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Total Synthesis of (±)-Indoxamycins A and B

and

(+)-Asperolide C

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presented by

Oliver Fabian Jeker

MSc ETH Chemistry

born December 1, 1982

Citizen of Olten, SO and Büsserach, SO

Accepted on the recommendation of

Prof. Dr. Erick M. Carreira, examiner

Prof. Dr. Karl-Heinz Altmann, co-examiner

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Publications

O. F. Jeker, E. M. Carreira

Total Synthesis and Stereochemical Reassignment of (±)-Indoxamycin B

Angewandte Chemie International Edition **2012**, *51*, 3474–3477.

O. F. Jeker, A. G. Kravina, E. M. Carreira

Total Synthesis of (+)-Asperolide C by Iridium-Catalyzed Enantioselective Polyene Cyclization

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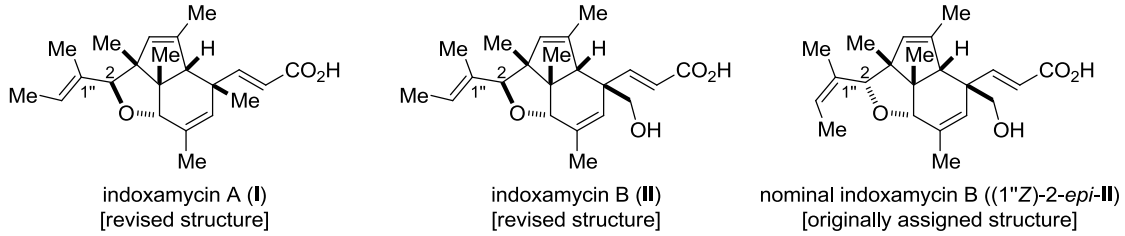
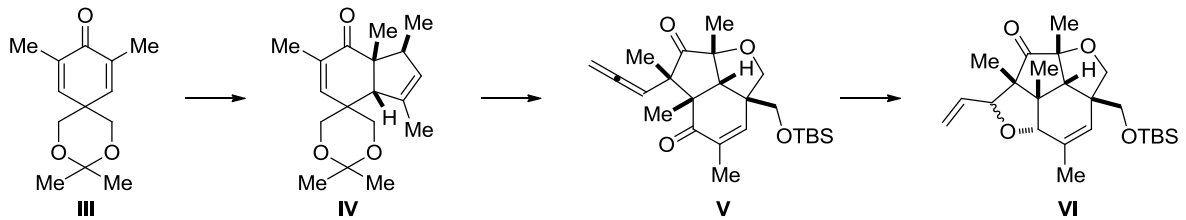
Abstract

The indoxamycins represent a novel class of polypropionates that were isolated from saline cultures of marine-derived actinomycetes (Scheme I). The tricyclic structure common to these natural products is distinguished by a pentamethylindenyl core with six contiguous stereogenic centers, an enoate side chain and an isobutenyl appendage. Their unique molecular architecture renders the indoxamycins notable targets for synthetic studies. The first chapter of this doctoral thesis describes the development of a divergent route to indoxamycins A (**I**) and B (**II**), which not only culminated in the first total synthesis of this unprecedented structural class, but also led to the stereochemical reassignment of these compounds (e.g. (1’’*Z*)-2-*epi*-**II** to **II**).



Scheme I: Revised structures of indoxamycins A (**I**) and B (**II**). Originally assigned structure of indoxamycin B ((1’’*Z*)-2-*epi*-**II**).

The successful synthesis of both target compounds relied on C_{2v}-symmetric cyclohexa-2,5-dienone precursor **III**, which was advanced to key dihydroindenone **IV** *via* a carboannulation sequence involving ketone crotylation, oxy-COPE rearrangement and Pd-catalyzed oxidative cycloalkenylation (Scheme II). Further elaboration to diketone **V** proceeded through Au(I)-catalyzed SAUCY–MARBET (propargyl CLAISEN) rearrangement to diastereoselectively install the vicinal quaternary centers. The formation of the tetrahydrofuran ring in **VI** was achieved by a second Au(I)-catalyzed transformation, namely an intramolecular allene hydroalkoxylation.

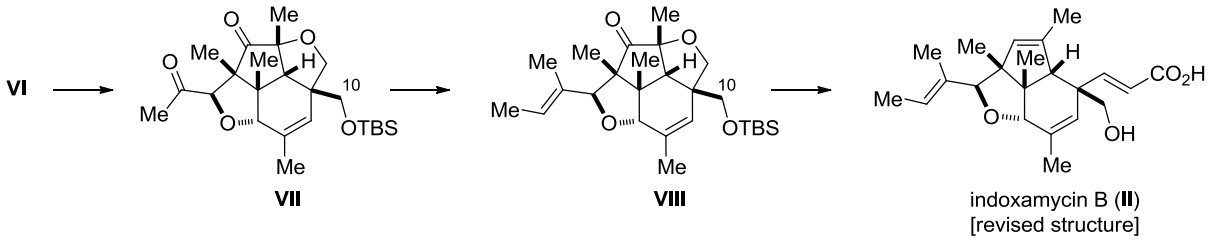


Scheme II: Synthesis of tetracyclic intermediate **VI**.

Tetracyclic intermediate **VI** was advanced to nominal indoxamycin B ((1’’*Z*)-2-*epi*-**II**). Surprisingly, the material obtained displayed spectral properties that did not match those

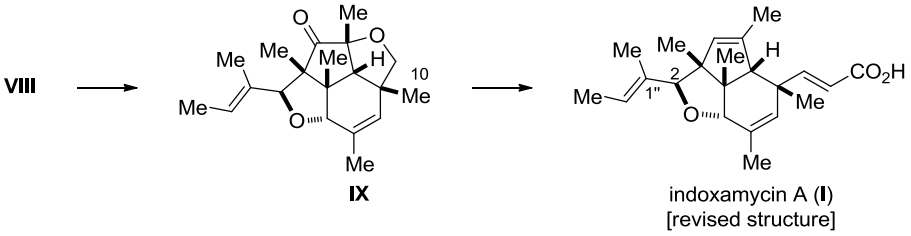
previously reported. Careful re-examination of published NMR data for several members of the indoxamycin family led to the conclusion that the relative configuration at C(2) had been misassigned by the isolation chemists. Furthermore, there was considerable ambiguity regarding the geometry of the trisubstituted olefin side chain. Comparison of ^{1}H NMR spectra for several synthetic intermediates with those of the natural products led to the hypothesis that indoxamycin B had the structure shown for **II** in Scheme I, which was subsequently targeted for synthesis.

Installation of the isobutenyl appendage proceeded from **VI** through methylketone **VII** to deliver intermediate **VIII**. Introduction of the enoate side chain and of the cyclopentene unsaturation completed the total synthesis of indoxamycin B (**II**) (Scheme III). The spectral data for **II** were all in excellent agreement with those reported for the natural product. This target molecule was obtained in 22 linear steps and 1.3% overall yield.



Scheme III: Elaboration of tetracyclic intermediate **VI** to indoxamycin B (**II**).

In order to gain access to indoxamycin A (**I**), the hydroxyl group at C(10) was removed by deprotection of **VIII** followed by radical deoxygenation (Scheme IV). Intermediate **IX** was successfully advanced to target molecule **I**. The synthesis described delivered indoxamycin A (**I**) in 24 linear steps and 0.8% overall yield.

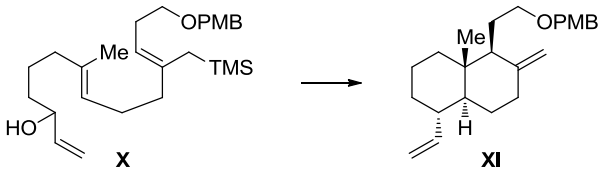


Scheme IV: Deoxygenation of intermediate **VIII** and completion of indoxamycin A.

Indoxamycins A (**I**) and B (**II**) were tested for cytotoxic activity in HT-29 and A-549 tumor cells. Surprisingly, the antiproliferative activity previously reported for natural indoxamycin A (**I**) in the HT-29 cell line could not be confirmed with the synthetic material.

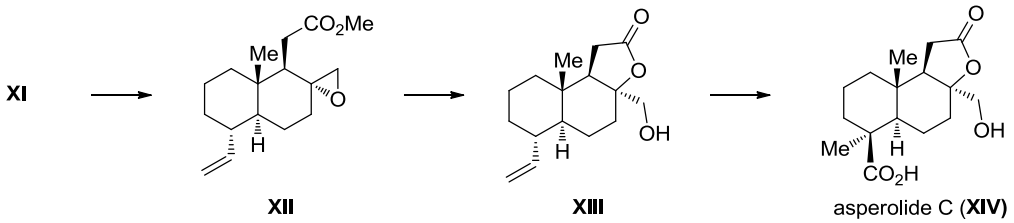
The second chapter of this thesis discusses a general synthetic entry into labdane-type diterpenoids, based on an iridium-catalyzed enantioselective polyene cyclization. The potential of this approach is showcased in the first total synthesis of the tetranorlabdane diterpene asperolide C (**XIV**).

In order to test the cascade reaction, a concise synthesis of the required polyunsaturated linear precursor **X** was devised. This intermediate underwent efficient polycyclization to deliver **XI** in optically pure form (Scheme V).



Scheme V: Polyene cyclization approach to labdane-type diterpenoids.

Decalin **XI** was further elaborated into epoxyester **XII**, which was subjected to acid-mediated oxirane opening to furnish γ-lactone **XIII** (Scheme VI). The assembly of asperolide C (**XIV**) was completed in a sequence of steps involving oxidative cleavage of the vinyl group and alkylation of an aldehyde enolate.

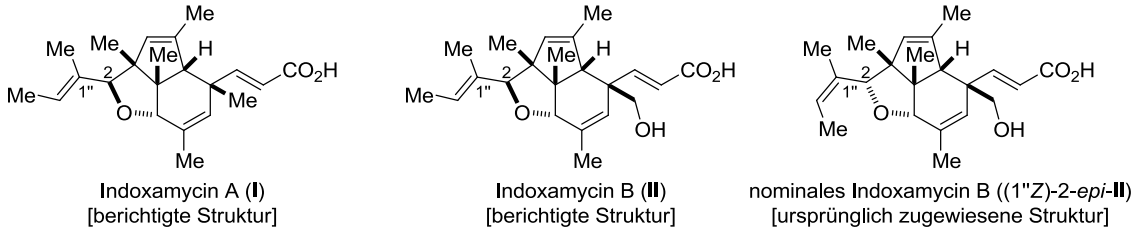


Scheme VI: Completion of asperolide C (**XIV**).

The first total synthesis of asperolide C (**XVII**) was achieved in 20 linear steps and 0.3% overall yield. It is one of the rare examples for the application of an enantioselective polyene cyclization in natural product synthesis. The synthetic strategy employed bears significant potential for the preparation of further target molecules.

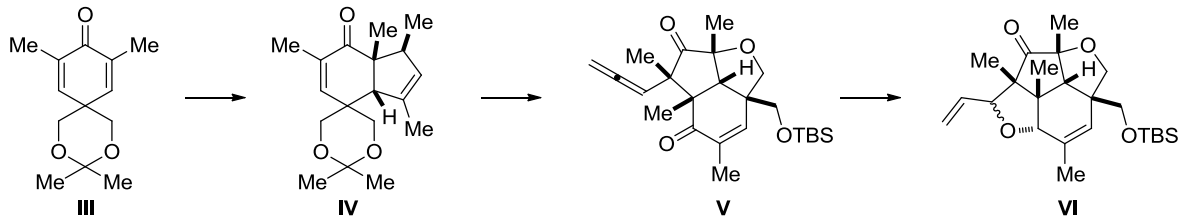
Zusammenfassung

Die Indoxamycine repräsentieren eine neuartige Klasse von Polypropionaten, die aus Salzwasserkulturen eines marinen Actinomyceten isoliert wurden (Schema I). Die tricyclische Struktur, die diesen Naturstoffen gemein ist, zeichnet sich durch einen Pentamethylindenyl-Kern mit sechs benachbarten Stereozentren, sowie einer Enoat-Seitenkette und einem Isobutenylrest aus. Ihre einzigartige molekulare Architektur macht die Indoxamycine zu interessanten Zielmolekülen für Synthesestudien. Das erste Kapitel dieser Dissertation beschreibt die Entwicklung einer divergenten Syntheseroute zu Indoxamycin A (**I**) und B (**II**). Neben der ersten Totalsynthese dieser neuartigen Strukturklasse führte diese Arbeit auch zur stereochemischen Strukturberichtigung der Zielverbindungen (z.B. (1’’*Z*)-2-*epi*-**II** zu **II**).



Schema I: Berichtigte Strukturen von Indoxamycin A (**I**) and B (**II**). Ursprünglich vorgeschlagene Struktur von Indoxamycin B ((1’’*Z*)-2-*epi*-**II**).

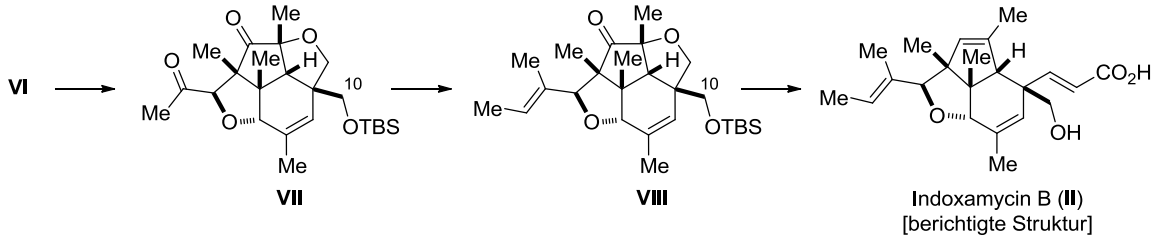
Die erfolgreiche Synthese beider Verbindungen basiert auf dem C_{2v}-symmetrischen Cyclohexa-2,5-dienon Vorläufer **III**, der durch eine Carboannelierungssequenz, bestehend aus Ketoncrotylierung, oxy-COPE Umlagerung und Pd-katalysierter oxidativer Cycloalkenylierung in Dihydroindenon **IV** umgewandelt wurde (Schema II). Der Ausbau zu Diketon **V** verlief über eine Au(I)-katalysierte SAUCY–MARBET (propargylische CLAISEN) Umlagerung, die zur diastereoselektiven Installation der vicinalen quartären Kohlenstoffzentren diente. Die Bildung des Tetrahydrofuran-Rings in **VI** wurde durch eine weitere Au(I)-katalysierte Transformation, nämlich durch die intramolekulare Hydroalkoxylierung eines Allens, erreicht.



Schema II: Synthese des tetracyclischen Zwischenproduktes **VI**.

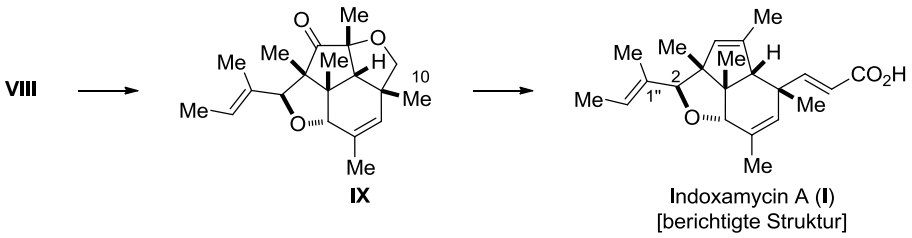
Intermediat **VI** wurde weiter zu nominalem Indoxamycin B ((1’’*Z*)-2-*epi*-**II**) umgesetzt. Überraschenderweise zeigte das erhaltene Material spektroskopische Eigenschaften, die nicht mit den zuvor beschriebenen übereinstimmten. Eine sorgfältige Überprüfung der publizierten NMR Daten verschiedener Mitglieder der Indoxamycin Naturstoff-Familie führte zu dem Schluss, dass die relative Konfiguration an C(2) durch die Isolationschemiker falsch zugewiesen worden war. Desweiteren bestanden erhebliche Zweifel bezüglich der Geometrie der dreifachsubstituierten Olefin-Seitenkette. Ein Vergleich der ^{1}H NMR Spektren verschiedener Syntheseintermediate mit jenen der Naturstoffe führte schliesslich zur Hypothese, dass Indoxamycin B die Struktur **II** in Schema I hat, die daraufhin synthetisiert wurde.

Die Installation des Isobutenylrests ausgehend von **VI** verlief über Methylketon **VII** und führte über Intermediat **VIII**. Durch Einführung der Enoat-Seitenkette und der Cyclopenten-Doppelbindung wurde die Synthese von Indoxamycin B (**II**) abgeschlossen (Schema III). Die spektroskopischen Daten für **II** stimmten allesamt hervorragend mit jenen des Naturstoffs überein. Die Zielverbindung wurde in 22 linearen Stufen und 1.3% Gesamtausbeute erhalten.



Schema III: Elaboration des tetracyclischen Intermediates **VI** zu Indoxamycin B (**II**).

Um Zugang zu Indoxamycin A (**I**) zu erhalten, wurde die Hydroxylgruppe an C(10) durch Entschützung und radikalische Deoxygenierung von **VIII** entfernt (Schema IV). Intermediat **IX** wurde erfolgreich weiter zu Zielverbindung **I** umgesetzt. Die beschriebene Synthese lieferte Indoxamycin A (**I**) in 24 linearen Stufen und 0.8% Gesamtausbeute.

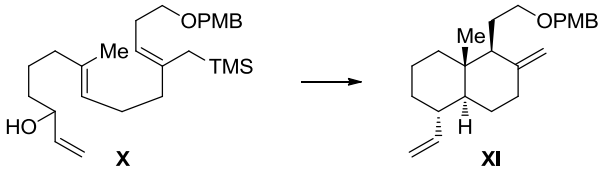


Schema IV: Deoxygenierung von Intermediat **VIII** und weitere Umsetzung zu Indoxamycin A.

Indoxamycin A (**I**) und B (**II**) wurden auf cytotoxische Aktivität in HT-29 und A-549 Tumorzellen getestet. Überraschenderweise konnte die antiproliferative Aktivität, die für natürliches Indoxamycin A in HT-29 Zellen beschrieben wurde, mit dem synthetischen Material nicht bestätigt werden.

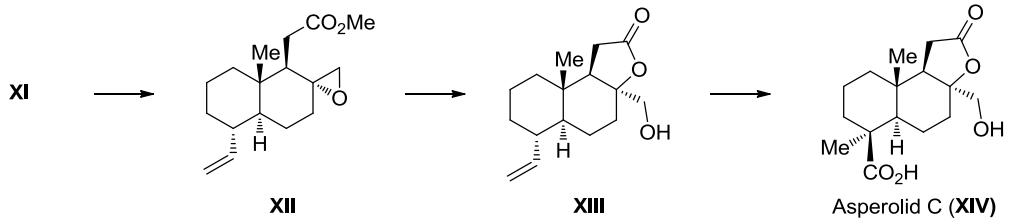
Das zweite Kapitel dieser Dissertation diskutiert einen allgemeinen synthetischen Zugang zu Labdan-artigen Diterpenoiden, beruhend auf einer Iridium-katalysierten enantioselektiven Polyencyclisierungskaskade. Das Potential dieses Ansatzes wird durch die erste Totalsynthese des Tetranorlabdan Diterpens Asperolid C (**XIV**) verdeutlicht.

Um die Kaskadenreaktion zu testen wurde eine Synthese für den mehrfach ungesättigten linearen Vorläufer **X** ausgearbeitet. Dieses Intermediat ging eine effiziente Polycyclisierung ein, bei der **XI** in optisch reiner Form anfiel (Schema V).



Schema V: Polyencyclisierungsansatz zu Labdan-artigen Diterpenoiden.

Decalin **XI** wurde weiter zu Epoxyester **XII** umgesetzt, der mittels einer säurevermittelten Oxiranöffnung in γ-Lakton **XIII** überführt wurde (Schema VI). Die Synthese von Asperolid C (**XVI**) wurde schliesslich durch eine Sequenz abgeschlossen, welche die oxidative Spaltung der Vinylgruppe und die Alkylierung eines Aldehyd-Enolats beinhaltete.



Schema VI: Vervollständigung von Asperolid C (**XIV**).

Die erste Totalsynthese von Asperolid C (**XIV**) wurde in 20 linearen Stufen und 0.3% Gesamtausbeute erzielt. Sie stellt eines der seltenen Beispiele für die erfolgreiche Anwendung einer katalytisch-enantioselektiven Polyencyclisierung in einer Naturstoffsynthese dar. Die verwendete Synthesestrategie hat beträchtliches Potential für die Darstellung weiterer Zielmoleküle.

List of Abbreviations Acronyms and Symbols

$[\alpha]_D^T$	specific rotation at temperature T at the sodium D line
Å	Ångström
Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
b.p.	boiling point
br	broad
brsm	based on recovered starting material
Bu	butyl
°C	degree centigrade
calcd	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
cm^{-1}	reciprocal centimeters
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
δ	NMR chemical shift in ppm downfield from a standard
d	day, doublet
DATMP	diethylaluminum 2,2,6,6-tetramethylpiperidine
DBU	diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminumhydride
DIPEA	diisopropylethylamine
DMAP	4-*N*,*N*'-dimethylamino pyridine
DMDO	dimethyldioxyrane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethyl formamide
DMP	DESS-MARTIN periodinane
DMSO	dimethylsulfoxide

dpm	2,2,6,6-tetramethyl-3, 5-heptanedionate
dppf	1,1’-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact ionization
ent	inversion of all stereogenic centers
epi	inversion of one stereogenic center
equiv	equivalent
e.r.	enantiomeric ratio
ESI	electron spray ionization
Et	ethyl
EtOAc	ethyl acetate
FT	FOURIER transformation
g	gram
h	hour
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IPNBSH	*N*-isopropylidene-*N*’-2-nitrobenzenesulfonyl hydrazine
IR	infrared
J	coupling constant
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
LDA	lithium diisopropyl amide
L-selectride	lithium tri-*sec*-butylborohydride
m	multiplet
m	*meta*
M	molecule ion, molar
MAD	methylaluminum bis(2,6-di-*tert*-butyl-4-alkylphenoxide)
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	megahertz

min	minute(s)
ml	milliliter
MOM	methoxymethyl
mp	melting point
µl	microliter
mmol	millimole
µm	micromole
mol%	mole per cent
Ms	methanesulfonyl
MS	molecular sieves, mass spectrometry
NBS	*N*-bromosuccinimide
NBSH	*o*-nitrobenzenesulfonylhydrazine
n.d.	not determined
NMR	nuclear magnetic resonance
nOe	nuclear OVERHAUSER enhancement
NOESY	nuclear OVERHAUSER effect spectroscopy
n.r.	no reaction
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pH	negative logarithm of hydrogen ion concentration
Ph	phenyl
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium 4-toluenesulfonate
Pr	propyl
q	quartet
quant.	quantitative
R_f	retention factor
RT	room temperature
s	singlet, second
satd.	saturated
Superhydride	lithium triethylborohydride

t	triplet
T	temperature, tesla
Tam	tamoxifen
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	4-methylphenylsulfonyl
UV	ultraviolet

1 Total Synthesis of Indoxamycins A & B

1.1 Introduction

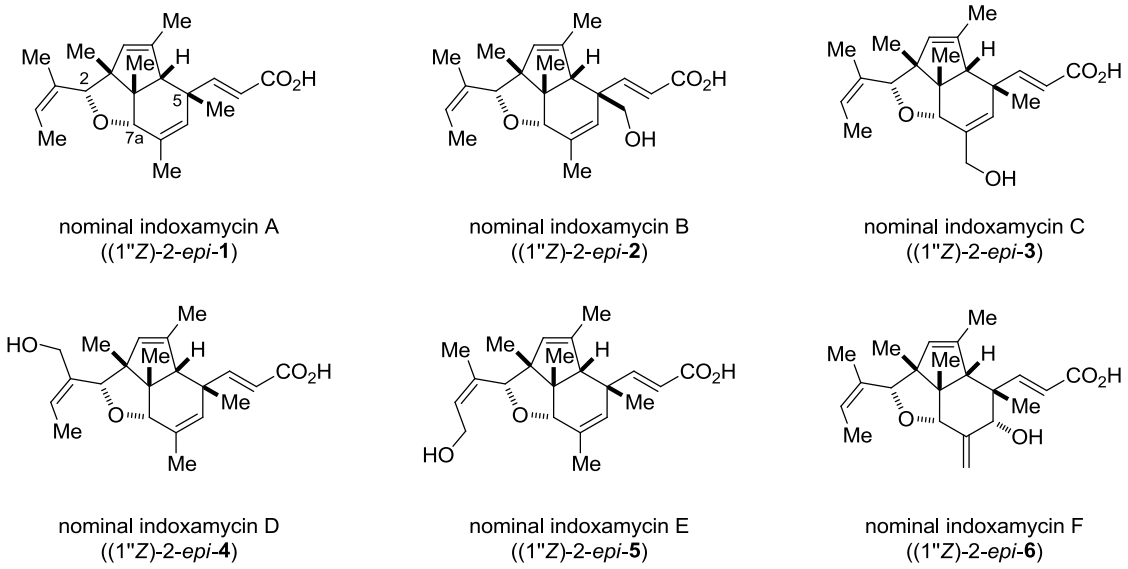
1.1.1 Marine Actinomycetes

The order *Actinomycetales* includes GRAM-positive microorganisms that have been a rich source of biologically active compounds, yielding more than 50% of all microbial antibiotics discovered to date [1]. Over the last five decades, most small-molecule discovery efforts focused on soil-derived actinomycetes. In contrast, microbes from marine sediments have only recently gained in importance as a source of structurally diverse natural products [2]. Given the fact that 70% of the Earth's surface is covered by the oceans, harboring most of the planet's biodiversity, this might be unexpected. However, sampling marine habitats often requires specialized equipment and less than 1% of the bacteria found in those environments form colonies on traditional agar nutrient media [3]. These factors are possible reasons why this resource has been largely unexplored for such a long period of time. In the 1950s the existence of marine bacteria has even been subject of debate [4]. Furthermore, until the 1990s it was surmised that the most important groups of drug-relevant microorganisms are not indigenous to the sea [5]. Nowadays, it is known that marine actinomycetes do exist [6-11] and the oceans are recognized as a highly complex microbiological ecosystem with typical microbial abundances of 10^6 per ml sea water and 10^9 per ml ocean sediment. Advanced biotechnological methods are now being applied to marine microbial ecology and although the field is in its infancy, scientists are at the beginning to appreciate the complex interplay between those highly adapted organisms [12].

1.1.2 Isolation of the Indoxamycins

In 2009 an industrial research group at NIPPON SUISAN KAISHA, Ltd. in Japan isolated multiple actinomycete strains from marine sediments and examined their 16S ribosomal DNA (rDNA) gene sequence homology against members of the *Streptomycetae* family [13, 14]. Actinomycete strain NPS-643 was obtained from a sediment sample collected at a depth of 30 m near Kochi Harbor (Japan) and required seawater for cultivation. Furthermore, this microbe was found to exhibit 96% 16S rDNA gene sequence identity with *Streptomyces cacaoi*, which was indicative of a new *Streptomyces* species [15]. The ethyl acetate extract of NPS-643

displayed *in vitro* cytotoxicity against the HT-29 human colon adenocarcinoma cell line. Activity-guided fractionation using various chromatographic techniques led to the isolation of six novel polyketides, subsequently named indoxamycins A−F (**1**−**6**, Scheme 1).



Scheme 1. Originally assigned structures of indoxamycins A−F (**1**−**6**).

The structural assignment of indoxamycin A (**1**) was based on extensive NMR studies (^{1}H, ^{13}C, HSQC, HMBC, 1D nOe, NOESY), which revealed the presence of eight olefinic carbons, of which five were methine groups. Furthermore, these experiments were suggestive of an additional three allylic methine groups, three quaternary centers, a carboxylate carbon and seven methyl groups. High-resolution mass spectrometry indicated a molecular formula of $C_{22}H_{30}O_3$ (HRMS (ESI-TOF): exact mass calculated for $C_{22}H_{31}O_3$ ($[M+H]^+$), 343.2275; found, 343.2270). Additional insight arose from the identification of a fragment ion peak at *m/z* = 325 ($[M+H-H_2O]^+$), which implicated the presence of a free hydroxyl group. This was corroborated by an IR absorption at 3423 cm^{-1}. Furthermore, an IR band at 1694 cm^{-1} was characteristic for a conjugated carbonyl functionality. The HMBC correlations suggested a pentamethylindenyl core structure with an ether bridge between C(2) and C(7a). In addition, the data indicated attachment of an isobutene group at C(2) and the presence of an enoate at C(5). The relative configuration of the indoxamycins was assigned by 1D nOe and NOESY experiments.

Indoxamycins B−F (**2**−**6**) had the molecular formula $C_{22}H_{30}O_4$, based on HRMS data. The NMR spectra of these compounds were found to be very similar to those of indoxamycin A (**1**). A comprehensive analysis of the spectral data revealed that the isomeric natural products differed from **1** by an additional hydroxyl group present at various positions on the carbogenic

scaffold. Indoxamycin F (**6**) was distinct as it showed a rearranged six-membered ring system with an exomethylene group and a secondary allylic alcohol.

1.1.3 Biosynthesis and Biological Activity

The biosynthetic origin of indoxamycin A (**1**) was probed through feeding experiments with the cultured broth of *Streptomyces* strain NPS-643. The use of sodium [1,2-^{13}C]-acetate and sodium [2-^{13}C]-acetate led to no incorporation of the label into the natural product. However, cultivation with sodium [1-^{13}C]-propionate resulted in isotopic enrichment at C(3), C(6), C(1'), C(2), C(4a) and C(7), as determined by ^{13}C NMR. These results showed that indoxamycin A (**1**) is composed of six propionate units (Figure 1). Interestingly, metabolites derived entirely from propionate are relatively rare in actinomycetes. Prominent examples are the erythromycins, macrolide antibiotics isolated from *Saccharopolyapora erythrea*, which are constructed from seven C_3 units [16, 17].

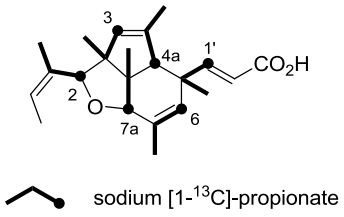


Figure 1. Sodium [1-^{13}C]-propionate labeling study with indoxamycin A (**1**).

Indoxamycins A−F (**1**−**6**) were tested for cytotoxic activity in the HT-29 tumor cell line. Indoxamycins A (**1**) and F (**6**) caused significant growth inhibition with IC_{50} values of 0.59 μM for **1** and 0.31 μM for **6**, respectively. On the other hand, indoxamycins B−E (**2**−**5**) did not exhibit any antiproliferative activity in this assay.

1.1.4 Conclusion

Their biological activity in conjunction with the highly congested and stereochemically dense structure renders the indoxamycins notable targets for total synthesis. At the commencement of this project, no synthetic studies towards any of these natural products had been reported in the literature. Consequently, the indoxamycins posed a stimulating synthetic challenge with significant scientific freedom, fueling potential innovation and discovery.

1.2 Synthetic Planning

1.2.1 General Considerations

Indoxamycin A (**1**) was originally chosen as the primary target for synthetic studies. The closely related indoxamycins B−F (**2**−**6**) were considered as additional target structures, as they presumably could be obtained at a later stage of the project through appropriate modification of advanced intermediates. The absence of any previous work towards the indoxamycins allowed for an unbiased analysis of the problem.

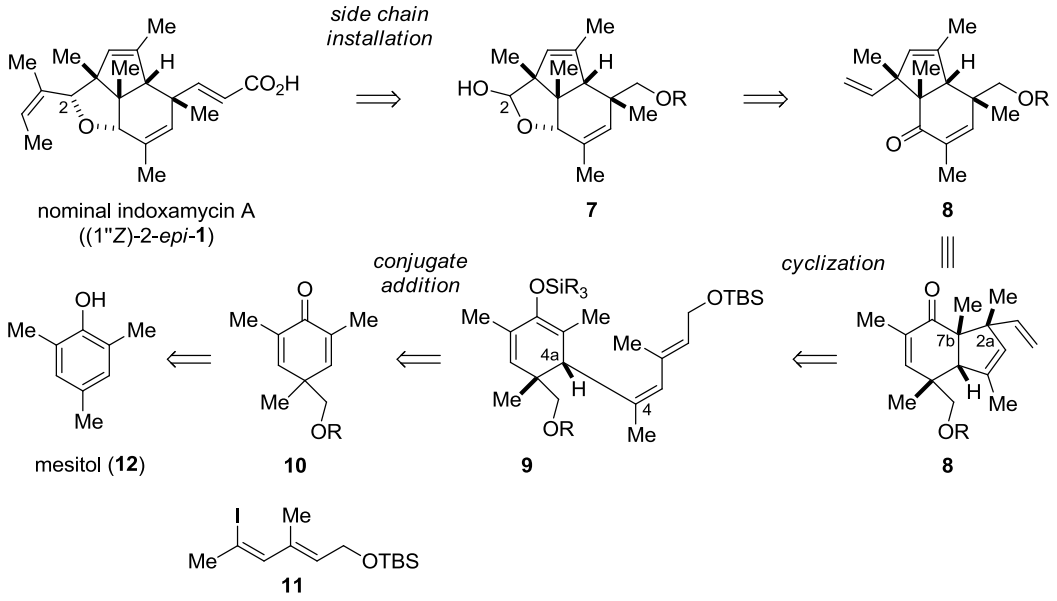
Among the analytical tools at disposal for synthetic planning, the retrosynthetic disconnection approach formalized by COREY *et al.* is widely regarded as the gold standard for complex molecule synthesis [18-22]. According to this technique, simpler precursors are deduced from target structures in an iterative manner until readily accessible building blocks are reached. The retrosynthetic analysis is usually guided by the concurrent use of several higher level strategies considering various aspects, such as possible key transformations, stereochemical implications, or potential starting materials [23]. Of particular importance for our retrosynthesis of the indoxamycins was the recognition of a symmetrical pattern in the target structure (*vide infra*).

The unique tricyclic skeleton common to the indoxamycin natural product family bears six contiguous asymmetric centers, an enoate side chain and an isobutene appendage. Three of the six stereogenic centers are quaternary, of which two are vicinal. At the outset, it seemed reasonable to focus efforts on the construction of the sterically congested pentamethylindenyl core and to defer the introduction of the side chains to a later stage in the synthesis. Strategies aiming at the construction of this motif would have to overcome the severe steric repulsion imposed by two adjacent quaternary centers.

1.2.2 Retrosynthetic Analysis

Scheme 2 shows the first generation retrosynthesis for nominal indoxamycin A ((1"*Z*)-2-*epi*-**1**). It was envisioned that the natural product could be accessed from tricyclic intermediate **7**, which bears the fully elaborated ring system of the target structure, through late-stage installation of the olefinic side chains. Opening of the tetrahydrofuran ring in **7** leads to dihydroindenone **8** as a possible precursor. In the forward sense, **7** could be obtained from this intermediate through selective reduction of the enone carbonyl and oxidative cleavage of the vinyl group. Key intermediate **8** in turn could arise from C_s-symmetric

cyclohexa-2,5-dienone **10** *via* a carboannulation sequence, which commences with conjugate addition of an organometallic species derived from vinyl iodide **11** to forge the C(4)−C(4a) bond. Subsequent cyclization of **9** would form the C(2a)−C(7b) junction. Precursor **10** should be accessible through dearomatization of commercially available mesitol (**12**).

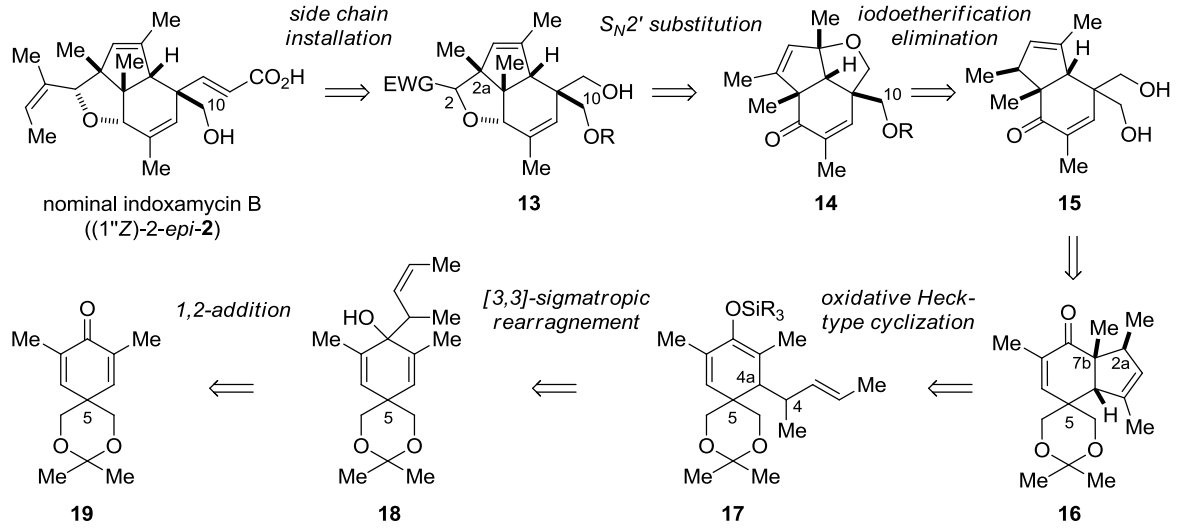


Scheme 2: Retrosynthetic analysis of nominal indoxamycin A ((1"*Z*)-2-*epi*-**1**) – first generation approach.

The critical steps in the first generation retrosynthesis included the diastereoselective introduction of the isobutene appendage at C(2) and the construction of the cyclopentene ring through cyclization of **9**. Furthermore, conjugate addition to cyclohexa-2,5-dienone **10** was potentially problematic due to the sterical hindrance of this substrate. A possible tactic to circumvent this problem was the 1,2-addition of allyl or crotyl nucleophiles, followed by [3,3]-sigmatropic rearrangement to generate the formal 1,4-adducts (Scheme 3). However, attaining facial selectivity in the carbonyl addition event was still challenging. The use of C_{2v}-symmetric cyclohexa-2,5-dienone **19** as a precursor would render the stereochemical outcome of this reaction inconsequential, but the resulting crotylation product **18** would bear two diastereotopic hydroxymethylene groups at C(5). It was presumed that these could be differentiated at a later stage of the synthesis. Consequently, the scaffold obtained would be hydroxylated at C(10), enabling the preparation of nominal indoxamycin B ((1"*Z*)-2-*epi*-**2**). Late stage deoxygenation of a suitable intermediate would grant access to the proposed structure of indoxamycin A ((1"*Z*)-2-*epi*-**1**).

Nominal indoxamycin B ((1"*Z*)-2-*epi*-**2**) was therefore the principal target in the second generation retrosynthesis. It was envisioned that this compound could be elaborated from tricyclic intermediate **13**. The vicinal quaternary centers and the tetrahydrofuran ring in **13**

might be constructed by employing an intramolecular S_N2' substitution, taking advantage of the primary alcohol at C(10) as a leaving group. The required electron withdrawing functionality would be introduced by reduction of the enone carbonyl in **14**, followed by alkylation of the intermediate secondary allylic alcohol. Based on hand-held models, it was reasonable to assume that tricyclic enone **14** could be obtained by differentiation of the primary alcohols in **15** through an iodoetherification-elimination sequence. The spirocyclic acetonide in **16** was chosen as a latent 1,3-diol. Furthermore, an oxidative Heck-type cyclization was considered suitable for the construction of the C(2a)−C(7b) bond to furnish dihydroindenone **16** from enol silane **17**. As pointed out, a sequence involving ketone crotylation followed by anionic oxy-COPE rearrangement to form the C(4)−C(4a) bond was considered to produce monocyclic intermediate **17** from cyclohexa-2,5-dienone **19**.

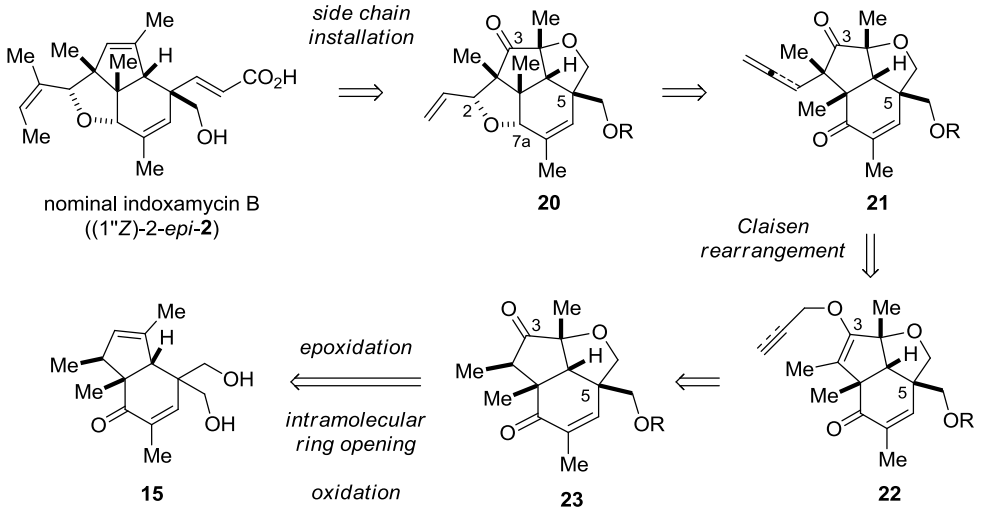


Scheme 3: Retrosynthetic analysis of nominal indoxamycin B ((1"*Z*)-2-*epi*-**2**) – second generation approach.

The formation of the C(2)−C(2a) bond in derivatives of **14** by S_N2' cyclization was a weak point in the second generation strategy, due to the considerable steric congestion of the bowl-like structure and the primary alcohol being a poor leaving group. In order to address the key-issue of installing the adjacent quaternary centers, the introduction of additional functionality in form of a ketone at C(3) was a taken into consideration. Although further synthetic operations would be required later in the synthesis to re-establish the cyclopentene unsaturation, this maneuver seemed worthwhile, as it would bestow significant flexibility for the installation of the adjacent quaternary centers.

The third generation retrosynthesis towards the indoxamycins is outlined in Scheme 4. Several elements of the second generation approach were conserved, such as late stage installation of the olefinic side chains and differentiation of the hydroxymethylene groups at

C(5) through intramolecular ether formation. It was reasoned that nominal indoxamycin B ((1"*Z*)-2-*epi*-**2**) could be obtained from tetracyclic intermediate **20**. Scission of the ether bridge between C(2) and C(7a) in **20** and oxidation state adjustment leads to enone **21** as a possible precursor. The vicinal quaternary centers in **21** might be constructed by CLAISEN rearrangement of substrates of type **22**. Both the propargyl and the vinyl species were taken into consideration for this transformation. It was envisaged that parent diketone **23** could be obtained from diol **15**, which was an intermediate in the second generation analysis.



Scheme 4: Retrosynthetic analysis of nominal indoxamycin B ((1"*Z*)-2-*epi*-**2**) – third generation approach.

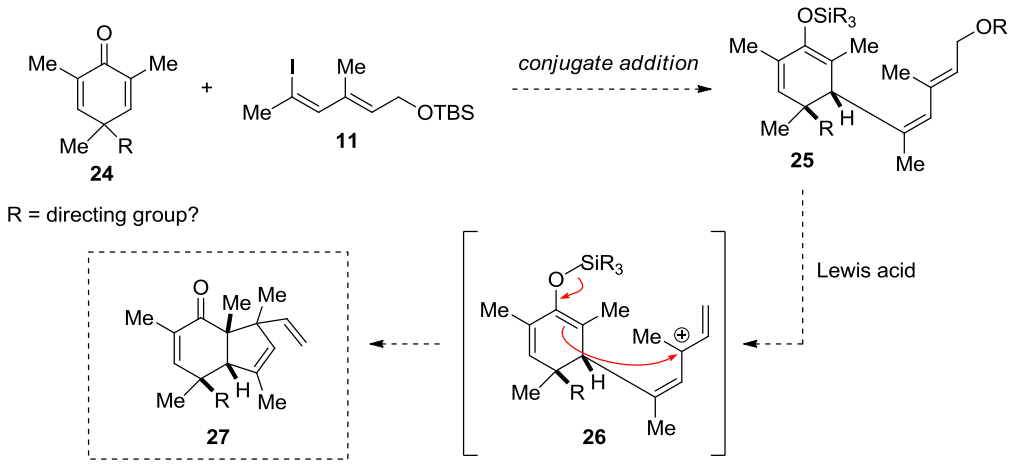
1.2.3 Conclusion

The devised third generation synthesis would provide an efficient route to the indoxamycins. The key issues to be addressed certainly include the significant steric repulsion in the stereochemically dense core framework. The utility of sigmatropic rearrangements in such a setting becomes apparent through the projected use of a CLAISEN and an oxy-COPE rearrangement. Another salient feature of the synthetic strategy is the employment of hidden symmetry for the rapid formation of molecular complexity.

1.3 Results and Discussion

1.3.1 First Generation Approach

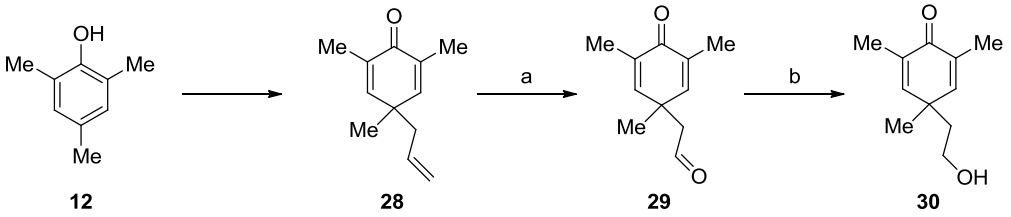
The original synthetic plan for the construction of the dihydroindenone core of indoxamycin A (**1**) involved conjugate addition of a vinyl metal species derived from **11** to a suitably substituted cyclohexa-2,5-dienone precursor **24** (Scheme 5). Subsequent cationic cyclization of an intermediate enolsilane **25** would then complete the assembly of the carbocyclic ring system. At the outset, it was unclear if such a transformation could overcome the severe steric strain imposed by the adjacent quaternary centers [24-26]. Furthermore, conjugate addition to cyclohexa-2,5-dienones bearing quaternary carbon atoms at the 4-position was expected to be difficult to realize. On the other hand, this approach seemed appealing, because commencing the synthesis with a starting material in which the six-membered ring is already elaborated with a large portion of the desired substitution pattern would allow for the efficient construction of the key intermediate.



Scheme 5: Original plan for the synthesis of the dihydroindenone core of indoxamycin A (**1**).

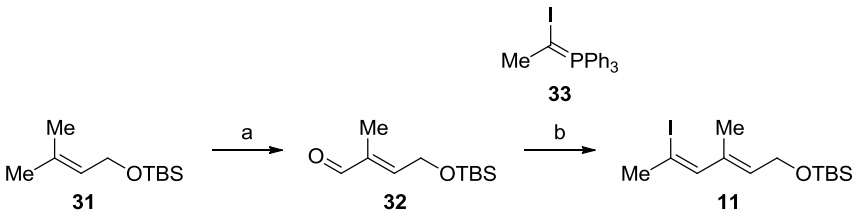
Another issue that had to be taken into consideration was stereocontrol. Cyclohexa-2,5-dienones of type **24** are achiral molecules that belong to the point group C_s. Hence, in the synthetic sequence envisioned, the first transformation to introduce a stereogenic center would be the conjugate addition. Although, this would in principle enable the use of a chiral catalyst to effect the enantioselective 1,4-addition under reagent control [27-29], substrates of type **24** are sterically biased to favor attack from the undesired diastereoface (R > Me). A possible solution for this problem is the installation of directing groups, which could also facilitate attack of the sterically congested substrate by the organometallic reagent.

Aromatic compounds provide a rich source of six-membered carbocycles with a myriad of different substitution patterns. A versatile arsenal of dearomatization protocols permits the conversion of these two-dimensional precursors into stereochemically dense, complex molecular architectures [30]. Among these transformations, the preparation of cyclohexadienones through the dearomatization of phenols is a prominent example [31]. Accordingly, **28** was conveniently obtained through the alkylation of mesitol (**12**) following a known procedure [32]. In order to introduce a flexible handle for the installation of various directing groups, intermediate **28** was subjected to selective oxidative cleavage of the terminal double bond by exposure to sodium periodate and catalytic osmium tetroxide (2.0 mol%) [33] (Scheme 6). The resulting aldehyde **29** was reduced to the corresponding primary alcohol in presence of the ketone carbonyl with *in situ* generated sodium triacetoxyborohydride [34] to furnish primary alcohol **30** in 66% yield. The latter proved to be a flexible intermediate and was used in further studies with a variety of different protective and directing groups (*vide infra*).



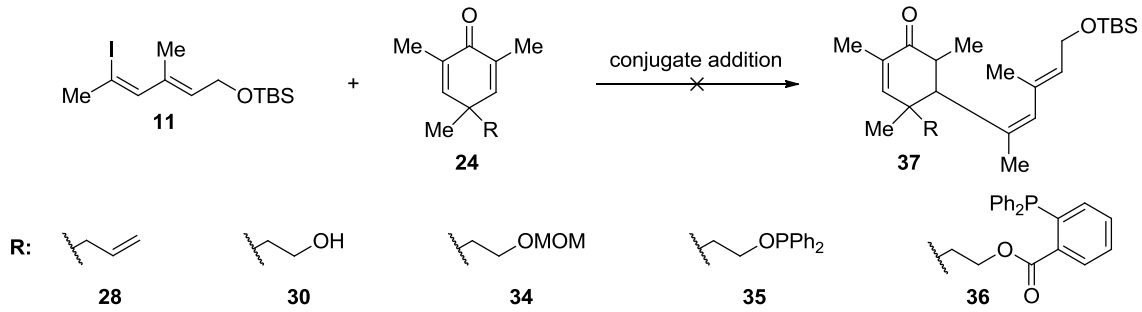
Scheme 6: Preparation of cyclohexa-2,5-dienone **30**. Reagents and conditions: a) OsO_4 (2.0 mol%), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), dioxane−H_2O, RT, 90%; b) $NaBH(OAc)_3$ (10 equiv), THF, 0 °C, 66%.

Vinyl iodide **11** was prepared from known compound **31**, which is readily available by TBS-protection of commercially available 3-methylbut-2-en-1-ol [35] (Scheme 7). Regioselective allylic oxidation, mediated by selenium dioxide (0.5 equiv) and with *tert*-butyl hydroperoxide (*t*-BuO_2H) as a stoichiometric oxidant (2.0 equiv), gave aldehyde **32** in a moderate yield of 44% [36]. ZHAO−STORK olefination with **33** afforded **11** exclusively as the (*Z*)-isomer [37].



Scheme 7: Preparation of vinyliodide **11**. Reagents and conditions: a) SeO_2 (0.5 equiv), *t*-BuO_2H (2.0 equiv), CH_2Cl_2, RT, 44%; b) **33** (2.0 equiv), THF, −78 °C, 57%.

With diene **11** and a flexible cyclohexa-2,5-dienone precursor in hand, the critical conjugate addition was examined (Scheme 8). Vinyl iodide **11** was transformed into the corresponding NORMANT cuprate and LIPSCHUTZ higher order cuprate [38] that were employed in the conjugate addition reaction in combination with boron trifluoride diethyletherate as a LEWIS acid [39]. Zinc organyls were also prepared and used with catalytic $Ni(acac)_2$. While in none of these cases the desired reaction was observed, the LIPSCHUTZ higher order cuprate derived from **11** readily underwent conjugate addition to the test substrate cyclohexenone (74% yield). Installation of directing groups, along with copper [40], zinc [41] and magnesium [42, 43] organyls, was also unsuccessful. The failure of this approach can be attributed to the severe steric hindrance of both the cyclohexa-2,5-dienones and the vinyl metal species.

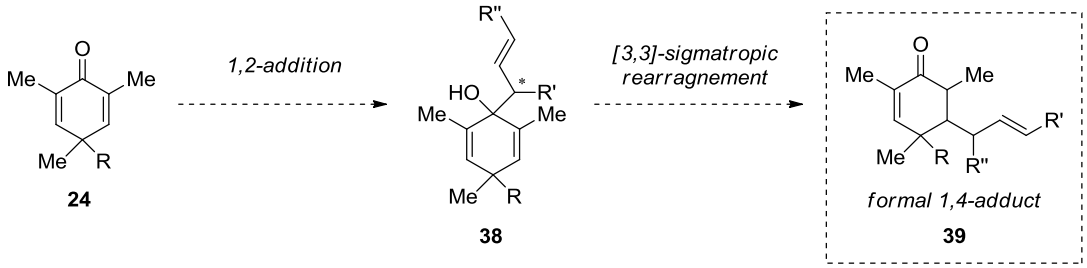


Scheme 8: Attempted conjugate addition of derivatives of **11** to cyclohexa-2,5-dienones.

1.3.2 Second Generation Approach

1.3.2.1 First Generation Dihydroindenone

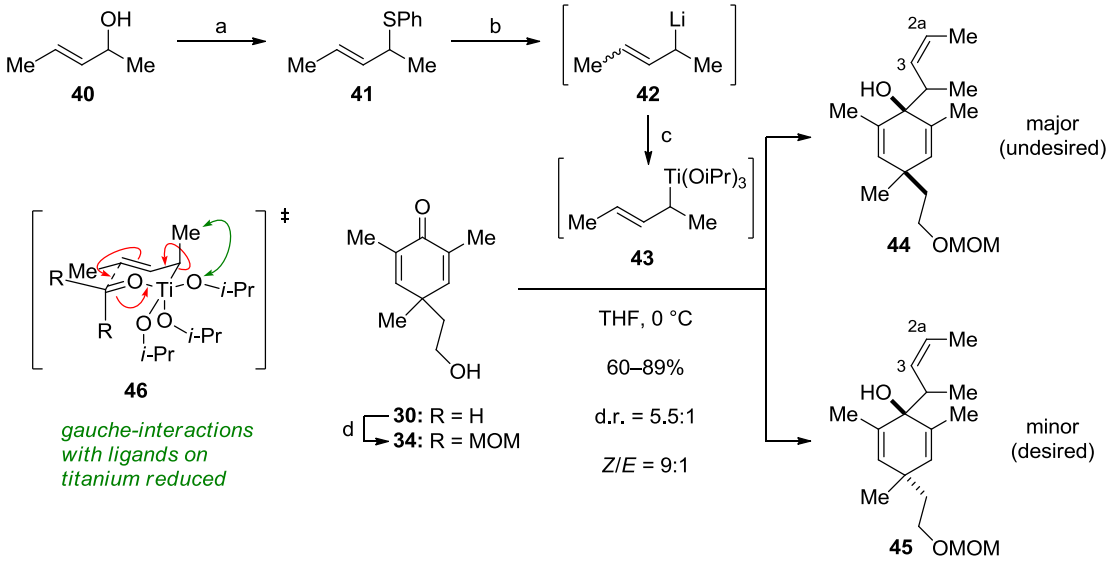
The reluctance of cyclohexa-2,5-dienones **28**, **30**, **34**, **35** and **36** to undergo conjugate addition required a revision of the synthetic strategy. A conventional tactic to address sterically hindered β-positions of α,β-unsaturated carbonyl compounds is 1,2-addition of allyl or crotyl nucleophiles, followed by [3,3]-sigmatropic rearrangement to generate the formal 1,4-adducts (**39**, Scheme 9). Since 1,2-adduct **38** would bear only one stereogenic center, an asymmetric synthesis could potentially be realized through enantioselective ketone crotylation, followed by stereospecific rearrangement. Compounds bearing a 3-hydroxy-1,5-hexadiene motif are formidable substrates for such a reaction, as they undergo facile oxy-COPE rearrangement. The primary enol products formed in this process are of higher stability than the starting materials, precluding undesired reaction equilibria [44, 45]. Furthermore, EVANS and GOLOB have shown that the oxy-COPE rearrangements can be performed at low temperatures by deprotonation of the hydroxyl groups and formation of the dissociated alkoxides to induce rate accelerations of 10^{10} to 10^{17} [46].



Scheme 9: Revised synthetic strategy with carbonyl 1,2-addition followed by [3,3]-sigmatropic rearrangement.

The addition of allyl and crotyl metal species to aldehydes has been extensively studied and constitutes a powerful method for the stereoselective synthesis of secondary alcohols [47]. In contrast, crotylation of sterically hindered ketones, which would be required in this approach, still poses a synthetic challenge. Most of the reagents used for this transformation are derived from alkali or alkaline earth metal complexes, which display dynamic behavior with multiple bonding hapticities and configurations. In order to avoid regioselectivity problems, it seemed reasonable to use a symmetrical 1,3-dimethylallyl precursor for the preparation of the crotylation reagent.

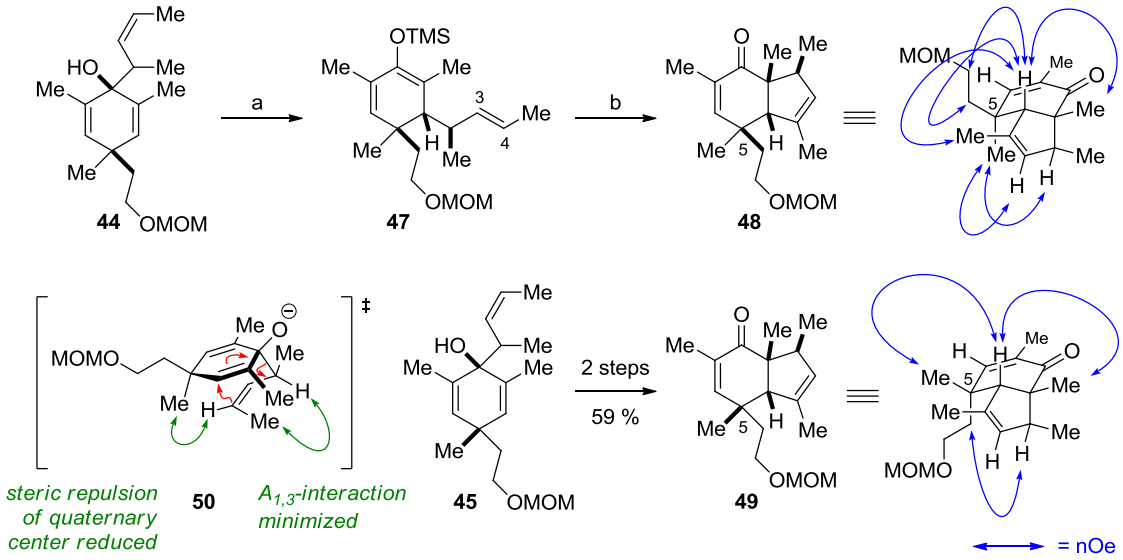
In initial studies, formation of the required GRIGNARD species was plagued by WURTZ-coupling [48] and polymerization of the starting 1,3-dimethylallyl halides. Therefore, an alternative protocol was employed, in which thioether **41** [49] was subjected to reductive cleavage with two aliquots of lithium naphthalenide to generate the resulting organolithium species **42** (Scheme 10). The latter was transmetalated with titanium(IV) isopropoxide to obtain crotylation reagent **43** [50]. Addition of **43** to cyclohexa-2,5-dienone **34** in THF at 0 °C delivered a 5.5:1 mixture of diastereomeric tertiary alcohols **44** and **45** (60−89% combined yield, both 9:1 mixture of (*Z*)/(*E*)-isomers). The ^{1}H NMR data for the major olefin isomers indicated (*Z*)-configuration, with the ^{3}J coupling constant for the C(2a) protons being 10.8 Hz. A plausible transition state for the crotylation reaction is shown in Scheme 10 (**46**). It can be seen that the allylic methyl group resides in an axial position to avoid gauche interactions with the ligands on titanium. The preference for metal-mediated allylation and crotylation reactions to yield (*Z*)-olefins has been discussed extensively [51].



Scheme 10: Ti-mediated crotylation of cyclohexa-2,5-dienone **34**. Only major olefin isomer for **44** and **45** shown. Reagents and conditions: a) $(PhS)_2$ (1.05 equiv), Bu_3P (1.05 equiv), MeCN, RT, 91%; b) Li naphthalenide (2.0 equiv), THF, −78 °C; c) $Ti(OiPr)_4$ (2.0 equiv), THF, −78 °C to 0 °C; d) MOMCl (2.2 equiv), DIPEA (2.5 equiv), CH_2Cl_2, RT, 97%.

Although the stereochemical outcome of the ketone crotylation was unknown at that point, the material obtained was taken forward in the synthesis (Scheme 11). Major diastereomer **44** was treated with potassium bis(trimethylsilyl)amide (KHMDS) in presence of 18-crown-6 ether to induce anionic oxy-COPE rearrangement. The intermediate ketone enolate was trapped as the corresponding trimethylsilyl enol ether to afford **47** in 40% yield. Analysis of the ^{1}H NMR spectrum of **47** showed the presence of an (*E*)-double bond with a ^{3}J coupling constant of 15.3 Hz for the C(3) and C(4) protons resonating at 5.44 ppm and 5.21 ppm,

respectively. It is reasonable to assume that the [3,3]-sigmatropic rearrangement of **44** to **47** proceeded through chair-like transition state **50**, in which the $A_{1,3}$-interaction of the (*Z*)-olefin, along with the steric repulsion between the quaternary center and the migrating allyl group, are minimized. Consequently, product **47** would have the relative stereochemistry as shown in Scheme 11.



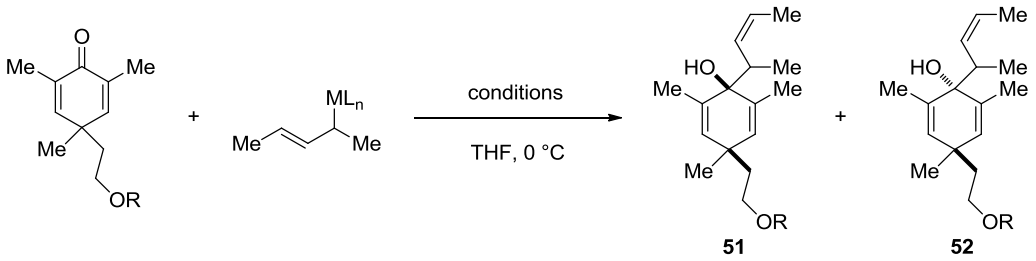
Scheme 11: Anionic oxy-Cope rearrangement and oxidative cyclization to dihydroindenones. Reagents and conditions: a) KHMDS (2.0 equiv), 18-crown-6 ether (2.0 equiv), THF, −10 °C; then TMSCl (2.5 equiv), −78 °C, 40%; b) $Pd(OAc)_2$ (1.1 equiv), MeCN−CH_2Cl_2, RT, 76%.

The palladium-mediated oxidative HECK-type cyclization of enol silanes with unfunctionalized olefins was discovered independently by the groups of ITO and KENDE [52-54] and further developed into a catalytic process by TOYOTA and co-workers [55, 56]. When **47** was exposed to stoichiometric palladium(II) acetate in MeCN−CH_2Cl_2, oxidative cycloalkenylation occurred to furnish dihydroindenone **48** (76%). The minor diastereomer obtained in the crotylation reaction (**45**) was advanced to dihydroindenone **49** in 59% overall yield following the same two-step procedure. The mechanistic details of the cycloalkenylation reaction will be discussed in detail later in this section (Schemes 16 and 17). Careful analysis of **48** and **49** by 2D NMR experiments, including nuclear OVERHAUSER effect spectroscopy (NOESY), revealed that dihydroindenone **48** derived from the major crotylation product had the undesired configuration at C(5).

A series of experiments was undertaken with the goal of reversing the stereochemical outcome of the crotylation reaction (Table 1). Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) has been reported to induce a switch of selectivity when employed as an additive in carbonyl additions [57]. However, when MAD was used as an additive in the

1,3-dimethylallylation of **34** (R = MOM), only a minor effect on the stereochemical outcome was observed (entry 3). Reaction of the respective GRIGNARD reagent with **34** gave a slightly diminished selectivity, still favoring **44** (entry 4). Use of the unprotected primary alcohol **30** as a substrate, along with a large excess of reagent, resulted in the same configurational outcome as with the MOM-protected analogue (entry 5). Altering MOM to a bulky TBS protective group led to no increase of diastereoselection (entry 6). These experimental observations suggest that the facial selectivity in the crotylation reaction is mainly governed by the steric demand of the alkyl compared to that of the methyl group, rather than by the nature of the substituent on the ethereal oxygen (either by steric bulk or directing interactions of heteroatom-bearing functionalities). Unfortunately, no conditions could be found to reverse this trend.

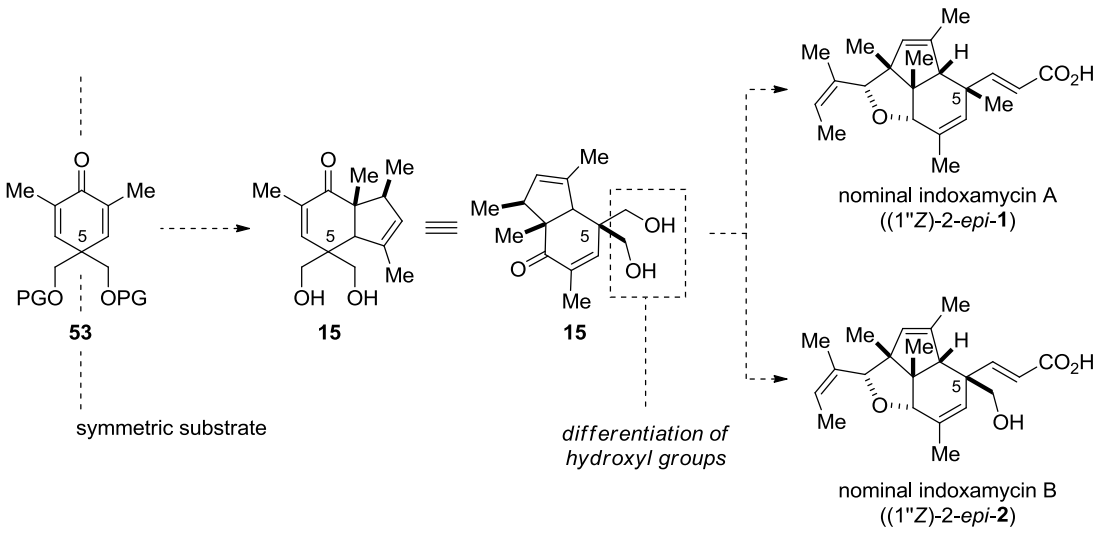
Table 1: Attempted reversal of stereochemical outcome of ketone crotylation.



Entry	R	ML_n	Additive	51:52	Yield
1	MOM	$Ti(OiPr)_3$	-	5.5:1	60−89%
2	MOM	$Ti(OEt)_3$	-	4.4:1	55%
3	MOM	$Ti(OiPr)_3$	MAD	4.4:1	92%
4	MOM	MgCl	-	3.2:1	66%
5	H	$Ti(OiPr)_3$	-	5.5:1	27%
6	TBS	$Ti(OiPr)_3$	-	5.4:1	73%

1.3.2.2 Second Generation Dihydroindenone

The failure to install the desired relative configuration at C(5) required an adaptation of the synthetic plan. Therefore, a route was conceived in which the carboannulation sequence was undertaken on a C_{2v}-symmetric cyclohexa-2,5-dienone substrate (Scheme 12, **53**). The resulting dihydroindenone **15** would bear two diastereotopic hydroxyl groups that could be differentiated at a later stage of the synthesis. If successful, such a tactic would not only allow for setting the C(5) stereocenter with the required diastereoselectivity, but also provide a functional group handle on both of the one-carbon residues at C(5), which would enable the synthesis of indoxamycin B (**2**).

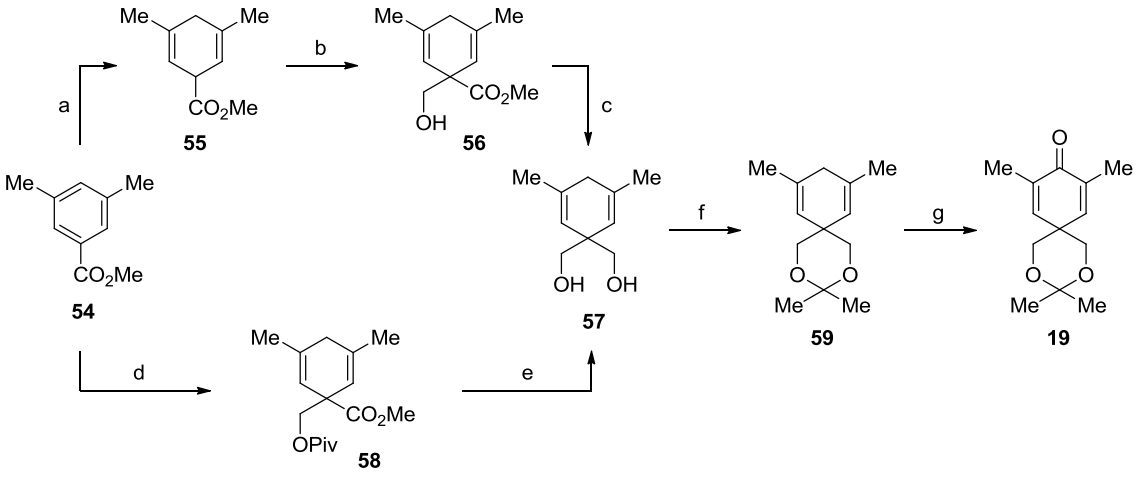


Scheme 12: Adapted synthetic route with C_{2v}-symmetric cyclohexa-2,5-dienone substrate.

Spirocyclic acetonide **19** was chosen as C_{2v}-symmetric substrate for ketone crotylation (Scheme 13). Synthesis of **19** commenced with BIRCH reduction [58] of commercially available methyl 3,5-dimethylbenzoate (**54**) with potassium metal as a reductant. The resulting cyclohexa-2,5-diene **55** was isolated in quantitative yield and treated with lithium diisopropylamide (LDA, 1.2 equiv) to generate the corresponding lithium enolate, which was subjected to aldol addition with monomeric formaldehyde [59]. The latter was generated by thermal depolymerization of paraformaldehyde (150 °C) and introduction of the gaseous monomer (b.p. −19 °C) into the reaction mixture using dry Ar as a carrier-gas. Reduction of **56** with lithium aluminumhydride furnished 1,3-diol **57** in 63% yield, which was converted to **59** under standard conditions.

Attempts to perform the aldol reaction on a decagram scale were hampered by variable yields (48−88%) and poor reproducibility, presumably due to residual water in the

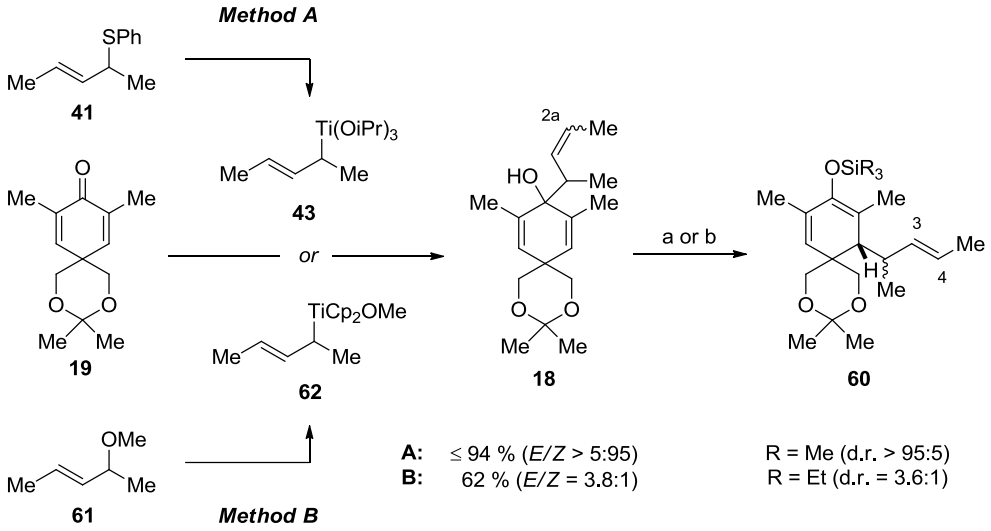
paraformaldehyde and re-polymerization of the monomeric species. In order to circumvent this problem, an improved reaction sequence was developed, which involved BIRCH reduction of **54** using lithium metal and *in situ* alkylation of the intermediate enolate with a suitable one carbon electrophile [60-62]. After testing a series of alkylating and acylating agents (ethyl formate, methyl chloroformate, paraformaldehyde), iodomethyl pivalate was identified as the reagent of choice [63, 64]. Under optimized conditions, spirocyclic acetonide **59** was obtained in 3 steps and 96% overall yield from commercially available **54** with only one chromatographic purification. Allylic oxidation to **19** was effected by exposure of **59** to *t*-BuO_2H (2.5 equiv) and catalytic palladium on carbon (2.5 mol%), employing the method disclosed by COREY and YU [65, 66]. Conditions based on catalytic chromium [67-69] or on the dirhodium(II) caprolactam catalyst developed by DOYLE and co-workers [70] gave comparable results.



Scheme 13: Synthesis of cyclohexa-2,5-dienone **19**. Reagents and conditions: a) K (2.5 equiv), *t*-BuOH (1.5 equiv), NH_3–THF, −78 °C, quant; b) LDA (1.2 equiv), THF, −78 °C; then CH_2O (gas), −20 °C, 48–88% (from **54**); c) $LiAlH_4$ (1.25 equiv), THF, 0 °C, 63%; d) Li (2.2 equiv), *t*-BuOH (1.05 equiv), NH_3–THF, −78 °C; then iodomethyl pivalate (1.0 equiv), −78 °C; e) $LiAlH_4$ (1.5 equiv), THF, 0 °C; f) TsOH (10 mol%), 2,2-dimethoxypropane, RT, 96% (from **54**, via d and e); g) Pd/C (10 wt%, 2.5 mol%), *t*-BuO_2H (2.5 equiv), K_2CO_3 (0.25 equiv), CH_2Cl_2, 0 °C, 61%.

With a reliable route to C_{2v}-symmetric cyclohexa-2,5-dienone **19** established, implementation of the crotylation-rearrangement sequence could be addressed. In initial studies, **19** was treated with titanium complex **43** to furnish **18** in high (*Z*)-selectivity (d.r. ≥ 95:5) and up to 94% yield (Scheme 14). The double bond configuration was determined by analysis of the ^{1}H NMR data for (*Z*)-**18**, which revealed an olefinic ^3J coupling constant of 10.8 Hz for the C(2a) proton resonating at 5.69 ppm. Hence, the crotylation reaction of **19** with **43** presumably proceeded through a six-membered transition state analogous to **46** (Scheme 10). Anionic oxy-COPE rearrangement of (*Z*)-**18** under optimized conditions afforded **60** (R = Me) as a single olefin isomer. The ^{1}H NMR spectrum of **60** showed the presence of

an (*E*)-double bond, with a ^3J coupling constant of 15.3 Hz for the C(3) and C(4) protons at 5.43 ppm and 5.24 ppm. The high diastereoselectivity of this reaction suggests a boat-like transition state for the [3,3]-sigmatropic rearrangement analogous to **50** (Scheme 11).

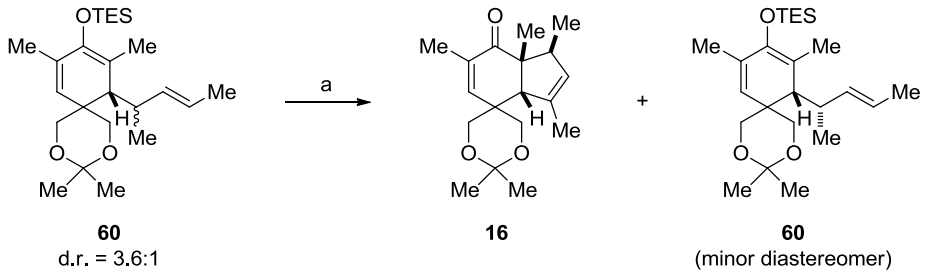


Scheme 14: Reagents and conditions: Method A: **41** (2.1 equiv), Li naphthalenide (4.0 equiv), THF, −78 °C; then $Ti(OiPr)_4$ (4.0 equiv), −78 °C to −40 °C; then **19** (1.0 equiv), −40 °C to 0 °C, 94%; Method B: $TiCp_2Cl_2$ (3.0 equiv), *n*-BuLi (6.0 equiv), THF, −78 °C; then **61** (1.5 equiv), −78 °C to RT; then **19** (1.0 equiv), −40 °C to 10 °C, 62%; a) *t*-BuOK (3.0 equiv), 18-crown-6 ether (3.0 equiv), THF, 0°C; then TMSCl (4.0 equiv), −78 °C, yield n.d.; b) *t*-BuOK (3.0 equiv), 18-crown-6 ether (3.0 equiv), THF, −78 °C to −40 °C; then TESCl (3.0 equiv), −78 °C, 70%.

In contrast to derivatives of **30**, for which ketone crotylation was a robust process (*vide supra*), crotylation of **19** was accompanied with the formation of various quantities of side-products. Moreover, the reaction suffered from poor reproducibility and attempted scale-up was met with failure. It was reasoned that the spirocyclic acetal in **19** might be sensitive to traces of residual lithium naphthalenide or the lithium thiophenoxide generated over the course of thioether cleavage. An alternative method for the generation of titanium(IV) allyl complexes is the cleavage of allylic ethers with low-valent titanium(II), as pioneered by SATO and co-workers [71]. In order to test this protocol, ether **61** was prepared according to literature procedures [72] and treated with the low-valent titanium(II) species generated by reduction of titanocene(IV) chloride with 2.0 equiv of *n*-butyllithium (*n*-BuLi) [73-75]. Exposure of **19** to the resulting crotylation reagent **62** afforded the desired tertiary alcohol **18** in 62% yield, although with diminished diastereoselectivity (3.8:1 vs. 1:9 ratio of olefin diastereomers) and favoring the (*E*)-isomer. The configuration of (*E*)-**18** was determined by analysis of the ^{1}H NMR spectrum, which exhibited a ^3J coupling constant of 15.3 Hz for the olefinic protons at 5.56 ppm and 5.44 ppm, respectively. When the 3.8:1 mixture of olefin isomers was subjected to anionic oxy-COPE rearrangement, **60** (R = Et) was obtained as a 3.6:1 mixture of diastereomers. Careful analysis of possible transition states by hand-held

models revealed that in the case of (*E*)-**18** the rearrangement presumably proceeded through a plurality of ill-defined boat- and chair-like transition states. Therefore, no stereochemical information seems to be translated over the course of this process. However, although diastereoselectivity was poor, this sequence proved to be highly reliable and scalable. Therefore, it was used to prepare ample amounts of **60**.

Although oxidative cyclization of **60** could be achieved with stoichiometric $Pd(OAc)_2$ on small scale (80% yield), this method was not amenable to multigram preparation of **16**, not only due to the high costs of $Pd(OAc)_2$, but also because of the palladium black that precipitated from the reaction mixture and complicated the work-up. LAROCK *et al.* have shown that enol silanes derived from aldehydes and ketones can be converted to the corresponding α,β-unsaturated carbonyl compounds with catalytic $Pd(OAc)_2$ (10 mol%) in DMSO under an atmosphere of oxygen [76]. The same conditions were later applied in the TOYOTA laboratory to oxidative cycloakenylation reactions [55, 56]. In accordance to their results, cyclization of **60** proceeded best (74% yield) using 10 mol% of $Pd(OAc)_2$ at a concentration of 0.05 M and a temperature of 45 °C. It is interesting to note that the minor diastereomer of **60** was recovered unchanged from this reaction. During optimization, the effect of the enol silane was briefly examined. Whereas TMS and TES gave comparable results, the analogous substrate bearing a TBS group was inferior.



60
d.r. = 3.6:1

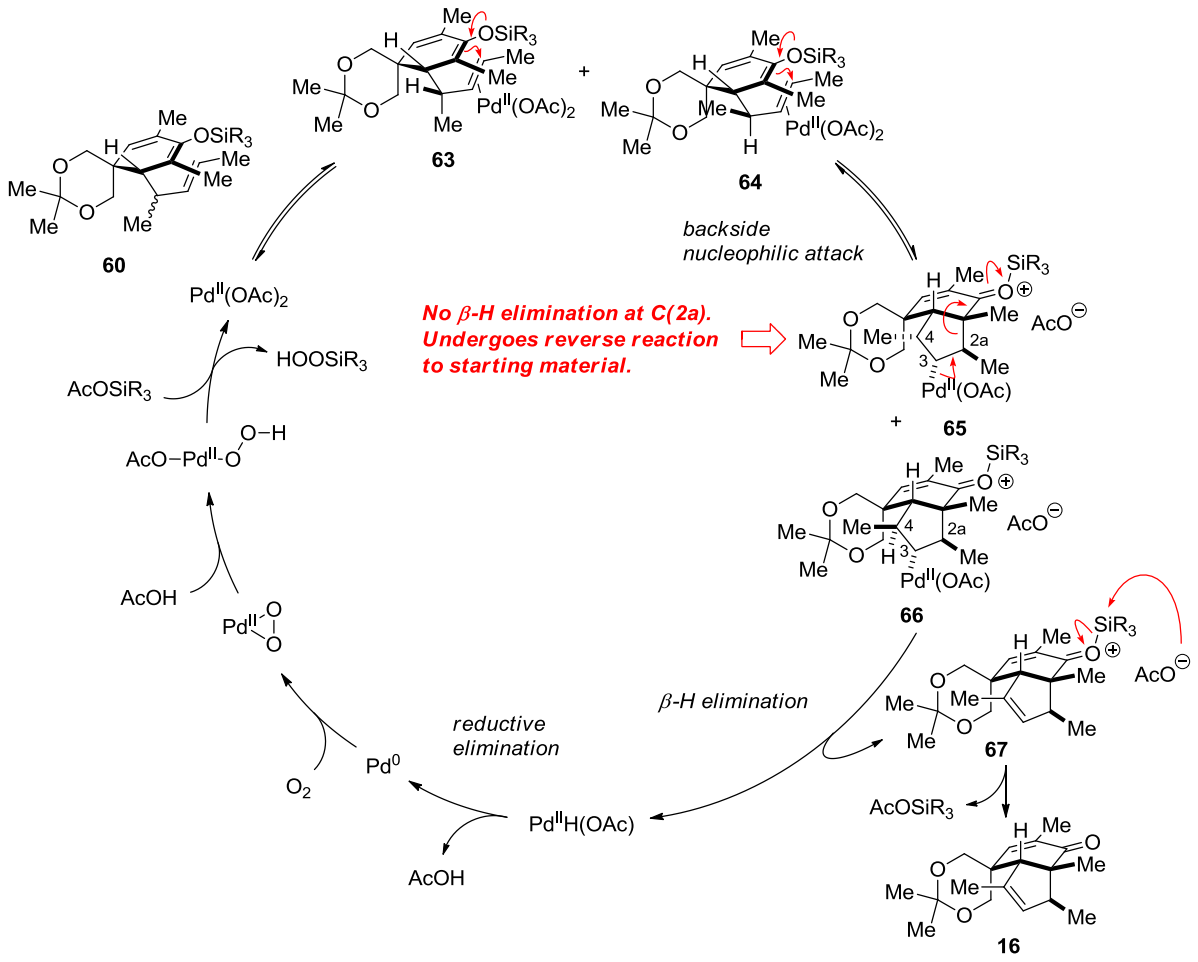
16

60
(minor diastereomer)

Scheme 15: Reagents and conditions: a) $Pd(OAc)_2$ (10 mol%), O_2 atmosphere, DMSO, 45 °C, 74%.

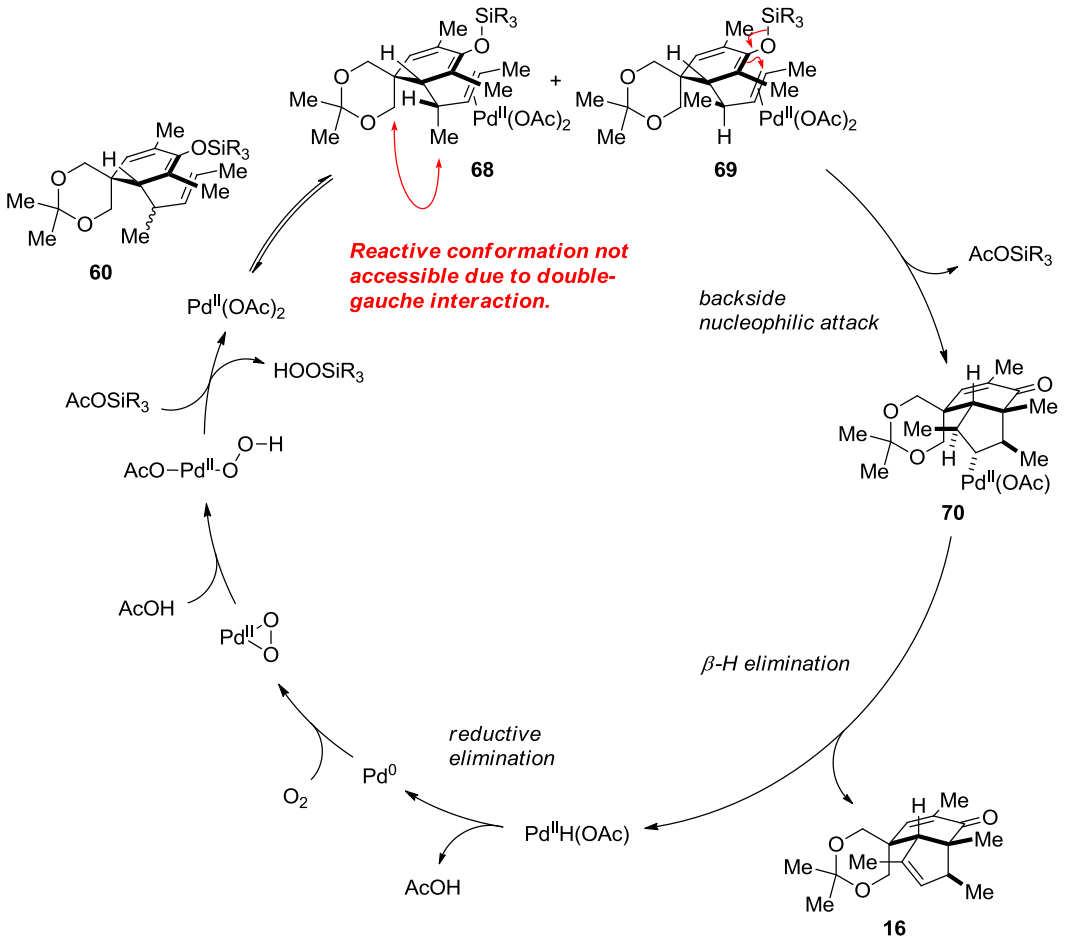
Based on these findings, two closely related mechanisms can be postulated for the oxidative cycloakenylation reaction (Schemes 16 and 17). The observation that the minor diastereomer of **60** remains unaffected, along with the absence of any α,β-desaturation product [77, 78], allows ruling out mechanistic pathways, which involve coordination of palladium(II) to the silyl enol ether followed by formation of a σ-bonded or oxo-π-palladium(II) intermediate and consecutive alkene insertion, as originally proposed by ITO *et al.* [52]. More plausible is a mechanism by KENDE and co-workers, which commences with backside nucleophilic attack of the enolsilane to the remote palladium-coordinated alkene [53]

(Scheme 16). For most substrates reported in the literature, a bulky TBS group is necessary to attenuate the reactivity of the silyl enol ether and to guide the palladium catalyst to the side chain olefin [55, 56]. However, TMS or TES are sufficient in this particular case, which is most probably due to the sterically congested nature of the substrate. The lack of reactivity for the minor diastereomer of **60** can be explained by two scenarios. In the first case (Scheme 16), both isomers undergo pre-coodination to palladium(II) (**63** and **64**), followed by cyclopentane formation without loss of the silyl group (**65** and **66**). Whereas major diastereomer **66** would bear a β-hydrogen atom at C(4), which is *syn* to the σ-bonded palladium(II) to enable productive β-hydride elimination, minor isomer **65** would undergo the reverse reaction to regenerate monocyclic starting material **60**. The reason why in both **65** and **66** no β-hydride elimination is observed at C(2a), despite the fact that the geometrical prerequisites are fulfilled, is speculative. A possible explanation is that the strong inductive effect caused by the oxonium ion in **65** and **66** attenuates the agostic interaction between the C(2a)−H bond and palladium to such an extent that β-hydride elimination is precluded [79]. Elimination of the silyl group in **67** would be the last step of the productive reaction pathway.



Scheme 16: Proposed mechanism for the oxidative cycloalkenylation reaction − option A.

The alternative scenario (Scheme 17) also involves reversible pre-coordination of both epimers of **60** to electrophilic palladium(II) (**68** and **69**), but minor diastereomer **68** would be unable to adopt the reactive conformation due to a double-gauche interaction of the allylic methyl group with one of the acetonide methylenes. Major isomer **69** would suffer backside nucleophilic attack of the enolsilane with concomitant loss of the silyl group, followed by β-hydride elimination of **70** to furnish product **16**. As in the first option, inductive effects would account for the selectivity in this event. A mechanism for the direct oxidation of the palladium(0) formed in this reaction by molecular oxygen to regenerate $Pd(OAc)_2$ through a palladium(II) peroxide intermediate [80] has been proposed by LAROCK and co-workers [76].

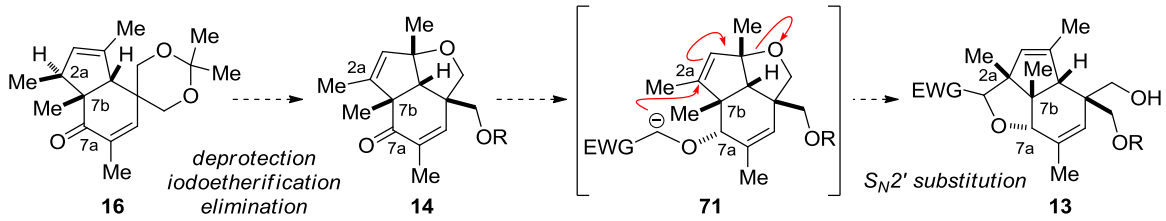


Scheme 17: Proposed mechanism for the oxidative cycloalkenylation reaction − option B.

1.3.2.3 Attempted Installation of Vicinal Quaternary Centers

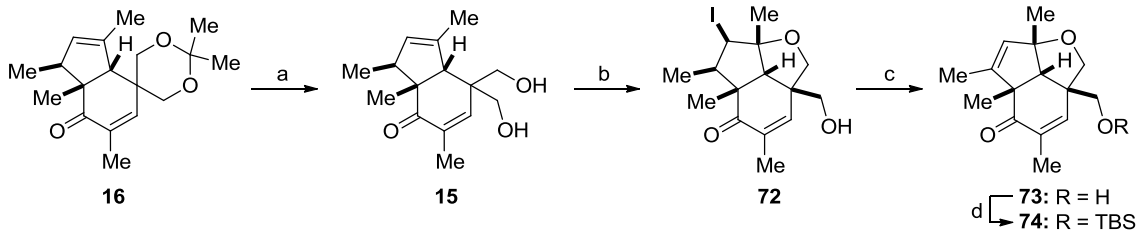
With dihydroindenone **16** in hand, the next critical task was the installation of the adjacent quaternary centers at C(2a) and C(7b). As any sequence to establish this structural motif would have to surmount considerable steric hindrance, it seemed prudent to devise a synthesis

that relied upon an intramolecular key transformation. Reduction of the enone carbonyl at C(7a) to the corresponding allylic alcohol would not only provide a flexible handle for the introduction of various functional groups, but also allow for the simultaneous construction of the tetrahydrofuran ring in the target structure. A variety of synthetic strategies, including C−H insertion at C(2a), were taken into consideration. Ultimately, a route involving transposition of the cyclopentene double bond through iodoetherification and elimination of the intermediate alkyl iodide seemed most promising, as it would not only render C(2a) susceptible to C−C bond formation, but also enable differentiation of the diastereotopic primary alcohols. S_N2' substitution would eventually complete construction of the tricyclic core framework.



Scheme 18: S_N2' substitution strategy for installation of vicinal quaternary carbon centers.

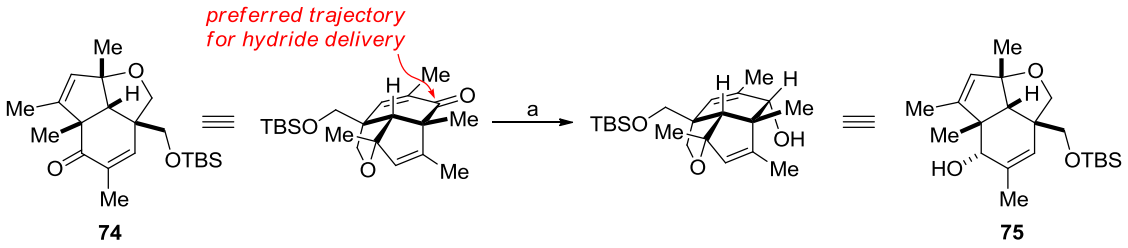
To this end, acetonide **16** was hydrolyzed in quantitative yield with aqueous hydrochloric acid in THF to liberate 1,3-diol **15** (Scheme 19). This compound was subjected to iodoetherification conditions to furnish tricyclic intermediate **72** as a single diastereomer, which was immediately subjected to elimination of hydrogen iodide by treatment with 1,8-diazabi-cyclo[5.4.0]undec-7-ene (DBU, 5.0 equiv) in benzene at 70 °C. Diene **73** was delivered efficiently with the cyclopentene olefin transposed (91% over two steps). Protection of the primary alcohol as a silyl ether proceeded in 90% yield under standard conditions to furnish enone intermediate **74**.



Scheme 19: Reagents and conditions: a) HCl (1.0 M in H_2O, 2.9 equiv), THF, RT, quant; b) I_2 (2.5 equiv), Na_2CO_3 (5.0 equiv), MeCN, RT; c) DBU (5.0 equiv), benzene, 70 °C, 91% from **15**; d) TBSCl (2.2 equiv), imidazole (2.5 equiv), DMF, 0 °C, 90%.

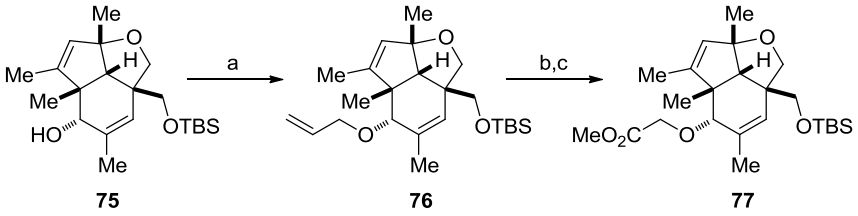
The enone carbonyl in **74** was selectively reduced to the corresponding allylic alcohol using the ate complex of *n*-BuLi and diisobutylaluminum hydride (LiAlH(*i*-Bu)$_2$*n*-Bu) to give

75 as a single diastereomer in 84% yield [81]. The excellent substrate stereocontrol exhibited in this reaction can be attributed to hydride delivery from the convex face of the bowl-shaped molecule (Scheme 20).



Scheme 20: Reagents and conditions: a) LiAlH(*i*-Bu)$_2$*n*-Bu (1.6 equiv), toluene, −78 °C, 84%.

Consequently, the newly formed hydroxyl group was oriented towards the concave side of the ring system, which rendered **75** remarkably inert towards alkylation. Whereas no product was observed in the reaction of the corresponding sodium alkoxide with methyl bromoacetate,[1] minor amounts (12−18%) of the corresponding ester were obtained with the more stable *tert*-butyl bromoacetate under phase transfer catalysis.[2] However, as allylation of **75** proceeded in good yield (84%, quant brsm, Scheme 21) under forcing conditions, a 4-step protocol was eventually employed, which involved selective oxidative cleavage of the allyl residue within **76**, followed by PINNICK oxidation [82-85] of the intermediate aldehyde. The carboxylic acid thus obtained was converted to the corresponding methyl ester using TMS diazomethane.



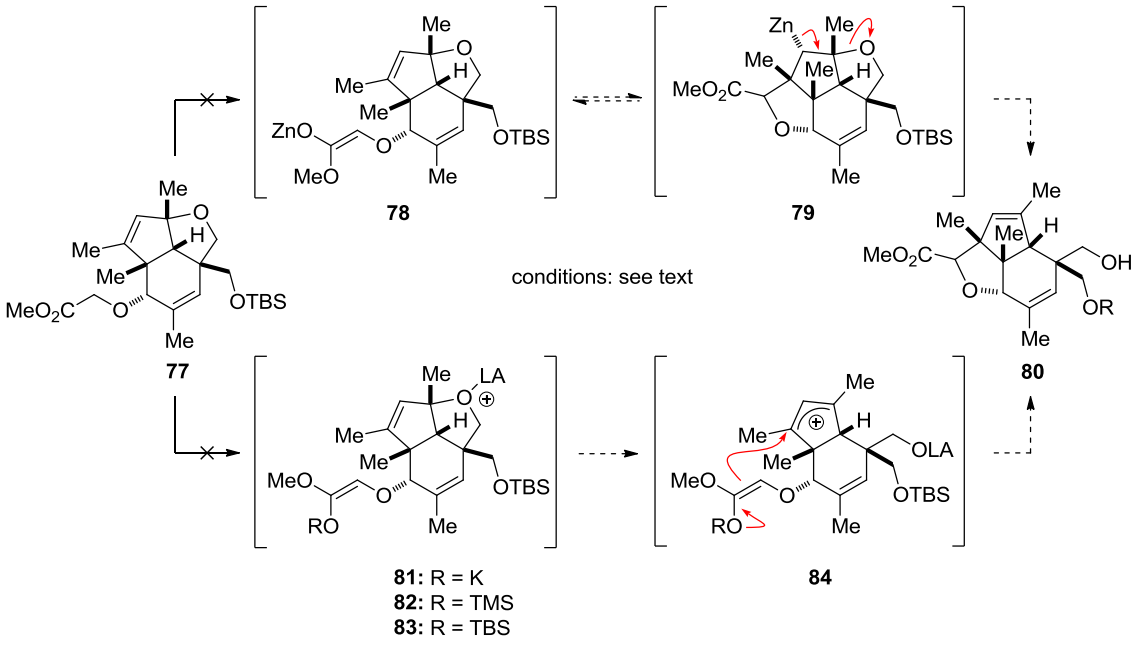
Scheme 21: Reagents and conditions: a) KH (4.0 equiv), allyl bromide (5.0 equiv), TBAI (0.2 equiv), THF, 60 °C, 84% (quant brsm); b) OsO_4 (3.0 mol%), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), dioxane−H_2O, RT, 82% (96% brsm); c) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (7.0 equiv), 2-methyl-2-butene (70 equiv), *t*-BuOH−H_2O, RT; then trimethylsilyl diazomethane (15 equiv), MeOH, 0°C to RT, 87%.

With a reliable route to **77** established, the critical 5-exo-trig cyclization to provide **80** could be examined (Scheme 22). Although additions of metal enolate derivatives to unactivated carbon-carbon multiple bonds have been extensively studied, examples for their use in complex natural product synthesis are still rare [86]. A possible reason for this is that

[1] The addition of TBAI, 15-crown-5 ether or HMPA had no influence on this transformation.
[2] Methyl bromoacetate presumably underwent elimination to ketene or hydrolysis under identical conditions.

the carbometalation of unactivated olefins with stabilized carbanions is *per se* an endothermic process. Nevertheless, there was encouraging precedence for the sought transformation from a report by NORMANT and co-workers, in which zinc enolates of δ,ε-unsaturated α-amino esters were cyclized to polysubstituted pyrrolidines [87]. Such a process would be particularly attractive for the system in hand, as the resulting organozinc intermediate **79** might suffer irreversible elimination of the primary hydroxyl group to deliver **80**. Unfortunately, all attempts to generate the zinc enolate by treatment of **77** with LDA, followed by addition of zinc(II) bromide to effect transmetalation and insertion into the cyclopentene double bond met with failure.

An alternative option to effect the desired transformation was the exposure of derivatives of **77**, such as enolate **81** or silyl ketene acetals **82** and **83**, to strong LEWIS acids to form carbocation **84**, which potentially could collapse to provide **80**. In the event, treatment of **77** with various bases, such as KHMDS or NEt_3, in combination with trimethylsilyl iodide or titanium(IV) iodide, either led to no reaction or decomposition. As attempts to generate and isolate ketene acetals **82** or **83** were unsuccessful, **77** was subjected to a series of experiments involving treatment with strong bases and quenching with D_2O. The fact that no deuterium incorporation was observed in any of these experiments led to the conclusion that ester **77** was sterically too congested to undergo enolization.

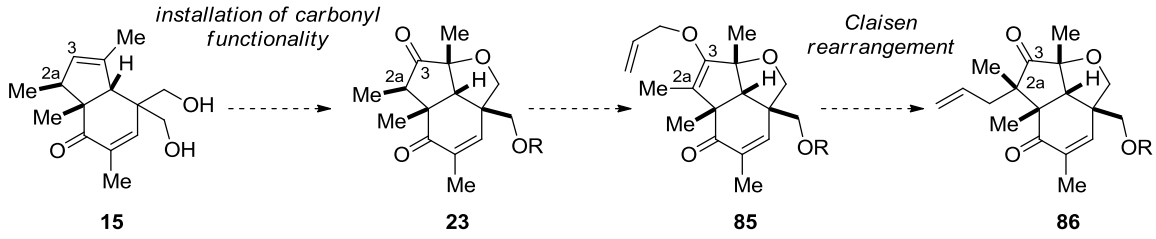


Scheme 22: Attempted 5-exo-trig cyclization.

1.3.3 Third Generation Approach

1.3.3.1 Claisen Rearrangement

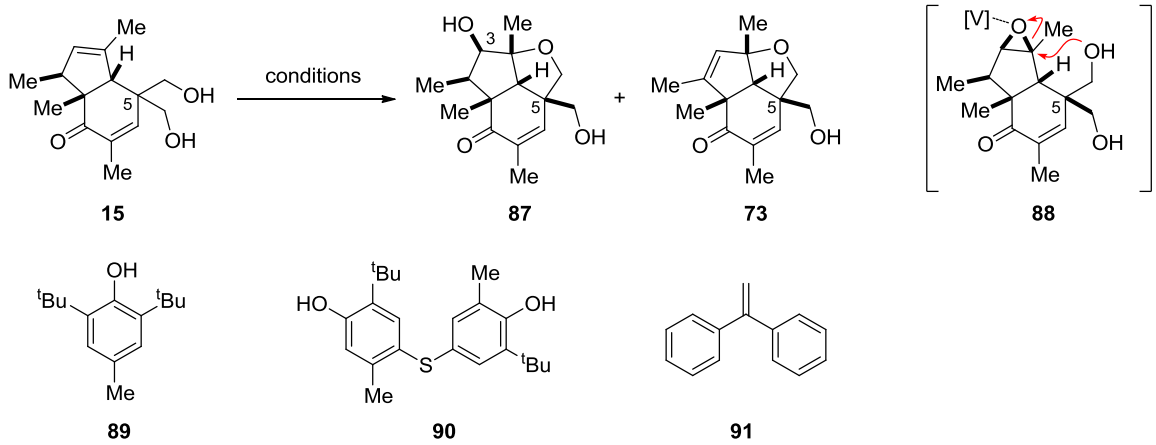
Due to the lack of success in the nucleophilic attack to C(2a) in the previous approach (*vide supra*), an alternative strategy was conceived, which involved an Umpolung of the reactivity at this position. Generally, the introduction of additional functional groups into intermediates in complex molecule synthesis is undesirable, as it often increases the number of steps and complicates the system. However, under certain circumstances, added functionality can open new reaction pathways, which potentially allows for overcoming synthetic obstacles that are otherwise impassable. In the case of **15**, installation of a ketone carbonyl at C(3) seemed particularly interesting, as formation of the enolate corresponding to **23** would enable a variety of C−C bond forming reactions, such as CLAISEN rearrangement of **85** to **86** (Scheme 23).



Scheme 23: CLAISEN approach for installation of vicinal quaternary centers.

In analogy to the previous iodoetherification approach, a sequence involving epoxidation, followed by diastereoselective opening of the intermediate oxirane seemed most attractive to install the required functional group pattern and simultaneously differentiate the hydroxymethylene groups attached to C(5) (Scheme 23). Consequently, different epoxidation reagents were examined, including *meta*-chloroperoxybenzoic acid (*m*-CPBA) and dimethyldioxirane (DMDO) [88, 89], which led to selective epoxidation of the cyclopentene double bond. However, stereocontrol was poor in both cases and the diastereomeric products formed were prone to spontaneous epoxide opening, complicating their isolation. After some experimentation, it was found that vanadium-catalyzed epoxidation of **15** [90] led to a tandem reaction, wherein the intermediate epoxide **88** underwent group-selective intramolecular ring opening to afford **87** as a single diastereomer (Table 2). Interestingly, diene **73**, previously prepared from **15** through iodoetherification and subsequent elimination of hydrogen iodide, was isolated from this reaction as a side product.

Table 2: Optimization of vanadium-catalyzed epoxidation-ring opening cascade.[a]



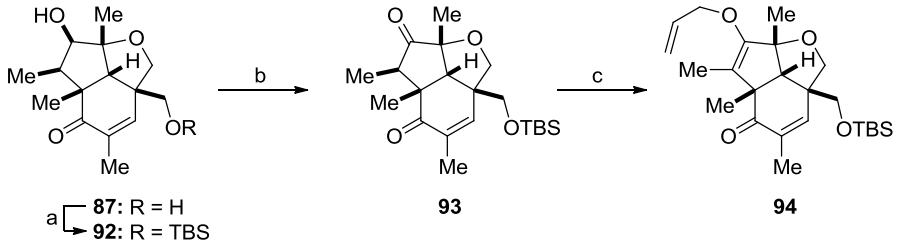
Entry	Vanadium Cat.	Additive	87 : 73[b]	Isolated Yield (87)
1	$VO(acac)_2$	-	2:1	46%
2	$V(OEt)_3$	-	1.3:1	31%
3	$VO(acac)_2$	**89** (0.1 equiv)	2:1	33%
4	$VO(acac)_2$	**91** (0.1 equiv)	1.4:1	38%
5	$VO(acac)_2$	**90** (0.25 equiv)	10:1	51%
6	$VO(acac)_2$	**90** (0.1 equiv)	7:1	55%
7	$VO(acac)_2$	**90** (0.05 equiv)	6:1	70%
8	$VO(acac)_2$	**90** (0.025 equiv)	7:1	75%
9	$VO(acac)_2$	**90** (0.02 equiv)	7:1	71%
10	$VO(acac)_2$	**90** (0.01 equiv)	3:1	65%

[a] Conditions: Vanadium catalyst (5.0 mol%), *t*-BuO_2H (3.0 equiv), 4 Å molecular sieves (30 wt%), additive, CH_2Cl_2 (0.10 M), 40 °C, 12 h. [b] Determined by ^1H NMR of the crude reaction mixture.

The formation of substantial amounts of **73** in the vanadium-catalyzed oxidative tandem reaction was not only surprising, but also hampered the overall efficiency of the process. Therefore, a series of experiments was undertaken with the goal to suppress this side reaction (Table 2). In addition to $VO(acac)_2$ (entry 1), $V(OEt)_3$ was tested as a catalyst [91], which gave inferior results (entry 2). As a radical mechanism could not be ruled out for the formation of **73**, the influence of radical inhibitors was also examined. 2,6-Di-*tert*-butyl-4-methylphenol (BHT, **89**, entry 3) and ethene-1,1-diyldibenzene (**91**, entry 4) had no

significant effect on the cascade. However, addition of the radical inhibitor developed by KISHI and co-workers (**90**, entries 5-10) resulted in a substantial increase of selectivity [92]. When 0.25 equiv of **90** were employed (entry 5), almost no side product was observed, but the isolated yield of **87** was still relatively low (51%). Interestingly, gradual reduction of the amount of **90** resulted in an increase of product yield with an only slight decrease in selectivity. Optimal results were achieved when just half an aliquot of **90** was used relative to the vanadium loading (entry 8). The mechanism for the formation of **73** and the mode of action of **90** are currently not understood. However, the fact that **90** was the only additive having an influence on the reaction, along with the result that a 1:2 stoichiometry between **90** and the vanadium catalyst afforded the best outcome, lead to the conclusion that **90**, or an oxidized form thereof, acts as a ligand on vanadium rather than as a radical inhibitor.

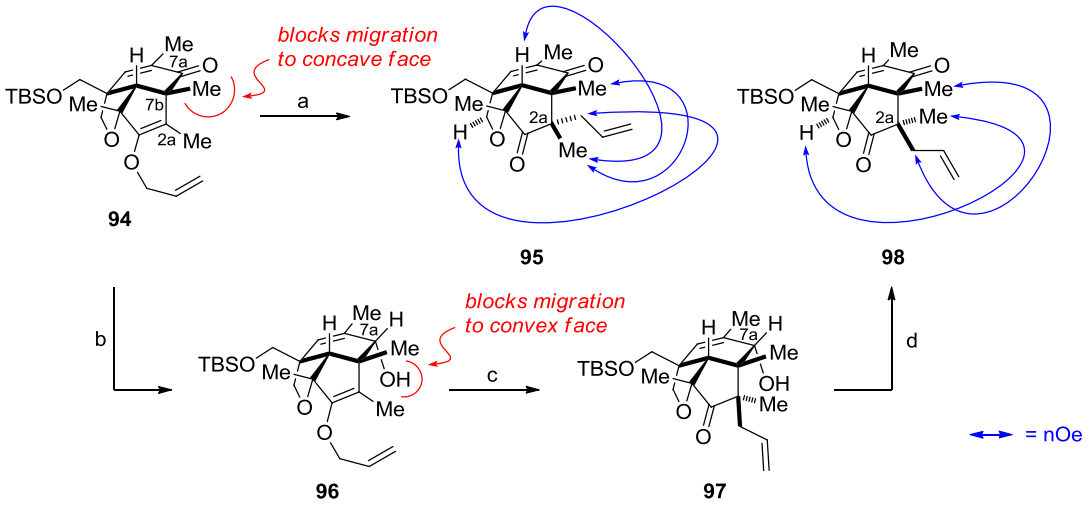
The primary hydroxyl group in **87** was selectively protected as a silyl ether (TBSCl, NEt_3, DMAP, 88%), and the remaining secondary alcohol in **92** was oxidized with DESS–MARTIN periodinane to afford ketone **93** [93] (Scheme 24). *O*-alkylation of the potassium enolate of **93** with allyl bromide in the presence of 18-crown-6 ether furnished allyl vinyl ether **94** in 94% yield.



Scheme 24: Synthesis of allyl vinyl ether **94**. Reagents and conditions: a) TBSCl (1.2 equiv), NEt_3 (2.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C to RT, 88%; b) DMP (1.5 equiv), CH_2Cl_2, 0 °C, 95%; c) KH (1.5 equiv), THF, RT; then 18-crwon-6 ether (2.0 equiv), allyl bromide (1.5 equiv), 0 °C, 94%.

With access to **94**, installation of the vicinal quaternary centers at C(2a) and C(7b) *via* CLAISEN rearrangement could be examined (Scheme 25). At this point, it was unclear whether the stereochemical outcome of the sought transformation would be favorable, as the convex face of the molecule seemed sterically more accessible. However, it was reasoned that the methyl group at C(7b) would significantly shield the 2a position, potentially leading to the introduction of the allyl residue from the concave side of the ring system. Precedence for this reaction came from studies by the LEY group in connection with their total synthesis of azadirachtin [94]. In the experiment, heating a solution of allyl vinyl ether **94** in *o*-xylene to 160 °C for 12 h resulted in formation of diketone **95** with excellent diastereoselectivity (d.r. = 95:5) in almost quantitative yield (98%). Intriguingly, the C(2a) epimer of **95** could be

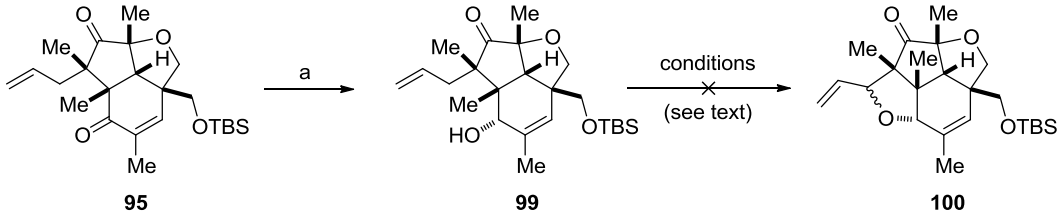
obtained *via* a sequence involving stereoselective reduction of the enone carbonyl in **94** to allylic alcohol **96**, followed by an analogous [3,3]-sigmatropic rearrangement (d.r. = 88:12, 88%). Oxidation of **97** with DMP delivered **98** in 92% yield [93]. The stereodivergent outcome of these reaction protocols can be attributed to the steric demand of the secondary hydroxyl group in **96**, which precludes the allyl substituent's ability to migrate to the concave face of the molecule. Hence, the stereochemical outcome of the CLAISEN rearrangement could be controlled by the oxidation state of C(7a). The relative stereochemistry of **95** and **98** was assigned by 2D NMR experiments, including nuclear OVERHAUSER effect spectroscopy (NOESY).



Scheme 25: Reagents and conditions: a) *o*-xylene, 160 °C, 12 h, d.r. = 95:5, 98%; b) LiAlH(*i*-Bu)$_2$*n*-Bu (1.6 equiv), toluene, −78 °C, quant; c) *o*-xylene, 160 °C, 14 h, d.r. = 88:12, 88%; d) DMP (5.0 equiv), CH_2Cl_2, RT, 92%.

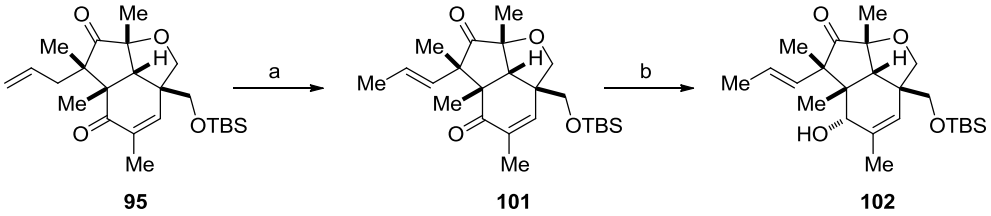
The successful installation of the adjacent quaternary carbon centers at C(2a) and C(7b) was a significant milestone in the synthesis of the indoxamycin core framework. With the goal in mind to complete the tricyclic scaffold prior to side chain installation, various options were considered for the construction of the remaining tetrahydrofuran ring, including allylic oxidation and subsequent cyclization (Scheme 26). In order to access intermediate **99**, the enone carbonyl of diketone **95** had to be chemoselectively reduced to the corresponding allylic alcohol (*vide supra*). Exposure of **95** to LiAlH(*i*-Bu)$_2$*n*-Bu, as previously employed for **78** and **94**, gave an inseparable 2:1 mixture of product isomers, reflecting a poor chemoselectivity. Inspired by a report by PAQUETTE and co-workers [95], LUCHE reduction of **95** [96-98] was examined. This reaction resulted in better chemoselectivity (4:1−11:1), but suffered from low conversion and poor reproducibility (21−47% yield). Nevertheless, closure of the tetrahydrofuran ring to give **100** was attempted by treatment of **99** with lead(IV) acetate under irradiation with a 500 W tungsten halogen lamp, but was unsuccessful with no product

observed. Furthermore, reaction of **99** with *N*-bromosuccinimide (NBS) under WOHL−ZIEGLER conditions exclusively yielded the 6-exo-trig bromoetherification product.[3]



Scheme 26: Attempted oxidative cyclization of **99**. Reagents and conditions: a) $NaBH_4$ (12 equiv), $CeCl_3 \cdot 7\ H_2O$ (2.0 equiv), EtOH−THF, 0 °C, 21−74%.

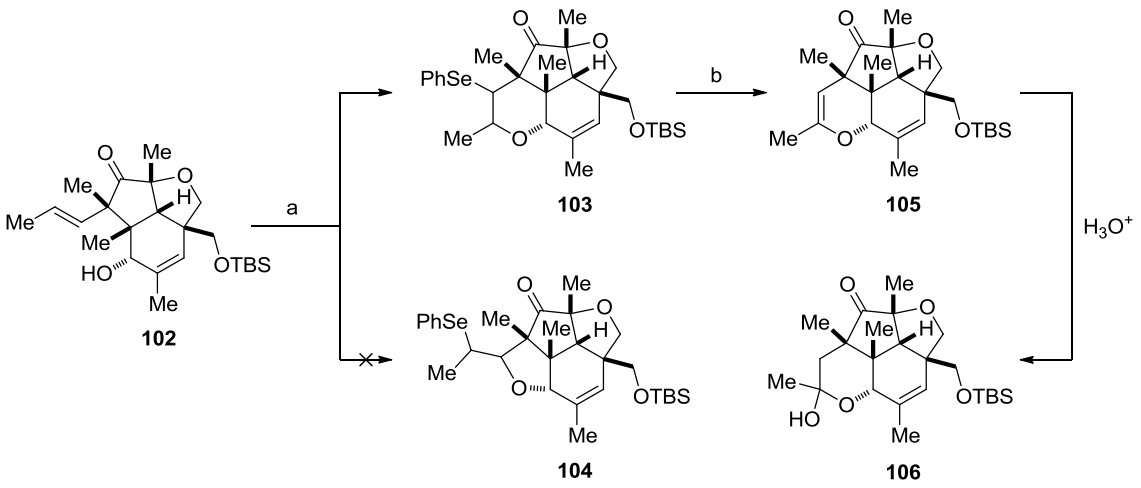
As direct cyclization of **99** appeared difficult, migration of the terminal double bond within **95** to the thermodynamically preferred internal position was examined (Scheme 27). This approach seemed promising, as selective reduction of resulting diketone **101** would yield **102**, in which the stage is set for cyclization through a suitable olefin activation protocol. The ruthenium-catalyzed isomerization of olefins has been studied extensively and has found application in total syntheses [99]. Among the conditions tested, the method by HANESSIAN and co-workers (2nd generation GRUBBS catalyst (10 mol%), MeOH, 60 °C) was most successful, affording **101** in 87% yield [100]. LUCHE reduction of **101** was sluggish, but proceeded in good chemoselectivity, when it was stopped at 50−60% conversion[4] to obtain **102** in 53% yield (91% brsm).



Scheme 27: Reagents and conditions: a) 2nd Generation GRUBBS catalyst (10 mol%), MeOH, 60 °C, 87%; b) $NaBH_4$ (5.0 equiv), $CeCl_3 \cdot 7\ H_2O$ (2.0 equiv), EtOH−THF, 0 °C, 53%, 91% brsm.

In order to effect 5-exo-trig cyclization of **102**, different protocols were tested. Standard iodoetherification (I_2, Na_2CO_3, MeCN, RT) led to a complex mixture of products. Treatment of **102** with phenyl selenyl chloride exclusively delivered 6-endo-trig cyclization product **103** (73% yield, Scheme 28). The structural assignment of **103** was confirmed by selenoxide elimination to afford enol ether **105**, which upon standing in deuterated chloroform, underwent facile hydrolysis to hemiketal **106** [101].

[3] As determined by ^{1}H NMR and HRMS.
[4] Determined by ^{1}H NMR of the crude product mixture.

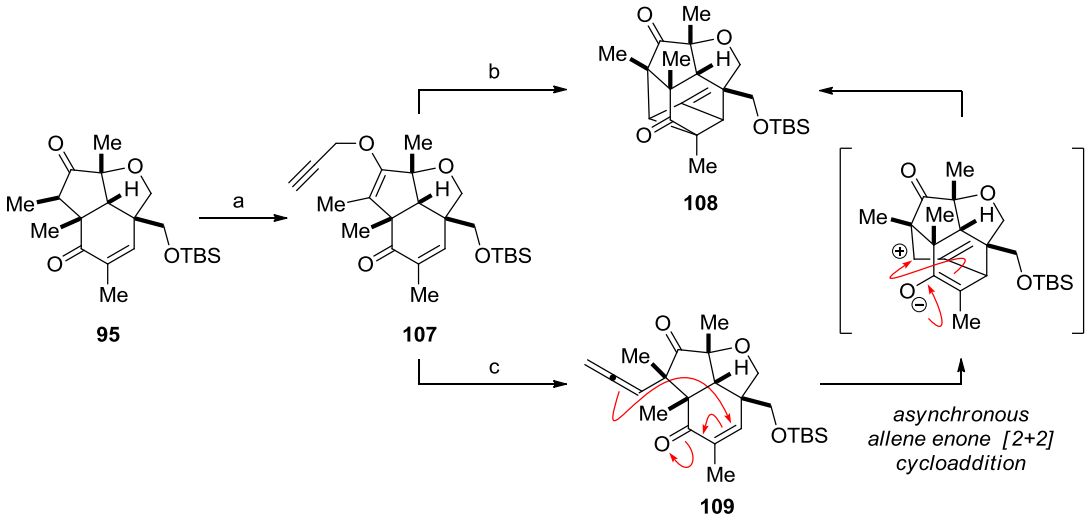


Scheme 28: Reagents and conditions: a) PhSeCl (1.5 equiv), CH_2Cl_2, −78 °C to RT, 73%; b) *m*-CPBA (1.0 equiv), CH_2Cl_2, 0 °C, then $(i\text{-Pr})_2NH$ (30 equiv), 0 °C to RT.

1.3.3.2 Saucy-Marbet Rearrangement

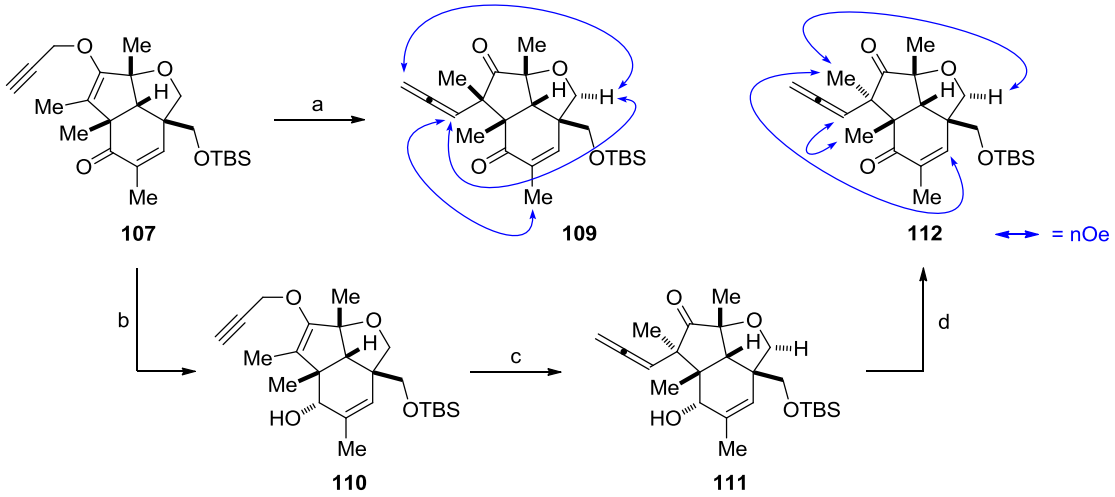
In previous experiments, cyclization of intermediates arising from CLAISEN rearrangement failed to deliver the desired tetrahydrofuran motif. Therefore, a related strategy encompassing SAUCY−MARBET (propargyl CLAISEN) rearrangement was examined [102-106]. In analogy to the corresponding allylation reaction, *O*-alkylation of the potassium enolate of **93** with propargyl bromide in presence of 18-crown-6 ether furnished propargyl vinyl ether **107** in 87% yield. Surprisingly, attempts at conducting the SAUCY–MARBET reaction under standard conditions (160 °C, *o*-xylene) proved unsuccessful to give tricyclic intermediate **109**. Instead, cage-like structure **108** was obtained as a single product in 91% yield.[5] It is reasonable to assume that the sought [3,3]-sigmatropic rearrangement to **109** was actually effective in this reaction. However, as in **109** the allyl residue is located in close proximity to the enone alkene, an intramolecular non-concerted [2+2] cycloaddition *via* intermediate **110** presumably occurred to furnish **108** as the final product. It was presumed that the high temperature required for the rearrangement (160 °C), was the cause for this problem and that the use of a suitable catalyst would permit milder conditions. Gratifyingly, **109** was obtained as the only detectable product (84%) by exposure of **107** to catalytic amounts (1.0 mol%) of the trinuclear Au(I)-oxo complex$[(Ph_3PAu)_3O]BF_4$ [107].

[5] The structure of **108** was unambiguously assigned by 2D NMR experiments.



Scheme 29: Reagents and conditions: a) KH (1.1 equiv), THF, RT; then 18-crwon-6 (1.5 equiv), propargyl bromide (1.2 equiv), 0 °C, 87%; b) *o*-xylene, 160 °C, 12 h, 91%; c) $[(Ph_3PAu)_3O]BF_4$ (1.0 mol%), dichloroethane, 75 °C, 84%.

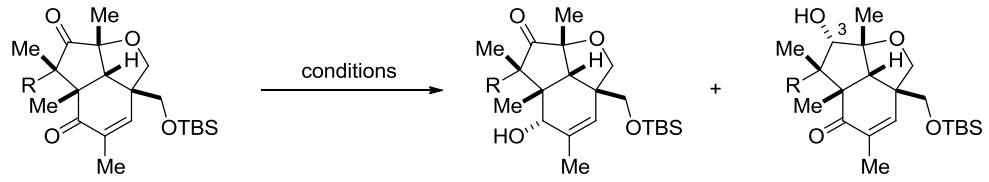
In order to secure the relative configuration of **109**, and to study the stereochemical behavior of the SAUCY–MARBET rearrangement, a series of experiments analogous to those carried out for the CLAISEN approach were conducted (Scheme 30). Reduction of the enone carbonyl in **107** (LiAlH(*i*-Bu)$_2$*n*-Bu, 91%) gave secondary allylic alcohol **110**, which, upon heating to 160 °C in *o*-xylene for 10 h, underwent a highly diastereoselective [3,3]-sigmatropic rearrangement to afford **111** in 88% yield (d.r. ≥ 95:5). Alternatively, the same transformation also proceeded at 75 °C under Au(I) catalysis (2.5 mol% of $[(Ph_3PAu)_3O]BF_4$) to furnish **111** in 81% yield, although as a 2:1 mixture of diastereomers. Oxidation of **111** with DMP delivered **112** in 56% yield [93], which was the C(2a) epimer of **109**. The relative configurations of **109** (desired) and **112** (undesired) were unambiguously assigned by 2D NMR studies.



Scheme 30: Reagents and conditions: a) $[(Ph_3PAu)_3O]BF_4$ (1.0 mol%), dichloroethane, 75 °C, d.r. ≥ 95:5, 84%; b) b) LiAlH(*i*-Bu)$_2$*n*-Bu (1.25 equiv), toluene, −78 °C, 91%; c) Method A: *o*-xylene, 160 °C, d.r. ≥ 95:5, 88%; Method B: $[(Ph_3PAu)_3O]BF_4$ (2.5 mol%), dichloroethane, 75 °C, d.r. = 2:1, 81%; d) DMP (3.0 equiv), CH_2Cl_2, RT, 56%.

The further elaboration of intermediate **109** to the indoxamycin core framework required chemoselective reduction of the enone carbonyl, a problem which was still challenging. Table 3 summarizes the experiments conducted for this purpose. Reduction with LiAlH(*i*-Bu)$_2$*n*-Bu reproducibly proceeded in good yields, but poor selectivities were observed with all substrates tested (entries 1, 3 and 8) [81]. LUCHE reduction of **95** and **101** gave better chemoselectivity [95-98], however, the results were erratic and the reaction was sluggish (entries 2 and 4). Reaction of **101** with L-selectride (LiBH(*s*-Bu)$_3$) resulted in exclusive conjugate reduction of the enone upon warming to ambient temperature (entry 5). Contrary to two reports by the BROWN laboratory, who had described the functional group tolerant reduction of conjugated aldehydes and ketones to the corresponding allylic alcohols with 9-BBN, **101** turned out to be inert toward this reagent (entry 6) [108, 109]. Exposure of **101** to DIBAL-H (entry 7) resulted in the formation of **102** (27%), along with significant amounts of double reduction product (22%, structure not shown), whereas treatment with LiAlH(*O*-*t*-Bu)$_3$ led to no reaction (entry 9). Borane *tert*-butylamine complex in CH_2Cl_2 at room temperature selectively reduced the cyclopentanone carbonyl in poor diastereoselectivity at C(3) (d.r. = 2:1, entry 10). Finally, it was found that reaction of **109** with Superhydride (LiBHEt$_3$) delivered **113** in excellent chemoselectivity and good yield (71−87% yield, entry 11).

Table 3: Optimization of chemo- and diastereoselective enone reduction.



95: R = $CH_2CH{=}CH_2$
101: R = $CH{=}CHCH_3$
109: R = $CH{=}C{=}CH_2$

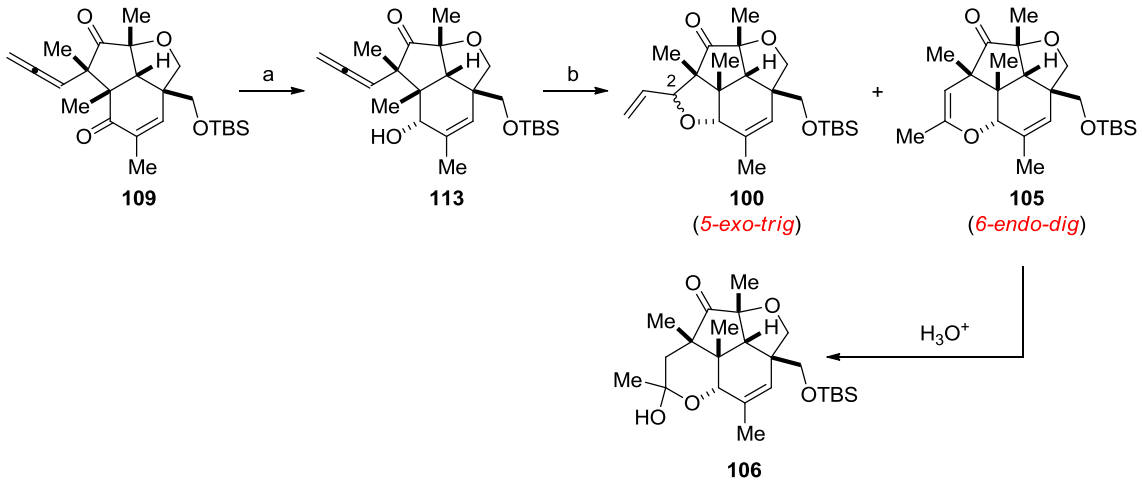
99: R = $CH_2CH{=}CH_2$
102: R = $CH{=}CHCH_3$
113: R = $CH{=}C{=}CH_2$

114: R = $CH_2CH{=}CH_2$
115: R = $CH{=}CHCH_3$
116: R = $CH{=}C{=}CH_2$

Entry	Substrate	Conditions	Selectivity	Yield[a]
1	**95**	LiAlH(*i*-Bu)$_2$*n*-Bu, THF, −78 °C	2:1	n.d.
2[b]	**95**	$CeCl_3 \cdot 7\ H_2O$, $NaBH_4$, EtOH−THF, 0 °C	7:1	33%
3	**101**	LiAlH(*i*-Bu)$_2$*n*-Bu, THF, −78 °C	1.6:1	80%
4	**101**	$CeCl_3 \cdot 7\ H_2O$, $NaBH_4$, EtOH−THF, 0 °C	2.4:1	53%
5[c]	**101**	LiBH(*s*-Bu)$_3$, THF, 0 °C to RT	-	-
6	**101**	9-BBN, THF, RT	-	n.r.
7[d]	**101**	DIBAL-H, toluene, −78 °C	1:0	27%
8[e]	**109**	LiAlH(*i*-Bu)$_2$*n*-Bu, THF, −78 °C	1.5:1	64%
9	**109**	LiAlH(O*t*-Bu)$_3$, −78 °C to 0 °C	-	n.r.
10	**109**	$BH_3 \cdot NH_2t$-Bu, CH_2Cl_2, RT	< 5:95[f]	n.d.
11	**109**	$LiBHEt_3$, THF, −78 °C	9:1	71−87%

[a] Isolated combined yield of isomeric secondary alcohols. [b] Average over 3 runs. [c] Only conjugate reduction of enone observed. [d] Significant amount (22%) of double reduction product observed. [e] Average over 4 runs. [f] Product **112** isolated as a separable 2:1 mixture of diastereomers (80% conversion).

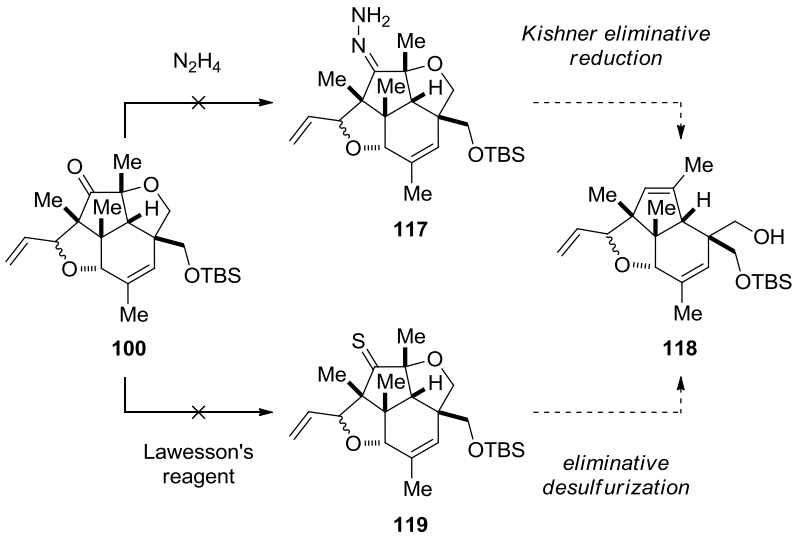
With a reliable protocol for chemo- and diastereoselective reduction of the cyclohexenone carbonyl in **109** disclosed, significant quantities of **113** could be prepared. The formation of the tetrahydrofuran ring in the indoxamycin framework was achieved through an intramolecular Au(I)-catalyzed allene hydroalkoxylation to form the desired 5-exo-trig cyclization product **100** as a 3.2:1 mixture of inseparable diastereomers at C(2) (72% combined yield, Scheme 31) [110]. In this reaction, a side product was obtained in 9% yield, which turned out to be identical to **105**, previously prepared by selenoxide elimination of **103** (*vide supra*). Consequently, a 6-endo-dig reaction pathway was operative in side reaction.



Scheme 31: Reagents and conditions: a) $LiBHEt_3$ (1.1 equiv), THF, −78 °C, 80%; b) chloro[2-(di-*tert*-butylphosphino)biphenyl]gold(I) (10 mol%), AgOTs (10 mol%), toluene, 60 °C, d.r. = 3.2:1, 72%.

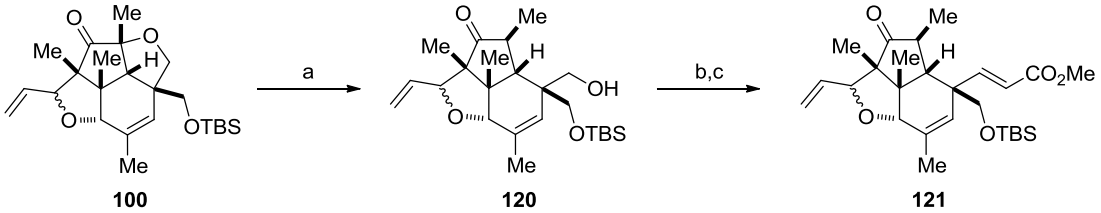
1.3.3.3 Synthesis of Nominal Indoxamycin B

With all of the rings of the indoxamycin core framework constructed, installation of both alkene side chains became the next objective in the synthesis. In this context, cleavage of the ether linkage in α-position to the ketone carbonyl was pivotal, because the primary hydroxyl group, which was masked as a tetrahydrofuran, had to be released to allow for introduction of the acrylate residue. An efficient method to achieve this transformation would be eliminative ketone reduction of **100** *via* hydrazone **117**, resulting in concomitant introduction of the cyclopentene unsaturation present in the natural product (KISHNER eliminative reduction; Scheme 32) [111-113]. Unfortunately, treatment of **100** with hydrazine hydrate or anhydrous hydrazine, even under forcing conditions (diethylene glycol, 120 °C) and prolonged reaction times (6 h), failed to produce hydrazone **117**. It was therefore attempted to convert **100** to thioketone **119**. The latter was not only expected to be more reactive towards nucleophiles, but potentially also susceptible to eliminative desulfurization. Disappointingly, **100** was inert towards thionation with Lawesson's reagent, even at temperatures as high as 160 °C [114, 115]. The lack of reactivity of **100** can be attributed in both cases to the fully substituted carbon atoms flanking the ketone carbonyl, imposing significant steric hindrance.



Scheme 32: Attempted eliminative ketone reduction.

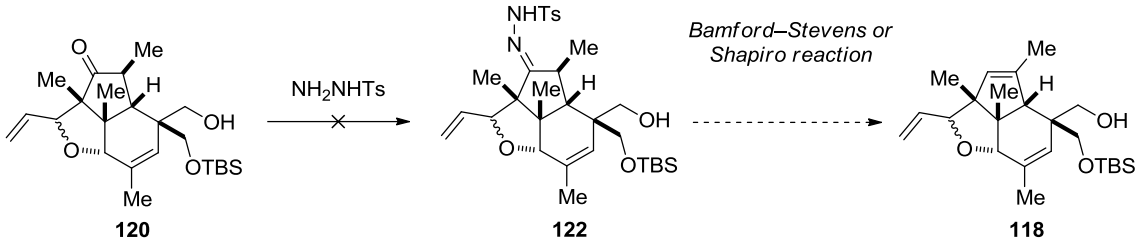
The reluctance of ketone **100** to be converted into carbonyl derivatives led to the investigation of single electron reduction reactions to effect the desired elimination. Although in such a scenario additional steps were necessary for the introduction of the required cyclopentene double bond, this approach seemed promising, as cleavage of the α-keto ether would bestow significant synthetic flexibility for the installation of this motif. Whereas treatment of **100** with aluminum amalgam in THF–EtOH gave only traces of elimination product **120** [116], exposure to freshly prepared samarium(II) iodide (2.0 equiv) in THF–MeOH resulted in efficient release of the primary alcohol. Intermediate **120** was oxidized to the corresponding aldehyde (DMP, 97%) [93], which was subjected to HORNER–WADSWORTH–EMMONS olefination to deliver α,β-unsaturated ester **121** in 92% yield as a single olefin isomer [117-120].



Scheme 33: Reagents and conditions: a) SmI_2 (2.0 equiv), THF−MeOH, RT, quant; b) DMP (1.25 equiv), CH_2Cl_2, 0 °C to RT, 97%; c) methyl diethylphosphonoacetate (5.0 equiv), NaH (5.0 equiv), THF, RT, 92%.

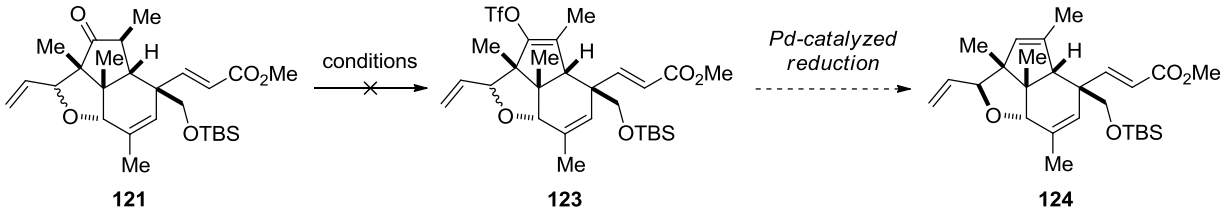
With a reliable sequence for installation of the enoate side chain established, the introduction of the cyclopentene unsaturation was next addressed (Scheme 34). Classical methods for the conversion of ketones to olefins are the BAMFORD–STEVENS or the SHAPIRO reaction, both of which involve the base-mediated decomposition of tosylhydrazones [121,

122]. Although many ketones can be readily transformed to the corresponding tosylhydrazones by reaction with tosylhydrazide, the formation of **122** from **120** failed. Similar to the attempted formation of hydrazone **117** (Scheme 32), the lack of reactivity of **120** can be attributed to steric reasons.



Scheme 34: Attempted formation of tosylhydrazone **122**.

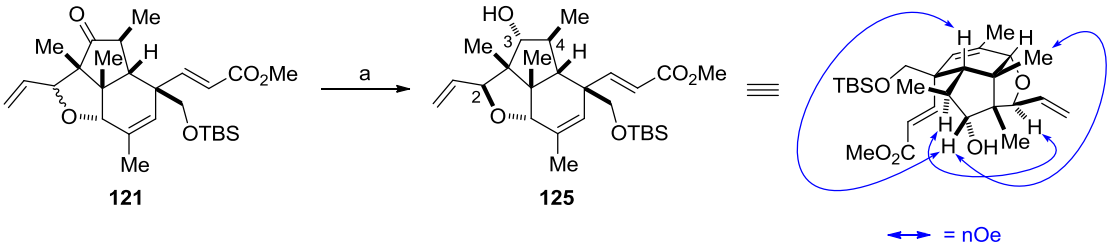
Enol triflates can be reduced to the parent olefins through palladium catalysis with a suitable hydride source, such as formic acid [123]. In order to test this reaction pathway, ketone **121** was treated with 2-NTf_2-pyridines in combination with various bases, such as KH, KHMDS or LDA [124]. Unfortunately, enol triflate **123** could not be obtained under these conditions.



Scheme 35: Attempted synthesis of enol triflate **123**.

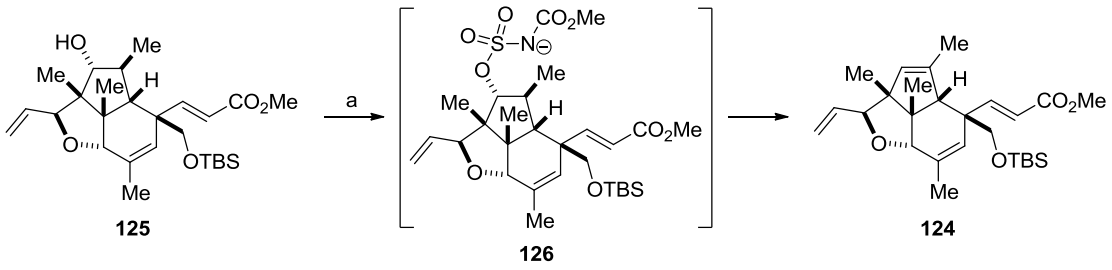
Another alternative to achieve the synthesis of **124** was reduction of ketone **121** to secondary alcohol **125**, followed by dehydration (Scheme 36). Treatment of **121** with sodium borohydride in methanol delivered **125**, but the reaction was sluggish and suffered from poor conversion (ca. 20%). Inspired by DU BOIS and HINMAN, who reported the chemoselective reduction of a sterically congested ketone in presence of an ester in the course of their total synthesis of (−)-tetrodotoxin [125], borane *tert*-butylamine complex was identified as reagent of choice for this functional group interconversion. Interestingly, ketone reduction in **121** furnished alcohol **125** in diastereoenriched form (d.r. = 9:1) due to a kinetic resolution of the initial isomer mixture (d.r. = 3.6:1). The relative configuration of **125** was determined by 2D NMR. These experiments revealed that in **124**, the relative stereochemistry at C(2) was opposite to that originally assigned for the natural product. Furthermore, it was found that the

C(3) hydroxyl group and the C(4) hydrogen atom were both oriented towards the concave face of the ring system.



Scheme 36: Reagents and conditions: a) $BH_3 \cdot t\text{-}BuNH_2$ (2.0 equiv), CH_2Cl_2, 40 °C, d.r. = 9:1, 88%.

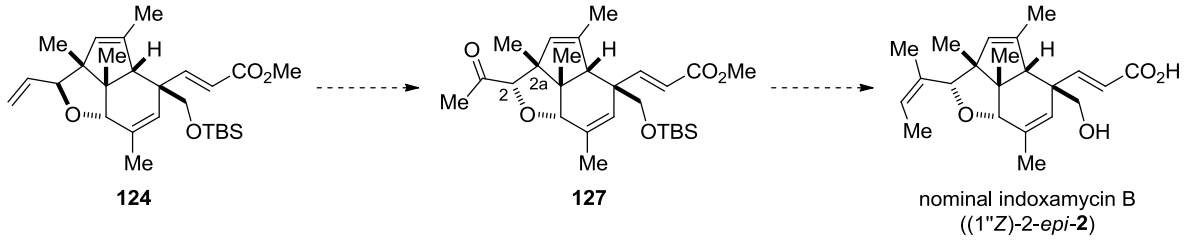
The configuration of **125** required a *syn*-elimination of the secondary alcohol to introduce the desired alkene. Although careful assessment of hand-held models indicated sufficient overlap of the σ(C−H) orbital with the antibonding σ*(C−O) orbital, mesylation of **125**, followed by treatment with DBU under forcing conditions either led to no reaction (benzene, 75 °C) or decomposition (DMF, 120 °C). Furthermore, the use of MARTIN sulfurane as a dehydrating reagent was unsuccessful [126]. Conversion of **125** to the corresponding xanthate proceeded uneventfully. However, attempted pyrolysis of the latter according to CHUGAEV met with failure [127, 128]. Eventually, it was found that olefin **124** could be delivered by dehydration with BURGESS' reagent [129, 130]. It is interesting to note that in this reaction a temperature of 60 °C was necessary to generate intermediate sulfamate ester **126**. The protonated form of **126** could be isolated,[6] if the temperature was not further increased. Heating to 90 °C induced *syn*-elimination to furnish **124**. After extensive optimization, if was found that the reaction worked best at 110 °C, resulting in a moderate yield of 44%.



Scheme 37: Reagents and conditions: a) Burgess' reagent (2.0 equiv), toluene, 110 °C, 44%.

[6] As judeged by ^{1}H NMR and HRMS.

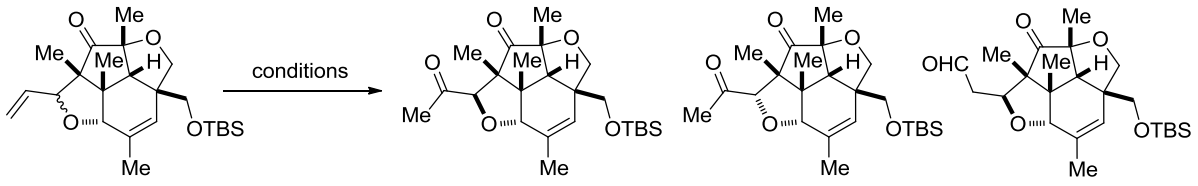
With the enoate residue in place, installation of the trisubstituted alkene side chain was next investigated. It was envisioned that the conversion of the terminal olefin in **124** to the corresponding methyl ketone **127** would not only set the stage for introduction of the (*Z*)-configured olefin, but also enable C(2) epimerization to arrive at the reported structure of indoxamycin B ((1"*Z*)-2-*epi*-**2**, Scheme 38).



Scheme 38: Synthetic plan for the completion of indoxamycin B (**2**).

The introduction of the trisubstituted olefin was studied with intermediate **100**, due to the limited amounts of **124** available. The first step in the planned sequence involved oxidation of the monosubstituted vinyl group to the corresponding methylketone (Table 4). A conventional method to effect this transformation is the WACKER oxidation, which originally had been developed in an industrial setting for the conversion of ethylene to acetaldehyde (WACKER–SMIDT process) [131, 132]. Later on, the scope of this reaction was extended to applications in complex molecule synthesis. Hence, terminal olefins nowadays can be regarded as synthetic equivalents for methyl ketones [133, 134]. However, the palladium-mediated oxidation of alkenes bearing heteroatom substituents in α-position is known to be problematic with respect to regioselectivity [135]. It was therefore no surprise that a standard WACKER oxidation of intermediate **100** gave exclusively aldehyde **130** (45% conversion, entry 1). Although the reason for this unusual behavior is not entirely understood, it is generally accepted that coordination of the nearby heteroatom to palladium plays a critical role. Moreover, the concentration of Cl^- ions in the reaction mixture and the oxidation state of copper were reported to have an influence on the outcome. In certain cases, the use of $CuCl_2$ instead of CuCl could even reverse the regioselectivity [135]. However, when the same experiment was repeated with $CuCl_2$, no reaction was observed (entry 2).

Table 4: Wacker-type oxidation of olefin **100** to the corresponding methylketone.

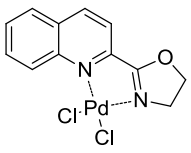


100 (d.r. = 3.2:1) **128** **129** **130**

Entry	Conditions	Product	Yield
1	$PdCl_2$ (1.0 equiv), CuCl (6.0 equiv), DMF−H_2O, O_2 atmosphere, RT	**130**	n.d.[a]
2	$PdCl_2$ (1.0 equiv), $CuCl_2$ (6.0 equiv), DMF−H_2O, O_2 atmosphere, 60 °C	-	n.r.
3	$Pd(quinox)Cl_2$ (0.3 equiv), $AqSbF_6$ (0.75 equiv), *t*-BuO_2H (18 equiv), CH_2Cl_2, 0 °C to RT	**129**	27%
4	$Hg(O_2CF_3)_2$ (1.2 equiv), MeOH, 0 °C to RT; then $PdCl_2$ (1.0 equiv),$CuCl_2$ (3.0 equiv), LiCl (2.0 equiv), 60 °C	**128/129 (3.3:1)**	64%

[a] 45% conversion.

SIGMAN and co-workers have developed a selective oxidation of terminal allylic alcohols and derivatives thereof to the corresponding methylketones using palladium complex **131** as catalyst precursor (Scheme 39) in combination with aqueous *t*-BuO_2H as stoichiometric oxidant [136-138]. Application of these conditions to substrate **100** gave a complex mixture of products, from which **129** was isolated as a single diastereomer in 27% yield (entry 3). Interestingly, **129** had the C(2) relative configuration that is opposite to the major diastereomer of **100**. It is reasonable to assume that this reaction was only productive with the minor diastereomer of **100**, whereas the major underwent decomposition.

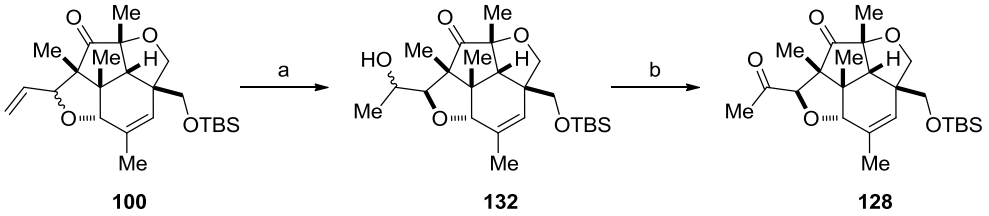


$Pd(quinox)Cl_2$ (**131**)

Scheme 39: Structure of catalyst-precursor **131**.

A well-established method to overcome regioselectivity problems in the WACKER oxidation of terminal olefins is oxymercuration, followed by transmetalation to palladium(II) and subsequent β-hydride elimination. Highly reactive mercury(II) trifluoroacetate was necessary to address the sterically congested olefin, as **100** turned out to be inert towards mercury(II) acetate. Transmetalation with palladium(II) chloride in presence of copper(II) chloride and lithium chloride in MeOH at 60 °C then furnished **128** and **129** as a 3.3:1

mixture of diastereomers in 64% combined yield (Table 4, entry 4). Although this protocol would have been capable to afford ample amounts of the desired methylketones, the use of stoichiometric amounts of mercury salts was highly undesirable.



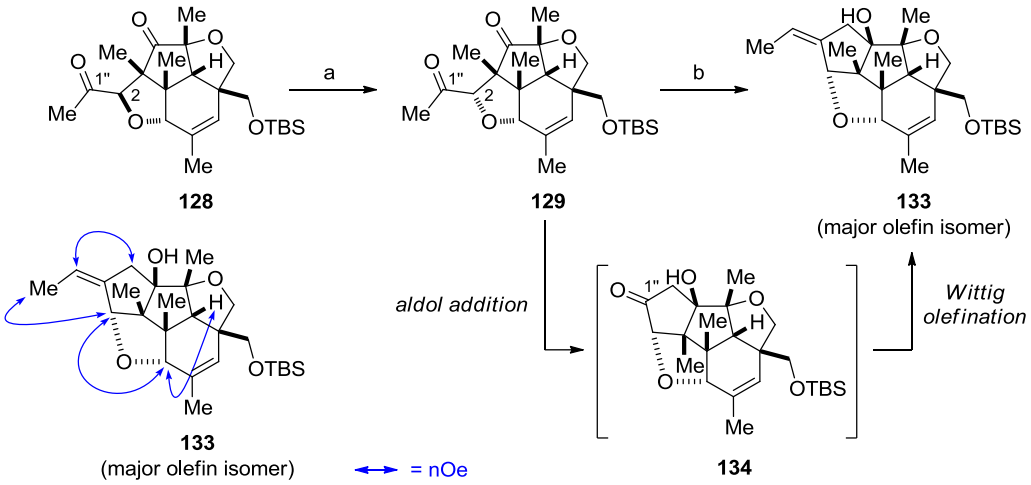
Scheme 40: Reagents and conditions: a) $Mn(dpm)_3$ (10 mol%), $PhSiH_3$ (2.5 equiv), O_2 atmosphere, EtOH, RT, d.r. = 1:1, 73%; b) DMP (1.5 equiv), CH_2Cl_2, 0 °C to RT, 72%.

In addition to direct oxidation, methylketones can also be derived from terminal alkenes *via* a two-step sequence involving MARKOVNIKOV hydration, followed by oxidation of the intermediate secondary alcohols. MUKAIYAMA and co-workers have developed a mild regioselective method for the formal hydration of alkenes, involving a cobalt- or manganese-catalyzed reduction-oxidation process [139-142]. Accordingly, reaction of **100** with phenylsilane and catalytic $Mn(dpm)_3$ (10 mol%) in EtOH under an atmosphere of oxygen furnished, after column chromatography, a 1:1 mixture of isomeric secondary alcohols **132** in 73% yield (Scheme 40) [143]. Oxidation with DESS-MARTIN periodinane gave **128** as a single diastereomer [93].

Diketone **128** was epimerized at C(2) by treatment with potassium carbonate in methanol to furnish **129** in 67% yield (Scheme 41). Stereoselective olefination of **129** was expected to be challenging, but encouraging precedence came from a report by STILL and co-workers, who described the (*Z*)-selective WITTIG reaction [144-148] of unstabilized ylides with α-alkoxy ketones under lithium-free conditions [149]. Although WITTIG olefination of aldehydes with unstabilized phosphonium ylides is a reliable process for the formation of (*Z*)-alkenes [150], reaction of ketones is often cumbersome, not only due to poor (*E*)/(*Z*)-selectivities, but also because sterically hindered substrates are prone to undergo enolization, rather than the desired olefination. An elegant solution for this problem is the use of *tert*-butoxide bases, as the presence of *tert*-butanol in the reaction mixture can reverse enolate formation and regenerate the ylide. Potassium *tert*-butoxide was therefore chosen as a base for WITTIG olefination of **129** with ethyltriphenylphosphonium bromide. Surprisingly, pentacyclic product **133** was obtained as a 8:1 mixture of olefin isomers.[7] The formation of

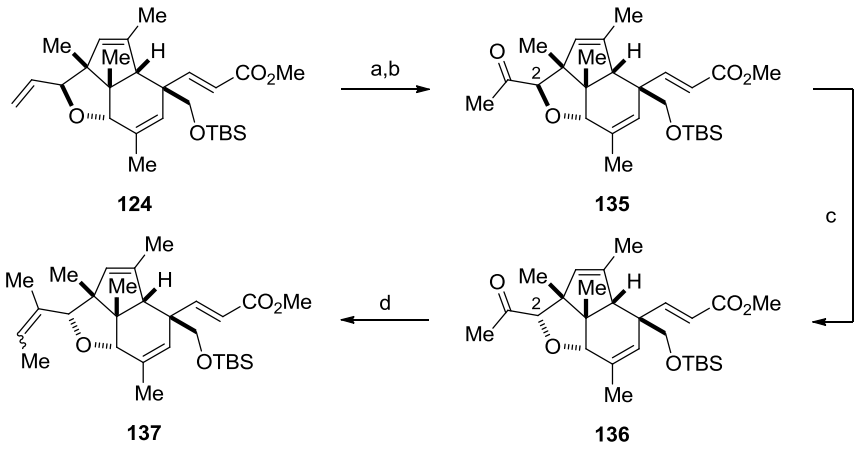
[7] The structure of **133** was determined by 2D NMR experiments, including NOESY to secure the relative configuration.

133 can be explained by enolization of the methyl ketone in **129**, followed by intramolecular aldol addition with the nearby cyclopentanone carbonyl. The resulting pentacyclic ketone then underwent olefination with excess or regenerated WITTIG reagent to furnish **133**.



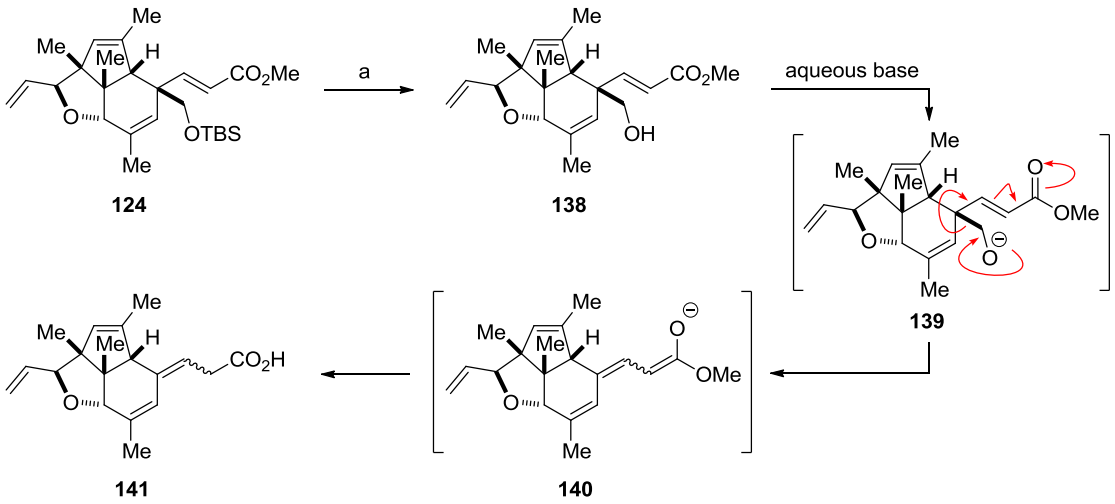
Scheme 41: Reagents and conditions: a) K_2CO_3 (10 equiv), MeOH, RT, 67%; b) Ph_3PEtBr (12 equiv), *t*-BuOK (10 equiv), THF, RT, 37%.

The close proximity of the carbonyl functionalities in diketone **129** was interfering with the olefination at C(1'). It seemed therefore reasonable to defer the installation of the trisubstituted alkene side chain to a later stage of the synthesis, where the cyclopentene unsaturation was already installed. Accordingly, tricyclic intermediate **124** was subjected to the hydration-oxidation protocol disclosed earlier to provide methyl ketone **135** as a single diastereomer at C(2) (42% over 2 steps, Scheme 42). Equilibration of **135** with its C(2) epimer **136** under the conditions disclosed previously (K_2CO_3, MeOH) mainly led to decomposition. However, treatment of **135** with DBU (5.0 equiv) in toluene at 100 °C delivered a 6:1 mixture of diastereomers, favoring **136**. Separation by chromatography on silica gel furnished **136** in 58% yield. When ketone **136** was subjected to WITTIG olefination, a 1.6:1 mixture of olefin isomers **137** was obtained (70%), which could not be separated.



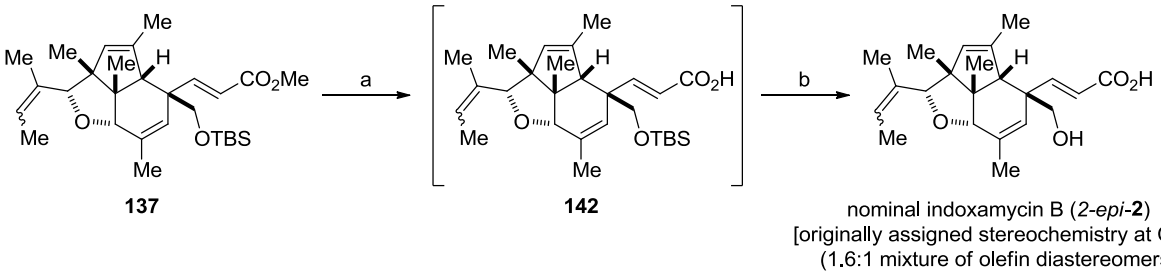
Scheme 42: Reagents and conditions: a) $Mn(dpm)_3$ (10 mol%), $PhSiH_3$ (2.5 equiv), O_2 atmosphere, EtOH, RT, d.r. = 1:1, 49%; b) DMP (2.0 equiv), CH_2Cl_2; 0 °C to RT, 85%; c) DBU (5.0 equiv), toluene, 100 °C, 58%; d) Ph_3PEtBr (6.0 equiv), KHMDS (5.0 equiv), THF−DMPU, 78 °C to 0 °C, 1:1.6 ratio of olefin isomers, 70%.

Intermediate **124** was selected as a test substrate to investigate protective group removal, which turned out to be nontrivial. Isolation and purification of carboxylic acids can be tedious, especially on small reaction scale. Hence, it was intended to cleave the TBS ether prior to hydrolysis of the methyl ester, as this order of operations would involve only one problematic purification step. In the event, reaction of **124** with *para*-toluenesulfonic acid monohydrate in methanol led to efficient release of the primary alcohol to furnish **138** in 80% yield (Scheme 43). Surprisingly, treatment of this intermediate with aqueous lithium hydroxide, to effect ester saponification, resulted in rapid decomposition. Careful analysis of the product mixture by ^1H NMR and HRMS revealed that alkoxide **139** presumably underwent a vinylogous retro-aldol reaction, leading to extinction of the quaternary carbon center bearing the primary hydroxyl group, to furnish **141** as a mixture of olefin isomers.



Scheme 43: Reagents and conditions: a) *p*-TsOH·H_2O (2.5 equiv), MeOH, RT, 80%.

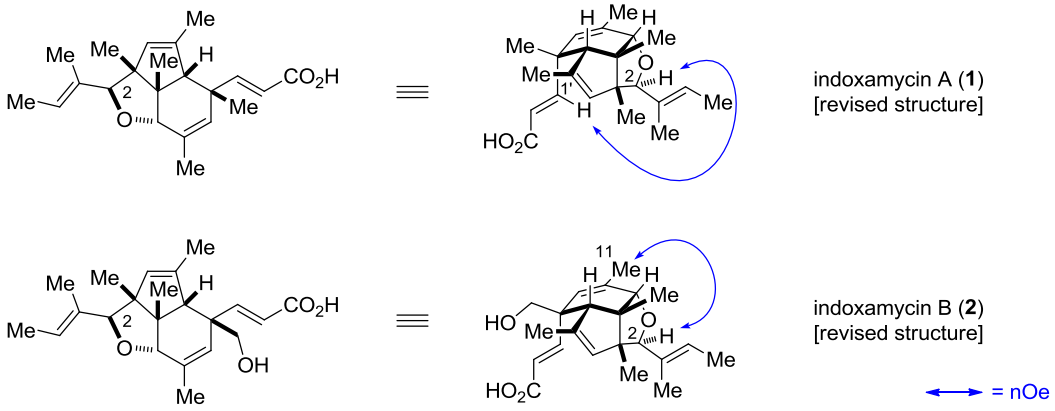
The unforeseen lability of indoxamycin B (**2**) and derivatives thereof towards basic reaction conditions required a revision of the deprotection tactic. After extensive experimentation, it was found that sequential removal of the protective groups could be achieved by ester saponification with aqueous lithium hydroxide, followed by addition of hydrochloric acid to attain removal of the silyl protective group (Scheme 44). Surprisingly, when this reaction sequence was applied to **137**, neither of the olefin isomers obtained displayed spectral properties (^{1}H and ^{13}C NMR) that matched those reported for the natural product.



Scheme 44: Reagents and conditions: a) LiOH (18 equiv), THF−MeOH−H_2O, RT; b) HCl (aq, 1.0 M, 53 equiv), RT, 73%.

1.3.3.4 Stereochemical Reassignment and Synthesis of Indoxamycin B

The discrepancy of the spectra for the synthetic material with those reported for the natural product required a careful re-examination of the published NMR data [13]. Analysis of the NOESY spectra reported for indoxamycins A (**1**) and B (**2**) revealed that in indoxamycin A (**1**), the C(2) proton exhibited a nuclear OVERHAUSER correlation with the proton at C(1') (Scheme 45). Furthermore, in indoxamycin B (**2**) a correlation was found between the protons at C(2) and C(11). These observations led to the conclusion that the relative configuration at C(2) had been misassigned by the isolation chemists. Moreover, there was considerable ambiguity regarding the geometry of the trisubstituted olefin side chain.

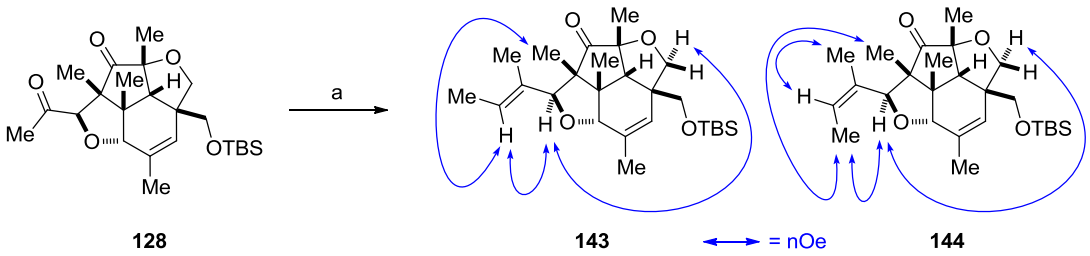


Scheme 45: Stereochemical reassignment of indoxamycins A (**1**) and B (**2**).

The results discussed above highlight that even in the days of modern structure elucidation, with an arsenal of advanced spectroscopic methods available, total synthesis still plays an important role in the assignment of structures to highly complex molecules. This can be underlined by the fact that in the period of 2010−2013, four structural revisions have been reported from our laboratory alone [151-154]. A comprehensive review about misassigned natural products and the role of chemical synthesis in modern structure elucidation has been provided by NICOLAOU and SNYDER [155].

In order to secure the configuration of the trisubstituted olefin, revised structures (1''*E*/*Z*)-**2** were targeted for synthesis. In contrast to the route previously discussed for the conversion of **100** to nominal indoxamycin B ((1"*Z*)-2-*epi*-**2**), it seemed prudent to install the C(2) side chain prior to manipulation of the cyclopentane ring, to compare the spectroscopic properties of olefins **143** and **144** with those of the natural product (Scheme 46). Accordingly, methylketone **128** was subjected to WITTIG olefination to afford a 1.9:1 mixture of **143** and **144**, with the double bond configuration unambiguously secured by NMR spectroscopic experiments (NOESY) of the separated isomers.[8] The similarity of the ^{1}H NMR resonances of diastereomer **143** to those reported for natural indoxamycin B led to the hypothesis that the natural product had an (*E*)-configuration, as shown in Scheme 45.

[8] Stereochemical assignment of **143** and **144** using *J*-based configuration analysis (HETLOC, HECADE and refocused HMBC) failed.



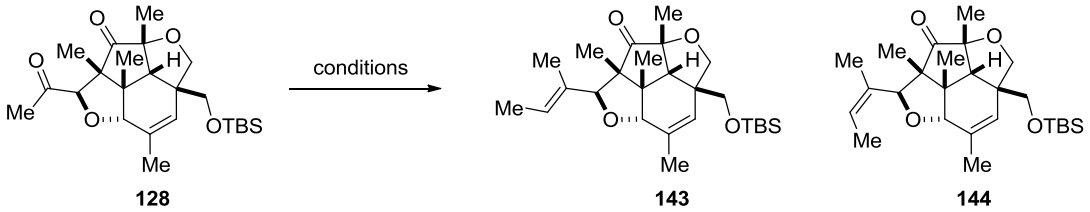
128 143 144

Scheme 46: Olefination of **128** and configurational assignment of alkene products. Reagents and conditions: a) Ph_3PEtBr (6.0 equiv), *t*-BuOK (5.0 equiv), THF, 0 °C, (*E*)/(*Z*) = 1.9:1.

Preferential formation of (*E*)-isomer **143** in the WITTIG reaction was surprising, as the (*Z*)-isomer was expected on the basis of the substrates examined by STILL and co-workers [149]. Therefore, an extensive investigation into the olefination of **128** was undertaken, as summarized in Table 5. The use of potassium *tert*-butoxide as a base, as initially conceived for ketone substrates (*vide supra*), resulted in a slight preference for **143** ((*E*)/(*Z*) = 1.9:1, entry 1). Addition of HMPA as a co-solvent and a decreased reaction temperature (−40 °C) only had a subtle effect on this result ((*E*)/(*Z*) = 2.3:1, entry 2). The conditions disclosed by the STILL laboratory (Ph_3PEtBr, KHMDS, THF−HMPA, −78 °C to RT) proved capricious and yielded **143** and **144** in a wide range of selectivities (e.g. entries 3 and 4). The preference for the formation of (*E*)-olefin **143** in the lithium salt-free WITTIG reaction with an unstabilized ylide leaves room for speculation. The presence of a bishomoallylic ketone in **143** and **144** may be responsible for the observed outcome. On the other hand, the good (*E*)-selectivity in the WITTIG olefination with *n*-BuLi as a base ((*E*)/(*Z*) = 8:1, entry 5) is in agreement with the generally observed trend.

The modified JULIA olefination is a reliable method for the stereoselective one-step conversion of aldehydes and ketones to the corresponding alkenes [156]. Encouraged by literature precedence for (*E*)-selective olefination of ketones [157, 158], the required benzothiazol-2-yl and 1-phenyl-1*H*-tetrazol-5-ly sulfones were prepared and tested in the reaction of **128** [159]. Although the olefination proceeded in excellent yields using LiHMDS or NaHMDS as a base, (*Z*)-isomer **144** was obtained as the major product (entries 6−8).

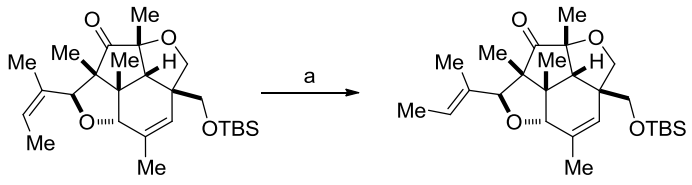
Table 5: Olefination of **128**.



128 **143** **144**

Entry	Conditions	143:144	Yield
1	Ph_3PEtBr (6.0 equiv), *t*-BuOK (5.0 equiv), THF, 0 °C	1.9:1	n.d.
2	Ph_3PEtBr (6.0 equiv), *t*-BuOK (5.0 equiv), THF−HMPA, −40 °C	2.3:1	39%
3	Ph_3PEtBr (14 equiv), KHMDS (12 equiv), THF−HMPA, −78 °C to 0 °C	2.5:1	n.d.
4	Ph_3PEtBr (15 equiv), KHMDS (12 equiv), THF−HMPA, −40 °C	7:1	41%
5	Ph_3PEtBr (6.0 equiv), *n*-BuLi (5.0 equiv), toluene, −78 °C to RT	8:1	88%
6	2-(ethylsulfonyl)benzo[*d*]thiazole (5.0 equiv), LiHMDS (5.0 equiv), THF, −78 °C to RT	1:3.3	n.d.
7	5-(ethylsulfonyl)-1-phenyl-1H-tetrazole (5.0 equiv), NaHMDS (5.0 equiv), THF, −78 °C to −30 °C	1:3.6	97%
8	5-(ethylsulfonyl)-1-phenyl-1H-tetrazole (4.0 equiv), LiHMDS (3.0 equiv), THF, −78 °C to −30 °C	1:3.2	92%

Although the WITTIG reaction of **128** with *n*-BuLi as a base granted access to **143** in good yield and selectivity, significant amounts of **144** were produced over the course of the olefination studies. In order to advance this material further in the synthesis, an isomerization protocol for the conversion into **143** was required. Initial attempts to effect this transformation with $Pd(PhCN)_2Cl_2$ were unsuccessful. However, photoisomerization with substoichiometric diphenyl disulfide (0.25 equiv) delivered **143** in 7.6:1 (*E*)/(*Z*)-isomer ratio (Scheme 47) [160-162].

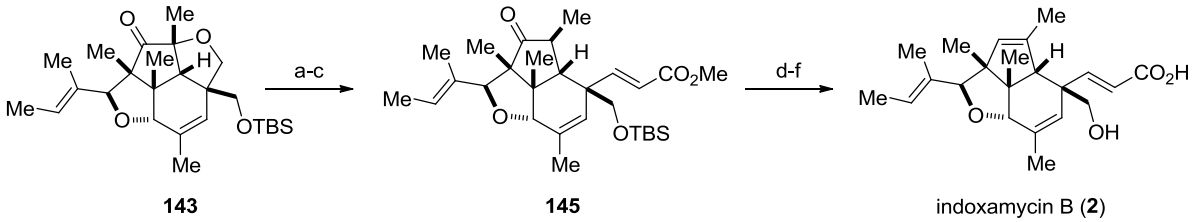


144
(*E*)/(*Z*) = 1:3.1

143
(*E*)/(*Z*) = 7.6:1

Scheme 47: Isomerization of olefin **144**. Reagents and conditions: a) $(PhS)_2$ (0.25 equiv), hν, cyclohexane−dioxane, RT, 89%.

With a reliable sequence for the installation of the trisubstituted olefin residue secured, completion of the synthesis of indoxamycin B (**2**) was addressed. Tetracyclic intermediate **143** was advanced by employing the sequence previously described for the conversion of **100** to **121** (*vide supra*), which involved samarium(II)-mediated α-keto ether cleavage, DMP oxidation and HWE olefination to furnish **145** in 98% yield over three steps (Scheme 48). Introduction of the cyclopentene unsaturation proceeded in 55% yield over two steps, following the analogous reduction–dehydration protocol. Sequential deprotection then completed the total synthesis of indoxamycin B (**2**, 96% yield).



Scheme 48: Reagents and conditions: a) SmI_2 (2.0 equiv), THF−MeOH, RT, 99%; b) DMP (1.25 equiv), CH_2Cl_2, 0 °C to RT, quant; c) methyl diethylphosphonoacetate (5.0 equiv), NaH (5.0 equiv), THF, RT, 99%; d) BH_3·*t*-BuNH_2 (2.0 equiv), CH_2Cl_2, 40 °C, 79%; e) Burgess' reagent (2.0 equiv), PhMe, 110 °C, 69%; f) LiOH (10 equiv), then HCl (aq, 1.0 M, 29 equiv), THF−MeOH−H_2O, RT, 96%.

The ^{1}H and ^{13}C NMR spectra for synthetic indoxamycin B (**2**) obtained from purification by column chromatography, or by preparative TLC (as previously described for the natural product), did not match precisely with those reported in the literature. However, the observed differences in the resonances were minor (^{1}H: $|\Delta\delta| \leq 0.33$ ppm; ^{13}C: $|\Delta\delta| \leq 6.5$ ppm). A systematic analysis of the spectral deviations revealed that the mismatch had to be associated with the enoate portion (Figure 2). Deeper insight came from the ^{13}C NMR chemical shift of the carboxylic acid carbon atom (C(3')). According to the literature, α,β-unsaturated carboxylic acids are expected to resonate at 172 ppm, whereas the corresponding carboxylates should display a chemical shift of 175 ppm [163]. The fact that C(3') in natural indoxamycin exhibited a chemical shift 175.7 ppm led to the conclusion that the natural product had been characterized as the carboxylate, and not as the free carboxylic acid.

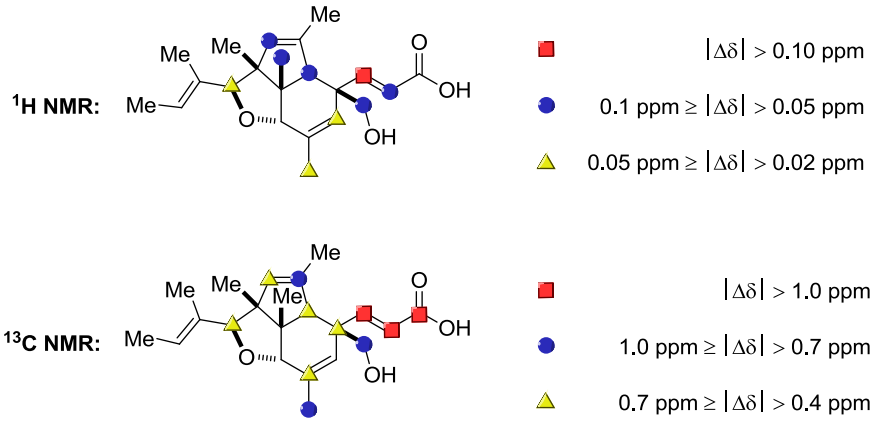
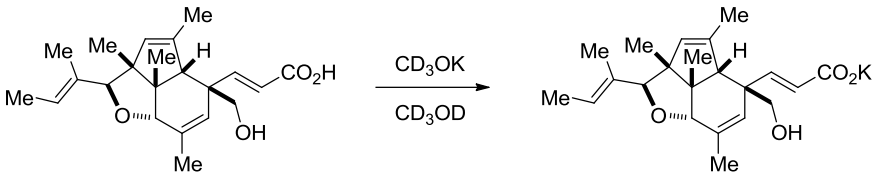


Figure 2: Systematic analysis of chemical shift deviations in synthetic indoxamycin B (**2**).

In order to test this hypothesis, an experiment was devised in which a solution of synthetic indoxamycin B in methanol-D_4 was titrated against potassium methoxide-D_3. Figure 3 shows the change in the olefinic region of the ^{1}H NMR spectrum over the course of incremental addition of potassium methoxide-D_3. It can be seen that the chemical shift of the proton in β-position of the carboxylic acid was particularly sensitive to the pH of the solution. Upon addition of just 1.0 equiv of base, a new set of signals in the ^{1}H and ^{13}C NMR spectra was obtained that was in full accordance with the data reported for the natural product.



indoxamycin B (**2**) indoxamycin B potassium salt (**146**)

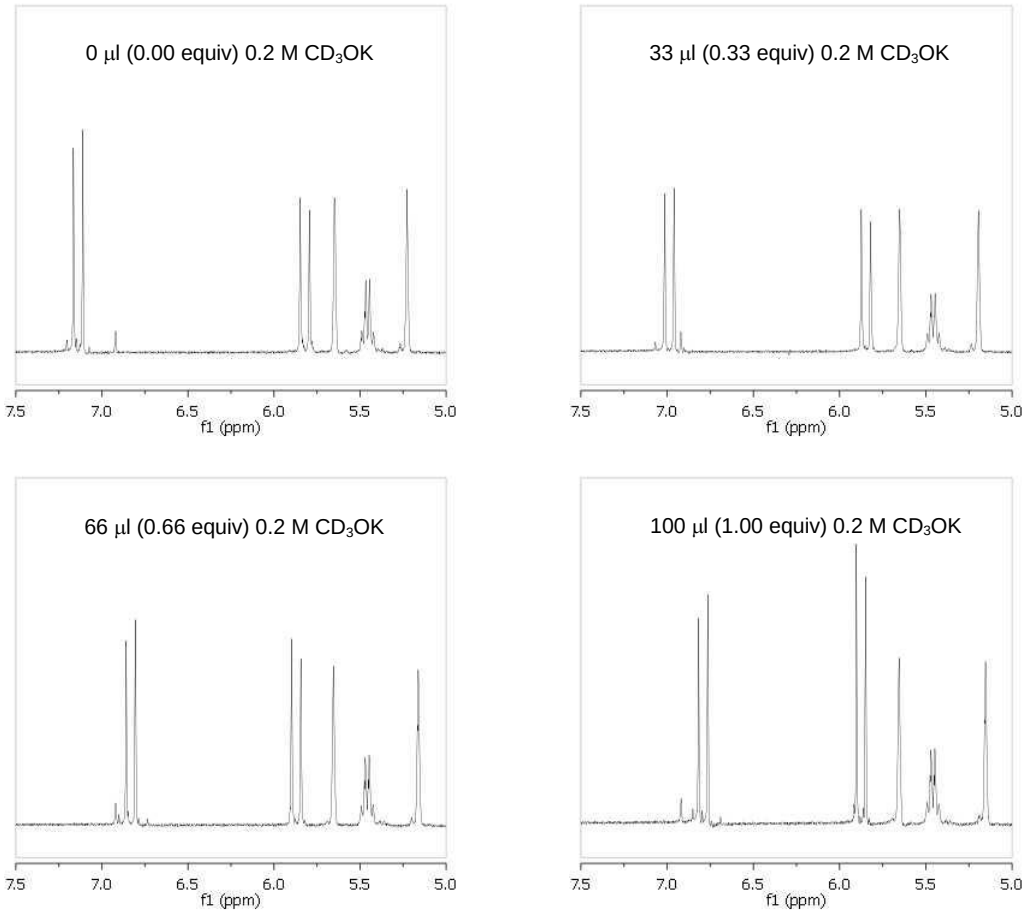


Figure 3: ^{1}H NMR titration of synthetic indoxamycin B.

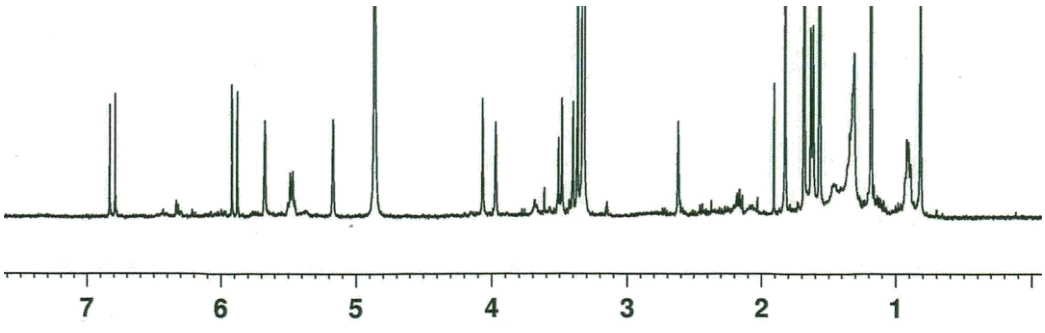


Figure 4: ^{1}H NMR spectrum of natural indoxamycin B [13].

Table 6: ^{1}H and ^{13}C NMR spectroscopic data for indoxamycin B (**2**).

Atom Nr.	^{1}H NMR Chemical Shifts (δ) Natural Indoxamycin B	^{1}H NMR Chemical Shifts (δ) Synthetic Indoxamycin B	Δδ	^{1}H NMR Chemical Shifts (δ) Synthetic Indoxamycin B Potassium Salt	Δδ
1	-	-	-	-	-
2	3.97 (s)	4.00 (s)	0.03	3.98 (s)	0.01
2a	-	-	-	-	-
3	5.17 (s)	5.23 (s)	0.06	5.18 (s)	0.01
4	-	-	-	-	-
4a	2.62 (s)	2.55 (s)	–0.07	2.62 (s)	0.00
5	-	-	-	-	-
6	5.68 (s)	5.65 (s)	–0.03	5.68 (s)	0.00
7	-	-	-	-	-
7a	4.07 (s)	4.07 (s)	0.00	4.07 (s)	0.00
7b	-	-	-	-	-
8	0.82 (s)	0.83 (s)	0.01	0.82 (s)	0.01
9	1.69 (s)	1.69 (s)	0.00	1.69 (s)	0.00
10	3.37, 3.50 (d, ^{2}J = 10.8 Hz)	3.46, 3.56 (d, ^{2}J = 10.8 Hz)	0.09, 0.06	3.39, 3.50 (d, ^{2}J = 11.0 Hz)	0.02, 0.00
11	1.83 (s)	1.86 (s)	0.03	1.83 (s)	0.00
12	1.19 (s)	1.12 (s)	–0.07	1.19 (s)	0.00
1'	6.81 (d, ^{3}J = 16.1 Hz)	7.14 (d, ^{3}J = 16.1 Hz)	0.33	6.81 (d, ^{3}J = 16.1 Hz)	0.00
2'	5.90 (d, ^{3}J = 16.1 Hz)	5.83 (d, ^{3}J = 16.1 Hz)	–0.07	5.90 (d, ^{3}J = 16.1 Hz)	0.00
3'	-	-	-	-	-
1''	-	-	-	-	-
2''	5.48 (q, ^{3}J = 6.7 Hz)	5.46 (q, ^{3}J = 6.8 Hz)	–0.02	5.48 (q, ^{3}J = 6.8 Hz)	0.00
3''	1.63 (d, ^{3}J = 6.7 Hz)	1.62 (d, ^{3}J = 6.8 Hz)	–0.01	1.63 (d, ^{3}J = 6.8 Hz)	0.00
4''	1.57 (s)	1.55 (s)	–0.02	1.57 (s)	0.00

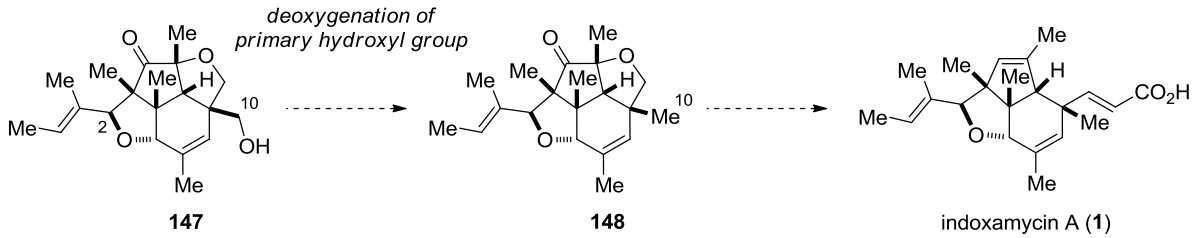
Atom Nr.	^{13}C NMR Chemical Shifts (δ) Natural Indoxamycin B	^{13}C NMR Chemical Shifts (δ) Synthetic Indoxamycin B	Δδ	^{13}C NMR Chemical Shifts (δ) Synthetic Indoxamycin B Potassium Salt	Δδ
1	-	-	-	-	-
2	91.2	91.86	0.7	91.17	0.0
2a	61.2	61.23	0.0	61.20	0.0
3	136.4	136.86	0.5	136.39	0.0
4	140.1	139.09	–1.0	140.08	0.0
4a	58.7	59.16	0.5	58.65	0.0
5	61.2	48.97	–12.2	48.56	–12.6[9]
6	128.1	127.97	-0.1	128.05	0.0
7	138.6	138.94	0.3	138.56	0.0
7a	84.4	84.77	0.4	84.80	0.4
7b	57.8	58.02	0.2	57.78	0.0
8	17.2	17.22	0.0	17.51	0.3
9	19.2	18.81	–0.3	19.21	0.0
10	70.1	69.29	–0.8	70.11	0.0
11	20.7	21.59	0.9	20.74	0.0
12	26.2	25.95	–0.2	26.20	0.0
1'	148.5	154.97	6.5	148.45	0.0
2'	128.0	121.93	–6.1	128.12	0.1
3'	175.7	170.14	–5.6	175.71	0.0
1''	138.6	134.86	–3.7	134.80	–3.8[10]
2''	120.0	120.36	0.4	120.01	0.0
3''	12.9	12.89	0.0	12.88	0.0
4''	14.3	14.27	0.0	14.29	0.0

[9] This signal was misassigned in the isolation literature. The HMBC data for synthetic indoxamycin B potassium salt indicate that the respecting carbon atom resonates at δ 48.6 ppm and is therefore hidden by the solvent signal.

[10] This signal was misassigned in the isolation literature. Although a strong ^{13}C resonance at δ 134.8 ppm can be found in the spectrum provided by Sato *et al.*, the chemical shift was not reported in the corresponding peak table. We attribute this to a typographical error.

1.3.3.5 Synthesis of Indoxamycin A

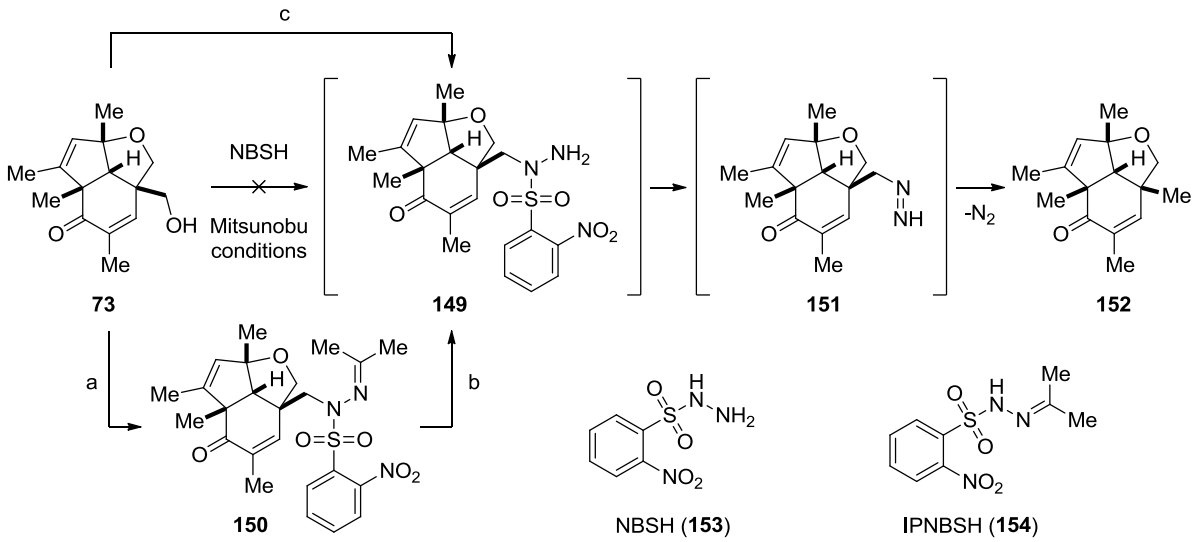
The synthesis of indoxamycin A (**1**) required an adaptation of the route, which would allow for deoxygenation of the primary alcohol at C(10) (Scheme 49). In order to deviate as little as possible from the sequence previously disclosed for indoxamycin B (**2**), a strategy was conceived, which encompassed late stage removal of the hydroxyl group. Primary neopentylic alcohols are known to be potentially problematic in deoxygenation events. Careful choice of the substrate for scission of the C−O bond was therefore essential. Tetracyclic alcohol **147** seemed promising, as the tetrahydrofuran ring with the desired stereochemistry at C(2) and the trisubstituted alkene side chain were already installed. Furthermore, the portion of the molecule flanking the primary hydroxyl group was largely devoid of functionality, which minimized the risk of unforeseen side reactions.



Scheme 49: Deoxygenation approach to indoxamycin A (**1**).

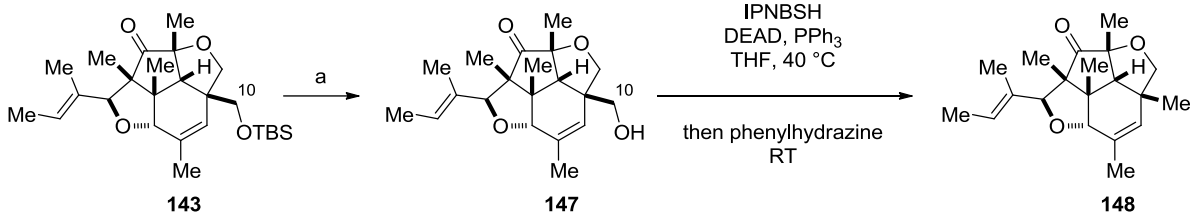
Alcohol **73** was chosen as a model substrate to study the removal of the C(10) hydroxyl group due to the limited amounts of **147** available (Scheme 50). Whereas the vast majority of methods for deoxygenation of alcohols involve multiple chemical transformations, the protocol by MYERS, MOVASSAGHI and ZHENG is remarkable as it allows for reductive removal of primary hydroxyl groups in a single step [164]. Treatment of **73** with *o*-nitrobenzenesulfonylhydrazine (NBSH, **153**) under MITSUNOBU conditions [165-167] led to recovery of starting material. The failure of this reaction to generate required intermediate **149** can be attributed to the low stability of **153**, which upon warming in solution (–15 °C or above) underwent decomposition, rather than MITSUNOBU displacement at the neopentylic position in **73**. In order to extend the scope of this reaction to sterically congested substrates, the more stable reagent IPNBSH (**154**) was developed by MOVASSAGHI *et al.* [168]. Gratifyingly, treatment of **73** with IPNBSH (**154**) at 40 °C led to the desired substitution reaction, furnishing **150** in 71% yield. Intermediate **150** was a stable species that required cleavage of the hydrazone to generate tosylhydrazide **149**. The latter then spontaneously underwent sulfinic acid elimination to form alkyl diazene **151**, which suffered nitrogen extrusion to yield the deoxygenated product **152**. It has been shown in mechanistic studies

that the decomposition of alkyl diazene intermediates proceeds through a free-radical process [169]. As a consequence, rapid hydrolysis of hydrazone **150** was desirable in order to generate high concentrations of diazene **151**, facilitating the reaction. Among the reagents tested for hydrazone cleavage (trifluoroethanol–H_2O, 1,1-dimethylamine, anhydrous hydrazine, methylhydrazine–*p*-TsOH·H_2O, 4-hydrazinyl-benzenesulfonic acid−pyridine), exposure of **150** to phenylhydrazine in THF at room temperature proved best for initiation of this process. The reaction was also realized in one pot through the addition of phenylhydrazine to the reaction mixture after MITSUNOBU displacement. Due to the high volatility of **152** no yields could be determined for the deoxygenation in model studies.



Scheme 50: Reagents and conditions: a) IPNBSH (**154**, 3.0 equiv), PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, 40 °C, 71%; b) phenylhydrazine, THF, RT; c) IPNBSH (**154**, 3.0 equiv), PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, 40 °C; then phenylhydrazine, RT.

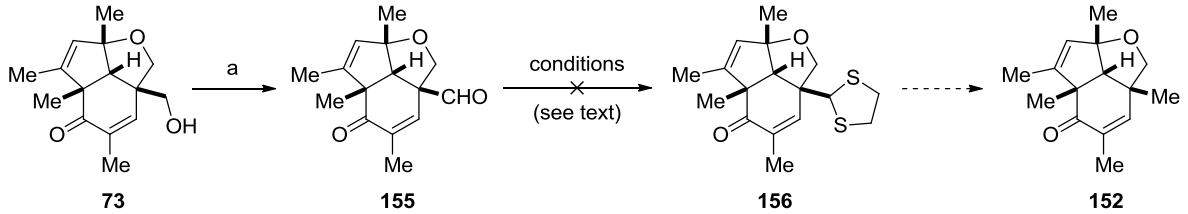
In order to test the one-pot deoxygenation with the fully elaborated system, the TBS protective group in **143** was cleaved with *para*-toluenesulfonic acid monohydrate (10 mol%) in methanol to furnish **147** in 89% yield (Scheme 51). When **147** was subjected to the described conditions, **148** could be detected in the crude product mixture by ^{1}H NMR. However, as chromatographic purification failed to deliver pure product in this reaction, alternative methods were considered for the deoxygenation.



143 147 148

Scheme 51: Reagents and conditions: a) *p*-TsOH·H_2O (10 mol%), MeOH, RT, 89%.

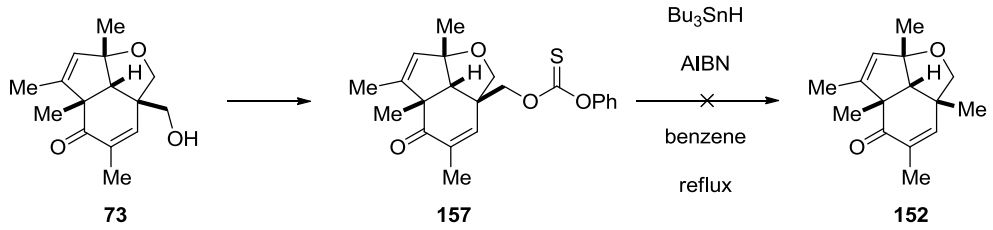
Scission of primary hydroxyl groups can also be effected through oxidation to the corresponding aldehyde followed by thioacetal formation and reductive desulfurization. Going back to the model system, alcohol **73** was oxidized with DESS−MARTIN periodinane to furnish aldehyde **155** in 69% yield (Scheme 52) [93]. Generation of dithiolane **156** was attempted with ethane-1,2-dithiol and catalytic borontrifluoride diethyletherate or with $Me_2AlSCH_2CH_2SAlMe_2$, as described by SNYDER and COREY [170]. Unfortunately, both sets of conditions proved unsuccessful.



73 155 156 152

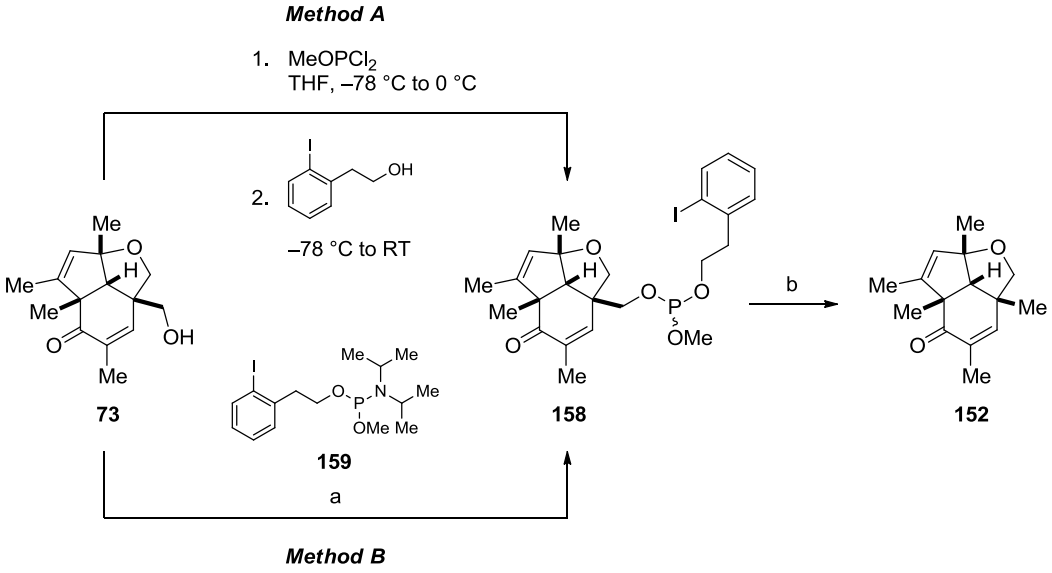
Scheme 52: Reagents and conditions: a) DMP (1.50 equiv), CH_2Cl_2, 0 °C to RT, 69%.

One of the most widely employed methods for deoxygenation of alcohols in complex molecule synthesis is the radical reaction of *O*-thiocarbonyl derivatives, known as the BARTON–MCCOMBIE radical deoxygenation [171-174]. Whereas this protocol is highly effective for the removal of secondary alcohols, its application to primary hydroxyl groups has met with mixed results, presumably due to the highly unstable nature of the primary radical intermediates generated. In order to test this method, alcohol **73** was converted to thionocarbonate **157**, which was subjected to radical deoxygenation conditions using tributyltin hydride and AIBN as radical initiator (Scheme 53). We were disappointed to find that the desired deoxygenation product **152** could not be obtained in this reaction.



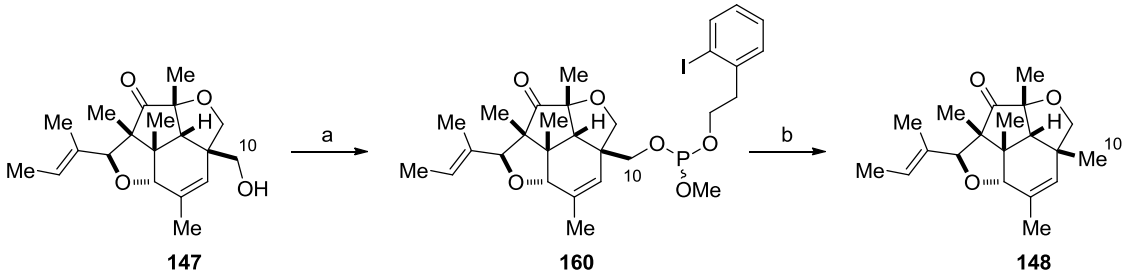
Scheme 53: Attempted BARTON–MCCOMBIE deoxygenation of alcohol **73**.

ZHANG and KOREEDA have disclosed a radical-based deoxygenation protocol for sterically hindered hydroxyl groups through phosphite derivatives [175]. Following this procedure, alcohol **73** was converted to phosphite **158** by successive treatment with dichloro(methoxy)phosphine and 2-(2-iodophenyl)ethanol (Method A, Scheme 54). Radical deoxygenation of **158** with Bu_3SnH and AIBN in benzene at 80 °C then delivered **152**. Although this deoxygenation was successful, the original protocol was not amenable to small quantities of advanced synthetic intermediates as chromatographic purification of **158** was required, which was hampered by the instability of the phosphite products. An improved version of this reaction was developed by MILLER and co-workers who disclosed an organocatalytic phosphoramidite transfer reaction (Method B, Scheme 54) [176]. Accordingly, alcohol **73** was coupled with **159** using catalytic phenyltetrazole (0.25 equiv), in presence of phenyl isocyanate as an amine scavenger, to furnish phosphite **158** as a 1:1 mixture of diastereomers at phosphorus. Radical deoxygenation of the crude reaction mixture under standard conditions then delivered **152**.



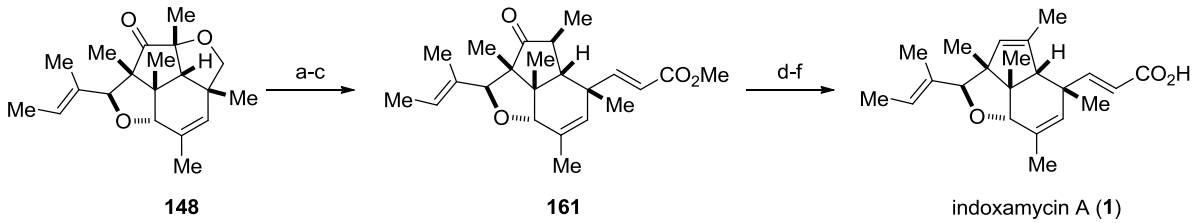
Scheme 54: Reagents and conditions: a) 2-iodophenethyl methyl diisopropylphosphoramidite (**159**, 2.5 equiv), phenyl isocyanate (2.5 equiv), phenyltetrazole (0.25 equiv), CH_2Cl_2, RT, 40%; b) Bu_3SnH (10 equiv), AIBN (5.0 equiv), benzene, 80 °C.

Encouraged by this result, alcohol **147** was subjected to catalytic phosphoramidite transfer to furnish phosphite **160** as an inconsequential 1:1 mixture of epimers. Radical deoxygenation of the crude reaction mixture afforded the C(10) deoxygenated product **148** in 63% yield over 2 steps.



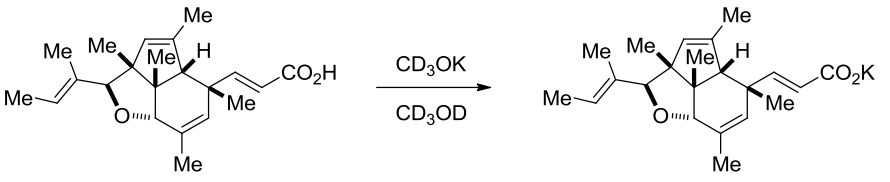
Scheme 55: Reagents and conditions: a) 2-iodophenethyl methyl diisopropylphosphoramidite (**159**, 1.2 equiv), phenyl isocyanate (1.2 equiv), phenyltetrazole (5.0 mol%), CH_2Cl_2, RT, d.r. = 1:1; b) tributyltin hydride (10 equiv), AIBN (5.0 equiv), benzene, 80 °C, 63% over 2 steps.

Intermediate **148** was advanced in the synthesis through the sequence previously described for the elaboration of indoxamycin B (**2**) (Scheme 48). Cleavage of the α-keto ether and installation of the enoate side chain proceeded in 81% yield to furnish **161** (Scheme 56). The cyclopentene unsaturation was introduced by the same reduction–dehydration protocol in 62% yield over two steps. Finally, saponification of the methyl ester furnished indoxamycin A (**1**) in 96% yield. In analogy to indoxamycin B (**2**), the spectral data for synthetic indoxamycin A (**1**) (^{1}H and ^{13}C NMR) deviated from those published in the literature.



