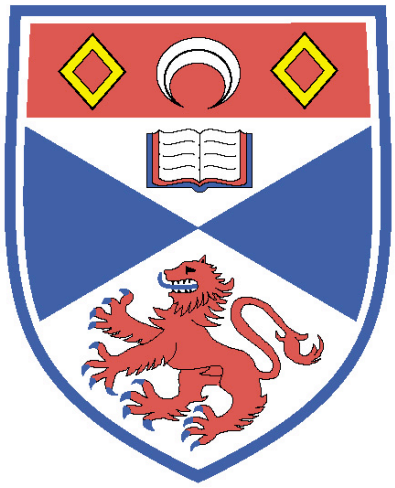
Studies Towards the Synthesis of the Palmerolides



University
of
St Andrews

School of Chemistry
Fife, Scotland

Scott Eadie
November 2013

Thesis submitted to the University of St Andrews in application for the degree of Doctor of Philosophy

Supervisor: Dr. G. J. Florence

Declarations

I, Scott Eadie, hereby certify that this thesis, which is approximately 34000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2007 and as a candidate for the degree of Doctor of Philosophy in November 2013; the higher study for which this is a record was carried out in the University of St Andrews between 2007 and 2013.

Date ……. signature of candidate ……

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctor of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date ……. signature of supervisor …….

Copyright Declarations

In submitting this thesis to the University of St Andrews I understand that I am giving permission for it to be made available for use in accordance with the regulations of the University Library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and the abstract will be published, and that a copy of the work may be made and supplied to any bona fide library or research worker, that my thesis will be electronically accessible for personal or research use unless exempt by award of an embargo as requested below, and that the library has the right to migrate my thesis into new electronic forms as required to ensure continued access to the thesis. I have obtained any third-party copyright permissions that may be required in order to allow such access and migration, or have requested the appropriate embargo below.

The following is an agreed request by candidate and supervisor regarding the electronic publication of this thesis:

Embargo on both all of printed copy and electronic copy for the same fixed period of two years on the following ground: publication would preclude future publication

Date …… signature of candidate ……..

Date …… signature of supervisor ……

Dedicated to my parents

Acknowledgements

Firstly, I would like to thank my supervisor Dr Gordon J. Florence for welcoming me into his group and putting up with me for so long. He has always been there with an open door policy, providing immeasurable support and advice, both in and out of the laboratory.

All of the GJF group past and present, whose companionship and support have helped throughout my time in St Andrews. I would particularly like to thank Dr Ross Murray for all his help with this project and for being a great friend during our time together; Dr Vanga Raghava Reddy for all his advice and help; Dr Eoin Gould for proof reading for me and Dr Joanne Morris for being a good friend and constant source of entertainment.

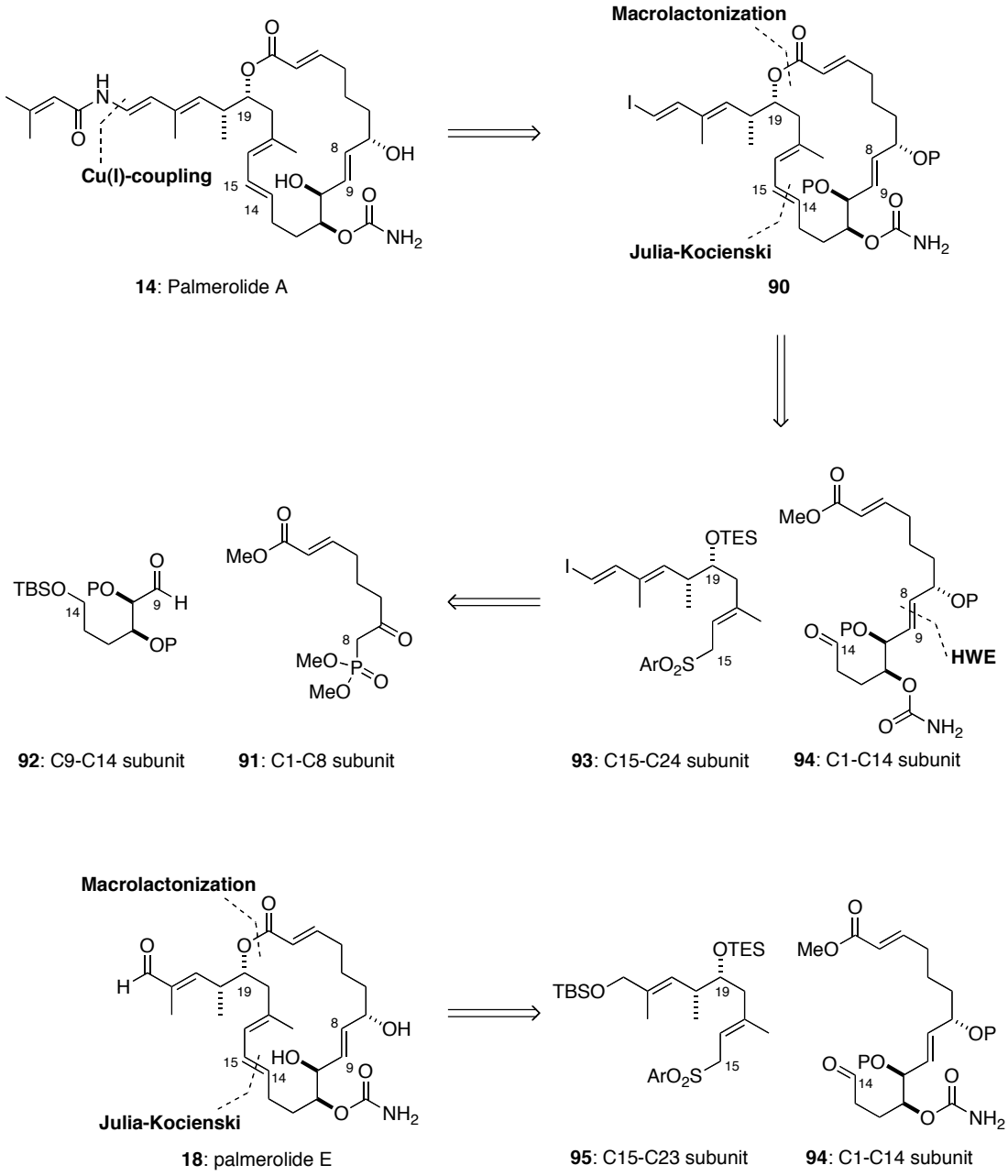
I am grateful to all technical and administrative staff at the School of Chemistry and at the Centre for Biomolecular Sciences. This includes Mrs Melanja Smith and Dr Tomas Lebl (NMR); and Mrs Caroline Horsburgh (Mass spectrometry) and also to the National Mass Spectrometry, Swansea. My thanks goes to the University of St Andrews, the EPSRC and CRUK for funding.

