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Synthetic and biosynthetic studies on the ambruticins

Synthetic and Biosynthetic Studies on the Ambruticins

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A thesis submitted to the University of Bristol as part of the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science

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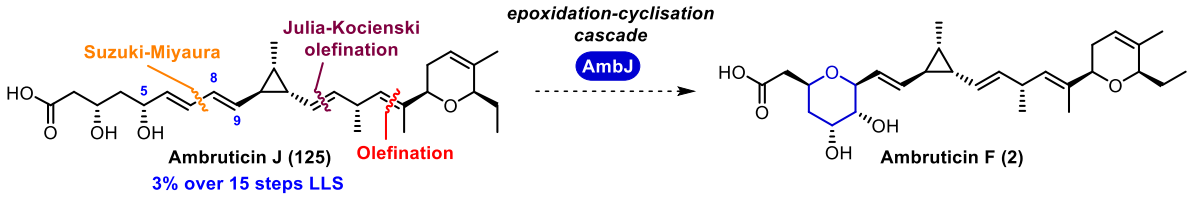
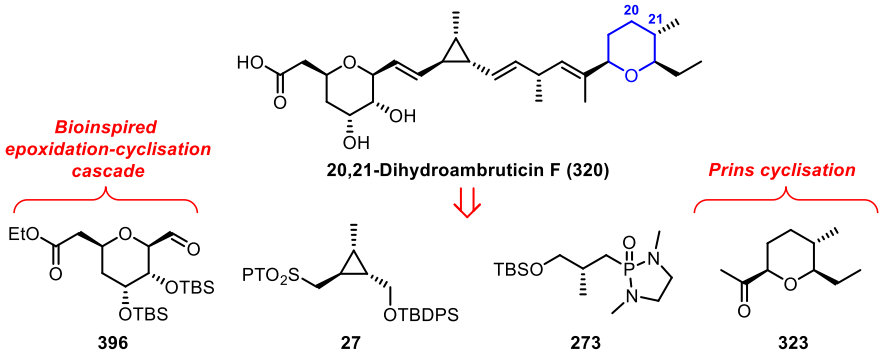
Abstract

Antifungal resistance is an area of growing concern which poses a severe threat to public healthcare and global food supplies. Research into novel acting antimycotics is urgently required to address the issues associated with antifungal resistance. This thesis describes investigations into the synthesis and biosynthesis of the ambruticins, a family of polyketide natural products which exhibit potent antifungal activity. **Chapter one** introduces the current state of antimycotics, the development of antifungal resistance, and a summary of synthetic and biosynthetic studies on the ambruticins.

Chapter two discusses the selectivity of intramolecular epoxide ring opening of 4,5-epoxy alcohols and investigations into tetrahydropyran ring formation in ambruticin biosynthesis. Model epoxidation-cyclisation studies are outlined and indicate that the 5-hydroxyl and 8,9-alkene of ambruticin J (**125**) may be responsible for controlling selectivity during AmbJ-catalysed epoxidation to form ambruticin F (**2**). A convergent total synthesis of the putative biosynthetic intermediate ambruticin J is also discussed, where four key fragments are united by a thallium accelerated Suzuki-Miyaura cross-coupling and two olefinations.



Chapter three outlines investigations into dihydropyran ring formation in ambruticin biosynthesis. The first total synthesis of the proposed biosynthetic intermediate 20,21-dihydroambruticin F (**320**) is reported, which employs a bioinspired epoxidation-cyclisation cascade and a Prins cyclisation to construct the two heterocyclic rings. The structure of 20,21-dihydroambruticin F (**320**) was confirmed by comparison with an authentic sample obtained from gene-knockout experiments, providing definitive proof of its existence as a biosynthetic intermediate. Finally, the modular route was adapted to complete the first total synthesis of ambruticin F and a biomimetic total synthesis of ambruticin S.



Acknowledgements

I would like to thank and dedicate this thesis to my friends and family who have supported me unconditionally throughout my life. Without their love, care, humour, and encouragement I would not be where I am today – thank you.

A special thanks to my supervisor, Prof. Chris Willis, who has been the best guide and mentor that I could have asked for. Your endless support and encouragement allowed me to develop both personally and as a scientist. Your positive and welcoming attitude continue to provide a safe environment for everyone to flourish. I am incredibly grateful for all that you have taught me. Thank you also to my co-supervisor, Prof. Matt Crump, for your enthusiasm and always being available for a chat.

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Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

James Ivor Bowen

April 2023

Abbreviations

δ	Chemical shift
Ac	Acetyl
ACP	Acyl carrier protein
AdoMet	*S*-Adenosyl methionine
AFD	Adenylate-forming domain
AIBN	Azobisisobutyronitrile
ap.	Apparent
APCI	Atmospheric pressure chemical isomerisation
Ar	Aromatic
AT	Acetyltransferase
Atm.	Atmospheric pressure
BAIB	(Diacetoxyiodo)benzene
BGC	Biosynthetic gene cluster
Bn	Benzyl
BORSM	Based on recovered starting material
Bpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
br.	Broad
c	Concentration
CD	Circular dichroism
CDI	1,1'-Carbonyldiimidazole
CoA	Coenzyme A
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
d	Doublet
DCM	Dichloromethane
DH	Dehydratase
DHP	Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine

DIPT	Diisopropyl tartrate
DMAP	*N*,*N*-Dimethylpyridin-4-amine
DME	1,2-Dimethoxyethane
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dr	Diastereomeric ratio
DTBMP	2,6-Di-*tert*-butylpyridine
DVC	Divinylcyclopropane
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EH	Epoxide hydrolase
er	Enantiomeric ratio
ER	Enoylreductase
ESI	Electrospray ionisation
Eq.	Equivalent
FAAL	Fatty acyl:adenylate ligase
FAD	Flavin adenine dinucleotide
FAS	Fatty acid synthase
FMO	Flavin-containing monooxygenase
GH-G2	Grubbs-Hoveyda 2nd generation
GLC	Gas-liquid chromatography
HDA	Hetero Diels-Alder
HFIP	Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HOG	High-osmolarity glycerol
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
hrs	Hours
Hz	Hertz

IERO	Intramolecular epoxide ring opening
IMOMA	Intramolecular oxa-Michael addition
Ipc	Isopinocampheyl
ISMS	Intramolecular silyl modified Sakurai
J	Coupling constant
JKO	Julia-Kocienski olefination
KR	Ketoreductase
KS	Ketosynthase
LC	Liquid chromatography
LDA	Lithium diisopropylamide
LLS	Longest linear sequence
LUMO	Lowest unoccupied molecular orbital
M	Molar
MAT	Malonyl acetyltransferase
Mb	Myoglobin
*m*CPBA	*meta*-Chloroperoxybenzoic acid
M.I.C	Minimal inhibition concentration
MIDA	*N*-Methylimidodiacetic acid
min	Minutes
MS	Mass spectrometry
MT	Methyltransferase
NADH	Reduced nicotinamide adenine dinucleotide
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
n.d	None detected
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
p	*Para*
ppm	Parts per million

PKS	Polyketide synthase
PT	Phenyl tetrazole
Px	Pyridoxal cofactor binding domain
q	Quartet
Q_o	Quinone outside
quant.	Quantitative
RCM	Ring-closing metathesis
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
Rf	Retention factor
rpm	Revolutions per minute
rt	Room temperature
s	Singlet
SAE	Sharpless asymmetric epoxidation
SAR	Structure activity relationship
SNAC	*N*-Acetylcysteamine
spp.	Species
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TE	Thioesterase
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	Triflyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tr	Trityl
TS	Transition state
Ts	Tosyl

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CHAPTER 1:

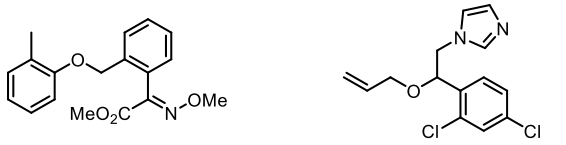
Antifungal Agents and the Ambruticins

1.1. Introduction

1.1.1. Antifungal Agents

Antimycotic agents have widespread use in both medicine and agriculture in order to fight infections and prevent fungal growth.[1,2] Fungal pathogens have been shown to dramatically reduce the quality, yield, and shelf life of crops by compromising the plants' immune system.[3] Fungicides are therefore utilised to protect plants from fungal infections.[4] The use of agricultural fungicides to improve crop growth is documented as early as 1807, where metallic copper was used to inhibit spore germination in *Tilletia caries*.[5] In recent times, the increased demand for food, due to rising population, and the reduced area of land used to grow crops has resulted in the further necessity to improve the yield and quality of crops.[6,7] As a result, the fungicide market is valued at 13.41 billion USD and expected to rise to 15.74 billion USD by 2025.[8]

Numerous classes of fungicides have been discovered and developed such as benzimidazoles, Q_o inhibitors, and azoles, each possessing a different mode of biological action.[1] For example, the broad-spectrum fungicide Kresoxim-methyl, developed from the natural product strobilurin A by BASF, is a Q_o inhibitor which prevents mitochondrial respiration and subsequently blocks fungal energy production (Figure **1**).[9] Alternatively, the azole class of antifungals, such as the general use fungicide Imazalil, act through suppression of ergosterol synthesis.[1]



Kresoxim-methyl (BASF) **Imazalil (Janssen Pharmaceuticals)**

Figure 1. Antifungal agents Kresoxim-methyl and Imazalil.

While fungal pathogens commonly infect plants, they can also affect humans. Although most fungal species are harmless to humans, a few hundred have been shown to cause diseases including *Aspergillus fumigatus* and *Candida* spp.[10] Human mycoses can range from superficial skin and nail infections, to more serious, invasive systemic infections which occur inside the body. In healthy humans, mycoses are generally limited to the skin as the immune system and raised body temperatures prevent internal infection.[11] Superficial skin infections, which affect roughly 25% of the world's population, such as thrush and athlete's foot, can be readily treated with local antifungals such as Clotrimazole and Terbinafine (Figure **2**).[12] However, humans with compromised immune systems or those under increased physiological stress can suffer from invasive fungal infections which are more

difficult to treat and can have mortality rates of greater than 50%.[1,13,14] For example, a leading cause of death for HIV patients is by aspergillosis, an infection caused by *Aspergillus fumigatus*.[15]

The development of antimycotic medicines has proven challenging due to the similarity between human and fungal cells. Both cells are eukaryotic, resulting in potential issues with selectivity when targeting mycoses within humans.[16] Nevertheless, systemic antifungal agents that treat internal infections have been developed. The first systemic antifungal agent, amphotericin B deoxycholate, was initially isolated from *Streptomyces nodosus* and later developed in 1958 by Squibb Laboratories (Figure **2**).[17] It is a potent, broad-spectrum antimycotic commonly used to treat aspergillosis, candidiasis and coccidioidomycosis. Since then, alternative medications have been introduced to combat invasive infections, such as the pyrimidine analogue Flucytosine and the azole Voriconazole (Figure **2**).[17] Nevertheless, most antifungal medicines are only effective for topical infections.[13] Furthermore, current systemic drugs show low efficacy and high toxicity, with no new antifungals approved in the clinic since 2002, highlighting the need for new medications.[18–20]

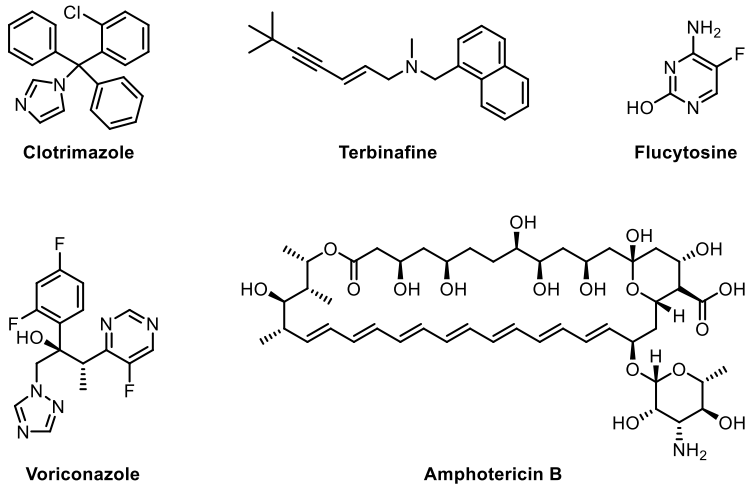


Figure 2. Local and systemic antifungal medications.

1.1.2. Rise in Fungal Infections and Antifungal Resistance

Estimates show that over a billion people are affected by fungal infections worldwide.[21] Of these cases, around 150 million result in a major detriment to quality of life and approximately 1.5 million are fatal. Moreover, reports suggest these figures are significantly underestimated due to poor diagnosis and data collection in the developing world.[14,21] Various factors are suggested to have caused the rise in fungal infections including the HIV epidemic, the use of antibiotics and immunosuppressive therapies, and the increase in surgery and intravascular catheters.[22] It is also predicted that the incidences of serious infections will rise.[11] Furthermore, the number of cases of emerging infectious diseases in plants has already dramatically increased (Figure **3**).[23]

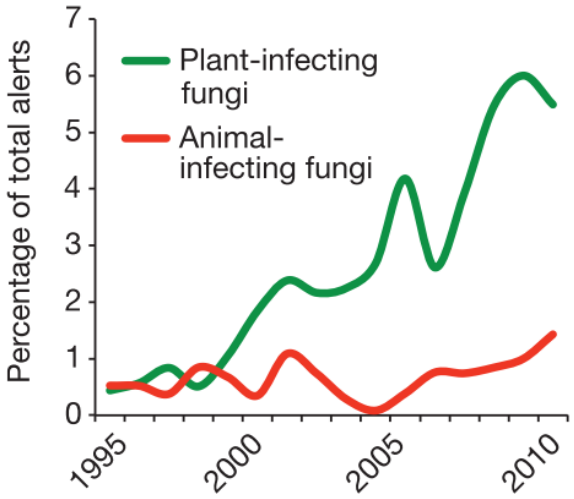


Figure 3. Alerts for pathogenic fungi in animals and plants from the ProMED database.[23]

Alongside the rise in fungal infections, there have been increased reports of antifungal resistance including the multidrug-resistant fungal pathogen *Candida auris*.[24,25,26] The cause of this resistance is similar to that observed in antibiotic resistance: the overuse of a narrow selection of antifungals, particularly in agriculture, and the ability for fungi to reproduce rapidly.[1] The broad use of azole antifungal agents has resulted in selection pressure and a growing concern for antifungal resistance in this class of drugs, both in agriculture and medicine.[14,27] This is evident in aspergillosis, where infections due to *Aspergillus fumigatus* have begun to show significant resistance to azole antifungal drugs.[15] Not only will the increase in antifungal resistance intensify the fungal medical problem, but crop growth will suffer, creating concerns for world food supplies.[28] The number of extinction events due to fungal pathogens has dramatically increased, with fungi accounting for the vast majority of all cases related to infectious diseases (Figure **4**).[23]

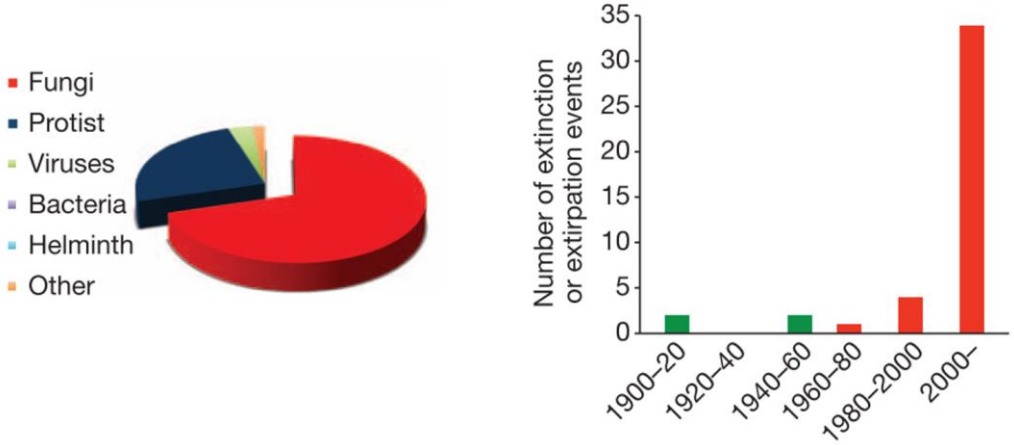


Figure 4. Relative proportions of extinction events due to infectious diseases (left) and their occurrence over time (right).[23]

Climate change is also predicted to exacerbate both healthcare and agricultural fungal issues.[11] At present, fungal infections in healthy humans are predominantly superficial due to the inability of fungi

to survive the internal temperatures of the body. However, thermal tolerances of fungal pathogens are expected to rise as a result of global warming, increasing the likelihood of invasive mycoses, even in healthy humans.[29] Experiments where frogs were infected with *Batrachochytrium dendrobatidis* indicated that rising temperatures may increase host susceptibility.[30] Moreover, global warming may result in the spread of fungi around the globe, causing more infections in both mammalian and plant species.[23]

Given the current limited arsenal of antifungal agents, alongside the ever-increasing prospect of antifungal resistance, novel acting antimycotics are required. Nature is a continued source of medicines through natural products, such as polyketides, which have evolved over millions of years to fight pathogens.[31,32] As such, there are continued efforts to isolate natural products and develop them into novel acting drugs.[33–35] Nevertheless, the complex architectures of natural product scaffolds has limited their development as therapeutics due to poor pharmacokinetic properties, poor synthetic tractability, and poor drug-likeness.[33,36,37] To develop truncated scaffolds of natural products which maintain potency whilst achieving desired pharmacokinetic profiles, a greater understanding of the structural features responsible for their observed bioactivities is required. Furthermore, it is vital to conduct research into the mechanism of resistance, in order to overcome the threat which antifungal resistance poses.[38]

1.1.3. Polyketides

Polyketide natural products are secondary metabolites produced by various microorganisms. The family shows remarkable diversity, containing a plethora of functional groups and structural frameworks, and have found wide use in medicine due to their potent biological activities.[39] For example, polyketides are used as antibiotic, anticancer, and cholesterol lowering drugs such as tetracycline, epothilone B, and lovastatin respectively (Figure **5**).[40,41]

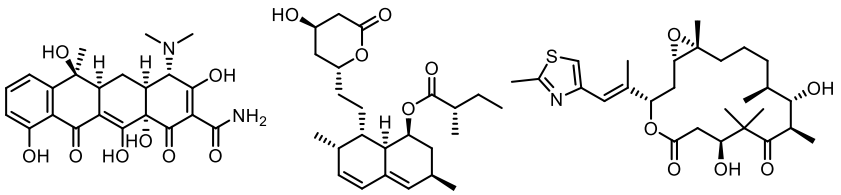
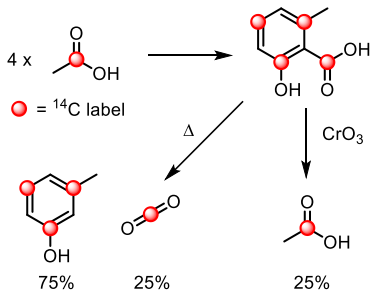


Figure 5. Examples of polyketide natural product medications.

Due to their complex structures and promising biological properties, polyketides present challenging targets for total synthesis.[42] Indeed, total synthesis is often required to confirm stereochemistry in

complex polyketides, provide larger quantities of compounds for biological testing, and facilitate the formation of natural product analogues for structure activity relationship (SAR) studies.[43] This can aid the development of safer and more effective new medications. Furthermore, the biosynthesis of polyketides has been extensively investigated over the past century.[44] A deeper understanding of natures' biological machinery aids the development of clean and efficient routes to bioactive compounds and novel biocatalysts to perform challenging transformations.[45]

The fundamental mechanism for the biosynthesis of polyketides, initially proposed by Collie in 1893, was outlined by Birch in 1953.[44] Feeding and degradation studies were conducted with radiolabelled [^{14}C]-acetic acid on the polyketide 3-methylsalycylic acid (Scheme **1**). The labelling pattern observed from these studies indicated that the acetate building blocks were arranged in a "head-to-tail" fashion. Birch concluded that polyketides were assembled through iterative condensation of the common starter unit. Since then, a detailed picture of polyketide biosynthesis has been developed, which is closely related to that of fatty acid biosynthesis (Scheme **2**).[39]

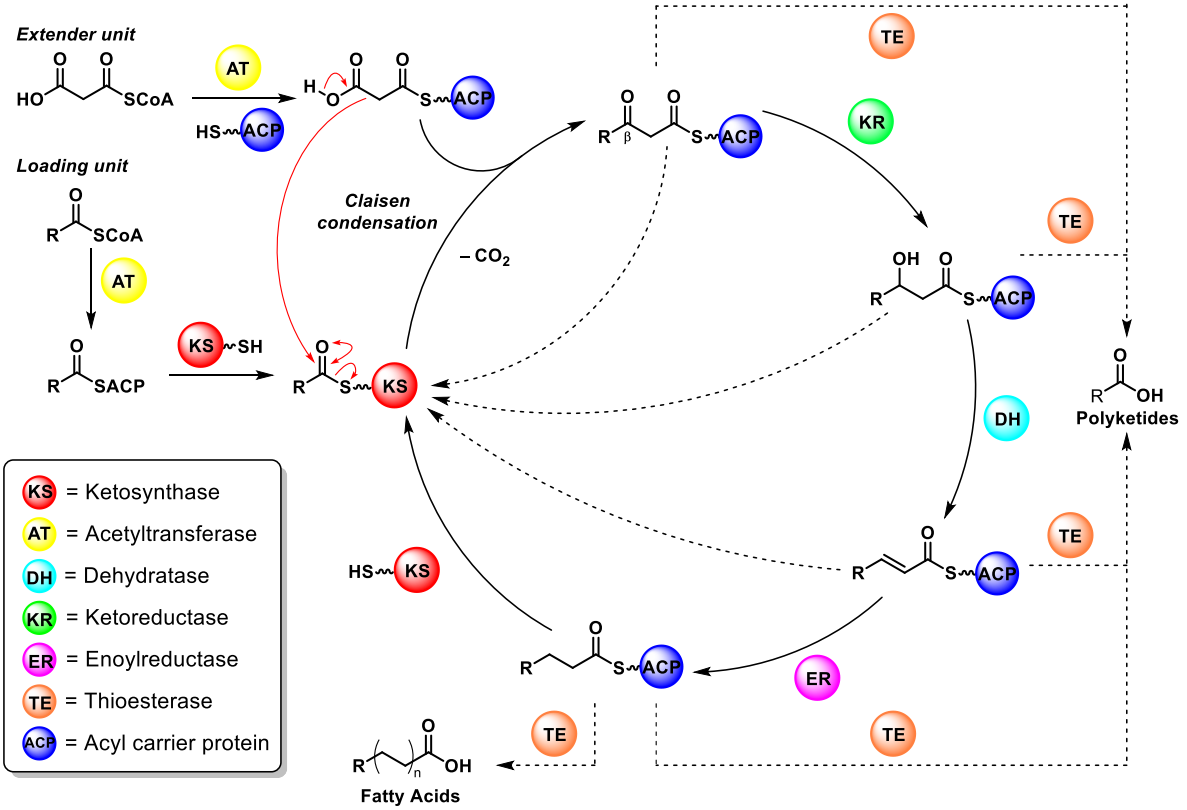


Scheme 1. Feeding and degradation studies of 3-methylsalycylic acid.[44]

While the biosynthesis of fatty acids is catalysed by fatty acid synthases (FASs), polyketide biosynthesis is performed by polyketide synthases (PKSs).[44] However, both adopt a general chain extension mechanism to generate their respective core molecular frameworks.[46] The multifunctional enzymes or multienzyme complexes (FASs and PKSs) conduct sequential catalytic steps, where each enzyme domain is responsible for a single biotransformation.[39] The catalytic domains which oversee a single chain extension cycle can be grouped into modules.

Both processes begin with the loading of an acetyl unit from coenzyme A (CoA) onto an acyl carrier protein (ACP), catalysed by an acetyltransferase (AT) domain (Scheme **2**). The acetyl unit is then transferred onto a ketosynthase (KS) domain where it is bound in the active site by a cysteine residue. The KS domain then proceeds to catalyse the key decarboxylative Claisen condensation between the KS-bound acyl unit and an ACP-bound extender unit, such as the ACP-bound malonyl unit depicted (Scheme **2**). Following this condensation, the extended chain, now residing on the ACP, can undergo β-tailoring steps where the ACP acts to deliver the β-ketothioester to the relevant tailoring enzymes.

Ketone reduction, dehydration, and alkene reduction are sequentially catalysed by ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) domains respectively, to afford the fully saturated chain. In the case of fatty acid biosynthesis, all three domains are always present, and a full reductive process occurs. In contrast, domains can be omitted in polyketide biosynthesis, allowing complexity to be rapidly incorporated into the backbone. Upon completion of an extension cycle, the chain can undergo further condensations, or be cleaved by a thioesterase (TE) through hydrolysis, lactonisation, or cyclisation to liberate the free polyketide.[47] In polyketides, post-PKS tailoring enzymes can further elaborate the molecule through a plethora of transformations such as epoxidation, methylation and transamination.[39,48,49] Another source of the diversity seen in polyketide natural products is the incorporation of alterative starter units such as chloroethylmalonyl-CoA, hydroxymalonyl-CoA and methoxymalonyl-CoA.[50]



Scheme 2. General mechanism of chain extension in fatty acid and polyketide biosynthesis.

PKSs can be classified as type I, II, or III according to their domain structural organisation, mechanism of action, and substrate specificity (Figure **6**).[51] Type I PKSs are large multifunctional proteins, which contain numerous catalytic domains, and are formed from covalently linked enzymes.[46] In contrast, type II PKSs are composed of non-covalently linked monofunctional enzymes which are able to aggregate into a protein complex and subsequently fully dissociate.[52] Finally, type III PKSs are small proteins which are readily distinguished from type I and II by their ability to employ acyl-CoA as the substrate for chain elongation as opposed to an ACP-bound substrate normally required.[39]

Type I PKSs can be further classified as either iterative or modular.[53] Iterative systems are composed of a limited set of domains, where each domain can be reused to facilitate polyketide chain extension or reductive processing.[54] In contrast, modular (non-iterative) systems are comparable to an assembly line, where the growing polyketide chain is passed between single acting catalytic domains. Finally, in modular type I PKSs the AT domains can be either non-covalently bound, free-standing enzymes (*trans*-AT), or covalently bound enzymes embedded in the PKS (*cis*-AT).[55] Whilst *trans*-AT domains can intercept the growing polyketide chain to provide an extender unit multiple times, *cis*-AT domains are only utilised once.

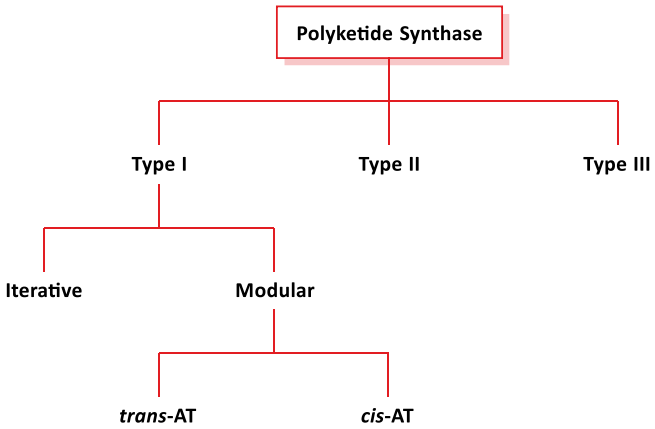
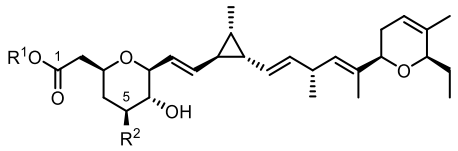


Figure 6. Classification of polyketide synthases.

Although a great deal is known about the biosynthesis of polyketides, there is still much uncertainty around the complex mechanisms involved in their formation. A greater understanding of these biosynthetic mechanisms may facilitate the development of novel biocatalysts to perform challenging chemical transformations.

1.1.4. The Ambruticins

The ambruticins are a family of polyketide natural products, originally isolated from the myxobacteria *Sorangium cellulosum* (Table **1**).[56,57] Ambruticins S and F were isolated in 1977, followed by the VS series in 1991.[58,59] Their structures and absolute configurations were elucidated through the combination of spectroscopic analysis, degradation studies, and single-crystal X-ray analysis.[60–62] These studies revealed a unique and complex structure, containing 3 *E*-alkenes, 10 stereocentres, and three distinct rings: a tetrahydropyran (THP), cyclopropane, and dihydropyran (DHP). Variation in the structure of this family occurs primarily at the C-5 position. Ambruticins S and F are alcohol epimers, whilst the VS series possess an amine at differing states of oxidation and methylation. Ambruticin VS-2 is the only member to contain a methyl ester as opposed to the carboxylic acid observed in the other molecules.



R^1	R^2	Ambruticin
H	OH	S (**1**)
H	OH (epimer)	F (**2**)
H	NH_2	VS-5 (**3**)
H	NHMe	VS-4 (**4**)
H	NMe_2	VS-3 (**5**)
H	NMe_3^+	VS-1 (**6**)
H	NMe_2O	VS-3 N-oxide (**7**)
Me	NMe_3^+	VS-2 (**8**)

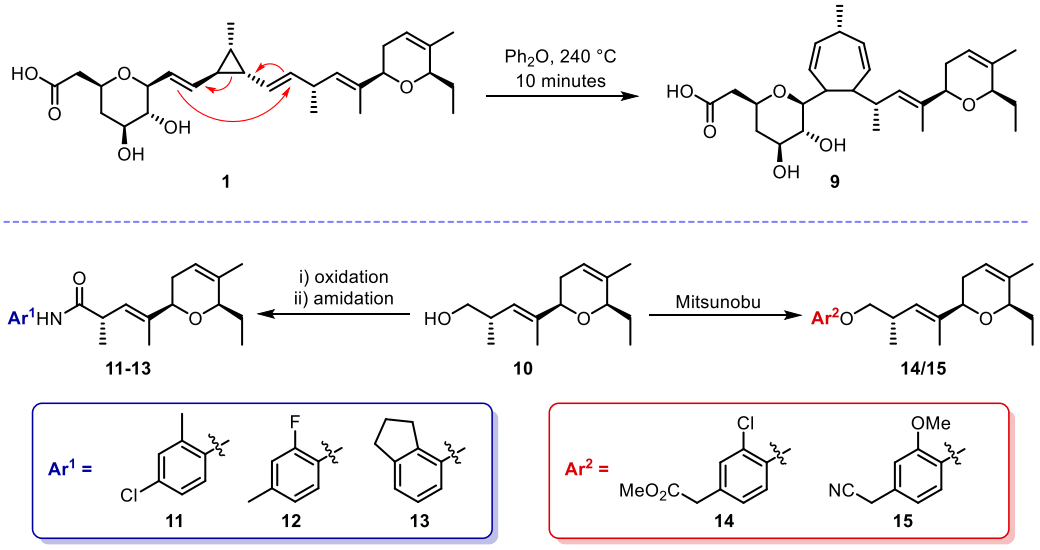
Table 1. Structure of the naturally occurring ambruticins.

Biological testing showed the ambruticins have potent and selective antifungal activity *in vitro* against a range of common fungal pathogens, alongside minimal toxicity in mammals (Table **2**).[58,63] Rats infected with *Coccidioides immitis* experienced a cure rate of 71-100% upon administration of ambruticin S at 50-100 mg/kg of bodyweight.[64] Furthermore, its activity against *Histoplasma capsulatum* was comparative to that of the commonly employed antimycotic amphotericin B.[65,66] The antimycotic activity of the ambruticins is proposed to originate from their interaction with the high-osmolarity glycerol (HOG) protein kinase signalling pathway.[67,68] This pathway is involved in osmoregulation in fungal cells and over stimulation, caused by the ambruticins, leads to the accumulation of glycerol and subsequent cell death. Given there is no direct human equivalent to the HOG pathway, the ambruticins present an exciting opportunity as a potential antimycotic medication.[69] Due to these promising biological properties, and the family's fascinating structure, the ambruticins have been the focus of many synthetic and biosynthetic studies.

Organism	M.I.C (μg/mL)
Coccidioides immitis	< 0.025
Histoplasma capsulatum	0.195
Blastomyces dermatitidis	0.04
Diplococcus pneumoniae	12.5

Table 2. Antifungal activity of ambruticins where M.I.C = Minimal inhibition concentration.[58,63]

In efforts to identify the structural features of the ambruticins which are fundamental to the family's antifungal activity, numerous analogues have been generated through synthesis and derivatisation of the natural products.[70–77] Following the initial isolation of ambruticin S, researchers at Warner-Lambert published the design and synthesis of a series of analogues targeting the central divinylcyclopropane (DVC) ring, the carboxylic acid, and the THP diol.[71–73] These studies indicated the central DVC was essential for biological activity as the cycloheptadiene analogue **9**, accessed through a thermal DVC rearrangement, showed no activity (Scheme **3**). It was suggested the DVC ring may impart sufficient rigidity to facilitate desired target binding.[57,71] It was also noted that significant modification of the polar functional groups of the western THP resulted in loss of antimycotic activity, although a slight increase in steric demand was tolerated. This was reinforced by reports from Shaw *et al*., whereby modification of the carboxylic acid and C-5 amine of ambruticin VS-5 often resulted in decreased antimycotic activity.[74,77] In an attempt to simplify the complex structure of the ambruticins, Hanessian *et al*. reported truncated analogues of ambruticin S which replaced the THP and cyclopropane rings with aryl amides and aryl ethers (Scheme **3**).[70] All analogues reported by Hanessian exhibited no biological activity, providing further evidence for the importance of the DVC ring and polar functionalities on the dehydroxylated THP acid.



Scheme 3. Divinylcyclopropane rearrangement of ambruticin S (top) and synthesis of truncated analogues of ambruticin S by Hanessian *et al*. (bottom).[70,71]

Although limited in scope, these SAR studies have highlighted the importance of all polar functionalities in the western portion of the ambruticins for biological activity, along with the potential requirement for the DVC moiety (Figure **7**). To date, no work has been published on the SAR of the eastern portion of the ambruticins. The jerangolids, a family of structurally related polyketide derived natural products isolated from *Sorangium cellulosum*, exhibit similar antifungal activity to the ambruticins (Figure **7**).[57,78] The presence of the conserved eastern fragment in both the ambruticins

and jerangolids may indicate its importance for interaction with the biological target. In order to fully exploit the promising pharmacological properties of the ambruticins, more detailed studies to probe their SAR are required. Towards this goal, many groups have reported approaches to the total syntheses of ambruticin S.

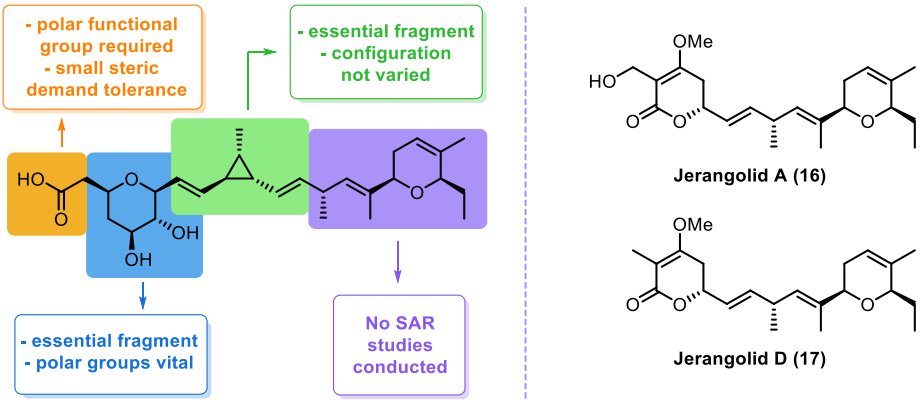


Figure 7. Summary of SAR studies on the ambruticins (left) and structures of jerangolids A and D (right).[57,78]

1.1.4.1. Total Syntheses of Ambruticin S

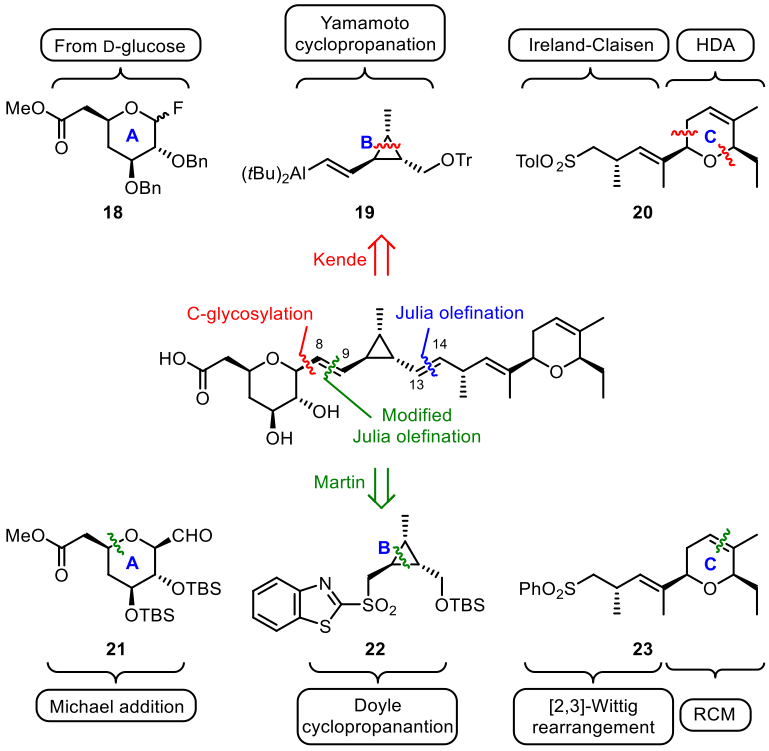
Five total syntheses of ambruticin S have been published by the groups of Kende (1990),[79] Martin (2001),[80] Jacobsen (2001),[81] Lee (2002),[82] and finally Hanessian (2010)[70] (Table **3**). Both Kende and Martin proceeded to report improvements to their originally published routes.[83,84] Overviews of the five syntheses, and their improvements, are discussed below. The synthesis of fragments towards the ambruticins have been reported and will be briefly discussed.[56]

Author	Date Published	Steps (LLS)/Yield	Total Steps/Yield
Kende[79,83]	1990	15/0.2%	35/0.1%
Martin[80,84]	2001	13/9.2%	28/0.7%
Jacobsen[81]	2001	16/12.0%	21/6%
Lee[82]	2002	17/4.8%	34/0.4%
Hanessian[70]	2010	17/5.0%	37/0.1%

Table 3. Total syntheses of ambruticin S. LLS = longest linear sequence.[57]

The first total synthesis of ambruticin S was reported by Kende *et al*. in 1990, inspired by previous work from Sinaÿ and co-workers.[56,79] A convergent approach was adopted, whereby the three constituent rings were synthesised and combined by a C-glycosylation and a Julia olefination (Scheme **4**).[85] THP **18** (ring A) was constructed in a total of 9 steps from protected D-glucose *via* a Barton deoxygenation, Arndt-Eistert homologation, various protecting group manipulations, and finally

fluorination. Yamamoto's dianion procedure was utilised to construct the trisubstituted cyclopropane in **19** (ring B).[86] Subsequent processing steps including selective hydrolysis, a Corey-Fuchs reaction, and hydroalumination provided the desired vinyl aluminium species **19** Finally, DHP **20** (ring C) was formed through a diastereoselective hetero-Diels-Alder (HDA), subsequent resolution, and a key Ireland-Claisen rearrangement. Overall, Kende's synthesis comprised 15 steps in the longest linear sequence (LLS), achieving a yield of 0.1%.

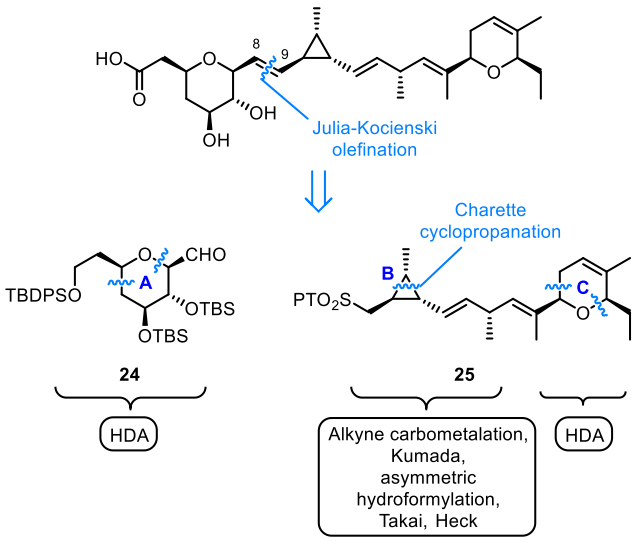


Scheme 4. Retrosynthetic analyses of ambruticin S by Kende and Martin.[79,80]

Martin adopted a similar convergent strategy to Kende, assembling the core structure of ambruticin S from the three individual ring fragments (Scheme **4**). However, in this instance, it was achieved through two Julia olefinations. Ring A (**21**) was assembled from commercially available L-glucono-1,5-lactone *via* an intramolecular oxa-Michael addition, followed by thermal equilibration of the resulting adducts to generate the most thermodynamically stable THP. The key oxa-Michael addition was similar to that previously reported in 1980 by Potvin *et al*. during studies to determine the absolute stereochemistry of ambruticin S.[61] For the synthesis of ring B (**22**), a rhodium-catalysed enantioselective intramolecular cyclopropanation of allylic diazoacetates developed by Martin and Doyle was employed.[80,87] This approach generated a cyclopropyl lactone which was subsequently opened, epimerised to achieve the desired cyclopropane stereochemistry, and transformed into cyclopropane benzothiazole sulfone **22**. Martin's construction of the ring C fragment in **23** made use of a selective epoxide ring opening and ring-closing metathesis (RCM). Further tailoring steps,

including Grignard addition and a [2,3]-Wittig rearrangement, were used to generate **23**, a similar sulfone as that used in Kende's synthesis (**20**). The use of a modified Julia olefination for the construction of the 8,9-alkene in ambruticin S provided a moderate *E*/*Z* ratio of 2.6:1. Nevertheless, the Julia olefination performed by Martin *et al*. for the construction of the 13,14-alkene achieved an improved *E*/*Z* ratio of 10:1 compared with a 4:1 ratio obtained by Kende and co-workers. Martin's synthesis improved upon Kende's in both yield and step count, with a yield of 9.2% over a LLS of 13 steps.

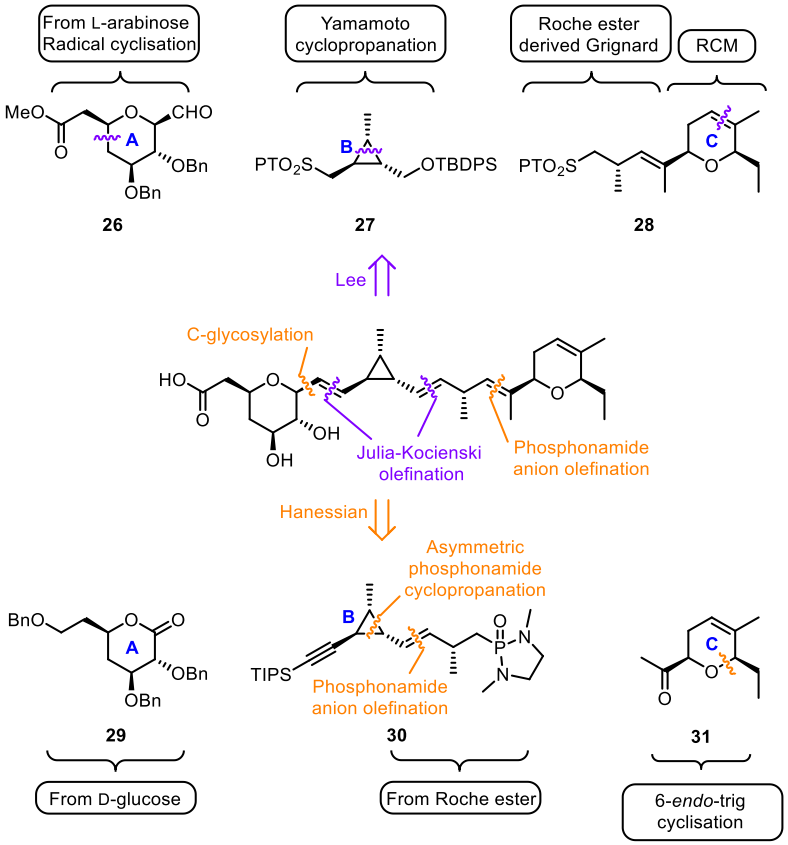
Shortly following Martin's synthesis, Jacobsen published an elegant total synthesis that adopted a less convergent, but higher yielding approach (Scheme **5**).[81] Both oxygen heterocycles were assembled utilising the asymmetric Cr-catalysed hetero-Diels-Alder methodology developed in their laboratories.[88] Fragment **25** was then generated by sequential chain elongation steps, including alkyne carbometallation, Kumada coupling, a key asymmetric hydroformylation, Takai olefination, and a Heck cross-coupling. Cyclopropane Ring B was then synthesised through a highly selective asymmetric Simmons-Smith cyclopropanation previously developed by Charette.[89] Fragments **24** and **25** were coupled *via* a Julia-Kocienski olefination (JKO), where excellent *trans*-selectivity (*E*/*Z* > 30:1) for the 8,9-alkene was achieved through the unprecedented use of LiHMDS in a mixture of polar solvents (4:1 ratio of DMF/HMPA).[90] Finally, global deprotection and selective oxidation afforded the natural product in an impressive yield of 12% over the 16 steps in the LLS.



Scheme 5. Jacobsen's synthetic approach to ambruticin S.[81]

In 2002, Lee reported a similar strategy for the synthesis of ambruticin S to that of Martin's in the previous year (Scheme **6**).[82] The core DVC unit was assembled through two JKOs, analogous to Martin's use of two Julia olefinations. Ring A in fragment **26** was constructed from L-arabinose by an oxa-Michael addition and a radical cyclisation. Yamamoto's dianion procedure was selected for the

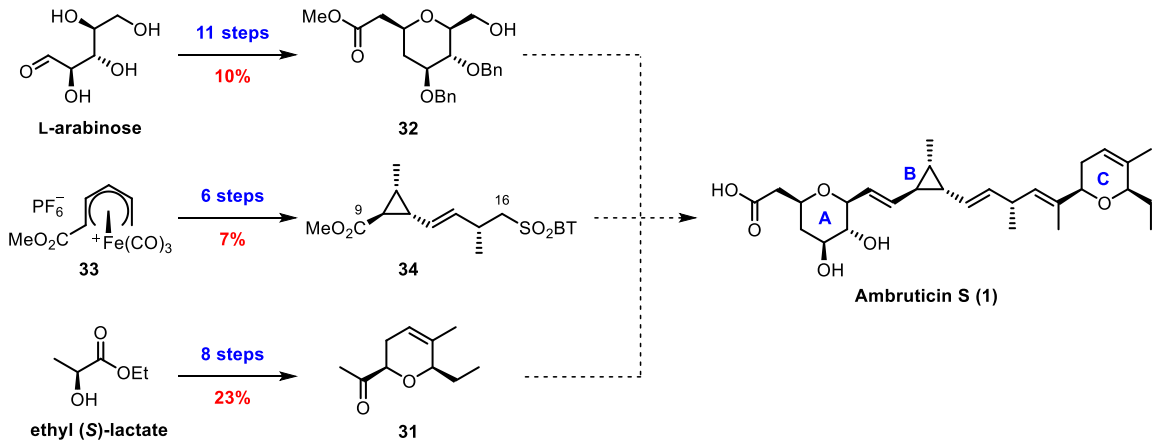
synthesis of cyclopropane ring B in the same fashion as Kende in 1990. The strategy adopted to generate ring C incorporated an asymmetric α-alkylation of an Evans-auxiliary adduct, followed by RCM. The ring was then elaborated by Grignard addition along with further transformations to form sulfone **28**. Lee's synthesis was the longest to date, with 17 steps and a yield of 4.8% over the LLS.



Scheme 6. Retrosynthetic analyses of ambruticin S by Lee and Hanessian.[70,82]

The final published total synthesis was completed in 2010 by Hanessian and co-workers (Scheme **6**).[70] Starting from α-methylated D-glucose, synthetic steps included a radical coupling and double bond isomerisation with Grubbs' catalyst to generate lactone **29**. Ring B was constructed with excellent stereoselectivity (dr = 99:1) by an asymmetric cyclopropanation with a chiral phosphonamide auxiliary previously developed in their group.[91] An olefination with a Roche ester-derived phosphonamide was employed to generate fragment **30**, which could then be used in a subsequent phosphonamide anion olefination with ketone **31**. Ring C in ketone **31** was assembled efficiently by a Lewis acid-catalysed 6-*endo*-trig cyclisation. Utilising numerous phosphonamide anion olefinations, Hanessian achieved excellent double bond stereoselectivity in the synthesis and obtained a yield of 5% over the 17 steps LLS. Due to the modular nature of the route, various truncated analogues which maintained the eastern sector of ambruticin S were synthesised and their biological activity tested. As previously discussed in section **1.1.4**, preliminary results showed no significant activity, indicating the importance of the western portion of ambruticin towards its antifungal potency.[70]

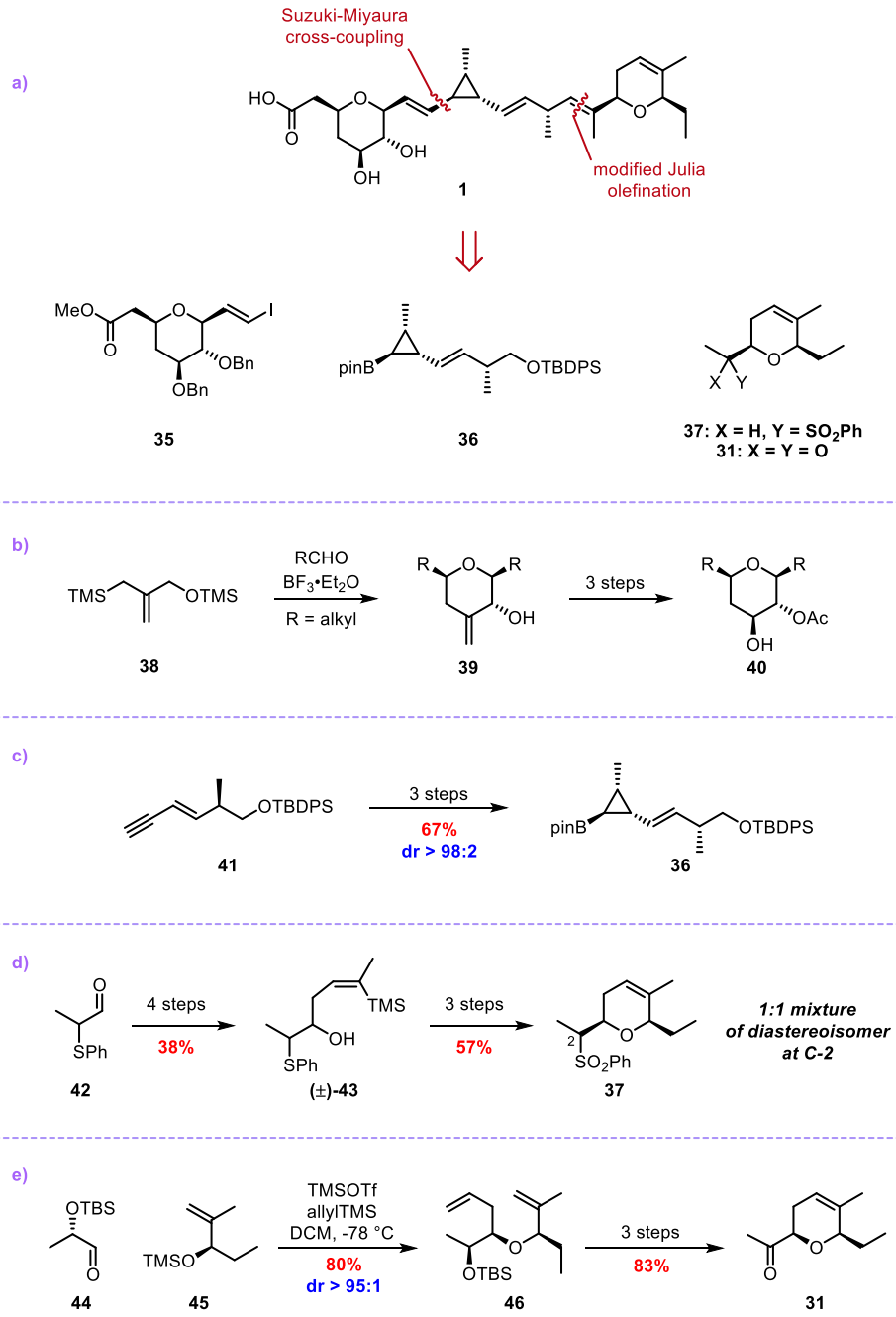
Groups including Donaldson,[92–95] Genêt,[56,96,97] Markó,[98–103] Sinaÿ,[56] Procter,[62,104] and Potvin[61] have also reported the syntheses of fragments and advanced intermediates of ambruticin S, many of which inspired the successful total syntheses. Genêt and Michelet published a detailed review highlighting the key synthetic strategies.[56] In particular, the groups of Donaldson and Markó made significant progress. Donaldson *et al*. successfully constructed all three ring systems of ambruticin S. The western THP ring **32** was assembled from L-arabinose in 10% yield over 11 steps (Scheme **7**).[92,95] The C-9 to C-16 segment of ambruticin S (**1**) containing the complex cyclopropane ring was constructed through organoiron methodology.[93] Finally, the dihydropyran ring **31** was synthesised in 23% yield over 8 steps from ethyl (*S*)-lactate, employing a key Lewis acid-catalysed HDA.[94]



Scheme 7. Partial synthesis of ambruticin S reported by Donaldson *et al*.[92–95]

Through a series of publications, Markó disseminated their progress towards the total synthesis of ambruticin S, where three fragments (**35**, **36** and **31**/**37**) were to be combined by a Suzuki-Miyaura cross-coupling and a modified Julia olefination (Scheme **8**). The construction of **40**, model fragments for THP **35**, were demonstrated through the use of an intramolecular silyl-modified Sakurai (ISMS) reaction developed in their group (Scheme **8B**).[103] The challenging cyclopropane fragment **36** was readily constructed from enyne **41** by hydroboration and subsequent palladium catalysed cyclopropanation with diazoethane.[98] Essentially a single diastereoisomer of **36** was obtained in an excellent yield of 67% from **41**. Finally, two strategies were developed for the synthesis of the DHP ring in the ambruticins. The first approach made use of the ISMS reaction previously applied to the synthesis of the THP **35**, forming sulfone **37** as a racemate in 21% yield over 7 steps from aldehyde **42**.[101] A mixture of epimers at C-2 was obtained, although this was of no consequence since the stereochemical information would later be lost. In a second more elegant approach, ketone **31** was constructed *via* a highly diastereoselective multicomponent silyl-modified Sakurai reaction between aldehyde **44**, silyl alcohol **45**, and allyltrimethylsilane, catalysed by TMSOTf.[99] Subsequent RCM and

tailoring steps afforded the desired ketone **31**, primed for Julia olefination. This strategy was applied to the total synthesis of jerangolid D, which contains a common eastern segment to the ambruticins.[100]



Scheme 8. (a) Synthetic strategy proposed by Markó. Syntheses of (b) THP **35**, (c) cyclopropane **36**, (d) sulfone **37**, and (e) ketone **31**.[56,98–103]

As outlined, a plethora of studies towards the synthesis of ambruticin S have been reported, culminating in five total syntheses. Nevertheless, to date, no other members of the ambruticins have been successfully synthesised. Routes to access these natural products may facilitate drug development of the ambruticins as antifungal agents, a goal not yet realised. Alongside these synthetic studies, research has been conducted in an attempt to elucidate the biosynthetic pathway to the ambruticins. It is hoped that the knowledge gained from these studies will inspire novel synthetic methods for the construction of complex molecules and aid in the development of biocatalysts.

1.1.4.2. Biosynthesis of the Ambruticins

Initial feeding studies with [2-^{13}C]-acetate units to cultures of *Sorangium cellulosum* indicated the ambruticins were polyketides in nature (Figure **8**).[105] Incorporation of both malonyl and methyl malonyl units was observed, alongside methyl units from adenosyl methionine. Of significant interest was the observed coupling between C-4 and C-5 ^{13}C labels, indicative of the excision of one carbon unit during the biosynthesis of the ambruticins.

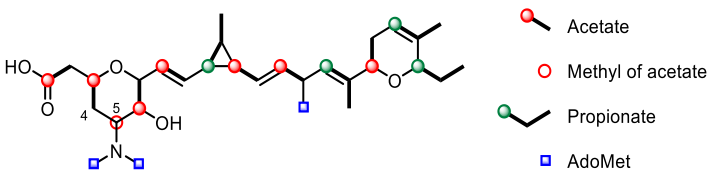
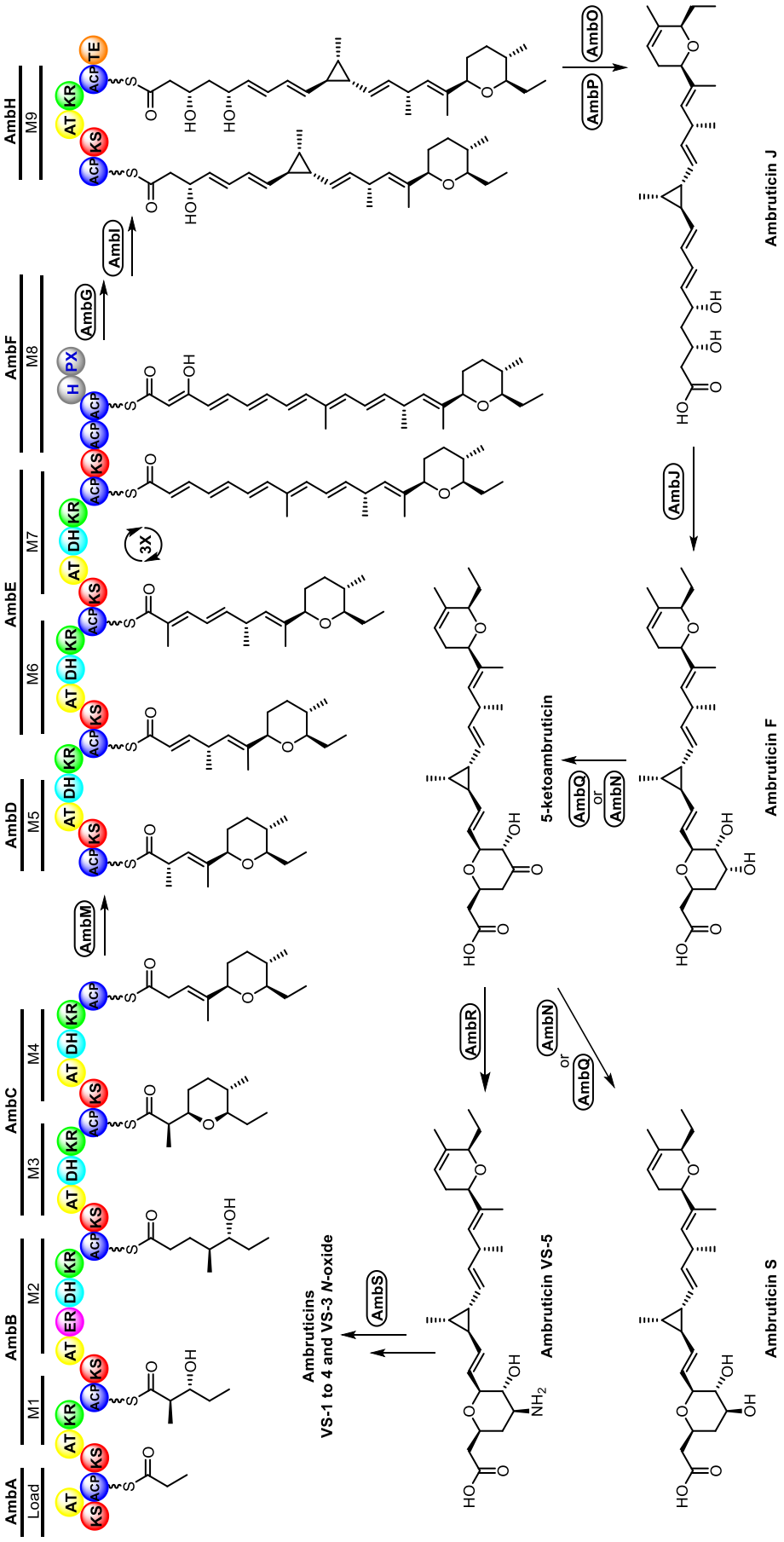


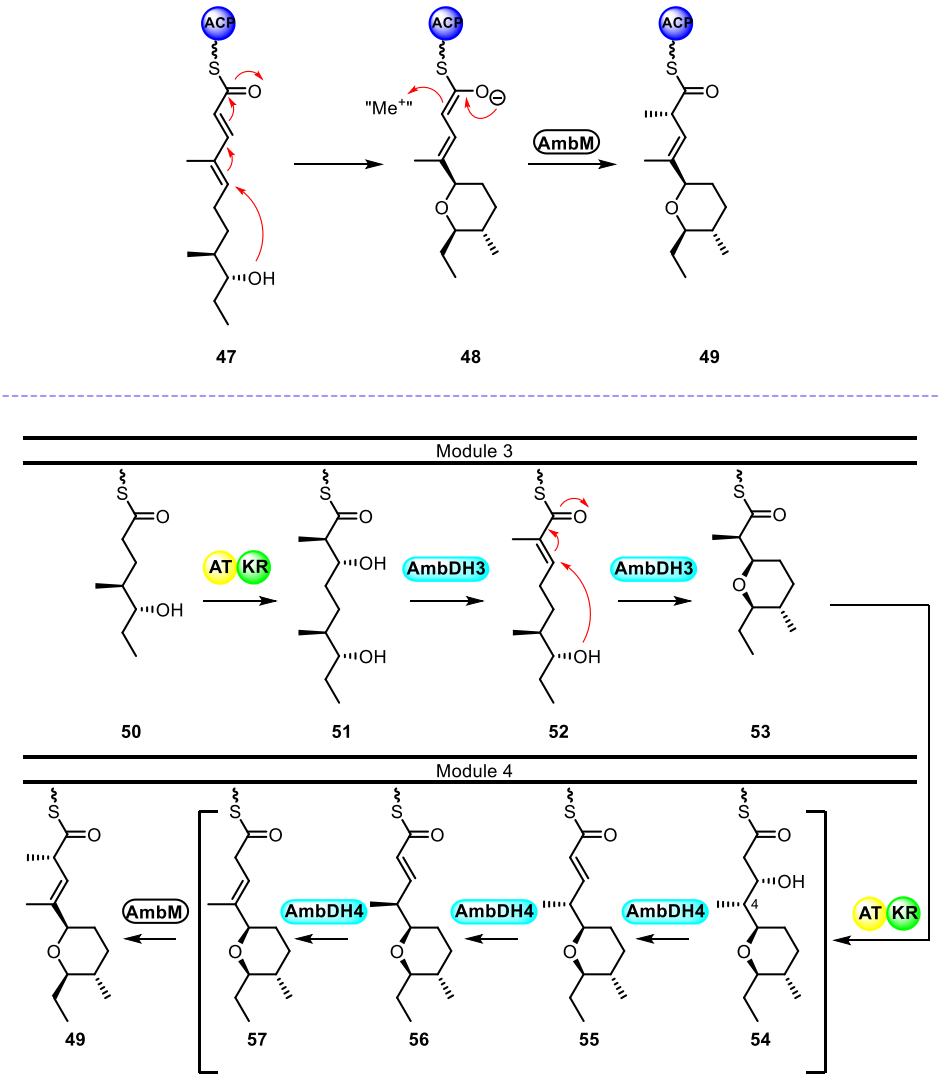
Figure 8. Feeding studies with ^{13}C labelled precursors for ambruticin VS-3.[105]

Through a combination of gene knockout experiments, gene cluster analysis, and *in vitro* enzymatic studies, a biosynthetic pathway to the ambruticins has been proposed (Scheme **9**).[57,105] In particular, the basis of the proposed biosynthetic pathway was established through an in-depth study conducted by Reeves *et al*.[105]

Modules 1 and 2 of the PKS conduct two elongations of the polyketide backbone in the canonical fashion of a type I PKS. Initially, Reeves proposed that modules 3 and 4 further elongated the backbone to generate dienoic acylthioester **47**, which undergoes a vinylogous oxa-Michael addition and subsequent C-methylation to generate the eastern heterocycle (Scheme **10**). However, no tailoring enzyme nor PKS domain could be identified to catalyse the proposed conjugate addition. Further investigations by the Hahn group led to the proposal of an unusual, alternative mechanism (Scheme **10**).[106–109]



Scheme 9. Proposed biosynthetic pathway to the ambruticins.[105]

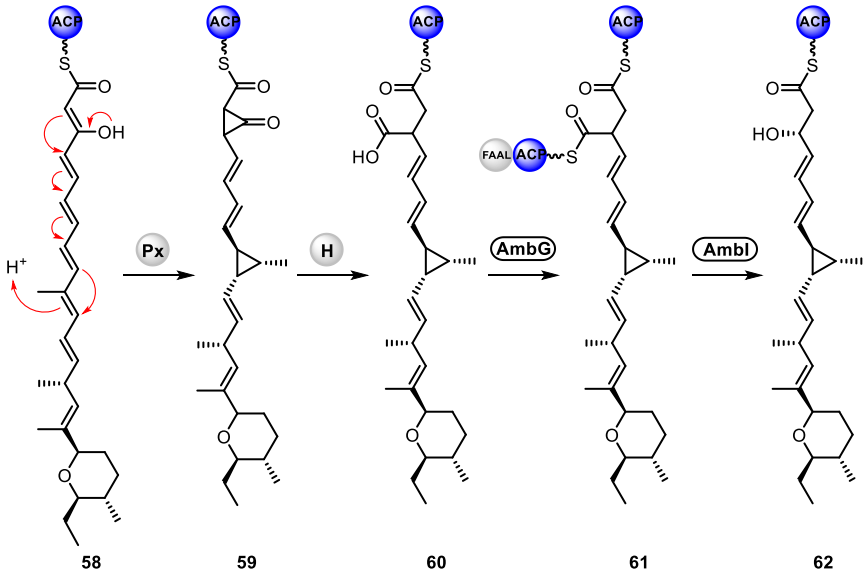


Scheme 10. Eastern THP formation proposed by Reeves *et al*. (top) and revised proposal by Hahn *et al*. (bottom).[105–107]

Initial chain elongation in module 3 generates α,β-unsaturated thioester **52** (Scheme **10**). This unsaturated system undergoes an intramolecular oxa-Michael addition, catalysed by the dehydratase domain AmbDH3, to selectively form THP **53** as a single diastereoisomer.[106,108] This unusual bifunctional activity of AmbDH3 was determined by incubating the *N*-acetylcysteamine (SNAC) thioester of **51** with heterologously expressed and purified protein. Further computational studies by Shi *et al*. provided further evidence for these transformations.[109] Following THP formation, further ketide elongation and reduction of the chain in module 4 affords β-hydroxythioester **54**, where concurrent C-4 epimerisation has occurred. Interestingly, a unique trifunctional activity of AmbDH4 as a DH, an epimerase and an enoylisomerase has been established through a similar *in vitro* strategy as that for AmbDH3. An equilibrium between **54-57** is set up, where the *trans*-acting methyl transferase AmbM only acts upon **57** to form **49** in an overall thermodynamically unfavourable process.[107] Although it is yet to be established when desaturation of the THP ring occurs, and which enzymes are

responsible, gene knockout experiments indicate the process is likely to be catalysed by either AmbO or AmbP. This is discussed further in chapter 3.

Following chain extension by modules 5 and 6, three consecutive alkenes are constructed by the iteratively acting module 7, a process which is uncommon in bacterial type I PKSs.[57,110] Although presently unproven, the mechanism of cyclopropane ring formation is proposed to proceed *via* a Favorskii rearrangement and a polyene shift, catalysed by a hydrolase (H) domain and a pyridoxal cofactor binding (Px) domain (Scheme **11**).[111,112] Bioinformatic analysis suggested the Px domain catalyses the intriguing Favorskii rearrangement, which is followed by the hydrolytic cleavage of cyclopropanone **59** catalysed by the H domain.[111] Carbon excision, which was initially predicted from ^{13}C feeding studies, appears to be catalysed by the adenylation (A)-ACP didomain, AmbG, and the flavin dependant monooxygenase, AmbI. Enzymatic *in vitro* studies conducted by Hahn *et al*. confirmed the adenylate-forming domain (AFD) of AmbG to be a fatty acyl:adenylate ligase (FAAL).[113] Nevertheless, further investigations to elucidate the intriguing steps in this part of the biosynthetic pathway are required. Module 9 of the PKS encodes for a final chain extension and subsequent TE-catalysed hydrolysis of the thioester, releasing ambruticin J (Scheme **9**, page **18**). The stereochemistry of the 1,3-diol in ambruticin J was assigned *via* the Rychnovsky method by analysis of the acetonide derived from the methyl ester of ambruticin J, although no spectral data were reported.[105,114]

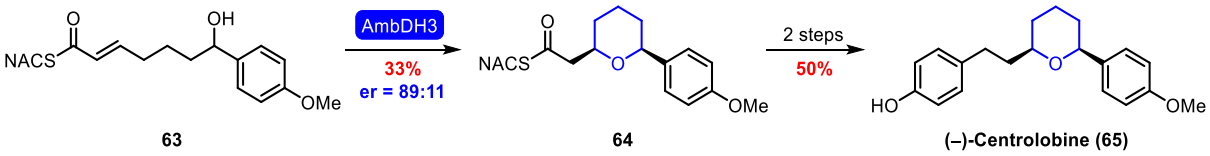


Scheme 11. Proposed mechanism of cyclopropane ring formation in ambruticin biosynthesis.[105]

Following release from the PKS, various tailoring enzymes are involved in generating all the members of the ambruticin family (Scheme **9**, page **18**). Formation of the THP ring is proposed to be catalysed by the monooxygenase enzyme, AmbJ, through epoxidation of ambruticin J and subsequent cyclisation to yield ambruticin F (Scheme **9**, page **18**). This process is discussed in greater detail in

Chapter **2**, section **2.1.5**. Formation of ambruticin S is proposed to occur *via* selective oxidation of the 5-hydroxyl in ambruticin F and subsequent reduction of the resultant ketone, catalysed by AmbQ and AmbN (Scheme **9**, page **18**). Cultures of the Δ*ambR* mutant in *Sorangium cellulosum* resulted in ceased production of the ambruticin VS series, implying the role of AmbR as a transaminase in the biosynthetic pathway. This is consistent with sequencing of the protein showing similarities with other aminotransferases.[105] Finally, the methyltransferase (MT) homolog AmbS is responsible for sequential methylations of the amino group in the VS series.

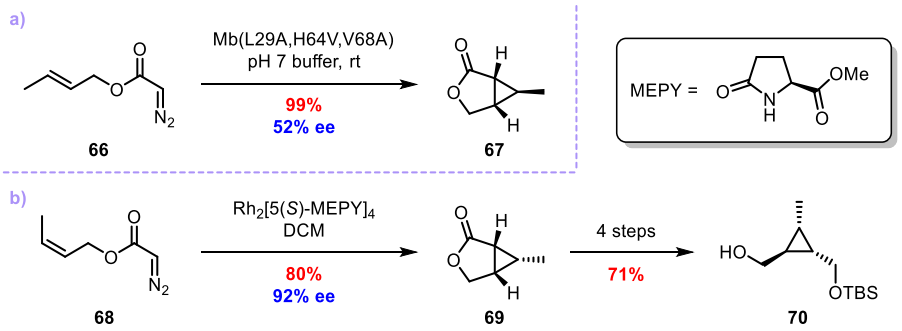
Overall, the ambruticin biosynthetic pathway is composed of many unusual processes and offers a suite of potentially valuable biocatalysts to perform challenging synthetic transformations. Biocatalysis has the capability to generate complex molecular scaffolds with exquisite selectivity in an efficient and cost-effective manner, with benefits to worldwide sustainability.[115–117] Furthermore, enzymatic transformations can supplement the already expansive library of reactions a synthetic chemist can apply to the construction of natural products, and numerous chemoenzymatic total syntheses have been reported.[118–120] Indeed, Hahn and co-workers have already demonstrated that the AmbDH3 cyclase domain from the ambruticin biosynthetic pathway is capable of synthesising THP rings on a gram scale.[121] This has been successfully applied to the chemoenzymatic total synthesis of (−)-centrolobine (Scheme **12**).



63 **64** **(–)-Centrolobine (65)**

Scheme 12. Chemoenzymatic total synthesis of (−)-centrolobine.[121]

The application of enzymes in synthesis is often limited to molecules that closely resemble the protein's native substrates. However, recent developments in engineering of enzymes to improve catalytic activity, substrate tolerance, and scalability may further facilitate the use of biocatalysts for the synthesis of pharmaceuticals and fine chemicals on an industrial scale.[117,122–124] For example, Fasan *et al*. reported a carbene transferase catalysed cyclopropanation reminiscent of the cyclopropane ring formation employed by Martin *et al*. in their total synthesis of ambruticin S (Scheme **13**).[80,87,125] Remodelling of the enzyme's active site through protein engineering allowed for stereodivergent selectivity and gram-scale assembly of trisubstituted cyclopropanes. This methodology was applied to the formal total syntheses of chrysanthemic acid and permethrin.[125]



Scheme 13. (a) Carbene transferase catalysed cyclopropanation reported by Fasan *et al*. and (b) synthesis of cyclopropane **70** by Martin *et al*. Mb = myoglobin.[80,87]

Developing a greater understanding of the structure and function of the enzymes involved in the biosynthesis of the ambruticins, and other polyketide natural products, may lay the foundations for the development of novel biocatalysts and inspire synthetic methods for the construction of complex molecules. Moreover, chemoenzymatic synthesis may provide rapid access to truncated scaffolds and analogues of the ambruticins in an attempt to improve upon their antifungal properties, synthetic tractability, and overall drug-like properties.[33,36,37] Further investigations are required to fully elucidate the biosynthetic pathway and take advantage of its biological machinery.

CHAPTER 2:

Tetrahydropyran Ring Formation in Ambruticin Biosynthesis

2.1. Introduction

During the course of these studies, we published a review on the synthetic and biosynthetic methods for controlling the cyclisation of 4,5-epoxy alcohols to generate THP rings.[126] The sections below provide an overview of the key topics from this review.

2.1.1. Tetrahydropyran Rings

Both aromatic and aliphatic ring systems are common structural features found in a plethora of natural products and small molecule drugs, with 96% of all marketed drugs containing a ring.[127] The importance of cyclic structures is well established due to their ability to affect key drug-like properties such as potency, lipophilicity, and solubility through modulation of molecular properties including scaffold rigidity, electronic distribution, and polarity.[128] Fully saturated ring systems, such as THPs, piperidines, and THFs, have the added benefit of increasing a molecule's three-dimensional character. Although not essential, evidence suggests that a greater degree of saturation in a drug molecule results in an improved chance of it progressing through the drug discovery process.[129] An increase in three-dimensionality of a drug can facilitate stronger and more specific binding to the desired biological target, imparting improved potency and selectivity by preventing off-target interactions.[130] Of these saturated ring systems, THPs are regularly employed in medicinal chemistry programs and indeed they are the sixth most prevalent ring system and fourth most common saturated ring system amongst all FDA approved small molecule drugs (Figure **9**).[128,131] Moreover, according to natural product databases, THPs are by far the most abundant heterocyclic ring system found in natural products, with many of these bioactive molecules having been developed into drugs (Figure **9**).[132]

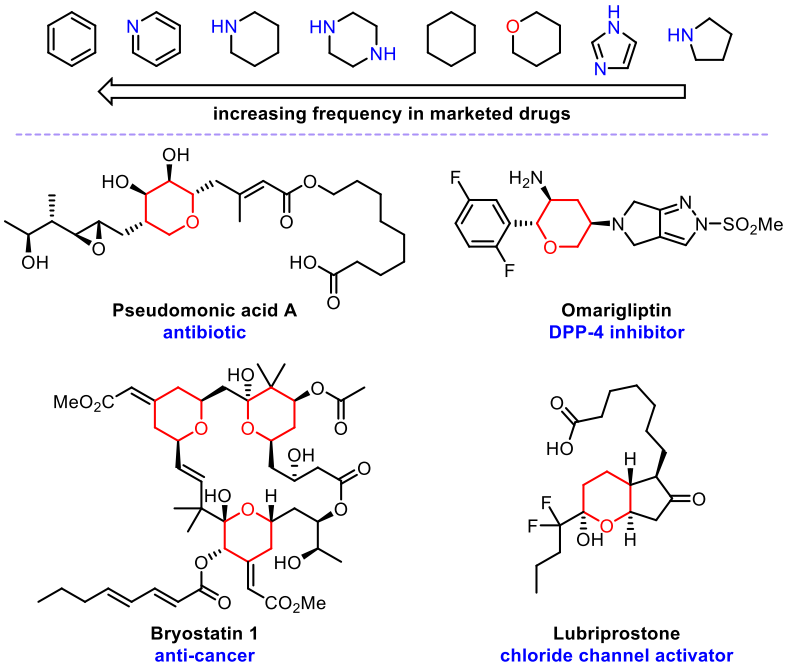
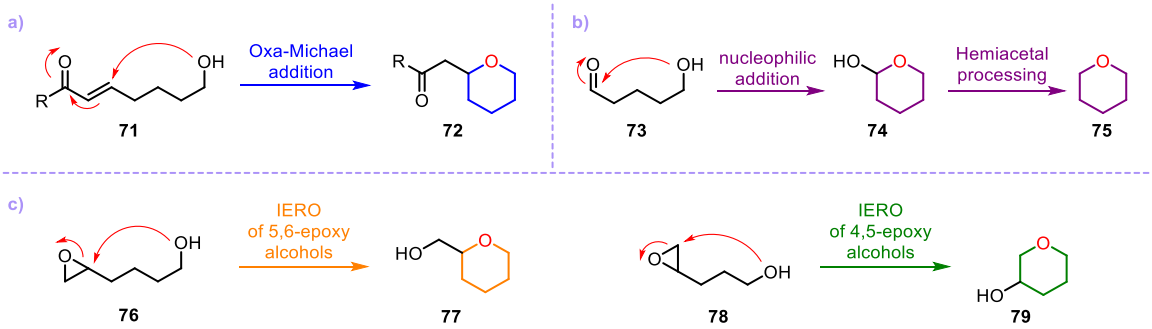


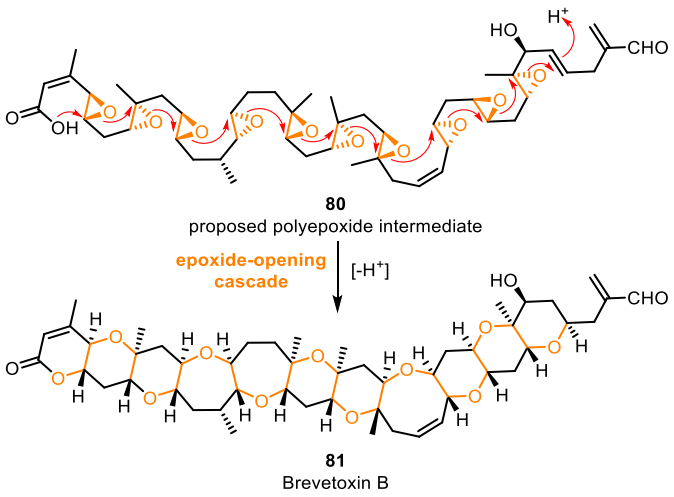
Figure 9. Frequency of ring systems in marketed drug molecules (top) and examples of THP-containing natural products and drug molecules (bottom).[128,131]

Due to the importance of THPs, numerous synthetic methods have been developed for their formation as described in various informative reviews.[133–136] Common approaches include the Prins cyclisations, hetero-Diels-Alder reactions, ring-closing metathesis, intramolecular epoxide ring opening, intramolecular oxa-Michael addition, and reductive etherification.[126,137–139] These methodologies have been applied to the construction of THPs in a plethora of complex natural products.[126,140–143] In addition to these synthetic studies, recent investigations into the biosynthesis of THPs in natural products has revealed three main processes for their formation in nature: oxa-Michael addition, modification of hemiacetals, and intramolecular nucleophilic opening of epoxides (Scheme **14**).[126,144,145]



Scheme 14. Biosynthetic methods for THP formation: (a) oxa-Michael addition, (b) processing of hemiacetals and (c) intramolecular epoxide ring opening of 5,6 and 4,5-epoxy alcohols.[144]

Indeed, intramolecular epoxide ring opening (IERO) is a well-established process for the formation of THP rings. For example, in 1983, Cane, Celmer, and Westley proposed the polyether ionophore class of natural products are formed *via* a cascade of IEROs.[146] Furthermore, the marine polycyclic polyethers such as brevetoxin B are proposed to be biosynthesised through a cascade of intramolecular opening of polyepoxide intermediates in what later was coined the "Nakanishi hypothesis" (Scheme **15**).[147–149] Of particular interest is the IERO of 4,5-epoxy alcohols as it has been extensively applied to the synthesis and biosynthesis of complex THP rings.[126]



Scheme 15. Proposed biosynthesis of brevetoxin B *via* an intramolecular epoxide-opening cascade.[147]

2.1.2. THP Ring Formation by Intramolecular Epoxide Ring Opening of 4,5-Epoxy Alcohols

IERO of 4,5-epoxy alcohols is a common method for the formation of oxygen heterocycles, giving either 5-membered THFs or 6-membered THPs depending on the site of alcohol attack onto the epoxide (Figure **10**).[126]

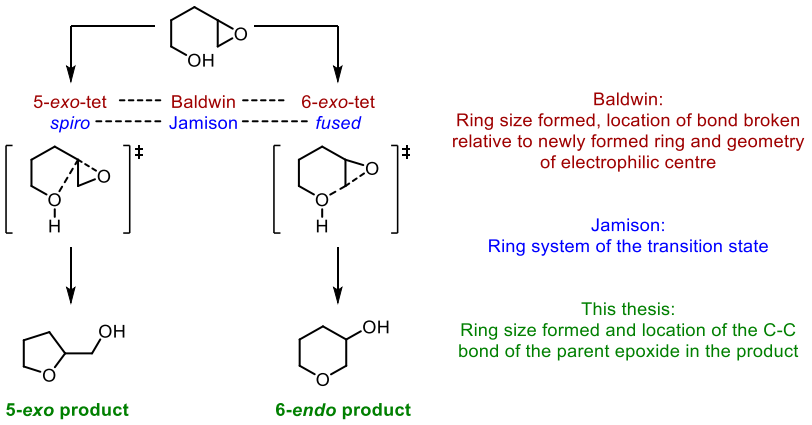


Figure 10. Intramolecular epoxide ring opening of 4,5-epoxy alcohols and corresponding nomenclature as described by Baldwin (red), Jamison (blue), and in this thesis (green).[149–151]

In the literature there has been significant confusion regarding the terminology utilised to describe these two processes, resulting in the misunderstanding that IERO of 4,5-epoxy alcohols that generate THPs are "anti-Baldwin" cyclisations. Historically, the formation of 5 and 6-membered rings by IERO have been mistakenly referred to as 5-*exo*-tet and 6-*endo*-tet processes.[150] This nomenclature originated from Baldwin's rules, a set of guidelines for predicting the outcome of ring-forming reactions, which were borne from experimental observations. In these processes defined by Baldwin, the numerical prefix defines the ring size formed, *exo* and *endo* refer to whether the bond broken during cyclisation is inside or outside of the newly formed ring, and the suffix indicates the geometry of the electrophile. It is evident from these rules that both cyclisations of 4,5-epoxy alcohols are *exo* processes since the C-O bonds broken during cyclisation are outside of the newly formed rings.[151,152] This has important implications as according to Baldwin's rules, both 5-*exo*-tet and 6-*exo*-tet are favoured processes, whilst 6-*endo*-tet cyclisations are disfavoured. As such, THP formation by IERO of 4,5-epoxy alcohols is not an "anti-Baldwin" cyclisation. This is further confirmed by considering the epoxide LUMO, generated through a combination of the relevant Walsh p-orbitals (Figure **11**).[151,152] It is apparent that the trajectory of the nucleophile onto the epoxide's 'banana bonds' resembles that of the trajectories in 5-*exo*-tet and 6-*endo*-trig processes, both of which are favoured according to Baldwin's rules.

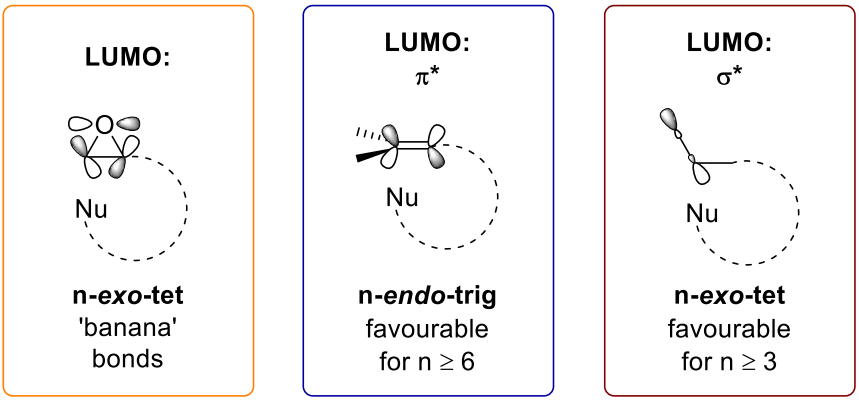


Figure 11. Molecular orbitals and cyclisation trajectories of *exo*-tet, *endo*-trig, and epoxide cyclisations.[151,152]

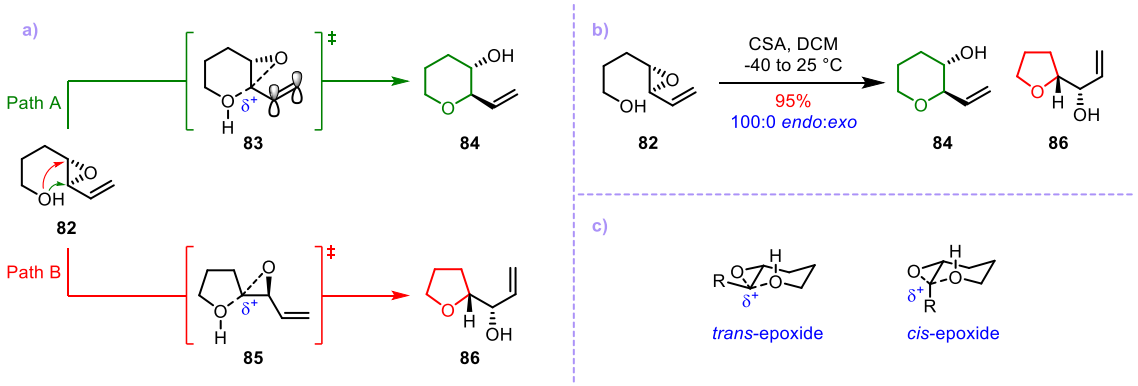
However, to avoid confusion, Jamison *et al*. have suggested an alternative nomenclature which refers to the transition state of the cyclisation as either 'spiro' or 'fused' for THF and THP formation respectively (Figure **10**).[148,149] Gilmore argued that it was better to consider the epoxide as a single functionality, where *exo*/*endo* can be used to indicate whether the C-C bond of the initial epoxide is located outside or inside the newly formed ring respectively.[151,152] As such, for the cyclisation of 4,5-epoxy alcohols, the THF can be referred to as the 5-*exo* product while the corresponding THP is the 6-*endo* product (Figure **10**). It is important to note that this nomenclature does not relate to Baldwin's rules. For clarity, this nomenclature of 5-*exo* and 6-*endo* processes will be adopted herein.

Whilst both THF and THP rings can be generated from 4,5-epoxy alcohols, the THF is often the major product as noted by Baldwin.[150] This selectivity originates from improved orbital overlap and a lower overall energetic barrier for formation in a 5-*exo* process.[153] Furthermore, formation of 5-membered rings is often preferred kinetically over the corresponding 6-membered rings. Therefore, to form THP rings through intramolecular epoxide ring opening of 4,5-epoxy alcohols, this inherent kinetic preference to form the 5-membered ring needs to be overcome. Many synthetic methods have been developed to favour THP formation using substrates and reaction conditions which either stabilise the 6-*endo* transition state or destabilise the 5-*exo* transition state. On the other hand, to achieve selectivity in natural product biosynthesis, enzymes known as epoxide hydrolases (EHs) are often employed.

2.1.3. Synthesis of THPs from 4,5-Epoxy Alcohols

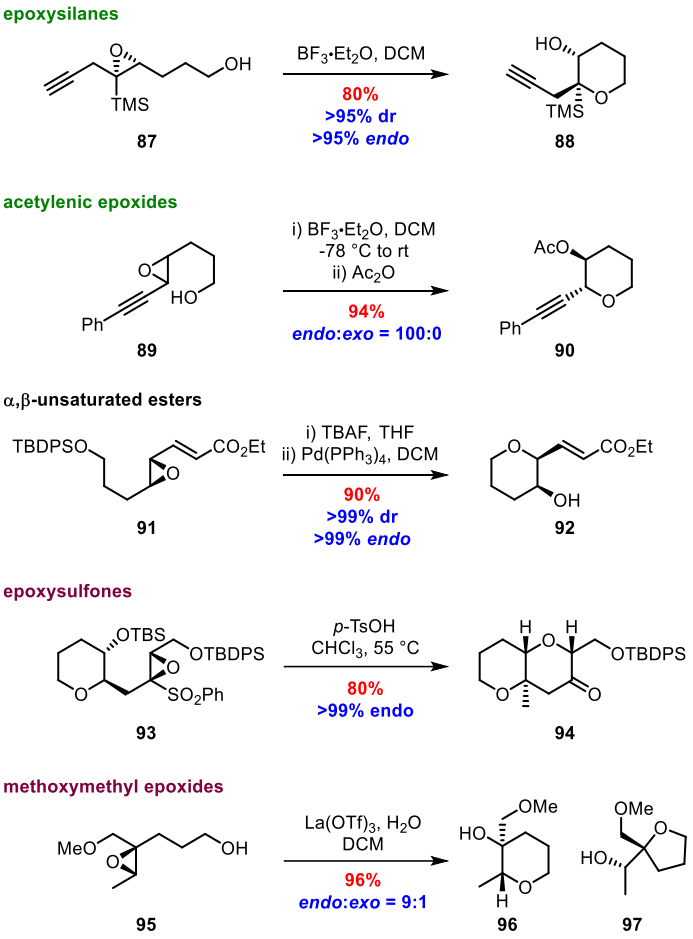
Due to widespread interest in marine polycyclic polyether natural products, such as the ladder polyether gambierol and the oxasqualenoid thyrsiferol, many groups have developed methods to achieve selective 6-*endo* ring closure of 4,5-epoxy alcohols.[148] Selective cyclisation is often achieved *via* stabilisation of the 6-*endo* transition state (TS) or destabilisation of the 5-*exo* TS through the use

of directing groups or reaction conditions. In the case of directing groups, an electronic or steric bias influences the site of nucleophilic attack on the epoxide. In 1985 Nicolaou reported studies towards the total synthesis of brevetoxin B in which selective cyclisation could be achieved by stabilisation of the incipient positive charge in the 6-*endo* transition state through the incorporation of a π-system adjacent to the epoxide (Scheme **16**).[154] Alkenyl epoxide **82** underwent acid-catalysed cyclisation to afford the desired 6-*endo* product **84** with complete regioselectivity in 95% yield.[155] Although *trans*-epoxides performed well under these conditions, poor regioselectivity was obtained with the corresponding *cis*-epoxides. Nicolaou proposed this is due to the inability of *cis*-epoxides to adopt the required planar geometry to achieve stabilisation in the transition state. This was supported by earlier studies conducted by Coxon *et al*. which illustrated that the cyclisation of *cis*-4,5-epoxy alcohols had a greater preference for 5-*exo* ring closure compared to the corresponding *trans*-epoxides.[156] The 6-*endo* transition state for *cis*-epoxides requires a group to be placed axially, resulting in steric clashes and an overall increased barrier for THP formation (Figure **16C**). The value of this methodology for the construction of THP rings has been exemplified through numerous natural product syntheses including preparation of amphidinol 3, meayamycin B, and mucocin.[157–164]



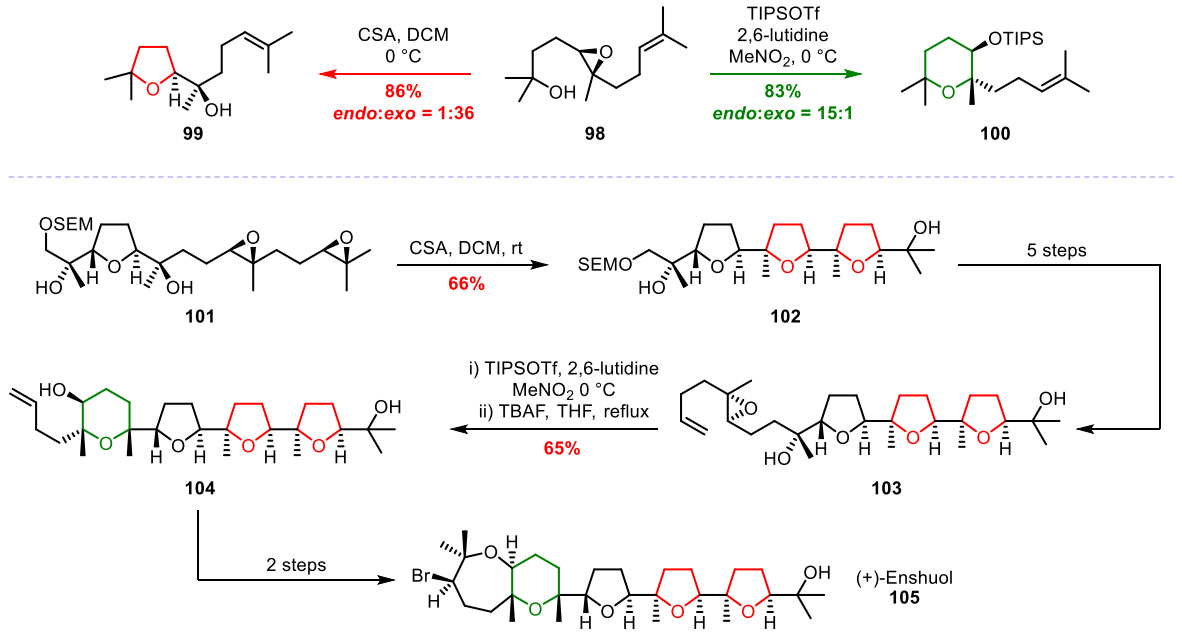
Scheme 16. (a) Stabilisation of 6-*endo* transition state by conjugation (b) CSA catalysed cyclisation of alkenyl epoxide **82** and (c) transition states of *trans* and *cis*-epoxides. CSA = camphorsulfonic acid.[126,154–156]

Since this pioneering work by Nicolaou, further methods of stabilising the 6-*endo* transition state have been developed such as through the use of epoxysilanes and acetylenic epoxides (Scheme **17**).[165–170] Alternatively, a number of approaches have been reported where selectivity is achieved by destabilisation of the 5-*exo* transition state through electronic influence or geometric constraints, such as in the cases of α,β-epoxysulfones and methoxymethyl substituted epoxides (Scheme **17**).[171–173]



Scheme 17. Examples of substrate-controlled selective 6-*endo* cyclisation of 4,5-epoxy alcohols.[126]

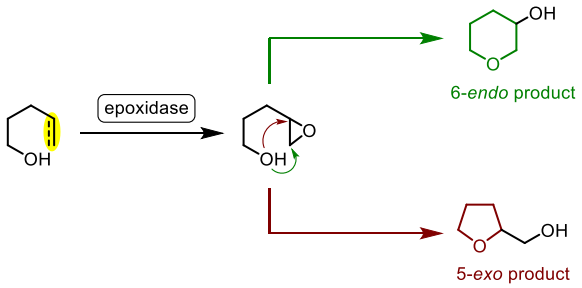
Although effective, the use of directing groups imposes substrate constraints. More recently, methods for selective 6-*endo* ring closure have been achieved through reagent control. This approach was elegantly demonstrated by Morimoto *et al*. where a judicious choice of reaction conditions facilitated reagent-controlled switching between the 5-*exo* and 6-*endo* products (Scheme **18**).[174,175] This methodology was applied to the construction of both 5 and 6-membered rings of (+)-enshuol.[176] Other examples of reagent controlled selective 6-*endo* cyclisations include the use of chiral phosphoric acid catalysis,[177] antibody catalysis,[178,179] π-anion catalysis,[180] and cyclisations in water.[181] Although not comprehensive, we have published a more extensive review of how the cyclisation of 4,5-epoxy alcohols can be controlled, and how these methods have been applied to the synthesis of natural products.[126]



Scheme 18. Reagent-controlled selective cyclisation of 4,5-epoxy alcohols (top) and its application in the total synthesis of (+)-enshuol (bottom).[174–176]

2.1.4. Biosynthesis of THPs from 4,5-Epoxy Alcohols

In natural product biosynthesis, a common method for THP formation is epoxidation of a 4,5-alkenyl alcohol and subsequent 6-*endo* IERO (Scheme **19**). The regioselective 6-*endo* cyclisation of the intermediate 4,5-epoxy alcohol can be achieved through structural features present in the substrate or *via* enzymatic control. However, in the absence of structural features which favour 6-*endo* cyclisation, enzymes known as epoxide hydrolases can overcome inherent 5-*exo* selectivity.



Scheme 19. Biosynthesis of THFs and THPS by epoxidation and selective intramolecular epoxide ring opening.

Epoxide hydrolases (EHs) are an abundant class of enzyme which play a crucial role in processes such as detoxification and blood pressure regulation.[182,183] They are robust, co-factor independent enzymes which catalyse the hydrolysis of epoxides with excellent regioselectivity and stereoselectivity.[184] Due to this exquisite control, EHs have been widely employed as biocatalysts for the hydrolysis of epoxides to generate chiral 1,2-diols, key building blocks in organic synthesis.[185] Indeed, a number of chemoenzymatic total syntheses of natural products have been reported where EHs are employed to

introduce chirality.[186] Furthermore, genetic engineering has been utilised to improve the substrate scope of various epoxide hydrolases, further enhancing their value as biocatalysts.[183,187]

EHs play a key role in the biosynthesis of THP-containing natural products by controlling the regioselectivity in intramolecular epoxide ring opening of 4,5-epoxy alcohols.[126] For example, the THP ring of pseudomonic acid A, the major component of the antibiotic mupirocin, is formed through an epoxidation-cyclisation cascade, catalysed by the Rieske non-haem oxygenase MupW and the EH MupZ (Figure **12**).[188] Through the use of whole-cell biotransformations, Willis, Crump, and co-workers demonstrated that MupW catalyses the intriguing selective oxidation of the non-activated 8,16-alkane in **106** to form 8,16-epoxide **107**, which in the presence of MupZ undergoes a selective 6-*endo* cyclisation to form THP **108**. In the absence of MupZ, the epoxide intermediate **107** underwent spontaneous 5-*exo* cyclisation to afford THF **109**. Furthermore, when the gene encoding for MupZ was deleted in *Pseudomonas fluorescens*, the mupirocin producing strain, only THF metabolites were isolated. Through a combination of molecular modelling, X-ray crystallography, and point mutation studies, it was revealed that MupZ catalyses epoxide ring opening through an acid-base mechanism. A glutamate residue (Glu54) acts as a general base to deprotonate the 5-hydroxyl group, while a tyrosine residue (Tyr41) protonates the epoxide to stabilise the desired transition state.

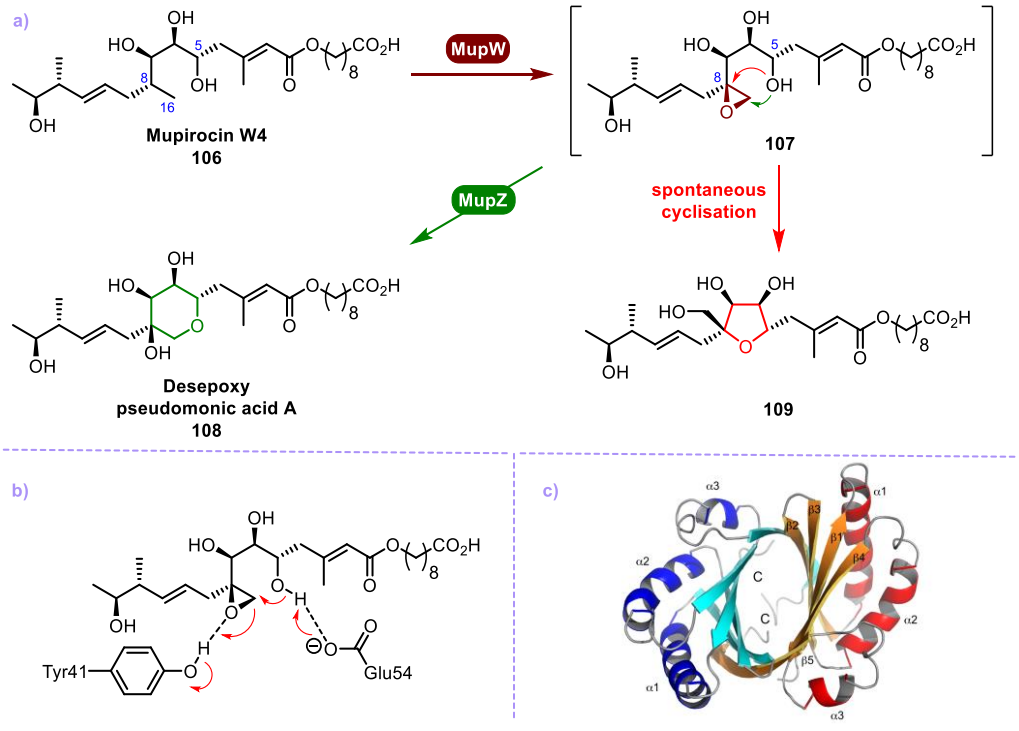
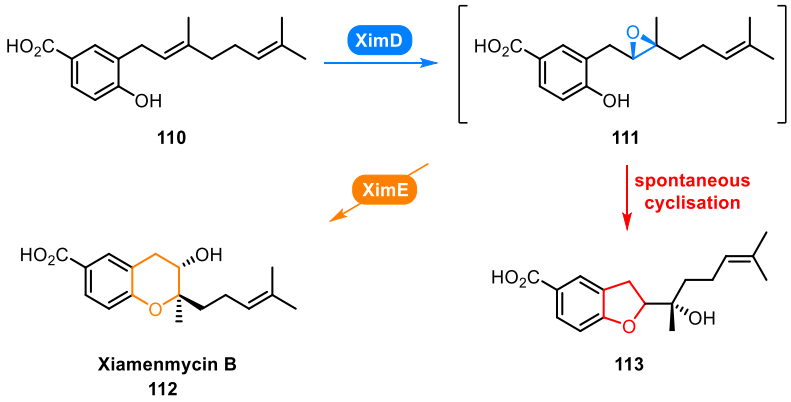


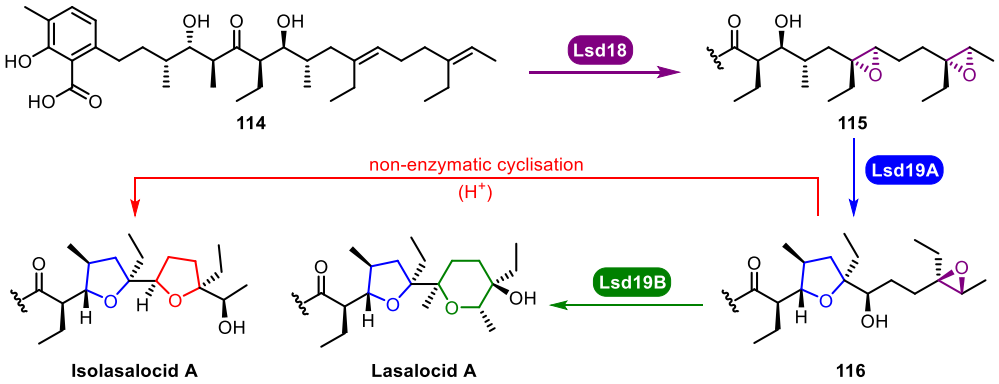
Figure 12. (a) MupW and MupZ catalysed THP ring formation in mupirocin biosynthesis (b) proposed general acid-base catalysis of MupZ and (c) X-ray crystal structure of MupZ.[126,188]

Epoxide hydrolase activity has been observed in the biosynthetic pathway of the xiamenmycins, a family of anti-inflammatory benzopyran natural products (Scheme **20**).[189] Following epoxidation by the flavin-dependant monooxygenase (FMO) XimD, pyran ring formation is controlled by XimE, a SnoaL-like cyclase. *In vitro* assays which incubated substrate **110** with XimD in the absence and presence of XimE afforded the furan and pyran products respectively. Furthermore, site directed mutagenesis, X-ray crystallography, and computational studies aided the identification of three residues responsible for this regioselectivity through a general acid-base mechanism.[189,190] The value of XimD and XimE as biocatalysts was demonstrated by He *et al*. where 14 products comprising 6 different benzoheterocyclic scaffolds were synthesised. These enzymes were also employed to generate structurally diverse benzoheterocyclic scaffolds through combinatorial biosynthesis.[191]



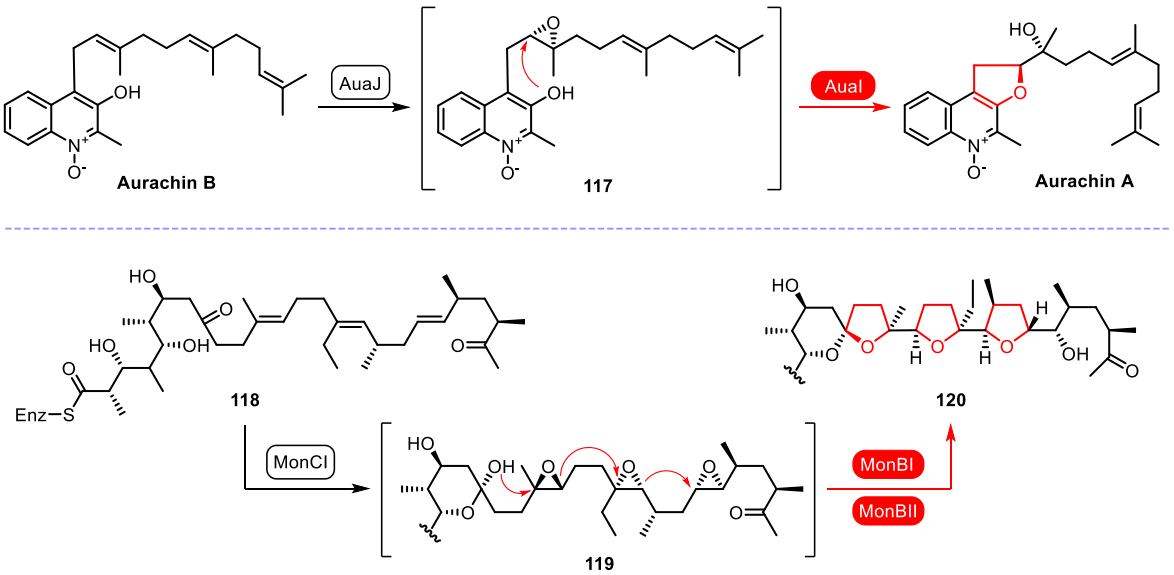
Scheme 20. XimD and XimE catalysed THP ring formation in xiamenmycin biosynthesis.[189]

The polyether natural product lasalocid A contains THF and THP moieties, both constructed *via* intramolecular epoxide ring opening of 4,5-epoxy alcohols (Scheme **21**). The groups of Minami and Oikawa demonstrated that the FMO Lsd18 catalyses the bis-epoxidation of linear diene **114** which, in the absence of an EH, undergoes two successive 5-*exo* cyclisations to afford isolasalocid A.[192,193] However, in the presence of the EH Lsd19, lasalocid A is produced through an initial kinetically favoured 5-*exo* cyclisation followed by a 6-*endo* cyclisation. These results highlight the ability of EH to overcome the bias towards 5-*exo* ring closure in the cyclisation of 4,5-epoxy alcohols. Further studies on Lsd19 by the groups of Leadlay and Hotta identified two catalytic domains, Lsd19A and Lsd19B, which catalyse the 5-*exo* and 6-*endo* cyclisations respectively.[194,195] Both domains are proposed to operate under general acid-base catalysis, similar to that previously seen in the biosyntheses of xiamenmycin and mupirocin. These findings provided early evidence to support the proposal that nucleophilic epoxide ring opening cascades were employed in the biosynthesis of numerous polyether natural products.[196]



Scheme 21. Heterocycle ring formation in lasalocid biosynthesis.[195]

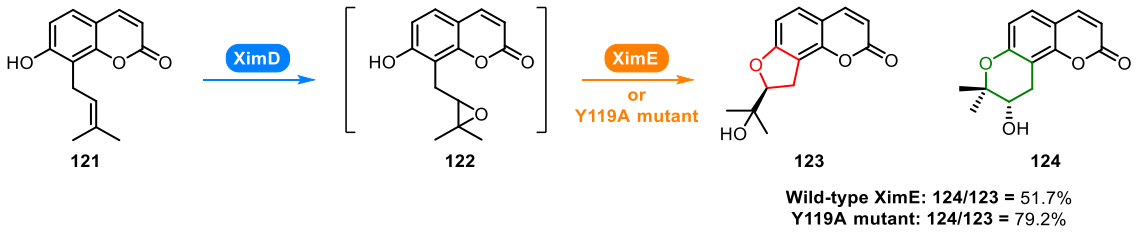
While these examples illustrate the ability of EHs to control the regioselectivity in IERO of 4,5-epoxy alcohols, there are numerous reported cases where their role is to solely catalyse cyclisations. In these cases, structural features of the substrate govern the selectivity of cyclisation to generate either THF or THP products. This is evident in the biosynthetic pathways of lasalocid, monensin, and aurachin, where EHs promote 5-*exo* cyclisation to forms THFs (Scheme **21** and Scheme **22**).[195,197,198] Furthermore, it is also unclear whether EHs can stabilise intermediate epoxides, facilitating the desired 5-*exo* or 6-*endo* ring closure.



Scheme 22. EH catalysed THF formation in the biosyntheses of aurachin (top) and monensin (bottom).[197,198]

EHs are potentially powerful biocatalysts for the formation of THP rings through IERO. Furthermore, rational protein engineering may expand the substrate scope of this class of enzyme and improve their catalytic activity and selectivity.[122] Xu *et al*. have used site-directed mutagenesis of the EH XimE to improve selectivity for the 6-*endo* cyclisation of an unnatural substrate (Scheme **23**).[191] The discovery

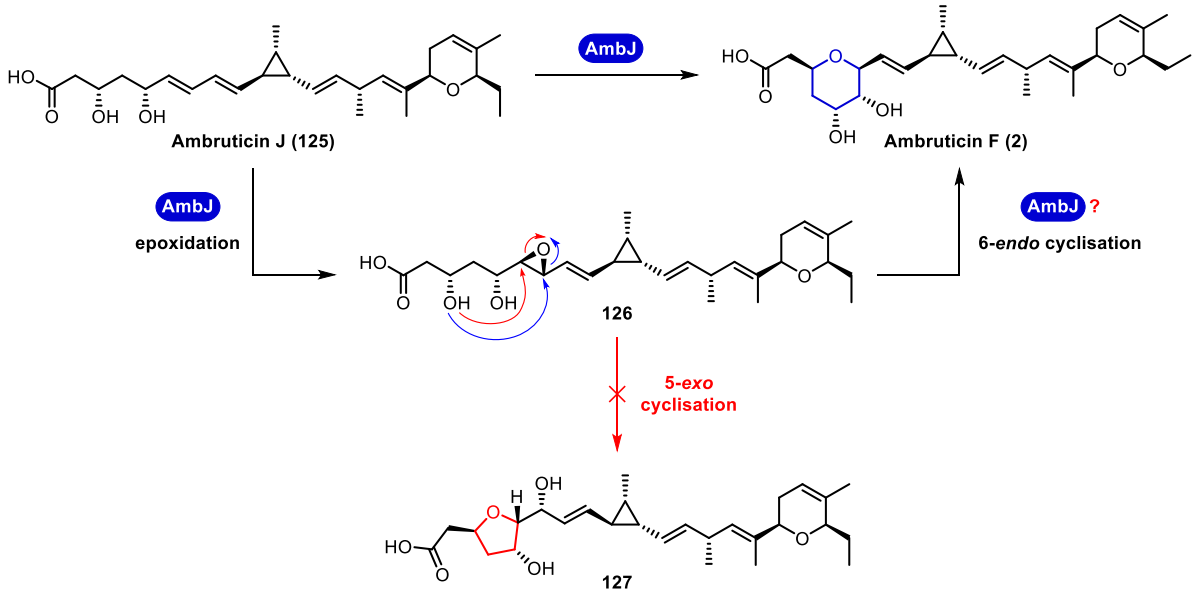
of more EHs, alongside investigations to probe their structure and function, may provide further tools for selective and sustainable THP ring formation.



Scheme 23. Biocatalytic synthesis of pyranocoumarins by wild-type and engineered XimE.[191]

2.1.5. Proposed THP Ring Formation in Ambruticin Biosynthesis

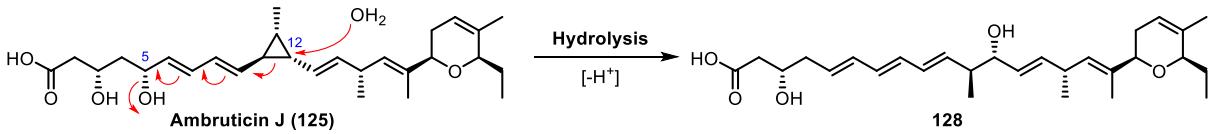
As discussed in section **1.1.4.2**, gene-knockout experiments conducted by Reeves *et al*. indicate that the formation of the THP ring in the ambruticins is catalysed by the flavin-dependent monooxygenase (FMO) AmbJ.[105] Cultures of *Sorangium cellulosum* where the *ambJ* gene was disrupted resulted in a build-up of ambruticin J and no THP ring formation was observed. AmbJ shows homology to epoxidases in polyether biosynthesis, suggesting it is responsible for selective epoxidation of ambruticin J to form epoxide **126** (Scheme **24**).[105] It is proposed the resultant 4,5-epoxy alcohol **126** undergoes selective 6-*endo* ring closure to generate the THP in ambruticin F. This epoxidation cyclisation-cascade is analogous to those processes discussed in section **2.1.4**.



Scheme 24. Proposed AmbJ catalysed THP ring formation in ambruticin biosynthesis.[105]

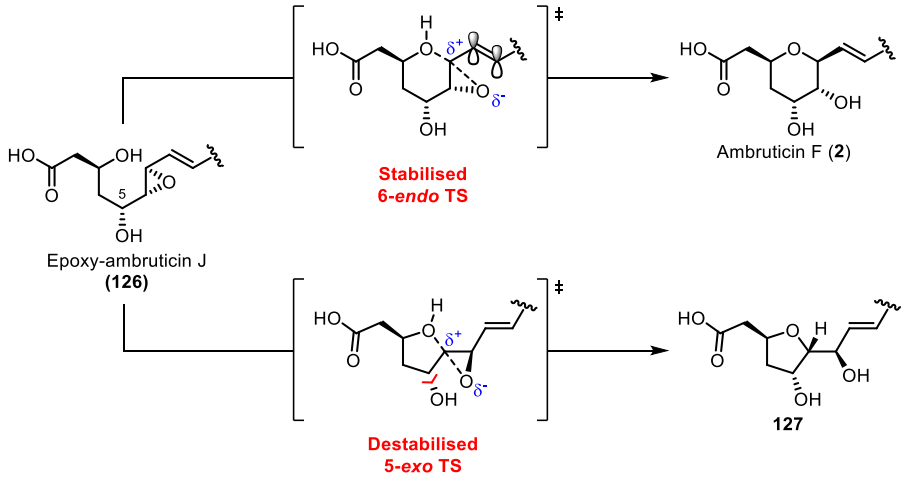
Interestingly, no THF products are observed in wild-type cultures of *Sorangium cellulosum*, indicating the epoxide ring opening step is highly selective. However, to date no EH has been identified in the ambruticin biosynthetic gene cluster. It is therefore unclear as to whether the apparent selectivity is due to inherent reactivity of the substrate, a yet to be identified EH, or the potentially unique

bifunctional role of AmbJ as both an epoxidase and EH. It is also not known whether the cyclisation occurs spontaneously under biological conditions, and if stabilisation of ambruticin J and epoxide **126** is required to prevent undesired reactivity. Indeed, Reeves *et al*. reported that the putative biosynthetic intermediate ambruticin J was prone to hydrolysis *via* opening of the cyclopropane ring by water at C-12 (Scheme **25**).



Scheme 25. Proposed mechanism of ambruticin J hydrolysis.[105]

Ambruticin J possesses structural features that may promote selective THP ring formation during cyclisation through both stabilisation of the 6-*endo* transition state and destabilisation of the *5-exo* transition state (Scheme **26**). As previously discussed in section **2.1.3**, Nicolaou *et al*. demonstrated that alkenic epoxides such as epoxy ambruticin J **126** often undergo selective 6-*endo* cyclisation due to stabilisation of the transition state by the adjacent π-system (Scheme **26**).[154] Moreover, the 5-hydroxyl group in epoxy-ambruticin J **126** may serve to further differentiate the energy of the two transition states through electron withdrawing destabilisation of the 5-*exo*-tet transition state.

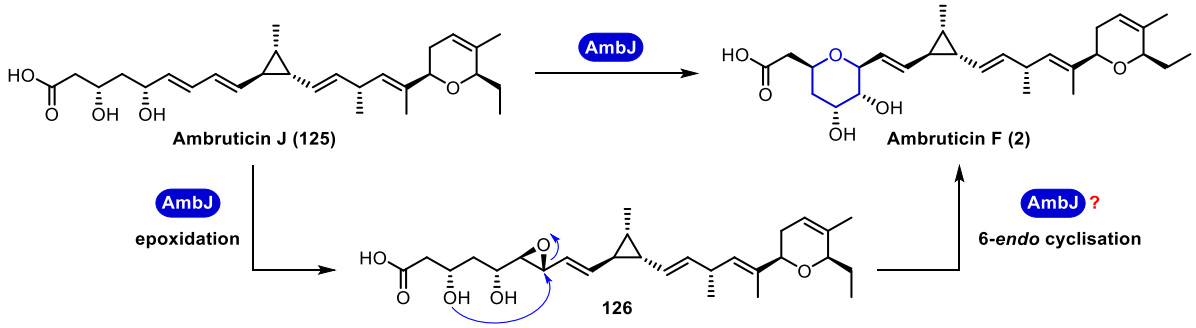


Scheme 26. Proposed intramolecular epoxide ring opening of epoxy-ambruticin J **126**.

Nevertheless, further investigations into this intriguing biosynthetic transformation are required to determine whether AmbJ has a unique role as not only an epoxidase but also an epoxide hydrolase. It is hoped that a greater understanding of these steps will provide clarity on whether AmbJ, or a yet to be identified EH, plays a role in controlling regioselectivity of IERO, stabilising biosynthetic intermediates, and accelerating the key cyclisation. Furthermore, studies into structure and function of AmbJ may facilitate the exploitation of nature's biosynthetic machinery for the development of a novel biocatalyst for THP ring formation.

2.2. Project Aims

The initial goal of this project was to confirm the function of AmbJ in formation of the THP in the ambruticins (Scheme **27**). Two steps are involved, epoxidation and ring formation. Hence a question remains of whether AmbJ plays a role in the oxidation and as an epoxide hydrolase to control cyclisation, or if a yet to be identified EH is required.



Scheme 27. Proposed THP formation in ambruticin biosynthesis.

To develop an understanding of the inherent selectivity for the cyclisation of epoxy ambruticin J **126**, we aimed to perform chemical epoxidation-cyclisation studies on model substrates of ambruticin J. Substrates **129**, **130**, and **131** were to be synthesised, then epoxidised in order to test the hypothesis that the 5-hydroxyl group and 8,9-alkene of ambruticin J play a role in controlling selectivity during cyclisation (Figure **13**). Although ambruticin J is a carboxylic acid, model studies were to be performed on ethyl esters for ease of handling.

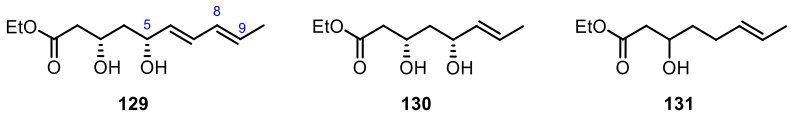
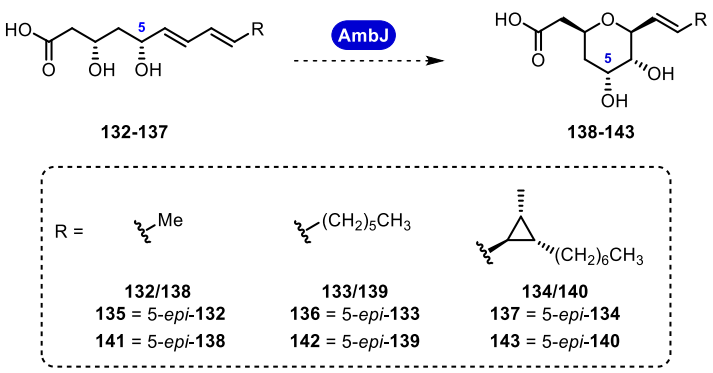


Figure 13. Model substrates of ambruticin J for chemical epoxidation-cyclisation studies.

To determine the function of AmbJ, simplified model substrates of ambruticin J were to be synthesised, then fed to heterologously expressed protein *in vivo* and *in vitro* (Scheme **28**). Initially, 3,5-dihydroxy acid **132** and the corresponding 6-*endo* cyclisation product **138** were to be prepared, where THP **138** was to serve as a synthetic reference to aid the analysis of assays. If no turnover was observed in assays of AmbJ with **132**, substrates which more closely resemble ambruticin J (**133** and **134)** were to be synthesised. Although Reeves *et al*. determined a 3,5-*syn* relationship for the alcohols in ambruticin J through Rychnovsky analysis, no spectral data for the acetonide was reported. As such, we also aimed to conduct assays of AmbJ with 3,5-*anti*-diols **135**, **136**, and **137** (Scheme **28**).



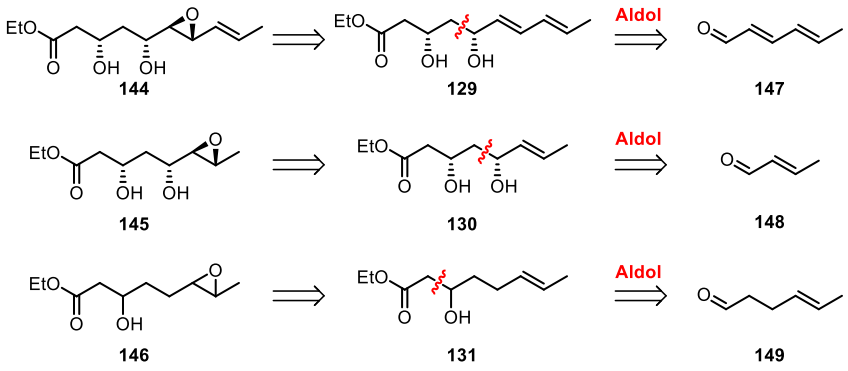
Scheme 28. Proposed assays of AmbJ with 3,5-dihydroxy esters **132**-**137** to form THPs **138**-**143**.

If assays with AmbJ and model substrates of ambruticin J were unsuccessful, the next aim was to complete the total synthesis of the putative biosynthetic intermediate ambruticin J (**125**). A modular approach was to be employed to facilitate the rapid synthesis of ambruticin J analogues for substrate specificity studies with AmbJ. Additionally, it was hoped that AmbJ could be utilised as a biocatalyst for THP ring formation and in the chemoenzymatic synthesis of ambruticin J analogues, with the aim to improve antifungal activity and assess SAR.

2.3. Results and Discussion

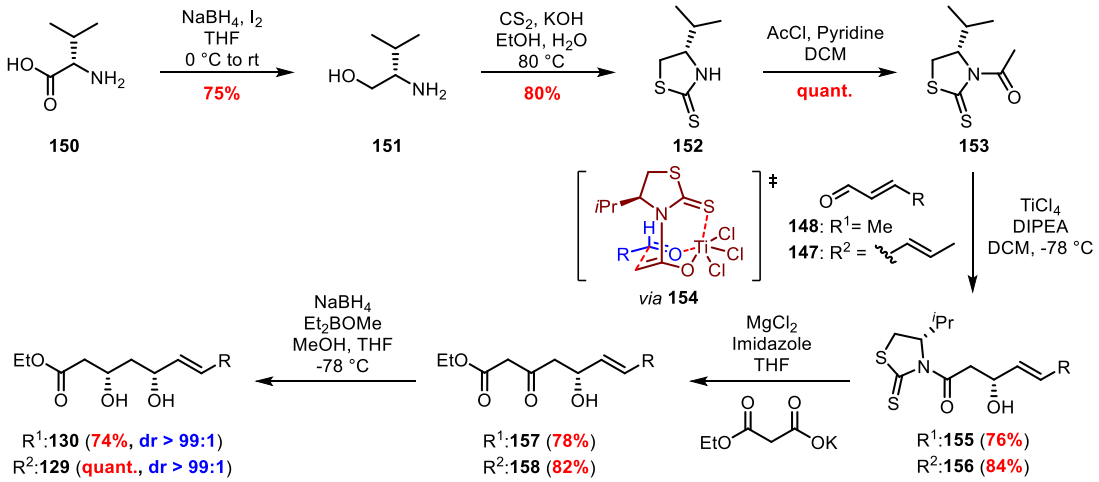
2.3.1. Model Epoxidation-Cyclisation Studies

In order to probe the inherent chemical reactivity of the proposed intramolecular epoxide ring opening in ambruticin biosynthesis, we aimed to prepare three epoxide substrates **144**, **145**, and **146** for use in model cyclisation studies (Scheme **29**). These studies would provide insights into how the structural features of ambruticin J (5-hydroxyl and 8,9-alkene) influence the outcome of cyclisation. We proposed the epoxides could be readily accessed by epoxidation of the corresponding alkenes, which in turn could be synthesised by aldol condensations with aldehydes **147**, **148** and **149** (Scheme **29**).



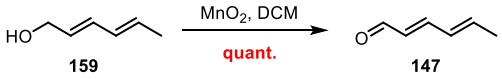
Scheme 29. Retrosynthetic analysis of epoxides **144**, **145**, and **146**.

Crimmins' auxiliaries are the thiazolidinethione variants of the Evans oxazolidinone auxiliaries which have been widely used in diastereoselective aldol reactions and are readily cleaved under mild conditions.[199] Acylated auxiliary **153** was synthesised on a multi-gram scale in 60% yield over 3 steps from L-valine using a literature procedure (Scheme **30**).[200] Titanium-catalysed asymmetric aldol condensations with acylated auxiliary **153** and either aldehyde **148** or **147** afforded the corresponding auxiliary adducts **155** and **156** in 76% and 84% yields respectively as single diastereoisomers.[201] In both cases, a major diastereoisomer was formed as expected (dr = 6:1 for **155** and 8:1 for **156**) with the reaction proceeding *via* transition state **154**, where strong coordination between titanium and sulfur prevents free rotation of the auxiliary.[202] Steric interactions in the Zimmerman-Traxler TS are minimised through orientation of the aldehyde side chain in an equatorial position to reduce 1,3-diaxial interactions, and by the aldehyde approaching from the back face of the auxiliary adduct as drawn.



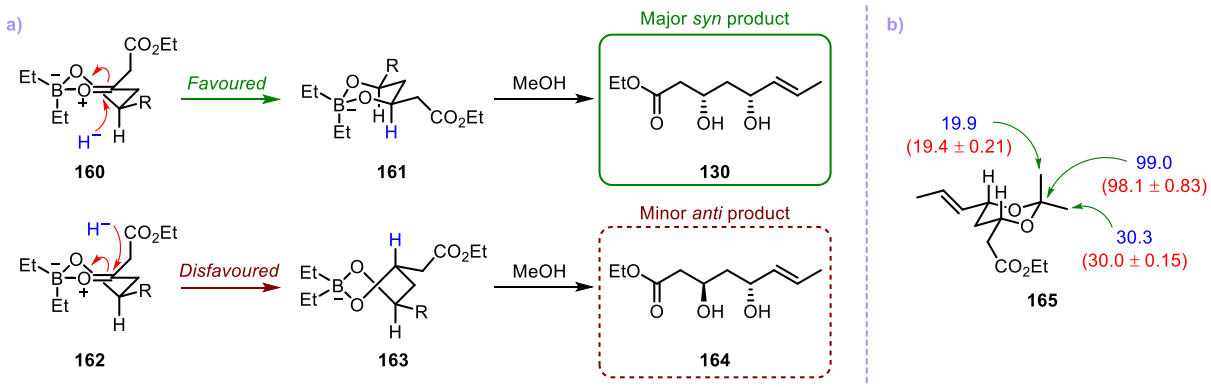
Scheme 30. Synthesis of acylated Crimmins' auxiliary **153** and alkenes **129** and **130**.

Unfortunately, commercially available sorbic aldehyde **147** comprised a 7:1 mixture of *trans*,*trans*:*cis*,*trans* olefins which were inseparable by column chromatography, resulting in a mixture of alkene isomers in auxiliary adduct **156**. If required, this issue could be circumvented by freshly preparing aldehyde **147** in quantitative yield by oxidation of geometrically pure *trans*,*trans*-2,4-hexadien-1-ol **159** with activated MnO_2 in DCM, without the need for column chromatography (Scheme **31**). Due to the volatility of sorbic aldehyde **147**, it was desirable to avoid column chromatography to prevent product loss during solvent evaporation. Although Dess-Martin Periodinane (DMP) oxidised alcohol **159** cleanly, separation from the by-products without column chromatography was challenging. Swern oxidation afforded sorbic aldehyde **147** in a 95% yield, however, 10% of the undesired *E*,*Z* isomer was observed.



Scheme 31. Oxidation of alcohol **159** to *trans*,*trans*-hexadienal **147**.

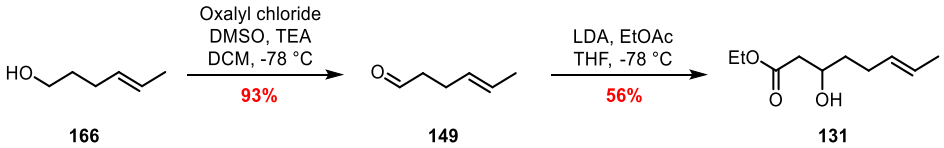
Following the asymmetric aldol condensation, the auxiliary adducts **155** and **156** were cleaved in a decarboxylative Claisen condensation to generate β-hydroxyketones **157** and **158** in 78% and 82% yield respectively (Scheme **30**).[199,203] In both cases auxiliary **152** was readily recovered in greater than 95% yield. Finally, diastereoselective Narasaka-Prasad reductions afforded **130** and **129** as exclusively the 1,3-*syn*-diols.[204] Rychnovsky analysis of acetonide **165** revealed a characteristic 10.4 ppm difference in ^{13}C-NMR chemical shift for the acetonide methyl groups, confirming the *syn*-diol relationship in **130** (Scheme **32**).[114,205] The diastereoselectivity observed in this reduction is due to intermolecular hydride delivery following the Fürst-Plattner rule.[206] This rule states that a nucleophile will approach a cyclohexene derivative from the face that will result in a chair-like TS (**161**) as opposed to a twist boat TS (**163**). In the reduction of ketone **157**, Et_2BOMe chelates to the substrate, generating a 6-membered ring, which is reduced by the intermolecular hydride from $NaBH_4$ (Scheme **32**).[204]



Scheme 32. (a) Diastereoselectivity of the Narasaka-Prasad reduction and (b) Rychnovsky analysis of acetonide **165**, where observed (blue) and average (red) ^{13}C-NMR chemical shifts for acetonides are depicted.[114,204,205]

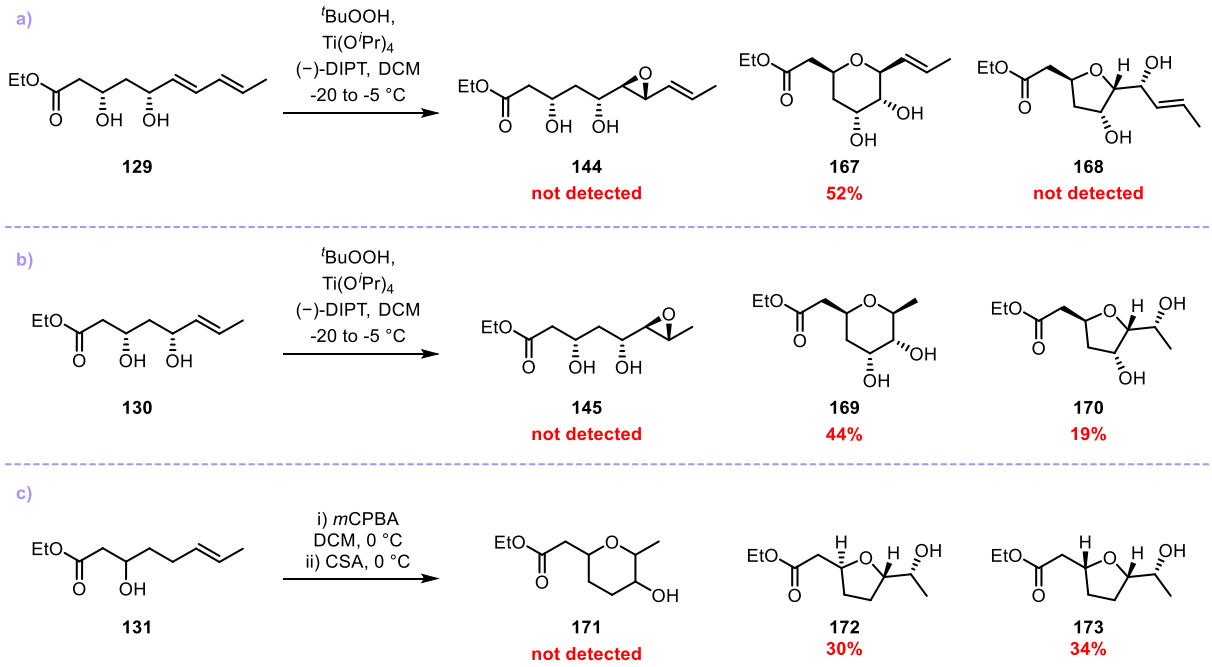
Initial attempts to form the *syn*-diol **130** through reduction of ketone **157** were low yielding due to the formation of the stable boronate **161** (Scheme **32**). Attempts to cleave the boronate with both acetic acid and aqueous 2 M HCl were unsuccessful. Nevertheless, successive azeotroping with methanol afforded the desired diol **130** without the need for further purification.

Finally, racemic alkene **131** was readily synthesised from (*E*)-hex-4-en-1-ol (**166**) in a two-step sequence of Swern oxidation and subsequent aldol condensation with EtOAc (Scheme **33**). Although the aldol reaction proceeded with a moderate yield of 56%, no optimisation was performed as the desired alkene **131** was obtained in sufficient quantity for the proposed epoxidation-cyclisation studies.



Scheme 33. Synthesis of alkene **131**.

With alkenes **129**, **130** and **131** in hand, the planned epoxidation-cyclisation studies were conducted (Scheme **34**). Alcohol-directed epoxidation of allylic alcohol **129** was performed under standard conditions developed by Sharpless, followed by an aqueous tartaric acid quench to afford THP **167** in 52% yield with no evidence of the corresponding THF **168** in the ^{1}H-NMR spectrum of the crude product.[207,208] Attempts to isolate the assumed epoxide intermediate **144** by quenching the reaction with either water or aqueous saturated $Na_2S_2O_3$ were unsuccessful. Moreover, no change in retention factor (Rf) for the newly formed product was observed by thin layer chromatography (TLC) analysis of the reaction mixture prior to and after quenching, indicating the cyclisation of the 4,5-epoxy alcohol **144** was spontaneous under the reaction conditions. It is known that such epoxy alcohols readily cyclise under these conditions.[209]



Scheme 34. Epoxidation-cyclisation studies on alkenes **129**, **130** and **131**.

Due to the similar connectivity of THF **168** and THP **167**, in-depth NMR analysis was required to confirm the structure of the product. The ^{1}H-NMR spectrum of **167** revealed peaks characteristic of a 6-membered ring (Figure **14**). In particular, 2-H exhibits one large $^{3}J_{ax\text{-}ax}$ coupling (9.8 Hz) and one smaller $^{3}J_{ax\text{-}eq}$ coupling (3.1 Hz). Furthermore, the signals assigned to the diastereotopic protons 4-H and 5-H exhibit expected coupling constants alongside a characteristic difference in chemical shift (0.38 ppm) for equatorial and axial protons in a 6-membered ring. This information, alongside the observed nuclear Overhauser effect (nOe) between 2-H and 5-H as well as 1-H and 6-H indicated the THP had formed preferentially over the THF. To conclusively assign the structure of the product, acetylation of the free alcohols and subsequent NMR analysis was conducted (Figure **15**). Upon acetylation of the diol in THP **167**, the signals assigned to 2-H and 3-H would shift downfield in the ^{1}H-NMR spectrum. On the other hand, acetylation of the alcohols in THF **168** would result in a downfield shift of the signals assigned to 1-H and 3-H. Indeed, upon acetylation with acetic anhydride in pyridine the signals for 2-H and 3-H shifted downfield, by 1.33 and 1.28 ppm respectively, whilst the signal assigned to 1-H exhibited a small downfield shift of 0.16 ppm.

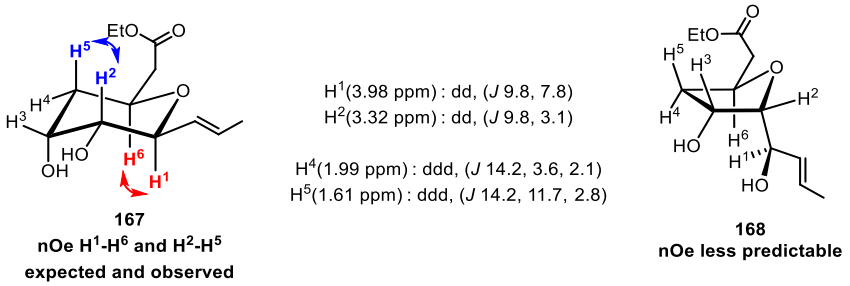


Figure 14. Selected ^{1}H-NMR chemical shifts, coupling constants, and nOe enhancements of **167**.

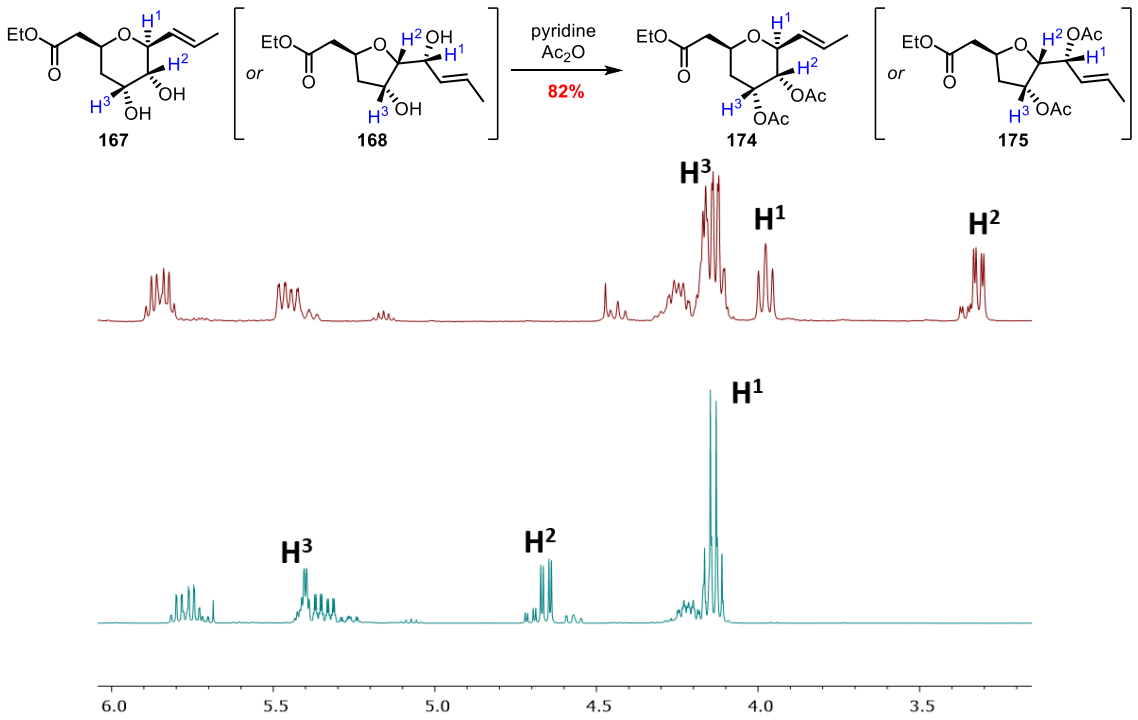


Figure 15. Acetylation of **167** or **168**. ^{1}H-NMR spectra of starting material (red) and product (blue).

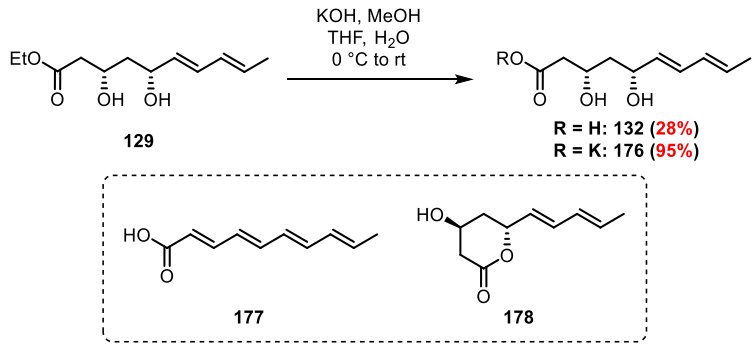
This observed selectivity for 6-*endo* ring closure of 4,5-epoxy alcohol **144** is likely to be due to stabilisation of the 6-*endo* transition state by the adjacent alkene and destabilisation of the 5-*exo* transition state by the 5-hydroxyl group. To test this hypothesis, alkene **130**, which lacked the adjacent alkene, was epoxidised under SAE conditions and after an aqueous tartaric acid work-up afforded a mixture of THP and THF products **169** and **170** in 44% and 19% isolated yields respectively, with no further products detected (Scheme **34**). Finally, *m*CPBA epoxidation of alkene **31** (lacking the 5-hydroxyl group and adjacent alkene) gave a mixture of epoxides which upon addition of CSA gave solely THF products **172** and **173** (Scheme **34**). The structures of products **169**, **170**, **172** and **173** were confirmed by NMR spectroscopy and derivatisation as the diacetates.

These results are in accord with the hypothesis that both the 5-hydroxyl group and 8,9-alkene of ambruticin J play a role in controlling regioselectivity in the IERO of epoxy-ambruticin J to form ambruticin F. Nevertheless, these simple model studies do not provide information on whether AmbJ or an unidentified EH is required to accelerate cyclisation or stabilise epoxy-ambruticin J to hydrolysis. Furthermore, since the selectivity of IERO is influenced by reaction conditions such as pH, the outcome of cyclisation may differ *in vivo*.[126] As such, assays with AmbJ and ambruticin J (or simplified model substrates of ambruticin J) are required to definitively confirm the function of AmbJ in ambruticin biosynthesis. To perform these bioassays, we required access to both the substrates and protein. The expression and isolation of AmbJ through heterologous expression in *E. coli* was conducted by Dr. Luoyi Wang and will not be discussed in this thesis.

2.3.2. Synthesis of Model Substrates for Ambruticin J

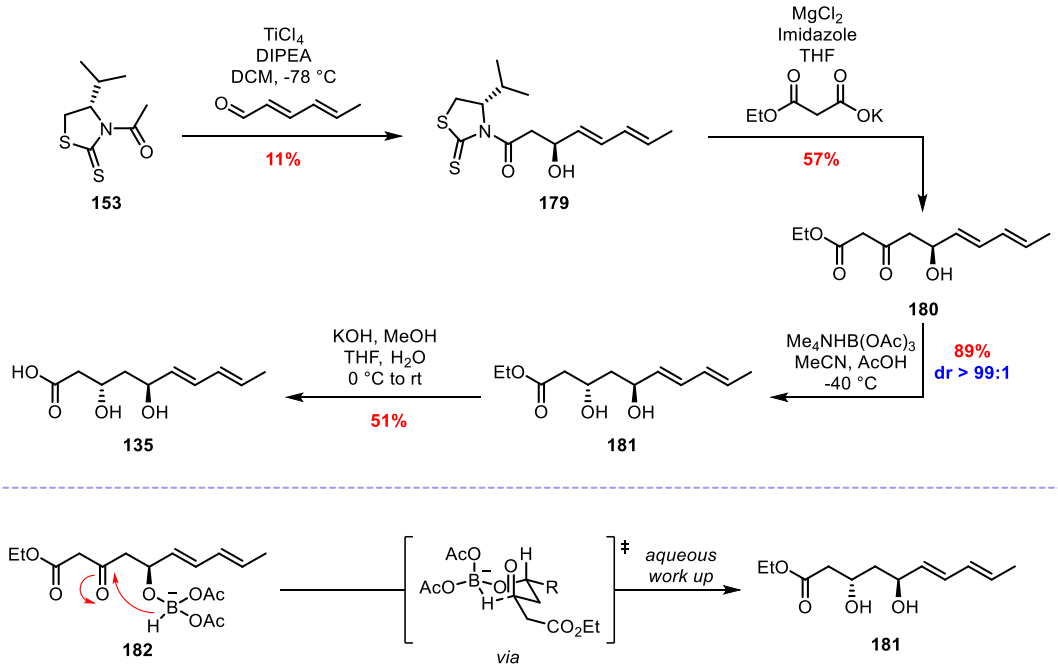
Next, we proceeded with the synthesis of 3,5-dihydroxy acid **132** as a model substrate of ambruticin J for use in bioassays with AmbJ (Scheme **28**, page **37**). Although Reeves *et al*. proposed that the structure of ambruticin J contained a 1,3-*syn*-diol, no spectroscopic data are available in the literature.[105] As such, we also targeted the synthesis of the corresponding 1,3-*anti*-diol **135** in the event that ambruticin J was incorrectly assigned.

While esters were employed in epoxidation-cyclisation studies for ease of handling, the corresponding carboxylic acids were required for bioassays. Access to 3,5-dihydroxyacid **132** *via* KOH catalysed hydrolysis of ethyl ester **129** (previously synthesised as outlined in Scheme **30**, page **39**) proved problematic due to formation of polyene **177** and lactone **178** (Scheme **35**). The formation of polyene **177** could be avoided by lowering the equivalents (eq.) of KOH from 10 to 0.5 eq. It became evident that lactonisation occurred during the acidic work-up with 2 M HCl and column chromatography on silica gel. As a result, a work-up procedure was developed which afforded the desired carboxylic acid **132**, albeit in only 28% yield, without the need for column chromatography (see experimental). However, if required, the potassium salt **176** could be isolated in 95% yield through use of 1 eq. of KOH followed by concentration of the reaction mixture. Since lactonisation was observed over time in $CDCl_3$, the NMR of **132** was run in acetone-D_6.



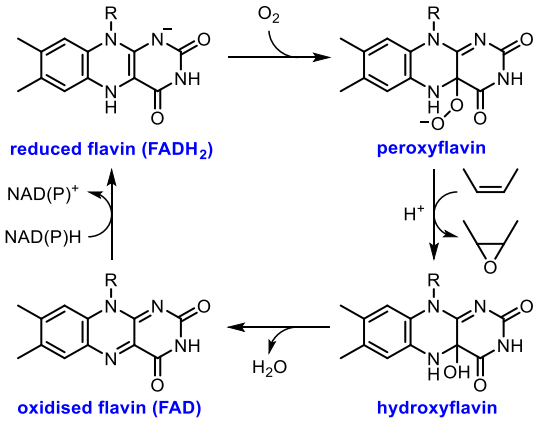
Scheme 35. Hydrolysis of ester **129** and observed side products **177** and **178**.

To synthesise 3,5-*anti*-diol **135**, the minor diastereoisomer obtained from the previous asymmetric aldol condensation (Scheme **30**, page **39**) was cleaved with ethyl potassium malonate and subsequently reduced under Evans-Saksena conditions (Scheme **36**).[210] In contrast to the Narasaka-Prasad reduction, this reduction achieves diastereoselectivity through intramolecular hydride delivery (Scheme **36**). Finally, hydrolysis of the ethyl ester afforded carboxylic acid **135** in a 51% yield. With the two desired substrates **132** and **135** in hand, we next performed bioassays with AmbJ, in collaboration with Dr. Luoyi Wang.



Scheme 36. Synthesis of *anti*-diol **135** (top) and mechanism of the Evans-Saksena reduction (bottom).[210]

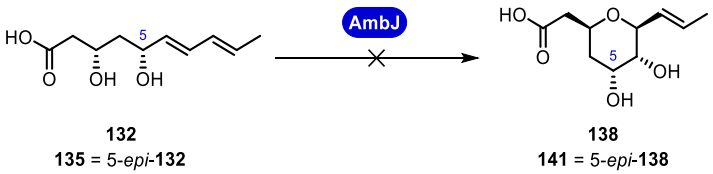
Flavin-dependent monooxygenases, such as AmbJ, oxidise substrates through a catalytic cycle that requires molecular oxygen and two cofactors: flavin adenine dinucleotide (FAD) and either reduced nicotinamide adenine dinucleotide phosphate (NADPH) or reduced nicotinamide adenine dinucleotide (NADH).[211] The catalytic cycle for a flavin-dependent epoxidase begins with reduction of oxidised flavin (FAD) by an external reducing agent, such as NADH, to generate $FADH_2$ (Scheme **37**). Oxidation with molecular oxygen forms peroxyflavin which subsequently epoxidises the substrate. Loss of water regenerates FAD and closes the catalytic cycle. For assays of AmbJ with substrates **132** and **135**, we initially attempted whole cell biotransformations with heterologously expressed AmbJ in *E. coli* in the hope that the cells would supply the required cofactors for catalytic activity.



Scheme 37. Simplified mechanism of FAD-catalysed epoxidation of alkenes.[211]

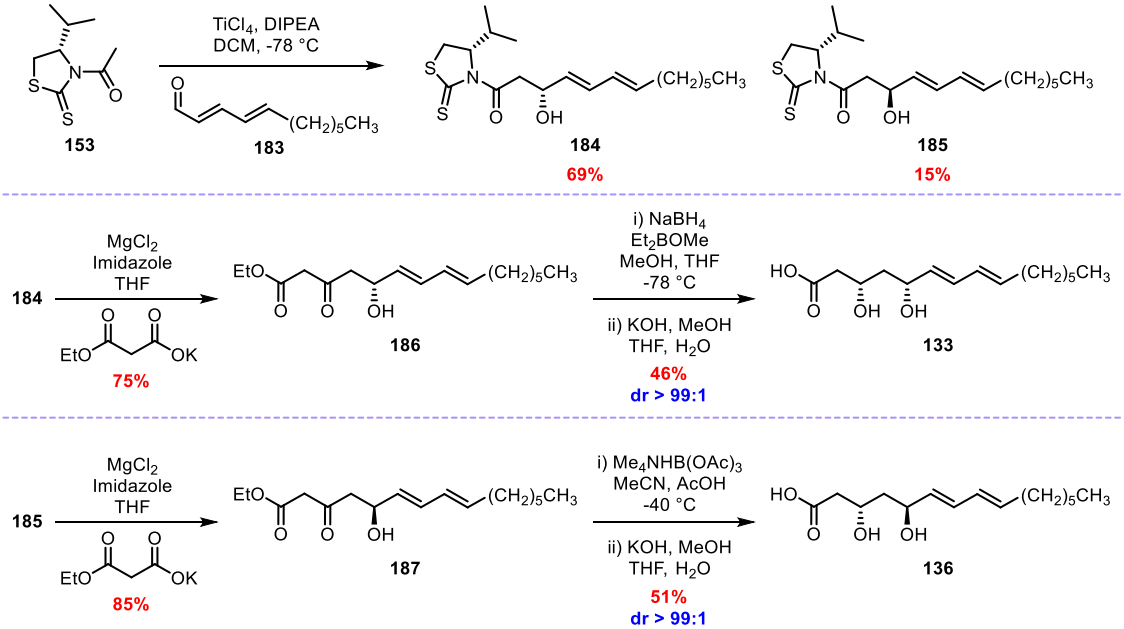
Carboxylic acids **132** and **135** were separately incubated with *E. coli* cells overexpressing AmbJ in pH 7.2 phosphate buffer at 30 °C overnight. As negative controls, substrates were also incubated with

blank *E. coli* cells. No new products were observed by HPLC-MS analysis of the assays. Next, assays were conducted with purified AmbJ by Dr. Luoyi Wang. Disappointingly, no turnover was also observed upon incubation of either **132** or **135** at 30 °C with purified AmbJ, FAD, and NADH or NADPH in a pH 7.5 phosphate buffer. There are many factors that may have prevented substrate turnover, such as the truncated substrate and cofactor concentrations. However, to avoid an extensive optimisation of the assay conditions on a largely simplified model substrate of ambruticin J, we turned attention to the synthesis of carboxylic acids **133** and **136** as the extended aliphatic chains would more closely mimic the amphiphilic nature of ambruticin J and may facilitate substrate recognition by the enzyme (Scheme **28**, page **37**).



Scheme 38. Bioassays of diols **132** and **135** with AmbJ.

Starting from the commercially available aldehyde **183**, both carboxylic acids were synthesised in 4 steps using the previously developed route (Scheme **39**). Both the major (**184**) and minor (**185**) diastereoisomers from the asymmetric aldol condensation were taken forward to generate the *syn*- and *anti*-diols **133** and **136** respectively through decarboxylative Claisen condensation, reduction, and ester hydrolysis.



Scheme 39. Synthesis of carboxylic acids **133** and **136** from aldehyde **183**.

To aid analysis of the enzyme assays by HPLC, THP **139** was synthesised as a reference of the proposed product. Epoxidation of **188** *via* a SAE-cyclisation cascade and subsequent hydrolysis gave **139** in 15%

yield (Figure **16**). The structure and stereochemistry of **139** was confirmed by X-ray crystallography. Unfortunately, no turnover was observed for either substrate **133** or **136** in whole cell or isolated AmbJ enzyme assays. As a result, we embarked on the synthesis of carboxylic acid **134**, a more complex model substrate containing the central trisubstituted cyclopropane of ambruticin J (Scheme **28**, page **37**).

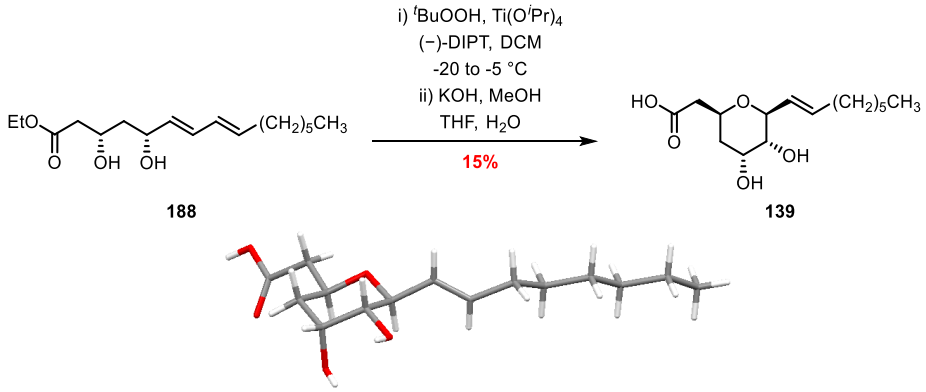
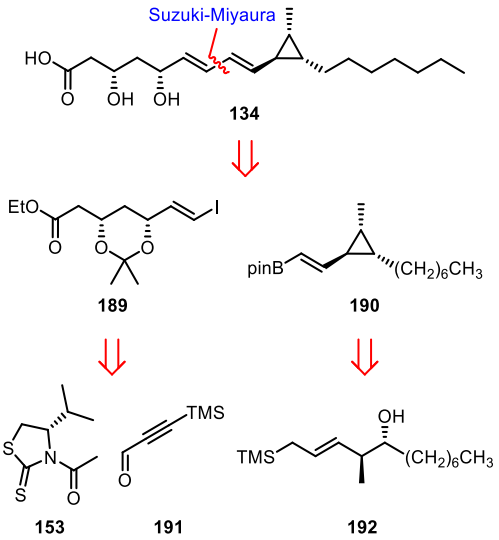


Figure 16. Synthesis and corresponding X-ray crystal structure of THP **139**.

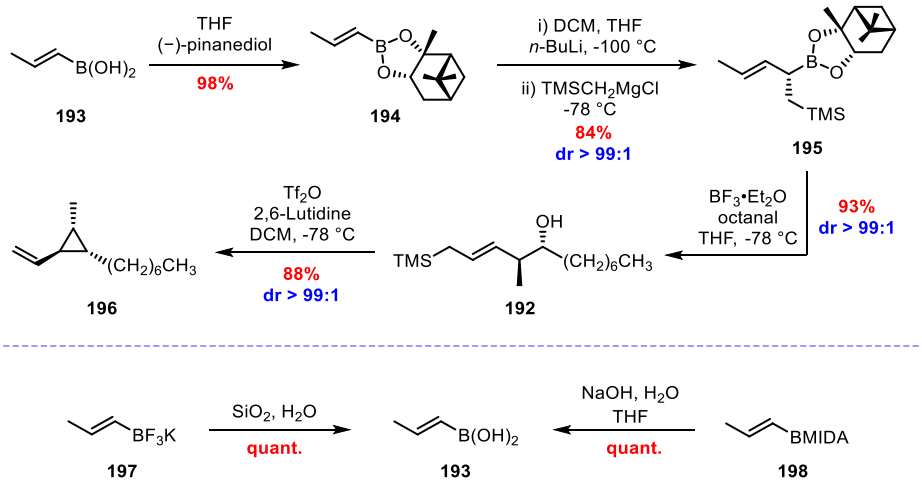
2.3.3. Synthesis of Cyclopropane-Containing Model Substrate 134 for Ambruticin J

We envisaged that carboxylic acid **134** would be prepared *via* a Suzuki-Miyaura cross-coupling of vinyl iodide **189** and vinyl boronic ester **190** (Scheme **40**). Building on our previous work, vinyl iodide **189** was to be generated through an asymmetric aldol condensation between acylated auxiliary **153** and aldehyde **191**, while the trisubstituted cyclopropane **190** was to be constructed from homoallylic alcohol **192** using a cation rearrangement developed by Taylor *et al*.[212] It was hoped that this modular approach could be adapted to the total synthesis of ambruticin J.



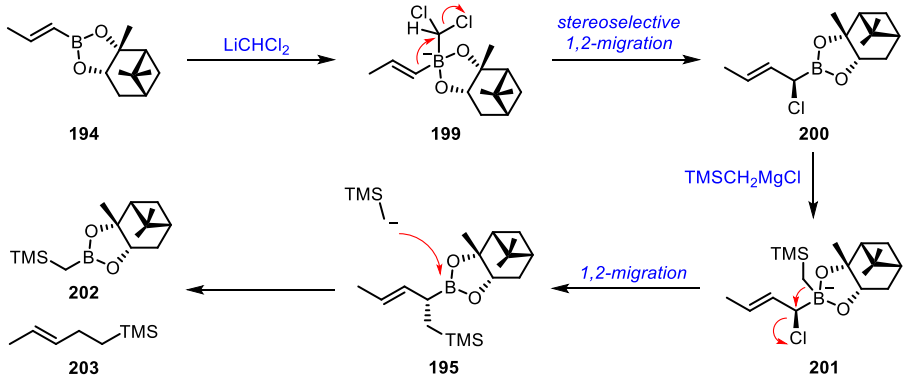
Scheme 40. Retrosynthetic analysis of carboxylic acid **134**.

We began with the synthesis of homoallylic alcohol **192**, the proposed substrate for the key cyclopropane ring forming step (Scheme **41**). We adapted a route developed by Hall *et al*. whereby homoallylic alcohols such as **192** were constructed *via* an asymmetric allylation of aldehydes with chiral allyl boronic ester **195**.[213] The required allyl boronic ester **195** was prepared as a single diastereoisomer by a Matteson homologation of vinyl boronate **194** with *in situ* addition of $TMSCH_2MgCl$. The stereochemical outcome of the reaction is influenced by the use of chiral boronic ester **194**, which was readily derived from (−)-pinanediol and *trans*-propenylboronic acid **193** in a 98% yield.[214] Although boronic acid **193** was commercially available, we encountered supply issues. Nevertheless, it could be accessed through hydrolysis of the corresponding potassium trifluoroborate salt **197** or the MIDA boronate **198** (Scheme **41**). If required, boronic acid **193** could also be synthesised through hydroboration of propyne.[215]



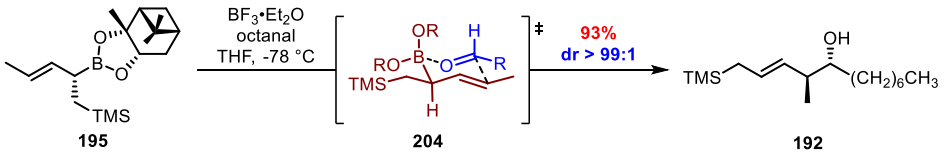
Scheme 41. Optimised synthesis of cyclopropane **196** (top) and vinyl boronic acid **193** (bottom).

Initially a modest 61% yield of the desired allyl boronic ester **195** was obtained from the Matteson homologation, alongside 10% of the undesired side product **202** (Scheme **42**). The formation of **202** was rationalised by the overreaction of **195** with the Grignard reagent. This may have occurred due to an excess of the Grignard reagent, or through collapse of the intermediate boronate **201** prior to complete consumption of the Grignard reagent. Therefore, we proposed that the formation of side product **202** could be reduced by slow and accurate addition of no greater than 1 equivalent of $TMSCH_2MgCl$, alongside precise temperature control. Pleasingly, careful control of these reaction parameters entirely eliminated the formation of **202** and increased the yield of the desired allyl boronic ester to 84%.



Scheme 42. Proposed mechanism for the formation of boronic ester **195** and side product **202**.[214]

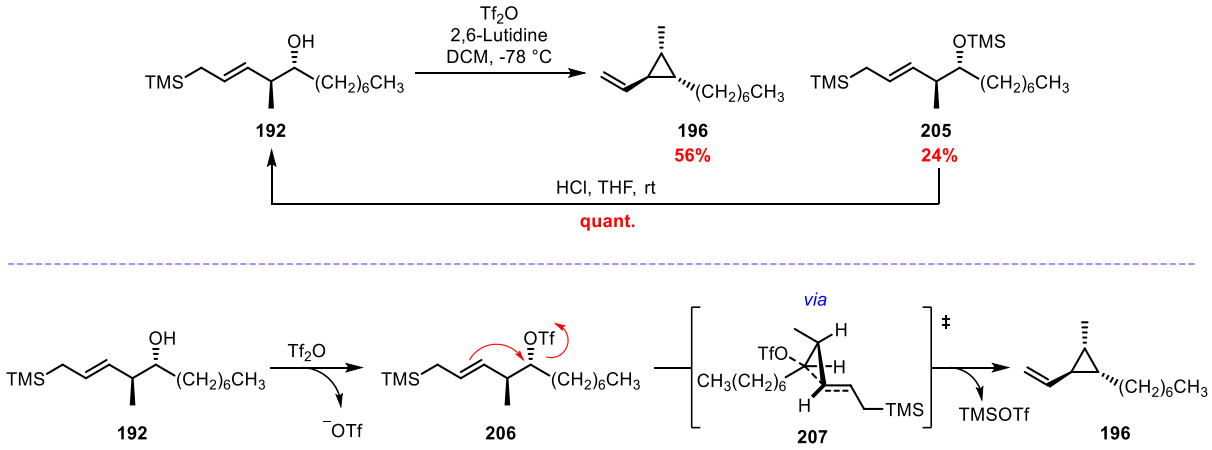
The Lewis acid-catalysed asymmetric allylation of **195** with octanal proceeded smoothly, affording homoallylic alcohol **192** as a single diastereoisomer in 93% yield. The stereochemical outcome of this reaction can be rationalised by the 6-membered transition state **204**, where steric interactions are minimised (Scheme **43**).[213] The octanal side chain occupies an equatorial position, whilst the facial approach of the aldehyde is dictated by the chirality of the boronate. Furthermore, the preestablished stereochemistry of the starting material dictates the orientation of the silyl group in an equatorial position, resulting in the observed *E*-olefin **192**.



Scheme 43. Transition state responsible for observed stereoselectivity in the allylation of boronate **195**.[213]

With homoallylic alcohol **192** in hand, we attempted the proposed cyclopropanation using triflic anhydride and 2,6-lutidine, conditions previously developed by Taylor *et al*. (Scheme **44**).[212] Initially we achieved a modest 56% yield of **196**, which was accompanied by silyl protected alcohol **205** isolated in 24% yield. The silyl protected alcohol could be readily deprotected with acid to return starting material in a quantitative yield. Nevertheless, it was desirable to prevent formation of silyl ether **205**. We proposed that TMSOTf, formed as a by-product in the reaction, reacts with alcohol **192** to generate the undesired silyl ether **205** (Scheme **44**). In particular, if activation of alcohol **192** with triflic anhydride is slow relative to subsequent cyclisation, then silyl protection may compete with the desired reaction pathway. Furthermore, the rate of triflic anhydride addition may influence the reaction, where slow addition would exacerbate the issue due to gradual consumption of the starting material. As such, the cyclopropanation was repeated with rapid injection of triflic anhydride, resulting in an improved 88% yield of **196**. However, fast addition of triflic anhydride was impractical on a larger scale of 5 mmol and significant quantities of silyl ether **205** were still apparent. Moreover, exotherms were observed upon addition causing a decrease in diastereoselectivity on scale. Although alternative

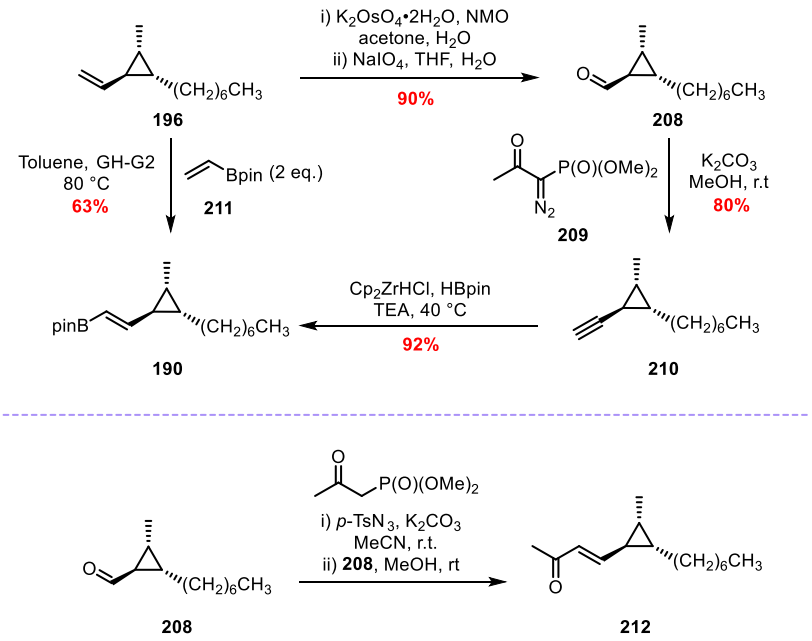
activating agents such as $SOCl_2$ could be explored, no further optimisation was performed at this stage.[212] Further improvements to the protocol are discussed in chapter **3**. The observed stereochemical outcome of the reaction is rationalised by TS **207**. Steric interactions are minimised and the reaction proceeds with stereochemical inversion of triflate **206** (Scheme **44**).



Scheme 44. Unoptimised synthesis (top) and proposed mechanism (bottom) for the formation of cyclopropane **196** and side product **205**.

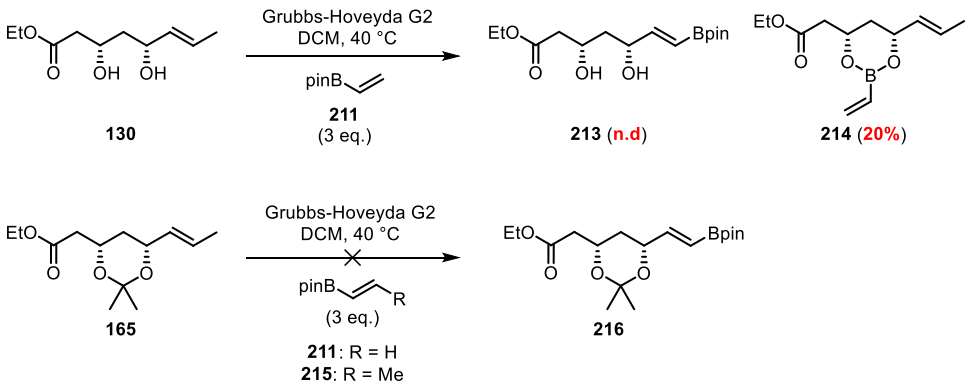
Two routes were developed to transform terminal olefin **196** into *E*-vinyl boronic ester **190** (Scheme **45**). The first approach began with dihydroxylation of alkene **196** and subsequent cleavage with $NaIO_4$ to afford aldehyde **208** in 90% yield over the two steps (Scheme **45**). Alkyne **210** was then obtained in 80% yield using a Seyferth-Gilbert homologation of aldehyde **208** with the Ohira-Bestmann reagent **209**, which was readily synthesised in 74% yield over two steps from 4-toluenesulfonyl chloride.[216] Unfortunately, an attempt to perform the one pot homologation with *in situ* formation of the Ohira-Bestmann reagent was unsuccessful due to competitive olefination forming enone **212** (Scheme **45**). Finally, hydroboration of the terminal alkyne with pinacolborane catalysed by the Schwartz reagent afforded vinyl boronic ester **190** in 92% yield solely as the *E*-olefin.[217] Overall, this route gave trisubstituted cyclopropane **190** in a 66% yield over four steps.

In an alternative route, cross-metathesis facilitated the conversion of alkene **196** to boronic ester **190** in 63% yield in only one step (Scheme **45**).[218] An initial attempt to form vinyl boronic ester **190** using Grubbs 1st generation catalyst in DCM at 40 °C gave a disappointing yield of 24%. This was attributed to a combination of poor conversion to the desired product and difficulty in separating the product from vinylboronic acid pinacol ester starting material. We found that performing the reaction with the thermally more stable Grubbs-Hoveyda 2nd generation (GH-G2) catalyst in toluene at 80 °C gave an improved yield of 63%.



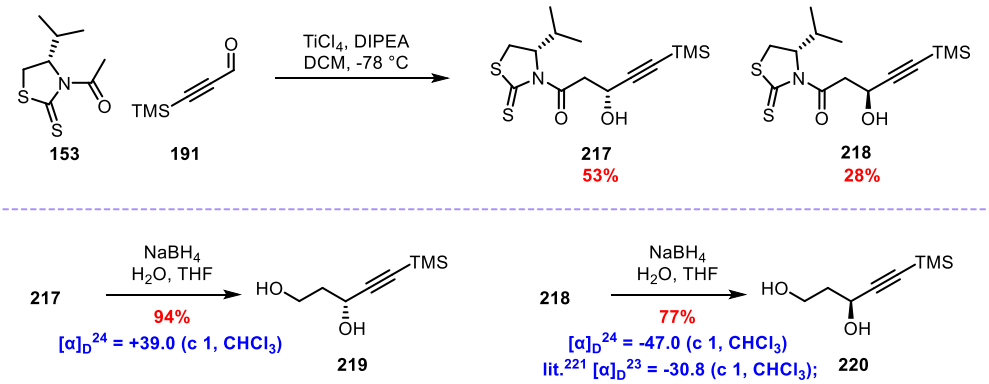
Scheme 45. Approach to the synthesis of vinyl boronic ester **190** (top) and formation of enone **212** (bottom).

Although we envisaged constructing vinyl iodide **189** *via* an asymmetric aldol condensation between acylated auxiliary **153** and aldehyde **191**, we initially attempted to synthesise **213** by cross-metathesis of vinyl boronic ester **211** with the previously prepared dihydroxy ester **130** (Scheme **46**). We proposed vinyl boronic ester **213** could then be converted to vinyl iodide **189** using a variety of literature methods.[219] Unfortunately, reaction of the unprotected diol **130** resulted in the formation of boronic ester **214** with no evidence of product **213** formation. Moreover, no reaction was observed when the corresponding dimethyl acetonide of **165** was subjected to the same conditions. Efforts to achieve reactivity by employing boronic ester **215** were to no avail.



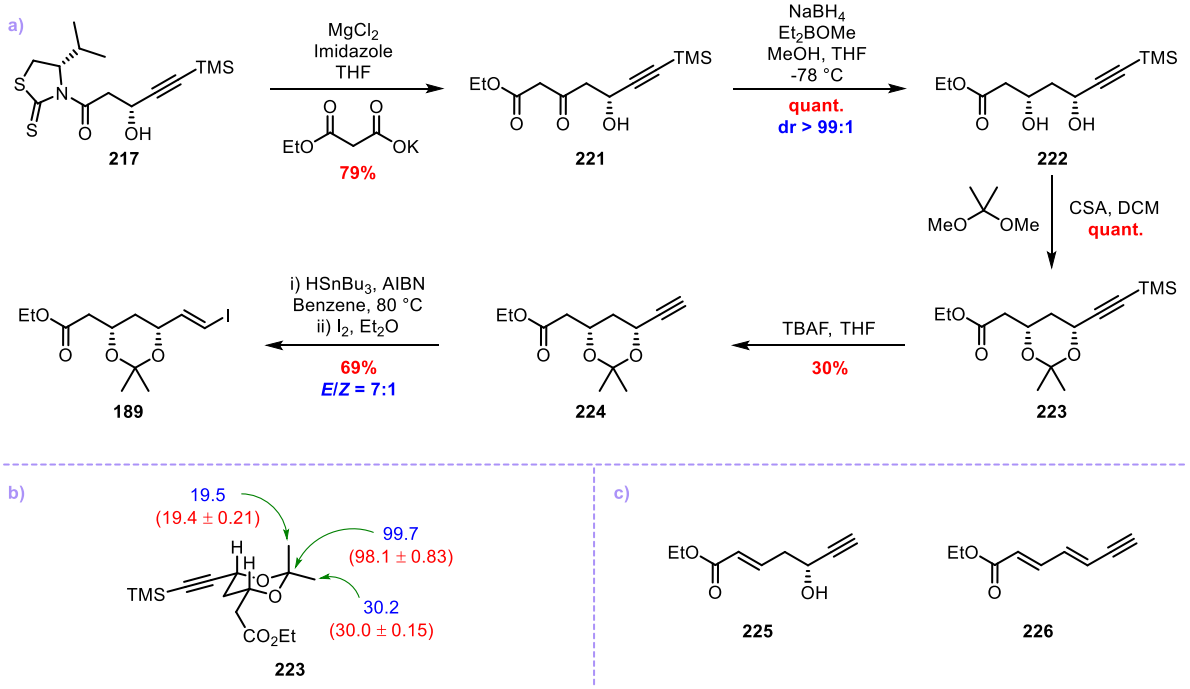
Scheme 46. Attempted cross-metathesis of alkenes **130** and **165**.

Nevertheless, vinyl iodide **189** was successfully prepared by employing an asymmetric aldol condensation analogous to the route used in the syntheses of model substrates of ambruticin J (Scheme **47**). The Lewis acid-catalysed asymmetric aldol condensation of acylated Crimmins' auxiliary **153** with aldehyde **191** afforded the desired adduct **217** in 53% isolated yield with 28% of the undesired diastereoisomer **218**. This poor diastereomeric ratio (dr) of 1.9:1 is attributed to the low steric demand of alkyne **191**, which results in a small energy difference between the transition states leading to the two diastereoisomers.[220] To confirm the stereochemistry of the two diastereoisomers, both products were reduced with sodium borohydride to afford known diols **219** and **220**, and their optical rotations were compared with the literature (Scheme **47**).[221]



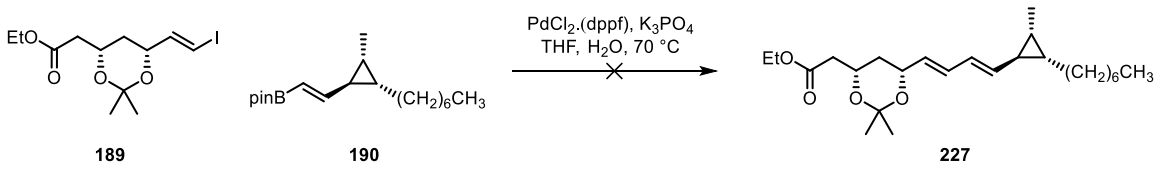
Scheme 47. Aldol condensation of **153** and **191** (top) and synthesis of known diols **219** and **220** (bottom).

The auxiliary in **217** was cleaved by a decarboxylative Claisen condensation to give ketone **221**, which was reduced to afford 1,3-*syn*-diol **222** in 79% yield over the two steps (Scheme **48**). The *syn*-diol was protected as the acetonide in quantitative yield with no need for purification by column chromatography. Rychnovsky analysis of acetonide **223** confirmed the formation of the desired *syn*-diol due to a characteristic 10.7 ppm difference in chemical shift for the acetonide methyl groups in the ^{13}C-NMR spectrum (Scheme **48**).[114,205] Unfortunately, silyl deprotection with TBAF afforded the desired product **224** in a 30% yield, which was separated from alkynes **225** and **226** by column chromatography. We proposed the mild basicity of TBAF-facilitated an E1cB elimination and subsequent further alcohol elimination. The synthesis of vinyl iodide **189** proved challenging, with methods catalysed by Cp_2ZrHCl resulting in acetonide deprotection, presumably due to the undesired acidity of the reaction mixture. Nevertheless, radical hydrostannylation and *in situ* trapping of the intermediate vinyl stannane with iodine afforded vinyl iodide **189** as a 7:1 mixture of *E*/*Z* isomers.[222]



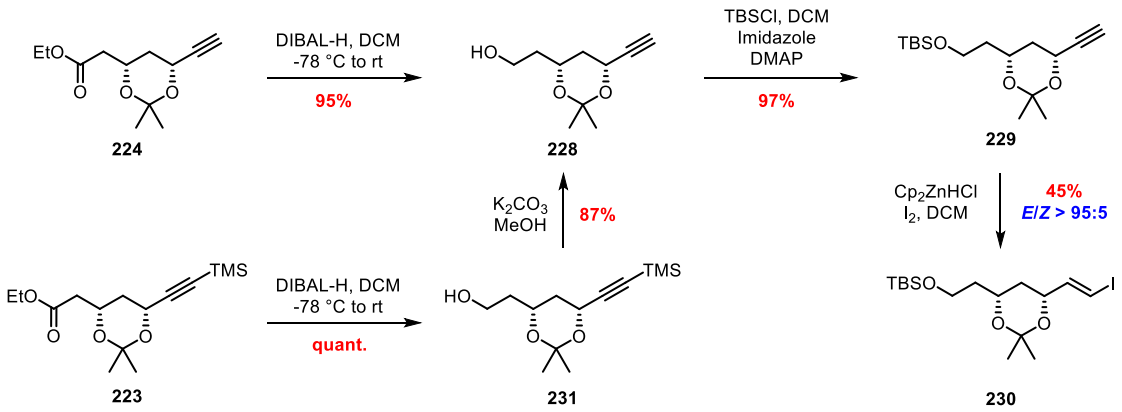
Scheme 48. (a) Synthesis of vinyl iodide **189** (b) Rychnovsky analysis of acetonide **223**, where observed (blue) and average (red) ^{13}C-NMR chemical shifts for acetonides are depicted and (c) elimination side products **225** and **226**.[114,205]

The proposed Suzuki-Miyaura cross-coupling to unite vinyl iodide **189** and vinyl boronic ester **190** was unsuccessful (Scheme **49**). Variation of base and palladium catalyst had no effect on the reaction in all cases. Furthermore, vinyl iodide **189** was not detected in the ^{1}H-NMR of the crude product and evidence of ester hydrolysis, acetonide deprotection, and alcohol elimination were observed. These results highlighted the propensity for vinyl iodide **189** to undergo E1cB elimination, as previously observed with alkyne **223** (Scheme **48**). As such, we opted to circumvent this issue by reduction of the problematic ester functional group to an alcohol then protection as the silyl ether (Scheme **50**).



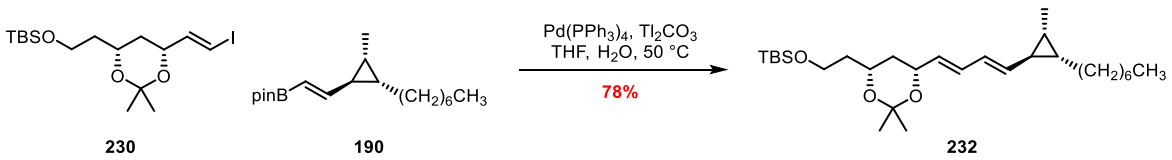
Scheme 49. Unsuccessful Suzuki-Miyaura cross-coupling between **189** and **190**.

Vinyl iodide **230** was readily prepared from both the previously synthesised terminal alkyne **224** and TMS alkyne **223**. Although both routes were robust, by starting from silyl protected alkyne **223**, the problematic E1cB elimination associated with TBAF-mediated TMS-alkyne deprotection could be avoided (Scheme **48**). Surprisingly, hydrozirconation of terminal alkyne **229** and *in situ* trapping with *N*-iodosuccinimide (NIS) afforded vinyl iodide **230** in only 20% yield. This was improved to 45% yield by trapping with molecular iodine, although further optimisation of this step may further increase the yield.



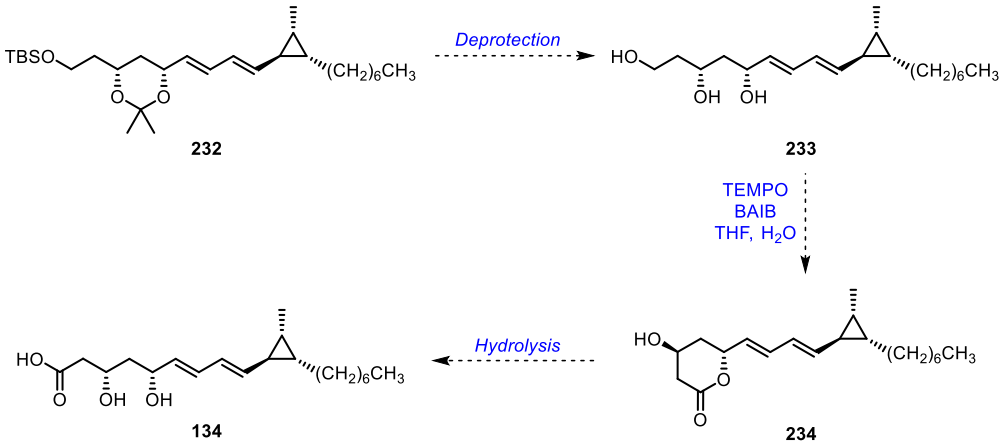
Scheme 50. Synthesis of vinyl iodide **230**.

To begin, performing the Suzuki-Miyaura cross-coupling with **230** and **190** under conditions of K_3PO_4 and $PdCl_2$(dppf) in THF and water at 80 °C gave none of the desired diene **232** (Scheme **51**). It is likely that prolonged periods at elevated temperatures (18 hours at 80 °C) resulted in hydrolysis of the product, in accordance with reports by Reeves *et al*. where ambruticin J underwent rapid solvolysis.[105] Pleasingly, the cross-coupled product **232** was obtained in 78% yield by performing the reaction with thallium carbonate and $Pd(Ph_3)_4$ at 50 °C for 2 hours. Thallium salts have been shown to promote challenging Suzuki-Miyaura cross-coupling under mild conditions with short reaction times.[223,224] We propose that by performing the reaction at a lower temperature for less time facilitated successful cross-coupling whilst simultaneously preventing degradation of the starting materials and product.



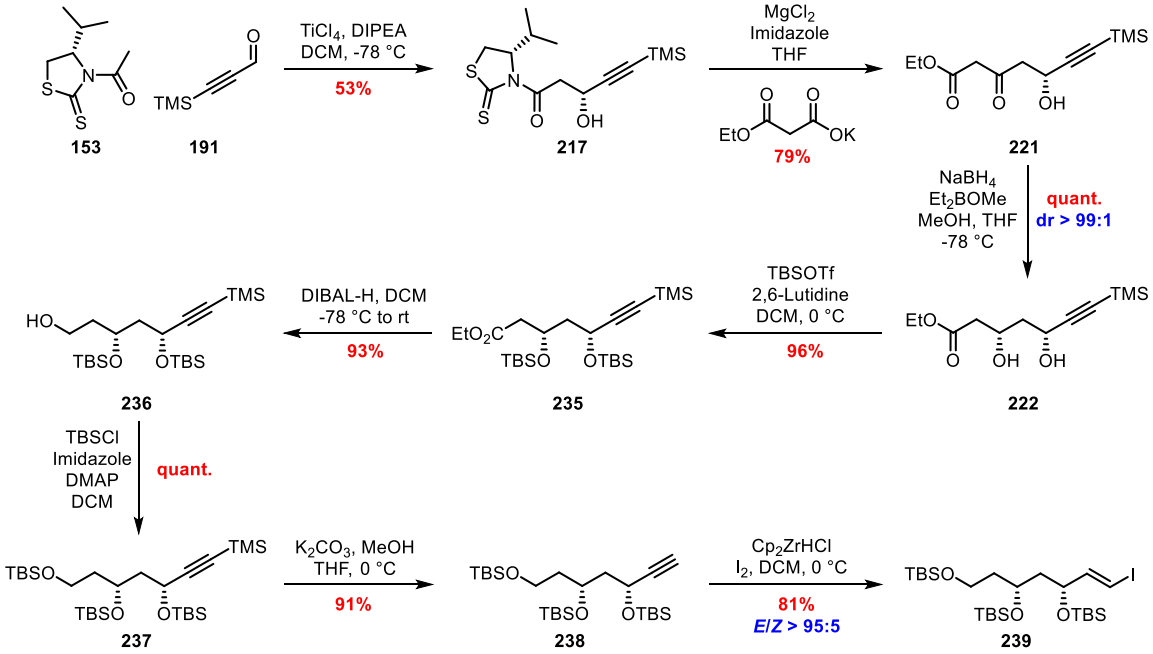
Scheme 51. Thallium-accelerated Suzuki-Miyaura cross-coupling of vinyl iodide **230** and vinyl boronic ester **190**.

With the carbon framework constructed, we envisaged the desired substrate **134** for enzyme assays could be accessed from acetonide **232** by global deprotection, selective oxidation of the primary alcohol to form lactone **234**, and finally hydrolysis (Scheme **52**). However, attempts at global deprotection of **232** with either HCl in DCM or *p*TsOH in toluene were unsuccessful, returning either unreacted starting material or a mixture of eliminated products. This prompted us to develop an alternative route whereby triol **233** could be liberated by global TBAF-mediated silyl deprotection.



Scheme 52. Proposed synthetic route from protected triol **232** to carboxylic acid **234**.

Hence, *syn*-diol **222** was prepared through the asymmetric aldol previously outlined (page **51**). Silyl protection of **222** with TBSCl provided a mixture of mono-protected products after 72 hours. However, using TBSOTf provided the desired product in 96% yield (Scheme **53**). Protected triol **238** was synthesised from ester **235** in 85% yield over 3 steps without the need for column chromatography as shown in scheme **53**. Employing the conditions previously optimised for the synthesis of vinyl iodide **230**, the desired *E*-vinyl iodide **239** was prepared in 81% yield.

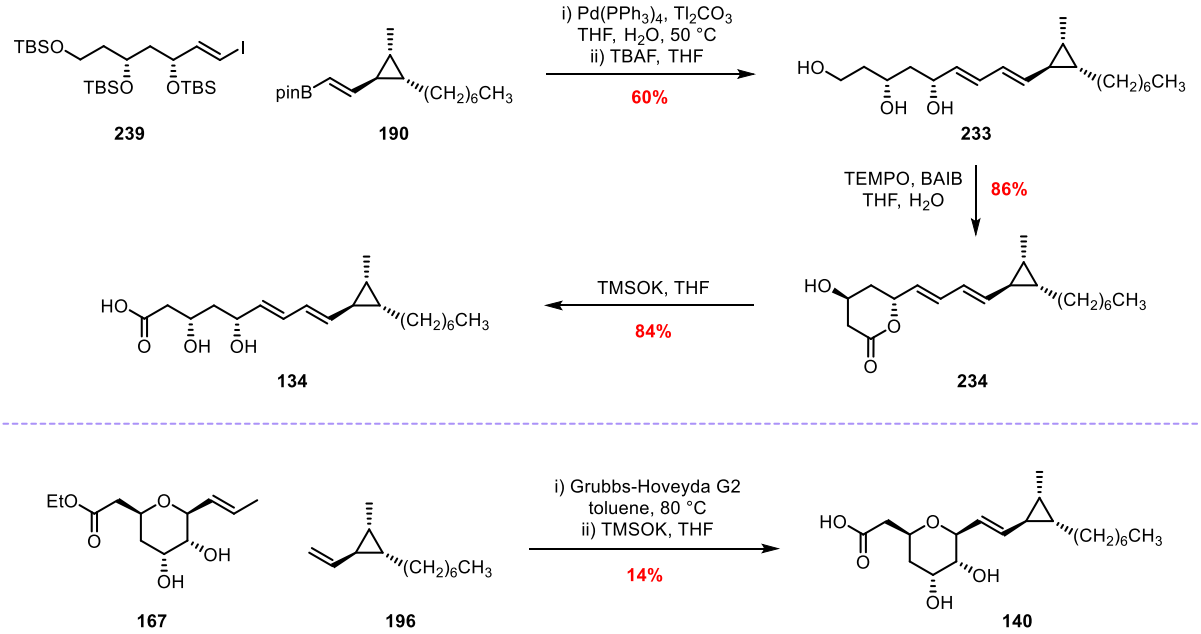


Scheme 53. Synthesis of vinyl iodide **239**.

Cross-coupling between vinyl iodide **239** and vinyl boronic ester **190** under thallium-mediated conditions proceeded smoothly, however, purification of the protected triol from non-polar impurities was problematic (Scheme **54**). As such, global deprotection of the crude product with TBAF gave pure diene **233** in 60% yield over two steps. Selective oxidation of the primary alcohol was achieved utilising

a procedure developed by Forsyth *et al*. whereby 1,5-diols are converted to the corresponding δ-lactones through the use of a TEMPO/*bis*-acetoxyiodobenzene (BAIB) oxidation system.[225] To avoid the issues that were previously encountered with potassium hydroxide mediated hydrolysis such as undesired lactonisation, alcohol elimination, and cyclopropane ring opening, alternative conditions were investigated. It has been reported that hydrolysis of substrates sensitive to elimination can proceed in excellent yields through the use of TMSOK in THF.[226,227] Indeed, we found that the hydrolysis of lactone **234** to carboxylic acid **134** proceeded in 84% yield under these conditions.

To aid the analysis of enzyme assays, a sample of the expected product **140** from epoxidation/cyclisation of **134** by AmbJ was prepared in 14% yield through a cross-metathesis between alkenes **167** and **196** followed by hydrolysis of the ethyl ester (Scheme **54**). Next, *in vivo* and *in vitro* assays were undertaken by Luoyi Wang using **134**, but no new products were detected by LC-MS. Whilst modification of the assay conditions may have proved necessary to achieve the desired reaction, it was deemed appropriate to prepare ambruticin J, the putative substrate for AmbJ, prior to performing any optimisation of the enzyme assays.

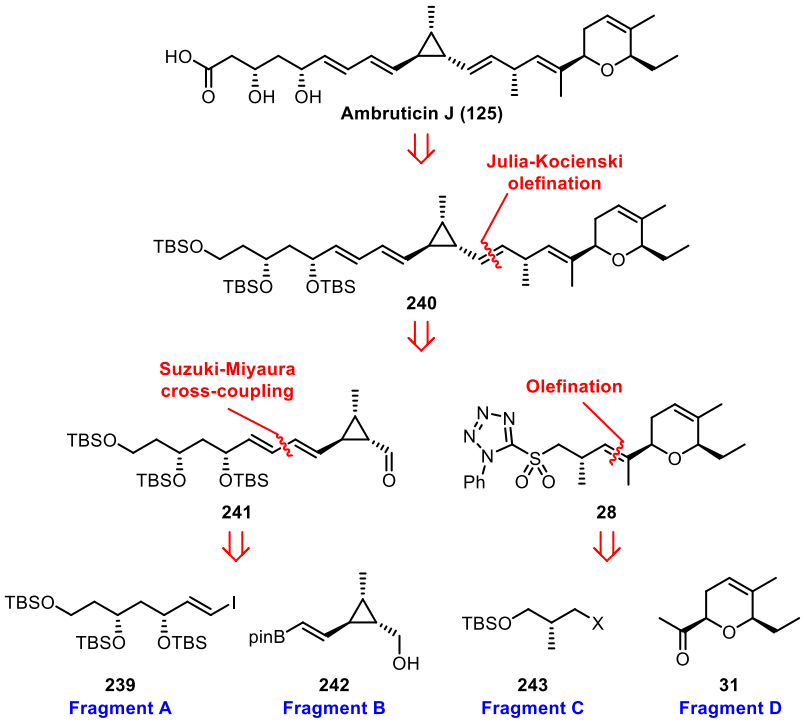


Scheme 54. Synthesis of carboxylic acid **134** (top) and THP **140** (bottom).

2.3.4. Total Synthesis of Ambruticin J

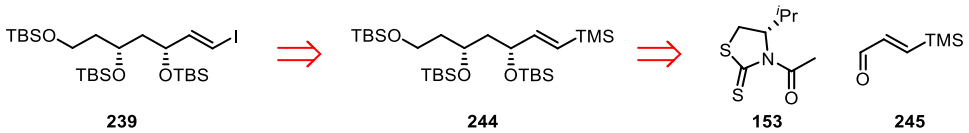
Our approach to the synthesis of ambruticin J built upon the routes developed for constructing truncated compounds for assays with AmbJ. Ambruticin J was to be accessed from protected triol **240** through a sequence analogous to that used for the formation of **134**, whereby the late-stage introduction of the carboxylic acid would be essential to prevent reported conjugate addition and cyclopropane ring opening (Scheme **55**).[105] The carbon framework of ambruticin J was to be

constructed in a modular fashion, where four fragments were to be combined by two olefinations and a Suzuki-Miyaura cross-coupling. We hoped that the modular route would facilitate the preparation of analogues of ambruticin J for substrate specificity studies with AmbJ. As we reached our final stages of our total synthesis of ambruticin J, Taylor *et al*. reported a synthesis which employed a similar strategy to that which we developed.[228] Nevertheless, the route described within this chapter was conducted prior to the disclosures made by Taylor and co-workers.[229]



Scheme 55. Retrosynthetic analysis of ambruticin J.

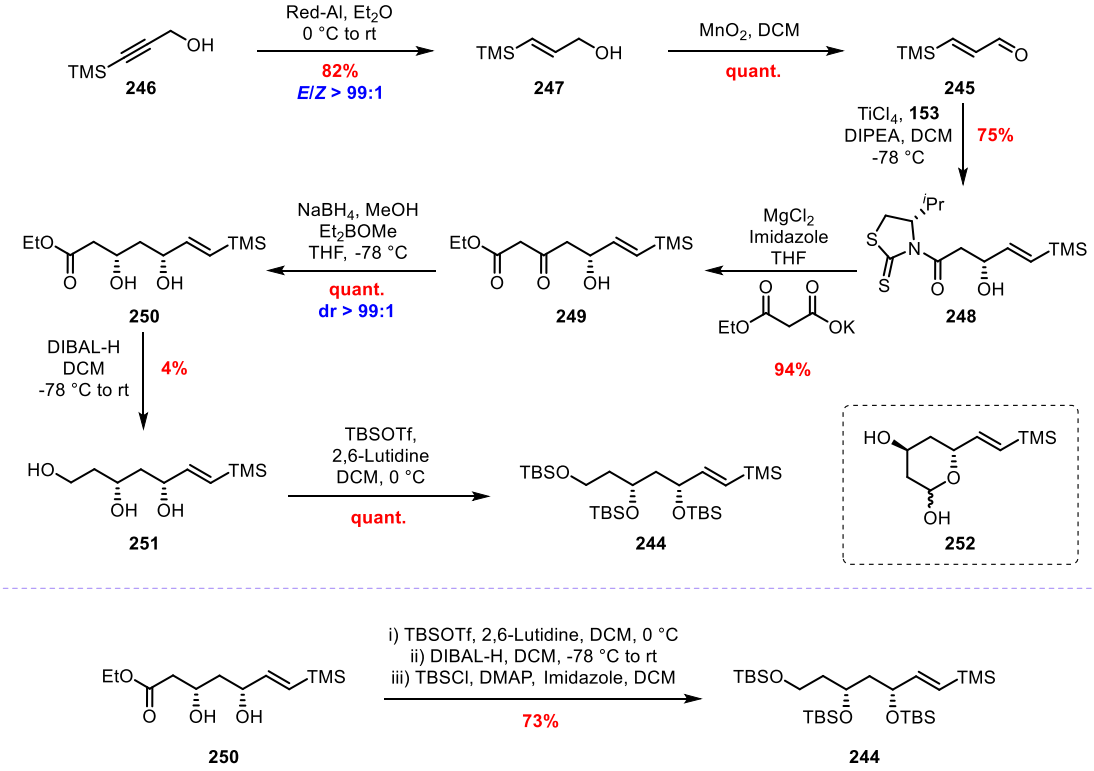
Significant progress had already been made towards our proposed strategy, with a robust route developed to vinyl iodide **239**, proof of concept for the end-game transformations, and a method for constructing the vinyl cyclopropane in fragment B. Nevertheless, the poor diastereoselectivity of the initial asymmetric aldol condensation in the construction of vinyl iodide **239** (Scheme **47**, page **51**) prompted us to develop an alternative, more efficient synthesis of fragment A. An asymmetric aldol condensation between aldehyde **245** and acylated auxiliary **153** was proposed to access vinyl silane **244**, with many methods known to convert vinyl silanes into vinyl iodides (Scheme **56**).[230]



Scheme 56. Retrosynthetic analysis of vinyl iodide **239**.

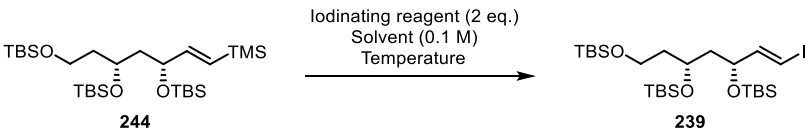
Asymmetric aldol condensation of acylated auxiliary **153** with aldehyde **245** gave **248** in 75% yield. Although aldehyde **245** is commercially available, it was readily synthesised from propargylic alcohol

246 in 82% yield over two steps. The previously established sequence of auxiliary cleavage and subsequent asymmetric reduction of **249** proceeded smoothly to afford diol **250** in 94% yield over the two steps. Finally, reduction of ester **251** and protection with TBSOTf provided the desired vinyl silane **244**. Disappointingly, a yield of only 4% was achieved for the reduction of ester **250** with DIBAL-H due to the competing formation of lactol **252** as a mixture of diastereoisomers in a 25% yield, presumably from Lewis acid-catalysed cyclisation of the intermediate aldehyde. Whilst alternative reducing agents may have supressed this competing pathway, we opted to initially protect diol **250** prior to reduction (Scheme **57**). All three steps in this new route were facile to perform and only one purification by column chromatography was required, resulting in a 73% yield of vinyl silane **244** from ester **250**.



Scheme 57. Synthesis of vinyl silane **244** (top) and optimised conversion ester **250** to vinyl silane **244** (bottom).

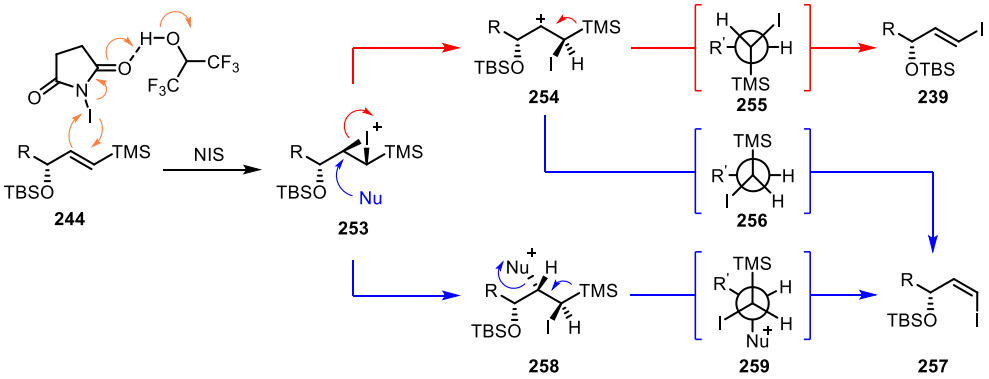
With vinyl silane **244** in hand, we moved on to the synthesis of vinyl iodide **239**. Several reagents have been shown to facilitate iododesilylation of vinyl silanes with varying levels of success for controlling double bond geometry.[230] Furthermore, many reagents result in decomposition of more complex substrates.[230] However, it has been demonstrated that NIS is a mild reagent which can perform the desired transformation with good selectivity in high yields. Hence, conversion of vinyl silane **244** to vinyl iodide **239** with NIS was investigated using various conditions (Table **4**). Initially, employing 2 eq. of NIS in either DCM or MeCN resulted in no reaction, even on warming to room temperature (entries 1 and 2).



Entry	Reagent	Solvent	Temp (°C)	Variation	Time (hrs)	Yield (%)[c]	*E*/*Z*[d]
1	NIS	DCM	0 – rt	-	24	0	-
2	NIS	MeCN	0 – rt	-	24	0	-
3	NIS	HFIP[b]	0	-	0.25	55	2:1
4	NIS	HFIP[b]	0	Reverse addition	0.25	-	2:1
5	NIS	HFIP[b]	0	Anhydrous	0.25	-	1:1
6	NIS	HFIP[b]	0	2,6-Lutidine	0.25	-	1.2:1
7	NIS	10:1 MeCN:HFIP	0 – rt	-	18	41	2.5:1
8	NIS	5:1 DCM:HFIP	0 – rt	-	24	-	1.5:1
9	NIS	5:1 MeCN:HFIP	-20 – rt	-	1	40	2.4:1
10	ICl[a]	MeCN	rt	-	0.5	-	-

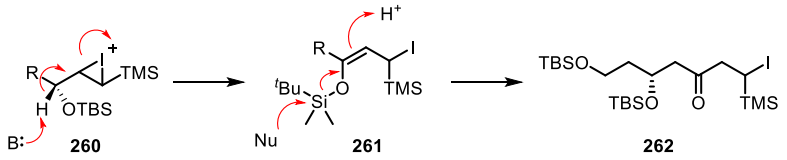
Table 4. Optimisation of vinyl iodide formation where standard procedure is to add iodinating reagent to starting material. [a]1.2 eq. used. [b]Reaction concentration of 0.3 M. [c]Isolated yields. [d]Determined from ^{1}H-NMR of the crude product.