Scheme 56: Reagents and conditions: a) SmI_2 (2.0 equiv), THF−MeOH, RT, 93%; b) DMP (1.5 equiv), CH_2Cl_2, 0 °C to RT, 93%; c) methyl diethylphosphonoacetate (5.0 equiv), NaH (5.0 equiv), THF, RT, 94%; d) BH_3·*t*-$BuNH_2$ (2.0 equiv), CH_2Cl_2, 40 °C, 99%; e) Burgess' reagent (2.0 equiv), PhMe, 110 °C, 63%; f) LiOH (8.4 equiv), THF−MeOH−H_2O, RT, 96%.

Incremental addition of potassium methoxide-D_3 to a solution of synthetic indoxamycin A (**1**) in methanol-D_4 resulted in a change of the ^{1}H and ^{13}C NMR chemical shifts (Figure 5). Interestingly, a set of signals in full accordance with the data reported for the natural product was obtained upon addition of 0.67 equiv of base. Consequently, natural indoxamycin A has been characterized by the isolation chemists as a 1:2 mixture of free carboxylic acid **1** and carboxylate **162**.



indoxamycin A (**1**) indoxamycin A potassium salt (**162**)

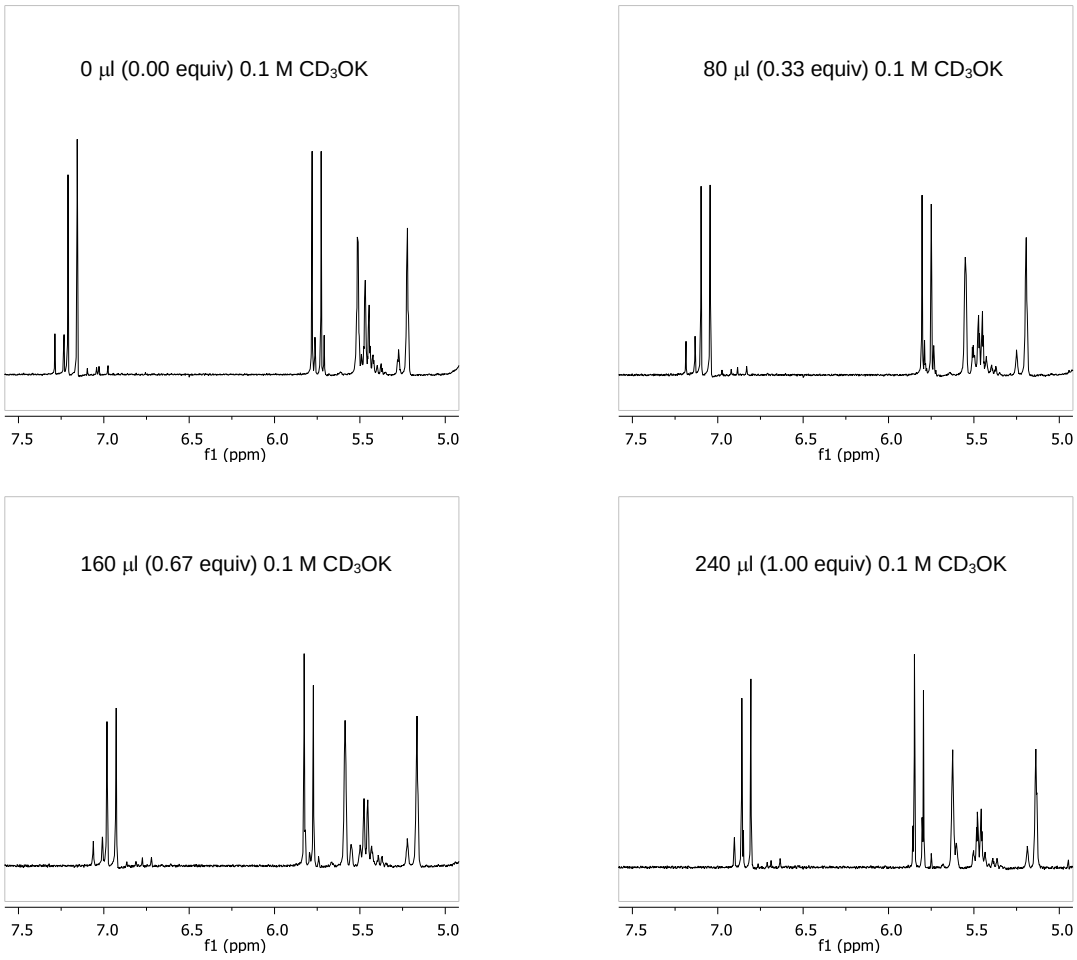


Figure 5: ^{1}H NMR titration of synthetic indoxamycin A.

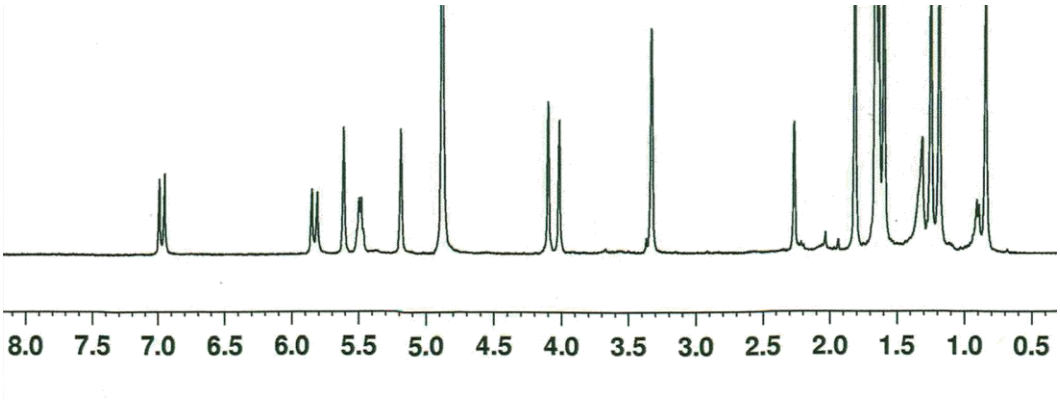


Figure 6: ^{1}H NMR spectrum of natural indoxamycin A [13].

Table 7: ^{1}H and ^{13}C NMR spectroscopic data for indoxamycin A.

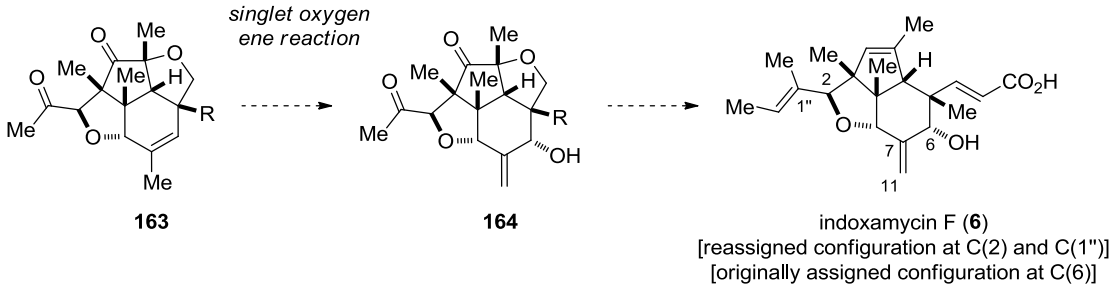
Atom No	^{1}H NMR Chemical Shifts (δ) Natural Indoxamycin A	^{1}H NMR Chemical Shifts (δ) Synthetic Indoxamycin A	Δδ	^{1}H NMR Chemical Shifts (δ) Synthetic Indoxamycin A Potassium Salt	Δδ
1	-	-	-	-	-
2	4.02 (s)	4.08 (s)	0.06	4.02 (s)	0.00
2a	-	-	-	-	-
3	5.19 (s)	5.23 (s)	0.04	5.19 (s)	0.00
4	-	-	-	-	-
4a	2.27 (s)	2.21 (s)	–0.06	2.27 (s)	0.00
5	-	-	-	-	-
6	5.61 (s)	5.52 (s)	–0.09	5.61 (s)	0.02
7	-	-	-	-	-
7a	4.10 (s)	4.10 (s)	0.00	4.10 (s)	0.00
7b	-	-	-	-	-
8	0.84 (s)	0.85 (s)	0.01	0.84 (s)	0.00
9	1.66 (s)	1.66 (s)	0.00	1.66 (s)	0.00
10	1.25 (s)	1.28 (s)	0.03	1.25 (s)	0.00
11	1.81 (s)	1.84 (s)	0.03	1.81 (s)	0.00
12	1.19 (s)	1.11 (s)	–0.08	1.18 (s)	–0.01
1'	6.97 (d, ^{3}J = 15.9 Hz)	7.19 (d, ^{3}J = 16.0 Hz)	0.22	6.98 (d, ^{3}J = 16.0 Hz)	0.01
2'	5.83 (d, ^{3}J = 15.9 Hz)	5.76 (d, ^{3}J = 16.0 Hz)	–0.07	5.83 (d, ^{3}J = 16.0 Hz)	0.00
3'	-	-	-	-	-
1"	-	-	-	-	-
2"	5.49 (q, ^{3}J = 6.3 Hz)	5.46 (q, ^{3}J = 6.8 Hz)	–0.03	5.49 (q, ^{3}J = 6.8 Hz)	0.00
3"	1.64 (d, ^{3}J = 6.3 Hz)	1.63 (d, ^{3}J = 6.8 Hz)	–0.01	1.64 (d, ^{3}J = 6.8 Hz)	0.00
4"	1.59 (s)	1.58 (s)	–0.01	1.59 (s)	0.00

Atom No	^{13}C NMR Chemical Shifts (δ) Natural Indoxamycin A	^{13}C NMR Chemical Shifts (δ) Synthetic Indoxamycin A	Δδ	^{13}C NMR Chemical Shifts (δ) Synthetic Indoxamycin A Potassium Salt	Δδ
1	-	-	-	-	-
2	92.1	92.79	0.7	92.10	0.0
2a	61.2	61.28	0.1	61.22	0.0
3	136.9	137.31	0.4	136.95	0.1
4	139.6	138.78	–0.8	139.61	0.0
4a	65.9	66.37	0.5	65.88	0.0
5	42.3	42.73	0.4	42.30	0.0
6	131.5	131.49	0.0	131.48	0.0
7	136.7	137.16	0.5	136.75	0.1
7a	85.1	85.11	0.0	85.07	0.0
7b	58.1	58.32	0.2	58.08	0.0
8	17.7	17.52	–0.2	17.74	0.0
9	19.0	18.59	–0.4	19.02	0.0
10	30.2	29.88	–0.3	30.20	0.0
11	20.7	21.62	–0.1	20.74	0.0
12	26.6	26.31	–0.3	26.63	0.0
1'	153.7	157.83	4.1	153.87	0.2
2'	123.7	119.15	–4.5	123.31	–0.4
3'	174.2	170.38	–3.8	173.94	–0.3
1"	135.2	135.38	0.2	135.19	0.0
2"	120.3	120.61	0.3	120.36	0.1
3"	12.9	12.92	0.0	12.91	0.0
4"	14.4	14.36	0.0	14.35	0.0

1.3.3.6 Studies Towards Indoxamycin F

The third structure that was targeted for total synthesis was indoxamycin F (**6**) (Scheme 57). In contrast to other members of this natural product family, which contain a cyclohexene ring, **6** is distinguished by a cyclohexane system with an exocyclic double bond at C(7) and an allylic alcohol at C(6). Careful re-examination of the spectral data published for natural indoxamycin F [13] called the original assignment of the relative stereochemistry at C(6) into question. Therefore, indoxamycin F (**6**) was not only an attractive target due to the synthetic challenge, but also because of the question regarding its relative configuration.

The synthetic plan for preparation of indoxamycin F (**6**) was based on the route previously disclosed for indoxamycins A (**1**) and B (**2**). It was envisioned that an intermediate of type **163** might be amenable to a singlet oxygen ene reaction, which, after reduction of the intermediate peroxide, would lead to allylic alcohol **164**. With the desired structural motif installed, **164** could be advanced to the putative structure of indoxamycin F (**6**), allowing for unambiguous stereochemical assignment. If required, inversion of the stereocenter at C(6) would enable the synthesis of the corresponding epimer.

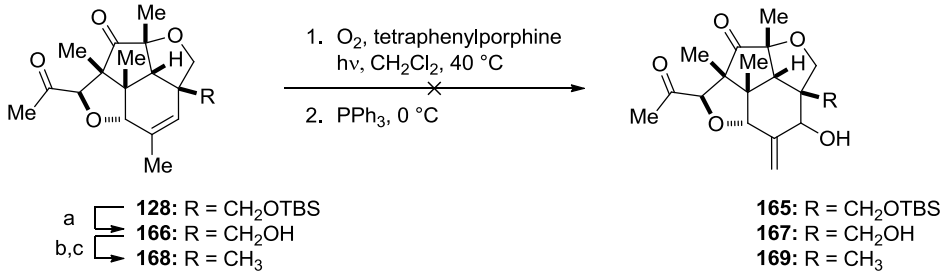


Scheme 57: Synthetic plan for indoxamycin F (**6**) exploiting a singlet oxygen ene reaction.

Synthetic investigations towards indoxamycin F (**6**) commenced with the attempted singlet oxygen ene reaction of intermediate **128** (Scheme 58). Singlet oxygen ($^1O_2$) refers to molecular oxygen in the first exited electronic state ($^1\Delta_g$), which lies 22.4 kcal mol^{-1} above the triplet ground state [177].[11] The highly electrophilic oxidant has to be prepared either *in situ* or immediately prior to use. Methods for the generation of singlet oxygen include dye-sensitized photoexcitation of triplet oxygen ($^3O_2$) [178-180], decomposition of phosphite ozonides [181], decomposition of transannular peroxides [182] and reaction of hydrogen peroxide with sodium hypochlorite [183-185].

[11] The second excited singlet state ($^1\Sigma_g^+$) has an energy of 37 kcal mol^{-1} relative to the ground state and a very short life time in solution (10^{-12} s), due to rapid spin-allowed relaxation to the longer-lived (10^{-3}–10^{-6} s) first excited singlet. Hence, $^1O_2$ in the $^1\Delta_g$ state can be regarded as the reactive species for the oxidation of organic compounds.

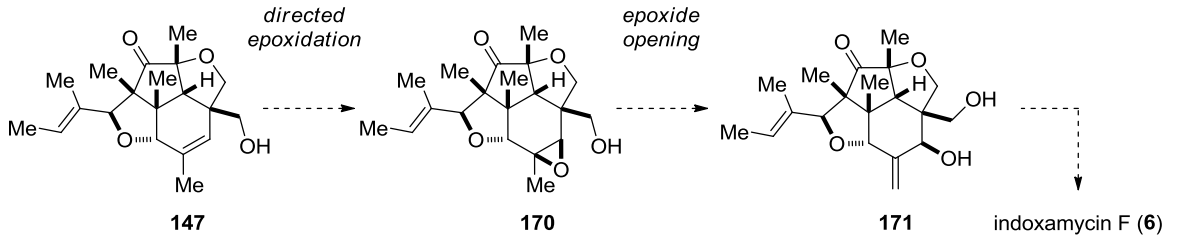
Using the first method, a solution of **128** in dichloromethane containing tetraphenylporphyrin as a sensitizer was irradiated with a 500 W tungsten halogen lamp while bubbling $^3O_2$ through it (Scheme 58). Surprisingly, no transformation of **128** occurred, even after prolonged reaction times (3 h).[12] Mechanistic studies have shown that the formal ene reaction of nonconjugated olefins with $^1O_2$ is not a pericyclic reaction but rather a stepwise process, in which hydrogen bond donors can have a directing effect [186]. It was therefore reasoned that the primary hydroxyl group, which was masked in **128** as a TBS ether, could facilitate the reaction. To this end, **128** was deprotected under standard conditions to furnish alcohol **166** in quantitative yield, which was subjected to the same $^1O_2$ ene conditions. Disappointingly, **166** turned out to be unreactive in this experiment, even when the solvent was changed to CCl_4, in which $^1O_2$ has a prolonged lifetime ($2.6\cdot10^{-2}$ s vs. $9.1\cdot10^{-5}$ s) [187]. The inertness of the cyclohexene olefin towards $^1O_2$ can be attributed to sterical hindrance and electronic deactivation by the nearby allylic ether. In order to reduce the steric congestion, alcohol **166** was deoxygenated, as previously described in the synthesis of indoxamycin A (**1**), to deliver **168** (66% over 2 steps). Subjecting **168** to $^1O_2$ led to recovery of starting material.



Scheme 58: Reagents and conditions: a) *p*-TsOH·H_2O (0.25 equiv), MeOH, RT, quant; b) 2-iodophenethyl methyl diisopropylphosphoramidite (**159**, 1.5 equiv), phenyl isocyanate (1.5 equiv), phenyltetrazole (10 mol%), CH_2Cl_2, RT, d.r. = 1:1; c) tributyltin hydride (20 equiv), AIBN (10 equiv), benzene, 80 °C, 66% over 2 steps.

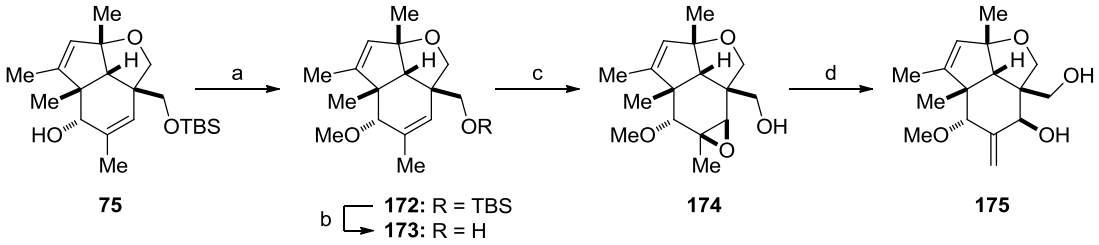
The failure to install the required functional group pattern through a singlet oxygen ene reaction required a revision of the synthetic plan. An alternative route was considered, which involved directed epoxidation of intermediate **147**, followed by isomerization of oxirane **170** to generate the allylic alcohol present in **171** (Scheme 59). Diol **171** could then be advanced to indoxamycin F (**6**).

[12] The reaction of α-pinene under identical conditions led, after reduction of the intermediate peroxide with PPh_3, to efficient formation of α-pineneoxide.



Scheme 59: Revised synthetic approach to indoxamycin F (**6**).

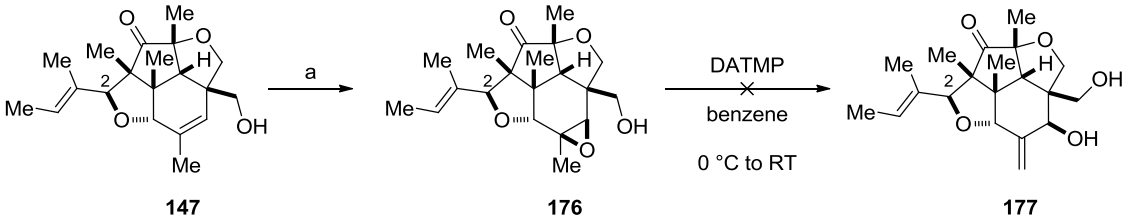
Intermediate **75** was converted into a test substrate for the epoxide isomerization reaction due to the restricted quantities of **147** available (Scheme 60). The secondary alcohol in **75** was transformed to methyl ether **172** (74%) and the TBS protective group was subsequently cleaved to yield primary alcohol **173** (96%). Vanadium-catalyzed epoxidation then delivered **174** in 83% yield [90]. The production of allylic alcohols from epoxides can be achieved by treatment with strong bases. Among them, lithium diethylamide has found particularly wide application. However, the rather vigorous reaction conditions required (Et_2O, reflux) and the sometimes poor regioselectivity limit the substrate scope of this reaction [177]. Diethylaluminum 2,2,6,6-tetramethylpiperidine (DATMP) has been developed by YAMAMOTO and co-workers as a milder alternative that allows for the highly selective isomerization of epoxides [188]. In their studies, the YAMAMOTO laboratory observed that proton abstraction in trisubstituted oxiranes generally occurs on the alkyl group located on the same side as the hydrogen atom ("steric approach control"). Further encouraged by a recent report where DATMP was employed on a closely related system [189], we were delighted to find that treatment of **174** with an excess (4.0 equiv) of DATMP led to clean formation of **175**.



Scheme 60: Reagents and conditions: a) KH (1.5 equiv), THF, RT; then 18-crown-6 (2.0 equiv), MeI (5.0 equiv), 0 °C, 74%; b) *p*-TsOH·H_2O (0.5 equiv), MeOH, RT, 96%; c) $VO(acac)_2$ (5.0 mol%), *t*-BuO_2H (3.0 equiv), 4 Å molecular sieves (50 wt%), CH_2Cl_2, RT, 83%; d) 2,2,6,6-tetramethylpiperidine (5.0 equiv), *n*-BuLi (4.0 equiv), Et_2AlCl (4.0 equiv), benzene, 0 °C to RT, 83%.

In order to test this strategy with the fully elaborated system, bishomoallylic alcohol **147** was subjected to site-selective epoxidation to furnish **176** in 92% yield (Scheme 61). Unfortunately, treatment of oxirane **176** with DATMP, as previously described for **174**, led to

decomposition of the material. Additional attempts at the isomerization were made using LDA (Et_2O, RT), Al_2O_3 (toluene, 100 °C), SiO_2 (toluene, RT) and TMSI (MeCN, 0 °C). However, no **177** could be isolated in any of these cases. Although the reason for the failure of this reaction is speculative, it seems that the decomposition of **176** is caused by the trisubstituted olefin on C(2), which enables facile cleavage of the allylic ether bond.



Scheme 61: Reagents and conditions: a) $VO(acac)_2$ (10 mol%), *t*-BuO_2H (4.0 equiv), 4 Å molecular sieves (200 wt%), CH_2Cl_2, RT, 92%.

1.4 Cytotoxicity Assays

Indoxamycins A (**1**) and B (**2**) were tested for cytotoxic activity against HT-29 and A-549 tumor cells, at concentrations of 1, 10 and 100 μM in three independent experiments with each condition run in triplicate (n = 9).[13] Surprisingly, both compounds proved inactive in these assays. This result stands in stark contrast to the findings of the isolation group, who reported an IC_{50} value of 0.59 μM for indoxamycin A (**1**) in the HT-29 cell line [13, 14]. An explanation for this discrepancy currently seems to be elusive. However, given the fact that indoxamycin A (**1**) caused no significant growth inhibition at concentrations exceeding the IC_{50} value of the previous study by a factor of 170, the described biological activity of this natural product has to be questioned.

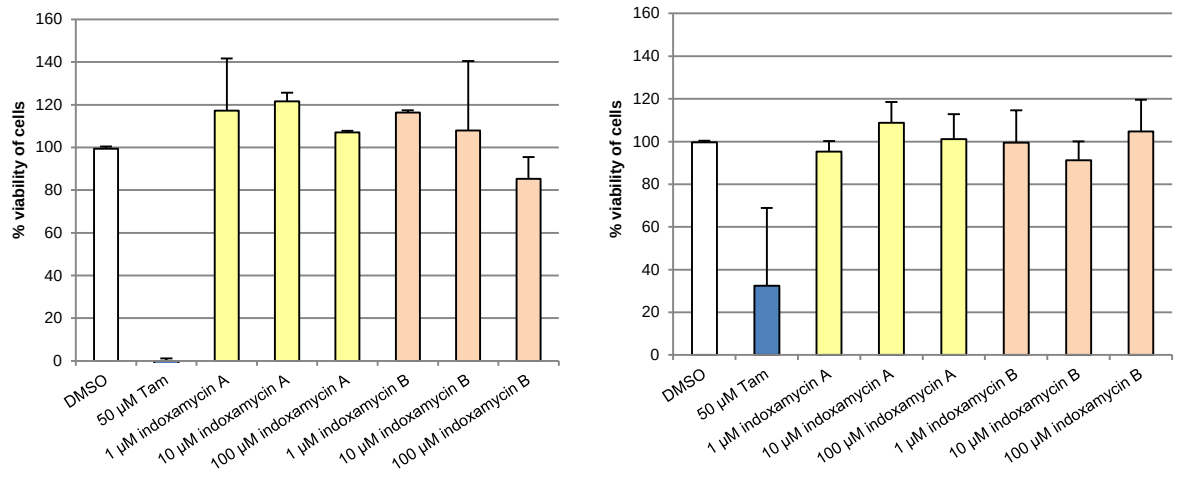


Figure 7: Cytotoxicity assays for indoxamycins A (**1**) and B (**2**) in HT-29 (left) and A-549 (right) cells. Shown are % viability of the cells following 24 hours of incubation with the indicated conditions relative to untreated cells. DMSO served as negative/solvent control while 50 μM Tam (tamoxifen) served as positive control for the assay. All data are shown as average ± standard deviation of three independent experiments each run in triplicate.

[13] Dr. SUSANNE WOLFRUM is gratefully acknowledged for conducting these experiments.

1.5 Conclusions and Outlook

In summary, we have described a divergent synthetic route to the polypropionate natural products indoxamycin A (**1**) and B (**2**). These studies have not only culminated in the first total synthesis of this unprecedented structural class, but also led to a configurational reassignment of the target molecules. The synthesis of indoxamycin B (**2**) proceeded in 22 linear steps and 1.3% overall yield, whereas indoxamycin A (**1**) was completed in 24 linear steps and 0.8% overall yield. Surprisingly, the reported cytotoxic activity of indoxamycin A (**1**) in the HT-29 tumor cell line could not be confirmed.

The synthetic strategy was based on the use of a symmetric cyclohexa-2,5-dienone precursor (**19**) and relied on a series of modern metal-catalyzed reactions to construct the tricyclic core framework. The salient features of the route include an efficient carboannulation sequence involving a Ti-mediated ketone crotylation and anionic oxy-Cope rearrangement, as well as a Pd-catalyzed oxidative cycloalkenylation reaction to rapidly access key dihydroindenone intermediate **16**. Moreover, a highly diastereoselective vanadium-catalyzed tandem reaction and a series of Au(I)-catalyzed transformations (SAUCY–MARBET rearrangement and allene hydroalkoxylation) allowed for the elaboration of the highly congested core framework. Tetracycle **100** proved to be a flexible key intermediate, which could be elaborated into the nominal structure of indoxamycin B ((1’’*Z*)-2-*epi*-**2**) by sequential installation of the alkene side chains. Following structural reassignment, the same compound also served as a precursor for the corrected structure of indoxamycin B (**2**).

The structural revision for indoxamycin B ((1’’*Z*)-2-*epi*-**2** to **2**) was shown to be valid for indoxamycin A ((1’’*Z*)-2-*epi*-**1** to **1**). To this end, an efficient deoxygenation protocol, taking advantage of a phosphite intermediate, was implemented into the synthesis, to effect cleavage of the primary neopentylic hydroxyl group in intermediate **147**. Furthermore, installation of the altered substitution pattern in the cyclohexane ring of indoxamycin F (**6**) has been successfully realized in a model system through regioselective isomerization of epoxide **174** to allylic alcohol **175**. Unfortunately, the execution of this reaction protocol on fully elaborated system **176** failed.

We propose that the stereochemical reassignment for indoxamycins A (**1**) and B (**2**) described herein is also valid for the other members of the natural product family. But the expansion of the described strategy to the synthesis of other indoxamycins awaits further experimentation. Future work might therefore involve the preparation of indoxamycins C−E (**3**−**5**) or the implementation of the described epoxide isomerization strategy to the total

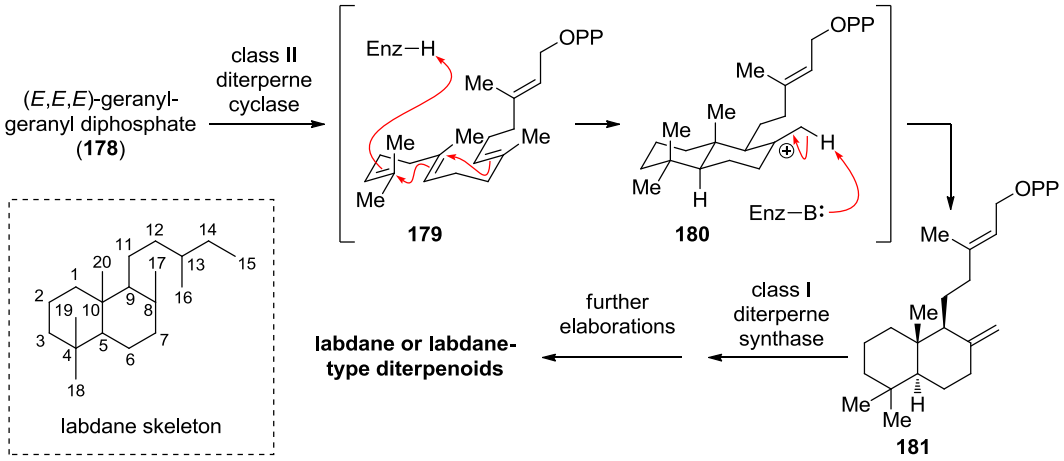
synthesis of indoxamycin F (**6**). The development of an asymmetric synthesis based on enantioselective ketone crotylation and stereospecific oxy-COPE rearrangement offers another opportunity for further research.

2 Total Synthesis of (+)-Asperolide C

2.1 Introduction

2.1.1 Labdane Diterpenoids

The labdane diterpenes encompass a structurally diverse class of natural products that are widely distributed in terrestrial and marine organisms, exhibiting a broad range of biological activities [190-192]. The carbon skeleton common to these compounds is biosynthetically assembled from (*E*,*E*,*E*)-geranylgeranyl diphosphate (**178**) through a cationic polyolefin cyclization pathway consistent with the stereochemical interpretation of the biogenetic isoprene rule, formulated more than half a century ago by ESCHENMOSER and STORK [193-195]. The currently accepted mechanism for the biogenesis of labdane-type diterpenoids involes protonation-initiated bicyclization of **178**, enabled by class II diterpene cyclases, to generate a labda-13-en-8-yl diphosphate cation [196]. Scheme 62 illustrates a common scenario, in which cation **180** is formed from linear precursor **178** through pro-chair-chair conformation **179**. This intermediate typically suffers deprotonation of the C(18) methyl group to produce copalyl pyrophosphate **181**, but can also undergo further cationic rearrangements to form labdane-like diterpenes. The intact allylic diphosphate in **181** is then engaged by class I diterpene synthases to induce other rearrangement and/or cyclization reactions. Moreover, the hydrocarbon backbone is normally tailored through a series of downstream biosynthetic modifications leading to the introduction of additional functionality.

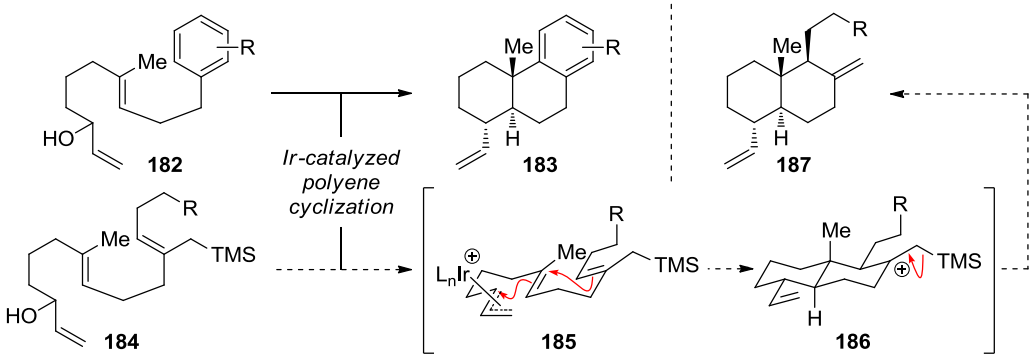


Scheme 62: Proposed biosynthesis of labdane or labdane-type diterpenoids.

The relative stereochemistry at the ring junction of the bicyclic core of these diterpenes is most often *trans*, with both enantioseries known. It is estimated that a significant number of polycyclic diterpenoids (~7000) arise from this initial cyclization event (e.g. **179** to **180**). In view of the interesting biological properties of the labdane diterpenoids, different procedures have been developed to access these natural products. Several labdane-type diterpenes are abundant in nature and commercially available. Isolation and chemical or biological manipulation is therefore a common preparative method for these compounds [192, 197]. Furthermore, this structural class has been target to numerous total syntheses [198].

2.1.2 Iridium-Catalyzed Polyene Cyclization

We became attracted to the labdane diterpenes in the course of the development of an iridium-catalyzed enantioselective polyene cyclization in our laboratories (Scheme 63) [199]. It was envisioned that this methodology, which was originally taking advantage of arenes to conclude the cationic cascade (e.g. **182** to **183**), could be expanded to a general entry into the labdane core structure by implementation of an allyl silane as terminating group. A linear precursor of type **184**, containing a branched allylic alcohol, would be subjected to polycyclization conditions to generate π-allyl iridium complex **185**. This reactive intermediate would then undergo a series of stereospecific cyclizations before being terminated by loss of a TMS group to form the exomethylene in **187**. The *trans*-decalin system thus obtained would be a valuable intermediate in the synthesis of various labdane or labdane-type diterpenoids.



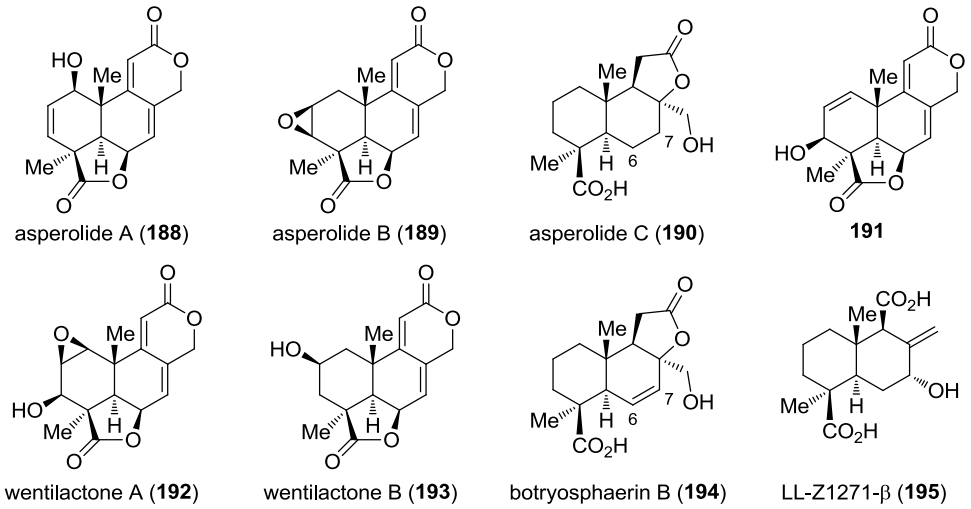
Scheme 63: Iridium-catalyzed enantioselective polyene cyclization.

A limited number of catalytic enantioselective polyene cyclizations have been reported in the literature, including BRØNSTED and LEWIS acid catalysis [200-202], organocatalysis [203-205], as well as transition metal catalyzed reactions [206, 207]. Interestingly, applications of these processes in natural product synthesis are very scarce. Prominent examples are the

pioneering studies by YAMAMOTO *et al.*, who achieved the synthesis of several diterpenes [208, 209].

2.1.3 Isolation of Asperolide C

Asperolide C (**190**) was isolated together with seven related tetranorlabdane diterpenoids from the culture extract of *Aspergillus wentii* EN-48, an entophytic fungus obtained from unidentified marine brown algae of the genus *Sargassum* (Scheme 64) [210]. Fungal identification of *A. wentii* was achieved by DNA amplification and sequencing of the ITS region [211]. It is worth noting that *A. wentii* is a common terrestrial species that is rarely found in marine environments.



Scheme 64: Structures of tetranorlabdane diterpenoids isolated from *Aspergillus wentii* EN-48.

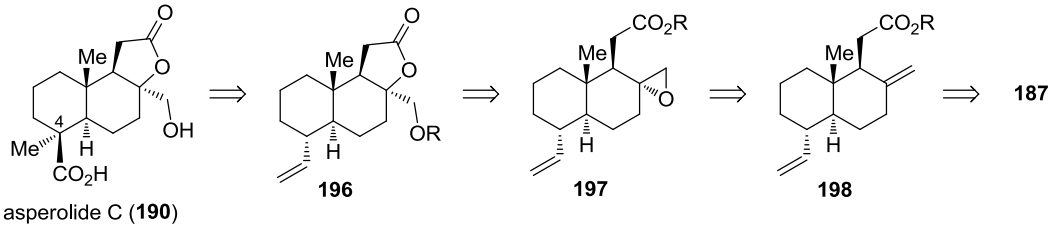
Asperolide C (**190**) was obtained as an inseparable 3:4 mixture with the known natural product botryosphaerin (**194**) that was previously isolated from the entophytic fungal strain *Botryosphaeria* sp. MHF [212]. The ^{13}C NMR signals of **190** and **194** were well separated, however, the ^{1}H NMR resonances could be resolved only in part. Furthermore, as a consequence of this mixture, it was impossible to acquire IR spectra or measure optical rotation. The structural assignment of **190** was assisted by 2D NMR experiments (COSY, HMQC, HMBC and NOESY) and guided by the similarity to **194**, which was found to be the C(6)−C(7) unsaturated analogue of **190**. This finding was corroborated by the HRMS data, which revealed a molecular formula of $C_{16}H_{24}O_5$ (HRMS (ESI): exact mass calculated for $C_{16}H_{24}O_5$ ($[M-H]^-$), 295.1545; found 295.1546), two hydrogen atoms more than in **194**. Based on the structural assignment for asperolides A (**188**) and B (**189**), it was assumed that asperolide C (**190**) had the absolute configuration as shown in Scheme 64.

2.2 Synthetic Planning

2.2.1 Retrosynthetic Analysis

The asperolides seemed to be ideal targets to study the thought synthetic entry into the labdane diterpenoids. The common structural feature rendering those natural products amenable for this strategy is the quaternary center at C(4) with a carboxylate pointing to the β-face of the ring system. It was envisioned that this motif could be conveniently accessed from the vinyl group generated in the iridium-catalyzed polyene cyclization through oxidative cleavage and enolate alkylation. Asperolide C (**190**) was chosen as the primary target, since the tricyclic scaffold of this tetranorlabdane diterpenoid would be rapidly accessible from a key-intermediate of type **187**.

The retrosynthesis of asperolide C is outlined in Scheme 65. As pointed out, target structure **190** presumably could be obtained from intermediate **196** through late-stage installation of the neopentylic carboxylate at C(4). γ-Lactone **196** was envisioned to be derived from epoxide **197** by cationic cyclization. It was reasoned that the oxirane in **197** could be installed through chemoselective epoxidation of the more electron-rich exomethylene group in **198**. This structure would be accessed from an intermediate of type **187**.



Scheme 65: Retrosynthetic analysis of asperolide C (**190**).

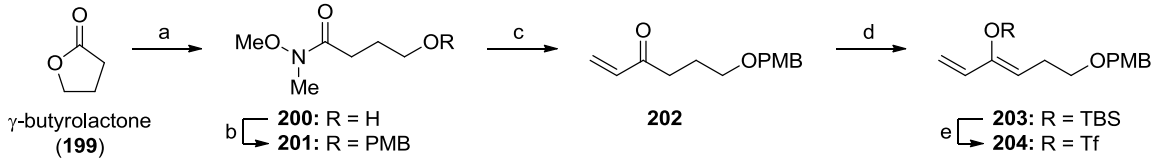
2.2.2 Conclusions

The proposed iridium-catalyzed enantioselective polyene cyclization employing an allyl silane as cascade terminating group would grant a general entry into the labdane or labdane-type diterpenoids. Asperolide C (**190**) poses an attractive target to study this synthetic strategy. The key-issues to be addressed are the preparation of a polyene precursor of type **184**, implementation of the iridium-catalyzed polycyclization, installation of the γ-lactone and construction of the quaternary center at C(4).

2.3 Results and Discussion

2.3.1 Synthesis of Polyene Precursor

The synthesis of asperolide C (**190**) commenced with LEWIS acid-mediated opening of commercially available γ-butyrolactone (**199**) to afford WEINREB amide **200**, which was used in the next step without further purification. The free hydroxyl group in **200** was protected as PMB ether by employing 4-methoxybenzyl trichloroacetimidate with catalytic camphorsulfonic acid (5 mol%) to furnish intermediate **201** in 70% yield over two steps [213, 214]. GRIGNARD addition of vinylmagnesium bromide proceeded best at 0 °C to afford enone **202** in 68% yield.[14] Initial attempts to directly transform vinyl ketone **202** to enol triflate **204** (LiHMDS, 2-NTf_2-5-chloropyridine, THF, −78 °C) proved unsuccessful. Therefore, a two-step protocol was examined, which involved conversion of **202** to the corresponding enol silane (**203**) followed by exchange of the silyl group with the required triflate. Formation of **203** under standard conditions was hampered by polymerization of **202**. However, the desired silyl enol ether **203** could be obtained in good yield (95%) and excellent (*Z*)-selectivity (d.r. > 95:5) when **202** was added to a pre-mixed solution of LiHMDS and *tert*-butyldimethylsilyl chloride in THF at −78 °C, using HMPA as a co-solvent.[15] Enol triflate **204** was obtained with complete retention of the olefin geometry in 96% yield by treatment of **203** with triflic fluoride generated *in situ*, following the procedure of COREY and co-workers [215]. The described route proved highly reliable and allowed for the efficient preparation of multigram quantities of **204**.

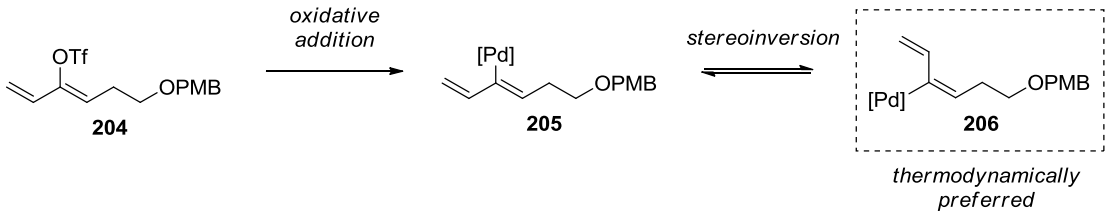


Scheme 66: Reagents and conditions: a) NHMe(OMe)·HCl (1.1 equiv), $AlMe_2Cl$ (1.1 equiv), CH_2Cl_2, 0 °C to RT, 83%; b) 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.6 equiv), CSA (5 mol%), CH_2Cl_2, 0 °C to RT, 81%; c) vinylmagnesium bromide (2.5 equiv), THF, 0 °C, 68 %; d) LiHMDS (1.25 equiv), TBSCl (1.25 equiv), THF−HMPA, d.r. > 95:5, 95%; e) $PhNTf_2$ (1.5 equiv), CsF (1.5 equiv), DME, RT, d.r. > 95:5, 96%.

Cross-coupling of enol triflate **204** to afford allyl silane **207** (Table 8) was expected to be difficult, as (*Z*)-dienylpalladium intermediates of type **205** are prone to undergo stereoinversion to the thermodynamically favored (*E*)-isomers (Scheme 67). NEGISHI and co-workers have shown in a systematic study that the widely accepted π−σ−π rearrangement

[14] Master's thesis Alberto Kravina.
[15] The addition of HMPA to this reaction was imperative, as the use of DMPU or the absence of co-solvent resulted in significantly diminished yields.

mechanism observed for ordinary allyl palladium derivatives [216] is not operational in this process [217]. However, a rationale for the isomerization has not been given thus far. In an extension of their work, the NEGISHI laboratory demonstrated that this stereoinversion can be suppressed through the use of sterically demanding ligands on palladium, such as *t*-Bu_3P [218-220] or *N*-heterocyclic carbenes [221-223] [224].



Scheme 67: Stereoinversion of dienylpalladium intermediate **205**.

Following the NEGISHI procedure, **204** was subjected to KUMADA [225-228] or NEGISHI [229-234] coupling using (*t*-$Bu_3P)_2Pd$ as a catalyst (2.5 mol%, entries 1 and 2, Table 8). Unfortunately, both reactions delivered (*E*)-isomer **208** as a major product (entries 1 and 2).[16] The double bond configuration of **207** and **208** was unambiguously assigned by 2D NMR experiments (NOESY).[17] Employment of *N*-heterocyclic carbene **213** and $Pd_2(dba)_3$ as catalyst precursors (5 mol% catalyst loading) had no beneficial influence on the reaction (entries 3 and 4). Furthermore, coupling with $Ni(acac)_2$ (10 mol%) as a catalyst resulted in a 9:1 mixture of olefin isomers, favoring undesired **208** (entry 5). A related NEGISHI cross-coupling has been reported by the FÜRSTNER group, who noted that the quality of the zinc organyl employed was pivotal to avoid isomerization [235]. It was speculated that the presence of magnesium(II) and zinc(II) salts in the reaction mixture might be responsible for olefin inversion.

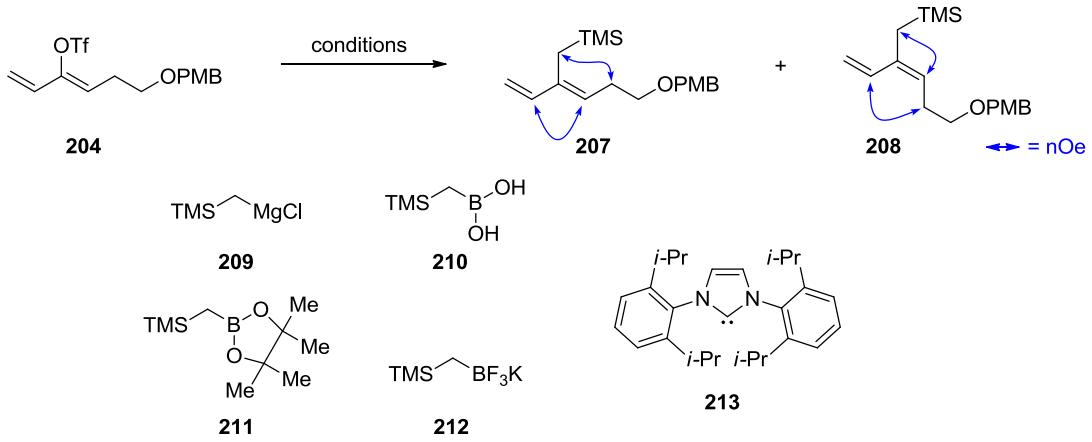
SUZUKI [236-238] coupling of **204** with known ((trimethylsilyl)methyl)boronic acid (**210**) was therefore examined [239]. The use of catalytic $Pd(PPh_3)_4$ (5 mol%) in combination with Na_2CO_3 as a base in 1,4-dioxane−water at 60 °C gave a 6:1 mixture of olefin diastereomers, favoring desired product **207** [240]. Unfortunately, the yield of this reaction was moderate (36%, entry 6). Considerable effort was undertaken to improve the efficiency of this process and the results of these studies are summarized in Table 8 (entries 7−12).

[16] The ((trimethylsilyl)methyl)magnesium chloride (**209**) required for these experiments was obtained from commercial sources, and the corresponding organozinc reagent was prepared by *in situ* treatment of **209** with $ZnBr_2$.
[17] Stereochemical assignment of **208** using *J*-based configuration analysis (HETLOC, HECADE) failed.

The employment of thallium bases has provided a solution for difficult SUZUKI couplings in numerous instances [241]. In the case of **204**, however, employment of Tl_2CO_3 in place of Na_2CO_3 resulted in a diminished yield of 15% (entry 7). Alternatively, the addition of silver salts has been reported to facilitate SUZUKI reactions involving triflates [242]. When freshly prepared Ag_2O was added to the coupling of **204** with **209**, an increased yield (54%) was observed, but the product was obtained as a 1.5:1 mixture of **207** and **208** (entry 8). The result that the presence of silver(I) in the SUZUKI coupling leads to the inversion of **205** to **206** is in agreement with the hypothesis that various metal salts can promote this process, as previously discussed for the KUMADA and NEGISHI reactions.

Bis((diphenylphosphino)ferrocene)palladium(II) chloride ($Pd(dppf)Cl_2$) is often the catalyst of choice for SUZUKI cross-couplings. Among other reasons, this can be ascribed to the bulky bidentate ligand on palladium facilitating reductive elimination of the transmetalated complex, which is particularly important for cases with *B*-alkyl substrates that are prone to undergo β-hydride elimination [241, 243]. When $Pd(dppf)Cl_2$ was employed in the coupling of **204** and **210** under otherwise identical conditions, the result obtained was similar to those with $Pd(PPh_3)_4$ (entry 9). However, the conditions by JOHNSON and BRAUN [244], using $Pd(dppf)Cl_2$ in combination with Cs_2CO_3 as a base and Ph_3As as co-ligand, were significantly more efficient [245]. Under optimized conditions, the desired product was produced as a 10:1 mixture of **207** and **208** in 62% yield (entry 10). SUZUKI couplings with other organoboron reagents, such as pinacolborane **211** or trifluoroborate **212**, were unsuccessful in our hands (entries 11, 12) [246].

Table 8: Cross-coupling of enol triflate **204**.

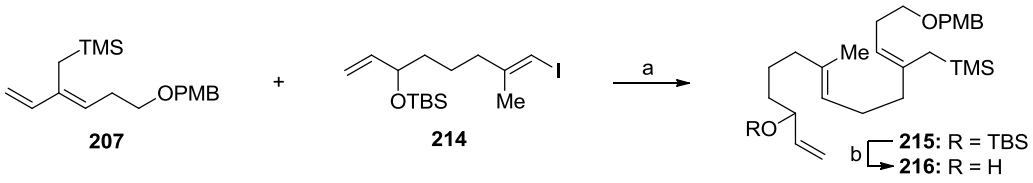


Entry	Conditions	207:208	Yield[a]
1	**209** (2.0 equiv), (t-Bu_3P)$_2$Pd (2.5 mol%), THF, RT	< 5:95	76%
2	**209** (2.0 equiv), $ZnBr_2$ (2.0 equiv), (t-Bu_3P)$_2$Pd (2.5 mol%), THF, RT	1:4	52%
3	**209** (2.0 equiv), **213** (5 mol%), $Pd_2(dba)_3$ (2.5 mol%), THF, RT	< 5:95	n.d.
4	**209** (2.0 equiv), $ZnBr_2$ (2.0 equiv), **213** (2 mol%), $Pd_2(dba)_3$ (2.5 mol%), THF, RT	< 5:95	n.d.
5	**209** (3.0 equiv), $Ni(acac)_2$ (10 mol%), THF, 0 °C	1:9	n.d.
6	**210** (2.5 equiv), $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (3.5 equiv), 1,4-dioxane–H_2O, 60 °C	6:1	36%
7	**210** (2.5 equiv), $Pd(PPh_3)_4$ (5 mol%), Tl_2CO_3 (3.5 equiv), 1,4-dioxane–H_2O, 60 °C	5:1	15%
8	**210** (2.5 equiv), $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (3.5 equiv), Ag_2O (3.5 equiv), 1,4-dioxane–H_2O, 60 °C	1.5:1	54%
9	**210** (2.5 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (5 mol%), Na_2CO_3 (3.5 equiv), 1,4-dioxane–H_2O, 60 °C	5:1	24%
10	**210** (1.5 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (10 mol%), Ph_3As (10 mol%), Cs_2CO_3 (2.5 equiv), THF–DMF–H_2O, 0 °C to RT	10:1	62%
11	**211** (1.25 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (5 mol%), Cs_2CO_3 (3.0 equiv), THF–H_2O, RT	-	n.r.
12	**212** (1.2 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (5 mol%), Cs_2CO_3 (3.0 equiv), THF–H_2O, 40 °C	-	n.r.

[a] Purification by column chromatography furnished **207** and **208** contaminated with various amounts of $TMSCH_2CH_2TMS$. The yields given in this table are corrected accordingly.

The terminal olefin in diene **207** was hydroborated with 9-BBN and the resulting trialkylborane was directly subjected to *B*-alkyl SUZUKI coupling with known vinyliodide **214** to afford polyene **215** in 61% yield [199]. Removal of the TBS protective group to release the allylic hydroxyl group in **215** required carefully chosen reaction conditions. Whereas attempts

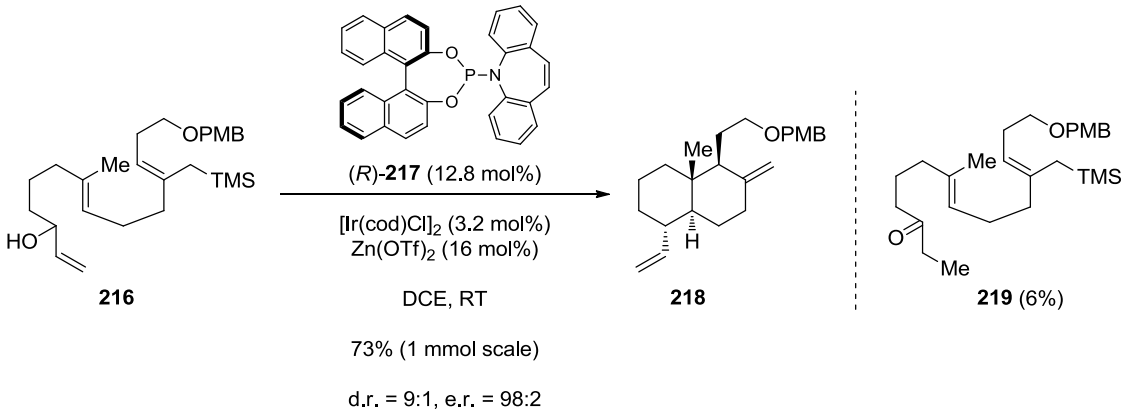
with TBAF or *para*-toluenesulfonic acid led to decomposition of the material, PPTS (10 mol%) was found to catalyze the desired transformation. However, due to the poor stability of the product under those conditions, the reaction was halted at 60% conversion, as determined by ^{1}H NMR of the crude reaction mixture. Re-subjection of the recovered starting material led to allylic alcohol **216** in 81% combined yield.



Scheme 68: Completion of polyene precursor **216**. Reagents and conditions: a) **207** (1.0 equiv), 9-BBN (1.0 equiv), THF, 0 °C to RT; then **214** (1.0 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.7 mol%), NaOH (3.0 equiv), THF−H_2O, 0 °C to RT, 61%; b) PPTS (10 mol%), MeOH, RT, 81% (2 iterations).

2.3.2 Polyene Cyclization and Synthesis of (+)-Asperolide C

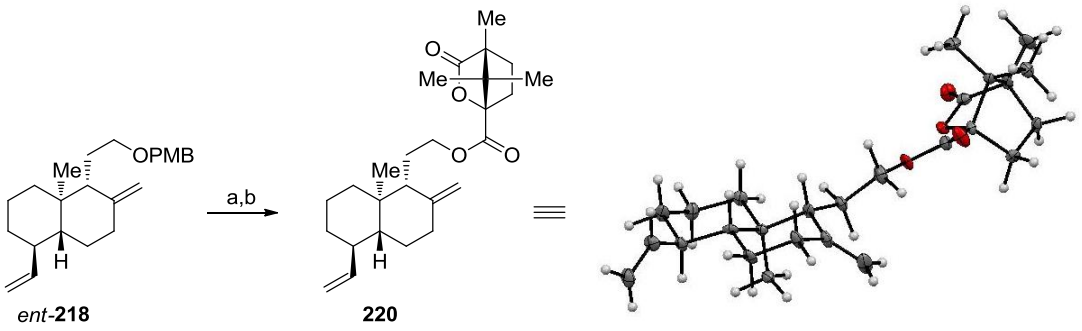
With polyene precursor **216** in hand, the pivotal iridium-catalyzed cyclization cascade was examined. Gratifyingly, reaction of **216** under standard conditions using $[Ir(cod)Cl]_2$ (3.2 mol%) and (*R*)-**217** (12.8 mol%) as catalyst precursors, along with $Zn(OTf)_2$ (16 mol%) as a LEWIS acid delivered decalin **218** in excellent stereoselectivity (d.r. = 9:1, e.r. = 98:2) and 73% yield (Scheme 69) [199]. The reaction proved highly robust and scalable. The only side product isolated was ethylketone **219** (6% yield).



Scheme 69: Iridium-catalyzed enantioselective polyene cyclization cascade.

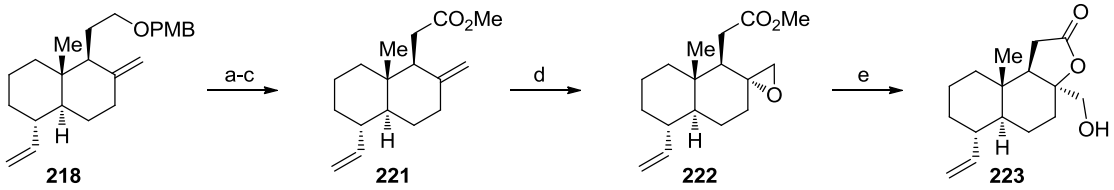
The configuration of the polyene cyclization product was determined by derivatization of *ent*-**218**, which was obtained through the same protocol using (*S*)-**217** as a ligand (Scheme 70). PMB deprotection of *ent*-**218** delivered the corresponding primary alcohol, which was

treated with (−)-camphanic acid chloride in presence of Et_3N to furnish camphanate **220** in 79% yield. Samples of this compound suitable for single crystal X-ray diffraction were obtained by crystallization from hexane−EtOAc.[18]



Scheme 70: Reagents and conditions: a) DDQ (1.1 equiv), pH 7 buffer, CH_2Cl_2, RT, 98%; b) (−)-camphanic acid chloride (2.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 °C to RT, 79%.

The synthesis of asperolide C (**190**) was continued with the PMB deprotection of **218**, followed by stepwise oxidation of the liberated hydroxyl group to the corresponding carboxylic acid, which was treated with trimethylsilyl diazomethane to afford methyl ester **221** (62% over 4 steps). Epoxidation of the exomethylene group in **221** with freshly prepared DMDO at −20 °C proceeded from the sterically more accessible α-face to deliver oxirane **222** in moderate yield (45%, 66% brsm).[19] Exposure of **222** to trifluoroacetic acid in anhydrous CH_2Cl_2 at 0 °C led to selective epoxide opening to furnish lactone **223** (70%).[20] Precedence for this transformation came from a report by BARRERO *et al.* who described a closely related process as a side reaction [247].



Scheme 71: Reagents and conditions: a) DDQ (1.1 equiv), pH 7 buffer, CH_2Cl_2, RT, 98%; b) DMP (1.5 equiv), CH_2Cl_2, RT, 80%; c) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-2-butene (70 equiv), *t*-BuOH−H_2O, RT; then trimethylsilyl diazomethane (1.1 equiv), MeOH, 0 °C to RT, 79%; d) DMDO (1.1 equiv), acetone, −78 °C to −20 °C, 45% (66% brsm); e) TFA (1.2 equiv), CH_2Cl_2, −20 °C to 0 °C, 70%.

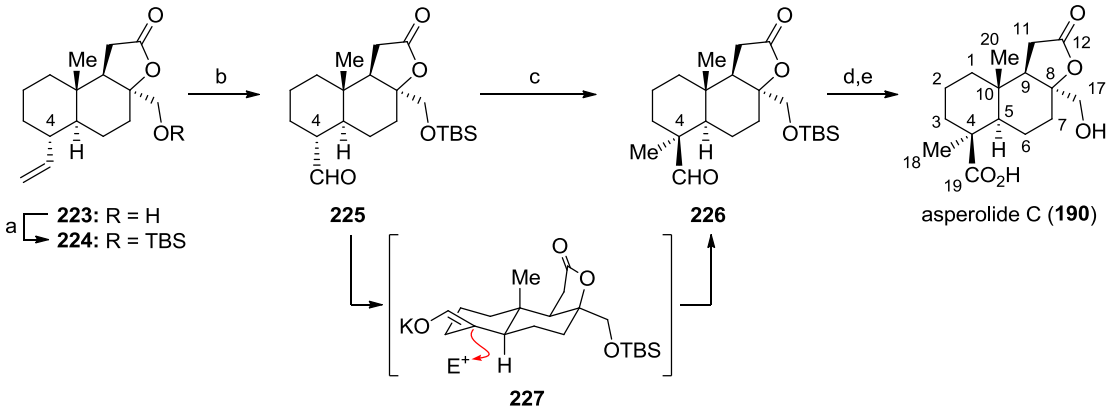
With the tricyclic scaffold of the target molecule constructed, the final stages of the total synthesis were addressed. After protection of the primary hydroxyl group in **223** as a TBS

[18] The corresponding diastereomer derived from **218** and (−)-camphanic acid chloride was an oil at ambient temperature (Master's thesis Alberto Kravina).

[19] Master's thesis Alberto Kravina.

[20] When this reaction was conducted at RT, the corresponding α,β-unsaturated δ-lactone was observed as a side product (25%, ^{1}H NMR).

ether (TBSCl, imidazole, DMAP, 89%), intermediate **224** was subjected to oxidative cleavage of the vinyl residue with sodium periodate and catalytic osmium tetroxide (20 mol%) to afford aldehyde **225** in 81% yield [33]. Introduction of the quaternary center at C(4) by enolate alkylation was expected to be difficult due to the presence of a γ-lactone in the same molecule. However, careful evaluation of the system revealed that his transformation might be feasible in high chemoselectivity by direct alkylation of aldehyde enolate **227**, which was supported by literature precedence [248, 249]. It was reasoned that the aldehyde in **225** might be selectively deprotonated in presence of the γ-lactone through thermodynamic enolate formation using potassium *tert*-butoxide as a base. In the event, treatment of a solution of **225** in THF at −20 °C with *t*-BuOK (1.25 equiv),[21] followed by addition of iodomethane (1.25 equiv) and warming to 0 °C delivered **226** as the only isolable product, although in only 36% yield. The high diastereoselectivity of this process can be attributed to steric congestion of the β-face in **227**, leading to alkylation from the more accessible α-face. PINNICK oxidation of aldehyde **226** to the corresponding carboxylic acid (76%) [82-85] and TBS deprotection (76%) delivered synthetic asperolide C (**190**).



Scheme 72: Reagents and conditions: a) TBSCl (3.0 equiv), imidazole (6.0 equiv), DMAP (10 mol%), CH_2Cl_2, RT, 89%; b) OsO_4 (20 mol%), $NaIO_4$ (5.0 equiv), 2,6-lutidine (2.0 equiv), 1,4-dioxane−H_2O, RT, 81%; c) *t*-BuOK (1.25 equiv), MeI (1.25 equiv), THF, −20 °C to 0 °C, 36%; d) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-2-butene (30 equiv), *t*-BuOH−H_2O, RT, 76%; e) TBAF (1.5 equiv), THF, 0 °C, 74%.

The ^1H and ^{13}C NMR spectra for the synthetic material were in agreement with those reported for natural asperolide C (Table 9).[22] With a pure sample of **190** in hand, the optical rotation $[\alpha]_D^{26}$ of the natural product could be determined to +2.5 (c = 0.25, MeOH).

[21] A slight excess of base instead of 0.9−0.95 equiv, as usually employed for thermodynamic enolate formation, was necessary to achieve full conversion. The small reaction scale (12 mg) is a plausible explanation for this finding.

[22] Three chemical shifts in the ^1H NMR spectrum of synthetic asperolide C showed a significant deviation from the literature data ($|\Delta\delta| \geq 0.1$ ppm). In light of the fact that natural asperolide C had been characterized as a mixture of two natural products, this can be ascribed to misassignments in the isolation literature.

Table 9: ^{1}H and ^{13}C NMR spectroscopic data for asperolide C (**190**).

Atom Nr.	^{1}H NMR Chemical Shifts (δ) Natural Asperolide C	^{1}H NMR Chemical Shifts (δ) Synthetic Asperolide C	Δδ
1	α 1.07 (m) β 1.70 (m)	1.04 (m) 1.68 (m)	−0.03 −0.02
2	1.52 (m) 1.86 (m)	1.43 (m) 1.86 (m)	−0.09 0.00
3	1.08 (m) 1.74 (m)	1.08 (dd, ^{2}J = 13.4 Hz, ^{3}J = 3.9 Hz) 2.19 (m)	0.00 0.45
5	1.16 (dd, ^{3}J = 10.5 Hz, 4.5 Hz)	1.17 (dd, ^{3}J = 11.1, 3.7 Hz)	0.01
6	α 1.87 (m) β 1.46 (dd, ^{2}J = 14.2 Hz, ^{3}J = 3.2 Hz)	1.95−1.89 (m)	0.02 0.43
7	2.07 (dd, ^{2}J = 14.2 Hz, ^{3}J = 3.2 Hz) 1.72 (m)	2.08 (m) 1.69 (m)	0.01 0.03
9	2.24 (m)	2.07 (m)	−0.17
11	2.90 (m) 2.35 (d, ^{2}J = 18.2 Hz)	2.93 (dd, ^{2}J = 18.1 Hz, ^{3}J = 8.4 Hz) 2.37 (d, ^{2}J = 18.1 Hz)	0.03 0.02
17	α 3.40 (d, ^{2}J = 10.3 Hz) β 3.34 (dt, ^{2}J = 10.3 Hz, ^{3}J = 2.1 Hz)	3.43 (d, ^{2}J = 11.6 Hz) 3.39 (d, ^{2}J = 11.6 Hz)	0.03 0.05
18	1.24 (s)	1.23 (s)	−0.01
20	0.84 (s)	0.84 (s)	0.00

Atom Nr.	^{13}C NMR Chemical Shifts (δ) Natural Asperolide C	^{13}C NMR Chemical Shifts (δ) Synthetic Asperolide C	Δδ
1	42.0	42.09	0.1
2	20.0	20.10	0.1
3	38.6	39.02	0.4
4	44.6	44.63	0.0
5	53.3	53.34	0.0
6	20.1	20.26	0.2
7	31.0	31.12	0.1
8	88.9	88.85	0.0
9	50.8	50.77	0.0
10	37.5	37.46	0.0
11	33.5	33.52	0.0
12	180.3	180.87	0.6
17	69.3	69.23	−0.1
18	29.3	29.39	0.1
19	181.0	181.29	0.3
20	14.6	14.64	0.0

2.4 Conclusions and Outlook

In conclusion, the first total synthesis of the tetranorlabdane diterpenoid asperolide C (**190**) has been achieved in 20 linear steps and 0.3% overall yield. This study represents one of the few examples for the use of an enantioselective polyene cyclization reaction in a natural product synthesis and the first that strategically relies on modern iridium catalysis to construct the carbobicyclic core scaffold.

The described route features a series of cross-coupling reactions to efficiently assemble the linear polyene precursor and a highly enantioselective iridium-catalyzed cyclization cascade to construct the carbobicyclic core scaffold. Specifically, the Pd-mediated coupling of a dienol triflate with $Me_3SiCH_2B(OH)_2$ provides a novel access route to allylic silanes. Moreover, a BRØNSTED acid-mediated epoxide opening leading to a lactone and the highly chemo- and diastereoselective alkylation of an aldehyde enolate were employed to complete the target structure. The synthetic strategy bestows a general entry into the labdane-type diterpenoids and bears significant potential for the total synthesis of further natural products.

3 Experimental

3.1 General Methods

Solvents and reagents: All chemicals and solvents were purchased from ABCR, ACROS, ALDRICH, J.T. BAKER, COMBI-BLOCKS, FLUKA, FLUOROCHEM, MERCK, TCI, STREM or LANCASTER and used as such with the following exceptions: Deuterated solvents were obtained from ARMAR CHEMICALS, Döttingen, Switzerland. THF, Et_2O, MeCN, CH_2Cl_2, DMF and toluene were dried by passage over two 4" × 36" columns of anhydrous neutral A-2 alumina (MACHEREY and NAGEL; activated over night at 300 °C under a flow of dry N_2) under an atmosphere of Ar (H_2O content < 30 ppm, as determined by KARL-FISCHER titration) [250]. Alternatively, the above solvents were dried on a LC TECHNOLOGY SOLUTIONS *SP-1* solvent purification system under N_2. DME, DMPU, DMSO, HMPA and *o*-xylene were distilled from calcium hydride under an atmosphere of dry N_2 and stored over 4 Å molecular sieves. MeOH was distilled from magnesium turnings under an atmosphere of dry N_2. Benzene was distilled from potassium/benzophenone ketyl radical under an atmosphere of dry N_2. Diisopropylamine and pyridine were distilled from KOH under an atmosphere of dry N_2. Ethyldiisopropylamine and triethylamine were distilled from calcium hydride under an atmosphere of dry N_2 immediately prior to use. Chlorotrimethylsilane and chlorotriethylsilane were distilled from calcium hydride and stored under an atmosphere of dry N_2. 18-crown-6 ether was dried azeotropically with dry THF immediately prior to use. Allyl bromide was distilled from calcium hydride under an atmosphere of dry N_2 immediately prior to use. Ethyltriphenylphosphonium bromide was azeotroped with dry THF and dried at 0.5 torr at 60 °C for 12 h. Cesium fluoride was dried at 0.5 torr at 220 °C for 12 h. 4-Dimethylaminopyridine (DMAP) was recrystallized from EtOAc prior to use. Commercial 1,2-diiodoethane was purified by dissolving in Et_2O, washing with satd. aq. $Na_2S_2O_3$, drying over $MgSO_4$, filtration and concentration under reduced pressure [251]. The purified 1,2-diiodoethane was stored at –20 °C in a N_2-filled glove box. pH 7 phosphate buffer (0.05 M) was prepared from NaH_2PO_4 (3 g, 25 mmol) and NaOH (0.6 g, 15 mmol) in H_2O (500 ml). pH 7 phosphate buffer (0.1 M) was prepared from NaH_2PO_4 (6 g, 50 mmol) and NaOH (1.2 g, 30 mmol) in H_2O (500 ml). DESS–MARTIN periodinane (DMP) [252], iodomethyl pivalate [253], (*E*)-pent-3-en-2-yl(phenyl)sulfane [49], (*E*)-4-methoxypent-2-ene [72], $[(Ph_3PAu)_3O]BF_4$ [254], *o*-nitrobenzenesulfonylhydrazine [165], *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazine [168], 2-iodophenethyl methyl diisopropylphosphoramidite

[255], 4-methoxybenzyl trichloroacetimidate [214], ((trimethylsilyl)methyl)boronic acid [239], 5-((11b*R*)-dinaphtho[2,1-d:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)-5*H*-dibenzo[b,*f*]azepine [199] and (*E*)-*tert*-butyl((8-iodo-7-methylocta-1,7-dien-3-yl)oxy)dimethylsilane [199] were prepared according to literature procedures.

Reaction handling: All non-aqueous reactions were performed in flame dried glassware under positive pressure of dry N_2 unless otherwise stated. Reactions were magnetically stirred and monitored by TLC unless otherwise noted. TLC was performed on Merck silica gel 60 F_{254} TLC glass plates and visualized with UV fluorescence quenching and potassium permanganate ($KMnO_4$) or ceric ammonium nitrate (CAN) stain. Concentrations under reduced pressure were performed by rotary evaporation at 40 °C at the appropriate pressure, unless otherwise noted. Column chromatographic purification was performed as flash column chromatography with 0.3–0.5 bar pressure using BRUNSCHWIG silica gel (32–63, 60 Å) or FLUKA silica gel (40–63, 60 Å) [256]. Distilled technical grade solvents were employed. The yields given refer to chromatographically purified compounds, unless stated otherwise.

Melting points: Melting points were measured on a BÜCHI B-540 melting point apparatus using open glass capillaries and are uncorrected.

Optical Rotations: Optical rotations were measured on a JASCO *DIP-2000* polarimeter at the sodium D line with 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$ (concentration (g/100 ml), solvent).

NMR Spectroscopy: NMR data was recorded on VARIAN *Mercury* (300 MHz), BRUKER *Ascend* (400 MHz), BRUKER *AV* (400 MHz, 600 MHz) or BRUKER *DRX* (400 MHz, 500 MHz, 600 MHz) spectrometers. Measurements were carried out at RT (*ca*. 22 °C). Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.00 ppm, methanol at 3.31 and 49.00 ppm for ^{1}H and ^{13}C spectroscopy, respectively), unless otherwise noted. The data is reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with complete ^{1}H-decoupling. Service measurements were performed by the NMR service team of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by Mr. PHILIPP ZUMBRUNNEN, Mr. RAINER FRANKENSTEIN and Mr. RENÉ ARNOLD under direction of Dr. MARC-OLIVIER EBERT.

IR Spectroscopy: Infrared spectra were recorded on a PERKIN ELMER *RXI* or on a PERKIN ELMER *BX* FT-IR instrument as thin films. Absorptions are given in wavenumbers (cm^{-1}).

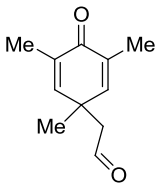
Mass Spectrometry: Mass spectrometric analyses were performed as high resolution ESI measurements on a BRUKER DALTONICS *maXis* (UHR-TOF) instrument or as high resolution EI measurements on a WATERS MICROMASS *AutoSpec Ultima* instrument by the mass spectrometry service of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by Mr. LOUIS BERTSCHI, Mr. ROLF HÄFLIGER and Mr. OSWALD GRETER under direction of Dr. XIANGYANG ZHANG.

SFC: Enantiomeric excesses were determined by chiral analytical chromatography on a JASCO *2080Plus* supercritical fluid chromatography apparatus. Columns and conditions are specified, retention times (t_R) are given in minutes.

X-Ray Diffraction: X-Ray diffraction analysis was performed on a BRUKER *Kappa Apex-II DUO* system equipped with a graphite monochromator by Dr. BERND SCHWEIZER and Mr. MICHAEL SOLAR at the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH. The data obtained for compound **220** has been submitted to the CAMBRIDGE CRYSTALLOGRAPHIC DATA CENTRE (CCDC Deposition Number: 955873).

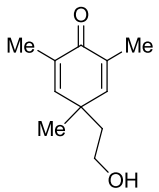
3.2 Total Synthesis of Indoxamycin A & B

3.2.1 First Generation Approach



2-(1,3,5-Trimethyl-4-oxocyclohexa-2,5-dien-1-yl)acetaldehyde (29). Osmium tetroxide, 4% in H_2O (2.50 ml, 0.40 mmol, 2.0 mol%) and sodium periodate (17.0 g, 79.0 mmol, 4.00 equiv) were added in this order to a stirred solution of olefin **28** (3.50 g, 19.8 mmol, 1.00 equiv) in dioxane / water 3:1 (80 ml), containing 2,6-lutidine (4.60 ml, 39.7 mmol, 2.00 equiv) at RT. After 1 h, the reaction mixture was diluted with water (200 ml), and the resulting mixture was extracted with EtOAc (3 x 100 ml). The combined organic extracts were washed with satd. aq. sodium thiosulfate (3 x 30 ml), H_2O (3 x 30 ml) and satd. aq. NaCl (30 ml), then dried over $MgSO_4$ and filtered. Concentration *in vacuo* afforded a black residue that was purified by chromatography on silica gel (hexane / EtOAc; 7:3 to 1:1 gradient) to furnish aldehyde **29** (3.2 g, 90%) as an amber oil.

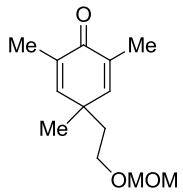
TLC: R_f = 0.40 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 9.43 (s, 1H), 6.67 (s, 2H), 2.55 (s, 2H), 1.91 (s, 6H), 1.30 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 199.88, 148.07, 135.06, 52.02, 38.90, 26.29, 16.32; **IR** (thin film): 3427, 3253, 2966, 2924, 2732, 1724, 1669, 1636, 1449, 1432, 1400, 1374, 1348, 1218, 1072, 1038, 1073, 1038, 989, 914, 769, 582 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{11}H_{14}O_2$ ($[M]^{\cdot+}$), 178.0989; found, 178.0988.



4-(2-Hydroxyethyl)-2,4,6-trimethylcyclohexa-2,5-dienone (30). To a suspension of sodium borohydride (6.79 g, 180 mmol, 10.0 equiv) in THF (150 ml) at 0 °C was added carefully over 30 min acetic acid (41.1 ml, 718 mmol, 40.0 equiv). **(Caution: Vigorous gas-evolution!)** After further 30 min, the mixture was allowed to warm up to RT and stirred for 1 h. The resulting mixture was cooled to 0 °C and a solution of aldehyde **29** (3.20 g, 18.0 mmol,

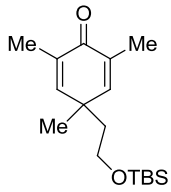
1.00 equiv) in THF (15 ml) was added. THF (5 ml) was used to assist the transfer. After 2 h, the reaction was quenched by pouring into satd. aq. NH_4Cl (800 ml). **(Caution: Vigorous gas-evolution!)** Extraction with CH_2Cl_2 (3 x 100 ml), washing with satd. aq. NaCl (50 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product as a colorless oil. Purification by column chromatography gave alcohol **30** (2.13 g, 66%) as a white crystalline solid.

TLC: R_f = 0.23 (hexane / EtOAc; 6:4; UV / $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.59 (s, 2H), 3.47 (m, 2H), 1.90 (m, 8H), 1.22 (m, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 187.17, 150.52, 134.39, 59.87, 43.54, 39.91, 26.78, 16.18; **IR** (thin film): 3434, 2962, 2924, 2872, 1667, 1628, 1448, 1401, 1374, 1218, 1053, 1026, 989, 914 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{11}H_{16}O_2$ ($[M]^{\cdot+}$), 180.1145; found, 180.1142.



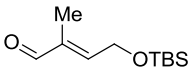
4-(2-(Methoxymethoxy)ethyl)-2,4,6-trimethylcyclohexa-2,5-dienone (34). To a stirred solution of alcohol **30** (500 mg, 2.77 mmol, 1.00 equiv) in CH_2Cl_2 (5.5 ml) was added DIPEA (1.20 ml, 6.94 mmol, 2.50 equiv), followed by chloromethyl methyl ether (0.49 ml, 6.10 mmol, 2.20 equiv). The resulting mixture was stirred at RT for 4 h. The reaction was quenched by pouring into satd. aq. NH_4Cl (20 ml). Extraction with CH_2Cl_2 (3 x 25 ml), washing with satd. aq. NaCl (5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished an amber crude. Purification by chromatography on silica gel (hexane / EtOAc; 7:3) gave product **34** (604 g, 97%) as a colorless oil.

TLC: R_f = 0.42 (hexane / EtOAc; 7:3; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.56 (s, 2H), 4.49 (s, 2H), 3.30 (m, 5H), 1.90 (m, 8H), 1.21 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 187.28, 150.50, 134.19, 96.50, 64.59, 55.20, 40.38, 39.71, 26.74, 16.23; **IR** (thin film): 2924, 2884, 1669, 1635, 1449, 1399, 1374, 1216, 1150, 1111, 1058, 1034, 914, 744 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{13}H_{20}NaO_3$ ($[M+Na]^+$), 247.1305; found, 247.1297.



4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2,4,6-trimethylcyclohexa-2,5-dienone (228). To a stirred solution of alcohol **30** (50 mg, 0.277 mmol, 1.00 equiv) in DMF (1.0 ml) at 0 °C was added imidazole (48.2 mg, 0.694 mmol, 2.50 equiv), followed by *tert*-butyldimethylsilyl chloride (50.7 mg, 0.333 mmol, 1.20 equiv). The resulting mixture was stirred at this temperature for 1 h. The reaction was quenched by pouring into satd. aq. NH_4Cl (10 ml). Extraction with Et_2O (3 x 10 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure gave the crude product that was purified by chromatography on silica gel (hexane / EtOAc; 95:5) to furnish silyl ether **228** (81 mg, 99%) as a colorless oil.

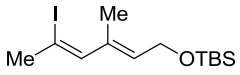
TLC: R_f = 0.25 (hexane / EtOAc; 95:5; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.57 (s, 2H), 3.43 (t, ^3J = 6.8 Hz, 2H), 1.88 (s, 6H), 3.82 (t, ^3J = 6.8 Hz, 2H), 1.19 (s, 3H), 0.85 (s, 9H), −0.02 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 187.42, 150.96, 133.80, 59.86, 43.62, 39.87, 26.68, 25.85, 18.16, 16.24, −5.44; **IR** (thin film): 2956, 2928, 2857, 1670, 1637, 1472, 1399, 1373, 1256, 1217, 1100, 1035, 989, 9112, 836, 776, 662 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{30}NaO_2Si$ ($[M+Na]^+$), 317.1907; found, 317.1901.



(*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-enal (32). Selenium dioxide (1.38 g, 12.4 mmol, 0.50 equiv) and *tert*-butyl hydroperoxide (9.00 ml, 49.9 mmol, 2.00 equiv) were combined in CH_2Cl_2 (220 ml), cooled to −20 °C and stirred for 30 min. A solution of *tert*-butyldimethyl((3-methylbut-2-en-1-yl)oxy)silane (**31**, 5.00 g, 24.95 mmol, 1.00 equiv) in CH_2Cl_2 (10 ml) was added via cannula over 10 min. CH_2Cl_2 (20 ml) was used to assist the transfer. The reaction was allowed to slowly warm up to RT and stirred for 60 h. The mixture was taken up in Et_2O (100 ml), washed with 40% aq. sodium bisulfite (3 x 70 ml) and sat. aq. NaCl (50 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure afforded a crude oil, which was purified by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient) to yield aldehyde **32** (2.36 g, 44%) as a slightly yellowish oil.

TLC: R_f = 0.21 (hexane / EtOAc; 97.5:2.5; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 6.52 (m, 1H), 4.51 (m, 2H), 1.73 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H); **^{13}C-NMR**

(100 MHz, $CDCl_3$): δ 194.57, 153.12, 137.74, 60.49, 25.83, 18.29, 9.37, −5.30; **IR** (thin film): 2956, 2860, 2711, 1700, 1473, 1380, 1332, 1255, 1200, 1062, 939, 834, 747, 677 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{11}H_{22}O_2Si$ ($[M]^{\cdot+}$), 214.1384; found, 214.1391.

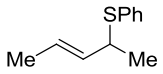


***tert*-Butyl(((2*E*,4*Z*)-5-iodo-3-methylhexa-2,4-dien-1-yl)oxy)dimethylsilane (11).** To a flask charged with ethyl triphenylphosphonium iodide (2.78 g, 6.53 mmol, 2.00 equiv) and THF (25 ml) was added at RT *n*-butyllithium, 1.5 M in hexanes (4.35 ml, 6.53 mmol, 2.00 equiv). The resulting suspension was stirred for 30 min, during which the reaction mixture became a deeply red homogeneous solution. This solution was slowly cannulated into a round bottom flask charged with iodine (1.66 g, 6.53 mmol, 2.00 equiv) and THF (25 ml) at −78 ºC, resulting in an orange suspension. THF (5 ml) was used to assist the transfer. The temperature of this suspension was raised to −20 °C and KHMDS (1.24 g, 6.20 mmol, 1.9 equiv) in THF (5 ml) was added dropwise. The resulting suspension was stirred for 20 min, before it was cooled to −78 °C. To this solution was then added a solution of aldehyde **32** (700 mg, 3.27 mmol, 1.00 equiv) in THF (5 ml). THF (5 ml) was used to assist the transfer. After 20 min, as TLC indicated full consumption of the starting material, the reaction was quenched by pouring into sat. aq. NH_4Cl (250 ml). The mixture was extracted with ether (3 x 50 ml). The combined organic phases were washed with satd. aq. NaCl (10 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 97.5:2.5 to 9:1 gradient) gave vinyliodide **11** (650 mg, 57%) as a colorless oil.

TLC: R_f = 0.28 (hexane / EtOAc; 97.5:2.5; UV / $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.00 (s, 1H), 5.61 (m, 1H), 4.28 (d, ^3J = 6.2 Hz, 2H), 2.56 (d, ^4J = 1.5 Hz, 3H), 1.77 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 137.38, 134.22, 131.19, 97.23, 60.16, 35.10, 26.07, 18.51, 16.34, −4.91; **IR** (thin film): 2955, 2928, 2856, 1472, 1378, 1256, 1111, 1082, 836, 775, 668 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_9H_{16}IOSi$ ($[M-C_4H_9]^+$), 295.0010; found, 295.0006.

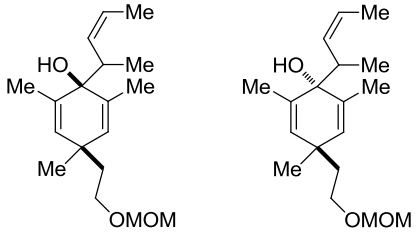
3.2.2 Second Generation Approach

3.2.2.1 First Generation Dihydroindenone



(*E*)-Pent-3-en-2-yl(phenyl)sulfane (41) [49]. A solution of (*E*)-pent-3-en-2-ol (**40**, 3.6 ml, 33.8 mmol, 1.00 equiv) and diphenyldisulfide (7.8 g, 35.5 mmol, 1.05 equiv) in MeCN (84 ml) was deoxygenated by bubbling Ar throgh it for 30 min. Tributylphosphine (8.9 ml, 35.5 mmol, 1.05 equiv) was added and the resulting mixture was stirred at RT for 17 h. The mixture was treated with 5% aq. NaOH (50 ml) and extracted with Et_2O (3 x 50 ml). The combined organic extracts were washed with satd. aq. NaCl (30 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 100:0 to 97:3 gradient) gave thioether **41** (5.5 g, 91%) as a clear colorless liquid.

TLC: R_f = 0.36 (hexane; UV / $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.40−7.36 (m, 2H), 7.31−7.19 (m, 3H), 5.49−5.32 (m, 2H), 3.79−3.69 (m, 1H), 1.62 (d, ^3J = 5.3 Hz, 3H), 1.36 (d, ^3J = 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.13, 132.73, 132.71, 128.54, 126.91, 125.99, 45.78, 20.72, 17.59. The spectral data were in accordance with those previously reported [49].

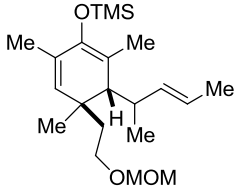


(1*SR*,4*RS*)-4-(2-(methoxymethoxy)ethyl)-2,4,6-trimethyl-1-(pent-3-en-2-yl)cyclohexa-2,5-dienol (44). (1*RS*,4*RS*)-4-(2-(methoxymethoxy)ethyl)-2,4,6-trimethyl-1-(pent-3-en-2-yl)cyclohexa-2,5-dienol (45). A solution of lithium naphthalenide [257, 258], 0.7 M in THF (2.55 ml, 1.78 mmol, 4.00 equiv) was diluted with THF (5.0 ml) and cooled to −78 °C. (*E*)-pent-3-en-2-yl(phenyl)sulfane (**41**) (159 mg, 0.892 mmol, 2.00 equiv) in THF (3.5 ml) was added dropwise over 10 min. Upon consumption of the lithium naphthalenide, the color of the dark-green mixture changed to red-brown. Titanium(IV) isopropoxide (0.534 ml, 1.78 mmol, 4.00 equiv) was added slowly at the same temperature. After 20 min of stirring, the mixture was warmed up to 0 °C and a solution of ketone **34** (100 mg, 0.446 mmol, 1.00 equiv) in THF (1.0 ml) was added via cannula. THF (0.5 ml) was used to assist the transfer. The mixture was

stirred at 0 °C for 2 h. The reaction was quenched by pouring into a mixture of pH 7 buffer (0.05 M) and satd. aq. Na-K-tartrate (1:1, 20 ml) and allowed to warm up to RT. Extraction with Et_2O (3 x 25 ml), washing with satd. aq. NaCl (5 ml) drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product. Purification by chromatography on silica gel (hexane / MTBE; 8:2 to 7:3 gradient) yielded tertiary alcohols **44** (65 mg, 50%) and **45** (13 mg, 10%) as colorless oils.

*(1SR,4RS)-4-(2-(methoxymethoxy)ethyl)-2,4,6-trimethyl-1-(pent-3-en-2-yl)cyclohexa-2,5-dienol (**44**):* **TLC:** R_f = 0.19 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (9:1 olefin geometrical isomer ratio, only major isomer reported, 300 MHz, $CDCl_3$): δ 5.67 (m, 1H), 5.42−5.33 (m, 3H), 4.54 (s, 2H), 3.40−3.35 (m, 2H), 3.32 (s, 3H), 3.04 (m, 1H), 2.13 (s, 1H), 1.87 (d, ^4J = 1.4 Hz, 3H), 1.74 (d, ^4J = 1.4 Hz, 3H), 1.72 (dd, ^3J = 6.8 Hz, ^4J = 1.8 Hz, 3H), 1.66−1.60 (m, 2H), 1.02 (s, 3H), 0.84 (d, ^3J = 6.9 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 134.57, 133.87, 133.57, 133.32, 132.90, 127.06, 96.48, 75.30, 65.48, 55.14, 41.90, 37.27, 36.35, 28.80, 19.83, 18.07, 16.78, 13.33; **IR** (thin film): 3458, 2952, 2928, 2882, 1451, 1406, 1372, 1292, 1218, 1150, 1110, 1038, 1001, 959, 926, 876, 748 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{30}NaO_3$ ($[M+Na]^+$), 317.2087; found, 317.2090.

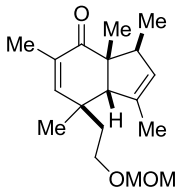
*(1RS,4RS)-4-(2-(methoxymethoxy)ethyl)-2,4,6-trimethyl-1-(pent-3-en-2-yl)cyclohexa-2,5-dienol (**45**):* **TLC:** R_f = 0.39 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (9:1 olefin geometrical isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 5.67 (m, 1H), 5.50 (s, 1H), 5.42 (s, 1H), 5.37 (dd, ^3J = 10.7 Hz, 1.8 Hz, 1H), 4.59 (s, 2H), 3.57−3.53 (m, 2H), 3.36 (s, 3H), 3.10 (m, 1H), 2.11 (s, 1H), 1.88 (d, ^4J = 1.2 Hz, 3H), 1.76 (d, ^4J = 1.2 Hz, 3H), 1.77 (dd, ^3J = 6.9 Hz, ^4J = 1.8 Hz, 3H), 1.67−1.63 (m, 2H), 1.05 (s, 3H), 0.87 (d, ^3J = 7.0 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 134.32, 134.12, 133.60, 133.02, 132.88, 127.16, 96.46, 75.10, 65.00, 55.11, 41.67, 37.42, 36.05, 28.23, 20.08, 18.31, 16.87, 13.34; **IR** (thin film): 3460, 2925, 2856, 1453, 1373, 1151, 1110, 1038, 1006, 960, 748 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{30}NaO_3$ ($[M+Na]^+$), 317.2087; found, 317.2087.



(((3*RS*,4*SR*)-4-(2-(methoxymethoxy)ethyl)-2,4,6-trimethyl-3-((E)-pent-3-en-2-yl)cyclohexa-1,5-dien-1-yl)oxy)trimethylsilane (47). To a solution of alcohol **44** (65 mg,

0.221 mmol, 1.00 equiv) and 18-crown-6 (117 mg, 0.442 mmol, 2.00 equiv) in THF (6 ml) at −10 °C was added KHMDS, 0.25 M in THF (1.76 ml, 0.442 mmol, 2.00 equiv). The resulting mixture was stirred at the same temperature for 2 h, before TMSCl (0.071 ml, 0.552 mmol, 2.50 equiv) was added. After 15 min, the reaction was quenched by addition of pH 7 buffer (0.05 M, 5 ml), allowed to warm up to RT and extracted with diethyl ether (3 x 20 ml). Drying over $MgSO_4$, filtration, and concentration under reduced pressure furnished the crude product, which was purified by column chromatography (hexane / EtOAc; 95:5) to furnish enolsilane **47** (32 mg, 40%) as a colorless oil.

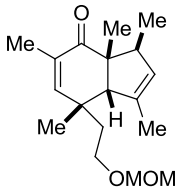
TLC: R_f = 0.38 (hexane / EtOAc; 95:5; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.44 (ddq, ^3J = 15.3 Hz, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H), 5.21 (ddq, ^3J = 15.3 Hz, ^3J = 6.3 Hz, ^4J = 1.0 Hz, 1H), 4.95 (s, 1H), 2.57 (m, 2H), 3.56 (m, 1H), 3.46 (m, 1H), 3.34 (s, 3H), 2.48 (m, 1H), 2.00 (m, 1H), 1.75 (s, 3H), 1.65 (d, ^4J = 1.5 Hz, 3H), 1.57 (dd, ^3J = 6.3 Hz, ^4J = 0.9 Hz, 3H), 1.49−1.42 (m, 2H), 1.06 (s, 3H), 0.97 (d, ^3J = 7.1 Hz, 3H), 0.22 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 145.24, 136.08, 132.57, 130.60, 121.50, 112.75, 96.39, 65.03, 55.89, 55.11, 39.40, 37.45, 36.57, 22.49, 20.68, 19.30, 18.12, 17.78, 0.94; **IR** (thin film): 2958, 2929, 2918, 2881, 1662, 1451, 1378, 1252, 1193, 1151, 1108, 1040, 968, 913, 844, 750 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{38}NaO_3Si$ ($[M+Na]^+$), 389.2482; found, 389.2468.



(1*SR*,3a*RS*,4*SR*,7a*RS*)-4-(2-(methoxymethoxy)ethyl)-1,3,4,6,7a-pentamethyl-3a,4-dihydro-1H-inden-7(7aH)-one (48). To a solution of enolsilane **47** (20.0 mg, 0.055 mmol, 1.00 equiv) in CH_2Cl_2 / MeCN (1:1, 4.0 ml) at RT was added palladium(II) acetate (13.5 mg, 0.060 mmol, 1.10 equiv). The reaction was stirred at the same temperature for 5 h. The resulting black suspension was evaporated to dryness under reduced pressure, taken up in with hexanes and filtered through a plug of celite. The filtrate was concentrated *in vacuo* to furnish a brown crude, which was purified by column chromatography (hexane / EtOAc; 85:15 to 75:25 gradient) to yield dihydroindenone **48** (12.2 mg, 76%) as a colorless oil.

TLC: R_f = 0.50 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 6.45 (s, 1H), 5.23 (s, 1H), 4.61 (m, 2H), 3.68 (m, 1H), 3.59 (m, 1H), 3.36 (s, 3H), 2.80 (m, 1H), 2.47 (s, 1H), 1.91 (m, 1H), 1.81 (s, 3H), 1.79 (d, ^4J = 1.3 Hz, 3H), 1.74

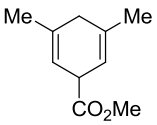
(m, 1H), 1.12 (d, ^3J = 7.2 Hz, 3H), 0.94 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$, relative to TMS): δ 204.57, 152.92, 138.33, 132.40, 132.26, 96.53, 64.75, 61.04, 55.29, 53.07, 45.11, 41.81, 37.44, 26.25, 23.40, 18.44, 16.26, 14.31; **IR** (thin film): 2959, 2927, 2876, 1664, 1450, 1376, 1251, 1216, 1150, 1110, 1072, 1039, 919, 833, 678 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{29}O_3$ ($[M+H]^+$), 293.2111; found, 293.2104.



(1*SR*,3a*RS*,4*RS*,7a*RS*)-4-(2-(methoxymethoxy)ethyl)-1,3,4,6,7a-pentamethyl-3a,4-dihydro-1H-inden-7(7aH)-one (49). Prepared from (1*RS*,4*RS*)-4-(2-(methoxymethoxy) ethyl)-2,4,6-trimethyl-1-(pent-3-en-2-yl)cyclohexa-2,5-dienol (**45**) according to the analogous procedure in 59% overall yield.

TLC: R_f = 0.29 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.32 (s, 1H), 5.23 (s, 1H), 4.55 (m, 2H), 3.56-3.47 (m, 2H), 3.33 (s, 3H), 2.90 (m, 1H), 2.29 (s, 1H), 1.81 (d, ^4J = 1.4 Hz, 3H), 1.79 (s, 3H), 1.70 (m, 1H), 1.50 (m, 1H), 1.15 (d, ^3J = 7.2 Hz, 3H), 1.05 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 205.14, 152.57, 137.11, 133.60, 133.14, 96.45, 67.07, 64.37, 55.29, 53.58, 44.74, 39.95, 36.88, 27.83, 24.57, 18.53, 16.32, 14.86; **IR** (thin film): 2959, 2929, 2876, 1668, 1448, 1375, 1251, 1215, 1150, 1110, 1039, 918, 835, 678 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{29}O_3$ ($[M+H]^+$), 293.2111; found, 293.2110.

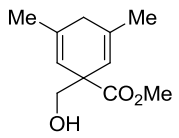
3.2.2.2 Second Generation Dihydroindenone



Methyl 3,5-dimethylcyclohexa-2,5-dienecarboxylate (55). NH_3 (990 ml) was condensed into a solution of methyl 3,5-dimethylbenzoate (**54**, 27.5 g, 167 mmol, 1.00 equiv) and *tert*-butanol (27.0 ml, 251 mmol, 1.50 equiv) in THF (330 ml) at –78 °C. Small pieces of potassium metal (16.4 g, 419 mmol, 2.50 equiv) were added, until a dark royal blue coloration persisted. After stirring at the same temperature for 60 min, the reaction was quenched by

careful addition of solid NH_4Cl (50 g). When the mixture had warmed up to RT and all of the ammonia had evaporated, the almost colorless residue was taken up in water (100 ml) and extracted with Et_2O (3 x 100 ml). Washing with satd. aq. NaCl (50 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure furnished cyclohexadiene **55** as a slightly yellowish oil, which was used as such in the following transformation. An analytically pure sample of **55** could be obtained by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient).

TLC: R_f = 0.55 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.50 (s, 2H), 3.69 (m, 4H), 2.56-2.40 (m, 2H), 1.74 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 173.81, 133.84, 116.22, 51.99, 44.08, 35.63, 23.02; **IR** (thin film): 2968, 2953, 2942, 2869, 2814, 1738, 1610, 1435, 1381, 1316, 1265, 1221, 1192, 1170, 1116, 1007, 928, 832, 761 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{10}H_{14}O_2$ ($[M]^+$), 166.0989; found, 166.0991.

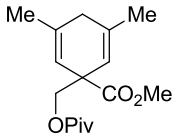


Methyl 1-(hydroxymethyl)-3,5-dimethylcyclohexa-2,5-dienecarboxylate (56). To a solution of diisopropylamine (2.75 ml, 19.3 mmol, 1.20 equiv) in THF (25 ml) at –78 °C was added *n*-butyllithium, 1.6 M in hexanes (12.1 ml, 19.3 mmol, 1.20 equiv). After 15 min of stirring, a solution of ester **55** (2.67 g, 16.1 mmol, 1.00 equiv) in THF (3.0 ml) was added. THF (2.0 ml) was used to assist the transfer. The resulting mixture was stirred for 15 min at the same temperature and then allowed to warm up to –20 °C. Gaseous formaldehyde[23] was bubbled into the solution for 30 min, using Ar as a carrier-gas. The reaction was quenched at –20 °C by addition of 1 M aq. HCl (25 ml). Extraction with EtOAc (3 x 50 ml), washing with satd. aq. $NaHCO_3$ (2 x 10 ml), satd. aq. NaCl (10 ml) and drying over $MgSO_4$, followed by filtration and concentration under reduced pressure furnished the crude product as an amber oil. Purification by column chromatography (hexane / EtOAc; 7:3) gave alcohol **56** (2.78 g, 88%) as a slightly yellowish oil. Yields ranged typically between 48% and 88%.

TLC: R_f = 0.44 (hexane / EtOAc; 6:4; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.47 (s, 2H), 3.70 (s, 3H), 3.63 (d, ^3J = 6.9 Hz, 2H), 2.58-2.46 (m, 2H), 2.01 (m, 1H), 1.78 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 174.85, 135.42, 118.49, 68.96, 53.01, 52.29, 36.12. 23.02;

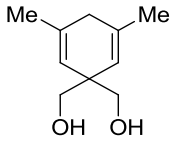
[23] Gaseous formaldehyde was generated by heating paraformaldehyde to 150 °C.

IR (thin film): 3450, 2966, 2951, 2935, 2914, 2876, 2855, 2811, 1726, 1435, 1383, 1242, 1198, 1078, 1041, 926, 914, 824, 743 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{11}H_{16}NaO_3$ ($[M+Na]^+$), 219.0992; found, 219.0993.



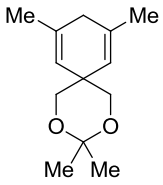
Methyl 3,5-dimethyl-1-((pivaloyloxy)methyl)cyclohexa-2,5-dienecarboxylate (58) [63, 64]. NH_3 (400 ml) was condensed into a solution of methyl 3,5-dimethylbenzoate (**54**, 10.0 g, 60.9 mmol, 1.00 equiv) and *tert*-butanol (6.12 ml, 63.9 mmol, 1.05 equiv) in THF (200 ml) at –78 °C. Small pieces of lithium metal (930 mg, 134 mmol, 2.20 equiv) were added and the resulting mixture was stirred for 30 min. During this period the color of the reaction mixture changed to amber, later to dark royal blue. The excess of lithium was destroyed by addition of 1,3-pentadiene (0.5 ml). To the resulting yellow solution was added via cannula over 10 min a solution of iodomethyl pivalate (14.74 g, 60.9 mmol, 1.00 equiv) in THF (50 ml). The yellow color of the reaction mixture disappeared towards the end of the addition. The reaction was stirred at –78 °C for 1 h and was then quenched by addition of solid NH_4Cl (20 g). After the mixture had warmed up to RT and all of the ammonia had evaporated, the yellow residue was taken up in water (100 ml) and extracted with Et_2O (3 x 50 ml). Washing with satd. aq. NaCl (25 ml), drying over $MgSO_4$ and concentration under reduced pressure furnished cyclohexadiene **58** as a slightly yellowish oil, which was used as such in the following transformation. An analytically pure sample of **58** could be obtained by column chromatography (hexane / EtOAc; 95:5).

TLC: R_f = 0.39 (hexane / EtOAc; 95:5; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.47 (s, 2H), 4.09 (s, 2H), 3.68 (s, 3H), 2.54–2.42 (m, 2H), 1.75 (s, 6H), 1.15 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 177.88, 173.48, 134.91, 118.24, 69.45, 52.18, 50.76, 38.82, 36.01, 27.06, 22.94; **IR** (thin film): 3042, 2972, 2957, 2935, 2914, 2872, 2857, 2810, 1733, 1480, 1450, 1435, 1417, 1395, 1364, 1282, 1249, 1219, 1197, 1152, 1094, 1081, 1035, 999, 980, 926, 827 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}NaO_4$ ($[M+Na]^+$), 303.1567; found, 303.1568.



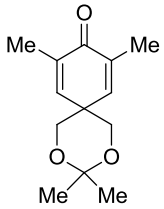
(3,5-Dimethylcyclohexa-2,5-diene-1,1-diyl)dimethanol (57). To a solution of cyclohexadiene **58** (ca. 61 mmol, 1.00 equiv) in THF (120 ml) at 0 °C was added dropwise over 20 min lithium aluminum hydride, 4.0 M in Et_2O (22.8 ml, 91.0 mmol, 1.50 equiv). The resulting mixture was stirred at this temperature for 30 min. The reaction was carefully quenched by slow addition of MeOH (5 ml). **Caution: Vigorous gas-evolution!** Satd. aq. $NaHCO_3$ (200 ml) and satd. aq. NaCl (200 ml) were added and the resulting mixture was extracted with EtOAc (3 x 150 ml). The combined organic extracts were washed with satd. aq. NaCl (100 ml), dried over $MgSO_4$ and concentrated under reduced pressure to furnish diol **57** as a white solid, which was used as such in the next transformation. An analytically pure sample of 57 be obtained by column chromatography (CH_2Cl_2 / MeOH; 95:5 to 9:1 gradient).

TLC: R_f = 0.30 (CH_2Cl_2 / MeOH; 95:5; $KMnO_4$); **Melting point:** 99 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.26 (s, 2H), 3.47 (s, 4H), 2.53 (s, 2H), 1.78 (s, 6H), 1.62 (br s, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 136.5, 121.1, 68.4, 47.3, 36.6, 23.1; **IR** (thin film): 3303, 3028, 2998, 2966, 2930, 2862, 2840, 2807, 1451, 1436, 1417, 1385, 1368, 1254, 1211, 1116, 1090, 1050, 1034, 1021, 928, 915, 896, 823, 728, 684 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{10}H_{17}O_2$ ($[M+H]^+$), 169.1223; found, 169.1219.



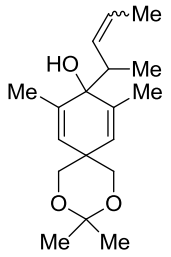
3,3,8,10-Tetramethyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (59). To a suspension of diol **57** (ca. 61 mmol, 1.00 equiv) in 2,2-dimethoxypropane (120 ml) at RT was added *p*-toluenesulfonic acid monohydrate (116 mg, 0.609 mmol, 0.01 equiv). After 30 min of stirring satd. aq. $NaHCO_3$ (100 ml) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 50 ml). The combined organic extracts were washed with satd. aq. NaCl (25 ml) and dried over $MgSO_4$. After evaporation of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (hexane / EtOAc; 95:5) to obtain pure spiroketal **59** (12.2 g, 96% over three steps) as a colorless oil.

TLC: R_f = 0.25 (hexane / EtOAc; 95:5; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.51 (s, 2H), 3.59 (s, 4H), 2.49 (s, 2H), 1.73 (s, 6H), 1.46 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 133.28, 121.83, 97.49, 69.29, 38.14, 36.93, 23.80, 22.96; **IR** (thin film): 2992, 2965, 2854, 2812, 2360, 2342, 1449, 1438, 1383, 1368, 1341, 1267, 1220, 1212, 1192, 1163, 1127, 1115, 1072, 1031, 927, 914, 840, 743, 730, 668, 520 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{13}H_{20}NaO_2$ ($[M+Na]^+$), 231.1356; found, 231.1353.



3,3,8,10-Tetramethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-9-one (19). To a solution of cyclohexadiene **59** (4.20 g, 20.1 mmol, 1.00 equiv) in CH_2Cl_2 (100 ml) at 0 °C was added in this order potassium carbonate (700 mg, 5.04 mmol, 0.25 equiv), palladium, 10% w/w on carbon (536 mg, 0.50 mmol, 0.025 equiv) and *tert*-butyl hydroperoxide, 5.5 M in decane (9.20 ml, 50.4 mmol, 2.5 equiv). The reaction was stirred at 0 °C for 16 h. The cold reaction mixture was filtered through a plug of celite (cold CH_2Cl_2, 3 x 20 ml used to rinse) and concentrated at 0 °C by rotary-evaporator. The resulting oil was immediately submitted to column chromatography (hexane / EtOAc; 9:1 to 8:2 gradient) to give cyclohexadienone **59** (2.71 g, 61%) as a white solid.

TLC: R_f = 0.35 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **Melting point:** 138 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.91 (s, 2H), 3.77 (s, 4H), 1.94 (s, 6H), 1.53 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 186.75, 143.38, 137.06, 98.32, 66.63, 40.59, 23.58, 16.41; **IR** (thin film): 2986, 2949, 2924, 2877, 1666, 1635, 1452, 1425, 1388, 1368, 1347, 1263, 1234, 1212, 1196, 1163, 1114, 1072, 1036, 1018, 908, 8333, 743 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{13}H_{18}NaO_3$ ($[M+Na]^+$), 245.1148; found, 245.1158.



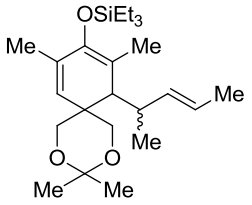
3,3,8,10-Tetramethyl-9-(pent-3-en-2-yl)-2,4-dioxaspiro[5.5]undeca-7,10-dien-9-ol (18). *Method A:* A solution of lithium naphthalenide [257, 258], 0.675 M in THF (13.3 ml, 9.00 mmol, 4.00 equiv) was diluted with THF (60 ml) and cooled to −78 °C. (*E*)-pent-3-en-2-yl(phenyl)sulfane (**41**) (842 mg, 4.72 mmol, 2.10 equiv) in THF (15.0 ml) was added dropwise over 5 min. Upon consumption of the lithium naphthalenide, the color of the dark-green mixture changed to red-brown. Titanium(IV) isopropoxide (2.69 ml, 9.00 mmol, 4.00 equiv) in THF (5.0 ml) was added slowly at the same temperature. After 30 min of stirring, the mixture was allowed to warm up to −40 °C and a solution of ketone **19** (500 mg, 2.25 mmol, 1.00 equiv) in THF (5.0 ml) was added via cannula. THF (5.0 ml) was used to assist the transfer. The mixture was allowed to slowly warm up to 0 °C over 1.5 h. The reaction was quenched by addition of a mixture of 1 M aq. NaOH and satd. aq. Na-K-tartrate (1:9, 150 ml), then allowed to reach RT. Extraction with Et_2O (3 x 100 ml), washing with satd. aq. NaCl (25 ml) drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product. Purification by chromatography on silica gel (hexane / MTBE; 8:2 to 7:3 gradient) yielded tertiary alcohol **18** (617 mg, 94%) as exclusive (*Z*)-isomer.

*(Z)-3,3,8,10-tetramethyl-9-(pent-3-en-2-yl)-2,4-dioxaspiro[5.5]undeca-7,10-dien-9-ol (Z-**18**):* **TLC:** R_f = 0.33 (hexane / MTBE; 8:2; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.78 (s, 1H), 5.72-5.64 (m, 2H), 5.34 (m, 1H), 3.63 (m, 4H), 3.02 (m, 1H), 2.28 (s, 1H), 1.93 (d, ^4J = 1.3 Hz, 3H), 1.81 (d, ^4J = 1.3 Hz, 3H), 1.74 (dd, ^3J = 6.8 Hz, ^4J = 1.8 Hz, 3H), 1.48 (s, 6H), 0.85 (d, ^3J = 7.0 Hz, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 137.24, 136.54, 132.17, 127.32, 126.72, 126.46, 97.53, 76.19, 68.88, 68.56, 37.58, 37.39, 23.90, 20.08, 18.45, 163.98, 13.57.

Method B: To a suspension of titanocene chloride (11.3 g, 45.5 mmol, 3.00 equiv) in THF (120 ml) at –78 °C was added dropwise over 15 min *n*-butyllithium, 1.6 M in hexanes (56.9 ml, 91.0 mmol, 6.00 equiv). The resulting mixture was stirred at –78 °C for 1 h. (*E*)-4-methoxypent-2-ene (**61**) (2.97 ml, 22.7 mmol, 1.50 equiv) was added dropwise. Stirring was continued for 30 min at –78 °C and then at RT for 20 min. The reaction was cooled to –40 °C and stirred for 10 min, before a solution of ketone **19** (3.37 g, 15.2 mmol, 1.00 equiv) in THF (20 ml) was added slowly via cannula. THF (10 ml) used to assist the transfer. The reaction

mixture was stirred and allowed to gradually warm up to 10 °C over 3 h. The reaction was quenched by addition of 1 M aq. NaOH (3 ml), followed by addition of celite (33 g) and NaF (33 g). Air was bubbled into the reaction mixture under vigorous stirring until the black color disappeared (ca. 20 min). The resulting yellow slurry was filtered through a plug of celite and the filter cake was washed with Et_2O (3 x 50 ml). The combined filtrate was concentrated under reduced pressure to give an orange oil that was purified by chromatography on silica gel (hexane / MTBE; 7:3) to furnish alcohol **18** (2.77 g, 62%) as a 3.8:1 mixture of olefin geometrical isomers.

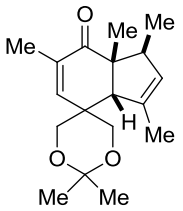
TLC: R_f = 0.33 (hexane / MTBE; 8:2; $KMnO_4$); **^{1}H-NMR** (3.8:1 olefin geometrical isomer ratio, asterisk denotes minor isomer signals, 400 MHz, $CDCl_3$): δ 5.78* (s, 1H), 5.76 (s, 1H), 5.73 (s, 1H), 5.68* (m, 1H), 5.56 (dq, ^3J = 15.3 Hz, 6.2 Hz, 1H), 5.44 (dd, ^3J = 15.3 Hz, 8.3 Hz, 1H), 5.33* (m, 1H), 3.61 (m, 4H), 3.02* (m, 1H), 2.55 (m, 1H), 2.27* (s, 1H), 2.21 (s,1H), 1.92* (s, 3H), 1.85 (s, 3H), 1.80* (s, 3H), 1.78 (s, 3H), 1.72 (m, 3H), 1.47 (s, 6H), 0.86 (d, ^3J = 7.1 Hz, 3H), 0.84 (d, ^3J = Hz, 7.1 Hz, 1H); **^{13}C-NMR** (asterisk denotes minor isomer signals, 100 MHz, $CDCl_3$): 137.56, 137.51*, 136.74, 133.27, 132.41*, 127.62, 126.99*, 126.94, 126.90, 126.76*, 97.65, 76.25*, 75.64, 68.69*, 68.61, 68.58, 42.89, 37.48*, 37.43, 37.27*, 23.74, 23.70, 20.01, 19.90*, 18.21*, 18.17, 18.08, 16.77*, 16.15, 13.35; **IR** (thin film): 3459, 2991, 2965, 2928, 2858, 1678, 1452, 1381, 1371, 1269, 1259, 1226, 1202, 1162, 1115, 1074, 1005, 968, 935, 847, 827, 753, 731, 519 cm^{-1}; **HRMS** (EI): exact mass calculated for $C_{17}H_{25}O_3$ ($[M–CH_3]^+$), 277.1799; found, 277.1797.

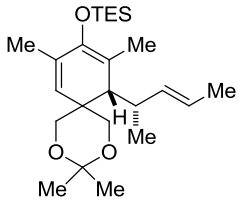


(*E*)-Triethyl((3,3,8,10-tetramethyl-11-(pent-3-en-2-yl)-2,4-dioxaspiro[5.5]undeca-7,9-dien-9-yl)oxy)silane (60). To a solution of potassium *tert*-butoxide (1.54 g, 13.7 mmol, 3.00 equiv) and 18-crow-6 ether (3.62 g, 13.7 mmol, 3.00 equiv) in THF (450 ml) at –78 °C was added via cannula a solution of alcohol **18** (1.34 g, 4.57 mmol, 1.00 equiv) in THF (15 ml). THF (10 ml) was used to rinse. The resulting mixture was stirred and allowed to warm up to –40 °C over 3 h, then kept at this temperature 2.5 h. The reaction was cooled to –78 °C, before triethylchlorosilane (2.30 ml, 13.7 mmol, 3.0 equiv) was added dropwise. After 30 min of stirring, the reaction was quenched by addition of pH 7 buffer, 0.05 M (300 ml). The mixture

was allowed to warm up to RT and extracted with diethyl ether (3 x 105 ml). The combined extracts were washed with satd. aq. NaCl (50 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product as a slightly yellowish oil. Purification by column chromatography (hexane / Et_2O; 98:2 to 96:4 gradient) yielded silyl enol ether **60** (1.31 g, 70%) as an inseparable 3.6:1 mixture of diastereomers.

TLC: R_f = 0.24 (hexane / Et_2O; 95:5; $KMnO_4$); **^{1}H-NMR** (3.6:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 400 MHz, $CDCl_3$): δ 5.43 (ddq, ^3J = 15.3 Hz, 8.3 Hz, ^4J = 1.5 Hz, 1H), 5.24 (dq, ^3J = 15.3 Hz, 6.4 Hz, 1H), 5.05* (s, 1H), 5.01 (s, 1H), 4.00 (d, ^2J = 11.8 Hz, 1H), 3.95* (d, ^2J = 11.7 Hz, 1H), 3.73–3.55 (m, 3H), 2.46 (m, 1H), 2.32 (br s, 1H), 1.78 (s, 3H), 1.70 (m, 3H), 1.63* (d, ^3J = 6.4 Hz, 3H), 5.57 (d, ^3J = 6.3 Hz, 3H), 1.42 (m, 6H), 1.00 (m, 12H), 0.71 (m, 6H); **^{13}C-NMR** (asterisk denotes minor diastereomer signals, 100 MHz, $CDCl_3$): 145.5, 145.0*, 137.6*, 136.0, 133.7*, 133.2, 125.7, 124.8*, 122.0, 121.9*, 112.0*, 111.6, 97.8, 66.8*, 66.7, 65.8*, 65.5, 48.4, 37.2, 37.1, 36.9*, 36.4*, 25.7*, 25.4, 22.32, 22.12*, 20.7, 19.2, 18.9*, 18.1*, 18.0, 15.7, 6.9, 5.6, 5.5*; **IR** (thin film): 2958, 2916, 2878, 1662, 1611, 1452, 1414, 1381, 1368, 1343, 1230, 1195, 1163, 1119, 1071, 1032, 1005, 974, 916, 893, 837, 799, 740 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{43}O_3Si$ ($[M+H]^+$), 407.2976; found, 407.2987.





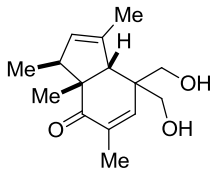
(1'*SR*,3a'*RS*,7a'*RS*)-1',2,2,3',6',7a'-Hexamethyl-1',7a'-dihydrospiro[[1,3]dioxane-5,4'-inden]-7'(3a'H)-one (16). Triethyl(((*R*S)-3,3,8,10-tetramethyl-11-((*SR*,*E*)-pent-3-en-2-yl)-2,4-dioxaspiro[5.5]undeca-7,9-dien-9-yl)oxy)silane (60). To a solution of silyl enol ether **60** (1.99 g, 4.90 mmol, 1.00 equiv) in DMSO (100 ml) was added at RT palladium(II) acetate (110 mg, 0.490 mmol, 0.10 equiv). The flask was evacuated and purged three times with oxygen. The reaction was heated to 45 °C under an atmosphere of oxygen for 72 h. The mixture was taken up in water (100 ml) and extracted with EtOAc (3 x 100 ml). The combined organic layers were washed with satd. aq. NaCl (50 ml) and dried over $MgSO_4$. Filtration and concentration under reduced pressure furnished a crude oil that was purified by chromatography on silica gel (hexane / MTBE; 9:1 to 8:2 gradient) to give dihydroindenone

16 (1.05 g, 74%) as a white solid, along with recovered enolsilane **60** (minor diastereomer, 353 mg, 18%) as an amber oil.

*(1'SR,3a'RS,7a'RS)-1',2,2,3',6',7a'-Hexamethyl-1',7a'-dihydrospiro[[1,3]dioxane-5,4'-inden]-7'(3a'H)-one (**16**):* **TLC:** R_f = 0.25 (hexane / MTBE; 9:1; UV / $KMnO_4$); **Melting point:** 69 °C; **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 7.17 (s, 1H), 5.29 (s, 1H), 4.03 (d, ^2J = 11.5 Hz, 1H), 3.99 (d, ^2J = 11.5 Hz, 1H), 3.48 (dd, ^2J = 11.6 Hz, ^4J = 2.1 Hz, 1H), 3.44 (dd, ^2J = 11.5 Hz, ^4J = 2.0 Hz, 1H), 2.70 (m, 1H), 2.04 (s, 1H), 1.92 (s, 3H), 1.87 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 1.10 (d, ^3J = 7.2 Hz, 3H), 1.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$, relative to TMS): δ 203.34, 147.30, 137.35, 133.21, 133.17, 98.55, 67.61, 67.07, 59.63, 53.91, 45.28, 37.90, 27.94, 22.35, 20.01, 18.83, 16.47, 13.90; **IR** (thin film): 2990, 2960, 2875, 1665, 1450, 1374, 1251, 1226, 1201, 1158, 1110, 1073, 1036, 930, 896, 832 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{26}NaO_3$ ($[M+Na]^+$), 313.1774; found, 313.1776.

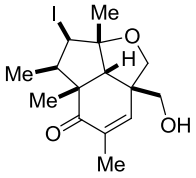
*Triethyl(((RS)-3,3,8,10-tetramethyl-11-((SR,E)-pent-3-en-2-yl)-2,4-dioxaspiro[5.5]undeca-7,9-dien-9-yl)oxy)silane (**60**):* **TLC:** R_f = 0.24 (hexane / Et_2O; 95:5; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.47 (ddq, ^3J = 15.3 Hz, ^3J = 6.6 Hz, ^4J = 1.5 Hz, 1H), 5.31 (ddq, ^3J = 15.3 Hz, ^3J = 6.2 Hz, ^4J = 1.2 Hz, 1H), 5.05 (s, 1H), δ 3.95 (dd, ^3J = 11.8 Hz, ^4J = 1.6 Hz, 1H), 3.71 (d, ^3J = 11.8 Hz, 1H), 3.64 (dd, ^3J = 11.2 Hz, ^4J = 1.6 Hz, 1H), 3.58 (d, ^3J = 11.2 Hz, 1H), 2.46 (m, 2H), 1.71 (d, ^3J = 1.5 Hz, 3H), 1.69 (s, 3H), 1.63 (d, ^3J = 6.3 Hz, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.02−0.95 (m, 12H), 0.74−0.65 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 145.01, 137.60, 133.66, 124.74, 121.87, 112.01, 97.75, 66.74, 65.83, 48.35, 36.89, 36.40, 25.66, 22.14, 18.86, 18.12, 17.96, 15.71, 6.92, 5.56; **IR** (thin film): 2991, 2957, 2938, 2917, 2878, 2860, 1663, 1612, 1451, 1414, 1382, 1368, 1343, 1230, 1193, 1163, 1120, 1072, 1032, 1005, 974, 935, 917, 875, 837, 738 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{43}O_3Si$ ($[M+H]^+$), 407.2976; found, 407.2981.

3.2.2.3 Attempted Installation of Vicinal Quaternary Centers



(1*SR*,3a*RS*,7a*RS*)-4,4-Bis(hydroxymethyl)-1,3,6,7a-tetramethyl-3a,4-dihydro-1H-inden-7(7aH)-one (15). To a solution of acetonide **16** (1.00 g, 3.44 mmol, 1.00 equiv) in THF (35 ml) at RT was added 1 M aq. HCl (10.0 ml, 10.0 mmol, 2.90 equiv). The resulting mixture was stirred at the same temperature for 8 h. The pH of the mixture was adjusted to 8–9 by the addition of concentrated ammonium hydroxide (ca. 1.5 ml). The resulting mixture was extracted with CH_2Cl_2 (5 x 25 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2 / MeOH; 95:5 to 93:7 gradient) to furnish diol **15** (860 mg, quantitative) as a white solid.

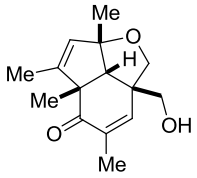
TLC: R_f = 0.23 (CH_2Cl_2 / MeOH; 95:5; UV / $KMnO_4$); **Melting point:** 82 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.71 (s, 1H), 5.30 (s, 1H), 4.05 (d, ^2J = 10.7 Hz, 1H), 3.63–3.47 (m, 3H), 2.97, (m, 1H), 2.07 (br s, 1H), 1.87 (s, 6H), 1.15 (d, ^3J = 7.4 Hz, 3H), 1.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 204.47, 144.84,138.09, 136.14, 133.81, 67.80, 67.51, 58.85, 53.73, 45.78, 45.20, 23.73, 18.70, 16.56, 14.63; **IR** (thin film): 3421, 2959, 2919, 2872, 1660, 1642, 1450, 1378, 1252, 1039, 914, 881, 810, 795 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{22}NaO_3$ ($[M+Na]^+$), 273.1461; found, 273.1449.



(2a*RS*,2a1*RS*,5a*SR*,6*RS*,7*RS*,7a*RS*)-2a-(hydroxymethyl)-7-iodo-4,5a,6,7a-tetramethyl-2,2a,5a,6,7,7a-hexahydroindeno[1,7-bc]furan-5(2a1H)-one (72). To a stirred solution of diol **15** (164 mg, 0.654 mmol, 1.00 equiv) in MeCN (30 ml) was added Na_2CO_3 (347 mg, 3.27 mmol, 5.00 equiv), followed by iodine (415 mg, 1.64 mmol, 2.50 equiv). The resulting mixture was stirred in the dark for 1 h. The reaction mixture was diluted with Et_2O (20 ml) and treated with satd. aq. sodium thiosulfate (30 ml). Extraction with Et_2O (3 x 25 ml), washing with satd. aq. NaCl (10 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure furnished iodoether **72** as an amber oil that was used as such in the

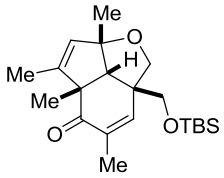
following transformation. An analytically pure sample of **72** could be obtained by column chromatography (CH_2Cl_2 / MeOH; 97.5:2.5).

TLC: R_f = 0.45 (CH_2Cl_2 / MeOH; 95:5; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.43 (s, 1H), 4.43 (d, ^3J = 6.7 Hz, 1H), 3.98 (d, ^2J = 9.5 Hz, 1H), 3.76 (d, ^2J = 9.5 Hz, 1H), 3.69 (dd, ^2J = 10.3 Hz, ^3J = 4.5 Hz, 1H), 3.62 (dd, ^2J = 10.3 Hz, ^3J = 5.7 Hz, 1H), 2.87 (m, 1H), 2.44 (s, 1H), 1.87 (d, ^4J = 1.4 Hz, 3H), 1.66 (m, 1H), 1.60 (s, 3H), 1.20 (s, 3H), 1.09 (d, ^3J = 7.5 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 201.91, 143.10, 134.94, 94.06, 76.59, 67.85, 58.52, 51.70, 48.65, 47.05, 44.21, 30.38, 23.38, 17.16, 16.15; **IR** (thin film): 3460, 2972, 2930, 2863, 1660, 1446, 1385, 1213, 1121, 1052, 993, 911, 831, 705 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{22}IO_3$ ($[M+H]^+$), 377.0608; found, 377.0614.



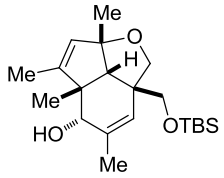
(2a*RS*,2a1*RS*,5a*SR*,7a*SR*)-2a-(hydroxymethyl)-4,5a,6,7a-tetramethyl-2,2a,5a,7a-tetrahydroindeno[1,7-bc]furan-5(2a1H)-one (73). To a solution of iodoether **72** (246 mg, 0.654 mmol, 1.00 equiv) in benzene (20 ml) was added DBU (0.500 ml, 3.27 mmol, 5.00 equiv). The resulting mixture was heated to 70 °C for 30 h. After cooling to RT, the mixture was diluted with Et_2O (50 ml) and washed with satd. aq. NaCl (10 x 3 ml). Drying over $MgSO_4$, filtration, and concentration under reduced pressure furnished a yellow crude that was purified by chromatography on silica gel (hex / EtOAc; 6:4) to deliver diene **73** (147 mg, 91% over two steps) as an amber oil.

TLC: R_f = 0.30 (hex / EtOAc; 6:4; UV / $KMnO_4$); **Melting point:** 78 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.45 (s, 1H), 5.22 (s, 1H), 3.87 (d, ^2J = 8.9 Hz, 1H), 3.62 (d, ^2J = 10.3 Hz, 1H), 3.49 (d, ^2J = 10.3 Hz, 1H), 3.40 (d, ^2J = 8.9 Hz, 1H), 2.20 (s, 1H), 1.81 (d, ^4J = 1.4 Hz, 3H), 1.45 (d, ^4J = 1.4 Hz, 3H), 1.50 (s, 3H), 1.30 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 199.40, 147.89, 142.89, 134.62, 129.08, 95.61, 72.45, 68.73, 60.10, 56.86, 49.64, 25.52, 25.47, 16.87, 13.13; **IR** (thin film): 3447, 2970, 2928, 2865, 1661, 1447, 1374, 1310, 1254, 1237, 1206, 1155, 1138, 1115, 1100, 1053, 1001, 969, 889, 861, 838, 778, 698, 553 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{20}NaO_3$ ($[M+Na]^+$), 271.1305; found, 271.1311.



(2a*SR*,2a1*RS*,5a*SR*,7a*SR*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,5a,7a-tetrahydroindeno[1,7-bc]furan-5(2a1H)-one (74). To a stirred solution of alcohol **73** (143 mg, 0.576 mmol, 1.00 equiv) in DMF (2.5 ml) at 0 °C was added imidazole (98 mg, 1.44 mmol, 2.50 equiv), followed by TBS chloride (195 mg, 1.27 mmol, 2.20 equiv). The resulting mixture was stirred at this temperature for 1h. The reaction was quenched by pouring into satd. aq. NH_4Cl (50 ml). Extraction with Et_2O (3 x 25 ml), washing with satd. aq. NaCl (3 ml), drying over $MgSO_4$, filtration, and concentration gave a crude oil. Purification by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient) yielded TBS protected alcohol **74** (189 mg, 90%) as a colorless oil.

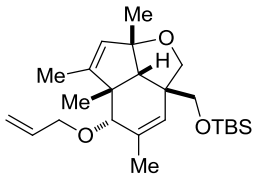
TLC: R_f = 0.48 (hex / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.48 (s, 1H), 5.22 (s, 1H), 3.88 (d, ^2J = 8.7 Hz, 1H), 3.55 (d, ^2J = 9.3 Hz, 1H), 3.36 (d, ^2J = 9.3 Hz, 1H), 3.32 (d, ^2J = 8.7 Hz, 1H), 2.03 (s, 1H), 1.79 (d, ^4J = 1.4 Hz, 3H), 1.58 (d, ^4J = 1.2 Hz, 3H), 1.48 (s, 3H), 1.28 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 199.55, 147.76, 144.49, 133.53, 129.30, 95.13, 71.94, 68.06, 60.18, 56.83, 49.82, 25.80, 25.75, 25.51, 18.23, 16.80, 13.16, −5.45, −5.50; **IR** (thin film): 2955, 2929, 2857, 1663, 1447, 1372, 1253, 1212, 1099, 1004, 972, 835, 776 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{35}O_3Si$ ($[M+H]^+$), 363.2350; found, 363.2351.



(2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*SR*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-5-ol (75). Diisobutylaluminum hydride, 1.0 M solution in hexane (1.00 ml, 1.00 mmol, 1.00 equiv) was diluted with toluene (2.40 ml) and the solution was cooled to 0 °C. *n*-Butyllithium, 1.6 M in hexane (0.60 ml, 1.00 mmol, 1.00 equiv) was added slowly and the resulting mixture was stirred for additional 30 min to give a clear colorless solution of ate complex (0.25 M). In a separate flask, a solution of enone **74** (137 mg, 0.378 mmol, 1.00 equiv) in toluene (7.6 ml) was cooled to –78 °C and ate complex, 0.25 M (2.4 ml, 0.605 mmol, 1.60 equiv) was added dropwise.

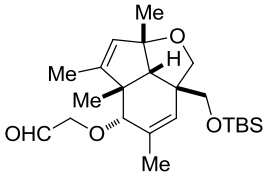
The resulting mixture was stirred at the same temperature for 1 h. The reaction was quenched at –78 °C by addition of a suspension of NaOMe in MeOH (1.0 wt%, 2 ml). After further 10 min of stirring, the cold mixture was poured into pH 7 buffer, 0.05 M (50 ml) and satd. aq. Na-K-tartrate (50 ml) was added. Extraction with Et_2O (3 x 25 ml), washing with stad. aq. NaCl (10 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure furnished the crude product. Purification by column chromatography gave secondary allylic alcohol **75** (115 mg, 84%) as a white solid.

TLC: R_f = 0.27 (hex / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.47 (q, ^4J = 1.5 Hz, 1H), 5.37 (q, ^4J = 1.5 Hz, 1H), 3.88 (d, ^3J = 9.1 Hz, 1H), 3.71 (d, ^2J = 9.0 Hz, 1H), 3.65 (d, ^2J = 9.0 Hz, 1H), 3.50 (d, ^2J = 9.4 Hz, 1H), 3.45 (d, ^2J = 9.4 Hz, 1H), 2.70 (d, ^3J = 9.1 Hz, 1H), 1.95 (s, 1H), 1.88 (d, ^4J = 1.5 Hz, 3H), 1.71 (d, ^4J = 1.5 Hz, 3H), 1.42 (s, 3H), 1.09 (s, 1H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 149.31, 136.90, 129.00, 126.65, 93.41, 73.10, 69.30, 61.00, 53.28, 49.58, 29.88, 26.04, 24.98, 23.55, 21.95, 18.51, 14.25, -5.15; **IR** (thin film): 3427, 2954, 2928, 2856, 1472, 1436, 1374, 1257, 1090, 1053, 1014, 938, 835, 775 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{36}NaO_3Si$ ($[M+Na]^+$), 387.2326; found, 387.2317.



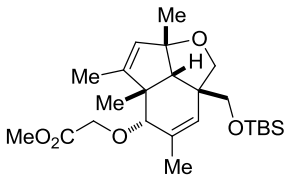
(((2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*SR*)-5-(allyloxy)-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-2a-yl)methoxy)(*tert*-butyl)dimethylsilane (76). A solu-tion of alcohol **75** (20.8 mg, 0.057 mmol, 1.00 equiv) in THF (0.5 ml) was added via cannula to a suspension of potassium hydride (9.2 mg, 0.228 mmol, 4.00 equiv) in THF (0.5 ml). THF (0.5 ml) was used to assist the transfer. Allyl bromide (0.025 ml, 0.285 mmol, 5.00 equiv) was added, followed by tetrabutylammonium iodide (4.2 mg, 0.011 mmol, 0.20 equiv). The reaction vessel was sealed and the mixture was heated to 60 °C for 30 h. The reaction was quenched by addition of pH 7 buffer, 0.05 M (3 ml) and the aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and the volatiles were evaporated *in vacuo*. Purification by chromatography on silica gel (hexane / EtOAc; 96:4 to 8:2 gradient) gave allyl ether **76** (19.5 mg, 84%, quant brsm) as a colorless oil, along with recovered starting material **75** (3.3 mg, 16%).

TLC: R_f = 0.56 (hex / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.93 (m, 1H), 5.34-5.24 (m, 2H), 5.17-5.11 (m, 2H), 4.17-4.10 (m, 1H), 4.01-3.94 (m, 1H), 3.83 (s, 1H), 3.68 (d, ^2J = 8.5 Hz, 1H), 3.42 (d, ^2J = 8.5 Hz, 1H), 3.38 (s, 2H), 2.01 (s, 1H), 1.79 (m, 3H), 1.67 (d, ^4J = 1.5 Hz, 3H), 1.42 (s, 3H), 1.25 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 148.38, 137.61, 134.81, 130.12, 126.49, 115.37, 93.80, 83.35, 74.21, 74.06, 67.92, 60.94, 53.86, 51.28, 26.07, 25.33, 19.35, 18.49, 15.78, −5.09, −5.14; **IR** (thin film): 2955, 2921, 2857, 1462, 1372, 1256, 1096, 1067, 1006, 919, 835, 775 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_3Si$ ($[M+Na]^+$), 427.2639; found, 427.2624.



2-(((2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*SR*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno [1,7-bc] furan-5-yl) oxy) acetaldehyde (229). To a solution of olefin **76** (15.0 mg, 0.037 mmol, 1.00 equiv) in 1,4-dioxane (1.0 ml) was added in this order 2,6-lutidine (8.6 µl, 0.074 mmol, 2.00 equiv), osmium tetroxide, 0.08% in H_2O (350 µl, 1.11 µmol, 0.03 equiv) and $NaIO_4$ (31.7 mg, 0.148 mmol, 4.00 equiv). The resulting mixture was stirred at RT for 6 h. As TLC indicated nearly full conversion, the reaction mixture was poured into water (5 ml), and extracted with EtOAc (3 x 10 ml). The organic layers were washed with satd. aq. NaCl (10 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography gave aldehyde **229** (12.3 mg, 82%, 96% brsm) as a white solid, along with recovered starting material (2.1 mg, 14%).

TLC: R_f = 0.24 (hex / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 9.80 (m, 1H), 5.30 (m, 1H), 5.21 (m, 1H), 4.21 (dd, ^2J = 17.3 Hz, ^3J = 1.3 Hz, 1H), 4.05 (dd, ^2J = 17.3 Hz, ^3J = 1.3 Hz, 1H), 3.91 (s, 1H), 3.67 (d, ^2J = 8.6 Hz, 1H), 3.43 (d, ^2J = 8.6 Hz, 1H), 3.39 (m, 2H), 2.02 (s, 1H), 1.82 (m, 3H), 1.70 (d, ^4J = 1.4 Hz, 3H), 1.44 (s, 3H), 1.28 (s, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 200.68, 147.73, 136.04, 130.54, 127.60, 93.74, 85.72, 78.64, 74.09, 68.16, 60.98, 53.92, 51.36, 26.13, 26.05, 25.44, 19.70, 18.47, 15.64, -5.10, -5.15; **IR** (thin film): 2953, 2927, 2856, 1740, 1472, 1439, 1373, 1256, 1098, 1062, 1002, 835, 776 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{23}H_{38}NaO_4Si$ ($[M+Na]^+$), 429.2432; found, 429.2438.

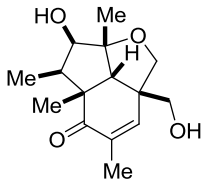


Methyl 2-(((2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*SR*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno [1,7-bc] furan-5-yl) oxy) acetate (77). To a stirred solution of aldehyde **229** (15.0 mg, 0.037 mmol, 1.00 equiv) in *tert*-butanol (0.5 ml) at RT was added 2-methyl-2-butene (0.270 ml, 2.58 mmol, 70 equiv), followed by a solution of sodium dihydrogen phosphate (31.0 mg, 0.258 mmol, 7.00 equiv) and sodium chlorite (25.0 mg, 0.221 mmol, 6.00 equiv) in 0.5 ml of H_2O. After 1.5 h, as TLC indicated full conversion, the mixture was diluted with water (3 ml) and extracted with Et_2O (5 x 5 ml). The combined organic extracts were washed with satd. aq. NaCl (1.5 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in methanol (2.0 ml) and the resulting solution was cooled to 0 °C. Trimethylsilyl diazomethane, 2.0 M in Et_2O (0.280 ml, 0.553 mmol, 15.0 equiv) was added until a slightly yellow color persisted. The mixture was allowed to warm up to RT and stirred for additional 30 min. Removal of the volatiles under reduced pressure and purification by chromatography on silica gel (hexane / EtOAc; 9:1 to 8:2 gradient) delivered ester **77** (14.0 mg, 87%) as a colorless oil.

TLC: R_f = 0.26 (hex / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.29 (m, 1H), 5.18 (m, 1H), 4.27 (d, ^2J = 15.7 Hz, 1H), 4.08 (d, ^2J = 15.7 Hz, 1H), 3.91 (s, 1H), 3.75 (s, 3H), 3.67 (d, ^2J = 8.5 Hz, 1H), 3.44 (d, ^2J = 8.5 Hz, 1H), 3.44 (m, 2H), 2.01 (s, 1H), 1.82 (m, 3H), 1.70 (d, ^4J = 1.4 Hz, 3H), 1.42 (s, 3H), 1.29 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.12, 148.23, 136.62, 130.17, 127.38, 93.75, 85.13, 74.21, 70.33, 67.97, 60.98, 54.09, 51.76, 51.38, 26.18, 26.05, 25.43, 19.72, 18.47, 15.55, -5.11, -5.16; **IR** (thin film): 2954, 2911, 2857, 1765, 1739, 1472, 1438, 1374, 1252, 1205, 1138, 1119, 1095, 1062, 836, 780 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_5Si$ ($[M+Na]^+$), 459.2537; found, 459.2531.

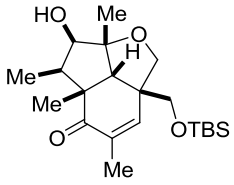
3.2.3 Third Generation Approach

3.2.3.1 Claisen Rearrangement



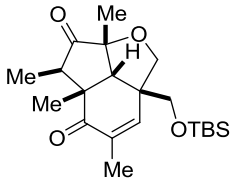
(2a*RS*,2a1*RS*,5a*RS*,6*RS*,7*RS*,7a*RS*)-7-Hydroxy-2a-(hydroxymethyl)-4,5a,6,7a-tetramethyl-2,2a,5a,6,7,7a-hexahydroindeno[1,7-bc]furan-5(2a1H)-one (87). To a mixture of diol **15** (860 mg, 3.44 mmol, 1.00 equiv) and 4 Å molecular sieves (powdered, 250 mg) in CH_2Cl_2 (35 ml) at RT was added 4,4'-thiobis(2-*tert*-butyl-5-methylphenol) (30.8 mg, 0.086 mmol, 0.025 equiv), vanadyl acetylacetonate (45.5 mg, 0.172 mmol, 0.05 equiv) and *tert*-butyl hydroperoxide, ca. 5.5 M in nonane (1.87 ml, 10.31 mmol, 3.00 equiv). Upon addition of the *tert*-butyl hydroperoxide, the initially green suspension turned brown immediately, later dark-red. The reaction was heated to reflux for 12 h. The mixture was filtered through a plug of celite. CH_2Cl_2 (15 ml) was used to rinse. The filtrate was washed with 40% aq. $NaHSO_3$ (30 ml). Water (60 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (CH_2Cl_2 / MeOH; 97:3 to 95:5 gradient) yielded diol **87** (686 mg, 75%) as a white solid.

TLC: R_f = 0.34 (hexane / EtOAc; 3:7; UV / $KMnO_4$); **Melting point:** 132 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.34 (s, 1H), 4.04 (d, ^2J = 9.2 Hz, 1H), 3.67 (m, 2H), 3.52 (br d, ^2J = 10.3 Hz, 1H), 3.43 (m, 1H), 2.52 (d, ^3J = 8.8 Hz, 1H), 2.32 (s, 1H), 1.89 (m, 1H), 1.82 (s, 3H), 1.62 (br s, 1H), 1.45 (s, 3H), 1.07 (s, 3H), 0.95 (d, ^3J = 6.7 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 200.69, 140.58, 134.15, 90.56, 82.88, 74.88, 68.64, 60.69, 50.39, 49.64, 48.47, 25.70, 18.53, 16.95, 11.64; **IR** (thin film): 3413, 2967, 2926, 2875, 1659, 1652, 1453, 1382, 1230, 1196, 1154, 1070, 1044, 1214, 889, 8839, 800 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{22}NaO_4$ ($[M+Na]^+$), 289.1410; found, 289.1410.



(2a*SR*,2a1*RS*,5a*RS*,6*RS*,7a*RS*)-2a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-hydroxy-4,5a,6,7a-tetramethyl-2,2a,5a,6,7,7a-hexahydroindeno[1,7-bc]furan-5(2a1H)-one (92). To a solution of diol **87** (680 mg, 2.55 mmol, 1.00 equiv) in CH_2Cl_2 (10 ml) at 0 °C was added triethylamine (720 µl, 5.11 mmol, 2.00 equiv), followed by DMAP (62.4 mg, 0.511 mmol, 0.20 equiv) and finally *tert*-butyldimethylsilyl chloride (462 mg, 3.06 mmol, 1.20 equiv). The resulting mixture was allowed to warm up to RT and stirred for 60 h. The reaction was quenched by pouring into satd. aq. NH_4Cl (50 ml). Extraction with CH_2Cl_2 (3 x 25 ml), drying over $MgSO_4$, filtration and concentration gave a crude oil. Column chromatography (CH_2Cl_2 / MeOH; 99:1 to 95:5 gradient) furnished pure alcohol **92** (857 mg, 88%) as a colorless oil.

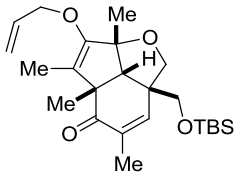
TLC: R_f = 0.44 (hexane / EtOAc; 7:3; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.35 (s, 1H), 4.07 (d, ^2J = 9.1 Hz, 1H), 3.62 (d, ^2J = 9.1 Hz, 1H), 3.54 (d, ^2J = 9.3 Hz, 1H), 3.41 (m, 2H), 2.50 (d, ^3J = 9.0 Hz, 1H), 2.19 (s, 1H), 1.88 (m, 1H), 1.80 (s, 3H), 1.43 (s, 3H), 1.05 (s, 3H), 0.95 (d, ^3J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 200.85, 141.85, 133.06, 90.31, 82.85, 74.50, 68.42, 60.69, 50.48, 49.59, 48.36, 30.31, 25.78, 25.60, 18.64, 16.87, 11.62, –5.49, –5.51; **IR** (thin film): 3482, 2953, 2930, 2857, 1665, 1472, 1452, 1372, 1255, 1115, 1055, 914, 837, 777, 745 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{37}O_4Si$ ($[M+H]^+$), 381.2456; found, 381.2450.



(2a*SR*,2a1*RS*,5a*SR*,6*RS*,7a*RS*)-2a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetra-methyl-2,2a,5a,6-tetrahydroindeno[1,7-bc]furan-5,7(2a1H,7aH)-dione (93). To a solution of alcohol **92** (850 mg, 2.233 mmol, 1.00 equiv) in CH_2Cl_2 (112 ml) was added at 0 °C DESS–MARTIN periodinane (1.42 g, 3.35 mmol, 1.50 equiv). The resulting reaction was stirred for 5 h, while it was allowed to warm up to RT. The reaction was diluted with CH_2Cl_2 (200 ml) and washed with a mixture of satd. aq. sodium thiosulfate solution (50 ml) and satd. aq. $NaHCO_3$ (50 ml). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 100 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under

reduced pressure. After chromatography on silica gel (hexane / EtOAc; 9:1) diketone **93** (800 mg, 95%) was obtained as a colorless oil.

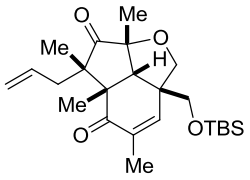
TLC: R_f = 0.23 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **Melting point:** 91 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.48 (s, 1H), 4.10 (d, ^2J = 9.5 Hz, 1H), 3.59 (d, ^2J = 9.4 Hz, 1H), 3.51 (d, ^2J = 9.5 Hz, 1H), 3.43 (d, ^2J = 9.4 Hz, 1H), 2.52 (q ^3J = 6.8 Hz, 1H), 2.33 (s, 1H), 1.86 (s, 3H), 1.43 (s, 3H), 1.03 (s, 3H), 0.96 (d, ^3J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 213.28, 199.67, 141.88, 132.56, 86.74, 74.14, 68.50, 57.26, 53.45, 50.27, 45.88, 25.76, 21.68, 19.23, 18.21, 16.99, 8.01, –5.45, –5.51; **IR** (thin film): 2955, 2930, 2858, 1752, 1669, 1471, 1452, 1384, 1254, 1115, 1054, 838, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{21}H_{38}NO_4Si$ ($[M+NH_4]^+$), 396.2565; found, 396.2561.



(2a*SR*,2a1*RS*,5a*SR*,7a*RS*)-7-(allyloxy)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,5a,7a-tetrahydroindeno[1,7-bc]furan-5(2a1H)-one (94). To a suspension of potassium hydride (4.5 mg, 0.11 mmol, 1.50 equiv) in THF (0.5 ml) was added dropwise via cannula a solution of ketone **93** (28.0 mg, 0.074 mmol, 1.00 equiv) in THF (1.0 ml). THF (0.5 ml) was used to assist the transfer. After a few minutes of stirring, the solution became deep-yellow. After 30 min the mixture was cooled to 0 °C and a solution of 18-crown-6 ether (39.1 mg, 0.148 mmol, 2.00 equiv) in THF (0.5 ml) was added, followed by allyl bromide (9.6 µl, 0.11 mmol, 1.50 equiv). Upon addition of 18-crown-6 ether, the mixture changed from yellow to deep-red. The red color disappeared a few minutes after the addition of allyl bromide. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by careful addition of pH 7 buffer, 0.05 M (3 ml). Extraction with Et_2O (3 x 5 ml), washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product. Purification by column chromatography (hexane / MTBE; 95:5 to 9:1 gradient) gave allyl vinyl ether **94** (29.1 mg, 94%) as a clear colorless oil.

TLC: R_f = 0.25 (hexane / MTBE; 95:5; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.47 (s, 1H), 6.00–5.91 (m, 1H), 5.31 (d, ^3J = 17.2 Hz, 1H), 5.18 (d, ^3J = 10.4 Hz, 1H), 4.55 (dd, ^2J = 12.8 Hz, ^3J = 5.4 Hz, 1H), 4.41 (dd, ^2J = 12.8 Hz, ^3J = 5.6 Hz, 1H), 3.91 (d, ^2J = 8.8

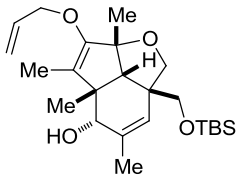
Hz, 1H), 3.54 (d, ^2J = 9.3 Hz, 1H), 3.38–3.34 (m, 2H), 2.00 (s, 1H), 1.79 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.24 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 199.52, 149.94, 143.68, 134.55, 133.32, 125.24, 116.78, 93.19, 72.25, 71.84, 68.05, 58.05, 50.77, 49.78, 25.80, 25.44, 24.11, 18.22, 16.84, 9.06, –5.46, –5.50; **IR** (thin film): 2956, 2929, 2858, 1664, 1472, 1373, 1312, 1258, 1163, 1112, 1074, 988, 919, 838, 777 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{39}O_4Si$ ($[M+H]^+$), 419.2612; found, 419.2627.



(2a*SR*,2a1*RS*,5a*SR*,6*SR*,7a*RS*)-6-allyl-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,5a,6-tetrahydroindeno[1,7-bc]furan-5,7(2a1H,7aH)-dione (95). A dry 50 ml air-free tube under N_2 was treated with a solution of BSA (1.5 ml) in hexanes (7.5 ml, HPLC grade) by warming to ca. 60 °C and repeated shaking of the closed vessel. The BSA solution was discarded and the tube was successively rinsed with hexanes (2 x 7.5 ml, HPLC grade) and dry Et_2O (7.5 ml). The tube was put under high vacuum at RT for 15 min. The prepared air-free tube was charged with a solution of allyl vinyl ether **94** (23.5 mg, 0.056 mmol, 1.00 equiv) in Et_2O (ca. 3 ml). The solvent was removed *in vacuo* and the remaining starting material was dried under high vacuum for 20 min. *o*-Xylene (5.0 ml) was added and the mixture was carefully degased (freeze-pump-thaw; 4 cycles). The air-free tube was sealed under a positive pressure of N_2 and placed in a preheated oil-bath (160 °C). The reaction was heated for 12 h. After cooling to RT, the solvent was removed by rotary evaporator at 60 °C water bath temperature to give crude tricycle **95** in greater than 95:5 diastereoselectivity. Column chromatography (hexane / EtOAc; 95:5) furnished **95** (23.0 mg, 98%) as a white solid.

TLC: R_f = 0.32 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **Melting point:** 98 °C; **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 6.49 (s, 1H), 5.59–5.51 (m, 1H), 5.04 (d, ^3J = 10.1 Hz, 1H), 4.93 (d, ^3J = 16.9 Hz, 1H), 4.07 (d, ^3J = 9.3 Hz, 1H), 3.86 (d, ^3J = 9.3 Hz, 1H), 3.61 (d, ^3J = 9.4 Hz, 1H), 3.53 (d, ^3J = 9.4 Hz, 1H), 2.64 (dd, ^2J = 13.7 Hz, ^3J = 6.0 Hz, 1H), 2.46 (s, 1H), 1.88 (s, 3H), 1.68 (dd, ^2J = 13.7 Hz, ^3J = 8.3 Hz, 1H), 1.38 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$, relative to TMS): δ 215.10, 199.96, 144.37, 136.64, 133.20, 118.64, 88.53, 75.15, 70.00, 58.35, 55.40, 51.49,

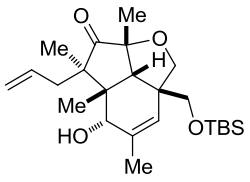
47.78, 40.11, 26.50, 25.77, 21.66, 18.22, 17.05, 16.70, –5.54; **IR** (thin film): 2954, 2929, 2857, 1746, 1662, 1472, 1462, 1447, 1384, 1255, 1105, 1074, 1044, 1006, 914, 838, 777, 744 cm^{-1}; **HRMS** (ESI): exact mass calculated for C24H38NaO4Si ($[M+H]^+$), 441.2432; found, 441.2430.



(2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*RS*)-7-(allyloxy)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-5-ol (96). A solution of DIBAL-H (1.0 ml, 1.0 mmol) was diluted with toluene (2.4 ml) and cooled to 0 °C. *n*-Butyllithium, 1.6 M in hexanes (0.6 ml, 1.0 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for additional 30 min to give a colorless solution of ate complex (0.25 M). In a separate flask, enone **94** (2.4 mg, 5.7 µmol, 1.0 equiv) was dissolved in toluene (1.0 ml) and cooled to –78 °C. Ate complex (34 µl, 8.6 mmol, 1.5 equiv) was added and the reaction mixture was stirred at this temperature for 15 min. The reaction was quenched at –78 °C by addition of NaOMe (5.4 mg, 0.1 mmol) in MeOH (0.2 ml). After further 10 min of stirring, pH 7 buffer, 0.05 M (1.5 ml) was added and the mixture was allowed to warm up to RT. Satd. aq. Na-K-tartrate (1.5 ml) was added and the mixture was extracted with Et_2O (3 x 5 ml). Washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product, which was purified by column chromatography (hexane / EtOAc; 9:1) to furnish alcohol **96** (2.4 mg, quantitative) as a colorless oil.

TLC: R_f = 0.34 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.03–5.94 (m, 1H), 5.46 (s, 1H), 5.32 (d, ^3J = 17.2 Hz, 1H), 5.19 (d, ^3J = 10.4 Hz, 1H), 4.46 (dd, ^2J = 12.7 Hz, ^3J = 5.5 Hz, 1H), 4.32 (dd, ^2J = 12.7 Hz, ^3J = 6.0 Hz, 1H), 3.89 (d, ^2J = 9.1 Hz, 1H), 3.69 (d, ^2J = 9.1 Hz, 1H), 3.66 (d, ^3J = 8.6 Hz, 1H), 3.51 (d, ^2J = 9.4 Hz, 1H), 3.44 (d, ^2J = 9.4 Hz, 1H), 2.60 (d, ^3J = 8.6 Hz, 1H), 1.92 (s, 1H), 1.88 (s, 3H), 1.62 (s, 3H), 1.45 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 150.89, 137.09, 134.54, 126.65, 126.49, 117.26, 91.95, 77.47, 73.18, 72.09, 69.23, 59.53, 49.13, 47.66, 25.83, 25.11, 22.00, 21.45, 18.27, 9.37, –5.46, –5.48; **IR** (thin film): 3462, 2954, 2930, 2854, 1680,

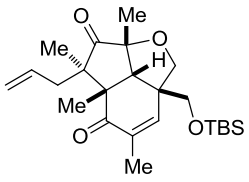
1666, 1472, 1446, 1373, 1312, 1256, 1100, 1013, 922, 836, 776 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_4Si$ ($[M+Na]^+$), 443.2588; found, 443.2586.



(2a*SR*,2a1*RS*,5*SR*,5a*SR*,6*RS*,7a*RS*)-6-allyl-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxy-4,5a,6,7a-tetramethyl-2,2a,5,5a,6,7a-hexahydroindeno[1,7-bc]furan-7(2a1H)-one (97). A dry 50 ml air-free tube under N_2 was treated with a solution of BSA (1.5 ml) in hexanes (7.5 ml, HPLC grade) by warming to ca. 60 °C and repeated shaking of the closed vessel. The BSA solution was discarded and the tube was successively rinsed with hexanes (2 x 7.5 ml, HPLC grade) and dry Et_2O (7.5 ml). The tube was put under high vacuum at RT for 15 min. The prepared air-free tube was charged with a solution of allyl vinyl ether **96** (2.7 mg, 6.4 µmol, 1.00 equiv) in Et_2O (ca. 3 ml). The solvent was removed *in vacuo* and the remaining starting material was dried under high vacuum for 20 min. *o*-Xylene (5.0 ml) was added and the mixture was carefully degased (freeze-pump-thaw; 4 cycles). The air-free tube was sealed under a positive pressure of N_2 and placed in a preheated oil-bath (160 °C). The reaction was heated for 14 h. After cooling to RT, the solvent was removed by rotary evaporator at 60 °C water bath temperature to give crude tricycle **97** as a 88:12 mixture of diastereomers. Column chromatography (hexane / EtOAc; 9:1) furnished **97** (2.4 mg, 88%) as a colorless oil.

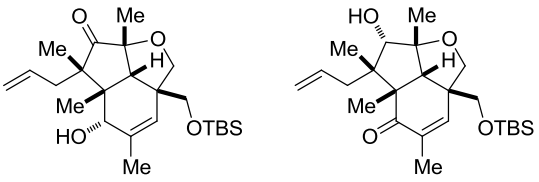
TLC: R_f = 0.43 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (12:1 diastereomeric ratio, only major diastereomer reported, 600 MHz, $CDCl_3$, relative to TMS): δ 5.67–5.60 (m, 1H), 5.43 (s, 1H), 5.11 (d, ^3J = 10.2 Hz, 1H), 5.05 (d, ^3J = 16.9 Hz, 1H), 4.03 (d, ^2J = 9.1 Hz, 1H), 3.64 (d, ^2J = 9.1 Hz, 1H), 3.55 (d, ^2J = 9.7 Hz, 1H), 3.53 (d, ^2J = 9.7 Hz, 1H), 3.46 (d, ^3J = 12.2 Hz, 1H), 2.88 (d, ^3J = 12.2 Hz, 1H), 2.38 (s, 1H), 2.29 (dd, ^2J = 14.3 Hz, ^3J = 6.2 Hz, 1H), 2.14 (dd, ^2J = 14.3 Hz, ^3J = 8.1 Hz, 1H), 1.89 (s, 3H), 1.40 (s, 3H), 1.23 (s, 3H), 0.92 (s, 9H), 0.86 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C-NMR** (12:1 diastereomeric ratio, only major diastereomer reported, 150 MHz, $CDCl_3$, relative to TMS): δ 214.32, 138.25, 132.87, 125.63, 118.54, 89.02, 76.54, 73.07, 68.67, 57.23, 54.04, 50.13, 46.37, 39.17, 25.92, 22.79, 20 .49, 19.30, 18.44, 14.36, –5.40, –5.44; **IR** (thin film): 3442, 2955, 2930, 2884, 2854, 1750, 1472, 1462, 1440, 1414, 1382, 1371, 1255, 1108, 1028, 1019, 1001, 913, 863, 837, 779 cm^{-1};

HRMS (ESI): exact mass calculated for $C_{24}H_{40}NaO_4Si$ ($[M+Na]^+$), 443.2588; found, 443.2576.



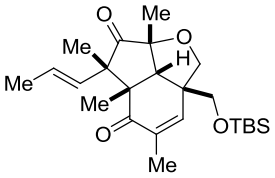
(2a*SR*,2a1*RS*,5a*SR*,6*RS*,7a*RS*)-6-allyl-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-2,2a,5a,6-tetrahydroindeno[1,7-bc]furan-5,7(2a1H,7aH)-dione (98). To a solution of alcohol **97** (2.3 mg, 5.5 µmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) was added at RT Dess–Martin periodinane (11.6 mg, 0.027 mmol, 5.00 equiv). The reaction was stirred at this temperature for 4.5 h. The mixture was diluted with CH_2Cl_2 (1.5 ml) and filtered through a plug of celite. CH_2Cl_2 (4.5 ml) was used to rinse. The filtrate was washed with satd. aq. sodium thiosulfate solution (1.5 ml) and satd. aq. $NaHCO_3$ (1.5 ml) successively and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane / EtOAc; 9:1) to obtain ketone **98** (2.1 mg, 92%) as a colorless oil.

TLC: R_f = 0.21 (hexane / EtOAc; 95:5; UV / $KMnO_4$); **^{1}H-NMR** (9:1 diastereomeric ratio, only major diastereomer reported, 500 MHz, $CDCl_3$, relative to TMS): δ 6.43 (s, 1H), 6.00–5.93 (m, 1H), 5.09–5.05 (m, 2H), 3.98 (d, ^2J = 9.4 Hz, 1H), 3.61 (d, ^2J = 9.4 Hz, 1H), 3.57 (d, ^2J = 9.3 Hz, 1H), 3.43 (d, ^2J = 9.3 Hz, 1H), 2.35 (s, 1H), 2.34–2.27 (m, 2H), 1.84 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 0.96 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (9:1 diastereomeric ratio, only major diastereomer reported, 125 MHz, $CDCl_3$, relative to TMS): δ 221.14, 200.63, 142.83, 136.67, 133.42, 118.47, 88.78, 73.18, 69.39, 57.80, 53.10, 50.54, 48.78, 39.98, 25.86, 25.77, 22.87, 21.04, 18.21, 16.74, –5.46, –5.47; **IR** (thin film): 2956, 2930, 2887, 2858, 1746, 1665, 1463, 1370, 1253, 1104, 1055, 1004, 8307, 777 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{42}NO_4Si$ ($[M+NH_4]^+$), 436.2878; found, 436.2881.



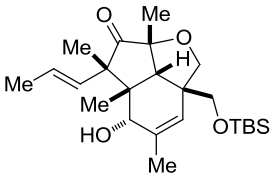
(2a*SR*,2a1*RS*,5*SR*,5a*SR*,6*SR*,7a*RS*)-6-allyl-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxy-4,5a,6,7a-tetramethyl-2,2a,5,5a,6,7a-hexahydroindeno[1,7-bc]furan-7(2a1H)-one (99). (2a*SR*,2a1*RS*,5a*SR*,6*SR*,7*SR*,7a*RS*)-6-allyl-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-hydroxy-4,5a,6,7a-tetramethyl-2,2a,5a,6,7,7a-hexahydroindeno[1,7-bc]furan-5(2a1H)-one (104). To a solution of diketone **95** (5.5 mg, 0.013 mmol, 1.00 equiv) in EtOH (1.0 ml) / THF (0.1 ml) at RT was added cerium(III) chloride heptahydrate (9.8 mg, 0.026 mmol, 2.00 equiv). Once homogeneous, the mixture was cooled to 0 °C and treated with sodium borohydride (3.0 mg, 0.079 mmol, 6.00 equiv). After 4 h, as TLC indicated incomplete conversion, a second portion of sodium borohydride (3.0 mg, 0.079 mmol, 6.00 equiv) was added and stirring was continued for 1.5 h. The reaction was quenched by addition of satd. aq. NH_4Cl (6 ml). Addition of satd. aq. NaCl (2 ml), extraction with Et_2O (3 x 5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure gave a white crude. Purification by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient) furnished a 4:1 mixture of alcohol **99** and the corresponding isomer **114** resulting from cyclopentanone reduction (2.6 mg, 47%). The chemoselectivity of this reaction usually ranged between 4:1 and 11:1, the yield between 21% and 47%.

TLC: R_f = 0.30 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (11:1 diastereomeric ratio, only major diastereomer reported, 600 MHz, $CDCl_3$, relative to TMS): δ 6.08 (m, 1H), 5.44 (s, 1H), 5.13 (d, ^3J = 17.0 Hz, 1H), 5.07 (d, ^3J = 10.0 Hz, 1H), 4.03 (d, ^2J = 9.1 Hz, 1H), 3.64 (d, ^2J = 9.1 Hz, 1H), 3.58 (d, ^3J = 11.8 Hz, 1H), 3.54 (d, ^2J = 9.8 Hz, 1H), 3.52 (d, ^2J = 9.8 Hz, 1H), 3.02 (d, ^3J = 11.8 Hz, 1H), 2.69 (dd, ^2J = 14.5 Hz, ^3J = 6.4 Hz, 1H), 2.62 (dd, ^2J = 14.5 Hz, ^3J = 8.8 Hz, 1H), 2.26 (s, 1H), 1.89 (d, ^4J = 1.5 Hz, 3H), 1.44 (s, 3H), 1.08 (s, 3H), 0.92 (s, 9H), 0.86 (s, 3H), 0.09 (s, 6H); **^{13}C-NMR** (11:1 diastereomeric ratio, only major diastereomer reported, 150 MHz, $CDCl_3$, relative to TMS): δ 216.47, 138.11, 135.18, 125.63, 117.37, 88.63, 76.60, 72.85, 68.75, 55.65, 54.52, 50.10, 46.63, 37.07, 25.91, 22.77, 21.45, 20.32, 20.09, 18.43, –5.41, –5.46; **IR** (thin film): 3436, 2954, 2928, 2880, 2853, 1749, 1659, 1637, 1471, 1462, 1447, 1409, 1384, 1370, 1254, 1109, 1094, 1026, 1018, 996, 911, 836, 780 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_4Si$ ($[M+Na]^+$), 443.2588; found, 443.2589.



(2a*SR*,2a1*RS*,5a*SR*,6*SR*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-6-((E)-prop-1-en-1-yl)-2,2a,5a,6-tetrahydroindeno[1,7-bc]furan-5,7(2a1H, 7aH)-dione (101). Terminal olefin **95** (10.7 mg, 0.026 mmol, 1.00 equiv) and 2nd generation Grubbs catalyst (2.2 mg, 2.6 µmol, 0.10 equiv) were suspended in MeOH (2.5 ml) at RT, before the mixture was heated to 60 °C. After ca. 30 min, the insoluble catalyst (red-brown) dissolved and the resulting orange-brown solution was stirred at the same temperature for 12 h. The solvent was evaporated under reduced pressure to furnish an amber crude, which was purified by chromatography on silica gel (hexane / EtOAc; 9:1) to furnish internal olefin **101** (9.3 mg, 87%) as a colorless oil.

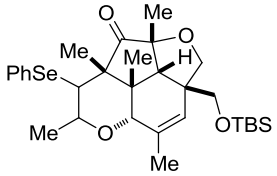
TLC: R_f = 0.32 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.43 (s, 1H), 5.35 (dq, ^3J = 15.6 Hz, 6.4 Hz, 1H), 5.12 (dq, ^3J = 15.6 Hz, ^4J = 1.4 Hz, 1H), 3.93 (d, ^2J = 8.9 Hz, 1H), 3.76 (d, ^2J = 8.9 Hz, 1H), 3.58 (d, ^2J = 9.3 Hz, 1H), 3.45 (d, ^2J = 8.9 Hz, 1H), 2.39 (s, 1H), 1.85 (s, 3H), 1.57 (dd, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 3H), 1.42 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 216.17, 200.10, 142.86, 135.79, 129.78, 126.97, 88.21, 69.38, 58.59, 57.73, 50.31, 48.44, 25.85, 25.78, 23.35, 21.07, 20.78, 18.22, 18.19, 16.55, –5.43, –5.46; **IR** (thin film): 2956, 2930, 2889, 2856, 1745, 1665, 1450, 1382, 1258, 1104, 1005, 838, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{39}O_4Si$ ($[M+H]^+$), 419.2612; found, 419.2617.



(2a*SR*,2a1*RS*,5*SR*,5a*SR*,6*SR*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxy-4,5a,6,7a-tetramethyl-6-((E)-prop-1-en-1-yl)-2,2a,5,5a,6,7a-hexahydroindeno [1,7-bc]furan-7(2a1H)-one (102). To a solution of diketone **101** (3.2 mg, 7.46 µmol, 1.00 equiv) in EtOH (1.0 ml) / THF (0.1 ml) at RT was added cerium(III) chloride heptahydrate (5.7 mg, 0.015 mmol, 2.00 equiv). Once homogeneous, the mixture was cooled to 0 °C and treated with sodium borohydride (1.4 mg, 0.038 mmol, 5.00 equiv). After 2 h, the reaction was quenched by addition of satd. aq. NH_4Cl (5 ml). Extraction with Et_2O (3 x 5 ml), drying

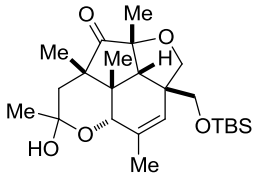
over $MgSO_4$, filtration and concentration under reduced pressure gave a white crude. Purification by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient) furnished alcohol **102** (1.7 mg, 53%, 91% brsm).

TLC: R_f = 0.23 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.05 (d, ^3J = 16.0 Hz, 1H), 5.65 (dq, ^3J = 16.0 Hz, 6.4 Hz, 1H), 5.43 (s, 1H), 4.04 (d, ^3J = 9.1 Hz, 1H), 3.65 (d, ^3J = 9.1 Hz, 1H), 3.54 (m, 2H), 3.39 (d, ^3J = 12.1 Hz, 1H), 3.05 (d, ^3J = 12.1 Hz, 1H), 2.32 (s, 1H), 1.87 (d, ^4J = 1.5 Hz, 3H), 1.80 (dd, ^3J = 6.4 Hz, ^4J = 1.6 Hz, 3H), 1.47 (s, 3H), 1.18 (s, 3H), 0.93 (s, 9H), 0.81 (s, 3H), 0.10 (s, 6H).



(2a*SR*,2a1*RS*,4a*SR*,4a1*SR*,7a*SR*,8a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4, 4a1,6,7a,8a-pentamethyl-7-(phenylselanyl)-2,2a,4a,4a1,6,7,7a,8a-octahydrofuro[2',3', 4':3,4]indeno[7,1-bc]pyran-8(2a1H)-one (103). To a solution of alcohol **102** (5.2 mg, 0.012 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) at −78 °C was added phenyl selenyl chloride (3.6 mg, 0.019 mmol, 1.50 equiv). The resulting mixture was allowed to warm up to RT over 20 min. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane / EtOAc; 9:1) to furnish selenoether **103** (5.2 mg, 73%).

TLC: R_f = 0.46 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.58 (m, 2H), 7.27 (m, 3H), 5.60 (s, 1H), 4.23 (m, 1H), 3.91 (d, ^2J = 8.7 Hz, 1H), 3.69 (d, ^2J = 8.7 Hz, 1H), 3.52 (d, ^2J = 9.5 Hz, 1H), 3.47 (d, ^2J = 9.5 Hz, 1H), 3.33 (s, 1H), 2.70 (d, ^3J = 9.9 Hz, 1H), 2.21 (s, 1H), 1.78 (d, ^4J = 1.5 Hz, 3H), 1.47 (s, 3H), 1.45 (s, 3H), 1.35 (d, ^3J = 6.3 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 3H), 0.07 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 217.41, 133.74, 133.06, 132.19, 129.19, 128.56, 127.35, 88.34, 75.08, 72.19, 68.17, 55.61, 55.33, 54.29, 51.22, 45.58, 25.86, 24.96, 22.43, 21.66, 21.43, 18.33, 15.66, –5.42, –5.45; **IR** (thin film): 2955, 2929, 2856, 1743, 1579, 1463, 1368, 1252, 1078, 1011, 837, 777, 739, 692 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{30}H_{45}O_4SeSi$ ($[M+H]^+$), 577.2249; found, 577.2253.

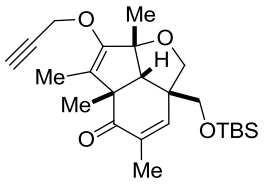


(2a*SR*,2a1*RS*,4a*SR*,4a1*SR*,7a*SR*,8a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-hydroxy-4,4a1,6,7a,8a-pentamethyl-2,2a,4a,4a1,6,7,7a,8a-octahydrofuro[2',3',4':3,4]indeno[7,1-bc]pyran-8(2a1H)-one (106). To selenoether **103** (1.7 mg, 2.95 µmol, 1.00 equiv) in CH_2Cl_2 (0.5 ml) at 0 °C was added a solution of *m*-CPBA, 70 wt% (0.7 mg, 2.95 µmol, 1.00 equiv) in CH_2Cl_2 (0.1 ml). The resulting mixture was stirred at this temperature for 15 min, before diisopropylamine (13 µl, 0.089 mmol, 30 equiv) was added. The reaction was allowed to warm up to RT and stirred for 10 h. The mixture was poured in to satd. aq. $NaHCO_3$ (3 ml) and extracted with Et_2O (3 x 5 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure gave the crude product that was purified by column chromatography (hexane / EtOAc; 9:1) to furnish enol ether **105** (yield not determined), which upon standing in $CDCl_3$, was quantitatively hydrolyzed to hemiketal **106**.

*(2aSR,2a1RS,4aSR,4a1SR,7aSR,8aRS)-2a-(((tert-butyldimethylsilyl)oxy)methyl)-4,4a1,6,7a,8a-pentamethyl-2,2a,4a,4a1,7a,8a-hexahydrofuro[2',3',4':3,4]indeno[7,1-bc]pyran-8(2a1H)-one (**105**):* **TLC:** R_f = 0.43 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.52 (s, 1H), 4.87 (s, 1H), 4.04 (s, 1H), 3.82 (d, ^2J = 8.5 Hz, 1H), 3.65 (d, ^2J = 8.5 Hz, 1H), 3.48 (m, 2H), 2.34 (s, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.49 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H), 0.90 (s, 9H), 0.05(m, 6H).

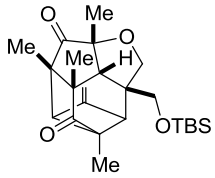
*(2aSR,2a1RS,4aSR,4a1SR,7aSR,8aRS)-2a-(((tert-butyldimethylsilyl)oxy)methyl)-6-hydroxy-4,4a1,6,7a,8a-pentamethyl-2,2a,4a,4a1,6,7,7a,8a-octahydrofuro[2',3',4':3,4]indeno[7,1-bc]pyran-8(2a1H)-one (**106**):* **TLC:** R_f = 0.51 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.69 (s, 1H), 3.87 (m, 2H), 3.64 (d, ^2J = 8.6 Hz, 1H), 3.55 (d, ^2J = 9.4 Hz, 1H), 3.47 (d, ^2J = 9.4 Hz, 1H), 2.37 (d, ^2J = 14.7 Hz, 1H), 2.12 (s, 1H), 1.85 (s, 1H), 1.82 (d, ^4J = 1.5 Hz, 3H), 1.66 (d, ^2J = 14.7 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 220.96, 133.21, 128.59, 97.19, 88.37, 72.81, 67.99, 54.43, 52.07, 51.61, 42.07, 39.66, 29.91, 25.85, 22.96, 22.59, 22.53, 18.29, –5.42, –5.43; **IR** (thin film): 3466, 2956, 2929, 2896, 2855, 1747, 1471, 1464, 1450, 1381, 1368, 1313, 1252, 1215, 1176, 1120, 1092, 1042, 1029, 1002, 972, 938, 909, 836, 777 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{44}NO_5Si$ ($[M+NH_4]^+$), 454.2983; found, 454.2974.

3.2.3.2 Saucy-Marbet Rearrangement



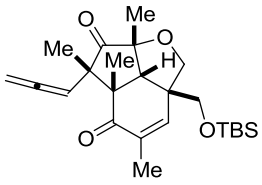
(2a*SR*,2a1*RS*,5a*SR*,7a*RS*)-2a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-7-(prop-2-yn-1-yloxy)-2,2a,5a,7a-tetrahydroindeno[1,7-bc]furan-5(2a1H)-one (107). To a suspension of potassium hydride (93.0 mg, 2.32 mmol, 1.10 equiv) in THF (10 ml) was added dropwise via cannula over 5 min a solution of ketone **95** (800 mg, 2.113 mmol, 1.00 equiv) in THF (15 ml). THF (5 ml) was used to assist the transfer. After a few minutes of stirring the solution became deep-yellow. After 30 min the mixture was cooled to 0 °C and a solution of 18-crown-6 ether (838 mg, 3.17 mmol, 1.50 equiv) in THF (10 ml) was added, followed by propargyl bromide (270 µl, 2.54 mmol, 1.20 equiv). Upon addition of 18-crown-6 ether, the mixture changed from yellow to deep-red. The red color disappeared a few minutes after the addition of propargyl bromide. The mixture was stirred at 0 °C for 15 min. The reaction was quenched by careful addition of pH 7 buffer, 0.05 M (50 ml). Extraction with Et_2O (3 x 50 ml), washing with satd. aq. NaCl (10 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product. Purification by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient) gave propargyl vinyl ether **107** (762 mg, 87%) as a clear colorless oil.

TLC: R_f = 0.38 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 4.66 (m, 2H), 3.94 (d, ^2J = 8.7 Hz, 1H), 3.54 (d, ^2J = 9.2 Hz, 1H), 3.47 (d, ^2J = 8.8 Hz, 1H), 3.36 (d, ^2J = 9.3 Hz, 1H), 2.45 (m, 1H), 2.01 (s, 1H), 1.81 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H), 1.25 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 198.78, 148.06, 143.46, 133.06, 127.67, 93.13, 79.76, 74.86, 72.35, 68.01, 58.61, 58.14, 50.88, 49.84, 26.00 25.76, 24.23, 18.45, 17.08, 9.41, –5.13, –5.17; **IR** (thin film): 3517, 3312, 3263, 2955, 2930, 2858, 1663, 1472, 1447, 1374, 1310, 1258, 1163, 1112, 1074, 1005, 972, 887, 838, 779 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{37}O_4Si$ ($[M+H]^+$), 417.2456; found, 417.2450.



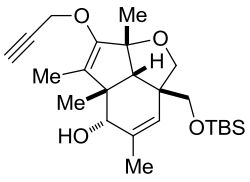
(2a*SR*,2a1*RS*,5a*SR*,6*SR*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-9-methylenehexahydro-4,6,3-(epiethane[1,1,2]triyl)indeno[1,7-bc]furan-5,7(2a1H,7aH)-dione (108). A dry 50 ml air-free tube under N_2 was treated with a solution of BSA (0.1 ml) in hexanes (7.5 ml, HPLC grade) by warming to ca. 60 °C and repeated shaking of the closed vessel. The BSA solution was discarded and the tube was successively rinsed with hexanes (2 x 7.5 ml, HPLC grade) and dry Et_2O (7.5 ml). The tube was put under high vacuum at RT for 15 min. The prepared air-free tube was charged with a solution of propargyl vinyl ether **107** (10.8 mg, 0.026 mmol, 1.00 equiv) in Et_2O (ca. 3 ml). The solvent was removed *in vacuo* and the remaining starting material was dried under high vacuum for 20 min. *o*-Xylene (5.0 ml) was added and the mixture was carefully degased (freeze-pump-thaw; 4 cycles). The air-free tube was sealed under a positive pressure of N_2 and placed in a preheated oil-bath (160 °C). The reaction was heated for 12 h. After cooling to RT, the solvent was removed by rotary evaporator at 60 °C water bath temperature. Column chromatography (hexane / EtOAc; 8:2) furnished **108** (9.8 mg, 91%) as a colorless oil.

TLC: R_f = 0.31 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.08 (s, 1H), 5.01 (s, 1H), 3.88 (d, ^2J = 8.8 Hz, 1H), 3.70 (d, ^2J = 8.8 Hz, 1H), 3.34 (d, ^2J = 10.3 Hz, 1H), 3.27 (d, ^2J = 10.3 Hz, 1H), 2.85 (d, ^4J = 3.3 Hz, 1H), 2.85 (s, 1H), 2.53 (d, ^4J = 4.7 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 218.34, 216.28, 144.00, 110.60, 88.84, 75.06, 64.94, 63.88, 62.10, 58.84, 57.30, 51.72, 49.73, 43.32, 25.75, 22.98, 18.36, 18.13, 16.03, 14.28, –5.61, –5.62; **IR** (thin film): 2956, 2929, 2886, 2858, 1740, 1679, 1472, 1465, 1452, 1385, 1374, 1362, 1334, 1279, 1258, 1200, 1105, 1061, 1042, 1008, 938, 883, 838, 815, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NO_4Si$ ($[M+NH_4]^+$), 434.2721; found, 434.2714.



(2a*SR*,2a1*RS*,5a*SR*,6*SR*,7a*RS*)-2a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a,5a,6-tetrahydroindeno[1,7-bc]furan-5,7(2a1H, 7aH)-dione (109). To a solution of propargyl vinyl ether **107** (760 mg, 1.824 mmol, 1.00 equiv) in 1,2-dichloroethane (36 ml) was added at RT $[(Ph_3PAu)_3O]BF_4$ (27.0 mg, 0.018 mmol, 0.01 equiv). The resulting mixture was heated to 75 °C for 12 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane / EtOAc; 95:5 to 9:1 gradient) to obtain allene **109** (640 mg, 84%) as a white amorphous solid.

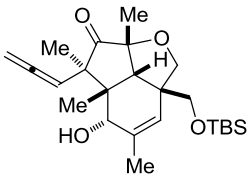
TLC: R_f = 0.29 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **Melting point:** 93 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.46 (s, 1H), 5.04 (m, 1H), 4.81 (dd, ^2J = 11.3 Hz, ^4J = 6.7 Hz, 1H), 4.76 (dd, ^2J = 11.4 Hz, ^4J = 6.5 Hz, 1H), 3.98 (d, ^2J = 9.1 Hz, 1H), 3.80 (d, ^2J = 9.1 Hz, 1H), 3.60 (d, ^2J = 9.4 Hz, 1H), 3.47 (d, ^2J = 9.4 Hz, 1H), 2.43 (s, 1H), 1.85 (s, 3H), 1.43 (s, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 214.86, 206.83, 199.42, 143.37, 136.10, 92.18, 88.28, 78.52, 73.78, 69.32, 57.80, 55.58, 50.60, 48.48, 25.80, 25.76, 22.88, 19.81, 18.20, 16.72, –5.46, –5.48; **IR** (thin film): 2956, 2930, 2891, 2858, 1954, 1750, 1667, 1472, 1469, 1464, 1445, 1383, 1369, 1258, 1112, 1070, 1043, 1003, 838, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{37}O_4Si$ ($[M+H]^+$), 417.2456; found, 417.2462.



(2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-7-(prop-2-yn-1-yloxy)-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-5-ol (110). A solution of DIBAL-H (1.0 ml, 1.0 mmol) was diluted with toluene (2.4 ml) and cooled to 0 °C. *n*-Butyllithium, 1.6 M in hexanes (0.6 ml, 1.0 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for additional 30 min to give a colorless solution of ate complex (0.25 M). In a separate flask, enone **107** (13.6 mg, 0.033 mmol, 1.00 equiv) was dissolved in toluene (1.6 ml) and cooled to –78 °C. Ate complex (160 µl, 0.041 mmol, 1.25 equiv) was added and the reaction mixture was stirred at this temperature for 1 h. The reaction

was quenched at −78 °C by addition of NaOMe (5.4 mg, 0.1 mmol) in MeOH (0.2 ml). After further 10 min of stirring, pH 7 buffer, 0.05 M (1.5 ml) was added and the mixture was allowed to warm up to RT. Satd. aq. Na-K-tartrate (1.5 ml) was added and the mixture was extracted with Et_2O (3 x 5 ml). Washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished the crude product, which was purified by column chromatography (hexane / EtOAc; 9:1) to furnish alcohol **110** (12.5 mg, 91%) as a colorless oil.

TLC: R_f = 0.31 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.46 (s, 1H), 4.56 (m, 2H), 3.88 (d, ^2J = 9.1 Hz, 1H), 3.75-3.72 (m, 2H), 3.50 (d, ^2J = 9.3 Hz, 1H), 3.43 (d, ^2J = 9.3 Hz, 1H), 2.50 (d, ^3J = 7.7 Hz, 1H), 2.46 (m, 1H), 1.93 (s, 1H),), 1.88 (d, ^4J = 1.4 Hz, 3H), 1.67 (s, 3H), 1.45 (s, 3H), 1.07 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 150.18, 137.05, 128.45, 126.46, 91.68, 79.90, 77.26, 74.73, 73.33, 68.98, 59.39, 58.73, 49.43, 47.88, 25.83, 25.24, 22.16, 21.93, 18.26, 9.51, –5.47; **IR** (thin film): 3462, 3311, 2953, 2928, 2889, 2855, 1686, 1671, 1472, 1462, 1444, 1373, 1310, 1254, 1191, 1160, 1147, 1117, 1097, 1051, 1012, 836, 815, 780 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_4Si$ ($[M+Na]^+$), 441.2432; found, 441.2437.

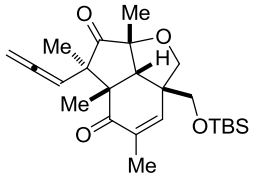


(2a*SR*,2a1*RS*,5*SR*,5a*SR*,6*RS*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxy-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a,5,5a,6,7a-hexahydro-indeno [1,7-bc]furan-7(2a1H)-one (111). *Method A:* A dry 50 ml air-free tube under N_2 was treated with a solution of BSA (0.5 ml) in hexanes (7.5 ml, HPLC grade) by warming to ca. 60 °C and repeated shaking of the closed vessel. The BSA solution was discarded and the tube was successively rinsed with hexanes (2 x 7.5 ml, HPLC grade) and dry Et_2O (7.5 ml). The tube was put under high vacuum at RT for 15 min. The prepared air-free tube was charged with a solution of allyl vinyl ether **110** (8.0 mg, 0.019 mmol, 1.00 equiv) in Et_2O (ca. 3 ml). The solvent was removed *in vacuo* and the remaining starting material was dried under high vacuum for 20 min. *o*-Xylene (5.0 ml) was added and the mixture was carefully degased (freeze-pump-thaw; 4 cycles). The air-free tube was sealed under a positive pressure of N_2 and placed in a preheated oil-bath (160 °C). The reaction was heated for 10 h. After cooling to

RT, the solvent was removed by rotary evaporator at 60 °C water bath temperature to give crude tricycle **111** as the only detectable diastereomer. Column chromatography (hexane / EtOAc; 9:1) furnished **111** (7.0 mg, 88%) as an amorphous solid.

Method B: To a solution of propargyl vinyl ether **110** (12.5 mg, 0.030 mmol, 1.00 equiv) in 1,2-dichloroethane (1.0 ml) at RT was added $[(Ph_3PAu)_3O]BF_4$ (1.1 mg, 0.746 μmol, 0.025 equiv). The resulting mixture was heated to 75 °C for 18 h. Removal of the solvent *in vacuo* gave the crude product as a 2:1 mixture of diastereomers, which could be separated by column chromatography (hexane / EtOAc; 85:15) to obtain allene **111** (7.1 mg, 57%) as a white amorphous solid, along with the corresponding diastereomer (3.0 mg, 24%).

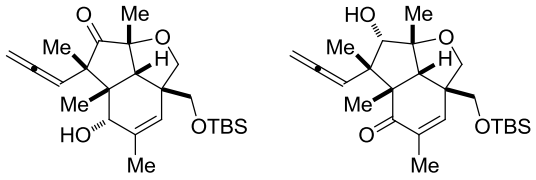
TLC: R_f = 0.32 (hexane / EtOAc; 85:15; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.45 (s, 1H), 2.21 (m, 1H), 4.90 (dd, ^2J = 11.2 Hz, ^4J = 6.7 Hz, 1H), 4.84 (dd, ^2J = 11.2 Hz, ^4J = 6.7 Hz, 1H), 4.04 (d, ^2J = 9.1 Hz, 1H), 3.64 (d, ^2J = 9.1 Hz, 1H), 3.57−3.52 (m, 2H), 3.47 (d, ^3J = 12.2 Hz, 1H), 2.97 (d, ^3J = 12.2 Hz, 1H), 2.36 (s, 1H), 1.89 (d, ^4J = 1.5 Hz, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H), 0.09 (s, 6H); **^{13}C-NMR** (MHz, $CDCl_3$): δ 212.00, 208.55, 138.05, 126.03, 92.02, 89.40, 78.50, 76.62, 72.98, 68.58, 58.36, 54.42, 50.08, 46.36, 25.91, 22.76, 21.30, 20.08, 18.42, 15.20, –5.42, –5.45; **IR** (thin film): 3441, 2958, 2930, 2884, 2857, 2360, 2343, 2251, 1953, 1756, 1472, 1447, 1411, 1370, 1259, 1213, 1194, 1158, 1096, 1020, 996, 936, 909, 864, 837, 814, 780, 735, 668, 620, 556 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_4Si$ ($[M+NH_4]^+$), 436.2878; found, 436.2882.



(2a*SR*,2a1*RS*,5a*SR*,6*RS*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a,5a,6-tetrahydroindeno[1,7-bc]furan-5,7(2a1H, 7aH)-dione (112). To a solution of alcohol **111** (6.8 mg, 0.016 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) at 0 °C was added Dess–Martin periodinane (20.7 mg, 0.049 mmol, 3.00 equiv). The reaction was stirred at this temperature for 6 h. The mixture was diluted with CH_2Cl_2 (1.5 ml) and filtered through a plug of celite. CH_2Cl_2 (10 ml) was used to rinse. The filtrate was washed with satd. aq. sodium thiosulfate solution (5 ml) and satd. aq. $NaHCO_3$ (5 ml) successively and dried over $MgSO_4$. The solvent was removed under reduced pressure and the

residue was purified by column chromatography (hexane / EtOAc; 9:1) to obtain ketone **112** (3.8 mg, 56%) as a colorless oil.

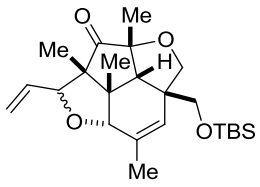
TLC: R_f = 0.53 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 6.45 (s, 1H), 5.10 (m, 1H), 4.89 (dd, ^2J = 11.0 Hz, ^2J = 6.7 Hz, 1H), 4.83 (dd, ^2J = 11.0 Hz, ^2J = 6.6 Hz, 1H), 3.99 (d, ^2J = 9.4 Hz, 1H), 3.60 (d, ^2J = 9.4 Hz, 1H), 3.57 (d, ^2J = 9.3 Hz, 1H), 3.44 (d, ^2J = 9.3 Hz, 1H), 2.39 (s, 1H), 1.85 (d, ^4J = 1.4 Hz, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.11 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (150 MHz, $CDCl_3$, relative to TMS): δ 218.38, 207.94, 199.52, 143.06, 136.54, 92.65, 89.04, 78.22, 73.37, 69.32, 57.41, 55.05, 50.40, 48.86, 27.32, 25.77, 22.57, 21.60, 18.21, 16.70, –5.46, –5.48; **IR** (thin film): 2955, 2929, 2857, 1957, 1750, 1666, 1462, 1451, 1372, 1257, 1105, 1000, 838, 777 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NO_4Si$ ($[M+NH_4]^+$), 434.2721; found, 434.2720.



(2a*SR*,2a1*RS*,5*SR*,5a*SR*,6*SR*,7a*RS*)-2a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-hydroxy-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a,5,5a,6,7a-hexahydroindeno [1,7-bc]furan-7(2a1H)-one (113). (2a*SR*,2a1*RS*,5a*SR*,6*SR*,7*SR*,7a*RS*)-2a-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-hydroxy-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a, 5a,6,7,7a-hexahydroindeno[1,7-bc]furan-5(2a1H)-one (116). To a solution of diketone **109** (650 mg, 1.56 mmol, 1.00 equiv) in THF (30 ml) at –78 °C was added dropwise lithium triethylborohydride, 1.0 M in THF (1.72 ml, 1.72 mmol, 1.10 equiv). The resulting mixture was stirred at the same temperature for 1 h. The reaction was quenched at –78 °C by addition of satd. aq. NH_4Cl (ca. 5 ml). After warming up to RT, the mixture was diluted with satd. aq. NH_4Cl (100 ml) and extracted with Et_2O (3 x 100 ml). The combined organic layers were washed with satd. aq. NaCl (25 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product as a 9:1 mixture of isomers. Purification by chromatography on silica gel (hexane / EtOAc; 9:1 to 8:2 gradient) gave alcohol **113** (521 mg, 80%) as a colorless oil and alcohol **116** (62.5 mg, 12%) as a white solid, along with recovered starting material **109** (52.3 mg, 8%). The isolated yield of **113** ranged between 71 and 87 %.

*(2aSR,2a1RS,5SR,5aSR,6SR,7aRS)-2a-(((tert-Butyldimethylsilyl)oxy)methyl)-5-hydroxy-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a,5,5a,6,7a-hexahydroindeno [1,7-bc]furan-7(2a1H)-one (**109**):* **TLC:** R_f = 0.43 (hexane / EtOAc; 85:15; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.44 (s, 1H), 4.90 (dd, ^2J = 10.6 Hz, ^4J = 6.8 Hz, 1H), 4.79 (dd, ^2J = 10.6 Hz, ^4J = 6.7 Hz, 1H), 4.03 (d, ^2J = 9.1 Hz, 1H), 3.63 (d, ^2J = 9.1 Hz, 1H), 3.54 (m, 3H), 2.90 (d, ^3J = 12.1 Hz, 1H), 2.34 (s, 1H), 1.87 (s, 3H), 1.45 (s, 3H), 1.19 (s, 3H), 0.91 (s, 9H), 0.83 (s, 3H), 0.09 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 214.79, 209.58, 137.86, 125.91, 91.48, 88.75, 76.57, 73.17, 68.52, 56.77, 54.55, 50.39, 47.59, 25.89, 22.67, 21.47, 19.64, 19.45, 18.40, –5.44, –5.49; **IR** (thin film): 3441, 2957, 2931, 2882, 2856, 1953, 1753, 1472, 1461, 1458, 1410, 1381, 1370, 1251, 1110, 1094, 1026, 1019, 995, 865, 838, 779 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{39}O_4Si$ ($[M+H]^+$), 419.2612; found, 419.2612.

*(2aSR,2a1RS,5aSR,6SR,7SR,7aRS)-2a-(((tert-butyldi-methylsilyl)oxy)methyl)-7-hydroxy-4,5a,6,7a-tetramethyl-6-(propa-1,2-dien-1-yl)-2,2a,5a,6,7,7a-hexahydroindeno[1,7-bc]furan-5(2a1H)-one (**116**):* **TLC:** R_f = 0.45 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **Melting point:** 113 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.30 (s, 1H), 5.53 (m, 1H), 4.73-4.64 (m, 2H), 3.98 (d, ^2J = 9.4 Hz, 1H), 3.88 (d, ^2J = 9.4 Hz, 1H), 3.55 (d, ^3J = 11.5 Hz, 1H), 3.51 (m, 2H), 2.33 (s, 1H), 2.21 (d, ^3J = 11.5 Hz, 1H), 1.78 (s, 3H), 1.41 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 208.47, 199.42, 144.43, 136.63, 92.38, 92.32, 83.22, 74.41, 70.00, 60.01, 51.73, 51.21, 50.63, 25.90, 25.78, 24.87, 23.61, 19.44, 18.25, 16.75, –5.48, –5.50; **IR** (thin film): 3570, 3479, 2957, 2930, 2886, 2856, 1953, 1754, 1665, 1472, 1462, 1451, 1409, 1383, 1371, 1361, 1253, 1148, 1112, 1062, 838, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{39}O_4Si$ ($[M+H]^+$), 419.2612; found, 419.2606.

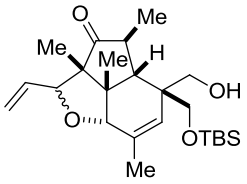


(2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*,7a*SR*)-5a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2a,2a1,3a,7-tetramethyl-2-vinyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (100). To a solution of allene **113** (520 mg, 1.24 mmol, 1.00 equiv) in toluene (62 ml) was added at RT chloro[2-(di-*tert*-butylphosphino)biphenyl]gold(I) (65.9 mg, 0.124 mmol, 0.10 equiv) and silver *p*-toluenesulfonate (34.7 mg, 0.124 mmol, 0.10

equiv). The resulting mixture was stirred at RT for 10 min, before it was degassed carefully (freeze-pump-thaw, 4 cycles). The reaction was heated to 60 °C for 15 h. Upon heating, the formation of a white precipitate could be observed. After cooling to RT, the mixture was filtered through a plug of silica (4 cm x 2 cm ø). Hexane / EtOAc (1:1, 20 ml) was used to rinse. The filtrate was concentrated under reduced pressure and purified by column chromatography to furnish tetracycle **100** (373 mg, 72%) as a 3.2:1 mixture of inseparable diastereomers, along with enol ether **105** (47 mg, 9%), which upon standing in $CDCl_3$, was quantitatively hydrolyzed to hemiketal **106**.

TLC: R_f = 0.51 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (3.2:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 400 MHz, $CDCl_3$): δ 5.98–5.84 (m, 1H), 5.81* (s, 1H), 5.64 (s, 1H), 5.37–5.26 (m, 2H), 4.60 (d, ^3J = 6.9 Hz, 1H), 4.02 (s, 1H), 3.84 (d, ^2J = 8.9 Hz, 1H), 3.83–3.76* (m, 2H), 3.56* (d, ^2J = 9.4 Hz, 1H), 3.52–3.46 (m, 1H), 3.43* (d, ^2J = 9.4 Hz, 1H), 3.38 (d, ^2J = 9.4 Hz, 1H), 3.29 (d, ^2J = 8.9 Hz, 1H), 1.99 (s, 1H), 1.97* (s, 1H), 1.94* (s, 3H), 1.85 (s, 3H), 1.44 (s, 3H), 1.32* (s, 3H), 1.18 (s, 3H), 1.09* (s, 3H), 1.08* (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C-NMR** (asterisk denotes minor diastereomer signals, 100 MHz, $CDCl_3$): δ 223.38, 133.73*, 133.33, 132.98. 132.76*, 128.99*, 127.44, 118.29*, 118.15, 90.89*, 90.12, 88.27*, 86.02*, 84.41, 84.17, 76.39, 67.95*, 67.83, 63.11, 57.28*, 56.26, 53.20*, 52.09, 49.09*, 47.22, 26.70, 25.84, 25.82, 24.98*, 25.84, 24.15*, 23.43*, 22.23, 18.27, 18.23*, 17.95*, 16.67, –5.45; **IR** (thin film): 2954, 2929, 2883, 2856, 1746, 1472, 1464, 1450, 1386, 1369, 1361, 1253, 1172, 1114, 1093, 1072, 1054, 1036, 1006, 956, 926, 836, 780 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{42}NO_4Si$ ($[M+NH_4]^+$), 436.2878; found, 436.2870.

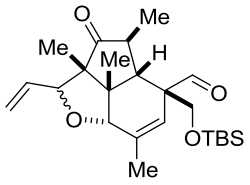
3.2.3.3 Synthesis of Nominal Indoxamycin B



(2a*RS*,2a1*SR*,4*SR*,4a*RS*,5*SR*,7a*SR*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(hydroxylmethyl)-2a,2a1,4,7-tetramethyl-2-vinyl-2,2a,4,4a,5,7a-hexahydroindeno[7,1-bc]furan-3(2a1H)-one (120). The THF employed in this reaction was degassed by freeze-pump-thaw (4 cycles) prior to use. To a suspension of samarium powder (450 mg, 3.01 mmol) in THF (6.6 ml) at RT was added via cannula a solution of diiodoethane (450 mg, 1.60 mmol)

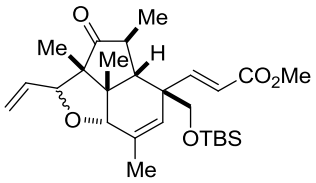
in THF (6.0 ml). THF (3.0 ml) was used to assist the transfer. The resulting mixture became royal blue after 15 min and was stirred at the same temperature for 2 h to give a solution of samarium diiodide (ca. 0.1 M). In a separate 100 ml Schlenk flask ketone **100** (225 mg, 0.537 mmol, 1.00 equiv) was dissolved in THF / MeOH (7:3, 54 ml) and the resulting mixture was degassed carefully (freeze-pump-thaw; 4 cycles). The fresh samarium diiodide solution (10.7 ml, 1.08 mmol, 2.00 equiv) was added dropwise via syringe to this mixture until a slightly blue coloration persisted for ca. 5 min. The reaction was quenched by addition of THF / H_2O (1:1; 20 ml). HCl (0.05 M in H_2O; 10 ml) was added and the mixture was extracted with Et_2O (3 x 50 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (10 ml) and satd. aq. NaCl (3 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure to furnished a green crude oil. Purification by chromatography on silica gel (hexane / EtOAc; 85:15) gave alcohol **120** (226 mg, quantitative) as a 3.2:1 mixture of inseparable diastereomers.

TLC: R_f = 0.29 (hexane / EtOAc; 85:15; $KMnO_4$); **^{1}H-NMR** (3.2:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 400 MHz, $CDCl_3$): δ 5.92–5.80 (m, 1H), 5.33–5.22 (br m, 3H), 4.46 (d, ^3J = 6.4 Hz, 1H), 4.06 (s, 1H), 3.83* (d, ^3J = 7.1 Hz, 1H), 3.73–3.55 (br m, 4H), 3.10 (m, 1H), 2.84* (m, 1H), 2.26 (d, ^3J = 10.0 Hz, 1H), 2.20–2.09 (m, 1H), 1.86* (s, 3H), 1.79 (s, 3H), 1.29 (s, 3H), 1.26 (d, ^3J = 7.1 Hz, 3H), 1.21* (s, 3H), 1.17* (d, ^3J = 6.5 Hz, 3H), 0.98* (s, 3H), 0.96 (s, 3H), 0.91 (s, 9H), 0.90* (s, 9H), 0.10–0.06 (m, 6H); **^{13}C-NMR** (3.2:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 100 MHz, $CDCl_3$): δ 223.99, 220.85*, 137.70, 134.97*, 133.71, 133.02*, 124.25*, 123.50, 118.18*, 117.40, 87.61*, 84.91, 84.71*, 84.26, 69.59, 69.23, 69.12*, 68.83*, 64.10, 62.75*, 49.26, 48.36*, 46.01*, 45.94*, 45.87, 45.68*, 45.51, 45.15, 26.33, 25.78, 24.67*, 21.44*, 20.17, 18.47, 18.11*, 18.08, 17.06*, 14.59*, 13.94, –5.52, –5.66*, –5.73; **IR** (thin film): 3503, 2953, 2929, 2884, 2856, 1736, 1472, 1463, 1406, 1388, 1376, 1361, 1253, 1234, 1121, 1089, 1080, 1044, 1006, 985, 957, 928, 864, 837, 815, 777 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{40}NaO_4Si$ ($[M+Na]^+$), 443.2588; found, 443.2592.



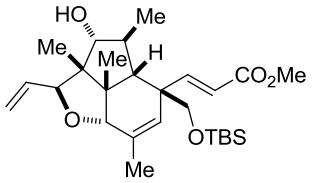
(2a*RS*,2a1*SR*,4*SR*,4a*SR*,5*RS*,7a*SR*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2a,2a1,4,7-tetra-methyl-3-oxo-2-vinyl-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7,1-bc]furan-5-carb-aldehyde (230). To a solution of alcohol **120** (225 mg, 0.535 mmol, 1.00 equiv) in CH_2Cl_2 (10.0 ml) at 0 °C was added Dess–Martin periodinane (284 mg, 0.669 mmol, 1.25 equiv). The resulting mixture was allowed to slowly warm up to RT. After 6 h of stirring the reaction mixture was taken up in CH_2Cl_2 (10 ml) and washed with a mixture of satd. aq. sodium thiosulfate solution (3 ml) and satd. aq. $NaHCO_3$ (3 ml). The organic phase was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography furnished aldehyde **230** (218 mg, 97%) as a 3.8:1 mixture of inseparable diastereomers.

TLC: R_f = 0.20 (hexane / EtOAc; 95:5; $KMnO_4$); **^{1}H-NMR** (3.8:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 9.70* (s, 1H), 5.91–5.68 (m, 2H), 5.33–5.22 (m, 2H), 4.41 (d, ^3J = 6.5 Hz, 1H), 4.05 (s, 1H), 3.85–3.75 (m, 2H), 2.36 (d, ^3J = 10.9 Hz, 1H), 2.22* (d, ^3J = 12.5 Hz, 1H), 2.17–2.03 (m, 1H), 1.95* (s, 3H), 1.88 (s, 3H), 1.29 (s, 3H), 1.21* (s, 3H), 1.06–1.01 (m, 3H), 0.96 (s, 3H), 0.95* (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); **^{13}C-NMR** (3.8:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 100 MHz, $CDCl_3$): δ 222.02, 218.20*, 203.56, 203.04*, 137.19, 135.32*, 133.09, 132.50*, 120.99*, 120.72, 118.29*, 117.89, 87.78*, 85.54, 84.59*, 83.84, 67.34, 67.21*, 63.29, 62.05*, 56.93, 56.69*, 48.83, 48.09*, 46.00, 45.77*, 45.39*, 44.52, 25.85, 25.71, 23.88*, 21.86*, 20.56, 18.16, 16.83, 14.93*, 14.24*, 13.62, –5.62, –5.66*, –5.71; **IR** (thin film): 2953, 2930, 2883, 2857, 1738, 1471, 1463, 1389, 1377, 1362, 1254, 1232, 1212, 1094, 1040, 1005, 988, 954, 928, 838, 814, 779 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{39}O_4Si$ ($[M+H]^+$), 419.2612; found, 419.2619.



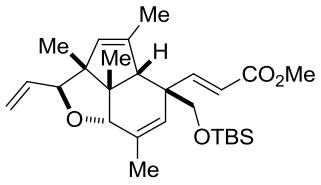
(*E*)-Methyl 3-((2a*RS*,2a1*SR*,4*SR*,4a*RS*,5*SR*,7a*SR*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-2a,2a1,4,7-tetramethyl-3-oxo-2-vinyl-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7,1-bc]furan-5-yl)acryl-ate (121). To a suspension of sodium hydride (60% in mineral oil, 84.0 mg, 2.09 mmol, 5.00 equiv) in THF (3.4 ml) was added dropwise at RT methyl diethylphosphonoacetate (393 µl, 2.09 mmol, 5.00 equiv). Strong gas evolution could be observed immediately. The resulting mixture was stirred for 30 min, before a solution of aldehyde **230** (175 mg, 0.418 mmol, 1.00 equiv) in THF (3.0 ml) was added via cannula. THF (2.0 ml) was used to assist the transfer. The reaction was stirred at RT for 48 h. The mixture was poured into satd. aq. $NaHCO_3$ (20 ml). Extraction with Et_2O (3 x 20 ml), washing with satd. aq. NaCl (3 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished a crude oil. Purification by chromatography on silica gel (hexane / EtOAc; 9:1 to 85:15 gradient) gave ester **121** (182 mg, 92%) as a 3.6:1 mixture of inseparable diastereomers.