I would also like to thank all the friends that I have made throughout my time here in St Andrews, within and out with the department, with a special thanks to everyone involved with Madras rugby club, making my time here so memorable, and helping me become the person I am now.

Finally I would like to send out my deepest thanks to my family; Mum, Dad, Blair and David who with out there continued support and motivation I would not be here now. Mum and Dad you have both provided so much for me and for that I will be eternally grateful. You have always supported me in everything I do and helped me out when ever possible, which is why this is dedicated to the both of you.

Abstract

In 2006, Baker reported the isolation of palmerolide A (**14**), a polyketide derived marine macrolide, from the Antarctic tunicate *Synoicum adareanum* collected in the shallow waters surrounding Anvers Island. This unique macrolide displayed potent levels of cytotoxic activity in the human melanoma cell lines (UACC-62, LC_{50} = 18 nM and M14 LC_{50} = 76 nM), while also inhibiting V-ATPase with an IC_{50} of 2 nM. There have been eight further palmerolides isolated from *Synoicum adareanum*, which have been shown to possess cytotoxicity activity. The synthetic route devised (Scheme A), was a convergent approach synthesising palmerolide A (14) from three key subunits (**91**, **92** and **93**), which could be coupled *via* a Horner-Wadsworth Emmons to give the C1-C14 subunit **94** followed by a Julia-Kocienski olefination and formation of the macrolcycle **90**. This approach offers both flexibility and convergence as alterations to the subunits would give access to other members of the palmerolide family and their analogues; as using the C15-C23 subunit **(95**) instead of the C15-C24 subunit (**93**) would give rise to palmerolide E (**18**). This thesis details the synthesis of these key fragments and efforts towards their coupling. The C1-C14 subunit synthesis is detailed in chapter 2; chapter 3 and 4 detail the synthesis of thr C15-C23 subunit **(95**) for palmerolide E (**18**) and the C15-C24 subunit **(94**) for palmerolide A (14) respectively. Chapter 5 describes the unsuccessful Julia-Kocienski olefination between the C1-C14 subunit (**94**) and the C15-C24 subunit (**95**)



14: Palmerolide A

90

92: C9-C14 subunit

91: C1-C8 subunit

93: C15-C24 subunit

94: C1-C14 subunit

18: palmerolide E

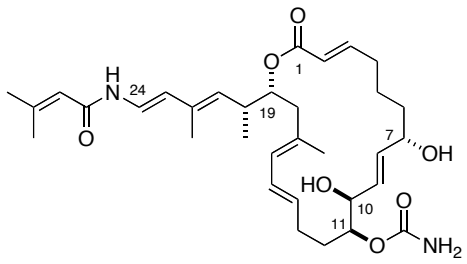
95: C15-C23 subunit

94: C1-C14 subunit

Scheme A

Compound Numbering

All compounds intended towards the total synthesis of palmerolide A (**14**) will be numbered according to the carbon chain of the natural product. This numbering is given on the structure.



14: Palmerolide A

The naming of the compounds in the experimental chapter uses IUPAC convention.

List of Abbreviations

α	alpha
p-ABSA	4-acetamidobenzenesulfonyl azide
Ac	acetate
ATP	adenosine triphosphate
ATPH	aluminium tris-(2,6-diphenylphenoxide)
β	beta
BAIB	[*bis*(acetoxy)iodo]benzene
Bz	benzoyl
9-BBN	9-borabicyclo[3.3.1]nonane dimer
calc.	calculated
CSA	camphor sulfonic acid
C	carbon
cat.	catalytic
CBS	Corey-Bakshi-Shibata
J	coupling constant
Cy	cyclohexyl
°C	degrees Celsius
DIP-Cl	B-chlorodiisopinocampheylborane
DMP	Dess-Martin periodinane
d.r.	diastereomeric ratio
DCM	dichloromethane
DDQ	2, 3-dichloro-5, 6-dicyanobenzoquinone
$(DHQ)_2PHAL$	bis(dihydroquinino)pthalazine
DHQD	dihydroquinidine
DIBAL	diisobutyl aluminium hydride
DIAD	diisopropylazodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide

eq.	equivalent
Et	ethyl
γ	gamma
g	gram
HMDS	hexamethyldisilazane
Hz	hertz
HRMS	high resolution mass spectrometry
h	hours
IC_{50}	concentration required for 50% inhibition
ImH	imidazole
IR	infrared
LDA	lithium diisopropylamide
L	Litres
Mes	mesityl
MeOH	methanol
MOM	methoxymethyl
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
Me	methyl
m	milli; multiplet
mL	millilitre
min	minutes
M	molarity
mol	mole
μ	micro
n	normal
NMR	nuclear magnetic resonance
Nu	unspecified nucleophile
p	para
ppm	parts per million
pH	$-\log[H^+]$
Ph	phenyl
PTSH	1-phenyl-1*H*-tetrazole-5-thiol
PMB	*para*-methoxybenzyl
i-Pr	*iso*-propyl