Studies by Zakarian *et al*. illustrated the role of hexafluoroisopropanol (HFIP) in accelerating the rate of reaction through activation of NIS, and providing improved stereoselectivity (Scheme **58**).[230] The reaction can proceed with either stereoinversion or stereoretention of the double bond geometry, depending on which mechanistic pathway is followed. Stereoretention (red, Scheme **58**) occurs by selective ring opening of iodonium ion **253** to generate the β-silyl stabilised carbocation **254**, which undergoes E1 elimination of the silyl group *via* the lowest energy conformer, affording the *E*-vinyl iodide **239**. Of the two conformers which provide the *syn*-periplanar alignment of the carbon 2p and $\sigma_{C\text{-}Si}$ orbitals which is required for E1 elimination, conformer **255** is often lower in energy due to reduced steric interactions. An alternative model which considers the principle of least rotation also leads to **239**, *via* formation of intermediate **255**.



Scheme 58. Proposed mechanism for iododesilylation of vinyl silane **244**. Only one iodonium diastereoisomer (**253**) depicted for clarity. Nu = nucleophile.

Alternatively, stereoinversion (blue) can occur by E1 elimination in **254** occurring *via* conformer **256**, or due to nucleophilic ring opening of iodonium **253** and subsequent E2 elimination *via* an *anti*-periplanar conformation. With nucleophilic solvents such as acetonitrile, stereoinversion often competes with stereoretention resulting in lower stereoselectivity. It is proposed that the poor nucleophilicity of HFIP, as a result of the electron withdrawing effect of the CF_3 groups, decreases the propensity of the reaction to follow the undesired pathway. However, we found that treatment of vinyl silane **244** with NIS in HFIP at 0 °C afforded a 55% yield of vinyl iodide **239** as an inseparable 2:1 mixture of *E* and *Z* isomers (Table **4**, entry 3). The formation of ketone **262** was observed in the reaction, accounting for the modest yield when compared to near quantitative literature yields for similar substrates (Scheme **59**).[231] We propose ketone **262** is formed through deprotonation of iodonium **260** to generate silyl enol ether **261**, which in the presence of acid undergoes protodesilylation. Alternatively, **262** could be formed *via* a semi-pinacol rearrangement of **260**.

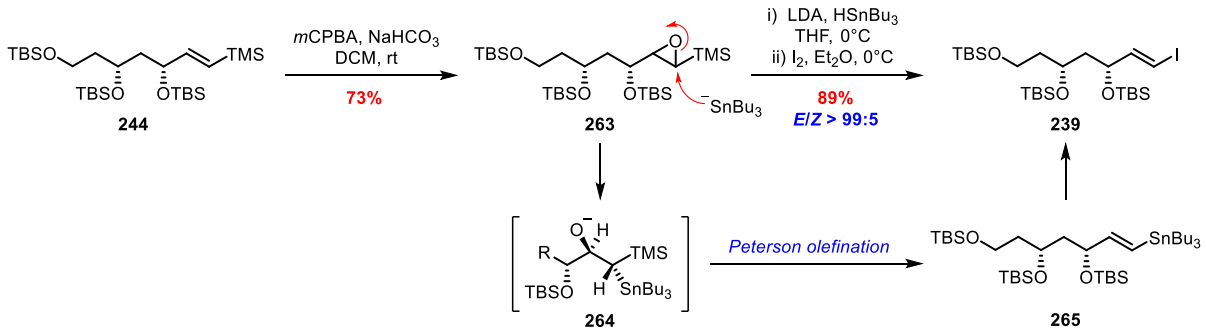


Scheme 59. Proposed mechanism for the formation of ketone **262**.

Alternative solvent systems, a reverse order of addition, use of anhydrous conditions, and the addition of 2,6-lutidine were all unsuccessful at improving stereoselectivity and preventing the formation of ketone **262** (entries 4 to 8). Zakarian proposed that buffering the reaction with 2,6-lutidine prevents the deprotection of acid-sensitive functional groups and therefore we hoped this may stop the formation of ketone **262**.[230] Although not attempted, Vilarrasa and co-workers reported the conversion of vinyl silanes which contained acid-sensitive functionalities to vinyl iodides through the addition of silver carbonate.[232]

Various reasons may account for the poor stereoselectivity observed in the reaction: (i) slow ring opening of iodonium ion **253** resulting in competing nucleophilic ring opening even with HFIP as the solvent; (ii) E1 elimination of **254** proceeding *via* conformer **256** (Scheme **58**); or (iii) the succinimide anion acting as the nucleophile to open iodonium ion **253**. In an attempt to improve the potential selectivity issue for E1 elimination between conformers **255** and **256**, the reaction was cooled to -20 °C (Table **4**, entry 9). We proposed that a lower temperature would limit access to the higher energy conformer and therefore improve stereoselectivity. A 5:1 MeCN:HFIP solvent system was used to prevent HFIP from freezing. Unfortunately, even at this dilution the reaction mixture froze at temperatures below -5 °C and higher dilutions resulted in no reaction. Finally, we opted to change iodinating reagent to ICl in the hope that this would prevent potential succinimide opening of

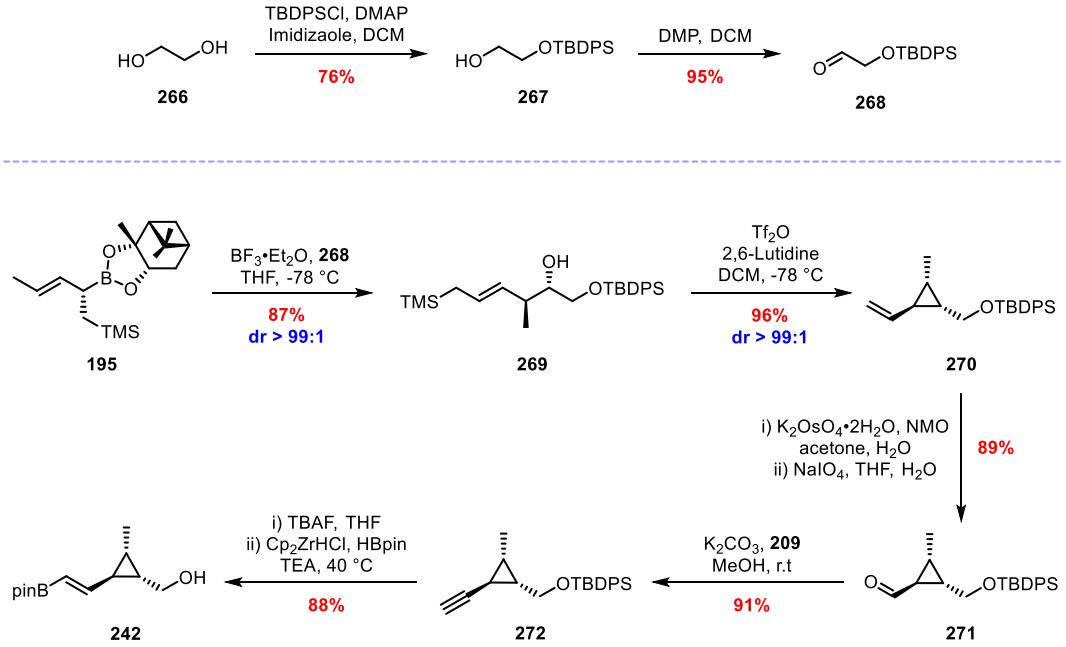
iodonium ion **253** (entry 10). Nevertheless, complete degradation of the starting material was observed in this case. At this stage we concluded that vinyl silane **244** may not be amenable to efficient iododesilylation. As such, a two-step protocol developed by Kobayashi *et al*. was utilised for this transformation (Scheme **60**).[233]



Scheme 60. Optimised synthesis of vinyl iodide **239** from vinyl silane **244**.[233]

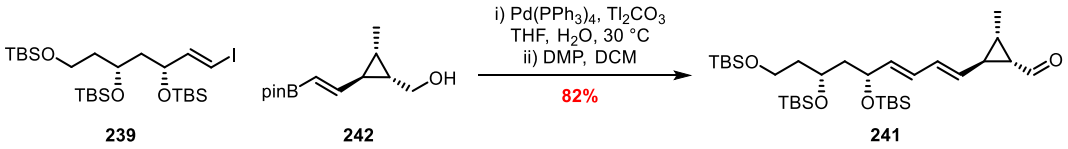
Epoxidation of vinyl silane **244** afforded epoxide **263** as a mixture of diastereoisomers in a 73% yield. Nucleophilic ring opening of the oxirane with tributyltin lithium and subsequent Peterson olefination followed by *in situ* trapping of the vinyl stannane **265** with iodine gave vinyl iodide **239** in 89% yield as exclusively the *E*-isomer, evident from a ^{3}J coupling constant of 14.4 Hz for the vinyl protons. This procedure offers a high yielding and stereoselective alternative to iododesilylation. This newly developed route gave vinyl iodide **239** (fragment A) in 33% over 8 steps, an improvement from 28% over 8 steps in the previous synthesis (Scheme **53**, page **54**).

Next, we turned our attention to the synthesis of vinyl boronic ester **242** (fragment B) which was to be accessed through a route analogous to that previously employed for the formation of cyclopropane **196** (Scheme **41**, page **47**). Aldehyde **268**, synthesised in 72% yield over two steps from ethylene glycol, underwent clean allylation with boronic ester **195** to generate homoallylic alcohol **269** in 87% yield as a single diastereoisomer (Scheme **61**).[213] Cyclopropanation using Taylor's cation rearrangement methodology afforded the desired trisubstituted cyclopropane in 96% yield.[212] As previously established, rapid addition of triflic anhydride was essential to prevent silyl protection of the starting material. As a result, the reaction could not be performed on greater than 3 mmol scale without detrimental silyl protection or loss of stereocontrol due to exotherms caused by the addition of triflic anhydride. Dihydroxylation of alkene **270** followed by cleavage of the resultant diol with $NaIO_4$ gave aldehyde **271**, which was converted to alkyne **272** by a Seyferth-Gilbert homologation with the Ohira-Bestmann reagent.[216] Silyl deprotection with TBAF and finally hydroboration of the terminal alkyne with pinacolborane catalysed by the Schwartz reagent provided vinyl boronic ester **242** in 88% yield over the two steps. Overall, vinyl boronic ester **242** was accessed on a multi-gram scale in a yield of 51% over 8 steps.[217]



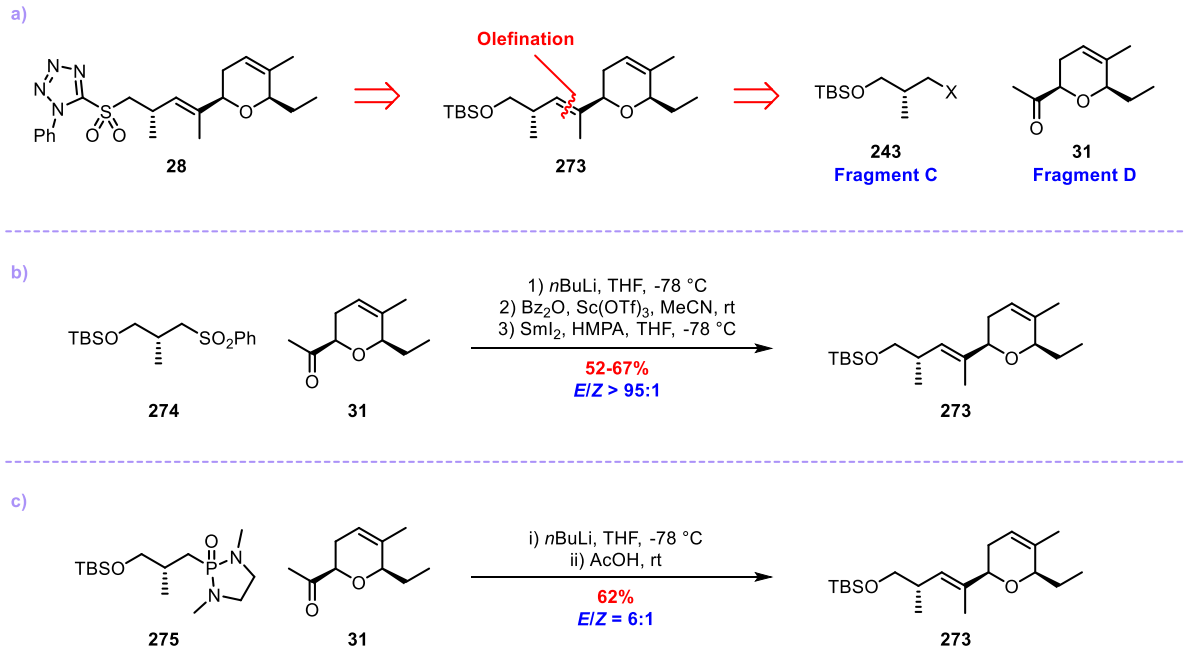
Scheme 61. Synthesis of aldehyde **268** (top) and vinyl boronic ester **242** (bottom).

Following the synthesis of vinyl iodide **239** and vinyl boronic ester **242**, the two fragments were united by a thallium-accelerated Suzuki-Miyaura cross-coupling.[224] The resultant primary alcohol was oxidised with DMP in DCM to afford aldehyde **241** in 82% yield over the two steps. Next, we embarked on the synthesis of sulfone **28** (Scheme **63**).



Scheme 62. Synthesis of aldehyde **241** from vinyl iodide **239** and vinyl boronic ester **242**.

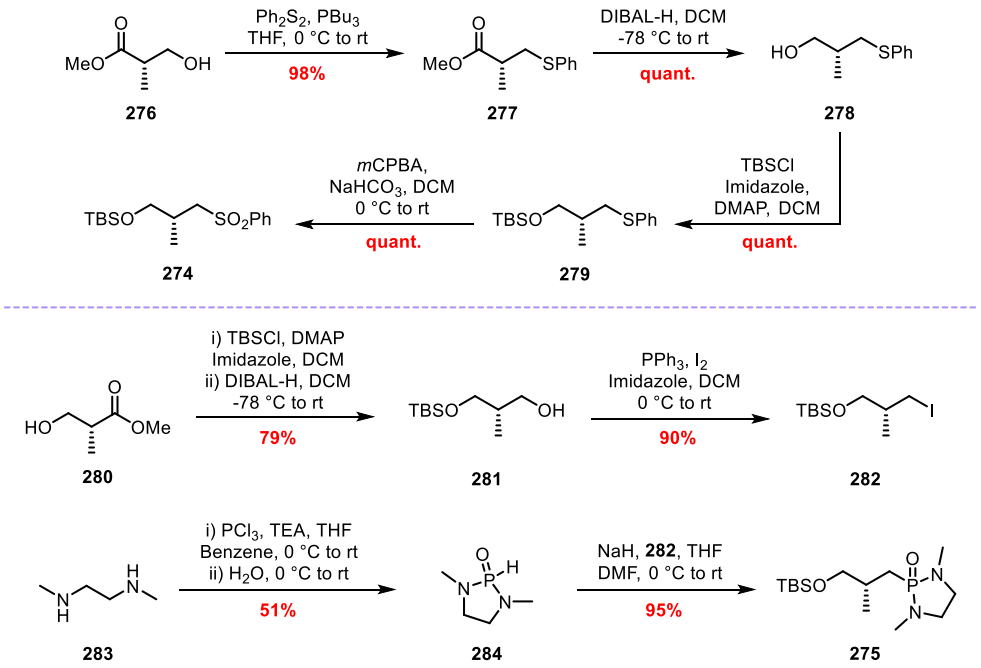
As discussed in chapter 1, various approaches for the formation of the trisubstituted double bond in **28** have been developed. In 2007, Markó reported the first total synthesis of jerangolid D, whereby the trisubstituted olefin was constructed through a Julia coupling between ketone **31** and sulfone **274** (Scheme **63**).[100] Later, in 2010 Hanessian employed a phosphonamide-anion olefination in the total syntheses of ambruticin S and jerangolid A to generate the same fragment.[70,234] It was anticipated that we would use one of these approaches to access the trisubstituted olefin **28**, where either sulfone **274** or phosphorus diamide **275** were to be coupled with ketone **31**. Hence both fragments were prepared in order to determine which method was preferred.



Scheme 63. (a) Retrosynthetic analysis of sulfone **28** (b) synthesis of trisubstituted olefin **273** by Markó and (c) synthesis of **273** by Hanessian.[70,100,234]

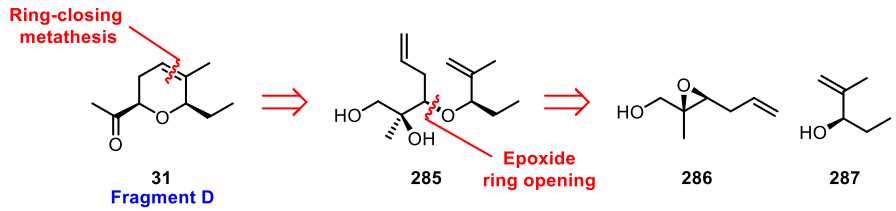
Sulfone **274** was synthesised from *S*-Roche ester **276** following a literature route in 98% yield over 4 steps (Scheme **64**).[100] Reaction of the alcohol in **276** with diphenyl disulfide and tributyl phosphine afforded sulfide **277** which was reduced to form alcohol **278**. Protection of the newly formed primary alcohol and subsequent oxidation of the sulfide with *m*CPBA gave phenyl sulfone **274**.

The alternative olefination reagent phosphorus diamide **275** was synthesised using a literature route from *R*-Roche ester (Scheme **64**).[70] Silyl protection of the primary alcohol followed by ester reduction and an Appel reaction afforded alkyl iodide **282** in 71% yield over 3 steps. Alkylation of diazaphospholidine **284**, synthesised through condensation of phosphorus trichloride with diamine **283** in 51% yield, with alkyl iodide **282** proceeded in an excellent yield of 95% to afford the desired phosphorus diamide **275** in 34% yield over 5 total steps. During the synthesis of diazaphospholidine **284**, significant polymerisation of PCl_3 with diamine **283** was observed. Increasing the scale of the reaction exacerbated this problem, resulting in a decrease in isolated yield of **284**. Although it was found that vigorous stirring of the reaction mixture and addition of PCl_3 diluted in benzene supressed this undesired reactivity, the reaction could not be performed on greater than 10 mmol scale without a significant drop in yield.



Scheme 64. Synthesis of sulfone **274** (top) and phosphorus diamide **275** (bottom).[70,100]

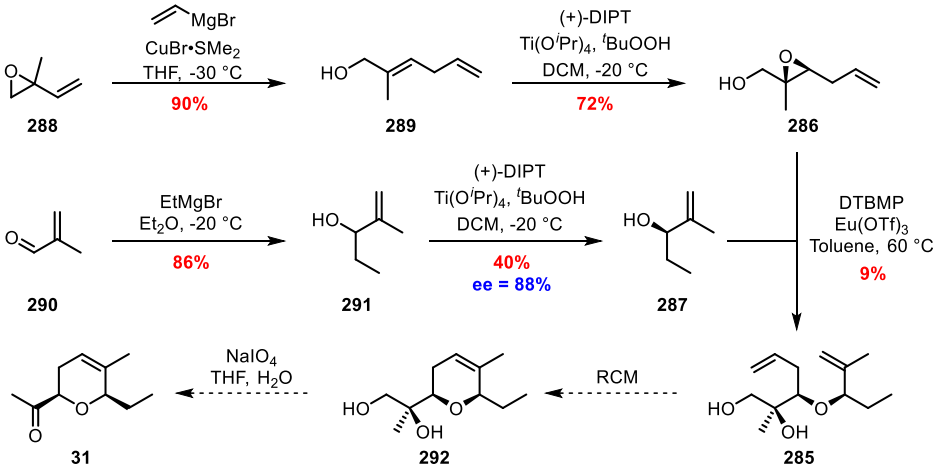
Our initial approach to dihydropyran **31** was centred around ring-closing metathesis and an intermolecular epoxide ring opening (Scheme **65**). A key feature of this proposed route was the selective C-3 ring opening of epoxide **286**. Indeed, various methods have been developed to direct the intermolecular epoxide ring opening of 2,3-epoxy alcohols such as the pioneering work by Sharpless involving coordination of the epoxy alcohol with titanium isopropoxide.[235]



Scheme 65. Retrosynthetic analysis of dihydropyran **31**.

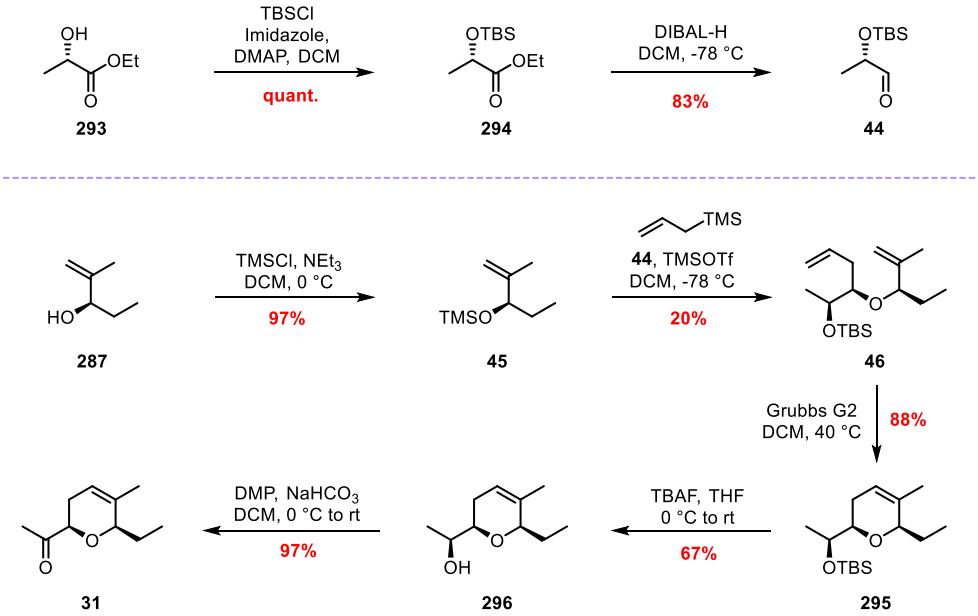
Allylic alcohol **287** was synthesised from methacrolein in 34% yield *via* a Grignard addition with ethyl magnesium bromide and a subsequent kinetic resolution of the two enantiomers by Sharpless asymmetric epoxidation (SAE) (Scheme **66**).[208] The enantiomeric excess (ee) of allylic alcohol **287** was determined as 88% by ^{1}H-NMR analysis of the corresponding Mosher's ester.[236] Epoxy alcohol **286** was prepared *via* an organocuprate addition into epoxide **288** followed by Sharpless asymmetric epoxidation of the resultant allylic alcohol. The enantiopurity of **286** was not determined at this stage.

In 2014, Iwabuchi and co-workers reported the $Eu(OTf)_3$-catalysed C-3 selective nucleophilic epoxide ring opening of 2,3-epoxy alcohols with excess (5 eq.) alcohol.[237] We were disappointed to find that reaction of epoxide **286** with 2 eq. of alcohol **287** under conditions described by Iwabuchi *et al*. provided only 9% of the desired product **285** due to the competing reaction with a second molecule of epoxy alcohol **286**. While this may have been alleviated by increasing the equivalents of alcohol **287**, it was deemed inefficient and was not tested. Further optimisation of the reaction conditions may have improved the yield of this process however, in many literature examples a large excess of nucleophilic alcohol is required to achieve the desired selectivity. Alternatively, protection of the epoxy alcohol **286** would prevent this unwanted pathway.[80] However, the increased number of synthetic transformations this would require dissuaded us from exploring this avenue. Although the apparent issues with this synthetic route may be overcome through further investigations, in the essence of time we opted to access ketone **31** through a previously developed route by Markó *et al* (Scheme **8E**, page **16**).[99]



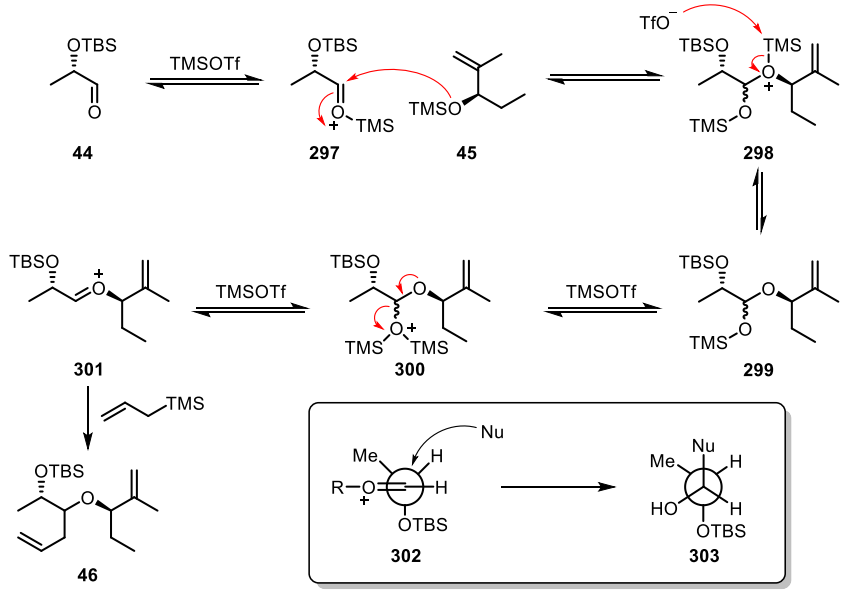
Scheme 66. Synthesis of diol **285** and proposed conversion to ketone **31**.

Markó synthesised dihydropyran **31** through a key RCM of **46**, which was generated by a diastereoselective multicomponent silyl-modified Sakurai reaction between silyl ether **45** and aldehyde **44** (Scheme **67**).[99] Aldehyde **44** was prepared in 83% yield from L-ethyl lactate by silyl protection and subsequent reduction. Initial attempts to reduce ester **294** to aldehyde **44** with DIBAL-H at -78 °C were unsuccessful due to over reduction to the corresponding alcohol. Nevertheless, we found that initial quenching of the reaction mixture at -78 °C with methanol prior to the addition of aqueous saturated potassium sodium tartrate supressed issues of over reduction. The required silyl alcohol **45** for the silyl-modified Sakurai reaction was synthesised from allylic alcohol **287** in 97% yield.



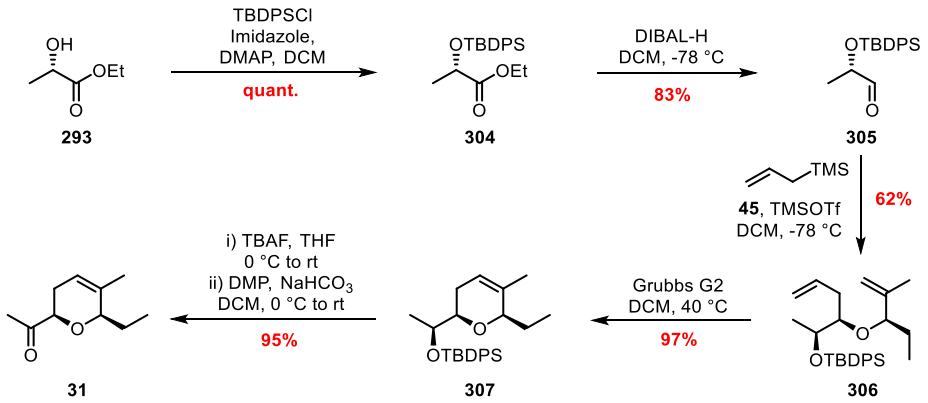
Scheme 67. Synthesis of ketone **31**.[100]

The proposed reaction mechanism for the multicomponent silyl-modified Sakurai reaction is depicted in scheme **68**. Following initial condensation of silyl ether **45** and activated aldehyde **297**, a sequence of silyl transfers generates oxocarbenium **301** which is trapped by allyltrimethylsilane in a manner typical of a Hosomi-Sakurai reaction.[238] The diastereoselectivity of the reaction is proposed to arise from this final step, where the preferred approach of the nucleophile can be rationalised using a Felkin-Anh model, such that steric interactions in transition state **302** are minimised.



Scheme 68. Proposed mechanism for silyl-modified Sakurai reaction of **44** and **45**.[99]

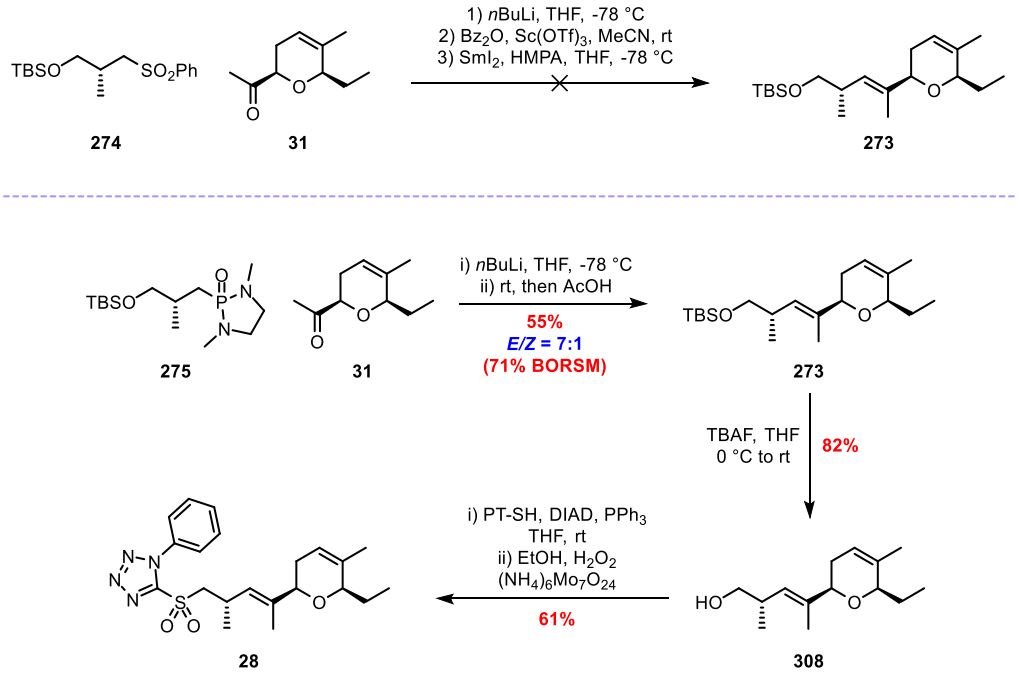
Although Markó reported an 80% yield for the multicomponent silyl-modified Sakurai reaction, in our hands a disappointing 20% yield of **46** was achieved even after rigorous purification of the starting materials and reagents (Scheme **67**).[100] Analysis of the crude product by NMR spectroscopy indicated silyl deprotection was occurring during the reaction. Furthermore, although readily separated by column chromatography, a mixture of diastereoisomers of **46** were also formed. After unsuccessful attempts to improve the yield of the reaction through alteration of the reaction procedure, we opted to perform the reaction with the TBDPS ether **305** in the hope that the more sterically hindered silyl group may prevent deprotection and the associated side products (Scheme **69**). Pleasingly the silyl-modified Sakurai reaction with aldehyde **305**, synthesised in 83% over 2 steps from L-ethyl lactate, gave ether **306** in 62% yield as a single diastereoisomer after purification by column chromatography. Ring-closing metathesis of **306** followed by silyl deprotection and finally oxidation of the resultant alcohol with DMP afforded ketone **31** in 47% over 6 steps from L-ethyl lactate. Ketone **31** was volatile and required care upon drying under vacuum.



Scheme 69. Synthesis of ketone **31**.

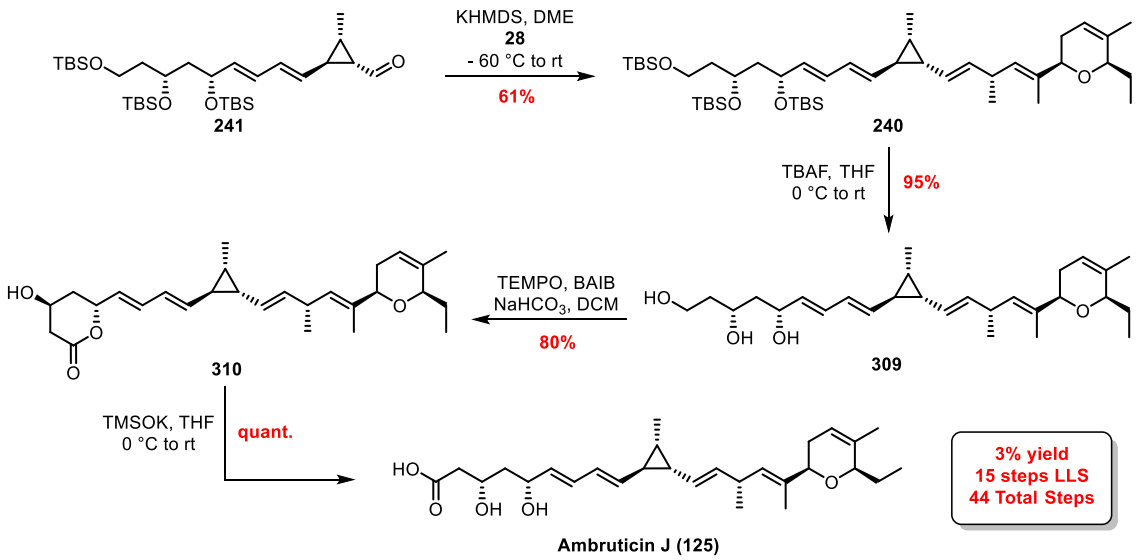
Having synthesised ketone **31**, sulfone **274** and phosphorus diamide **275**, we focussed on the olefination to assemble the trisubstituted alkene **273** (Scheme **70**). Unfortunately, we were unable to reproduce literature results reported by Markó *et al*. for the Julia coupling of sulfone **274** with ketone **31** and a complex mixture of inseparable products was formed. Hanessian and co-workers pioneered the use of phosphorus diamides to perform challenging olefinations with ketones, generating *trans*-alkenes with excellent control.[239,240] Initial attempts to replicate the work of Hanessian by coupling phosphorus diamide **275** with ketone **31** resulted in a 27% yield of **273** in a 20:1 ratio of *E*/*Z* isomers due to competing self-aldol condensation of ketone **31**. Nevertheless, this undesired pathway was avoided *via* the addition of neat ketone **31**, resulting in a 55% yield of **273** as a 7:1 mixture of olefin isomers. Unreacted ketone **31** was easily recovered by flash column chromatography. The olefin isomers were readily separated by column chromatography after silyl deprotection, affording alcohol **308** as solely the *E*-isomer in 45% yield from ketone **31**.

Alcohol **308** was converted to sulfone **28** using a Mitsunobu reaction with phenyl tetrazole thiol followed by oxidation of the resultant sulfide with molybdate and H_2O_2 in ethanol (Scheme **70**). Initially a one-pot Mitsunobu-oxidation procedure was carried out, giving only 41% yield of the desired sulfone due to competing epoxidation of the trisubstituted olefins. It proved necessary to isolate and purify the intermediate sulfide, which upon oxidation provided an improved 61% yield of sulfone **28**. Strict monitoring of the reaction was required to maximise oxidation of the sulfide and intermediate sulfoxide while minimising undesired epoxidation.



Scheme 70. Attempted Julia coupling of sulfone **274** with ketone **31** (top) and synthesis of sulfone **28** (bottom).

A Julia-Kocienski olefination was used to unite sulfone **28** and aldehyde **241**, completing the assembly of the carbon skeleton of ambruticin J (Scheme **71**).[90,241] Performing the reaction with equimolar amounts of sulfone **28** and aldehyde **241** under standard conditions of KHMDS in DME afforded the *E*-alkene **240**, albeit in only 44% isolated yield. However, we found that the yield could be improved to 61% by using 1.3 eq. of sulfone **28**. The total synthesis of ambruticin J was completed *via* global deprotection with TBAF to liberate triol **309**, selective oxidation of the primary alcohol to lactone **310**, and mild hydrolysis with TMSOK in THF. Overall, ambruticin J had been prepared in 3% yield over 15 steps in the longest linear sequence and 44 total synthetic transformations.

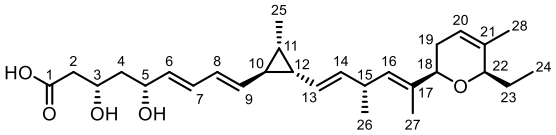


Scheme 71. Julia-Kocienski olefination of sulfone **28** and aldehyde **241** and final stage transformations to ambruticin J.

Comparison of the NMR data for the synthetic sample of ambruticin J with the data reported by Reeves *et al*. revealed discrepancies which prompted us to further interrogate the spectral data (Tables **5** and **6**).[105] Unfortunately, an authentic sample of ambruticin J from *Sorangium cellulosum* was not available for us to use to compare the structure of the natural product and our synthetic sample.

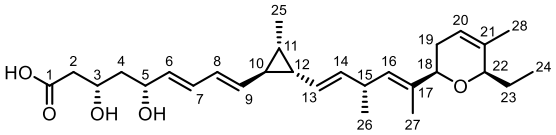
The chemical shifts and coupling constants in the ^{1}H-NMR spectrum of our synthetic sample of ambruticin J were in excellent agreement with those reported by Reeves *et al*. with the exception of the signals corresponding to 2-H_2, where slight deviations were observed (Table **5**). These differences are rationalised by considering the exchange/protonation state of the carboxylic acid, where small changes caused by differences in pH and/or concentration are expected to lead to conformational changes in ambruticin J and concomitant changes in chemical shift. Similar chemical shift discrepancies for the signals assigned as C-1 and C-2 in the ^{13}C-NMR spectra were observed (Table **6**). Attempts to reconcile the data with that reported by Reeves and co-workers by pH changes were unsuccessful due to decomposition of the sample.

Further discrepancies were noted in the ^{13}C-NMR spectra (Table **6**). We confirmed through HSQC analysis that differences for the chemical shifts in the ^{13}C-NMR for signals associated with C-3, C-4, C-5, and C-16 arose due to misassignment of the original spectra by Reeves *et al*. Indeed, C-3 and C-5 assignments were interchanged as were the signals corresponding to C-4 and C-12. Comparison of the C-12 chemical shift for our synthetic sample of ambruticin J with that reported for ambruticin S (30.6 ppm and 29.7 ppm respectively) provided further confirmation of our correct assignment (Table **7**).[242]



Position	Synthetic Ambruticin J 500 MHz (CD_3OD): δ_H (multiplet, J (Hz))	Natural Ambruticin J 400 MHz (CD_3OD): δ_H (multiplet, J (Hz))[105]
1-H	-	-
2-H_a	2.40 (dd, 15.4, 8.0)	2.35 (dd, 15.2, 7.8)
2-H_b	2.47 (dd, 15.4, 4.9)	2.42 (dd, 15.2, 5.0)
3-H	4.08	4.07
4-H_2	1.72 and 1.65	1.72
5-H	4.25 (ap. q, 7.2)	4.25 (dd, 13.8, 7.0)
6-H	5.53	5.49
7-H	6.16 (dd, 15.2, 10.5)	6.15 (dd, 15.0, 10.5)
8-H	6.05 (dd, 14.8, 10.5)	6.05 (dd, 14.8, 10.5)
9-H	5.32 (dd, 14.8, 8.9)	5.31 (dd, 14.8, 8.5)
10-H	1.12	1.10
11-H	1.10	1.10
12-H	1.49	1.52
13-H	5.16 (dd, 15.2, 8.8)	5.15 (dd, 15.2, 8.6)
14-H	5.46	5.45
15-H	3.09	3.10
16-H	5.25 (d, 8.9)	5.25 (d, 9)
18-H	3.82	3.82
19-H_a	1.86	1.85
19-H_b	2.10	2.09
20-H	5.58	5.57 (dd, 3.8, 1.9)
22-H	4.08	4.08
23-H_a	1.52	1.53
23-H_b	1.73	1.74
24-H_3	0.88 (t, 7.3)	0.88 (t, 7.5)
25-H_3	1.06	1.06, (d, 3.6)
26-H_3	1.04 (d, 7.1)	1.05
27-H_3	1.64 (d, 1.5)	1.63
28-H_3	1.59 (s)	1.58

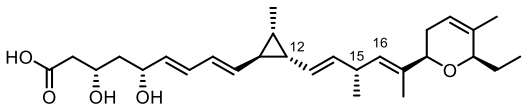
Table 5. Comparison of ^{1}H-NMR data for synthetic and natural ambruticin J.[105]



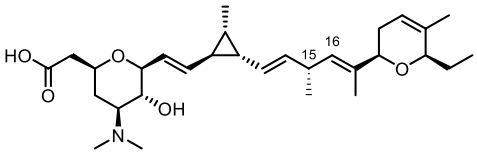
Position	Synthetic Ambruticin J 126 MHz (CD_3OD): δ_C	Natural Ambruticin J 100 MHz (CD_3OD): δ_C [105]
C-1	175.4	177.0
C-2	43.3	44.0
C-3	67.5	71.7
C-4	45.0	30.5
C-5	71.6	67.8
C-6	133.1	133.2
C-7	132.4	132.3
C-8	128.4	128.5
C-9	138.6	138.4
C-10	32.1	32.1
C-11	22.8	22.8
C-12	30.6	45.0
C-13	126.9	126.9
C-14	136.3	136.3
C-15	36.3	36.3
C-16	130.9	124.3
C-17	136.2	136.2
C-18	79.54	79.5
C-19	31.1	31.1
C-20	122.1	122.1
C-21	136.1	136.1
C-22	79.48	79.5
C-23	26.6	26.6
C-24	8.7	8.7
C-25	13.4	13.4
C-26	21.6	21.6
C-27	12.7	12.6
C-28	19.1	19.0

Table 6. Comparison of ^{13}C-NMR data for synthetic and natural ambruticin J.[105]

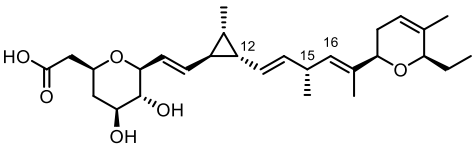
Finally, a large difference in chemical shift (6.6 ppm) for the signal assigned as C-16 in the ^{13}C-NMR was observed (Table **6**). Comparison of the C-16 chemical shifts for our synthetic sample of ambruticin J and that of natural ambruticin S revealed a difference of 0.1 ppm, providing some support for our assignment.[242] This encouraged us to interrogate the chemical shifts of signals assigned as C-16 for other products reported by Reeves *et al*. (Table **7**). In particular, we noted that the C-16 chemical shift of 15-desmethylambruticin VS3 (**311**) exhibited no difference with that reported by Reeves for ambruticin J. We expected that the lack of the C-15 methyl group in 15-desmethylambruticin VS3 would impart a significant change in chemical shift for the signal assigned as C-16. Indeed, comparison of the chemical shifts of C-16 signals of ambruticin VS3 and 15-desmethylambruticin VS3 revealed an expected significant difference of 6.4 ppm.[59] Furthermore, a chemical shift of 130.7 ppm for the C-16 signal of ambruticin VS3 is in agreement with our reported chemical shift of 130.9 ppm for ambruticin J. These points indicate an error was made in the original assignment of ambruticin J by Reeves *et al*. either due to a transcription error or impurities present in their sample.



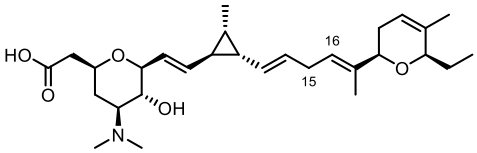
Ambruticin J (125)



Ambruticin VS3 (5)



Ambruticin S (1)



15-Desmethylambruticin VS3 (311)

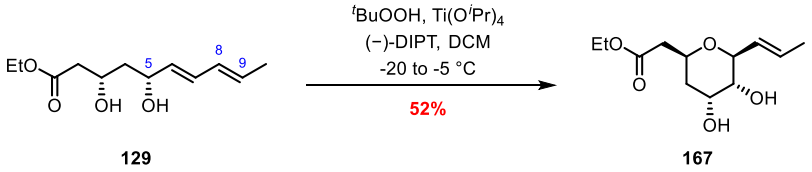
Compound	δ_C: C-12 (ppm)	δ_C: C-16 (ppm)
Synthesised ambruticin J (**125**)	30.6	130.9
Natural ambruticin J (**125**)	45.0	124.3
Ambruticin S (**1**)	29.7	130.8
15-Desmethylambruticin VS3 (**311**)	29.9	124.3
Ambruticin VS3 (**5**)	29.8	130.7

Table 7. Ambruticin C-12 and C-16 ^{13}C-NMR signals.[59,105,242]

As discussed, Taylor reported the total synthesis of ambruticin J shortly after we completed our route.[228] Comparison of the NMR data of our synthetic sample with that reported by Taylor shows good agreement (see chapter **4**). A similar analysis of discrepancies in the spectral data of ambruticin J to that discussed above was made by Taylor, providing further evidence we have successfully synthesised ambruticin J.

2.4. Conclusions and Future Work

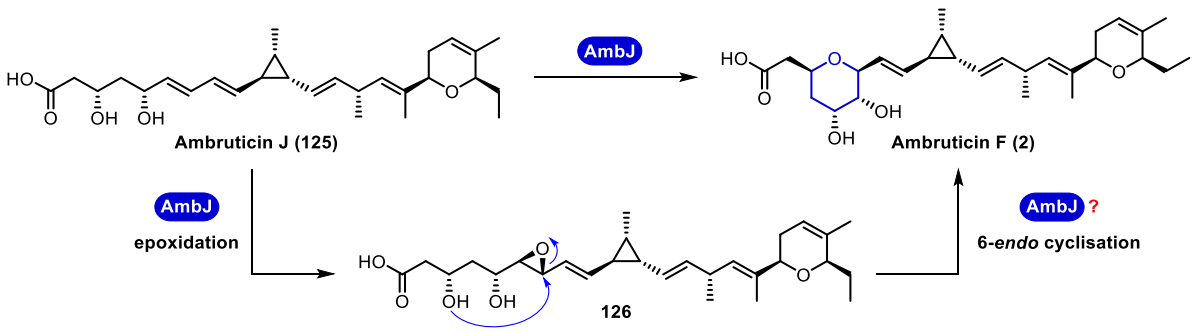
In conclusion, epoxidation-cyclisation studies on model substrates of ambruticin J (**125**) have been conducted to probe the inherent reactivity of epoxy ambruticin J to cyclisation. These results indicate the 5-hydroxyl and 8,9-alkene of ambruticin J may play a role in directing 6-*endo* intramolecular epoxide ring opening, suggesting an epoxide hydrolase may not be required to achieve THP ring formation in ambruticin biosynthesis. Nevertheless, it is unclear whether AmbJ, or a yet to be determined epoxide hydrolase, is required to promote cyclisation, or stabilise the epoxide intermediate.



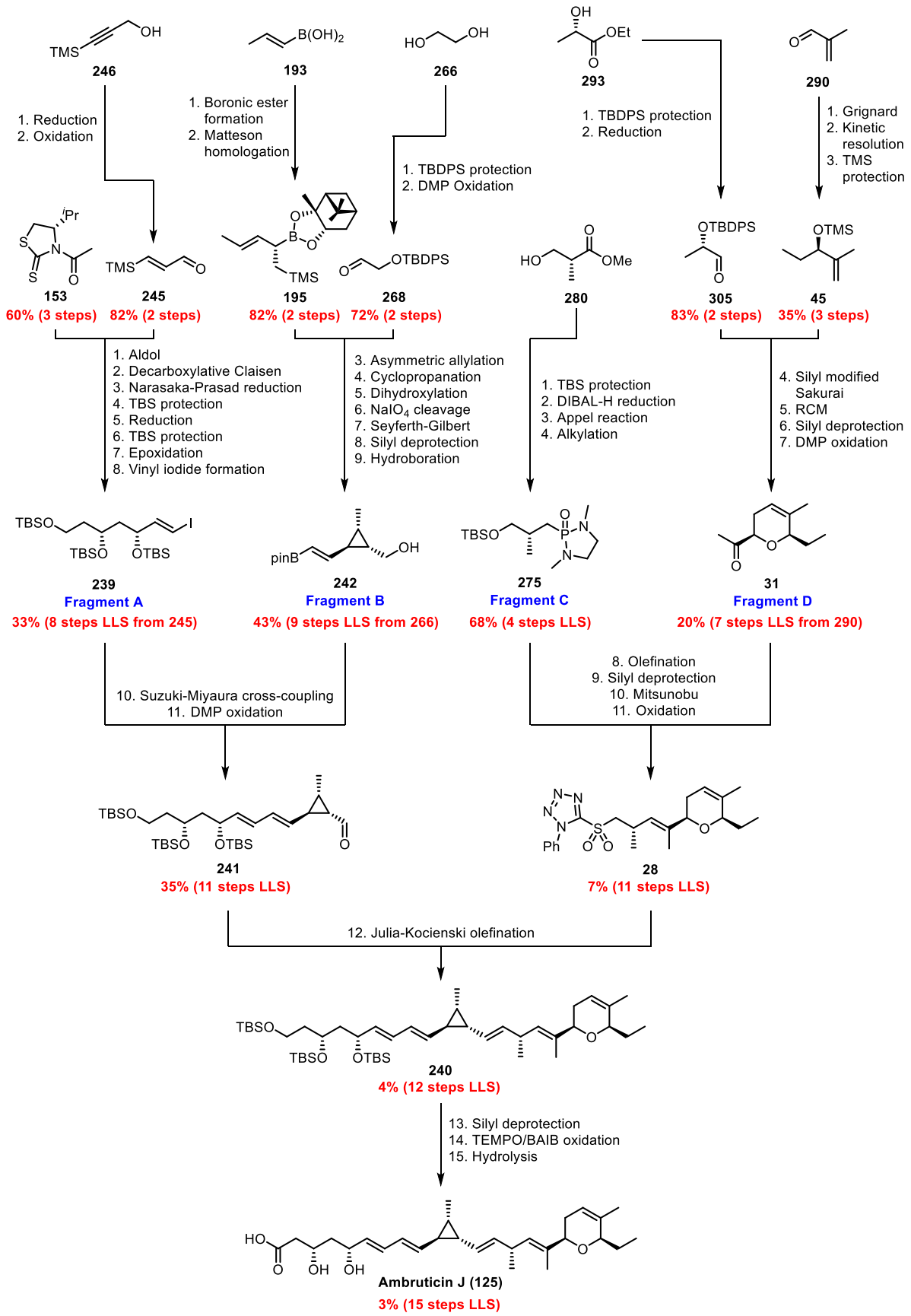
Scheme 72. Epoxidation-cyclisation of dihydroxy ester **129** to THP **167**.

Towards the goal of probing the structure and function of AmbJ in ambruticin biosynthesis, we have completed the total synthesis of the protein's putative substrate, ambruticin J. A convergent approach was developed, where four fragments were combined by a thallium accelerated Suzuki-Miyaura cross-coupling and two olefinations (Scheme **74**). Two synthetic routes to fragment A (**239**) were developed which employed a key asymmetric aldol condensation, decarboxylative Claisen condensation sequence. The trisubstituted cyclopropane in fragment B (**242**) was constructed by employing a cation rearrangement methodology developed by Taylor *et al*. Finally, ketone **31** was synthesised employing a diastereoselective silyl-modified Sakurai reaction, while phosphorus diamide **275** was accessed from *R*-Roche ester. A summary of the optimised synthetic route to ambruticin J is depicted in scheme **74**.

Assays with the synthetic sample of ambruticin J and AmbJ are currently underway in collaboration with Dr. Luoyi Wang at the Chinese Academy of Sciences in Beijing, China (Scheme **73**). With a robust route to ambruticin J realised, we plan to synthesise analogues of ambruticin J to probe the substrate specificity of AmbJ. Furthermore, the biological activities of these ambruticin analogues will be tested to study the SAR of the ambruticins.



Scheme 73. Ongoing biosynthetic transformation of ambruticin J with AmbJ.



Scheme 74. Summary of the total synthesis of ambruticin J.

CHAPTER 3:

Dihydropyran Ring Formation in Ambruticin Biosynthesis

3.1. Introduction

The ambruticins contain three rings, two of which are oxygen heterocycles. Whilst chapter 2 outlined our investigations into the synthesis and biosynthesis of the tetrahydropyran (THP) ring of the ambruticins, this chapter discusses the formation of the dihydropyran (DHP) ring. DHPs are 6-membered oxygen heterocycles which contain a double bond between C-5 and C-6 in the case of 3,4-dihydropyrans, or C-3 and C-4 for 5,6-dihydropyrans (Figure **17**).

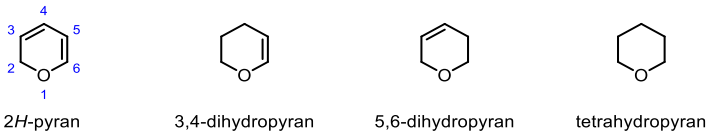


Figure 17. Structures of pyrans, DHPs, and THPs.

Although less abundant than THPs, DHPs are found in many classes of biologically active natural products and drug molecules such as the antifungal agent monocillin VII, the antibiotic blasticidin S, and the anticancer agent aspergillide C (Figure **18**).[243–245] Numerous methods have been developed for the synthesis of DHP rings with key methods including, but not limited to, hetero Diels-Alder cycloadditions, Prins and silyl-Prins reactions, and ring closing metatheses.[244] Nevertheless, additional methods for their efficient construction are desirable.[245]

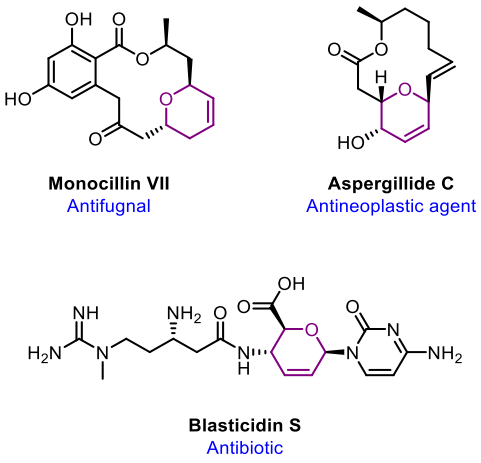
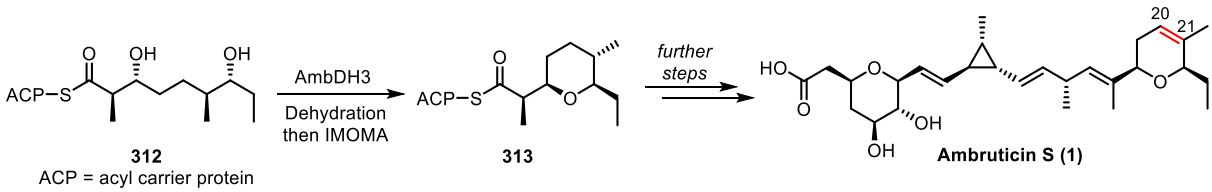


Figure 18. DHP-containing biologically active natural product and drug molecules.[243–245]

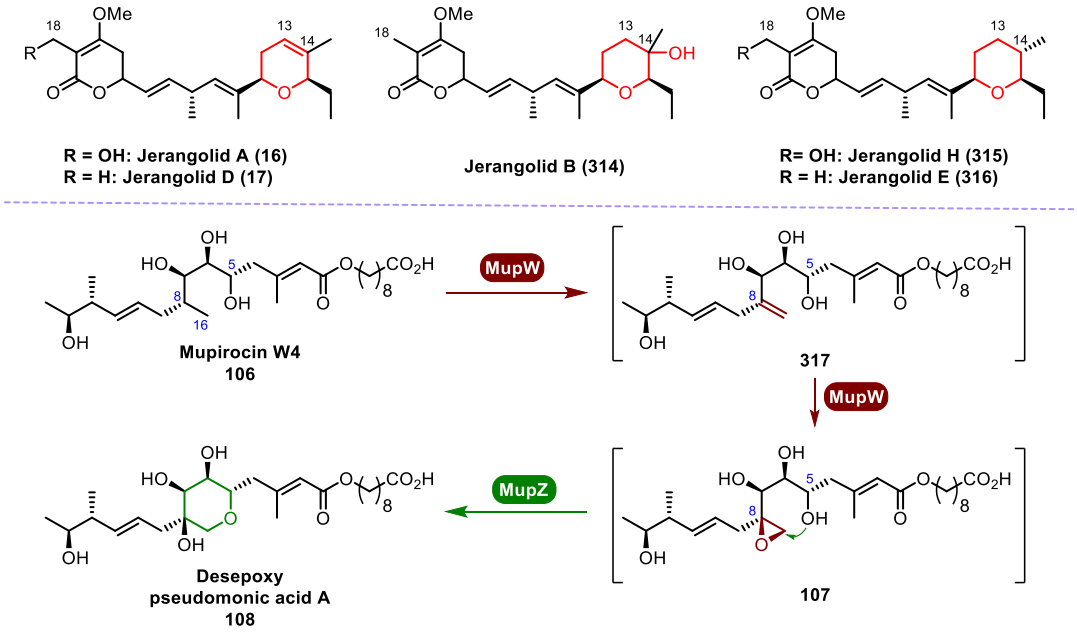
The formation of DHPs in nature has been less well studied than formation of THPs, with dehydration of saturated heterocycles being the most widely reported process.[144] As discussed in chapter 1, Hahn and co-workers revealed that the DHP ring in the ambruticins is initially formed as THP **313** from linear polyketide **312** *via* AmbDH3 catalysed dehydration and subsequent intramolecular oxa-Michael addition (IMOMA) (Scheme **75**).[106] Gene knockout experiments conducted by Reeves *et al*. indicated that oxidation of the THP to the DHP occurs later in the biosynthetic pathway, catalysed by the Rieske oxygenase AmbP and the NAD(P)/FAD-dependent oxidoreductase AmbO, although the exact timing

of this process is not known.[105] Reeves observed by LC-MS that the 20,21-dihydro analogues of the ambruticins were present in wild-type cultures of *Sorangium cellulosum*, although their structures were not definitively assigned.[105] They concluded that the desaturation event may occur at any point in the biosynthetic pathway, even whilst the growing polyketide chain is still bound to the PKS.[105]



Scheme 75. Proposed DHP ring formation in the ambruticins from linear polyketide **312**.[57]

Whilst desaturation was proposed to be catalysed by AmbP, Reeves *et al*. suggested that AmbO played a role in the regeneration of the Rieske oxygenase.[105] Both enzymes exhibit significant homology to JerP and JerO from the jerangolid biosynthetic gene cluster, which are proposed to perform an analogous desaturation.[57,105] Indeed, the THP, DHP, and hydroxylated THP rings are all present in the jerangolid family of natural products (Figure **76**). JerL, a close homolog to AmbP and JerP, is responsible for the late-stage C-18 hydroxylation in the jerangolid biosynthetic pathway. Taken together, this information indicates that DHP ring formation in ambruticin biosynthesis may occur *via* AmbP catalysed hydroxylation of the THP followed by elimination of the resultant alcohol. Similar reactivity has been reported in mupirocin biosynthesis where the Rieske oxygenase MupW catalyses epoxide formation from the unactivated alkane **106**, presumably *via* the intermediate alkene (Scheme **76**).[188]



Scheme 76. Jerangolids A, B, D, E and H (top) and THP ring formation in mupirocin biosynthesis (bottom).[57,188]

As discussed previously, the presence of the ambruticins and their 20,21-dihydro analogues in cultures of wild-type *Sorangium cellulosum* indicates the desaturation event to form the DHP may occur at multiple points in the biosynthetic pathway.[105] This suggests the enzymes responsible for this intriguing desaturation may possess a degree of substrate tolerance. This apparent promiscuity, alongside the challenge of performing such a transformation chemically, make these interesting proteins for further study. Indeed, in recent years Rieske oxygenases have been shown to catalyse a range of biosynthetic transformations and further investigations into this class of enzyme are required to fully reveal their potential as biocatalysts.[246]

3.2. Project Aims

Towards the goal of investigating DHP ring formation in ambruticin biosynthesis, we aimed to synthesise substrates to be used in bioassays with AmbP and AmbO, the proteins proposed to catalyse the key desaturation step. These proteins will be expressed by Dr. Luoyi Wang at the Chinese Academy of Sciences in Beijing, China.

As it is hypothesised that desaturation may occur at multiple points in the biosynthetic pathway,[105] our initial target was carboxylic acid **318**, a proposed truncated analogue of the PKS-bound growing polyketide chain (Figure **19**). Furthermore, since carboxylic acid **318** would still be attached to the PKS, the thioester derivative **319** was also required as the pantetheine unit will mimic the phosphopantetheine arm of the PKS ACP and therefore facilitate substrate recognition with AmbP. Although alternative thioester units could be incorporated, such as *N*-acetylcysteamine (SNAC), the pantetheine moiety provides a close mimic to the phosphopantetheine arm whilst remaining synthetically facile to incorporate.

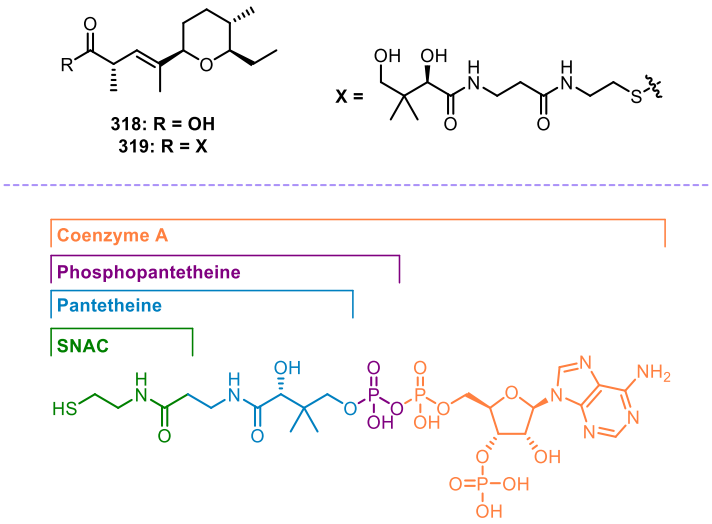
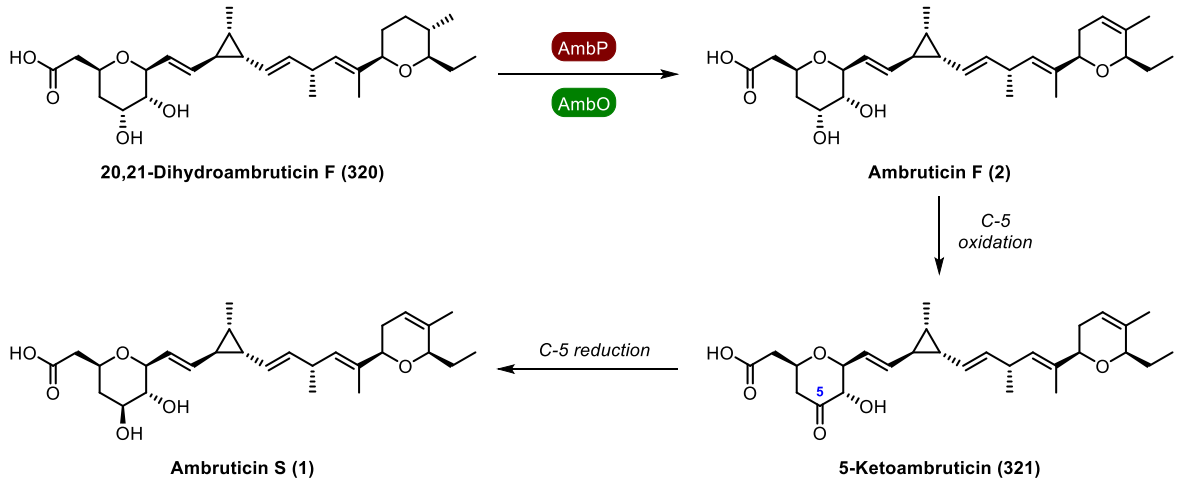


Figure 19. Carboxylic acid **318** and thioester **319** as substrates for bioassays (top) and structures of SNAC, pantetheine, phosphopantetheine, and coenzyme A (bottom).

Next, in collaboration with Dr. Luoyi Wang, we aimed to isolate 20,21-dihydroambruticin F (**320**) from culture extracts of a mutant strain of *Sorangium cellulosum* where the genes encoding for AmbP and AmbO are disrupted, alongside the genes responsible for further tailoring of C-5 of the THP ring (Scheme **77**). An authentic sample of 20,21-dihydroambruticin F (**320**) was required to confirm the structure of the proposed biosynthetic intermediate and to provide a further substrate for bioassays with AmbP and AmbO (Scheme **77**).

To provide standards to aid the analysis of bioassays with 20,21-dihydroambruticin F and AmbP/AmbO, a further goal was to complete the first total synthesis of ambruticin F (**2**) by adapting

the synthetic route previously developed to ambruticin J. Furthermore, ambruticin F will also act as a synthetic reference for the assays with AmbJ and ambruticin J described in chapter 2.



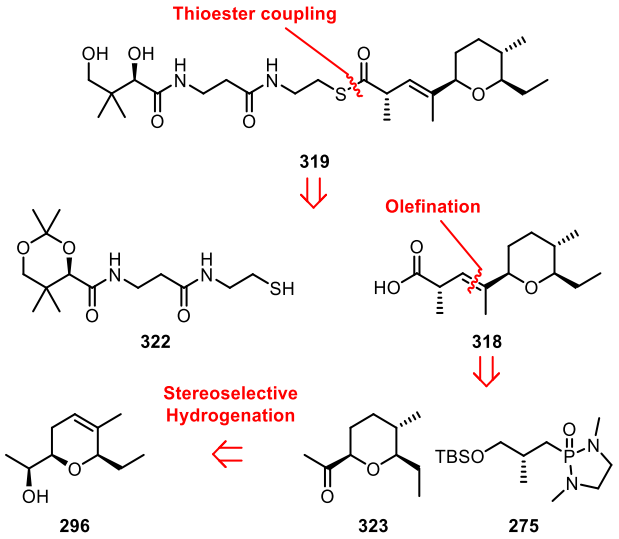
Scheme 77. Proposed bioassays of 20,21-dihydroambruticin F (**320**) with AmbP and AmbO, and proposed biomimetic synthesis of ambruticin S from ambruticin F.

Finally, as only partial spectral data for ambruticin F have been reported in the literature,[60] we wished to prepare ambruticin S from ambruticin F *via* a biomimetic oxidation/reduction sequence to epimerise the 5-hydroxyl group (Scheme **77**). Spectral data for the synthetic sample of ambruticin S would then be compared with the literature. Isolation of ambruticin F *via* gene knockout experiments was also to be undertaken to provide further confirmation of the proposed structure.

3.3. Results and Discussion

3.3.1. Synthesis of Proposed Biosynthetic Intermediates 318 and 319

Our initial goal was to synthesise carboxylic acid **318**, which could be readily converted to the corresponding thioester **319** *via* coupling with the acetonide protected pantetheine **322**. We envisaged a key olefination between ketone **323** and phosphorus diamide **275** would generate the trisubstituted alkene in **318**. Hanessian *et al*. previously illustrated an analogous olefination in the total synthesis of jerangolid A which we employed in our total synthesis of ambruticin J.[229,234] While we had previously accessed phosphorus diamide **275**, a route towards ketone **323** was required.



Scheme 78. Retrosynthetic analysis of thioester **319**.

Hahn and co-workers previously synthesised ketone **323** in 30% yield over 13 steps by employing a intramolecular oxa-Michael addition to construct the THP ring.[247] However, we wished to explore the conversion of the previously accessed DHP **296** (see chapter 2) to THP **323** through a stereoselective hydrogenation. Conformational analysis of DHP **323** revealed that in both half-chair cyclohexene conformers the alcohol is positioned on the top face of the alkene as drawn (Figure **20**). Therefore, it was anticipated that the alcohol would direct hydrogenation to the top face of the alkene to generate the desired THP.

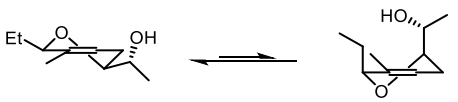
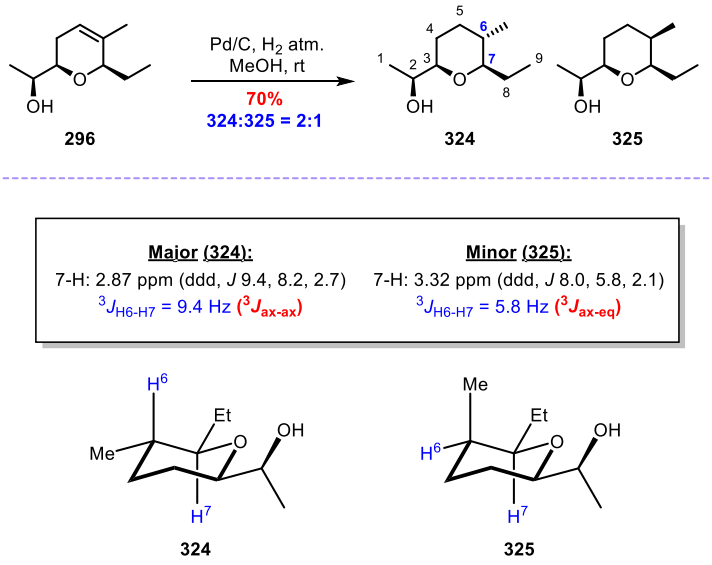


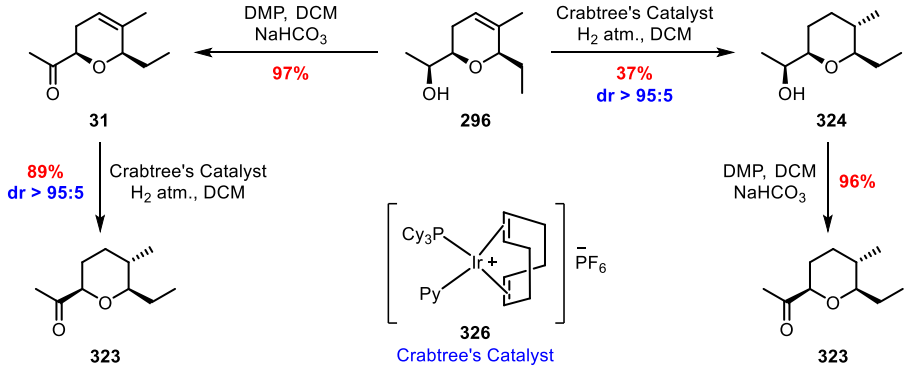
Figure 20. Conformational analysis of DHP **323**.

We found that hydrogenation of alkene **296** with palladium on carbon in methanol under an atmospheric pressure of hydrogen yielded an inseparable mixture of THPs **324** and **325** in a 2:1 ratio in favour of the desired product (Scheme **79**). The structures of the products were confirmed by analysis of the coupling constants in the ^{1}H-NMR spectra. In particular, a characteristic $^{3}J_{ax\text{-}ax}$ coupling of 9.4 Hz was apparent for 7-H in the major product **324**, whilst a $^{3}J_{ax\text{-}eq}$ coupling constant of 5.8 Hz was observed for 7-H in the minor product **325**.



Scheme 79. Hydrogenation of DHP **296** (top) and NMR analysis used to confirm relative stereochemistry (bottom).

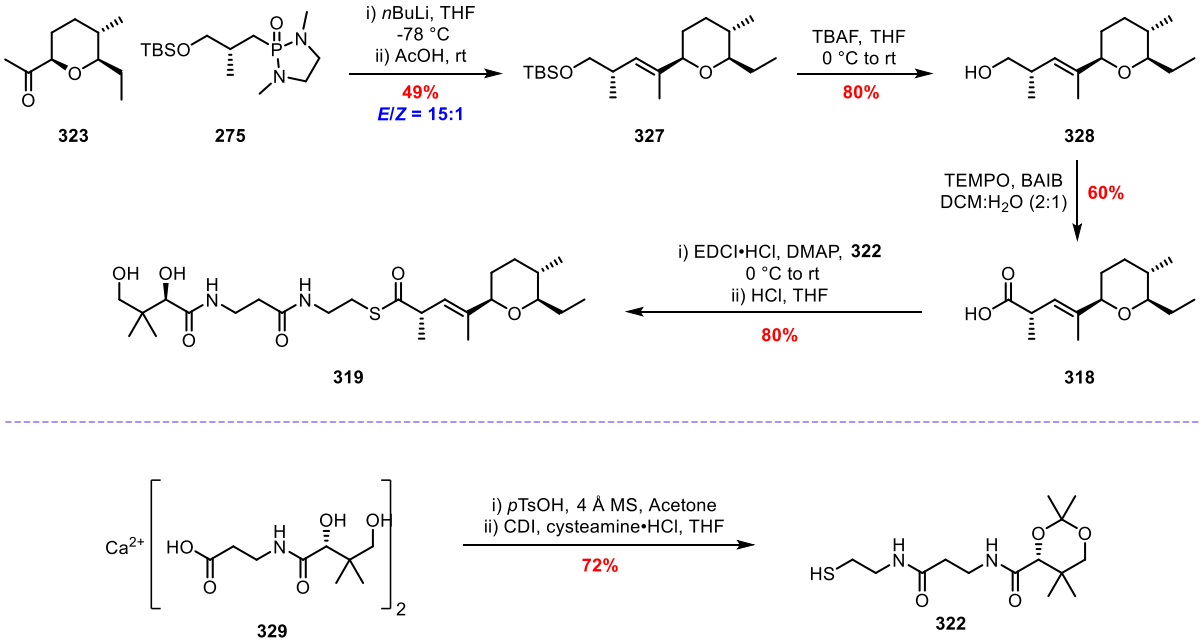
In 1986, Crabtree *et al*. reported the substrate directed hydrogenation of alkenes with iridium catalyst **326**, later referred to as Crabtree's catalyst (Scheme **80**).[248] Employing Crabtree's catalyst for the hydrogenation of DHP **296** gave THP **324** in 37% yield along with a side product which could not be characterised. Alcohol **324** was subsequently oxidised to THP **323** in 96% yield, where comparison of the NMR data with that reported by Hahn *et al*. provided further confirmation that the desired diastereoisomer had been formed.[247]



Scheme 80. Synthesis of THP ketone **323** *via* hydrogenation with Crabtree's catalyst.

Crabtree *et al*. reported that ketones may also direct hydrogenation through coordination with the catalyst.[247] Gratifyingly, hydrogenation of DHP ketone **31** under Crabtree's conditions resulted in an 89% yield of THP **323** whilst maintaining an excellent diastereoselectivity of greater than 95:5 for the desired diastereoisomer (Scheme **80**). Scaling the reaction from 0.5 mmol to 5 mmol resulted in a dramatic drop in yield to 25% for THP **323** which was isolated alongside unreacted starting material. Nevertheless, after significant optimisation, a yield of 81% was achieved on a 6.5 mmol scale by increasing catalyst loading from 2.5 to 5 mol% and increasing the time hydrogen was bubbled through the reaction mixture from 5 minutes to 20 minutes.

Ketone **323** was reacted with phosphorus diamide **275** as previously discussed in chapter 2 (Scheme **70**, page **67**), providing the trisubstituted alkene **327** in 49% yield as a 15:1 mixture of *E*/*Z* isomers (Scheme **81**). Deprotection of the silyl ether with TBAF afforded **328** as solely the *E*-alkene after purification in 80% yield. Finally, carboxylic acid **318** was generated in 60% yield by oxidation of the primary alcohol in **328** with catalytic TEMPO and stoichiometric BAIB as a co-oxidant in a mixture of DCM and water. The corresponding thioester **319** was readily synthesised from **318** *via* an EDCI mediated coupling with thiol **322**, accessed in two steps from D-pantothenic acid hemicalcium salt, and subsequent acid-catalysed acetonide deprotection.

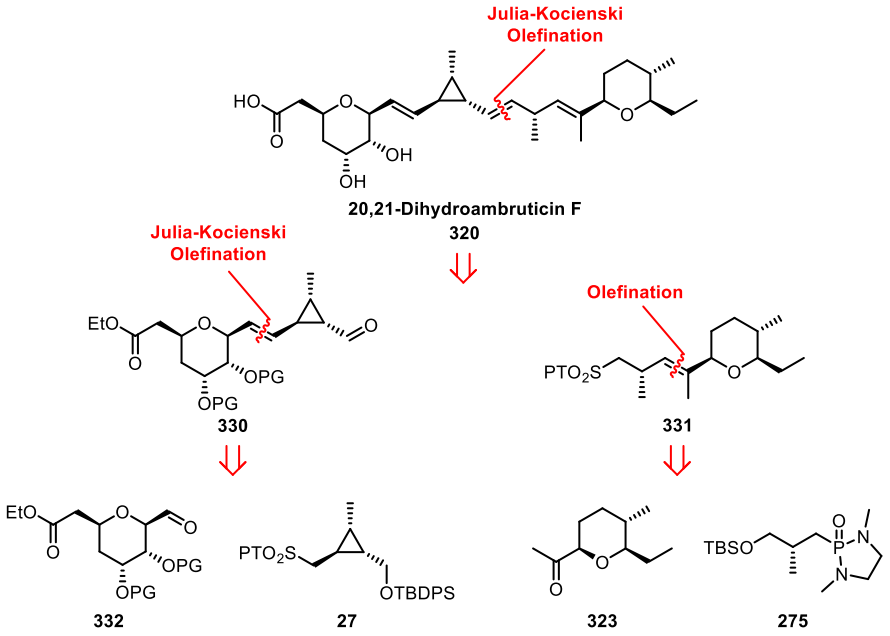


Scheme 81. Synthesis of carboxylic acid **318** and thioester **319** (top) and synthesis of thiol **322** (bottom).

Investigations into DHP ring formation using substrates **318** and **319** with AmbP and AmbO are currently underway in the laboratories of Dr. Luoyi Wang. Next, we investigated the total synthesis of 20,21-dihydroambruticin F (**320**), a proposed post-PKS substrate for DHP ring formation in the ambruticin biosynthetic pathway.

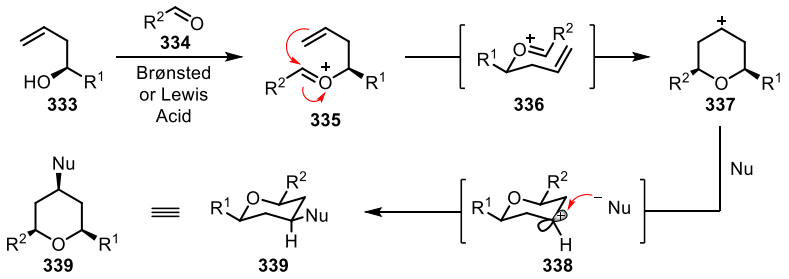
3.3.2. Total Synthesis of 20,21-Dihydroambruticin F

We envisaged that our previous route to ambruticin J could be adapted for the synthesis of 20,21-dihydroambruticin F, where a key Julia-Kocienski olefination between aldehyde **330** and sulfone **331** would generate the carbon skeleton (Scheme **82**). A second Julia-Kocienski olefination between aldehyde **332** and sulfone **27** would construct the alkene in **330**, and the THP in aldehyde **332** would be generated *via* a biomimetic epoxidation-cyclisation cascade as discussed in chapter 2. Finally, sulfone **331** could be readily accessed from ketone **323** and phosphorus diamide **275** by a route analogous to that previously discussed in section **2.3.4**.



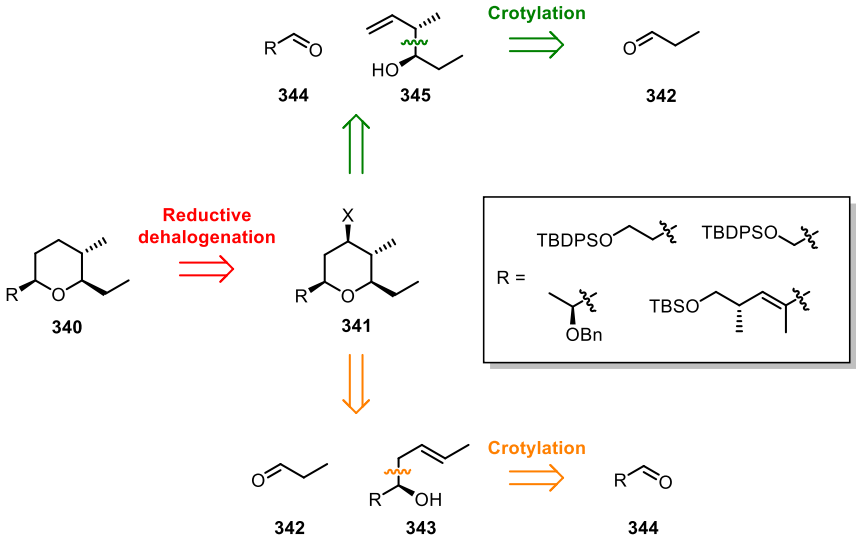
Scheme 82. Retrosynthetic analysis of 20,21-dihydroambruticin F.

Although we have previously prepared THP ketone **323** through asymmetric hydrogenation of the corresponding DHP **31**, we wished to develop a more concise route prior to embarking on the total synthesis of 20,21-dihydroambruticin F. The Prins cyclisation has been widely applied to the construction of THP rings in natural product synthesis.[137] A typical Prins cyclisation proceeds *via* an acid-catalysed condensation of a homoallylic alcohol with an aldehyde to form oxocarbenium **335**, which undergoes stereoselective cyclisation (Scheme **83**). In most cases a 2,6-*syn* relationship in carbocation **337** is achieved as the substituents prefer adopting a pseudoequatorial position in **336** to minimise 1,3-diaxial interactions.[249] Following cyclisation, the resultant carbocation is trapped with a nucleophile which will preferentially attack carbocation **337** from an equatorial position as this approach minimises undesired steric interactions whilst providing improved orbital overlap between the empty p-orbital and the HOMO of the incoming nucleophile.[249]



Scheme 83. Mechanism for the Prins cyclisation of homoallylic alcohol **333** and aldehyde **334**.[249]

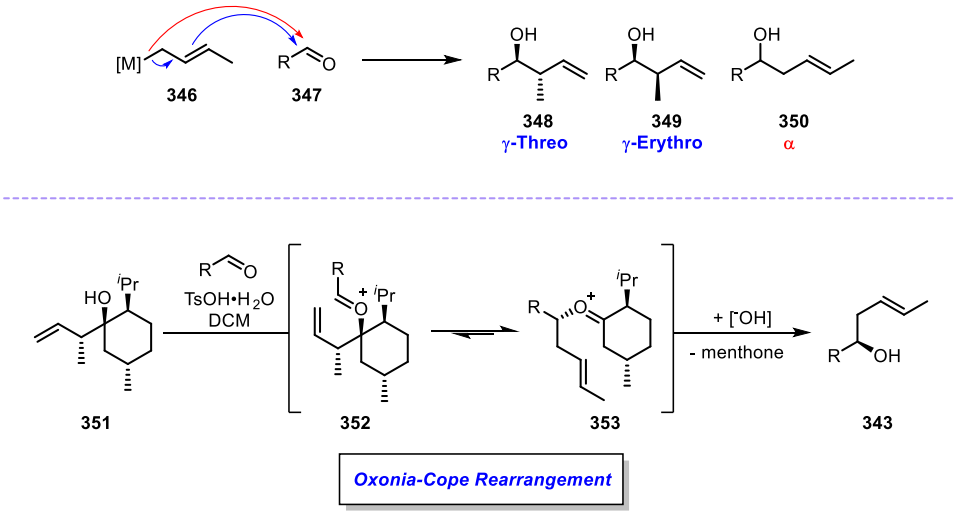
We proposed the THP in **340** could be synthesised by reductive dehalogenation of alkyl halide **341**, which in turn could be constructed *via* two different Prins cyclisation approaches (Scheme **84**). Various alkyl chains could be incorporated into aldehyde **344** or homoallylic alcohol **343**, however preinstallation of the trisubstituted alkene would be particularly attractive to circumvent the moderately yielding olefination. In both instances, crotylations could be employed to generate the required homoallylic alcohols.



Scheme 84. Retrosynthetic analysis of THP **340** *via* Prins cyclisation.

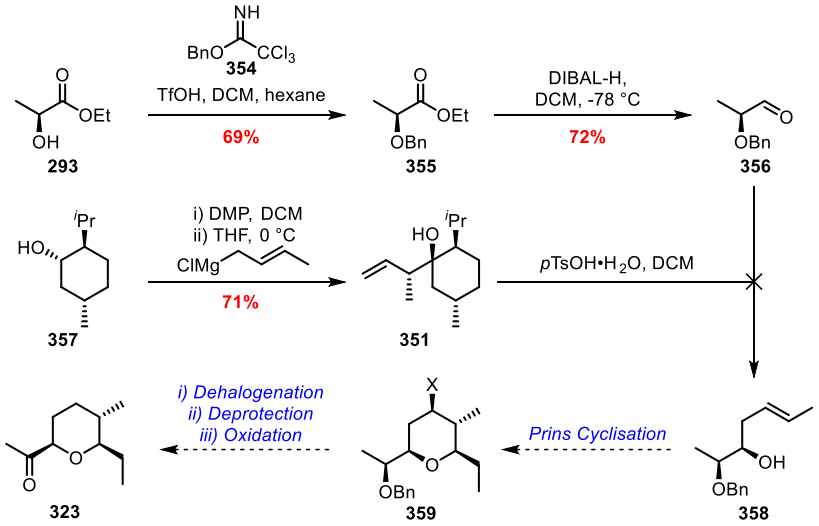
We initially opted to synthesise THP **341** *via* the condensation of propanal with various homoallylic alcohols, which were to be prepared through a Nokami crotylation (orange in scheme **84**).[250] The reaction of aldehydes with allylic metals to form α-adducts of the homoallylic alcohols such as **343** can be challenging due to the propensity of these reactions to form almost exclusively the γ-adducts (Scheme **85**).[251] However, In 2001, Nokami *et al*. reported the enantioselective crotylation of aldehydes to generate homoallylic alcohols as the α-adducts (Scheme **85**).[250] The reaction proceeds *via* condensation of an aldehyde with homoallylic alcohol **351**, derived from γ-crotylation of (+)-menthone, where the resultant oxocarbenium ion **352** undergoes an oxonia-Cope rearrangement to generate the thermodynamically more stable ion **353**. Hydrolysis of **353** under the reaction conditions

then generates homoallylic alcohol **343**, where a net allyl transfer from homoallylic alcohol **351** to aldehyde **344** has occurred. Importantly, the *E*-olefin is obtained exclusively and the optical purity of the starting homoallylic alcohol **351** maintained. Furthermore, both enantiomers of crotyl transfer reagent **351** are readily available from either (+) or (−)-menthol in excellent levels of enantiopurity. The key to the success of the reaction is the relative stabilities of the two oxocarbenium ions **352** and **353**, with **353** lower in energy due to a more thermodynamically stable internal alkene alongside a more stable and less sterically hindered oxocarbenium ion.[250,251]



Scheme 85. Crotylation to form α- and γ-adducts (top) and Nokami crotylation (bottom).[250]

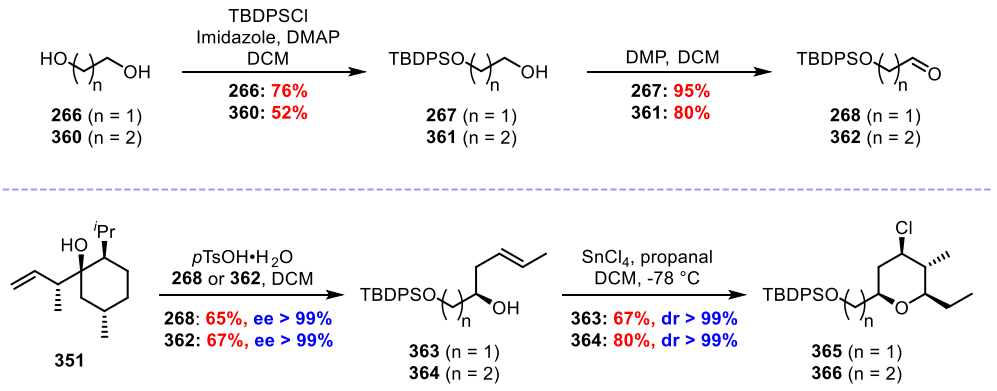
The required Nokami reagent **351** was synthesised on a multi-gram scale in two steps from (+)-menthol by oxidation with DMP and subsequent reaction with crotyl magnesium chloride (Scheme **86**).[250] The Nokami crotylation was initially investigated with aldehyde **356**, which was readily synthesised from L-ethyl lactate in two steps by benzyl protection and reduction of the ester with DIBAL-H. Unfortunately, treatment of aldehyde **356** and homoallylic alcohol **351** with *p*TsOH.H_2O in DCM returned only starting material. Although it was unclear why no reactivity was observed, a survey of the literature returned no instances of where an α-disubstituted aldehyde such as **356** underwent successful crotylation under these conditions. We hypothesised that the steric bulk around aldehyde **356** may prevent the condensation with homoallylic alcohol **351**, or the desired oxonia-Cope rearrangement from occurring. Hence, alternative aldehydes **268** and **362** were used in the reaction (Scheme **87**).



Scheme 86. Synthesis of Nokami reagent **351** and proposed synthesis of THP **358**.

Aldehydes **268** and **362** were synthesised from ethylene glycol and propane-1,3,-diol respectively by mono-protection as the TBDPS ether and subsequent oxidation with DMP (Scheme **87**). In both cases, excess of the diol (> 2 eq. with respect to TBDPSCl) was required to prevent bis-protection. The Nokami crotylation of aldehydes **268** and **362** with homoallylic alcohol **351** provided the desired homoallylic alcohols **363** and **364** in 65% and 67% yields respectively as solely the *E*-alkenes. ^{1}H-NMR analysis of the Mosher's esters of **363** and **364** indicated both were formed as essentially single enantiomers, consistent with results reported for similar aldehydes by Nokami *et al*.[250]

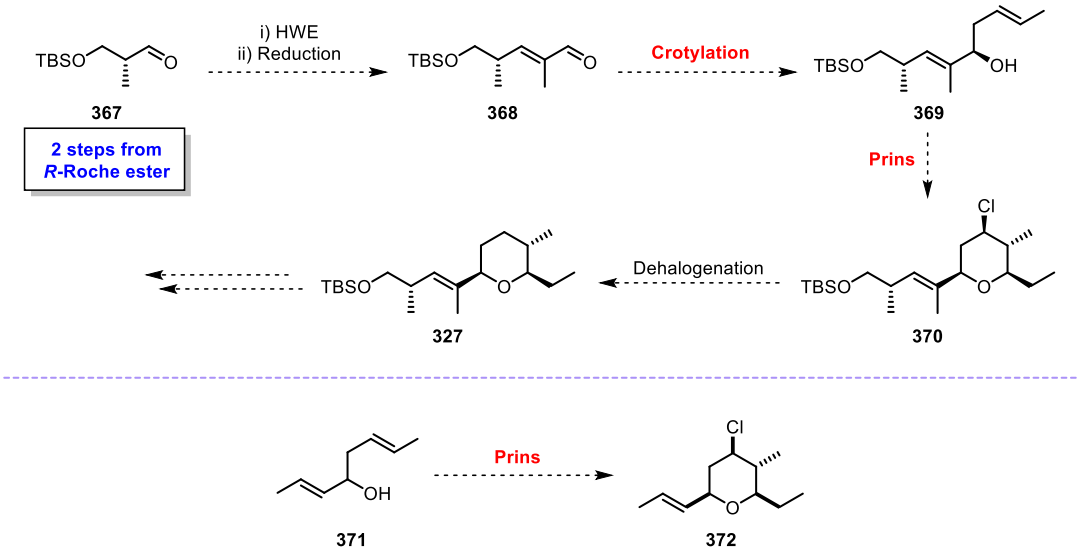
Numerous catalysts have been employed in the literature to facilitate the Prins cyclisation.[137] Since we intended to remove the trapping nucleophile at the 4-position on the newly formed THP ring by reductive dehalogenation, we opted to use $SnCl_4$ as the Lewis acid to promote cyclisation. Treatment of either homoallylic alcohol **363** or **364** with $SnCl_4$ and propanal in DCM gave the corresponding THPs **365** and **366** in 67% and 80% yield respectively (Scheme **87**). Importantly, excellent stereocontrol was achieved in both cases. No further optimisation of reaction conditions was performed.



Scheme 87. Synthesis of aldehydes **268** and **362** (top) and synthesis of THPs **365** and **366** (bottom).

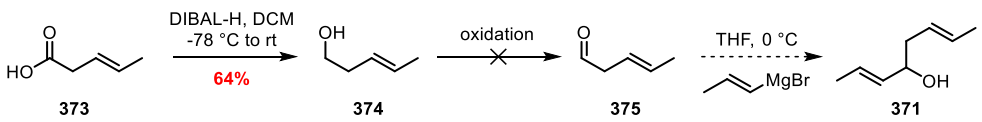
Although in both cases the THP rings were constructed in excellent yield and stereoselectivity, the number of synthetic transformations required to access the desired ketone fragment **323** from silyl ethers **365** and **366** prompted us to consider alternative routes. As previously discussed, the preinstallation of the trisubstituted olefin would be advantageous, thus we aimed to develop a route with this in mind.

Our new strategy centred on the crotylation of aldehyde **368** followed by a Prins cyclisation analogous to those previously performed (Scheme **88**). This route would rapidly construct silyl ether **327**, however both the α-crotylation of α,β-unsaturated aldehydes such as **368** and the Prins cyclisation with allylic homoallylic alcohols such as **369** were unprecedented in the literature. Due to these uncertainties, and the relative complexity of aldehyde **368** (to be prepared in 4 steps from *R*-Roche ester), we opted to investigate the feasibility of the route on the simplified racemic alcohol **371** (Scheme **88**).



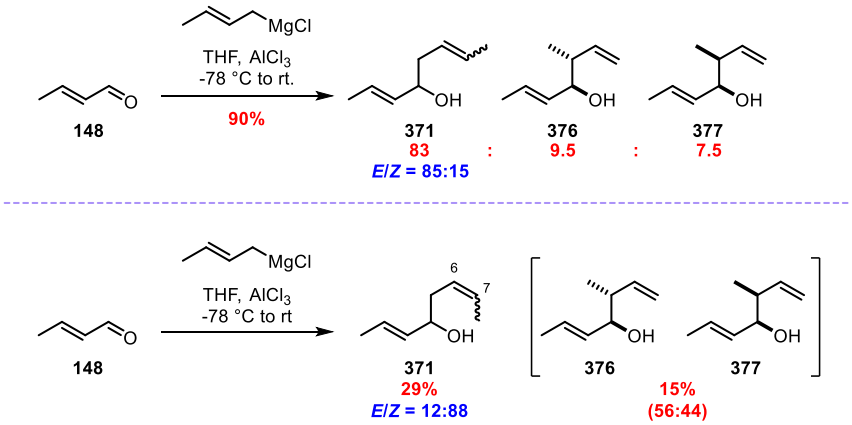
Scheme 88. Proposed synthesis of silyl ether **327** (top) and model system for Prins cyclisation (bottom).

Initial attempts to synthesise alcohol **371** from carboxylic acid **373** were unsuccessful (Scheme **89**). We anticipated that addition of propenyl magnesium bromide to aldehyde **375** would afford alcohol **371** as a racemate. Whilst reduction of carboxylic acid **373** afforded the primary alcohol **374** in 64% yield, we were unable to isolate aldehyde **375** after oxidation due to both degradation and volatility of the product. After attempting various oxidation conditions including DMP, Swern, and Ley-Griffith, we opted to explore alternative routes to alcohol **371**.



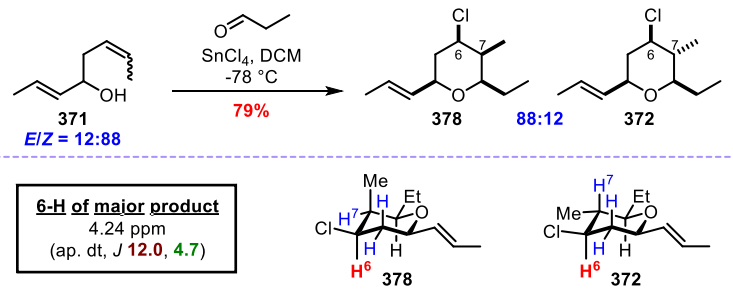
Scheme 89. Unsuccessful synthesis of alcohol **371**.

In 1983, Yamamoto and co-workers reported the synthesis of alcohol **371** as a mixture with the two γ-adducts **376** and **377** in 90% yield by addition of crotylmagnesium chloride to crotonaldehyde in the presence of aluminium trichloride (Scheme **90**).[252] To our surprise, when we conducted the reaction under the Yamamoto conditions, alcohol **371** was isolated in only 29% yield alongside an inseparable mixture of alcohols **376** and **377** in 15% yield. Most striking was the apparent preferential formation of the *Z*-alkene in **371**, with only 12% of the desired *E*-alkene observed. The alkene geometry of the major isomer of **371** was determined by analysis of the ^{1}H-NMR, where a $^{3}J_{7H\text{-}6H}$ coupling of 10.9 Hz was consistent with a *Z*-geometry. In the research reported by Yamamoto *et al*., the product ratio was determined by gas-liquid chromatography (GLC) with no discussion of how double bond configuration was established. It is possible that the configuration of the alkene was assumed to be retained from *E*-crotylmagnesium chloride when in fact isomerisation occurs under the reaction conditions.



Scheme 90. Selective crotylation of crotonaldehyde **148** reported by Yamamoto *et al*. (top) and by us (bottom).

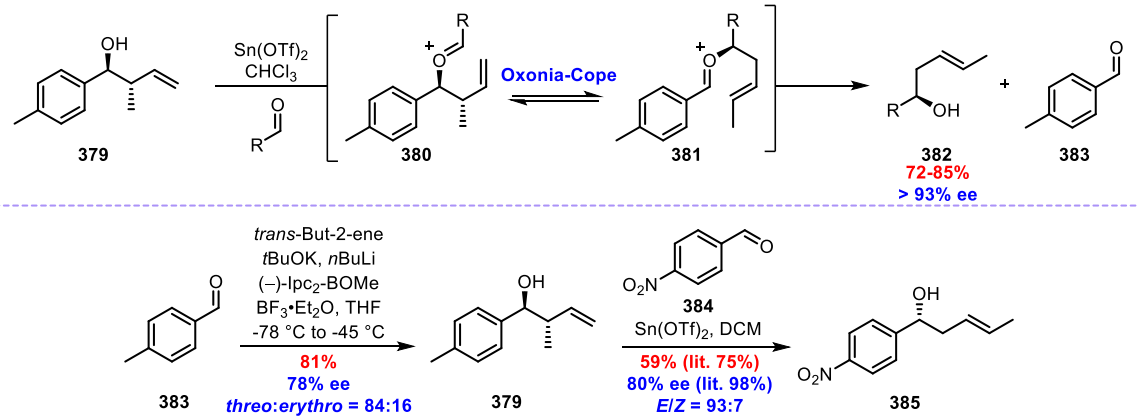
Nevertheless, alcohol **371** was taken forward to the Prins cyclisation with propanal and afforded a mixture of THPs **378** and **372** in 79% yield (Scheme **91**). The structure of the major product **378** was confirmed by analysis of the ^{1}H-NMR spectrum, where only one large $^{3}J_{ax\text{-}ax}$ coupling constant of 12.0 Hz was observed for 6-H. It is expected that **372**, the corresponding C-7 epimer of **378**, would exhibit two $^{3}J_{ax\text{-}ax}$ coupling constants for 6-H. This provided further support for our structural assignment of the major product in the crotylation of **148** as ***Z*-371**. At this stage we were confident that the Prins cyclisation of homoallylic alcohol **369** with propanal would provide the desired THP **370** (Scheme **88**, page **87**). We therefore turned our attention to investigating whether alcohol **369** could be prepared by crotylation of α,β-unsaturated aldehyde **368**.



Scheme 91. Prins cyclisation of homoallylic alcohol **371** (top) and analysis of coupling constants for 6-H in the ^{1}H-NMR of the major product (bottom).

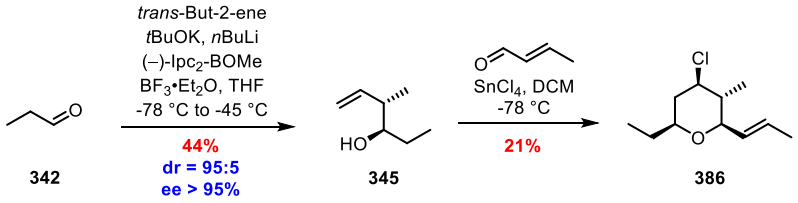
Although we were able to successfully access homoallylic alcohols **363** and **364** by employing the Nokami crotylation (Scheme **87**, page **86**), it was unclear as to whether these conditions would be amenable to α,β-unsaturated aldehydes such as **368**, as a literature search returned no examples of the Nokami crotylation with such molecules. Indeed, attempts to perform the Nokami crotylation with both crotonaldehyde and tiglic aldehyde were unsuccessful, returning unreacted starting materials. We hypothesised that in both cases, the corresponding oxocarbenium ion **352** does not undergo the required oxonia-Cope rearrangement due to increased stabilisation by the adjacent alkene (Scheme **85**, page **85**).

In 2009, Kocovsky *et al*. reported the asymmetric allyl transfer of a variety of aliphatic and aromatic aldehydes (Scheme **92**).[253,254] Although this methodology was not applied to α,β-unsaturated aldehydes, we were encouraged by the impressive results achieved for aromatic aldehydes. In a similar manner to the Nokami crotylation, this methodology relies on the relative stability of the two oxocarbenium ions **380** and **381** to induce a net allyl transfer to generate the desired homoallylic alcohols. We found that reaction of aldehyde **384** with homoallylic alcohol **379**, synthesised *via* Brown allylation of *p*-tolualdehyde **383**, afforded homoallylic alcohol **385** (Scheme **92**).[255] However, the reaction proved unsuccessful with both crotonaldehyde and tiglic aldehyde. At this stage due to the apparent issues with accessing homoallylic alcohol **369** *via* crotylation of α,β-unsaturated aldehyde **368**, this route towards the THP ring in **327** was not explored further.



Scheme 92. Lewis acid-catalysed allyl transfer methodology developed by Kocovsky *et al*. (top) and synthesis of homoallylic alcohol **385** (bottom).[253]

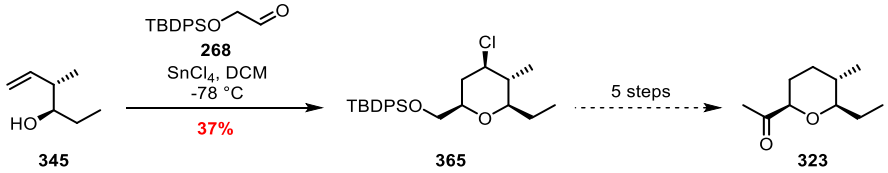
Having explored the synthesis of THP **340** through the Prins cyclisation of propanal with homoallylic alcohols, next the alternative Prins cyclisation was investigated (Scheme **84**, page **84**). As previously discussed, we proposed that the THP ring in sulfone **331** could be constructed *via* cyclisation of homoallylic alcohol **345** with various aldehydes. The required homoallylic alcohol **345** for the envisaged Prins cyclisation was synthesised in 44% yield (dr > 95:5) by Brown crotylation of propanal (Scheme **93**).[255] Derivatisation of the primary alcohol as the Mosher's ester and subsequent analysis of the ^{1}H-NMR data indicated homoallylic alcohol **345** was formed in > 95% ee.



Scheme 93. Synthesis of homoallylic alcohol **345** and subsequent Prins cyclisation with crotonaldehyde.

Reaction of homoallylic alcohol **345**, crotonaldehyde and $SnCl_4$ in DCM at -78 °C gave a complex mixture from which THP **386** was isolated in 21% yield by column chromatography (Scheme **93**). Although we had deemed it preferable to preinstall the trisubstituted olefin into the side chain of the aldehyde, this initial study indicated the Prins cyclisation may not be amenable to the required substrates. As a result, alternative aldehydes were investigated to access THP **340**.

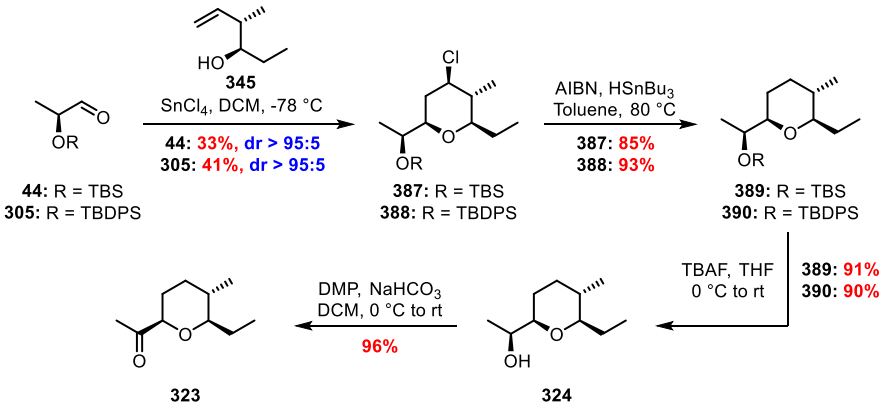
Homoallylic alcohol **345** underwent Prins cyclisation with aldehyde **268** to give THP **365** albeit in only 37% yield (Scheme **94**). The low yield was attributed to a competing oxonia-Cope rearrangement to generate the more stable internal alkene.[256] This undesired pathway has been reported to be detrimental to both the yield and selectivity of the Prins cyclisation and has been widely studied by the groups of Willis and Rychnovsky.[257–259]



Scheme 94. Prins cyclisation of homoallylic alcohol **345** and aldehyde **268**.

As previously discussed, conversion of silyl ether **365** to the desired ketone **323** would require several synthetic steps. Hence, the Prins cyclisation between homoallylic alcohol **345** and aldehyde **44** was investigated to shorten the synthetic route to ketone **323** (Scheme **95**). Pleasingly, the proposed Prins cyclisation of homoallylic alcohol **345** with aldehyde **44** afforded THP **387** in 33% yield as a single diastereoisomer after purification. Due to concerns about the lability of the TBS group, the reaction was repeated with aldehyde **305** containing a TBDPS protected alcohol. This modification resulted in an improved yield of 41%. In both cases, analysis of the crude products by ^{1}H-NMR spectroscopy

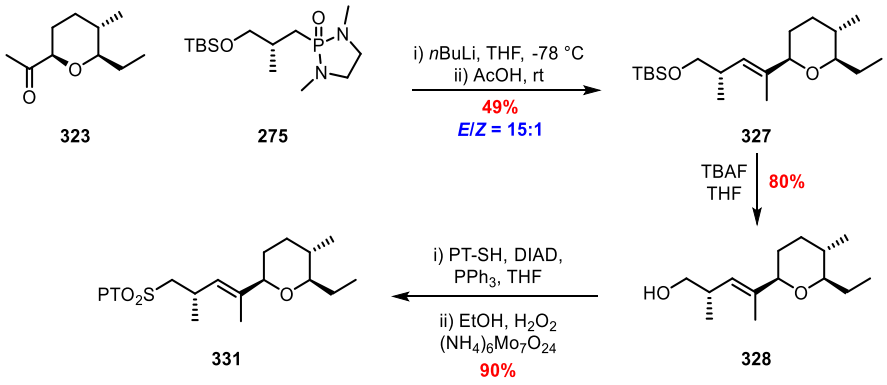
provided evidence for the formation of side-products resulting from the oxonia-Cope rearrangement, however, these side-products were not isolated and characterised.[259] Further optimisation of the protecting group or reaction conditions may result in improved yields for the Prins cyclisation. Nevertheless, as the desired THP ring was constructed rapidly and with excellent stereocontrol, a yield of 41% was deemed acceptable at this stage.



Scheme 95. Synthesis of ketone **323** *via* Prins cyclisation of aldehydes **44** and **305**.

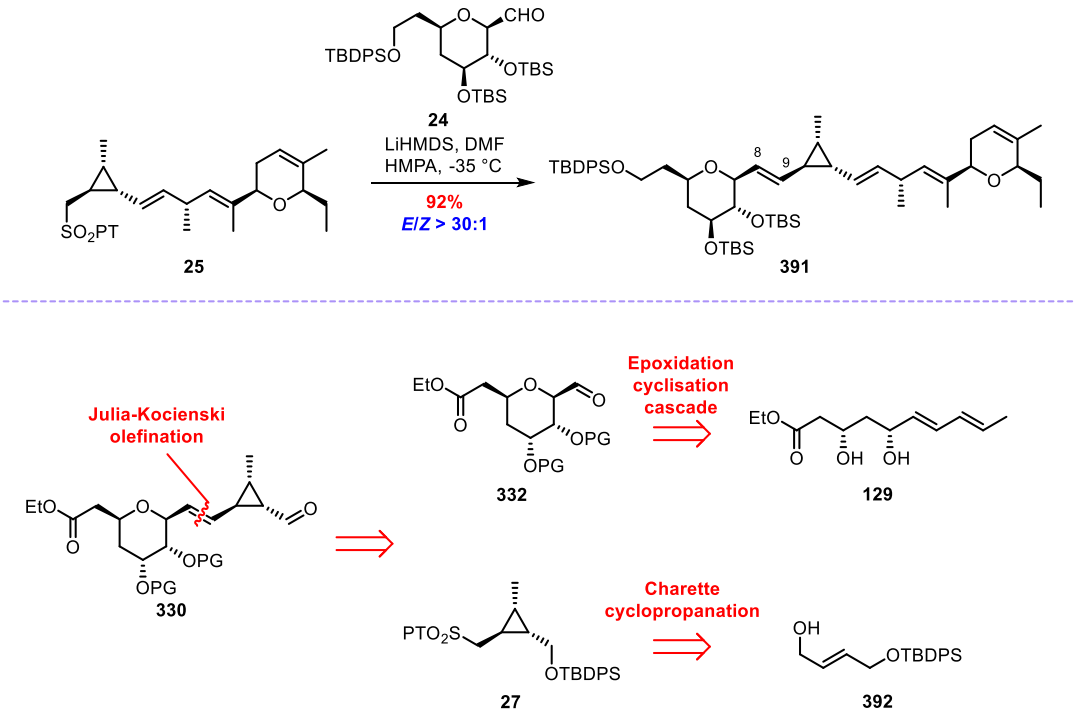
Both alkyl chlorides **387** and **388** were converted to the desired ketone **323** through a sequence of reductive dehalogenation, silyl deprotection, and finally oxidation of the secondary alcohol with DMP. Overall, this new route provided ketone **323** in 27% yield over 6 steps in the LLS (7 steps total) from L-ethyl lactate. This was a significant improvement from the previous route discussed in section **3.3.1** which employed an asymmetric hydrogenation to access ketone **323** in 18% yield over 8 steps in the LLS (10 steps total). With a robust route to ketone **323** developed, we turned our attention to completing the synthesis of 20,21-dihydroambruticin F.

As previously outlined in section **3.3.1**, ketone **323** was reacted with the lithium anion of phosphorus diamide **275** to give alcohol **328** in 39% yield following silyl deprotection (Scheme **96**). Finally, the alcohol in **328** was converted to the corresponding phenyl tetrazole sulfone in 90% yield by a Mitsunobu reaction and subsequent oxidation of the intermediate sulfide. A greatly improved yield was achieved for this transformation when compared with the same sequence performed for the conversion of the corresponding DHP of **328** in the total synthesis of ambruticin J, where undesired alkene epoxidation proved problematic (Chapter **2**, Section **2.3.4**, Scheme **70**, page **67**). With the sulfone fragment **331** synthesised, the construction of aldehyde **330** required for the proposed Julia-Kocienski olefination was investigated (Scheme **82**, page **83**).



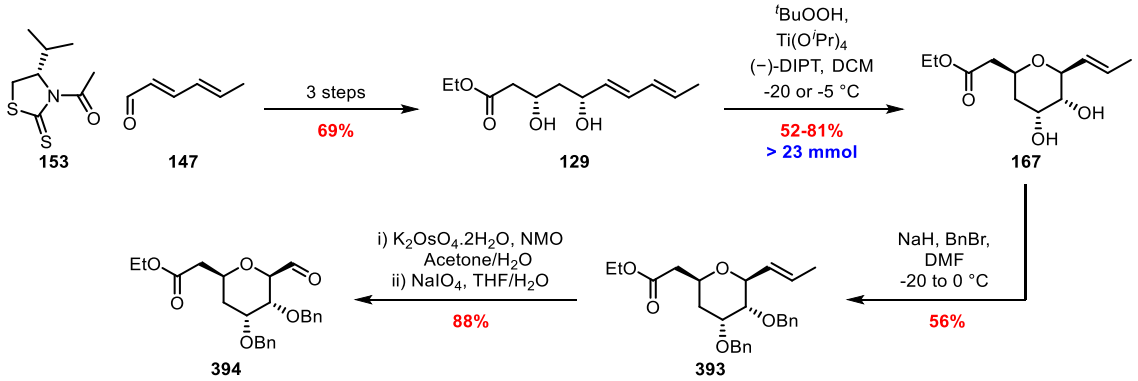
Scheme 96. Synthesis of phenyl tetrazole sulfone **331**.

In 2001, Jacobsen *et al*. published a total synthesis of ambruticin S in which the 8,9-alkene was assembled *via* a Julia-Kocienski olefination between sulfone **25** and aldehyde **24** (Scheme **97**). We proposed that aldehyde **330** could be accessed by a similar olefination between aldehyde **332** and sulfone **27**. Aldehyde **332** would be synthesised from dihydroxy ester **129** through the bioinspired epoxidation-cyclisation cascade previously developed in section **2.3.1** of chapter **2** (Scheme **97**). While a number of protecting groups could be employed for the diol in THP **332**, it was essential they would be stable to conditions that would later be used to deprotect the primary TBDPS ether. Finally, we planned to explore whether a Charette cyclopropanation of allylic alcohol **392** could be utilised to access sulfone **27**.



Scheme 97. Julia-Kocienski olefination by Jacobsen (top) and our retrosynthetic analysis of aldehyde **330** (bottom).[81]

As outlined in section **2.3.1** of chapter **2**, dihydroxy ester **129** was synthesised in 69% yield over 3 steps from acylated thiazolidinethione auxiliary **153** and aldehyde **147** (Scheme **98**). Previously we found that Sharpless asymmetric epoxidation of **129** with *in situ* 6-*endo* cyclisation afforded THP **167** in 52% yield on a 0.25 mmol scale. Further optimisation of the conditions led to an increased 81% yield of the desired THP **167** on a 0.44 mmol scale. Important changes included increasing the loading of titanium isopropoxide and (−)-DIPT from both 0.12 eq. to 0.2 and 0.3 eq. respectively, alongside performing the reaction at -20 °C overnight as opposed to -5 °C for 5 hours. Furthermore, on a 0.44 mmol scale we noted that the order of addition for the reagents did not significantly impact the outcome of the reaction. Finally, quenching the reaction with an aqueous solution of $FeSO_4$ and citric acid instead of a 10% aqueous tartaric acid solution resulted in less emulsion during the work-up.

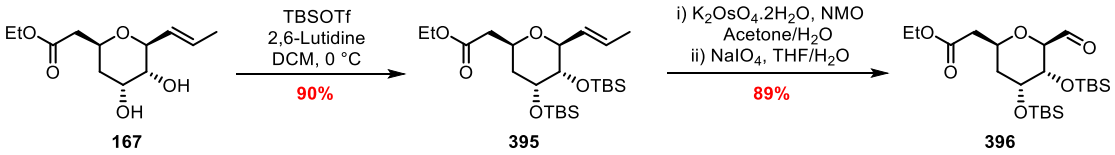


Scheme 98. Bioinspired synthesis of THP **394**.

However, when the reaction was conducted on a > 10 mmol scale, poor conversion of the starting material to the desired product was observed, resulting in a 48% yield of **167**. A 76% yield (89% based on recovered starting material (BORSM)) was achieved on 23.22 mmol scale by further increasing the equivalents of titanium isopropoxide and (−)-DIPT to 0.5 and 0.6 respectively. While on a < 1 mmol scale the timing and order of reagent addition did not significantly impact the yield of the reaction, upon scale up it was necessary to control these factors to achieve maximum conversion to the product. It proved essential to pre-mix both titanium isopropoxide and (−)-DIPT prior to the addition of dihydroxy ester **129**. The resultant solution also required stirring for 30 minutes before the addition of peroxide (see chapter **4** for detailed procedure).

Initially, the hydroxyl groups in **167** were protected as benzyl ethers as these would be stable to silyl deprotection conditions which would be employed for the liberation of the primary alcohol after the proposed Julia-Kocienski olefination (Scheme **98**). Deprotonation of the diol with 3 eq. of NaH in DMF at -20 °C followed by addition of 2.5 eq. of benzyl bromide afforded only a 56% yield of the bis-protected product **393**. Increasing the equivalents of both benzyl bromide and NaH to 5 eq. or

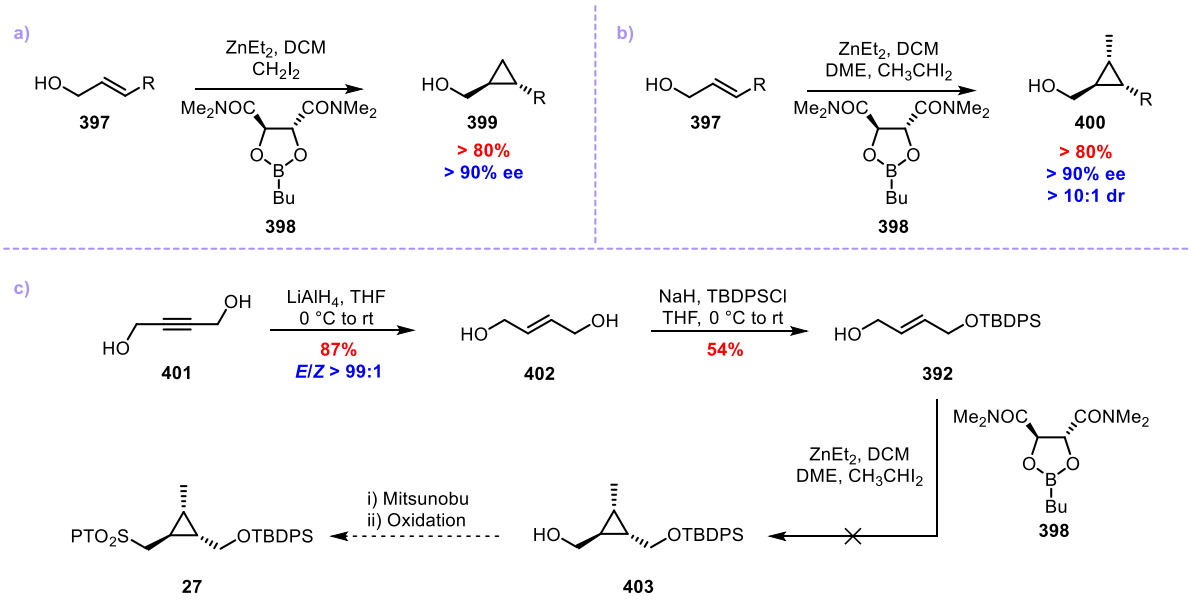
increasing the reaction temperature to 0 °C resulted in a decrease in yield. Triflic acid-catalysed protection with benzyl trichloroacetimidate was also unsuccessful, returning starting diol **167** alongside a mixture of mono-protected products. Although the desired product **393** was readily converted to aldehyde **394** by dihydroxylation of the alkene and cleavage of the resultant diol, the yield for the protection encouraged us to investigate alternative protecting groups. Treatment of **167** with TBSOTf, gave **395** in 90% yield, which underwent dihydroxylation followed by reductive cleavage to afford aldehyde **396** in 45% yield over 7 steps from acylated auxiliary **153**. This bioinspired THP synthesis allowed rapid access to > 11 mmol of the desired aldehyde **396** from commercially available starting materials and reagents.



Scheme 99. Synthesis of aldehyde **396** from diol **167**.

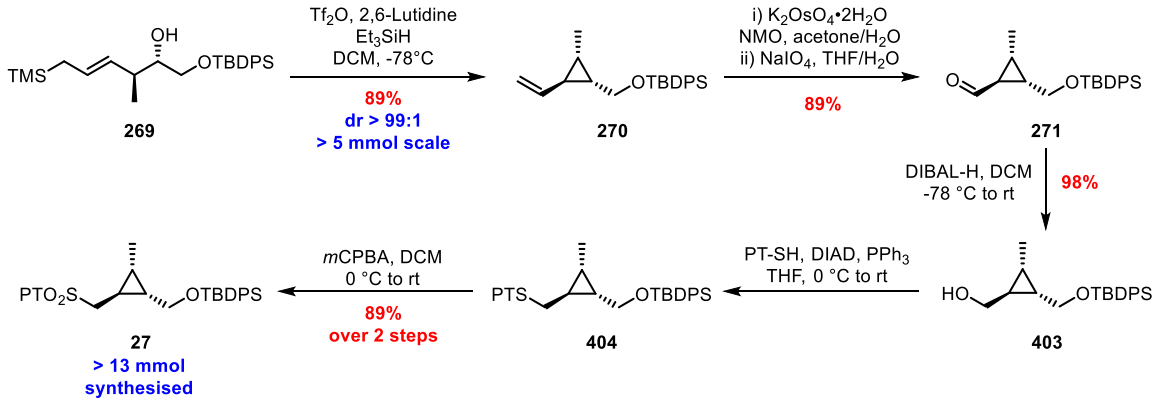
For the synthesis of sulfone **27**, an enantioselective Simmons-Smith cyclopropanation of allylic alcohol **392** was investigated (Scheme **100C**).[260] Charette and co-workers demonstrated that using dioxaborolane ligands in the Simmons-Smith reaction resulted in excellent levels of enantioselectivity during the cyclopropanation of allylic alcohols to generate disubstituted cyclopropanes (Scheme **100A**).[89] It was later reported that trisubstituted cyclopropanes could be accessed with exquisite stereocontrol by employing 1,1-diiodoethane in place of 1,1-diiodomethane (Scheme **100B**).[260]

Although available commercially, allylic alcohol **392** was synthesised in 47% yield from 1,4-butynediol **401** by selective alkyne reduction to form *E*-alkene **402** which was mono-protected as the TBDPS ether (Scheme **100C**). However, no reaction was observed when allylic alcohol **392** was subjected to Charette cyclopropanation conditions where diethyl zinc was added as a 1 M solution in hexane. A survey of the literature revealed that it was commonplace to add diethyl zinc as a neat reagent, with only a handful of examples employing a diluted solution of the reagent. As attempts to source diethyl zinc as a neat solution were unsuccessful, sulfone **27** was prepared from the previously accessed aldehyde **271** (Scheme **101**). In the future, we wish to conduct further investigations into the cyclopropanation of allylic alcohol **392** as this route would provide rapid access to sulfone **27**.



Scheme 100. (a) Charette asymmetric cyclopropanation to disubstituted and (b) trisubstituted cyclopropanes. (c) Proposed synthesis of sulfone **27**.[89,260]

In section **2.3.4** of chapter **2**, the synthesis of aldehyde **271** was described using Taylor's cation rearrangement methodology to construct the cyclopropane ring (Scheme **61**, page **61**).[229] During the course of those studies, it was found that scaling up the cyclopropanation of homoallylic alcohol **269** was accompanied with decreases in either yield or diastereoselectivity. In the total synthesis of ambruticin J reported by Taylor *et al.*, this issue was circumvented through the addition of sub-stoichiometric triethyl silane.[228] Repeating the reaction under these conditions with homoallylic alcohol **269** gave **270** in 89% yield on a > 5 mmol scale whilst maintaining excellent stereocontrol (Scheme **101**). Although Taylor did not indicate the role of triethyl silane in the reaction, it may act as a scavenger to prevent the formation of TMSOTf and therefore the undesired silyl protection of alcohol **269**.

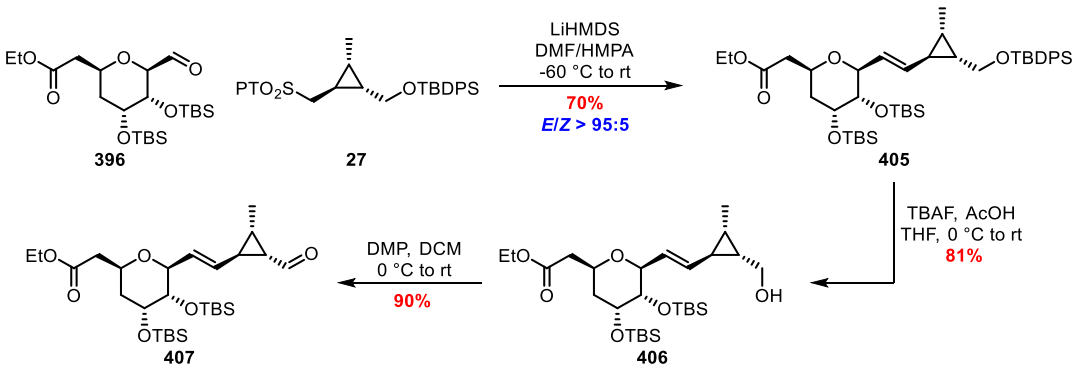


Scheme 101. Synthesis of sulfone **27** from homoallylic alcohol **269**.

Following oxidative cleavage of the alkene, aldehyde **271** was converted to sulfone **27** by reduction to the alcohol, a Mitsunobu reaction, and finally oxidation of the sulfide with *m*CPBA (Scheme **101**). Although oxidation of the intermediate sulfide **404** with molybdate and H_2O_2 in ethanol gave similar yields of sulfone **27**, the reaction was less amenable to scale due to the large quantities of solvent required.[261] Overall sulfone **27** was prepared in 47% yield over 8 steps in the LLS (10 steps total). Although this route required numerous synthetic transformations, all were high-yielding and excellent stereocontrol was achieved in the cyclopropanation step, allowing us to synthesise > 13 mmol of the desired sulfone **27**.

The Julia-Kocienski olefination conditions developed by Jacobsen *et al*. during their total synthesis of ambruticin S were used to unite aldehyde **396** and sulfone **27** (Scheme **102**).[81] While Jacobsen and co-workers reported a 92% yield for the olefination of aldehyde **24** with sulfone **25** with LiHMDS in DMF/HMPA at -35 °C (Scheme **97**, page **92**), we found replicating these conditions resulted in no product formation and a complex ^{1}H-NMR spectrum was observed for the crude material after work-up. A possible competing reaction is the deprotonation of THP **396** at -35 °C, resulting in unwanted reactivity. Pleasingly, by performing the reaction at -60 °C a 70 % yield of solely the *E*-alkene **405** was obtained on a multi-gram scale (Scheme **102**). Furthermore, while Jacobsen indicated the reaction was to be warmed to room temperature immediately after aldehyde addition, we found that it was vital to maintain the reaction at -60 °C for a minimum of one hour to achieve full conversion to the desired product. Alternative bases and solvents were investigated but, in all cases, the desired product was obtained in a lower yield or as a mixture of alkene isomers.

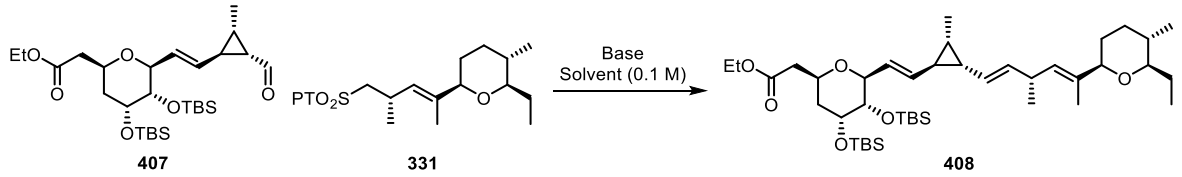
Selective deprotection of the primary silyl ether **405** with acetic acid buffered TBAF afforded alcohol **406** which was readily oxidised with DMP to provide aldehyde **407** in 73% yield over the two steps (Scheme **102**). The next goal was formation of the 13-14-alkene of 20,21-dihydroambruticin F which would set the stage for the end-game transformations towards the proposed biosynthetic intermediate.



Scheme 102. Synthesis of aldehyde **407**.

A screen of Julia-Kocienski olefination conditions was conducted to unite aldehyde **407** and sulfone **331**, and selected results are summarised in table **8**. With greater quantities of aldehyde **407** than sulfone **331** available, most tests were performed with excess aldehyde. Using KHMDS in DME to effect the desired coupling, a set of conditions we had previously utilised in our total synthesis of ambruticin J, the desired product **408** was obtained in a 36% yield as a 10:1 mixture of *E*/*Z* alkene isomers (entry 1).[229] The use of both sodium and lithium bases in a variety of solvents was investigated. NaHMDS in a mixture of THF/HMPA gave a significant increase in yield to 78%, however, it was accompanied by a decrease in selectivity for the *E*-alkene (entry 2). Based on the previous Julia-Kocienski olefination with aldehyde **396** and sulfone **27** (Scheme **102**, page **96**), LiHMDS in DMF/HMPA was used but the conditions gave only a 57% yield of **408** as a 3:1 mixture of isomers (entry 3). Finally, when sulfone **331** was used in excess (1.5 eq. relative to aldehyde **407**), no improvement in either yield or selectivity was observed (entry 4).

From this optimisation, conditions were identified to synthesise alkene **408** in either low yield with excellent stereocontrol (entry 1), or in high yield with poor control of the alkene geometry (entry 2). As the two alkene isomers were inseparable by column chromatography, and it was unclear whether they could be separated later in the synthesis, we proceeded with the conditions that provided alkene **408** as a 10:1 mixture of *E*/*Z* isomers. In an attempt to improve the efficiency of the reaction upon scale up, the equivalents of aldehyde **407** were lowered to 1.2 (entry 5). Pleasingly, a 40% yield was achieved under these conditions, generating 0.34 mmol of alkene **408**.



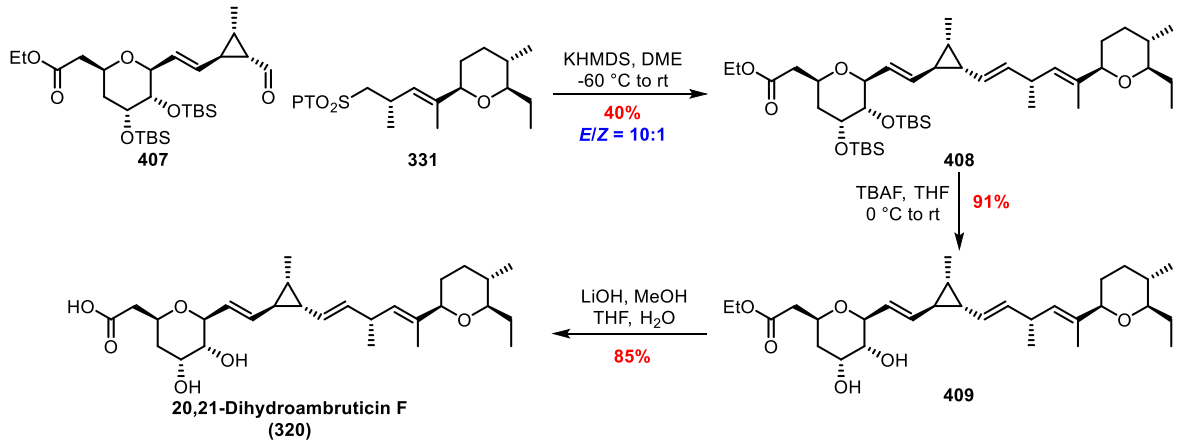
407 **331** **408**

Entry	Base (eq.)	Solvent	Temperature	Eq. of 407	Eq. of 331	Yield (%)[a]	*E*/*Z*[b]
1	KHMDS (1.2)	DME	-60 °C to rt	1.3	1.0	36%	10:1
1	NaHMDS (1.2)	THF/HMPA (4:1)	-78 °C to rt	1.3	1.0	78%	3:1
3	LiHMDS (1.2)	DMF/HMPA (4:1)	-78 °C to rt	1.3	1.0	57%	3:1
4	KHMDS (1.5)	DME	-60 °C to rt	1.0	1.5	34%	10:1
5[c]	KHMDS (1.2)	DME	-60 °C to rt	1.2	1.0	40%	10:1

Table 8. Optimisation of the Julia-Kocienski olefination between aldehyde **407** and sulfone **331**. All reactions performed with 0.05 mmol of the limiting reagent unless otherwise noted. [a]Isolated yields. [b]Determined by ^{1}H-NMR analysis of the product. [c]0.84 mmol of sulfone **331** used.

Having assembled the complete carbon skeleton of 20,21-dihydroambruticin F, the total synthesis was completed by silyl deprotection with TBAF followed by basic hydrolysis of the ethyl ester (Scheme

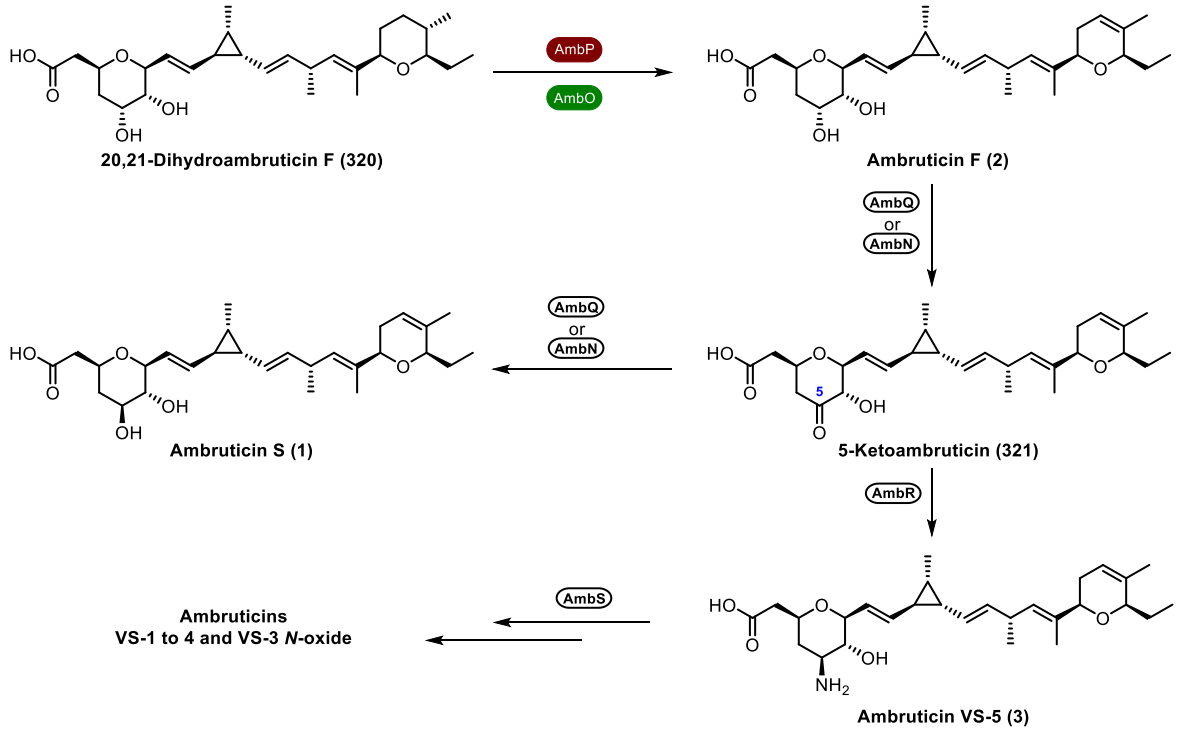
103). Overall, 20,21-dihydroambruticin F (**320**) was prepared using a modular approach in 8% yield in 14 steps over the LLS (37 steps in total). This provided us access to the proposed biosynthetic intermediate **320** for use in bioassays with AmbP and AmbO to investigate DHP ring formation in ambruticin biosynthesis. These studies are currently ongoing in the laboratories of Dr. Luoyi Wang.



Scheme 103. Final transformations for the synthesis of 20,21-dihydroambruticin F.

To confirm the structure of 20,21-dihydroambruticin F and provide definitive proof of its existence as an intermediate in the biosynthesis of the ambruticins, it was desirable to the compare spectral data obtained from our synthetic sample with an authentic sample produced by *Sorangium cellulosum*. Isolation and characterisation of 20,21-dihydroambruticin F from cultures of wild-type *Sorangium cellulosum* would be extremely challenging as the intermediate is proposed to undergo further biotransformations (Scheme **104**).[105] Nevertheless, disruption of the genes in the biosynthetic gene cluster (BGC) of the ambruticins responsible for downstream transformations of 20,21-dihydroambruticin F may result in accumulation of the intermediate and therefore facilitate its isolation.

Indeed, when Xiaotong Zhong and Kaining Gao (researchers in the Wang laboratories) cultured hygromycin (Hyg) resistant *Sorangium cellulosum* So ce10 cells where the genes *ambP-S* had been deleted, HPLC-MS analysis of the culture extracts revealed a new peak with m/z of 476, consistent with the production of 20,21-dihydroambruticin F (Figure **21**). Furthermore, the retention time of this new compound matched that of our synthetic reference of 20,21-dihydroambruticin F. Purification of the new product afforded 20,21-dihydroambruticin F and the spectral data matched that obtained from our synthetic sample, confirming the structure of the biosynthetic intermediate (see chapter **4**, page **223** for detailed comparison). Studies in collaboration with Dr. Luoyi Wang are ongoing to determine the timing and mechanism of DHP ring formation in ambruticin biosynthesis.



Scheme 104. Proposed tailoring of 20,21-dihydroambruticin F in ambruticin biosynthesis.[105]

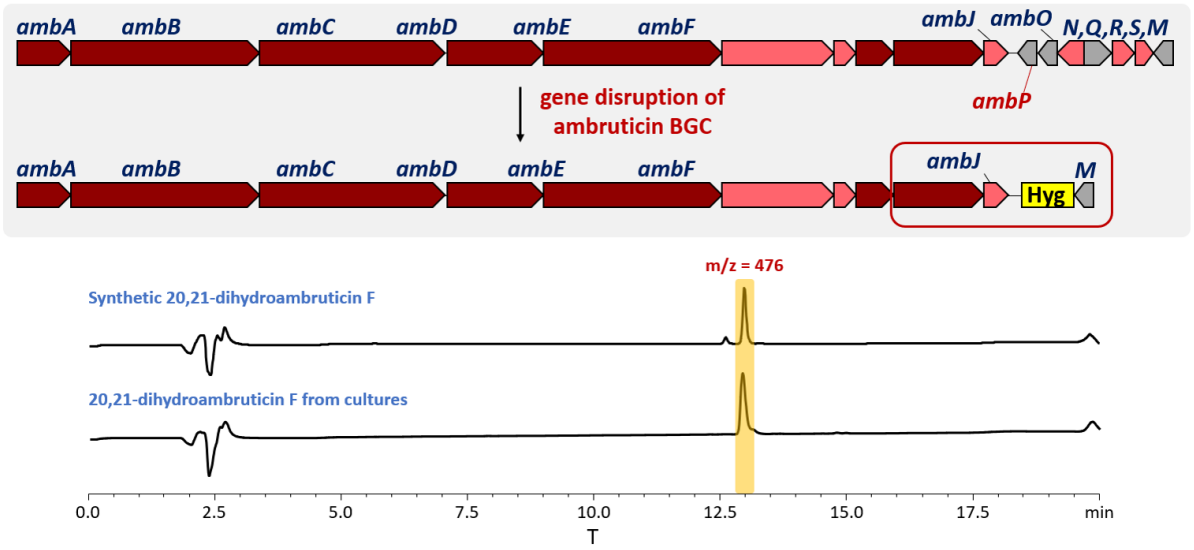
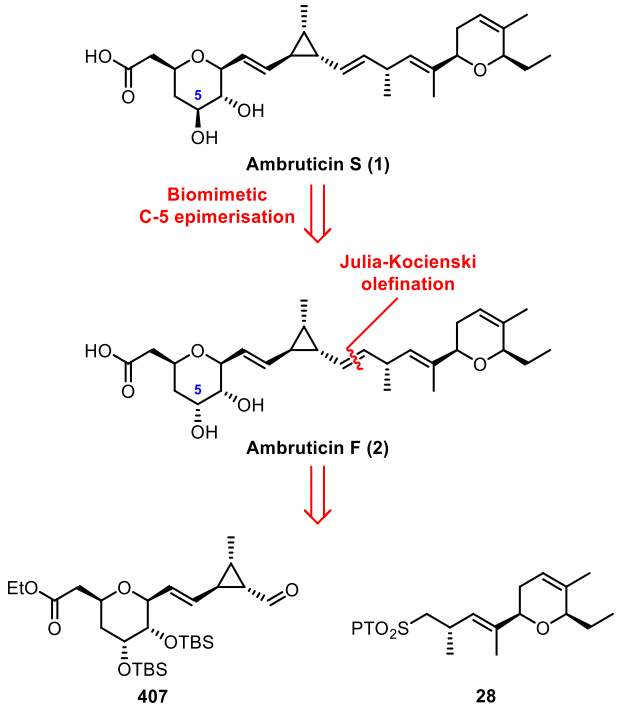


Figure 21. Disruption of genes *ambP-S* in the ambruticin BGC (top) and HPLC traces of 20,21-dihydroambruticin F (bottom).

3.3.3. Total Synthesis of Ambruticin F and S

To aid in the analysis of bioassays of AmbP and AmbO with 20,21-dihydroambruticin F (**320**), a reference of the proposed assay product ambruticin F (**2**) was required. Comparing HPLC traces of the crude assay extracts with the synthetic reference would help identify whether ambruticin F is being formed in bioassays with 20,21-dihydroambruticin F. Furthermore, since full NMR data of ambruticin F have not been reported in the literature, a sample of the natural product will be useful for confirming the structure of the product from bioassays by NMR analysis. In addition, ambruticin F (**2**) is the proposed product of the AmbJ catalysed epoxidation-cyclisation of ambruticin J described in chapter 2, hence **2** will therefore also serve as a synthetic reference to aid the analysis of bioassays being performed with AmbJ and ambruticin J.

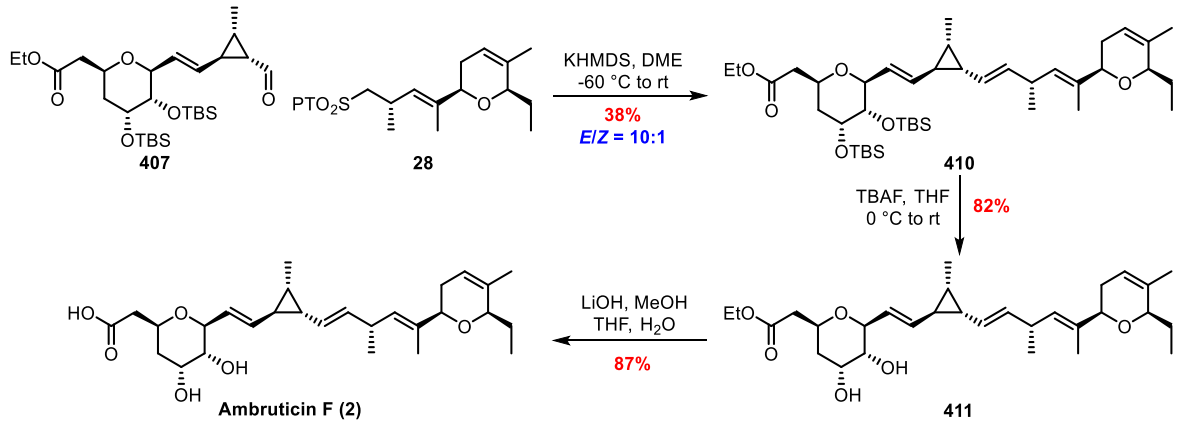
Our synthetic route to 20,21-dihydroambruticin F was to be adapted to prepare ambruticin F, demonstrating the flexibility of the modular approach (Scheme **105**). A Julia-Kocienski olefination between the previously synthesised aldehyde **407** and sulfone **28** would construct the carbon skeleton of ambruticins F and S. To definitively confirm the structure of synthetic ambruticin F, the spectral data obtained would be compared with those obtained from a sample of the natural product isolated from cultures of *Sorangium cellulosum* where the relevant genes in the BGC had been disrupted. Furthermore, the biomimetic total synthesis of ambruticin S from F was to be investigated and the obtained spectral data compared with that reported in the literature for ambruticin S.



Scheme 105. Retrosynthetic analysis of ambruticins S and F.

Using the optimised conditions established previously, Julia-Kocienski olefination between aldehyde **407** and sulfone **28** using KHMDS in DME afforded alkene **410** in 38% yield as a 10:1 mixture of *E*/*Z* isomers (Scheme **106**). As previously established, the yield of the reaction could be significantly improved to 80% at the cost of selectivity (*E*/*Z* = 3:1) through the use of NaHMDS in a mixture of THF and HMPA. This represents an attractive alternative to the lower yielding conditions if control of the alkene geometry is not essential. Deprotection of silyl ether **410** with TBAF in THF followed by saponification of the ethyl ester with LiOH completed the first total synthesis of ambruticin F.

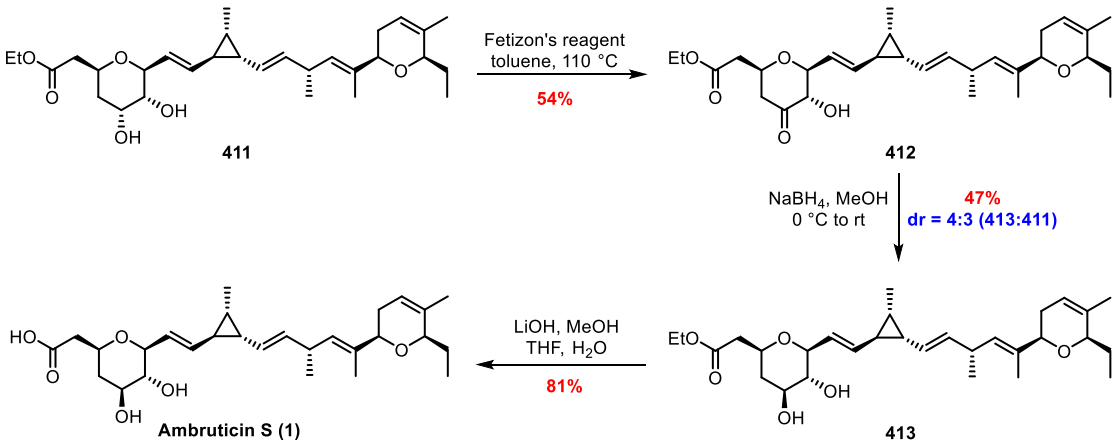
Next, in collaboration with Dr. Luoyi Wang we isolated ambruticin F through engineering the biosynthetic pathway in *Sorangium cellulosum*. Previous studies by Reeves and co-workers demonstrated that disrupting *ambQ* from the ambruticin biosynthetic gene cluster led to accumulation of ambruticin F alongside ambruticin S and the VS series of compounds found in the wild-type strain, potentially due to the function of AmbQ being complemented by AmbN.[105] Wang and co-workers found that fermentation of a *ΔambN-S* mutant strain of *S. cellulosum* So ce10, which was constructed by replacing the continuous region of *ambN*, *ambQ*, *ambR* and *ambS* genes with a hygromycin selection marker, afforded ambruticin F as the major metabolite. The NMR data obtained from purified natural ambruticin F were in excellent agreement with those from the synthetic sample, confirming the structure of the natural product (see chapter **4**, page **230** for detailed comparison). Nevertheless, to provide definitive proof for the structure of our synthetic sample of ambruticin F, the biomimetic conversion of ambruticin F to ambruticin S was investigated.



Scheme 106. Synthesis of ambruticin F.

Attempts to oxidise the 5-hydroxyl of diol **411** with DMP were problematic, with yields varying dramatically and never exceeding 33% (Scheme **107**). The low yield for the desired product alongside the inability to recover starting material may be due to undesired oxidative cleavage of the vicinal diol, a process which is known to be promoted by DMP.[262] Nevertheless, diol **411** underwent selective oxidation with Fetizon's reagent (Ag_2CO_3 on celite) to generate 5-ketoambruticin ethyl ester (**412**) in

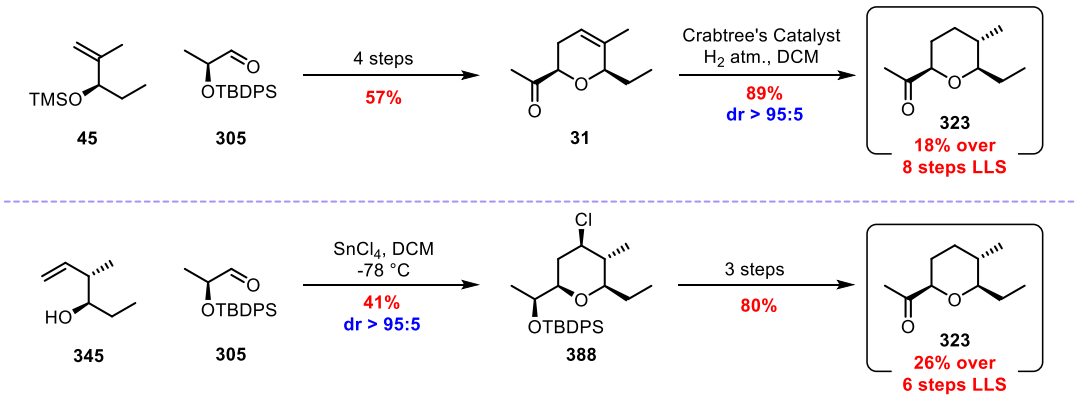
54% yield.[242] Reduction of ketone **412** with sodium borohydride in methanol gave a separable mixture of alcohol epimers **413** and **411** in 47% and 35% yield respectively. Finally, hydrolysis of ethyl ester **413** gave ambruticin S (**1**), with spectral data consistent with those reported for the natural product in the literature (see chapter **4**, page **237** for detailed comparison). As a result, since we accessed ambruticin S from the ethyl ester of ambruticin F, we can be confident of the assignment of the structure of ambruticin F.



Scheme 107. Biomimetic synthesis of ambruticin S from the ethyl ester of ambruticin F.

3.4. Conclusions and Future Work

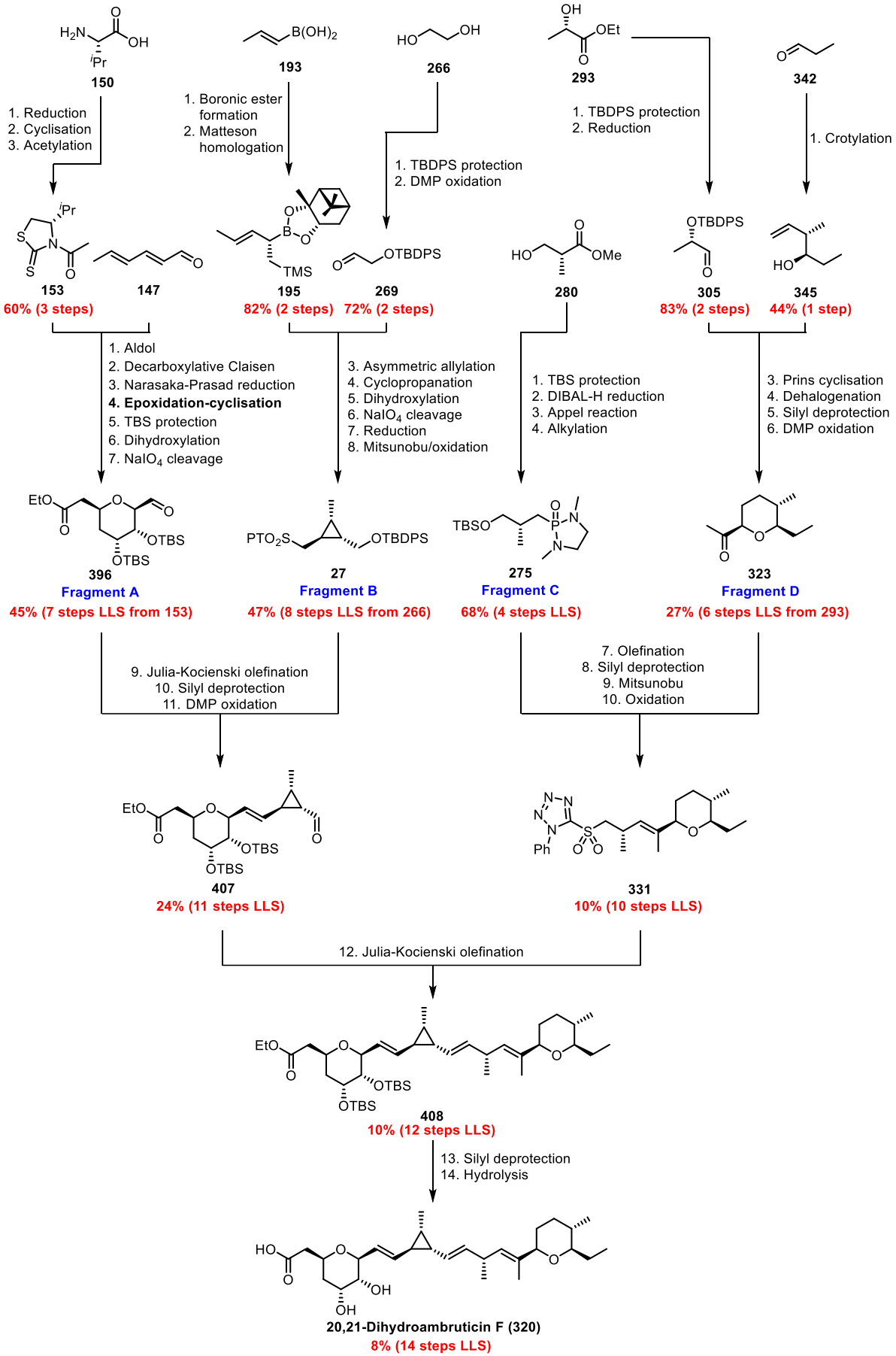
Towards the goal of understanding DHP ring formation in ambruticin biosynthesis, two synthetic routes to the THP ring in 20,21-dihydroambruticin F (**320**) have been developed. The first strategy employs an asymmetric hydrogenation of DHP **31** with Crabtree's catalyst, whilst the second approach rapidly assembles the desired ring with excellent stereocontrol through a Prins cyclisation between homoallylic alcohol **345** and aldehyde **305** (Scheme **108**). Alternative Prins cyclisations for the construction of the THP were also investigated and in the future will be explored in more detail to further improve the synthesis of THP **323**.



Scheme 108. Synthesis of THP **323** *via* asymmetric hydrogenation (top) and Prins cyclisation (bottom).

In collaboration with Dr. Luoyi Wang, 20,21-dihydroambruticin F (**320**) was isolated through gene-knockout experiments with *Sorangium cellulosum*. The first total synthesis of 20,21-dihydroambruticin F (**320**) was completed to confirm its structure and provide further quantities of the biosynthetic intermediate for subsequent bioassays (Scheme **109**). Overall, 20,21-dihydroambruticin F (**320**) was synthesised in 8% yield over 14 steps in the LLS where a key component of the route was a bioinspired epoxidation-cyclisation cascade to generate the THP ring of the ambruticins. In future, in an attempt to optimise our synthetic route to the ambruticins, the Charette cyclopropanation for the formation of the trisubstituted cyclopropane ring **27** will be investigated further (Scheme **109**).

To aid the analysis of bioassays of 20,21-dihydroambruticin F with AmbP and AmbO, our modular route was adapted to complete the first total synthesis of ambruticin F (**2**), the proposed assay product. These bioassays are underway in collaboration with Dr. Luoyi Wang. Furthermore, ambruticin F and 20,21-dihydroambruticin F were isolated from cultures of the *ΔambN-S* and *ΔambP-S* mutant strains of *S. cellulosum* respectively. Finally, the total synthesis of ambruticin S was completed through a biomimetic epimerisation of the 5-hydroxyl of ambruticin F. Having developed a robust and modular route, in future, analogues of the ambruticins could be prepared to study SAR in an effort to improve antifungal activity and other biological properties.



Scheme 109. Summary of our total synthesis of 20,21-dihydroambruticin F (**320**).

CHAPTER 4:

Experimental

4.1 General Experimental

All reactions were carried out using standard Schlenk syringe-septa techniques in flame dried glassware under a positive pressure of nitrogen in anhydrous solvents unless otherwise stated. Reagents and solvents were purchased from commercial suppliers and used without further purification unless reported. Anhydrous THF, Et_2O, hexane, DCM, toluene and MeCN were dried by passing through a modified Grubbs system of alumina columns and stored under nitrogen. MeOH, EtOH, EtOAc, DIPEA and TEA were dried by distillation from calcium hydride and stored under nitrogen and over 3 Å molecular sieves. Degassed solvents were prepared by freeze-pump-thaw cycling under nitrogen or by sparging with nitrogen.

Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} analytical plates and were developed using UV fluorescence (254 nm) or $KMnO_4$ / Δ. Flash column chromatography was carried out on Sigma Aldrich silica gel 60 Å (43-63 µm) and an organic solvent system as stated.

Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer spectrum 2 with selected peaks of interested reported as absorption maxima (cm^{-1}). Mass spectrometry (MS) and High-resolution mass spectrometry (HRMS) were performed by the University of Bristol mass spectrometry service using electrospray ionisation (ESI) on a Bruker microOTOF II (TOF) or atmospheric pressure chemical ionisation (APCI) on a Thermo Scientific Orbitrap Elite (LC-Orbitrap). Optical rotation was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter and is quoted in (° ml)(g dm)$^{-1}$. Melting points of solid products were recorded on a Stuart MP20.

NMR spectra were recorded on Varian 400-MR (400 MHz), Jeol ECS400 (400 MHz), Jeol ECZ400 (400 MHz), JeolVAR ECZ400 (400 MHz), BrukerNano400 (400 MHz), Bruker Avance III HD 500 Cryo (500 MHz), Bruker Neo 600 Cryo (600 MHz), and Bruker Avance III HD Cryo700 (700 MHz) spectrometers at ambient temperature. Spectra were recorded in deuterochloroform referenced to residual $CHCl_3$ (^1H, 7.26 ppm; ^{13}C, 77.2 ppm), deuterated methanol referenced to residual CD_2HOD (^1H, 3.30 ppm; ^{13}C, 49.0 ppm) or deuterated acetone referenced to residual $(CD_3)(CD_2H)CO$ (^1H, 2.09 ppm; ^{13}C, 30.6 ppm). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to describe multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), br. (broad), ap. (apparent). COSY, HMBC, and HSQC NMR spectra were routinely used to definitively assign the signals of ^1H and ^{13}C NMR spectra. For clarity, the numbering of atoms does not correspond to the compound names. X-ray diffraction experiments were performed and structure solved by Dr. H. A. Sparks and Dr. N. E. Pridmore at the University of Bristol.

4.2 Protein Expression, Enzymatic Assays, and Gene-Knockout Experiments

4.2.1. General Experimental Procedures

Size exclusion column chromatographic separations were carried out by using Sephadex LH-20 (Cytiva) as packing materials. LC-MS data were obtained on a SHIMADZU LCMS system comprising SHIMADZU SIL-20A autosampler, SHIMADZU LC-20AD HPLC pump, SHIMADZU SPD-M40 Diode Array detector and SHIMADZU LCMS-2010 mass spectrometer. HPLC grade H_2O and MeCN were added with 0.1% formic acid as solvent system. Analytical LC-MS data were obtained using a Phenomenex Kinetex column (C18, 150 × 4.60 mm, 5 µm) at a flow rate of 1 mL/min. Preparative HPLC purification were carried out using a SilGreen column (C18, 250 × 10 mm, 5 µm) at a flow rate of 4 mL/min. The work described in sections **4.2.2 - 4.2.7** was performed by Dr. Luoyi Wang.

4.2.2. AmbJ Protein Expression and Purification:

A plasmid encoding for AmbJ was transformed into *E. coli* BL21 (DE3) cells and these cells were gown overnight on an agar plate at 37 °C. One colony was picked and added to 20 mL of LB medium inoculated with kanamycin. The pre-culture was incubated at 37 °C/200 rpm overnight. The pre-culture was added to 1 L of auto induction medium and shaken at 37 °C/200 rpm until the optical density at 600 nm reached 0.6 (roughly 3 hours). The culture was then shaken at 18 °C/200 rpm overnight (for whole cell biotransformation, see section **4.2.3**).

The cells were harvested by centrifugation (4 °C/6000 rpm for 15 min) and resuspended in buffer A (50 mM Tris/HCl pH 7.5, 150 mM NaCl). The cells were lysed by sonication (6 × 10 s pulsed cycle) on ice, and the debris was removed by centrifugation (4 °C/15000 rpm for 30 min). The clarified supernatant was loaded onto a pre-equilibrated Ni-NTA agarose column, which was then washed with a gradient of buffer B (50 mM Tris/HCl pH 7.5, 150 mM NaCl, 1 M imidazole). Fractions containing the target protein of interest, as established by monitoring the absorbance of the column eluent at 280 nm followed by SDS-PAGE analysis, were pooled and concentrated. Concentrated protein samples were subjected to Superdex 75 or 200 size exclusion column for further purification, eluted with Buffer A to yield final protein samples with > 95% purity.

4.2.3. Whole-Cell Biotransformations with AmbJ:

50 mL of overnight culture of *E. coli* BL21 (DE3) cells overexpressing AmbJ were centrifuged at 6000 rpm for 5 min. Cell pellets were resuspended in 2 mL of 100 mM potassium phosphate buffer pH 7.2 supplemented with 20 mM glucose. Substrates dissolved in 50 µL of MeOH were then added and the reactions were incubated at 30 °C, 200 rpm for overnight. As negative controls, substrates were incubated with blank *E. coli* BL21 (DE3) cells.

Reactions were quenched by adding equal volume of acetonitrile, vortexed and centrifuged. The acetonitrile layer was injected for HPLC-MS analysis. The aqueous layer was dried *in vacuo*, resuspended in acetonitrile, and injected for HPLC-MS analysis.

4.2.4. *In Vitro* Enzymatic Assays with AmbJ:

Reaction mixture contains 0.5 mg/mL AmbJ, 100 µM FAD, 5 mM NADH, 100 µM substrates at the final volume of 200 µL in buffer A. The mixture was incubated at 30 °C in water for 12 hours in the plastic tube with the lid open for air supplementation. To analyse the products, the reaction mixture was extracted with EtOAc (3 × 300 µL). The combined extracts were dried by a sample concentrator and then dissolved in 200 µL of methanol for HPLC-MS analysis.

4.2.5. Gene Disruption in *Sorangium cellulosum* So ce10:

A plasmid containing the hygromycin selection marker flanked by the upstream and downstream fragments of the target gene or region was constructed and introduced into *Sorangium* cells *via* electroporation. Double crossover clones with the target gene or region replaced by the antibiotic selection marker were screened by PCR on HS agar (0.15% Casitone, 0.1% KNO_3, 0.1% $MgSO_4 \cdot 7H_2O$, 0.008% Fe-EDTA, 0.4% glucose, 0.0075% $CaCl_2 \cdot 2H_2O$, 0.00625% K_2HPO_4, 1.5% agar) containing 100 µg/mL of hygromycin.

4.2.6. Fermentation Procedure for Mutant Strains of *Sorangium cellulosum* So ce10:

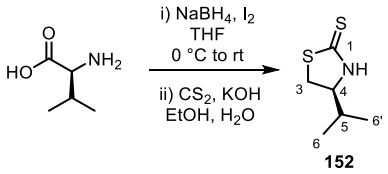
Mutant strains of *Sorangium cellulosum* So ce10 were inoculated on HS agar plates and incubated 3 days at 30 °C. Seed medium was inoculated in a 500 mL flask with 100 mL of liquid HS medium by scrape colonies from the HS agar plate and incubated 2-3 days at 220 rpm at 30 °C. Production fermentation was inoculated with 20% of seed culture in SF1-P medium (0.3% soy peptone, 0.6% fructose, 0.1% $MgSO_4 \cdot 7H_2O$, 0.1% $CaCl_2 \cdot 2H_2O$, 0.008% ferric citrate and 0.05 M HEPES, pH 7.6). Ferric citrate and HEPES were filter sterilized and added after autoclaving. The culture was incubated at 30°C at 220 rpm for 7 days and supplemented with 0.5 g/L of fructose every 48 hours, and then extracted with EtOAc for three times. The combined EtOAc extracts were evaporated in vacuo to give a crude extract, which was subjected to LC-MS analysis or further purification.

4.2.7. Isolation and Purification of Ambruticin F and 20,21-Dihydroambruticin F

A 2.0 L scale fermentation of *ΔambP-S* mutant of *Sorangium cellulosum* So ce10 was carried out as per the general procedure described above. The crude extract was purified by Sephadex LH-20 column chromatography eluting with MeOH to give a crude 20,21-dihydroambruticin F fraction, which was further purified by HPLC eluting with a gradient of 70 to 95% MeCN in water over 20 min to yield 20,21-dihydroambruticin F (7 mg). Ambruticin F was isolated from the fermentation of *ΔambN-S* mutant of *Sorangium cellulosum* So ce10 using a similar purification protocol at a yield of 2 mg/L.

4.3 Synthetic Procedures

(*S*)-4-Isopropylthiazolidine-2-thioneacid (152)



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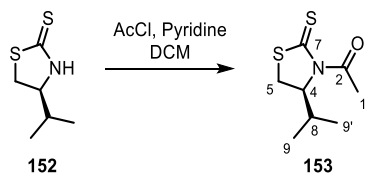
L-Valine (8.03 g, 68.3 mmol) was dissolved in THF (180 mL) under nitrogen and cooled to 0 °C then $NaBH_4$ (6.20 g, 163.9 mmol) was added in one portion. After stirring for 5 minutes, iodine (17.30 g, 68.3 mmol) in THF (20 mL) was added dropwise over 20 minutes. The reaction mixture was warmed slowly to room temperature and then refluxed for 24 hours. The reaction mixture was cooled to room temperature and methanol was added until the solution became clear and the solvent was removed *in vacuo*. The crude material was dissolved in 1 M aqueous KOH solution (200 mL) and stirred for 4 hours then the solution was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford L-valinol (5.31 g, 75%) as a colourless oil. The crude product was dissolved in ethanol (17 mL) then CS_2 (7.85 mL) was added. KOH (7.64 g, 136.1 mmol) in water/MeOH 1:1 (50 mL) was added by an addition funnel over 20 minutes. The reaction mixture was refluxed for 3 days before being cooled to room temperature and the solvent removed *in vacuo*. The solution was dissolved in 2 M HCl (30 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford **152** (6.50 g, 80%) as a yellow solid; $[\alpha]_D^{23}$ = -41.0 (*c* 1, $CHCl_3$), lit.[263] $[\alpha]_D^{20}$ = -35.9 (*c* 1, $CHCl_3$); ν_{max} (UATR) 3176, 2960, 2869, 1661, 1482, 1268, 1029, 977; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, 6-H_3), 1.03 (3H, d, *J* 6.8, 6'-H_3), 1.92 – 2.02 (1H, m, 5-H), 3.31 (1H, dd, *J* 11.1, 8.4, 3-*H*H), 3.50 (1H, dd, *J* 11.1, 8.2, 3-H*H*), 4.01 – 4.08 (1H, m, 4-H), 8.22 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 18.4 (C-6), 19.0 (C-6'), 32.2 (C-5), 36.2 (C-3), 70.2 (C-4), 201.3 (C-1); m/z (ESI): $[M+H]^+$ = 175.1. Data consistent with the literature.[263]

(*S*)-1-(4-Isopropyl-2-thioxothiazolidin-3-yl)ethan-1-one (153)



152 **153**

Auxiliary **152** (1.40 g, 8.70 mmol) was dissolved in DCM (35 mL) under nitrogen then AcCl (0.92 mL, 13.0 mmol) was added. Pyridine (1.05 mL, 13.0 mmol) was added dropwise and the reaction mixture was stirred for 2 hours. The reaction mixture was filtered, and the solvent removed *in vacuo*. The

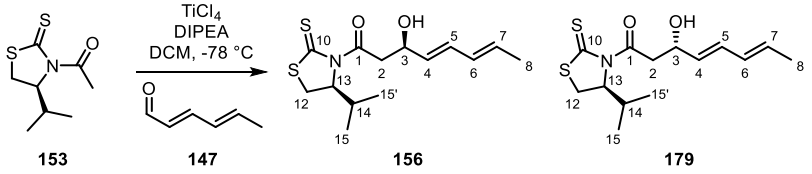
crude material was purified by flash column chromatography (10% EtOAc in petroleum ether 60:40) to afford acylated auxiliary **153** (1.77 g, quant.) as a yellow oil; $[\alpha]_D^{23}$ = +412.0 (*c* 1, $CHCl_3$), lit.[263] $[\alpha]_D^{20}$ = +442.1 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.9, 9-H_3), 1.05 (3H, d, *J* 6.8, 9'-H_3), 2.29 – 2.43 (1H, m, 8-H), 2.76 (3H, s, 1-H_3), 3.02 (1H, dd, *J* 11.5, 1.1, 5-*H*H), 3.50 (1H, dd, *J* 11.5, 8.0, 5-H*H*), 5.11 – 5.17 (1H, m, 4-H); δ_C (101 MHz, $CDCl_3$) 17.9 (C-9), 19.2 (C-9'), 27.1 (C-1), 30.6 (C-8), 30.9 (C-5), 71.4 (C-4), 170.9 (C-2), 203.4 (C-7); m/z (ESI): $[M+H]^+$ = 204.05. Data consistent with the literature.[263]

(2*E*,4*E*)-Hexa-2,4-dienal (147)

147

2*E*,4*E*-Hexa-2,4-dienol (0.34 g, 4.40 mmol) was dissolved in DCM (20 mL) under nitrogen then activated MnO_2 (11.54 g, 133 mmol) was added and the reaction mixture was stirred for 24 hours. The mixture was filtered over Celite, washed with DCM (50 mL) and the solvent removed *in vacuo* to afford volatile aldehyde **147** (0.42 g, quant.) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 1.87 (3H, d, *J* 5.7, 6-H_3), 6.01 (1H, dd, *J* 15.5, 8.0, 2-H), 6.17 – 6.36 (2H, m, 4-H and 5-H), 6.96 – 7.09 (1H, ddd, *J* 15.5, 9.1, 1.1 3-H), 9.49 (1H, dd, *J* 8.0, 1.1, 1-H); δ_C (101 MHz, $CDCl_3$) 19.0 (C-6), 130.0 (C-2), 130.2 (C-4), 142.1 (C-5), 152.8 (C-3), 194.1 (C-1); m/z (ESI): $[M+H]^+$ = 97.06. Data consistent with the literature.[264]

(*R*,4*E*,6*E*)-3-Hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)octa-4,6-dien-1-one (156)



153 **147** **156** **179**

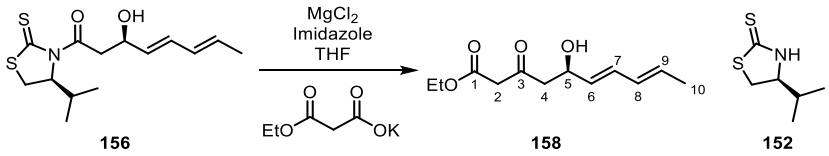
Acylated auxiliary **153** (2.00 g, 9.84 mmol) was dissolved in DCM (100 mL) under nitrogen and cooled to -78 °C then $TiCl_4$ (1 M in DCM, 9.84 mL, 9.84 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 20 minutes then DIPEA (2.10 mL, 11.8 mmol) was added dropwise. The reaction mixture was stirred for 1 hour then aldehyde **147** (1.10 mL, 9.84 mmol) was added dropwise. After stirring at -78 °C for 1 hour, aqueous saturated NH_4Cl (25 mL) was added and the reaction mixture was stirred for a further hour at room temperature. The solution was extracted with DCM (3 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (18% EtOAc in petroleum ether 60:40) to afford aldol products **156** (2.48 g, 84%) and **179** (0.32 g, 11%) as yellow oils.

156: $[\alpha]_D^{25}$ = +182.0 (*c* 1, Acetone); ν_{max} (film) 3430, 2962, 1689, 1468, 1162, 725; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.9, 15-H_3), 1.05 (3H, d, *J* 6.8, 15'-H_3), 1.75 (3H, d, *J* 6.5, 8-H_3), 2.30 – 2.41 (1H, m, 14-H),

3.02 (1H, d, *J* 11.5, 12-*H*H), 3.33 (1H, dd, *J* 17.5, 8.8, 2-*H*H), 3.51 (1H, dd, *J* 11.5, 7.5, 12-H*H*), 3.61 (1H, dd, *J* 17.5, 3.0, 2-H*H*), 4.64 – 4.78 (1H, m, OH), 5.14 (1H, ap. t, *J* 7.5, 13-H), 5.60 (1H, dd, *J* 15.3, 6.2, 4-H), 5.67 – 5.78 (1H, m, 7-H), 5.98 – 6.09 (1H, m, 6-H), 6.24 (1H, dd, *J* 15.3, 10.5, 5-H); δ_C (101 MHz, $CDCl_3$) 18.0 (C-15), 18.3 (C-8), 19.3 (C-15'), 30.8 (C-12), 31.0 (C-14), 45.5 (C-2), 68.7 (C-3), 71.6 (C-13), 130.7 (C-4), 130.8 (C-6 and C-7), 131.3 (C-5), 172.6 (C-1), 203.2 (C-10); HRMS (ESI) calc. for $[C_{14}H_{21}NO_2S_2Na]$ 322.0906 Found 322.0898.

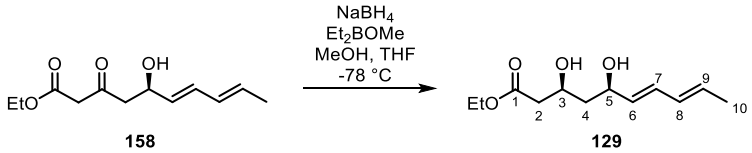
179: $[\alpha]_D^{25}$ = +105.0 (*c* 1, Acetone); ν_{max} (film) 3430, 2963, 1688, 1468, 1157, 729; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.9, 15-H_3), 1.05 (3H, d, *J* 6.8, 15'-H_3), 1.74 (3H, d, *J* 6.3, 8-H_3), 2.28 – 2.41 (1H, m, 14-H), 3.03 (1H, d, *J* 11.5, 12-*H*H), 3.38 (1H, dd, *J* 17.3, 3.4, 2-*H*H), 3.51 (1H, dd, *J* 11.5, 7.5, 12-H*H*), 3.60 (1H, dd, *J* 17.3, 8.8, 2-H*H*), 4.54 – 4.72 (1H, m, OH), 5.16 (1H, ap. t, *J* 7.5, 13-H), 5.59 (1H, dd, *J* 15.3, 6.2, 4-H), 5.65 – 5.77 (1H, m, 7-H), 6.03 (1H, dd, *J* 15.2, 10.5, 6-H), 6.23 (1H, dd, *J* 15.3, 10.5, 5-H); δ_C (101 MHz, $CDCl_3$) 18.0 (CH_3), 18.3 (C-8), 19.3 (CH_3), 30.7 (C-12), 30.9 (C-14), 45.3 (C-2), 69.1 (C-3), 71.5 (C-13), 130.7 (C-4), 130.8 (C-7), 130.9 (C-6), 131.4 (C-5), 173.0 (C-1), 203.2 (C-10); HRMS (ESI) calc. for $[C_{14}H_{21}NO_2S_2Na]$ 322.0906 Found 322.0898.

Ethyl (*R*,6*E*,8*E*)-5-hydroxy-3-oxodeca-6,8-dienoate (158)



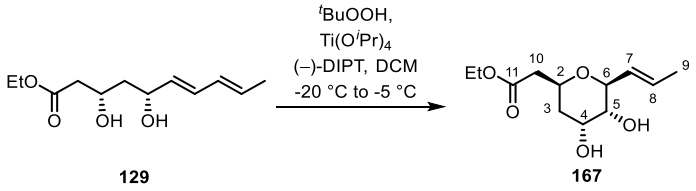
Potassium-3-ethoxy-2-methyl-3-oxopropanoate (5.19 g, 30.49 mmol) and $MgCl_2$ (1.45 g, 15.24 mmol) were added to a solution of aldol product **156** (4.15 g, 13.86 mmol) in THF (50 mL) under nitrogen and stirred for 45 minutes. Imidazole (1.04 g, 15.24 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (100 mL) and washed with 1 M HCl (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (5% Et_2O in DCM) to afford **158** (2.58 g, 82%) as a yellow oil and auxiliary **152** (2.16 g, 97%) as a white solid; $[\alpha]_D^{22}$ = +6.0 (*c* 1, Acetone); ν_{max} (film) 3443, 2981, 2914, 1737, 1709, 988; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2, OCH_2CH_3), 1.73 – 1.76 (3H, m, 10-H_3), 2.68 – 2.74 (1H, br. s, OH), 2.74 – 2.80 (2H, m, 4-H_2), 3.47 (2H, s, 2-H_2) , 4.19 (2H, q, *J* 7.2, OCH_2CH_3), 4.61 (1H, ap. q, *J* 6.5, 5-H), 5.53 (1H, ddq, *J* 15.2, 6.4, 0.7, 9-H), 5.71 (1H, dd, *J* 15.0, 6.5, 6-H), 5.97 – 6.04 (1H, m, 8-H), 6.17 – 6.26 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) 14.2 (OCH_2CH_3), 18.3 (C-10), 49.8 (C-4), 50.2 (C-2), 61.7 (OCH_2CH_3), 68.4 (C-5), 130.6 (C-9), 130.7 (C-6), 130.9 (C-8), 131.4 (C-7), 167.1 (C-1), 203.0 (C-3); HRMS (ESI) calc. for $[C_{12}H_{18}O_4Na]$ 249.1097 Found 249.1093.

Ethyl (3*S*,5*R*,6*E*,8*E*)-3,5-dihydroxydeca-6,8-dienoate (129)



Ketone **158** (1.01 g, 4.42 mmol) was dissolved in THF (25 mL) and MeOH (7 mL) under nitrogen and cooled to -78 °C then Et_2BOMe (0.70 mL, 5.30 mmol) was added dropwise and the reaction mixture was stirred for 15 minutes. $NaBH_4$ (0.19 g, 5.08 mmol) was added in one portion and the reaction mixture was stirred for 3 hours then AcOH (3 mL) was added and the mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc (30 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in methanol (20 mL) and the solvent removed *in vacuo* to afford diol **129** (1.02 g, quant., dr > 99:1) as a yellow oil; $[\alpha]_D^{22}$ = -8.0 (*c* 1, Acetone); ν_{max} (film) 3396, 2981, 2914, 1716, 1164, 987; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.57 – 1.72 (2H, m, 4-H_2), 1.73 – 1.77 (3H, m, 10-H_3), 2.42 – 2.52 (2H, m, 2-H_2), 3.07 (1H, br. s, OH), 3.74 (1H, br. s, OH), 4.16 (2H, q, *J* 7.1, OCH_2CH_3), 4.22 – 4.31 (1H, m, 3-H), 4.42 (1H, m, 5-H), 5.54 (1H, dd, *J* 15.2, 6.6, 6-H), 5.71 (1H, dd, *J* 15.0, 6.8, 9-H), 5.97 – 6.08 (1H, m, 8-H), 6.20 (1H, dd, *J* 15.2, 10.4, 7-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 18.3 (C-10), 41.8 (C-2), 42.9 (C-4), 61.0 (OCH_2CH_3), 68.5 (C-3), 72.6 (C-5), 130.5 (C-9), 130.85 (C-8), 130.93 (C-7), 132.4 (C-6), 172.7 (C-1); HRMS (ESI) calc. for [$C_{12}H_{20}O_4Na$] 251.1254 Found 251.1252.

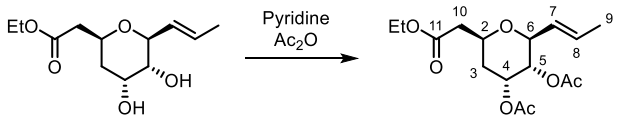
Ethyl 2-((2*S*,4*R*,5*R*,6*S*)-4,5-dihydroxy-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)acetate (167)



In a flame dried flask at -20 °C under nitrogen was added 4 Å molecular sieves (20 mg) and DCM (2 mL) followed by $Ti(O^iPr)_4$ (0.01 mL, 0.03 mmol) and (−)-DIPT (0.01 mL, 0.03 mmol). The reaction mixture was stirred for 5 minutes then allyl alcohol **129** (57 mg, 0.25 mmol) in DCM (1 mL) was added and the solution was stirred for 30 minutes. ^{t}BuOOH (5.5 M in decane, 0.09 mL, 0.50 mmol) was added dropwise and the reaction mixture was stirred at -5 °C for 5 hours. The reaction mixture was quenched with 10 wt.% aqueous tartaric acid (3 mL) and warmed to room temperature. The organic layer was separated and the aqueous extracted with DCM (3 × 15 mL). The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*.

The crude product was purified by flash column chromatography (65% EtOAc in petroleum ether 60:40) to afford tetrahydropyran **167** (32 mg, 52%) as a colourless oil; $[\alpha]_D^{22}$ = -34.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3431, 2984, 2920, 1729, 1373, 1071; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.61 (1H, ddd, *J* 14.2, 11.7, 2.8, 3-H_{ax}), 1.74 (3H, dd, *J* 6.5, 1.7, 9-H_3), 1.99 (1H, ddd, *J* 14.2, 3.6, 2.1, 3-H_{eq}), 2.16 (1H, br. s, OH), 2.38 (1H, dd, *J* 15.2, 5.9, 10-*H*H), 2.54 (1H, dd, *J* 15.2, 7.3, 10-H*H*), 2.63 (1H, br. s, OH), 3.32 (1H, dd, *J* 9.8, 3.1, 5-H), 3.98 (1H, dd, *J* 9.8, 7.8, 6-H), 4.07 – 4.18 (3H, m, OCH_2CH_3 and 4-H), 4.20 – 4.30 (1H, m, 2-H), 5.45 (1H, ddq, *J* 15.4, 7.8, 1.7, 7-H), 5.79 – 5.91 (1H, dq, *J* 15.4, 6.5, 8-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 18.1 (C-9), 37.1 (C-3), 40.8 (C-10), 60.6 (OCH_2CH_3), 66.6 (C-4), 68.0 (C-2), 71.0 (C-5), 76.9 (C-6), 128.9 (C-7), 132.0 (C-8), 171.0 (C-11); HRMS (ESI) calc. for $[C_{12}H_{21}O_5]$ 245.1384 Found 245.1379.

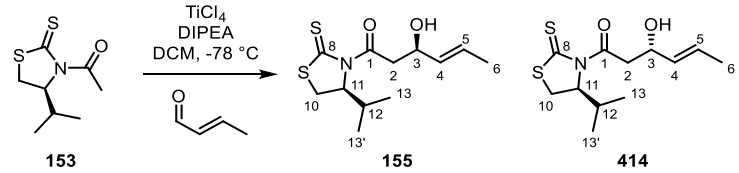
(2*S*,3*R*,4*R*,6*S*)-6-(2-Ethoxy-2-oxoethyl)-2-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-3,4-diyl diacetate (174)



167 174

Diol **167** (30 mg, 0.12 mmol) was dissolved in pyridine (0.25 mL, 3.01 mmol) and Ac_2O (0.11 mL, 1.2 mmol) and stirred under nitrogen for 16 hours. The reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 15 mL). The combined organic layers were washed sequentially with 2 M HCl (2 × 5 mL), aqueous saturated $NaHCO_3$ (2 × 10 mL) and brine (25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc in petroleum ether 60:40) to afford diacetate **174** (32 mg, 82%) as a colourless oil; $[\alpha]_D^{18}$ = -20.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2981, 2938, 1736, 1370, 1243, 1055; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.67 (3H, dd, *J* 6.6, 1.7, 9-H_3), 1.70 – 1.77 (1H, m, 3-*H*H), 1.91 – 1.95 (1H, m, 3-H*H*), 1.96 (3H, s, OAc), 2.13 (3H, s, OAc), 2.38 (1H, dd, *J* 15.5, 5.8, 10-*H*H), 2.58 (1H, dd, *J* 15.5, 7.3, 10-H*H*), 4.11 – 4.17 (3H, m, OCH_2CH_3 and 6-H), 4.18 – 4.25 (1H, m, 2-H), 4.66 (1H, dd, *J* 10.1, 3.1, 5-H), 5.34 (1H, ddq, *J* 15.3, 7.2, 1.7, 7-H), 5.40 (1H, ap. q, *J* 3.1, 4-H), 5.72 – 5.82 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 18.1 (C-9), 21.0 (OAc), 21.3 (OAc), 35.6 (C-3), 40.6 (C-10), 60.8 (OCH_2CH_3), 67.4 (C-4), 68.8 (C-2), 70.9 (C-5), 75.0 (C-6), 127.8 (C-7), 131.1 (C-8), 170.1 (OAc), 170.4 (OAc), 170.9 (C-11); HRMS (ESI) calc. for $[C_{16}H_{24}O_7Na]$ 315.1414 Found 315.1402.

(*R*,*E*)-3-Hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)hex-4-en-1-one (155)



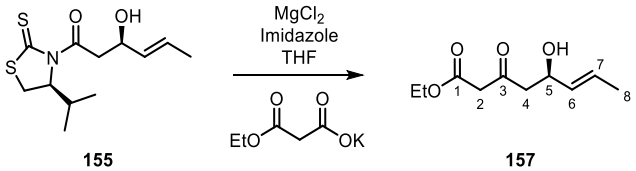
153 155 414

Acylated auxiliary **153** (1.69 g, 8.37 mmol) was dissolved in DCM (85 mL) under nitrogen and cooled to -78 °C then $TiCl_4$ (1 M in DCM, 8.37 mL, 8.37 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 20 minutes then DIPEA (1.75 mL, 10.04 mmol) was added dropwise. The reaction mixture was stirred for 1 hour then crotonaldehyde (0.69 mL, 8.37 mmol) was added dropwise. After stirring at -78 °C for 1 hour, aqueous saturated NH_4Cl (25 mL) was added and the reaction mixture was stirred for a further hour at room temperature. The solution was extracted with DCM (3 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% EtOAc in petroleum ether 60:40) to afford aldol products **155** (1.73 g, 76%) and **414** (0.29 g, 13%) as yellow oils.

155: $[\alpha]_D^{22}$ = +251.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3419, 2962, 1688, 1156; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.0, 13-H_3), 1.06 (3H, d, *J* 6.8, 13'-H_3), 1.71 (3H, dd, *J* 6.5, 1.5, 6-H_3), 2.30 – 2.43 (1H, m, 12-H), 2.76 (1H, d, *J* 4.0, OH), 3.03 (1H, dd, *J* 11.5, 1.1, 10-*H*H), 3.29 (1H, dd, *J* 17.5, 9.0, 2-*H*H), 3.52 (1H, dd, *J* 11.5, 8.0, 10-H*H*), 3.61 (1H, dd, *J* 17.5, 2.9, 2-H*H*), 4.61 (1H, m, 3-H), 5.16 (1H, ddd, *J* 8.0, 6.2, 1.1, 11-H), 5.51 – 5.60 (1H, ddq, *J* 15.4, 6.4, 1.5, 4-H), 5.69 – 5.83 (1H, dqd, *J* 15.4, 6.5, 1.1, 5-H); δ_C (101 MHz, $CDCl_3$) 17.9 (C-6), 18.0 (C-13), 19.3 (C-13'), 30.8 (C-10), 31.0 (C-12), 45.6 (C-2), 68.9 (C-3), 71.6 (C-11), 127.6 (C-5), 131.9 (C-4), 172.8 (C-8), 203.16 (C-1); HRMS (ESI) calc. for [$C_{12}H_{19}NO_2S_2Na$] 296.0749 Found 296.0743.

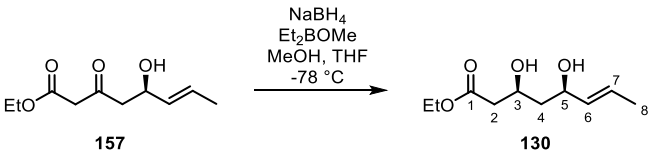
414: $[\alpha]_D^{22}$ = +177.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3418, 2962, 2875, 1689, 1156; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.9, 13-H_3), 1.06 (3H, d, *J* 6.9, 13'-H_3), 1.70 (3H, dd, *J* 6.5, 1.5, 6-H), 2.27 – 2.43 (1H, m, 12-H), 3.04 (1H, dd, *J* 11.5, 1.2, 10-*H*H), 3.18 (1H, d, *J* 4.2, OH), 3.36 (1H, dd, *J* 17.5, 3.2, 2-*H*H), 3.52 (1H, dd, *J* 11.5, 8.0, 10-H*H*), 3.59 (1H, dd, *J* 17.5, 9.1, 2-H*H*), 4.45 – 4.57 (1H, br. m, 3-H), 5.18 (1H, ddd, *J* 8.0, 6.3, 1.2, 11-H), 5.55 (1H, ddq, *J* 14.8, 6.5, 1.5, 4-H), 5.75 (1H, dqd, *J* 14.8, 6.5, 1.2, 5-H); δ_C (101 MHz, $CDCl_3$) 17.9 (C-6), 18.0 (C-13), 19.3 (C-13), 30.8 (C-10), 30.9 (C-12), 45.4 (C-2), 69.3 (C-3), 71.5 (C-11), 127.7 (C-5), 132.0 (C-4), 173.28 (C-8), 203.2 (C-1); HRMS (ESI) calc. for [$C_{12}H_{19}NO_2S_2Na$] 296.0749 Found 296.0756.

Ethyl (*R*,*E*)-5-hydroxy-3-oxooct-6-enoate (157)



Potassium-3-ethoxy-2-methyl-3-oxopropanoate (1.89 g, 11.10 mmol) and $MgCl_2$ (0.53 g, 5.60 mmol) were added to a solution of aldol product **155** (1.38 g, 5.05 mmol) in THF (20 mL) under nitrogen and stirred for 45 minutes. Imidazole (0.38 g, 5.55 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (50 mL) and washed with 1 M HCl (20 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (50 mL) and the aqueous layer extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (30% EtOAc in petroleum ether 60:40) to afford **157** (0.79 g, 78%) as a yellow oil; $[\alpha]_D^{23}$ = -4.0 (*c* 1, Acetone); ν_{max} (film) 3427, 2982, 2920, 1737, 1709, 1027; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2, $OCH_2\mathit{CH_3}$), 1.69 (3H, dd, *J* 6.5, 1.7, 8-H_3), 2.65 (1H, br. s, OH), 2.75 (2H, d, *J* 6.5, 4-H_2), 3.47 (1H, s, 2-H_2), 4.19 (2H, q, *J* 7.2, $O\mathit{CH_2}CH_3$), 4.54 (1H, ap. br. q, *J* 6.5, 5-H), 5.48 (1H, ddq, *J* 15.3, 6.5, 1.7, 6-H), 5.73 (1H, dqd, *J* 15.3, 6.5, 1.0, 7-H); δ_C (101 MHz, $CDCl_3$) 14.3 ($OCH_2\mathit{C}H_3$), 17.8 (C-8), 49.8 (C-4), 50.2 (C-2), 61.7 ($O\mathit{C}H_2CH_3$), 68.7 (C-5), 127.7 (C-7), 131.9 (C-6), 167.1 (C-1), 203.2 (C-3); HRMS (ESI) calc. for [$C_{10}H_{16}O_4Na$] 223.0941 Found 223.0948.

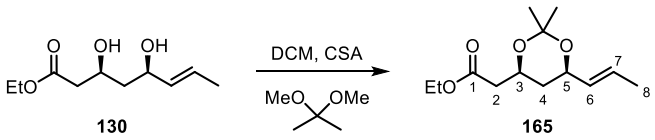
Ethyl (3*S*,5*R*,*E*)-3,5-dihydroxyoct-6-enoate (130)



Ketone **157** (750 mg, 3.75 mmol) was dissolved in THF (25 mL) and MeOH (7 mL) under nitrogen and cooled to -78 °C then Et_2BOMe (0.59 mL, 4.49 mmol) was added dropwise and the reaction mixture was stirred for 15 minutes. $NaBH_4$ (163 mg, 4.30 mmol) was added in one portion and the reaction mixture was stirred for 3 hours then AcOH (4 mL) was added and the mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc (25 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in methanol (20 mL) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (45% EtOAc in petroleum ether 60:40) to afford diol **130** (561 mg, 74%, dr > 99:1) as a yellow oil; $[\alpha]_D^{23}$ = +56.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3406, 2938, 1731, 1160, 966; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, $OCH_2\mathit{CH_3}$), 1.59

(1H, ap. dt, *J* 14.3, 3.2, 4-*H*H), 1.64 – 1.75 (4H, m, 4-H*H* and 8-H_3), 2.39 – 2.56 (2H, m, 2-H_2), 2.98 (1H, d, *J* 2.1, 5-OH), 3.72 (1H, d, *J* 2.8, 3-OH), 4.17 (2H, q, *J* 7.1, O*C*$H_2$$CH_3$), 4.20 – 4.31 (1H, m, 3-H), 4.31 – 4.38 (1H, m, 5-H), 5.48 (1H, ddq, *J* 15.3, 7.0, 1.6, 6-H), 5.70 (1H, dqd, *J* 15.3, 6.6, 0.9, 7-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2*C*H_3), 17.8 (C-8), 41.8 (C-2), 42.9 (C-4), 61.0 (O*C*$H_2$$CH_3$), 68.5 (C-3), 73.0 (C-5), 127.1 (C-7), 133.6 (C-6), 172.7 (C-1); HRMS (ESI) calc. for [$C_{10}H_{19}O_4$] 203.1278 Found 203.1281.

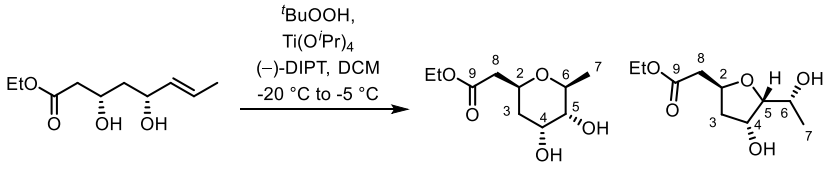
Ethyl 2-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-prop-1-en-1-yl)-1,3-dioxan-4-yl)acetate (165)



130 165

Diol **130** (100 mg, 0.49 mmol) was dissolved in DCM (5 mL) under nitrogen then 2,2-dimethoxypropane (1.50 mL, 12.00 mmol) and CSA (57 mg, 0.25 mmol) were added and the reaction mixture was stirred at room temperature for 1 hour. The solution was diluted with aqueous saturated $NaHCO_3$ (10 mL), the organic layer separated and the aqueous extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford acetonide **165** (116 mg, 99%) as a yellow oil; $[\alpha]_D^{23}$ = +15.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2997, 1735, 1198, 1164, 965, 949; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2*C*H_3), 1.29 – 1.36 (1H, m, 4-*H*H), 1.40 (3H, s, $OCCH_3$), 1.49 (3H, s, $OCCH_3$), 1.60 (1H, ap. dt, *J* 12.8, 2.5, 4-H*H*), 1.69 (3H, dd, *J* 6.5, 1.6, 8-H_3), 2.38 (1H, dd, *J* 15.5, 6.1, 2-*H*H), 2.54 (1H, dd, *J* 15.5, 7.0, 2-H*H*), 4.08 – 4.22 (2H, m, O*C*$H_2$$CH_3$), 4.28 – 4.38 (2H, m, 3-H and 5-H), 5.40 – 5.50 (1H, m, 6-H), 5.72 (1H, dq, *J* 15.5, 6.5, 7-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH_2*C*H_3), 18.0 (C-8), 19.9 (CH_3), 30.3 (CH_3), 36.9 (C-4), 41.6 (C-2), 60.7 (O*C*$H_2$$CH_3$), 65.9 (C-3), 70.2 (C-5), 99.0 (OCO), 128.2 (C-7), 131.7 (C-6), 171.1 (C-1); HRMS (ESI) calc. for [$C_{13}H_{22}O_4Na$] 265.1410 Found 265.1401.

Ethyl 2-((2*S*,4*R*,5*R*,6*S*)-4,5-dihydroxy-6-methyltetrahydro-2H-pyran-2-yl)acetate (169) and ethyl 2-((2*S*,4*R*,5*R*)-4-hydroxy-5-((*R*)-1-hydroxyethyl)tetrahydrofuran-2-yl)acetate (170)



130 169 170

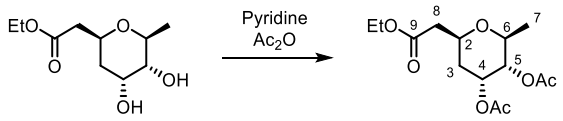
In a flame dried flask at -20 °C under nitrogen was added 4 Å molecular sieves (30 mg) and DCM (2.5 mL) followed by $Ti(O^iPr)_4$ (0.03 mL, 0.10 mmol) and (−)-DIPT (0.03 mL, 0.12 mmol). The reaction mixture was stirred for 5 minutes then allyl alcohol **130** (100 mg, 0.49 mmol) in DCM (0.5 mL) was added and the solution was stirred for 30 minutes. ^{t}BuOOH (5.5 M in decane, 0.18 mL, 0.99 mmol)

was added dropwise and the reaction mixture was stirred at -5 °C for 5 hours. The reaction mixture was quenched with 10 wt.% aqueous tartaric acid (5 mL) and warmed to room temperature. The organic layer was separated and the aqueous extracted with DCM (3 × 15 mL). The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (70% EtOAc in petroleum ether 60:40) to afford tetrahydropyran **169** (47 mg, 44%) and tetrahydrofuran **170** (20 mg, 19%) as colourless oils.

169: $[\alpha]_D^{22}$ = -85.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3436, 2983, 2923, 1731, 1372, 1180, 1061; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.2, 7-H_3), 1.23 (3H, t, *J* 7.1, OCH_2CH_3). 1.58 (1H, ddd, *J* 14.0, 11.6, 2.6, 3-H_{ax}), 1.94 (1H, ddd, *J* 14.0, 3.5, 2.0, 3-H_{eq}), 2.34 (1H, dd, *J* 15.2, 5.6, 8-*H*H), 2.49 (1H, dd, *J* 15.2, 7.7, 8-H*H*), 2.82 (1H, br. s, 5-OH), 3.00 (1H, br. s, 4-OH), 3.20 (1H, m, 5-H), 3.64 (1H, dq, *J* 9.5, 6.2, 6-H), 4.07 (1H, m, 4-H), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 4.18 (1H, ddd, *J* 7.7, 5.6, 2.0, 2-H); δ_C (101 MHz, $CDCl_3$) 14.3 (C-7), 18.4 (OCH_2CH_3), 38.0 (C-3), 40.9 (C-8), 60.8 (OCH_2CH_3), 67.4 (C-4), 68.1 (C-2), 71.8 (C-6), 73.4 (C-5), 171.6 (C-9); HRMS (ESI) calc. for [$C_{10}H_{19}O_5$] 219.1227 Found 219.1223.

170: $[\alpha]_D^{23}$ = +3.0 (*c* 0.67, $CHCl_3$); ν_{max} (film) 3419, 2981, 2925, 1732, 1062; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.34 (3H, d, *J* 6.6, 7-H_3), 1.71 – 1.81 (1H, m, 3-*H*H), 2.21 (1H, ddd, *J* 13.2, 5.6, 1.1, 3-H*H*), 2.53 (1H, dd, *J* 15.5, 5.5, 8-*H*H), 2.61 (1H, dd, *J* 15.5, 7.3, 8-H*H*), 3.08 (1H, s, 6-OH), 3.68 (1H, dd, *J* 4.9, 3.3, 5-H), 4.00 (1H, s, 4-OH), 4.12 – 4.20 (3H, m, OCH_2CH_3 and 6-H), 4.48 – 4.61 (1H, m, 4-H), 4.62 – 4.76 (1H, m, 2-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH_2CH_3), 18.9 (C-7), 40.9 (C-8), 41.8 (C-3), 60.8 (OCH_2CH_3), 67.9 (C-6), 73.3 (C-4), 74.8 (C-2), 84.4 (C-5), 171.5 (C-9); HRMS (ESI) calc. for [$C_{10}H_{19}O_5$] 219.1227 Found 219.1230.

(2*S*,3*R*,4*S*,6*S*)-2-(2-Ethoxy-2-oxoethyl)-6-methyltetrahydro-2H-pyran-4,5-diyl diacetate (415)

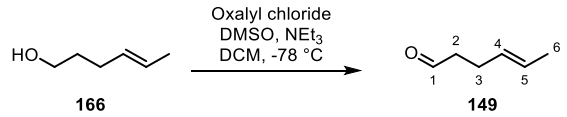


169 **415**

Diol **169** (40 mg, 0.18 mmol) was dissolved in pyridine (0.37 mL, 4.57 mmol) and Ac_2O (0.17 mL, 1.8 mmol) and stirred under nitrogen for 16 hours. The reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 15 mL). The combined organic layers were washed with 2 M HCl (2 × 5 mL), $NaHCO_3$ (2 × 10 mL) and brine (25 mL). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford diacetate **415** (51 mg, 94%) as a yellow oil; $[\alpha]_D^{23}$ = -115.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2988, 2928, 1736, 1370, 1245, 1053; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.2, 7-H_3), 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.71 (1H, ddd, *J* 14.4, 11.6, 2.6, 3-H_{ax}), 1.92 (1H, ddd, *J* 14.4, 3.7, 2.2, 3-

H_{eq}), 1.99 (3H, s, OAc), 2.10 (3H, s, OAc), 2.35 (1H, dd, *J* 15.4, 5.3, 8-*H*H), 2.52 (1H, dd, *J* 15.4, 7.8, 8-H*H*), 3.87 (1H, dq, *J* 10.0, 6.2, 6-H), 4.15 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 4.18 – 4.22 (1H, m, 2-H), 4.52 (1H, dd, *J* 10.0, 3.0, 5-H), 5.39 (1H, m, 4-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 18.1 (C-7), 21.0 (OAc), 21.20 (OAc), 35.8 (C-3), 40.7 (C-8), 60.8 (O*C*H$_2$CH$_3$), 67.3 (C-4), 69.0 (C-2), 70.2 (C-6), 73.1 (C-5), 170.2 (OAc), 170.3 (OAc), 171.0 (C-9); HRMS (ESI) calc. for [$C_{14}H_{23}O_7$] 303.1438 Found 303.1427.

