., Chem. Commun.* **1995**, 1321–1322.

[28] W. Herz, R. N. Mirrington, H. Young, *Tetrahedron Lett.* **1968**, *9*, 405–407.

[29] W. Herz, R. N. Mirrington, H. Young, Y. Yeng Lin, *J. Org. Chem.* **1968**, *33*, 4210–4219.

[30] R. B. Kelly, J. Eber, H. K. Hung, *Can. J. Chem.* **1973**, *51*, 2534–2541.

[31] R. F. Church, R. E. Ireland, J. A. Marshall, *J. Org. Chem.* **1966**, *31*, 2526–2530.

[32] R. Pappo, D. S. Allen, Jr., R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478–479.

[33] T. S. Osdene, G. M. Timmis, M. H. Maguire, G. Shaw, H. Goldwhite, B. C. Saunders, E. R. Clark, P. F. Epstein, M. Lamchen, A. M. Stephen, et al., *J. Chem. Soc.* **1955**, 2038.

[34] R. M. Cory, D. M. T. Chan, Y. M. A. Naguib, M. H. Rastall, R. M. Renneboog, *J. Org. Chem.* **1980**, *45*, 1852–1863.

[35] R. C. Cambie, K. N. Joblin, N. K. McCallum, *Aust. J. Chem.* **1995**, *9*, 1943–1455.

[36] E. Wenkert, *Chem. Ind.* **1955**, 282–284.

[37] M. Toyota, T. Wada, K. Fukumoto, M. Ihara, *J. Am. Chem. Soc.* **1998**, *120*, 4916–4925.

[38] M. Toyota, T. Wada, Y. Nishikawa, K. Yanai, K. Fukumoto, *Synlett* **1994**, *1994*, 597–598.

[39] A. Abad, C. Agulló, A. C. Cuñat, I. de Alfonso Marzal, I. Navarro, A. Gris, *Tetrahedron*

2006, *62*, 3266–3283.

[40] M. J. R. Richter, M. Schneider, M. Brandstätter, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2018**, jacs.8b09685.

[41] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146–146.

[42] A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5846.

[43] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1983**, *24*, 5425–5428.

[44] A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chemie Int. Ed.* **2006**, *45*, 497–500.

[45] W. Nagata, M. Yoshioka, S. Hirai, *J. Am. Chem. Soc.* **1972**, *94*, 4635–4643.

[46] T. Ghaffar, A. W. Parkins, *Tetrahedron Lett.* **1995**, *36*, 8657–8660.

[47] H. L. Riley, J. F. Morley, N. A. C. Friend, *J. Chem. Soc.* **1932**, 1875.

[48] J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 6676–6677.

[49] T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020–5023.

[50] T. Nemoto, Z. Zhao, T. Yokosaka, Y. Suzuki, R. Wu, Y. Hamada, *Angew. Chemie Int. Ed.* **2013**, *52*, 2217–2220.

[51] M. Yoshida, T. Nozaki, T. Nemoto, Y. Hamada, *Tetrahedron* **2013**, *69*, 9609–9615.

[52] T. Nemoto, R. Wu, Z. Zhao, T. Yokosaka, Y. Hamada, *Tetrahedron* **2013**, *69*, 3403–3409.

[53] Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye, S.-L. You, *Angew. Chemie Int. Ed.* **2011**, *50*, 4455–4458.

[54] Q. Xiao, J. J. Jackson, A. Basak, J. M. Bowler, B. G. Miller, A. Zakarian, *Nat. Chem.* **2013**, *5*, 410.

[55] S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 9282–9285.

[56] R.-Q. Xu, Q. Gu, W.-T. Wu, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2014**, *136*, 15469–15472.

[57] K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang, W. Tang, *Angew. Chemie - Int. Ed.* **2015**, *54*,

3033–3037.

[58] I. Yamamura, Y. Fujiwara, T. Yamato, O. Irie, K. Shishido, *Tetrahedron Lett.* **1997**, *38*, 4121–4124.

[59] G. Zhao, G. Xu, C. Qian, W. Tang, *J. Am. Chem. Soc.* **2017**, *139*, 3360–3363.

[60] C. Li, D. Lee, T. N. Graf, S. S. Phifer, Y. Nakanishi, J. P. Burgess, S. Riswan, F. M. Setyowati, A. M. Saribi, D. D. Soejarto, et al., *Org. Lett.* **2005**, *7*, 5709–5712.

[61] S. Zheng, Y. R. Santosh Laxmi, E. David, A. T. Dinkova-Kostova, K. H. Shiavoni, Y. Ren, Y. Zheng, I. Trevino, R. Bumeister, I. Ojima, et al., *J. Med. Chem.* **2012**, *55*, 4837–4846.

[62] W. Ren, Y. Xia, S.-J. Ji, Y. Zhang, X. Wan, J. Zhao, *Org. Lett.* **2009**, *11*, 1841–1844.

[63] W. Tang, B. Qu, A. G. Capacci, S. Rodriguez, X. Wei, N. Haddad, B. Narayanan, S. Ma, N. Grinberg, N. K. Yee, et al., *Org. Lett.* **2010**, *12*, 176–179.

[64] S. a Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **1997**, *119*, 7165–7166.

[65] T. J. Senter, M. C. O'Reilly, K. M. Chong, G. A. Sulikowski, C. W. Lindsley, *Tetrahedron Lett.* **2015**, *56*, 1276–1279.

[66] A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5846–5850.

[67] T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451–2458.