TLC: R_f = 0.30 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (3.6:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 400 MHz, $CDCl_3$): δ 7.22 (d, ^3J = 16.3 Hz, 1H), 7.21* (d, ^3J = 16.3 Hz, 1H), 5.93–5.70 (br m, 2H), 5.46 (s, 1H), 5.43* (s, 1H), 5.34–5.22 (br m, 2H), 4.48 (d, ^3J = 6.6 Hz, 1H), 4.04 (s, 1H), 3.81* (d, ^3J = 6.8 Hz, 1H), 3.75 (s, 3H), 3.70* (s, 1H), 3.60* (d, ^2J = 10.0 Hz, 1H), 3.55 (d, ^2J = 10.2 Hz, 1H), 3.45* (d, ^2J = 10.0 Hz, 1H), 3.42 (d, ^2J = 10.2 Hz, 1H), 2.26 (d, ^3J = 10.4 Hz, 1H), 2.15* (d, ^3J = 12.2 Hz, 1H), 1.94* (s, 3H), 1.93–1.89 (m, 1H), 1.87 (s, 3H), 1.30 (s, 3H), 1.21* (s, 3H), 1.03–1.00 (m, 3H), 0.95 (s, 3H), 0.94* (s, 3H), 0.91 (s, 9H), 0.90* (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (3.6:1 diastereomer ratio, asterisk denotes minor diastereomer signals, 100 MHz, $CDCl_3$): δ 223.62, 219.61*, 167.04*, 166.99, 154.08*, 153.60, 137.45, 134.39*, 133.33, 132.75*, 124.43*, 123.33, 118.33*, 118.23*, 118.12, 117.72, 88.03*, 85.38, 84.41*, 83.56, 68.62*, 68.18, 64.28, 62.68*, 51.60, 51.57*, 48.72, 48.11*, 47.88, 47.67*, 47.30, 47.26*, 47.00*, 45.88, 26.03, 25.79, 24.18*, 22.09*, 20.95, 18.67, 18.22, 16.54*, 14.47*, 13.84, –5.46, –5.59*, –5.62; **IR** (thin film): 2951, 2929, 2855, 1726, 1646, 1471, 1463, 1450, 1435, 1388, 1373, 1360, 1312, 1302, 1274, 1259, 1231, 1212, 1193, 1167, 1094, 1042, 1009, 953, 930, 863, 839, 814, 779 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{43}O_5Si$ ($[M+H]^+$), 475.2874; found, 475.2868.



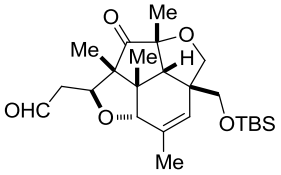
(*E*)-Methyl 3-((2*SR*,2a*SR*,2a1*SR*,3*RS*,4*SR*,4a*RS*,5*SR*,7a*SR*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2a,2a1,4,7-tetramethyl-2-vinyl-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7,1-bc] furan-5-yl)acrylate (125). To a solution of ketone **121** (85.0 mg, 0.179 mmol, 1.00 equiv) in CH_2Cl_2 (3.6 ml) was added at RT borane *tert*-butylamine complex (31.1 mg, 0.358 mmol, 2.00 equiv). The resulting mixture has heated to 40 °C for 16 h. After cooling to RT 1 M aq. HCl (5 ml) was added. The resulting mixture was stirred vigorously for 30 min before it was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (3 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 9:1 to 85:15 gradient) gave alcohol **125** (75.0 mg, 88%) as a 9:1 mixture of inseparable diastereomers.

TLC: R_f = 0.33 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (9:1 diastereomer ratio, only major diastereomer reported, 400 MHz, $CDCl_3$): δ 7.15 (d, ^3J = 16.3 Hz, 1H), 5.92–5.83 (m, 2H), 5.54 (s, 1H), 5.27 (m, 1H), 5.15 (m, 1H), 4.15 (d, ^3J = 5.8 Hz, 1H), 3.83 (s, 1H), 3.74 (s, 3H), 3.37 (d, ^2J = 9.9 Hz, 1H), 3.29 (d, ^2J = 16.3 Hz, 1H), 3.18 (dd, ^3J = 9.9 Hz, 4.9 Hz, 1H), 1.83 (s, 3H), 1.73 (d, ^3J = 11.2 Hz, 1H), 1.65–1.61 (m, 2H), 1.11 (s, 3H), 0.97 (s, 3H), 0.94 (d, ^3J = 6.0 Hz, 1H), 0.89 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); **^{13}C-NMR** (9:1 diastereomer ratio, only major diastereomer reported, 100 MHz, $CDCl_3$): δ 167.21, 154.03, 137.42, 136.30, 125.66, 118.10, 115.80, 85.64, 83.31, 81.57, 68.69, 56.51, 52.65, 51.46, 50.09, 46.70, 40.69, 25.99, 25.80, 20.54, 19.41, 18.23, 17.75, –5.47, –5.63; **IR** (thin film): 3471, 2953, 2927, 2908, 2855, 1724, 1707, 1644, 1472, 1463, 1447, 1435, 1410, 1389, 1375, 1362, 1312, 1304, 1275, 1258, 1197, 1172, 1111, 1089, 1062, 1043, 1014, 990, 957, 918, 854, 838, 814, 777, 733, 670 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{45}O_5Si$ ($[M+H]^+$), 477.3031; found, 477.3035.



(*E*)-Methyl 3-((2*SR*,2a*RS*,2a1*SR*,4a*RS*,5*SR*,7a*SR*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-2a,2a1,4,7-tetramethyl-2-vinyl-2,2a,2a1,4a,5,7a-hexahydroindeno[7,1-bc]furan-5-yl)acrylate (124). To a solution of (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (75.0 mg, 0.315 mmol, 2.00 equiv) in toluene (8.0 ml) at RT was added via cannula solution of alcohol **125** (75.0 mg, 0.157 mmol, 1.00 equiv) in toluene (5.0 ml). Toluene (3.0 ml) was used to assist the transfer. The resulting mixture was heated to reflux for 14 h. After cooling to RT, H_2O (5 ml) was added and the mixture was extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with satd. aq. NaCl (3 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (hexane / EtOAc; 95:5) to yield olefin **124** (31.8 mg, 44%) as a colorless oil.

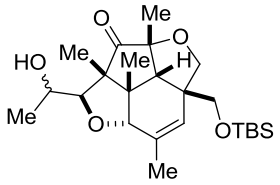
TLC: R_f = 0.44 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.23 (d, ^3J = 16.3 Hz, 1H), 5.91–5.82 (m, 2H), 5.50 (s, 1H), 5.23–5.13 (m, 3H), 4.06 (d, ^3J = 7.0 Hz, 1H), 4.02 (s, 1H), 3.72 (s, 3H), 3.52 (d, ^2J = 9.8 Hz, 1H), 3.34 (d, ^2J = 9.8 Hz, 1H), 2.84 (s, 1H), 1.85 (s, 3H), 1.51 (s, 3H), 1.18 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 167.22, 154.63, 138.73, 138.44, 136.28, 136.00, 124.81, 118.29, 116.16, 87.73, 84.36, 69.36, 60.16, 56.01, 55.05, 51.43, 47.07, 25.79, 24.94, 20.87, 18.78, 18.21, 17.68, –5.48, –5.58; **IR** (thin film): 3079, 3020, 2955, 2928, 2884, 2857, 1726, 1644, 1471, 1468, 1447, 1434, 1406, 1378, 1361, 1308, 1258, 1194, 1172, 1115, 1093, 1055, 1015, 1006, 996, 965, 938, 922, 847, 838, 815, 776, 731, 670 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{46}NO_4Si$ ($[M+NH_4]^+$), 476.3191; found, 476.3191.



2-((2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*,7a*SR*)-5a-(((*tert*-butyldimethylsilyl)oxy) methyl)-2a,2a1,3a,7-tetramethyl-3-oxo-2a,2a1,3,3a,3a1,5,5a,7a-octahydro-2H-indeno[1, 7-bc:4,3-b'c']difuran-2-yl)acetaldehyde (130). To a solution of olefin **100** (2.0 mg, 4.78 µmol, 1.00 equiv) in DMF (0.84 ml) / H_2O (0.12 ml) at RT were added palladium(II) chloride

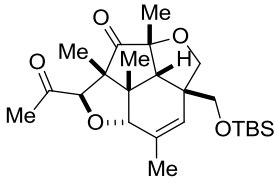
(0.8 mg, 4.78 µmol, 1.00 equiv) and copper(I) chloride (2.8 mg, 0.029 mmol, 6.00 equiv). The reaction mixture was stirred at this temperature for 48 h under an atmosphere of oxygen. The solution was diluted with H_2O (3 ml), the layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 9:1 to 8:2 gradient) gave aldehyde **130** (yield not determined), along with recovered **100**.

TLC: R_f = 0.31 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 9.74 (dd, ^3J = 3.6 Hz, 1.3 Hz, 1H), 5.63 (s, 1H), 4.58 (dd, ^3J = 10.8 Hz, 3.4 Hz, 1H), 3.94 (s, 1H), 3.85 (d, ^2J = 9.0 Hz, 1H), 3.74 (d, ^2J = 9.4 Hz, 1H), 3.38 (d, ^2J = 9.4 Hz, 1H), 3.28 (d, ^2J = 9.0 Hz, 1H), 2.62 (ddd, ^2J = 15.8 Hz, ^3J = 10.7 Hz, 3.6 Hz, 1H), 2.54 (ddd, ^2J = 15.8 Hz, ^3J = 3.7 Hz, 1.4 Hz, 1H), 2.02 (s, 1H), 1.79 (d, ^4J = 1.1 Hz, 3H), 1.45 (s, 3H), 1.25 (s, 3H), 1.09 (s, 3H), 0.09 (s, 9H), 0.06 (s, 6H); **^{13}C-NMR** (150 MHz, $CDCl_3$, relative to TMS): δ 222.65, 199.73, 133.15, 127.75, 90.82, 84.33, 76.44, 76.28, 68.00, 62.19, 56.22, 51.74, 47.23, 43.47, 26.94, 25.83, 24.56, 21.54, 18.27, 15.76, –5.43; **IR** (thin film): 2953, 2926, 2853, 1745, 1728, 1469, 1462, 1450, 1387, 1370, 1252, 1172, 1094, 1072, 1056, 1034, 1004, 996, 913, 834 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{38}NaO_5Si$ ($[M+Na]^+$), 457.2381; found, 457.2373.



(2*RS*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5aSR,7a*SR*)-5a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(1-hydroxyethyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (132): To a solution of olefin **100** (140 mg, 0.334 mmol, 1.00 equiv) in anhydrous EtOH (6.7 ml) was added at RT $Mn(dpm)_3$ (20.2 mg, 0.033 mmol, 0.10 equiv). The reaction flask was purged with oxygen, before phenylsilane (107 µl, 0.836 mmol, 2.50 equiv) was added dropwise by syringe-pump (1.0 µl / min). After the addition was complete, stirring was continued for 1 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (hexane / EtOAc; 8:2) to obtain alcohol **132** (106 mg, 73%) as an inseparable 1:1 mixture of epimers.

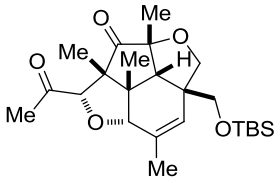
TLC: R_f = 0.44 (hexane / EtOAc; 7:3; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.61 (s, 1H), 5.55 (s, 1H), 4.08–3.13 (br m, 8H), 2.05 (s, 1H), 2.04 (s, 1H), 1.83 (s, 3H), 1.75 (s, 3H), 1.47 (s, 3H), 1.45 (s, 3H), 1.32–1.22 (br m, 9H), 0.90 (m 9H), 0.05 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 225.14, 222.69, 133.90, 133.53, 127.63, 127.59, 92.49, 90.40, 85.22, 84.97, 84.75, 81.89, 76.29, 75.90, 68.44, 67.71, 66.45, 65.06, 62.50, 62.34, 56.44, 56.43, 52.02, 50.73, 48.08, 47.31, 27.56, 26.29, 25.83, 25.80, 24.92, 23.87, 21.71, 21.09, 20.76, 20.22, 18.27, 18.24, 15.89, 15.47, –5.46; **IR** (thin film): 3477, 2956, 2930, 2885, 2857, 1747, 1472, 1464, 1450, 1388, 1373, 1362, 1255, 1173, 1097, 1073, 1054, 1037, 1003, 836, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{44}NO_5Si$ ($[M+NH_4]^+$), 454.2983; found, 454.2990.



(2*RS*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*,7a*SR*)-2-Acetyl-5a-(((*tert*-butyldimethylsilyl) oxy) methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (128): To a solution of alcohol **132** (120 mg, 0.275 mmol, 1.00 equiv) in CH_2Cl_2 (5.5 ml) was added at 0 °C DESS–MARTIN periodinane (175 mg, 0.412 mmol, 1.50 equiv). The resulting mixture was stirred at this temperature for 2 h, then allowed to warm up to RT and stirred for further 4 h. The reaction mixture was diluted with CH_2Cl_2 (3 ml) and filtered through a plug of celite. CH_2Cl_2 (6 ml) was used to rinse. The filtrate was washed with a mixture of satd. aq. sodium thiosulfate (3 ml) and satd. aq. $NaHCO_3$ (3ml). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 8:2) gave diketone **128** (86 mg, 72%) as a colorless oil.

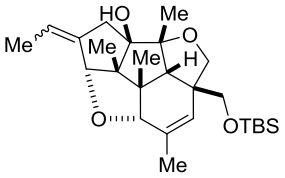
TLC: R_f = 0.43 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 5.61 (s, 1H), 4.58 (s, 1H), 4.23 (s, 1H), 3.86 (d, ^2J = 8.9 Hz, 1H), 3.47 (d, ^2J = 9.5 Hz, 1H), 3.40 (d, ^2J = 9.5 Hz, 1H), 3.36 (d, ^2J = 8.9 Hz, 1H), 2.28 (s, 3H), 2.09 (s, 1H), 1.83 (s, 3H), 1.47 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C-NMR** (150 MHz, $CDCl_3$, relative to TMS): δ 221.07, 207.18, 133.64, 127.99, 90.37, 85.54, 85.49, 76.46, 67.65, 63.18, 56.55, 52.08, 47.53, 29.03, 26.20, 25.84, 24.73, 21.52, 18.29, 16.26, –5.45; **IR**

(thin film): 2955, 2930, 2857, 1750, 1772, 1471, 1463, 1451, 1385, 1271, 1360, 1253, 1172, 1093, 1071, 1038, 1007, 836, 781 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{42}NO_5Si$ ($[M+NH_4]^+$), 452.2827; found, 452.2831.



(2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*,7a*SS*)-2-acetyl-5a-(((*tert*-butyldimethylsilyl)oxy) methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (129). To a solution of ketone **128** (1.5 mg, 3.45 µmol, 1.00 equiv) in MeOH (0.5 ml) at RT was added K_2CO_3 (4.77 mg, 0.035 mmol, 10.0 equiv). The resulting mixture was stirred at this temperature for 24 h. Satd. aq. $NaHCO_3$ (3 ml) was added and the mixture was extracted with Et_2O (3 x 5 ml). Drying over $MgSO_4$, filtation, and concentration under reduced pressure furnished the crude product. Purification by column chromatography (hexane / EtOAc; 9:1) gave epimerized ketone **129** (1 mg, 67%).

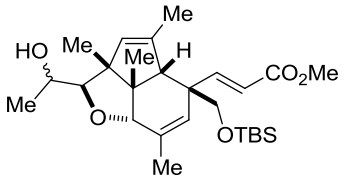
TLC: R_f = 0.50 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.77 (s, 1H), 3.87 (d, ^2J = 8.8 Hz, 1H), 3.68 (s, 1H), 3.66 (s, 1H), 3.51 (d, ^2J = 9.4 Hz, 1H), 3.40 (d, ^2J = 9.4 Hz, 1H), 3.33 (d, ^2J = 8.8 Hz, 1H), 2.17 (s, 3H), 2.02 (s, 1H), 1.92 (d, ^4J = 1.5 Hz, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.13 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).



Compound 133. To a suspension of ethyltriphenylphosphonium bromide (45.3 mg, 0.121 mmol, 25.0 equiv) in THF (0.5 ml) at RT was added potassium *tert*-butoxide, 1 M in THF (0.11 ml, 0.11 mmol, 22.5 equiv). The resulting mixture was stirred at this temperature for 5 min to give an orange solution. A part of this solution (0.27 ml, 48.7 µmol, 10.1 equiv) was taken up with a syringe and added to ketone **129** (2.1 mg, 4.83 µmol, 1.00 equiv) in THF (0.5 ml) at RT. The reaction was stirred at at this temperature for 30 min. The mixture was diluted with water (3 ml) and extracted with ether (3 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was

purified by chromatography on silica gel (hexane / EtOAc; 9:1 to 8:2 gradient) to yield product **133** (0.8 mg, 37%) as a colorless oil.

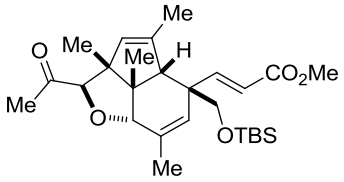
TLC: R_f = 0.43 (hexane / EtOAc; 8:2; $KMnO_4$); **^{1}H-NMR** (8:1 olefin geometrical isomer ratio, only major isomer reported, 600 MHz, $CDCl_3$, relative to TMS): δ 5.61 (s, 1H), 5.44 (m, 1H), 4.36 (s, 1H), 3.84 (d, ^2J = 8.6 Hz, 1H), 3.77 (s, 1H), 3.70 (d, ^2J = 8.6 Hz, 1H), 3.46 (s, 2H), 3.38 (d, ^2J = 16.9 Hz, 1H), 2.14 (s, 1H), 2.09 (d, ^2J = 16.9 Hz, 1H), 1.84 (d, ^4J = 1.2 Hz, 3H), 1.70 (d, ^3J = 6.9 Hz, 3H), 1.31 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); **^{13}C-NMR** (8:1 olefin geometrical isomer ratio, only major isomer reported,150 MHz, $CDCl_3$, relative to TMS): δ 139.84, 134. 58, 129.88, 121.40, 96.80, 90.86, 90.10, 86.85, 77.73, 68.81, 68.65, 51.62, 51.40, 44.08, 29.70, 25.82, 25.20, 22.53, 22.15, 18.24, 16.53, 14.48, −5.45, −5.49; **IR** (thin film): 3456, 2955, 2928, 2856, 1464, 1378, 1253, 1104, 1043, 839, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{43}O_4Si$ ($[M+H]^+$), 447.2925; found, 447.2925.



(*E*)-Methyl 3-((2*RS*,2a*RS*,2a1*SR*,4a*RS*,5*SR*,7a*SR*)-5-(((*tert*-butyldimethylsilyl)oxy) methyl)-2-(1-hydroxyethyl)-2a,2a1,4,7-tetramethyl-2,2a,2a1,4a,5,7a-hexahydroindeno [7,1-bc]furan-5-yl)acryl-ate (231). To a solution of olefin **124** (30.0 mg, 0.065 mmol, 1.00 equiv) in anhydrous EtOH (3.3 ml) was added at RT $Mn(dpm)_3$ (4.0 mg, 6.54 µmol, 0.10 equiv). The reaction flask was purged with oxygen before phenylsilane (21 µl, 0.164 mmol, 2.50 equiv) was added slowly by syringe-pump (10 µl/h). The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (hexane / EtOAc; 8:2) to obtain alcohol **231** (15.2 mg, 49%) as an inseparable 1:1 mixture of epimers.

TLC: R_f = 0.35 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (1:1 diastereomer ratio, 400 MHz, $CDCl_3$): δ 7.19 (d, ^3J = 16.3 Hz, 1H), 5.88 (d, ^3J = 16.3 Hz, 1H), 5.57 (s, 1H), 5.54 (s, 1H), 5.21 (s, 1H), 5.11 (s, 1H), 3.99 (s, 1H), 3.94 (s, 1H), 3.78 (m, 1H), 3.73 (s, 3H), 3.50–3.45 (m. 1H), 3.33–3.30 (m, 1H), 3.20 (d, ^2J = 7.3 Hz, 1H), 3.06 (d, ^2J = 8.7 Hz, 1H), 2.77 (s, 1H), 2.74 (s, 1H), 2.42 (s, 1H), 1.82 (s, 3H), 1.80 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H), 1.26 (d, ^3J = 6.1 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 1.16 (d, ^3J = 6.2 Hz, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); **^{13}C-NMR** (1:1 diastereomer ratio, 100 MHz, $CDCl_3$):

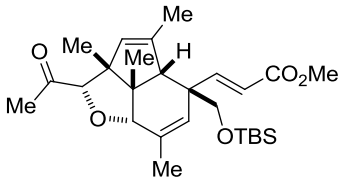
δ 167.16, 167.11, 154.51, 154.27, 138.56, 138.15, 138.08, 137.53, 136.67, 135.63, 125.73, 125.58, 118.81, 118.69, 89.81, 89.79, 83.86, 83.64, 69.12, 69.04, 67.19, 66.43, 59.09, 58.36, 57.05, 56.74, 56.60, 56.48, 51.46, 47.34, 47.23, 25.77, 25.69, 25.28, 22.01, 20.29, 20.03, 19.65, 18.78, 18.77, 18.20, 16.46, 15.88, –5.47, –5.60; **IR** (thin film): 3467, 2951, 2926, 2854, 1724, 1642, 1470, 1462, 1434, 1378, 1304, 1275, 1254, 1206, 1168, 1094, 1056, 1010, 838, 779 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{44}NaO_5Si$ ($[M+Na]^+$), 499.2850; found, 499.2848.



(*E*)-Methyl 3-((2*RS*,2a*RS*,2a1*SR*,4a*RS*,5*SR*,7a*SR*)-2-acetyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2a,2a1,4,7-tetramethyl-2,2a,2a1,4a,5,7a-hexahydroindeno[7,1-bc] furan-5-yl)acrylate (135). To a solution of alcohol **231** (16.0 mg, 0.034 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) was added at 0 °C Dess–Martin periodinane (28.5 mg, 0.067 mmol, 2.00 equiv). The resulting mixture was stirred at this temperature for 2 h, then allowed to warm up to RT and stirred for further 3 h. The reaction mixture was diluted with CH_2Cl_2 (3 ml) and filtered through a plug of celite. CH_2Cl_2 (6 ml) was used to rinse. The filtrate was washed with a mixture of satd. aq. sodium thiosulfate (3 ml) and satd. aq. $NaHCO_3$ (3ml). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 9:1) gave ketone **135** (13.5 mg, 85%) as a colorless oil.

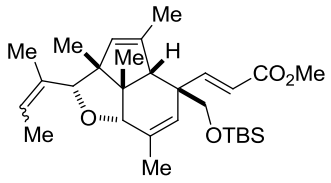
TLC: R_f = 0.20 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 7.14 (d, ^3J = 16.3 Hz, 1H), 5.86 (d, ^3J = 16.3 Hz, 1H), 5.54 (s, 1H), 5.30 (s, 1H), 4.23 (s, 1H), 4.08 (s, 1H), 3.72 (s, 3H), 3.52 (d, ^2J = 9.7 Hz, 1H), 3.39 (d, ^2J = 9.7 Hz, 1H), 2.75 (s, 1H), 2.16 (s, 3H), 1.85 (s, 3H), 1.59 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H), 0.89 (s, 9H), 0.02 (s, 6H); **^{13}C-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 209.64, 167.07, 153.48, 139.03, 137.47, 135.15, 126.32, 119.21, 91.49, 85.11, 69.01, 60.60, 56.58, 56.19, 51.51, 47.31, 28.04, 25.78, 24.73, 20.95, 18.59, 18.21, 17.33, –5.45, –5.54; **IR** (thin film): 29.52, 2930, 2855, 1723, 1642, 1469, 1462, 1434, 1378, 1352, 1312, 1272, 1254,

1199, 1172, 1093, 1033, 1006, 1093, 1033, 1006, 964, 938, 920, 847, 838, 778 cm^{-1}; ; **HRMS** (ESI): exact mass calculated for $C_{27}H_{43}O_5Si$ ($[M+H]^+$), 475.2874; found, 475.2872.



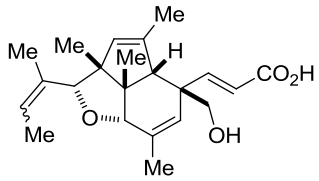
(*E*)-Methyl 3-((2*SR*,2a*RS*,2a1*SR*,4a*RS*,5*SR*,7a*SR*)-2-acetyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2a,2a1,4,7-tetramethyl-2,2a,2a1,4a,5,7a-hexahydroindeno[7,1-bc] furan-5-yl)acrylate (136). To a solution of ketone **135** (10.7 mg, 0.023 mmol, 1.00 equiv) in toluene (1.0 ml) was added at RT 1,8-diazabicyclo[5.4.0]undec-7-ene (17 µl, 0.113 mmol, 5.00 equiv). The resulting mixture was heated to 100 °C for 36 h. After cooling to RT, the mixture was diluted with Et_2O (15 ml) and washed with satd. aq. NaCl (3 x 1.5 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure furnished a white residue. Purification by chromatography on silica gel (hexane / EtOAc; 95:5 to 9:1 gradient) gave diastereomer **136** (6.2 mg, 58%) as a colorless oil.

TLC: R_f = 0.26 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 7.22 (d, ^3J = 16.5 Hz, 1H), 5.74 (d, ^3J = 16.5 Hz, 1H), 5.45 (s, 1H), 4.96 (s, 1H), 3.78 (s, 1H), 3.69–3.66 (m, 5H), 3.52 (d, ^2J = 9.6 Hz, 1H), 2.70 (s, 1H), 2.23 (s, 3H), 1.92 (s, 3H), 1.55 (s, 3H), 1.16 (s, 3H), 1.03 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 210.49, 167.16, 153.02, 141.26, 134.90, 131.35, 128.67, 117.72, 92.98, 85.26, 68.74, 60.79, 57.01, 54.27, 51.38, 47.24, 28.63, 25.80, 23.28, 22.79, 20.34, 18.29, 18.21, –5.43, –5.46; **IR** (thin film): 2953, 2928, 2857, 1718, 1638, 1471, 1463, 1435, 1378, 1354, 1313, 1257, 1200, 1172, 1101, 1084, 1043, 1020, 1006, 938, 838, 816, 776, 728, 671 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{42}NaO_5Si$ ($[M+Na]^+$), 497.2694; found, 497.2683.



(*E*)-Methyl 3-((2*RS*,2a*RS*,2a1*SR*,4a*RS*,5*SR*,7a*SR*)-2-((*Z*)-but-2-en-2-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2a,2a1,4,7-tetramethyl-2,2a,2a1,4a,5,7a-hexahydro-indeno[7,1-bc]furan-5-yl)acrylate (137). To a suspension of ethyltriphenylphosphonium bromide (35.5 mg, 0.095 mmol, 6.00 equiv) in THF (0.5 ml) / DMPU (0.4 ml) was added at RT KHMDS, 1.0 M in THF (80 µl, 0.080 mmol, 5.00 equiv). The resulting mixture was stirred at this temperature for 10 min. The mixture was cooled to –78 °C and stirred for 5 min, before a solution of ketone **136** (7.5 mg, 0.016 mmol, 1.00 equiv) in THF (0.5 ml) was added dropwise. THF (0.5 ml) was used to assist the transfer. The reaction was stirred for 2 h, while it was allowed to warm up to 0 °C. The mixture was diluted with water (3 ml) and extracted with Et_2O (3 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 98:2 to 95:5 gradient) gave olefin **137** (5.4 mg, 70%) as a 1.6:1 mixture of mixture of *E/Z*-isomers.

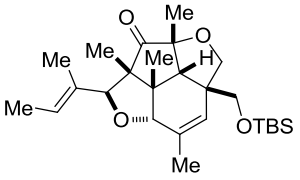
TLC: R_f = 0.46 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (1.6:1 olefin geometrical isomer ratio, asterisk denotes minor isomer signals, 600 MHz, $CDCl_3$, relative to TMS): δ 7.26-7.23 (m, 1H), 5.75–5.70 (m, 1H), 5.51* (q, ^3J = 6.7 Hz, 1H), 5.46 (q, ^3J = 7.0 Hz, 1H), 5.39* (s, 1H), 5.38 (s, 1H), 5.01 (s, 1H), 4.92* (s, 1H), 4.37 (s, 1H), 3.78* (s, 1H), 3.70–3.63 (m, 5H), 3.51–3.48 (m, 1H), 2.72 (s, 1H), 2.71* (s, 1H), 1.89 (s, 3H), 1.75–1.63 (m, 6H), 1.53 (s, 3H), 1.52* (s, 3H), 1.07 (s, 3H), 1.05* (s, 3H), 1.00 (s, 3H), 0.99* (s, 3H), 0.89 (s, 9H), 0.05–0.04 (m, 6H); **^{13}C-NMR** (1.6:1 olefin geometrical isomer ratio, asterisk denotes minor isomer signals, 600 MHz, $CDCl_3$, relative to TMS): δ 167.30, 154.01*, 153.92, 138.89*, 138.79, 136.09*, 135.99, 133.95, 133.92*, 133.44, 132.82*, 127.17, 127.07*, 122.68, 121.61*, 117.51*, 117.35, 92.80*, 85.63, 85.04, 84.42*, 69.08*, 68.96, 61.90, 60.28*, 56.93, 56.73*, 54.12*, 53.84, 51.33*, 51.25, 47.32, 47.23*, 25.83, 23.80, 23.76*, 22.70, 22.65*, 21.54, 19.97, 19.91*, 18.48*, 18.40, 18.22, 14.23, 14.07*, 13.15*, –5.43, –5.47; **IR** (thin film): 2954, 2929, 2857, 1725, 1643, 1471, 1462, 1445, 1434, 1378, 1361, 1309, 1293, 1269, 1257, 1197, 1170, 1099, 1083, 1059, 1042, 1022, 1006, 938, 850, 838, 815, 777, 729 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{29}H_{47}O_4Si$ ($[M+H]^+$), 487.3238; found, 487.3240.

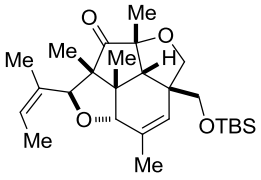


Nominal Indoxamycin B (2-*epi*-2). To a solution of ester **137** (5.4 mg, 0.011 mmol, 1.00 equiv) in THF / MeOH (3:1; 0.8 ml) was added at RT a solution of lithium hydroxide (1 M in H_2O, 0.2 ml, 0.20 mmol, 18.0 equiv). The resulting mixture was stirred at RT for 12 h. As TLC indicated full consumption of starting material, hydrochloric acid (6 M in H_2O, 0.1 ml, 0.60 mmol, 53.1 equiv) was added. Stirring was continued at RT for 18 h. Brine (1.5 ml) was added and the mixture was extracted with EtOAc (5 x 3 ml). The combined organic extracts were dried over Na_2SO_4. Concentration under reduced pressure gave a white crude, which was purified by column chromatography (hexane / EtOAc / AcOH; 25:50:2.5) to furnish nominal indoxamycin B (2-*epi*-**2**) (2.9 mg, 73%) as a 1.5:1 mixture of olefin geometrical isomers.

TLC: R_f = 0.42 (hexane / EtOAc / AcOH; 25:50:2.5; UV / $KMnO_4$); **^{1}H-NMR** (1.5:1 olefin geometrical isomer ratio, 600 MHz, CD_3OD): δ 7.26–7.21 (m, 1H), 5.70 (s, 1H), 5.67 (s, 1H), 5.55–5.52 (m, 2H), 5.46 (q, ^3J = 7.0 Hz, 1H), 5.00 (s, 1H), 4.41 (s, 1H), 4.91 (s, 1H), 4.41 (s, 1H), 3.79 (s, 1H), 3.73–3.64 (s, 2H), 3.56–3.53 (m, 1H), 2.64 (s, 1H), 2.60 (s, 1H), 1.93 (s, 3H), 1.92 (s, 3H), 1.93 (d, ^4J = 1.5 Hz, 3H), 1.92 (d, ^4J = 1.5 Hz, 3H), 1.73–1.60 (m, 9H), 1.07–1.04 (m, 6H); **^{13}C-NMR** (1.5:1 olefin geometrical isomer ratio, 150 MHz, CD_3OD): δ 170.42, 155.03, 154.94, 140.07, 136.31, 136.26, 135.27, 135.23, 134.70, 133.86, 130.28, 130.04, 123.59, 122.48, 119.48, 95.17, 87.76, 86.30, 85.65, 68.96, 63.04, 61.43, 59.32, 59.21, 55.57, 55.15, 24.06, 24.03, 23.31, 23.28, 22.38, 20.78, 20.75, 18.37, 14.58, 14.41, 13.13; **IR** (thin film): 3404, 2962, 2925, 2861, 1691, 1634, 1445, 1415, 1380, 1292, 1257, 1216, 1179, 1103, 1041, 1021, 1008, 866, 756 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{30}NaO_4$ ($[M+Na]^+$), 381.2036; found, 381.2039.

3.2.3.4 Stereochemical Reassignment and Synthesis of Indoxamycin B



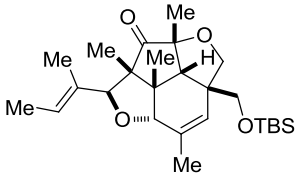


(2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5a-(((*tert*-butyldimethylsilyl)oxy)methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c'] difuran-3(2aH)-one (143). (2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*, 7a*SR*)-2-((*Z*)-But-2-en-2-yl)-5a (((*tert*-butyldimethyl-silyl)oxy)methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c'] difuran-3(2aH)-one (144). A typical experiment was carried out as follows: To a suspension of ethyltriphenylphosphonium bromide (103 mg, 0.275 mmol, 1.20 equiv) in toluene (0.26 ml) at RT was added *n*-BuLi (0.144 ml, 0.230 mmol, 1.00 equiv). The resulting mixture was stirred at this temperature for 30 min to give a deep-orange solution of phosphonium ylide. In a separate flask, ketone **128** (5.0 mg, 0.012 mmol, 1.00 equiv) was dissolved in toluene and cooled to –78 °C. Ylide solution (0.10 ml, 0.060 mmol, 5.00 equiv) was added dropwise. The resulting mixture was stirred at this temperature for 30 min and then allowed to slowly warm up to RT. The mixture was diluted with water (3 ml) and extracted with Et_2O (3 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 95:5) gave a 8:1 mixture of olefin geometrical isomers **143** and **144** (4.5 mg, 88%). Both olefins **143** and **144** could be obtained in isomerically enriched form by repeated column-chromatography on silica gel (hexane / EtOAc; 95:5).

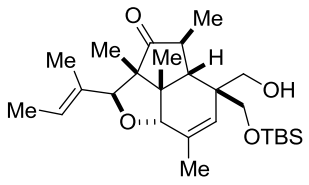
*(2SR,2aRS,2a1SR,3aRS,3a1RS,5aSR,7aSR)-2-((E)-But-2-en-2-yl)-5a-(((tert-butyldimethyl-silyl) oxy)methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c'] difuran-3(2aH)-one (**143**):* **TLC:** R_f = 0.39 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (12:1 (E)/(Z)-isomer ratio, only major isomer reported, 600 MHz, $CDCl_3$, relative to TMS): δ 5.65 (q, ^3J = 6.8 Hz, 1H), 5.50 (s, 1H), 4.12 (s, 1H), 4.03 (s, 1H), 3.85 (d, ^2J = 8.7 Hz, 1H), 3.55 (d, ^2J = 8.7 Hz, 1H), 3.44 (d, ^2J = 9.6 Hz, 1H), 3.41 (d, ^2J = 9.6 Hz, 1H), 2.16 (s, 1H), 1.77 (s, 3H), 1.67 (s, 3H), 1.65 (d, ^3J = 6.8 Hz, 3H), 1.44 (s, 3H), 1.28, (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H); **^{13}C-NMR** (1:12 (E)/(Z)-isomer ratio, only major isomer reported, 150 MHz, $CDCl_3$, relative to TMS): δ 220.44, 136.50, 132.14, 127.93, 121.95, 91.57, 84.09, 83.84, 76.48, 67.49, 63.40, 56.84, 51.39, 47.92, 27.04, 25.86, 24.73, 19.95, 18.32, 17.13, 14.23, 13.04,–5.45, –5.47; **IR** (thin film): 2954, 2929, 2885, 2857, 1745,

1471, 1463, 1448, 1384, 1367, 1313, 1253, 1172, 1095, 1056, 1003, 972, 938, 835, 778 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{43}O_4Si$ ($[M+H]^+$), 447.2925; found, 447.2927.

*(2SR,2aRS,2a1SR,3aRS,3a1RS,5aSR,7aSR)-2-((Z)-But-2-en-2-yl)-5a (((tert-butyldimethyl-silyl) oxy)methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c'] difuran-3(2aH)-one (**144**):* **TLC:** R_f = 0.39 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$, relative to TMS): δ 5.59 (s, 1H), 5.51 (q, ^3J = 7.1 Hz, 1H), 4.92 (s, 1H), 4.10 (s, 1H), 3.85 (d, ^2J = 8.7 Hz, 1H), 3.51–3.48 (m, 2H), 3.42 (d, ^2J = 9.5 Hz, 1H), 2.10 (s, 1H), 1.82 (s, 3H), 1.75 (s, 3H), 1.70 (d, ^3J = 7.1 Hz, 3H), 1.44 (s, 3H), 1.24 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C-NMR** (150 MHz, $CDCl_3$, relative to TMS): δ 221.96, 135.79, 133.04, 127.51, 125.60, 90.39, 85.01, 81.47, 76.50, 67.44, 64.48, 57.00, 52.11, 48.28, 26.29, 25.86, 24.89, 21.18, 20.96, 18.31, 16.77, 13.78, ,–5.43, –5.44; **IR** (thin film): 2955, 2929, 2884, 2857, 1746, 1472, 1463, 1448, 1383, 1368, 1362, 1254, 1171, 1163, 1115, 1095, 1071, 1059, 1028, 1005, 975, 939, 837, 815, 779; cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{42}NaO_4Si$ ($[M+Na]^+$), 469.2745; found, 469.2751.

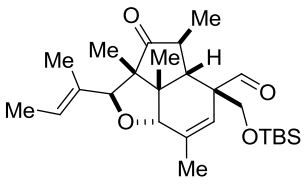


(2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*SR*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5a-(((*tert*-butyldimethylsilyl)oxy)methyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c'] difuran-3(2aH)-one (143). A solution of isomeric olefins **143** and **144** ((*E*)/(*Z*) = 1:3.1, 38 mg, 0.085 mmol, 1.00 equiv) and diphenyl disulfide (4.6 mg, 0.021 mmol, 0.25 equiv) in cyclohexane (4.0 ml) / dioxane (0.2 ml) at RT was irradiated with a medium pressure mercury vapor lamp for 4 h. The mixture was poured into satd. aq. $NaHCO_3$ (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic layer was washed with a satd. aq. NaCl solution, dried over $MgSO_4$ filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 95:5 to 9:1 gradient) gave olefin **143** ((*E*)/(*Z*) = 7.6:1, 34 mg, 89%).



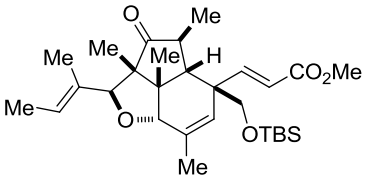
(2*SR*,2a*RS*,2a1*SR*,4*SR*,4a*RS*,5*SR*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5-(((*tert*-butyldimethylsilyl) oxy)methyl)-5-(hydroxymethyl)-2a,2a1,4,7-tetramethyl-2,2a,4,4a,5,7a-hexahydroindeno[7,1-bc] furan-3(2a1H)-one (232). The THF employed in this reaction was degassed by freeze-pump-thaw (4 cycles) prior to use. To a suspension of samarium powder (150 mg, 1.00 mmol) in THF (2.2 ml) at RT was added via cannula a solution of diiodoethane (150 mg, 0.532 mmol) in THF (2.0 ml). THF (1.0 ml) was used to assist the transfer. The resulting mixture became royal blue after 15 min and was stirred at the same temperature for 2 h to give a solution of samarium diiodide (ca. 0.1 M). In a separate 50 ml Schlenk tube ketone **143** (27.6 mg, 0.062 mmol, 1.00 equiv) was dissolved in THF / MeOH (7:3, 6.2 ml) and the resulting mixture was degassed carefully (freeze-pump-thaw; 4 cycles). To this mixture the fresh samarium diiodide solution (1.24 ml, 0.124 mmol, 2.00 equiv) was added dropwise via syringe until a slightly blue coloration persisted for ca. 5 min. The reaction was quenched by addition of THF / H_2O (1:1; 3 ml). HCl (0.05 M in H_2O; 3 ml) was added and the mixture was extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (3 ml) and satd. aq. NaCl (1.5 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure to furnished a crude oil that was purified by chromatography on silica gel (hexane / EtOAc; 9:1 to 8:2 gradient) to give alcohol **232** (27.5 mg, 99%) as a 12:1 mixture of (*E*)/(*Z*)-isomers.

TLC: R_f = 0.28 (hexane / EtOAc; 85:15; $KMnO_4$); **^{1}H-NMR** (12:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 5.55 (q, ^3J = 6.8 Hz, 1H), 5.26 (s, 1H), 4.13 (s, 1H), 3.98 (s, 1H), 3.73 (d, ^2J = 10.7 Hz, 1H), 3.64 (m, 2H), 3.52 (d, ^2J = 10.2 Hz, 1H), 3.09 (m, 1H), 2.33 (m, 1H), 2.14 (d, ^3J = 9.7 Hz, 1H), 1.75 (s, 3H), 1.64 (d, ^3J = 6.8 Hz, 3H), 1.57 (s, 3H), 1.27 (s, 3H), 1.24 (d, ^3J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C-NMR** (12:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 222.38, 139.49, 132.43, 125.29, 121.31, 86.25, 84.65, 69.31, 68.13, 63.45, 52.59, 46.97, 45.44, 44.90, 26.65, 25.76, 18.93, 18.08, 17.45, 14.36, 14.23, 12.95, –5.55, –5.75; **IR** (thin film): 3514, 2955, 2929, 2886, 2858, 1731, 1472, 1463, 1434, 1386, 1361, 1319, 1255, 1232, 1123, 1082, 1062, 1006, 971, 858, 838, 814, 781, 734 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{44}NaO_4Si$ ($[M+Na]^+$), 471.2901; found, 471.2900.



(2*SR*,2a*RS*,2a1*SR*,4*SR*,4a*SR*,5*RS*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5-(((*tert*-butyldimethyl-silyl) oxy)methyl)-2a,2a1,4,7-tetramethyl-3-oxo-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7 ,1-bc]furan-5-carbaldehyde (233). To a solution of alcohol **232** (27.0 mg, 0.061 mmol, 1.00 equiv) in CH_2Cl_2 (3.0 ml) was added at 0 °C Dess–Martin periodinane (32.5 mg, 0.077 mmol, 1.25 equiv). The resulting mixture was stirred for 4 h, while it was allowed to warm up to RT. The reaction mixture was diluted with CH_2Cl_2 (3 ml) and filtered through a plug of celite. CH_2Cl_2 (6 ml) was used to rinse. The filtrate was washed with aq. sodium thiosulfate solution (5 ml) and $NaHCO_3$ (5 ml) successively and was dried over $MgSO_4$. Purification by column chromatography (hexane / EtOAc; 95:5) gave aldehyde **233** (27.5 mg, quantitative) as a 12:1 mixture of (*E*)/(*Z*)-isomers.

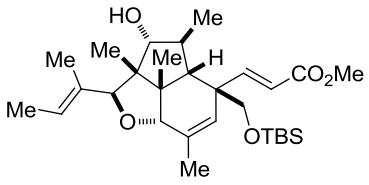
TLC: R_f = 0.26 (hexane / EtOAc; 95:5; $KMnO_4$); **^{1}H-NMR** (12:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 5.95 (s, 1H), 5.54 (q, ^3J = 6.8 Hz, 1H), 4.13 (s, 1H), 3.89 (s, 1H), 3.74 (d, ^2J = 10.3 Hz, 1H), 3.67 (d, ^2J = 10.3Hz, 1H), 2.28 (m, 2H), 1.82 (s, 3H), 1.62 (d, ^3J = 6.8 Hz, 3H), 1.54 (s, 3H), 1.29 (s, 3H), 1.03 (d, ^3J = 6.5 Hz, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C-NMR** (12:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): 219.97, 203.75, 139.41, 131.93, 122.28, 121.49, 86.50, 84.54, 66.10, 62.84, 56.80, 52.37, 47.08, 44.01, 26.67, 25.69, 19.11, 18.14, 15.97, 14.09, 13.70, 12.92, –5.61, –5.77; **IR** (thin film): 2954, 2930, 2883, 2858, 1792, 1471, 1464, 1446, 1388, 1379, 1362, 1321, 1254, 1231, 1092, 1014, 1006, 994, 974, 939, 897, 839, 814, 779, 746, 722, 671 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{43}NaO_4Si$ ($[M+H]^+$), 447.2925; found, 447.2923.



(*E*)-methyl 3-((2*SR*,2a*RS*,2a1*SR*,4*SR*,4a*RS*,5*SR*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5-(((*tert*-butyldi-methylsilyl)oxy)methyl)-2a,2a1,4,7-tetramethyl-3-oxo-2,2a,2a1,3,4,4a,5,7a-octa-hydroindeno[7,1-bc] furan-5-yl)acrylate (145). To a suspension of sodium hydride (60% in mineral oil, 12.3 mg, 0.308 mmol, 5.00 equiv) in THF (1.0 ml) was added dropwise at RT

methyl diethylphosphonoacetate (58.0 µl, 0.308 mmol, 5.00 equiv). Strong gas evolution could be observed immediately. The resulting mixture was stirred for 30 min, before a solution of aldehyde **233** (27.5 mg, 0.062 mmol, 1.00 equiv) in THF (1.0 ml) was added via cannula. THF (0.5 ml) was used to assist the transfer. The reaction was stirred at RT for 48 h. The mixture was poured into satd. aq. $NaHCO_3$ (5 ml). Extraction with Et_2O (3 x 10 ml), washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished a crude oil. Purification by chromatography on silica gel (hexane / EtOAc; 95:5 to 9:1 gradient) gave ester **145** (30.6 mg, 99%) as a 11:1 mixture of (*E*)/(*Z*)-isomers.

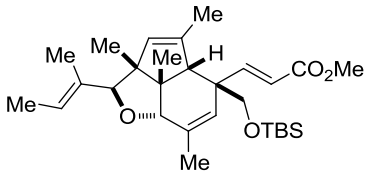
TLC: R_f = 0.28 (hexane / EtOAc; 85:15; UV / $KMnO_4$); **^{1}H-NMR** (11:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 7.20 (d, ^3J = 16.4 Hz, 1H), 5.89 (d, ^3J = 16.3 Hz, 1H), 5.61 (s, 1H), 5.55 (q, ^3J = 6.8 Hz, 1H), 4.14 (s, 1H), 3.98 (s, 1H), 3.76 (s, 3H), 3.47 (d, ^2J = 10.2 Hz, 1H), 3.36 (d, ^2J = 10.2 Hz, 1H), 2.15 (d, ^3J = 10.1 Hz, 1H), 2.09 (m, 1H), 1.82 (s, 3H), 1.64 (d, ^3J = 6.8 Hz, 3H), 1.56 (s, 3H), 1.30 (s, 3H), 1.02 (d, ^3J = 4.7 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (11:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 221.67, 166.94, 153.21, 139.80, 132.37, 124.41, 121.41, 118.41, 86.37, 84.38, 67.30, 63.77, 52.17, 51.60, 48.90, 47.73, 45.43, 26.68, 25.77, 19.57, 18.21, 17.74, 14.23, 14.09, 12.96, –5.45, –5.66; **IR** (thin film): 2953, 2931, 2857, 1728, 1648, 1472, 1463, 1435, 1395, 1377, 1361, 1313, 1305, 1275, 1259, 1194, 1176, 1167, 1088, 1059, 1007, 972, 839, 813, 780, 731 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{29}H_{50}NO_5Si$ ($[M+NH_4]^+$), 520.3453; found, 520.3441.



(*E*)-methyl 3-((2*SR*,2a*SR*,2a1*SR*,3*RS*,4*SR*,4a*RS*,5*SR*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2a,2a1,4,7-tetramethyl-2,2a,2a1,3,4,4a,5,7a-octahydro-indeno[7,1-bc]furan-5-yl)acrylate (234). To a solution of ketone **145** (30.6 mg, 0.061 mmol, 1.00 equiv) in CH_2Cl_2 (1.2 ml) was added at RT borane *tert*-butylamine complex (10.6 mg, 0.122 mmol, 2.00 equiv). The resulting mixture was heated to 40 °C for 16 h. After cooling to RT, CH_2Cl_2 (3 ml) was added, followed by 1 M aq. HCl (5 ml). The resulting mixture was stirred vigorously for 30 min. The mixture was extracted with CH_2Cl_2

(3 x 10 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (3 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 9:1 to 85:15 gradient) gave alcohol **234** (24.3 mg, 79%) as a colorless oil.

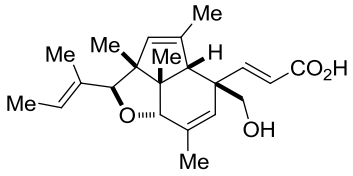
TLC: R_f = 0.25 (hexane / EtOAc; 85:15; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.09 (d, ^3J = 16.2 Hz, 1H), 5.81 (d, ^3J = 16.2 Hz, 1H), 5.52 (q, ^3J = 6.7 Hz, 1H), 5.42 (s, 1H), 4.27 (s, 1H), 3.85 (s, 1H), 3.71 (s, 3H), 3.45 (d, ^2J = 9.6 Hz, 1H), 3.38 (d, ^2J = 9.6 Hz, 1H), 3.19 (dd, ^3J = 10.1 Hz, 5.1 Hz, 1H), 1.86 (s, 3H), 1.75–1.66 (m, 1H), 1.64 (m, 9H), 1.55 (d, ^3J = 5.5 Hz, 1H), 0.98 (m, 9H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 167.26, 153.04, 135.68, 135.58, 126.78, 120.98, 119.02, 85.64 (2C), 83.40, 69.44, 56.73, 52.43, 51.39, 49.86, 46.62, 40.30, 25.84, 24.53, 21.99, 18.72, 18.29, 17.84, 14.30, 13.06, –5.45, –5.55; **IR** (thin film): 3453, 2955, 2927, 2856, 1724, 1704, 1644, 1472, 1463, 1448, 1435, 1378, 1362, 1313, 1278, 1258, 1197, 1171, 1107, 1091, 1089, 1013, 991, 837, 814, 782 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{29}H_{52}NO_5Si$ ($[M+NH_4]^+$), 522.3609; found, 522.3615.



(*E*)-methyl 3-((2*SR*,2a*RS*,2a1*SR*,4a*RS*,5*SR*,7a*SR*)-2-((*E*)-But-2-en-2-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2a,2a1,4,7-tetramethyl-2,2a,2a1,4a,5,7a-hexahydro-indeno[7,1-bc]furan-5-yl)acrylate (235). To a solution of (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (23.0 mg, 0.096 mmol, 2.00 equiv) in toluene (2.5 ml) at RT was added via cannula solution of alcohol **234** (24.3 mg, 0.048 mmol, 1.00 equiv) in toluene (1.5 ml). Toluene (1.0 ml) was used to assist the transfer. The resulting mixture was heated to 110 °C for 14 h. After cooling to RT, H_2O (5 ml) was added and the mixture was extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with satd. aq. NaCl (1.5 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (hexane / EtOAc; 97:3 to 95:5 gradient) to yield olefin **235** (16.1 mg, 69%) as a colorless oil.

TLC: R_f = 0.23 (hexane / EtOAc; 95:5; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, ^3J = 16.3 Hz, 1H), 5.90 (d, ^3J = 16.3 Hz, 1H), 5.55 (s, 1H), 5.50 (q, ^3J = 6.8 Hz, 1H),

5.17 (s, 1H), 4.07 (s, 1H), 3.83 (s, 1H), 3.72, (s, 3H), 3.50 (d, ^2J = 9.7 Hz, 1H), 3.31 (d, ^2J = 9.7 Hz, 1H), 2.76 (s, 1H), 1.81 (s, 3H), 1.62 (d, ^3J = 6.8 Hz, 3H), 1.55 (m, 6H), 1.18 (s, 3H), 0.88 (s, 9H), 0.80 (s, 3H), 0.00 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 167.19, 154.70, 139.11, 137.86, 136.38, 133.56, 124.94, 119.46, 118.71, 90.19, 83.79, 68.83, 60.09, 56.80, 56.46, 51.41, 47.30, 25.78, 25.43, 20.10, 18.80, 18.21, 17.50, 14.20, 12.85, –5.47, –5.60; **IR** (thin film): 3024, 2955, 2928, 2885, 2859, 1727, 1645, 1471, 1463, 1435, 1378, 1362, 1313, 1304, 1272, 1256, 1199, 1173, 1093, 1013, 1006, 971, 848, 838, 814, 779, 730, 703, 670, 626 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{29}H_{47}NO_4Si$ ($[M+H]^+$), 487.3238; found, 487.3226.



Indoxamycin B (2). To a solution of ester **235** (10.0 mg, 0.021 mmol, 1.00 equiv) in THF / MeOH (3:1; 0.8 ml) was added at RT a solution of lithium hydroxide (1.0 M in H_2O, 0.20 ml, 0.20 mmol, 9.74 equiv). The resulting mixture was stirred at RT for 10 h. As TLC indicated full consumption of starting material, hydrochloric acid (6.0 M in H_2O, 0.10 ml, 0.60 mmol, 29.1 equiv) was added. Stirring was continued at RT for 14 h. Satd. aq. NaCl solution (3 ml) was added and the mixture was extracted with EtOAc (5 x 3 ml). The combined organic extracts were dried over Na_2SO_4. Concentration under reduced pressure gave a white crude that was purified by column chromatography (hexane / EtOAc / AcOH; 25:50:2.5) to furnish synthetic indoxamycin B (**2**) (7.1 mg, 96%) as a colorless oil, which became a white amorphous solid upon prolonged standing.

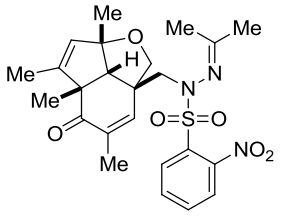
TLC: R_f = 0.42 (hexane / EtOAc / AcOH; 25:50:2.5; UV / $KMnO_4$); **^{1}H-NMR** (500 MHz, CD_3OD): δ 7.14 (d, ^3J = 16.1 Hz, 1H), 5.83 (d, ^3J = 16.1 Hz, 1H), 5.65 (s, 1H), 5.46 (q, ^3J = 6.8 Hz, 1H), 5.23 (s, 1H), 4.07 (s, 1H), 4.00 (s, 1H), 3.56 (d, ^2J = 10.8 Hz, 1H), 3.46 (d, ^2J = 10.8 Hz, 1H), 2.55 (s, 1H), 1.86 (s, 3H), 1.69 (s, 3H), 1.62 (d, ^3J = 6.8 Hz, 3H), 1.55 (s, 3H), 1.12 (s, 3H), 0.83 (s, 3H); **^{13}C-NMR** (125 MHz, CD_3OD): δ 170.14, 154.97, 139.09, 138.94, 136.94, 134.86, 127.97, 121.93, 120.36, 91.86, 84.77, 69.29, 61.23, 59.16, 58.02, 25.95, 21.59, 18.81, 17.22, 14.27, 12.89; **IR** (thin film): 3416, 2964, 2920, 2864,1693, 1643, 1446, 1380, 1291, 1260, 1208, 1052, 1012, 670, 864, 805, 755 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{30}NaO_4$ ($[M+Na]^+$), 381.2036; found, 381.2037. The ^{1}H and ^{13}C NMR data

for the synthetic material did not precisely match with does previously reported for natural indoxamycin B [13, 14].

A sample of (**2**) that exhibits NMR resonances, which are in full accordance with the literature data, could be reproducibly prepared as follows: An NMR tube (178 mm x 5 mm ø) was charged with a solution of indoxamycin B (**2**) (7.1 mg, 0.020 mmol, 1.00 equiv) in CD_3OD (0.5 ml). A solution of CD_3OK (0.2 M in CD_3OD, freshly prepared from CD_3OD and potassium hydride) was added in increments of 33 µl with continuous monitoring by ^1H NMR. When 100 µl (0.020 mmol, 1.00 equiv) of CD_3OK was added, the ^1H NMR spectrum obtained was identical to that reported for natural indoxamycin B. Furthermore, the ^{13}C NMR chemical shifts were in excellent agreement.

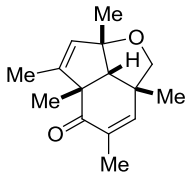
^{1}H-NMR (500 MHz, CD_3OD): δ 6.81 (d, ^3J = 16.1 Hz, 1H), 5.90 (d, ^3J = 16.1 Hz, 1H), 5.68 (s, 1H), 5.48 (q, ^3J = 6.8 Hz, 1H), 5.18 (s, 1H), 4.07 (s, 1H), 3.98 (s, 1H), 3.50 (d, ^2J = 11.0 Hz, 1H), 3.39 (d, ^2J = 11.0 Hz, 1H), 2.62 (s, 1H), 1.83 (s, 3H), 1.69 (s, 3H), 1.63 (d, ^3J = 6.8 Hz, 1H), 1.57 (s, 1H), 1.19 (s, 3H), 0.82 (s, 3H); **^{13}C-NMR** (125 MHz, CD_3OD): δ 175.71, 148.45, 140.08, 138.56, 136.39, 134.80, 128.12, 128.05, 120.01, 91.17, 84.80, 70.11, 61.20, 58.65, 57.78, 26.20, 20.74, 19.21, 17.51, 14.29, 12.88.

3.2.3.5 Synthesis of Indoxamycin A



2-nitro-N'-(propan-2-ylidene)-N-(((2a*RS*,2a1*RS*,5a*SR*,7a*SR*)-4,5a,6,7a-tetramethyl-5-oxo-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-2a-yl)methyl)benzenesulfonohydrazide (150). A solution of alcohol **73** (30 mg, 0.121 mmol, 1.00 equiv), triphenylphosphine (IPNBSH, **154**, 63.4 mg, 0.242 mmol, 2.00 equiv) and 2-nitro-N'-(propan-2-ylidene)benzenesulfonohydrazide [168] (93 mg, 0.362 mmol, 3.00 equiv) in THF (1.20 ml) was degassed carefully (freeze-pump-thaw; 4 cycles), before DEAD (38 µl, 0.242 mmol, 2.00 equiv) was added. The resulting mixture was heated to 40 °C for 22 h. After cooling to RT, the reaction-mixture was concentrated by rotary-evaporator. Purification by column chromatography (hexane / EtOAc; 6:4 to 1:1 gradient) gave alcohol **150** (41.6 mg, 71%) as an amber solid.

TLC: R_f = 0.29 (hexane / EtOAc; 4:6; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.98 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H), 7.73 (m, 2H), 7.57 (dd, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H), 6.16 (s, 1H), 5.20 (s, 1H), 3.87 (d, ^2J = 12.9 Hz, 1H), 3.55 (d, ^2J = 9.0 Hz, 1H), 3.36 (d, ^2J = 9.0 Hz, 1H), 3.01 (d, ^2J = 12.9 Hz, 1H), 2.79 (s, 1H), 2.07 (s, 3H), 2.00 (s, 3H), 1.71 (d, ^4J = 1.3 Hz, 3H), 1.60 (s, 3H), 1.59 (d, ^4J = 1.4 Hz, 1H), 1.33 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 198.99, 183.36, 149.54, 147.75, 144.74, 134.22, 133.21, 131.10, 130.66, 128.94, 128.79, 123.85, 96.41, 74.26, 60.46, 59.78, 56.75, 49.11, 26.40, 25.41, 25.05, 22.53, 16.79, 13.08; **IR** (thin film): 3092, 2967, 2923, 2860, 1659, 1548, 1439, 1374, 1309, 1295, 1256, 1238, 1214, 1176, 1128, 1099, 1059, 963, 914, 891, 861, 851, 820, 787, 772, 731, 699, 651, 615, 586, 578, 538 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{30}N_3O_6S$ ($[M+H]^+$), 488.1850; found, 488.1842.

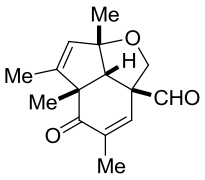


(2aR,2a1R,5aS,7aS)-2a,4,5a,6,7a-pentamethyl-2,2a,5a,7a-tetrahydroindeno[1,7-bc]furan-5(2a1H)-one (152). *From Hydrazone **150**:* To a solution of hydrazone **150** (10 mg, 0.021 mmol, 1.00 equiv) in THF (1.0 ml) at RT was added phenylhydrazine (10 µl, 0.103 mmol, 5.00 equiv). The resulting mixture was stirred at this temperature for 2 h. The mixture was taken up in Et_2O (5 ml) and washed with water (5 ml). The aqueous layer was extracted with Et_2O (2 x 5 ml) and the combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure gave the crude product, which was purified by chromatography on silica gel (hexane / EtOAc; 9:1) to furnish deoxygenated species **152** as a colorless oil.

*One-Pot Deoxygenation of **73**:* To a degassed solution of alcohol **73** (30 mg, 0.121 mmol, 1.00 equiv), triphenylphosphine (63.4 mg, 0.242 mmol, 2.00 equiv) and 2-nitro-N'-(propan-2-ylidene)benzenesulfonohydrazide [168] (IPNBSH, **154**, 93 mg, 0.362 mmol, 3.00 equiv) in THF (1.2 ml) at RT was added DEAD (38.3 µl, 0.242 mmol, 20.. equiv). The resluting mixture was heated to 40 °C for 12 h. After cooling to RT, phenylhydrazine (59.9 µl, 0.604 mmol, 5.00 equiv) was added and the mixture was stirred at this temperature for 2 h. The resulting mixture was stirred at this temperature for 2 h. The mixture was taken up in Et_2O (5 ml) and washed with water (5 ml). The aqueous layer was extracted with Et_2O (2 x 5 ml) and the combined organic extracts were dried over $MgSO_4$. Filtration and concentration under

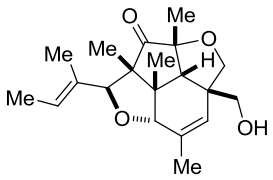
reduced pressure gave the crude product, which was purified by chromatography on silica gel (hexane / EtOAc; 9:1) to furnish deoxygenated species **152** as a colorless oil.

TLC: R_f = 0.36 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.34 (s, 1H), 5.19 (s, 1H), 3.58 (d, ^2J = 8.3 Hz, 1H), 3.41 (d, ^2J = 8.3 Hz, 1H), 2.08 (s, 1H), 1.78 (d, ^4J = 1.3 Hz, 3H), 1.60 (d, ^4J = 1.5 Hz, 3H),1.52 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H).



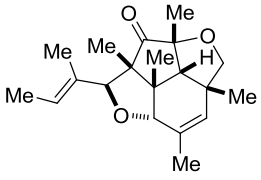
(2a*SR*,2a1*RS*,5a*SR*,7a*SR*)-4,5a,6,7a-tetramethyl-5-oxo-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-2a-carbaldehyde (155). To a solution of alcohol **73** (47 mg, 0.189 mmol, 1.00 equiv) in CH_2Cl_2 (1.9 ml) at 0 °C was added DESS-MARTIN periodinane (120 mg, 0.284 mmol, 1.50 equiv). The resulting mixture was allowed to slowly warm up to RT and stirred for 6 h. The reaction was taken up in CH_2Cl_2 (10ml) and washed with a mixture of aq. sodium thiosulfate solution (3 ml) and satd. aq. $NaHCO_3$ (3 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure gave the crude product, which was purified by chromatography on silica gel (hexane / EtOAc; 9:1 to 6:4 gradient) to furnish aldehyde **155** (32 mg, 69%) as a colorless oil.

TLC: R_f = 0.23 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 6.45 (s, 1H), 5.26 (s, 1H), 4.24 (d, ^2J = 9.3 Hz, 1H), 3.51 (d, ^2J = 9.3 Hz, 1H), 2.84 (s, 1H), 1.84 (d, ^4J = 1.4 Hz, 3H), 1.62 (d, ^4J = 1.4 Hz, 3H), 1.53 (s, 3H), 1.35 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 198.32, 198.08, 148.21, 135.84, 135.59, 128.97, 96.52, 72.18, 59.83, 56.88, 56.43, 25.69, 24.68, 16.95, 13.18; **IR** (thin film): 3039, 2970, 2927, 2861, 2720, 1728, 1664, 1448, 1374, 1311, 1258, 1239, 1211, 1199, 1153, 1132, 1118, 1099, 1067, 1041, 1025, 1001, 969, 954, 931, 913, 885, 858 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{15}H_{19}O_3$ ($[M+H]^+$), 247.1329; found, 247.1336.



(2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-5a-(hydroxymethyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (147). To a solution of silylether **143** (40.0 mg, 0.09 mmol, 1.00 equiv) in MeOH (5.0 ml) at RT was added *p*-toluenesulfonic acid monohydrate (1.7 mg, 9.0 µmol, 0.10 equiv). The resulting mixture was stirred at this temperature for 18 h. The reaction was quenched by addition of satd. aq. $NaHCO_3$ (10 ml) and the mixture was extracted with Et_2O (3 x 5 ml). Washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure afforded a white crude. Purification by column chromatography (hexane / EtOAc; 1:1) gave alcohol **147** (26.5 mg, 89%) as a colorless oil.

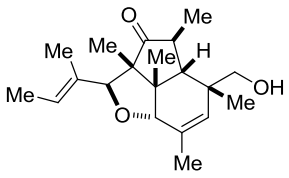
TLC: R_f = 0.26 (hexane / EtOAc; 6:4; $KMnO_4$); **^{1}H-NMR** (12:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 5.64 (q, ^3J = 6.7 Hz, 1H), 5.51 (s, 1H), 4.13 (s, 1H), 4.11 (s, 1H), 3.81 (d, ^2J = 9.0 Hz, 1H), 3.57 (d, ^2J = 9.0 Hz, 1H), 3.56-3.46 (m, 2H), 2.18 (s, 1H), 1.81 (s, 3H), 1.67–1.64 (m, 6H), 1.46 (s, 3H), 1.31, (s, 3H), 1.00 (s, 3H); **^{13}C-NMR** (12:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 220.59, 137.90, 131.94, 126.37, 122.17, 91.79, 84.03, 83.91, 68.50, 63.18, 57.03, 51.41, 47.93, 27.09, 24.50, 20.38, 17.04, 14.21, 13.04; **IR** (thin film): 3476, 2969, 2916. 2863, 1742, 1466, 1448, 1383, 1370, 1314, 1233, 1063, 1031, 998, 972, 890, 853, 835, 802, 730, 717 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{20}H_{28}NaO_4$ ($[M+Na]^+$), 355.1880; found, 355.1877.



(2*SR*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-2a,2a1,3a,5a,7-pentamethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (148). To a solution of alcohol **147** (25.0 mg, 0.075 mmol, 1.00 equiv) in CH_2Cl_2 (1.5 ml) at RT was added phenyltetrazole (0.6 mg, 3.8 µmol, 0.05 equiv), followed by 2-iodophenethyl methyl diisopropylphosphoramidite (37 µl, 0.090 mmol, 1.20 equiv). The reaction was allowed to stir for 10 min, before the addition of phenyl isocyanate (10 µl, 0.090 mmol, 1.20 equiv). After 4 h, TLC indicated full consumption of the starting material. Water (ca. 30 µl)

was added and allowed to stir for 10 min to hydrolyze any remaining phosphoramidite. The entire reaction mixture was added to a separatory funnel with satd. aq. $NaHCO_3$ (3 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting white solid was dissolved in benzene (2.0 ml) and tributyltin hydride (200 µl, 0.758 mmol, 10.0 equiv) was added. The mixture was heated to reflux for 4 h, while a solution of AIBN (61.7 mg, 0.376 mmol, 5.00 equiv) in benzene (1 ml) was added slowly by syringe-pump (0.25 ml/h). After cooling to RT, the volatiles were removed under reduced pressure to furnish the crude product. Purification by chromatography on a stationary phase comprising silica gel (90% w/w) and finely ground KF (10% w/w) [259] (hexane / EtOAc; 9:1) gave deoxygenated tetracycle **148** (15.0 mg, 63%) as a 9:1 mixture of (*E*)/(*Z*)-isomers.

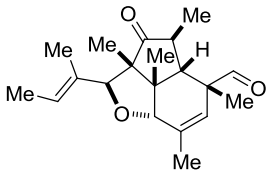
TLC: R_f = 0.32 (hexane / MTBE; 9:1; $KMnO_4$); **^{1}H-NMR** (9:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 5.65 (q, ^3J = 6.3 Hz, 1H), 5.50 (s, 1H), 4.15 (s, 1H), 4.05 (s, 1H), 3.65 (d, ^2J = 8.6 Hz, 1H), 3.63 (d, ^2J = 8.6 Hz, 1H), 1.96 (s, 1H), 1.75 (s, 3H), 1.66–1.64 (m, 6H), 1.46 (s, 3H), 1.28, (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H); **^{13}C-NMR** (9:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 220.37, 134.48, 132.26, 131.44, 121.99, 91.42, 84.47, 83.42, 80.90, 63.64, 61.88, 48.29, 44.92, 27.50, 25.95, 24.97, 19.80, 17.03, 14.21, 13.02; ; **IR** (thin film): 2968, 2924, 2867, 1744, 1450, 1383, 1314, 1258, 1224, 1164, 1090, 1065, 1033, 998, 973, 893 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{20}H_{28}NaO_3$ ($[M+Na]^+$), 339.1931; found, 339.1930.



(2*SR*,2a*RS*,2a1*SR*,4*SR*,4a*RS*,5*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-5-(hydroxymethyl)-2a,2a1,4,5,7-pentamethyl-2,2a,4,4a,5,7a-hexahydroindeno[7,1-bc]furan-3(2a1H)-one (236). The THF employed in this reaction was degassed by freeze-pump-thaw (4 cycles) prior to use. To a suspension of samarium powder (150 mg, 1.00 mmol) in THF (2.2 ml) at RT was added via cannula a solution of diiodoethane (150 mg, 0.532 mmol) in THF (2.0 ml). THF (1.0 ml) was used to assist the transfer. The resulting mixture became royal blue after 15 min and was stirred at the same temperature for 2 h to give a solution of samarium diiodide (ca. 0.1 M). In a separate 10 ml Schlenk tube ketone **148** (15.0 mg, 0.047 mmol, 1.00 equiv) was

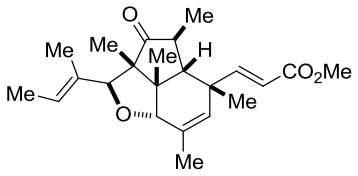
dissolved in THF / MeOH (7:3, 2.0 ml) and the resulting mixture was degassed carefully (freeze-pump-thaw; 4 cycles). To this mixture the fresh samarium diiodide solution (0.95 ml, 0.095 mmol, 2.00 equiv) was added dropwise via syringe until a slightly blue coloration persisted for ca. 5 min. The reaction was quenched by addition of THF / H_2O (1:1; 1 ml). HCl (0.05 M in H_2O; 1.5 ml) was added and the mixture was extracted with Et_2O (3 x 5 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (1.5 ml) and satd. aq. NaCl (1.5 ml). Drying over $MgSO_4$, filtration and concentration under reduced pressure to furnished a crude oil that was purified by chromatography on silica gel (hexane / EtOAc; 9:1 to 7:3 gradient) to give alcohol **236** (14.0 mg, 93%) as a 8:1 mixture of (*E*)/(*Z*)-isomers.

TLC: R_f = 0.42 (hexane / EtOAc; 7:3; $KMnO_4$); **^{1}H-NMR** (8:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 5.56 (q, ^3J = 6.8 Hz, 1H), 5.40 (s, 1H), 4.15 (s, 1H), 4.02 (s, 1H), 3.57 (dd, ^2J = 10.6 Hz, ^3J = 5.1 Hz, 1H), 3.50 (dd, ^2J = 10.6 Hz, ^3J = 5.1 Hz, 1H), 2.39 (dq, ^3J = 9.5 Hz, ^3J = 7.0 Hz, 1H), 1.76 (s, 3H), 1.67 (d, ^3J = 9.5 Hz, 1H), 1.64 (d, ^3J = 6.8 Hz, 3H), 1.58 (s, 3H), 1.29 (s, 3H), 1.21 (d, ^3J = 7.0 Hz, 3H), 1.18 (s, 3H), 0.89 (s, 3H); **^{13}C-NMR** (8:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 222.37, 136.35, 132.56, 129.56, 121.30, 86.59, 84.61, 70.11, 63.21, 53.36, 53.00, 45.13, 40.88, 26.98, 25.58, 19.17, 17.56, 14.30, 14.26, 12.98; **IR** (thin film): 3477, 2970, 2915, 2877, 1727, 1448, 1382, 1317, 1254, 1232, 1054, 1014, 968 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{20}H_{30}NaO_3$ ($[M+Na]^+$), 341.2087; found, 3412082.



(2*SR*,2a*RS*,2a1*SR*,4*SR*,4a*SR*,5*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-2a,2a1,4,5,7-pentamethyl-3-oxo-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7,1-bc]furan-5-carbaldehyde (237). To a solution of alcohol **236** (14.0 mg, 0.044 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) was added at 0 °C Dess–Martin periodinane (28.0 mg, 0.066 mmol, 1.50 equiv). The resulting mixture was stirred at this temperature for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 (3 ml) and filtered through a plug of celite. CH_2Cl_2 (6 ml) was used to rinse. The filtrate was washed with a mixture of satd. aq. sodium thiosulfate (1.5 ml) and satd. aq. $NaHCO_3$ (1.5 ml) and was dried over $MgSO_4$. Purification by column chromatography (hexane / EtOAc; 9:1) gave aldehyde **237** (12.9 mg, 93%) as a 6:1 mixture of (*E*)/(*Z*)-isomers.

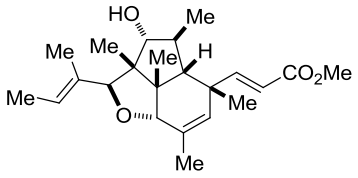
TLC: R_f = 0.27 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 5.98 (s, 1H), 5.56 (q, ^3J = 6.8 Hz, 1H), 4.18 (s, 1H), 3.93 (s, 1H), 2.30 (dq, ^3J =10.0 Hz, ^3J = 7.0 Hz, 1H), 1.87-1.80 (m, 4H), 1.64 (d, ^3J = 6.8 Hz, 3H), 1.56 (s, 3H), 1.35 (s, 3H), 1.27 (s,1H), 1.05 (d, ^3J = 7.0 Hz, 3H), 0.90 (s, 3H); **^{13}C-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 220.22, 202.19, 137.58, 132.09, 124.60, 121.60, 86.75, 84.52, 62.83, 52.92, 52.68, 50.84, 44.73, 27.20, 22.47, 19.16, 16.21, 14.16, 13.89, 12.96; **IR** (thin film): 2975, 2918, 2876, 1730, 1448, 1384, 1320, 1232, 1083, 1059, 1020, 991, 971, 900 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{20}H_{29}O_3$ ($[M+H]^+$), 317.2221; found, 317.2119.



(*E*)-methyl 3-((2*SR*,2a*RS*,2a1*SR*,4*SR*,4a*RS*,5*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-2a,2a1,4,5,7-pentamethyl-3-oxo-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7,1-bc]furan-5-yl)acrylate (161). To a suspension of sodium hydride (60% in mineral oil, 8.2 mg, 0.204 mmol, 5.00 equiv) in THF (0.5 ml) was added dropwise at RT methyl diethylphosphonoacetate (38 µl, 0.204 mmol, 5.00 equiv). Strong gas evolution could be observed immediately. The resulting mixture was stirred for 30 min, before a solution of aldehyde **237** (12.9 mg, 0.041 mmol, 1.00 equiv) in THF (0.6 ml) was added via cannula. THF (0.5 ml) was used to assist the transfer. The reaction was stirred at RT for 12 h. The mixture was poured into satd. aq. $NaHCO_3$ (3 ml). Extraction with Et_2O (3 x 3 ml), washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration and concentration under reduced pressure furnished a crude oil. Purification by chromatography on silica gel (hexane / EtOAc; 95:5 to 9:1 gradient) gave ester **161** (14.3 mg, 94%) as a 6:1 mixture of (*E*)/(*Z*)-isomers.

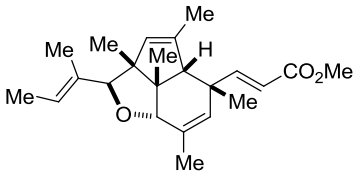
TLC: R_f = 0.26 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 400 MHz, $CDCl_3$): δ 6.97 (d, ^3J = 16.1 Hz, 1H), 5.84 (d, ^3J = 16.1 Hz, 1H), 5.69 (s, 1H), 5.57 (q, ^3J = 6.8 Hz, 1H), 4.16 (s, 1H), 4.01 (s, 1H), 3.76 (s, 3H), 2.14 (dq, ^3J = 9.6 Hz, ^3J = 7.1 Hz, 1H), 1.83-1.80 (m, 4H), 1.65 (d, ^3J = 6.8 Hz, 3H), 1.85 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.05 (d, ^3J = 7.1 Hz, 3H), 0.89 (s, 3H)); **^{13}C-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 100 MHz, $CDCl_3$): δ 221.86, 167.12, 155.78, 136.57, 132.44, 128.04, 121.49, 117.46, 86.55, 84.22, 63.68, 56.50, 52.59, 51.68,

46.26, 41.63, 27.84, 27.40, 19.32, 18.05, 14.34, 14.27, 12.99; **IR** (thin film): 2971, 2952, 2923, 1728, 1648, 1434, 1377, 1315, 1299, 1282, 1230, 1193, 1170, 1108,. 1084, 1059, 1015, 980, 932, 915, 862, 818, 731 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{23}H_{32}NaO_4$ ($[M+Na]^+$), 395.2193; found, 395.2189.



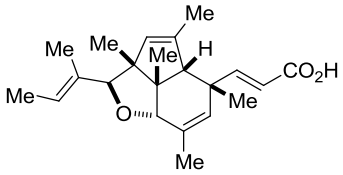
(*E*)-methyl 3-((2*SR*,2a*SR*,2a1*SR*,3*RS*,4*SR*,4a*RS*,5*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-3-hydroxy-2a,2a1,4,5,7-pentamethyl-2,2a,2a1,3,4,4a,5,7a-octahydroindeno[7,1-bc]furan-5-yl)acrylate (238). To a solution of ketone **161** (14.3 mg, 0.038 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) was added at RT borane *tert*-butylamine complex (6.7 mg, 0.077 mmol, 2.00 equiv). The resulting mixture was heated to 40 °C for 12 h. After cooling to RT, CH_2Cl_2 (3 ml) was added, followed by 1 M aq. HCl (1.5 ml). The resulting mixture was stirred vigorously for 30 min. The mixture was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (1.5 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 8:2) gave alcohol **238** (14.2 mg, 99%) as a 7:1 mixture of (*E*)/(*Z*)-isomers.

TLC: R_f = 0.38 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H-NMR** (7:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 600 MHz, $CDCl_3$): δ 7.01 (d, ^3J = 16.0 Hz, 1H), 5.75 (d, ^3J = 16.0 Hz, 1H), 5.53 (q, ^3J = 6.7 Hz, 1H), 5.33 (s, 1H), 4.34 (s, 1H), 3.87 (s, 1H), 3.71 (s, 3H), 3.19 (dd, ^3J = 10.2 Hz, ^3J = 5.1 Hz, 1H), 1.85 (s, 3H), 1.80-1.72 (m, 2H), 1.67 (d, ^3J = 5.1 Hz, 1H), 1.64-1.62 (m, 6H), 1.21 (s, 3H), 0.99-0.97 (m, 6H), 0.95 (s, 3H); **^{13}C-NMR** (7:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 150 MHz, $CDCl_3$): δ 167.39, 155.81, 135.67, 133.44, 130.51, 120.65, 117.16, 85.68, 85.47, 83.17, 56.82, 56.72, 52.78, 51.45, 40.52, 40.39, 29.57, 24.84, 22.15, 18.68, 17.77, 14.27, 13.05; **IR** (thin film): 3458, 2959, 2922, 2867, 1722, 1706, 1639, 1462, 1448, 1435, 1376, 1312, 1288, 1240, 1194, 1174, 1102, 1089, 1067, 1037, 1016, 983, 944, 912, 860, 843, 814, 732 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{23}H_{35}O_4$ ($[M+H]^+$), 375.2530; found, 375.2518.



(*E*)-methyl 3-((2*SR*,2a*RS*,2a1*SR*,4a*RS*,5*RS*,7a*SR*)-2-((*E*)-but-2-en-2-yl)-2a,2a1,4,5,7-penta-methyl-2,2a,2a1,4a,5,7a-hexahydroindeno[7,1-bc]furan-5-yl)acrylate (239). To a solution of (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (18.1 mg, 0.076 mmol, 2.00 equiv) in toluene (1.3 ml) at RT was added via cannula solution of alcohol **238** (14.2 mg, 0.038 mmol, 1.00 equiv) in toluene (1.5 ml). Toluene (1.0 ml) was used to assist the transfer. The resulting mixture was heated to 110 °C for 14 h. After cooling to RT, H_2O (3 ml) was added and the mixture was extracted with Et_2O (3 x 5 ml). The combined organic extracts were washed with satd. aq. NaCl (1.5 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (hexane / EtOAc; 97:3 to 95:5 gradient) to yield olefin **239** (8.5 mg, 63%) as a 5:1 mixture of (*E*)/(*Z*)-isomers.

TLC: R_f = 0.26 (hexane / EtOAc; 95:5; UV / $KMnO_4$); **^{1}H-NMR** (5:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 500 MHz, $CDCl_3$): δ 7.18 (d, ^3J = 16.1 Hz, 1H), 5.82 (d, ^3J = 16.1 Hz, 1H), 5.51–5.47 (m, 2H), 5.18 (s, 1H), 4.07 (s, 1H), 3.94 (s, 1H), 3.71, (s, 3H), 2.21 (s, 1H), 1.82 (s, 3H), 1.62 (d, ^3J = 6.8 Hz, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 0.81 (s, 3H); **^{13}C-NMR** (5:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 125 MHz, $CDCl_3$): δ 167.46, 156.63, 137.54, 136.51, 136.40, 133.79, 128.96, 119.48, 117.22, 90.66, 83.64, 64.54, 60.10, 56.91, 51.45, 41.52, 29.26, 26.13, 20.68, 18.56, 17.38, 14.26, 12.86; **IR** (thin film): 2965, 2917, 2869, 1725, 1644, 1435, 1380, 1305, 1291, 1272, 1192, 1170, 1068, 1014, 998, 968, 856, 805, 734, 703 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{23}H_{33}O_3$ ($[M+H]^+$), 357.2424; found, 357.2421.



Indoxamycin A (1). To a solution of ester **239** (8.5 mg, 0.024 mmol, 1.00 equiv) in THF / MeOH (3:1; 0.8 ml) was added at RT a solution of lithium hydroxide (1.0 M in H_2O, 0.20 ml, 0.20 mmol, 8.39 equiv). The resulting mixture was stirred at RT for 7 h. Satd. aq. NaCl solution (1.5 ml) was added and the pH of the mixture was adjusted to ca. 3 with 1 M aq.

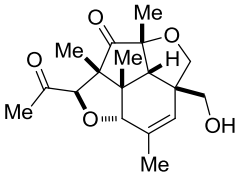
$NaHSO_4$. The aqueous layer was extracted with EtOAc (5 x 3 ml). The combined organic extracts were dried over Na_2SO_4. Concentration under reduced pressure gave the crude product that was purified by column chromatography (hexane / EtOAc / AcOH; 9:1:0.1) to furnish synthetic indoxamycin A (**1**) (7.8 mg, 96%) as a 6:1 mixture of (*E*)/(*Z*)-isomers (white amorphous solid).

TLC: R_f = 0.32 (hexane / EtOAc; 6:4; UV / $KMnO_4$); **^{1}H-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 600 MHz, CD_3OD): δ 7.19 (d, ^3J = 16.0 Hz, 1H), 5.76 (d, ^3J = 16.0 Hz, 1H), 5.52 (s, 1H), 5.46 (q, ^3J = 6.8 Hz, 1H), 5.23 (s, 1H), 4.10 (s, 1H), 4.08 (s, 1H), 2.21 (s, 1H), 1.84 (s, 3H), 1.66 (s, 3H), 1.63 (d, ^3J = 6.8 Hz, 3H), 1.58 (s, 3H), 1.28 (s, 3H), 1.11 (s, 3H), 0.85 (s, 3H); **^{13}C-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 150 MHz, CD_3OD): δ 170.38, 157.83, 138.78, 137.31, 137.16, 135.38, 131.49, 120.61, 119.15, 92.79, 85.11, 66.37, 61.28, 58.32, 42.73, 29.88, 26.31, 21.62, 18.59, 17.52, 14.36, 12.92; **IR** (thin film): 3019, 2964, 2914, 2870, 2686, 2590, 1691, 1637, 1443, 1416, 1378, 1305, 1291, 1225, 1066, 1051, 1014, 997, 968, 913, 866, 849, 805, 732, 701, 624 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{29}O_3$ ($[M–H]^-$), 341.2122; found, 341.2117. The ^{1}H and ^{13}C NMR data for the synthetic material did not precisely match with does previously reported for natural indoxamycin A [13, 14].

A sample of (**1**) that exhibits NMR resonances, which are in full accordance with the literature data, could be reproducibly prepared as follows: An NMR tube (178 mm x 5 mm ø) was charged with a solution of indoxamycin A (**1**) (8.2 mg, 0.024 mmol, 1.00 equiv) in CD_3OD (0.5 ml). A solution of CD_3OK (0.1 M in CD_3OD, freshly prepared from CD_3OD and potassium hydride) was added in increments of 80 µl with continuous monitoring by ^{1}H NMR. When 160 µl (0.016 mmol, 0.67 equiv) of CD_3OK was added, the ^{1}H NMR spectrum obtained was identical to that reported for natural indoxamycin A. Furthermore, the ^{13}C NMR chemical shifts were in excellent agreement.

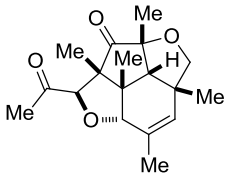
^{1}H-NMR (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 600 MHz, CD_3OD): δ 6.98 (d, ^3J = 16.0 Hz, 1H), 5.83 (d, ^3J = 16.0 Hz, 1H), 5.61 (s, 1H), 5.49 (q, ^3J = 6.8 Hz, 1H), 5.19 (s, 1H), 4.10 (s, 1H), 4.02 (s, 1H), 2.27 (s, 1H), 1.81 (s, 3H), 1.66 (s, 3H), 1.64 (d, ^3J = 6.8 Hz, 3H), 1.59 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H), 0.84 (s, 3H); **^{13}C-NMR** (6:1 (*E*)/(*Z*)-isomer ratio, only major isomer reported, 150 MHz, CD_3OD): δ 173.49, 153.87, 139.61, 136.95, 136.75, 135.19, 131.48, 120.36, 223.31, 92.10, 85.07, 65.88, 61.22, 58.08, 42.30, 30.20, 26.63, 20.74, 19.02, 17.74, 14.35, 12.91.

3.2.3.6 Studies Towards Indoxamycin F



(2*RS*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*RS*,7a*SR*)-2-acetyl-5a-(hydroxymethyl)-2a,2a1,3a,7-tetramethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (166). To a solution of silyl ether **128** (30 mg, 0.069 mmol, 1.00 equiv) in MeOH (3.5 ml) at RT was added *p*-TsOH·H_2O (3.3 mg, 0.017 mmol, 0.25 equiv). The resulting mixture was stirred at this temperature for 12 h. The reaction was quenched by addition of satd. aq. $NaHCO_3$ (10 ml) and the mixture was extracted with Et_2O (3 x 5 ml). Washing with satd. aq. NaCl (1.5 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure afforded a white crude. Purification by column chromatography (hexane / EtOAc; 1:1) gave alcohol **166** (22.7 mg, quantitative) as a colorless oil.

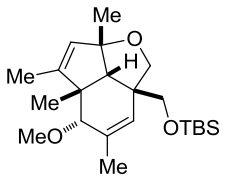
TLC: R_f = 0.20 (hexane / EtOAc; 1:1; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.61 (s, 1H), 4.61 (s, 1H), 4.27 (s, 1H), 3.82 (d, ^2J = 9.1 Hz, 1H), 3.59 (dd, ^2J = 10.4 Hz, ^3J = 4.4 Hz, 1H), 3.49 (dd, ^2J = 10.4 Hz, ^3J = 6.5 Hz, 1H), 3.36 (d, ^2J = 9.2 Hz, 1H), 2.28 (s, 3H), 2.17 (s, 1H), 1.86 (d, ^4J = 1.2 Hz, 3H), 1.64 (m, 1H), 1.49 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 221.40, 207.08, 135.28, 126.50, 90.56, 85.53, 76.90, 68.62, 62.95, 56.62, 52.02, 47.52, 29.16, 26.13, 24.59, 21.92, 16.26; **IR** (thin film): 3480, 2970, 2920, 2869, 1748, 1716, 1468, 1450, 1368, 1372, 1355, 1227, 1173, 1094, 1066, 1034, 1009, 987, 967, 921, 883 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{25}O_5$ ($[M+H]^+$), 321.1697; found, 321.1694.



(2*RS*,2a*RS*,2a1*SR*,3a*RS*,3a1*RS*,5a*RS*,7a*SR*)-2-acetyl-2a,2a1,3a,5a,7-pentamethyl-2a1,3a,3a1,5,5a,7a-hexahydro-2H-indeno[1,7-bc:4,3-b'c']difuran-3(2aH)-one (168). To a solution of alcohol **166** (16 mg, 0.050 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 ml) at RT was added phenyltetrazole (0.7 mg, 5.00 µmol, 0.10 equiv), followed by 2-iodophenethyl methyl diisopropylphosphoramidite (31 µl, 0.075 mmol, 1.50 equiv). The reaction stirred for 10 min, before the addition of phenyl isocyanate (8 µl, 0.075 mmol, 1.50 equiv). After 2.5 h, TLC

indicated full consumption of the starting material. Water (ca. 30 µl) was added and allowed to stir for 10 min to hydrolyze any remaining phosphoramidite. The entire reaction mixture was added to a separatory funnel with satd. aq. $NaHCO_3$ (3 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting white solid was dissolved in benzene (2.0 ml) and tributyltin hydride (260 µl, 1.00 mmol, 20.0 equiv) was added. The mixture was heated to reflux for 8 h, while a solution of AIBN (82 mg, 0.50 mmol, 10.0 equiv) in benzene (1 ml) was added slowly by syringe-pump (0.125 ml/h). After cooling to RT, the volatiles were removed under reduced pressure to furnish the crude product. Purification by chromatography on a stationary phase comprising silica gel (90% w/w) and finely ground KF (10% w/w) [259] (hexane / EtOAc; 9:1) gave deoxygenated tetracycle **168** (10.0 mg, 66%).

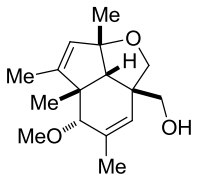
TLC: R_f = 0.27 (hexane / EtOAc; 9:1; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.56 (s, 1H), 4.61 (s, 1H), 4.25 (s, 1H), 3.62 (d, ^2J = 8.6 Hz, 1H), 3.40 (d, ^2J = 8.6 Hz, 1H), 2.26 (s, 3H), 1.91 (s, 1H), 1.82 (d, ^4J = 1.2 Hz, 3H), 1.50 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 221.57, 207.33, 132.20, 131.23, 90.33, 85.75, 85.26, 81.11, 63.18, 62.13, 47.98, 45.78, 29.12, 28.05, 26.56, 24.98, 21.63, 16.17; **IR** (thin film): 2969, 2927, 2870, 1748, 1716, 1468, 1451, 1372, 1354, 1222, 1175, 1094, 1070, 1036, 1009, 973, 924, 881, 836 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{24}NaO_4$ ($[M+Na]^+$), 327.1567; found, 327.1569.



***tert*-butyl(((2a*SR*,2a1*RS*,5*SR*,5a*SR*,7a*SR*)-5-methoxy-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-2a-yl)methoxy)dimethylsilane (172).** A solution of alcohol **75** (58 mg, 0.159 mmol, 1.00 equiv) in THF (2.0 ml) was added via cannula to a suspension of potassium hydride (9.6 mg, 0.239 mmol, 1.50 equiv) in THF (1.0 ml) at RT. THF (1.0 ml) was used to assist the transfer. Slow gas-evolution could be observed. The resulting mixture was stirred at this temperature for 30 min. After cooling to 0 °C, 18-crown-6 ether (84 mg, 0.318 mmol, 2.00 equiv) was added, followed by iodomethane (50 µl, 0.795 mmol, 5.00 equiv). The resulting mixture was allowed to slowly warm up to RT and stirred

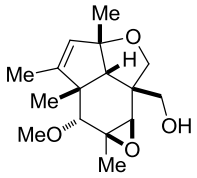
for 12 h. The reaction was quenched by addition of pH 7 buffer, 0.05 M (5 ml). The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification of the residue by chromatography on silica gel (hexane / EtOAc; 96:4 to 94:6 gradient) gave methyl ether **172** (45 mg, 74%) as a colorless oil.

TLC: R_f = 0.28 (hexane / EtOAc; 96:4; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.26 (s, 1H), 5.16 (s, 1H), 3.68 (d, ^2J = 8.5 Hz, 1H), 3.64 (s, 1H), 3.43–3.39 (m, 5H), 3.37 (d, ^2J = 9.4 Hz, 1H), 1.98 (s, 1H), 1.80 (s, 3H), 1.62 (s, 3H), 1.42 (s, 3H), 1.24 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 148.73, 137.67, 130.20, 126.66, 93.27, 85.65, 74.22, 68.00, 61.13, 60.96, 53.83, 51.13, 25.96, 25.85, 25.04, 19.24, 18.24, 15.29, –5.43, –5.49; **IR** (thin film): 3032, 2954, 2927, 2889, 2854, 2822, 1644, 1471, 1462, 1444, 1372, 1255, 1192, 1152, 1136, 1104, 1066, 1004, 983, 964, 938, 890, 852, 835, 815, 776 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{38}NaO_3Si$ ([M+Na]$^+$), 401.2482; found, 401.2481.



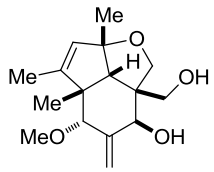
((2aRS,2a1RS,5SR,5aSR,7aSR)-5-methoxy-4,5a,6,7a-tetramethyl-2,2a,2a1,5,5a,7a-hexahydroindeno[1,7-bc]furan-2a-yl)methanol (173). To a solution of silyl ether **172** (45 mg, 0.119 mmol, 1.00 equiv) in MeOH (2.4 ml) at RT was added *p*-TsOH·H_2O (11.3 mg, 0.059 mmol, 0.50 equiv). The resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of satd. aq. $NaHCO_3$ (5 ml) and the mixture was extracted with Et_2O (3 x 10 ml). Drying over $MgSO_4$, filtration, and concentration under reduced pressure afforded a white crude. Purification by column chromatography (hexane / EtOAc; 1:1 to 3:7 gradient) gave alcohol **173** (30 mg, 96%) as a colorless oil.

TLC: R_f = 0.28 (hexane / EtOAc; 6:4; $KMnO_4$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.23 (s, 1H), 5.13 (s, 1H), 3.67–3.63 (m, 2H), 3.47–3.44 (m, 6H), 1.99 (s, 1H), 1.84 (s, 3H), 1.63 (s, 3H), 1.60 (s, 1H), 1.46 (s, 3H), 1.27 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 149.07, 139.36, 129.89, 124.72, 94.00, 85.59, 74.26, 69.18, 61.43, 61.20, 53.46, 51.08, 25.64, 24.98, 19.34, 15.36; **IR** (thin film): 3417, 2965, 2918, 2865, 2818, 1660, 1644, 1444, 1372, 1310, 1282, 1255, 1192, 1149, 1103, 1075, 1050, 985, 889, 863, 831, 743, 711, 690 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}NaO_3$ ([M+Na]$^+$), 287.1618; found, 287.1618.



((2a*SR*,2a1*SR*,4a*SR*,5*RS*,5a*RS*,6a*RS*,6b*SR*)-5-methoxy-2a,4,4a,5a-tetramethyl-1,2a, 2a1,4a,5,5a,6a,6b-octahydrooxireno[2',3':5,6]indeno[1,7-bc]furan-6b-yl)methanol (174). To a solution of homoallylic alcohol **173** (25 mg, 0.095 mmol 1.00 equiv) in CH_2Cl_2 (1.9 ml) at RT were added in this order 4 Å molecular sieves (powdered, 12 mg), vanadyl acetylacetonate (1.3 mg, 4.7 µmol, 0.05 equiv) and *tert*-butyl hydroperoxide, ca. 5.5 M in nonane (52 µl, 0.284 mmol, 3.00 equiv). Upon addition of the *tert*-butyl hydroperoxide, the initially red green solution turned dark-red immediately. The reaction was stirred at RT for 2 h. During this period, the mixture lost its red color. The mixture was filtered through a plug of celite. CH_2Cl_2 (10 ml) was used to rinse. The filtrate was washed with satd. aq. sodium thiosulfate (3 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 1:1) gave epoxide **174** (22 mg, 83%) as a withe solid.

TLC: R_f = 0.35 (hexane / EtOAc; 1:1; $KMnO_4$); **Melting point:** 151 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.21 (s, 1H), 3.80 (d, ^2J = 8.9 Hz, 1H), 3.73 (d, ^2J = 8.9 Hz, 1H), 3.66 (dd, ^2J = 10.9 Hz, ^3J = 5.7 Hz, 1H), 3.66 (dd, ^2J = 10.9 Hz, ^3J = 7.0 Hz, 1H), 3.51 (s, 3H), 3.06 (s, 1H), 2.93 (s, 1H), 2.22 (m 1H), 1.73 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 147.31, 130.55, 93.61, 87.54, 72.82, 67.33, 62.51, 61.11, 60.87, 58.96, 51.87, 48.58, 26.30, 25.90, 19.11, 14.85; **IR** (thin film): 3420, 2966, 2927, 2869, 2828, 1666, 1441, 1373, 1314, 1241, 1197, 1146, 1098, 1064, 1044, 996, 962, 949, 903, 888, 862, 837 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}NaO_4$ ($[M+Na]^+$), 303.1567; found, 303.1576.



(2a*SR*,2a1*SR*,3*RS*,5*RS*,5a*SR*,7a*SR*)-2a-(hydroxymethyl)-5-methoxy-5a,6,7a-trimethyl-4-methylene-2,2a,2a1,3,4,5,5a,7a-octahydroindeno[1,7-bc]furan-3-ol (175). 2,2,6,6-Tetramethylpiperidine (36 µl, 0.214 mmol, 5.00 equiv) was dissolved in benzene (1.0 ml) and cooled to 0 °C. *n*-BuLi, 1.6 M in hexanes (107 µl, 0.171 mmol, 4.00 equiv) was added and the resulting mixture was stirred at 0 °C for 30 min. Diethylaluminium chloride, 1.0 M in benzene (0.171 ml, 0.171 mmol, 4.00 equiv) was added and stirring was continued at 0 °C. After 40 min, a solution of epoxide **174** (12 mg, 0.043 mmol, 1.00 equiv) in benzene (0.5 ml) was added dropwise via cannula. Benzene (0.5 ml) was used to assist the transfer. The resulting mixture was stirred for 3.5 h, while it was allowed to warm up to RT. The reaction was quenched by addition of satd. aq. $NaHCO_3$ (3 ml). Satd. aq. Na-K-tartrate (1.5 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 8:2 to 2:8 gradient) gave diol **175** (10 mg, 83%) as a white solid.

TLC: R_f = 0.24 (hexane / EtOAc; 1:1; $KMnO_4$); **Melting point:** 154 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.09 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.14 (s, 1H), 4.02 (s, 1H), 3.63 (dd, ^2J = 10.8 Hz, ^3J = 5.1 Hz, 1H), 3.59–3.53 (m, 2H), 3.35 (s, 3H), 3.16 (d, ^2J = 8.7 Hz, 1H), 2.74 (m, 1H), 2.20 (d, ^2J = 2.3 Hz, 1H), 1.94 (s, 1H), 1.70 (d, ^4J = 1.4 Hz, 3H), 1.41 (s, 3H), 1.28 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 149.08, 145.27, 129.24, 109.79, 94.04, 83.46, 75.70, 69.68, 66.68, 58.86, 58.36, 54.37, 52.83, 27.36, 26.20, 15.30; **IR** (thin film): 3383, 3029, 2964, 2922, 2872, 2830, 1657, 1434, 1373, 1308, 1266, 1220, 1196, 1133, 1104, 1071, 1068, 1051, 1026, 1002, 979, 962, 879, 868, 849, 836, 739, 708, 691 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}NaO_4$ ($[M+Na]^+$), 303.1567; found, 303.1561.

3.2.4 Cytotoxicity Measurements[24]

3.2.4.1 Cell culture

The human colorectal cancer cell line HT-29 and the human lung carcinoma cell line A-549 were maintained in DMEM (INVITROGEN) containing 10% fetal bovine serum (INVITROGEN) and 1% penicillin streptomycin (INVITROGEN) at 37 °C in a humidified incubator with 5% CO_2.

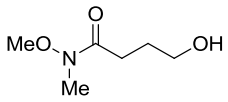
3.2.4.2 Cell viability analysis

Logarithmically growing cells were washed once with PBS (INVITROGEN) before they were trypsinized with 0.05% trypsin-EDTA (INVITROGEN) and re-suspended in 10 ml growth medium. HT-29 were plated at a density of 5 x 10^4 per 96-well in a flat bottom microtiter plate while A-549 cells were plated at a density of 2 x 10^4 cells per 96-well. Following 24 h incubation in standard culture medium, the cells were either left untreated (growth control) or treated with up to 1% DMSO (solvent control), 50 µM Tamoxifen (positive control) and various concentrations (1µM, 10 µM and 100 µM) of indoxamycin A (**1**) or B (**2**) dissolved in growth medium without phenol red for 24 h. 10 mM stock solutions were used to prepare the dilutions of the chemicals. Afterwards 5 mg/ml diphenyltetrazolium-bromide (MTT) solution was added to each well to reach a final concentration of 0.5 mg/ml and culture was continued at 37 °C and 5% CO_2 for 4 h before the medium was removed and the formed formazan crystals were solubilized in acidic *i*-PrOH (*i*-PrOH plus 1:100 dilution of 4M HCl and 0.1% NP40). The diluted formazan was quantified by reading the absorbance at 570 nm (test wavelength) and 650 nm (reference wavelength). Cell viability was calculated using the formula: Cell viability (%) = [(OD value of treated well – OD value of the blank) x 100%] / (OD value of untreated well – OD value of the blank). The average cell viability was determined from three independent experiments run in triplicate per condition.

[24] Dr. SUSANNE WOLFRUM is gratefully acknowledged for conducting these experiments.

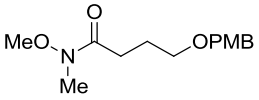
3.3 Total Synthesis of Asperolide C

3.3.1 Synthesis of Polyene Precursor



4-Hydroxy-*N*-methoxy-*N*-methylbutanamide (200). *N*,*O*-Dimethylhydroxylamine hydrochloride (19.9 g, 200 mmol, 1.10 equiv) was dissolved in CH_2Cl_2 (1000 ml) and cooled to 0 °C. Dimethylaluminum chloride, 1.0 M in hexane (200 ml, 200 mmol, 1.10 equiv) was added dropwise *via* cannula over 55 min and the resulting mixture was stirred at this temperature for 1 h. γ-Butyrolactone (**199**, 14.0 ml, 182 mmol, 1.0 equiv) was added slowly over 15 min and the mixture was allowed to warm up to RT. After 30 h of stirring, the reaction was quenched by slow addition of water (200 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 200 ml) and the combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure yielded alcohol **200** (22.1 g, 83%) as a clear colorless oil, which was used as such in the following transformation. An analytically pure sample of **200** could be obtained by column chromatography (hexane / EtOAc; 3:1).

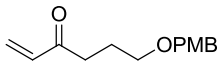
TLC: R_f = 0.35 (hexane / EtOAc; 3:1; $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.63 (t, ^3J = 6.8 Hz, 2H), 3.14 (s, 3H), 3.04 (s, 1H), 2.54 (t, ^3J = 6.8 Hz, 2H), 1.81−1.88 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.79, 62.44, 61.18, 32.16, 29.13, 27.17; **IR** (thin film): 3426, 2939, 1644, 1444, 1388, 1180, 1059, 997, 943 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_6H_{13}NNaO_3$ ($[M+Na]^+$), 170.0788; found, 170.0784.



***N*-Methoxy-4-((4-methoxybenzyl)oxy)-*N*-methylbutanamide (201).** To a solution of alcohol **200** (22.0 g, 149 mmol, 1.00 equiv) CH_2Cl_2 (150 ml) at 0 °C was added dropwise *via* cannula 4-methoxybenzyl 2,2,2-trichloroacetimidate [214] (67.6 g, 239 mmol, 1.60 equiv) in CH_2Cl_2 (50 ml) over 25 min. CH_2Cl_2 (2 x 50 ml) was used to assist the transfer. Camphorsulfonic acid (1.74 g, 7.47 mmol, 5.0 mol%) was added and the reaction was allowed to slowly warm to RT. After 18 h of stirring, the reaction was quenched by addition of sat. aq. $NaHCO_3$ (250 ml). The aqueous phase extracted with CH_2Cl_2 (4 x 100 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by

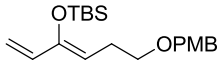
chromatography on silica gel (hexane / EtOAc; 7:3 to 1:3 gradient) to furnish PMB ether **201** as an orange oil (32.2 g, 81%).

TLC: R_f = 0.35 (hexane / EtOAc; 7:3; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, ^3J = 8.7 Hz, 2H), 6.87 (d, ^3J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.51 (t, ^3J = 6.2 Hz, 2H), 3.17 (s, 3H), 2.53 (t, ^3J = 7.2 Hz, 2H), 1.97−1.90 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.17, 159.01, 130.55, 129.09, 113.62, 72.31, 69.14, 61.06, 55.14, 32.11, 28.43, 24.52; **IR** (thin film): 2936, 2858, 1666, 1613, 1513, 1463, 1302, 1200, 1174, 1097, 1034, 820 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{14}H_{21}NNaO_4$ ($[M+Na]^+$), 290.1363; found, 290.1363.



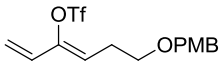
6-((4-Methoxybenzyl)oxy)hex-1-en-3-one (202). To a solution of WEINREB amide **201** (4.30 g, 15.0 mmol, 1.00 equiv) in THF (150 ml) at 0 °C was added *via* cannula vinylmagnesium bromide, 1.0 M in THF (37.5 ml, 37.5 mmol, 2.50 equiv) over 20 min. The resulting mixture was stirred at this temperature for 30 min. The reaction was quenched by addition of pre-cooled satd. aq. NH_4Cl (100 ml) and the aqueous layer extracted with EtOAc (3 x 150 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography afforded enone **202** (2.40 g, 68%) as a colorless oil.

TLC: R_f = 0.75 (hexane / EtOAc; 3:2; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, ^3J = 8.7 Hz, 2H), 6.87 (d, ^3J = 8.7 Hz, 2H), 6.35 (dd, ^3J = 17.7 Hz, 10.5 Hz, 1H), 6.21 (dd, ^3J = 17.7 Hz, ^2J = 1.3 Hz, 1H), 5.81 (dd, ^3J = 10.5 Hz, ^2J = 1.3 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.48 (t, ^3J = 6.2 Hz, 2H), 2.70 (t, ^3J = 7.2 Hz, 2H), 1.96−1.89 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.47, 159.15, 136.60, 130.52, 129.22, 127.94, 113.77, 72.51, 68.98, 55.26, 36.18, 23.97; **IR** (thin film): 3075, 2861, 1613, 1513, 1495, 1426, 1379, 1210, 1142, 1033, 821 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{14}H_{18}NaO_3$ ($[M+Na]^+$), 257.1148; found, 257.1147.



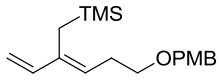
(Z)-*tert*-Butyl((6-((4-methoxybenzyl)oxy)hexa-1,3-dien-3-yl)oxy)dimethylsilane (203). LiHMDS (5.39 g, 32.2 mmol, 1.25 equiv) was dissolved in THF (60 ml) and HMPA (15.7 ml, 90.0 mmol, 3.50 equiv) was added. The resulting mixture was cooled to −78 °C, before a solution of *tert*-butyldimethylchlorosilane (4.86 g, 32.2 mmol, 1.25 equiv) in THF (15 ml) was added. A solution of vinyl ketone **202** (6.04 g, 25.8 mmol, 1.00 equiv) in THF (22 ml) was added dropwise via cannula. THF (2 x 4 ml) was used to assist the transfer. The resulting mixture was stirred at −78 °C for 35 min. The reaction was quenched at this temperature by addition of satd. aq. $NaHCO_3$ (150 ml) and extracted with Et_2O (4 x 100 ml). The combined organic extracts were washed with satd. aq. NaCl (20 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 20:1 to 9:1 gradient) furnished silyl enol ether **203** (8.52 g, 95%) as a yellowish oil.

TLC: R_f = 0.29 (hexane / EtOAc; 96:4; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (d, ^3J = 8.7 Hz, 2H), 6.91 (d, ^3J = 8.7 Hz, 2H), 6.16 (dd, ^3J = 17.2 Hz, 10.8 Hz, 1H), 5.31 (d, ^3J = 17.2 Hz, 1H), 4.98 (d, ^3J = 10.8 Hz, 1H), 4.85 (t, ^3J = 7.2 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.45 (t, ^3J = 7.0 Hz, 2H), 2.43 (m, 2H), 1.01 (s, 9H), 0.12 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.12, 149.46, 135.49, 130.60, 129.26, 113.74, 112.47, 111.46, 72.48, 69.34, 55.25, 26.79, 25.96, 18.42, 3.64; **IR** (thin film): 2954, 2929, 2856, 1610, 1512, 1361, 1249, 1097, 1048, 839 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{20}H_{32}NaO_3Si$ ($[M+Na]^+$), 371.2013; found, 371.2009.



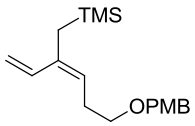
(*Z*)-6-((4-Methoxybenzyl)oxy)hexa-1,3-dien-3-yl trifluoromethanesulfonate (204). To a solution of silyl enol ether **203** (6.13 g, 17.6 mmol, 1.00 equiv) in DME (35 ml) was added *N*-phenyl-bis(trifluoromethanesulfonimide) (9.42 g, 26.4 mmol, 1.50 equiv), followed by cesium fluoride (6.68 g, 44.0 mmol, 2.50 equiv). The reaction-vessel was sealed and the mixture was stirred at RT for 4 h. **Caution: Reaction builds up pressure! Use blast-shield for protection!** The reaction was quenched by addition of pH 7 buffer 0.05 M (150 ml) and the mixture was extracted with Et_2O (4 x 100 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane / acetone; 95:5) delivered enol triflate **204** (6.18 g, 96%) as a slightly yellowish oil.

TLC: R_f = 0.35 (hexane / acetone; 9:1; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, ^3J = 8.6 Hz, 2H), 6.89 (d, ^3J = 8.6 Hz, 2H), 6.22 (dd, ^3J = 17.2 Hz, 11.3 Hz, 1H), 5.67 (t, ^3J = 7.4 Hz, 1H), 5.51 (d, ^3J = 17.2 Hz, 1H), 5.26 (d, ^3J = 11.3 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.53 (t, ^3J = 6.2 Hz, 2H), 2.56 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.26, 146.13, 130.09, 129.53, 129.25, 122.63, 118.45 (q, ^1J = 319.7 Hz), 116.10, 113.79, 72.57, 67.77, 55.19, 27.10; **^{19}F NMR** (376 MHz, $CDCl_3$): δ −73.70; **IR** (thin film): 3001, 2907, 2861, 1612, 1514, 1417, 1302, 1210, 1189, 1099, 995, 900, 821, 628 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{20}H_{32}F_3NaO_5S$ ($[M+Na]^+$), 389.0641; found, 389.0640.



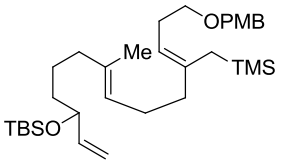
(*Z*)-(5-((4-Methoxybenzyl)oxy)-2-vinylpent-2-en-1-yl)trimethylsilane (207). To a solution of enol triflate **204** (732 mg, 2.00 mmol, 1.00 equiv) in DMF (4.7 ml) was added ((trimethylsilyl)methyl)boronic acid (**210**, 541 mg, 4.09 mmol, 1.50 equiv) in THF (4.7 ml). Water (1.6 ml), cesium carbonate (2.22 g, 6.82 mmol, 2.50 equiv) and triphenylarsine (84 mg, 0.27 mmol, 10 mol%) were added, and the resulting mixture was deoxygenated by bubbling N_2 through it for 20 minutes. The mixture was cooled to 0°C, before $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (223 mg, 0.27 mmol, 10 mol%) was added. The reaction was allowed to slowly warm up to RT. After stirring for further 60 h, the entire mixture was directly subjected to column chromatography (hexane / EtOAc; 16:1) to afford allyl silane **207** (381 mg, 62%) as a 10:1 mixture of olefin geometrical isomers (colorless oil).

TLC: R_f = 0.45 (hexane / acetone; 16:1; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, ^3J = 8.7 Hz, 2H), 6.88 (d, ^3J = 8.7 Hz, 2H), 6.30 (dd, ^3J = 17.4 Hz, 10.9 Hz, 1H), 5.36 (t, ^3J = 7.1 Hz, 1H), 5.01 (d, J = 17.4 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.47 (t, ^3J = 7.2 Hz, 2H), 2.38 (m, 2H), 1.72 (s, 2H), 0.00 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.15, 141.40, 137.73, 130.55, 129.28, 125.94, 113.77, 111.20, 72.62, 69.44, 55.28, 29.52, 16.57, –0.52; **IR** (thin film): 2954, 2855, 1614, 1514, 1247, 1172, 1098, 1037, 854 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{28}NaO_2Si$ ($[M+Na]^+$), 327.1751; found, 327.1752.



(*E*)-(5-((4-methoxybenzyl)oxy)-2-vinylpent-2-en-1-yl)trimethylsilane (208). ((Trimethylsilyl)methyl)magnesium chloride, 1.3 M in THF (0.21 ml, 0.273 mmol, 2.00 equiv) was diluted with THF (1.0 ml). Enoltriflate **204** (50 mg, 0.136 mmol, 1.00 equiv) in THF (0.5 ml) was then added *via* syringe, followed by (*tert*-$Bu_3P)_2Pd$ (1.7 mg, 3.4 µmol, 2.5 mol%). The resulting mixture was stirred at RT of 2 h. The reaction was quenched by dropwise addition of water (ca. 0.1 ml), then further diluted with water (5 ml) and extracted with Et_2O (3 x 8 ml). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (1.5 ml) and satd. aq. NaCl (1.5 ml). Drying over $MgSO_4$, filtration, and concentration under reduced pressure furnished a crude oil. Purification by chromatography on silica gel (hexane / EtOAc; 95:5) furnished allyl silane **208** (32 mg, 76%) as a colorless oil.

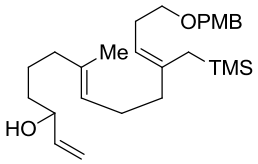
TLC: R_f = 0.24 (hexane / EtOAc; 97:3; UV / $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28 (d, ^3J = 8.8 Hz, 2H), 6.89 (d, ^3J = 8.8 Hz, 2H), 6.74 (ddd, ^3J = 17.3 Hz, 10.9 Hz, ^4J = 0.9 Hz, 1H), 5.23 (t, ^3J = 7.6 Hz, 1H), 5.17 (d, ^3J = 17.3 Hz, 1H), 5.11 (d, ^3J = 10.9 Hz, 1H), 4.46 (s, 2H), 3.81 (s, 3H), 3.47 (t, ^3J = 7.1 Hz, 2H), 2.51 (m, 2H), 1.67 (s, 2H), 0.00 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 159.08, 135.68, 133.40, 130.57, 129.19, 124.26, 114.09, 113.70, 72.50, 70.02, 55.20, 28.11, 22.40, –1.09; **IR** (thin film): 3087, 3001, 2952, 2896, 2853, 2835, 1614, 1586, 1512, 1463, 1455, 1440, 1420, 1405, 1359, 1301, 1246, 1208, 1180, 1171, 1160, 1099, 1037, 1009, 987, 902, 846, 759, 727, 694, 668, 637, 572, 511 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{18}H_{28}NaO_2Si$ ($[M+Na]^+$), 327.1751; found, 327.1752.



***tert*-Butyl(((7*E*,11*Z*)-14-((4-methoxybenzyl)oxy)-7-methyl-11-((trimethylsilyl)methyl) tetradeca-1,7,11-trien-3-yl)oxy)dimethylsilane (215).** To a solution of diene **207** (1.14 g, 3.26 mmol, 1.00 equiv) in THF (1.0 ml) at 0 °C was added 9-BBN, 0.5 M in THF (7.2 ml, 3.60 mmol, 1.10 equiv). The resulting mixture was kept at this temperature for 30 min, before it was allowed to warm up to RT and stirred for further 24 h. After re-cooling to 0 °C, sodium hydroxide, 3.0 M in water (3.3 ml, 9.90 mmol, 3.00 equiv) was added, followed by vinyl iodide **214** [199] (1.24 g, 3.26 mmol, 1.00 equiv) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (71.9 mg, 0.09

mmol, 2.7 mol%). The reaction was allowed to slowly warm up to RT and stirred for 4 d. Satd. aq. NH_4Cl (15 ml) was added the aqueous layer extracted with Et_2O (4 x 25 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / EtOAc; 99:1 to 9:1 gradient) furnished polyene **215** (1.12 g, 61%) as an amber oil, along with recovered vinyl iodide **214** (500 mg, 40%).

TLC: R_f = 0.28 (hexane / EtOAc; 98:2; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, ^3J = 8.7 Hz, 2H), 6.88 (d, ^3J = 8.7 Hz, 2H), 5.83−5.75 (m, 1H), 5.15−5.07 (m, 2H), 5.03−4.98 (m, 2H), 4.45 (s, 2H), 4.08 (m, 1H), 3.80 (s, 3H), 3.41 (t, ^3J = 7.4 Hz, 2H), 2.26 (m, 2H), 2.10−2.05 (m, 2H), 1.97−1.91 (m, 4H), 1.57 (s, 3H), 1.53 (s, 2H), 1.45−1.38 (m, 4H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.09, 141.87, 138.99, 134.94, 130.73, 129.23, 124.31, 116.85, 113.73, 113.40, 73.75, 72.52, 70.08, 55.26, 39.51, 39.16, 37.56, 29.16, 26.83, 25.90, 23.36, 21.57, 18.27, 15.80, –0.65, –4.37, –4.79; **IR** (thin film): 2952, 2855, 1613, 1513, 1248, 1096, 836 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{33}H_{62}NO_3Si_2$ ($[M+NH_4]^+$), 576.4263; found, 576.4264.

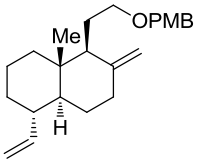


(7*E*,11*Z*)-14-((4-Methoxybenzyl)oxy)-7-methyl-11-((trimethylsilyl)methyl)tetradeca-1,7,11-trien-3-ol (216). To a solution of silyl ether **215** (1.12 g, 2.00 mmol, 1.00 equiv) in MeOH (40 ml) at RT was added PPTS (50.0 mg, 0.20 mmol, 10 mol%). The resulting mixture was stirred this temperature for 20 h. Satd. aq. $NaHCO_3$ (10 ml) was added and the mixture was extracted with Et_2O (4 x 25 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification column chromatography (hexane / EtOAc; 9:1 to 4:1 gradient) afforded alcohol **216** (550 mg, 62%) along with recovered starting material **215** (400 mg, 36%). Re-subjection to another round yielded **216** (720 mg) in 81% combined yield.

TLC: R_f = 0.44 (hexane / EtOAc; 8:2; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, ^3J = 8.7 Hz, 2H), 6.88 (d, ^3J = 8.7 Hz, 2H), 5.90−5.81 (m, 1H), 5.21 (d, ^3J = 17.2, Hz, 1H), 5.11−5.08 (m, 2H), 5.00 (t, ^3J = 6.9 Hz, 1H), 4.45 (s, 2H), 4.11−4.06 (m, 1H), 3.80 (s, 3H), 3.41 (t, ^3J = 7.3 Hz, 2H), 2.28−2.23 (m, 2H), 2.11−2.04 (m, 2H), 1.98−1.92 (m, 4H),

1.62 (s, 1H), 1.58 (s, 3H), 1.53 (s, 2H), 1.49−1.41 (m, 4H), 0.01 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.08, 141.27, 138.83, 134.69, 130.69, 129.24, 124.53, 116.99, 114.50, 113.73, 73.13, 72.48, 70.03, 55.25, 39.41, 39.09, 36.54, 29.12, 26.71, 23.53, 21.52, 15.83, –0.66; **IR** (thin film): 3434, 2934, 2857, 1613, 1516, 1247, 1095, 1037, 855 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{44}NaO_3Si$ ($[M+Na]^+$), 467.2952; found, 467.2942.

3.3.2 Polyene Cyclization and Synthesis of Asperolide C



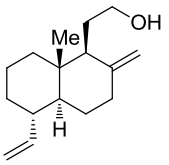
(1*S*,4a*S*,5*S*,8a*S*)-1-(2-((4-Methoxybenzyl)oxy)ethyl)-8a-methyl-2-methylene-5-vinyldecahydronaphthalene (218). $[IrCl(cod)]_2$ (20.4 mg, 0.03 mmol, 3.2 mol%) and ligand *(R)*-**217** (59.9 mg, 0.118 mmol, 12.8 mol%) were placed in a conical flask. Dichloroethane (3.3 ml) was added, the reaction vessel was quickly purged with N_2, closed, and the mixture was stirred vigorously for 15 min, during which the solution turned dark red. The mixture was taken up with a syringe and added to a separate flask containing polyene **216** (410 mg, 0.922 mmol, 1.00 equiv). Dichloroethane (2 x 1.0 ml) was used to assist the transfer. After 30 s of stirring, $Zn(OTf)_2$ (53.6 mg, 0.148 mmol, 16 mol%) was added. The reaction was purged with N_2, before it was stirred for 16 h. Silica (4 g) was added and the volatiles were removed under reduced pressure. Purification by column chromatography (dry pack; hexane / EtOAc; 9:1) yielded decaline **218** (240 mg, 73%) as a 9:1 mixture of diastereomers (colorless oil), along with ethyl ketone **219** (24.7 mg, 6%).

*(1S,4aS,5S,8aS)-1-(2-((4-Methoxybenzyl)oxy)ethyl)-8a-methyl-2-methylene-5-vinyl-decahydronaphthalene (**218**):* **TLC:** R_f = 0.38 (hexane / EtOAc; 20:1; UV / $KMnO_4$); **Optical Rotation** $[\alpha]_D^{25}$ (c = 1.00, $CHCl_3$): +16.4; **^{1}H NMR** (9:1 diastereomer ratio, only major diastereomer reported, 400 MHz, $CDCl_3$): δ 7.25 (d, ^3J = 8.7 Hz, 2H), 6.87 (d, ^3J = 8.7 Hz, 2H), 5.52 (ddd, ^3J = 17.1 Hz, 10.2 Hz, 8.9 Hz, 1H), 4.95−4.88 (m, 2H), 4.82 (s, 1H), 4.54 (s, 1H), 4.45−4.38 (m, 2H), 3.80 (s, 3H), 3.58−3.53 (m, 1H), 3.36−3.30 (m, 1H), 2.34−2.24 (m, 1H), 1.97−1.75 (m, 5H), 1.71−1.44 (m, 6H), 1.19−1.01 (m, 3H), 0.65 (s, 3H); **^{13}C NMR** (9:1 diastereomer ratio, only major diastereomer reported, 100 MHz, $CDCl_3$): δ 159.04, 148.70, 144.04, 130.85, 129.14, 113.72, 113.55, 106.79, 72.44, 69.79, 55.27, 51.35, 50.40, 43.49, 38.97, 38.21, 37.72, 33.99, 28.35, 24.28, 21.73, 12.75; **IR (thin film)**: 3076, 2935, 2361,

1644, 1645, 1587, 1515, 1456, 1247, 1097, 907 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{24}H_{35}O_2$ ($[M+Na]^+$), 355.2632; found, 355.2631; **SFC** (OJ-H column; CO_2 / *i*-PrOH; 98:2; 2.00 ml/min, 100 bar, 25 °C): major enantiomer t_r = 15.0 min, minor enantiomer t_r = 20.1 min, 96% ee.

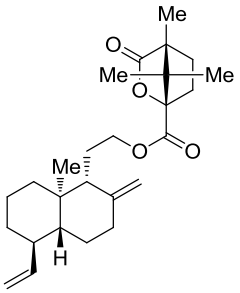
*(7E,11Z)-14-((4-methoxybenzyl)oxy)-7-methyl-11-((trimethylsilyl)methyl)tetradeca-7,11-dien-3-one (**219**):* **TLC:** R_f = 0.30 (hexane / EtOAc; 9:1; UV / $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, ^3J = 8.7 Hz, 2H), 6.87 (d, ^3J = 8.7 Hz, 2H), 5.09 (t, ^3J = 7.1 Hz, 1H), 4.99 (t, ^3J = 6.9 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.41 (t, ^3J = 7.4 Hz, 2H), 2.40 (q, ^3J = 7.3 Hz, 2H), 2.34 (m, 2H), 2.25 (m, 2H), 2.08 (m, 2H), 1.93 (m, 4H), 1.67 (m, 2H), 1.57 (s, 3H), 1.53 (s, 2H), 1.04 (t, ^3J = 7.3 Hz, 3H), 0.01 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.80, 159.09, 138.85, 134.24, 130.72, 129.24, 125.03, 116.98, 113.73, 72.52, 70.05, 55.27, 41.61, 39.09, 38.98, 35.94, 29.16, 26.76, 21.92, 21.55, 15.73, 7.86, −0.66; **IR (thin film)**: 2914, 1715, 1614, 1513, 1247, 1096, 838 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{27}H_{44}NaO_3Si$ ($[M+Na]^+$), 467.2952; found, 467.2950.

A racemic sample of **218** was obtained following the same procedure, using the achiral ligand 5-(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)-5H-dibenzo[*b*,*f*]azepine. The correspondding enantiomer *ent*-**218** was prepared with ligand (*S*)-**217**: **Optical Rotation** $[\alpha]_D^{25}$ (c = 1.00, $CHCl_3$): −16.3; **SFC** (OJ-H column; CO_2 / *i*-PrOH; 98:2; 2.00 ml/min, 100 bar, 25 °C): minor enantiomer t_r = 14.9 min, major enantiomer t_r = 19.4 min, 97% ee.



2-((1*S*,4a*S*,5*S*,8a*S*)-8a-methyl-2-methylene-5-vinyldecahydronaphthalen-1-yl)ethanol (240). To a solution of PMB ether **218** (260 mg, 0.733 mmol, 1.00 equiv) in CH_2Cl_2 (13 ml) was added pH 7 phosphate buffer, 0.1 M (1.3 ml), followed by DDQ (183 mg, 0.807 mmol, 1.10 equiv). The biphasic reaction mixture was stirred vigorously for 1 h. A mixture of sat. aq. $Na_2S_2O_3$ and satd. aq. $NaHCO_3$ (1:1, 20 ml) was added. The aqueous phase was extracted with Et_2O (4 x 40 ml) and the combined organic extracts were dried over Na_2SO_4. Concentration under reduced pressure and purification by chromatography on silica gel (hexane / EtOAc; 9:1) afforded alcohol **240** (170 mg, 98%).

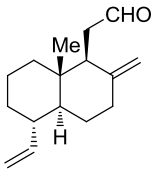
TLC: R_f = 0.22 (hexane / EtOAc; 9:1; $KMnO_4$); **Optical Rotation** $[\alpha]_D^{25}$ (c = 1.00, $CHCl_3$): +14.3; **^{1}H NMR** (9:1 diastereomer ratio, only major diastereomer reported, 400 MHz, $CDCl_3$): δ 5.53 (ddd, ^3J = 17.1 Hz, 10.2 Hz, 8.9 Hz, 1H), 4.95−4.88 (m, 2H), 4.86 (s, 1H), 4.56 (s, 1H), 3.75 (s, 1H), 3.55 (s, 1H), 2.32 (d, ^3J = 12.8 Hz, 1H), 1.99−1.78 (m, 5H), 1.72−1.44 (m, 6H), 1.24 (m, 1H), 1.12−1.01 (m, 3H), 0.66 (s, 3H); **^{13}C NMR** (9:1 diastereomer ratio, only major diastereomer reported, 100 MHz, $CDCl_3$): δ 148.80, 143.97, 113.61, 106.90, 62.57, 51.10, 50.43, 43.49, 38.94, 38.23, 37.74, 33.97, 28.34, 27.27, 21.73, 12.79; **IR** (thin film): 3338, 3078, 2921, 1640, 1601, 1578, 1542, 1442, 1262, 1035, 889 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{27}O$ ($[M+H]^+$), 235.2056; found, 235.2057.



(1*S*,4*R*)-2-((1*R*,4a*R*,5*R*,8a*R*)-8a-Methyl-2-methylene-5-vinyldecahydronaphthalen-1-yl)ethyl 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (220). To a solution of alcohol *ent*-**240** (13.3 mg, 0.057 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 ml) at RT was added Et_3N (40 µl, 0.284 mmol, 5.00 equiv). The resulting mixture was cooled to 0 °C and (−)-camphanic acid chloride (30.7 mg, 0.142 mmol, 2.50 equiv) was added in one portion. The reaction was stirred at 0 °C for 30 min and was then allowed to warm up to RT. After 1 h of further stirring, the reaction mixture was taken up in Et_2O (3 ml) and transferred into a separatory funnel with satd. aq. $NaHCO_3$ (5 ml). The mixture was extracted with Et_2O (3 x 5 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane / EtOAc; 9:1) furnished ester **220** (18.6 mg, 79%) as a white crystalline solid.

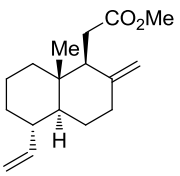
TLC: R_f = 0.30 (hexane / EtOAc; 9:1; $KMnO_4$); **Optical Rotation** $[\alpha]_D^{25}$ (c = 1.00, $CHCl_3$): −23.4; **^{1}H NMR** (9:1 diastereomer ratio, only major diastereomer reported, 400 MHz, $CDCl_3$): δ 5.52 (ddd, ^3J = 17.0 Hz, 10.2 Hz, 8.9 Hz, 1H), 4.94−4.89 (m, 3H), 4.59 (s, 1H), 4.38 (m, 1H), 4.09 (m, 1H), 2.42 (m, 1H), 2.33 (m, 1H), 2.06−1.84 (m, 6H), 1.79−1.74 (m, 8H), 1.20−1.02 (m, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.66 (s, 3H); **^{13}C NMR** (9:1 diastereomer ratio, only major diastereomer reported, 100 MHz, $CDCl_3$): δ 178.16, 167.53,

147.84, 143.78, 113.75, 107.21, 91.15, 65.54, 54.78, 54.09, 51.25, 50.43, 43.43, 38.98, 38.22, 37.61, 33.87, 30.65, 28.98, 28.25, 23.32, 21.65, 16.82, 16.81, 12.71, 9.72; **IR** (thin film): 3075, 2967, 2929, 1794, 1752, 1730, 1641, 1444, 1396, 1380, 1342, 1315, 1267, 1229, 1168, 1105, 1062, 1018, 994, 958, 931, 902, 795, 740, 664, 586 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{26}H_{39}O_4$ ($[M+H]^+$), 415.2843; found, 415.2841.



2-((1*S*,4a*S*,5*S*,8a*S*)-8a-methyl-2-methylene-5-vinyldecahydronaphthalen-1-yl) acetaldehyde (241). DESS-MARTIN periodinane (497 mg, 1.17 mmol, 1.50 equiv) was added to a solution of alcohol **240** (183 mg, 0.78 mmol, 1.00 equiv) in CH_2Cl_2 (15 ml) at RT. After 5 h of stirring, the reaction was quenched by addition of a mixture of sat. $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 10 ml). The aqueous layer was extracted with CH_2Cl_2 (4 x 15 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography gave aldehyde **241** (145 mg, 80%) as a colorless oil.

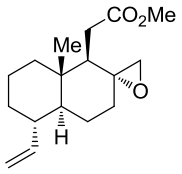
TLC: R_f = 0.60 (hexane / EtOAc; 9:1; $KMnO_4$); **Optical Rotation** $[\alpha]_D^{25}$ (c = 0.10, $CHCl_3$): −6.8; **^{1}H NMR** (9:1 diastereomer ratio, only major diastereomer reported, 400 MHz, $CDCl_3$): δ 9.66 (t, ^3J = 2.0, 1H), 5.54 (ddd, J = 17.0 Hz, 10.2 Hz, 8.9 Hz, 1H), 4.96−4.91 (m, 2H), 4.85 (s, 1H), 4.41 (s, 1H), 4.51−4.49 (m, 2H), 2.44−2.33 (m, 2H), 2.06 (m, 1H), 1.95−1.86 (m, 1H), 1.74−1.59 (m, 4H), 1.52−1.43 (m, 1H), 1.22−1.07 (m, 4H), 0.69 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.44, 148.52, 143.56, 113.98, 108.45, 50.17, 49.34, 43.41, 39.99, 38.61, 38.47, 37.02, 33.84, 27.78, 21.60, 13.12; **IR** (thin film): ν 3078, 2927, 2849, 2714, 1718, 1670, 1637, 1438, 1380, 1260, 1025, 908, 800 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}NaO$ ($[M+Na]^+$), 255.1719; found, 255.1719.



Methyl-2-((1*S*,4a*S*,5*S*,8a*S*)-8a-methyl-2-methylene-5-vinyldecahydronaphthalen-1-yl)acetate (221). To a solution of aldehyde **241** (140 mg, 0.603 mmol, 1.00 equiv) in *tert*-

BuOH (7.0 ml) at RT was added 2-methyl-2-butene (4.5 ml, 42.2 mmol, 70 equiv), followed by a solution of $NaClO_2$ (218 mg, 2.41 mmol, 4.00 equiv) and $NaH_2PO_4 \cdot 2H_2O$ (434 mg, 3.62 mmol, 6.00 equiv) in water (7.0 ml). The reaction was stirred at this temperature for 4 h, before it was quenched by addition of a mixture of sat. aq. $NaHCO_3$ and satd. aq. $Na_2S_2O_3$ (1:1, 10 ml). The resulting mixture was extracted with EtOAc (4 x 10 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in methanol (10 ml) and the solution was cooled to 0 °C. Trimethylsilyl diazomethane, 2.0 M in Et_2O (0.33 ml, 0.60 mmol, 1.10 equiv) was added until a slightly yellow color persisted. The mixture was allowed to warm up to RT and stirred for additional 30 min. Removal of the volatiles under reduced pressure and purification by chromatography on silica gel (hexane / EtOAc; 9:1) delivered ester **221** (125 mg, 79%) as a colorless oil.

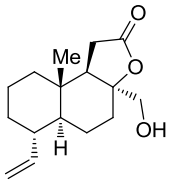
TLC: R_f = 0.65 (hexane / EtOAc; 9:1; $KMnO_4$); **Optical Rotation** $[\alpha]_D^{25}$ (c = 0.33, $CHCl_3$): −7.6; **^{1}H NMR** (9:1 diastereomer ratio, only major diastereomer reported, 400 MHz, $CDCl_3$): δ 5.53 (ddd, *J* = 17.0 Hz, 10.2 Hz, 8.9 Hz, 1H), 4.95−4.89 (m, 2H), 4.78 (s, 1H), 4.50 (s, 1H), 3.65 (s, 3H), 2.54−2.49 (m, 1H), 2.44−2.36 (m, 2H), 2.34−2.29 (m, 1H), 2.10−2.02 (m, 1H), 1.93−1.84 (m, 1H), 1.72−1.44 (m, 5H), 1.21−1.00 (m, 4H), 0.67 (s, 3H); **^{13}C NMR** (9:1 diastereomer ratio, only major diastereomer reported, 100 MHz, $CDCl_3$): δ 174.42, 149.11, 143.75, 113.81, 106.71, 51.61, 50.90, 50.01, 43.42, 38.45, 38.18, 37.08, 33.87, 30.92, 27.89, 21.64, 12.91; **IR** (thin film) 3077, 2922, 1739, 1644, 1435, 1381, 1322, 1224, 1159, 996, 891 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{27}O_2$ ($[M+H]^+$), 263.2006; found, 263.2013.



Methyl-2-((1*R*,2*R*,4a*S*,5*S*,8a*S*)-8a-methyl-5-vinyloctahydro-1H-spiro[naphthalene-2,2'-oxiran]-1-yl)acetate (222). To a solution of olefin **221** (53.0 mg, 0.202 mmol, 1.00 equiv) in acetone (4.3 ml) at –78 °C was added dropwise over 7 min freshly prepared DMDO, 0.06 M in acetone (3.7 ml, 0.22 mmol, 1.10 equiv). The resulting mixture was allowed to warm up to –20 °C and was stirred for 3d. The reaction was quenched by addition of a mixture of sat. aq. $Na_2S_2O_3$ and satd. aq. $NaHCO_3$ (1:1, 2 ml). Extraction with Et_2O (3 x 5 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure gave a crude oil.

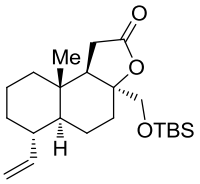
Purification by column chromatography epoxide **222** (25 mg, 45%, 58% brsm) as a colorless oil.

TLC: R_f = 0.40 (hexane / EtOAc; 9:1; $KMnO_4$); **Optical Rotation** $[\alpha]_D^{26}$ (c = 0.33, $CHCl_3$): −7.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.53 (ddd, ^3J = 17.0 Hz, 10.2 Hz, 8.9 Hz, 1H), 4.97−4.91 (m, 2H), 3.65 (s, 3H), 2.67 (m, 1H), 2.52 (d, ^3J = 4.8 Hz, 1H), 2.35 (m, 1H), 2.12 (dd, ^2J = 15.8 Hz, ^3J = 6.2 Hz, 1H), 1.98−1.87 (m, 3H), 1.82−1.76 (m, 1H), 1.68−1.63 (m, 1H), 1.60−1.46 (m, 3H), 1.35−1.31 (m, 1H), 1.23−1.08 (m, 4H), 0.8 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.16, 143.47, 114.11, 58.59, 51.69, 50.70, 49.45, 48.33, 43.08, 38.89, 37.93, 35.23, 33.60, 27.60, 25.54, 20.84, 12.98; **IR** (thin film): 2922, 1739, 1640, 1435, 1305, 1164, 997, 910 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{17}H_{26}NaO_3$ ($[M+Na]^+$), 301.1774; found, 301.1770.



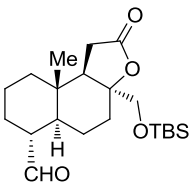
(3a*S*,5a*S*,6*S*,9a*S*,9b*R*)-3a-(Hydroxymethyl)-9a-methyl-6-vinyldecahydronaphtho[2,1-b]furan-2(3aH)-one (223). To a solution of epoxide **222** (24 mg, 0.09 mmol, 1.00 equiv) in CH_2Cl_2 (4.3 ml) at –20 °C was added TFA (7.7 µl, 0.103 mmol, 1.20 equiv). The resulting mixture was allowed to warm up to 0 °C over 40 min. The reaction was quenched by addition of satd. aq. $NaHCO_3$ (2 ml). Extraction with Et_2O (3 x 5 ml), drying over Na_2SO_4, filtration and concentration under reduced pressure gave the crude product. Purification by chromatography on silica gel (hexane / EtOAc; 9:1 to 4:1 gradient) furnished lactone **223** (16 mg, 70%) as a colorless oil.

TLC: R_f = 0.58 (hexane / EtOAc; 7:3; $KMnO_4$); **Optical Rotation** $[\alpha]_D^{26}$ (c = 1.00, $CHCl_3$): −10.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.51 (ddd, ^3J = 17.1 Hz, 10.1 Hz, 8.8 Hz, 1H), 5.00−4.94 (m, 2H), 3.50 (m, 2H), 2.88 (dd, ^2J = 18.2, ^3J = 8.9 Hz, 1H), 2.43 (d, ^2J = 18.2 Hz, 1H), 2.29 (m, 1H), 2.12−1.93 (m, 3H), 1.72−1.46 (m, 6H), 1.33−1.24 (m, 1H), 1.20−1.10 (m, 1H), 1.05−0.95 (m, 1H), 0.91 (s, 3H), 0.90−0.84 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 178.21, 142.99, 114.75, 87.12, 70.00, 48.74, 45.56, 43.26, 40.13, 35.17, 33.40, 32.26, 28.42, 20.89, 20.34, 14.21; **IR** (thin film): 3448, 3074, 2926, 1751, 1638, 1458, 1203, 1042, 910 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}NaO_3$ ($[M+Na]^+$), 287.1618; found, 287.1616.



(3a*S*,5a*S*,6*S*,9a*S*,9b*R*)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-9a-methyl-6-vinyl-decahydronaphtho[2,1-b]furan-2(3aH)-one (224). To a solution of alcohol **223** (33 mg, 0.13 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 ml) at RT was added imidazole (51 mg, 0.75 mmol, 6.00 equiv), TBSCl (56 mg, 0.37 mmol, 3.00 equiv) and DMAP (1.6 mg, 0.013 mmol, 0.10 equiv). The resulting mixture was stirred at this temperature for 12 h. Satd. aq. $NaHCO_3$ (2 ml) was added and the mixture was extracted with Et_2O (3 x 5 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (hexane / EtOAc; 95:5) yielded silyl ether **224** as a white powder (42 mg, 89%).

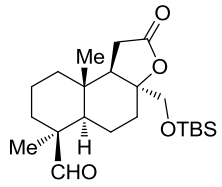
TLC: R_f = 0.60 (hexane / EtOAc; 9:1; CAN / $KMnO_4$); **Optical Rotation** $[\alpha]_D^{24}$ (c = 1.00, $CHCl_3$): +1.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.51 (ddd, 3*J* = 17.1 Hz, 10.1 Hz, 8.8 Hz, 1H), 4.99−4.94 (m, 2H), 3.45 (d, ^2J = 10.4 Hz, 1H), 3.37 (d, ^2J = 10.4 Hz, 1H), 2.84 (dd, ^2J = 17.9 Hz, ^3J = 8.8 Hz, 1H), 2.34 (d, ^2J = 17.9 Hz, 1H), 2.04−1.89 (m, 3H), 1.69−1.64 (m, 1H), 1.62−1.41 (m, 5H), 1.30−1.21 (m, 1H), 1.17−1.07 (m, 1H), 0.97−0.93 (m, 1H), 0.89 (s, 9H), 0.87 (s, 3H), 0.83−0.76 (m, 1H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 178.02, 143.14, 114.61, 86.63, 70.01, 48.82, 45.77, 43.16, 40.11, 35.03, 33.43, 32.33, 28.37, 25.81, 20.93, 20.33, 18.18, 14.07, –5.59, –5.67; **IR** (thin film): 2930, 2857, 1762, 1638, 1472, 1252, 1111, 1055, 983, 838 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{39}O_3Si$ ($[M+H]^+$), 379.2663; found, 379.2665.



(3a*S*,5a*S*,6*R*,9a*S*,9b*R*)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-9a-methyl-2-oxo-dodecahydronaphtho[2,1-b]furan-6-carbaldehyde (225). To a solution of olefin **224** (42 mg, 0.11 mmol, 1.00 equiv) in dioxane (4.1 ml) / water (1.4 ml) at RT was added $NaIO_4$ (119 mg, 0.55 mmol, 5.0 equiv) and 2,6-lutidine (26 μL, 0.22 mmol, 2.00 equiv), followed by OsO_4, 4% w/w in water (140 μl, 0.02 mmol, 20 mol%). The reaction was stirred at this

temperature for 12 h. A mixture of sat. aq. $Na_2S_2O_3$ and satd. aq. $NaHCO_3$ (1:1, 3 ml) was added. The aqueous phase was extracted with Et_2O (3 x 5 ml) and the combined organic extracts were dried over $MgSO_4$. Concentration under reduced pressure and purification by chromatography on silica gel (hexane / EtOAc; 9:1) afforded aldehyde **225** (34 mg, 81%) as a white solid.

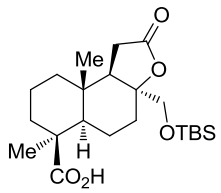
TLC: R_f = 0.38 (hexane / EtOAc; 8:2; CAN); **Optical Rotation** $[\alpha]_D^{25}$ (c = 1.30, $CHCl_3$): −8.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.54 (d, ^3J = 10.4 Hz, 1H), 3.47 (d, ^2J = 10.4 Hz, 1H), 3.40 (d, ^2J = 10.4 Hz, 1H), 2.87 (dd, ^2J = 18.0 Hz, ^3J =8.8 Hz, 1H), 2.34 (d, ^2J = 18.0 Hz, 1H), 2.32−2.27 (m, 1H), 2.10 (d, ^3J = 8.6 Hz, 1H), 2.03−1.99 (m, 1H), 1.85−1.81 (m, 1H), 1.71−1.62 (m, 3H), 1.55−1.21 (m, 6H), 1.01−0.93 (m, 1H), 0.89 (s, 9H), 0.88 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 204.34, 177.60, 86.13, 69.91, 50.83, 48.50, 41.08, 39.35, 34.50, 32.28, 28.01, 26.18, 25.82, 21.30, 19.48, 18.20, 14.08, –5.58, –5.65; **IR** (thin film): 2932, 2857, 1765, 1730, 1471, 1258, 1203, 1156, 1118, 1042, 934, 839 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{41}O_5Si$ ($[M+MeOH+H]^+$), 413.2718; found, 413.2721.



(3a*S*,5a*R*,6*S*,9a*S*,9b*R*)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-6,9a-dimethyl-2-oxo-dodecahydronaphtho[2,1-b]furan-6-carbaldehyde (226). To a solution of aldehyde **225** (12.0 mg, 0.032 mmol, 1.00 equiv) in THF (1.0 ml) at −20 °C was added *tert*-BuOK, 0.5 M in THF (79 µl, 0.039 mmol, 1.25 equiv). The resulting mixture was stirred at this temperature for 5 min, before MeI, 0.5 M in THF (79 µl, 0.039 mmol, 1.25 equiv) was added. The reaction was stirred and allowed to warm up to 0 °C over 35 min. After keeping the reaction at this temperature for a further 10 min, it was quenched by addition of satd. aq. $NaHCO_3$ (2 ml). Extraction with Et_2O (3 x 5 ml), drying over $MgSO_4$, filtration, and concentration under reduced pressure delivered a yellow oil. Purification by column chromatography afforded aldehyde **226** (4.5 mg, 36%) as a slightly yellowish oil.

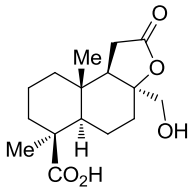
TLC: R_f = 0.22 (hexane / EtOAc; 9:1; CAN); **Optical Rotation** $[\alpha]_D^{26}$ (c = 0.50, $CHCl_3$): −8.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.76 (d, ^4J = 1.4 Hz, 1H), 3.47 (d, ^2J = 10.4 Hz, 1H), 3.40 (d, ^2J = 10.4 Hz, 1H), 2.84 (dd, ^2J = 18.0 Hz, ^3J = 8.6 Hz, 1H), 2.30 (d, ^2J = 18.0 Hz,

1H), 2.21−2.12 (m, 2H), 2.07 (d, ^3J = 8.5 Hz, 1H), 1.97−1.87 (m, 1H), 1.86−1.78 (m, 1H), 1.73−1.67 (m, 1H), 1.65−1.62 (m, 1H), 1.52−1.46 (m, 2H), 1.19 (dd, ^3J = 12.1, 3.3 Hz, 1H), 1.06 (s, 3H), 1.03−0.95 (m, 2H), 0.90 (s, 9H), 0.77 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.01, 177.51, 85.97, 69.40, 52.15, 49.28, 47.86, 40.44, 35.85, 33.99, 32.47, 29.78, 25.81, 24.32, 18.20, 18.00, 17.26, 14.90, −5.56, −5.63; **IR** (thin film): 2931, 1774, 1718, 1464, 1255, 1208, 1159, 1118, 1050, 936, 839, 780 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{39}O_4Si$ ($[M+H]^+$), 395.2612; found, 395.2604.



(3a*S*,5a*R*,6*S*,9a*S*,9b*R*)-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-6,9a-dimethyl-2-oxo-dodecahydronaphtho[2,1-b]furan-6-carboxylic acid (242). To a solution of aldehyde **226** (9.5 mg, 0.024 mmol, 1.00 equiv) in *tert*-BuOH (1.0 ml) at RT was added 2-methyl-2-butene (85 μl, 0.722 mmol, 30.0 equiv), followed by a solution of $NaClO_2$ (13.0 mg, 0.144 mmol, 6.0 equiv) and $NaH_2PO_4{\cdot}2H_2O$ (22.5 mg, 0.144 mmol, 6.0 equiv) in water (0.5 ml). The resulting mixture was stirred at this temperature for 12 h, before it was diluted with water (2 ml). Extraction with EtOAc (4 x 5 ml), drying over Na_2SO_4, filtration, and concentration under reduced pressure gave a crude oil, which was purified by chromatography on silica gel (hexane / EtOAc / AcOH; 8:2:0.02) to afford carboxylic acid **242** as a white solid (7.5 mg, 76%).

TLC: R_f = 0.20 (hexane / EtOAc / AcOH; 8:2:0.02; CAN); **Optical Rotation** $[\alpha]_D^{26}$ (c = 0.44, $CHCl_3$): +2.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.46 (d, ^2J = 10.4 Hz, 1H), 3.39 (d, ^2J = 10.4 Hz, 1H), 2.85 (dd, ^2J = 17.9 Hz, ^3J = 8.5 Hz, 1H), 2.32 (d, ^2J = 17.9 Hz, 1H), 2.24−2.21 (m, 1H), 2.09 (m, 1H), 2.03 (d, ^3J = 8.2 Hz, 1H), 1.99−1.90 (m, 1H), 1.88−1.77 (m, 2H), 1.67−1.56 (m, 2H), 1.52−1.41 (m, 2H), 1.37−1.31 (m, 1H), 1.27 (s, 3H), 1.10−1.04 (m, 2H), 0.89 (s, 9H), 0.83 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.02, 177.84, 86.32, 69.44, 52.45, 49.69, 43.53, 41.17, 37.65, 36.27, 32.60, 29.92, 28.87, 25.83, 18.92, 18.77, 18.20, 14.22, −5.56, −5.63; **IR** (thin film): 3500−2500, 1774, 2929, 1769, 1694, 1470, 1258, 1209, 1158, 1116, 1046, 934, 839, 775, 669 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{22}H_{39}O_5Si$ ($[M+H]^+$), 411.2561; found, 411.2563.



Asperolide C (190). To a solution of silyl ether **242** (7.5 mg, 0.018 mmol, 1.00 equiv) in THF (1.0 ml) at 0 °C was added TBAF, 1.0 M in THF (28 μl, 0.027 mmol, 1.5 equiv). The resulting mixture was stirred at this temperature for 7 h. Satd. aq. NH_4Cl (3 ml) was added and the mixture was extracted with EtOAc (5 x 5 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification column chromatography (hexane / EtOAc / AcOH; 1:1:0.02) afforded synthetic asperolide C (**190**) as a white amorphous solid (4.0 mg, 74%).

TLC: R_f = 0.32 (hexane / EtOAc / AcOH; 6:4:0.02; CAN); **Optical Rotation** $[\alpha]_D^{26}$ (c = 0.25, MeOH): +2.5; **^{1}H NMR** (400 MHz, CD_3OD): δ 3.43 (d, ^2J = 11.6 Hz, 1H), 3.39 (d, ^2J = 11.6 Hz, 1H), 2.93 (dd, ^2J = 18.1 Hz, ^3J = 8.4 Hz, 1H), 2.37 (d, ^2J = 18.1 Hz, 1H), 2.19 (m, 1H), 2.08 (m, 1H), 2.07 (m, 1H) 1.95−1.89 (m, 1H), 1.86 (m, 1H), 1.69(m, 1H), 1.68 (m, 1H), 1.43 (m, 1H), 1.23 (s, 3H), 1.17 (dd, ^3J = 11.2 Hz, 3.7 Hz, 1H), 1.04 (m, 1H), 1.08 (dd, ^2J = 13.4 Hz, ^3J = 3.9 Hz, 1H), 0.84 (s, 3H); **^{13}C NMR** (150 MHz, CD_3OD): δ 181.29, 180.87, 88.85, 69.23, 53.34, 50.77, 44.63, 42.09, 39.02, 37.46, 33.52, 31.12, 29.39, 20.26, 20.10, 14.64; **IR** (thin film): 3419, 2930, 1755, 1694, 1464, 1203, 1090, 1043, 989, 931, 797, 756 cm^{-1}; **HRMS** (ESI): exact mass calculated for $C_{16}H_{24}O_5$ ($[M+H]^+$), 297.1697; found, 297.1699.

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5 Appendix

5.1 X-Ray Crystallographic Data for Compound 220

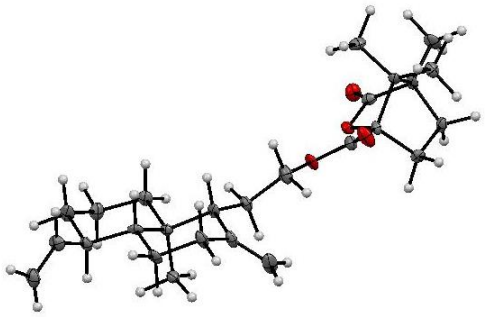


Table 1: Crystal data and structure refinement for CCDC 955873.

Crystal Data

Empirical formula:	$C_{26}H_{38}O_4$	
Formula weight:	414.56	
Temperature:	100(2) K	
Wavelength:	0.71073 Å	
Crystal System, Space Group:	Triclinic, P1	
Unit Cell Dimensions:	a = 7.122(2) Å	α = 86.822(6)°
	b = 7.145(2) Å	β = 75.055(8)°
	c = 12.775(3) Å	γ = 67.155(6)°
Volume:	578.1(3) $Å^3$	
Z:	1	
Calculated Density:	1.194 Mg/m^3	
Absorption Coefficient:	0.078 mm^{-1}	
F(000):	226	
Crystal Size:	0.40 x 0.20 x 0.08 mm	

Data Collection

Theta Range for Data Collection:	3.10−27.56°
Limiting Indices:	$-9 \le h \le 9, -5 \le k \le 9, -16 \le l \le 16$
Reflections Collected / Unique:	3472 / 3472 [R(int) = 0.0000]
Completeness to Theta = 27.56:	96.3%
Absorption Correction:	SADABS, multiscan

Solution Refinement

Refinement Method:	Full-matrix least-squares on F^2
Data / Restraints / Parameters:	3472 / 3 / 285
Goodness-of-Fit on F^2:	1.982
Final R indices [I>2sigma(I)]:	R1 = 0.0831, wR2 = 0.2461
R Indices (all data):	R1 = 0.0870, wR2 = 0.2479
Absolute Structure Parameter:	−1(2)
Largest Diff. Peak and Hole:	0.461 and −0.616 $eÅ^{-3}$

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for CCDC 955873. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(17)	-10555(6)	-4035(5)	3273(3)	17(1)
O(19)	-9520(7)	-5184(6)	1531(3)	27(1)
O(21)	-12564(6)	-275(5)	2861(3)	15(1)
O(30)	-13736(7)	3161(6)	2940(3)	23(1)
C(1)	-7943(9)	-8033(8)	077(4)	16(1)
C(2)	-7935(10)	-10039(8)	4759(4)	21(1)
C(3)	-6064(10)	-11864(8)	4912(4)	23(1)
C(4)	-6022(9)	-11857(8)	6114(4)	19(1)
C(5)	-5789(9)	-9889(8)	7666(4)	17(1)
C(6)	-5652(10)	-7911(8)	7960(5)	23(1)
C(7)	-7510(10)	-6031(8)	7789(5)	22(1)
C(8)	-7754(9)	-6041(8)	6631(4)	19(1)
C(9)	-8000(8)	-7979(8)	6315(4)	14(1)
C(10)	-6022(8)	-9868(8)	6472(4)	15(1)
C(11)	-9489(13)	-10235(10)	4404(5)	33(2)
C(12)	-3897(9)	-11677(8)	7793(5)	22(1)
C(13)	-3921(11)	-13069(9)	8537(5)	26(1)
C(14)	-10062(8)	-8065(8)	6990(4)	18(1)
C(15)	-9632(9)	-6137(8)	4762(4)	18(1)
C(16)	-9131(10)	-6022(8)	3528(5)	24(1)
C(18)	-10541(9)	-3853(9)	2230(4)	20(1)
C(20)	-11914(8)	-1775(7)	1971(4)	13(1)
C(22)	-13110(8)	1597(8)	2387(4)	16(1)
C(23)	-12857(9)	1224(8)	1200(4)	16(1)
C(24)	-14605(9)	481(8)	1183(4)	17(1)
C(25)	-13943(8)	-1612(7)	1692(4)	16(1)
C(26)	-10843(8)	-788(8)	990(4)	15(1)
C(27)	-8901(9)	-554(9)	1162(5)	23(1)
C(28)	-10295(9)	-1851(8)	-125(4)	20(1)
C(29)	-12794(10)	3016(8)	504(5)	24(1)

Table 3: Bond lengths [Å] and angles [°] for CCDC 955873.

O(17)-C(18)	1.330(6)
O(17)-C(16)	1.467(6)
O(19)-C(18)	1.205(7)
O(21)-C(22)	1.392(6)
O(21)-C(20)	1.461(6)
O(30)-C(22)	1.219(7)
C(1)-C(2)	1.509(8)
C(1)-C(15)	1.539(7)
C(1)-C(9)	1.574(7)
C(1)-H(1)	1.09

C(2)-C(11)	1.356(10)
C(2)-C(3)	1.507(8)
C(3)-C(4)	1.544(7)
C(3)-H(3A)	1.09
C(3)-H(3B)	1.09
C(4)-C(10)	1.517(8)
C(4)-H(4A)	1.09
C(4)-H(4B)	1.09
C(5)-C(12)	1.493(7)
C(5)-C(6)	1.527(8)
C(5)-C(10)	1.574(7)
C(5)-H(5)	1.09
C(6)-C(7)	1.529(8)
C(6)-H(6A)	1.09
C(6)-H(6B)	1.09
C(7)-C(8)	1.534(8)
C(7)-H(7A)	1.09
C(7)-H(7B)	1.09
C(8)-C(9)	1.548(7)
C(8)-H(8A)	1.09
C(8)-H(8B)	1.09
C(9)-C(14)	1.521(7)
C(9)-C(10)	1.577(7)
C(10)-H(10)	1.09
C(11)-H(11A)	0.93
C(11)-H(11B)	0.93
C(12)-C(13)	1.338(8)
C(12)-H(12)	1.08
C(13)-H(13A)	1.06(6)
C(13)-H(13B)	0.95(9)
C(14)-H(14A)	1.0899
C(14)-H(14B)	1.0899
C(14)-H(14C)	1.0899
C(15)-C(16)	1.529(7)
C(15)-H(15A)	1.09
C(15)-H(15B)	1.09
C(16)-H(16A)	1.09
C(16)-H(16B)	1.09
C(18)-C(20)	1.502(7)
C(20)-C(25)	1.536(7)
C(20)-C(26)	1.573(7)
C(22)-C(23)	1.506(7)
C(23)-C(29)	1.526(7)
C(23)-C(24)	1.536(8)
C(23)-C(26)	1.562(7)
C(24)-C(25)	1.544(7)
C(24)-H(24A)	1.09
C(24)-H(24B)	1.09
C(25)-H(25A)	1.09
C(25)-H(25B)	1.09
C(26)-C(27)	1.526(8)
C(26)-C(28)	1.537(7)
C(27)-H(27A)	1.0899
C(27)-H(27B)	1.0899
C(27)-H(27C)	1.0899
C(28)-H(28A)	1.0899
C(28)-H(28B)	1.0899
C(28)-H(28C)	1.0899
C(29)-H(29A)	1.0899
C(29)-H(29B)	1.0899
C(29)-H(29C)	1.0899
C(18)-O(17)-C(16)	114.3(4)

C(22)-O(21)-C(20)	105.0(4)
C(2)-C(1)-C(15)	115.2(5)
C(2)-C(1)-C(9)	109.5(4)
C(15)-C(1)-C(9)	112.9(4)
C(2)-C(1)-H(1)	106.2
C(15)-C(1)-H(1)	106.2
C(9)-C(1)-H(1)	106.2
C(11)-C(2)-C(3)	121.7(6)
C(11)-C(2)-C(1)	124.2(5)
C(3)-C(2)-C(1)	114.1(5)
C(2)-C(3)-C(4)	108.5(5)
C(2)-C(3)-H(3A)	110
C(4)-C(3)-H(3A)	110
C(2)-C(3)-H(3B)	110
C(4)-C(3)-H(3B)	110
H(3A)-C(3)-H(3B)	108.4
C(10)-C(4)-C(3)	111.3(4)
C(10)-C(4)-H(4A)	109.4
C(3)-C(4)-H(4A)	109.4
C(10)-C(4)-H(4B)	109.4
C(3)-C(4)-H(4B)	109.4
H(4A)-C(4)-H(4B)	108
C(12)-C(5)-C(6)	110.6(5)
C(12)-C(5)-C(10)	110.7(4)
C(6)-C(5)-C(10)	110.2(4)
C(12)-C(5)-H(5)	108.4
C(6)-C(5)-H(5)	108.4
C(10)-C(5)-H(5)	108.4
C(5)-C(6)-C(7)	112.4(5)
C(5)-C(6)-H(6A)	109.1
C(7)-C(6)-H(6A)	109.1
C(5)-C(6)-H(6B)	109.1
C(7)-C(6)-H(6B)	109.1
H(6A)-C(6)-H(6B)	107.9
C(6)-C(7)-C(8)	111.5(4)
C(6)-C(7)-H(7A)	109.3
C(8)-C(7)-H(7A)	109.3
C(6)-C(7)-H(7B)	109.3
C(8)-C(7)-H(7B)	109.3
H(7A)-C(7)-H(7B)	108
C(7)-C(8)-C(9)	113.1(4)
C(7)-C(8)-H(8A)	109
C(9)-C(8)-H(8A)	109
C(7)-C(8)-H(8B)	109
C(9)-C(8)-H(8B)	109
H(8A)-C(8)-H(8B)	107.8
C(14)-C(9)-C(8)	110.8(4)
C(14)-C(9)-C(1)	109.2(4)
C(8)-C(9)-C(1)	110.5(4)
C(14)-C(9)-C(10)	112.2(4)
C(8)-C(9)-C(10)	107.5(4)
C(1)-C(9)-C(10)	106.5(4)
C(4)-C(10)-C(5)	112.3(4)
C(4)-C(10)-C(9)	112.1(4)
C(5)-C(10)-C(9)	111.6(4)
C(4)-C(10)-H(10)	106.8
C(5)-C(10)-H(10)	106.8
C(9)-C(10)-H(10)	106.8
C(2)-C(11)-H(11A)	120
C(2)-C(11)-H(11B)	120
H(11A)-C(11)-H(11B)	120
C(13)-C(12)-C(5)	125.0(6)

C(13)-C(12)-H(12)	117.5
C(5)-C(12)-H(12)	117.5
C(12)-C(13)-H(13A)	114(3)
C(12)-C(13)-H(13B)	122(5)
H(13A)-C(13)-H(13B)	124(6)
C(9)-C(14)-H(14A)	109.5
C(9)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(9)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(16)-C(15)-C(1)	109.8(4)
C(16)-C(15)-H(15A)	109.7
C(1)-C(15)-H(15A)	109.7
C(16)-C(15)-H(15B)	109.7
C(1)-C(15)-H(15B)	109.7
H(15A)-C(15)-H(15B)	108.2
O(17)-C(16)-C(15)	107.9(4)
O(17)-C(16)-H(16A)	110.1
C(15)-C(16)-H(16A)	110.1
O(17)-C(16)-H(16B)	110.1
C(15)-C(16)-H(16B)	110.1
H(16A)-C(16)-H(16B)	108.4
O(19)-C(18)-O(17)	124.9(5)
O(19)-C(18)-C(20)	121.3(5)
O(17)-C(18)-C(20)	113.7(4)
O(21)-C(20)-C(18)	111.9(4)
O(21)-C(20)-C(25)	106.3(4)
C(18)-C(20)-C(25)	115.9(5)
O(21)-C(20)-C(26)	102.3(4)
C(18)-C(20)-C(26)	115.6(4)
C(25)-C(20)-C(26)	103.4(4)
O(30)-C(22)-O(21)	120.2(5)
O(30)-C(22)-C(23)	131.8(5)
O(21)-C(22)-C(23)	108.0(4)
C(22)-C(23)-C(29)	114.3(5)
C(22)-C(23)-C(24)	104.3(4)
C(29)-C(23)-C(24)	116.2(4)
C(22)-C(23)-C(26)	98.6(4)
C(29)-C(23)-C(26)	118.3(5)
C(24)-C(23)-C(26)	102.8(4)
C(23)-C(24)-C(25)	104.4(4)
C(23)-C(24)-H(24A)	110.9
C(25)-C(24)-H(24A)	110.9
C(23)-C(24)-H(24B)	110.9
C(25)-C(24)-H(24B)	110.9
H(24A)-C(24)-H(24B)	108.9
C(20)-C(25)-C(24)	101.6(4)
C(20)-C(25)-H(25A)	111.5
C(24)-C(25)-H(25A)	111.5
C(20)-C(25)-H(25B)	111.5
C(24)-C(25)-H(25B)	111.5
H(25A)-C(25)-H(25B)	109.3
C(27)-C(26)-C(28)	109.7(4)
C(27)-C(26)-C(23)	114.1(5)
C(28)-C(26)-C(23)	113.7(4)
C(27)-C(26)-C(20)	112.5(4)
C(28)-C(26)-C(20)	114.9(4)
C(23)-C(26)-C(20)	91.0(4)
C(26)-C(27)-H(27A)	109.5
C(26)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5

C(26)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(26)-C(28)-H(28A)	109.5
C(26)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(26)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(23)-C(29)-H(29A)	109.5
C(23)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(23)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4: Anisotropic displacement parameters ($Å^2$ x 10^3) for CCDC 955873. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(17)	22(2)	8(2)	16(2)	7(1)	-9(1)	0(1)
O(19)	40(3)	11(2)	20(2)	2(2)	-8(2)	2(2)
O(21)	16(2)	14(2)	13(2)	0(1)	1(1)	-4(1)
O(30)	29(2)	15(2)	23(2)	-2(2)	-8(2)	-5(2)
C(1)	22(3)	8(2)	21(2)	8(2)	-13(2)	-3(2)
C(2)	33(3)	15(3)	17(2)	4(2)	-12(2)	-7(2)
C(3)	41(4)	13(3)	17(2)	4(2)	-12(2)	-9(2)
C(4)	28(3)	12(2)	19(3)	8(2)	-9(2)	-9(2)
C(5)	22(3)	13(3)	17(2)	6(2)	-10(2)	-6(2)
C(6)	33(3)	10(3)	32(3)	11(2)	-20(3)	-10(2)
C(7)	29(3)	14(3)	24(3)	-2(2)	-11(2)	-6(2)
C(8)	24(3)	8(2)	24(3)	3(2)	-8(2)	-4(2)
C(9)	15(3)	13(2)	16(2)	2(2)	-5(2)	-6(2)
C(10)	15(2)	7(2)	21(2)	4(2)	-1(2)	-5(2)
C(11)	62(5)	25(3)	29(3)	11(2)	-26(3)	-25(3)
C(12)	20(3)	14(3)	29(3)	9(2)	-10(2)	-3(2)
C(13)	33(3)	19(3)	27(3)	9(2)	-18(3)	-7(2)
C(14)	16(3)	22(3)	17(2)	5(2)	-5(2)	-8(2)
C(15)	24(3)	15(3)	15(2)	6(2)	-8(2)	-6(2)
C(16)	26(3)	18(3)	23(3)	3(2)	-11(2)	0(2)
C(18)	20(3)	23(3)	20(3)	6(2)	-8(2)	-9(2)
C(20)	14(2)	11(2)	12(2)	2(2)	-6(2)	-1(2)
C(22)	15(3)	11(2)	21(2)	2(2)	-5(2)	-5(2)
C(23)	23(3)	6(2)	22(2)	9(2)	-12(2)	-7(2)
C(24)	23(3)	11(2)	22(2)	6(2)	-15(2)	-7(2)
C(25)	15(3)	8(2)	26(3)	5(2)	-8(2)	-4(2)

C(26)	19(3)	13(2)	16(2)	6(2)	-7(2)	-8(2)
C(27)	18(3)	26(3)	26(3)	-1(2)	0(2)	-12(2)
C(28)	25(3)	16(3)	16(2)	-1(2)	-5(2)	-6(2)
C(29)	39(4)	10(3)	26(3)	8(2)	-10(2)	-13(2)

Table 5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for CCDC 955873.

	x	y	z	U(eq)
H(1)	-6425	-8009	4632	20
H(3A)	-4613	-11800	4394	28
H(3B)	-6188	-13255	4691	28
H(4A)	-7396	-12088	6618	23
H(4B)	-4616	-13111	6226	23
H(5)	-7184	-10007	8217	21
H(6A)	-4188	-7840	7463	27
H(6B)	-5611	-7906	8806	27
H(7A)	-7268	-4668	7946	26
H(7B)	-8954	-5988	8366	26
H(8A)	-6377	-5919	6064	22
H(8B)	-9133	-4713	6557	22
H(10)	-4635	-9695	5943	18
H(11A)	-10426	-8779	4132	50
H(11B)	-10497	-10714	5063	50
H(11C)	-8795	-11370	3731	50
H(12)	-2396	-11863	7244	26
H(13A)	-2390(90)	-14100(90)	8570(50)	10(14)
H(13B)	-5190(140)	-13100(120)	8990(70)	40(20)
H(14A)	-11362	-6641	6940	27
H(14B)	-9997	-8292	7833	27
H(14C)	-10303	-9322	6680	27
H(15A)	-11178	-6211	5066	22
H(15B)	-9671	-4775	5128	22
H(16A)	-7497	-6193	3205	29
H(16B)	-9360	-7237	3165	29
H(24A)	-14699	336	355	20
H(24B)	-16130	1528	1659	20
H(25A)	-15139	-1643	2416	20
H(25B)	-13639	-2829	1115	20
H(27A)	-9281	151	1966	34
H(27B)	-8409	400	548	34
H(27C)	-7625	-2047	1097	34
H(28A)	-9981	-850	-761	29
H(28B)	-11614	-2202	-200	29
H(28C)	-8900	-3254	-205	29

H(29A)	-12410	2556	-350	36
H(29B)	-11597	3498	642	36
H(29C)	-14329	4273	723	36

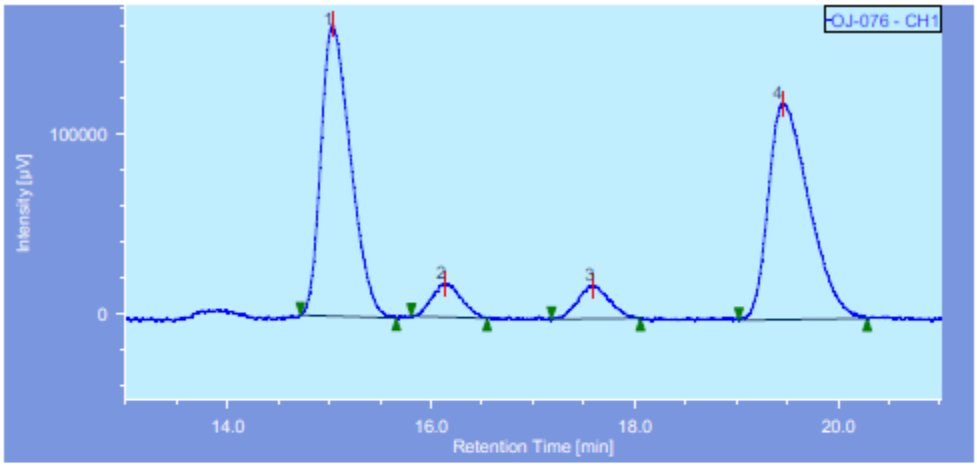
Table 6: Torsion angles [°] for CCDC 955873.

C(15)-C(1)-C(2)-C(11)	-11.7(8)
C(9)-C(1)-C(2)-C(11)	116.9(6)
C(15)-C(1)-C(2)-C(3)	170.7(4)
C(9)-C(1)-C(2)-C(3)	-60.7(6)
C(11)-C(2)-C(3)-C(4)	-119.8(6)
C(1)-C(2)-C(3)-C(4)	57.9(6)
C(2)-C(3)-C(4)-C(10)	-55.2(7)
C(12)-C(5)-C(6)-C(7)	177.3(5)
C(10)-C(5)-C(6)-C(7)	54.6(6)
C(5)-C(6)-C(7)-C(8)	-54.3(7)
C(6)-C(7)-C(8)-C(9)	56.3(7)
C(7)-C(8)-C(9)-C(14)	66.2(6)
C(7)-C(8)-C(9)-C(1)	-172.6(5)
C(7)-C(8)-C(9)-C(10)	-56.7(6)
C(2)-C(1)-C(9)-C(14)	-64.3(5)
C(15)-C(1)-C(9)-C(14)	65.5(6)
C(2)-C(1)-C(9)-C(8)	173.6(5)
C(15)-C(1)-C(9)-C(8)	-56.6(6)
C(2)-C(1)-C(9)-C(10)	57.1(5)
C(15)-C(1)-C(9)-C(10)	-173.1(4)
C(3)-C(4)-C(10)-C(5)	-175.2(5)
C(3)-C(4)-C(10)-C(9)	58.2(6)
C(12)-C(5)-C(10)-C(4)	53.6(6)
C(6)-C(5)-C(10)-C(4)	176.3(4)
C(12)-C(5)-C(10)-C(9)	-179.5(4)
C(6)-C(5)-C(10)-C(9)	-56.8(6)
C(14)-C(9)-C(10)-C(4)	61.7(6)
C(8)-C(9)-C(10)-C(4)	-176.2(4)
C(1)-C(9)-C(10)-C(4)	-57.7(5)
C(14)-C(9)-C(10)-C(5)	-65.3(6)
C(8)-C(9)-C(10)-C(5)	56.7(5)
C(1)-C(9)-C(10)-C(5)	175.3(4)
C(6)-C(5)-C(12)-C(13)	112.8(7)
C(10)-C(5)-C(12)-C(13)	-124.7(7)
C(2)-C(1)-C(15)-C(16)	-67.8(6)
C(9)-C(1)-C(15)-C(16)	165.3(5)
C(18)-O(17)-C(16)-C(15)	-169.3(5)
C(1)-C(15)-C(16)-O(17)	-170.5(5)
C(16)-O(17)-C(18)-O(19)	2.1(9)
C(16)-O(17)-C(18)-C(20)	-176.8(5)
C(22)-O(21)-C(20)-C(18)	158.7(4)
C(22)-O(21)-C(20)-C(25)	-73.8(5)
C(22)-O(21)-C(20)-C(26)	34.3(5)
O(19)-C(18)-C(20)-O(21)	-165.1(6)
O(17)-C(18)-C(20)-O(21)	13.8(7)
O(19)-C(18)-C(20)-C(25)	72.8(7)
O(17)-C(18)-C(20)-C(25)	-108.3(5)
O(19)-C(18)-C(20)-C(26)	-48.5(8)
O(17)-C(18)-C(20)-C(26)	130.4(5)
C(20)-O(21)-C(22)-O(30)	179.5(5)

C(20)-O(21)-C(22)-C(23)	2.0(5)
O(30)-C(22)-C(23)-C(29)	19.0(9)
O(21)-C(22)-C(23)-C(29)	-163.8(5)
O(30)-C(22)-C(23)-C(24)	-108.9(7)
O(21)-C(22)-C(23)-C(24)	68.3(5)
O(30)-C(22)-C(23)-C(26)	145.5(6)
O(21)-C(22)-C(23)-C(26)	-37.3(5)
C(22)-C(23)-C(24)-C(25)	-67.5(5)
C(29)-C(23)-C(24)-C(25)	165.7(5)
C(26)-C(23)-C(24)-C(25)	35.0(5)
O(21)-C(20)-C(25)-C(24)	69.6(4)
C(18)-C(20)-C(25)-C(24)	-165.3(4)
C(26)-C(20)-C(25)-C(24)	-37.7(5)
C(23)-C(24)-C(25)-C(20)	1.7(5)
C(22)-C(23)-C(26)-C(27)	-62.8(5)
C(29)-C(23)-C(26)-C(27)	60.8(6)
C(24)-C(23)-C(26)-C(27)	-169.7(4)
C(22)-C(23)-C(26)-C(28)	170.4(5)
C(29)-C(23)-C(26)-C(28)	-66.0(6)
C(24)-C(23)-C(26)-C(28)	63.5(5)
C(22)-C(23)-C(26)-C(20)	52.4(4)
C(29)-C(23)-C(26)-C(20)	176.1(5)
C(24)-C(23)-C(26)-C(20)	-54.4(4)
O(21)-C(20)-C(26)-C(27)	62.8(5)
C(18)-C(20)-C(26)-C(27)	-59.1(6)
C(25)-C(20)-C(26)-C(27)	173.1(4)
O(21)-C(20)-C(26)-C(28)	-170.6(4)
C(18)-C(20)-C(26)-C(28)	67.5(6)
C(25)-C(20)-C(26)-C(28)	-60.3(5)
O(21)-C(20)-C(26)-C(23)	-53.8(4)
C(18)-C(20)-C(26)-C(23)	-175.7(5)
C(25)-C(20)-C(26)-C(23)	56.5(4)

Symmetry transformations used to generate equivalent atoms:

5.2 SFC Data for Compound 218



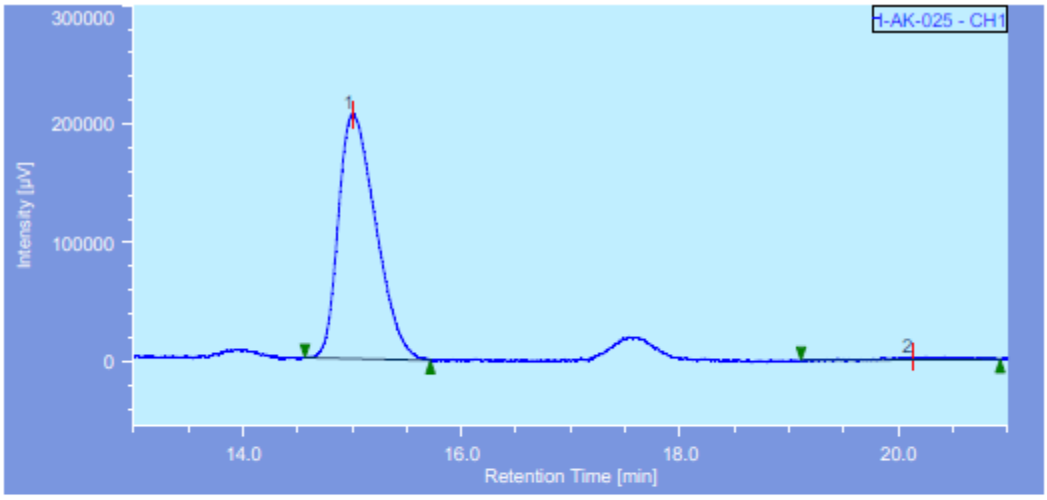
Chromatogram Information

User Name	sfc
Date Modified	22.03.2013 15:21:09
Description	
HPLC System Name	Jasco SFC
Injection Date	22.03.2013 11:53:38
Volume	10.00 [µL]
Sample Number	1
Project Name	EMC-SFC
Acquisition Time	30.0 [min]
Acquisition Sequence	OJ-22.3.13
Control Method	column1-98CO2-25C-flow2-30min
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	OJ-076-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	15.033	3272570	162195	44.153	50.729	N/A	12473	2.047	1.361	
2	Unknown	1	16.142	375565	18549	5.067	5.801	N/A	13901	2.604	1.131	
3	Unknown	1	17.600	401590	18519	5.418	5.792	N/A	14965	2.827	1.013	
4	Unknown	1	19.450	3362205	120469	45.362	37.678	N/A	11155	N/A	1.532	

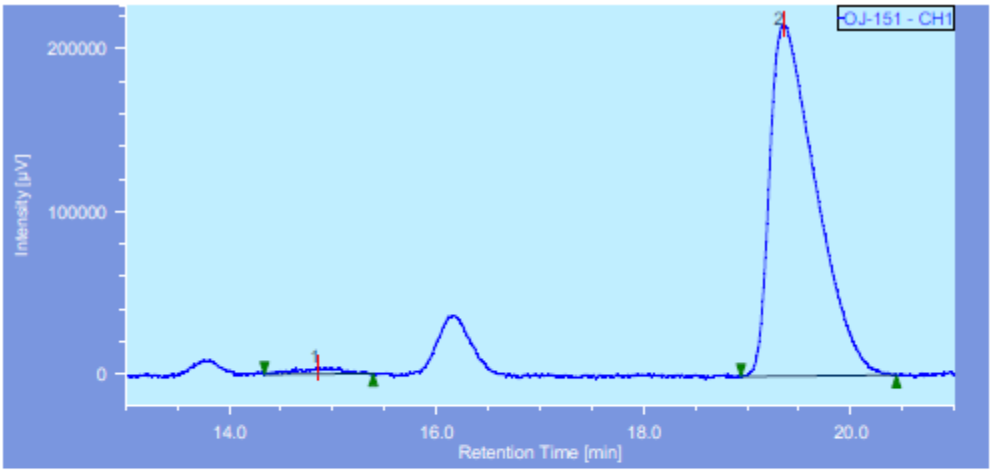


Chromatogram Information	
User Name	sfc
Date Modified	22.03.2013 15:59:07
Description	
HPLC System Name	Jasco SFC
Injection Date	22.03.2013 12:25:14
Volume	10.00 [µL]
Sample Number	2
Project Name	EMC-SFC
Acquisition Time	30.0 [min]
Acquisition Sequence	OJ-22.3.13
Control Method	column1-98CO2-25C-flow2-30min
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	I-AK-025-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	15.008	4896179	205921	98.248	98.913	N/A	8855	3.426	1.403	
2	Unknown	1	20.125	87320	2264	1.752	1.087	N/A	1167	N/A	0.901	



Chromatogram Information

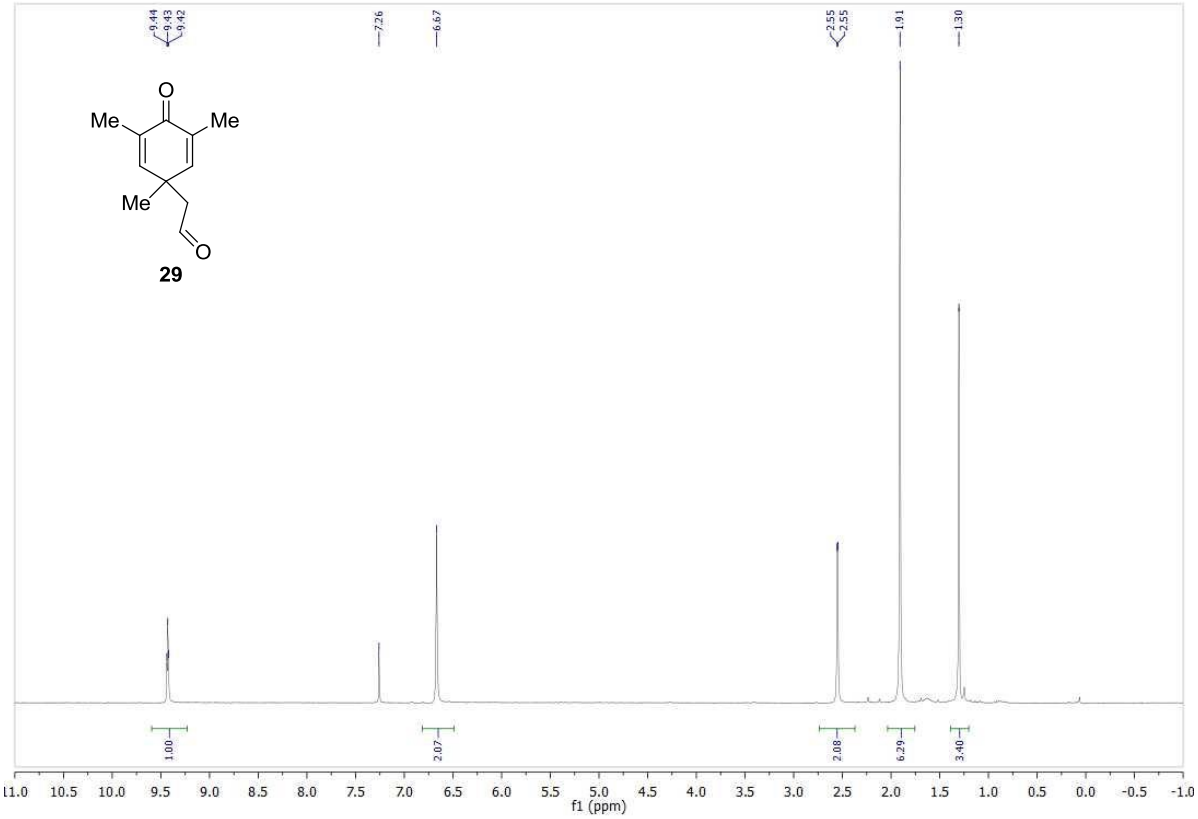
User Name	sfc
Date Modified	22.03.2013 15:20:13
Description	
HPLC System Name	Jasco SFC
Injection Date	22.03.2013 13:24:07
Volume	10.00 [µL]
Sample Number	3
Project Name	EMC-SFC
Acquisition Time	30.0 [min]
Acquisition Sequence	OJ-22.3.13
Control Method	column1-98CO2-25C-flow2-30min
Peak ID Table	
Calibration Method	
Additional Information	

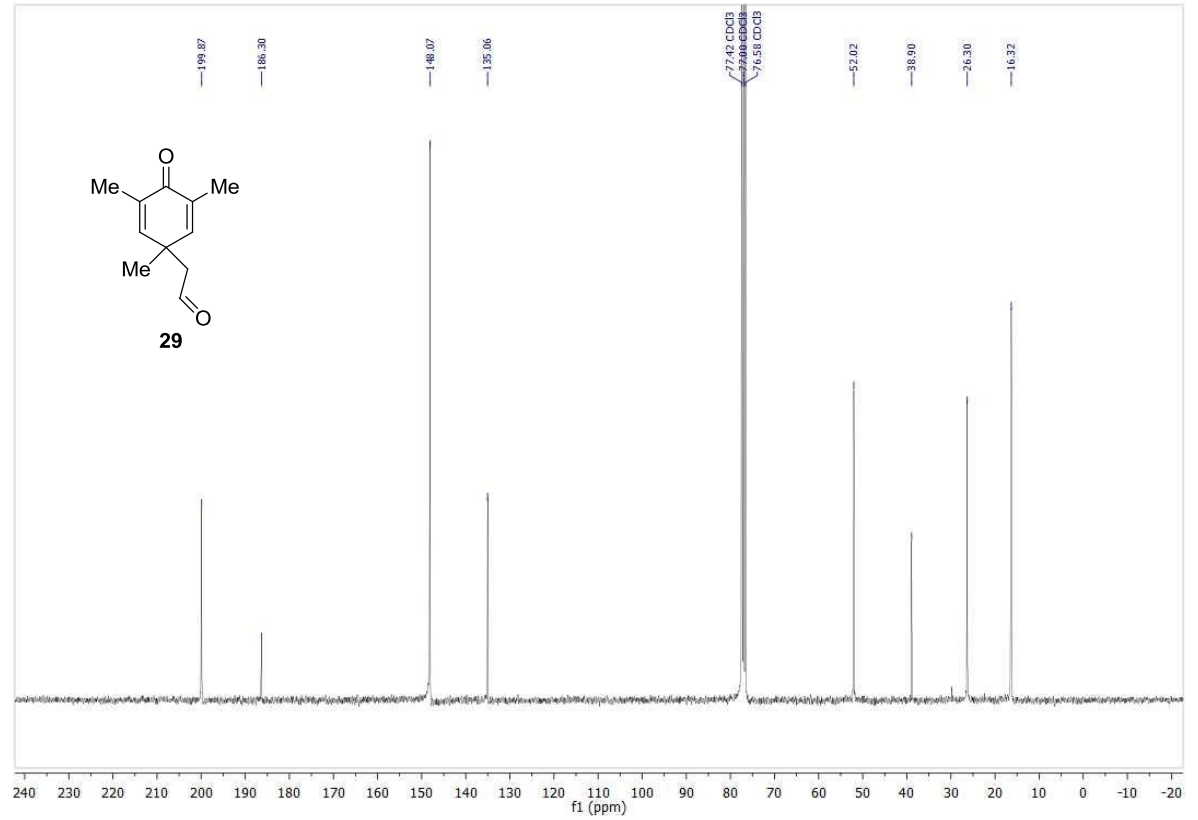
Channel & Peak Information Table

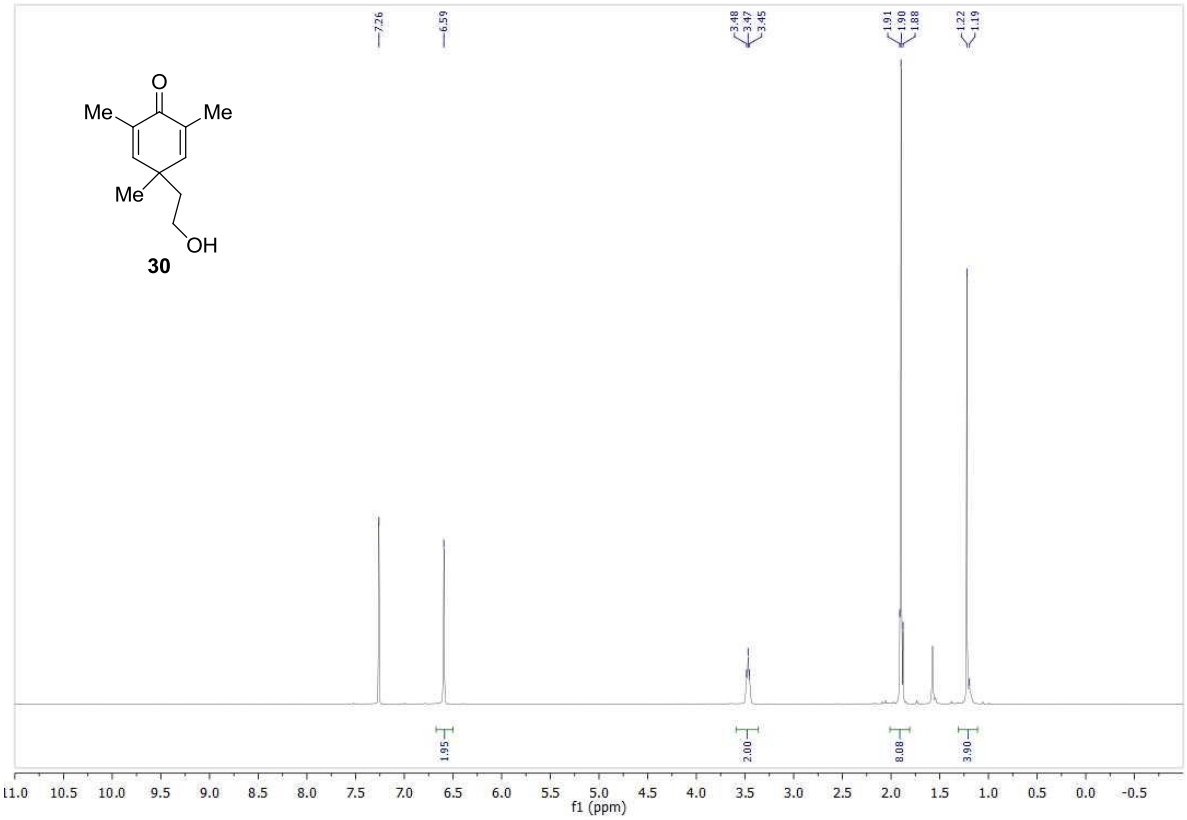
Chromatogram Name	OJ-151-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	14.867	113012	3772	1.660	1.714	N/A	2954	4.686	0.997	
2	Unknown	1	19.350	6695584	216350	98.340	98.286	N/A	8813	N/A	1.948	

5.3 NMR Spectra



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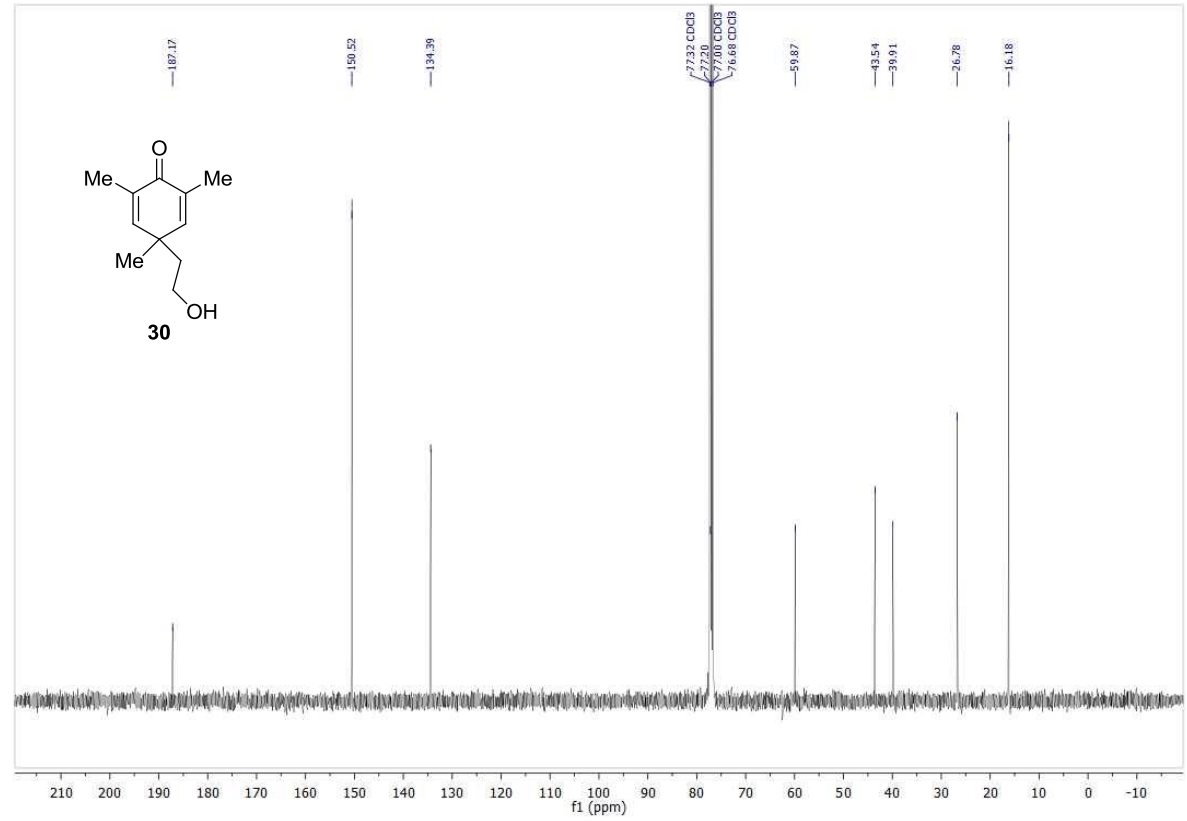
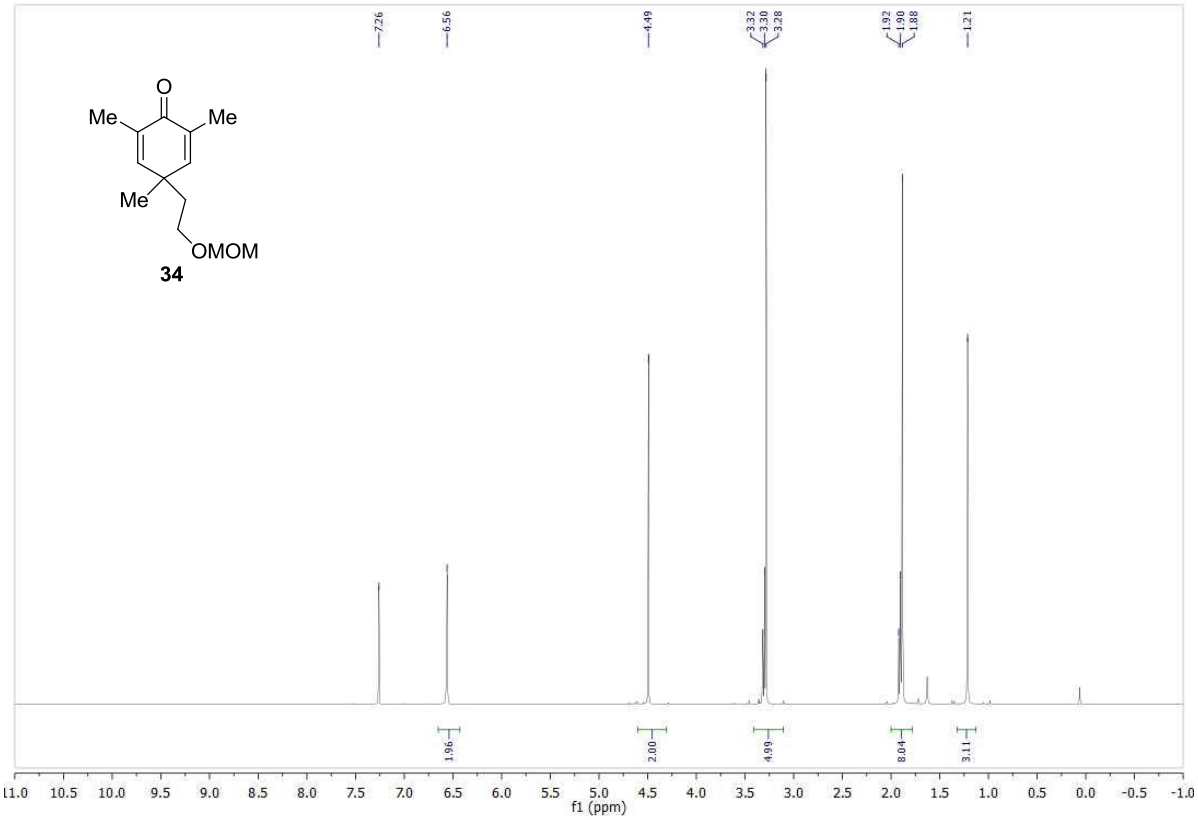
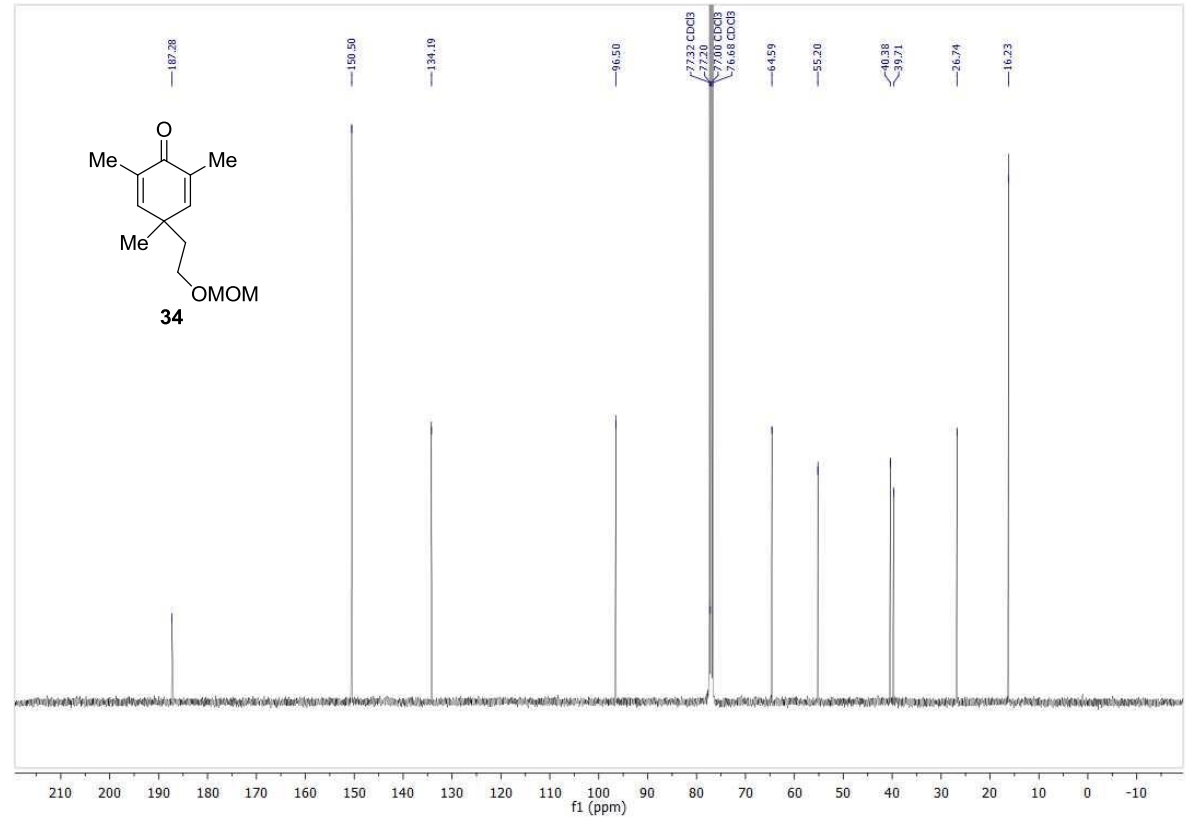
6.59
3.48
3.47
3.45
1.91
1.90
1.88
1.22
1.19
Me
Me
Me
O
OH
30
1.95
2.00
8.08
3.90
f1 (ppm)


187.17
150.52
134.39
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
59.87
43.54
39.91
26.78
16.18
Me
Me
Me
O
OH
30
f1 (ppm)


7.26
6.56
4.49
3.32
3.30
3.28
1.92
1.90
1.88
1.21
O
Me
Me
Me
OMOM
34
1.96
2.00
4.99
8.04
3.11
f1 (ppm)