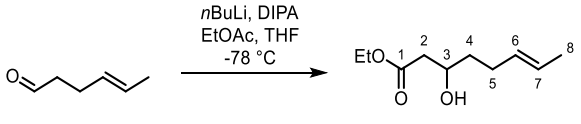
(*E*)-Hex-4-enal (149)



166 **149**

Oxalyl chloride (1.69 mL, 20.0 mmol) was dissolved in DCM (50 mL) and cooled to -78 °C under nitrogen then DMSO (2.13 mL, 30.0 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes then alcohol **166** (1.18 mL, 10.0 mmol) was added dropwise and the mixture was stirred for an additional hour. Triethylamine (6.27 mL, 45.0 mmol) was added and the reaction mixture was warmed to room temperature. Water (40 mL) was added and the organic layer separated. The aqueous was extracted with further DCM (2 × 50 mL). The combined organic layers were washed sequentially with 2 M HCl (2 × 30 mL), aqueous saturated $NaHCO_3$ (2 × 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* at 0 °C to afford volatile aldehyde **149** (912 mg, 93%) as an orange oil; ν_{max} (film) 2919, 2856, 2721, 1724, 966; δ_H (400 MHz, $CDCl_3$) 1.63 – 1.66 (3H, m, 6-H$_3$), 2.28 – 2.36 (2H, m, 3-H$_2$), 2.45 – 2.53 (2H, m, 2-H$_2$), 5.37 – 5.55 (2H, m, 4-H and 5-H), 9.76 (1H, t, *J* 1.7, 1-H); δ_C (101 MHz, $CDCl_3$) 18.0 (C-6), 25.3 (C-3), 43.7 (C-2), 126.6 (C-5) , 129.1 (C-4), 202.7 (C-1); m/z (ESI): $[M+H]^+$ = 99.08. Data consistent with the literature.[265]

(±)-Ethyl (*E*)-3-hydroxyoct-6-enoate (131)

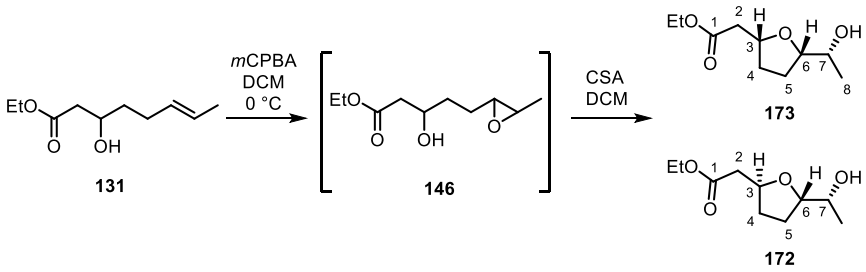


149 **131**

DIPA (1.41 mL, 10.09 mmol) was dissolved in THF (40 mL) under nitrogen and cooled to 0 °C then 1.5 M *n*BuLi in hexanes (6.11 mL, 9.17 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 20 minutes and then cooled to -78 °C. EtOAc (2.69 mL, 27.51 mmol) was added dropwise and the reaction mixture was stirred for 20 minutes. Aldehyde **149** (601 mg, 6.11 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 2 hours then quenched with aqueous saturated NH_4Cl (10 mL). The reaction mixture was warmed to room temperature and extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with brine (50 mL), dried

over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford alcohol **131** (640 mg, 56%) as a yellow oil; ν_{max} (film) 3450, 2920, 1732, 1717, 1157; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, $OCH_2\mathit{CH_3}$), 1.38 – 1.52 (1H, m, 4-*H*H), 1.52 – 1.62 (1H, m, 4-H*H*), 1.62-1.66 (3H, m, 8-H_3) 1.98 – 2.20 (2H, m, 5-H_2), 2.40 (1H, dd, *J* 16.4, 8.9, 2-*H*H), 2.49 (1H, dd, *J* 16.4, 3.3, 2-H*H*), 2.93 (1H, d, *J* 4.0, OH), 3.89 – 4.08 (1H, m, 3-H), 4.17 (1H, q, *J* 7.1, $O\mathit{CH_2}CH_3$), 5.35 – 5.54 (2H, m, 6-H and 7-H); δ_C (101 MHz, $CDCl_3$) 14.4 ($OCH_2\mathit{C}H_3$), 18.1 (C-8), 28.7 (C-5), 36.4 (C-4), 41.4 (C-2), 60.9 ($O\mathit{C}H_2CH_3$), 67.7 (C-3), 125.8 (C-7), 130.7 (C-6), 173.2 (C-1); HRMS (ESI) calc. for [$C_{10}H_{19}O_3$] 187.1329 Found 187.1329.

(±)-Ethyl 2-(5-(1-hydroxyethyl)tetrahydrofuran-2-yl)acetate (172 and 173)



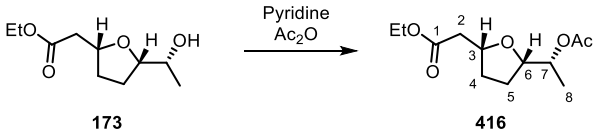
Alkene **131** (300 mg, 1.61 mmol) was dissolved in DCM (10 mL) under nitrogen and cooled to 0 °C then *m*CPBA (70 wt.%, 596 mg, 2.42 mmol) was added and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with aqueous saturated $Na_2S_2O_3$ solution (15 mL) and DCM (10 mL). The organic layer was separated and the aqueous extracted with further DCM (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (70% Et_2O in petroleum ether 60:40) to afford a complex mixture. The crude mixture was dissolved in DCM (10 mL) and CSA (32 mg, 0.14 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature then quenched with aqueous saturated $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (50% EtOAc in petroleum ether 60:40) to afford tetrahydrofuran **173** (112 mg, 34%) and tetrahydrofuran **172** (98 mg, 30%) as colourless oils. The diastereoisomers were determined by nOe analysis showing enhancements between 3-H and 6-H for **173**.

173: ν_{max} (film) 3453, 2977, 2880, 1733, 1067; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.6, 8-H_3), 1.26 (3H, t, *J* 7.2, $OCH_2\mathit{CH_3}$), 1.61 – 1.71 (1H, m, 4-*H*H), 1.71 – 1.83 (1H, m, 5-*H*H), 1.94 1H, (ap. dq, *J* 12.4, 8.0, 5-H*H*), 2.06 (1H, ap. dtd, *J* 12.0, 8.0, 7.0, 4-H*H*), 2.45 – 2.57 (2H, m, 2-H_2), 2.67 – 2.75 (1H, m, OH), 3.85 (1H, ddd, *J* 8.0, 7.0, 3.0, 6-H), 3.93 – 4.04 (1H, m, 7-H), 4.07 – 4.26 (2H, m, $O\mathit{CH_2}CH_3$), 4.33 (1H, ap. tt, *J* 7.0, 5.6, 3-H); δ_C (101 MHz, $CDCl_3$) 14.3 ($OCH_2\mathit{C}H_3$), 18.0 (C-8), 23.3 (C-5), 31.2 (C-4), 41.0 (C-2), 60.9

(O*C*H$_2$CH$_3$), 67.3 (C-7), 75.7 (C-3), 84.0 (C-6), 171.7 (C-1); HRMS (ESI) calc. for [$C_{10}H_{18}NaO_4$] 225.1097 Found 225.1100.

172: ν_{max} (film) 3453, 2976, 2876, 1733, 1064; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.5, 8-H$_3$), 1.26 (3H, t, *J* 7.1, OCH$_2$*CH$_3$*), 1.57 – 1.70 (1H, m, 4-*H*H), 1.83 – 1.96 (2H, m, 5-H$_2$), 2.08 – 2.20 (2H, m, OH and 4-H*H*), 2.45 (1H, dd, *J* 15.2, 6.0, 2-*H*H), 2.59 (1H, dd, *J* 15.2, 7.5, 2-H*H*), 3.84 – 4.02 (2H, m, 6-H and 7-H), 4.15 (2H, q, *J* 7.1, O*CH$_2$*CH$_3$), 4.40 (1H, ap. tt, *J* 7.5, 6.0, 3-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 18.1 (C-8), 24.9 (C-5), 32.2 (C-4), 41.0 (C-2), 60.7 (O*C*H$_2$CH$_3$), 68.0 (C-7), 76.3 (C-3), 82.9 (C-6), 171.4 (C-1); HRMS (ESI) calc. for [$C_{10}H_{18}NaO_4$] 225.1097 Found 225.1105.

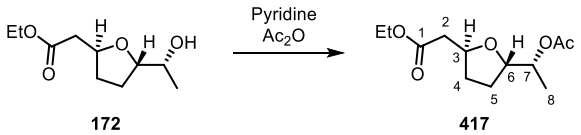
(±)-Ethyl 2-((2*R*,5*S*)-5-((*R*)-1-acetoxyethyl)tetrahydrofuran-2-yl)acetate (416)



173 416

Alcohol **173** (50 mg, 0.25 mmol) was dissolved in pyridine (0.34 mL, 4.20 mmol) and Ac_2O (0.24 mL, 2.50 mmol) and stirred under nitrogen for 16 hours. The reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 15 mL). The combined organic layers were washed with 2 M HCl (2 × 5 mL), aqueous saturated $NaHCO_3$ (2 × 10 mL) and brine (25 mL). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford acetate **416** (63 mg, quant.) as a yellow oil; ν_{max} (film) 2981, 2878, 1732, 1238, 1033; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.4, 8-H$_3$), 1.24 (3H, t, *J* 7.1, OCH$_2$*CH$_3$*), 1.60 (1H, ap. ddt, *J* 11.9, 8.5, 6.7, 4-*H*H), 1.77 (1H, ap. ddt, *J* 12.5, 8.5, 7.0, 5-*H*H), 1.94 (1H, ap. dq, *J* 12.5, 7.0, 5-H*H*), 2.00 – 2.11 (4H, m, 4-H*H* and OAc), 2.41 (1H, dd, *J* 15.1, 6.6, 2-*H*H), 2.60 (1H, dd, *J* 15.1, 6.7, 2-H*H*), 3.91 (1H, ap. td, *J* 7.0, 4.7, 6-H), 4.07 – 4.19 (2H, m, O*CH$_2$*CH$_3$), 4.30 (1H, m, 3-H), 4.90 (1H, ap. qd, *J* 6.4, 4.7, 7-H); δ_C (101 MHz, $CDCl_3$) 14.7 (OCH$_2$*C*H$_3$), 16.5 (C-8), 21.9 (OAc), 27.3 (C-5), 31.3 (C-4), 41.5 (C-2), 61.0 (O*C*H$_2$CH$_3$), 72.2 (C-7), 76.6 (C-3), 81.6 (C-6), 171.0 (OAc), 171.7 (C-1); HRMS (ESI) calc. for [$C_{12}H_{20}NaO_5$] 267.1203 Found 267.1192.

(±)-Ethyl 2-((2*S*,5*S*)-5-((*R*)-1-acetoxyethyl)tetrahydrofuran-2-yl)acetate (417)

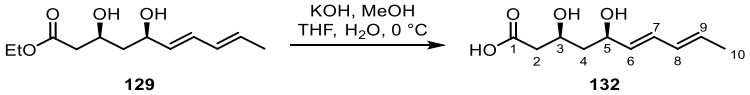


172 417

Alcohol **172** (25 mg, 0.13 mmol) was dissolved in pyridine (0.17 mL, 2.10 mmol) and Ac_2O (0.12 mL, 1.25 mmol) and stirred under nitrogen for 16 hours. The reaction mixture was diluted with water (10 mL) and extracted with DCM (2 × 15 mL). The combined organic layers were washed with 2 M HCl (2 × 5 mL), aqueous saturated $NaHCO_3$ (2 × 10 mL) and brine (25 mL). The combined organics were dried

over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% EtOAc in petroleum ether 60:40) to afford acetate **417** (26 mg, 83%) as a colourless oil; ν_{max} (film) 2981, 2939, 1731, 1371, 1238; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5, 8-H_3), 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.49 – 1.67 (1H, m, 4-*H*H), 1.67 – 1.86 (1H, m, 5-*H*H), 1.94 – 2.08 (4H, m, 5-H*H* and OAc), 2.08 – 2.21 (1H, m, 4-H*H*), 2.41 (1H, dd, *J* 15.2, 6.8, 2-*H*H), 2.62 (1H, dd, *J* 15.2, 6.5, 2-H*H*), 4.00 (1H, ap. td, *J* 7.2, 4.8, 6-H), 4.13 (2H, q, *J* 7.1, OCH_2CH_3), 4.26 – 4.38 (1H, m, 3-H), 4.90 (1H, ap. qd, *J* 6.5, 4.8, 7-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 15.9 (C-8), 21.5 (OAc), 27.5 (C-5), 31.8 (C-4), 40.8 (C-2), 60.6 (OCH_2CH_3), 72.3 (C-7), 76.3 (C-3), 80.7 (C-6), 170.7 (OAc), 171.2 (C-1); HRMS (ESI) calc. for [$C_{12}H_{20}NaO_5$] 267.1203 Found 267.1196.

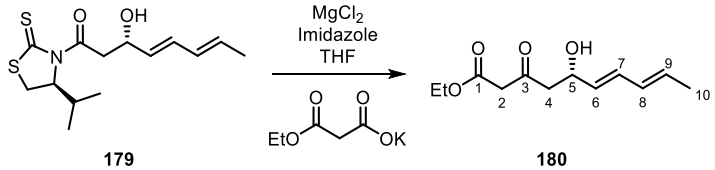
(3*S*,5*R*,6*E*,8*E*)-3,5-Dihydroxydeca-6,8-dienoic acid (132)



129 **132**

Ester **129** (50 mg, 0.22 mmol) was dissolved in THF (0.7 mL), MeOH (0.3 mL) and water (0.3 mL) and cooled to 0 °C then 25% aqueous KOH solution (0.06 mL) was added and the reaction mixture was stirred for 4 hours. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 mL) and solid NH_4Cl was added until saturation. The mixture was washed with EtOAc (5 mL) and the organic layer discarded. The aqueous phase was acidified with 3 drops of 2 M HCl and extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **132** (12 mg, 28%) as a colourless oil; $[\alpha]_D^{23}$ = -20.0 (*c* 1, Acetone); ν_{max} (film) 3392, 3021, 2973, 1708, 1246, 987; δ_H (400 MHz, $(CD_3)_2CO$) 1.68 – 1.79 (5H, m, 10-H_3 and 4-H_2), 2.43 – 2.57 (2H, m, 2-H_2), 2.78 – 3.08 (2H, m, 3-OH and 5-OH), 4.23 (1H, ap. p, *J* 5.9, 3-H), 4.39 (1H, ap. q, *J* 6.5, 5-H), 5.62 (1H, dd, *J* 15.1, 6.5, 6-H), 5.70 (1H, dq, *J* 14.8, 6.9, 9-H), 6.09 (1H, ddq, *J* 14.8, 10.5, 1.8, 8-H), 6.23 (1H, dd, *J* 15.1, 10.5, 7-H); δ_C (126 MHz, $(CD_3)_2CO$) 18.2 (C-10), 42.8 (C-2), 44.6 (C-4), 68.1 (C-3), 71.7 (C-5), 129.4 (C-9), 130.6 (C-8), 132.3 (C-7), 135.1 (C-6), 173.4 (C-1); HRMS (ESI) calc. for [$C_{10}H_{15}O_4$] 199.0970 Found 199.0976.

Ethyl (*S*,6*E*,8*E*)-5-hydroxy-3-oxodeca-6,8-dienoate (180)

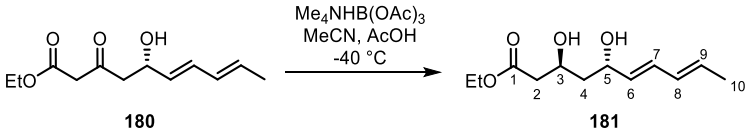


179 **180**

Potassium-3-ethoxy-2-methyl-3-oxopropanoate (374 mg, 2.20 mmol) and $MgCl_2$ (105 mg, 1.10 mmol) were added to a solution of aldol product **179** (290 mg, 1.00 mmol) in THF (5 mL) under nitrogen and

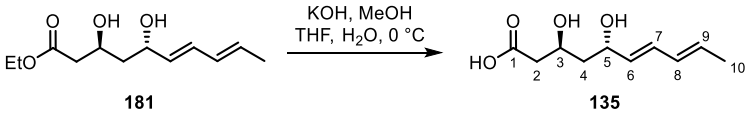
stirred for 45 minutes. Imidazole (175 mg, 1.10 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (20 mL) and washed with 1 M HCl (10 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (10 mL) and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether 60:40) to afford **180** (129 mg, 57%) as a yellow oil; $[\alpha]_D^{24}$ = -13.0 (*c* 1, Acetone); ν_{max} (film) 3439, 2980, 2912, 1740, 1709, 980; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.75 (3H, d, *J* 7.0, 10-H_3), 2.65 (1H, br. s, OH) 2.78 (2H, m, 4-H_2), 3.48 (2H, s, 2-H_2), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 4.62 (1H, ap. q, *J* 6.5, 5-H), 5.54 (1H, dd, *J* 15.3, 6.5, 6-H), 5.73 (1H, dq, *J* 15.0, 7.0, 9-H), 6.02 (1H, dd, *J* 15.0, 10.4, 8-H), 6.23 (1H, dd, *J* 15.3, 10.4, 7-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 18.3 (C-10), 49.8 (C-4), 50.2 (C-2), 61.7 (OCH_2CH_3), 68.4 (C-5), 130.6 (C-6), 130.7 (C-9), 131.0 (C-8), 131.5 (C-7), 167.1 (C-1), 203.1 (C-3); HRMS (ESI) calc. for [$C_{12}H_{18}O_4Na$] 249.1097 Found 249.1091.

Ethyl (3*S*,5*S*,6*E*,8*E*)-3,5-dihydroxydeca-6,8-dienoate (181)



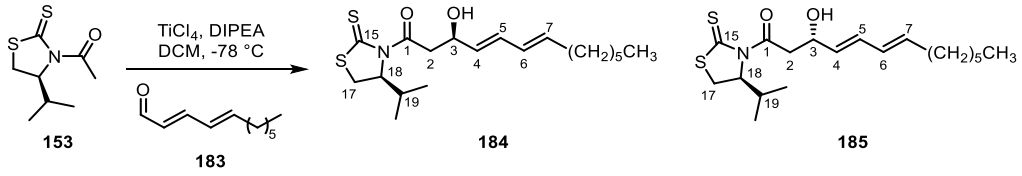
$Me_4NHB(OAc)_3$ (1390 mg, 5.28 mmol) was dissolved in MeCN (4 mL) and AcOH (3 mL) and stirred for 30 minutes at room temperature under nitrogen. The solution was cooled to -40 °C then ketone **180** (150 mg, 0.66 mmol) in MeCN (4 mL) was added dropwise. The reaction mixture was stirred for 5 hours then aqueous saturated sodium potassium tartrate (10 mL) was added and the mixture was warmed to room temperature and stirred for 1 hour. Aqueous saturated $NaHCO_3$ (15 mL) was added and the solution was extracted with DCM (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford diol **181** (134 mg, 89%, dr > 99:1) as a yellow oil; $[\alpha]_D^{24}$ = -30.0 (*c* 1, Acetone); ν_{max} (film) 3416, 2960, 2934, 2914, 1716, 987; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2, OCH_2CH_3), 1.64 (1H, ddd, *J* 14.4, 7.8, 3.1, 4-*H*H), 1.71 – 1.84 (4H, m, 4-H*H* and 10-H_3), 2.41 – 2.56 (2H, m, 2-CH_2), 2.68 (1H, br. s, OH), 3.50 (1H, br. s, OH), 4.16 (2H, q, *J* 7.2, OCH_2CH_3), 4.29 – 4.39 (1H, m, 3-H), 4.42 – 4.50 (1H, m, 5-H), 5.60 (1H, dd, *J* 15.3, 6.3, 6-H), 5.70 (1H, dq, *J* 14.8, 7.1, 9-H), 6.04 (1H, ddd, *J* 14.8, 10.3, 1.7, 8-H), 6.23 (1H, dd, *J* 15.3, 10.3, 7-H); δ_C (101 MHz, $CDCl_3$) δ 14.3 (OCH_2CH_3), 18.3 (C-10), 41.5 (C-2), 42.3 (C-4), 61.0 (OCH_2CH_3), 65.7 (C-3), 69.9 (C-5), 130.2 (C-9), 130.7 (C-7), 130.9 (C-8), 132.7 (C-6), 173.0 (C-1); HRMS (ESI) calc. for [$C_{12}H_{20}O_4Na$] 251.1254 Found 251.1253.

(3*S*,5*S*,6*E*,8*E*)-3,5-Dihydroxydeca-6,8-dienoic acid (135)



Ester **181** (40 mg, 0.18 mmol) was dissolved in THF (0.7 mL), MeOH (0.3 mL) and water (0.3 mL) and cooled to 0 °C then 25% aqueous KOH solution (0.06 mL) was added and the reaction mixture was stirred for 4 hours. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 mL) and solid NH_4Cl was added until saturation. The mixture was washed with EtOAc (5 mL) and the organic layer discarded. The aqueous phase was acidified with 3 drops of 2 M HCl and extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **135** (18 mg, 51%) as a yellow oil; $[\alpha]_D^{22}$ = +13.0 (*c* 1, Acetone); ν_{max} (film) 3376, 3019, 2915, 1704, 1255, 987; δ_H (400 MHz, $(CD_3)_2CO$) 1.61 – 1.66 (2H, m, 4-H_2), 1.70 – 1.75 (3H, m, 10-H_3), 2.40 – 2.54 (2H, m, 2-H_2), 4.26 – 4.35 (1H, m, 3-H), 4.41 (1H, ap. q , *J* 6.0, 5-H), 5.59 – 5.70 (2H, m, 6-H and 9-H), 6.06 (1H, ddd, *J* 15.0, 10.4, 1.7, 8-H), 6.17 – 6.25 (1H, m, 7-H); δ_C (101 MHz, $(CD_3)_2CO$) 18.2 (C-10), 42.9 (C-2), 44.8 (C-4), 66.1 (C-3), 69.3 (C-5), 129.1 (C-9), 130.0 (C-8), 132.4 (C-7), 135.7 (C-6), 173.5 (C-1); HRMS (ESI) calc. for $[C_{10}H_{15}O_4]$ 199.0970 Found 199.0974.

(*R*,4*E*,6*E*)-3-Hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)trideca-4,6-dien-1-one (184)



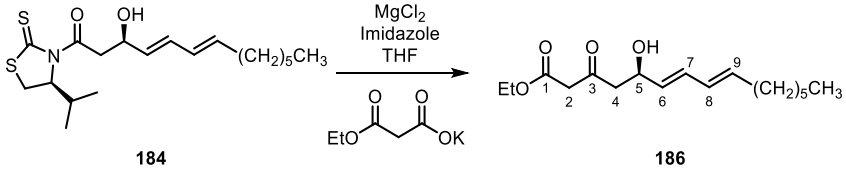
Acylated auxiliary **153** (1.0 g, 4.92 mmol) was dissolved in DCM (50 mL) under nitrogen and cooled to -78 °C then $TiCl_4$ (1 M in DCM, 5 mL, 4.92 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 20 minutes then DIPEA (1.05 mL, 5.90 mmol) was added dropwise. The reaction mixture was stirred for 1 hour then aldehyde **183** (0.55 mL, 4.92 mmol) was added dropwise. After stirring at -78 °C for 1 hour, aqueous saturated NH_4Cl (25 mL) was added and the reaction mixture was stirred for a further hour at room temperature. The solution was extracted with DCM (3 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (17% EtOAc in petroleum ether 60:40) to afford aldol products **184** (1.26 g, 69%) and **185** (0.28 g, 15%) as yellow oils.

184: $[\alpha]_D^{22}$ = +154.0 (*c* 1, Acetone); ν_{max} (film) 3429, 2958, 2925, 2871, 2854, 1694, 1466, 1159; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.5, 13-H_3), 0.98 (3H, d, *J* 7.0, 19-CH_3), 1.06 (3H, d, *J* 7.0, 19-CH_3), 1.19 – 1.34 (8H, m, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 2.02 – 2.12 (2H, m, 8-H_2), 2.36 (1H, ap. h, *J* 7.0, 19-H), 3.03 (1H,

d, *J* 11.5, 17-*H*H), 3.33 (1H, dd, *J* 17.6, 8.8, 2-*H*H), 3.52 (1H, dd, *J* 11.5, 7.9, 17-H*H*), 3.62 (1H, dd, *J* 17.6, 3.0, 2-H*H*), 4.63 – 4.76 (1H, m, 3-H), 5.14 (1H, dd, *J* 7.9, 7.0, 18-H), 5.62 (1H, dd, *J* 15.3, 6.2, 4-H), 5.65 – 5.78 (1H, m, 7-H), 6.01 (1H, dd, *J* 15.2, 10.4, 6-H), 6.25 (1H, dd, *J* 15.3, 10.4, 5-H); δ_C (101 MHz, $CDCl_3$) 14.2 (C-13), 17.9 (CH_3), 19.2 (CH_3), 22.7 (CH_2), 28.9 (CH_2), 29.3 (CH_2), 30.8 (C-17), 30.9 (C-19), 31.8 (CH_2), 32.7 (C-8), 45.4 (C-2), 68.6 (C-3), 71.5 (C-18), 129.3 (C-6), 130.9 (C-4), 131.4 (C-5), 136.3 (C-7), 172.6 (C-1), 203.1 (C-15); HRMS (ESI) calc. for [$C_{19}H_{31}NO_2S_2Na$] 392.1688 Found 392.1688.

185: $[\alpha]_D^{22}$ = +132.0 (*c* 1, Acetone); ν_{max} (film) 3425, 2959, 2924, 2871, 2854, 1693, 1466, 1157; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.8, 13-H_3), 0.98 (3H, d, *J* 6.9, 19-CH_3), 1.06 (3H, d, *J* 6.9, 19-CH_3), 1.22 – 1.32 (8H, m, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 2.03 – 2.10 (2H, m, 8-H_2), 2.35 (1H, ap. h, *J* 6.9, 19-H), 3.03 (1H, dd, *J* 11.5, 1.2, 17-*H*H), 3.39 (1H, dd, *J* 17.3, 3.4, 2-*H*H), 3.51 (1H, dd, *J* 11.5, 8.0, 17-H*H*), 3.62 (1H, dd, *J* 17.3, 8.9, 2-H*H*), 4.57 – 4.64 (1H, m, 3-H), 5.17 (1H, ddd, *J* 8.0, 6.9, 1.2, 18-H), 5.62 (1H, dd, *J* 15.3, 6.2, 4-H), 5.71 (1H, dt, *J* 15.0, 7.0, 7-H), 6.01 (1H, dd, *J* 15.0, 10.5, 6-H), 6.25 (1H, dd, *J* 15.3, 10.5, 5-H); δ_C (101 MHz, $CDCl_3$) 14.3 (C-13), 18.0 (CH_3), 19.3 (CH_3), 22.8 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 30.8 (C-17), 30.9 (C-19), 31.9 (CH_2), 32.8 (C-8), 45.3 (C-2), 69.2 (C-3), 71.5 (C-18), 129.4 (C-6), 131.6 (C-4), 131.6 (C-5), 136.4 (C-7), 173.1 (C-1), 203.2 (C-15); HRMS (ESI) calc. for [$C_{19}H_{31}NO_2S_2Na$] 392.1688 Found 392.1683.

Ethyl (*R*,6*E*,8*E*)-5-hydroxy-3-oxopentadeca-6,8-dienoate (186)

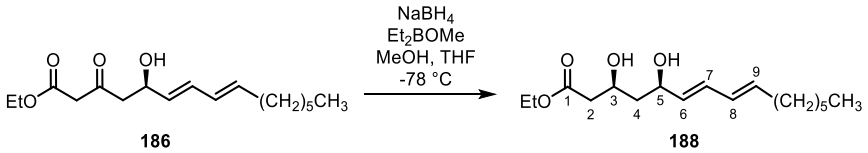


184 186

Potassium-3-ethoxy-2-methyl-3-oxopropanoate (1226 mg, 7.20 mmol) and $MgCl_2$ (343 mg, 3.60 mmol) were added to a solution of aldol product **184** (1200 mg, 3.25 mmol) in THF (20 mL) under nitrogen and stirred for 45 minutes. Imidazole (245 mg, 3.60 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (30 mL) and washed with 1 M HCl (10 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (15 mL) and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether 60:40) to afford **186** (709 mg, 75%) as a yellow oil; $[\alpha]_D^{22}$ = +17.0 (*c* 1, Acetone); ν_{max} (film) 3410, 2962, 2925, 2859, 1745, 1710, 1031, 988; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.6, 15-H_3), 1.20 – 1.34 (11H, m, OCH_2CH_3, 11-H_2, 12-H_2, 13-H_2 and 14-H_2), 2.07 (2H, ap. q, *J* 7.0, 10-H_2), 2.78 (2H, d, *J* 6.0, 4-H_2), 3.48 (2H, s, 2-H_2), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 4.55 – 4.68 (1H, m, 5-H), 5.55 (1H, dd, *J* 15.2, 6.4, 6-H), 5.71

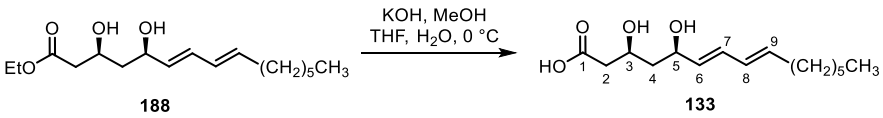
(1H, dt, *J* 15.0, 7.0, 9-H), 5.99 (1H, dd, *J* 15.0, 10.2, 8-H), 6.23 (1H dd, *J* 15.2, 10.2, 7-H); δ_C (101 MHz, $CDCl_3$) 14.23 ($OCH_2\mathit{CH_3}$ and C-15), 22.8 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 32.8 (C-10), 49.8 (C-4), 50.2 (C-2), 61.7 ($O\mathit{C}H_2CH_3$), 68.4 (C-5), 129.2 (C-8), 130.8 (C-6), 131.7 (C-7), 136.6 (C-9), 167.1 (C-1), 203.0 (C-3); HRMS (ESI) calc. for [$C_{17}H_{28}O_4Na$] 319.1880 Found 319.1879.

Ethyl (3*S*,5*R*,6*E*,8*E*)-3,5-dihydroxypentadeca-6,8-dienoate (188)



Ketone **186** (650 mg, 2.20 mmol) was dissolved in THF (16 mL) and MeOH (5 mL) under nitrogen and cooled to -78 °C then Et_2BOMe (0.38 mL, 2.91 mmol) was added dropwise and the reaction mixture was stirred for 15 minutes. $NaBH_4$ (105 mg, 2.78 mmol) was added in one portion and the reaction mixture was stirred for 3 hours then AcOH (2 mL) was added and the mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc (25 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in methanol (20 mL) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (30% EtOAc in petroleum ether 60:40) to afford diol **188** (415 mg, 63%, dr > 99:1) as a yellow oil; $[\alpha]_D^{22}$ = -7.0 (*c* 1, Acetone); ν_{max} (film) 3389, 2956, 2925, 2855, 1717, 987; δ_H (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* 6.6, 15-H_3), 1.19 – 1.40 (11H, m, $OCH_2\mathit{CH_3}$, 11-H_2, 12-H_2, 13-H_2 and 14-H_2), 1.58 – 1.76 (2H, m, 4-H_2), 2.02 – 2.10 (2H, m, 10-H_2), 2.48 (2H, dd, *J* 6.2, 2.6, 2-H_2), 3.03 (1H, s, OH), 3.73 (1H, s, OH), 4.17 (2H, q, *J* 7.1, $O\mathit{CH_2}CH_3$), 4.22 – 4.31 (1H, m, 3-H), 4.38 – 4.47 (1H, m, 5-H), 5.56 (1H, dd, *J* 15.3, 6.7, 6-H), 5.70 (dt, *J* = 15.0, 7.0 Hz, 9-H), 6.00 (1H, dd, *J* 15.0, 10.4, 8-H), 6.21 (1H, dd, *J* 15.3, 10.4, 7-H); δ_C (101 MHz, $CDCl_3$) 14.27 (C-15), 14.34 ($OCH_2\mathit{C}H_3$), 22.8 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 32.8 (C-10), 41.8 (C-2), 42.9 (C-4), 61.0 ($O\mathit{C}H_2CH_3$), 68.5 (C-3), 72.7 (C-5), 129.4 (C-8), 131.2 (C-7), 132.6 (C-6), 136.2 (C-9), 172.7 (C-1); HRMS (ESI) calc. for [$C_{17}H_{30}O_4Na$] 321.2036 Found 321.2029.

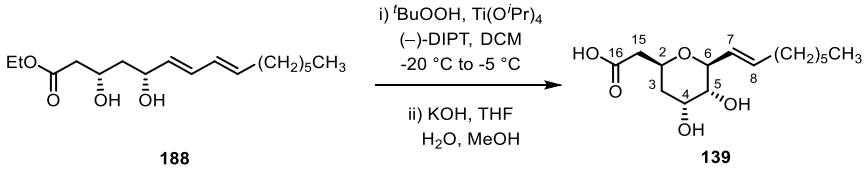
(3*S*,5*R*,6*E*,8*E*)-3,5-Dihydroxypentadeca-6,8-dienoic acid (133)



Ester **188** (100 mg, 0.34 mmol) was dissolved in THF (1.4 mL), MeOH (0.6 mL) and water (0.6 mL) and cooled to 0 °C when 25% aqueous KOH solution (0.12 mL) was added and the reaction mixture was stirred for 4 hours. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 mL) and solid

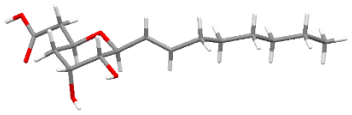
NH_4Cl was added until saturation. Two drops of 2 M HCl were added and the aqueous phase extracted with EtOAc (5 × 30 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **133** (67 mg, 73%) as a colourless oil; $[\alpha]_D^{22}$ = -16.0 (*c* 1, Acetone); ν_{max} (film) 3443, 3285, 2921, 2852, 1703, 990; δ_H (400 MHz, $(CD_3)_2CO$) 0.85 (3H, d, *J* 6.4, 15-H_3), 1.22 – 1.38 (8H, m, 11-H_2, 12-H_2, 13-H_2 and 14-H_2), 1.64 (2H, m, 4-H_2), 2.01 – 2.08 (2H, m, 10-H_2), 2.36 – 2.49 (2H, m, 2-H_2), 4.11 – 4.20 (1H, m, 3-H), 4.34 (1H, m, 5-H), 5.57 (1H, dd, *J* 15.2, 6.5, 6-H), 5.65 (1H, dt, *J* 15.0, 7.0, 9-H), 6.01 (1H, dd, *J* 15.0, 10.5, 8-H), 6.16 (1H, dd, *J* 15.2, 10.5, 7-H); δ_C (126 MHz, $(CD_3)_2CO$) 14.3 (C-15), 23.2 (C-13), 29.6 (C-14), 30.0 (C-11), 32.4 (C-12), 33.2 (C-10), 42.7 (C-2), 44.5 (C-4), 68.0 (C-3), 71.7 (C-5), 130.6 (C-7), 130.9 (C-8), 135.0 (C-9), 135.2 (C-6), 173.3 (C-1); HRMS (ESI) calc. for $[C_{15}H_{26}O_4]$ 269.1753 Found 269.1754.

2-((2*S*,4*R*,5*R*,6*S*)-4,5-Dihydroxy-6-((*E*)-oct-1-en-1-yl)tetrahydro-2H-pyran-2-yl)acetic acid (139)



In a flame dried flask at -20 °C under nitrogen was added 4 Å molecular sieves (30 mg) and DCM (2 mL) followed by $Ti(O^iPr)_4$ (0.02 mL, 0.07 mmol) and (−)-DIPT (0.02 mL, 0.08 mmol). The reaction mixture was stirred for 5 minutes then allylic alcohol **188** (100 mg, 0.34 mmol) in DCM (1 mL) was added and the solution was stirred for 30 minutes. ^{t}BuOOH (5.5 M in decane, 0.13 mL, 0.68 mmol) was added dropwise and the reaction mixture was stirred at -5 °C for 5 hours. The reaction mixture was quenched with 10 wt.% aqueous tartaric acid (5 mL) and warmed to room temperature. The organic layer was separated and the aqueous extracted with DCM (3 × 15 mL). The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (50% EtOAc in petroleum ether 60:40) to afford crude tetrahydropyran (30 mg, 28%) as a colourless oil. The crude material was dissolved in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) then 25% aqueous KOH solution (0.1 mL) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with aqueous saturated NH_4Cl (3 mL) and the aqueous phase was extracted with Et_2O (10 mL). The organic layer was discarded and the aqueous phase was acidified with 2 M HCl (2 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo* to afford acid **139** (15 mg, 52%) as a white solid; m.p. 94-98 °C (Et_2O/hexane); $[\alpha]_D^{23}$ = -48.0 (*c* 0.5, $CHCl_3$); ν_{max} (UATR) 3506, 3179, 2925, 1713, 1191, 1071; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.6, 14-H_3), 1.16 – 1.42 (8H, m, 4 × CH_2), 1.62 (1H, ap. t, *J* 12.9, 3-H_{ax}), 1.99 – 2.10 (3H, m, 3-H_{eq} and 9-H_2), 2.46 (1H, dd, *J* 15.8, 5.6, 15-*H*H), 2.60 (1H, dd, *J* 15.8, 7.2, 15-H*H*), 3.34

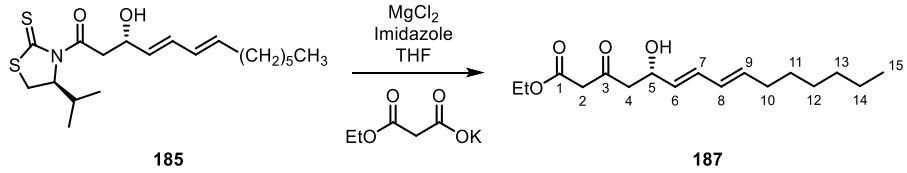
(1H, m, 5-H), 4.02 (1H, ap. t, *J* 7.7, 6-H), 4.15 – 4.23 (1H, m, 4-H), 4.22 – 4.29 (1H, m, 2-H), 5.42 (1H, dd, *J* 14.7, 7.7, 7-H), 5.85 (1H, dt, *J* 14.7, 6.6, 8-H); δ_C (101 MHz, $CDCl_3$) 14.2 (C-14), 22.7 (CH_2), 28.95 (CH_2), 29.01 (CH_2), 31.7 (CH_2), 32.6 (9-CH_2), 36.9 (C-3), 40.3 (C-15), 66.4 (C-4), 67.8 (C-2), 70.9 (C-5), 77.4 (C-6), 126.9 (C-7), 137.8 (C-8), 175.0 (C-16); HRMS (ESI) calc. for [$C_{15}H_{27}O_5$] 287.1853 Found 287.1847.



Crystal obtained by recrystallisation from Et_2O/hexane

Space group: $P2_1$ (monoclinic)

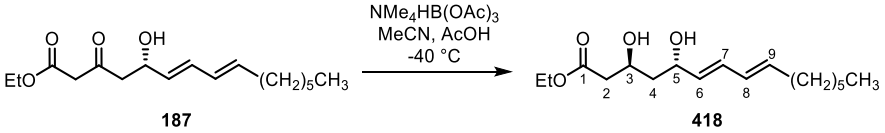
Ethyl (*S*,6*E*,8*E*)-5-hydroxy-3-oxopentadeca-6,8-dienoate (187)



185 **187**

Potassium-3-ethoxy-2-methyl-3-oxopropanoate (255 mg, 1.50 mmol) and $MgCl_2$ (71 mg, 0.75 mmol) were added to a solution of aldol product **185** (250 mg, 0.68 mmol) in THF (20 mL) under nitrogen and stirred for 45 minutes. Imidazole (51 mg, 0.75 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (20 mL) and washed with 1 M HCl (5 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (10 mL) and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether 60:40) to afford **187** (170 mg, 85%) as a yellow oil; $[\alpha]_D^{22}$ = -23.0 (*c* 1, Acetone); ν_{max} (film) 3401, 2963, 2920, 2845, 1745, 1711, 1033, 987; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.5, 15-H_3), 1.28 (11H, m, OCH_2CH_3, 11-H_2, 12-H_2, 13-H_2 and 14-H_2), 2.07 (2H, ap. q, *J* 7.0, 10-H_2), 2.78 (2H, d, *J* 6.0, 4-H_2), 3.48 (2H, s, 2-H_2), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 4.56 – 4.73 (1H, m, 5-H), 5.55 (1H, dd, *J* 15.2, 6.4, 6-H), 5.72 (1H, dt, *J* 15.0, 7.0, 9-H), 5.99 (1H, dd, *J* 15.0, 10.3, 8-H), 6.23 (1H, dd, *J* 15.2, 10.3, 7-H); δ_C (101 MHz, $CDCl_3$) 14.2 (OCH_2CH_3 and C-15), 22.7 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 32.7 (C-10), 49.7 (C-4), 50.1 (C-2), 61.6 (OCH_2CH_3), 68.4 (C-5), 129.2 (C-8), 130.7 (C-6), 131.6 (C-7), 136.6 (C-9), 167.0 (C-1), 202.9 (C-3); HRMS (ESI) calc. for [$C_{17}H_{28}O_4Na$] 319.1880 Found 319.1877.

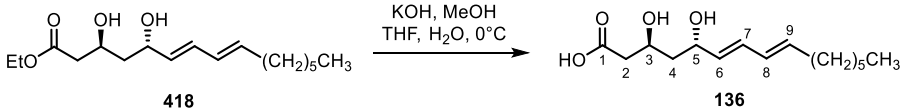
Ethyl (3*S*,5*S*,6*E*,8*E*)-3,5-dihydroxypentadeca-6,8-dienoate (418)



187 **418**

$Me_4NHB(OAc)_3$ (1.18 g, 4.47 mmol) was dissolved in MeCN (6 mL) and AcOH (2 mL) and stirred for 30 minutes at room temperature under nitrogen. The solution was cooled to -40 °C then ketone **187** (150 mg, 0.51 mmol) in MeCN (4 mL) was added dropwise. The reaction mixture was stirred for 5 hours then aqueous saturated sodium potassium tartrate (5 mL) was added and the mixture was warmed to room temperature and stirred for 1 hour. Aqueous saturated $NaHCO_3$ (15 mL) was added and the solution was extracted with DCM (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (30% EtOAc in petroleum ether 60:40) to afford diol **418** (93 mg, 61%, dr > 99:1) as a yellow oil; $[\alpha]_D^{22}$ = +9.0 (*c* 1, Acetone); ν_{max} (film) 3416, 2956, 2924, 2855, 1717, 988; δ_H (400 MHz, $CDCl_3$) 0.85 – 0.90 (3H, m, 15-H_3), 1.23 – 1.29 (11H, m, OCH_2CH_3, 11-H_2, 12-H_2, 13-H_2 and 14-H_2), 1.66 (1H, ddd, *J* 14.4, 7.8, 3.2, 4-*H*H), 1.78 (1H, ddd, *J* 14.4, 9.0, 3.4, 4-H*H*), 2.07 (2H, ap. q, *J* 7.0, 10-H_2), 2.48 – 2.51 (2H, m, 2-H_2), 2.59 (1H, d, *J* 4.3, OH), 3.46 (1H, d, *J* 3.7, OH), 4.17 (2H, q, *J* 7.1, OCH_2CH_3), 4.28 – 4.39 (1H, m, 3-H), 4.47 (1H, s, 5-H), 5.62 (1H, dd, *J* 15.3, 6.3, 6-H), 5.70 (1H, dt, *J* 15.0, 7.0, 9-H), 6.02 (1H, dd, *J* 15.0, 10.3, 8-H), 6.24 (1H, dd, *J* 15.3, 10.3, 7-H); δ_C (101 MHz, $CDCl_3$) 14.27 (C-15), 14.34 (OCH_2CH_3), 22.8 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 32.8 (C-10), 41.4 (C-2), 42.2 (C-4), 61.0 (OCH_2CH_3), 65.6 (C-3), 70.0 (C-5), 129.4 (C-8), 131.0 (C-7), 132.8 (C-6), 136.0 (C-9), 173.0 (C-1); HRMS (ESI) calc. for [$C_{17}H_{30}O_4Na$] 321.2036 Found 321.2028.

(3*S*,5*S*,6*E*,8*E*)-3,5-Dihydroxypentadeca-6,8-dienoic acid (136)

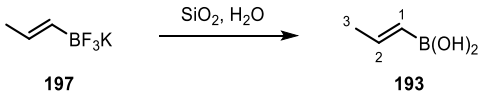


418 **136**

Ester **418** (50 mg, 0.17 mmol) was dissolved in THF (0.7 mL), MeOH (0.3 mL) and water (0.3 mL) and cooled to 0 °C then 25% aqueous KOH solution (0.06 mL) was added and the reaction mixture was stirred for 4 hours. The reaction mixture was quenched with aqueous saturated NH_4Cl (2 mL) and solid NH_4Cl was added until saturation. Two drops of 2 M HCl were added and the aqueous phase extracted with EtOAc (5 × 30 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **136** (38 mg, 83%) as a colourless oil; $[\alpha]_D^{22}$ = +6.0 (*c* 1, Acetone); ν_{max} (film) 3445, 3361, 2921, 2850, 1687, 991; δ_H (400 MHz, $(CD_3)_2CO$) 0.87 – 0.96 (3H, m, 15-H_3), 1.26 – 1.44 (8H, m, 11-H_2, 12-H_2, 13-H_2 and 14-H_2), 1.64 – 1.70 (2H, m, 4-H_2), 2.10 – 2.15 (2H, m, 10-H_2), 2.50 (2H, dd, *J* 9.0, 6.4, 2-H_2), 4.28 – 4.39 (1H, m, 3-H), 4.44 (1H, ap. q, *J* 6.0, 5-H), 5.64 – 5.73 (2H, m, 6-H and 9-H), 6.09 (1H, dd, *J* 15.1, 10.5, 8-H), 6.25 (1H, dd, *J* 15.0, 10.5, 7-H); δ_C (126 MHz, $(CD_3)_2CO$) 14.3 (C-15), 23.2 (C-13), 29.6 (C-14), 30.0 (C-11), 32.4 (C-12), 33.2 (C-10), 42.9 (C-2), 44.6 (C-4), 66.0 (C-3), 69.23 (C-5), 130.0 (C-7), 131.0 (C-8), 134.7 (C-9), 135.9 (C-6), 173.4 (C-1); HRMS (ESI) calc. for [$C_{15}H_{26}O_4$] 269.1753 Found 269.1762.

(*E*)-Prop-1-en-1-ylboronic acid (193)

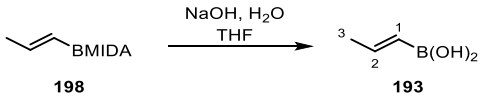
Method 1:



197 193

To a solution of potassium trifluoroborate salt **197** (4.50 g, 30.41 mmol) in water (100 mL) under nitrogen was added silica gel (1.83 g, 30.41 mmol). The reaction mixture was stirred for 3 hours at room temperature, filtered and the residue washed with EtOAc (200 mL). The layers were separated and the aqueous phase extracted with further EtOAc (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford boronic acid **193** (2.62 g, quant.) as a white solid which was used directly in the next step; δ_H (400 MHz, $CDCl_3$) 1.91 (3H, dd, *J* 6.4, 1.7, 3-H_3), 5.55 (1H, dt, *J* 17.5, 1.7, 1-H), 6.98 (1H, dq, *J* 17.5, 6.5, 2-H); δ_C (101 MHz, $CDCl_3$) 21.8 (C-3), 152.9 (C-2). Data consistent with the literature.[266]

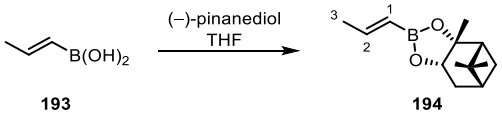
Method 2:



198 193

Boronate **198** (9.67 g, 49.12 mmol) was dissolved in THF (250 mL) and 1 M NaOH (147 mL, 147 mmol) then stirred for 30 minutes. The reaction mixture was diluted with aqueous saturated NH_4Cl (100 mL) and the resulting solution was extracted with Et_2O (3 × 300 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford boronic acid **193** (4.25 g, quant.) as a white solid which was used directly in the next step. Data consistent with previously reported.

(–)-Pinanediol (*E*)-1-propen-1-ylboronate (194)

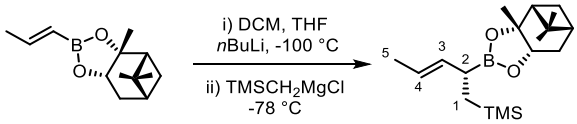


193 194

Boronic acid **193** (922 mg, 10.7 mmol) and (−)-pinanediol (1830 mg, 10.7 mmol) were dissolved in THF (22 mL) and stirred for 30 minutes. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford boronate **194** (2316 mg, 98%) as a white crystalline solid; $[\alpha]_D^{25}$ = -24.0 (*c* 1, $CHCl_3$) lit. enantiomer[213] $[\alpha]_D^{23}$ = +24.2 (*c* 1.3, $CHCl_3$); ν_{max} (UATR) 2942, 2912, 1636, 1358, 986; δ_H (400 MHz, $CDCl_3$) 0.84 (3H, s, pinanyl CH_3), 1.14 (1H, d, *J* 10.9, pinanyl H), 1.28 (3H, s, pinanyl CH_3), 1.39 (3H, s, pinanyl CH_3), 1.85 (3H, dd, *J* 6.4, 1.7, 3-CH_3), 1.87 – 1.93 (2H, m, CH_2), 2.05 (1H, dd, *J* 6.0, 4.9, pinanyl CH), 2.16 – 2.24 (1H, m, pinanyl CH),

2.34 (1H, ddt, *J* 14.0, 8.7, 2.2, pinanyl CH), 4.29 (1H, dd, *J* 8.7, 1.9, CHOB), 5.47 (1H, dq, *J* 17.9, 1.7, 1-H), 6.64 (1H, dq, *J* 17.9, 6.4, 2-H); δ_C (101 MHz, $CDCl_3$) 21.9, 24.2, 26.6, 27.3, 28.8, 35.7, 38.3, 39.7, 51.5, 77.8 (OCH), 85.6 (OC), 120.1 (br, C-1), 149.7 (C-2). Data consistent with the literature.[213]

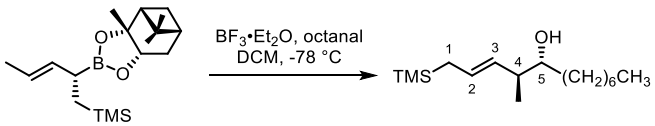
Trimethyl (*S*,*E*)-2-((−)-pinanediol boronate)-pent-3-en-1-yl)silane (195)



194 195

DCM (2.86 mL) and THF (80 mL) were cooled to -100 °C under nitrogen then 2.45 M *n*BuLi in THF (11.68 mL, 28.62 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 20 minutes then boronic ester **194** (6.30 g, 28.62 mmol) in THF (15 mL) was added dropwise over 10 minutes. The reaction mixture was stirred for 2 minutes then warmed to 0 °C. After 40 minutes the reaction mixture was cooled to -78 °C then 1.3 M $TMSCH_2MgCl$ in THF (22.0 mL, 28.62 mmol) was added dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 3 hours, room temperature for 18 hours then quenched with aqueous saturated NH_4Cl (25 mL). The resulting solution was diluted with Et_2O (250 mL) and water (150 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (3% Et_2O in petroleum ether 60:40) to afford boronic ester **195** (7.66 g, 84%, dr > 99:1) as a colourless oil; $[\alpha]_D^{25}$ = -22.0 (*c* 1, $CHCl_3$) lit.[213] $[\alpha]_D^{25}$ = -11.75 (*c* 0.45, $CHCl_3$); ν_{max} (film) 2916, 1367, 1246, 1031, 857, 834; δ_H (400 MHz, $CDCl_3$) -0.03 (9H, s, $Si(CH_3)_3$), 0.63 (1H, dd, *J* 14.5, 7.6, 1-*H*H), 0.82 (1H, dd, *J* 14.5, 7.6, 1-H*H*), 0.83 (3H, s, CH_3), 1.11 (1H, d, *J* 10.9, C*H*H), 1.27 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.61 – 1.65 (3H, m, 5-H_3), 1.78 – 1.85 (1H, m, C*H*H), 1.85 – 1.91 (2H, m, 2-H and CH), 2.04 (1H, t, *J* 5.6, CH), 2.13 – 2.22 (1H, m, CH*H*), 2.32 (1H, ddt, *J* 14.4, 8.7, 2.4, C*H*H), 4.25 (1H, dd, *J* 8.7, 2.0, BOCH), 5.33 – 5.47 (2H, m, 3-H and 4-H); δ_C (101 MHz, $CDCl_3$) -0.8 ($Si(CH_3)_3$), 17.9 (C-1), 18.2 (C-5), 24.2 (CH_3), 26.3 (CH_2), 27.3 (CH_3), 28.7 (CH_3), 35.7 (CH_2), 38.4 (C), 39.6 (CH), 51.6 (CH), 77.9 (CH), 85.6 (OC), 123.1 (C-4), 134.6 (C-3); HRMS (ESI) calc. for [$C_{18}H_{34}BO_2Si$] 321.2419 Found 321.2404. Data consistent with the literature.[213]

(4*S*,5*R*,*E*)-4-Methyl-1-(trimethylsilyl)dodec-2-en-5-ol (192)

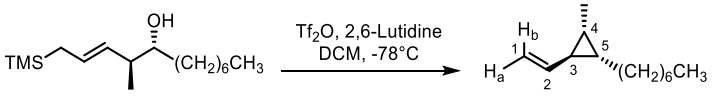


195 192

Boronic ester **195** (3.00 g, 9.36 mmol) and octanal (1.46 mL, 9.36 mmol) were dissolved in DCM (47 mL) under nitrogen and cooled to -78 °C. $BF_3.Et_2O$ (1.16 mL, 9.36 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 4 hours. Aqueous saturated $NaHCO_3$ (30 mL) was added and the reaction mixture was warmed to room temperature. The organic layer was separated and the aqueous extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether 60:40) to afford alcohol **192** (2.36 g, 93%, dr > 99:1) as a colourless oil; $[\alpha]_D^{22}$ = -10.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3367, 2955, 2925, 2855, 1247, 839; δ_H (400 MHz, $CDCl_3$) 0.00 (1H, s, TMS), 0.86 – 0.90 (3H, m, 12-H_3), 0.99 (3H, d, *J* 6.8, 4-CH_3), 1.20 – 1.37 (11H, m, 6-*H*H and 7,8,9,10,11-H_2), 1.46 (2H, dd, *J* 8.1, 1.3, 1-H_2), 1.47 – 1.53 (1H, m, 6-H*H*), 1.61 (1H, d, *J* 3.5, OH), 2.05 – 2.16 (1H, m, 4-H), 3.28 (1H, ddd, *J* 7.9, 6.4, 3.5, 5-H), 5.13 (1H, ddt, *J* 15.2, 8.6, 1.3, 3-H), 5.50 (1H, dtd, *J* 15.2, 8.1, 0.9, 2-H); δ_C (101 MHz, $CDCl_3$) -1.8 (TMS), 14.3 (C-12), 17.4 (CH_3-4), 22.9 (CH_2), 23.2 (C-1), 26.0 (C-7), 29.5 (CH_2), 30.0 (CH_2), 32.1 (CH_2), 34.4 (C-6), 43.8 (C-4), 75.2 (C-5), 129.2 (C-2), 130.4 (C-3); HRMS (ESI) calc. for [$C_{16}H_{34}OSiNa$] 293.2271 Found 293.2279.

(1*S*,2*R*,3*S*)-1-Heptyl-2-methyl-3-vinylcyclopropane (196)

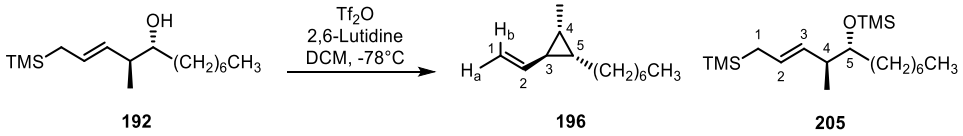
Method 1:



192 **196**

Alcohol **192** (700 mg, 2.59 mmol) was dissolved in DCM (30 ml) and cooled to -78 °C under nitrogen then 2,6-lutidine (0.39 mL, 3.37 mmol) was added and the reaction mixture was stirred for 5 minutes. Tf_2O (0.52 mL, 3.11 mmol) was added within 5 seconds then the reaction mixture was stirred for 3 minutes before quenching with DIPEA (5.5 mL, 30.0 mmol). The mixture was warmed to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether 60:40) to afford alcohol **196** (412 mg, 88%, dr > 99:1) as a colourless oil; $[\alpha]_D^{22}$ = -11.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2956, 2924, 2855, 1636, 1465, 1248, 888, 839; δ_H (400 MHz, $CDCl_3$) 0.73 – 0.80 (1H, m, 3-H), 0.83 – 0.92 (5H, m, 12-H_3, 4-H and 5-H), 1.06 (3H, d, *J* 6.2, 4-CH_3), 1.23 – 1.39 (12H, m, 6,7,8,9,10 and 11-H_2), 4.78 (1H, dd, *J* 10.3, 1.8, 1-H_a), 4.95 (1H, dd, *J* 17.1, 1.8, 1-H_b), 5.42 (1H, ddd, *J* 17.1, 10.3, 8.3, 2-H); δ_C (101 MHz, $CDCl_3$) 12.6 (CH_3-4), 14.3 (C-12), 19.7 (C-4), 22.9 (C-5), 26.1 (C-3), 27.9 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 30.5 (CH_2), 32.1 (CH_2), 110.5 (C-2), 142.9 (C-1); HRMS (ESI) calc. for [$C_{13}H_{24}$] 181.1951 Found 181.1947.

Method 2:



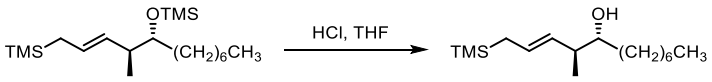
192 **196** **205**

Alcohol **192** (2.60 g, 9.61 mmol) was dissolved in DCM (96 ml) and cooled to -78 °C under nitrogen then 2,6-lutidine (1.45 mL, 12.49 mmol) was added and the reaction mixture was stirred for 5 minutes. Tf_2O (1.94 mL, 11.53 mmol) was added within 1 minute and the reaction mixture was stirred for 3 minutes before quenching with DIPEA (15.0 mL, 96.10 mmol). The mixture was warmed to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether 60:40) to afford alcohol **196** (964 mg, 56%) and silyl ether **205** (803 mg, 24%) as colourless oils.

196: Data as previously reported.

205: δ_H (400 MHz, $CDCl_3$) -0.01 (9H, s, $Si(CH_3)_3$), 0.10 (9H, s, $Si(CH_3)_3$), 0.84 – 0.91 (3H, m, 12-H_3), 0.95 (3H, d, *J* 6.9, 4-CH_3), 1.20 – 1.38 (12H, m, 6 × CH_2), 1.39 – 1.45 (2H, m, 1-H_2), 2.10 – 2.25 (1H, m, 4-H), 3.48 (1H, ap. dt, *J* 8.3, 4.0, 5-H), 5.19 (1H, m, 3-H), 5.31 – 5.40 (1H, m, 2-H); δ_C (101 MHz, $CDCl_3$) δ -1.8 ($Si(CH_3)_3$), 0.7 ($Si(CH_3)_3$), 14.3 (C-12), 16.5 (CH_3-4), 22.86 (CH_2), 22.93 (C-1), 26.4 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 32.1 (CH_2), 33.8 (CH_2), 42.9 (C-4), 77.0 (C-5), 126.3 (C-2), 131.1 (C-3); HRMS (ESI) calc. for [$C_{19}H_{43}OSi_2$] 343.2847 Found 343.2837.

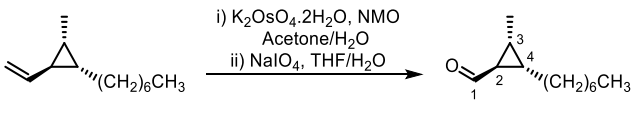
(4*S*,5*R*,*E*)-4-Methyl-1-(trimethylsilyl)dodec-2-en-5-ol (192)



205 **192**

Silyl ether **205** (800 mg, 2.33 mmol) was dissolved in THF (12 mL) and 2 M HCl (12 mL) and stirred for 3 hours. The reaction mixture was diluted with water (30 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford alcohol **192** (634 mg, quant.) as a colourless oil. Data consistent with previously reported.

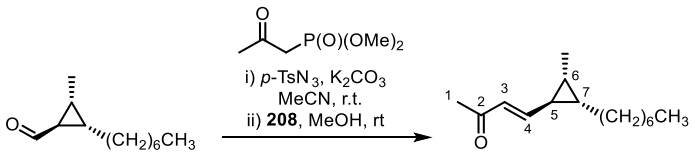
(2*S*,3*R*,4*S*)-4-Heptyl-3-methylcyclopropane-2-carbaldehyde (208)



196 **208**

Alkene **196** (50 mg, 0.28 mmol) was dissolved in acetone (1.2 mL) and water (0.2 mL) then a spatula tip of potassium osmate dihydrate and NMO (49 mg, 0.42 mmol) were added sequentially and the reaction mixture was stirred at room temperature. After 18 hours the reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated and the aqueous was extracted with further EtOAc (2 × 10 mL). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude diol was dissolved in THF (1 mL) and water (0.7 mL) and $NaIO_4$ (84 mg, 0.39 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The solution was filtered through a pad of Celite and washed with DCM (30 mL). The organic phase was washed with aqueous saturated $Na_2S_2O_3$ (15 mL) and the aqueous extracted with DCM (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford aldehyde **208** (46 mg, 90%) as a colourless oil; $[\alpha]_D^{23}$ = +41.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2956, 2925, 2855, 1705, 1465, 1065; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.6, 11-H_3), 1.14 (3H, d, *J* 6.3, 3-CH_3), 1.21 – 1.34 (10H, m, 5 × CH_2), 1.38 (3H, m, 2-H and 5-H_2), 1.53 (1H, m, 4-H), 1.64 (1H, m, 3-H), 9.05 (1H, d, *J* 5.4, 1-H); δ_C (101 MHz, $CDCl_3$) 12.0 (CH_3-3), 14.2 (C-11), 22.3 (C-3), 22.8 (CH_2), 27.0 (C-5), 28.5 (C-4), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 38.9 (C-2), 201.5 (C-1); HRMS (ESI) calc. for [$C_{12}H_{22}O$] 183.1743 Found 183.1737.

(*E*)-4-((5*S*,6*S*,7*R*)-2-Heptyl-3-methylcyclopropyl)but-3-en-2-one (212)

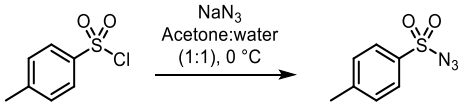


208 **212**

Dimethyl 2-oxopropylphosphonate (33 mg, 0.20 mmol) was added to a suspension of K_2CO_3 (66 mg, 0.48 mmol) and TsN_3 (39 mg, 0.20 mmol) in MeCN (1.6 mL) under nitrogen. The reaction mixture was stirred for 2 hours then aldehyde **208** (30 mg, 0.16 mmol) in MeOH (0.4 ml) was added. The reaction mixture was stirred for 16 hours and the solvent was removed *in vacuo*. The crude material was dissolved in Et_2O (10 mL) and washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% EtOAc in petroleum ether 60:40) to afford enone **212** (7 mg, 20%) as a colourless oil; $[\alpha]_D^{23}$ = +21.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2925, 2855, 1667, 1612, 1257; δ_H (400 MHz, $CDCl_3$) 0.80 – 0.91 (3H, m, 14-H_3), 0.92 – 0.98 (1H, m, 5-H), 1.03 – 1.09 (1H, m, 7-H), 1.09 – 1.14 (4H, m, 6-H and 6-CH_3), 1.21 – 1.43 (12H, m, 6 × CH_2), 2.18 (3H, s, 1-H_3), 6.08 (1H, d, *J* 15.6, 3-H), 6.39 (1H, dd, *J* 15.6, 9.8, 4-H); δ_C (101 MHz, $CDCl_3$) 12.5 (CH_3-6), 14.3 (C-14), 22.8 (C-6), 23.1 (CH_2), 27.1 (C-1),

27.7 (CH_2), 29.3 (C-7), 29.4 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 30.50 (C-5), 32.0 (CH_2), 127.4 (C-3), 154.1 (C-4), 198.0 (C-2); HRMS (ESI) calc. for [$C_{15}H_{27}O$] 223.2056 Found 223.2065.

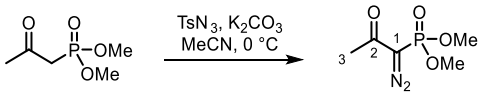
4-Methylbenzenesulfonyl azide (419)



419

To a stirred solution of 4-toluenesufonyl chloride (5.01 g, 26.28 mmol) in acetone (75 mL) and water (75 mL) at 0 °C was added sodium azide (1.74 g, 26.78 mmol) and the reaction mixture was stirred at 0 °C for 3 hours. The solvent volume was reduced by half *in vacuo* and the resulting solution was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford azide **419** (5.09 g, 99%) as a colourless oil; ν_{max} (film) 2123, 1596, 1368, 1164, 1086; δ_H (400 MHz, $CDCl_3$) 2.48 (3H, s, CH_3), 7.35 – 7.48 (2H, m, ArH), 7.67 – 7.96 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 21.9 (CH_3), 127.7 (ArCH), 130.5 (ArCH), 135.7 (ArC), 146.4 (ArC); m/z (ESI): $[M+Na]^+$ = 220.01. Data consistent with the literature.[216]

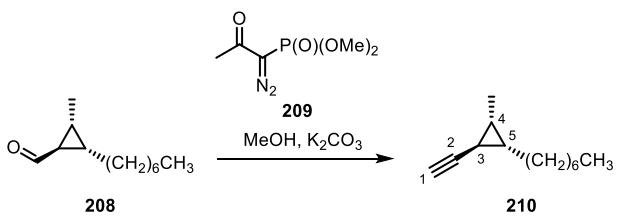
Dimethyl (1-diazo-2-oxopropyl)phosphonate (209)



209

K_2CO_3 (274 mg, 1.98 mmol) and TsN_3 (392 mg, 1.98 mmol) were added to a stirred solution of dimethyl 2-oxopropylphosphonate (300 mg, 1.80 mmol) in MeCN (4 mL) at 0 °C under nitrogen. After stirring for 4 hours the solvent was removed *in vacuo*. The crude residue was dissolved in DCM (30 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (90% EtOAc in petroleum ether 60:40) to afford phosphonate **209** (259 mg, 75%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, 3-H_3), 3.83 (6H, d, *J* 12.0, 2 × OMe); δ_C (101 MHz, $CDCl_3$) 27.3 (C-3), 53.7 (d, *J* 5.4, OMe), 190.1 (d, *J* 13.0, C-2); m/z (ESI): $[M+H]^+$ = 193.04. Data consistent with the literature.[267]

(3*S*,4*R*,5*S*)-1-Ethynyl-2-heptyl-3-methylcyclopropane (210)



208 **210**

To a stirred solution of aldehyde **208** (254 mg, 1.39 mmol) in MeOH (12 mL) under nitrogen was added K_2CO_3 (384 mg, 2.78 mmol) followed by phosphonate **209** (321 mg, 1.67 mmol) in MeOH (2 mL). After 16 hours the reaction mixture was diluted with Et_2O (25 mL) and washed sequentially with aqueous saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (5% Et_2O in petroleum ether 60:40) to afford alkyne **210** (198 mg, 80%) as a colourless oil; $[\alpha]_D^{23}$ = +6.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3317, 2956, 2925, 2855, 2119, 1465, 638; δ_H (400 MHz, $CDCl_3$) 0.53 – 0.61 (1H, m, 3-H), 0.88 (3H, t, *J* 6.8, 12-H_3), 1.00 – 1.11 (4H, m, 4-H and 4-CH_3), 1.11 – 1.20 (1H, m, 5-H), 1.22 – 1.35 (10H, m, 5 × CH_2), 1.36 – 1.43 (2H, m, 6-H_2), 1.81 (1H, d, *J* 2.1, 1-H); δ_C (101 MHz, $CDCl_3$) 12.4 (CH_3-4), 13.5 (C-3), 14.3 (C-12), 21.3 (C-5), 22.9 (CH_2), 27.4 (C-4), 27.7 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 63.9 (C-1), 88.0 (C-2); HRMS (ESI) calc. for [$C_{13}H_{22}$] 179.1794 Found 179.1788.

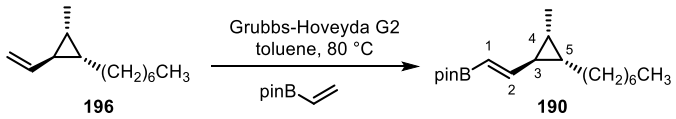
2-((*E*)-2-((1*S*,2*S*,3*R*)-2-Heptyl-3-methylcyclopropyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (190)

Method 1:

210 **190**

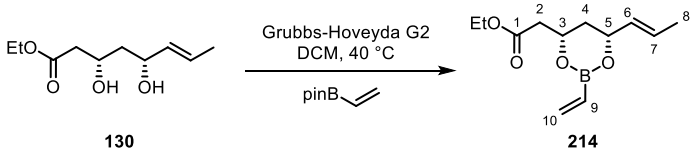
HBpin (0.04 mL, 0.28 mmol), triethylamine (0.01 mL, 0.03 mmoL) and Cp_2ZrHCl (2 mg, 0.01 mmol) were added sequentially to alkyne **210** (47 mg, 0.26 mmol) stirring under nitrogen and the reaction mixture was heated at 40 °C for 18 hours. The reaction mixture was cooled to room temperature, quenched with water (10 mL) and diluted with DCM (15 mL). The organic layer was separated and the aqueous extracted with further DCM (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (5% Et_2O in petroleum ether 60:40) to afford vinyl boronic ester **190** (72 mg, 92%, *E*/*Z* > 99:1) as a colourless oil; $[\alpha]_D^{24}$ = -9.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2977, 2956, 2925, 2855, 1630, 1352, 1139; δ_H (400 MHz, $CDCl_3$) 0.83 – 0.97 (5H, m, 3-H, 5-H and 12-H_3), 0.98 – 1.09 (4H, m, 4-H and 4-CH_3), 1.19 – 1.41 (24H, m, 6 × CH_2 and Bpin), 5.36 (1H, d, *J* 17.8, 1-H), 6.19 (1H, dd, *J* 17.8, 8.9, 2-H); δ_C (101 MHz, $CDCl_3$) 12.6 (CH_3-4), 14.3 (C-12), 21.4 (C-3/4/5), 22.9 (CH_2), 24.93 (Bpin CH_3), 24.94 (Bpin CH_3), 27.7 (C-3/4/5), 27.8 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 33.1 (C-3/4/5), 83.0 (Bpin C), 114.0 (C-1), 159.0 (C-2); HRMS (ESI) calc. for [$C_{19}H_{36}BO_2$] 307.2806 Found 307.2794.

Method 2:



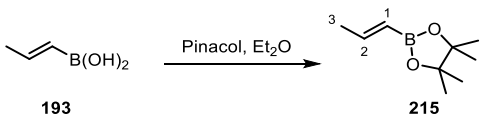
Alkene **196** (54 mg, 0.30 mmol) was dissolved in degassed toluene (3 mL) under nitrogen then vinyl boronic pinacol ester (0.10 mL, 0.60 mmol) followed by Hoveyda-Grubbs Catalyst G2 (19 mg, 0.03 mmol) were added. The reaction mixture was heated at 80 °C for 20 hours. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (4% Et_2O in petroleum ether 60:40) to afford alkene **190** (58 mg, 63%, *E*/*Z* > 99:1) as a yellow oil. Data consistent with previously reported.

Ethyl 2-((3*R*,5*S*)-6-((*E*)-prop-1-en-1-yl)-2-vinyl-1,3,2-dioxaborinan-4-yl)acetate (214)



Hoveyda-Grubbs Catalyst G2 (7.5 mg, 0.01 mmol) was dissolved in DCM (1 mL) under nitrogen then alkene **130** (50 mg, 0.25 mmol) in DCM (1 mL) and vinyl boronic pinacol ester (0.13 mL, 0.74 mmol) were added. The reaction mixture was heated at 40 °C for 16 hours. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (18% EtOAc in petroleum ether 60:40) to afford alkene **214** (12 mg, 20%) as a yellow oil; ν_{max} (film) 2974, 2920, 1736, 1399, 1300; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.51 (1H, ap. dt, *J* 13.8, 11.4, 4-*H*H), 1.71 (3H, d, *J* 6.7, 8-H_3), 2.05 (1H, ap. dt, *J* 13.8, 2.8, 4-H*H*), 2.46 (1H, dd, *J* 15.4, 6.3, 2-*H*H), 2.64 (1H, dd, *J* 15.4, 7.0, 2-H*H*), 4.17 (2H, ap. qd, *J* 7.1, 1.3, OCH_2CH_3), 4.41 – 4.54 (2H, m, 3-H and 5-H), 5.47 (1H, ddq, *J* 15.3, 6.5, 1.6, 6-H), 5.70 – 5.83 (2H, m, 7-H and 9-H), 5.87 (1H, dd, *J* 13.4, 4.6, 10-H), 6.06 (1H, dd, *J* 19.1, 4.6, 10-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH_2CH_3), 17.8 (C-8), 38.9 (C-4), 42.3 (C-2), 60.8 (OCH_2CH_3), 68.3 (C-3), 72.1 (C-5), 127.6 (C-6), 131.7 (C-7), 134.8 (C-10), 170.9 (C-1).

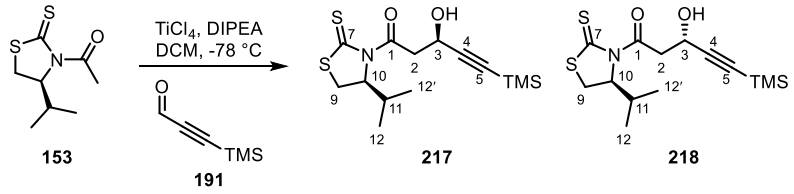
(*E*)-4,4,5,5-Tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane (215)



Boronic acid **193** (100 mg, 1.16 mmol), pinacol (137 mg, 1.16 mmol) and anhydrous $MgSO_4$ (100 mg) were dissolved in Et_2O (4 mL) and stirred for 4 hours. The reaction mixture was filtered over a pad of silica, eluting with 10% EtOAc in petroleum ether 60:40 to afford boronate **215** (170 mg, 87%) as a

colourless oil; δ_H (400 MHz, $CDCl_3$) 1.26 (12H, s, 4 × CH_3), 1.84 (3H, dd, *J* 6.4, 1.7, 3-H_3), 5.45 (1H, dq, *J* 17.8, 1.7, 1-H), 6.65 (1H, dq, *J* 17.8, 6.4, 2-H); δ_C (101 MHz, $CDCl_3$) 21.9 (C-3), 24.9 (4 × CH_3), 83.2 (COB), 149.9 (C-2); m/z (ESI): $[M+H]^+$ = 169.14. Data consistent with the literature.[268]

(*R*)-3-Hydroxy-1-((*S*)-10-isopropyl-7-thioxothiazolidin-8-yl)-5-(trimethylsilyl)pent-4-yn-1-one (217)

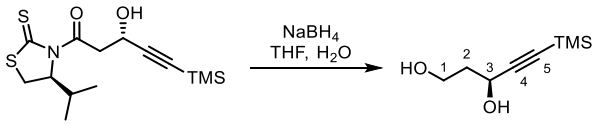


Acylated auxiliary **153** (2.01 g, 9.84 mmol) was dissolved in DCM (100 mL) under nitrogen and cooled to -78 °C then $TiCl_4$ (1 M in DCM, 9.85 mL, 9.85 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 20 minutes then DIPEA (2.05 mL, 11.8 mmol) was added dropwise. The reaction mixture was stirred for 1 hour then aldehyde **191** (1.45 mL, 9.83 mmol) was added dropwise. After stirring at -78 °C for 1 hour, aqueous saturated NH_4Cl (25 mL) was added and the reaction mixture was stirred for a further hour at room temperature. The solution was washed with DCM (3 × 50 mL) dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (17% EtOAc in petroleum ether 60:40) to afford aldol products **217** (1.72 g, 53%) and **217** (0.90 g, 28%) as yellow oils.

217: $[\alpha]_D^{22}$ = +533.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3428, 2962, 2174, 1693, 1249, 1167, 843; δ_H (400 MHz, $CDCl_3$) 0.17 (9H, s, $Si(CH_3)_3$), 0.98 (3H, d, *J* 7.0, 12-H_3), 1.06 (3H, d, *J* 6.8, 12'-H_3), 2.28 – 2.44 (1H, m, 11-H), 2.96 (1H, d, *J* 6.2, OH), 3.05 (1H, dd, *J* 11.5, 1.0, 9-*H*H), 3.54 (1H, dd, *J* 11.5, 7.9, 9-H*H*), 3.59 – 3.72 (2H, m, 2-H_2), 4.81 – 4.91 (1H, m, 3-H), 5.14 (1H, ddd, *J* 7.9, 6.3, 1.0, 10-H); δ_C (101 MHz, $CDCl_3$) 0.0 ($Si(CH_3)_3$), 18.0 (C-12), 19.3 (C-12), 30.97 (C-9), 31.05 (C-11), 45.9 (C-2), 59.3 (C-3), 71.5 (C-10), 90.1 (C-5), 104.7 (C-4), 172.0 (C-1), 203.0 (C-7); HRMS (ESI) calc. for [$C_{14}H_{23}NO_2S_2Si$] 330.1012 Found 330.1005.

218: $[\alpha]_D^{22}$ = +425.0 (*c* 1, $CHCl_3$); ν_{max} (cm^{-1}) 3439, 2962, 2178, 1690, 1248, 839; δ_H (400 MHz, $CDCl_3$) 0.16 (9H, s, $Si(CH_3)_3$), 0.98 (3H, d, *J* 6.9, 12-H_3), 1.06 (3H, d, *J* 6.7, 12'-H_3), 2.27 – 2.42 (1H, m, 11-H), 3.05 (1H, dd, *J* 11.5, 1.2, 9-*H*H), 3.24 (1H, d, *J* 6.5, OH), 3.46 (1H, dd, *J* 17.6, 3.8, 2-*H*H), 3.53 (1H, dd, *J* 11.5, 8.0, 9-H*H*), 3.96 (1H, dd, *J* 17.6, 7.9, 2-H*H*), 4.80 (1H, ddd, *J* 7.9, 6.5, 3.8, 3-H), 5.19 (1H, ddd, *J* 8.0, 6.4, 1.2, 10-H); δ_C (101 MHz, $CDCl_3$) 0.0 ($Si(CH_3)_3$), 18.0 (C-12), 19.3 (C-12), 30.8 (C-9), 30.9 (C-11), 45.7 (C-2), 59.6 (C-3), 71.5 (C-10), 90.0 (C-5), 104.7 (C-4), 172.0 (C-1), 203.0 (C-7); HRMS (ESI) calc. for [$C_{14}H_{23}NO_2S_2Si$] 330.1012 Found 330.1002.

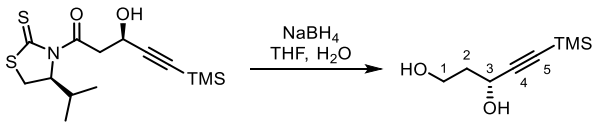
(*S*)-5-(Trimethylsilyl)pent-4-yne-1,3-diol (220)



218 **220**

Alcohol **218** (200 mg, 0.61 mmol) was dissolved in THF (8 mL) under nitrogen then $NaBH_4$ (69 mg, 1.82 mmol) was added followed by water (10 drops). The reaction mixture was stirred at room temperature for 30 minutes and quenched with 2 M HCl (2 mL). The resulting solution was extracted with DCM (3 × 10 mL). The combined organic layers were washed sequentially with aqueous saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc in petroleum ether 60:40) to afford diol **220** (81 mg, 77%) as a colourless oil; $[\alpha]_D^{24}$ = -47.0 (*c* 1, $CHCl_3$), lit.[221] $[\alpha]_D^{23}$ = -30.8 (*c* 1, $CHCl_3$); ν_{max} (film) 3334, 2957, 2897, 2172, 1249; δ_H (400 MHz, $CDCl_3$) 0.17 (9H, s, $Si(CH_3)_3$), 1.83 – 2.08 (2H, m, 2-H_2), 2.18 (1H, s, 1-OH), 2.69 (1H, s, 3-OH), 3.81 – 3.92 (1H, m, 1-*H*H), 3.92 – 4.07 (1H, m, 1-H*H*), 4.63 (1H, ap. t, *J* 5.5, 3-H); δ_C (101 MHz, $CDCl_3$) 0.0 ($Si(CH_3)_3$), 39.1 (C-2), 60.6 (C-1), 62.3 (C-3), 90.3 (C-5), 106.1 (C-4); HRMS (ESI) calc. for [$C_8H_{16}O_2SiNa$] 195.0812 Found 195.0806. Data consistent with the literature.[221]

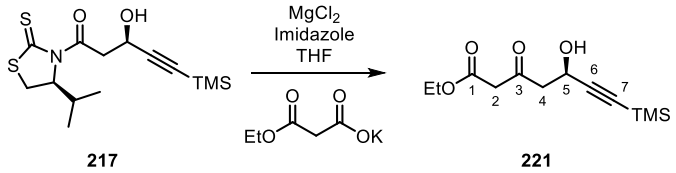
(*R*)-5-(Trimethylsilyl)pent-4-yne-1,3-diol (219)



217 **219**

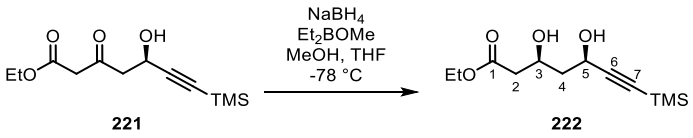
Alcohol **217** (100 mg, 0.30 mmol) was dissolved in THF (4 mL) under nitrogen then $NaBH_4$ (35 mg, 0.91 mmol) was added followed by water (5 drops). The reaction mixture was stirred at room temperature for 30 minutes and quenched with 2 M HCl (2 mL). The resulting solution was extracted with DCM (3 × 10 mL). The combined organic layers were washed sequentially with aqueous saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (40% EtOAc in petroleum ether 60:40) to afford diol **219** (49 mg, 94%) as a colourless oil; $[\alpha]_D^{21}$ = +39.0 (*c* 1, $CHCl_3$). All other spectral data consistent with previous synthesised enantiomer (**220**).

Ethyl (*R*)-5-hydroxy-3-oxo-7-(trimethylsilyl)hept-6-ynoate (221)



Potassium-3-ethoxy-2-methyl-3-oxopropanoate (1719 mg, 10.10 mmol) and $MgCl_2$ (481 mg, 5.05 mmol) were added to a solution of aldol product **217** (1510 mg, 4.59 mmol) in THF (15 mL) under nitrogen and stirred for 45 minutes. Imidazole (344 mg, 5.05 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (75 mL) and washed with 1 M HCl (30 mL). The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (30 mL) and the aqueous layer extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (4% Et_2O in DCM) to afford **221** (929 mg, 79%) as a colourless oil; $[\alpha]_D^{24}$ = +13.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3475, 2962, 2174, 1740, 1716, 1250, 844; δ_H (400 MHz, $CDCl_3$) 0.16 (9H, s, $Si(CH_3)_3$), 1.29 (3H, t, *J* 7.1, $OCH_2\mathit{CH_3}$), 2.77 (1H, d, *J* 4.0, OH), 2.94 (1H, dd, *J* 17.5, 4.0, 4-*H*H), 3.03 (1H, dd, *J* 17.5, 8.1, 4-H*H*), 3.49 (2H, s, 2-H_2), 4.21 (2H, q, *J* 7.1, $O\mathit{CH_2}CH_3$), 4.83 (1H, ap. dt, *J* 8.1, 4.0, 5-H); δ_C (101 MHz, $CDCl_3$) -0.1 ($Si(CH_3)_3$), 14.3 ($OCH_2\mathit{C}H_3$), 49.9 (C-4), 50.0 (C-2), 58.8 (C-5), 61.8 ($O\mathit{C}H_2CH_3$), 90.4 (C-7), 104.4 (C-6), 166.83 (C-1), 201.7 (C-3); HRMS (ESI) calc. for [$C_{12}H_{20}O_4SiNa$] 279.1023 Found 279.1018.

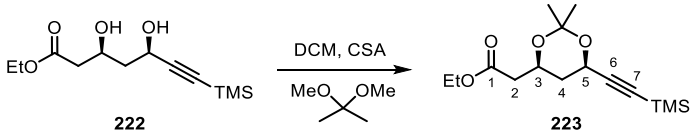
Ethyl (3*S*,5*R*)-3,5-dihydroxy-7-(trimethylsilyl)hept-6-ynoate (222)



Ketone **221** (1010 mg, 3.94 mmol) was dissolved in THF (26 mL) and MeOH (8 mL) under nitrogen and cooled to -78 °C then Et_2BOMe (0.62 mL, 4.73 mmol) was added dropwise and the reaction mixture was stirred for 15 minutes. $NaBH_4$ (171 mg, 4.53 mmol) was added in one portion and the reaction mixture was stirred for 3 hours then AcOH (4 mL) was added and the mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc (75 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in methanol (20 mL) and the solvent removed *in vacuo* to afford diol **222** (1023 mg, quant., dr > 99:1) as a yellow oil; $[\alpha]_D^{22}$ = -24.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3416, 2960, 2173, 1718, 1250, 843; δ_H (400 MHz, $CDCl_3$) 0.17 (9H, s, $Si(CH_3)_3$), 1.28 (3H, t, *J* 7.1, $OCH_2\mathit{CH_3}$), 1.85 (1H, ddd, *J* 14.2, 4.8, 3.0, 4-*H*H), 1.96 (1H, ddd, *J* 14.2, 9.6, 8.2, 4-H*H*), 2.48

– 2.56 (2H, m, 2-H_2), 4.18 (2H, q, *J* 7.1, O*C*H_2CH$_3$), 4.29 (1H, ap. dtd, *J* 9.6, 6.2, 3.0, 3-H), 4.66 (1H, dd, *J* 8.2, 4.8, 5-H); δ_C (101 MHz, $CDCl_3$) 0.0 (Si(CH_3)$_3$), 14.3 (OCH$_2$*C*H$_3$), 41.4 (C-2), 43.4 (C-4), 61.1 (O*C*H$_2$CH$_3$), 67.7 (C-5), 62.3 (C-3), 89.9 (C-7), 105.9 (C-6), 172.7 (C-1); HRMS (ESI) calc. for [$C_{12}H_{22}O_4SiNa$] 281.1180 Found 281.1167.

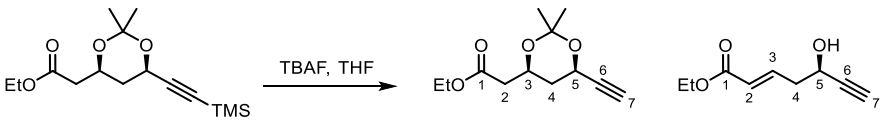
Ethyl 2-((4*S*,6*R*)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)acetate (223)



222 **223**

Diol **222** (982 mg, 3.80 mmol) was dissolved in DCM (40 mL) under nitrogen then 2,2-dimethoxypropane (10 mL, 81 mmol) and CSA (441 mg, 1.90 mmol) were added and the reaction mixture was stirred at room temperature for 1 hour. The solution was diluted with aqueous saturated $NaHCO_3$ (40 mL), the organic layer separated and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford acetonide **223** (1170 mg, quant.) as a yellow oil; $[\alpha]_D^{22}$ = -13.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2961, 2178, 1737, 843; δ_H (400 MHz, $CDCl_3$) 0.16 (9H, s, Si(CH_3)$_3$), 1.26 (3H, t, *J* 7.2, OCH$_2$*CH*$_3$), 1.42 (3H, s, OCCH_3), 1.46 (3H, s, OCCH_3), 1.53 – 1.71 (1H, m, 4-*H*H), 1.84 (1H, ap. dt, *J* 13.0, 2.6, 4-H*H*), 2.38 (1H, dd, *J* 15.7, 6.0, 2-*H*H), 2.53 (1H, dd, *J* 15.7, 7.0, 2-H*H*), 4.07 – 4.22 (2H, m, O*C*H$_2$CH$_3$), 4.22 – 4.36 (1H, m, 3-H), 4.70 (1H, dd, *J* 11.8, 2.6, 5-H); δ_C (101 MHz, $CDCl_3$) -0.0 (Si(CH_3)$_3$), 14.4 (OCH$_2$*C*H$_2$), 19.5 (OC*C*H$_3$), 30.2 (OC*C*H$_3$), 37.1 (C-4), 41.2 (C-2), 60.8 (C-5 and O*C*H$_2$CH$_3$), 65.7 (C-3), 89.6 (C-7), 99.7 (OCO), 103.8 (C-6), 170.8 (C-1); HRMS (ESI) calc. for [$C_{15}H_{26}O_4SiNa$] 321.1493 Found 312.1485.

Ethyl 2-((4*S*,6*R*)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate (224)



223 **224** **225**

TMS alkyne **223** (1100 mg, 3.69 mmol) was dissolved in THF (18 mL) under nitrogen then 1 M TBAF in THF (5.54 mL, 5.54 mmol) was added dropwise. The reaction mixture was stirred for 1 hour, diluted with water (20 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (25% Et_2O in petroleum ether 60:40) to afford alkynes **224** (250 mg, 30%) and **225** (212 mg, 34%) as orange oils.

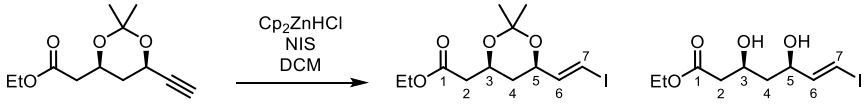
224: $[\alpha]_D^{25}$ = +15.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3271, 2992, 2114, 1731, 1160; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH$_2$*CH*$_3$), 1.42 (3H, s, OC*CH*$_3$), 1.47 (3H, s, OC*CH*$_3$), 1.56 – 1.73 (1H, m, 4-*H*H), 1.84 (1H, ap. dt,

J 13.0, 2.5, 4-H*H*), 2.39 (1H, dd, *J* 15.7, 6.0, 2-*H*H), 2.46 (1H, d, *J* 2.2, 7-H), 2.54 (1H, dd, *J* 15.7, 7.0, 2-H*H*), 4.07 – 4.22 (2H, m, O*CH*$_2$CH$_3$), 4.31 (1H, dddd, *J* 11.6, 7.0, 6.0, 2.5, 3-H), 4.69 (1H, dt, *J* 11.7, 2.5, 5-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 19.4 (OC*C*H$_3$), 30.1 (OC*C*H$_3$), 36.9 (C-4), 41.2 (C-2), 60.2 (C-5), 60.8 (O*C*H$_2$CH$_3$), 65.6 (C-3), 73.04 (C-7), 82.4 (C-6), 99.7 (OCO), 170.8 (C-1); HRMS (ESI) calc. for [$C_{12}H_{19}O_4$] 227.1278 Found 227.1278.

225: $[\alpha]_D^{25}$ = +71.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3418, 3291, 2940, 2117, 1699, 1037; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH$_2$*CH*$_3$), 2.23 (1H, d, *J* 6.0, 7-H), 2.52 (1H, d, *J* 2.1, OH), 2.62 (2H, ddd, *J* 7.5, 6.0, 1.5, 4-H$_2$), 4.19 (2H, q, *J* 7.2, O*CH*$_2$CH$_3$), 4.51 (1H, ap. qd, *J* 6.0, 2.1, 5-H), 5.96 (1H, ap. dt, *J* 15.7, 1.5, 2-H), 6.98 (1H, ap. dt, *J* 15.7, 7.5, 3-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 40.3 (C-4), 60.6 (O*C*H$_2$CH$_3$), 61.0 (C-5), 74.2 (C-7), 83.7 (C-6), 125.0 (C-2), 142.9 (C-3), 166.4 (C-1); HRMS (ESI) calc. for [$C_9H_{13}O_3$] 169.0859 Found 169.0857.

Ethyl 2-((4*S*,6*R*)-6-((*E*)-2-iodovinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (189)

Method 1:



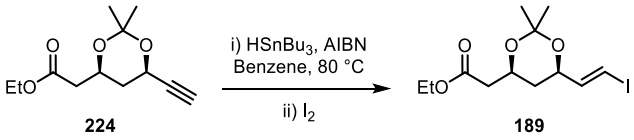
224 **189** **420**

Cp_2ZrHCl (85 mg, 0.33 mmol) was added to a stirred solution of alkyne **224** (47 mg, 0.21 mmol) in DCM (2.5 mL) under nitrogen and the reaction mixture was stirred for 30 mins. NIS (99 mg, 0.44 mmol) was added and the reaction mixture was stirred for an additional 30 minutes. Aqueous saturated $NaHCO_3$ (5 mL) was added and the reaction mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (5-20% Et_2O in petroleum ether 60:40) to afford vinyl iodides **189** (9 mg, 12%, *E*/*Z* > 95:5) and **420** (22 mg, 33%, *E*/*Z* > 95:5) as yellow oils.

189: $[\alpha]_D^{22}$ = +25.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2992, 2924, 1735, 1380, 1164; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2, OCH$_2$*CH*$_3$), 1.28 – 1.36 (1H, m, 4-*H*H), 1.39 (3H, s, OCCH$_3$), 1.47 (3H, s, OCCH$_3$), 1.67 (1H, ap. dt, *J* 12.8, 2.5, 4-H*H*), 2.38 (1H, dd, *J* 15.6, 6.1, 2-*H*H), 2.54 (1H, dd, *J* 15.6, 6.9, 2-H*H*), 4.00 – 4.27 (2H, m, O*CH*$_2$CH$_3$), 4.26 – 4.44 (2H, m, 3-H and 5-H), 6.41 (1H, dd, *J* 14.5, 1.2, 7-H), 6.52 (1H, dd, *J* 14.5, 5.5, 6-H); δ_C (126 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 19.8 (OC*C*H$_3$), 30.1 (OC*C*H$_3$), 36.0 (C-4), 41.4 (C-2), 60.8 (O*C*H$_2$CH$_3$), 65.7 (C-3), 71.5 (C-5), 78.5 (C-7), 99.3 (OCO), 145.6 (C-6), 170.9 (C-1); HRMS (ESI) calc. for [$C_{12}H_{19}INaO_4$] 377.0220 Found 377.0202.

420: $[\alpha]_D^{22}$ = +9.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3419, 2983, 2923, 1718, 1183; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2, OCH_2CH_3), 1.59 – 1.78 (2H, m, 4-H_2), 2.40 – 2.59 (2H, m, 2-H_2), 3.66 (1H, s, OH), 3.70 – 3.82 (1H, m, OH), 4.17 (2H, q, *J* 7.2, OCH_2CH_3), 4.22 – 4.35 (1H, m, 3-H), 4.35 – 4.43 (1H, m, 5-H), 6.41 (1H, dd, *J* 14.4, 1.2, 7-H), 6.55 (1H, dd, *J* 14.4, 5.8, 6-H); δ_C (101 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 41.5 (C-2), 41.8 (C-4), 61.2 (OCH_2CH_3), 68.3 (C-3), 74.4 (C-5), 77.8 (C-7), 147.57 (C-6), 172.7 (C-1); HRMS (ESI) calc. for [$C_9H_{15}INaO_4$] 336.9907 Found 336.9915.

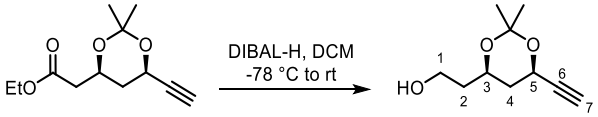
Method 2:



224 **189**

Alkyne **224** (50 mg, 0.22 mmol) was dissolved in benzene (2.2 mL) then AIBN (11 mg, 0.07 mmol) and $HSnBu_3$ (0.12 mL, 0.44 mmol) were added sequentially. The reaction vessel was sealed and heated at 80 °C for 2 hours. The reaction mixture was cooled to room temperature and a solution of iodine (1 M in Et_2O) was added until a red colour persisted. A further 0.25 mL of the iodine solution was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ (5 mL) and diluted with Et_2O (10 mL). The organic layer was separated and the organic phase washed with 1 M aqueous KF solution (3 × 15 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% EtOAc in petroleum ether 60:40) to afford vinyl iodide **189** (54 mg, 69%) as a colourless oil in a 7:1 *E*/*Z* ratio determined by ^{1}H-NMR analysis. Data consistent with previously reported.

2-((4*R*,6*R*)-6-Ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethan-1-ol (228)

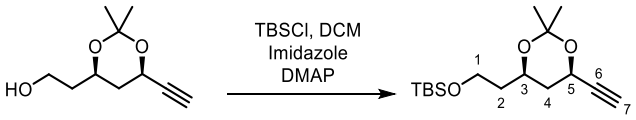


224 **228**

Ester **224** (149 mg, 0.66 mmol) was dissolved in DCM (7 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (1.45 mL, 1.45 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was cooled to 0 °C, aqueous saturated potassium sodium tartrate solution (10 mL) was added and the mixture was stirred for 30 minutes at room temperature. The layers were separated and the aqueous layer extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (40%

EtOAc in petroleum ether 60:40) to afford alcohol **228** (110 mg, 95%) as a yellow oil; $[\alpha]_D^{23}$ = +24.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3416, 3288, 2994, 2926, 2883, 2125, 1381; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.67 – 1.80 (4H, m, 2-H_2 and 4-H_2), 2.31 (1H, br. s, OH), 2.46 (1H, d, *J* 2.1, 7-H), 3.64 – 3.84 (2H, m, 1-H_2), 4.04 – 4.17 (1H, m, 3-H), 4.63 – 4.72 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 19.6 (CH_3), 30.3 (CH_3), 37.1 (C-4), 38.0 (C-2), 60.3 (C-5), 60.4 (C-1), 68.4 (C-3), 73.0 (C-7) , 82.5 (C-6), 99.5 (OCO); HRMS (ESI) calc. for [$C_{10}H_{16}NaO_3$] 207.0992 Found 207.0996.

***tert*-Butyl(2-((4*R*,6*R*)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (229)**

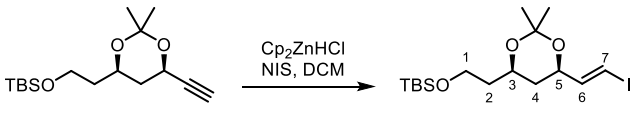


228 **229**

To a solution of alcohol **228** (80 mg, 0.43 mmol) in DCM (5 mL) was added imidazole (59 mg, 0.87 mmol), TBSCl (149 mg, 0.99 mmol) and a spatula tip of DMAP and the reaction mixture was stirred at room temperature for 24 hours. Water (5 mL) was added and the solution was acidified with 2 M HCl (2 mL). The organic layer was separated and the aqueous extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (10% EtOAc in petroleum ether 60:40) to afford alkyne **229** (124 mg, 97%) as a colourless oil; $[\alpha]_D^{25}$ = +21.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3319, 2957, 2928, 2857, 1380, 1095; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.43 (3H, s, $OCCH_3$), 1.45 (3H, s, $OCCH_3$), 1.61 – 1.72 (3H, m, 2-H_2 and 4-*H*H), 1.75 (1H, ap. dt, *J* 13.1, 2.5, 4-H*H*), 2.45 (1H, d, *J* 2.5, 7-H), 3.64 (1H, ap. dt, *J* 10.2, 5.3, 1-*H*H), 3.72 (1H, ddd, *J* 10.2, 7.9, 5.3, 1-H*H*), 4.05 (1H, dddd, *J* 11.9, 7.5, 4.9, 2.5, 3-H), 4.67 (1H, ap. dt, *J* 11.7, 2.5, 5-H); δ_C (101 MHz, $CDCl_3$) -5.2 ($Si(CH_3)_2$), 19.6 ($OCCH_3$), 26.1 ($SiC(CH_3)_3$), 30.3 ($OCCH_3$), 37.6 (C-4), 39.2 (C-2), 58.7 (C-1), 60.5 (C-5), 65.3 (C-3), 72.8 (C-7), 82.9 (C-6), 99.4 (OCO); HRMS (ESI) calc. for [$C_{16}H_{31}SiO_3$] 299.2037 Found 299.2035.

***tert*-Butyl(2-((4*R*,6*R*)-6-((*E*)-2-iodovinyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (230)**

Method 1:

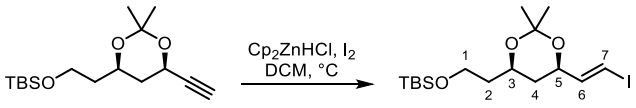


229 **230**

Cp_2ZrHCl (136 mg, 0.53 mmol) was added to a stirred solution of alkyne **229** (105 mg, 0.35 mmol) in DCM (4 mL) under nitrogen and the reaction mixture was stirred for 1 hour. NIS (157 mg, 0.70 mmol) was added and the reaction mixture was stirred for an additional 45 minutes. Aqueous saturated $NaHCO_3$ (5 mL) was added and the reaction mixture was extracted with DCM (3 × 10 mL). The

combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (4% Et_2O in petroleum ether 60:40) to afford vinyl iodide **230** (30 mg, 20%, *E*/*Z* > 95:5) as a colourless oil; $[\alpha]_D^{21}$ = +33.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2952, 2928, 2856, 1381, 1256, 1094; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.29 (1H, ap. q, *J* 12.0, 4-*H*H), 1.40 (3H, s, $OCCH_3$), 1.44 (3H, s, $OCCH_3$), 1.51 – 1.73 (3H, m, 2-H_2 and 4-H*H*), 3.64 (1H, ap. dt, *J* 10.2, 5.3, 1-*H*H), 3.72 (1H, ddd, *J* 10.2, 7.9, 5.3, 1-H*H*), 4.06 (1H, dddd, *J* 12.0, 7.5, 5.0, 2.4, 3-H), 4.34 (1H, dddd, *J* 12.0, 5.5, 2.6, 1.1, 5-H), 6.38 (1H, dd, *J* 14.5, 1.1, 7-H), 6.53 (1H, dd, *J* 14.5, 5.5, 6-H); δ_C (101 MHz, $CDCl_3$) -5.3 ($Si(CH_3)_2$), 18.4 ($SiC(CH_3)_3$), 19.8 ($OCCH_3$), 26.0 ($SiC(CH_3)_3$), 30.2 ($OCCH_3$), 36.6 (C-4), 39.3 (C-2), 58.7 (C-1), 65.2 (C-3), 71.7 (C-5), 78.2 (C-7), 98.9 (OCO), 146.0 (C-6); HRMS (ESI) calc. for [$C_{16}H_{31}SiIO_3$] 449.0985 Found 449.0979.

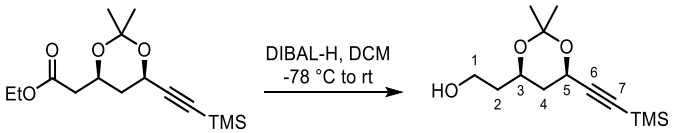
Method 2:



229 **230**

Cp_2ZrHCl (67 mg, 0.26 mmol) was added to a stirred solution of alkyne **229** (50 mg, 0.17 mmol) in DCM (2 mL) under nitrogen at 0 °C and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0 °C and a solution of iodine in DCM (0.5 M) was added until the red colour remained (*ca*. 1 mL) and the mixture was stirred for a further 15 minutes. Aqueous saturated $NaHCO_3$ (5 mL) and aqueous saturated $Na_2S_2O_3$ (2 mL) were added and the organic layer was separated. The aqueous phase was extracted with DCM (2 × 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (4% Et_2O in petroleum ether 60:40) to afford vinyl iodide **230** (32 mg, 45%, *E*/*Z* > 95:5) as a colourless oil. Data consistent with previously reported.

2-((4*R*,6*R*)-2,2-Dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)ethan-1-ol (231)

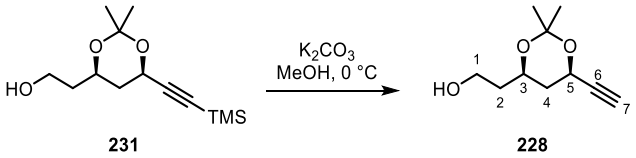


223 **231**

Ester **223** (1110 mg, 3.69 mmol) was dissolved in DCM (37 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (8.11 mL, 8.11 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was cooled to 0 °C, aqueous saturated potassium sodium tartrate solution (20 mL) was added and the mixture was stirred for 30 minutes at room temperature. The layers were separated and the aqueous layer extracted with DCM

(2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford alcohol **231** (998 mg, quant.) as a yellow oil; $[\alpha]_D^{22}$ = +45.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3426, 2993, 2958, 2182, 1379, 840; δ_H (400 MHz, $CDCl_3$) 0.17 (9H, s, $Si(CH_3)_3$), 1.44 (3H, s, $OCCH_3$), 1.47 (3H, s, $OCCH_3$), 1.67 – 1.79 (4H, m, 2-H_2 and 4-H_2), 2.27 (1H, dd, *J* 6.4, 4.2, OH), 3.68 – 3.85 (2H, m, 1-H_2), 4.04 – 4.18 (1H, m, 3-H), 4.65 – 4.75 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) -0.1 ($Si(CH_3)_3$), 19.5 ($OCCH_3$), 30.2 ($OCCH_3$), 37.3 (C-4), 37.9 (C-2), 60.6 (C-1), 60.8 (C-5), 68.7 (C-3), 89.5 (C-7), 99.4 (OCO), 103.7 (C-6); HRMS (ESI) calc. for [$C_{13}H_{24}NaO_3Si$] 279.1387 Found 279.1375.

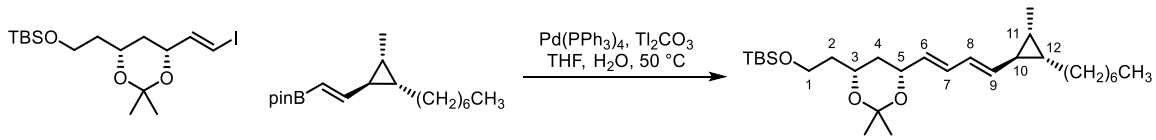
2-((4*R*,6*R*)-6-Ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)ethan-1-ol (228)



231 228

TMS alkyne **231** (1100 mg, 4.29 mmol) was dissolved in MeOH (43 mL) and cooled to 0 °C then K_2CO_3 (178 mg, 1.29 mmol) was added. The reaction mixture was stirred at 0 °C for 5 hours then the solvent was removed *in vacuo*. The resulting material was dissolved in water (20 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous extracted with further EtOAc (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford terminal alkyne **228** (690 mg, 87%) as a yellow oil. Data consistent with previously reported.

***tert*-Butyl(2-((4*R*,6*R*)-6-((1*E*,3*E*)-4-((1*S*,2*S*,3*R*)-2-heptyl-3-methylcyclopropyl)buta-1,3-dien-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (232)**

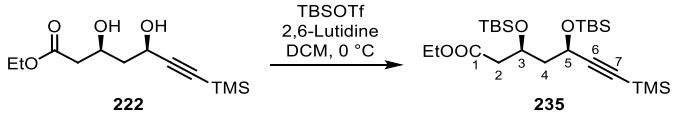


230 190 232

To a stirred solution of Boronic ester **190** (22 mg, 0.07 mmol) in degassed THF (0.25 mL) and water (0.25 mL) under nitrogen was added vinyl iodide **230** (30 mg, 0.07 mmol) in degassed THF (0.5 mL) followed by $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and the reaction mixture was stirred at room temperature for 5 minutes. Tl_2CO_3 (66 mg, 0.14 mmol) was added and the reaction mixture was heated at 50 °C for 2 hours. The reaction mixture was filtered over Celite, eluting with ether (20 mL) and water (20 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (4% Et_2O in petroleum ether 60:40) to afford diene **232** (26 mg, 78%) as a colourless oil; $[\alpha]_D^{21}$ = +4.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2927, 2856, 1379, 1256, 1214, 745; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.71 – 0.81 (1H, m, 10-H), 0.83 – 0.95

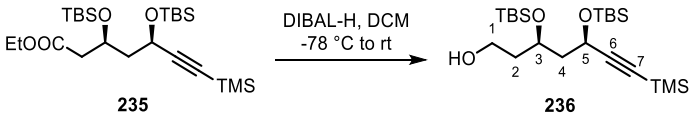
(14H, m, SiC(CH_3)$_3$, 11-H, 12-H and 19-H_3), 1.05 (3H, d, *J* 6.1, 11-CH_3), 1.22 – 1.38 (13H, m, 4-*H*H and 6 × CH_2), 1.40 (3H, s, OCCH_3), 1.46 (3H, s, OCCH_3), 1.52 (1H, ap. dt, *J* 13.0, 2.5, 4-H*H*), 1.57 – 1.71 (2H, m, 2-H_2), 3.61 – 3.67 (1H, ap. dt, *J* 10.1, 5.5, 1-*H*H), 3.73 (1H, ddd, *J* 10.1, 7.9, 5.3, 1-H*H*), 4.06 (1H, dddd, *J* 11.8, 7.4, 4.8, 2.5, 3-H), 4.31 – 4.39 (1H, m, 5-H), 5.31 (1H, dd, *J* 15.0, 8.8, 9-H), 5.47 (1H, dd, *J* 15.2, 6.6, 6-H), 5.99 (1H, dd, *J* 15.0, 10.5, 8-H), 6.15 (1H, dd, *J* 15.2, 10.5, 7-H); δ_C (101 MHz, $CDCl_3$) -5.2 (Si(CH_3)$_2$), 12.7 (CH_3-11), 14.3 (C-19), 18.5 (Si*C*(CH_3)$_3$), 20.1 (OC*C*H_3), 20.6 (C-12), 22.9 (CH_2), 26.1 (SiC(*C*H_3)$_3$), 26.9 (C-11), 27.9 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 30.0 (C-10), 30.5 (OC*C*H_3), 32.1 (CH_2), 37.5 (C-4), 39.6 (C-2), 59.0 (C-1), 65.5 (C-3), 70.3 (C-5), 98.7 (OCO), 126.3 (C-8), 129.7 (C-6), 131.7 (C-7), 140.0 (C-9); HRMS (ESI) calc. for [$C_{29}H_{54}O_3SiNa$] 501.3734 Found 501.3746.

Ethyl (3*S*,5*R*)-3,5-bis((*tert*-butyldimethylsilyloxy)-7-(trimethylsilyl)hept-6-ynoate (235)



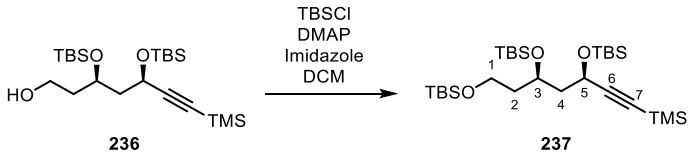
Diol **222** (900 mg, 3.48 mmol) was dissolved in DCM (35 mL) under nitrogen and cooled to 0 °C then 2,6-lutidine (2.03 mL, 17.42 mmol) was added and the reaction mixture was stirred for 5 minutes. TBSOTf (4.00 mL, 17.42 mmol) was added and the reaction mixture was stirred for 30 minutes before the addition of aqueous saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 30 mL). The combined organic layers were washed sequentially with 2 M HCl (20 mL) and brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (4% Et_2O in petroleum ether 60:40) to afford silyl ether **235** (1632 mg, 96%) as a colourless oil; $[\alpha]_D^{21}$ = +25.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2957, 2930, 2858, 2176, 1740, 1251; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, Si(CH_3)), 0.10 (3H, s, Si(CH_3)), 0.11 (3H, s, Si(CH_3)), 0.13 (3H, s, Si(CH_3)), 0.16 (9H, s, Si(CH_3)$_3$), 0.86 (9H, s, SiC(CH_3)$_3$), 0.90 (9H, s, SiC(CH_3)$_3$), 1.25 (3H, t, *J* 7.1, OCH$_2$*CH*$_3$), 1.81 (1H, ddd, *J* 13.5, 7.5, 5.5, 4-*H*H), 1.92 (1H, ap. dt, *J* 13.5, 7.0, 4-H*H*), 2.45 (1H, dd, *J* 14.6, 7.0, 2-*H*H), 2.53 (1H, dd, *J* 14.6, 5.5, 2-H*H*), 4.03 – 4.18 (2H, m, O*CH*$_2$CH$_3$), 4.34 (1H, ap. tt, *J* 7.0, 5.5, 3-H), 4.47 (1H, dd, *J* 7.5, 7.0, 5-H); δ_C (101 MHz, $CDCl_3$) -4.8 (Si(CH_3)), -4.6 (Si(CH_3)), -4.5 (Si(CH_3)), -4.4 (Si(CH_3)), -0.0 (Si(CH_3)$_3$), 14.4 (OCH$_2$*C*H$_3$), 18.1 (Si*C*(CH_3)$_3$), 18.4 (Si*C*(CH_3)$_3$), 25.95 (SiC(*C*H_3)$_3$), 25.99 (SiC(*C*H_3)$_3$), 43.3 (C-2), 46.0 (C-4), 60.5 (O*C*H$_2$CH$_3$), 61.2 (C-5), 67.0 (C-3), 89.8 (C-7), 107.1 (C-6), 171.5 (C-1); HRMS (ESI) calc. for [$C_{24}H_{51}O_4Si_3$] 487.3090 Found 487.3089.

(3*R*,5*R*)-3,5-Bis((*tert*-butyldimethylsilyloxy)-7-(trimethylsilyl)hept-6-yn-1-ol (236)



Ester **235** (1600 mg, 3.29 mmol) was dissolved in DCM (33 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (7.23 mL, 7.23 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was cooled to 0 °C, aqueous saturated potassium sodium tartrate solution (20 mL) was added and the mixture was stirred for 30 minutes at room temperature. The layers were separated and the aqueous layer extracted with DCM (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford alcohol **236** (1358 mg, 93%) as a colourless oil; $[\alpha]_D^{23}$ = +29.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3360, 2956, 2930, 2887, 2858, 2173, 1251; δ_H (400 MHz, $CDCl_3$) 0.10 (3H, s, $SiCH_3$), 0.11 – 0.11 (6H, m, 2 × $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.16 (9H, s, $Si(CH_3)_3$), 0.86 – 0.94 (18H, m, 2 × $SiC(CH_3)_3$), 1.65 – 1.74 (1H, m, 2-*H*H), 1.80 – 1.99 (3H, m, 2-H*H* and 4-H_2), 2.36 (1H, dd, *J* 6.2, 4.3, OH), 3.67 – 3.78 (1H, m, 1-*H*H), 3.81 – 3.92 (1H, m, 1-H*H*), 4.12 – 4.20 (1H, m, 3-H), 4.44 (1H, ap. t, *J* 6.8, 5-H); δ_C (101 MHz, $CDCl_3$) -4.8 ($SiCH_3$), -4.5 ($SiCH_3$), -4.4 ($SiCH_3$), -4.3 ($SiCH_3$), -0.1 ($Si(CH_3)_3$), 18.1 (Si*C*(CH_3)$_3$), 18.4 (Si*C*(CH_3)$_3$), 25.96 (SiC(*C*H_3)$_3$), 26.01 (SiC(*C*H_3)$_3$), 38.2 (C-2), 45.0 (C-4), 60.2 (C-1), 61.3 (C-5), 69.1 (C-3), 89.8 (C-7), 107.2 (C-6); HRMS (ESI) calc. for [$C_{22}H_{49}O_3Si_3$] 445.2984 Found 445.2999.

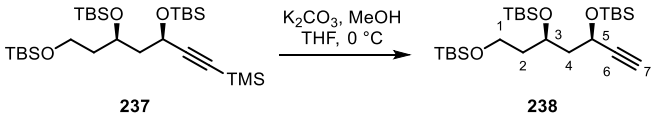
(5*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-2,2,3,3,11,11,12,12-octamethyl-5-((trimethylsilyl)ethynyl)-4,10-dioxa-3,11-disilatridecane (237)



Alcohol **236** (1300 mg, 2.92 mmol) was dissolved in DCM (30 mL) then imidazole (380 mg, 5.84 mmol) was added. The reaction mixture was cooled to 0 °C then TBSCl (880 mg, 5.84 mmol) and a spatula tip of DMAP were added. The reaction mixture was stirred at room temperature for 2 hours then water (10 mL) was added and the solution acidified to pH 2 with 2 M HCl. The organic layer was separated and the aqueous extracted with further DCM (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in toluene (50 mL) and the solvent removed *in vacuo* to afford TBS protected triol **237** (1650 mg, quant.) as a colourless oil; $[\alpha]_D^{22}$ = +15.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2956, 2930, 2887, 2858, 2173, 1719, 1251; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, 2 × $Si(CH_3)_2$), 0.06 (3H, s, $Si(CH_3)_2$), 0.08 (3H, s, $Si(CH_3)_2$), 0.11 (3H, s, $Si(CH_3)_2$), 0.13 (3H, s, $Si(CH_3)_2$), 0.15 (9H, s, $Si(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.66 – 1.74 (2H, m, 2-H_2), 1.74 – 1.87 (2H, m, 4-H_2), 3.61 – 3.72 (2H, m, 1-H_2), 4.01 (1H, dq, *J* 7.7, 5.6, 3-H), 4.49 (1H, dd, *J* 7.9, 6.5, 5-H); δ_C (101 MHz, $CDCl_3$) -5.13 ($SiCH_3$), -5.08 ($SiCH_3$), -4.7 ($SiCH_3$), -4.43 ($SiCH_3$), -4.36 ($SiCH_3$), -4.3 ($SiCH_3$), 0.00 ($SiCH_3$)$_3$), 18.2 (Si*C*(CH_3)$_3$), 18.5

(2 × Si*C*$(CH_3)_3$), 26.0 (SiC(*C*$H_3)_3$), 26.1 (SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 40.9 (C-2), 46.2 (C-4), 59.7 (C-1), 61.7 (C-5), 66.9 (C-3), 89.5 (C-7), 107.6 (C-6); HRMS (ESI) calc. for [$C_{28}H_{62}NaO_3Si_4$] 581.3668 Found 581.3670.

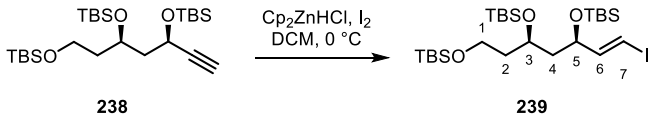
(5*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-ethynyl-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane (238)



237 **238**

TMS alkyne **237** (1650 mg, 2.95 mmol) was dissolved in MeOH (20 mL) and THF (10 mL) and cooled to 0 °C then K_2CO_3 (408 mg, 0.89 mmol) was added. The reaction mixture was stirred at room temperature for 5 hours and the solvent was removed *in vacuo*. The resulting material was dissolved in water (20 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous extracted with further EtOAc (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford terminal alkyne **238** (1306 mg, 91%) as a yellow oil; $[\alpha]_D^{22}$ = +26.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3313, 2955, 2929, 2887, 2858, 1252; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, 2 × $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.89 (18H, s, 2 × SiC(*C*$H_3)_3$), 0.90 (9H, s, SiC(*C*$H_3)_3$), 1.67 – 1.74 (2H, m, 2-H_2), 1.82 – 1.86 (2H, m, 4-H_2), 2.39 (1H, d, *J* 2.1, 7-H), 3.62 – 3.69 (2H, m, 1-H_2), 3.98 – 4.07 (1H, m, 3-H), 4.49 (1H, ddd, *J* 7.6, 6.7, 2.1, 5-H); δ_C (101 MHz, $CDCl_3$) -5.2 (2 × $SiCH_3$), -4.9 ($SiCH_3$), -4.5 (2 × $SiCH_3$), -4.2 ($SiCH_3$), 18.2 (Si*C*$(CH_3)_3$), 18.40 (Si*C*$(CH_3)_3$), 18.43 (Si*C*$(CH_3)_3$), 26.0 (SiC(*C*$H_3)_3$), 26.06 (SiC(*C*$H_3)_3$), 26.14 (SiC(*C*$H_3)_3$), 40.8 (C-2), 46.4 (C-4), 59.6 (C-1), 61.0 (C-5), 66.8 (C-3), 72.9 (C-7), 85.6 (C-6); HRMS (ESI) calc. for [$C_{25}H_{55}O_3Si_3$] 487.3453 Found 487.3455.

***tert*-Butyl(2-((4*R*,6*R*)-6-((*E*)-2-iodovinyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (239)**

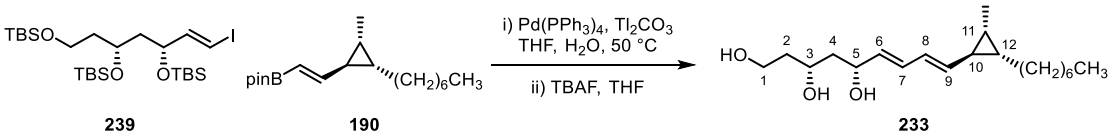


238 **239**

Cp_2ZrHCl (108 mg, 0.42 mmol) was added to a stirred solution of alkyne **238** (100 mg, 0.21 mmol) in DCM (3 mL) under nitrogen at 0 °C and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0 °C and a solution of iodine in DCM (0.5 M) was added until the red colour remained (*ca*. 1 mL) and the mixture was stirred for a further 30 minutes. Aqueous saturated $Na_2S_2O_3$ (5 mL) was added and the organic layer was separated. The aqueous phase was extracted with DCM (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (1.5% Et_2O in petroleum ether 60:40) to afford vinyl iodide **239** (105 mg, 81%, *E*/*Z* > 95:5) as a colourless oil;

$[\alpha]_D^{21}$ = +10.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2954, 2929, 2886, 2857, 1472, 1255, 1093, 835; δ_H (400 MHz, $CDCl_3$) -0.01 – 0.10 (18H, m, 3 × $Si(CH_3)_2$), 0.86 – 0.96 (27H, m, 3 × $SiC(CH_3)_3$), 1.48 – 1.75 (4H, m, 2-H_2 and 4-H_2), 3.66 (2H, m, 1-H_2), 3.89 (1H, ap. p, *J* 6.1, 3-H), 4.21 (1H, ap. qd, *J* 6.5, 1.1, 5-H), 6.23 (1H, dd, *J* 14.4, 1.1, 7-H), 6.54 (1H, dd, *J* 14.4, 6.5, 6-H); δ_C (101 MHz, $CDCl_3$) -5.1 (2 × $SiCH_3$), -4.6 ($SiCH_3$), -4.23 ($SiCH_3$), -4.22 ($SiCH_3$), -4.1 ($SiCH_3$), 18.2 (Si*C*$(CH_3)_3$), 18.3 (Si*C*$(CH_3)_3$), 18.5 (Si*C*$(CH_3)_3$), 26.0 (SiC(*C*$H_3)_3$), 26.1 (SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 40.4 (C-2), 45.9 (C-4), 59.8 (C-1), 66.5 (C-3), 72.7 (C-5), 76.3 (C-7), 149.2 (C-6); HRMS (ESI) calc. for [$C_{25}H_{55}O_3Si_3I$] 615.2550 Found 615.2568.

(3*R*,5*R*,6*E*,8*E*)-9-((1*S*,2*S*,3*R*)-2-Heptyl-3-methylcyclopropyl)nona-6,8-diene-1,3,5-triol (233)



239 **190** **233**

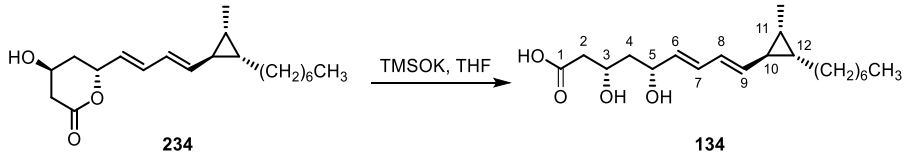
To a stirred solution of boronic ester **190** (196 mg, 0.64 mmol) in degassed THF (5 mL) and water (2.5 mL) under nitrogen was added vinyl iodide **239** (393 mg, 0.64 mmol) in degassed THF (2.5 mL) followed by $Pd(PPh_3)_4$ (74 mg, 0.06 mmol) and the reaction mixture was stirred at room temperature for 5 minutes. Tl_2CO_3 (600 mg, 1.28 mmol) was added and the reaction mixture was heated at 50 °C for 16 hours. The reaction mixture was filtered over Celite, eluting with ether (50 mL) and water (20 mL). The layers were separated, and the aqueous phase extracted with further Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (1.6% Et_2O in petroleum ether 60:40) to afford the crude cross-coupled product. The crude material was dissolved in THF (2.5 mL) under nitrogen then 1 M TBAF in THF (5.10 mL, 5.10 mmol) was added dropwise. The reaction mixture was stirred for 16 hours, diluted with aqueous saturated NH_4Cl (20 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (100% EtOAc) to afford triol **233** (125 mg, 60%) as a colourless oil; $[\alpha]_D^{24}$ = -10.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3342, 2924, 2854, 1654, 1457, 1062, 985; δ_H (400 MHz, $CDCl_3$) 0.73 – 0.82 (2H, m, 10-H and 12-H), 0.84 – 0.90 (4H, m, 11-H and 19-H_3), 1.06 (3H, d, *J* 6.2, 11-CH_3), 1.22 – 1.39 (12H, m, 6 × CH_2), 1.59 (1H, m, 4-*H*H), 1.66 – 1.79 (3H, m, 2-H_2 and 4-H*H*), 2.68 – 2.83 (2H, m, OH), 3.79 – 3.92 (2H, m, 1-H_2), 3.99 (1H, m, OH), 4.10 – 4.19 (1H, m, 3-H), 4.36 – 4.44 (1H, m, 5-H), 5.33 (1H, dd, *J* 15.0, 8.6, 9-H), 5.52 (1H, dd, *J* 15.1, 7.0, 6-H), 6.00 (1H, dd, *J* 15.0, 10.5, 8-H), 6.15 (1H, dd, *J* 15.1, 10.5, 7-H); δ_C (101 MHz, $CDCl_3$) 12.6 (CH_3-11), 14.3 (C-19), 20.7 (C-11), 22.9 (CH_2), 27.0 (C-12), 27.9 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.9 (C-10), 30.0 (CH_2), 32.1 (CH_2), 38.9 (C-2), 43.5 (C-4), 61.6 (C-1), 72.6 (C-3), 73.9 (C-5), 125.9 (C-8), 131.2 (C-7), 131.3 (C-6), 140.5 (C-9); HRMS (ESI) calc. for [$C_{20}H_{36}O_3Na$] 347.2557 Found 347.2568.

(4*S*,6*R*)-6-((1*E*,3*E*)-4-((1*S*,2*S*,3*R*)-2-Heptyl-3-methylcyclopropyl)buta-1,3-dien-1-yl)-4-hydroxytetrahydro-2H-pyran-2-one (234)

233 234

Triol **233** (13 mg, 0.04 mmol) was dissolved in DCM (1 mL) under nitrogen then BAIB (41 mg, 0.13 mmol), $NaHCO_3$ (13 mg, 0.16 mmol) and TEMPO (0.01 mmol, 2 mg) were added sequentially. The reaction mixture was stirred at room temperature for 6 hours and then quenched with aqueous saturated $Na_2S_2O_3$ (1 mL) and water (5 mL). The solution was extracted with Et_2O (2 × 10 mL) and the combined organic layers washed sequentially with aqueous saturated $NaHCO_3$ (10 mL) and water (10 mL). The combined aqueous layers were extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 ml), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (50% EtOAc in petroleum ether 60:40) to afford lactone **234** (11 mg, 86%) as a colourless oil; $[\alpha]_D^{24}$ = -36.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3427, 2957, 2925, 2855, 1730, 1655, 1247; δ_H (500 MHz, $CDCl_3$) 0.75 – 0.85 (2H, m, 10-H and 12-H), 0.85 – 0.94 (4H, m, 11-H and 19-H_3), 1.07 (3H, d, *J* 6.2, 11-CH_3), 1.21 – 1.39 (12H, m, 6 × CH_2), 1.80 – 1.91 (2H, m, OH and 4-*H*H), 1.97 – 2.04 (1H, m, 4-H*H*), 2.61 (1H, ddd, *J* 17.7, 4.1, 1.6, 2-*H*H), 2.76 (1H, dd, *J* 17.7, 5.0, 2-H*H*), 4.35 – 4.43 (1H, m, 3-H), 5.18 (1H, ddd, *J* 10.4, 6.7, 3.4, 5-H), 5.38 (1H, dd, *J* 15.1, 8.8, 9-H), 5.51 (1H, dd, *J* 15.2, 6.7, 6-H), 6.02 (1H, dd, *J* 15.1, 10.5, 8-H), 6.24 (1H, dd, *J* 15.2, 10.5, 7-H); δ_C (126 MHz, $CDCl_3$) 12.6 (CH_3-11), 14.3 (C-19), 20.9 (C-11), 22.9 (CH_2), 27.2 (C-12), 27.9 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.0 (10-H and CH_2), 32.1 (CH_2), 36.7 (C-4), 38.9 (C-2), 63.0 (C-3), 76.3 (C-5), 125.5 (C-8), 125.8 (C-6), 133.5 (C-7), 141.9 (C-9), 170.0 (C-1); HRMS (ESI) calc. for [$C_{20}H_{33}O_3$] 321.2424 Found 321.2409.

(3*S*,5*R*,6*E*,8*E*)-9-((1*S*,2*S*,3*R*)-2-Heptyl-3-methylcyclopropyl)-3,5-dihydroxynona-6,8-dienoic acid (134)



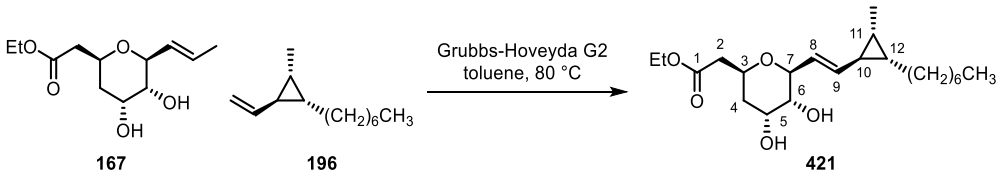
234 134

Lactone **234** (17 mg, 0.05 mmol) was dissolved in THF (0.5 mL) under nitrogen then TMSOK (34 mg, 0.27 mmol) was added. The reaction mixture was stirred for 4 hours then quenched with aqueous saturated NH_4Cl (5 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **134** (15 mg, 84%) as a yellow oil; $[\alpha]_D^{22}$ = -24.0 (*c* 0.5, $CHCl_3$); ν_{max}

(film) 3399, 2953, 2925, 2854, 1713, 987; δ_H (500 MHz, $CDCl_3$) 0.74 – 0.83 (2H, m, 10-H and 12-H), 0.85 – 0.91 (4-H, m, 11-H and 19-H_3), 1.07 (3H, d, *J* 6.3, 11-CH_3), 1.23 – 1.38 (12H, m, 6 × CH_2), 1.57 – 1.81 (2H, m, 4-H_2), 2.41 – 2.63 (2H, m, 2-H_2), 4.23 – 4.36 (1H, m, 3-H), 4.37 – 4.47 (1H, m, 5-H), 5.34 (1H, dd, *J* 15.0, 8.6, 9-H), 5.50 (1H, dd, *J* 15.2, 6.8, 6-H), 5.99 (1H, dd, *J* 15.0, 11.0, 8-H), 6.15 (1H, dd, *J* 15.2, 11.0, 7-H); δ_C (126 MHz, $CDCl_3$) 12.7 (CH_3-11), 14.3 (C-19), 20.7 (C-11), 22.9 (CH_2), 27.1 (C-12), 27.9 (CH_2), 29.5 (CH_2), 29.7 (C-10), 29.9 (CH_2), 30.0 (CH_2), 32.1 (CH_2), 41.7 (C-2), 42.6 (C-4), 63.0 (C-5), 73.3 (C-3), 125.9 (C-8), 130.7 (C-6), 131.6 (C-7), 140.7 (C-9), 170.0 (C-1); HRMS (ESI) calc. for [$C_{20}H_{34}O_4Na$] 361.2349 Found 361.2352.

NMR data in $(CD_3)_2CO$: δ_H (500 MHz, $(CD_3)_2CO$) 0.78 – 0.84 (2H, m, 10-H and 12-H), 0.88 (4H, m, 11-H and 19-H_3), 1.07 (3H, d, *J* 6.2, 11-CH_3), 1.24 – 1.44 (12H, m, 6 × CH_2), 1.61 – 1.68 (2H, m, 4-H_2), 2.42 (1H, dd, *J* 15.6, 7.7, 2-*H*H), 2.48 (1H, dd, *J* 15.6, 5.0, 2-H*H*), 4.15 – 4.21 (1H, m, 3-H), 4.31 – 4.37 (1H, m, 5-H), 5.31 (1H, dd, *J* 15.0, 8.5, 9-H), 5.53 (1H, dd, *J* 15.1, 6.6, 6-H), 6.03 (1H, dd, *J* 15.0, 10.5, 8-H), 6.15 (1H, dd, *J* 15.1, 10.5, 7-H); δ_C (126 MHz, $(CD_3)_2CO$) 12.4 (CH_3-11), 14.1 (C-19), 20.37 (C-11), 20.42 (CH_2), 23.02 (CH_2), 26.8 (C-12), 28.1 (CH_2), 29.8 (CH_2), 30.1 (C-10), 30.3 (CH_2), 32.3 (CH_2), 42.4 (C-2), 44.3 (C-4), 67.7 (C-5), 71.5 (C-3), 127.3 (C-8), 130.5 (C-6), 133.4 (C-7), 138.9 (C-9), 172.9 (C-1).

Ethyl 2-((2*S*,4*R*,5*R*,6*S*)-6-((*E*)-2-((1*S*,2*S*,3*R*)-2-heptyl-3-methylcyclopropyl)vinyl)-4,5-dihydroxytetrahydro-2H-pyran-2-yl)acetate (421)

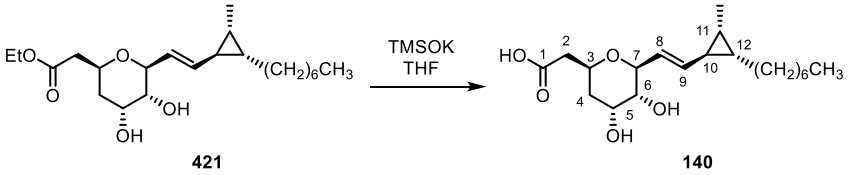


167 196 421

Alkene **167** (85 mg, 0.35 mmol) and alkene **196** (77 mg, 0.42 mmol) were dissolved in toluene (4 mL) under nitrogen, then Hoveyda-Grubbs Catalyst G2 (22 mg, 0.04 mmol) was added and the reaction mixture was heated at 80 °C for 24 hours. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (75% Et_2O in petroleum ether 60:40) to afford alkene **421** (29 mg, 22%, *E*/*Z* > 95:5) as an orange oil; $[\alpha]_D^{22}$ = -23.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3441, 2923, 2855, 1951, 1735, 1036; δ_H (500 MHz, $CDCl_3$) 0.73 – 0.82 (2H, m, 10-H and 12-H), 0.83 – 0.92 (4H, m, 11-H and 19-H_3), 1.05 (3H, d, *J* 6.2, 11-CH_3), 1.17 – 1.37 (15H, m, OCH_2CH_3 and 6 × CH_2), 1.60 (1H, m, 4-*H*H), 1.98 (1H, m, 4-H*H*), 2.31 – 2.41 (2H, m, OH and 2-*H*H), 2.49 – 2.58 (2H, m, OH and 2-H*H*), 3.30 (1H, dd, *J* 9.5, 2.9, 6-H), 3.93 (1H, dd, *J* 9.5, 7.2, 7-H), 4.07 – 4.18 (4H, m, OCH_2CH_3 and 5-H), 4.19 – 4.26 (1H, m, 3-H), 5.36 (1H, dd, *J* 15.6, 7.2, 8-H), 5.41 (1H, dd, *J* 15.6, 7.6, 9-H); δ_C (101 MHz, $CDCl_3$) 12.4 (CH_3-11), 14.1 (OCH_2CH_3), 14.2 (C-19), 20.0 (C-11), 22.7 (CH_2), 26.3 (C-12), 27.7 (CH_2), 29.2 (C-10), 29.3 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 37.0 (C-4), 40.7 (C-2), 60.5 (OCH_2CH_3), 66.4 (C-6), 68.1 (C-7), 71.1 (C-

5), 77.0 (C-3), 123.4 (C-8), 141.3 (C-9), 170.9 (C-1); HRMS (ESI) calc. for [$C_{22}H_{38}O_5Na$] 405.2611 Found 405.2610.

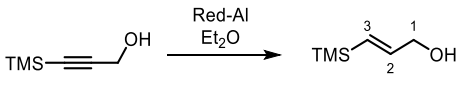
2-((2*S*,4*R*,5*R*,6*S*)-6-((*E*)-2-((1*S*,2*S*,3*R*)-2-Heptyl-3-methylcyclopropyl)vinyl)-4,5-dihydroxytetrahydro-2H-pyran-2-yl)acetic acid (140)



421 140

Ester **421** (29 mg, 0.08 mmol) was dissolved in THF (1 mL) under nitrogen then TMSOK (49 mg, 0.38 mmol) was added. The reaction mixture was stirred for 4 hours and quenched with aqueous saturated NH_4Cl (5 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (6% MeOH in DCM) to afford carboxylic acid **140** (18 mg, 63%) as a yellow oil; $[\alpha]_D^{22}$ = +22.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3406, 2924, 2855, 1714, 1072; δ_H (500 MHz, $CDCl_3$) 0.70 – 0.85 (2H, m, 10-H and 12-H), 0.84 – 0.93 (4H, m, 11-H and 19-H_3), 1.06 (3H, d, *J* 6.2, 11-CH_3), 1.19 – 1.43 (12H, m, 6 × CH_2), 1.57 – 1.66 (1H, m, 4-*H*H), 1.98 – 2.06 (1H, m, 4-H*H*), 2.47 (1H, dd, *J* 15.7, 5.6, 2-*H*H), 2.59 (1H, dd, *J* 15.7, 7.4, 2-H*H*), 3.33 (1H, dd, *J* 9.5, 3.0, 6-H), 3.98 (1H, dd, *J* 9.5, 7.8, 7-H), 4.16 – 4.27 (2H, m, 3-H and 5-H), 5.36 (1H, dd, *J* 15.3, 7.8, 8-H), 5.45 (1H, dd, *J* 15.3, 8.3, 9-H); δ_C (126 MHz, $CDCl_3$) 12.5 (CH_3-11), 14.3 (C-19), 20.3 (C-11), 22.9 (CH_2), 26.6 (C-12), 27.9 (CH_2), 29.3 (C-10), 29.5 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 32.1 (CH_2), 36.9 (C-4), 40.3 (C-2), 66.4 (C-6), 68.0 (C-7), 71.1 (C-5), 77.4 (C-3), 123.0 (C-8), 142.3 (C-9), 174.3 (C-1); HRMS (ESI) calc. for [$C_{20}H_{33}O_5$] 353.2328 Found 353.2337.

(*E*)-3-(Trimethylsilyl)prop-2-en-1-ol (247)

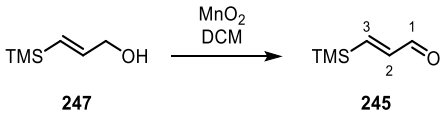


246 247

A 70% solution of Red-Al in toluene (3.48 mL, 14.04 mmol) was dissolved in Et_2O (40 mL) under nitrogen and cooled to 0 °C then propargylic alcohol **246** (1.01 g, 7.80 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour then quenched with 1 M H_2SO_4 (20 mL). The layers were separated and the organic layer washed with water (2 × 20 mL) and brine (20 mL). The combined aqueous phases were extracted with Et_2O (2 × 60 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (40% Et_2O in pentane) to afford the volatile allylic alcohol **247** (0.84 g, 82%,

E/*Z* > 99:1) as a colourless oil; ν_{max} (film) 3314, 2955, 2899, 1622, 1247, 861, 832; δ_H (400 MHz, $CDCl_3$) 0.07 (9H, s, $Si(CH_3)_3$), 1.52 (1H, t, *J* 6.0, OH), 4.18 (2H, ddd, *J* 6.0, 4.4, 1.8, 1-H_2), 5.92 (1H, dt, *J* 18.8, 1.8, 3-H), 6.18 (1H, dt, *J* 18.8, 4.4, 2-H); δ_C (101 MHz, $CDCl_3$) -1.2 ($Si(CH_3)_3$), 65.7 (C-1), 129.7 (C-3), 145.0 (C-2). Data consistent with the literature.[269]

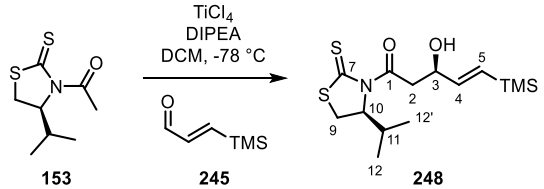
(*E*)-3-(Trimethylsilyl)acrylaldehyde (245)



247 **245**

Alcohol **247** (0.98 g, 7.52 mmol) was dissolved in DCM (38 mL) under nitrogen then activated MnO_2 (13.02 g, 150.01 mmol) was added. The reaction mixture was stirred for 1 hour, filtered over Celite, washed with DCM (100 mL) and the solvent removed *in vacuo* to afford the volatile aldehyde **245** (0.97 g, quant.) as a colourless oil; ν_{max} (film) 2957, 2799, 1692, 1250, 837; δ_H (400 MHz, $CDCl_3$) 0.17 (9H, s, $Si(CH_3)_3$), 6.50 (1H, dd, *J* 18.7, 7.6, 2-H), 7.18 (1H, d, *J* 18.7, 3-H), 9.49 (1H, d, *J* 7.6, 1-H); δ_C (101 MHz, $CDCl_3$) -1.8 ($Si(CH_3)_3$), 144.3 (C-2), 159.0 (C-3), 195.0 (C-1); m/z (APCI): $[M+H]^+$ = 129.10. Data consistent with the literature.[269]

(*R*,*E*)-3-Hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-5-(trimethylsilyl)pent-4-en-1-one (248)

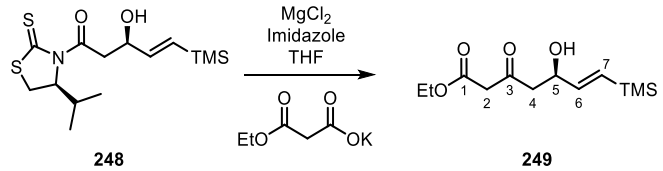


153 **245** **248**

Acylated auxiliary **153** (1.45 g, 7.14 mmol) was dissolved in DCM (70 mL) under nitrogen and cooled to -78 °C then $TiCl_4$ (1 M in DCM, 7.14 mL, 7.14 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 20 minutes then DIPEA (1.49 mL, 8.57 mmol) was added dropwise. The reaction mixture was stirred for 1 hour then aldehyde **245** (0.92 g, 7.14 mmol) in DCM (5 mL) was added dropwise. After stirring at -78 °C for 1 hour, aqueous saturated NH_4Cl (25 mL) was added and the reaction mixture was stirred for a further hour at room temperature. The solution was washed with DCM (3 × 50 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (22% EtOAc in petroleum ether 60:40) to afford aldol product **248** (1.768 g, 75%) as a single diastereoisomer and as a yellow oil; $[\alpha]_D^{22}$ = +308.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3436, 2958, 1688, 1246, 1156, 835; δ_H (400 MHz, $CDCl_3$) 0.07 (9H, s, $Si(CH_3)_3$), 0.98 (3H, d, *J* 6.8, 12-H_3), 1.07 (3H, d, *J* 6.8, 12'-H_3), 2.19 – 2.48 (1H, m, 11-H), 2.82 (1H, s, br. s, OH), 3.04 (1H, dd, *J* 11.5, 1.1, 9-*H*H), 3.29 (1H, dd, *J* 17.6, 9.0, 2-*H*H), 3.41 – 3.55 (1H, dd, *J* 11.5, 7.7, 9-H*H*), 3.55 – 3.73 (1H, dd, *J* 17.6, 8.0, 2-H*H*), 4.54 – 4.77 (1H, m, 3-H), 5.15 (1H, ddd, *J* 7.7, 6.3,

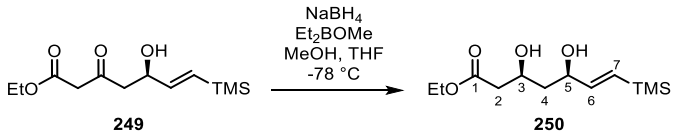
1.1, 10-H), 5.96 (1H, dd, *J* 18.8, 1.4, 5-H), 6.08 (1H, dd, *J* 18.8, 4.6, 4-H); δ_C (101 MHz, $CDCl_3$) -1.2 ($Si(CH_3)_3$), 18.0 (C-12), 19.3 (C-12'), 30.9 (C-9), 31.0 (C-11), 45.1 (C-2), 70.4 (C-3), 71.6 (C-10), 130.5 (C-5), 145.8 (C-4), 172.7 (C-1), 203.1 (C-7); HRMS (ESI) calc. for $[C_{14}H_{26}NO_2S_2Si]$ 332.1169 Found 332.1162.

Ethyl (*R*,*E*)-5-hydroxy-3-oxo-7-(trimethylsilyl)hept-6-enoate (249)



Potassium-3-ethoxy-2-methyl-3-oxopropanoate (1243 mg, 7.30 mmol) and $MgCl_2$ (348 mg, 3.65 mmol) were added to a solution of aldol product **248** (1100 mg, 3.32 mmol) in THF (11 mL) under nitrogen and stirred for 45 minutes. Imidazole (248 mg, 3.65 mmol) was added and the reaction mixture was stirred for 72 hours. The mixture was diluted with EtOAc (50 mL) and washed with 1 M HCl (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (30 mL) and the aqueous layer extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (5% Et_2O in DCM) to afford alcohol **249** (810 mg, 94%) as a yellow oil; $[\alpha]_D^{21}$ = +14.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3464, 2957, 1742, 1714, 1248, 1215, 750; δ_H (400 MHz, $CDCl_3$) 0.06 (9H, s, $Si(CH_3)_3$), 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 2.68 – 2.77 (2H, m, OH and 4-*H*H), 2.80 (1H, dd, *J* 17.3, 4.0, 4-H*H*), 3.48 (2H, s, 2-H_2), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 4.59 (1H, ap. dtd, *J* 8.6, 4.0, 1.1, 5-H), 5.93 (1H, dd, *J* 18.7, 1.1, 7-H), 6.02 (1H, dd, *J* 18.7, 4.0, 6-H); δ_C (101 MHz, $CDCl_3$) -1.2 ($Si(CH_3)_3$), 14.3 (OCH_2CH_3), 49.4 (C-4), 50.2 (C-2), 61.7 (OCH_2CH_3), 70.0 (C-5), 130.5 (C-7), 145.8 (C-6), 167.1 (C-1), 203.1 (C-3); HRMS (ESI) calc. for $[C_{12}H_{22}O_4SiNa]$ 281.1180 Found 281.1191.

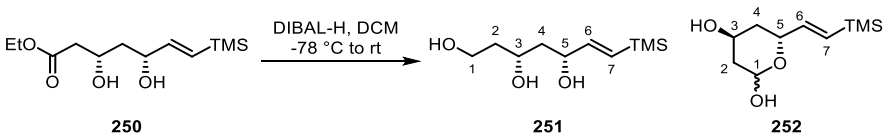
Ethyl (3*S*,5*R*,*E*)-3,5-dihydroxy-7-(trimethylsilyl)hept-6-enoate (250)



Ketone **249** (680 mg, 2.63 mmol) was dissolved in THF (18 mL) and MeOH (5 mL) under nitrogen and cooled to -78 °C then Et_2BOMe (0.42 mL, 3.16 mmol) was added dropwise and the reaction mixture was stirred for 15 minutes. $NaBH_4$ (114 mg, 3.02 mmol) was added in one portion and the reaction mixture was stirred for 3 hours then AcOH (4 mL) was added and the mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc (25 mL) and the resulting solution was washed with aqueous saturated $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in methanol (20 mL) and the solvent

removed *in vacuo* to afford diol **250** (689 mg, quant., dr > 99:1) as a yellow oil; $[\alpha]_D^{21}$ = +12.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3412, 2955, 1733, 1248, 866, 838; δ_H (400 MHz, $CDCl_3$) 0.06 (9H, s, $Si(CH_3)_3$), 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.62 – 1.70 (2H, m, 4-H_2), 2.48 – 2.51 (2H, m, 2-H_2), 4.18 (2H, q, *J* 7.1, OCH_2CH_3), 4.26 – 4.33 (1H, m, 4-H), 4.35 – 4.41 (1H, m, 5-H), 5.90 (1H, dd, *J* 18.7, 0.9, 7-H), 6.03 (1H, dd, *J* 18.7, 5.0, 6-H); δ_C (101 MHz, $CDCl_3$) -1.2 ($Si(CH_3)_3$), 14.3 (OCH_2CH_3), 41.8 (C-2), 42.4 (C-4), 61.0 (OCH_2CH_3), 68.8 (C-3), 74.6 (C-5), 129.6 (C-7), 147.6 (C-6), 172.7 (C-1); HRMS (ESI) calc. for [$C_{12}H_{24}O_4SiNa$] 283.1336 Found 283.1334.

(3*R*,5*R*,*E*)-7-(Trimethylsilyl)hept-6-ene-1,3,5-triol (251)



250 **251** **252**

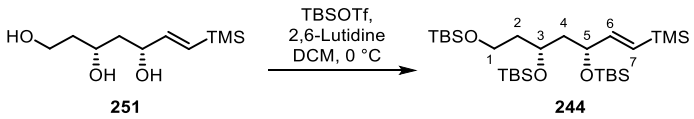
Ester **250** (670 mg, 2.57 mmol) was dissolved in DCM (26 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (2.57 mL, 2.57 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 hours. TLC analysis showed the presence of starting material so the reaction mixture was cooled to -78 °C and further 1 M DIBAL-H in hexane (2.57 mL, 2.57 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was cooled to 0 °C, aqueous saturated potassium sodium tartrate solution (30 mL) was added and the mixture was stirred for 3 hours at room temperature. The layers were separated and the aqueous layer extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (60-100% EtOAc in petroleum ether 60:40) to afford triol **251** (24 mg, 4%) and lactol **252** (141mg, 25%) as yellow oils.

251: $[\alpha]_D^{22}$ = +7.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3326, 2952, 1423, 1247, 864, 836; δ_H (400 MHz, $CDCl_3$) 0.04 (9H, s, $Si(CH_3)_3$), 1.55 – 1.78 (4H, m, 2-H_2 and 4-H_2), 3.49 (1H, br. s, OH), 3.71 – 3.87 (3H, m, OH and 1-H_2), 4.07 – 4.17 (1H, m, 3-H), 4.33 (1H, ap. qd, *J* 5.0, 1.0, 5-H), 4.40 (1H, s, OH), 5.85 (1H, dd, *J* 18.7, 1.0, 7-H), 6.01 (1H, dd, *J* 18.7, 5.0, 6-H); δ_C (101 MHz, $CDCl_3$) -1.2 ($Si(CH_3)_3$), 38.9 (C-2), 43.0 (C-4), 60.9 (C-1), 72.0 (C-3), 75.0 (C-5), 129.3 (C-7), 147.9 (C-6); HRMS (ESI) calc. for [$C_{10}H_{22}O_3SiNa$] 241.1230 Found 241.1231.

252 (2:1 ratio of unknown diastereoisomers) where NMR data is reported for the major diastereoisomer: ν_{max} (film) 3369, 2954, 1247, 861, 834; δ_H (400 MHz, $CDCl_3$) 0.07 (9H, s, $Si(CH_3)_3$), 1.58 – 1.63 (1H, m, 4-*H*H), 1.78 – 1.85 (1H, m, 2-*H*H), 1.85 – 1.92 (1H, m, 4-H*H*), 1.94 – 1.98 (1H, m, 2-H*H*), 3.19 (1H, m, OH), 4.09 (1H, m, OH), 4.21 – 4.29 (1H, m, 3-H), 4.69 – 4.80 (1H, m, 5-H), 5.39 (1H, ap. t, *J* 4.7, 1-H), 5.94 (1H, dd, *J* 18.8, 1.1, 7-H), 6.04 (1H, dd, *J* 18.8, 4.8, 6-H); δ_C (101 MHz, $CDCl_3$) -1.2

($Si(CH_3)_3$), 35.1 (C-2), 38.1 (C-4), 65.0 (C-3), 65.5 (C-5), 93.3 (C-1), 130.8 (C-7), 145.6 (C-6); HRMS (ESI) calc. for [$C_{10}H_2O_3SiNa$] 239.1074 Found 239.1069.

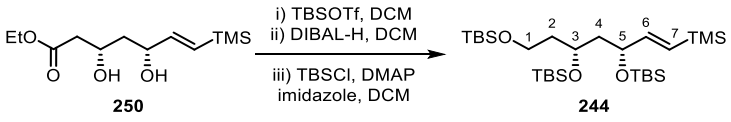
(3*R*,5*R*,*E*)-7-(Trimethylsilyl)hept-6-ene-1,3,5-(*tert*-butyldimethylsilyloxy)-triol (244)



251 **244**

Triol **251** (20 mg, 0.09 mmol) was dissolved in DCM (2 mL) under nitrogen and cooled to 0 °C then 2,6-lutidine (0.05 mL, 0.40 mmol) was added and the reaction mixture was stirred for 5 minutes. TBSOTf (0.11 mL, 0.50 mmol) was added and the reaction mixture was stirred for 5 minutes before the addition of aqueous saturated $NaHCO_3$ solution (2 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (1% Et_2O in petroleum ether 60:40) to afford silyl ether **244** (50 mg, quant.) as a colourless oil; $[\alpha]_D^{21}$ = +14.0 (*c* 1, $CHCl_3$); ν_{max} (film) 1955, 2930, 2887, 1472, 1250, 833; δ_H (400 MHz, $CDCl_3$) 0.00 – 0.06 (27H, m, $Si(CH_3)_3$ and 3 × $Si(CH_3)_2$), 0.86 – 0.90 (27H, m, 3 × $SiC(CH_3)_3$), 1.53 – 1.80 (4H, m, 2-H_2 and 4-H_2), 3.67 (2H, m, 1-H_2), 3.89 (1H, ap. tt, *J* 6.8, 5.1, 3-H), 4.17 (1H, ap. dtd, *J* 7.2, 6.0, 1.1, 5-H), 5.76 (1H, dd, *J* 18.6, 1.1, 7-H), 5.95 (1H, dd, *J* 18.6, 6.0, 6-H); δ_C (101 MHz, $CDCl_3$) -5.1 ($Si(CH_3)$), -4.5 ($Si(CH_3)$), -4.2 ($Si(CH_3)$), -4.2 ($Si(CH_3)$), -3.9 ($Si(CH_3)$), -2.8 ($Si(CH_3)$), -1.2 ($Si(CH_3)$), 18.2 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 40.4 (C-2), 46.1 (C-4), 60.1 (C-1), 66.9 (C-3), 73.4 (C-5), 129.2 (C-7), 149.2 (C-6); HRMS (ESI) calc. for [$C_{28}H_{64}NaO_3Si_4$] 583.3825 Found 583.3831.

(3*R*,5*R*,*E*)-7-(Trimethylsilyl)hept-6-ene-1,3,5-(*tert*-butyldimethylsilyloxy)-triol (244)



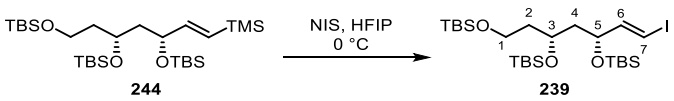
250 **244**

Diol **250** (0.85 g, 3.26 mmol) was dissolved in DCM (33 mL) under nitrogen and cooled to 0 °C then TBSOTf (4.50 mL, 19.58 mmol) was added dropwise. The reaction mixture was stirred for 20 minutes and quenched with a solution of aqueous saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 20 mL). The combined organic layers were washed sequentially with 2 M HCl (20 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was dissolved in DCM (33 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (7.17 mL, 7.17 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was cooled to 0 °C, aqueous saturated potassium sodium tartrate solution (40 mL) was added and the mixture was stirred for 5

hours at room temperature. The layers were separated and the aqueous layer extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The material was dissolved in DCM (33 mL) and imidazole (424 mg, 6.52 mmol), TBSCl (0.98 g, 6.52 mmol) and a spatula tip of DMAP were added. The reaction mixture was stirred for 3 hours then water (20 mL) was added and the solution was acidified with 2 M HCl (15 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (0-1% Et_2O in petroleum ether 60:40) to afford TBS alcohol **244** (1.34 g, 73%) as a colourless oil. Data consistent with previously reported.

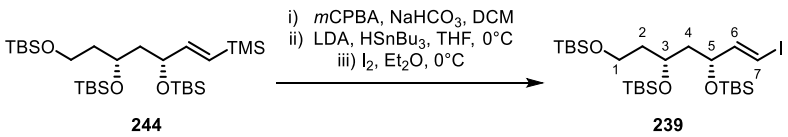
(3*R*,5*R*,*E*)-7-Iodo-hept-6-ene-1,3,5-(*tert*-butyldimethylsilyloxy)-triol (239)

Method 1:



Vinyl silane **244** (50 mg, 0.09 mmol) was dissolved in HFIP (0.3 mL) and cooled to 0 °C then NIS (30 mg, 0.18 mmol) was added. The reaction mixture was stirred for 15 minutes and then quenched with water (1 mL). The solution was diluted with DCM (10 mL) and the organic layer was washed sequentially with aqueous saturated solutions of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (1% Et_2O in petroleum ether 60:40) to afford vinyl iodide **239** (31 mg, 55%, *E*/*Z* = 2:1) as a colourless oil; $[\alpha]_D^{21}$ = +10.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2954, 2929, 2886, 2857, 1472, 1255, 1093, 835; δ_H (400 MHz, $CDCl_3$) -0.01 – 0.10 (18H, m, 3 × $Si(CH_3)_2$), 0.86 – 0.96 (27H, m, 3 × $SiC(CH_3)_3$), 1.48 – 1.75 (4H, m, 2-H_2 and 4-H_2), 3.66 (2H, m, 1-H_2), 3.89 (1H, ap. p, *J* 6.1, 3-H), 4.21 (1H, ap. qd, *J* 6.5, 1.1, 5-H), 6.23 (1H, dd, *J* 14.4, 1.1, 7-H), 6.54 (1H, dd, *J* 14.4, 6.5, 6-H); δ_C (101 MHz, $CDCl_3$) -5.1 (2 × $SiCH_3$), -4.6 ($SiCH_3$), -4.23 ($SiCH_3$), -4.22 ($SiCH_3$), -4.1 ($SiCH_3$), 18.2 (Si*C*$(CH_3)_3$), 18.3 (Si*C*$(CH_3)_3$), 18.5 (Si*C*$(CH_3)_3$), 26.0 (SiC(*C*$H_3)_3$), 26.1 (SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 40.4 (C-2), 45.9 (C-4), 59.8 (C-1), 66.5 (C-3), 72.7 (C-5), 76.3 (C-7), 149.2 (C-6) HRMS (ESI) calc. for [$C_{25}H_{55}O_3Si_3I$] 615.2550 Found 615.2568.

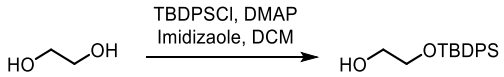
Method 2:



Vinyl silane **244** (542 mg, 0.97 mmol) was dissolved in DCM (10 mL) under nitrogen and cooled to 0 °C then $NaHCO_3$ (180 mg, 2.13 mmol) and *m*CPBA (70 wt.%, 476 mg, 1.93 mmol) were added sequentially and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was diluted with aqueous saturated $Na_2S_2O_3$ solution (30 mL) and DCM (50 mL). The organic layer was separated and the aqueous extracted with further DCM (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (2% Et_2O in petroleum ether 60:40) to afford crude epoxide **263** (410 mg, 73%) as a colourless oil and a 3:1 mixture of diastereoisomers.

DIPA (0.30 mL, 2.13 mmol) was dissolved in THF (10 mL) under nitrogen and cooled to 0 °C then 2.45 M *n*BuLi in hexanes (0.72 mL, 1.78 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 30 minutes. $HSnBu_3$ (0.38 mL, 1.42 mmol) was added, and the reaction mixture was stirred for a further 30 minutes. Epoxide **263** (410 mg, 0.71 mmol) in THF (3 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 3 hours then aqueous saturated NH_4Cl (10 mL) was added. The resulting solution was extracted with hexane (3 × 40 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was dissolved in Et_2O (7 mL) and cooled to 0 °C then I_2 (198 mg, 0.78 mmol) in Et_2O (4 mL) was added dropwise. The reaction mixture was stirred for 30 minutes then quenched with aqueous saturated $Na_2S_2O_3$ (10 mL). The organic layer was separated and the aqueous extracted with hexane (3 × 20 mL). The combined organic layers were washed with 3 M NaOH (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% DCM in petroleum ether 60:40) to afford vinyl iodide **239** (389 mg, 65% over two steps, *E*/*Z* > 95:5) as a colourless oil. Data consistent with previously reported.

2-(*tert*-Butyldiphenylsilyloxy)ethan-1-ol (267)

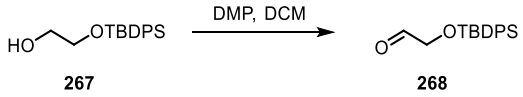


267

To a solution of ethylene glycol (22.30 mL, 400 mmol) in DCM (100 mL) under nitrogen was added imidazole (3.00 g, 44 mmol) and a spatula tip of DMAP. TBDPSCl (10.50 mL, 40 mmol) was added dropwise and the reaction mixture was stirred for 24 hours. Water (50 mL) was added and the solution was acidified with 2 M HCl (10 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether 60:40) to afford alcohol **267** (8.66 g, 76%) as a yellow oil; ν_{max} (film)

3385, 2930, 2857, 1427, 1110, 699; δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, $SiC(CH_3)_3$), 2.13 (1H, t, *J* 6.2, OH), 3.65 – 3.71 (2H, m, CH_2), 3.74 – 3.79 (2H, m, CH_2OH), 7.36 – 7.45 (5H, m, ArH), 7.65 – 7.70 (3H, m, ArH); δ_C (101 MHz, $CDCl_3$) 19.4 ($SiC(CH_3)_3$), 27.0 ($SiC(CH_3)_3$), 63.9 (CH_2), 65.2 (CH_2OH), 128.0 (ArC), 130.0 (ArC), 133.5 (ArC), 135.7 (ArC). Data consistent with the literature.[270]

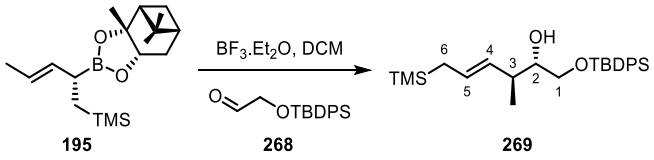
2-(*tert*-Butyldiphenylsilyloxy)ethan-1-al (268)



267 **268**

Alcohol **267** (4.00 g, 14.1 mmol) was dissolved in DCM (70 mL) under nitrogen then DMP (7.17 g, 16.9 mmol) was added and the reaction mixture was stirred for 1 hour. Aqueous saturated $NaHCO_3$ (50 mL) was added and the organic phase separated. The aqueous phase was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL) dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was filtered through a pad of silica and washed with Et_2O (200 mL) and the solvent removed *in vacuo* to afford aldehyde **268** (3.77 g, 95%) as a colourless oil which was used directly in the next step without further purification; ν_{max} (film) 2931, 2857, 1738, 1427, 1111, 699; δ_H (400 MHz, $CDCl_3$) 1.10 (9H, s, $SiC(CH_3)_3$), 4.22 (2H, d, *J* 1.0, CH_2), 7.35 – 7.47 (6H, m, ArH), 7.63 – 7.68 (4H, m, ArH), 9.73 (1H, t, *J* 1.0, HCO); δ_C (101 MHz, $CDCl_3$) 19.4 ($SiC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$), 70.2 (CH_2), 128.1 (ArCH), 130.3 (ArC), 132.7 (ArC), 135.7 (ArCH), 201.9 (CO). Data consistent with the literature.[270]

(2*S*,3*S*,*E*)-1-(*tert*-Butyldiphenylsilyloxy)-3-methyl-6-(trimethylsilyl)hex-4-en-2-ol (269)

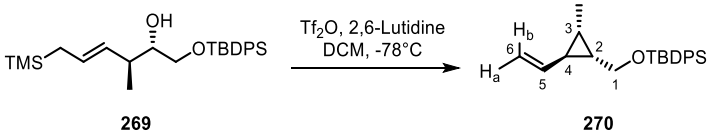


195 **268** **269**

Boronic ester **195** (9.40 g, 29.34 mmol) and aldehyde **268** (9.12 g, 32.27 mmol) were dissolved in DCM (150 mL) under nitrogen and cooled to -78 °C. $BF_3.Et_2O$ (3.62 mL, 29.34 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 4 hours. Aqueous saturated $NaHCO_3$ (50 mL) was added and the reaction mixture was warmed to room temperature. Et_2O (50 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford alcohol **269** (11.26 g, 87%, dr > 99:1) as a colourless oil; $[\alpha]_D^{22}$ = -8.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3583, 3473, 2956, 2858, 1428, 1111, 699; δ_H (400 MHz, $CDCl_3$) -0.05 (9H, s, TMS), 0.96 (3H, d, *J* 7.0, 3-CH_3), 1.06 (9H, s, $SiC(CH_3)_3$), 1.41 (2H, dd, *J* 8.0, 1.3, 6-H_2), 2.28 (1H, m, 3-H), 2.36 (1H, d, *J*

3.2, OH), 3.48 – 3.56 (1H, m, 2-H), 3.59 (1H, dd, *J* 10.0, 7.2, 1-*H*H), 3.67 (1H, dd, *J* 10.0, 3.6, 1-H*H*), 5.20 (1H, ap. ddt, *J* 15.5, 8.3, 1.3, 4-H), 5.40 (1H, ap. dt, *J* 15.5, 8.0, 5-H), 7.34 – 7.46 (6H, m, ArH), 7.64 – 7.69 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) -1.8 (TMS), 17.4 (CH_3-3), 19.4 (Si*C*$(CH_3)_3$), 23.0 (C-6), 27.0 (SiC(*C*$H_3)_3$), 39.8 (C-3), 66.4 (C-1), 75.6 (C-2), 127.8 (C-5), 127.9 (ArCH), 129.9 (ArCH), 130.0 (C-4), 133.5 (ArC), 135.8 (ArCH); HRMS (ESI) calc. for [$C_{26}H_{40}O_2Si_2Na$] 463.2459 Found 463.2459.

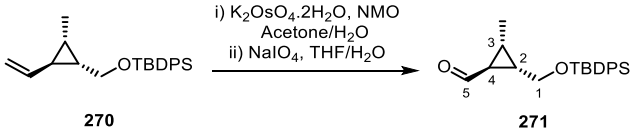
tert-Butyl(((1*S*,2*S*,3*S*)-2-methyl-3-vinylcyclopropyl)methoxy)diphenylsilane (270)



269 **270**

Alcohol **269** (1.158 g, 2.63 mmol) was dissolved in DCM (26 ml) and cooled to -78 °C under nitrogen then 2,6-lutidine (0.40 mL, 3.42 mmol) was added and the reaction mixture was stirred for 5 minutes. Tf_2O (0.53 mL, 3.16 mmol) was added within 5 seconds and the reaction mixture was stirred for 3 minutes before quenching with DIPEA (4.5 mL, 24.5 mmol). The mixture was warmed to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (2% Et_2O in petroleum ether 60:40) to afford alcohol **270** (0.882 g, 96%, dr > 99:1) as a colourless oil; $[\alpha]_D^{22}$ = -45.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2959, 2935, 2858, 1428, 1111, 1086, 699; δ_H (500 MHz, $CDCl_3$) 0.92 – 1.00 (2H, m, 3-H and 4-H), 1.07 (9H, s, SiC$(CH_3)_3$), 1.09 (3H, d, *J* 6.1, 3-CH_3), 1.16 – 1.22 (1H, m, 2-H), 3.61 (1H, dd, *J* 11.1, 8.3, 1-H*H*), 3.85 (1H, dd, *J* 11.1, 6.1, 1-*H*H), 4.82 (1H, dd, *J* 10.3, 1.8, 6-H_a), 4.97 (1H, ddd, *J* 17.1, 1.8, 0.6, 6-H_b), 5.42 (1H, ddd, *J* 17.1, 10.3, 8.4, 5-H), 7.35 – 7.44 (6H, m, ArH), 7.66 – 7.73 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 12.7 (CH_3), 19.4 (Si*C*$(CH_3)_3$), 19.6 (C-2/3), 27.0 (SiC(*C*$H_3)_3$, 27.6 (C-2/3), 28.6 (C-4), 63.2 (C-1), 111.5 (C-6), 127.8 (ArCH), 129.7 (ArCH), 134.2 (ArC), 135.8 (ArCH), 141.7 (C-5); HRMS (ESI) calc. for [$C_{23}H_{31}OSi$] 351.2139 Found 351.2142.

(2*S*,3*R*,4*S*)-2-((_tert_-Butyldiphenylsilyloxy)methyl)-3-methylcyclopropane-1-carbaldehyde (271)

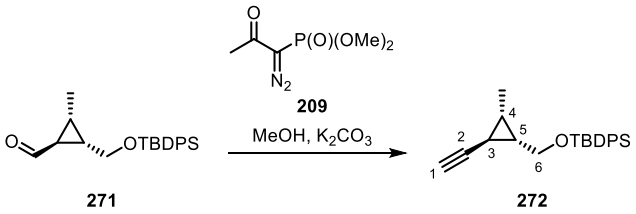


270 **271**

Alkene **270** (500 mg, 1.43 mmol) was dissolved in acetone (6 mL) and water (1 mL) then potassium osmate dihydrate (5 mg, 0.02 mmol) and NMO (251 mg, 2.15 mmol) were added sequentially and the reaction mixture was stirred at room temperature. After 18 hours the reaction mixture was diluted with EtOAc (75 mL) and water (50 mL). The organic layer was separated and the aqueous was extracted with further EtOAc (2 × 50 mL). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude diol was dissolved in THF (5 mL) and water (3.5 mL) then $NaIO_4$ (428 mg,

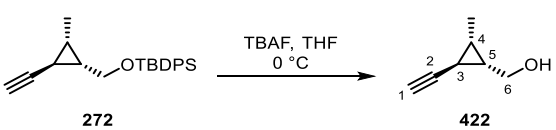
2.00 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The solution was filtered through a pad of Celite and washed with DCM (50 mL). The organic phase was washed with aqueous saturated $Na_2S_2O_3$ (20 mL) and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford aldehyde **271** (448 mg, 89%) as a light brown oil; $[\alpha]_D^{25}$ = +7.0 (*c* 0.7, $CHCl_3$); ν_{max} (film) 2930, 2857, 1710, 1428, 1111, 702; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, SiC(CH_3)$_3$), 0.99 (3H, d, *J* 6.3, 3-CH_3), 1.31 (1H, ap. td, *J* 9.5, 5.0, 4-H), 1.53 (1H, dqd, *J* 9.5, 6.3, 4.5, 3-H), 1.72 (1H, dddd, *J* 9.5, 7.5, 6.3, 4.5, 2-H), 3.55 (1H, dd, *J* 11.2, 7.5, 1-*H*H), 3.65 (1H, dd, *J* 11.2, 6.3, 1-H*H*), 7.18 – 7.33 (6H, m, ArH), 7.46 – 7.58 (4H, m, ArH), 8.93 (1H, d, *J* 5.0, 5-H); δ_C (101 MHz, $CDCl_3$) 12.1 (CH_3-3), 19.4 (Si*C*(CH_3)$_3$), 21.5 (C-3), 27.0 (SiC(*C*H_3)$_3$), 29.3 (C-2), 36.4 (C-4), 61.6 (C-1), 127.9 (ArCH), 129.9 (ArCH), 130.0 (ArCH), 133.7 (ArC), 135.8 (ArCH), 135.8 (ArCH), 200.6 (C-5); HRMS (ESI) calc. for [$C_{22}H_{28}O_2SiNa$] 375.1751 Found 375.1764.

tert-Butyl(((1*S*,2*S*,3*S*)-2-ethynyl-3-methylcyclopropyl)methoxy)diphenylsilane (272)



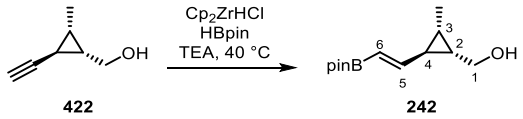
To a stirred solution of aldehyde **271** (4.70 g, 13.33 mmol) in MeOH (123 mL) under nitrogen was added K_2CO_3 (3.68 g, 26.66 mmol) followed by phosphonate **209** (3.84 g, 20.00 mmol) in MeOH (10 mL). After 16 hours the reaction mixture was diluted with Et_2O (500 mL) and washed sequentially with aqueous saturated $NaHCO_3$ (250 mL) and brine (250 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3% Et_2O in petroleum ether 60:40) to afford alkyne **272** (4.24 g, 91%) as a colourless oil; $[\alpha]_D^{22}$ = +68.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3313, 2931, 2858, 2120, 1428, 1112, 1084; δ_H (400 MHz, $CDCl_3$) 0.77 (1H, ap. td, *J* 5.0, 2.1, 3-H), 1.06 (9H, s, SiC(*CH*$_3$)$_3$), 1.08 (3H, d, *J* 6.4, 4-CH_3), 1.27 (1H, dqd, *J* 9.0, 6.4, 5.0, 4-H), 1.47 (1H, dddd, *J* 9.0, 8.1, 6.0, 5.0, 5-H), 1.82 (1H, d, *J* 2.1, 1-H), 3.53 (1H, dd, *J* 11.2, 8.1, 6-*H*H), 3.81 (1H, dd, *J* 11.2, 6.0, 6-H*H*), 7.34 – 7.45 (6H, m, ArH), 7.66 – 7.71 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 12.0 (C-3), 12.5 (CH_3-4), 19.4 (Si*C*(CH_3)$_3$), 21.2 (C-4), 27.0 (SiC(*C*H_3)$_3$), 28.6 (C-5), 62.5 (C-6), 64.4 (C-1), 87.0 (C-2), 127.9 (ArCH), 129.8 (ArCH), 133.89 (ArC), 133.91 (ArC), 135.78 (ArCH), 135.80 (ArCH); HRMS (ESI) calc. for [$C_{23}H_{28}OSiNa$] 371.1802 Found 371.1808.

((1*S*,2*S*,3*S*)-2-Ethynyl-3-methylcyclopropyl)methanol (422)



Silyl ether **272** (4.23 g, 12.14 mmol) was dissolved in THF (100 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (36.4 mL, 36.4 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 18 hours and then quenched with aqueous saturated NH_4Cl (100 mL) and diluted with Et_2O (300 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (40% Et_2O in petroleum ether 60:40) to afford alcohol **422** (1.26 g, 94%) as a colourless oil; $[\alpha]_D^{22}$ = +57.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3291, 3017, 2960, 2932, 2877, 2116, 1071, 1024; δ_H (400 MHz, $CDCl_3$) 0.88 (1H, ap. td, *J* 4.9, 2.1, 3-H), 1.15 (3H, d, *J* 6.4, 4-CH_3), 1.26 – 1.38 (1H, m, 4-H), 1.39 – 1.52 (2H, m, OH and 5-H), 1.85 (1H, d, *J* 2.1, 1-H), 3.54 (1H, dd, *J* 11.6, 8.2, 6-*H*H), 3.76 (1H, dd, *J* 11.6, 6.7, 6-H*H*); δ_C (101 MHz, $CDCl_3$) 12.3 (C-3), 12.4 (CH_3-4), 21.0 (C-4), 28.7 (C-5), 61.6 (C-6), 64.9 (C-1), 86.4 (C-2); HRMS (APCI) calc. for [$C_7H_{10}O$] 111.0804 Found 111.0807.

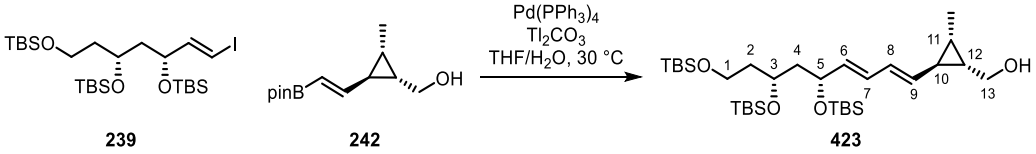
((1*S*,2*S*,3*S*)-2-Methyl-3-((*E*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclopropyl)methanol (242)



422 242

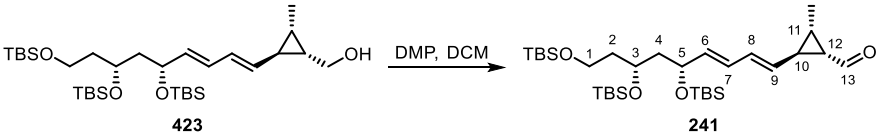
HBpin (0.73 mL, 5.06 mmol), triethylamine (0.04 mL, 0.25 mmol) and Cp_2ZrHCl (16 mg, 0.06 mmol) were added sequentially to alkyne **422** (279 mg, 2.53 mmol) stirring under nitrogen and the reaction mixture was heated at 40 °C for 18 hours. The reaction mixture was cooled to 0 °C, quenched with water (30 mL) and diluted with DCM (50 mL). The organic layer was separated and the aqueous extracted with further DCM (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (55% Et_2O in petroleum ether 60:40 + 0.1% TEA) to afford vinyl boronic ester **242** (587 mg, 97%, *E*/*Z* > 99:1) as a colourless oil; $[\alpha]_D^{24}$ = +6.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3419, 2977, 2930, 2877, 1630, 1353, 1139; δ_H (400 MHz, $CDCl_3$) 1.13 – 1.20 (5H, m, 3-H, 4-H and 3-CH_3), 1.25 (12H, s, Bpin), 1.31 – 1.39 (1H, m, 2-H), 3.58 (1H, ddd, *J* 11.7, 8.2, 4.5, 1-*H*H), 3.78 (1H, ddd, *J* 11.7, 6.7, 5.3, 1-H*H*), 5.43 (1H, d, *J* 17.8, 6-H), 6.17 (1H, dd, *J* 17.8, 8.8, 5-H); δ_C (101 MHz, $CDCl_3$) 12.5 (3-CH_3), 20.8 (C-3), 24.9 (Bpin CH_3), 29.0 (C-2), 31.0 (C-4), 62.0 (Bpin C), 83.2 (C-1), 156.8 (C-5); HRMS (ESI) calc. for [$C_{13}H_{23}BO_3Na$] 261.1635 Found 261.1646.

((1*S*,2*S*,3*S*)-2-Methyl-3-((1*E*,3*E*,5*R*,7*R*)-5,7,9-tris((*tert*-butyldimethylsilyl)oxy)nona-1,3-dien-1-yl)cyclopropyl)methanol (423)



To a stirred solution of boronic ester **242** (54 mg, 0.23 mmol) in degassed THF (2 mL) and water (1 mL) under nitrogen was added vinyl iodide **239** (141 mg, 0.23 mmol) in degassed THF (1 mL) followed by $Pd(PPh_3)_4$ (26 mg, 0.02 mmol) and the reaction mixture was stirred at room temperature for 5 minutes. Tl_2CO_3 (216 mg, 0.46 mmol) was added and the reaction mixture was heated at 30 °C for 3 hours. The reaction mixture was filtered over Celite, eluting with ether (50 mL) and water (20 mL). The layers were separated, and the aqueous phase extracted with further Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30 % Et_2O in petroleum ether 60:40) to afford diene **423** (117 mg, 85%) as a colourless oil; $[\alpha]_D^{24}$ = +12.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3348, 2954, 2929, 2885, 1655, 1252, 1074, 933, 773; δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.02 – 0.04 (15H, m, 5 × $SiCH_3$), 0.86 – 0.89 (27H, m, 3 × SiC(*CH*$_3$)$_3$), 0.99 – 1.08 (2H, m, 11-H and 12-H), 1.15 (3H, d, *J* 5.8, 11-CH_3), 1.18 – 1.27 (1H, m, 10-H), 1.29 – 1.33 (1H, m, OH), 1.50 – 1.78 (4H, m, 2-CH_2 and 4-CH_2), 3.58 (1H, dd, *J* 11.3, 8.6, 13-*H*H), 3.61 – 3.73 (2H, m, 1-CH_2), 3.79 (1H, dd, *J* 11.3, 6.6, 13-H*H*), 3.82 – 3.92 (1H, m, 3-H), 4.20 (1H, ap. q, *J* 6.7, 5-H), 5.19 – 5.29 (1H, m, 9-H), 5.43 – 5.53 (1H, m, 6-H), 5.97 – 6.07 (2H, m, 7-H and 8-H); δ_C (101 MHz, $CDCl_3$) -5.14 ($SiCH_3$), -5.12 ($SiCH_3$), -4.6 ($SiCH_3$), -4.2 (2 × $SiCH_3$), -3.9 ($SiCH_3$), 12.7 (CH_3-11), 18.2 (Si*C*$(CH_3)_2$), 18.3 (Si*C*$(CH_3)_2$), 18.5 (Si*C*$(CH_3)_2$), 20.0 (12-H), 26.1 (SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 28.1 (11-H), 28.3 (10-H), 40.4 (C-2), 46.8 (C-4), 60.1 (C-1), 62.3 (C-13), 66.9 (C-3), 70.9 (C-5), 127.9 (C-7/8), 129.6 (C-7/8), 134.1 (C-6), 136.5 (C-9); HRMS (ESI) calc. for [$C_{32}H_{66}O_4Si_3Na$] 621.4162 Found 621.4158.

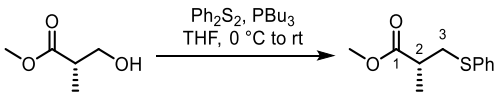
(1*S*,2*S*,3*S*)-2-Methyl-3-((1*E*,3*E*,5*R*,7*R*)-5,7,9-tris(*tert*-butyldimethylsiloxy)nona-1,3-dien-1-yl)cyclopropane-1-carbaldehyde (241)



Alcohol **423** (30 mg, 0.05 mmol) was dissolved in DCM (0.5 mL) under nitrogen and cooled to 0 °C, then DMP (25 mg, 0.06 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature then quenched with aqueous saturated $Na_2S_2O_3$ (2 mL) and aqueous saturated $NaHCO_3$

(2 mL) and stirred for 10 minutes. The aqueous phase was extracted with DCM (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% Et_2O in petroleum ether 60:40) to afford aldehyde **241** (29 mg, 97%) as a colourless oil; $[\alpha]_D^{22}$ = +27.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2954, 2928, 2856, 1704, 1472, 1214, 835, 751; δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.02 – 0.04 (15H, m, 5 × $SiCH_3$), 0.84 – 0.91 (27H, m, 3 × $SiC(CH_3)_3$), 1.31 (3H, d, *J* 6.4, 11-CH_3), 1.51 – 1.77 (5H, m, 2-H_2, 4-H_2 and 11-H), 1.97 (1H, ap. dt, *J* 9.1, 4.5, 12-H), 2.17 (1H, ddd, *J* 8.6, 6.3, 4.5, 10-H), 3.60 – 3.71 (2H, m, 1-H_2), 3.86 (1H, ap. p, *J* 6.2, 3-H), 4.22 (1H, ap. q, *J* 6.6, 5-H), 5.22 (1H, dd, *J* 14.8, 8.6, 9-H), 5.57 (1H, dd, *J* 14.9, 6.6, 6-H), 6.04 (1H, dd, *J* 14.9, 10.5, 7-H), 6.13 (1H, dd, *J* 14.8, 10.5, 8-H), 9.48 (1H, d, *J* 4.5, 13-H); δ_C (101 MHz, $CDCl_3$) -5.14 ($SiCH_3$), -5.12 ($SiCH_3$), -4.6 ($SiCH_3$), -4.2 (2 × $SiCH_3$), -4.0 ($SiCH_3$), 12.8 (CH_3-11), 18.2 (Si*C*$(CH_3)_3$), 18.3 (Si*C*$(CH_3)_3$), 18.5 (Si*C*$(CH_3)_3$), 26.1 (2 × SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 27.0 (C-11), 33.3 (C-10), 37.6 (C-12), 40.4 (C-2), 46.6 (C-4), 60.0 (C-1), 66.8 (C-3), 70.6 (C-5), 128.9 (C-7), 130.4 (C-8), 132.5 (C-9), 136.0 (C-6), 199.9 (C-13); HRMS (ESI) calc. for [$C_{32}H_{64}O_4Si_3Na$] 619.4005 Found 619.3999.

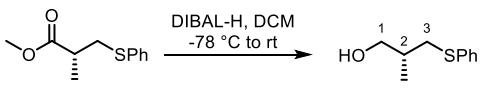
Methyl (*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate (277)



276 **277**

Alcohol **276** (2.81 ml, 25.40 mmol) was dissolved in THF (50 mL) under nitrogen and cooled to 0 °C then diphenyl disulfide (8.32 g, 38.09 mmol) and tributylphosphine (9.83 mL, 39.37 mmol) were added sequentially. The reaction was stirred at room temperature for 18 hours and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (10% Et_2O in petroleum ether 60:40) to afford sulfide **277** (5.26 g, 98%) as a colourless oil; $[\alpha]_D^{22}$ = +87.0 (*c* 1, $CHCl_3$), lit.[100] $[\alpha]_D^{20}$ = +74.6 (*c* 1.20, CH_2Cl_2); ν_{max} (film) 3059, 2976, 2951, 2878, 1733, 1437, 1162, 738; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, 2-CH_3), 2.70 (1H, ap. h, *J* 7.0, 2-H), 2.93 (1H, dd, *J* 13.4, 7.0, 3-*H*H), 3.27 (1H, dd, *J* 13.4, 7.0, 3-H*H*), 3.66 (3H, s, OCH_3), 7.17 – 7.23 (1H, m, ArH), 7.25 – 7.32 (2H, m, ArH), 7.34 – 7.41 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 16.9 (CH_3-2), 37.5 (C-3), 39.8 (C-2), 52.0 (OCH_3), 126.6 (ArCH), 129.1 (ArCH), 130.2 (ArCH), 135.8 (ArC), 175.5 (C-1); HRMS (ESI) calc. for [$C_{11}H_{14}O_2SNa$] 233.0607 Found 233.0600. Data consistent with the literature.[100]

(*R*)-2-Methyl-3-(phenylthio)propan-1-ol (278)



277 **278**

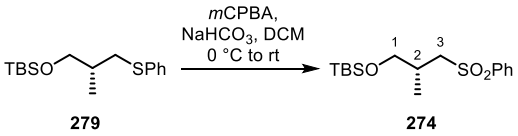
Ester **277** (5.24 g, 24.92 mmol) was dissolved in DCM (125 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (57.3 mL, 57.3 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was cooled to -78 °C then quenched with 2 M HCl (50 mL). The resulting solution was stirred vigorously for 30 minutes at room temperature. The organic layer was separated and the aqueous extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford alcohol **278** (4.53 g, quant.) as a yellow oil; $[\alpha]_D^{22}$ = -17.0 (*c* 1, $CHCl_3$), lit.[100] $[\alpha]_D^{20}$ = -20.9 (*c* 1.05, CH_2Cl_2); ν_{max} (film) 3345, 2958, 2924, 2872, 1583, 1480, 1438, 1025; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.8, 2-CH_3), 1.57 (1H, s, OH), 1.87 – 2.03 (1H, m, 2-H), 2.84 (1H, dd, *J* 12.9, 6.9, 3-*H*H), 3.07 (1H, dd, *J* 12.9, 6.5, 3-H*H*), 3.56 – 3.69 (2H, m, 1-H_2), 7.09 – 7.22 (1H, m, ArH), 7.24 – 7.33 (2H, m, ArH), 7.33 – 7.41 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 16.7 (CH_3-2), 35.7 (C-2), 37.6 (C-3), 67.0 (C-1), 126.1 (ArCH), 129.1 (ArCH), 129.2 (ArCH), 136.9 (ArC); HRMS (ESI) calc. for [$C_{10}H_{14}OSNa$] 205.0658 Found 205.0657. Data consistent with the literature.[100]

(*R*)-*tert*-Butyldimethyl(2-methyl-3-(phenylthio)propoxy)silane (279)

278 **279**

To a solution of alcohol **278** (4.46 g, 24.47 mmol) in DCM (80 mL) was added imidazole (3.33 g, 48.94 mmol), TBSCl (5.53 g, 36.70 mmol) and a spatula tip of DMAP and the reaction mixture was stirred for 24 hours. The reaction was quenched with 2 M HCl (20 mL) and water (50 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 60 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O in petroleum ether 60:40) to afford silyl ether **279** (7.26 g, quant.) as a colourless oil; $[\alpha]_D^{22}$ = -9.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2955, 2928, 2885, 2856, 1585, 1471, 1250, 1086, 834; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, *J* 6.5, 2-CH_3), 1.90 (1H, ap. dtt, *J* 7.7, 6.5, 5.5, 2-H), 2.68 (1H, dd, *J* 13.0, 7.7, 3-*H*H), 3.16 (1H, dd, *J* 13.0, 5.5, 3-H*H*), 3.49 (1H, dd, *J* 9.9, 6.5, 1-*H*H), 3.59 (1H, dd, *J* 9.9, 5.5, 1-H*H*), 7.08 – 7.17 (1H, m, ArH), 7.20 – 7.29 (2H, m, ArH), 7.29 – 7.40 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) -5.26 ($SiCH_3$), -5.23 ($SiCH_3$), 16.5 (2-CH_3), 18.5 (Si*C*$(CH_3)_3$), 26.1 (SiC(*C*$H_3)_3$), 36.0 (C-2), 37.0 (C-3), 66.8 (C-1), 125.6 (ArCH), 128.6 (ArCH), 129.0 (ArCH), 137.6 (ArC); HRMS (ESI) calc. for [$C_{16}H_{28}NaSSiO$] 319.1522 Found 319.1537. Data consistent with the literature.[100]

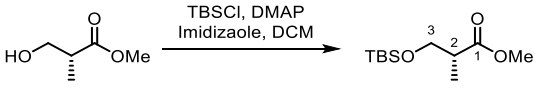
(*R*)-*tert*-Butyldimethyl(2-methyl-3-(phenylsulfonyl)propoxy)silane (274)



279 274

Sulfide **279** (1.00 g, 3.37 mmol) was dissolved in DCM (35 mL) and cooled to 0 °C, then $NaHCO_3$ (2.26g, 26.96 mmol) and 70 wt.% *m*CPBA (1.83g, 7.41 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 4 hours, then quenched with water (30 mL) and aqueous saturated $Na_2S_2O_3$ (10 mL). The organic layer was separated and the aqueous extracted with further DCM (2 × 50 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (3 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford sulfone **274** (1.14 g, quant.) as a white oil; $[\alpha]_D^{22}$ = -7.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2955, 2929, 2889, 2857, 1305, 1147, 1084, 836; δ_H (400 MHz, $CDCl_3$) -0.03 (3H, s, $SiCH_3$), -0.02 (3H, s, $SiCH_3$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.06 (3H, d, *J* 6.8, 2-CH_3), 1.93 – 2.37 (1H, m, 2-H), 2.86 (1H, dd, *J* 14.2, 8.0, 3-*H*H), 3.35 (1H, dd, *J* 9.9, 6.5 1-*H*H, 1H), 3.41 (1H, dd, *J* 14.2, 4.3, 3-H*H*), 3.54 (1H, dd, *J* 9.9, 4.8, 1-H*H*), 7.50 – 7.58 (2H, m, ArH), 7.59 – 7.68 (1H, m, ArH), 7.87 – 7.96 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) -5.4 ($SiCH_3$), -5.3 ($SiCH_3$), 16.9 (CH_3-2), 18.3 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 31.8 (C-2), 59.1 (C-3), 66.6 (C-2), 128.0 (ArCH), 129.4 (ArCH), 133.7 (ArCH), 140.2 (ArC); HRMS (ESI) calc. for $[C_{16}H_{28}SiO_3SNa]$ 351.1421 Found 351.1436. Data consistent with the literature.[100]

Methyl (*R*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate (424)

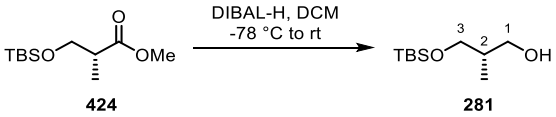


280 424

Alcohol **280** (5.00 g, 42.00 mmol) was dissolved in DCM (150 mL) then imidazole (5.76 g, 85.00 mmol) was added. The reaction mixture was cooled to 0 °C then TBSCl (14.60 g, 97.00 mmol) and a spatula tip of DMAP were added. The reaction mixture was stirred at room temperature for 24 hours then water (100 mL) was added and the solution acidified to pH 2 with 2 M HCl. The organic layer was separated and the aqueous extracted with further DCM (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford TBS protected alcohol **424** (9.70 g, 99%) as a colourless oil; $[\alpha]_D^{22}$ = -16.0 (*c* 1, $CHCl_3$), lit.[271] $[\alpha]_D^{20}$ = -19.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2951, 2928, 2850, 1740, 838; δ_H (400 MHz,$CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.13 (3H, d, *J* 7.0, 2-CH_3), 2.65 (1H, ap. h, *J* 7.0, 2-H), 3.65 (1H, dd, *J* 9.7, 6.0, 3-*H*H), 3.67 (3H, s, OCH_3), 3.77 (1H, dd, *J* 9.7, 7.0, 3-H*H*); δ_C (101 MHz, $CDCl_3$) -5.3 ($Si(CH_3)_2$), 13.6

(Si*C*(CH_3)$_3$), 18.4 (CH_3-2), 26.0 (SiC(*C*H_3)$_3$), 42.7 (C-2), 51.7 (OCH_3), 65.4 (C-3), 175.7 (C-1). Data consistent with the literature.[271]

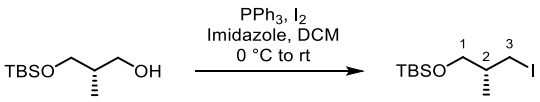
(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-1-ol (281)



424 **281**

Ester **424** (9.70 g, 41.74 mmol) was dissolved in DCM (150 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (94.00 mL, 94.00 mmol) was added slowly. The reaction mixture was stirred for 1 hour at room temperature and poured onto a solution of 1 M HCl (100 mL) at 0 °C. The resulting solution was stirred for 30 minutes. The organic layer was separated and the aqueous extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford alcohol **281** (6.86 g, 80%) as a colourless oil; $[\alpha]_D^{24}$ = -9.0 (*c* 1, $CHCl_3$), lit.[271] $[\alpha]_D^{24}$ = -11.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3350, 2934, 2854, 770; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, Si(CH_3)$_2$), 0.82 (3H, d, *J* 6.9, 2-CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 1.86 – 1.99 (1H, m, 2-H), 2.84 (1H, br. s, OH), 3.53 (1H, dd, *J* 10.0, 8.0, 1-*H*H), 3.57 – 3.67 (2H, m, 3-H_2), 3.72 (1H, ddd, *J* 10.0, 4.4, 0.8, 1-H*H*); δ_C (101 MHz, $CDCl_3$) -5.43 ($SiCH_3$), -5.37 ($SiCH_3$), 13.3 (CH_3), 18.4 (Si*C*(CH_3)$_3$), 26.0 (SiC(*C*H_3)$_3$, 37.2 (C-2), 68.6 (CH_2), 69.0 (CH_2). Data consistent with the literature.[271]

(*R*)-*tert*-Butyl(3-iodo-2-methylpropoxy)dimethylsilane (282)

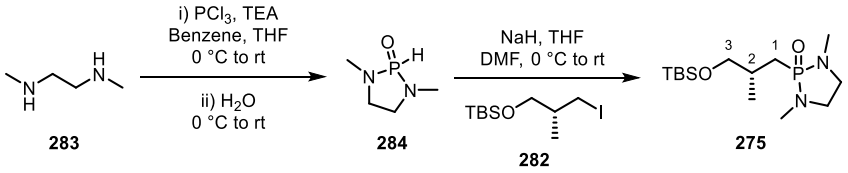


281 **282**

Alcohol **281** (7.20 g, 35.23 mmol), PPh_3 (12.01 g, 45.79 mmol) and imidazole (3.60 g, 52.88 mmol) were dissolved in DCM (150 mL) under nitrogen and cooled to 0 °C, then I_2 (12.07 g, 47.56 mmol) was added portionwise. The reaction mixture was warmed to room temperature and stirred in the dark for 16 hours. The reaction mixture was diluted with Et_2O (350 mL) and filtered over Celite. The organic layer was washed sequentially with aqueous saturated $Na_2S_2O_3$ (150 mL), aqueous saturated $NaHCO_3$ (150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (10% DCM in petroleum ether 60:40) to afford iodide **282** (9.99 g, 90%) as a colourless oil; $[\alpha]_D^{20}$ = -13.0 (*c* 1, $CHCl_3$), lit.[234] $[\alpha]_D^{20}$ = -9.5 (*c* 4.03, $CHCl_3$); ν_{max} (film) 2955, 2929, 2895, 1471, 1098, 834, 774; δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.95 (3H, d, *J* 6.7, 2-CH_3), 1.56 – 1.71 (1H, m, 2H), 3.25 (1H, dd, *J* 9.5, 5.6, 3-*H*H), 3.30 (1H, dd, *J* 9.5, 5.2, 3-H*H*), 3.39 (1H, dd, *J* 10.0, 6.9, 1-*H*H), 3.52 (1H, dd, *J* 10.0,

5.0, 1-H*H*); δ_C (101 MHz, $CDCl_3$) -5.2 ($SiCH_3$), 14.1 (C-3), 17.4 (CH_3-2), 18.5 (Si*C*(CH_3)$_3$), 26.1 (SiC(*C*H_3)$_3$), 37.6 (C-2), 66.9 (C-1); m/z (APCI): $[M+H]^+$ = 314.10. Data consistent with the literature.[234]

(*R*)-2-(3-(*tert*-Butyldimethylsiloxy)-2-methylpropyl)-1,3-dimethyl-1,3,2-diazaphospholidine 2-oxide (275)

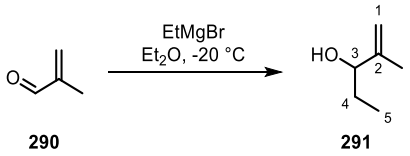


To a vigorously stirred solution of amine **283** (1.00 mL, 9.29 mmol) and degassed triethylamine (5.18 mL, 37.16 mmol) in degassed THF (11 mL) and degassed benzene (7.45 mL) at 0 °C under nitrogen was added PCl_3 (0.81 mL, 9.29 mmol) in degassed benzene (3.7 mL) dropwise. The reaction mixture was stirred for 1 hour at room temperature then cooled to 0 °C. A solution of water (0.17 mL, 9.29 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was dissolved in a mixture of benzene (5 mL) and THF (5 mL) and filtered over Celite, eluting with a solution of benzene (5 mL) and THF (5 mL). The solvent was removed *in vacuo* to afford phosphorus acid diamide **284**[234] (629 mg, 51%) as an orange oil which was used in the next step without further purification.

Alkyl iodide **282** (499 mg, 1.59 mmol) and phosphorus acid diamide **284** (490 mg, 3.65 mmol) were dissolved in THF (6.5 mL) and DMF (1.5 mL) under nitrogen and cooled to 0 °C. NaH (127 mg, 3.18 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with aqueous saturated NH_4Cl (5 mL) and diluted with EtOAc (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water (3 × 15 mL), brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% EtOH in EtOAc) to afford phosphorus diamide **275** (482 mg, 95%) as a colourless oil; $[\alpha]_D^{20}$ = -3.2 (*c* 1, $CHCl_3$), lit.[234] $[\alpha]_D^{20}$ = -6.3 (*c* 3.6, $CHCl_3$); ν_{max} (film) 2954, 2927, 2885, 2855, 1471, 1225, 1083, 834, 774; δ_H (400 MHz, $CDCl_3$) 0.03 (6H, s, Si(CH_3)$_2$), 0.88 (9H, s, SiC(CH_3)$_3$), 0.97 (3H, d, *J* 6.7, 2-CH_3), 1.54 (1H, ap. td, *J* 15.7, 8.8, 1-*H*H), 1.68 – 1.85 (1H, m, 2-H), 2.12 (1H, ddd, *J* 17.3, 15.7, 3.7, 1-H*H*), 2.64 (3H, d, *J* 3.1, NCH_3), 2.66 (3H, d, *J* 3.2, NCH_3), 3.03 – 3.12 (2H, m, NCH_2), 3.16 – 3.25 (2H, m, NCH_2), 3.33 (1H, dd, *J* 9.6, 6.8, 3-*H*H), 3.42 (1H, ddd, *J* 9.6, 5.7, 2.4, 3-H*H*); δ_C (101 MHz, $CDCl_3$) -5.24 ($SiCH_3$), -5.21 ($SiCH_3$), 18.0 (d, *J* 4.7, CH_3-2), 18.5 (Si*C*(CH_3)$_3$), 26.1 (SiC(*C*H_3)$_3$), 30.0 (d, *J* 116.9, C-1)), 31.8 (d, *J* 3.9, C-2), 32.0 (d, *J* 5.3, NCH_3), 32.2 (d, *J* 5.3, NCH_3), 48.3 (d, *J* 7.8, NCH_2), 48.5 (d, *J* 7.8, NCH_2), 68.6 (d, *J* 14.9,

C-3); δ_P (162 MHz, $CDCl_3$) 42.03; [$C_{14}H_{33}N_2O_2PSiNa$] 343.1941 Found 343.1931. Data consistent with the literature.[234]

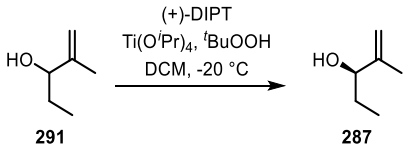
2-Methylpent-1-en-3-ol (291)



290 **291**

Aldehyde **290** (1.18 mL, 14.28 mmol) was dissolved in Et_2O (30 mL) under nitrogen and cooled to -20 °C then 1 M EtMgBr in THF (18.56 mL, 18.56 mmol) was added dropwise. The reaction mixture was stirred for 20 minutes then quenched with aqueous saturated NH_4Cl (30 mL). The layers were separated, and the aqueous phase extracted with further Et_2O (2 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude material was purified by flash column chromatography (DCM) to afford alcohol **291** (1.23 g, 86%) as a colourless oil; ν_{max} (film) 3367, 2964, 2936, 2877, 1651, 1455, 896; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.5, 5-H_3), 1.48 – 1.64 (2H, m, 4-H_2), 1.67 – 1.74 (3H, m, 2-CH_3), 3.99 (1H, t, *J* 6.7, 3-H), 4.79 – 4.86 (1H, m, 1-*H*H), 4.89 – 4.95 (1H, m, 1-H*H*); δ_C (101 MHz, $CDCl_3$) 10.0 (C-5), 17.6 (C-4), 27.9 (CH_3-2), 77.5 (C-3), 111.31 (C-1), 147.5 (C-2); HRMS (APCI) calc. for [C_6H_{11}] 83.0855 Found 83.0850. Data consistent with the literature.[272]

(*R*)-2-Methylpent-1-en-3-ol (287)



291 **287**

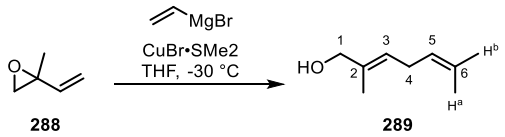
To a mixture of alcohol **291** (3.13 g, 31.25 mmol) and 4 Å molecular sieves (0.94 g) in DCM (156 mL) under nitrogen at -20 °C was added (+)-DIPT (0.98 mL, 4.69 mmol) and $Ti(O^iPr)_4$ (0.93 mL, 3.13 mmol). The reaction mixture was stirred for 30 minutes then ^{t}BuOOH (3.13 mL, 17.19 mmol) was added dropwise and the reaction mixture was stirred at -20 °C for 48 hours. The reaction mixture was quenched with an aqueous solution of $FeSO_4$/citric acid (16.5 g of $FeSO_4$ and 5.5 g of citric acid in 50 mL of H_2O). The solution was stirred vigorously for 30 minutes at room temperature then extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (DCM) to afford resolved alcohol **287** (1.25 g, 40%) as a colourless oil. ^{1}H-NMR analysis of the Mosher's ester indicated an 88% ee. $[\alpha]_D^{22}$ = +4.0 (*c* 1, $CHCl_3$) lit.[272] $[\alpha]_D^{20}$ = +4.1 (*c* 1, $CHCl_3$). Data consistent with alcohol **291** as previously reported.[272]

(*R*)-2-Methylpent-1-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (425)

287 **425**

Alcohol **287** (20 mg, 0.20 mmol) and (+)-MTPA (145 mg, 0.62 mmol) were dissolved in DCM (2 mL) under nitrogen, then DCC (128 mg, 0.62 mmol) and DMAP (76 mg, 0.62 mmol) were added sequentially and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was filtered, and the solvent removed *in vacuo*. ^{1}H-NMR analysis of the crude material indicated an 88% de.