H	proton
PPTS	pyridinium *p*-toluenesulfonate
pin	pinacol
RCM	ring closing metathesis
R	unspecified alkyl group
R_f	thin layer chromatography retention factor
s	singlet
[α]	specific rotation
t	*tert* (tertiary)
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TEMPO	2, 2, 6, 6-tetramethyl-1-piperidinyloxy
tlc	thin layer chromatography
Ts	*para*-toluenesulfonyl
TCA	trichloroacetimidate
TCCN	trichloroacetyl isocyanate
TES	triethyl silyl
TIPS	triisopropylsilyl
Tf	triflate
TMS	trimethylsilyl
t	triplet
UV	ultraviolet

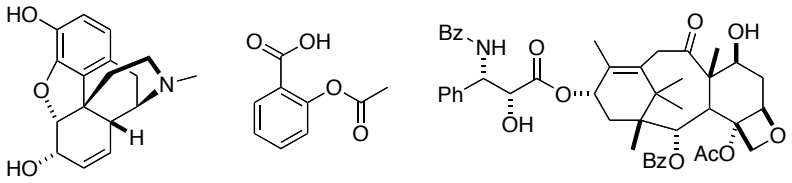
Table of Contents

Introduction

1.1: Natural products in drug discovery

Nature has proven to be an extensive resource of structurally diverse secondary metabolites that can be isolated from both terrestrial and marine sources. Many of these secondary metabolites possess important functions directed to their host organism's continual survival by acting as a defence against predators, parasites, diseases and also facilitating their reproductive processes.[1] Due to this, secondary metabolites often exhibit unique and potent biological properties such as antibiotic, antifungal, cytotoxic and pesticidal activity, which can provide an extremely large library of potential lead agents for both pharmaceutical and agrochemical development.[2]

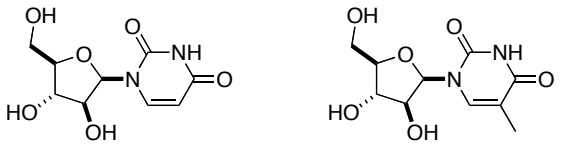
The use of natural products in the search for biologically active compounds is a powerful method for the identification of lead compounds in the drug discovery process. To date 60–70% of pharmaceuticals in clinical use have natural product origins, from the pain killing drugs of morphine (**1**) and aspirin (**2**) to various anticancer agents of which 47% originate from natural products, with one of the most well known being Taxol (**3**) (Figure 1.1), which was isolated from the bark of the Pacific yew tree, *Taxus brevifolia*.[3,4,5]



1: morphine **2**: aspirin **3**: Taxol

Figure 1.1: Structures of morphine (**1**), aspirin (**2**) and Taxol (**3**).

Biologically active natural products can arise from many different sources. One area playing an ever-increasing role are compounds isolated from marine extracts.[6] Two of the first notable discoveries from marine extracts were spongouridine (**4**) and spongothymidine (**5**), isolated by Bergmann from the Caribbean sponge *Crypotheca crypta* in the early 1950s (Figure 1.2).[7] These showed that for a nucleoside to have biological activity it did not require ribose or deoxyribose as the sugar unit and the base also could contain differing heterocycles.

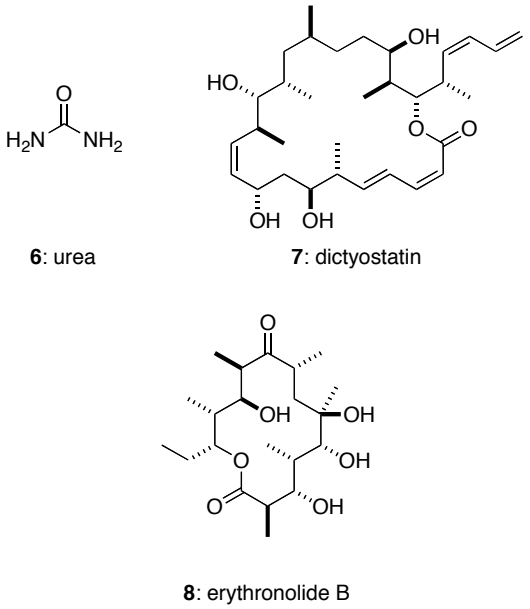


4: spongouridine **5**: spongothymidine

Figure 1.2: Structure of spongouridine (**4**) and spongothymidine (**5**).