187.28
150.50
134.19
96.50
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
64.59
55.20
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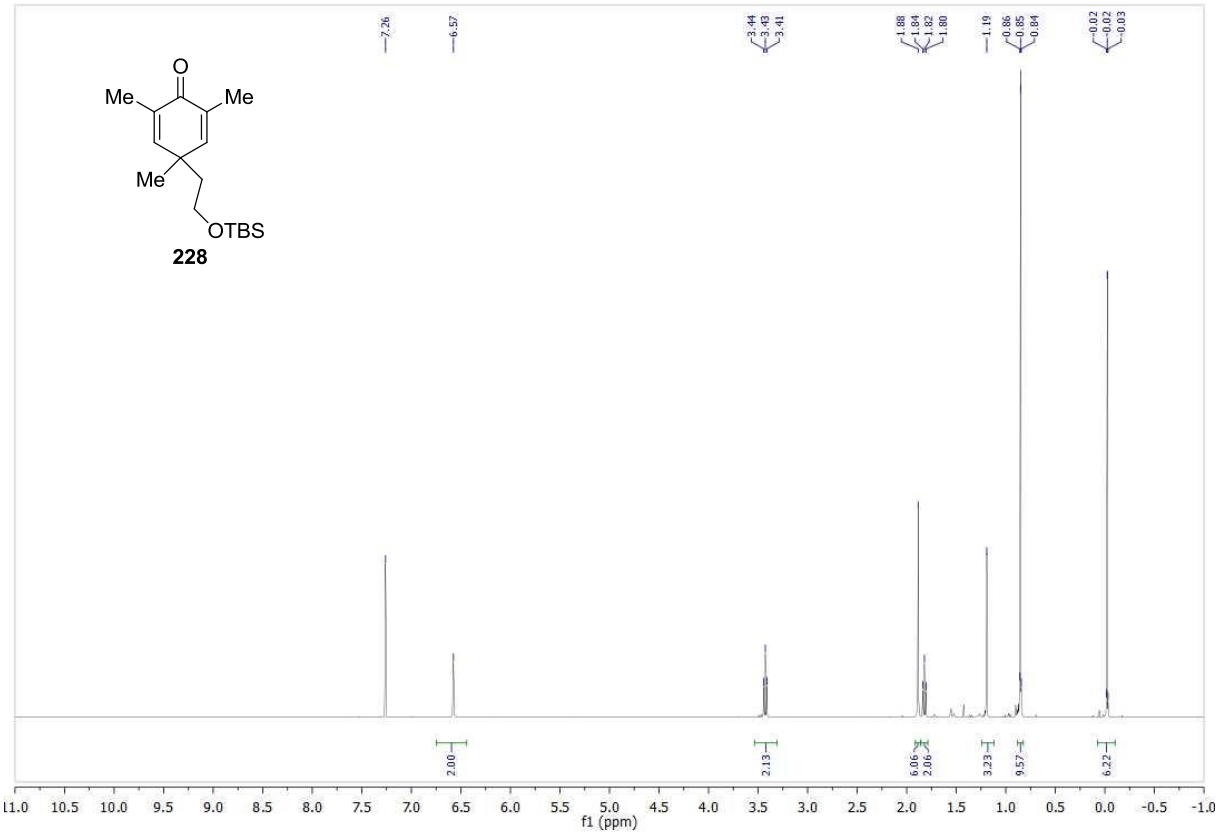
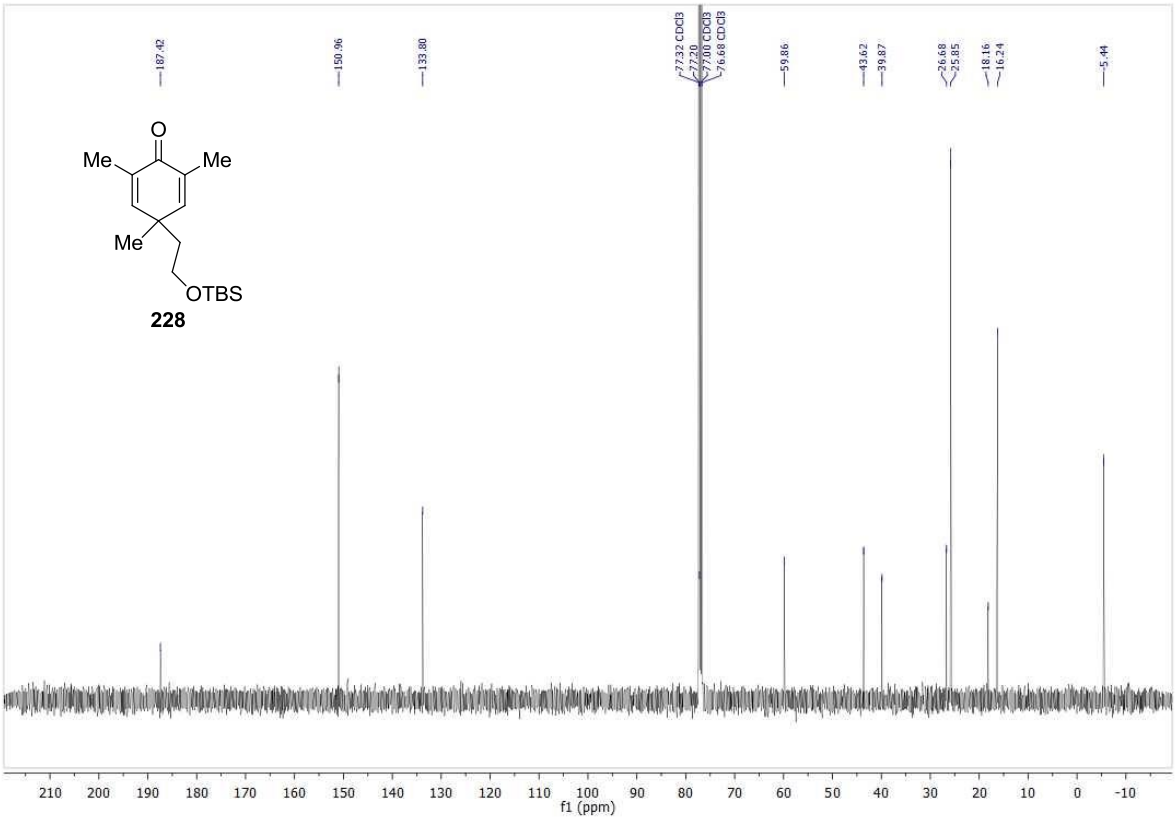
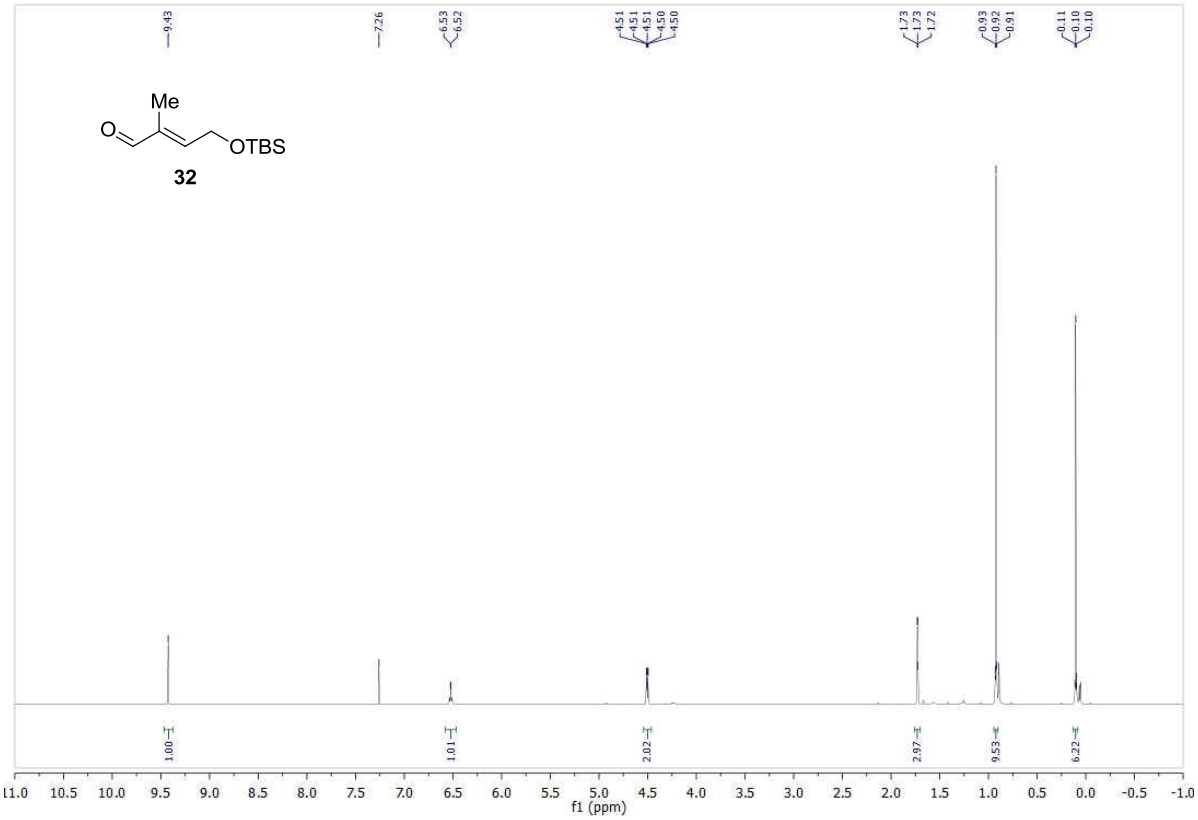
39.71
26.74
16.23
O
Me
Me
Me
OMOM
34
f1 (ppm)


Me
Me
Me
O
OTBS
228
7.26
6.57
3.44
3.43
3.41
1.88
1.84
1.82
1.80
1.19
0.86
0.85
0.84
0.02
0.02
0.03
2.00
2.13
6.06
2.06
3.23
9.57
6.22
f1 (ppm)


Me
Me
Me
O
OTBS
228
187.42
150.96
133.80
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
59.86
43.62
39.87
26.68
25.85
18.16
16.24
-5.44
f1 (ppm)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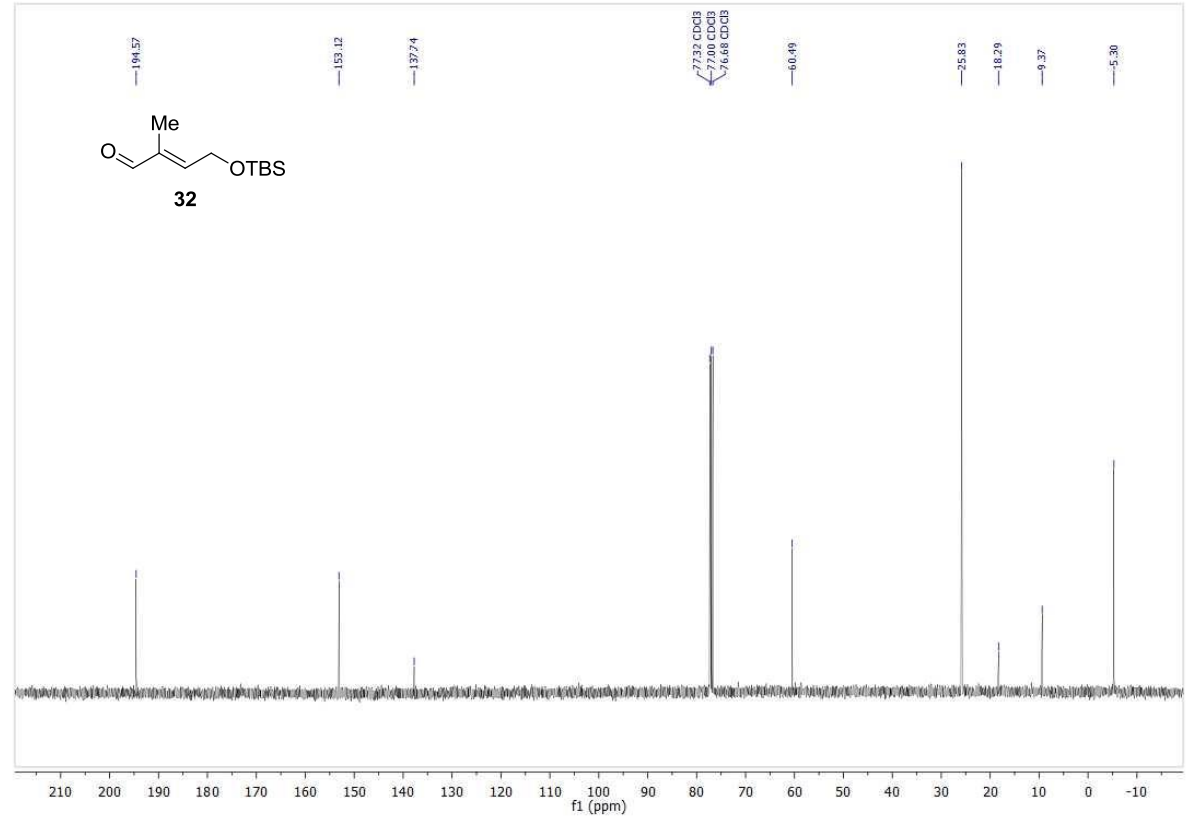
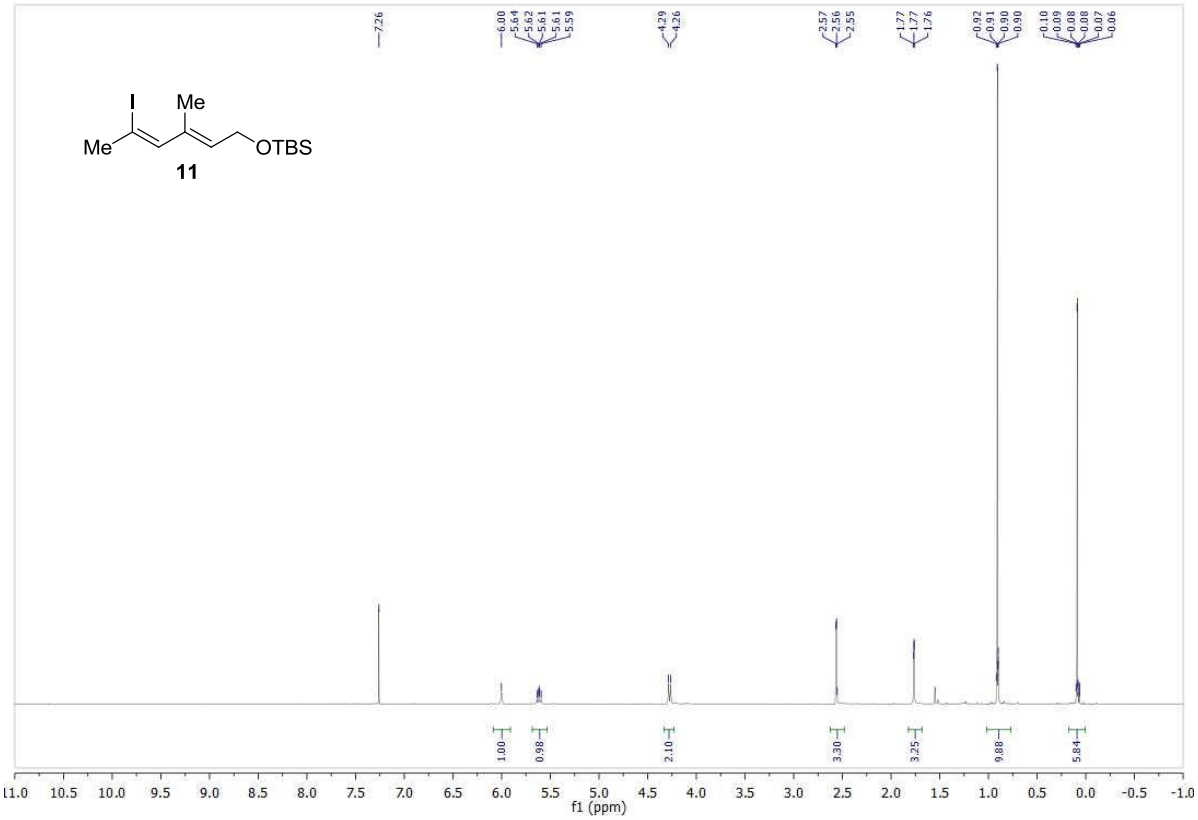
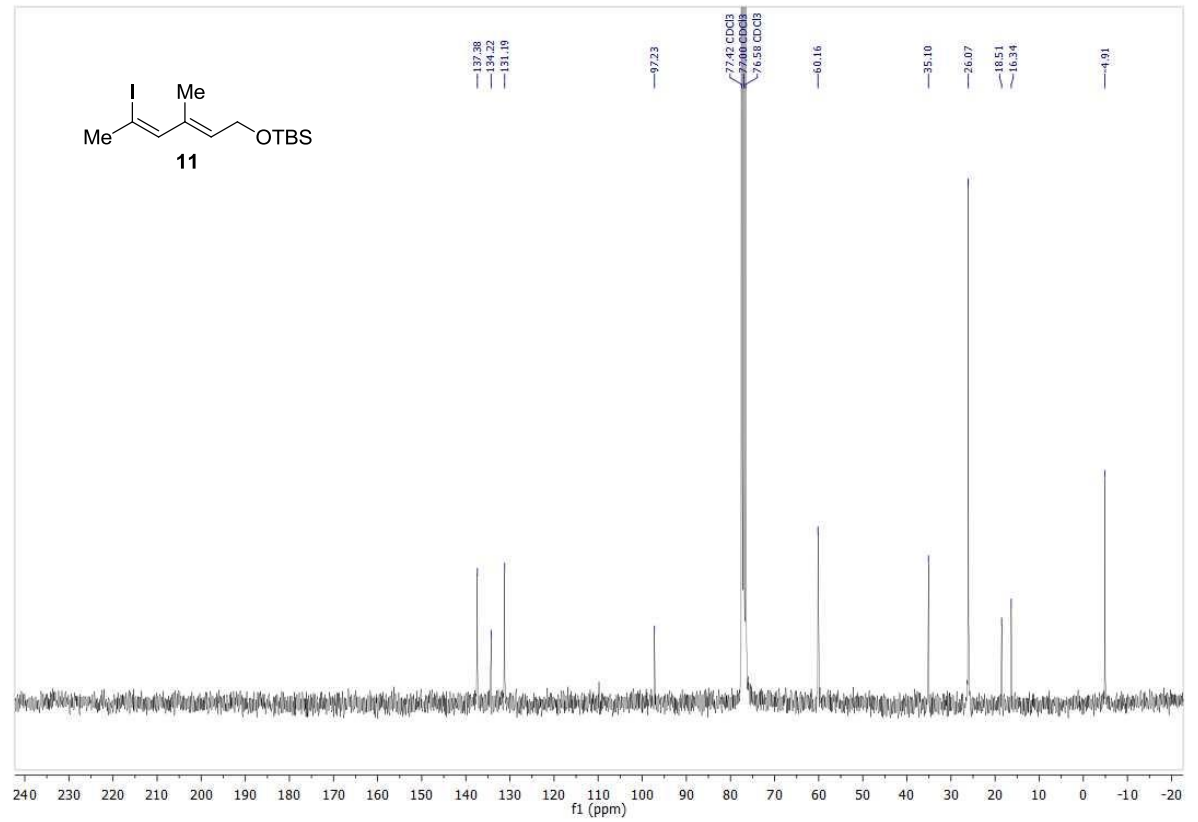
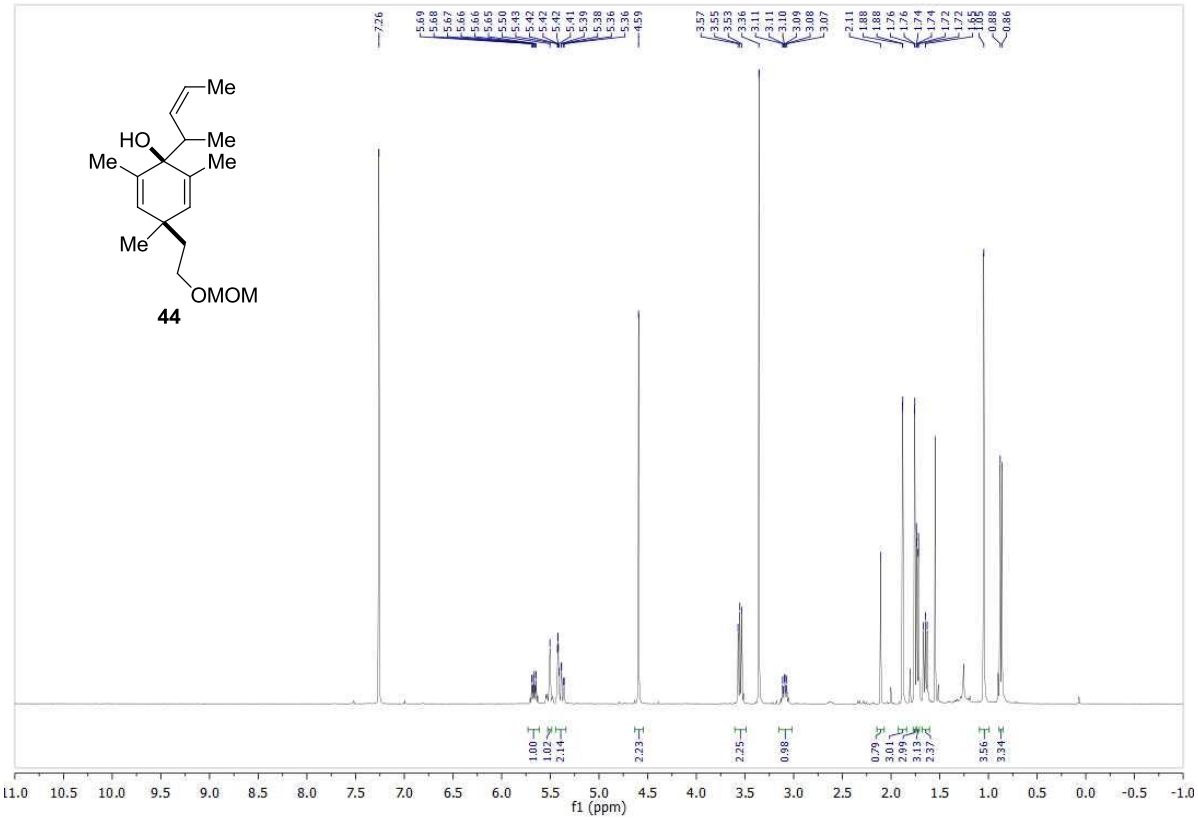
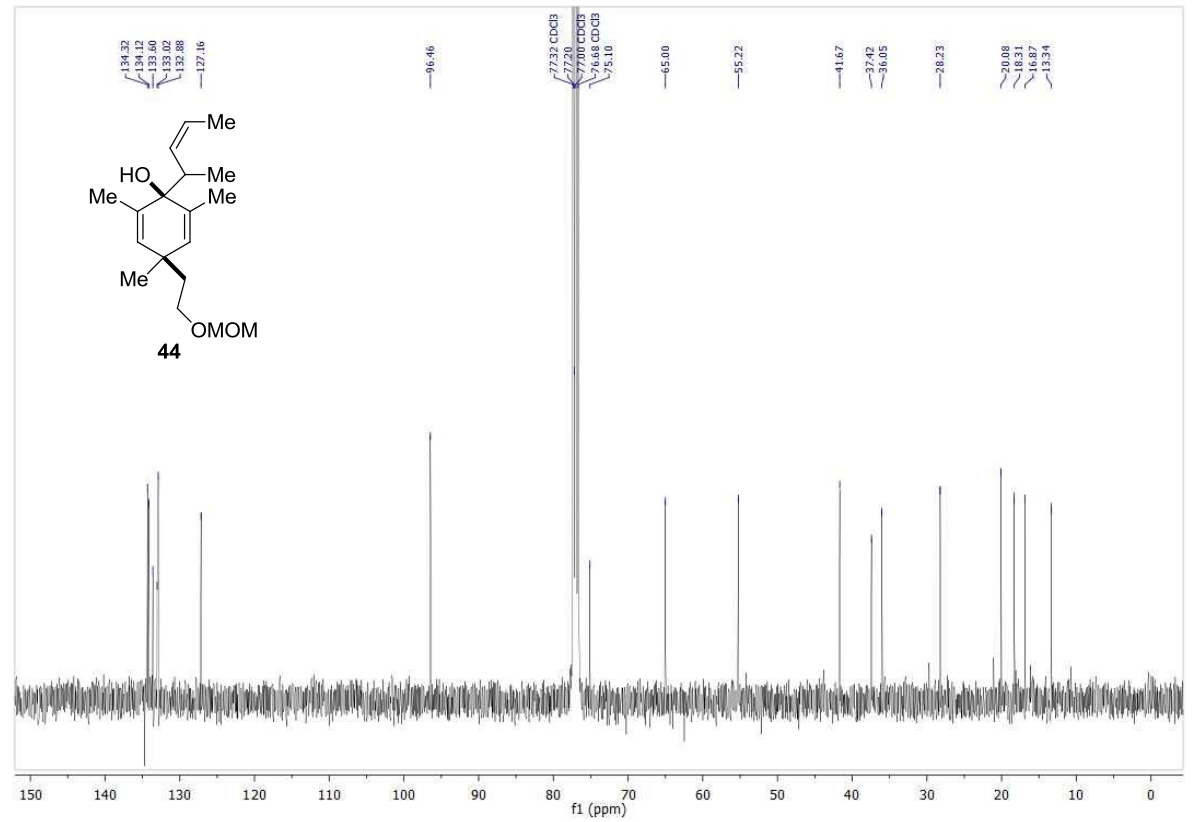
7.26
6.53
6.52
4.51
4.51
4.51
4.50
4.50
1.73
1.73
1.72
0.93
0.92
0.91
0.11
0.10
0.10
Me
O
OTBS
32
1.00
1.01
2.02
2.97
9.53
6.22
f1 (ppm)

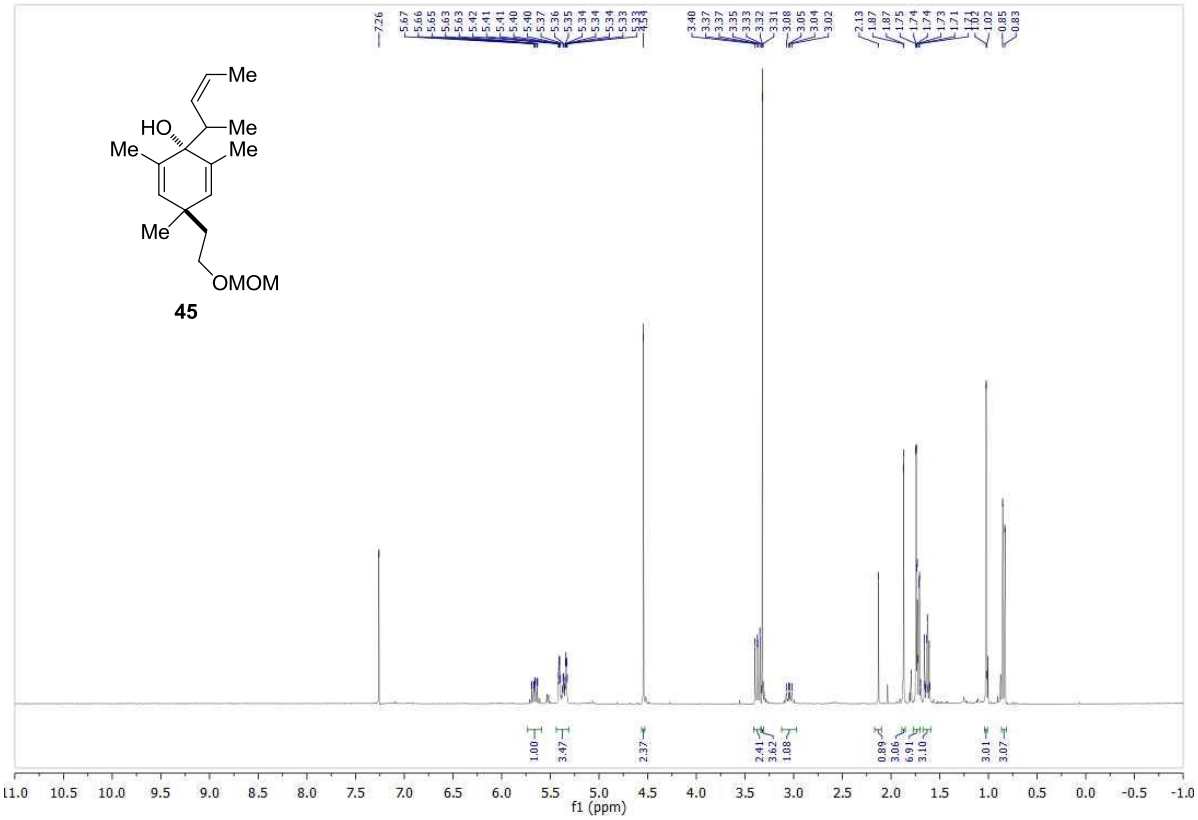

194.57
153.12
137.74
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
60.49
25.83
18.29
9.37
-5.30
Me
O
OTBS
32
f1 (ppm)

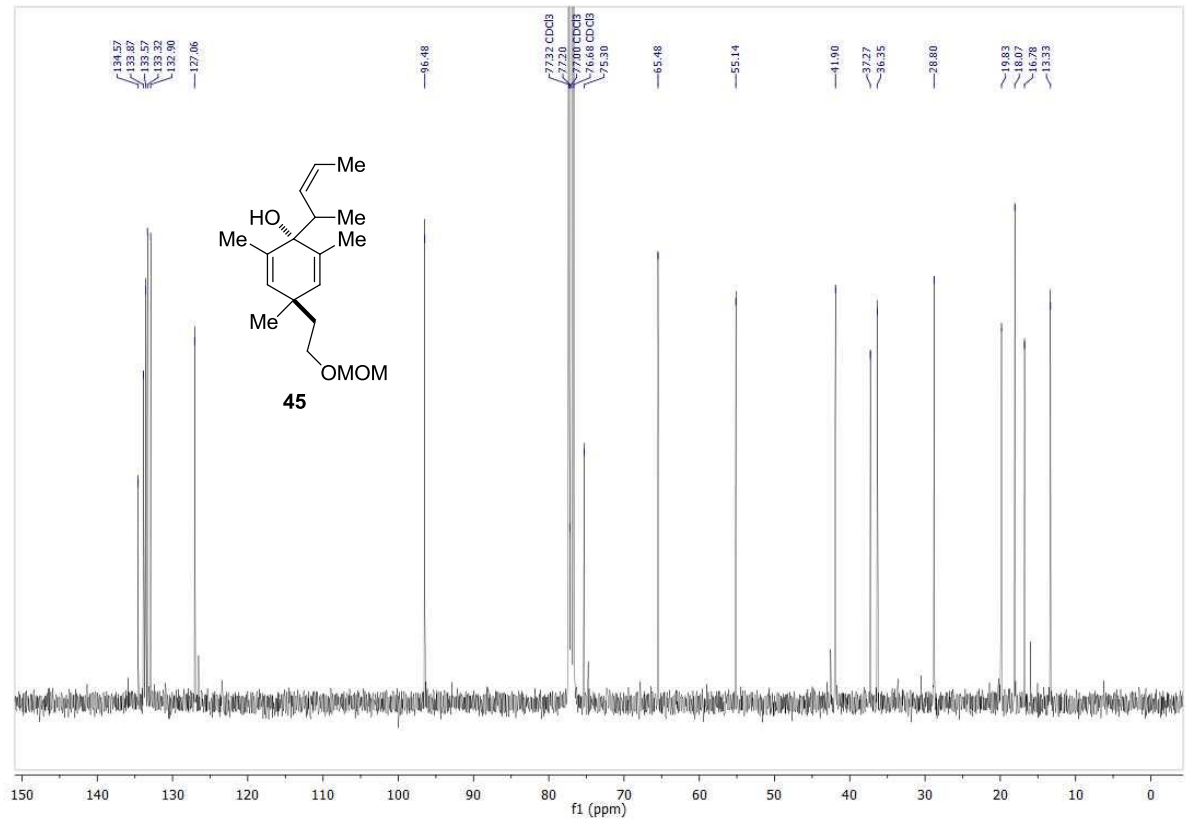

Me
I
Me
OTBS
11
f1 (ppm)

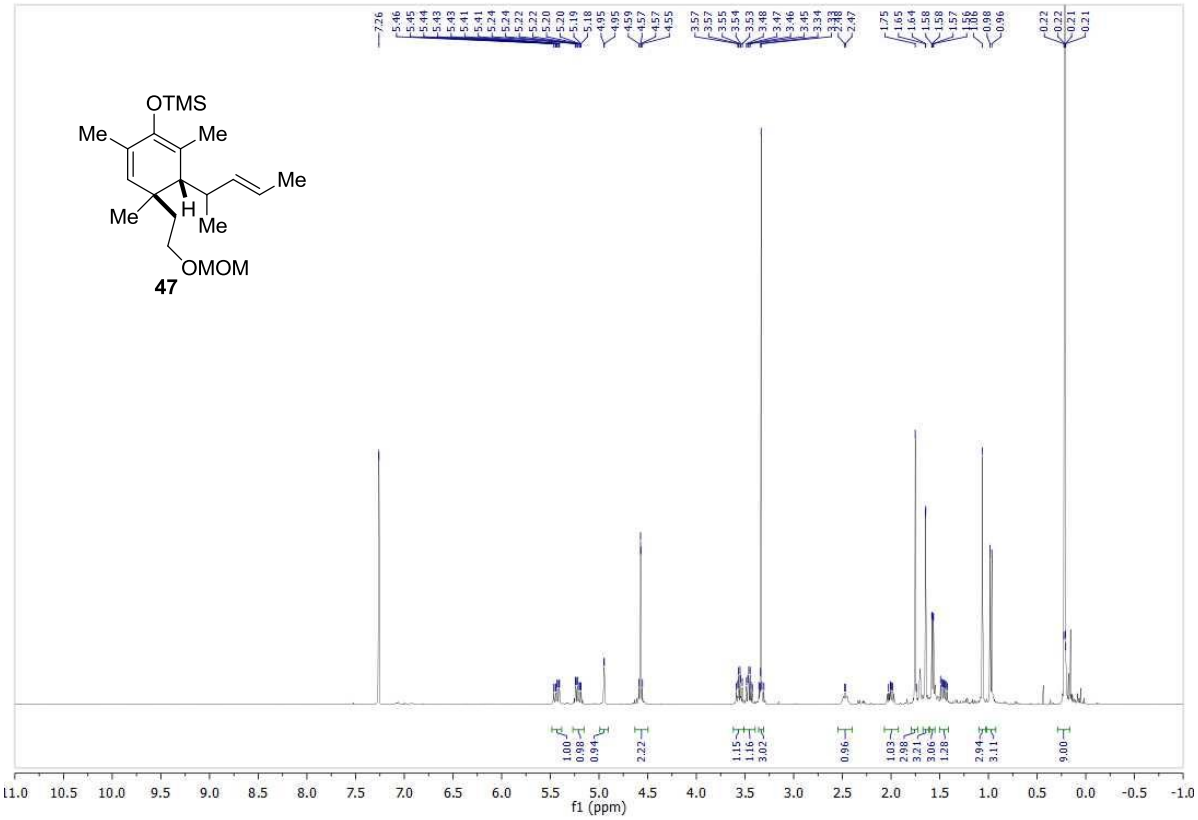

Me
I
Me
OTBS
11
f1 (ppm)

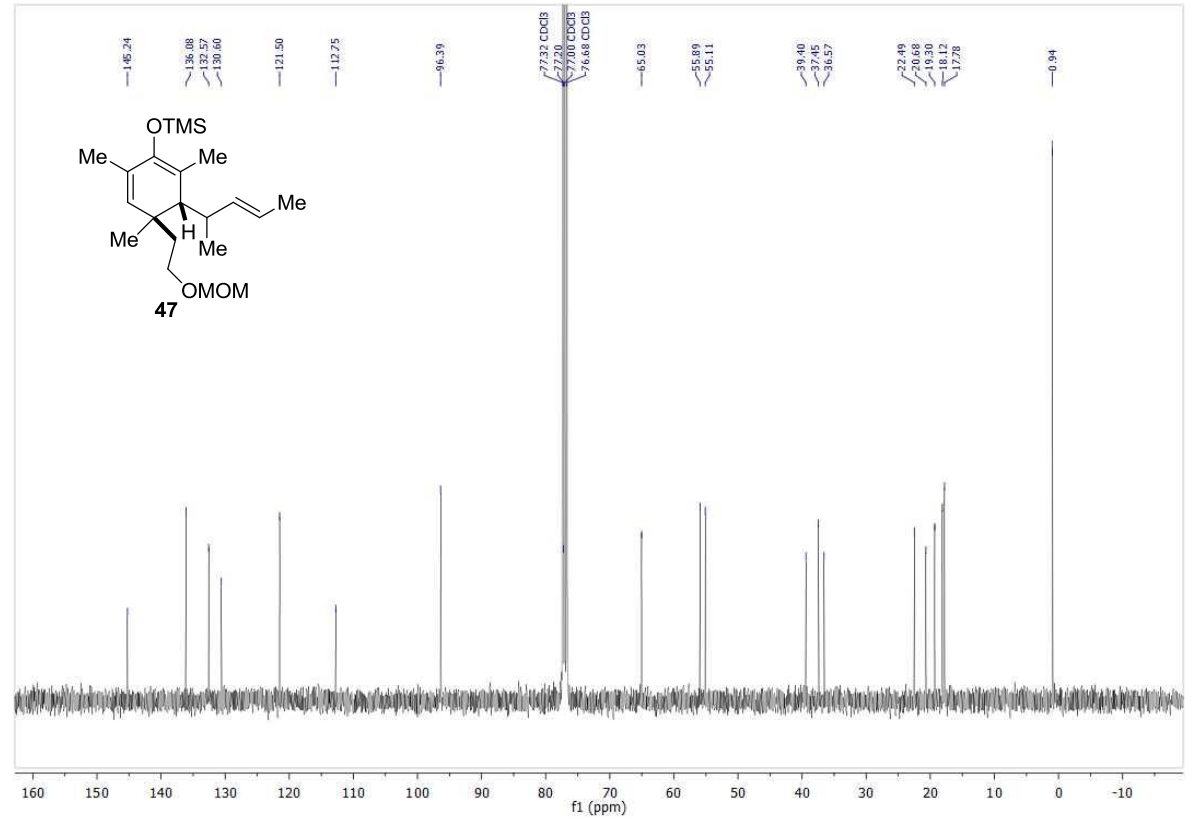

Me
HO
Me
Me
Me
Me
OMOM
44
f1 (ppm)

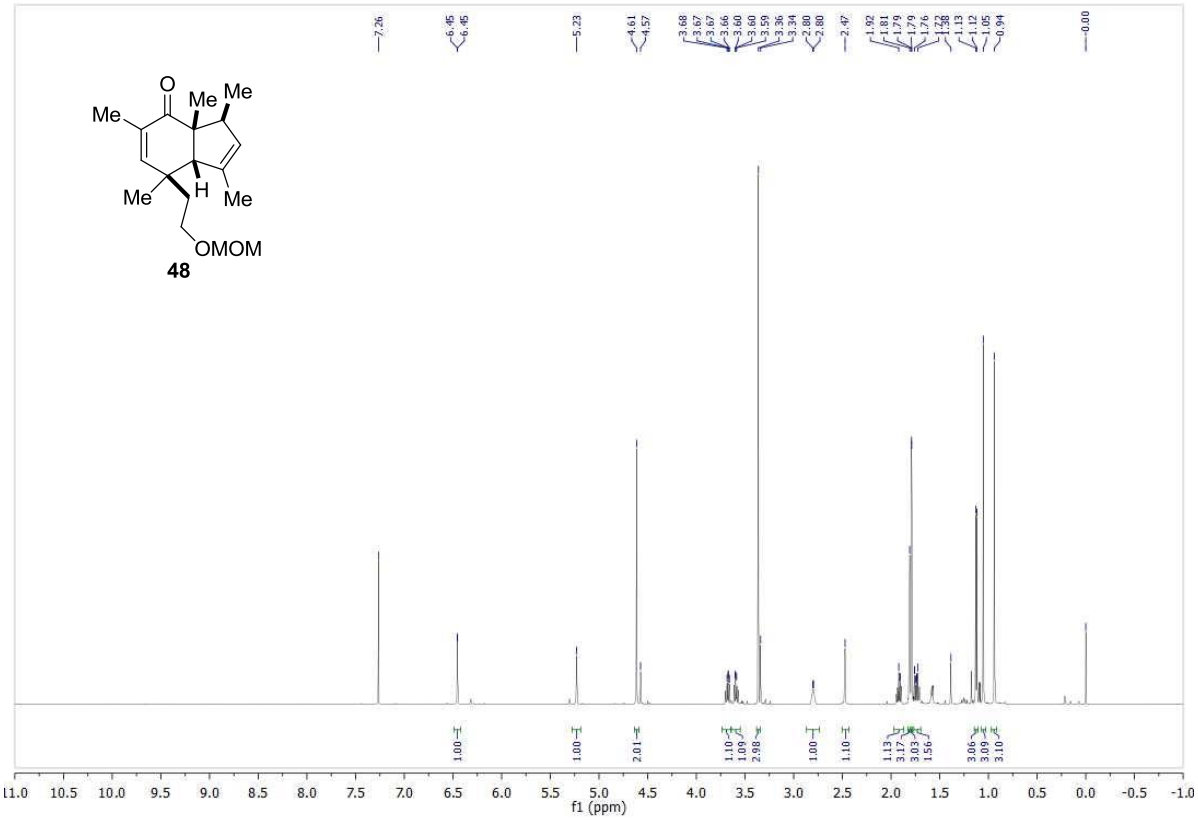

Me
HO
Me
Me
Me
Me
OMOM
44
f1 (ppm)

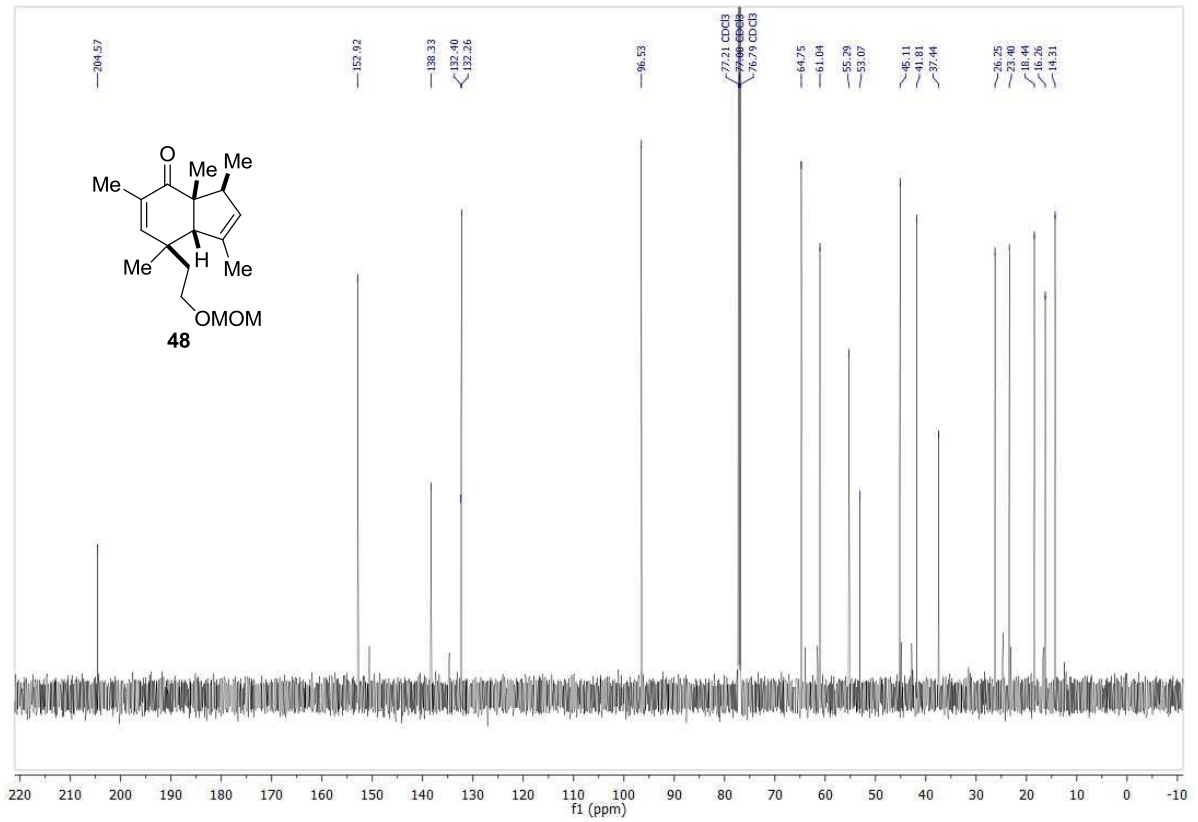

Me
HO
Me
Me
Me
Me
OMOM
45
f1 (ppm)

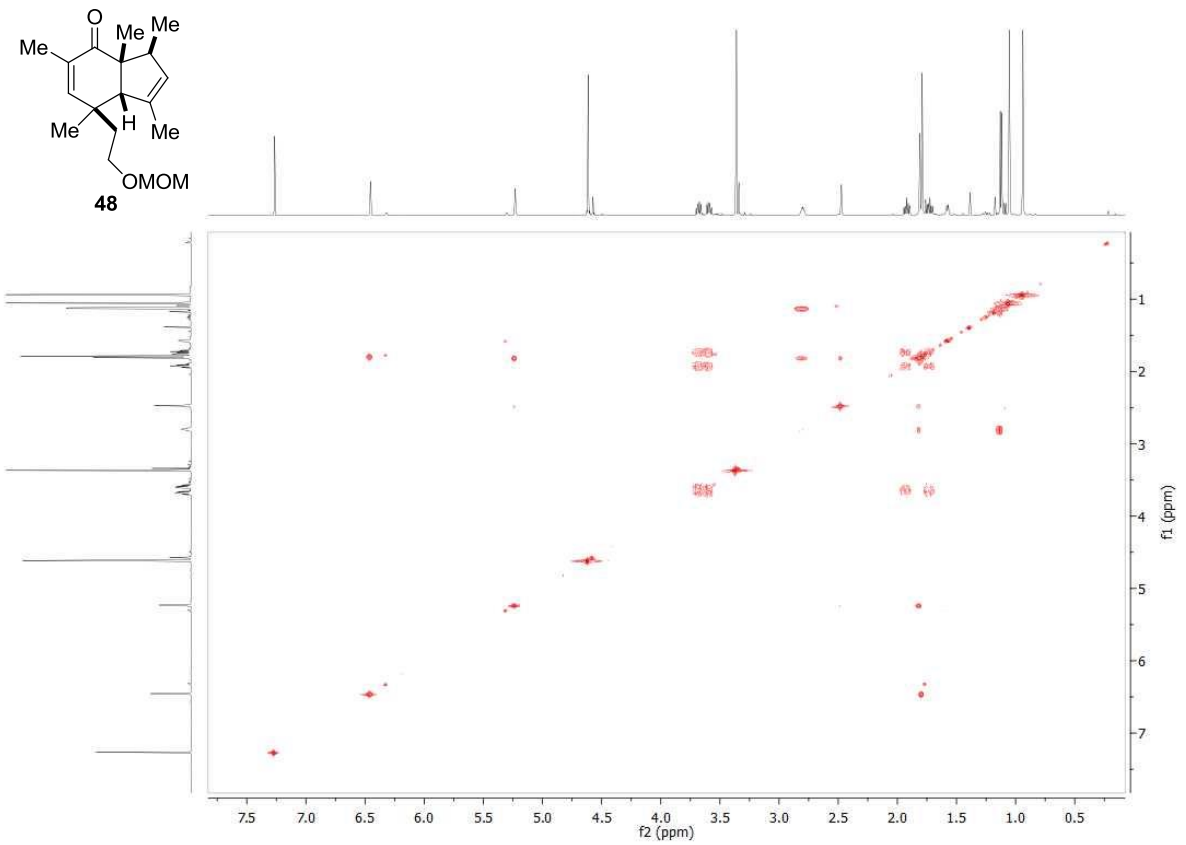

Me
HO
Me
Me
Me
Me
OMOM
45
f1 (ppm)

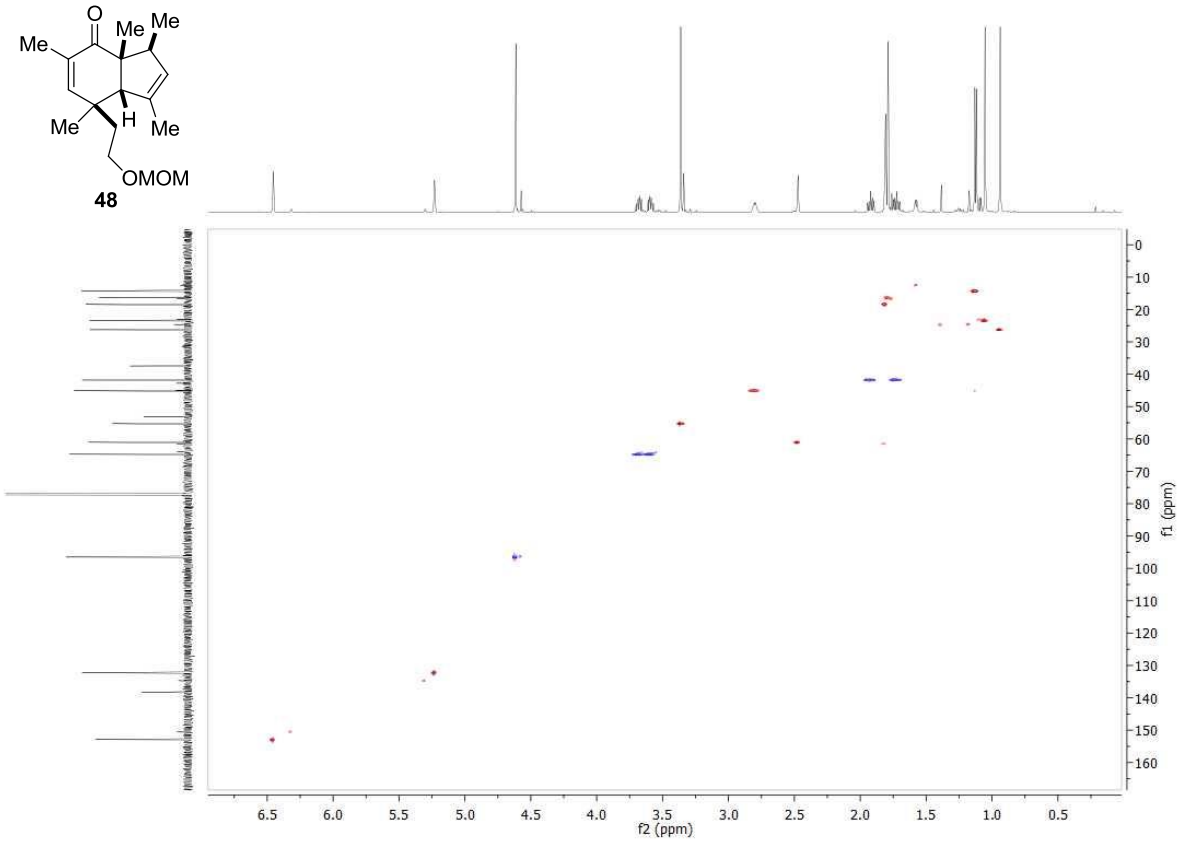

OTMS
Me
Me
Me
H
Me
Me
OMOM
47
f1 (ppm)

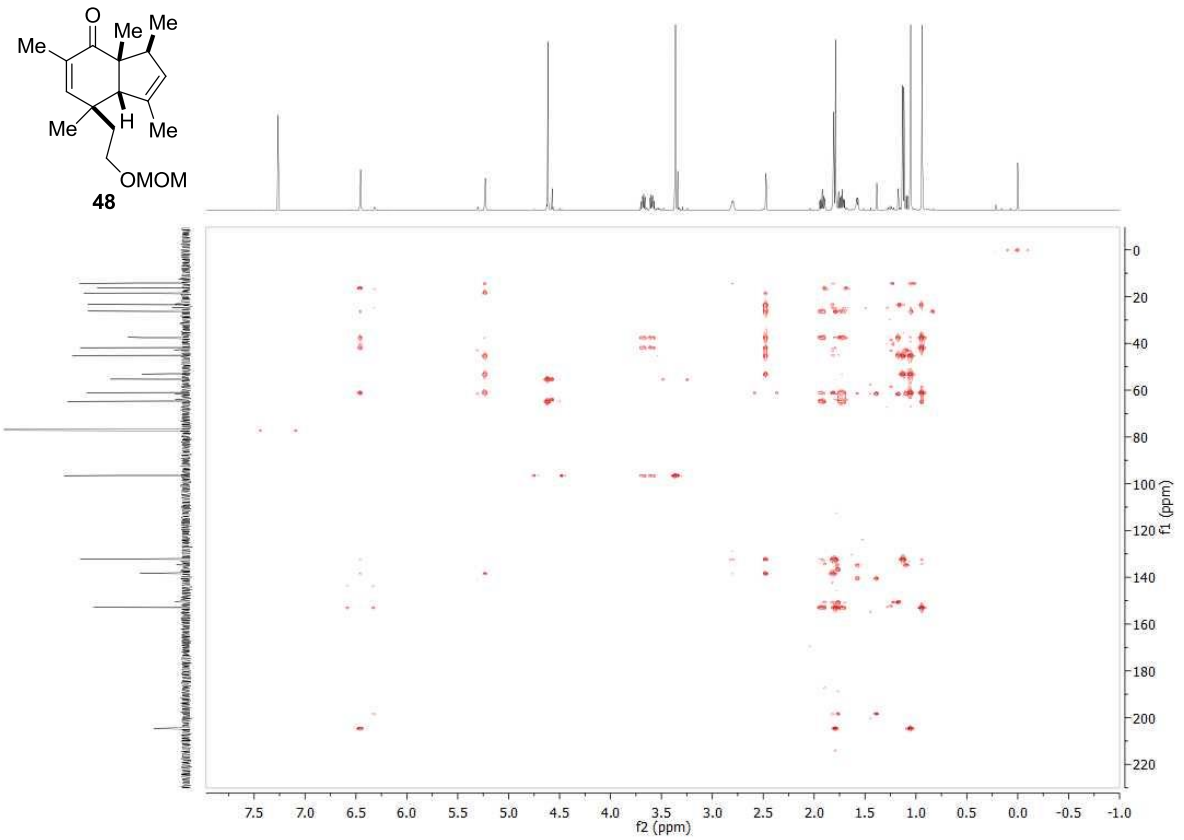

OTMS
Me
Me
Me
H
Me
Me
OMOM
47
f1 (ppm)

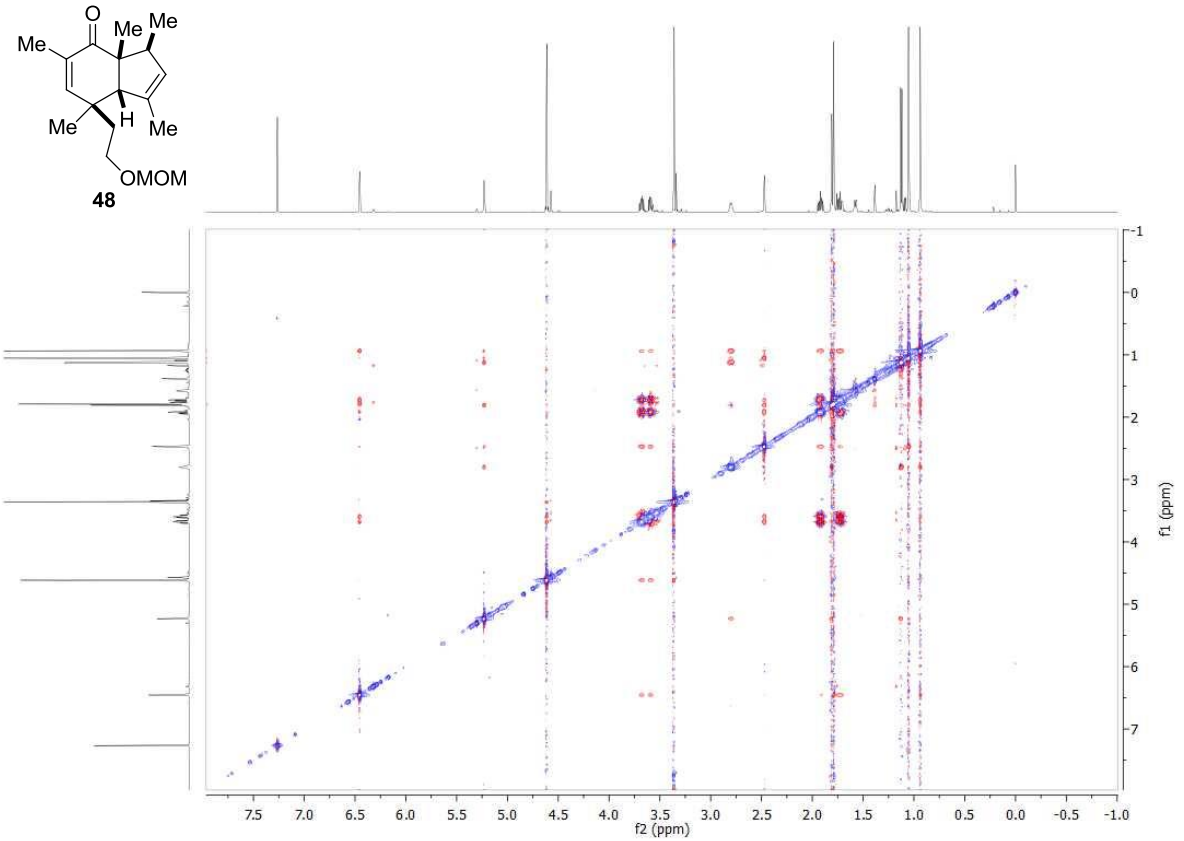

O
Me
Me
Me
Me
H
Me
OMOM
48
f1 (ppm)

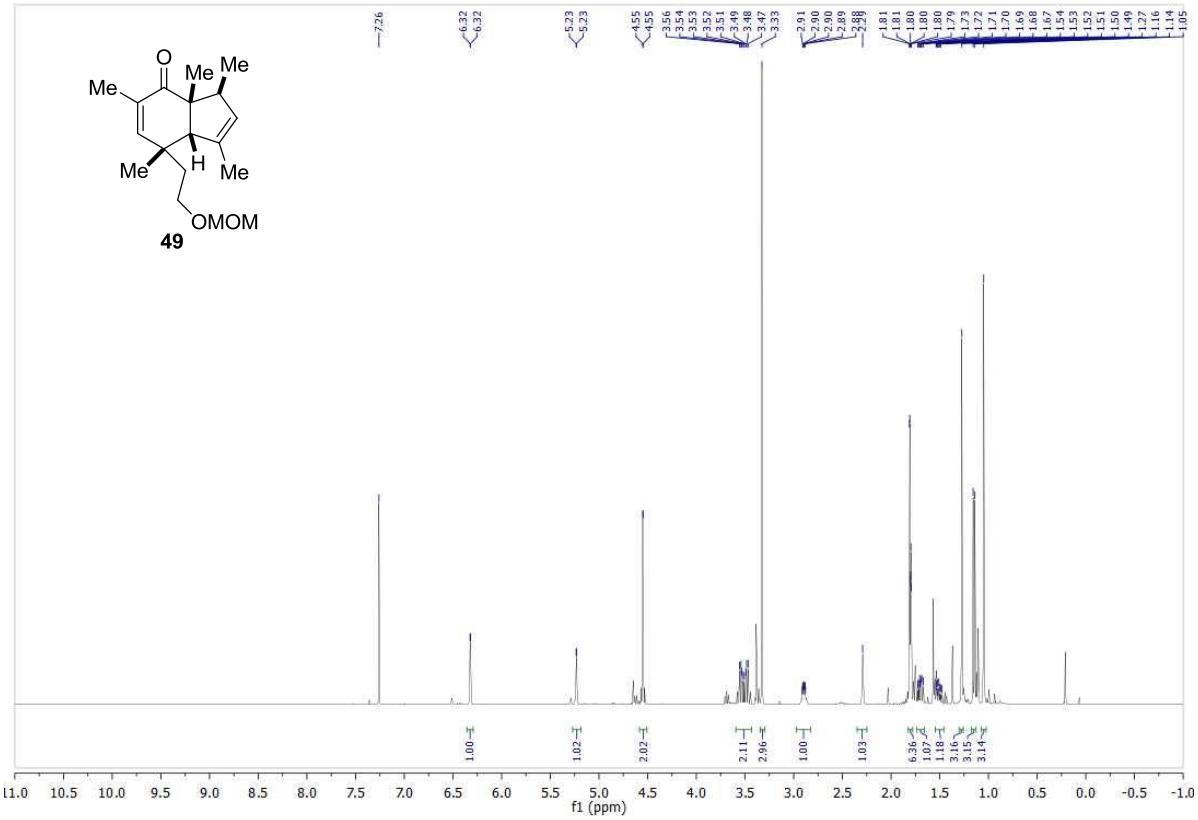

O
Me
Me
Me
Me
H
Me
OMOM
48
f1 (ppm)

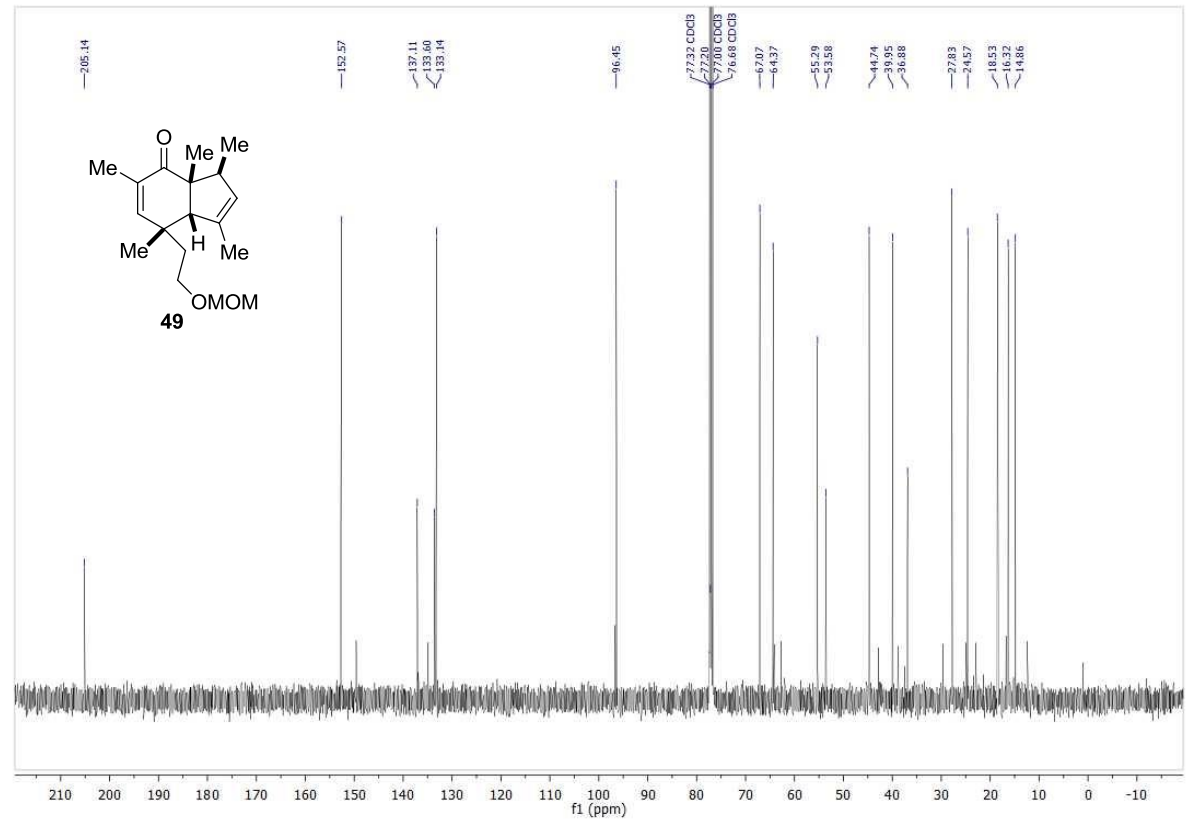

O
Me
Me
Me
Me
H
Me
OMOM
48
f2 (ppm)
f1 (ppm)

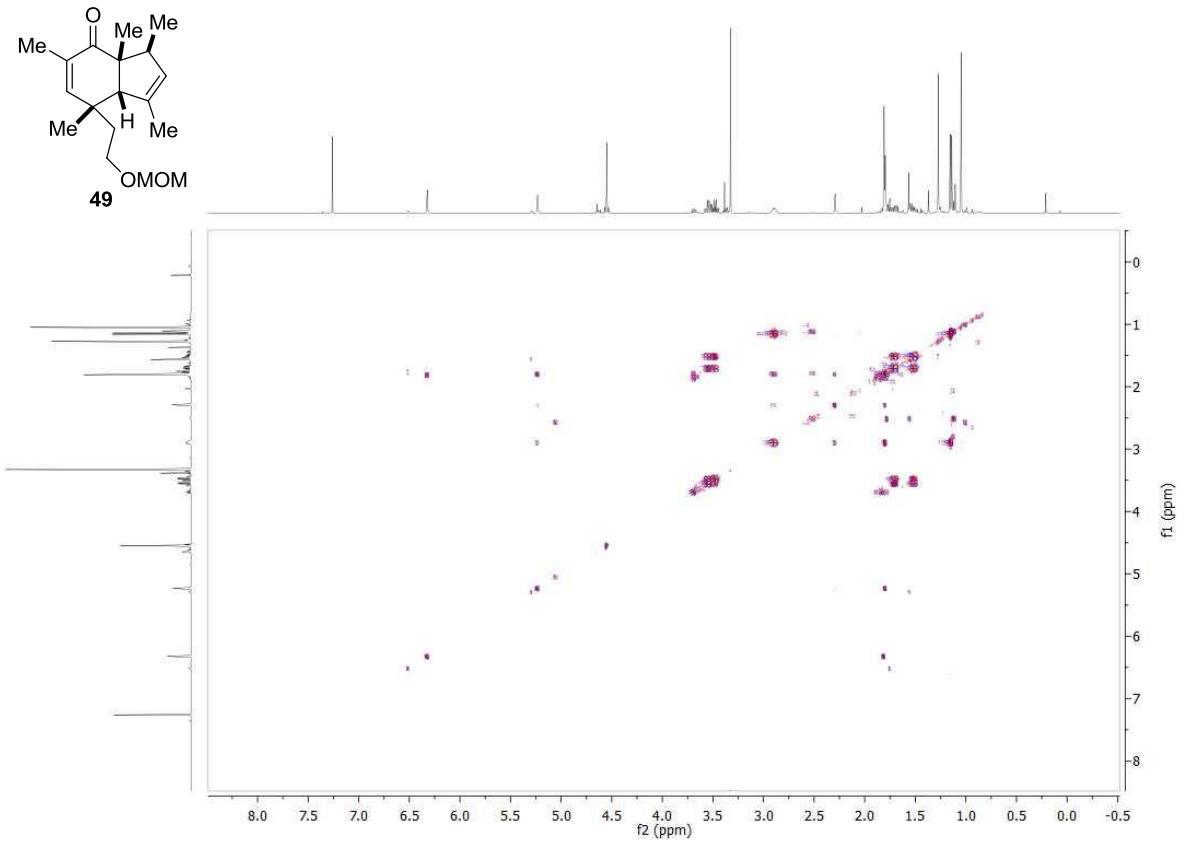

O
Me
Me
Me
Me
H
Me
OMOM
48
f2 (ppm)
f1 (ppm)

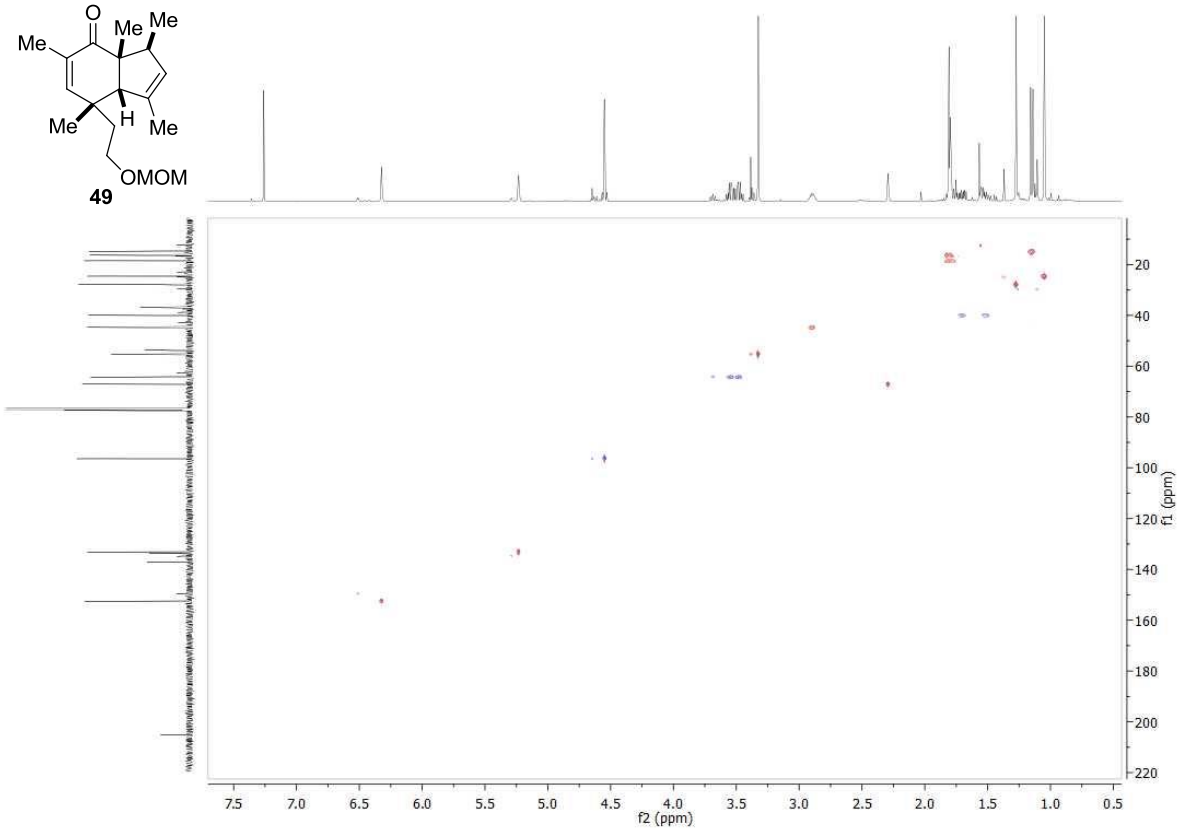

O
Me
Me
Me
Me
H
Me
OMOM
48
f2 (ppm)
f1 (ppm)

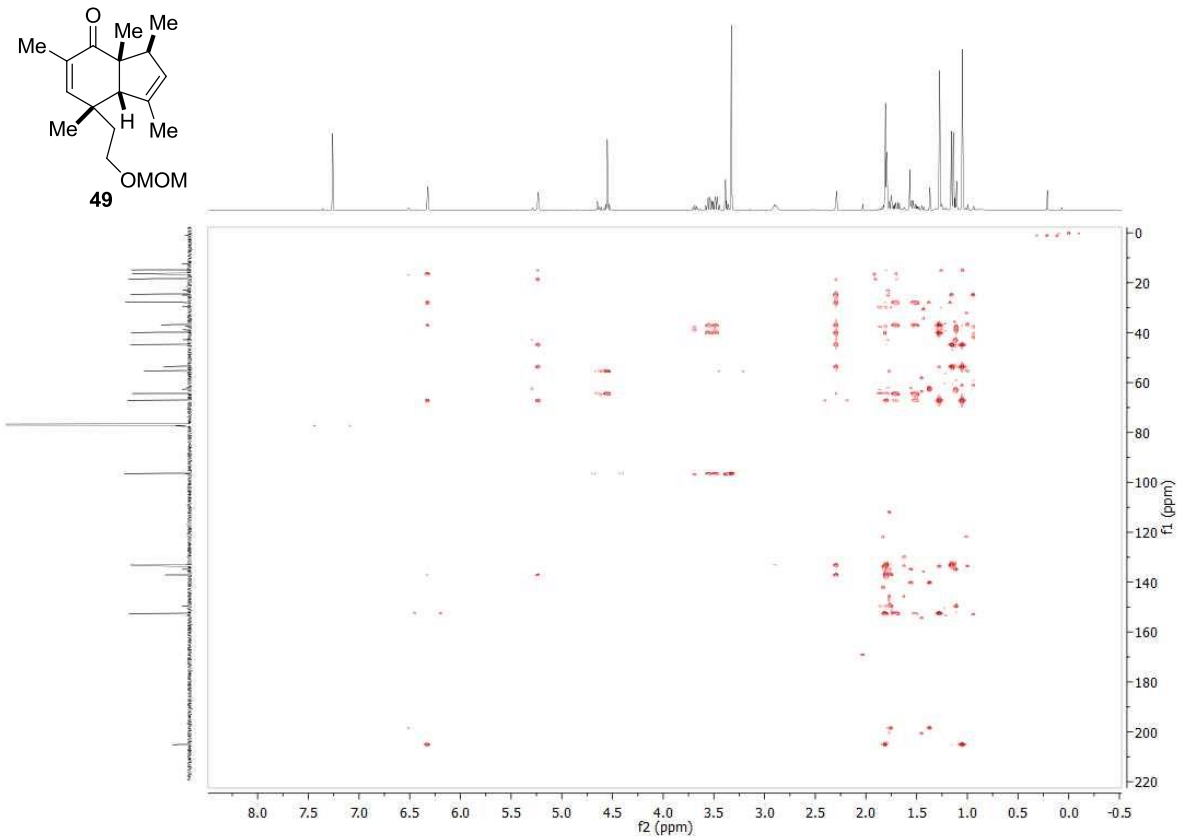

O
Me
Me
Me
Me
H
Me
OMOM
48
f2 (ppm)
f1 (ppm)

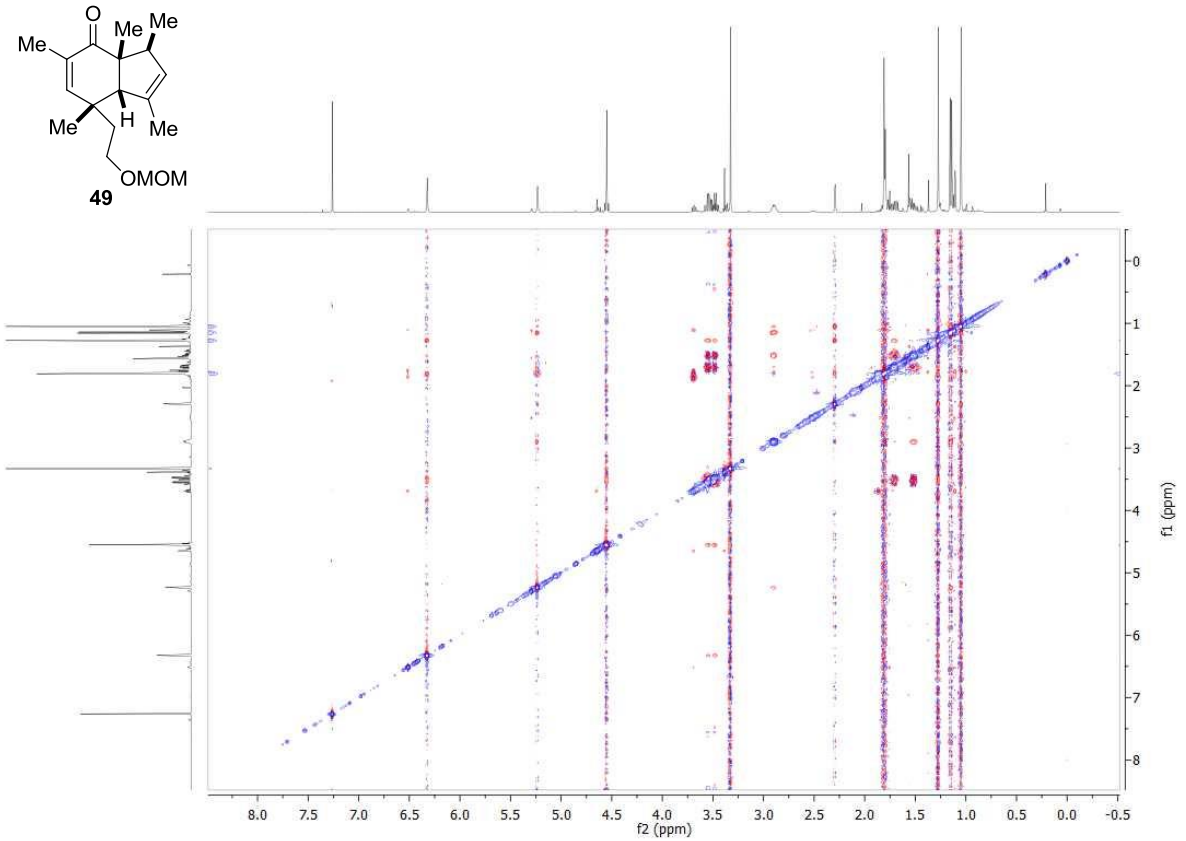

O
Me
Me
Me
Me
H
Me
OMOM
49
f1 (ppm)

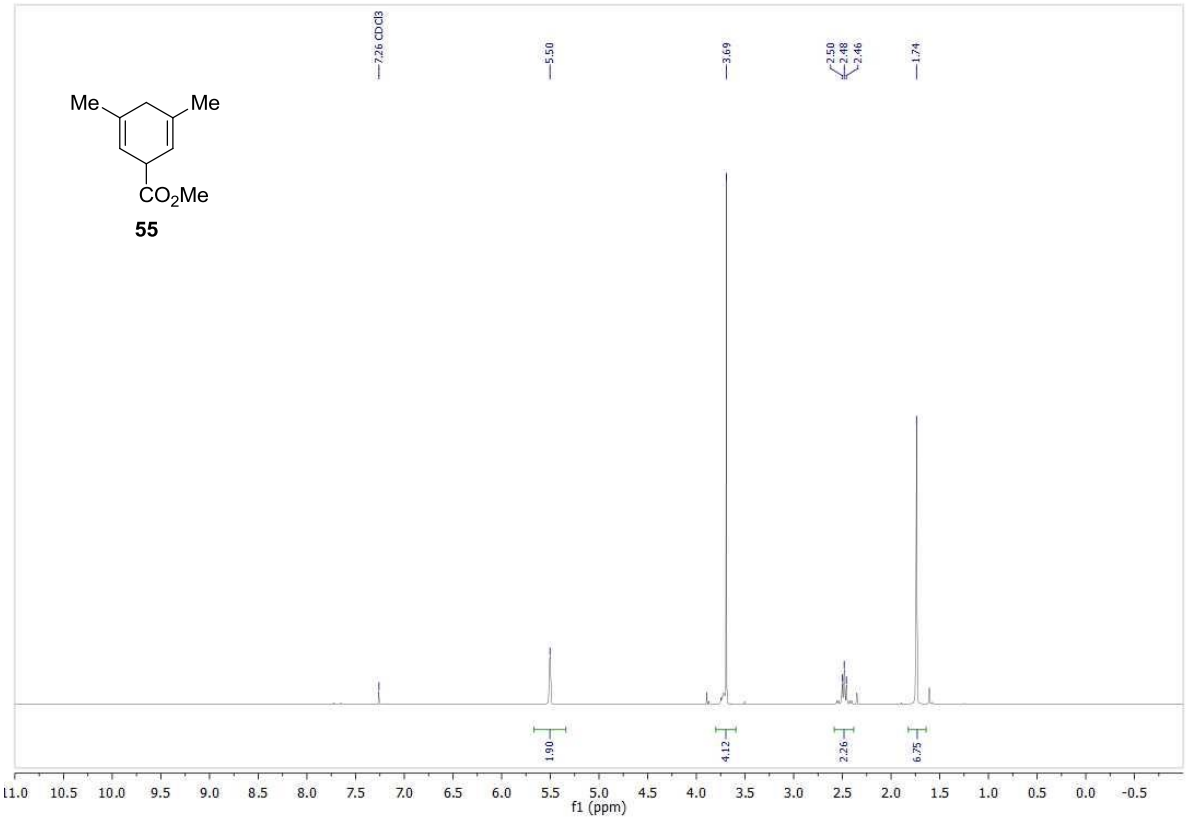

O
Me
Me
Me
Me
H
Me
OMOM
49
f1 (ppm)

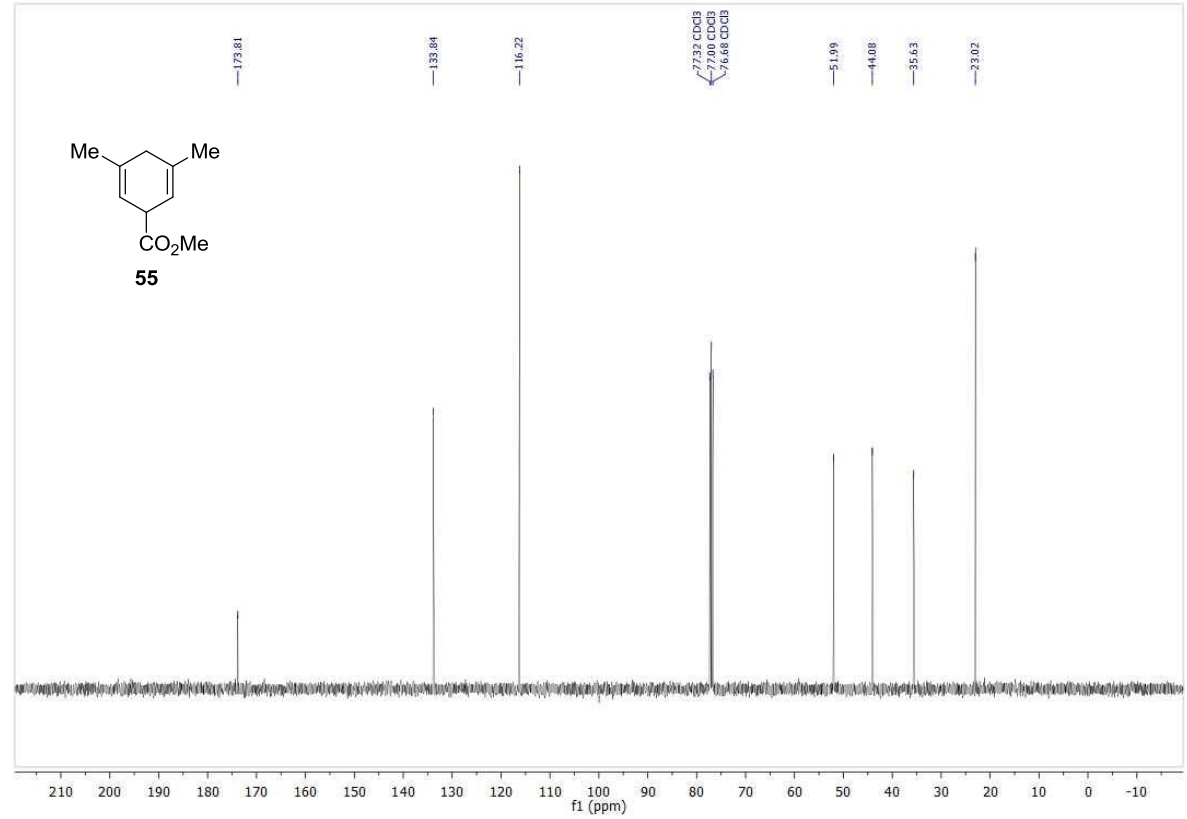

O
Me
Me
Me
Me
H
Me
OMOM
49
f2 (ppm)
f1 (ppm)

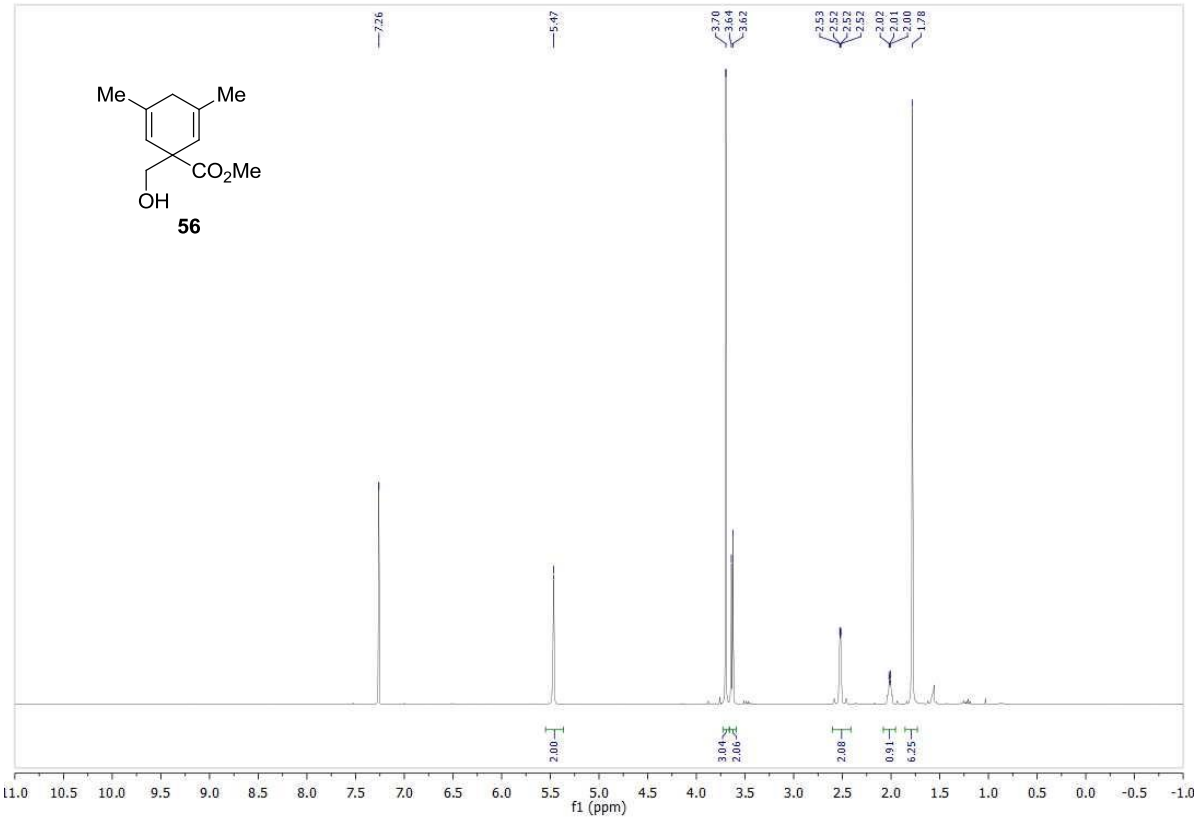

O
Me
Me
Me
Me
H
Me
OMOM
49
f2 (ppm)
f1 (ppm)

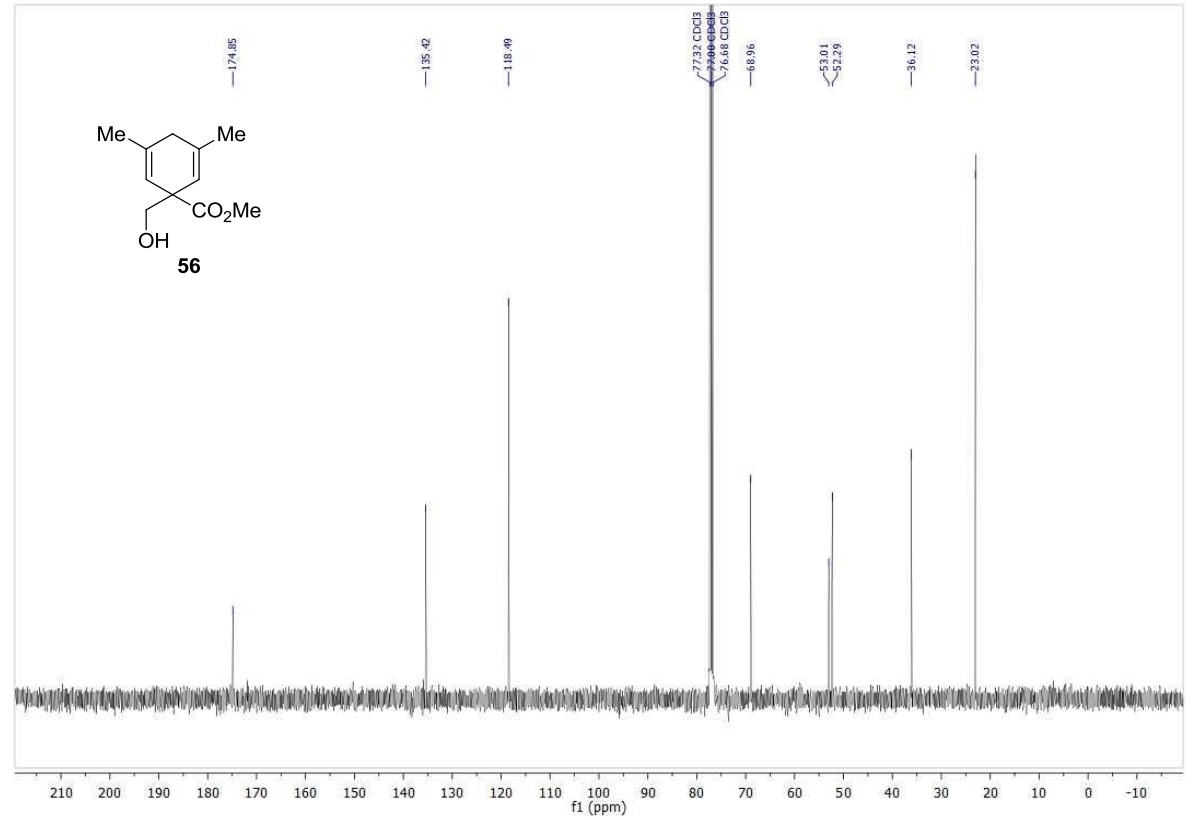

O
Me
Me
Me
Me
H
Me
OMOM
49
f2 (ppm)
f1 (ppm)

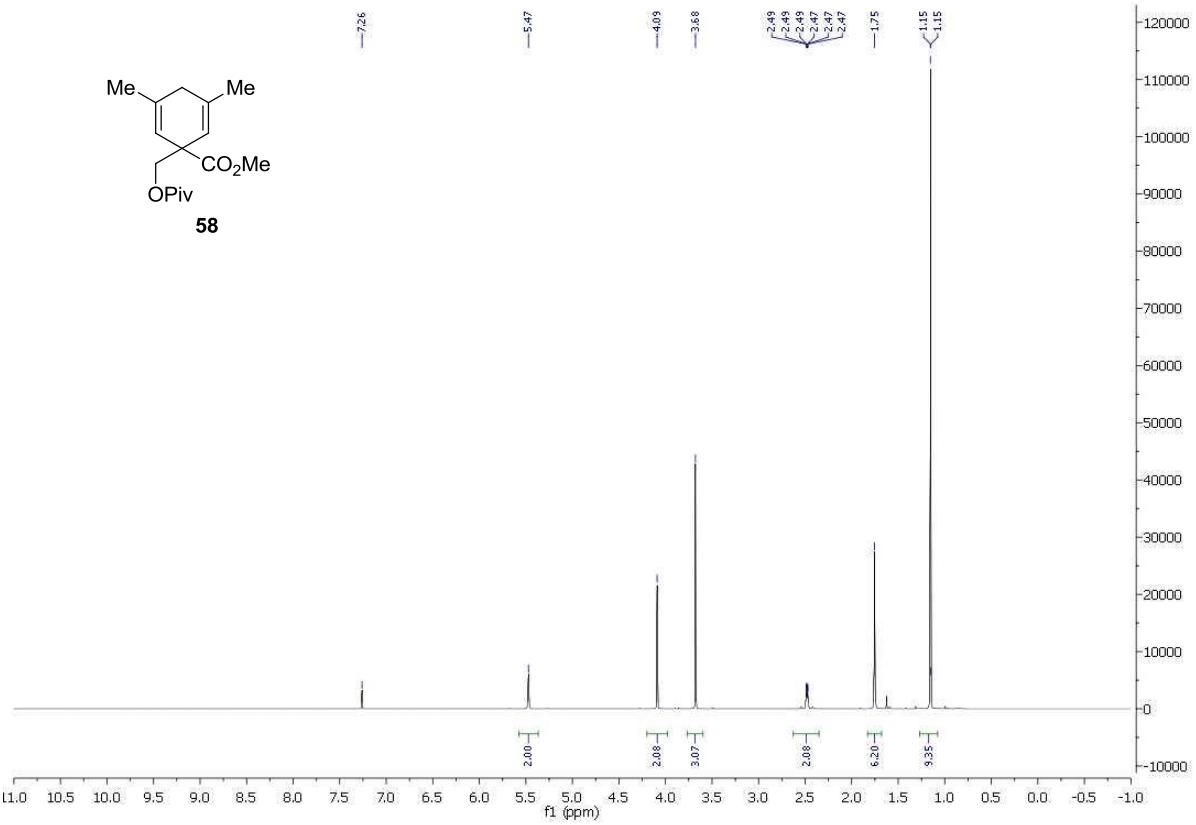

O
Me
Me
Me
Me
H
Me
OMOM
49
f2 (ppm)
f1 (ppm)

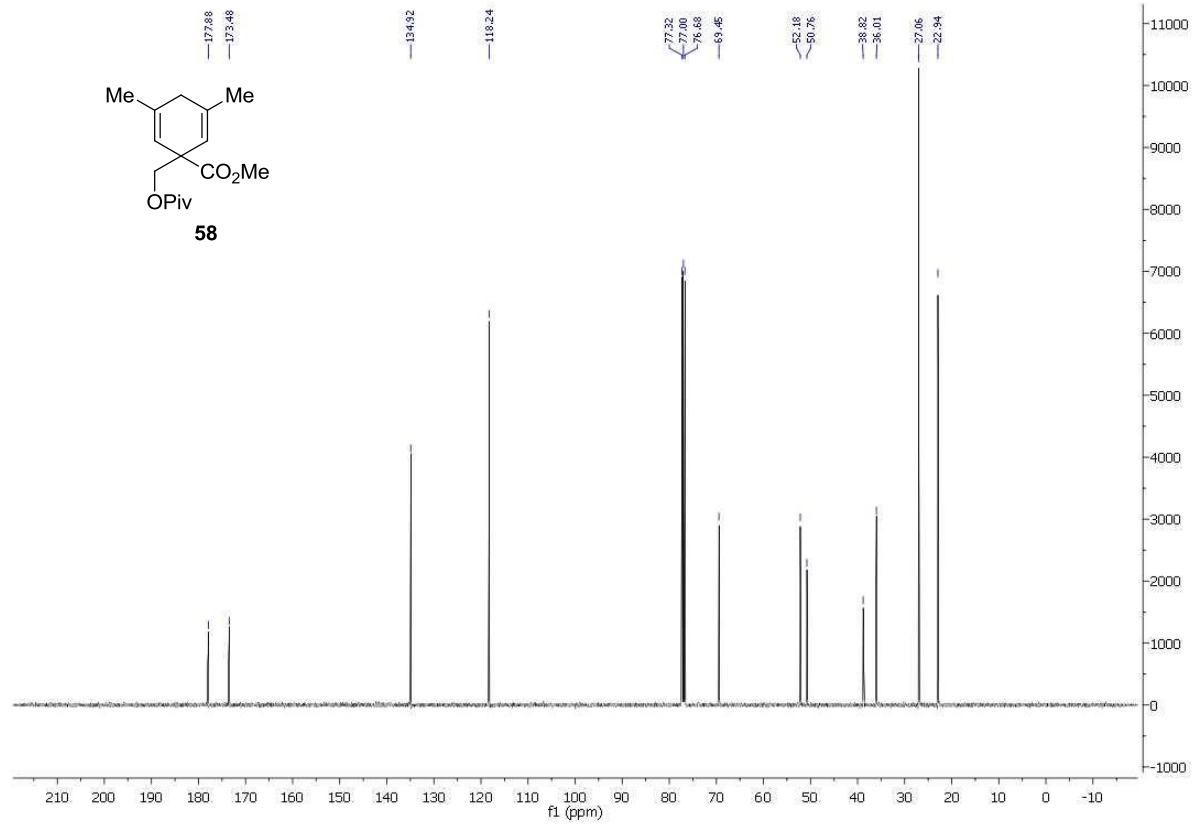

7.26 CDCl3
5.50
3.69
2.50
2.48
2.46
1.74
Me
Me
CO2Me
55
1.90
4.12
2.26
6.75
f1 (ppm)

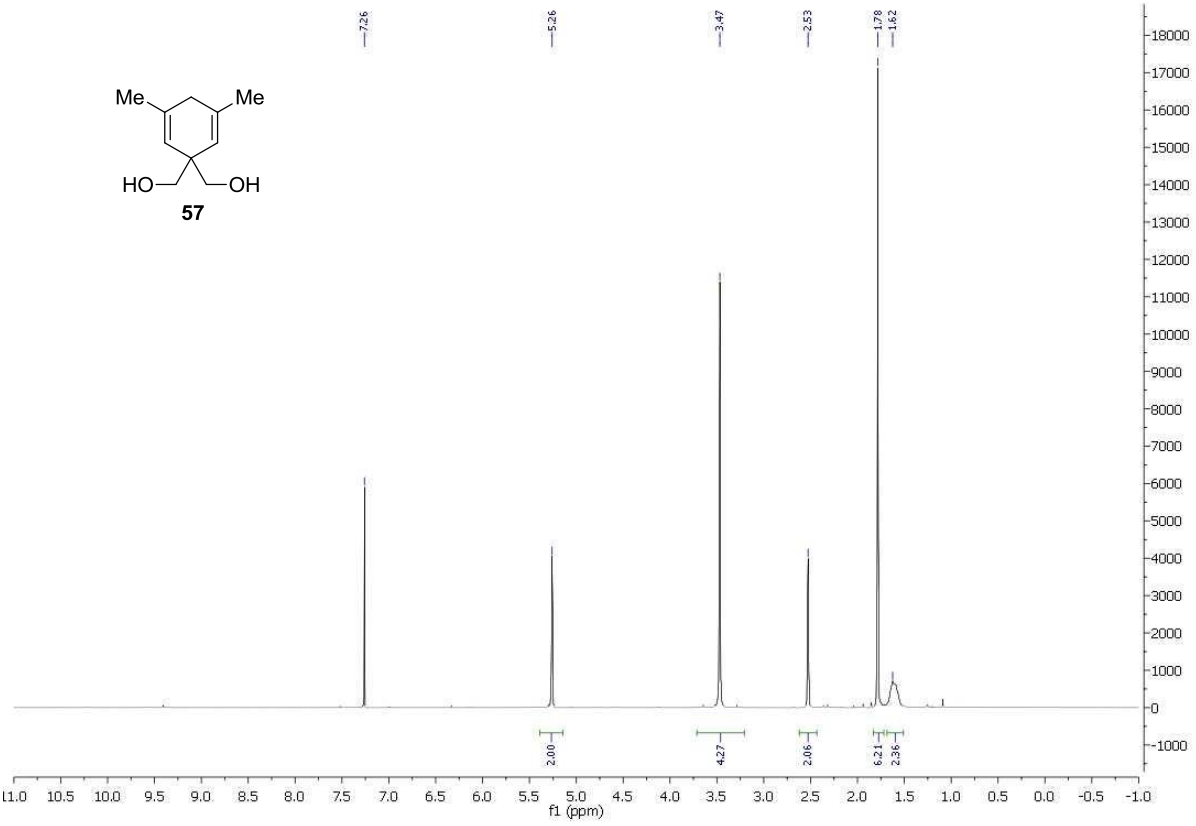

173.81
133.84
116.22
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
51.99
44.08
35.63
23.02
Me
Me
CO2Me
55
f1 (ppm)

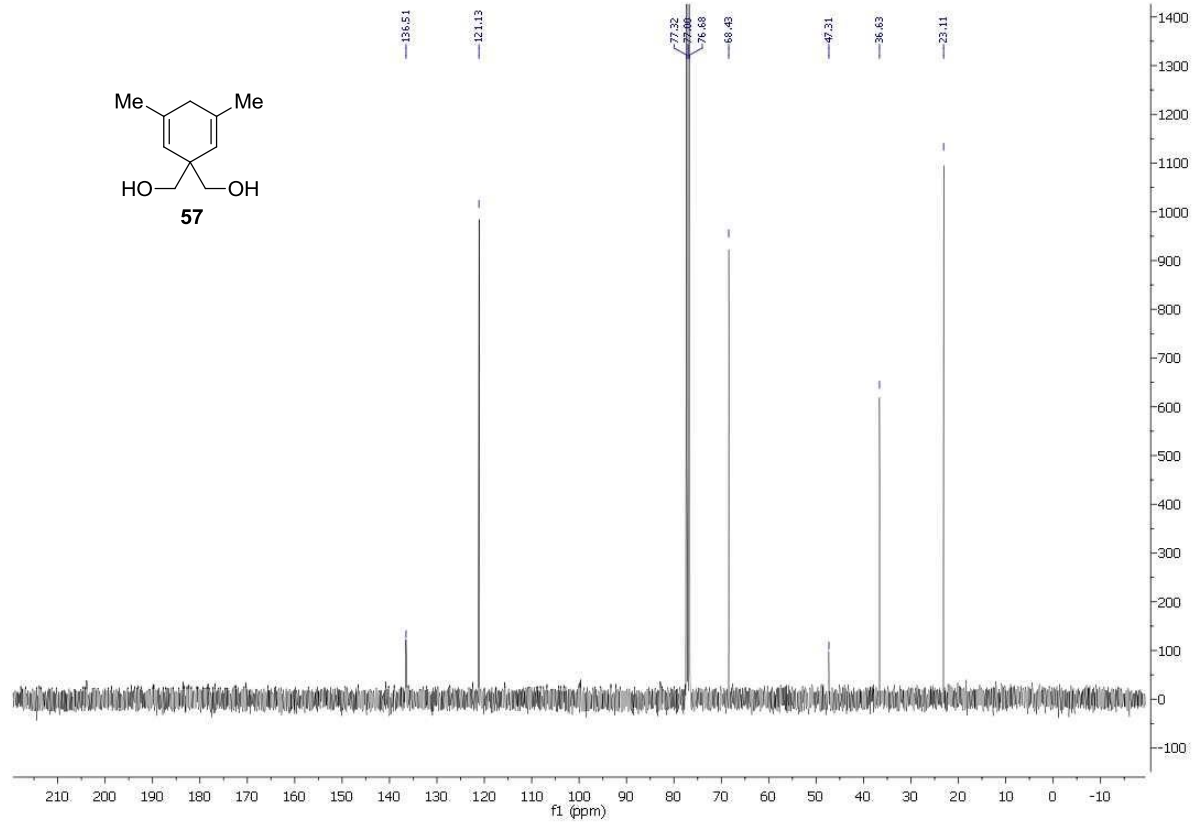

Me
Me
CO2Me
OH
56
7.26
5.47
3.70
3.64
3.62
2.53
2.52
2.52
2.52
2.02
2.01
2.00
1.78
2.00
3.04
2.06
2.08
0.91
6.25
f1 (ppm)

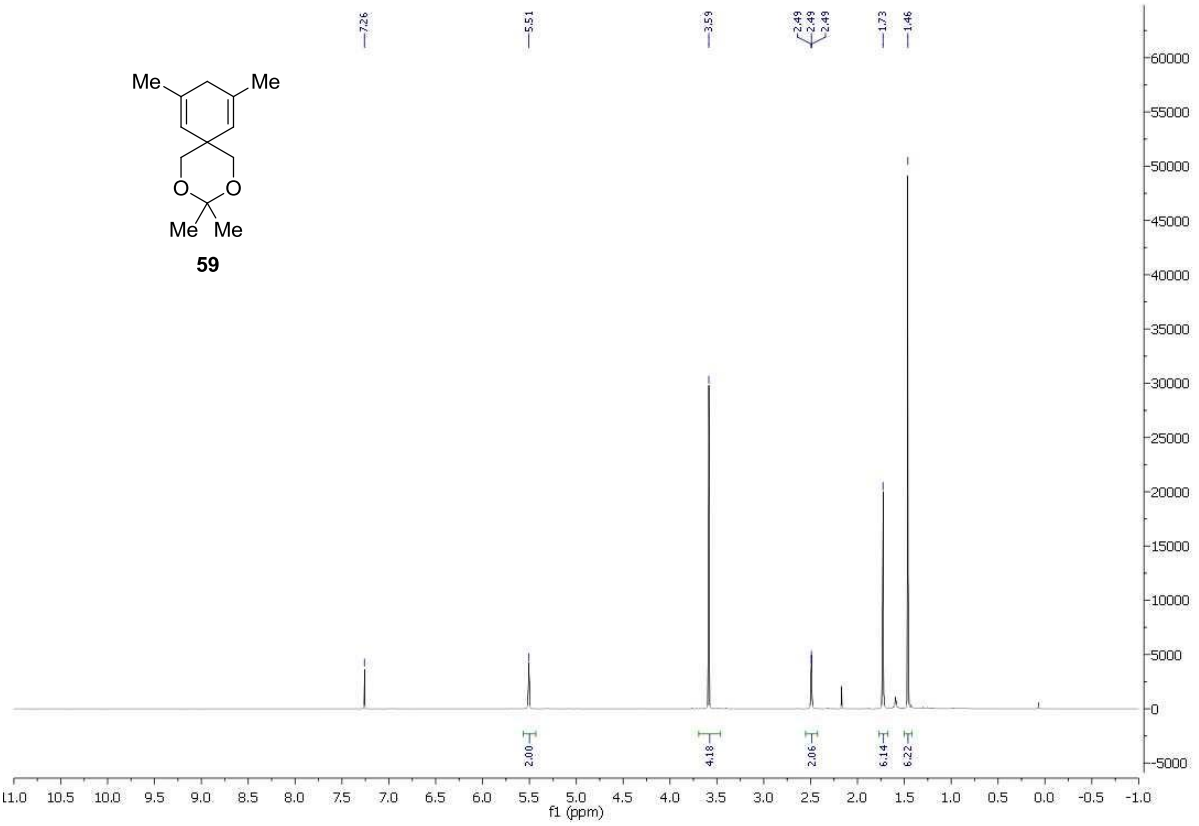

Me
Me
CO2Me
OH
56
174.85
135.42
118.49
77.32 CDCl3
76.68 CDCl3
68.96
53.01
52.29
36.12
23.02
f1 (ppm)

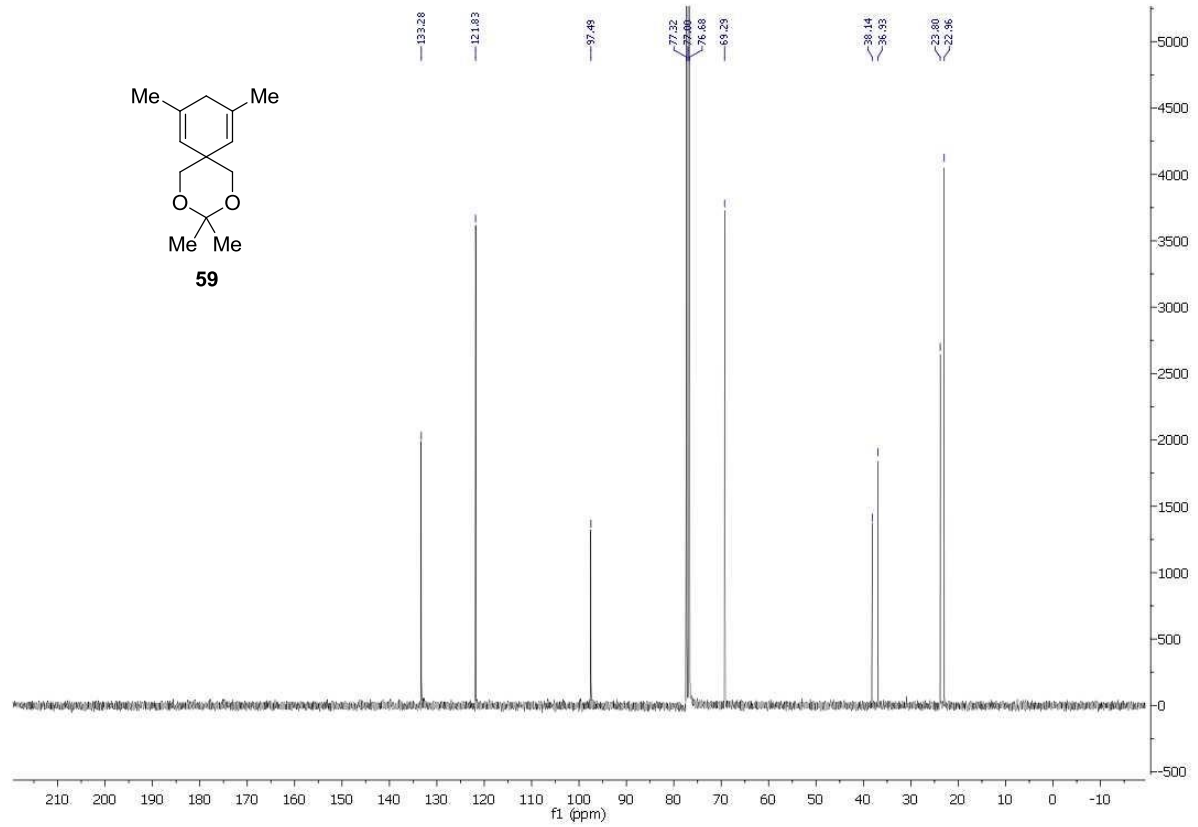

Me
Me
CO2Me
OPiv
58
7.26
5.47
4.09
3.68
2.49
2.49
2.49
2.47
2.47
2.47
1.75
1.15
1.15
2.00
2.08
3.07
2.08
6.20
9.35
f1 (ppm)

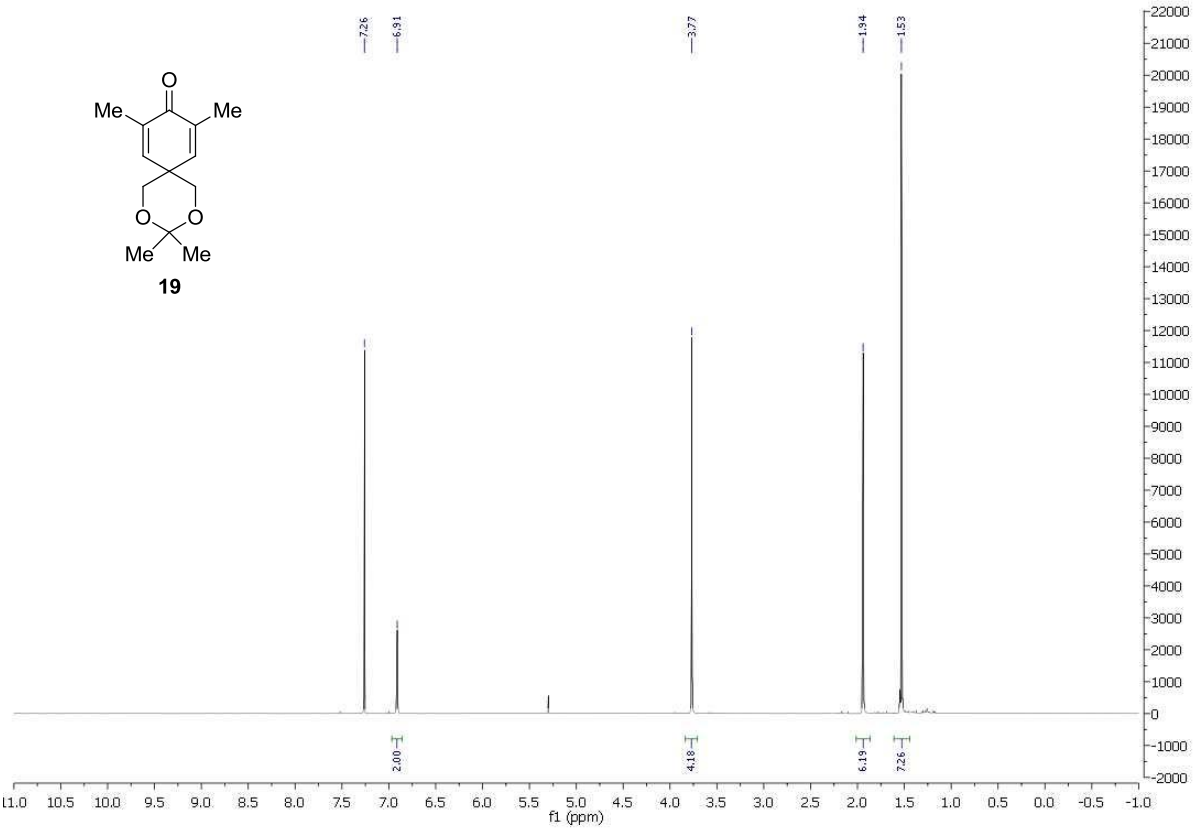

Me
Me
CO2Me
OPiv
58
177.88
173.48
134.92
118.24
77.32
77.00
76.68
69.46
52.18
50.76
38.82
36.01
27.06
22.94
f1 (ppm)

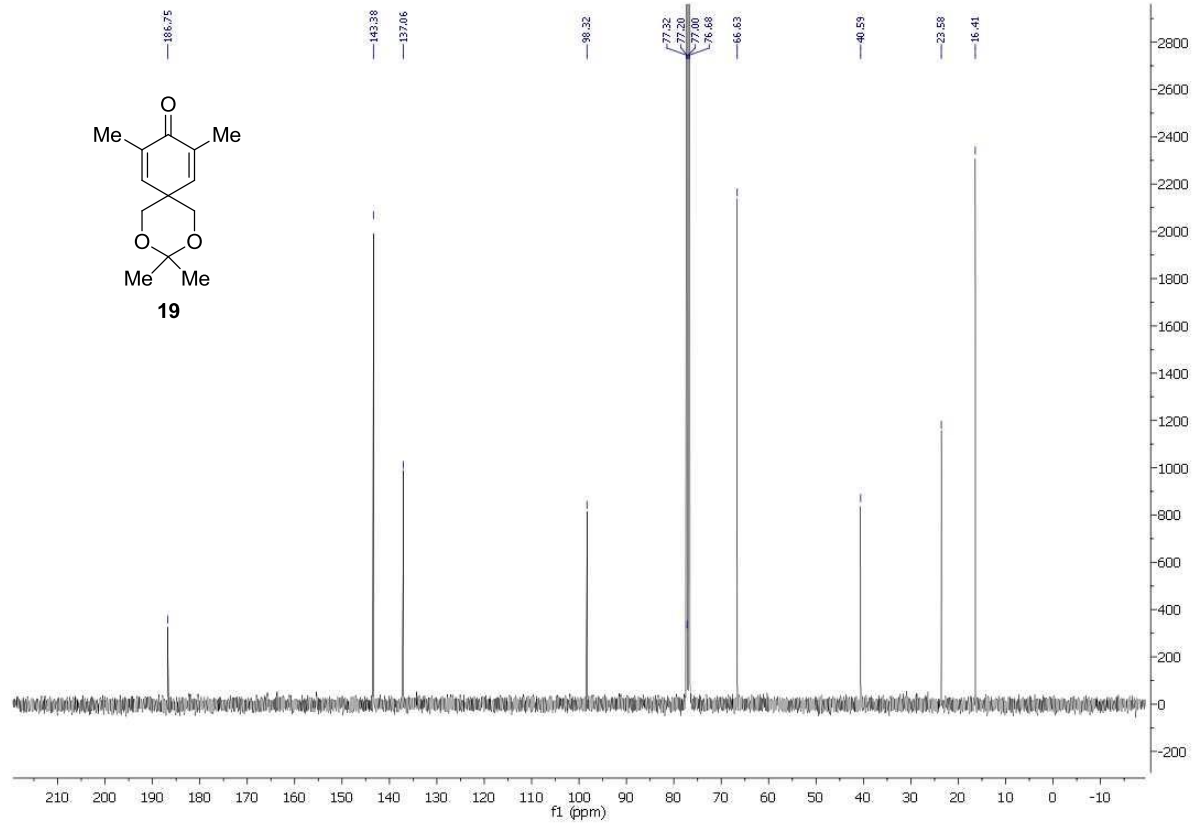

Me
Me
HO
OH
57
7.26
5.26
3.47
2.53
1.78
1.62
2.00
4.27
2.06
6.21
2.36
f1 (ppm)

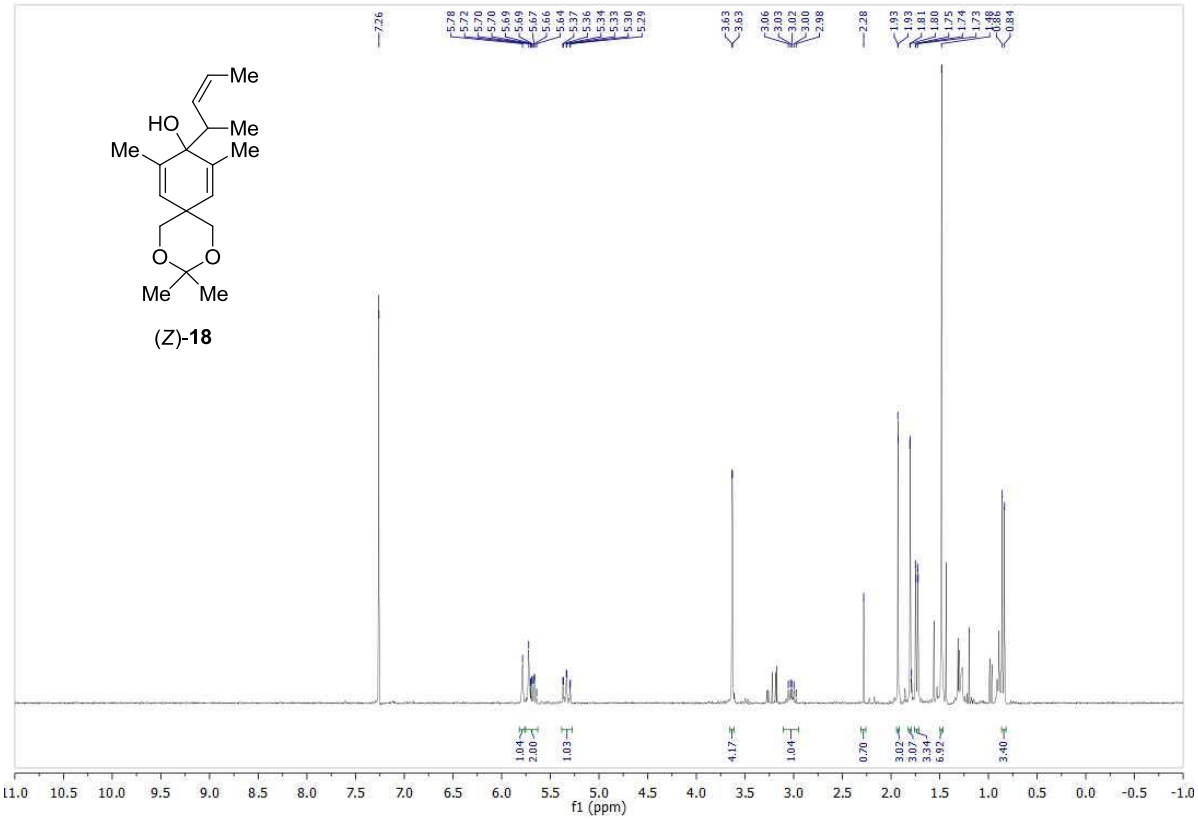

Me
Me
HO
OH
57
136.51
121.13
77.32
76.68
68.49
47.31
36.63
23.11
f1 (ppm)

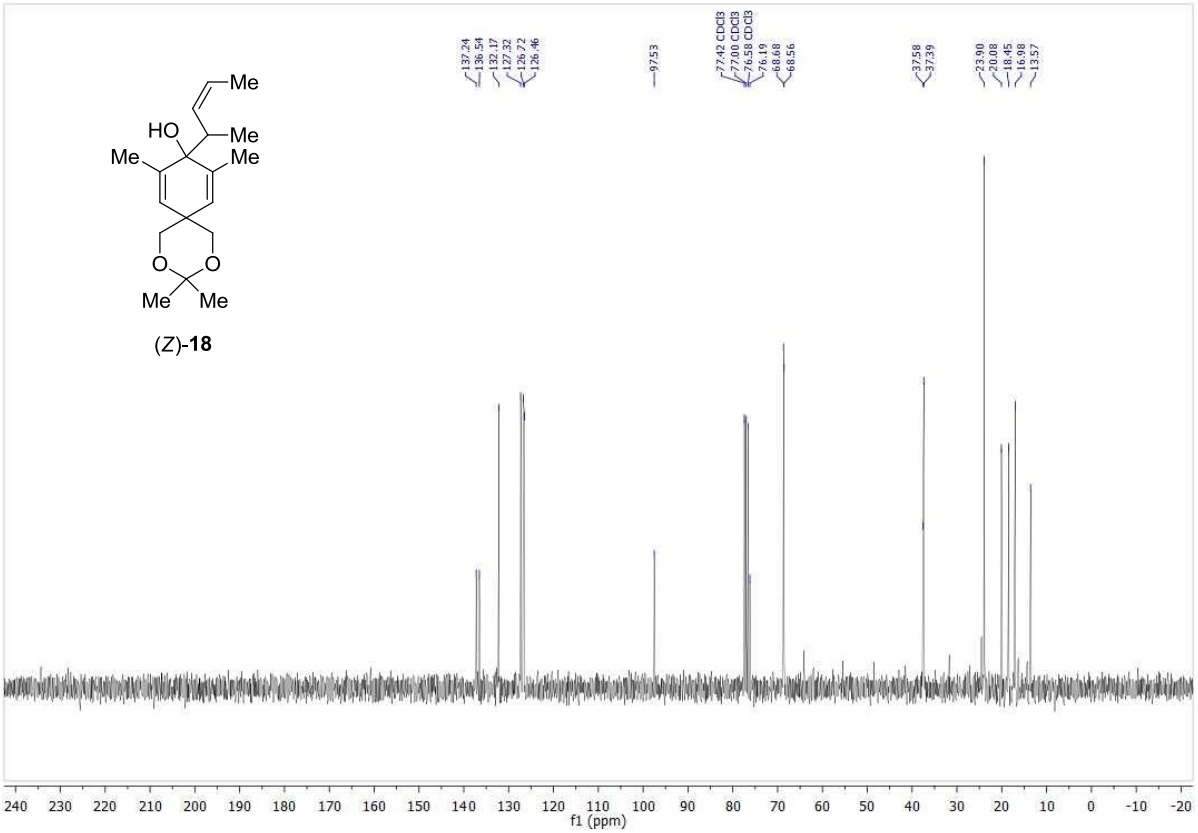

Me
Me
O
O
Me
Me
59
7.26
5.51
3.59
2.49
2.49
2.49
1.73
1.46
2.00
4.18
2.06
6.14
6.22
f1 (ppm)

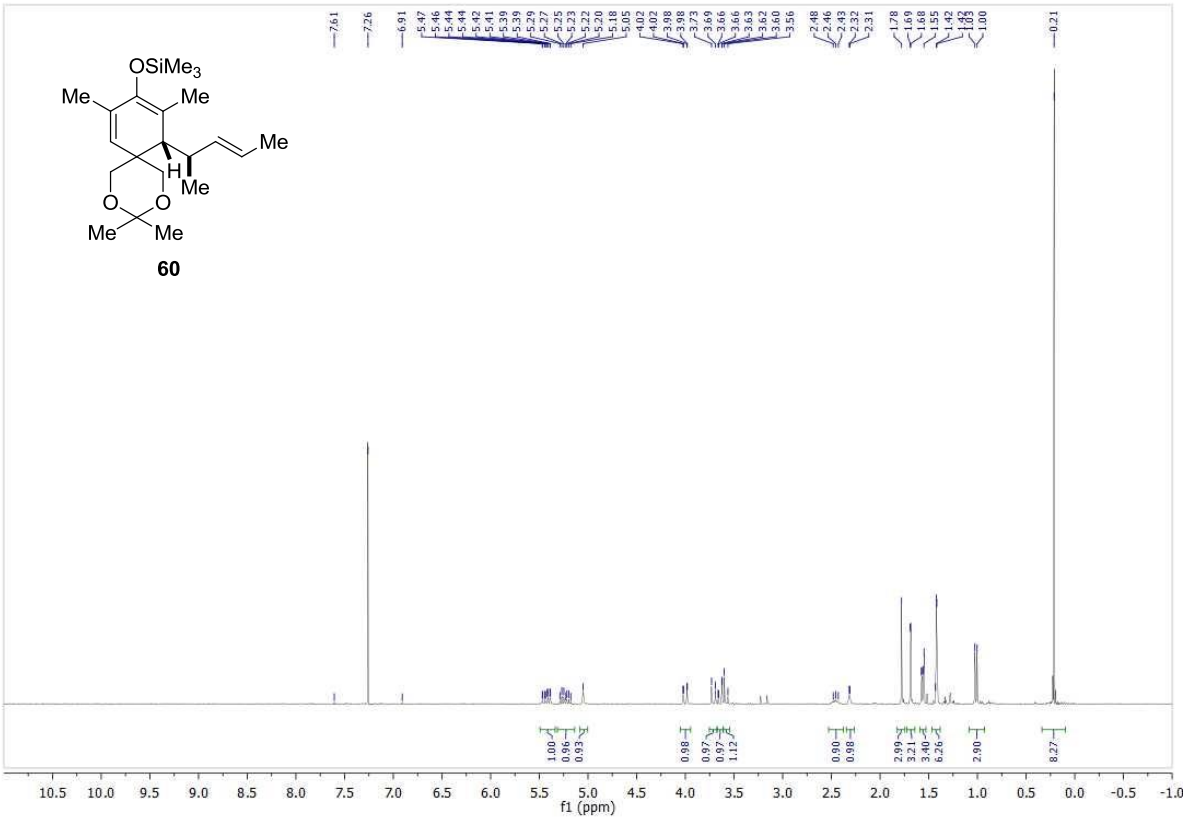

Me
Me
O
O
Me
Me
59
133.28
121.83
97.49
77.32
76.68
69.29
38.14
36.53
23.80
22.96
f1 (ppm)


Me
Me
O
O
O
Me
Me
19
7.26
6.91
3.77
1.94
1.53
2.00
4.18
6.19
7.26
f1 (ppm)

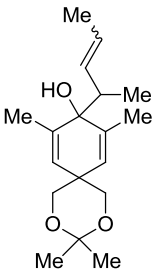

Me
Me
O
O
O
Me
Me
19
186.75
143.38
137.06
98.32
77.32
77.20
77.00
76.68
66.63
40.59
23.58
16.41
f1 (ppm)


Me
HO
Me
Me
Me
O
O
Me
Me
(Z)-18
f1 (ppm)

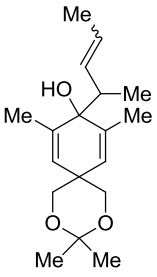

Me
HO
Me
Me
Me
O
O
Me
Me
(Z)-18
f1 (ppm)



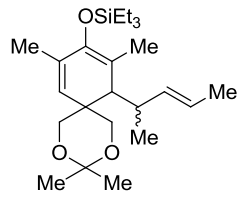
60



18
(*E*)/(*Z*) = 3.8:1

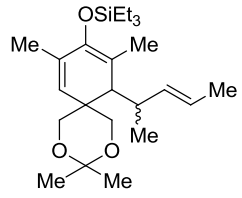


18
(*E*)/(*Z*) = 3.8:1


OSiEt3
Me
Me
Me
Me
O
O
Me
Me

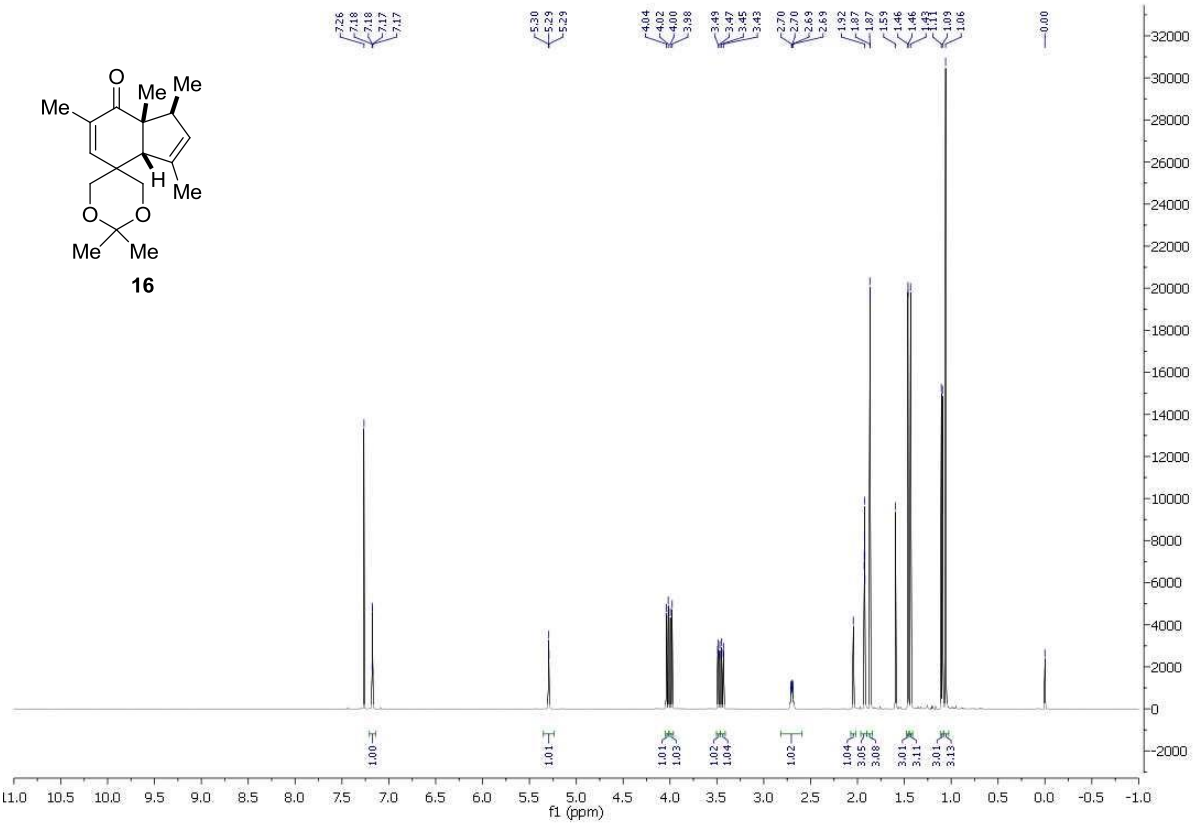
60

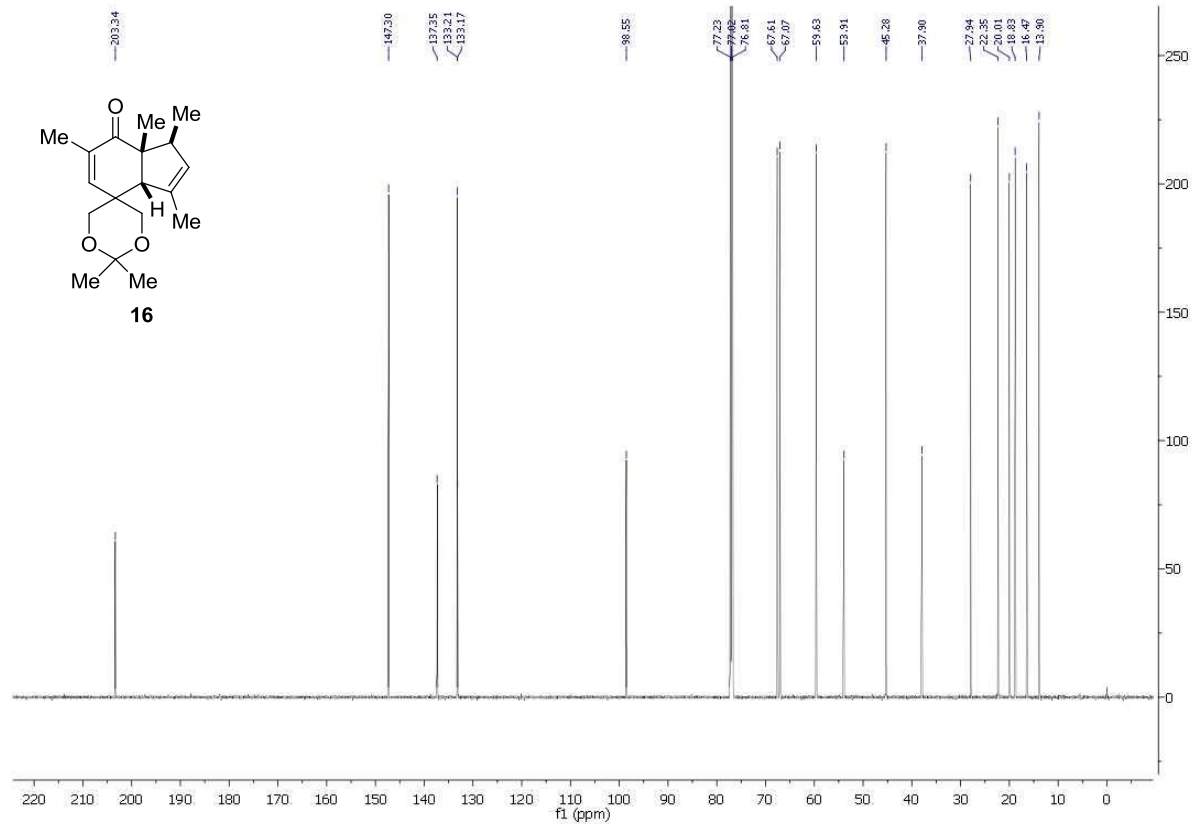
f1 (ppm)

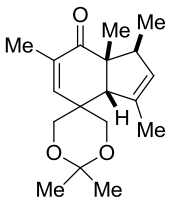

OSiEt3
Me
Me
Me
Me
O
O
Me
Me

60

f1 (ppm)

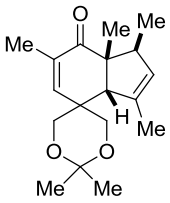

O
Me
Me
Me
H
Me
O
O
Me
Me
16
f1 (ppm)


O
Me
Me
Me
H
Me
O
O
Me
Me
16
f1 (ppm)


O
Me
Me
Me
H
Me
O
O
Me
Me

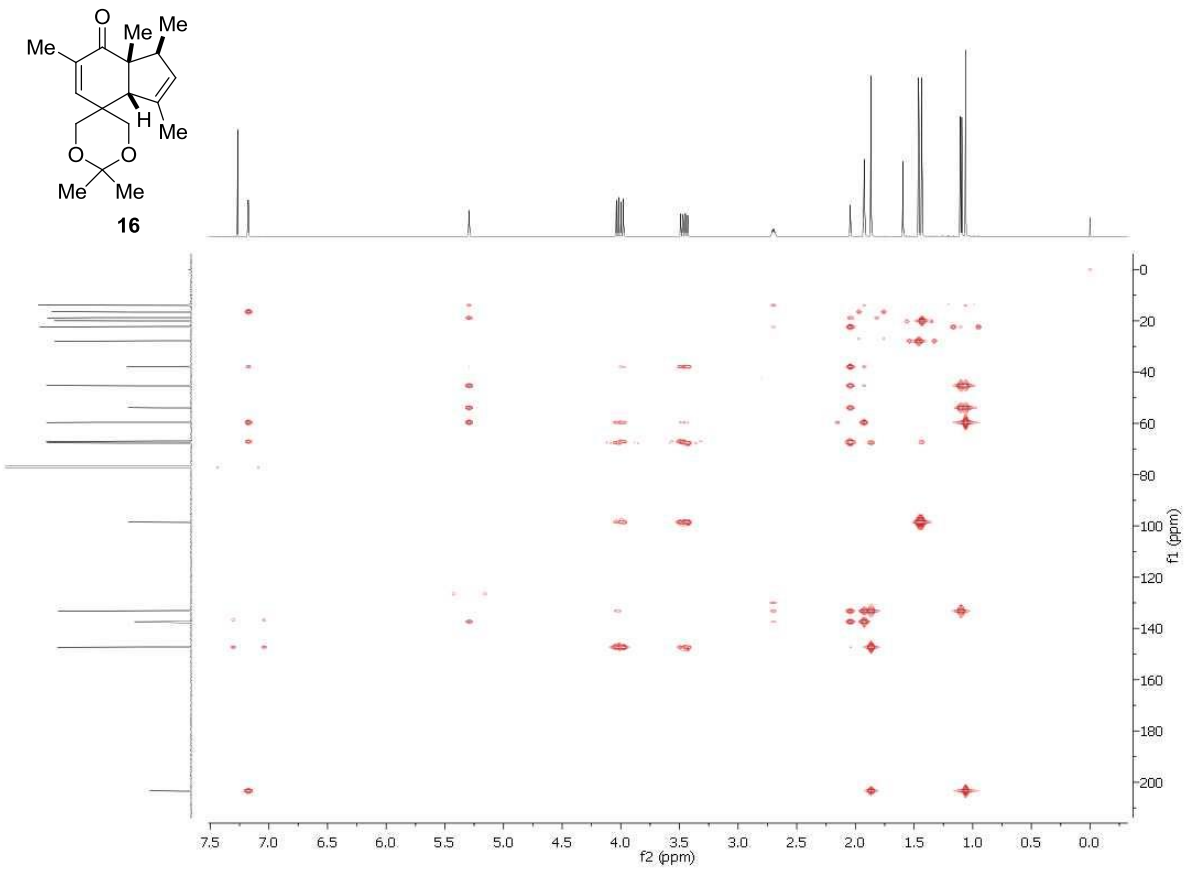
16

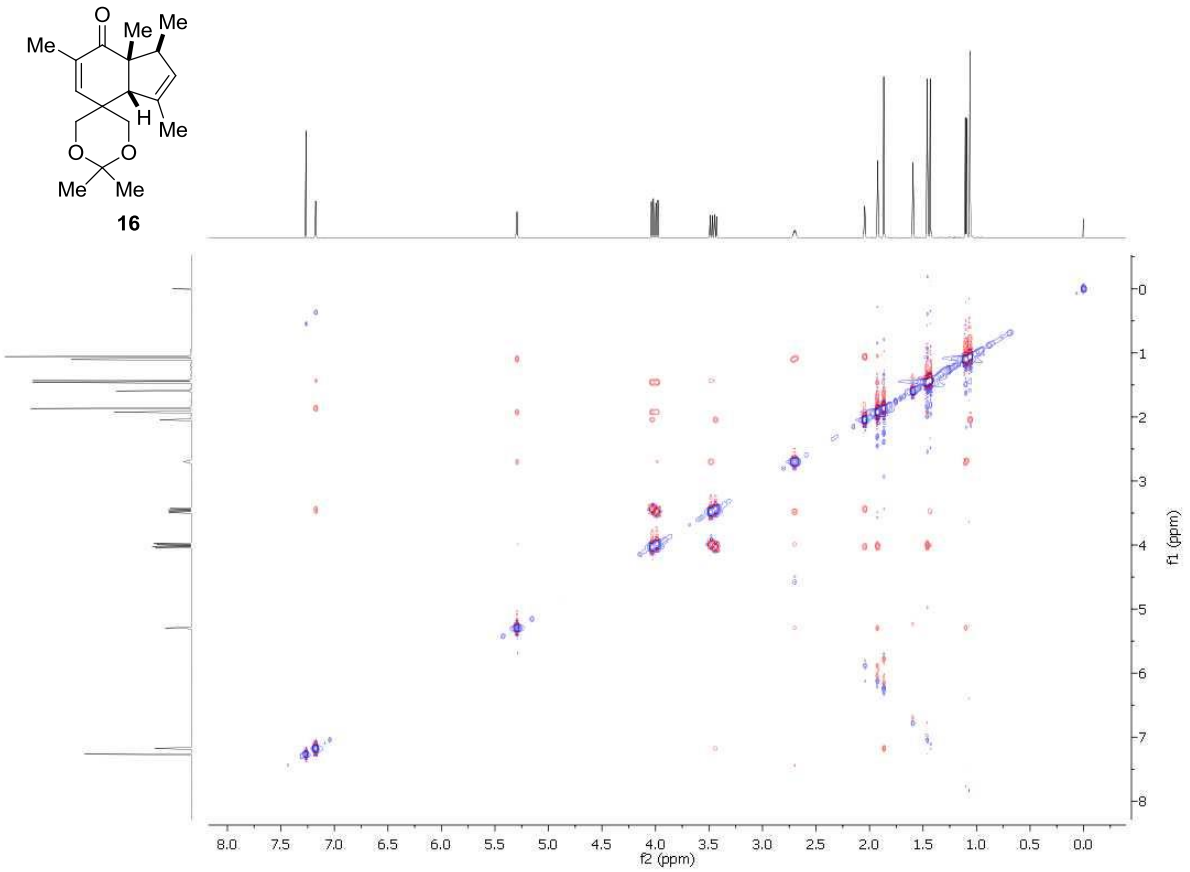
f2 (ppm)
f1 (ppm)

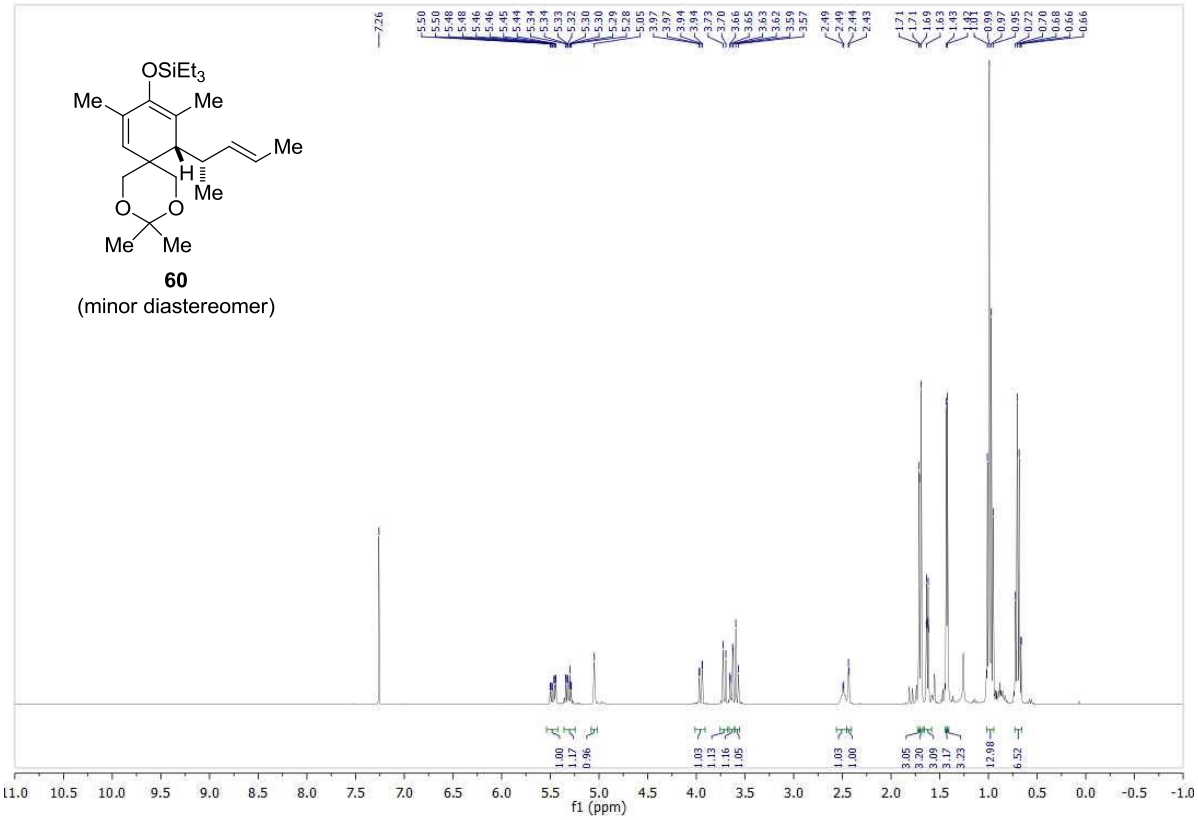

O
Me
Me
Me
H
Me
O
O
Me
Me

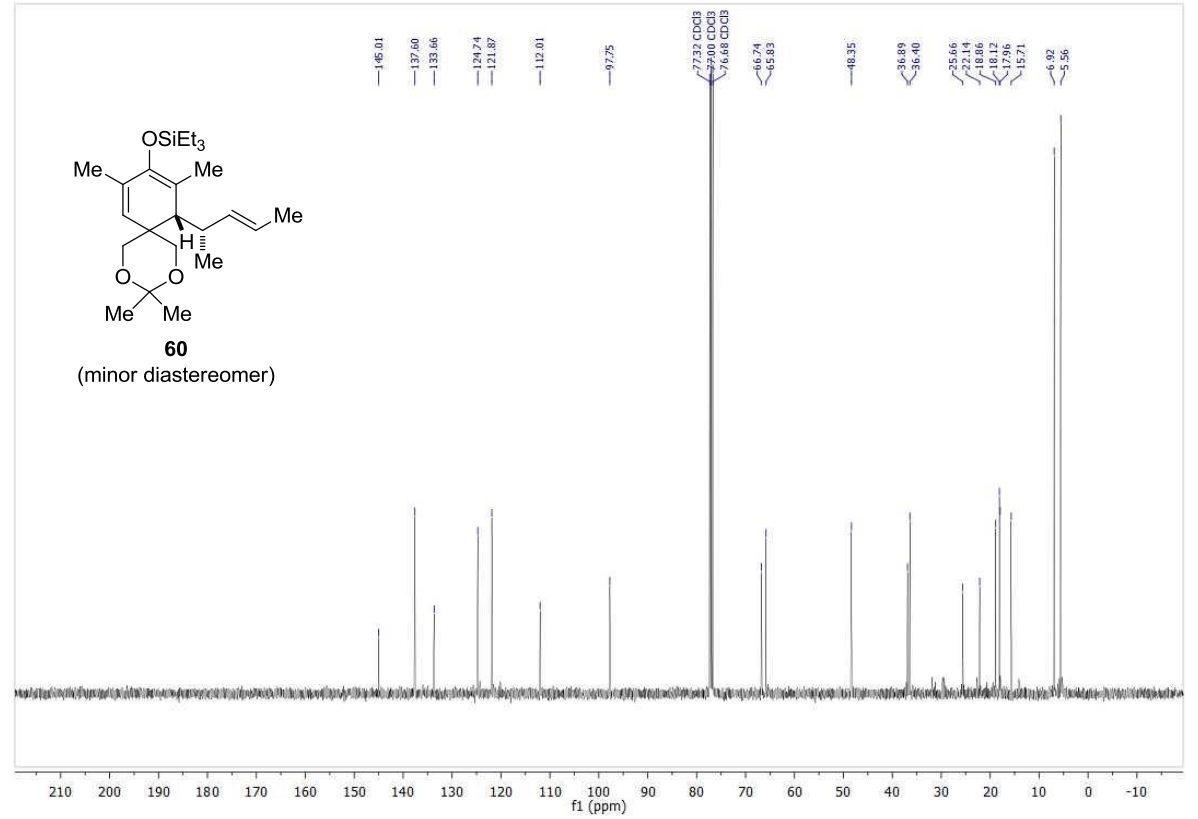
16

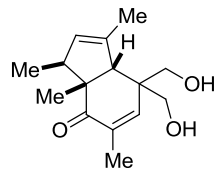
f2 (ppm)
f1 (ppm)


O
Me
Me
Me
H
Me
O
O
Me
Me
16
f1 (ppm)
f2 (ppm)

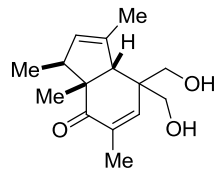

O
Me
Me
Me
H
Me
O
O
Me
Me
16
f1 (ppm)
f2 (ppm)


OSiEt3
Me
Me
Me
H
Me
O
O
Me
Me
60
(minor diastereomer)
f1 (ppm)

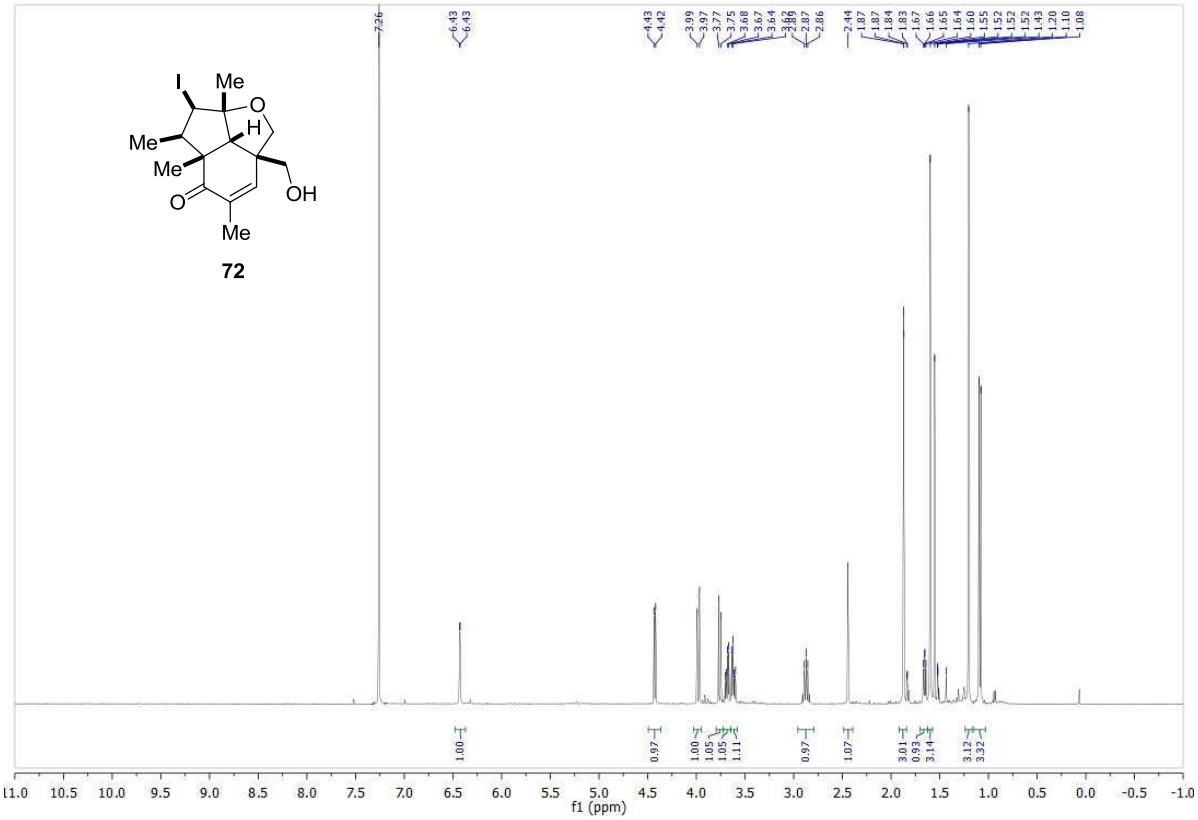

OSiEt3
Me
Me
Me
H
Me
O
O
Me
Me
60
(minor diastereomer)
f1 (ppm)

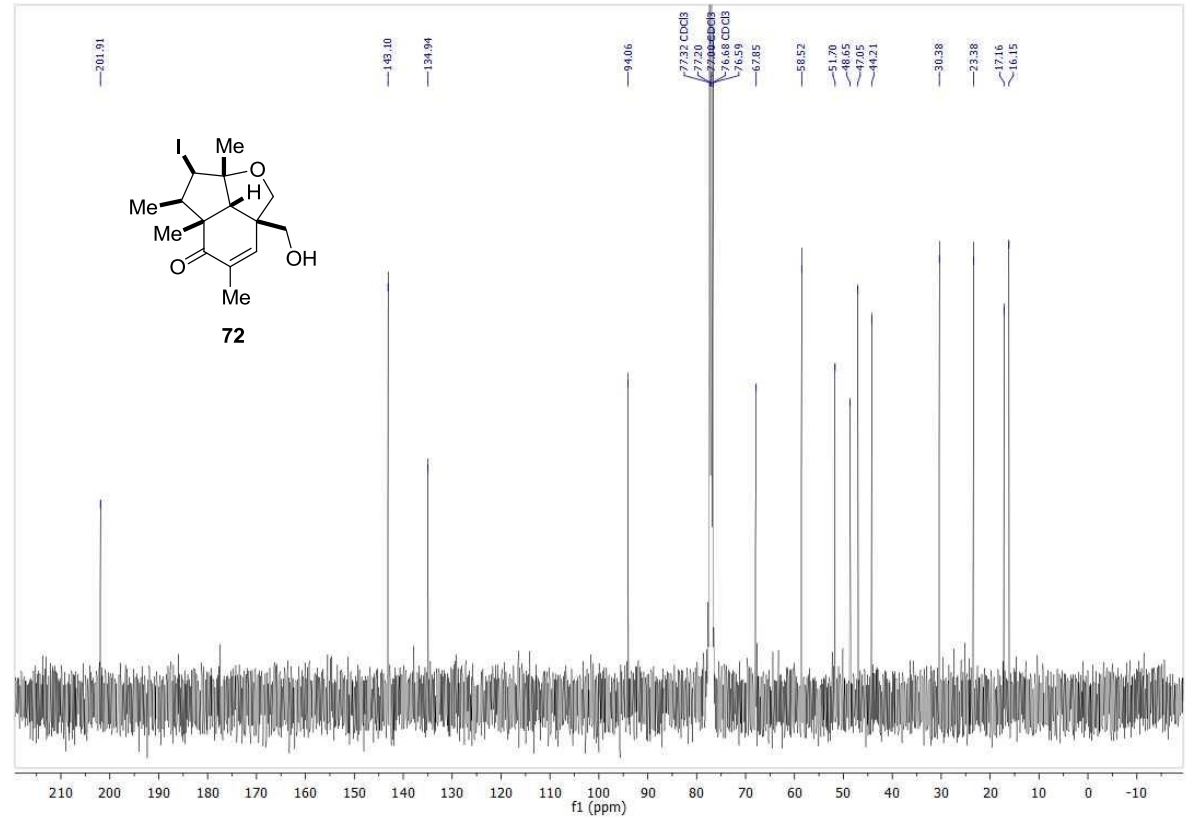


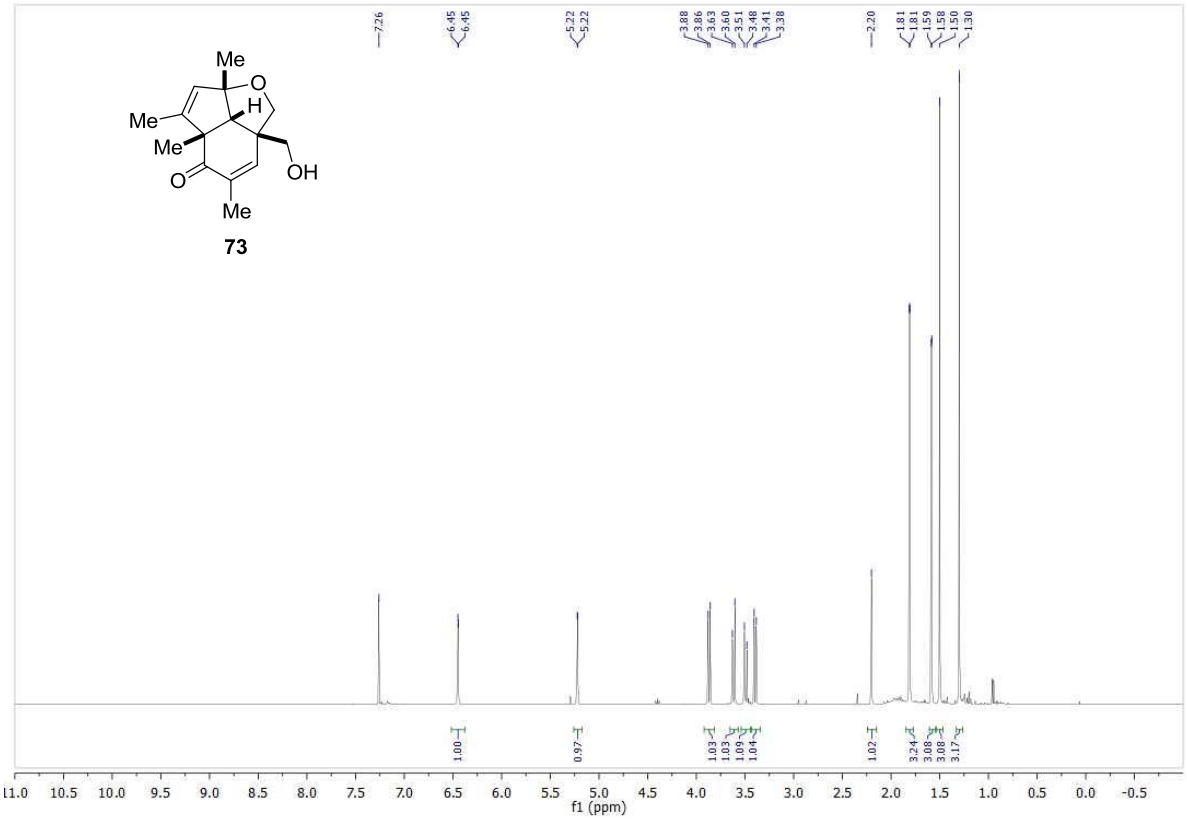
15



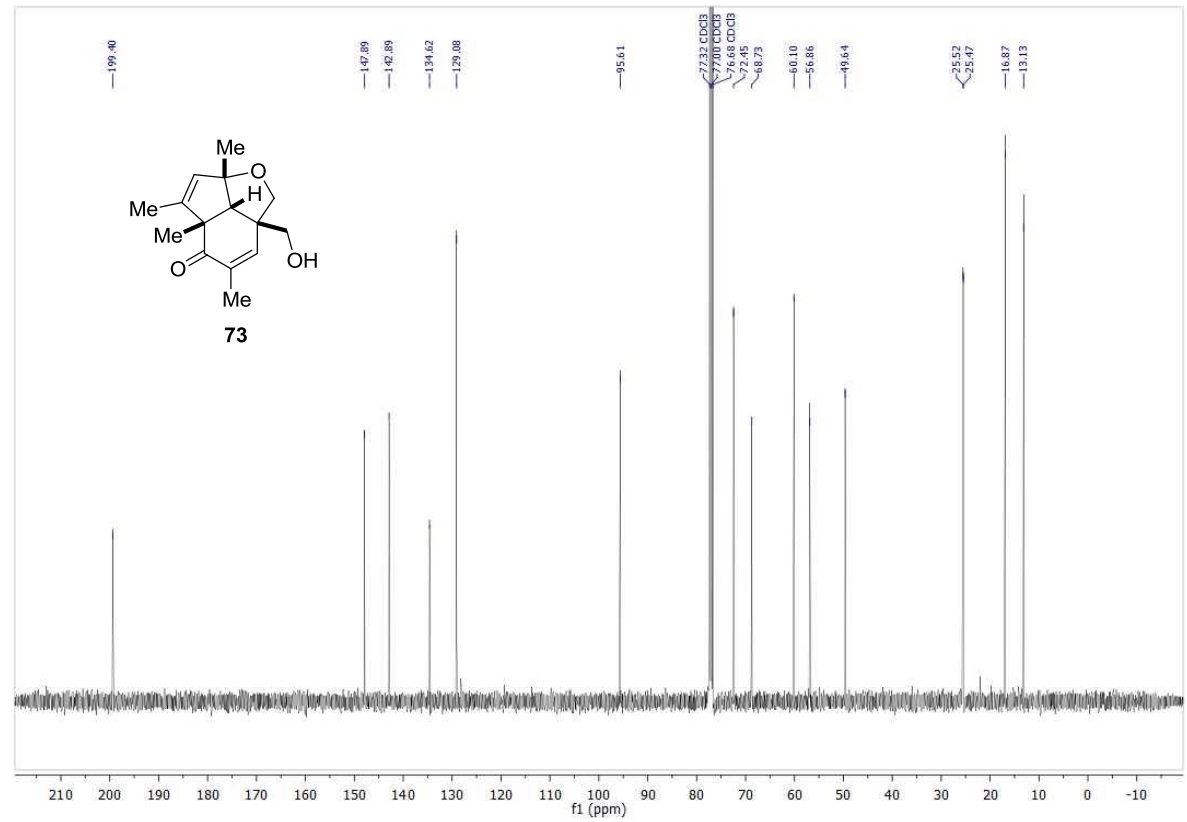
15


I
Me
O
H
Me
Me
O
OH
Me
72
f1 (ppm)

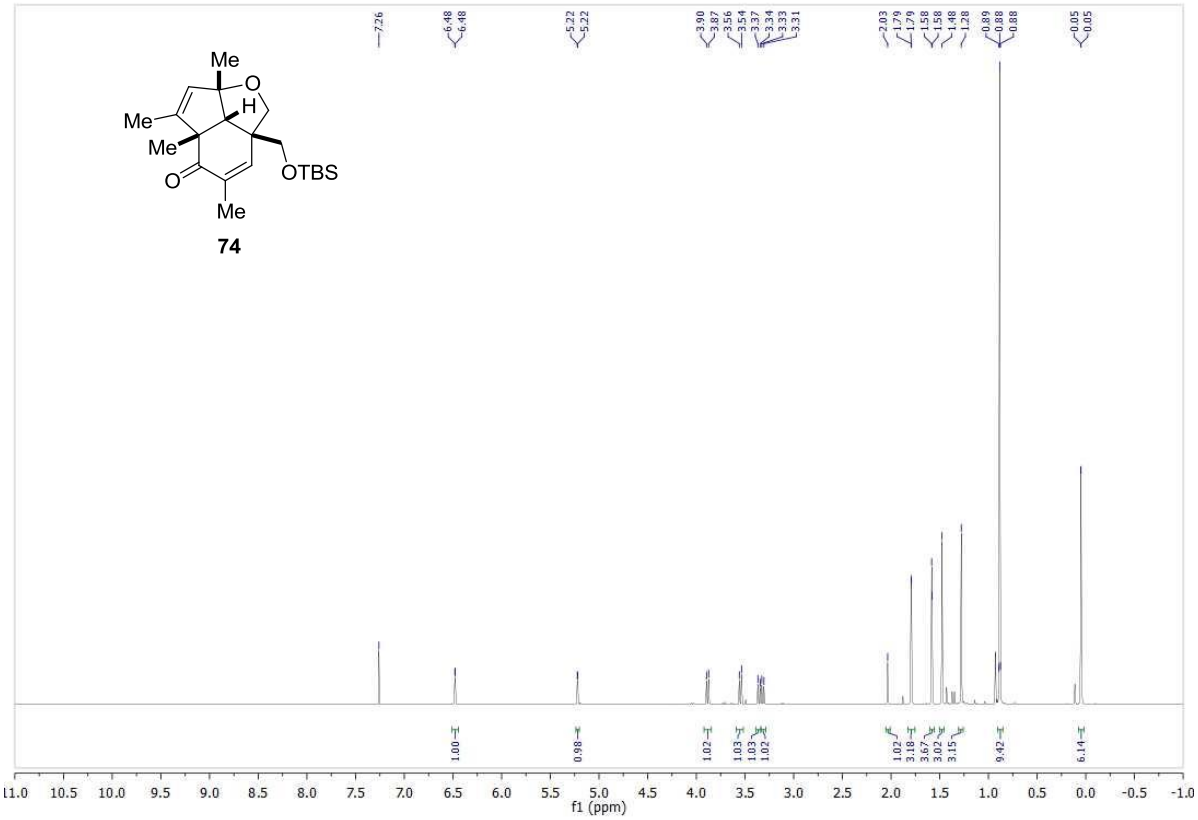

I
Me
O
H
Me
Me
O
OH
Me
72
f1 (ppm)

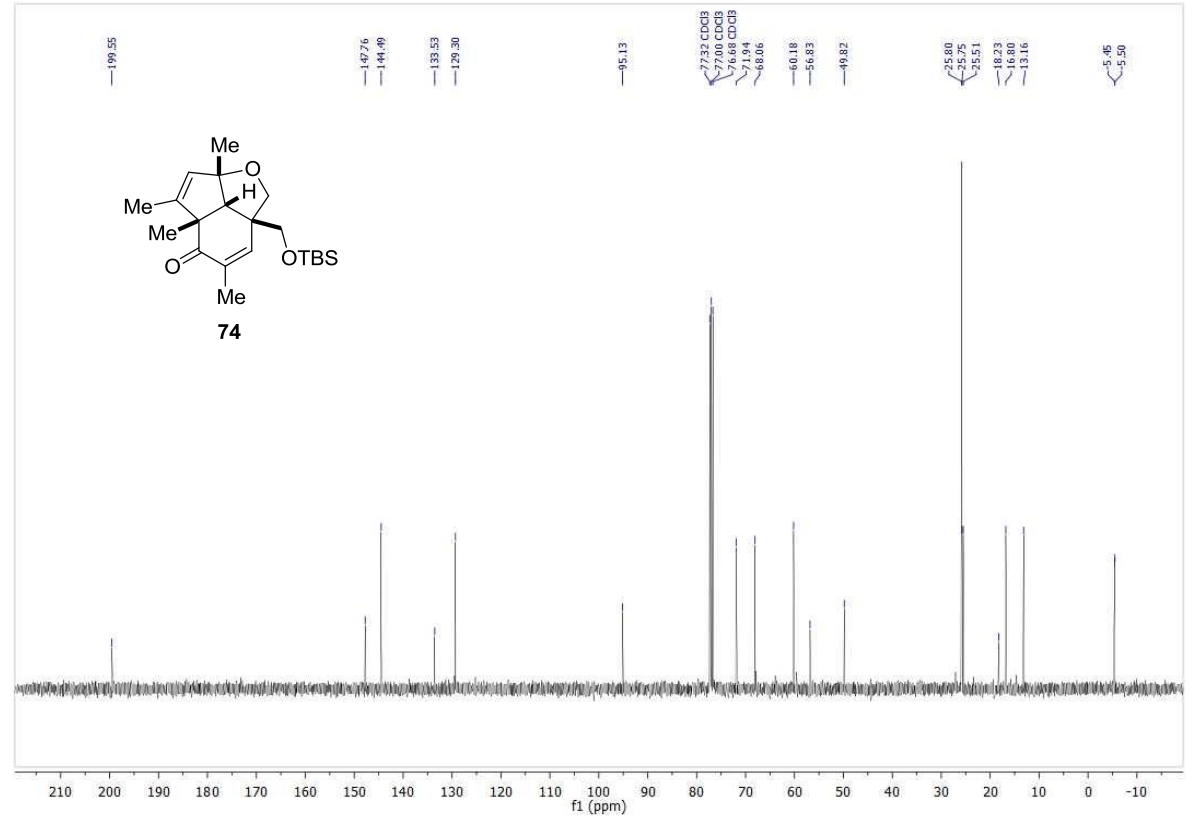

Me
O
H
Me
Me
O
OH
Me
7.26
6.45
6.45
5.22
5.22
3.88
3.86
3.63
3.60
3.51
3.48
3.41
3.38
2.20
1.81
1.81
1.59
1.58
1.50
1.30
1.00
0.97
1.03
1.03
1.09
1.04
1.02
3.24
3.08
3.08
3.17
f1 (ppm)

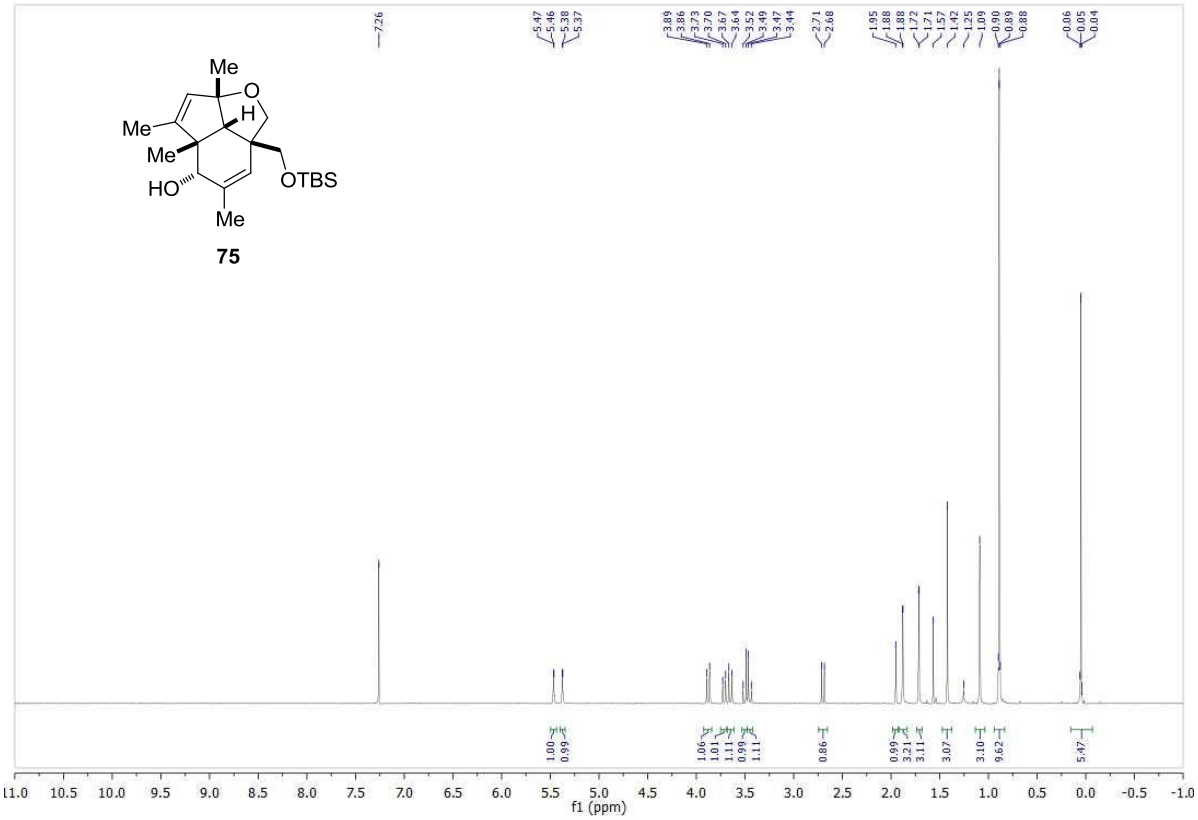
73

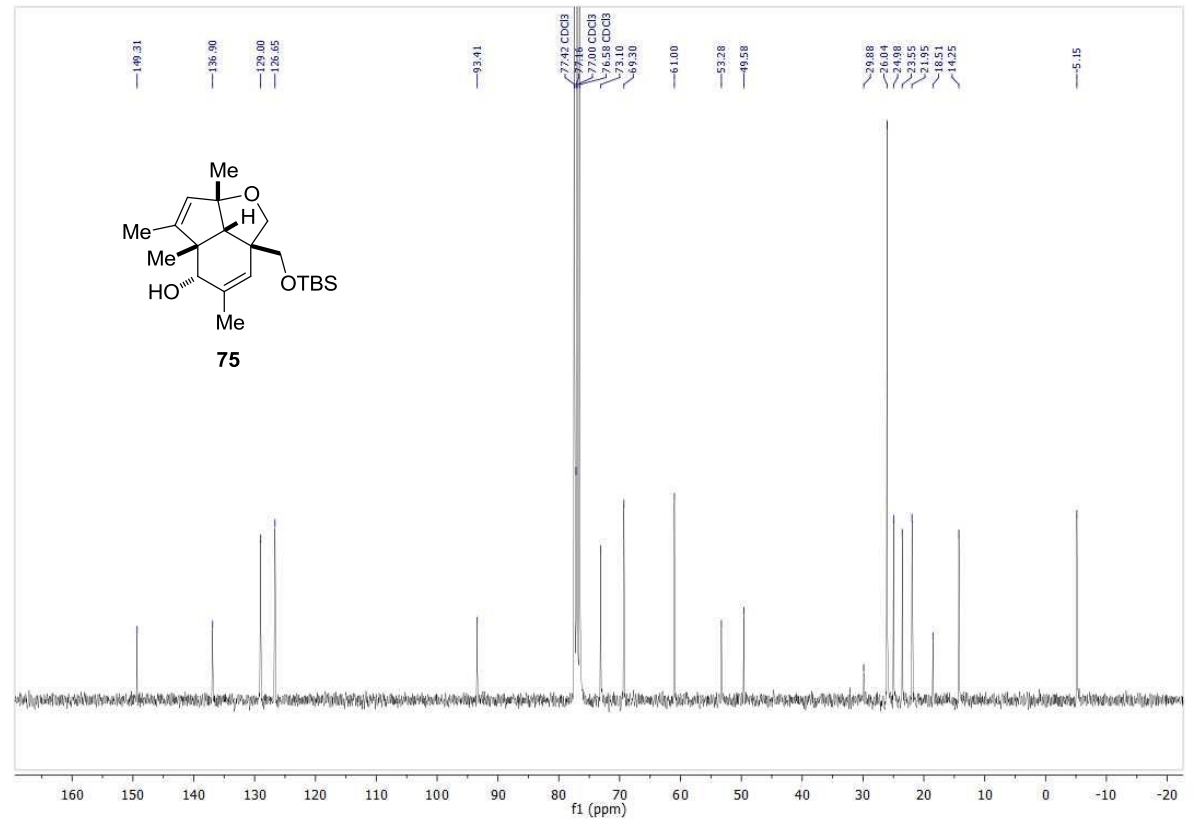

Me
O
H
Me
Me
O
OH
Me
199.40
147.89
142.89
134.62
129.08
95.61
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
72.45
68.73
60.10
56.86
49.64
25.52
25.47
16.87
13.13
f1 (ppm)

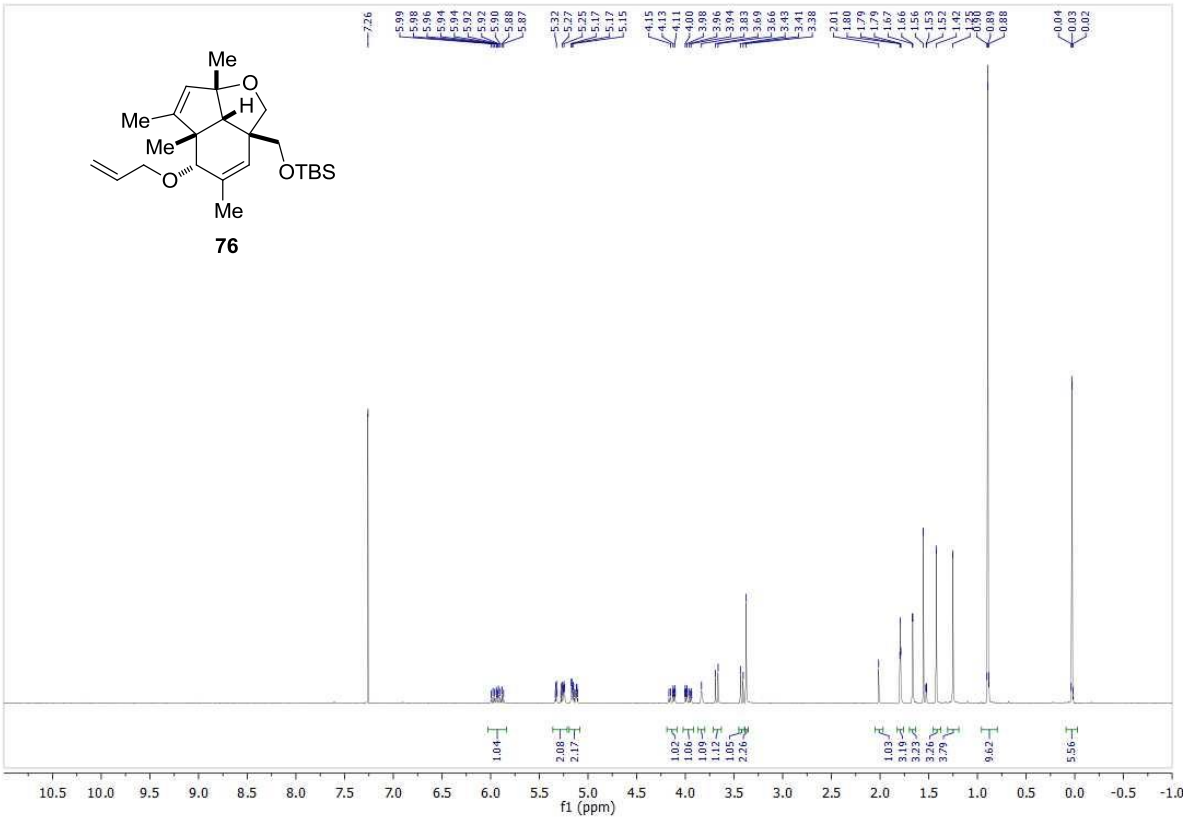
73

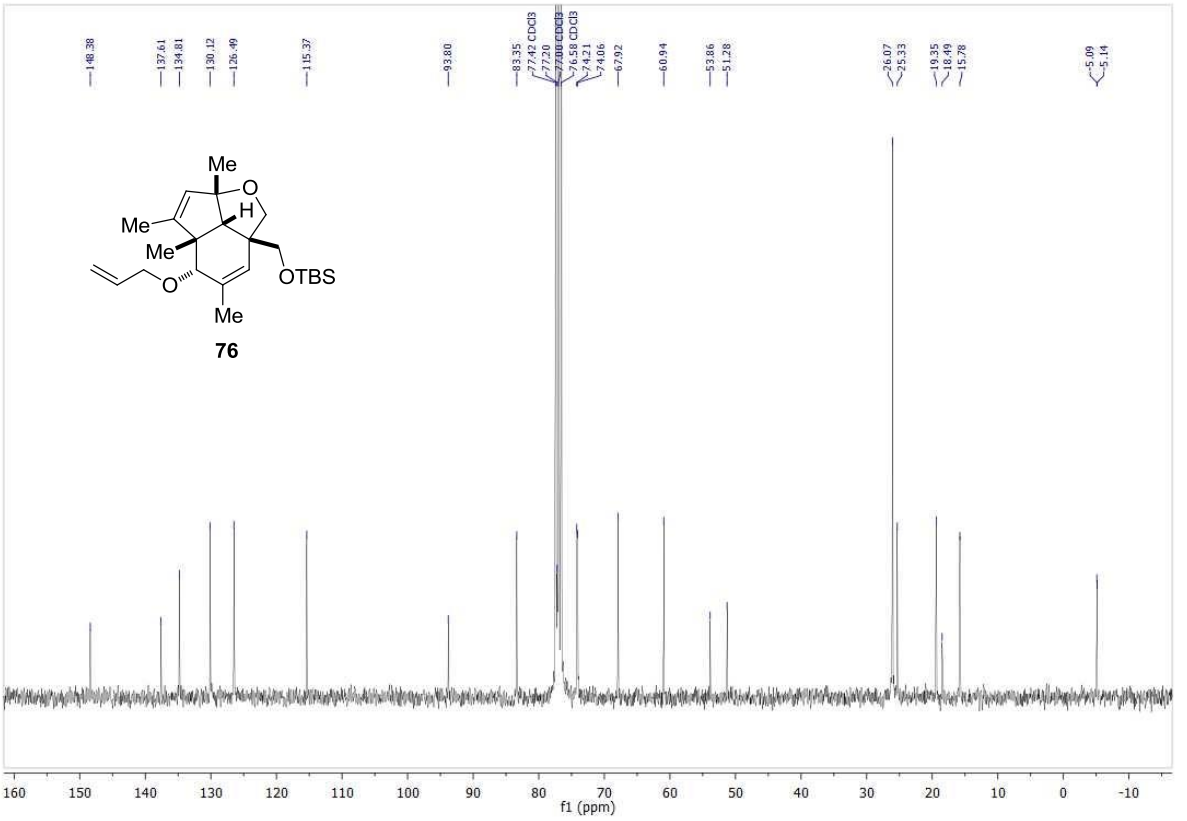

Me
O
H
Me
Me
O
OTBS
Me
74
f1 (ppm)

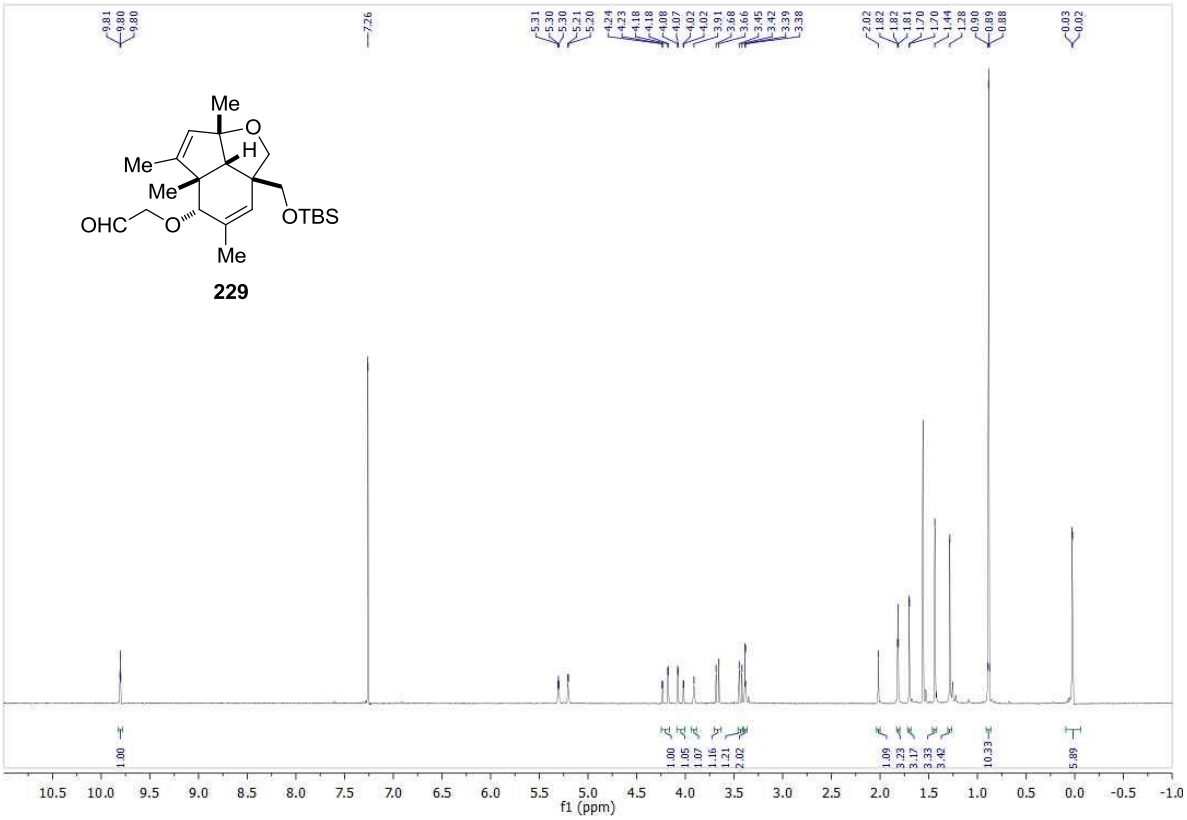

Me
O
H
Me
Me
O
OTBS
Me
74
f1 (ppm)

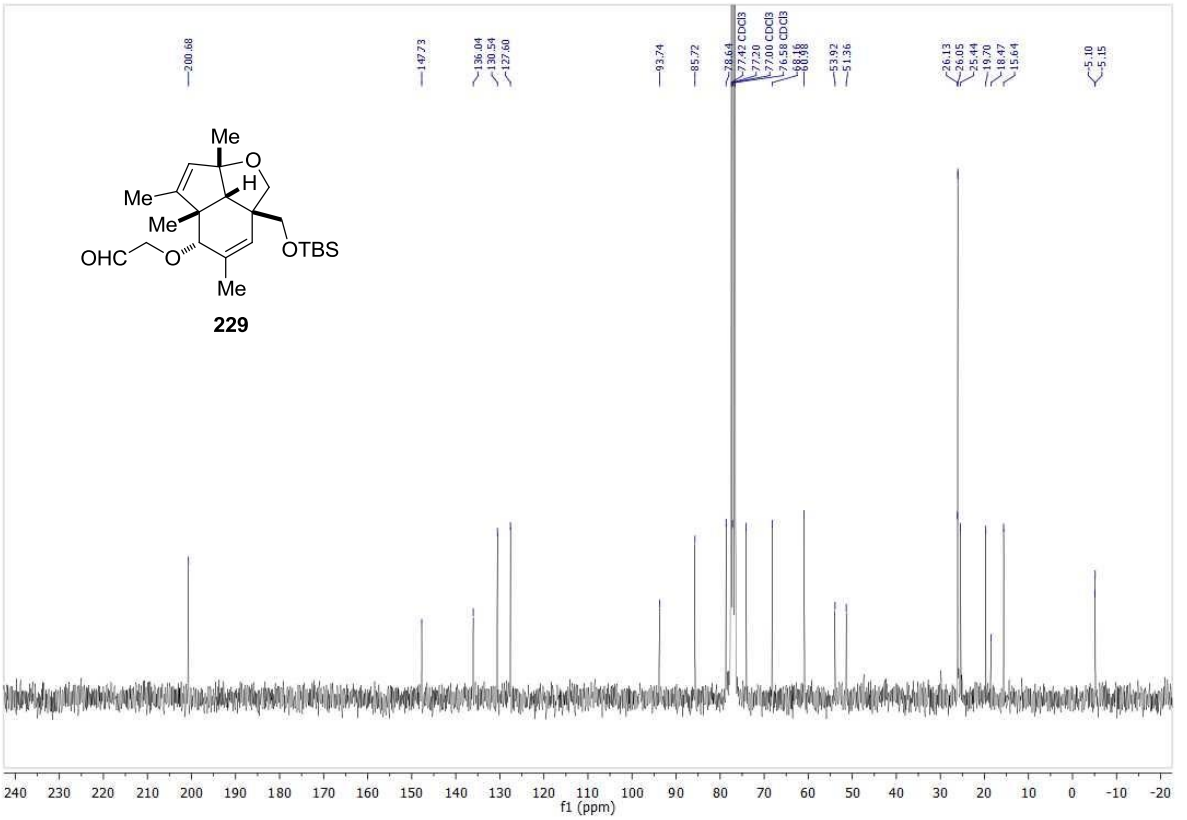

Me
O
H
Me
Me
HO
OTBS
Me
75
f1 (ppm)

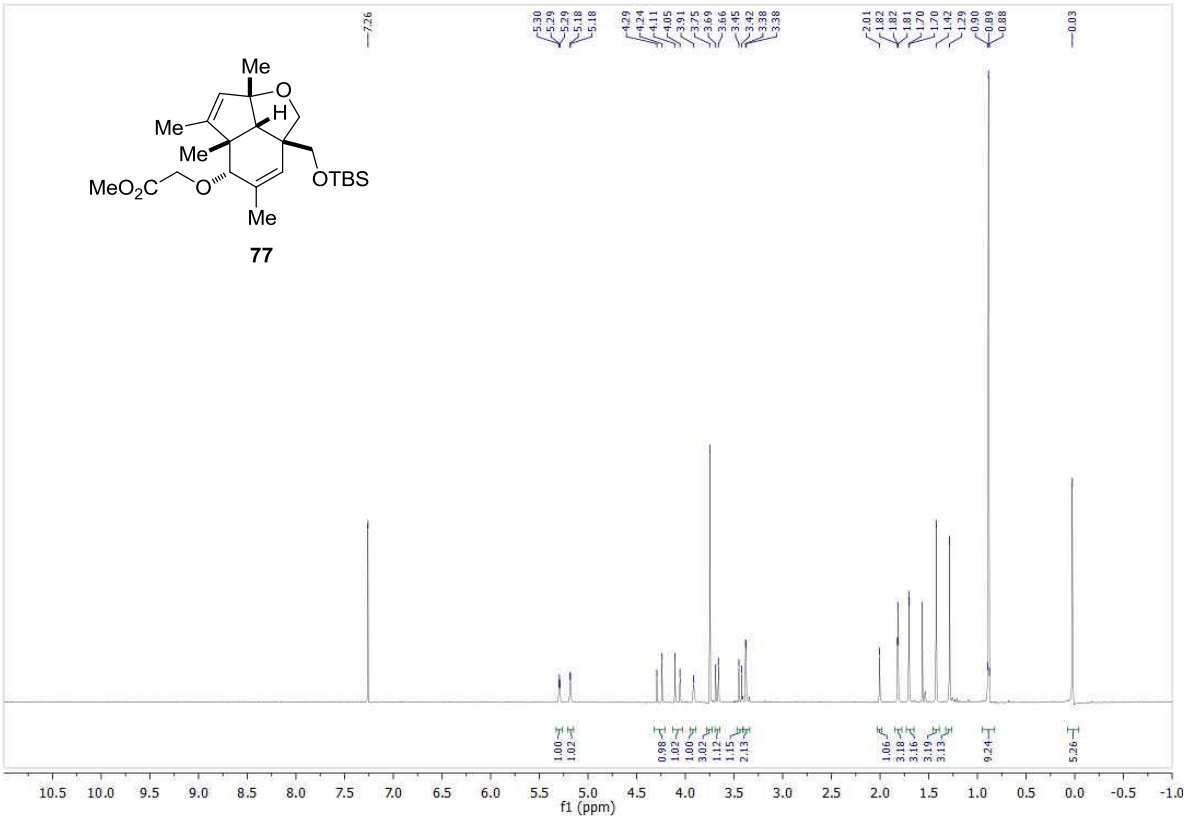

Me
O
H
Me
Me
HO
OTBS
Me
75
f1 (ppm)

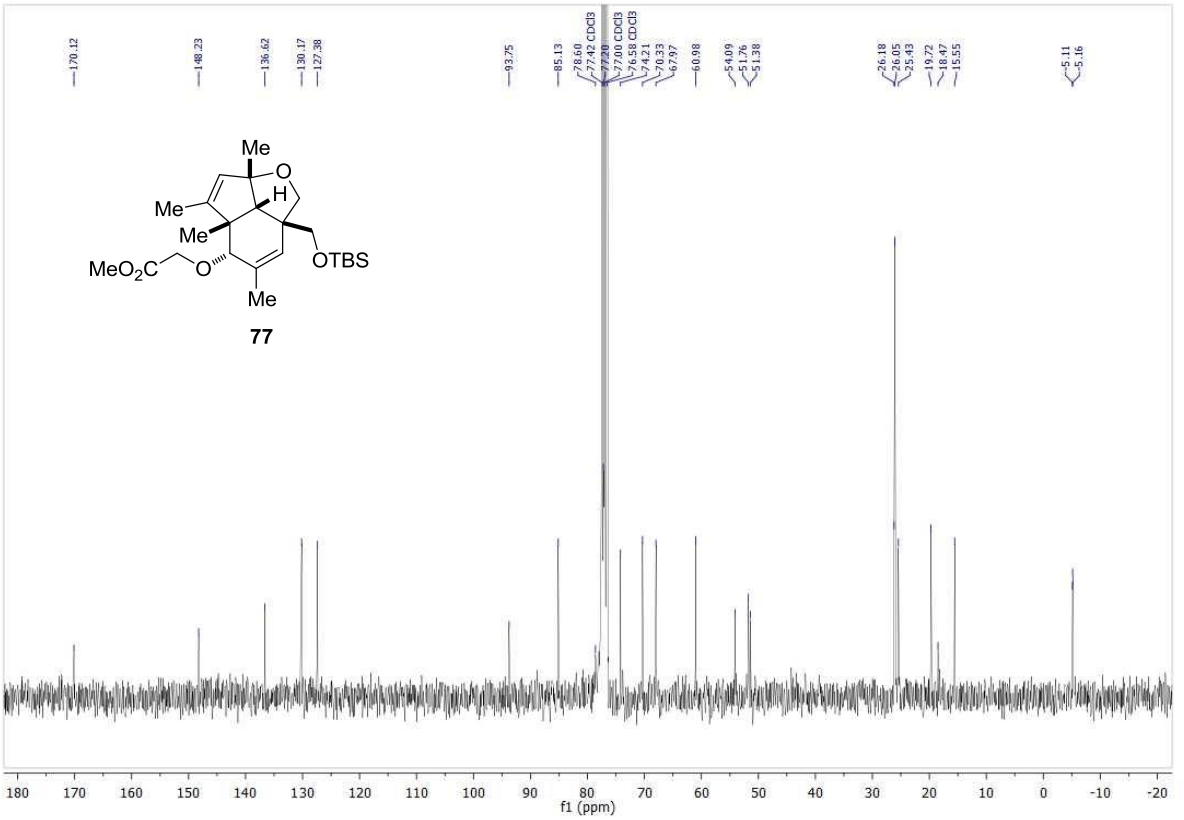

Me
O
H
Me
Me
O
OTBS
Me
76
f1 (ppm)

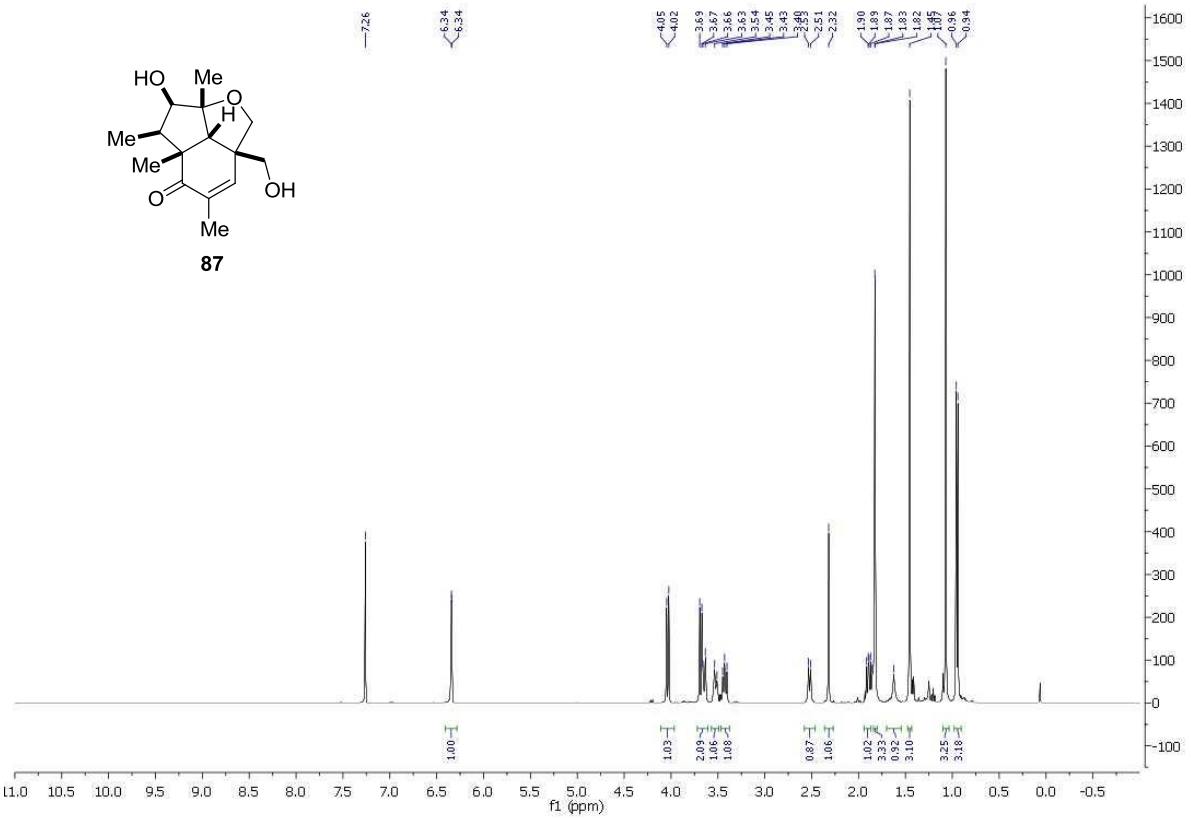

Me
O
H
Me
Me
O
OTBS
Me
76
f1 (ppm)

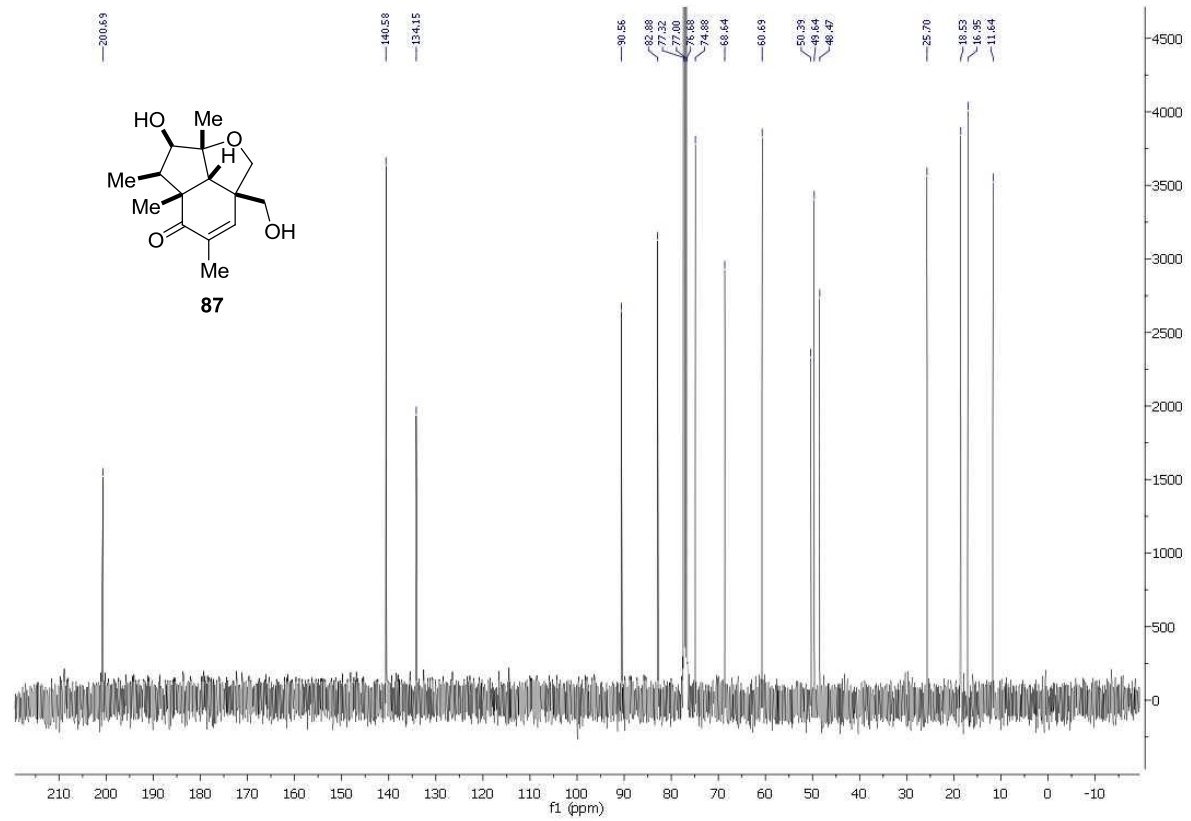

Me
O
H
Me
Me
OHC
O
OTBS
Me
229
f1 (ppm)

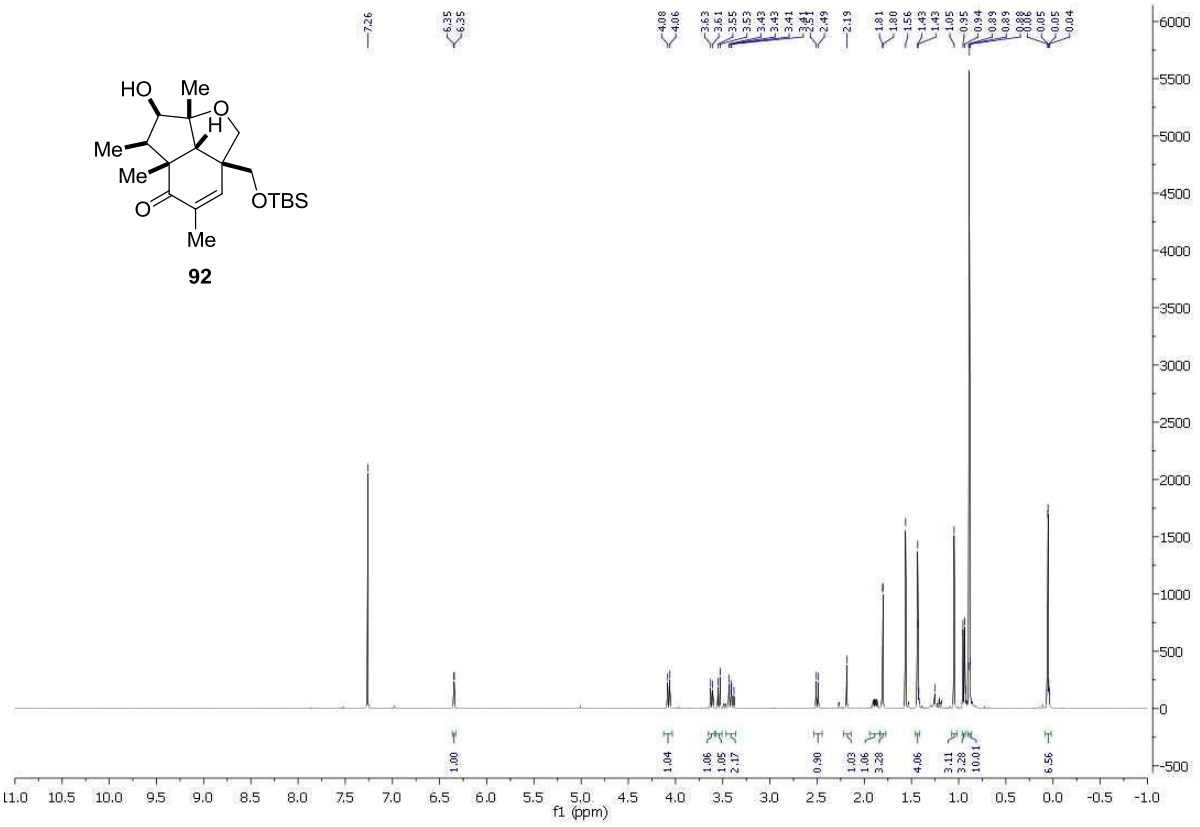

Me
O
H
Me
Me
OHC
O
OTBS
Me
229
f1 (ppm)

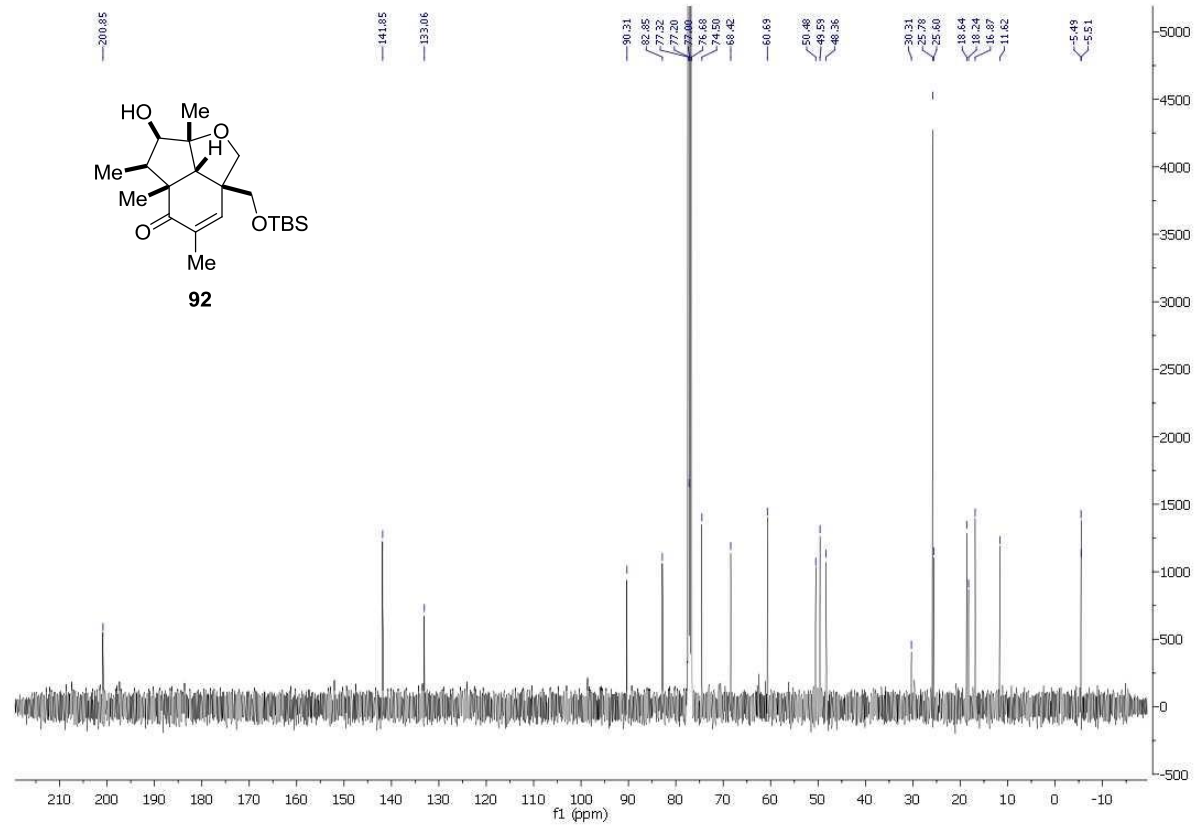

Me
O
H
Me
Me
MeO2C
O
OTBS
Me
77
7.26
5.30
5.29
5.29
5.18
5.18
4.29
4.24
4.11
4.05
3.91
3.75
3.69
3.66
3.45
3.42
3.38
3.38
2.01
1.82
1.82
1.81
1.70
1.70
1.42
1.29
0.90
0.89
0.88
0.03
1.00
1.02
0.98
1.02
1.00
3.02
1.12
1.15
2.13
1.06
3.18
3.16
3.19
3.13
9.24
5.26
f1 (ppm)