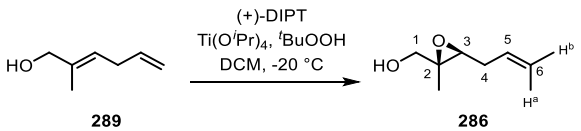
(*E*)-2-Methylhexa-2,5-dien-1-ol (289)



288 **289**

Epoxide **288** (2.33 mL, 23.78 mmol) was dissolved in THF (120 mL) under nitrogen and cooled to -30 °C then $CuBr.SMe_2$ (244 mg, 1.19 mmol) was added. A solution of 1 M Vinyl magnesium bromide in THF (40.00 mL, 40.00 mmol) was added dropwise over an hour and the reaction mixture was stirred for a further 2 hours at -30 °C. The reaction mixture was warmed to -20 °C and quenched with aqueous saturated NH_4Cl (30 mL) and brine (20 mL). The solution was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (35% Et_2O in petroleum ether 60:40) to afford alcohol **289** (2.39 g, 90%) as a colourless oil; ν_{max} (film) 3310, 3080, 2978, 2916, 1634, 993, 908; δ_H (400 MHz, $CDCl_3$) 1.43 – 1.52 (1H, m, OH), 1.67 (3H, br. s, 2-CH_3), 2.77 – 2.84 (2H, m, 4-H_2), 4.02 (2H, d, *J* 4.7, 1-H_2), 4.97 (1H, ap. dq, *J* 10.1, 1.7, 6-H^b), 5.03 (1H, ap. dq, *J* 17.0, 1.7, 6-H^a), 5.45 (1H, ap. ddq, *J* 7.3, 5.8, 1.4, 3-H), 5.80 (1H, ddt, *J* 17.0, 10.1, 6.3, 5-H); δ_C (101 MHz, $CDCl_3$) 13.8 (CH_3-2), 32.1 (C-4), 68.9 (C-1), 114.9 (C-6), 123.3 (C-3), 136.2 (C-2), 136.8 (C-5); HRMS (APCI) calc. for [$C_7H_{12}O$] 95.0855 Found 95.0857. Data consistent with the literature.[273]

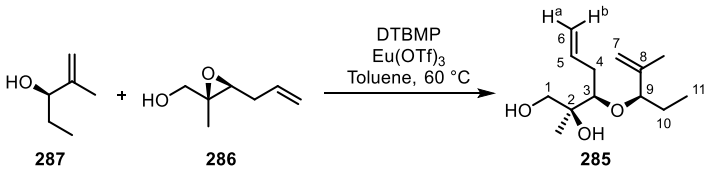
((2*S*,3*S*)-2-Methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (286)



289 **286**

(+)-DIPT (0.09 mL, 0.45 mmol) and 4 Å molecular sieves (250 mg) were dissolved in DCM (17 mL) under nitrogen and cooled to -20 °C, then Ti(^{i}OPr)$_4$ (0.11 mL, 0.36 mmol) and 5.5 M ^{t}BuOOH in decane (1.62 mL, 8.92 mmol) were added sequentially. The reaction mixture was stirred for 20 minutes, then allylic alcohol **289** (500 mg, 4.46 mmol) in DCM (5 mL) was added dropwise. The reaction mixture was stirred for 4 hours, then quenched with an aqueous solution of $FeSO_4$/citric acid (3.3 g of $FeSO_4$ and 1.1 g of citric acid in 10 mL of H_2O). The solution was stirred vigorously for 30 minutes at room temperature then extracted with DCM (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (50% Et_2O in petroleum ether 60:40) to afford epoxide **286** (410 mg, 72%) as a colourless oil; $[\alpha]_D^{23}$ = -20.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3420, 3081, 2978, 2930, 1642, 1429, 1035, 915; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, 2-CH_3), 1.84 (1H, dd, *J* 8.5, 4.5, OH), 2.28 (1H, dtt, *J* 15.0, 6.5, 1.5, 4-*H*H), 2.41 (1H, dtt, *J* 15.0, 6.5, 1.5, 4-H*H*), 3.13 (1H, ap. t, *J* 6.5, 3-H), 3.59 (1H, dd, *J* 12.2, 8.5, 1-*H*H), 3.69 (1H, dd, *J* 12.2, 4.5, 1-H*H*), 5.09 – 5.18 (2H, m, 6-H_2), 5.85 (1H, ddt, *J* 16.9, 10.3, 6.5, 5-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3-2), 32.9 (C-4), 58.9 (C-3), 61.0 (C-2), 65.4 (C-1), 117.4 (C-6), 133.5 (C-5); HRMS (ESI) calc. for [$C_7H_{12}NaO_2$] 151.0730 Found 151.0725.

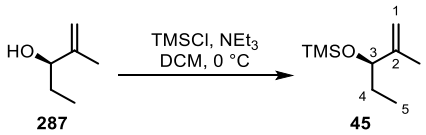
(2*S*,3*R*)-2-Methyl-3-(((*R*)-2-methylpent-1-en-3-yl)oxy)hex-5-ene-1,2-diol (285)



287 286 285

Alcohol **287** (68 mg, 0.68 mmol) and epoxide **286** (44 mg, 0.34 mmol) were dissolved in toluene (0.5 mL) under nitrogen, then DTBMP (14 mg, 0.07 mmol) and $Eu(OTf)_3$ (41 mg, 0.07 mmol) were added sequentially and the reaction mixture was stirred at 60 °C for 24 hours. The solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (60% Et_2O in petroleum ether 60:40) to afford diol **285** (7 mg, 9%) as a colourless oil; $[\alpha]_D^{26}$ = -8.0 (*c* 0.25, $CHCl_3$); ν_{max} (film) 3420, 3075, 2971, 2937, 2877, 1732, 1641, 1456, 1377, 1078; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.5, 11-H_3), 1.11 (3H, s, 2-CH_3), 1.47 – 1.55 (1H, m, 10-*H*H), 1.65 (3H, s, 8-CH_3), 1.66 – 1.71 (1H, m, 10-H*H*), 2.18 – 2.32 (1H, m, 4-*H*H), 2.30 – 2.40 (1H, m, 4-H*H*), 2.62 – 2.74 (1H, m, 1-OH), 2.85 (1H, s, 2-OH), 3.37 (1H, dd, *J* 11.2, 7.5, 1-*H*H), 3.50 (1H, t, *J* 5.8, 3-H), 3.71 – 3.85 (2H, m, 1-*H*H and 9-H), 4.79 – 4.95 (2H, m, 7-H_2), 5.01 (1H, ap. dq, *J* 10.2, 1.5, 6-H^a), 5.07 (1H, ap. dq, *J* 17.1, 1.5, 6-H^b), 5.85 (1H, ddt, *J* 17.1, 10.2, 7.0, 5-H); δ_C (101 MHz, $CDCl_3$) 10.0 (C-11), 17.0 (CH_3-8), 21.3 (CH_3-2), 25.8 (C-10), 36.3 (C-4), 68.0 (C-1), 75.0 (C-2), 84.3 (C-3), 87.5 (C-9), 114.5 (C-7), 116.8 (C-6), 135.9 (C-5), 144.3 (C-8); HRMS (ESI) calc. for [$C_{13}H_{24}NaO_3$] 251.1618 Found 251.1616.

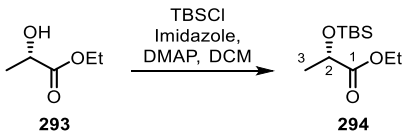
(*R*)-Trimethyl((2-methylpent-1-en-3-yl)oxy)silane (45)



287 **45**

Alcohol **287** (1.20 g, 11.98 mmol) was dissolved in DCM (60 mL) and cooled to 0 °C then NEt_3 (6.68 mL, 47.92 mmol) and TMSCl (3.04 mL, 23.96 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 30 minutes then quenched with water (30 mL). The organic layer was separated and the aqueous extracted with further DCM (40 mL). The combined organic layers were washed sequentially with ice cold 1 M HCl (25 mL) and aqueous saturated $NaHCO_3$ (25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (1% Et_2O in pentane) to afford to afford volatile silyl ether **45** (2.01 g, 97%) as a yellow oil; $[\alpha]_D^{22}$ = +14.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2960, 2928, 2873, 1250, 841; δ_H (400 MHz, $CDCl_3$) 0.09 (9H, s, $Si(CH_3)_3$), 0.84 (3H, t, *J* 7.4, 5-H_3), 1.50 (2H, qd, *J* 7.4, 6.5, 4-H), 1.67 (3H, dd, *J* 1.5, 0.9, 2-CH_3), 3.88 – 3.97 (1H, m, 3-H), 4.73 – 4.78 (1H, m, 1-*H*H), 4.80 – 4.88 (1H, m, 1-H*H*); δ_C (101 MHz, $CDCl_3$) 0.3 ($Si(CH_3)_3$) , 10.4 (C-5), 17.4 (C-4), 29.1 (CH_3-2), 78.3 (C-3), 110.8 (C-1), 147.8 (C-2); HRMS (ESI) calc. for $[C_9H_{20}OSi]$ 173.1356 Found 173.1352.

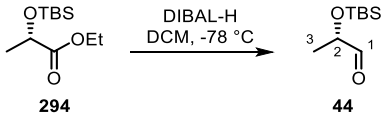
Ethyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (294)



293 **294**

To a solution of alcohol **293** (5.91 g, 50.00 mmol) in DCM (150 mL) was added imidazole (4.08 g, 68.08 mmol), TBSCl (8.29 g, 55 mmol) and a spatula tip of DMAP and the reaction mixture was stirred for 24 hours. The reaction was quenched with 2 M HCl (20 mL) and water (50 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 60 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford silyl alcohol **294** (11.64 g, quant.) as a colourless oil; $[\alpha]_D^{24}$ = -40.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2983, 2955, 2931, 2888, 2858, 1754, 1736, 1252, 1142, 829; δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, $Si(CH_3)$), 0.09 (3H, s, $Si(CH_3)$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.38 (3H, d, *J* 6.7, 3-H_3), 4.12 – 4.22 (2H, m, OCH_2CH_3), 4.30 (1H, q, *J* 6.7, 2-H); δ_C (101 MHz, $CDCl_3$) -5.1 ($SiCH_3$), -4.8 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.5 ($SiC(CH_3)_3$), 21.5 (C-3), 25.9 ($SiC(CH_3)_3$), 60.9 (OCH_2CH_3), 68.6 (C-2), 174.3 (C-1); HRMS (ESI) calc. for $[C_{11}H_{24}NaSiO_3]$ 255.1387 Found 255.1396. Data consistent with the literature.[274]

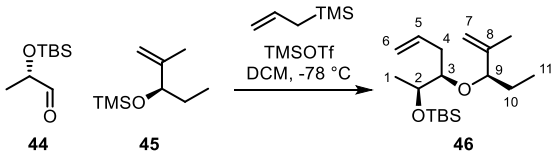
(*S*)-2-(*tert*-Butyldimethylsilyloxy)propanal (44)



294 **44**

Ester **294** (1.00 g, 4.30 mmol) was dissolved in DCM (15 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexanes (4.73 mL, 4.73 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 hour, then quenched with dropwise addition of MeOH (1 mL) followed by aqueous saturated sodium potassium tartrate solution (50 mL). The reaction mixture was warmed to room temperature and stirred vigorously for 1 hour. The organic layer was separated and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (5% Et_2O in petroleum ether 60:40) to afford aldehyde **44** (673 mg, 83%) as a colourless oil; $[\alpha]_D^{25}$ = -19.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2955, 2930, 2857, 2886, 1739, 1253, 832, 776; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.28 (3H, d, *J* 6.8, 3-H_3), 4.09 (1H, qd, *J* 6.8, 1.3, 2-H), 9.61 (1H, d, *J* 1.3, 1-H); δ_C (101 MHz, $CDCl_3$) -4.63 ($SiCH_3$), -4.57 ($SiCH_3$), 18.4 ($SiC(CH_3)_3$), 18.7 (C-3), 25.9 ($SiC(CH_3)_3$), 74.0 (C-2), 204.4 (C-1); HRMS (ESI) calc. for [$C_9H_{20}O_2Si$] 189.1305 Found 189.1304. Data consistent with the literature.[274]

***tert*-Butyldimethyl(((2*S*,3*R*)-3-(((*R*)-2-methylpent-1-en-3-yl)oxy)hex-5-en-2-yl)oxy)silane (46)**

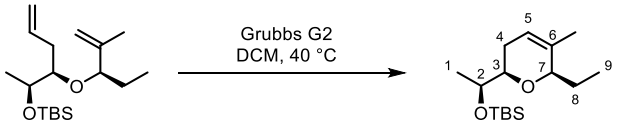


44 **45** **46**

Aldehyde **44** (188 mg, 1.00 mmol) and silyl ether **45** (184 mg, 1.07 mmol) were dissolved in DCM (2 mL, ethanol free) under nitrogen and cooled to -78 °C, then freshly distilled allyltrimethylsilane (0.18 mL, 1.1 mmol) followed by freshly distilled TMSOTf (0.02 mL, 0.1 mmol) were added sequentially. The reaction mixture was stirred at -78 °C for 48 hours. The reaction mixture was warmed to 0 °C over 2 hours, then quenched with DIPEA (0.04 mL, 0.2 mmol). The reaction mixture was warmed to room temperature and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (90% petroleum ether 60:40 in DCM) to afford ether **46** (63 mg, 20%) as a single diastereoisomer and as a colourless oil; $[\alpha]_D^{22}$ = +16.0 (*c* 2, $CHCl_3$) lit.[100] $[\alpha]_D^{20}$ = +10.6 (*c* 3.33, $CHCl_3$); ν_{max} (film) 2957, 1930, 2885, 2857, 1472, 1463, 1091, 833, 774; δ_H (400 MHz, $CDCl_3$) 0.03 – 0.06 (6H, m, $Si(CH_3)_2$), 0.87 – 0.90 (12H, m, 11-H and $SiC(CH_3)_3$), 1.14 (3H, d, *J* 6.3 Hz, 1-H), 1.42 – 1.55 (2H, m, 10-H_2), 1.63 – 1.65 (3H, m, 8-CH_3), 2.12 (1H, m, 4-*H*H), 2.22 (1H, m, 4-H*H*), 3.34 (1H, ap. td, *J* 6.3, 3.1, 3-H), 3.76 – 3.87 (1H, m, 2-H), 3.88 – 3.98 (1H, m, 9-H), 4.81 – 4.88 (1H, m, 7-*H*H), 4.85 – 4.92 (1H, m,

7-H*H*), 4.93 – 5.09 (2H, m, 6-H_2), 5.70 – 5.87 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) -4.6 ($SiCH_3$), -4.3 ($SiCH_3$), 10.4 (C-11), 16.7 (CH_3-8), 18.2 (Si*C*(CH_3)$_3$), 18.5 (C-1), 26.0 (SiC(*C*H_3)$_3$), 26.1 (C-10), 36.8 (C-4), 70.7 (C-2), 80.5 (C-9), 85.6 (C-3), 114.0 (C-7), 116.5 (C-6), 136.1 (C-5), 145.2 (C-8); HRMS (ESI) calc. for [$C_{18}H_{36}O_2SiNa$] 335.2377 Found 335.2384. Data consistent with the literature.[100]

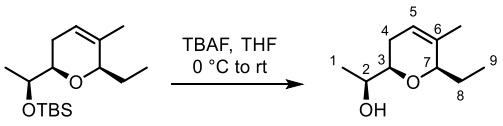
tert-Butyl((*S*)-1-((2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)ethoxy)dimethylsilane (295)



46 **295**

Ether **46** (50 mg, 0.16 mmol) was dissolved in DCM (4 mL) under nitrogen and heated at 40 °C, then Grubbs Catalyst G2 (3 mg, 0.01 mmol) in DCM (1 mL) was added. The reaction mixture was heated at 40 °C for 16 hours. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (1% Et_2O in petroleum ether 60:40) to afford pyran **295** (40 mg, 88%) as a colourless oil; $[\alpha]_D^{24}$ = +52.0 (*c* 1, $CHCl_3$) lit.[100] $[\alpha]_D^{20}$ = +34.8 (*c* 1.36, $CHCl_3$); ν_{max} (film) 2958, 2930, 2886, 2857, 1119, 1092, 832, 774; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.88 (9H, s, SiC(CH_3)$_3$), 0.91 (3H, t, *J* 7.3, 9-H_3), 1.18 (3H, d, *J* 6.1, 1-H_3), 1.37 – 1.53 (1H, m, 8-*H*H), 1.56 – 1.60 (3H, m, 6-CH_3), 1.68 – 1.80 (1H, m, 8-H*H*), 1.92 – 2.10 (2H, m, 4-H_2), 3.14 – 3.23 (1H, m, 3-H), 3.71 (1H, ap. p, *J* 6.1, 2-H), 3.91 – 4.00 (1H, m, 7-H), 5.52 – 5.57 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) -4.5 ($SiCH_3$), -4.2 ($SiCH_3$), 9.2 (C-9), 18.3 (Si*C*(CH_3)$_3$), 19.1 (CH_3-6), 21.1 (C-1), 25.97 (C-8), 26.04 (SiC(*C*H_3)$_3$), 27.5 (C-4), 71.4 (C-2), 78.3 (C-3), 78.7 (C-7), 121.0 (C-5), 135.5 (C-6). HRMS (ESI) calc. for [$C_{16}H_{32}O_2SiNa$] 307.2064 Found 307.2063. Data consistent with the literature.[100]

(*S*)-1-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)ethan-1-ol (296)

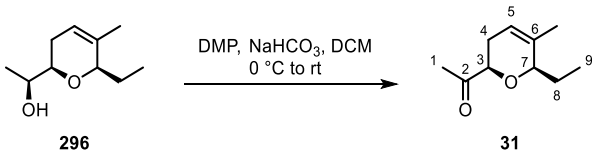


295 **296**

Silyl ether **295** (30 mg, 0.11 mmol) was dissolved in THF (1 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (0.21 mL, 0.21 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 5 hours and then quenched with water (10 mL) and Et_2O (10 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford alcohol **296** (12 mg, 67%) as a colourless oil; $[\alpha]_D^{24}$ = +6.0 (*c* 1, $CHCl_3$) lit.[100] $[\alpha]_D^{20}$ = +4.2 (*c* 1.04, $CHCl_3$); ν_{max} (film) 3405, 2966, 2935, 1454, 1265, 1116, 1057, 906, 729; δ_H (400 MHz, $CDCl_3$) 0.88

(3H, t, *J* 7.2, 9-H_3), 1.14 (3H, d, *J* 6.7, 1-H_3), 1.51 (1H, m, 8-*H*H), 1.57 – 1.61 (3H, m, 6-CH_3), 1.75 (1H, ap. dtd, *J* 14.3, 7.2, 3.0, 8-H*H*), 1.78 – 1.85 (1H, m, 4-*H*H), 2.09 – 2.19 (1H, m, 4-H*H*), 2.22 (1H, d, *J* 3.5, OH), 3.42 (1H, ap. dt, *J* 10.8, 3.5, 3-H), 3.91 (1H, ap. qt, *J* 6.7, 3.5, 2-H), 4.02 – 4.11 (1H, m, 7-H), 5.53 – 5.60 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 8.6 (C-9), 17.6 (C-1), 19.1 (CH_3-6), 24.4 (C-4), 25.8 (C-8), 69.3 (C-2), 76.2 (C-3), 78.3 (C-7), 120.6 (C-5), 135.2 (C-6); HRMS (ESI) calc. for [$C_{10}H_{18}O_2Na$] 193.1199 Found 193.1198. Data consistent with the literature.[100]

1-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)ethan-1-one (31)



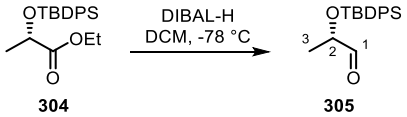
Alcohol **296** (1.20 g, 7.05 mmol) was dissolved in DCM (70 mL) under nitrogen and cooled to 0 °C, then $NaHCO_3$ (2.37 g, 28.20 mmol) and DMP (3.59 g, 8.46 mmol) were added sequentially. The reaction mixture was stirred for 2 hours at room temperature, filtered over Celite eluting with Et_2O (100 mL), and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (7% Et_2O in pentane) to afford the volatile ketone **31** (1.15 g, 97%) as a colourless oil; $[\alpha]_D^{20}$ = +166 (*c* 0.25, $CHCl_3$) lit.[100] $[\alpha]_D^{20}$ = +181 (*c* 0.257, $CHCl_3$); ν_{max} (film) 2966, 2936, 1720, 1353, 1115, 1057; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, 9-H_3), 1.44 – 1.58 (1H, m, 8-*H*H), 1.56 – 1.62 (3H, m, 6-CH_3), 1.81 (1H, dqd, *J* 14.8, 7.3, 3.5, 8-H*H*), 1.98 – 2.20 (2H, m, 4-H_2), 2.24 (3H, s, 1-H_3), 3.91 (1H, dd, *J* 10.5, 4.2, 3-H), 4.06 – 4.12 (1H, m, 7-H), 5.46 – 5.64 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 8.8 (C-9), 19.1 (CH_3-6), 25.8 (C-8), 25.9 (C-1), 27.5 (C-4), 78.5 (C-7), 78.9 (C-3), 119.7 (C-5), 135.8 (C-6), 210.2 (C-2); HRMS (ESI) calc. for [$C_{10}H_{16}O_2Na$] 191.1043 Found 191.1045. Data consistent with the literature.[100]

Ethyl (*S*)-2-(*tert*-butyldiphenylsiloxy)propanoate (304)

To a solution of alcohol **293** (2.36 g, 20.00 mmol) in DCM (70 mL) under nitrogen was added imidazole (1.63 g, 24 mmol), TBDPSCl (5.72 mL, 24 mmol) and a spatula tip of DMAP and the reaction mixture was stirred for 24 hours. The reaction was quenched with 2 M HCl (20 mL) and water (50 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 60 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford silyl alcohol **304** (7.42 g, quant.) as a colourless oil; $[\alpha]_D^{23}$ = -69.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3072, 2933, 2894, 2858, 1752, 1733, 1428, 1133, 1106; δ_H (400 MHz, $CDCl_3$) 1.10 (9H, s, $SiC(CH_3)_3$), 1.15 (3H, t, *J*

7.0, OCH_2CH_3), 1.37 (3H, d, *J* 6.8, 3-H_3), 4.02 (2H, q, *J* 7.0, OCH_2CH_3), 4.27 (1H, q, *J* 6.8, 2-H), 7.31 – 7.48 (6H, m, ArH), 7.62 – 7.73 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 14.2 (OCH_2CH_3), 19.4 ($SiC(CH_3)_3$), 21.4 (C-3), 27.0 ($SiC(CH_3)_3$), 66.0 (OCH_2CH_3), 69.1 (C-2), 127.7 (ArCH), 127.8 (ArCH), 129.9 (ArCH), 133.4 (ArC), 133.8 (ArC), 135.9 (ArCH), 136.1 (ArCH), 173.9 (C-1); HRMS (ESI) calc. for [$C_{21}H_{28}NaSiO_3$] 379.1700 Found 379.1689.

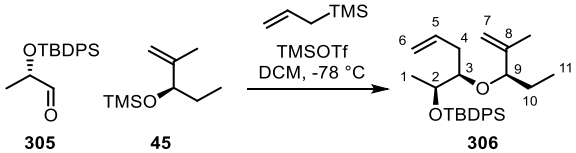
(*S*)-2-(*tert*-Butyldiphenylsiloxy)propanal (305)



304 **305**

Ester **304** (2.00 g, 5.60 mmol) was dissolved in DCM (20 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexanes (6.20 mL, 6.20 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 hour, then quenched with dropwise addition of MeOH (1 mL) followed by aqueous saturated sodium potassium tartrate solution (50 mL). The reaction mixture was warmed to room temperature and stirred vigorously for 1 hour. The organic layer was separated and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3% Et_2O in petroleum ether 60:40) to afford aldehyde **305** (1.45 g, 83%) as a colourless oil; $[\alpha]_D^{23}$ = -26.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3072, 2959, 2932, 2858, 1738, 1428, 1110, 699; δ_H (400 MHz, $CDCl_3$) 1.11 (9H, s, $SiC(CH_3)_3$), 1.22 (3H, d, *J* 6.8, 3-H_3), 4.09 (1H, qd, *J* 6.8, 1.2, 2-H), 7.34 – 7.47 (6H, m, ArH), 7.62 – 7.68 (4H, m, ArH), 9.64 (1H, d, *J* 1.2, C-1); δ_C (101 MHz, $CDCl_3$) 18.6 (C-3), 19.4 ($SiC(CH_3)_3$), 27.0 ($SiC(CH_3)_3$), 74.6 (C-2), 127.95 (ArCH), 128.03 (ArCH), 130.16 (ArCH), 130.23 (ArCH), 133.1 (ArC), 133.5 (ArC), 135.89 (ArCH), 135.92 (ArCH), 204.0 (C-1); HRMS (ESI) calc. for [$C_{19}H_{24}NaO_2Si$] 335.1438 Found 335.1436.

***tert*-Butyl(((2*S*,3*R*)-3-(((*R*)-2-methylpent-1-en-3-yl)oxy)hex-5-en-2-yl)oxy)diphenylsilane (306)**

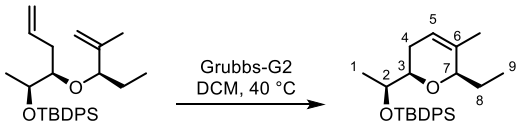


305 **45** **306**

Aldehyde **305** (10.34 g, 33.08 mmol) and silyl ether **45** (6.10 g, 35.40 mmol) were dissolved in DCM (65 mL, ethanol free) under nitrogen and cooled to -78 °C, then a precooled (-78 °C) mixture of freshly distilled allyltrimethylsilane (5.78 mL, 36.39 mmol) and freshly distilled TMSOTf (0.60 mL, 3.31 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at -78 °C for 5 hours. The reaction mixture was warmed to 0 °C over 1 hour, then quenched with freshly distilled DIPEA (1.15 mL, 6.62 mmol).

The reaction mixture was warmed to room temperature and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (75% petroleum ether 60:40 in DCM) to afford ether **306** (8.90 g, 62%) as a single diastereoisomer and as a colourless oil; $[\alpha]_D^{23}$ = +20.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3072, 2962, 2932, 2858, 1642, 1590, 1428, 1104,700; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.5, 11-H_3), 1.01 (3H, d, *J* 6.3, 1-H_3), 1.08 (9H, s, SiC(CH_3)$_3$), 1.45 – 1.56 (1H, m, 10-*H*H), 1.63 (3H, s, 8-CH_3), 1.65 – 1.74 (1H, m, 10-H*H*), 1.98 – 2.11 (1H, m, 4-*H*H), 2.16 – 2.27 (1H, m, 4-H*H*), 3.44 (1H, td, *J* 6.6, 2.3, 3-H), 3.88 (1H, qd, *J* 6.3, 2.3, 2-H), 3.97 (1H, dd, *J* 8.1, 6.1, 9-H), 4.76 – 4.78 (1H, m, 7-*H*H), 4.86 – 4.97 (3H, m, 6-H_2 and 7-H*H*), 5.56 – 5.69 (1H, m, 5-H), 7.31 – 7.47 (6H, m, ArH), 7.69 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 10.4 (C-11), 16.6 (CH_3-8), 18.0 (C-1), 19.4 (Si*C*(CH_3)$_3$), 26.3 (C-10), 27.2 (SiC(*C*H_3)$_3$), 36.8 (C-4), 71.7 (C-2), 80.2 (C-3), 85.4 (C-9), 114.2 (C-7), 116.4 (C-5), 127.6 (ArCH), 127.7 (ArCH), 129.7 (ArCH), 129.8 (ArCH), 134.1 (ArC), 134.8 (ArC), 136.0 (C-5), 136.2 (ArCH), 145.0 (C-8); HRMS (ESI) calc. for [$C_{28}H_{40}O_2SiNa$] 459.2690 Found 459.2703.

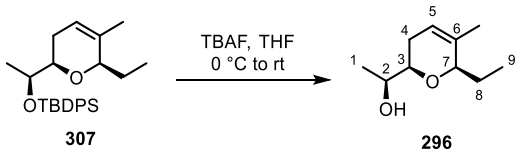
***tert*-Butyl((*S*)-1-((2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)ethoxy)diphenylsilane (307)**



306 307

Ether **306** (150 mg, 0.34 mmol) was dissolved in DCM (6 mL) under nitrogen and heated at 40 °C, then Grubbs Catalyst G2 (6 mg, 0.01 mmol) in DCM (1 mL) was added. The reaction mixture was heated at 40 °C for 16 hours. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (15% DCM in petroleum ether 60:40) to afford pyran **307** (135 mg, 97%) as a colourless oil; $[\alpha]_D^{21}$ = +23.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3071, 2962, 2931, 2856, 1427, 1111, 700; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3, 9-H_3), 1.03 (3H, d, *J* 6.3, 1-H_3), 1.05 (3H, s, 6-CH_3), 1.44 (1H, m, 8-*H*H), 1.52 – 1.66 (9H, m, SiC(CH_3)$_3$), 1.75 (1H, dqd, *J* 14.7, 7.3, 3.2, 8-H*H*), 1.94 – 2.06 (1H, m, 4-*H*H), 2.06 – 2.17 (1H, m, 4-H*H*), 3.31 (1H, ddd, *J* 10.3, 5.0, 3.4, 3-H), 3.87 (1H, dq, *J* 6.3, 5.0, 2-H), 3.92 – 4.02 (1H, m, 7-H), 5.50 – 5.59 (1H, m, 5-H), 7.31 – 7.44 (6H, m, ArH), 7.65 – 7.80 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 9.1 (OCH_2*C*H_3), 19.1 (CH_3-6), 19.6 (Si*C*(CH_3)$_3$), 20.3 (C-1), 26.0 (C-8), 27.0 (C-4), 27.2 (SiC(*C*H_3)$_3$), 72.3 (C-2), 78.2 (C-3), 78.7 (C-7), 120.9 (C-5), 127.6 (ArCH), 129.56 (ArCH), 129.61 (ArCH), 134.3 (ArC), 135.2 (ArC), 135.6 (C-6), 136.2 (ArCH), 136.3 (ArCH); HRMS (ESI) calc. for [$C_{26}H_{36}O_2SiNa$] 431.2377 Found 431.2378.

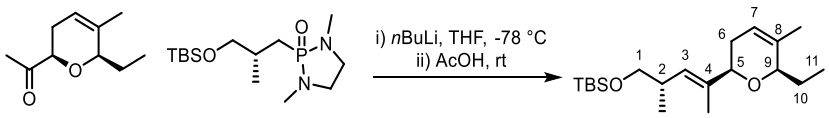
(*S*)-1-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)ethan-1-ol (296)



307 296

Silyl ether **307** (200 mg, 0.5 mmol) was cooled to 0 °C under nitrogen then 1 M TBAF in THF (1.0 mL, 1.0 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 24 hours and then quenched with water (10 mL) and Et_2O (10 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (25% Et_2O in petroleum ether 60:40) to afford alcohol **296** (83 mg, 98%) as a colourless oil. Data consistent with previously reported.

***tert*-Butyl((*S*, *E*)-4-((2*R*, 6*R*)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-2-methylpent-3-enyloxy)dimethylsilane (273)**

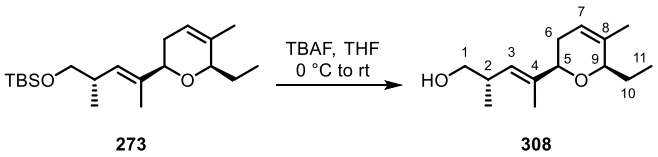


31 275 273

Phosphorus diamide **275** (3.98 g, 12.42 mmol) was dissolved in THF (38 mL) under nitrogen and cooled to -78 °C then 2.5 M *n*BuLi in hexane (4.29 mL, 10.74 mmol) was added dropwise and the reaction mixture was stirred for 2 hours. Neat ketone **31** (0.95 g, 5.65 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 1 hour. The reaction mixture was warmed to room temperature then quenched with AcOH (3.23 mL, 56.5 mmol) and stirred for an additional 20 minutes at room temperature. Aqueous saturated $NaHCO_3$ (50 mL) was added and the resulting solution was extracted with DCM (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3% Et_2O in petroleum ether 60:40) to afford alkene **273** (1.06 g, 55%, *E*/*Z* = 7:1) as a colourless oil and ketone **31** (209 mg, 22%); $[\alpha]_D^{20}$ = +38.0 (*c* 0.5, $CHCl_3$), lit.[234] $[\alpha]_D^{20}$ = +47.7 (*c* 1.37, $CHCl_3$); ν_{max} (film) 2957, 2929, 2857, 1463, 1255, 1090, 836; δ_H (400 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.89 (12H, m, $SiC(CH_3)_3$ and 11-H_3), 0.96 (3H, d, *J* 6.7, 2-CH_3), 1.47 – 1.57 (1H, m, 10-*H*H), 1.53 – 1.62 (3H, m, CH_3-8), 1.67 (3H, d, *J* 1.5, CH_3-4), 1.77 (1H, m, 10-H*H*), 1.83 – 1.90 (1H, m, 6-*H*H), 2.06 – 2.16 (1H, m, 6-H*H*), 2.50 – 2.63 (1H, m, 2-H), 3.35 (1H, dd, *J* 9.7, 7.4, 1-*H*H), 3.45 (1H, dd, *J* 9.7, 5.9, 1-H*H*), 3.83 (1H, dd, *J* 10.6, 3.0, 5-H), 4.03 – 4.15 (1H, m, 9-H), 5.21 (1H, dq, *J* 9.3, 1.5, 3-H), 5.52 – 5.58 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) -5.2 ($SiCH_3$), -5.1 ($SiCH_3$), 8.4 (C-11), 12.8 (CH_3-4), 17.4 (Si*C*$(CH_3)_3$), 18.5 (CH_3-8), 19.2 (CH_3-

2), 25.8 (C-10), 26.1 (SiC(*C*H$_3$)), 30.4 (C-6), 35.2 (C-2), 68.1 (C-1), 78.1 (C-5), 78.2 (C-9), 121.2 (C-7), 128.3 (C-3), 135.3 (C-8), 136.5 (C-4); HRMS (ESI) calc. for [$C_{20}H_{38}O_2SiNa$] 361.2533 Found 361.2549. Data consistent with the literature.[234]

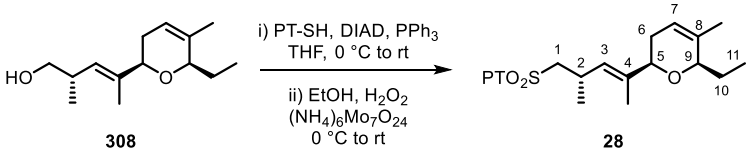
(*S*,*E*)-4-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-2-methylpent-3-en-1-ol (308)



273 **308**

Silyl ether **273** (998 mg, 2.95 mmol, *E*/*Z* = 7:1) was dissolved in THF (30 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (4.43 mL, 4.43 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 3 hours and then quenched with aqueous saturated NH_4Cl (50 mL) and the organic solvents removed *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 150 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (17% EtOAc in petroleum ether 60:40) to afford alcohol **308** (542 mg, 82%, *E*/*Z* > 95:5) as a colourless oil; $[\alpha]_D^{21}$ = +41.0 (*c* 1, $CHCl_3$) lit.[234] $[\alpha]_D^{20}$ = +57.1 (*c* 1.52, $CHCl_3$); ν_{max} (film) 3377, 2962, 2930, 2871, 1453, 1028, 733; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.5, 11-H$_3$), 0.96 (3H, d, *J* 6.5, 2-CH$_3$), 1.46 – 1.57 (1H, m, 10-*H*H), 1.59 (3H, dd, *J* 2.6, 1.3, 8-CH$_3$), 1.70 (3H, d, *J* 1.5, 4-CH$_3$), 1.73 – 1.84 (1H, m, 10-H*H*), 1.87 – 1.98 (1H, m, 6-*H*H), 2.05 – 2.21 (1H, m, 6-H*H*), 2.58 – 2.74 (1H, m, 2-H), 3.36 (1H, m, 1-*H*H), 3.47 (1H, m, 1-H*H*), 3.85 (1H, dd, *J* 10.7, 3.1, 5-H), 4.02 – 4.13 (1H, m, 9-H), 5.21 (1H, m, 3-H), 5.50 – 5.61 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) 8.5 (C-11), 13.3 (CH$_3$-4), 17.1 (CH$_3$-2), 19.1 (CH$_3$-8), 25.8 (C-10), 30.5 (C-6), 35.2 (C-2), 68.0 (C-1), 77.7 (C-5), 78.2 (C-9), 120.9 (C-7), 127.2 (C-3), 135.3 (C-8), 138.6 (C-4); HRMS (ESI) calc. for [$C_{14}H_{24}O_2Na$] 247.1669 Found 247.1679. Data consistent with the literature.[234]

5-(((*S*,*E*)-4-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-2-methylpent-3-en1-yl)sulfonyl)-1-phenyl-1H-tetrazole (28)



308 **28**

One-pot synthesis:

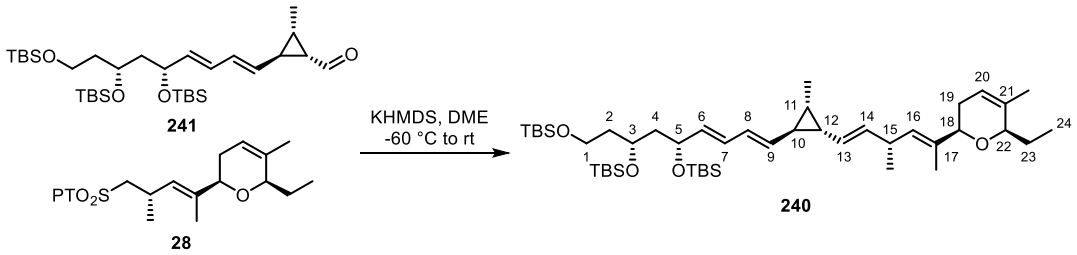
Alcohol **308** (23 mg, 0.11 mmol), PT-SH (23 mg, 0.13 mmol) and PPh_3 (34 mg, 0.12 mmol) were dissolved in THF (1.5 mL) under nitrogen and cooled the 0 °C then DIAD (0.03 mL, 0.13 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature then cooled to 0 °C and EtOH (4 mL) was added followed by a premixed solution of molybdate (27 mg, 0.02 mmol) in a

30% aqueous solution of H_2O_2 (0.11 mL, 1.1 mmol). The reaction mixture was stirred at room temperature for 16 hours. EtOAc (20 mL) and water (20 mL) were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed sequentially with water (20 mL) then brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% EtOAc in petroleum ether 60:40) to afford sulfone **28** (10 mg, 22%) as a colourless oil which contained small amounts of sulfoxide and epoxide impurities; $[\alpha]_D^{23}$ = +8.0 (*c* 1, $CHCl_3$) lit.[234] $[\alpha]_D^{20}$ = +12.6 (*c* 1.04, $CHCl_3$); ν_{max} (film) 2965, 2929, 1775, 1728, 1489, 1345, 1151, 761; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.4, 11-H_3), 1.17 (3H, d, *J* 6.7, 2-CH_3), 1.49 – 1.60 (4H, m, 8-CH_3 and 10-*H*H), 1.62 (3H, d, *J* 1.4, 4-CH_3), 1.72 – 1.98 (3H, m, 6-H_2 and 10-H*H*), 3.21 – 3.37 (1H, m, 2-H), 3.59 (1H, dd, *J* 14.6, 6.1, 1-*H*H), 3.67 – 3.73 (1H, m, 5-H), 3.77 (1H, dd, *J* 14.6, 7.6, 1-H*H*), 4.02 – 4.13 (1H, m, 9-H), 5.19 (1H, dt, *J* 9.8, 1.4, 3-H), 5.45 – 5.58 (1H, m, 7-H), 7.54 – 7.73 (5H, m, 5 × ArH); δ_C (101 MHz, $CDCl_3$) 8.4 (C-11), 13.1 (CH_3-4), 19.1 (CH_3-8), 21.0 (CH_3-2), 25.7 (C-10), 27.8 (C-2), 30.2 (C-6), 61.9 (C-1), 77.0 (C-5), 78.2 (C-9), 120.8 (C-7), 125.4 (C-3), 125.6 (ArCH), 129.8 (ArCH), 131.7 (ArCH), 133.3 (ArC), 135.3 (C-8), 138.5 (C-4), 154.2 (ArNCN); HRMS (ESI) calc. for [$C_{21}H_{28}N_4O_3SNa$] 439.1774 Found 439.1789. Data consistent with the literature.[234]

Two-pot synthesis:

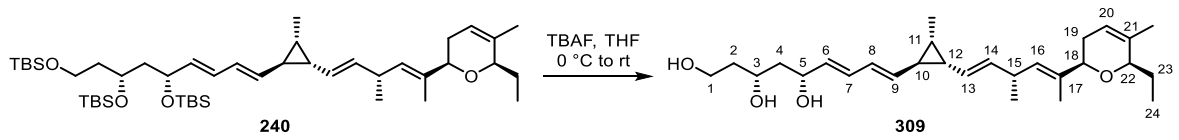
Alcohol **308** (270 mg, 1.20 mmol), PT-SH (278 mg, 1.56 mmol) and PPh_3 (409 mg, 1.56 mmol) were dissolved in THF (12 mL) under nitrogen and cooled the 0 °C then DIAD (0.31 mL, 1.56 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature then quenched with aqueous saturated $NHCl_4$ (20 mL). The resulting solution was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was filtered over a small plug of silica eluting with 20% EtOAc in petroleum ether 60:40 and the solvent removed *in vacuo*. The crude material was dissolved in EtOH (40 mL) and cooled to 0 °C then a premixed solution of molybdate (297 mg, 0.24 mmol) in a 30% aqueous solution of H_2O_2 (1.23 mL, 12.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 17 hours then quenched with water (50 mL) and brine (30 mL). The resulting solution was extracted with DCM (3 × 100 mL) and the combined organic layers dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford sulfone **28** (303 mg, 61%) as a colourless oil. Data consistent with previously reported.

(5*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-((1*E*,3*E*)-4-((1*S*,2*S*,3*S*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)buta-1,3-dien-1-yl)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane (240)



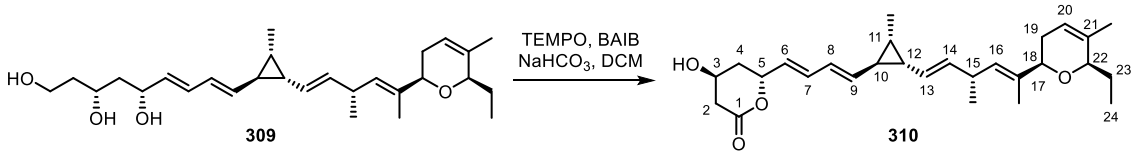
Sulfone **28** (76 mg, 0.18 mmol) was dissolved in DME (0.5 mL) under nitrogen and cooled to -60 °C then 1 M KHMDS in THF (0.2 mL, 0.2 mmol) was added dropwise. The reaction mixture was stirred for 15 minutes, then aldehyde **241** (85 mg, 0.14 mmol) in DME (0.5 mL) was added dropwise. The reaction mixture was stirred for 1 hour at -60 °C then 7 hours at room temperature. Water (10 mL) and Et_2O (10 mL) were added and the organic layer separated. The aqueous was further extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (1% Et_2O in petroleum ether 60:40) to afford alkene **240** (67 mg, 61%, *E*/*Z* > 95:5) as a yellow oil; $[\alpha]_D^{22}$ = +8.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3019, 2958, 2927, 1214, 1080, 746; δ_H (400 MHz, $CDCl_3$) -0.04 – 0.11 (18H, m, 6 × $SiCH_3$), 0.79 – 0.97 (30H, m, 24-H_3 and 3 × $SiC(CH_3)_3$), 1.05 (3H, d, *J* 7.0, 15-CH_3), 1.06 – 1.08 (3H, m, 11-CH_3), 1.09 – 1.14 (2H, m, 10-H and 11-H), 1.47 – 1.54 (3H, m, 4-*H*H, 12-H and 23-*H*H), 1.57 – 1.60 (3H, m, 21-CH_3), 1.62 – 1.67 (3H, m, 17-CH_3), 1.67 – 1.81 (4H, m, 2-H_2, 4-H*H* and 23-H*H*), 1.82 – 1.90 (1H, m, 19-*H*H), 2.07 – 2.16 (1H, m, 19-H*H*), 3.07 (1H, dqd, *J* 8.4, 7.0, 1.5, 15-H), 3.60 – 3.71 (2H, m, 1-H_2), 3.79 – 3.90 (2H, m, 3-H and 18-H), 4.05 – 4.14 (1H, m, 22-H), 4.19 (1H, ap. q, *J* 6.6, 5-H), 5.10 (1H, ddd, *J* 15.3, 8.9, 1.4, 13-H), 5.20 – 5.36 (2H, m, 9-H and 16-H), 5.42 – 5.52 (2H, m, 6-H and 14-H), 5.52 – 5.58 (1H, m, 20-H), 5.93 – 6.08 (2H, m, 7-H and 8-H); δ_C (101 MHz, $CDCl_3$) -5.11 ($SiCH_3$), -5.10 ($SiCH_3$), -4.5 ($SiCH_3$), -4.18 ($SiCH_3$), -4.16 ($SiCH_3$), -3.9 ($SiCH_3$), 8.4 (C-24), 12.5 (CH_3-17), 13.3 (CH_3-11), 18.2 (Si*C*$(CH_3)_3$), 18.4 (Si*C*$(CH_3)_3$), 18.5 (Si*C*$(CH_3)_3$), 19.2 (CH_3-21), 21.3 (CH_3-15), 22.1 (C-11), 25.8 (C-23), 26.10 (SiC(*C*$H_3)_3$), 26.11 (SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 29.7 (C-12), 30.3 (C-19), 31.3 (C-10), 34.4 (C-15), 40.4 (C-2), 46.8 (C-4), 60.1 (C-1), 66.9 (C-3), 71.0 (C-5), 78.1 (C-22), 78.2 (C-18), 121.1 (C-20), 125.6 (C-13), 127.5 (C-7/8), 129.7 (C-9/16), 129.9 (C-7/8), 133.7 (C-6/14), 135.31 (C-21), 135.54 (C-6/14), 135.95 (C-17), 137.0 (C-9/16); HRMS (ESI) calc. for [$C_{46}H_{86}O_4Si_3Na$] 809.5726 Found 809.5700.

(3*R*,5*R*,6*E*,8*E*)-9-((1*S*,2*S*,3*S*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)nona-6,8-diene-1,3,5-triol (309)



Silyl ether **240** (120 mg, 0.15 mmol) was dissolved in THF (1 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (1.35 mL, 1.35 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 hours. Aqueous saturated NH_4Cl (10 mL) was added and the resulting solution was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (100% EtOAc) to afford triol **309** (64 mg, 95%) as a yellow oil; $[\alpha]_D^{23}$ = +48.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3361, 2962, 2931, 1655, 1451, 1368, 1115, 1050, 987; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.05 (3H, d, *J* 6.5, 15-CH_3), 1.06 – 1.09 (4H, m, 11-H and 11-CH_3), 1.12 (1H, ap. dt, *J* 8.8, 4.0, 10-H), 1.46 – 1.57 (2H, m, 12-H and 23-*H*H), 1.57 – 1.61 (3H, m, 21-CH_3), 1.64 (4H, m, 4-*H*H and 17-CH_3), 1.67 – 1.81 (4H, m, 2-H_2, 4-H*H* and 23-H*H*), 1.82 – 1.90 (1H, m, 19-*H*H), 2.06 – 2.17 (1H, m, 19-H*H*), 2.67 (2H, s, 2 × OH), 3.07 (1H, ap. dq, *J* 8.5, 6.5, 15-H), 3.72 – 3.90 (3H, m, 1-H_2 and 18-H), 3.92 (1H, s, OH), 4.09 (1H, s, 22-H), 4.14 (1H, ap. tdt, *J* 6.9, 4.2, 2.2, 3-H), 4.40 (1H, ddd, *J* 9.9, 6.8, 3.1, 5-H), 5.09 (1H, dd, *J* 15.2, 8.8, 13-H), 5.25 (1H, dt, *J* 8.5, 1.4, 16-H), 5.33 (1H, dd, *J* 15.0, 8.8, 9-H), 5.48 (1H, dd, *J* 15.2, 6.5, 14-H), 5.52 – 5.58 (2H, m, 6-H and 20-H), 6.03 (1H, dd, *J* 15.0, 10.5, 8-H), 6.15 (1H, dd, *J* 15.1, 10.5, 7-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.5 (CH_3-17), 13.3 (CH_3-11), 19.2 (CH_3-21), 21.3 (CH_3-15), 22.2 (C-11), 25.8 (C-23), 29.8 (C-12), 30.4 (C-19), 31.2 (C-10), 35.2 (C-15), 38.9 (C-2), 43.5 (C-4), 61.7 (C-1), 72.7 (C-3), 73.8 (C-5), 78.06 (C-22), 78.12 (C-18), 121.1 (C-20), 125.4 (C-13), 126.9 (C-8), 129.7 (C-16), 130.9 (C-7), 132.0 (C-6), 135.30 (C-17/21), 135.31 (C-17/21), 135.7 (C-14), 138.7 (C-9); HRMS (ESI) calc. for [$C_{28}H_{44}O_4Na$] 467.3132 Found 467.3121.

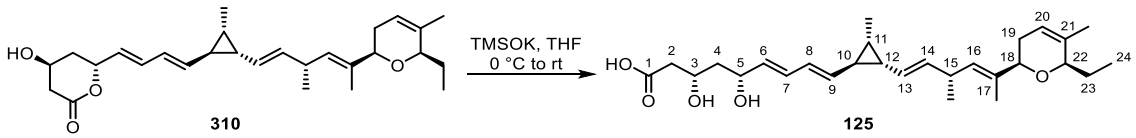
(4*S*,6*R*)-6-((1*E*,3*E*)-4-((1*S*,2*S*,3*S*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-Ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)buta-1,3-dien-1-yl)-4-hydroxytetrahydro-2H-pyran-2-one (310)



Triol **309** (50 mg, 0.11 mmol) was dissolved in DCM (1 mL) under nitrogen then BAIB (116 mg, 0.36 mmol), $NaHCO_3$ (37 mg, 0.44 mmol) and TEMPO (4 mg, 0.02 mmol) were added sequentially. The

reaction mixture was stirred at room temperature for 6 hours and then quenched with aqueous saturated $Na_2S_2O_3$ (2 mL) and water (10 mL). The solution was extracted with Et_2O (2 × 30 mL) and the combined organic layers washed sequentially with aqueous saturated $NaHCO_3$ (20 mL) and water (20 mL). The combined aqueous layers were extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (30 ml), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (60% EtOAc in petroleum ether 60:40) to afford lactone **310** (39 mg, 80%) as a yellow oil; $[\alpha]_D^{23}$ = +24.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3416, 2962, 2928, 1727, 1215, 908, 753, 731; δ_H (500 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.4, 24-H_3), 1.07 (3H, d, *J* 6.9, 15-CH_3), 1.09 – 1.12 (4H, m, 11-H and 11-CH_3), 1.13 – 1.18 (1H, m, 10-H), 1.51 – 1.59 (2H, m, 12-H and 23-*H*H), 1.61 (3H, d, *J* 1.3, 21-CH_3), 1.67 (3H, d, *J* 1.4, 17-CH_3), 1.76 – 1.82 (1H, m, 23-H*H*), 1.84 – 1.93 (2H, m, 4-*H*H and 19-*H*H), 1.99 – 2.05 (1H, m, 4-H*H*), 2.11 – 2.17 (1H, m, 19-H*H*), 2.63 (1H, dd, *J* 17.7, 4.0, 2-*H*H), 2.77 (1H, dd, *J* 17.7, 5.0, 2-H*H*), 3.06 – 3.14 (1H, m, 15-H), 3.86 (1H, dd, *J* 10.7, 3.1, 18-H), 4.08 – 4.15 (1H, m, 22-H), 4.37 – 4.43 (1H, m, 3-H), 5.12 (1H, dd, *J* 15.3, 8.8, 13-H), 5.18 – 5.24 (1H, m, 5-H), 5.28 (1H, dq, *J* 8.8, 1.4, 16-H), 5.40 (1H, dd, *J* 15.1, 8.9, 9-H), 5.51 (1H, dd, *J* 15.3, 6.2, 14-H), 5.54 – 5.60 (2H, m, 6-H and 20-H), 6.07 (1H, dd, *J* 15.1, 10.5, 8-H), 6.26 (1H, dd, *J* 15.2, 10.5, 7-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.5 (CH_3-17), 13.3 (CH_3-11), 19.1 (CH_3-21), 21.3 (CH_3-15), 22.3 (C-11), 25.8 (C-23), 30.0 (C-12), 30.3 (C-19), 31.3 (C-10), 35.2 (C-15), 36.6 (C-4), 38.9 (C-2), 62.9 (C-3), 76.2 (C-5), 78.05 (C-22), 78.12 (C-18), 121.1 (C-20), 125.2 (C-13), 126.4 (C-6), 126.5 (C-8), 129.6 (C-16), 133.1 (C-7), 135.3 (C-17/21), 135.3 (C-17/21), 135.8 (C-14), 140.0 (C-9), 170.1 (C-1); HRMS (ESI) calc. for [$C_{28}H_{40}O_4Na$] 463.2819 Found 463.2819.

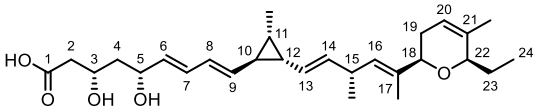
Ambruticin J (125)



Lactone **310** (7.7 mg, 0.02 mmol) was dissolved in THF (0.2 mL) under nitrogen and cooled to 0 °C then TMSOK (11.0 mg, 0.09 mmol) was added. The reaction mixture was stirred for 3 hours at room temperature then quenched with aqueous saturated NH_4Cl (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% MeOH in DCM + 0.25% AcOH). The combined column fractions containing product were washed with water (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to afford ambruticin J (8 mg, quant.) as a yellow oil; $[\alpha]_D^{25}$ = +52.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3383, 2962, 2926, 2875, 2857, 1714, 1049; δ_H (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* 7.4, 24-H_3), 1.05 (3H, d, *J* 6.8,

15-CH_3), 1.06 – 1.09 (4H, m, 11-H and 11-CH_3), 1.10 – 1.15 (1H, m, 10-H), 1.46 – 1.57 (2H, m, 12-H and 23-*H*H), 1.52 – 1.61 (3H, m, 21-CH_3), 1.63 – 1.68 (4H, m, 4-*H*H and 17-CH_3), 1.70 – 1.80 (2H, m, 4-H*H* and 23-H*H*), 1.81 – 1.88 (1H, m, 19-*H*H), 2.06 – 2.17 (1H, m, 19-H*H*), 2.47 – 2.57 (2H, m, 2-H_2), 3.00 – 3.13 (1H, m, 15-H), 3.84 (1H, dd, *J* 10.7, 3.1, 18-H), 4.03 – 4.12 (1H, m, 22-H), 4.25 – 4.34 (1H, m, 3-H), 4.38 – 4.45 (1H, m, 5-H), 5.09 (1H, ddd, *J* 15.1, 8.9, 1.4, 13-H), 5.25 (1H, d, *J* 8.9, 16-H), 5.34 (1H, dd, *J* 14.9, 8.8, 9-H), 5.45 – 5.58 (3H, m, 6-H, 14-H and 20-H), 6.03 (1H, dd, *J* 14.9, 10.5, 8-H), 6.16 (1H, dd, *J* 15.1, 10.5, 7-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.5 (CH_3-17), 13.3 (CH_3-11), 19.2 (CH_3-21), 21.3 (CH_3-15), 22.2 (C-11), 25.8 (C-23), 29.9 (C-12), 30.4 (C-19), 31.3 (C-10), 35.2 (C-15), 41.4 (C-2), 42.5 (C-4), 68.4 (C-3), 73.2 (C-5), 78.07 (C-22), 78.13 (C-18), 121.1 (C-20), 125.3 (C-13), 126.8 (C-8), 129.7 (C-16), 131.2 (C-6) , 131.4 (C-7), 135.30 (C-17/21), 135.31 (C-17/21), 135.8 (C-14), 139.0 (C-9), 175.1 (C-1); HRMS (ESI) calc. for [$C_{28}H_{42}O_5Na$] 481.2924 Found 481.2939.

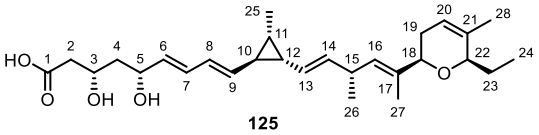
δ_H (500 MHz, (CD_3OD)) 0.88 (3H, t, *J* 7.3, 24-H_3), 1.04 (3H, d, *J* 7.1, 15-CH_3), 1.05 – 1.10 (4H, m, 11-H and 11-CH_3), 1.09 – 1.14 (1H, m, 10-H), 1.45 – 1.56 (2H, m, 12-H and 23-*H*H), 1.59 (3H, s, 21-CH_3), 1.64 (3H, d, *J* 1.5, 17-CH_3), 1.64 – 1.79 (3H, m, 4-H_2 and 23-H*H*), 1.81 – 1.91 (1H, m, 19-*H*H), 2.03 – 2.16 (1H, m, 19-H*H*), 2.40 (1H, dd, *J* 15.4, 8.0, 2-*H*H), 2.47 (1H, dd, *J* 15.4, 4.9, 2-H*H*), 3.04 – 3.14 (1H, m, 15-H), 3.79 – 3.85 (1H, m, 18-H), 4.03 – 4.13 (2H, m, 3-H and 22-H), 4.25 (1H, ap. q, *J* 7.1, 5-H), 5.16 (1H, dd, *J* 15.2, 8.8, 13-H), 5.25 (1H, d, *J* 8.9, 16-H), 5.32 (1H, dd, *J* 14.8, 8.9, 9-H), 5.42 – 5.52 (1H, m, 14-H), 5.53 – 5.62 (2H, m, 6-H and 20-H), 6.05 (1H, dd, *J* 14.8, 10.5, 8-H), 6.16 (1H, dd, *J* 15.2, 10.5, 7-H); δ_C (126 MHz, (CD_3OD)) 8.7 (C-24), 12.7 (CH_3-17), 13.4 (CH_3-11), 19.1 (CH_3-21), 21.6 (CH_3-15), 22.8 (C-11), 26.6 (C-23), 30.6 (C-12), 31.1 (C-19), 32.1 (C-10), 36.3 (C-15), 43.3 (C-2), 45.0 (C-4), 67.5 (C-3), 71.6 (C-5), 79.48 (C-22), 79.54 (C-18), 122.1 (C-20), 126.9 (C-13), 128.4 (C-8), 130.9 (C-16), 132.4 (C-7), 133.1 (C-6), 136.1 (C-21), 136.2 (C-17), 136.3 (C-14), 138.6 (C-9), 175.4 (C-1). ^1H and ^{13}C NMR spectra are consistent with those reported in the literature (see Tables **9** and **10**).[105,228]



125

Position	Our Synthetic Ambruticin J 500 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))	Taylor's Synthetic Ambruticin J 500 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))[228]
1-H	-	-
2-H_a	2.40 (dd, 15.4, 8.0)	2.38 (dd, 15.3, 8.0)
2-H_b	2.47 (dd, 15.4, 4.9)	2.42 (dd, 15.3, 4.5)
3-H	4.08	4.08
4-H_2	1.72 and 1.65	1.72 and 1.62
5-H	4.25 (ap. q, 7.2)	4.26 (ddd, 7.5, 6.5, 6.5)
6-H	5.53	5.50 (dd, 15.0, 7.5)
7-H	6.16 (dd, 15.2, 10.5)	6.17 (dd, 15.0, 10.5)
8-H	6.05 (dd, 14.8, 10.5)	6.06 (dd, 15.0, 10.5)
9-H	5.32 (dd, 14.8, 8.9)	5.33 (dd, 15.0, 9.0)
10-H	1.12	1.12
11-H	1.10	1.12
12-H	1.49	1.48
13-H	5.16 (dd, 15.2, 8.8)	5.16 (ddd, 15.0, 9.0, 1.0)
14-H	5.46	5.46 (dd, 15.0, 6.5)
15-H	3.09	3.10
16-H	5.25 (d, 8.9)	5.26 (dt, 9.0, 1.0)
18-H	3.82	3.83 (dd, 10.5, 2.5)
19-H_a	1.86	1.88
19-H_b	2.10	2.11
20-H	5.58	5.58 (dd, 5.5, 1.0)
22-H	4.08	4.08
23-H_a	1.52	1.53
23-H_b	1.73	1.75
24-H_3	0.88 (t, 7.3)	0.89 (t, 7.0)
25-H_3	1.06	1.07, (d, 1.0)
26-H_3	1.04 (d, 7.1)	1.04 (d, 6.5)
27-H_3	1.64 (d, 1.5)	1.65 (d, 1.5)
28-H_3	1.59 (s)	1.59 (d, 1)

Table 9. Comparison of ^{1}H-NMR of our synthetic ambruticin J with that reported by Taylor.[228]



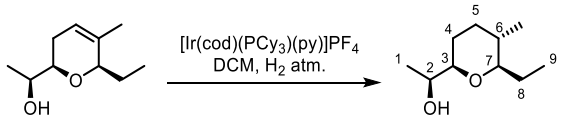
125

Position	Our Synthetic Ambruticin J 126 MHz (CD_3OD): δ_C	Taylor's Synthetic Ambruticin J 125 MHz (CD_3OD): δ_C[228]
C-1	175.4	177.1
C-2	43.3	44.0
C-3	67.5	67.9
C-4	45.0	44.9
C-5	71.6	71.7
C-6	133.1	133.2
C-7	132.4	132.3
C-8	128.4	128.4
C-9	138.6	138.5
C-10	32.1	32.0
C-11	22.8	22.8
C-12	30.6	30.5
C-13	126.9	126.9
C-14	136.3	136.3
C-15	36.3	36.3
C-16	130.9	130.9
C-17	136.2	136.2
C-18	79.54	79.5
C-19	31.1	31.1
C-20	122.1	122.1
C-21	136.1	136.0
C-22	79.48	79.5
C-23	26.6	26.6
C-24	8.7	8.7
C-25	13.4	13.3
C-26	21.6	21.6
C-27	12.7	12.7
C-28	19.1	19.0

Table 10. Comparison of ^{13}C-NMR of our synthetic ambruticin J and that report by Taylor.[228]

(*S*)-1-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethan-1-ol (324)

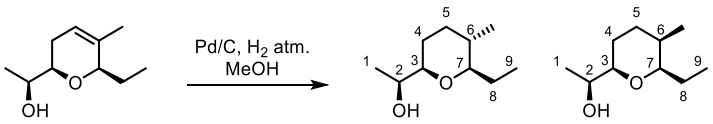
Method 1:



296 **324**

Alcohol **296** (85 mg, 0.5 mmol) was dissolved in degassed DCM (1 mL) under nitrogen at room temperature then Crabtree's catalyst (10 mg, 0.013 mmol) was added. Using a balloon, H_2 was bubbled through the reaction mixture for 2 minutes then the reaction mixture was stirred under H_2 at atmospheric pressure for 30 minutes. The solvent was removed *in vacuo* and the resulting material dissolved in Et_2O (5 mL), filtered over Celite and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford alcohol **324** (32 mg, 37%) as a single diastereoisomer and a colourless oil; $[\alpha]_D^{22}$ = +36.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3398, 2929, 2875, 1457, 1379, 1214, 747; δ_H (500 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.6, 6-CH_3), 0.92 (3H, t, *J* 7.5, 9-H_3), 1.13 (3H, d, *J* 6.5, 1-H_3), 1.14 – 1.19 (1H, m, 5-*H*H), 1.26 – 1.33 (1H, m, 6-H), 1.33 – 1.43 (2H, m, 4-*H*H and 8-*H*H), 1.55 (1H, ap. ddt, *J* 13.1, 5.1, 2.5, 4-H*H*), 1.68 (1H, dqd, *J* 14.9, 7.5, 2.7, 8-H*H*), 1.79 (1H, ap. dq, *J* 13.2, 3.6, 5-H*H*), 2.20 – 2.28 (1H, m, OH), 2.87 (1H, ddd, *J* 9.4, 8.2, 2.7, 7-H), 3.19 (1H, ddd, *J* 11.4, 4.0, 2.5, 3-H), 3.73 – 3.83 (m, 1H); δ_C (101 MHz, $CDCl_3$) 9.9 (C-9), 17.9 (CH_3-6), 18.0 (C-1), 25.6 (C-4), 26.1 (C-8), 32.7 (C-5), 35.0 (C-6), 69.8 (C-2), 80.7 (C-3), 84.7 (C-7); HRMS (ESI) calc. for [$C_{10}H_{20}O_2Na$] 195.1356 Found 195.1363.

Method 2:

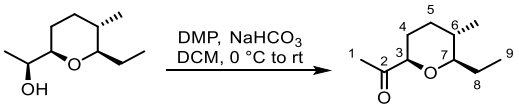


296 **324** **325**

Alcohol **296** (85 mg, 0.5 mmol) was dissolved in MeOH (5 mL) under nitrogen at room temperature then 10 wt.% Pd/C (50 mg, 0.05 mmol) was added. Using a balloon, H_2 was bubbled through the reaction mixture for 2 minutes then the reaction mixture was stirred under H_2 at atmospheric pressure for 1 hour. The reaction mixture was filtered over Celite, eluting with MeOH (30 mL), and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford an inseparable 2:1 mixture of alcohol **324** and alcohol **325** (60 mg, 70%) as a colourless oil. Data for **324** consistent with previously reported. Data for **325** not reported due to overlapping signals.

1-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethan-1-one (323)

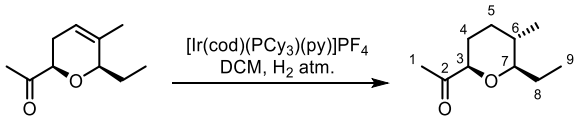
Method 1:



324 **323**

Alcohol **324** (88 mg, 0.51 mmol) was dissolved in DCM (5 mL) under nitrogen and cooled to 0 °C, then $NaHCO_3$ (171 mg, 2.04 mmol) and DMP (260 mg, 0.61 mmol) were added sequentially. The reaction mixture was stirred for 2 hours at room temperature, filtered over Celite eluting with Et_2O (100 mL) and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in pentane) to afford ketone **323** (83 mg, 96%) as a colourless oil; $[\alpha]_D^{22}$ = +172 (*c* 1, $CHCl_3$); ν_{max} (film) 2961, 2930, 2877, 1721, 1215, 1103, 746; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.5, 6-CH_3), 0.97 (3H, t, *J* 7.5, 9-H_3), 1.17 – 1.27 (1H, m, 5-*H*H), 1.30 – 1.49 (3H, m, 4-*H*H, 6-H and 8-*H*H), 1.73 (1H, dqd, *J* 14.0, 7.5, 2.8, 8-H*H*), 1.79 – 1.89 (2H, m, 4-H*H* and 5-H*H*), 2.20 (3H, s, 1-H_3), 2.89 (1H, ddd, *J* 9.5, 8.4, 2.8, 7-H), 3.70 (1H, dd, *J* 11.6, 2.5, 3-H); δ_C (101 MHz, $CDCl_3$) 9.9 (C-9), 17.8 (CH_3-6), 26.02 (C-8), 26.04 (C-1), 28.5 (C-4), 32.7 (C-5), 34.5 (C-6), 83.2 (C-3), 84.8 (C-7), 210.6 (C-2); HRMS (ESI) calc. for [$C_{10}H_{18}O_2Na$] 193.1199 Found 193.1199. Data consistent with the literature.[247]

Method 2:



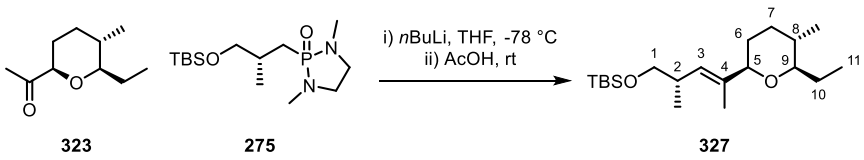
31 **323**

Ketone **31** (73 mg, 0.45 mmol) was dissolved in degassed DCM (2 mL) under nitrogen at room temperature then Crabtree's catalyst (17 mg, 0.02 mmol) was added. Using a balloon, H_2 was bubbled through the reaction mixture for 5 minutes then the reaction mixture was stirred under H_2 at atmospheric pressure for 3 hours. The solvent was removed *in vacuo* and the resulting material dissolved in Et_2O (5 mL), filtered over Celite eluting with Et_2O (10 mL) and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in pentane) to afford ketone **323** (65 mg, 89%) as a single diastereoisomer and a colourless oil; $[\alpha]_D^{22}$ = +172 (*c* 1, $CHCl_3$); ν_{max} (film) 2961, 2930, 2877, 1721, 1215, 1103, 746; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.5, 6-CH_3), 0.97 (3H, t, *J* 7.5, 9-H_3), 1.17 – 1.27 (1H, m, 5-*H*H), 1.30 – 1.49 (3H, m, 4-*H*H, 6-H and 8-*H*H), 1.73 (1H, dqd, *J* 14.0, 7.5, 2.8, 8-H*H*), 1.79 – 1.89 (2H, m, 4-H*H* and 5-H*H*), 2.20 (3H, s, 1-H_3), 2.89 (1H, ddd, *J* 9.5, 8.4, 2.8, 7-H), 3.70 (1H, dd, *J* 11.6, 2.5, 3-H); δ_C (101 MHz, $CDCl_3$) 9.9 (C-9), 17.8 (CH_3-6), 26.02 (C-8), 26.04 (C-1), 28.5 (C-4), 32.7 (C-5), 34.5 (C-6), 83.2 (C-3), 84.8 (C-7), 210.6 (C-2); HRMS (ESI) calc. for [$C_{10}H_{18}O_2Na$] 193.1199 Found 193.1199. Data consistent with previously reported.

Method 2 scale-up procedure:

Ketone **31** (1100 mg, 6.45 mmol) was dissolved in degassed DCM (26 mL) under nitrogen at room temperature. Using a balloon, H_2 was bubbled through the solution for 1 minute then Crabtree's catalyst (264 mg, 0.33 mmol) was added. Using a balloon, H_2 was bubbled through the reaction mixture for 20 minutes then the reaction mixture was stirred under H_2 at atmospheric pressure for 3 hours. The solvent was removed *in vacuo* and the resulting material dissolved in Et_2O (25 mL), filtered over Celite eluting with Et_2O (25 mL) and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in pentane) to afford ketone **323** (889 mg, 81%) as a single diastereoisomer and a colourless oil. Data consistent with previously reported.

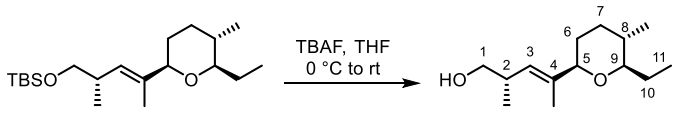
***tert*-Butyl(((*S*,*E*)-4-((2*R*,5*S*,6*R*)-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)-2-methylpent-3-en-1-yl)oxy)dimethylsilane (327)**



323 275 327

Phosphorus diamide **275** (3.15 g, 9.82 mmol) was dissolved in THF (30 mL) under nitrogen and cooled to -78 °C, then 2.5 M *n*BuLi in hexane (3.39 mL, 8.47 mmol) was added dropwise and the reaction mixture was stirred for 2 hours. Neat ketone **323** (0.76 g, 4.46 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 hour. The reaction mixture was warmed to room temperature and quenched with AcOH (2.55 mL, 44.6 mmol) then stirred for an additional 20 minutes at room temperature. Aqueous saturated $NaHCO_3$ (50 mL) was added and the resulting solution was extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3% Et_2O in petroleum ether 60:40) to afford alkene **327** (0.75 g, 49%, *E*/*Z* = 15:1) as a colourless oil and ketone **323** (212 mg, 28%); $[\alpha]_D^{24}$ = +22.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2956, 2929, 2856, 1215, 753; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.6, 8-CH_3), 0.88 (9H, s, $SiC(CH_3)_3$), 0.95 (3H, d, *J* 1.1, 2-CH_3), 0.95 – 0.98 (3H, m, 11-H_3), 1.17 – 1.25 (1H, m, 7-*H*H), 1.30 – 1.38 (1H, m, 8-H), 1.38 – 1.48 (2H, m, 6-*H*H and 10-*H*H), 1.56 – 1.72 (5H, m, 4-CH_3, 6-H*H* and 10-H*H*), 1.74 – 1.82 (1H, m, 7-H*H*), 2.51 – 2.60 (1H, m, 2-H), 2.90 (1H, ddd, *J* 9.5, 7.5, 3.0, 9-H), 3.26 – 3.36 (1H, m, 1-*H*H), 3.42 – 3.52 (1H, m, 1-H*H*), 3.54 – 3.62 (1H, m, 5-H), 5.14 – 5.18 (1H, m, 3-H); δ_C (101 MHz, $CDCl_3$) -6.16 ($SiCH_3$), -6.09 ($SiCH_3$), 8.6 (C-11), 12.6 (CH_3-4), 16.5 (CH_3-2), 17.0 (CH_3-8), 17.5 (Si*C*$(CH_3)_3$), 25.08 (C-10), 25.14 (SiC(*C*$H_3)_3$), 30.0 (C-6), 32.4 (C-7), 33.4 (C-8), 34.2 (C-2), 67.1 (C-1), 81.2 (C-5), 83.5 (C-9), 126.3 (C-3), 136.1 (C-4); HRMS (ESI) calc. for [$C_{20}H_{40}O_2SiNa$] 363.2701 Found 363.2690.

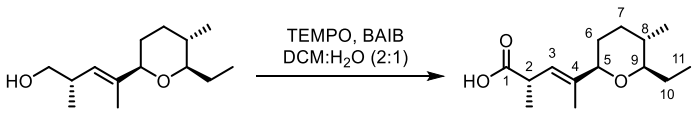
(*S*,*E*)-4-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)-2-methylpent-3-en-1-ol (328)



327 **328**

Silyl ether **327** (737 mg, 2.16 mmol, *E*/*Z* = 15:1) was dissolved in THF (20 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (3.25 mL, 3.25 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 3 hours and then quenched with aqueous saturated NH_4Cl (30 mL) and the organic solvent removed *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (35% Et_2O in petroleum ether 60:40) to afford alcohol **328** (391 mg, 80%, *E*/*Z* > 95:5) as a colourless oil; $[\alpha]_D^{23}$ = +20.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3403, 2956, 2928, 2873, 2850, 1457, 1380, 1084, 1031; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.5, 8-CH_3), 0.92 – 0.98 (6H, m, 2-CH_3 and 11-H_3), 1.15 – 1.26 (1H, m, 7-*H*H), 1.30 – 1.46 (3H, m, 6-*H*H, 8-H and 10-*H*H), 1.52 (1H, s, OH), 1.62 – 1.74 (5H, m, 4-CH_3, 6-H*H* and 10-H*H*), 1.80 (1H, ap. dq, *J* 13.0, 3.6, 7-H*H*), 2.60 – 2.70 (1H, m, 2-H), 2.90 (1H, ddd, *J* 9.5, 7.6, 3.0, 9-H), 3.36 (1H, dd, *J* 10.5, 7.8, 1-*H*H), 3.43 – 3.49 (1H, m, 1-H*H*), 3.61 (1H, m, 5-H), 5.13 – 5.20 (1H, m, 3-H); δ_C (126 MHz, $CDCl_3$) 9.7 (C-11), 13.9 (CH_3-4), 17.1 (CH_3-2), 17.9 (CH_3-8), 26.1 (C-10), 31.1 (C-6), 33.4 (C-7), 34.5 (C-8), 35.2 (C-2), 68.0 (C-1), 81.9 (C-5), 84.6 (C-9), 126.6 (C-3), 139.3 (C-4); HRMS (ESI) calc. for [$C_{14}H_{26}O_2Na$] 249.1825 Found 249.1820.

(*S*,*E*)-4-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)-2-methylpent-3-enoic acid (318)

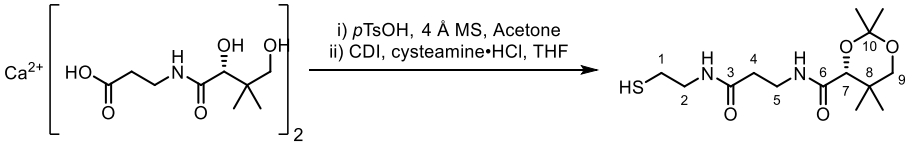


328 **318**

Alcohol **328** (56 mg, 0.25 mmol) was dissolved in DCM (2 mL) and water (1 mL) then TEMPO (20 mg, 0.13 mmol) and BAIB (199 mg, 0.62 mmol) were added, and the reaction mixture was stirred vigorously for 3 hours. Aqueous saturated $Na_2S_2O_3$ (5 mL) and DCM (5 mL) were added, and the reaction mixture was stirred vigorously for 10 minutes. The organic layer was separated and the aqueous extracted with further DCM (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (40% Et_2O in petroleum ether 60:40) to afford alcohol **318** (36 mg, 60%) as a yellow oil; $[\alpha]_D^{23}$ = +94.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3074 (broad), 2932, 2875, 2850, 1707, 1457; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.6, 8-CH_3), 0.95 (3H, t, *J* 7.4, 11-H_3), 1.15 – 1.22 (1H, m, 7-*H*H), 1.26 (3H, d, *J* 7.0, 2-CH_3), 1.30 – 1.46

(3H, m, 6-*H*H, 8-H and 10-*H*H), 1.62 – 1.73 (5H, m, 4-CH_3, 6-H*H* and 10-H*H*), 1.75 – 1.84 (1H, m, 7-H*H*), 2.91 (1H, ddd, *J* 10.1, 7.5, 2.9, 9-H), 3.38 (1H, dq, *J* 9.0, 7.0, 2-H), 3.53 – 3.73 (1H, m, 5-H), 5.45 (1H, d, *J* 9.0, 3-H); δ_C (126 MHz, $CDCl_3$) 9.6 (C-11), 13.4 (CH_3-4), 17.9 (CH_3-8), 18.0 (CH_3-2), 26.0 (C-10), 30.8 (C-6), 33.6 (C-7), 34.3 (C-8), 38.5 (C-2), 81.7 (C-5), 84.5 (C-9), 123.1 (C-3), 139.5 (C-4), 181.2 (C-1); HRMS (ESI) calc. for [$C_{14}H_{23}O_3$] 239.1647 Found 239.1655.

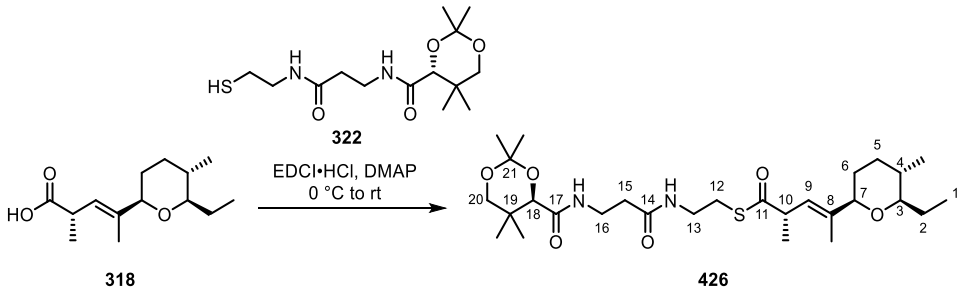
***O,O'*-Isopropylidene-D-pantetheine (322)**



To a suspension of calcium D-pantothenate **329** (5.00 g, 10.5 mmol) and 4 Å MS (5.00 g) in acetone (100 mL) under nitrogen was added *p*TsOH.H_2O (4.79 g, 25.2 mmol) and the reaction mixture was stirred for 20 hours. The reaction mixture was filtered, washed with EtOAc (100 mL) and the solvent removed *in vacuo*. The crude material was dissolved in EtOAc (50 mL), and hexane (25 mL) and the resulting solution decanted. The solvent was removed *in vacuo* to afford crude *O,O'*-isopropylidene D-pantothenic acid as a white solid.

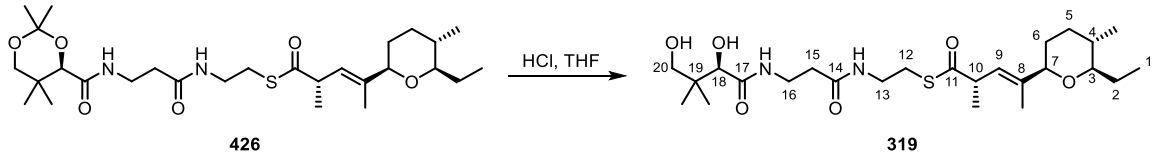
The crude material was dissolved in THF (100 mL) then CDI (5.11 g, 31.5 mmol) was added, and the reaction mixture was stirred for 1 hour under nitrogen. Cysteamine hydrochloride was added and the reaction mixture was stirred for a further 20 hours. The solvent was removed *in vacuo* then the crude material was dissolved in DCM (100 mL). The solution was washed with aqueous saturated NH_4Cl (2 × 100 mL), brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was recrystallised from EtOAc/hexane to afford thiol **322** (4.80 g, 72%) as a white crystalline solid; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, s, 8-CH_3), 1.04 (3H, s, 8-CH_3'), 1.36 (1H, t, *J* 8.5, SH), 1.42 (3H, s, 10-CH_3), 1.46 (3H, s, 10-CH_3'), 2.42 – 2.53 (2H, m, 4-H_2), 2.61 – 2.74 (2H, m, 1-H_2), 3.28 (1H, d, *J* 11.7, 9-*H*H), 3.34 – 3.64 (4H, m, 2-H_2 and 5-H_2), 3.68 (1H, d, *J* 11.7, 9-H*H*), 4.08 (1H, s, 7-H), 6.16 – 6.29 (1H, m, NH), 6.91 – 7.07 (1H, m, NH); δ_C (101 MHz, $CDCl_3$) 18.9 (CH_3-10), 19.1 (CH_3-8), 22.3 (CH_3'-8), 24.8 (C-1), 29.7 (CH_3'-10), 33.2 (C-8), 35.0 (C-5), 36.4 (C-4), 42.6 (C-2), 71.6 (C-9), 77.4 (C-7), 99.3 (C-10), 170.5 (C-3), 171.2 (C-6); m/z (ESI): $[M+H]^+$ = 319.17. Data consistent with the literature.[275]

_S_-(2-(3-((_R_)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carboxamido)propanamido)ethyl) (_S_,_E_)-4-((2_R_,5_S_,6_R_)-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)-2-methylpent-3-enethioate (426)



Carboxylic acid **318** (25 mg, 0.10 mmol) was dissolved in DCM (1 mL) under nitrogen and cooled to 0 °C then EDCI.HCl (29 mg, 0.15 mmol) was added, and the reaction mixture was stirred for 5 minutes. Thiol **322** (33 mg, 0.11 mmol) and DMAP (37 mg, 0.30 mmol) were added, and the reaction mixture was stirred at room temperature for 18 hours. Aqueous saturated NH_4Cl (10 mL) was added and the resulting solution was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (85% EtOAc in petroleum ether 60:40) to afford thioester **426** (45 mg, 82%) as a colourless oil; $[\alpha]_D^{22}$ = +90.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3429, 3313, 2933, 2873, 1660, 1526, 1098; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.6, 4-CH_3), 0.93 (3H, t, *J* 7.4, 1-H_3), 0.96 (3H, s, 19-CH_3), 1.03 (3H, s, 19-CH_3'), 1.15 – 1.22 (1H, m, 5-*H*H), 1.24 (3H, d, *J* 6.9, 10-CH_3), 1.30 – 1.43 (6H, m, 2-*H*H, 4-H, 6-*H*H and 21-CH_3), 1.45 (3H, s, 21-CH_3'), 1.62 – 1.72 (5H, m, 2-H*H*, 6-H*H* and 8-CH_3), 1.75 – 1.82 (1H, m, 5-H*H*), 2.30 – 2.44 (2H, m, 15-H_2), 2.87 – 2.93 (1H, m, 3-H), 2.93 – 2.98 (2H, m, 12-H_2), 3.27 (1H, d, *J* 11.7, 20-*H*H), 3.32 – 3.59 (5H, m, 10-H, 13-H_2 and 16-H_2), 3.61 – 3.70 (2H, m, 7-H and 20-H*H*), 4.06 (1H, s, 18-H), 5.34 – 5.44 (1H, m, 9-H), 6.05 – 6.15 (1H, m, NH), 6.97 – 7.06 (1H, m, NH); δ_C (126 MHz, $CDCl_3$) 9.4 (C-1), 13.3 (CH_3-8), 17.7 (CH_3-4), 18.1 (CH_3-10), 18.7 (CH_3-21), 18.9 (CH_3-19), 22.2 (CH_3'-19), 25.9 (C-2), 28.4 (C-12), 29.5 (CH_3'-21), 30.6 (C-6), 32.98 (C-5), 33.04 (C-19), 34.1 (C-4), 34.8 (C-16), 35.9 (C-15), 39.6 (C-13), 47.4 (C-10), 71.5 (C-20), 77.2 (C-18), 81.6 (C-7), 84.2 (C-3), 99.1 (C-21), 122.7 (C-9), 140.7 (C-8), 170.1 (C-17), 171.1 (C-14), 202.3 (C-11); HRMS (ESI) calc. for [$C_{28}H_{48}N_2O_6SNa$] 563.3125 Found 563.3111.

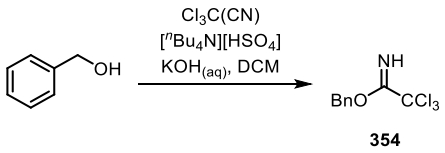
_S_-(2-(3-((_R_)-2,4-Dihydroxy-3,3-dimethylbutanamido)propanamido)ethyl) (_S_,_E_)-4-((2_R_,5_S_,6_R_)-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)-2-methylpent-3-enethioate (319)



Acetonide **426** (20.5 mg, 0.038 mmol) was dissolved in THF (4 mL) and 1 M HCl (2 mL) then stirred for 3 hours at room temperature. Aqueous saturated $NaHCO_3$ (10 mL) and EtOAc (20 mL) were added and

the organic layer was separated. The aqueous layer was extracted with EtOAc (4 × 20 mL) and the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (5% MeOH in EtOAc) to afford thioester **319** (18.6 mg, 98%) as a colourless oil; $[\alpha]_D^{22}$ = +62.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3315, 2971, 2932, 2874, 1649, 1532, 1214, 744; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.4, 4-CH_3), 0.91 (3H, s, 19-CH_3), 0.94 (3H, t *J* 7.5, 1-H_3), 1.01 (3H, s, 19-CH_3'), 1.15 – 1.27 (4H, m, 5-*H*H and 10-CH_3), 1.29 – 1.46 (3H, m, 2-*H*H, 4-H and 6-*H*H), 1.62 – 1.72 (5H, m, 2-H*H*, 6-H*H* and 8-CH_3), 1.76 – 1.82 (1H, m, 5-H*H*), 1.91 (1H, br. s, OH), 2.39 (2H, t, *J* 5.9, 15-H_2), 2.91 (1H, ddd, *J* 10.0, 7.6, 2.8, 3-H), 2.93 – 3.05 (2H, m, 12-H_2), 3.39 (2H, m, 13-H_2), 3.48 (2H, m, 20-H_2), 3.52 – 3.58 (3H, m, 10-H and 16-H_2), 3.64 (1H, m, 7-H), 3.99 (1H, d, *J* 5.0, 18-H), 4.07 (1H, d, *J* 5.0, OH), 5.39 (1H, d, *J* 9.5, 9-H), 6.30 (1H, t, *J* 5.7, NH), 7.39 (1H, t, *J* 6.0, NH); δ_C (126 MHz, $CDCl_3$) 9.6 (C-1), 13.7 (CH_3-8), 17.9 (CH_3-4), 18.3 (CH_3-10), 20.6 (CH_3-19), 21.8 (CH_3'-19), 26.0 (C-2), 28.4 (C-12), 30.7 (C-6), 33.2 (C-5), 34.4 (C-4), 35.3 (C-16), 35.8 (C-15), 39.5 (C-13), 39.8 (C-19), 47.6 (C-10), 71.1 (C-20), 77.8 (C-18), 81.7 (C-7), 84.6 (C-3), 122.7 (C-9), 140.8 (C-8), 171.8 (C-14), 173.7 (C-17), 203.0 (C-11); HRMS (ESI) calc. for [$C_{25}H_{44}N_2O_6SNa$] 523.2812 Found 523.2804.

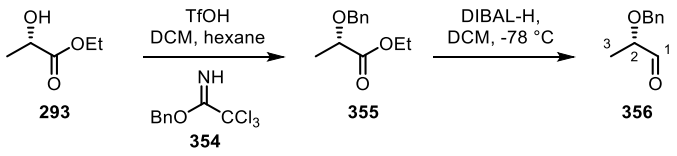
Benzyl 2,2,2-trichloroacetimidate (354)



354

Benzyl alcohol (0.96 mL, 9.25 mmol) was dissolved in DCM (10 mL) and cooled to -15 °C then tetrabutylammonium hydrogensulfate (15 mg, 0.04 mmol) and a 50% aqueous KOH solution (10 mL) were added. The reaction mixture was stirred for 5 minutes then trichloroacetonitrile (1.11 mL, 11.1 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes at -15 °C then 30 minutes at room temperature. The layers were separated, and the aqueous layer extracted with DCM (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford **354** (2.33 g, quant.) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 5.35 (2H, s, CH_2), 7.32 – 7.48 (5H, m, ArH), 8.40 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 70.9 (CH_2), 91.6 (CCl_3), 127.9 (ArC), 128.5 (ArC), 128.7 (ArC), 135.6 (ArC), 162.8 (CNH). Data consistent with the literature.[276]

(*S*)-2-(Benzyloxy)propanal (356)

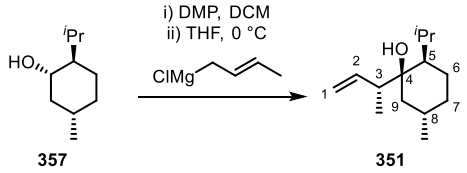


293 **354** **355** **356**

To a solution of alcohol **293** (0.70 mL, 6.15 mmol) in DCM (2 mL) and hexane (4 mL) under nitrogen was added **354** (2.33 g, 9.23 mmol) followed by dropwise addition of TfOH (0.016 mL, 0.18 mmol). The reaction mixture was stirred at room temperature for 18 hours and filtered, washing with hexane (10 mL). The filtrate was washed sequentially with water (20 mL) then aqueous saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford benzyl ether **355** (0.88 g, 69%) as a yellow oil which was used directly in the next step without purification.

Ester **355** (0.88 g, 4.23 mmol) was dissolved in DCM (20 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexanes (4.65 mL, 4.65 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 hour, then quenched by dropwise addition of MeOH (0.5 mL) followed by aqueous saturated sodium potassium tartrate solution (30 mL). The reaction mixture was warmed to room temperature and stirred vigorously for 1 hour. The organic layer was separated and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford aldehyde **356** (500 mg, 72%) as a colourless oil; $[\alpha]_D^{23}$ = -48.0 (*c* 1, $CHCl_3$), lit.[Ref] $[\alpha]_D^{23}$ = -52.6 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, 3-H_3), 3.90 (1H, qd, *J* 6.9, 1.8, 2-H), 4.61 (1H, d, *J* 11.7, C*H*H), 4.66 (1H, d, *J* 11.7, CH*H*), 7.31 – 7.39 (5H, m, ArH), 9.68 (1H, d, *J* 1.8, 1-H); δ_C (101 MHz, $CDCl_3$) 15.5 (C-3), 72.2 (C-2), 79.6 (CH_2), 128.1 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 137.5 (ArC), 203.7 (C-1). Data consistent with the literature.[274]

(1*S*,2*R*,5*S*)-1-((*R*)-But-3-en-2-yl)-2-isopropyl-5-methylcyclohexan-1-ol (351)

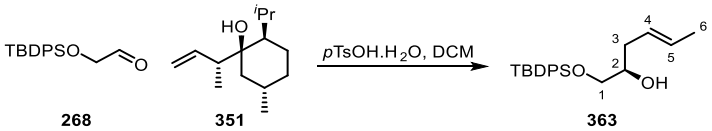


357 351

(+)-Menthol (3.13 g, 20.0 mmol) was dissolved in DCM (100 mL) under nitrogen then DMP (11.88 g, 28.0 mmol) was added. The reaction mixture was stirred at room temperature for 4 hours then aqueous saturated $NaHCO_3$ (50 mL) and aqueous saturated $Na_2S_2O_3$ (50 mL) were added and the reaction mixture was stirred vigorously for 30 minutes. The resulting solution was diluted with Et_2O (250 mL) and the layers were separated. The aqueous layer was extracted with further Et_2O (2 × 200 mL) and the combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to give (+)-menthone (3.05 g, 99%) as a yellow oil which was used in the next step without further purification. Freshly distilled crotyl chloride (3.31 mL, 34.0 mmol) in THF (35 mL) was added dropwise to magnesium turnings (0.83 g, 34.0 mmol) in THF (70 mL) under nitrogen at room temperature. (Note: the addition of a few crystals of iodine and gentle heating were required to

initiate the reaction). When bubbling stopped, the solution was cooled to 0 °C and a solution of (+)-menthone (3.09 g, 20.0 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours then quenched with aqueous saturated NH_4Cl (100 mL) and water (50 mL). The resulting solution was filtered, extracted with EtOAc (2 × 200 mL) and the combined organic layers washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (2% EtOAc in petroleum ether 60:40) to afford homoallylic alcohol **351** (2.97 g, 71%, dr > 95:5) as a colourless oil; $[\alpha]_D^{24}$ = -24.0 (*c* 1, $CHCl_3$) lit.[250] $[\alpha]_D^{25}$ = -25.2 (*c* 1, $CHCl_3$); ν_{max} (film) 3574, 2950, 2920, 2970, 2844, 1634, 1456, 1378, 1007; δ_H (400 MHz, $CDCl_3$) 0.76-1.01 (2H, m), 0.85 (3H, d, *J* 6.4, 8-CH_3), 0.90 (3H, d, *J* 2.2, 3-CH_3), 0.92 (3H, d, *J* 2.1, ^{i}Pr-Me), 0.96 (3H, d, *J* 7.0, ^{i}Pr-Me'), 1.25 (1H, m), 1.30 – 1.41 (2H, m), 1.46 – 1.54 (2H, m), 1.64 – 1.79 (2H, m), 2.08 (1H, ap. pd, *J* 7.0, 1.9, ^{i}Pr-H), 2.59 (1H, ap. p, *J* 7.2, 3-H), 5.08 – 5.16 (2H, m, 1-H_2), 5.87 (1H, ddd, *J* 16.7, 10.6, 8.3, 2-H); δ_C (101 MHz, $CDCl_3$) 14.8, 18.2, 20.8, 22.8, 23.6, 25.2, 27.7, 35.4, 41.7, 45.4, 46.1, 76.4, 116.9, 141.0; m/z (APCI): $[M-H]^+$ = 209.2. Data consistent with the literature.[250]

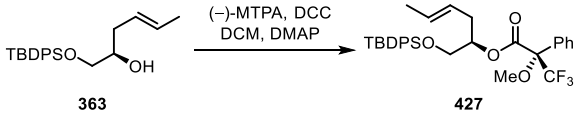
(*R*,*E*)-1-(*tert*-Butyldiphenylsiloxy)hex-4-en-2-ol (363)



268 351 363

Aldehyde **268** (1.00 g, 3.36 mmol) and (*S*)-Nokami reagent **351** (1.41 g, 6.72 mmol) were dissolved in DCM (34 mL) under nitrogen, then *p*TsOH.H_2O (64 mg, 0.34 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours. Triethylamine (0.18 mL) was added followed by aqueous saturated $NaHCO_3$ (30 mL) and the reaction mixture was stirred vigorously for 15 minutes. The layers were separated, and the aqueous phase extracted with DCM (2 × 50 mL). The combined organic layers were wash with aqueous saturated $NaHCO_3$, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (15% Et_2O in petroleum ether 60:40) to afford homoallylic alcohol **363** (0.77 g, 65%, *E*/*Z* > 95:5) as a yellow oil. ^{1}H-NMR analysis of the Mosher's ester indicated a > 99% ee; $[\alpha]_D^{24}$ = +4.0 (*c* 1, $CHCl_3$) lit. enantiomer[277] $[\alpha]_D^{25}$ = -1.2 (*c* 8.1, $CHCl_3$); ν_{max} (film) 3439, 3019, 2931, 2858, 1428, 1214, 1113, 741, 702; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, SiC(CH_3)$_3$), 1.64 (3H, dq, *J* 6.3, 1.3, 6-H_3), 2.13 – 2.20 (2H, m, 3-H_2), 2.43 (1H, d, *J* 4.0, OH), 3.55 (1H, dd, *J* 10.1, 6.8, 1-*H*H), 3.66 (1H, dd, *J* 10.1, 3.8, 1-H*H*), 3.70 – 3.76 (1H, m, 2-H), 5.34 – 5.43 (1H, m, 4-H), 5.44 – 5.54 (1H, m, 5-H), 7.37 – 7.45 (6H, m, ArH), 7.64 – 7.69 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 18.2 (C-6), 19.4 (Si*C*(CH_3)$_3$), 27.0 (SiC(*C*H_3)$_3$), 36.5 (C-3), 67.5 (C-2), 71.8 (C-1), 126.8 (C-4), 127.9 (ArCH), 128.4 (C-5), 130.0 (ArCH), 133.4 (ArC), 135.0 (ArC), 135.7 (ArCH); HRMS (ESI) calc. for [$C_{22}H_{30}O_2SiNa$] 377.1913 Found 377.1907. Data consistent with the literature.[277]

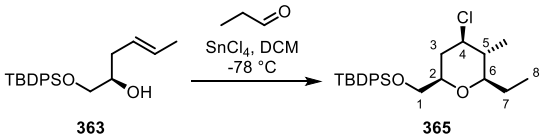
(*R*,*E*)-1-(*tert*-Butyldiphenylsiloxy)hex-4-en-2-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (427)



363 427

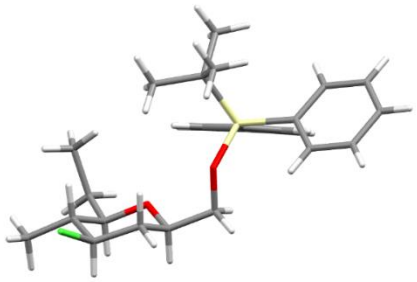
Alcohol **363** (18 mg, 0.05 mmol) and (−)-MTPA (23 mg, 0.10 mmol) were dissolved in DCM (1 mL) under nitrogen, then DCC (31 mg, 0.15 mmol) and DMAP (12 mg, 0.10 mmol) were added sequentially and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was filtered, and the solvent removed *in vacuo*. ^{1}H-NMR analysis of the crude material indicated a > 99% de.

***tert*-Butyl(((2*R*,4*R*,5*R*,6*R*)-4-chloro-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)methoxy)diphenylsilane (365)**



363 365

Homoallylic alcohol **363** (100 mg, 0.28 mmol) and propionaldehyde (0.061 mL, 0.85 mmol) were dissolved in DCM (1.5 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 0.56 mL, 0.56 mmol) was added dropwise. The reaction mixture was stirred for 4 hours then quenched with aqueous saturated $NaHCO_3$ (2 mL) and warmed to room temperature. The resultant solution was diluted with DCM (15 mL) and water (15 mL) and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 15 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (15% DCM in petroleum ether 60:40) to afford tetrahydropyran **365** (81 mg, 67%) as a single diastereoisomer and as a white solid; $[\alpha]_D^{22}$ = +8.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2961, 2931, 2857, 1472, 1428, 1116; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.4, 8-H_3), 1.01 – 1.12 (12H, m, SiC(CH_3)$_3$ and 5-CH_3), 1.47 (1H, m, 7-*H*H), 1.52 – 1.62 (1H, m, 5-H), 1.66 – 1.80 (2H, m, 3-H_{ax} and 7-H*H*), 2.27 (1H, ddt, *J* 12.8, 5.0, 1.5, 3-H_{eq}), 2.96 (1H, ddd, *J* 10.2, 8.0, 2.6, 6-H), 3.48 (1H, dtt, *J* 8.5, 5.0, 1.5, 2-H), 3.60 (1H, ddd, *J* 10.4, 5.0, 1.5, 1-*H*H), 3.67 – 3.78 (1H, m, 1H*H* and 4-H), 7.35 – 7.46 (6H, m, ArH), 7.70 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 9.7 (CH_3-5), 14.7 (C-8), 19.5 (Si*C*(CH_3)$_3$), 26.3 (C-7), 27.0 (SiC(*C*H_3)$_3$), 39.9 (C-3), 44.2 (C-5), 64.7 (C-4), 66.9 (C-1), 77.2 (C-2), 83.1 (C-6), 127.9 (2 × ArCH), 129.9 (2 × ArCH), 133.81 (ArC), 133.83 (ArC), 135.87 (ArCH), 135.91 (ArCH); HRMS (MALDI) calc. for [$C_{25}H_{35}O_2SiClNa$] 453.1987 Found 453.1996.



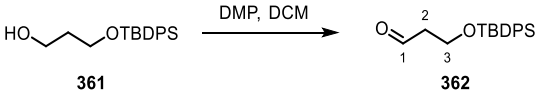
Crystal obtained by recrystallisation from MeOH/Et_2O/hexane. Space group: $P2_1$ (monoclinic).

3-(*tert*-Butyldiphenylsiloxy)propan-1-ol (361)

360 **361**

To a solution of 1,3-propanediol (6.50 mL, 90.0 mmol) in DCM (60 mL) under nitrogen was added imidazole (3.06 g, 45.0 mmol) and a spatula tip of DMAP. TBDPSCl (7.80 mL, 30.0 mmol) was added dropwise and the reaction mixture was stirred for 24 hours. Water (50 mL) was added and the solution was acidified with 2 M HCl (10 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc in petroleum ether 60:40) to afford alcohol **361** (4.94 g, 52%) as a white solid; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, $SiC(CH_3)_3$), 1.81 (2H, ap. p, *J* 5.7, 2-H_2), 2.36 (1H, t, *J* 5.4, OH), 3.82 – 3.88 (4H, m, 1-H_2 and 3-H_2), 7.37 – 7.46 (6H, m, ArH), 7.65 – 7.72 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 19.3 ($SiC(CH_3)_3$), 27.0 ($SiC(CH_3)_3$), 34.4 (C-2), 62.2 (C-1/3), 63.5 (C-1/3), 128.0 (ArCH), 130.0 (ArCH), 33.4 (ArC), 135.7 (ArCH); m/z (ESI): $[M+H]^+$ = 315.18. Data consistent with the literature.[278]

3-(*tert*-Butyldiphenylsilyloxy)propan-1-al (362)

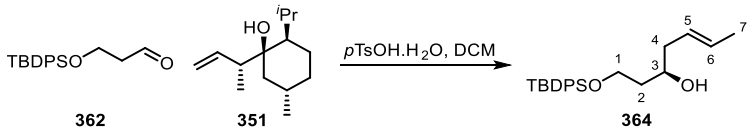


361 **362**

Alcohol **361** (4.50 g, 14.32 mmol) was dissolved in DCM (140 mL) under nitrogen then DMP (7.29 g, 17.19 mmol) was added and the reaction mixture was stirred for 1 hour. Aqueous saturated $NaHCO_3$ (50 mL) was added and the organic phase separated. The aqueous phase was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL) dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford aldehyde **362** (3.56 g, 80%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, $SiC(CH_3)_3$), 2.61 (2H, td, *J* 6.0, 2.2, 2-H_2), 4.03 (2H, t, *J* 6.0, 3-H_2), 7.28 – 7.57 (6H, m, ArH), 7.61 – 7.74 (4H, m, ArH), 9.83 (1H, t, *J* 2.2, 1-H); δ_C (101 MHz, $CDCl_3$) 19.3 ($SiC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$),

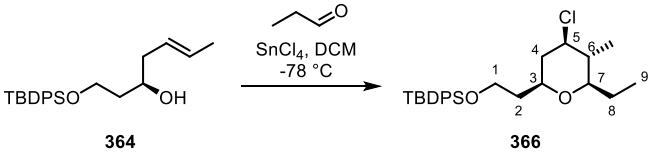
46.6 (C-2), 58.5 (C-3), 128.0 (ArCH), 130.0 (ArCH), 133.4 (ArC), 135.7 (ArCH), 202.1 (C-1); m/z (ESI): $[M+Na]^+$ = 335.10. Data consistent with the literature.[278]

(*R*,*E*)-1-(*tert*-Butyldiphenylsiloxy)hept-5-en-3-ol (364)



Aldehyde **362** (679 mg, 2.17 mmol) and (*S*)-Nokami reagent **351** (914 mg, 4.34 mmol) were dissolved in DCM (22 mL) under nitrogen, then *p*TsOH.H_2O (41 mg, 0.22 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours. Triethylamine (0.10 mL) was added followed by aqueous saturated $NaHCO_3$ (20 mL) and the reaction mixture was stirred vigorously for 15 minutes. The layers were separated, and the aqueous phase extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (15% Et_2O in petroleum ether 60:40) to afford homoallylic alcohol **364** (536 mg, 67%, *E*/*Z* > 95:5) as a yellow oil. ^{1}H-NMR analysis of the Mosher's ester indicated a > 99% ee; $[\alpha]_D^{22}$ = +4.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3459, 3019, 2932, 2858, 1428, 1215, 1111; δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, $SiC(CH_3)_3$), 1.63 – 1.79 (5H, m, 2-H_2 and 7-H_3), 2.16 – 2.23 (2H, m, 4-H_2), 3.78 – 3.93 (3H, m, 1-H_2 and 3-H), 5.41 – 5.59 (2H, m, 5-H and 6-H), 7.36 – 7.46 (6H, m, ArH), 7.65 – 7.71 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 18.3 (C-7), 19.2 ($SiC(CH_3)_3$), 27.0 ($SiC(CH_3)_3$), 38.0 (C-2), 40.9 (C-4), 63.5 (C-1), 71.4 (C-3), 127.5 (C-5), 128.0 (2 × ArCH), 128.3 (C-6), 130.0 (2 × ArCH), 133.2 (ArC), 133.3 (ArC), 135.7 (ArCH), 135.8 (ArCH); HRMS (ESI) calc. for $[C_{23}H_{32}O_2Si]$ 369.2244 Found 369.2243.

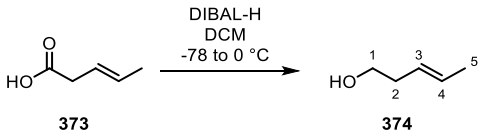
***tert*-Butyl(2-((2*S*,4*R*,5*R*,6*R*)-4-chloro-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethoxy)diphenylsilane (366)**



Homoallylic alcohol **364** (475 mg, 1.29 mmol) and propionaldehyde (0.28 mL, 3.87 mmol) were dissolved in DCM (17 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 2.58 mL, 2.58 mmol) was added dropwise. The reaction mixture was stirred for 6 hours then quenched with aqueous saturated $NaHCO_3$ (10 mL) and warmed to room temperature. The resultant solution was diluted with DCM (30 mL) and water (20 mL) and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 40 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$

and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% DCM in petroleum ether 60:40) to afford tetrahydropyran **366** (457 mg, 80%) as a single diastereoisomer and a colourless oil; $[\alpha]_D^{21}$ = +8.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3019, 2931, 2857, 1215; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, ap. t, *J* 7.4, 9-H_3), 0.99 – 1.10 (12H, m, $SiC(CH_3)_3$ and 6-CH_3), 1.35 – 1.47 (1H, m, 8-*H*H), 1.48 – 1.55 (1H, m, 6-H), 1.61 – 1.82 (4H, m, 2-H_2, 4-H_{ax} and 8-H*H*), 2.15 (1H, ddd, *J* 12.8, 4.5, 2.0, 4-H_{eq}), 2.89 (1H, ddd, *J* 9.5, 8.3, 2.7, 7-H), 3.56 (1H, dddd, *J* 11.3, 8.0, 4.5, 2.0, 3-H), 3.64 – 3.76 (2H, m, 1-*H*H and 5-H), 3.85 (1H, ddd, *J* 10.2, 8.2, 5.2, 1-H*H*), 7.35 – 7.47 (6H, m, 6 × ArCH), 7.57 – 7.72 (4H, m, 4 × ArCH); δ_C (101 MHz, $CDCl_3$) 9.9 (C-9), 14.7 (CH_3-6), 19.4 ($SiC(CH_3)_3$), 26.4 (C-8), 27.1 ($SiC(CH_3)_3$), 38.9 (C-2), 43.5 (C-4), 44.5 (C-6), 60.2 (C-1), 64.7 (C-5), 73.1 (C-3), 83.0 (C-7), 127.81 (ArCH), 127.82 (ArCH), 129.76 (ArCH), 129.78 (ArCH), 134.1 (2 × ArC), 135.71 (ArCH), 135.72 (ArCH); HRMS (ESI) calc. for $[C_{11}H_{19}O_{35}Cl]$ 445.2324 Found 445.2321.

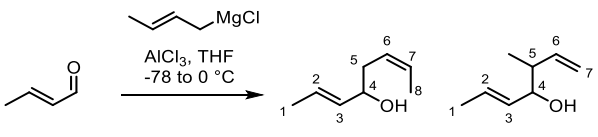
(*E*)-Pent-3-en-1-ol (374)



373 **374**

Carboxylic acid **373** (1.50 mL, 14.8 mmol) was dissolved in DCM (60 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexane (60 mL, 60 mmol) was added dropwise over 20 minutes. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was cooled to 0 °C, quenched with aqueous saturated sodium potassium tartrate solution (150 mL) and stirred vigorously for 16 hours. The organic layer was separated and the aqueous layer extracted with further DCM (2 × 150 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (35% Et_2O in petroleum ether 60:40) to afford the volatile aldehyde **374** (822 mg, 64%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.56 (1H, t, *J* 5.8, OH), 1.68 (3H, ap. dq, *J* 6.4, 1.4, 5-H_3), 2.21 – 2.28 (2H, m, 2-H_2), 3.61 (2H, ap. q, *J* 5.8, 1-H_2), 5.39 (1H, dtq, *J* 15.3, 6.9, 1.4, 3-H), 5.56 (1H, dqt, *J* 15.3, 6.4, 1.3, 4-H); δ_C (101 MHz, $CDCl_3$) 18.2 (C-5), 36.1 (C-2), 62.2 (C-1), 127.3 (C-3), 128.7 (C-4); HRMS (APCI) calc. for $[C_5H_{10}O]$ 87.0804 Found 87.0803. Data consistent with the literature.[279]

(2*E*,6*Z*)-Octa-2,6-dien-4-ol (371)



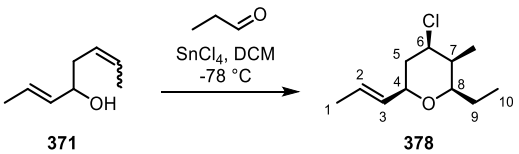
148 **371** **428**

Freshly distilled crotyl chloride (1.46 mL, 15.00 mmol) was added dropwise to magnesium turnings (364 mg, 15.00 mmol) in THF (15 mL) under nitrogen at room temperature. (Note: the addition of a few crystals of iodine and gentle heating were required to initiate the reaction). When bubbling had stopped, the solution was cooled to -78 °C then a precooled (0 °C) solution of $AlCl_3$ (2000 mg, 15.00 mmol) in THF (7.5 mL) was added dropwise and the reaction mixture was stirred for 10 minutes. Crotonaldehyde (0.414 mL, 5.00 mmol) was added dropwise and the reaction mixture was warmed to 0 °C over 30 minutes. The reaction mixture was quenched with aqueous saturated NH_4Cl (30 mL) and warmed to room temperature. The resulting solution was extracted with EtOAc (3 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford volatile alcohol **371** (containing 12% of the *E,E*-isomer, 186 mg, 29%) as a colourless oil, and alcohol **428** as an inseparable mixture of diastereoisomers (95 mg, 15%) as a colourless oil.

371 (data reported for the major *E*,*Z*-isomer only): ν_{max} (film) 3355, 3019, 2964, 2918, 2858, 1440, 1030, 964; δ_H (700 MHz, $CDCl_3$) 1.63 (3H, ddt, *J* 6.8, 1.8, 0.8, 8-H_3), 1.69 (3H, ddd, *J* 6.5, 1.7, 0.8, 1-H_3), 2.22 – 2.27 (1H, m, 5-*H*H), 2.32 (1H, ddddd, *J* 14.3, 7.9, 6.8, 1.5, 0.8, 5-H*H*), 4.08 (1H, ap. q, *J* 6.8, 4-H), 5.38 – 5.43 (1H, m, 6-H), 5.51 (1H, ddq, *J* 15.3, 6.8, 1.7, 3-H), 5.62 (1H, dqt, *J* 10.9, 6.8, 1.5, 7-H), 5.67 (1H, dqd, *J* 15.3, 6.5, 1.1, 2-H); δ_C (101 MHz, $CDCl_3$) 13.2 (C-8), 17.9 (C-1), 35.2 (C-5), 72.6 (C-4), 125.8 (C-6), 127.0 (C-2/7), 127.4 (C-2/7), 133.7 (C-3); HRMS (APCI) calc. for [C_8H_{13}] 109.1012 Found 109.1012.

428: ν_{max} (film) 3386, 2966, 2935, 2919, 2879, 965; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.8, 5-CH_3 minor), 1.01 (3H, d, *J* 6.9, 5-CH_3 major), 1.51 – 1.61 (1H, m, OH major), 1.62 – 1.66 (1H, m, OH minor), 1.67 – 1.74 (6H, m, 1-H_3 major and minor), 2.16 – 2.28 (1H, m, 5-H minor), 2.29 – 2.40 (1H, m, 5-H major), 3.78 (1H, ap. t, *J* 7.4, 4-H minor), 3.95 (1H, ap. t, *J* 6.2, 4-H major), 5.04 – 5.16 (4H, m, 7-H_2 major and minor), 5.40 – 5.51 (2H, m, 3-H major and minor), 5.60 – 5.84 (4H, m, 2-H and 6-H major and minor); δ_C (101 MHz, $CDCl_3$) 15.0 (CH_3-5 major), 16.3 (CH_3-5 minor), 17.9 (C-1 major and minor), 43.8 (C-5 major), 44.8 (C-5 minor), 76.1 (C-4 major), 76.4 (C-4 minor), 115.8 (C-7 major), 116.6 (C-7 minor), 128.1 (C-2/6 major), 128.7 (C-2/6 minor), 131.6 (C-3 major), 132.0 (C-3 minor), 140.3 (C-2/6 major), 140.8 (C-2/6 minor); HRMS (APCI) calc. for [C_8H_{13}] 109.1012 Found 109.1012.

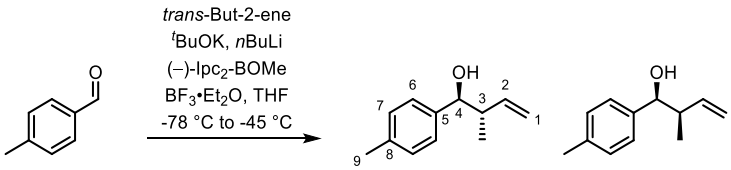
(±)-(2*R*,3*S*,4*R*,6*R*)-4-Chloro-2-ethyl-3-methyl-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran (378)



371 378

Homoallylic alcohol **371** (25 mg, 0.20 mmol, *E*/*Z* = 12:18) and propionaldehyde (0.043 mL, 0.60 mmol) were dissolved in DCM (1 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 0.4 mL, 0.4 mmol) was added dropwise. The reaction mixture was stirred for 15 minutes then quenched with aqueous saturated $NaHCO_3$ (1 mL) and warmed to room temperature. The resultant solution was diluted with DCM (10 mL) and water (10 mL) and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 10 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% DCM in petroleum ether 60:40) to afford tetrahydropyran **378** (32 mg, 79%) as a colourless oil which contained 12% of the C-7 epimer; ν_{max} (film) 2954, 2937, 2879, 2839, 1678, 1454, 1090; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, ap. t, *J* 7.5, 10-H_3), 0.98 (3H, d, *J* 6.9, 7-CH_3), 1.34 – 1.49 (1H, m, 9-*H*H), 1.58 – 1.66 (1H, m, 9-H*H*), 1.68 (3H, dd, *J* 6.6, 1.8, 1-H_3), 1.73 – 1.89 (2H, m, 5-H_2), 1.91 – 2.02 (1H, m, 7-H), 3.26 (1H, ap. td, *J* 6.9, 1.9, 8-H), 3.77 (1H, ddd, *J* 10.2, 6.5, 2.9, 4-H), 4.24 (1H, ap. dt, *J* 12.0, 4.7, 6-H), 5.48 (1H, ddd, *J* 15.4, 6.5, 1.8, 3-H), 5.64 – 5.75 (1H, m, 2-H); δ_C (101 MHz, $CDCl_3$) 6.0 (CH_3-7), 10.4 (C-10), 18.0 (C-1), 26.2 (C-9), 37.1 (C-5), 38.2 (C-7), 62.0 (C-6), 78.1 (C-4), 81.4 (C-8), 128.2 (C-2), 131.0 (C-3); HRMS (ESI) calc. for [$C_{11}H_{19}OCl$] 202.1119 Found 202.1114.

(1*S*,2*S*)-2-Methyl-1-(*p*-tolyl)but-3-en-1-ol (379)

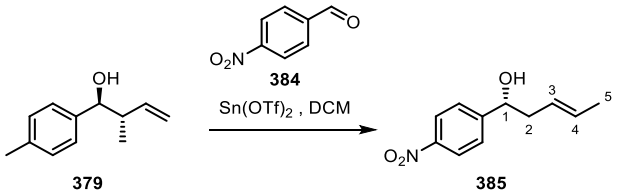


383 **379** **429**

A 1 M solution of *t*BuOK in THF (10.67 mL, 10.67 mmol) was dissolved in THF (20 mL) and cooled to -78 °C then condensed *trans*-but-2-ene (2.20 mL, 24.60 mmol) was added *via* cannula. A solution of 2.5 M *n*BuLi in hexane (4.27 mL, 10.67 mmol) was added dropwise over 15 minutes and the reaction mixture was stirred for 10 minutes at -45 °C then cooled to -78 °C. A 1 M solution of (−)-Ipc_2BOMe in Et_2O (13.12 mL, 13.12 mmol) was added dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 30 minutes then $BF_3.Et_2O$ (1.82 mL, 14.76 mmol) was added dropwise over 5 minutes followed by a solution of aldehyde **383** (0.98 mL, 8.2 mmol) in THF (13 mL) over 15 minutes. The reaction mixture was stirred for 4 hours, quenched with 3 M NaOH (6 mL) and 30% H_2O_2 (3 mL), then stirred at room temperature for 16 hours. The resulting solution was diluted with Et_2O (100 mL) and water (100 mL). The organic layer was separated and the aqueous extracted with further Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (15% DCM in petroleum ether 60:40) to afford an inseparable mixture of alcohols **379** and **429** (1165 mg, 81%,

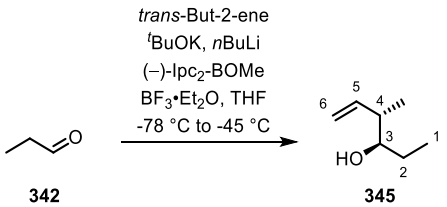
379:**429** = 84:16) as a colourless oil. ^{1}H-NMR analysis of the Mosher's ester indicated a 78% ee for **379**; $[\alpha]_D^{22}$ = -70.0 (*c* 1, $CHCl_3$); lit.[253] $[\alpha]_D^{25}$ = -72.46 (*c* 1.86, $CHCl_3$); ν_{max} (film) 3433, 3019, 2976, 1638, 1515, 1456, 1218; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 7.0, 3-CH_3), 2.12 (1H, d, *J* 2.5, OH), 2.35 (3H, s, 9-H_3), 2.47 (1H, ap. h, *J* 7.3, 3-H), 4.32 (1H, dd, *J* 8.0, 2.5, 4-H), 5.14 – 5.26 (2H, m, 1-H_2), 5.76 – 5.88 (1H, m, 2-H), 7.12 – 7.27 (4H, m, 4 × ArH); δ_C (101 MHz, $CDCl_3$) 16.8 (CH_3-3), 21.4 (C-9), 46.5 (C-3), 78.0 (C-4), 116.9 (C-1), 127.0 (ArCH), 129.2 (ArCH), 137.5 (ArC), 139.7 (ArC), 141.1 (C-2); m/z (APCI): $[M+H-H_2O]^+$ = 159.1. Data consistent with the literature.[253]

(*R*,*E*)-1-(4-Nitrophenyl)pent-3-en-1-ol (385)



Allylic alcohol **379** (50 mg, 0.28 mmol, 84:16 *threo*:*erythro*, 78% ee) and aldehyde **834** (129 mg, 0.85 mmol) were dissolved in DCM (4 mL) under nitrogen then $Sn(OTf)_2$ (4 mg, 0.01 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc (30 mL) and washed with aqueous saturated $NaHCO_3$ (2 × 20 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford allylic alcohol **385** (34 mg, 59%, *E*/*Z* = 93:7) as a colourless oil; ^{1}H-NMR analysis of the Mosher's ester indicated an 80% ee; $[\alpha]_D^{21}$ = +56.0 (*c* 0.5, $CHCl_3$); lit.[253] $[\alpha]_D^{23}$ = +61.5 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3444, 3020, 2925, 1730, 1521, 1347, 1214; δ_H (400 MHz, $CDCl_3$) 1.70 (3H, dd, *J* 6.4, 1.5, 5-H_3), 2.09 – 2.28 (1H, m, OH), 2.35 (1H, ap. dtt, *J* 14.0, 8.0, 1.0, 2-*H*H), 2.44 – 2.53 (1H, m, 2-H*H*), 4.79 (1H, dd, *J* 8.0, 4.4, 1-H), 5.39 (1H, dddq, *J* 15.5, 8.0, 6.3, 1.5, 3-H), 5.62 (1H, ap. dqt, *J* 15.5, 6.4, 1.0, 4-H), 7.42 – 7.57 (2H, m, ArH), 8.15 – 8.26 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 18.3 (C-5), 43.1 (C-2), 72.5 (C-1), 123.8 (ArCH), 125.7 (C-3), 126.7 (ArCH), 131.1(C-4), 147.4 (ArC), 151.5 (ArC); HRMS (ESI) calc. for $[C_{11}H_{13}NO_3]$ 207.0890 Found 207.0888. Data consistent with the literature.[253]

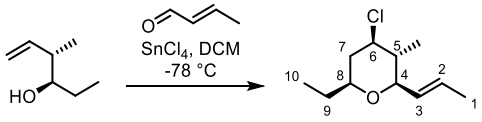
(3*R*,4*S*)-4-Methylhex-5-en-3-ol (345)



*t*BuOK (561 mg, 5.0 mmol) was dissolved in THF (15 mL) under nitrogen and cooled to -78 °C then condensed *trans*-but-2-ene (0.90 mL, 10.0 mmol) was added *via* cannula. A solution of 2.5 M *n*BuLi in

hexane (2.00 mL, 5.0 mmol) was added dropwise over 15 minutes and the reaction mixture was stirred for 10 minutes at -45 °C then cooled to -78 °C. A 0.92 M solution of (−)-Ipc_2BOMe in THF (6.52 mL, 6.0 mmol) was added dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 30 minutes then $BF_3.Et_2O$ (0.83 mL, 6.7 mmol) was added dropwise over 5 minutes followed by propionaldehyde (0.51 mL, 7.0 mmol) over 5 minutes. The reaction mixture was stirred for 4 hours, quenched with 3 M NaOH (4 mL) and 30% H_2O_2 (2 mL), then stirred at room temperature for 16 hours. The resulting solution was diluted with Et_2O (150 mL) and water (100 mL). The organic layer was separated and the aqueous extracted with further Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% Et_2O in pentane) to afford alcohol **345** (252 mg, 44%, dr = 95:5) as a colourless oil. ^{1}H-NMR analysis of the Mosher's ester indicated a > 95% ee; $[\alpha]_D^{21}$ -8.0 (*c* 1, $CHCl_3$); lit.[280] $[\alpha]_D^{25}$ = -8.7 (*c* 0.3, $CHCl_3$); ν_{max} (film) 3385, 3077, 2964, 2935, 2877, 1639, 1457, 1215; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.4, 1-H_3), 1.03 (3H, d, *J* 6.8, 4-CH_3), 1.35 – 1.44 (1H, m, 2-*H*H), 1.52 – 1.64 (2H, m, OH and 2-H*H*), 2.14 – 2.29 (1H, m, 4-H), 3.22 – 3.40 (1H, m, 3-H), 5.09 (1H, m, 6-*H*H), 5.12 (1H, m, 6-H*H*), 5.69 – 5.84 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 10.1 (C-1), 16.5 (CH_3-4), 27.1 (C-2), 43.9 (C-4), 76.2 (C-3), 116.4 (C-6), 140.6 (C-5); HRMS (APCI) calc. for [$C_7H_{14}O$] 97.1012 Found 97.1008. Data consistent with the literature.[280]

(2*R*,3*R*,4*R*,6*S*)-4-Chloro-6-ethyl-3-methyl-2-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran (386)

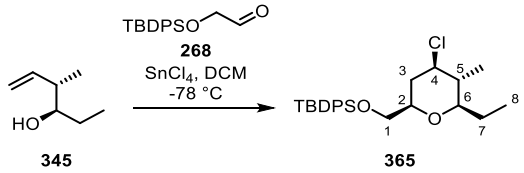


345 **386**

Homoallylic alcohol **345** (42 mg, 0.37 mmol) and crotonaldehyde (0.09 mL, 1.10 mmol) were dissolved in DCM (2 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 0.74 mL, 0.74 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes at -78 °C, warmed to room temperature, then quenched with aqueous saturated $NaHCO_3$ (2 mL). The resultant solution was diluted with DCM (10 mL) and water (10 mL) and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 10 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (15% DCM in petroleum ether 60:40) to afford tetrahydropyran **386** (16 mg, 21%) as a colourless oil; $[\alpha]_D^{21}$ -48.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2966, 2929, 2878, 2837, 1457, 1215; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5, 10-H_3), 0.99 (3H, d, *J* 6.6, 5-CH_3), 1.43 – 1.69 (4H, m, 5-H, 7-H_{ax}, 9-H_2), 1.72 (3H, dd, *J* 6.5, 1.6, 1-H_3), 2.18 (1H, ddd, *J* 12.9, 4.6, 1.9, 7-H_{eq}), 3.28 (1H, ap. dtd, *J* 11.2, 6.2, 1.9, 8-H), 3.40 (1H, dd, *J* 9.7, 7.9, 4-H), 3.70 (1H, ddd, *J* 11.9, 10.6, 4.6, 6-H), 5.43 (1H, ddq, *J* 15.3, 7.9, 1.6, 3-H), 5.67

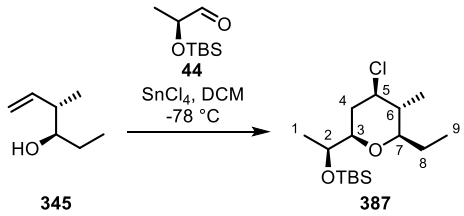
– 5.77 (1H, m, 2-H); δ_C (101 MHz, $CDCl_3$) 9.9 (C-10), 15.2 (CH_3-5), 18.0 (C-1), 28.8 (C-9), 42.4 (C-7), 44.8 (C-5), 64.3 (C-6), 77.8 (C-8), 83.9, (C-4) 130.4 (C-2 and C-3); HRMS (EI) calc. for [$C_{11}H_{19}O^{35}Cl$] 202.1119 Found 202.1119.

***tert*-Butyl(((2*R*,4*R*,5*R*,6*R*)-4-chloro-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)methoxy)diphenylsilane (365)**



Homoallylic alcohol **345** (57 mg, 0.5 mmol) and aldehyde **268** (179 mg, 0.6 mmol) were dissolved in DCM (5 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 1.0 mL, 1.0 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes then quenched with aqueous saturated $NaHCO_3$ (5 mL) and warmed to room temperature. The resultant solution was diluted with DCM (15 mL) and water (15 mL), and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 15 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (15% DCM in petroleum ether 60:40) to afford tetrahydropyran **365** (79 mg, 37%) as a single diastereoisomer and as white solid; $[\alpha]_D^{23}$ = +10.0 (*c* 1, $CHCl_3$). Data consistent with previously reported.

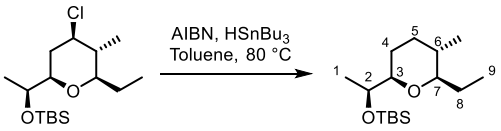
***tert*-Butyl((*S*)-1-((2*R*,4*R*,5*R*,6*R*)-4-chloro-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethoxy)dimethylsilane (387)**



Homoallylic alcohol **345** (91 mg, 0.80 mmol) and aldehyde **44** (100 mg, 0.53 mmol) were dissolved in DCM (5 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 1.1 mL, 1.1 mmol) was added dropwise. The reaction mixture was stirred for 2 hours then quenched with aqueous saturated $NaHCO_3$ (5 mL) and warmed to room temperature. The resultant solution was diluted with DCM (15 mL) and water (15 mL), and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 15 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10%

DCM in petroleum ether 60:40) to afford tetrahydropyran **387** (56 mg, 33%) as a single diastereoisomer and as a colourless oil; $[\alpha]_D^{25}$ = +16.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2930, 2857, 1463, 1379, 1251, 1214, 1099; δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.95 (3H, ap. t, *J* 7.5, 9-H_3), 1.03 (3H, d, *J* 6.5, 6-CH_3), 1.16 (3H, d, *J* 6.2, 1-H_3), 1.40 (1H, ddq, *J* 14.3, 9.0, 7.5, 8-*H*H), 1.47 – 1.56 (1H, m, 6-H), 1.65 – 1.78 (2H, m, 4-H_{ax} and 8-H*H*), 2.35 (1H, ddd, *J* 12.7, 4.6, 1.9, 4-H_{eq}), 2.88 (1H, ap. td, *J* 9.0, 2.6, 7-H), 3.04 (1H, ddd, *J* 11.3, 6.1, 1.9, 3-H), 3.64 – 3.74 (2H, m, 2-H and 5-H); δ_C (101 MHz, $CDCl_3$) -4.4 ($SiCH_3$), -4.3 $Si(CH_3)$, 10.1 (C-9) , 14.7 (CH_3-6), 18.24 (Si*C*$(CH_3)_3$), 21.0 (C-1), 26.0 (SiC(*C*$H_3)_3$), 26.4 (C-8), 39.0 (C-4), 44.7 (C-6), 65.2 (C-5), 70.9 (C-2), 81.1 (C-3), 83.3 (C-7); HRMS (EI) calc. for [$C_{16}H_{33}O_2Si^{35}Cl$] 263.1229 Found 263.1229.

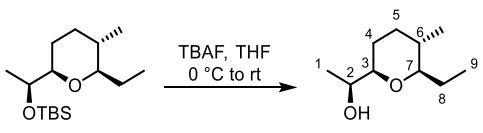
tert-Butyl((*S*)-1-((2*R*,5*S*,6*R*)-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethoxy)dimethylsilane (389)



387 **389**

Alkyl chloride **387** (95 mg, 0.30 mmol) was dissolved in degassed toluene (3 mL) under nitrogen and heated to 50 °C then tributyltin hydride (0.24 mL, 0.89 mmol) was added followed by AIBN (10 mg). The reaction mixture was heated at 80 °C for 1 hour, cooled to room temperature and diluted with aqueous saturated potassium fluoride (25 mL) and EtOAc (50 mL). The organic layer was separated and washed with aqueous saturated potassium fluoride (25 mL), then brine (25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% DCM in petroleum ether 60:40) to afford tetrahydropyran **389** (72 mg, 85%) as a colourless oil; $[\alpha]_D^{22}$ = +40.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2958, 2927, 2889, 1462, 1250, 1099; δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.80 (3H, d, *J* 6.5, 6-CH_3), 0.88 (9H, s, $SiC(CH_3)_3$), 0.94 (3H, ap. t, *J* 7.4, 9-H_3), 1.12 (1H, m, 5-*H*H), 1.18 (3H, d, *J* 6.1, 1-H_3), 1.20 – 1.35 (3H, m, 4-*H*H, 6-H and 8-*H*H), 1.65 – 1.73 (1H, m, 8-H*H*), 1.74 – 1.87 (2H, m, 4-H*H* and 5-H*H*), 2.77 (1H, ap. td, *J* 9.3, 2.6, 7-H), 2.96 (1H, ddd, *J* 11.0, 6.9, 2.0, 3-H), 3.58 – 3.67 (1H, m, 2-H); δ_C (101 MHz, $CDCl_3$) -4.5 ($SiCH_3$), -4.2 ($SiCH_3$), 10.3 (C-9), 18.0 (CH_3-6), 18.3 (Si*C*$(CH_3)_3$), 21.2 (C-1), 26.1 (SiC(*C*$H_3)_3$), 26.3 (C-8), 28.3 (C-4), 33.0 (C-5), 35.5 (C-6), 71.6 (C-2), 82.4 (C-3), 85.0 (C-7); HRMS (EI) calc. for [$C_{16}H_{34}O_2Si^{35}$] 299.1618 Found 299.1617.

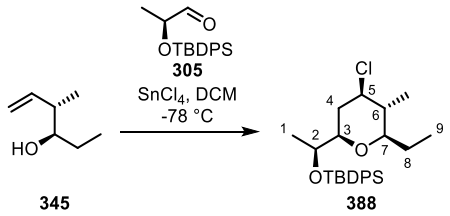
(*S*)-1-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethan-1-ol (324)



389 **324**

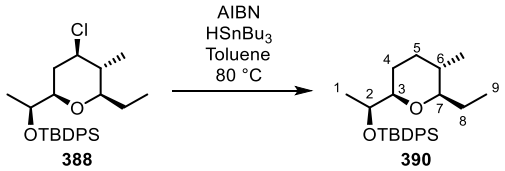
Silyl ether **389** (60 mg, 0.21 mmol) was cooled to 0 °C under nitrogen then 1 M TBAF in THF (0.42 mL, 0.42 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 24 hours and then quenched with water (10 mL) and Et_2O (10 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford alcohol **324** (33 mg, 91%) as a colourless oil. Data consistent with previously reported.

***tert*-Butyl((*S*)-1-((2*R*,4*R*,5*R*,6*R*)-4-chloro-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethoxy)diphenylsilane (388)**



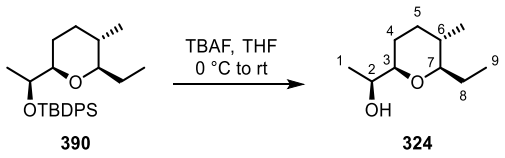
Homoallylic alcohol **345** (387 mg, 3.39 mmol) and aldehyde **305** (1060 mg, 3.39 mmol) were dissolved in DCM (40 ml) at -78 °C under nitrogen then $SnCl_4$ (1 M in DCM, 6.78 mL, 6.78 mmol) was added dropwise. The reaction mixture was stirred for 3 hours then quenched with aqueous saturated $NaHCO_3$ (20 mL) and warmed to room temperature. The resultant solution was diluted with DCM (50 mL) and water (30 mL), and the organic layer separated. The aqueous layer was extracted with further DCM (2 × 40 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (12% DCM in petroleum ether 60:40) to afford tetrahydropyran **388** (614 mg, 41%) as a single diastereoisomer and as a white crystalline solid; $[\alpha]_D^{23}$ = -12.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2965, 2931, 2857, 1473, 1428, 1376, 1111; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, 9-H_3), 1.00 – 1.05 (6H, m 1-H_3 and, 6-CH_3), 1.06 (9H, s, $SiC(CH_3)_3$), 1.33 – 1.46 (1H, m, 8-*H*H), 1.47 – 1.60 (1H, m, 6-H), 1.70 – 1.76 (1H, m, 8-H*H*), 1.82 (1H, ap. q, *J* 12.0, 4-H_{ax}), 2.33 (1H, ddd, *J* 12.8, 4.6, 2.0, 4-H_{eq}), 2.88 (1H, ap. td, *J* 9.1, 2.5, 7-H), 3.15 (1H, ddd, *J* 11.4, 4.5, 2.0, 3-H), 3.69 (1H, ap. td, *J* 11.3, 4.6, 5-H), 3.86 (1H, qd, *J* 6.3, 4.5, 2-H), 7.32 – 7.47 (6H, m, 6 × ArH), 7.68 – 7.75 (4H, m, 4 × ArH); δ_C (101 MHz, $CDCl_3$) 10.1 (C-9), 14.7 (CH_3-6), 19.6 (Si*C*$(CH_3)_3$), 20.2 (C-1), 26.4 (C-8), 27.2 (SiC(*C*$H_3)_3$), 38.3 (C-4), 44.7 (C-6), 65.3 (C-5), 71.8 (C-2), 81.0 (C-3), 83.4 (C-7), 127.66 (ArCH), 127.70 (ArCH), 129.7 (ArCH), 129.80 (ArCH), 134.0 (ArC), 135.0 (ArC), 136.2 (ArCH), 136.45 (ArCH); HRMS (EI) calc. for [$C_{26}H_{37}O_2Si^{35}Cl$] 387.1542 Found 387.1546.

***tert*-Butyl((*S*)-1-((2*R*,5*S*,6*R*)-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethoxy)diphenylsilane (390)**



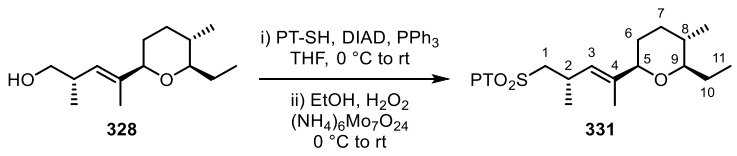
Alkyl chloride **388** (430 mg, 0.97 mmol) was dissolved in degassed toluene (10 mL) under nitrogen and heated to 50 °C then tributyltin hydride (0.78 mL, 2.90 mmol) was added followed by AINB (32 mg). The reaction mixture was heated at 80 °C for 1 hour, cooled to room temperature and diluted with aqueous saturated potassium fluoride (25 mL) and EtOAc (50 mL). The organic layer was separated and washed with aqueous saturated potassium fluoride (25 mL), then brine (25 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (13% DCM in petroleum ether 60:40) to afford tetrahydropyran **390** (372 mg, 93%) as a colourless oil; $[\alpha]_D^{22}$ = +12.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2960, 2930, 2856, 1463, 1427, 1105; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.5, 6-CH_3), 0.94 (3H, ap. t, *J* 7.4, 9-H_3), 1.04 (3H, d, *J* 6.2, 1-H_3), 1.06 (9H, s, $SiC(CH_3)_3$), 1.10 – 1.22 (1H, m, 5-*H*H), 1.24 – 1.45 (3H, m, 4-*H*H, 6-H and 8-*H*H), 1.63 – 1.75 (1H, m, 8-H*H*), 1.76 – 1.86 (2H, m, 4-H*H* and 5-H*H*), 2.79 (1H, ap. td, *J* 9.2, 2.6, 7-H), 3.09 (1H, ddd, *J* 11.1, 5.4, 2.0, 3-H), 3.75 – 3.88 (1H, m, 2-H), 7.31 – 7.47 (6H, m, ArH), 7.62 – 7.81 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 10.2 (C-9), 18.0 (CH_3-6), 19.6 ($SiC(CH_3)_3$), 20.4 (C-1), 26.3 (C-8), 27.2 ($SiC(CH_3)_3$), 27.6 (C-4), 33.1 (C-5), 35.4 (C-6), 72.6 (C-2), 82.4 (C-3), 85.0 (C-7), 127.5 (ArCH), 127.6 (ArCH), 129.5 (ArCH), 129.6 (ArCH), 134.4 (ArC), 135.3 (ArC), 136.2 (ArCH), 136.3 (ArCH); HRMS (EI) calc. for $[C_{26}H_{38}O_2Si]$ 353.1931 Found 353.1929.

(*S*)-1-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)ethan-1-ol (324)



Silyl ether **390** (350 mg, 0.79 mmol) was cooled to 0 °C under nitrogen then 1 M TBAF in THF (1.57 mL, 1.57 mmol) was added dropwise. The reaction mixture was stirred under nitrogen at room temperature for 24 hours and then quenched with water (20 mL) and Et_2O (50 mL). The organic layer was separated and the aqueous extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford alcohol **324** (122 mg, 90%) as a colourless oil. Data consistent with previously reported.

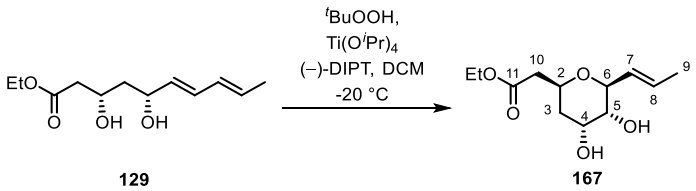
5-(((*S*,*E*)-4-((2*R*,5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2H-pyran-2-yl)-2-methylpent-3-en-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (331)



Alcohol **328** (340 mg, 1.50 mmol), PT-SH (348 mg, 1.96 mmol) and PPh_3 (514 mg, 1.96 mmol) were dissolved in THF (15 mL) under nitrogen and cooled to 0 °C then DIAD (0.39 mL, 1.96 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature then quenched with aqueous saturated $NHCl_4$ (20 mL) and brine (20 mL). The resulting solution was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was filtered over a small plug of silica eluting with 20% Et_2O in petroleum ether 60:40 and the solvent removed *in vacuo* to afford sulfide (552 mg, 95%) as a yellow oil.

The sulfide was dissolved in EtOH (47 mL) and cooled to 0 °C then a premixed solution of molybdate (347 mg, 0.28 mmol) in a 30% aqueous solution of H_2O_2 (1.43 mL, 14.1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 hours then quenched with water (50 mL). The resulting solution was extracted with DCM (3 × 100 mL) and the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% EtOAc in petroleum ether 60:40) to afford sulfone **331** (542 mg, 90% over two steps) as a yellow oil; $[\alpha]_D^{24}$ = -16.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3019, 2927, 1498, 1459, 1347, 1214; δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.6, 8-CH_3), 0.95 (3H, t, *J* 7.4, 11-H_3), 1.16 (3H, d, *J* 6.8, 2-CH_3), 1.18 – 1.20 (1H, m, 7-*H*H), 1.20 – 1.23 (1H, m, 6-*H*H), 1.28 – 1.35 (1H, m, 8-H), 1.42 (ap. dp, *J* 14.5, 7.4, 10-*H*H), 1.52 – 1.57 (1H, m, 6-H*H*), 1.61 (3H, d, *J* 1.4, 4-CH_3), 1.70 (1H, dqd, *J* 14.5, 7.4, 2.9, 10-H*H*), 1.74 – 1.80 (1H, m, 7-H*H*), 2.87 (1H, ddd, *J* 9.9, 7.4, 2.9, 9-H), 3.27 (1H, m, 2-H), 3.48 (1H, d, *J* 9.7, 5-H), 3.57 (1H, dd, *J* 14.7, 6.3, 1-*H*H), 3.83 (1H, dd, *J* 14.7, 7.5, 1-H*H*), 5.13 (1H, dt, *J* 9.7, 1.4, 3-H), 7.54 – 7.68 (5H, m, ArH); δ_C (101 MHz, $CDCl_3$) 9.7 (C-11), 13.7 (CH_3-4), 17.9 (CH_3-8), 21.0 (CH_3-2), 26.0 (C-10), 27.9 (C-2), 30.6 (C-6), 33.2 (C-7), 34.3 (C-8), 61.9 (C-1), 81.1 (C-5), 84.7 (C-9), 125.1 (C-3), 125.7 (2 × ArCH), 129.7 (2 × ArCH), 131.6 (ArCH), 133.3 (ArC), 138.9 (C-4), 154.2 (NCN); HRMS (ESI) calc. for [$C_{21}H_{30}N_4O_3S$] 419.2111 Found 419.2113.

Ethyl 2-((2*S*,4*R*,5*R*,6*S*)-4,5-dihydroxy-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)acetate (167)



Optimised procedure on < 1 mmol scale of allylic alcohol 129:

In a flame dried flask at -20 °C under nitrogen was added 4 Å molecular sieves (30 mg), allylic alcohol **129** (100 mg, 0.44 mmol) and DCM (2.5 mL) followed by titanium isopropoxide (0.03 mL, 0.09 mmol) and (−)-DIPT (0.03 mL, 0.13 mmol). The reaction mixture was stirred for 30 minutes then 5.5 M ^{t}BuOOH in decane (0.16 mL, 0.88 mmol) was added dropwise and the reaction mixture was stirred at -20 °C for 24 hours. The reaction mixture was quenched with a precooled (0 °C) aqueous solution of $FeSO_4$/citric acid (660 mg of $FeSO_4$ and 220 mg of citric acid in 3 mL of H_2O). The solution was stirred vigorously for 30 minutes at room temperature then extracted with DCM (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (70% EtOAc in petroleum ether 60:40) to afford tetrahydropyran **167** (87 mg, 81%) as a colourless oil. Data consistent with previously reported.

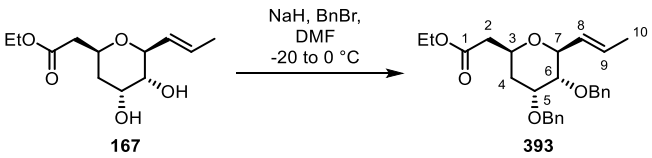
Optimised scale-up procedure:

In a flame dried flask at -20 °C under nitrogen was added 4 Å powdered molecular sieves (1.60 g), DCM (100 mL) and (−)-DIPT (2.92 mL, 13.93 mmol). The mixture was stirred for 30 minutes then titanium isopropoxide (3.44 mL, 11.61 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes then allylic alcohol **129** (5.30 g, 23.22 mmol) in DCM (15 mL) was added dropwise. The reaction mixture was stirred for a further 30 minutes then 5.5 M ^{t}BuOOH in decane (8.44 mL, 46.44 mmol) was added dropwise and the reaction mixture was stirred at -20 °C for 24 hours. The reaction mixture was poured into a precooled (0 °C) aqueous solution of $FeSO_4$/citric acid (20 g of $FeSO_4$ and 6.4 g of citric acid in 60 mL of H_2O) and the resulting solution was stirred for 10 minutes at room temperature. The mixture was filtered over Celite, washing with EtOAc (500 mL) and water (200 mL). The organic layer was separated and the aqueous extracted with further EtOAc (2 × 500 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (50% Et_2O in DCM) to afford tetrahydropyran **167** (4.31 g, 76%, 89% BORSM) as a colourless oil and unreacted allylic alcohol **129** (0.75 g, 14%). Data consistent with previously reported.

Procedure for alternative quench with $Na_2S_2O_3$:

In a flame dried flask at -20 °C under nitrogen was added 4 Å powdered molecular sieves (600 mg), DCM (26 mL) and (−)-DIPT (1.04 mL, 4.97 mmol). The mixture was stirred for 15 minutes then titanium isopropoxide (1.23 mL, 4.14 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes then allylic alcohol **129** (1890 mg, 8.28 mmol) in DCM (15 mL) was added dropwise. The reaction mixture was stirred for a further 30 minutes then 5.5 M ^{t}BuOOH in decane (3.01 mL, 16.56 mmol) was added dropwise and the reaction mixture was stirred at -20 °C for 24 hours. The reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ (40 mL) then stirred vigorously for 1 hour at 0 °C. The reaction mixture was diluted with water (100 mL) and EtOAc (200 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 × 150 mL) then the combined organic layers washed with Brine (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (60% Et_2O in DCM) to afford tetrahydropyran **167** (1167 mg, 58%) as a yellow oil. Data consistent with previously reported.

Ethyl 2-((2*S*,4*R*,5*R*,6*S*)-4,5-bis(benzyloxy)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)acetate (393)

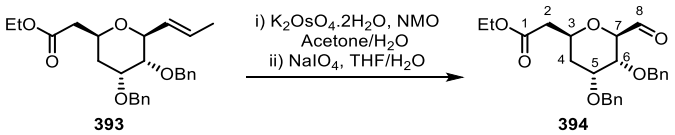


167 393

Diol **167** (74 mg, 0.30 mmol) in DMF (0.5 mL) was added dropwise to a suspension of a 60% dispersion of NaH in mineral oil (36 mg, 0.91 mmol) in DMF (1 mL) under nitrogen at -20 °C. The reaction mixture was stirred at -20 °C for 30 minutes, then benzyl bromide (0.09 mL, 0.75 mmol) was added dropwise. The reaction mixture was stirred at -20 °C for 30 minutes then for 1 hour at 0 °C. Aqueous saturated NH_4Cl (10 mL) was added, and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford tetrahydropyran **393** (72 mg, 56%) as a colourless oil; $[\alpha]_D^{26}$ = -83.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3030, 2916, 1737, 1679, 1454, 1175, 1074; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.2, OCH_2CH_3), 1.33 – 1.41 (1H, m, 4-H_{ax}), 1.69 – 1.76 (3H, m, 10-H_3), 2.04 – 2.16 (1H, m, 4-H_{eq}), 2.37 (1H, dd, 15.2, 6.7, 2-*H*H), 2.58 (1H, dd, *J* 15.2, 6.8, 2-H*H*), 3.14 (1H, dd, *J* 9.6, 2.9, 6-H), 3.90 – 4.00 (1H, m, 5-H), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.23 – 4.38 (2H, m, 3-H and 7-H), 4.45 (1H, d, *J* 12.0, OC*H*HPh), 4.54 (1H, d, *J* 12.0, OCH*H*Ph), 4.67 (1H, d, *J* 12.5 Hz, OC*H*HPh), 4.72 (1H, d, *J* 12.5, OC*H*HPh), 5.43 – 5.54 (1H, m, 8-H), 5.78 – 5.97 (1H, m, 9-H), 7.26 – 7.41 (10H, m, 10 × ArH); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH_2CH_3), 18.3 (C-10), 35.1 (C-4), 40.9 (C-2), 60.6 (OCH_2CH_3), 68.2 (C-3), 71.0 (C-5), 71.4 (OCH_2Ph), 71.6 (OCH_2Ph), 75.7 (C-7),

79.5 (C-6), 127.7 (ArCH), 127.8 (ArCH), 127.87 (ArCH), 127.92 (ArCH), 128.0 (ArCH), 128.5 (ArCH), 129.58 (C-8), 129.62 (C-9), 138.4 (ArC), 138.9 (ArC), 171.2 (C-1); HRMS (ESI) calc. for [$C_{26}H_{32}O_5Na$] 447.2142 Found 447.2141.

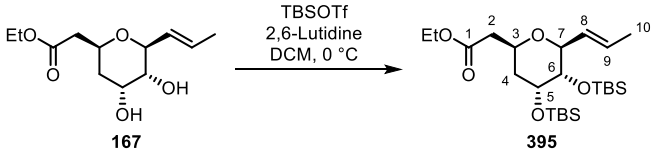
Ethyl 2-((2*S*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-formyltetrahydro-2H-pyran-2-yl)acetate (394)



393 394

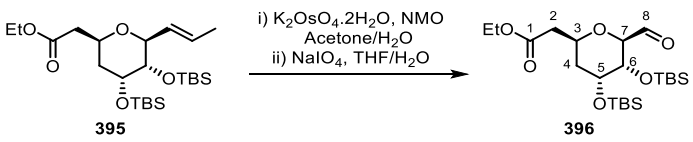
Alkene **393** (50 mg, 0.118 mmol) was dissolved in acetone (0.5 mL) and water (0.1 mL) then potassium osmate dihydrate (0.5 mg, 0.001 mmol) and NMO (21 mg, 0.177 mmol) were added sequentially and the reaction mixture was stirred at room temperature. After 18 hours the reaction mixture was diluted with EtOAc (15 mL) and water (15 mL). The organic layer was separated and the aqueous was extracted with further EtOAc (2 × 15 mL). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude diol was dissolved in THF (0.4 mL) and water (0.3 mL) and $NaIO_4$ (35 mg, 0.165 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The solution was filtered through a pad of Celite and washed with DCM (50 mL). The organic phase was washed with aqueous saturated $Na_2S_2O_3$ (20 mL) and the aqueous extracted with DCM (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (80% Et_2O in petroleum ether 60:40) to afford aldehyde **394** (43 mg, 88%) as a colourless oil; $[\alpha]_D^{20}$ = -129.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2872, 1733, 1265, 1092; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.37 – 1.41 (1H, m, 4-*H*H), 2.12 (1H, ddd, *J* 14.1, 4.0, 2.0, 4-H*H*), 2.41 (1H, dd, *J* 15.6, 6.7, 2-*H*H), 2.64 (1H, dd, *J* 15.6, 6.7, 2-H*H*), 3.52 (1H, dd, *J* 10.1, 2.5, 6-H), 4.03 (1H, ap. dt, *J* 4.0, 2.5, 5-H), 4.10 – 4.20 (2H, m, OCH_2CH_3), 4.32 (1H, ap. dtd, *J* 11.6, 6.7, 2.0, 3-H), 4.42 (1H, d, *J* 11.7, OC*H*HPh), 4.49 (1H, dd, *J* 10.1, 1.0, 7-H), 4.56 (1H, d, *J* 11.7, OCH*H*Ph), 4.68 (1H, d, *J* 12.1, OC*H*HPh), 4.73 (1H, d, *J* 12.1, OCH*H*Ph), 7.27 – 7.39 (10H, m, 10 × ArH), 9.75 (1H, d, *J* 1.0, 8-H); δ_C (101 MHz, $CDCl_3$) 14.4 (OCH_2CH_3), 34.5 (C-4), 40.4 (C-2), 60.8 (OCH_2CH_3), 68.6 (C-3), 70.2 (C-5), 71.3 (OCH_2Ph), 71.6 (OCH_2Ph), 76.1 (C-6), 78.4 (C-7), 127.9 (ArCH), 128.0 (2 × ArCH), 128.1 (2 × ArCH), 128.2 (ArCH), 128.6 (2 × ArCH), 128.7 (2 × ArCH), 137.4 (ArC), 138.4 (ArC), 170.8 (C-1), 199.5 (C-8); HRMS (ESI) calc. for [$C_{27}H_{28}O_6$] 413.1959 Found 413.1960.

Ethyl 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-((*E*)-prop-1-en-1-yl)tetrahydro-2H-pyran-2-yl)acetate (395)



Diol **167** (3.60 g, 14.74 mmol) was dissolved in DCM (150 mL) under nitrogen and cooled to 0 °C then 2,6-lutidine (10.30 mL, 88.44 mmol) was added and the reaction mixture was stirred for 5 minutes. TBSOTf (13.54 mL, 58.96 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 45 minutes at 0 °C then quenched with aqueous saturated $NaHCO_3$ solution (50 mL). The resulting solution was diluted with water (100 mL) and DCM (200 mL). The organic layer was separated and the aqueous extracted with DCM (2 × 100 mL). The combined organic layers were washed sequentially with 2 M HCl (100 mL) then brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford silyl ether **395** (6.28 g, 90%) as a colourless oil; $[\alpha]_D^{21}$ = -46.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3020, 2954, 2929, 2887, 2857, 1739, 1473, 1214; δ_H (400 MHz, $CDCl_3$) δ 0.00 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.53 (1H, ddd, *J* 13.4, 11.4, 2.1, 4-H_{ax}), 1.68 (3H, dd, *J* 6.5, 1.6, 10-H_3), 1.82 (1H, ddd, *J* 13.4, 4.1, 2.1, 4-H_{eq}), 2.34 (1H, dd, *J* 14.8, 7.6, 2-*H*H), 2.60 (1H, dd, *J* 14.8, 6.2, 2-H*H*), 3.28 (1H, dd, *J* 9.2, 2.1, 6-H), 4.00 (1H, ap. dt, *J* 4.1, 2.1, 5-H), 4.07 – 4.18 (3H, m, O$CH_2$$CH_3$ and 7-H), 4.27 (1H, dddd, *J* 11.4, 7.6, 6.2, 2.1, 3-H), 5.38 (1H, ddq, *J* 15.4, 7.3, 1.6, 8-H), 5.69 (1H, dqd, *J* 15.4, 6.5, 1.0, 9-H); δ_C (101 MHz, $CDCl_3$) -4.4 (2 × $SiCH_3$), -4.2 ($SiCH_3$), -3.4 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.2 (C-10), 18.3 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 26.3 ($SiC(CH_3)_3$), 39.7 (C-4), 41.2 (C-2), 60.6 (OCH_2CH_3), 67.9 (C-3), 69.6 (C-5), 73.9 (C-6), 76.7 (C-7), 129.2 (C-9), 130.4 (C-8), 171.2 (C-1); HRMS (ESI) calc. for $[C_{24}H_{48}O_5Si_2]$ 473.3113 Found 473.3114.

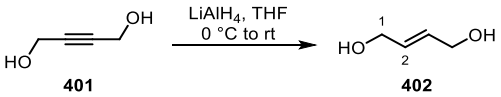
Ethyl 2-((2*S*,4*R*,5*S*,6*R*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-formyltetrahydro-2H-pyran-2-yl)acetate (396)



Alkene **395** (5.99 g, 12.67 mmol) was dissolved in acetone (50 mL) and water (6.5 mL) then potassium osmate dihydrate (47 mg, 0.13 mmol) and NMO (2.23 g, 19.04 mmol) were added sequentially, and the reaction mixture was stirred at room temperature. After 18 hours the reaction mixture was diluted

with EtOAc (200 mL), water (100 mL) and brine (50 mL). The organic layer was separated and the aqueous was extracted with further EtOAc (2 × 150 mL). The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude diol was dissolved in THF (42 mL) and water (32 mL) and $NaIO_4$ (3.80 g, 17.77 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 3 hours then further $NaIO_4$ (3.80 g, 17.77 mmol) was added and the reaction mixture was stirred for 3 hours. The solution was filtered through a pad of Celite and washed with DCM (300 mL). The organic phase was washed with aqueous saturated $Na_2S_2O_3$ (200 mL) and the aqueous extracted with DCM (2 × 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (50% Et_2O in petroleum ether 60:40) to afford aldehyde **396** (5.23 g, 89%) as a colourless oil; $[\alpha]_D^{22}$ = -76.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3019, 2953, 2929, 2887, 2858, 1739, 1214; δ_H (400 MHz, $CDCl_3$) 0.01 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.25 (3H, t, *J* 7.1, $OCH_2\mathit{CH_3}$), 1.57 (1H, ddd, *J* 13.6, 11.5, 2.0, 4-H_{ax}), 1.86 (1H, ddd, *J* 13.6, 4.2, 2.1, 4-H_{eq}), 2.40 (1H, dd, *J* 15.2, 6.8, 2-*H*H), 2.67 (1H, dd, *J* 15.2, 6.8, 2-H*H*), 3.67 (1H, dd, *J* 9.6, 2.0, 6-H), 4.06 (1H, ap. dt, *J* 4.2, 2.0, 5-H), 4.13 (2H, ap. qd, *J* 7.1, 2.2, $O\mathit{CH_2}CH_3$), 4.29 (1H, ap. dtd, *J* 11.5, 6.8, 2.1, 3-H), 4.39 (1H, dd, *J* 9.6, 1.4, 7-H), 9.72 (1H, d, *J* 1.4, 8-H); δ_C (101 MHz, $CDCl_3$) -4.9 ($SiCH_3$), -4.4 ($SiCH_3$), -4.1 ($SiCH_3$), -3.5 ($SiCH_3$), 14.4 ($OCH_2\mathit{C}H_3$), 18.2 ($Si\mathit{C}(CH_3)_3$), 18.3 ($Si\mathit{C}(CH_3)_3$), 26.0 ($SiC(\mathit{C}H_3)_3$), 26.1 ($SiC(\mathit{C}H_3)_3$), 39.0 (C-4), 40.6 (C-2), 60.8 ($O\mathit{C}H_2CH_3$), 68.2 (C-3), 69.4 (C-5), 71.4 (C-6), 79.5 (C-7), 170.8 (C-1), 200.5 (C-8); HRMS (ESI) calc. for $[C_{22}H_{44}O_6Si_2]$ 461.2749 Found 461.2761.

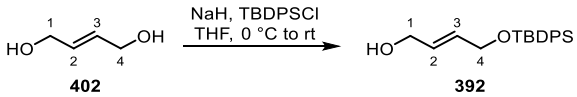
(*E*)-But-2-ene-1,4-diol (402)



401 **402**

A solution of 1,4-butyne diol **401** (8.61 g, 100 mmol) in THF (50 mL) was added dropwise to a suspension of $LiAlH_4$ (5.69 g, 150 mmol) in THF (150 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 15 minutes followed by 24 hours at room temperature. The reaction mixture was cooled to 0 °C and quenched with water (6 mL), then 3 M NaOH (6 mL) and then further water (18 mL). The reaction mixture was stirred at room temperature for 30 minutes then $MgSO_4$ was added. The resulting suspension was filtered over Celite, washed with Et_2O (250 mL) and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (EtOAc) to afford diol **402** (7.67 g, 87%, *E*/*Z* > 99:1) as a colourless oil; ν_{max} (film) 3268, 3009, 2939, 2873, 1452, 1398, 1369, 1080,973; δ_H (400 MHz, $CDCl_3$) 1.50 – 1.58 (2H, m, 2 × OH), 4.18 (4H, dd, *J* 5.3, 2.8, 2 × CH_2), 5.90 (2H, tt, *J* 2.7, 1.2, 2 × CH); δ_C (101 MHz, $CDCl_3$) 63.1 (C-1), 130.7 (C-2); m/z (APCI): $[M+Na]^+$ = 111.1. Data consistent with the literature.[281]

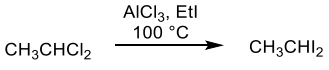
(*E*)-4-(*tert*-Butyldiphenylsiloxy)but-2-en-1-ol (392)



402 **392**

A solution of diol **402** (1.00 g, 11.35 mmol) in THF (7 mL) was added dropwise to a suspension of a 60% dispersion of NaH in mineral oil (454 mg, 11.35 mmol) in THF (25 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 1 hour then TBDPSCl (2.95 mL, 11.35 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for a further hour then cooled to 0 °C and quenched with water (20 mL). The resulting solution was diluted with DCM (100 mL) and water (70 mL), and the organic layer separated. The aqueous was extracted with further DCM (2 × 100 mL) and the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (40% Et_2O in petroleum ether 60:40) to afford homoallylic alcohol **392** (2.00 g, 54%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, $SiC(CH_3)_3$), 1.29 (1H, s, OH), 4.15 (2H, ap. dq, *J* 5.5, 1.4, 1-H_2), 4.23 (2H, ap. dq, *J* 4.5, 1.7, 4-H_2), 5.79 (1H, dtt, *J* 15.4, 4.5, 1.4, 3-H), 5.93 (1H, dtt, *J* 15.4, 5.5, 1.7, 2-H), 7.35 – 7.44 (6H, m, ArH), 7.65 – 7.71 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 19.4 ($SiC(CH_3)_3$), 27.0 ($SiC(CH_3)_3$), 63.4 (C-1), 63.9 (C-4), 127.9 (4 × ArCH), 129.0 (C-3), 129.9 (2 × ArCH), 130.8 (C-2), 133.8 (2 × ArC), 135.7 (4 × ArCH); m/z (ESI): $[M+Na]^+$ = 349.10. Data consistent with the literature.[282]

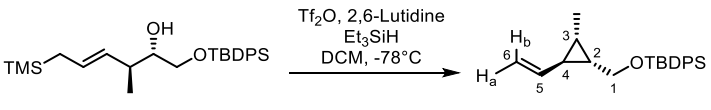
1,1-Diiodoethane (430)



430

1,1-Dichloroethane (2.0 gm 20.21 mmol) and iodoethane (4.87 mL, 60.63 mmol) were stirred under nitrogen at room temperature, then $AlCl_3$ (269 mg, 2.02 mmol) was added and the reaction mixture was refluxed at 100 °C for 4 hours. The reaction mixture was cooled to 0 °C, diluted with Et_2O (100 mL) and the resulting solution washed with 10% aqueous $Na_2S_2O_3$ (50 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (pentane) to afford 1,1-diiodoethane **430** (0.634 g, 11%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.92 (3H,d, *J* 6.7, CH_3), 5.19 – 5.26 (1H, q, *J* 6.7, CH); δ_C (101 MHz, $CDCl_3$) 39.1 (CH_3). Data consistent with the literature.[283]

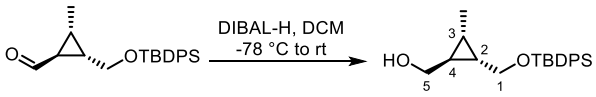
***tert*-Butyl(((1*S*,2*S*,3*S*)-2-methyl-3-vinylcyclopropyl)methoxy)diphenylsilane (270)**



269 **270**

Alcohol **269** (2.50 g, 5.67 mmol) was dissolved in DCM (57 ml) and cooled to -78 °C under nitrogen then 2,6-lutidine (2.64 mL, 22.68 mmol) and Et_3SiH (0.23 mL, 1.42 mmol) were added and the reaction mixture was stirred for 5 minutes. Tf_2O (2.88 mL, 17.02 mmol) was added dropwise and the reaction mixture was stirred for 30 minutes at -78 °C then 2 hours at 0 °C. The reaction mixture was quenched with dropwise addition of aqueous saturated $NaHCO_3$ (40 mL) and water (50 mL) and the resulting solution was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (2% Et_2O in petroleum ether 60:40) to afford alcohol **270** (1.77 g, 89%, dr > 99:1) as a colourless oil. Data consistent with previously reported.

((1*S*,2*S*,3*S*)-2-((*tert*-Butyldiphenylsiloxy)methyl)-3-methylcyclopropyl)methanol (403)

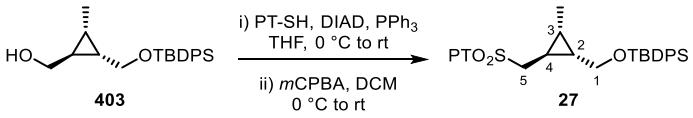


271 **403**

Aldehyde **271** (5.90 g, 16.74 mmol) was dissolved in DCM (170 mL) under nitrogen and cooled to -78 °C then 1 M DIBAL-H in hexanes (18.41 mL, 18.41 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour, cooled to 0 °C, then quenched with dropwise addition of aqueous saturated sodium potassium tartrate solution (75 mL). The reaction mixture was warmed to room temperature, diluted with water (75 mL) and DCM (50 mL) and stirred vigorously for 1 hour. The organic layer was separated and the aqueous extracted with DCM (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (45% Et_2O in petroleum ether 60:40) to afford alcohol **403** (5.83 g, 98%) as a colourless oil; $[\alpha]_D^{24}$ = +4.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3347, 3018, 2957, 2931, 2858, 1428, 1214; δ_H (400 MHz, $CDCl_3$) 0.66 (1H, m, 4-H), 0.79 – 0.89 (1H, m, 3-H), 0.97 (1H, dddd, *J* 9.1, 7.6, 6.8, 4.7, 2-H), 1.03 – 1.08 (12H, m, 3-CH_3 and $SiC(CH_3)_3$), 1.23 (1H, m, OH), 3.37 (1H, ddd, *J* 11.7, 7.1, 4.5, 5-*H*H), 3.50 (1H, ap. dt, *J* 11.7, 6.2, 5-H*H*), 3.66 (1H, dd, *J* 11.0, 7.6, 1-*H*H), 3.72 (1H, dd, *J* 11.0, 6.8, 1-H*H*), 7.34 – 7.45 (6H, m, 6 × ArH), 7.65 – 7.71 (4H, m, 4 × ArH); δ_C (101 MHz, $CDCl_3$) 12.9 (CH_3-3), 15.8 (C-3), 19.4 (Si*C*$(CH_3)_3$), 23.8 (C-2), 27.0 (SiC(*C*$H_3)_3$), 27.5 (C-4), 63.3 (C-1), 66.8 (C-5), 127.8 (2 × ArCH), 129.8 (2 × ArCH), 134.1 (ArC), 134.2 (ArC), 135.8 (2 × ArCH); HRMS (ESI) calc. for [$C_{22}H_{30}O_2Si$] 366.1907 Found 377.1911. Data consistent with the literature.[82]

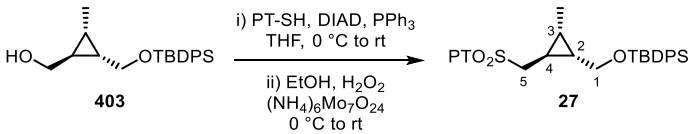
5-((((1*S*,2*R*,3*R*)-2-((*tert*-Butyldiphenylsiloxy)methyl)-3-methylcyclopropyl)methyl)sulfonyl)-1-phenyl-1H-tetrazole (27)

Method 1:



Alcohol **403** (5.31 g, 15.00 mmol), PT-SH (3.48 g, 19.50 mmol) and PPh_3 (5.11 g, 19.50 mmol) were dissolved in THF (150 mL) under nitrogen and cooled to 0 °C then DIAD (3.84 mL, 19.50 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 3 hours at room temperature then quenched with aqueous saturated NH_4Cl (150 mL). The resulting solution was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was filtered through a small plug of silica eluting with 50% Et_2O in petroleum ether 60:40 and the solvent removed *in vacuo*. The crude material was dissolved in DCM (75 mL) and cooled to 0 °C then *m*CPBA (70 wt.%, 12.94 g, 52.50 mmol) was added over 15 minutes. The reaction mixture was stirred at room temperature for 18 hours then quenched with aqueous saturated $Na_2S_2O_3$ (50 mL) and aqueous saturated $NaHCO_3$ (50 mL) then stirred vigorously for 1 hour. The resulting solution was diluted with water (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford sulfone **27** (7.34 g, 89%) as a yellow oil; $[\alpha]_D^{22}$ = +4.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3019, 2932, 2858, 1214; δ_H (400 MHz, $CDCl_3$) 0.76 – 0.84 (1H, m, 2-H or 4-H), 0.99 – 1.05 (1H, m, $SiC(CH_3)_3$ and 3-CH_3), 1.05 – 1.08 (1H, m, 3-H), 1.17 – 1.24 (1H, m, 2-H or 4-H), 3.52 – 3.61 (2H, m, 1-*H*H and 5-*H*H), 3.73 (1H, dd, *J* 6.3, 3.4, 1-H*H* or 5-H*H*), 3.77 (1H, d, *J* 6.3 1-H*H* or 5-H*H*), 7.34 – 7.44 (6H, m, ArH), 7.53 – 7.69 (9H, m, ArH); δ_C (101 MHz, $CDCl_3$) 12.4 (CH_3-3), 15.9 (C-2/4), 17.9 (C-3), 19.3 (Si*C*$(CH_3)_3$), 25.3 (C-2/4), 27.0 ($SiC(CH_3)_3$), 60.8 (C-1/5), 62.4 (C-1/5), 125.3 (2 × ArCH), 127.9 (2 × ArCH), 129.9 (2 × ArCH), 131.6 (ArCH), 133.2 (ArC), 133.8 (ArC), 133.8 (ArC), 135.7 (2 × ArCH), 153.9 (NCN); HRMS (ESI) calc. for $[C_{29}H_{34}N_4O_3SSiNa]$ 569.2019 Found 569.2018. Data consistent with the literature.[82]

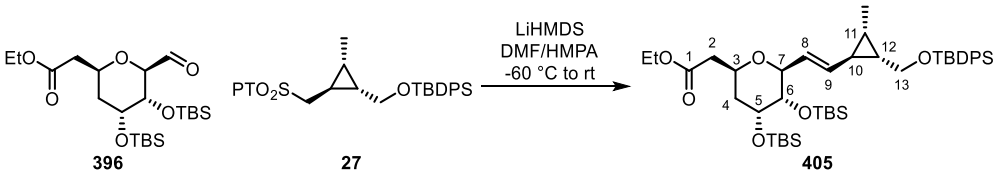
Method 2:



Alcohol **403** (250 mg, 0.71 mmol), PT-SH (164 mg, 0.92 mmol) and PPh_3 (241 mg, 0.92 mmol) were dissolved in THF (7 mL) under nitrogen and cooled to 0 °C then DIAD (0.18 mL, 0.92 mmol) was added

dropwise. The reaction mixture was stirred for 3 hours at room temperature then quenched with aqueous saturated NH_4Cl (20 mL). The resulting solution was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was filtered over a small plug of silica eluting with 50% Et_2O in petroleum ether 60:40 and the solvent removed *in vacuo*. The crude material was dissolved in EtOH (24 mL) and cooled to 0 °C then a premixed solution of molybdate (175 mg, 0.14 mmol) in a 30% aqueous solution of H_2O_2 (0.73 mL, 7.1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 hours then quenched with water (100 mL). The resulting solution was extracted with DCM (3 × 150 mL) and the combined organic layers dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (30% Et_2O in petroleum ether 60:40) to afford sulfone **27** (351 mg, 90%) as a colourless oil. Data consistent with previously reported.

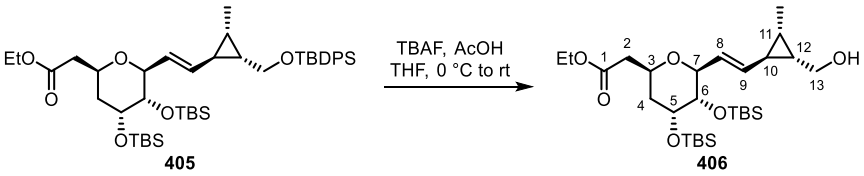
Ethyl 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-((*E*)-2-((1*S*,2*S*,3*S*)-2-((*tert*-butyldiphenylsiloxy)methyl)-3-methylcyclopropyl)vinyl)tetrahydro-2H-pyran-2-yl)acetate (405)



Sulfone **27** (5.28 g, 9.65 mmol) was dissolved in DMF (48 mL) and HMPA (12 mL) and cooled to -60 °C then 1 M LiHMDS in THF (9.65 mL, 9.65 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 5 minutes then aldehyde **396** (3.60 g, 7.82 mmol) in DMF (16 mL) and HMPA (4 mL) was added dropwise. The orange solution was stirred at -60 °C for 3 hours then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was quenched by dropwise addition of water (25 mL) then was diluted with water (75 mL), brine (100 mL) and Et_2O (250 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 250 mL). The combined organic layers were washed with brine (2 × 250 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford alkene **405** (4.28 g, 70%, *E*/*Z* > 95:5) as a colourless oil; $[\alpha]_D^{21}$ = -20.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2954, 2929, 2857, 1738, 1472, 1253, 1214; δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.88 – 0.90 (1H, m, 10-H), 0.91 (9H, s, $SiC(CH_3)_3$), 0.92 – 0.93 (1H, m, 11-H), 1.04 (9H, s, $SiC(CH_3)_3$), 1.08 (3H, d, *J* 6.2, 11-CH_3), 1.17 (1H, m, 12-H), 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.53 (1H, ddd, *J* 13.5, 11.6, 2.1, 4-H_{ax}), 1.82 (1H, ddd, *J* 13.5, 4.2, 2.1, 4-H_{eq}), 2.34 (1H, dd, *J* 14.8, 7.5, 2-*H*H), 2.61 (1H, dd, *J* 14.8, 6.1, 2-H*H*),

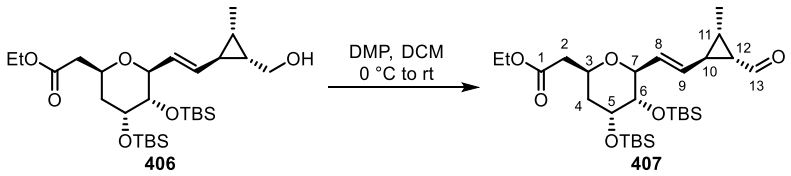
3.26 (1H, dd, *J* 9.1, 2.4, 6-H), 3.47 (1H, dd, *J* 11.0, 8.9, 13-*H*H), 3.88 (1H, dd, *J* 11.0, 5.4, 13-H*H*), 3.99 (1H, m, 5-H), 4.04 – 4.16 (3H, m, O*CH*$_2$CH$_3$ and 7-H), 4.24 (1H, m, 3-H), 5.22 (1H, dd, *J* 15.3, 8.6, 9-H), 5.33 (1H, dd, *J* 15.3, 7.3, 8-H), 7.34 – 7.45 (6H, m, 4 × ArH), 7.66 – 7.70 (4H, m, 4 × ArH); δ_C (101 MHz, $CDCl_3$) -4.4 ($SiCH_3$), -4.3 ($SiCH_3$), -4.2 ($SiCH_3$), -3.5 ($SiCH_3$), 12.7 (CH_3-11), 14.4 (OCH_2CH_3), 18.2 (Si*C*$(CH_3)_3$), 18.3 (Si*C*$(CH_3)_3$), 19.4 (Si*C*$(CH_3)_3$), 19.6 (C-11), 26.0 (SiC(*C*$H_3)_3$), 26.3 (SiC(*C*$H_3)_3$), 27.0 (SiC(*C*$H_3)_3$), 27.4 (C-12), 27.6 (C-10), 39.7 (C-4), 41.2 (C-2), 60.6 (OCH_2CH_3), 63.2 (C-13), 67.8 (C-3), 69.6 (C-5), 73.9 (C-6), 76.7 (C-7), 126.6 (C-8), 127.8 (2 × ArCH), 129.7 (2 × ArCH), 134.17 (2 × ArC), 135.8 (2 × ArCH), 137.1 (C-9), 171.2 (C-1); HRMS (ESI) calc. for [$C_{44}H_{72}O_6Si_3Na$] 803.4529 Found 803.4524.

Ethyl 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-((*E*)-2-((1*S*,2*S*,3*S*)-2-(hydroxymethyl)-3-methylcyclopropyl)vinyl)tetrahydro-2H-pyran-2-yl)acetate (406)



Silyl ether **405** (4.68 g, 6.00 mmol) was dissolved in THF (60 mL) under nitrogen and cooled to 0 °C then AcOH (0.343 mL, 6.00 mmol) and 1 M TBAF in THF (6.00 mL, 6.00 mmol) were added sequentially. The reaction mixture was stirred for 18 hours at room temperature then quenched with aqueous saturated $NaHCO_3$ (20 mL). The resulting solution was diluted with water (30 mL) and extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (50% Et_2O in petroleum ether 60:40) to afford alcohol **406** (2.63 mg, 81%) as a colourless oil; $[\alpha]_D^{21}$ = -38.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3441, 2953, 2929, 2885, 2857, 1738, 1472, 1252, 1115; δ_H (400 MHz, $CDCl_3$) 0.03 (6H, s, 2 × $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.88 (9H, s, SiC$(CH_3)_3$), 0.91 (9H, s, SiC$(CH_3)_3$), 0.95 – 1.02 (2H, m, 10-H and 11-H), 1.12 (3H, d, *J* 5.7, 11-CH_3), 1.15 – 1.20 (1H, m, 12-H), 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.43 (1H, s, OH), 1.53 (1H, ddd, *J* 13.4, 11.4, 1.9, 4-H_{ax}), 1.82 (1H, ddd, *J* 13.5, 4.2, 2.1, 4-H_{eq}), 2.34 (1H, dd, *J* 14.8, 7.5, 2-*H*H), 2.60 (1H, dd, *J* 14.8, 6.0, 2-H*H*), 3.27 (1H, dd, *J* 9.1, 2.4, 6-H), 3.51 (1H, dd, *J* 11.4, 8.6, 13-*H*H), 3.77 (1H, dd, *J* 11.4, 6.3, 13-H*H*), 3.97 – 4.02 (1H, m, 5-H), 4.05 – 4.16 (3H, m, O*CH*$_2$CH$_3$ and 7-H), 4.20 – 4.30 (1H, m, 3-H), 5.24 (1H, dd, *J* 15.3, 8.3, 9-H), 5.39 (1H, dd, *J* 15.3, 7.4, 8-H); δ_C (101 MHz, $CDCl_3$) -4.4 ($SiCH_3$), -4.3 ($SiCH_3$), -4.2 ($SiCH_3$), -3.4 ($SiCH_3$), 12.6 (CH_3-11), 14.4 (OCH_2CH_3), 18.26 (Si*C*$(CH_3)_3$), 18.32 (Si*C*$(CH_3)_3$), 19.4 (C-11), 26.0 (SiC(*C*$H_3)_3$), 26.3 (SiC(*C*$H_3)_3$), 27.6 (C-12), 28.0 (C-10), 39.6 (C-4), 41.1 (C-2), 60.6 (OCH_2CH_3), 62.3 (C-13), 67.8 (C-3), 69.5 (C-5), 74.0 (C-6), 76.6 (C-7), 127.1 (C-8), 136.6 (C-9), 171.1 (C-1); HRMS (ESI) calc. for [$C_{28}H_{54}O_6Si_2Na$] 565.3351 Found 565.3350.

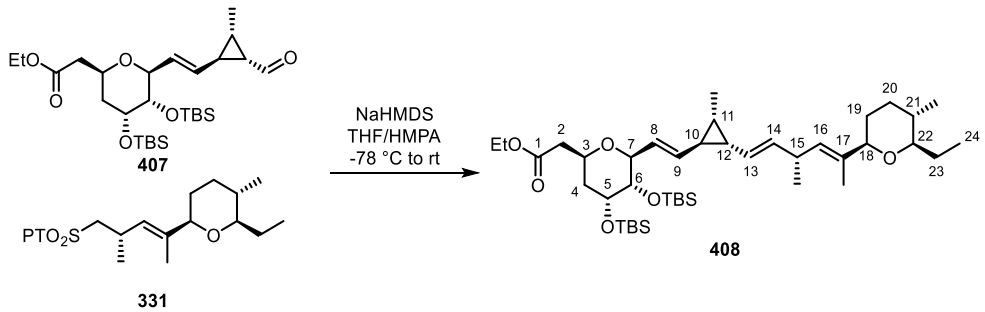
Ethyl 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-((*E*)-2-((1S,2S,3S)-2-formyl-3-methylcyclopropyl)vinyl)tetrahydro-2H-pyran-2-yl)acetate (407)



Alcohol **406** (2.60 g, 4.79 mmol) was dissolved in DCM (50 mL) under nitrogen and cooled to 0 °C, then DMP (2.64 g, 6.23 mmol) was added. The reaction mixture was stirred for 1 hour at room temperature then quenched with aqueous saturated $Na_2S_2O_3$ (30 mL) and aqueous saturated $NaHCO_3$ (30 mL) then stirred vigorously for 30 minutes. The aqueous phase was extracted with DCM (3 × 75 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2O in petroleum ether 60:40) to afford aldehyde **407** (2.33 g, 90%) as a white solid; $[\alpha]_D^{23}$ = -6.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2954, 2020, 2887, 2857, 1738, 1700, 1472; δ_H (400 MHz, $CDCl_3$) 0.02 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.27 (3H, d, *J* 6.4, 11-CH_3), 1.51 – 1.61 (2H, m, 4-H_{ax} and 11-H), 1.82 (1H, ddd, *J* 13.5, 4.1, 2.0, 4-H_{eq}), 1.96 (1H, ap. dt, *J* 9.1, 4.6, 12-H), 2.12 (1H, ddd, *J* 8.8, 6.4, 4.6, 10-H), 2.34 (1H, dd, *J* 14.9, 7.2, 2-*H*H), 2.58 (1H, dd, *J* 14.9, 6.4, 2-H*H*), 3.27 (1H, dd, *J* 9.1, 2.0, 6-H), 4.00 (1H, ap. dt, *J* 4.1, 2.0, 5-H), 4.07 – 4.17 (3H, m, O$CH_2$$CH_3$ and 7-H), 4.25 (1H, ap. dtd, *J* 11.4, 6.8, 2.0, 3-H), 5.25 (1H, ddd, *J* 15.3, 8.8, 1.1, 9-H), 5.58 (1H, dd, *J* 15.3, 7.0, 8-H), 9.47 (1H, d, *J* 4.6, 13-H); δ_C (101 MHz, $CDCl_3$) -4.4 ($SiCH_3$), -4.3 ($SiCH_3$), -4.2 ($SiCH_3$), -3.4 ($SiCH_3$), 12.7 (CH_3-11), 14.4 (OCH_2CH_3), 18.27 ($SiC(CH_3)_3$), 18.32 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 26.7 (C-11), 33.2 (C-10), 36.9 (C-12), 39.6 (C-4), 41.1 (C-2), 60.6 (OCH_2CH_3), 68.0 (C-3), 69.5 (C-5), 74.0 (C-6), 76.0 (C-7), 129.9 (C-8), 132.6 (C-9), 171.1 (C-1), 200.0 (C-13); HRMS (ESI) calc. for [$C_{28}H_{52}O_6Si_2$] 541.3375 Found 541.3369.

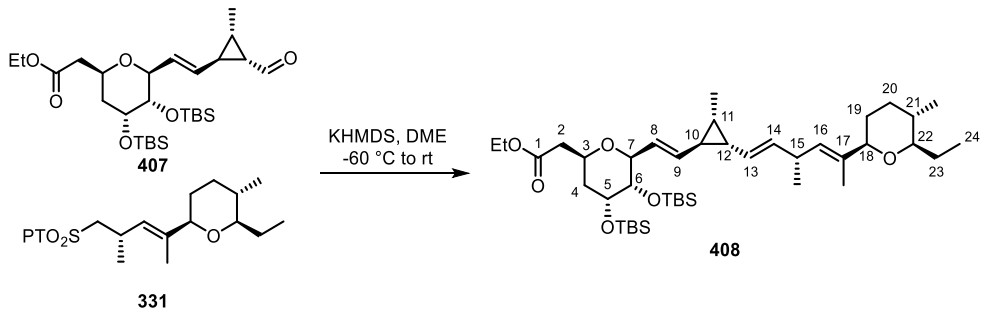
Ethyl 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-((*E*)-2-((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,5*S*,6*R*)-6-ethyl-5-methyltetrahydro-2H-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)vinyl)tetrahydro-2H-pyran-2-yl)acetate (408)

Method 1:



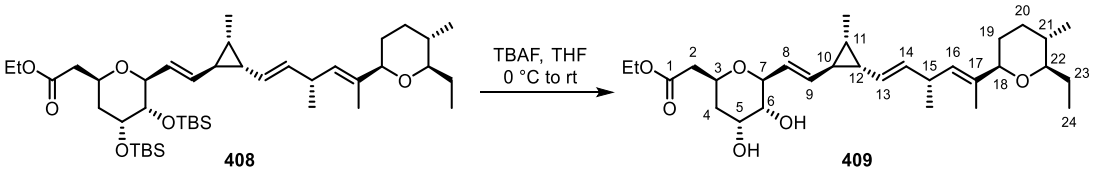
Sulfone **331** (20 mg, 0.048 mmol) was dissolved in THF (0.67 mL) and HMPA (0.13 mL) and cooled to -78 °C then 1 M NaHMDS in THF (0.06 mL, 0.06 mmol) was added dropwise over 1 minutes. The reaction mixture was stirred for 15 minutes then aldehyde **407** (32 mg, 0.06 mmol) in THF (0.28 mL) and HMPA (0.07 mL) were added dropwise sequentially. The orange solution was stirred at -78 °C for 2 hours then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was quenched with dropwise addition of water (1 mL) then was diluted with water (25 mL), brine (10 mL) and Et_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford alkene **408** (27 mg, 78%, *E*/*Z* = 3:1) as a colourless oil; $[\alpha]_D^{24}$ = -10.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2955, 2928, 2856, 1739, 1463, 1214; δ_H (500 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.80 (3H, d, *J* 6.6, 21-CH_3), 0.88 (9H, s, $SiC(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.94 (3H, t, *J* 7.4, 24-H_3), 1.00 – 1.04 (7H, m, 11-H, 11-CH_3 and 15-CH_3), 1.05 – 1.07 (1H, m, 10-H), 1.16 – 1.21 (1H, m, 20-*H*H), 1.24 (3H, t, *J* 7.3, OCH_2CH_3), 1.31 – 1.36 (1H, m, 21-H), 1.39 – 1.48 (3H, m, 12-H, 19-*H*H and 23-*H*H), 1.52 – 1.54 (1H, m, 4-H_{ax}), 1.59 – 1.61 (1H, m, 19-H*H*), 1.62 (3H, d, *J* 1.3, 17-CH_3), 1.68 – 1.72 (1H, m, 23-H*H*), 1.75 – 1.84 (2H, m, 4-H_{eq} and 20-H*H*), 2.33 (1H, dd, *J* 15.0, 7.7, 2-*H*H), 2.61 (1H, dd, *J* 15.0, 5.9, 2-H*H*), 2.90 (1H, ddd, *J* 9.9, 7.2, 2.9, 22-H), 2.98 – 3.08 (1H, m, 15-H), 3.27 (1H, dd, *J* 9.1, 2.4, 6-H), 3.61 (1H, d, *J* 10.8, 18-H), 3.98 – 4.01 (1H, m, 5-H), 4.07 – 4.15 (3H, m, O*CH*$_2$$CH_3$ and 7-H), 4.20 – 4.29 (1H, m, 3-H), 5.07 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.21 (1H, dt, *J* 8.8, 1.3, 16-H), 5.25 (1H, dd, *J* 15.4, 8.6, 9-H), 5.36 (dd, *J* 15.4, 7.5, 8-H), 5.42 (1H, dd, *J* 15.3, 6.5, 14-H); δ_C (126 MHz, $CDCl_3$) -4.4 ($SiCH_3$), -4.24 ($SiCH_3$), -4.20 ($SiCH_3$), -3.4 ($SiCH_3$), 9.5 (C-24), 13.0 (CH_3-17), 13.3 (CH_3-11), 14.4 (OCH_2CH_3), 18.0 (CH_3-21), 18.28 (Si*C*$(CH_3)_3$), 18.34 (Si*C*$(CH_3)_3$), 21.40 (CH_3-15), 21.44 (C-11) 26.1 ($SiC(CH_3)_3$ and C-23), 26.3 ($SiC(CH_3)_3$), 28.8 (C-12), 31.0 (C-10), 31.1 (C-19), 33.4 (C-20), 34.2 (C-21), 35.1 (C-15), 39.7 (C-4), 41.2 (C-2), 60.6 (OCH_2CH_3), 67.8 (C-3), 69.6 (C-5), 74.0 (C-6), 77.4 (C-7), 82.5 (C-18), 84.3 (C-22), 125.6 (C-13), 126.5 (C-8), 129.2 (C-16), 135.5 (C-9), 135.8 (C-17), 137.2 (C-9), 171.1 (C-1); HRMS (MALDI) calc. for [$C_{42}H_{76}O_6Si_2Na$] 755.5073 Found 755.5081.

Method 2:



Sulfone **331** (350 mg, 0.84 mmol) was dissolved in DME (7 mL) and cooled to -60 °C then 1 M KHMDS in THF (1.00 mL, 1.00 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred for 10 minutes then aldehyde **407** (543 mg, 1.00 mmol) in DME (4 mL) was added dropwise over 10 minutes. The deep red solution was stirred at -60 °C for 3 hours then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was quenched with dropwise addition of water (5 mL) then was diluted with water (30 mL), brine (40 mL) and Et_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford alkene **408** (244 mg, 40%, *E*/*Z* = 10:1) as a colourless oil. Data consistent with previously reported.

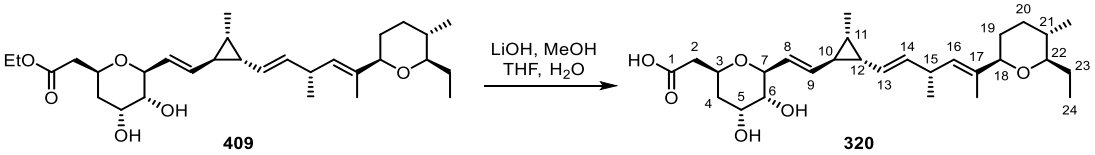
20,21-Dihydroambruticin F ethyl ester (409)



Silyl ether **408** (175 mg, 0.24 mmol, *E*/*Z* = 10:1) was dissolved in THF (2.50 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (1.20 mL, 1.20 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 hours and then quenched with aqueous saturated NH_4Cl (3 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (50% EtOAc in petroleum ether 60:40) to afford alcohol **409** (110 mg, 91%, *E*/*Z* = 10:1) as a colourless oil; $[\alpha]_D^{22}$ = +28.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3439, 2961, 2926, 2874, 1736; δ_H (600 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.5, 21-CH_3), 0.94 (3H, t, *J* 7.4, 24-H_3), 1.03 (3H, d, *J* 6.8, 15-CH_3), 1.04 – 1.06 (4H, m, 11-H and 11-CH_3), 1.09 – 1.14 (1H, m, 10-H), 1.18 – 1.21 (1H, m, 20-*H*H), 1.22 – 1.27 (3H, m, OCH_2CH_3), 1.31 – 1.37 (1H, m, 21-H), 1.39 – 1.47 (2H, m, 19-*H*H and 23-*H*H), 1.47 – 1.52 (1H, m, 12-H), 1.57 – 1.65 (5H, m, 17-CH_3, 19-H*H* and 4-H_{ax}), 1.67 – 1.71 (1H, m, 23-H*H*), 1.78 (1H, ap. dq, *J* 13.0, 3.6, 20-H*H*), 1.94 (1H, s, OH), 1.99 (1H, ddd, *J* 14.1, 3.6, 2.1, 4-H_{eq}), 2.37 (1H, dd, *J* 15.1, 5.9, 2-*H*H), 2.40 (1H, s, OH), 2.55 (1H, dd, *J* 15.1, 7.2, 2-H*H*), 2.90 (1H, ddd, *J* 9.9, 7.4, 2.9, 22-H), 3.05 (1H, m, 15-H), 3.32 (1H, dd, *J* 9.5, 3.1, 6-H), 3.60 (1H, d, *J* 11.3, 18-H), 3.95 (1H, dd, *J* 9.5, 6.8, 7-H), 4.10 – 4.19 (3H, m, O*CH*$_2$$CH_3$ and 5-H), 4.20 – 4.27 (1H, m, 3-H), 5.07 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.21 (1H, dt, *J* 8.8, 1.4, 16-H), 5.41 – 5.49 (3H, m, 8-H, 9-H and 14-H); δ_C (126 MHz, $CDCl_3$) 9.6 (C-24), 13.1 (CH_3-17), 13.2 (CH_3-11), 14.4 (OCH_2CH_3), 18.0 (CH_3-21), 21.4 (CH_3-15), 21.8 (C-11), 26.1 (C-23), 29.3 (C-12), 30.7 (C-10), 31.1 (C-19), 33.4 (C-20), 34.3 (C-21), 35.2 (C-15),

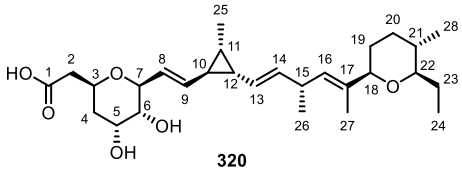
37.1 (C-4), 40.9 (C-2), 60.7 (O*C*H$_2$CH$_3$), 66.6 (C-5), 68.2 (C-3), 71.2 (C-6), 77.0 (C-7), 82.3 (C-18), 84.4 (C-22), 124.5 (C-8), 125.2 (C-13), 129.0 (C-16), 135.9 (C-17), 136.0 (C-14), 139.9 (C-9), 171.0 (C-1); HRMS (ESI) calc. for [$C_{30}H_{48}O_6$] 505.3524 Found 505.3527.

20,21-Dihydroambruticin F (320)



409 320

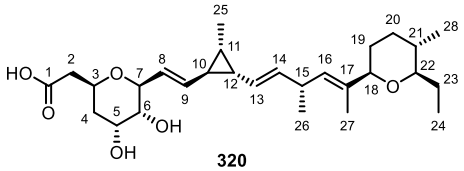
Ester **409** (30 mg, 0.06 mmol, *E*/*Z* = 10:1) was dissolved in THF (1 mL) and MeOH (0.1 mL) then a solution of LiOH (71 mg, 2.97 mmol) in water (0.4 mL) was added. The reaction mixture was stirred at room temperature for 3 hours then quenched with 1 M HCl (2 mL). The resulting solution was diluted with water (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% MeOH in DCM) to afford 20,21-dihydroambruticin F **320** (24 mg, 85%, *E*/*Z* = 10:1) as a colourless oil; $[\alpha]_D^{21}$ = +20.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3420, 2961, 2925, 2858, 1715, 1214; δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.5, 21-CH_3), 0.94 (3H, t, *J* 7.4, 24-H_3), 1.03 (3H, d, *J* 6.8, 15-CH_3), 1.04 – 1.07 (4H, m, 11-H and 11-CH_3), 1.09 – 1.16 (1H, m, 10-H), 1.17 – 1.23 (1H, m, 20-*H*H), 1.31 – 1.37 (1H, m, 21-H), 1.38 – 1.47 (2H, m, 19-*H*H and 23-*H*H), 1.48 – 1.54 (1H, m, 12-H), 1.56 – 1.61 (2H, m, 19-H*H* and 4-H_{ax}), 1.63 (3H, d, *J* 1.3, 17-CH_3), 1.67 – 1.73 (1H, m, 23-*H*H), 1.78 (1H, ap. dq, *J* 12.8, 3.5, 20-H*H*), 2.02 (1H, d, *J* 14.0, 4-H_{eq}), 2.44 (1H, dd, *J* 15.7, 5.8, 2-*H*H), 2.60 (1H, dd, *J* 15.7, 7.0, 2-H*H*), 2.91 (1H, ddd, *J* 10.0, 7.3, 3.1, 22-H), 2.98 – 3.11 (1H, m, 15-H), 3.33 (1H, dd, *J* 9.0, 3.0, 6-H), 3.60 (1H, d, *J* 10.9, 18-H), 3.98 (1H, dd, *J* 9.0, 7.1, 7-H), 4.18 (1H, m, 5-H), 4.22 (1H, m, 3-H), 5.07 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.21 (1H, dq, *J* 8.9, 1.3, 16-H), 5.40 – 5.52 (3H, m, 8-H, 9-H and 14-H); δ_C (126 MHz, $CDCl_3$) 9.6 (C-24), 13.18 (CH_3-17), 13.21 (CH_3-11), 17.9 (CH_3-21), 21.3 (CH_3-15), 21.8 (C-11), 26.0 (C-23), 29.3 (C-12), 30.6 (C-10), 31.0 (C-19), 33.4 (C-20), 34.3 (C-21), 35.2 (C-15), 37.0 (C-4), 40.4 (C-2), 66.6 (C-5), 68.0 (C-3), 71.2 (C-6), 77.1 (C-7), 82.3 (C-18), 84.4 (C-22), 124.1 (C-8), 125.1 (C-13), 129.0 (C-16), 135.8 (C-17), 136.1 (C-14), 140.1 (C-9), 174.7 (C-1); HRMS (MALDI) calc. for [$C_{28}H_{44}O_6Na$] 499.3030 Found 499.3036.



320

Position	Synthetic 20,21-dihydroambruticin F 400 MHz ($CDCl_3$): δ_H (multiplet, *J* (Hz))	Natural 20,21-dihydroambruticin F 500 MHz ($CDCl_3$): δ_H (multiplet, *J* (Hz))
28-H	0.80 (d, 6.5)	0.81 (d, 6.5)
24-H	0.94 (t, 7.4)	0.94 (t, 7.4)
26-H	1.03 (d, 6.8)	1.04 (d, 6.8)
11-H	1.04 – 1.07 (m)	1.05 – 1.07 (m)
25-H	1.04 – 1.07 (m)	1.05 – 1.07 (m)
10-H	1.09 – 1.16 (m)	1.10 – 1.15 (m)
20-*H*H	1.17 – 1.23 (m)	1.16 – 1.24 (m)
21-H	1.31 – 1.37 (m)	1.31 – 1.38 (m)
19-*H*H	1.38 – 1.47 (m)	1.40 – 1.46 (m)
23-*H*H	1.38 – 1.47 (m)	1.40 – 1.46 (m)
12-H	1.48 – 1.54 (m)	1.48 – 1.54 (m)
19-*H*H	1.56 – 1.61 (m)	1.56 – 1.61 (m)
4-*H*H	1.56 – 1.61 (m)	1.56 – 1.61 (m)
27-H	1.63 (d, 1.3)	1.63 (d, 1.4)
23-H*H*	1.67 – 1.73 (m)	1.70 (dqd, 14.9, 7.4, 3.0)
20-H*H*	1.78 (ap. dq, 12.8, 3.5)	1.79 (dq, 13.0, 3.5)
4-H*H*	2.02 (d, 14.0)	2.02 (d, 13.9)
2-*H*H	2.44 (dd, 15.7, 5.8)	2.45 (d, 15.1)
2-H*H*	2.60 (dd, 15.7, 7.0)	2.55 – 2.63 (m)
22-H	2.91 (ddd, 10.0, 7.3, 3.1)	2.90 (ddd, 10.0, 7.4, 3.0)
15-H	2.98 – 3.11 (m)	3.00 – 3.10 (m)
6-H	3.33 (dd, 9.5, 3.0)	3.33 (d, 9.3)
18-H	3.60 (d, 10.9)	3.61 (dd, 11.1, 2.0)
7-H	3.98 (dd, 9.0, 7.1)	3.99 (ap. t, 8.1)
5-H	4.18 (m)	4.17 (m)
3-H	4.22 (m)	4.21 (m)
13-H	5.07 (ddd, 15.3, 8.8, 1.4)	5.07 (dd, 15.1, 8.6)
16-H	5.21 (dq, 8.9, 1.3)	5.21 (d, 8.9)
8-H	5.40 – 5.52 (m)	5.39 – 5.51 (m)
9-H	5.40 – 5.52 (m)	5.39 – 5.51 (m)
14-H	5.40 – 5.52 (m)	5.39 – 5.51 (m)

Table 11. Comparison of ^{1}H-NMR data between synthetic and natural 20,21-dihydroambruticin F.