Due to the low abundance of many of these natural products, extraction from natural sources is often not practical, and as a result total synthesis remains the most viable option. Synthesis of natural products began in 1828 with the synthesis of urea (**6**) by Wöhler.[8] Total synthesis has developed since then, through the continual development of new technologies and techniques for the

determination of compound structures and with the development of new reaction methodology. Now it is possible to synthesize highly complex molecules with many different stereocentres and functional groups such as dictyostatin (**7**) and erythronolide B (**8**, Figure 1.3).[9,10]



6: urea

7: dictyostatin

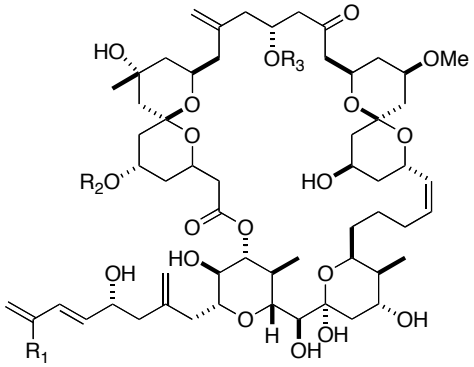
8: erythronolide B

Figure 1.3: Structure of urea (**6**), dictyostatin (**7**) and erythronolide B (**8**)

1.2: Classification of marine macrolides

Polyketides are secondary metabolites, which often display anticancer, antibiotic, antifungal, immunosuppressant and other biological properties. They have a generic 1,3–hydroxyl motif containing alternating carbonyl and methylene groups and are commonly biosynthesized *via* decarboxylative condensation of malonyl-CoA extender units *via* a Claisen condensation.[11] The polyketide chains are assembled by multi-domain polyketide synthase enzymes (PKS's).

One of the most prominent classes of polyketides are the macrolides. Macrolides are a class of compounds characterized by a macrocyclic lactone ring acting as a conformational constraint, which can be adorned with many stereocentres and a range of functional groups.[12] These compounds can be isolated from a variety of sources and possess a diverse range of biological properties. Many marine macrolides, such as the spongistatins (**9**-**13**, Figure 1.4) have been shown to be potent against cell growth in numerous cancer cell lines, which has led to their development as possible lead structures in the discovery of new anticancer agents.[13]



	R_1	R_2	R_3
9: spongistatin 1	Cl	Ac	Ac
10: spongistatin 2	H	Ac	Ac
11: spongistatin 3	Cl	H	Ac
12: spongistatin 4	Cl	Ac	H
13: spongistatin 6	H	Ac	H

Figure 1.4: Structure of spongistatins 1-6 (**9**-**13**)

The study of how these macrolides interact with their corresponding protein targets could help provide many new opportunities in finding novel cancer treatments. As there is a low natural abundance of these macrolides, large scale harvesting is neither practical due to the associated financial costs nor ecologically acceptable.[14] Therefore practical synthetic routes, in principal, have the most potential for supplying sufficient quantities of natural products to further investigate their activity and mode of interaction with their corresponding proteins. Due to their complex structures, synthesis still

presents a formidable challenge; in some cases the structure possesses in excess of thirty stereocentres, they can contain many di- or tri- substituted double bonds, and unusual structural motifs.

Total synthesis is also important for confirming, or in some cases determining the absolute and relative configuration of the target natural product. The common spectroscopic and crystallographic methods used to determine natural product structure may not have been able to fully assign the molecule or may have mis-assigned the relative and absolute configuration. The synthetic strategy devised must also be able to deliver sufficient quantities of pure material to enable further preclinical testing and biological evaluation, while also being flexible enough to allow access to structural analogues.

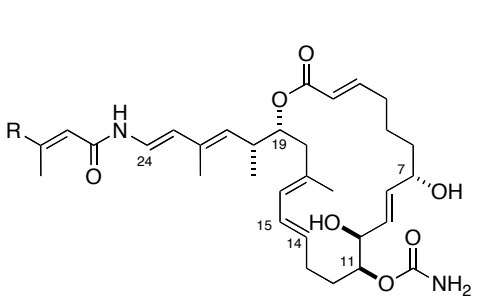
1.3: The palmerolides

1.3.1: Isolation of the palmerolides

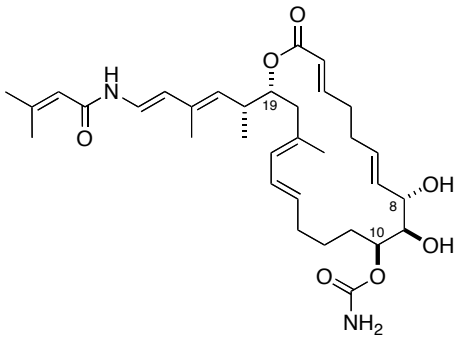
Antarctica is one of the least accessible marine environments, due to its extreme isolation and severe climate. Predation and competition are the dominant forces that determine the species composition and distribution of such an ecosystem. Antarctica is home to many distinct organisms that produce novel secondary metabolites, possessing unique molecular structures with distinctive biological properties, essential for survival in this harsh environment. Its seas sustain a largely unexplored indigenous population of fauna and algae, due to the Antarctic polar front isolating this marine

ecosystem, for over 20 million years.[15] During this time the Antarctic biota has evolved in a relatively stable system without the influence from other habitats. Due to this isolation, the Antarctic seas offer a unique collection of compounds, isolated from fauna that have evolved differently to organisms from more temperate climates. These species flourish in cold seas and have also developed unusual chemical defences to combat predators. Antarctic organisms are therefore of great interest in the search for novel compounds.[16]

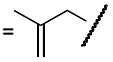
In 2006, Baker and co-workers isolated the palmerolide family from the circumpolar tunicate *Synoicum adareanum*, which is found in the shallow waters near Palmer station on Anvers Island.[17] This family consists of nine polyketide-derived macrolides termed palmerolide A-H and K (**14**-**22**, Figure 1.5).[18]