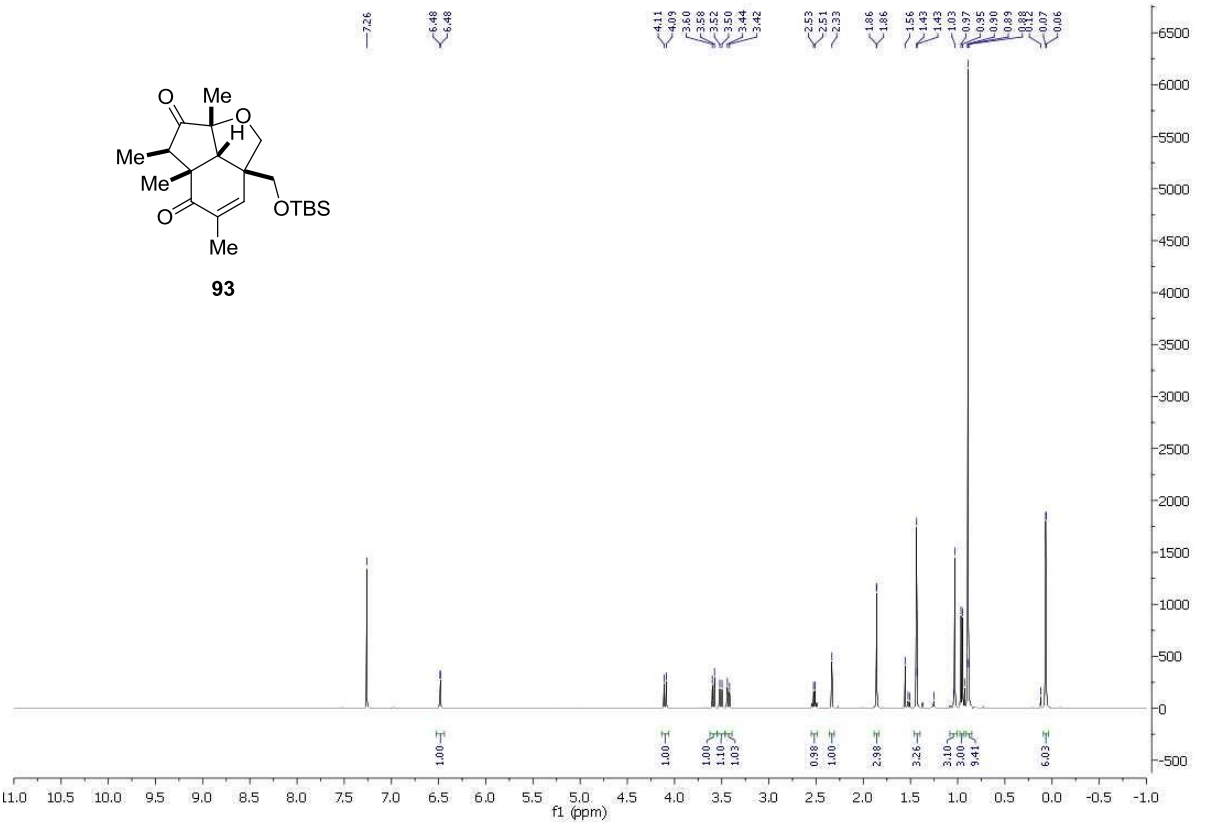

Me
O
H
Me
Me
MeO2C
O
OTBS
Me
77
170.12
148.23
136.62
130.17
127.38
93.75
85.13
78.60
77.42 CDCl3
77.00 CDCl3
76.58 CDCl3
74.21
70.33
67.97
60.98
54.09
51.76
51.38
26.18
26.05
25.43
19.72
18.47
15.55
5.11
5.16
f1 (ppm)

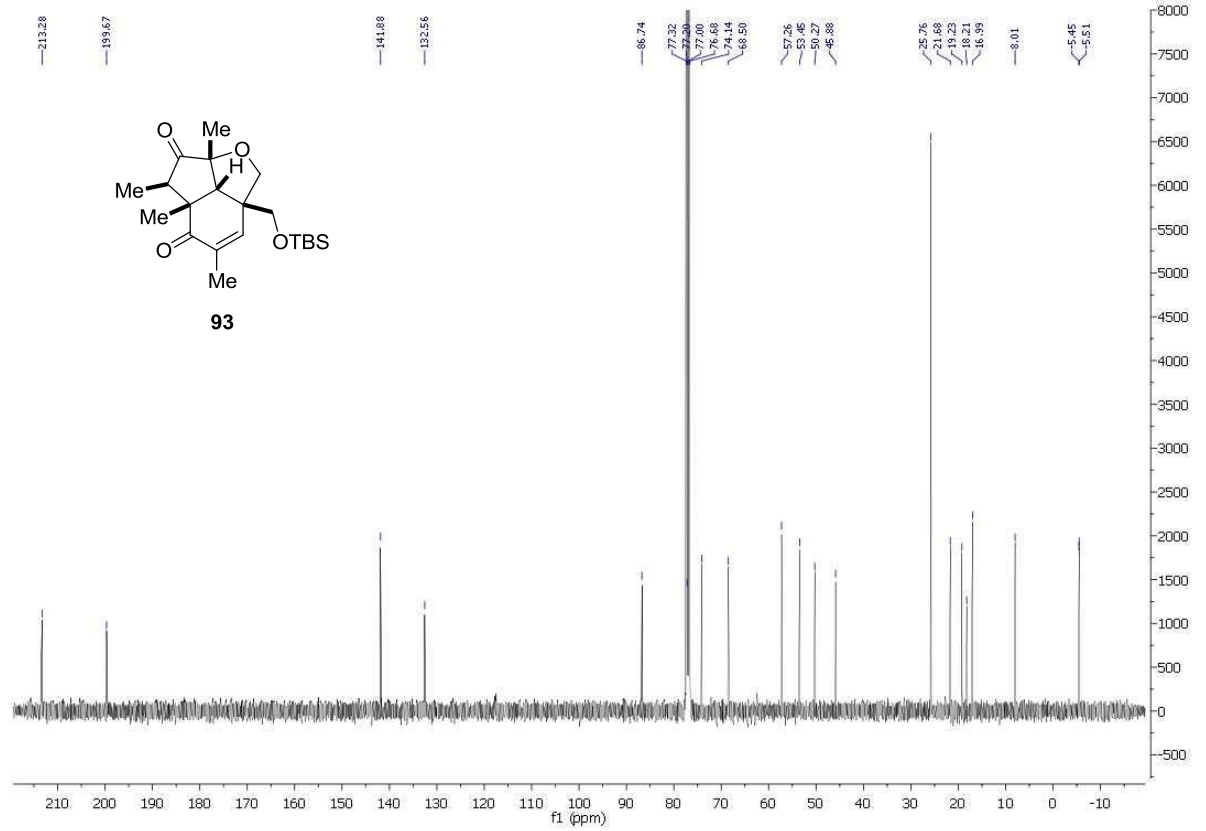

HO
Me
O
H
Me
Me
O
OH
Me
87
f1 (ppm)

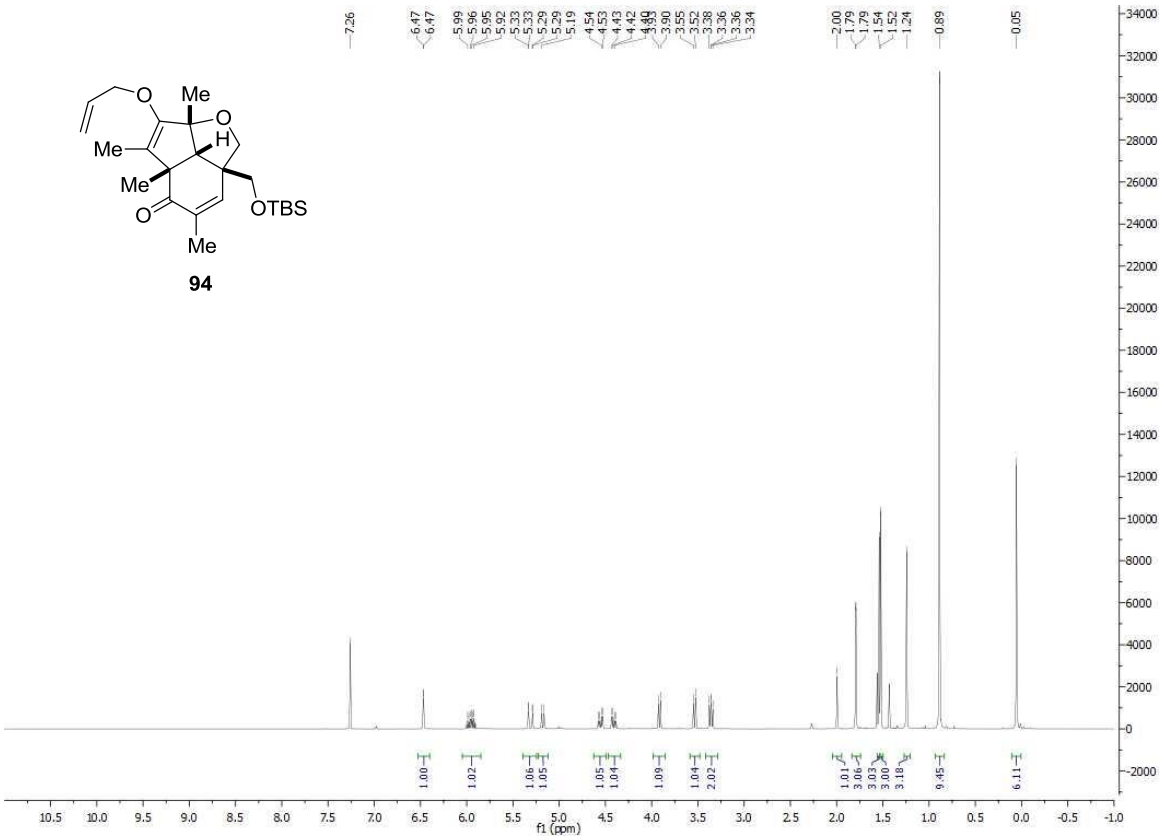

HO
Me
O
H
Me
Me
O
OH
Me
87
f1 (ppm)


HO
Me
O
H
Me
Me
O
OTBS
Me
92
f1 (ppm)


HO
Me
O
H
Me
Me
O
OTBS
Me
92
f1 (ppm)

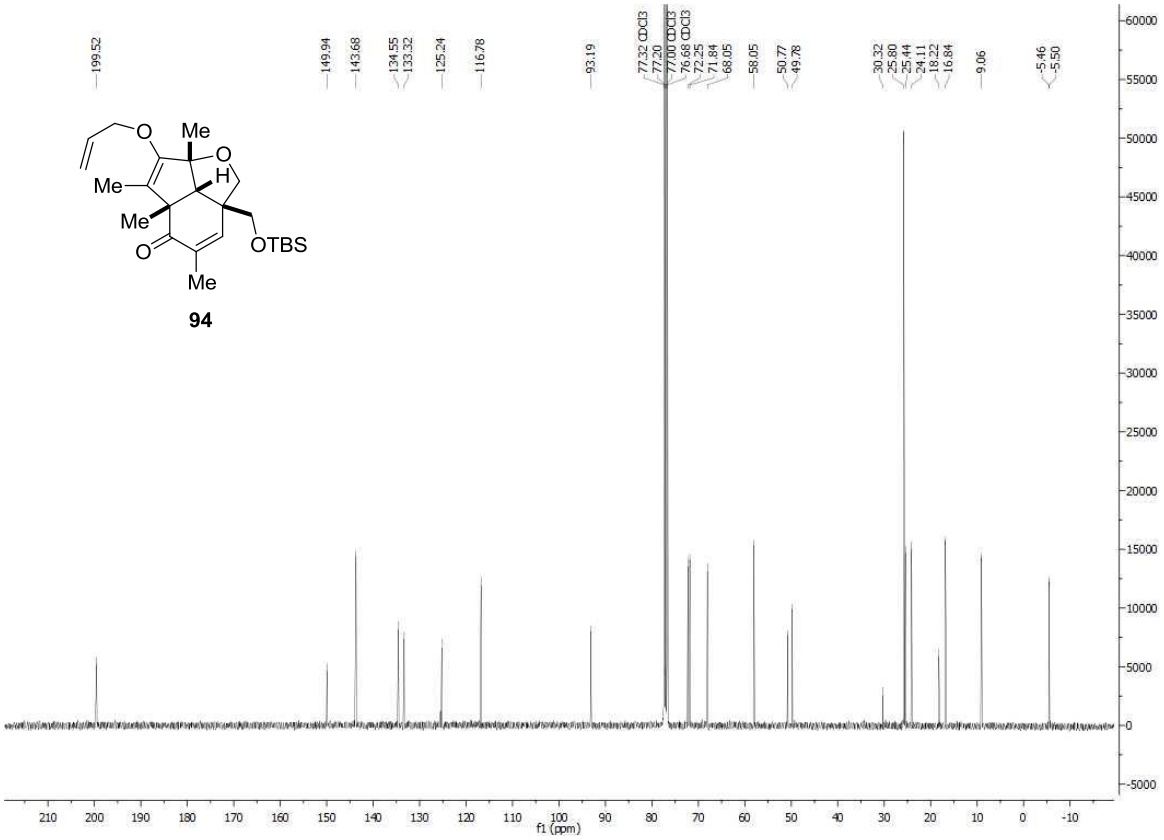

Me
O
O
H
Me
Me
O
OTBS
Me
93
f1 (ppm)


Me
O
O
H
Me
Me
O
OTBS
Me
93
f1 (ppm)


7.26
6.47
6.47
5.99
5.96
5.95
5.92
5.33
5.33
5.29
5.29
5.19
4.54
4.53
4.43
4.42
3.90
3.55
3.52
3.38
3.36
3.36
3.34
2.00
1.79
1.79
1.54
1.52
1.24
0.89
0.05
1.00
1.02
1.06
1.05
1.05
1.04
1.09
1.04
2.02
1.01
3.06
3.03
3.00
3.18
9.45
6.11
f1 (ppm)

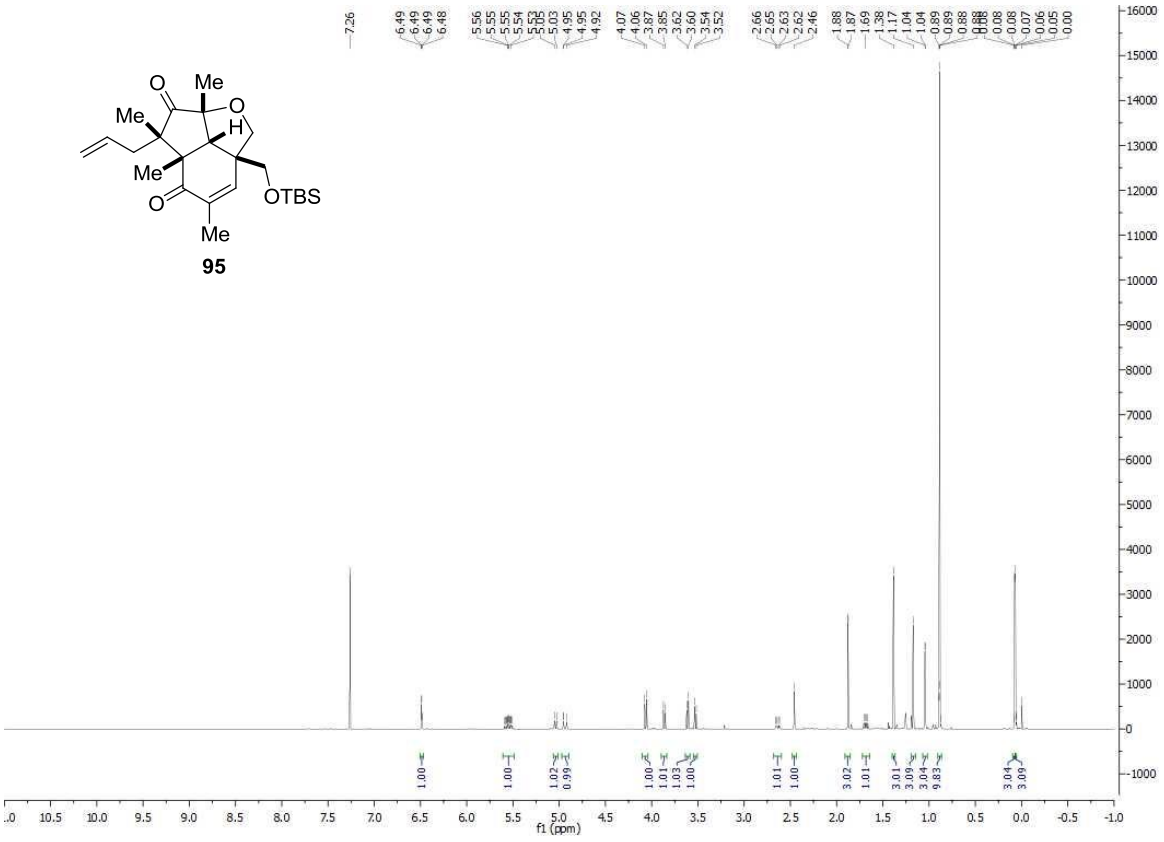
O
Me
O
H
Me
Me
O
OTBS
Me

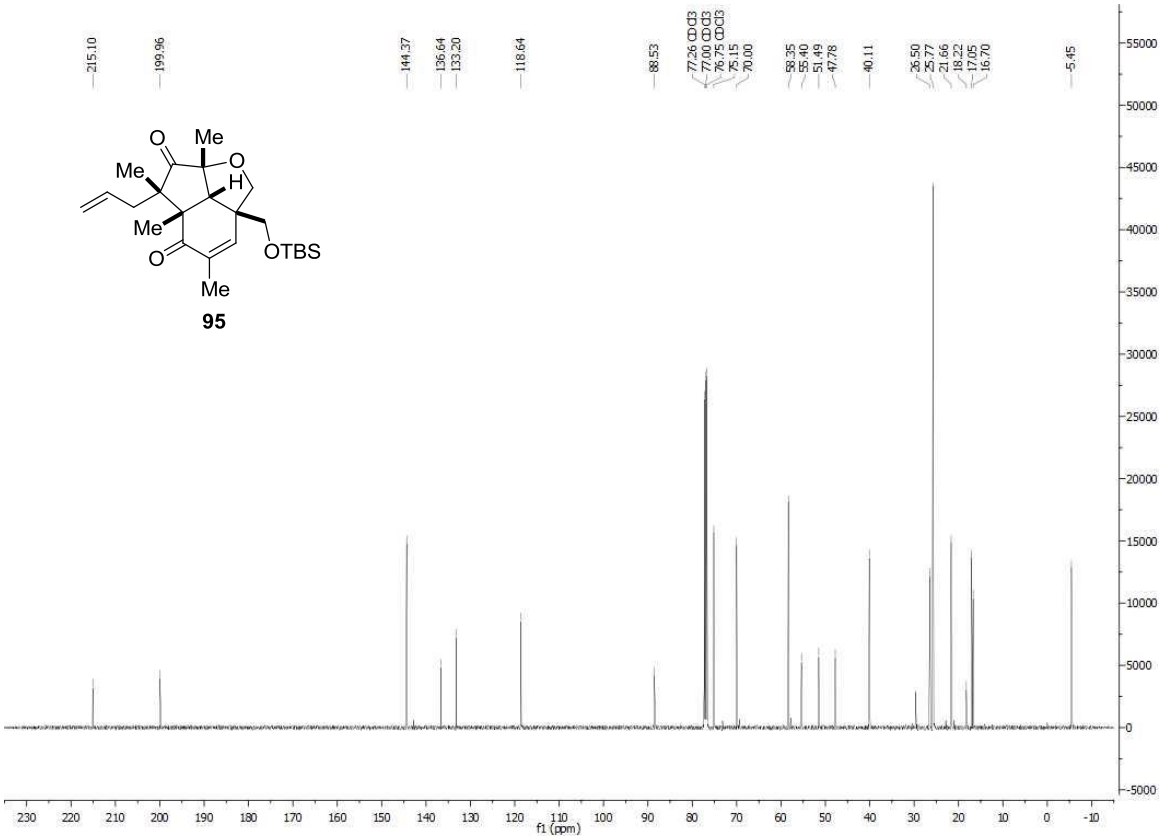
94

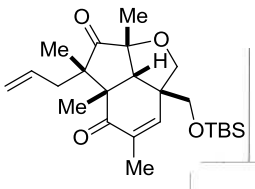

199.52
149.94
143.68
134.55
133.32
125.24
116.78
93.19
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
72.25
71.84
68.05
58.05
50.77
49.78
30.32
25.80
25.44
24.11
18.22
16.84
9.06
-5.46
-5.50
f1 (ppm)

O
Me
O
H
Me
Me
O
OTBS
Me

94

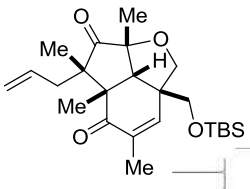

Me
O
Me
O
H
Me
O
OTBS
Me
95


Me
O
Me
O
H
Me
O
OTBS
Me
95

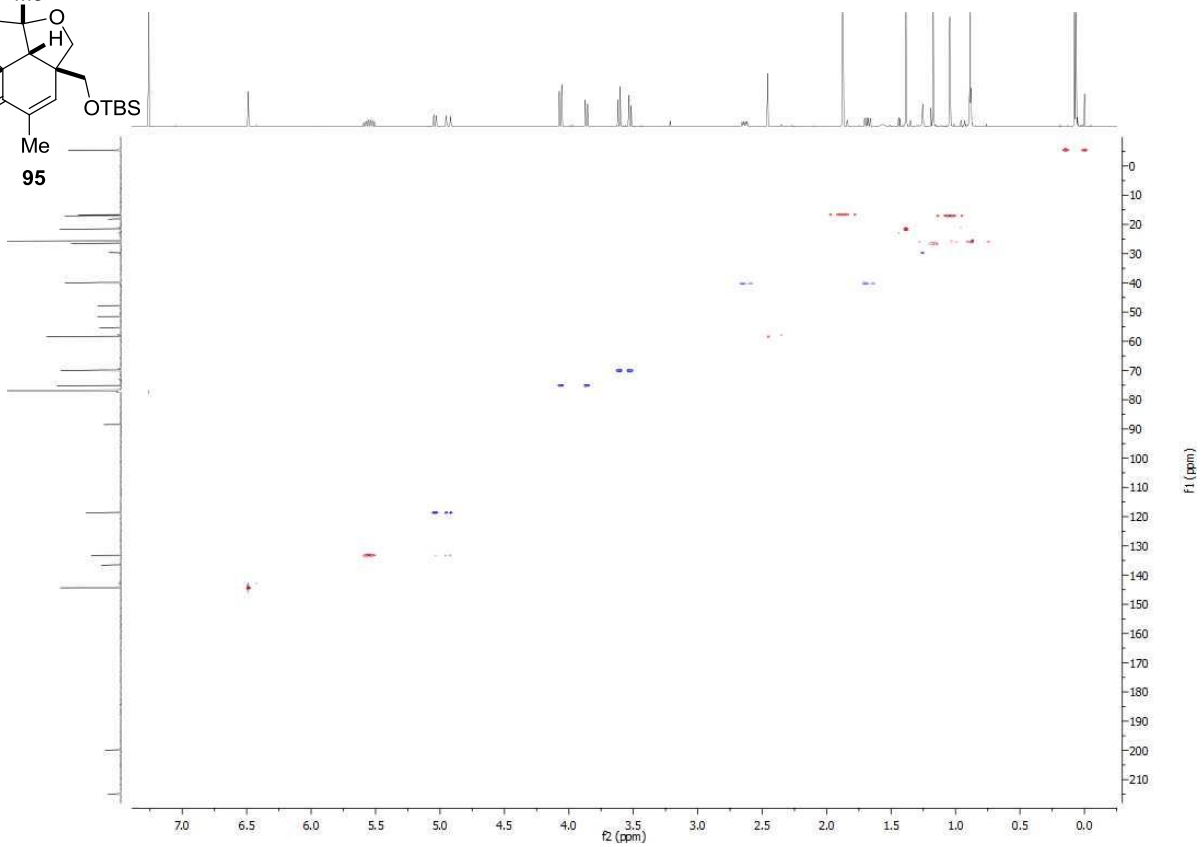

O
Me
Me
O
H
Me
O
OTBS
Me

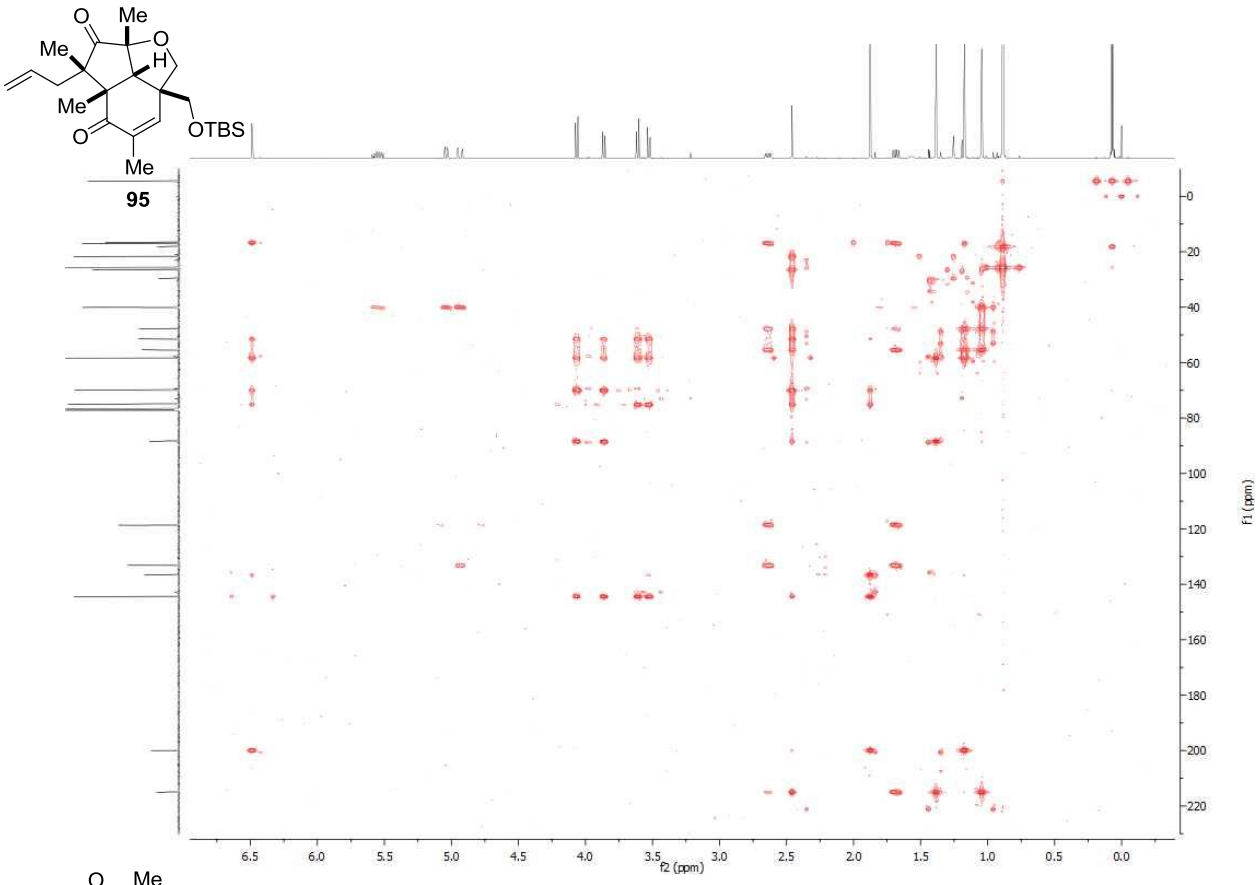
95

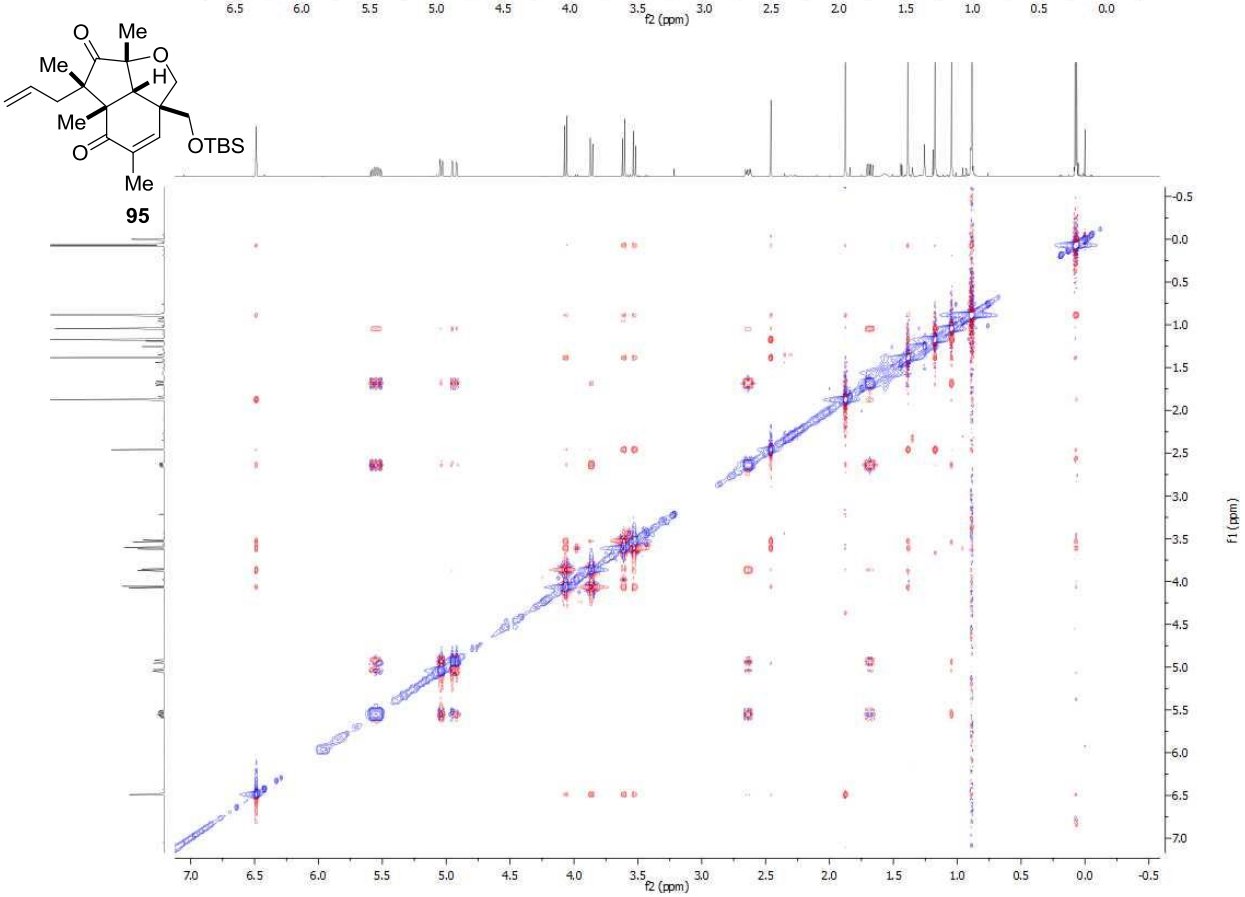
f2 (ppm)
f1 (ppm)

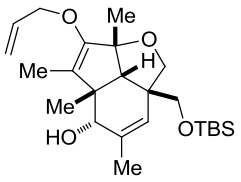

O
Me
Me
O
H
Me
O
OTBS
Me

95


f2 (ppm)
f1 (ppm)

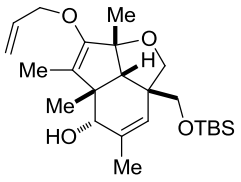

Me
O
Me
O
H
Me
OTBS
O
Me
95
f2 (ppm)
f1 (ppm)


Me
O
Me
O
H
Me
OTBS
O
Me
95
f2 (ppm)
f1 (ppm)


O
Me
O
H
Me
Me
HO
OTBS
Me

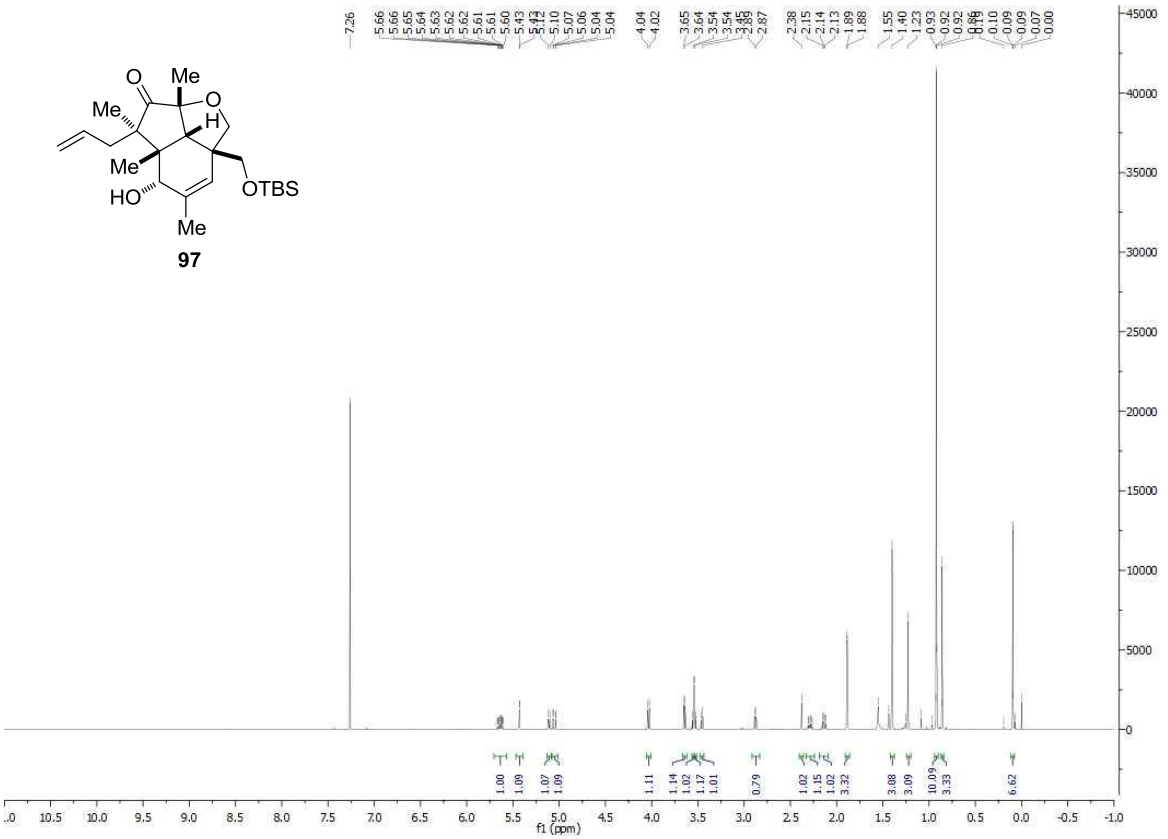
96

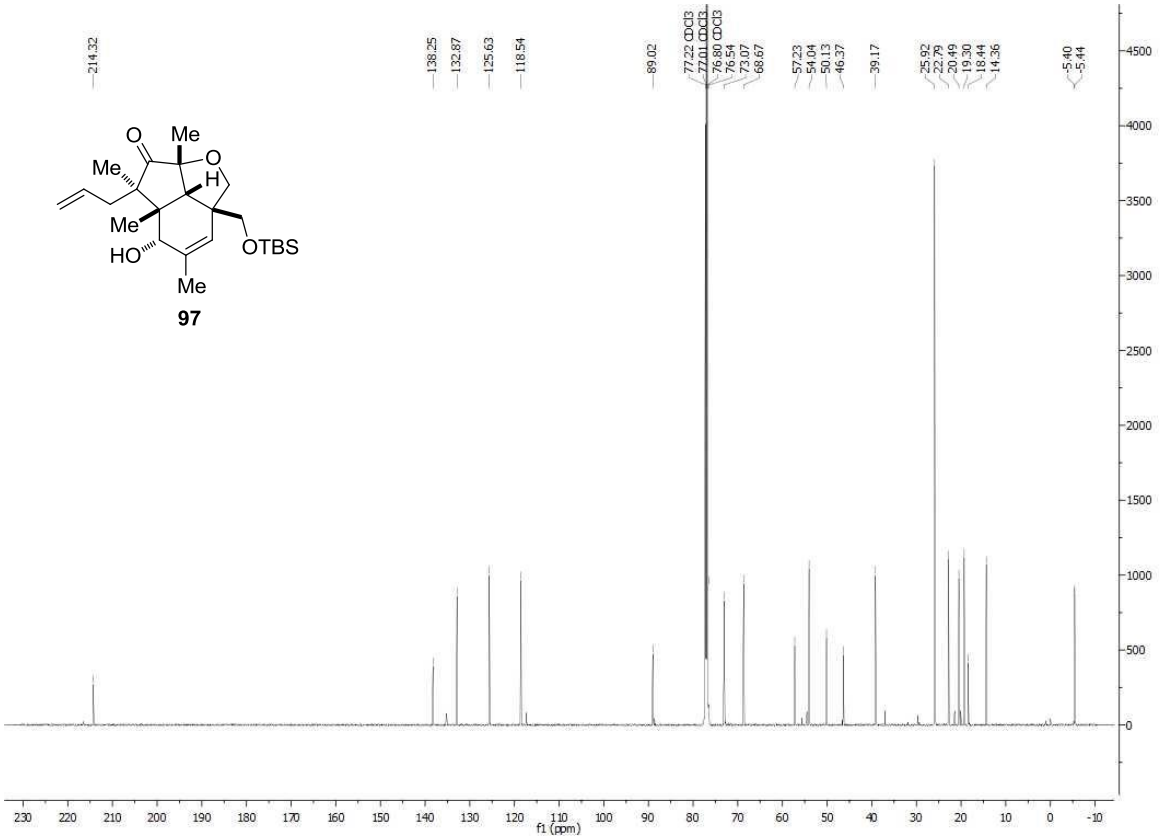
7.26
6.03
6.02
6.01
5.99
5.98
5.96
5.95
5.94
5.46
5.46
5.34
5.33
5.20
4.45
4.43
4.34
4.33
3.90
3.88
3.71
3.68
3.67
3.65
3.49
3.46
2.61
2.59
1.92
1.88
1.87
1.62
1.45
1.25
1.05
0.90
0.89
0.89
0.88
0.07
0.06
0.05
0.04
0.03
1.00
0.98
1.09
1.04
1.02
1.01
0.99
1.01
0.97
1.03
0.98
0.89
1.03
2.98
3.05
3.01
3.09
9.49
6.26
f1 (ppm)

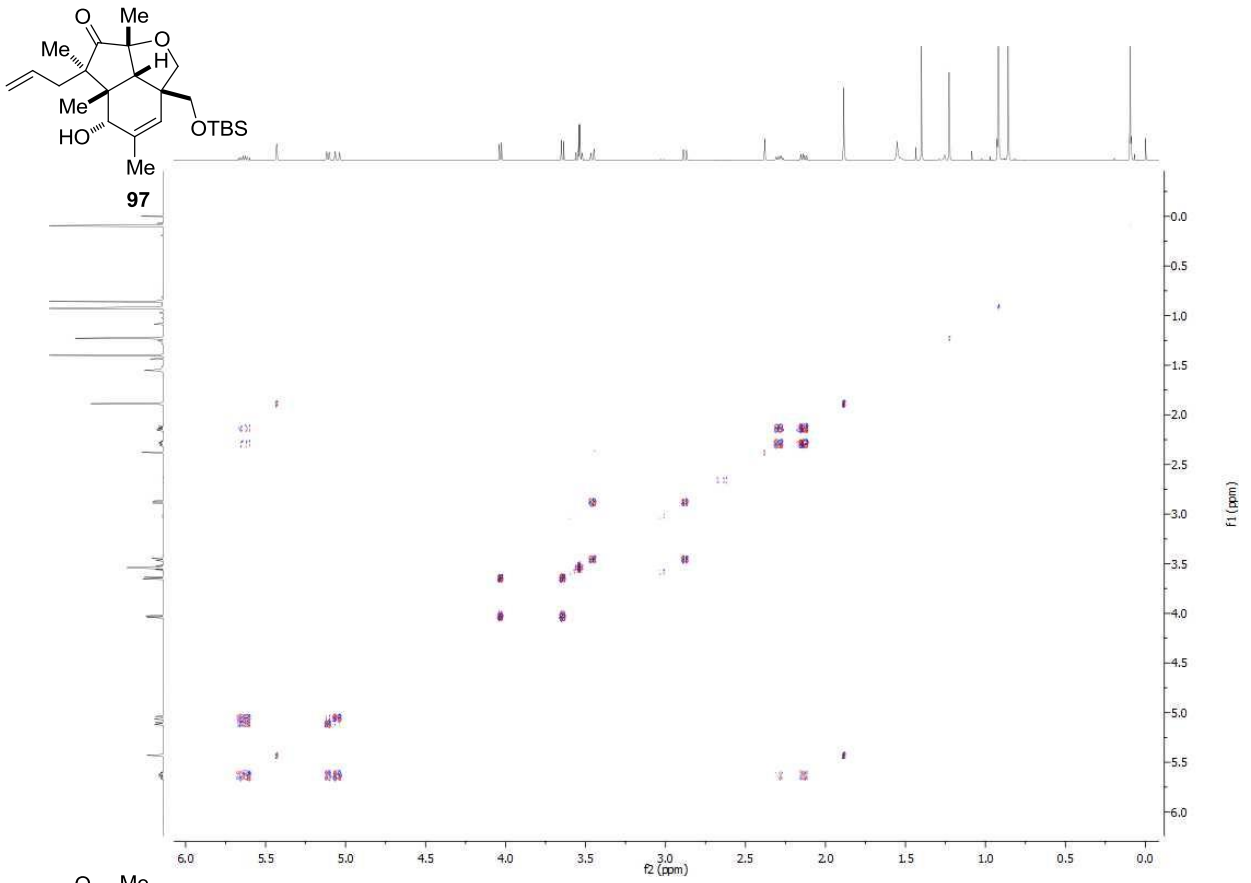

O
Me
O
H
Me
Me
HO
OTBS
Me

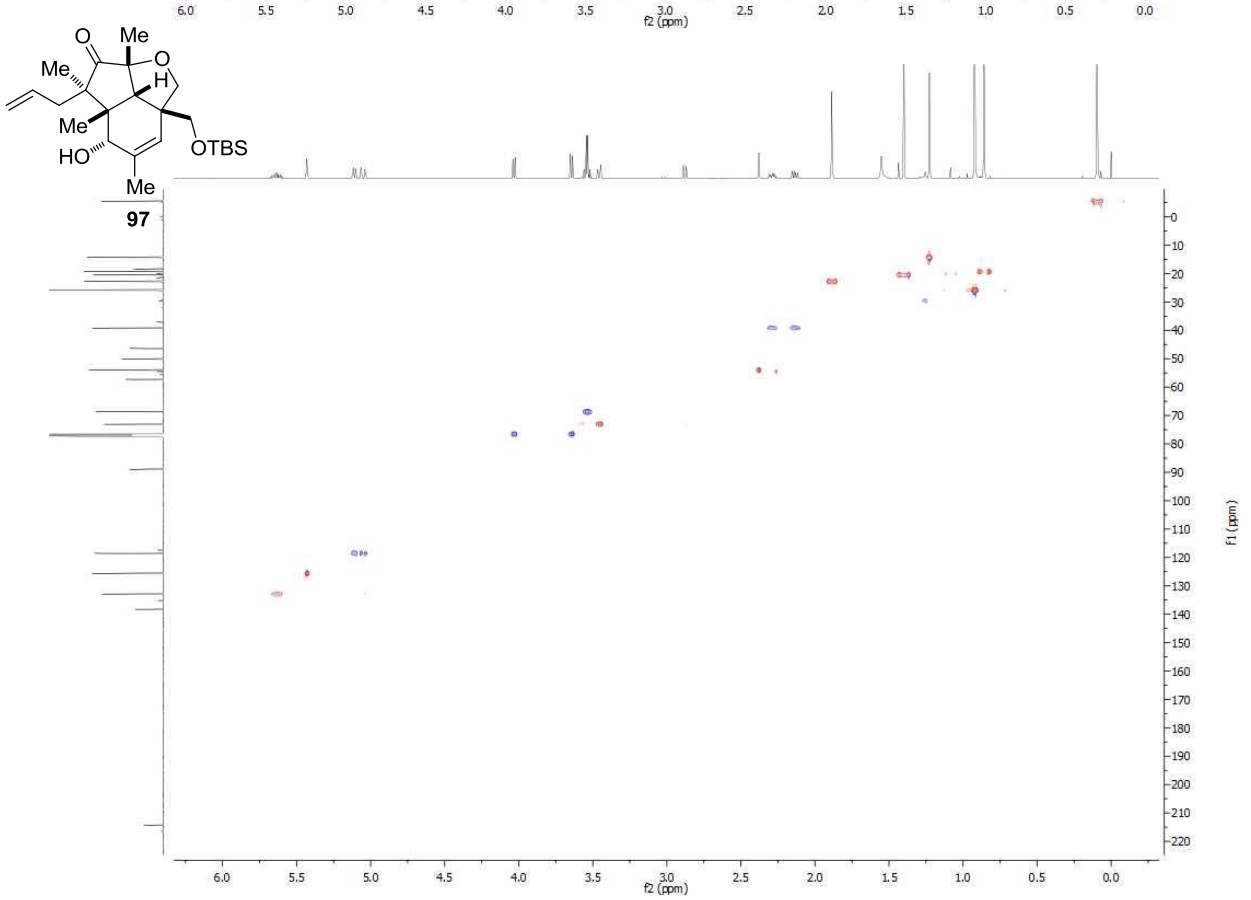
96

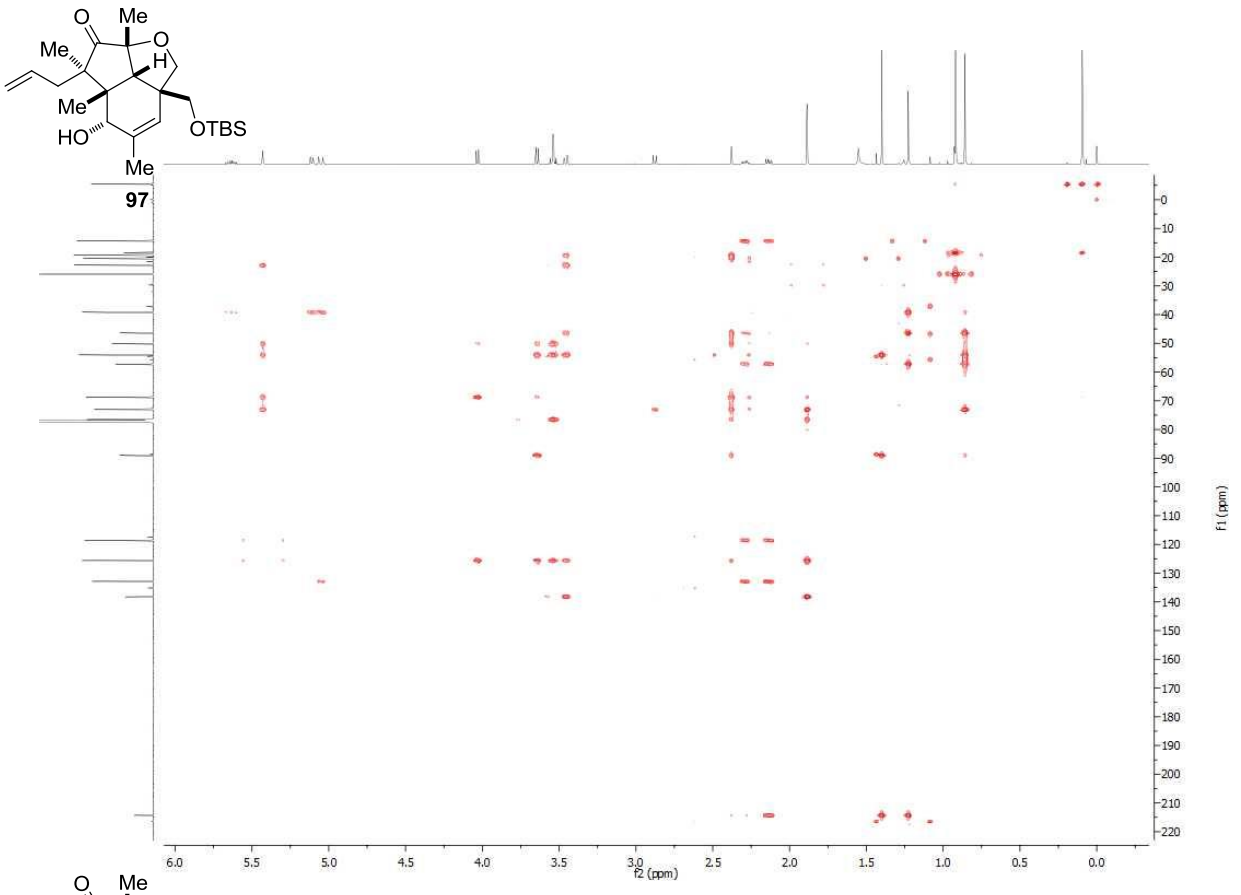
150.89
137.09
134.54
126.65
126.49
117.26
91.95
77.47
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
73.18
72.09
69.23
59.53
49.13
47.66
25.83
25.11
22.00
21.45
18.27
9.37
-5.46
-5.48
f1 (ppm)

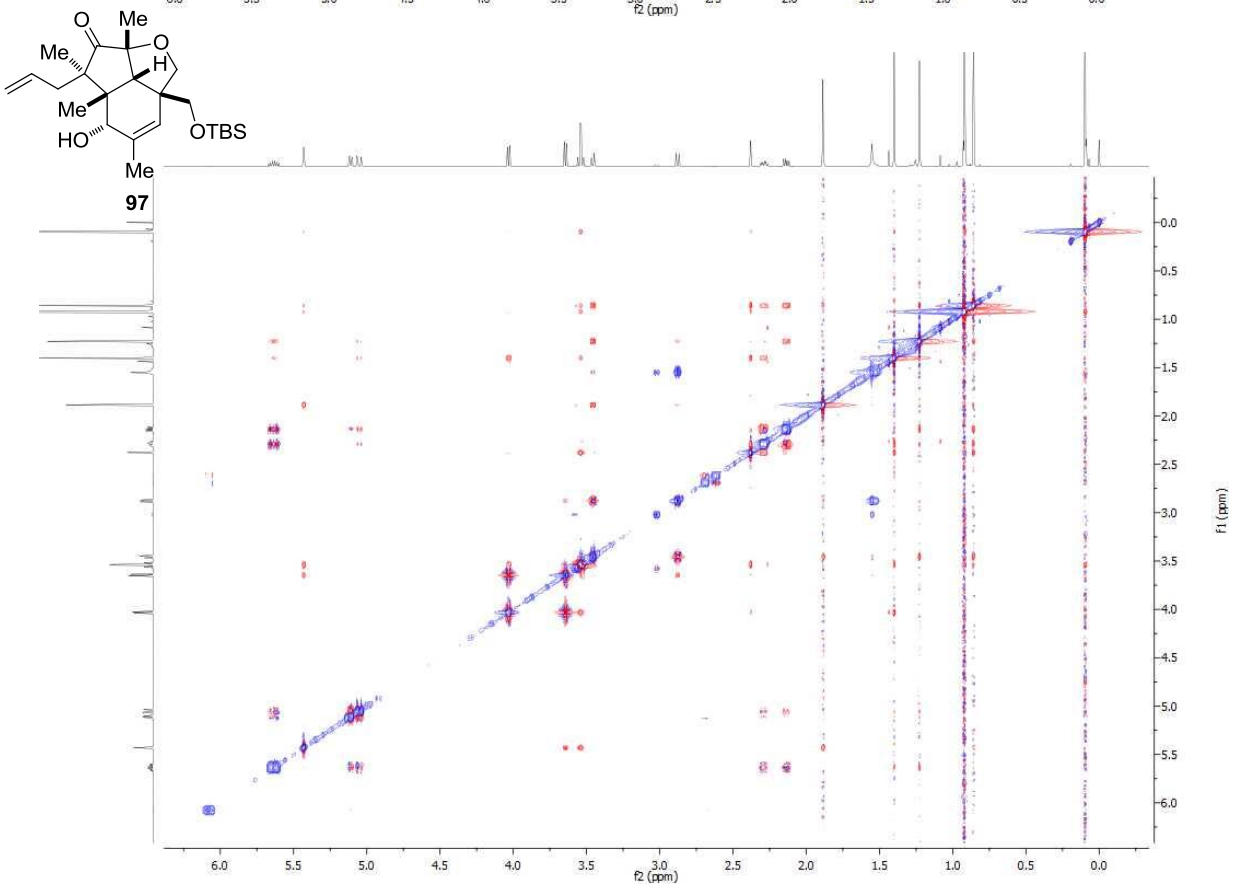

O
Me
Me
O
H
Me
HO
OTBS
Me
97
f1 (ppm)

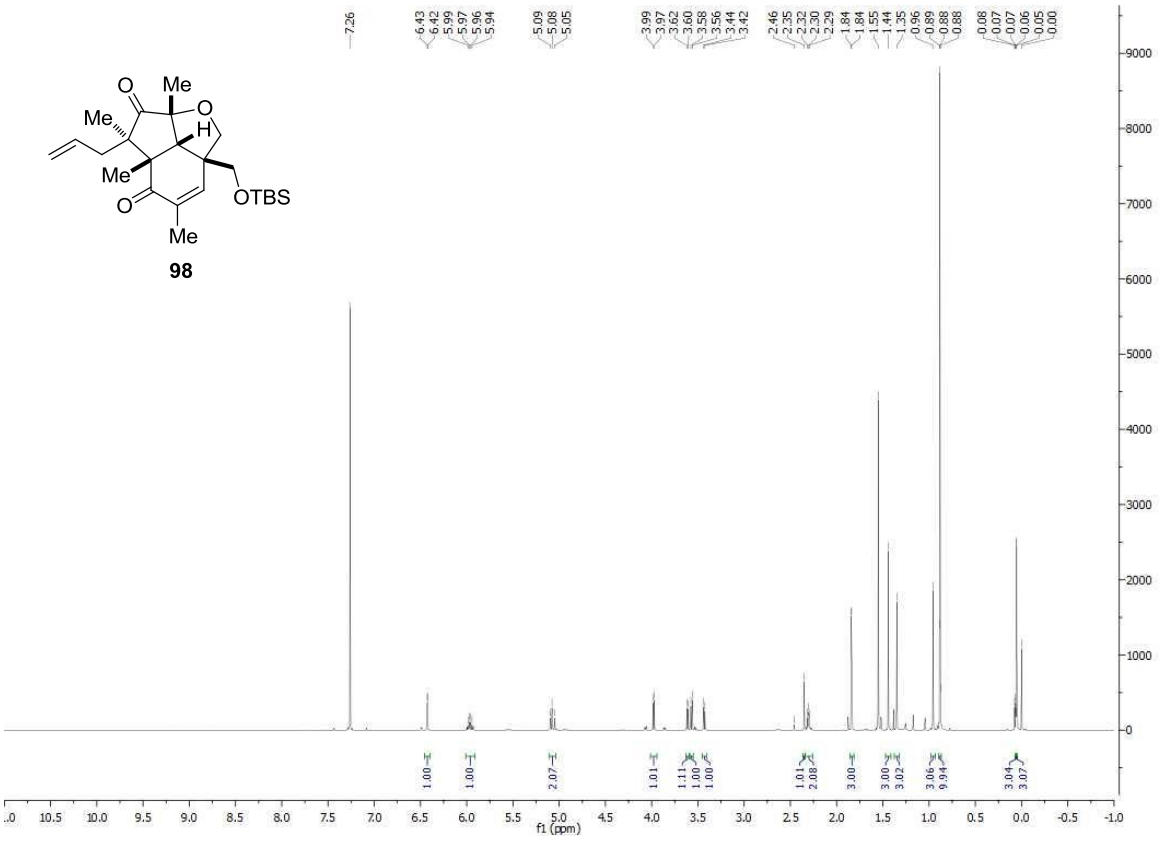

O
Me
Me
O
H
Me
HO
OTBS
Me
97
f1 (ppm)

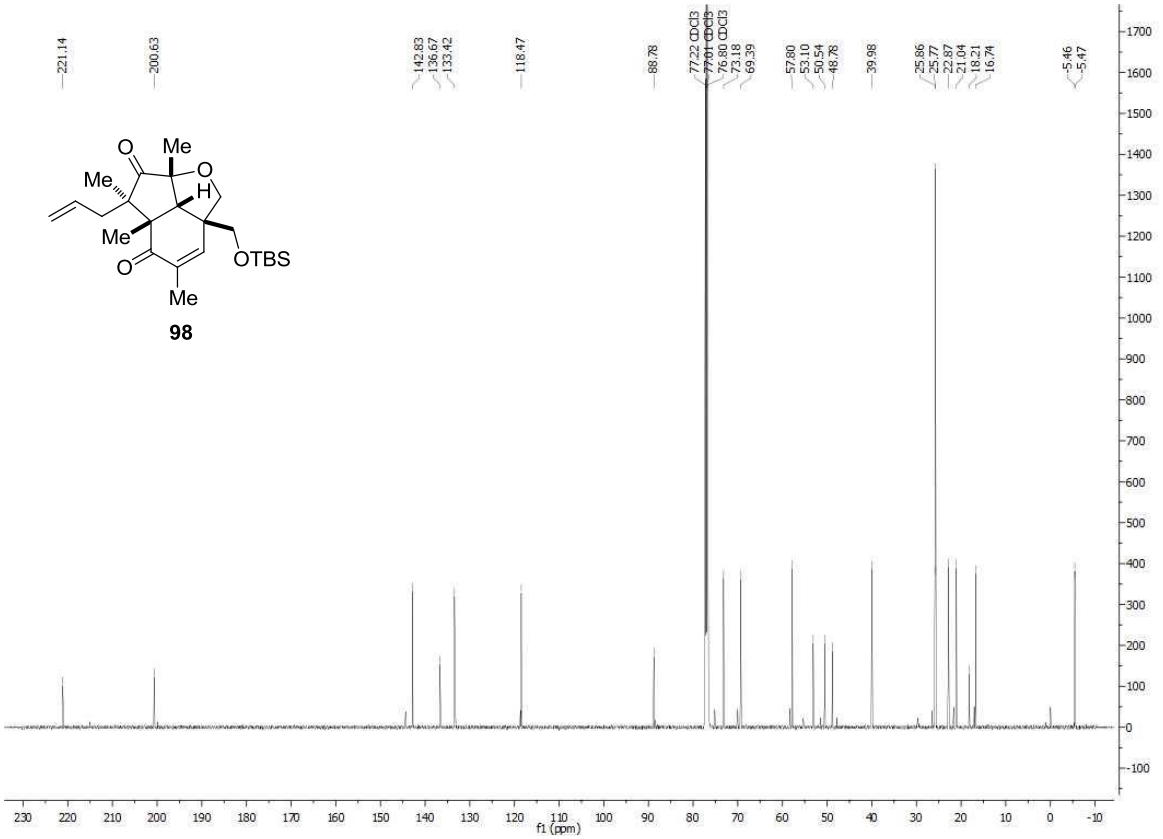

O
Me
Me
O
H
Me
HO
OTBS
Me
97
f2 (ppm)
f1 (ppm)


O
Me
Me
O
H
Me
HO
OTBS
Me
97
f2 (ppm)
f1 (ppm)


O
Me
Me
O
H
Me
HO
OTBS
Me
97
f2 (ppm)
f1 (ppm)


O
Me
Me
O
H
Me
HO
OTBS
Me
97
f2 (ppm)
f1 (ppm)


7.26
6.43
6.42
5.99
5.97
5.96
5.94
5.09
5.08
5.05
3.99
3.97
3.62
3.60
3.58
3.56
3.44
3.42
2.46
2.35
2.32
2.30
2.29
1.84
1.84
1.55
1.44
1.35
0.96
0.89
0.88
0.88
0.08
0.07
0.07
0.07
0.06
0.05
0.00
1.00
1.00
2.07
1.01
1.11
1.00
1.00
1.01
2.08
3.00
3.00
3.02
3.06
9.94
3.04
3.07
f1 (ppm)

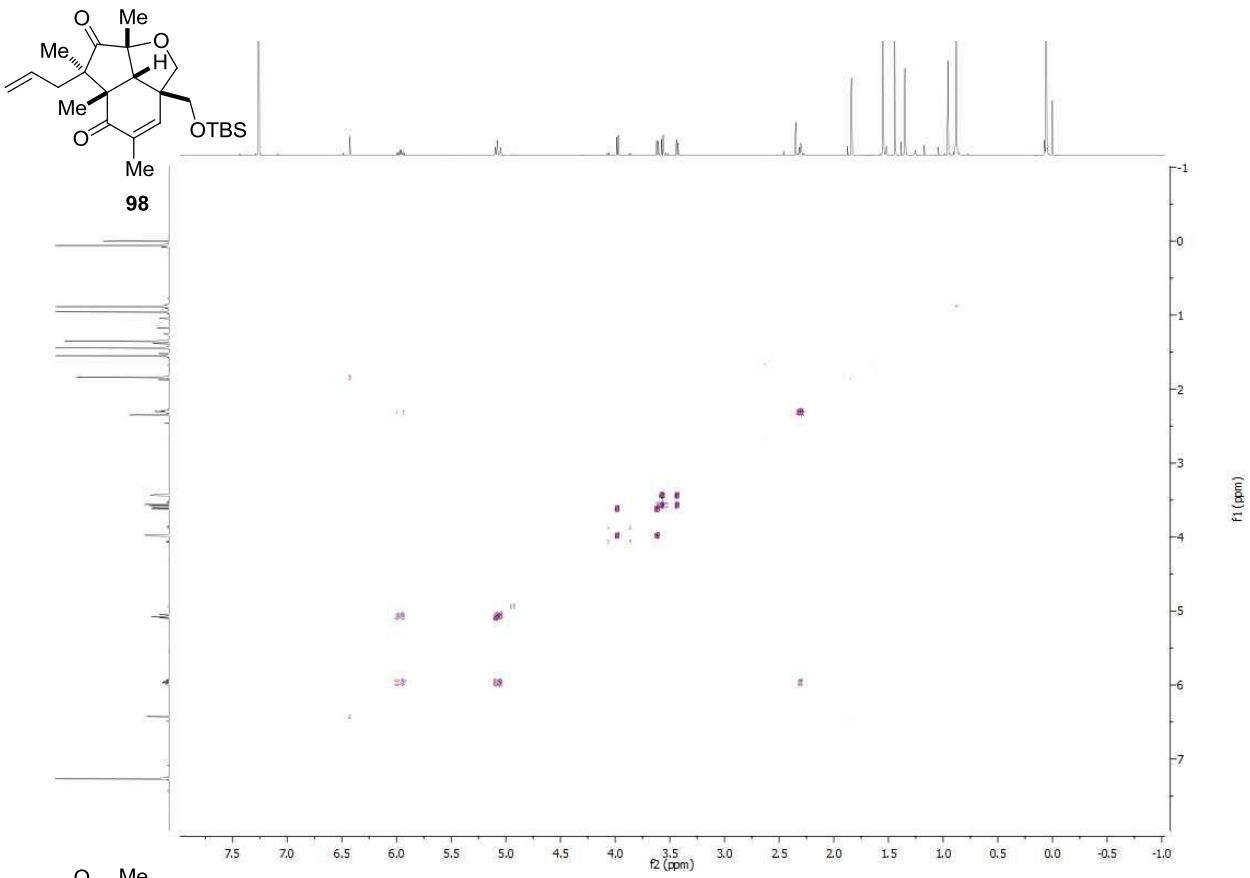

221.14
200.63
142.83
136.67
133.42
118.47
88.78
77.22 CDCl3
77.01 CDCl3
76.80 CDCl3
73.18
69.39
57.80
53.10
50.54
48.78
39.98
25.86
25.77
22.87
21.04
18.21
16.74
-5.46
-5.47
f1 (ppm)

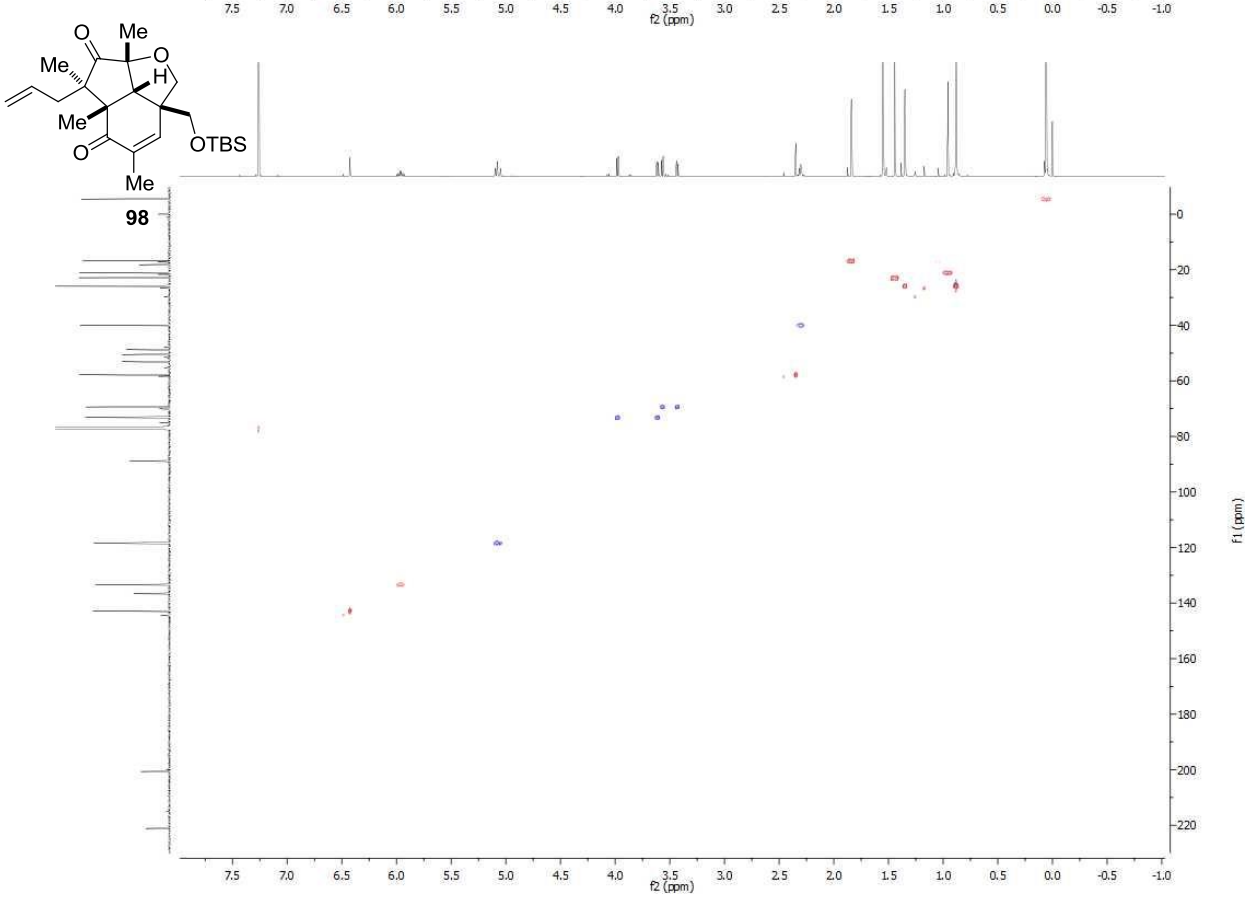
O
Me
Me
O
H
Me
OTBS
O
Me

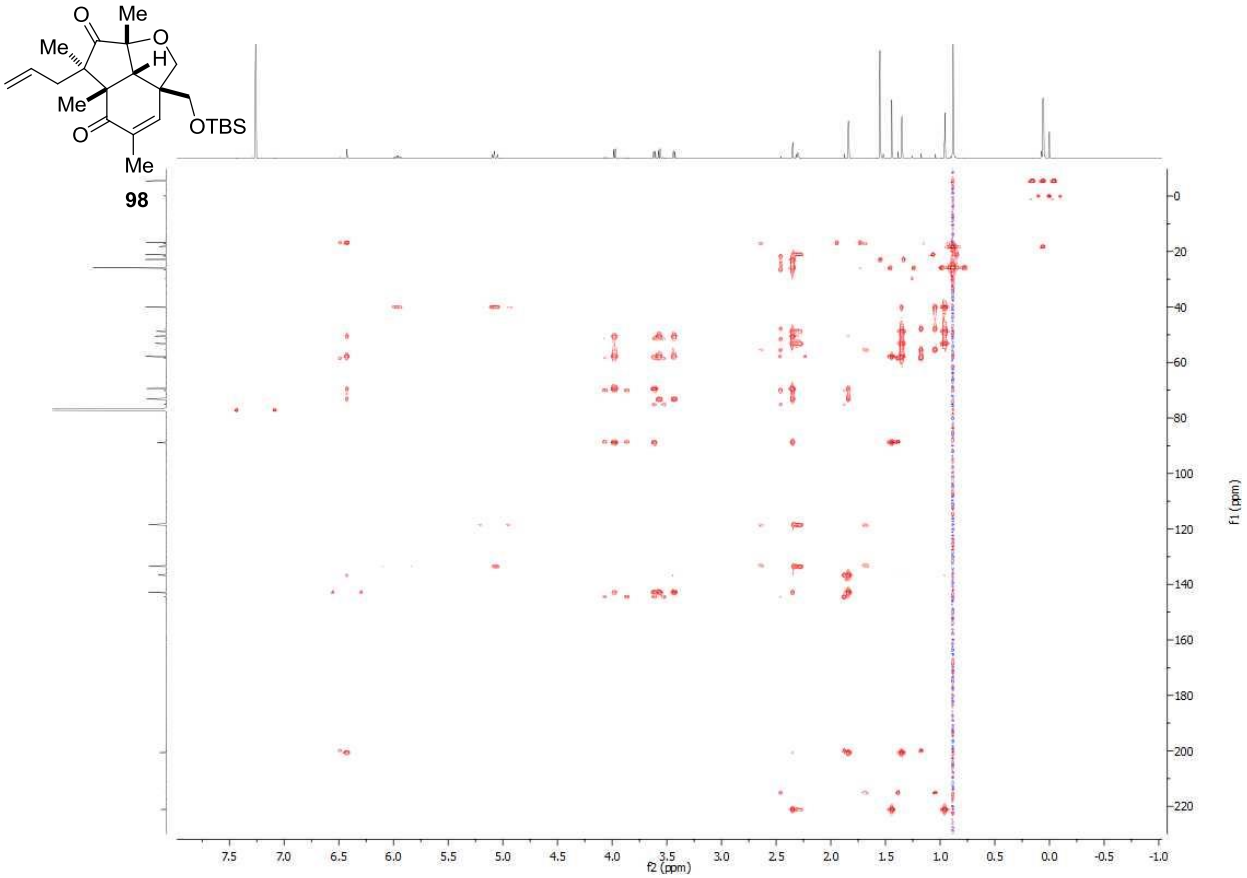
98

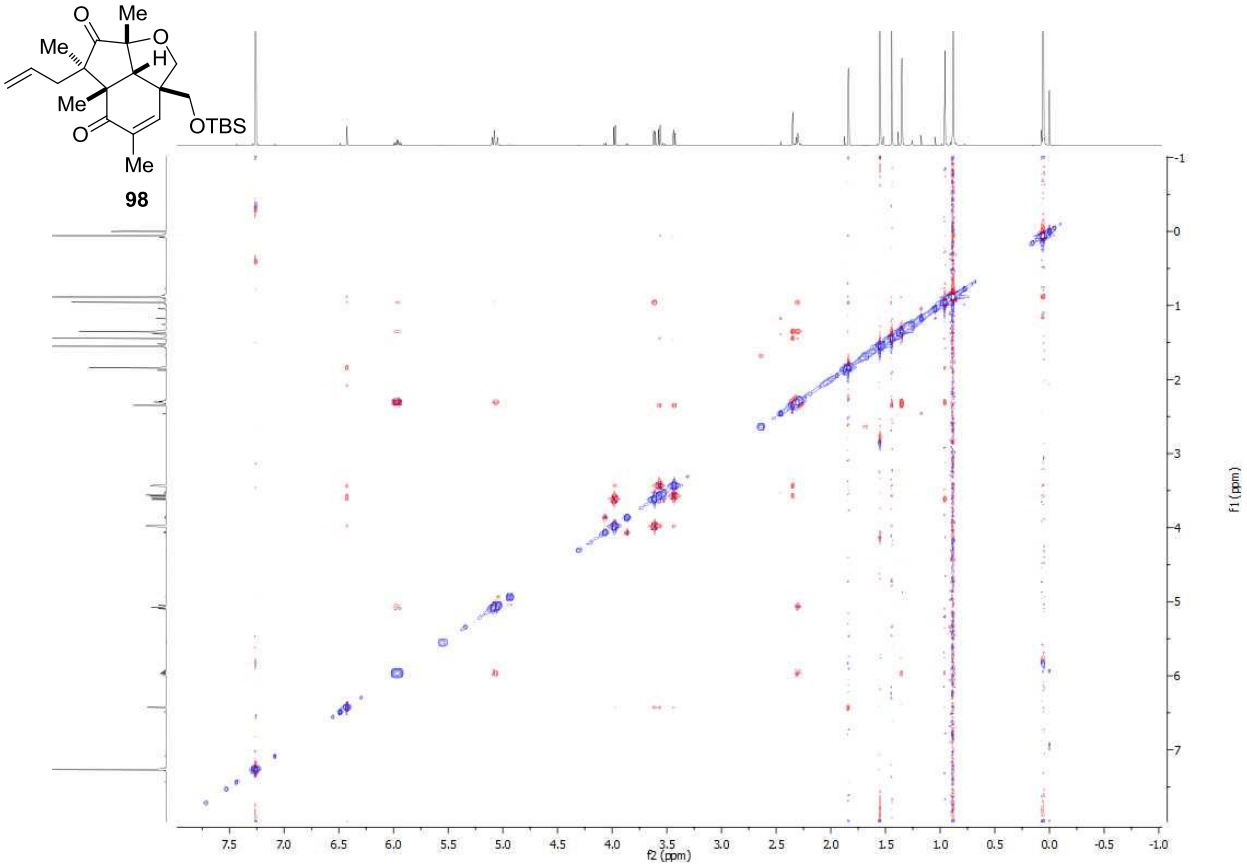
O
Me
Me
O
H
Me
OTBS
O
Me

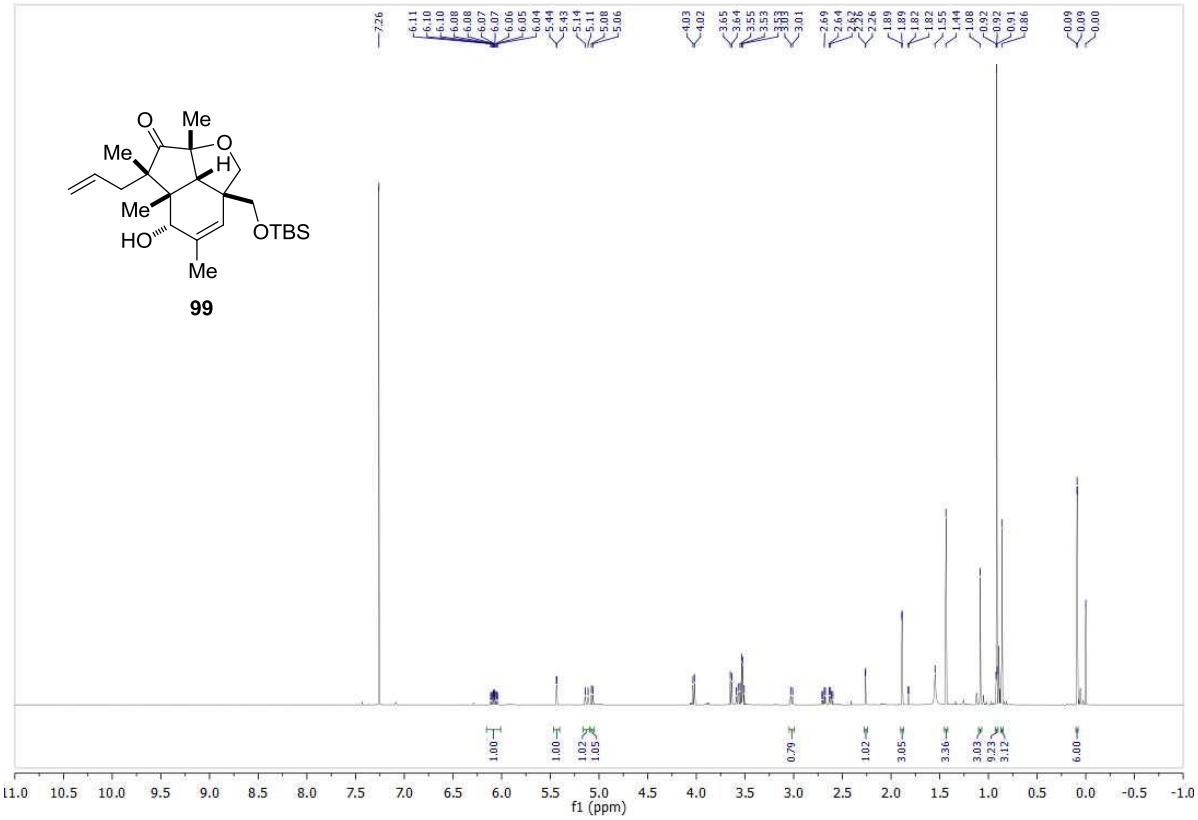
98

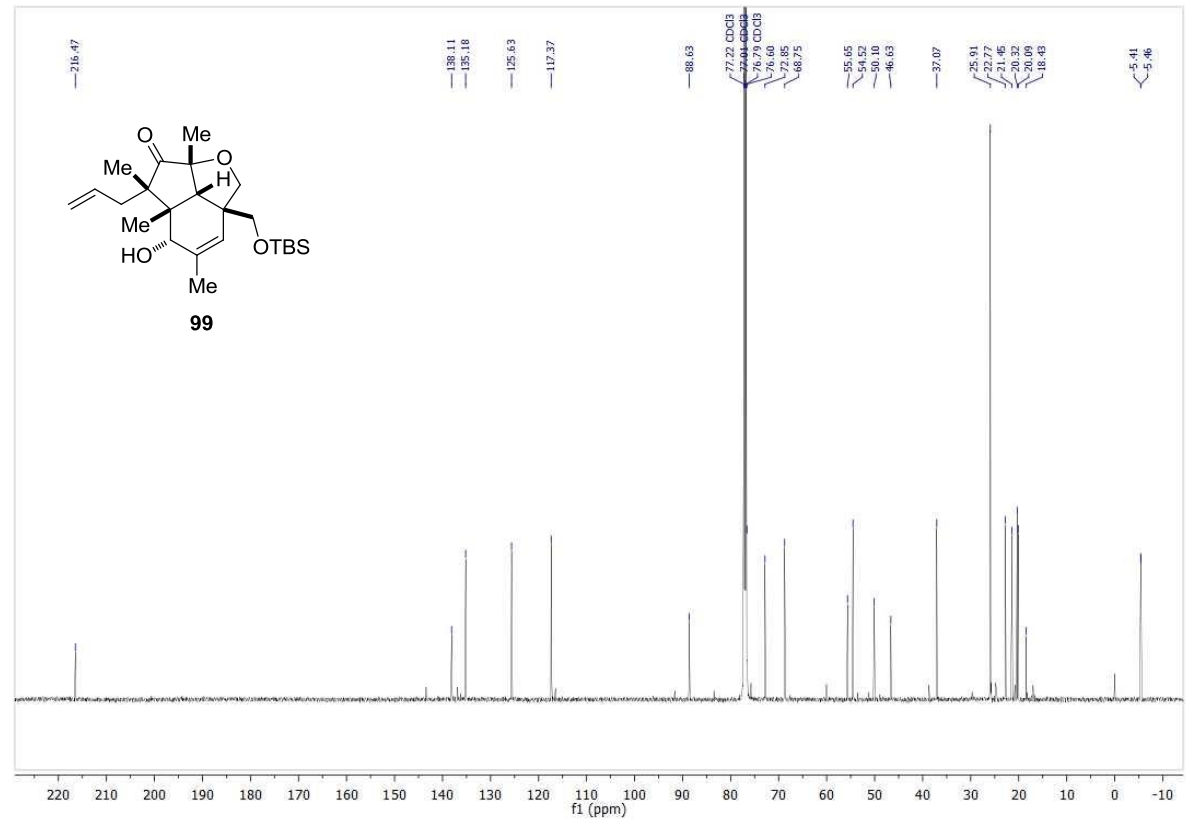

Me
O
Me
O
H
Me
OTBS
O
Me
98
f2 (ppm)
f1 (ppm)

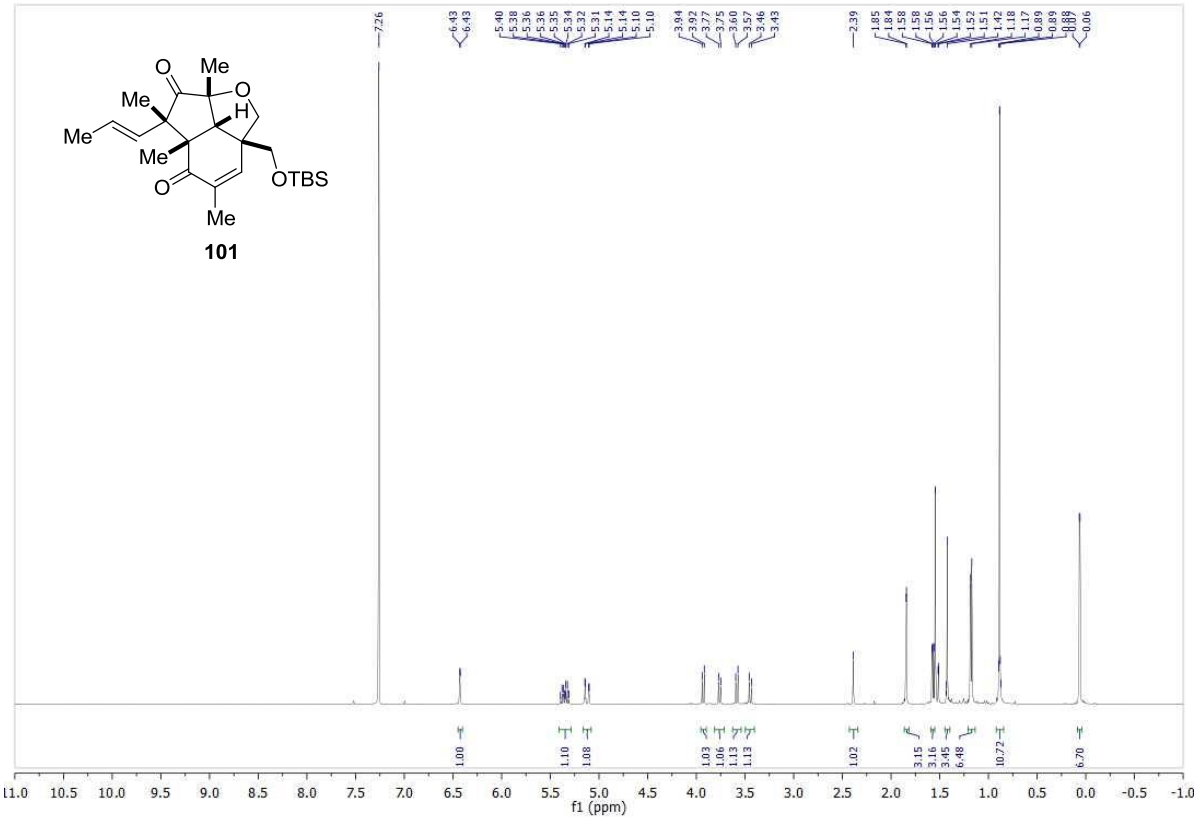

Me
O
Me
O
H
Me
OTBS
O
Me
98
f2 (ppm)
f1 (ppm)

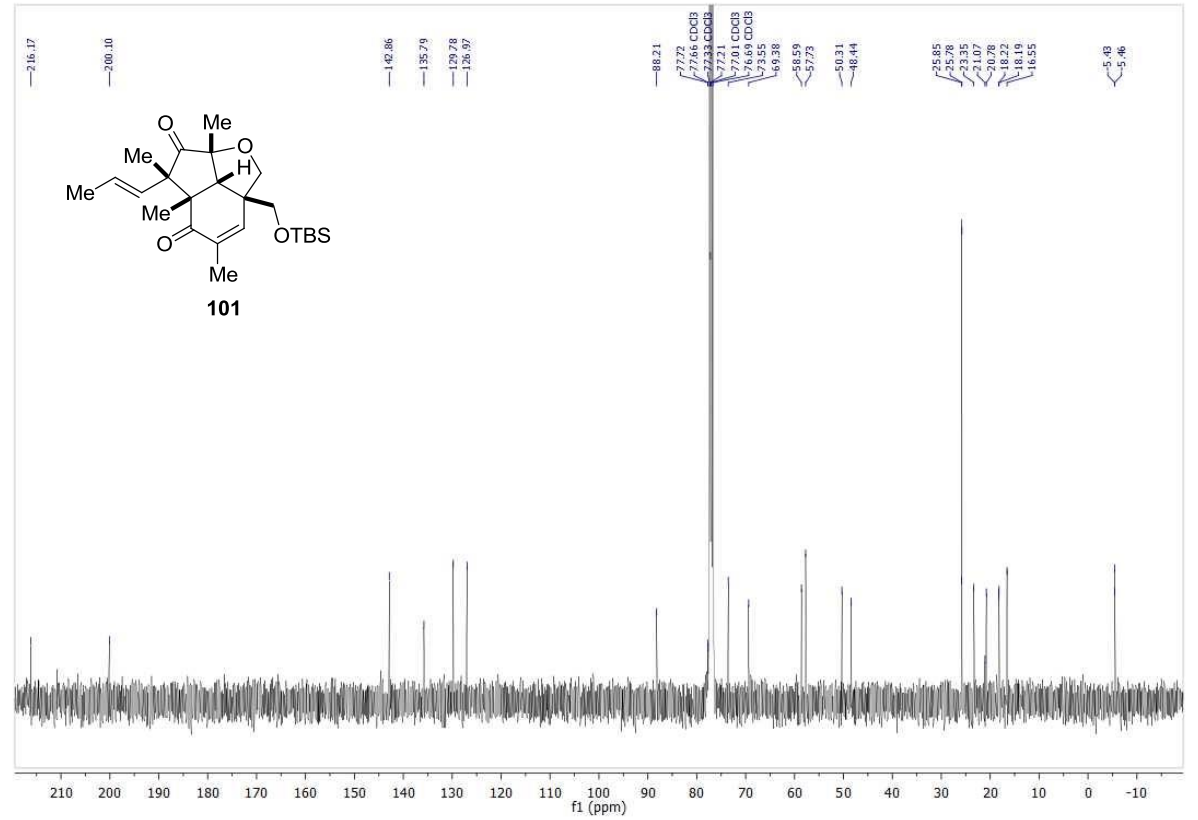

Me
O
Me
O
H
Me
OTBS
O
Me
98
f2 (ppm)
f1 (ppm)

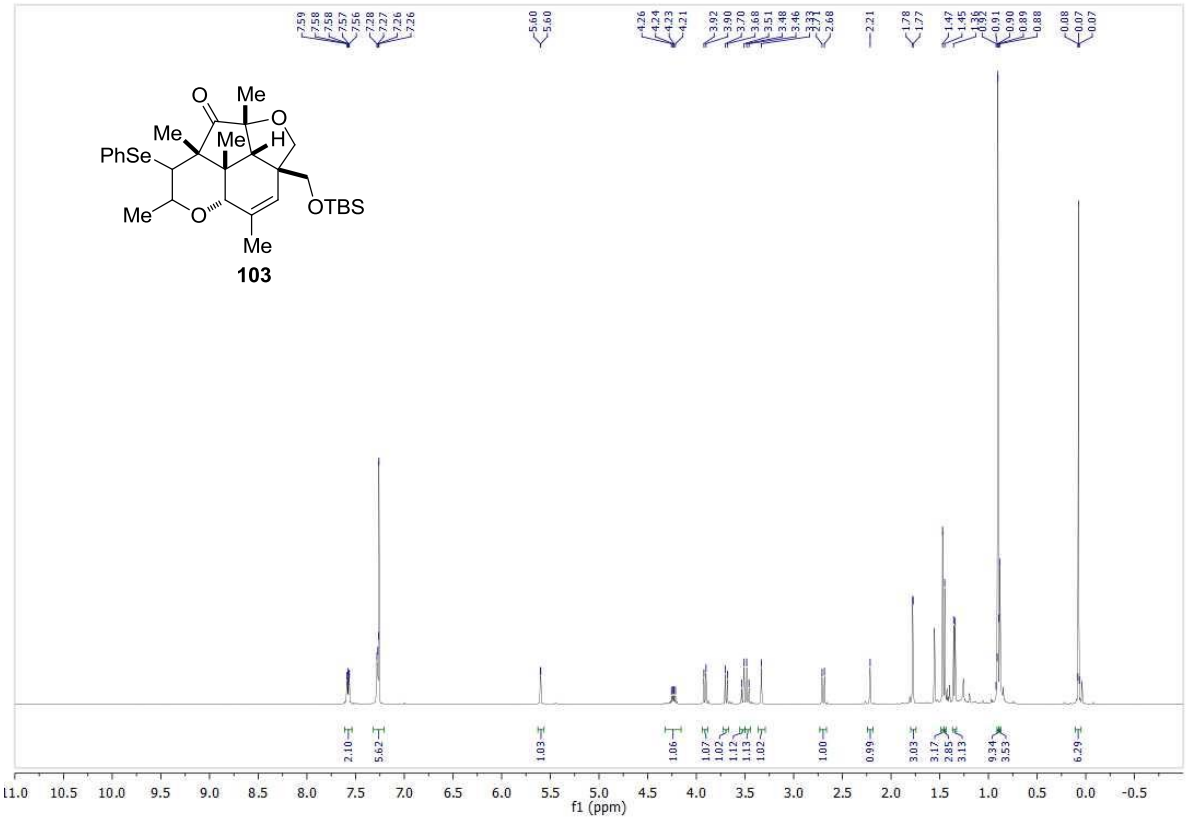

Me
O
Me
O
H
Me
OTBS
O
Me
98
f2 (ppm)
f1 (ppm)

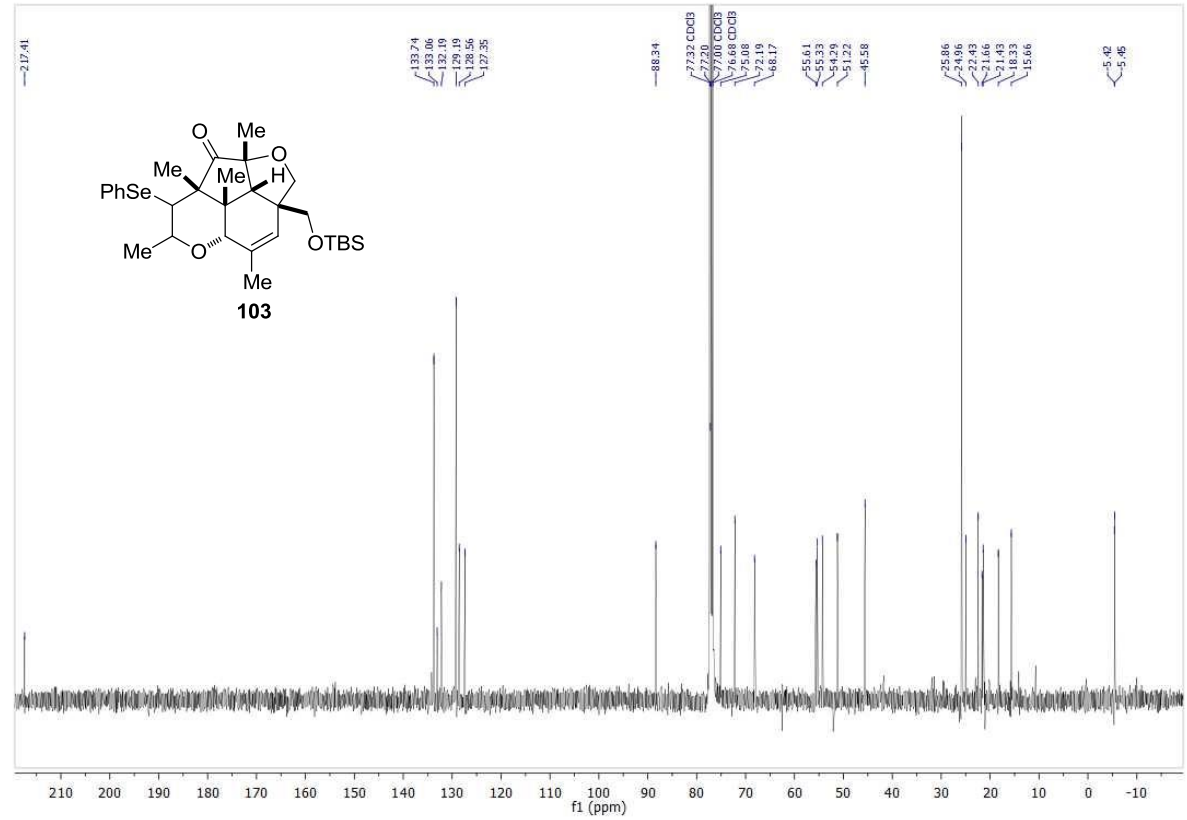

O
Me
Me
O
H
Me
HO
OTBS
Me
99
f1 (ppm)

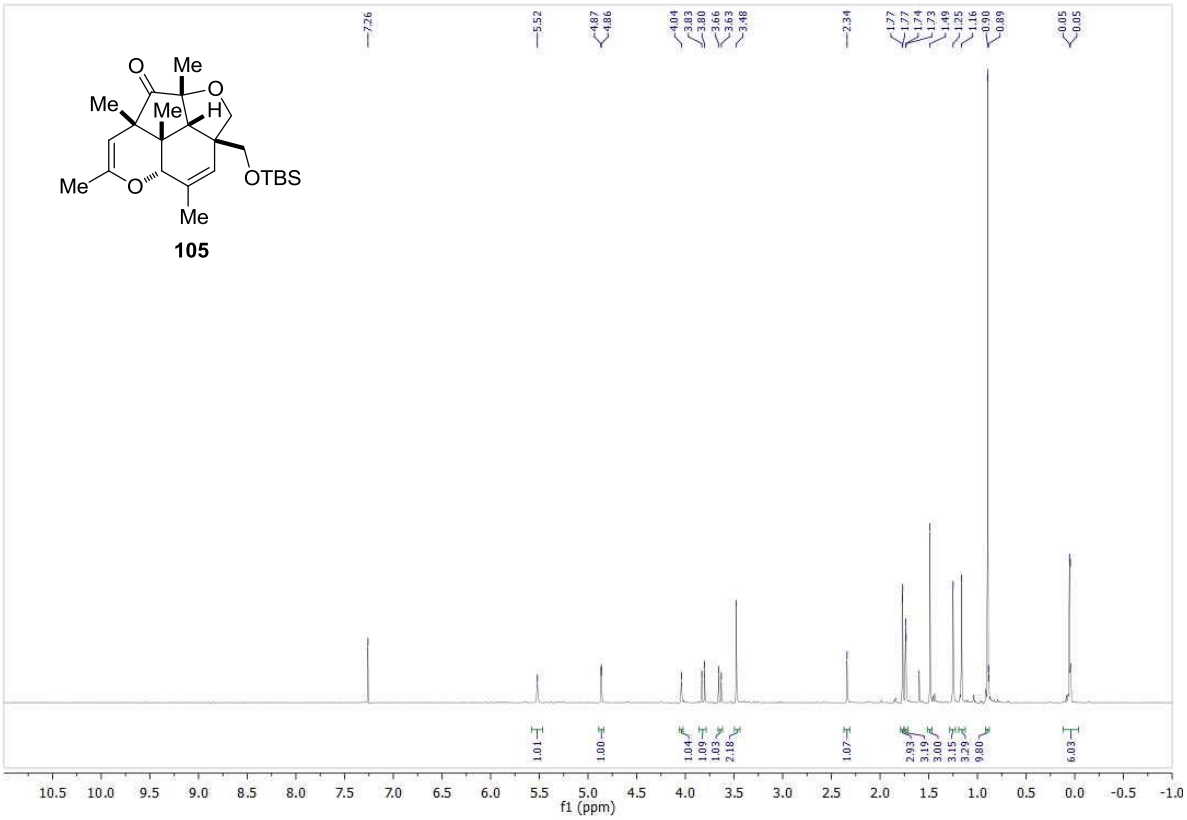

O
Me
Me
O
H
Me
HO
OTBS
Me
99
f1 (ppm)

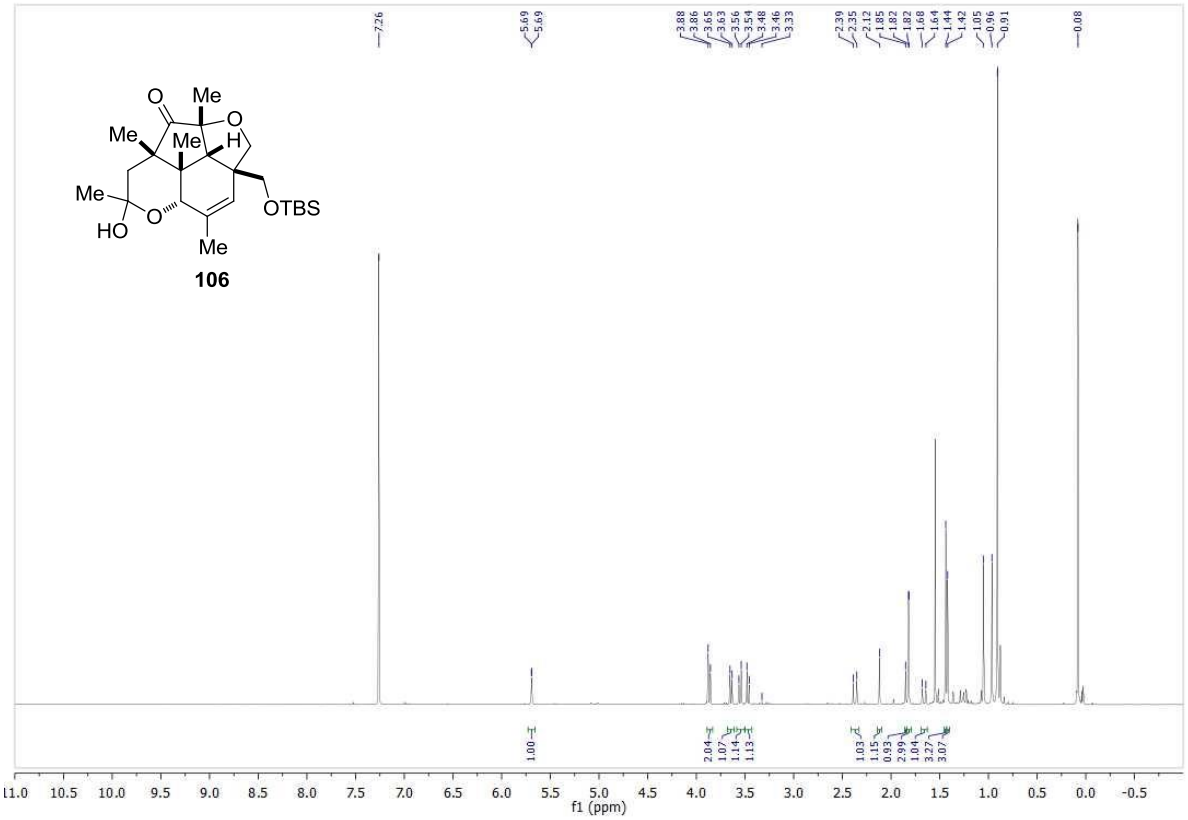

Me
O
Me
O
H
Me
Me
OTBS
O
Me
101
f1 (ppm)

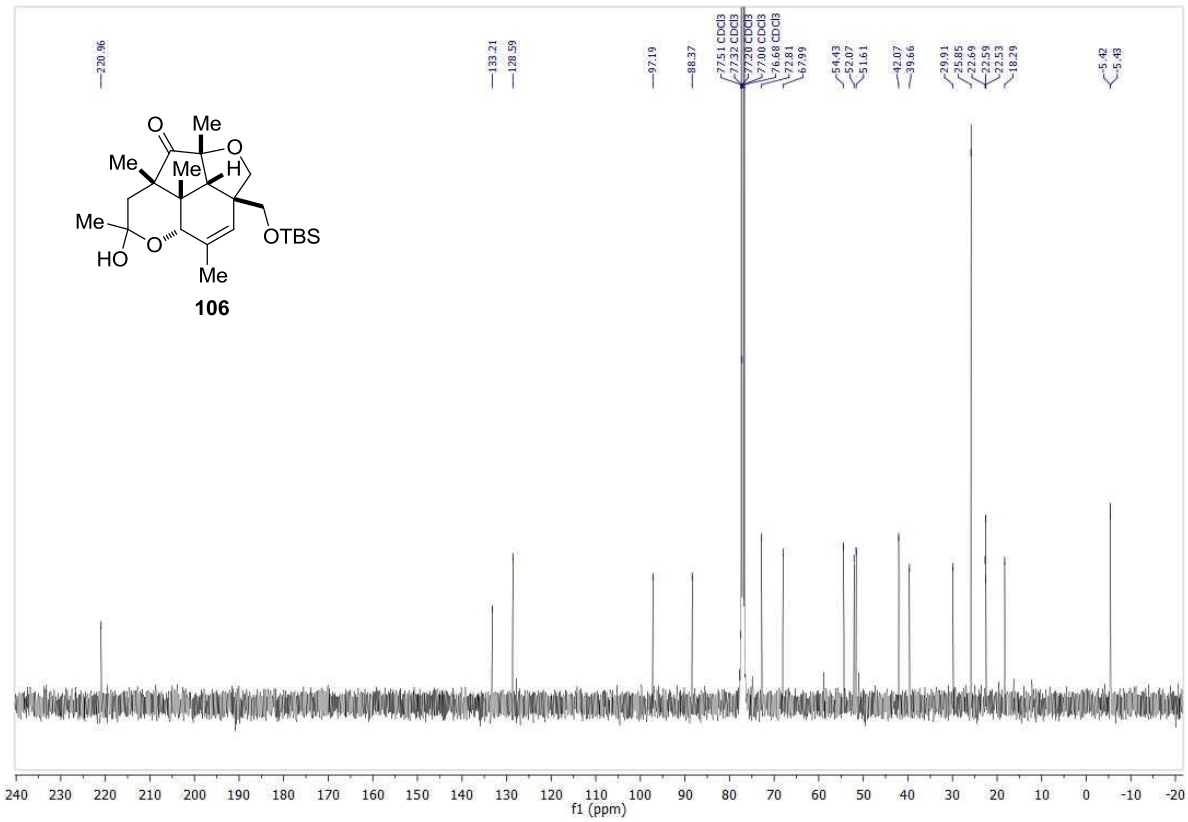

Me
O
Me
O
H
Me
Me
OTBS
O
Me
101
f1 (ppm)


O
Me
O
Me
Me
H
PhSe
OTBS
Me
O
Me
103
f1 (ppm)


O
Me
O
Me
Me
H
PhSe
OTBS
Me
O
Me
103
f1 (ppm)


O
Me
O
Me
Me
H
Me
O
OTBS
Me
105
7.26
5.52
4.87
4.86
4.04
3.83
3.80
3.66
3.63
3.48
2.34
1.77
1.77
1.74
1.73
1.49
1.25
1.16
0.90
0.89
0.05
0.05
1.01
1.00
1.04
1.09
1.03
2.18
1.07
2.93
3.19
3.00
3.15
3.29
9.80
6.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


7.26
5.69
5.69
3.88
3.86
3.65
3.63
3.56
3.54
3.48
3.46
3.33
2.39
2.35
2.12
1.85
1.82
1.82
1.68
1.64
1.44
1.42
1.05
0.96
0.91
0.08
1.00
2.04
1.07
1.14
1.13
1.03
1.15
0.93
2.99
1.04
3.27
3.07
f1 (ppm)


220.96
133.21
128.59
97.19
88.37
77.51 CDCl3
77.32 CDCl3
77.20 CDCl3
77.00 CDCl3
76.68 CDCl3
72.81
67.99
54.43
52.07
51.61
42.07
39.66
29.91
25.85
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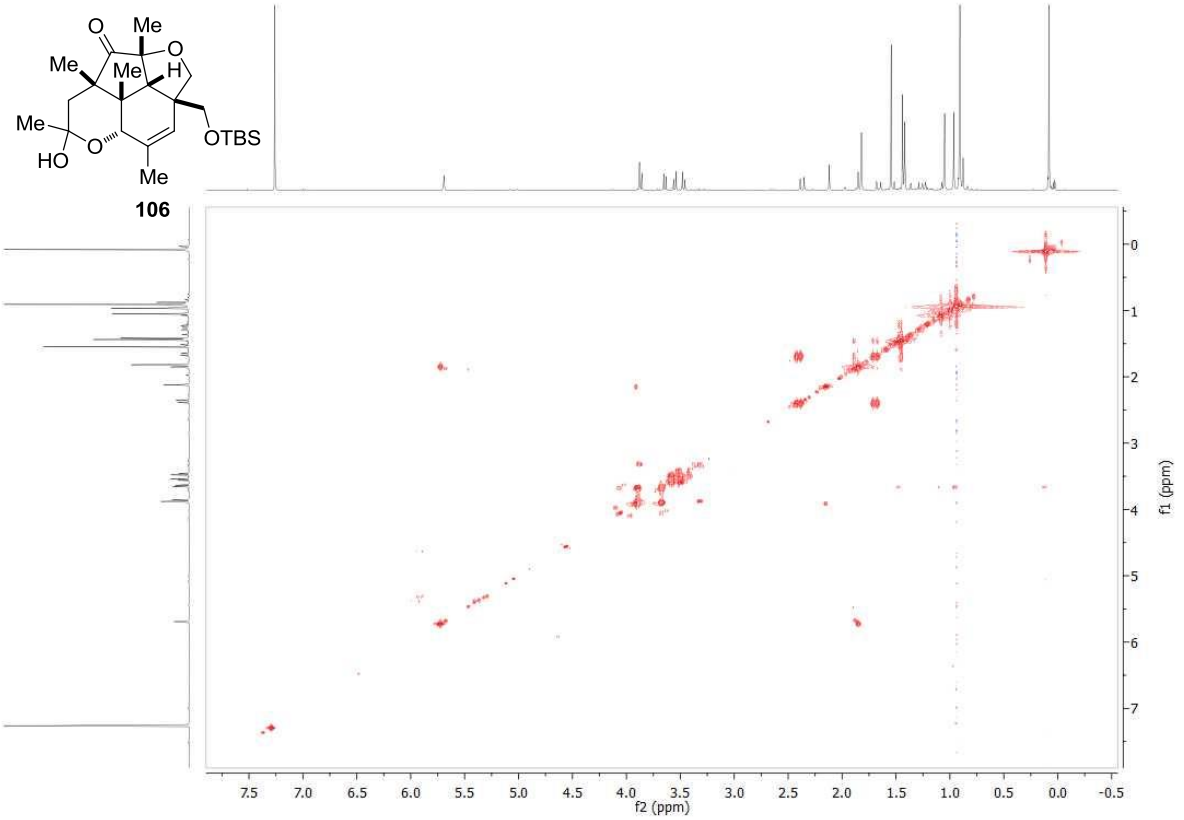
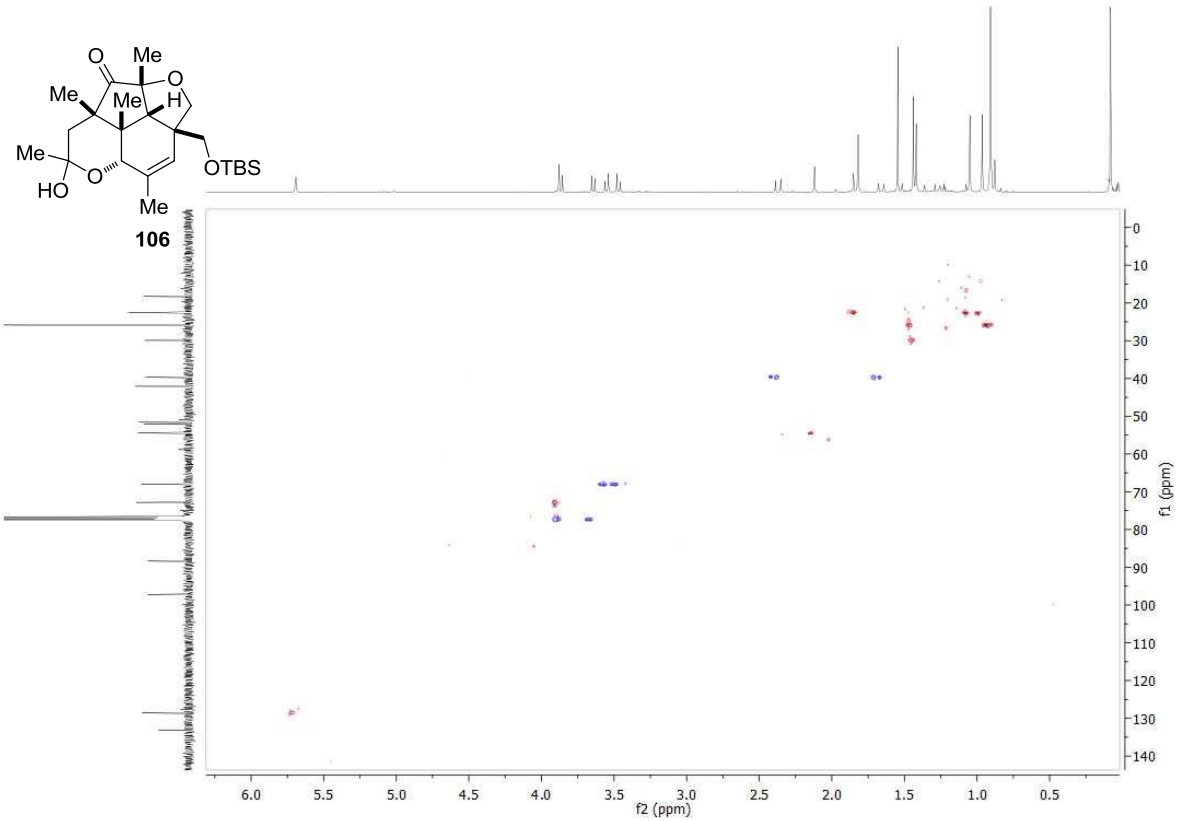
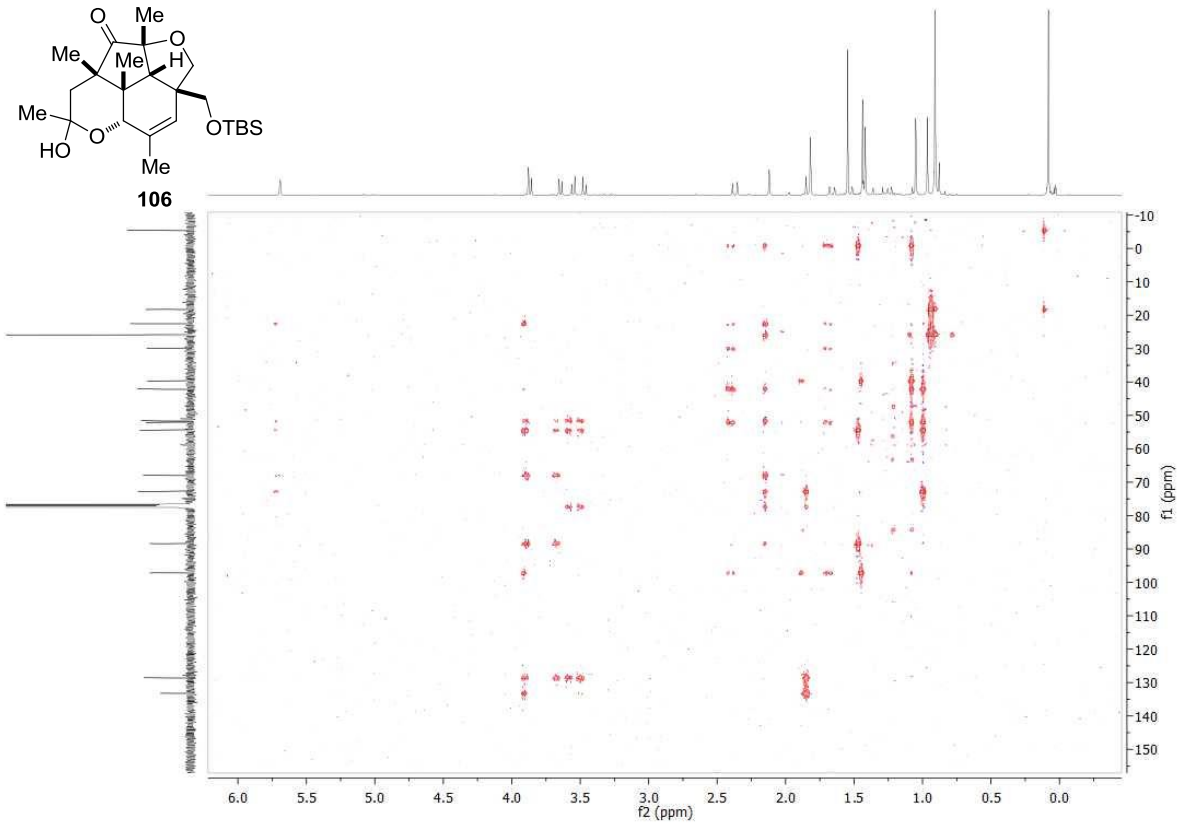
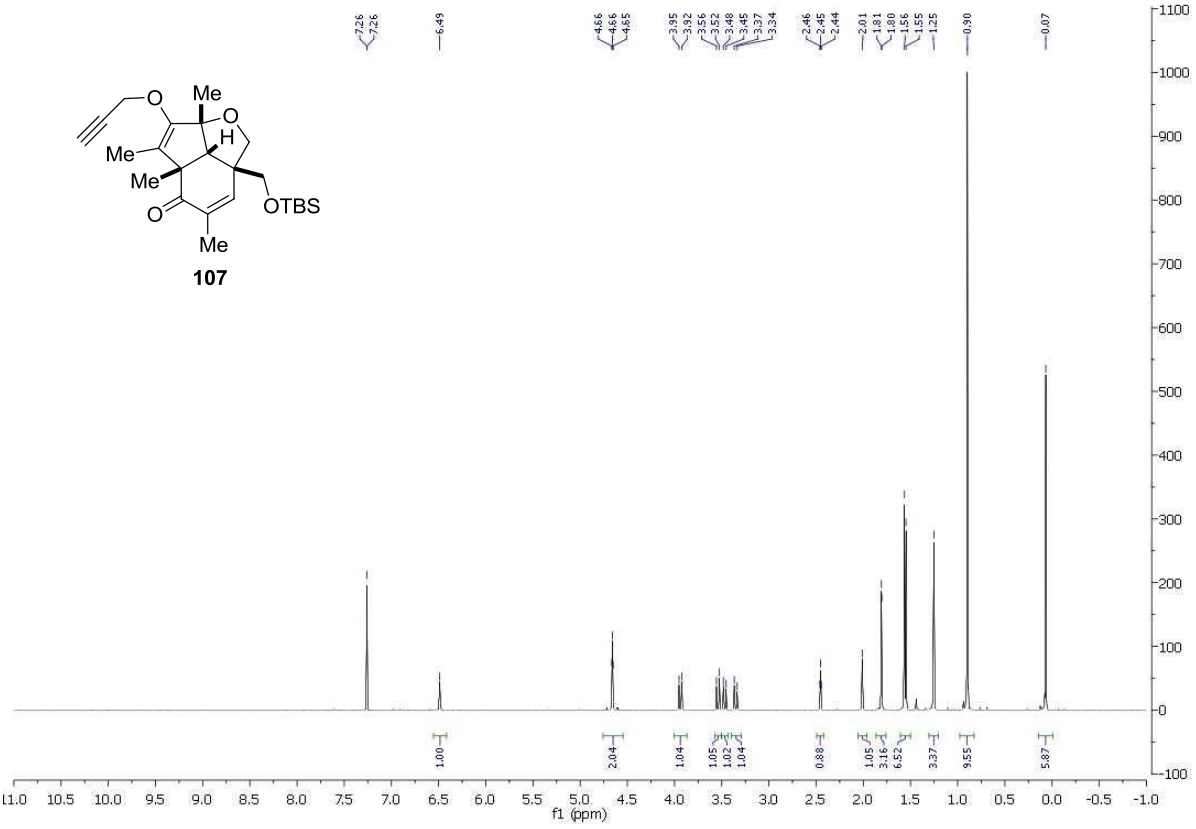
22.53
18.29
5.42
5.43
f1 (ppm)

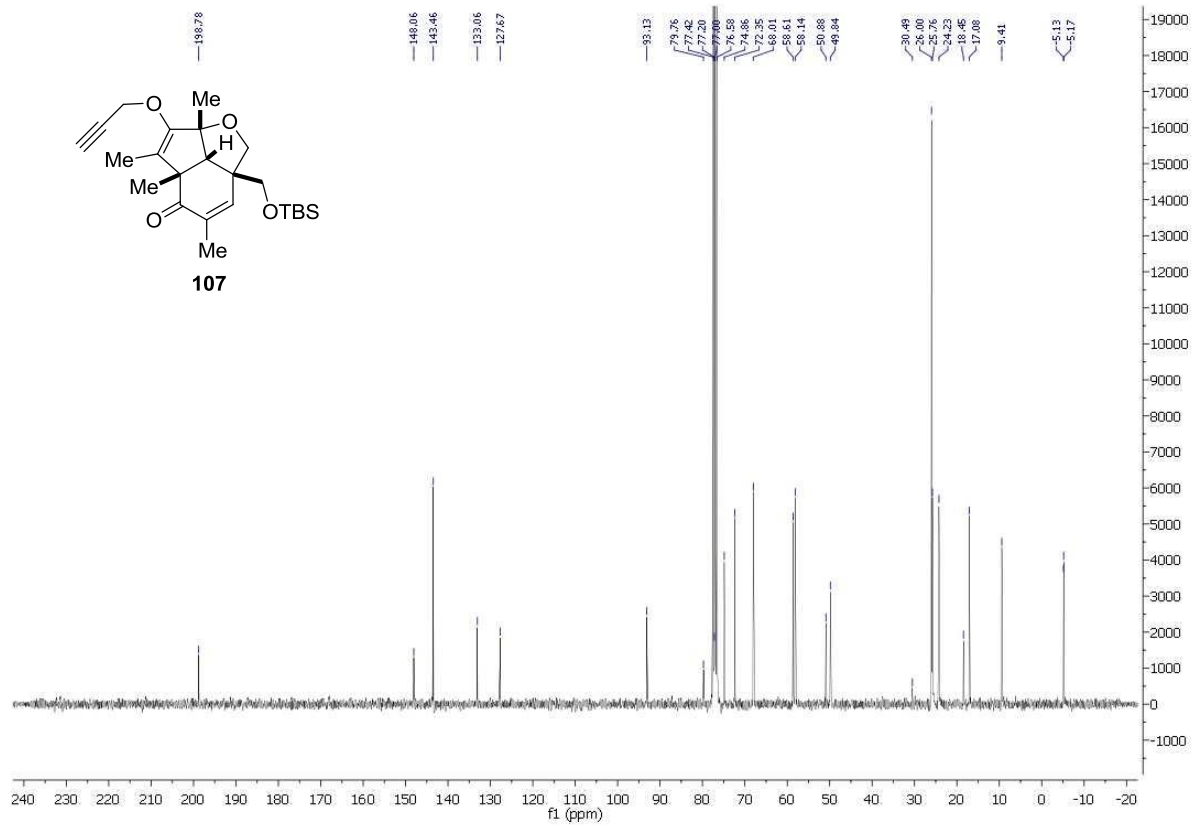
106

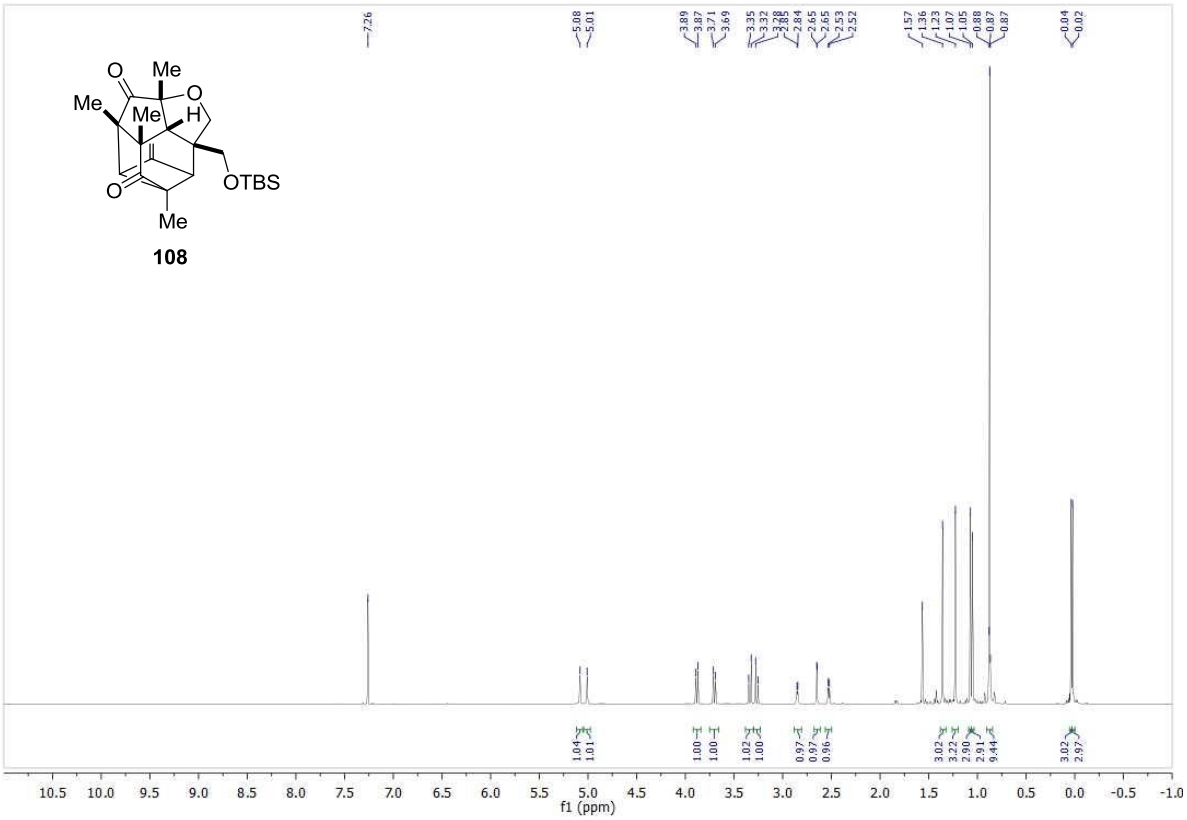

O
Me
Me
Me
O
H
Me
HO
O
OTBS
Me
106
f2 (ppm)
f1 (ppm)

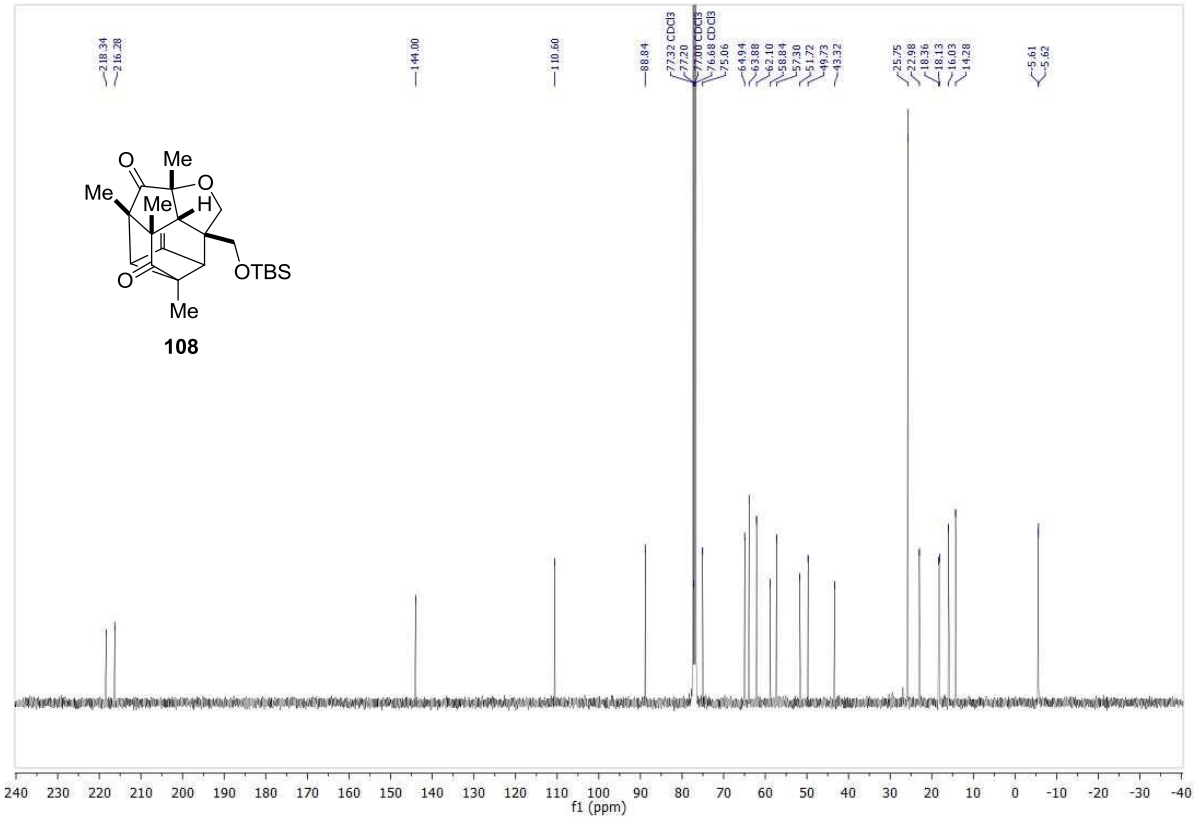

O
Me
Me
Me
O
H
Me
HO
O
OTBS
Me
106
f2 (ppm)
f1 (ppm)

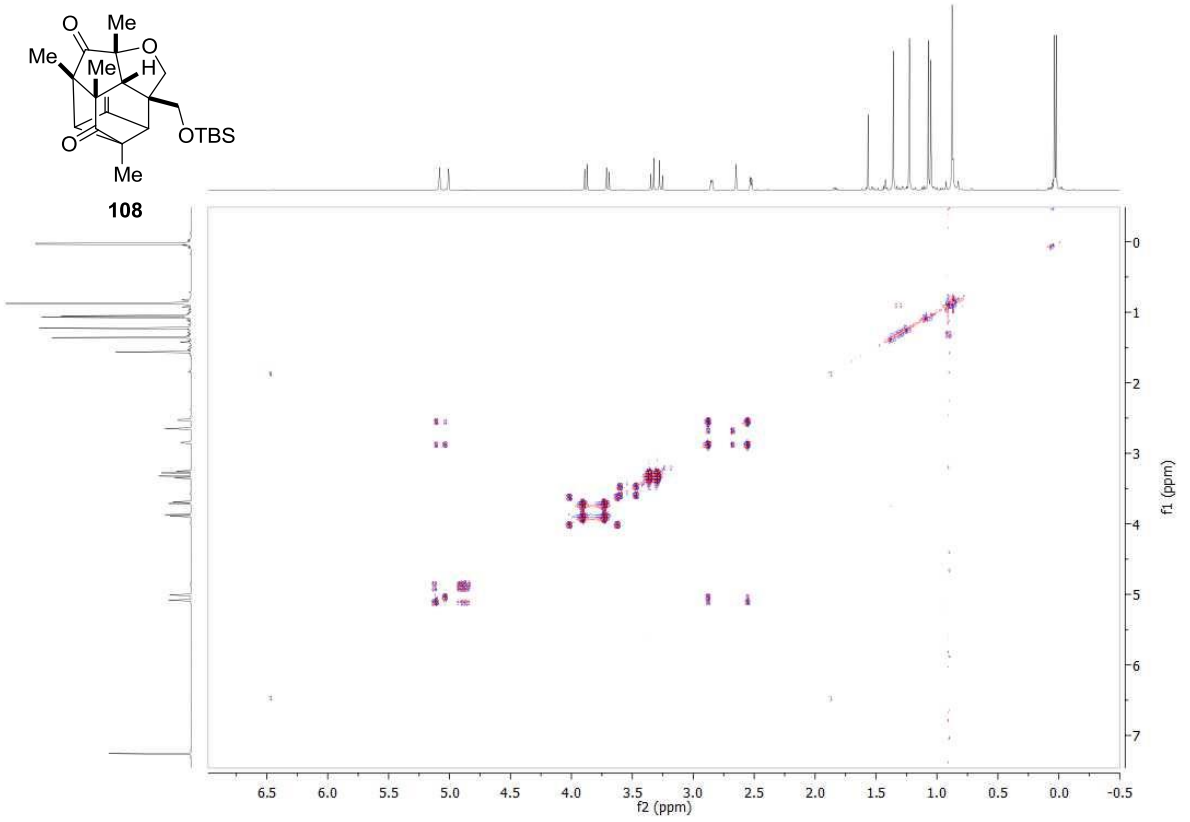

O
Me
O
Me
Me
H
Me
OTBS
HO
O
Me
106
f2 (ppm)
f1 (ppm)


Me
O
O
H
Me
Me
O
OTBS
Me
107
f1 (ppm)

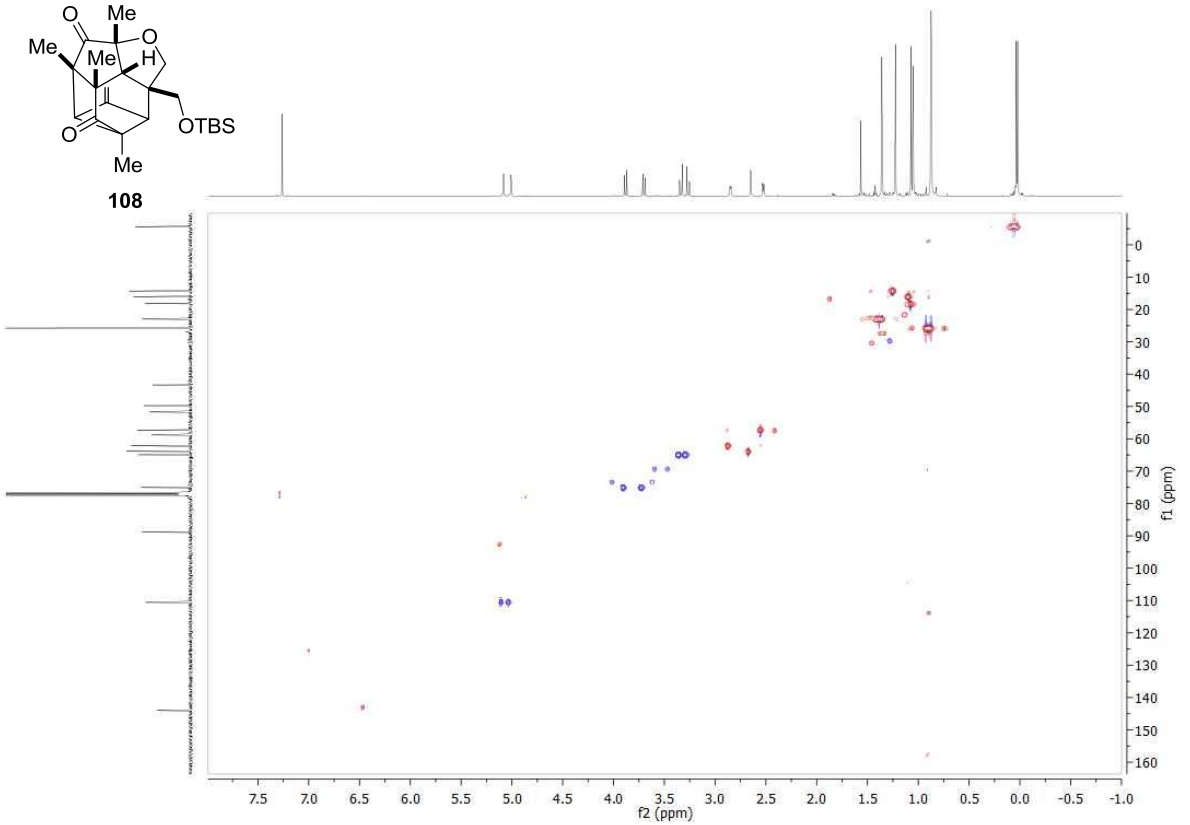

Me
O
O
H
Me
Me
O
OTBS
Me
107
f1 (ppm)


Me
O
Me
O
Me
H
O
OTBS
Me
108
f1 (ppm)


Me
O
Me
O
Me
H
O
OTBS
Me
108
f1 (ppm)


O
Me
Me
O
Me
H
OTBS
O
Me
f2 (ppm)
f1 (ppm)

108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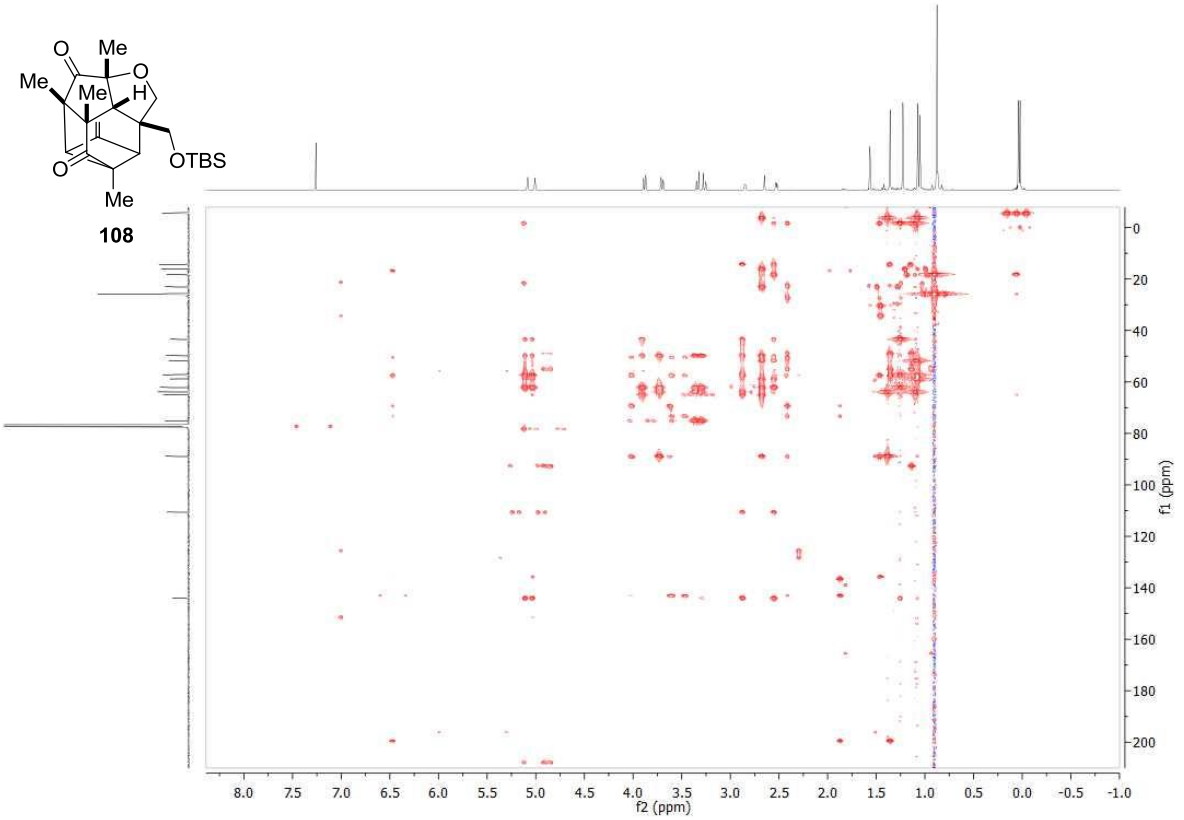
Me
Me
O
Me
H
OTBS
O
Me
f2 (ppm)
f1 (ppm)

108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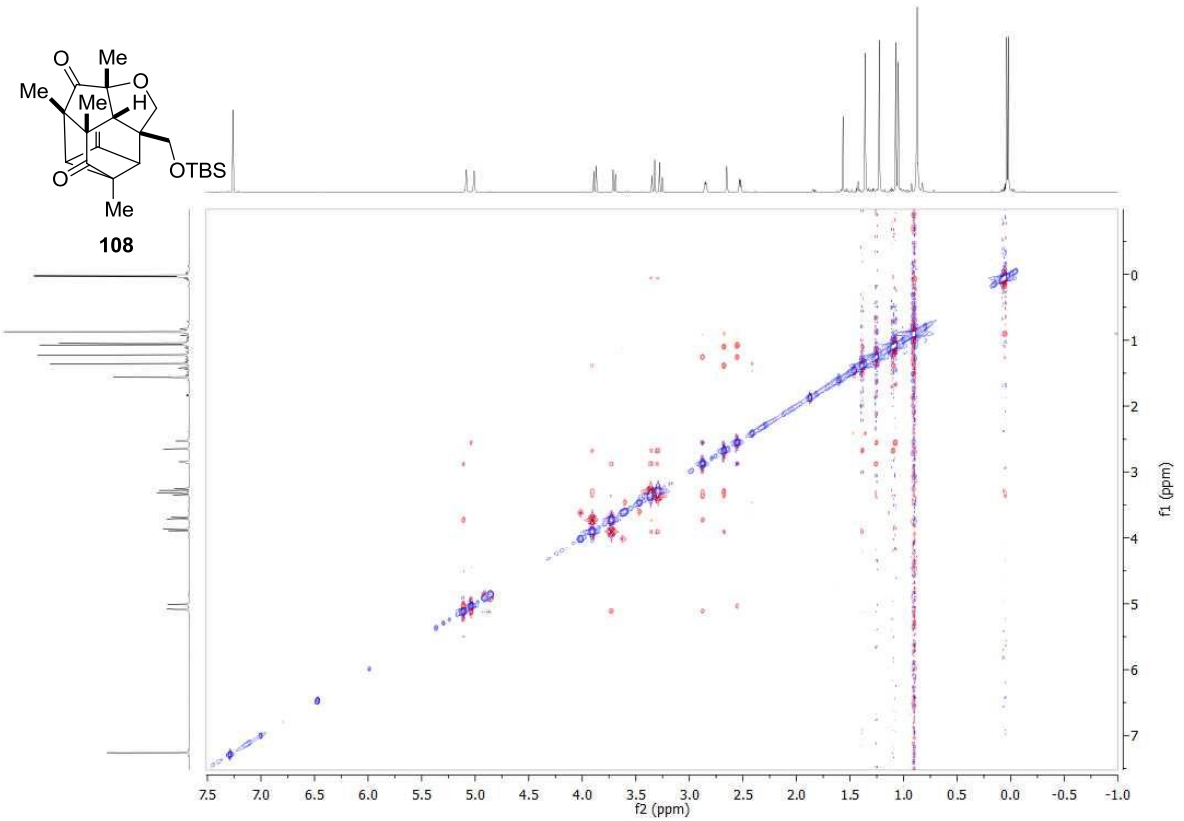
108
f2 (ppm)
f1 (ppm)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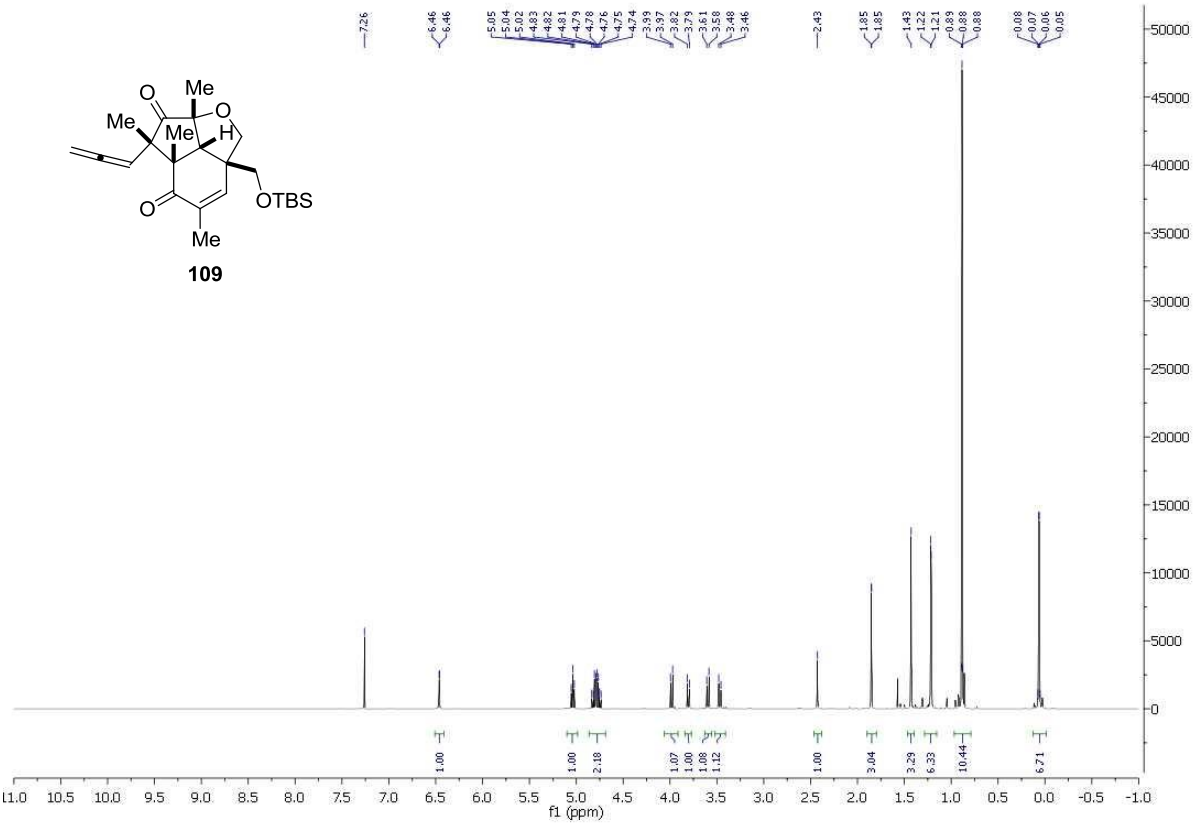
f1 (ppm)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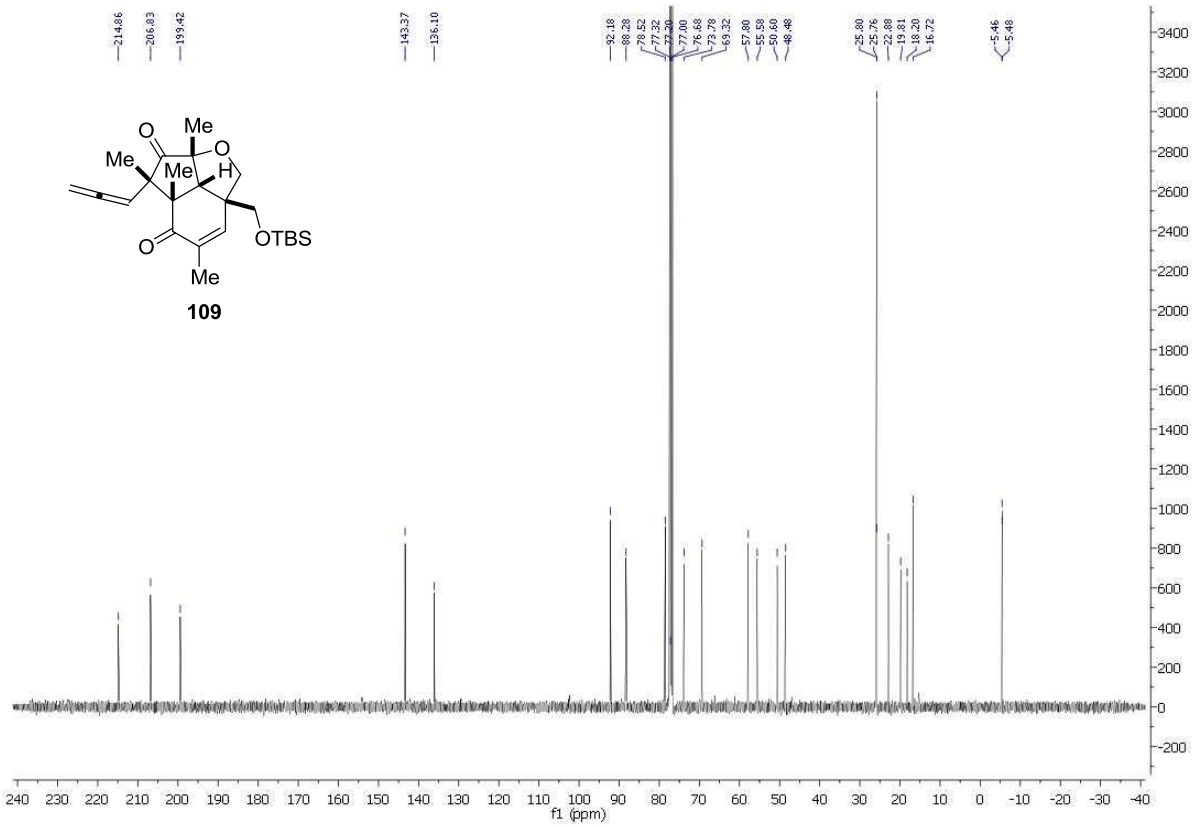
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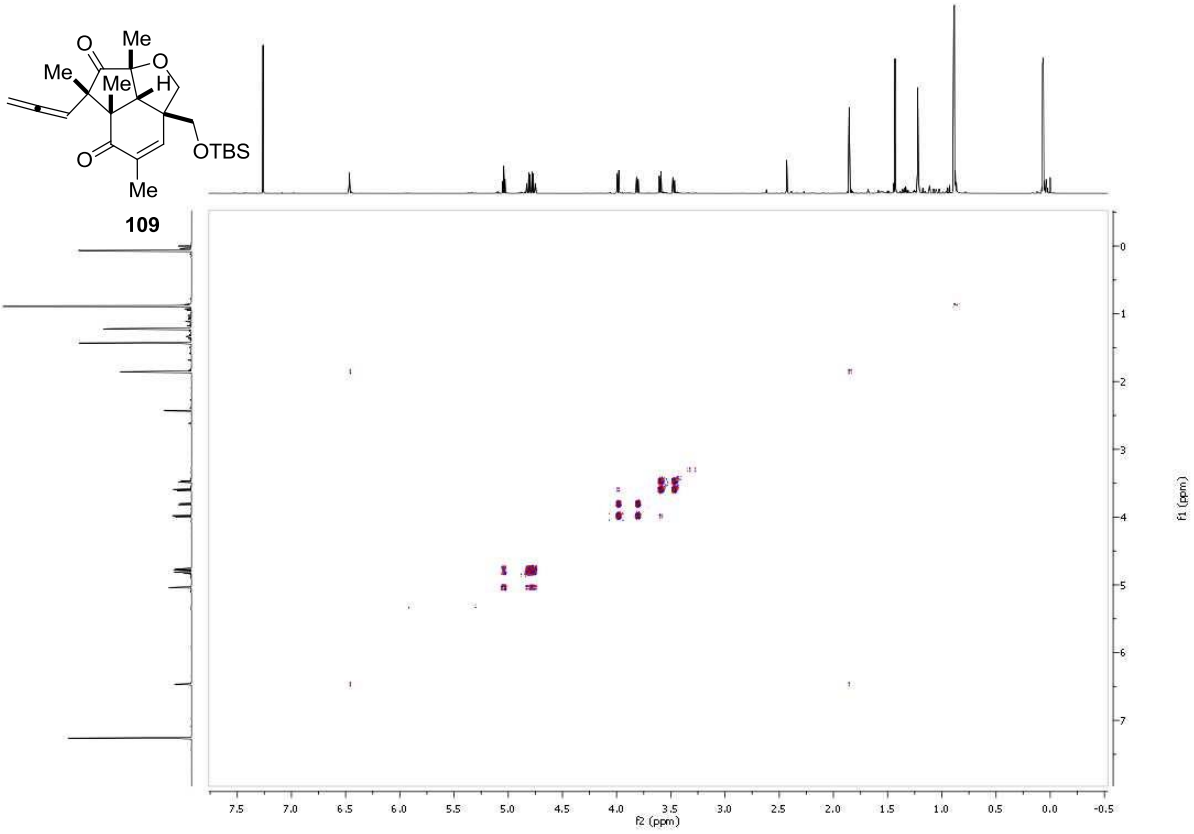
f1 (ppm)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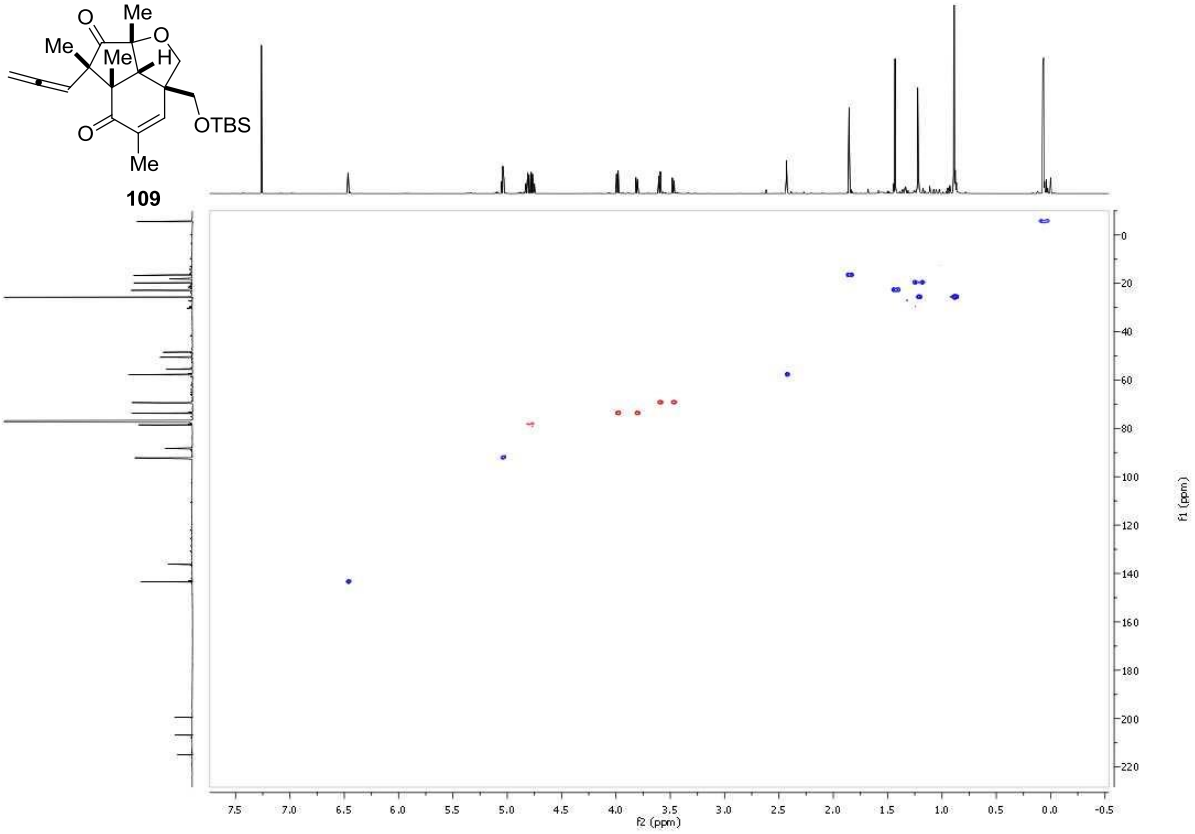
f2 (ppm)
f1 (ppm)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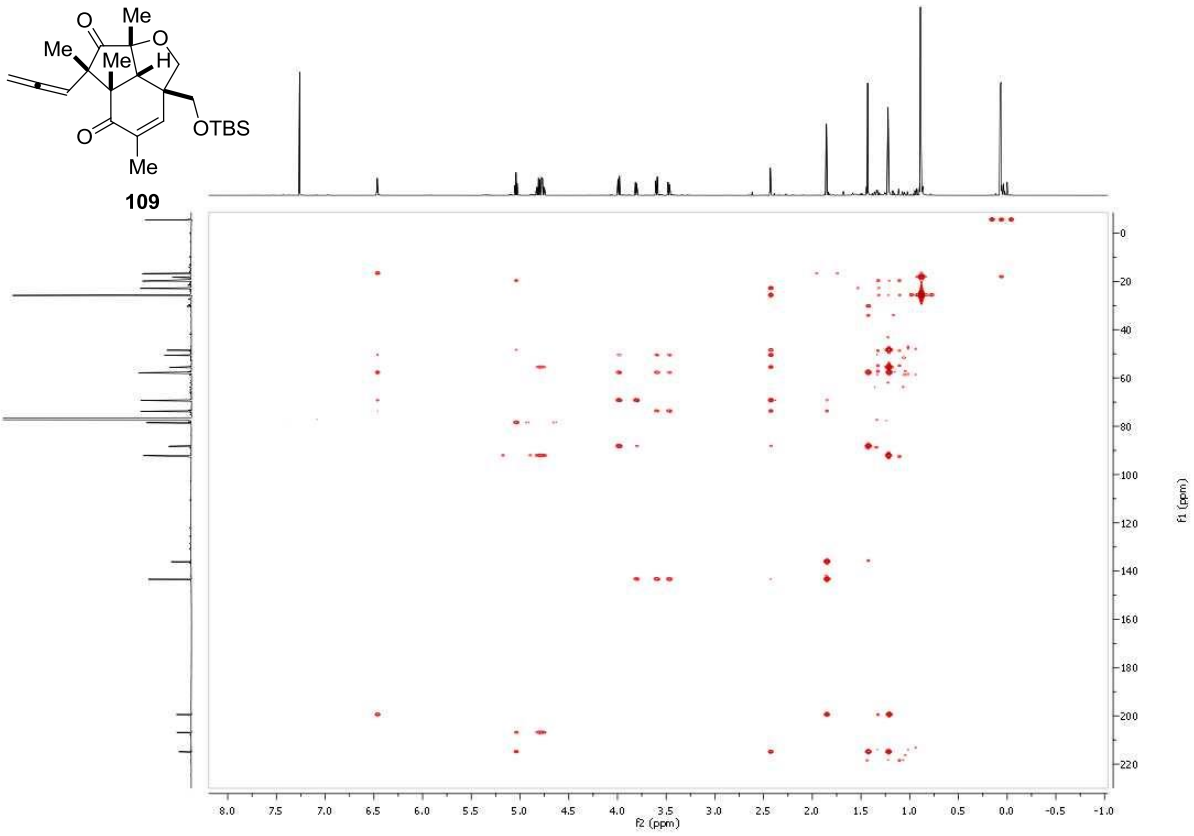
f1 (ppm)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OTBS
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Me
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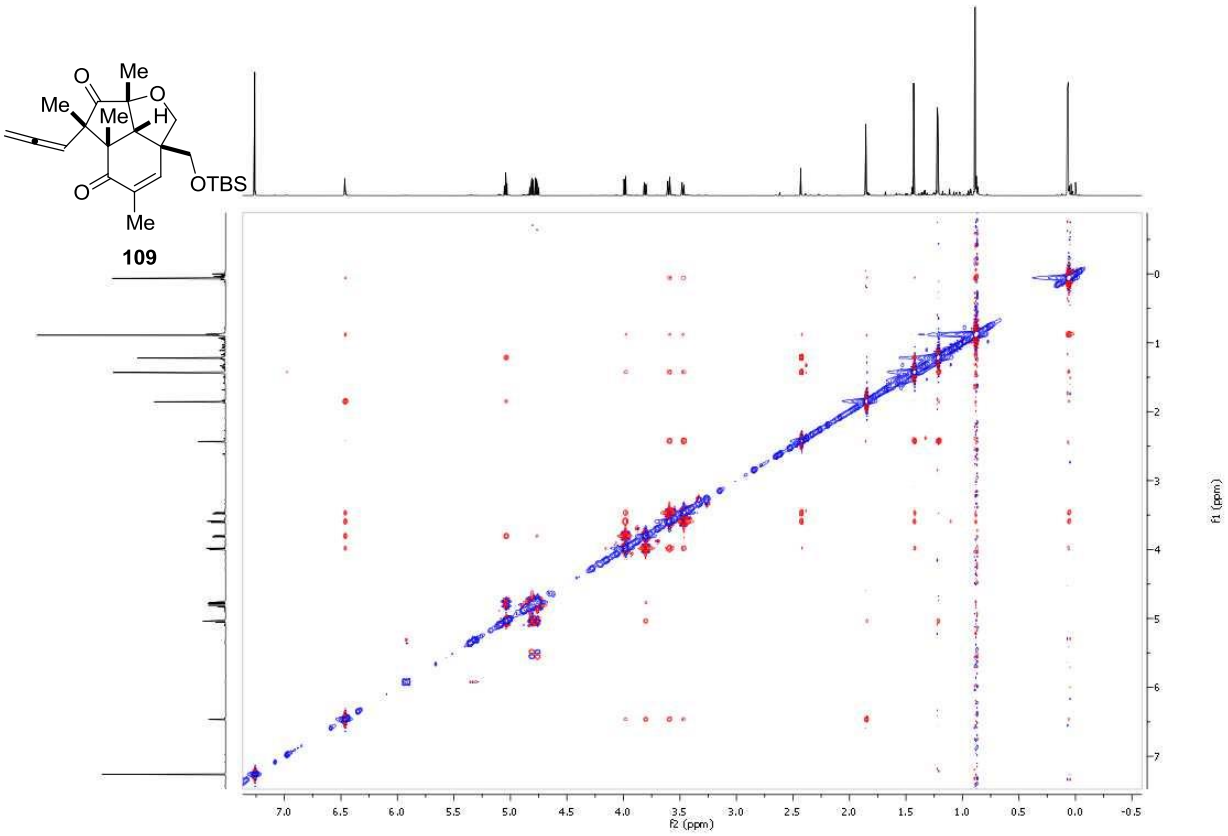
f2 (ppm)
f1 (ppm)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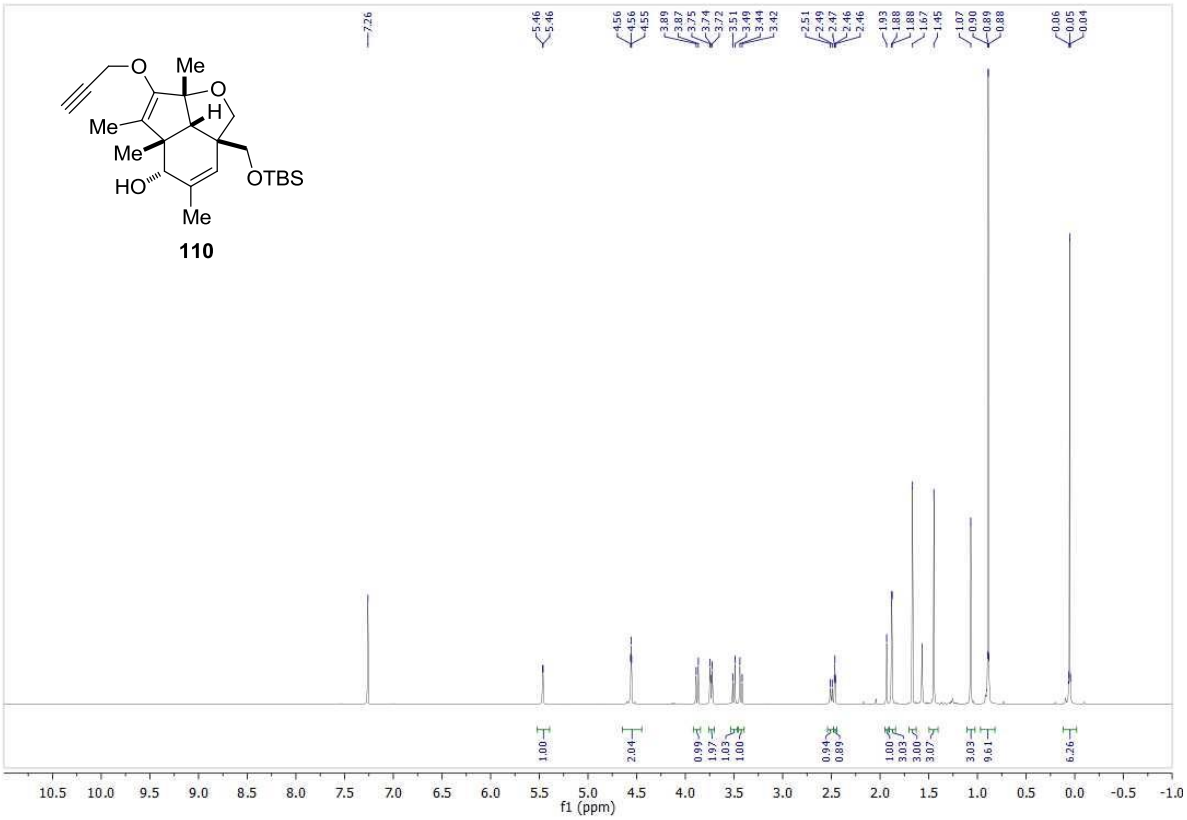
f2 (ppm)
f1 (ppm)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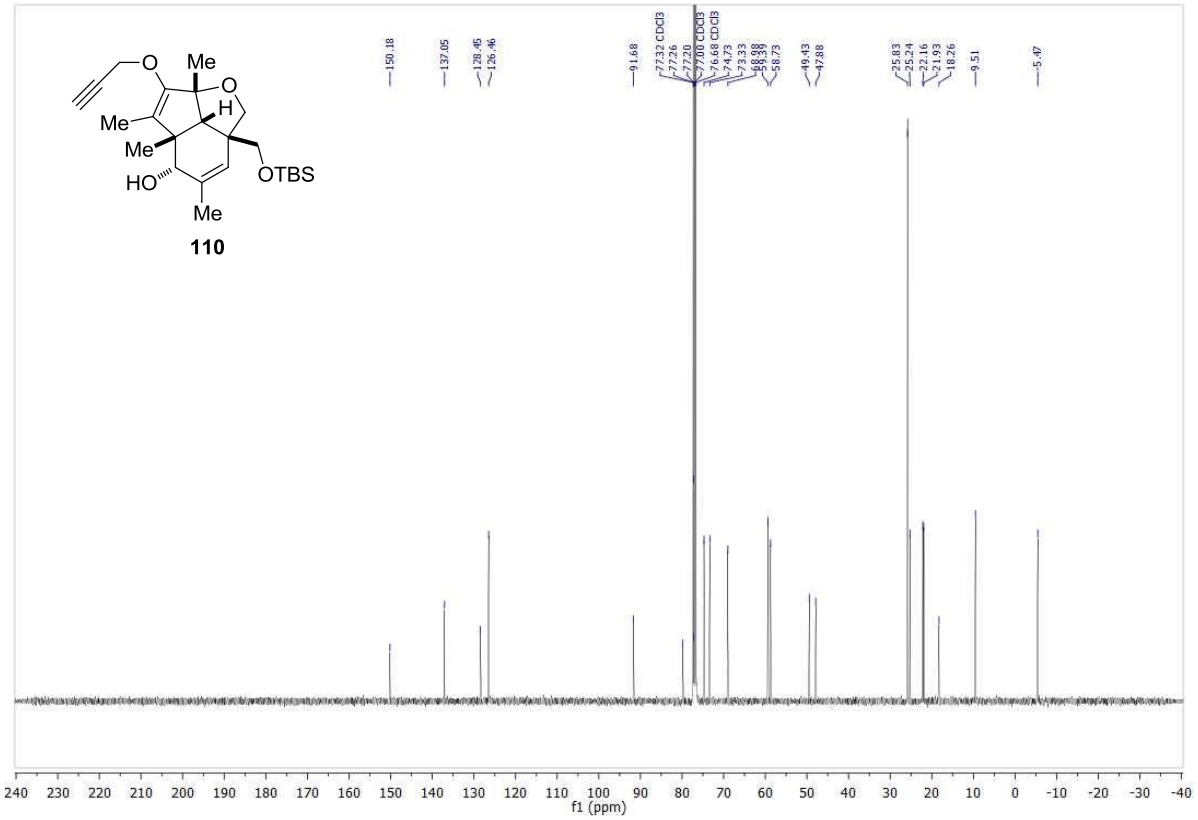
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HO
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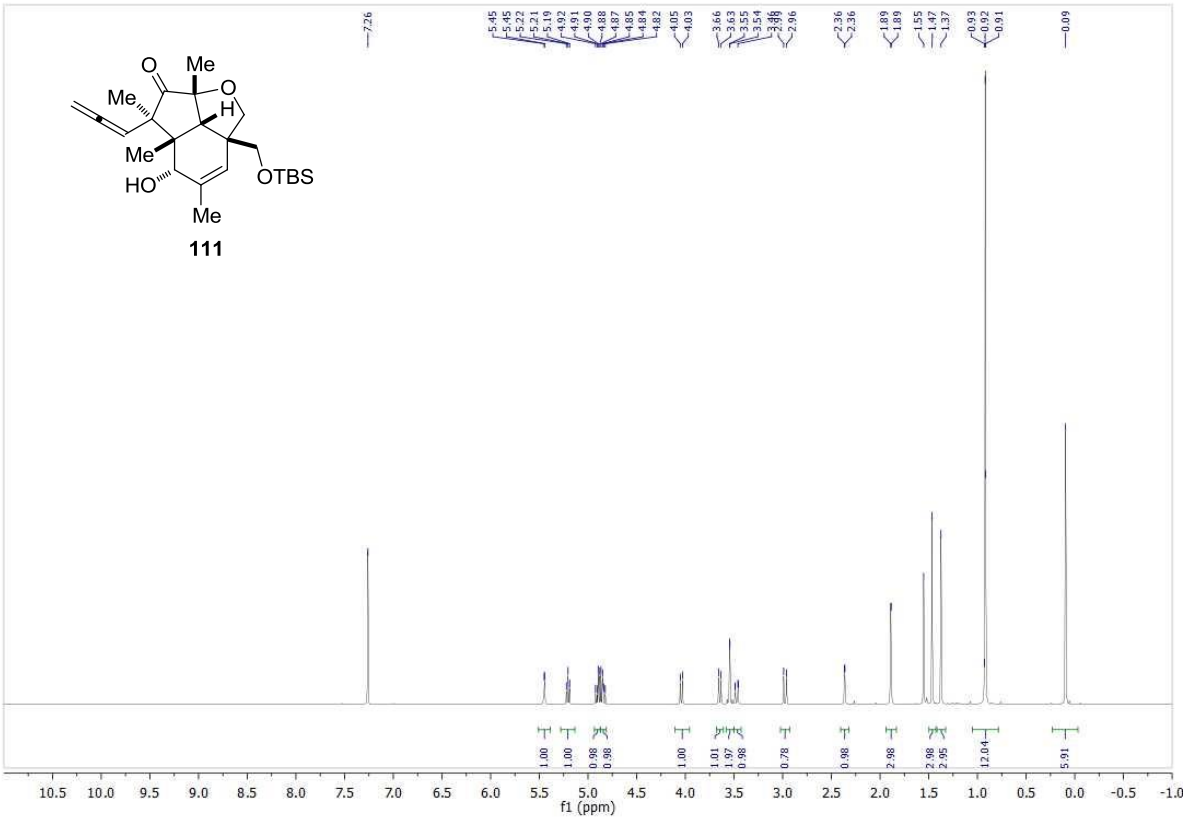
f1 (ppm)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H
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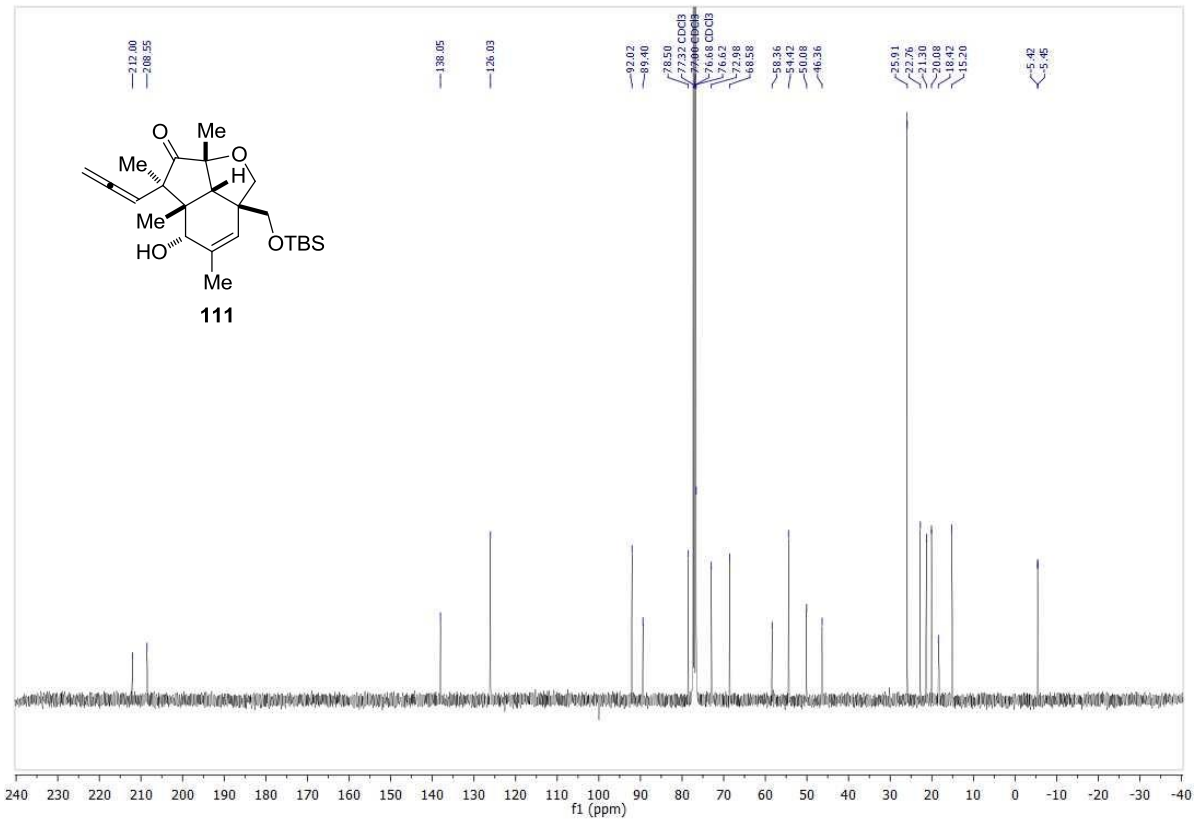
HO
OTBS
Me
111
f1 (ppm)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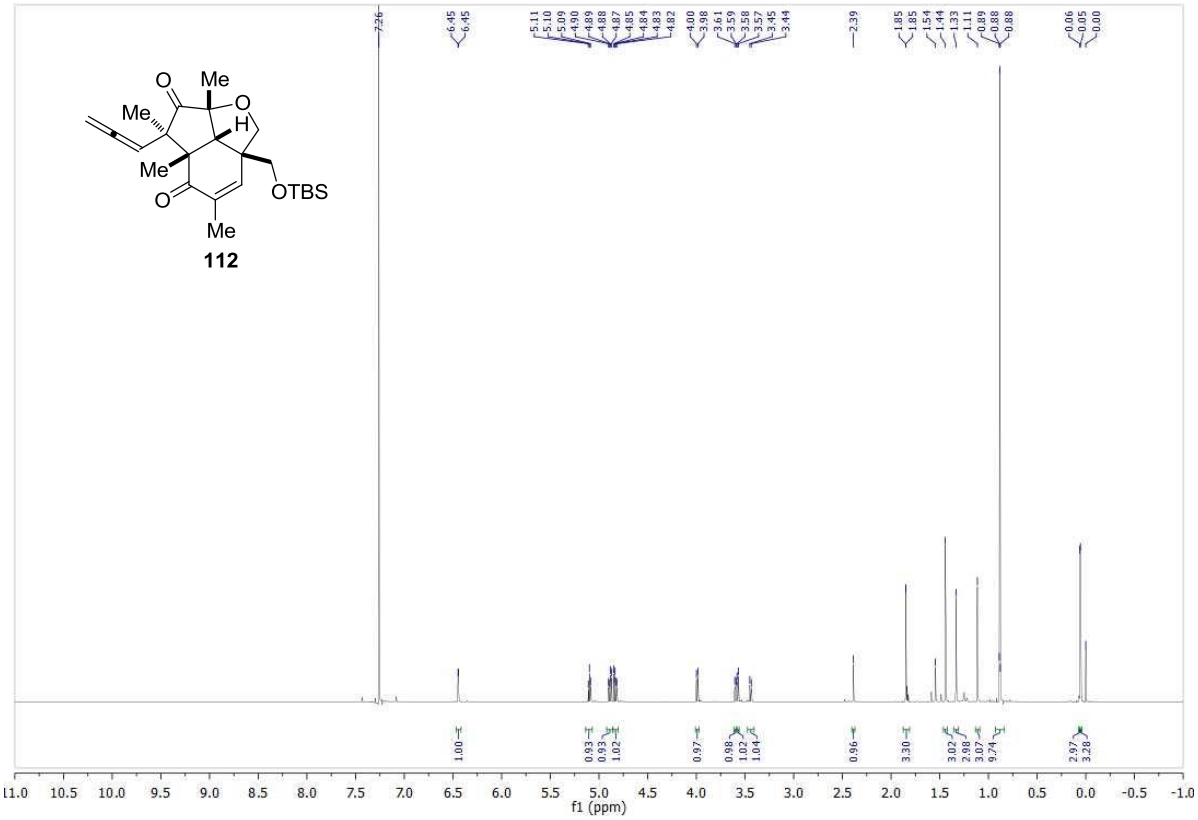
Me
O
H
Me
HO
OTBS
Me
111
f1 (ppm)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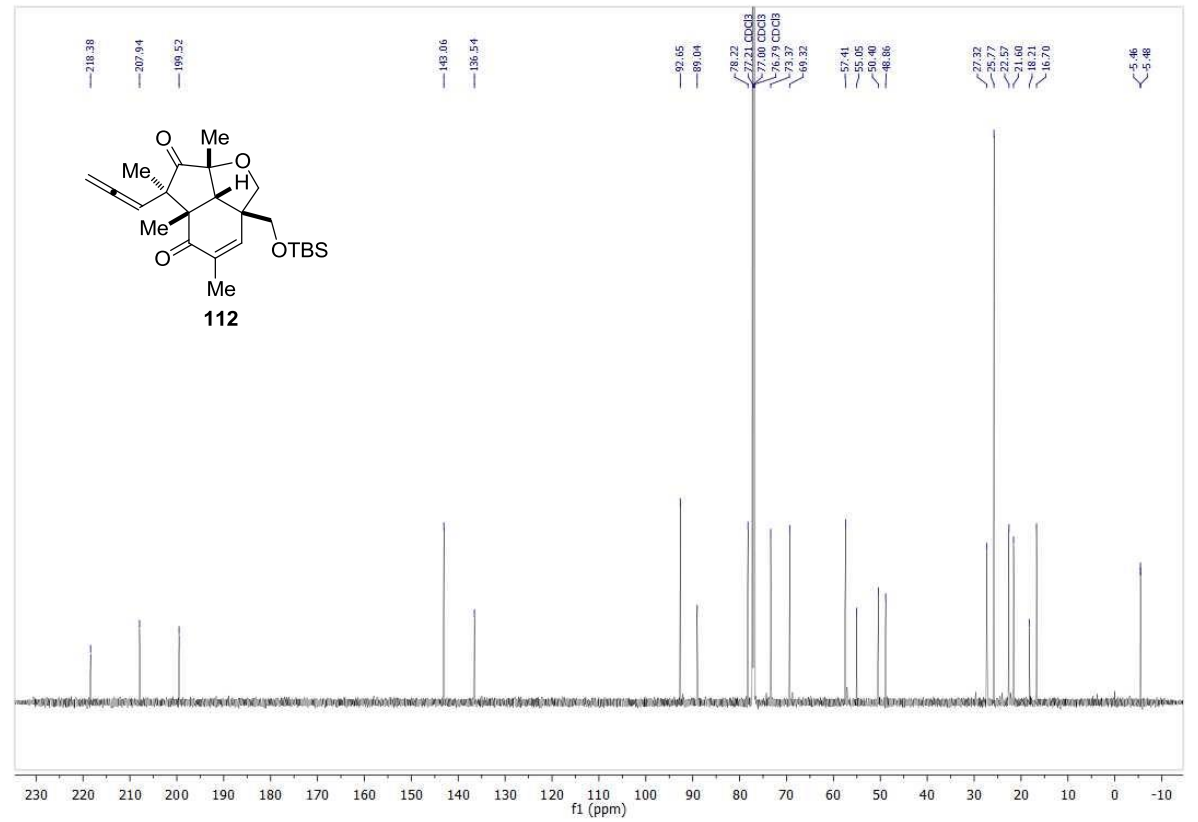
OTBS
O
Me
112
f1 (ppm)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Me
O
H
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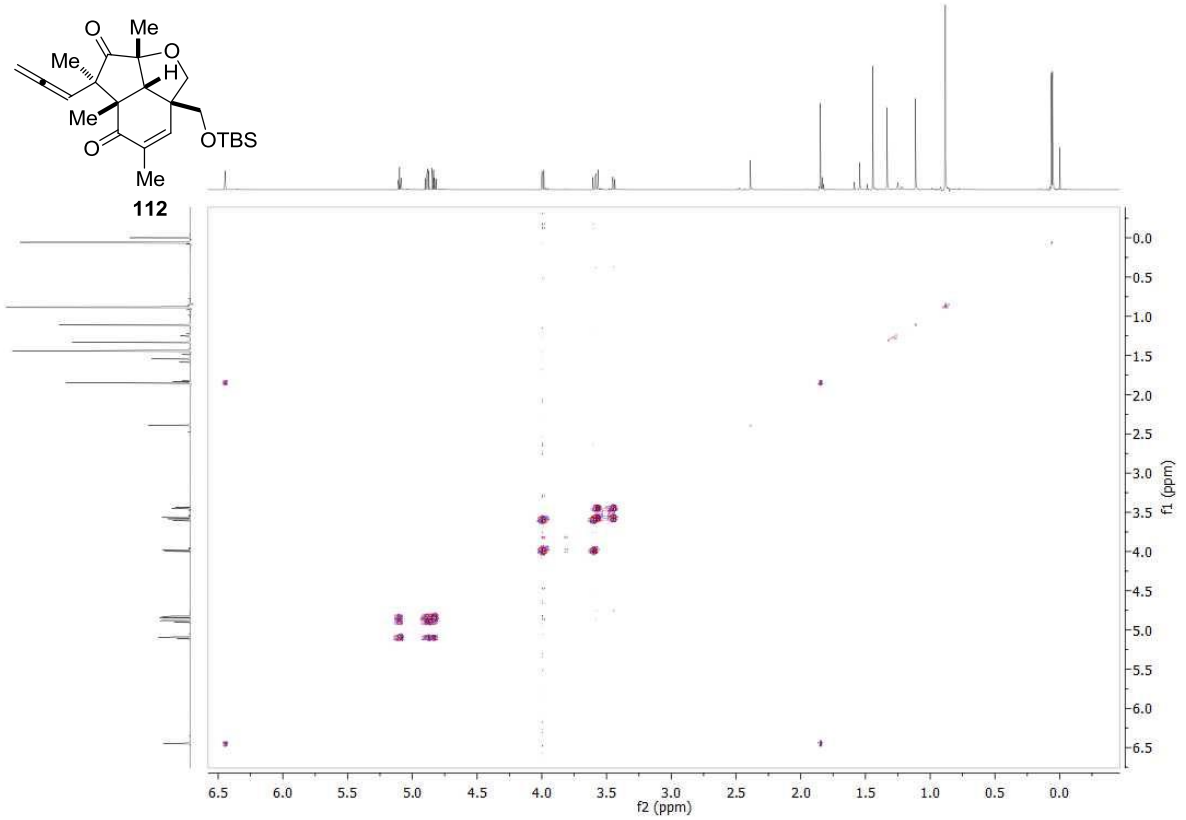
OTBS
O
Me
112
f1 (ppm)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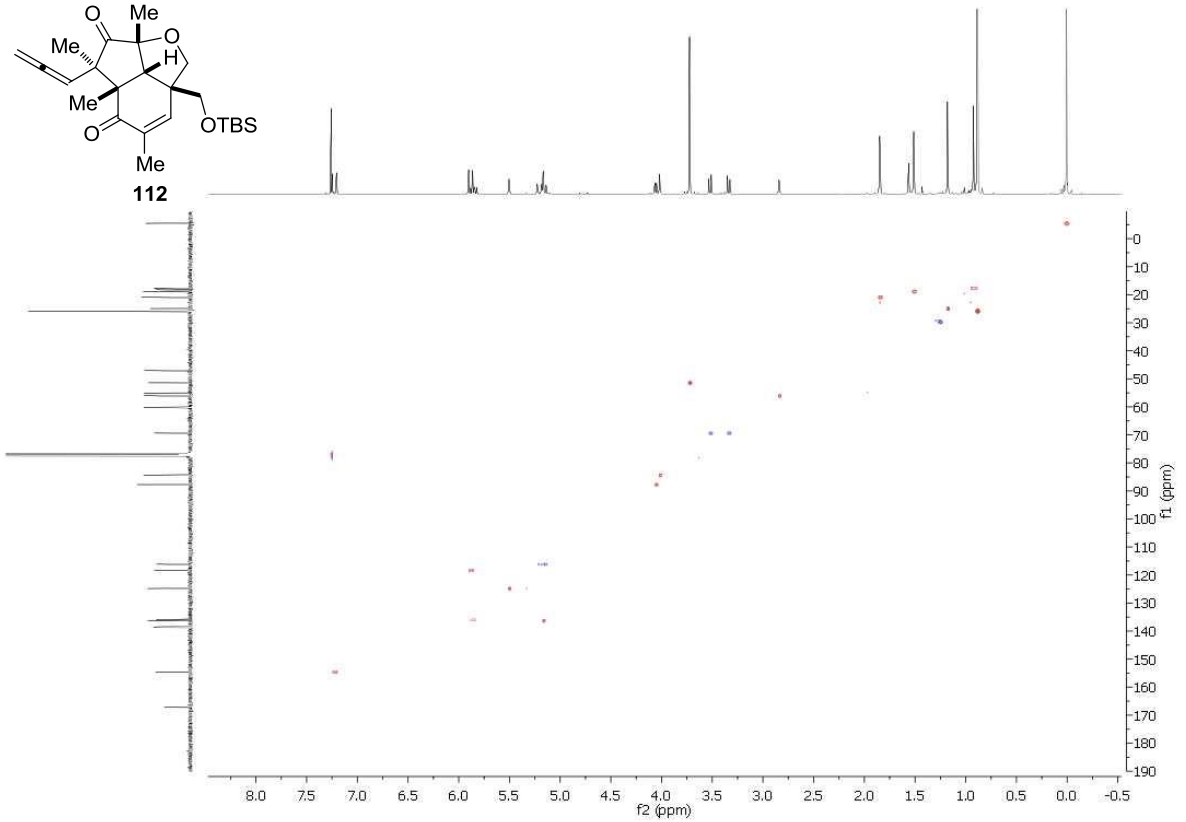
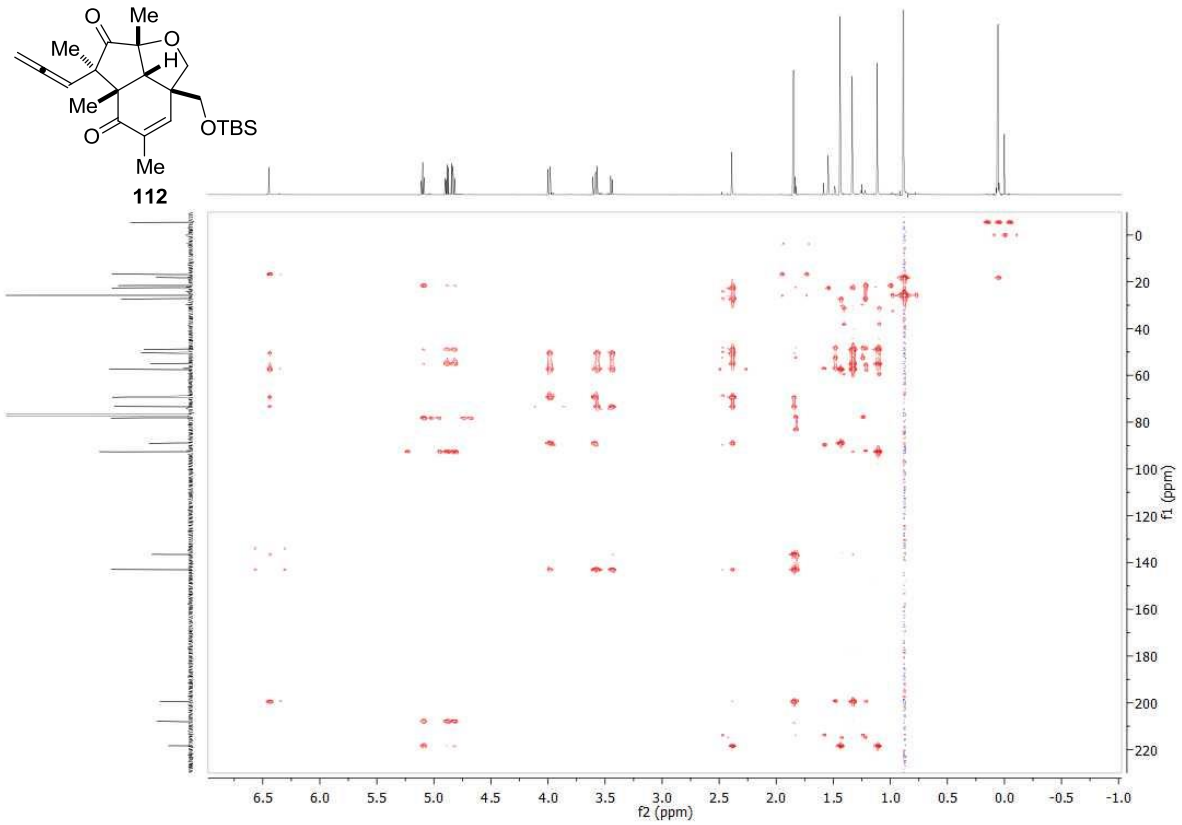
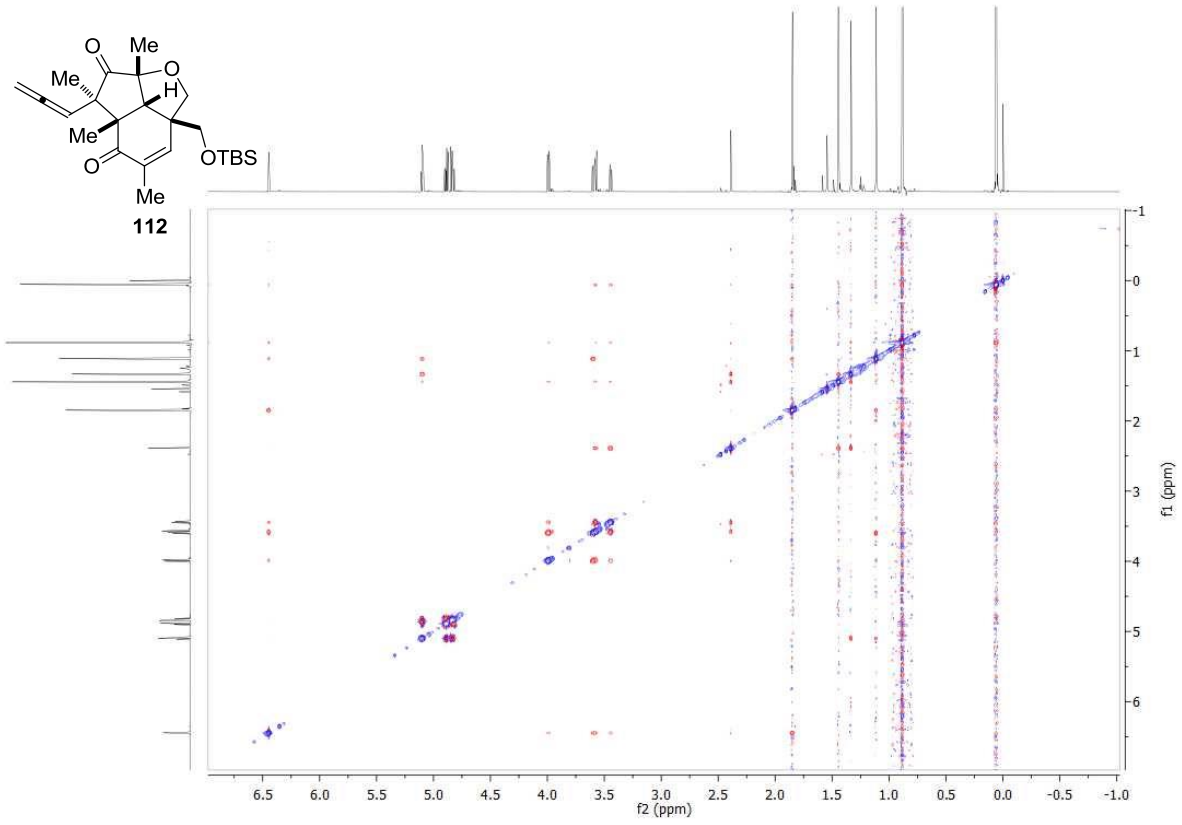
Me
O
H
Me
O
OTBS
Me
f2 (ppm)
f1 (ppm)

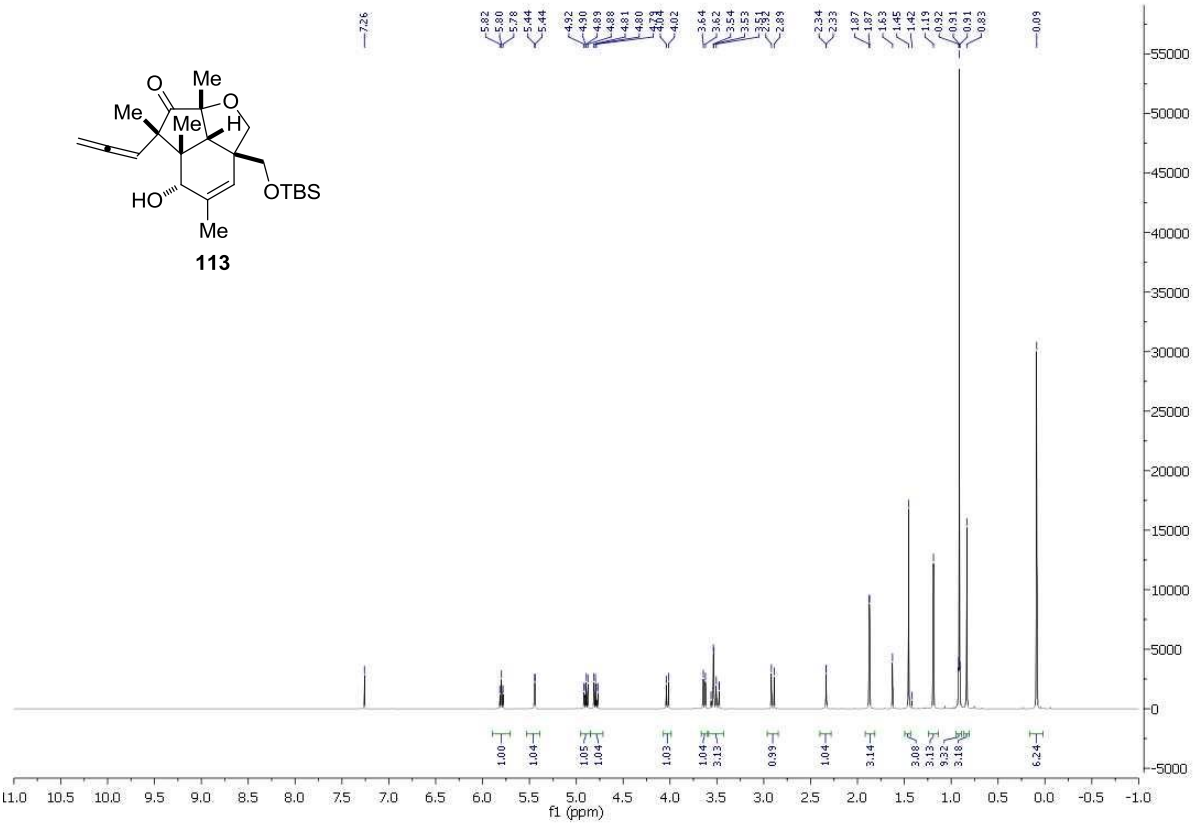
112


O
Me
Me
O
H
Me
O
OTBS
Me
f2 (ppm)
f1 (ppm)

112

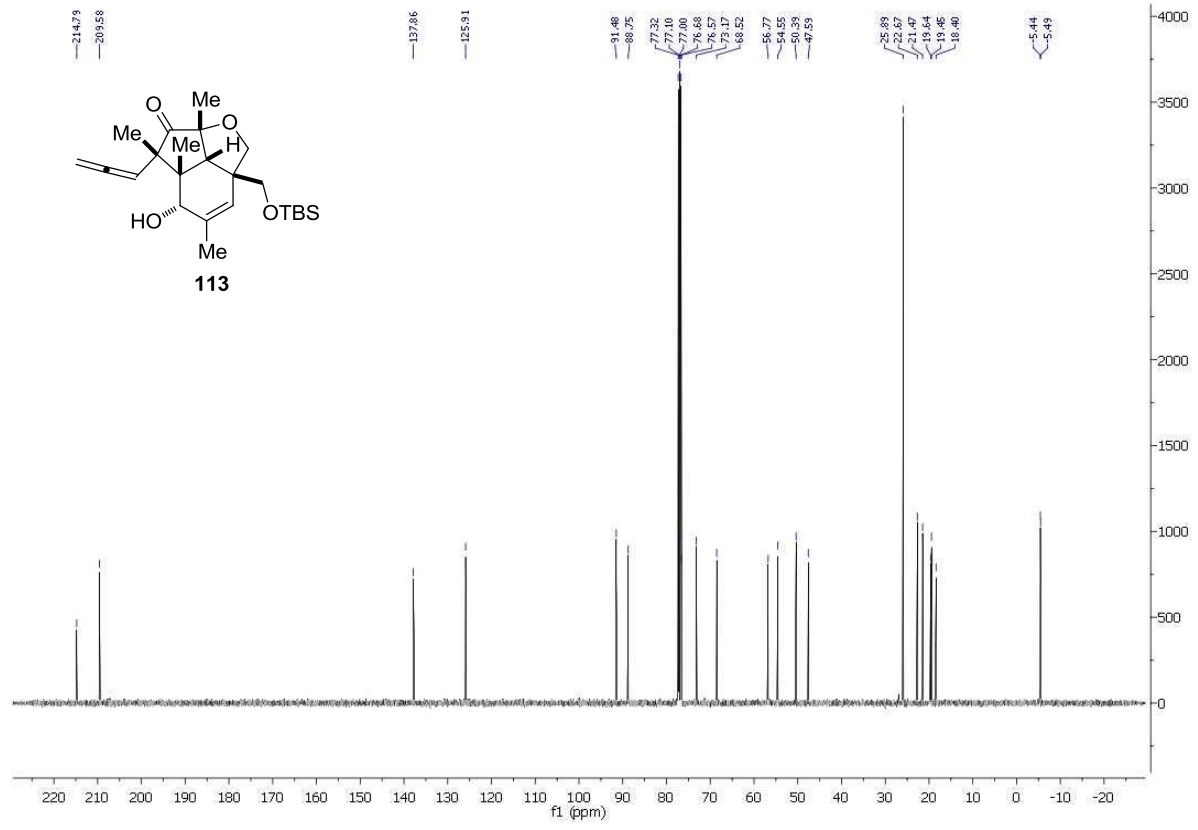

O
Me
Me
O
H
Me
O
OTBS
Me
112
f2 (ppm)
f1 (ppm)


O
Me
Me
O
H
Me
O
OTBS
Me
112
f2 (ppm)
f1 (ppm)


O
Me
Me
O
Me
H
HO
OTBS
Me

113

7.26
5.82
5.80
5.78
5.44
5.44
4.92
4.90
4.89
4.88
4.81
4.80
4.02
3.64
3.62
3.54
3.53
2.89
2.34
2.33
1.87
1.87
1.63
1.45
1.42
1.11
0.92
0.91
0.91
0.83
0.09
1.00
1.04
1.05
1.04
1.03
1.04
3.13
0.99
1.04
3.14
3.08
3.13
9.32
3.18
6.24
f1 (ppm)


O
Me
Me
O
Me
H
HO
OTBS
Me

113

214.79
209.58
137.86
125.91
91.48
88.75
77.32
77.10
77.00
76.68
76.57
73.17
68.52
56.77
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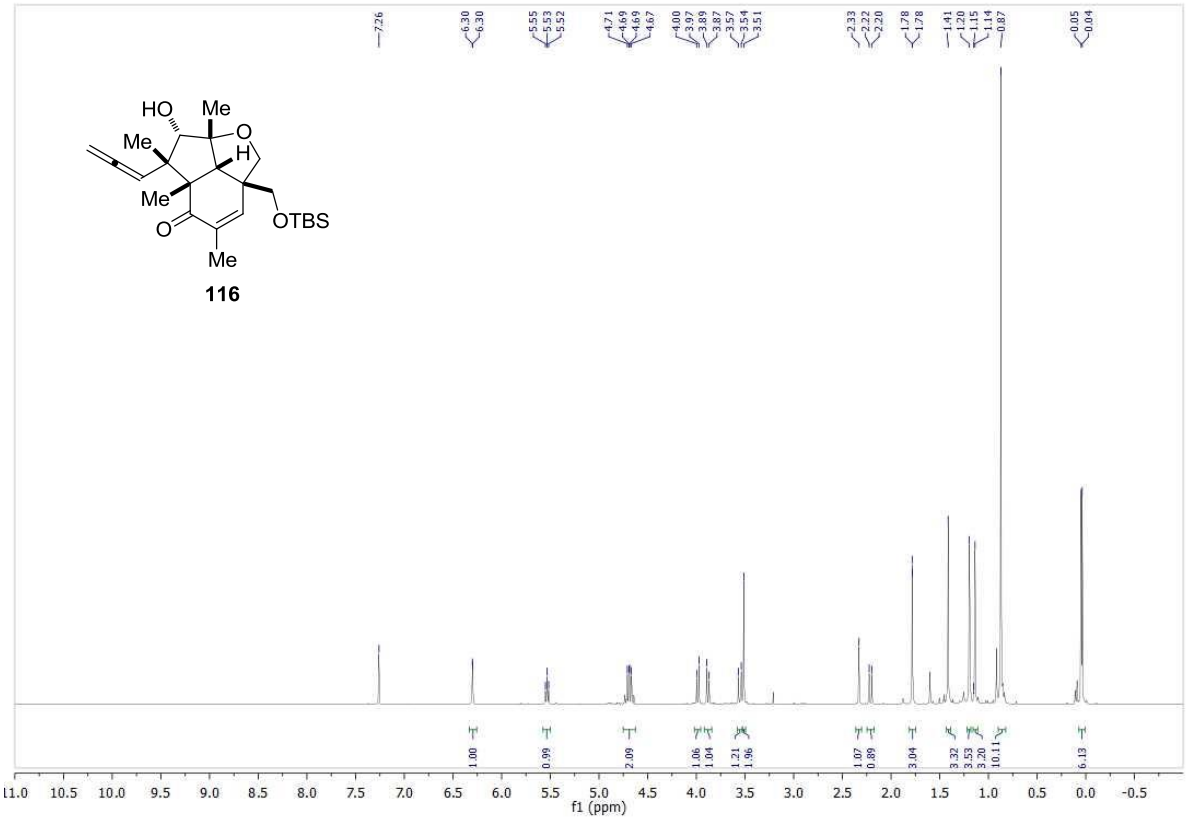
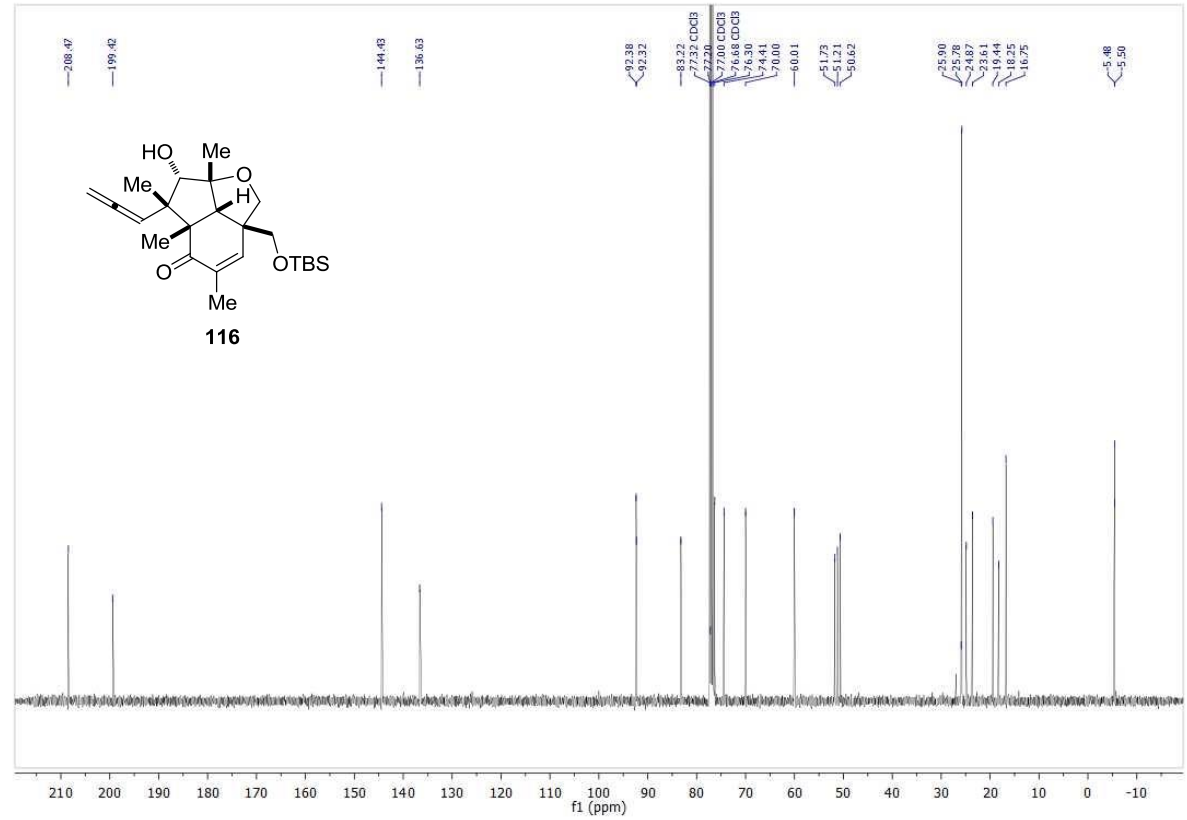
19.46
18.40
5.44
5.49
f1 (ppm)