320

Position	Synthetic 20,21-dihydroambruticin F 126 MHz ($CDCl_3$): δ_C	Natural 20,21-dihydroambruticin F 126 MHz ($CDCl_3$): δ_C
C-24	9.6	9.6
C-27	13.18	13.19
C-25	13.21	13.23
C-28	17.9	18.0
C-26	21.3	21.3
C-11	21.8	21.8
C-23	26.0	26.0
C-12	29.3	29.3
C-10	30.6	30.6
C-19	31.0	31.0
C-20	33.4	33.4
C-21	34.3	34.3
C-15	35.2	35.2
C-4	37.0	37.0
C-2	40.4	40.5
C-5	66.6	66.6
C-3	68.0	68.0
C-6	71.2	71.2
C-7	77.1	77.1
C-18	82.3	82.3
C-22	84.4	84.4
C-8	124.1	124.2
C-13	125.1	125.1
C-16	129.0	129.0
C-17	135.8	135.8
C-14	136.1	136.0
C-9	140.1	140.1
C-1	174.7	174.7

Table 12. Comparison of ^{13}C-NMR data between synthetic and natural 20,21-dihydroambruticin F.

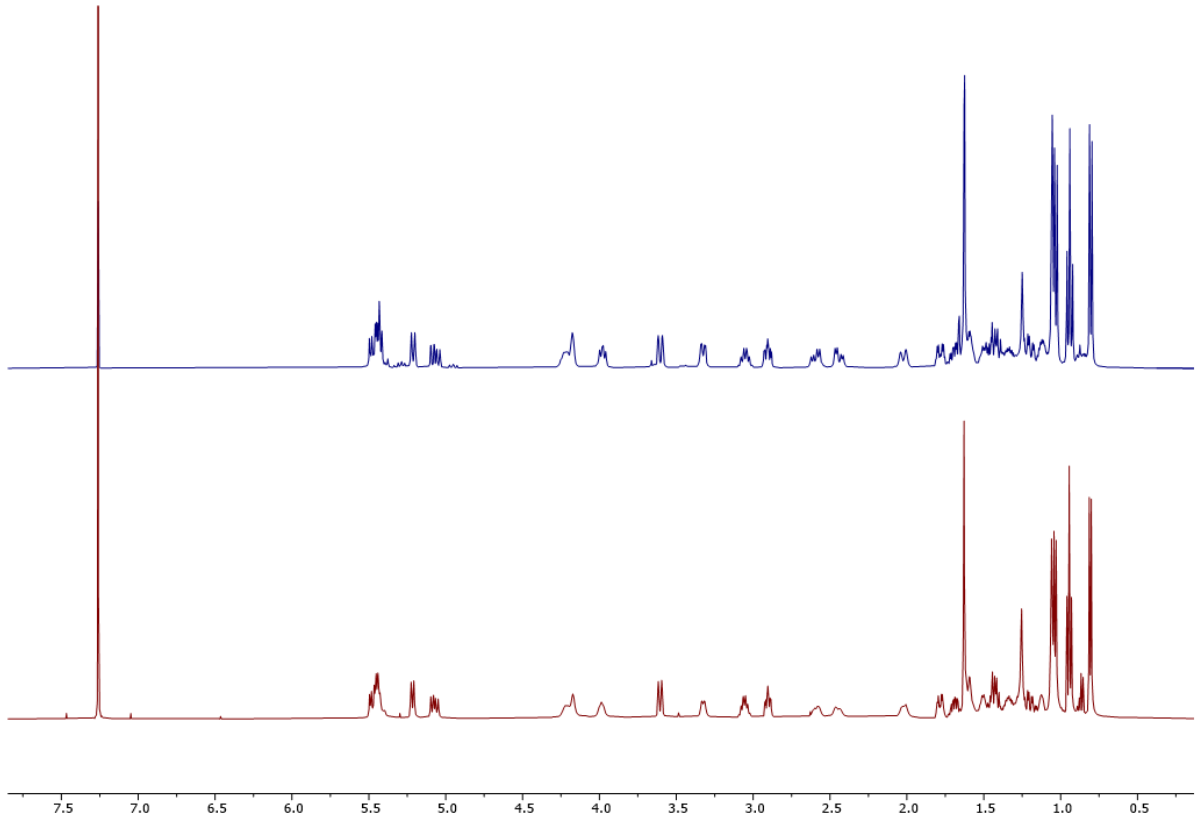


Figure 22. ^{1}H-NMR spectra of synthetic (blue) and natural (red) 20,21-dihydroambruticin F.

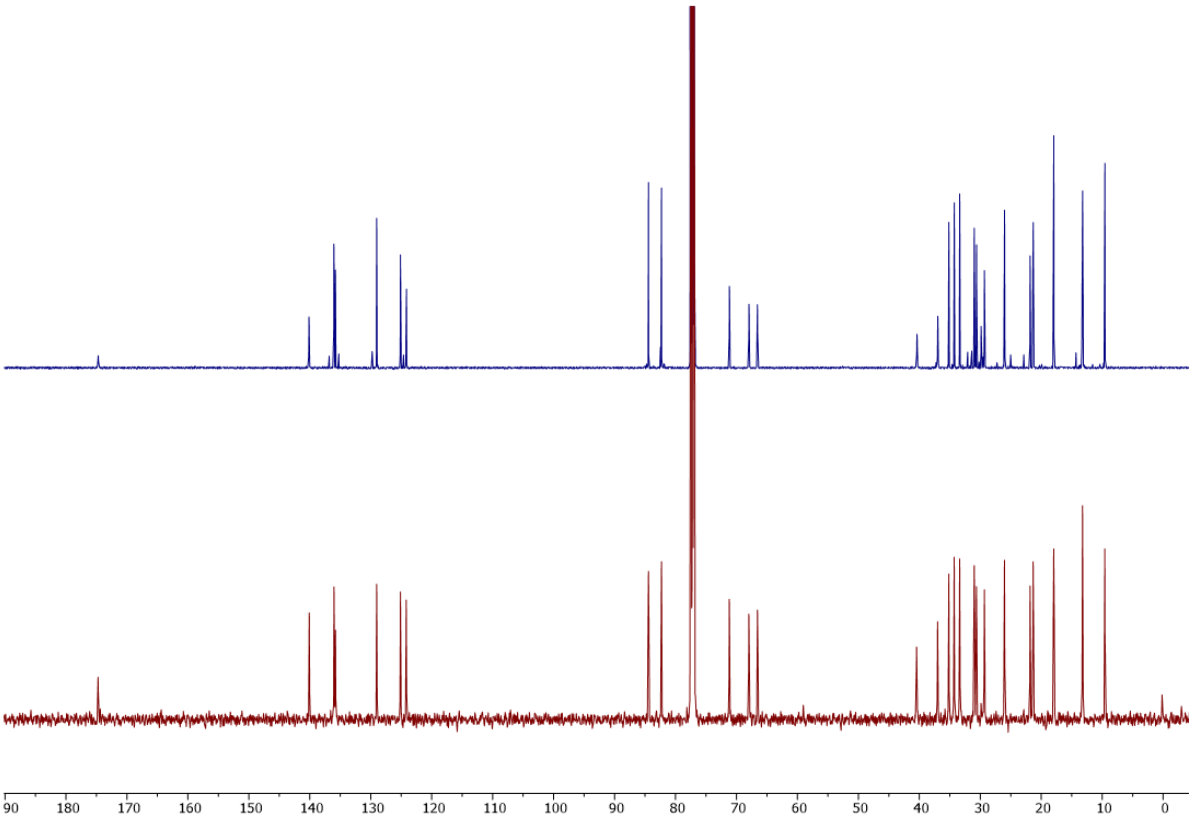
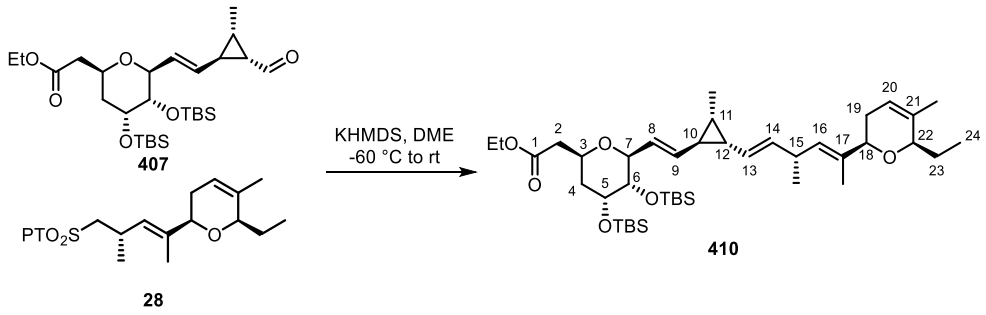


Figure 23. ^{13}C-NMR spectra of synthetic (blue) and natural (red) 20,21-dihydroambruticin F.

Ethyl 2-((2*S*,4*R*,5*S*,6*S*)-4,5-bis(*tert*-butyldimethylsiloxy)-6-((*E*)-2-((1*S*,2*S*,3*R*)-2-((*R*,1*E*,4*E*)-5-((2*R*,6*R*)-6-ethyl-5-methyl-3,6-dihydro-2H-pyran-2-yl)-3-methylhexa-1,4-dien-1-yl)-3-methylcyclopropyl)vinyl)tetrahydro-2H-pyran-2-yl)acetate (410)

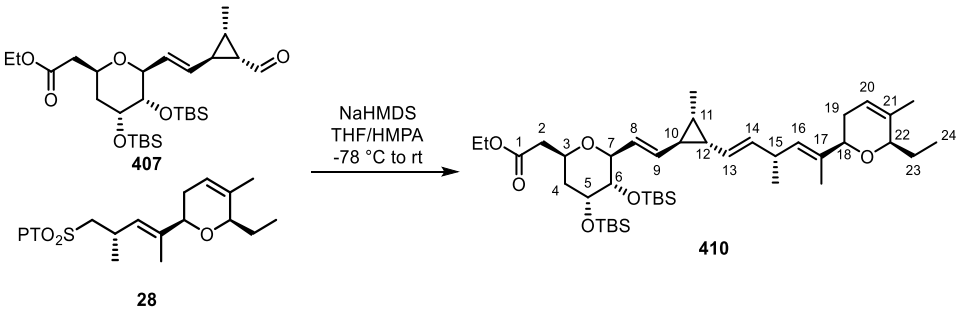
Method 1:



Sulfone **28** (551 mg, 1.32 mmol) was dissolved in DME (13 mL) and cooled to -60 °C then 1 M KHMDS in THF (1.98 mL, 1.98 mmol) was added dropwise over 8 minutes. The reaction mixture was stirred for 10 minutes then aldehyde **407** (1070 mg, 1.98 mmol) in DME (5 mL) was added dropwise over 10 minutes. The deep red solution was stirred at -60 °C for 3 hours then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was quenched with dropwise addition of water (10 mL) then was diluted with water (30 mL), brine (40 mL) and Et_2O (100 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford alkene **410** (367 mg, 38%, *E*/*Z* = 10:1) as a colourless oil; $[\alpha]_D^{27}$ = +14.0 (*c* 1, $CHCl_3$); ν_{max} (film) 2958, 2929, 2857, 1738, 1215; δ_H (400 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.86 – 0.89 (12H, m, $SiC(CH_3)_3$ and 24-H_3), 0.91 (9H, s, $SiC(CH_3)_3$), 0.96 – 1.01 (1H, m, 11-H), 1.02 – 1.03 (3H, m, 15-CH_3), 1.04 (3H, s, 11-CH_3), 1.05 – 1.08 (1H, m, 10-H), 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.46 (1H, ap. dt, *J* 8.5, 4.3, 12-H), 1.49 – 1.56 (2H, m, 4-H_{ax} and 23-H*H*), 1.57 – 1.60 (3H, m, 21-CH_3), 1.63 (3H, d, *J* 1.4, 17-CH_3), 1.73 – 1.88 (3H, m, 4-H_{eq}, 19-*H*H and 23-H*H*), 2.06 – 2.18 (1H, m, 19-H*H*), 2.33 (1H, dd, *J* 15.0, 7.7, 2-*H*H), 2.61 (1H, dd, *J* 15.0, 5.9, 2-H*H*), 3.05 (1H, ap. h, *J* 7.0, 15-H), 3.27 (1H, dd, *J* 9.1, 2.5, 6-H), 3.84 (1H, dd, *J* 10.7, 3.0, 18-H), 3.97 – 4.01 (1H, m, 5-H), 4.06 – 4.16 (4H, m, OCH_2CH_3, 7-H and 22-H), 4.20 – 4.29 (1H, m, 3-H), 5.07 (1H, ddd, *J* 15.2, 8.8, 1.3, 13-H), 5.20 – 5.28 (2H, m, 9-H and 16-H), 5.32 – 5.45 (2H, m, 8-H and 14-H), 5.54 – 5.59 (1H, m, 20-H); δ_C (101 MHz, $CDCl_3$) -4.4 ($SiCH_3$), -4.3 ($SiCH_3$), -4.2 ($SiCH_3$), -3.4 ($SiCH_3$), 8.3 (C-24), 12.2 (CH_3-17), 13.3 (CH_3-11), 14.4 (OCH_2CH_3), 18.27 ($SiC(CH_3)_3$), 18.32 ($SiC(CH_3)_3$), 19.2 (CH_3-21), 21.38 (CH_3-15), 21.43 (C-11), 25.8 (C-23), 26.0 ($SiC(CH_3)_3$), 26.3 ($SiC(CH_3)_3$), 28.8 (C-12), 30.3 (C-19), 31.1 (C-10), 35.2 (C-15), 39.6 (C-4), 41.2 (C-2), 60.6 (OCH_2CH_3), 67.8 (C-3), 69.6 (C-5), 74.0 (C-6), 76.8 (C-7), 77.9 (C-

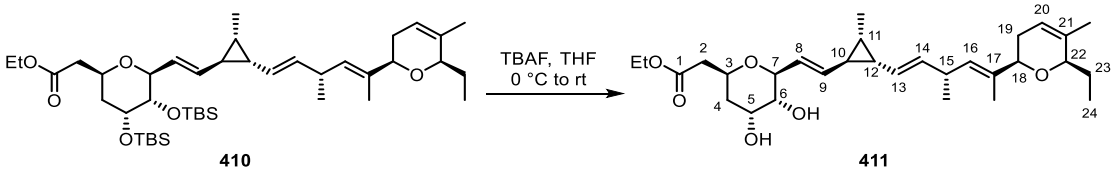
22), 78.4 (C-18), 121.2 (C-20), 125.7 (C-13), 126.5 (C-8), 130.0 (C-16), 135.2 (C-17 and C-21), 135.4 (C-14), 137.2 (C-9), 171.1 (C-1); HRMS (ESI) calc. for [$C_{42}H_{74}O_6Si_2Na$] 753.4916 Found 753.1919.

Method 2:



Sulfone **28** (25 mg, 0.06 mmol) was dissolved in THF (0.70 mL) and HMPA (0.18 mL) and cooled to -78 °C then 1 M NaHMDS in THF (0.08 mL, 0.08 mmol) was added dropwise over 1 minute. The reaction mixture was stirred for 15 minutes then aldehyde **407** (42 mg, 0.08 mmol) in THF (0.30 mL) and HMPA (0.08 mL) were added dropwise sequentially. The orange solution was stirred at -78 °C for 2 hours then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was quenched with dropwise addition of water (1 mL) then was diluted with water (25 mL), brine (10 mL) and Et_2O (40 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (8% Et_2O in petroleum ether 60:40) to afford alkene **410** (35 mg, 80%, *E*/*Z* = 3:1) as a colourless oil. Data consistent with previously reported.

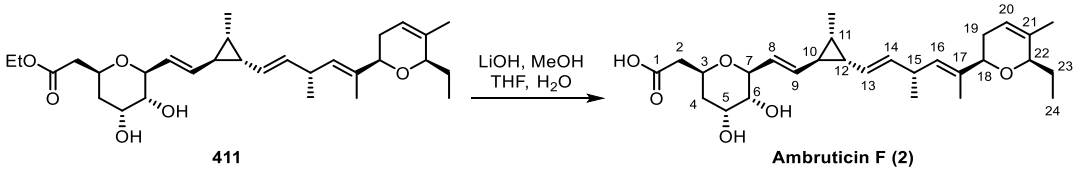
Ambruticin F ethyl ester (411)



Silyl ether **410** (367 mg, 0.50 mmol, *E*/*Z* = 10:1) was dissolved in THF (5 mL) under nitrogen and cooled to 0 °C then 1 M TBAF in THF (4.0 mL, 4.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 hours and then quenched with aqueous saturated NH_4Cl (10 mL) and water (40 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (50% EtOAc in petroleum ether 60:40) to afford diol **411** (206 mg, 82%, *E*/*Z* = 10:1) as a yellow oil; $[\alpha]_D^{22}$ = +54.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3438, 2963, 2923, 1735, 1214; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.02 – 1.07 (7H, m, 11-H, 11-CH_3

and 15-CH_3), 1.10 – 1.14 (1H, m, 10-H), 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 1.46 – 1.51 (1H, m, 12-H), 1.52 – 1.57 (1H, m, 23-*H*H), 1.59 (3H, ap. dq, *J* 2.4, 1.2, 21-CH_3), 1.60 – 1.62 (1H, m, 4-H_{ax}), 1.64 (3H, d, *J* 1.3, 17-CH_3), 1.77 (1H, m, 23-H*H*), 1.83 – 1.90 (1H, m, 19-*H*H), 1.94 – 2.01 (2H, m, 4-H_{eq} and OH), 2.08 – 2.16 (1H, m, 19-H*H*), 2.32 – 2.42 (2H, m, 2-*H*H and OH), 2.55 (1H, dd, *J* 15.2, 7.5, 2-H*H*), 3.06 (1H, dpd, *J* 8.2, 6.7, 1.4, 15-H), 3.31 (1H, dd, *J* 9.5, 3.1, 6-H), 3.84 (1H, dd, *J* 10.4, 2.7, 18-H), 3.95 (1H, dd, *J* 9.5, 6.6, 7-H), 4.07 – 4.11 (1H, m, 22-H), 4.13 (2H, ap. qd, *J* 7.1, 1.1, OCH_2CH_3), 4.16 – 4.18 (1H, m, 5-H), 4.23 (1H, dddd, *J* 11.7, 7.5, 6.1, 2.0, 3-H), 5.07 (1H, ddd, *J* 15.3, 8.7, 1.4, 13-H), 5.25 (1H, dq, *J* 8.9, 1.3, 16-H), 5.40 – 5.44 (2H, m, 8-H and 9-H), 5.44 – 5.48 (1H, m, 14-H), 5.53 – 5.59 (1H, m, 20-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.4 (CH_3-17), 13.2 (CH_3-11), 14.4 (OCH_2CH_3), 19.2 (CH_3-21), 21.3 (CH_3-15), 21.8 (C-11), 25.8 (C-23), 29.3 (C-12), 30.3 (C-19), 30.7 (C-10), 35.2 (C-15), 37.1 (C-4), 40.9 (C-2), 60.7 (OCH_2CH_3), 66.6 (C-5), 68.2 (C-3), 71.2 (C-6), 77.0 (C-7), 78.0 (C-22), 78.2 (C-18), 121.1 (C-20), 124.6 (C-8), 125.3 (C-13), 129.7 (C-16), 135.26 (C-21), 135.31 (C-17), 135.9 (C-14), 139.9 (C-9), 171.0 (C-1); HRMS (ESI) calc. for $[C_{30}H_{46}O_6]$ 503.3367 Found 503.3383.

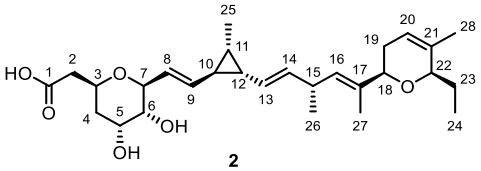
Ambruticin F (2)



Ester **411** (15.0 mg, 0.03 mmol, *E*/*Z* = 10:1) was dissolved in THF (0.8 mL) and MeOH (0.2 mL) then a solution of LiOH (36 mg, 1.50 mmol) in water (0.4 mL) was added. The reaction mixture was stirred at room temperature for 1 hour then quenched with 1 M HCl (2 mL). The resulting solution was diluted with water (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% MeOH in DCM) to afford ambruticin F (**2**) (12.7 mg, 87%, *E*/*Z* = 10:1) as a colourless oil; $[\alpha]_D^{23}$ = +50.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3411, 2962, 2925, 1714, 1214; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.02 – 1.07 (7H, m, 11-H, 11-CH_3 and 15-CH_3), 1.10 – 1.16 (1H, m, 10-H), 1.48 – 1.57 (2H, m, 12-H and 23-*H*H), 1.59 (3H, d, *J* 1.5, 21-CH_3), 1.60 – 1.62 (1H, m, 4-H_{ax}), 1.64 (3H, d, *J* 1.4, 17-CH_3), 1.77 (1H, dqd, *J* 14.2, 7.3, 3.7, 23-H*H*), 1.81 – 1.92 (1H, m, 19-*H*H), 1.97 – 2.06 (1H, m, 4-H_{eq}), 2.07 – 2.17 (1H, m, 19-H*H*), 2.46 (1H, dd, *J* 15.7, 5.6, 2-*H*H), 2.59 (1H, dd, *J* 15.7, 7.2, 2-H*H*), 3.02 – 3.13 (1H, m, 15-H), 3.33 (1H, dd, *J* 9.5, 3.0, 6-H), 3.84 (1H, dd, *J* 10.7, 3.1, 18-H), 3.99 (1H, dd, *J* 9.5, 7.0, 7-H), 4.07 – 4.15 (1H, m, 22-H), 4.18 (1H, ap. q, *J* 3.0, 5-H), 4.20 – 4.28 (1H, m, 3-H), 5.07 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.25 (1H, dq, *J* 8.9, 1.4, 16-H), 5.41 – 5.50 (3H, m, 8-H, 9-H and 14-H), 5.57 (1H, dq, *J* 6.4, 1.5, 20-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.5 (CH_3-17), 13.2 (CH_3-11), 19.2 (CH_3-21), 21.3 (CH_3-15), 21.9 (C-11), 25.8 (C-23), 29.4 (C-12), 30.3 (C-19), 30.6 (C-10), 35.2 (C-15), 36.9

(C-4), 40.3 (C-2), 66.5 (C-5), 68.0 (C-3), 71.1 (C-6), 77.2 (C-7), 78.1 (C-22), 78.2 (C-18), 121.1 (C-20), 124.1 (C-8), 125.2 (C-13), 129.7 (C-16), 135.2 (C-21), 135.3 (C-17), 136.0 (C-14), 140.4 (C-9), 174.3 (C-1); HRMS (ESI) calc. for [$C_{28}H_{42}O_6Na$] 497.2874 Found 497.2970.

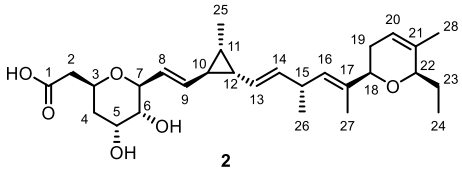
δ_H (600 MHz, MeOD) δ 0.91 (3H, ap. t, *J* 7.3, 24-H_3), 1.06 (3H, d, *J* 6.9, 15-CH_3), 1.07 (4H, m, 11-H and 11-CH_3), 1.13 (1H, m, 10-H), 1.48 (1H, m, 12-H), 1.52 – 1.57 (1H, m, 23-*H*H), 1.57 – 1.60 (1H, m, 4-H_{ax}), 1.60 – 1.63 (3H, m, 21-CH_3), 1.66 (3H, d, *J* 1.4, 17-CH_3), 1.78 (1H, dqd, *J* 14.8, 7.3, 3.6, 23-H*H*), 1.85 – 1.90 (1H, m, 19-*H*H), 1.92 (1H, ddd, *J* 13.9, 3.5, 2.1, 4-H_{eq}), 2.09 – 2.16 (1H, m, 19-H*H*), 2.37 (1H, dd, *J* 15.2, 5.4, 2-*H*H), 2.44 (1H, dd, *J* 15.2, 7.9, 2-H*H*), 3.07 – 3.14 (1H, m, 15-H), 3.22 (1H, dd, *J* 9.7, 3.5, 6-H), 3.85 (1H, dd, *J* 10.8, 3.0, 18-H), 3.99 (1H, dd, *J* 9.7, 6.5, 7-H), 4.04 (1H, ap. q, *J* 3.5, 5-H), 4.10 (1H, m, 22-H), 4.19 – 4.26 (1H, m, 3-H), 5.17 (1H, ddd, *J* 15.3, 8.7, 1.3, 13-H), 5.27 (1H, dq, *J* 9.0, 1.4, 16-H), 5.40 (1H, dd, *J* 15.4, 8.6, 9-H), 5.47 (1H, dd, *J* 15.3, 6.6, 14-H), 5.50 (1H, dd, *J* 15.4, 6.5, 8-H), 5.59 – 5.62 (1H, m, 20-H); δ_C (151 MHz, $CDCl_3$) 8.7 (C-24), 12.6 (CH_3-17), 13.4 (CH_3-11), 19.1 (CH_3-21), 21.7 (CH_3-15), 22.3 (C-11), 26.6 (C-23), 29.8 (C-12), 31.1 (C-19), 31.8 (C-10), 36.3 (C-15), 39.2 (C-4), 41.8 (C-2), 68.5 (C-5), 69.4 (C-3), 73.0 (C-6), 77.4 (C-7), 79.5 (C-18), 79.6 (C-22), 122.1 (C-20), 126.9 (C-8), 127.0 (C-13), 131.0 (C-16), 136.1 (C-21), 136.21 (C-14), 136.22 (C-17), 137.9 (C-9), 175.2 (C-1).



2

Position	Synthetic Ambruticin F 600 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))	Natural Ambruticin F 500 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))
24-H	0.91 (ap. t, 7.3)	0.90 (ap. t, 7.3)
26-H	1.06 (d. 6.9)	1.05 (d, 6.9)
11-H	1.07 (m)	1.07 (m)
25-H	1.07 (m)	1.07 (m)
10-H	1.13 (m)	1.12 (ddd, 8.6, 6.4, 3.2)
12-H	1.48 (m)	1.47 (m)
23-*H*H	1.52 – 1.57 (m)	1.51 – 1.55 (m)
4-*H*H	1.57 – 1.60 (m)	1.55 – 1.59 (m)
28-H	1.60 – 1.63 (m)	1.60 (ap. dq, 2.4, 1.2)
27-H	1.66 (d, 1.4)	1.65 (d, 1.4)
23-H*H*	1.78 (dqd, 14.8, 7.3, 3.6)	1.77 (dqd, 14.8, 7.3, 3.6)
19-*H*H	1.85 – 1.90 (m)	1.84 – 1.89 (m)
4-*H*H	1.92 (ddd, 13.8, 3.5, 2.1)	1.91 (ddd, 14.0, 3.5, 1.9)
19-H*H*	2.09 – 2.16 (m)	2.07 – 2.17 (m)
2-*H*H	2.37 (dd, 15.2, 5.4)	2.35 (dd, 15.2, 5.4)
2-H*H*	2.44 (dd, 15.2, 7.9)	2.43 (dd, 15.2, 7.8)
15-H	3.07 – 3.14 (m)	3.05 – 3.15 (m)
6-H	3.22 (dd, 9.7, 3.5)	3.21 (dd, 9.7, 3.5)
18-H	3.85 (dd, 10.8, 3.0)	3.84 (dd, 10.7, 3.0)
7-H	3.99 (dd, 9.7, 6.5)	3.98 (dd, 9.7, 6.6)
5-H	4.04 (ap. q, 3.5)	4.04 (ap. q, 3.5)
22-H	4.10 (m)	4.10 (m)
3-H	4.19 – 4.26 (m)	4.16 – 4.25 (m)
13-H	5.17 (ddd, 15.3, 8.7, 1.3)	5.17 (ddd, 15.3, 8.8, 1.3)
16-H	5.27 (dq, 9.0, 1.4)	5.26 (dq, 9.1, 1.4)
9-H	5.40 (dd, 15.4, 8.6)	5.39 (dd, 15.4, 8.6)
14-H	5.47 (dd, 15.3, 6.6)	5.46 (dd, 15.3, 6.9)
8-H	5.50 (dd, 15.4, 6.5)	5.49 (dd, 15.4, 6.6)
20-H	5.59 – 5.62 (m)	5.56 – 5.61 (m)

Table 13. Comparison of ^{1}H-NMR data between synthetic and natural ambruticin F.



2

Position	Synthetic Ambruticin F 151 MHz (CD_3OD): δ_C	Natural Ambruticin F 126 MHz (CD_3OD): δ_C
C-24	8.7	8.7
C-27	12.6	12.6
C-25	13.4	13.4
C-28	19.1	19.1
C-26	21.7	21.7
C-11	22.3	22.3
C-23	26.6	26.6
C-12	29.8	29.8
C-19	31.1	31.1
C-10	31.8	31.8
C-15	36.3	36.3
C-4	39.2	39.2
C-2	41.8	42.1
C-5	68.5	68.5
C-3	69.4	69.5
C-6	73.0	73.0
C-7	77.4	77.4
C-18	79.5	79.5
C-22	79.6	79.6
C-20	122.1	122.1
C-8	126.9	126.9
C-13	127.0	127.0
C-16	131.0	131.0
C-21	136.1	136.0
C-17	136.21	136.20
C-14	136.22	136.22
C-9	137.9	138.0
C-1	175.2	175.3

Table 14. Comparison of ^{13}C-NMR data between synthetic and natural ambruticin F.

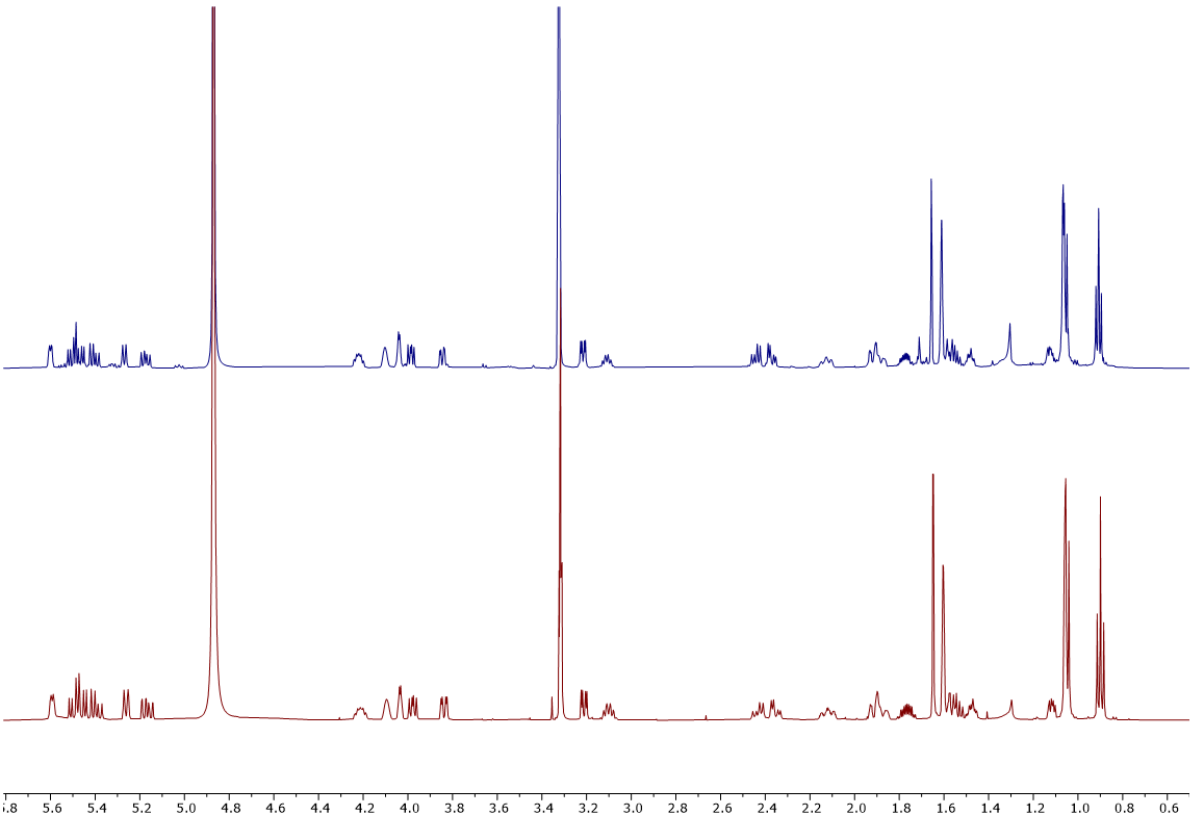


Figure 24. ^{1}H-NMR spectra of synthetic ambruticin F (blue) and natural ambruticin F (red).

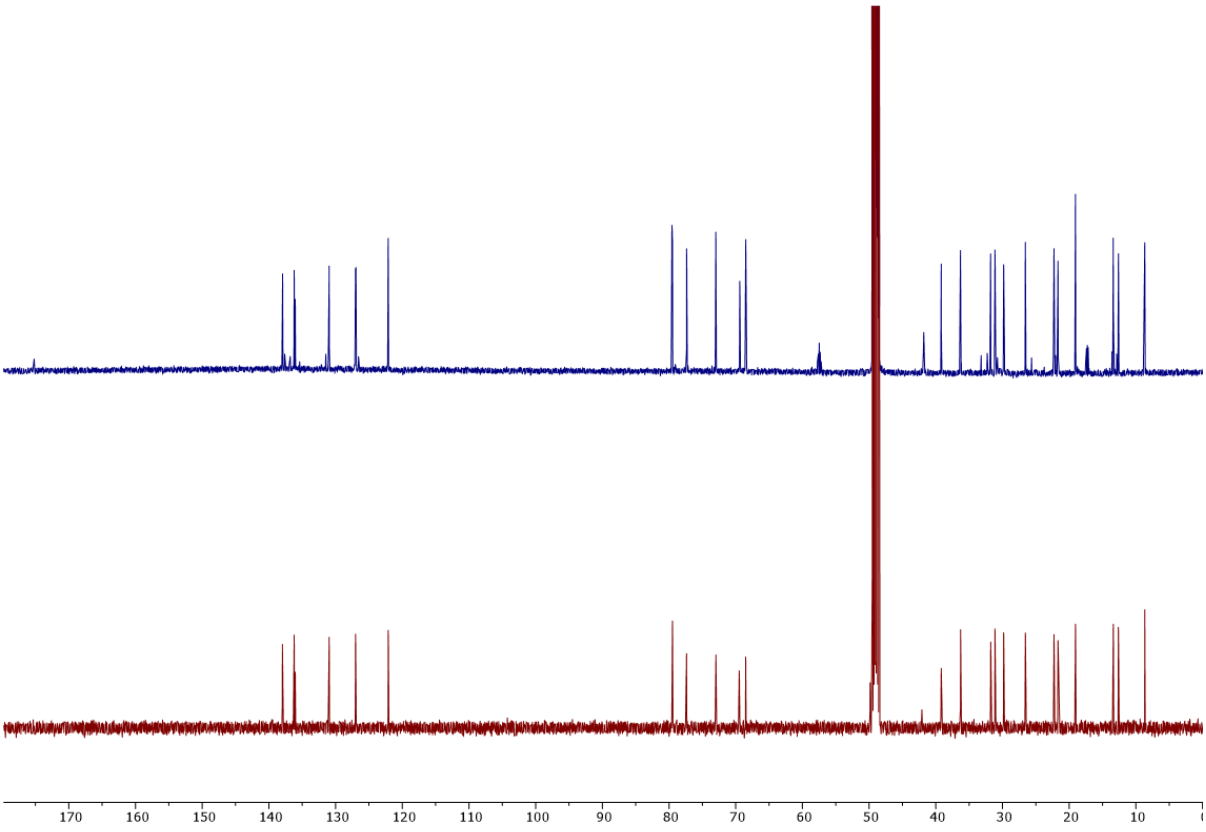
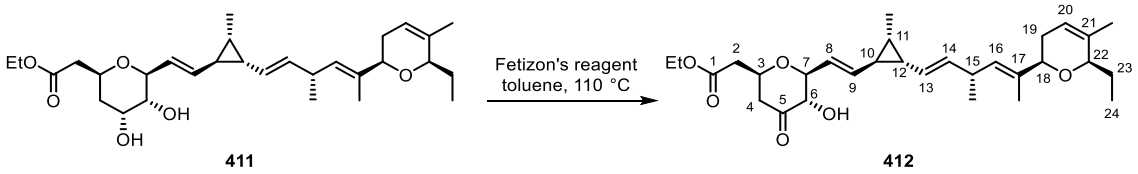


Figure 25. ^{13}C-NMR spectra of synthetic ambruticin F (blue) and natural ambruticin F (red).

5-Ketoambruticin F ethyl ester (412)

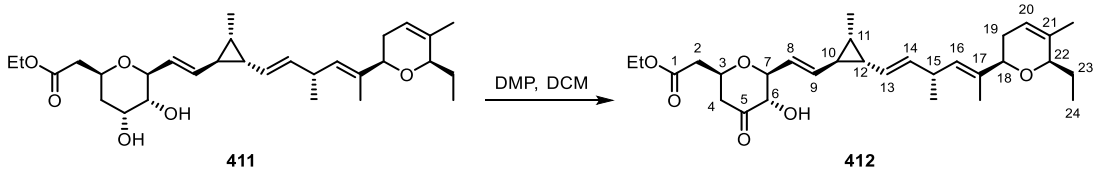
Method 1:



411 412

Diol **411** (99 mg, 0.20 mmol) was dissolved in toluene (40 mL) under nitrogen and Fetizon's reagent (~ 50 wt.% Ag_2CO_3 on Celite, 1000 mg) was added. The reaction mixture was heated at 110 °C with vigorous stirring for 2 hours by which time the reaction mixture had turned black. Further Fetizon's reagent (1000 mg) was added and the reaction mixture was stirred for a further 2 hours. Further Fetizon's reagent (1000 mg) was added and the reaction mixture was heated at 110 °C for 2 hours. The reaction mixture was filtered over Celite and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (25% EtOAc in petroleum ether 60:40) to afford ketone **412** (53 mg, 54%, *E*/*Z* = 10:1) as a colourless oil; $[\alpha]_D^{25}$ = +48.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3486, 2963, 2929, 2876, 1725, 1214; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.01 – 1.09 (7H, m, 11-H, 11-CH_3 and 15-CH_3), 1.16 (1H, ap. dt, *J* 9.0, 4.4, 10-H), 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.46 – 1.55 (2H, m, 12-H and 23-*H*H), 1.59 (3H, ap. dq, *J* 2.6, 1.3, 21-CH_3), 1.64 (3H, d, *J* 1.3, 17-CH_3), 1.77 (1H, dqd, *J* 14.2, 7.3, 3.6, 23-H*H*), 1.83 – 1.89 (1H, m, 19-*H*H), 2.08 – 2.17 (1H, m, 19-H*H*), 2.52 – 2.61 (2H, m, 2-*H*H and 4-H_{ax}), 2.71 (1H, dd, *J* 13.7, 2.4, 4-H_{eq}), 2.76 (1H, dd, *J* 15.6, 6.6, 2-H*H*), 3.03 – 3.12 (1H, m, 15-H), 3.54 (1H, d, *J* 3.7, 6-OH), 3.70 (1H, ddd, *J* 9.6, 6.4, 1.0, 7-H), 3.85 (1H, dd, *J* 10.5, 3.0, 18-H), 3.93 (1H, ddd, *J* 9.6, 3.7, 1.5, 6-H), 4.05 – 4.12 (2H, m, 3-H and 22-H), 4.16 (2H, q, *J* 7.1, OCH_2CH_3), 5.08 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.25 (1H, dq, *J* 8.8, 1.3, 16-H), 5.39 – 5.50 (2H, m, 9-H and 14-H), 5.55 – 5.59 (1H, m, 20-H), 5.61 (1H, dd, *J* 15.3, 6.4, 8-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.4 (CH_3-17), 13.2 (CH_3-11), 14.4 (OCH_2CH_3), 19.2 (CH_3-21), 21.4 (CH_3-15), 21.7 (C-11), 25.8 (C-23), 29.2 (C-12), 30.4 (C-19), 30.8 (C-10), 35.2 (C-15), 41.1 (C-2), 45.8 (C-4), 61.1 (OCH_2CH_3), 73.9 (C-3), 77.0 (C-6), 78.0 (C-22), 78.2 (C-18), 83.1 (C-7), 121.1 (C-20), 123.7 (C-8), 125.4 (C-13), 129.8 (C-16), 135.28 (C-21), 135.30 (C-17), 135.8 (C-14), 138.7 (C-9), 170.0 (C-1), 206.4 (C-5); HRMS (ESI) calc. for [$C_{30}H_{44}O_6Na$] 523.3030 Found 523.3026.

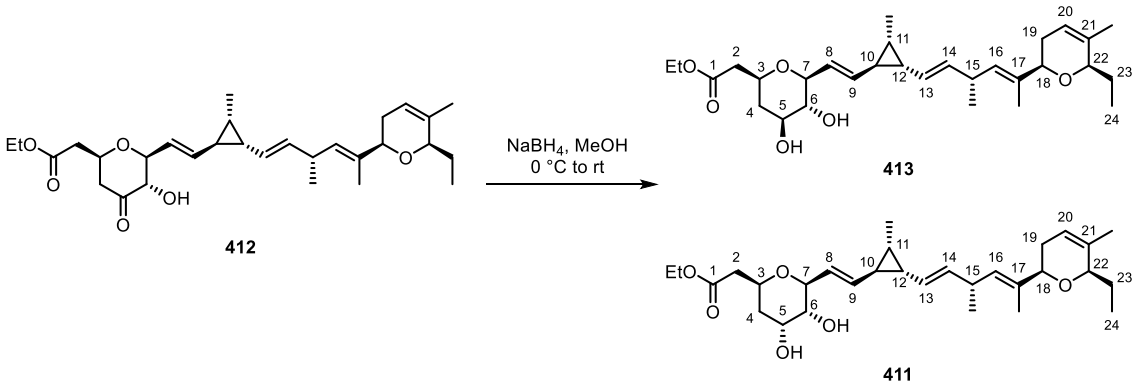
Method 2:



411 412

Diol **411** (10.0 mg, 0.02 mmol) was dissolved in DCM (0.4 mL, non-anhydrous) under nitrogen then DMP (12.7 mg, 0.03 mmol) was added. The reaction mixture was stirred at room temperature for 4 hours, quenched with aqueous saturated $NaHCO_3$ (5 mL) then washed with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (25% EtOAc in petroleum ether 60:40) to afford ketone **412** (3.3 mg, 33%, *E*/*Z* = 10:1) as a colourless oil. Data consistent with previously reported.

Ambruticin S ethyl ester (413)

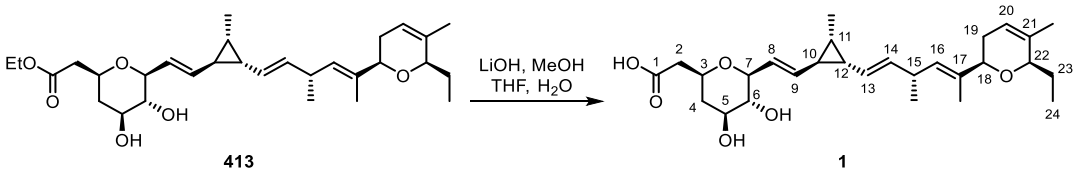


Ketone **412** (25 mg, 0.05 mmol) was dissolved in MeOH (5 mL) under nitrogen and cooled to 0 °C then $NaBH_4$ (19 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours then quenched with aqueous saturated NH_4Cl (30 mL). The resulting solution was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2OS_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (60% EtOAc in petroleum ether 60:40) to afford 1,2-*anti*-diol **413** (11.8 mg, 47%, *E*/*Z* = 10:1) and 1,2-*syn*-diol **411** (8.8 mg, 35%, *E*/*Z* = 10:1) as colourless oils. Data for 1,2-*syn*-diol **411** consistent with previously reported.

1,2-*anti*-diol **413**: $[\alpha]_D^{24}$ = +66.0 (*c* 1, $CHCl_3$); ν_{max} (film) 3395, 2962, 2925, 2872, 1736, 1214; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.01 – 1.08 (7H, m, 11-H, 11-CH_3 and 15-CH_3), 1.10 – 1.16 (1H, m, 10-H), 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.42 – 1.50 (2H, m, 4-H_{ax} and 12-H), 1.52 – 1.57 (1H, m, 23-*H*H), 1.58 – 1.60 (3H, m, 21-CH_3), 1.64 (3H, d, *J* 1.3, 17-CH_3), 1.77 (1H, dqd, *J* 14.3, 7.3, 3.7, 23-H*H*), 1.86 (1H, dddq, *J* 16.6, 6.5, 3.0, 1.4, 19-*H*H), 2.02 (1H, s, OH), 2.06 – 2.13 (2H, m, 4-H_{eq} and 19-H*H*), 2.39 – 2.48 (2H, m, OH and 2-*H*H), 2.63 (1H, dd, *J* 15.5, 6.5, 2-H*H*), 3.03 – 3.10 (1H, m, 15-H), 3.13 (1H, ap. t, *J* 9.0, 6-H), 3.53 (1H, ddd, *J* 9.0, 4.6, 2.2, 7-H), 3.66 – 3.73 (1H, m, 5-H), 3.84 (1H, dd, *J* 10.6, 3.0, 18-H), 3.91 (1H, ap. dtd, *J* 11.5, 6.5, 1.9, 3-H), 4.07 – 4.11 (1H, m, 22-H), 4.14 (2H, q, *J* 7.1, O*CH*$_2$CH$_3$), 5.07 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.25 (1H, dq, *J* 8.9, 1.3, 16-H), 5.39 – 5.49 (3H, m, 8-H, 9-H and 14-H), 5.57 (1H,

dq, *J* 6.5, 1.7, 20-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.4 (CH_3-17), 13.2 (CH_3-11), 14.4 (OCH_2CH_3), 19.2 (CH_3-21), 21.3 (CH_3-15), 21.8 (C-11), 25.8 (C-23), 29.3 (C-12), 30.4 (C-19), 30.7 (C-10), 35.2 (C-15), 38.3 (C-4), 40.9 (C-2), 60.8 (OCH_2CH_3), 72.0 (C-3), 72.4 (C-5), 75.9 (C-6), 78.0 (C-22), 78.2 (C-18), 80.9 (C-7), 121.1 (C-20), 123.8 (C-8), 125.2 (C-13), 129.7 (C-16), 135.27 (C-21), 135.32 (C-17), 135.9 (C-14), 139.9 (C-9), 170.9 (C-1); HRMS (ESI) calc. for $[C_{30}H_{46}O_6Na]$ 525.3187 Found 525.3182.

Ambruticin S (1)

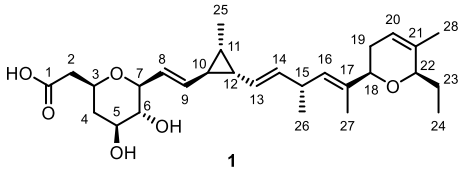


413 1

Ester **413** (10.0 mg, 0.02 mmol, *E*/*Z* = 10:1) was dissolved in THF (0.8 mL) and MeOH (0.2 mL) then a solution of LiOH (24 mg, 1.00 mmol) in water (0.4 mL) was added. The reaction mixture was stirred at room temperature for 1 hour then quenched with 1 M HCl (2 mL). The resulting solution was diluted with water (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (10% MeOH in DCM) to afford ambruticin S (**1**) (7.7 mg, 81%, *E*/*Z* = 10:1) as a colourless oil; $[\alpha]_D^{21}$ = +64.0 (*c* 0.5, $CHCl_3$), lit.[81] $[\alpha]_D^{23}$ = +58.0 (*c* 0.1, $CHCl_3$); ν_{max} (film) 3398, 2960, 2926, 1715, 1064; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.02 – 1.08 (7H, m, 11-H, 11-CH_3 and 15-CH_3), 1.10 – 1.16 (1H, m, 10-H), 1.44 – 1.49 (1H, m, 4-H_{ax}), 1.49 – 1.53 (1H, m, 12-H), 1.53 – 1.57 (1H, m, 23-*H*H), 1.59 (3H, dd, *J* 2.5, 1.3, 21-CH_3), 1.64 (3H, d, *J* 1.4, 17-CH_3), 1.77 (1H, dqd, *J* 14.2, 7.3, 3.7, 23-H*H*), 1.86 (1H, m, 19-H*H*), 2.07 – 2.16 (2H, m, 4-H_{eq} and 19-H*H*), 2.51 (1H, dd, *J* 16.1, 5.9, 2-*H*H), 2.67 (1H, dd, *J* 16.1, 7.1, 2-H*H*), 3.03 – 3.12 (1H, m, 15-H), 3.15 (1H, ap. t, *J* 8.9, 6-H), 3.52 – 3.61 (1H, m, 7-H), 3.67 – 3.75 (1H, m, 5-H), 3.85 (1H, dd, *J* 10.7, 3.0, 18-H), 3.87 – 3.93 (1H, m, 3-H), 4.07 – 4.12 (1H, m, 22-H), 5.07 (1H, ddd, *J* 15.3, 8.8, 1.4, 13-H), 5.25 (1H, dq, *J* 8.9, 1.4, 16-H), 5.40 – 5.52 (3H, m, 8-H, 9-H and 14-H), 5.56 – 5.58 (1H, m, 20-H); δ_C (126 MHz, $CDCl_3$) 8.4 (C-24), 12.5 (CH_3-17), 13.2 (CH_3-11), 19.2 (CH_3-21), 21.3 (CH_3-15), 21.8 (C-11), 25.8 (C-23), 29.3 (C-12), 30.3 (C-19), 30.7 (C-10), 35.2 (C-15), 38.2 (C-4), 40.3 (C-2), 71.7 (C-3), 72.1 (C-5), 75.8 (C-6), 78.1 (C-22), 78.2 (C-18), 81.1 (C-7), 121.1 (C-20), 123.5 (C-8), 125.2 (C-13), 129.7 (C-16), 135.26 (C-21), 135.32 (C-17), 136.0 (C-14), 140.2 (C-9), 174.0 (C-1); HRMS (MALDI) calc. for $[C_{28}H_{42}O_6Na]$ 497.2874 Found 497.2869.

δ_H (500 MHz, CD_3OD) 0.89 (3H, t, *J* 7.3, 24-H_3), 1.04 (3H, d, *J* 6.8, 15-CH_3), 1.05 – 1.08 (4H, m, 11-H and 11-CH_3), 1.10 – 1.14 (1H, m, 10-H), 1.35 – 1.39 (1H, m, 4-*H*H), 1.45 – 1.50 (1H, m, 12-H), 1.52 – 1.57 (1H, m, 23-*H*H), 1.60 (3H, d, *J* 1.1, 21-CH_3), 1.64 (3H, d, *J* 1.3, 17-CH_3), 1.74 – 1.80 (1H, m, 23-H*H*), 1.84 – 1.90 (1H, m, 19-*H*H), 2.05 (1H, ddd, *J* 12.6, 5.0, 1.6, 4-H*H*), 2.08 – 2.15 (1H, m, 19-H*H*), 2.44 (1H, dd,

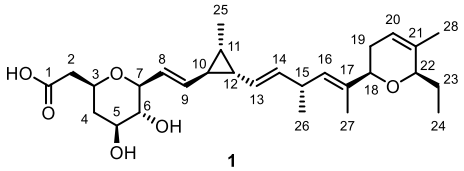
J 15.6, 5.4, 2-*H*H), 2.50 (1H, dd, *J* 15.6, 7.6, 2-H*H*), 2.97 (1H, ap. t, *J* 9.1, 6-H), 3.07 – 3.13 (1H, m, 15-H), 3.51 (1H, dd, *J* 9.1, 6.6, 7-H), 3.53 – 3.57 (1H, m, 5-H), 3.83 (1H, dd, *J* 11.1, 3.3, 18-H), 3.85 – 3.89 (1H, m, 3-H), 4.08 – 4.11 (1H, m, 22-H), 5.16 (1H, ddd, *J* 15.2, 8.7, 1.3, 13-H), 5.26 (1H, dq, *J* 9.0, 1.3, 16-H), 5.38 (1H, dd, *J* 15.4, 8.6, 9-H), 5.46 (1H, dd, *J* 15.2, 6.5, 14-H), 5.50 (1H, dd, *J* 15.4, 6.6, 8-H), 5.57 – 5.61 (1H, m, 20-H); δ_C (126 MHz, CD_3OD) 8.7 (C-24), 12.6 (CH_3-17), 13.4 (CH_3-11), 19.1 (CH_3-21), 21.7 (CH_3-15), 22.3 (C-11), 26.6 (C-23), 29.8 (C-12), 31.1 (C-19), 31.7 (C-10), 36.3 (C-15), 40.2 (C-4), 41.6 (C-2), 73.3 (C-5), 73.4 (C-5), 77.1 (C-6), 79.5 (C-18), 79.6 (C-22), 81.8 (C-7), 122.1 (C-20), 126.2 (C-8), 126.9 (C-13), 130.9, (C-16) 136.1 (C-21), 136.2 (C-17), 136.3 (C-14), 138.2 (C-9), 174.7 (C-1). Data consistent with the literature.[70,81,242]



1

Position	Synthetic Ambruticin S 500 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))	Natural Ambruticin S 400 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))	Hanessian's Synthetic Ambruticin S 500 MHz (CD_3OD): δ_H (multiplet, *J* (Hz))
24-H	0.89 (t, 7.3)	0.93 (t, 7.3)	0.91 (t, 7.3)
26-H	1.04 (d, 6.8)	1.08 (d, 7.0)	1.06 (d, 6.8)
11-H	1.05 – 1.08 (m)	1.13 (m)	1.04 – 1.06 (m)
25-H	1.05 – 1.08 (m)	1.09 (s)	1.06 – 1.07 (m)
10-H	1.10 – 1.14 (m)	1.16 (m)	1.13 – 1.15 (m)
4-*H*H	1.35 – 1.39 (m)	1.38 (m)	1.36 (q, 12.0)
12-H	1.45 – 1.50 (m)	1.54 (m)	1.48 – 1.51 (m)
23-*H*H	1.52 – 1.57 (m)	1.58 (m)	1.52 – 1.59 (m)
28-H	1.60 (d, 1.1)	1.64 (m)	1.62 (d, 1.1)
27-H	1.64 (d, 1.3)	1.68 (d, 1.3)	1.66 (d, 1.3)
23-H*H*	1.74 – 1.80 (m)	1.80 (m)	1.75 – 1.81 (m)
19-*H*H	1.84 – 1.90 (m)	1.90 (m)	1.86 – 1.91 (m)
4-*H*H	2.05 (ddd, 12.6, 5.0, 1.6)	2.08 (ddd, 12.6, 5.1, 1.9)	2.06 (ddd, 12.6, 5.0, 1.6)
19-H*H*	2.08 – 2.15 (m)	2.13 (m)	2.11 – 2.16 (m)
2-*H*H	2.44 (dd, 15.6, 5.4)	2.47 (dd, 15.6, 5.5)	2.46 (dd, 15.5, 5.3)
2-H*H*	2.50 (dd, 15.6, 7.6)	2.55 (dd, 15.6, 7.4)	2.52 (dd, 15.3, 7.6)
6-H	2.97 (ap.t, 9.1)	3.01 (dd, 9.1, 9.0)	2.99 (dd, 9.0, 9.0)
15-H	3.07 – 3.13 (m)	3.14 (m)	3.09 – 3.13 (m)
7-H	3.51 (dd, 9.1, 6.6)	3.55 (dd, 9.1, 6.5)	3.53 (dd, 9.2, 7.0)
5-H	3.53 – 3.57 (m)	3.57 (m)	3.56 (ddd, 11.5, 8.8, 5.0)
18-H	3.83 (dd, 11.1, 3.3)	3.87 (dd, 10.6, 3.0)	3.85 (dd, 10.8, 2.9)
3-H	3.85 – 3.89 (m)	3.91 (m)	3.87 – 3.90 (m)
22-H	4.08 – 4.11 (m)	4.13 (m)	4.11 (br s)
13-H	5.16 (ddd, 15.2, 8.7, 1.3)	5.20 (ddd, 15.3 8.8,1.2)	5.18 (ddd, 15.3, 8.8, 1.1)
16-H	5.26 (dq, 9.0, 1.3)	5.29 (dq, 9.0, 1.3)	5.27 (dq, 9.0, 1.1)
9-H	5.38 (dd, 15.4, 8.6)	5.42 (dd, 15.4, 8.4)	5.39 (dd. 15.4, 8.7)
14-H	5.46 (dd, 15.2, 6.5)	5.50 (dd, 15.3, 6.4)	5.48 (dd, 15.2, 6.5)
8-H	5.50 (dd, 15.4, 6.6)	5.54 (dd, 15.4, 6.5)	5.52 (dd, 15.4, 6.6)
20-H	5.57 – 5.61 (m)	5.63 (m)	5.60, 5.61 (m)

Table 15. Comparison of ^{1}H-NMR data between synthetic and natural ambruticin S.[70,81,242]



1

Position	Synthetic Ambruticin S 126 MHz (CD_3OD): δ_C	Natural Ambruticin S 75.5 MHz (CD_3OD): δ_C	Hanessian's Synthetic Ambruticin S 125 MHz (CD_3OD): δ_C
C-24	8.7	8.6	8.7
C-27	12.6	12.6	12.6
C-25	13.4	13.3	13.4
C-28	19.1	19.0	19.1
C-26	21.7	21.6	21.7
C-11	22.3	22.2	22.3
C-23	26.6	26.5	26.6
C-12	29.8	29.7	29.8
C-19	31.1	31.0	31.1
C-10	31.7	31.6	31.7
C-15	36.3	36.2	36.3
C-4	40.2	40.1	40.2
C-2	41.6	41.5	41.6
C-3	73.3	73.2	73.3
C-5	73.4	73.3	73.3
C-6	77.1	77.0	77.0
C-18	79.5	79.4	79.4
C-22	79.6	79.4	79.5
C-7	81.8	81.4	81.8
C-20	122.1	122.0	122.1
C-8	126.2	126.1	126.1
C-13	126.9	126.8	126.9
C-16	130.9	130.8	130.9
C-21	136.1	136.0	136.0
C-17	136.2	136.1	136.2
C-14	136.3	136.2	136.2
C-9	138.2	138.0	138.2
C-1	174.7	174.6	174.8

Table 16. Comparison of ^{13}C-NMR data between synthetic and natural ambruticin S.[70,81,242]

CHAPTER 5:

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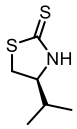
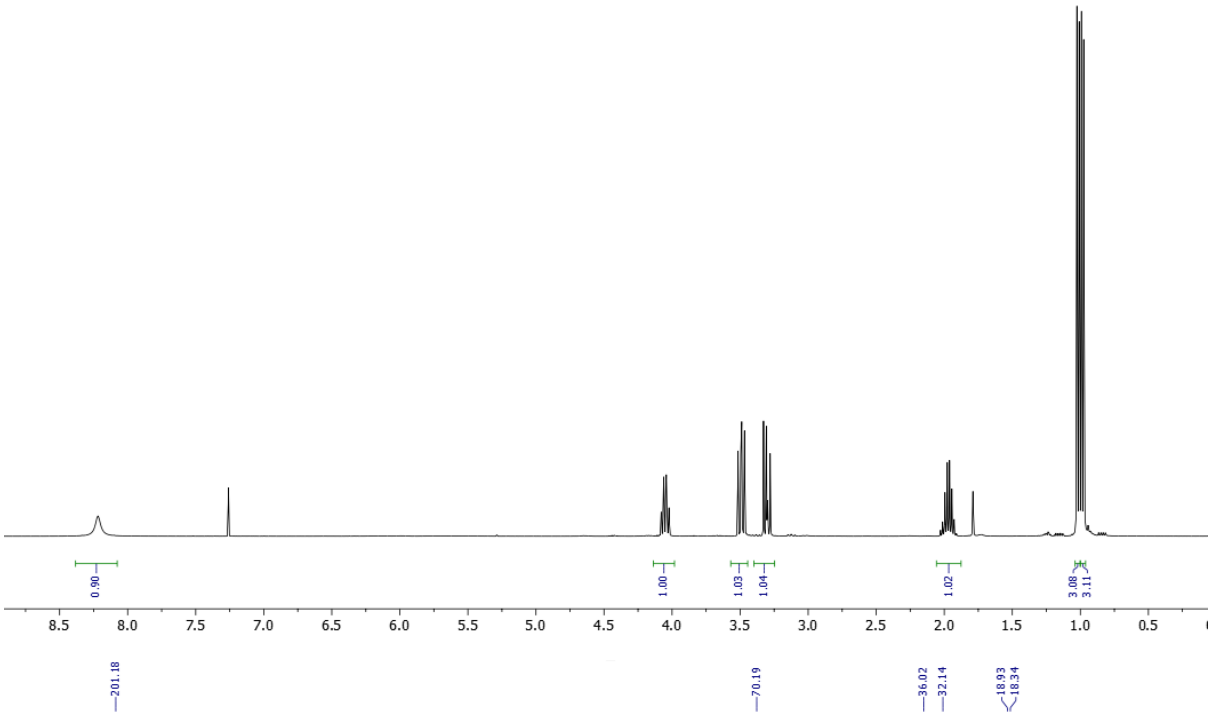
CHAPTER 6:

Spectra


S
S
NH

152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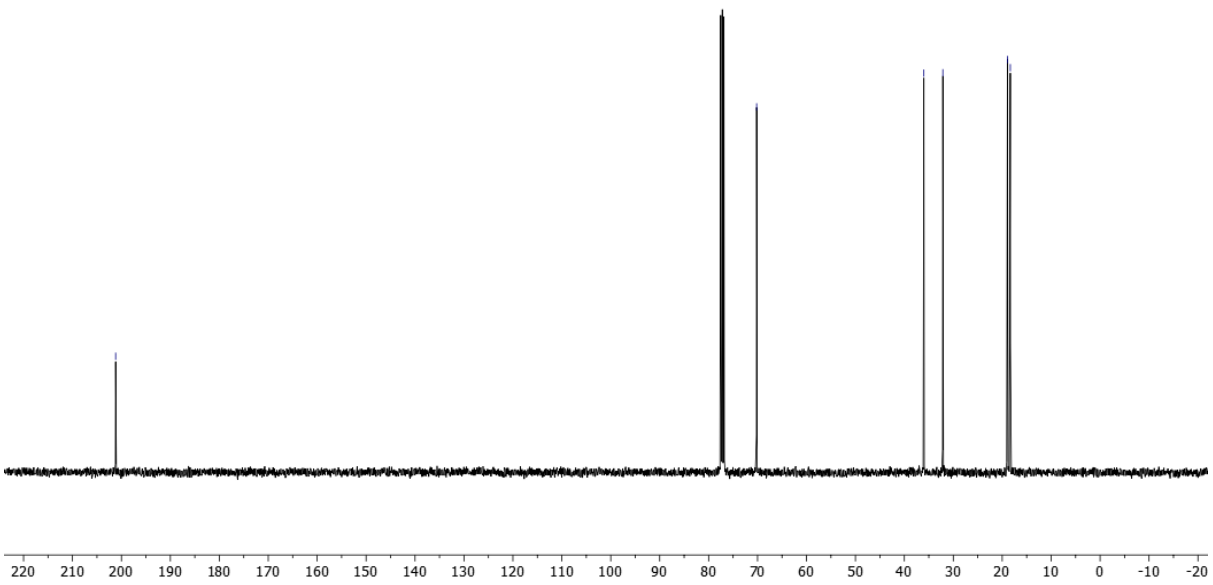
1.00
1.03
1.04
1.02
3.08
3.11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

201.18
70.19
36.02
32.14
18.93
18.34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210
200
190
180
170
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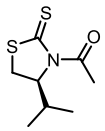
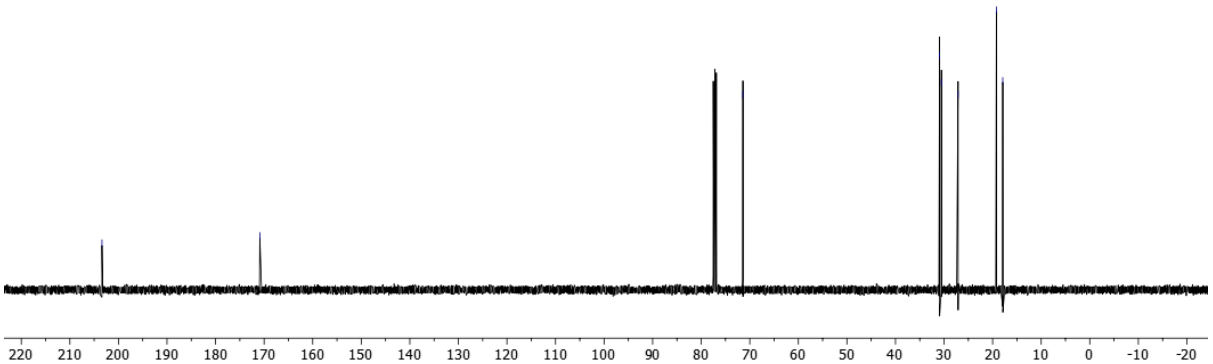
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20



153

1.00
1.03
1.04
3.10
1.01
3.17
3.20
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
203.39
170.88
71.42
30.93
30.55
27.11
19.22
17.91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210
200
190
180
170
160
150
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120
110
100
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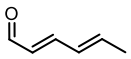
80
70
60
50
40
30
20
10
0
-10
-20



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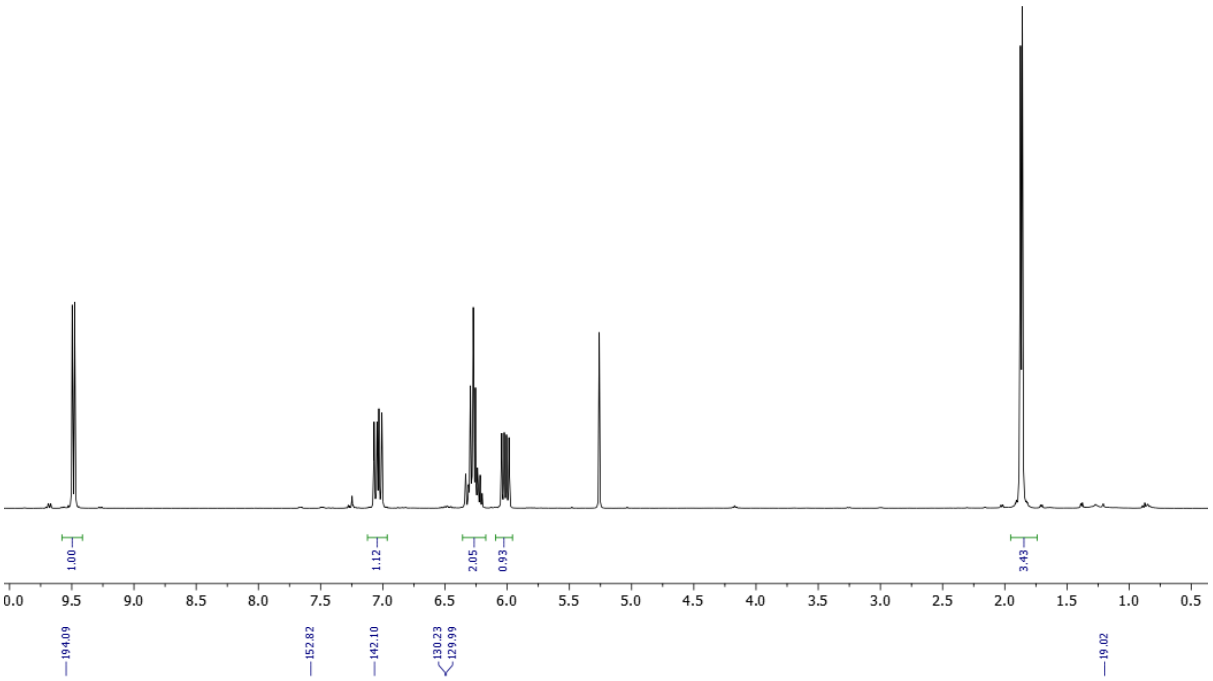
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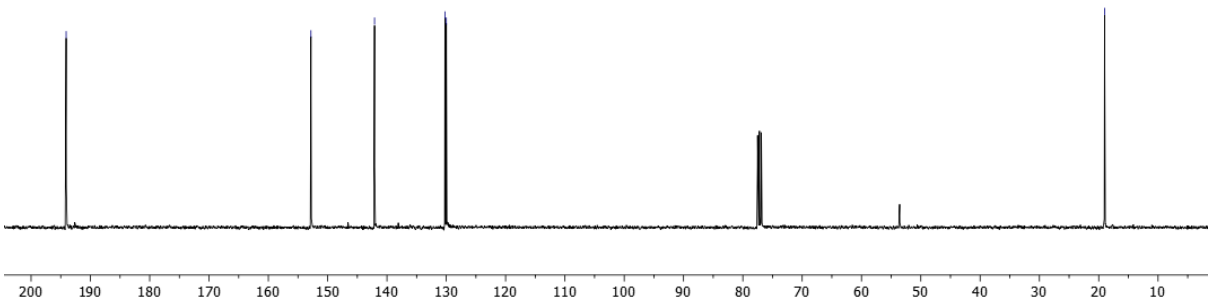
1.12
2.05
0.93
3.43
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
194.09
152.82
142.10
130.23
129.99
19.02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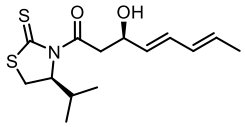
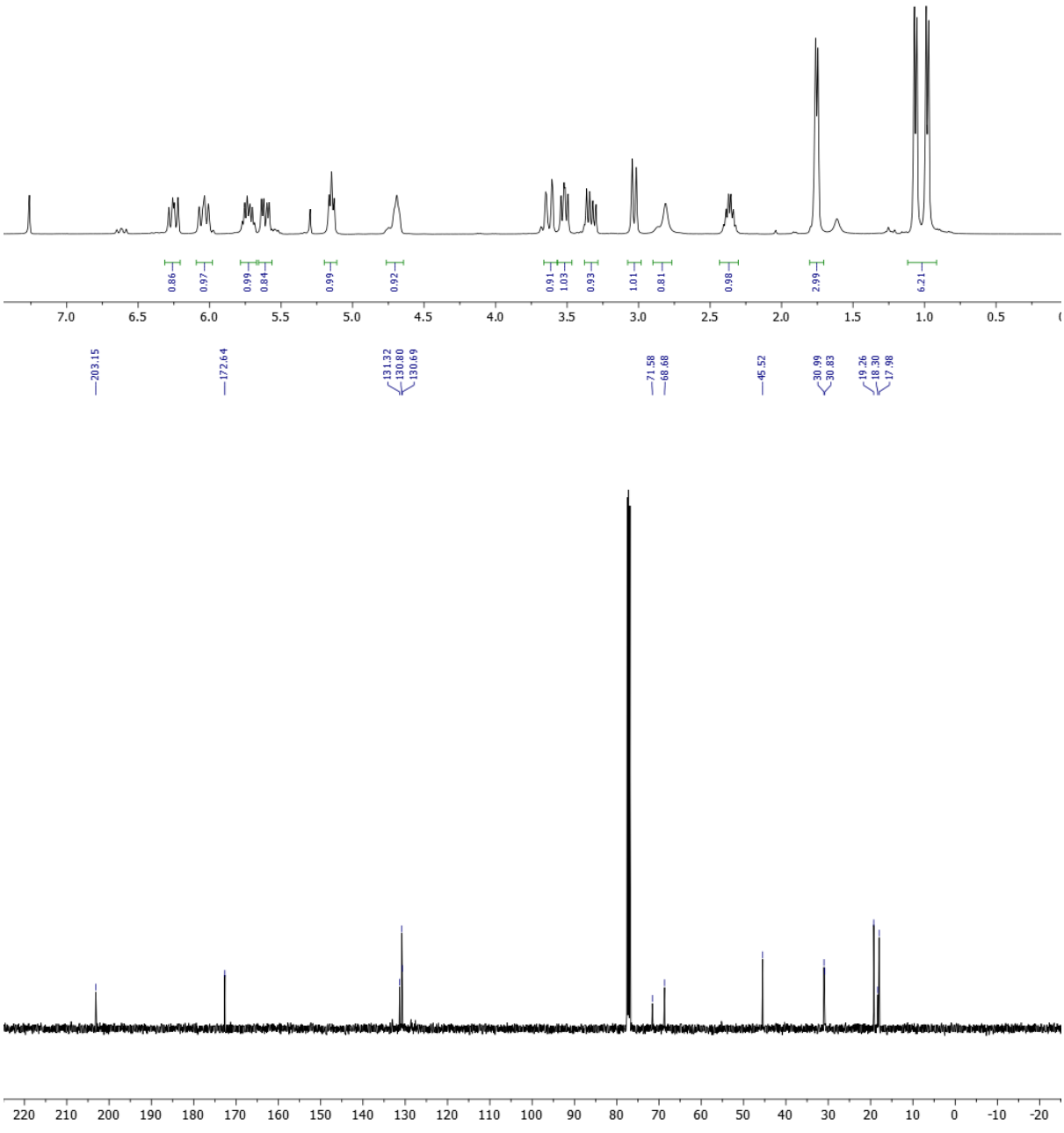

S
O
OH
N
S

156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0.97
0.99
0.84
0.99
0.92
0.91
1.03
0.93
1.01
0.81
0.98
2.99
6.21
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
203.15
172.64
131.32
130.80
130.69
71.58
68.68
45.52
30.99
30.83
19.26
18.30
17.98
220
210
200
190
180
170
160
150
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130
120
110
100
90
80
70
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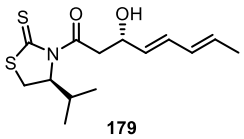
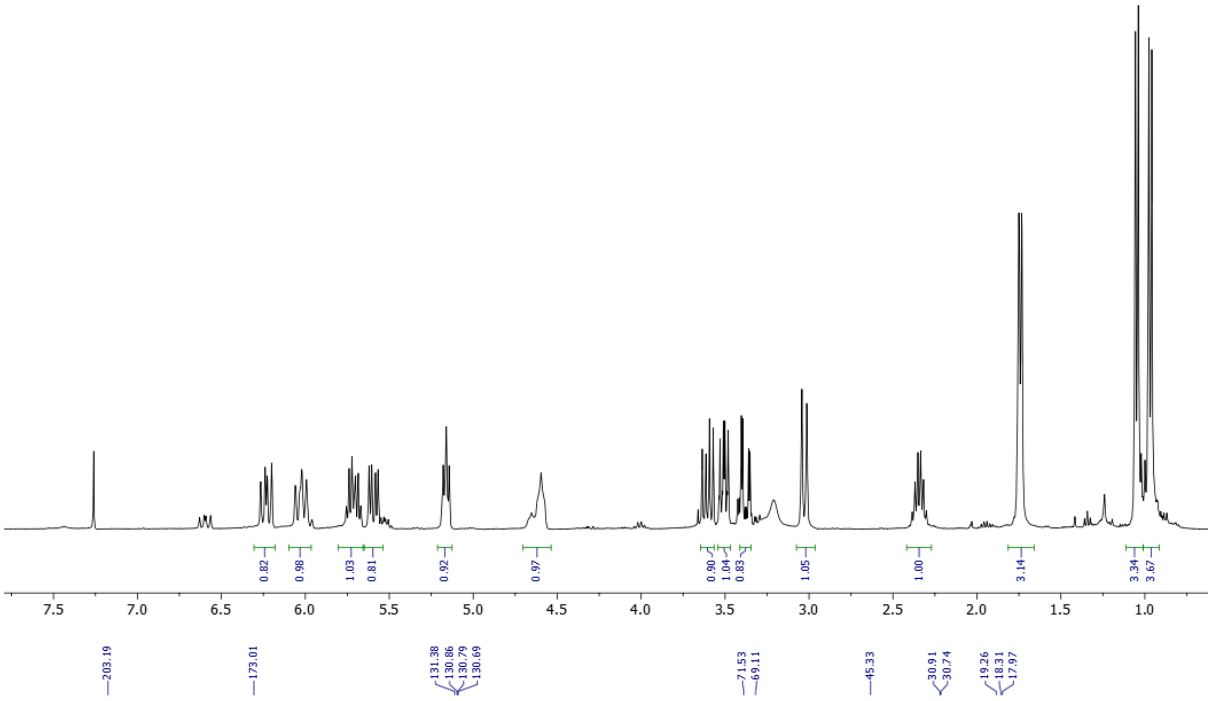
50
40
30
20
10
0
-10
-20



179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0.98
1.03
0.81
0.92
0.97
0.90
1.04
0.83
1.05
1.00
3.14
3.34
3.67
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
203.19
173.01
131.38
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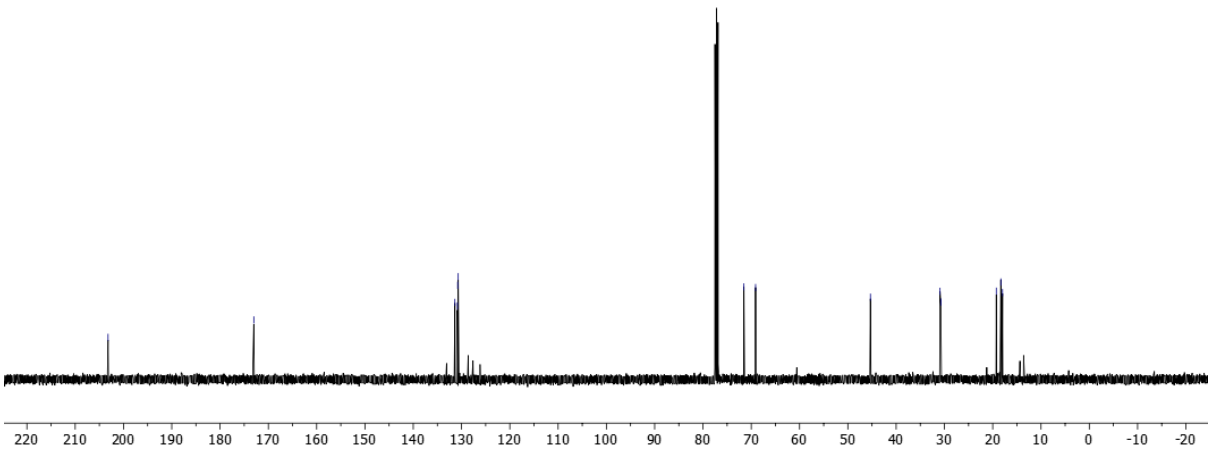
30.91
30.74
19.26
18.31
17.97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210
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180
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80
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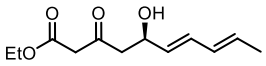
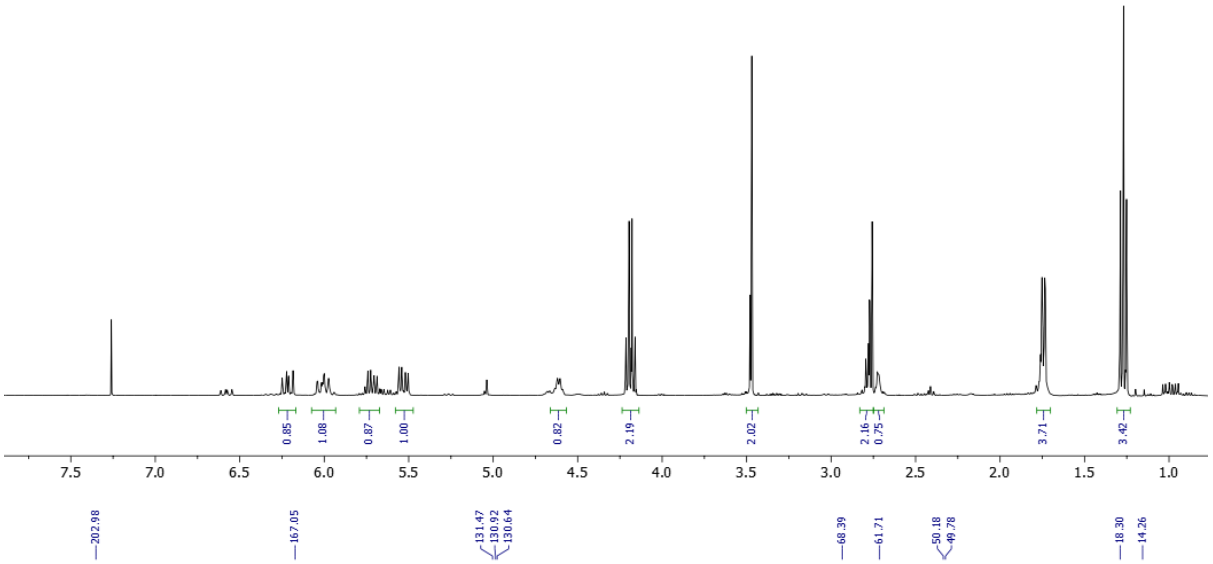
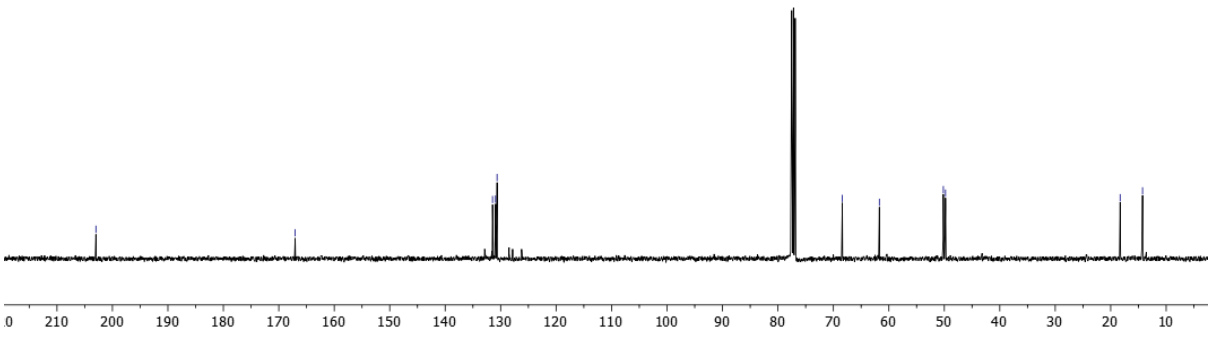
50
40
30
20
10
0
-10
-20


O
O
OH
EtO

158


0.85
1.08
0.87
1.00
0.82
2.19
2.02
2.16
0.75
3.71
3.42
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

202.98
167.05
131.47
130.92
130.64
68.39
61.71
50.18
49.78
18.30
14.26


210
200
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180
170
160
150
140
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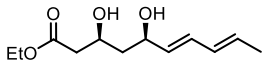
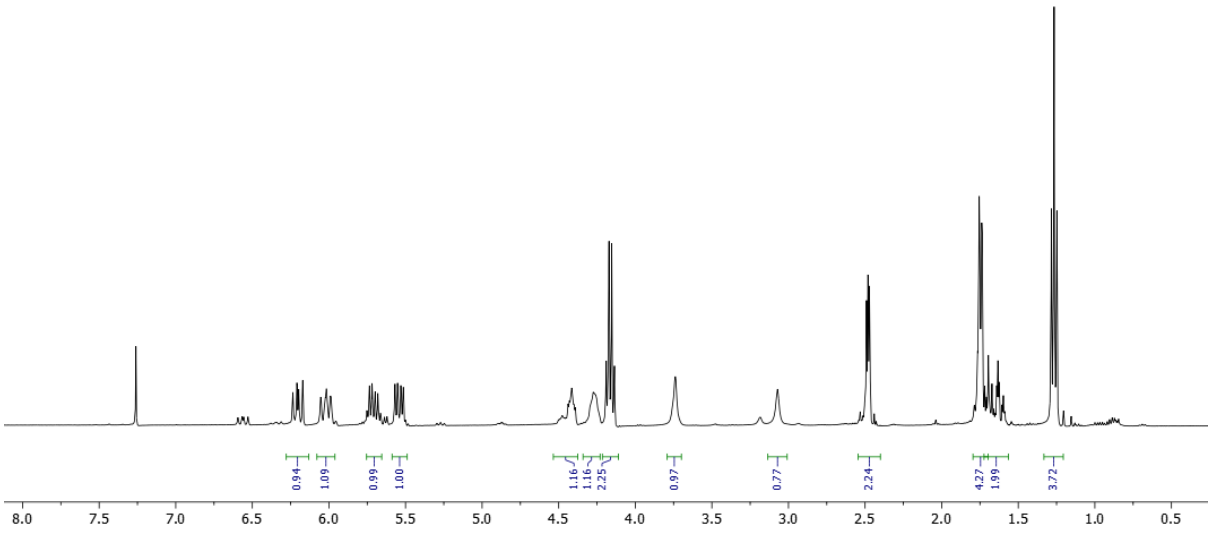
120
110
100
90
80
70
60
50
40
30
20
10


O
OH
OH
EtO

129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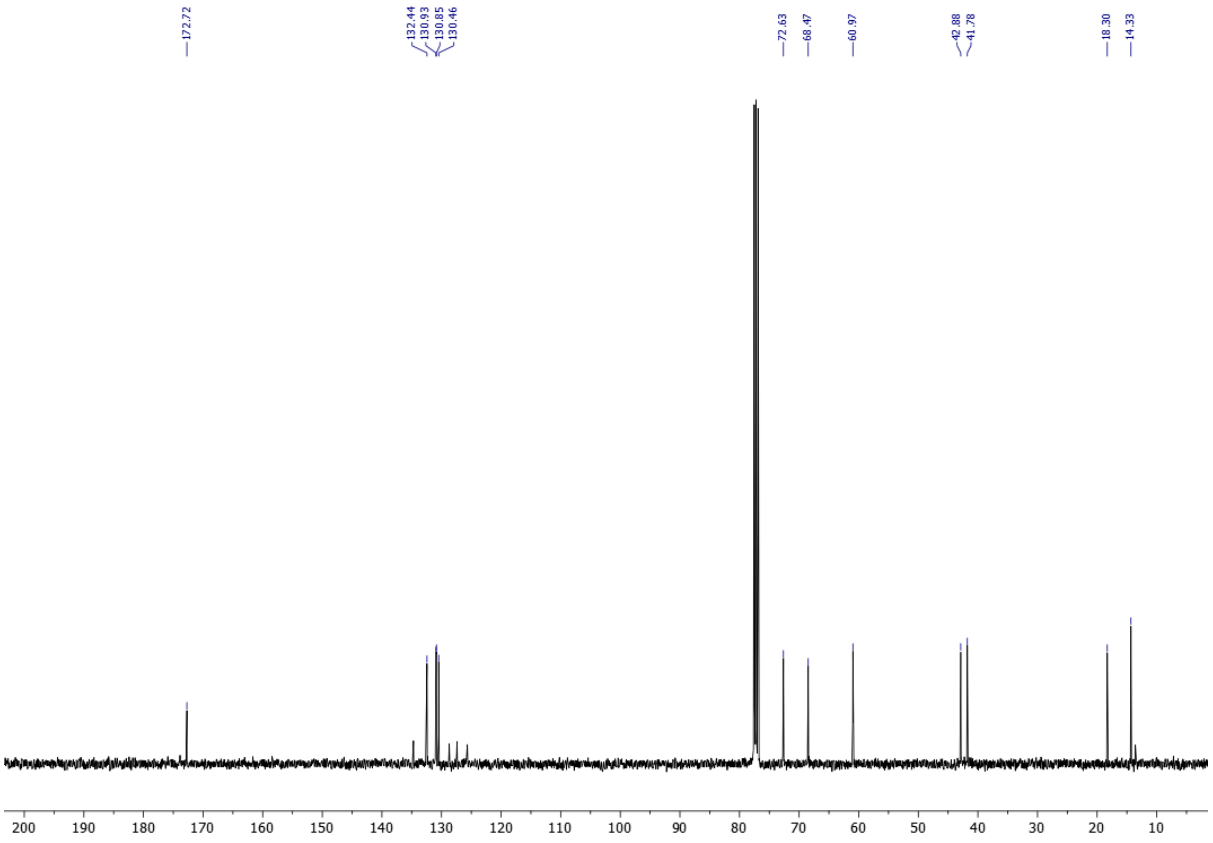
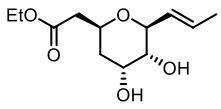
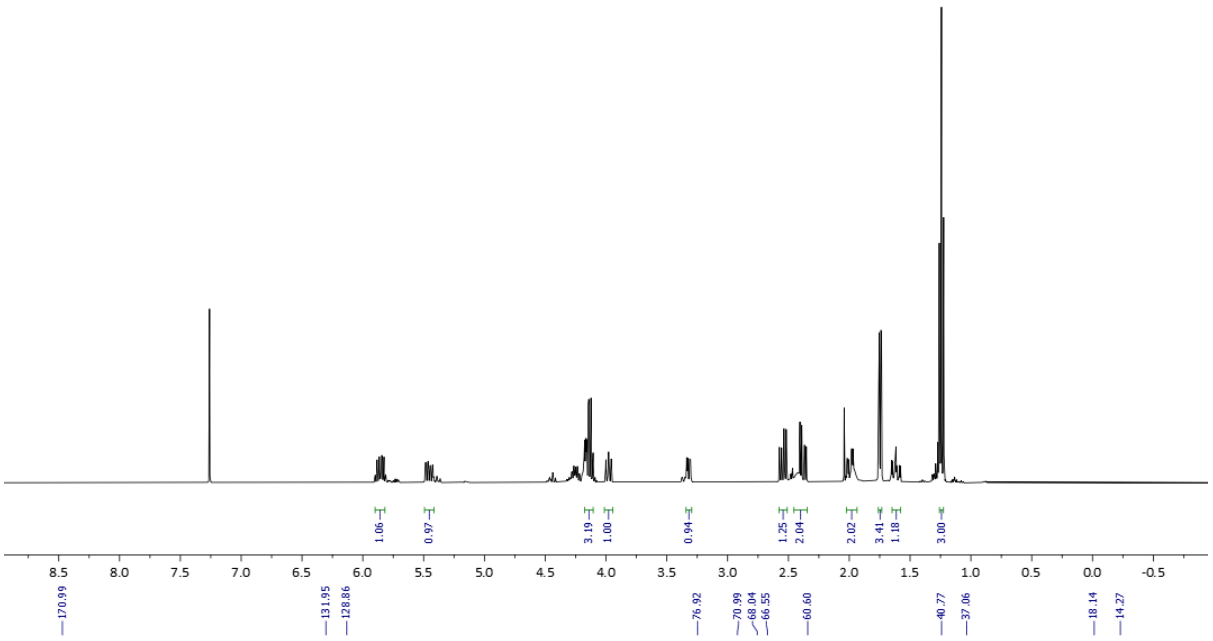
1.09
0.99
1.00
1.16
1.16
2.25
0.97
0.77
2.24
4.27
1.99
3.72
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

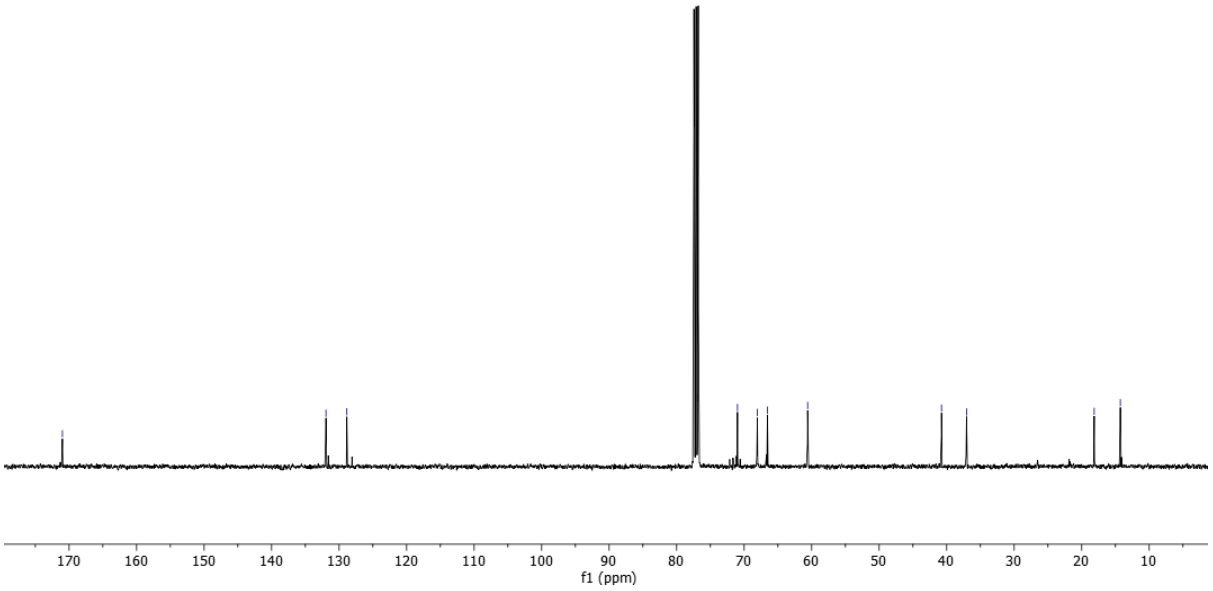
Z

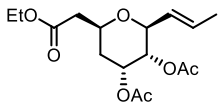

172.72
132.44
130.93
130.85
130.46
72.63
68.47
60.97
42.88
41.78
18.30
14.33
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
O
OH
OH

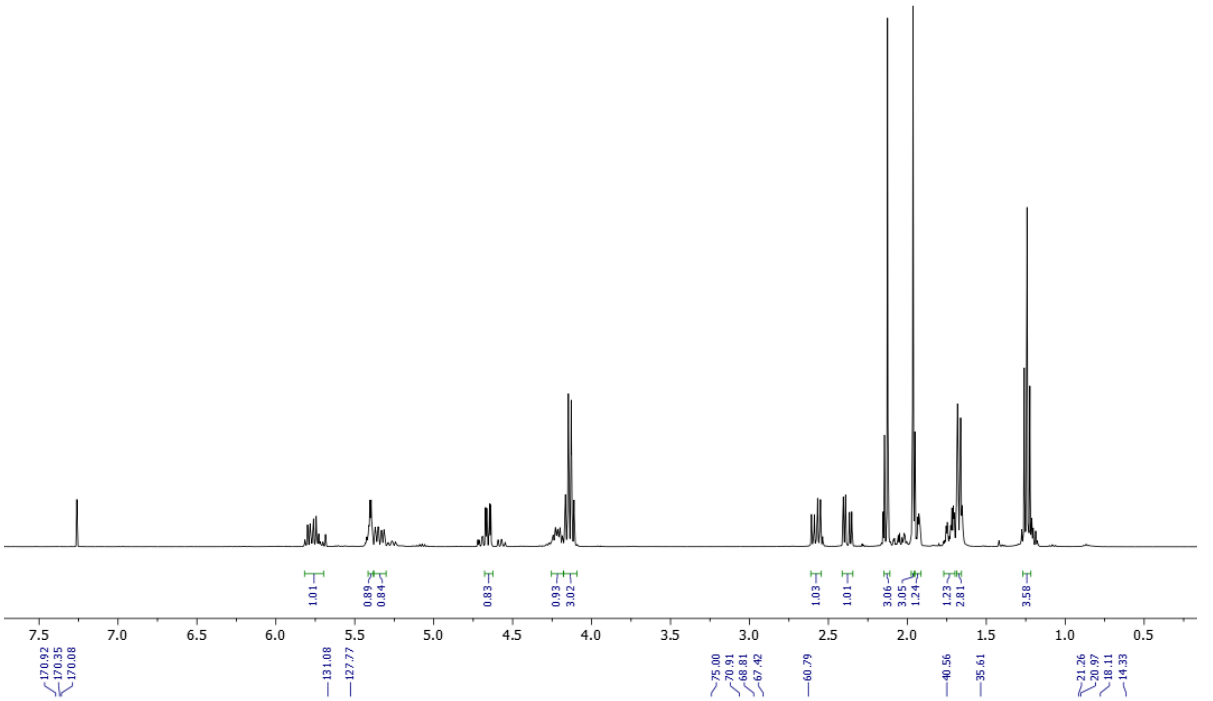
167

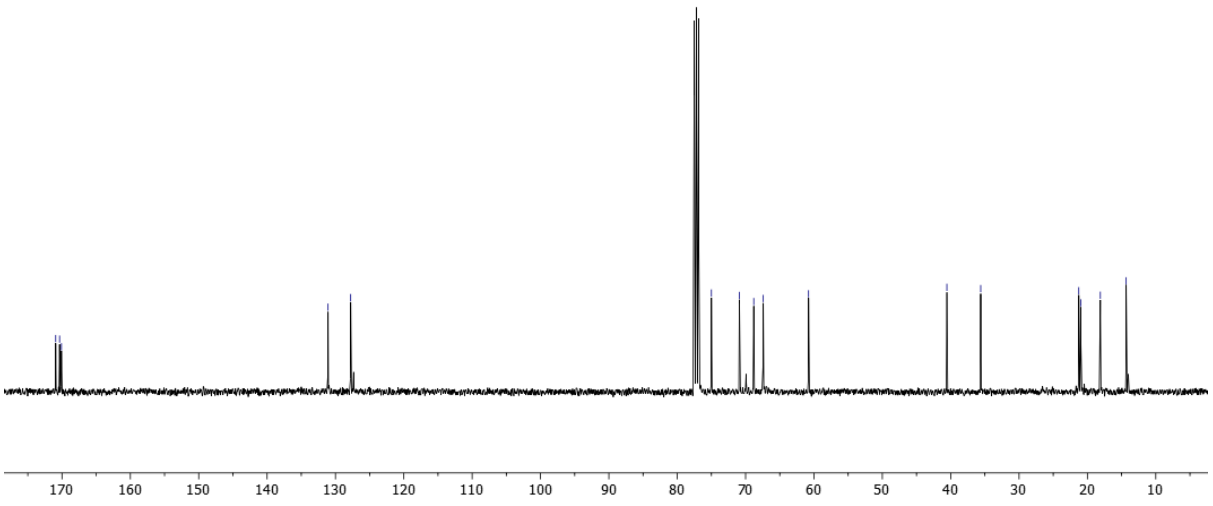

1.06
0.97
3.19
1.00
0.94
1.25
2.04
2.02
3.41
1.18
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
170.99
131.95
128.86
76.92
70.99
68.04
66.55
60.60
40.77
37.06
18.14
14.27


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


EtO
O
O
OAc
OAc

174


1.01
0.89
0.84
0.83
0.93
3.02
1.03
1.01
3.06
3.05
1.24
1.23
2.81
3.58
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
170.92
170.35
170.08
131.08
127.77
75.00
70.91
68.81
67.42
60.79
40.56
35.61
21.26
20.97
18.11
14.33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160
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140
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100
90
80
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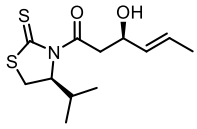
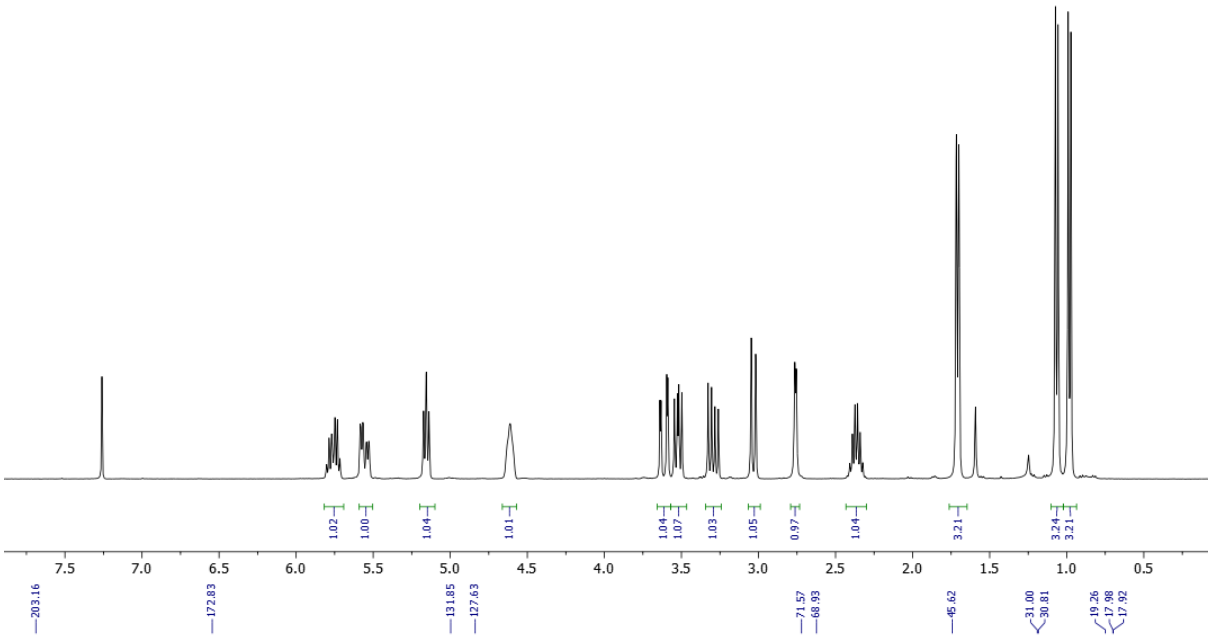
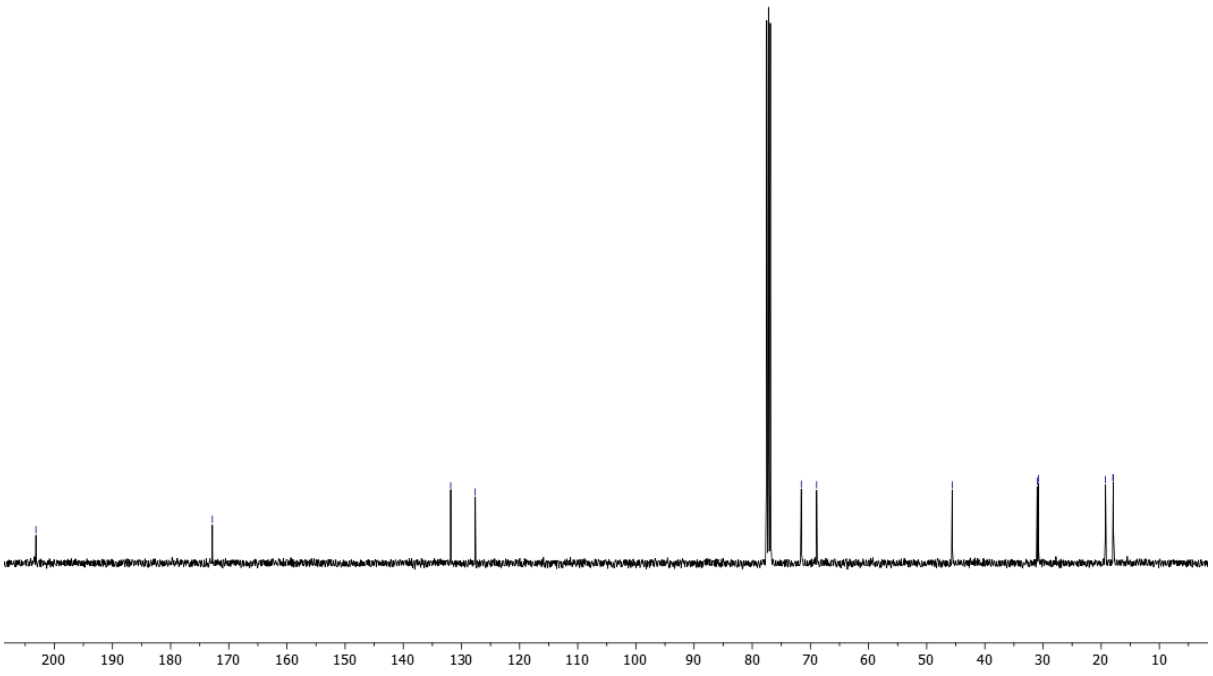
60
50
40
30
20
10


S
O
OH
N
S

155


1.02
1.00
1.04
1.01
1.04
1.07
1.03
1.05
0.97
1.04
3.21
3.24
3.21
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
203.16
172.83
131.85
127.63
71.57
68.93
45.62
31.00
30.81
19.26
17.98
17.92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190
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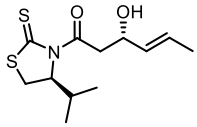
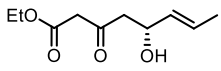
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

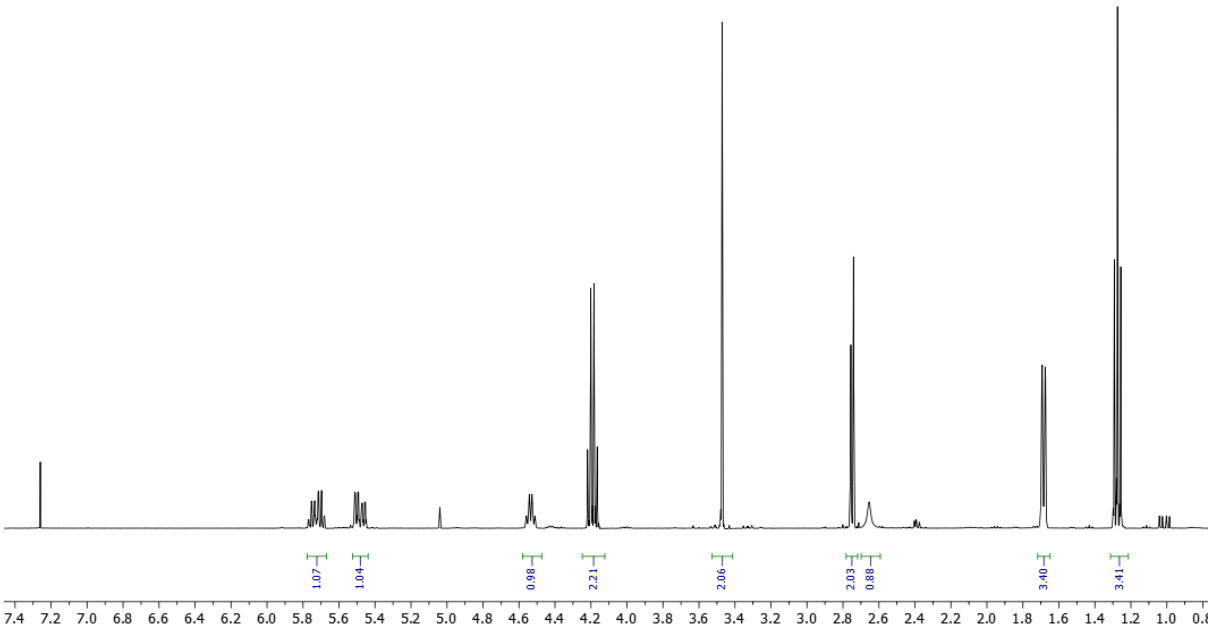

S
O
OH
N
S

414

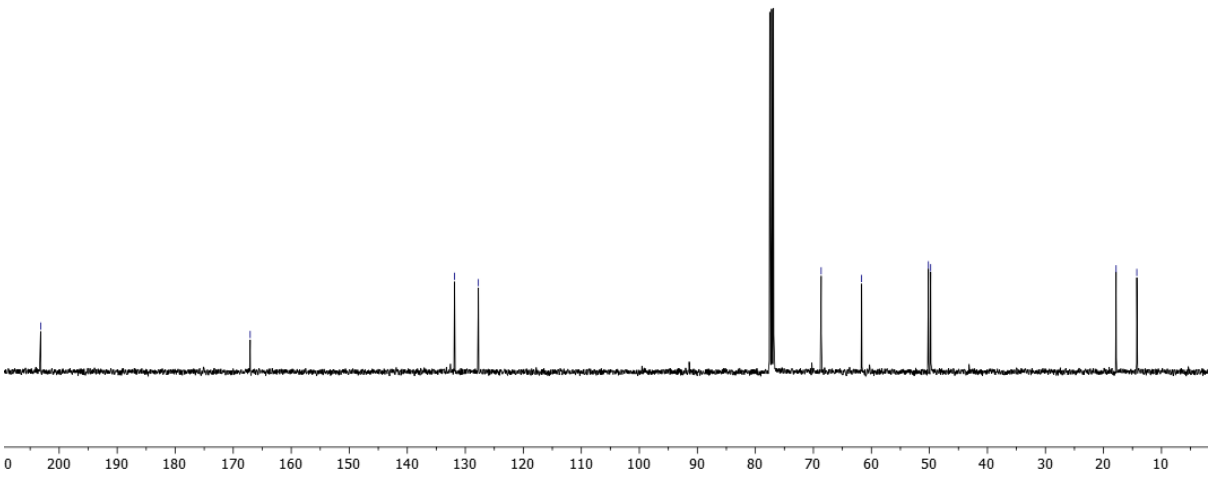
0.95
0.96
0.99
0.92
0.96
1.18
1.08
0.89
0.98
1.00
3.02
3.21
3.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
203.20
173.28
131.96
127.65
71.52
69.34
45.38
30.92
30.75
19.26
17.98
17.91
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
O
OH

157


1.07
1.04
0.98
2.21
2.06
2.03
0.88
3.40
3.41
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0


203.19
167.08
131.85
127.74
68.66
61.69
50.17
49.79
17.82
14.25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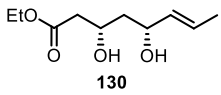
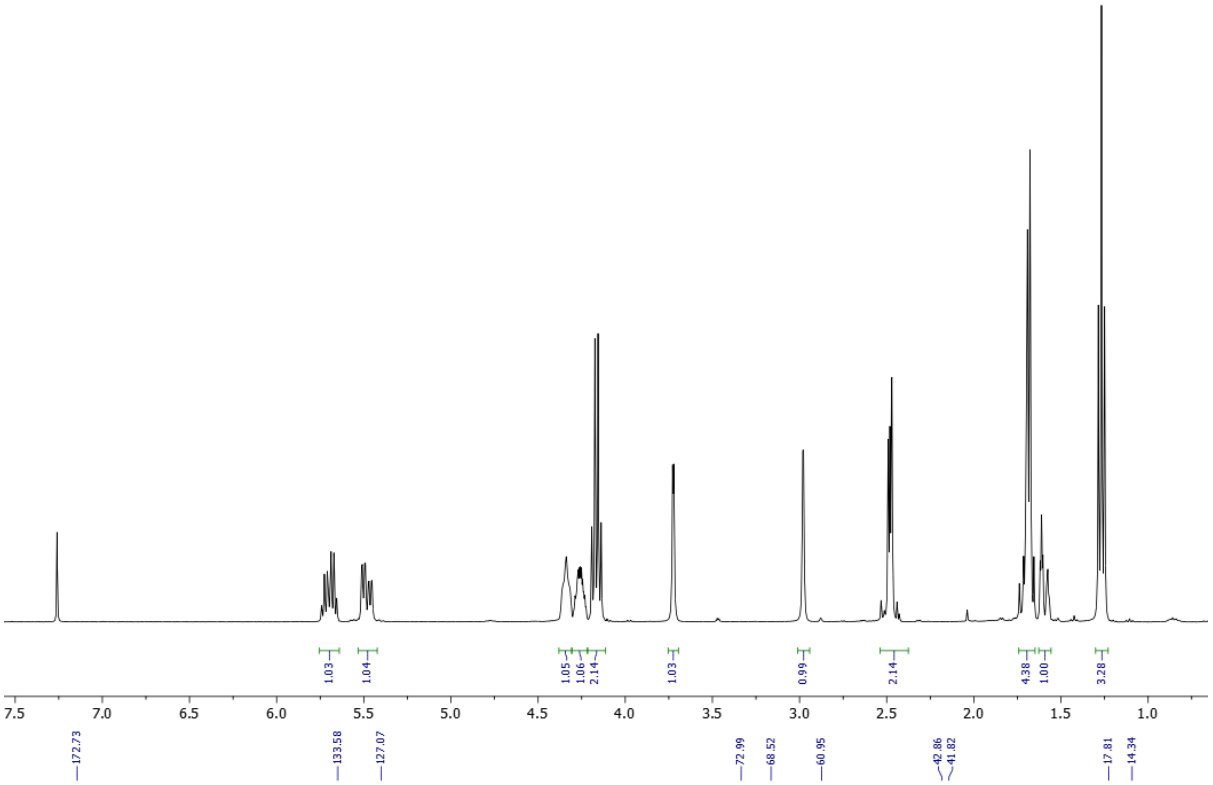
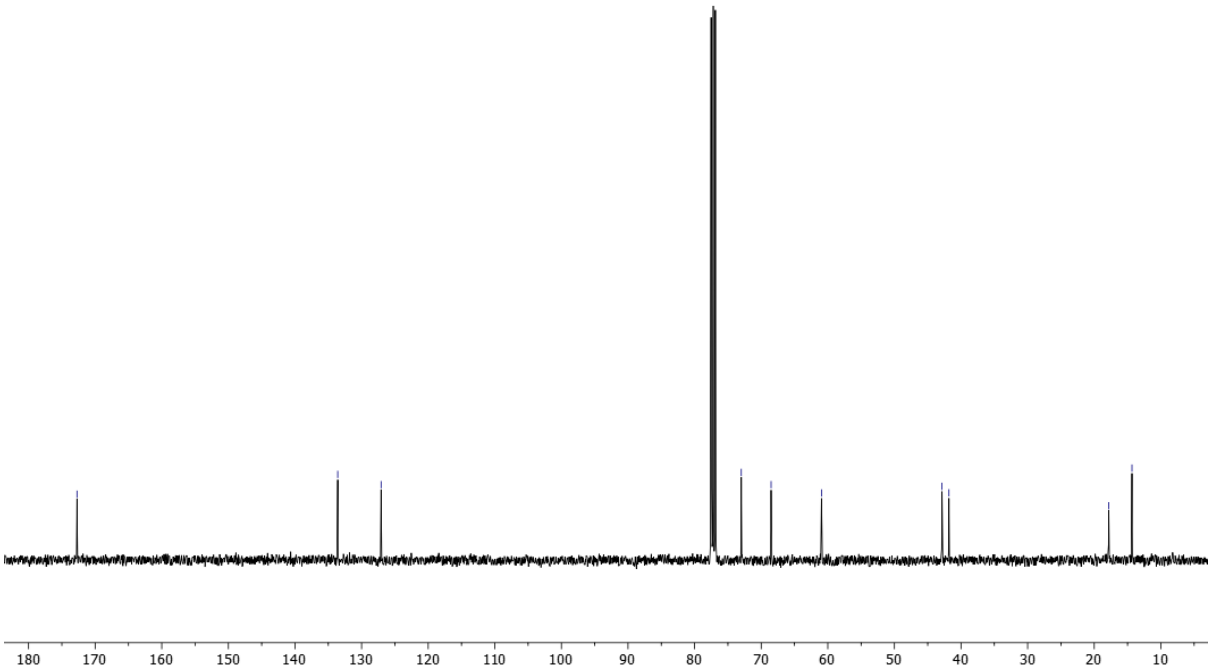
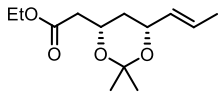

EtO
O
OH
OH

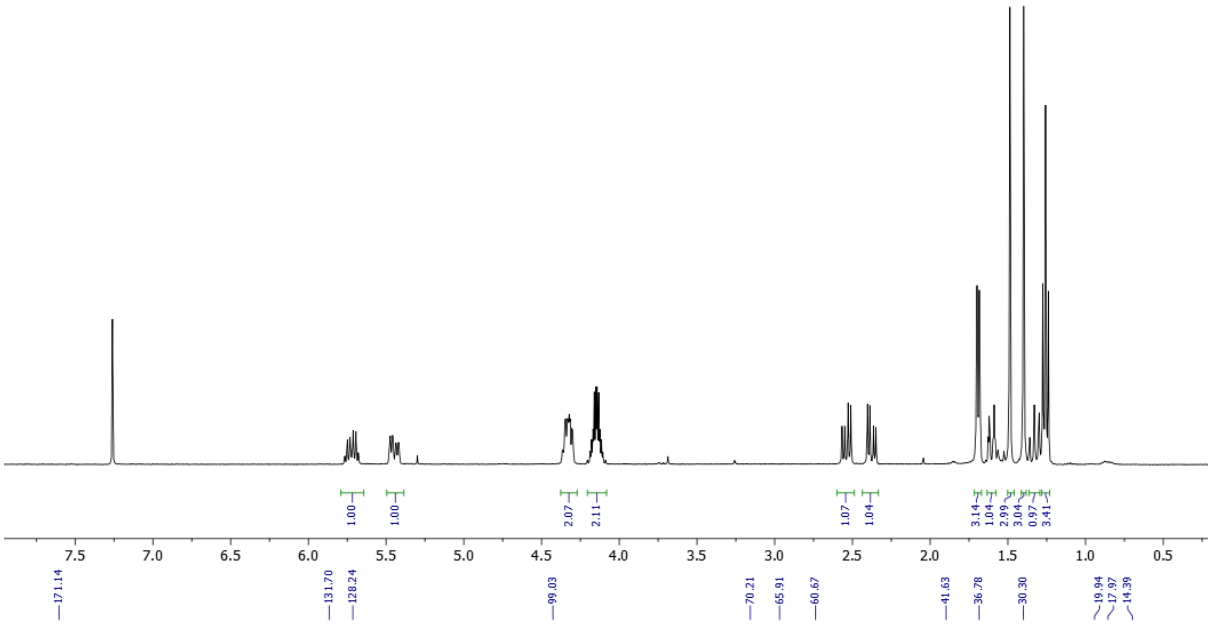
130

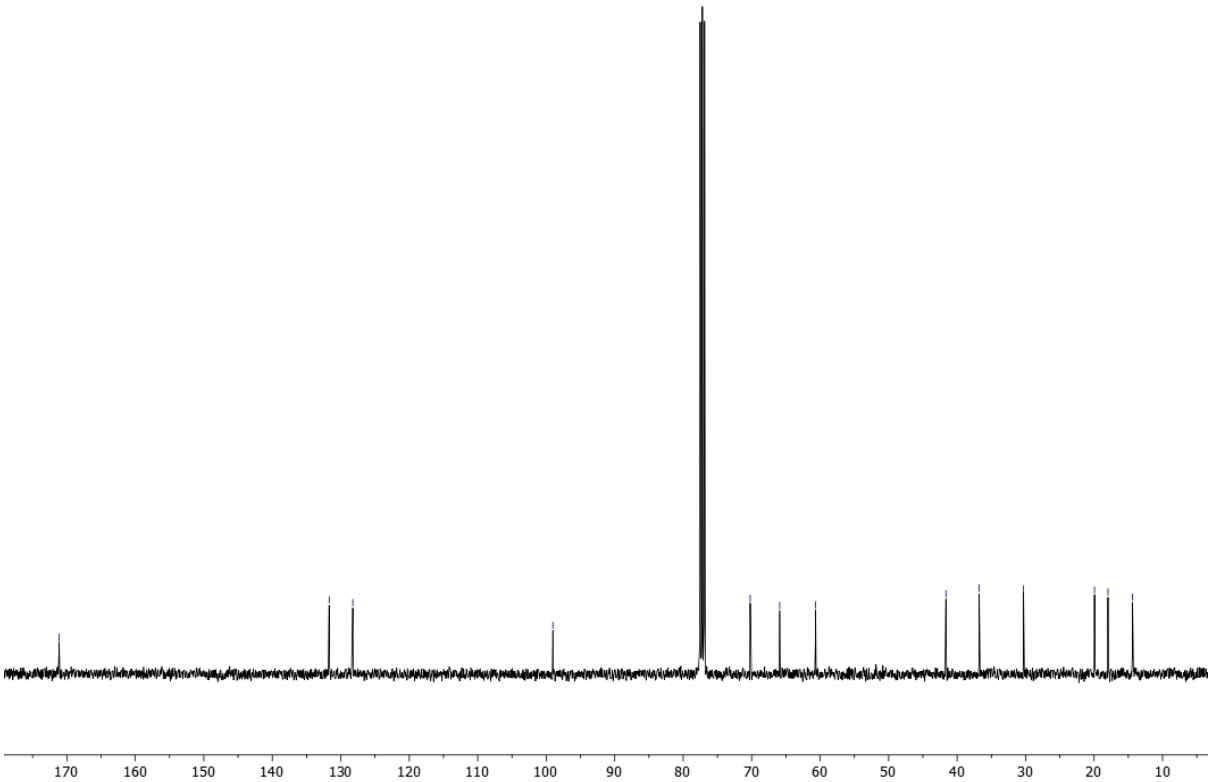

1.03
1.04
1.05
1.06
2.14
1.03
0.99
2.14
4.38
1.00
3.28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
172.73
133.58
127.07
72.99
68.52
60.95
42.86
41.82
17.81
14.34

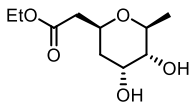

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
O
O

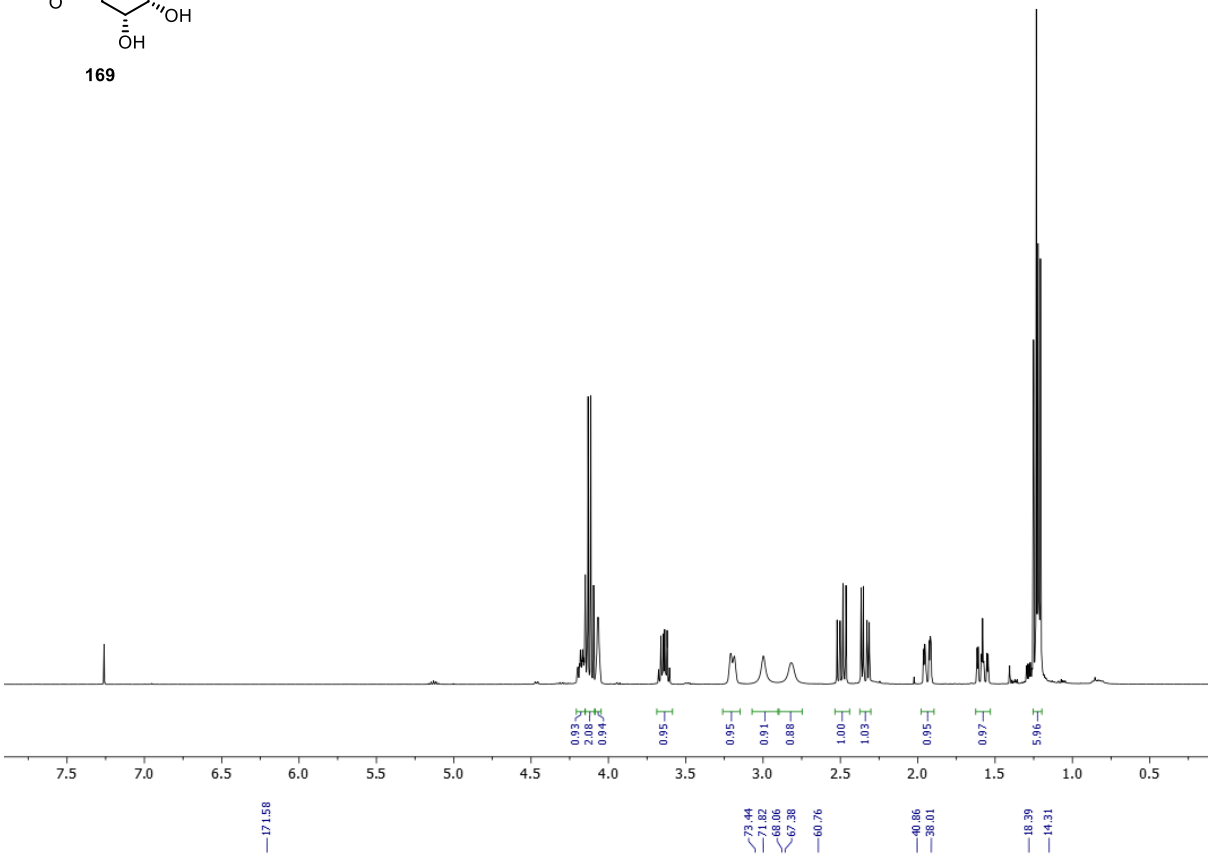
165

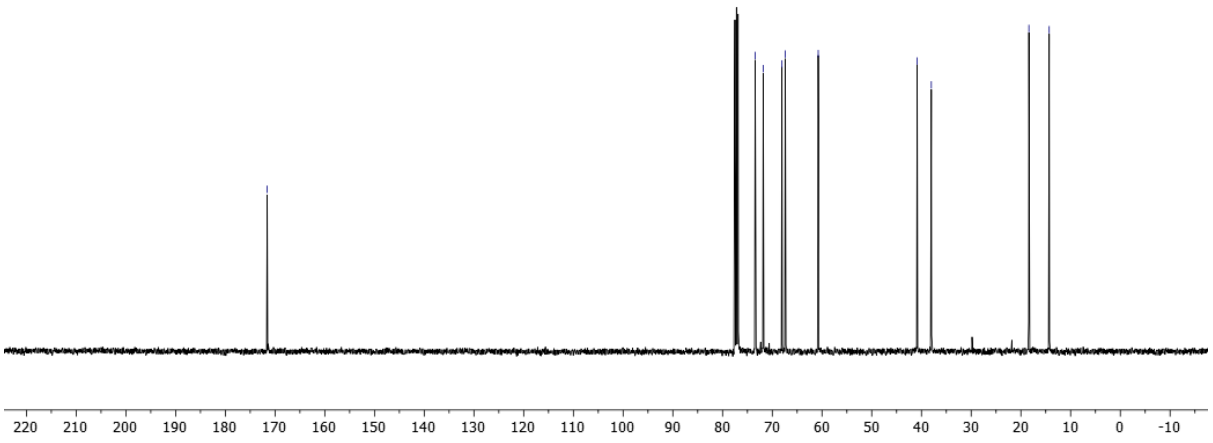

1.00
1.00
2.07
2.11
1.07
1.04
3.14
1.04
2.99
3.04
0.97
3.41
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

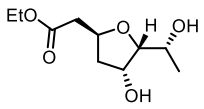

171.14
131.70
128.24
99.03
70.21
65.91
60.67
41.63
36.78
30.30
19.94
17.97
14.39
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
O
OH
OH

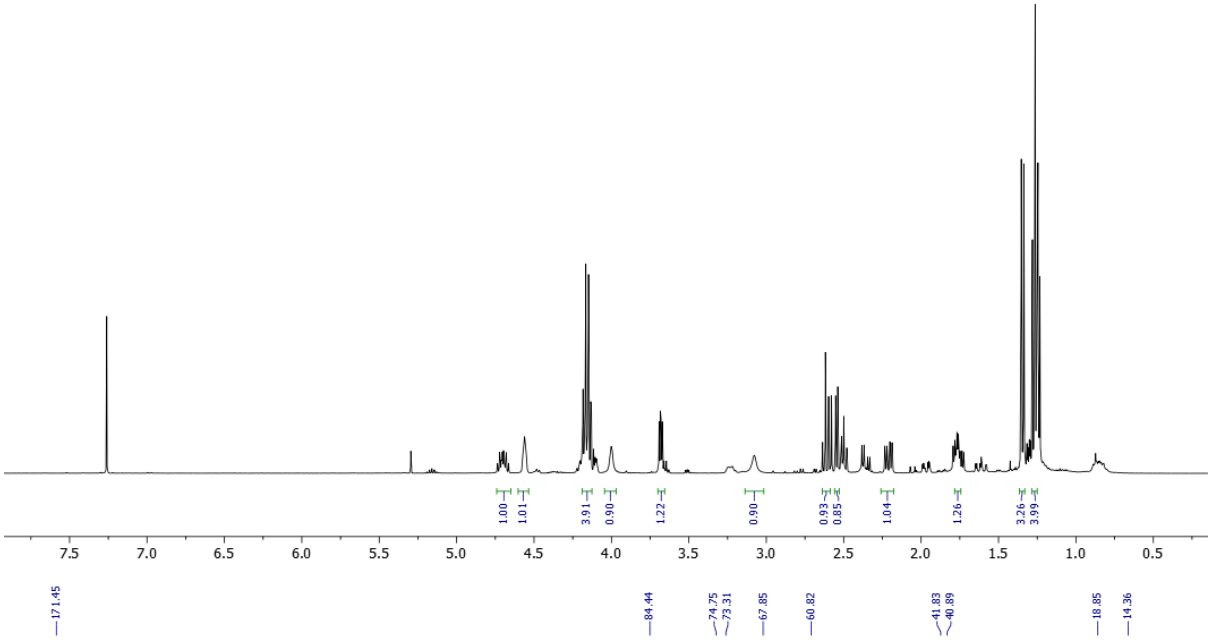
169


0.93
2.08
0.94
0.95
0.95
0.91
0.88
1.00
1.03
0.95
0.97
5.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
171.58
73.44
71.82
68.06
67.38
60.76
40.86
38.01
18.39
14.31

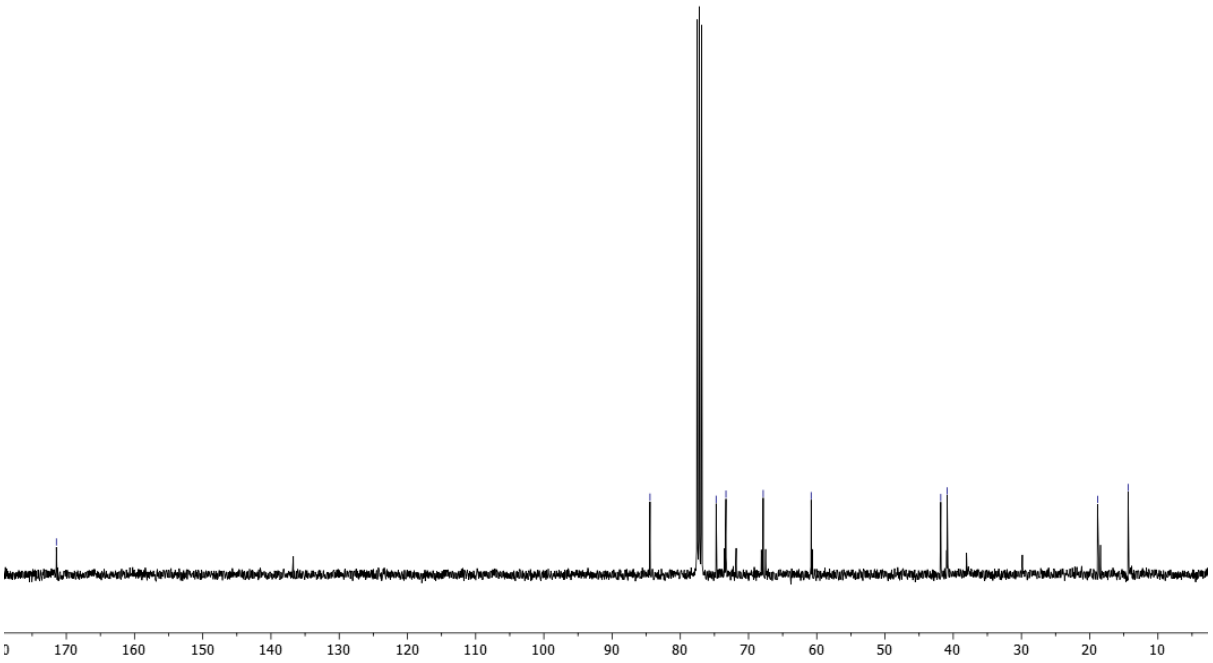

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


EtO
O
O
H
OH
OH

170


1.00
1.01
3.91
0.90
1.22
0.90
0.93
0.85
1.04
1.26
3.26
3.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

171.45
84.44
74.75
73.31
67.85
60.82
41.83
40.89
18.85
14.36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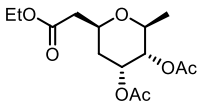
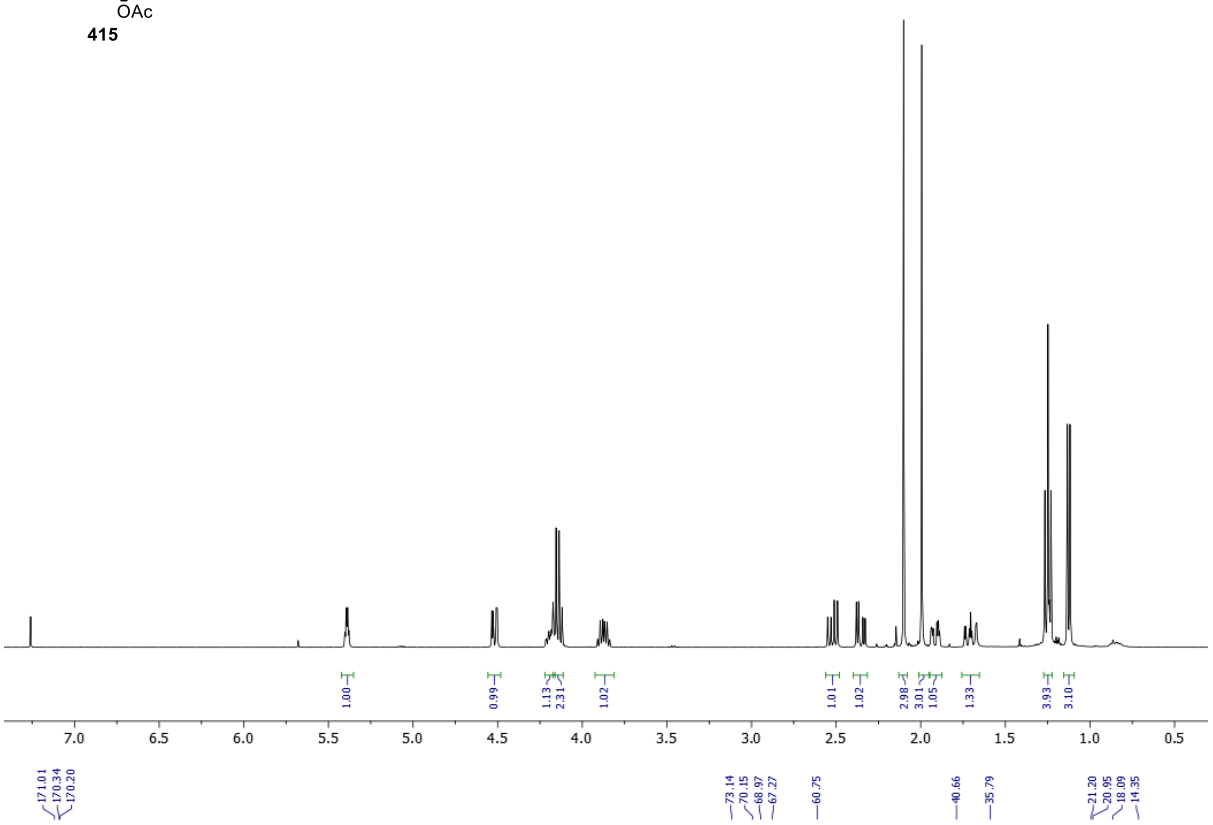
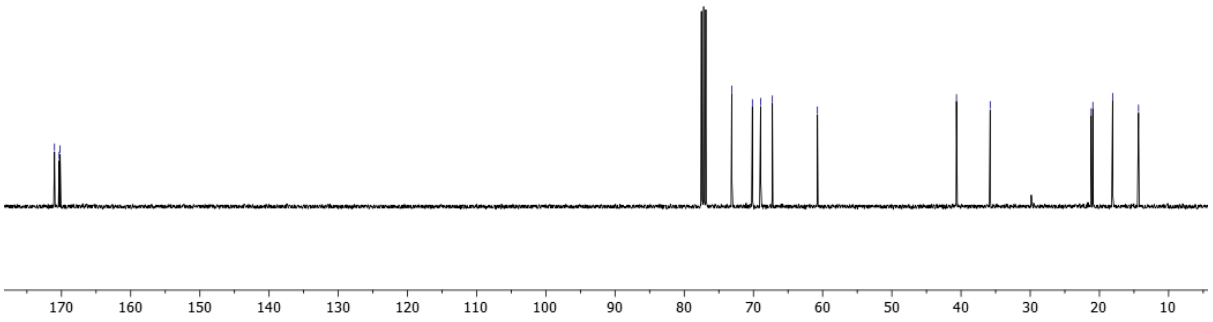
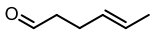
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
O
OAc
OAc

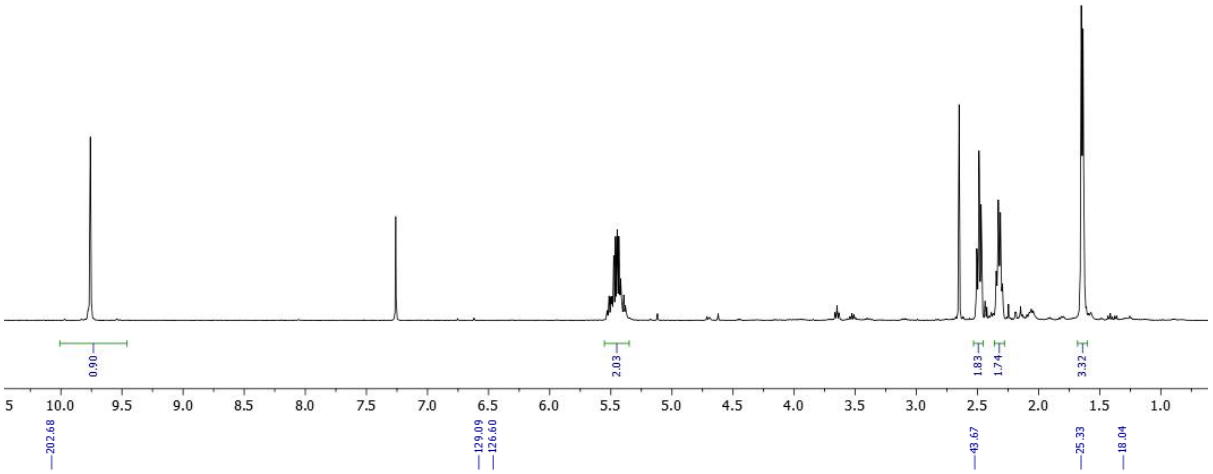
415

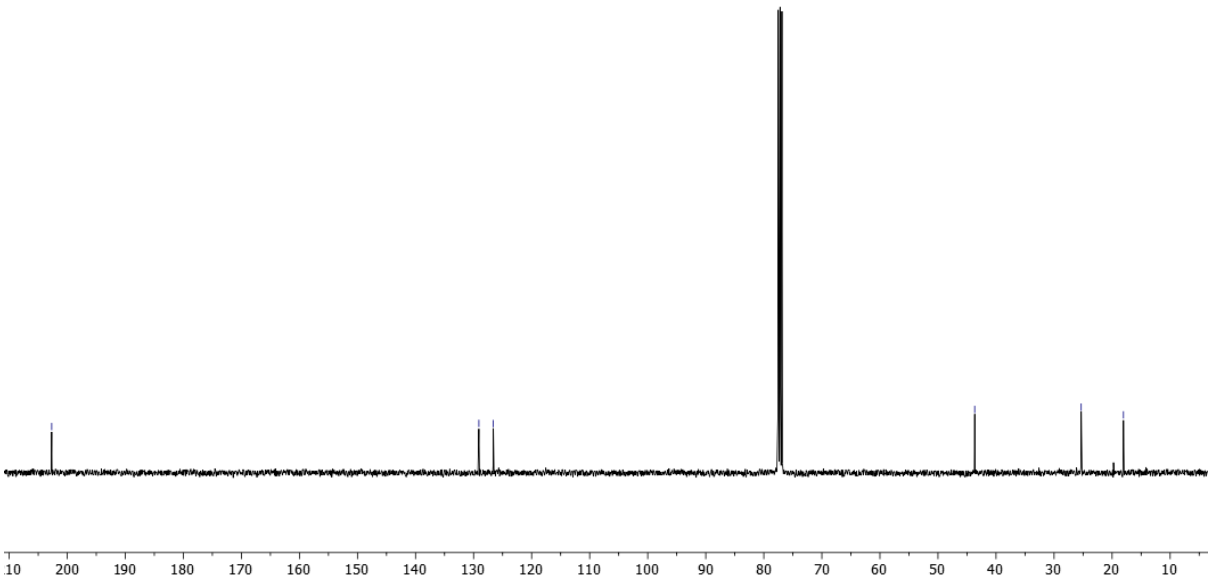

1.00
0.99
1.13
2.31
1.02
1.01
1.02
2.98
3.01
1.05
1.33
3.93
3.10
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
171.01
170.34
170.20
73.14
70.15
68.97
67.27
60.75
40.66
35.79
21.20
20.95
18.09
14.35

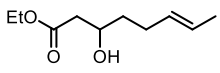

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



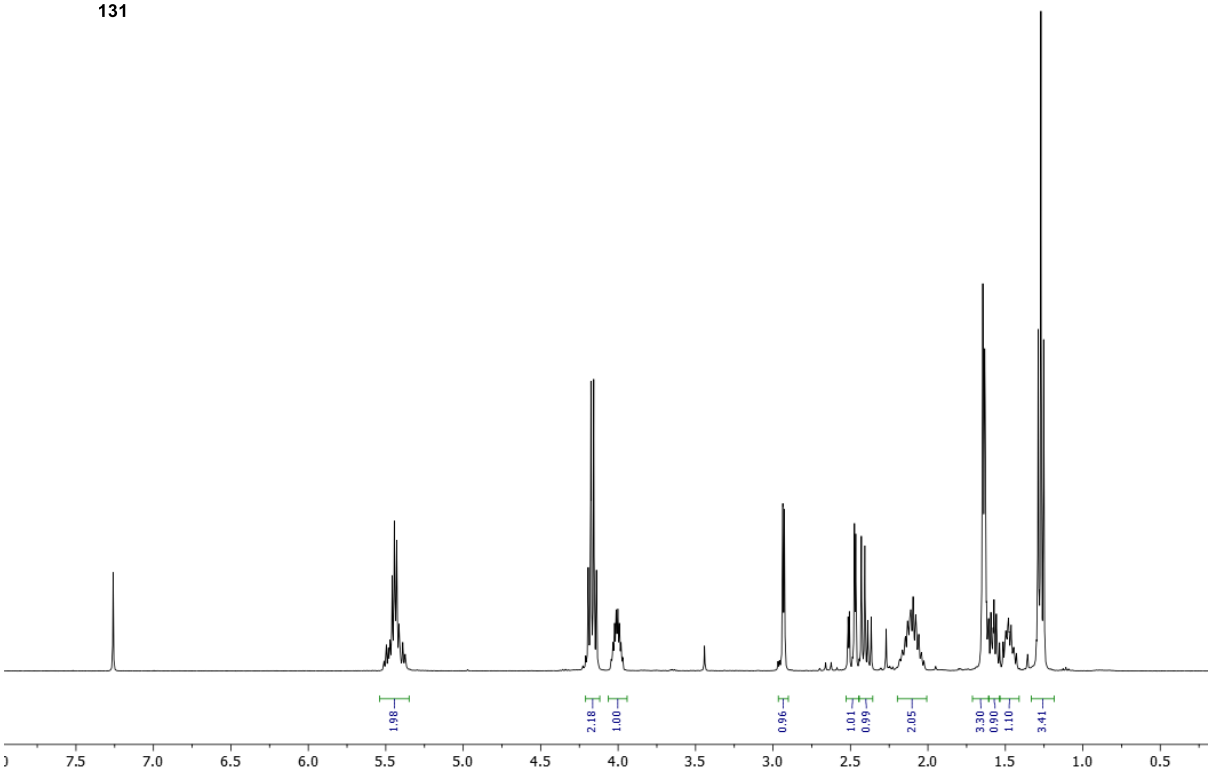
149

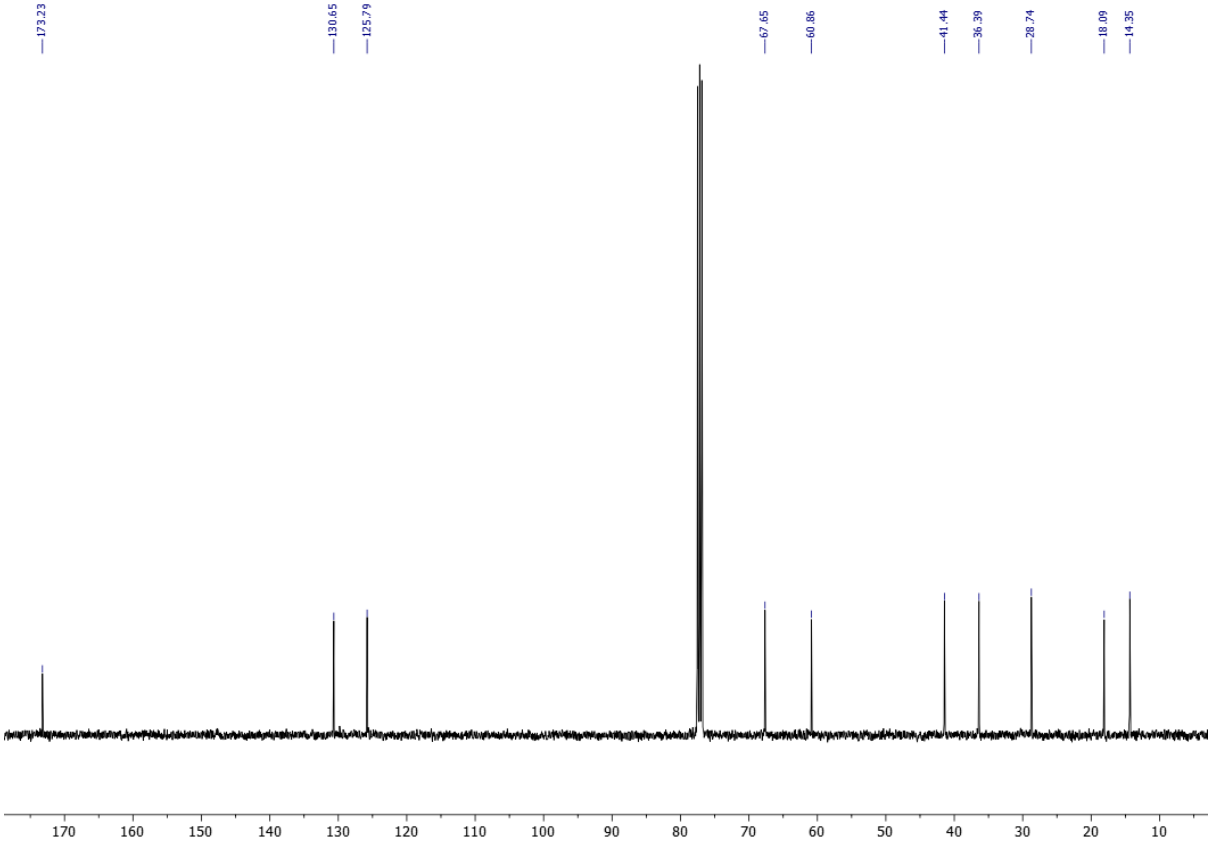

0.90
2.03
1.83
1.74
3.32
5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
202.68
129.09
126.60
43.67
25.33
18.04

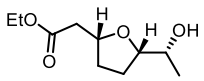

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
OH

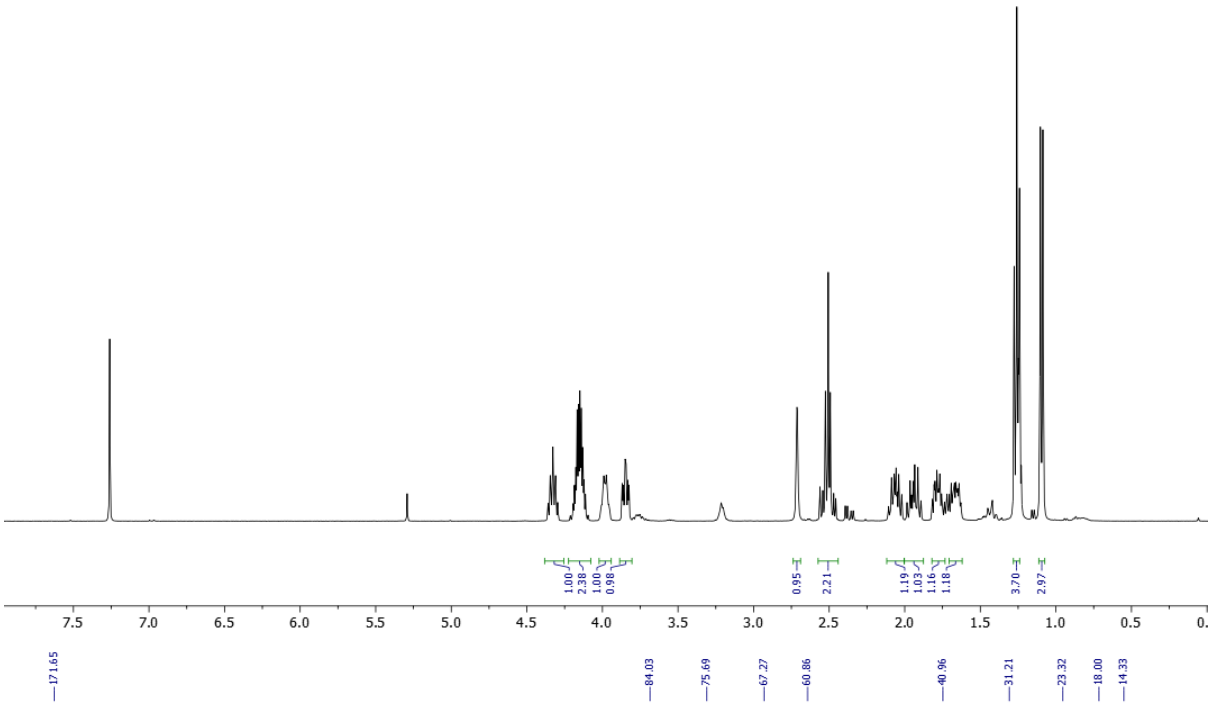
131


1.98
2.18
1.00
0.96
1.01
0.99
2.05
3.30
0.90
1.10
3.41
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

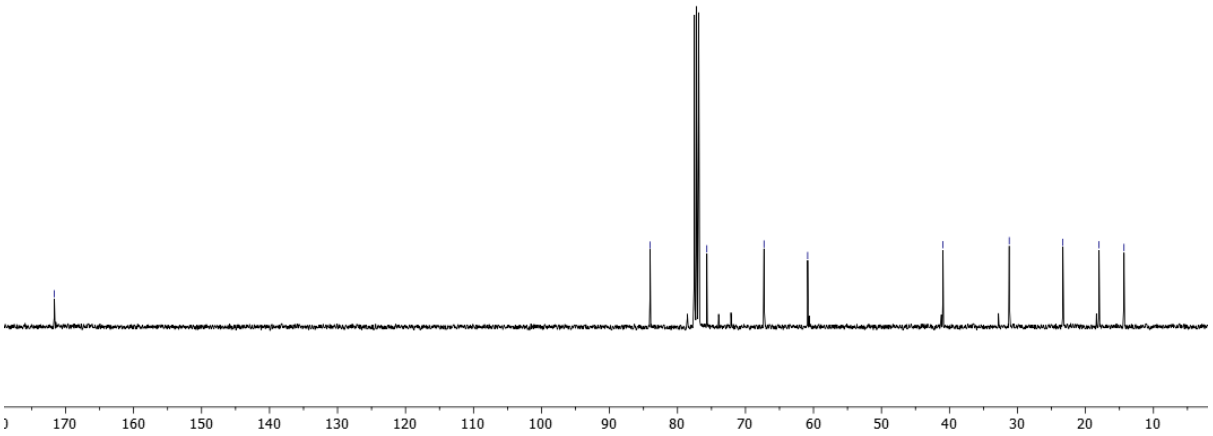

173.23
130.65
125.79
67.65
60.86
41.44
36.39
28.74
18.09
14.35
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
H
O
H
OH

173


1.00
2.38
1.00
0.98
0.95
2.21
1.19
1.03
1.16
1.18
3.70
2.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.

171.65
84.03
75.69
67.27
60.86
40.96
31.21
23.32
18.00
14.33


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

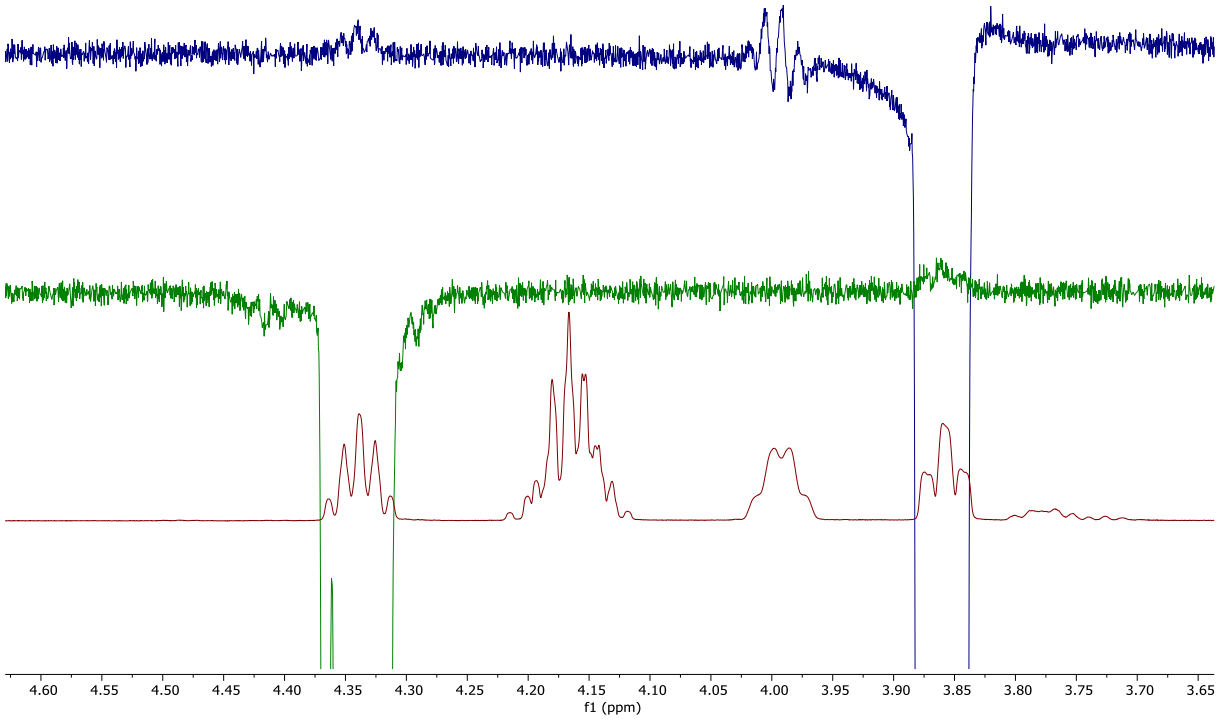
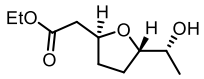
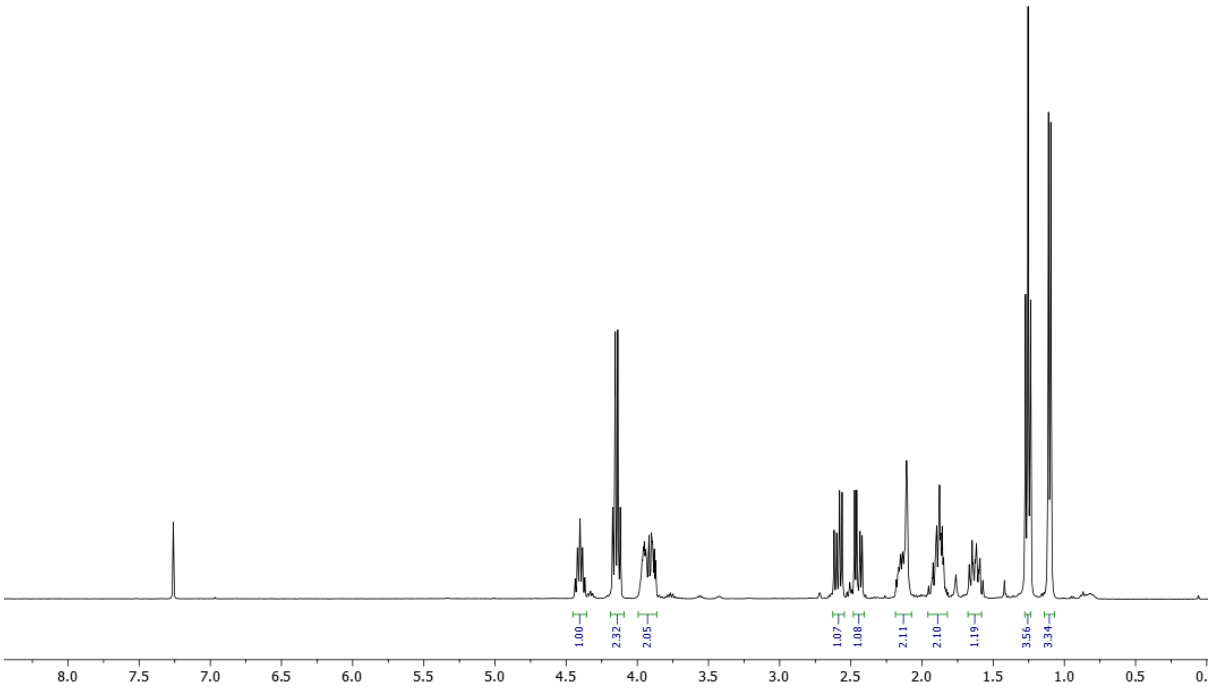
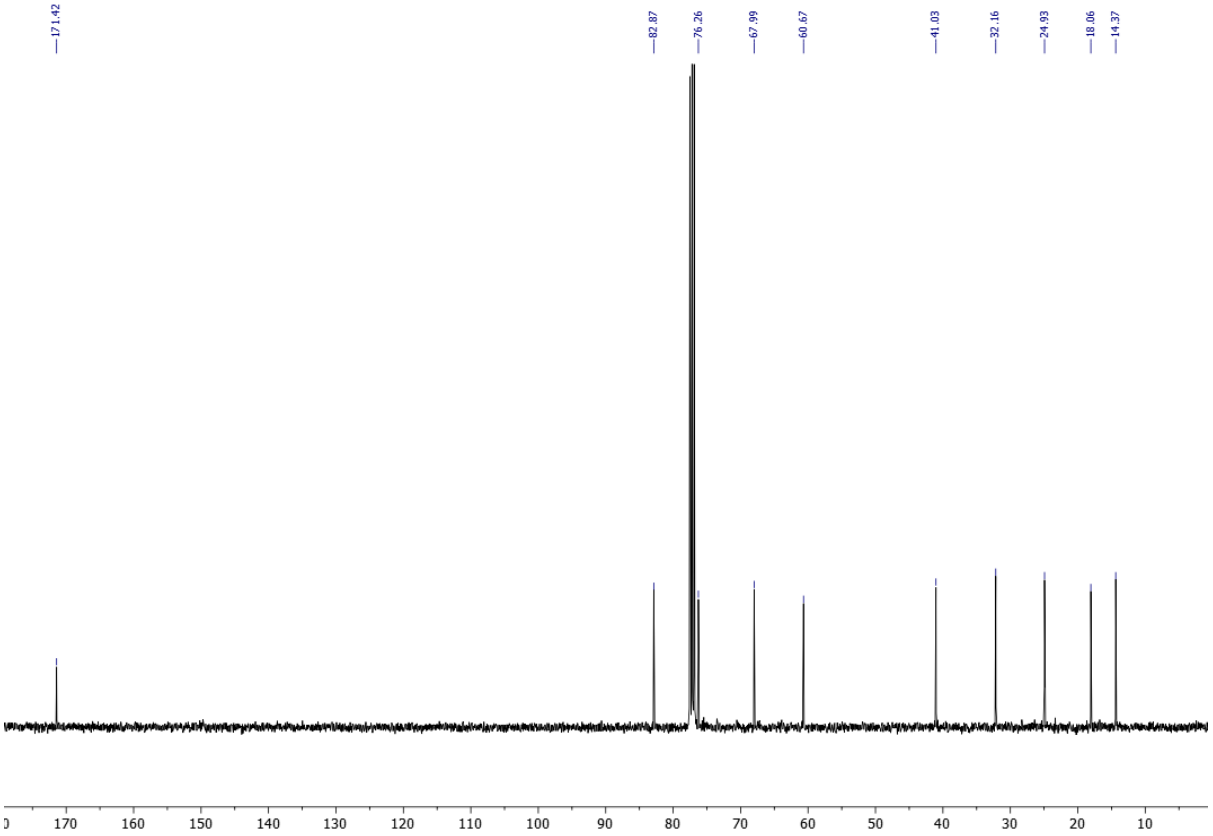


Figure 26. nOe experiment on THF **173**. Blue: Irradiation of 6-H (3.85 ppm) and corresponding nOe enhancement of 3-H (4.33 ppm). Green: Irradiation of 3-H (4.33 ppm) and corresponding nOe enhancement of 6-H (3.85 ppm). Red: ^{1}H-NMR of THF **173**.


EtO
O
H
O
H
OH

172


1.00
2.32
2.05
1.07
1.08
2.11
2.10
1.19
3.56
3.34
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.


171.42
82.87
76.26
67.99
60.67
41.03
32.16
24.93
18.06
14.37
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

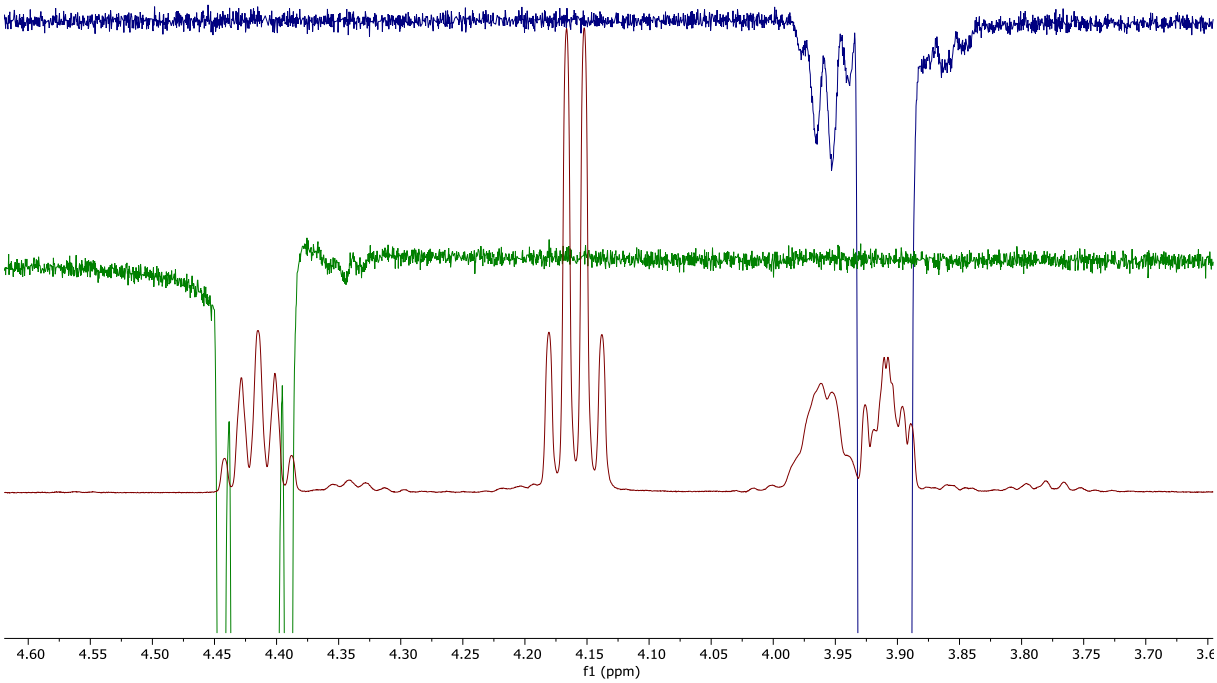
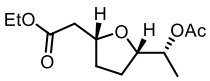
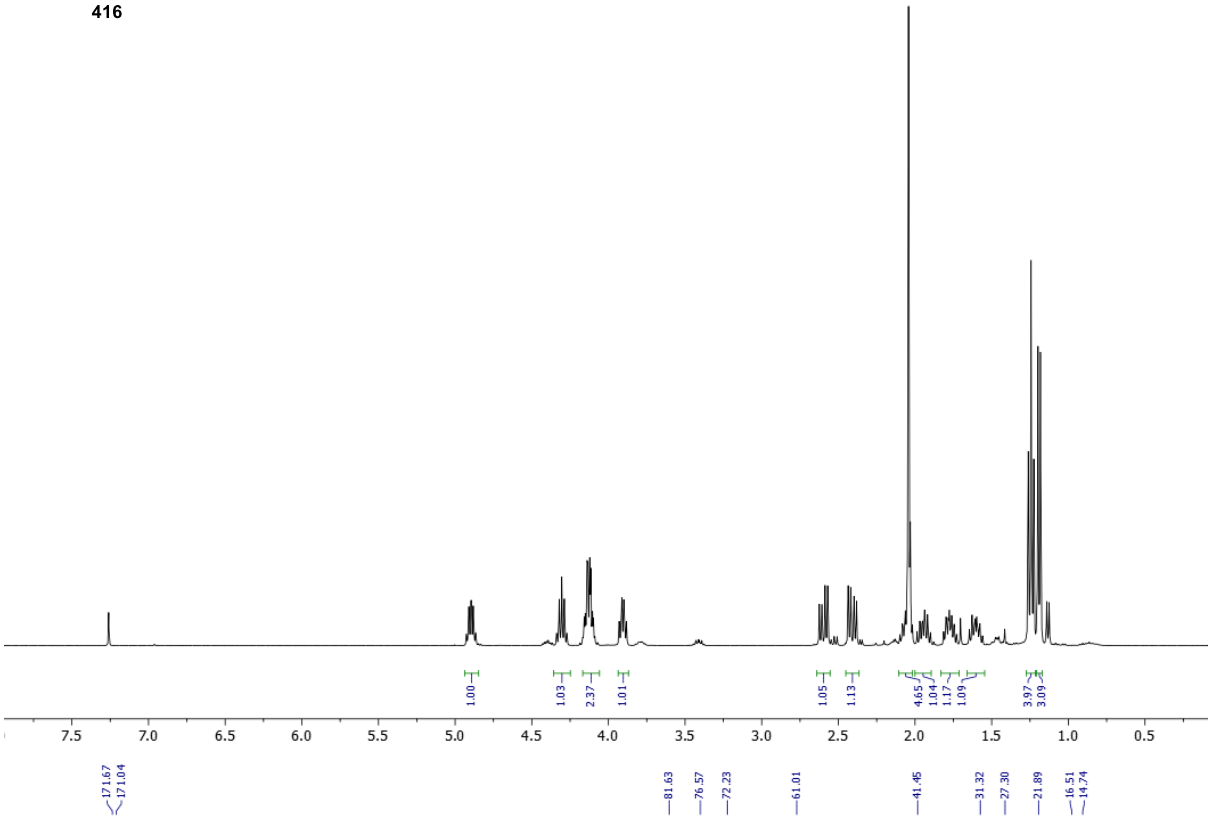


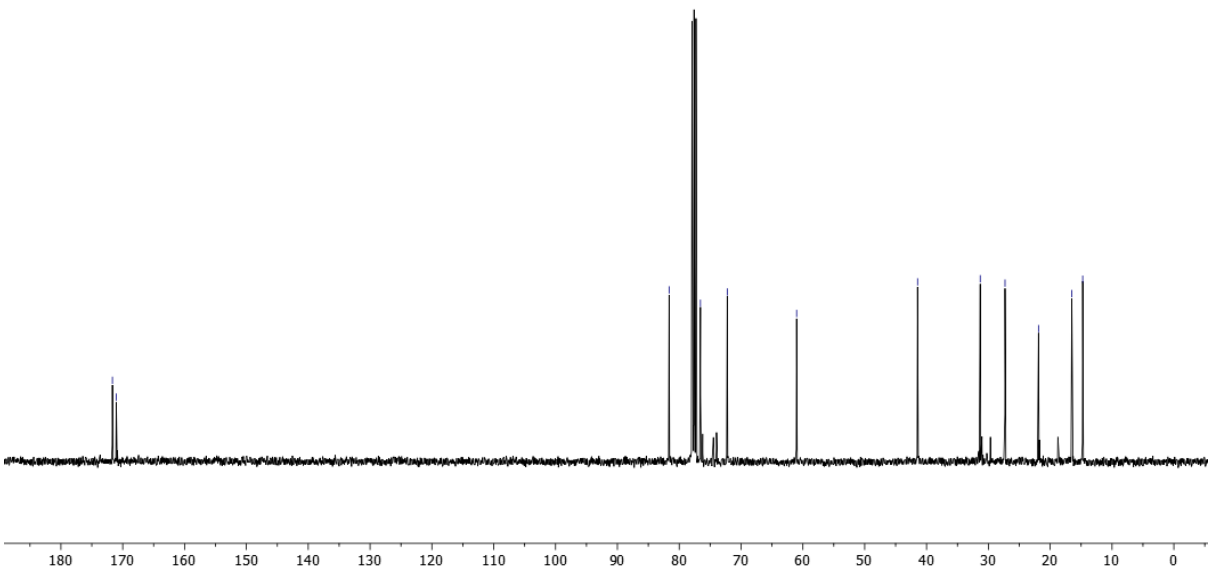
Figure 27. nOe experiment on THF **172**. Blue: Irradiation of 6-H (3.90 ppm) and no observed nOe enhancement of 3-H (4.40 ppm). Green: Irradiation of 3-H (4.40 ppm) and no observed nOe enhancement of 6-H (3.90 ppm). Red: ^{1}H-NMR of THF **172**.


EtO
O
H
O
H
OAc

416


1.00
1.03
2.37
1.01
1.05
1.13
4.65
1.04
1.17
1.09
3.97
3.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

171.67
171.04
81.63
76.57
72.23
61.01
41.45
31.32
27.30
21.89
16.51
14.74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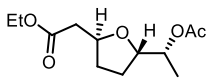
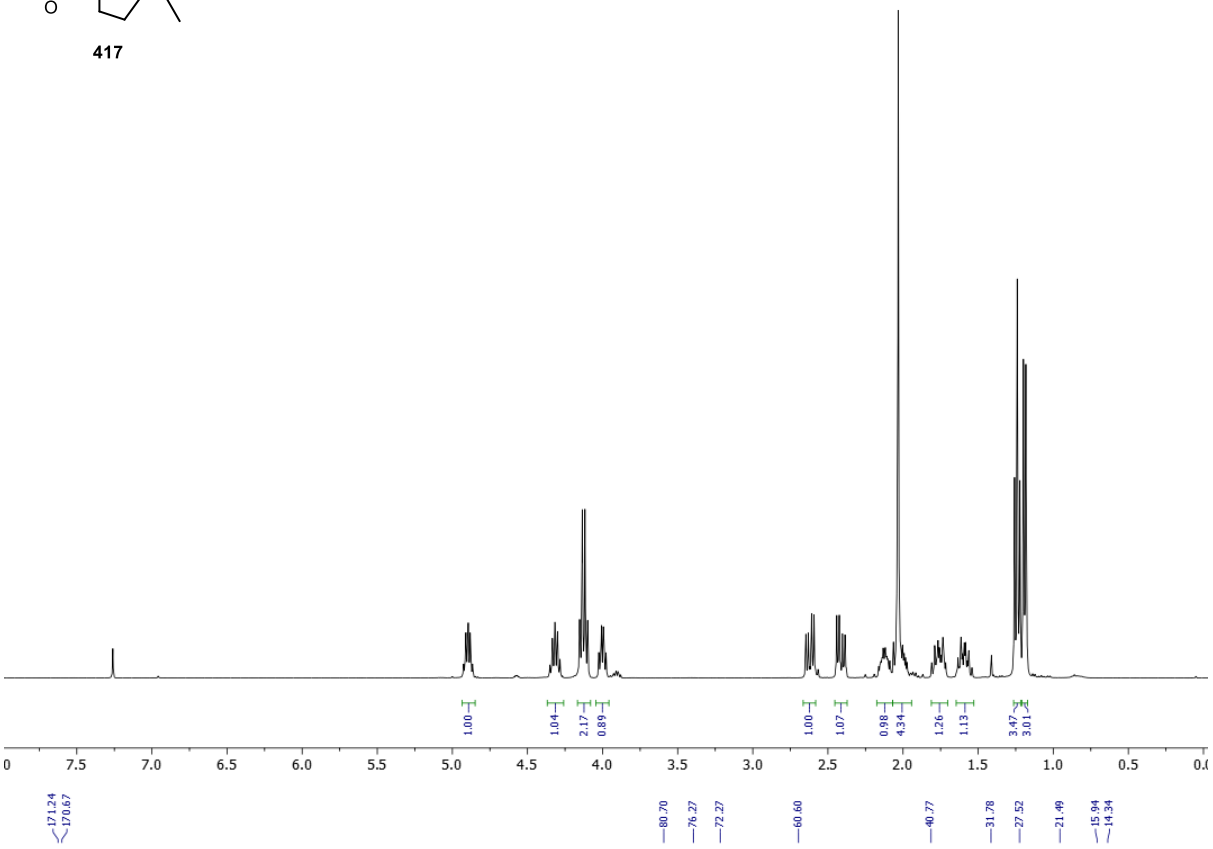

EtO
O
H
O
H
OAc

417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1.26
1.13
3.47
3.01
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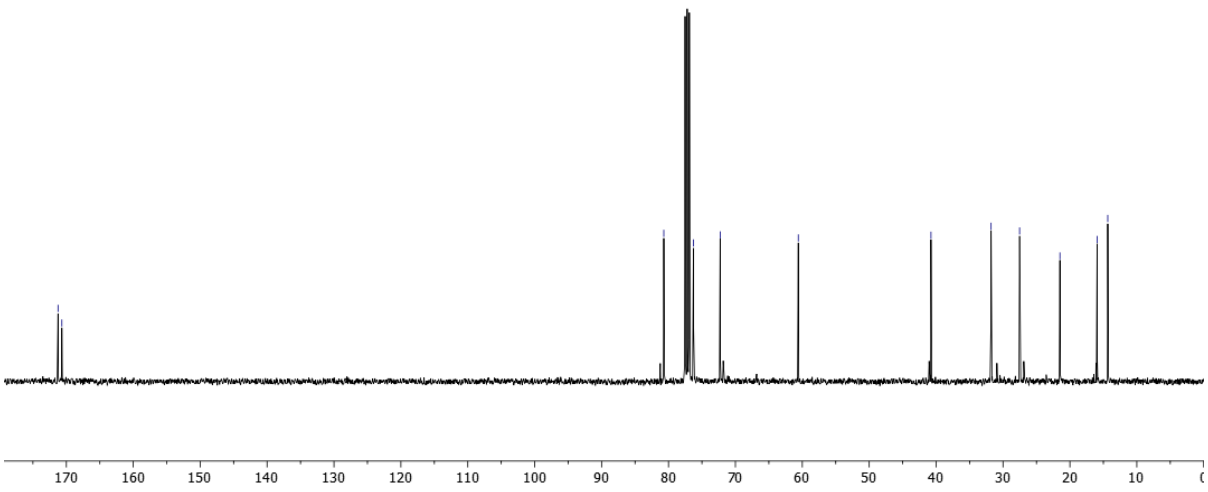
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

171.24
170.67
80.70
76.27
72.27
60.60
40.77
31.78
27.52
21.49
15.94
14.34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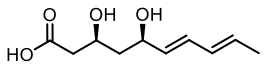
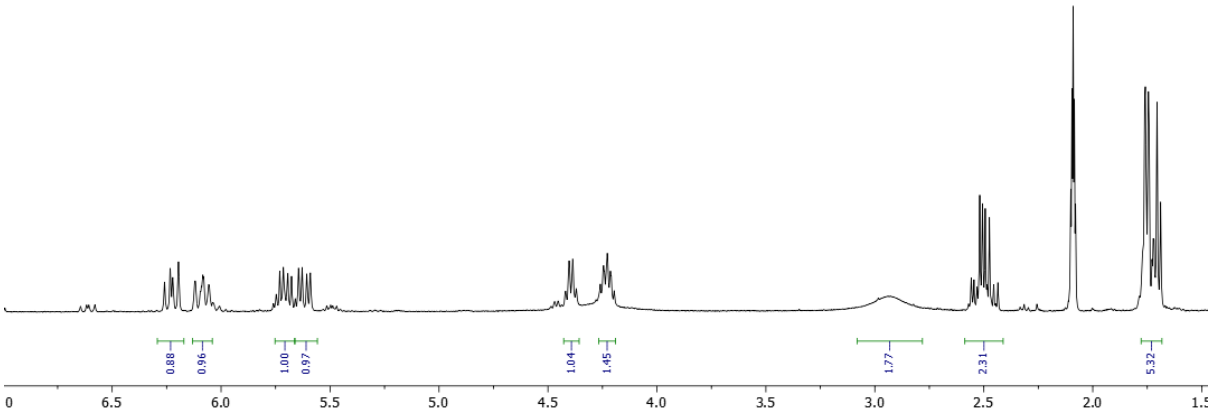

O
OH
OH
HO

132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1.77
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5.32
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6.5
6.0
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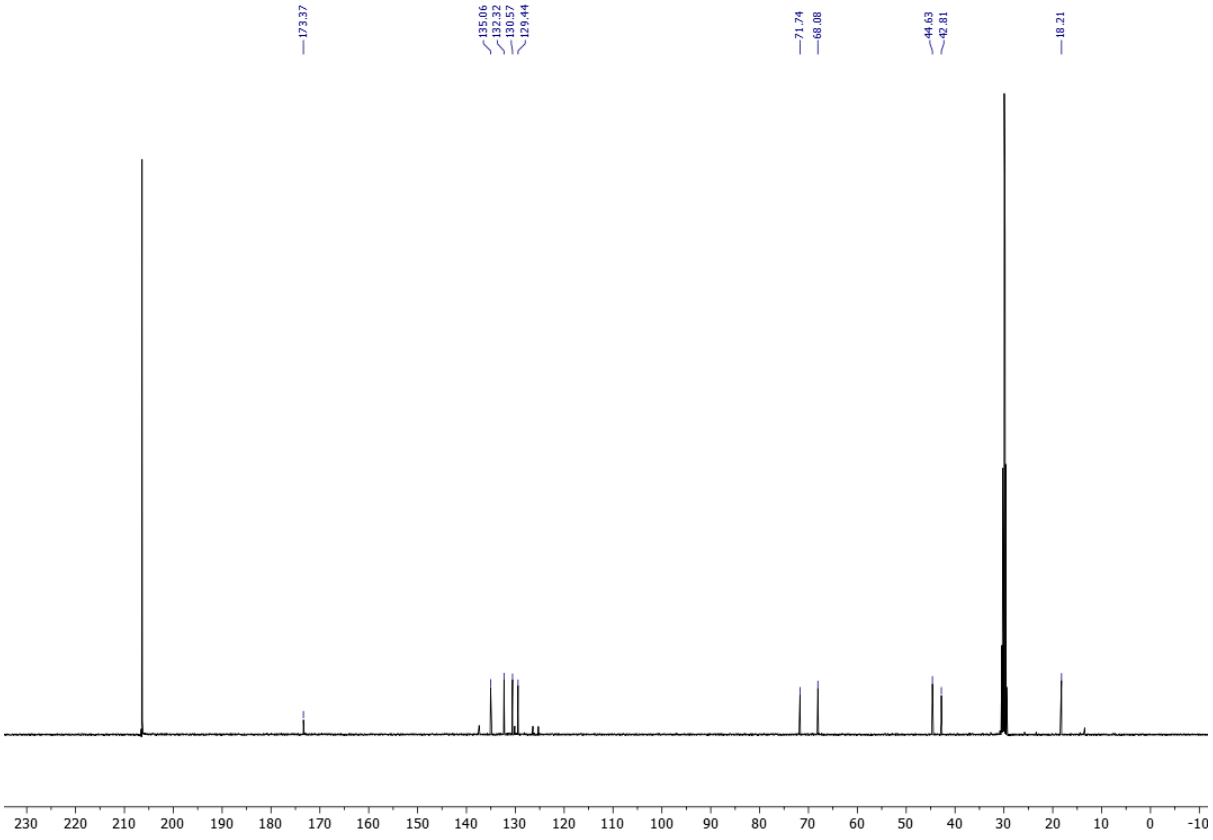
4.5
4.0
3.5
3.0
2.5
2.0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132.32
130.57
129.44
71.74
68.08
44.63
42.81
18.21
230
220
210
200
190
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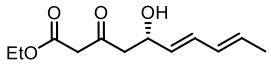
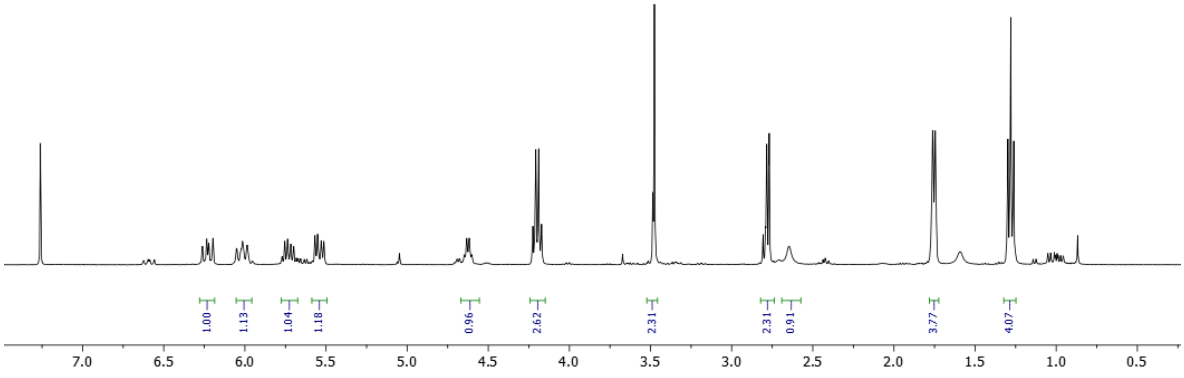

O
O
OH
EtO

180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1.04
1.18
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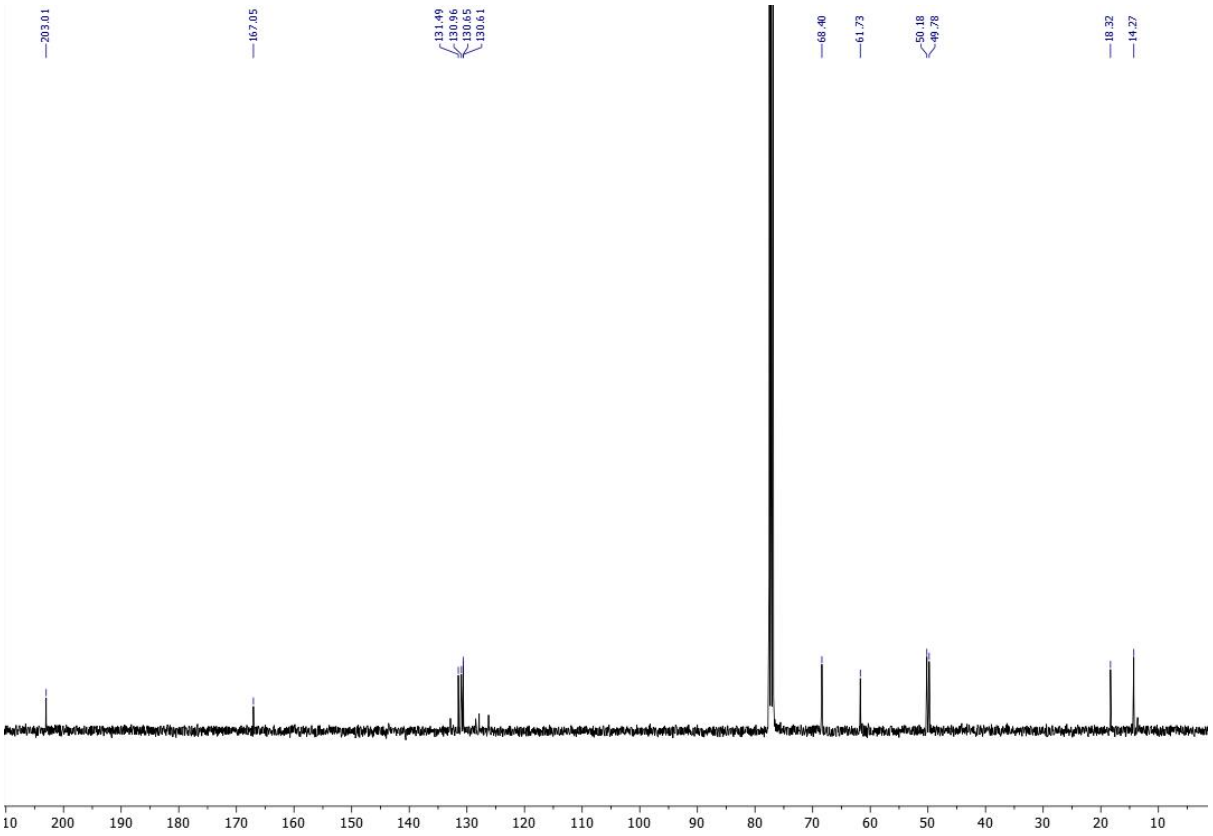
2.31
2.31
0.91
3.77
4.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


203.01
167.05
131.49
130.96
130.65
130.61
68.40
61.73
50.18
49.78
18.32
14.27
210
200
190
180
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160
150
140
130
120
110
100
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80
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40
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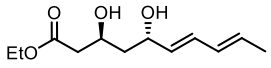
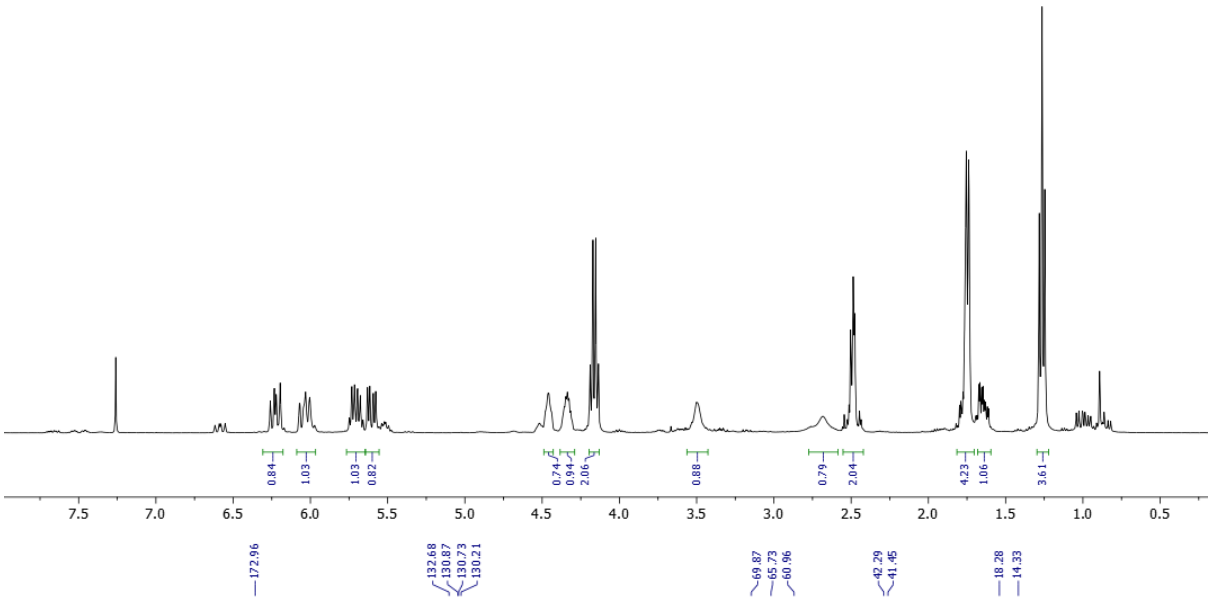
20
10


O
OH
OH
EtO

181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1.03
0.82
0.74
0.94
2.06
0.88
0.79
2.04
4.23
1.06
3.61
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

172.96
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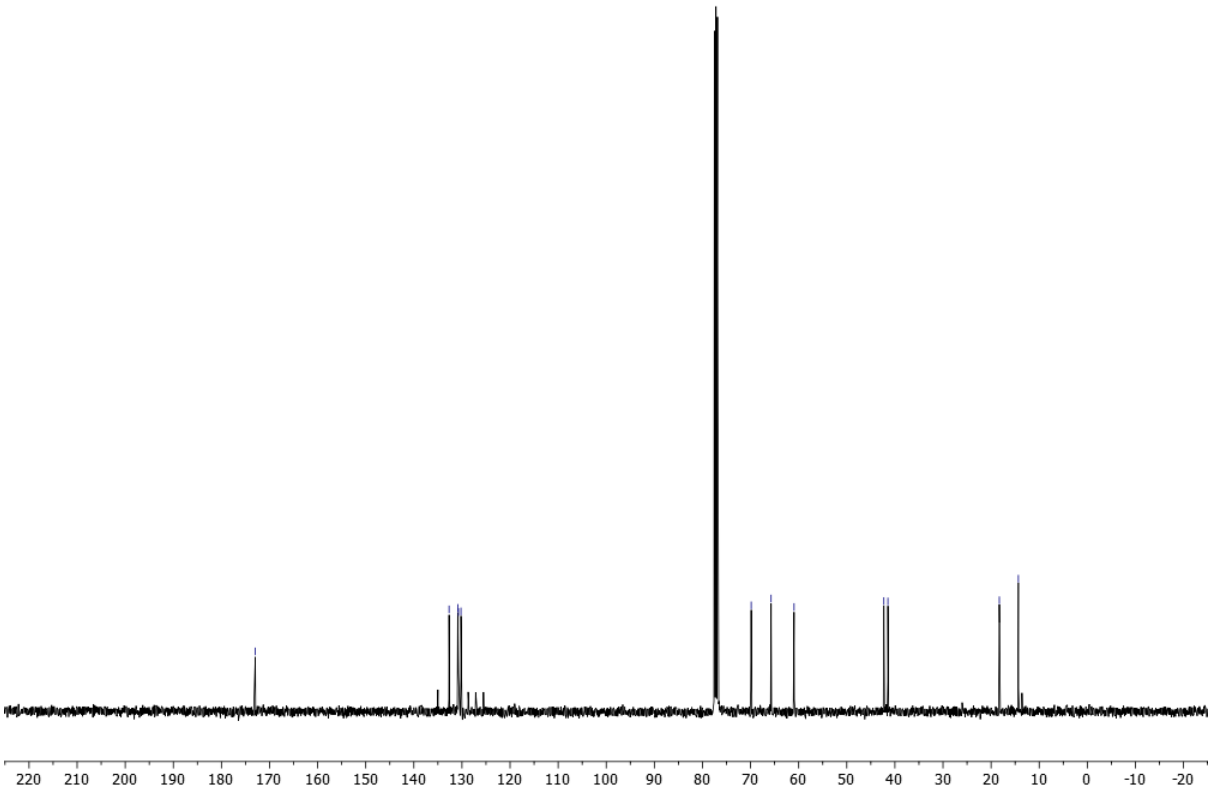
130.87
130.73
130.21
69.87
65.73
60.96
42.29
41.45
18.28
14.33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180
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120
110
100
90
80
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50
40
30
20
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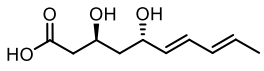
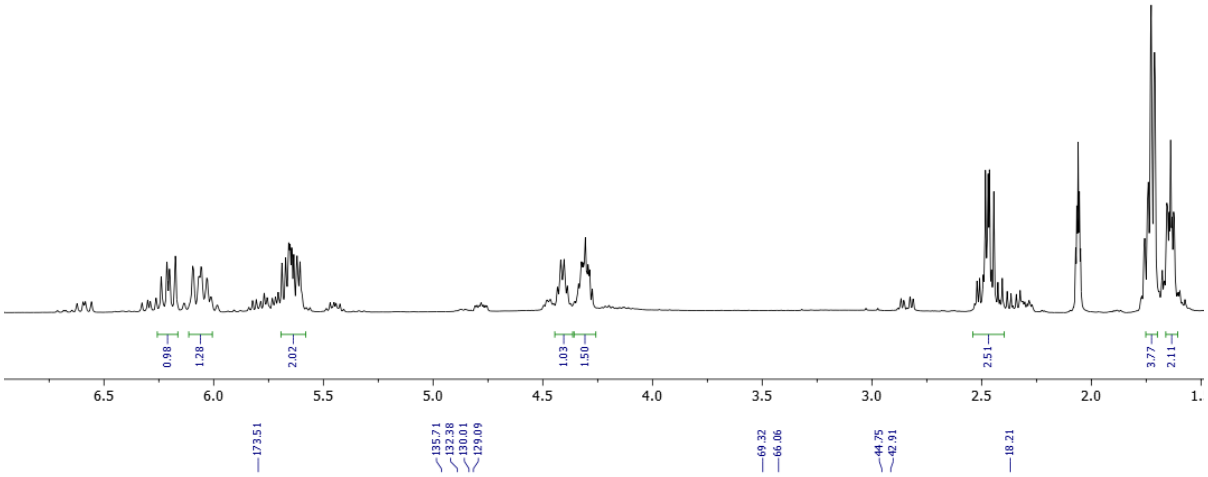
0
-10
-20


O
OH
OH
HO

135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2.51
3.77
2.11
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.
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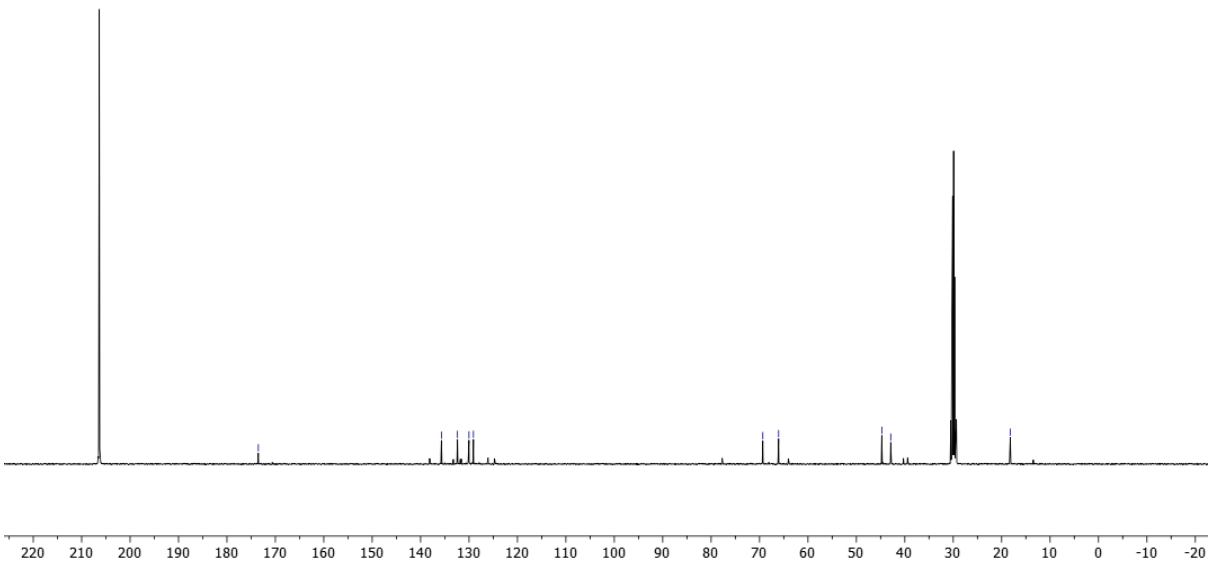
130.01
129.09
69.32
66.06
44.75
42.91
18.21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180
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110
100
90
80
70
60
50
40
30
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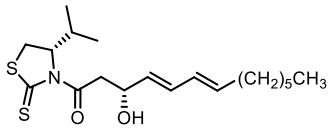
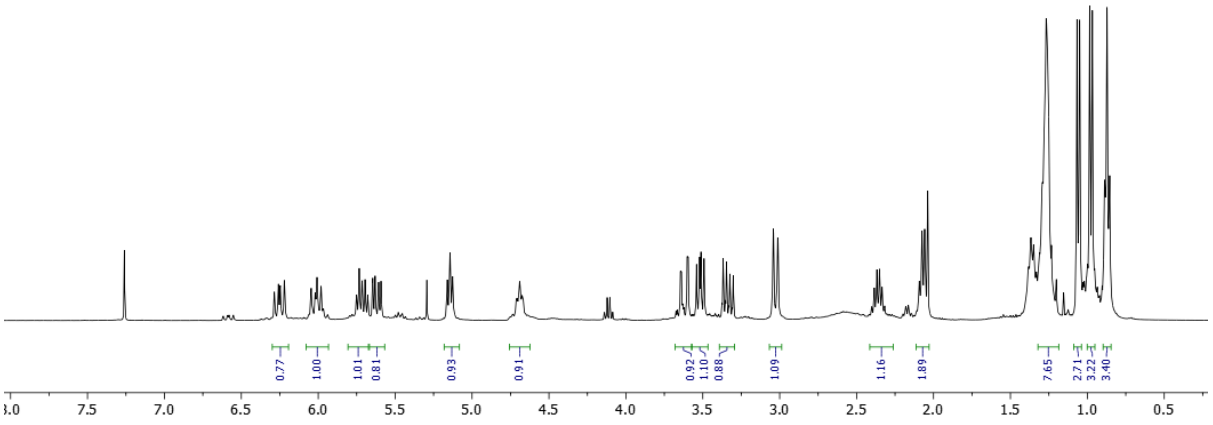
10
0
-10
-20


S
N
S
O
OH
(CH2)5CH3

184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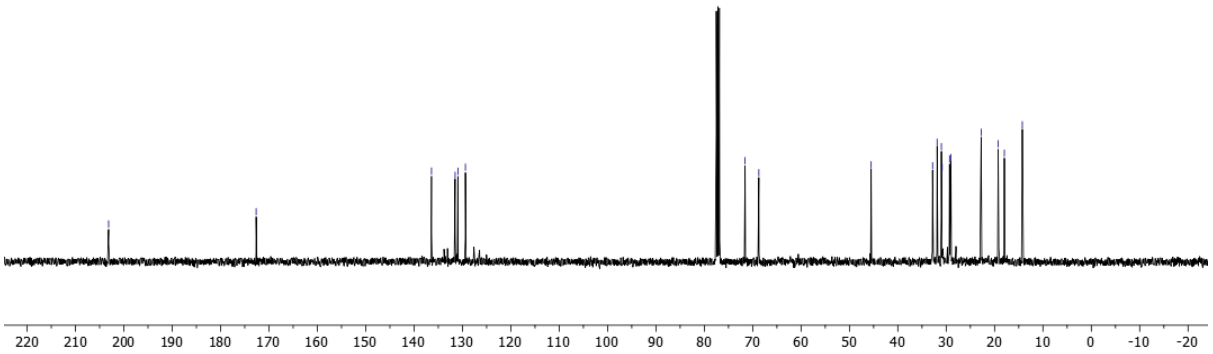
0.93
0.91
0.92
1.10
0.88
1.09
1.16
1.89
7.65
2.71
3.22
3.40
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


203.15
172.65
136.40
131.52
130.94
129.39
71.58
68.73
45.51
32.82
31.88
31.00
30.83
29.32
29.03
22.77
19.25
17.98
14.26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210
200
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180
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110
100
90
80
70
60
50
40
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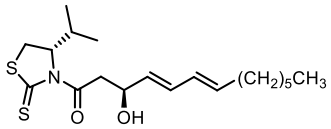
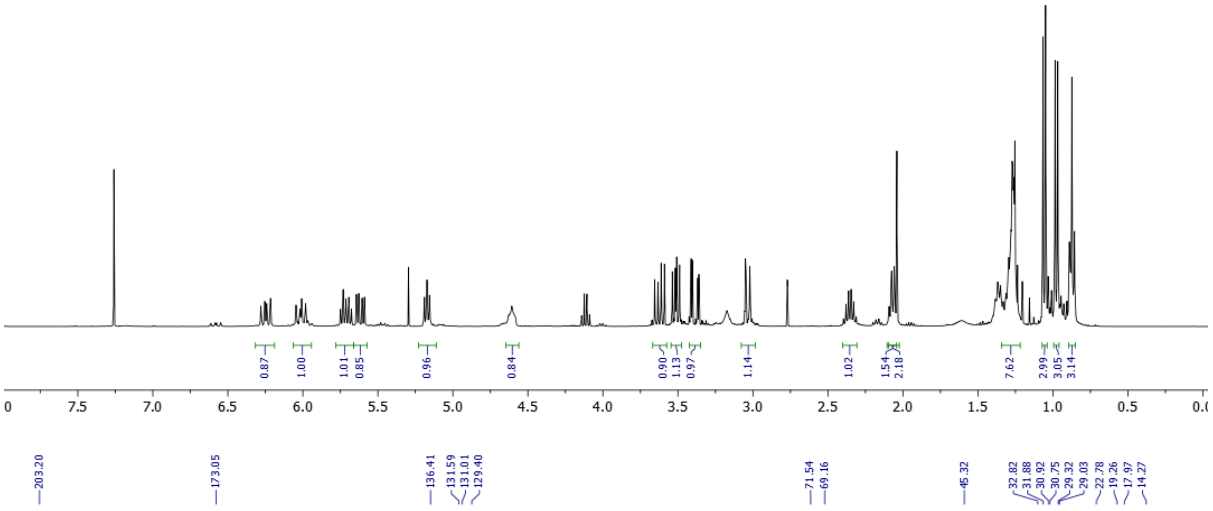
0
-10
-20


S
N
S
O
OH
(CH2)5CH3

185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0.90
1.13
0.97
1.14
1.02
1.54
2.18
7.62
2.99
3.05
3.14
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

203.20
173.05
136.41
131.59
131.01
129.40
71.54
69.16
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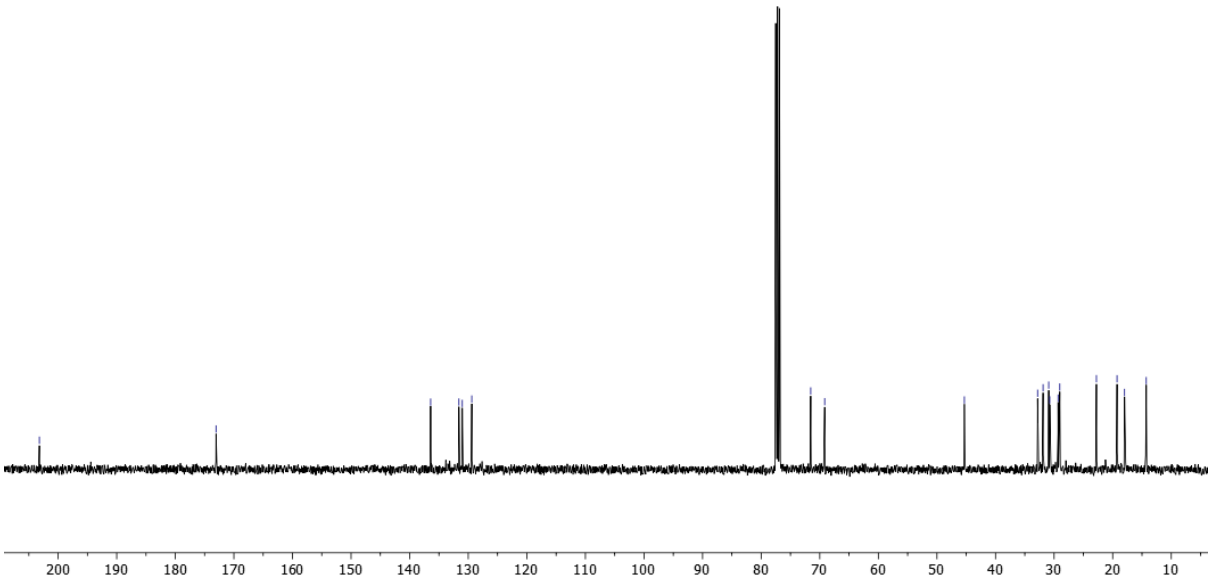
32.82
31.88
30.92
30.75
29.32
29.03
22.78
19.26
17.97
14.27