[68] H. Chu, J. M. Smith, J. Felding, P. S. Baran, *ACS Cent. Sci.* **2017**, *3*, 47–51.

[69] Z. Lu, H. Li, M. Bian, A. Li, *J. Am. Chem. Soc.* **2015**, *137*, 13764–13767.

[70] J. Li, W. Zhang, F. Zhang, Y. Chen, A. Li, *J. Am. Chem. Soc.* **2017**, *139*, 14893–14896.

[71] E. M. Simmons, J. F. Hartwig, *Nature* **2012**, *483*, 70–73.

[72] R. Tapia, H. Bouanou, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun, E. Alvarez-Manzaneda, *J. Org. Chem.* **2014**, *79*, 4405–4413.

[73] H. Zhu, P. Tu, *Synth. Commun.* **2005**, *35*, 71–78.

[74] M. Ohba, N. Kawase, T. Fujii, K. Aoe, K. Okamura, R. Fathi-Afshar, T. M. Allen, *Tetrahedron Lett.* **1995**, *36*, 6101–6104.

[75] N. Kornblum, H. E. DeLaMare, *J. Am. Chem. Soc.* **1951**, *73*, 880–881.

[76] P. S. Fier, K. M. Maloney, *Org. Lett.* **2016**, *18*, 2244–2247.

[77] G. Shan, X. Yang, L. Ma, Y. Rao, *Angew. Chemie Int. Ed.* **2012**, *51*, 13070–13074.

[78] H. Greenfield, H. W. Sternberg, R. A. Friedel, J. H. Wotiz, R. Markby, I. Wender, *J. Am. Chem. Soc.* **1956**, *78*, 120–124.

[79] K. Speck, T. Magauer, *Chem. - A Eur. J.* **2017**, *23*, 1157–1165.

[80] J. Deschamp, T. Hermant, O. Riant, *Tetrahedron* **2012**, *68*, 3457–3467.

[81] D. Xu, M. A. Drahl, L. J. Williams, *Beilstein J. Org. Chem.* **2011**, *7*, 937–943.

[82] J. Yu, B. Yu, *Chinese Chem. Lett.* **2015**, *26*, 1331–1335.

[83] F. Gallier, A. Martel, G. Dujardin, *Angew. Chemie - Int. Ed.* **2017**, *56*, 12424–12458.

[84] T. Ohgi, T. Kondo, T. Goto, *Tetrahedron Lett.* **1977**, *18*, 4051–4054.

[85] A. Klemer, H. Stegt, *J. Carbohydr. Chem.* **1985**, *4*, 205–213.

[86] M. L. Lewbart, J. J. Schneider, *J. Org. Chem.* **1969**, *34*, 3505–3512.

[87] G. A. Morrison, J. B. Wilkinson, *J. Chem. Soc. Perkin Trans. 1* **1990**, 345.

[88] T. J. Tewson, M. J. Welch, *J. Org. Chem.* **1978**, *43*, 1090–1092.

[89] J. Zhu, D. Ma, *Angew. Chemie Int. Ed.* **2003**, *42*, 5348–5351.

[90] A. Ichihara, M. Ubukata, S. Sakamura, *Tetrahedron Lett.* **1977**, *18*, 3473–3476.

[91] R. Wakharkar, M. Sahasrabuddhe, H. Borate, M. Gurjar, *Synthesis (Stuttg).* **2004**, *2004*, 1830–1834.

[92] W. A. Szarek, A. Zamojski, K. N. Tiwari, E. R. Ison, *Tetrahedron Lett.* **1986**, *27*, 3827–3830.

[93] G. G. Haraldsson, T. Stefansson, H. Snorrason, W. Chen, Á. G. Kristjánsdóttir, O. Matsson, K. V. Mikkelsen, A. Senning, *Acta Chem. Scand.* **1998**, *52*, 824–826.

[94] M. Yamashita, N. Ohta, T. Shimizu, K. Matsumoto, Y. Matsuura, I. Kawasaki, T. Tanaka, N. Maezaki, S. Ohta, *J. Org. Chem.* **2003**, *68*, 1216–1224.

[95] W. G. Overend, M. Stacey, L. F. Wiggins, *J. Chem. Soc.* **1949**, 1358.

[96] S. Miyamoto, T. Doi, T. Takahashi, *Synlett* **2002**, *2002*, 0097–0099.

[97] S. Manabe, C. Nishino, *Tetrahedron* **1986**, *42*, 3461–3470.

[98] R. D. Evans, J. W. Magee, J. H. Schauble, *Synthesis (Stuttg).* **1988**, *1988*, 862–868.

[99] C. L. Hugelshofer, T. Magauer, *J. Am. Chem. Soc.* **2016**, *138*, 6420–6423.

[100] G. Alvernhe, D. Anker, A. Laurent, G. Haufe, C. Beguin, *Tetrahedron* **1988**, *44*, 3551–3563.

[101] B. Hong, H. Li, J. Wu, J. Zhang, X. Lei, *Angew. Chemie Int. Ed.* **2015**, *54*, 1011–1015.

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

[103] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879–1880.

[104] *Org. Synth.* **1983**, *61*, 147.

[105] H. Du, D. Zhao, K. Ding, *Chem. - A Eur. J.* **2004**, *10*, 5964–5970.

[106] S. A. Kozmin, S. He, V. H. Rawal, in *Org. Synth.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2003**, pp. 152–152.

[107] G. Li, X. Wang, Y. Zhang, Z. Tan, P. DeCroos, J. C. Lorenz, X. Wei, N. Grinberg, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2017**, *82*, 5456–5460.