HO
Me
Me
O
H
Me
O
OTBS
Me
116
f1 (ppm)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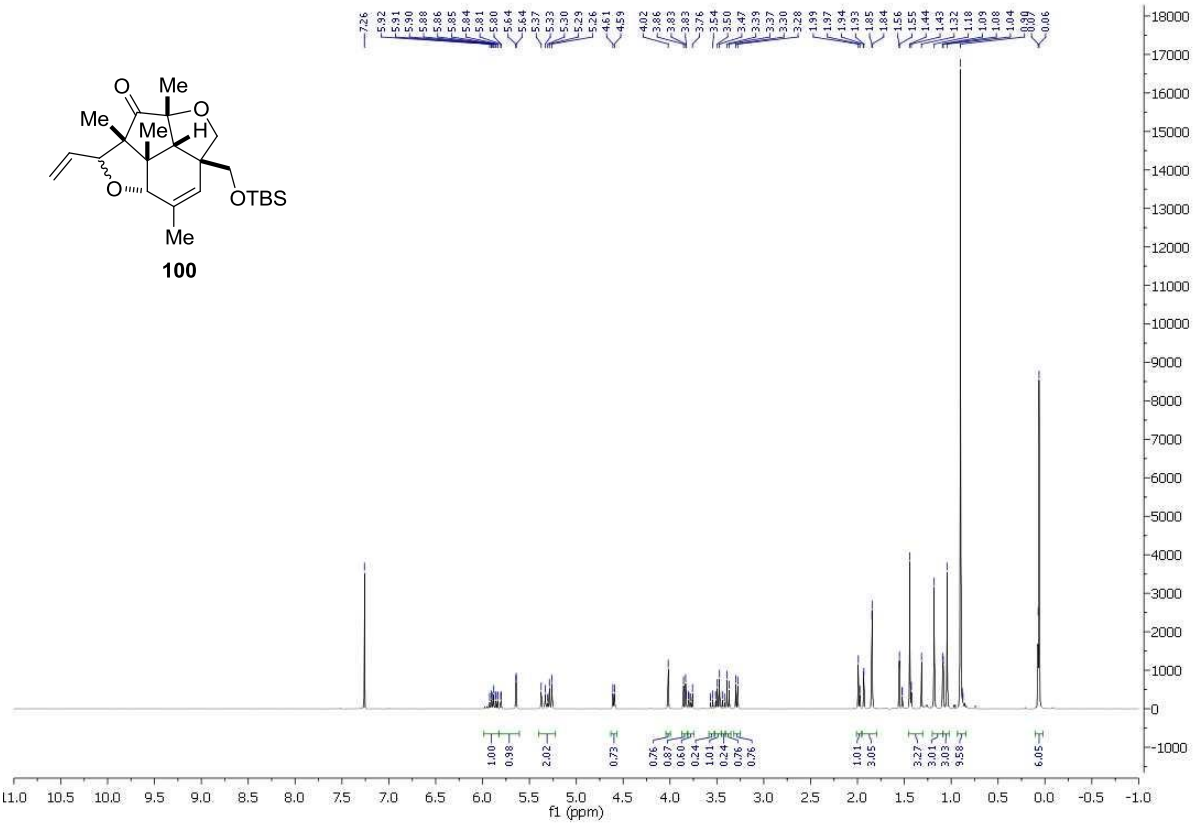
Me
Me
O
H
Me
O
OTBS
Me
116
f1 (ppm)



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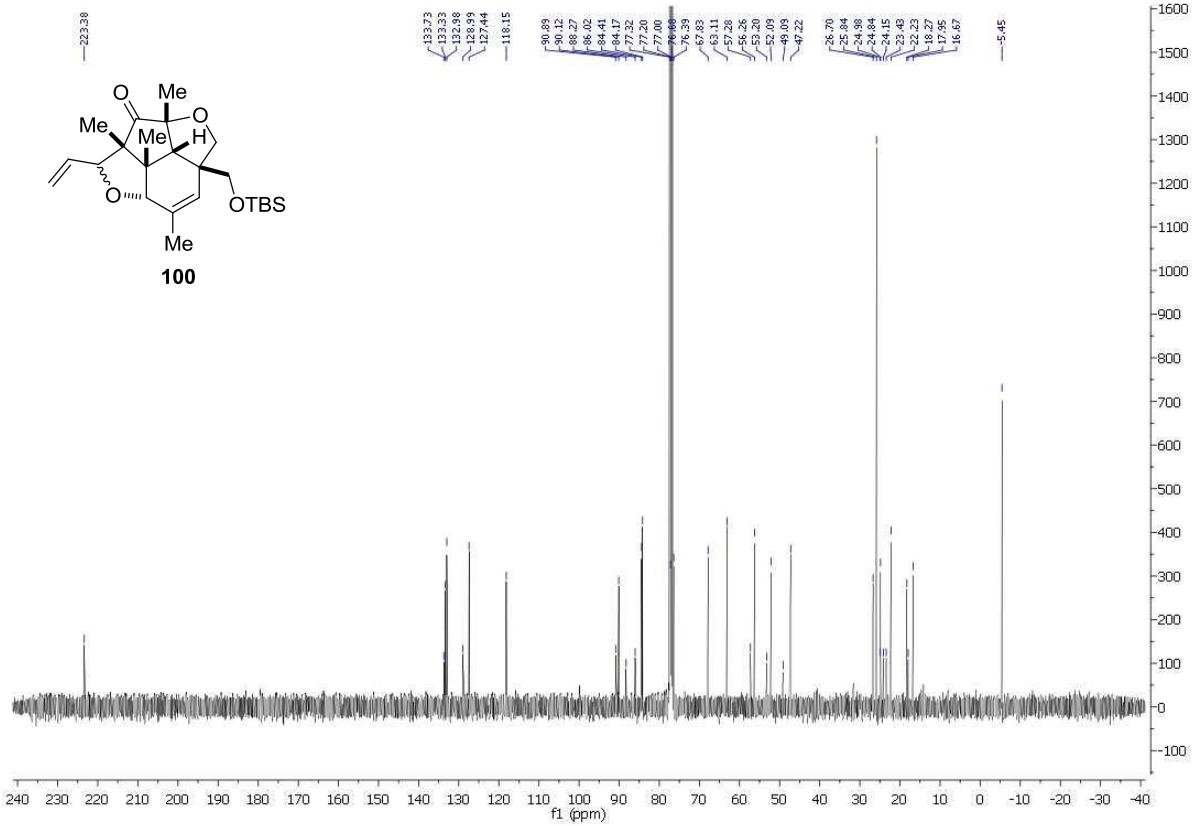

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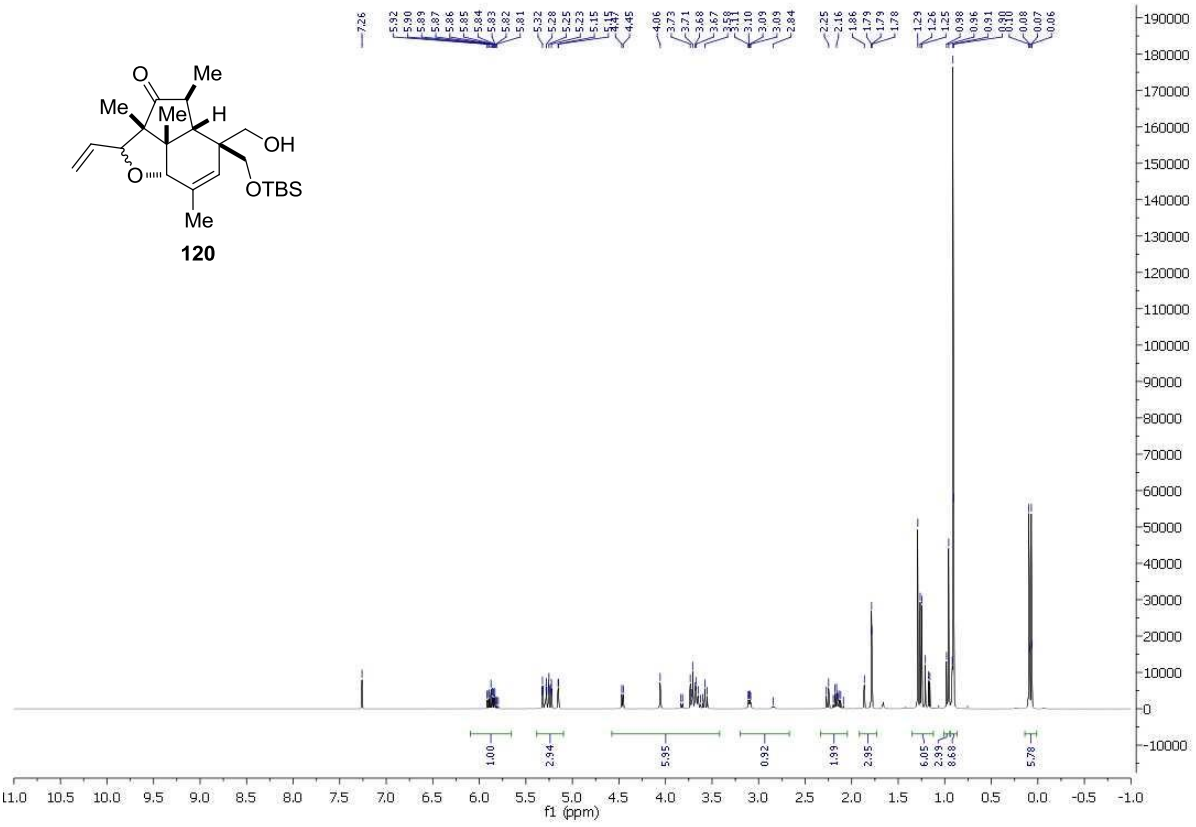
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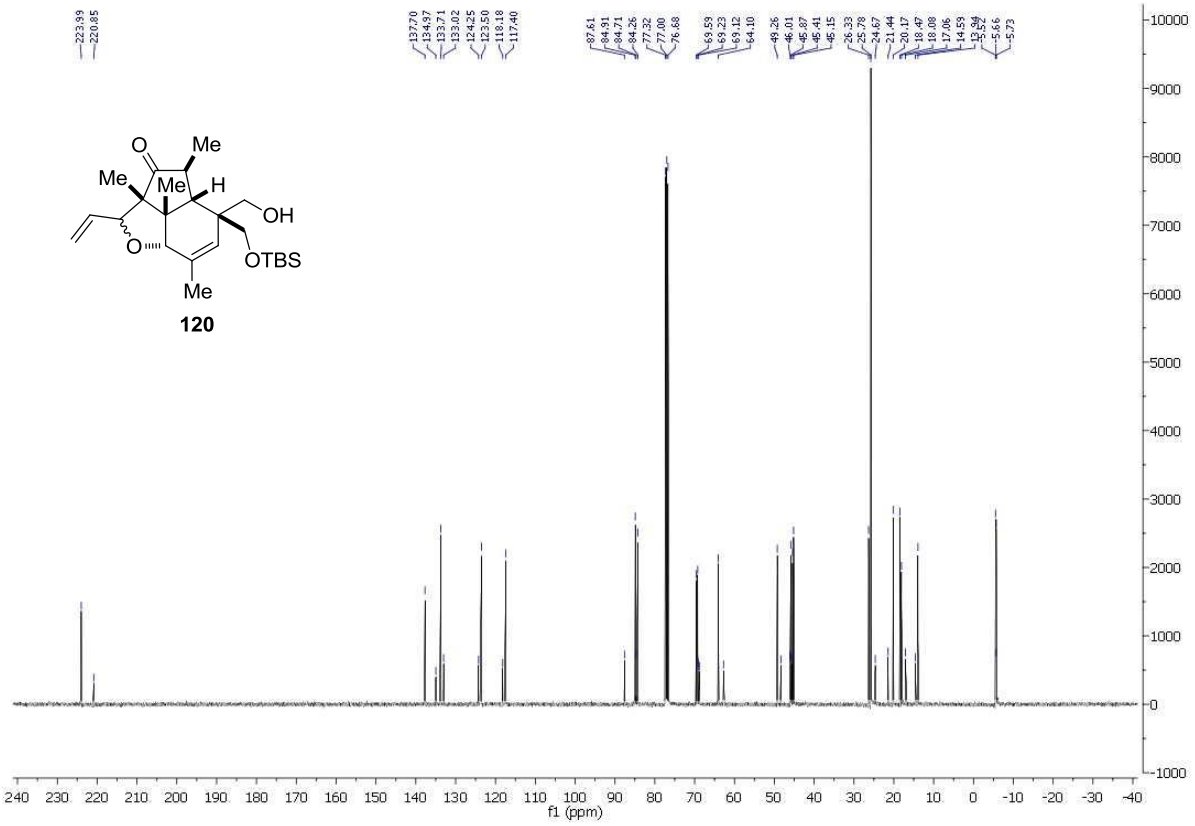
Me
Me
Me
H
OH
O
OTBS
Me
120
f1 (ppm)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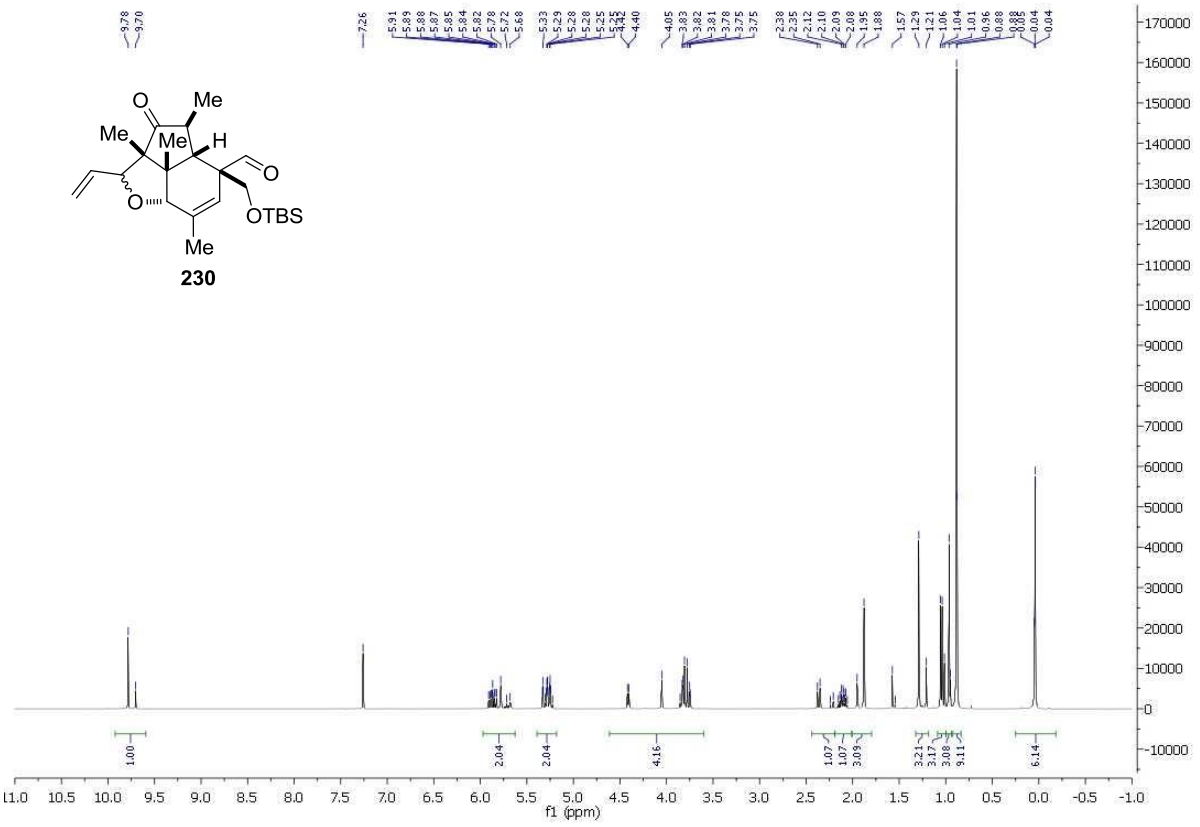
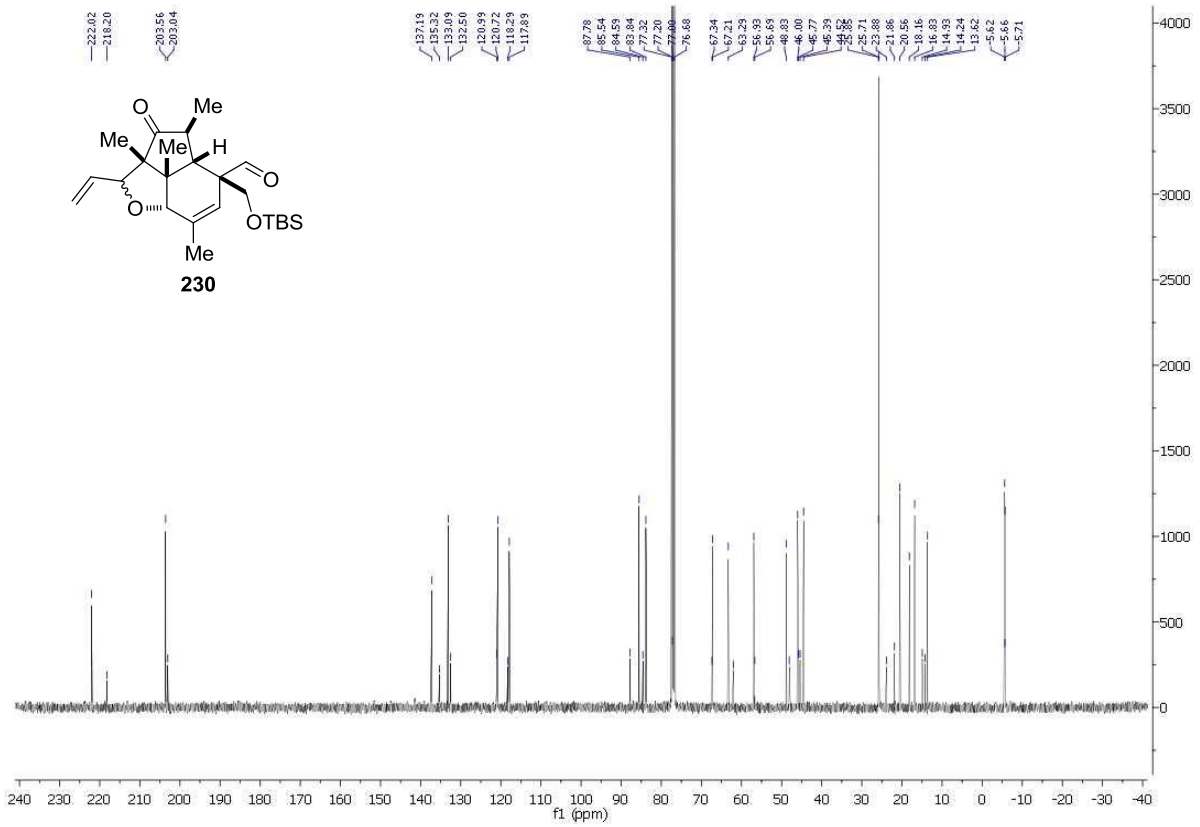
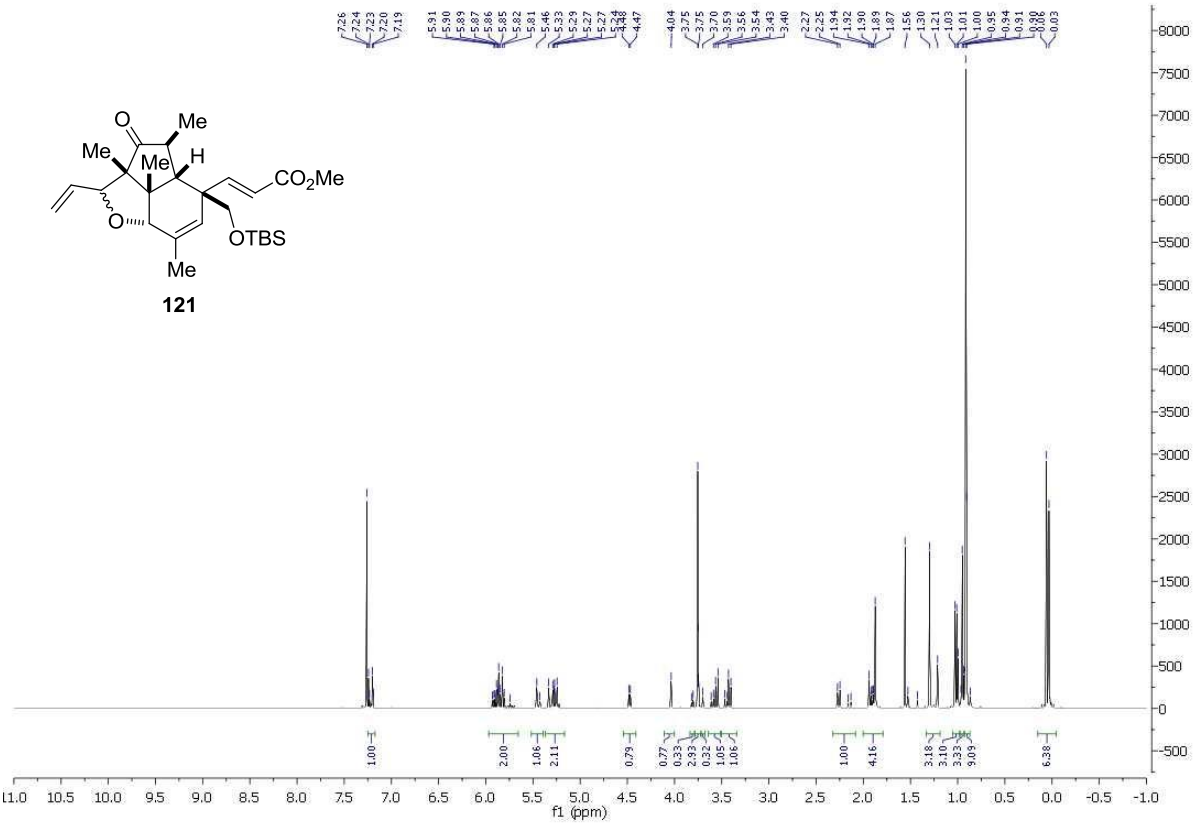
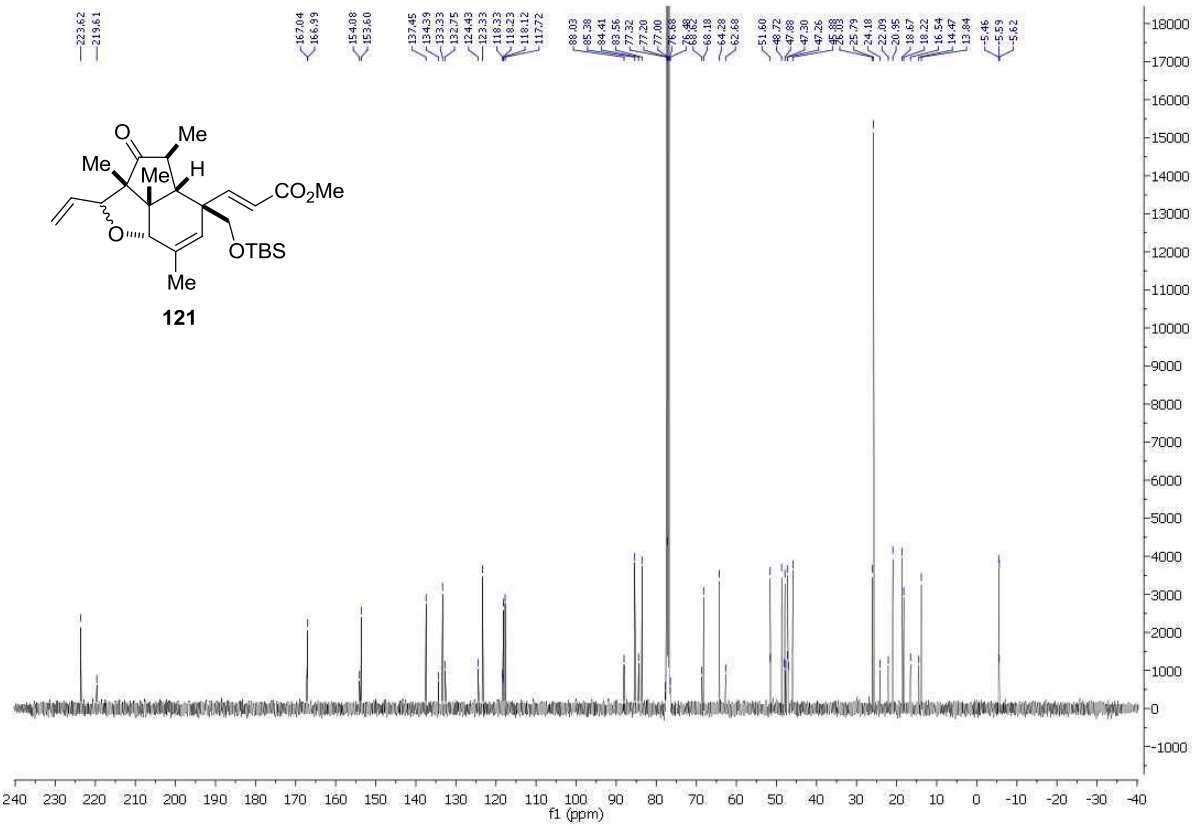
Me
Me
Me
H
OH
O
OTBS
Me
120
f1 (ppm)


O
Me
Me
Me
H
O
O
OTBS
Me
230
f1 (ppm)


O
Me
Me
Me
H
O
O
OTBS
Me
230
f1 (ppm)


O
Me
Me
Me
H
CO2Me
O
OTBS
Me
f1 (ppm)

121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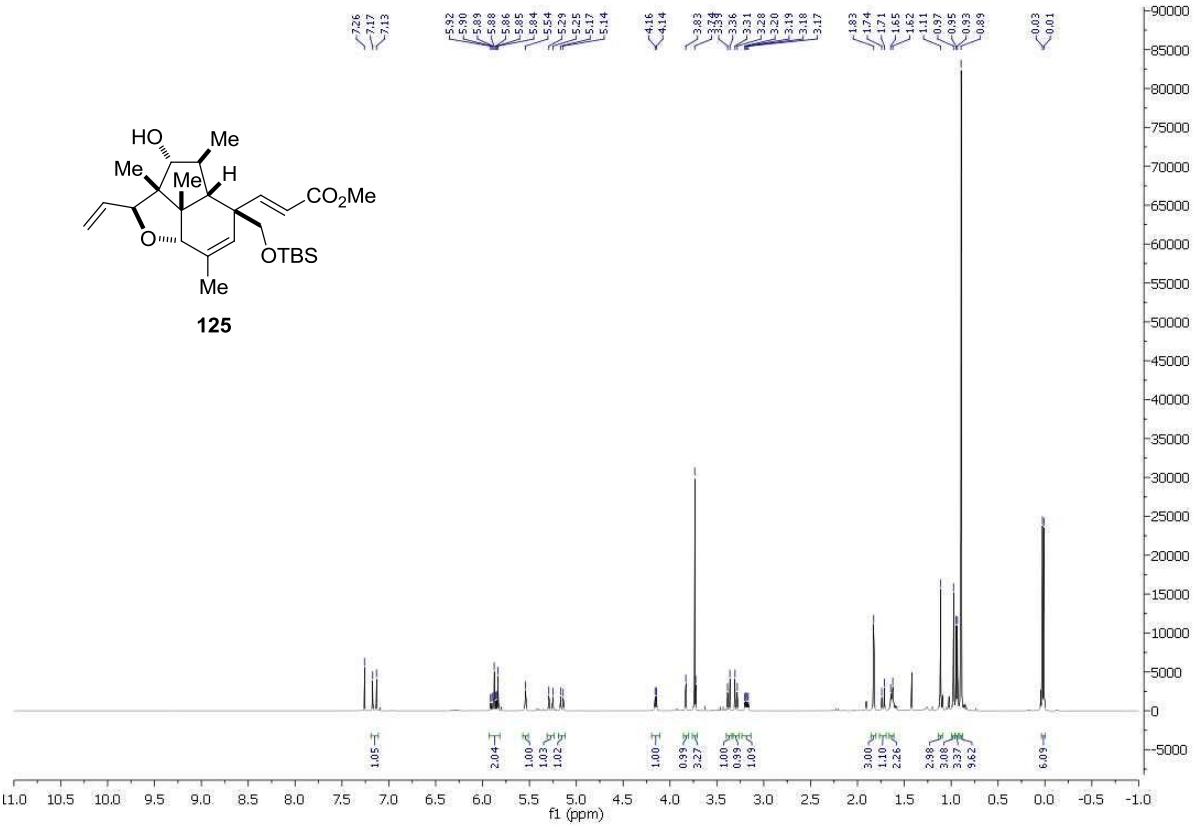
Me
Me
Me
H
CO2Me
O
OTBS
Me
f1 (ppm)

121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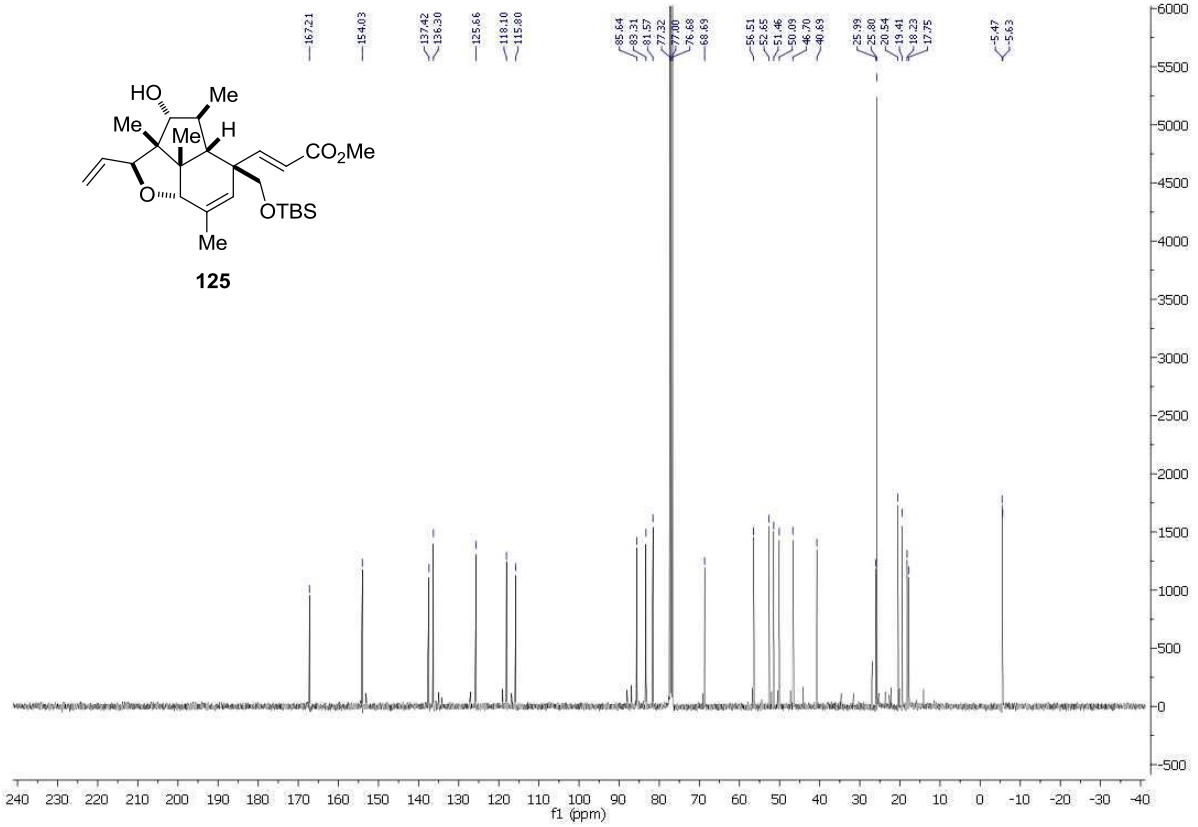
Me
Me
H
CO2Me
O
OTBS
Me
f1 (ppm)

125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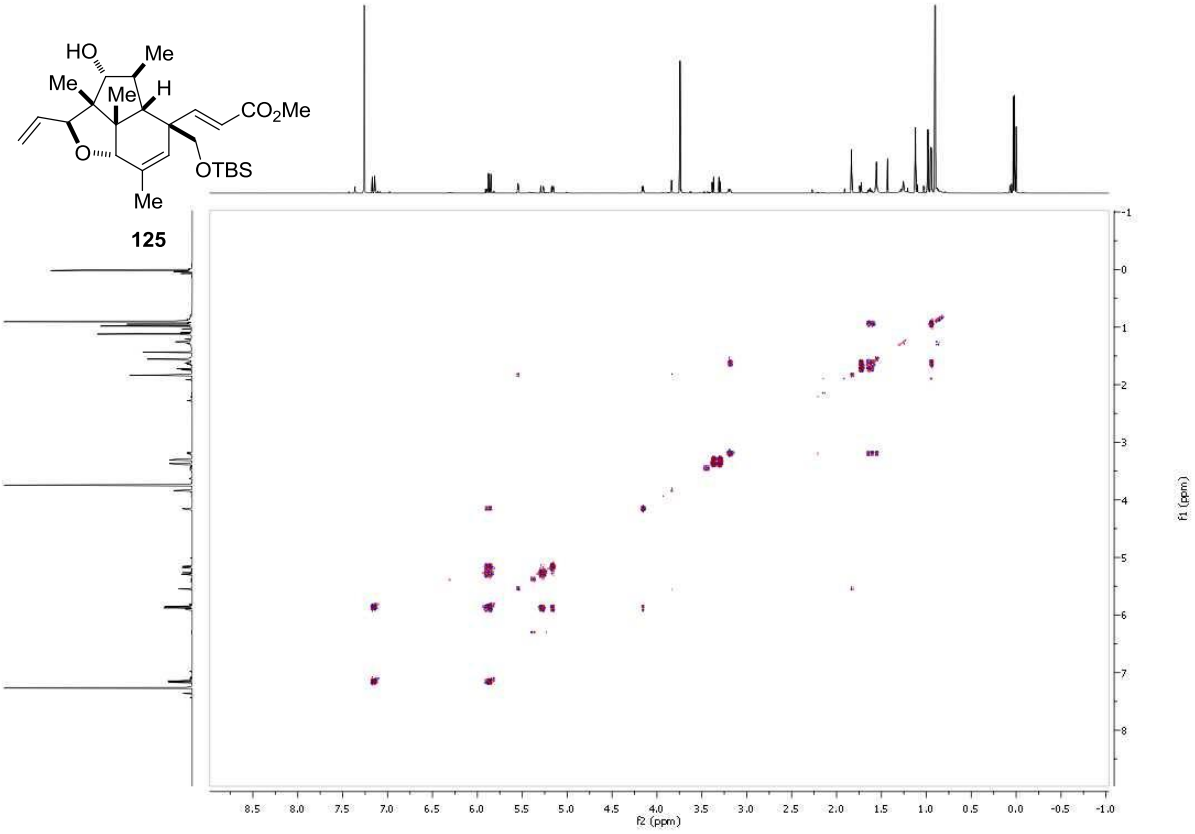
Me
H
CO2Me
O
OTBS
Me
f1 (ppm)

125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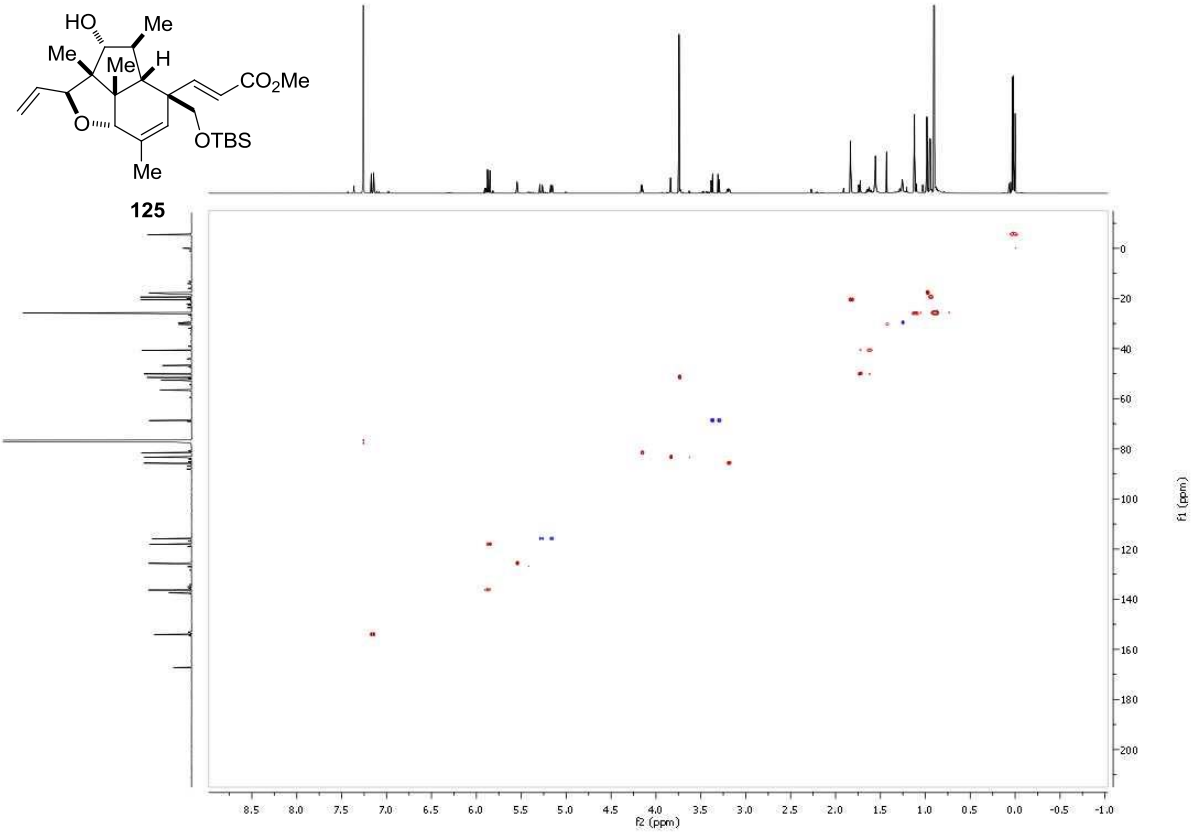
Me
H
CO2Me
O
OTBS
Me
125
F2 (ppm)
F1 (ppm)


HO
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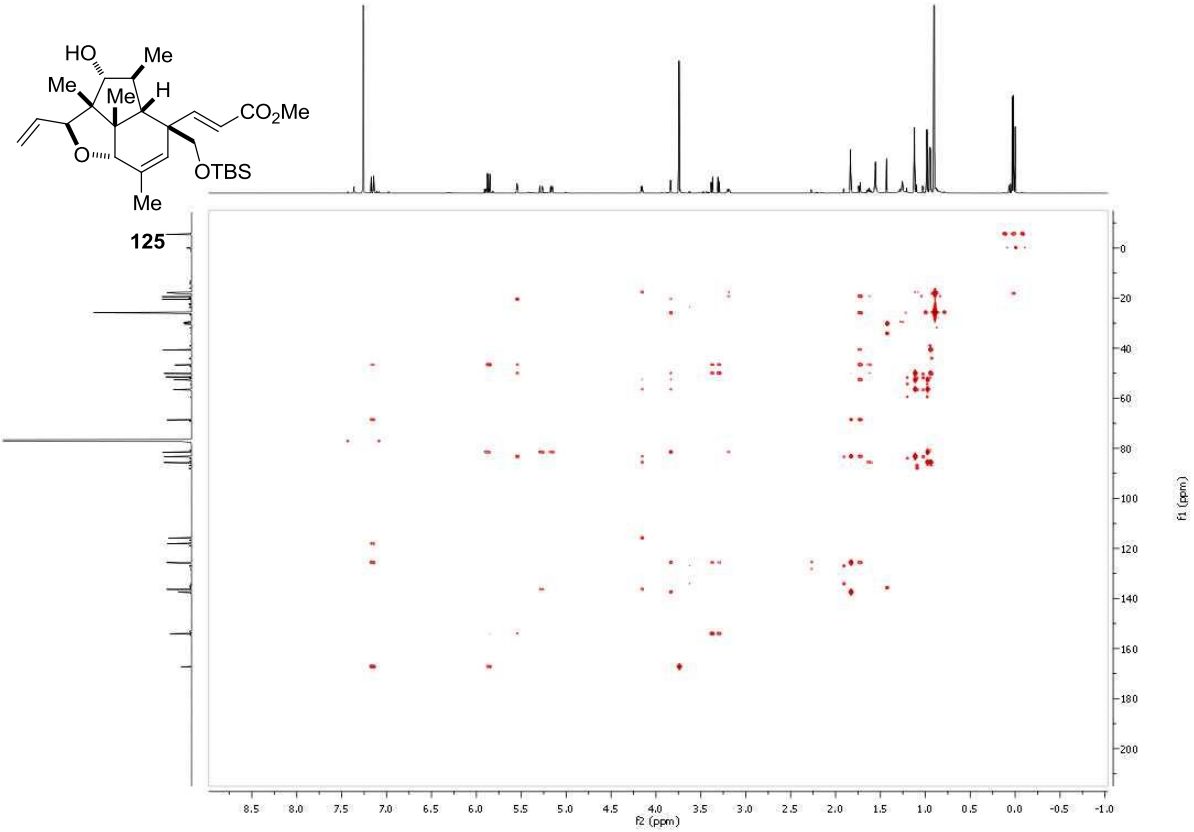
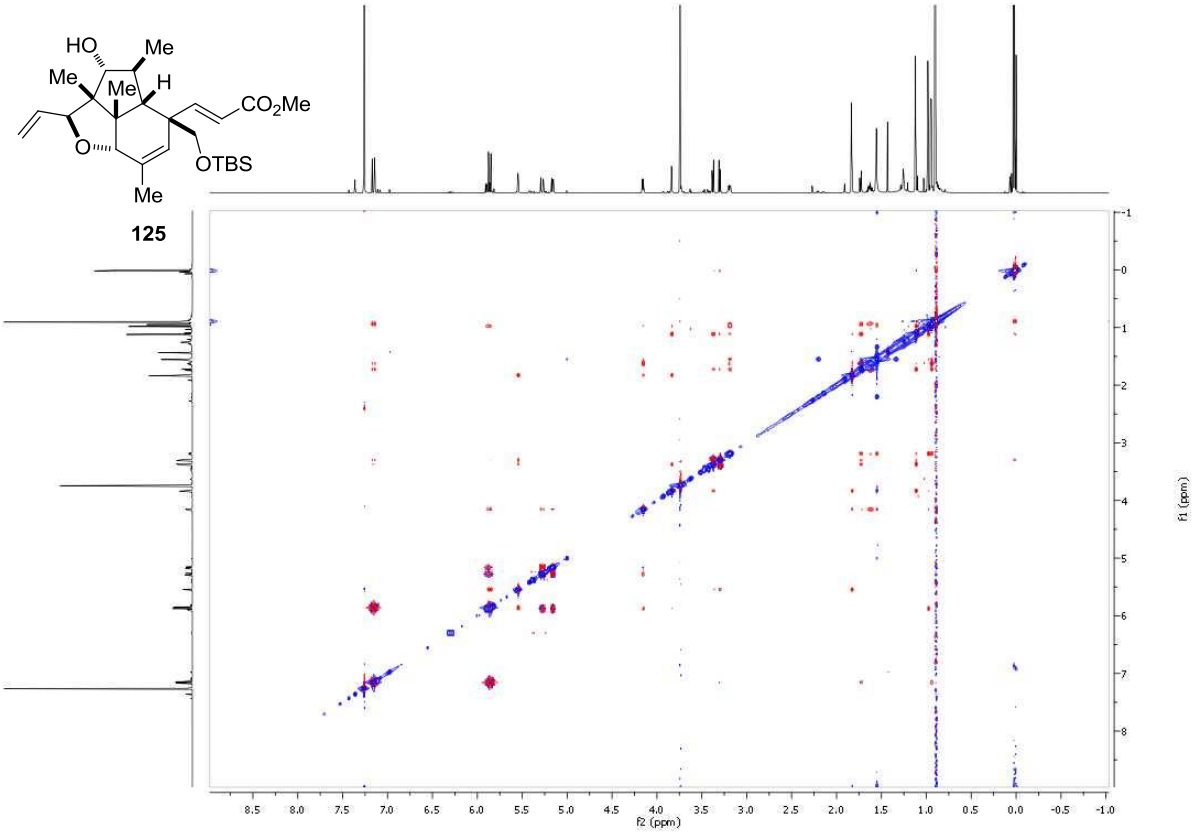
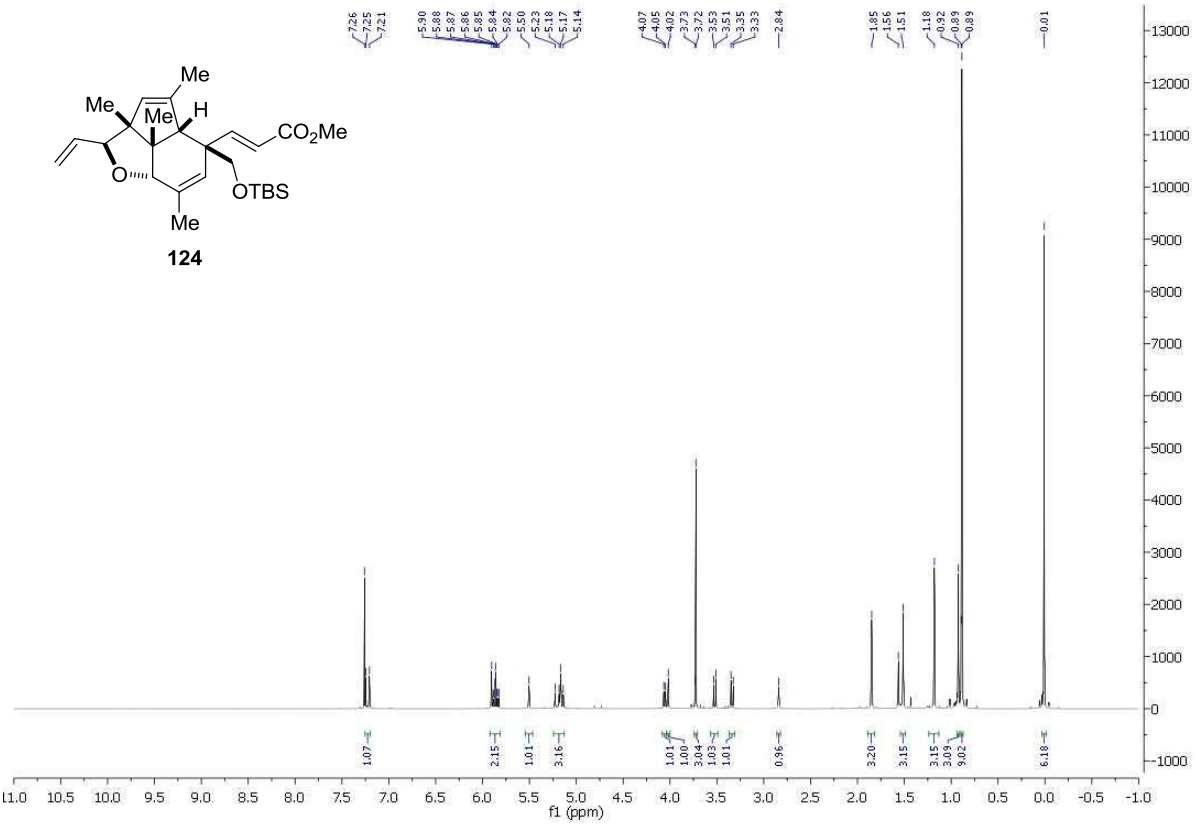
Me
H
CO2Me
O
OTBS
Me
125
F2 (ppm)
F1 (ppm)


HO
Me
Me
Me
H
CO2Me
O
OTBS
Me
125
F2 (ppm)
F1 (ppm)


HO
Me
Me
Me
H
CO2Me
O
OTBS
Me
125
F2 (ppm)
F1 (ppm)


Me
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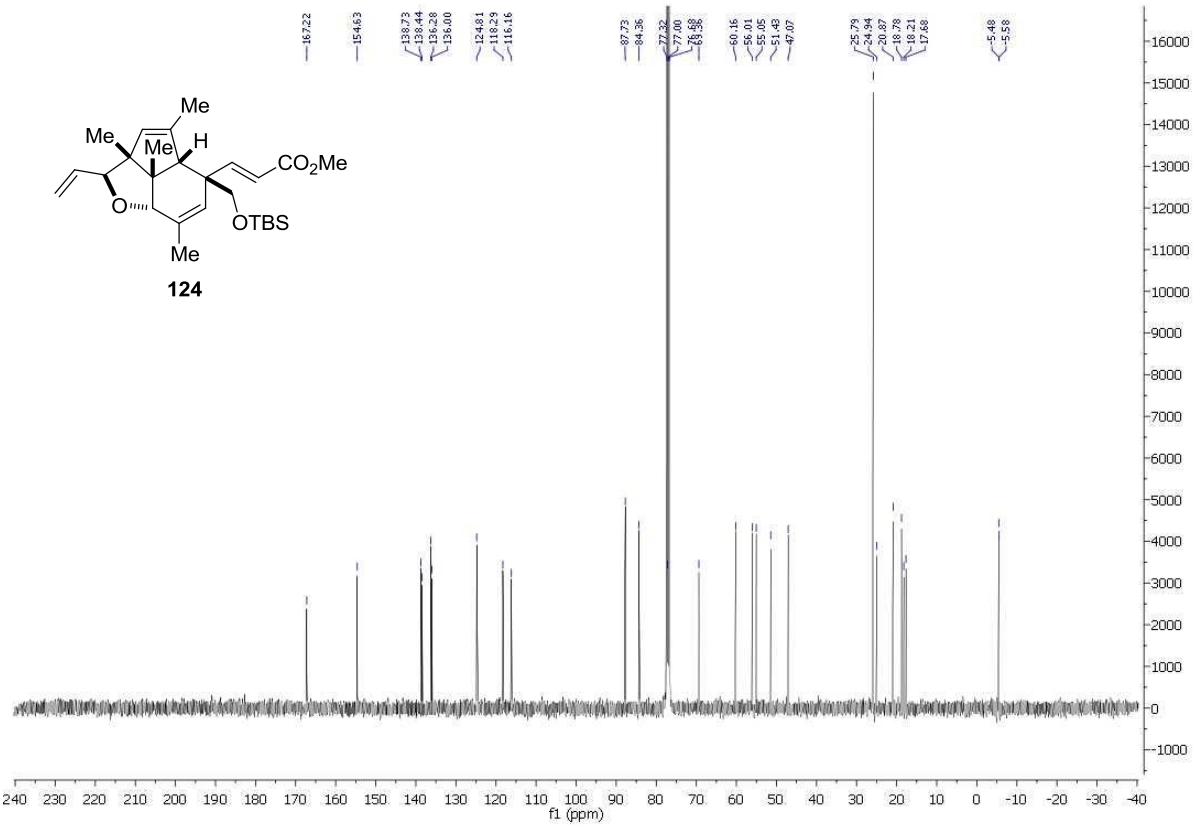
Me
H
CO2Me
O
OTBS
Me
124
f1 (ppm)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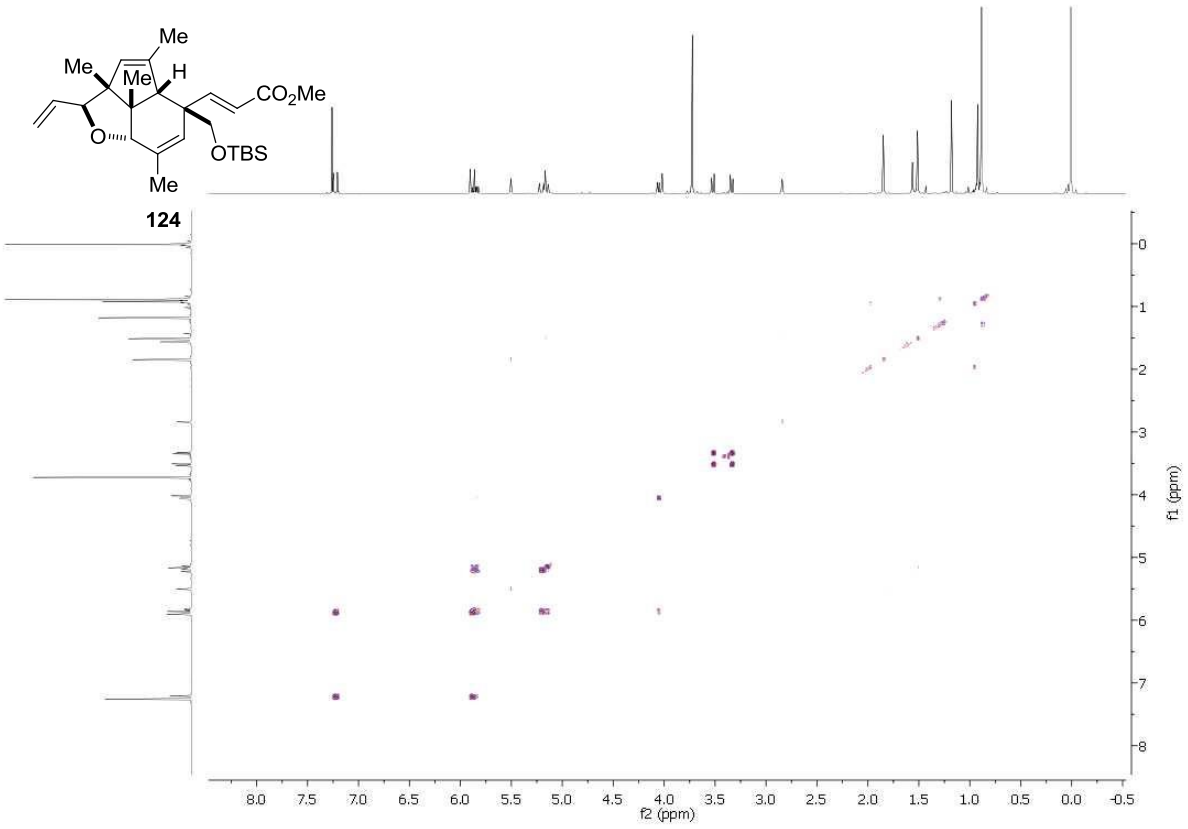
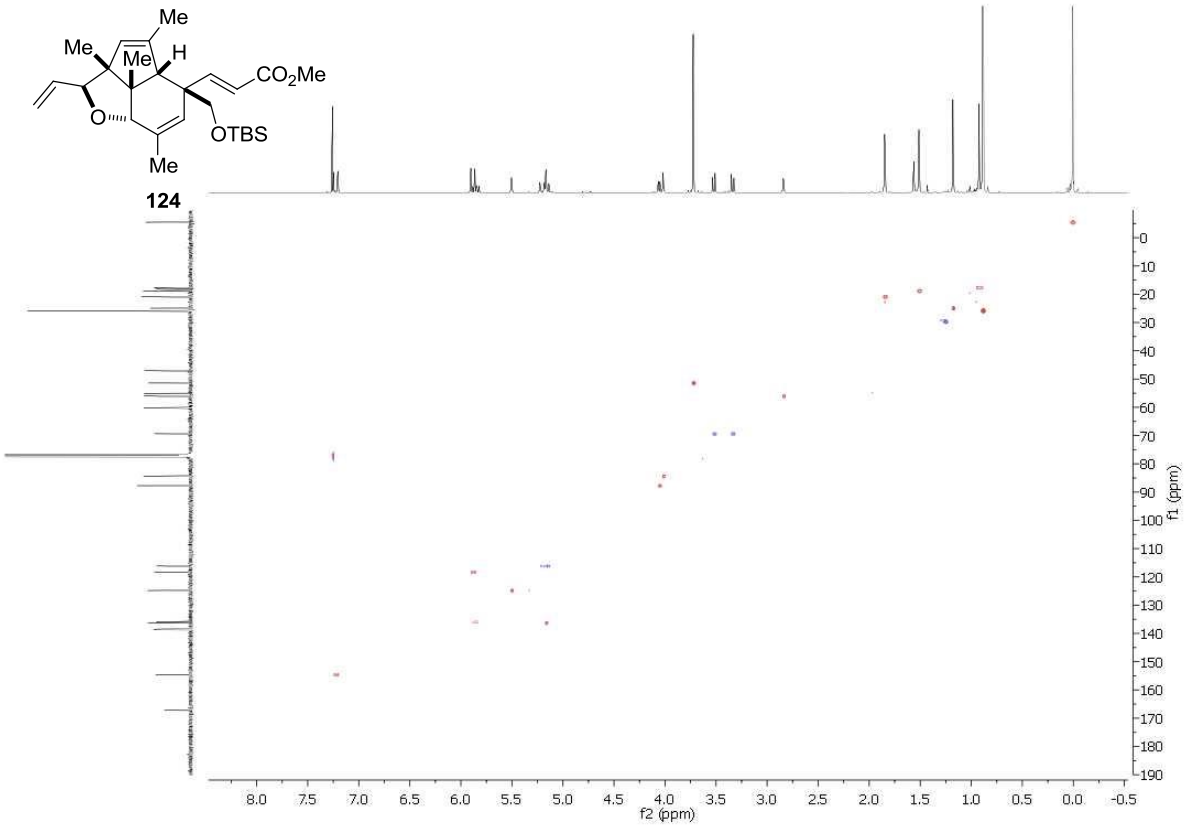
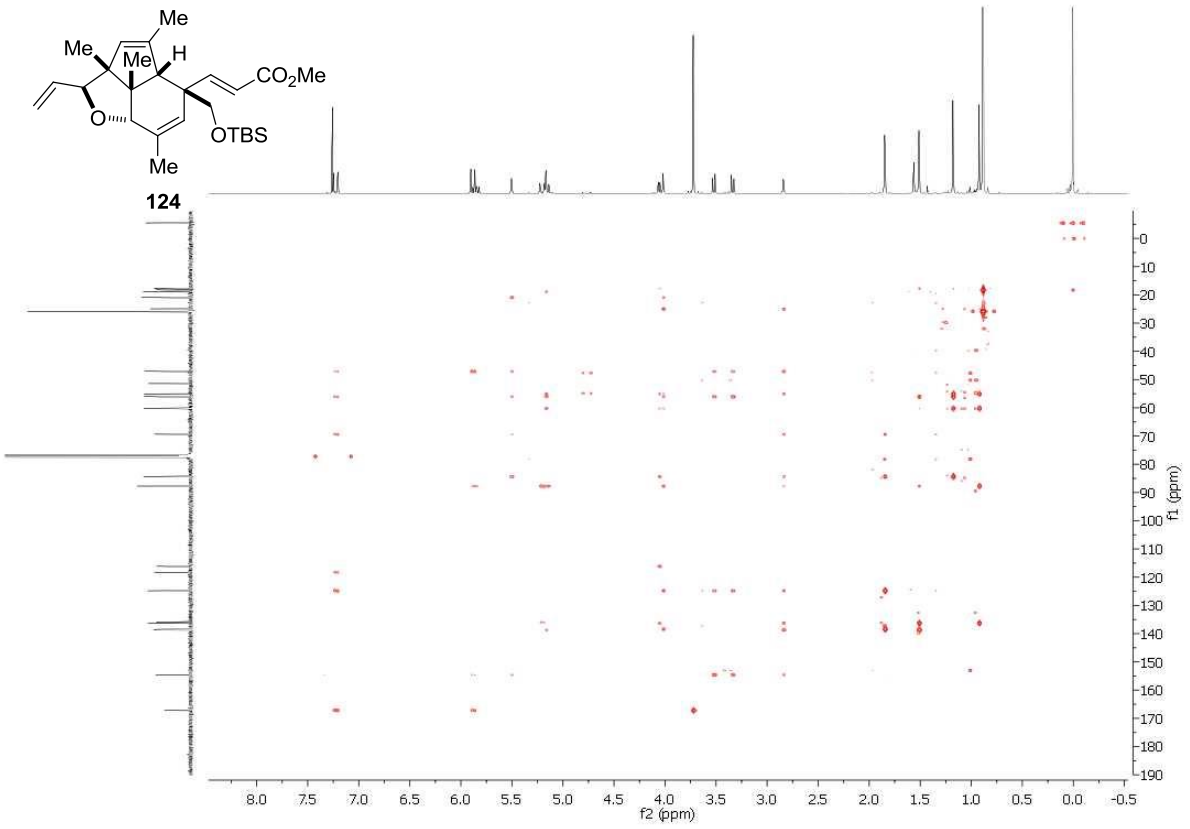
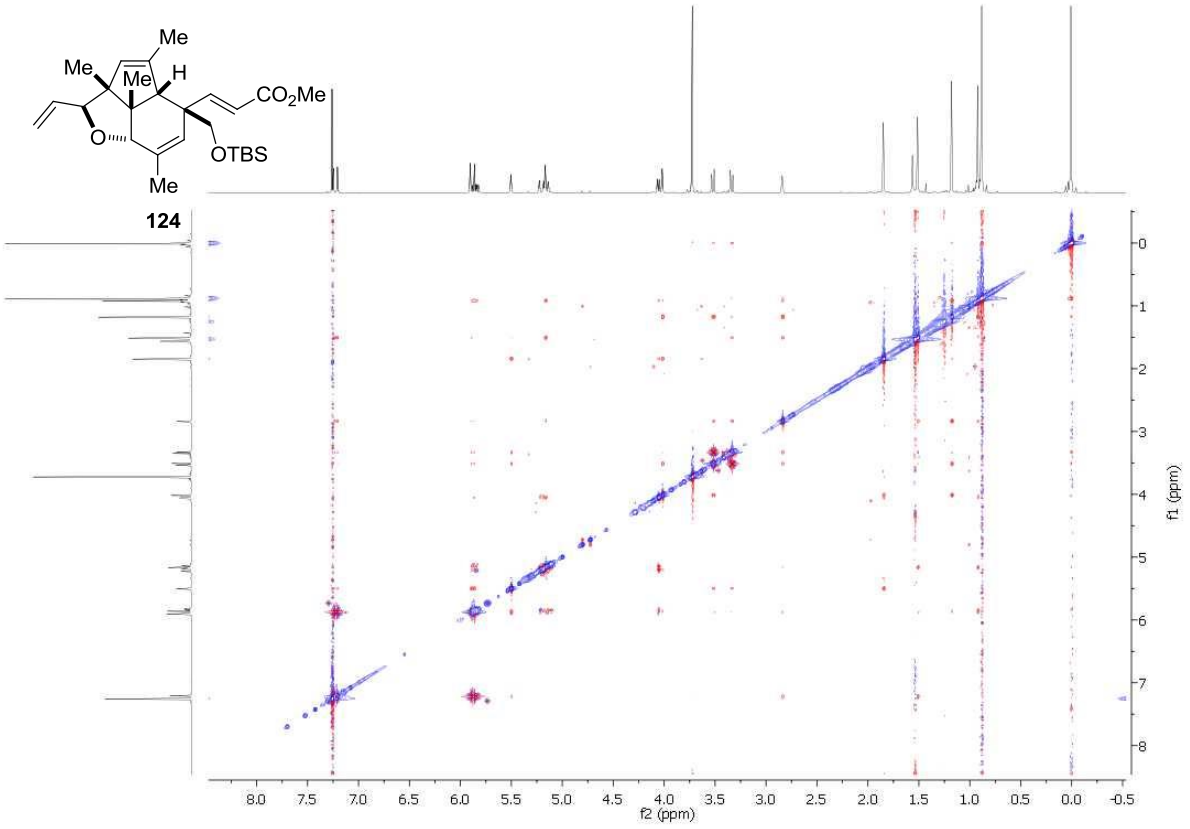
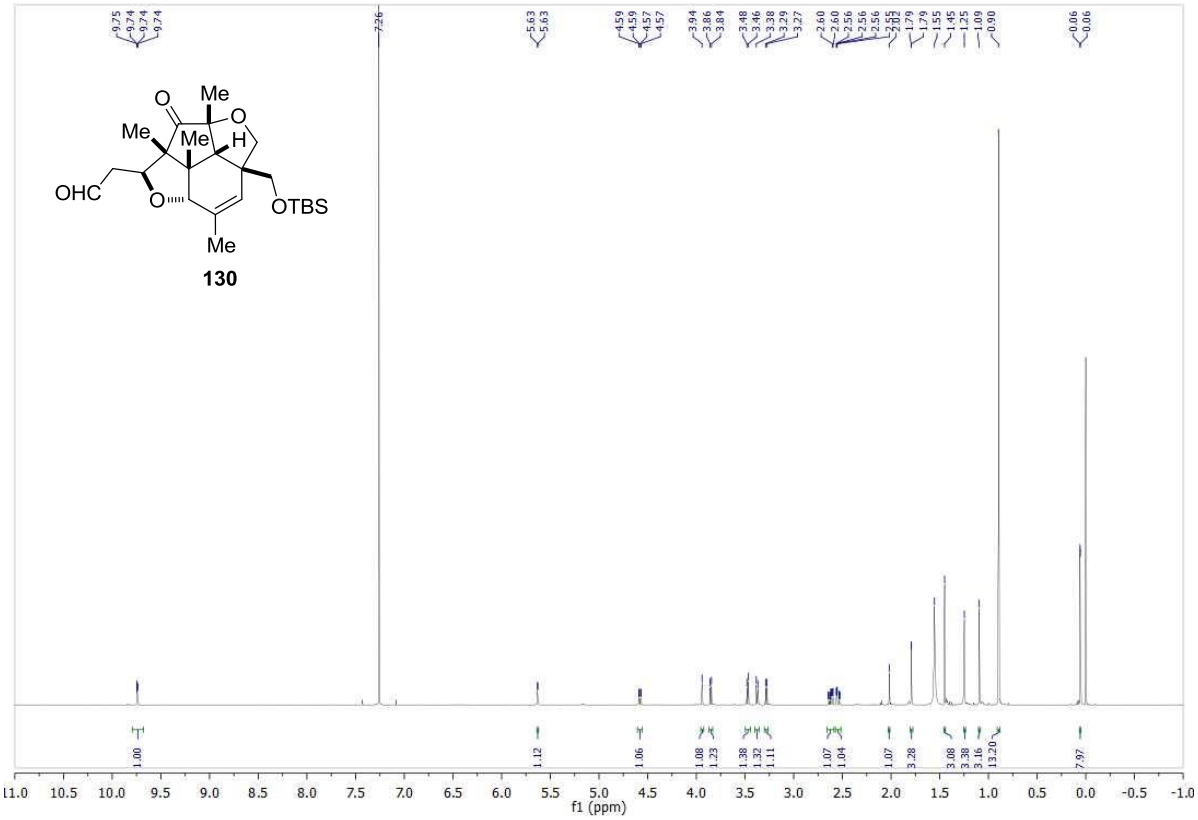
Me
H
CO2Me
O
OTBS
Me
124
f1 (ppm)

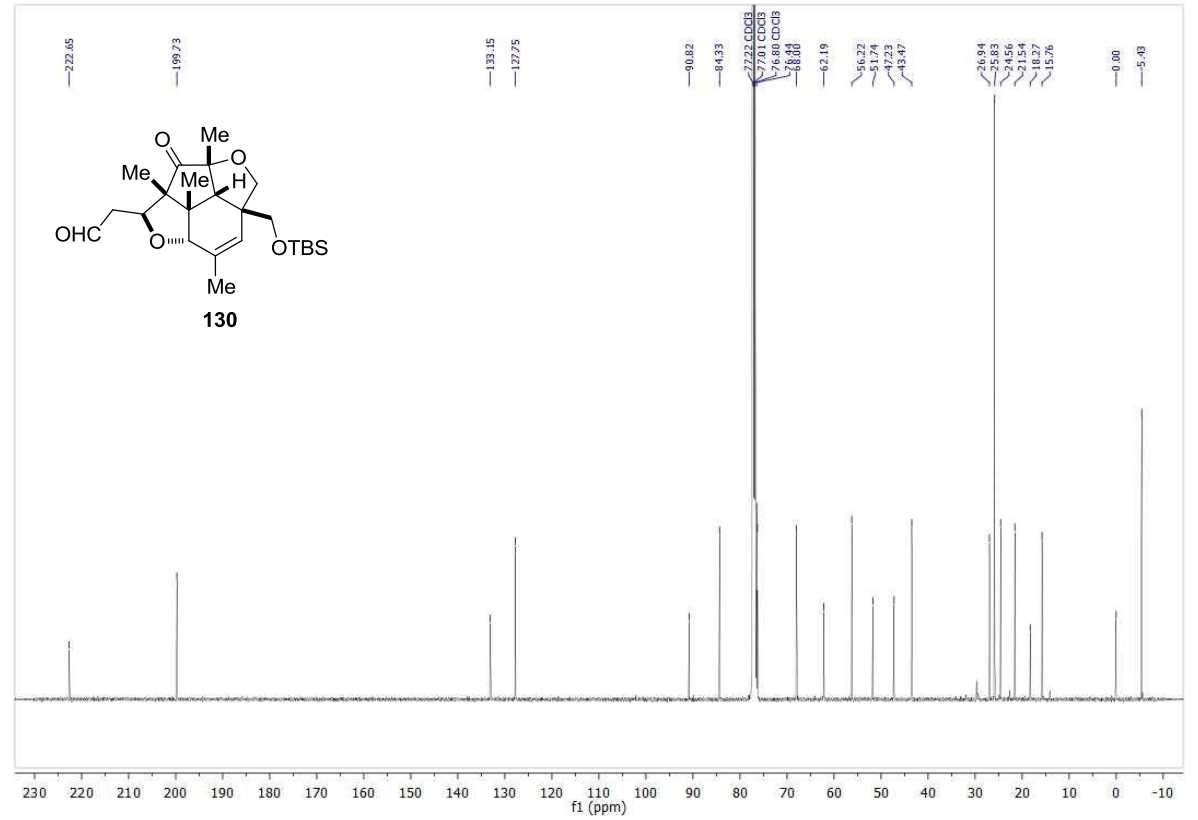

Me
Me
Me
H
CO2Me
O
OTBS
Me
124
f2 (ppm)
f1 (ppm)

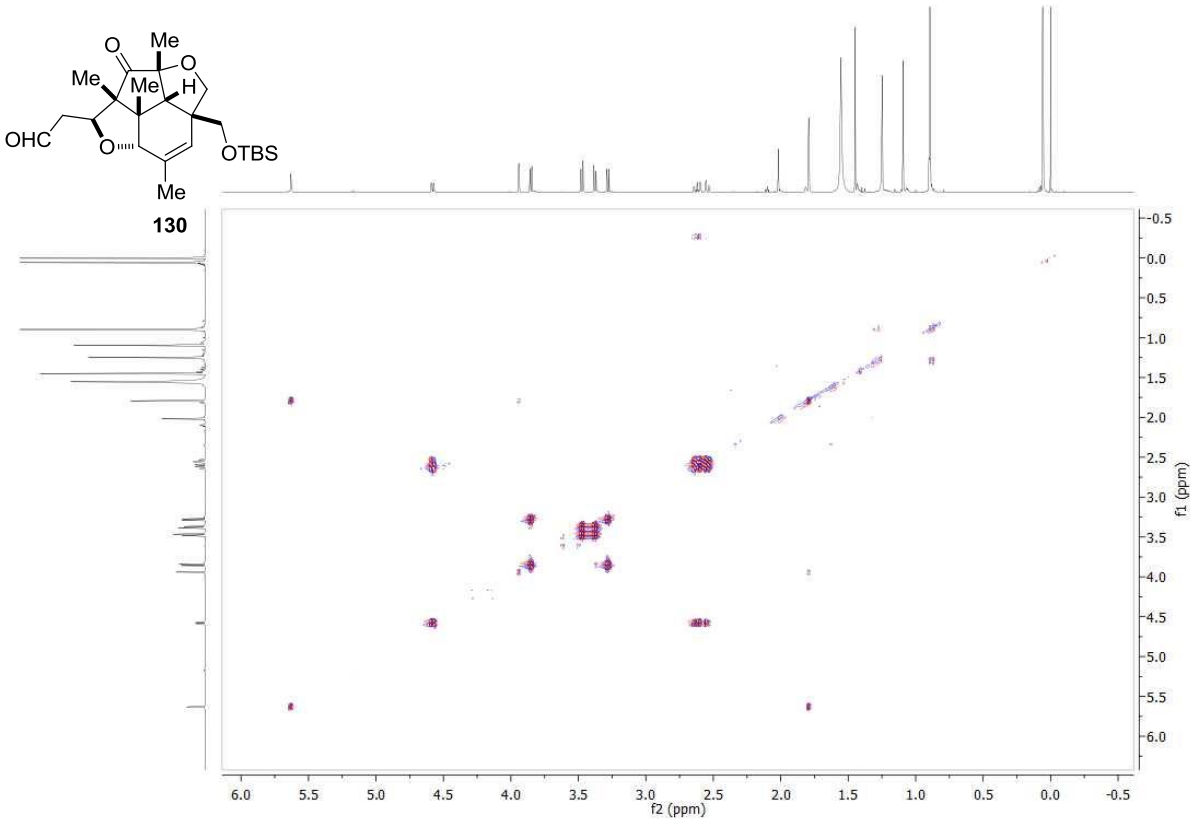

Me
Me
Me
H
CO2Me
O
OTBS
Me
124
f2 (ppm)
f1 (ppm)

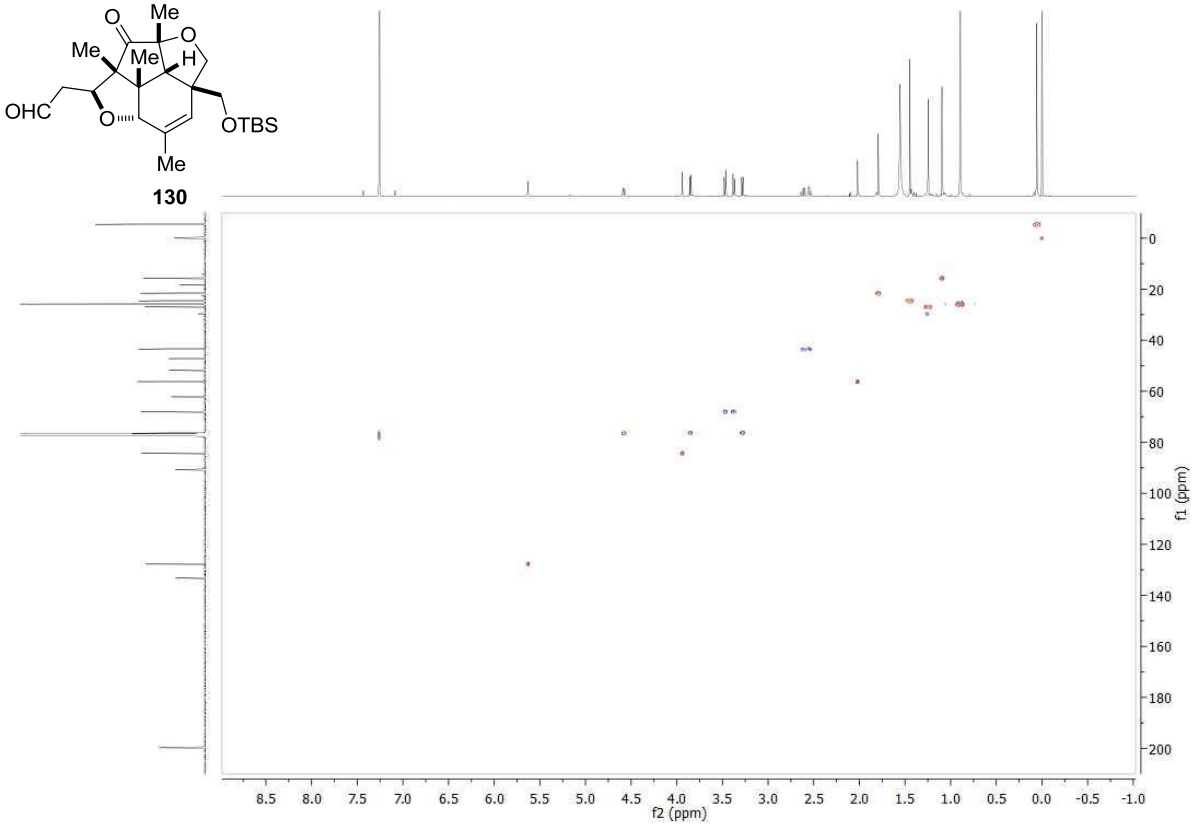

Me
Me
Me
H
CO2Me
O
OTBS
Me
124
f2 (ppm)
f1 (ppm)

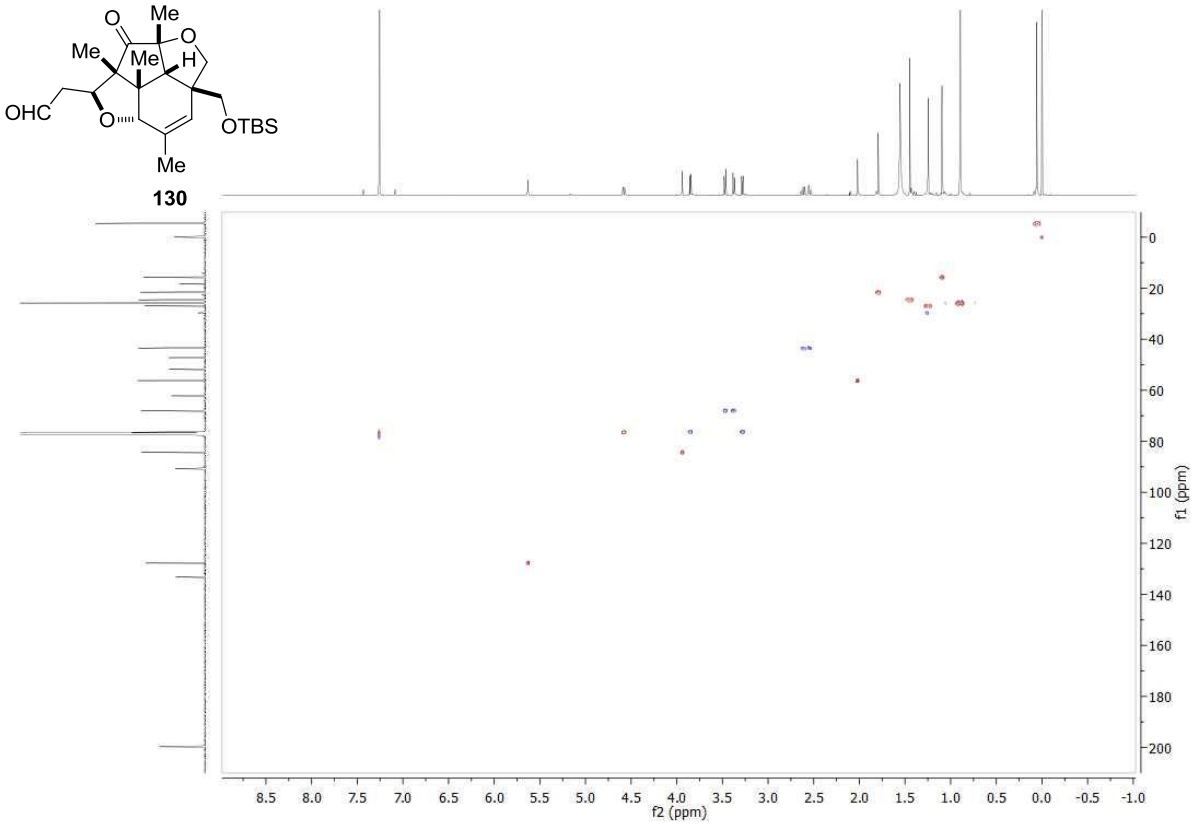

Me
Me
Me
H
CO2Me
O
OTBS
Me
124
f2 (ppm)
f1 (ppm)

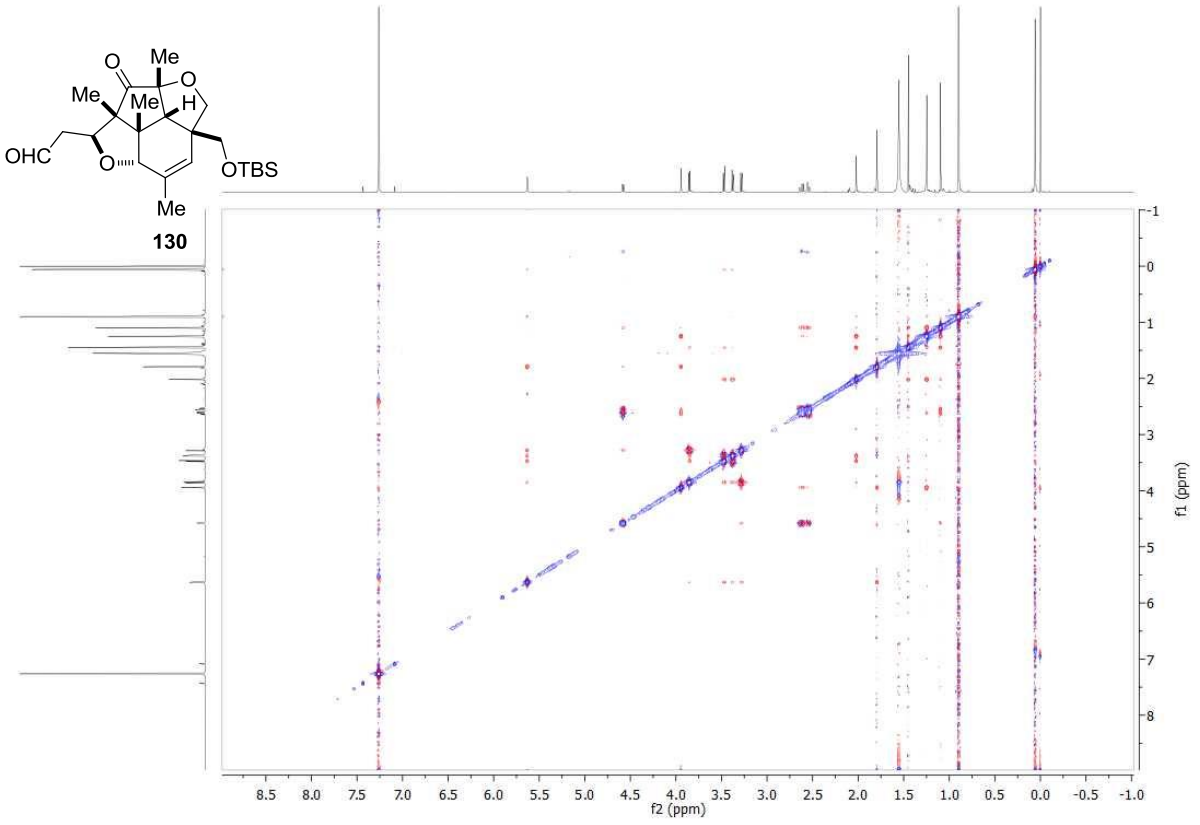

Me
O
O
Me
Me
H
OHC
O
OTBS
Me
130
f1 (ppm)

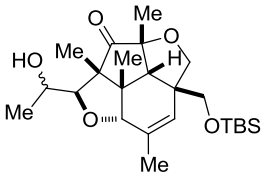

Me
O
O
Me
Me
H
OHC
O
OTBS
Me
130
f1 (ppm)


O
Me
O
Me
Me
H
OHC
O
OTBS
Me
130
f2 (ppm)
f1 (ppm)


O
Me
O
Me
Me
H
OHC
O
OTBS
Me
130
f2 (ppm)
f1 (ppm)

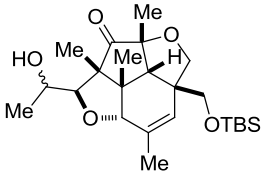

O
Me
O
Me
Me
H
OHC
O
OTBS
Me
130
f2 (ppm)
f1 (ppm)


O
Me
O
Me
Me
H
OHC
O
OTBS
Me
130
f2 (ppm)
f1 (ppm)


O
Me
O
HO
Me
Me
H
Me
O
OTBS
Me

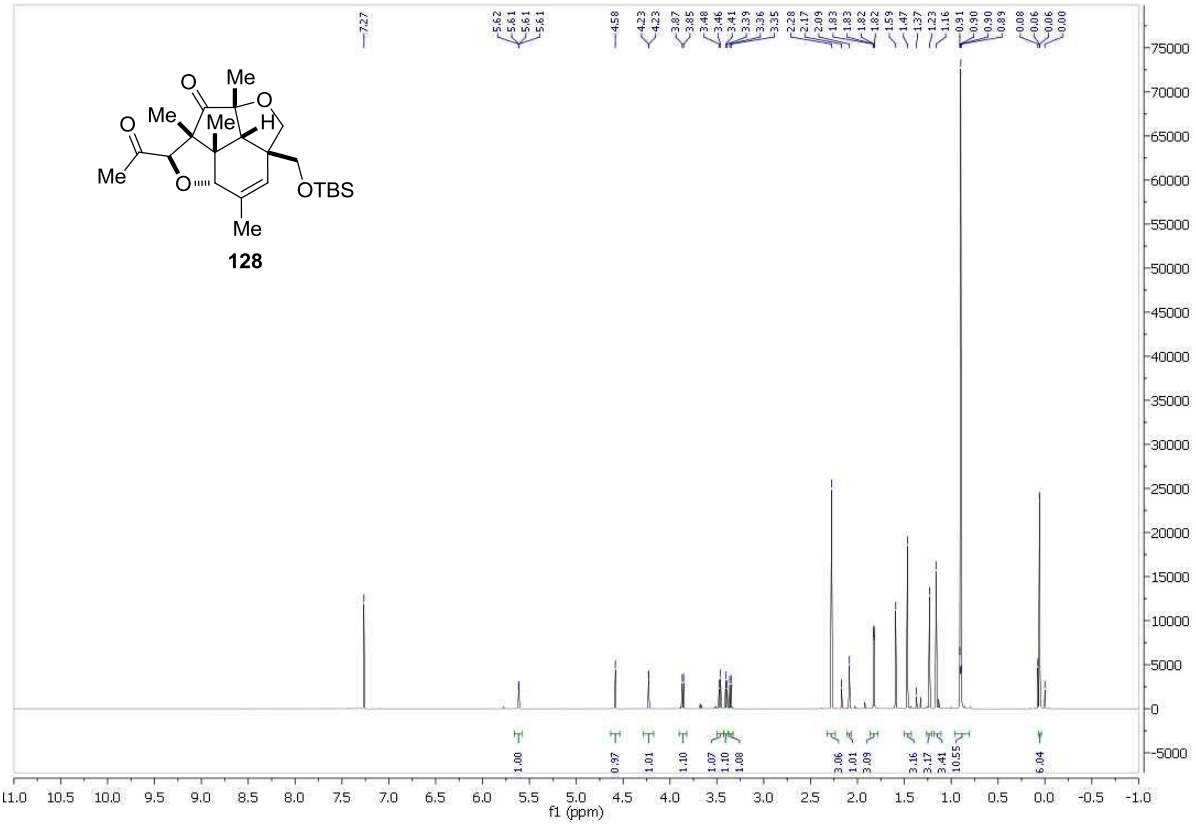
132

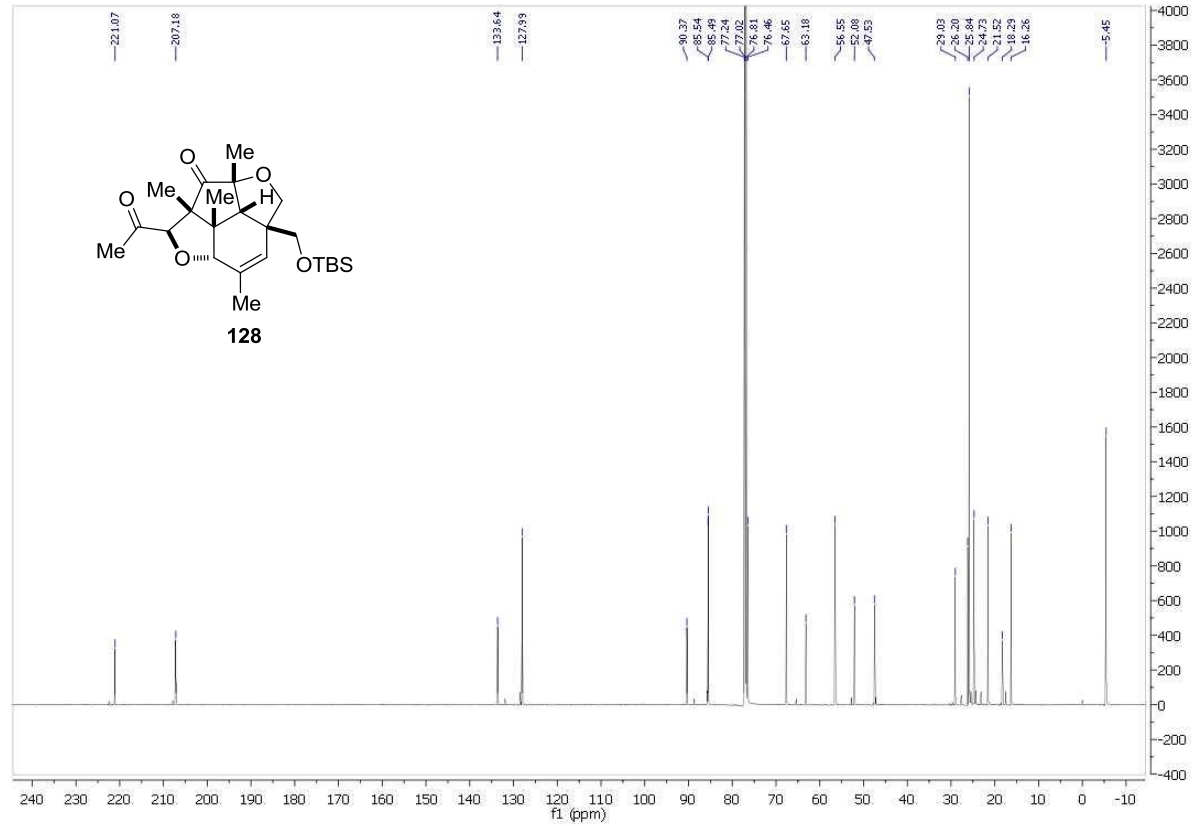
7.26
5.61
5.55
4.08
3.93
3.88
3.86
3.84
3.82
3.75
3.74
3.48
3.46
3.43
3.39
3.37
3.36
3.32
3.30
3.27
3.17
3.15
2.05
1.83
1.75
1.57
1.47
1.45
1.32
1.31
1.29
1.24
1.22
0.91
0.90
0.88
0.07
0.06
0.05
0.04
1.00
8.00
1.01
3.03
3.00
9.70
9.85
6.15
f1 (ppm)

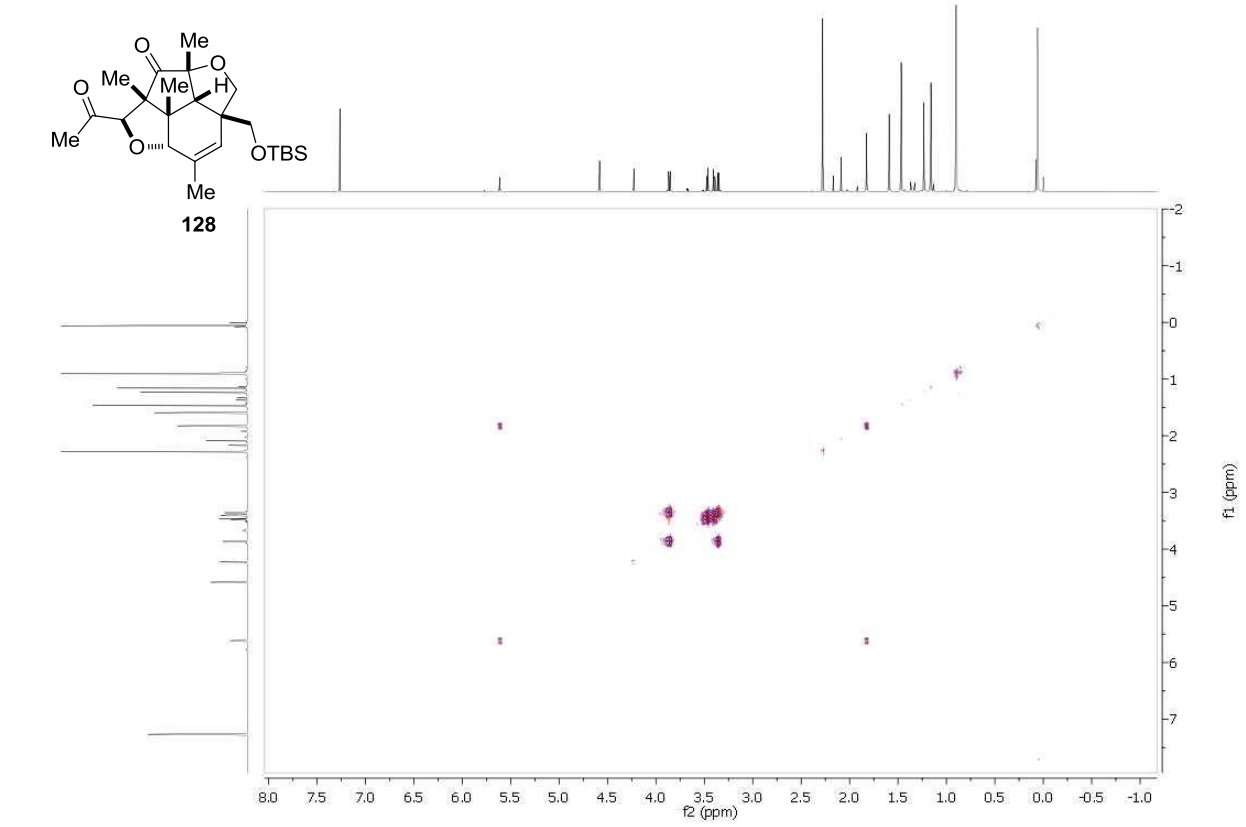

O
Me
O
HO
Me
Me
H
Me
O
OTBS
Me

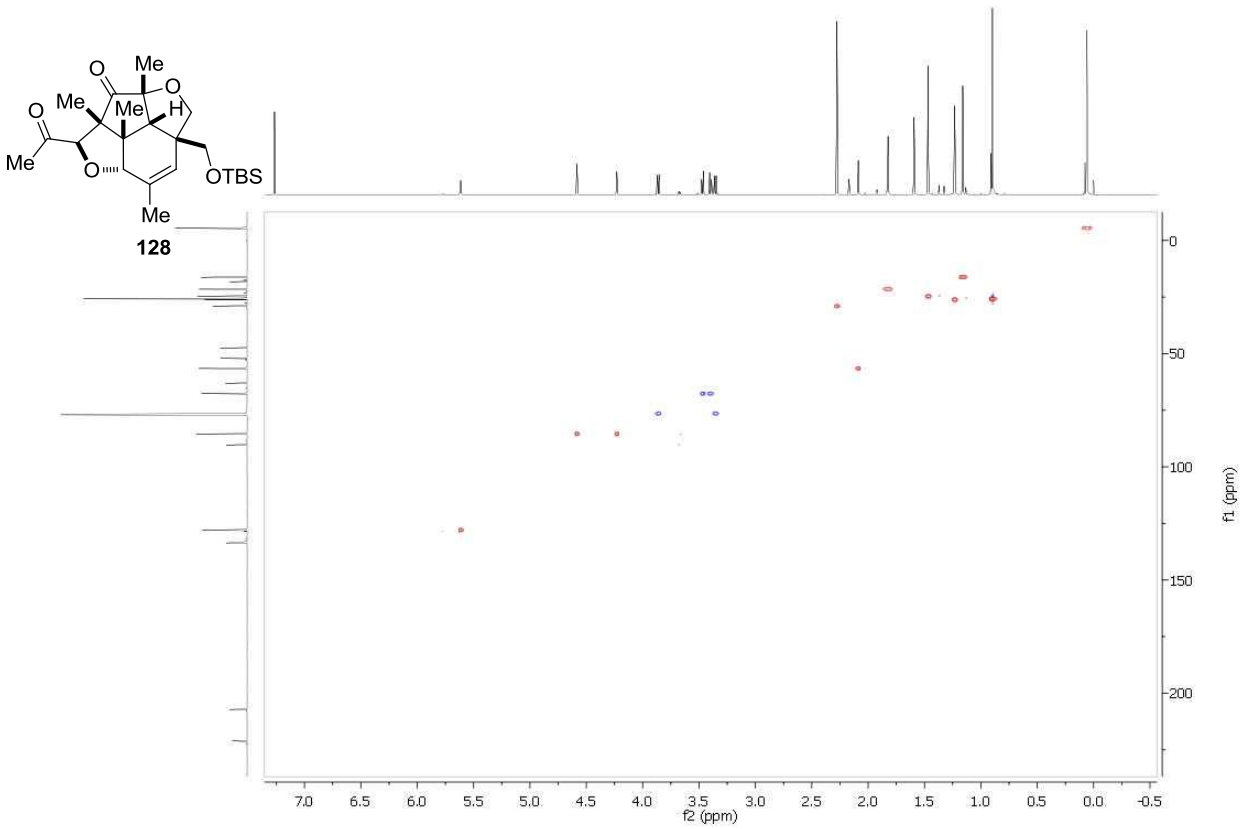
132

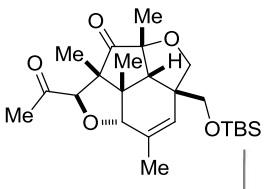
225.14
222.89
133.90
133.53
127.63
127.59
92.49
90.40
85.22
84.97
84.75
81.89
77.32
77.20
77.00
76.68
76.29
75.90
68.44
67.71
66.46
65.06
62.34
56.44
52.02
48.08
47.31
26.29
25.83
25.80
24.92
23.67
21.71
21.09
20.76
20.22
15.89
15.48
f1 (ppm)


Me
O
Me
O
Me
Me
H
O
Me
O
OTBS
Me
128
f1 (ppm)


Me
O
Me
O
Me
Me
H
O
Me
O
OTBS
Me
128
f1 (ppm)

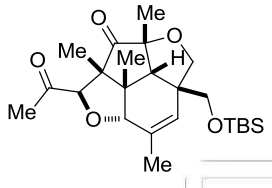

Me
O
Me
O
Me
Me
H
O
Me
O
OTBS
Me
128
f2 (ppm)
f1 (ppm)


O
Me
Me
O
Me
Me
H
O
Me
OTBS
Me
128
f2 (ppm)
f1 (ppm)


O
Me
O
Me
Me
H
O
Me
O
OTBS
Me

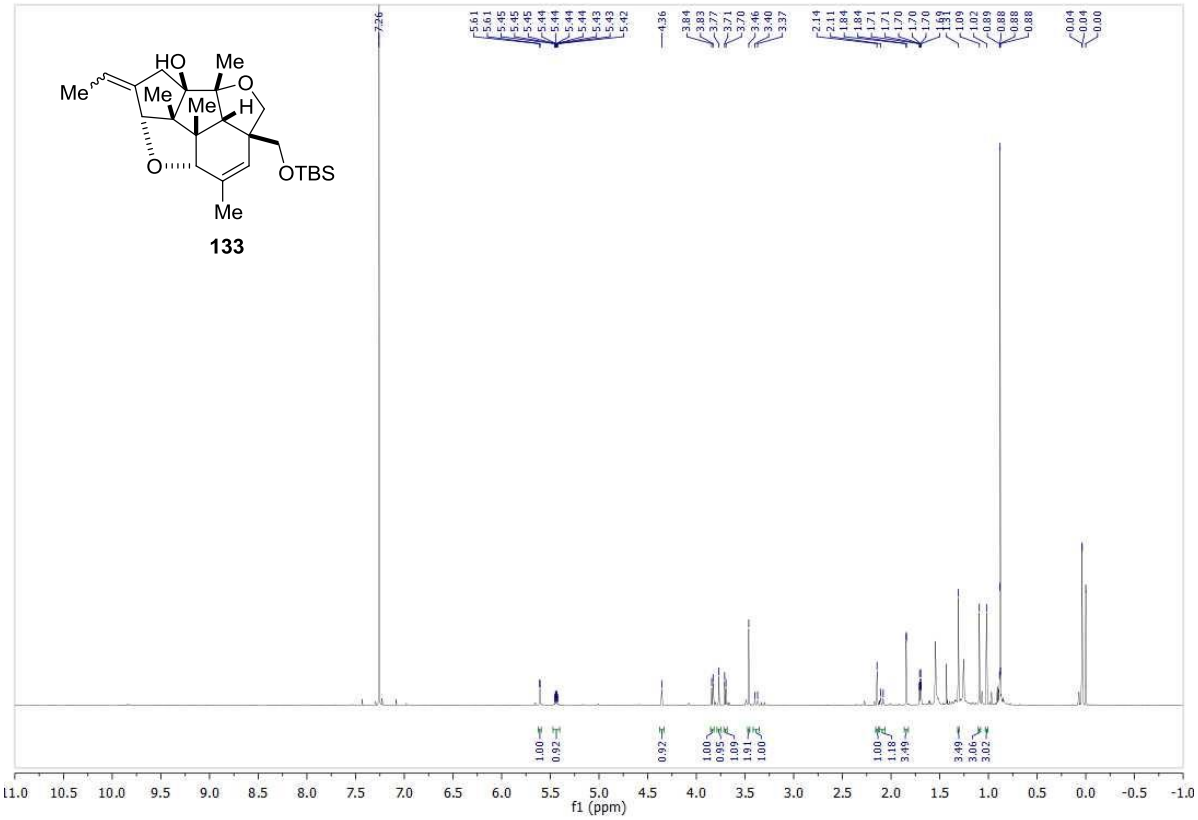
128

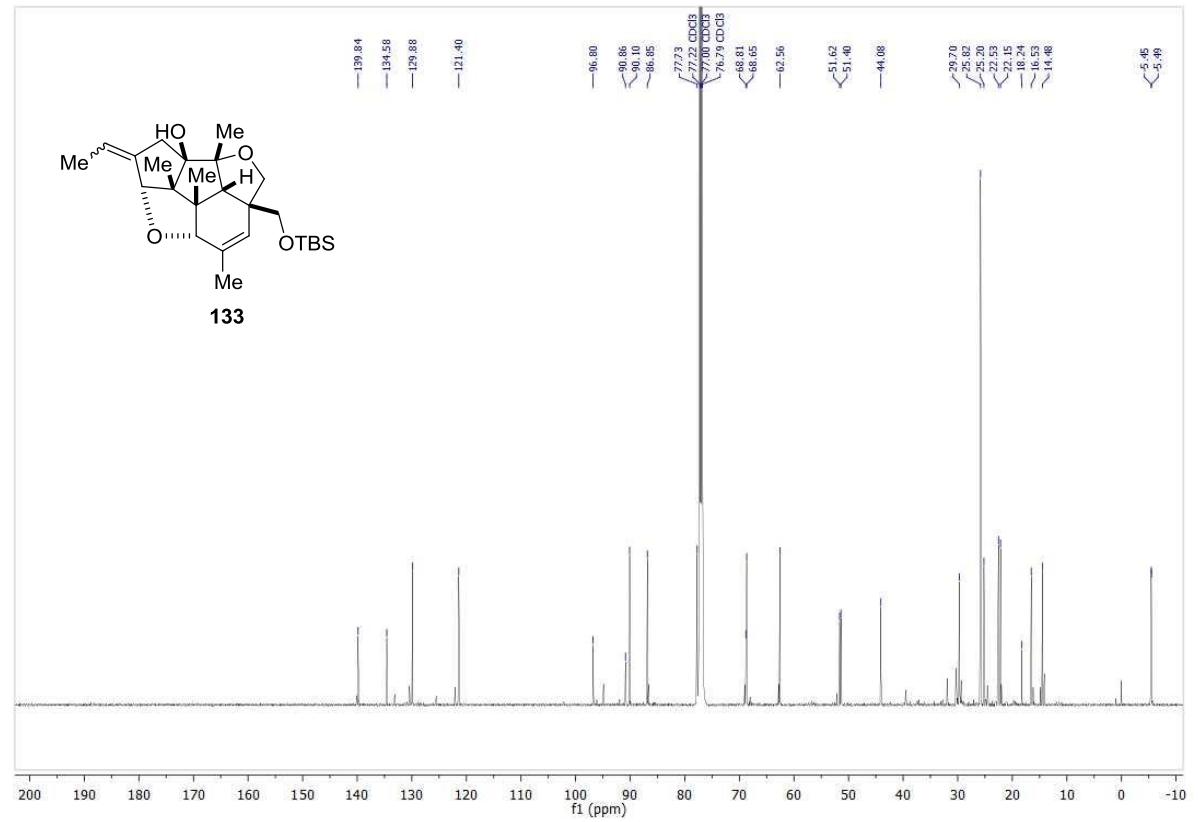
0
50
100
150
200
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)

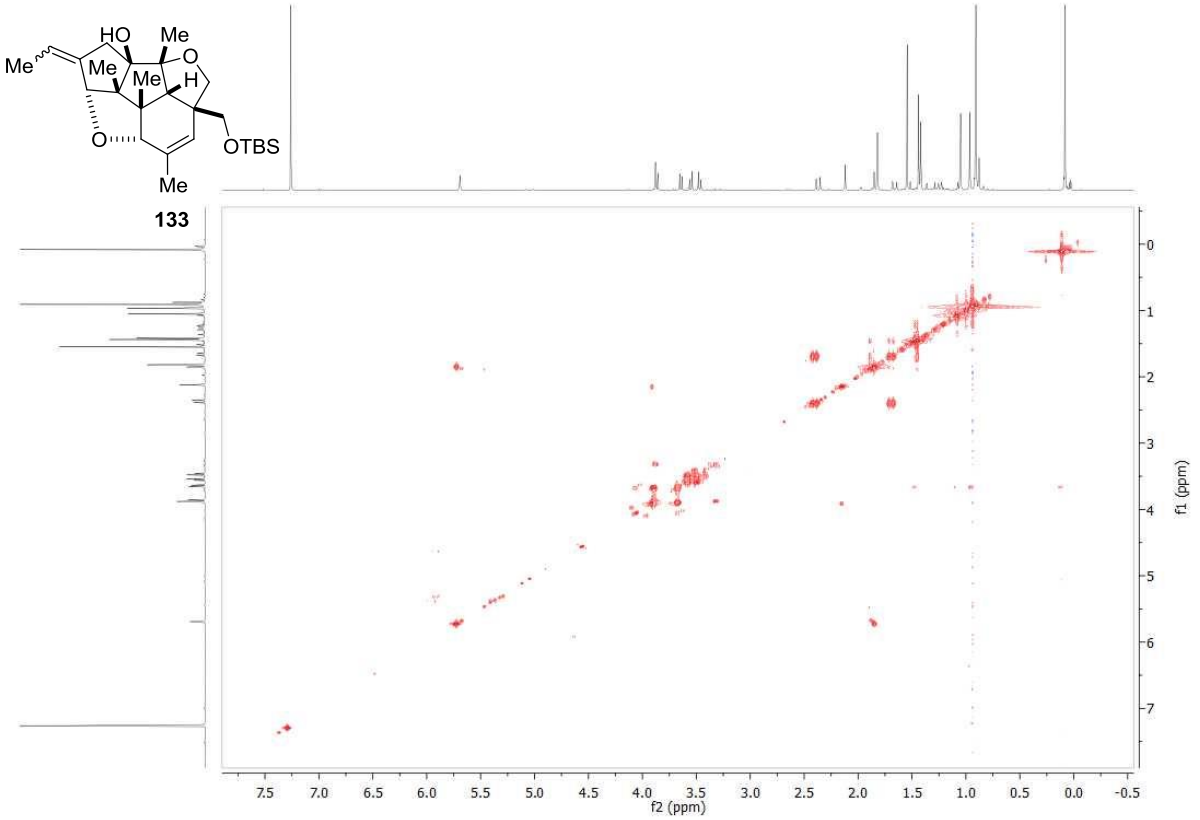

O
Me
O
Me
Me
H
O
Me
O
OTBS
Me

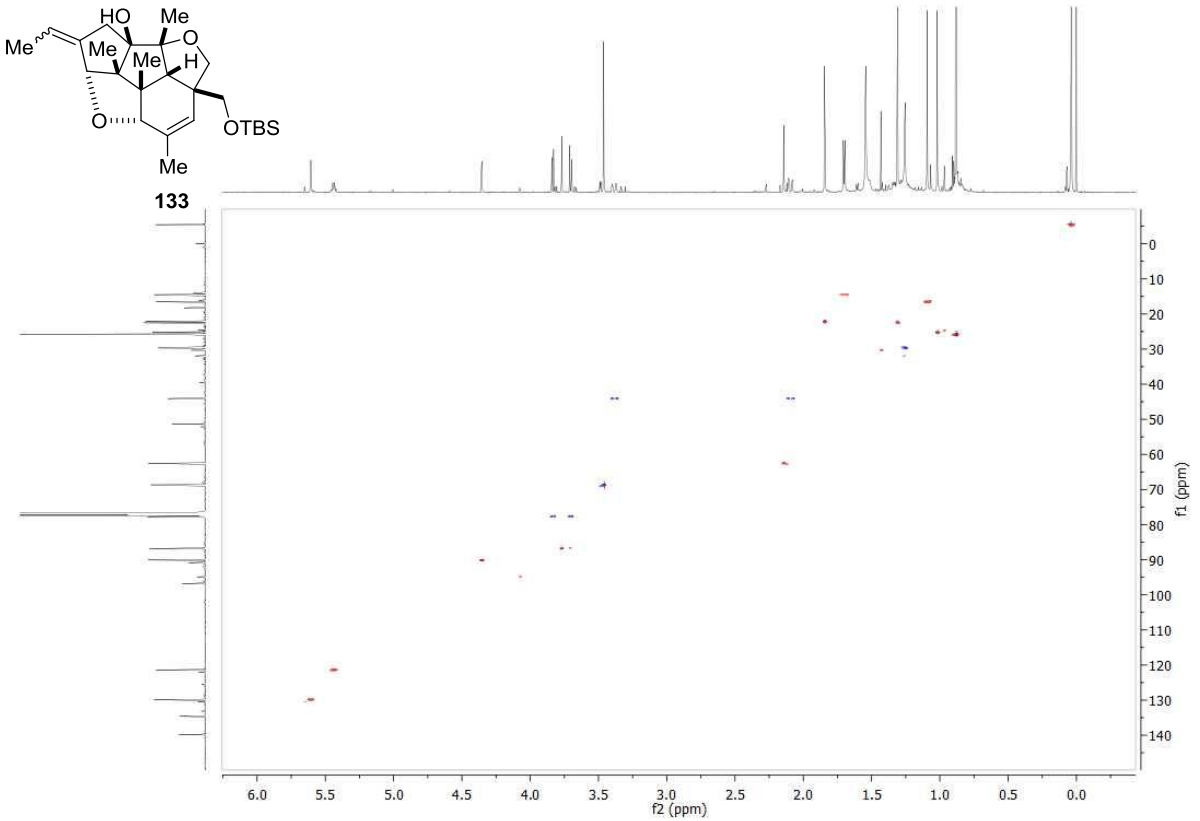
128

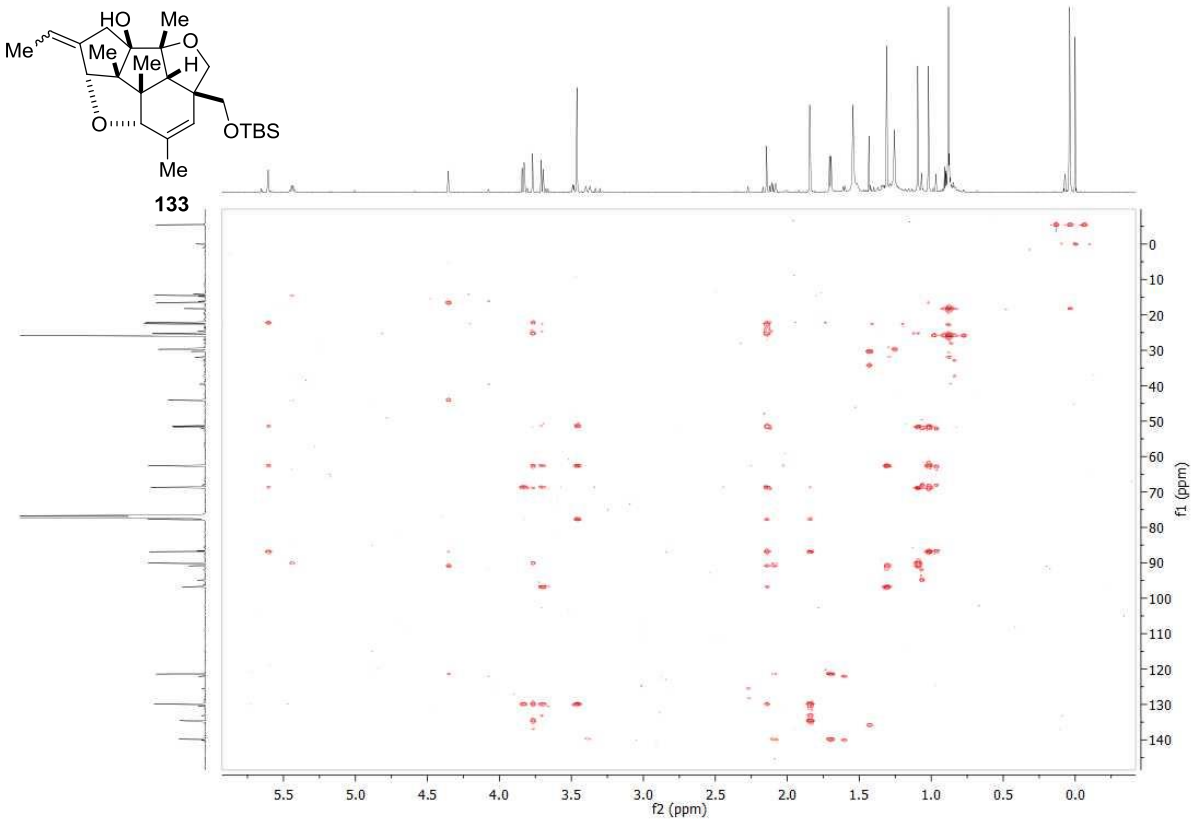
-1
0
1
2
3
4
5
6
7
8
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f2 (ppm)

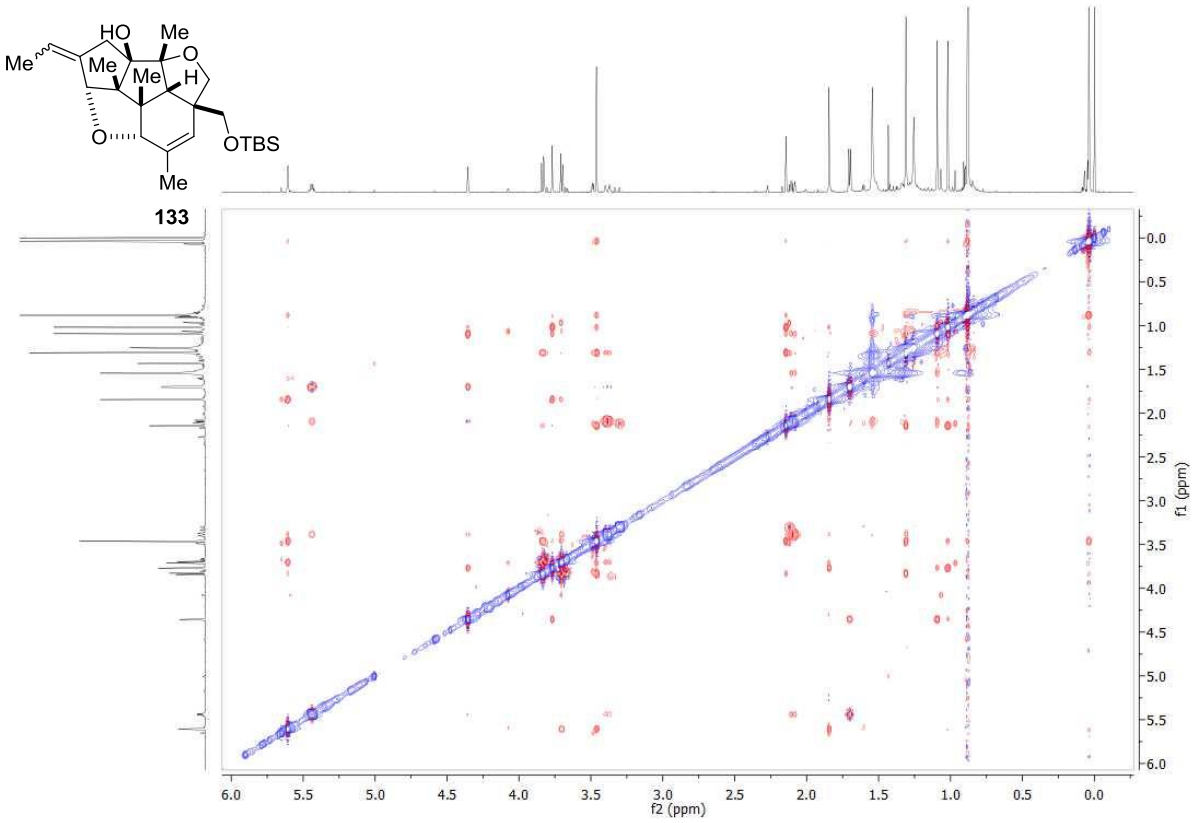

HO
Me
Me
O
Me
Me
H
Me
O
OTBS
Me
133
f1 (ppm)

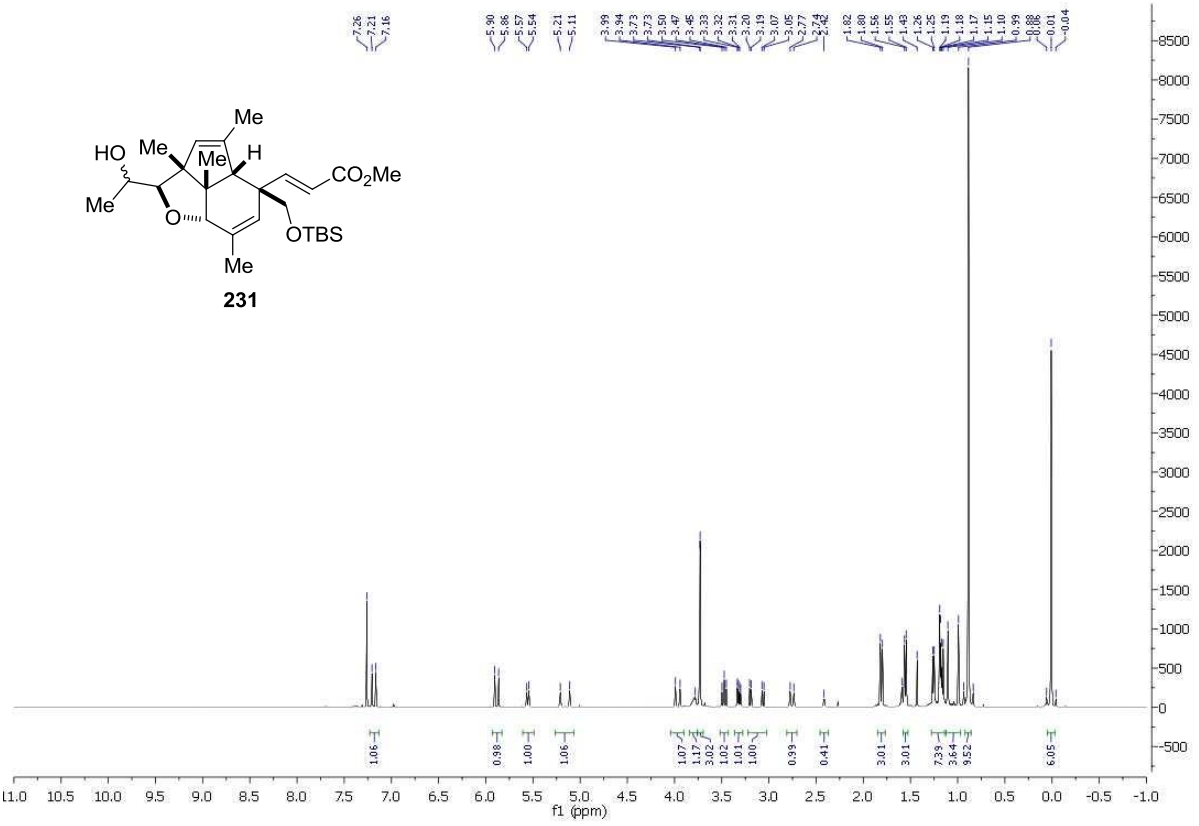

HO
Me
Me
O
Me
Me
H
Me
O
OTBS
Me
133
f1 (ppm)


HO
Me
Me
Me
Me
O
H
O
OTBS
Me
133
f2 (ppm)
f1 (ppm)

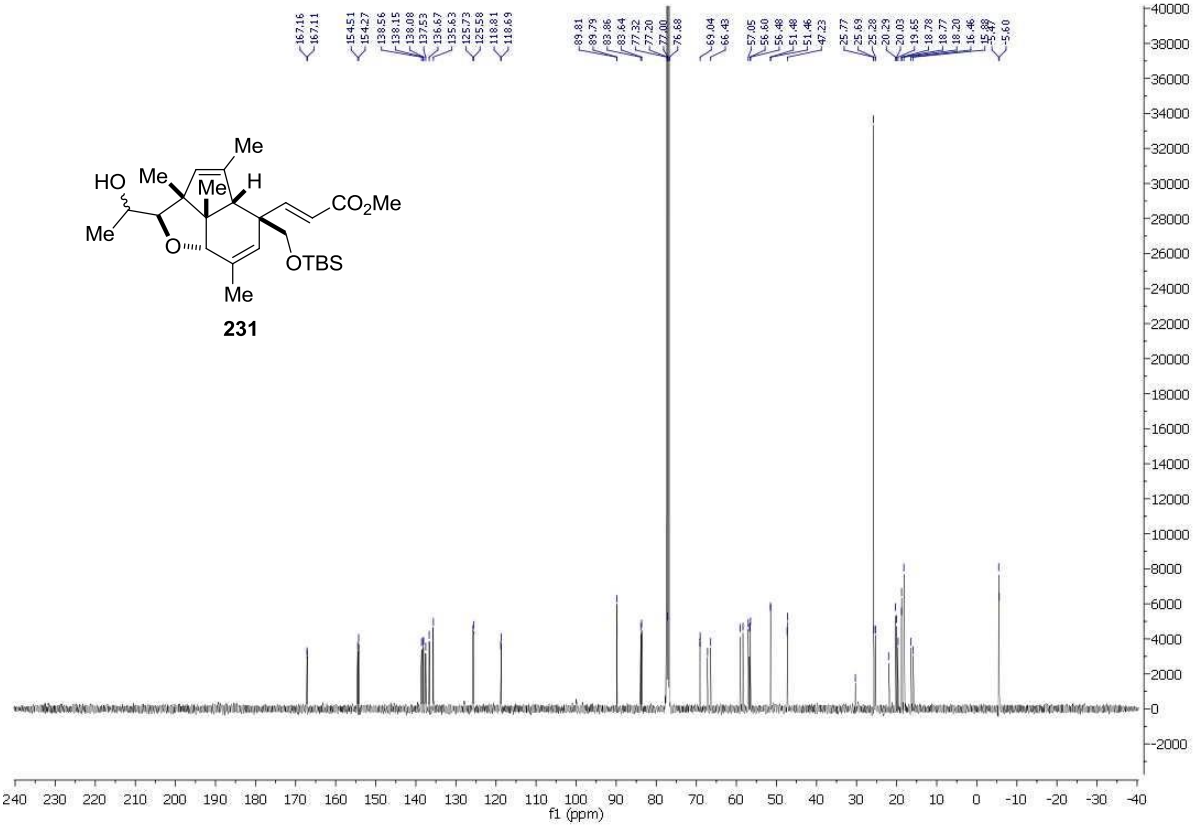

HO
Me
Me
Me
Me
O
H
O
OTBS
Me
133
f2 (ppm)
f1 (ppm)


HO
Me
Me
Me
Me
O
H
O
OTBS
Me
133
f2 (ppm)
f1 (ppm)

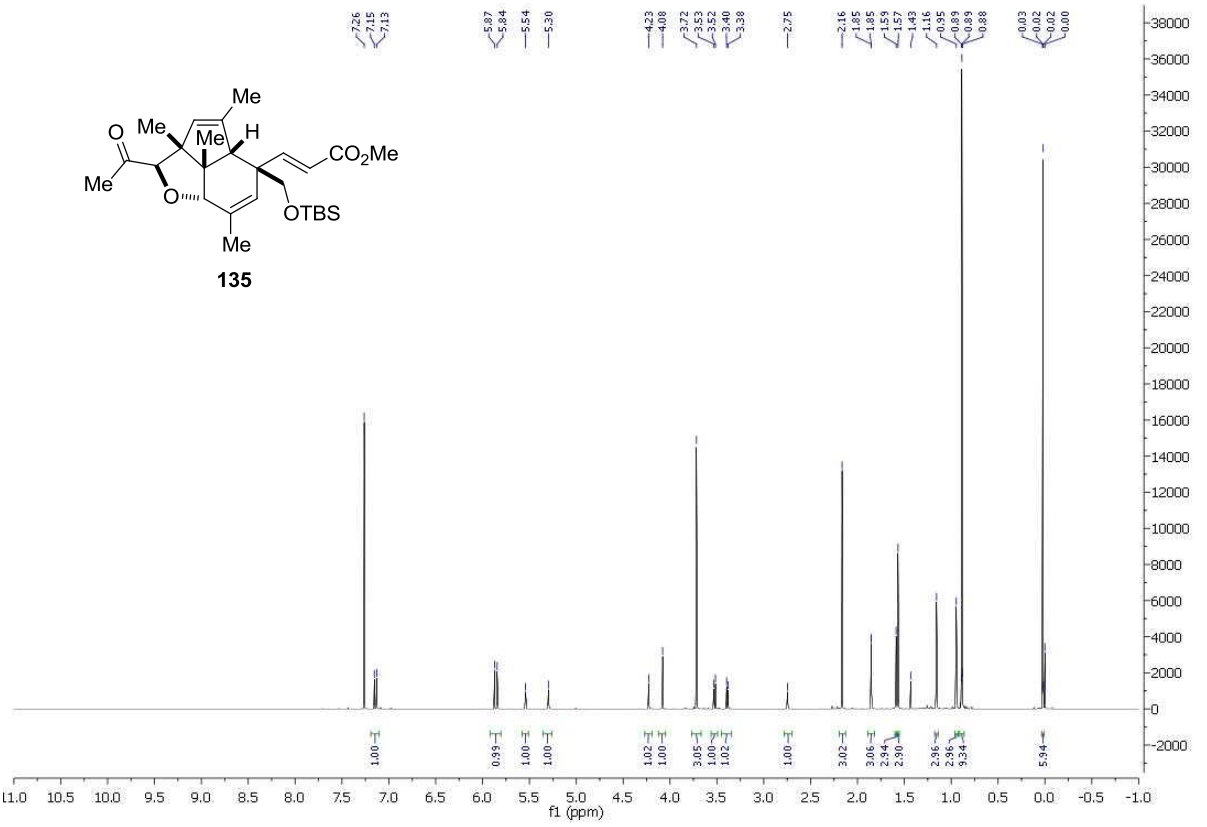

HO
Me
Me
Me
Me
O
H
O
OTBS
Me
133
f2 (ppm)
f1 (ppm)

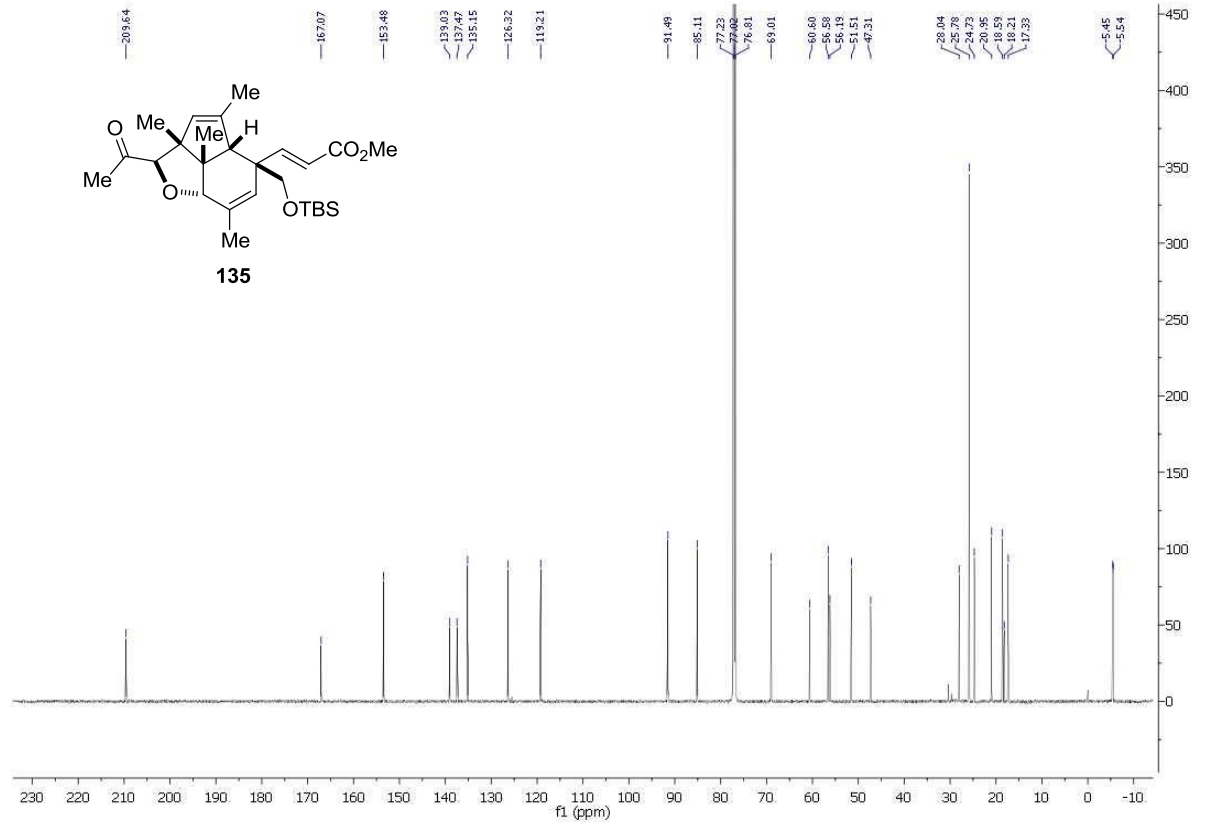

HO
Me
Me
Me
H
Me
O
CO2Me
OTBS
Me
f1 (ppm)

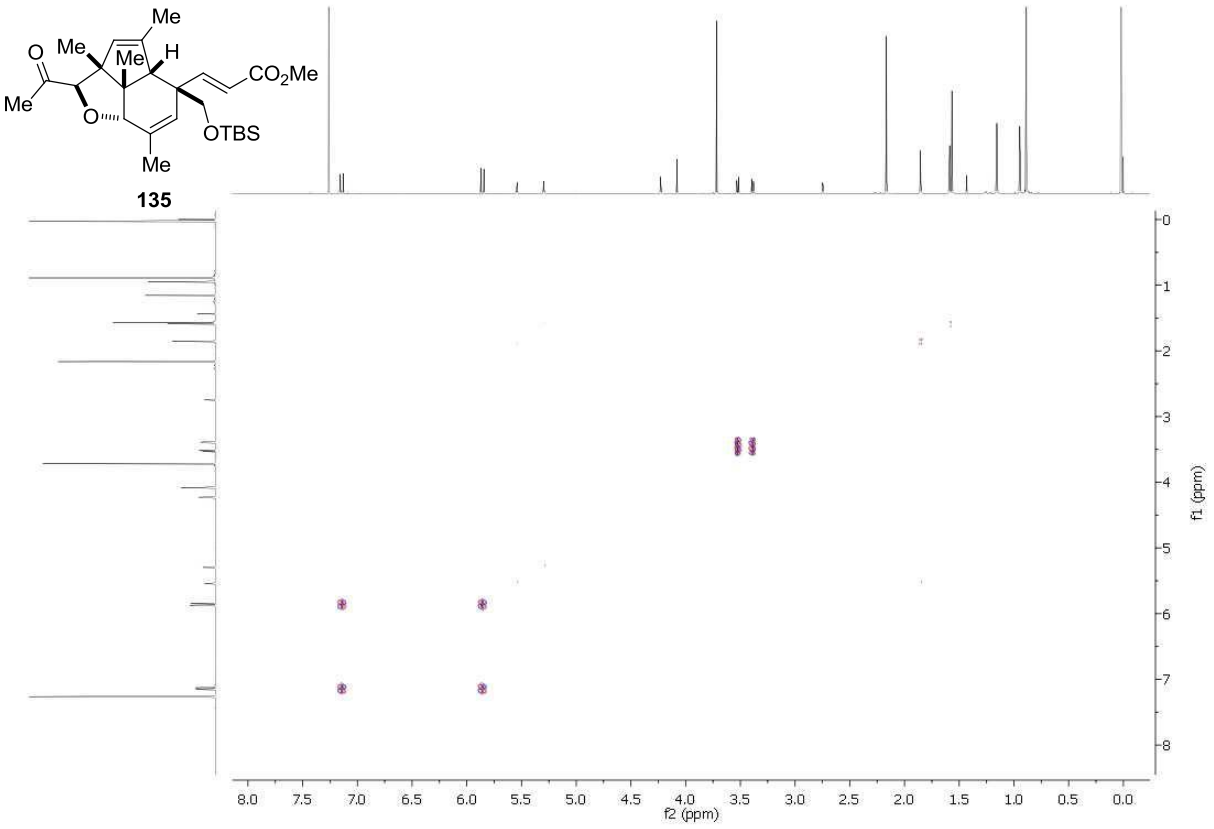
231


HO
Me
Me
Me
H
Me
O
CO2Me
OTBS
Me
f1 (ppm)

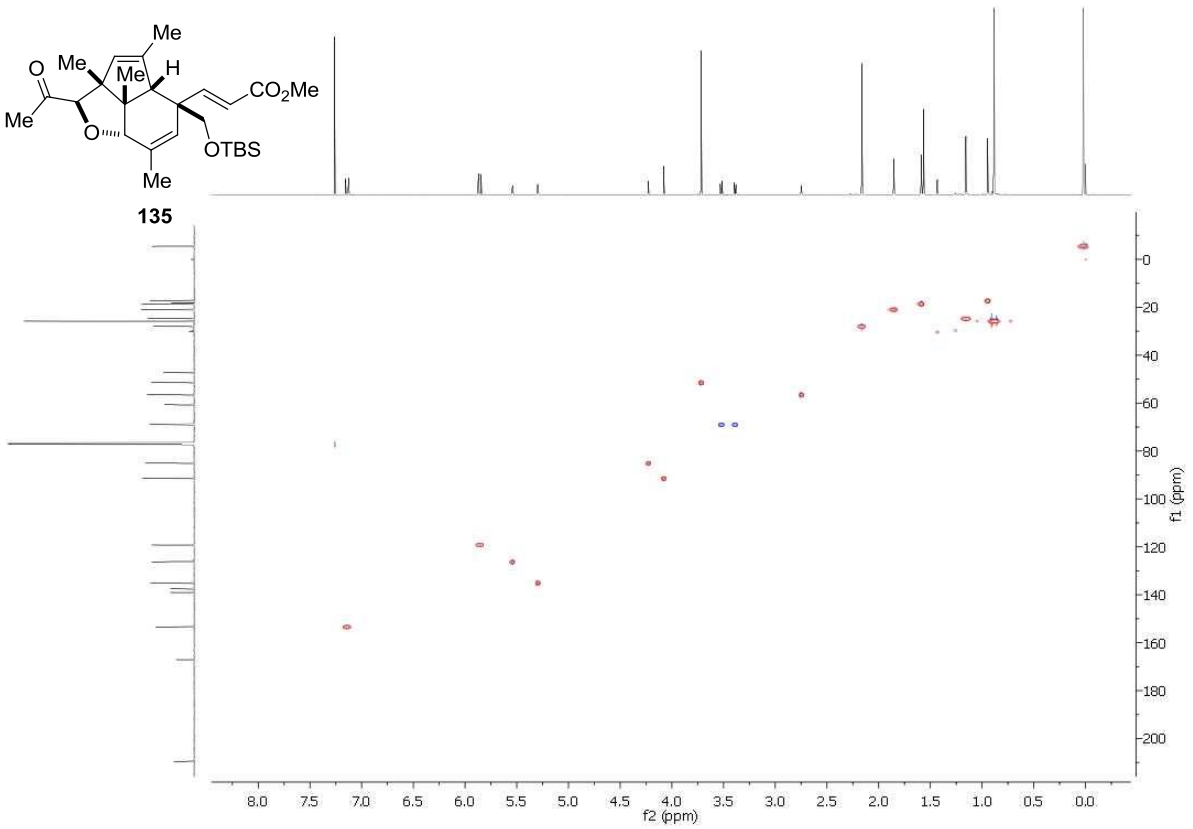
231


Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
135
f1 (ppm)

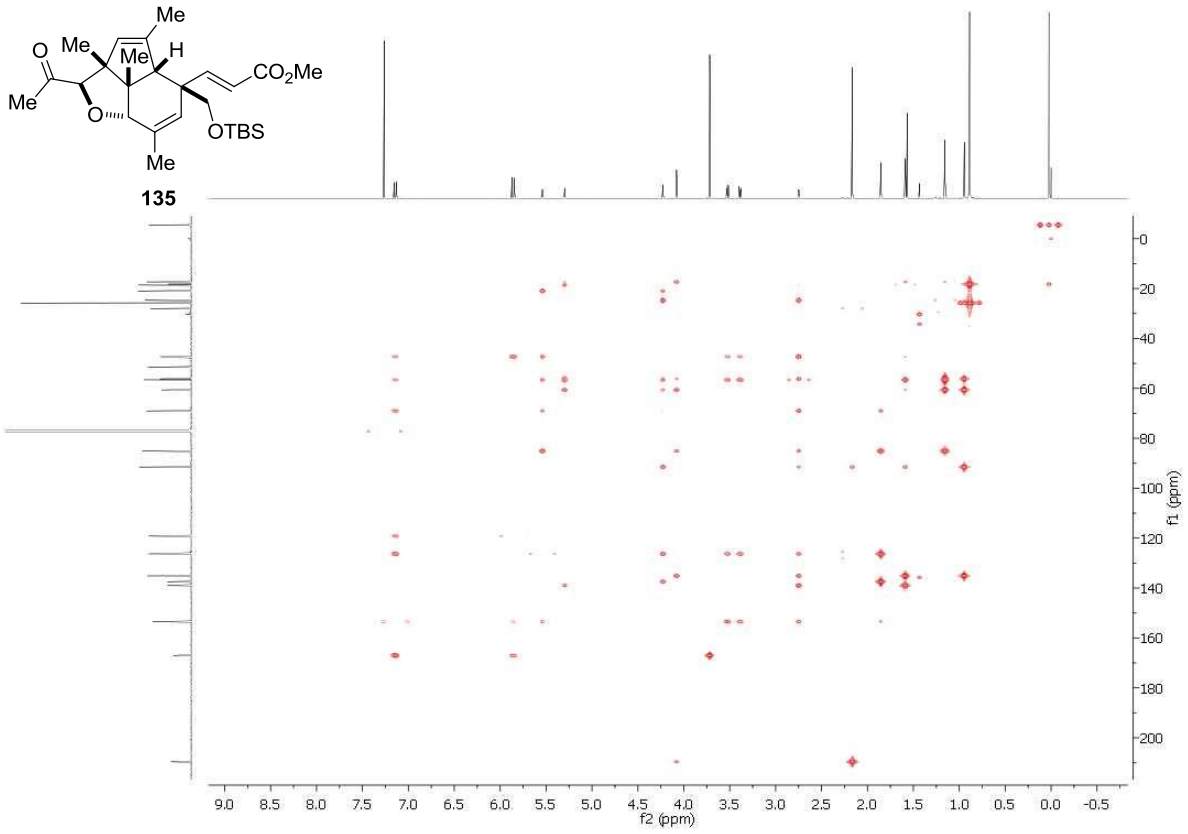

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
135
f1 (ppm)

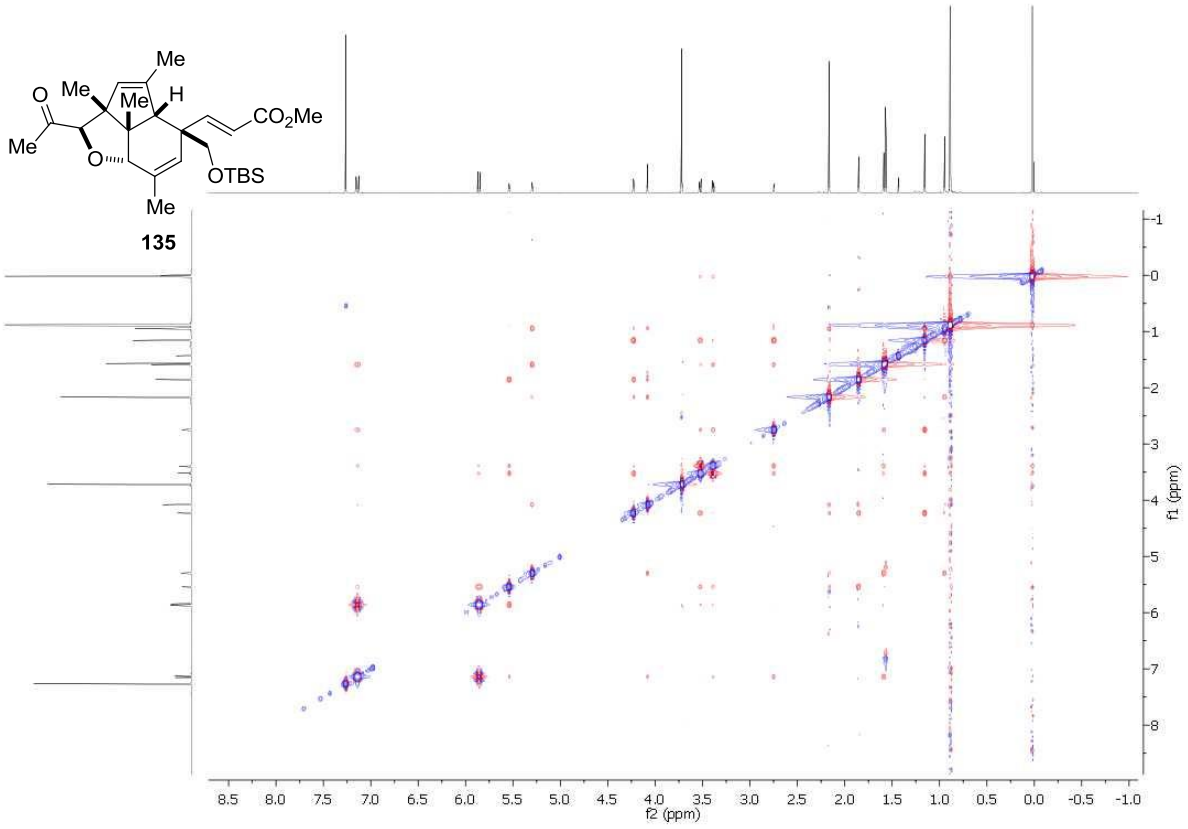

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
f2 (ppm)
f1 (ppm)

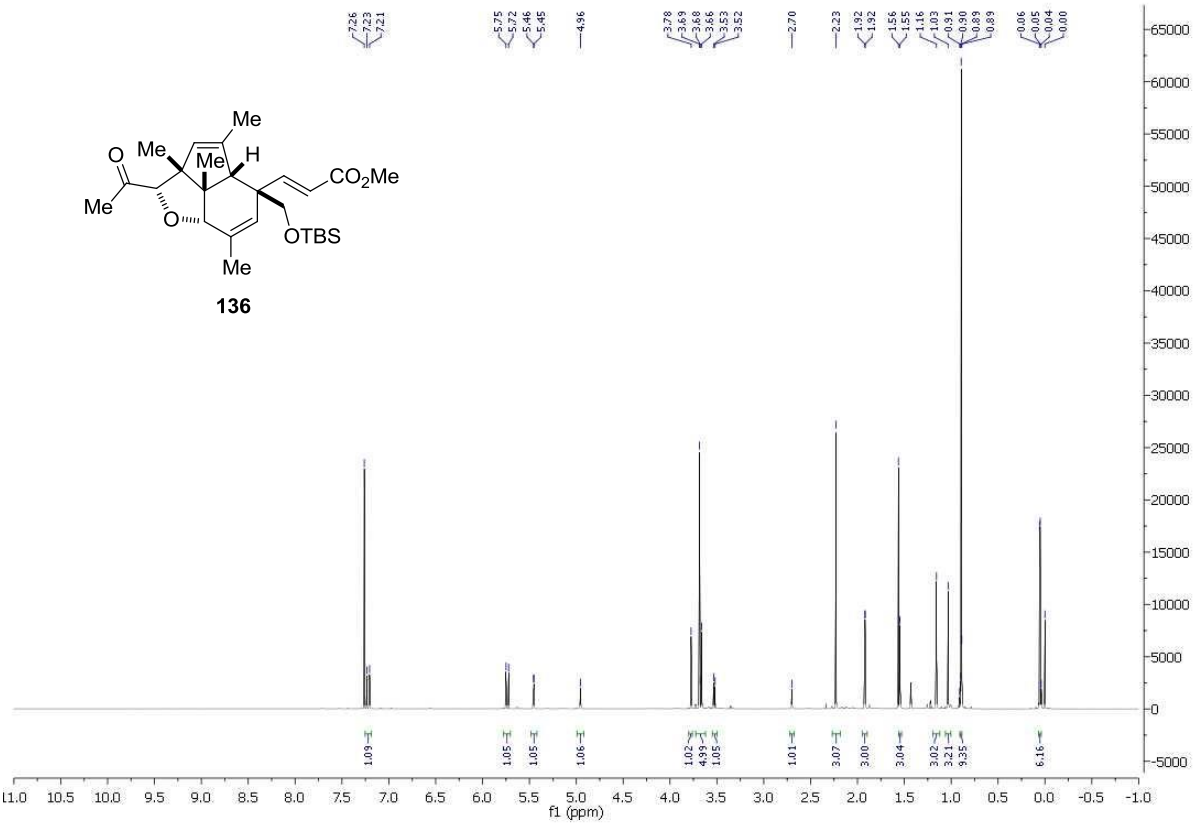
135

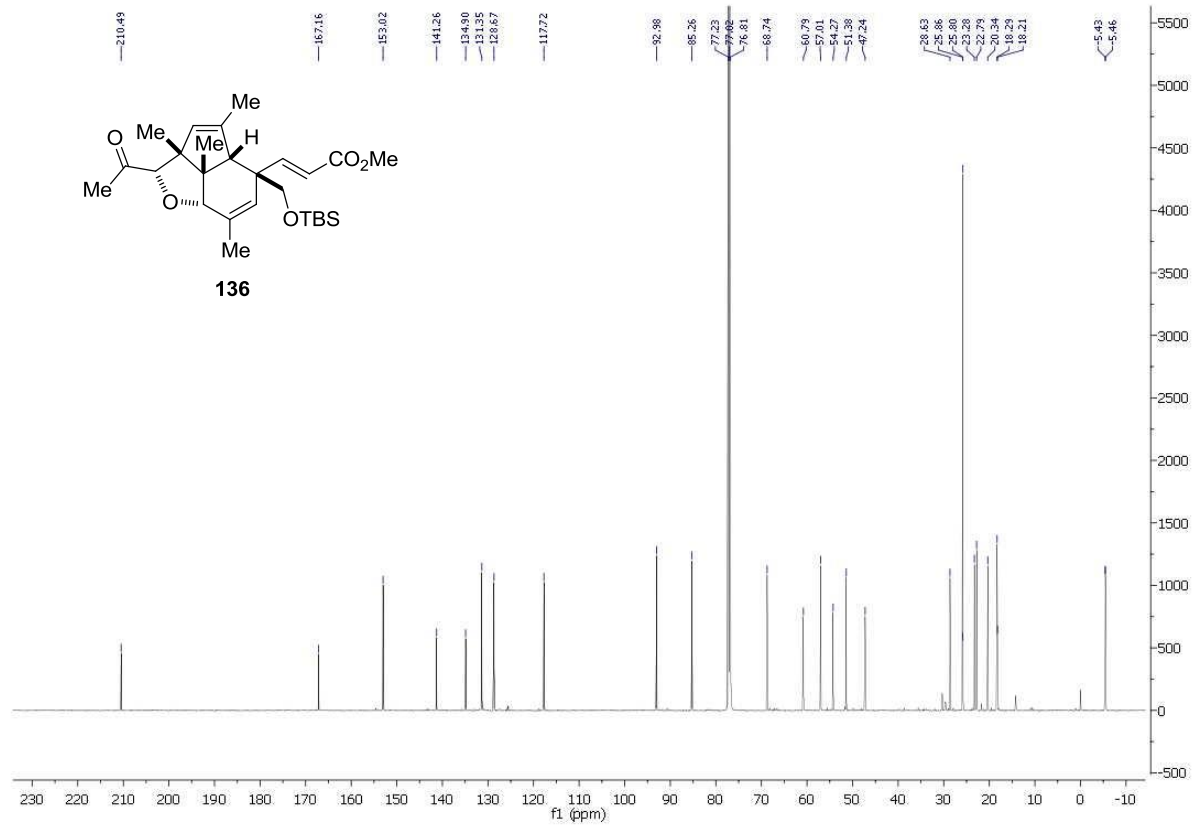

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
f2 (ppm)
f1 (ppm)

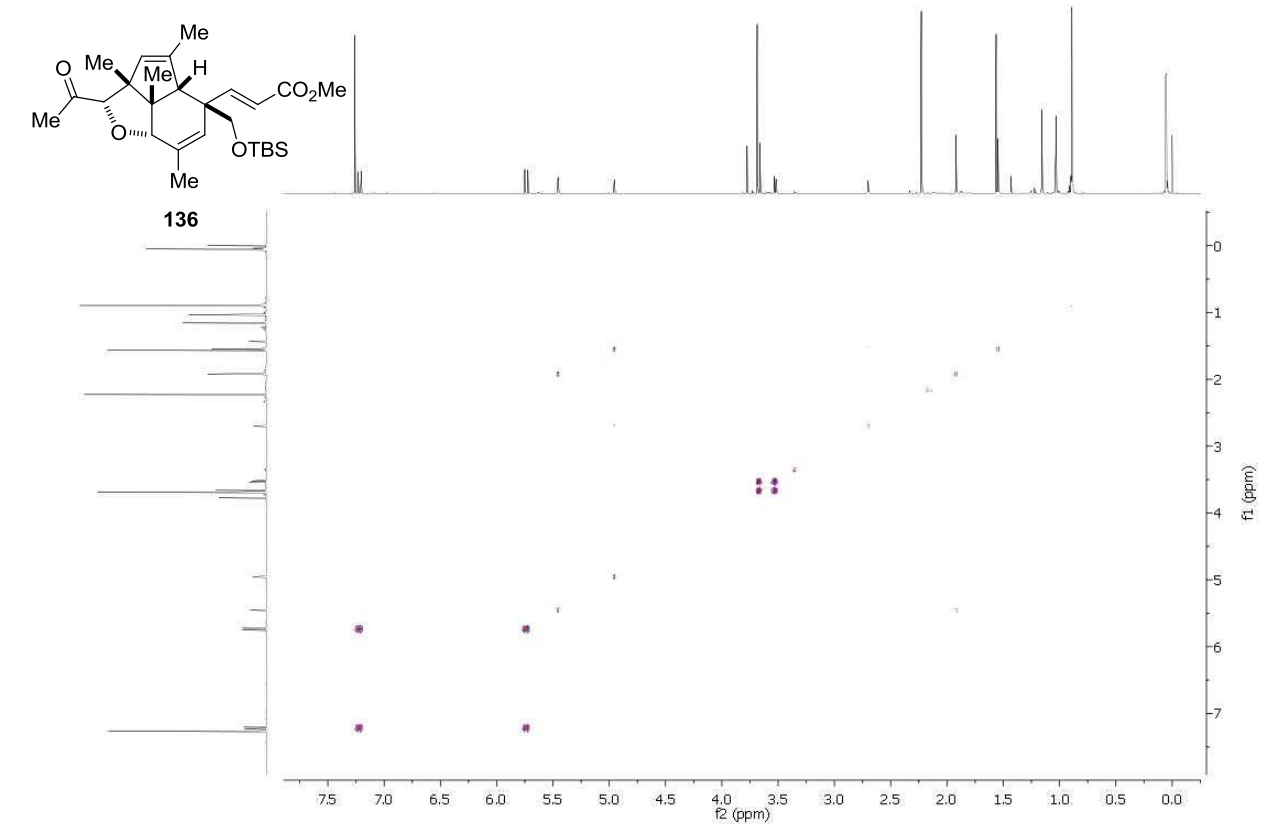
135

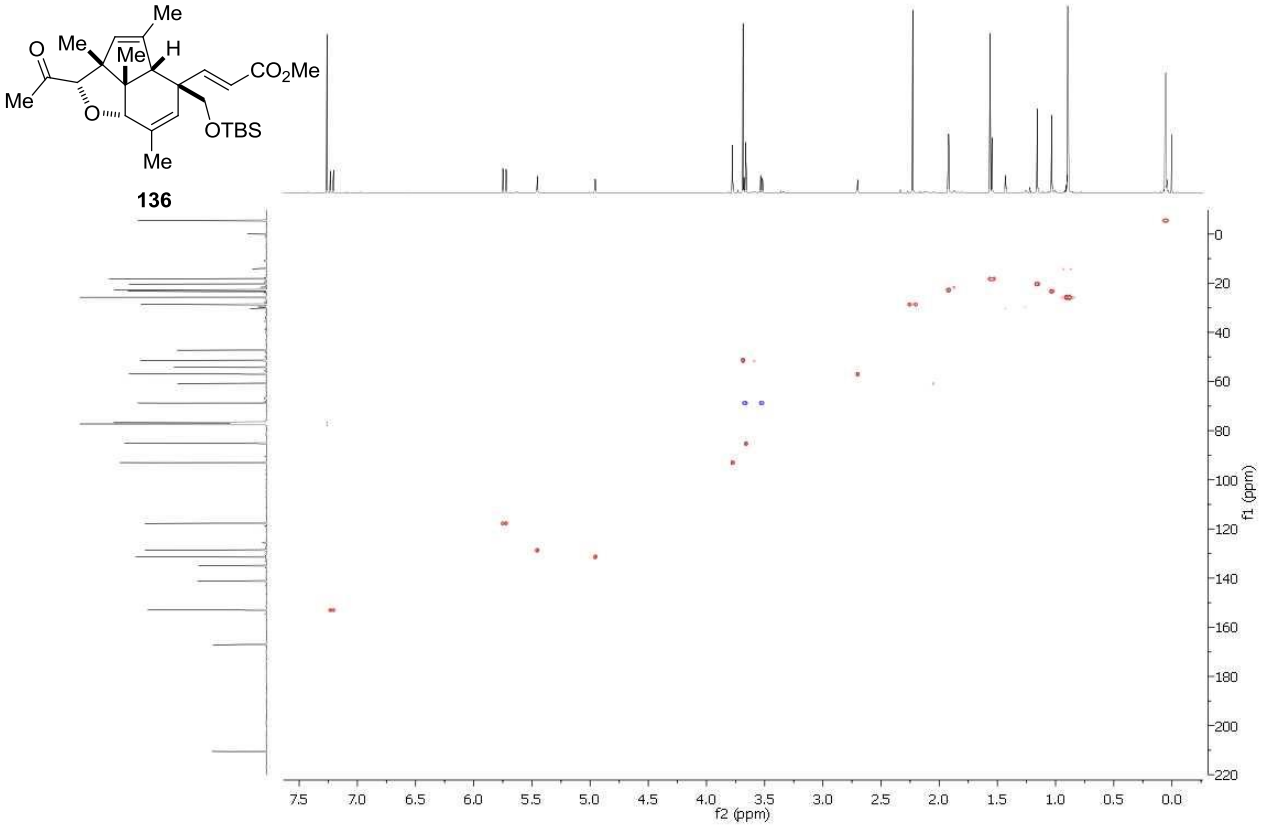

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
135
f2 (ppm)
f1 (ppm)

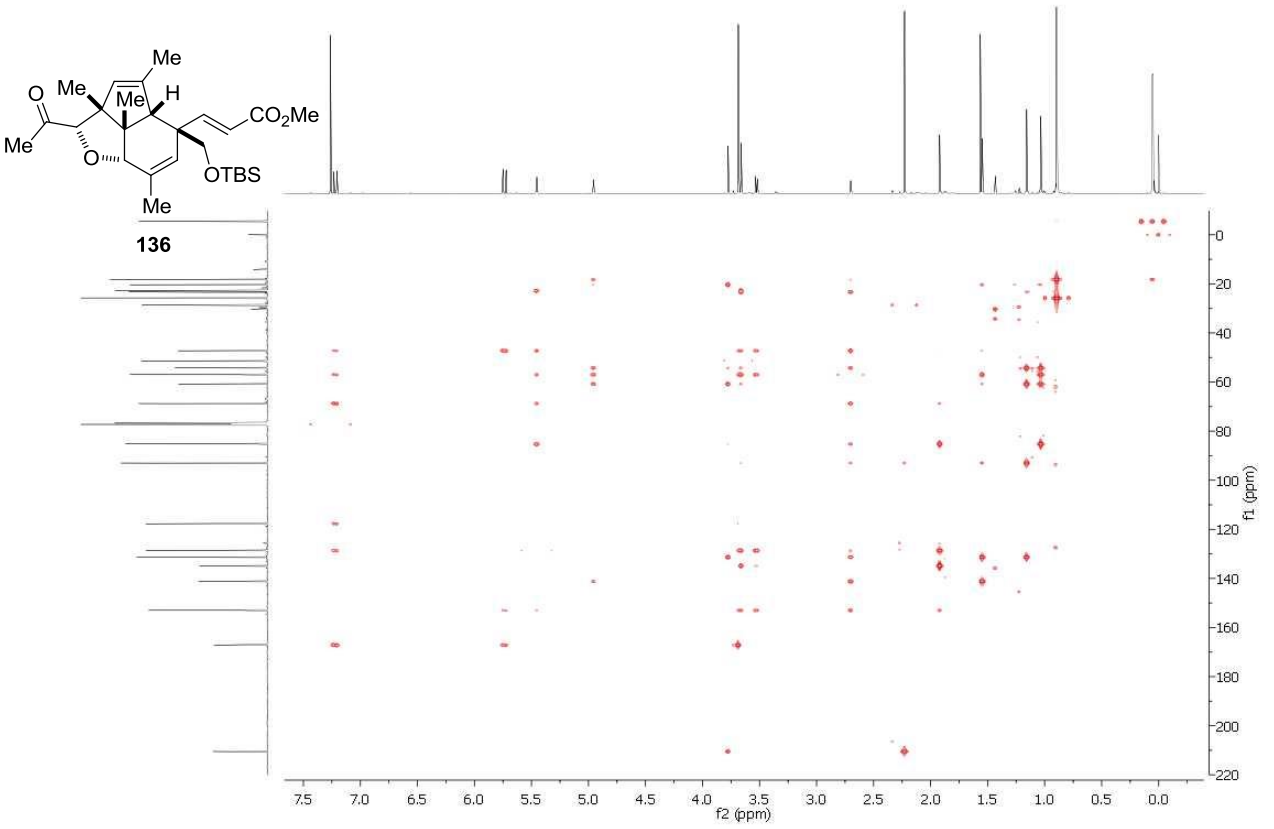

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
135
f2 (ppm)
f1 (ppm)

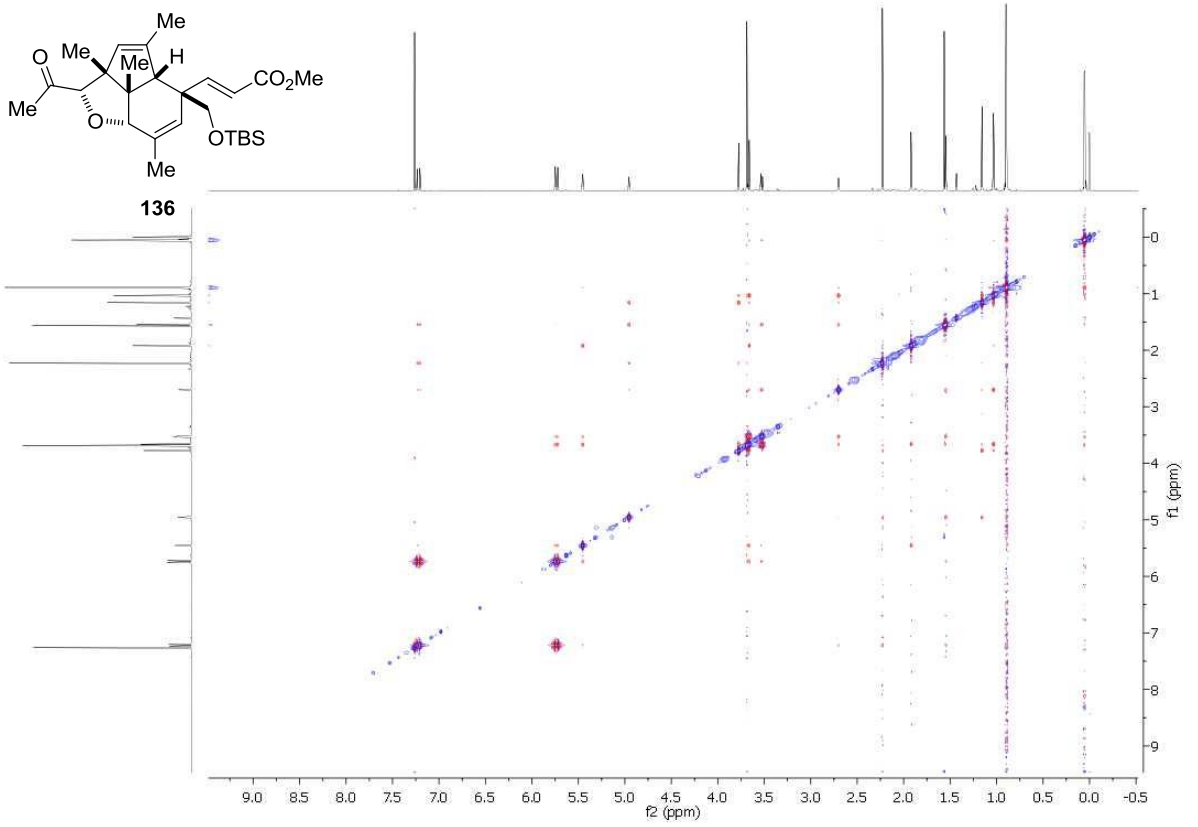

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
136
f1 (ppm)

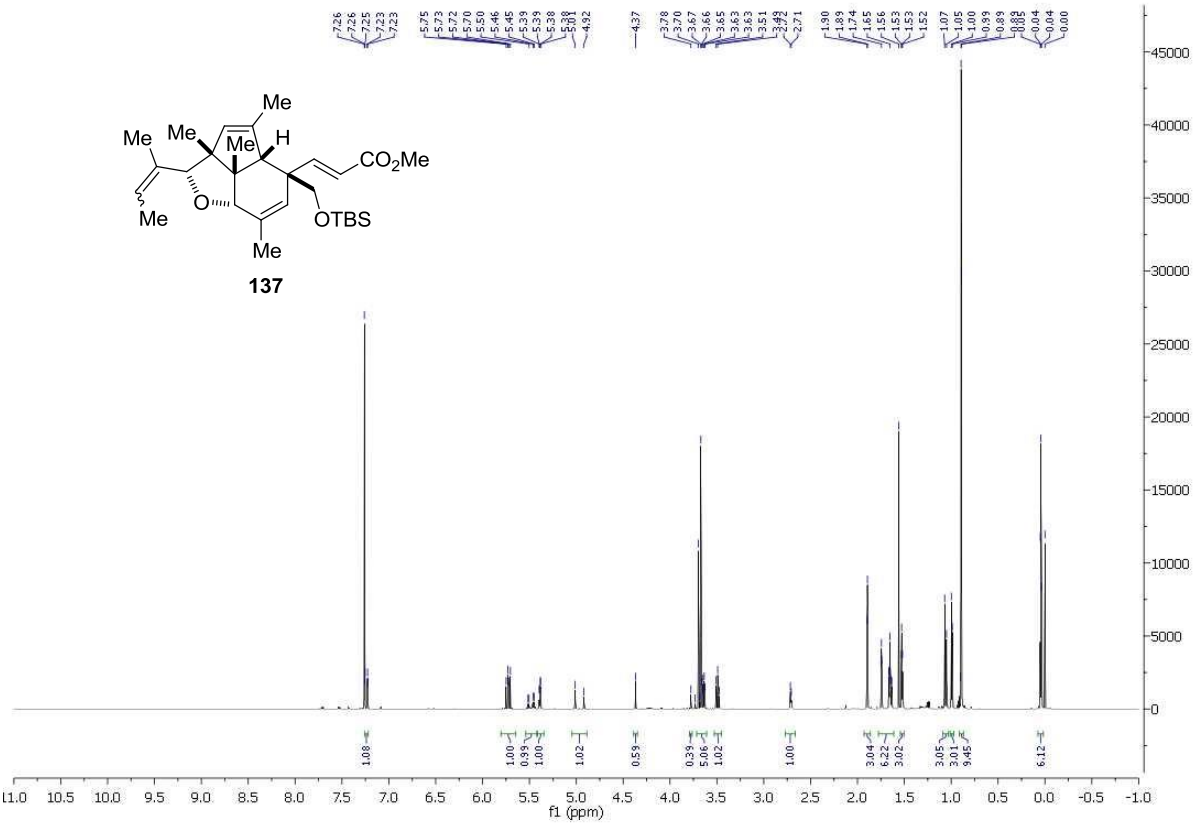

Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
136
f1 (ppm)


Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
136
f1 (ppm)
f2 (ppm)


Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
136
f1 (ppm)
f2 (ppm)


Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
136
f2 (ppm)
f1 (ppm)


Me
O
Me
Me
H
CO2Me
Me
O
OTBS
Me
136
f2 (ppm)
f1 (ppm)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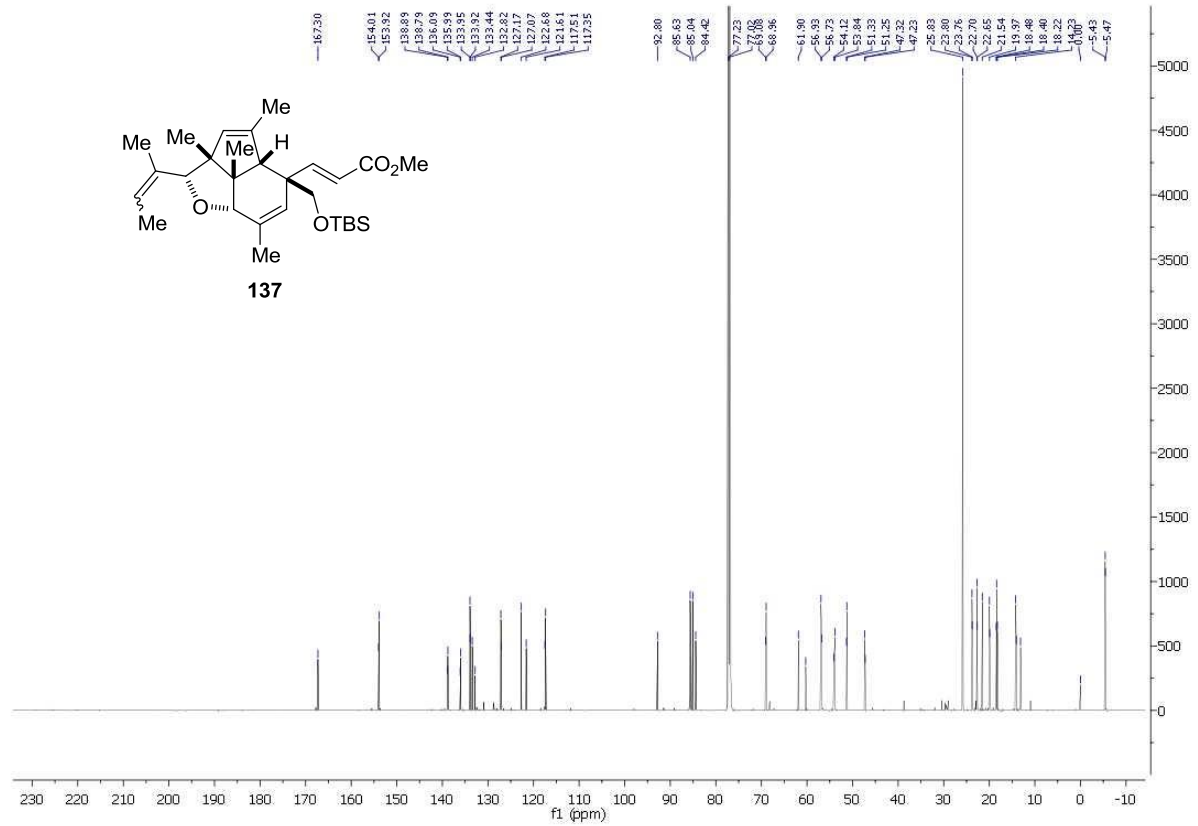
Me
Me
Me
H
CO2Me
O
Me
OTBS
Me
f1 (ppm)

137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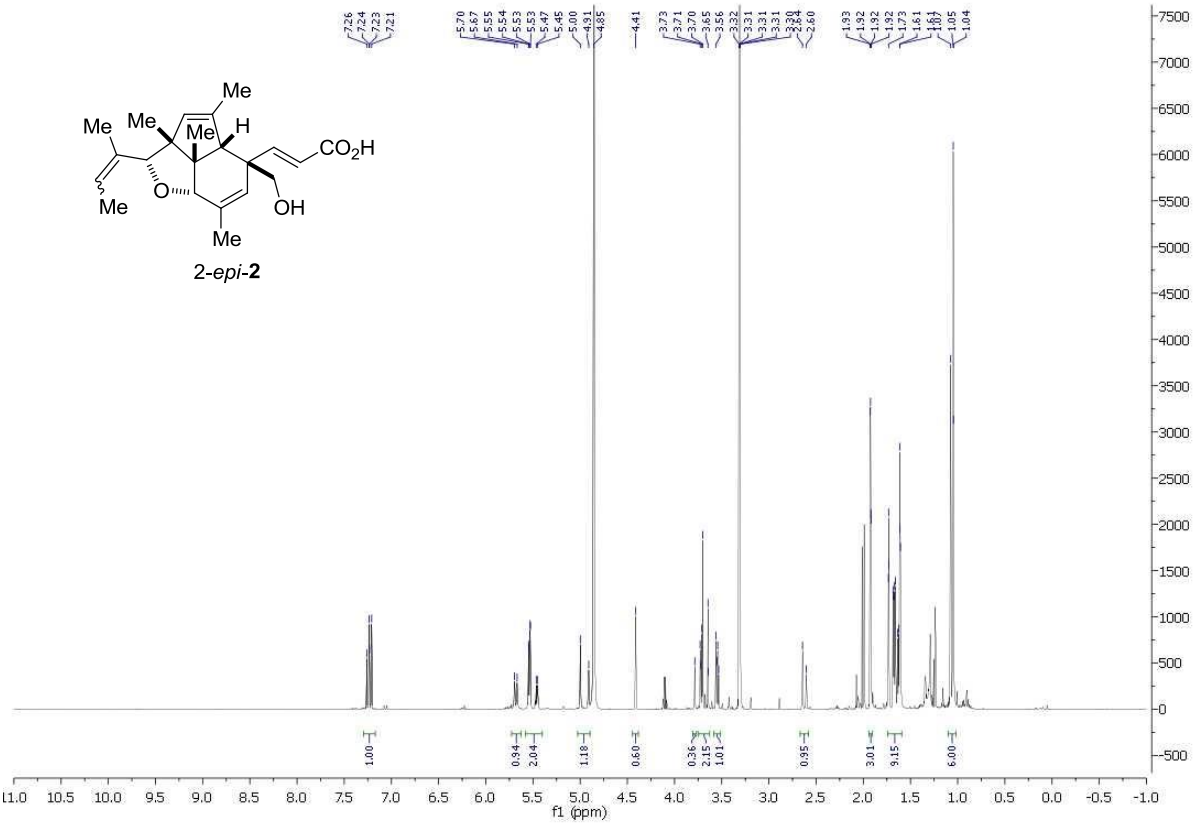
Me
Me
Me
H
CO2Me
O
Me
OTBS
Me
f1 (ppm)

137



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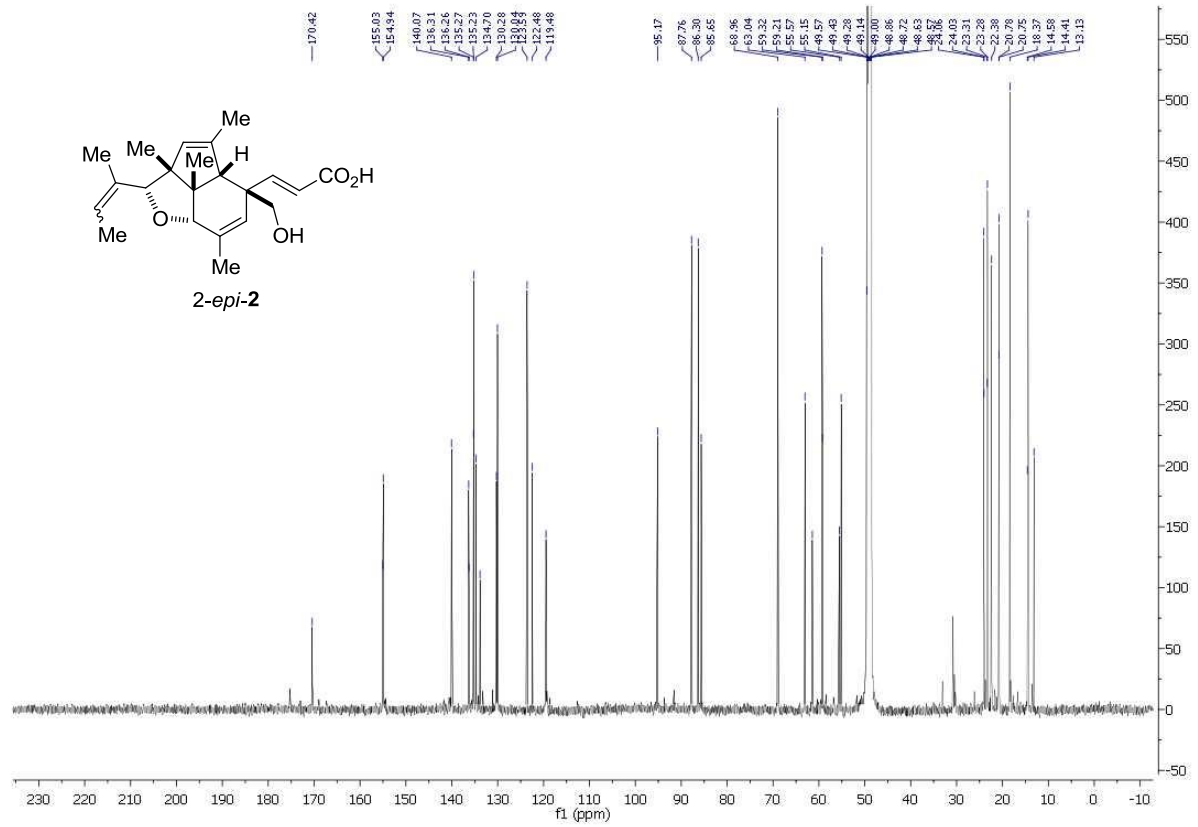
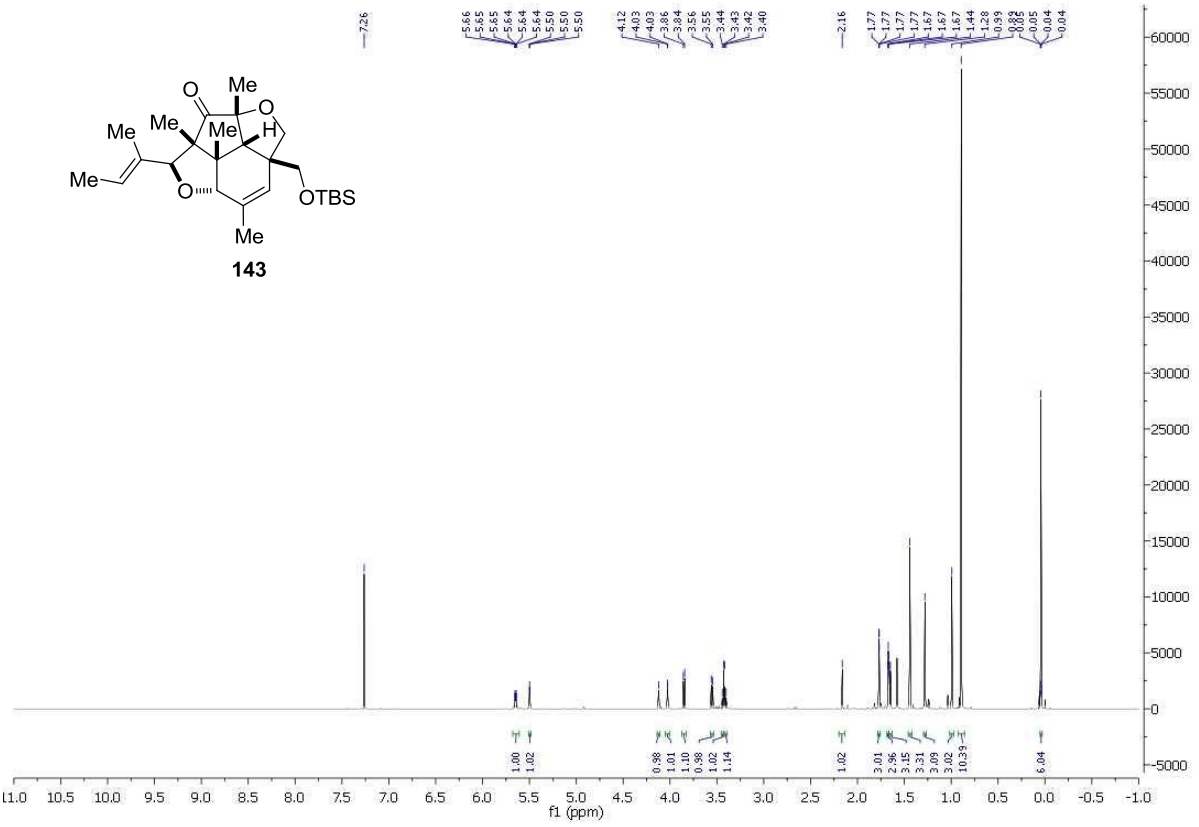


2-*epi*-**2**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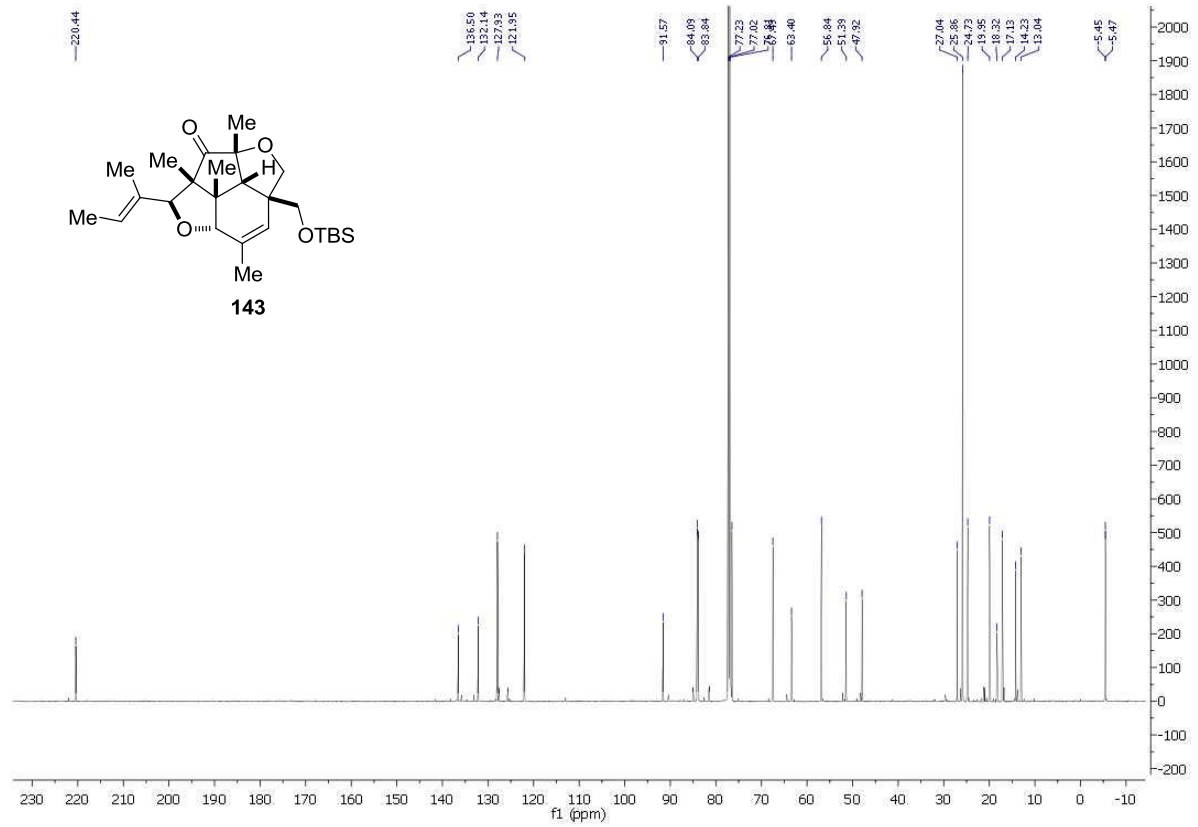
Me
O
Me
Me
Me
H
Me
O
OTBS
Me
143
f1 (ppm)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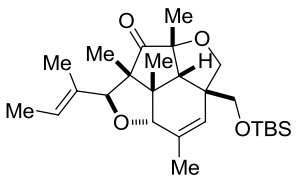
H
Me
O
OTBS
Me
143
f1 (ppm)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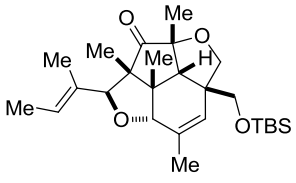
Me
Me
Me
H
Me
O
OTBS
Me

143

f1 (ppm)
f2 (ppm)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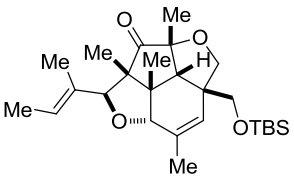
Me
Me
Me
H
Me
O
OTBS
Me

143

f1 (ppm)
f2 (ppm)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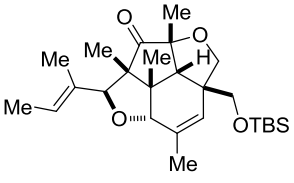
Me
Me
O
H
Me
Me
O
OTBS
Me

143

f1 (ppm)
f2 (ppm)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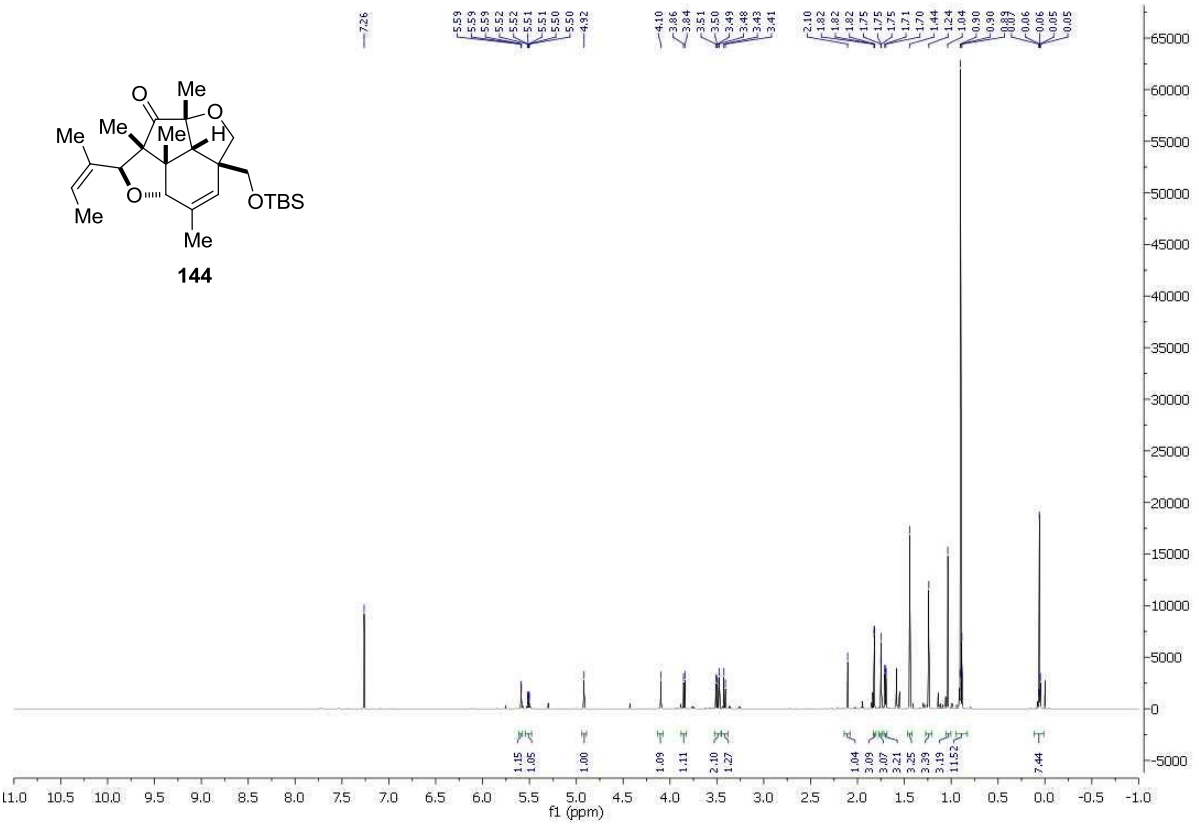
O
H
Me
Me
O
OTBS
Me

143

f1 (ppm)
f2 (ppm)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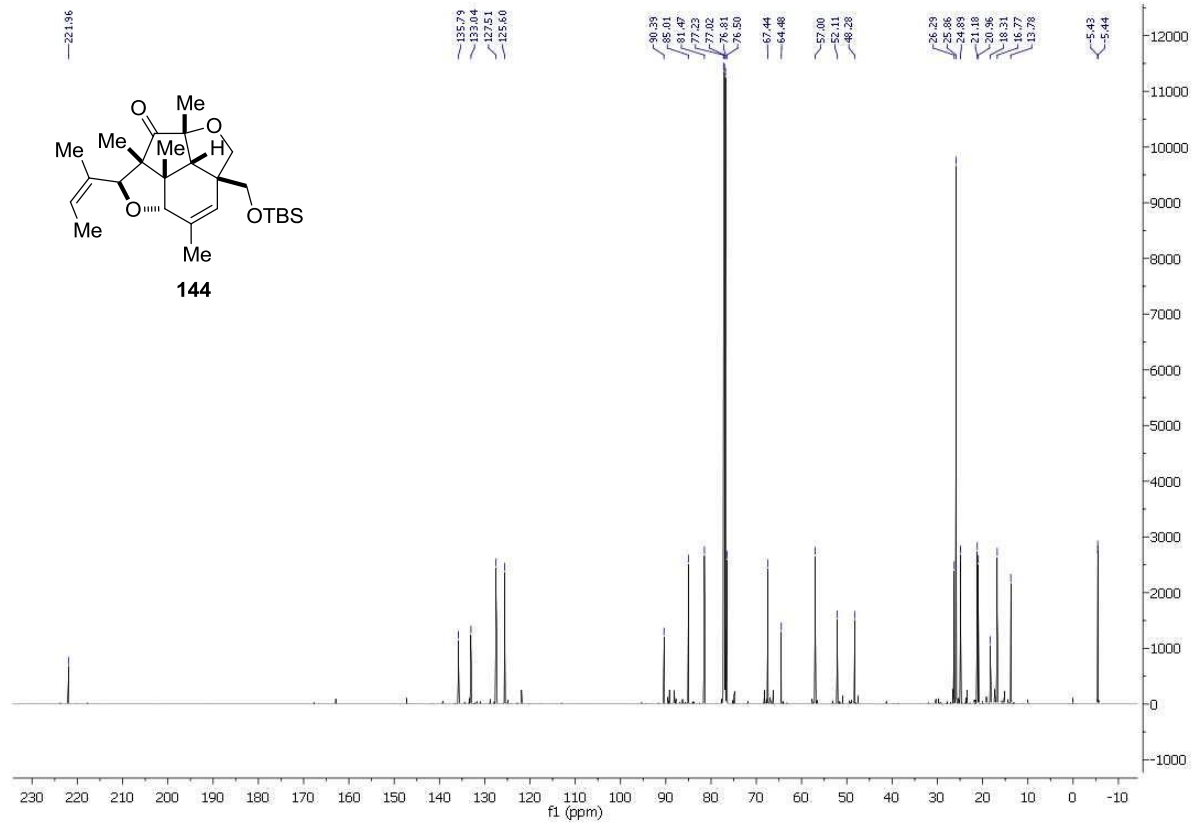
O
Me
Me
Me
H
O
OTBS
Me
Me
144
f1 (ppm)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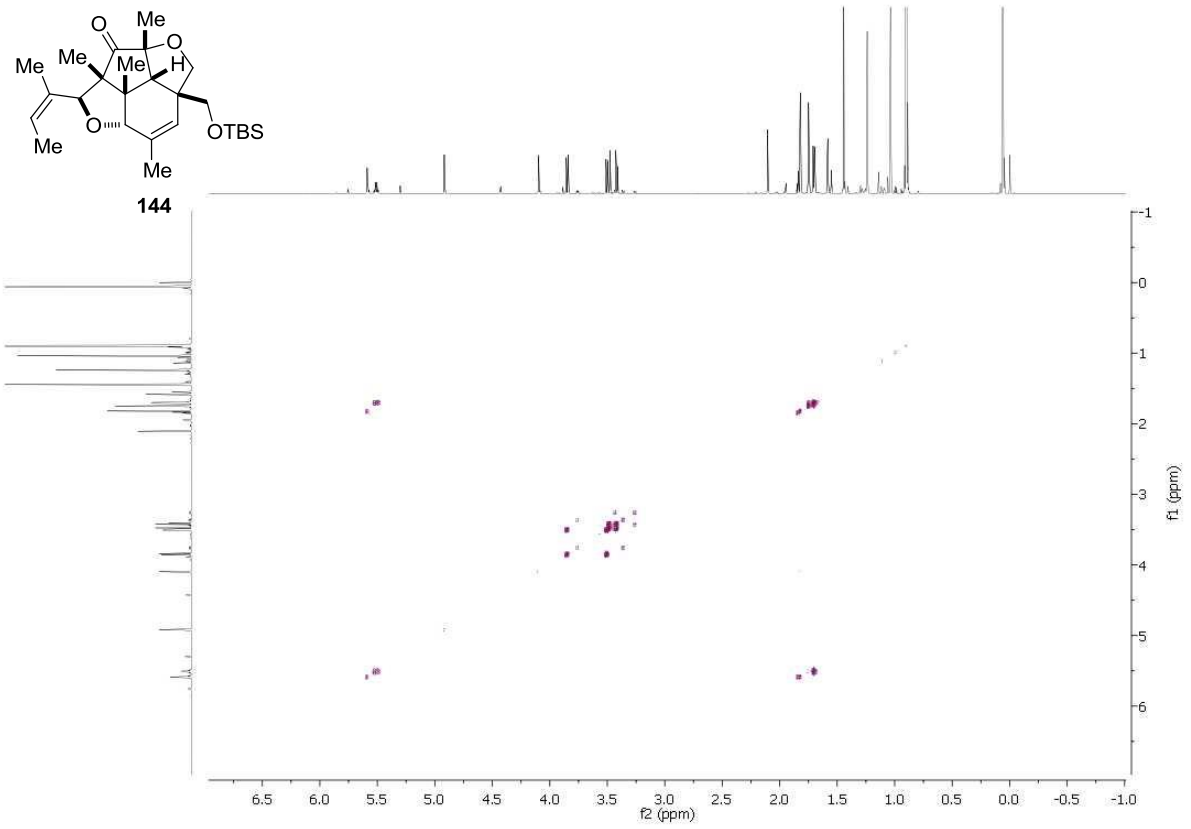
Me
H
O
OTBS
Me
Me
144
f1 (ppm)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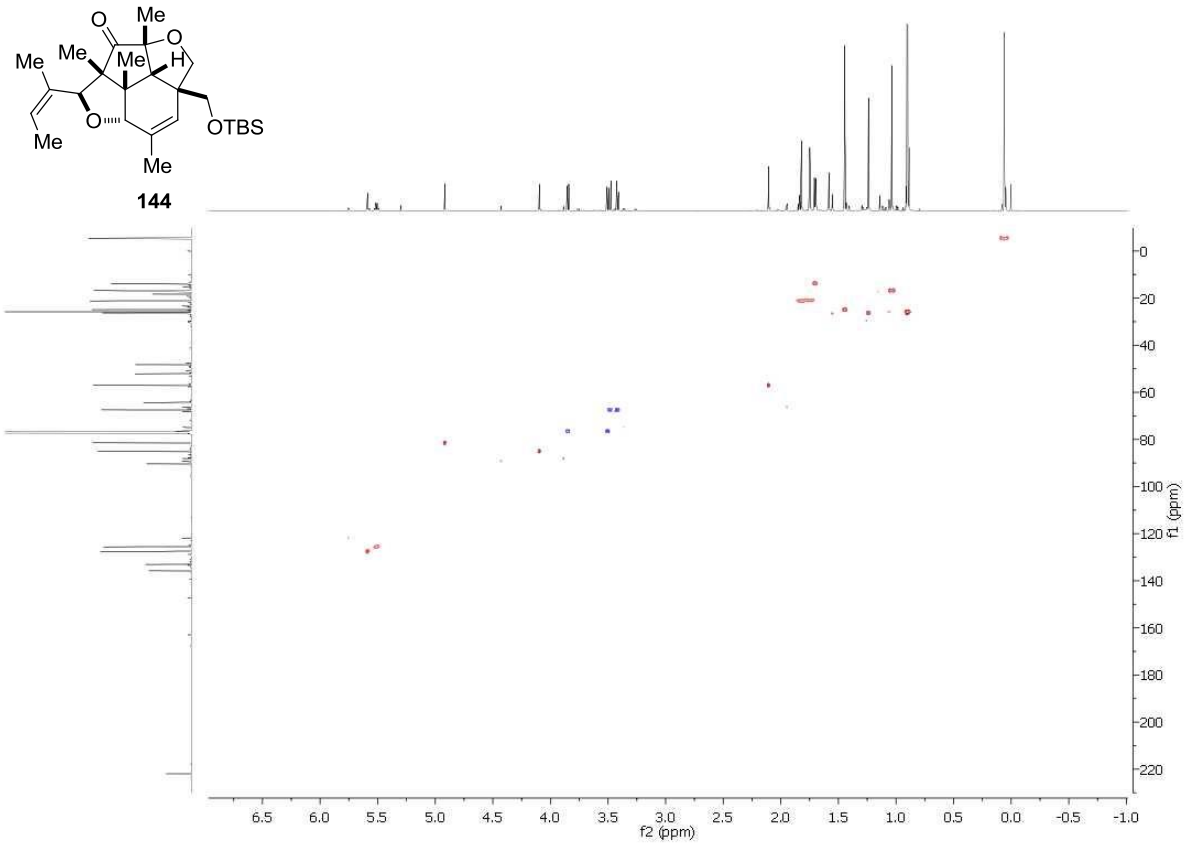
Me
O
Me
Me
Me
H
O
OTBS
Me
Me
144
f1 (ppm)
f2 (ppm)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Me
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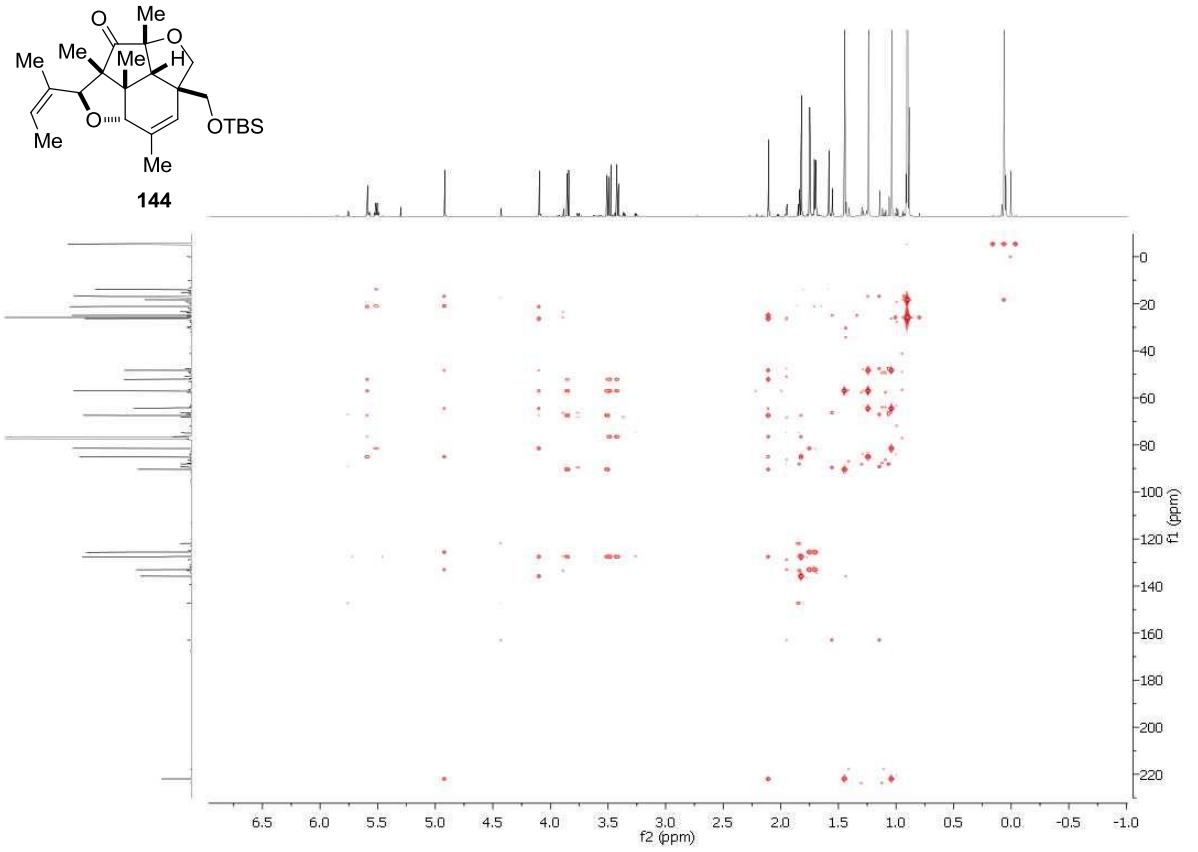
OTBS
Me
Me
144
f1 (ppm)
f2 (ppm)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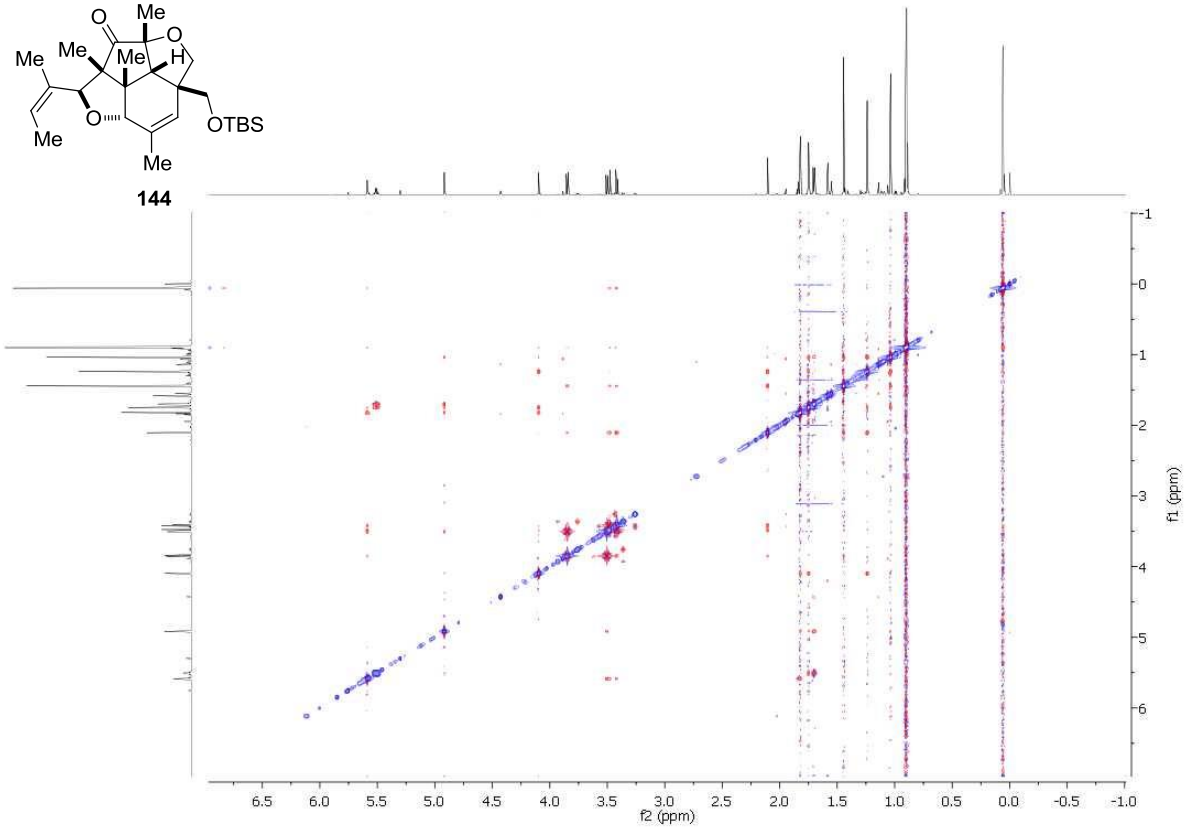
Me
O
Me
Me
H
Me
O
OTBS
Me
Me
144
f2 (ppm)
f1 (ppm)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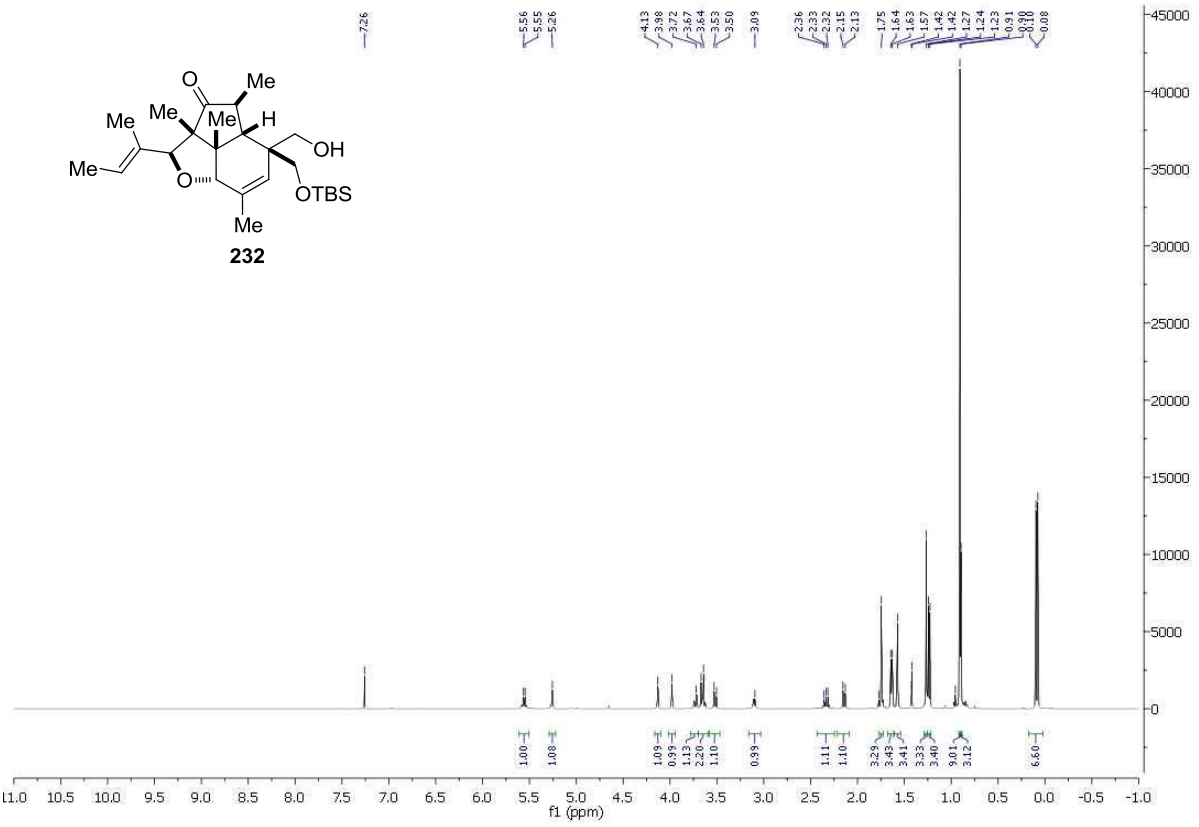
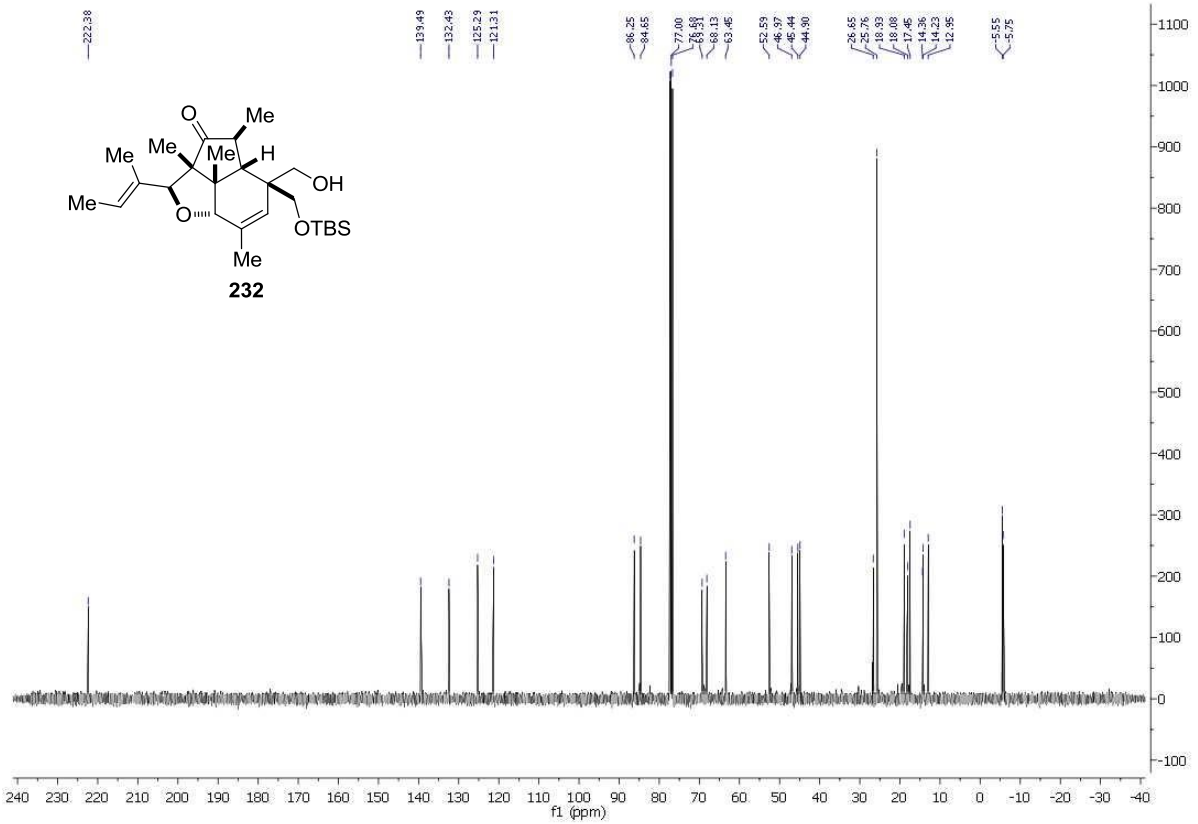
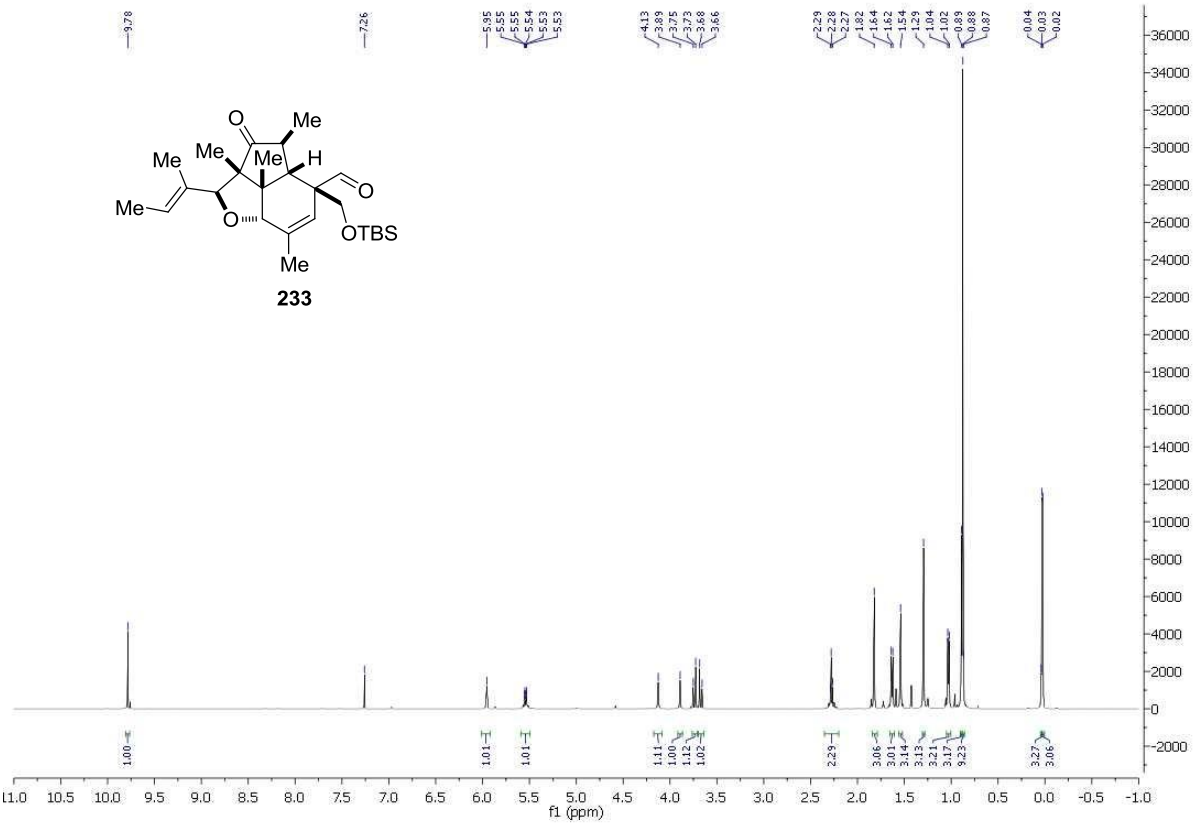
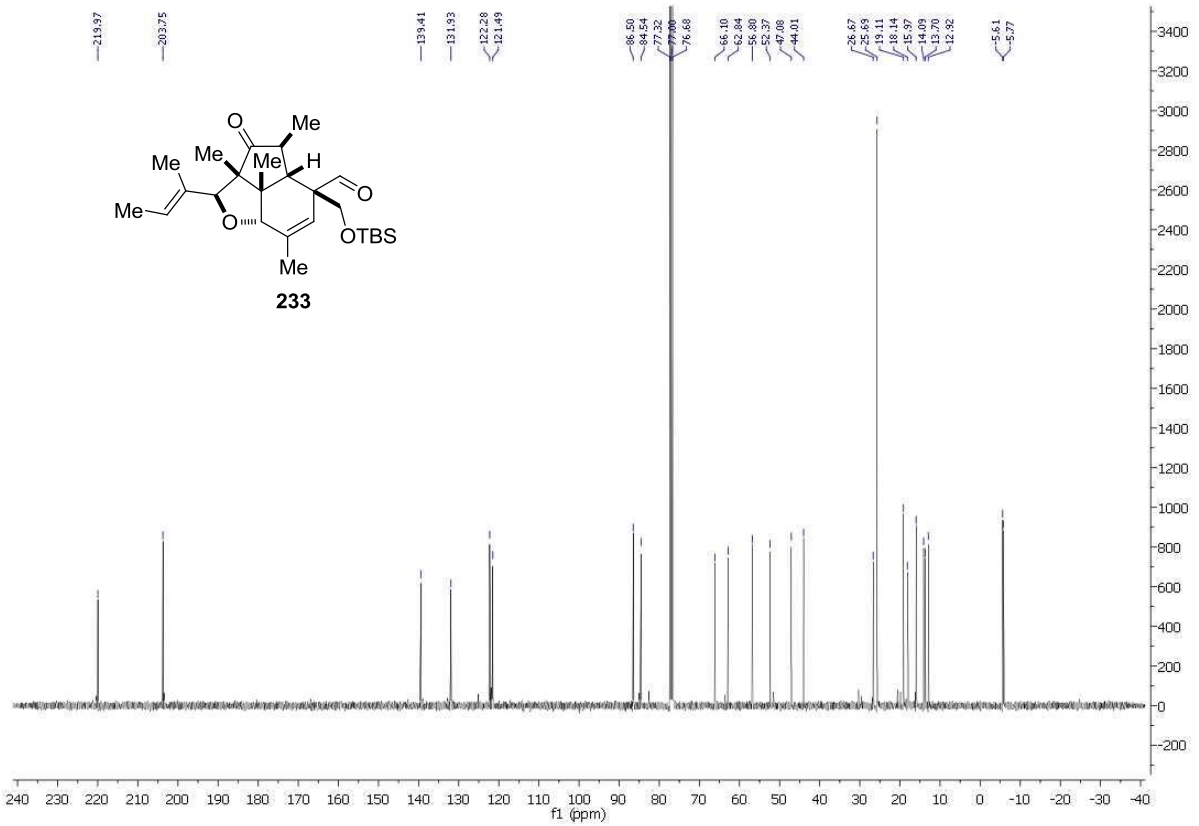
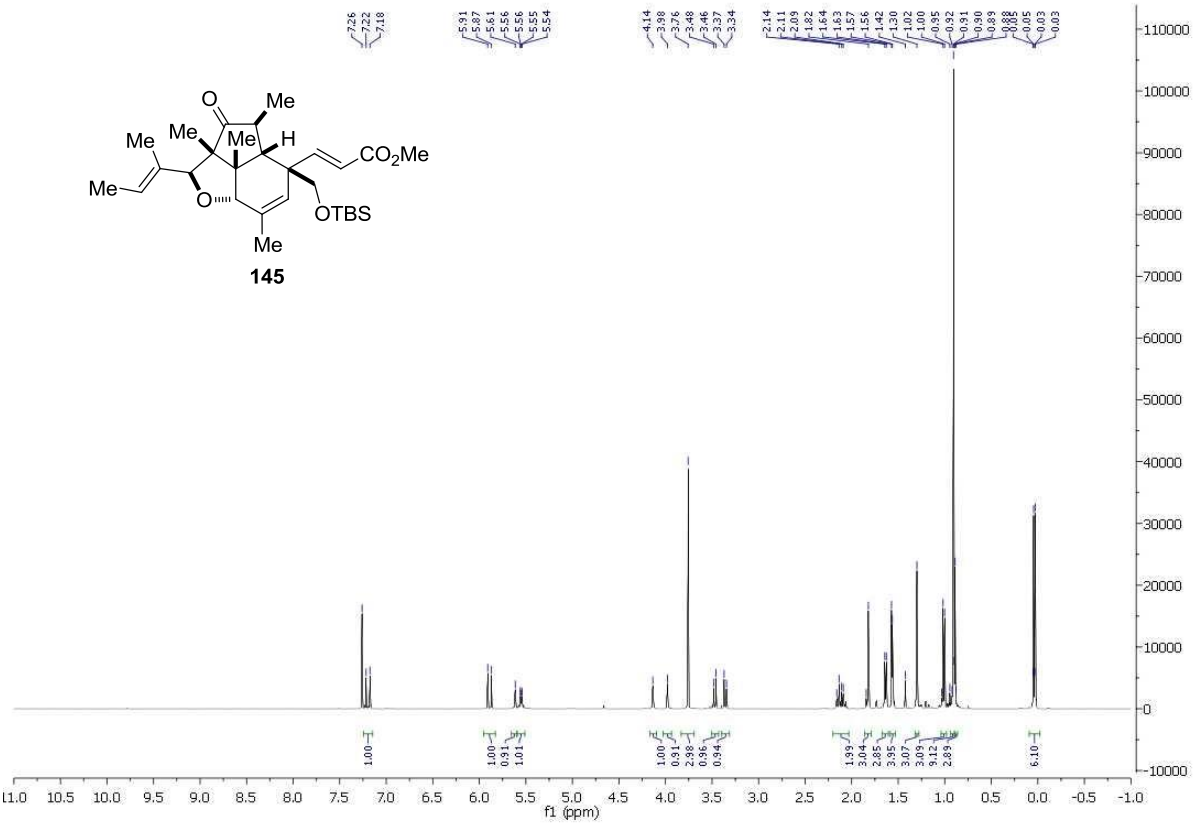
O
Me
O
Me
Me
H
Me
O
OTBS
Me
Me
144
f2 (ppm)
f1 (ppm)