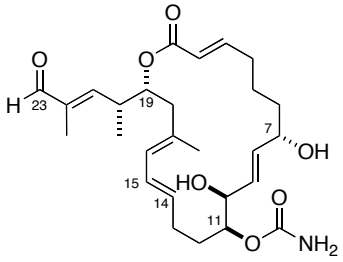


14: palmerolide A, R = Me

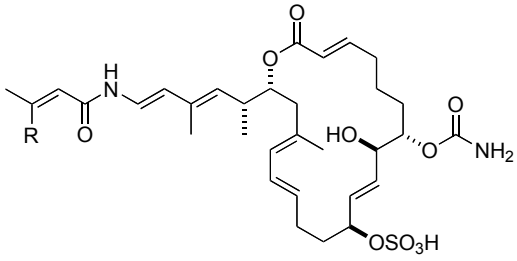


16: palmerolide C

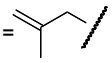
17: palmerolide D, R = 

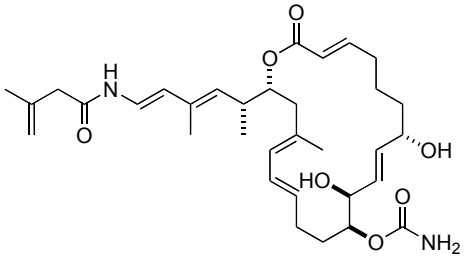


18: palmerolide E

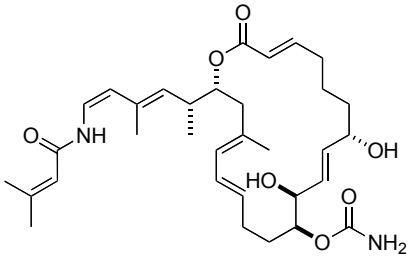


15: palmerolide B, R = Me

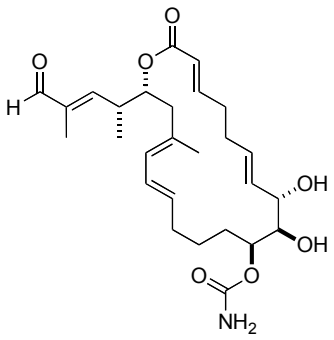
21: palmerolide H, R = 



19: palmerolide F



20: palmerolide G



22: palmerolide K

Figure 1.5: Palmerolide A-H and K (**14**-**22**)

Structurally each of the nine palmerolides A-H and K (**14**-**22**), are similar, each bearing a 20-membered macrolide, containing four *E*-olefins and four

stereocentres. Palmerolide A (**14**) bears an unsaturated *N*-acyl dienamide side chain bearing another stereocentre attached at C-19, whereas palmerolide E (**18**) supports a truncated C-19 enal side chain. The gross structure of palmerolide A (**14**) was assigned using a number of analytical techniques, including MS, and NMR spectroscopy.

Palmerolide D-G (**17**-**22**) are all presumed to have the same relative and absolute configuration as palmerolide A (**14**), assuming a common biogenesis. Palmerolide D (**17**) has been shown to bear an extended enamide side chain with the same macrolide core as palmerolide A, whereas palmerolide F (**19**) is a tautomer of palmerolide A (**14**) bearing the C29-C30 olefin at the C30-C32 terminus. Palmerolide G (**20**) is a geometric isomer of palmerolide A (**14**) with the (Z)-C23-C24 olefin. Palmerolide B (**15**) and H (**21**) both contain a carbamate moiety at C7 and a sulfonate at C11. Palmerolide K (**22**) contains the same structural variations as palmerolide C (**16**) in the macrolide core with hydroxyls at C8 and C9 and the carbamate at C10, but like palmerolide E (**18**) it lacks the enamide side chain while supporting a C19 enal side chain.

1.3.2: Structure of palmerolide A

Baker and co-workers attempted to establish the configuration of the C7 and C10 stereocentres through Mosher ester analysis,[19] where the (*R*)- and (*S*)-MTPA esters of palmerolide A showed both the C7 and C10 to convey the (*R*) configuration which was later shown to be incorrect. The C11 stereocentre was then assigned based on the C10 Mosher ester analysis. This was achieved

using *J*-coupling based conformational analysis of the C10/C11 coupling constants which showed a gauche relationship between H10 and H11 based on the small $^{3}J_{HH}$ and large $^{2}J_{CH}$ for both H10/C11 and H11/C10 relationships (Figure 1.6).[20]

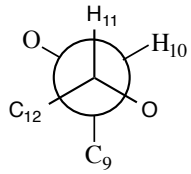
		$^{3}J_{HH}$ (Hz)	$^{2}J_{CH}$ (Hz)
C10/C11		2.2	C11/H10: 5.5 C10/H11: 4.2

Figure 1.6: *J*-coupling based conformational analysis

This method, developed by Murata and co-workers, is based on heteronuclear spin-coupling constants ($^{2,3}J_{CH}$) as well as homonuclear ($^{3}J_{HH}$) coupling constants (Figure 1.7).[20] In systems with conformational flexibility, the observed coupling constants exist as a weighted average for each conformer, so the most favourable conformer will govern the result. The dihedral angle dependence of proton to proton coupling constants ($^{3}J_{HH}$) and the Karplus relationship is frequently used to aid conformational analysis. This alone is inadequate for confident relative stereochemical determination, as two gauche rotamers cannot be distinguished, thus determination of the $^{2,3}J_{CH}$ coupling constants is necessary for stereochemical assignment.