200
190
180
170
160
150
140
130
120
110
100
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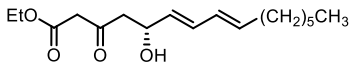
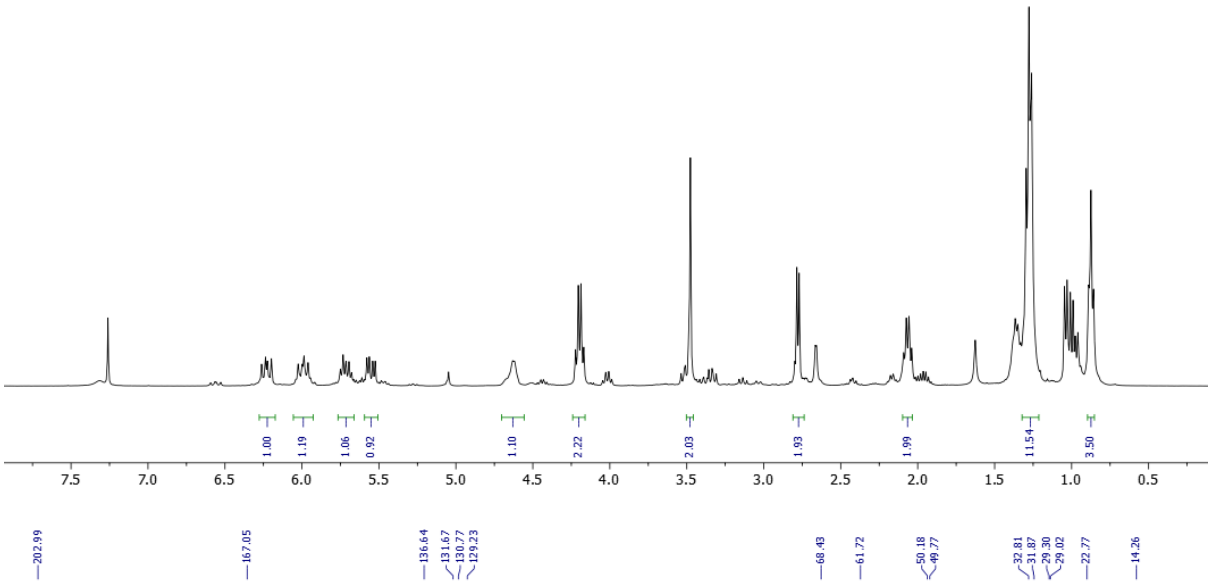
80
70
60
50
40
30
20
10


EtO
O
O
OH
(CH2)5CH3

186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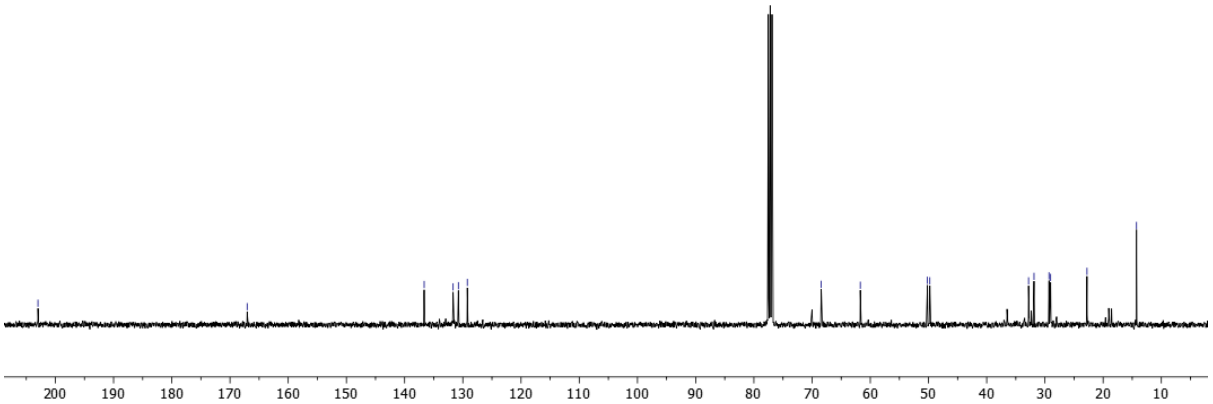
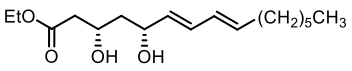
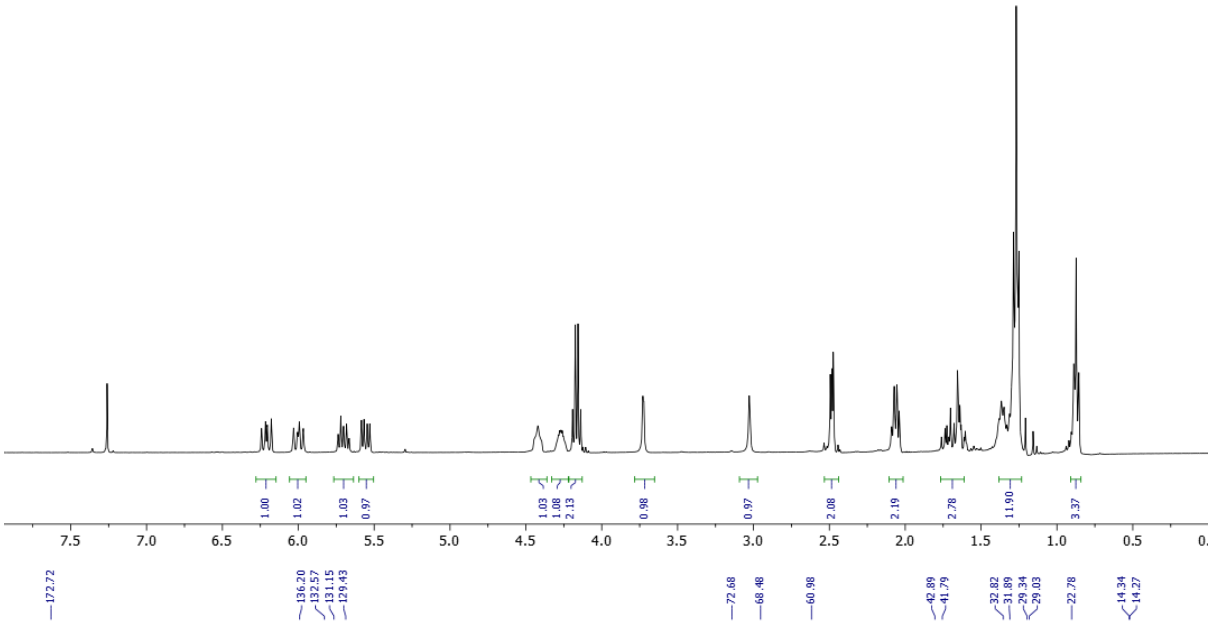
1.06
0.92
1.10
2.22
2.03
1.93
1.99
11.54
3.50
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

202.99
167.05
136.64
131.67
130.77
129.23
68.43
61.72
50.18
49.77
32.81
31.87
29.30
29.02
22.77
14.26


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


EtO
O
OH
OH
(CH2)5CH3

188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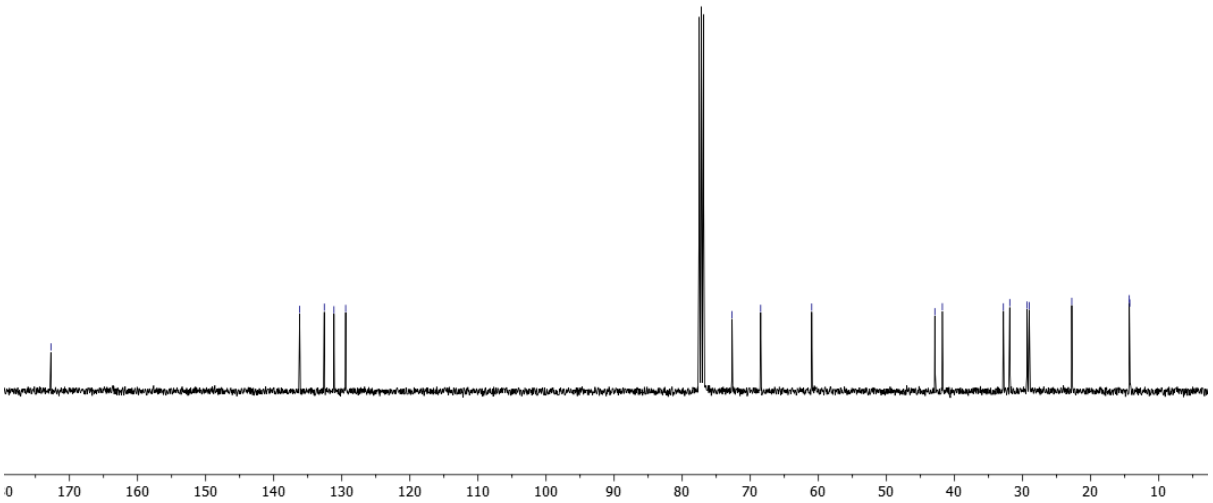
1.03
1.08
2.13
0.98
0.97
2.08
2.19
2.78
11.90
3.37
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
172.72
136.20
132.57
131.15
129.43
72.68
68.48
60.98
42.89
41.79
32.82
31.89
29.34
29.03
22.78
14.34
14.27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120
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100
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40
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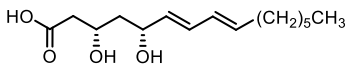
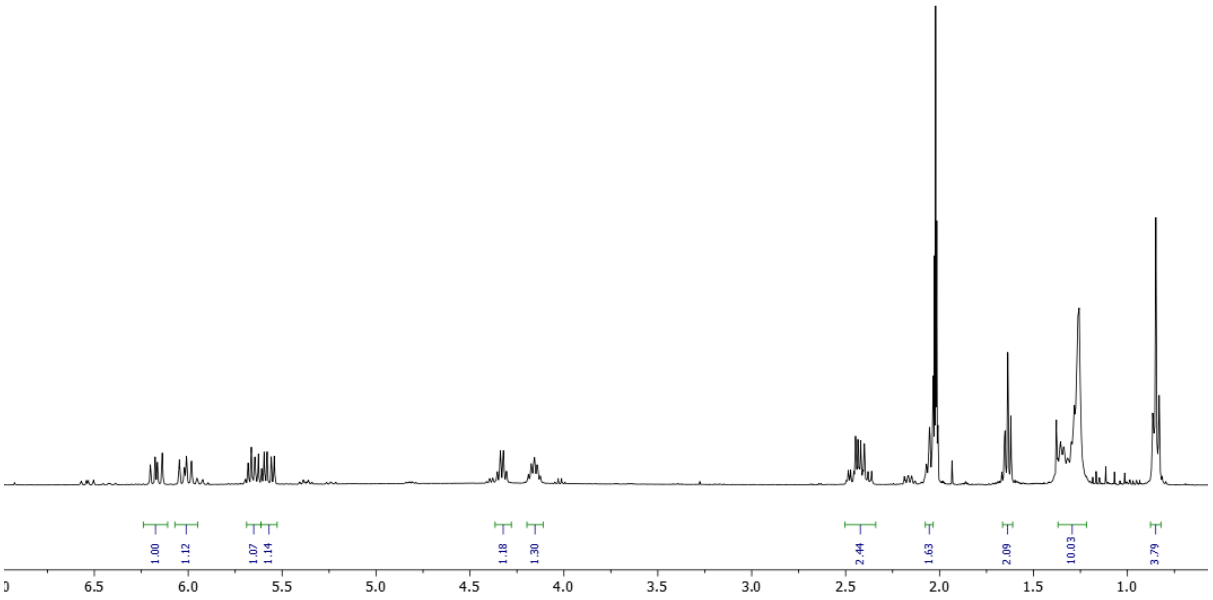
20
10


HO
O
OH
OH
(CH2)5CH3

133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1.07
1.14
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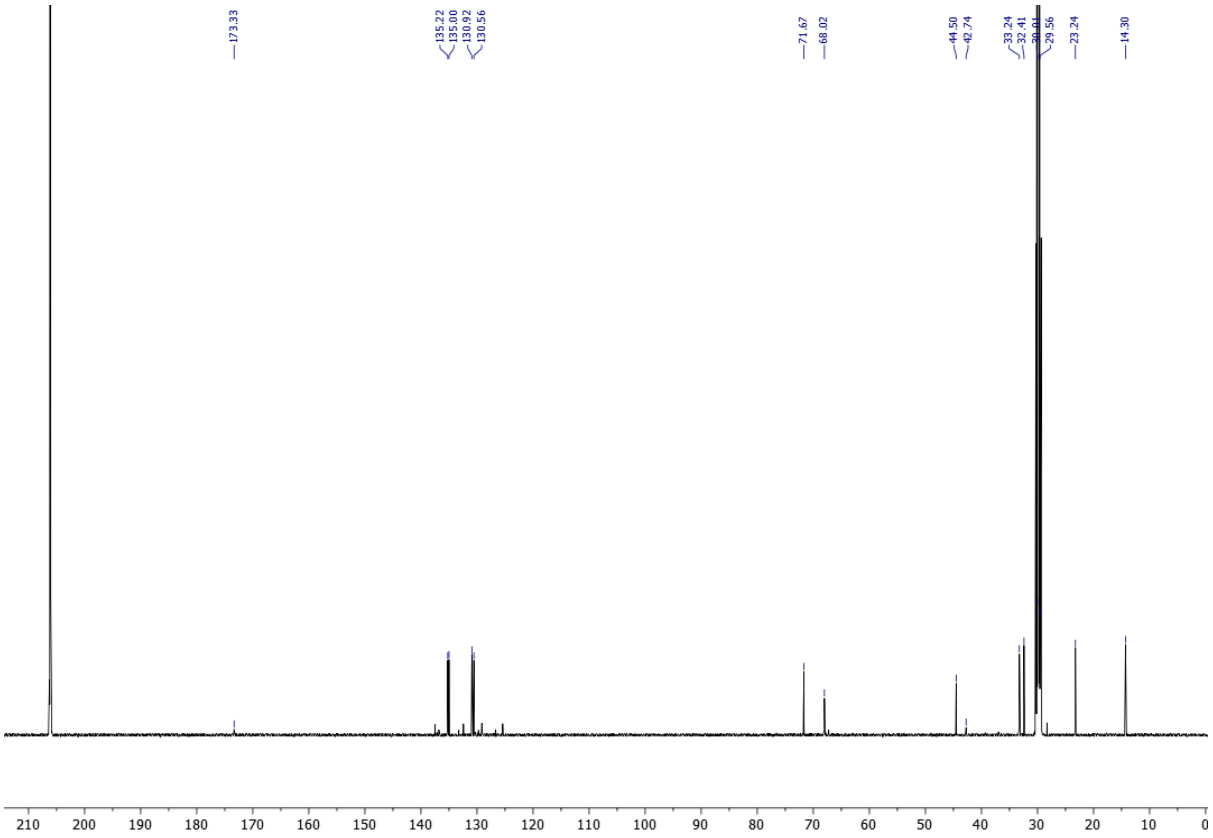
1.30
2.44
1.63
2.09
10.03
3.79
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0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135.22
135.00
130.92
130.56
71.67
68.02
44.50
42.74
33.24
32.41
30.01
29.56
23.24
14.30
210
200
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150
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110
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70
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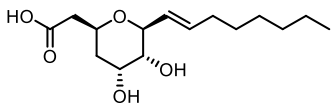
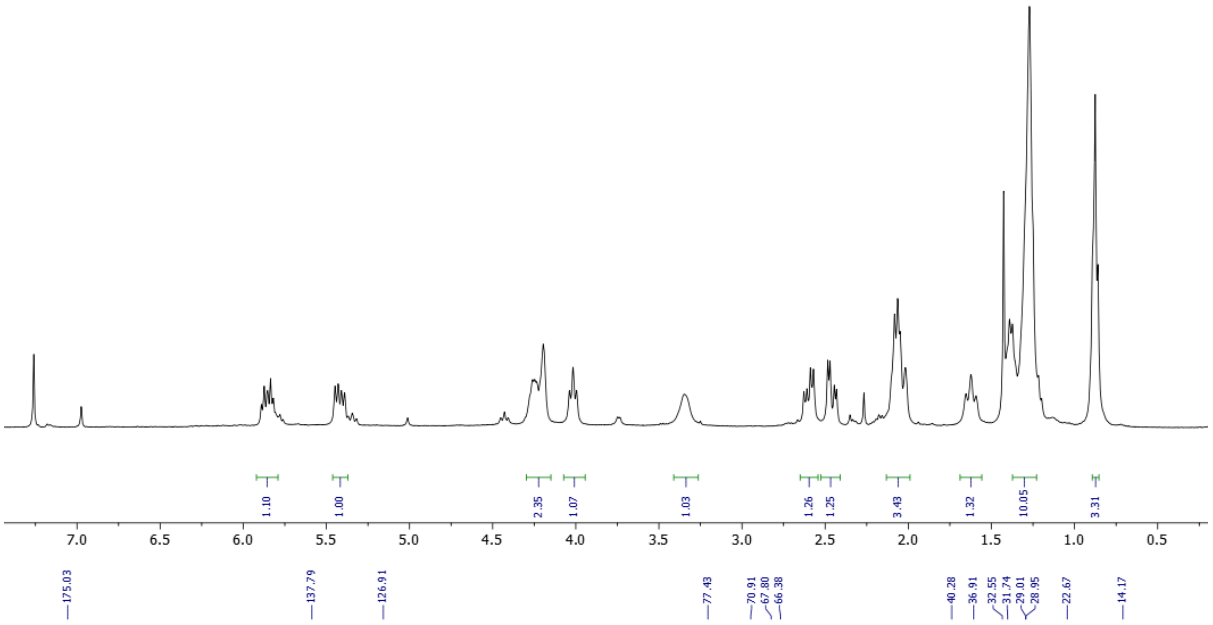
50
40
30
20
10
0


HO
O
O
OH
OH

139


1.10
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1.07
1.03
1.26
1.25
3.43
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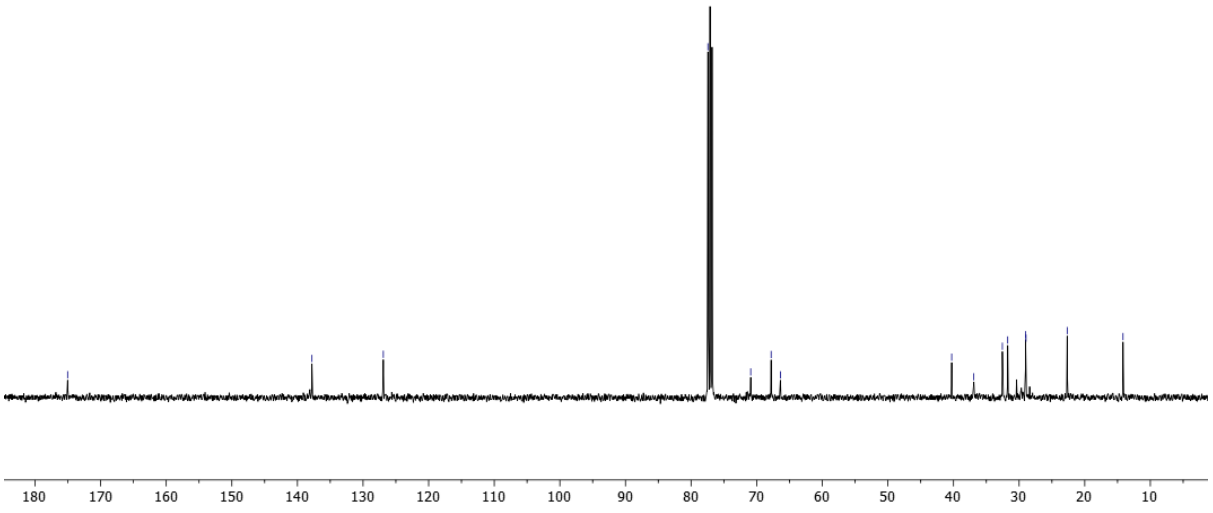
10.05
3.31
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
175.03
137.79
126.91
77.48
70.91
67.80
66.38
40.28
36.91
32.55
31.74
29.01
28.95
22.67
14.17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170
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150
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100
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80
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20
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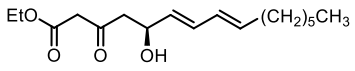
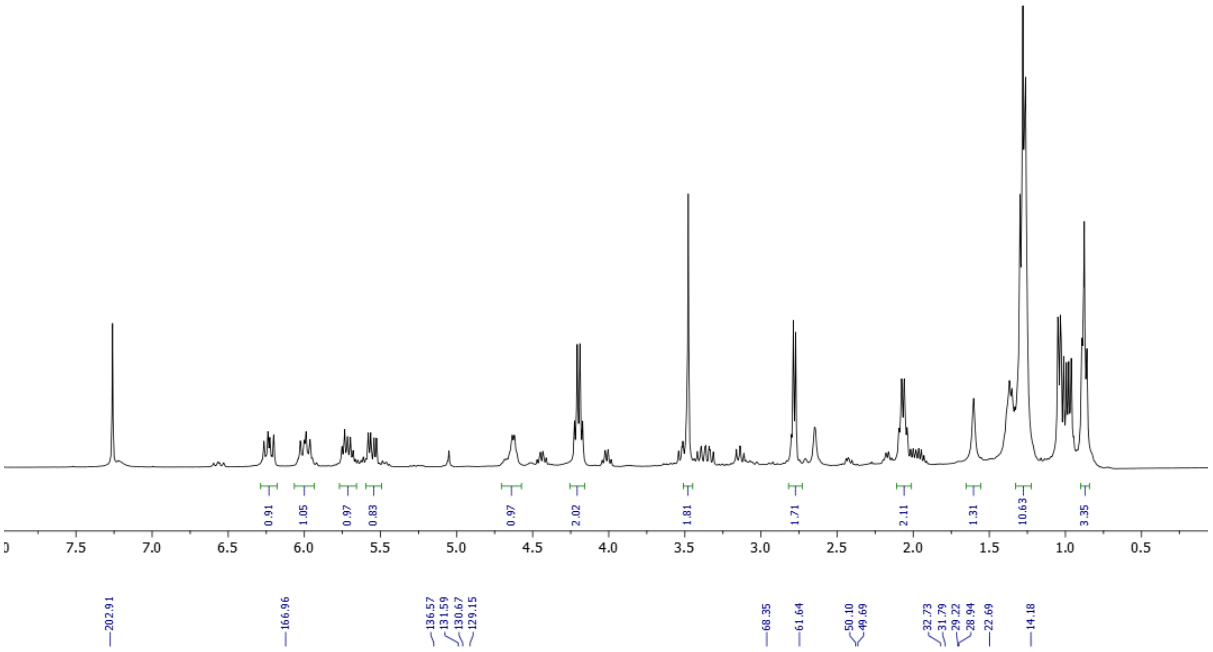

EtO
O
O
OH
(CH2)5CH3

187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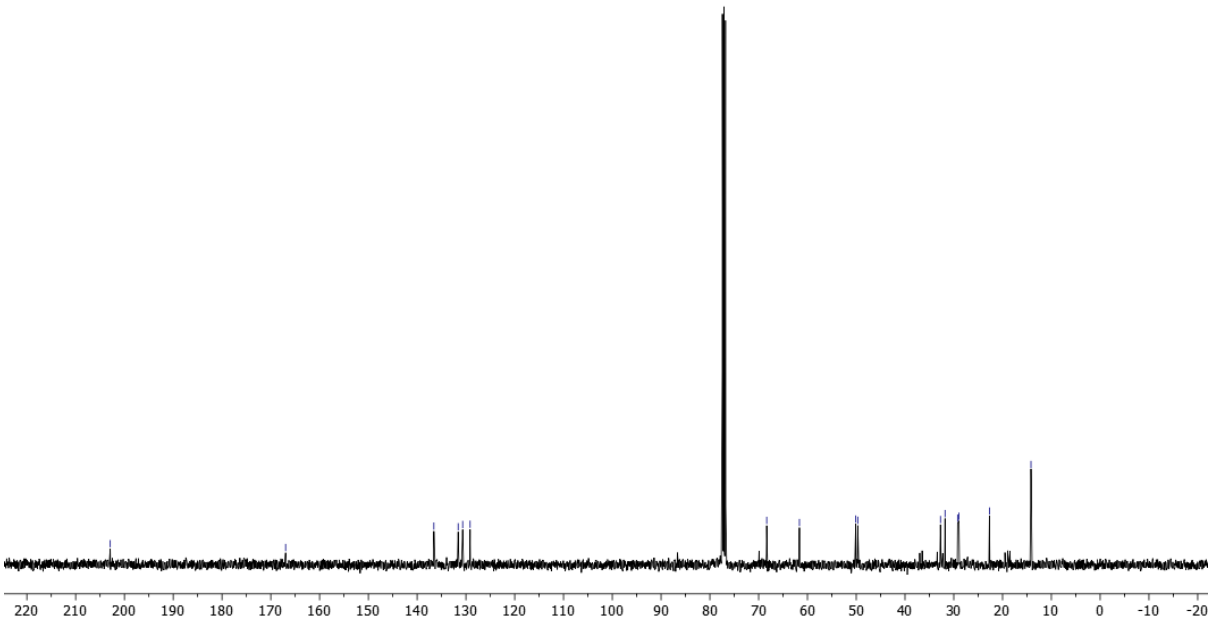
1.05
0.97
0.83
0.97
2.02
1.81
1.71
2.11
1.31
10.63
3.35
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

202.91
166.96
136.57
131.59
130.67
129.15
68.35
61.64
50.10
49.69
32.73
31.79
29.22
28.94
22.69
14.18


220
210
200
190
180
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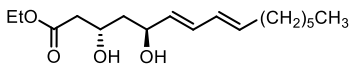
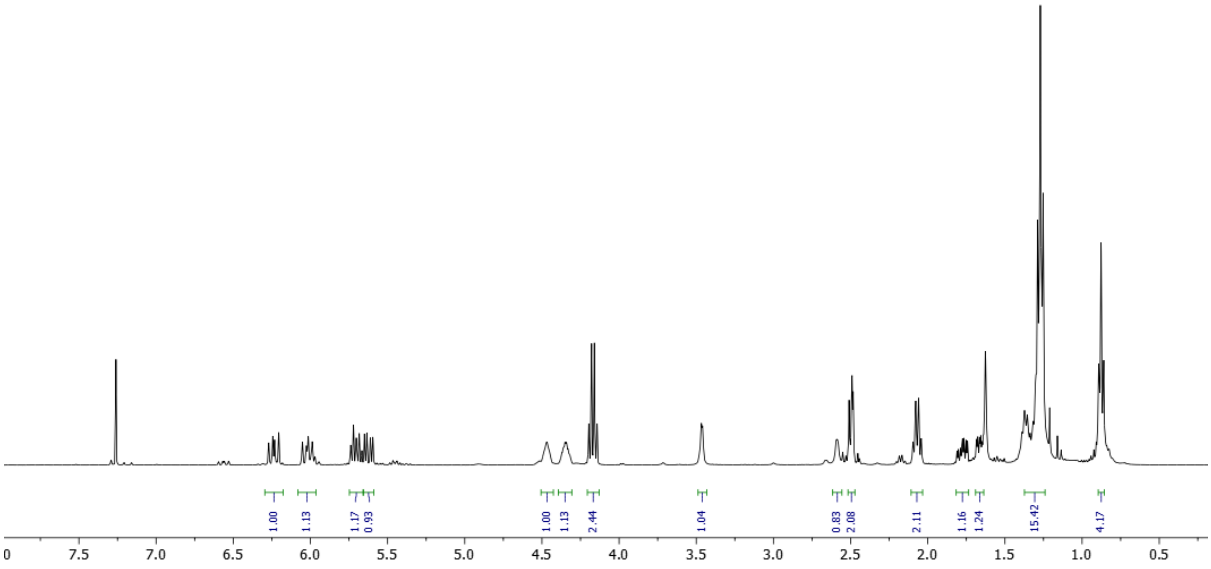
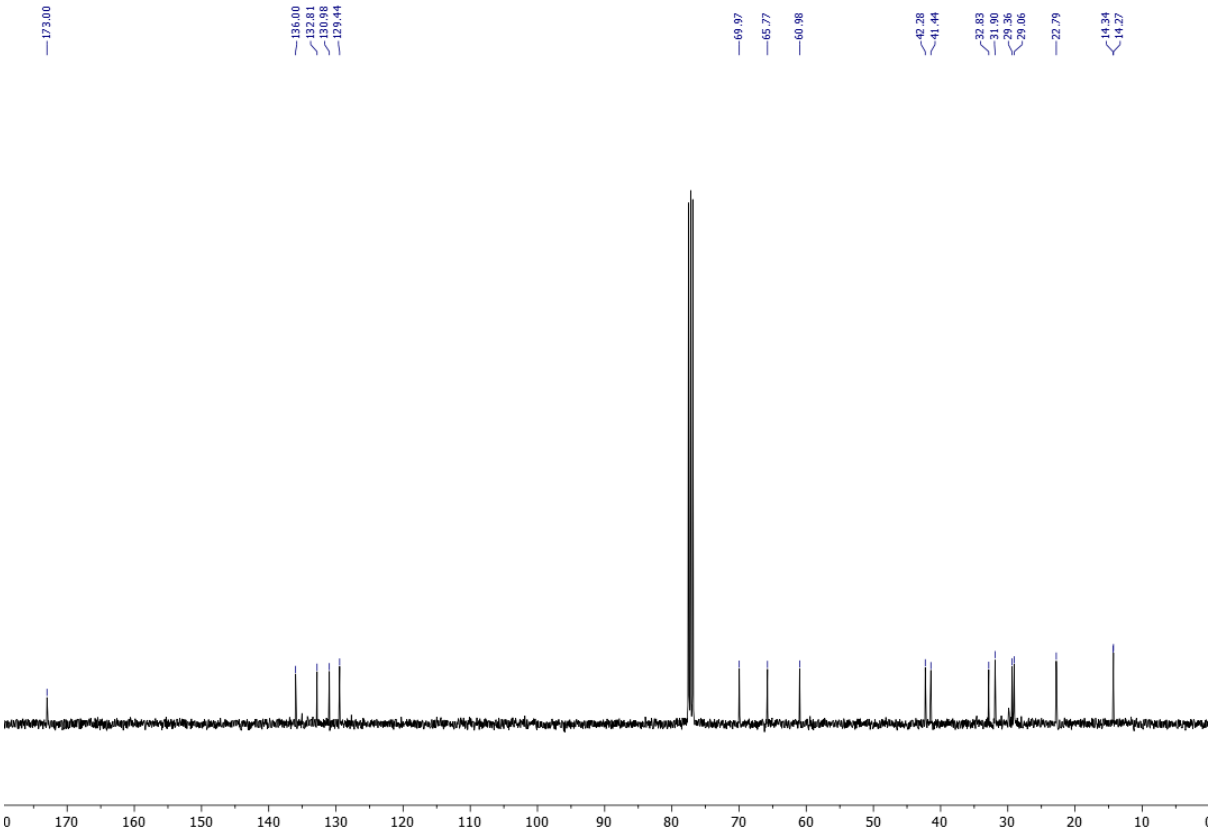
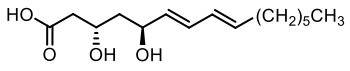
10
0
-10
-20


EtO
O
OH
OH
(CH2)5CH3

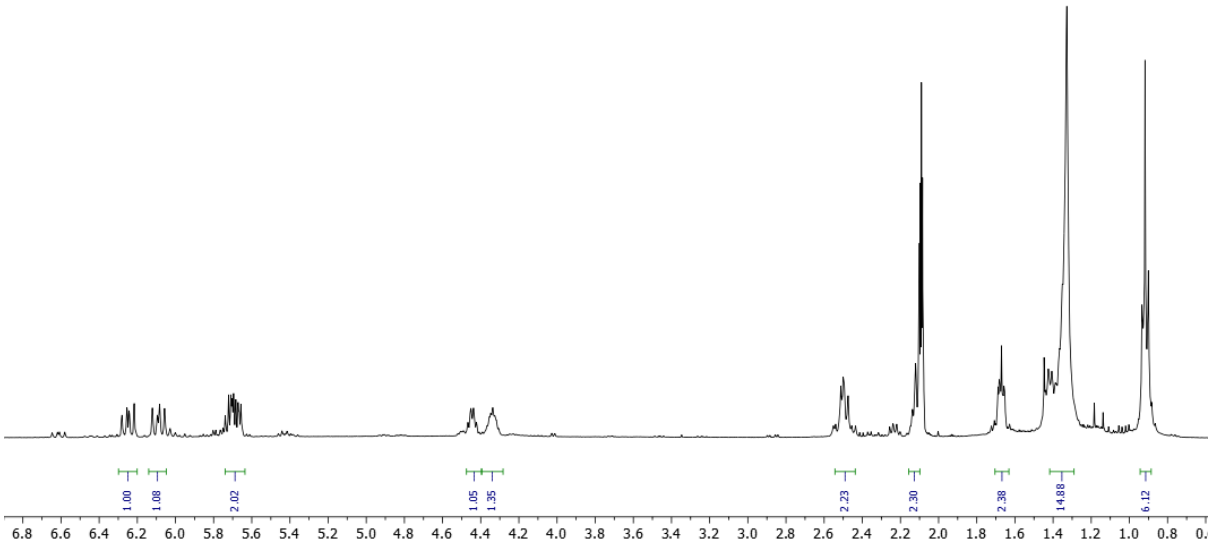
418

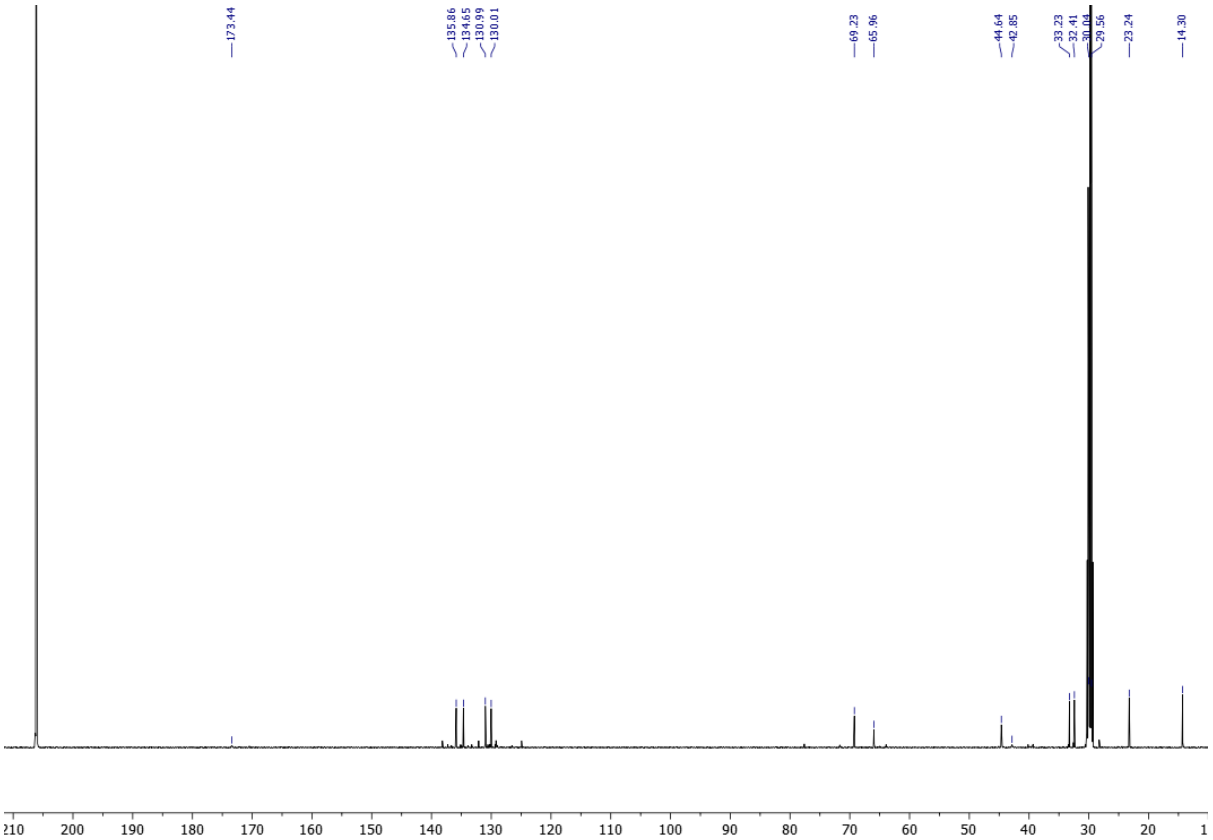

1.00
1.13
1.17
0.93
1.00
1.13
2.44
1.04
0.83
2.08
2.11
1.16
1.24
15.42
4.17
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

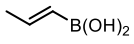

173.00
136.00
132.81
130.98
129.44
69.97
65.77
60.98
42.28
41.44
32.83
31.90
29.36
29.06
22.79
14.34
14.27
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


HO
O
OH
OH
(CH2)5CH3

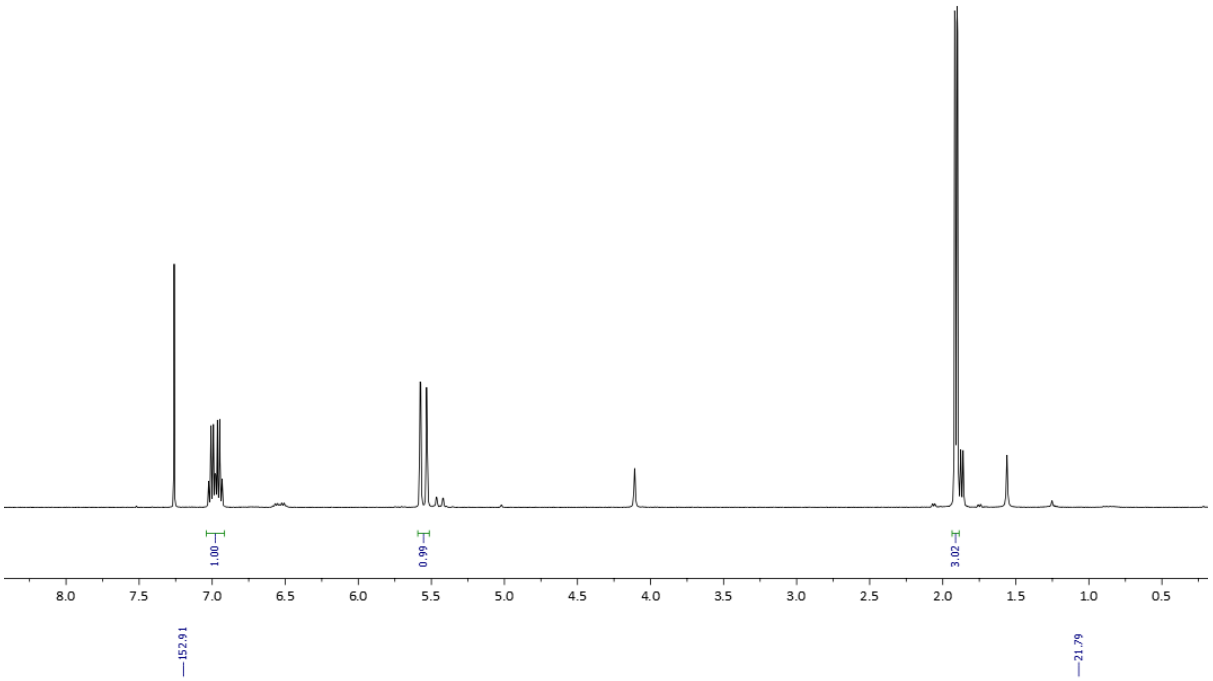
136

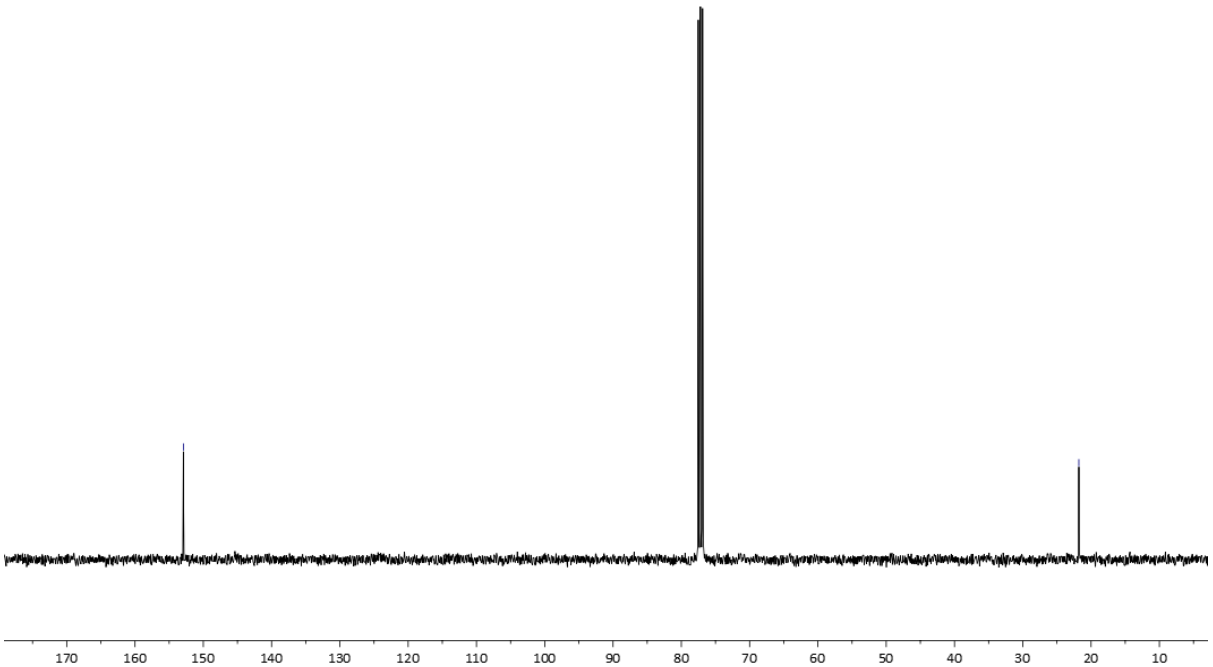

1.00
1.08
2.02
1.05
1.35
2.23
2.30
2.38
14.88
6.12
6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8


173.44
135.86
134.65
130.99
130.01
69.23
65.96
44.64
42.85
33.23
32.41
30.04
29.56
23.24
14.30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 1


B(OH)2

193


1.00
0.99
3.02
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
152.91
21.79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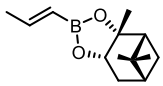
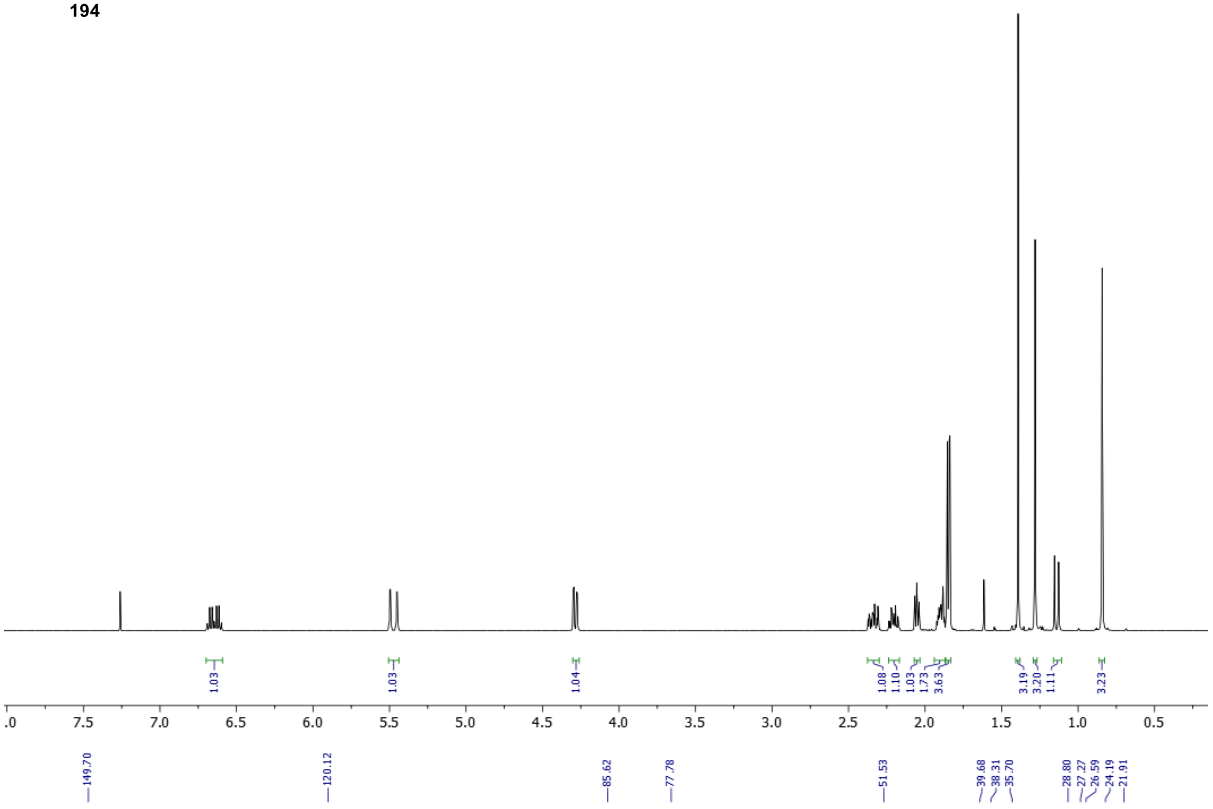
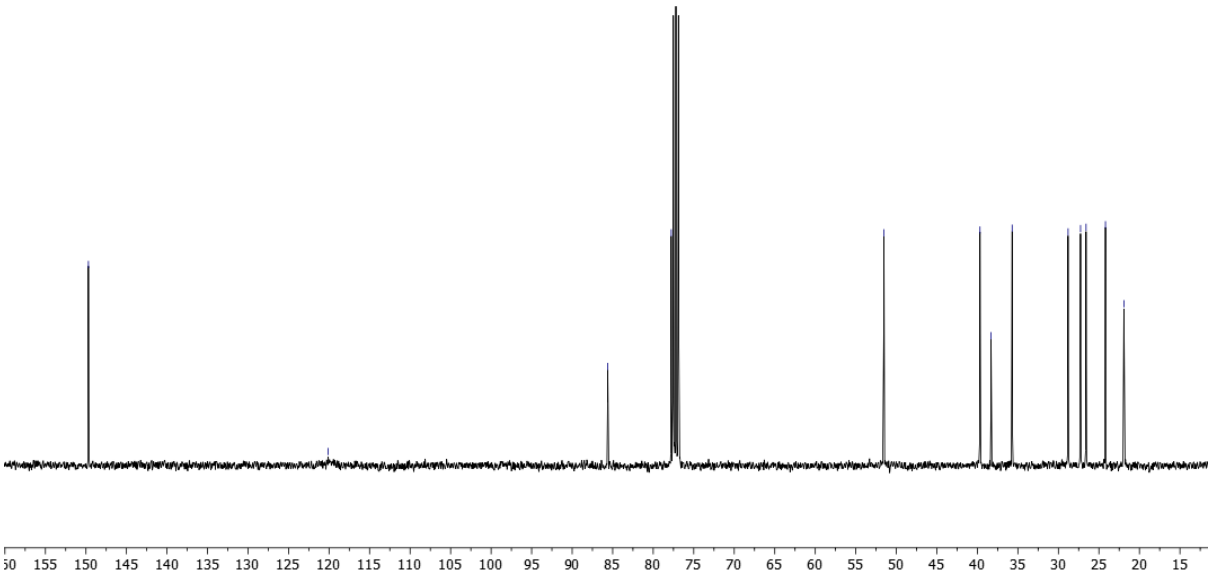
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



194


1.03
1.03
1.04
1.08
1.10
1.03
1.73
3.63
3.19
3.20
1.11
3.23
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
149.70
120.12
85.62
77.78
51.53
39.68
38.31
35.70
28.80
27.27
26.59
24.19
21.91


155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
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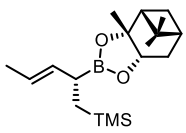
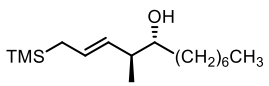
35
30
25
20
15


O
B
O
TMS

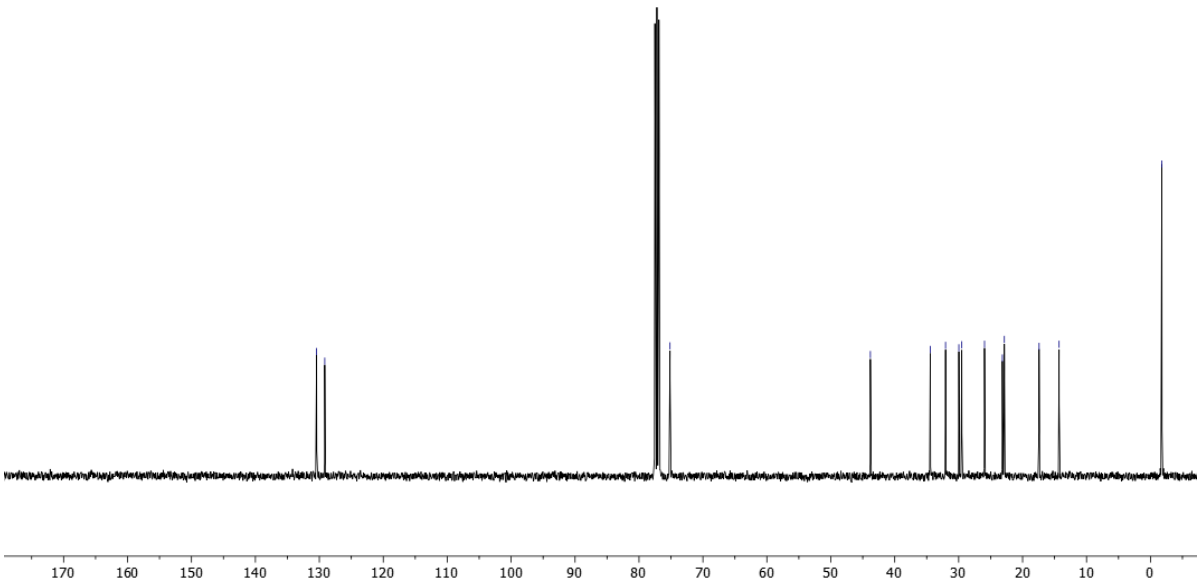
195

1.91
0.99
1.05
1.04
1.04
1.87
1.16
2.91
3.16
3.17
1.03
4.18
0.97
8.60
134.62
123.11
85.56
77.85
51.55
39.60
38.39
35.67
28.67
27.25
26.31
24.17
18.18
17.93
-0.79


OH
TMS
(CH2)6CH3

192

1.07
1.06
1.05
1.07
1.05
1.15
2.73
11.13
3.06
3.18
9.34
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
130.43
129.15
75.15
43.81
34.44
32.05
29.97
29.51
25.95
23.16
22.85
17.42
14.29
-1.78


170
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150
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120
110
100
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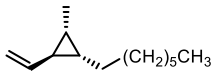
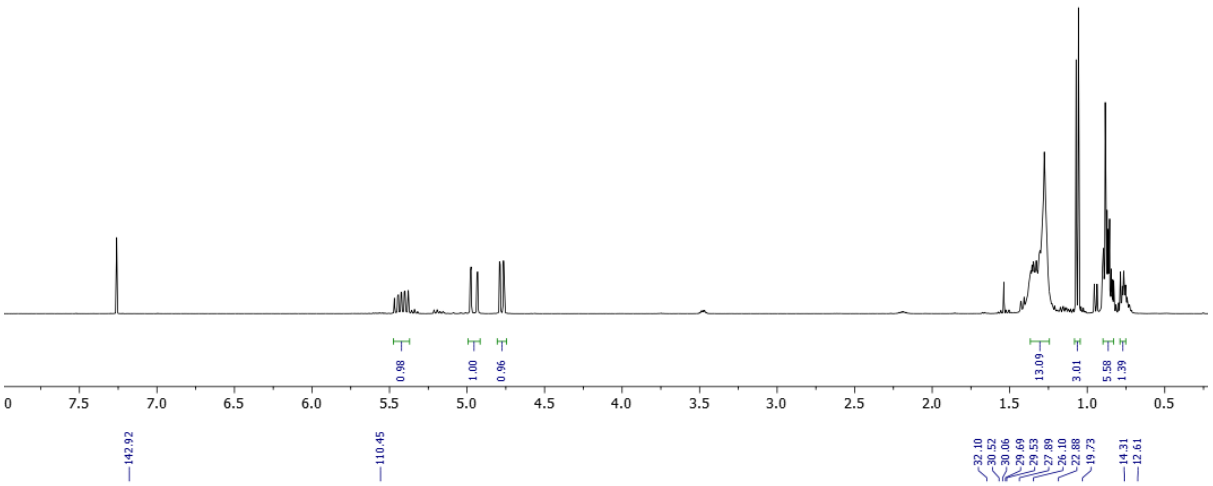
70
60
50
40
30
20
10
0


(CH2)5CH3

196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0.96
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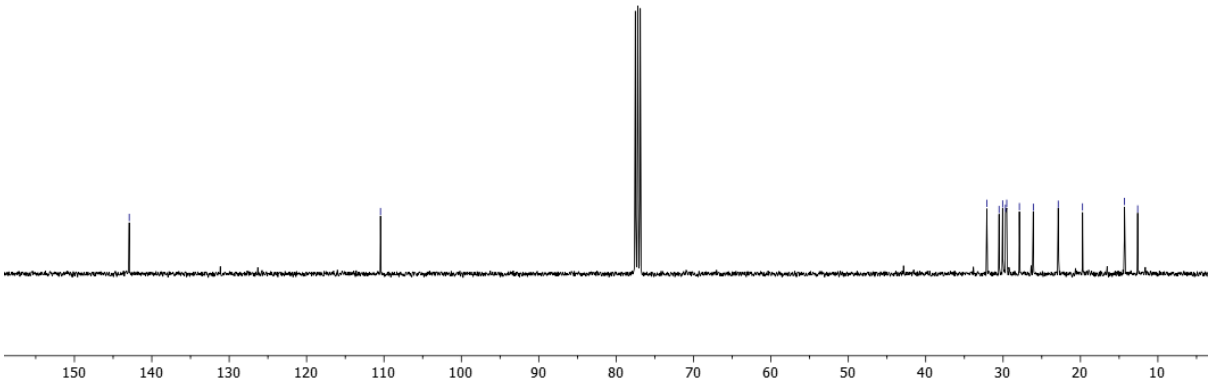
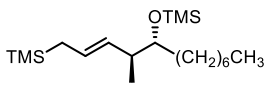
5.58
1.39
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
142.92
110.45
32.10
30.52
30.06
29.69
29.53
27.89
26.10
22.88
19.73
14.31
12.61


150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


OTMS
TMS
(CH2)6CH3

205

1.00
0.99
0.97
0.99
2.57
12.76
3.12
3.77
9.44
9.44
131.13
126.31
76.97
42.86
33.82
32.07
29.95
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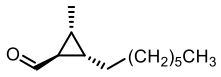
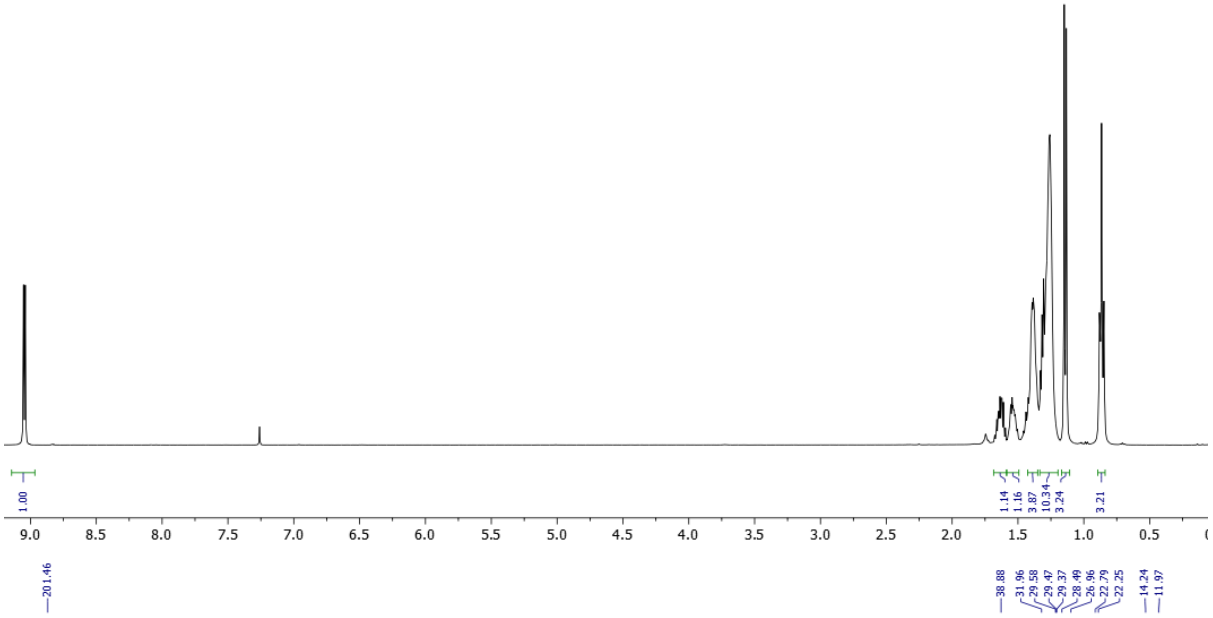
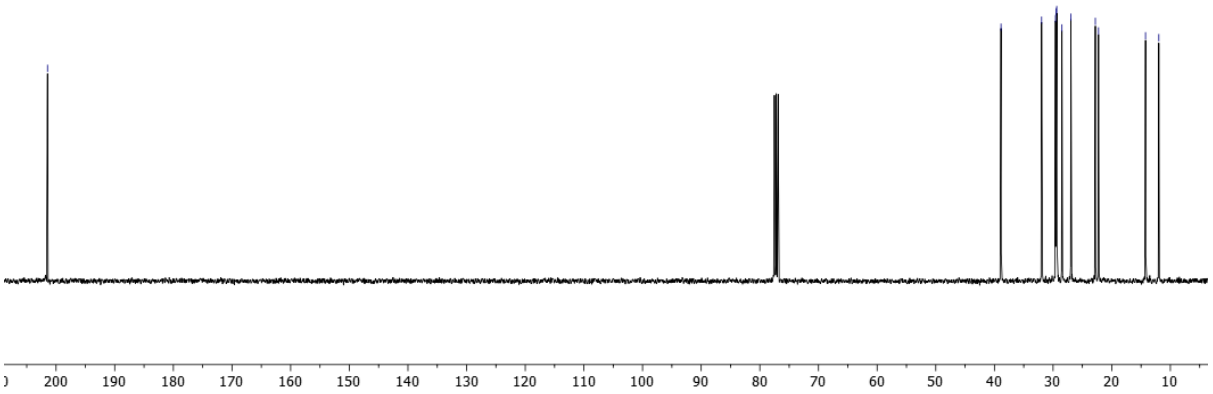
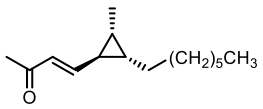
22.93
22.86
16.54
14.30
0.72
-1.77


O
(CH2)5CH3

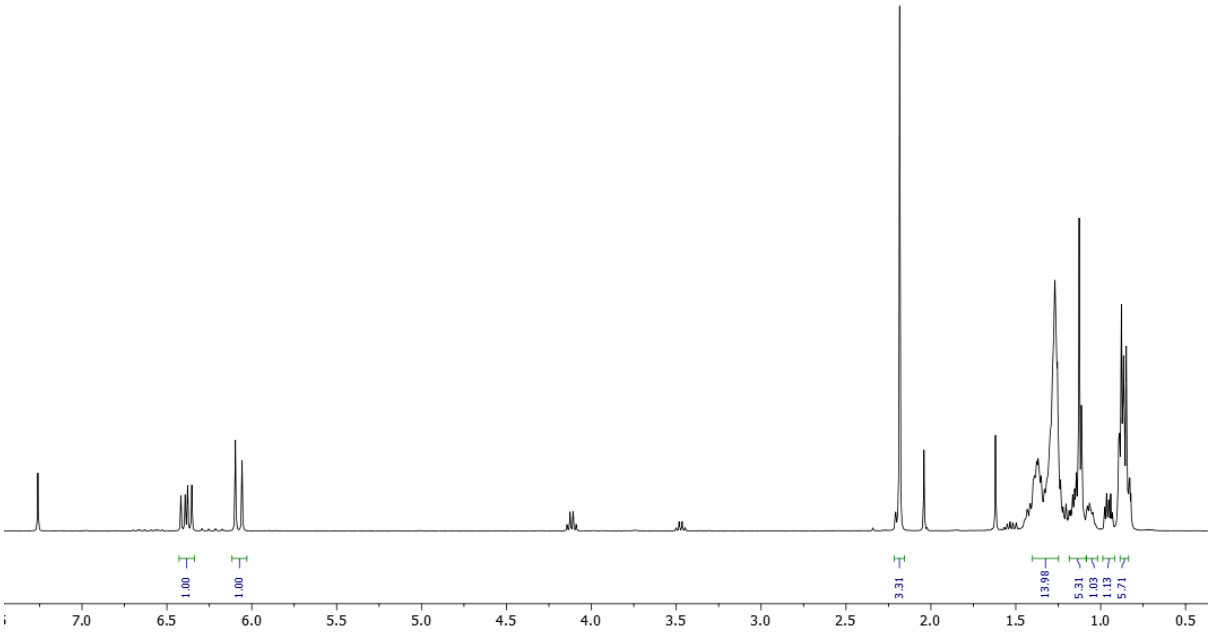
208


1.00
1.14
1.16
3.87
10.34
3.24
3.21
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
201.46
38.88
31.96
29.58
29.47
29.37
28.49
26.96
22.79
22.25
14.24
11.97


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


(CH2)5CH3
O

212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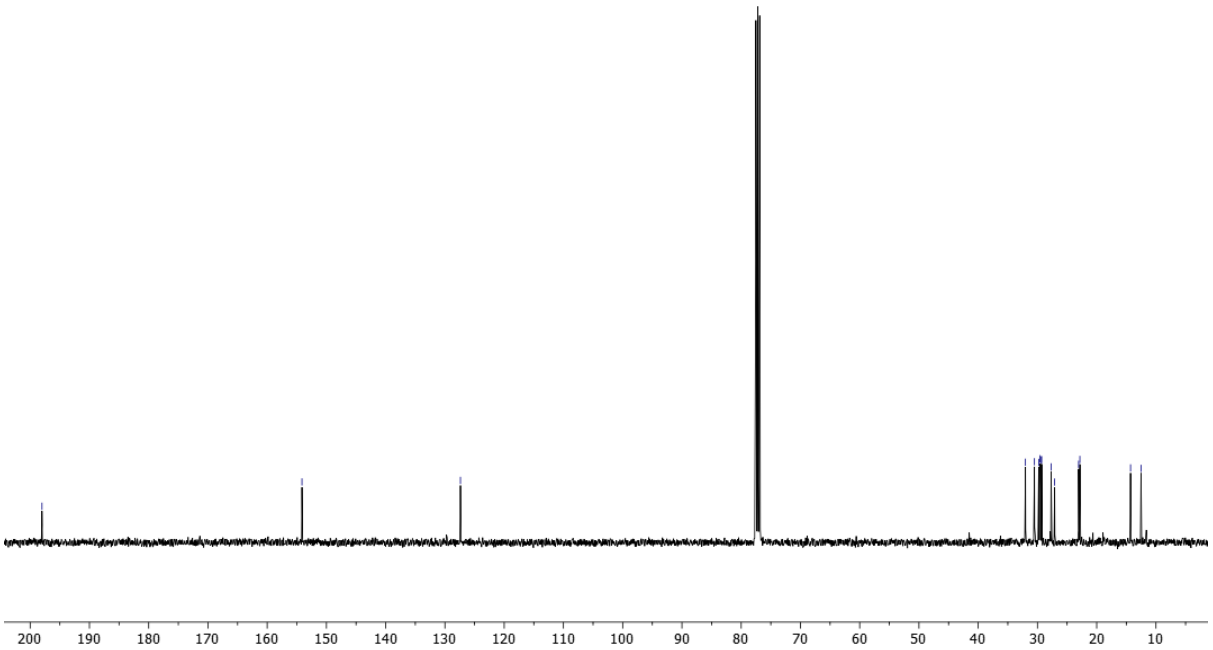
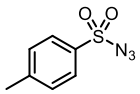
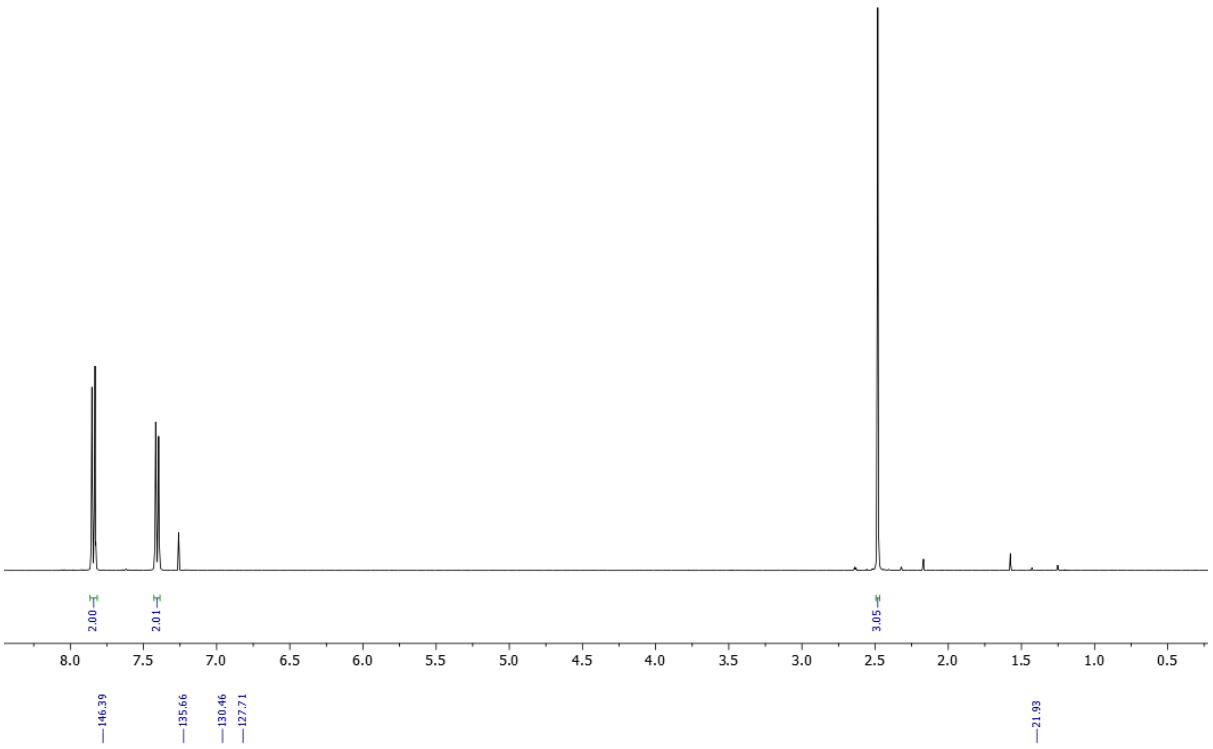
1.00
3.31
13.98
5.31
1.03
1.13
5.71
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

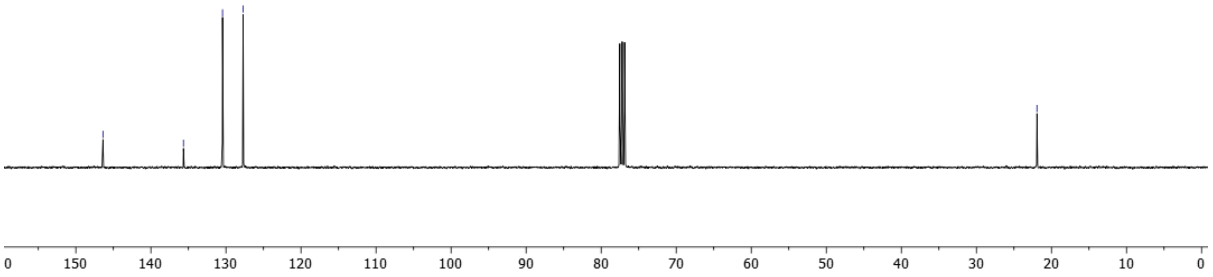

198.01
154.13
127.38
32.02
30.50
29.78
29.58
29.44
29.29
27.69
27.10
23.05
22.84
14.29
12.52

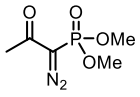

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



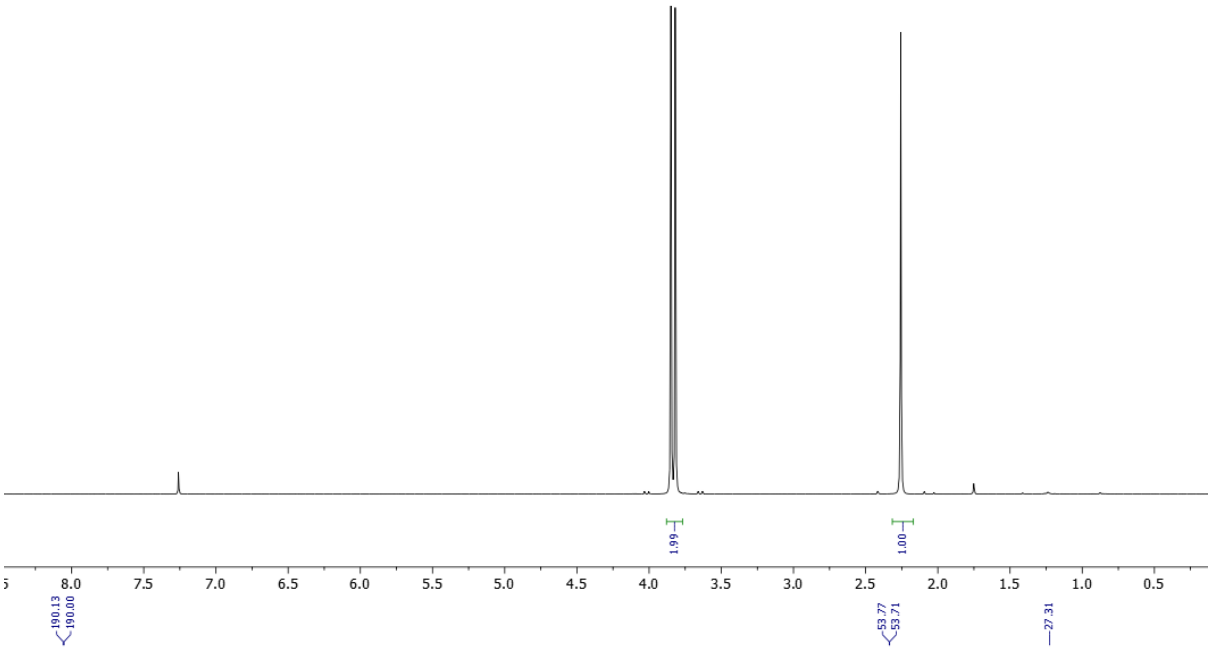
419


2.00
2.01
3.05
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
146.39
135.66
130.46
127.71
21.93


0
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



209


1.99
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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
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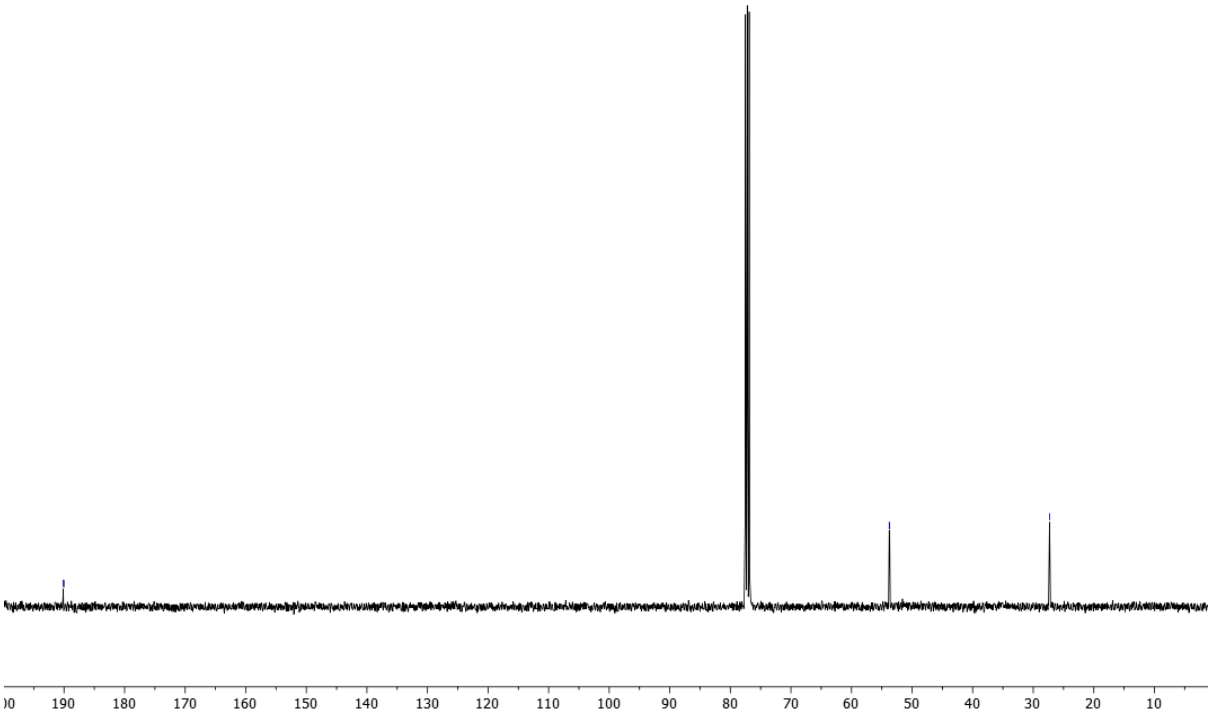
27.31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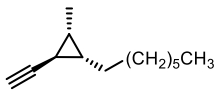
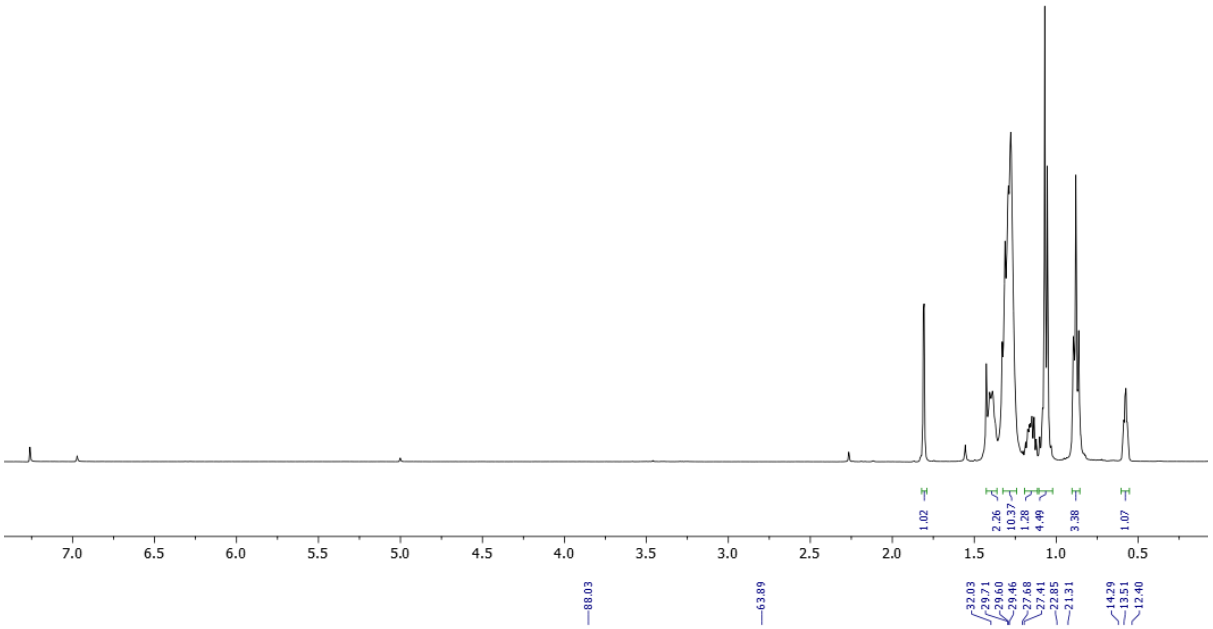

(CH2)5CH3

210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2.26
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1.28
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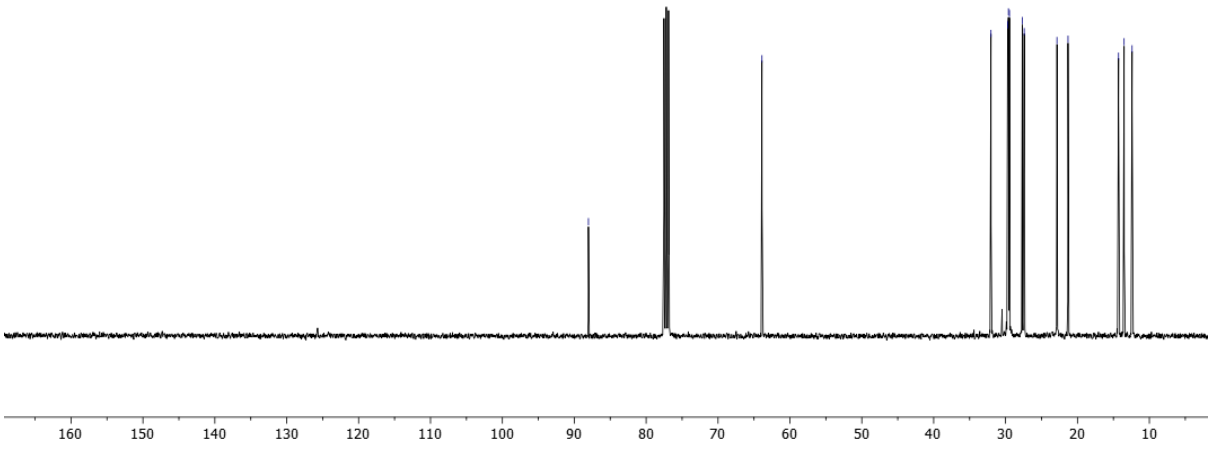
3.38
1.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
88.03
63.89
32.03
29.71
29.60
29.46
27.68
27.41
22.85
21.31
14.29
13.51
12.40


160
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110
100
90
80
70
60
50
40
30
20
10


pinB
(CH2)5CH3

190

1.09
1.09
26.86
4.31
5.54
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
159.04
113.97
83.01
76.88
33.06
32.05
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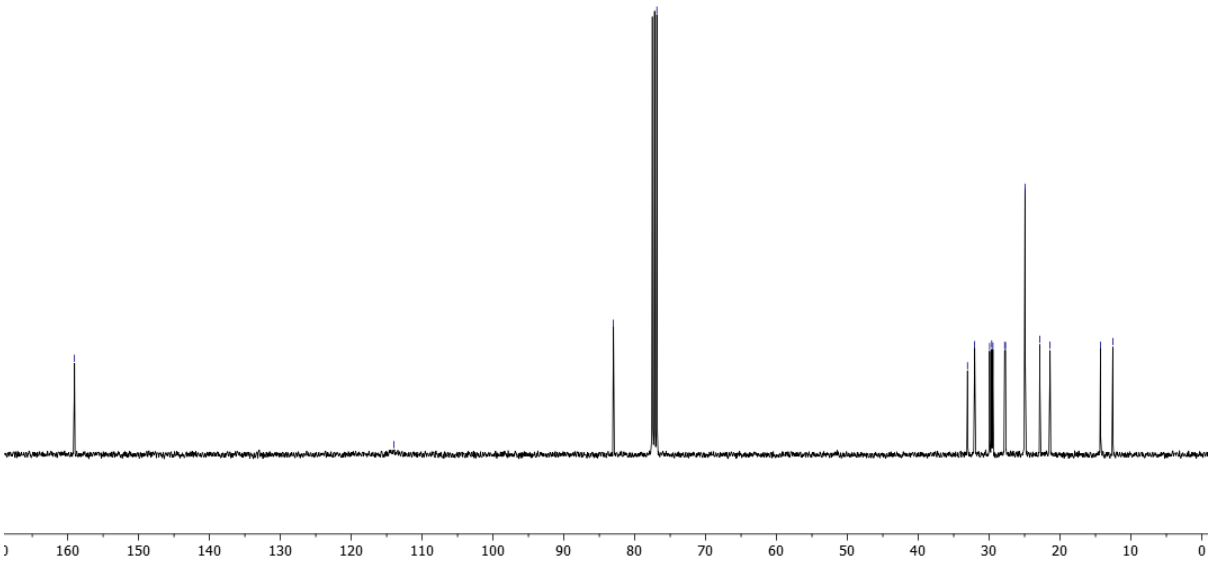
29.47
27.82
27.69
24.94
24.93
22.85
21.41
14.30
12.55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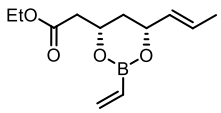
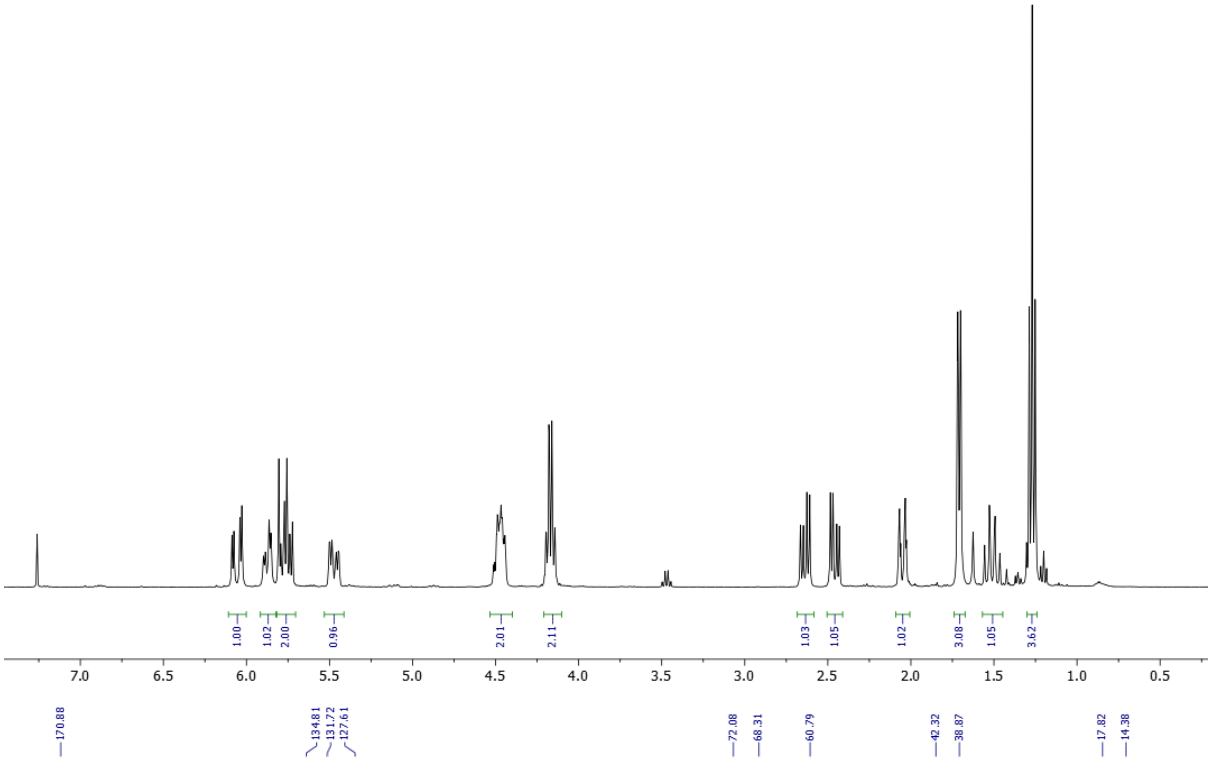
0


EtO
O
O
B
O

214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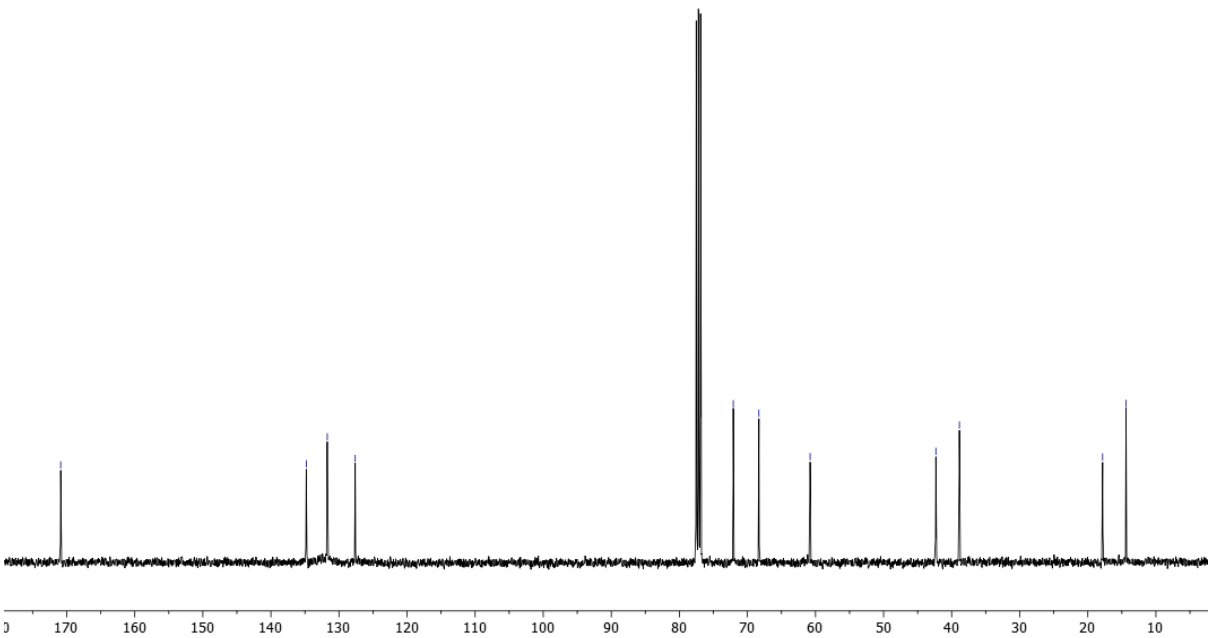
2.11
1.03
1.05
1.02
3.08
1.05
3.62
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

170.88
134.81
131.72
127.61
72.08
68.31
60.79
42.32
38.87
17.82
14.38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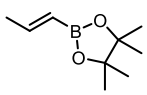
20
10



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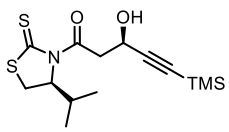
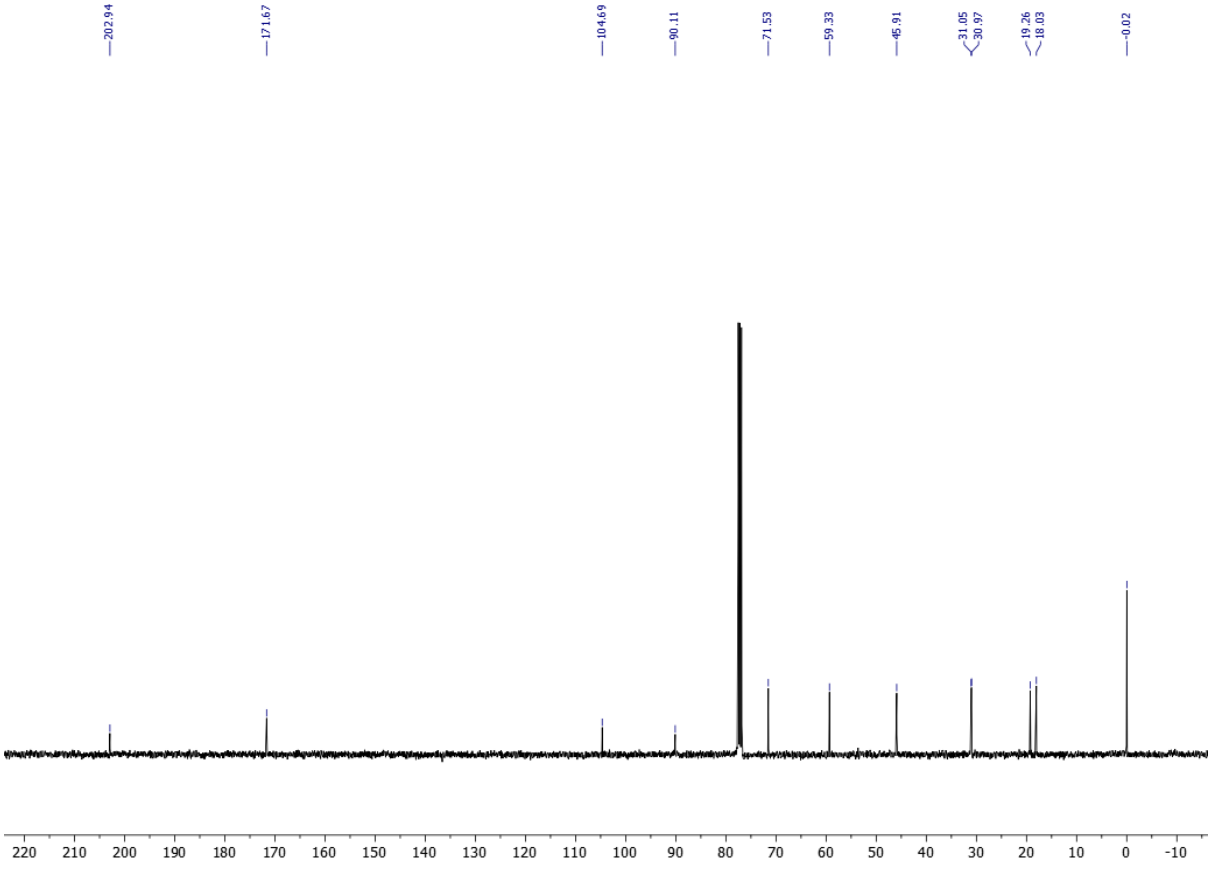

S
O
OH
N
S
TMS

217

1.00
1.00
2.06
1.06
1.07
1.01
1.05
3.37
3.48
9.69
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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171.67
104.69
90.11
71.53
59.33
45.91
31.05
30.97
19.26
18.03
-0.02
220
210
200
190
180
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140
130
120
110
100
90
80
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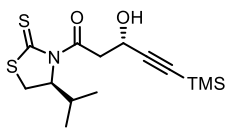
60
50
40
30
20
10
0
-10


S
O
OH
N
S
TMS

218

1.00
0.97
0.96
1.04
1.13
0.98
1.01
1.03
6.40
9.24
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
203.00
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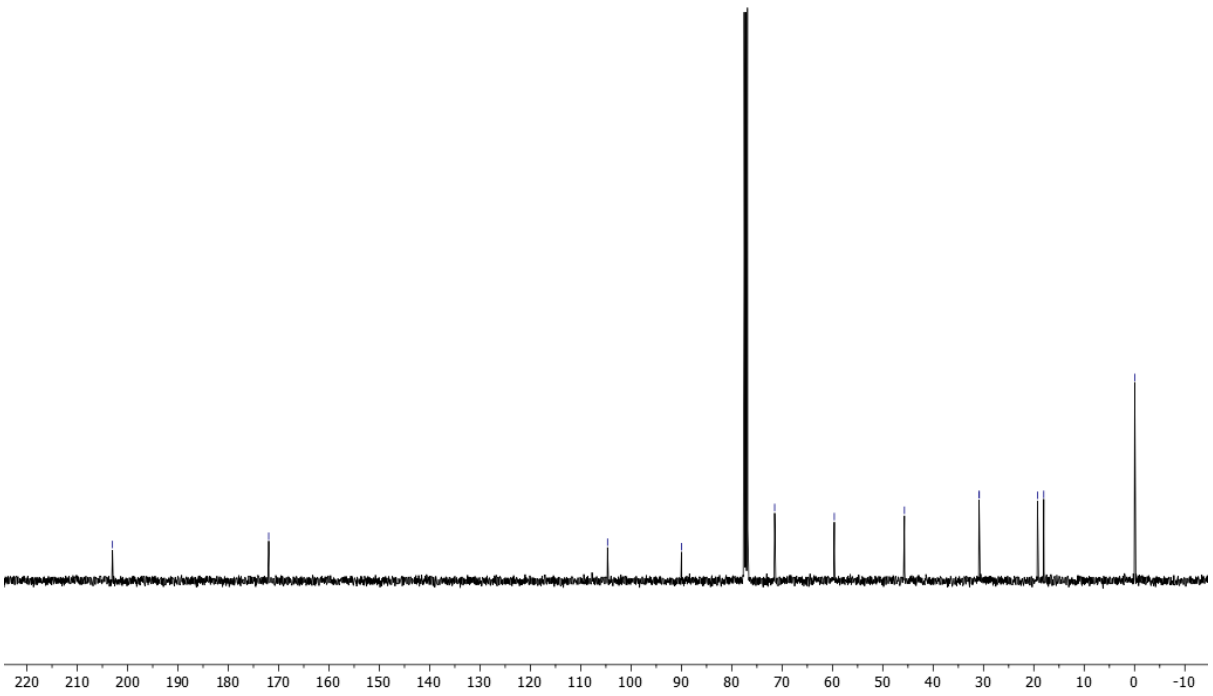
104.67
89.99
71.48
59.63
45.70
30.89
30.84
19.28
18.03
-0.04


220
210
200
190
180
170
160
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140
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120
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100
90
80
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60
50
40
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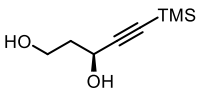
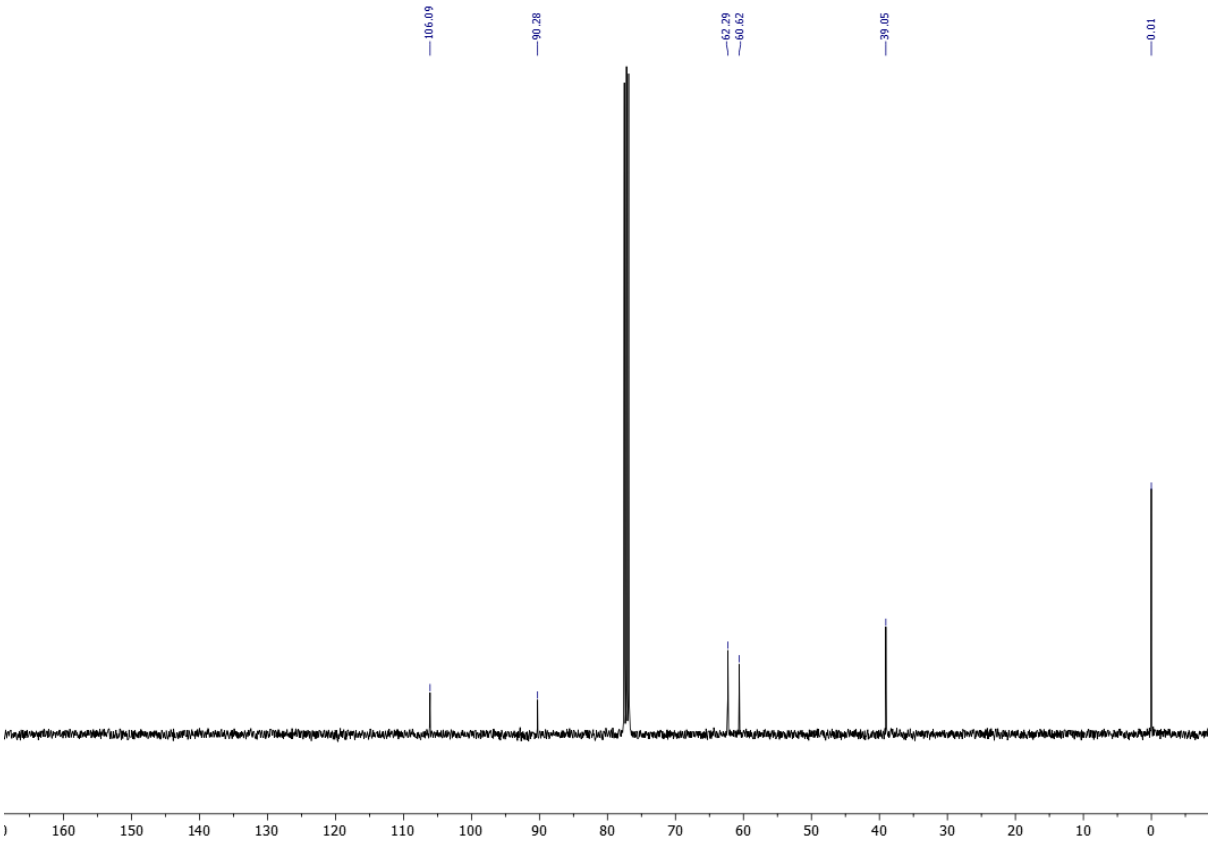
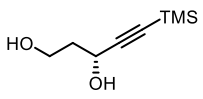
20
10
0
-10


TMS
HO
OH

220

1.04
1.03
1.06
0.95
0.96
2.12
9.54
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


106.09
90.28
62.29
60.62
39.05
0.01
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMS
HO
OH

219

1.00
1.03
1.06
0.96
0.85
2.19
9.53
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
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0.5
0.0
-0.5
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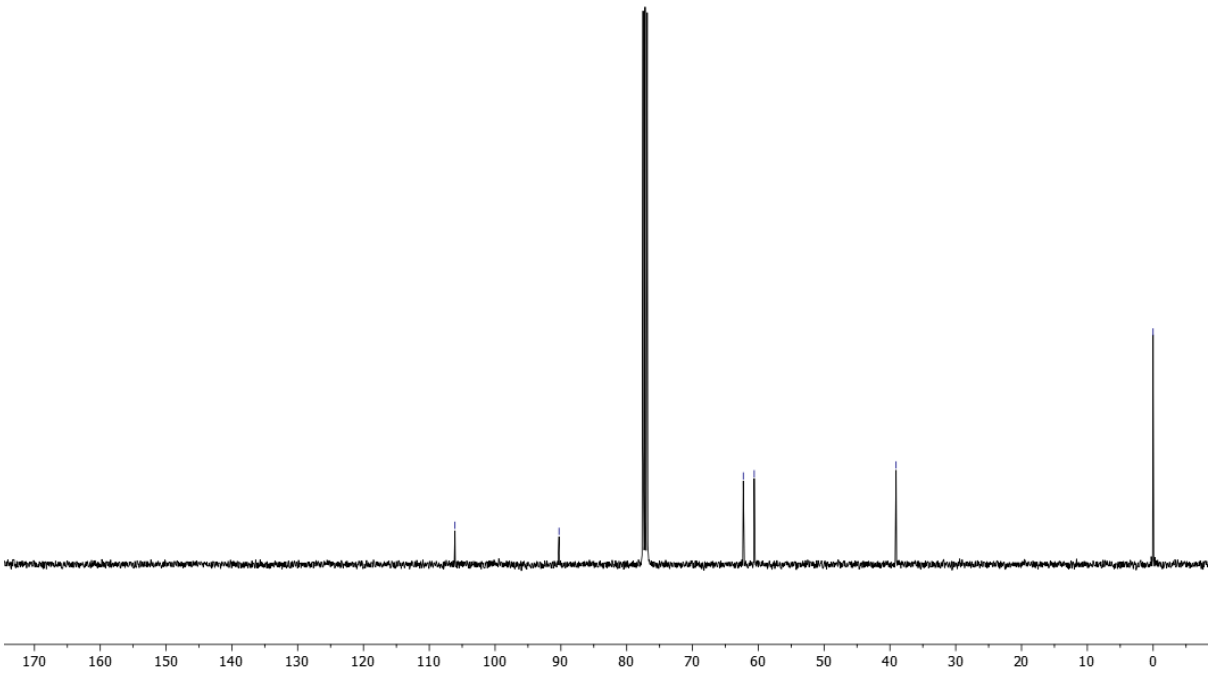
90.28
62.28
60.62
39.06
0.01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160
150
140
130
120
110
100
90
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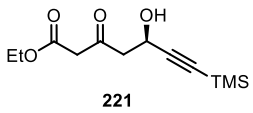
70
60
50
40
30
20
10
0


O
O
OH
EtO
TMS

221

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2.24
2.05
0.99
0.99
0.98
3.46
10.27
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
201.68
166.83
104.38
90.37
61.81
58.78
50.02
49.87
14.27
-0.07
220
210
200
190
180
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140
130
120
110
100
90
80
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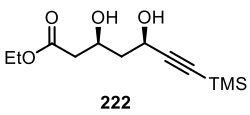
60
50
40
30
20
10
0
-10


O
OH
OH
EtO
TMS

222

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1.00
2.09
2.05
1.04
1.01
3.20
9.39
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
172.69
105.87
89.88
67.67
62.25
61.07
43.36
41.43
14.33
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150
140
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120
110
100
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70
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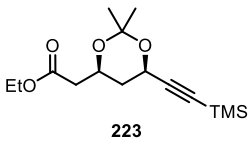
30
20
10
0


O
O
O
EtO
TMS

223

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0.99
2.06
1.05
1.02
1.12
1.24
3.01
3.01
3.31
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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
170.84
103.79
99.69
89.57
65.72
60.77
41.26
37.14
30.18
19.46
14.38
-0.00
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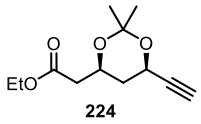
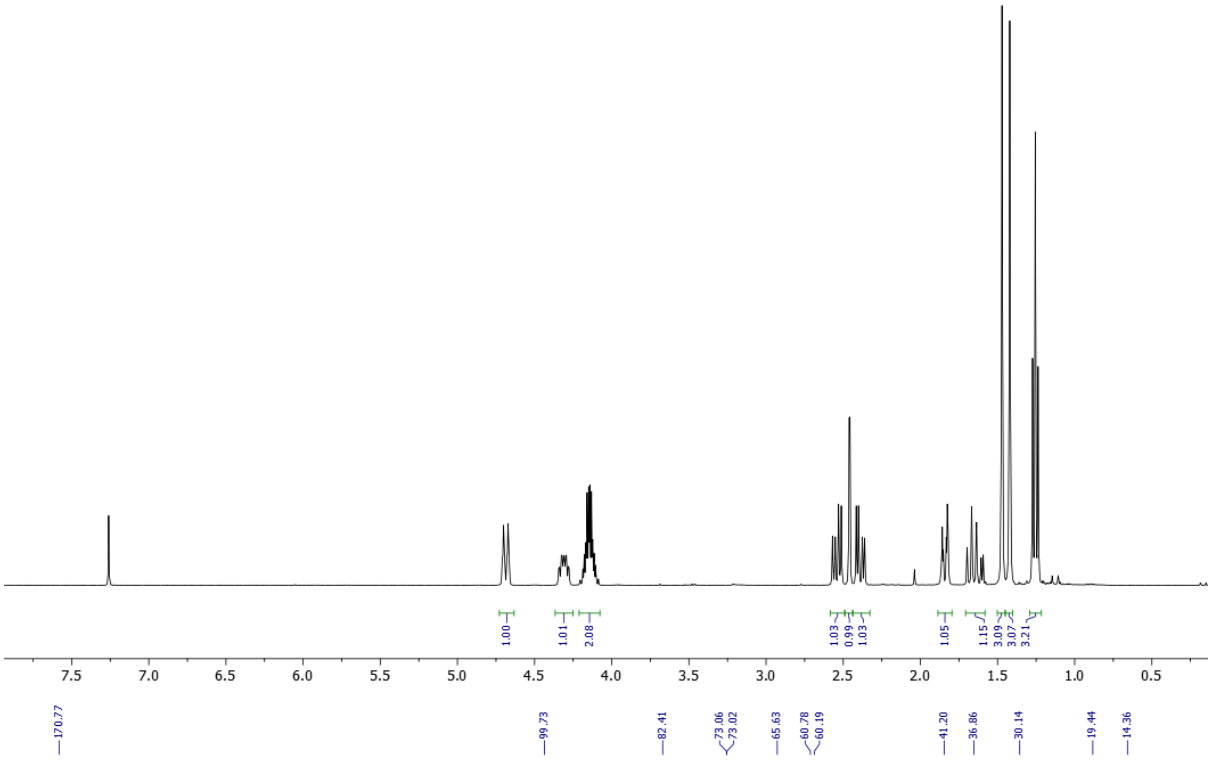
10
0
-10


O
O
O
EtO

224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1.01
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1.03
0.99
1.03
1.05
1.15
3.09
3.07
3.21
7.5
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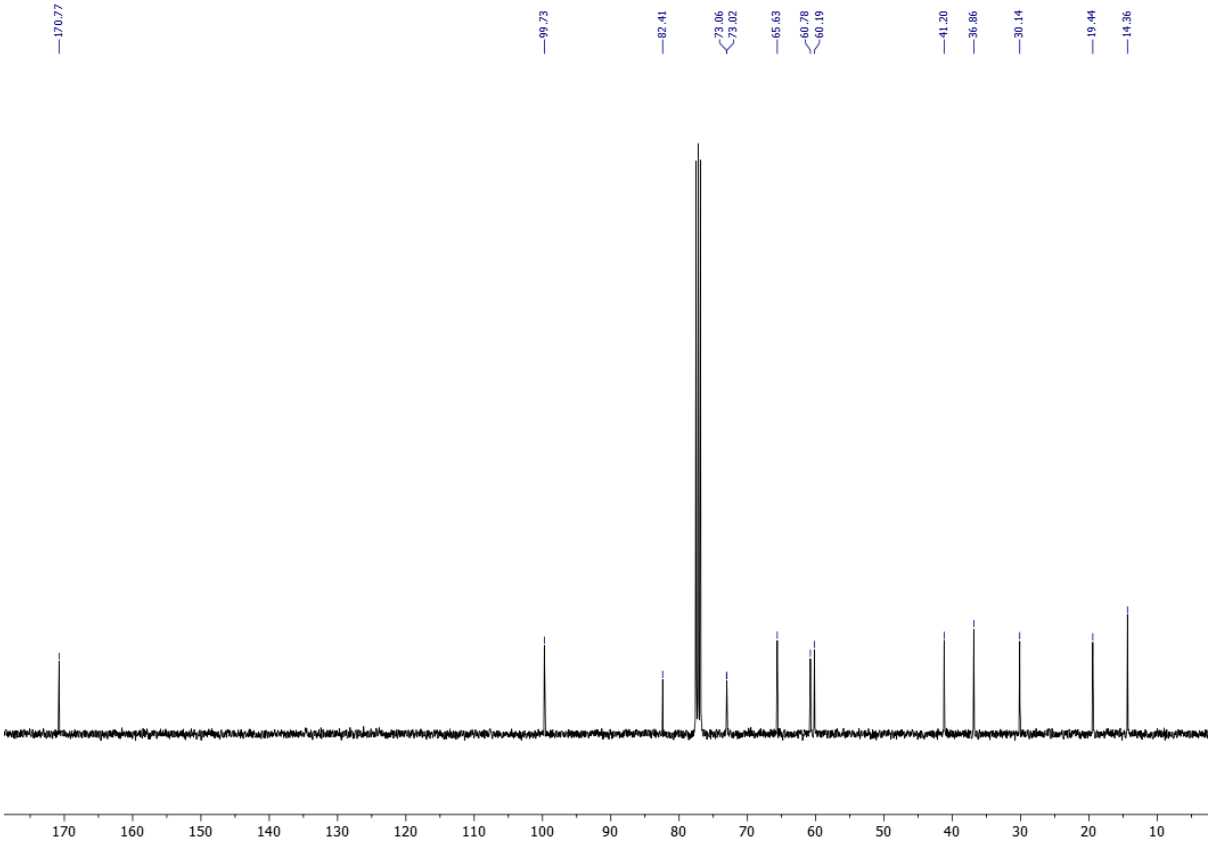
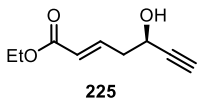
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


170.77
99.73
82.41
73.06
73.02
65.63
60.78
60.19
41.20
36.86
30.14
19.44
14.36
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


O
OH
EtO

225

1.00
1.02
1.02
2.12
2.11
0.98
1.03
3.27
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
166.35
142.85
125.04
83.66
74.23
60.96
60.83
40.28
14.40
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150
140
130
120
110
100
90
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70
60
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30
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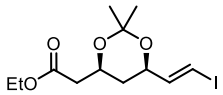
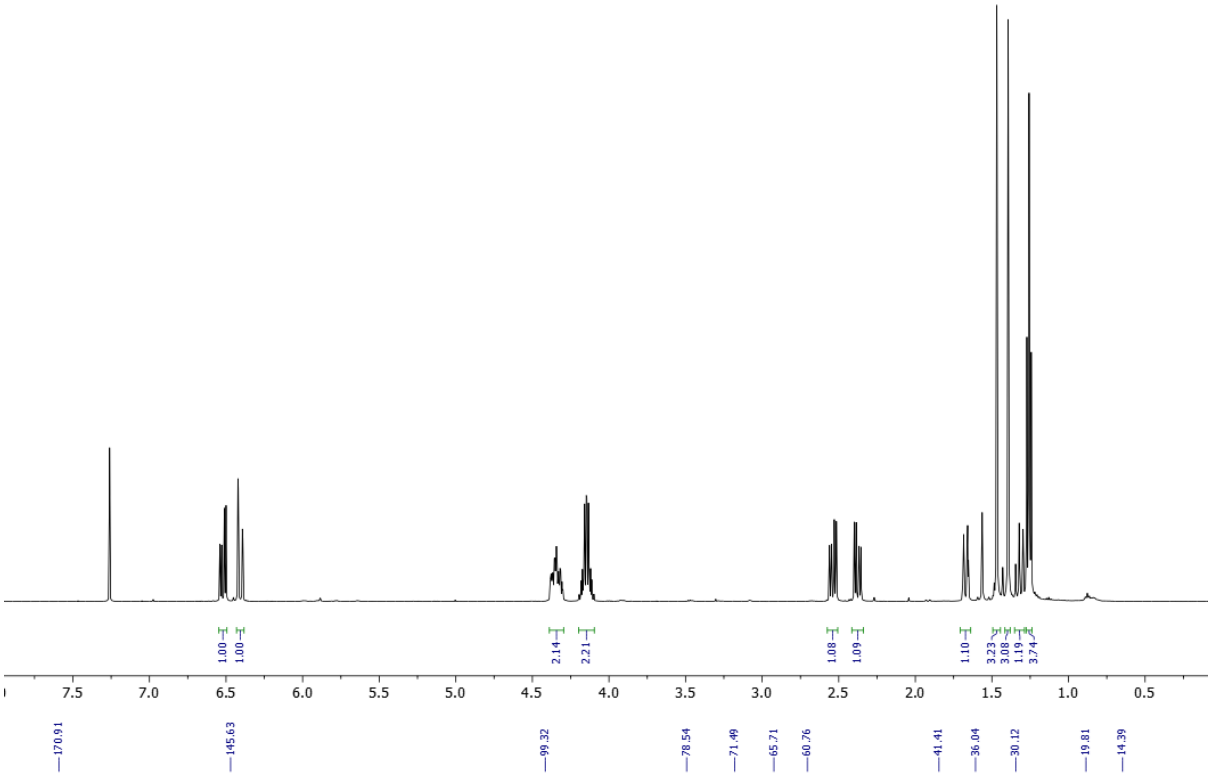
10
0


EtO
O
O
O
I

189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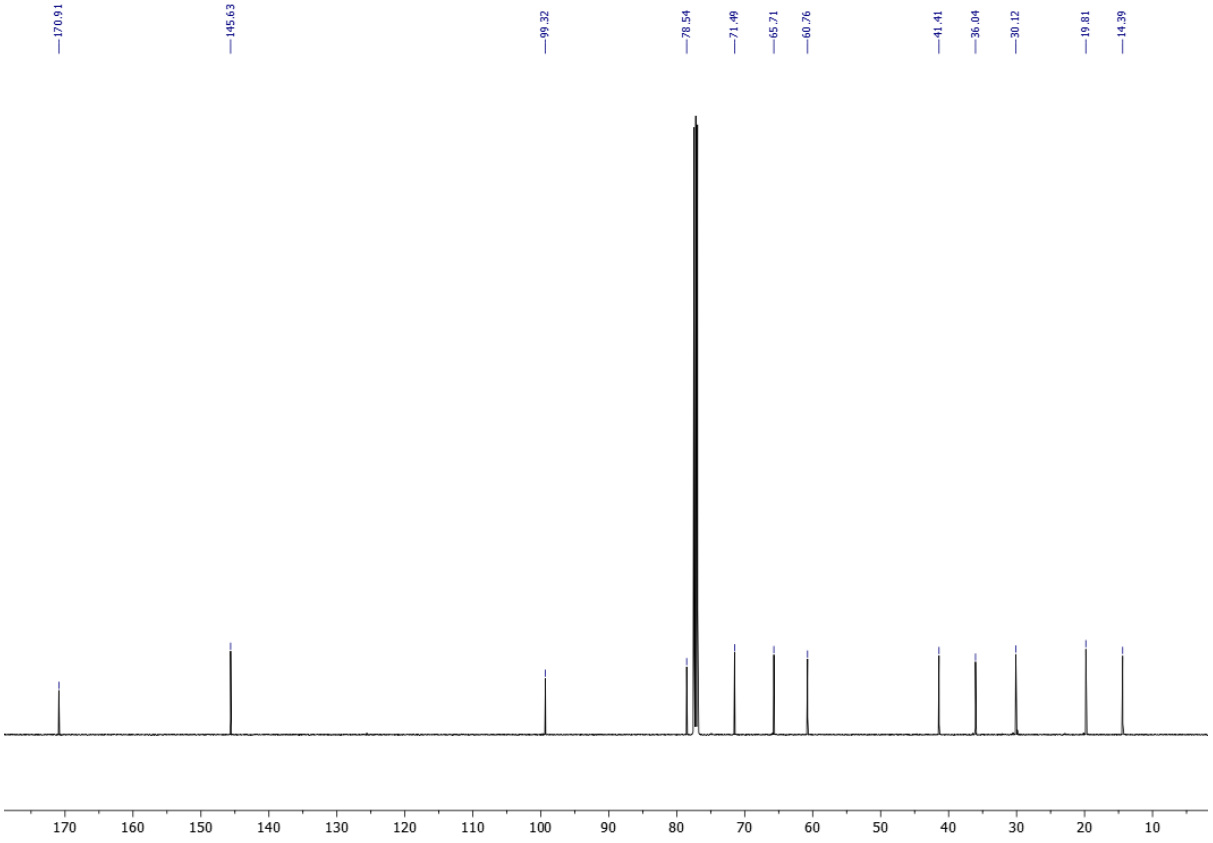
1.00
2.14
2.21
1.08
1.09
1.10
3.23
3.08
1.19
3.74
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5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145.63
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78.54
71.49
65.71
60.76
41.41
36.04
30.12
19.81
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120
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80
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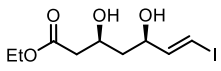
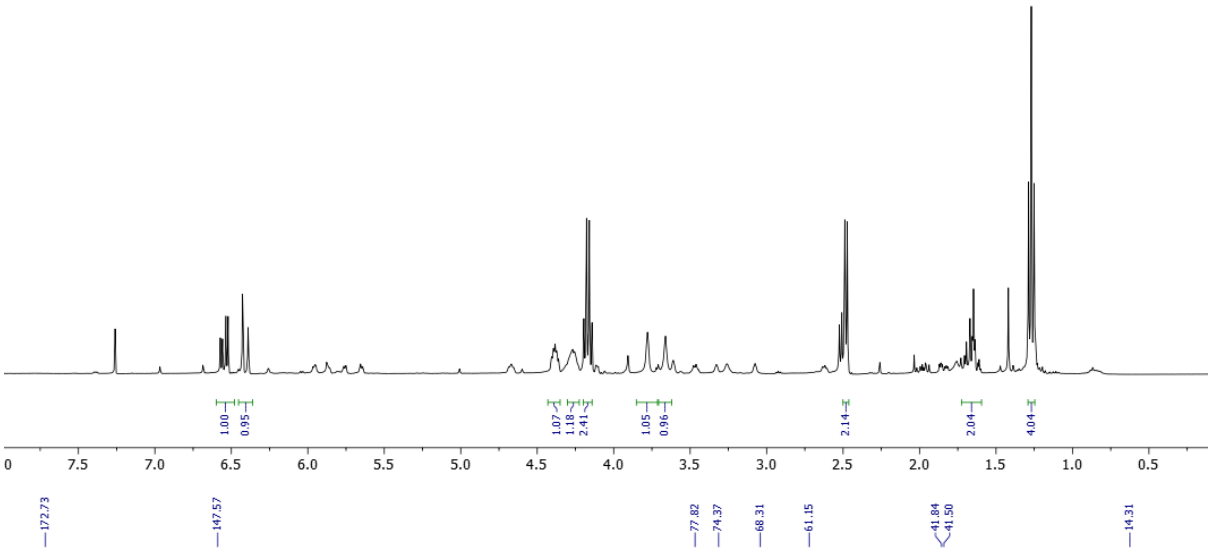
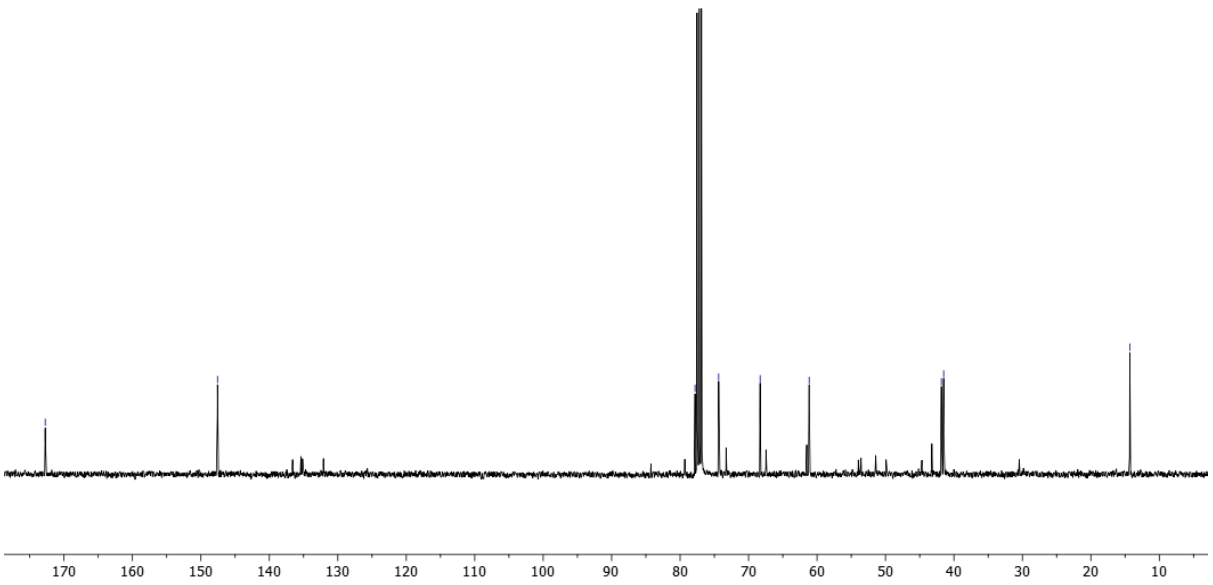
30
20
10

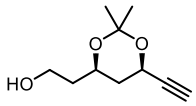

O
OH
OH
EtO
I

420

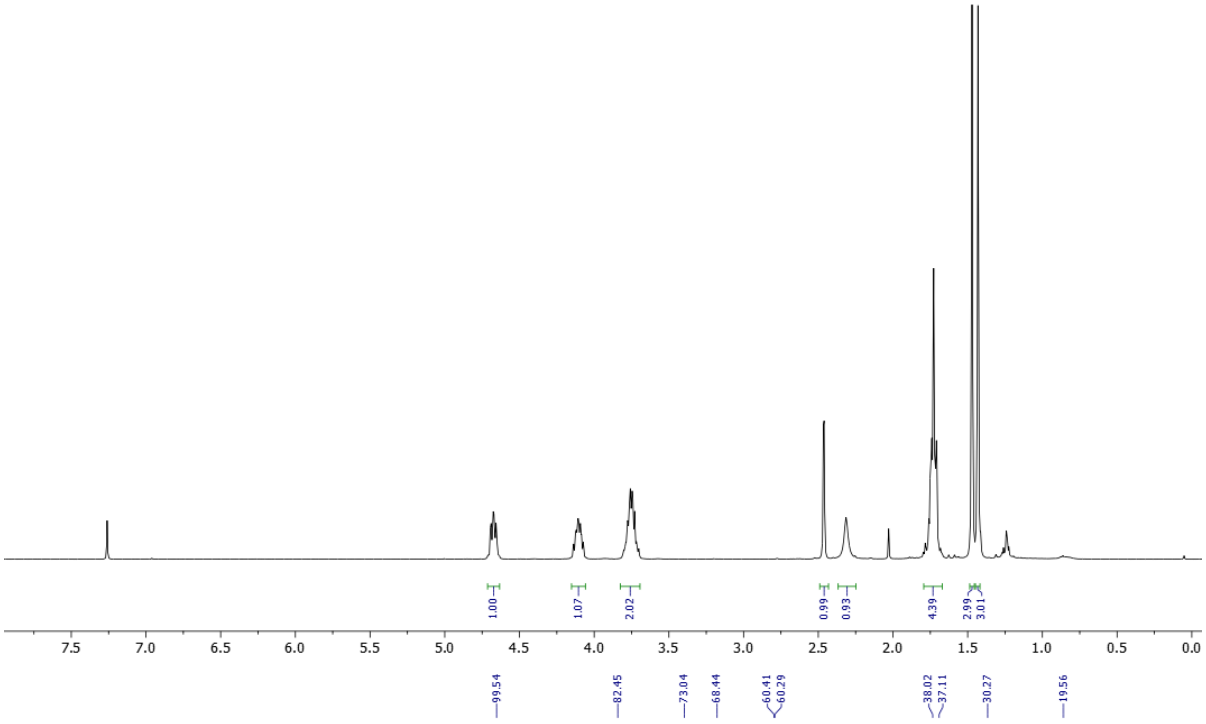

1.00
0.95
1.07
1.18
2.41
1.05
0.96
2.14
2.04
4.04
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

172.73
147.57
77.82
74.37
68.31
61.15
41.84
41.50
14.31

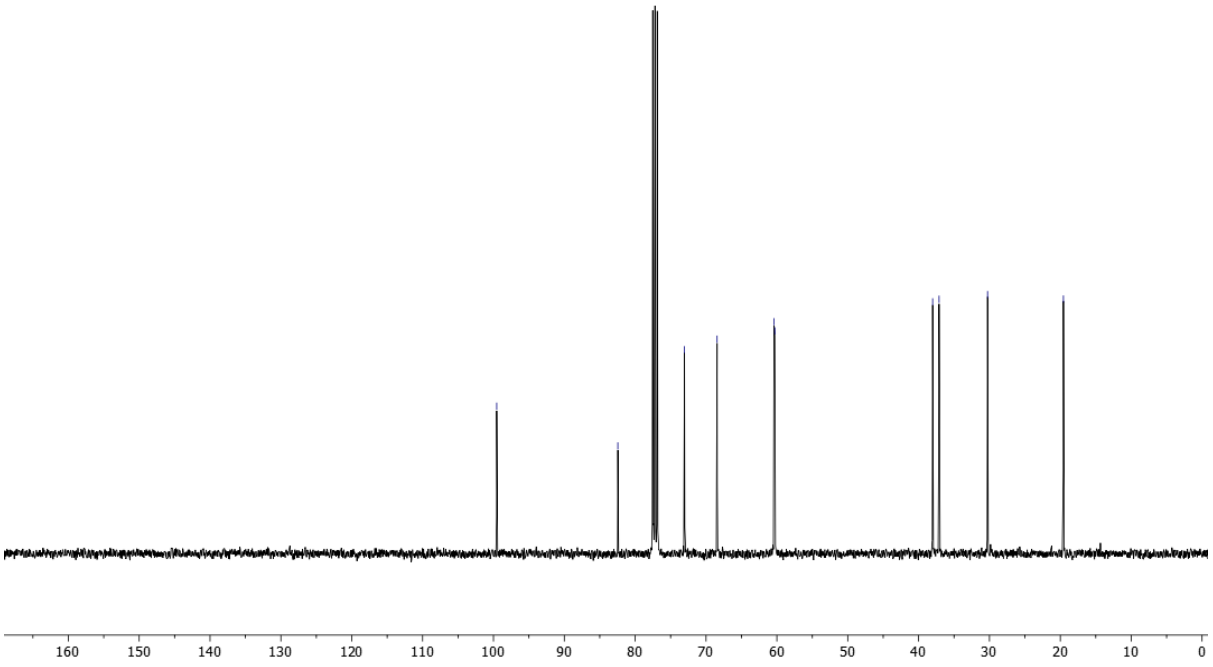

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

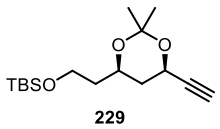

HO
O
O

228


1.00
1.07
2.02
0.99
0.93
4.39
2.99
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

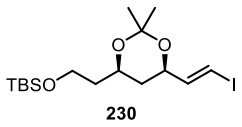
99.54
82.45
73.04
68.44
60.41
60.29
38.02
37.11
30.27
19.56


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
O
O

229

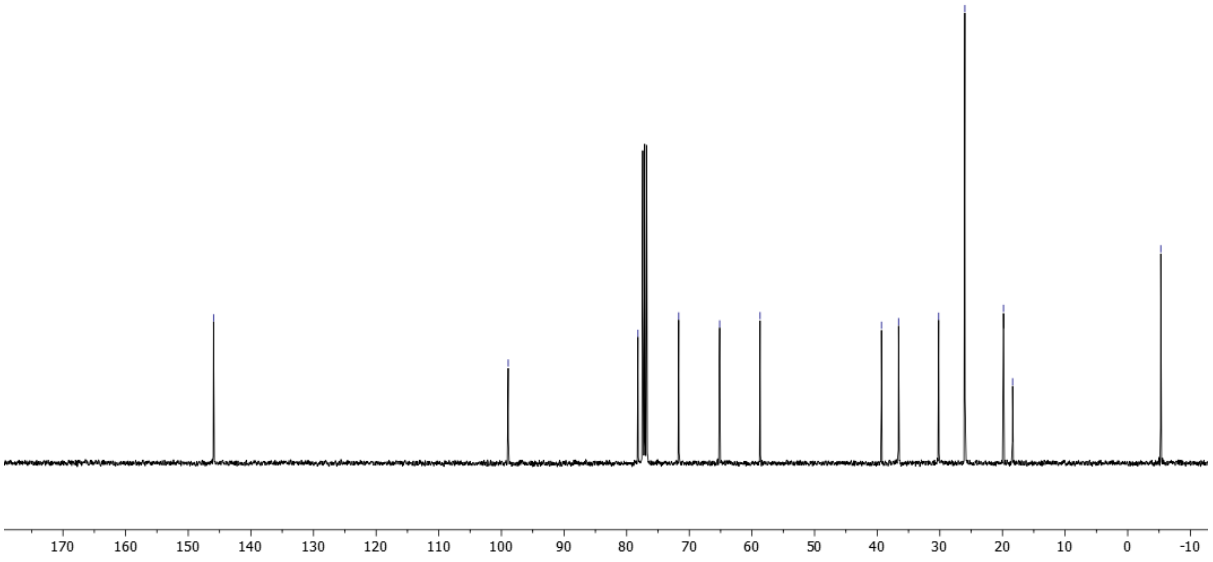
1.05
1.05
1.07
1.09
0.99
1.09
3.05
3.08
3.06
9.93
6.51
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
99.44
82.88
72.77
65.29
60.46
58.69
39.22
37.59
30.34
26.09
19.58
5.20
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

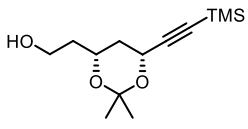

TBSO
O
O
I

230

1.00
1.01
1.03
1.06
1.07
1.07
3.22
3.33
3.26
1.33
9.86
6.61
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

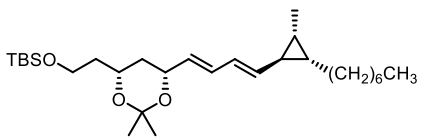
145.96
98.92
78.20
71.69
65.15
58.70
39.32
36.59
30.18
26.01
19.84
18.38
-5.28


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


HO
TMS
O
O

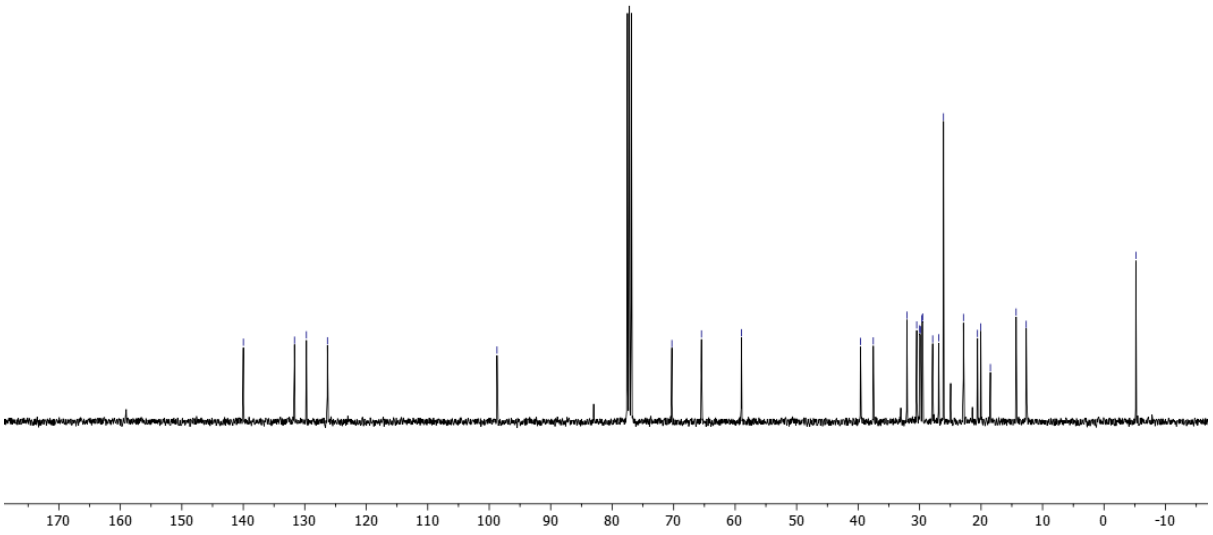
231

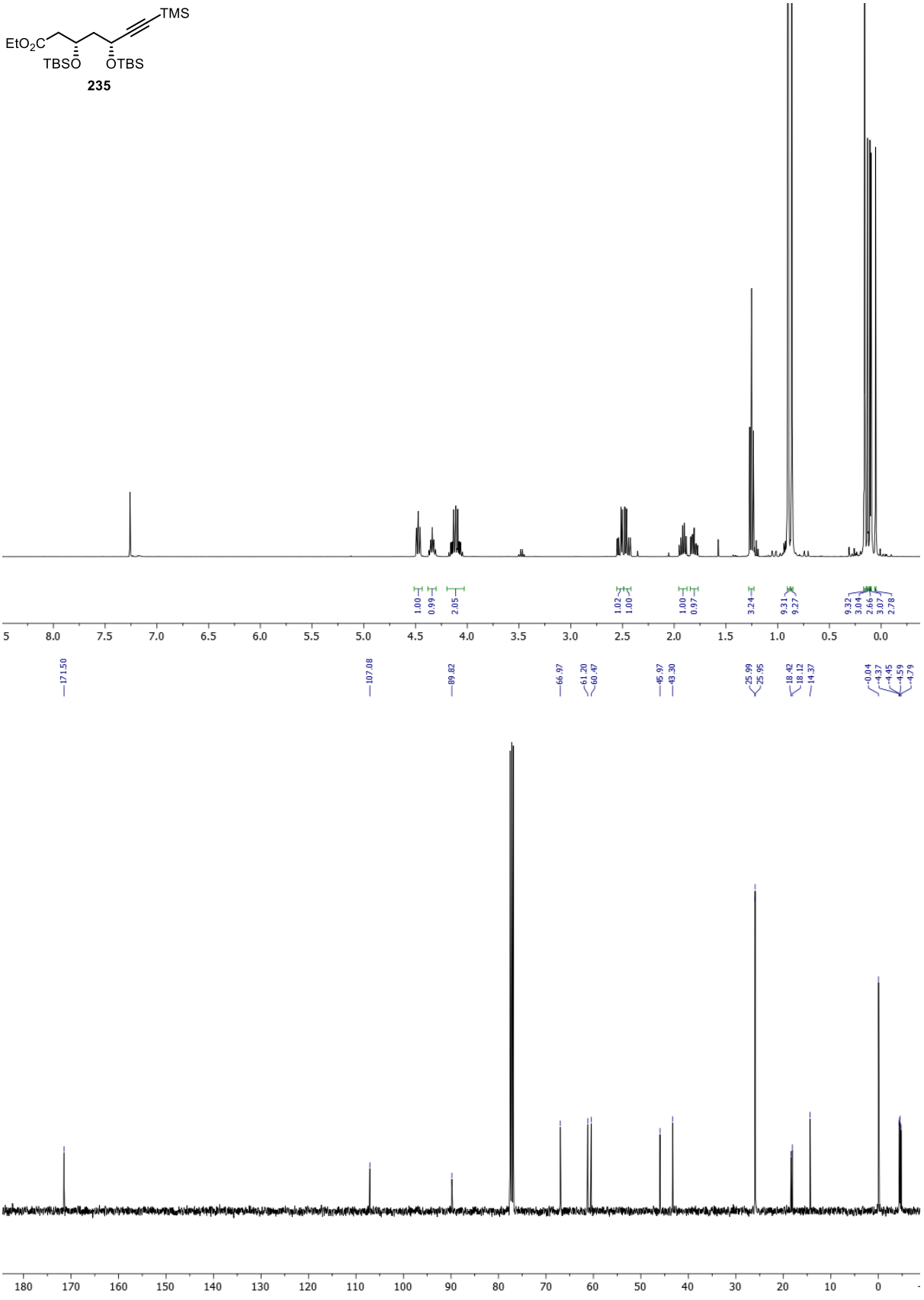
1.00
0.97
2.06
0.96
4.17
2.91
3.06
9.61
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
103.74
99.44
89.52
68.70
60.80
60.57
37.92
37.28
30.24
19.50
-0.08
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

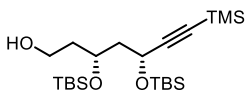

TBSO
O
O
(CH2)6CH3

232

1.07
1.00
1.01
1.09
1.04
1.06
1.10
1.11
2.45
2.26
1.43
3.64
16.04
4.12
14.49
1.47
7.14
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
139.99
131.67
129.73
126.31
98.74
70.29
65.48
58.98
39.61
37.53
32.06
30.47
29.99
29.87
29.63
29.50
27.87
26.90
26.11
22.87
20.58
20.05
18.49
14.30
12.66
-5.18

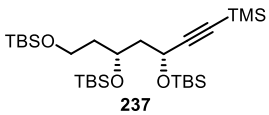

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


TMS
EtO2C
TBSO
OTBS
235
1.00
0.99
2.05
1.02
1.00
1.00
0.97
3.24
9.31
9.27
9.32
3.04
2.66
3.07
2.78
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
171.50
107.08
89.82
66.97
61.20
60.47
45.97
43.30
25.99
25.95
18.42
18.12
14.37
-0.04
-4.37
-4.45
-4.59
-4.79
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

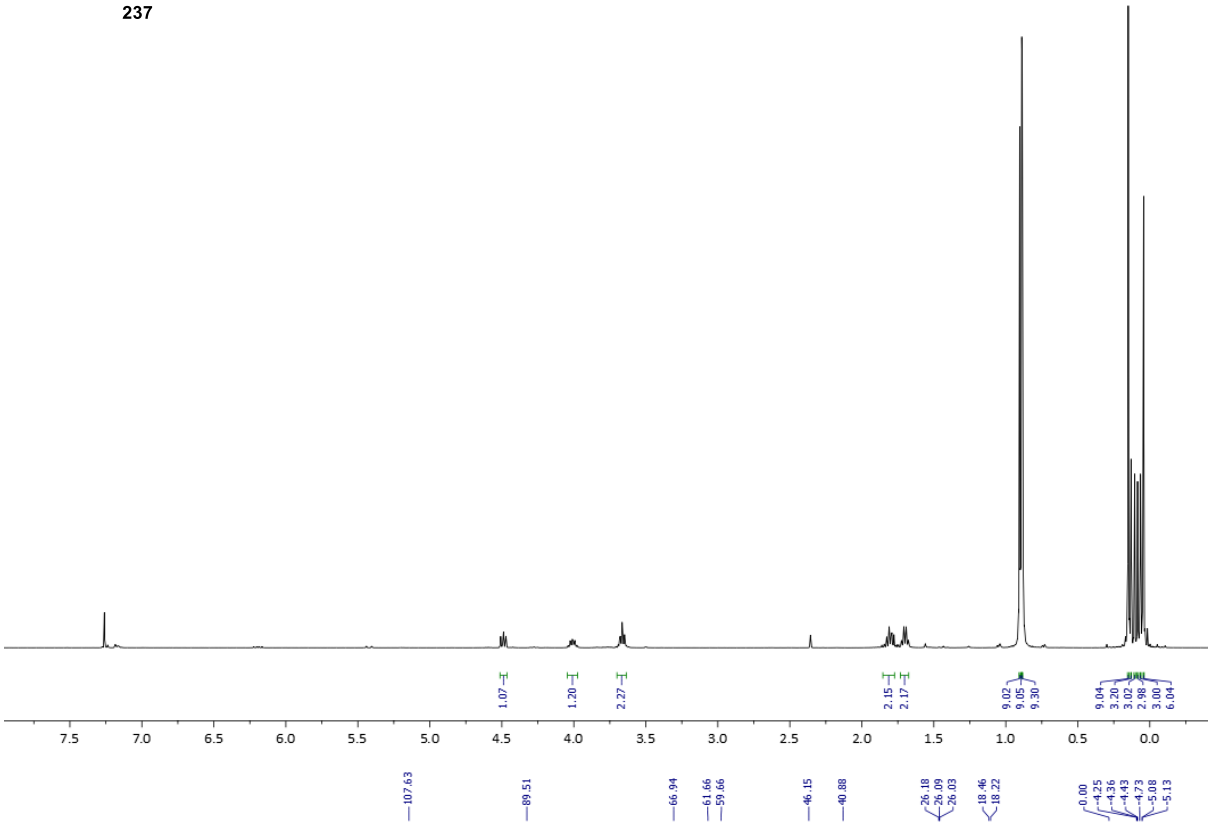

HO
TBSO
OTBS
TMS

236

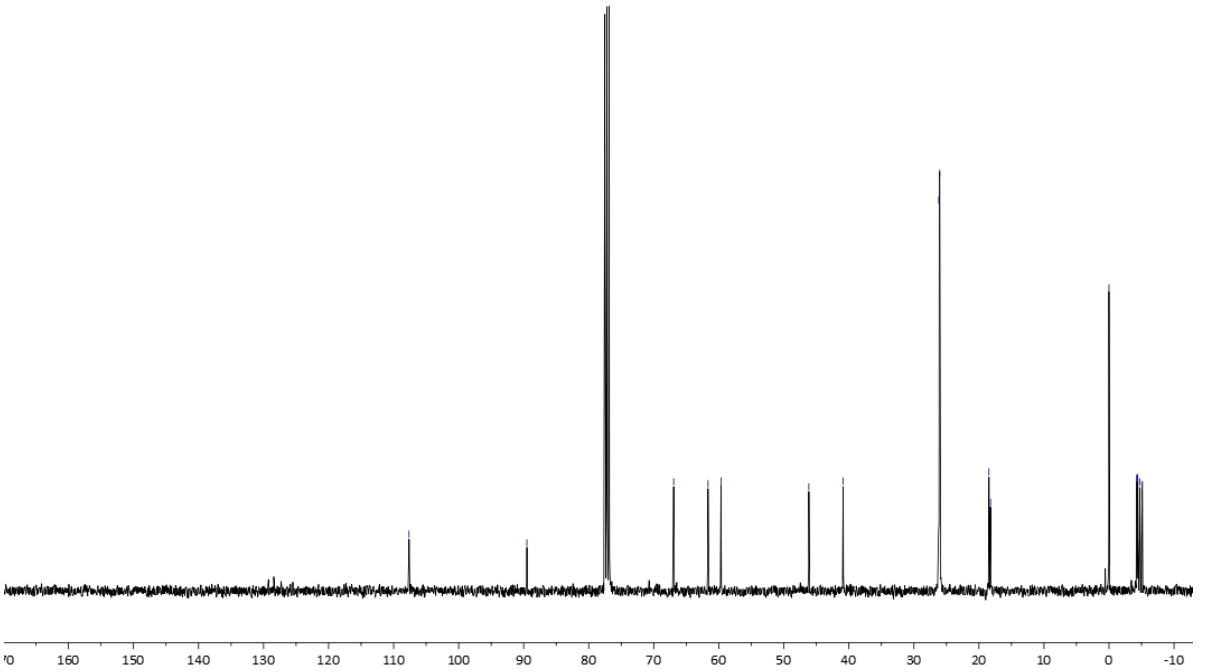
1.00
1.11
1.21
1.09
1.04
3.39
1.14
20.50
9.59
2.97
6.02
3.61
107.21
89.76
69.11
61.33
60.17
44.99
38.18
26.01
25.96
18.40
18.10
-0.05
-4.33
-4.43
-4.46
-4.83

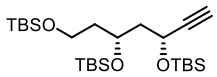

TMS
TBSO
TBSO
OTBS

237


1.07
1.20
2.27
2.15
2.17
9.02
9.05
9.30
9.04
3.20
3.02
2.98
3.00
6.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

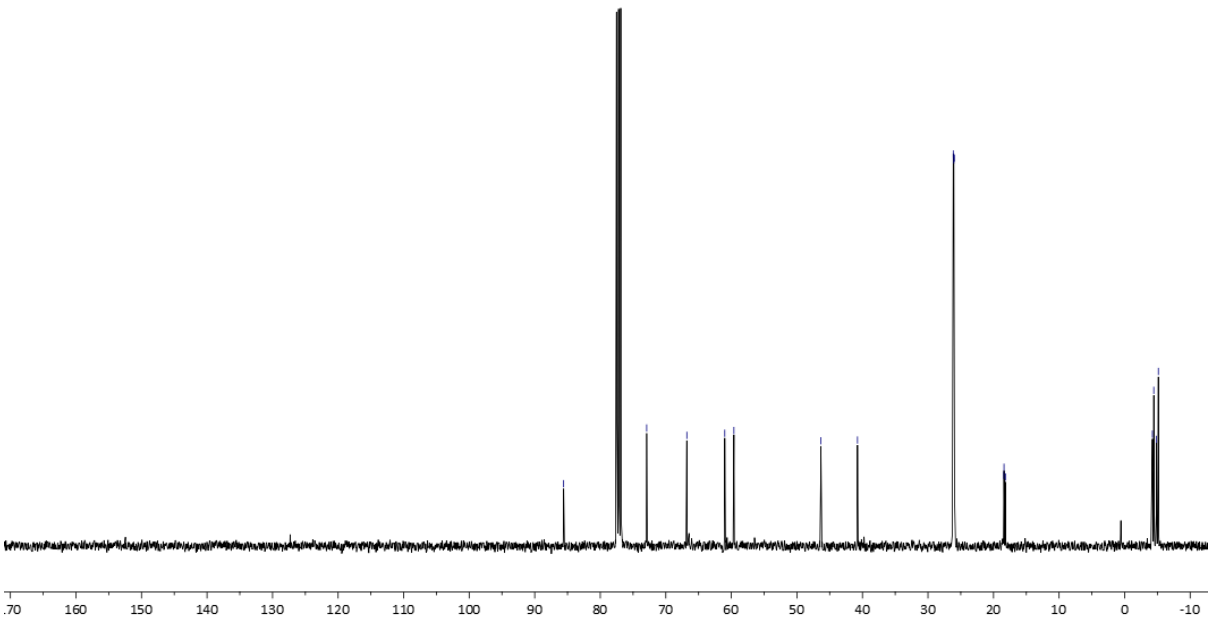
107.63
89.51
66.94
61.66
59.66
46.15
40.88
26.18
26.09
26.03
18.46
18.22
0.00
-4.25
-4.36
-4.43
-4.73
-5.08
-5.13

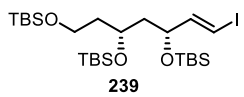

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


TBSO
TBSO
OTBS

238

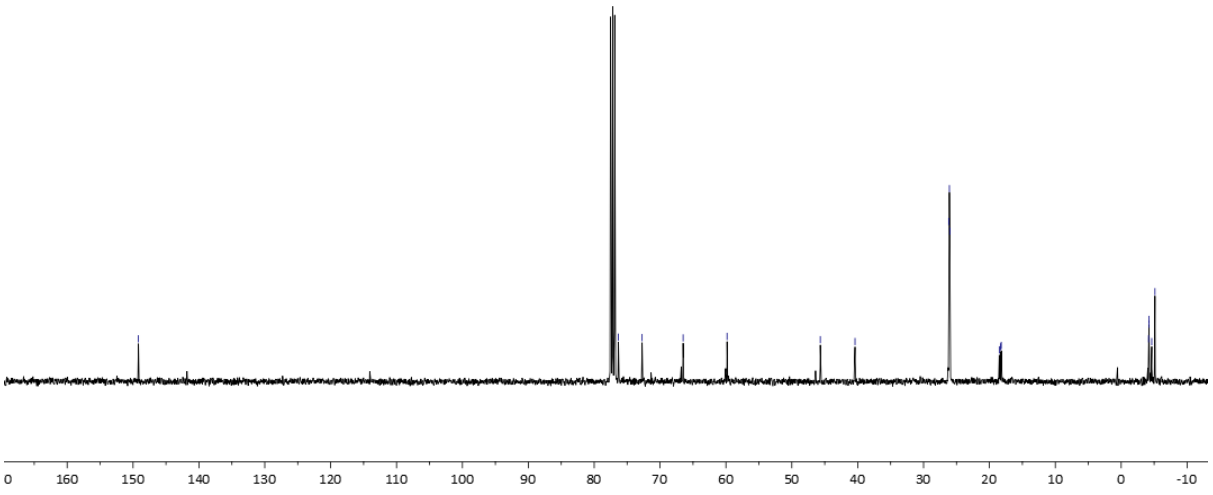
1.08
1.19
2.38
1.08
2.14
2.16
9.06
18.10
3.00
2.95
3.08
3.15
6.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
85.59
72.92
66.79
61.01
59.61
46.35
40.76
26.14
26.06
25.98
18.43
18.40
18.18
4.24
4.45
4.86
5.15

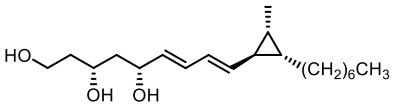

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


TBSO
TBSO
OTBS
I

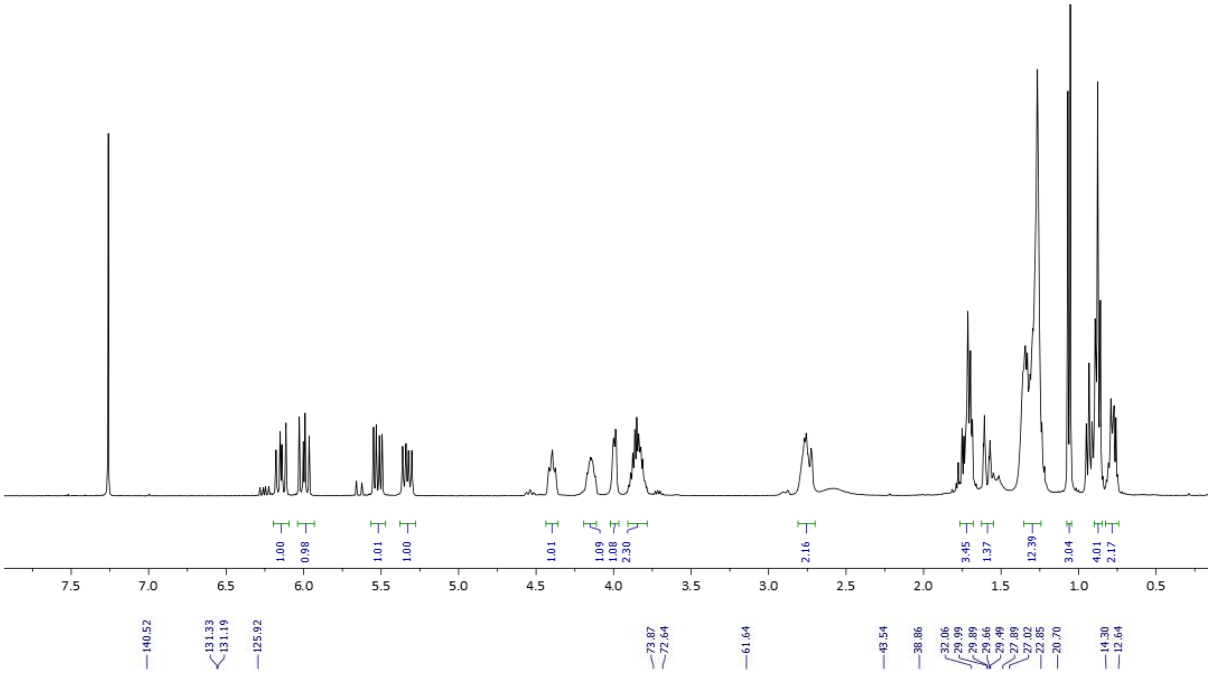
239

1.00
1.03
1.03
1.07
2.24
4.29
29.04
18.71
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
149.18
76.32
72.73
66.50
59.83
45.68
40.40
26.18
26.08
26.02
18.51
18.33
18.21
-4.17
-4.22
-4.23
-4.64
-5.13

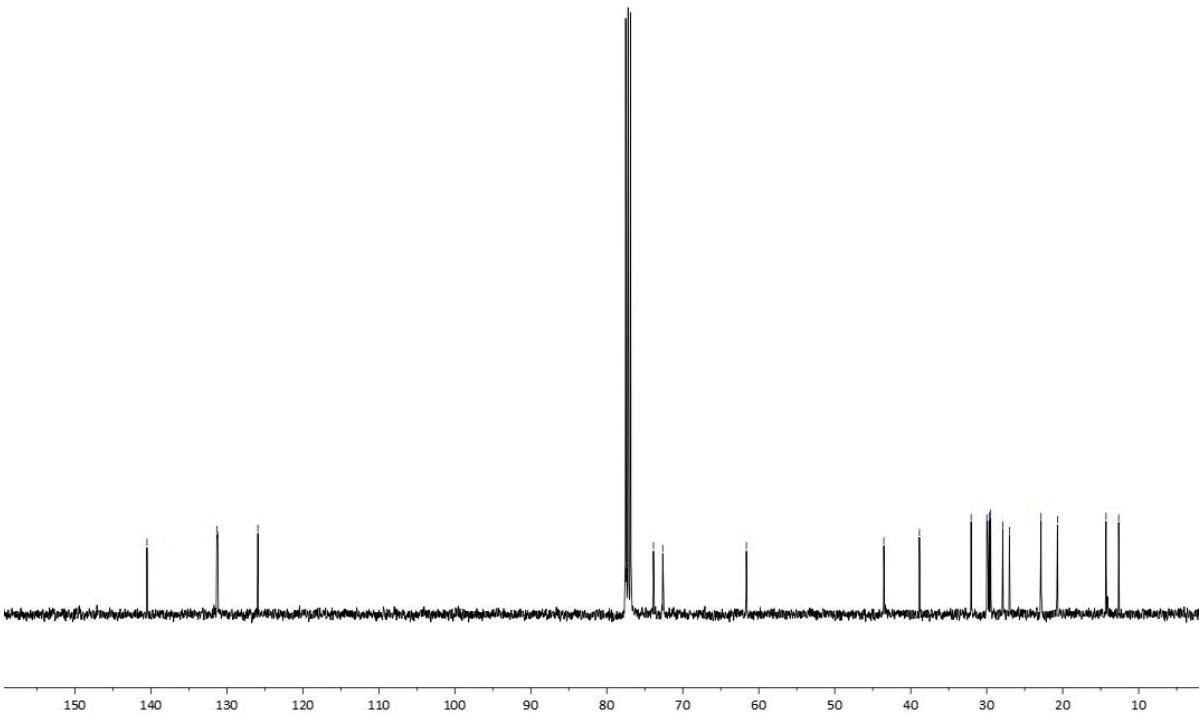

0
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

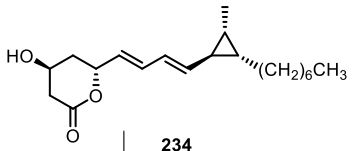

HO
OH
OH
(CH2)6CH3

233

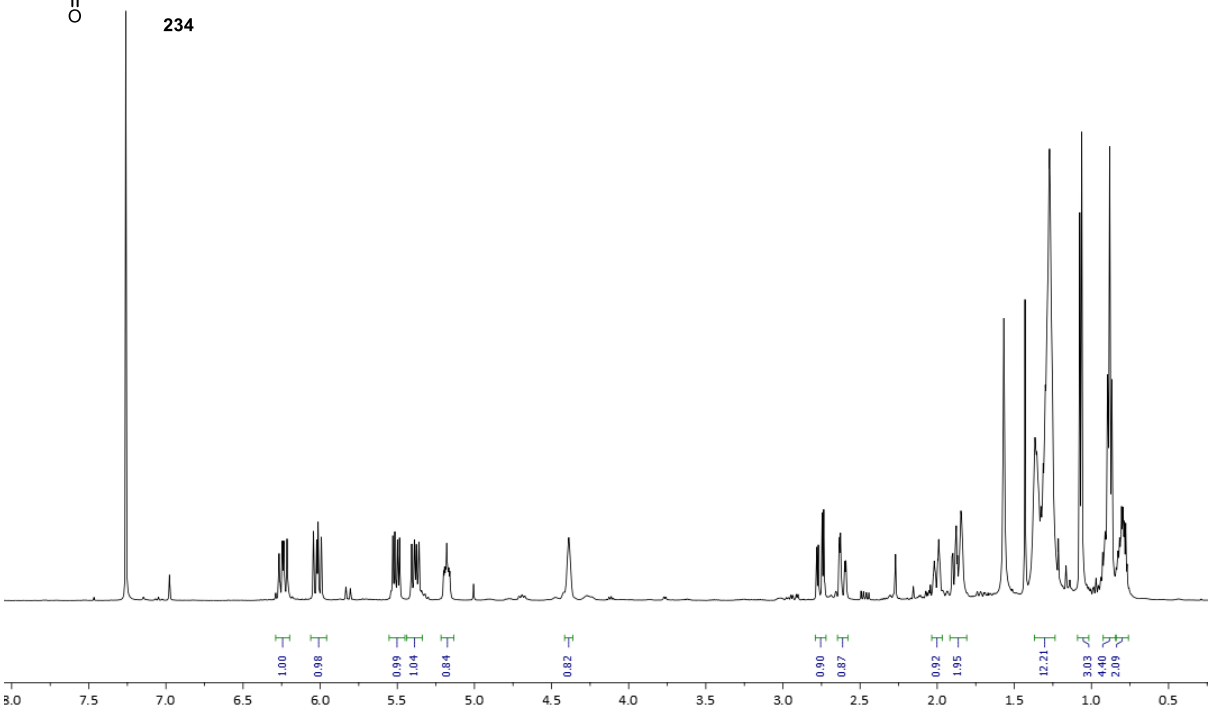

1.00
0.98
1.01
1.00
1.01
1.09
1.08
2.30
2.16
3.45
1.37
12.39
3.04
4.01
2.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

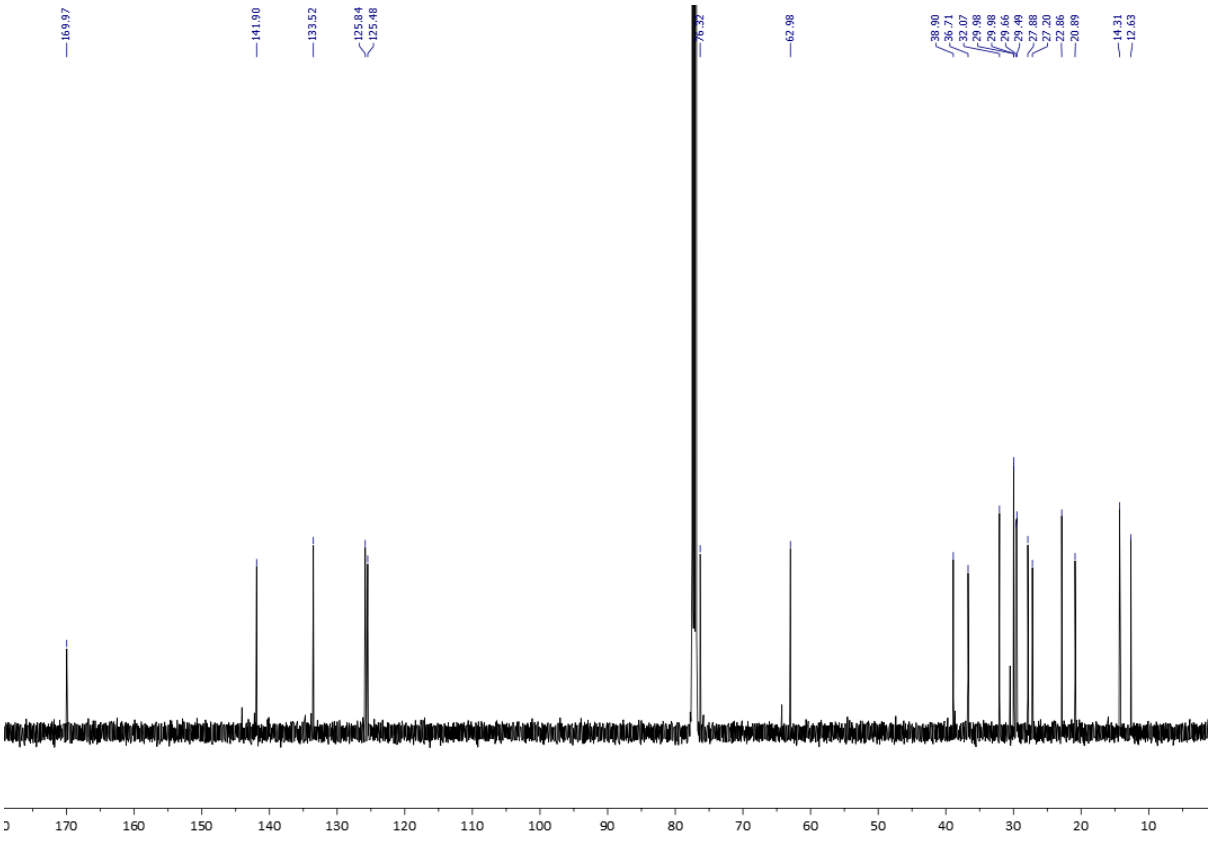
140.52
131.33
131.19
125.92
73.87
72.64
61.64
43.54
38.86
32.06
29.99
29.89
29.66
29.49
27.89
27.02
22.85
20.70
14.30
12.64

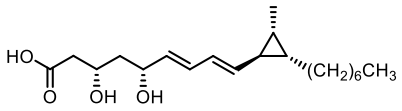

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


HO
O
O
$(CH_2)_6CH_3$

234

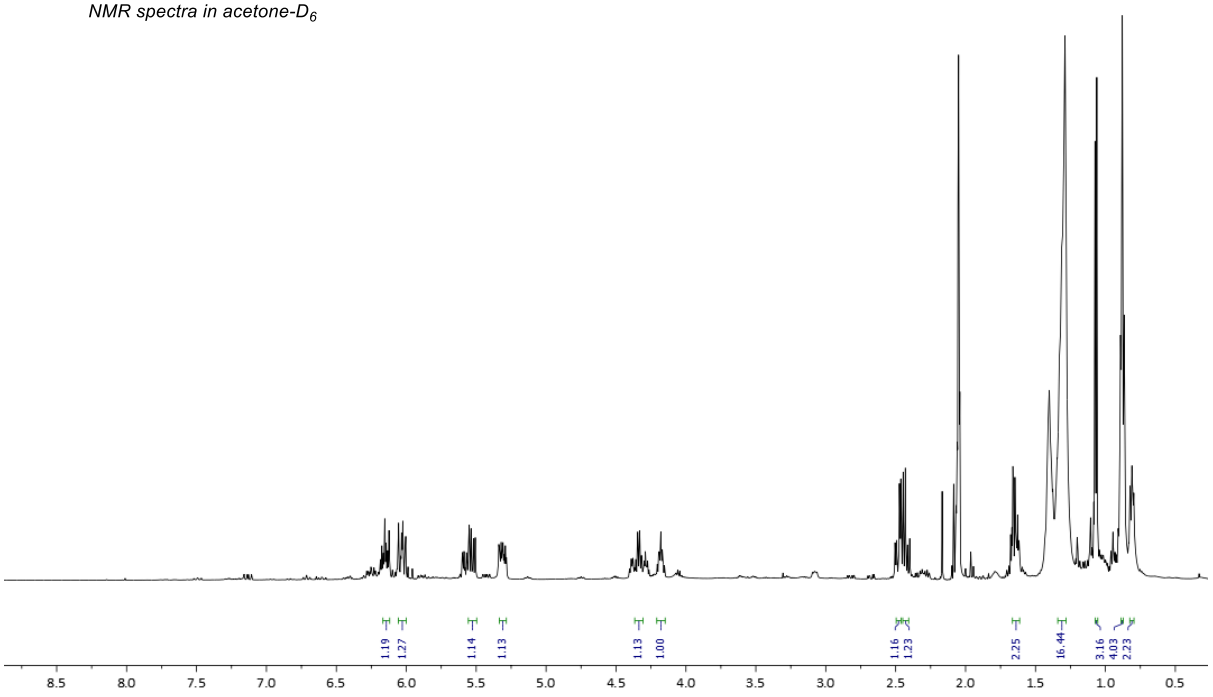

1.00
0.98
0.99
1.04
0.84
0.82
0.90
0.87
0.92
1.95
12.21
3.03
4.40
2.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

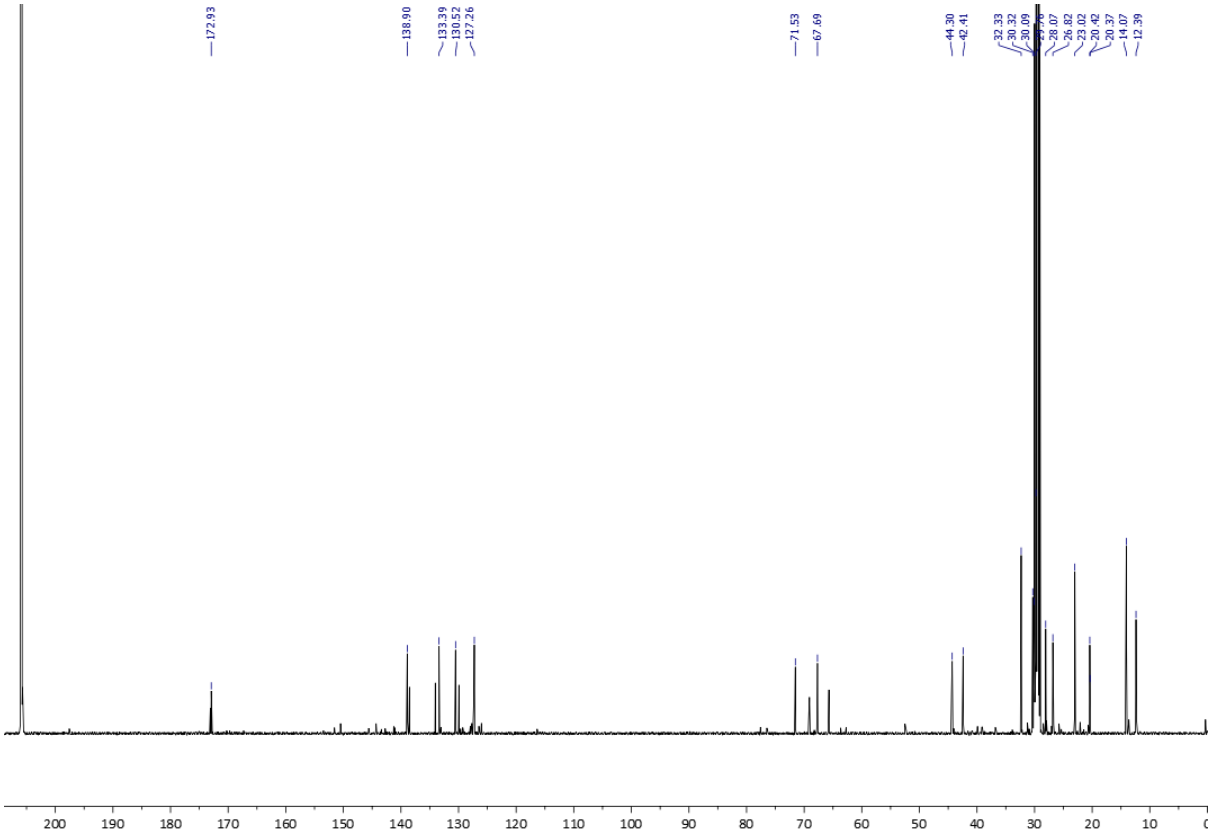

169.97
141.90
133.52
125.84
125.48
76.32
62.98
38.90
36.71
32.07
29.98
29.98
29.66
29.49
27.88
27.20
22.86
20.89
14.31
12.63
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

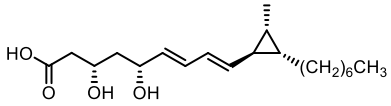


134

NMR spectra in acetone-D_6

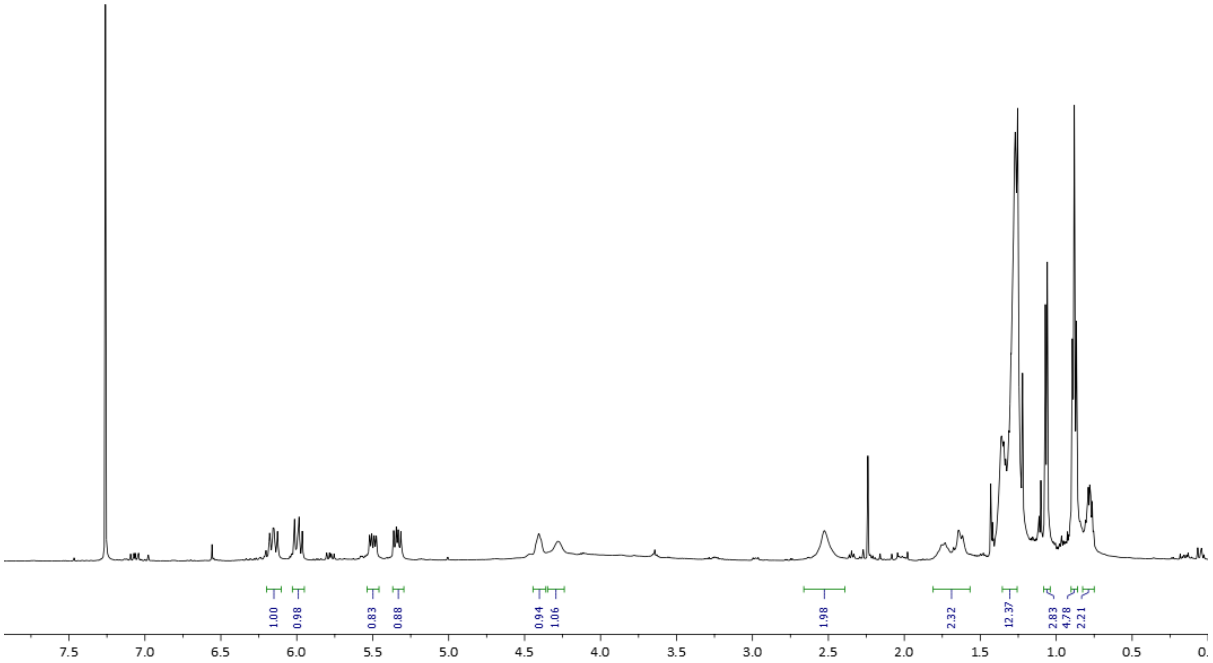


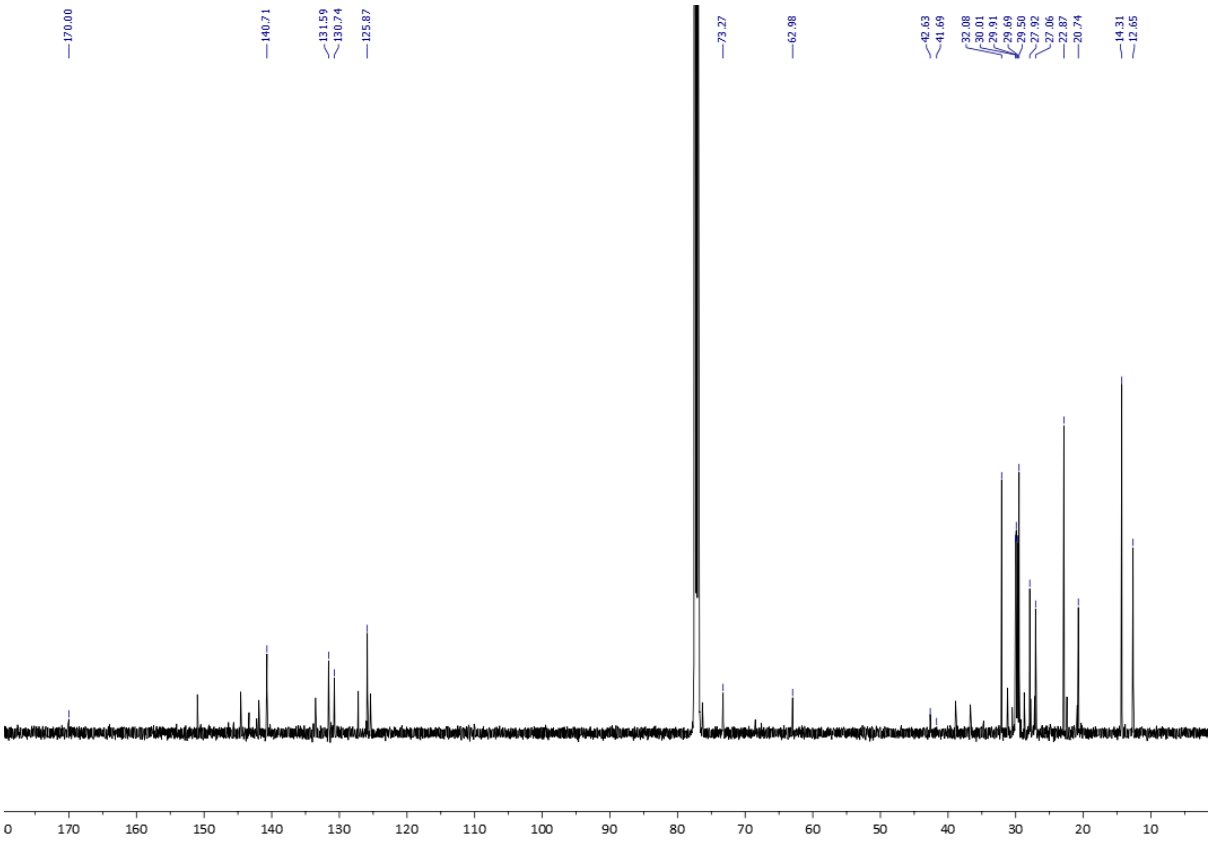


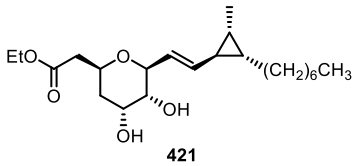


134

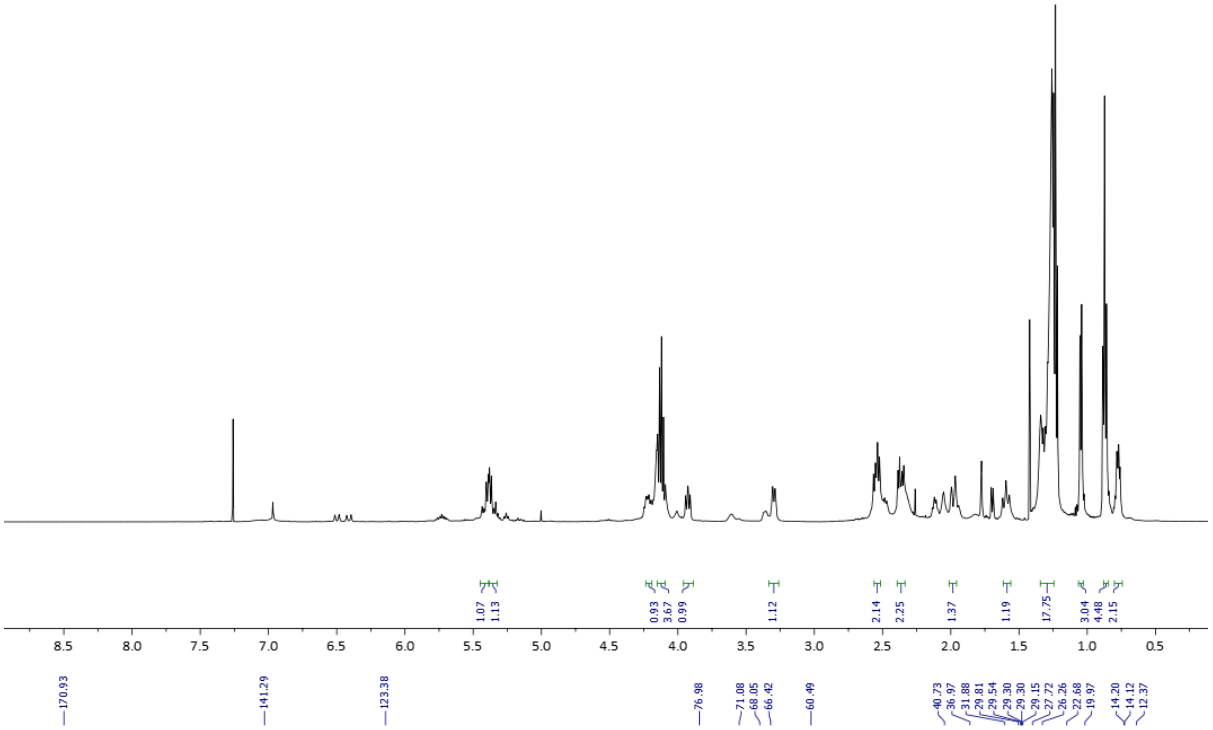
NMR spectra in methanol-D_4

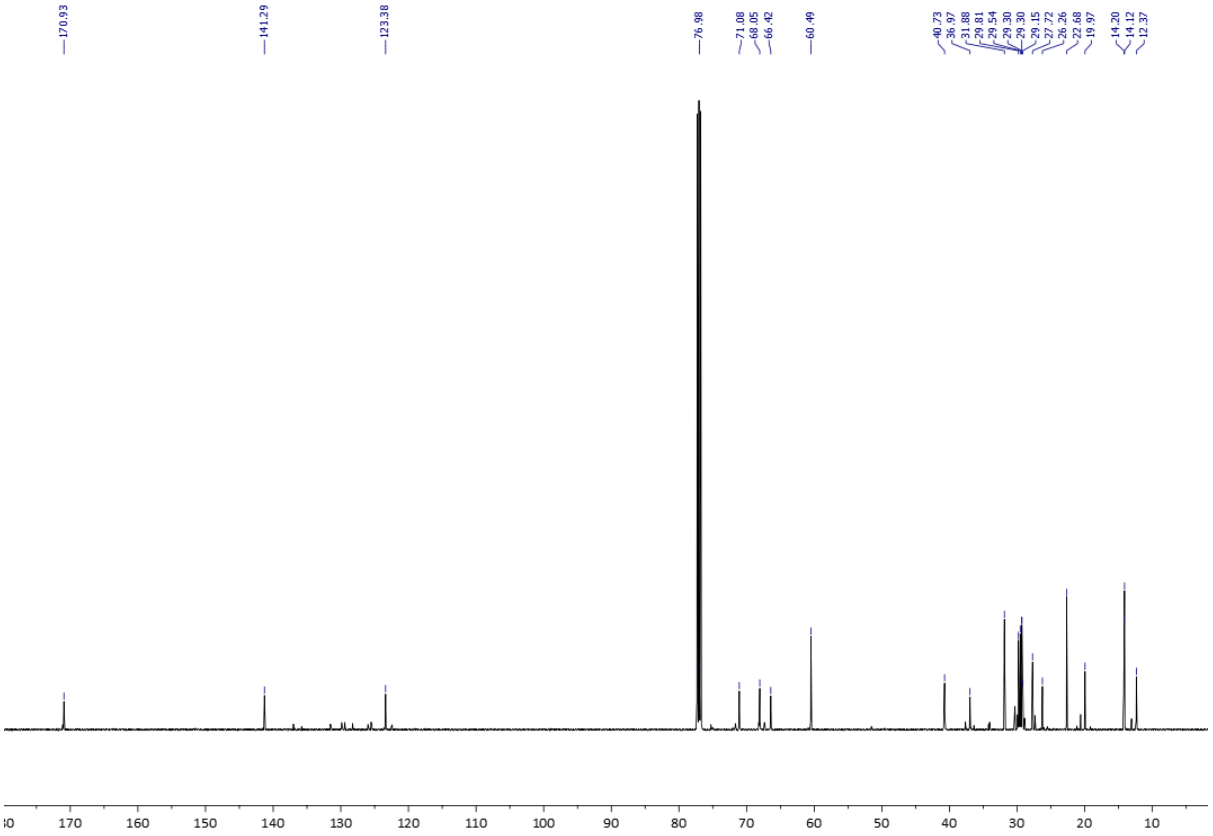


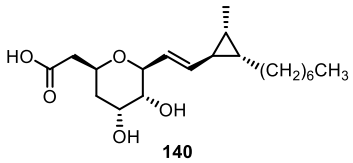



EtO
O
O
OH
OH
(CH2)6CH3

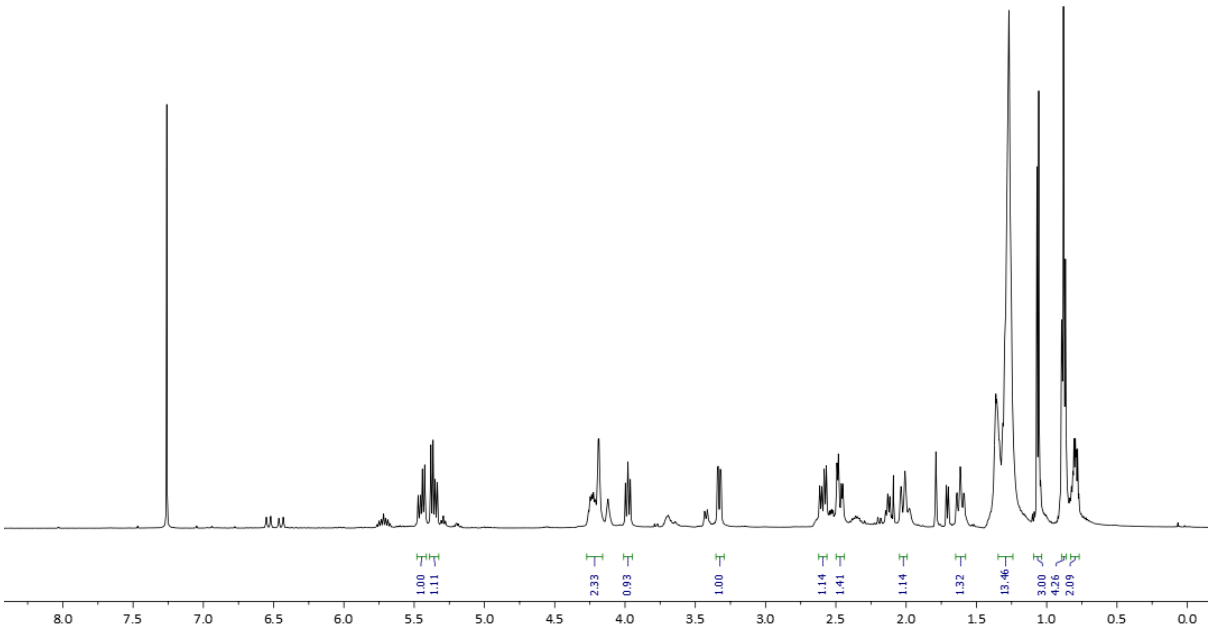
421

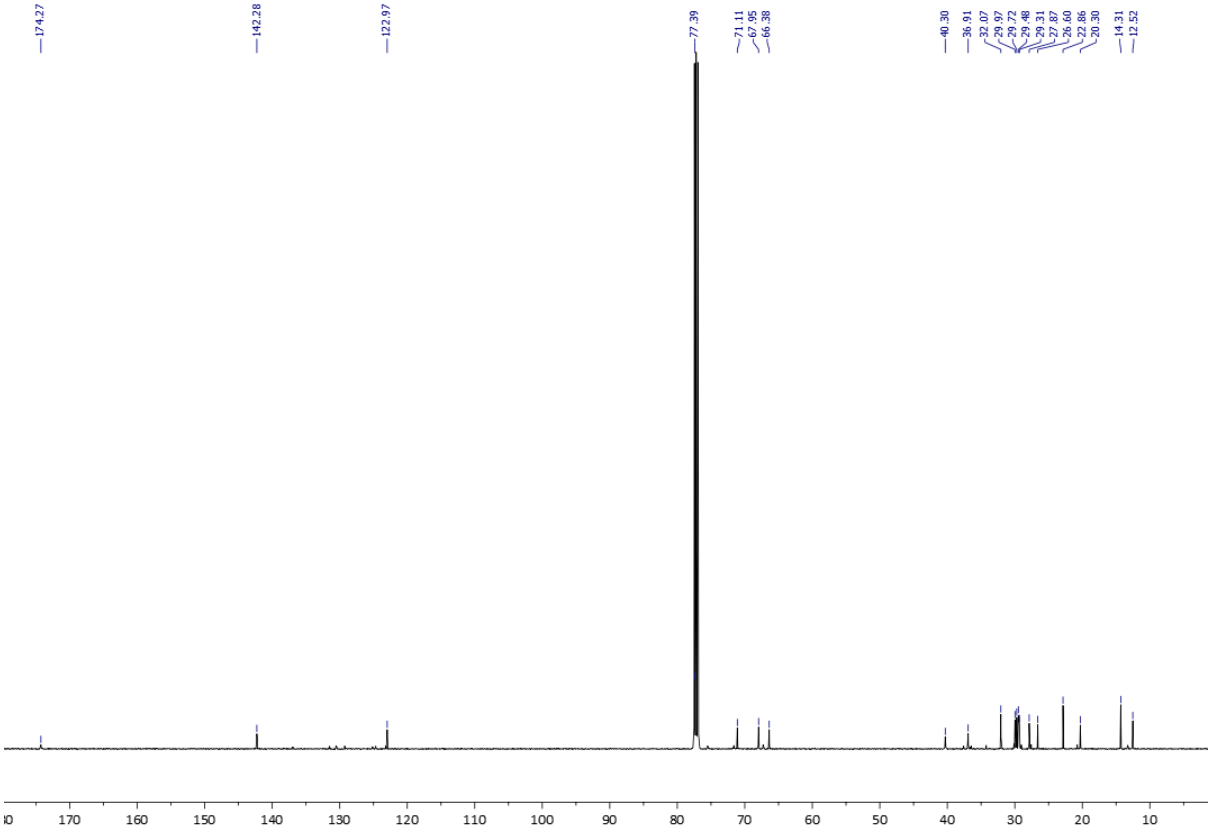

1.07
1.13
0.93
3.67
0.99
1.12
2.14
2.25
1.37
1.19
17.75
3.04
4.48
2.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

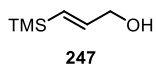

170.93
141.29
123.38
76.98
71.08
68.05
66.42
60.49
40.73
36.97
31.88
29.81
29.54
29.30
29.30
29.15
27.72
26.26
22.68
19.97
14.20
14.12
12.37
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


HO
O
O
OH
OH
$(CH_2)_6CH_3$

140

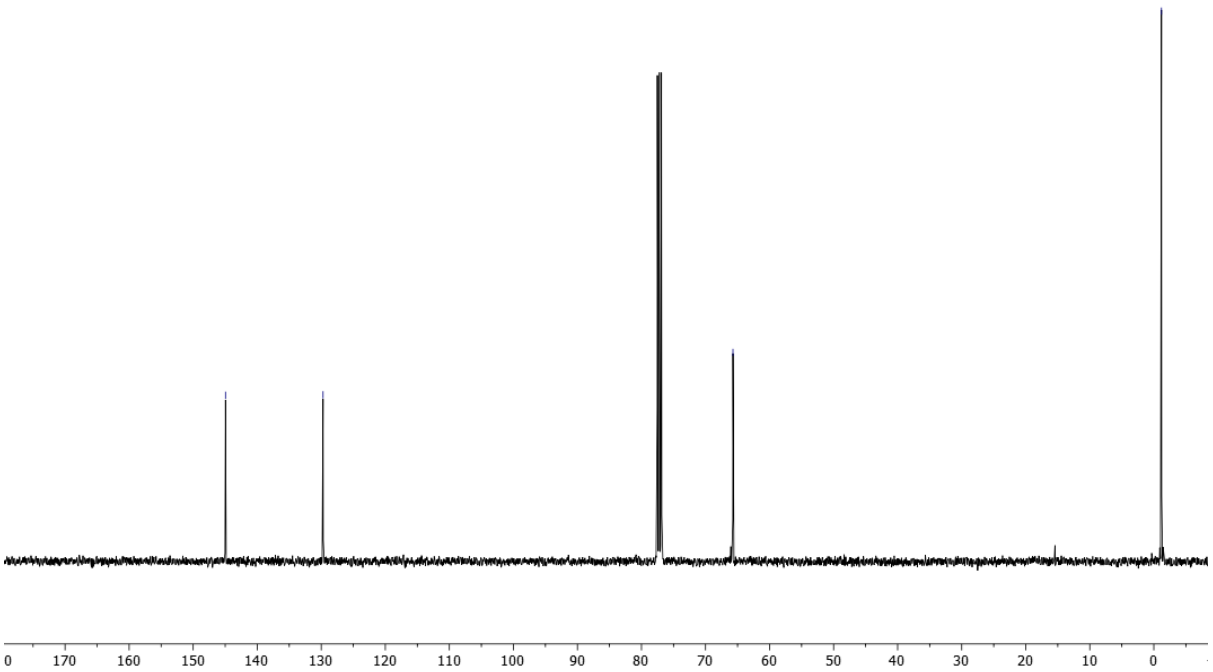

1.00
1.11
2.33
0.93
1.00
1.14
1.41
1.14
1.32
13.46
3.00
4.26
2.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

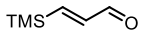

174.27
142.28
122.97
77.39
71.11
67.95
66.38
40.30
36.91
32.07
29.97
29.72
29.48
29.31
27.87
26.60
22.86
20.30
14.31
12.52
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


TMS
OH

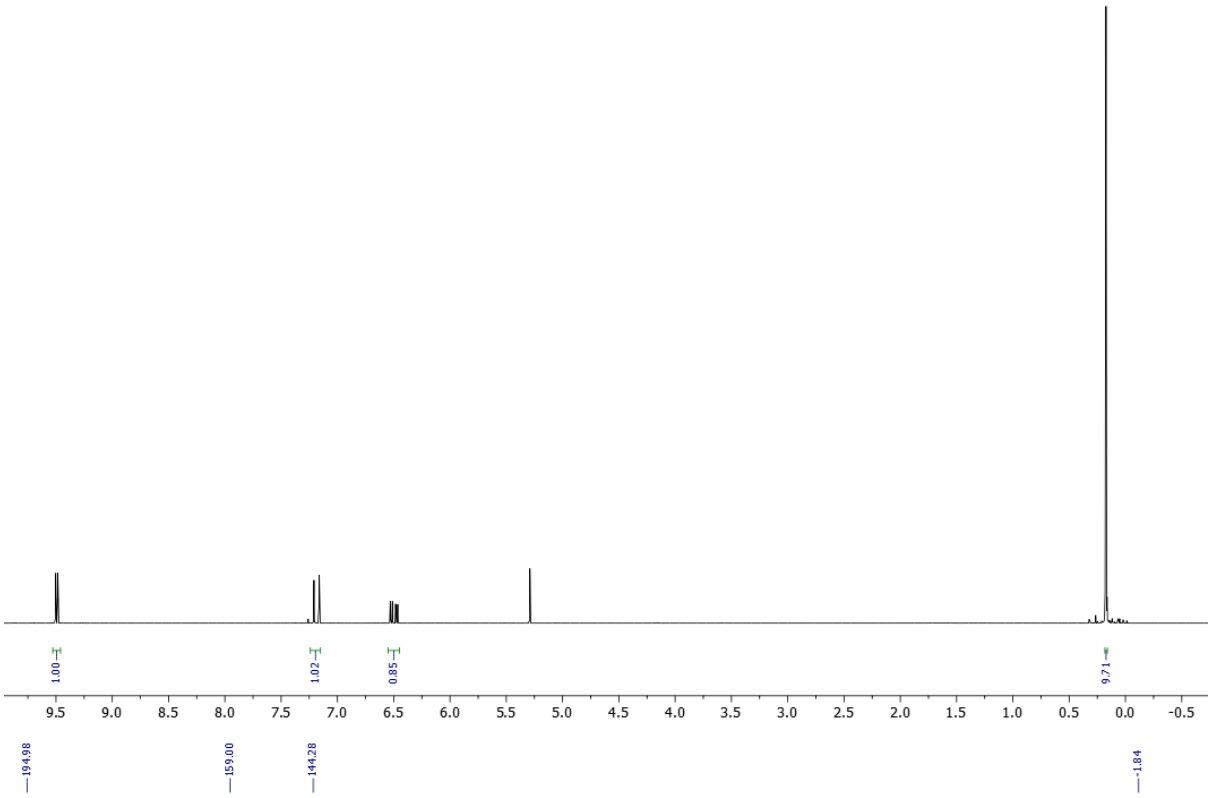
247

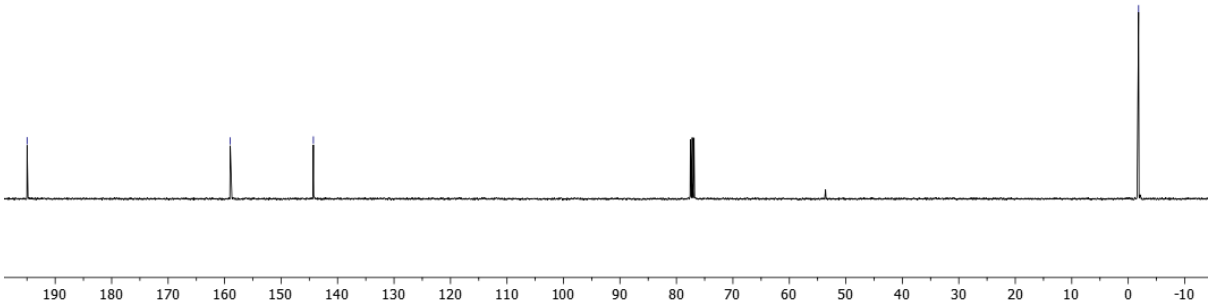
1.00
1.00
2.09
1.00
9.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
144.95
129.72
65.72
-1.19

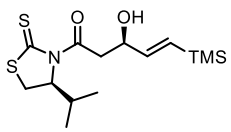

0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMS
O

245

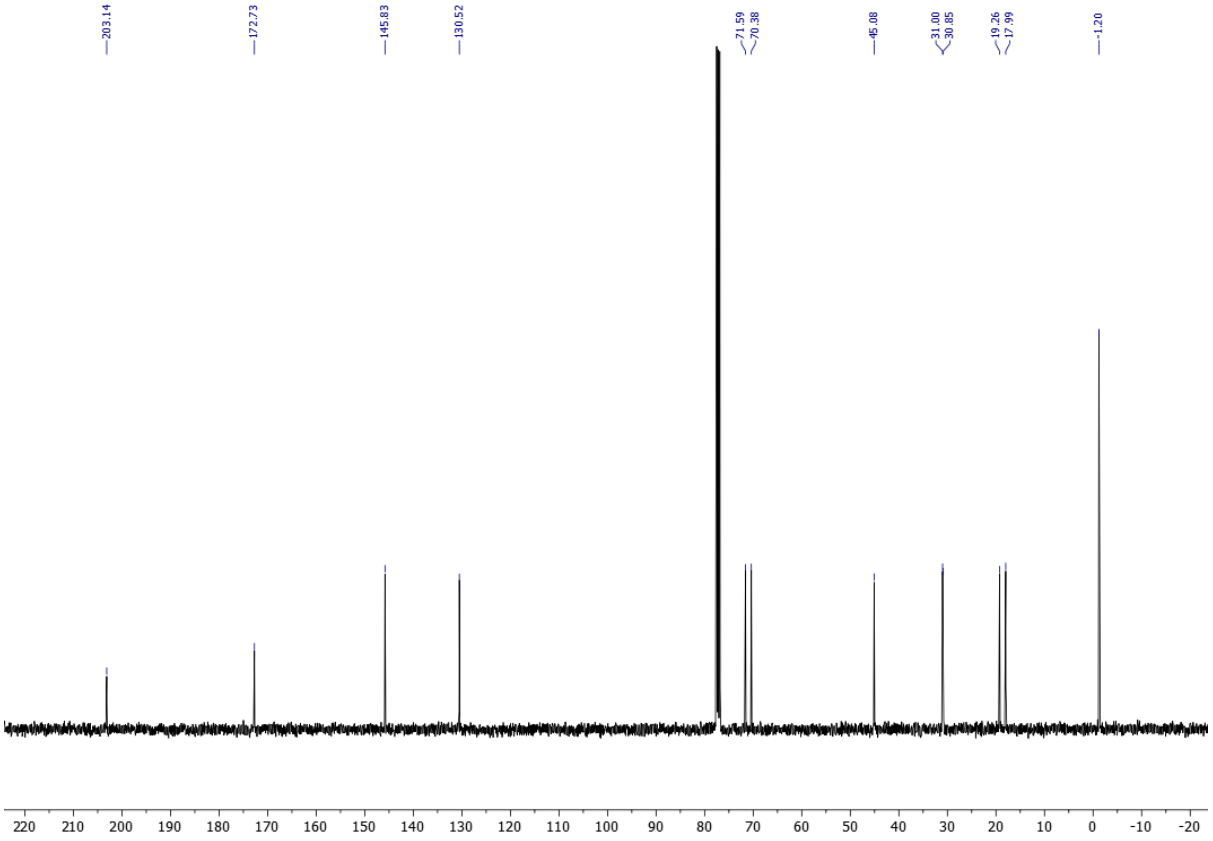

1.00
1.02
0.85
9.71
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
194.98
159.00
144.28
1.84

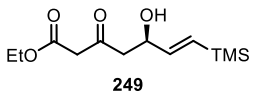

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


S
O
OH
N
S
TMS

248

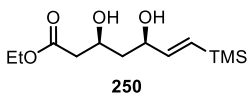
1.00
1.00
1.01
1.00
1.00
1.03
1.01
1.01
0.96
1.01
2.99
3.07
9.16
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


203.14
172.73
145.83
130.52
71.59
70.38
45.08
31.00
30.85
19.26
17.99
-1.20
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20


O
O
OH
EtO
TMS

249

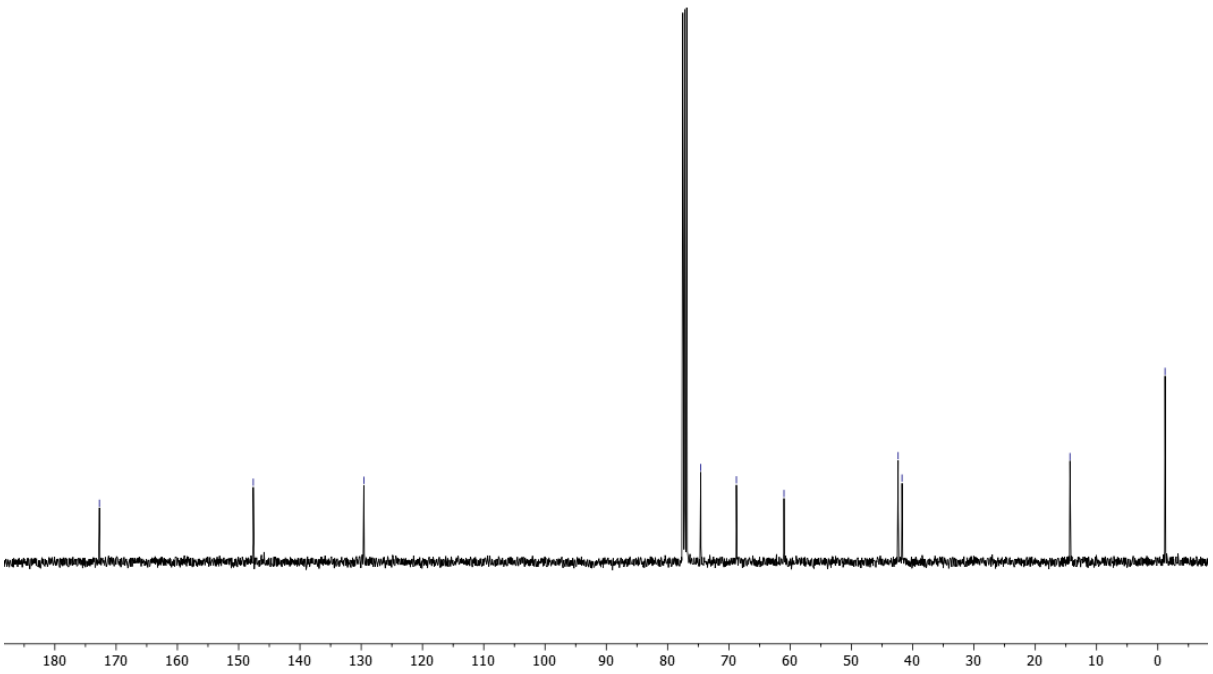
1.00
1.01
0.97
2.14
1.96
1.01
1.95
3.25
9.23
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
203.10
167.06
145.83
130.50
69.99
61.73
50.16
49.35
14.27
-1.24
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

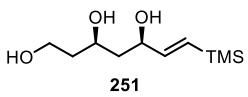

O
OH
OH
EtO
TMS

250

1.00
1.00
1.01
1.02
2.15
0.97
0.98
1.96
3.38
9.60
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

172.72
147.62
129.57
74.59
68.77
61.01
42.38
41.75
14.34
-1.18

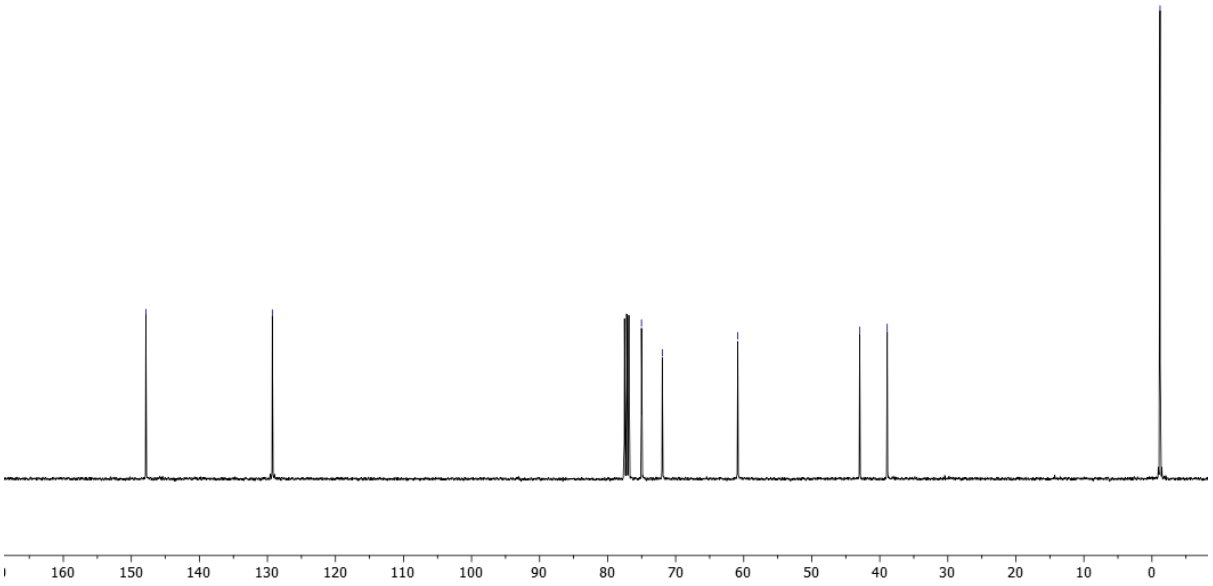

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

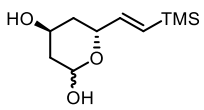

OH
OH
HO
TMS

251

1.00
0.99
0.88
1.05
1.03
2.97
0.88
4.07
9.31
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