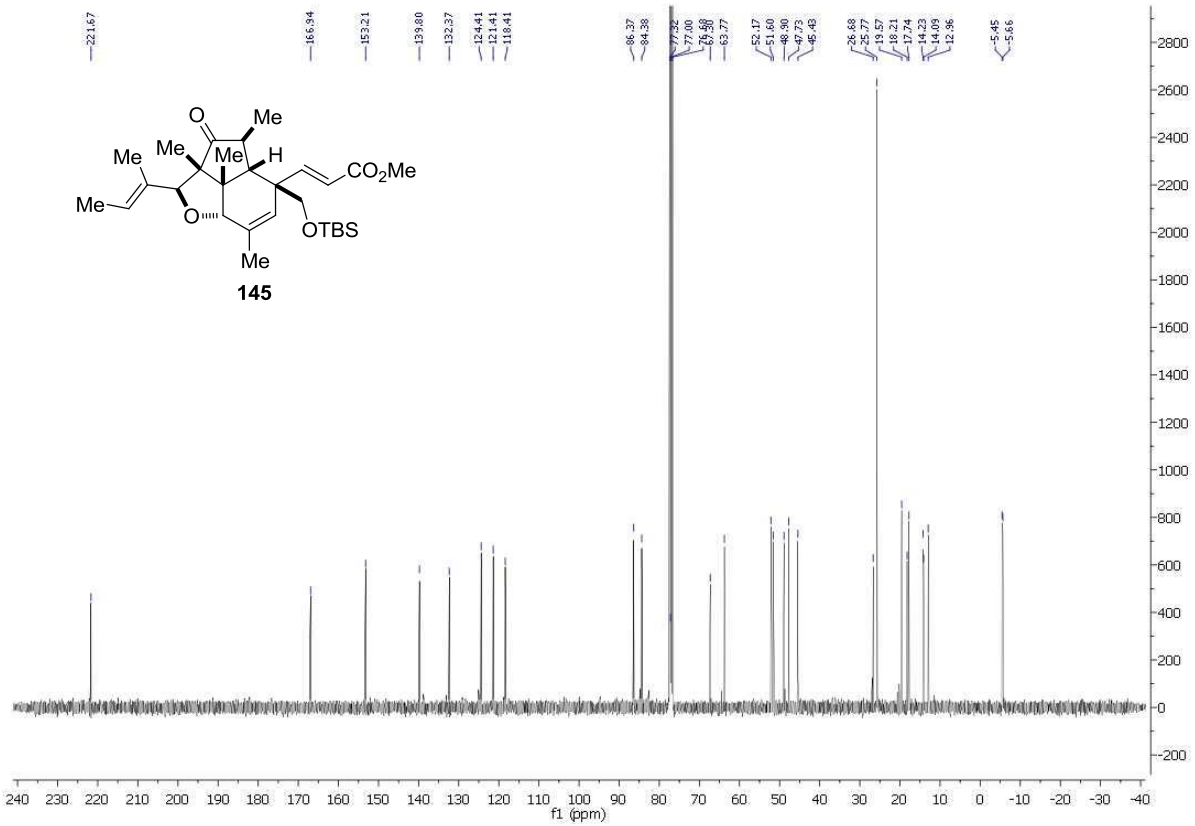

Me
O
Me
Me
Me
H
OH
Me
O
OTBS
Me
232
f1 (ppm)

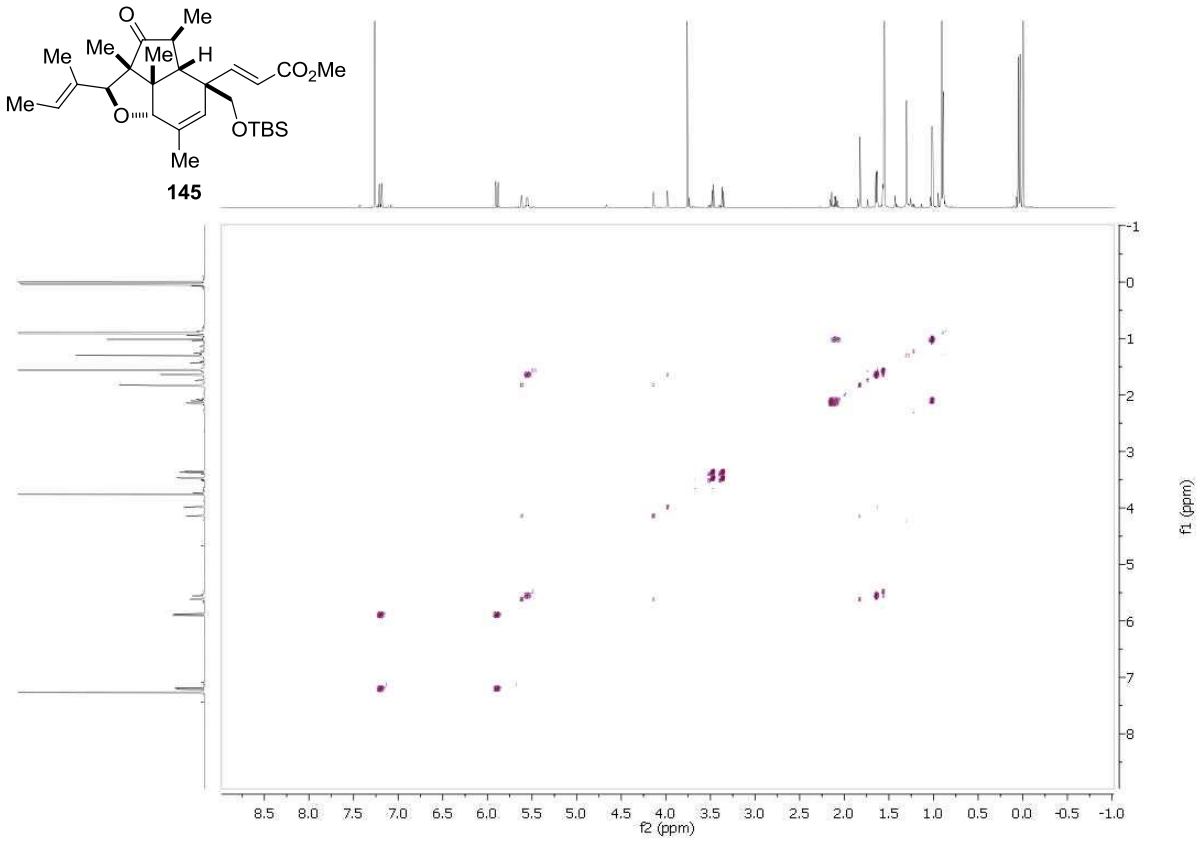

Me
O
Me
Me
Me
H
OH
Me
O
OTBS
Me
232
f1 (ppm)

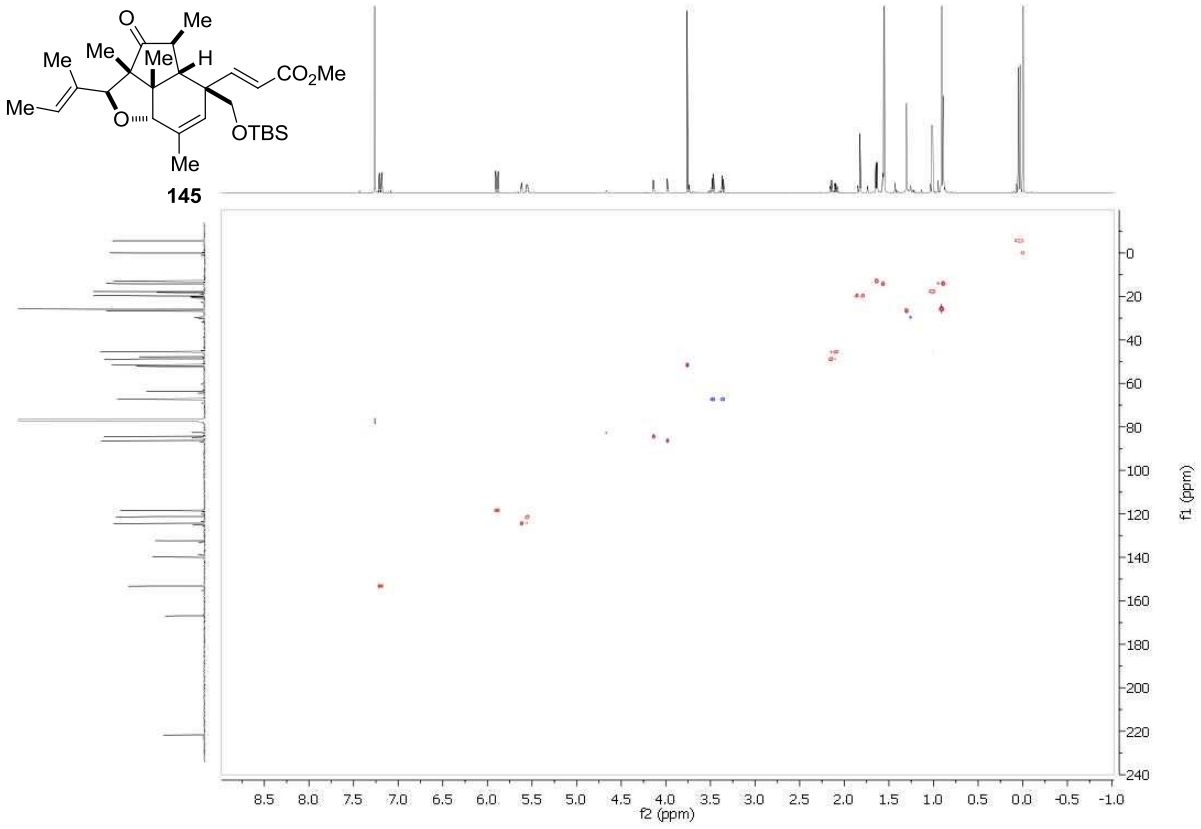

Me
Me
Me
Me
Me
H
O
O
O
OTBS
Me
233
f1 (ppm)


Me
Me
Me
Me
Me
H
O
O
O
OTBS
Me
233
f1 (ppm)


Me
Me
Me
Me
H
O
O
CO2Me
OTBS
Me
Me
145
f1 (ppm)


Me
Me
Me
Me
H
O
O
CO2Me
OTBS
Me
Me
145
f1 (ppm)


O
Me
Me
Me
Me
H
Me
CO2Me
Me
O
OTBS
Me
145
f2 (ppm)
f1 (ppm)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Me
Me
Me
H
Me
CO2Me
Me
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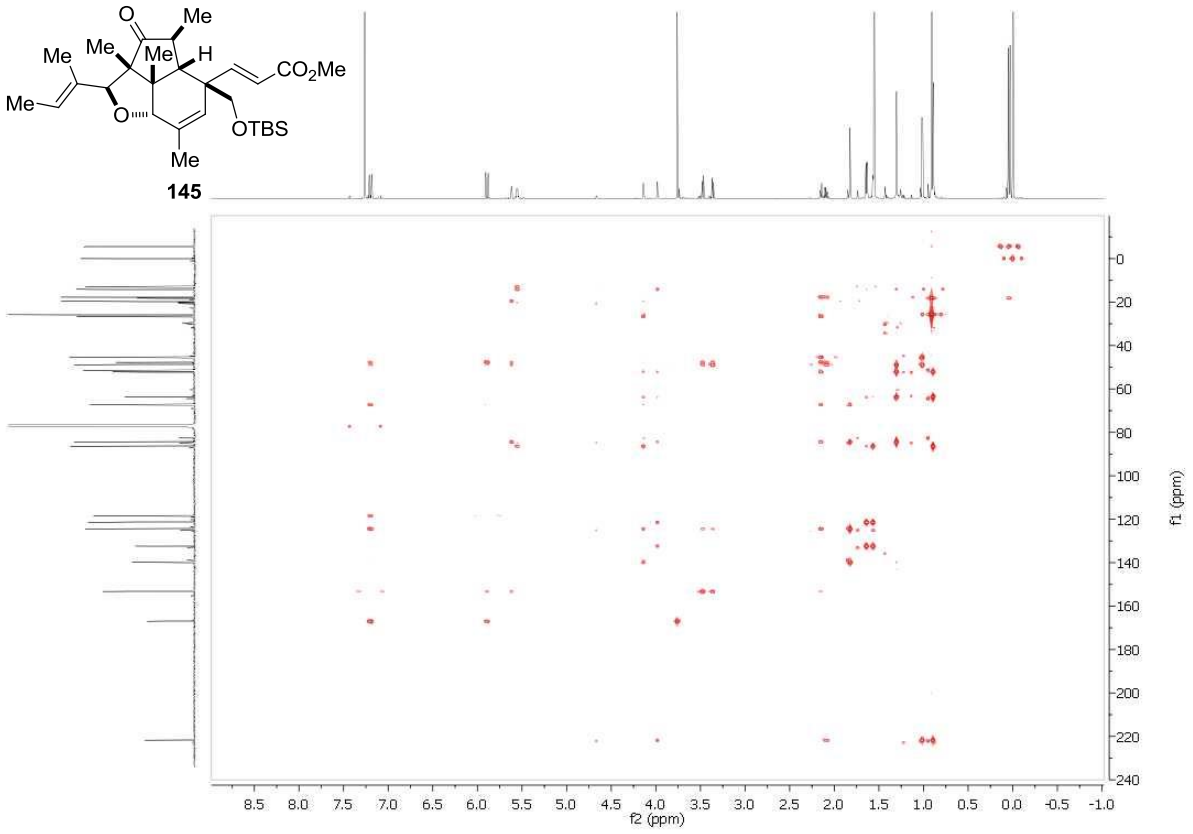
OTBS
Me
145
f2 (ppm)
f1 (ppm)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Me
Me
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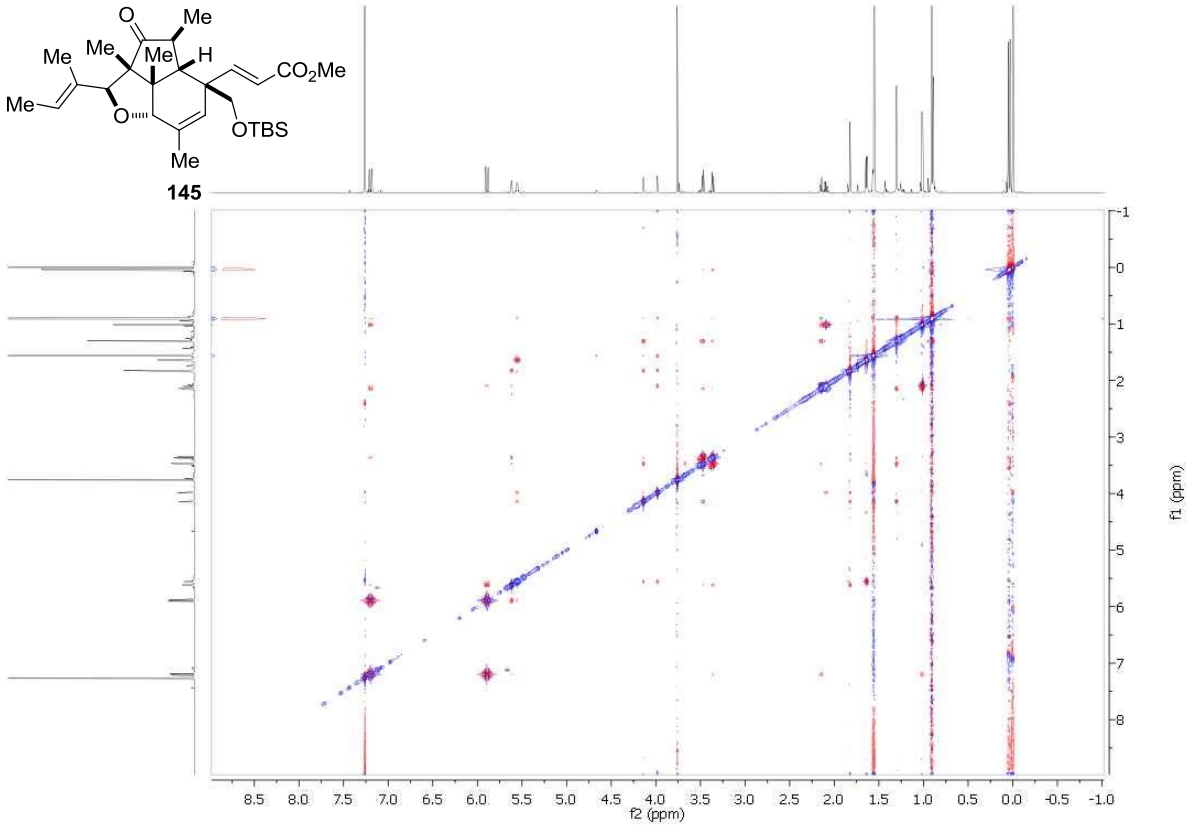
H
CO2Me
Me
O
OTBS
Me
145
f2 (ppm)
f1 (ppm)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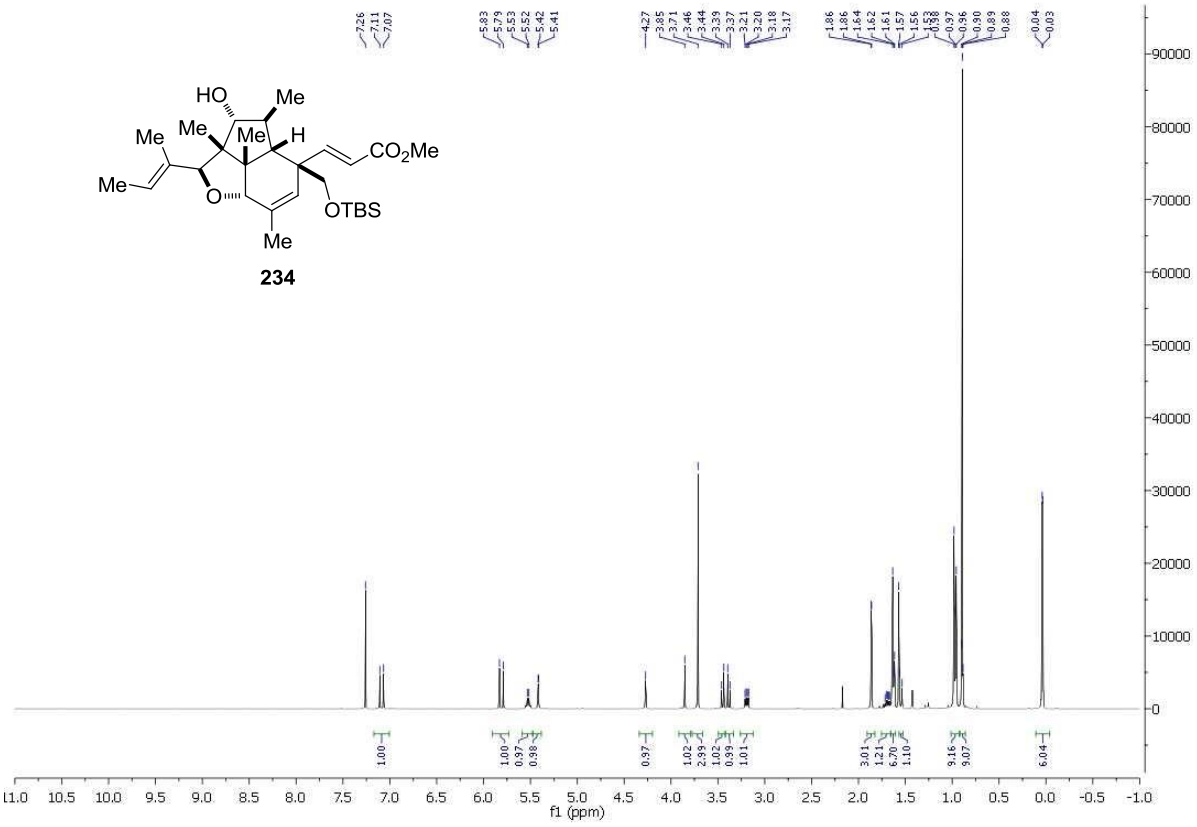
Me
Me
Me
H
CO2Me
Me
O
OTBS
Me
145
f2 (ppm)
f1 (ppm)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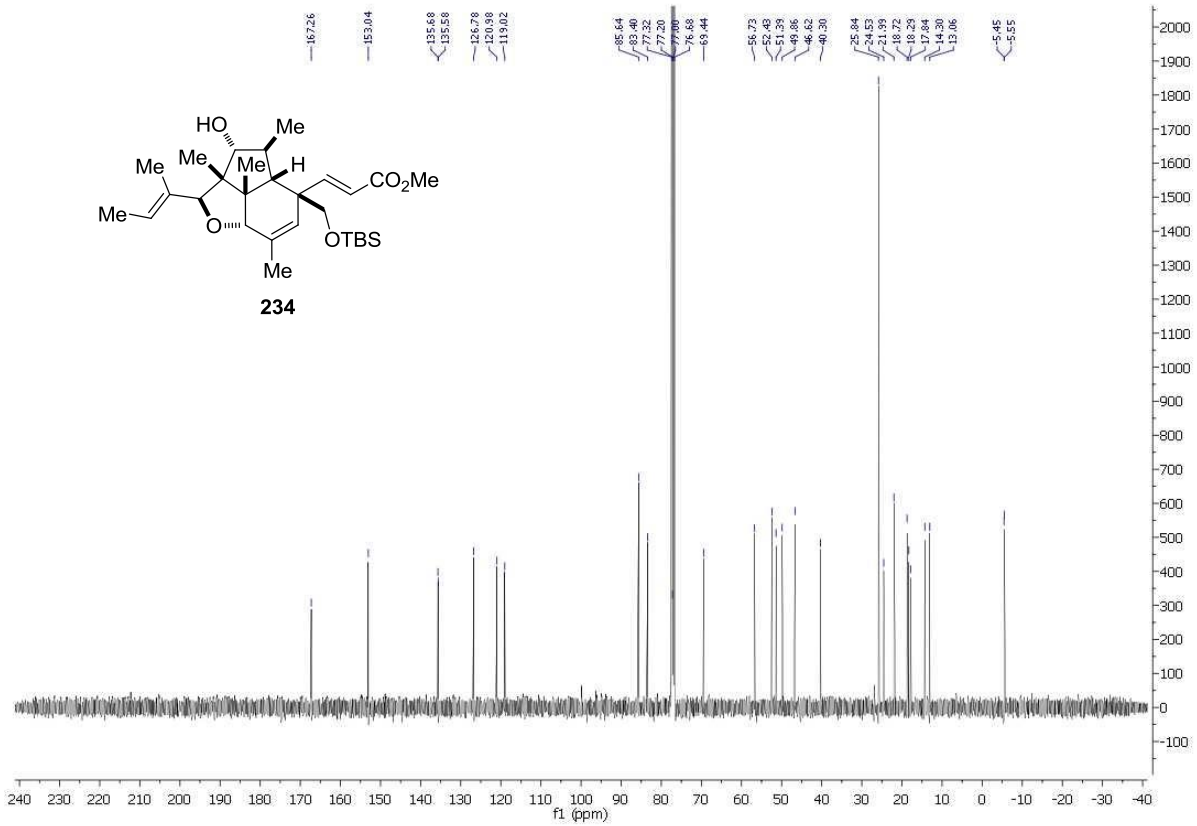
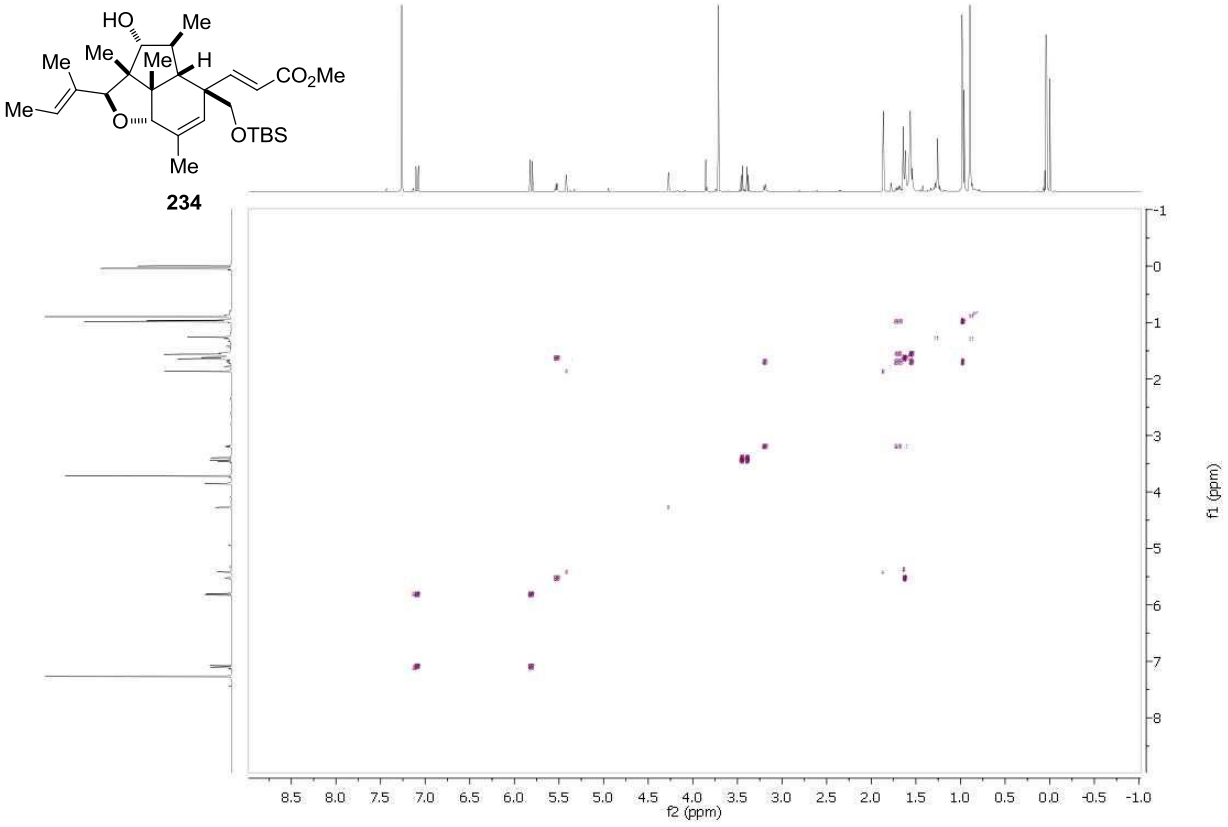
Me
Me
Me
H
CO2Me
Me
O
OTBS
Me
234
f1 (ppm)


HO
Me
Me
Me
Me
H
CO2Me
Me
O
OTBS
Me
234
f1 (ppm)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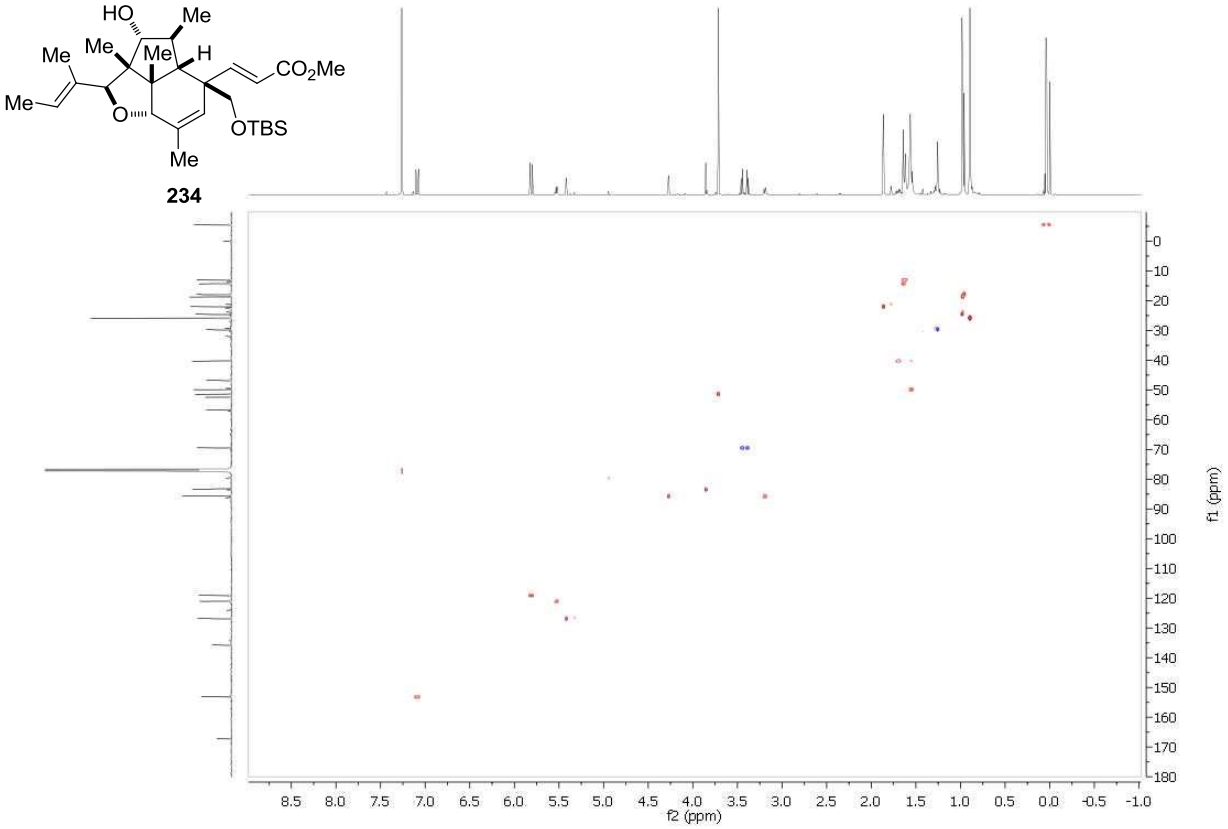
Me
Me
Me
H
Me
CO2Me
O
OTBS
Me
234
f2 (ppm)
f1 (ppm)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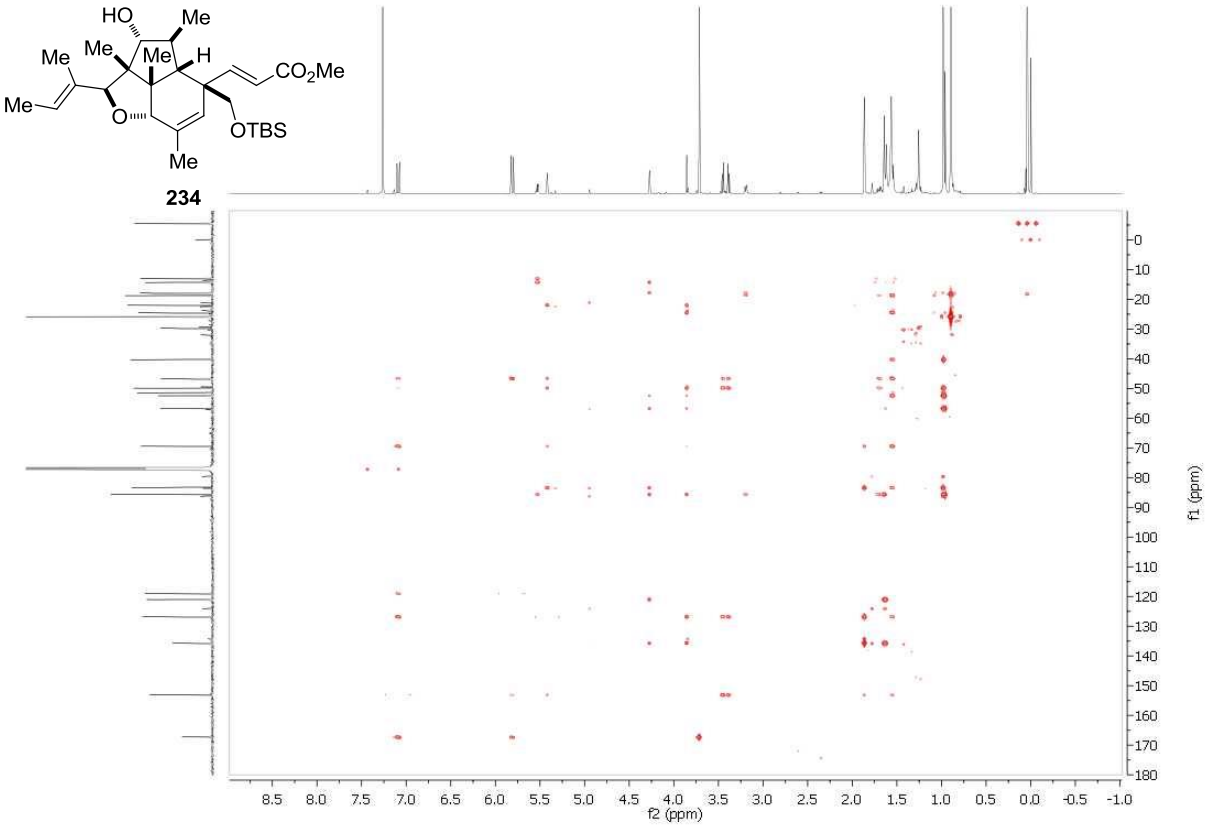
Me
Me
Me
H
Me
CO2Me
O
OTBS
Me
234
f2 (ppm)
f1 (ppm)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Me
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H
CO2Me
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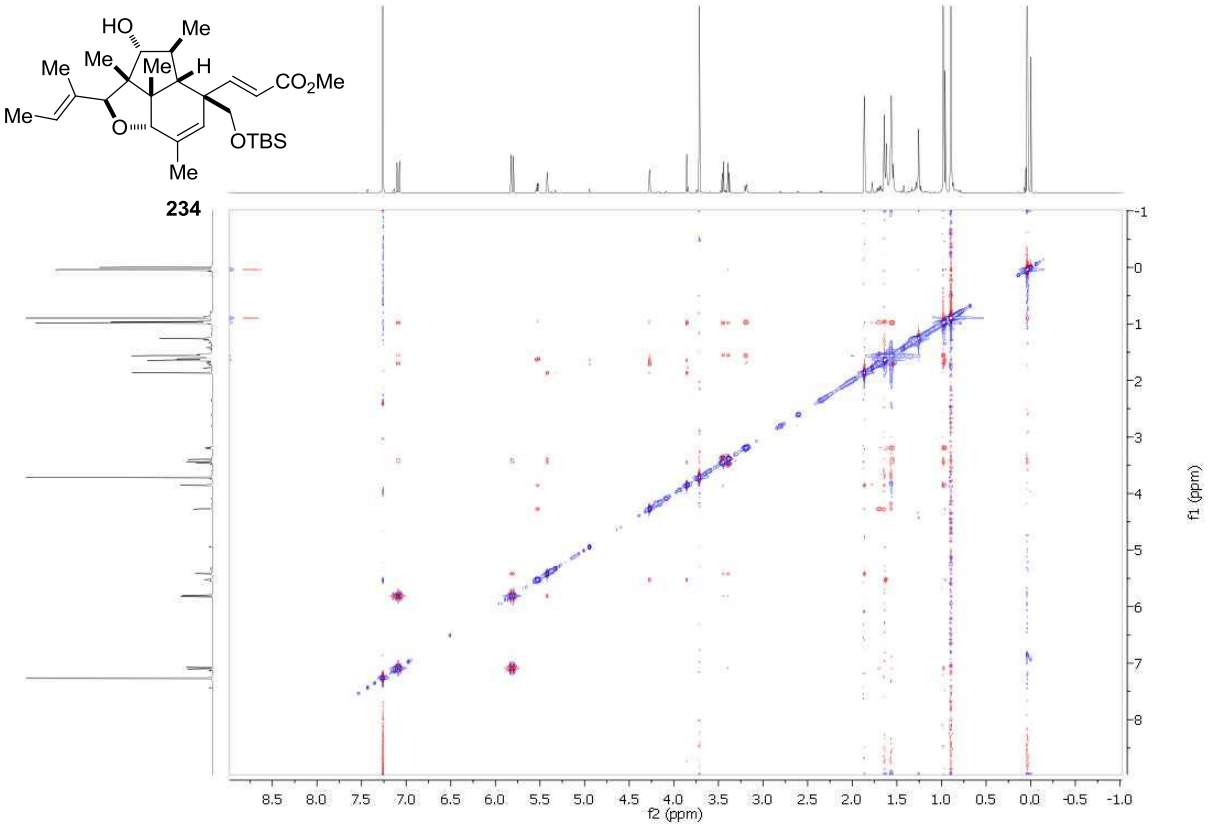
OTBS
Me
234
f2 (ppm)
f1 (ppm)


HO
Me
Me
Me
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H
CO2Me
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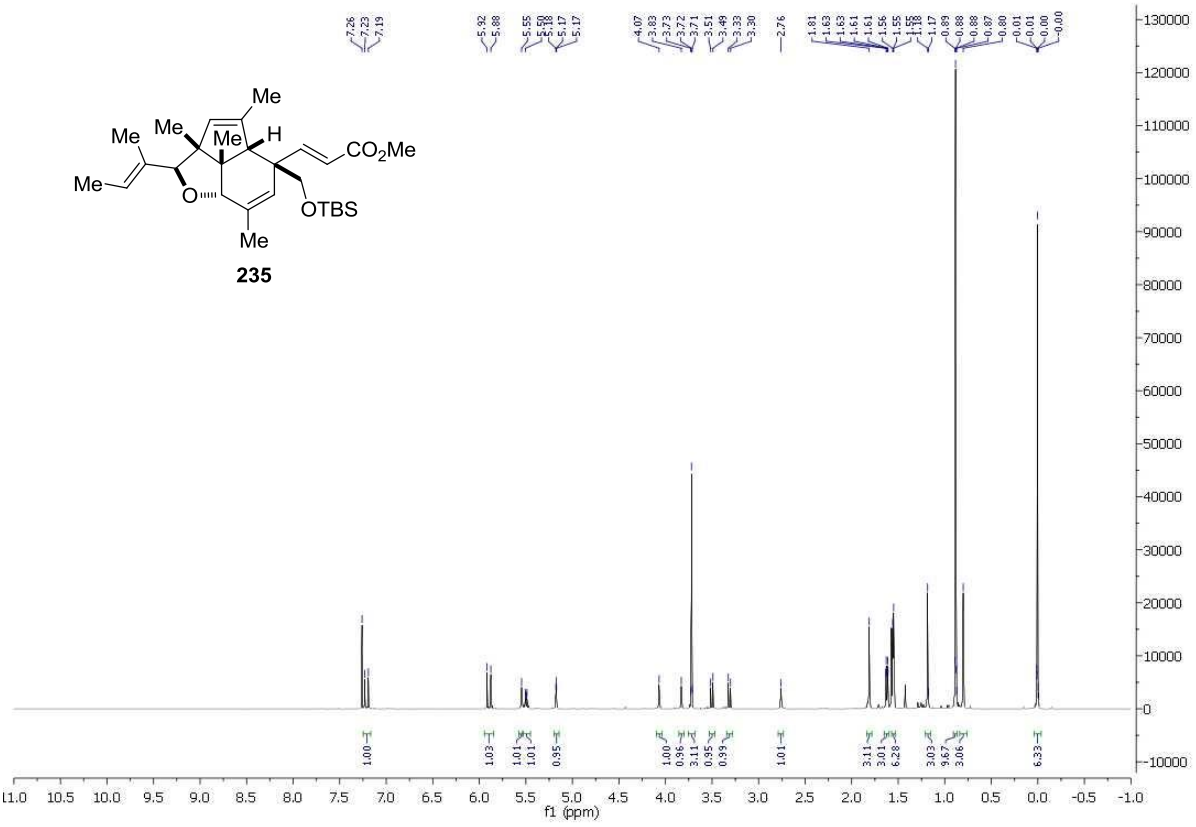
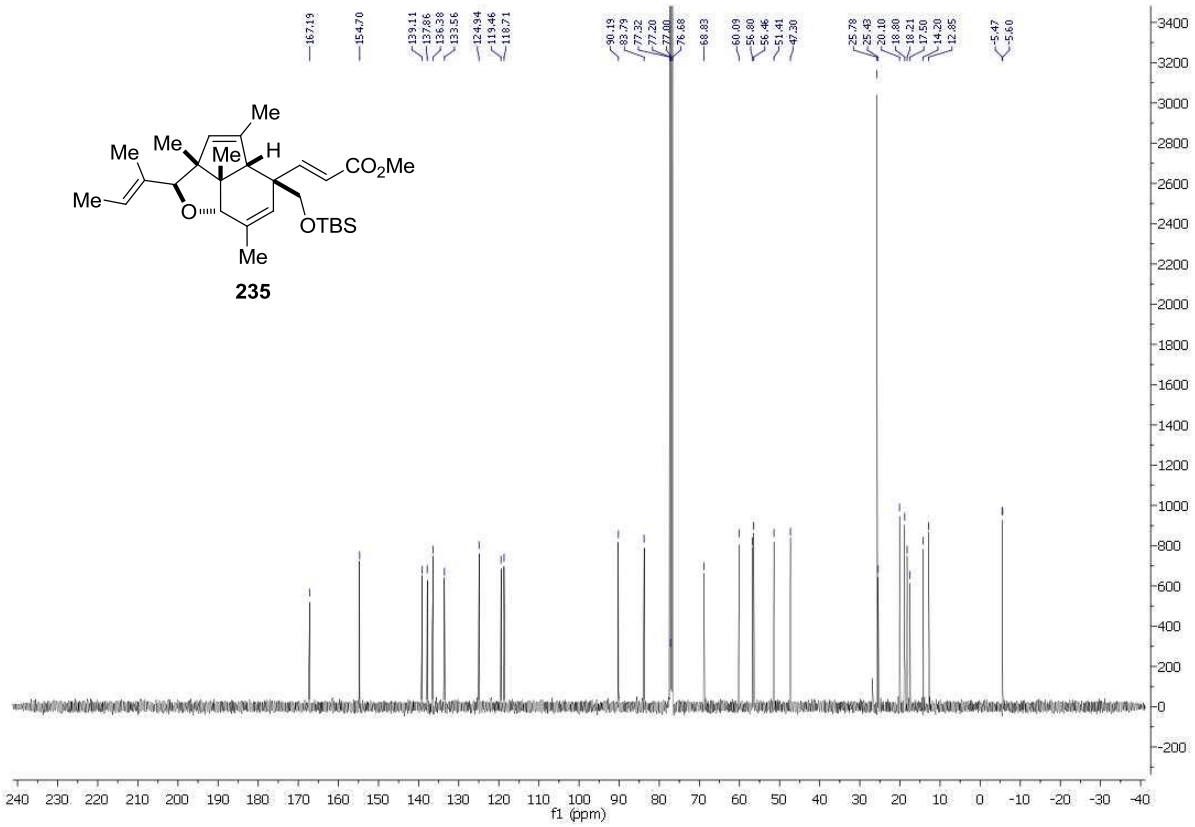
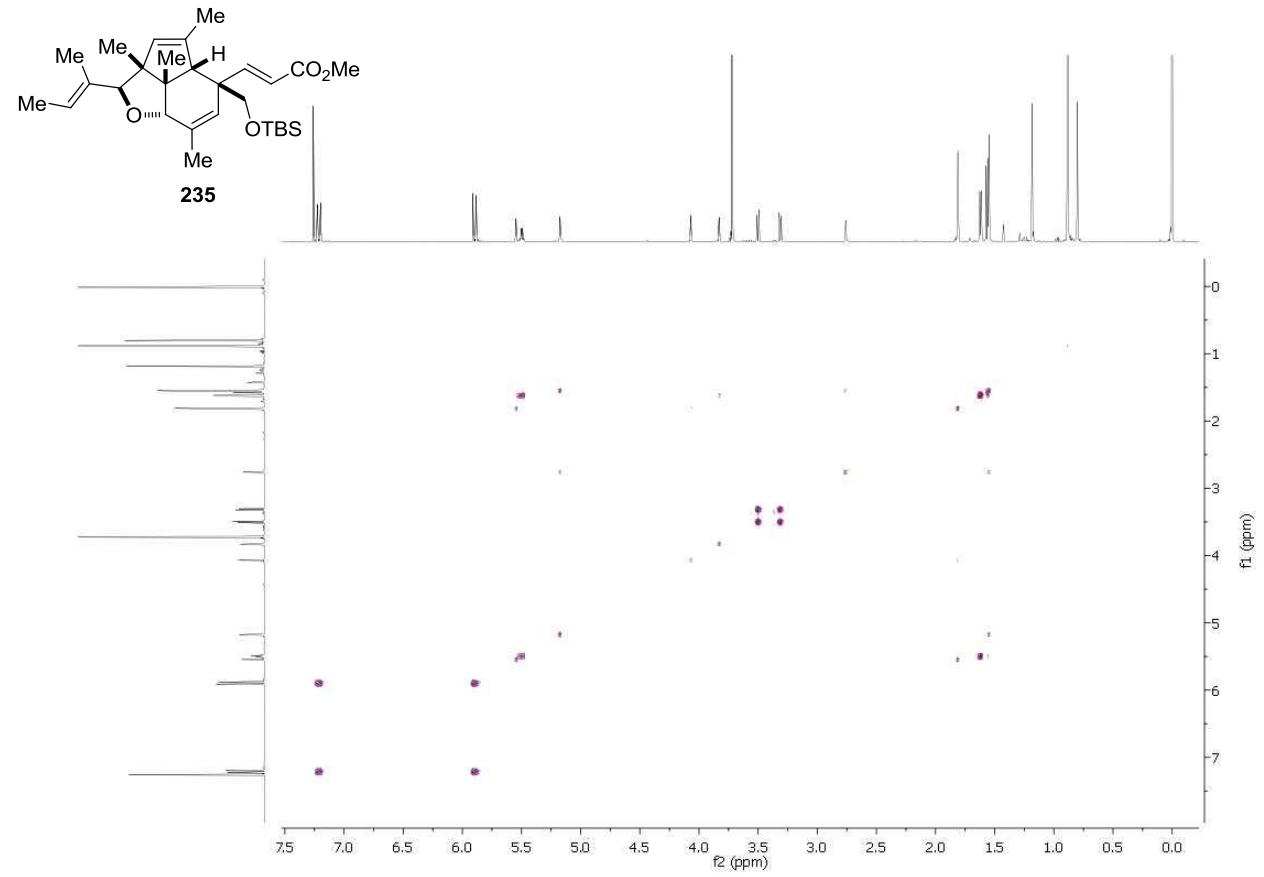
O
OTBS
Me
234
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2Me
Me
O
OTBS
Me
235
f1 (ppm)


Me
Me
Me
Me
H
CO2Me
Me
O
OTBS
Me
235
f1 (ppm)


Me
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Me
Me
H
CO2Me
Me
O
OTBS
Me
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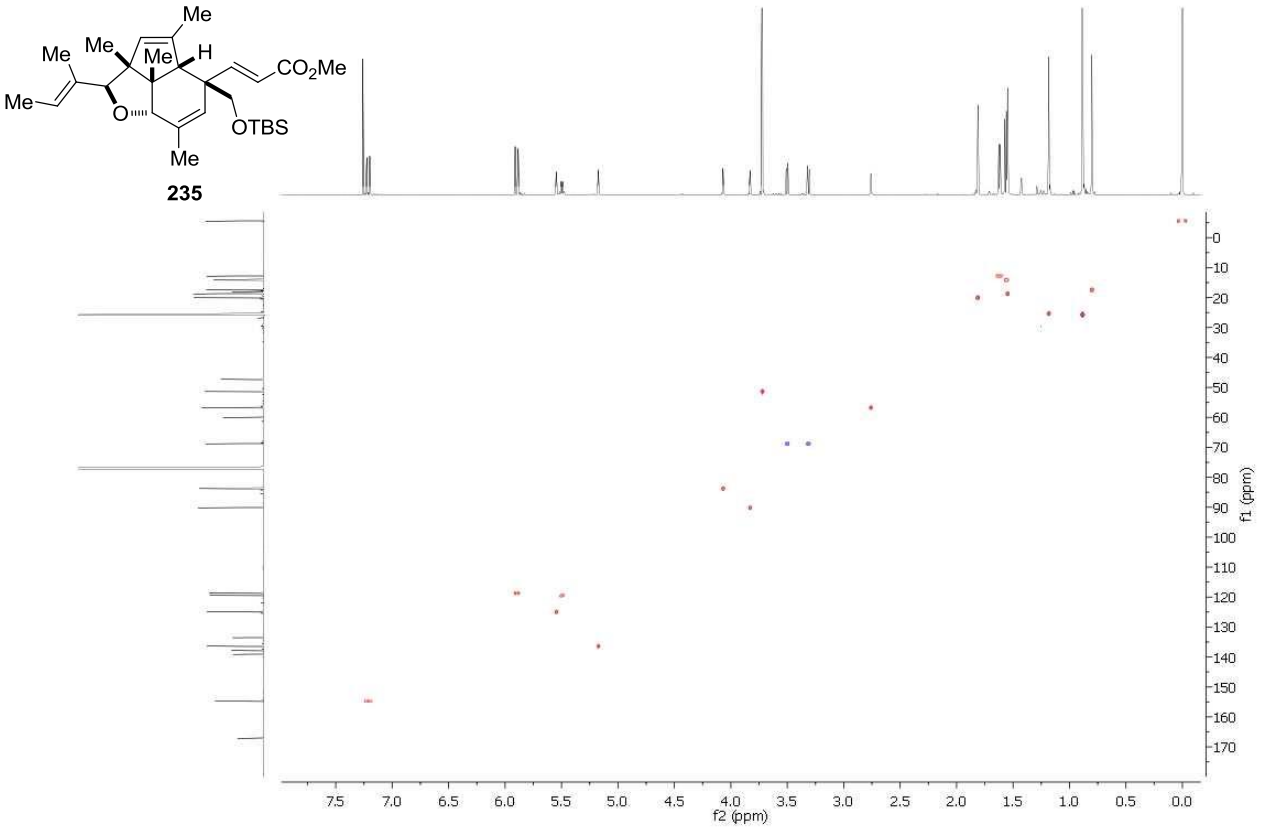
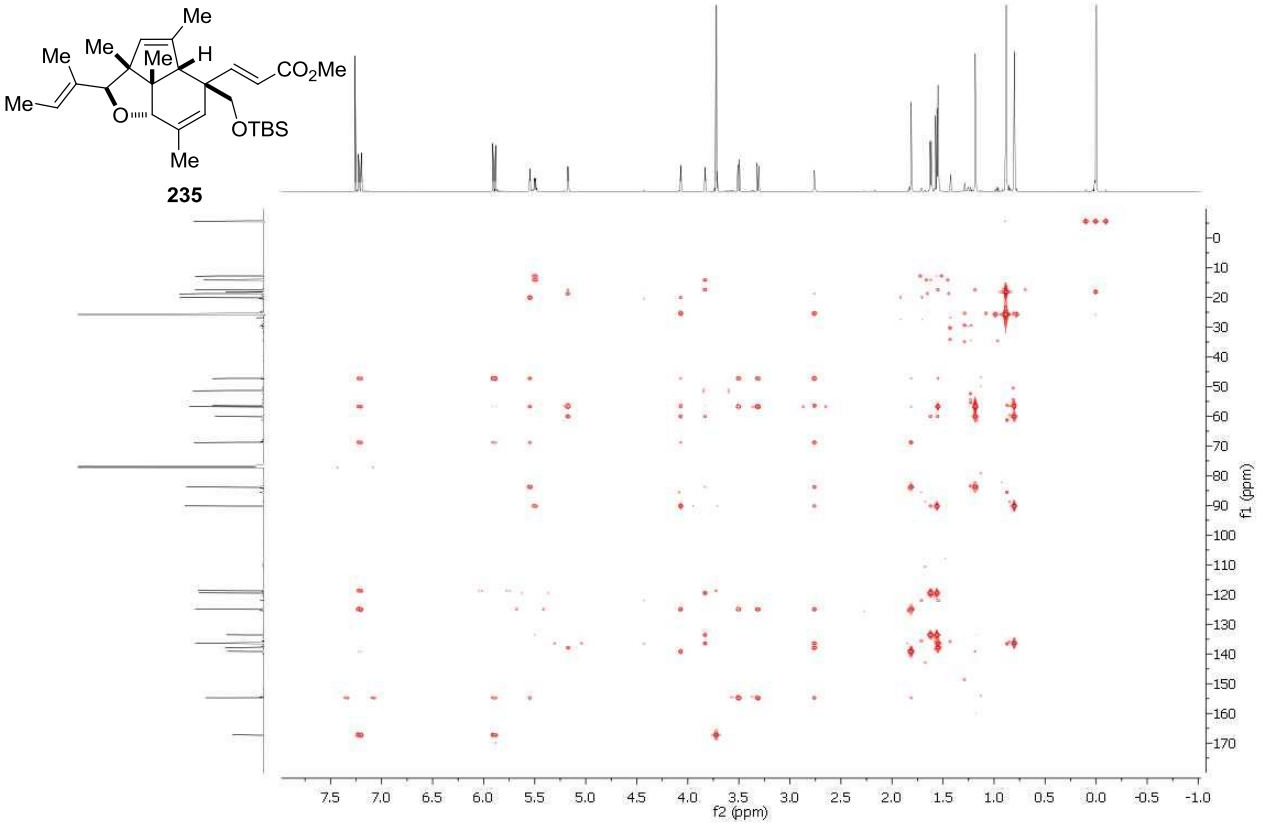
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2Me
Me
O
OTBS
Me
235
f2 (ppm)
f1 (ppm)


Me
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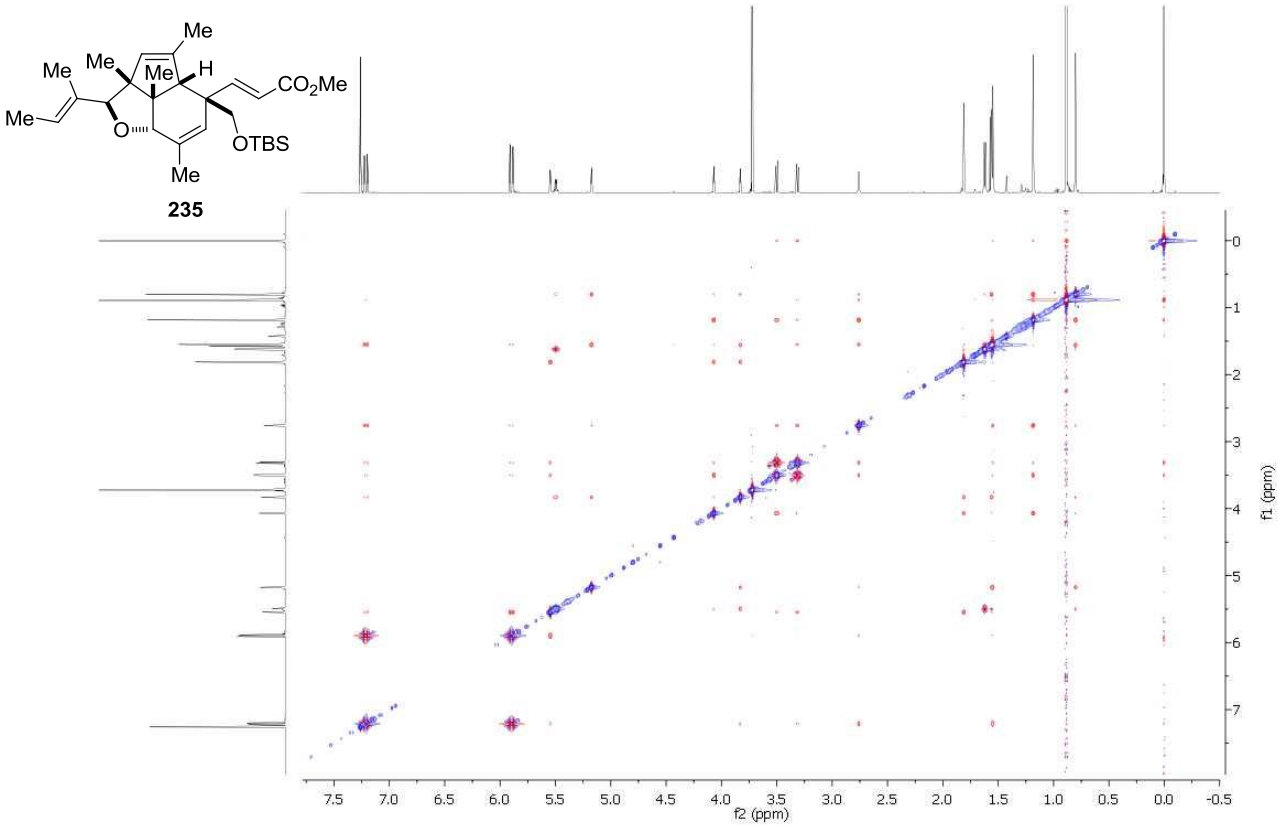
H
CO2Me
Me
O
OTBS
Me
235
f2 (ppm)
f1 (ppm)


Me
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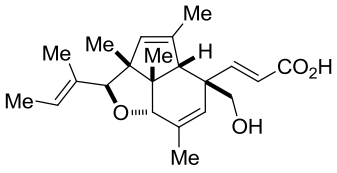
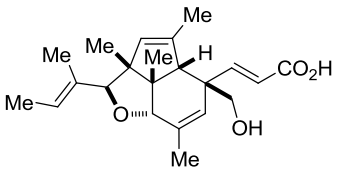
Me
Me
H
CO2Me
Me
O
OTBS
Me
235
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2H
Me
O
OH
Me

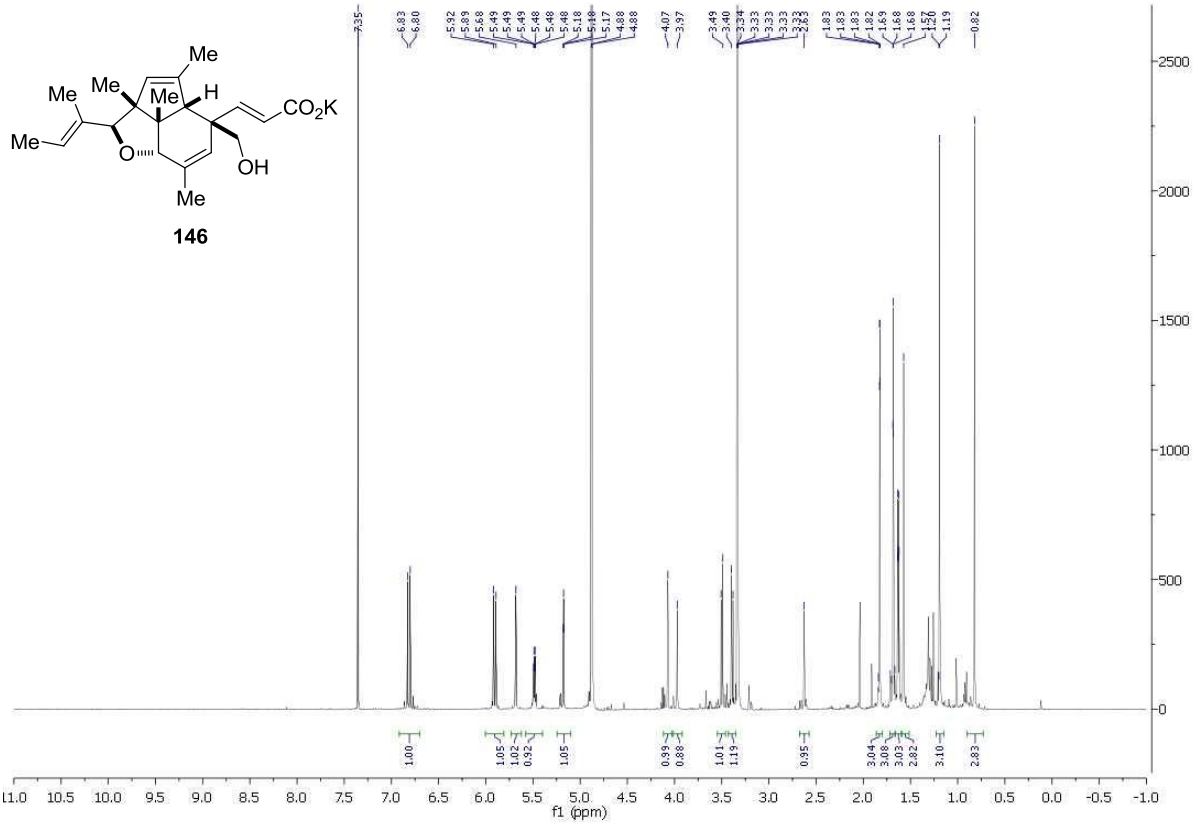
2

f1 (ppm)

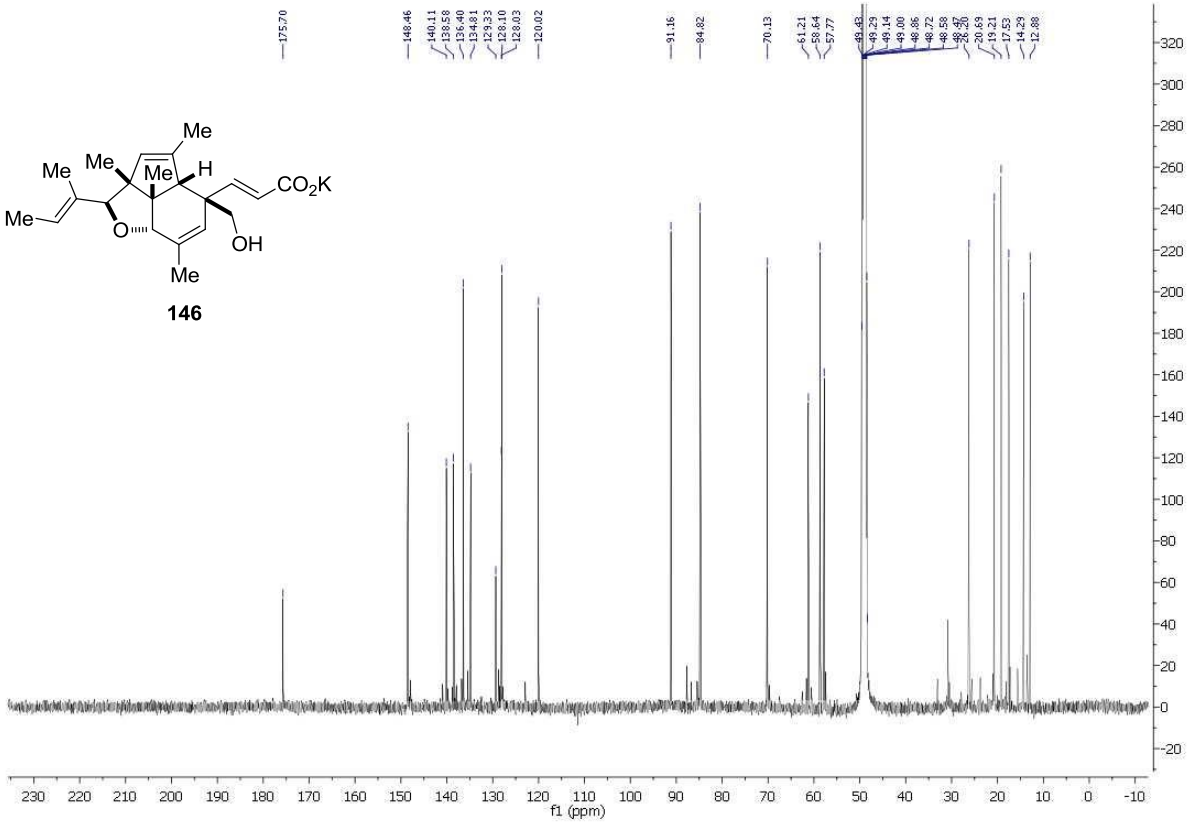

Me
Me
Me
Me
H
CO2H
Me
O
OH
Me

2

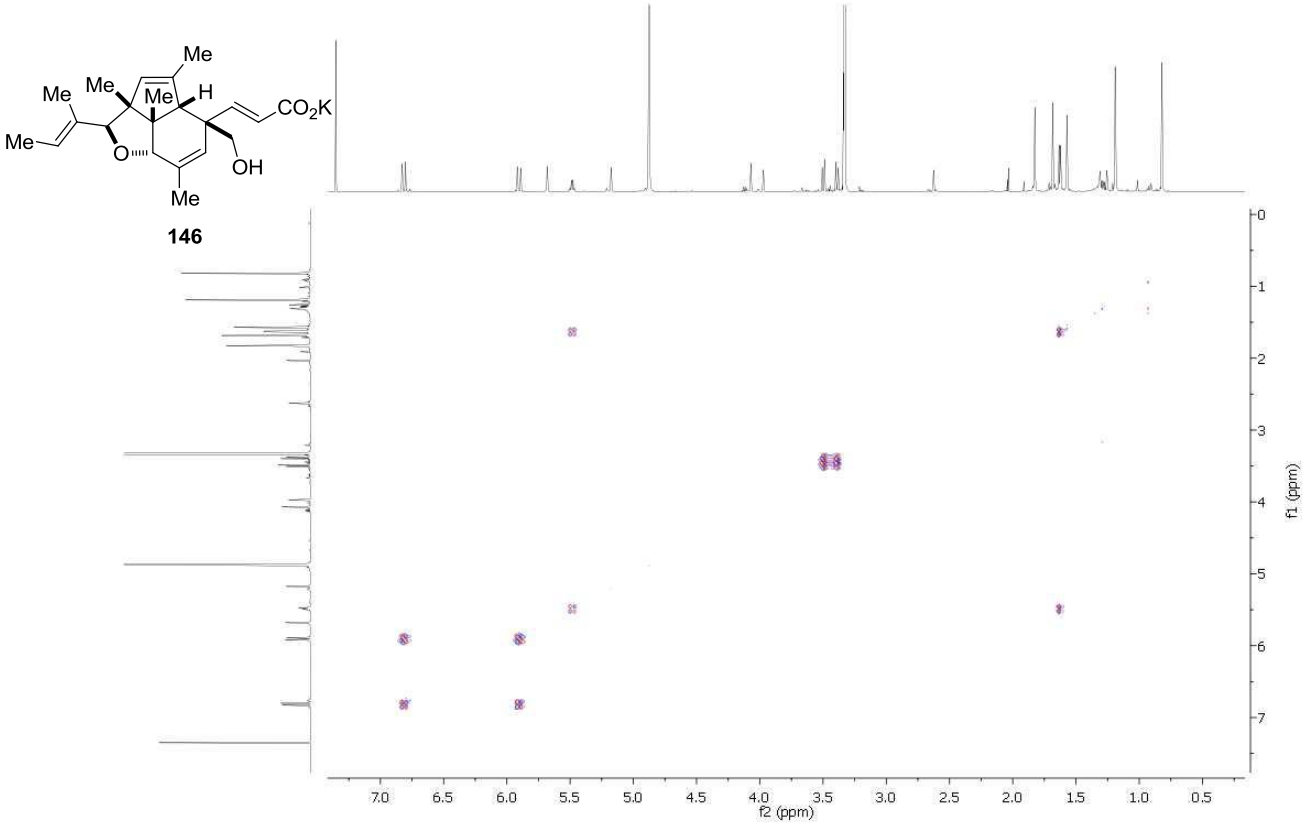
f1 (ppm)

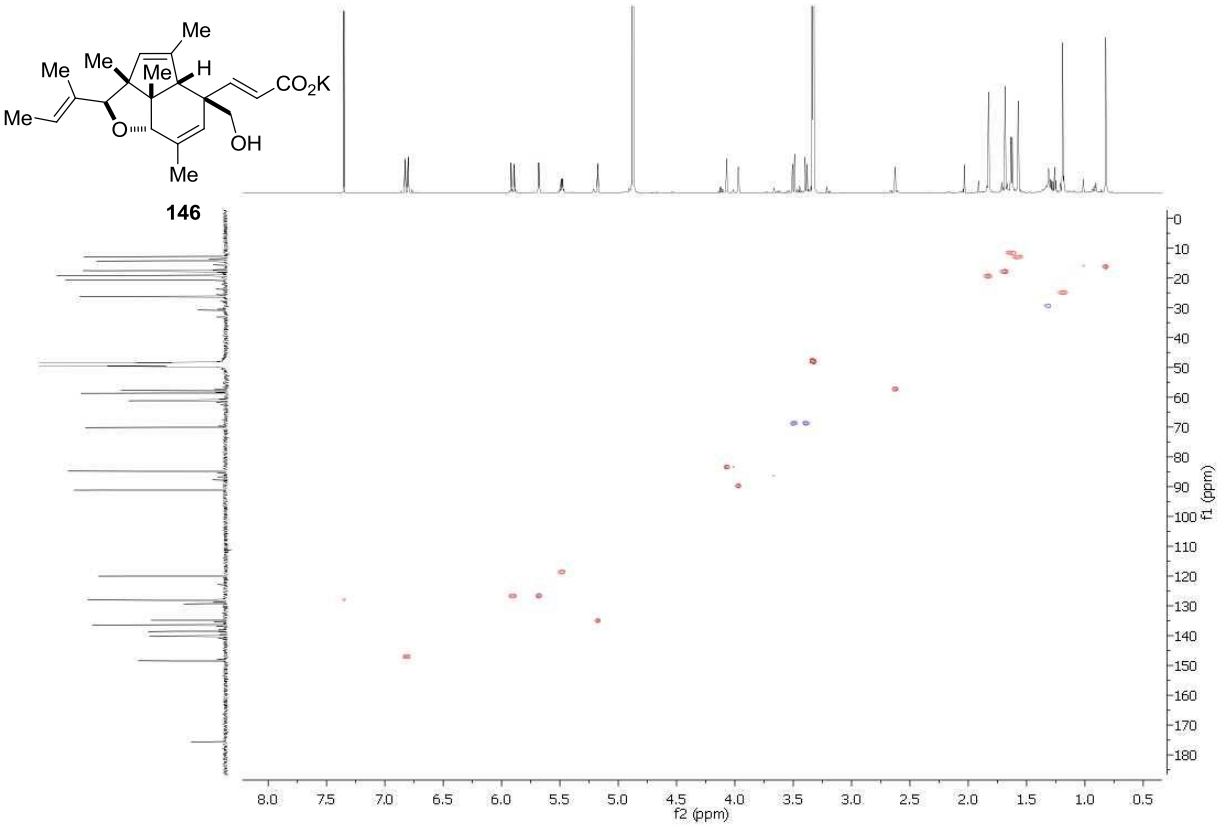

Me
Me
Me
H
Me
CO2K
Me
O
OH
Me
f1 (ppm)

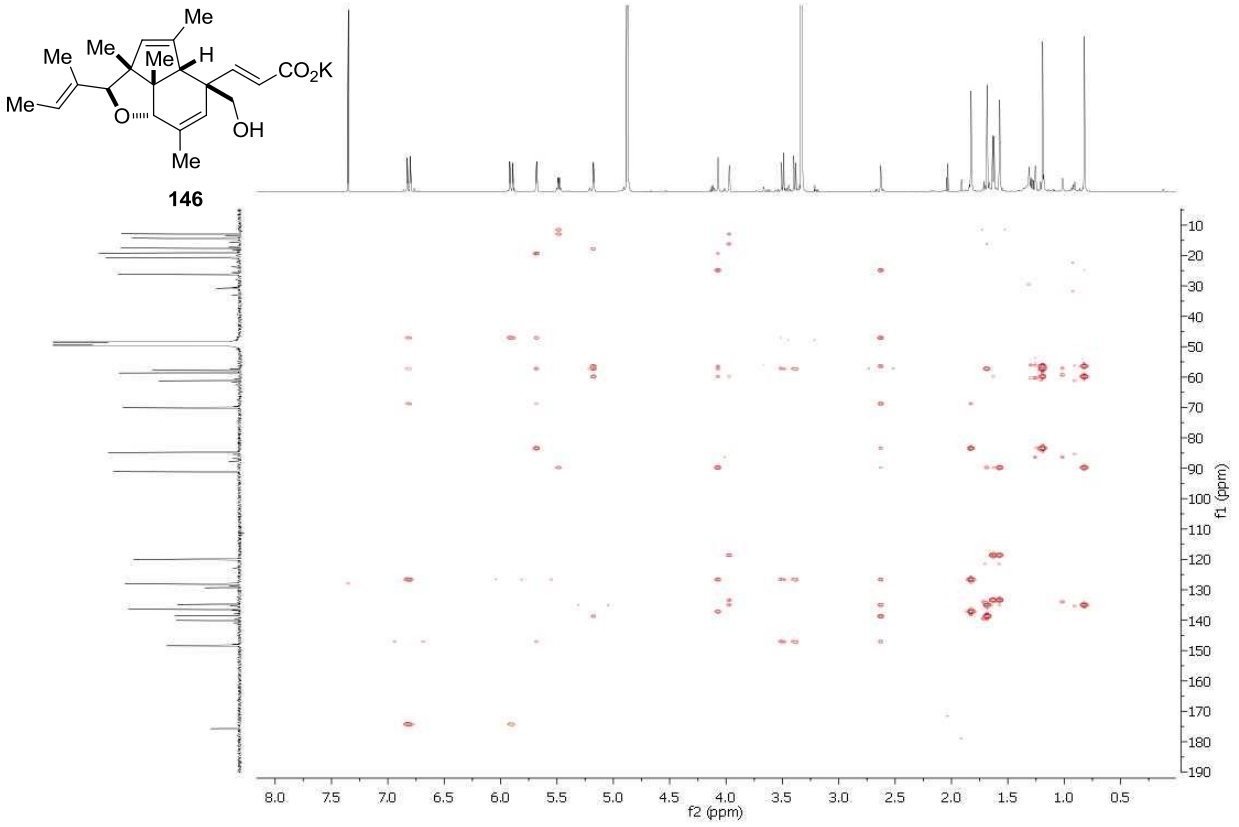
146


Me
Me
Me
H
Me
CO2K
Me
O
OH
Me
f1 (ppm)

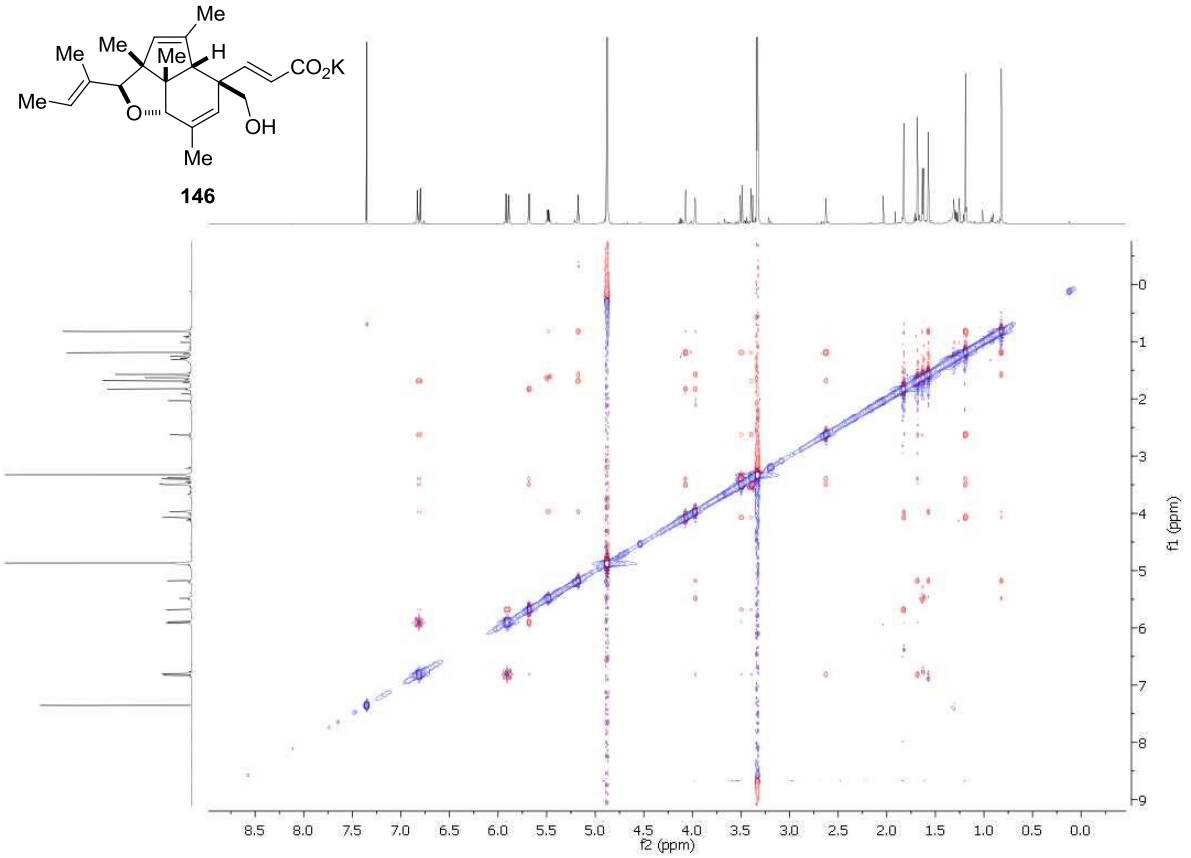
146


Me
Me
Me
Me
H
CO2K
Me
O
OH
Me
146
f2 (ppm)
f1 (ppm)

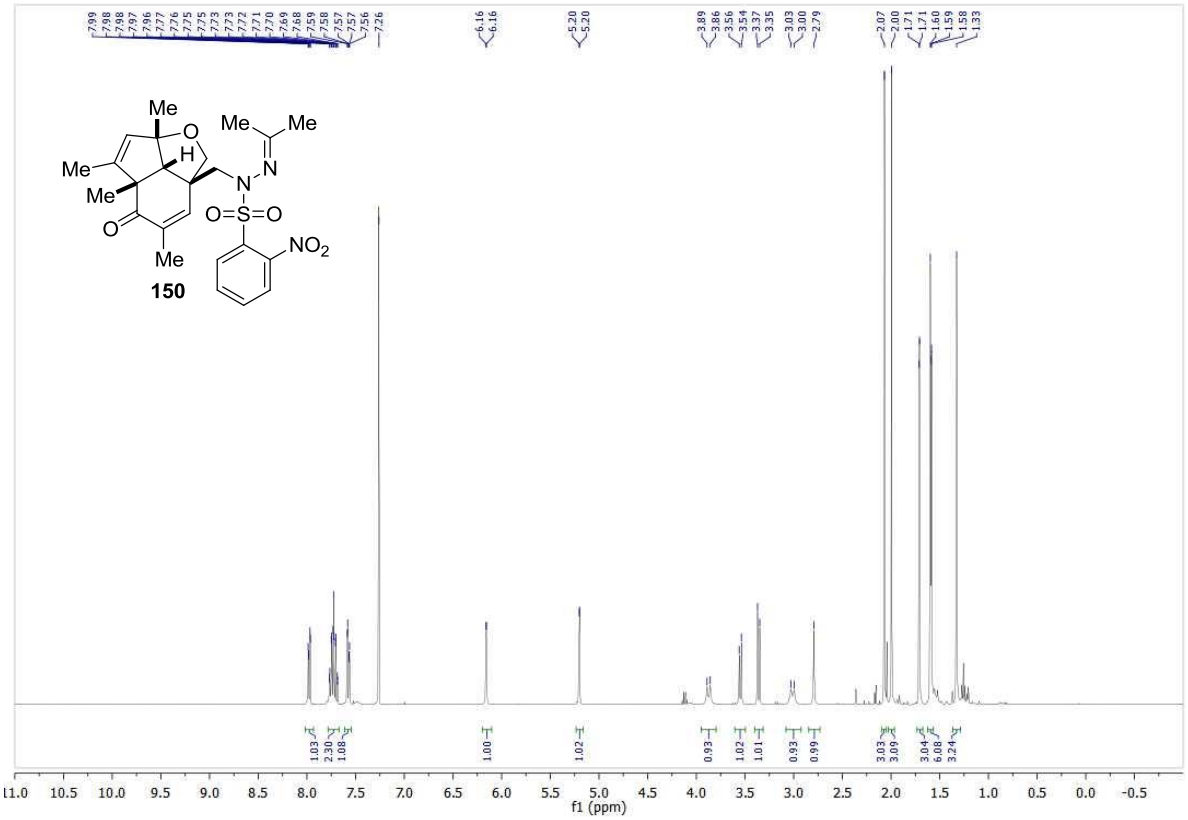

Me
Me
Me
Me
H
CO2K
Me
O
OH
Me
146
f2 (ppm)
f1 (ppm)

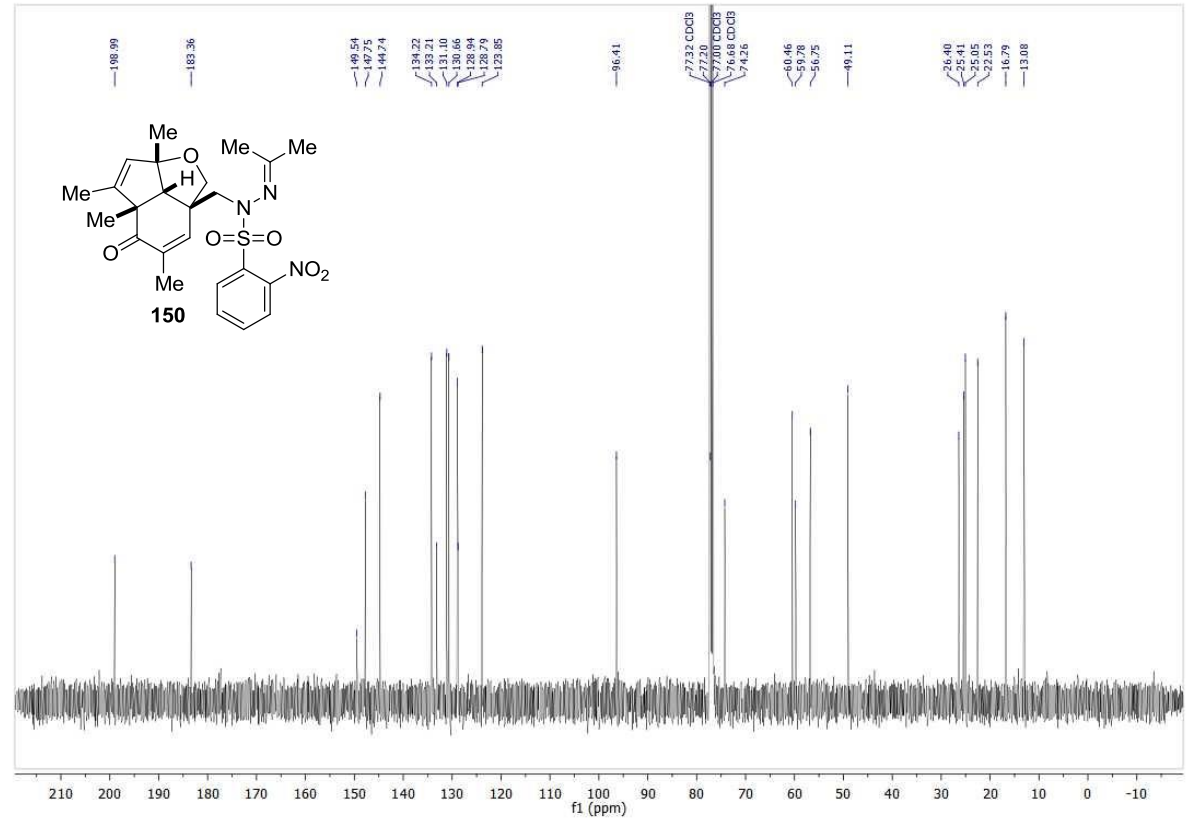

Me
Me
Me
Me
H
CO2K
Me
O
OH
Me
f2 (ppm)
f1 (ppm)

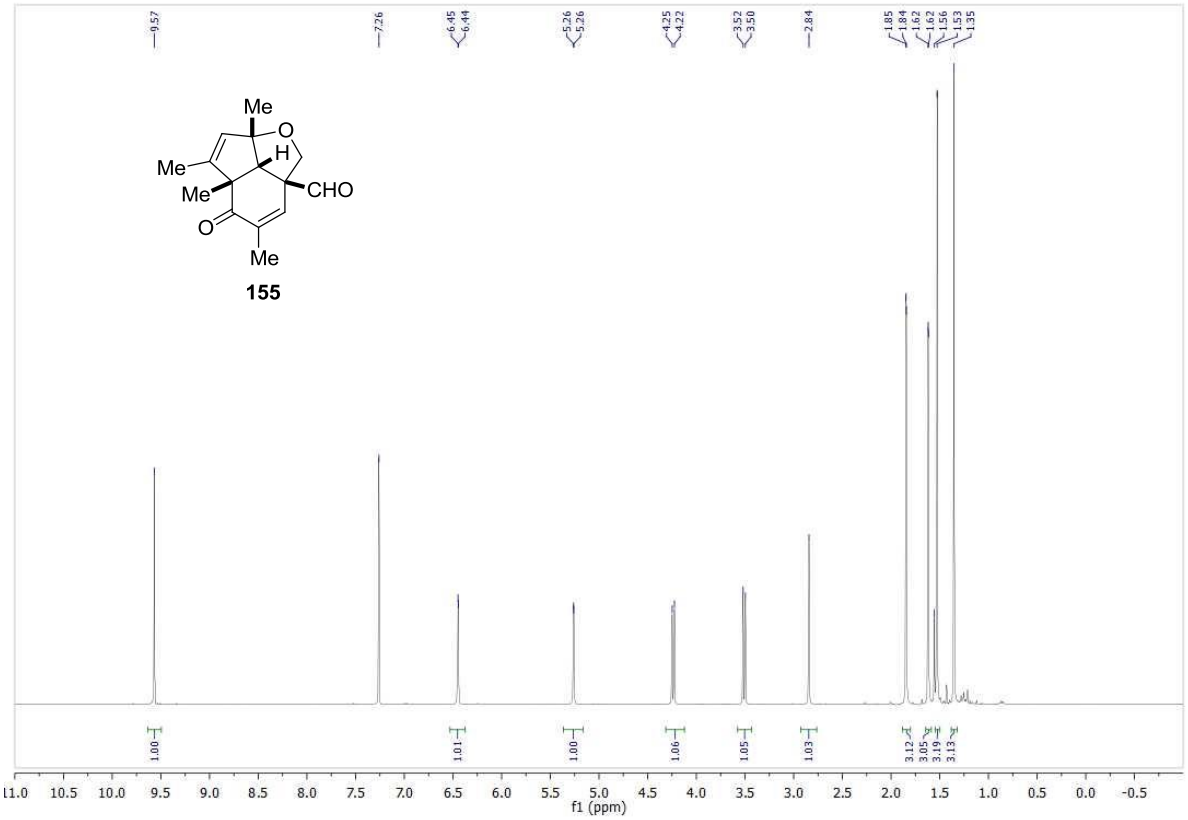
146

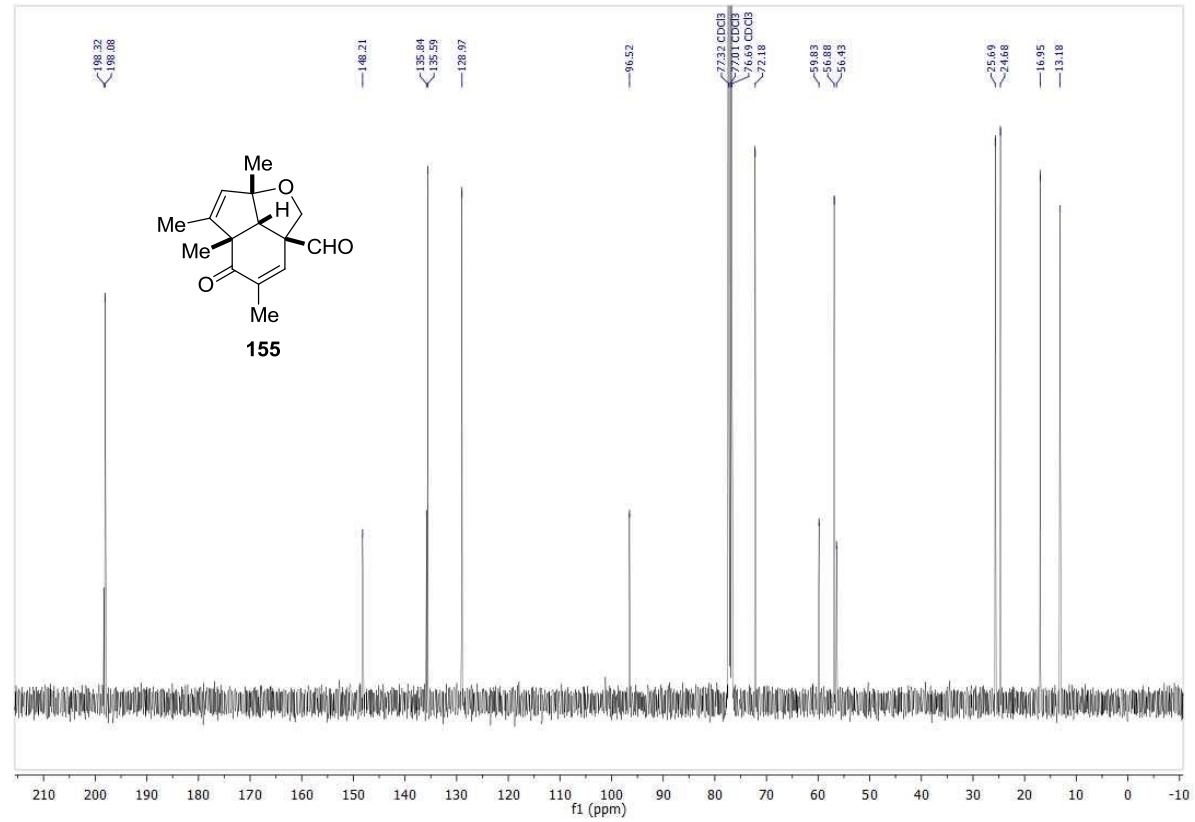

Me
Me
Me
Me
H
CO2K
Me
O
OH
Me
f2 (ppm)
f1 (ppm)

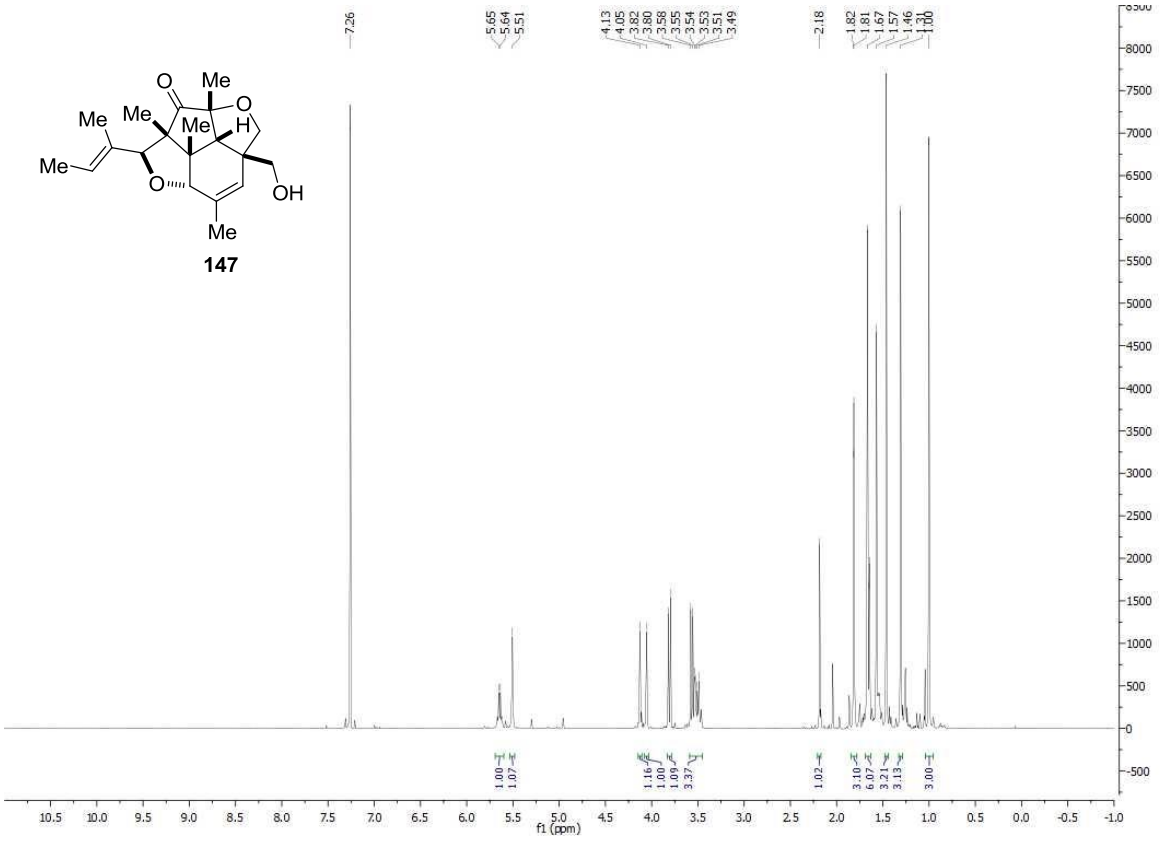
146


Me
O
H
Me
Me
Me
Me
N
N
O=S=O
O
Me
NO2
150
f1 (ppm)


Me
O
H
Me
Me
Me
Me
N
N
O=S=O
O
Me
NO2
150
f1 (ppm)

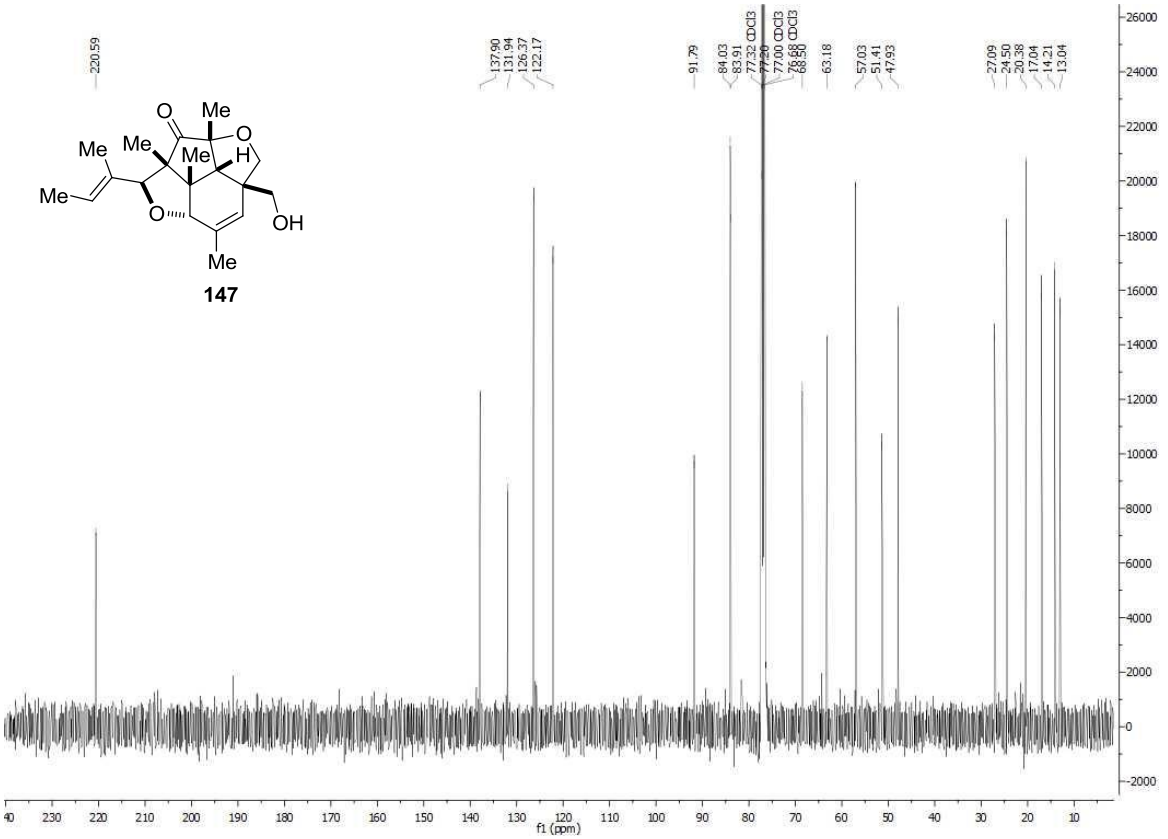

9.57
7.26
6.45
6.44
5.26
5.26
4.25
4.22
3.52
3.50
2.84
1.85
1.84
1.62
1.62
1.56
1.53
1.35
Me
O
H
Me
Me
CHO
O
Me
155
1.00
1.01
1.00
1.06
1.05
1.03
3.12
3.05
3.19
3.13
f1 (ppm)


198.32
198.08
148.21
135.84
135.59
128.97
96.52
77.32 CDCl3
77.01 CDCl3
76.69 CDCl3
72.18
59.83
56.88
56.43
25.69
24.68
16.95
13.18
Me
O
H
Me
Me
CHO
O
Me
155
f1 (ppm)


7.26
5.65
5.64
5.51
4.13
4.05
3.82
3.80
3.58
3.55
3.54
3.53
3.51
3.49
2.18
1.82
1.81
1.67
1.57
1.46
1.31
1.00
1.00
1.07
1.16
1.00
1.09
3.37
1.02
3.10
6.07
3.21
3.13
3.00
f1 (ppm)

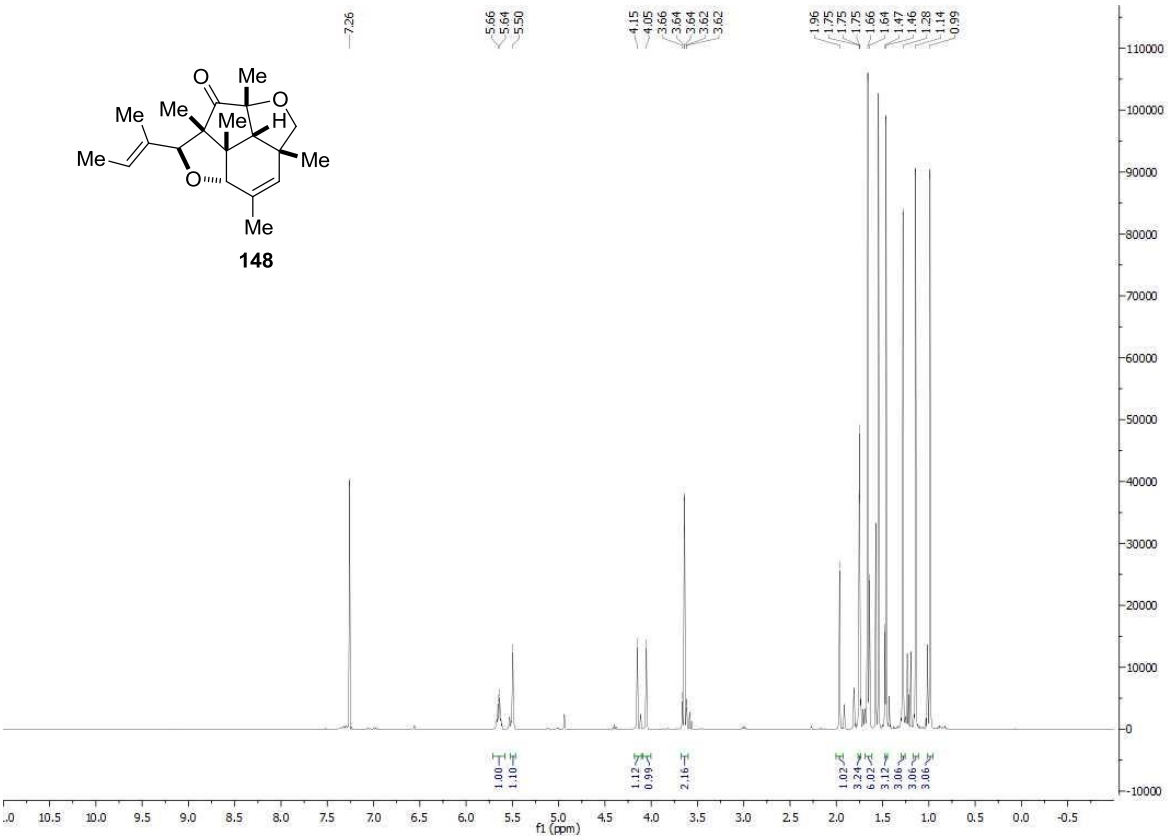
O
Me
Me
Me
Me
O
H
Me
O
OH
Me

147

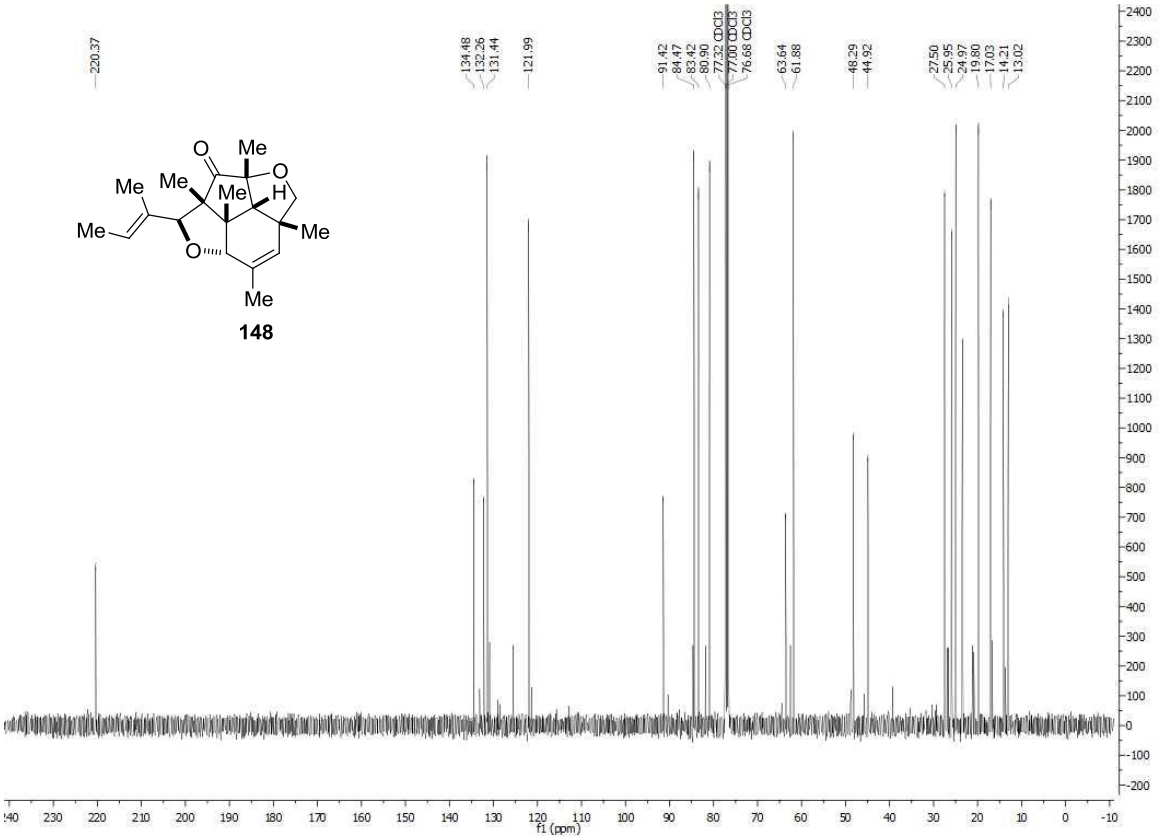

220.59
137.90
131.94
126.37
122.17
91.79
84.03
83.91
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
68.50
63.18
57.03
51.41
47.93
27.09
24.50
20.38
17.04
14.21
13.04
f1 (ppm)

O
Me
Me
Me
Me
O
H
Me
O
OH
Me

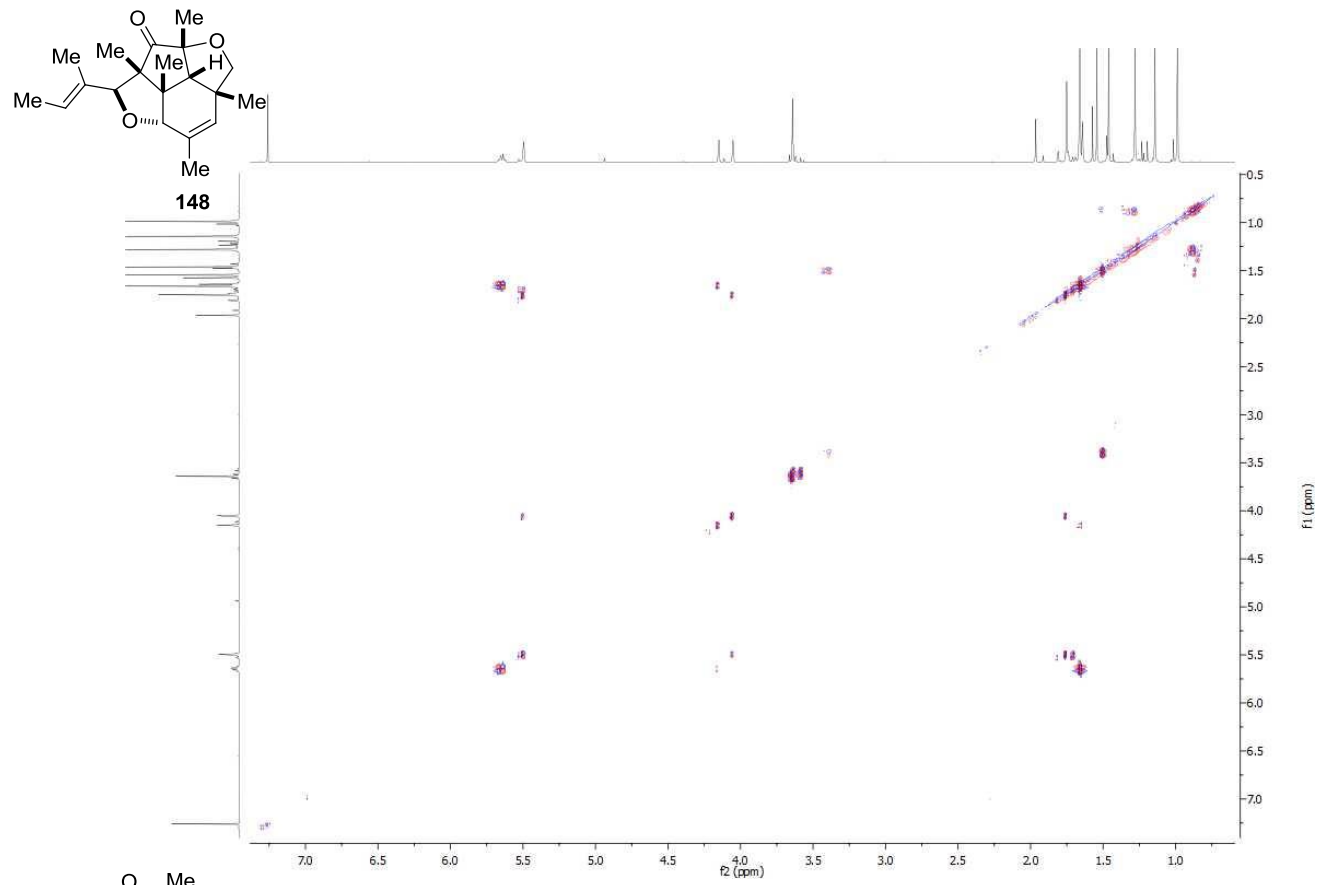
147

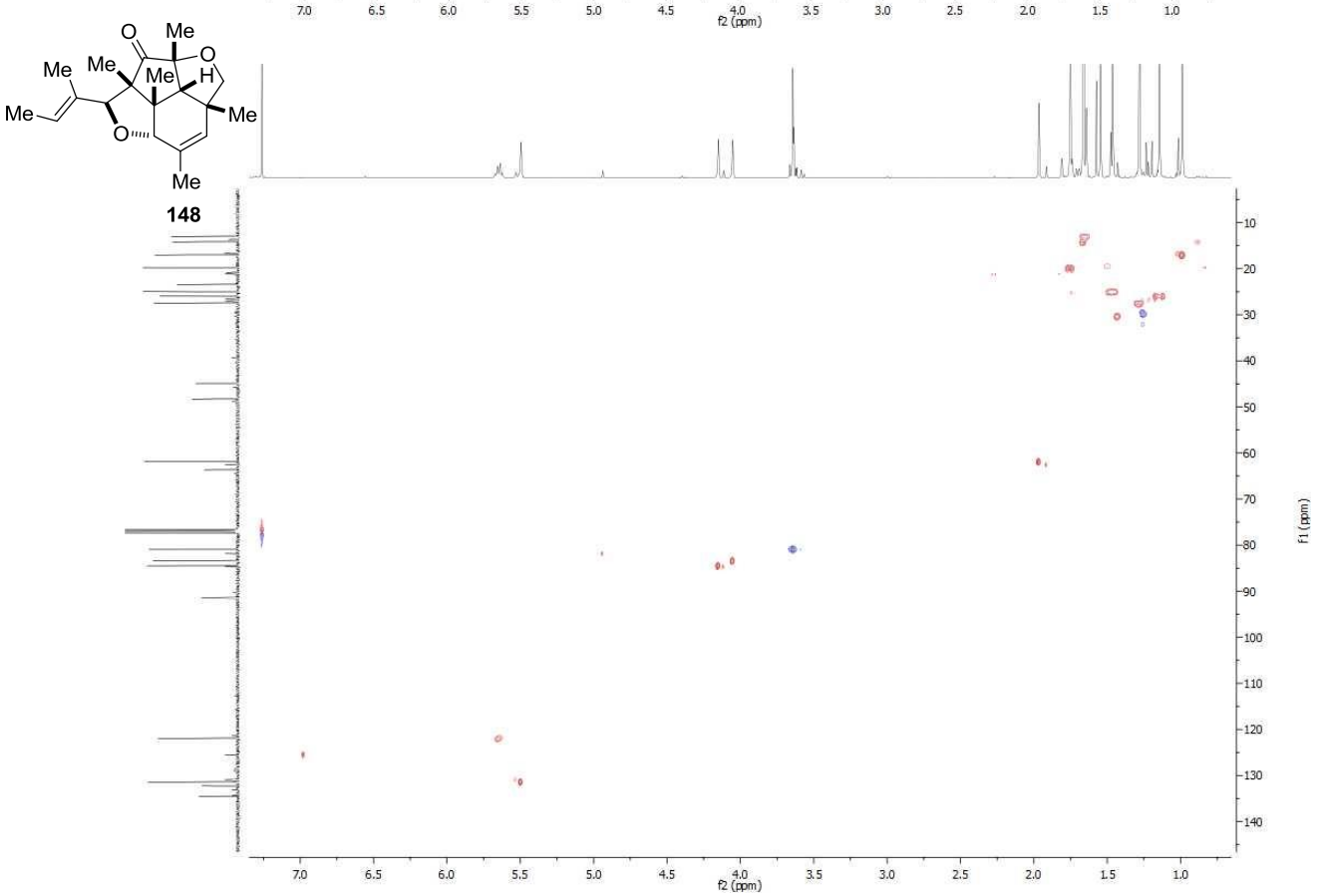

7.26
5.66
5.64
5.50
4.15
4.05
3.66
3.64
3.64
3.62
3.62
1.96
1.75
1.75
1.75
1.66
1.64
1.47
1.46
1.28
1.14
0.99
1.00
1.10
1.12
0.99
2.16
1.02
3.24
6.02
3.12
3.06
3.06
3.06
f1 (ppm)

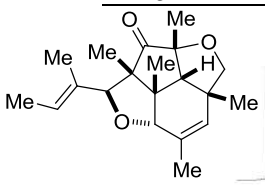
148


220.37
134.48
132.26
131.44
121.99
91.42
84.47
83.42
80.90
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
63.64
61.88
48.29
44.92
27.50
25.95
24.97
19.80
17.03
14.21
13.02
f1 (ppm)

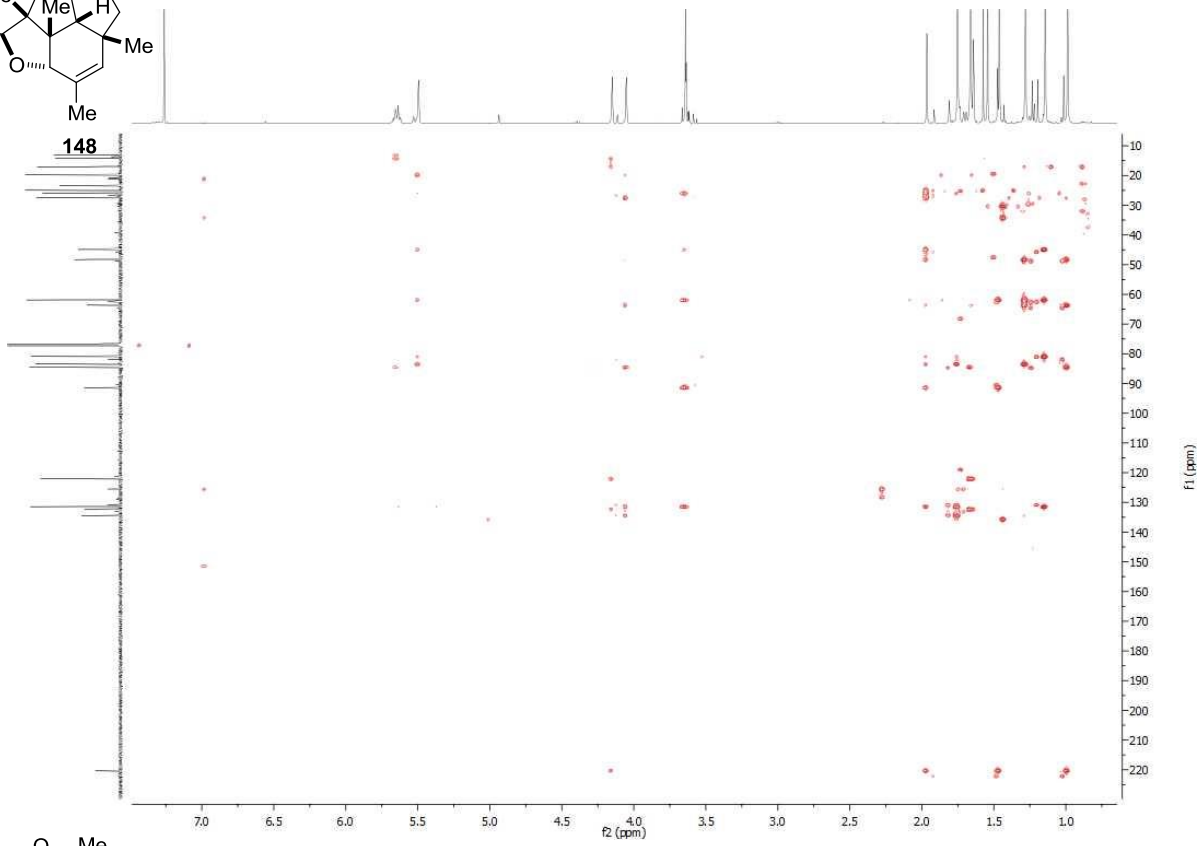
148

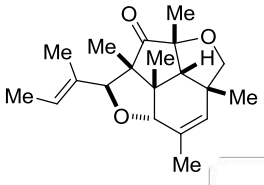

148
f2 (ppm)
f1 (ppm)


148
f2 (ppm)
f1 (ppm)


O
Me
Me
Me
Me
O
Me
H
Me
O
Me

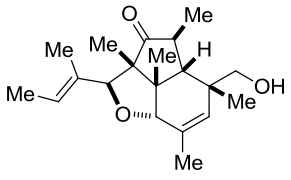
148


f2 (ppm)
f1 (ppm)


O
Me
Me
Me
Me
O
Me
H
Me
O
Me

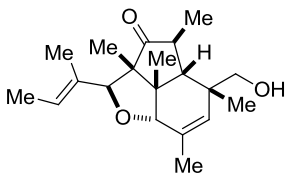
148

f2 (ppm)
f1 (ppm)


O
Me
Me
Me
Me
H
Me
OH
Me
O
Me

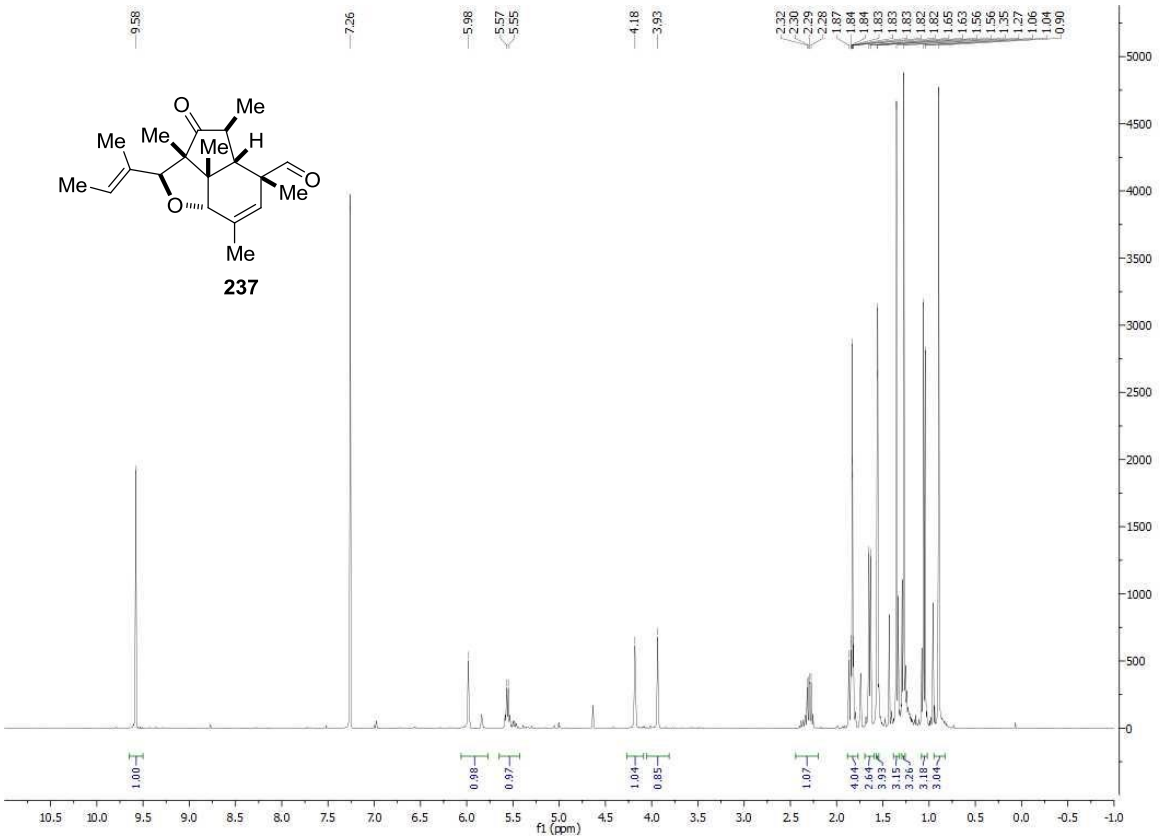
236

7.26
5.57
5.55
5.40
4.15
4.02
3.56
3.55
3.52
3.50
2.41
2.39
2.38
2.37
1.76
1.76
1.76
1.68
1.66
1.65
1.63
1.58
1.56
1.29
1.22
1.20
1.18
0.89
f1 (ppm)


O
Me
Me
Me
Me
H
Me
OH
Me
O
Me

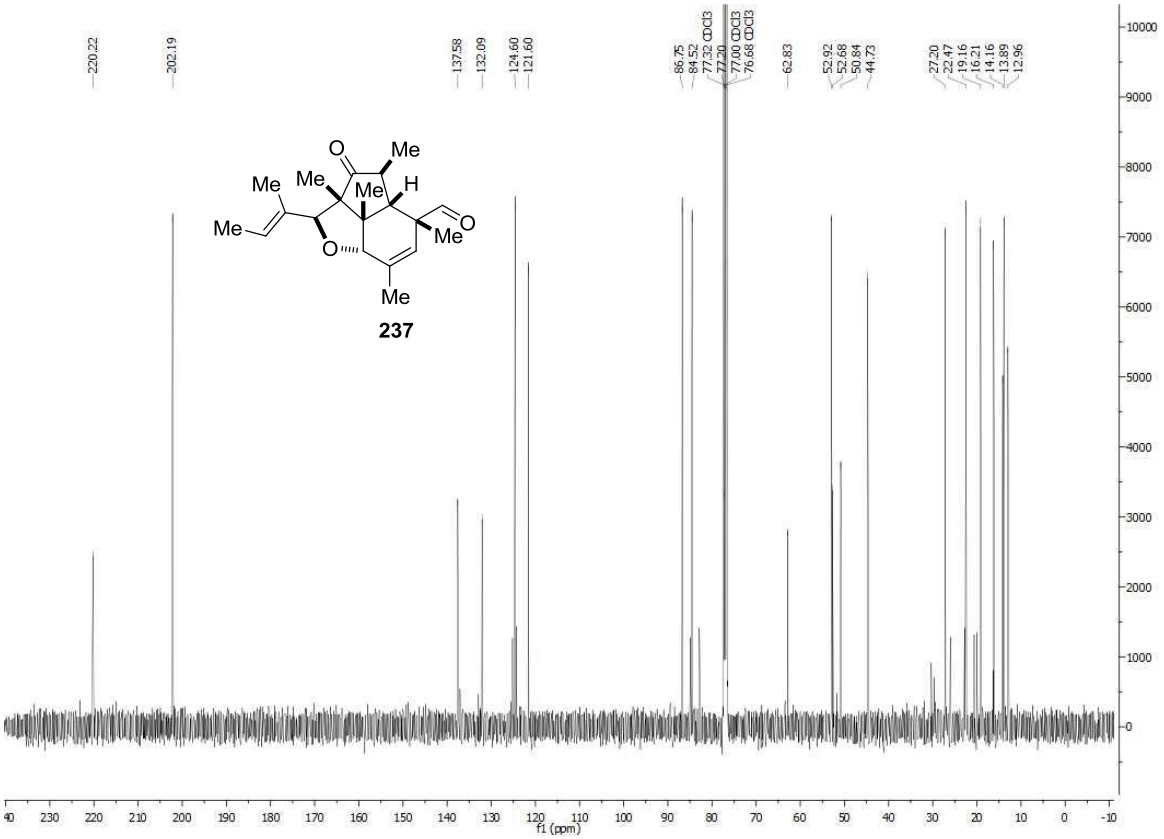
236

222.37
136.35
132.56
129.56
121.30
86.59
84.61
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
70.11
63.21
53.36
53.00
45.13
40.88
26.98
25.58
19.17
17.56
14.30
14.26
12.98
f1 (ppm)


9.58
7.26
5.98
5.57
5.55
4.18
3.93
2.32
2.30
2.29
2.28
1.87
1.84
1.84
1.84
1.83
1.83
1.83
1.82
1.82
1.65
1.63
1.56
1.56
1.35
1.27
1.06
1.04
0.90
1.00
0.98
0.97
1.04
0.85
1.07
4.04
2.64
3.93
3.15
3.26
3.18
3.04
f1 (ppm)

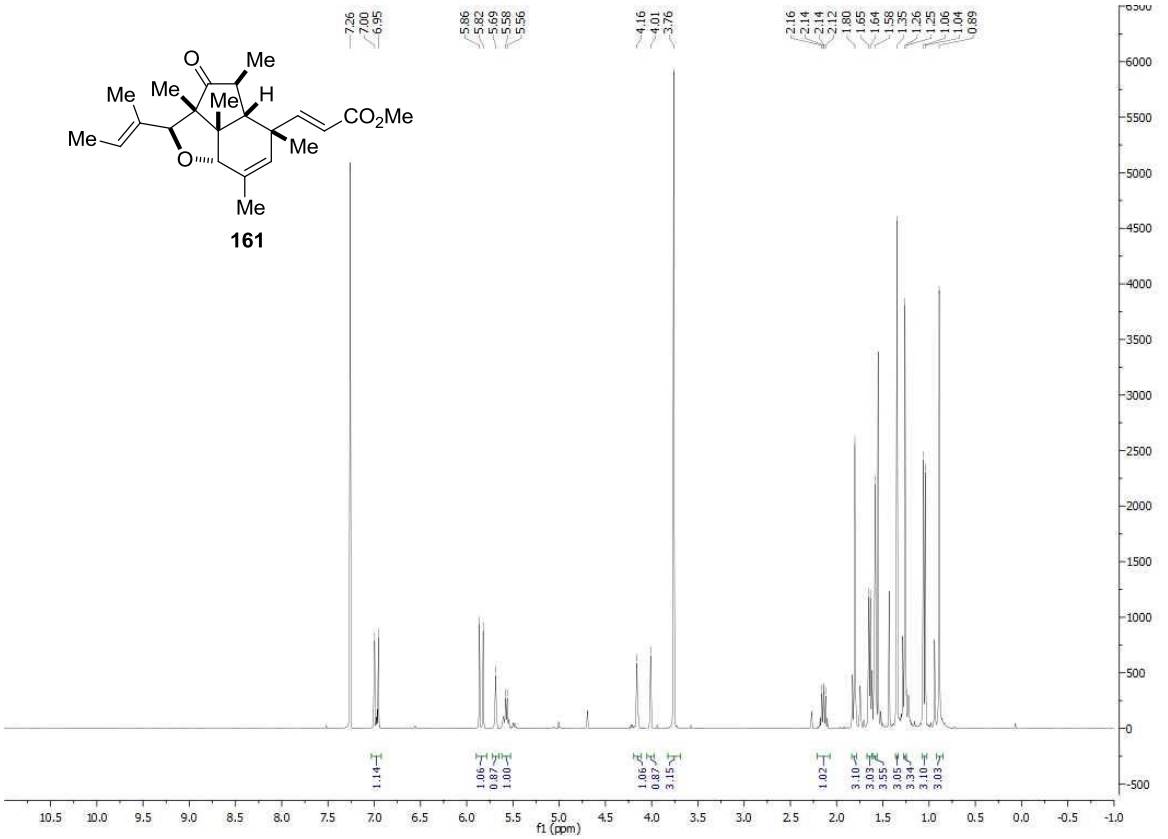
O
Me
Me
Me
Me
H
Me
O
Me
O
Me

237

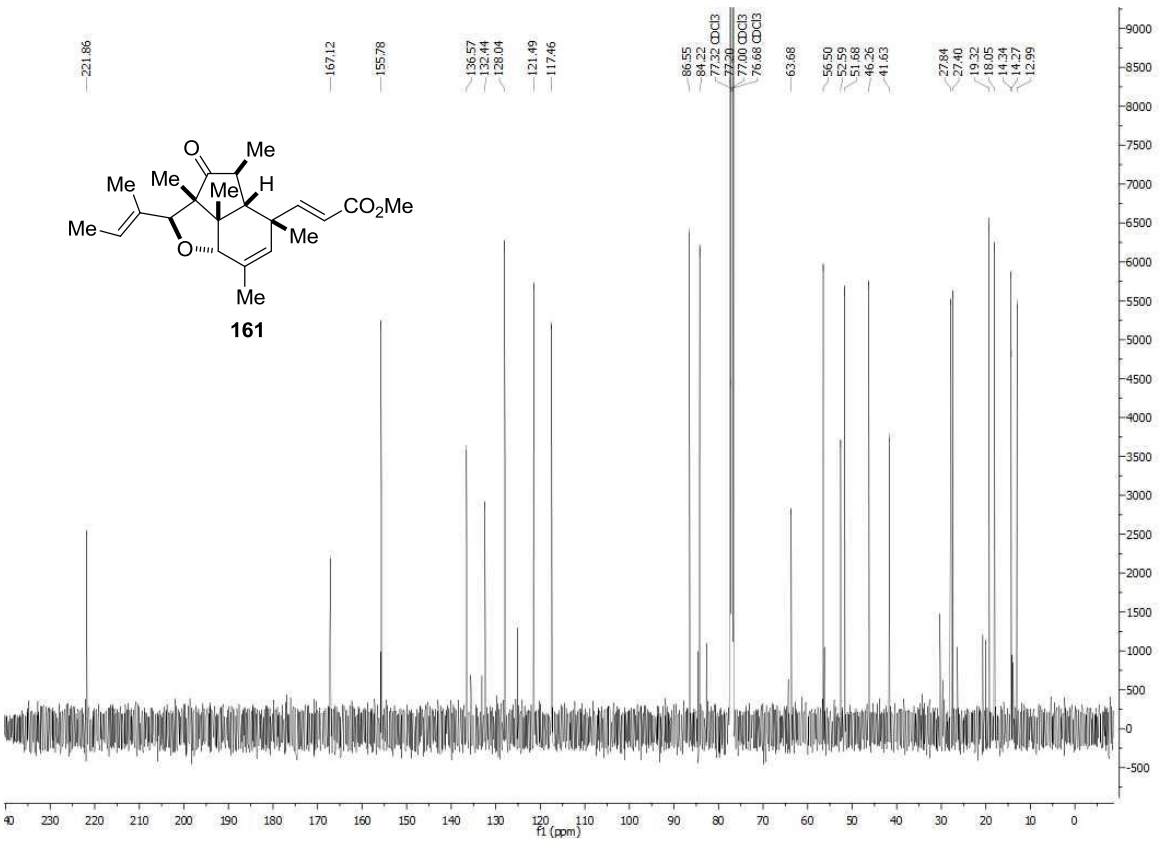

220.22
202.19
137.58
132.09
124.60
121.60
86.75
84.52
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
62.83
52.92
52.68
50.84
44.73
27.20
22.47
19.16
16.21
14.16
13.89
12.96
f1 (ppm)

O
Me
Me
Me
Me
H
Me
O
Me
O
Me

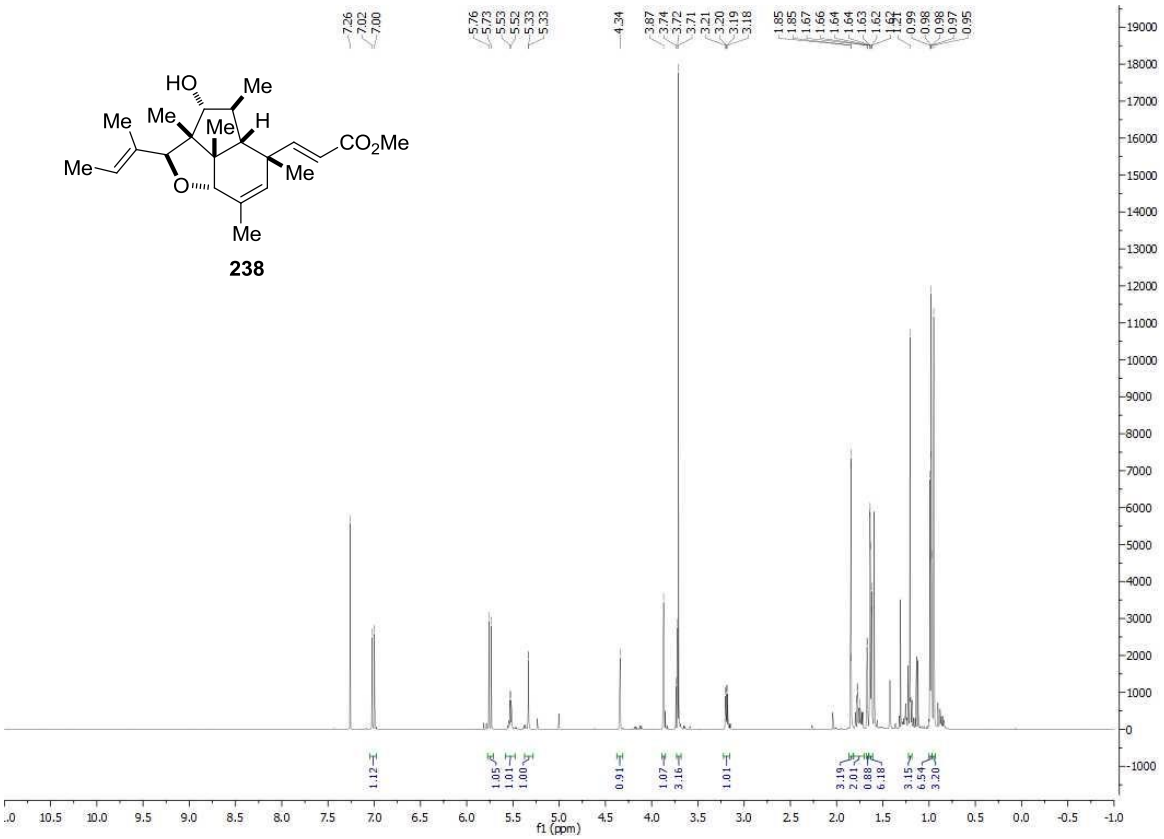
237

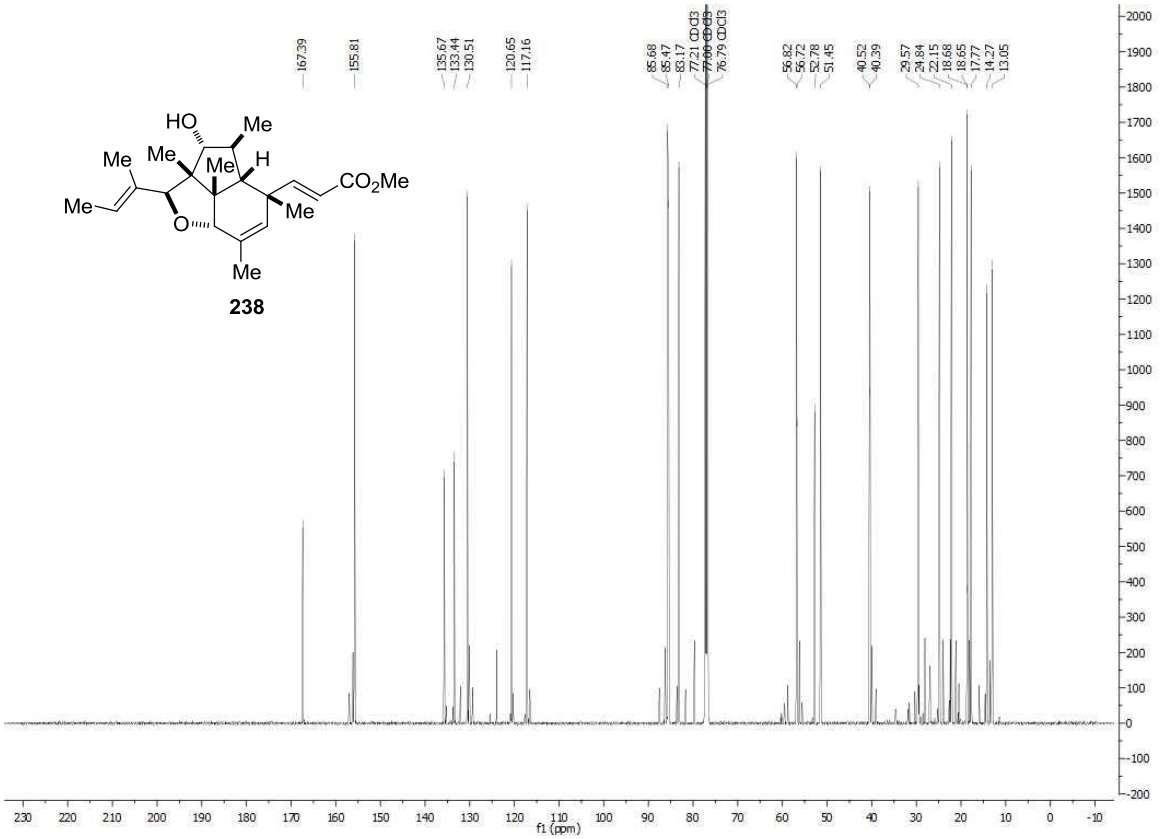

Me
Me
Me
Me
O
Me
H
CO2Me
Me
Me
O
Me
161

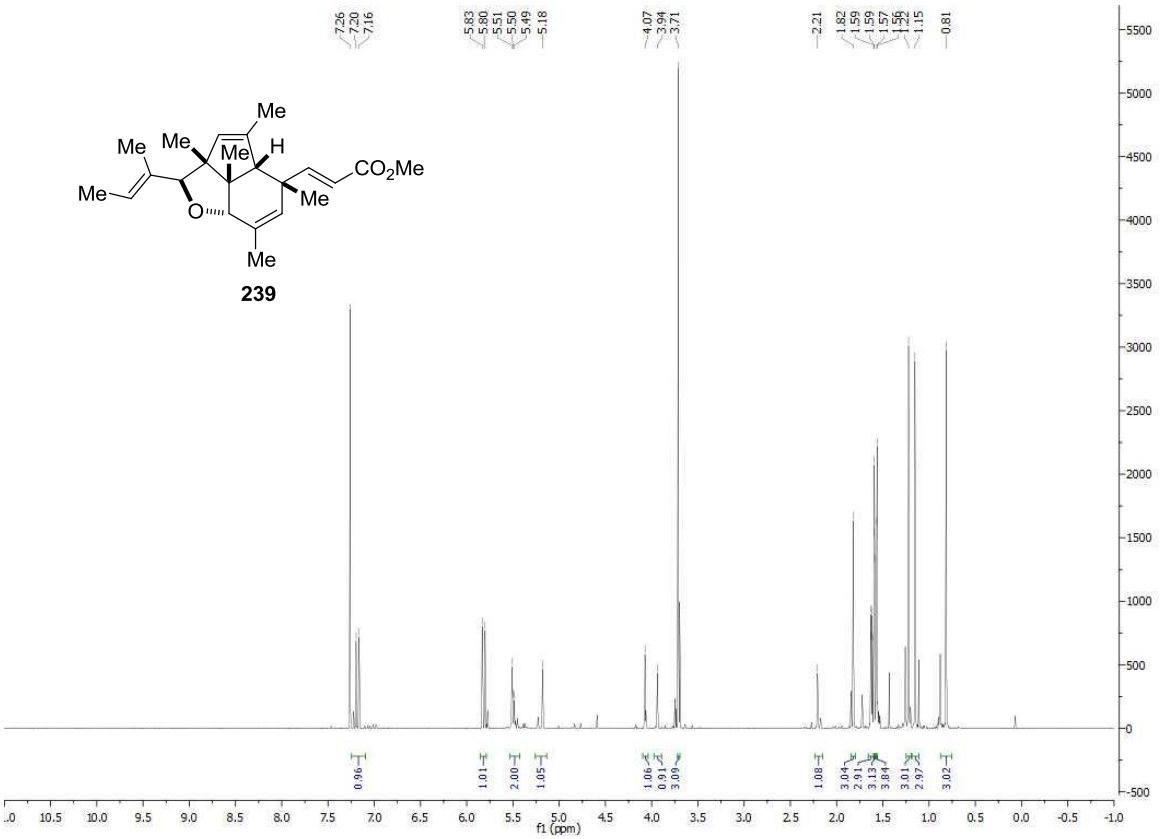
7.26
7.00
6.95
5.86
5.82
5.69
5.58
5.56
4.16
4.01
3.76
2.16
2.14
2.14
2.12
1.80
1.65
1.64
1.58
1.35
1.26
1.25
1.06
1.04
0.89
1.14
1.06
0.87
1.00
1.06
0.87
3.15
1.02
3.10
3.03
3.55
3.04
3.10
3.03
f1 (ppm)


Me
Me
Me
Me
O
Me
H
CO2Me
Me
Me
O
Me
161

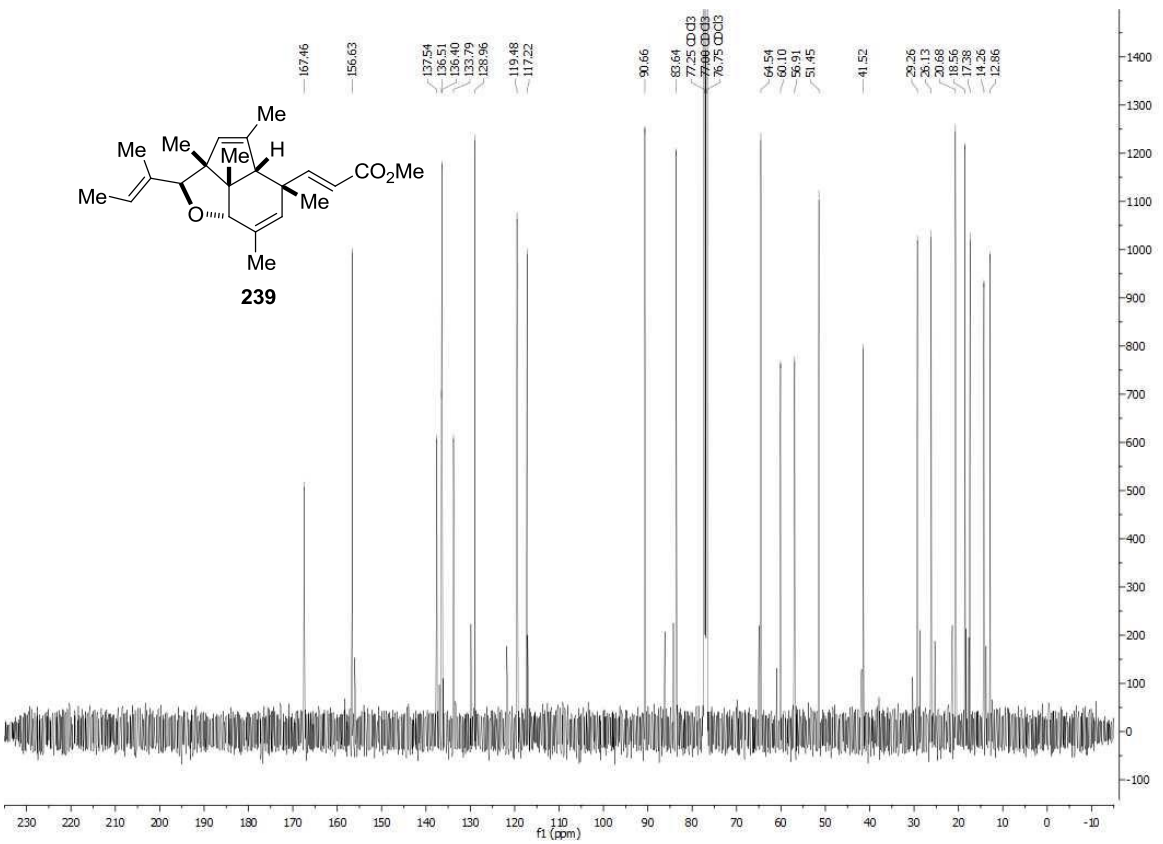
221.86
167.12
155.78
136.57
132.44
128.04
121.49
117.46
86.55
84.22
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
63.68
56.50
52.59
51.68
46.26
41.63
27.84
27.40
19.32
18.05
14.34
14.27
12.99
f1 (ppm)


HO
Me
Me
Me
Me
H
Me
CO2Me
Me
O
Me
238
7.26
7.02
7.00
5.76
5.73
5.53
5.52
5.33
5.33
4.34
3.87
3.74
3.72
3.71
3.21
3.20
3.19
3.18
1.85
1.85
1.67
1.66
1.64
1.64
1.63
1.62
1.61
0.99
0.98
0.98
0.97
0.95
1.12
1.05
1.01
1.00
0.91
1.07
3.16
1.01
3.19
2.01
0.88
6.18
3.15
6.54
3.20
f1 (ppm)

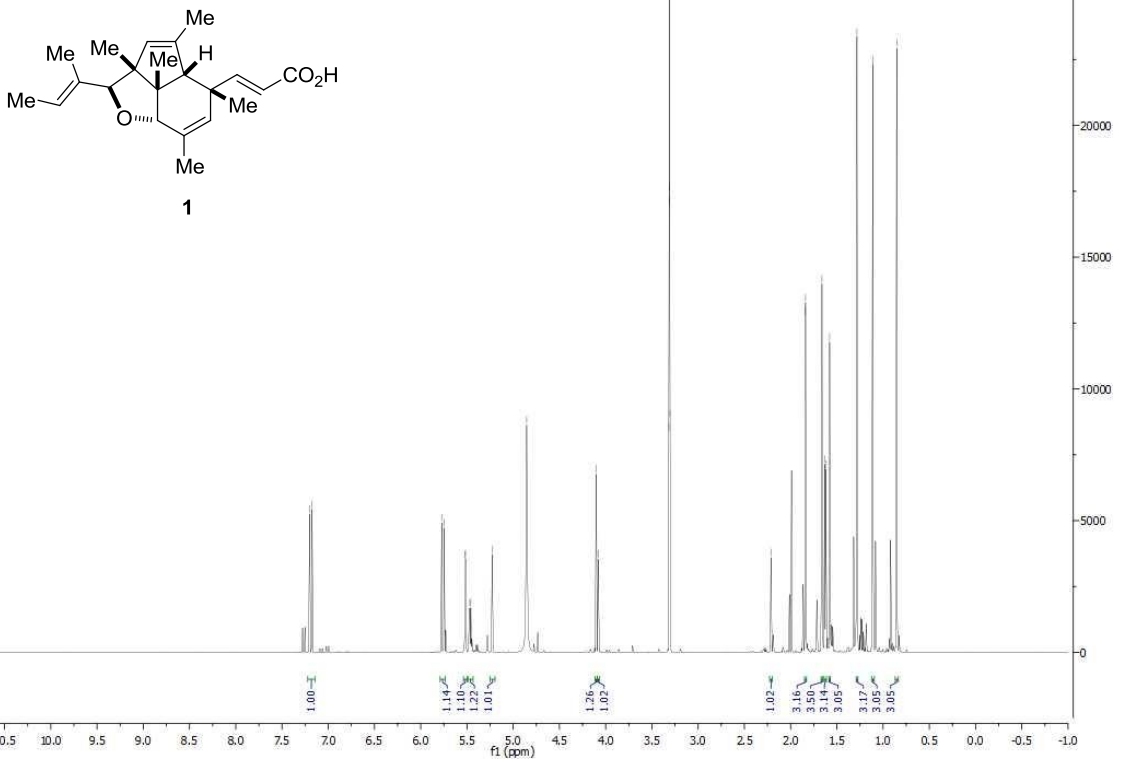

HO
Me
Me
Me
Me
H
Me
CO2Me
Me
O
Me
238
167.39
155.81
135.67
133.44
130.51
120.65
117.16
85.68
85.47
83.17
77.21 CDCl3
77.00 CDCl3
76.79 CDCl3
56.82
56.72
52.78
51.45
40.52
40.39
29.57
24.84
22.15
18.68
18.65
17.77
14.27
13.05
f1 (ppm)

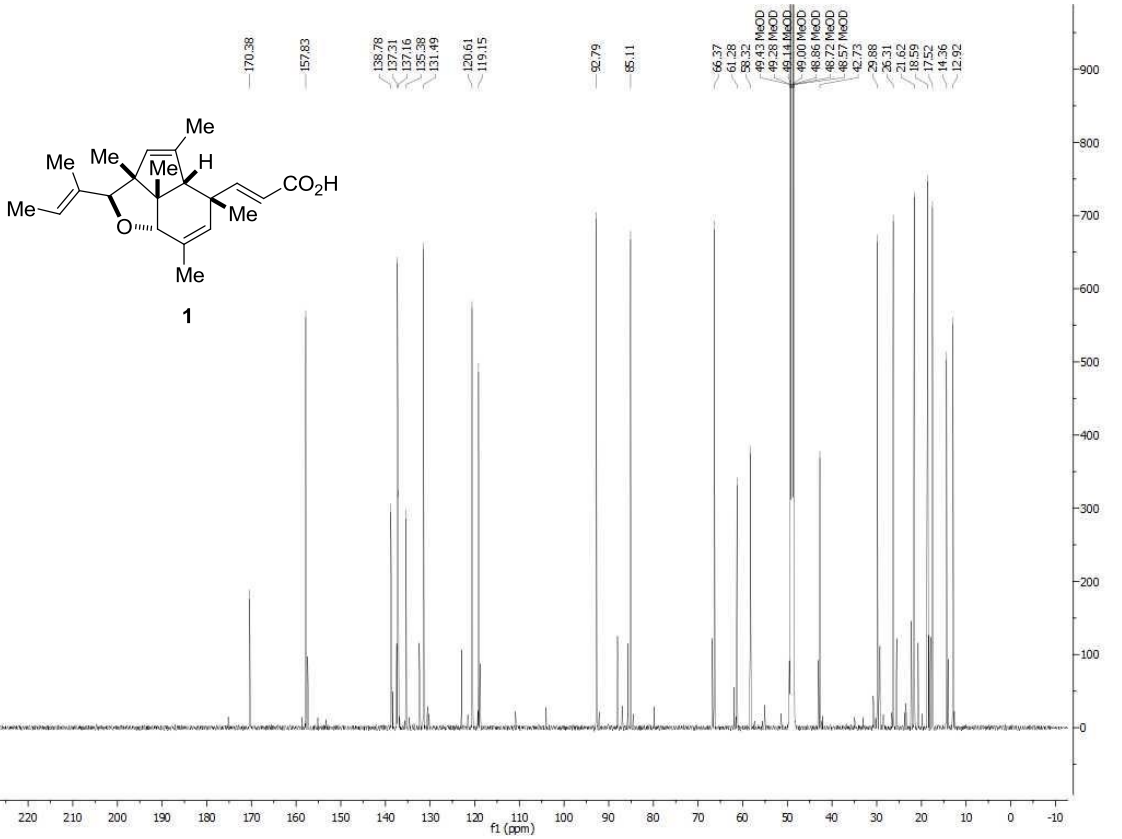

Me
Me
Me
Me
H
Me
CO2Me
Me
O
Me
239

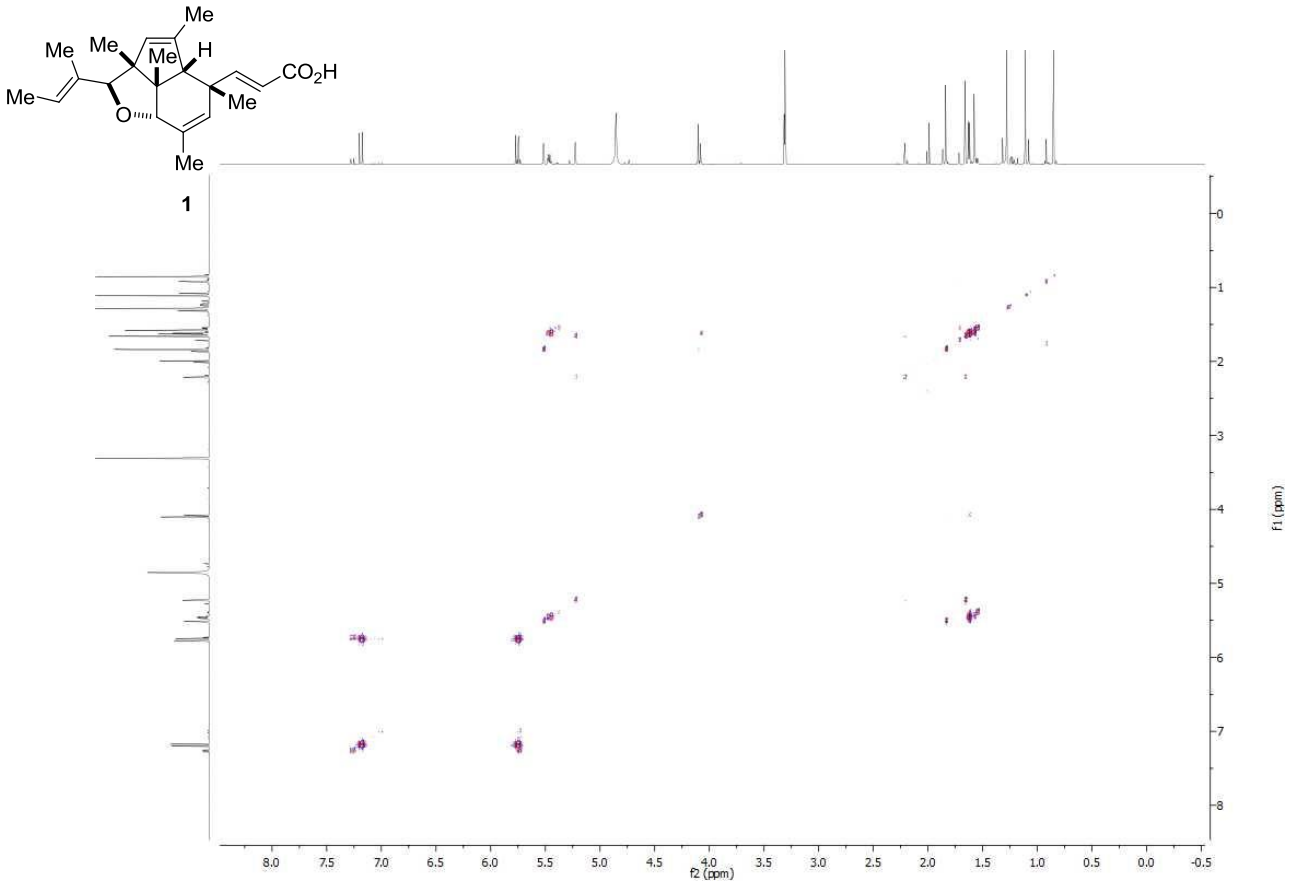
7.26
7.20
7.16
5.83
5.80
5.51
5.50
5.49
5.18
4.07
3.94
3.71
2.21
1.82
1.59
1.59
1.57
1.15
0.81
f1 (ppm)

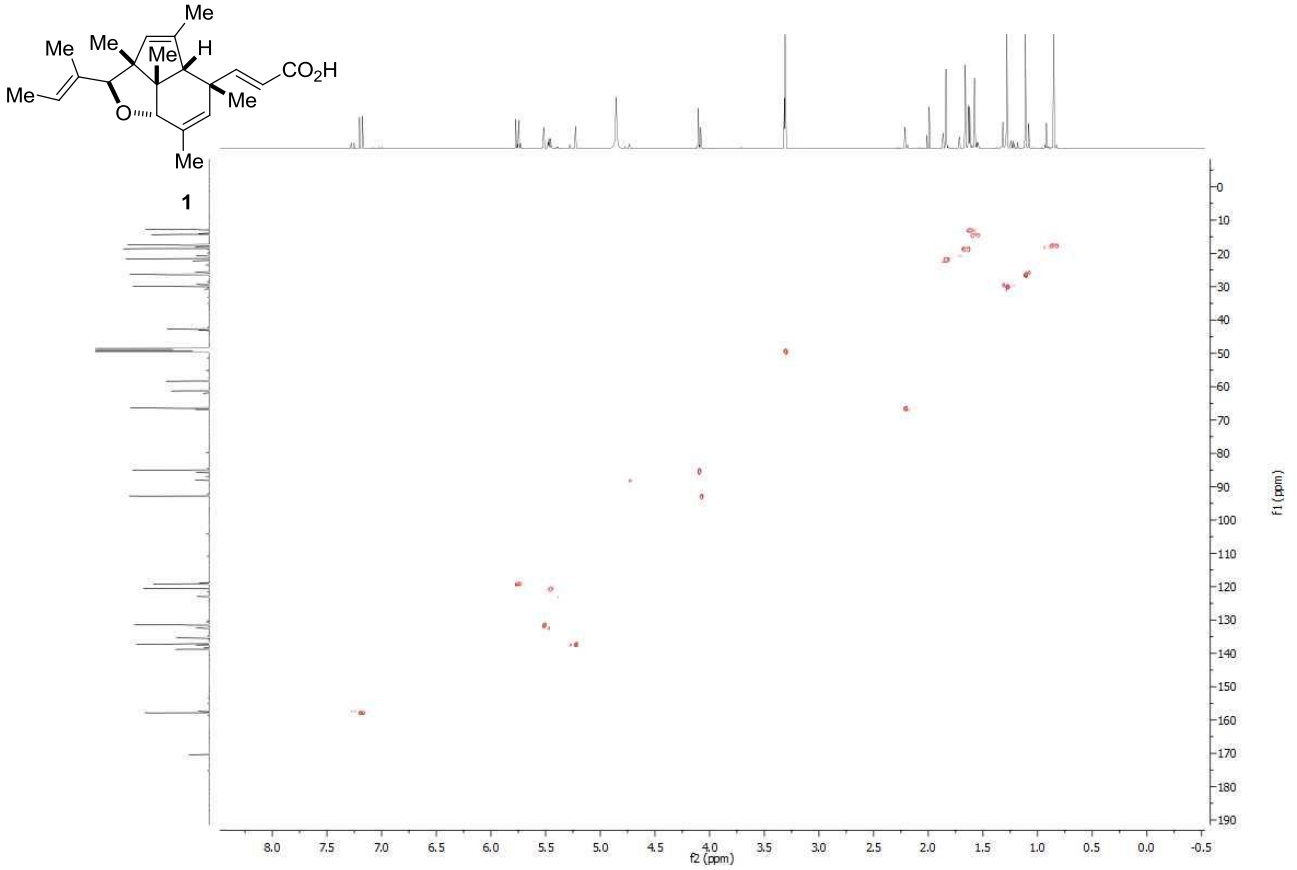

Me
Me
Me
Me
H
Me
CO2Me
Me
O
Me
239

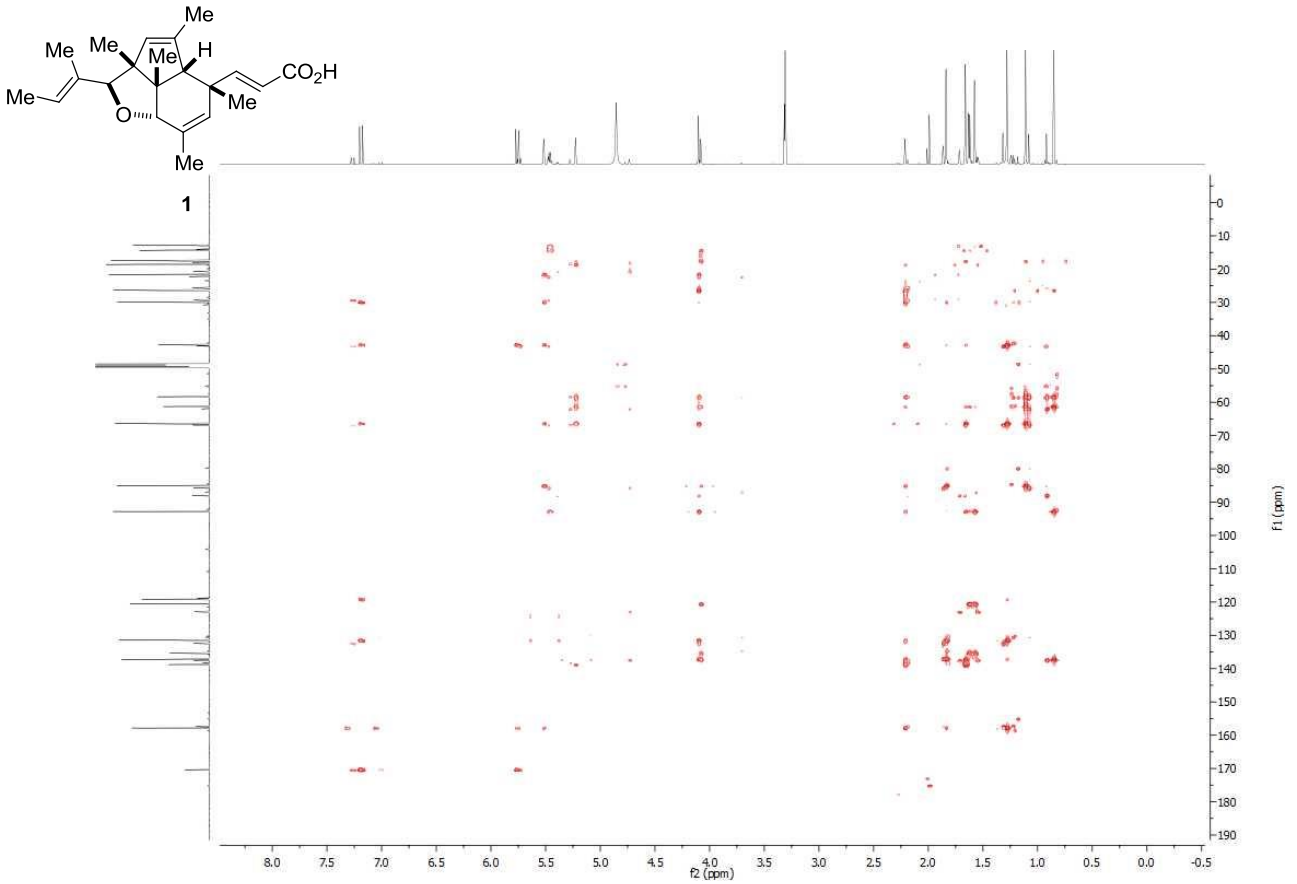
167.46
156.63
137.54
136.51
136.40
133.79
128.96
119.48
117.22
90.66
83.64
77.25 CDCl3
76.75 CDCl3
64.54
60.10
56.91
51.45
41.52
29.26
26.13
20.68
18.56
17.38
14.26
12.86
f1 (ppm)

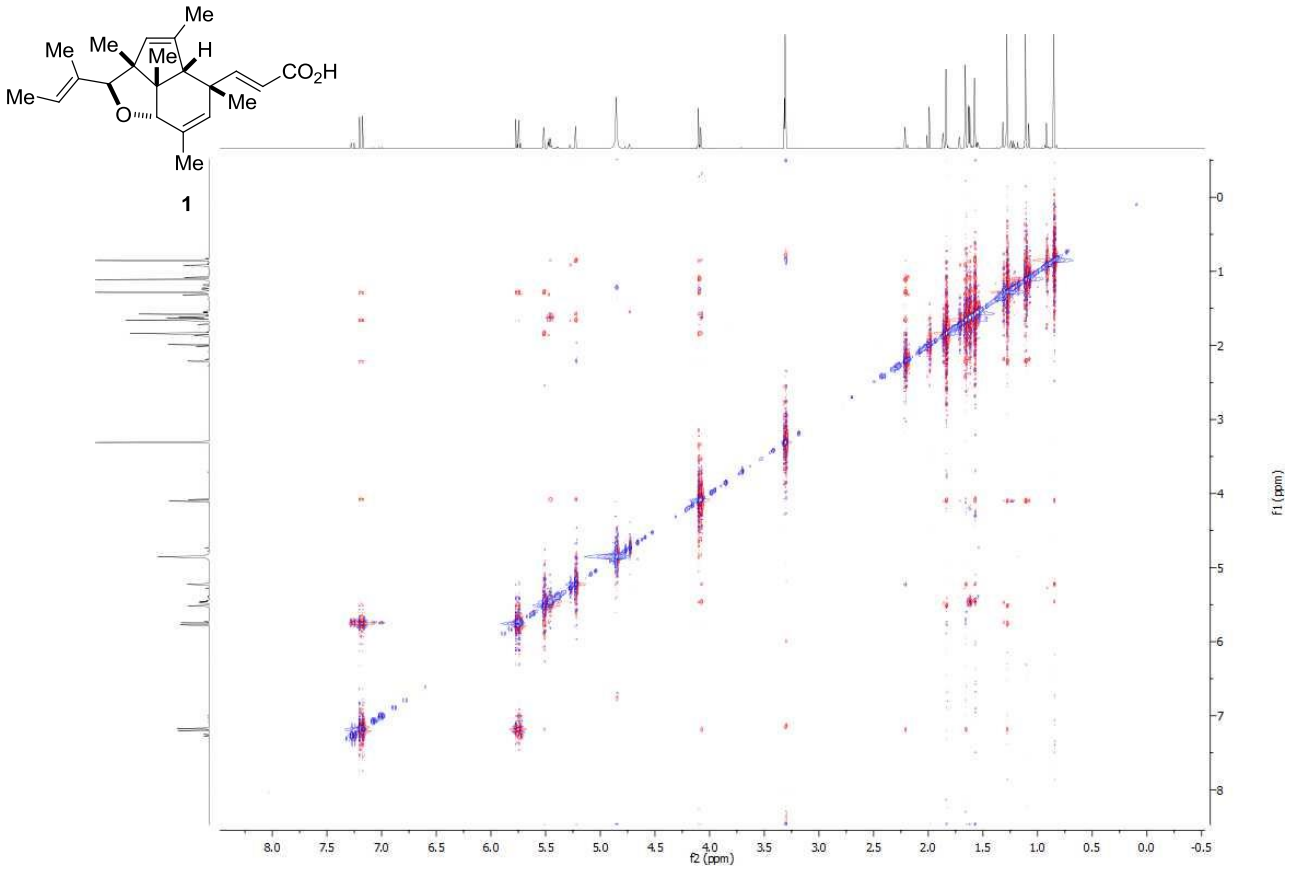

7.20
7.17
5.77
5.75
5.52
5.52
5.47
5.46
5.23
4.85
4.10
4.08
3.32
3.31
3.31
3.31
3.30
2.21
1.84
1.84
1.66
1.63
1.62
1.58
1.28
1.11
0.85
Me
Me
Me
Me
H
CO2H
Me
O
Me
Me
1
f1 (ppm)

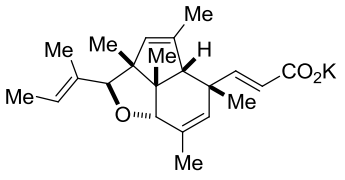

170.38
157.83
138.78
137.31
137.16
135.38
131.49
120.61
119.15
92.79
85.11
66.37
61.28
58.32
49.43 MeOD
49.28 MeOD
49.14 MeOD
49.00 MeOD
48.86 MeOD
48.72 MeOD
48.57 MeOD
42.73
29.88
26.31
21.62
18.59
17.52
14.36
12.92
Me
Me
Me
Me
H
CO2H
Me
O
Me
Me
1
f1 (ppm)


Me
Me
Me
Me
H
CO2H
Me
Me
O
Me
1
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2H
Me
Me
O
Me
1
f2 (ppm)
f1 (ppm)

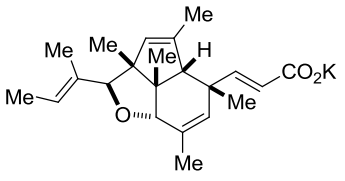

Me
Me
Me
Me
H
CO2H
Me
Me
O
Me
1
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2H
Me
Me
O
Me
1
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
Me
CO2K
Me
O
Me

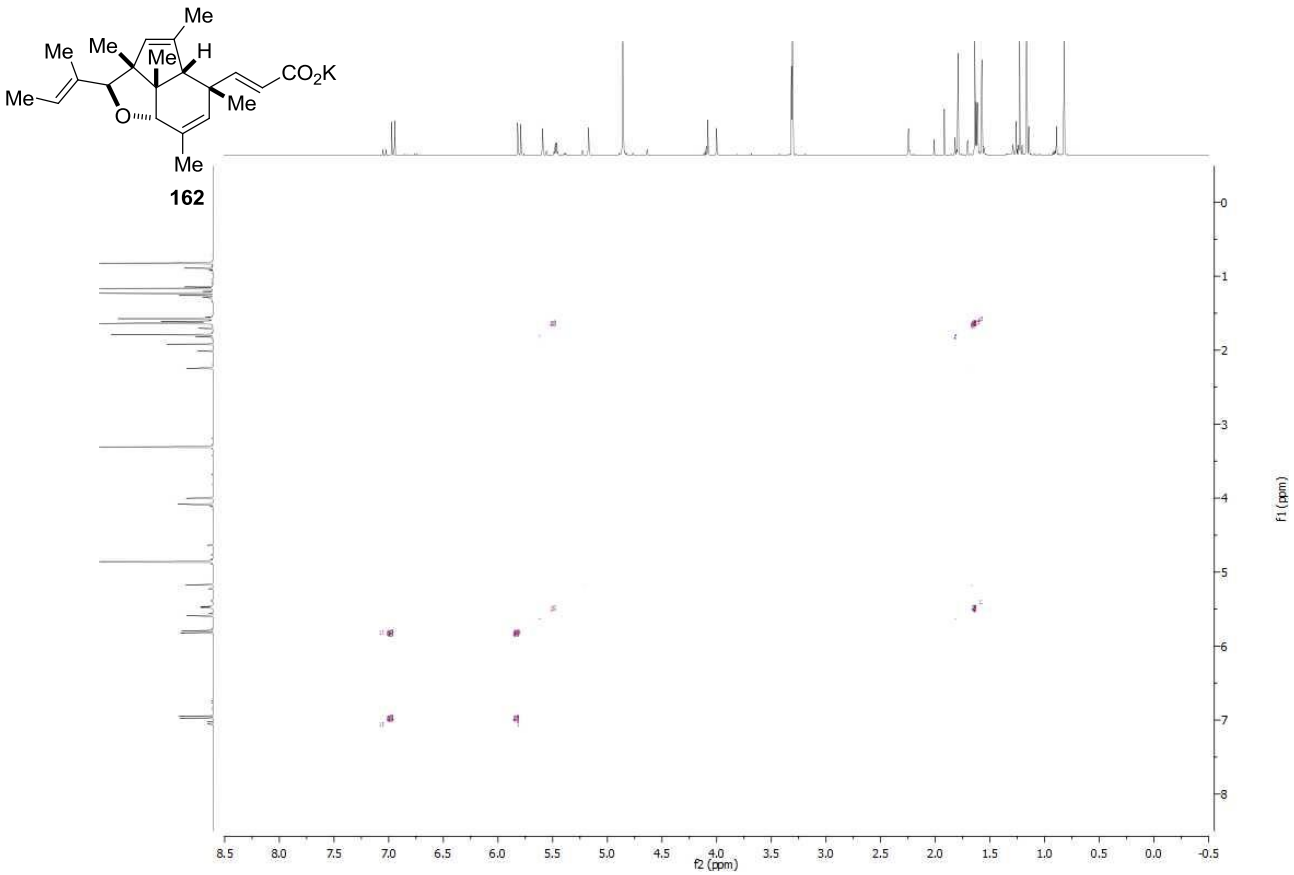
162

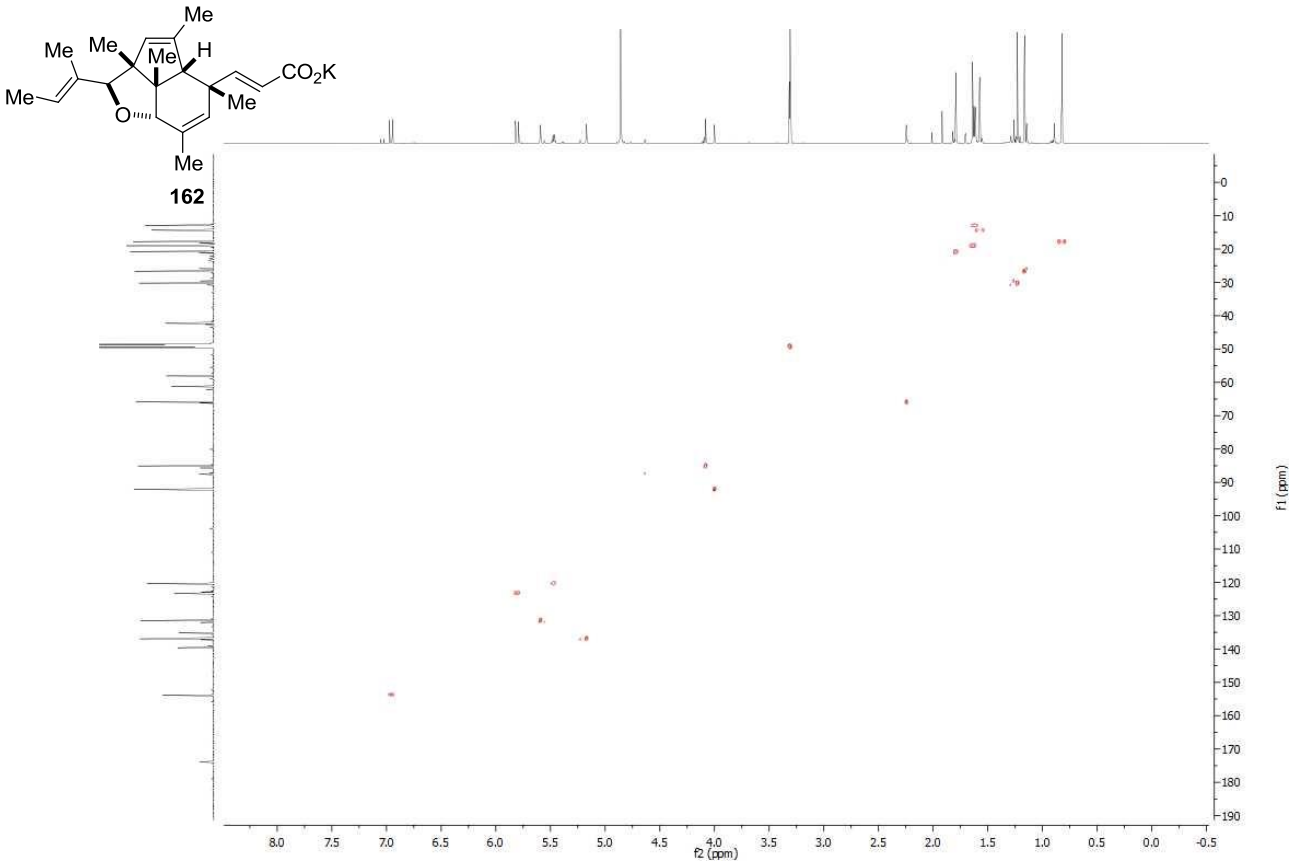
6.99
6.96
5.84
5.81
5.61
5.50
5.48
5.19
4.88
4.10
4.02
3.33
3.33
3.33
3.33
3.32
2.26
1.81
1.66
1.65
1.63
1.59
1.25
1.18
0.84
f1 (ppm)

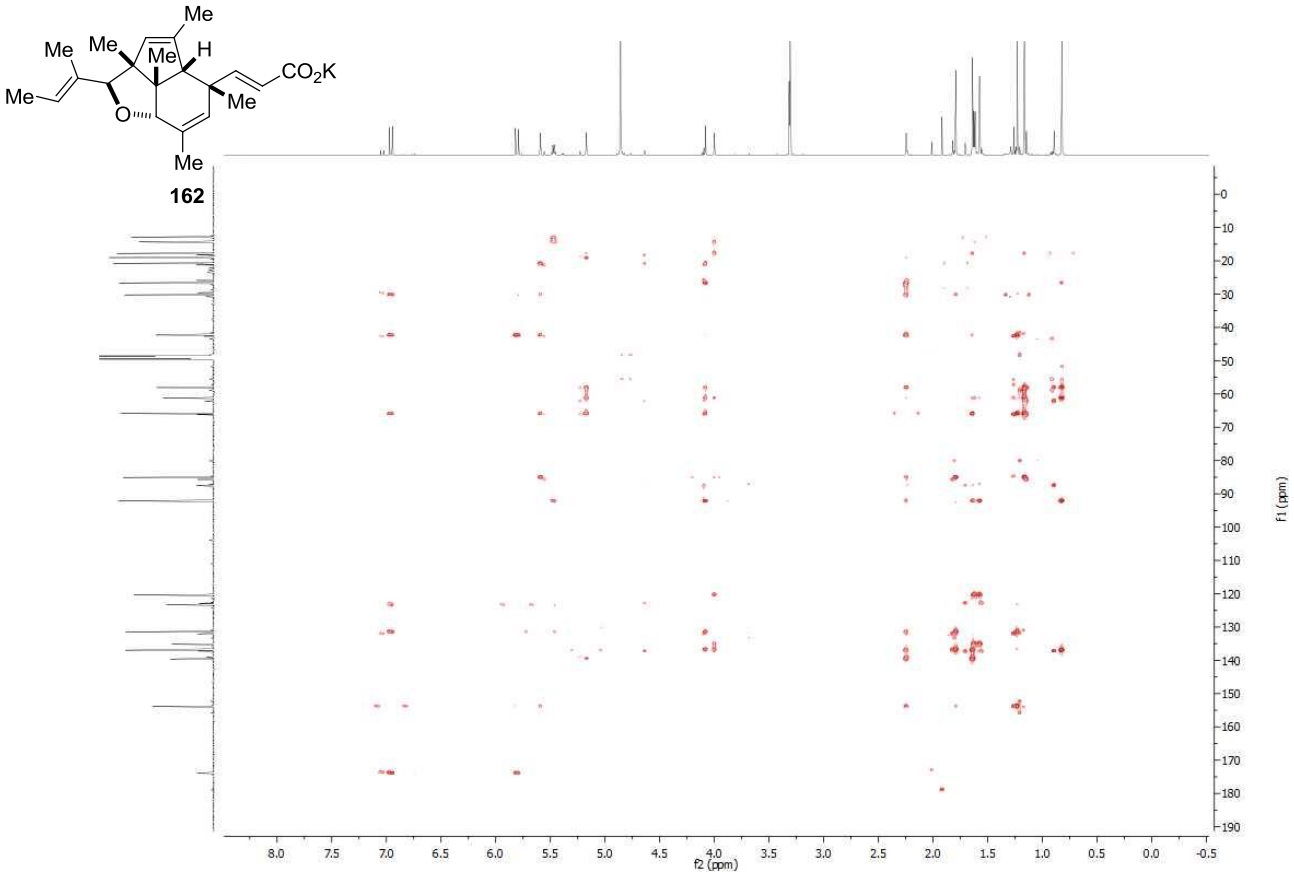

Me
Me
Me
Me
H
Me
CO2K
Me
O
Me

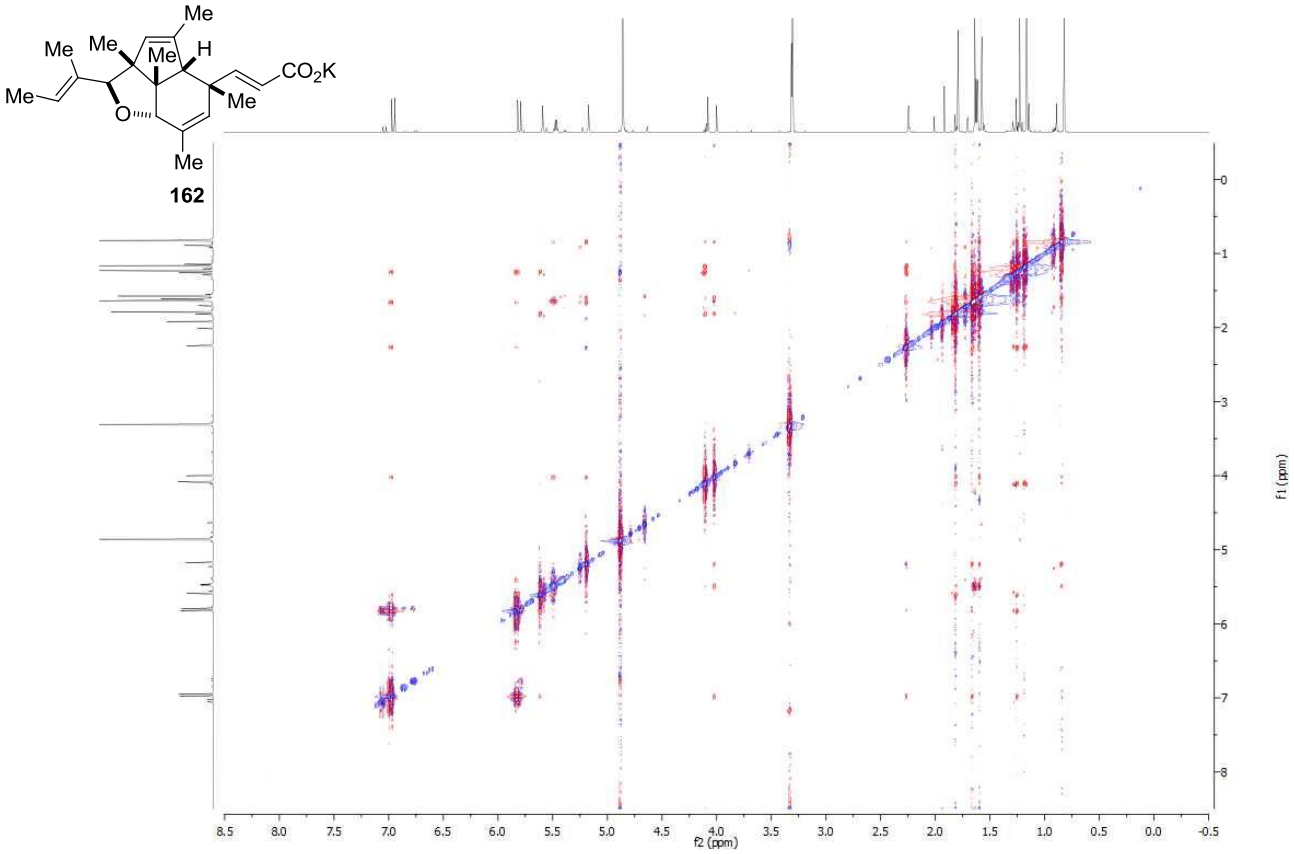
162

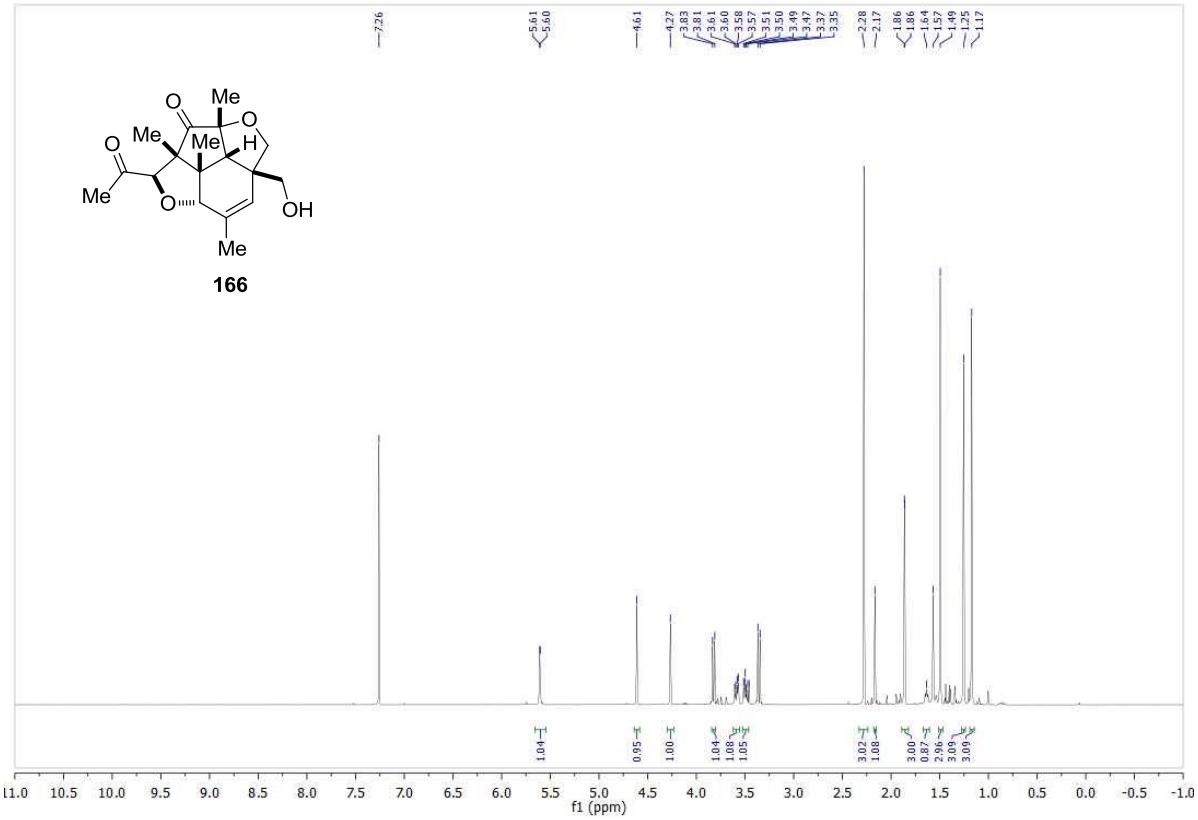
173.94
153.87
139.61
136.95
136.75
135.19
131.48
123.31
120.36
92.10
85.07
65.88
61.22
58.08
49.14 MeOD
49.00 MeOD
48.86 MeOD
48.72 MeOD
42.58
30.20
26.63
20.74
19.02
17.74
14.35
12.91
f1 (ppm)

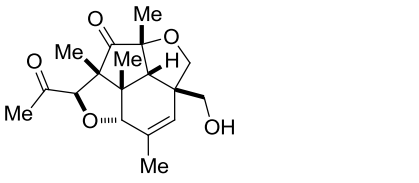

Me
Me
Me
Me
H
Me
Me
O
CO2K
Me
Me
162
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
Me
Me
O
CO2K
Me
Me
162
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2K
Me
Me
O
Me
162
f2 (ppm)
f1 (ppm)


Me
Me
Me
Me
H
CO2K
Me
Me
O
Me
162
f2 (ppm)
f1 (ppm)


7.26
5.61
5.60
4.61
4.27
3.83
3.81
3.61
3.60
3.58
3.57
3.51
3.50
3.49
3.47
3.37
3.35
2.28
2.17
1.86
1.86
1.64
1.57
1.49
1.25
1.17
1.04
0.95
1.00
1.04
1.08
1.05
3.02
1.08
3.00
3.02
2.67
3.09
3.09
f1 (ppm)

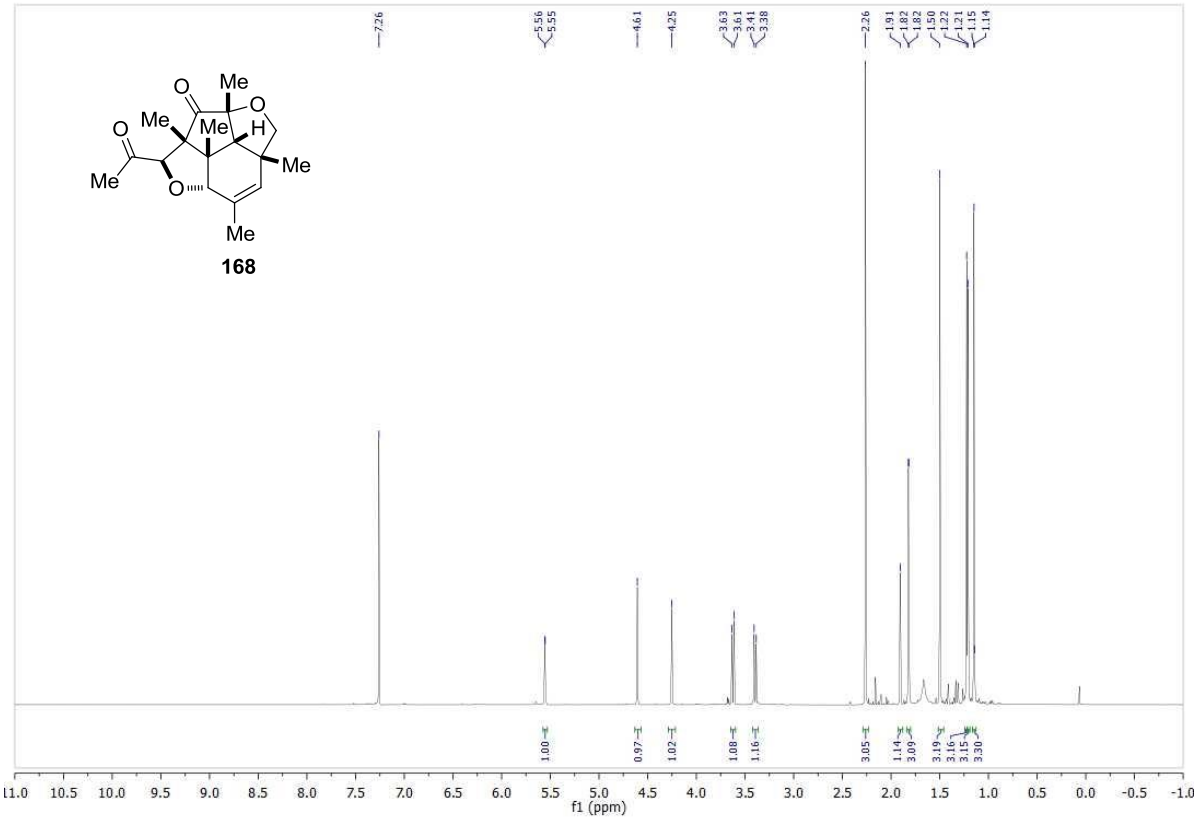

Me
O
O
Me
Me
H
O
Me
O
OH
Me

166

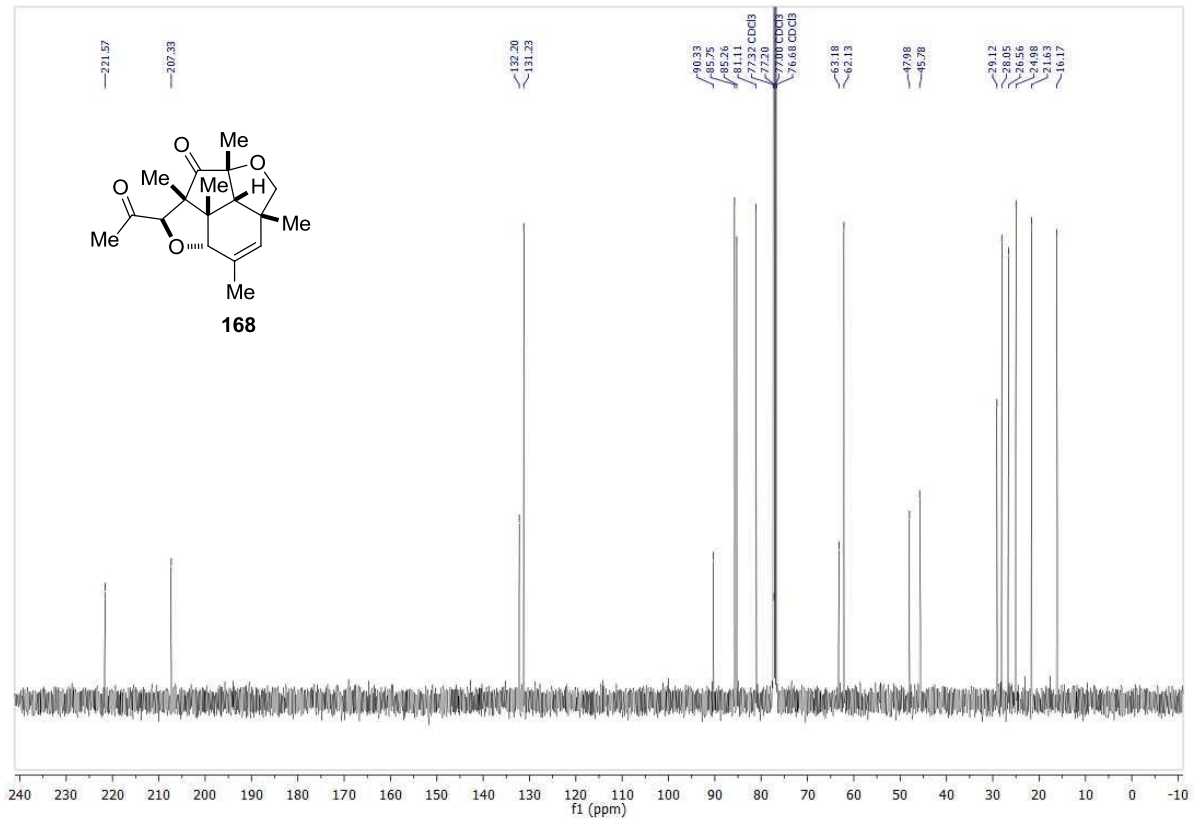
221.40
207.08
135.28
126.50
90.56
85.53
77.32 CDCl3
77.20 CDCl3
76.90 CDCl3
76.68 CDCl3
68.62
62.95
56.62
53.02
47.52
29.16
26.13
24.59
21.92
16.26
f1 (ppm)