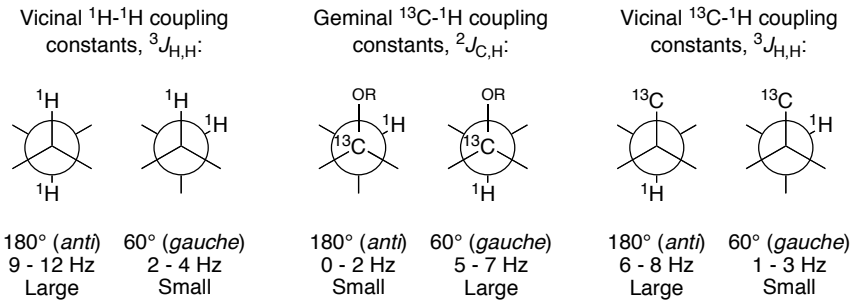
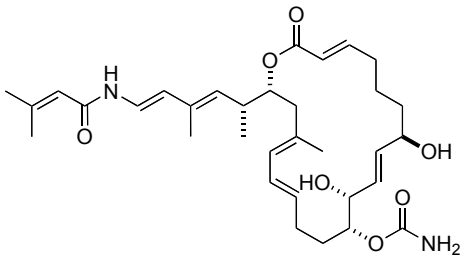


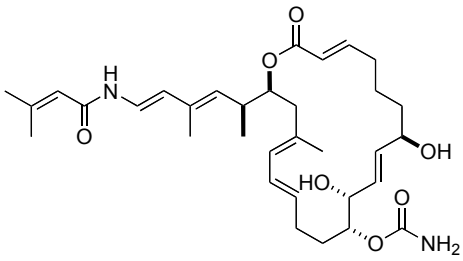
Figure 1.7: Coupling constants size dependence on dihedral angle

The remote C19 and C20 stereocentres were assigned on the basis of nOe and ROESY correlation experiments, which was achievable due to the constraints placed in the macrolide by the four olefins.[17]

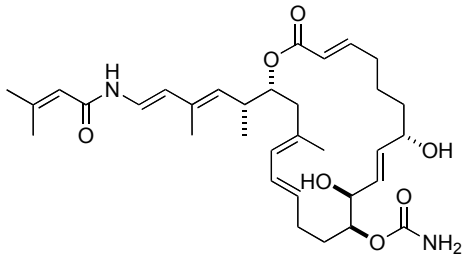
The relative and absolute configuration of the five stereocentres, which was proposed by Baker and co-workers, was subsequently proved to be incorrect by De Brabander in 2007 (Figure 1.8).[21] Total synthesis of the proposed diastereoisomer (**23**) showed that the synthetic compound's ^{1}H and ^{13}C NMR spectra did not match the natural isolate. De Brabander then synthesised the diastereoisomer with inversion of the C19 and C20 stereocentres, which he believed to be the most tenuous assignments to give (**24**). This isomer was shown to have an identical NMR with the natural isolate but was found to be antipodal as the optical rotation and circular dichroism were essentially opposite, confirming the relative and absolute configuration as shown in (**14**).



23: proposed structure of palmerolide A



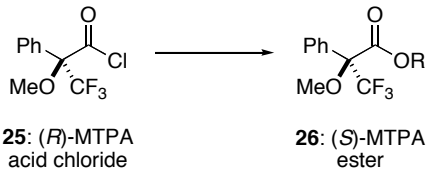
24: antipode of palmerolide A



14: revised structure of palmerolide A

Figure 1.8: Structure reassignment of palmerolide A

The structural mis-assignment of the C7, C10 and C11 stereocentres by Baker and co-workers occurred due to a simple but common mistake in the Mosher ester analysis. In using Mosher acid chlorides in forming the MTPA ester, which under Cahn-Ingold priority gives a reversal of assignment in stereochemistry, so the (*R*)-MTPA acid chloride (**25**) gives the (*S*)-MTPA ester (**26**, Figure 1.9).[19] Unfortunately, Baker and co-workers did not notice this not uncommon oversight and the assignments of the C7 and C10 stereocentres were erroneously reported as (*R*) instead of (*S*). This had a knock on effect throughout the structure, as the assignment of the C11 stereocentre was also reported incorrectly as *J*-based conformational analysis between the C10-C11 stereocentres was used to assign the relative stereochemistry. Therefore since the C10 stereocentre was mis-assigned as (*R*), the C11 was also mis-assigned as (*R*) when both should have been (*S*).



25: (*R*)-MTPA acid chloride

26: (*S*)-MTPA ester

Figure 1.9: (*R*)-MTPA acid chloride (**25**) to (*S*)-MTPA ester (**26**).

1.3.3: Structure of palmerolide C

Palmerolide C (**16**) contains significant structural variations within the macrolide core compared with palmerolide A (**14**). Until recently the absolute and relative configuration of the C8, C9 and C10 stereocentres were unknown but after work carried out within our group and in collaboration with Professor Baker,[22] the macrolide was shown to have the 8*R*, 9*S* and 10*S* configuration. This was achieved by comparison of the synthetic degradation fragments **27**-**30** with the natural equivalent (Figure 1.10).