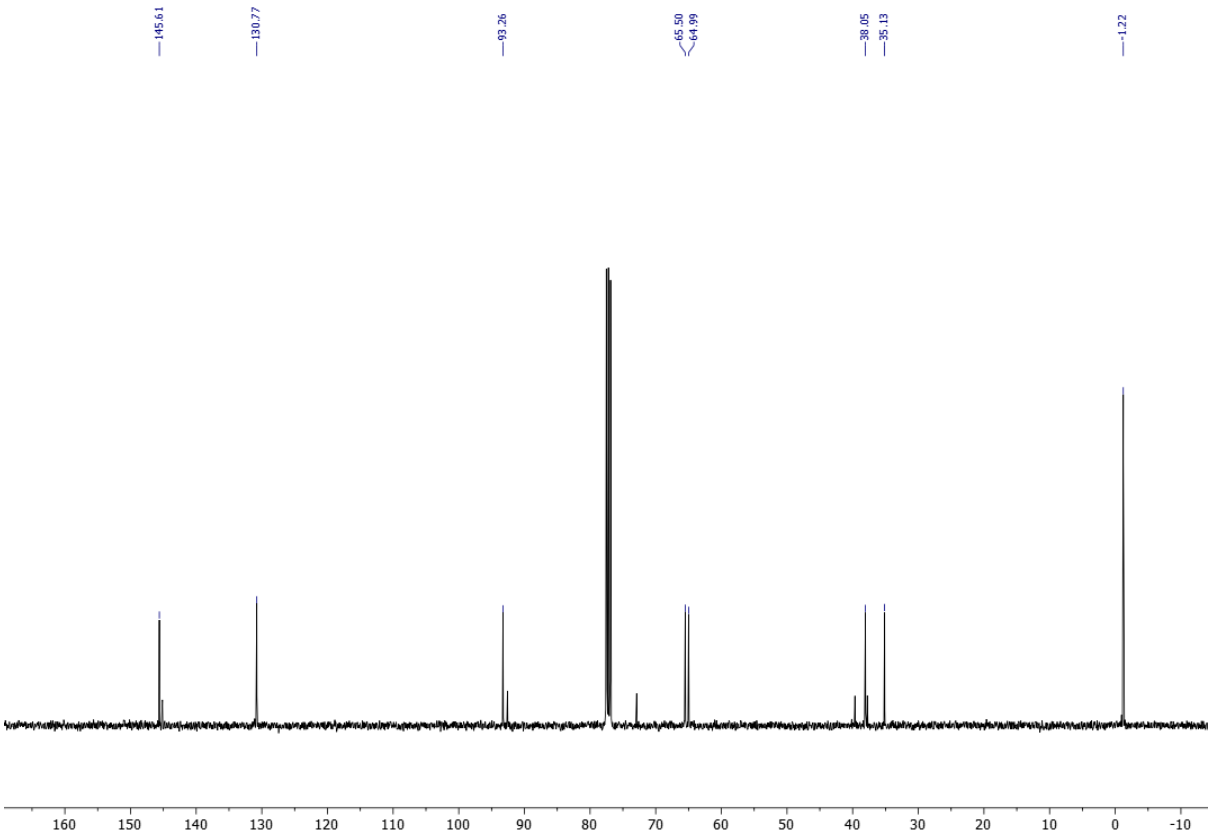
147.86
129.28
75.02
71.96
60.87
42.96
38.91
-1.19

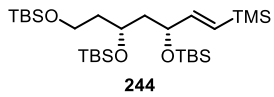

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


HO
TMS
O
OH

252

1.59
1.52
1.04
0.45
1.03
0.51
0.51
1.06
1.02
0.47
1.00
0.58
0.91
1.08
1.10
3.06
8.57
4.51
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


145.61
130.77
93.26
65.50
64.99
38.05
35.13
-1.22
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


TBSO
TMS
TBSO
OTBS

244

1.00
1.01
1.04
1.04
2.17
4.47
28.14
27.30
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

149.16
129.23
73.40
66.85
60.09
46.12
40.44
26.20
26.11
25.89
18.53
18.40
18.24
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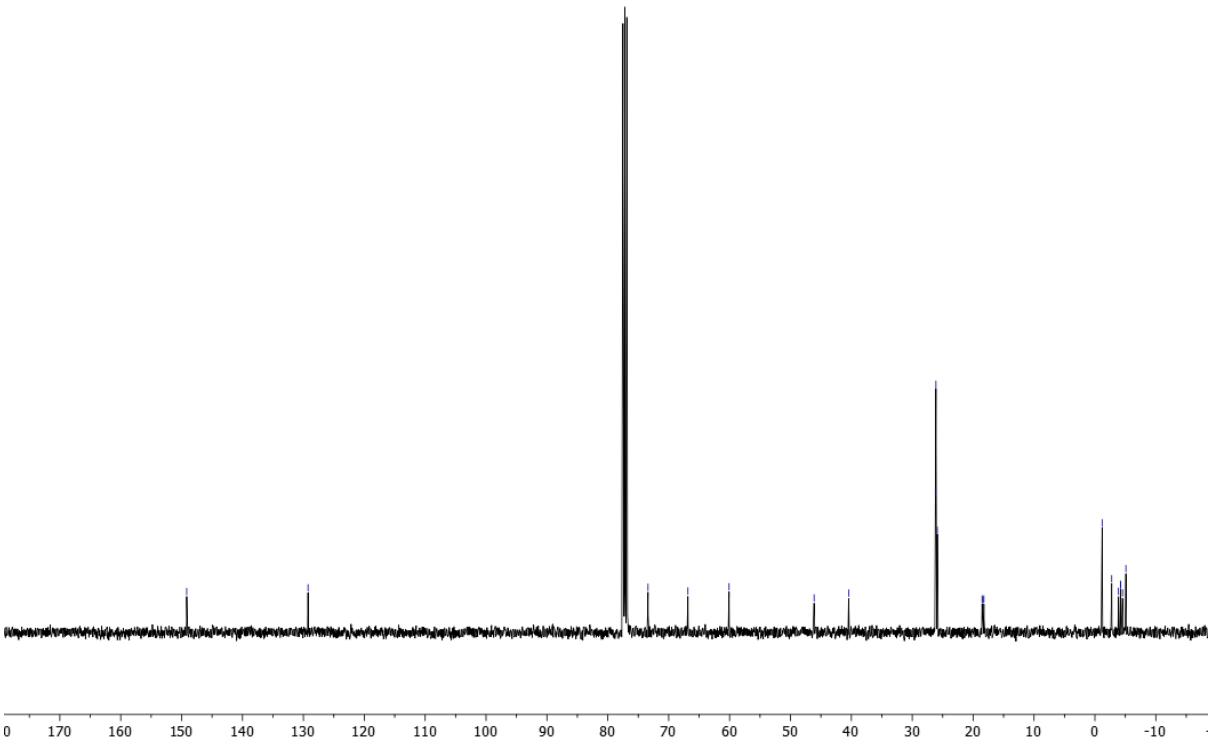
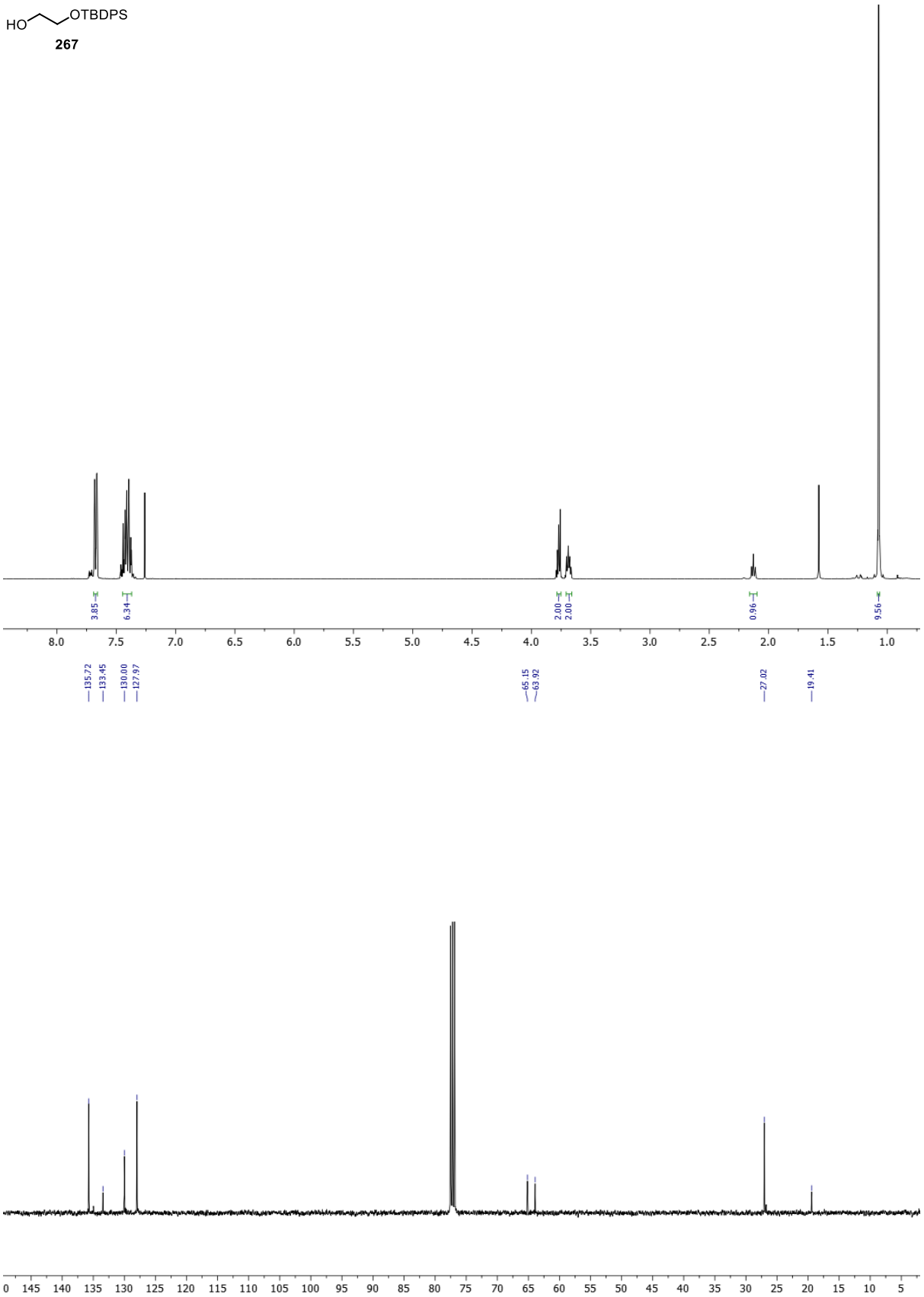
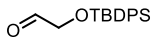
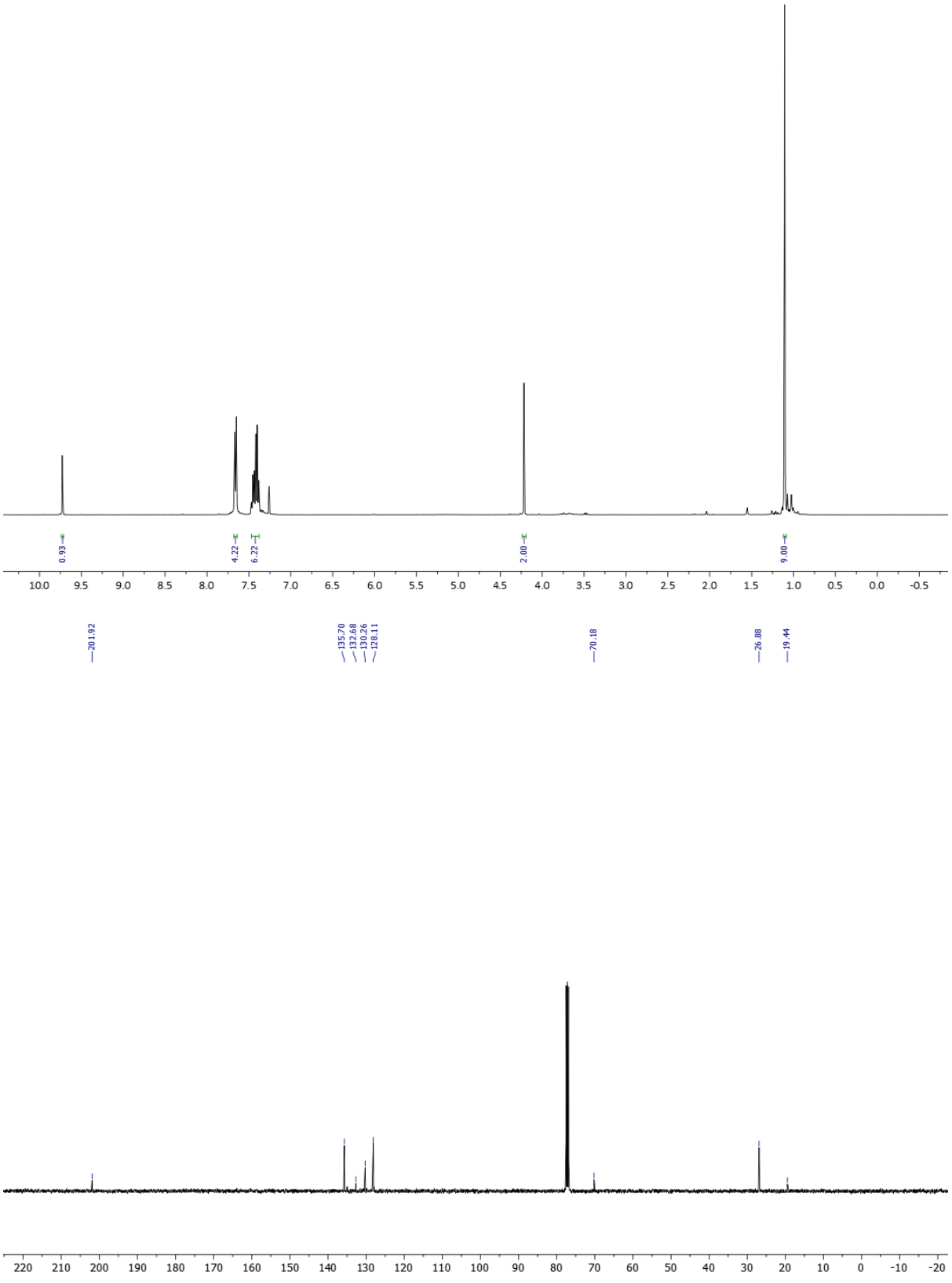
-3.88
-4.19
-4.22
-4.54
-5.09

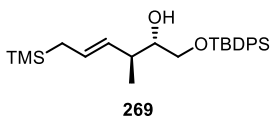

0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


HO
OTBDPS
267
3.85
6.34
2.00
2.00
0.96
9.56
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
135.72
133.45
130.00
127.97
65.15
63.92
27.02
19.41
0
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5


OTBDPS
O

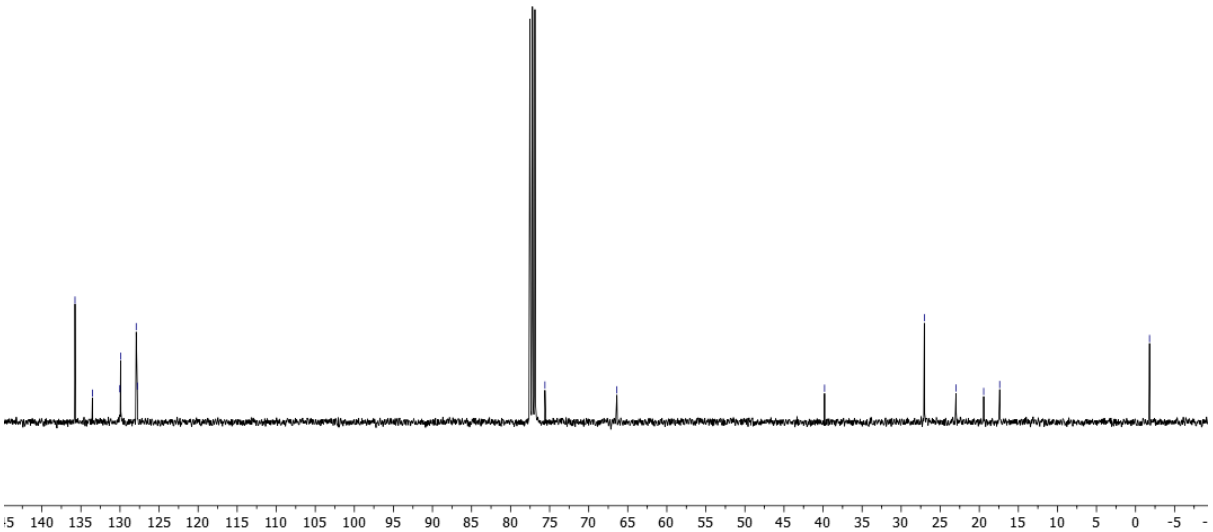
268

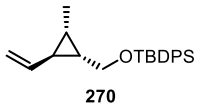

0.93
4.22
6.22
2.00
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
201.92
135.70
132.68
130.26
128.11
70.18
26.88
19.44
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


OH
TMS
OTBDPS

269

3.99
5.95
1.02
1.00
1.00
1.03
1.03
0.98
1.05
2.13
9.53
3.16
8.95
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
135.76
133.53
130.02
129.92
127.92
127.78
75.60
66.40
39.81
27.04
22.98
19.44
17.39
-1.79


140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5


OTBDPS

270

4.18
6.10
1.00
0.99
0.98
0.99
1.01
1.13
2.99
9.05
2.08
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
141.66
135.83
135.81
134.23
129.72
127.77
111.50
63.20
28.60
27.55
27.03
19.60
19.40
12.74
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140
130
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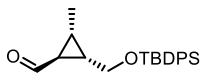
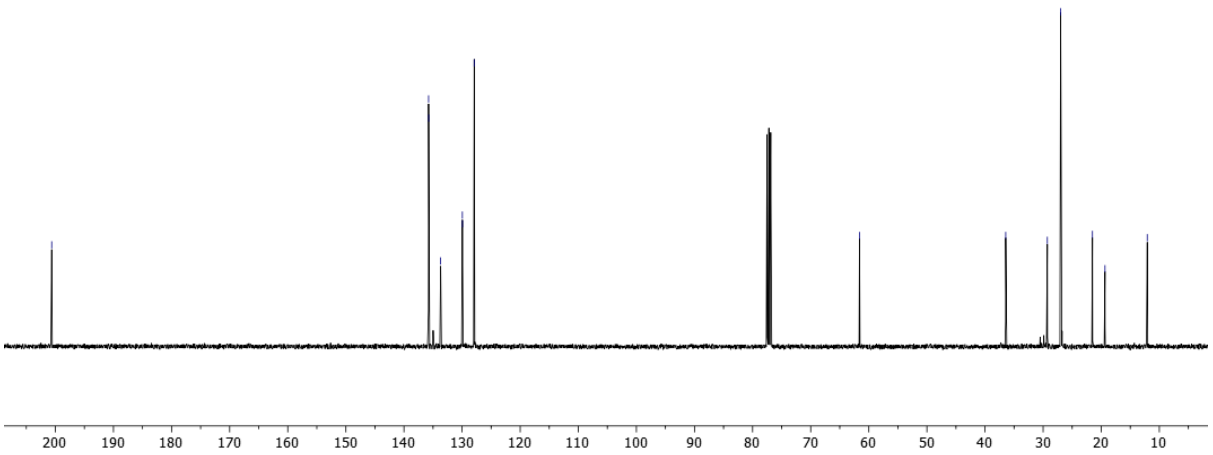
10
0


O
OTBDPS

271

1.00
4.47
7.03
1.09
1.10
1.15
1.27
1.36
3.26
8.65
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
200.63
135.76
135.75
133.69
129.95
129.94
127.91
61.60
36.44
29.28
26.99
21.51
19.35
12.08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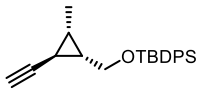
OTBDPS

272

4.04
6.02
1.00
1.06
0.98
1.17
1.21
3.08
9.00
0.99
135.80
135.78
133.91
133.89
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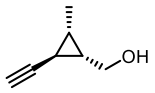
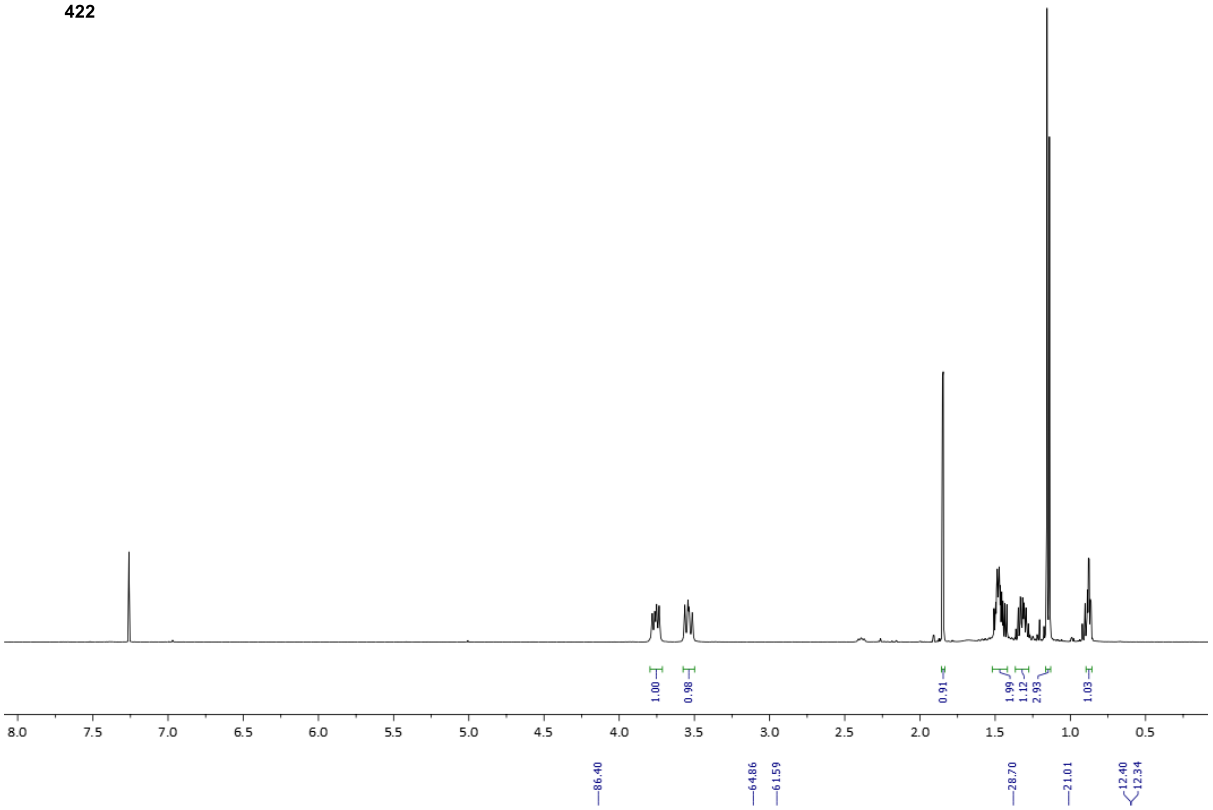
87.00
64.40
62.47
28.56
27.00
21.16
19.38
12.53
11.99


OH

422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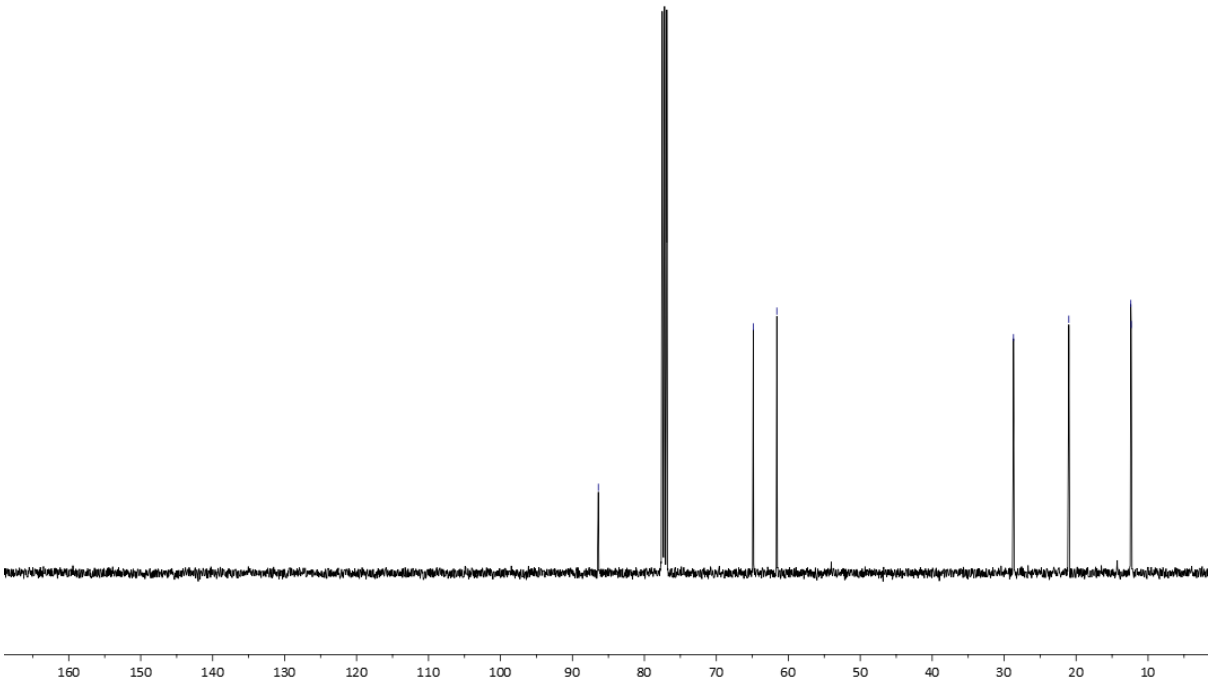
0.98
0.91
1.99
1.12
2.93
1.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
86.40
64.86
61.59
28.70
21.01
12.40
12.34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150
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110
100
90
80
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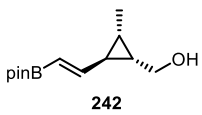
60
50
40
30
20
10


pinB
OH

242

1.04
1.03
1.12
1.01
1.35
12.59
4.94
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
156.83
83.18
62.00
31.04
28.99
24.91
20.78
12.53
170
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150
140
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120
110
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70
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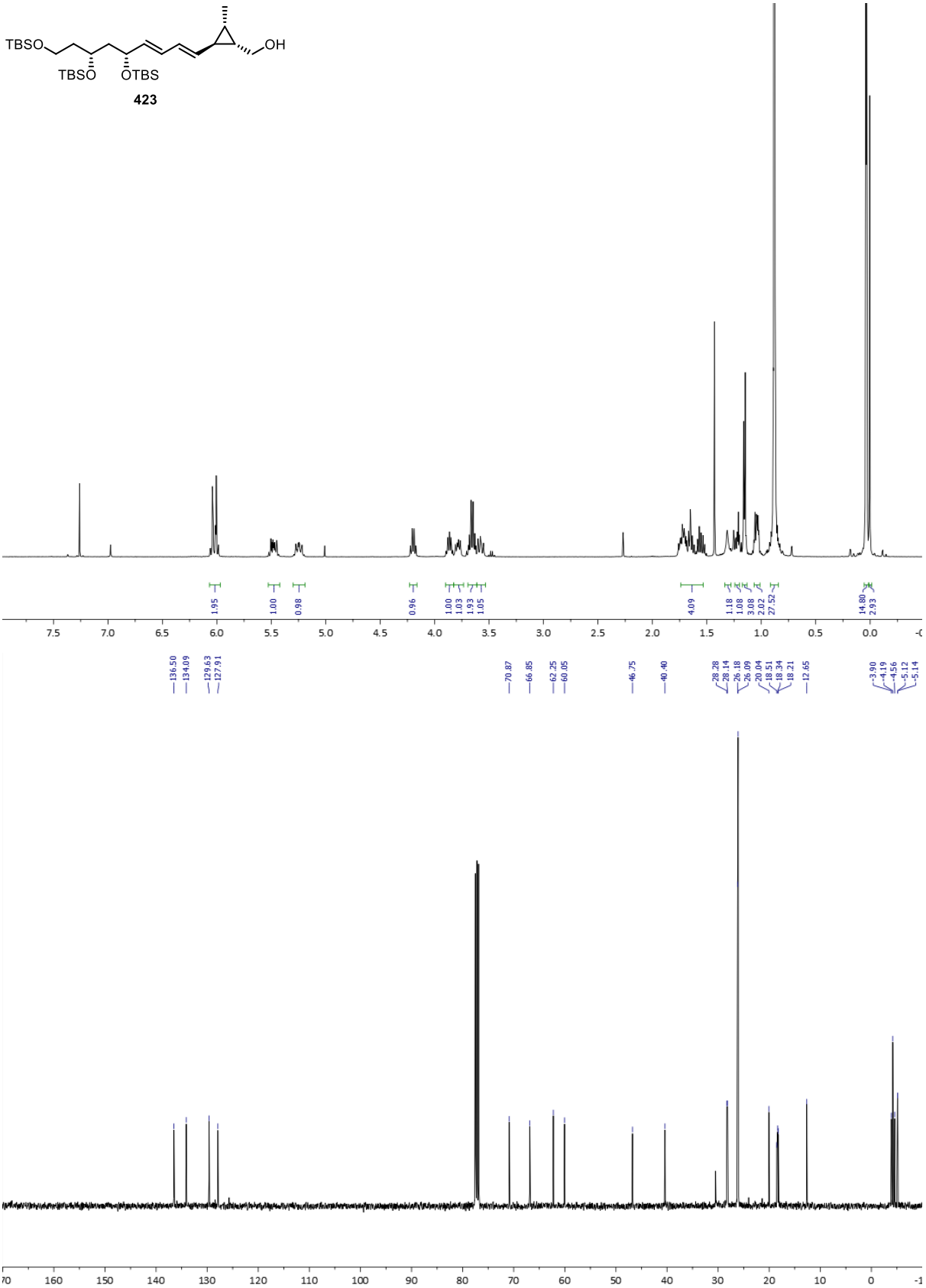
20
10
0


TBSO
TBSO
OTBS
OH
423
1.95
1.00
0.98
0.96
1.00
1.03
1.93
1.05
4.09
1.18
1.08
3.08
2.02
27.52
14.80
2.93
136.50
134.09
129.63
127.91
70.87
66.85
62.25
60.05
46.75
40.40
28.28
28.14
26.18
26.09
20.04
18.51
18.34
18.21
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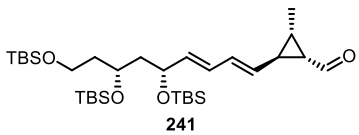
-3.90
-4.19
-4.56
-5.12
-5.14


TBSO
TBSO
OTBS
O

241

1.02
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0.99
1.00
0.97
0.99
1.02
2.15
1.01
1.03
5.12
3.31
27.18
15.23
3.03
199.92
136.04
132.53
130.44
128.86
70.63
66.78
60.00
46.59
40.41
37.57
33.34
26.98
26.18
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18.34
18.21
12.84
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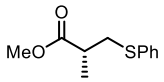
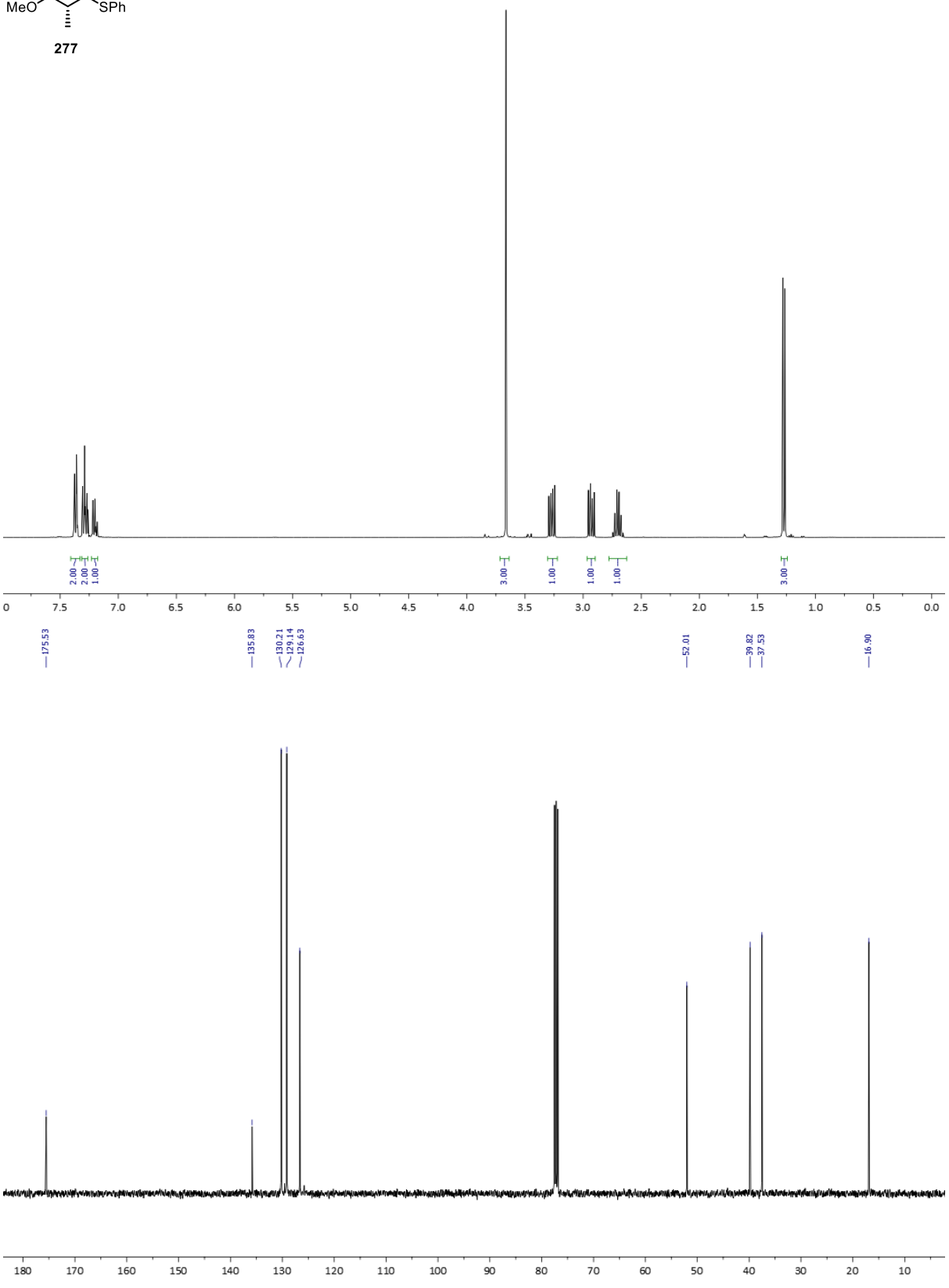
-4.19
-4.56
-5.12
-5.14


O
MeO
SPh

277


2.00
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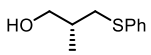
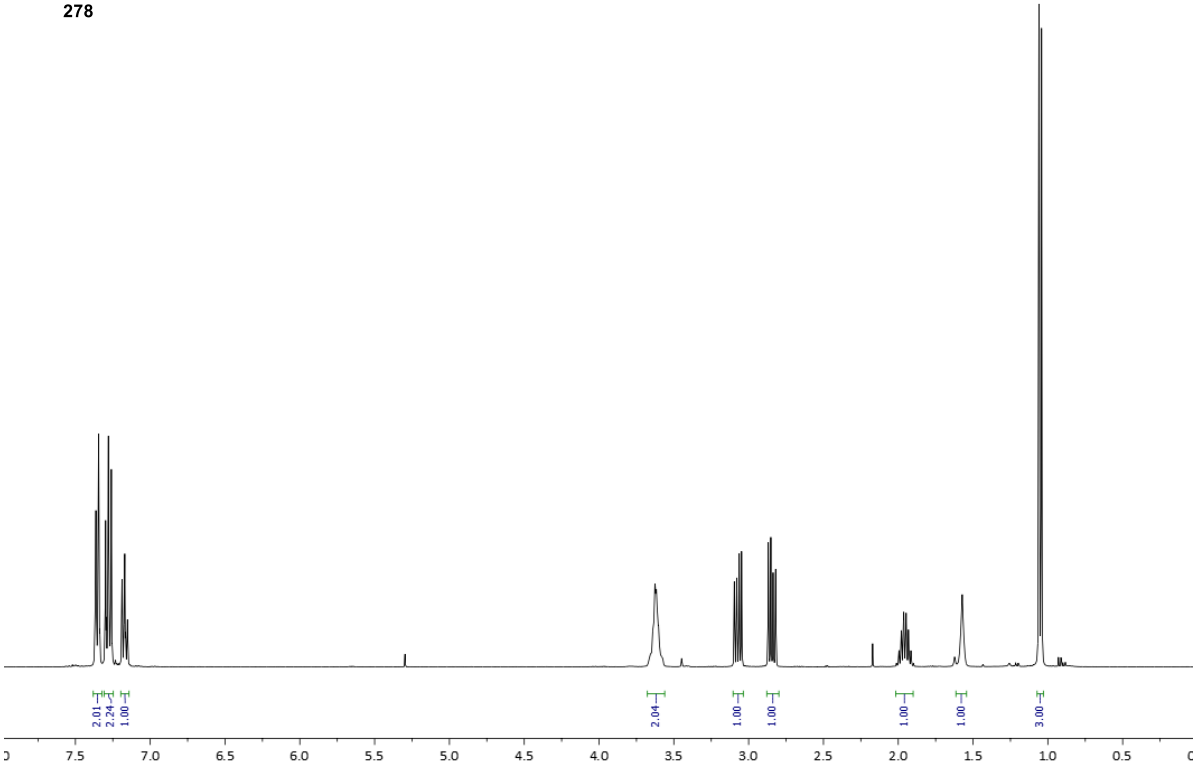
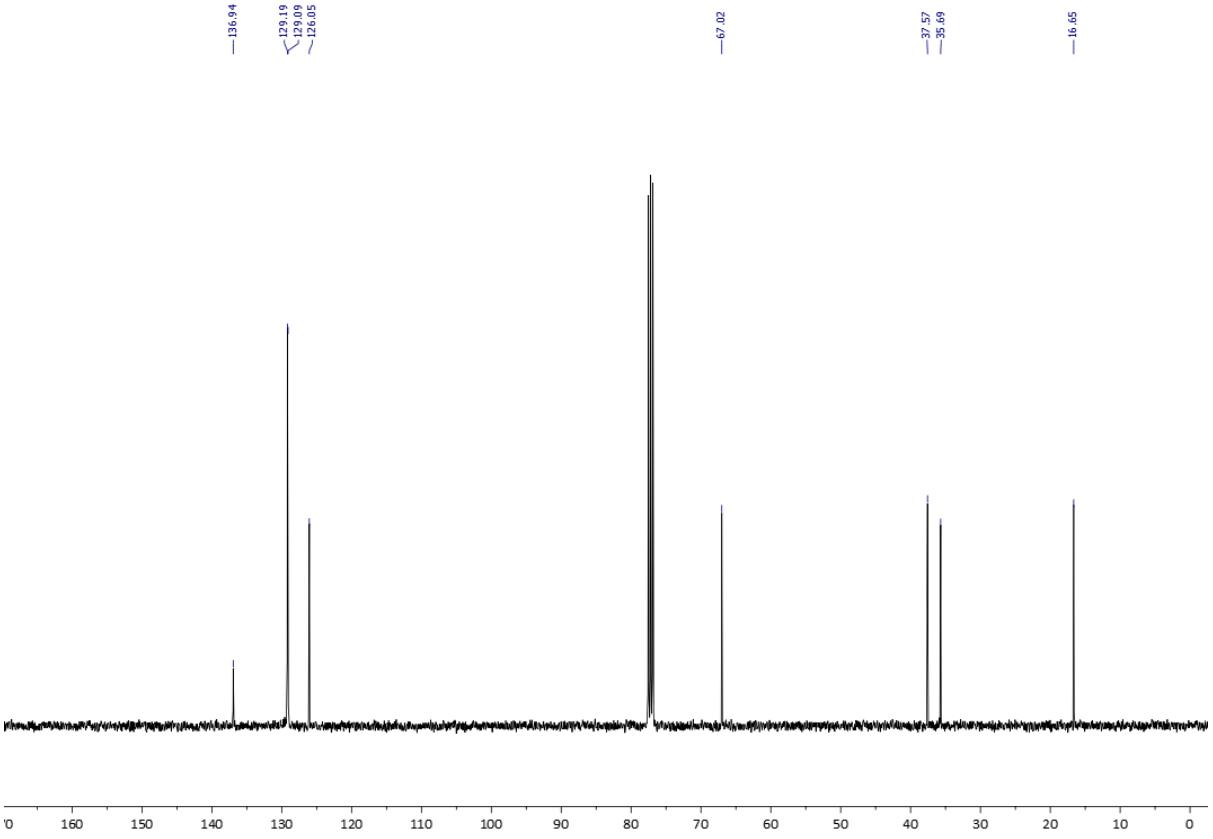
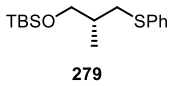
3.00
1.00
1.00
1.00
3.00
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
175.53
135.83
130.21
129.14
126.63
52.01
39.82
37.53
16.90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


HO
SPh

278


2.01
2.24
1.00
2.04
1.00
1.00
1.00
1.00
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

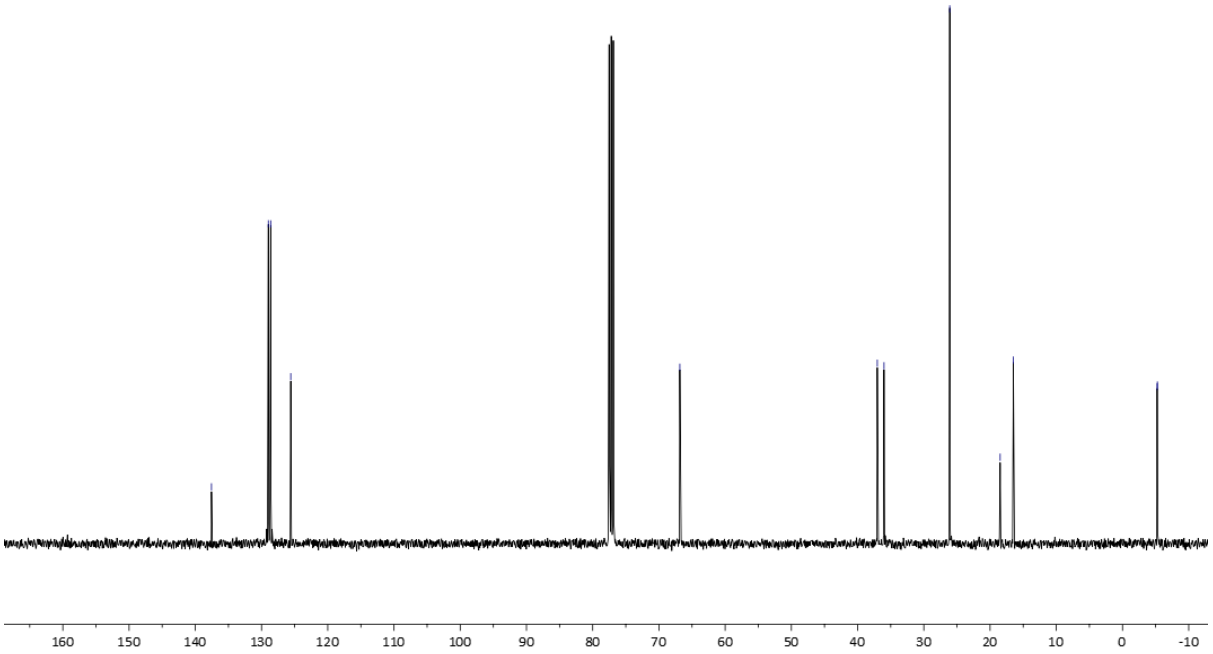

136.94
129.19
129.09
126.05
67.02
37.57
35.69
16.65
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
SPh

279

1.98
2.30
1.05
1.00
1.00
0.99
0.99
0.98
2.99
9.12
6.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

137.56
128.97
128.61
125.59
66.84
37.03
36.01
26.09
18.48
16.49
-5.23
-5.26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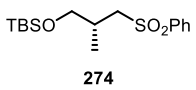
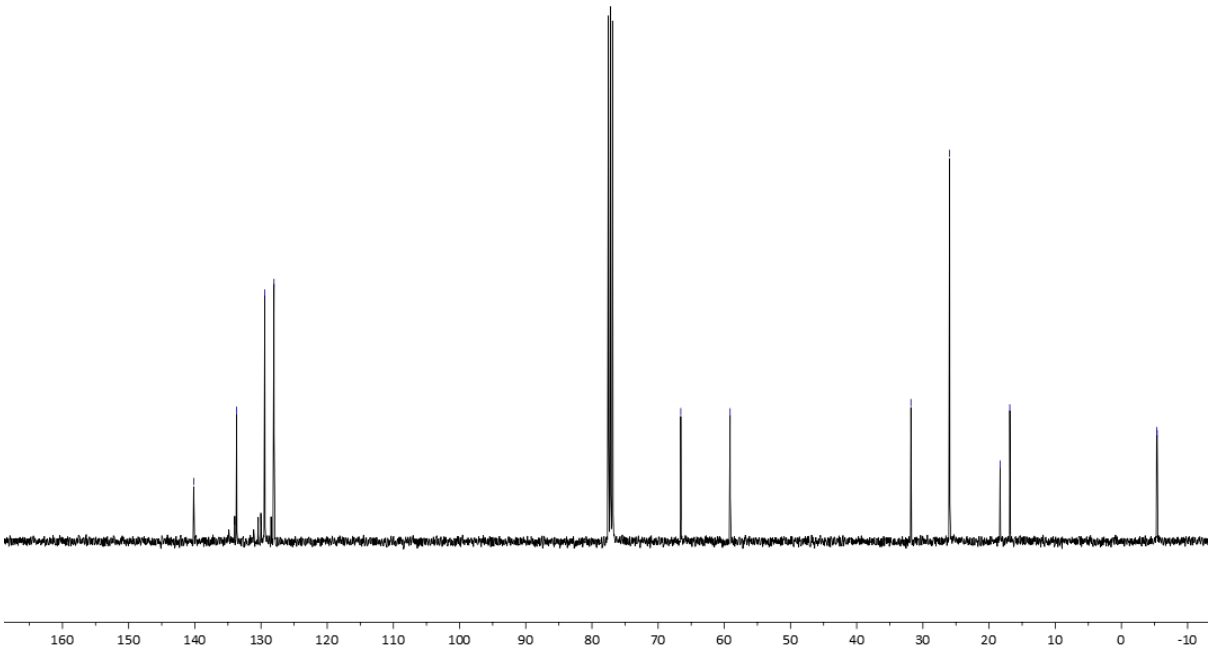
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


TBSO
SO2Ph

274

1.97
0.99
1.98
1.00
1.00
1.01
0.98
0.97
3.01
9.16
2.85
2.92
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
140.17
133.68
129.43
128.04
66.58
59.12
31.80
25.96
18.33
16.86
5.32
5.40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120
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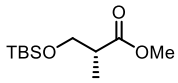
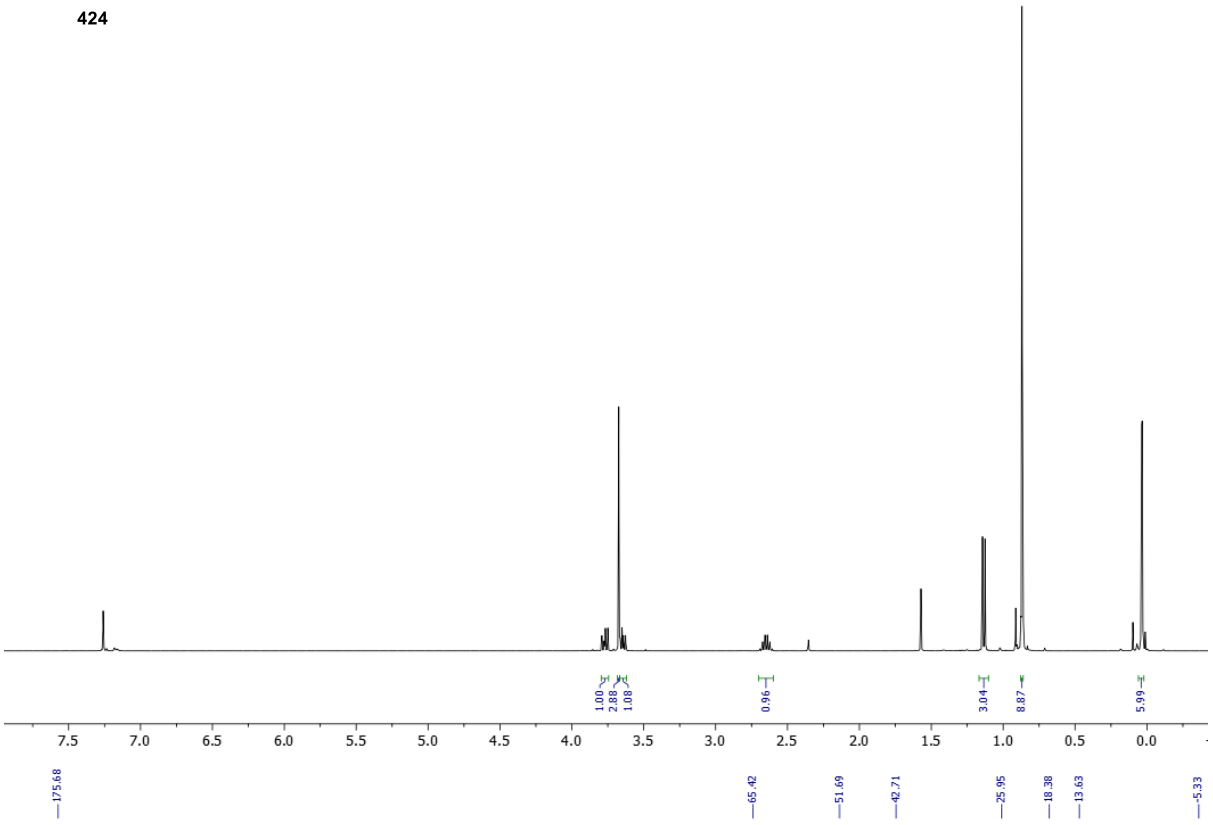
100
90
80
70
60
50
40
30
20
10
0
-10


TBSO
O
OMe

424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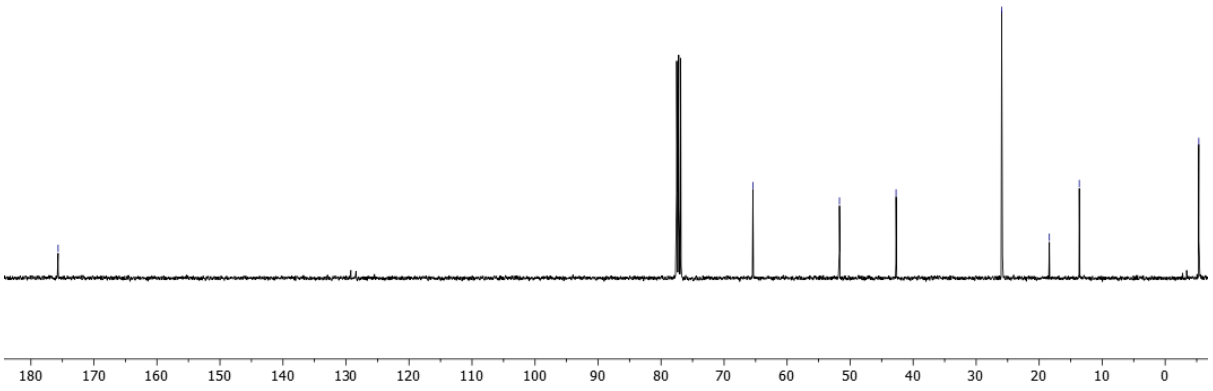
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

175.68
65.42
51.69
42.71
25.95
18.38
13.63
-5.33


180
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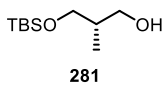
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
OH

281

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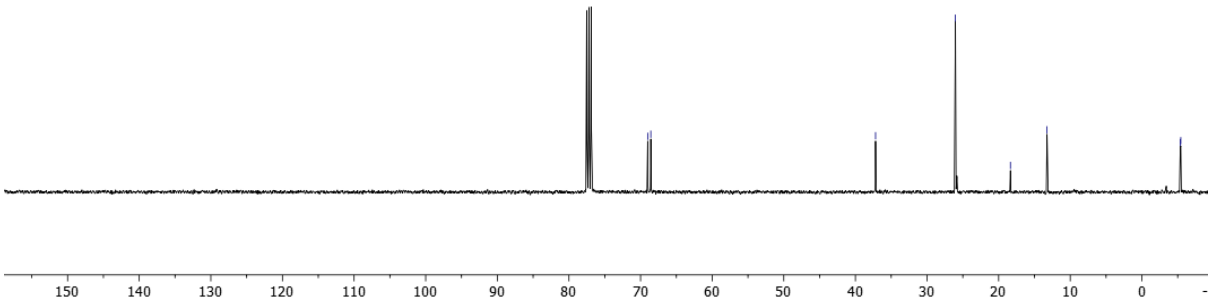
6.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
69.00
68.57
37.18
26.03
18.35
13.25
-5.37
-5.43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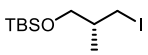
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
I

282

1.00
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6.10
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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
66.87
37.55
26.08
18.45
17.43
14.05
-5.19
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130
120
110
100
90
80
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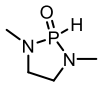
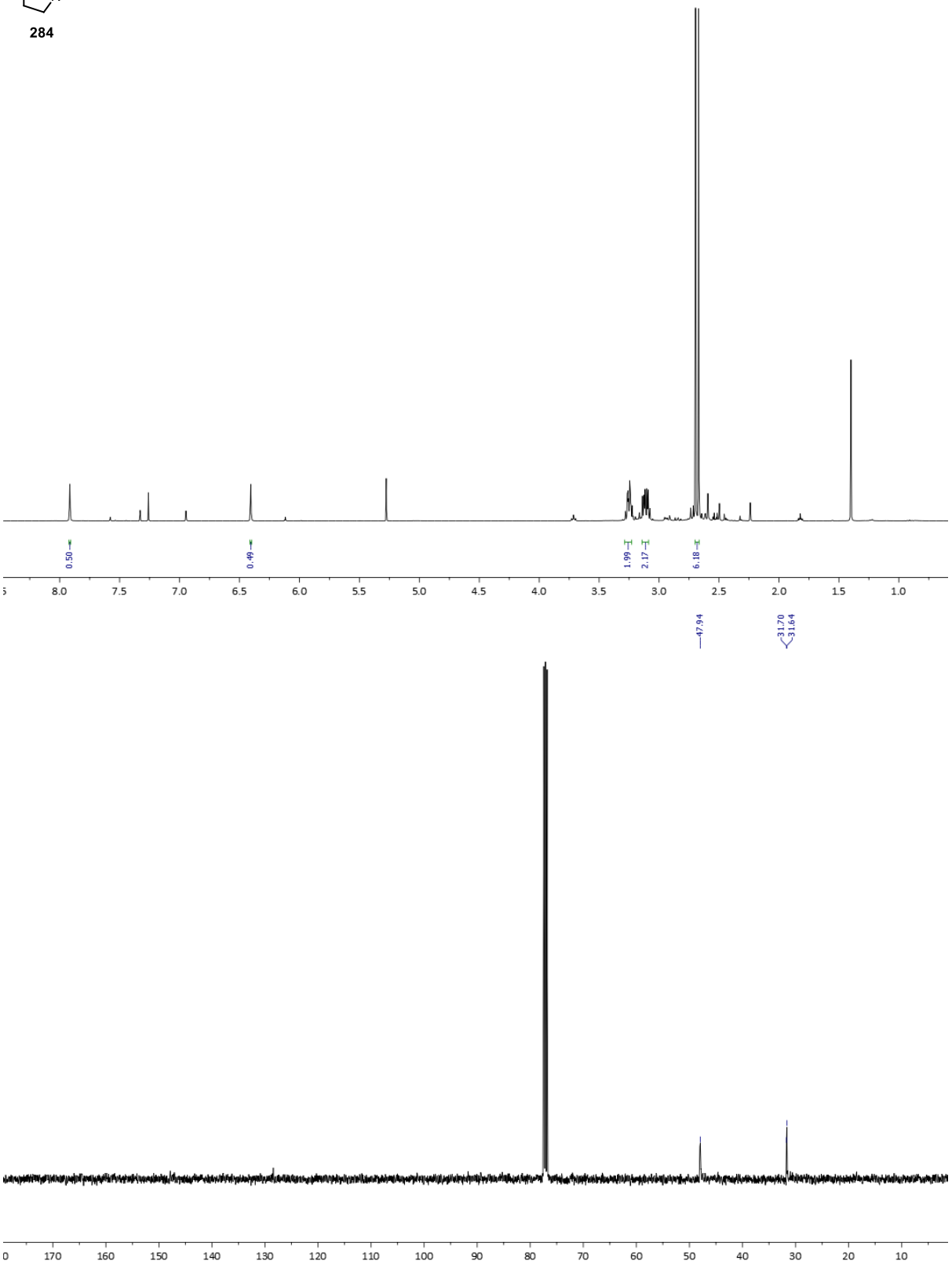
60
50
40
30
20
10
0
-10



284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7.0
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
47.94
31.70
31.64
170
160
150
140
130
120
110
100
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80
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50
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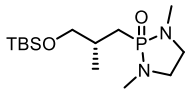
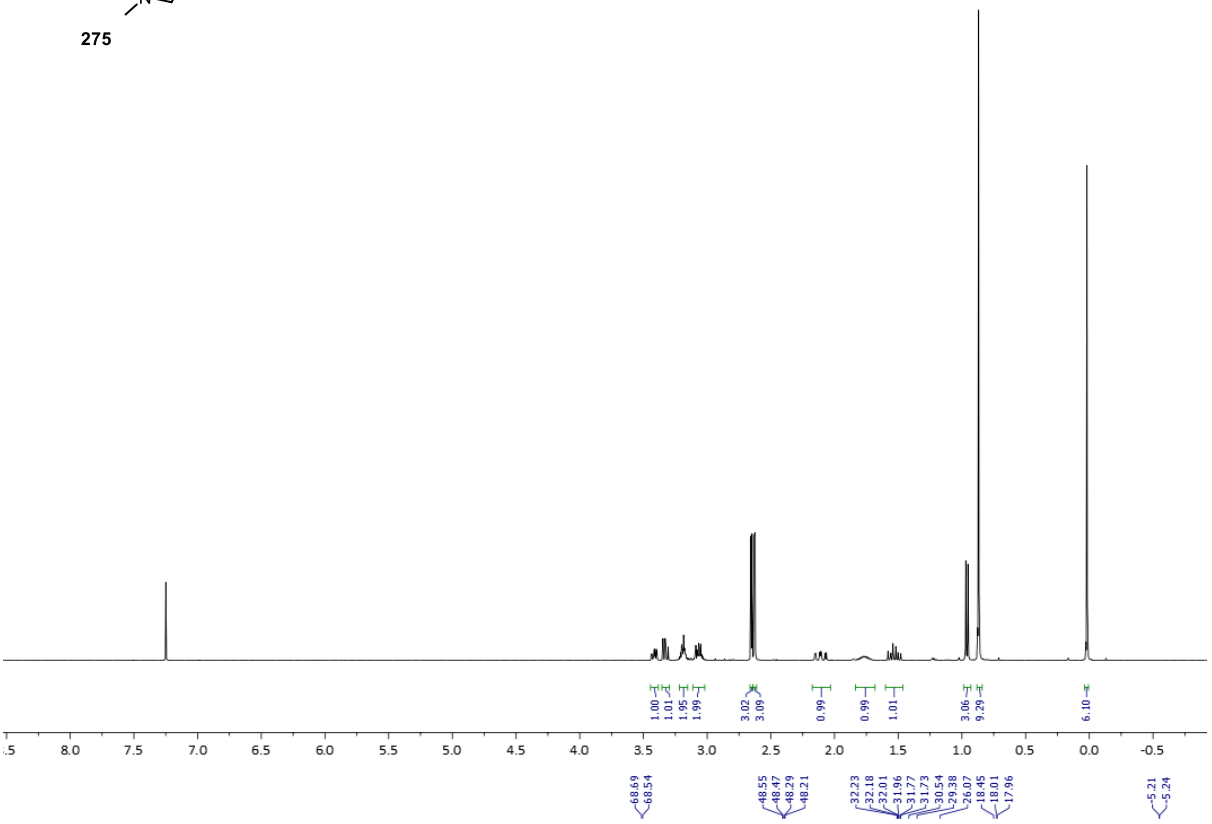
30
20
10


TBSO
O
P
N
N

275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3.02
3.09
0.99
0.99
1.01
3.06
9.29
6.10
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

68.69
68.54
48.55
48.47
48.29
48.21
32.23
32.18
32.01
31.96
31.77
31.73
30.54
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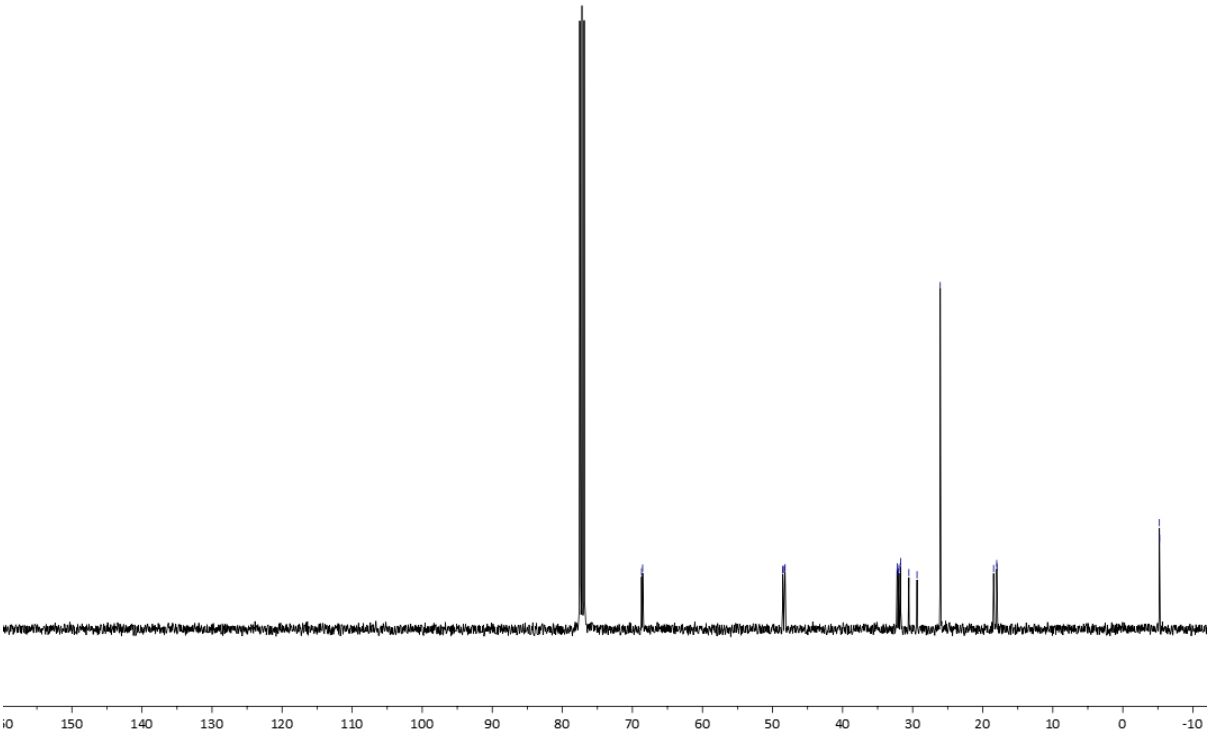
18.45
18.01
17.96
-5.21
-5.24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140
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100
90
80
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60
50
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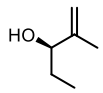
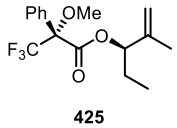
30
20
10
0
-10

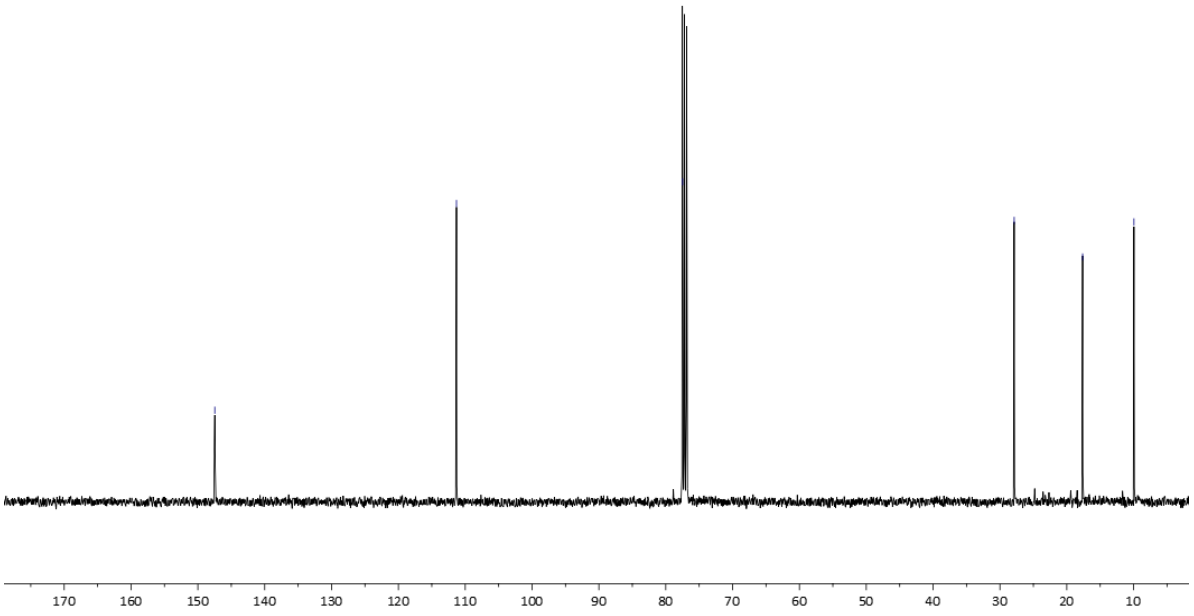


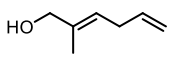
287



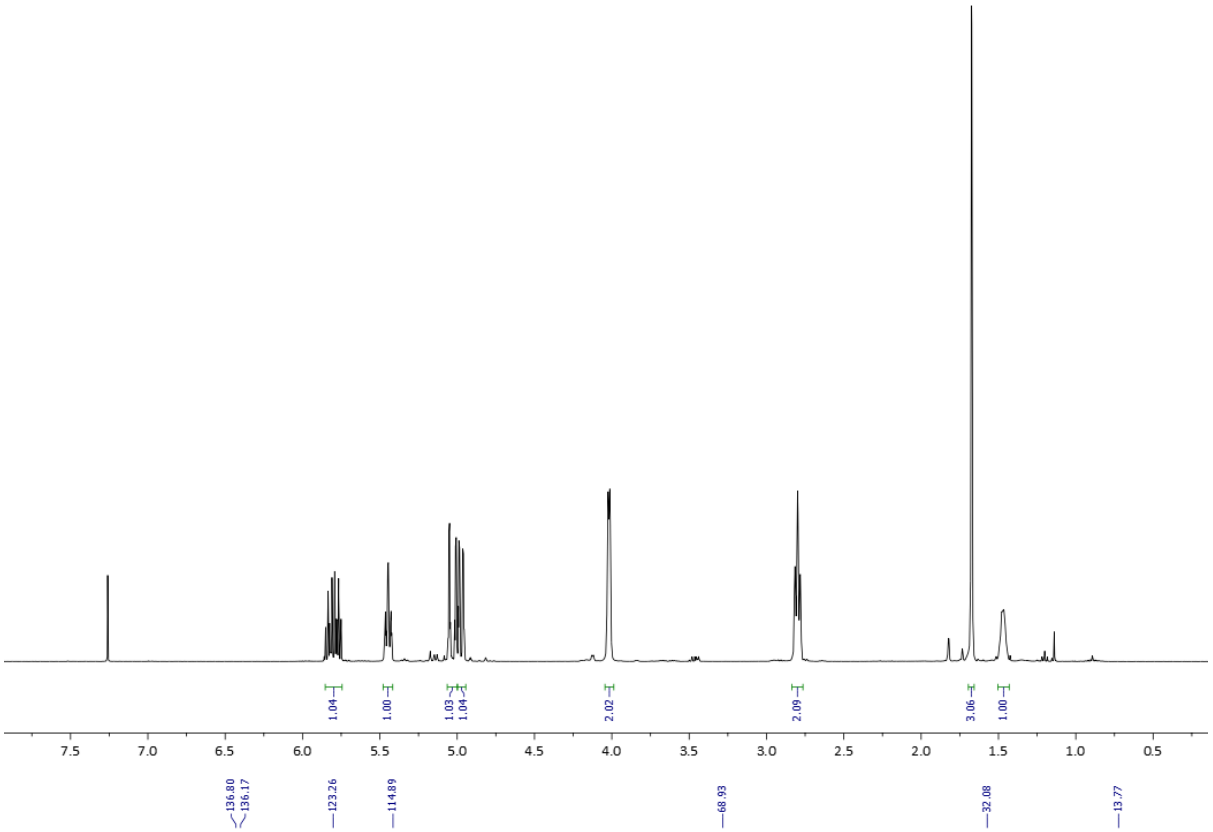
425

Figure 28. ^{1}H-NMR of (–)-Mosher's ester **425** showing an 88% de.




HO

289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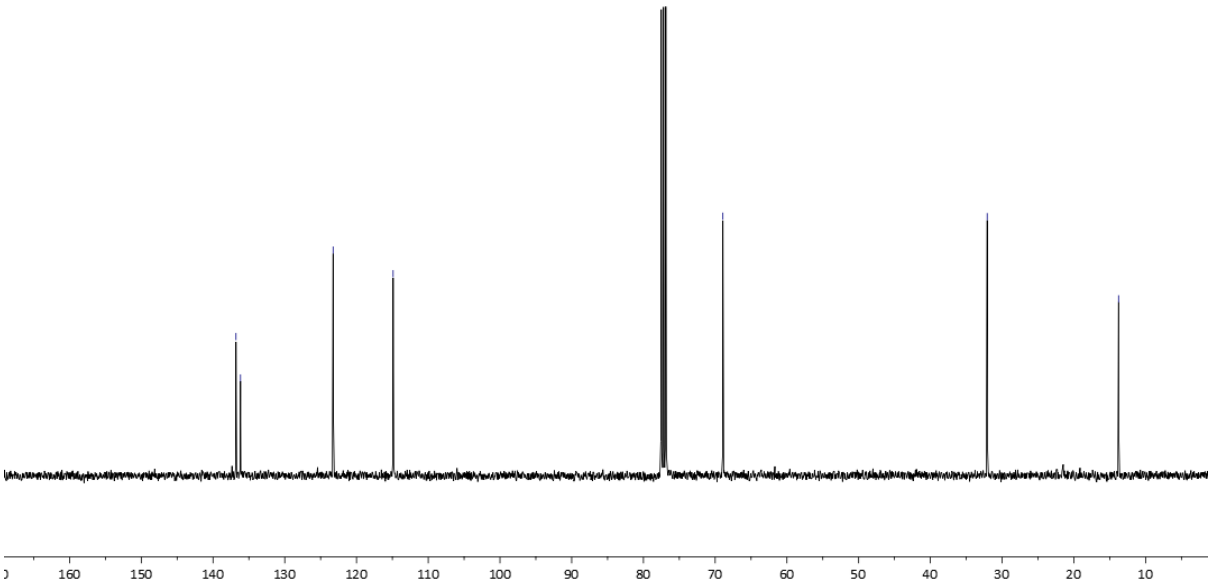
1.00
1.03
1.04
2.02
2.09
3.06
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

136.80
136.17
123.26
114.89
68.93
32.08
13.77


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

286

0.90
1.91
1.00
0.94
0.91
0.96
0.97
0.91
2.86
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
133.47
117.44
65.42
61.04
58.91
32.86
14.30
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160
150
140
130
120
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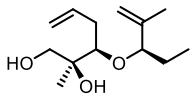
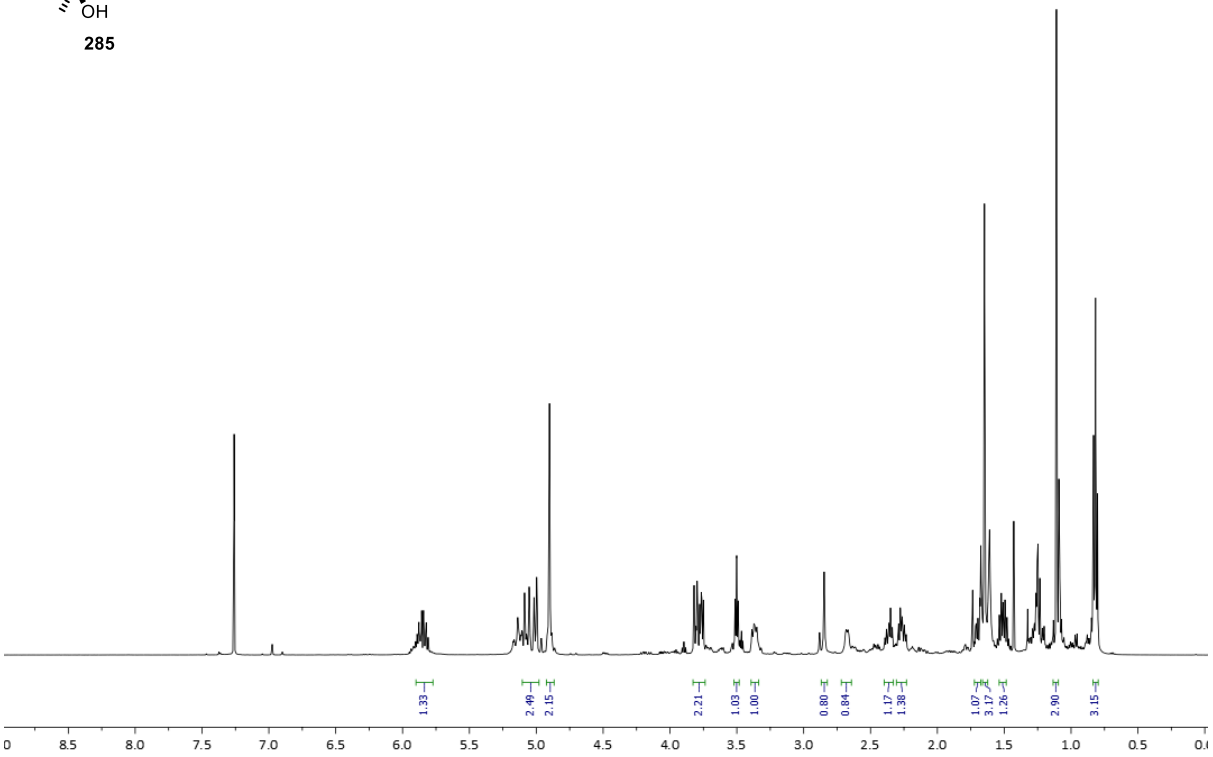
100
90
80
70
60
50
40
30
20
10


HO
OH
O

285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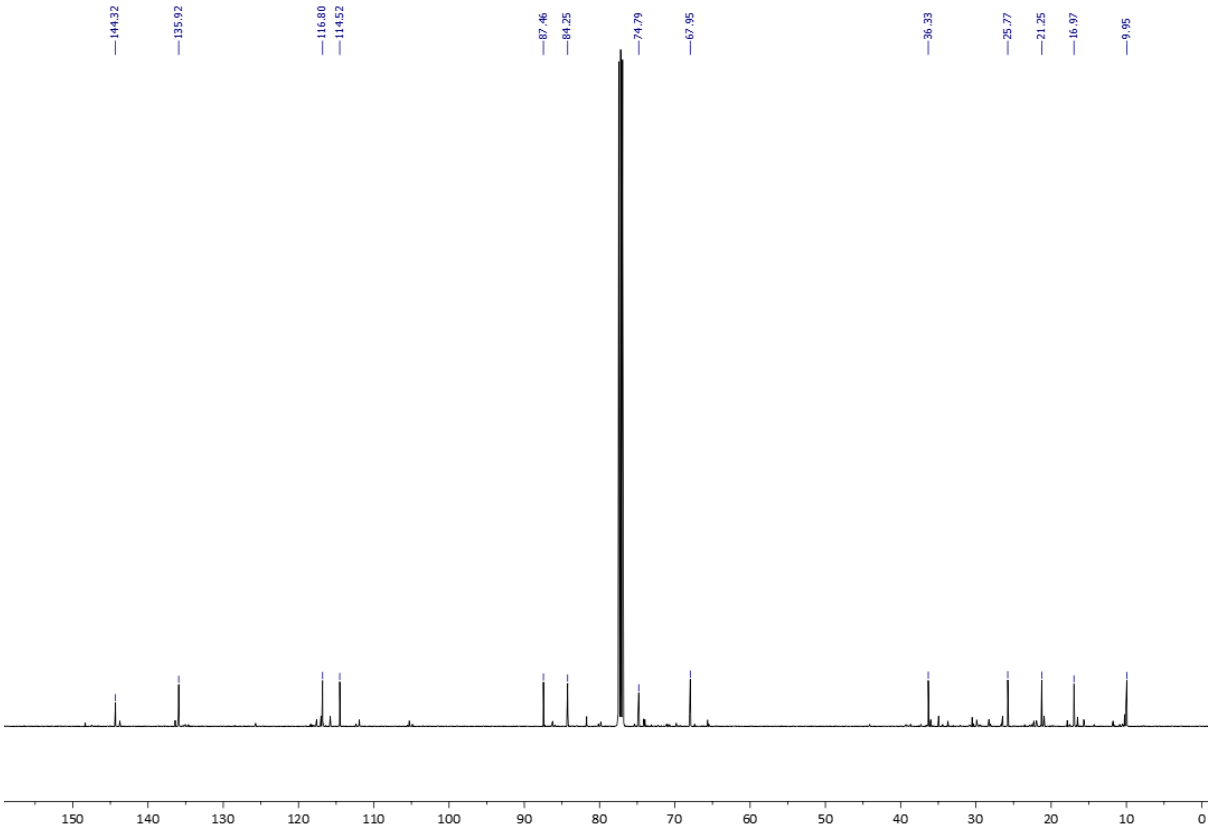
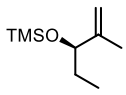
2.49
2.15
2.21
1.03
1.00
0.80
0.84
1.17
1.38
1.07
3.17
1.26
2.90
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


144.32
135.92
116.80
114.52
87.46
84.25
74.79
67.95
36.33
25.77
21.25
16.97
9.95
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMSO

45

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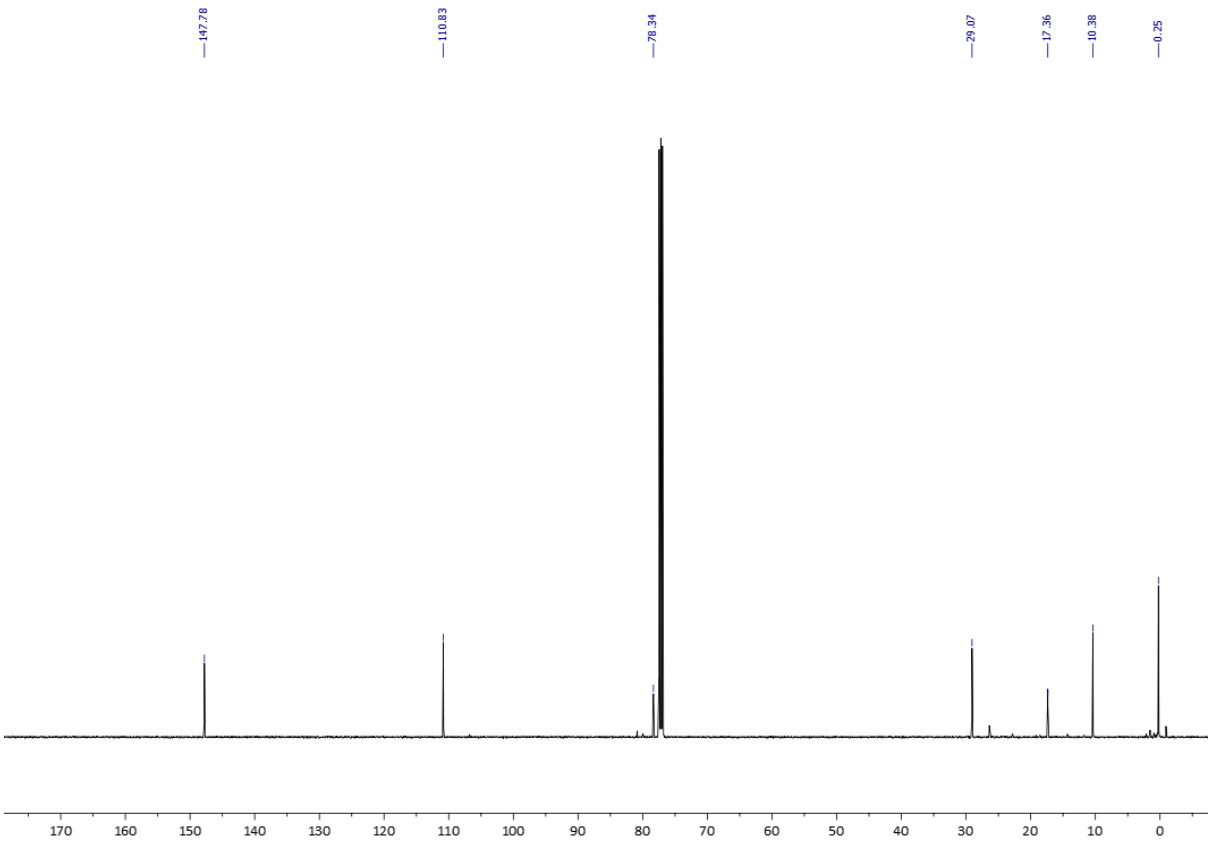
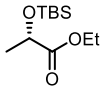
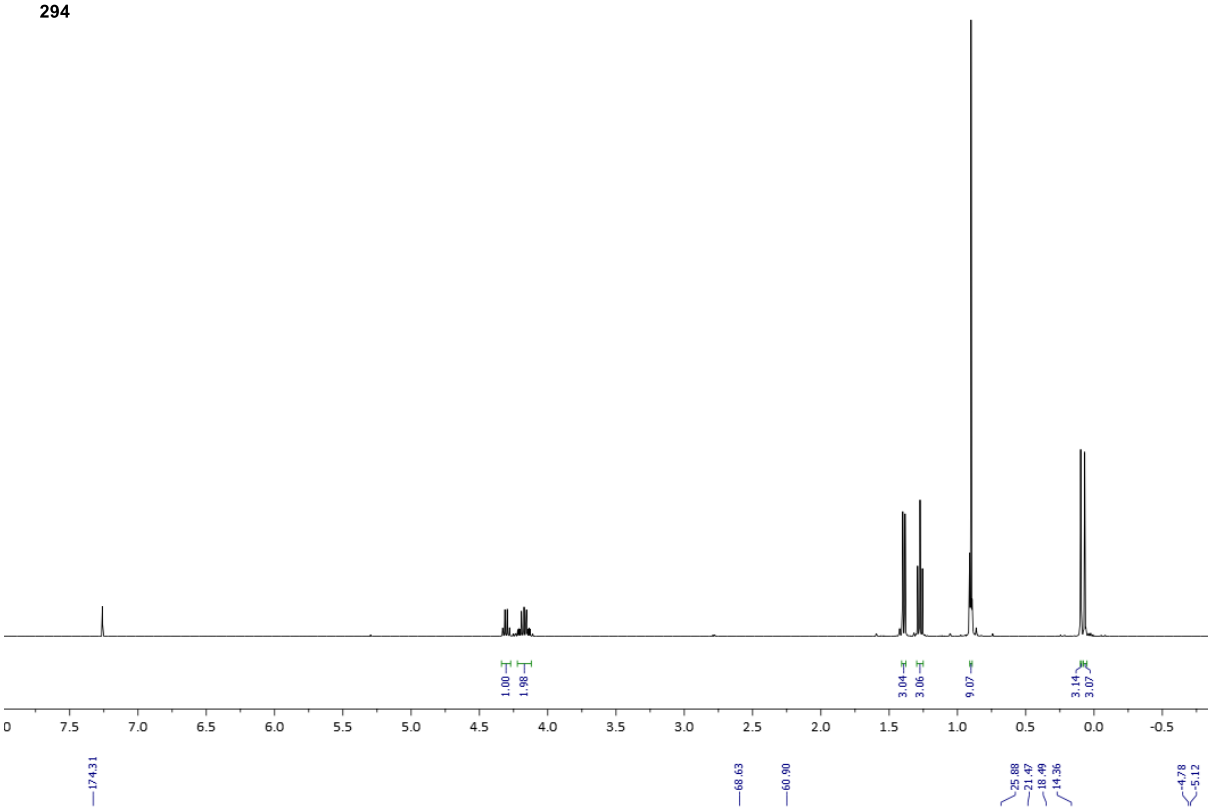
1.00
0.97
3.04
2.18
3.10
9.00
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

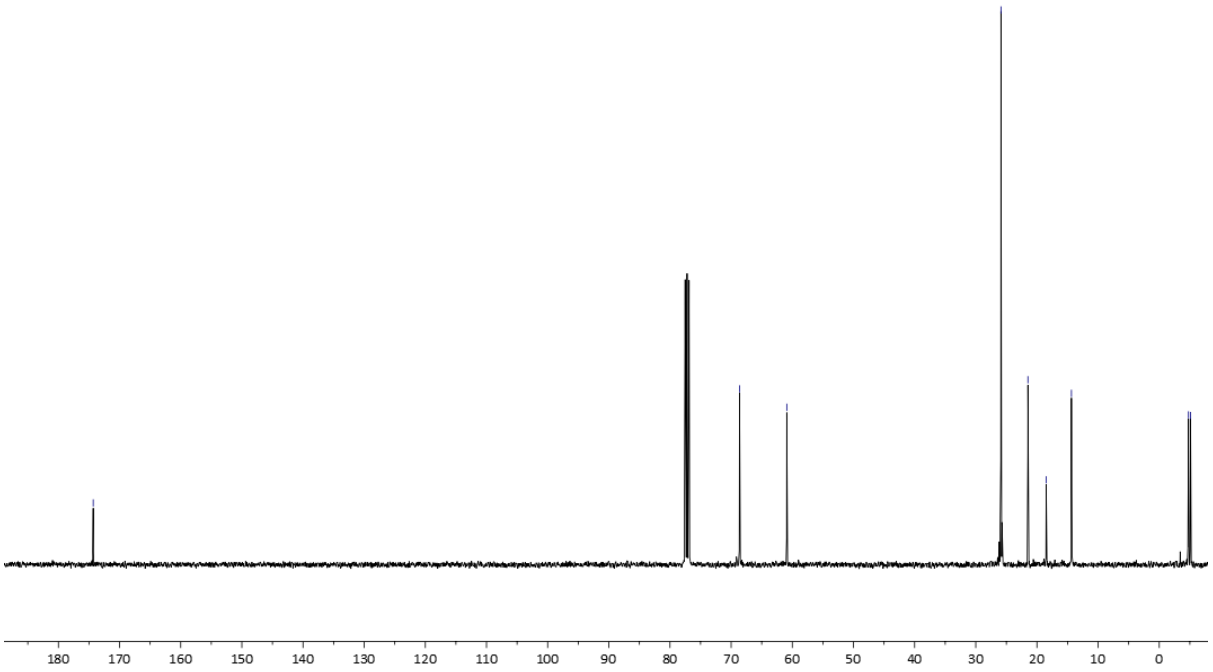

147.78
110.83
78.34
29.07
17.36
10.38
0.25
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OTBS
OEt
O

294


1.00
1.98
3.04
3.06
9.07
3.14
3.07
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

174.31
68.63
60.90
25.88
21.47
18.49
14.36
-4.78
-5.12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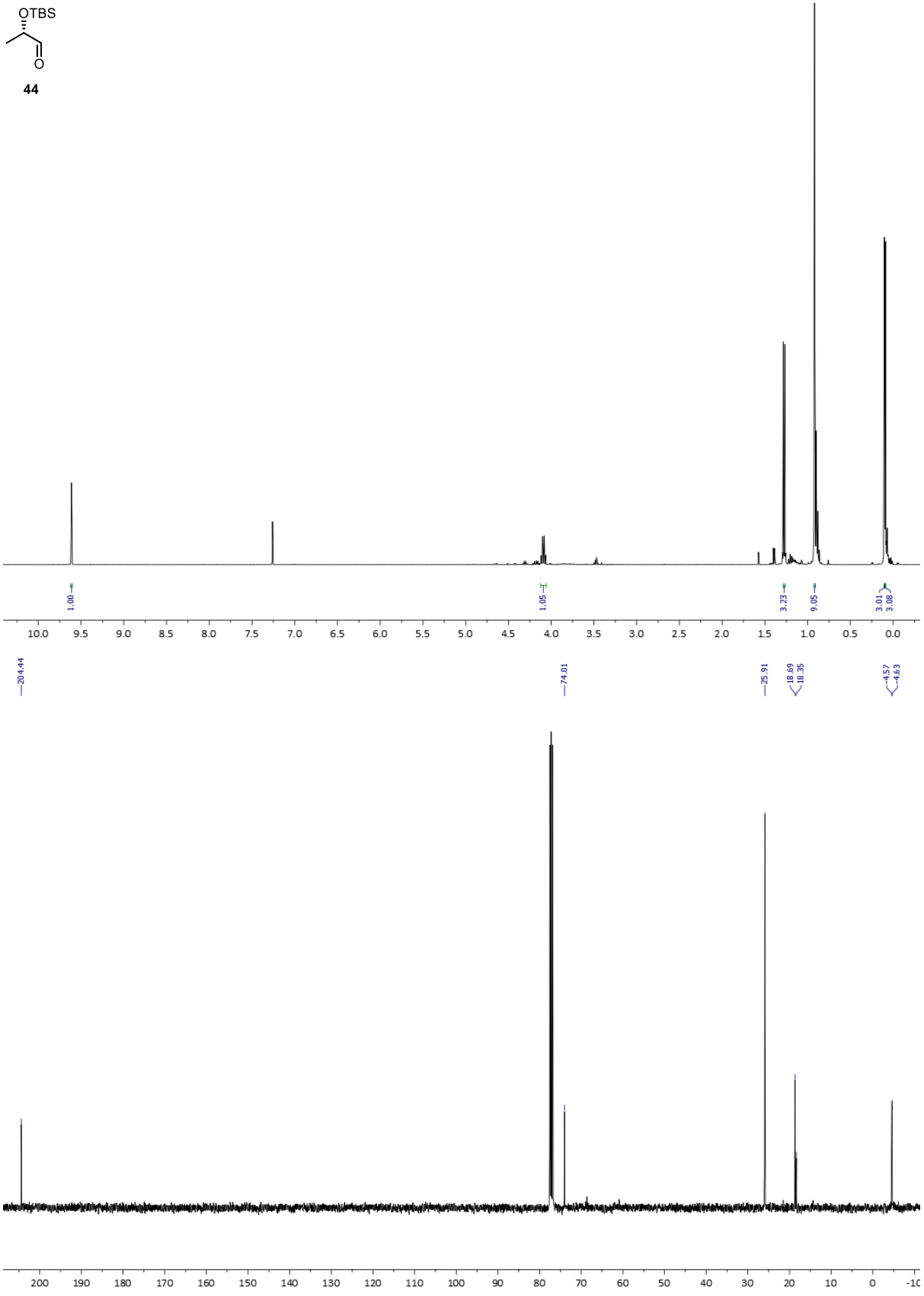
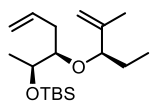
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OTBS
O
44
1.00
1.05
3.23
9.05
3.01
3.08
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
204.44
74.01
25.91
18.69
18.35
-4.57
-4.63
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


OTBS

46

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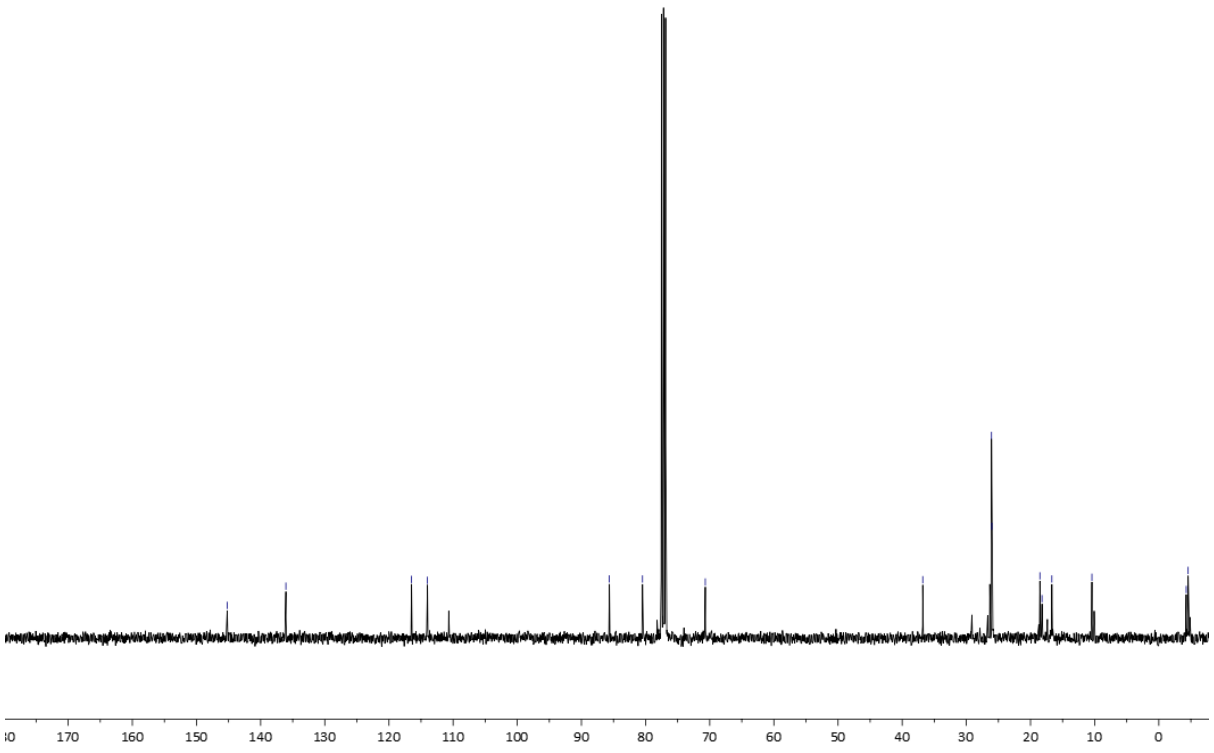
2.15
1.03
1.00
0.97
1.05
0.96
1.12
1.11
4.28
1.21
3.10
9.10
3.97
6.13
5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

145.21
136.06
116.48
113.99
85.64
80.48
70.69
36.79
26.08
26.03
18.53
18.21
16.67
10.43
-4.27
-4.57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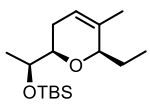
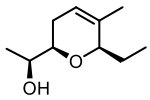
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OTBS

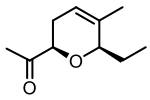
295

1.05
1.28
1.07
1.00
1.94
1.29
3.58
1.33
3.31
3.61
9.33
2.62
3.40
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
135.50
120.95
78.74
78.34
71.42
27.53
26.04
25.97
21.07
19.11
18.26
9.19
-4.19
-4.50
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

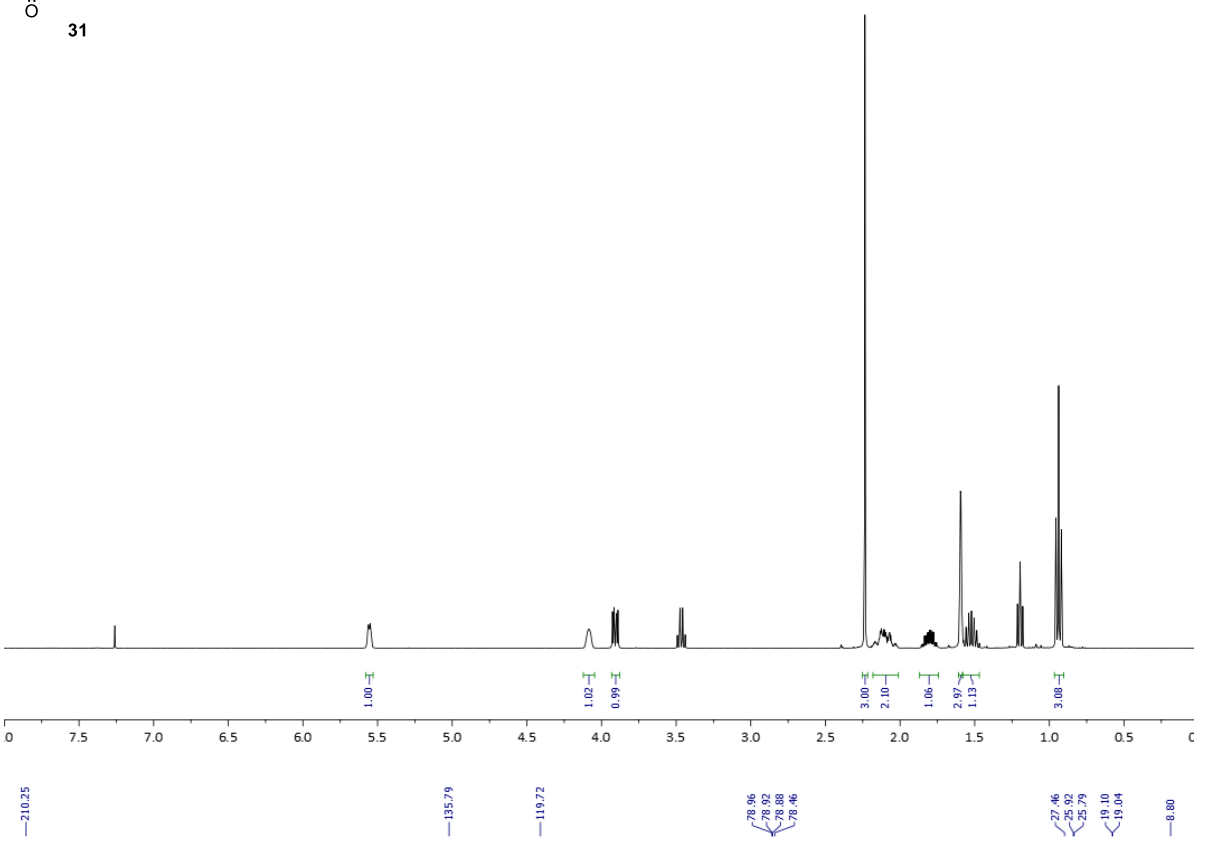

OH
O

296

1.00
1.03
1.03
1.02
0.96
1.14
1.09
1.05
3.13
1.22
3.07
3.28
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
135.22
120.61
78.28
76.21
69.33
25.79
24.44
19.07
17.61
8.60
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



31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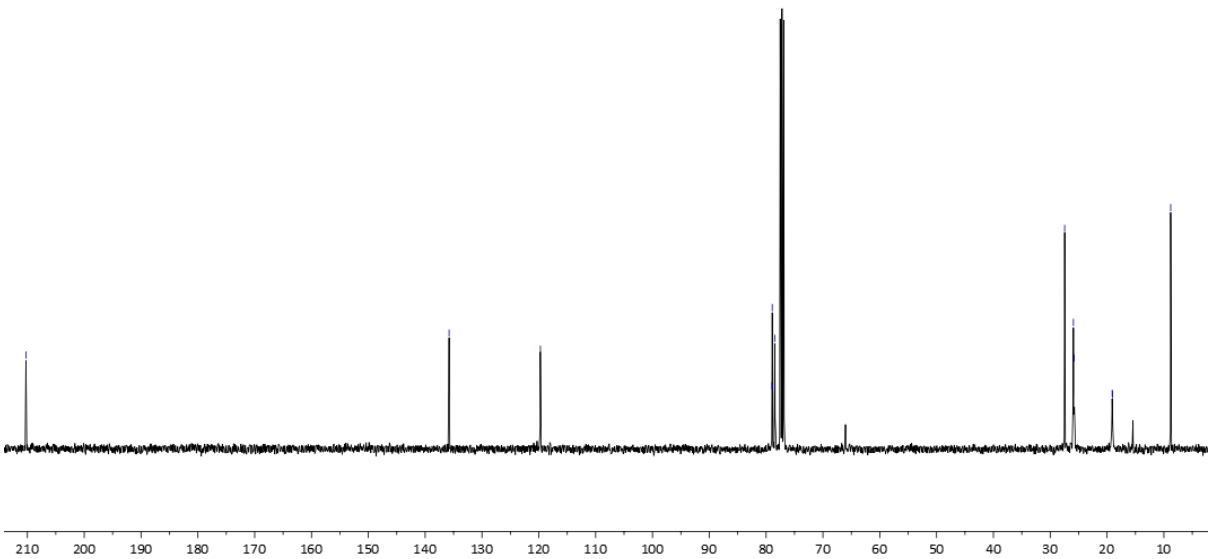
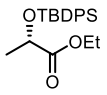
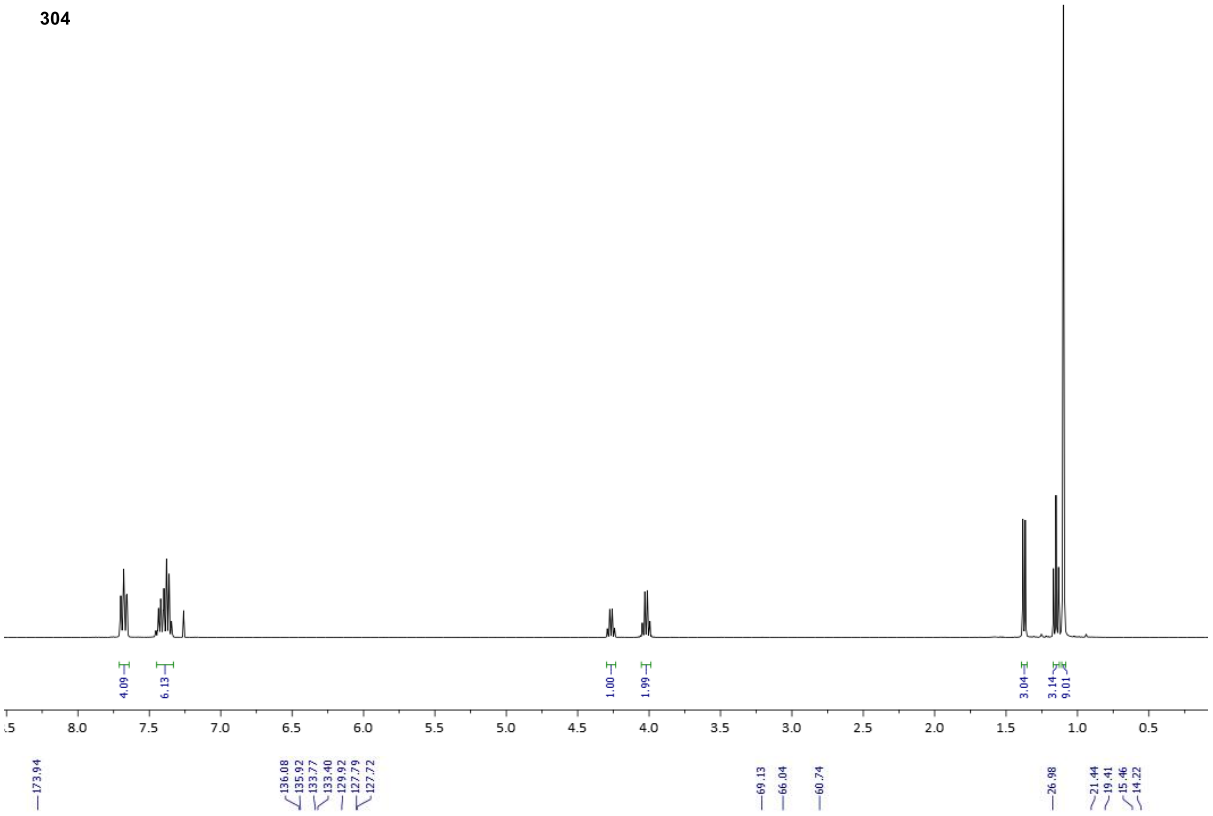
1.02
0.99
3.00
2.10
1.06
2.97
1.13
3.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

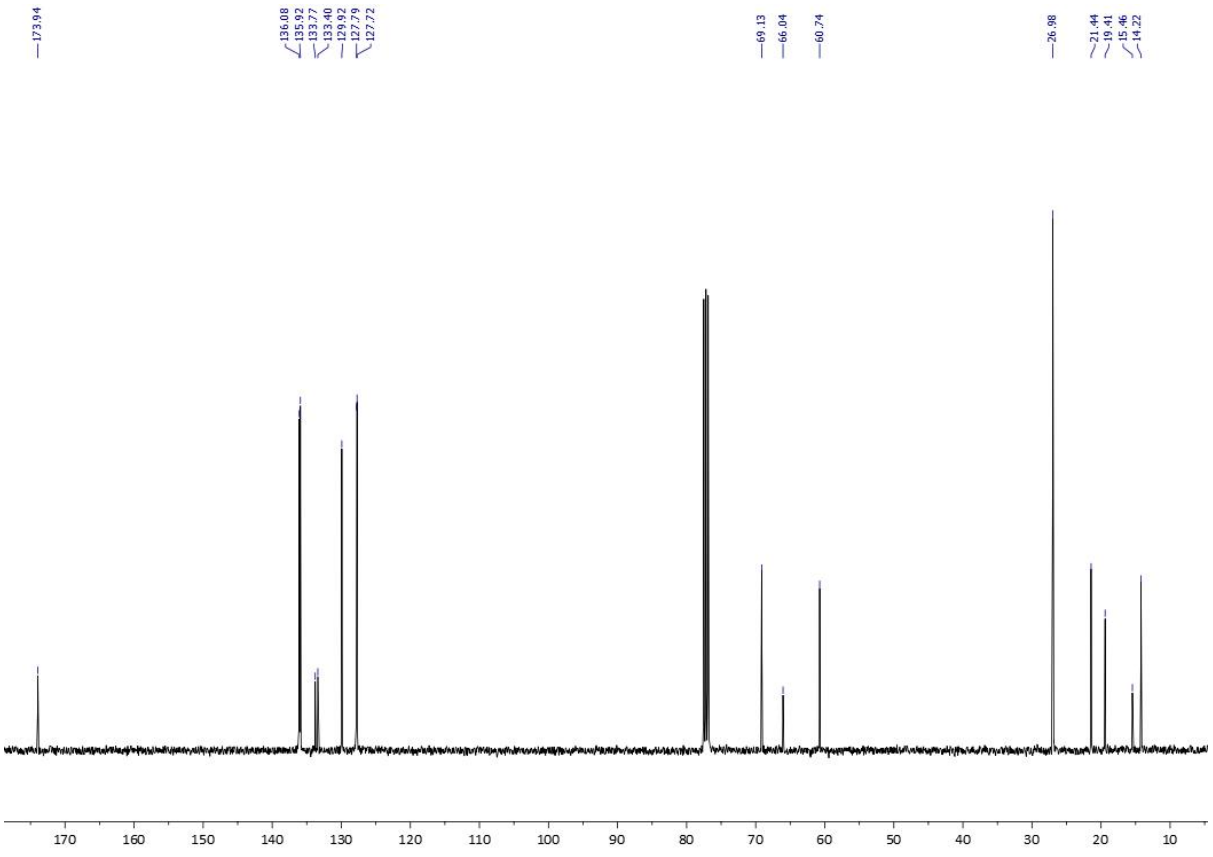
210.25
135.79
119.72
78.96
78.92
78.88
78.46
27.46
25.92
25.79
19.10
19.04
8.80


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


OTBDPS
OEt
O

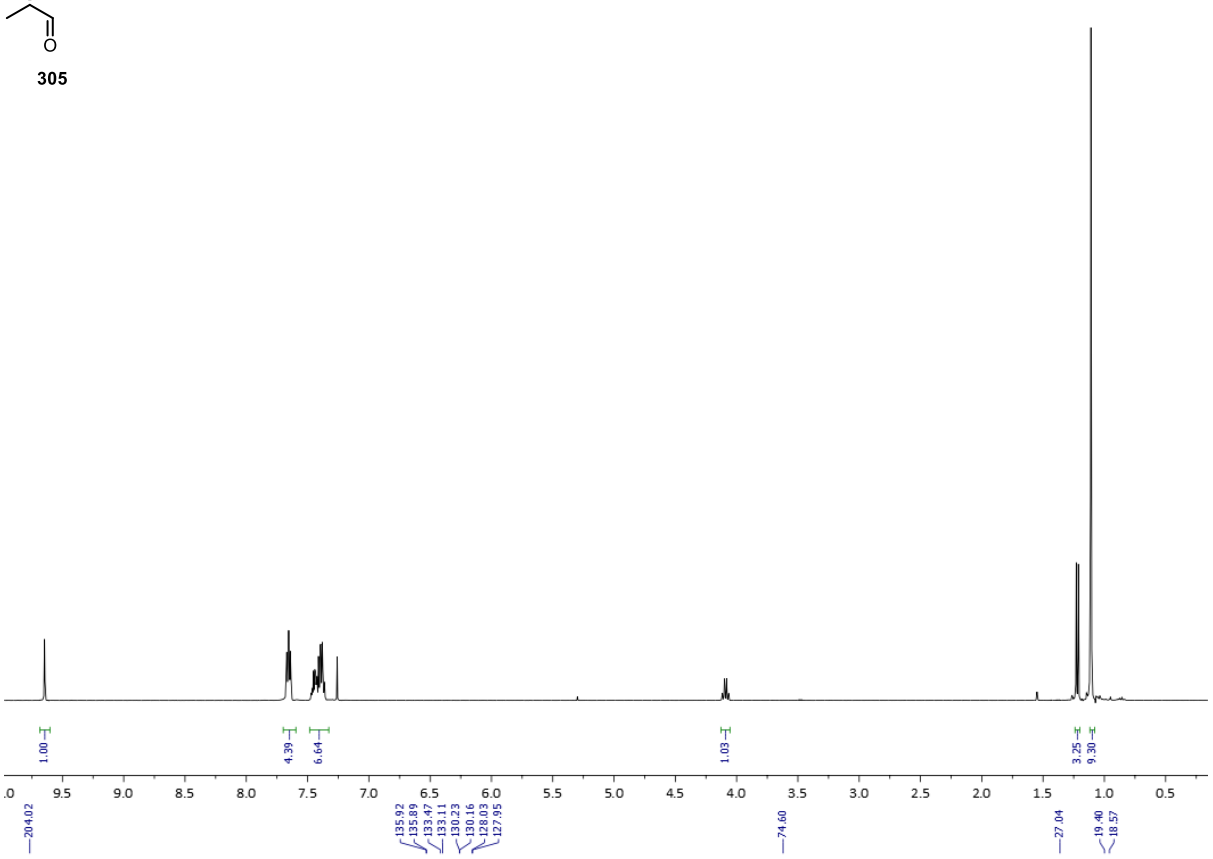
304


4.09
6.13
1.00
1.99
3.04
3.14
9.01
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


173.94
136.08
135.92
133.77
133.40
129.92
127.79
127.72
69.13
66.04
60.74
26.98
21.44
19.41
15.46
14.22
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


OTBDPS
O

305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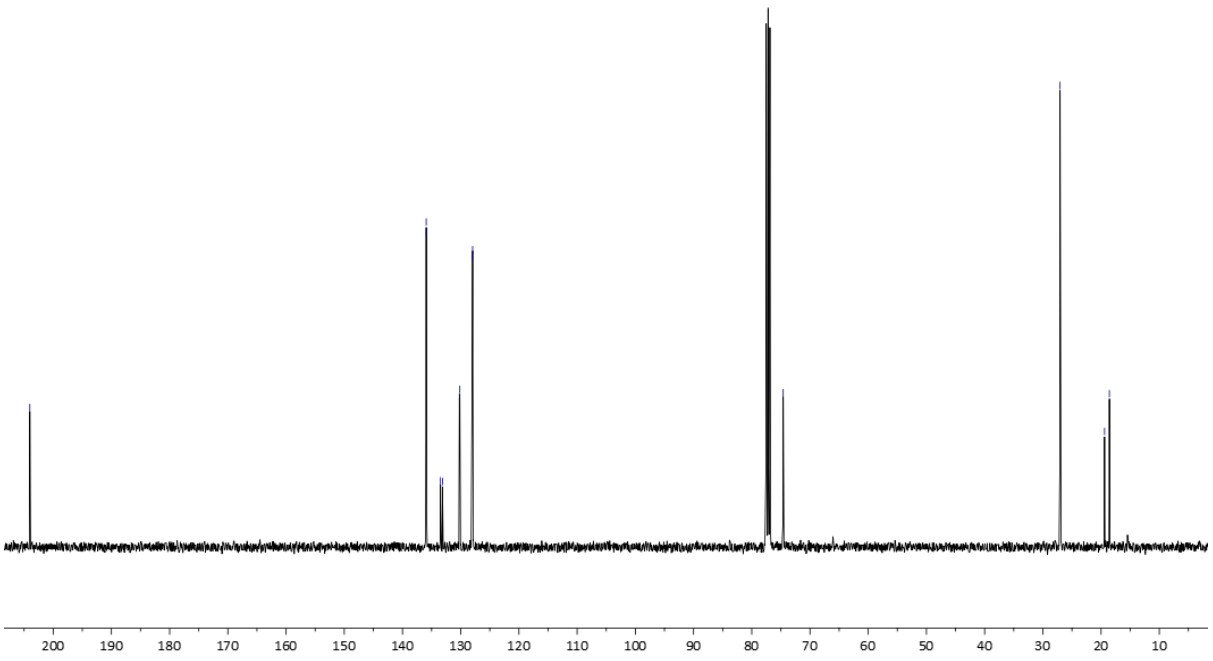
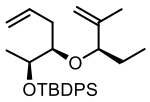
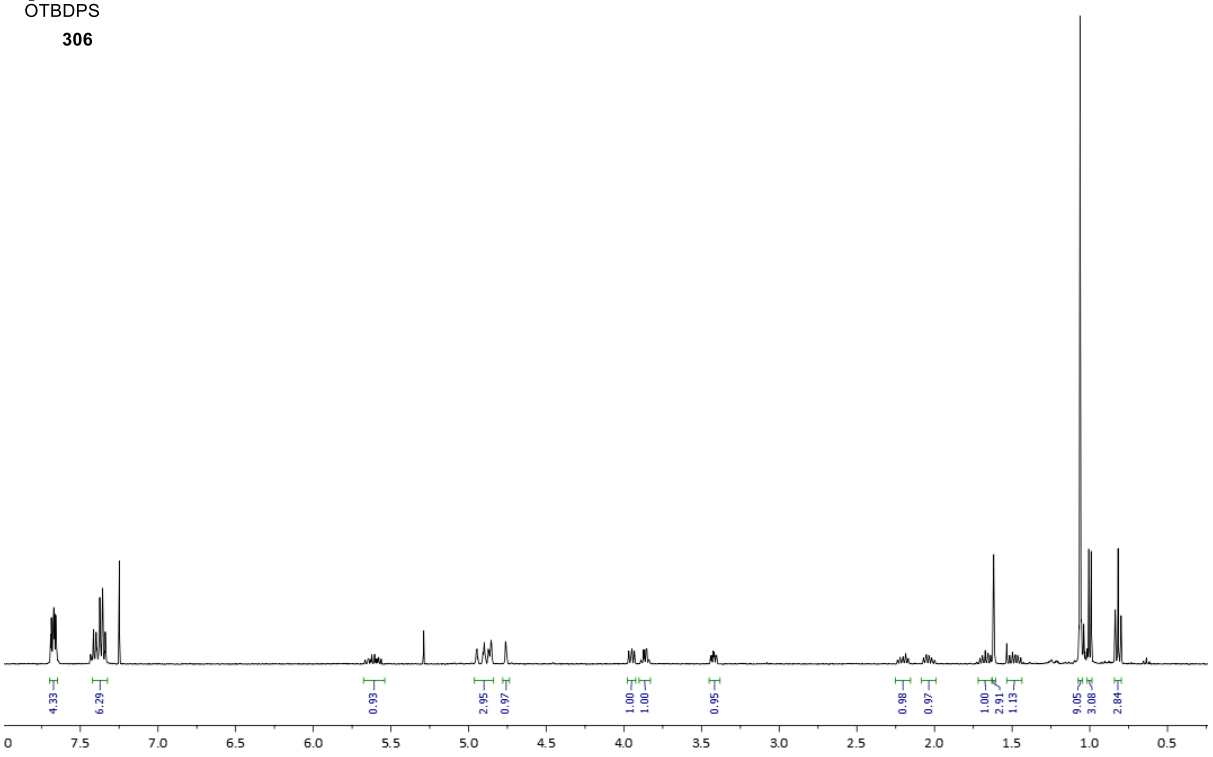
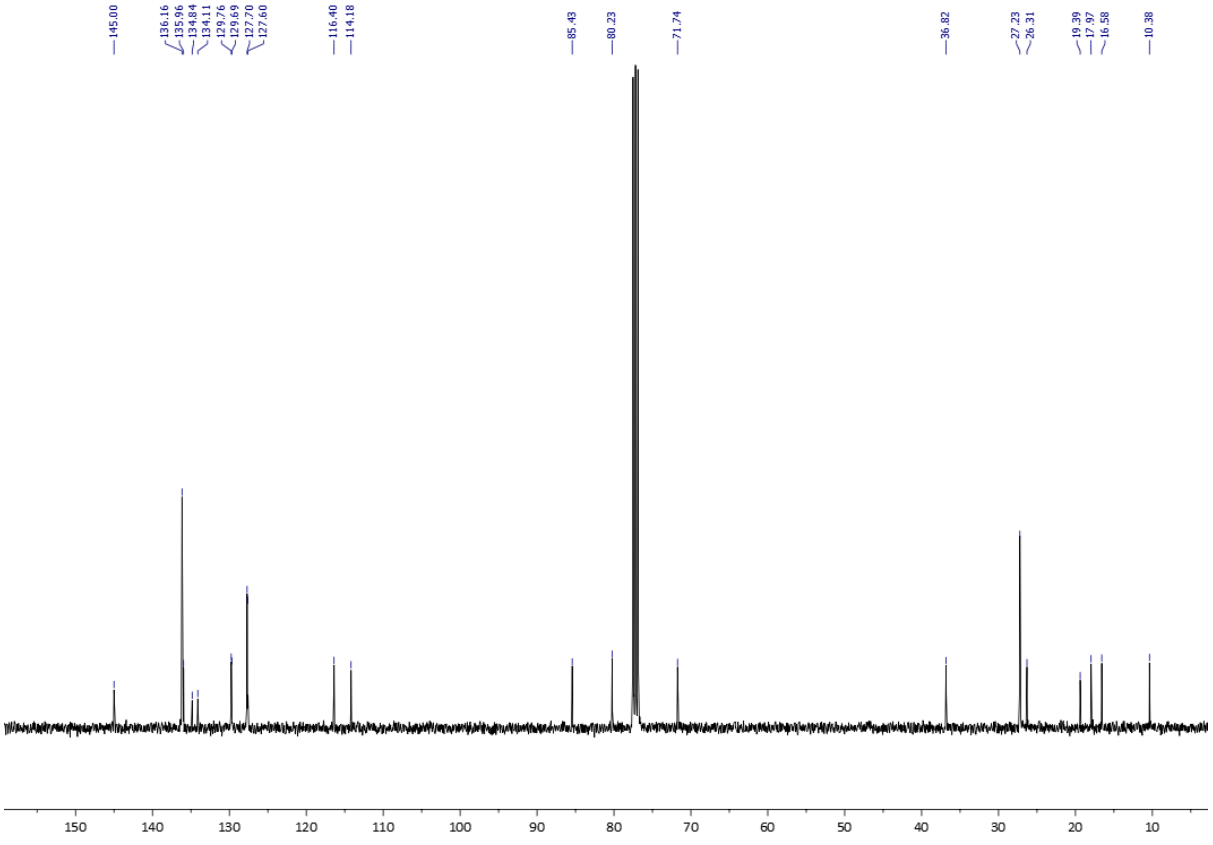
4.39
6.64
1.03
3.25
9.30
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
204.02
135.92
135.84
133.47
133.11
130.23
130.16
129.03
127.95
74.60
27.04
19.40
18.57


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


OTBDPS

306


4.33
6.29
0.93
2.95
0.97
1.00
1.00
0.95
0.98
0.97
1.00
2.91
1.13
9.05
3.08
2.84
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


145.00
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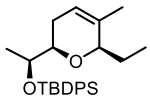
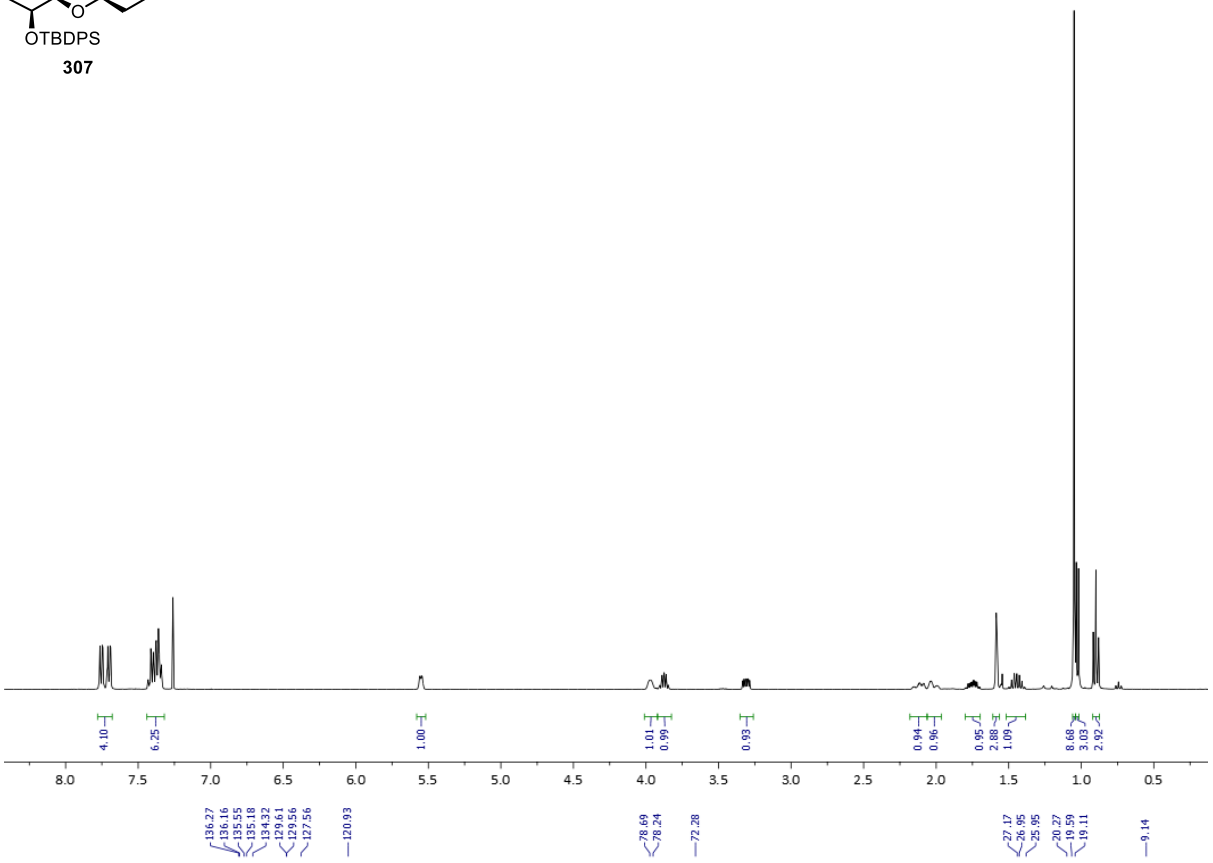
135.96
134.84
134.11
129.76
129.69
127.70
127.60
116.40
114.18
85.43
80.23
71.74
36.82
27.23
26.31
19.39
17.97
16.58
10.38
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


O
OTBDPS

307


4.10
6.25
1.00
1.01
0.99
0.93
0.94
0.96
0.95
2.88
1.09
8.68
3.03
2.92
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
136.27
136.16
135.55
135.18
134.32
129.61
129.56
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78.24
72.28
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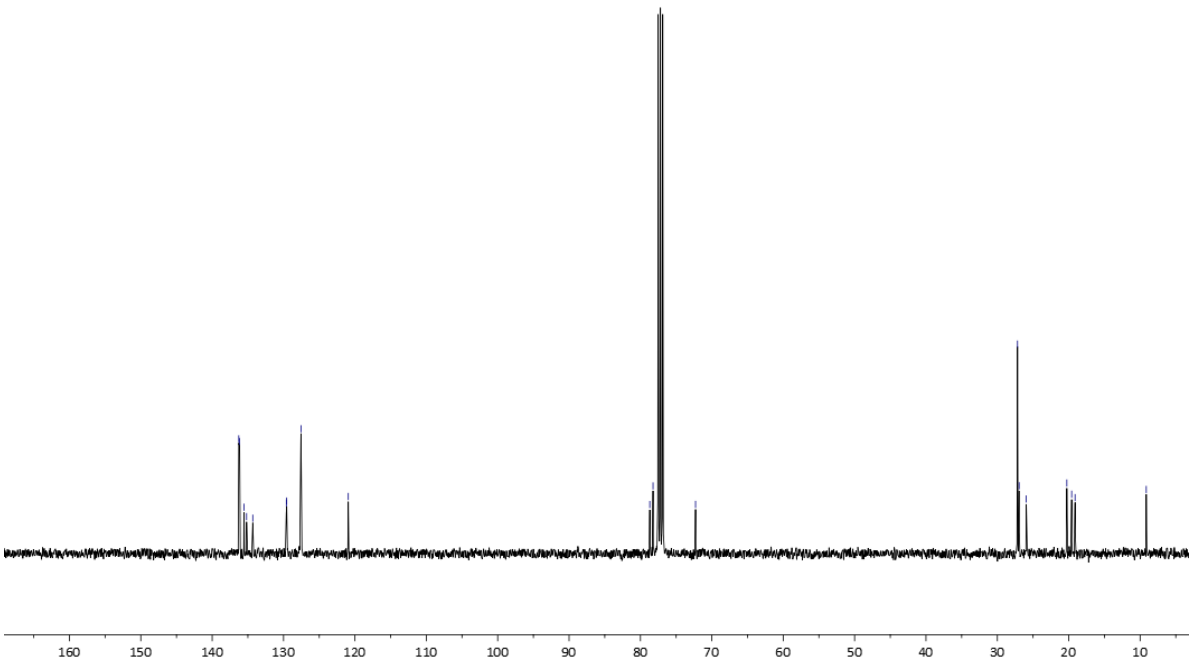
25.95
20.27
19.59
19.11
9.14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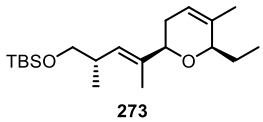
TBSO
O

273

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1.00
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1.00
1.01
1.10
2.91
3.34
1.06
3.07
9.18
6.24
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
136.52
135.27
128.24
121.15
78.15
78.04
68.03
35.15
30.31
26.12
25.79
19.17
18.53
17.40
12.78
8.41
-5.10
-5.17
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10
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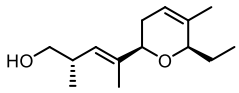
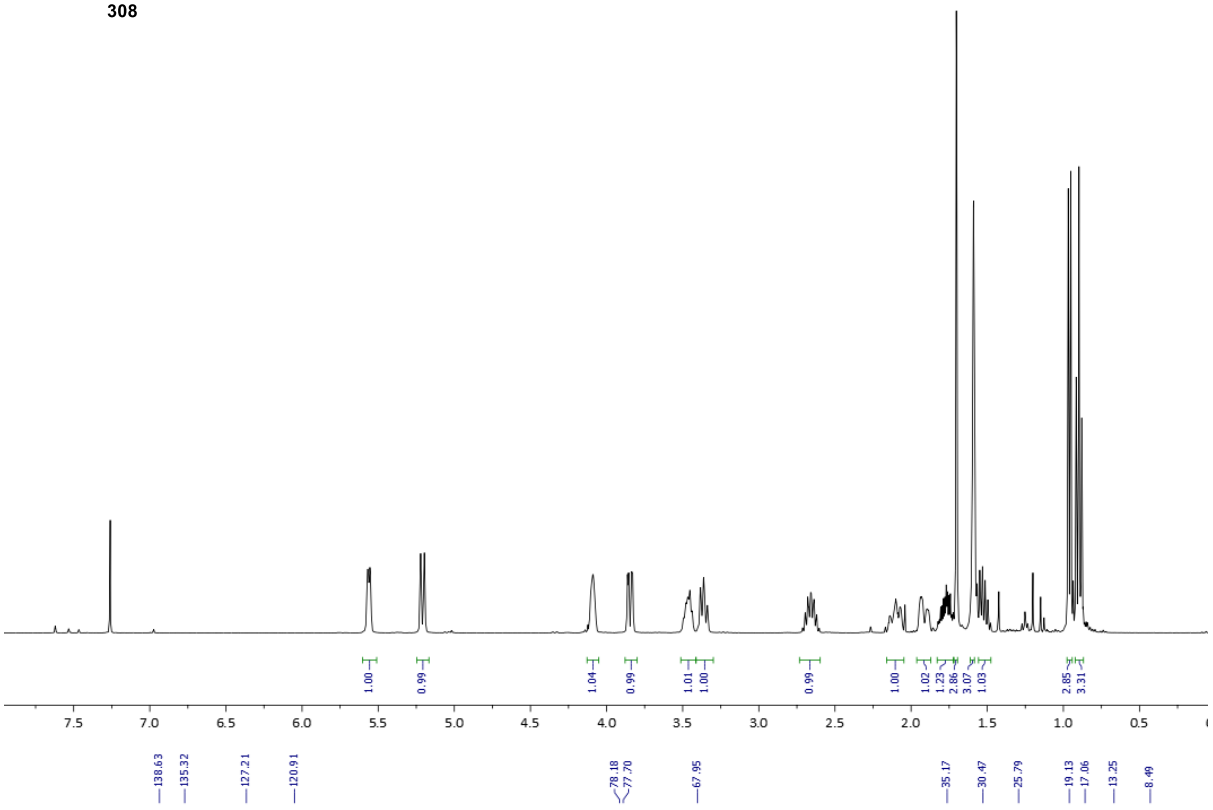

HO
O

308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1.00
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1.23
2.86
3.07
1.03
2.85
3.31
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

138.63
135.32
127.21
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77.70
67.95
35.17
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25.79
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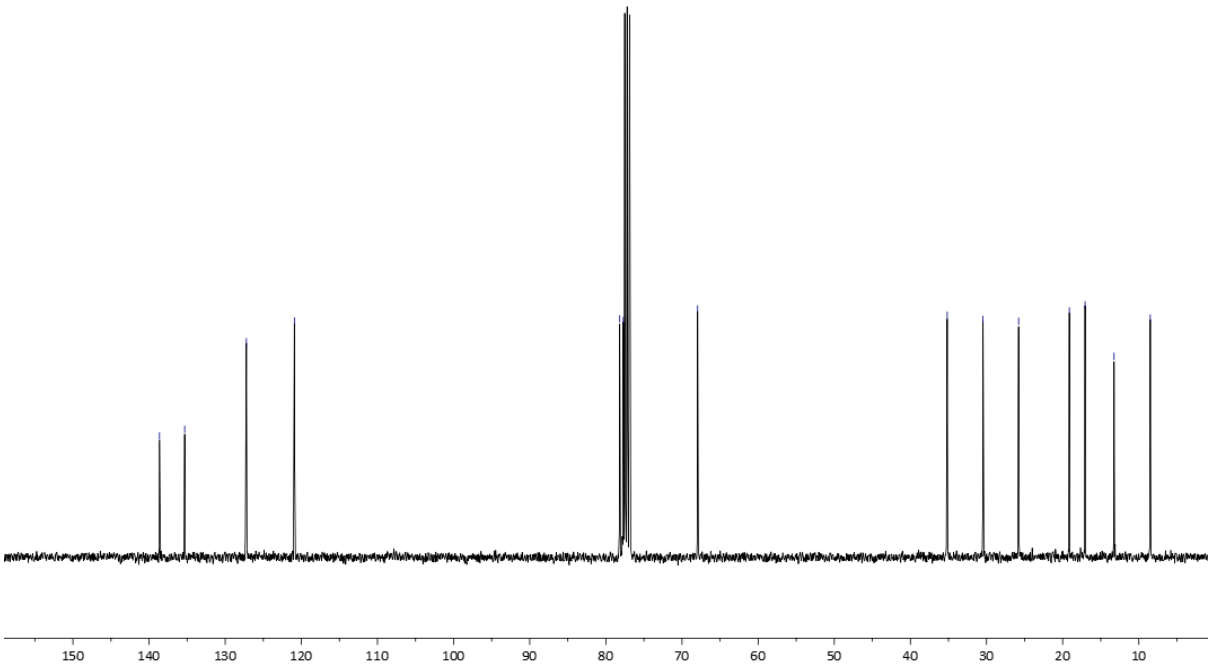
17.06
13.25
8.49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70
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40
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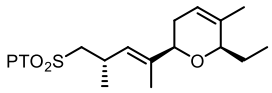
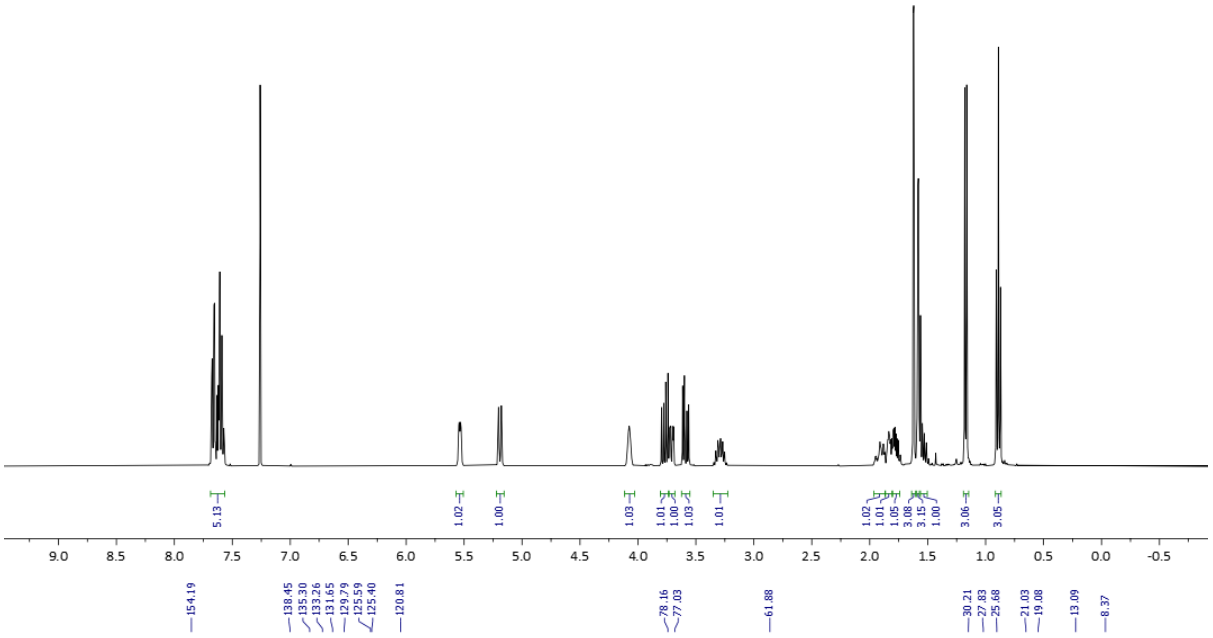
10


PTO2S
O

28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1.00
1.03
1.01
1.00
1.03
1.01
1.02
1.01
1.05
3.08
3.15
1.00
3.06
3.05
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

154.19
138.45
135.30
133.26
131.65
129.79
125.59
125.40
120.81
78.16
77.03
61.88
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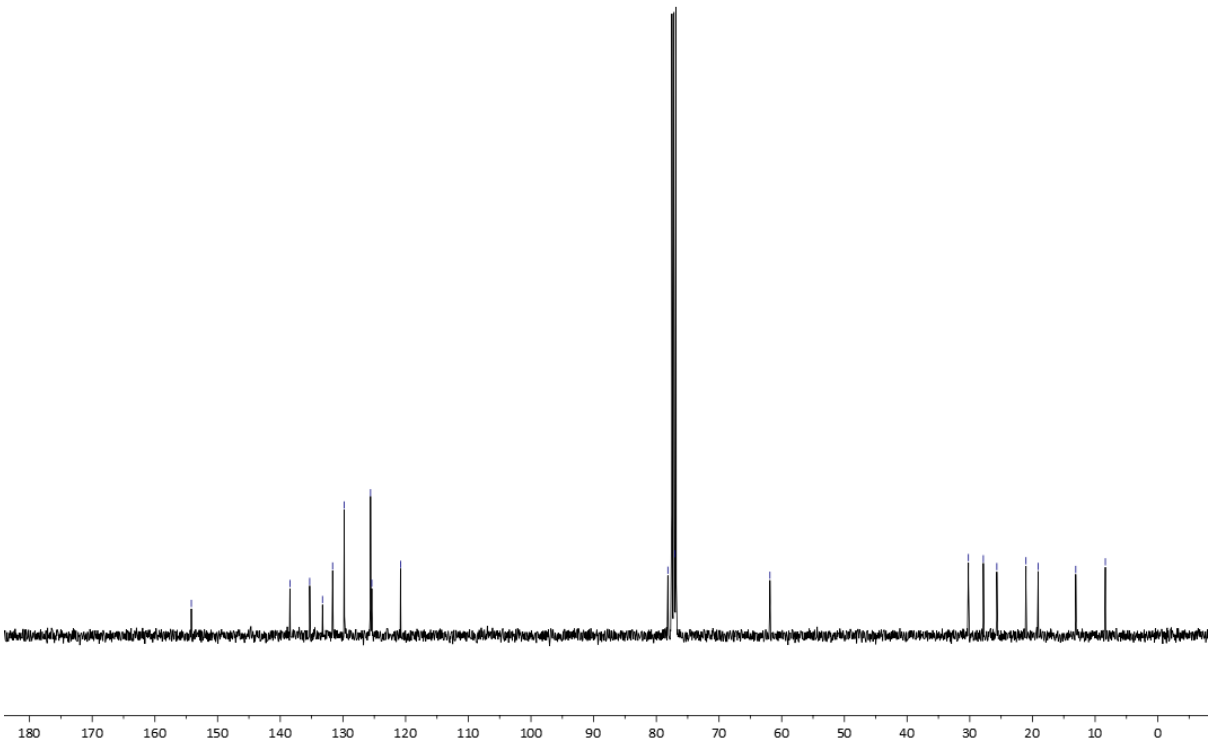
27.83
25.68
21.03
19.08
13.09
8.37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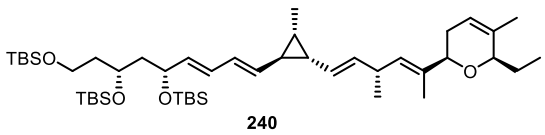
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
TBSO
OTBS
O

240

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1.07
1.92
1.99
0.97
1.00
1.10
2.05
2.16
0.94
1.01
1.02
4.27
3.19
3.41
3.05
1.93
3.01
2.92
30.23
18.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
136.95
135.55
135.31
135.29
133.73
129.87
129.74
127.53
125.58
121.12
78.16
70.96
66.89
60.08
46.82
40.42
35.18
31.29
30.36
29.71
26.20
26.11
26.10
25.82
22.06
21.33
19.16
18.53
18.35
18.23
13.32
12.46
8.41
-3.86
-4.17
-4.18
-4.54
-5.10
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150
140
130
120
110
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90
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70
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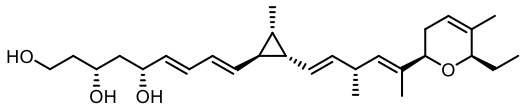
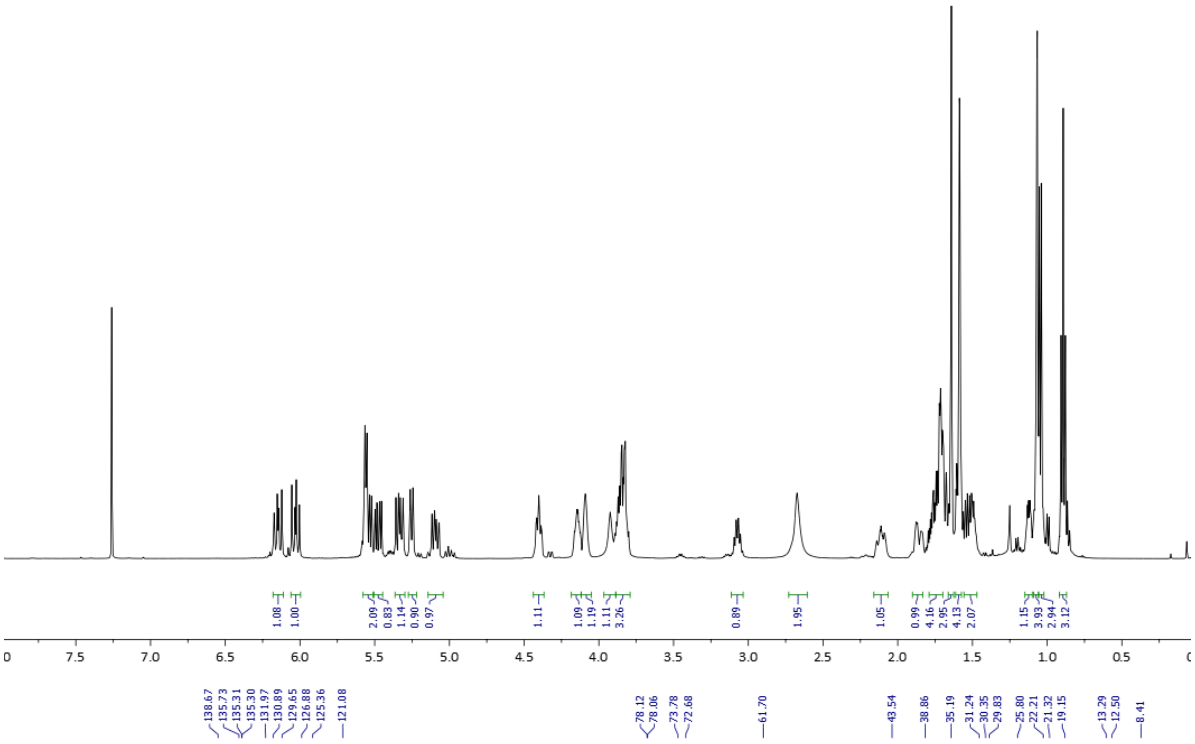
50
40
30
20
10
0


HO
OH
OH
O

309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1.00
2.09
0.83
1.14
0.90
0.97
1.11
1.09
1.19
1.11
3.26
0.89
1.95
1.05
0.99
4.16
2.95
4.13
2.07
1.15
3.93
2.94
3.12
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

138.67
135.73
135.31
135.30
131.97
130.89
129.65
126.88
125.36
121.08
78.12
78.06
73.78
72.68
61.70
43.54
38.86
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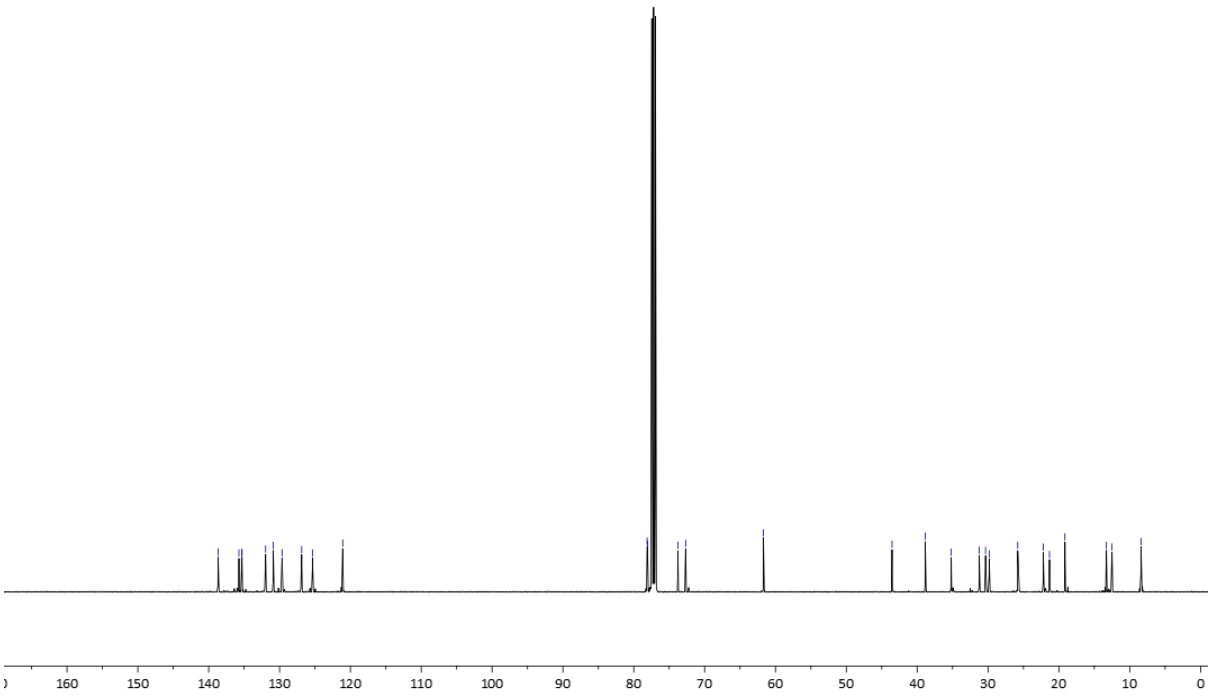
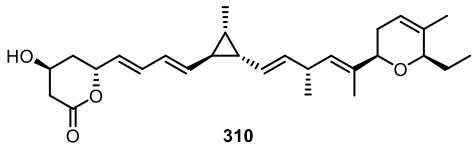
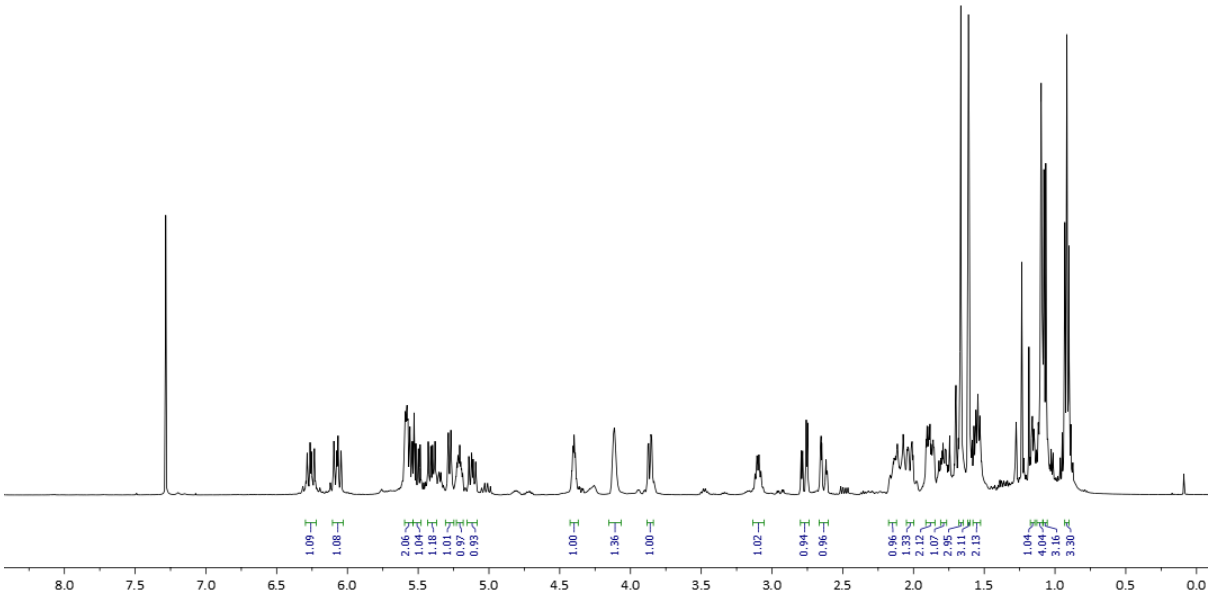
31.24
30.35
29.83
25.80
22.21
21.32
19.15
13.29
12.50
8.41


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


HO
O
O

310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1.08
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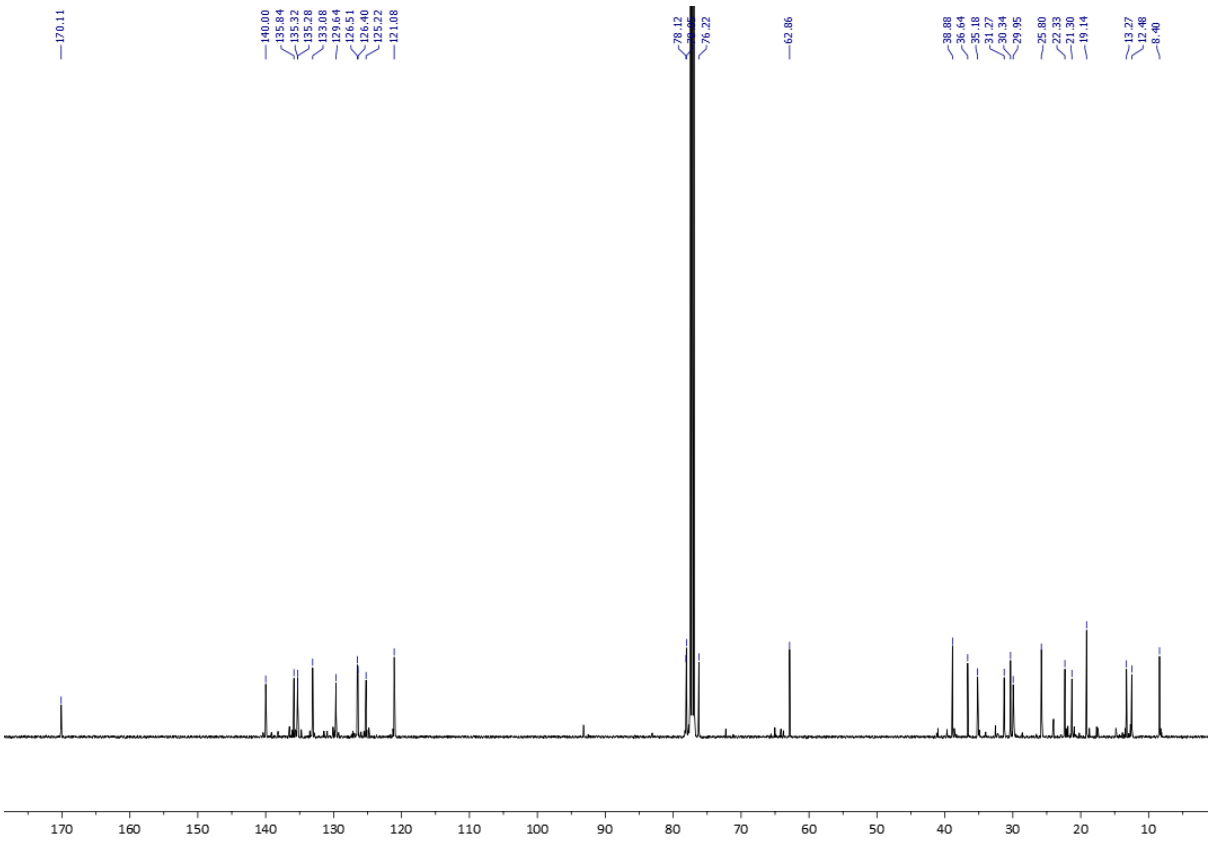
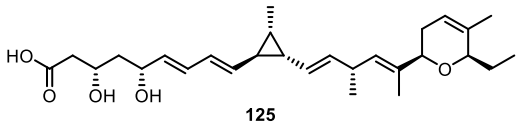
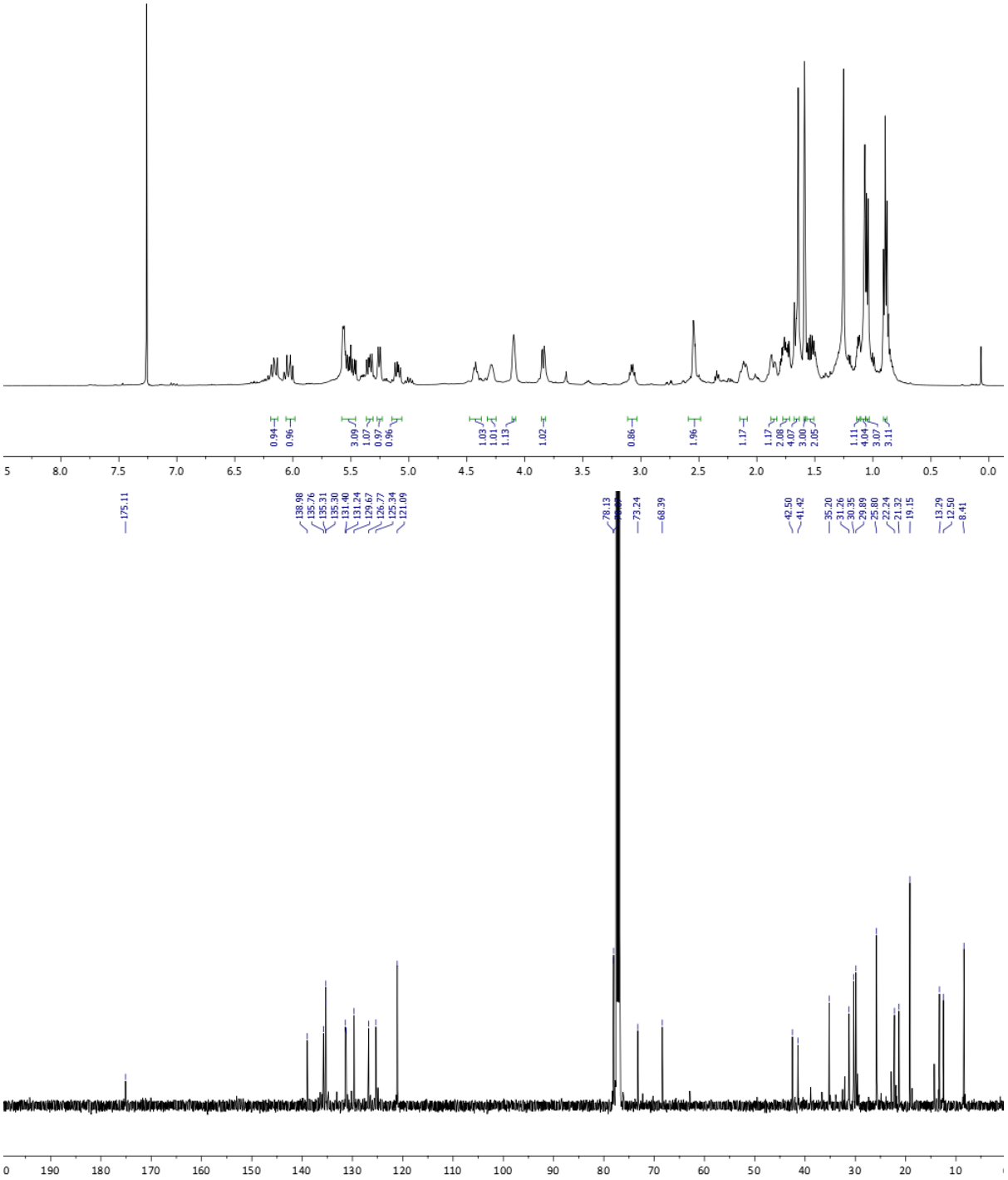
1.04
1.18
1.01
0.97
0.93
1.00
1.36
1.00
1.02
0.94
0.96
0.96
1.33
2.12
1.07
2.95
3.11
2.13
1.04
4.04
3.16
3.30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

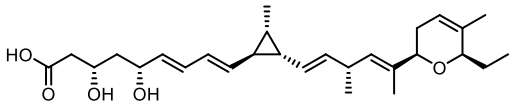

170.11
140.00
135.84
135.32
135.28
133.08
129.64
126.51
126.40
125.22
121.08
78.12
76.22
62.86
38.88
36.64
35.18
31.27
30.34
29.95
25.80
22.33
21.30
19.14
13.27
12.48
8.40
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



125

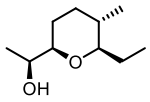
NMR spectra in $CDCl_3$



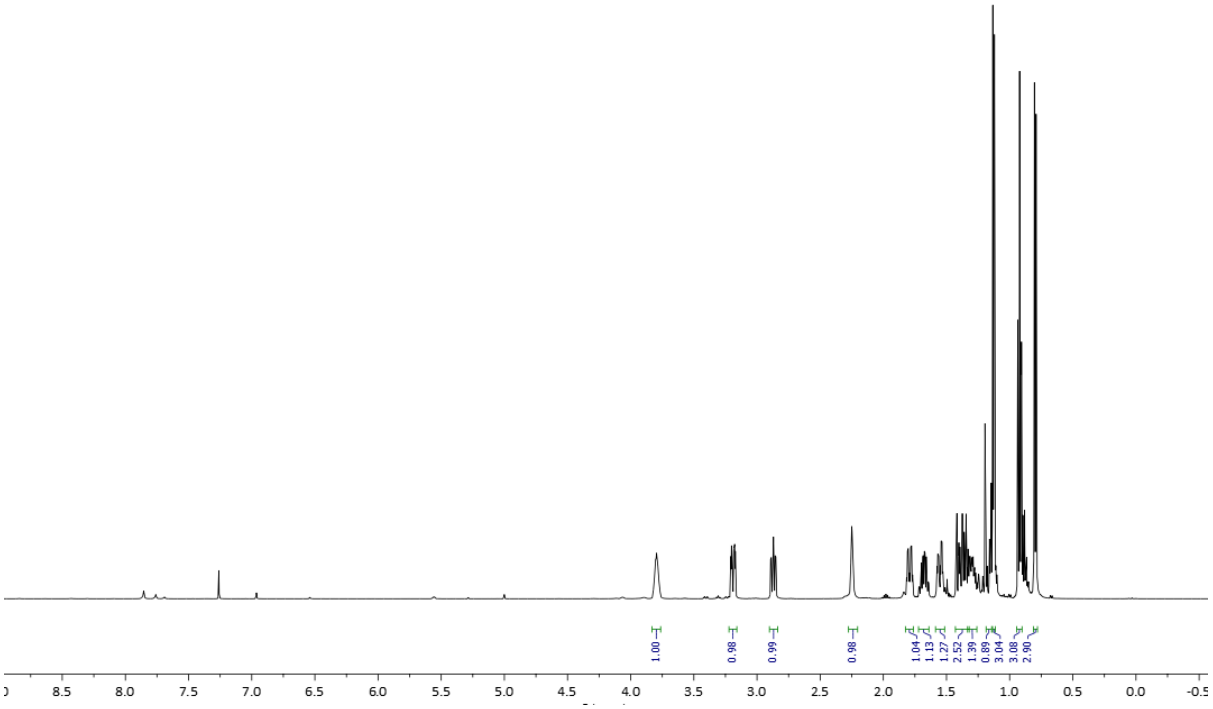


125

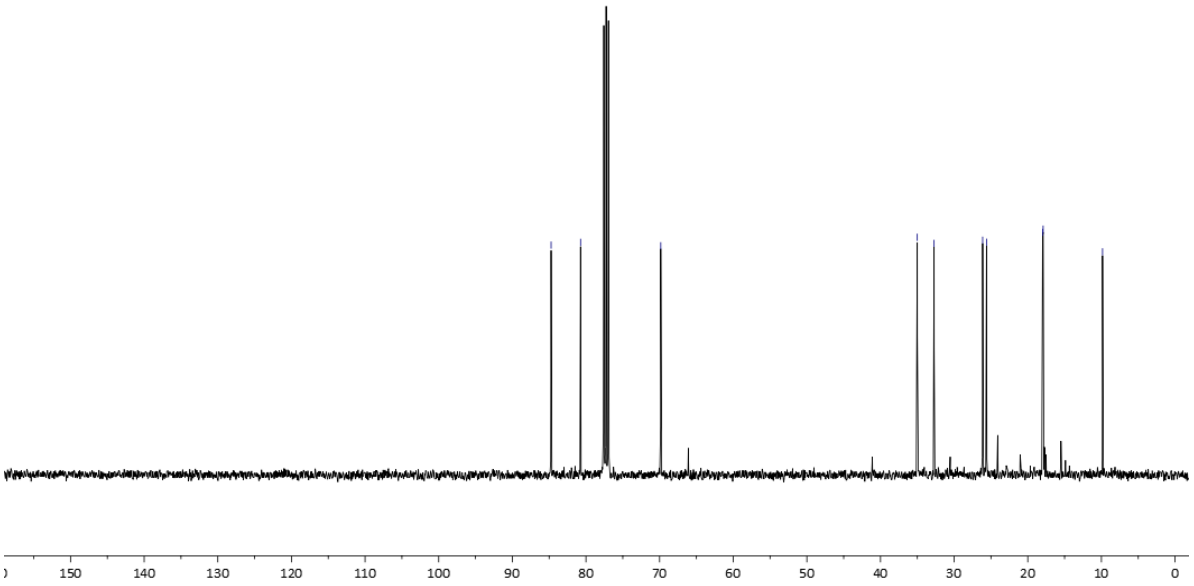
NMR spectra in methanol-D_4


OH
O

324


1.00
0.98
0.99
0.98
1.04
1.13
1.27
2.52
1.39
0.89
3.04
3.08
2.90
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


84.74
80.73
69.84
35.01
32.73
26.13
25.61
17.99
17.91
9.85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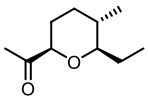
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



323

1.00
1.03
3.16
2.15
1.19
3.18
1.14
3.20
3.18
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
210.62
84.75
83.15
34.52
32.66
28.51
26.04
26.02
17.80
9.85
210
200
190
180
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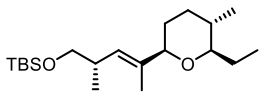
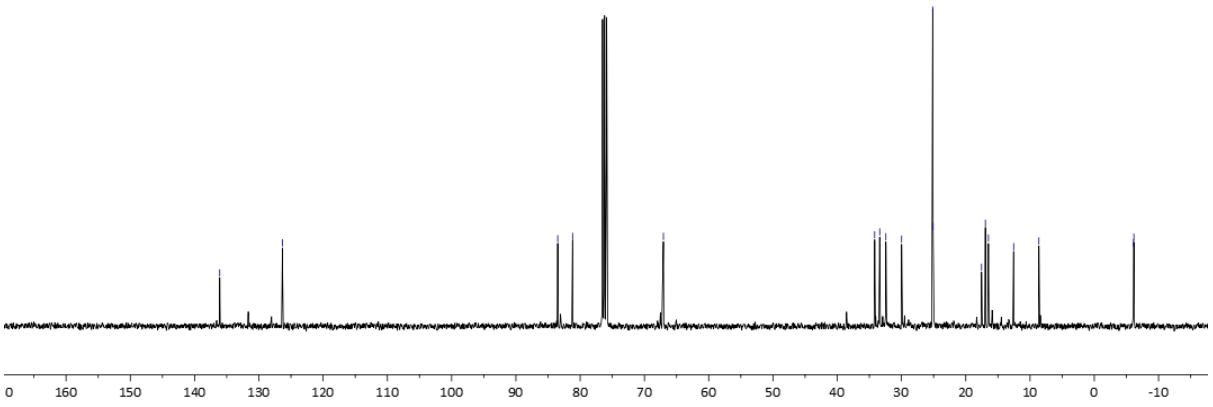
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
O

327

1.00
0.98
1.13
1.13
1.05
0.96
1.24
5.42
2.23
1.20
1.04
3.26
2.86
9.09
3.27
6.28
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
136.09
126.32
83.49
81.18
67.05
34.17
33.39
32.43
29.98
25.14
25.08
17.54
16.95
16.47
12.55
8.62
-6.09
-6.16


0
160
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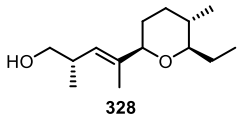
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


HO
O

328

1.00
1.02
1.12
1.02
1.01
1.06
1.09
5.25
1.02
3.18
1.34
6.00
3.02
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
139.31
126.59
84.60
81.87
68.04
35.20
34.46
33.38
31.12
26.10
17.92
17.10
13.89
9.67
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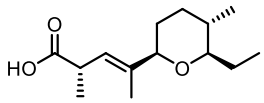
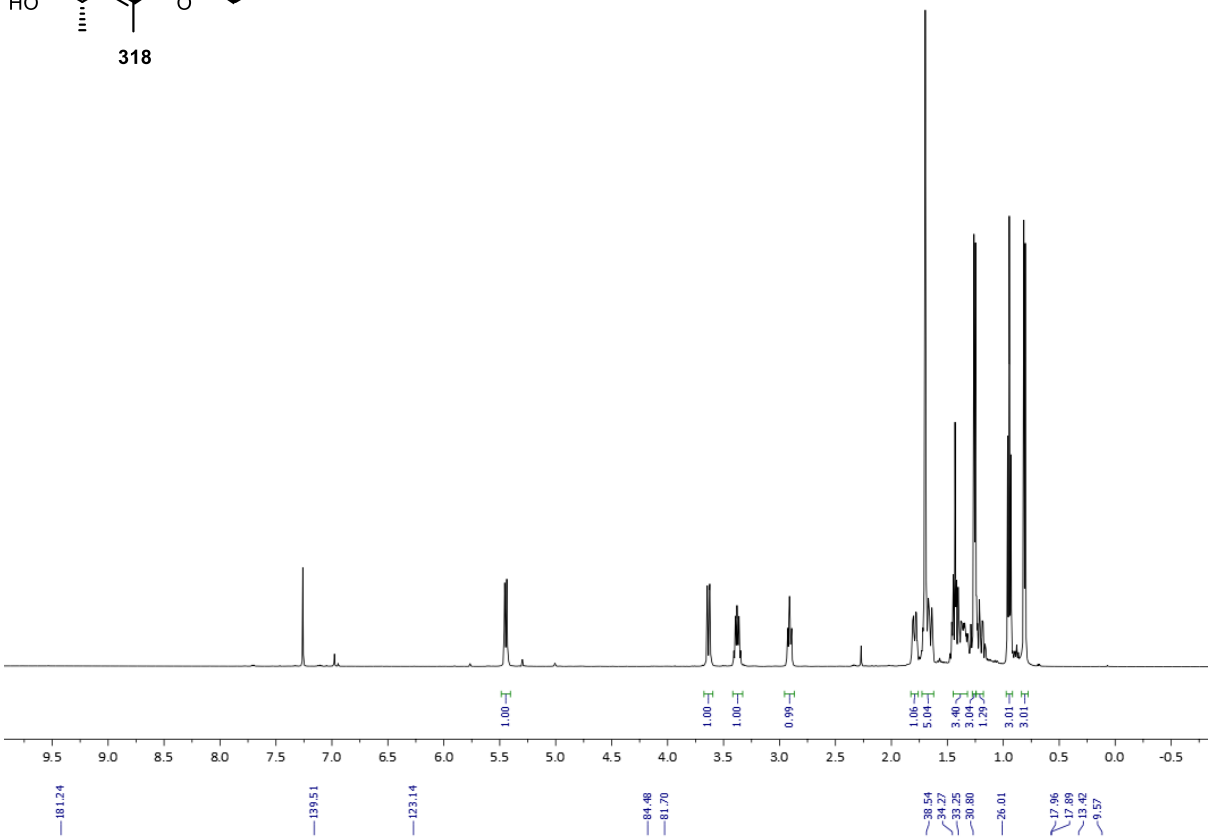
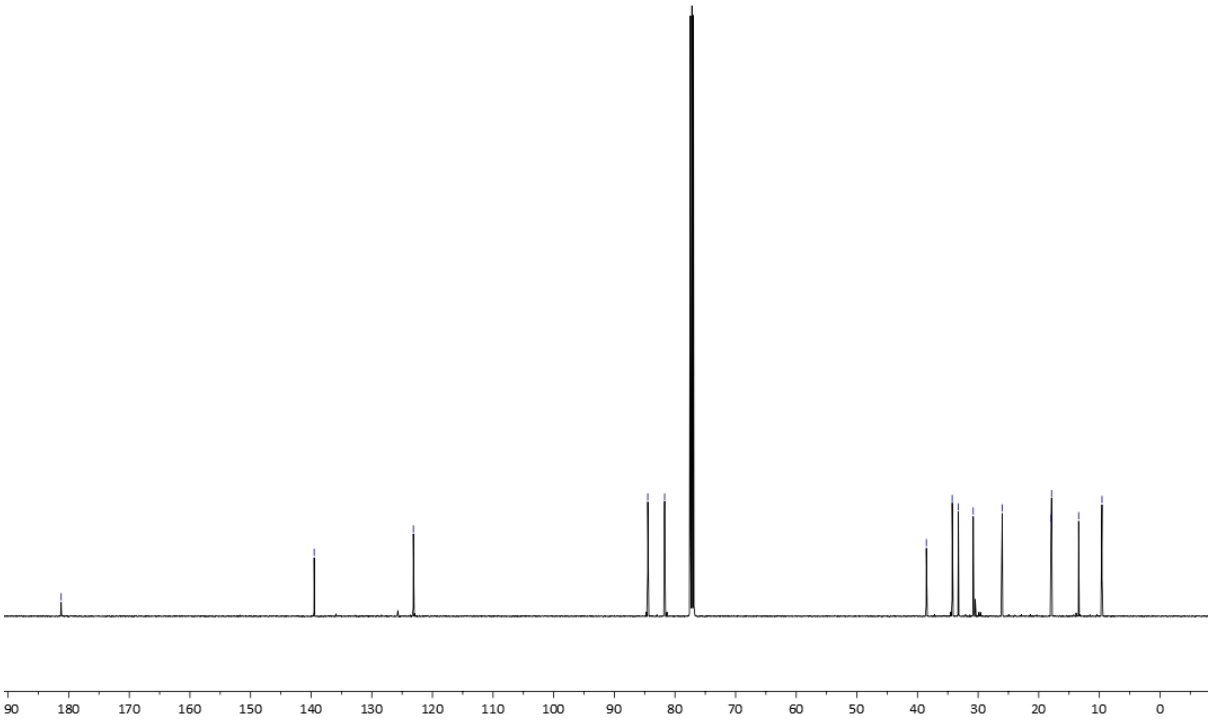
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

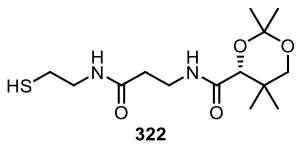

O
HO
O

318

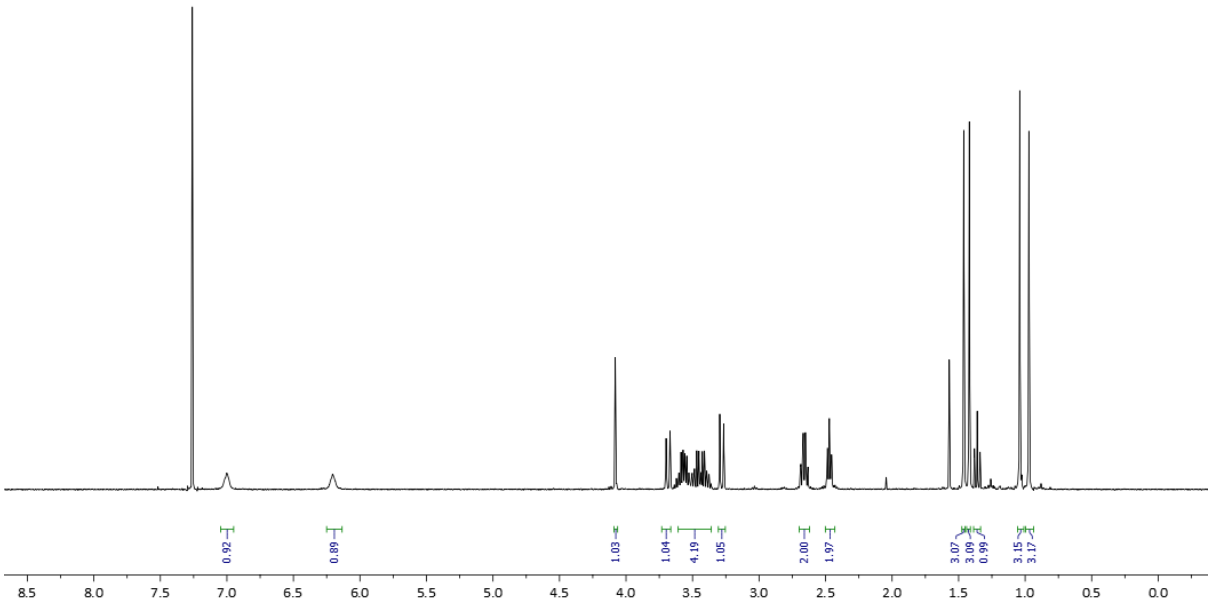

1.00
1.00
1.00
0.99
1.06
5.04
3.40
3.04
1.29
3.01
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

181.24
139.51
123.14
84.48
81.70
38.54
34.27
33.25
30.80
26.01
17.96
17.89
13.42
9.57


90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



322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1.03
1.04
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1.05
2.00
1.97
3.07
3.09
0.99
3.15
3.17
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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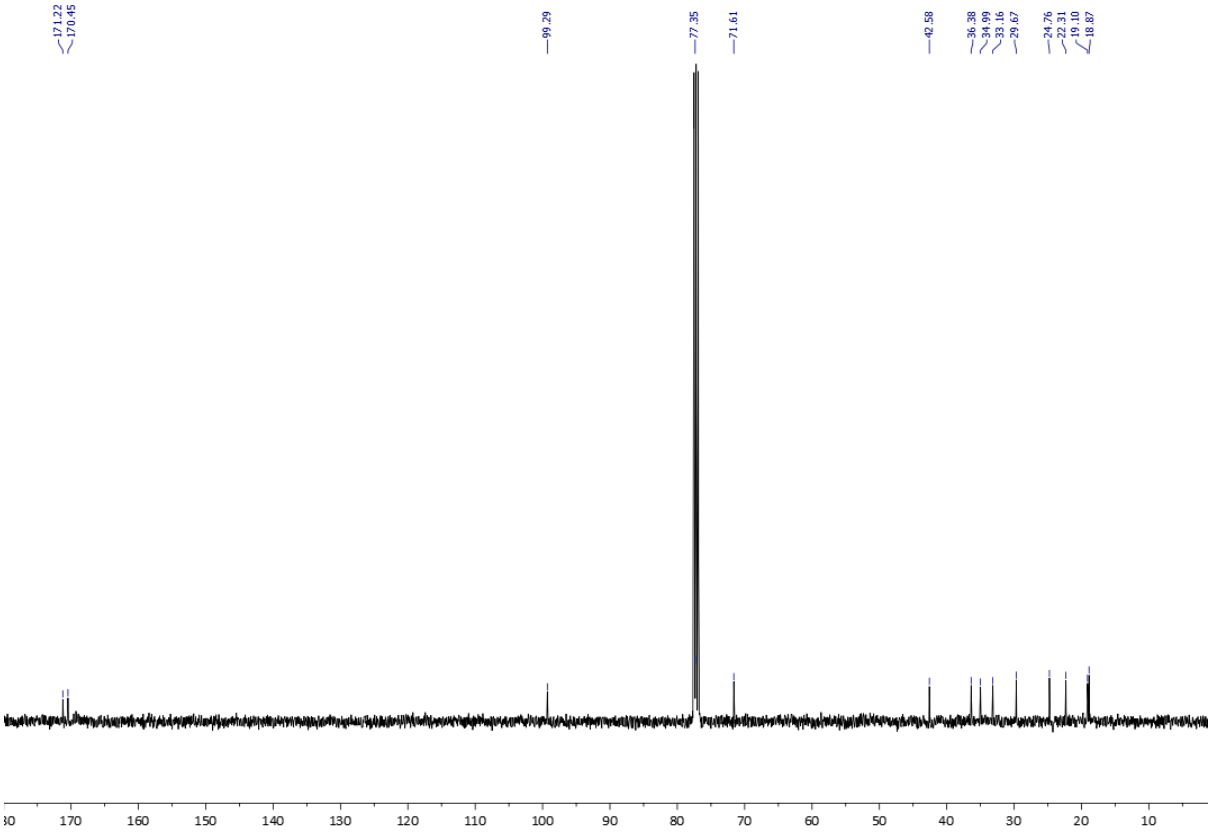
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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99.29
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42.58
36.38
34.99
33.16
29.67
24.76
22.31
19.10
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160
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120
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20
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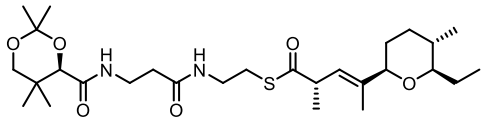
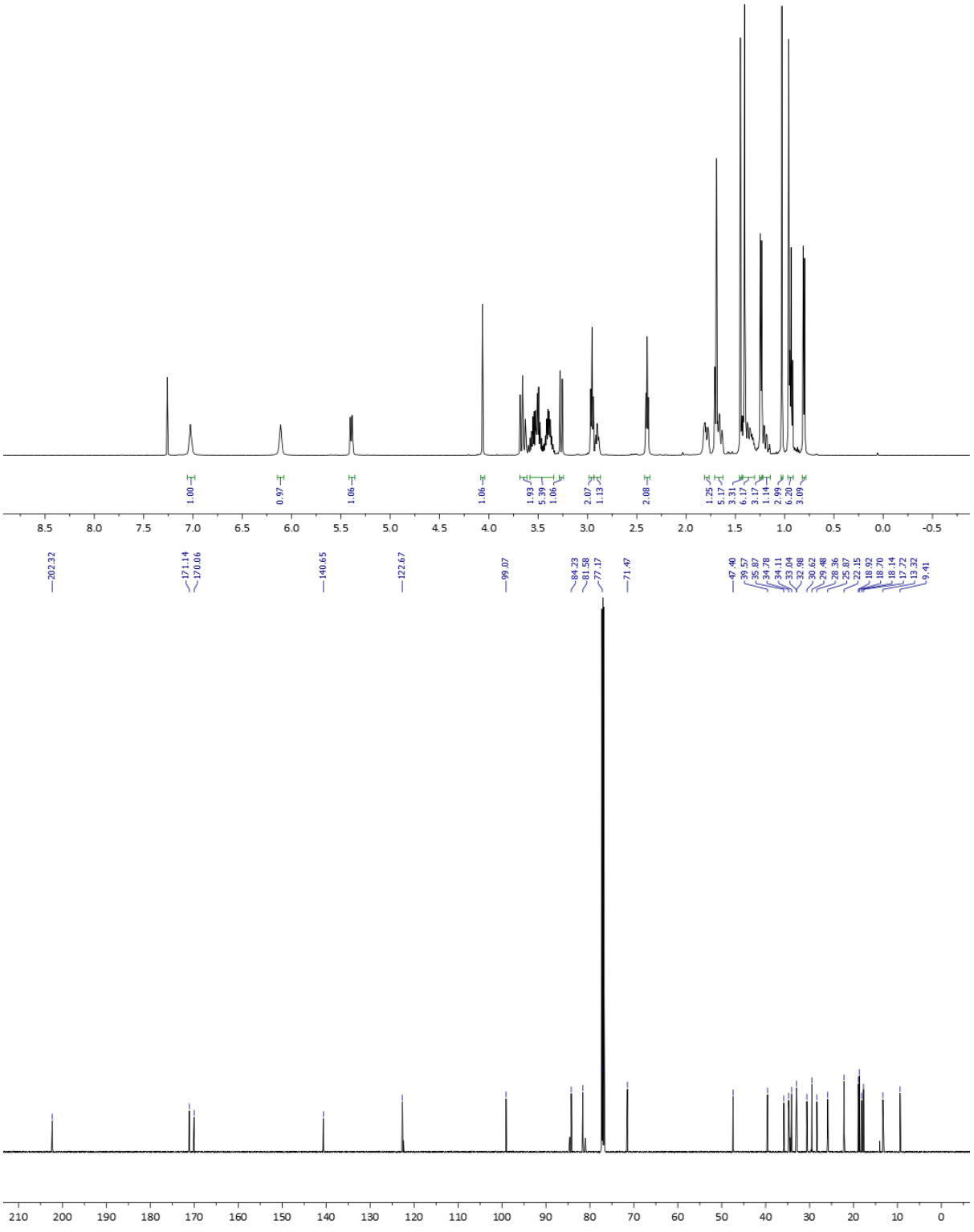


426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5.39
1.06
2.07
1.13
2.08
1.25
5.17
3.31
6.17
3.17
1.14
2.99
6.20
3.09
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
202.32
171.14
170.06
140.65
122.67
99.07
84.23
81.58
77.17
71.47
47.40
39.57
35.87
34.78
34.11
33.04
32.98
30.62
29.48
28.36
25.87
22.15
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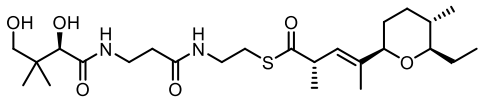
18.70
18.14
17.72
13.32
9.41
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



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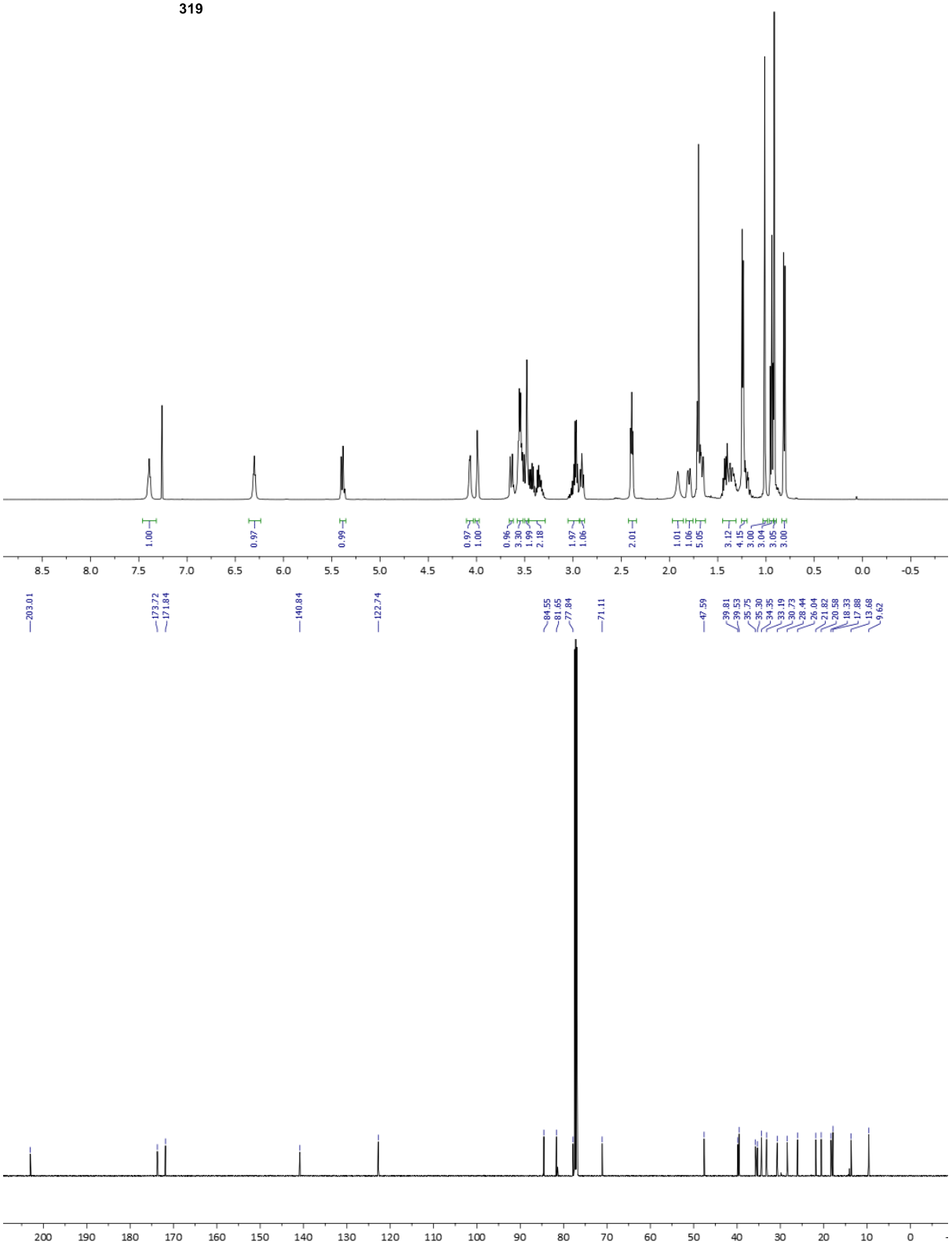

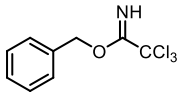
NH
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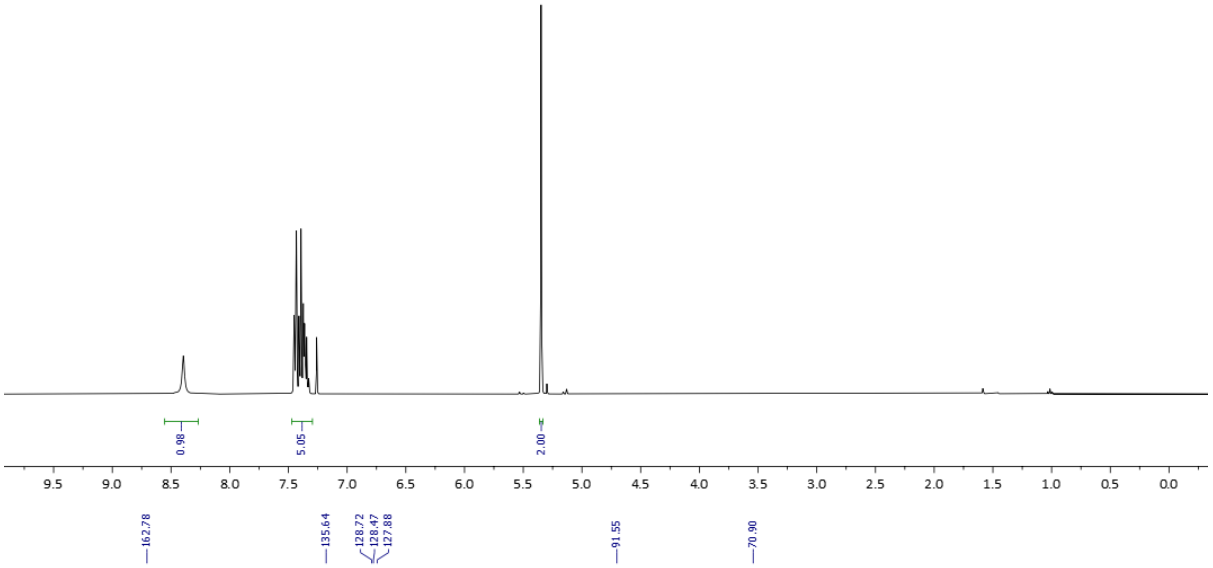
CCl3

354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7.5
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6.5
6.0
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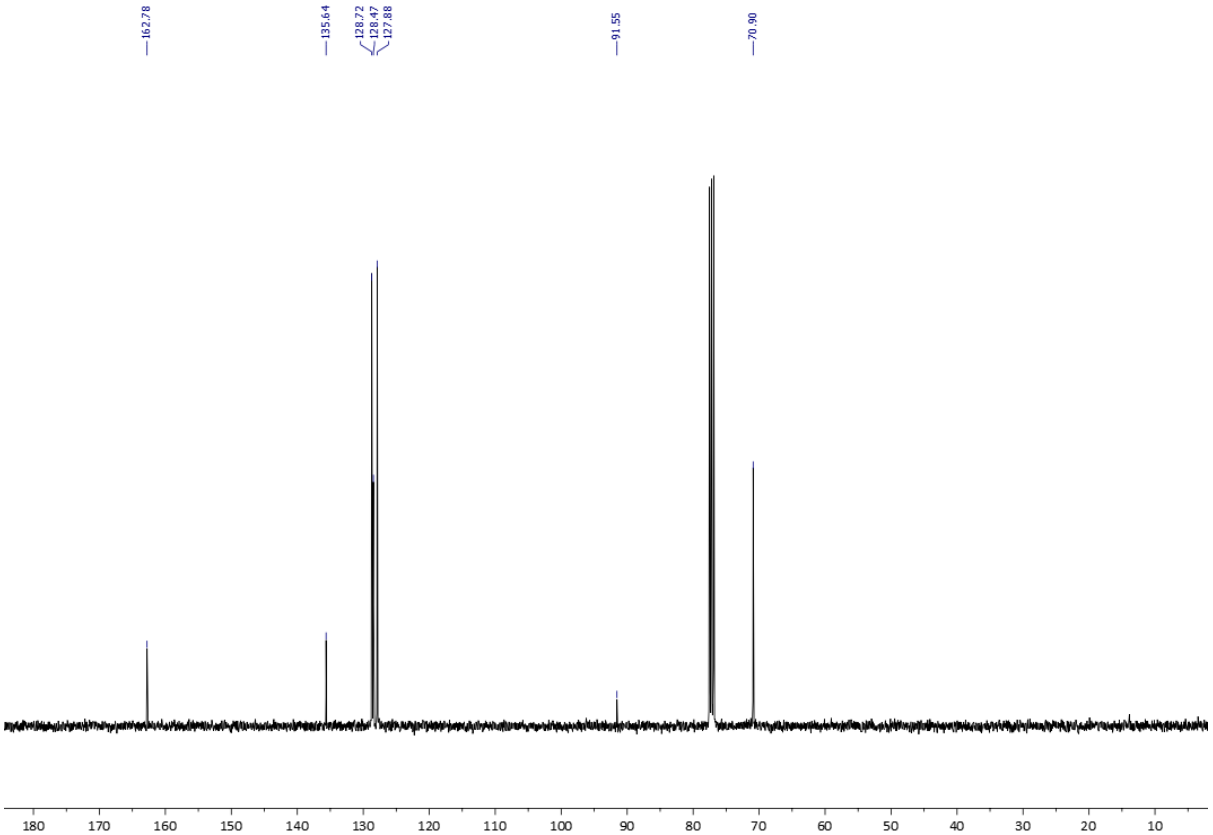
0.0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135.64
128.72
128.47
127.88
91.55
70.90
180
170
160
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140
130
120
110
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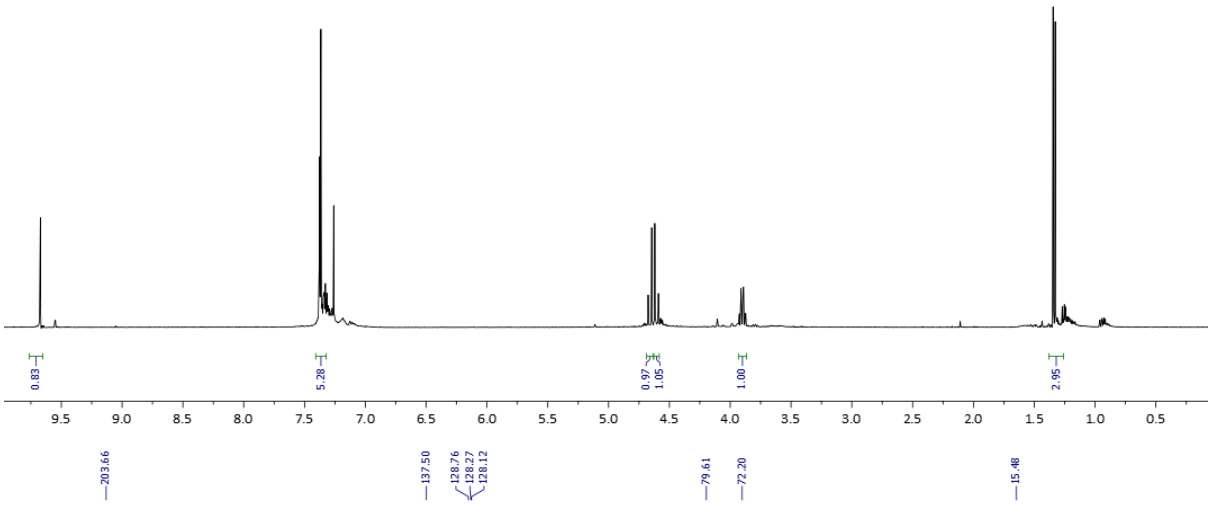
90
80
70
60
50
40
30
20
10


OBn
O

356


0.83
5.28
0.97
1.05
1.00
2.95
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
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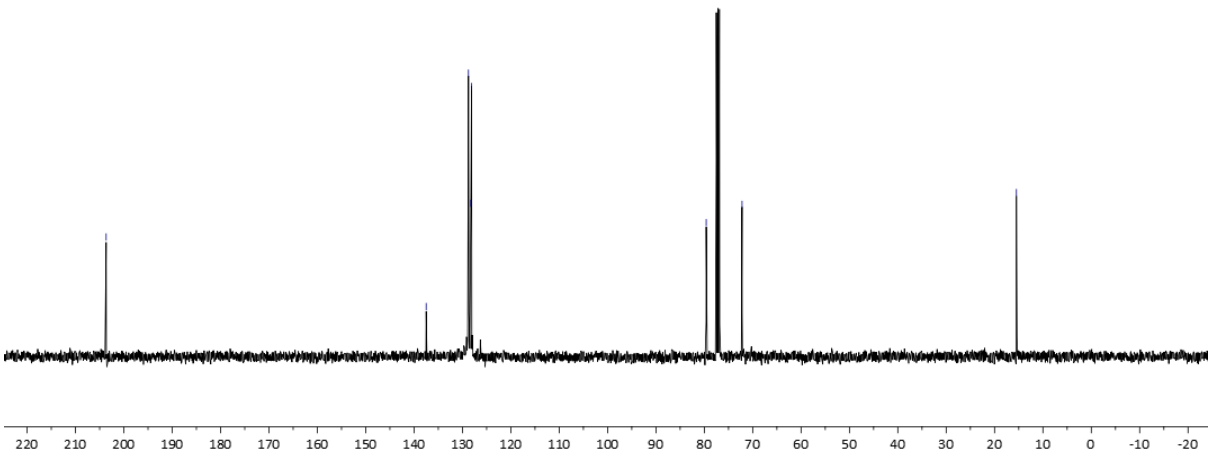
137.50
128.76
128.27
128.12
79.61
72.20
15.48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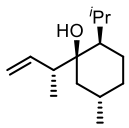
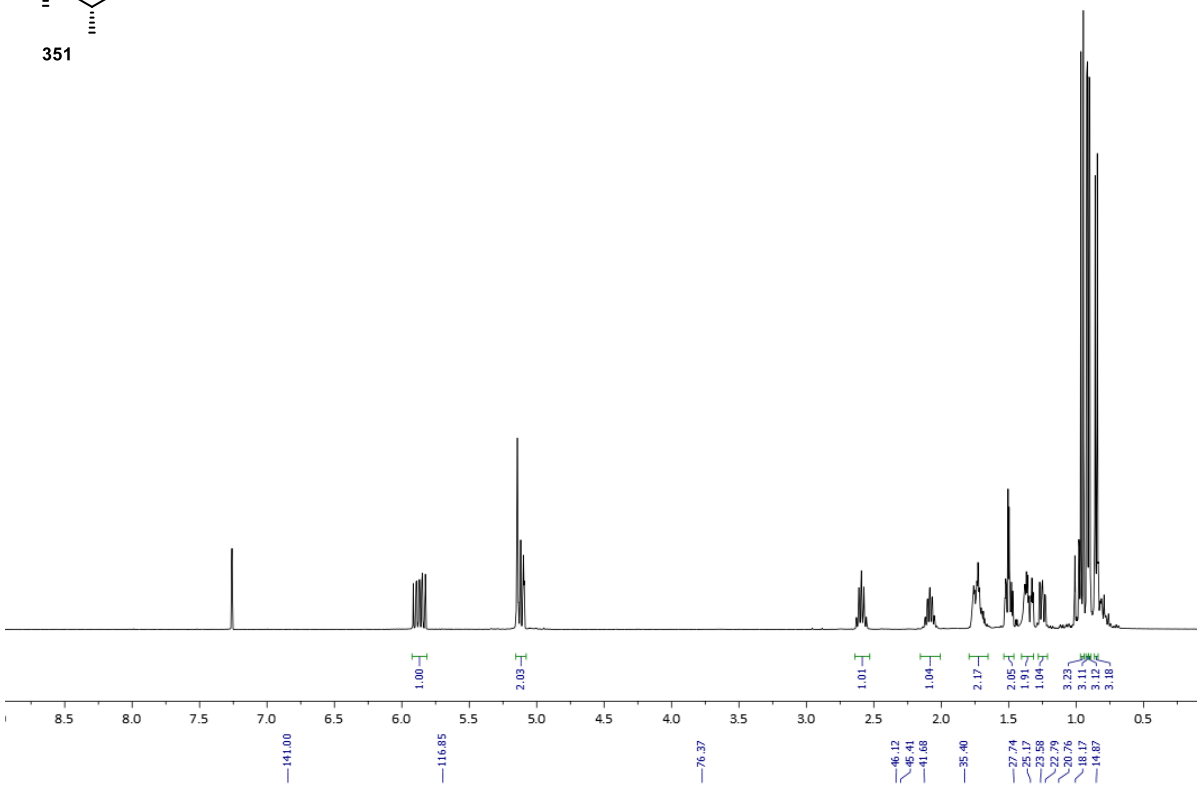

HO
iPr

351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1.01
1.04
2.17
2.05
1.91
1.04
3.23
3.11
3.12
3.18
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
141.00
116.85
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45.41
41.68
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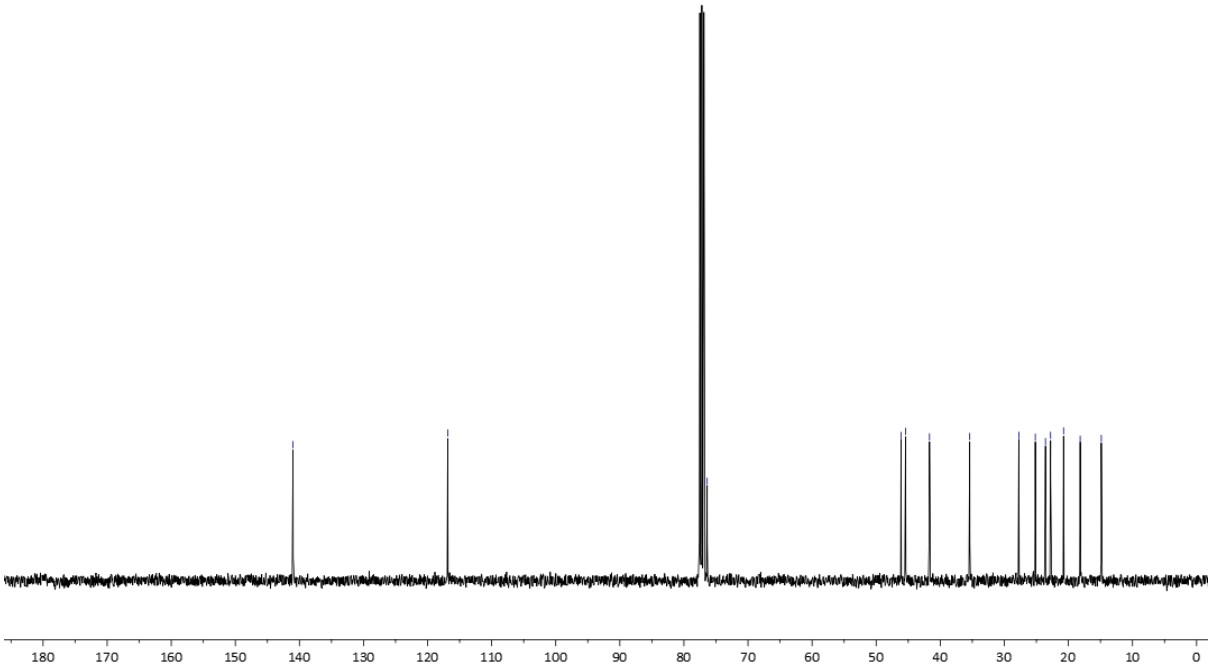
27.74
25.17
23.58
22.79
20.76
18.17
14.87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150
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100
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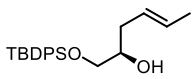
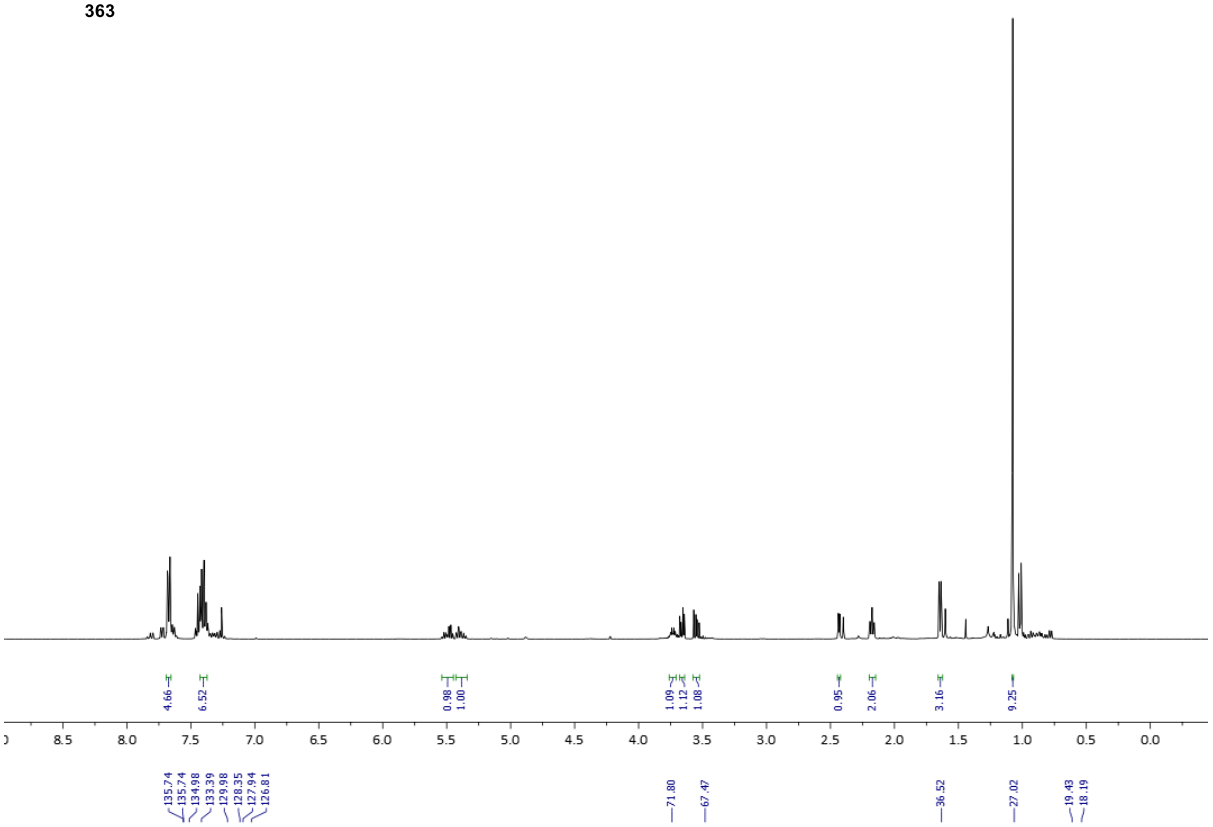
10
0