Me
O
O
Me
Me
H
O
Me
O
OH
Me

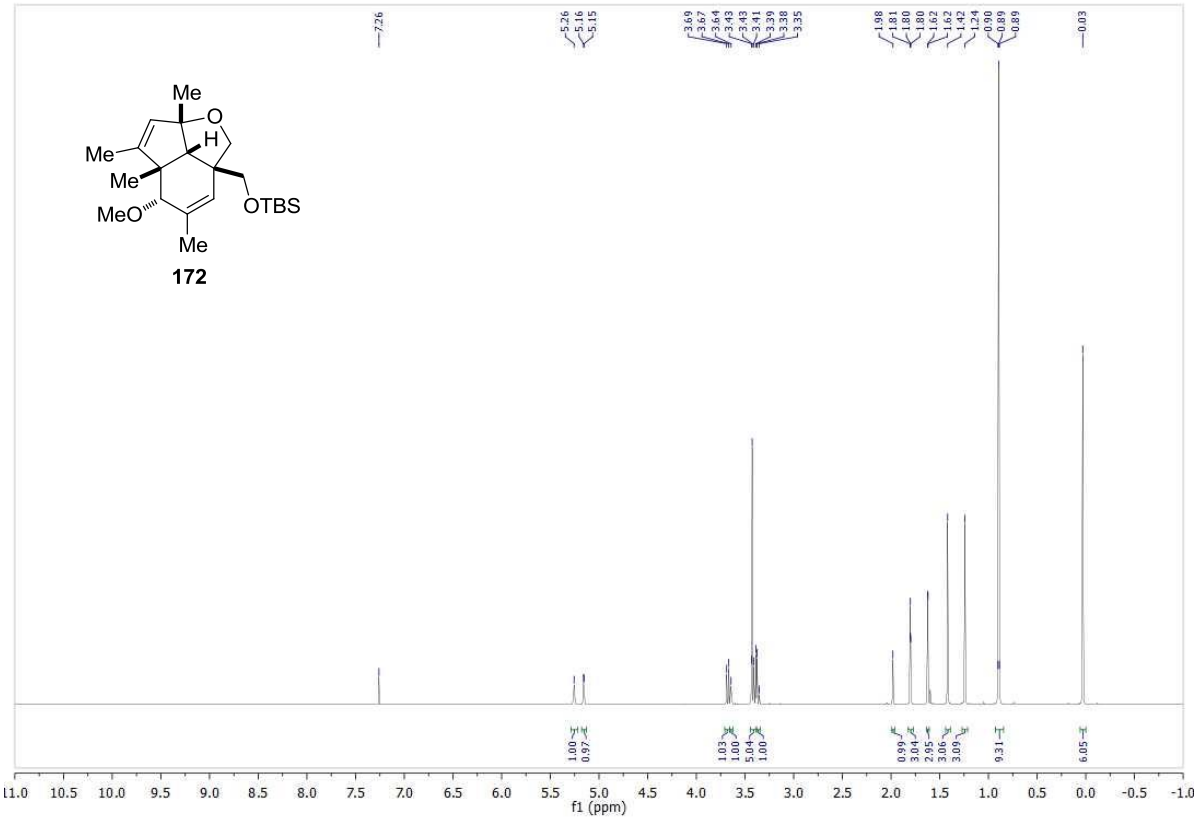
166

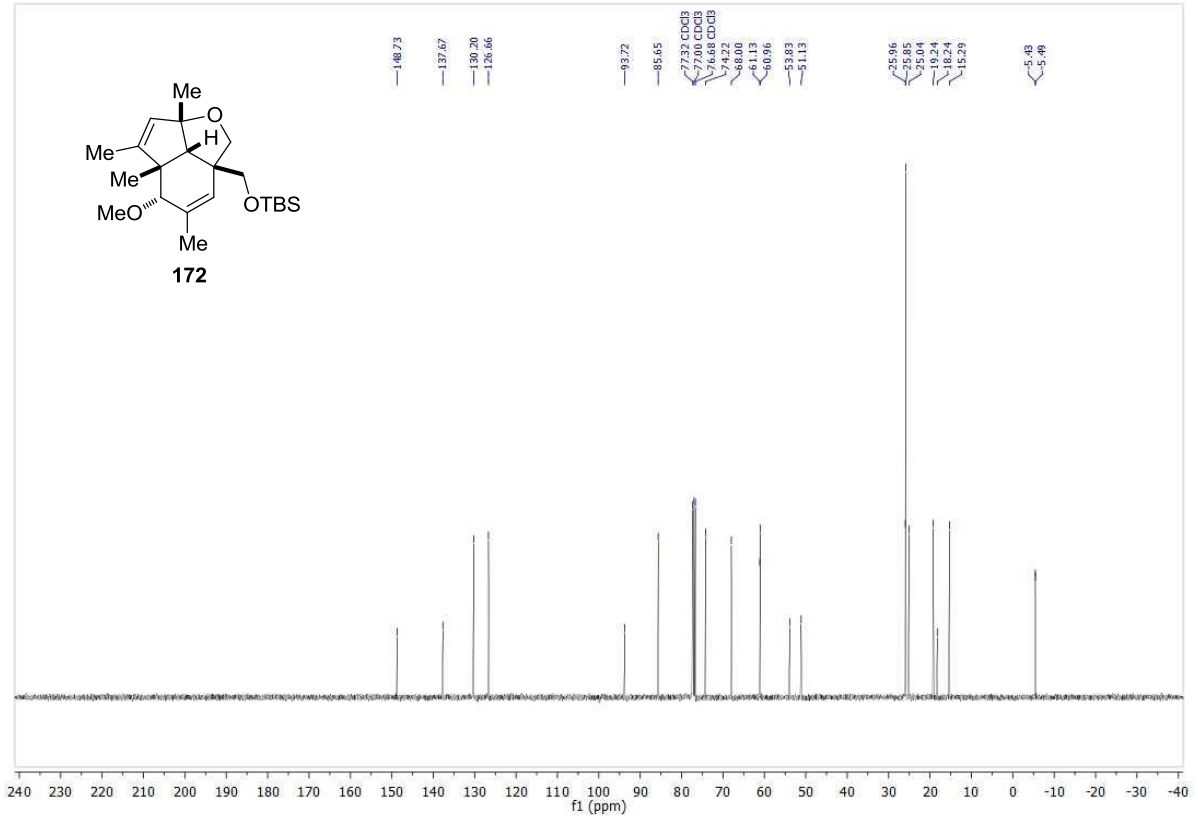

7.26
5.56
5.55
4.61
4.25
3.63
3.61
3.41
3.38
2.26
1.91
1.82
1.82
1.50
1.22
1.21
1.15
1.14
1.00
0.97
1.02
1.08
1.16
3.05
1.14
3.09
3.19
3.16
3.15
3.30
f1 (ppm)

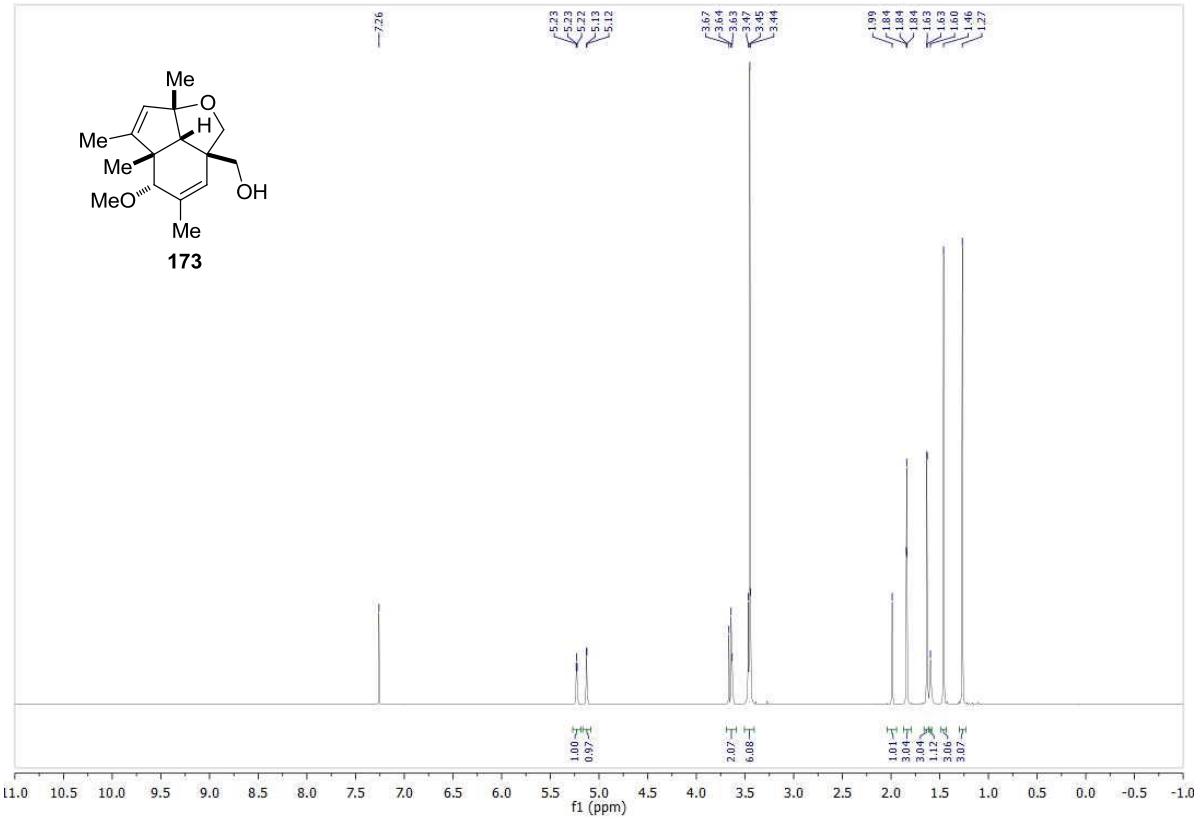
168

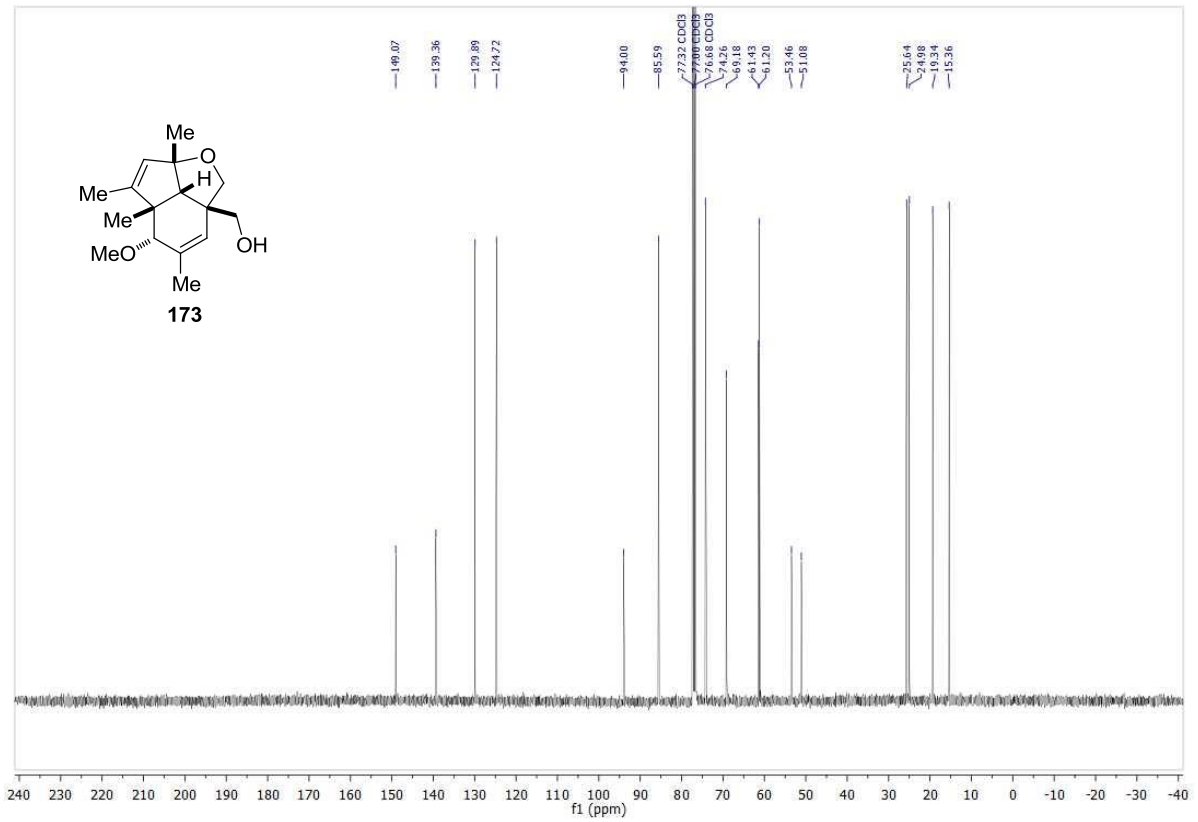

221.57
207.33
132.20
131.23
90.33
85.75
85.26
81.11
77.32 CDCl3
77.20
77.00 CDCl3
76.68 CDCl3
63.18
62.13
47.98
45.78
29.12
28.05
26.56
24.98
21.63
16.17
f1 (ppm)

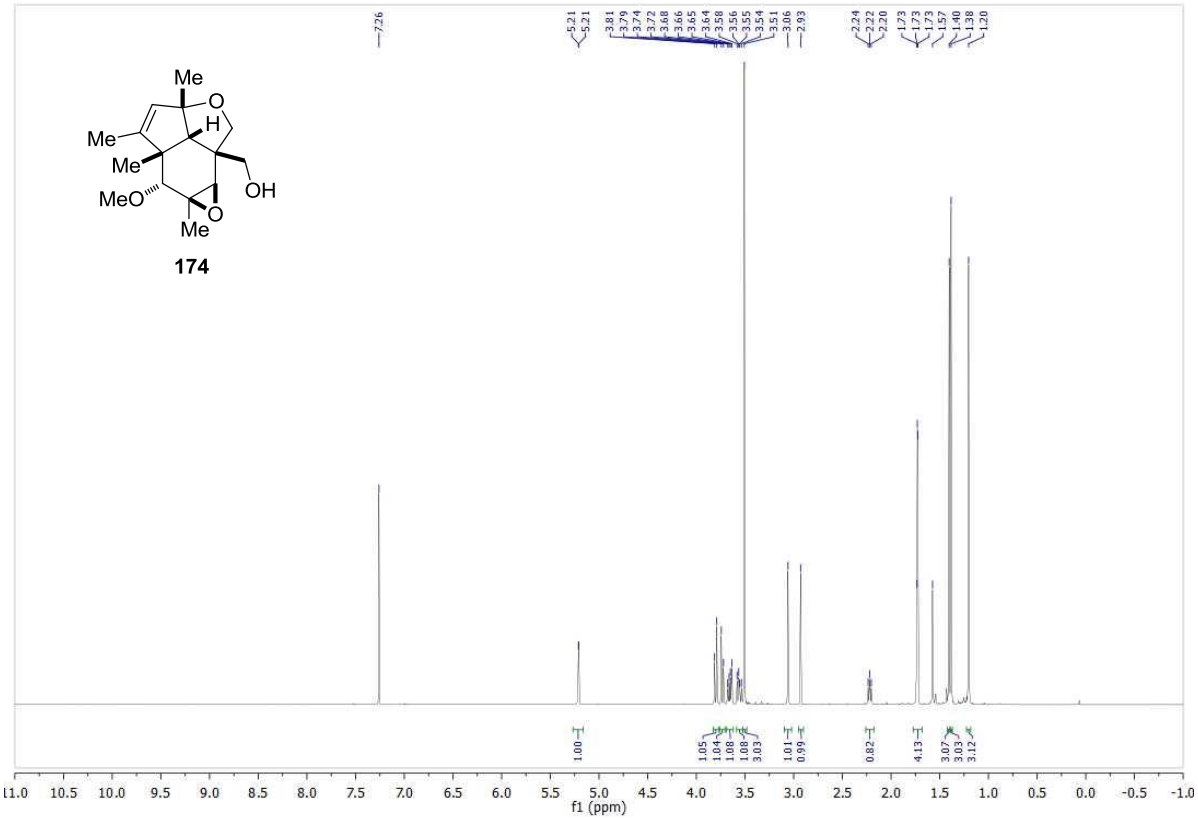
168

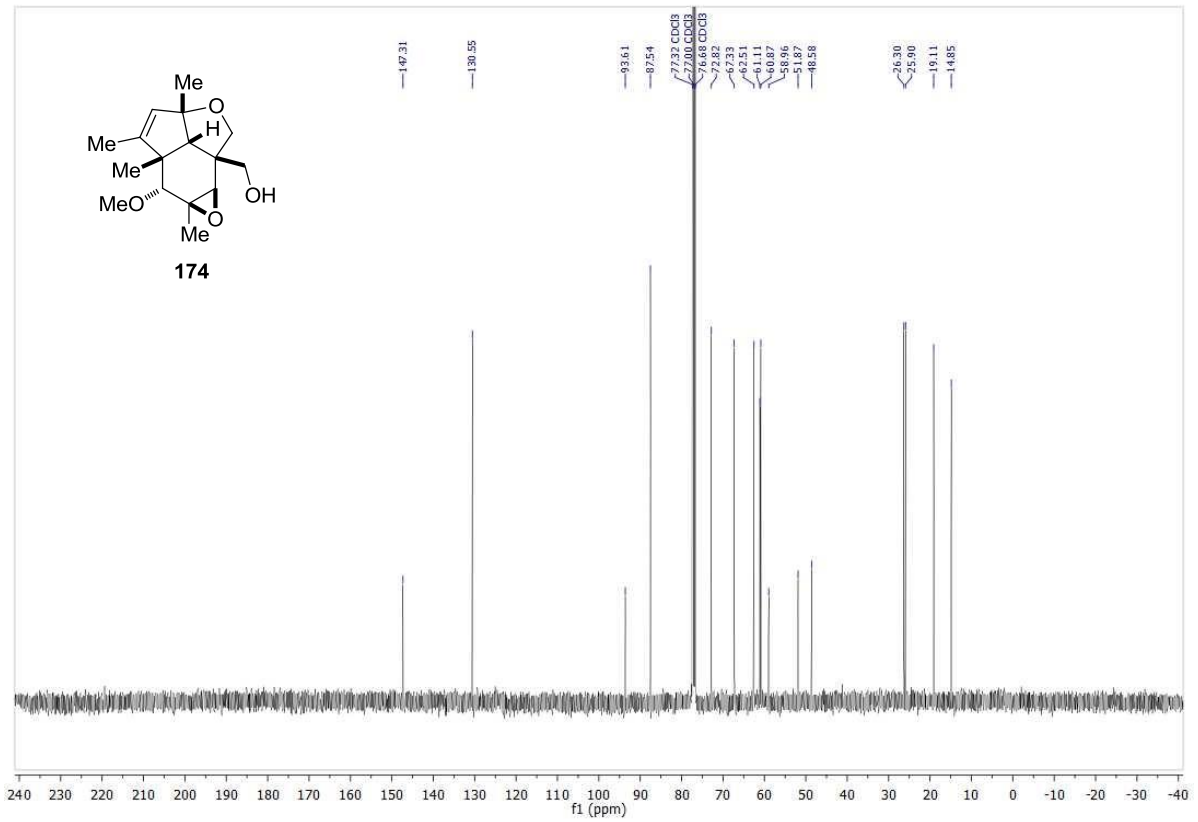

Me
O
H
Me
Me
MeO
OTBS
Me
172
f1 (ppm)

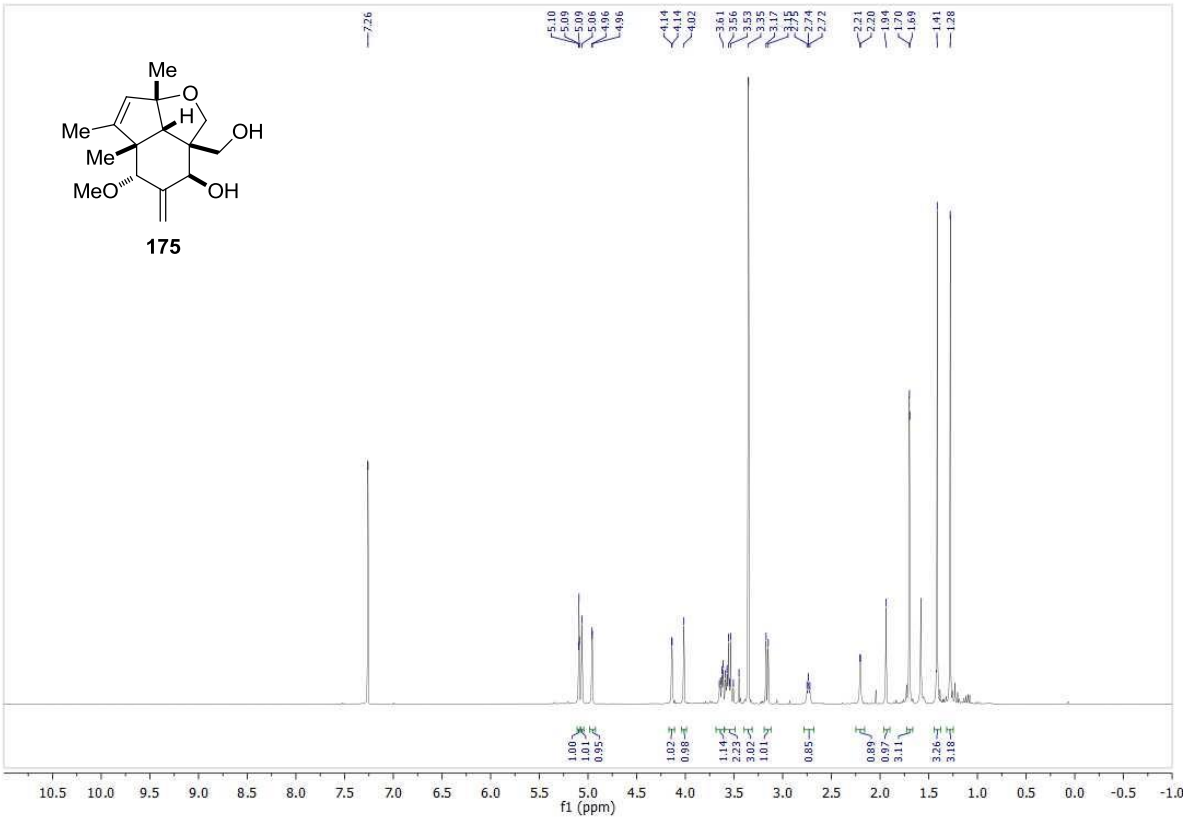

Me
O
H
Me
Me
MeO
OTBS
Me
172
f1 (ppm)

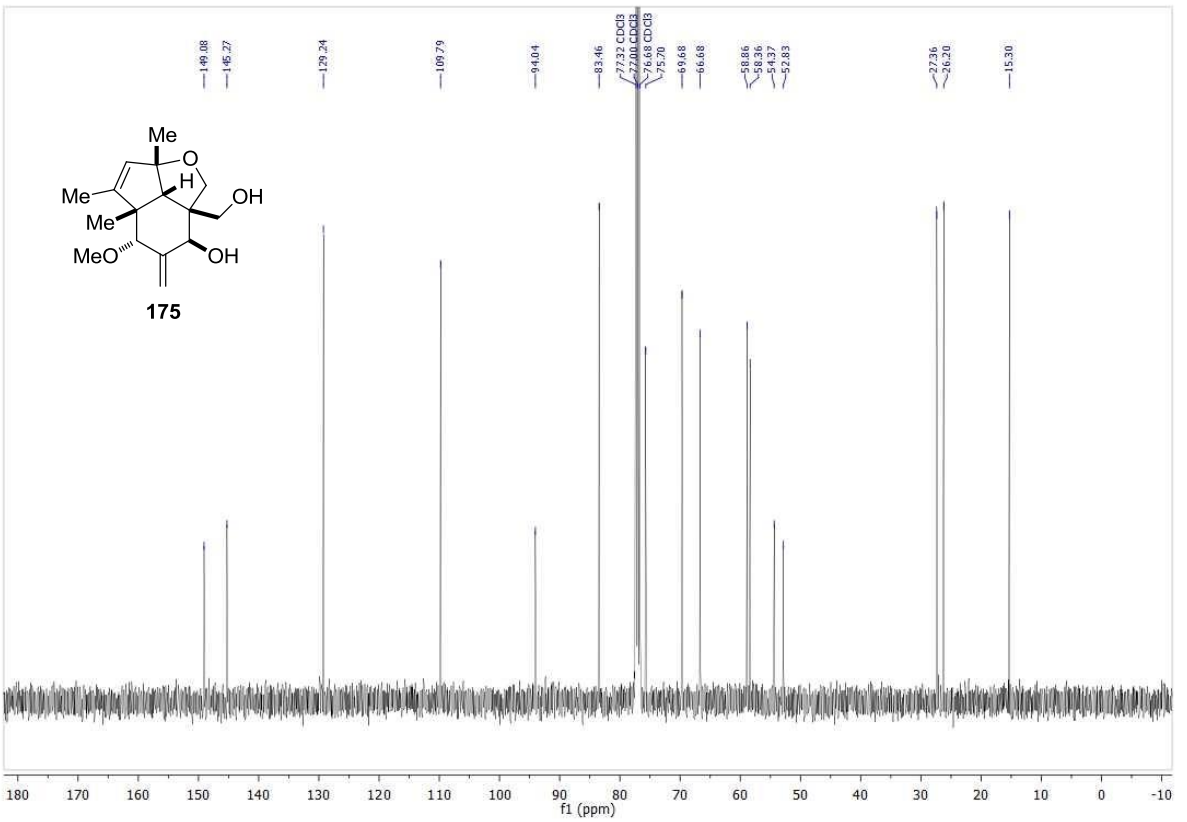

Me
O
H
Me
Me
MeO
OH
Me
173
7.26
5.23
5.23
5.22
5.13
5.12
3.67
3.64
3.63
3.47
3.45
3.44
1.99
1.84
1.84
1.84
1.63
1.63
1.60
1.46
1.27
1.00
0.97
2.07
6.08
1.01
3.04
3.04
1.12
3.06
3.07
f1 (ppm)

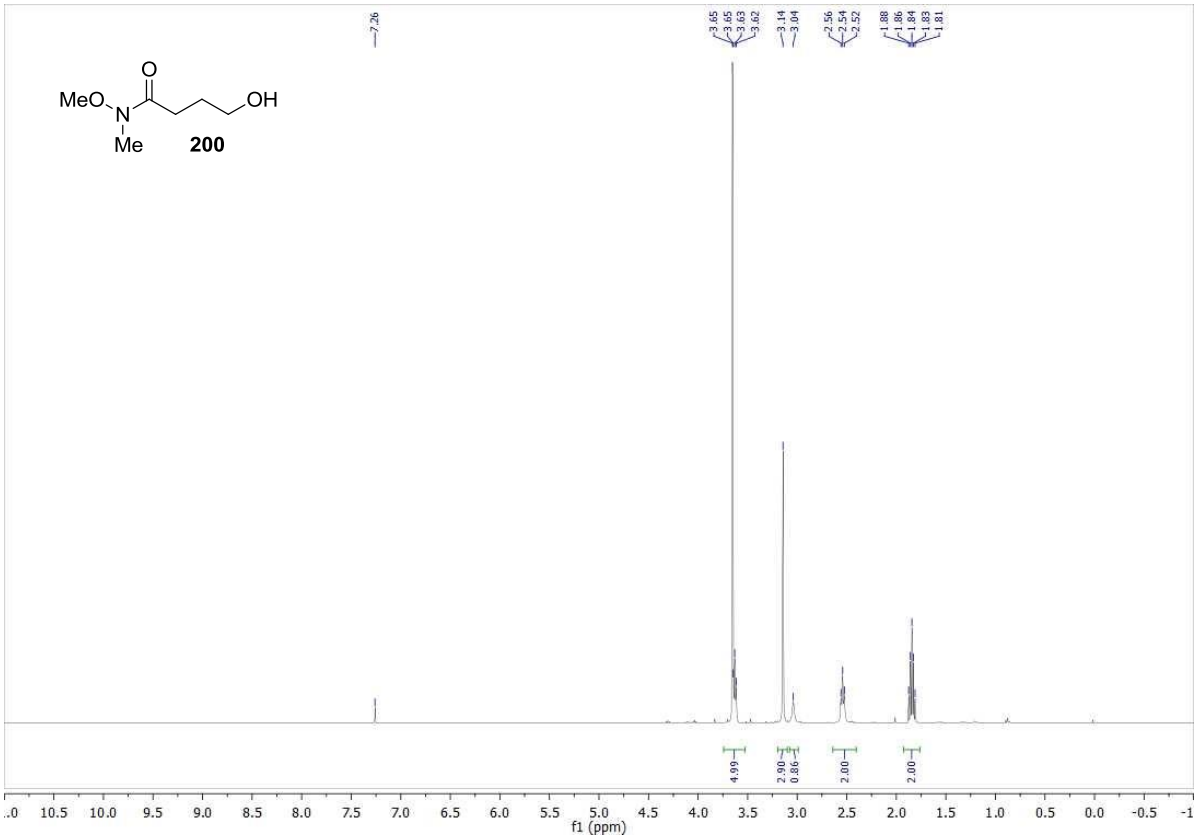

Me
O
H
Me
Me
MeO
OH
Me
173
149.07
139.36
129.89
124.72
94.00
85.59
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
74.26
69.18
61.43
61.20
53.46
51.08
25.64
24.98
19.34
15.36
f1 (ppm)

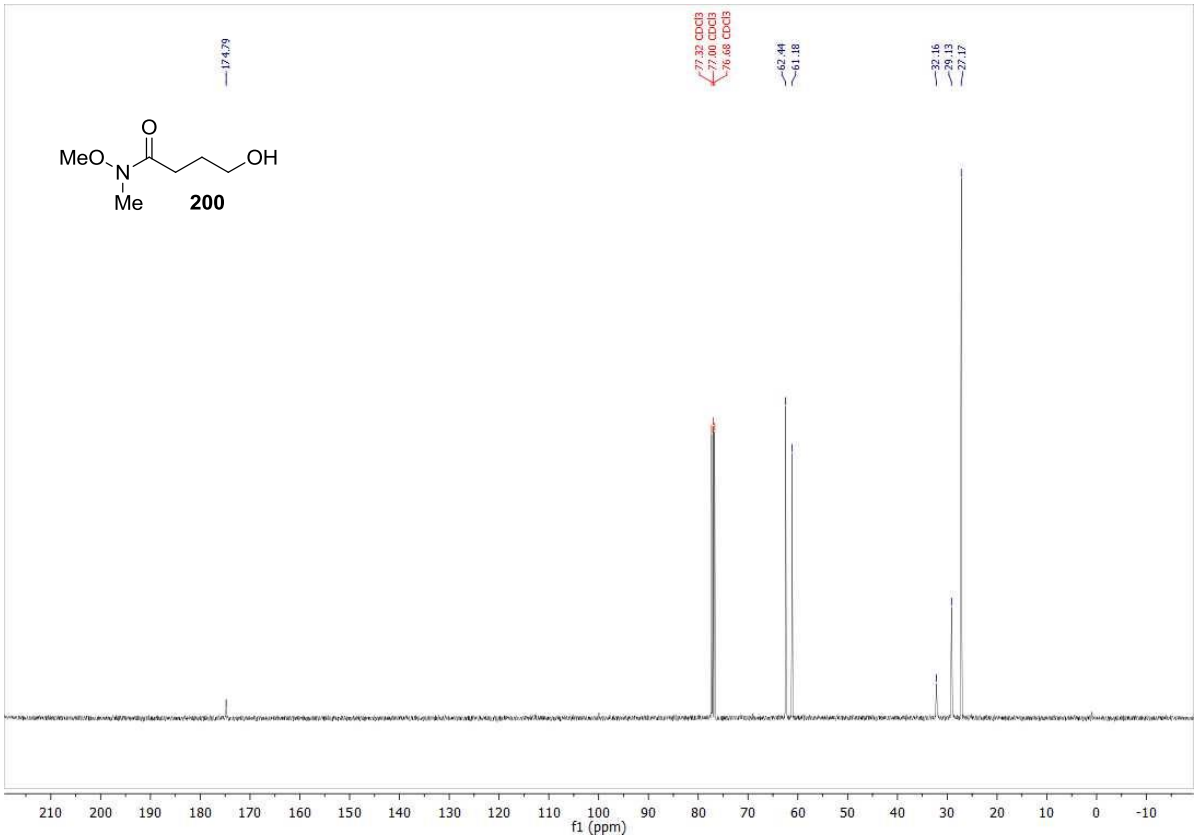

Me
O
H
Me
Me
MeO
OH
O
Me
174
f1 (ppm)

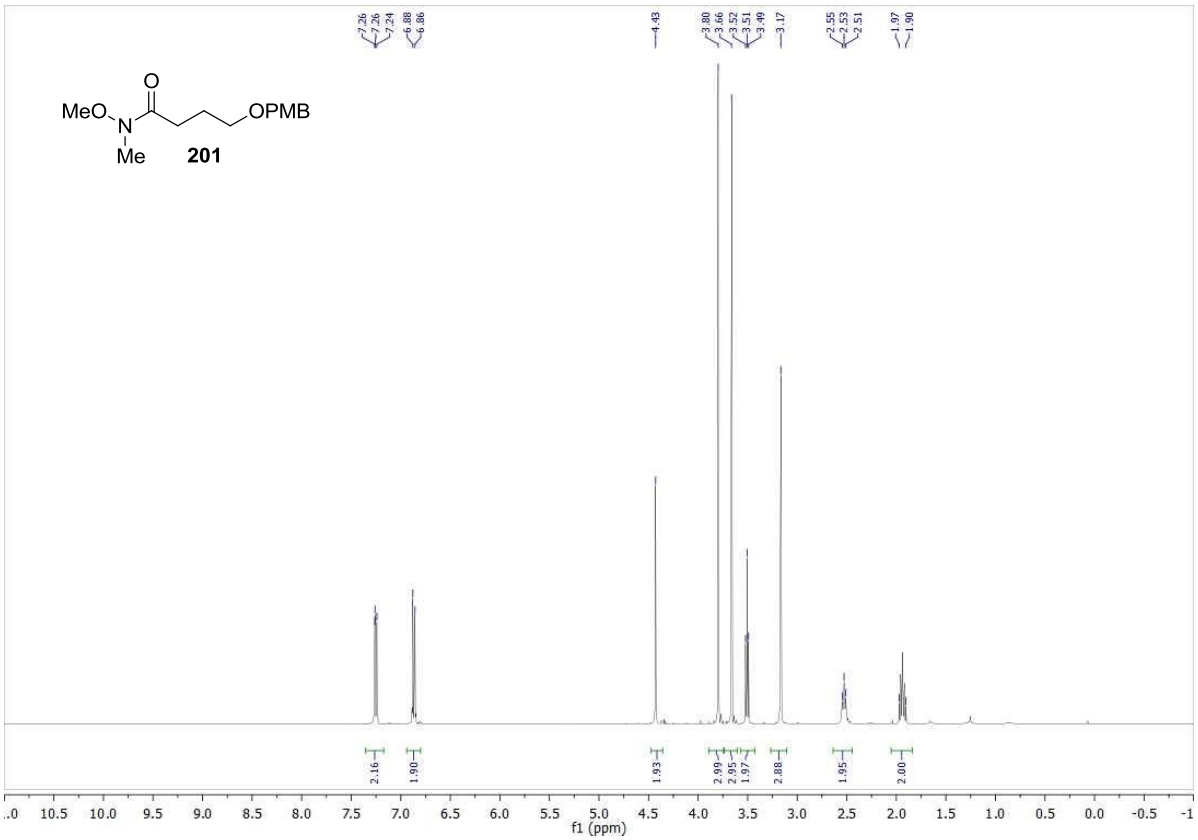

Me
O
H
Me
Me
MeO
OH
O
Me
174
f1 (ppm)

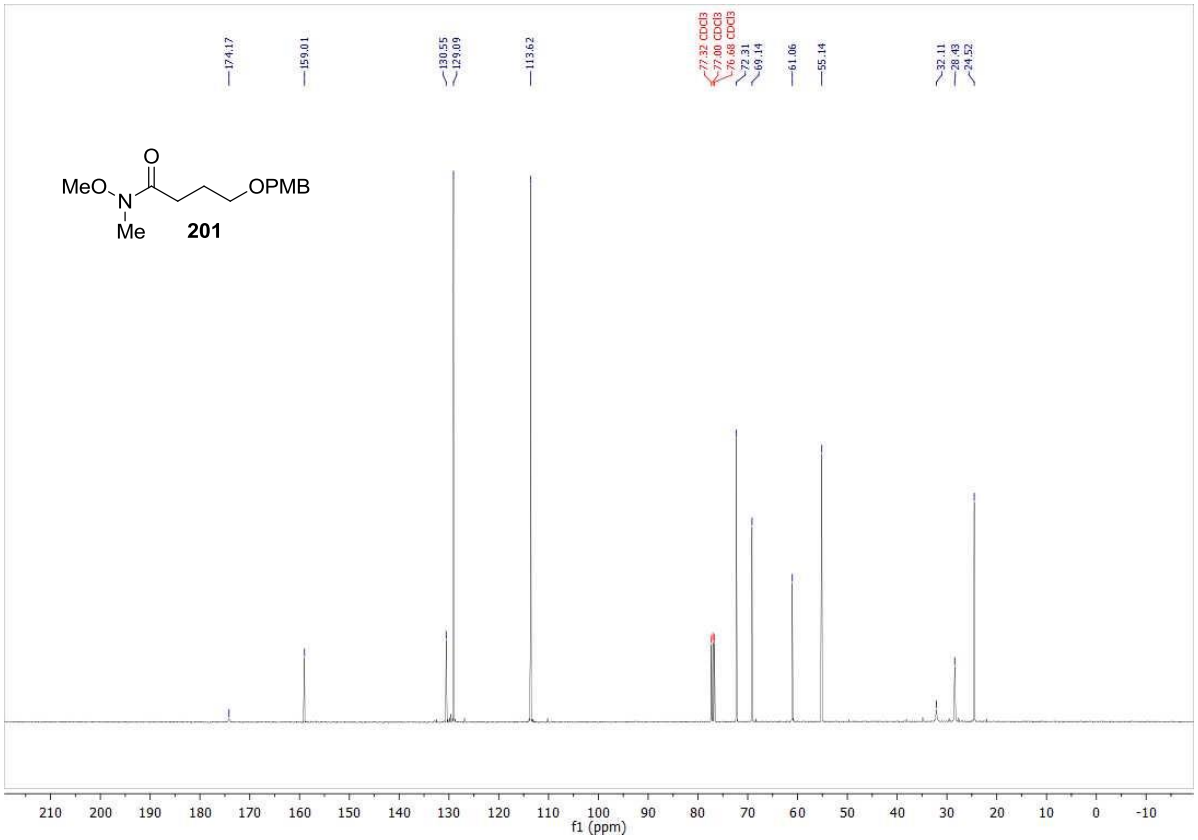

Me
O
H
Me
Me
OH
MeO
OH
175
7.26
5.10
5.09
5.09
5.06
5.06
4.96
4.14
4.14
4.02
3.61
3.56
3.53
3.35
3.17
3.15
2.74
2.72
2.21
2.20
1.94
1.70
1.69
1.41
1.28
1.00
1.01
0.95
1.02
0.98
1.14
2.23
3.02
1.01
0.85
0.89
0.97
3.11
3.26
3.18
f1 (ppm)

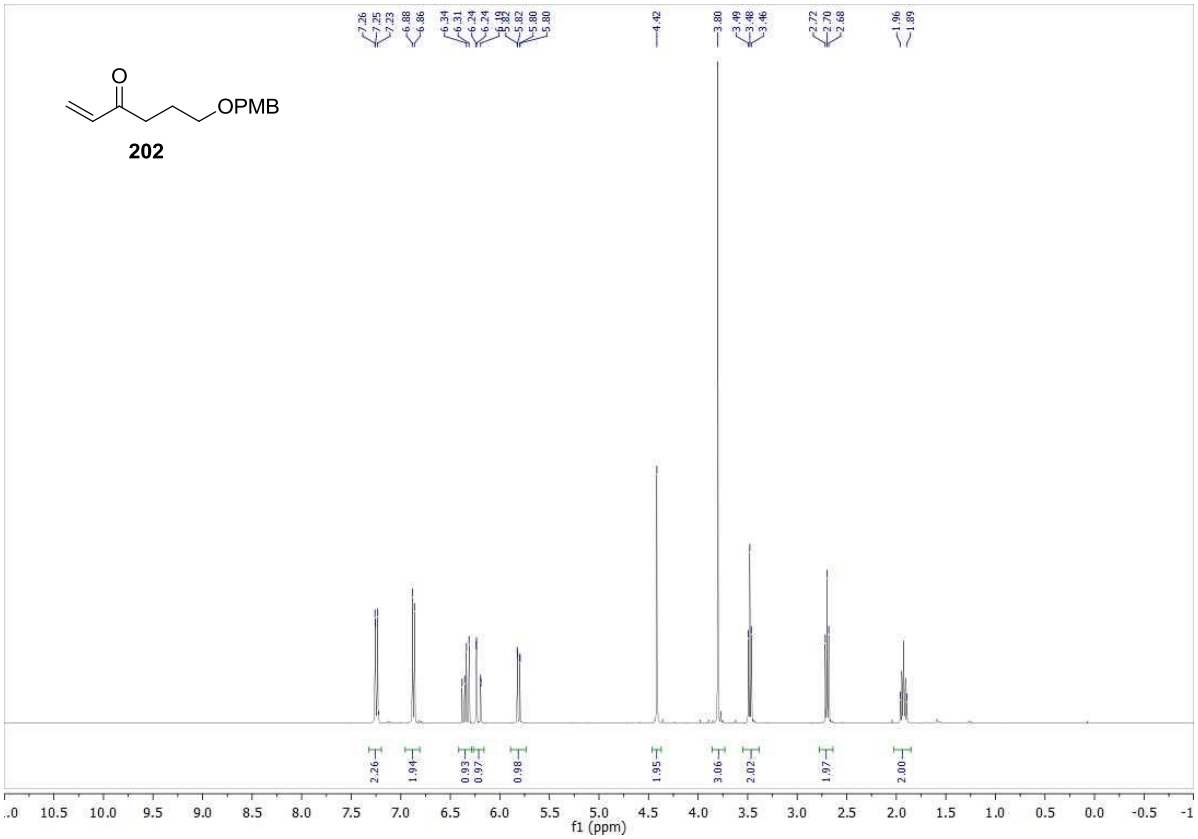

Me
O
H
Me
Me
OH
MeO
OH
175
149.08
145.27
129.24
109.79
94.04
83.46
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
75.70
69.68
66.68
58.86
58.36
54.37
52.83
27.36
26.20
15.30
f1 (ppm)

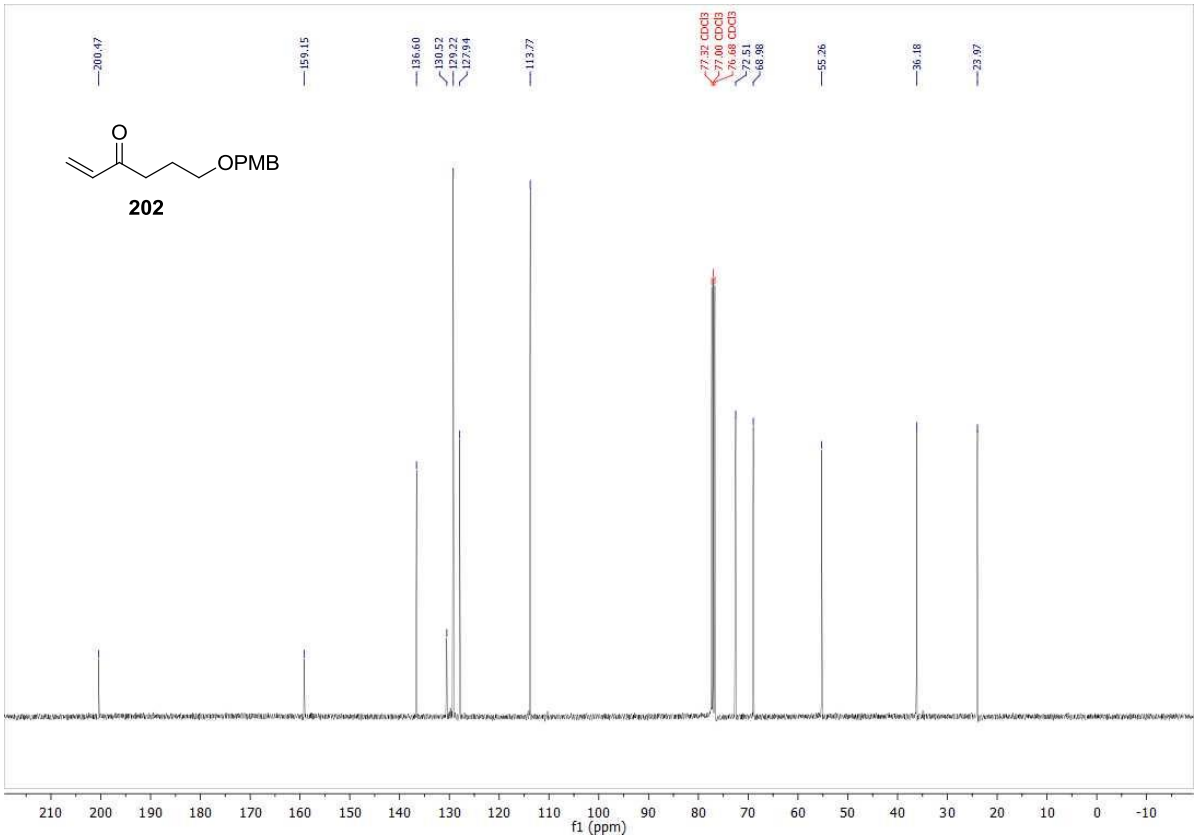

MeO
N
Me
O
OH
200
7.26
3.65
3.65
3.63
3.62
3.14
3.04
2.56
2.54
2.52
1.88
1.86
1.84
1.83
1.81
4.99
2.90
0.86
2.00
2.00
f1 (ppm)

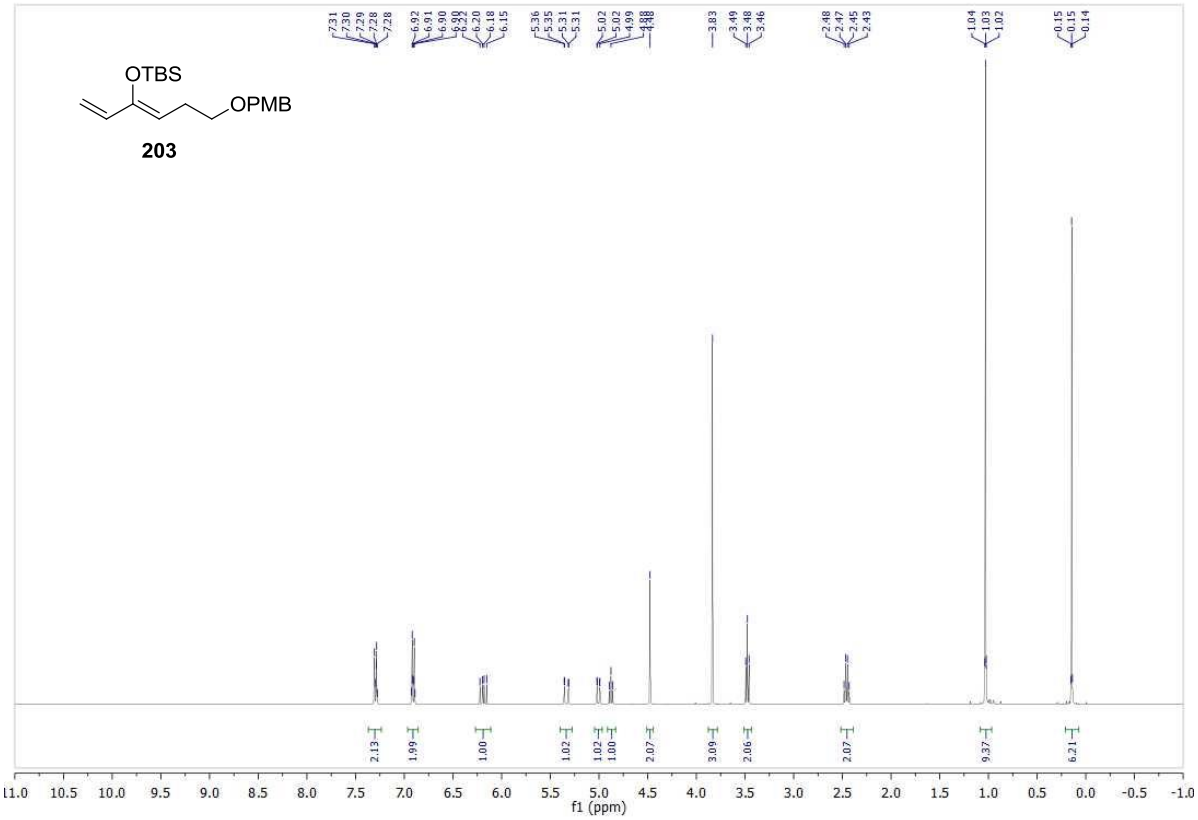

MeO
N
Me
O
OH
200
174.79
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
62.44
61.18
32.16
29.13
27.17
f1 (ppm)

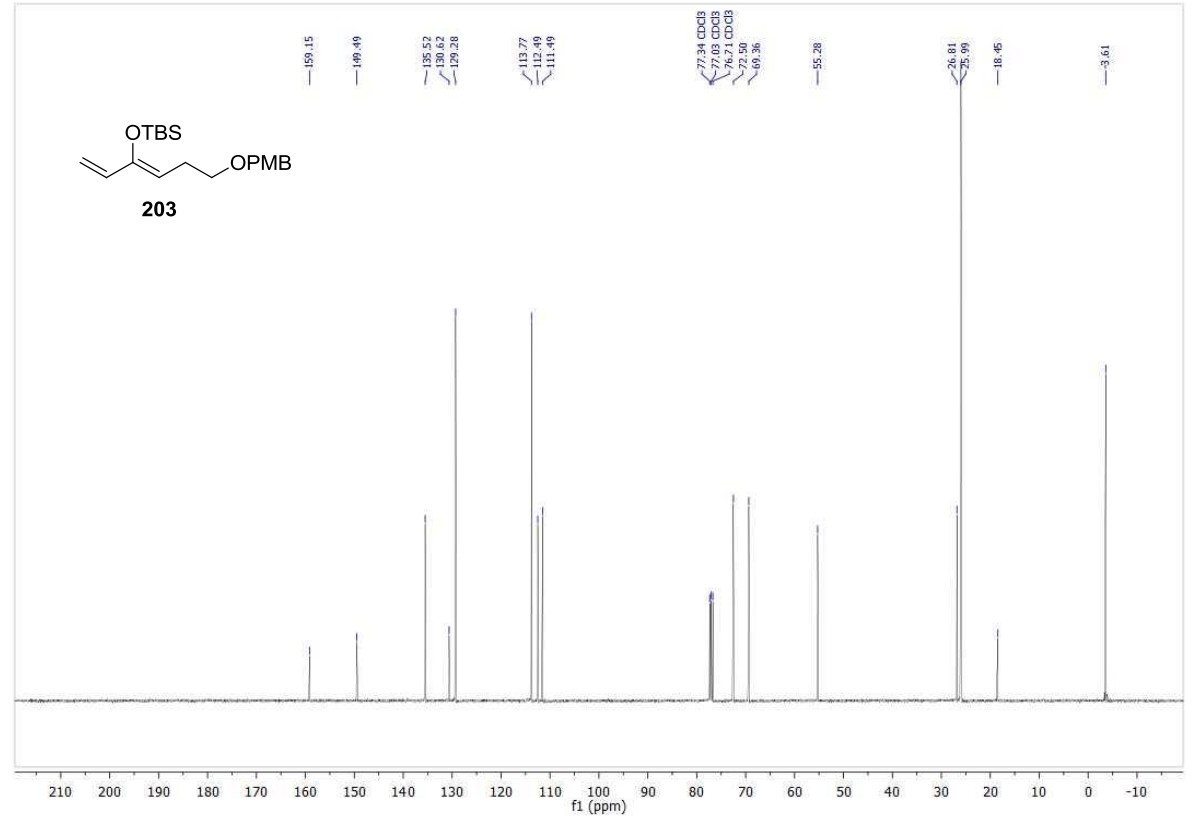

MeO
N
Me
O
OPMB
201
f1 (ppm)

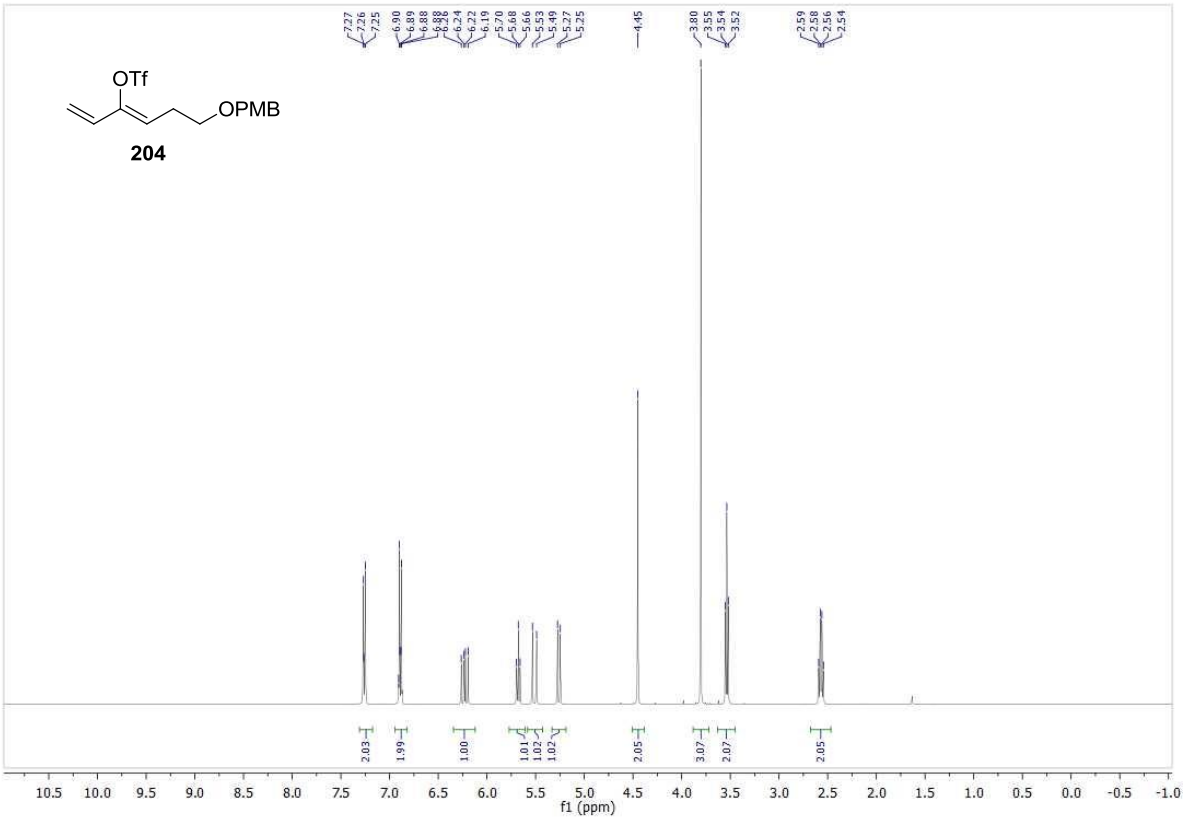

MeO
N
Me
O
OPMB
201
f1 (ppm)


O
OPMB
202
7.26
7.25
7.23
6.88
6.86
6.34
6.31
6.24
6.19
5.82
5.80
5.80
4.42
3.80
3.49
3.48
3.46
2.72
2.70
2.68
1.96
1.89
2.26
1.94
0.93
0.97
0.98
1.95
3.06
2.02
1.97
2.00
f1 (ppm)


O
OPMB
202
200.47
159.15
136.60
130.52
129.22
127.94
113.77
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
72.51
68.98
55.26
36.18
23.97
f1 (ppm)


OTBS
OPMB
203
f1 (ppm)


OTBS
OPMB
203
f1 (ppm)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OPMB
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7.25
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6.89
6.88
6.24
6.22
6.19
5.70
5.68
5.66
5.53
5.49
5.27
5.25
4.45
3.80
3.55
3.54
3.52
2.59
2.58
2.56
2.54
2.03
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1.01
1.02
1.02
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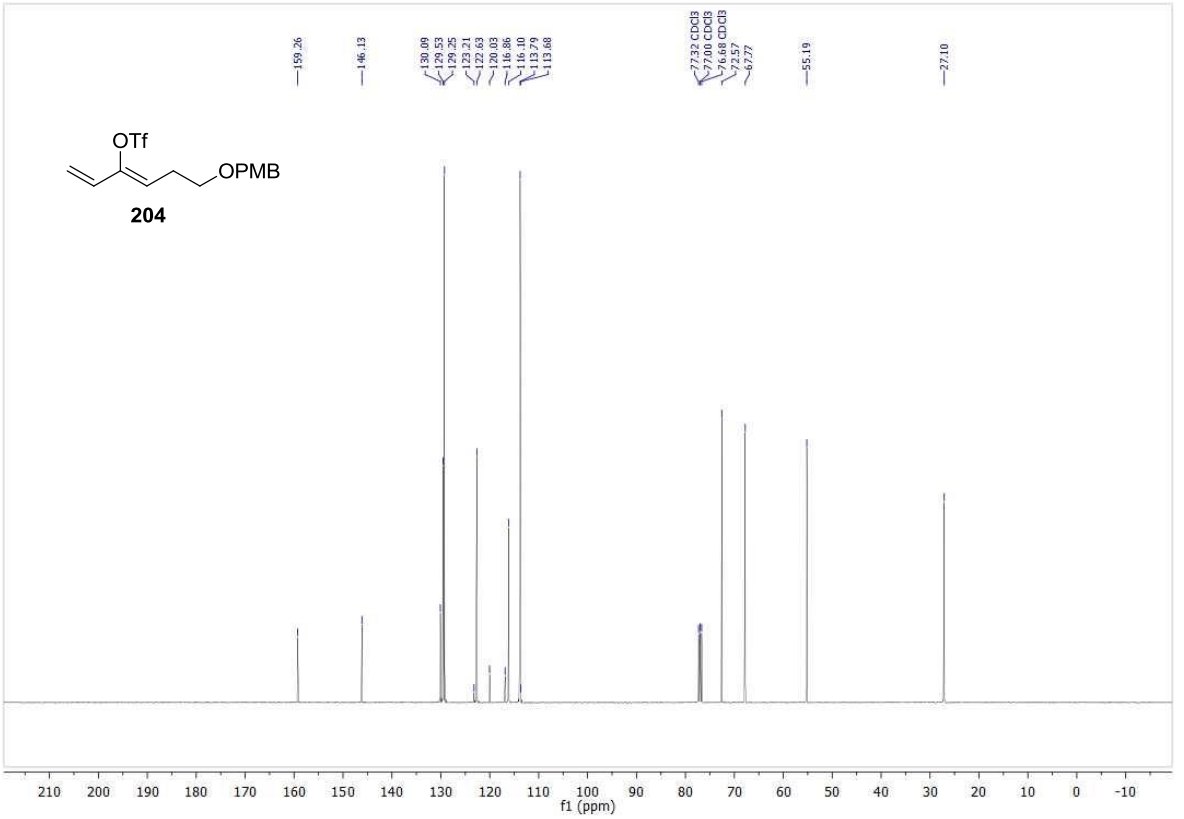
3.07
2.07
2.05
f1 (ppm)


OTf
OPMB
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130.09
129.53
129.25
123.21
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116.86
116.10
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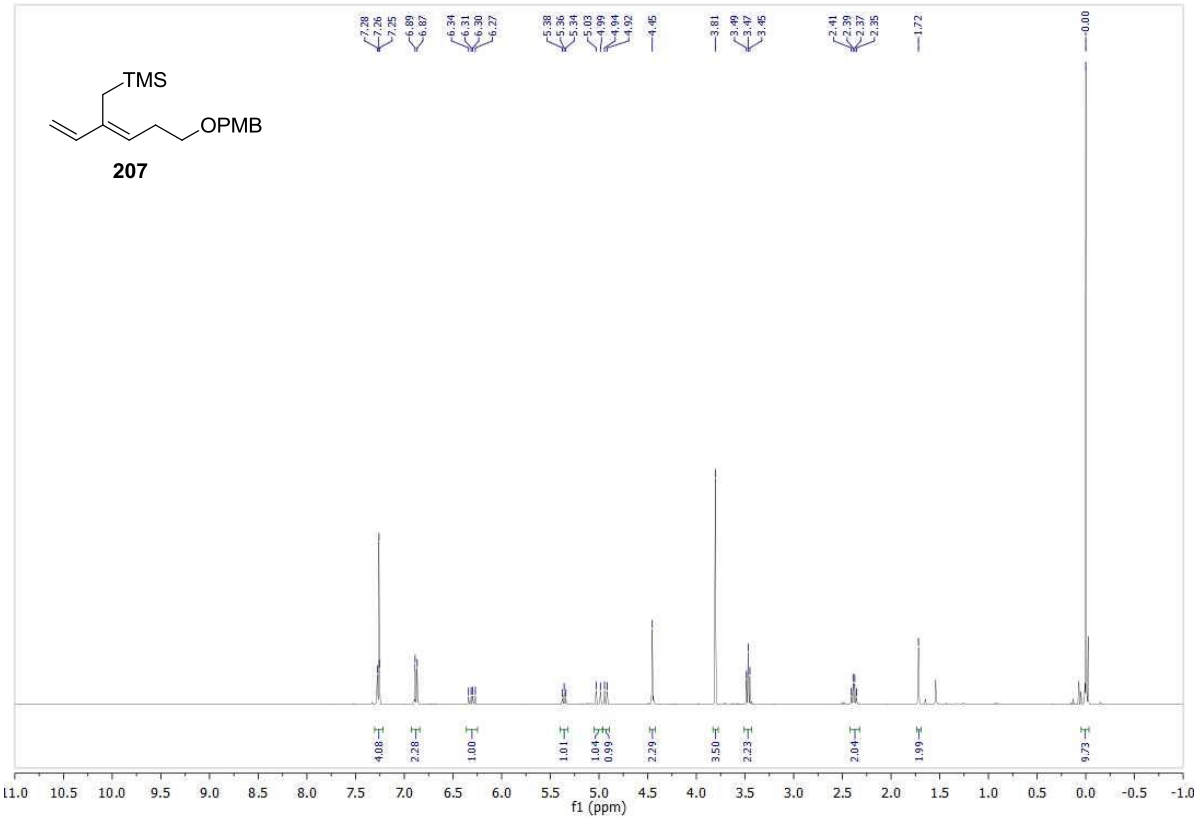
113.68
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
72.57
67.77
55.19
27.10
f1 (ppm)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OPMB
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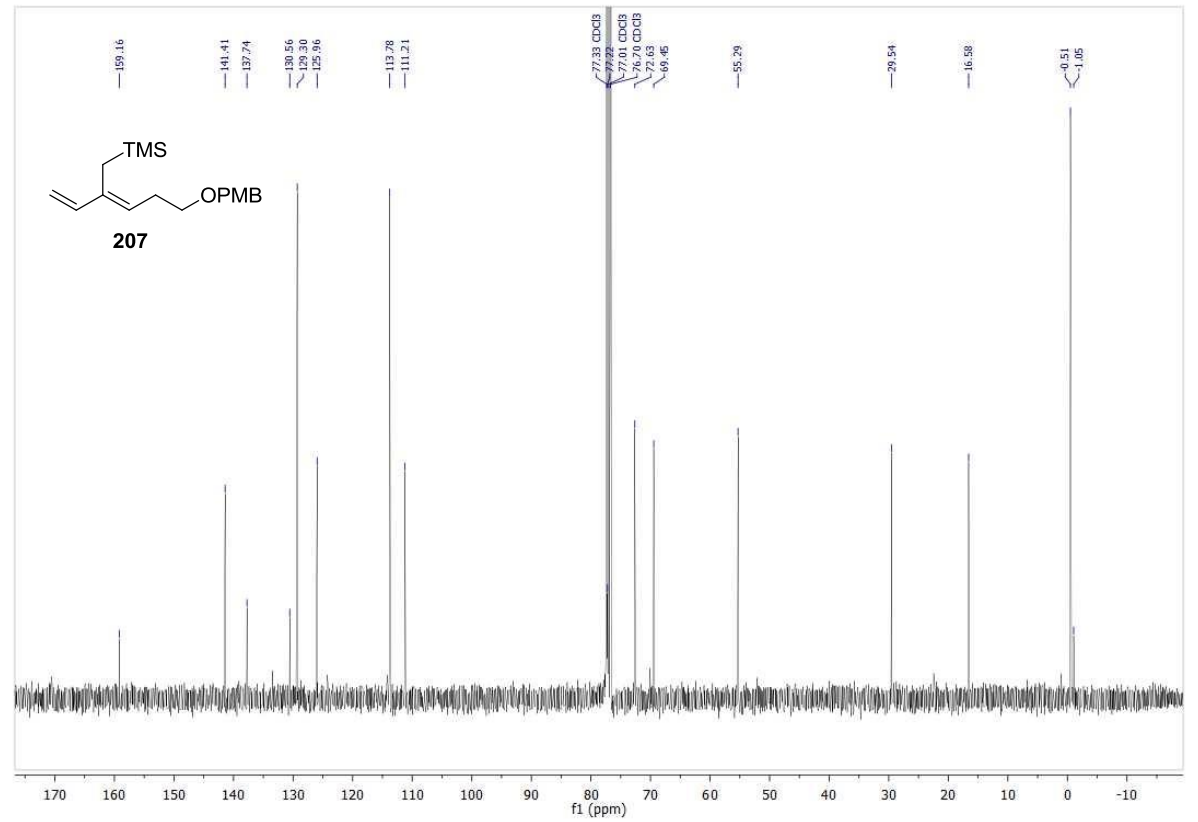
f1 (ppm)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OPMB
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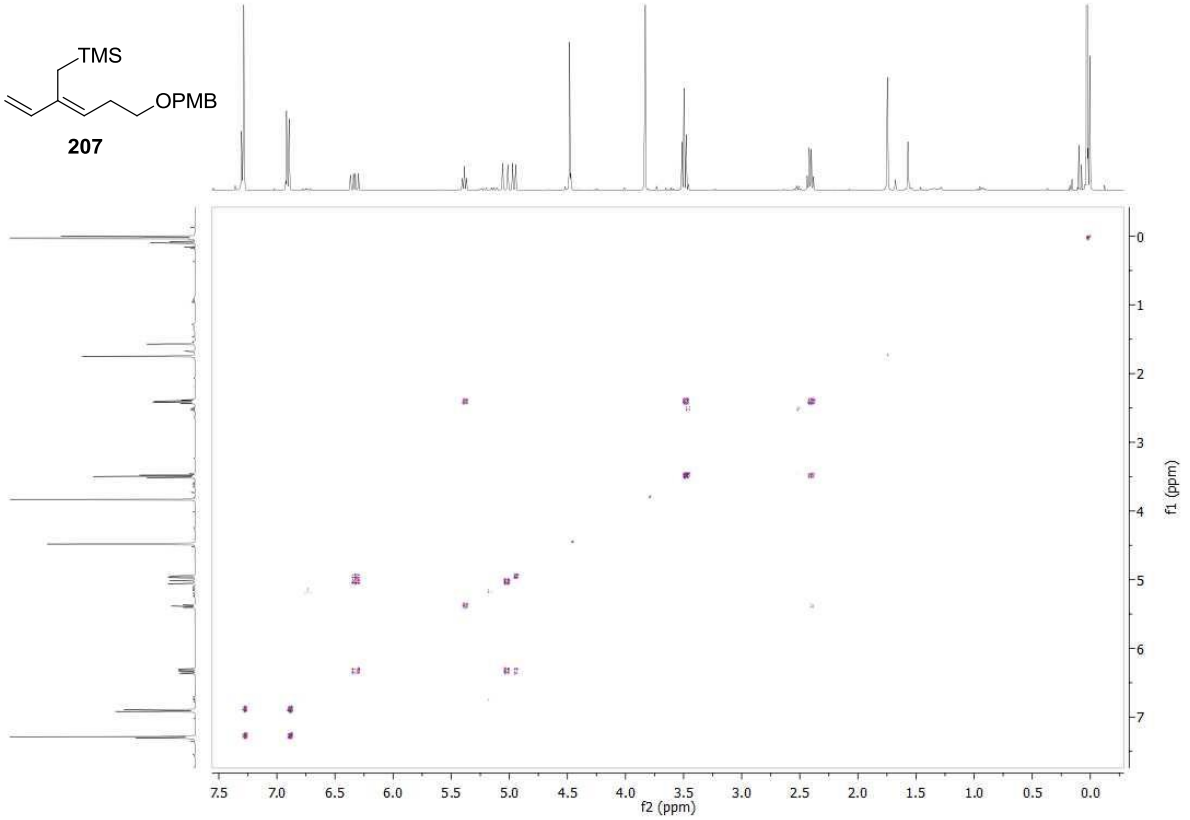
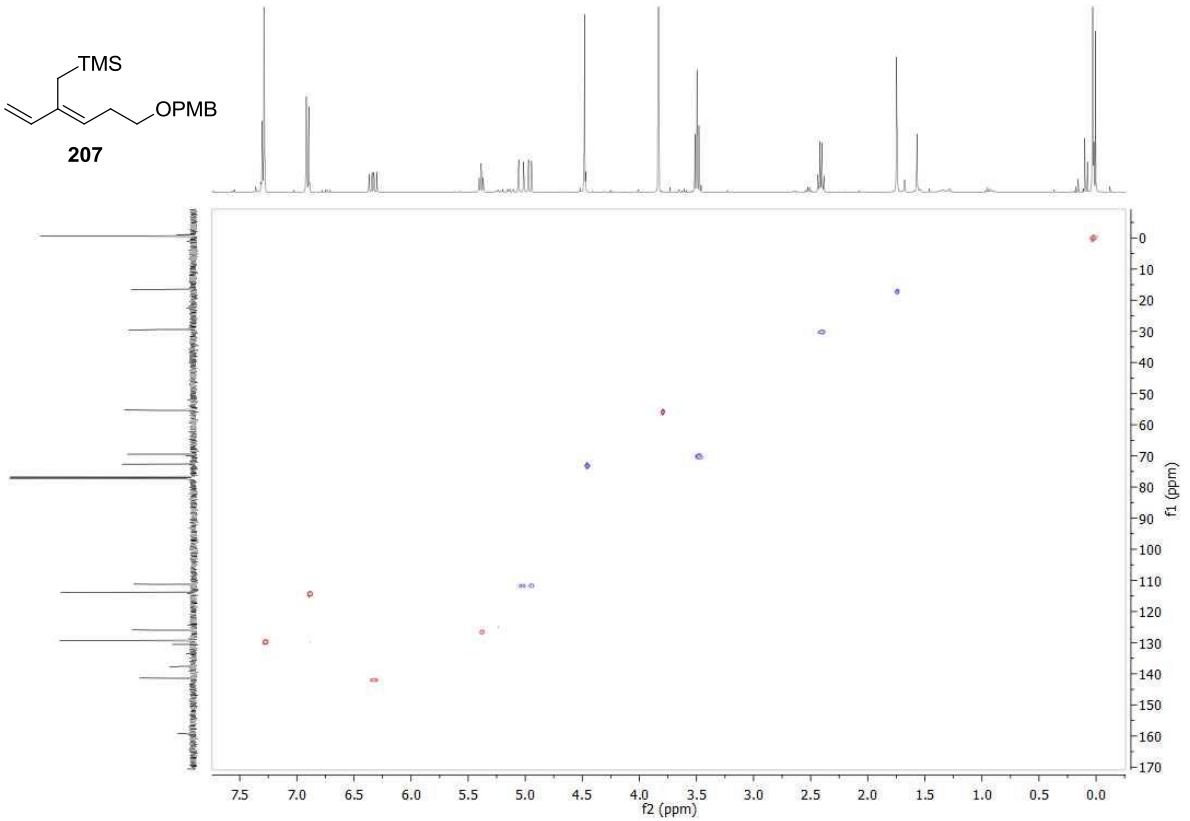
f1 (ppm)


TMS
OPMB
207
f2 (ppm)
f1 (ppm)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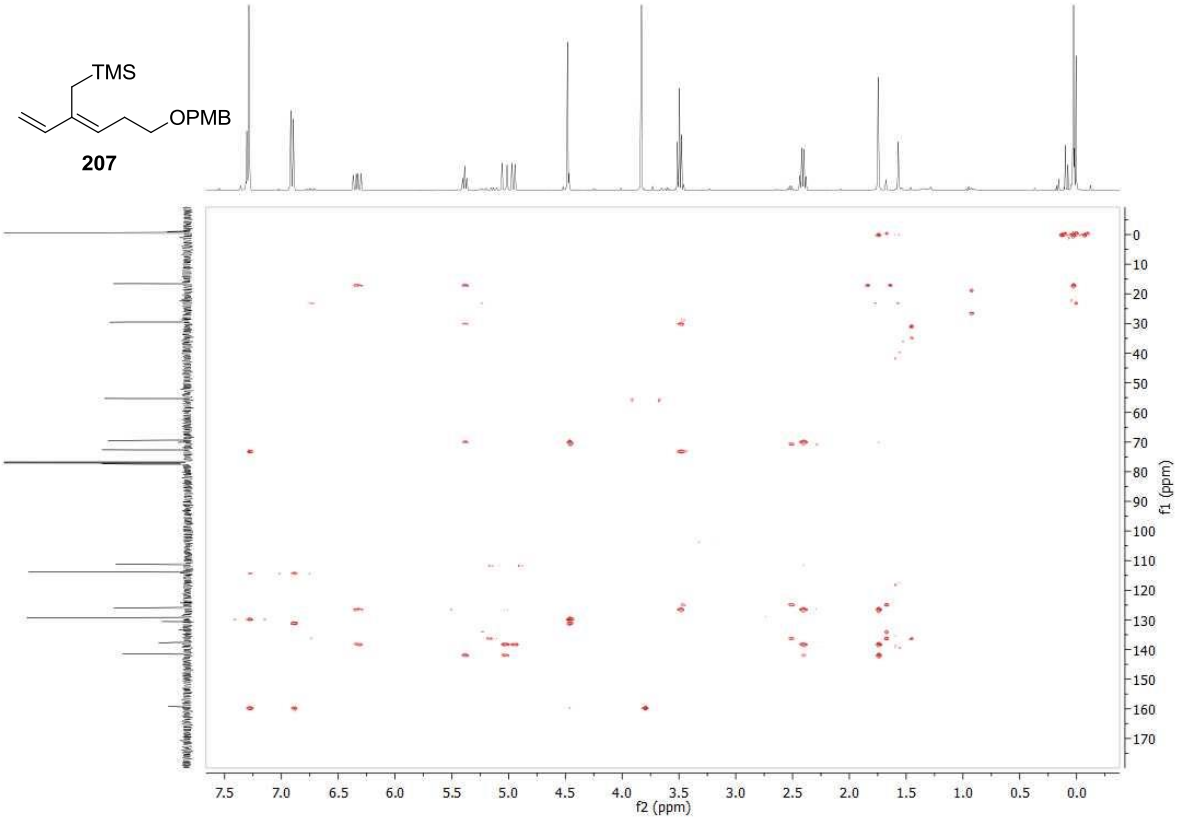
f2 (ppm)
f1 (ppm)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OPMB
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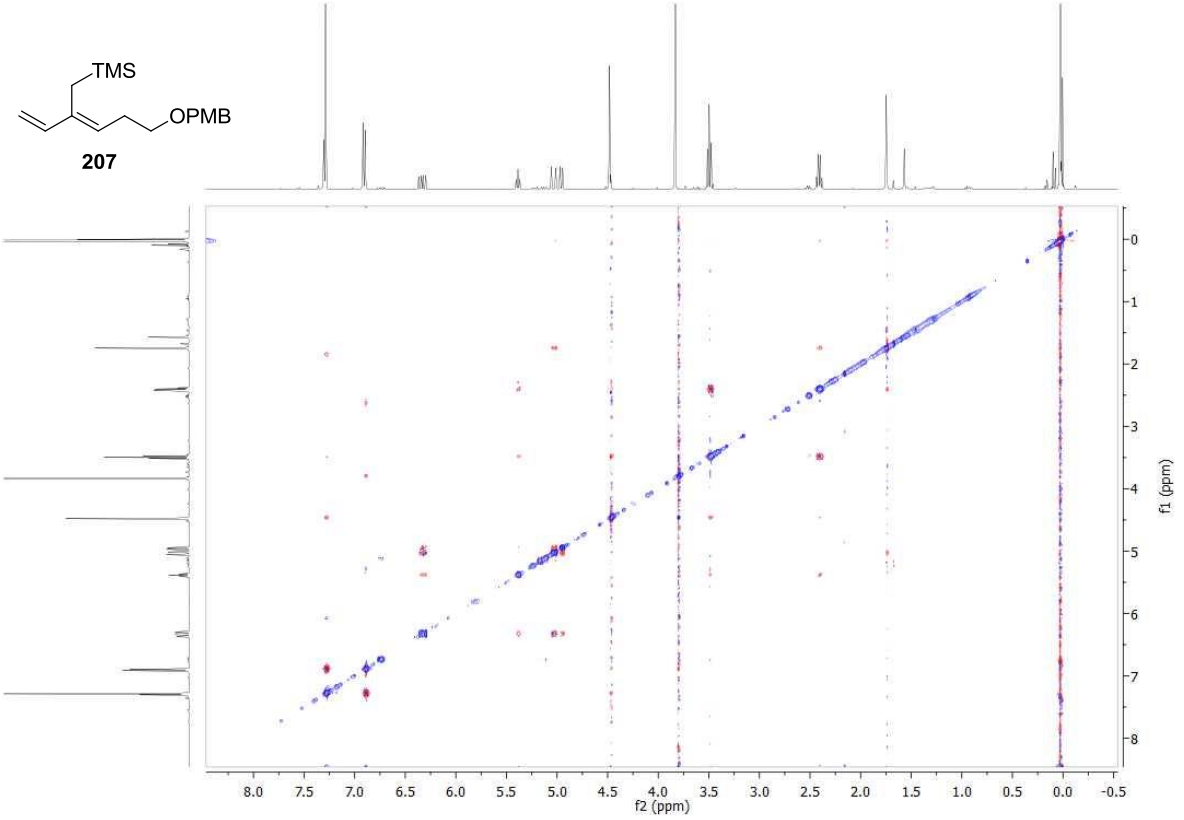
f2 (ppm)
f1 (ppm)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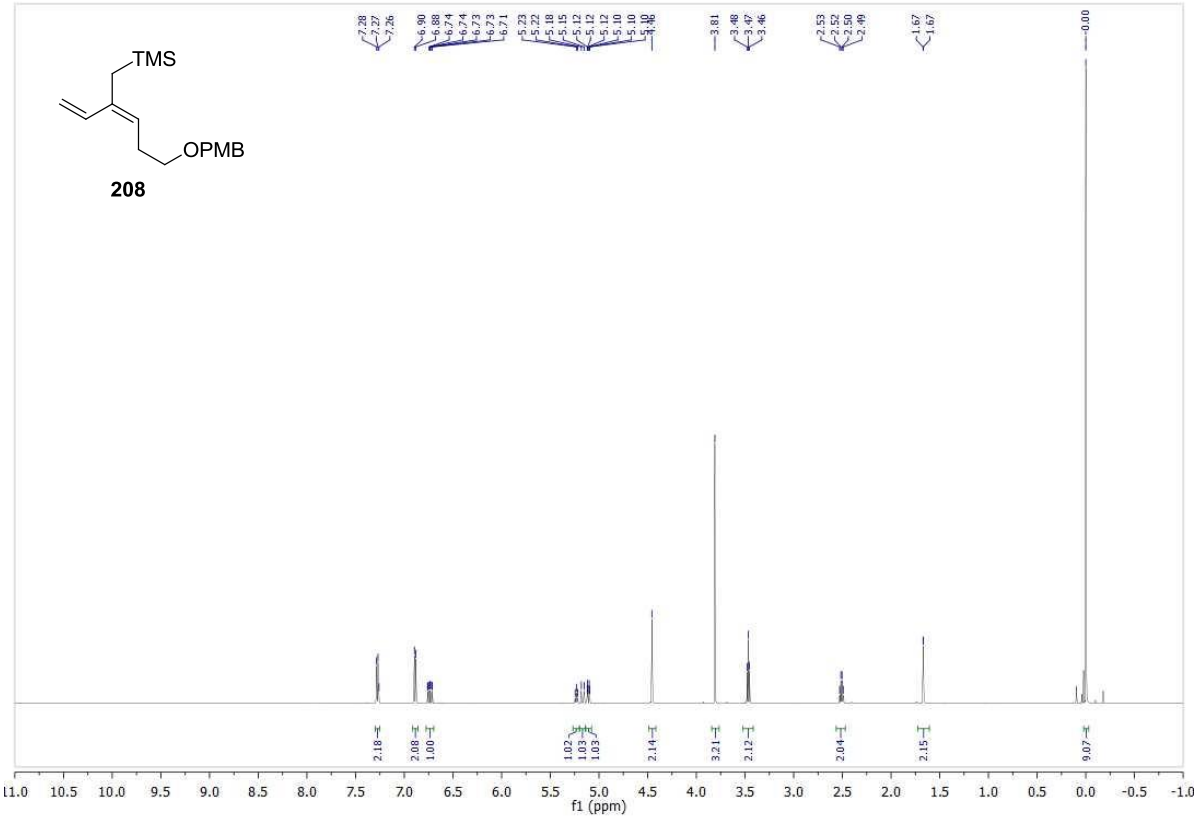
f2 (ppm)
f1 (ppm)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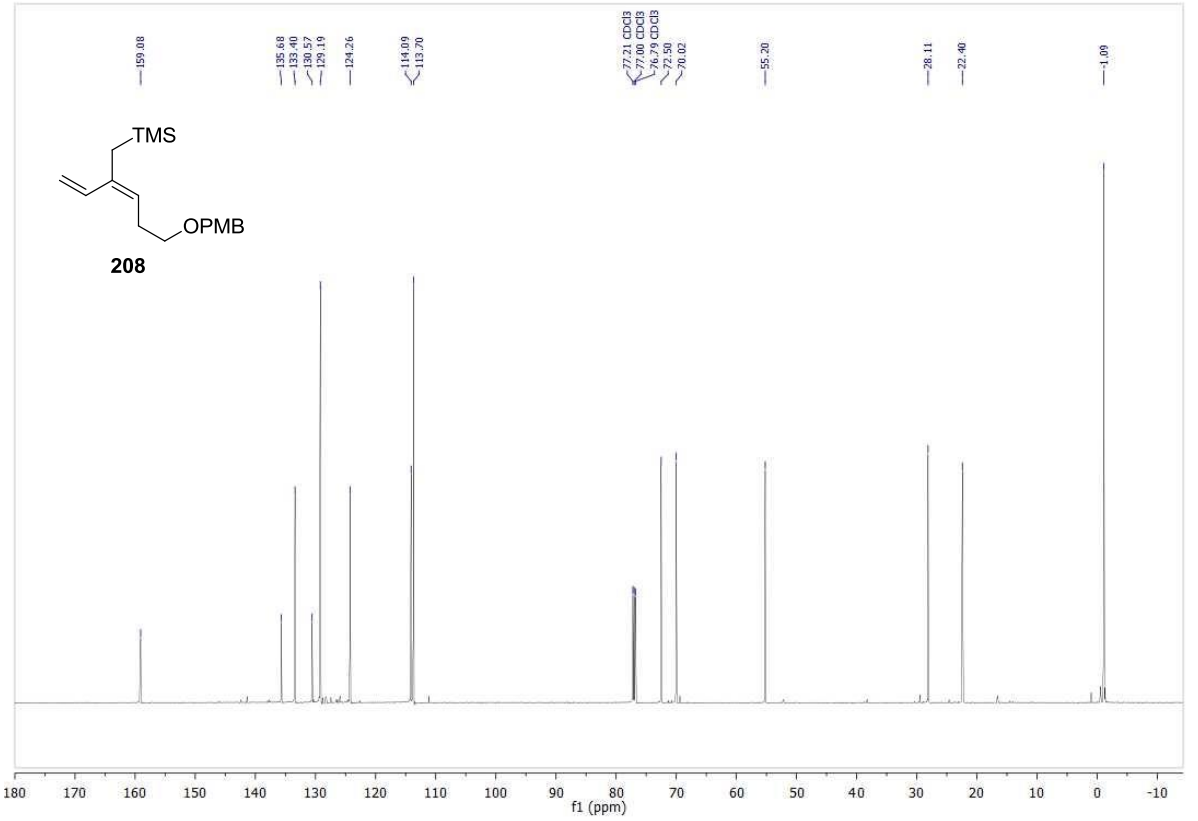
f1 (ppm)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OPMB
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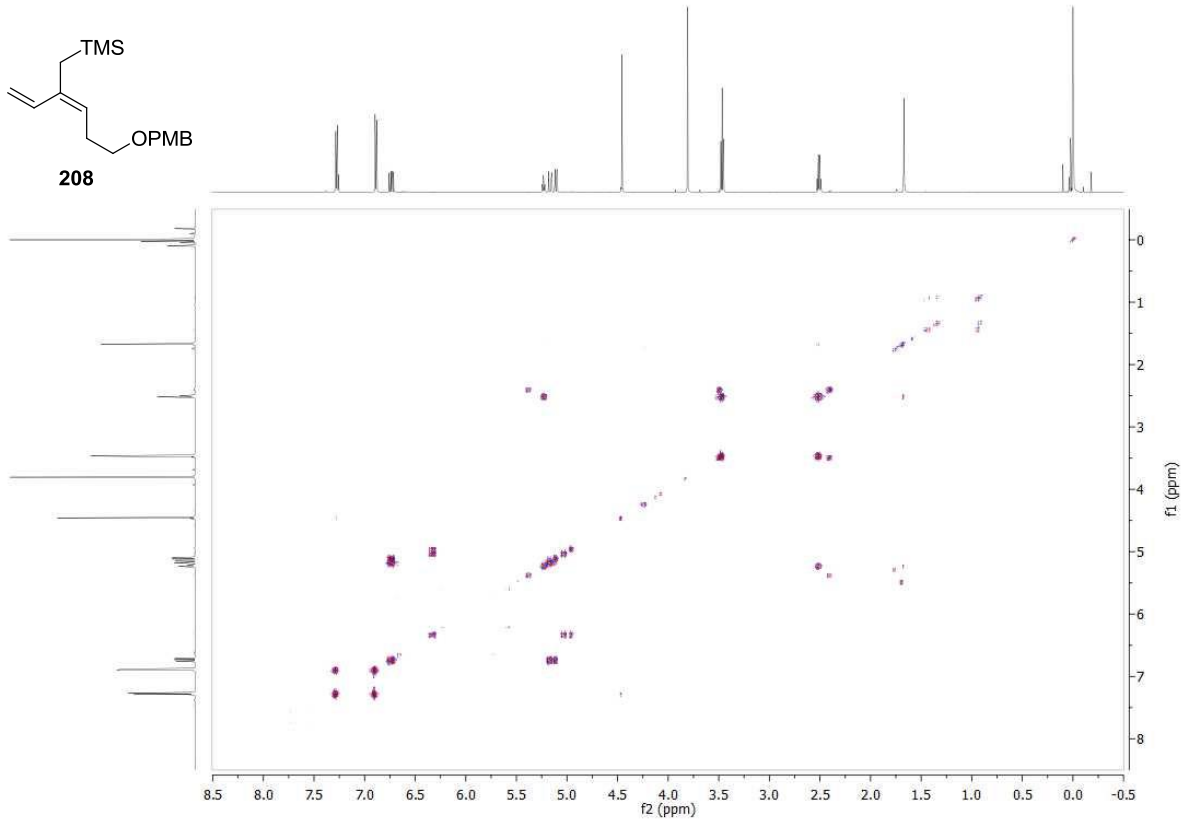
f1 (ppm)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OPMB
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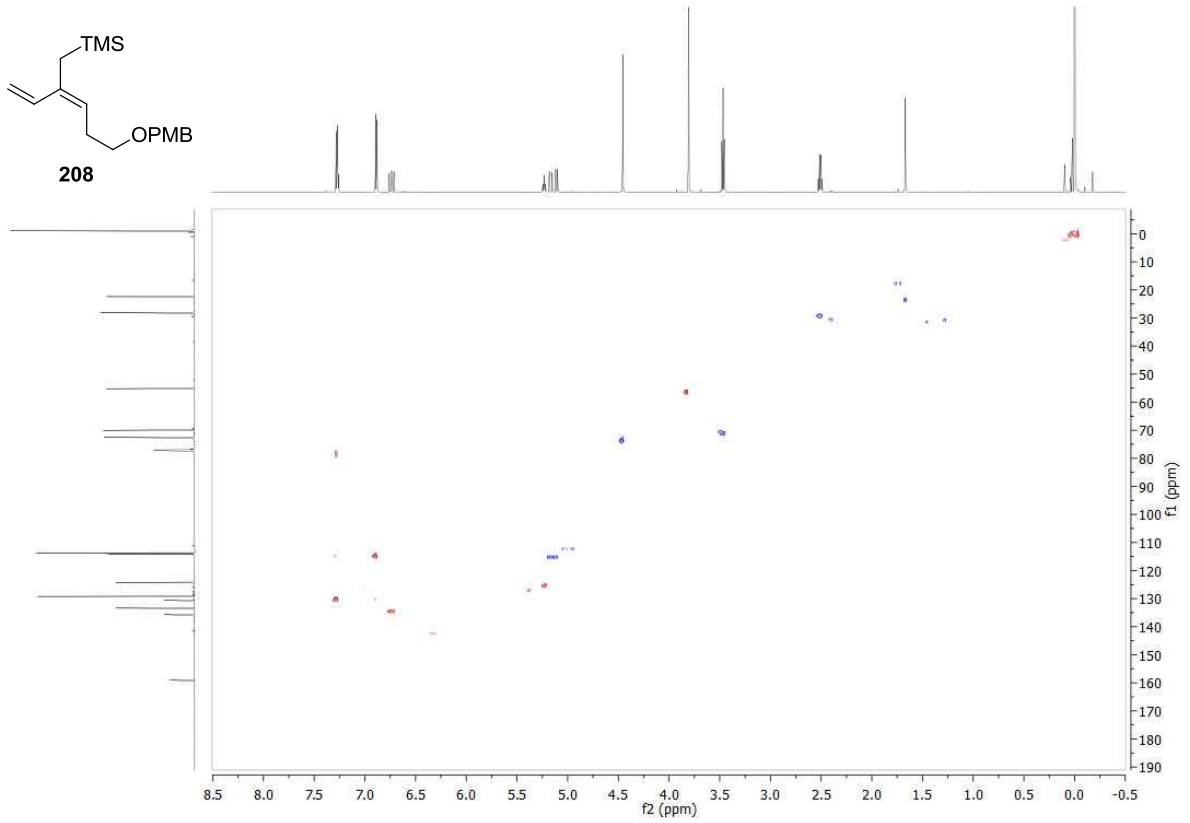
f2 (ppm)
f1 (ppm)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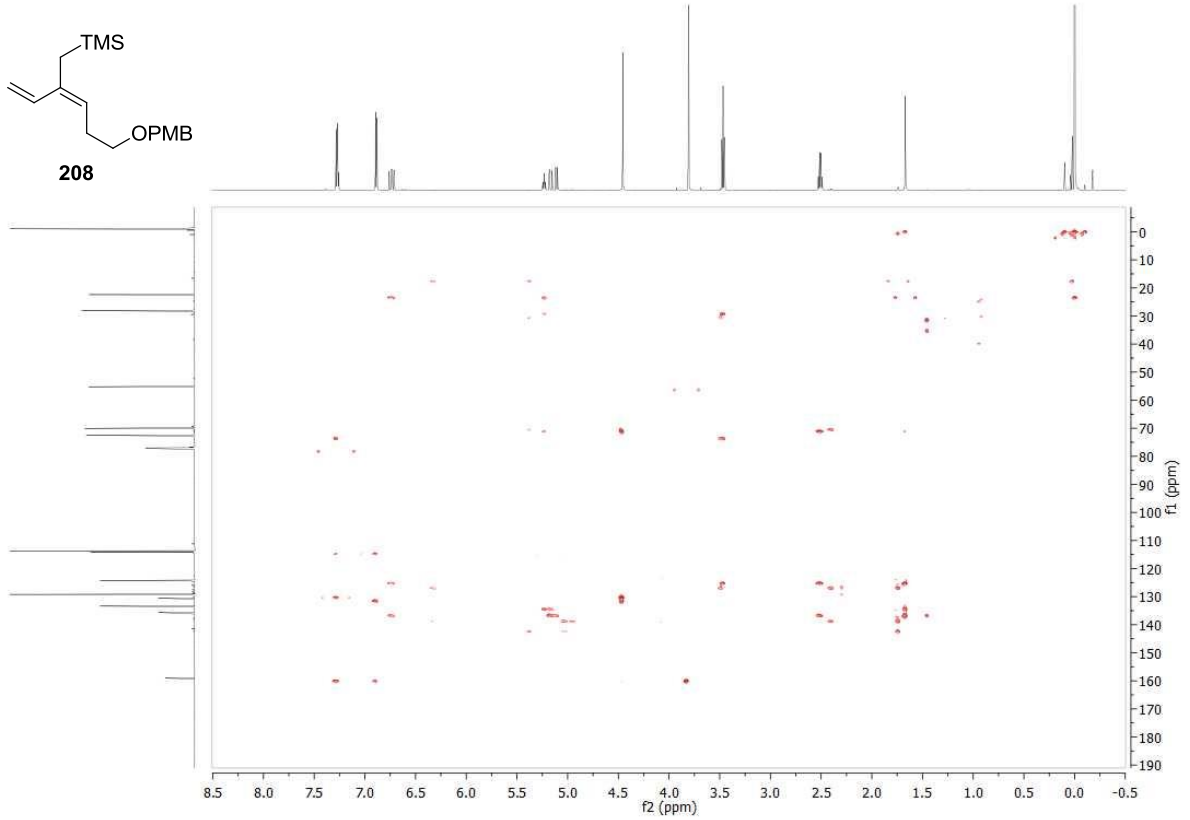
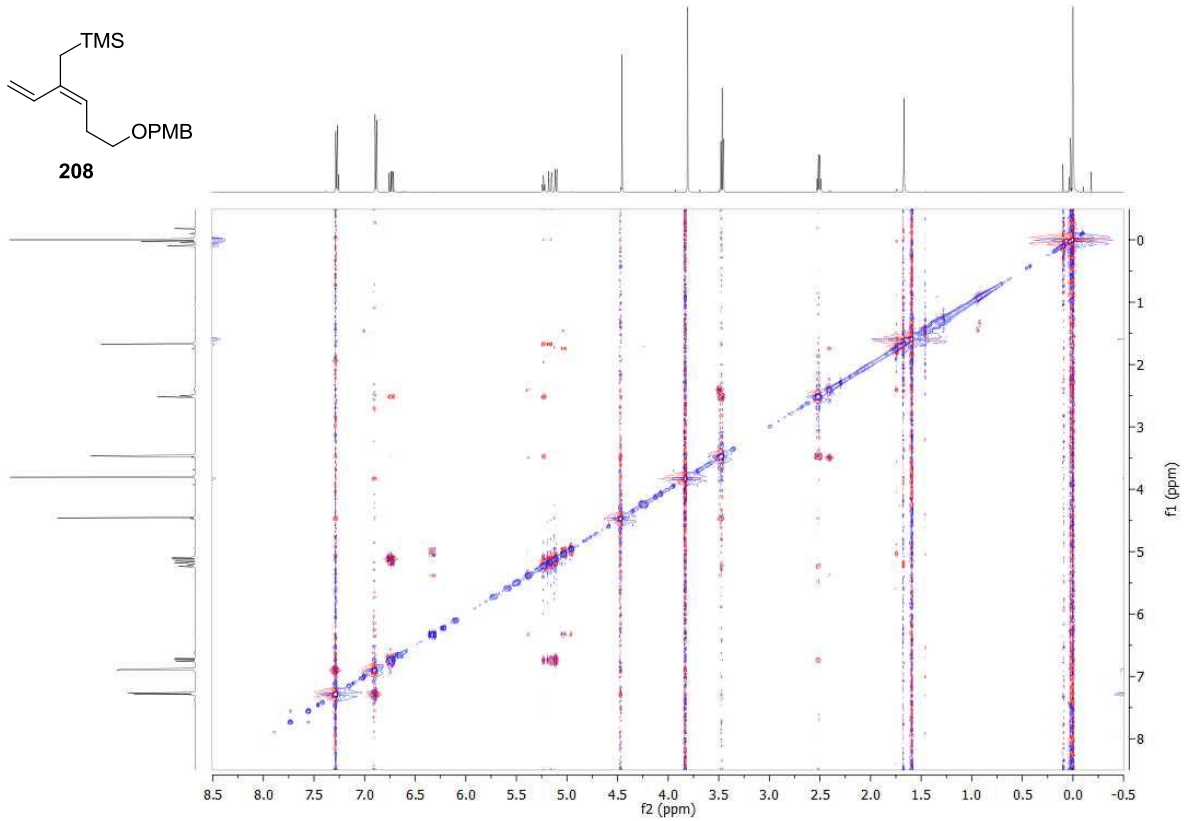
OPMB
208
f2 (ppm)
f1 (ppm)


TMS
OPMB
208
f2 (ppm)
f1 (ppm)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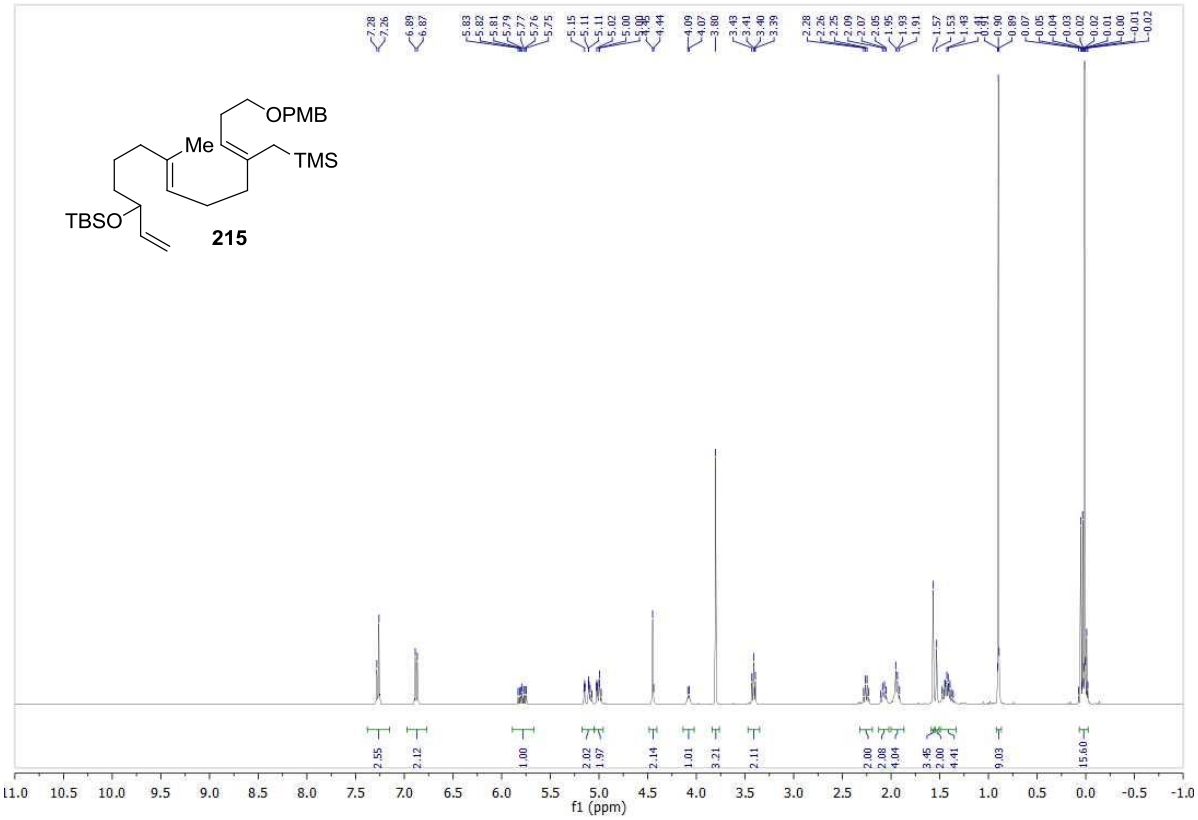
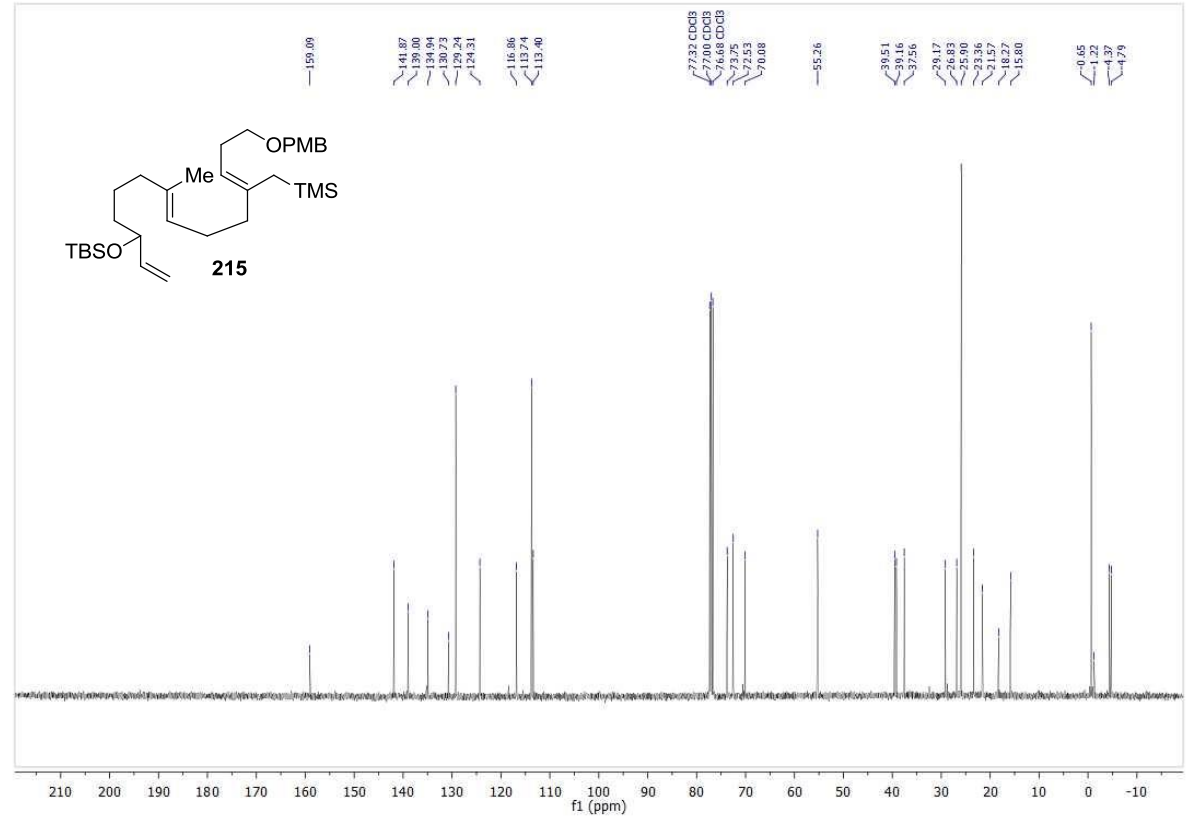
OPMB
208
f2 (ppm)
f1 (ppm)


OPMB
Me
TMS
TBSO
215
f1 (ppm)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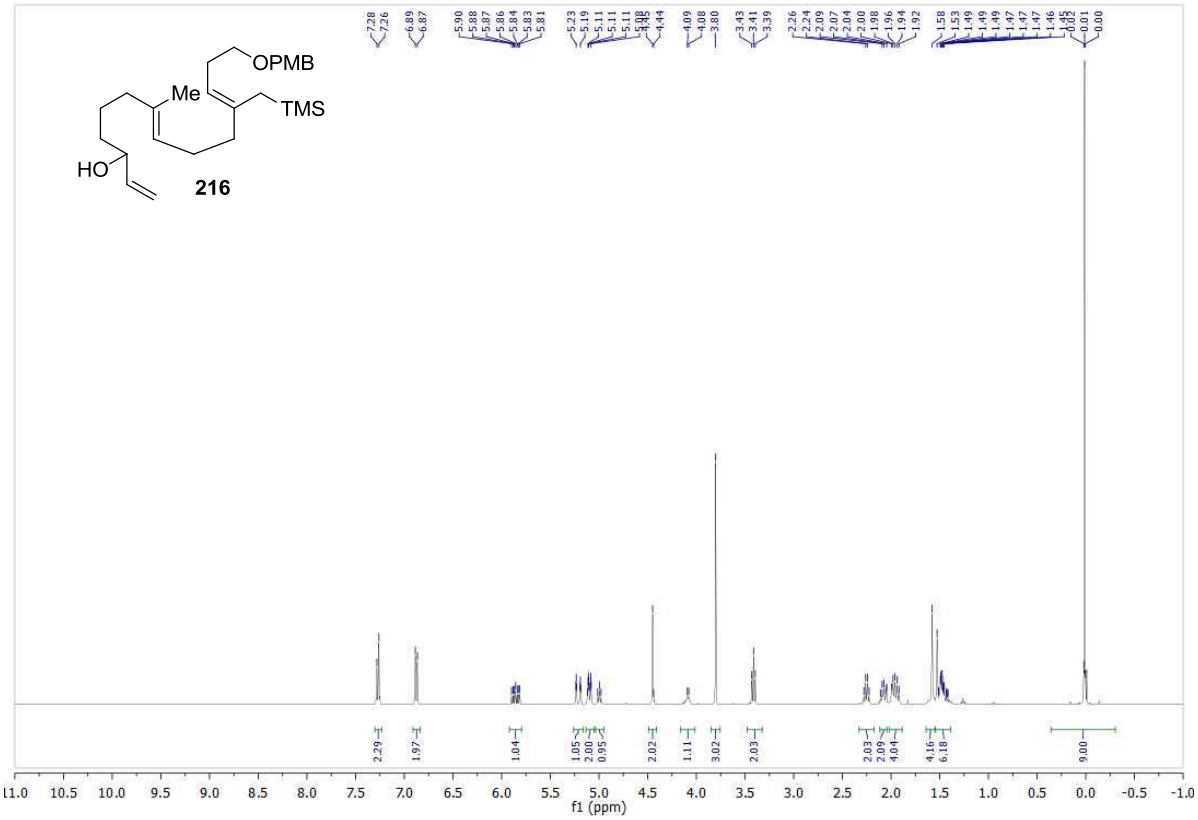
TMS
TBSO
215
f1 (ppm)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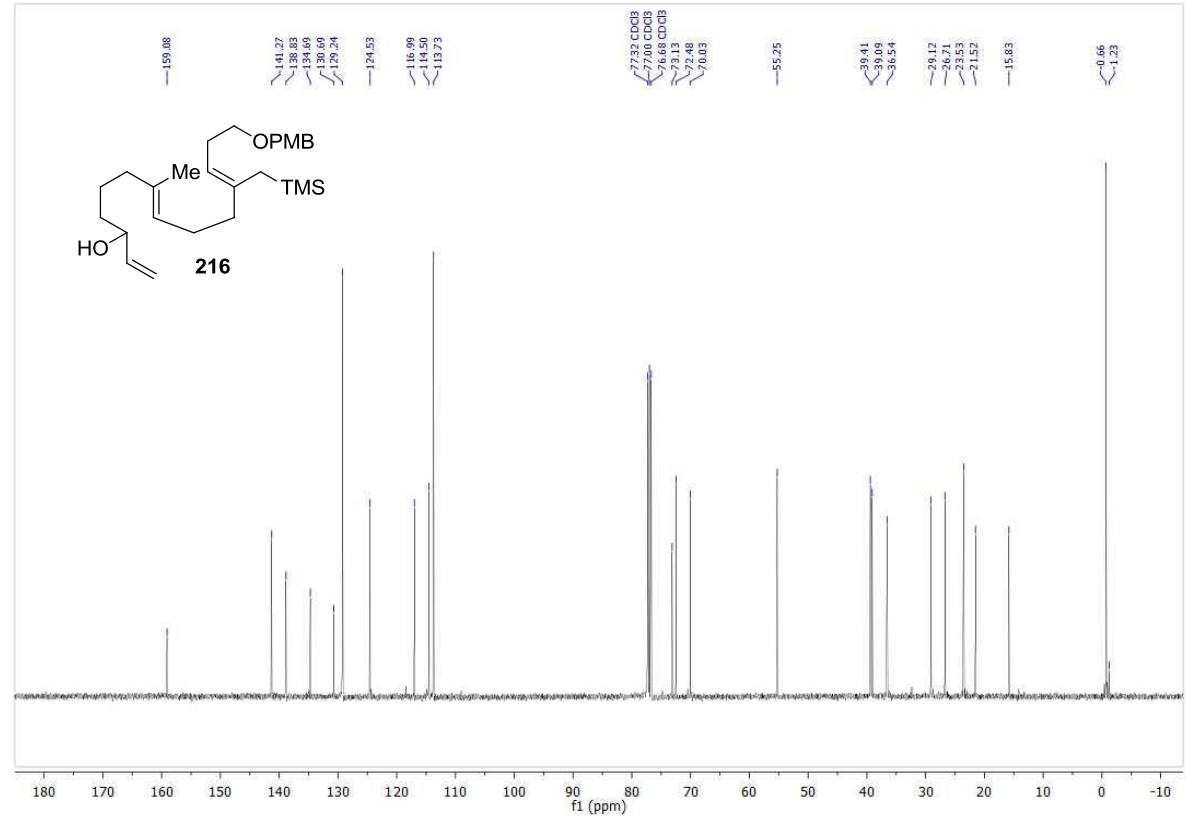
TMS
HO
216
f1 (ppm)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TMS
HO
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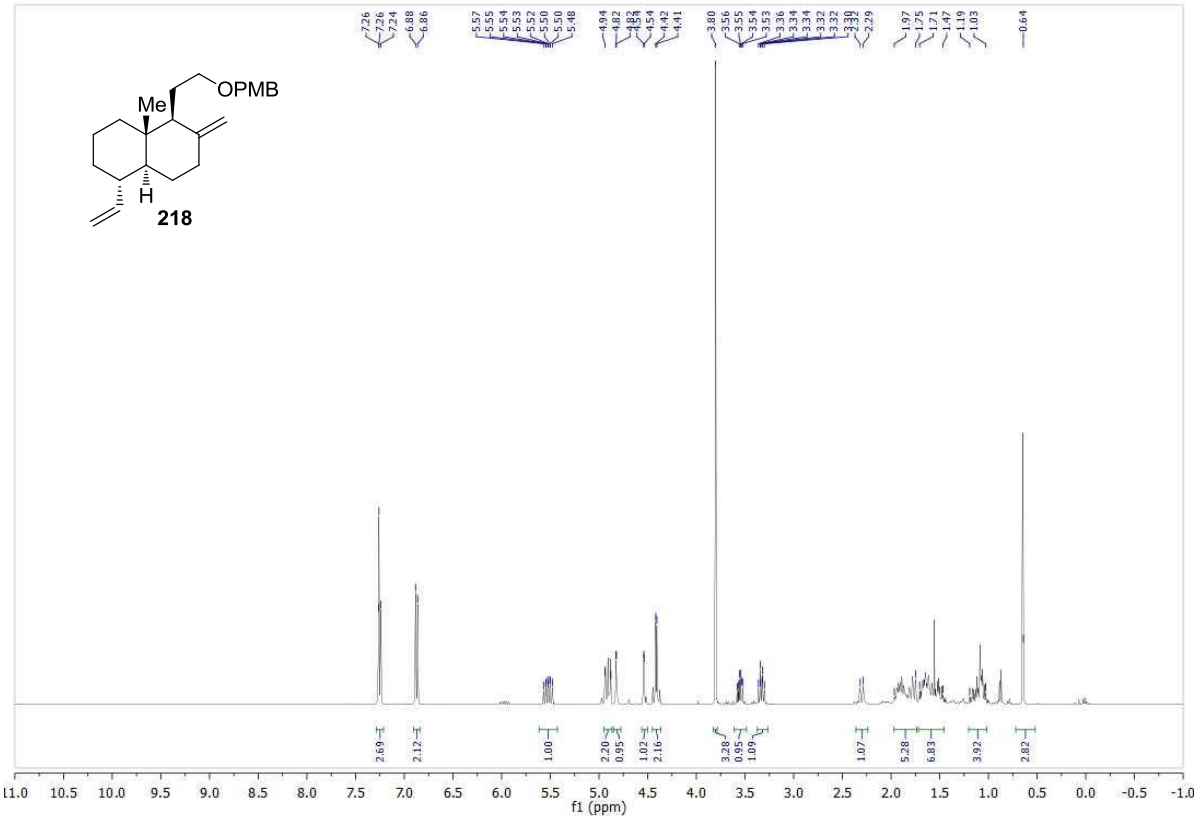
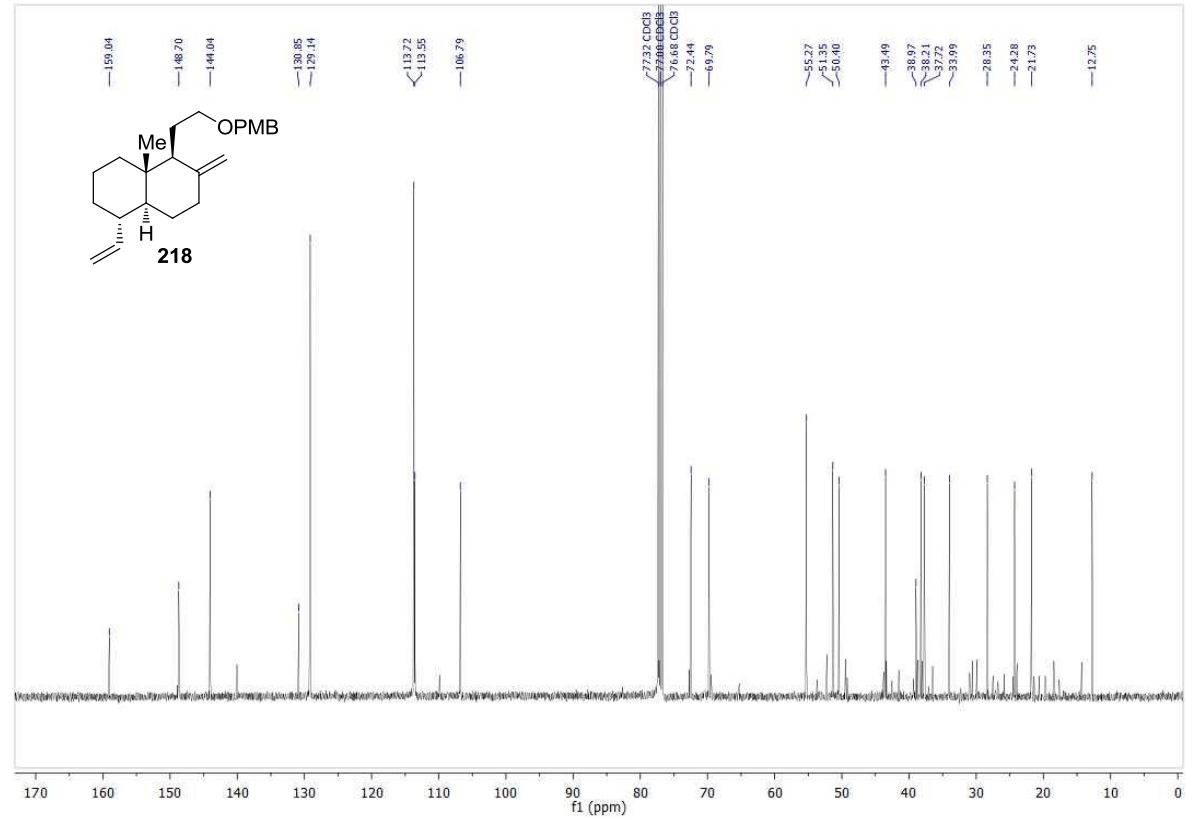
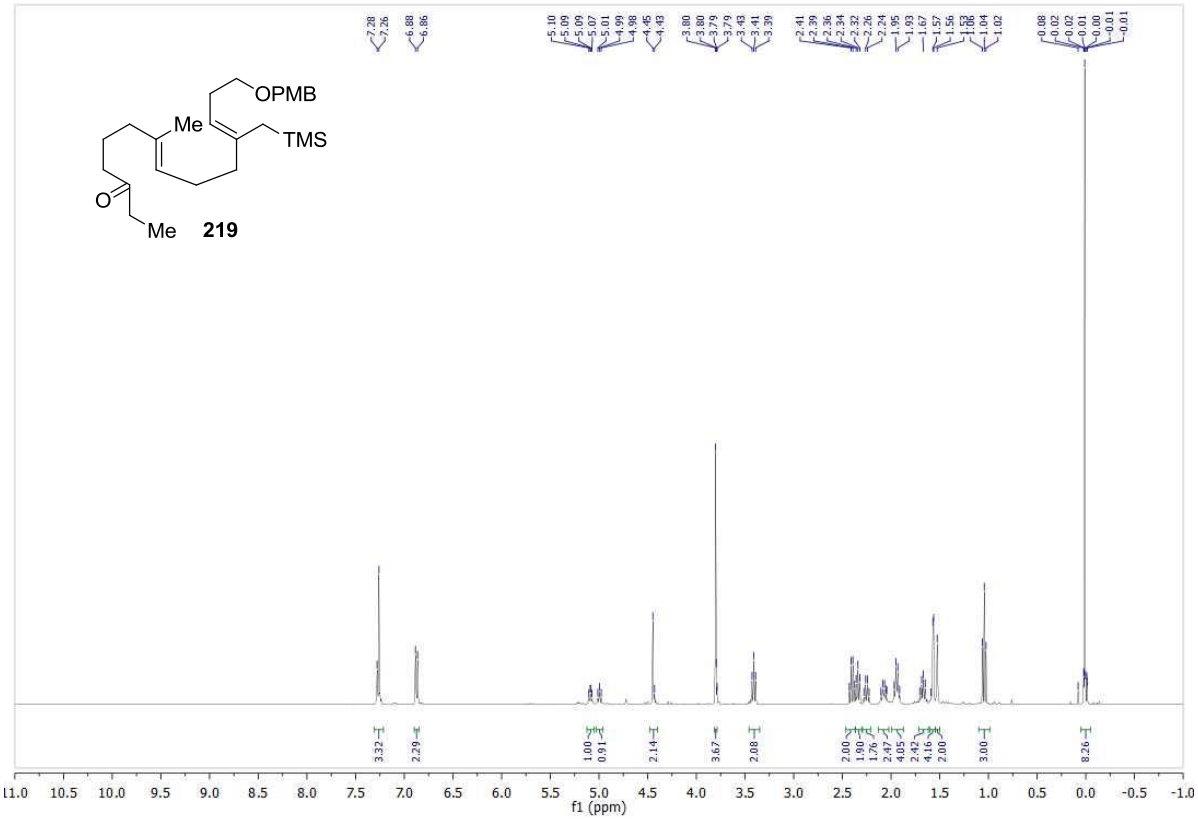
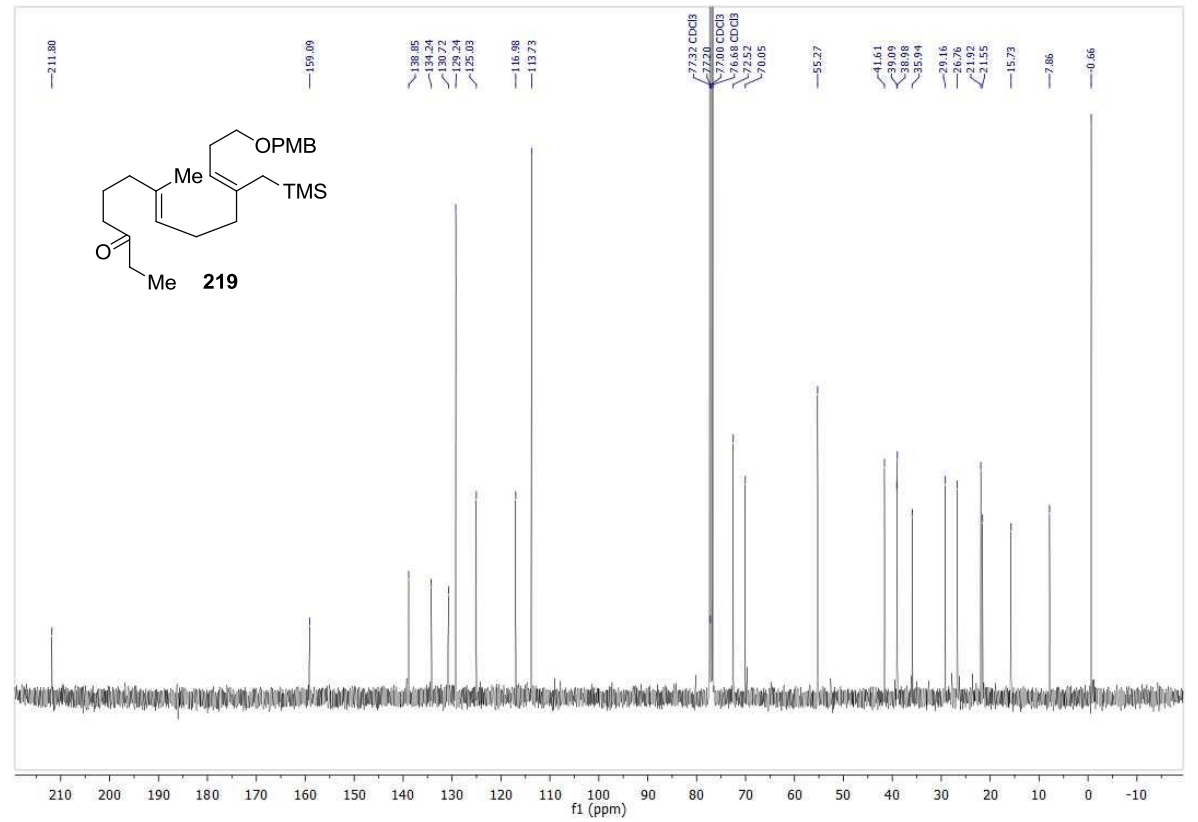
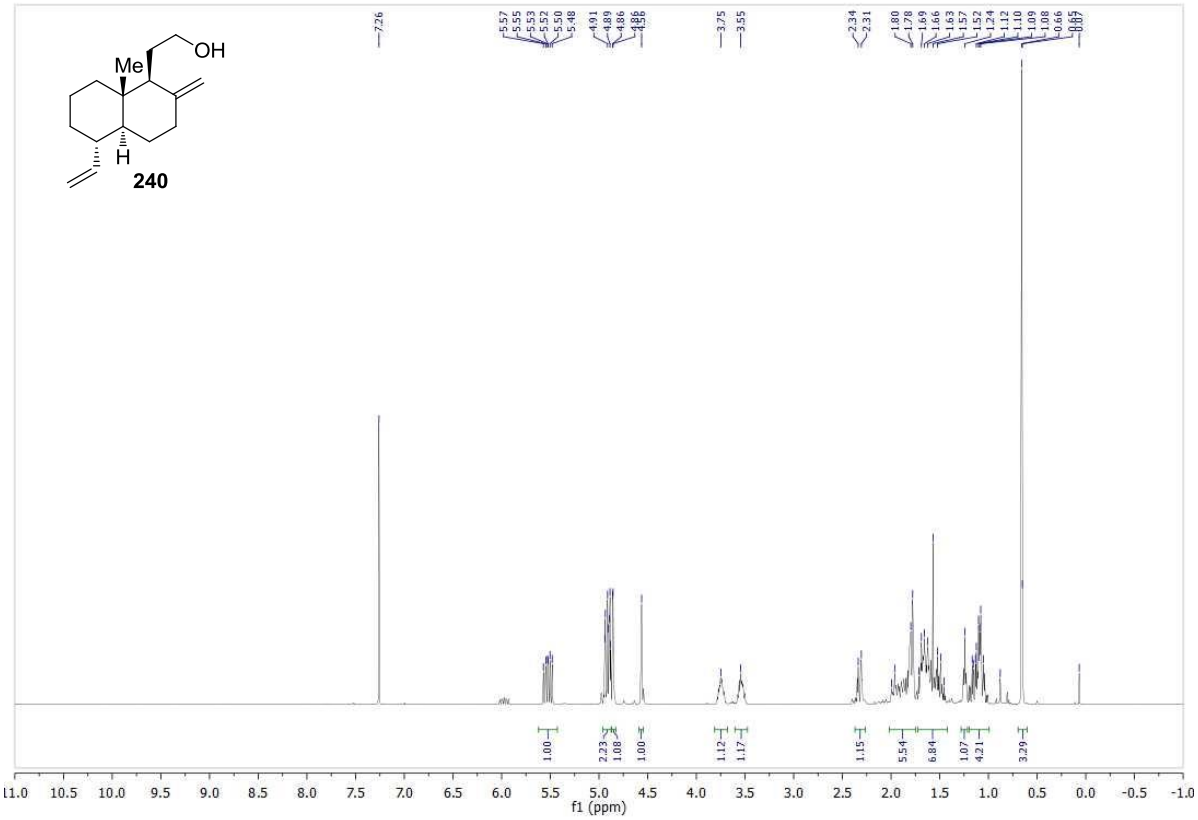
f1 (ppm)


OPMB
Me
H
218
f1 (ppm)


OPMB
Me
H
218
f1 (ppm)


OPMB
Me
TMS
O
Me
219
f1 (ppm)


OPMB
Me
TMS
O
Me
219
f1 (ppm)


OH
Me
H
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5.52
5.50
5.48
4.91
4.89
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4.86
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1.78
1.69
1.66
1.63
1.57
1.52
1.24
1.12
1.10
1.09
1.08
0.66
0.65
0.65
1.00
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1.07
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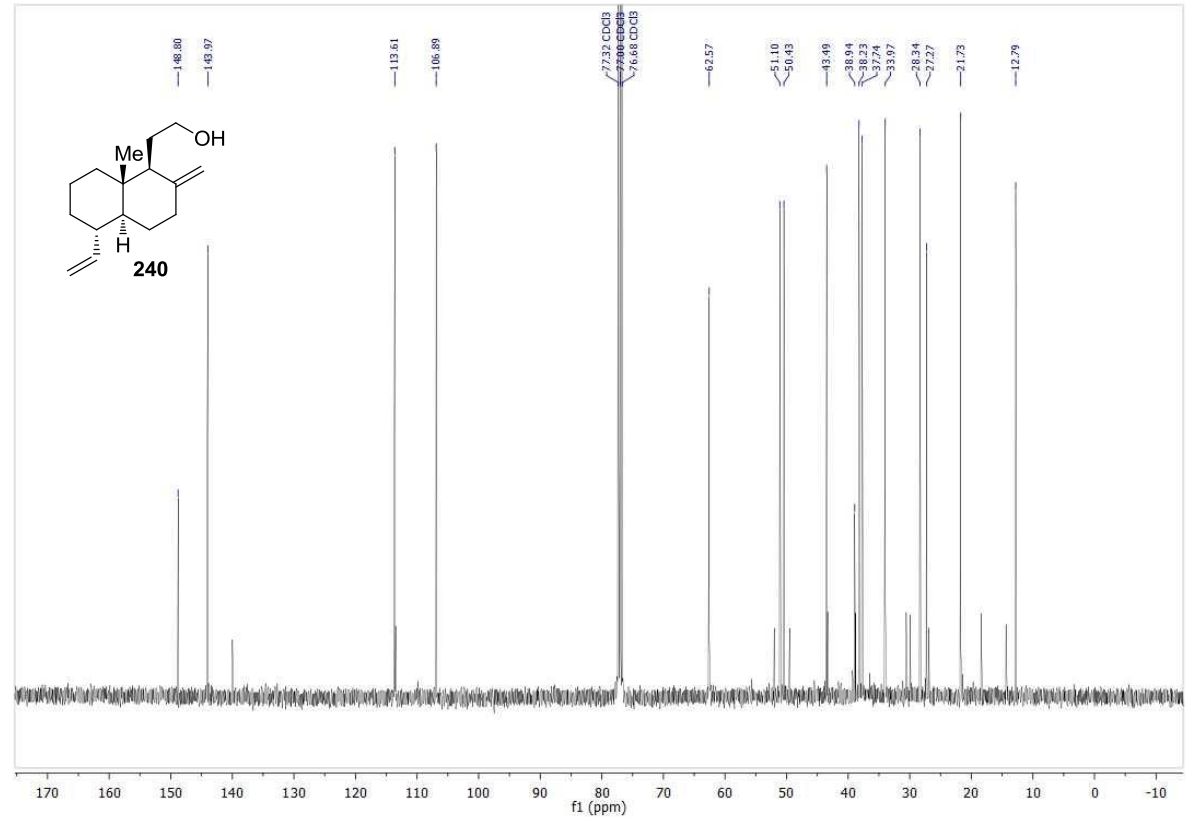
3.29
f1 (ppm)


OH
Me
H
240
148.80
143.97
113.61
106.89
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
62.57
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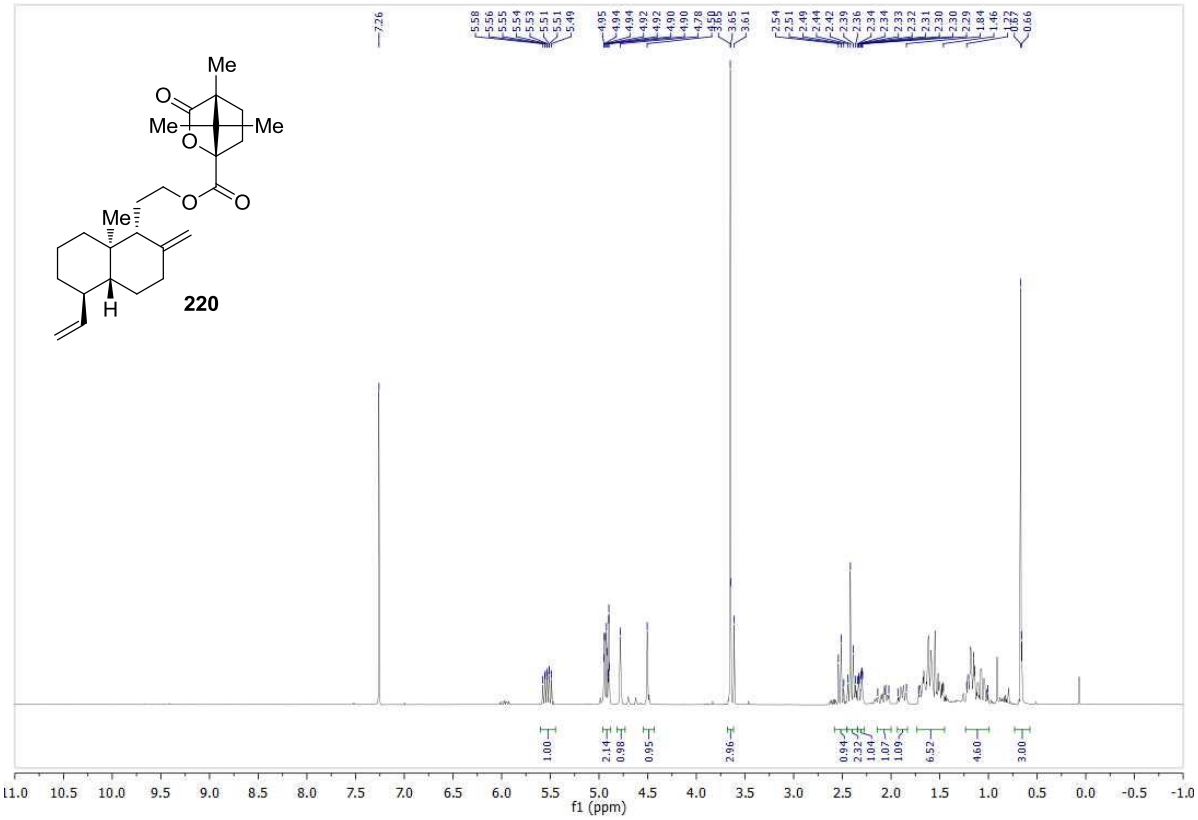
50.43
43.49
38.94
38.23
37.74
33.97
28.34
27.27
21.73
12.79
f1 (ppm)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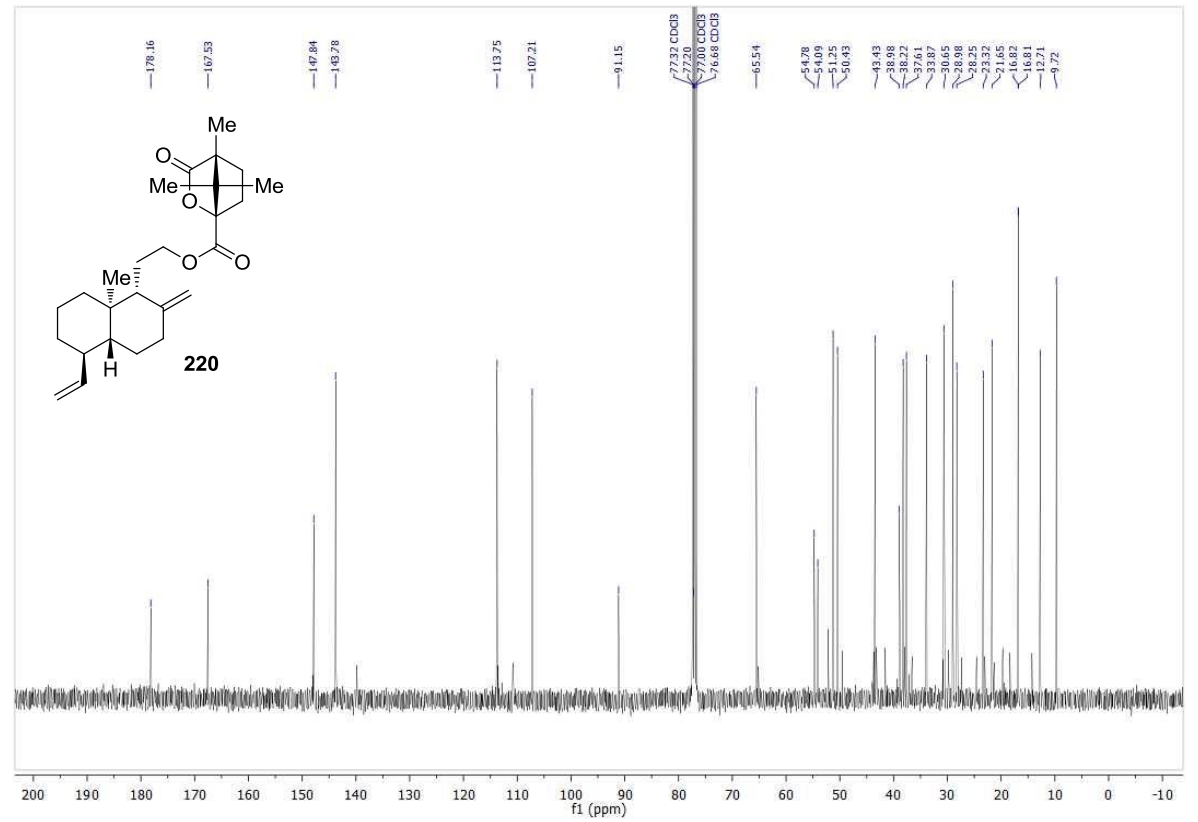
Me
Me
O
O
O
Me
H
220
f1 (ppm)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Me
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O
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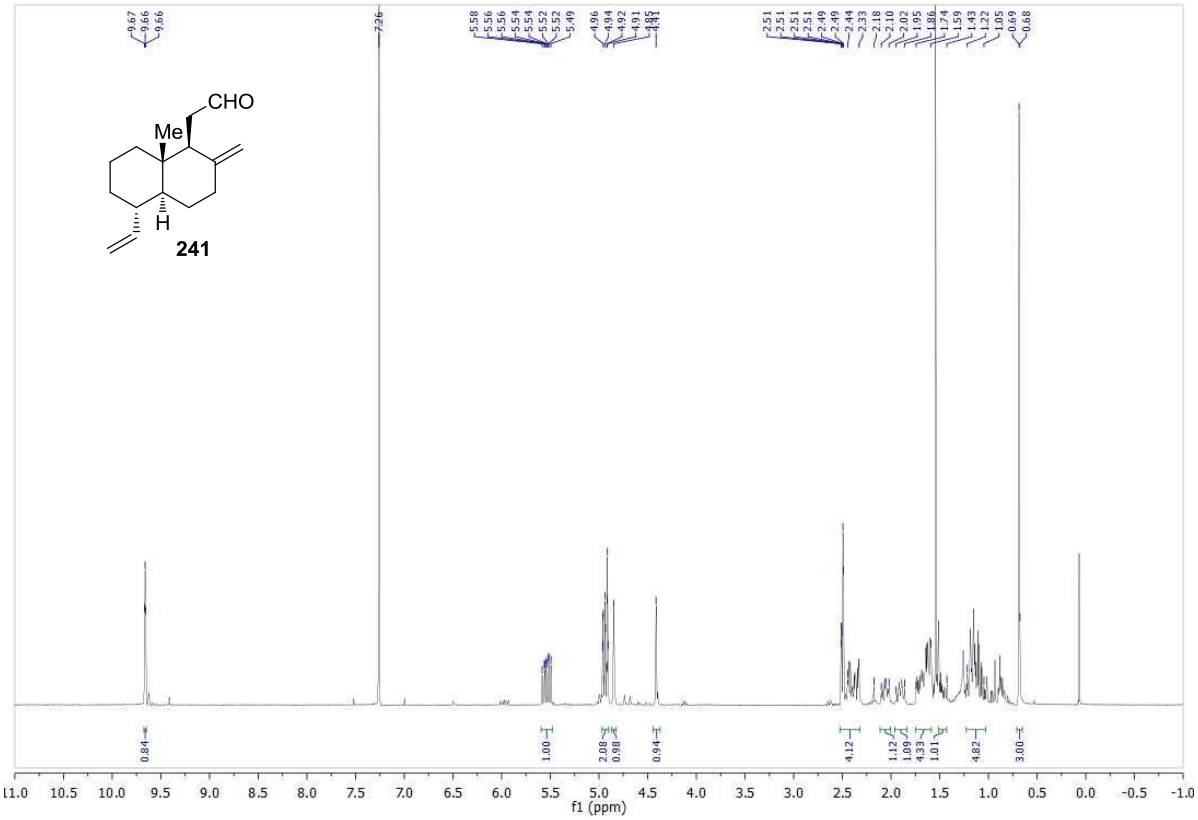
Me
H
220
f1 (ppm)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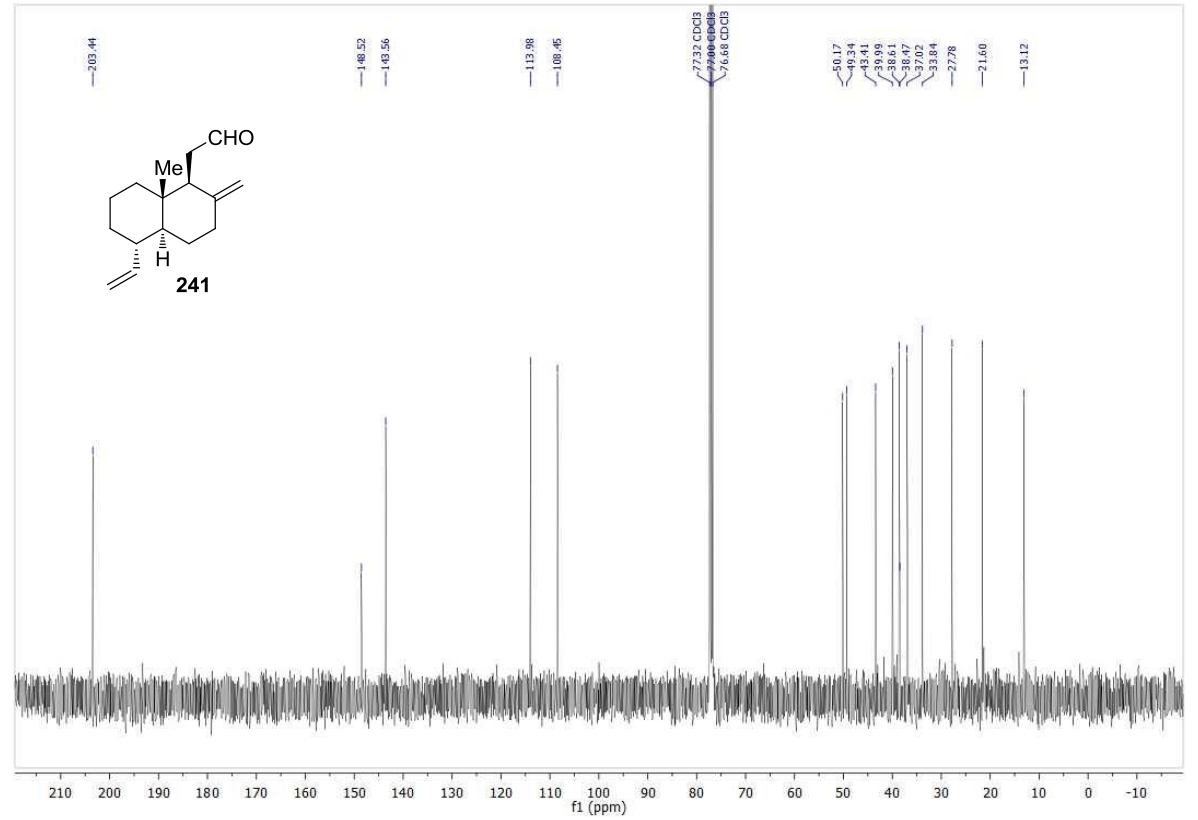
H
241
f1 (ppm)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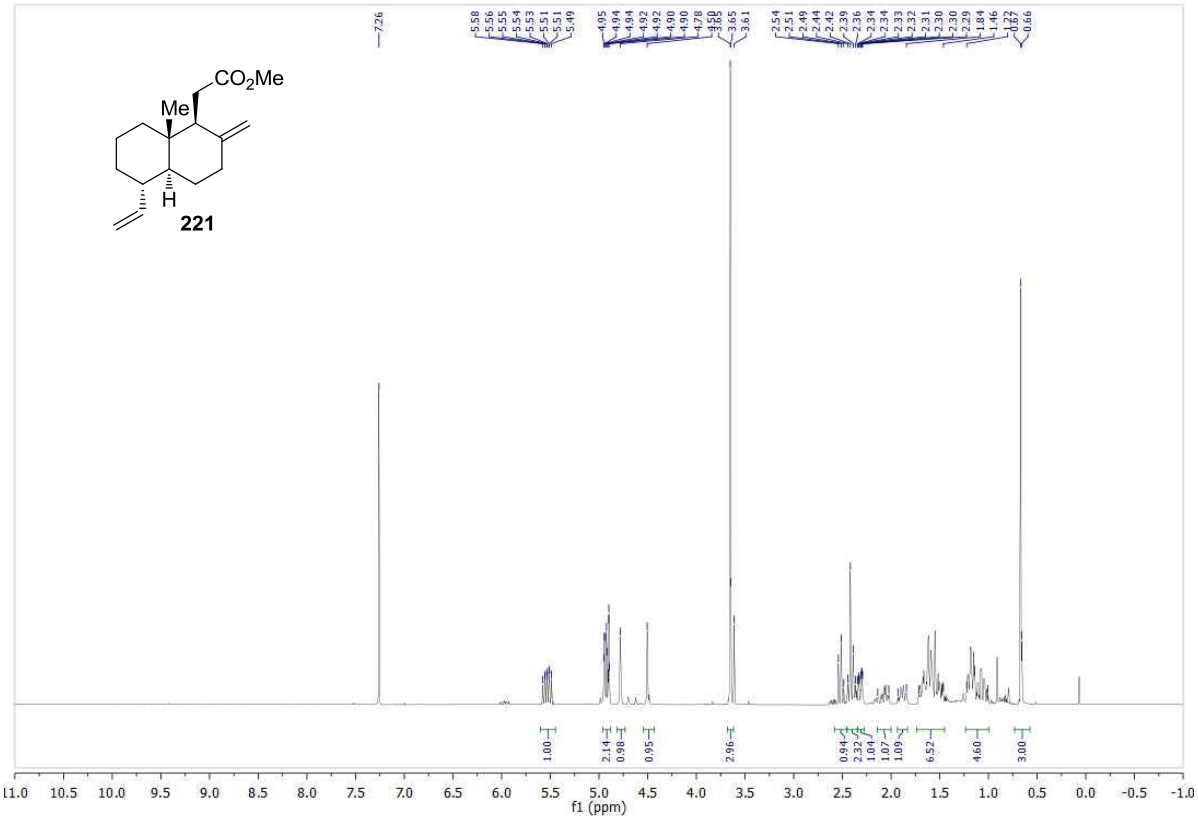
f1 (ppm)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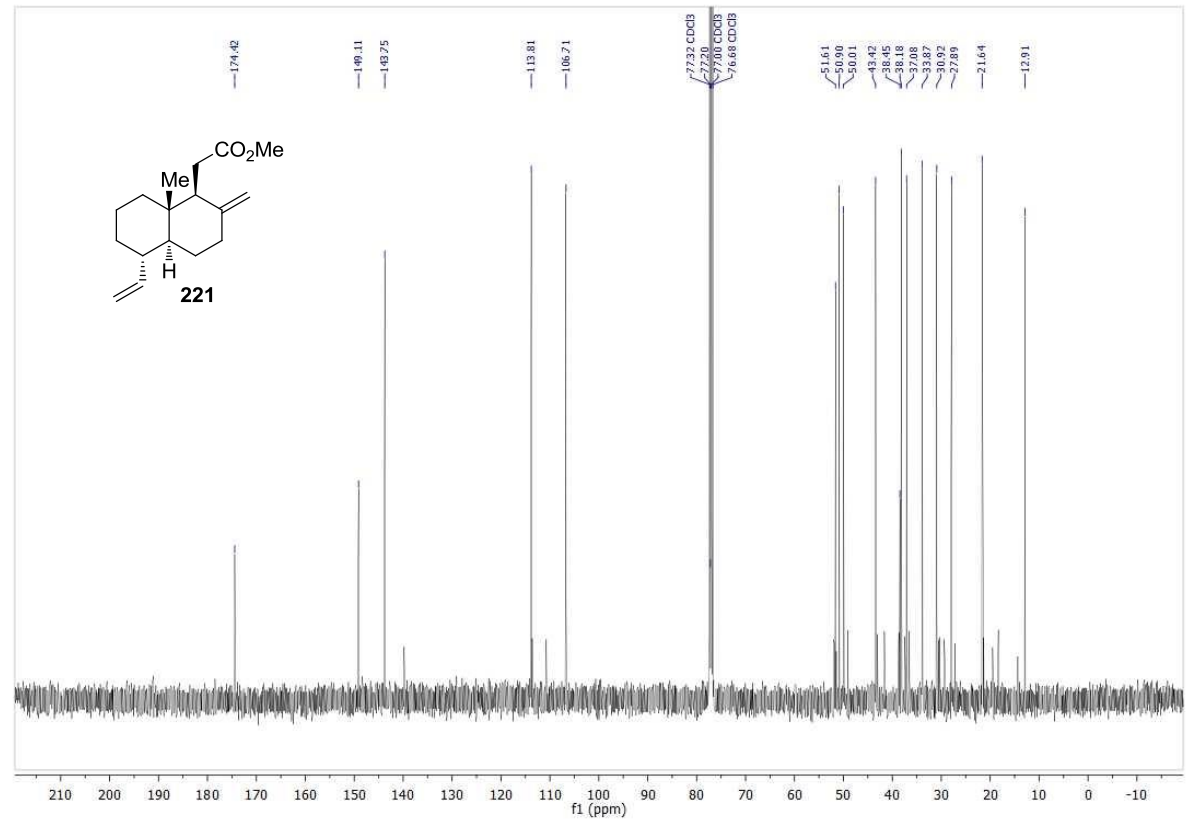
Me
H
221
f1 (ppm)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Me
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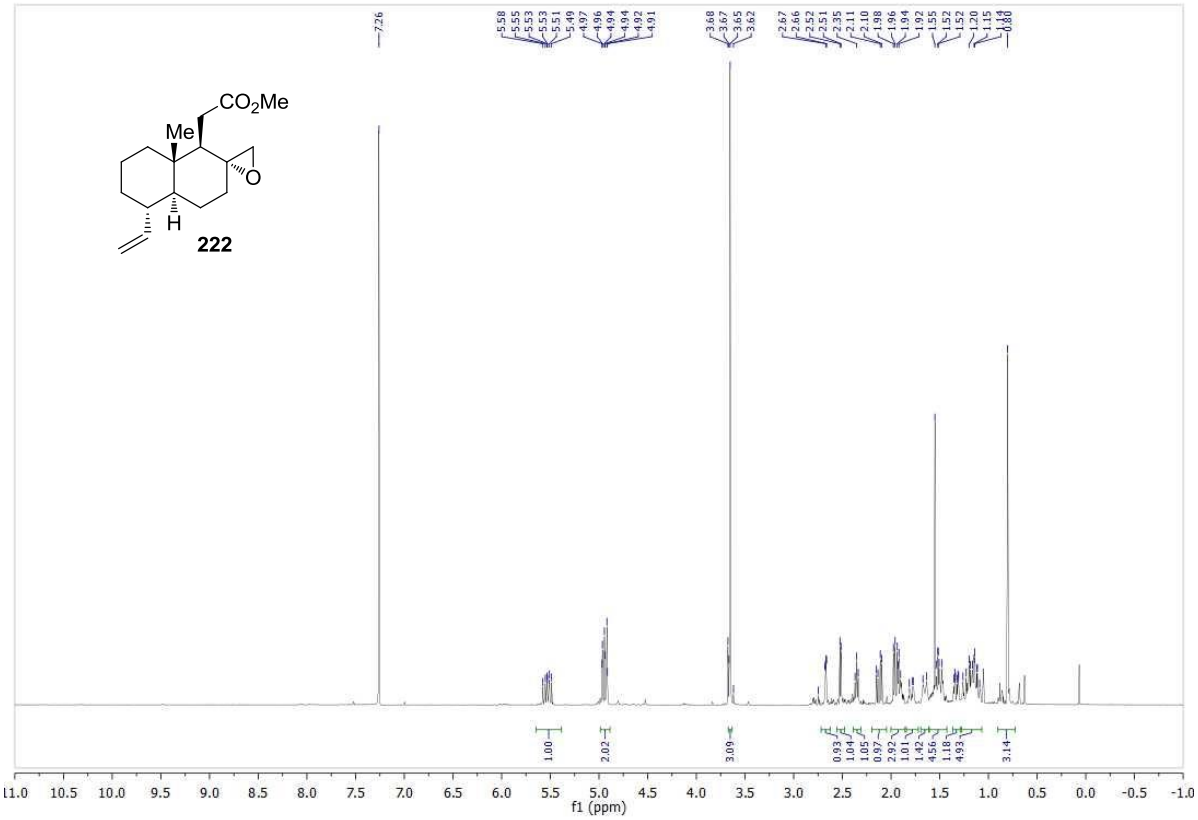
f1 (ppm)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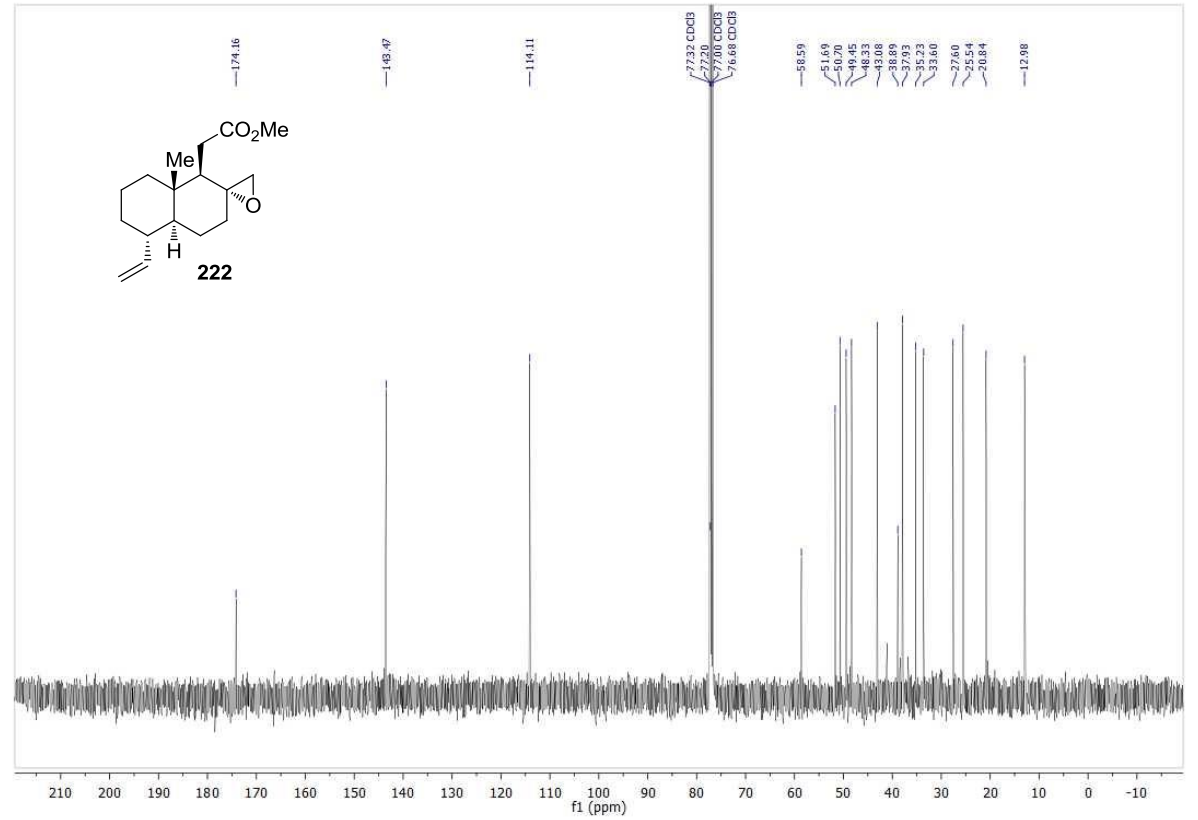
Me
O
H
222
f1 (ppm)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O
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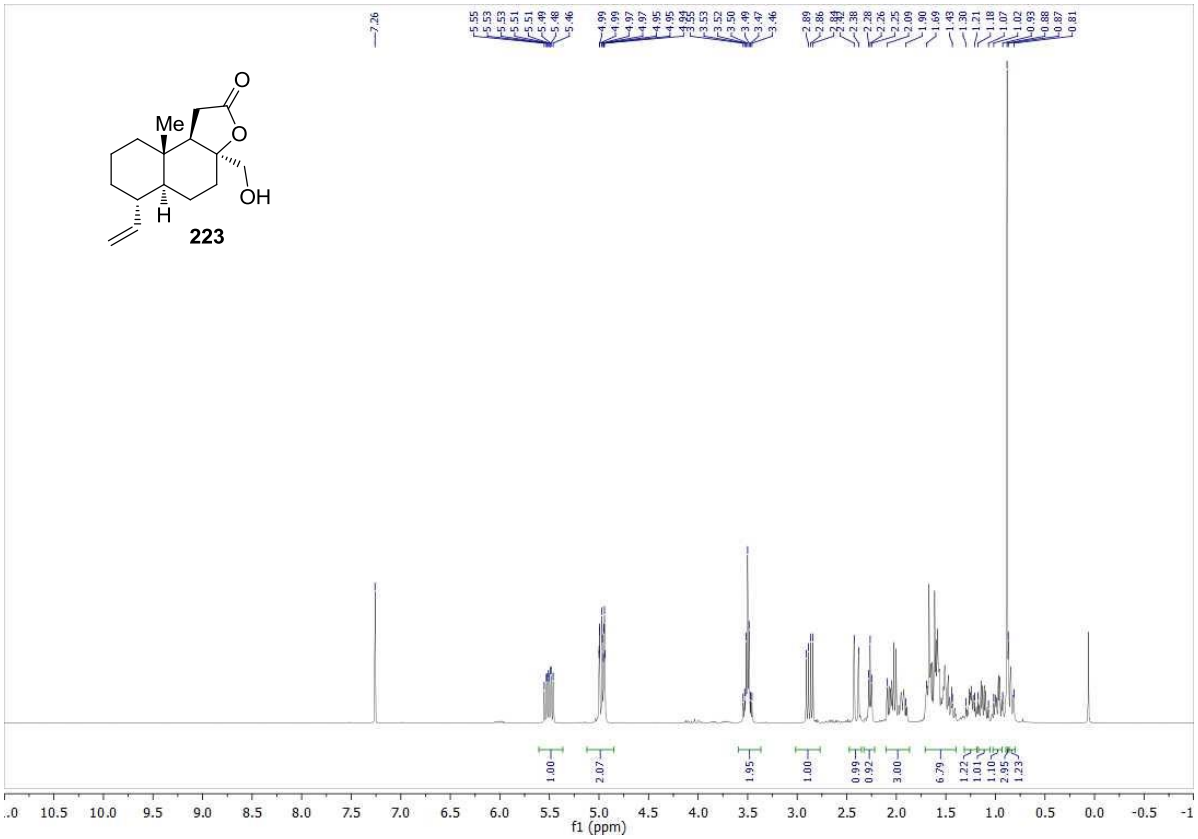
222
f1 (ppm)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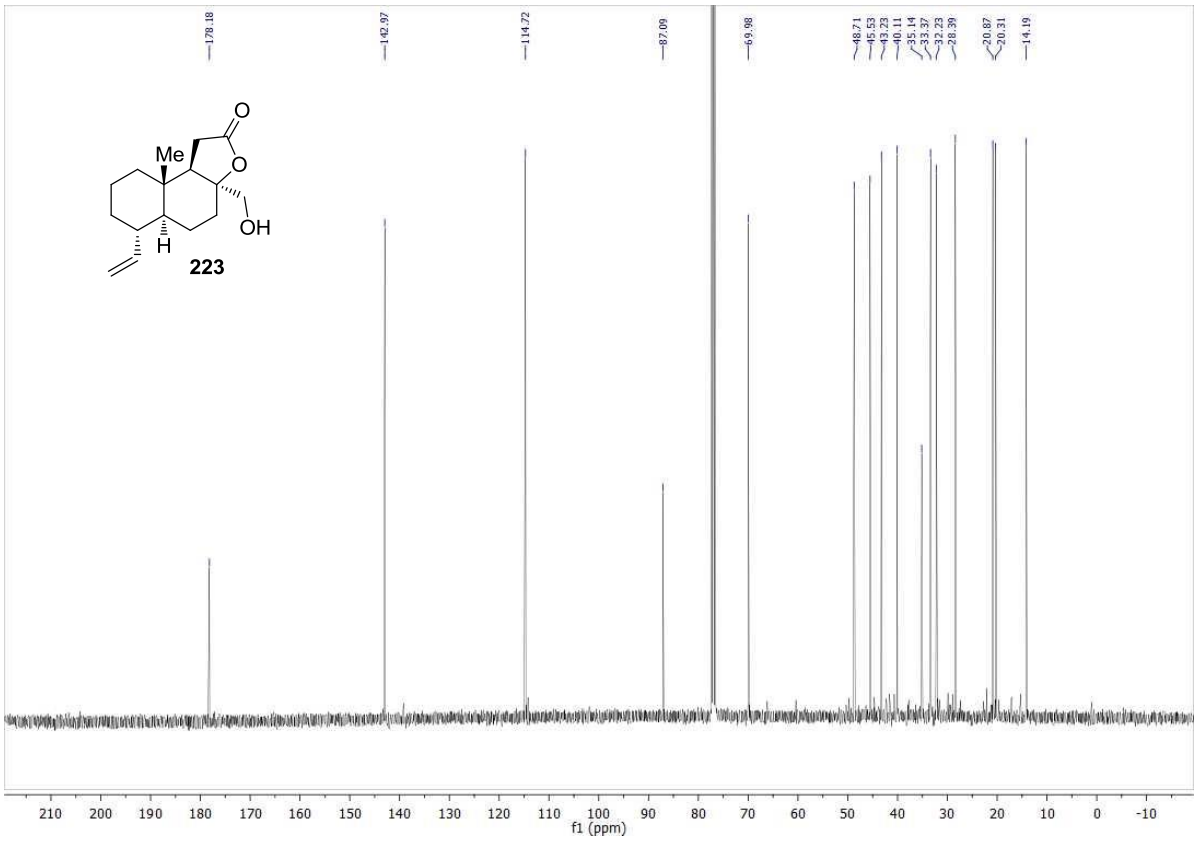
O
OH
H
223
f1 (ppm)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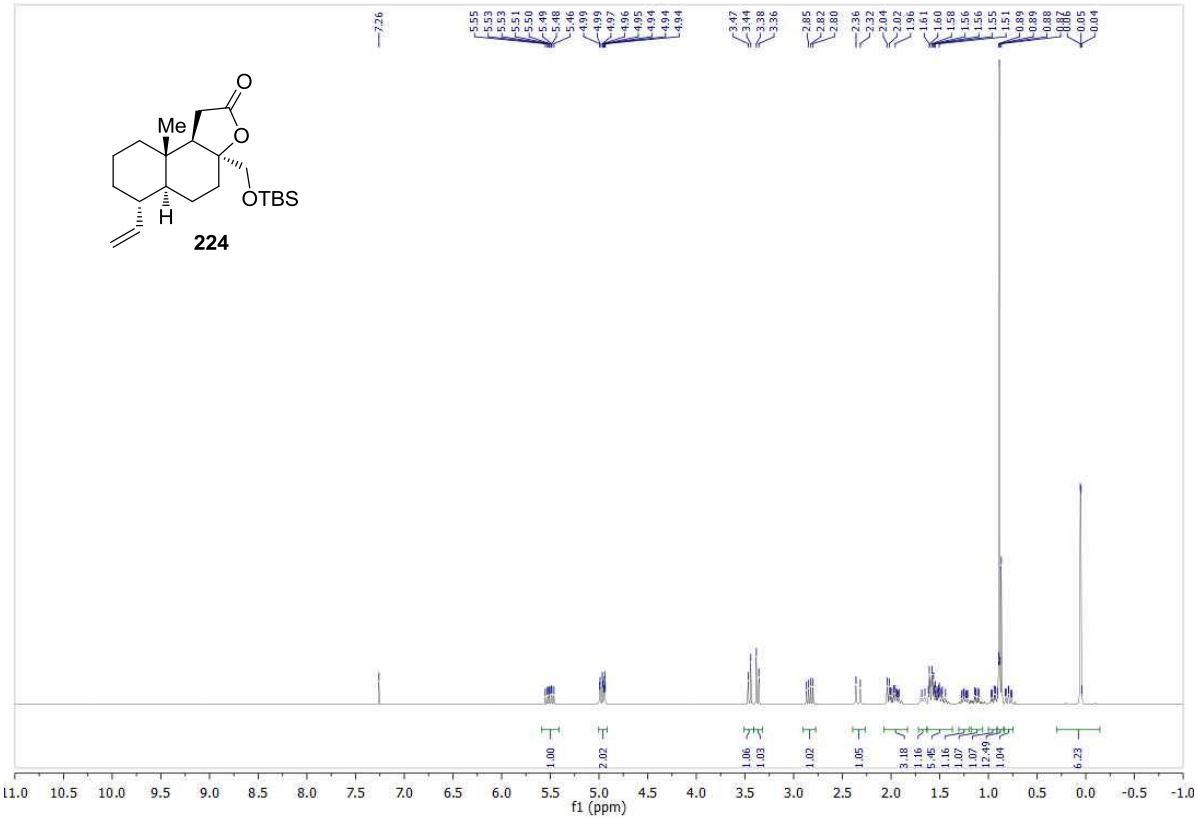
f1 (ppm)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OTBS
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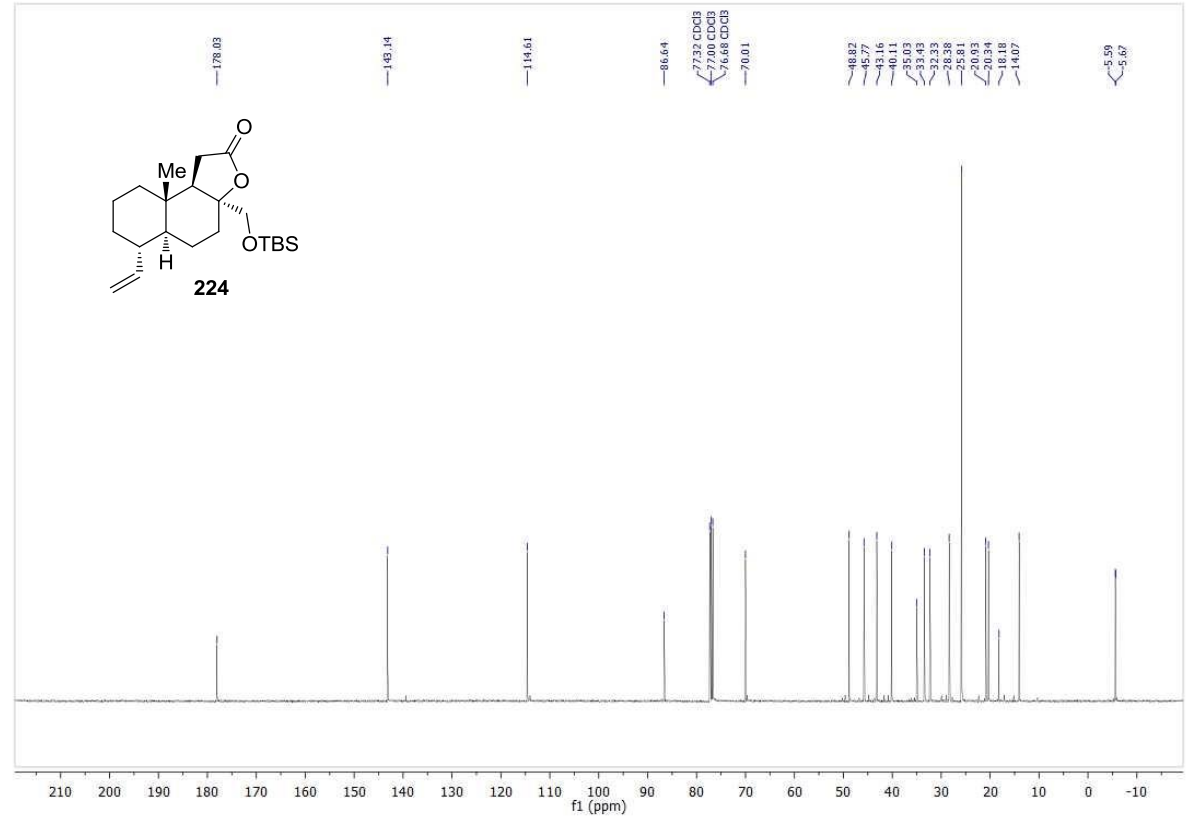
f1 (ppm)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OTBS
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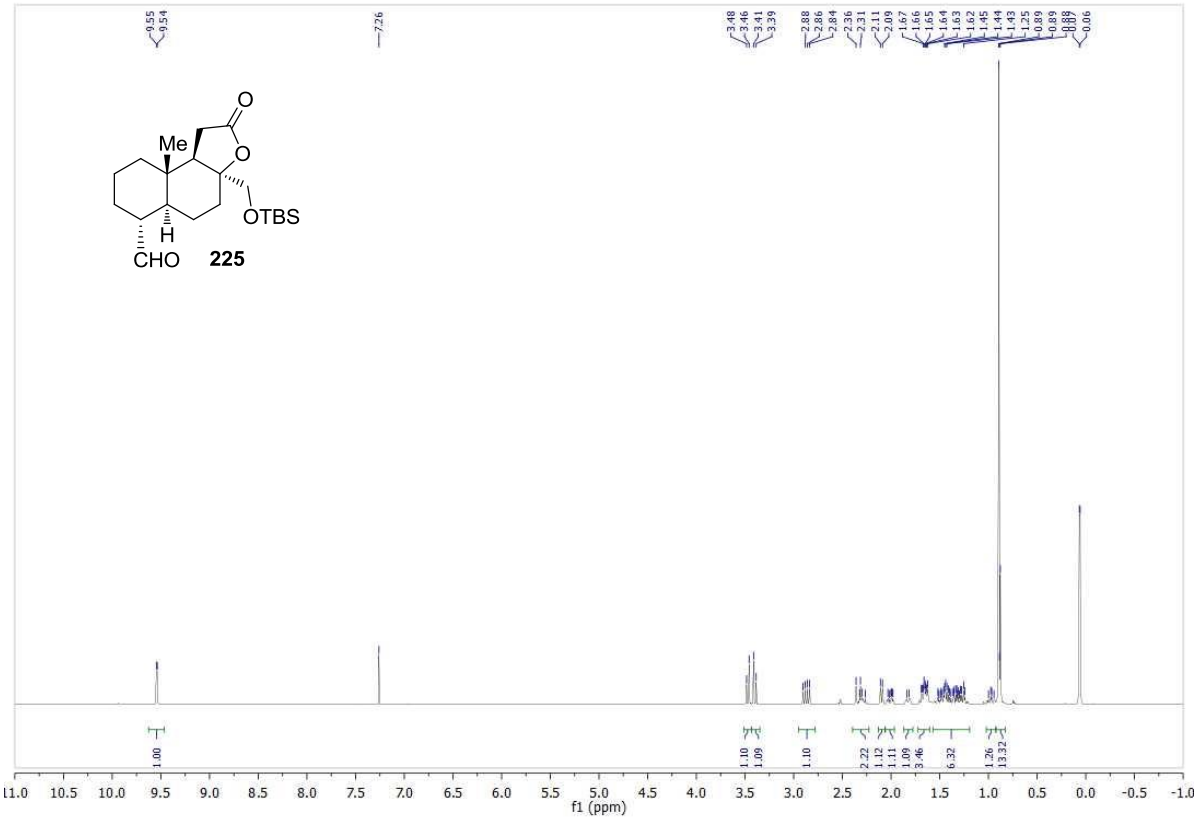
f1 (ppm)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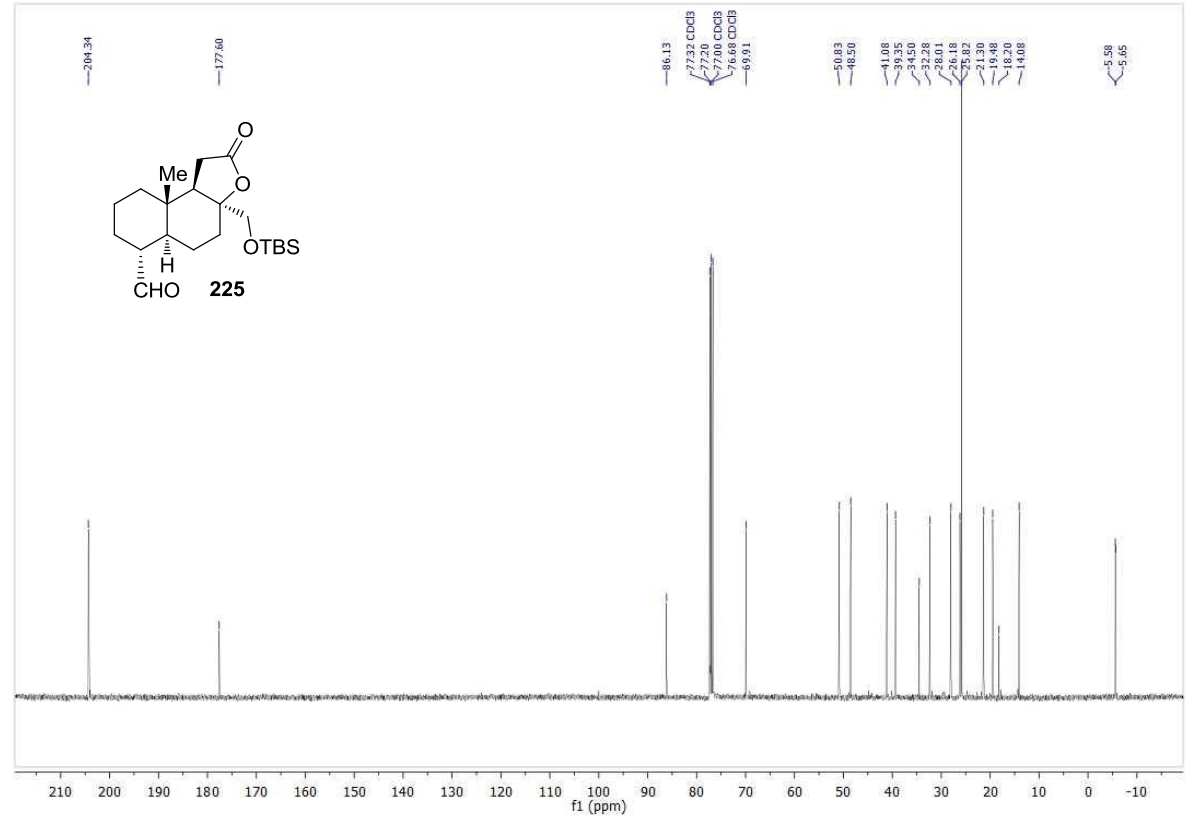
O
OTBS
H
CHO
225
f1 (ppm)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OTBS
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CHO
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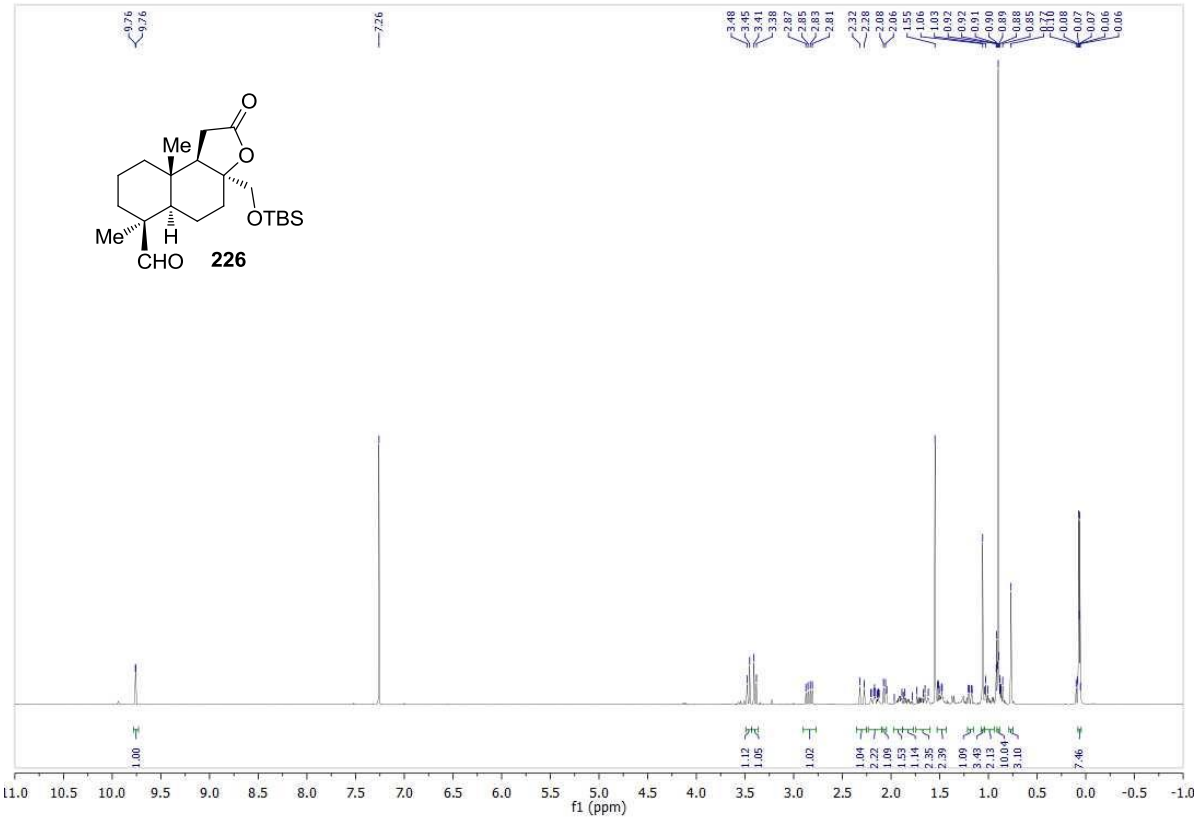
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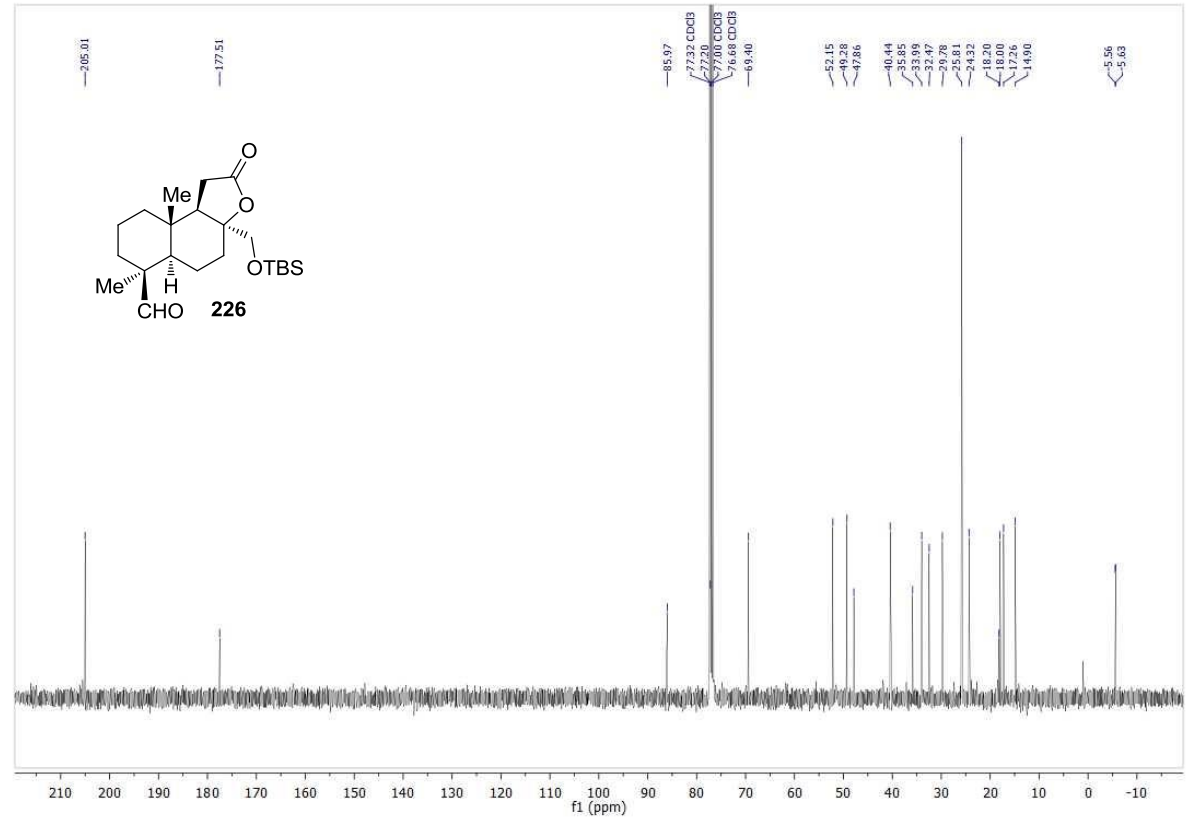
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OTBS
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H
CHO
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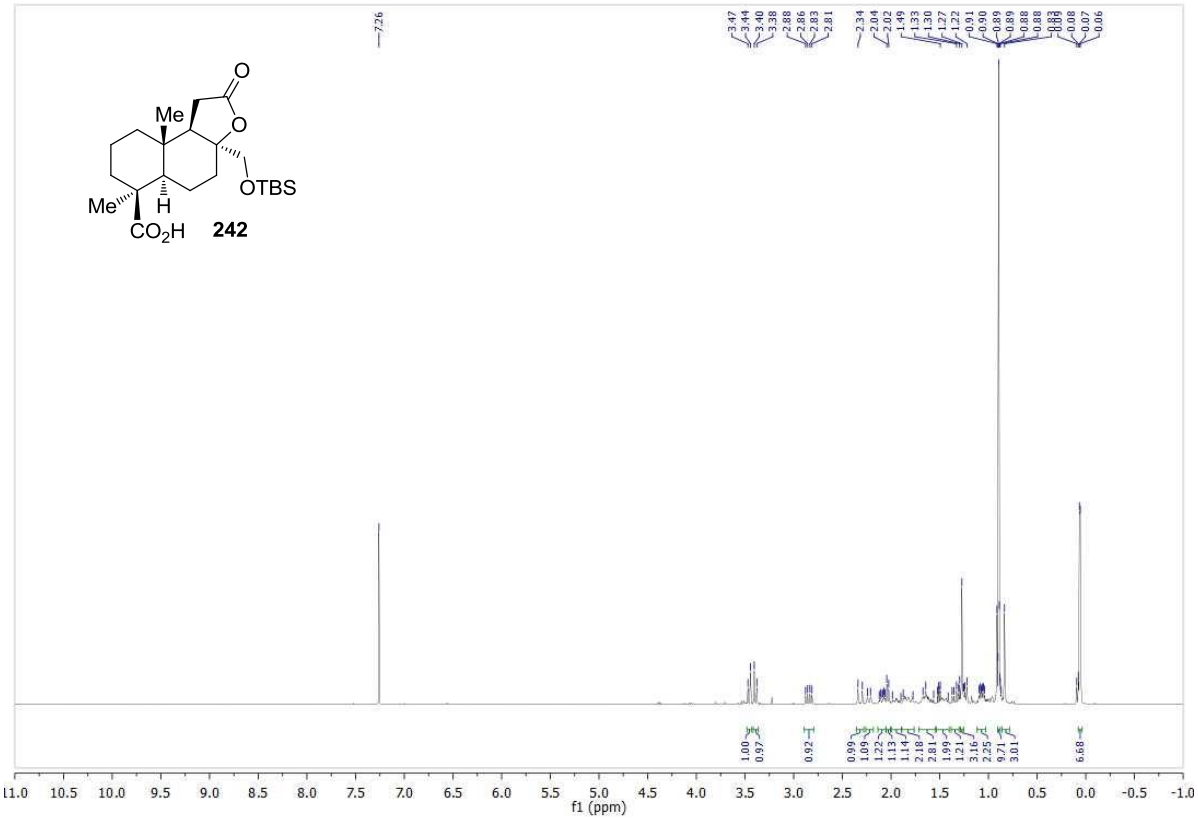
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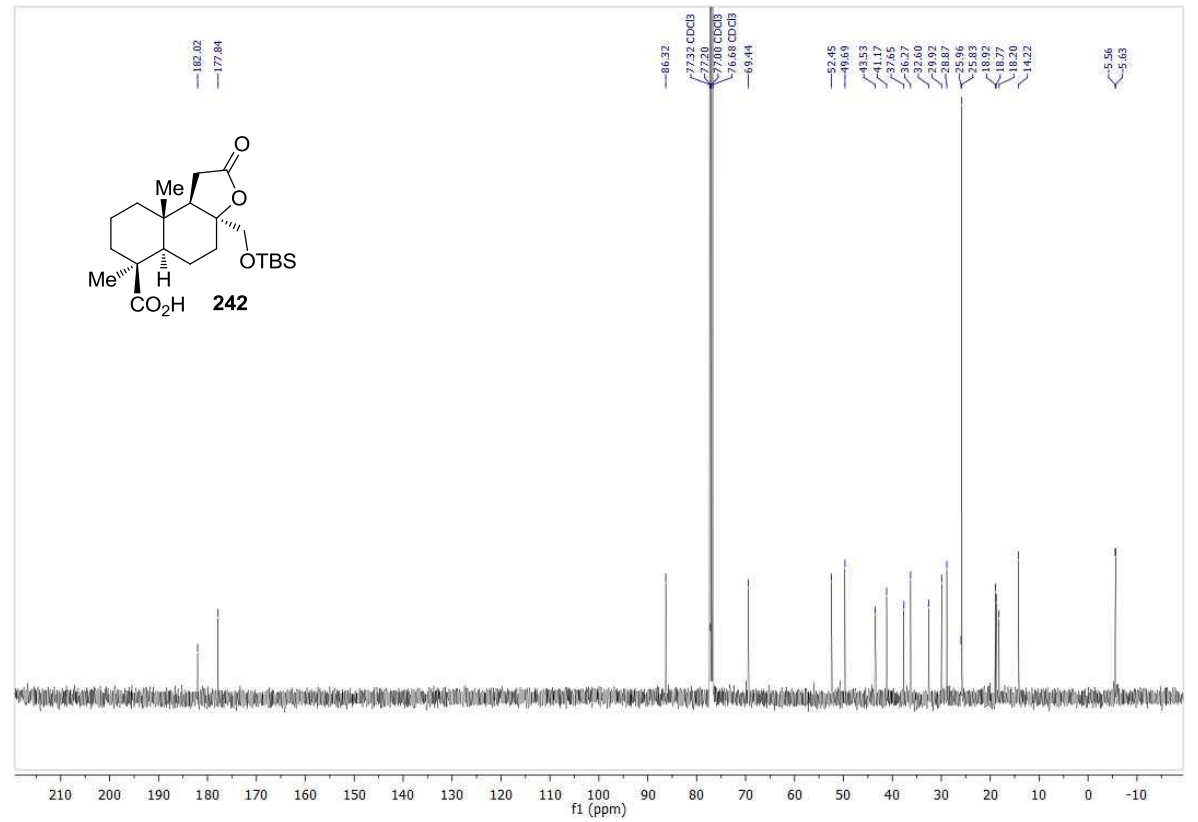
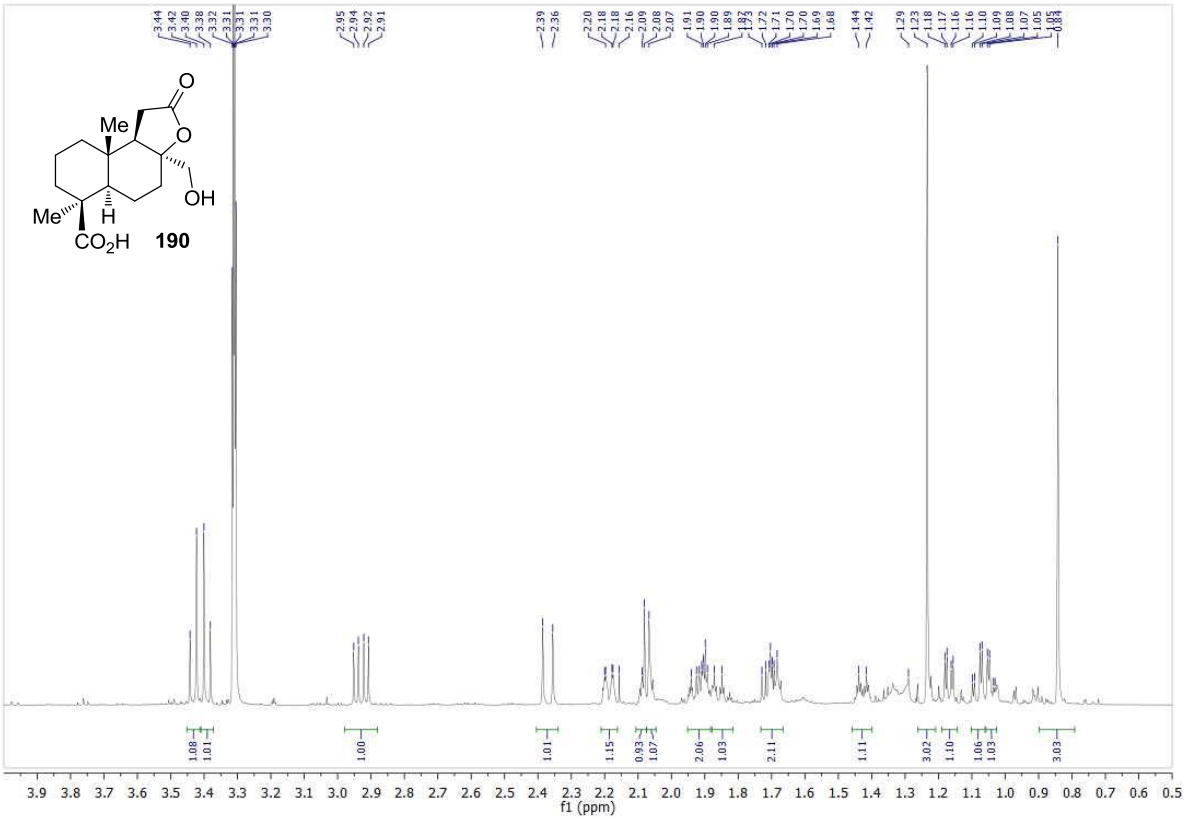
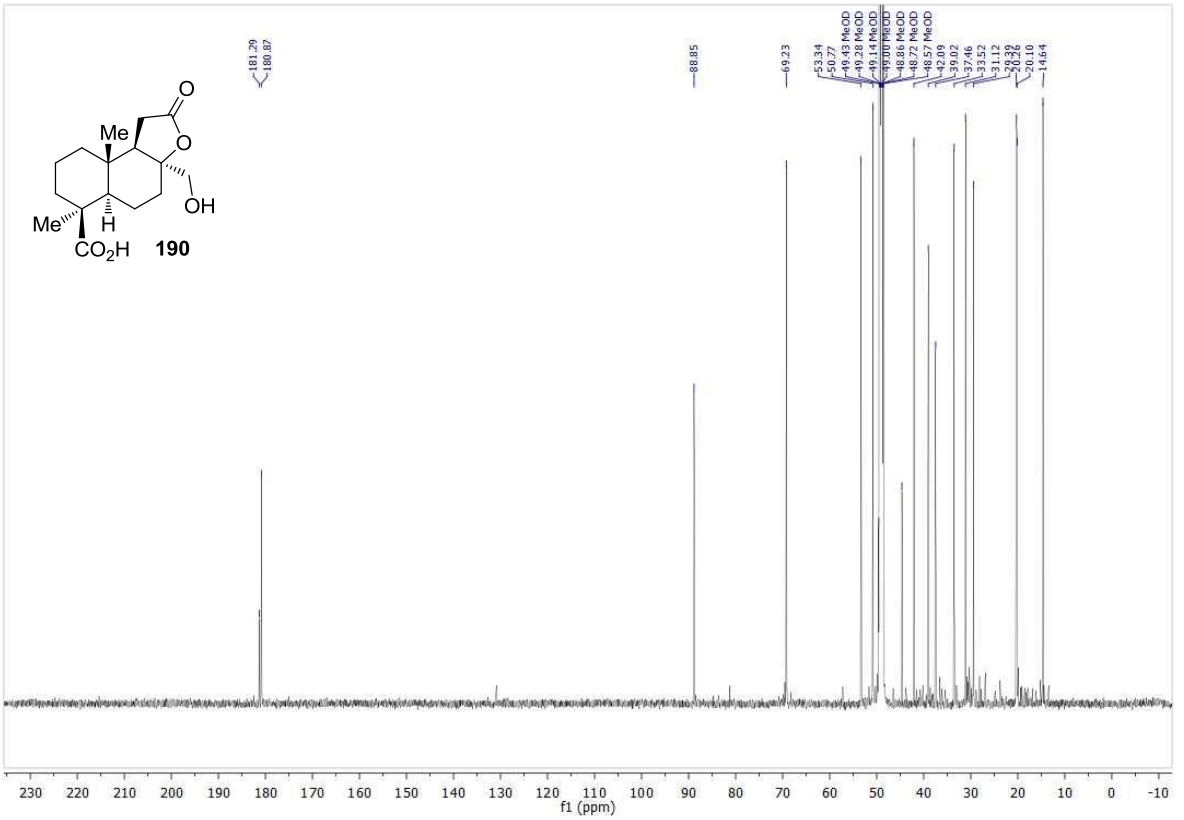
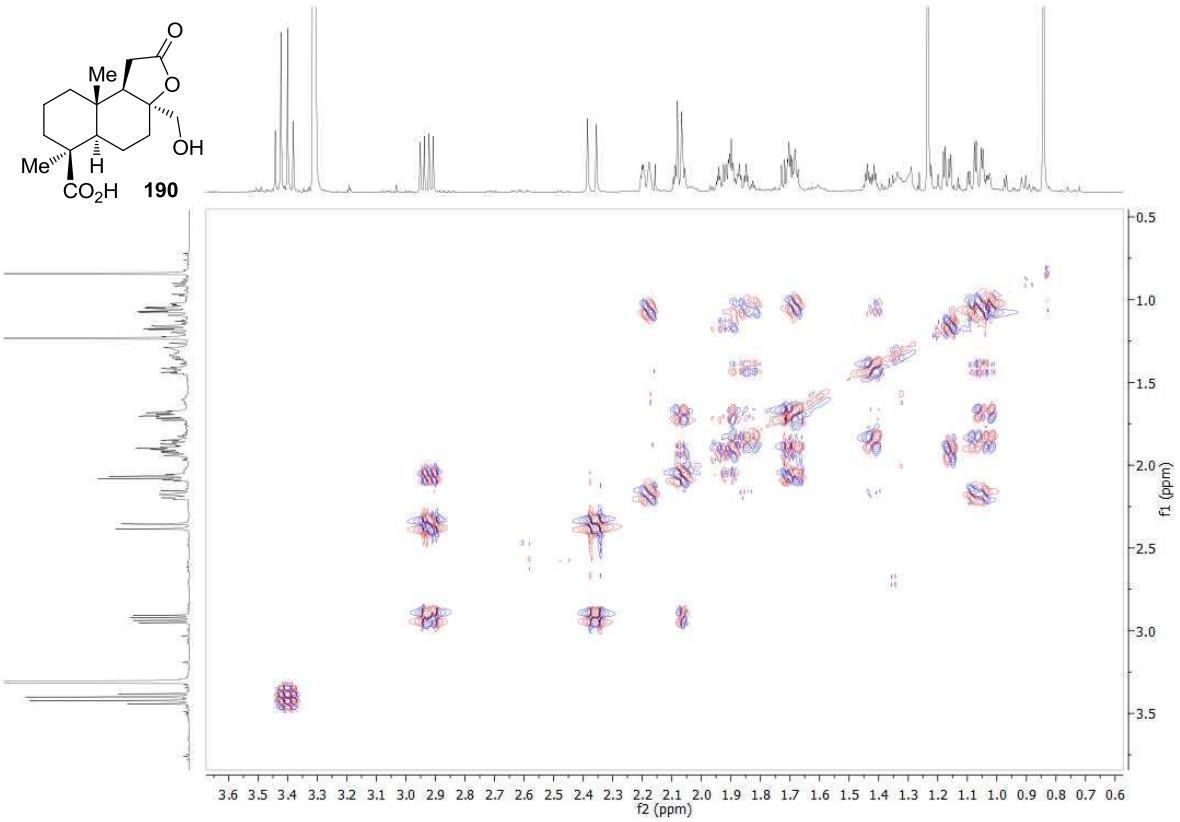
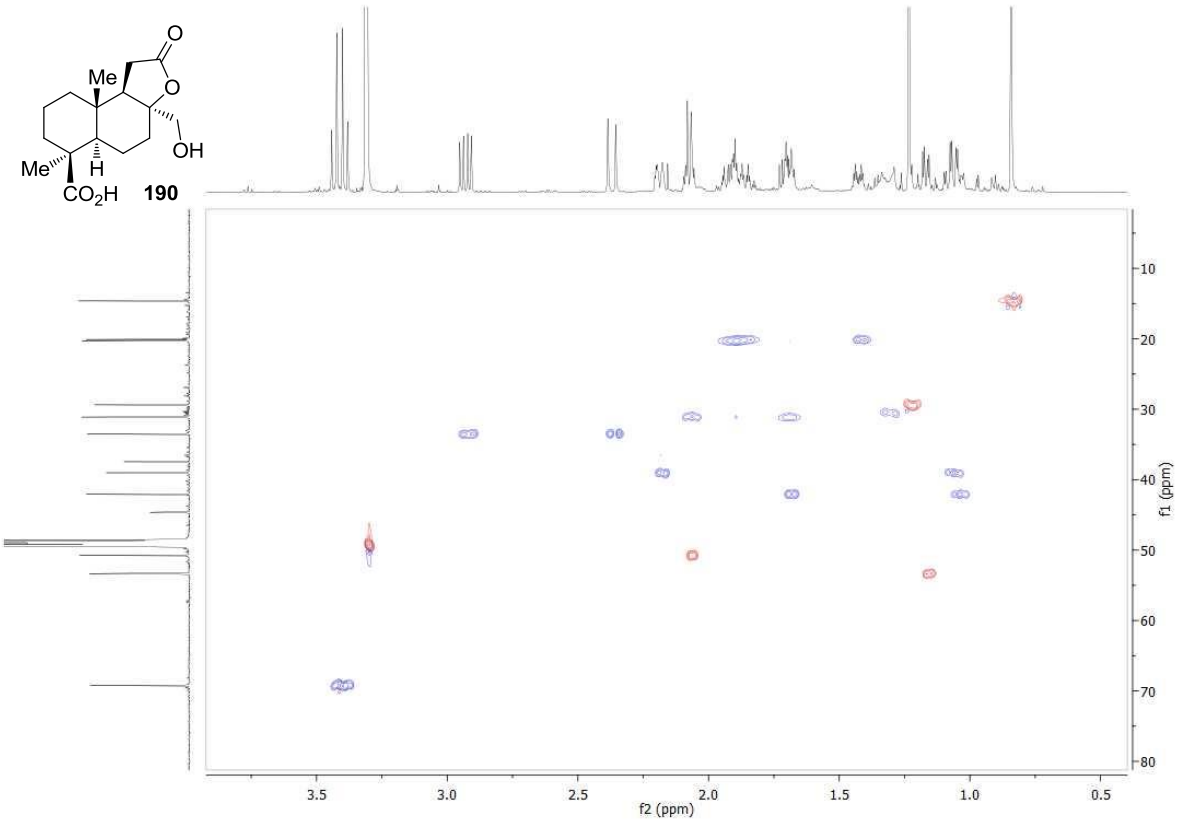
O
OTBS
Me
H
CO2H
242
f1 (ppm)

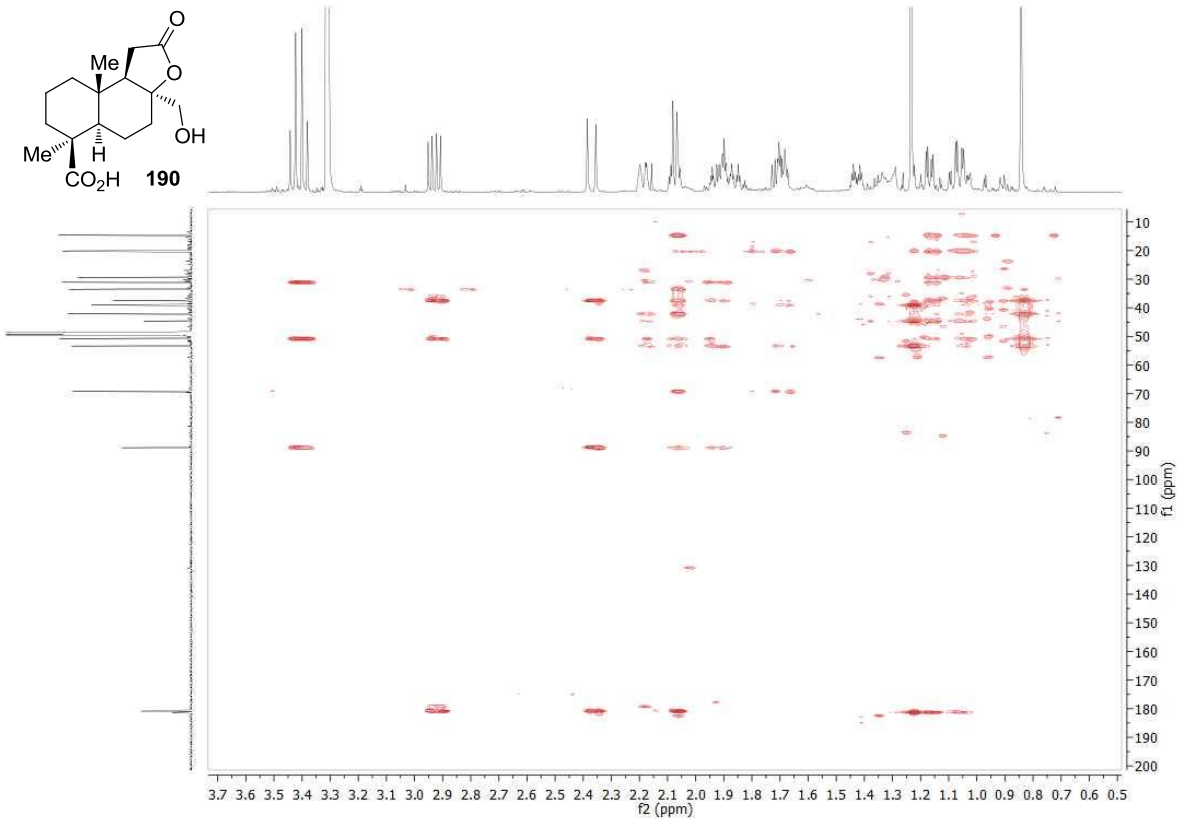

Me
O
O
OTBS
Me
H
CO2H
242
f1 (ppm)

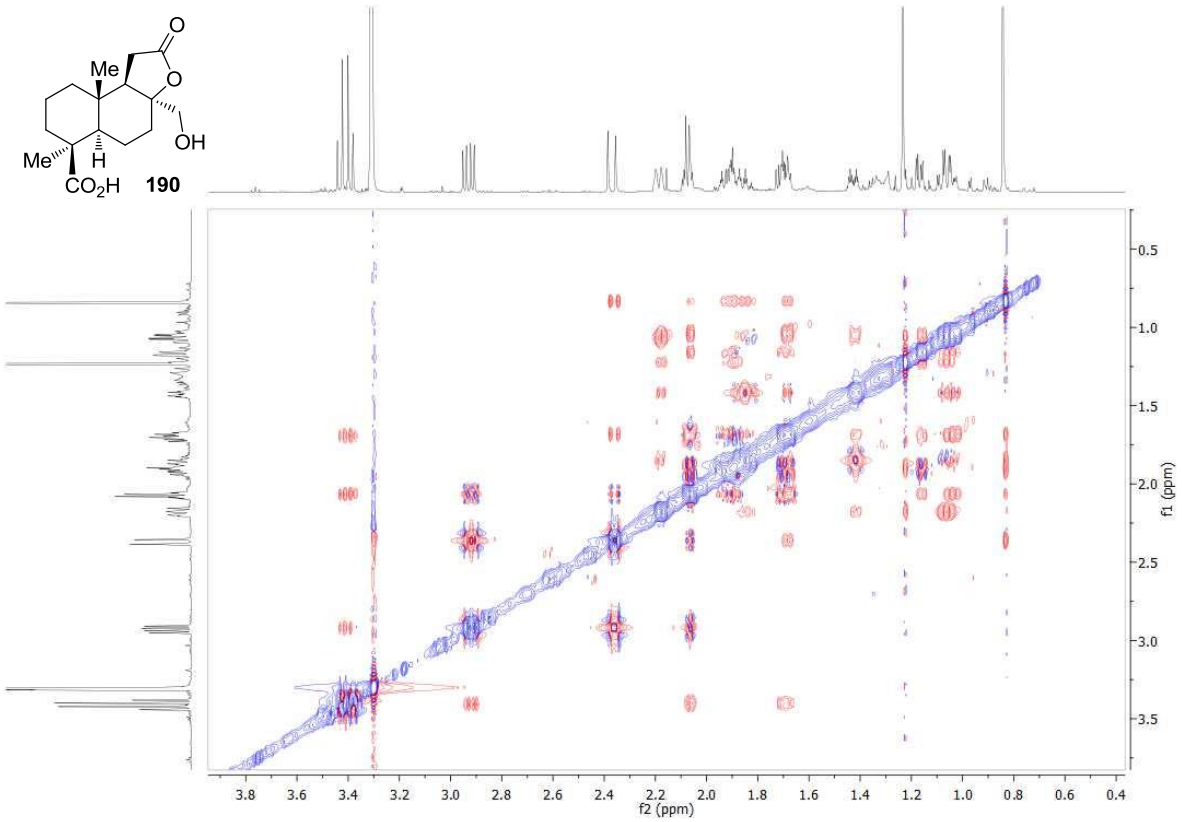

Me
O
O
OH
Me
H
CO2H
190
f1 (ppm)


Me
O
O
OH
Me
H
CO2H
190
f1 (ppm)


Me
O
O
OH
Me
H
CO2H
190
f1 (ppm)
f2 (ppm)


Me
O
O
OH
Me
H
CO2H
190
f1 (ppm)
f2 (ppm)


Me
O
O
OH
Me
H
CO2H
190
f1 (ppm)
f2 (ppm)


Me
O
O
OH
Me
H
CO2H
190
f1 (ppm)
f2 (ppm)