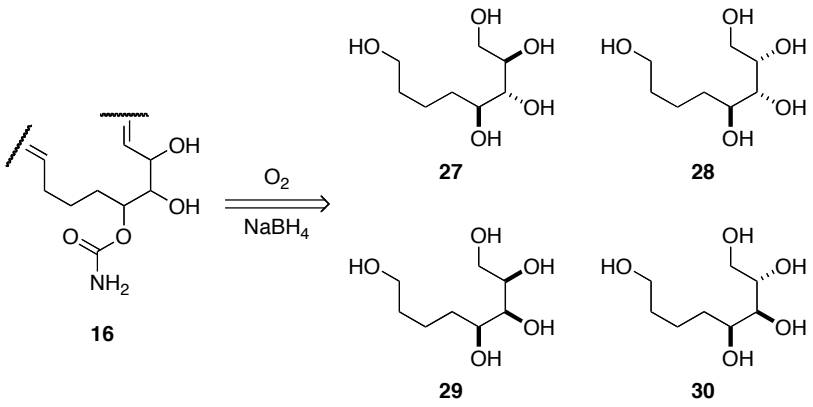
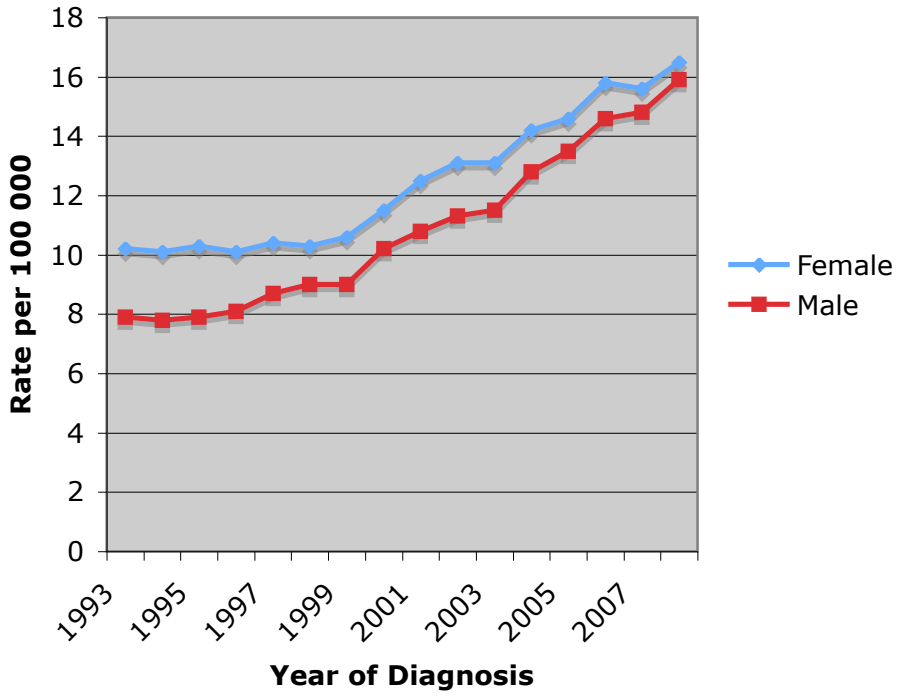


Figure 1.10: Degradation fragments **27**-**30** of palmerolide C (**16**)

1.3.4: Malignant melanoma

Cancer is often thought of as a single disease, with each class having the same mechanism of action and behaving in the same manner, which is a common misconception. Instead cancer is the name given to a range of specific illnesses caused by the body's cells displaying unregulated growth, which invade and destroy healthy tissue including organs. There are over 200 different types of cancer, which can occur from different causes and have differing symptoms, requiring different therapeutic strategies.

One of the most common cancers is skin cancer of which there are two main types, malignant melanoma and non-melanoma skin cancer. Malignant melanoma is the less common of the two but it is significantly more serious. Over the last thirty years malignant melanoma incidence rates have more than quadrupled, rising faster than any of the other more common cancers in both males and females (Graph 1.1).[23] In 2008 approximately 12,000 new cases of malignant melanoma were diagnosed in the UK, and more than 98,800 non-melanoma skin cancers. In the same year around 2,560 people died from skin cancer, with 2,070 of these deaths from malignant melanoma and only around 500 from non-melanoma skin cancer. [24]



Graph 1.1: Incidence rates of melanoma in the UK

The rates of malignant melanoma have been rising over the past thirty years, but due to early detection so are the survival rates which are amongst the highest for any cancer. The latest survival rates for malignant melanoma show that 81% of men and 90% of women survive the disease.[25] However if it is not detected early enough the survival rates rapidly decrease. Patients with early stage melanoma (stage 0, I and IIA), when the tumours are thin and have no nodal spread, can be treated by surgery alone and have survival rates in excess of 95%.[25] As tumor depth increases it becomes increasingly difficult to remove the entire tumor through surgery. Therefore the survival rates decrease, as the risk of developing nodal metastasis relates directly to tumor thickness. Patients with stage IIB and above melanoma are at risk of recurrence as there are currently no effective chemotherapies available.

Consequently further research into the understanding of this disease is required, as the process of melanoma pathogenesis is not fully understood. However a number of key genes and pathways have been implanted with the disease. It has been shown that the melanocortin receptor gene, *MC1R*, influences skin pigmentation, and polymorphisms are common within this gene.[26] These variants have been linked to an increased risk of melanoma and also there is some evidence that polymorphisms in the oculocutaneous albinism gene, *OCA2*, may also increase risk.[26a,27]

1.3.5: Bioactivity of the palmerolides

Of the nine palmerolides isolated, A, C, and E (**14**, **16**, **18**) exhibited the most interesting biological profiles. Initial screening of palmerolide A (**14**) in the NCI 60 cell line panel revealed inhibition of human melanoma cell lines (UACC-62, LC_{50} = 18 nM and M14 LC_{50} = 76 nM) as well as activity against renal and colon cancer cell lines.[18] Further screening of palmerolide A (**14**) revealed that it also inhibited V-ATPase (IC_{50} = 2 nM), although the specific binding site within the V-ATPase protein is currently unknown.