TBDPSO
OH

363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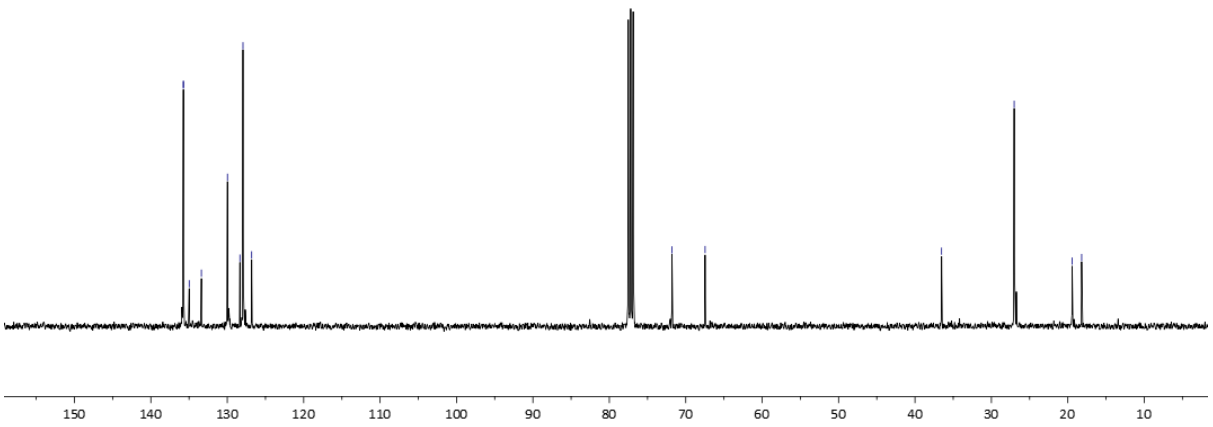
1.00
1.09
1.12
1.08
0.95
2.06
3.16
9.25
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
135.74
135.74
134.98
133.39
129.98
128.35
127.94
126.81
71.80
67.47
36.52
27.02
19.43
18.19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40
30
20
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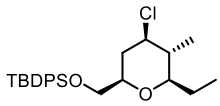
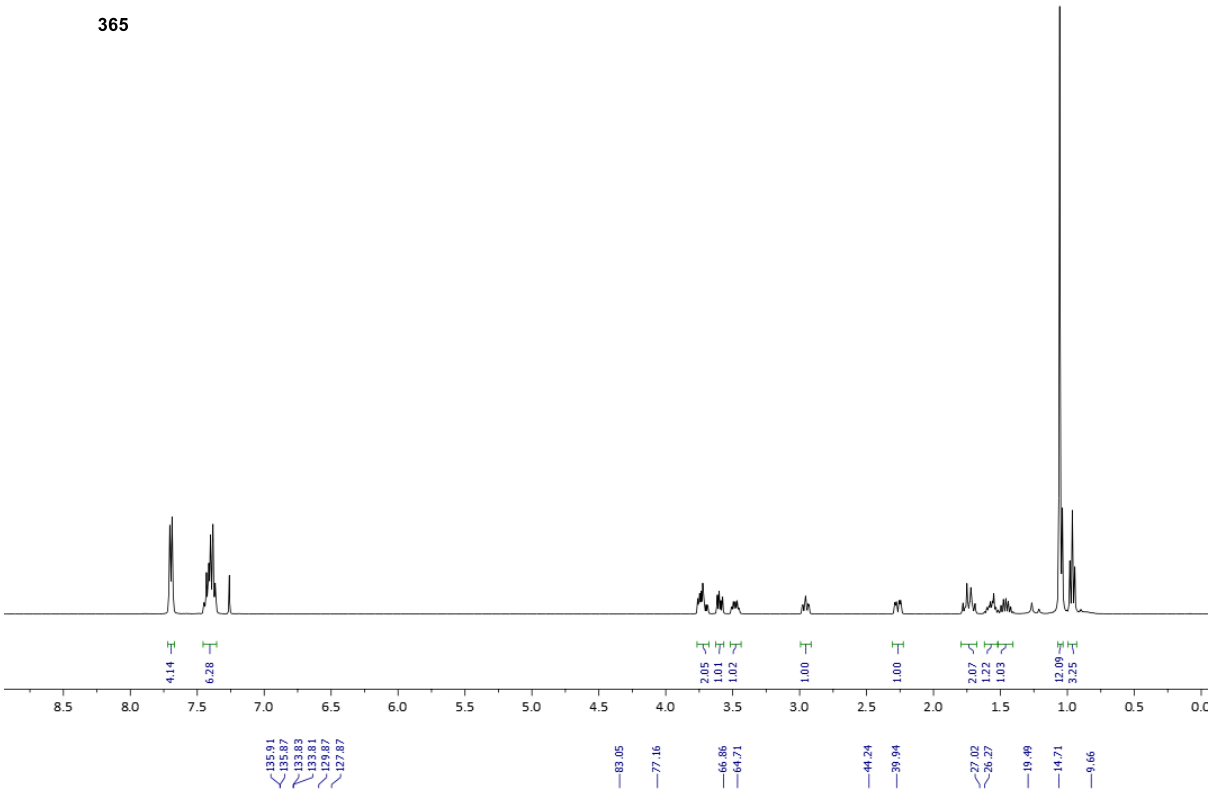

Cl
TBDPSO
O

365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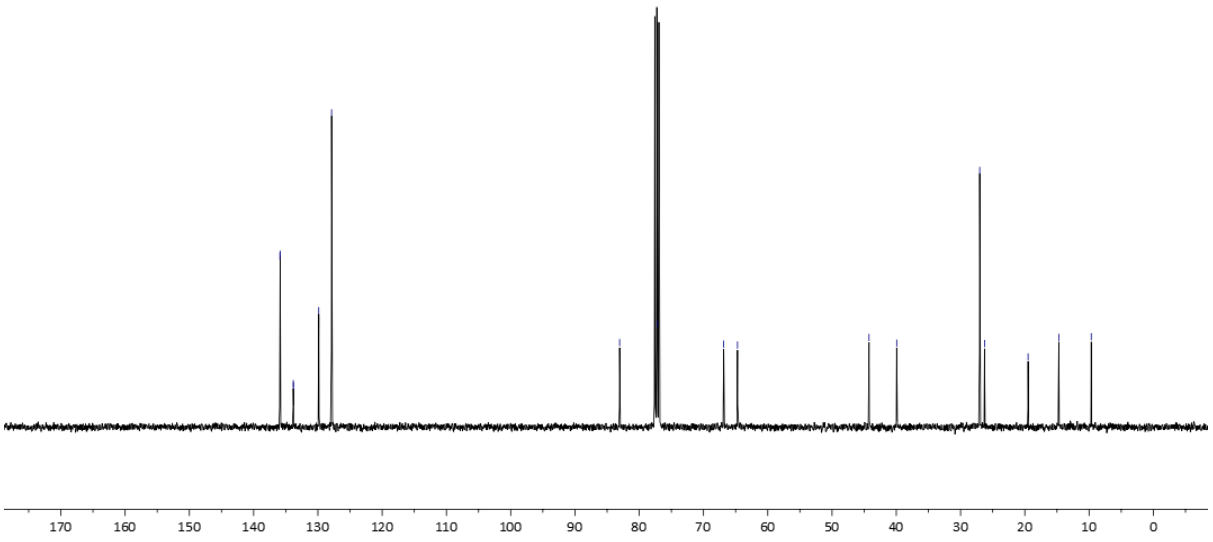
2.05
1.01
1.02
1.00
1.00
2.07
1.22
1.03
12.09
3.25
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
135.91
135.87
133.83
133.81
129.87
127.87
83.05
77.16
66.86
64.71
44.24
39.94
27.02
26.27
19.49
14.71
9.66


170
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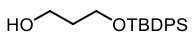
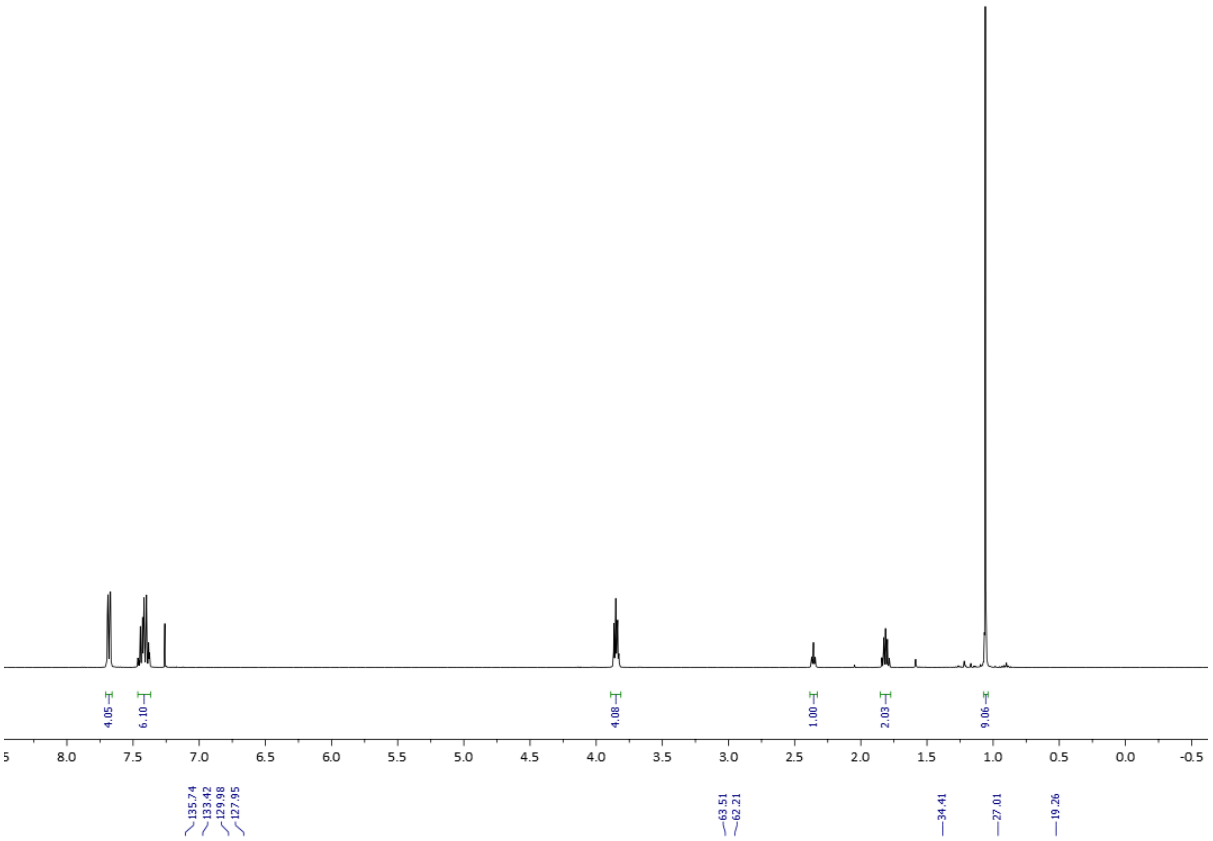
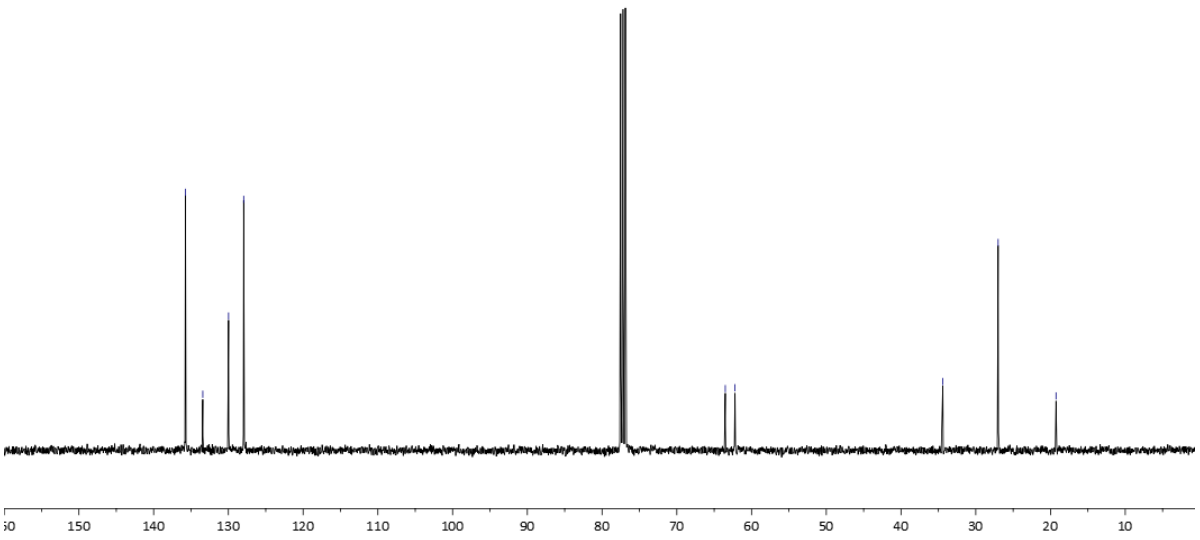
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


HO
OTBDPS

361


4.05
6.10
4.08
1.00
2.03
9.06
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
135.74
133.42
129.98
127.95
63.51
62.21
34.41
27.01
19.26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140
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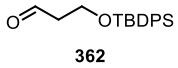
120
110
100
90
80
70
60
50
40
30
20
10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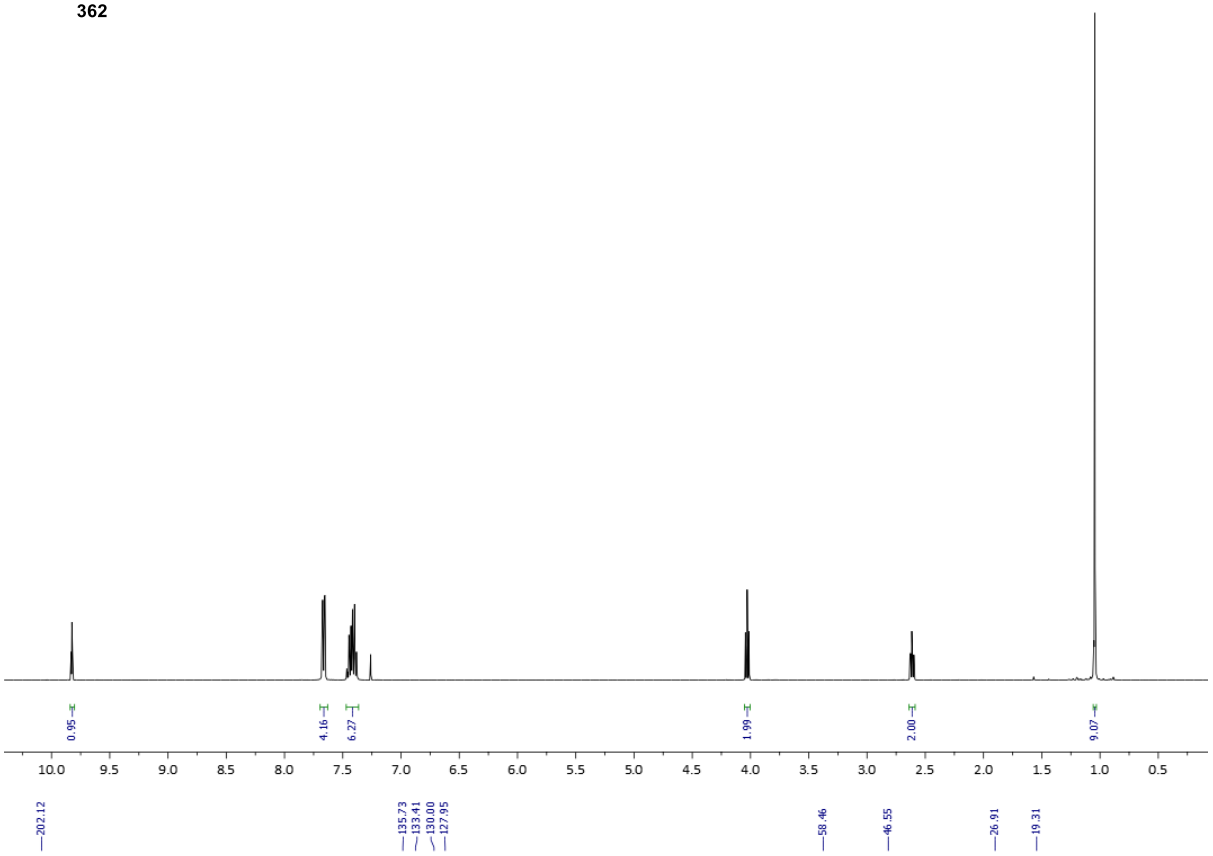
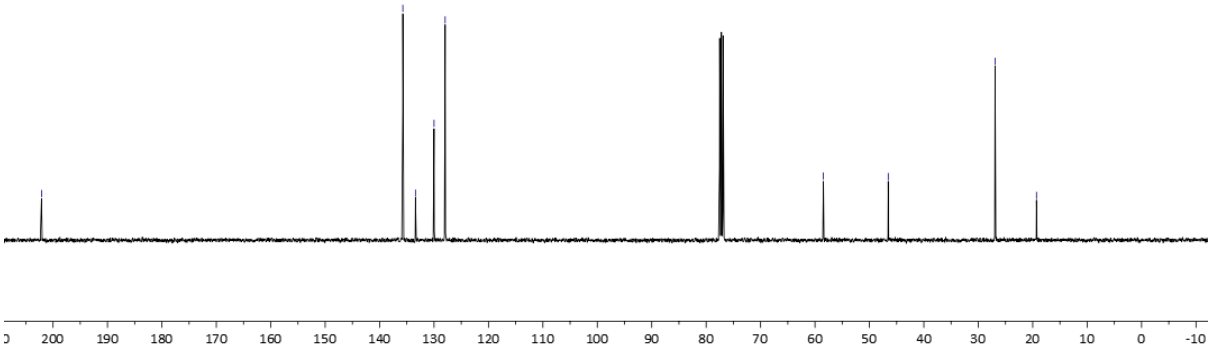
OTBDPS

362


0.95
4.16
6.27
1.99
2.00
9.07
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
202.12
135.73
133.41
130.00
127.95
58.46
46.55
26.91
19.31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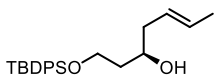
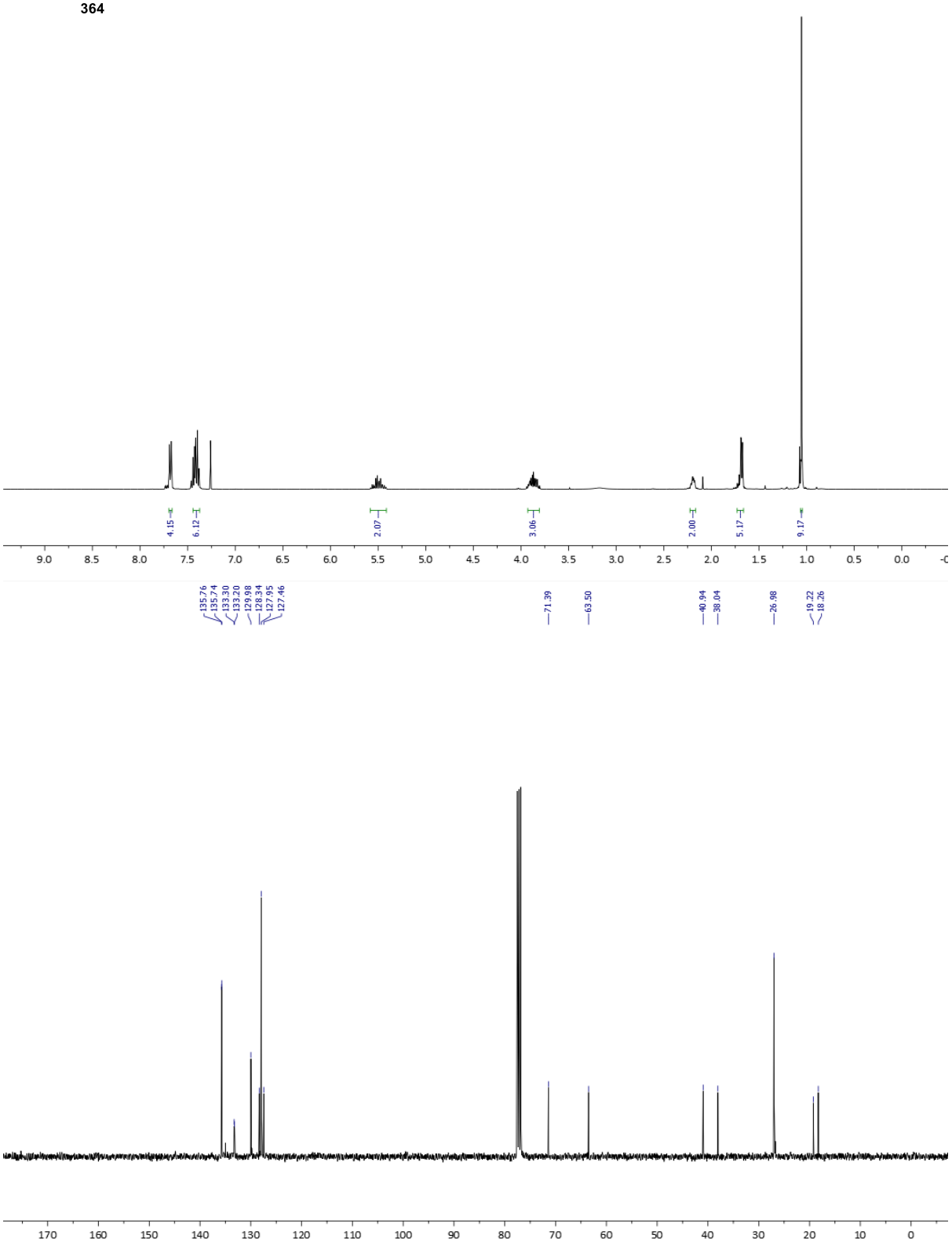

TBDPSO
OH

364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6.12
2.07
3.06
2.00
5.17
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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
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133.20
129.98
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127.95
127.46
71.39
63.50
40.94
38.04
26.98
19.22
18.26
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70
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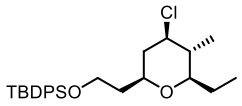
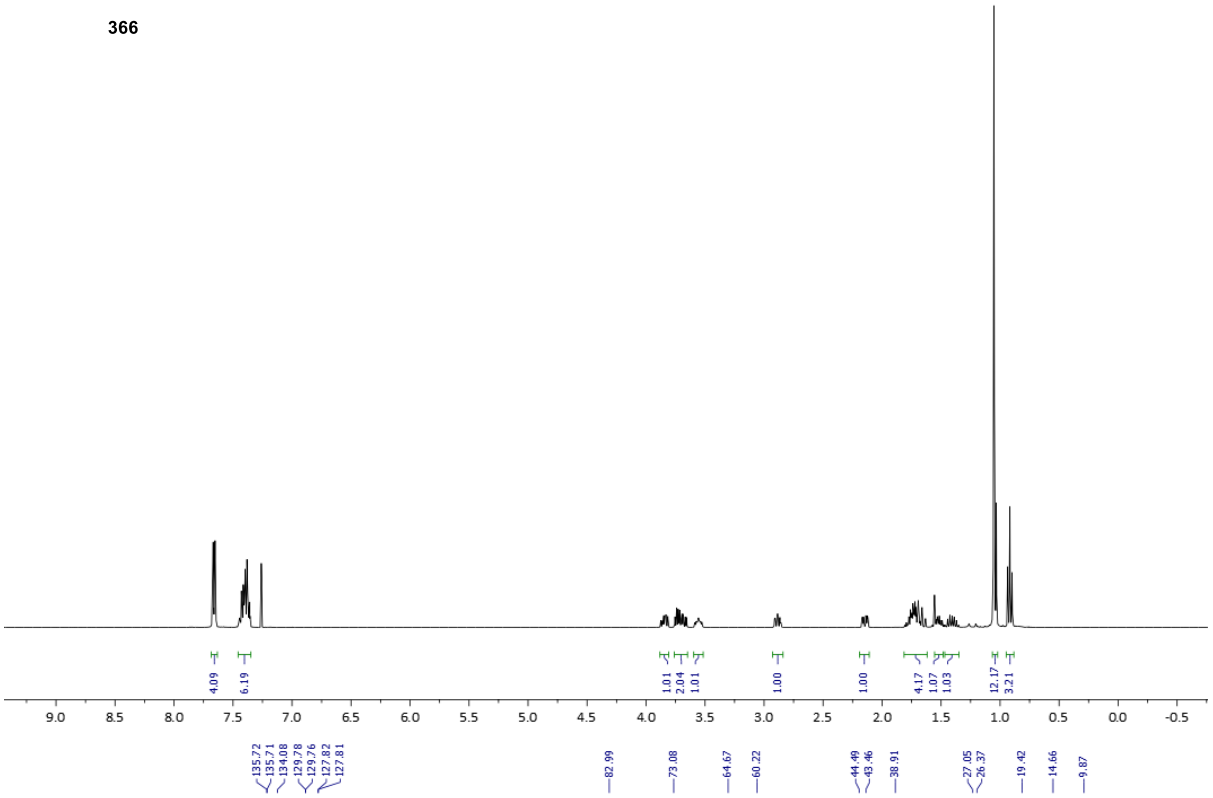
10
0


Cl
TBDPSO
O

366


4.09
6.19
1.01
2.04
1.01
1.00
1.00
4.17
1.07
1.03
12.17
3.21
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
135.72
135.71
134.08
129.78
129.76
127.82
127.81
82.99
73.08
64.67
60.22
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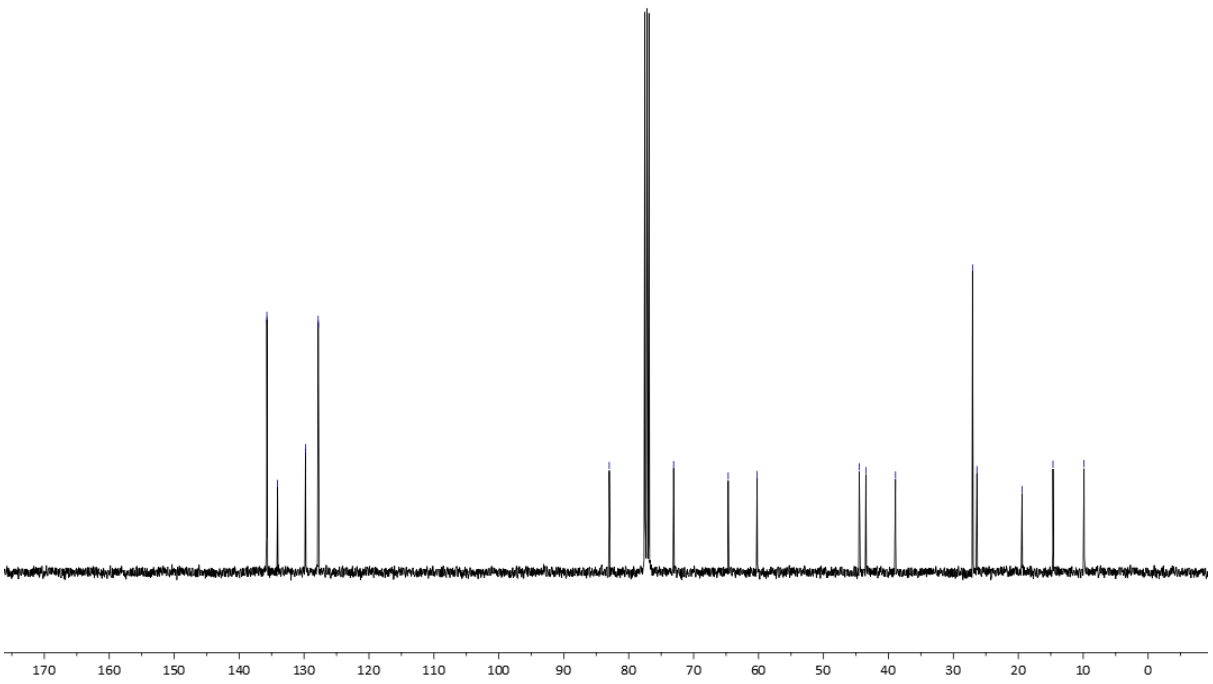
43.46
38.91
27.05
26.37
19.42
14.66
9.87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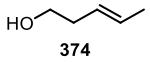
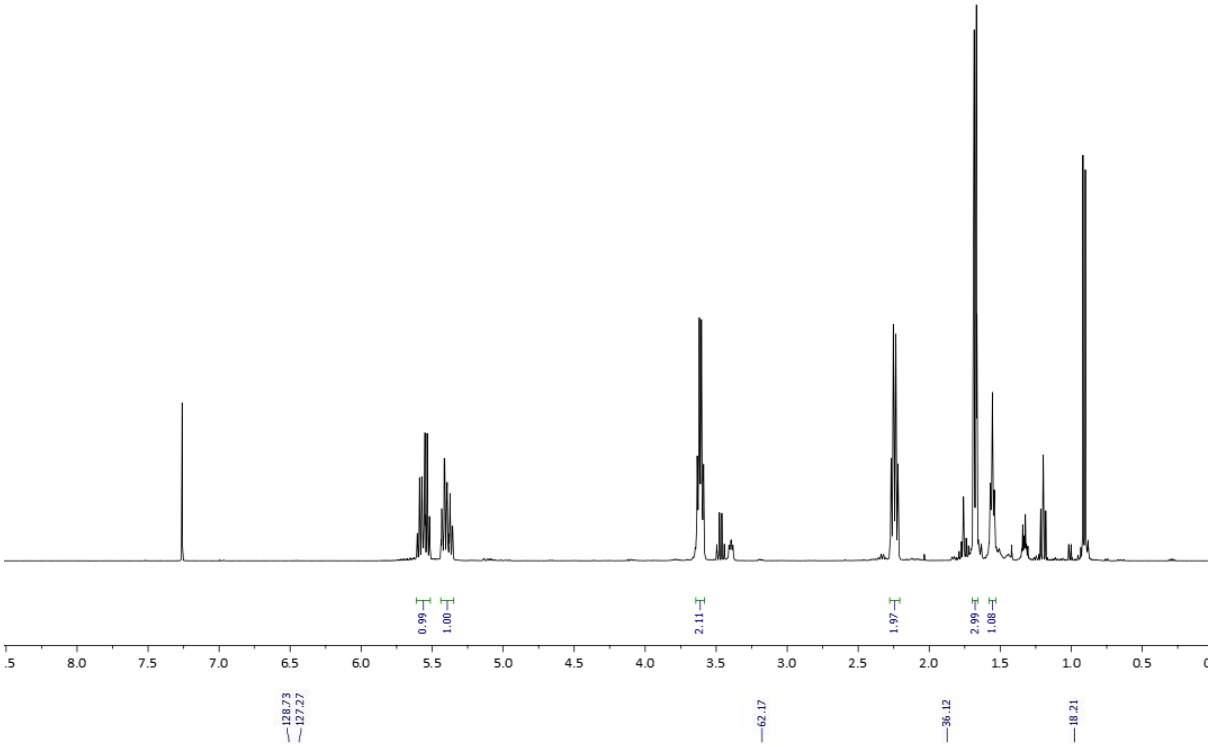
20
10
0



374


0.99
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1.97
2.99
1.08
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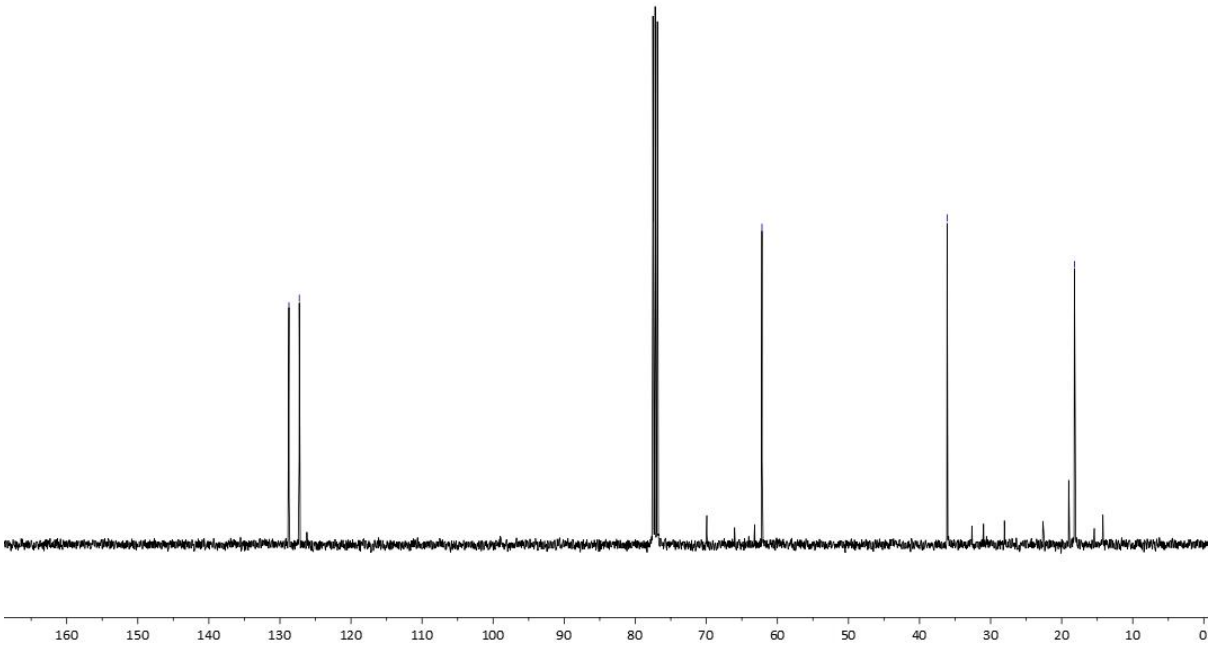
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

128.73
127.27
62.17
36.12
18.21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150
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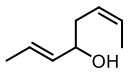
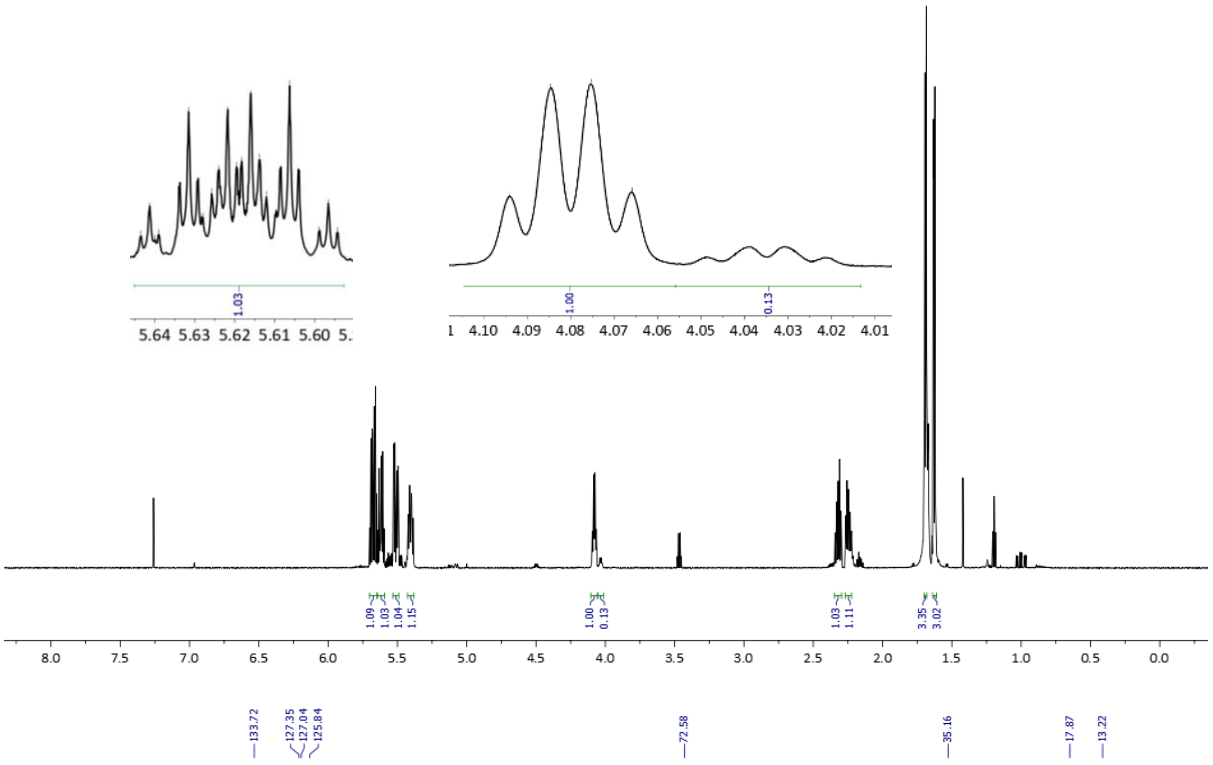
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OH

371

E/*Z* = 12:88


1.03
5.64 5.63 5.62 5.61 5.60 5.
1.00
0.13
4.10 4.09 4.08 4.07 4.06 4.05 4.04 4.03 4.02 4.01
1.09
1.03
1.04
1.15
1.00
0.13
1.03
1.11
3.35
3.02
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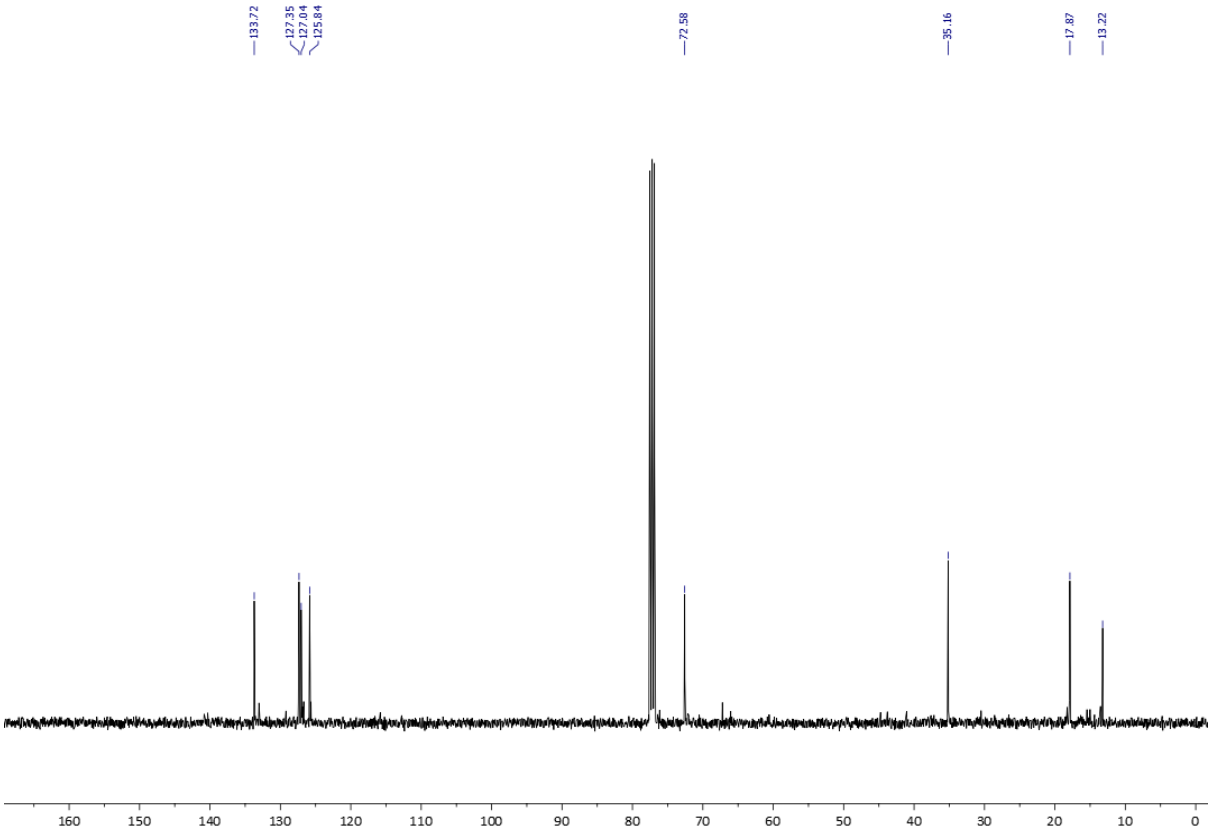

133.72
127.35
127.04
125.84
72.58
35.16
17.87
13.22
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

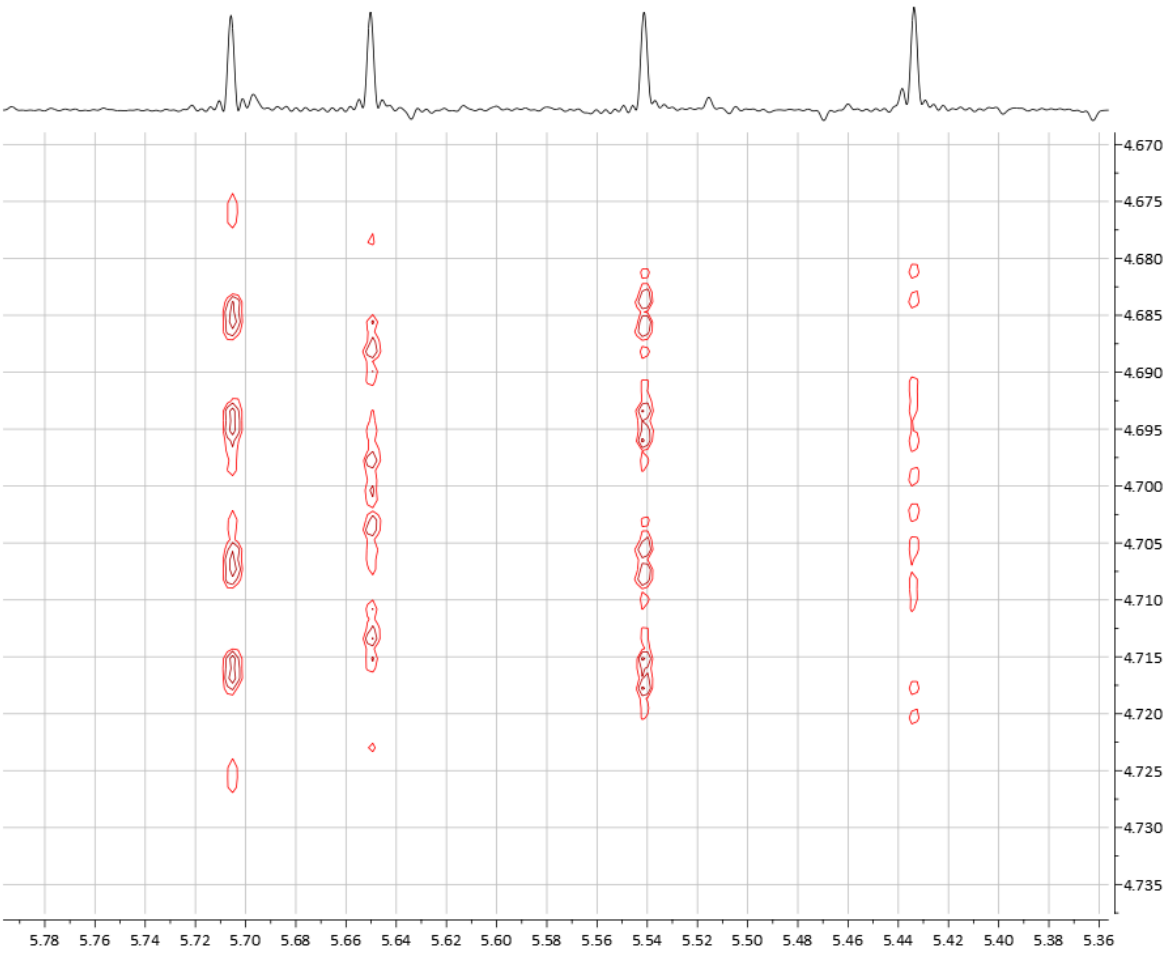
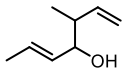
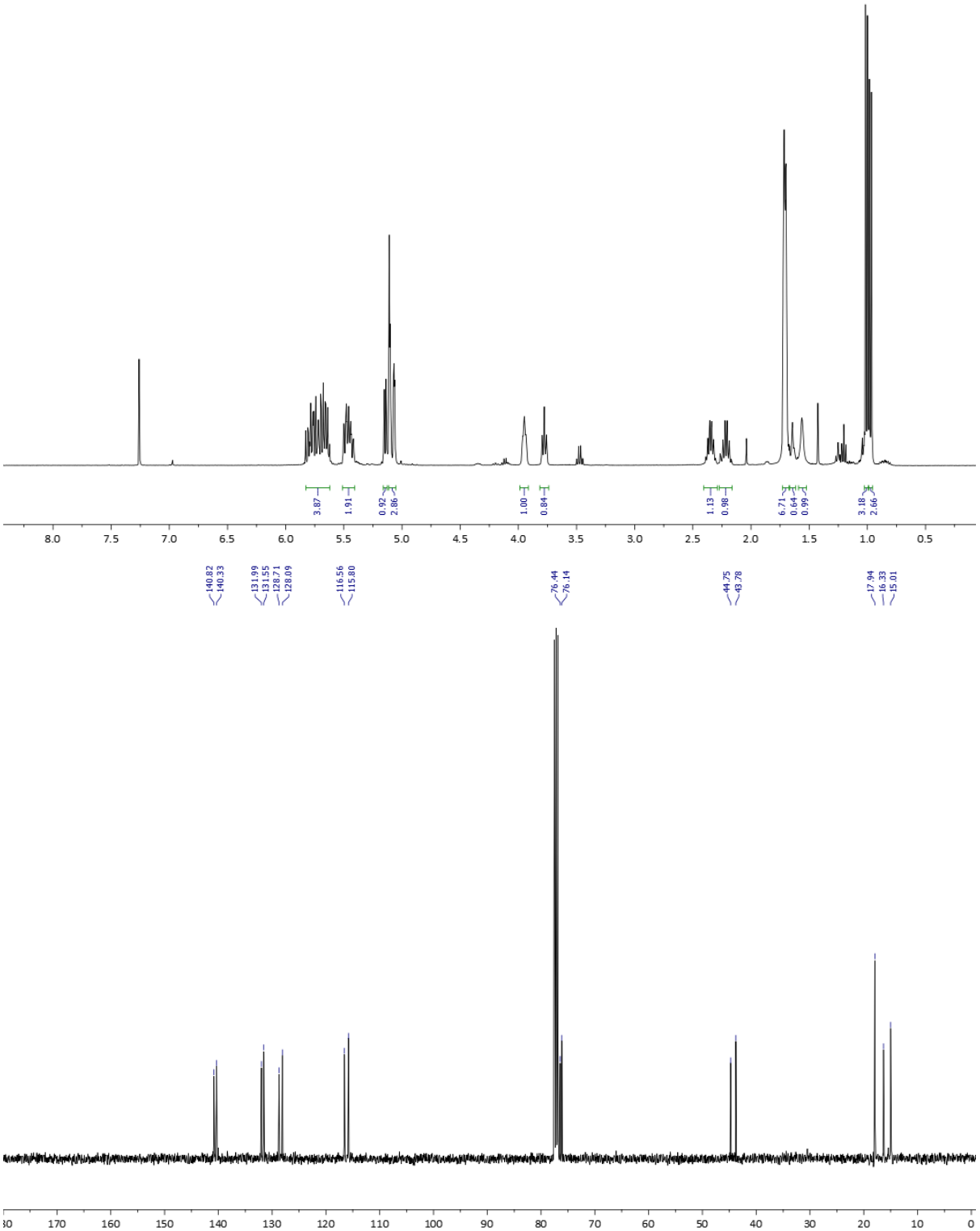


Figure 29. 2DJ-PYSCHE ^{1}H-NMR of **371** used to determine geometry of major alkene isomer.


OH

428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1.91
0.92
2.86
1.00
0.84
1.13
0.98
6.71
0.64
0.99
3.18
2.66
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
140.82
140.33
131.99
131.55
128.71
128.09
116.56
115.80
76.44
76.14
44.75
43.78
17.94
16.33
15.01
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70
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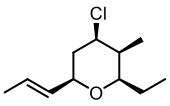
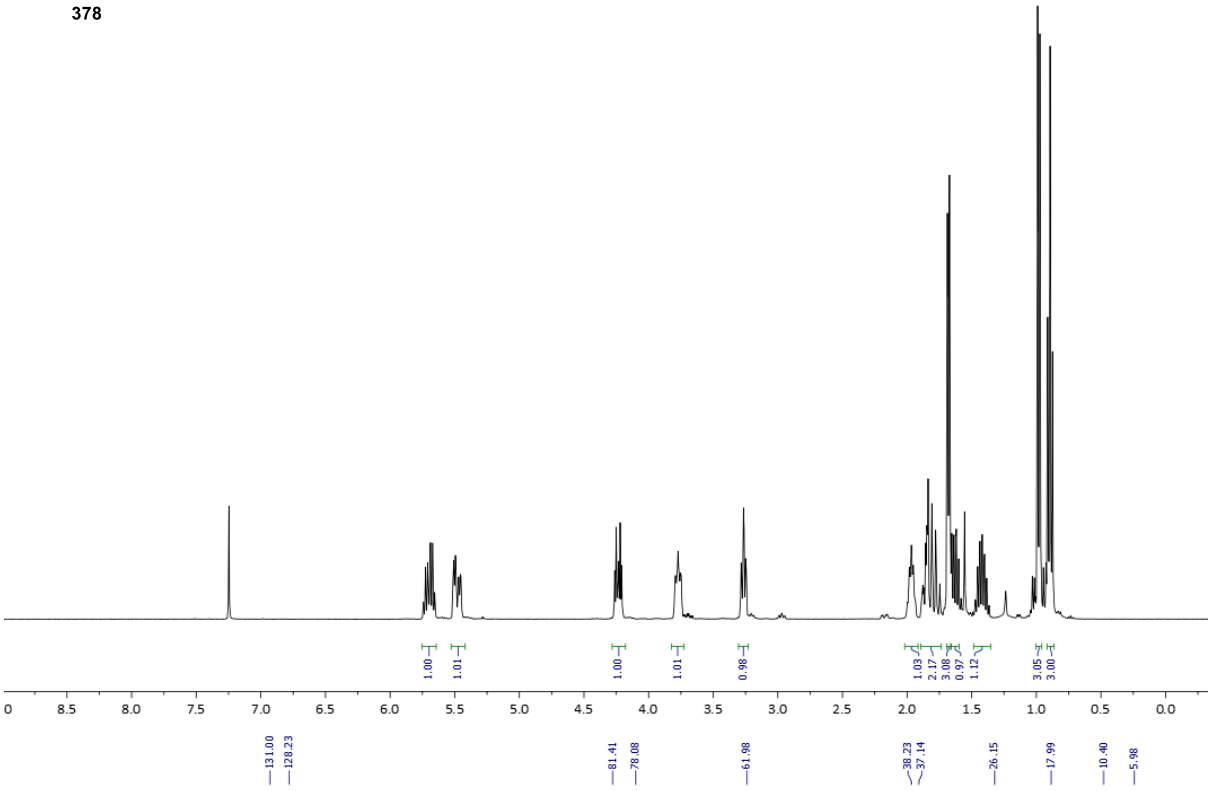
40
30
20
10
0


Cl
O

378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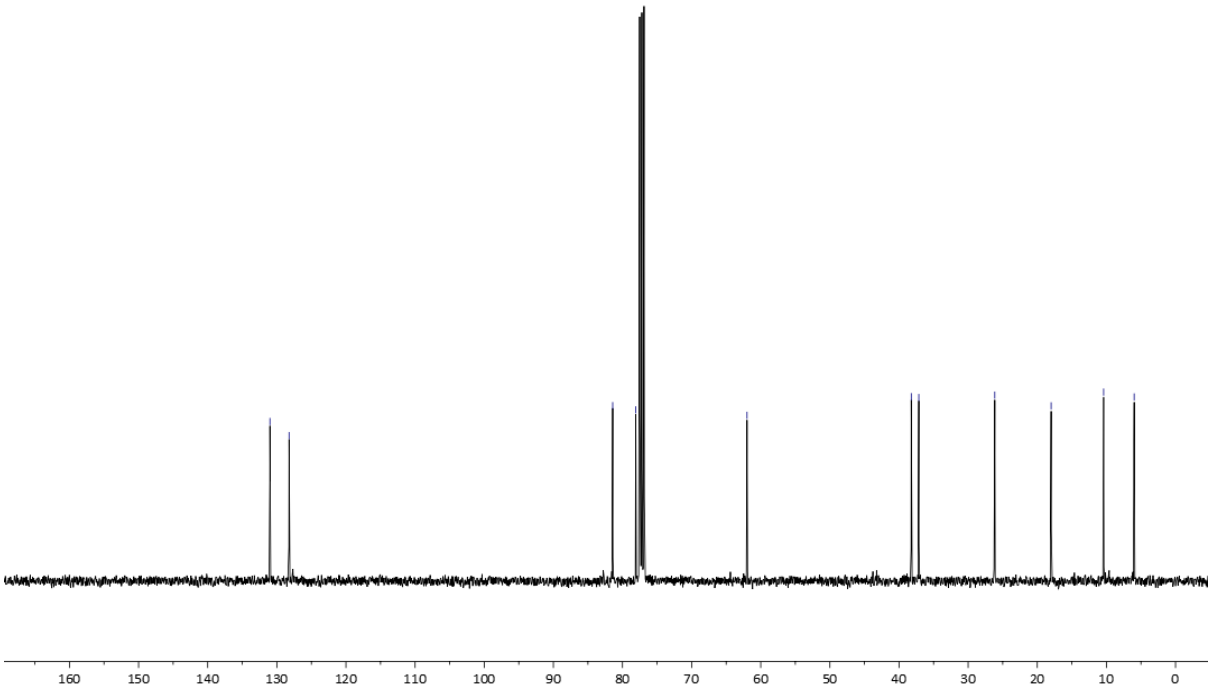
1.01
1.00
1.01
0.98
1.03
2.17
3.08
0.97
1.12
3.05
3.00
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

131.00
128.23
81.41
78.08
61.98
38.23
37.14
26.15
17.99
10.40
5.98


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

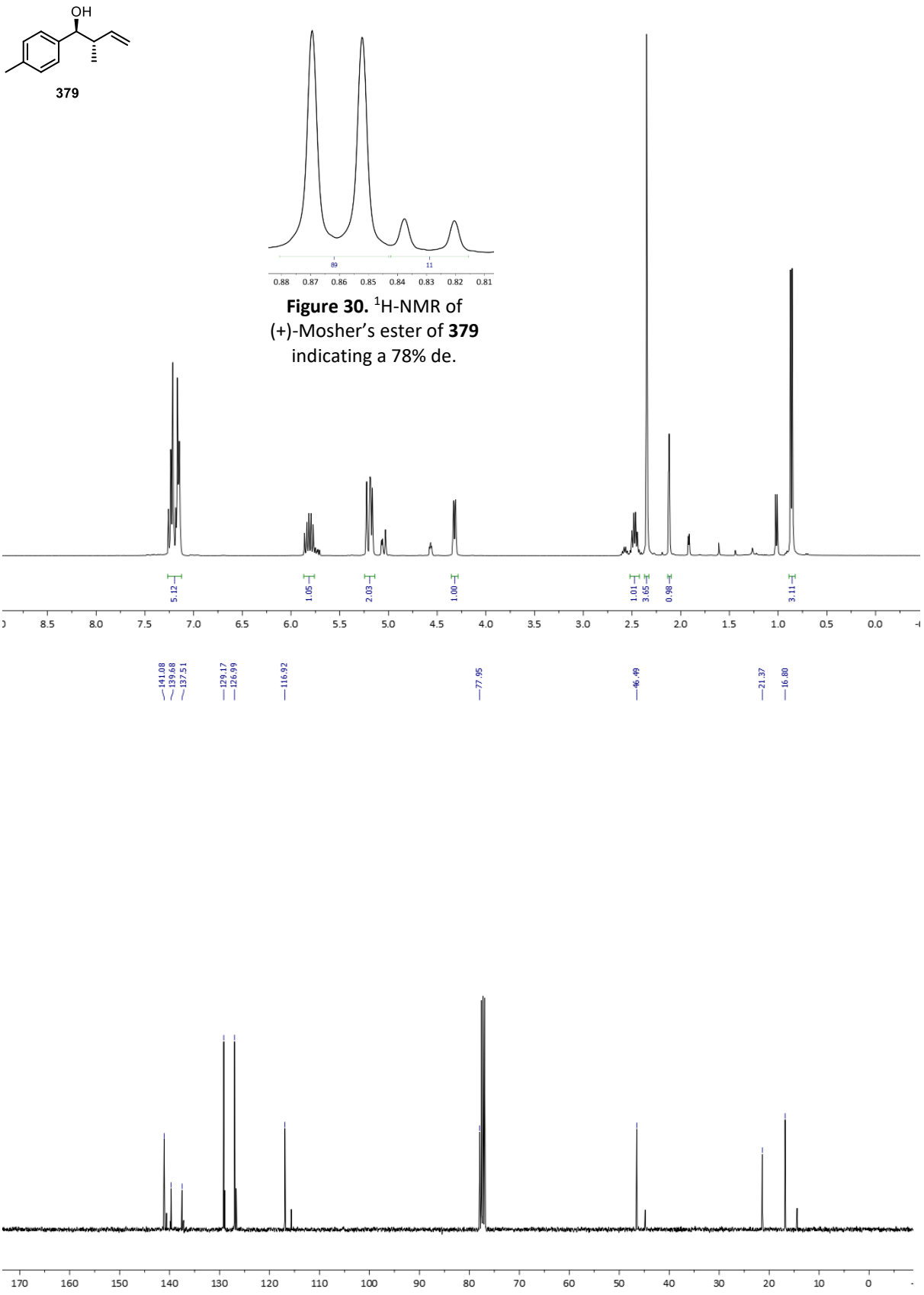
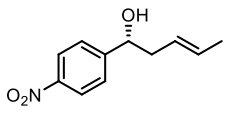


Figure 30. ^{1}H-NMR of (+)-Mosher's ester of **379** indicating a 78% de.



385

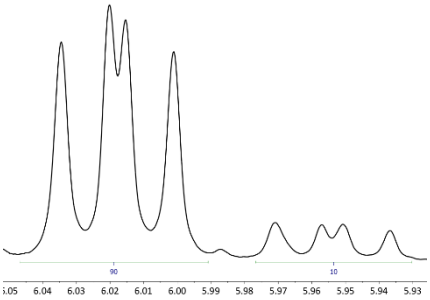
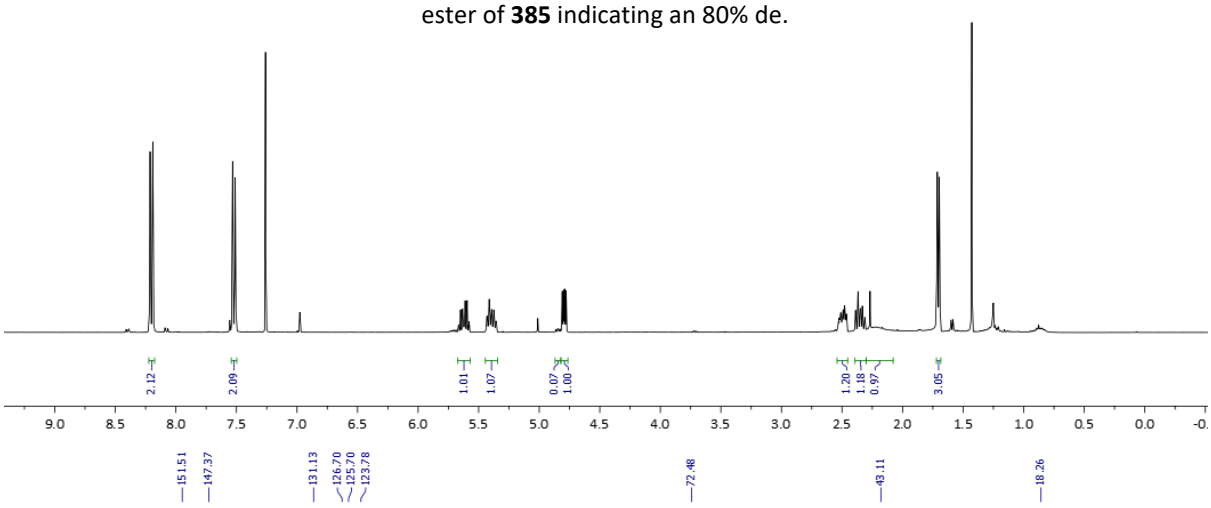
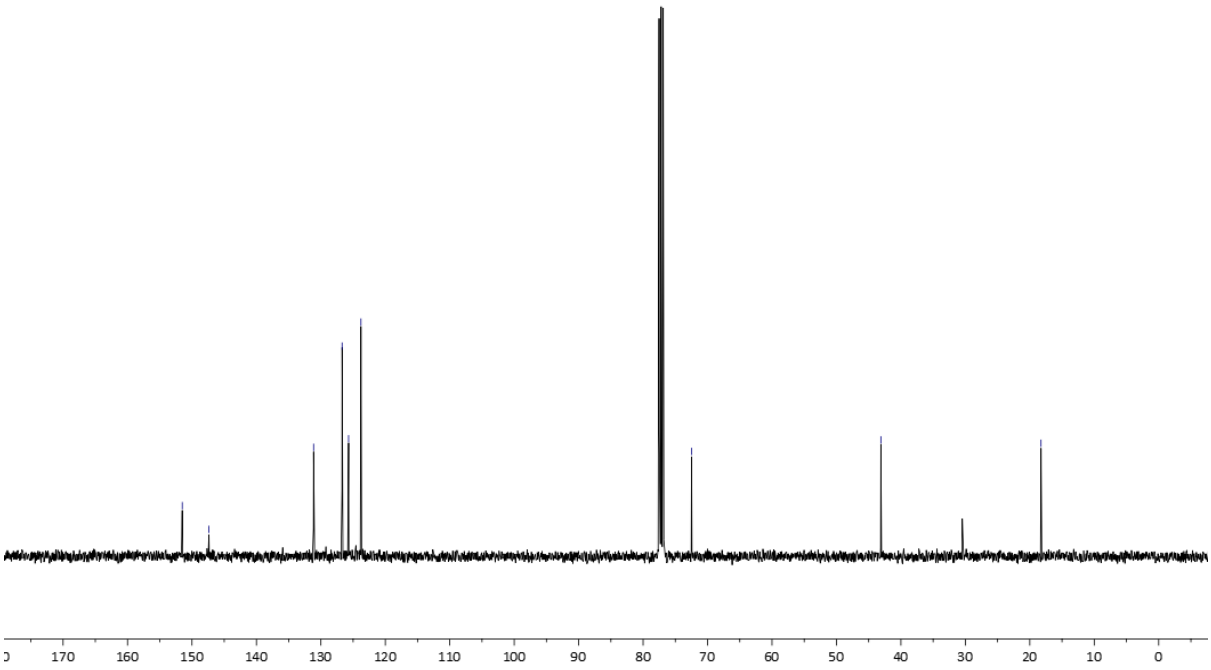
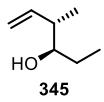


Figure 31. ^{1}H-NMR of (+)-Mosher's ester of **385** indicating an 80% de.






HO

345

4.9
95.1
3.45 3.43 3.41 3.39 3.37 3.35 3.33 3.31 3.29 3.27 3.25
1.00
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1.01
1.00
1.05
2.10
1.13
3.13
3.24
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
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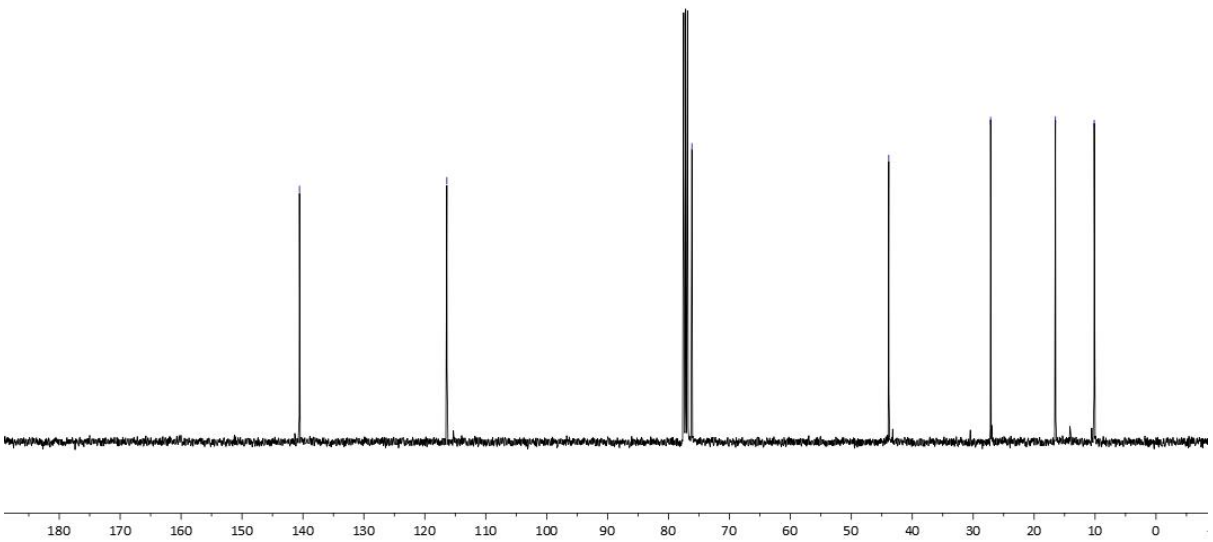
76.17
43.86
27.14
16.50
10.14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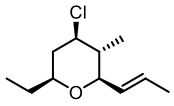
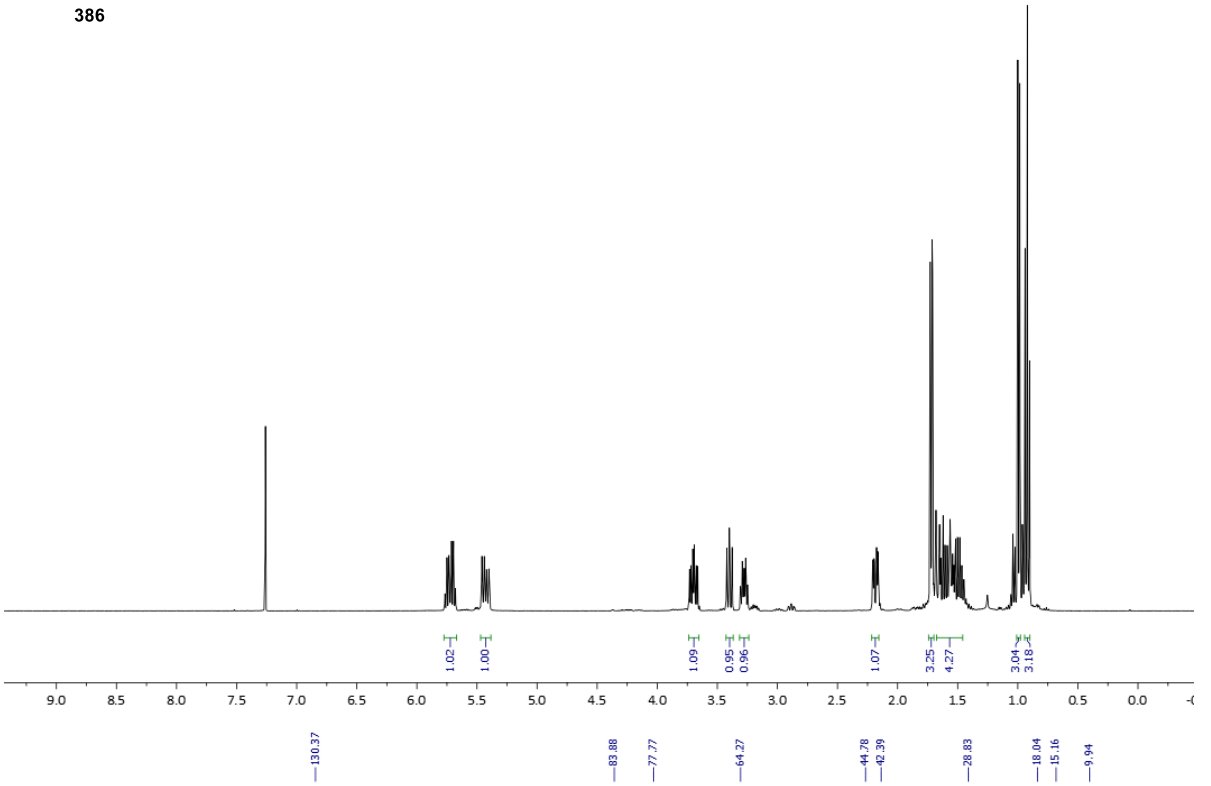

Cl
O

386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0.95
0.96
1.07
3.25
4.27
3.04
3.18
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

130.37
83.88
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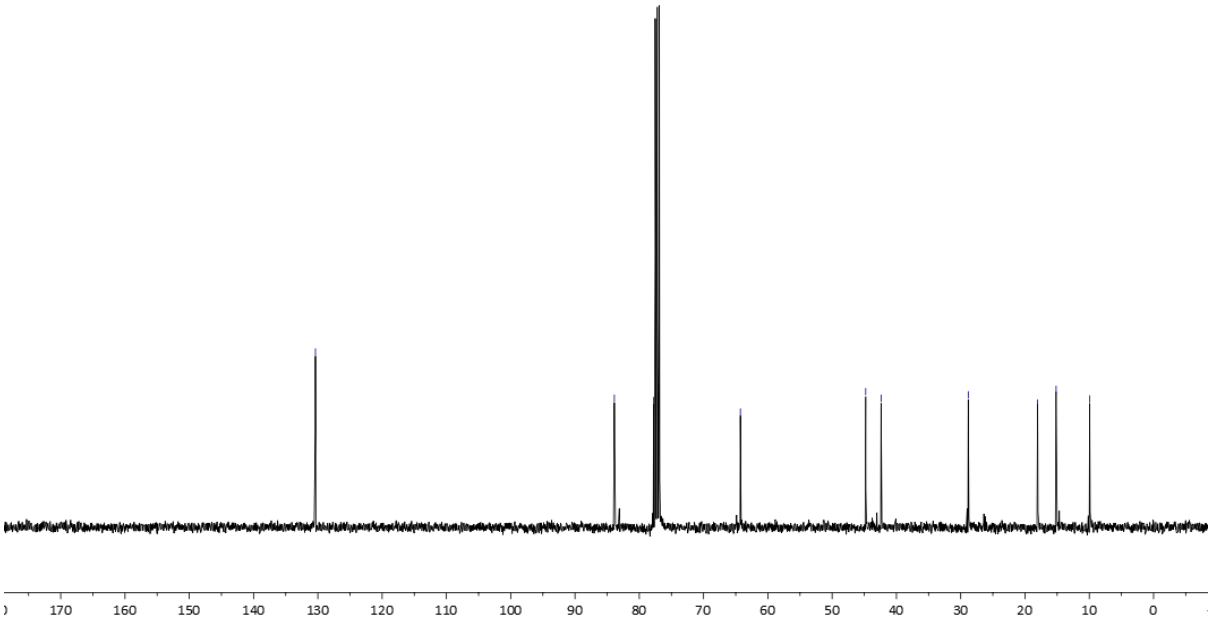
64.27
44.78
42.39
28.83
18.04
15.16
9.94


170
160
150
140
130
120
110
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90
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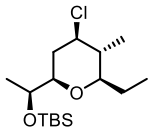
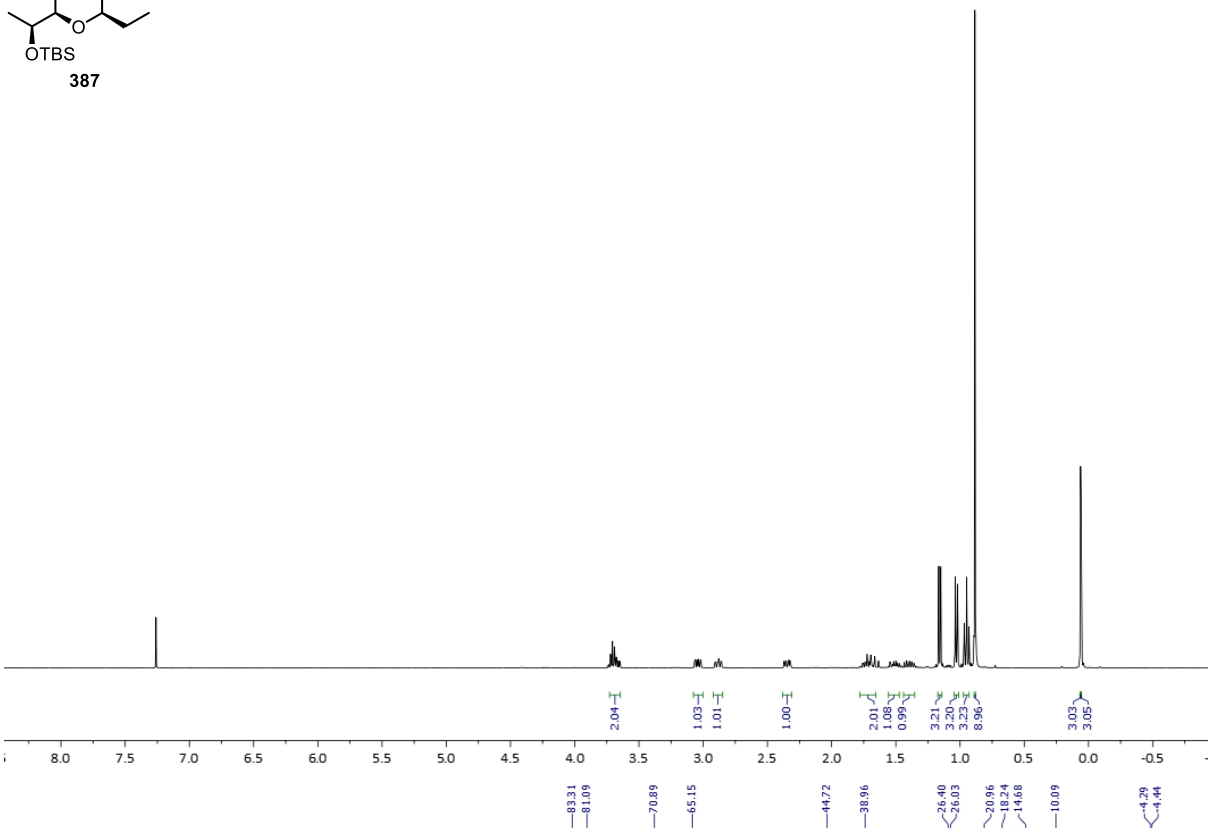
70
60
50
40
30
20
10
0


Cl
O
OTBS

387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1.03
1.01
1.00
2.01
1.08
0.99
3.21
3.20
3.23
8.96
3.03
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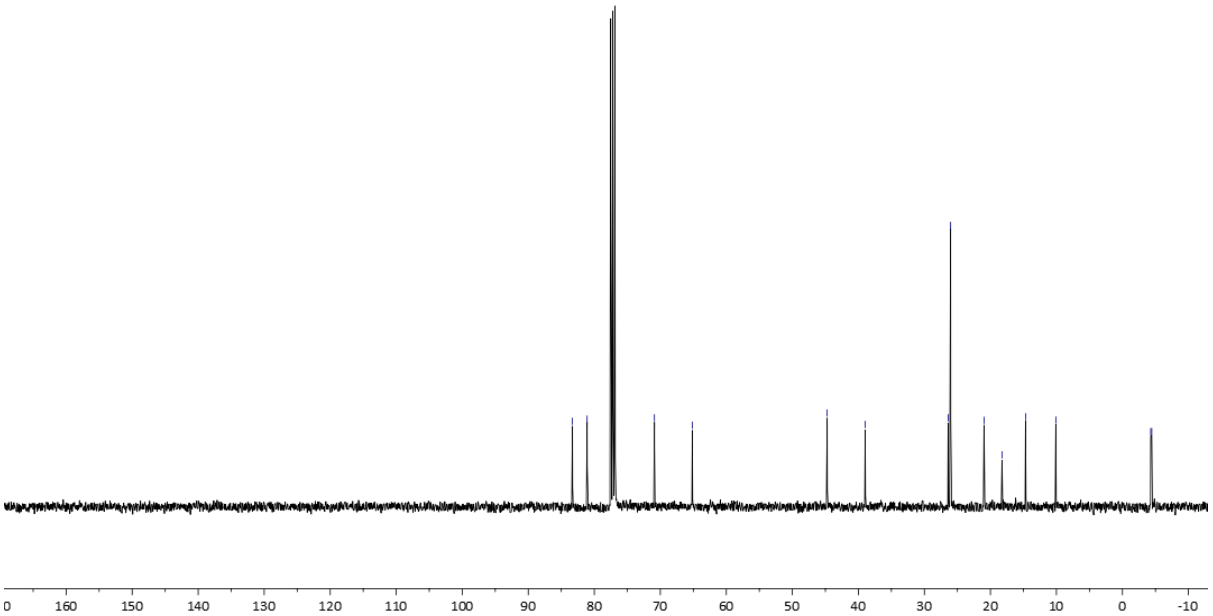
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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81.09
70.89
65.15
44.72
38.96
26.40
26.03
20.96
18.24
14.68
10.09
4.29
4.44
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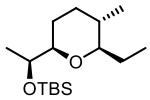
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
OTBS

389

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0.95
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2.02
1.05
3.15
3.46
1.01
3.39
8.94
2.93
3.12
3.06
85.04
82.44
71.63
35.54
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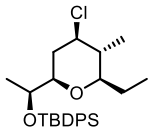
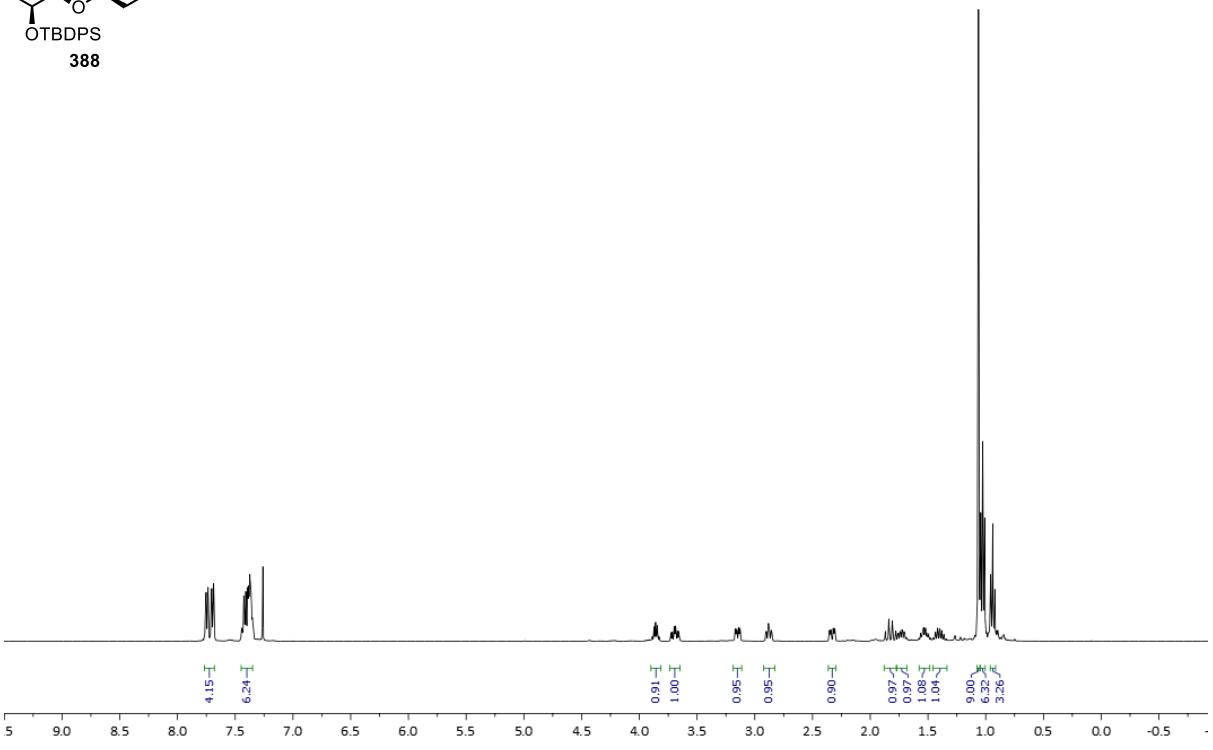
28.32
26.30
26.07
21.24
18.27
18.00
10.32
-4.20
-4.45


Cl
O
OTBDPS

388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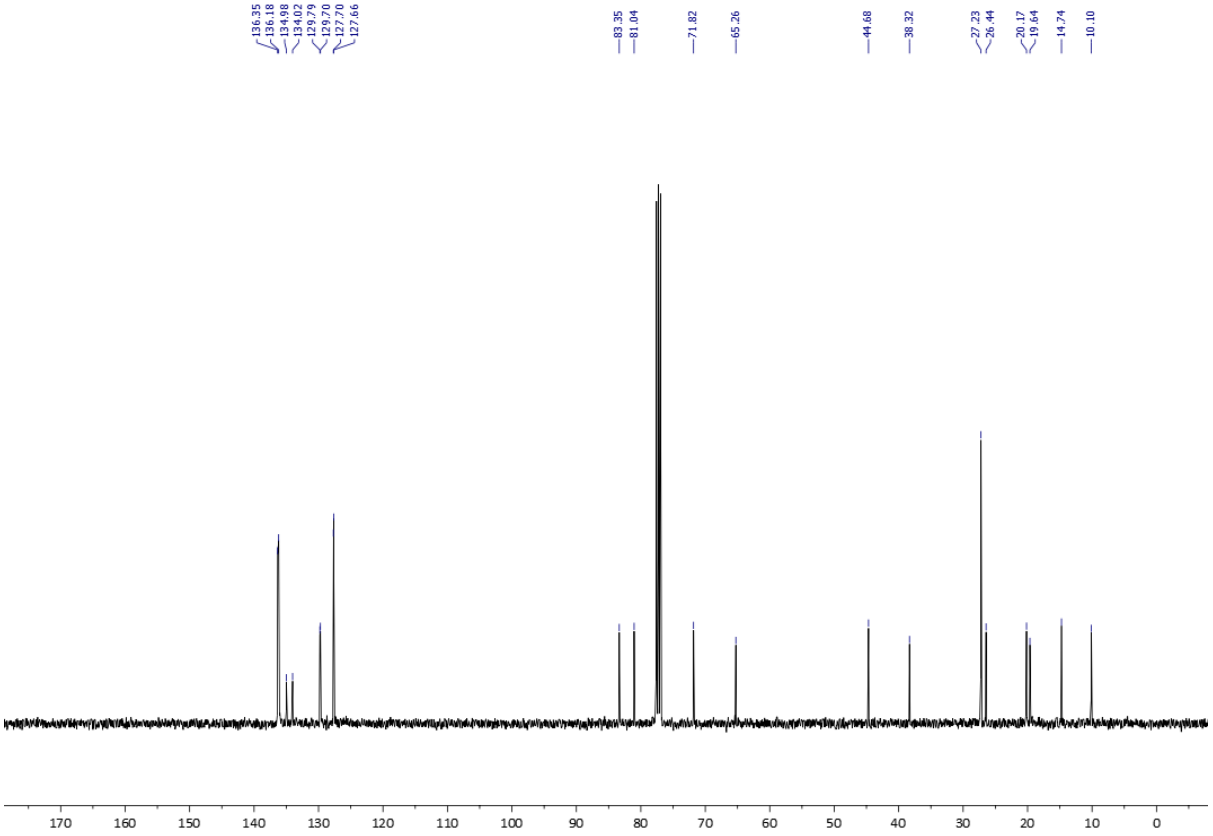
6.24
0.91
1.00
0.95
0.95
0.90
0.97
0.97
1.08
1.04
9.00
6.32
3.26
5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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136.18
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134.02
129.79
129.70
127.70
127.66
83.35
81.04
71.82
65.26
44.68
38.32
27.23
26.44
20.17
19.64
14.74
10.10
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120
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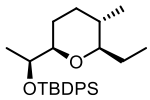
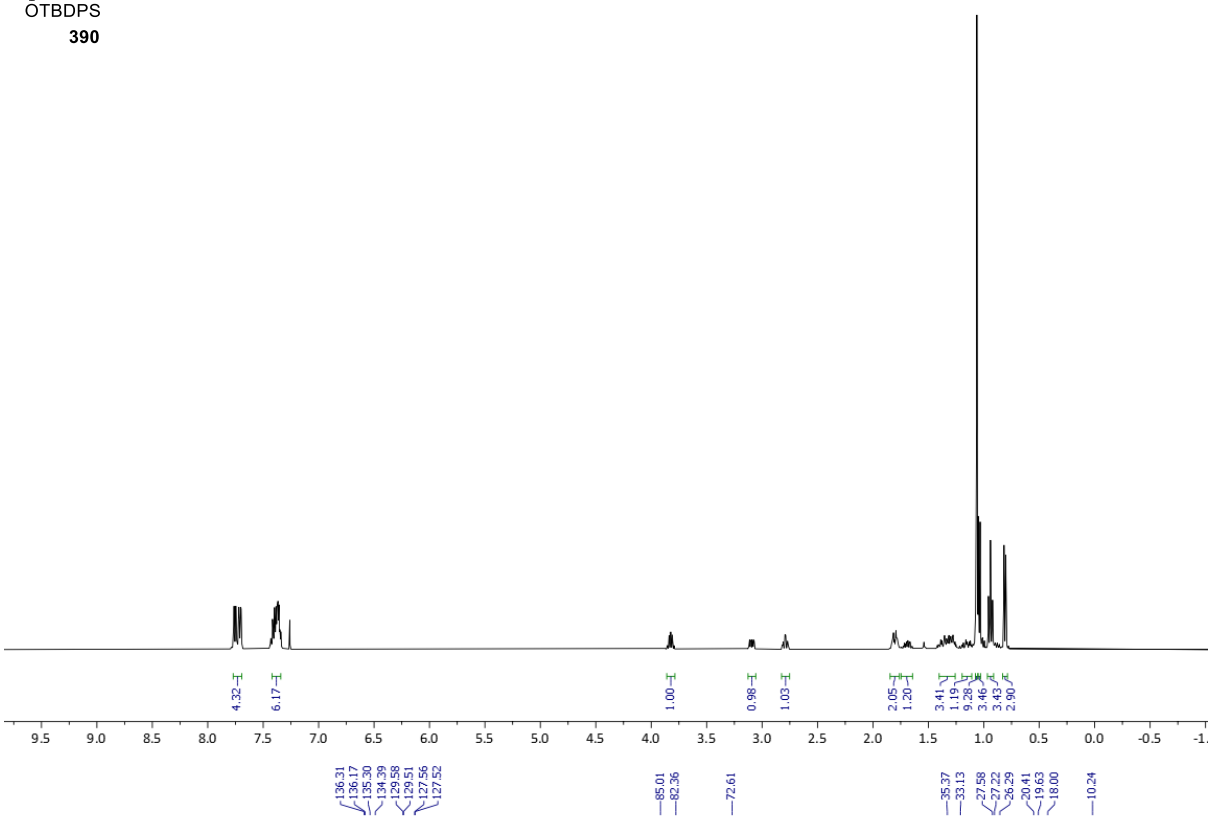
80
70
60
50
40
30
20
10
0


O
OTBDPS

390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0.98
1.03
2.05
1.20
3.41
1.19
9.28
3.46
3.43
2.90
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
136.31
136.17
135.30
134.39
129.58
129.51
127.56
127.52
85.01
82.36
72.61
35.37
33.13
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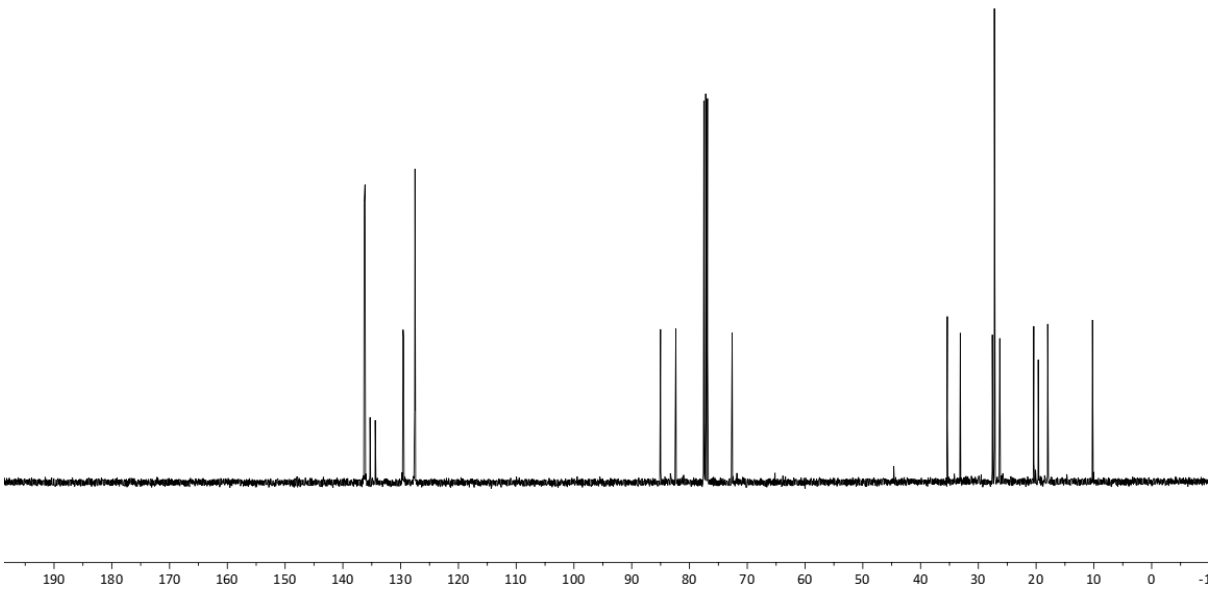
27.22
26.29
20.41
19.63
18.00
10.24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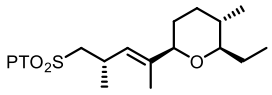
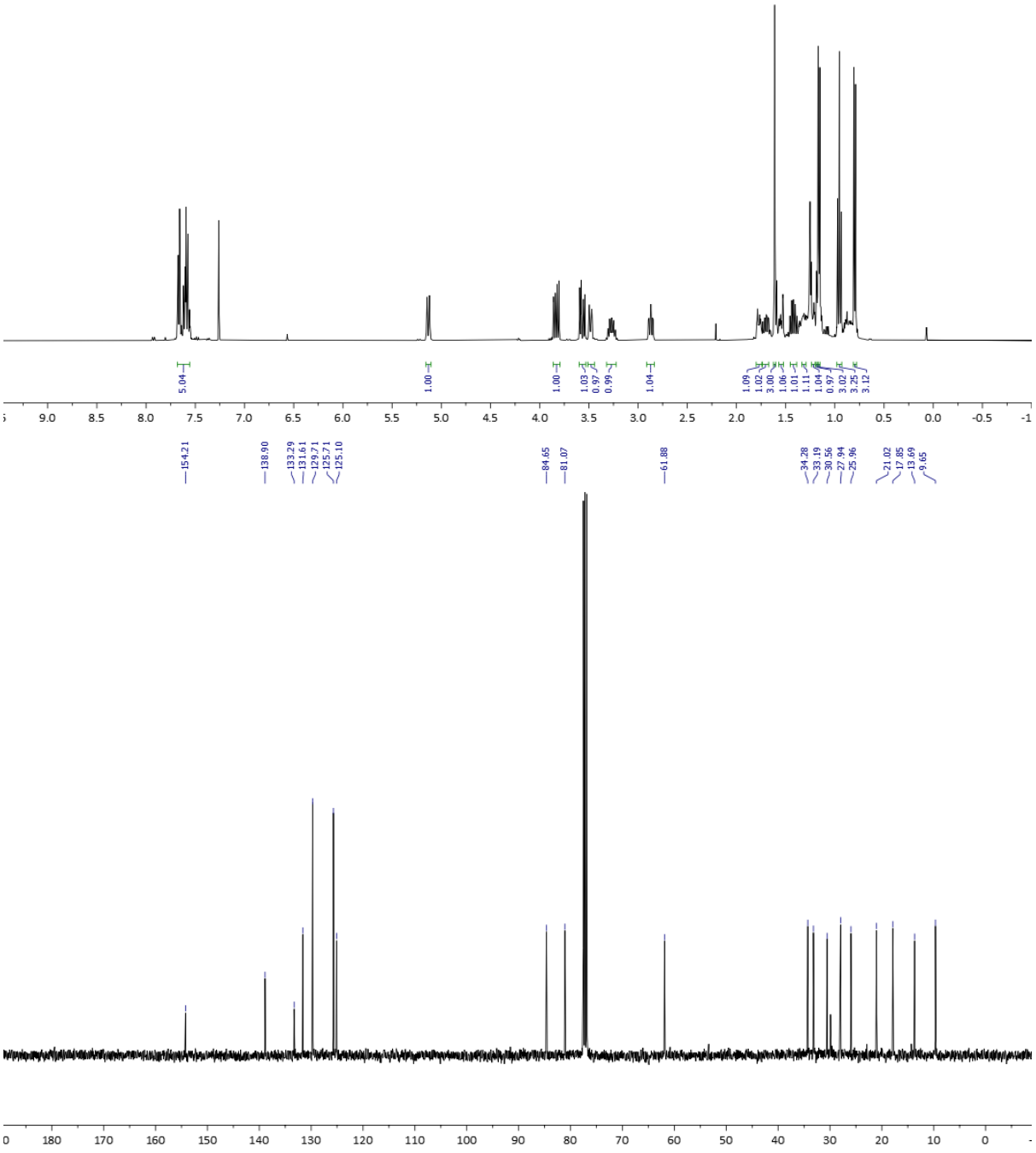

PTO2S
O

331


5.04
1.00
1.00
1.03
0.97
0.99
1.04
1.09
1.02
3.00
1.06
1.01
1.11
1.04
0.97
3.02
3.25
3.12
154.21
138.90
133.29
131.61
129.71
125.71
125.10
84.65
81.07
61.88
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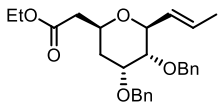
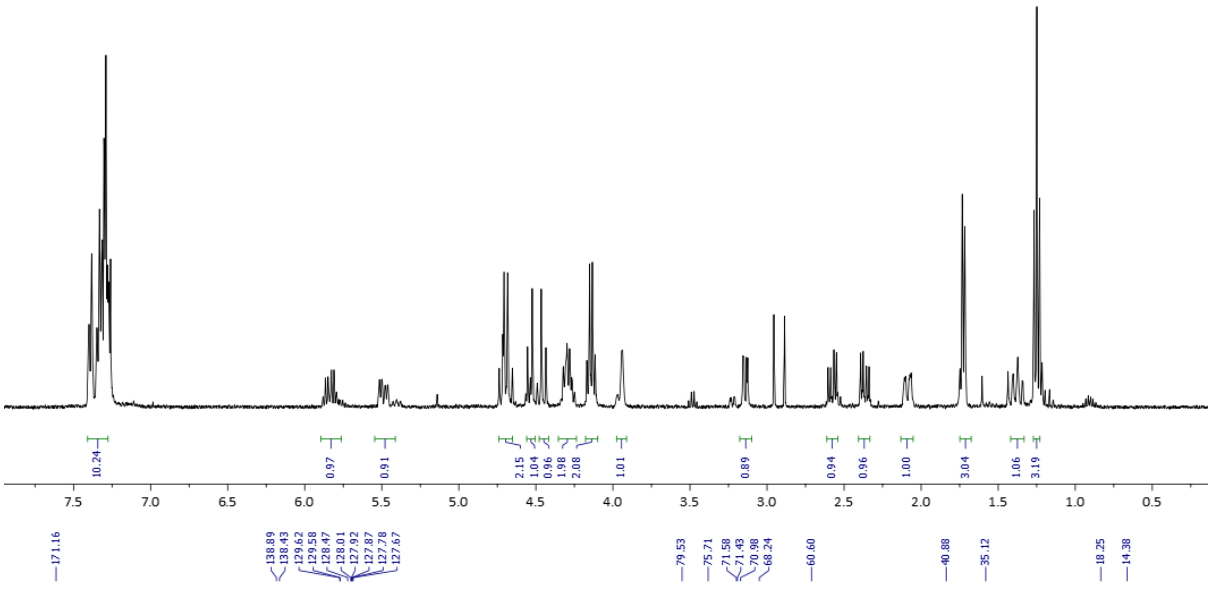
25.96
21.02
17.85
13.69
9.65


EtO
O
O
OBn
OBn

393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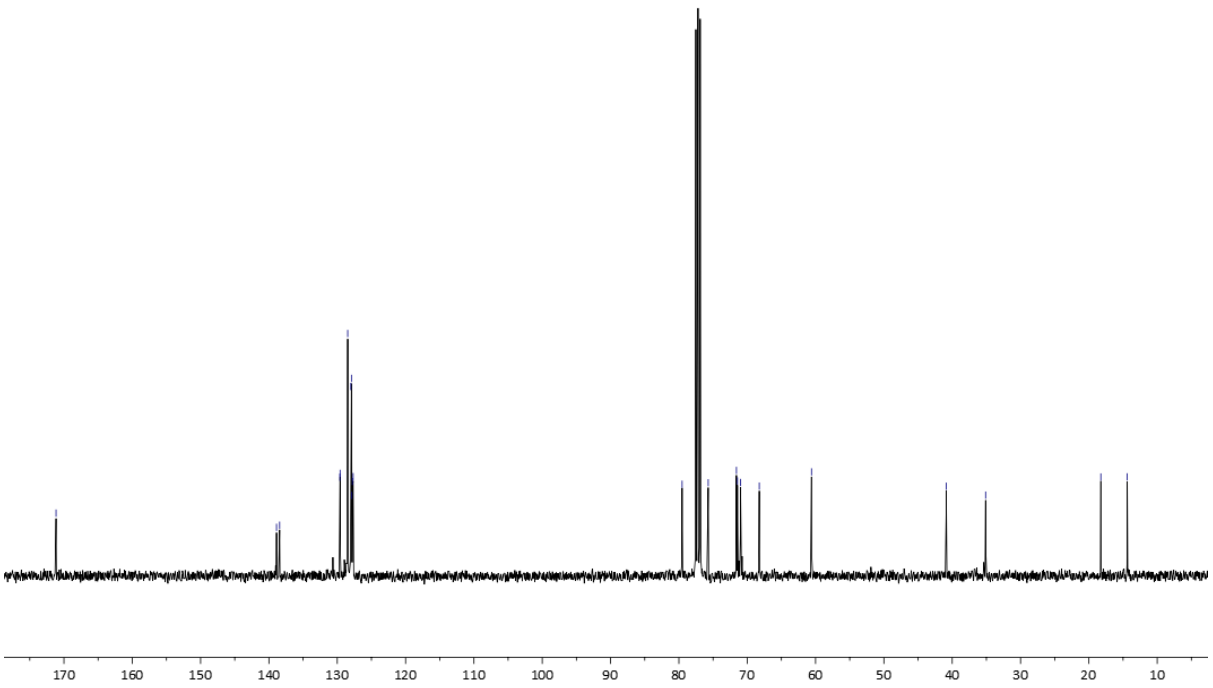
0.91
2.15
1.04
0.96
1.98
2.08
1.01
0.89
0.94
0.96
1.00
3.04
1.06
3.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

171.16
138.89
138.43
129.62
129.58
128.47
128.01
127.92
127.87
127.78
127.67
79.53
75.71
71.58
71.43
70.98
68.24
60.60
40.88
35.12
18.25
14.38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20
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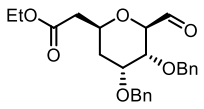
EtO
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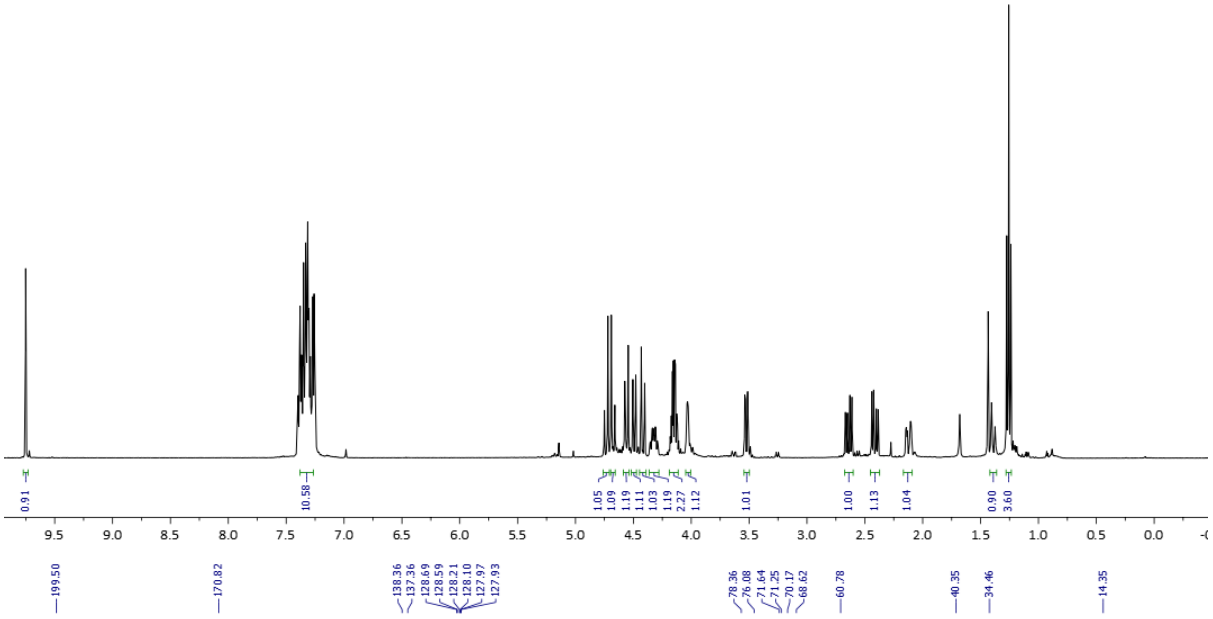
O
O
OBn
OBn

394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1.19
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1.12
1.01
1.00
1.13
1.04
0.90
3.60
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
199.50
170.82
138.36
137.36
128.69
128.59
128.21
128.10
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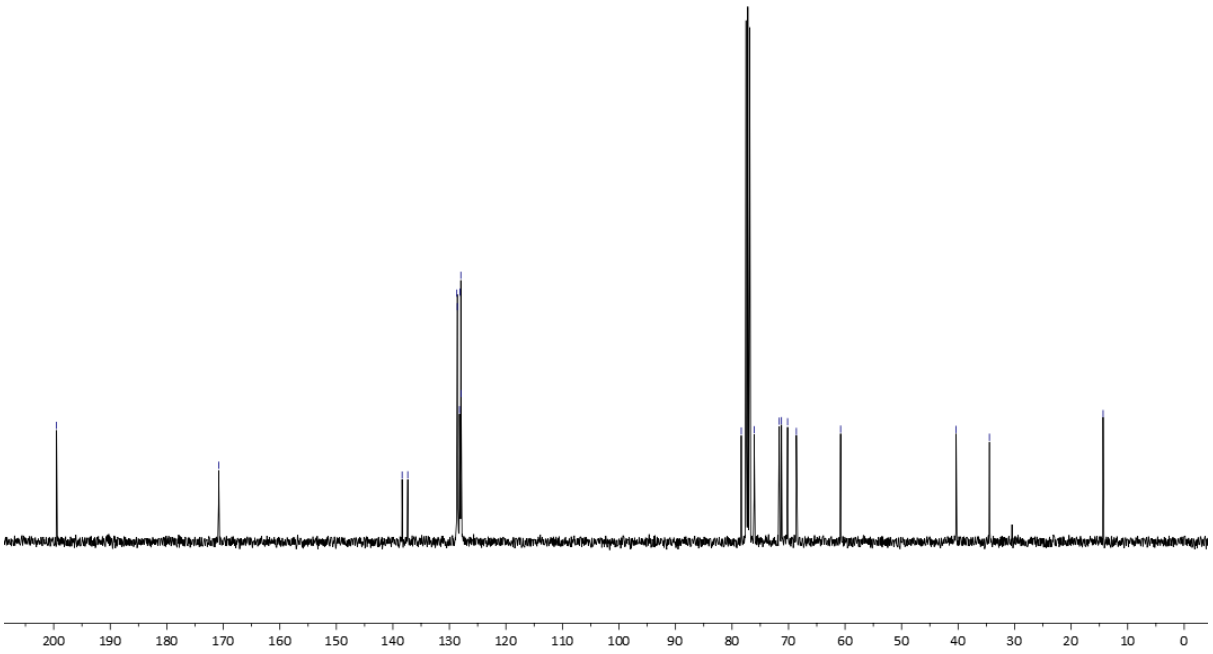
14.35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30
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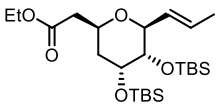
10
0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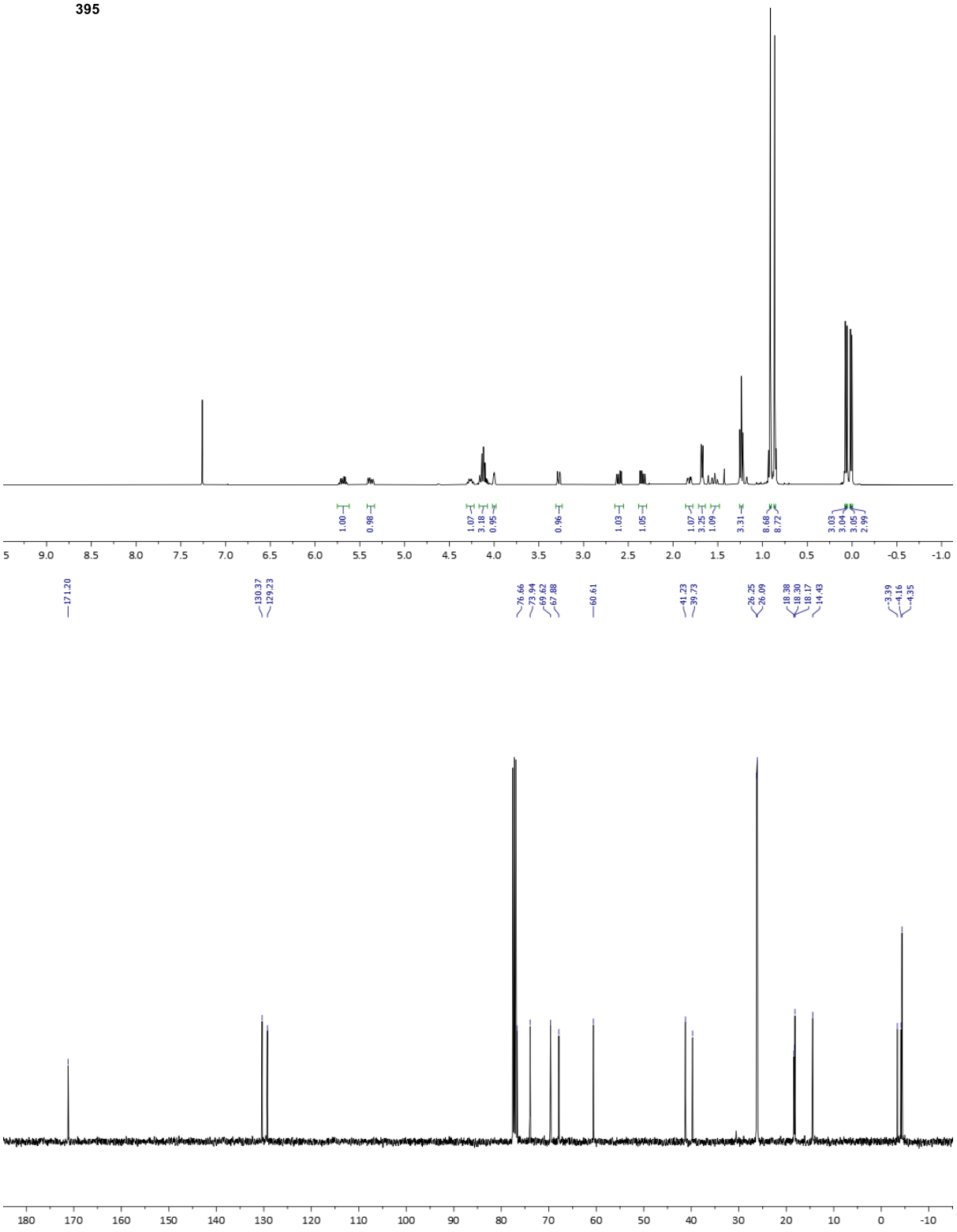
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3.25
1.09
3.31
8.68
8.72
3.03
3.04
3.05
2.99
5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
171.20
130.37
129.23
76.66
73.94
69.62
67.88
60.61
41.23
39.73
26.25
26.09
18.38
18.30
18.17
14.43
-3.39
-4.16
-4.35
180
170
160
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100
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30
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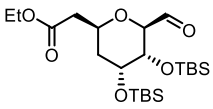
-10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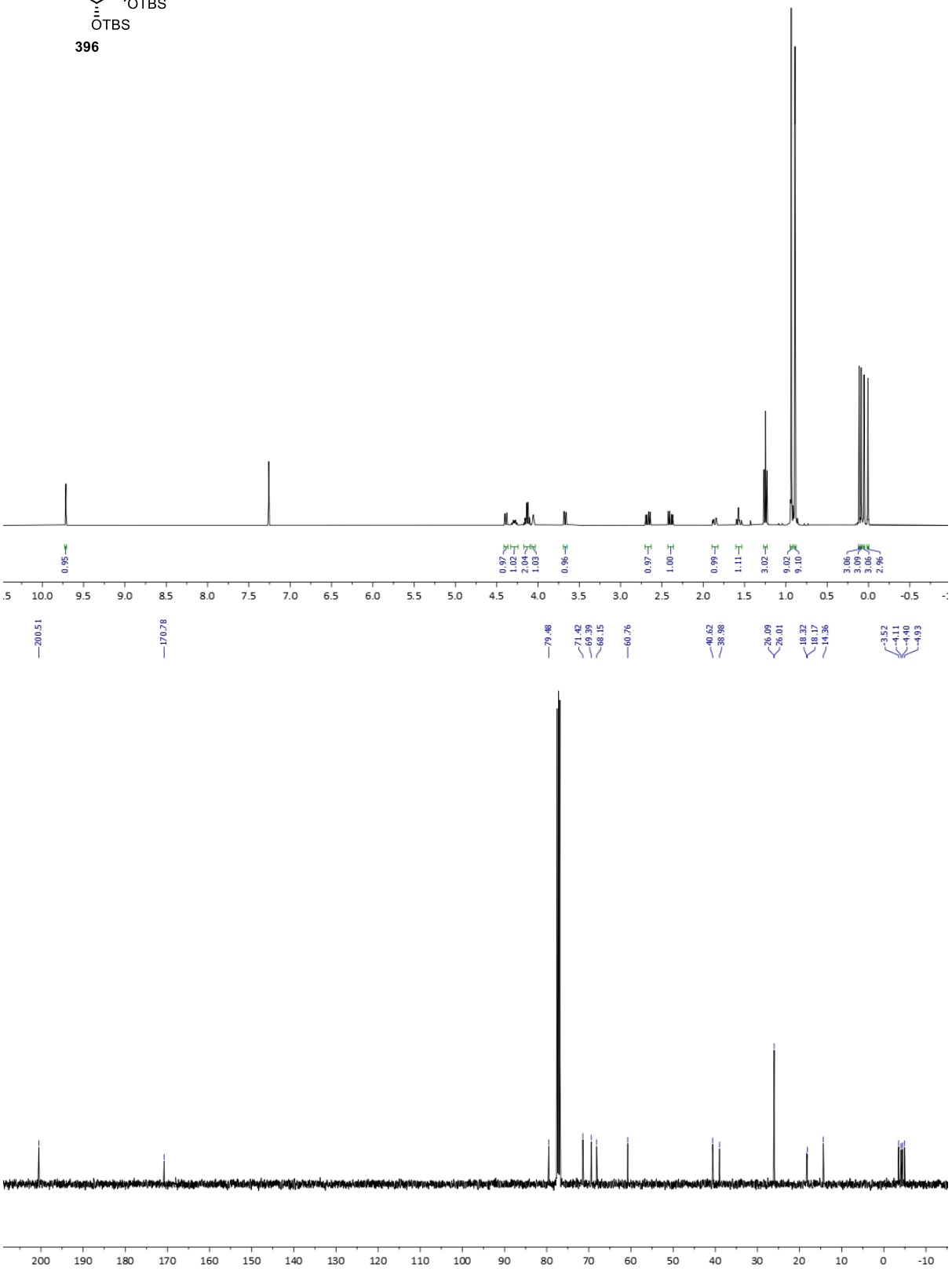
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0.99
1.11
3.02
9.02
9.10
3.06
3.09
3.06
2.96
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
200.51
170.78
79.48
71.42
69.39
68.15
60.76
40.62
38.98
26.09
26.01
18.32
18.17
14.36
-3.52
-4.11
-4.40
-4.93
200
190
180
170
160
150
140
130
120
110
100
90
80
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60
50
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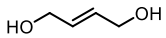
20
10
0
-10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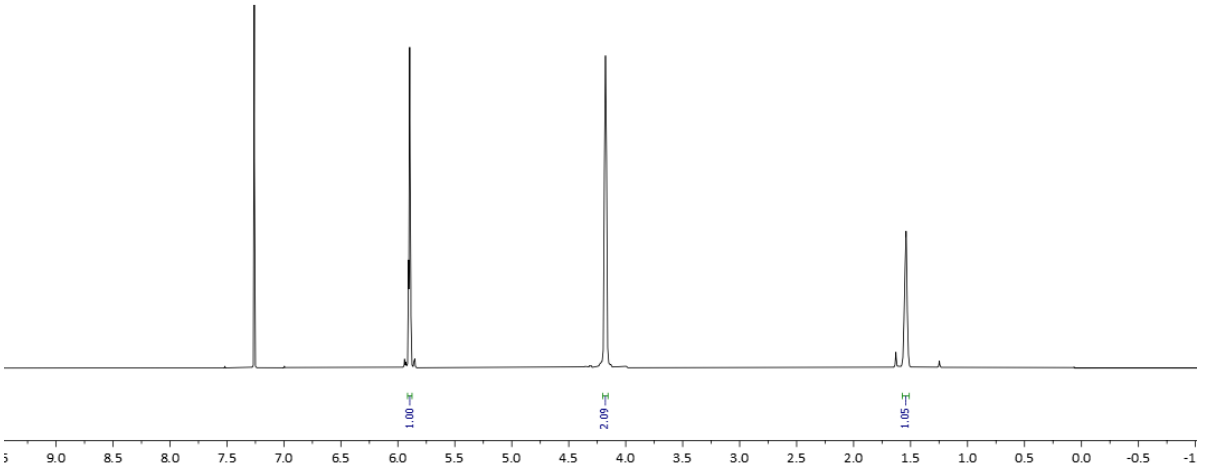
OH

402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2.09
1.05
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
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2.0
1.5
1.0
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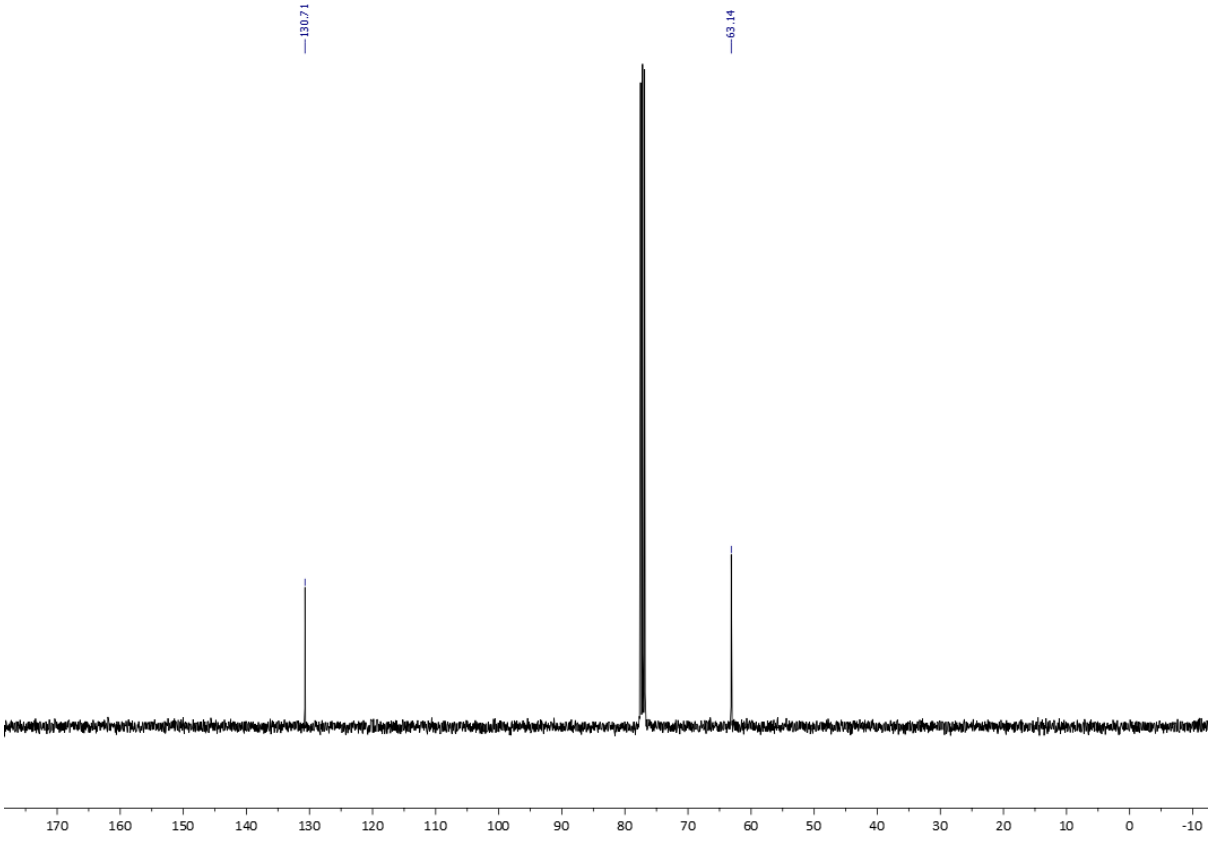
0.0
-0.5
-1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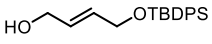
-10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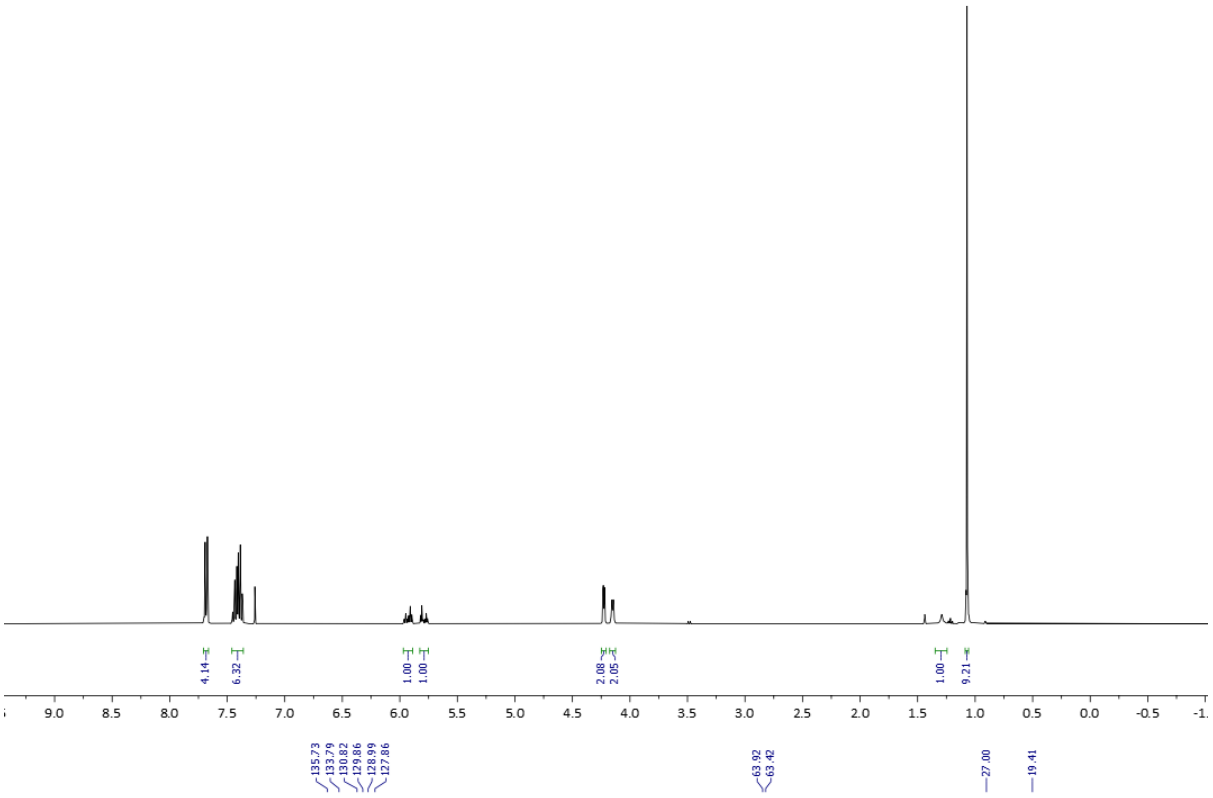
392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6.32
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2.08
2.05
1.00
9.21
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8.5
8.0
7.5
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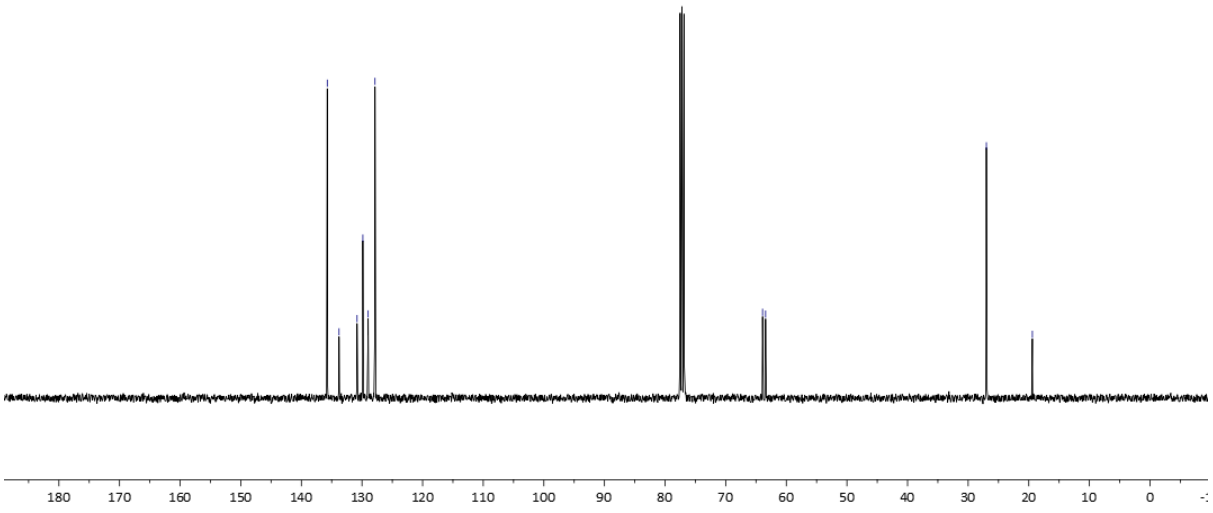
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

135.73
133.79
130.62
129.86
128.99
127.86
63.92
63.42
27.00
19.41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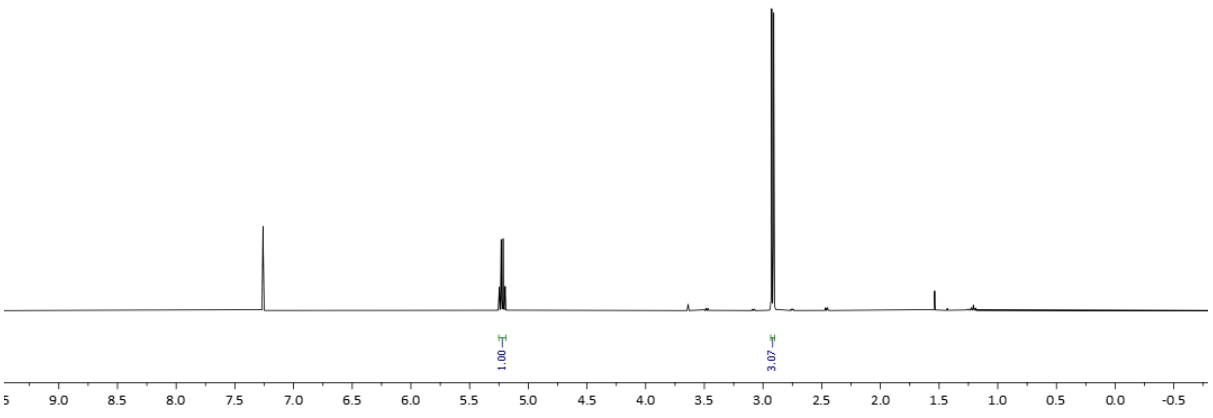
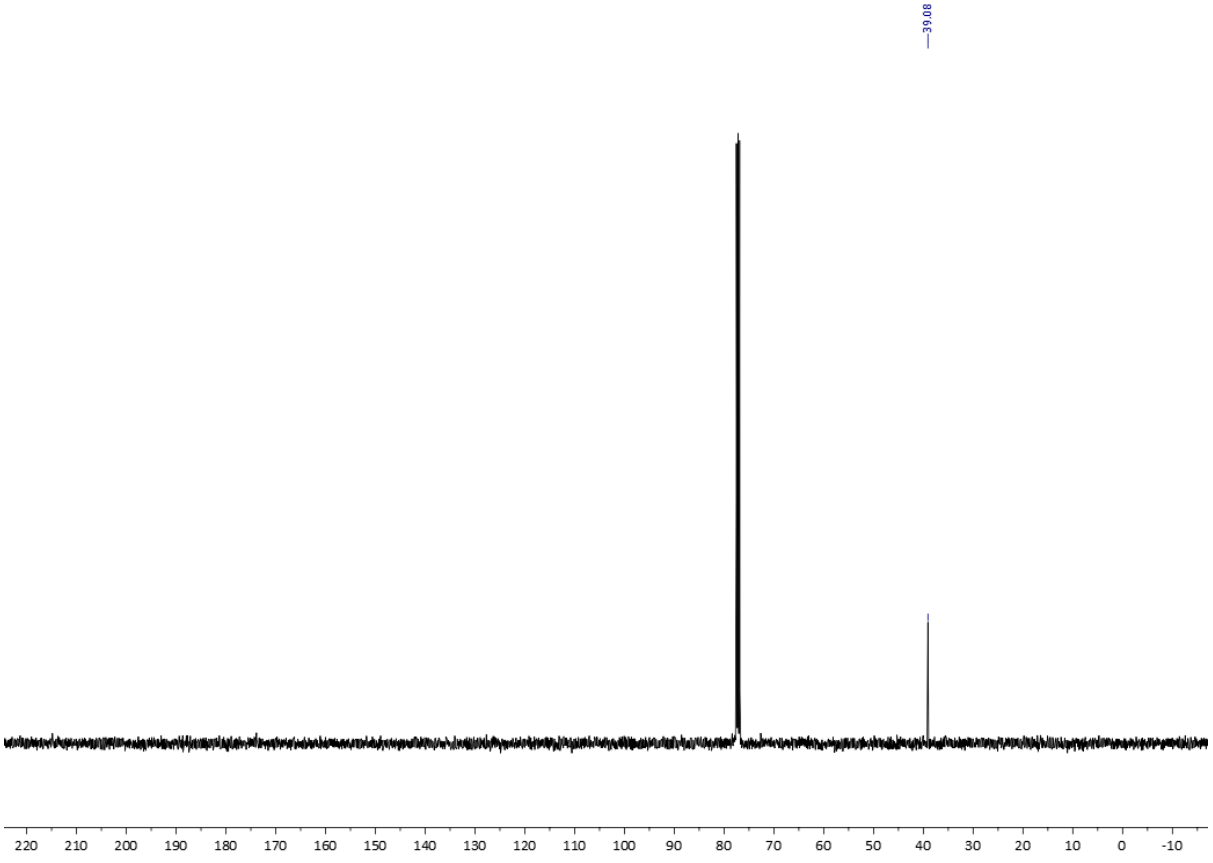
30
20
10
0

CH_3CHI_2

430


1.00
3.07
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


39.08
220
210
200
190
180
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140
130
120
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100
90
80
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60
50
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30
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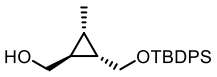
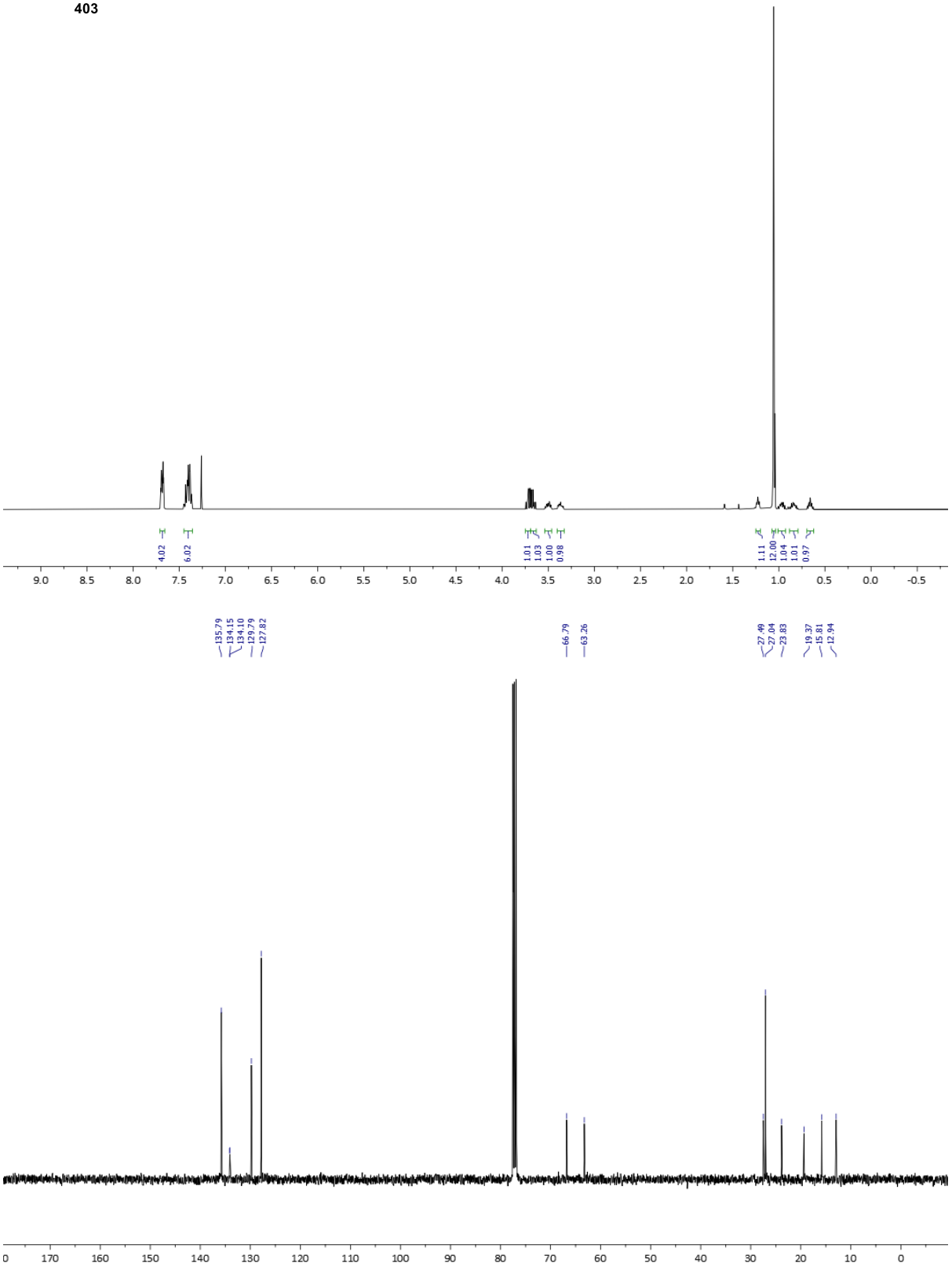
10
0
-10


HO
OTBDPS

403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1.03
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1.11
12.00
1.04
1.01
0.97
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
135.79
134.15
134.10
129.79
127.82
66.79
63.26
27.49
27.04
23.83
19.37
15.81
12.94
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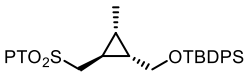
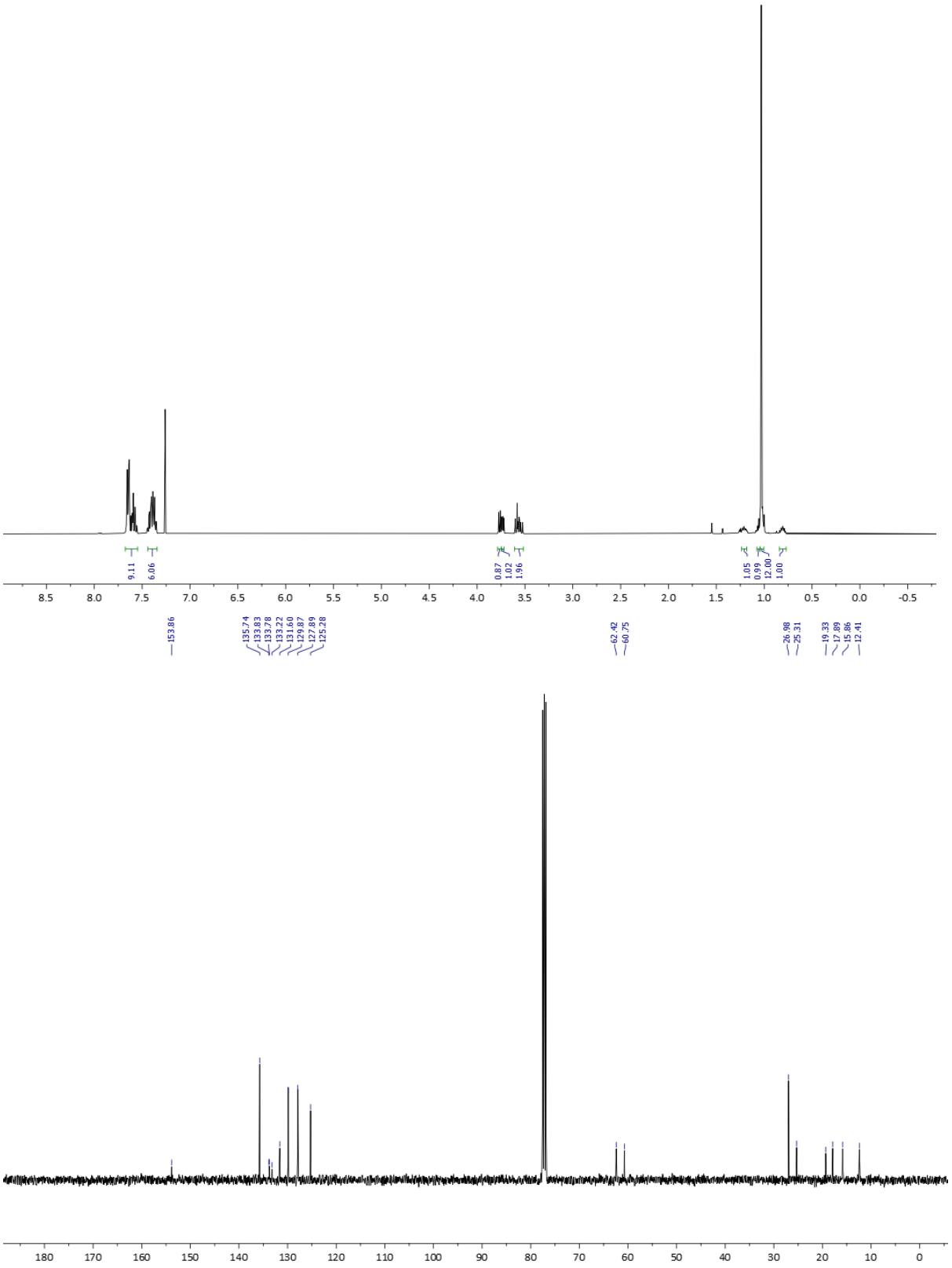
110
100
90
80
70
60
50
40
30
20
10
0


PTO2S
OTBDPS

27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12.00
1.00
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8.0
7.5
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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
153.86
135.74
133.83
133.78
133.22
131.60
129.87
127.89
125.28
62.42
60.75
26.98
25.31
19.33
17.89
15.86
12.41
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150
140
130
120
110
100
90
80
70
60
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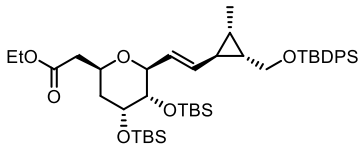
30
20
10
0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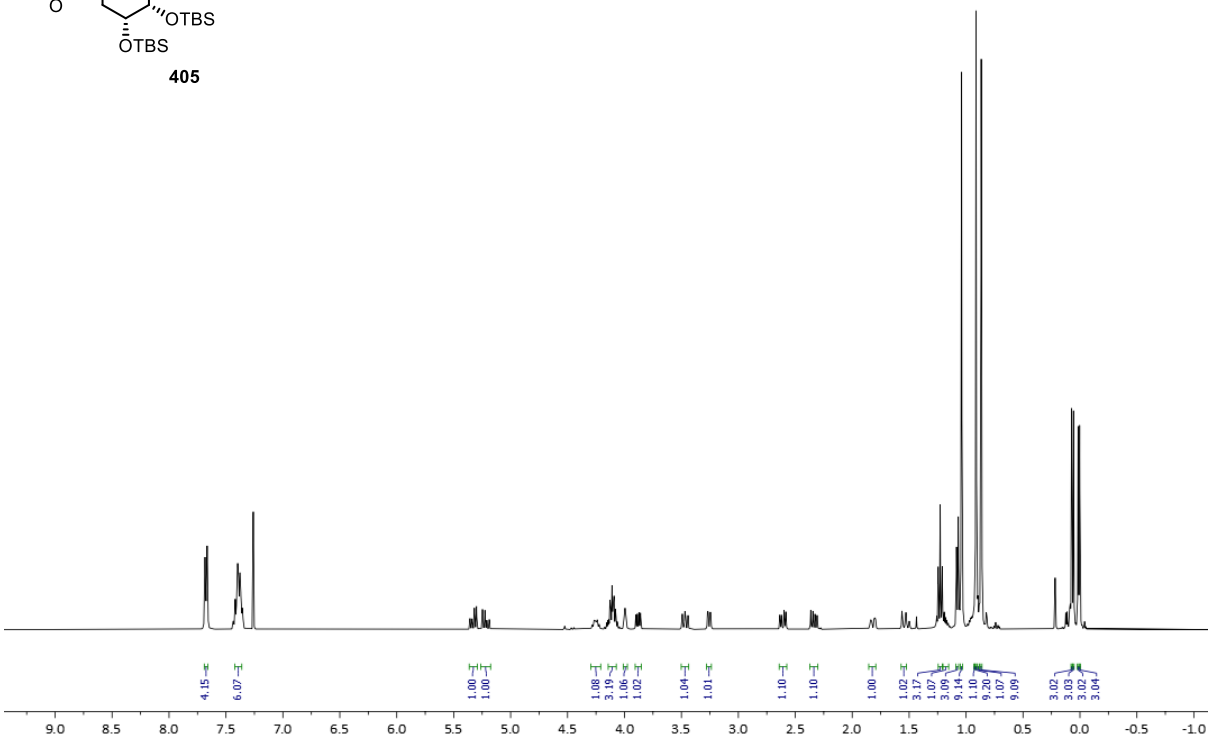
OTBS
OTBS
OTBDPS

405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1.00
1.08
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1.06
1.02
1.04
1.01
1.10
1.10
1.00
1.02
3.17
1.07
3.09
9.14
1.10
9.20
1.07
9.09
3.02
3.03
3.02
3.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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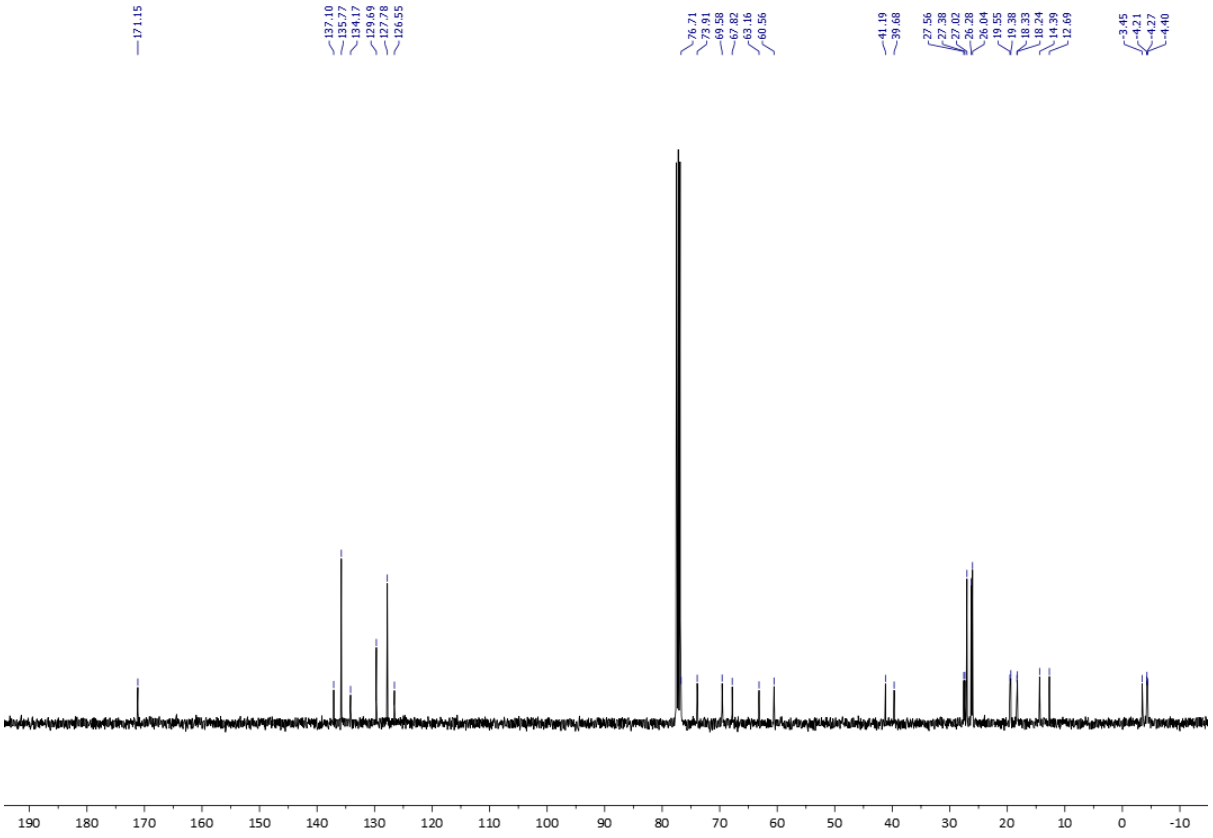
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0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127.78
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69.58
67.82
63.16
60.56
41.19
39.68
27.56
27.38
27.02
26.28
26.04
19.55
19.38
18.33
18.24
14.39
12.69
-3.45
-4.21
-4.27
-4.40
190
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120
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100
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80
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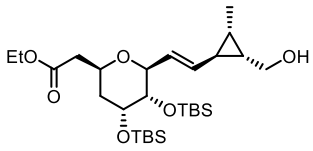
-10


EtO
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OTBS
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406

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1.00
1.03
1.00
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1.03
1.05
1.03
1.10
1.14
3.12
1.11
3.03
2.06
9.13
9.11
3.00
3.03
6.04
9.0
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8.0
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7.0
6.5
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4.5
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2.5
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73.96
69.54
67.84
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60.58
41.14
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27.99
27.55
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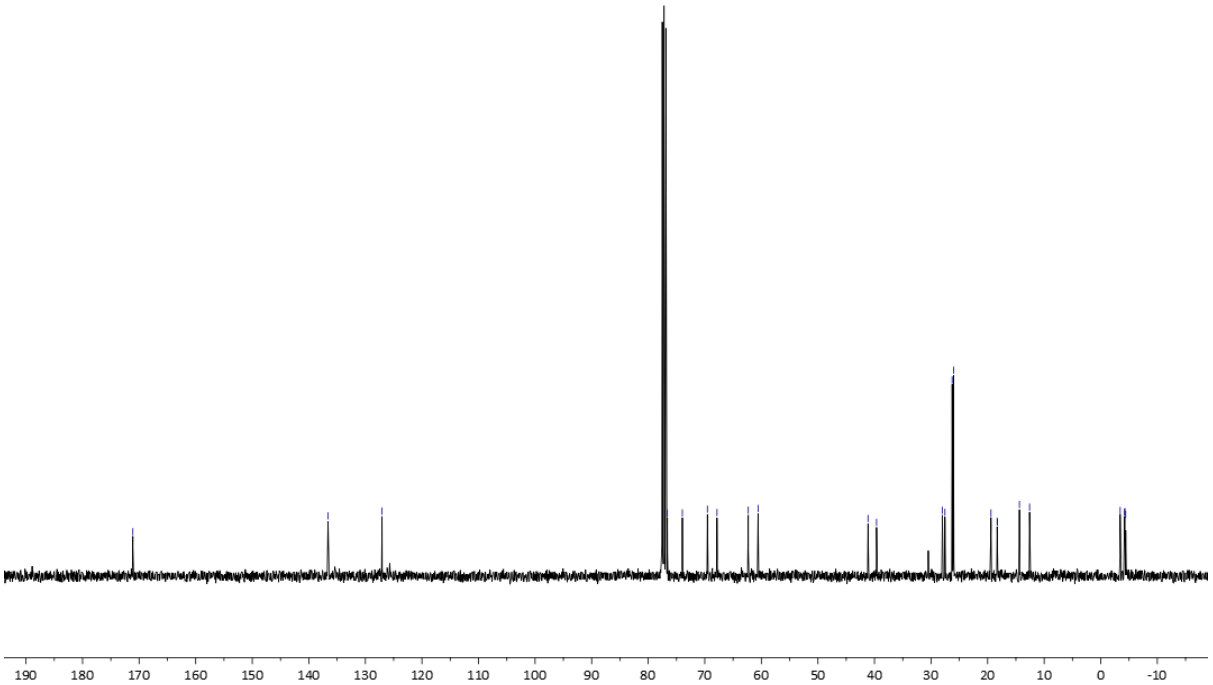
190
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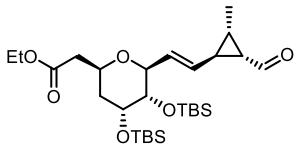
EtO
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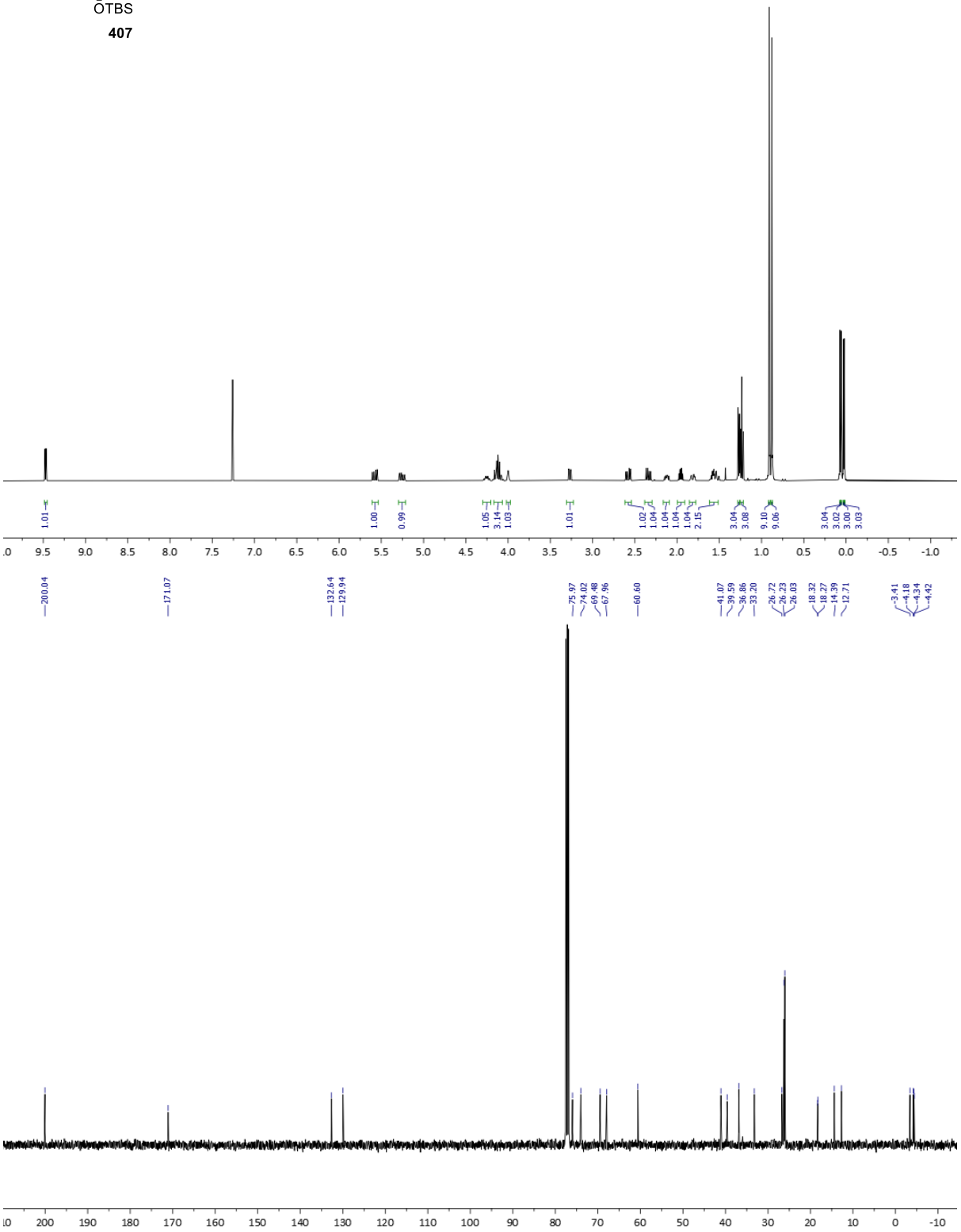
O
OTBS
OTBS
O

407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1.01
1.02
1.04
1.04
1.04
2.15
3.04
3.08
9.10
9.06
3.04
3.02
3.00
3.03
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
200.04
171.07
132.64
129.94
75.97
74.02
69.48
67.96
60.60
41.07
39.59
36.86
33.20
26.72
26.23
26.03
18.32
18.27
14.39
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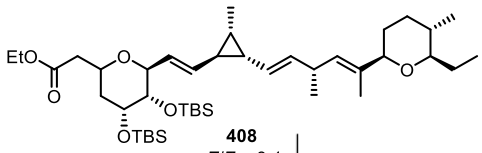
-3.41
-4.18
-4.34
-4.42
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



408

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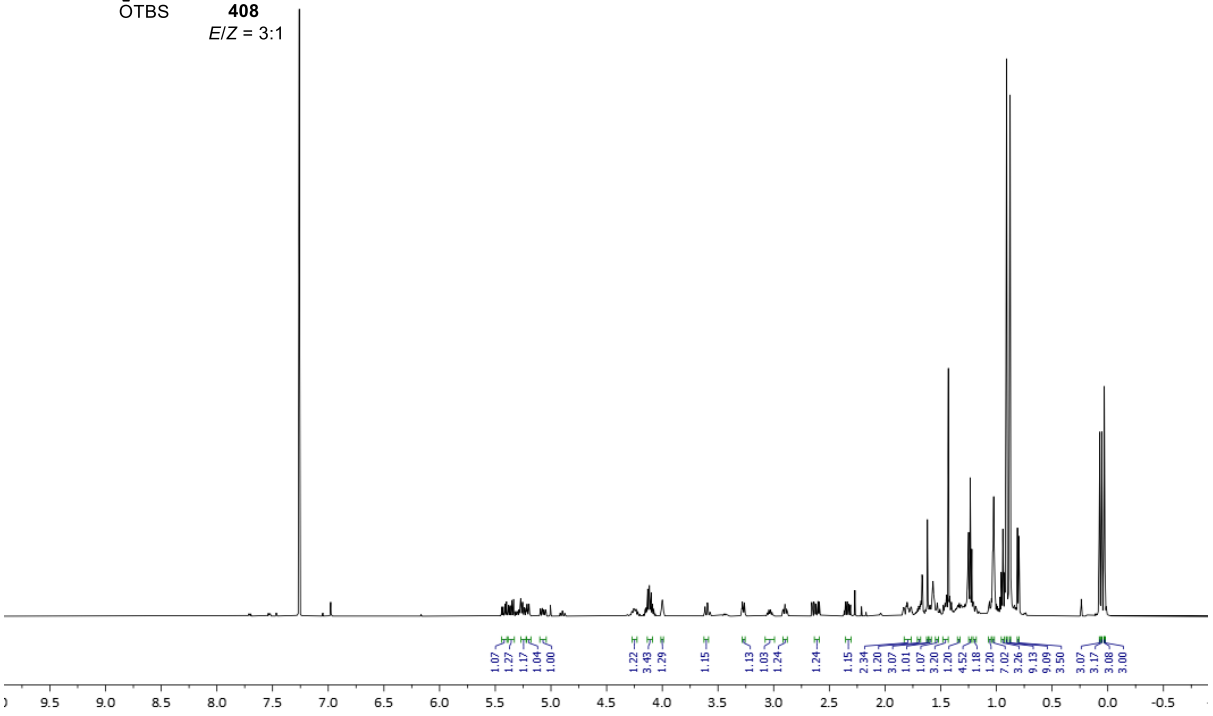

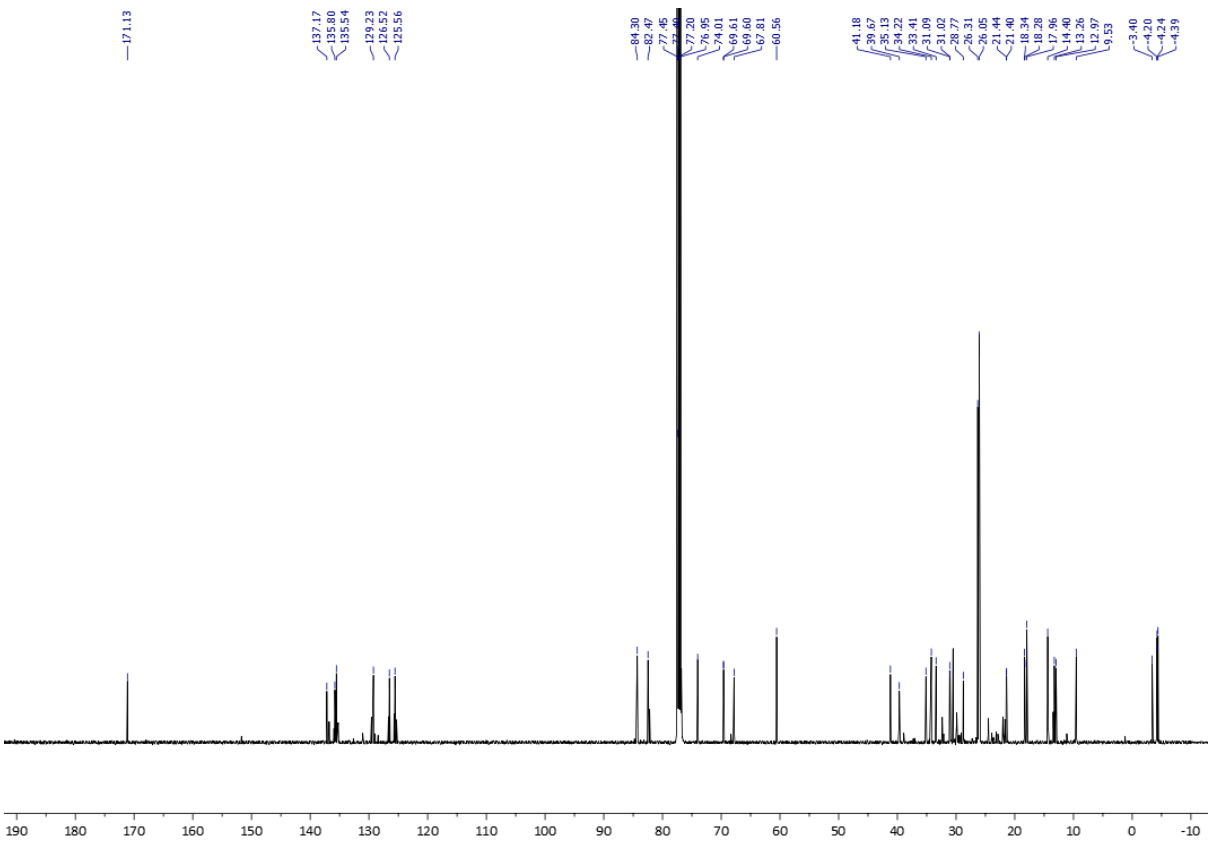

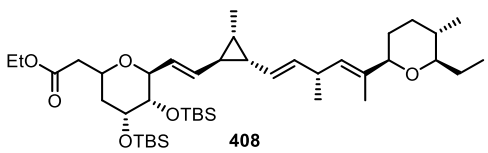
EtO
O
O
OTBS
OTBS

408

E/*Z* = 10:1

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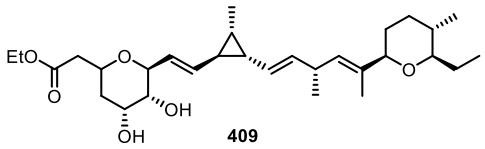
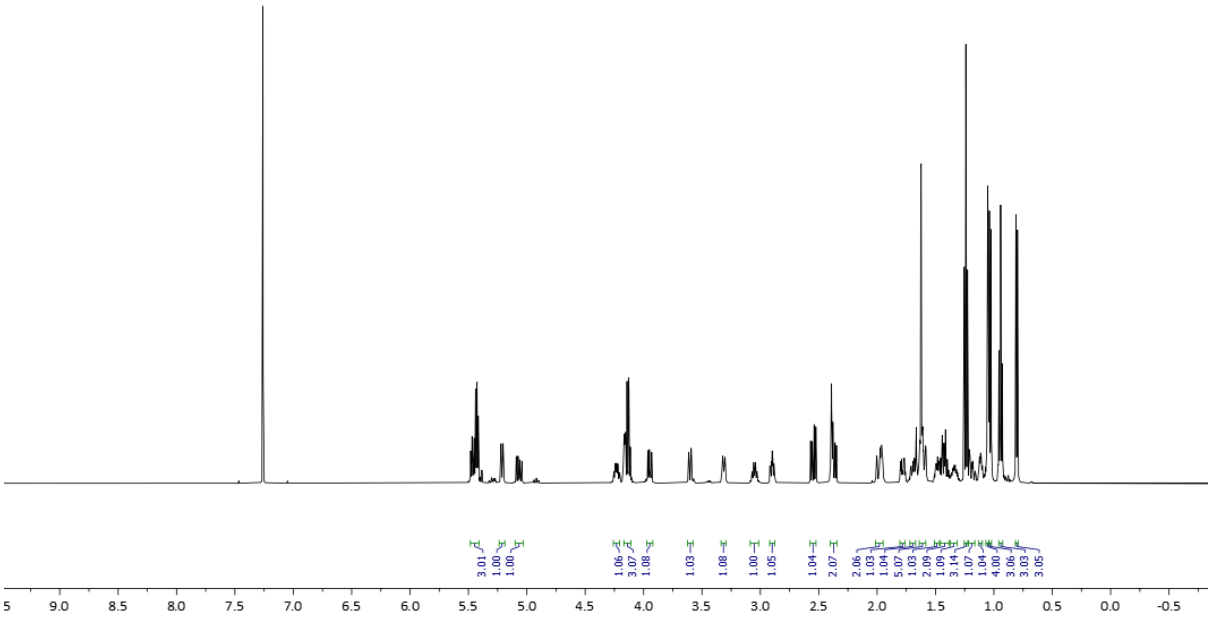
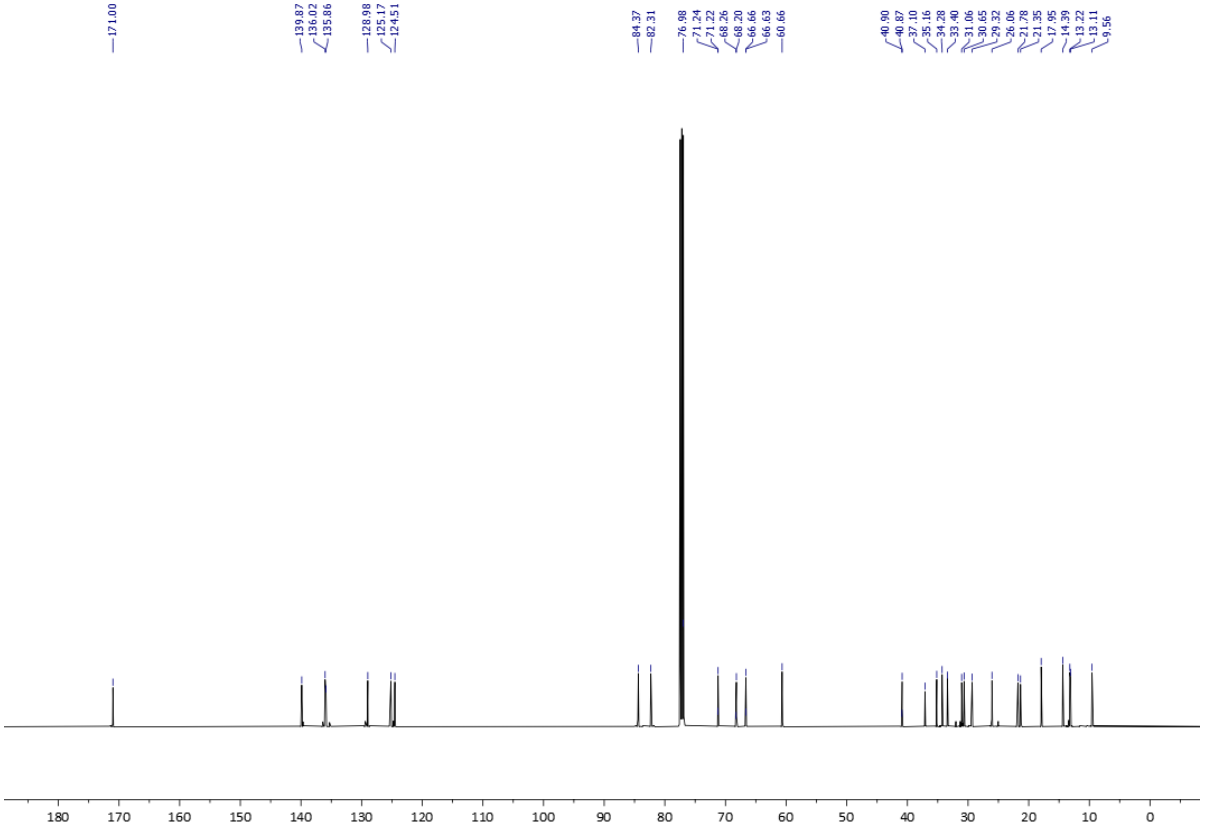
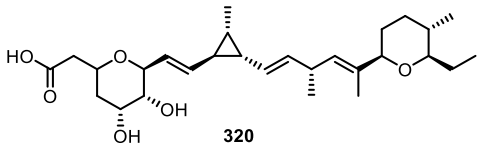
1.06
1.03
1.00
1.02
3.09
1.08
1.01
1.02
1.01
1.04
1.06
1.00
2.01
1.10
3.00
1.04
1.05
3.02
1.10
3.02
1.08
1.01
7.08
3.06
9.09
9.11
3.01
3.08
3.05
3.01
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
171.13
137.18
135.80
135.54
129.24
126.52
125.56
84.30
82.47
74.01
69.61
67.89
67.81
60.57
41.21
41.18
39.67
35.14
34.22
33.41
31.09
31.03
28.77
26.31
26.05
21.44
21.40
18.34
18.34
18.29
17.96
14.40
13.26
12.97
9.53
-3.40
-4.20
-4.23
-4.39
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


EtO
O
O
OH
OH
O

409
E/*Z* = 10:1

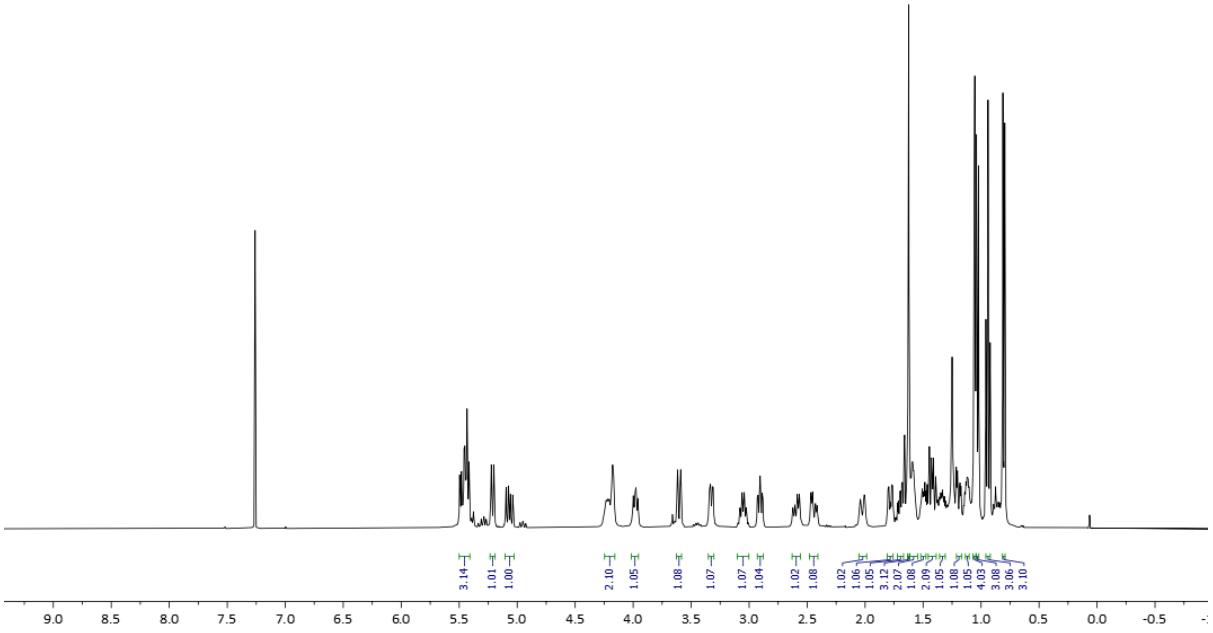

3.01
1.00
1.00
1.06
3.07
1.08
1.03
1.08
1.00
1.05
1.04
2.07
2.06
1.03
1.04
5.07
1.03
2.09
1.09
3.14
1.07
1.04
4.00
3.06
3.03
3.05
5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

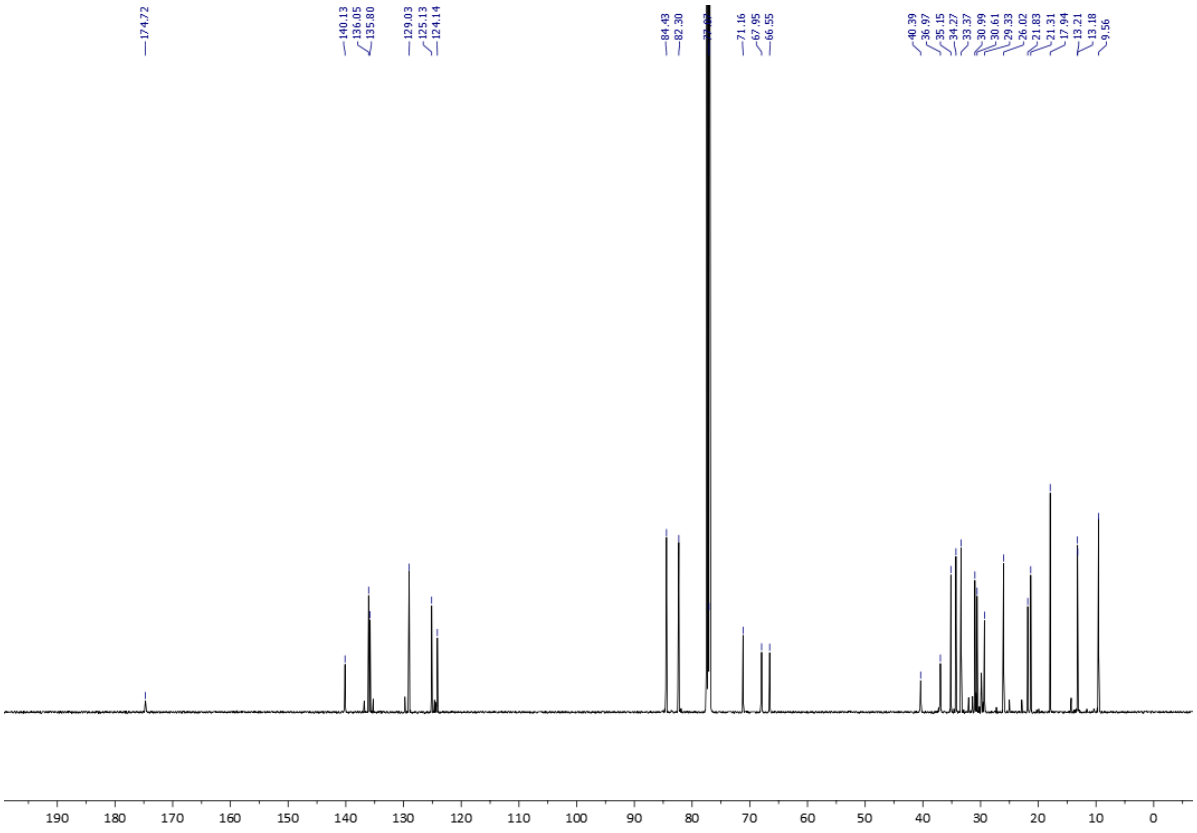

171.00
139.87
136.02
135.86
128.98
125.17
124.51
84.37
82.31
76.98
71.24
71.22
68.26
68.20
66.66
66.63
60.66
40.90
40.87
37.10
35.16
34.28
33.40
31.06
30.65
29.32
26.06
21.78
21.35
17.95
14.39
13.22
13.11
9.56
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

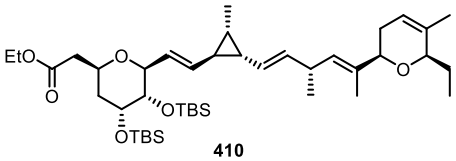

HO
O
O
OH
OH

320

E/*Z* = 10:1


3.14
1.01
1.00
2.10
1.05
1.08
1.07
1.07
1.04
1.02
1.08
1.02
1.06
1.05
3.12
2.07
1.08
2.09
1.05
1.08
1.05
4.03
3.08
3.06
3.10
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


174.72
140.13
136.05
135.80
129.03
125.13
124.14
84.43
82.30
71.16
67.95
66.55
40.39
36.97
35.15
34.27
33.37
30.99
30.61
29.33
26.02
21.83
21.31
17.94
13.21
13.18
9.56
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


EtO
O
O
OTBS
OTBS

410

E/*Z* = 10:1

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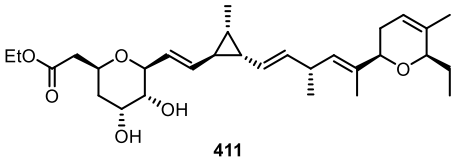
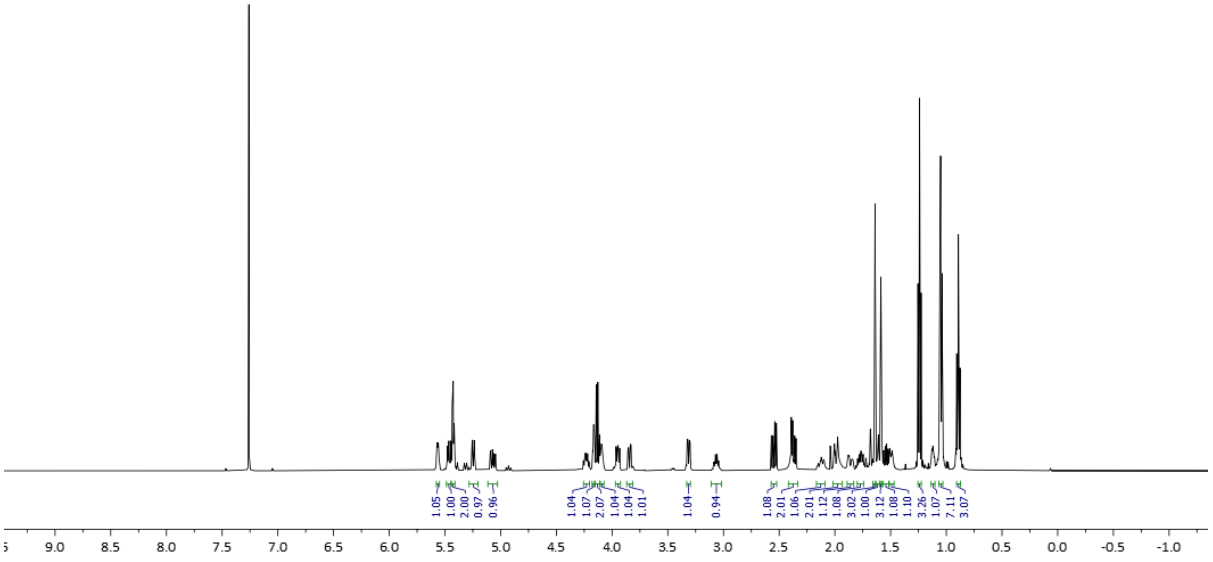
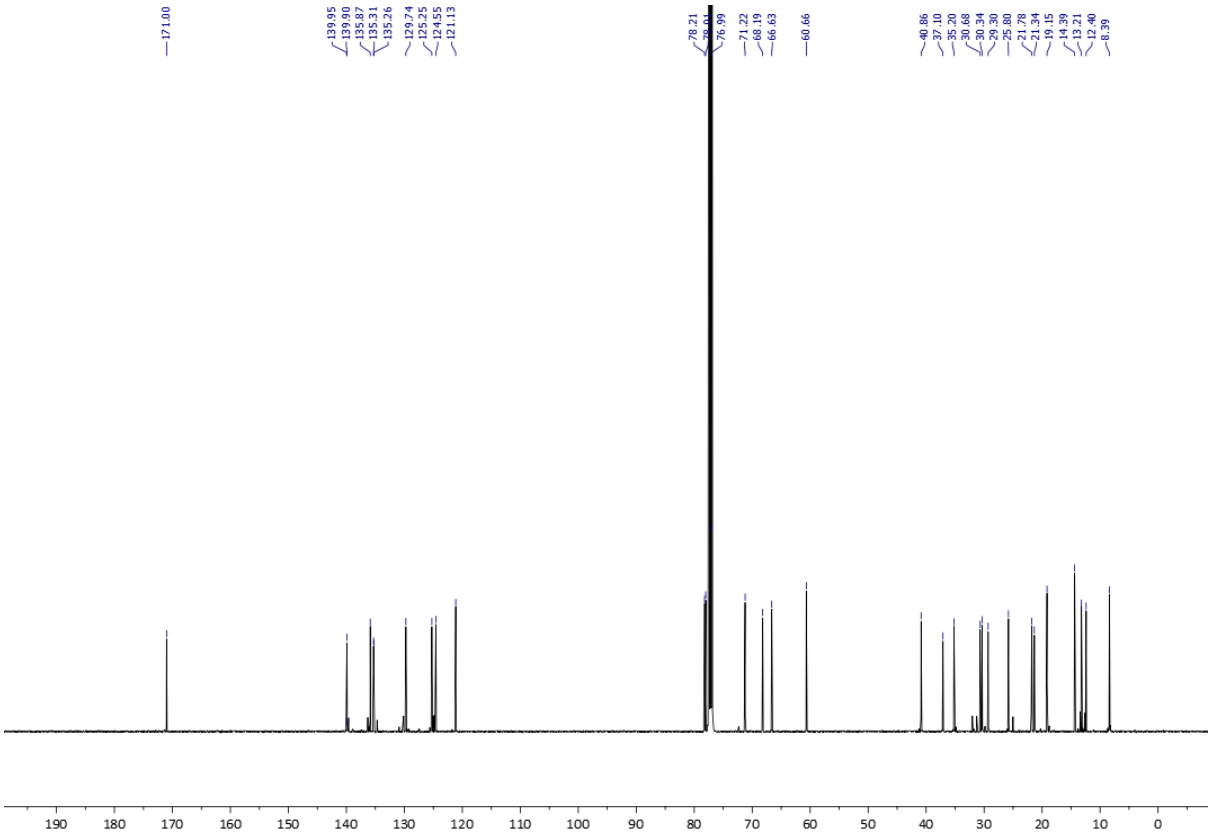
2.07
2.01
1.00
1.09
4.10
1.08
1.01
1.06
1.00
1.03
1.00
1.08
3.16
3.02
3.05
2.02
1.00
3.14
1.08
3.08
3.15
1.04
9.05
12.05
3.05
3.05
3.03
3.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
171.12
137.23
135.35
135.20
130.02
126.53
125.65
121.19
78.35
77.93
76.82
73.95
69.57
67.79
60.56
41.15
39.64
35.19
31.06
30.30
28.75
26.29
26.04
25.78
21.43
21.38
19.16
18.32
18.27
14.38
13.25
12.24
8.33
-3.41
-4.22
-4.25
-4.41
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

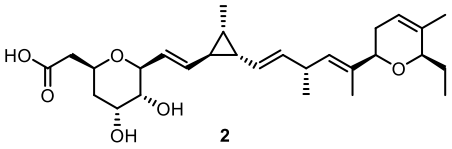

EtO
O
O
OH
OH

411

E/*Z* = 10:1


1.05
1.00
2.00
0.97
0.96
1.04
1.07
2.07
1.04
1.04
1.01
1.04
0.94
1.08
2.01
1.06
2.01
1.12
1.08
3.02
1.00
3.12
1.08
1.10
3.26
1.07
7.11
3.07
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

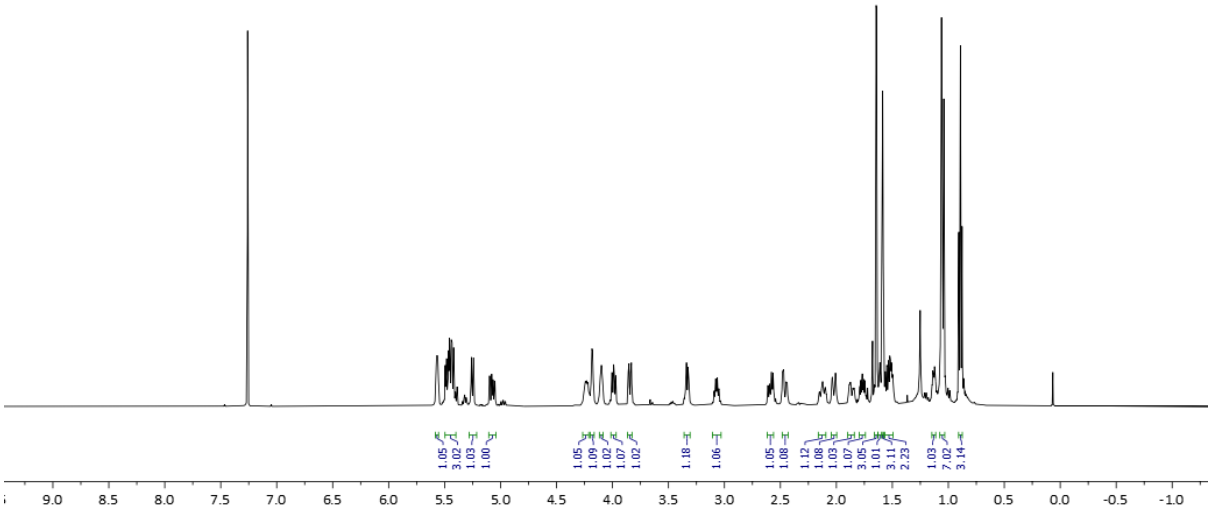

171.00
139.95
139.90
135.87
135.31
135.26
129.74
125.25
124.55
121.13
78.21
78.01
76.99
71.22
68.19
66.63
60.66
40.86
37.10
35.20
30.68
30.34
29.30
25.80
21.78
21.34
19.15
14.39
13.21
12.40
8.39
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

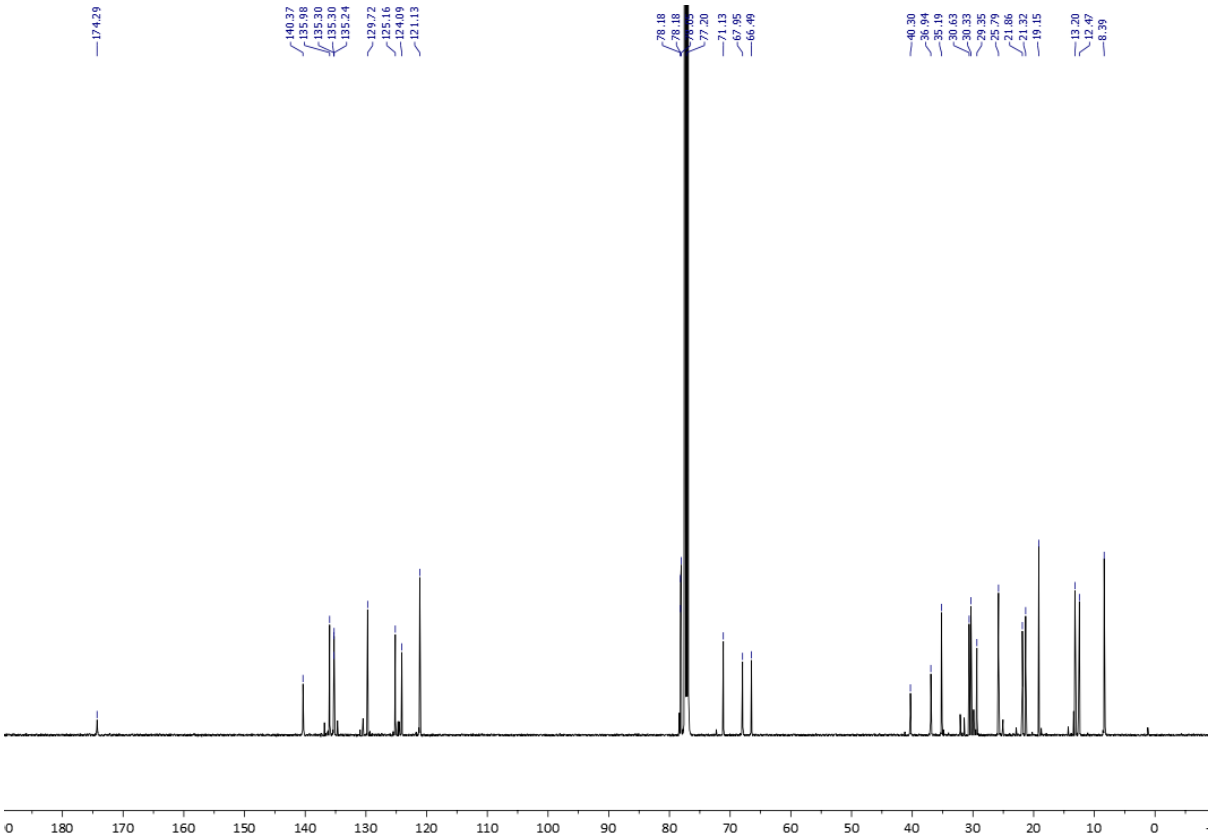


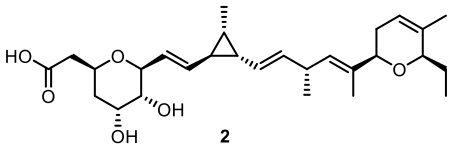
2

E/*Z* = 10:1

NMR spectra in $CDCl_3$



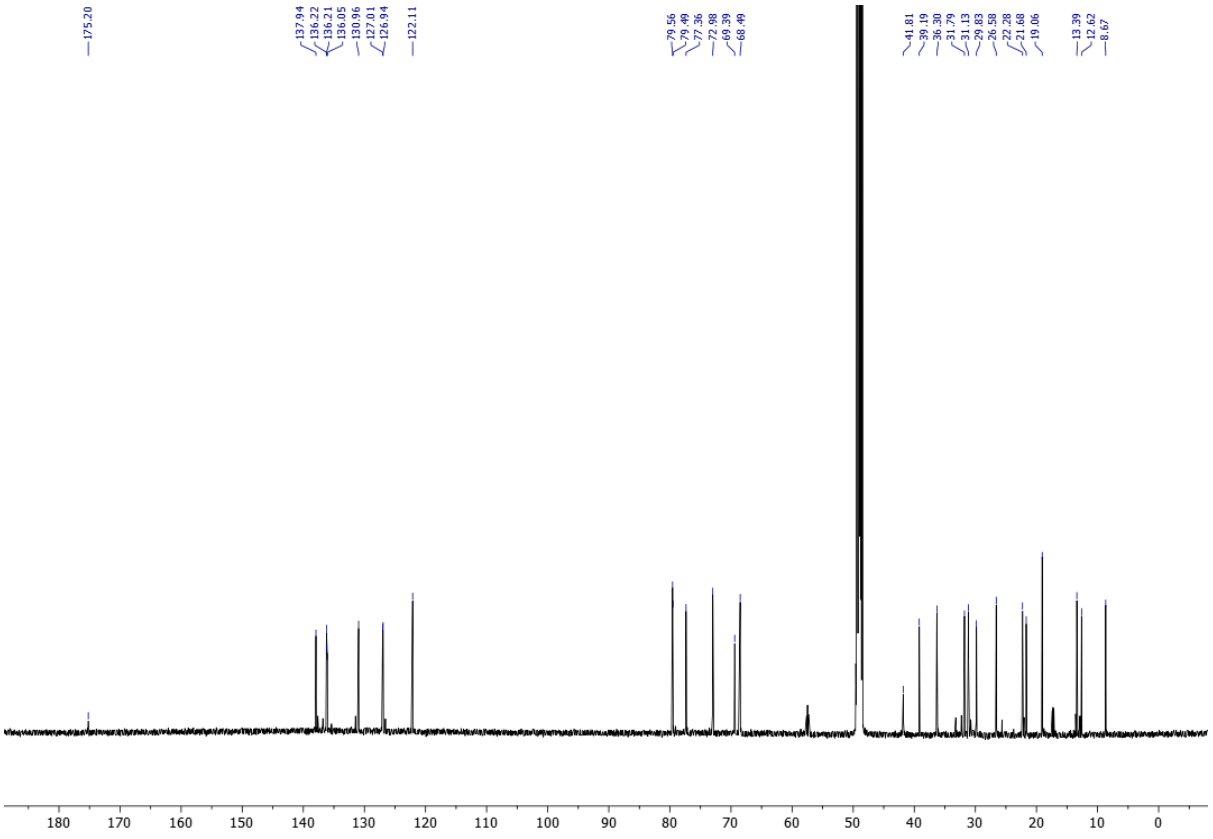


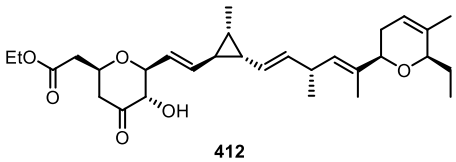


2

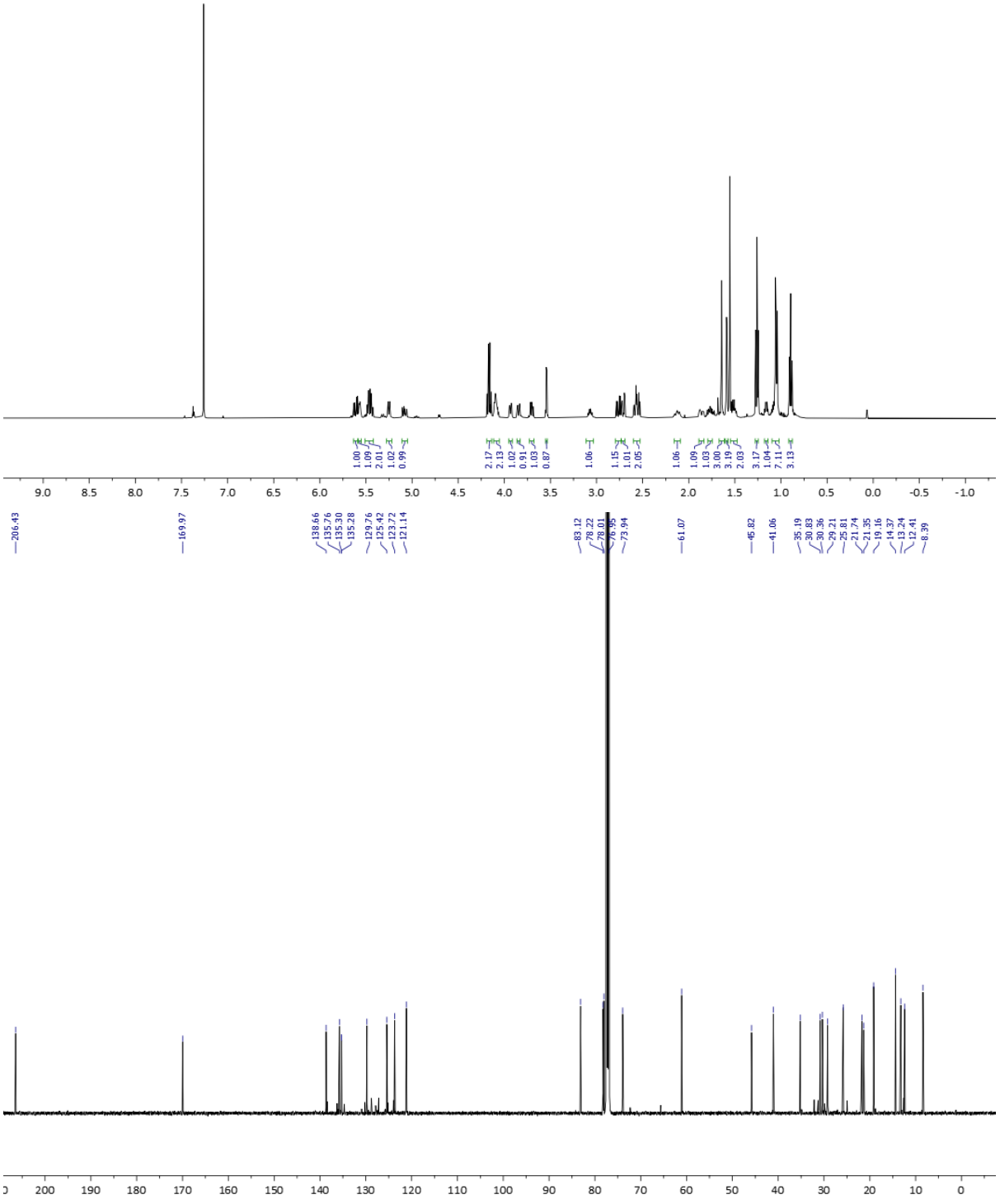
E/*Z* = 10:1

NMR spectra in methanol-D_6




EtO
O
O
OH
O

412
E/*Z* = 10:1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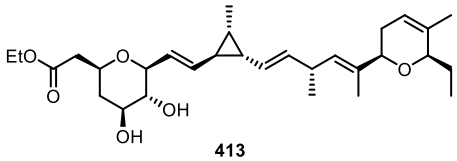
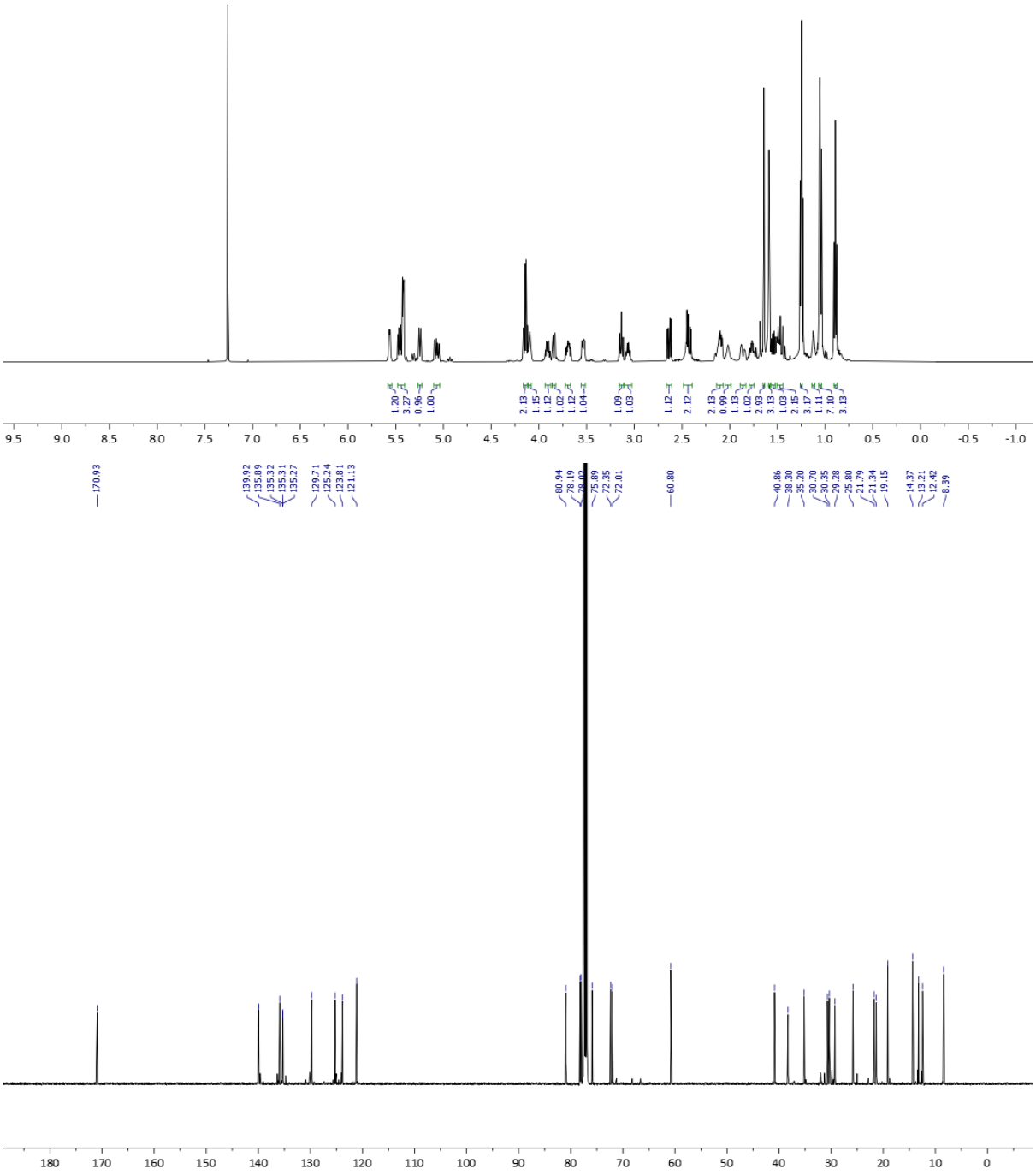
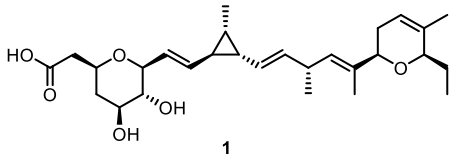
1.09
2.01
1.02
0.99
2.17
2.13
1.02
0.91
1.03
0.87
1.06
1.15
1.01
2.05
1.06
1.09
1.03
3.00
3.19
2.03
3.17
1.04
7.11
3.13
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
206.43
169.97
138.66
135.76
135.30
135.28
129.76
125.42
123.72
121.14
83.12
78.22
78.01
76.95
73.94
61.07
45.82
41.06
35.19
30.83
30.36
29.21
25.81
21.74
21.35
19.16
14.37
13.24
12.41
8.39
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


EtO
O
O
OH
OH

413

E/*Z* = 10:1

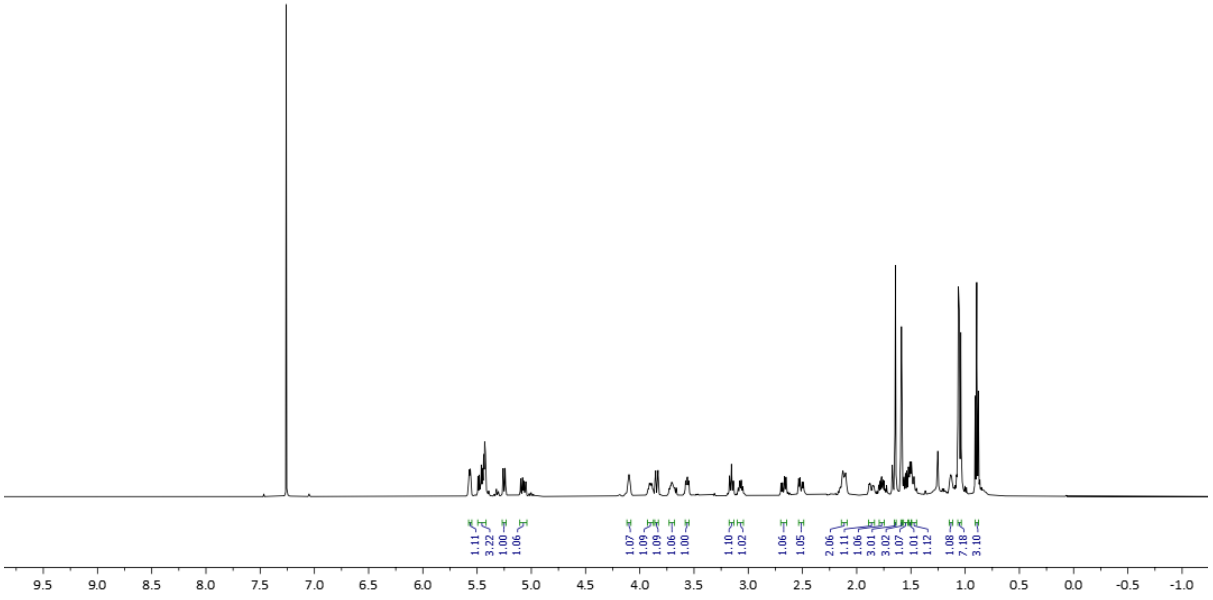

1.20
3.27
0.96
1.00
2.13
1.15
1.12
1.02
1.12
1.04
1.09
1.03
1.12
2.12
2.13
0.99
1.13
1.02
2.93
3.13
1.03
2.15
3.17
1.11
7.10
3.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
170.93
139.92
135.89
135.32
135.31
135.27
129.71
125.24
123.81
121.13
80.94
78.19
78.00
75.89
72.35
72.01
60.80
40.86
38.30
35.20
30.70
30.35
29.28
25.80
21.79
21.34
19.15
14.37
13.21
12.42
8.39
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

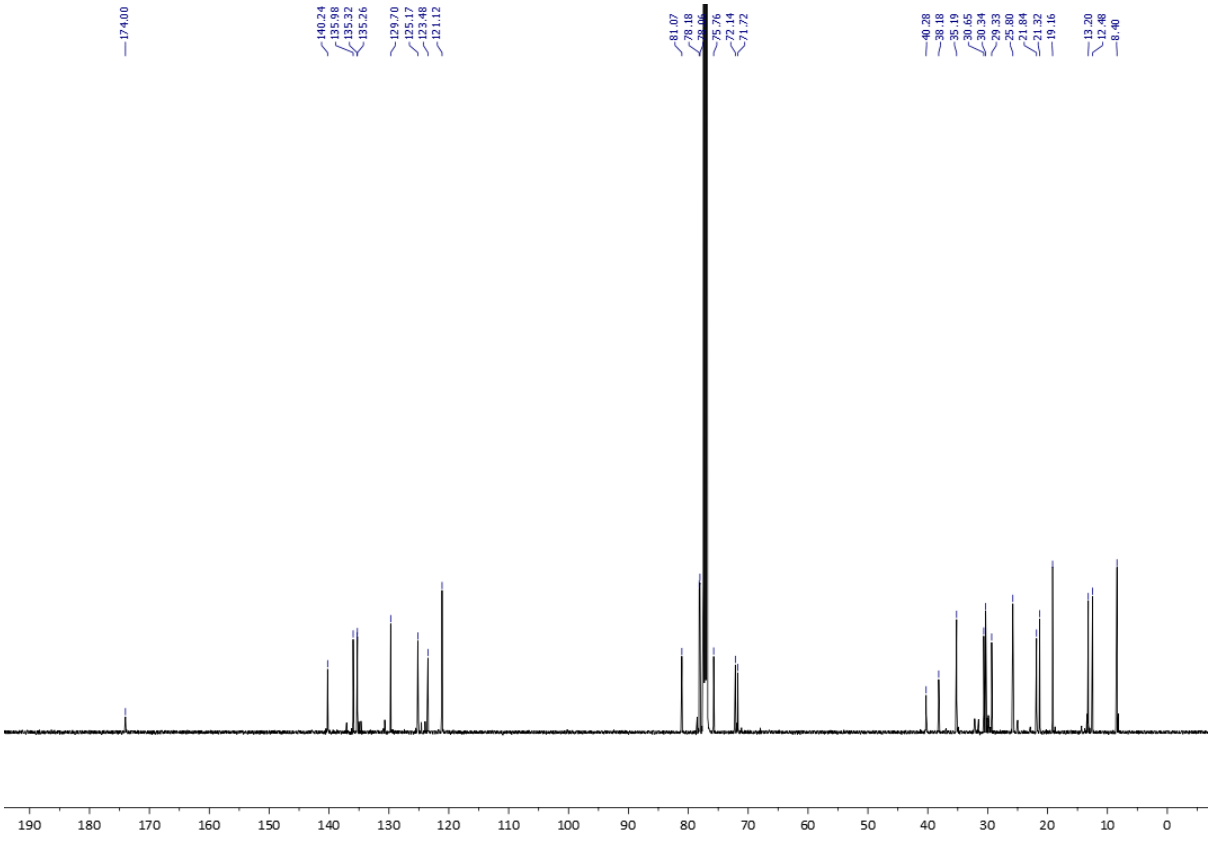


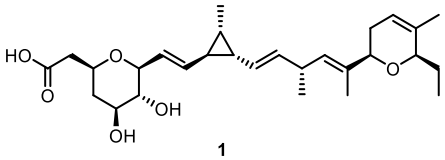
1

E/*Z* = 10:1

NMR spectra in $CDCl_3$







1

E/*Z* = 10:1

NMR spectra in methanol-D_4