The V-ATPase comprises a class of enzymes that are widely distributed throughout eukaryotes. These enzymes occur in many tissues of multicellular organisms. V-ATPases perform many diverse functions within eukaryotic organisms, such as receptor mediated endocytosis, intracellular targeting of lysosomal enzymes, protein processing and degradation and transport of small molecules.[28] V-ATPases are proton-translocating pumps involved in the

regulation of pH for eukaryotic cells and are found in many intracellular compartments. The pumps work by transferring protons out of the cytoplasm into the organelle, where the hydrolysis of adenosine triphosphate (ATP) creates an electrochemical potential across the membrane that drives the transport of ions and solutes. It has been shown that V-ATPases are involved in the onset of diseases such as osteoporosis, diabetes, pancreatitis and melanoma.[29]

Palmerolide A (**14**) has additionally demonstrated significant *in vivo* activity in the NCI's hollow fibre assay. The NCI hollow fiber assay is a standard bioassay used by the National Cancer Institute to determine *in vivo* cytotoxicity of anticancer agents.[30] The hollow fibre assay has established as a very efficient bioassay that can provide quantitative information of drug efficacy with minimum expenditures of time and materials. Palmerolide A (**14**) tested negative in COMPARE pattern recognition analyses during the NCI hollow fibre assay,[18a] suggesting a novel mode of action as its mean-graph profiles did not reveal any significant correlations to the profiles of known antitumor compounds contained in the NCI's standard agent database.[30a]

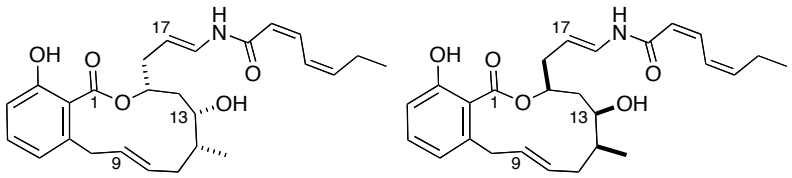
Palmerolide E (**18**) was shown to possess similar activity to palmerolide A (**14**).[18a] This information coupled with the relative instability of enamides at bodily pH suggests that *in vivo* palmerolide A (**14**) may be acting as a prodrug of the one carbon less palmerolide E (**18**). The similarity in activity between palmerolide A (**14**) and E (**18**) is believed to occur due to the C23 aldehyde in

palmerolide E's acting as the unmasked enamide, suggesting the aldehyde performs a major role in the activity of these molecules. Palmerolide C (**16**) was also found (in the NCI 60 cell line panel) to inhibit human melanoma cell line UACC-62 with an LC_{50} = 76 nM, which suggests the macrolide core is important to the activity.[18a]

1.4: Salicylihalamide

In 1997, Boyd and co-workers reported the isolation of salicylihalamide A (**31**) and salicylihalamide B (**32**) from the marine sponge *Haliclona*, collected off the southwest Australian coast (Figure 1.11).[31] The structure was assigned on the basis of NMR and mass spectroscopy and the absolute stereochemistry was assigned by Mosher esters analysis. The salicylihalamides represent a novel class of macrocyclic benzolactones incorporating salicylic acid, and decorated with a highly unsaturated *N*-acyl enamine side chain.

Once again due to the failure to take into account the change of priority by the conversion of the Mosher's acid chloride to the MTPA ester, the stereocentres at C12, C13 and C15 were assigned incorrectly.[32] As a result, the configuration of C13 is inverted to (*R*) and the biologically active forms are assigned as (-)-salicylihalamide A (**33**) and (-)-salicylihalamide B (**34**).



31: (+)-salicylihalamide A: 17*E* **33**: (-)-salicylihalamide A: 17*E*

32: (+)-salicylihalamide B: 17*Z* **34**: (-)-salicylihalamide B: 17*Z*

Figure 1.11: Structure of (±)-salicylihalamide A (**31** and **33**) and (±)-salicylihalamide B (**32** and **34**)

Screening of (-)-salicylihalamide A (**33**) showed some promising hits and had a unique cytotoxicity profile in the NCI 60-cell line human tumour screen. The mean GI_{50} concentration was 15 nM across the NCI 60 cell line panel, with a sensitivity range of ≤ 10^3.[31] The melanoma cell lines were shown to have the highest average tumour-type subpanel sensitivity (GI_{50} = 7 nM, TGI = 60 nM) and (-)-salicylihalamide A (**33**) has also been identified as a target for the V-ATPase enzyme (IC_{50} < 1.0 nM).

Structure-activity relationships (SARs) studies carried out on (-)-salicylihalamide A,[33] showed the side-chain analogues **35**–**39** all maintain the ability to inhibit V-ATPase, with similar concentrations to those of **33** (Figure 1.12).[33a] The analogues **40** and **41** without the enamide suggest that the enamide side chain is irreversibly binding to the protein target, as the activities of these molecules are both dramatically reduced in *in vitro* testing. Smith and Zheng tested analogues **42**, missing the C12 methyl and C13 hydroxyl, and **43** missing the C9-10 olefin, C12 methyl and C13 hydroxyl, which both retained some activity at reduced levels from **33**. From these

results it was hypothesised that the structure of the macrolide is important for activity, but not decisive.[33b/c]

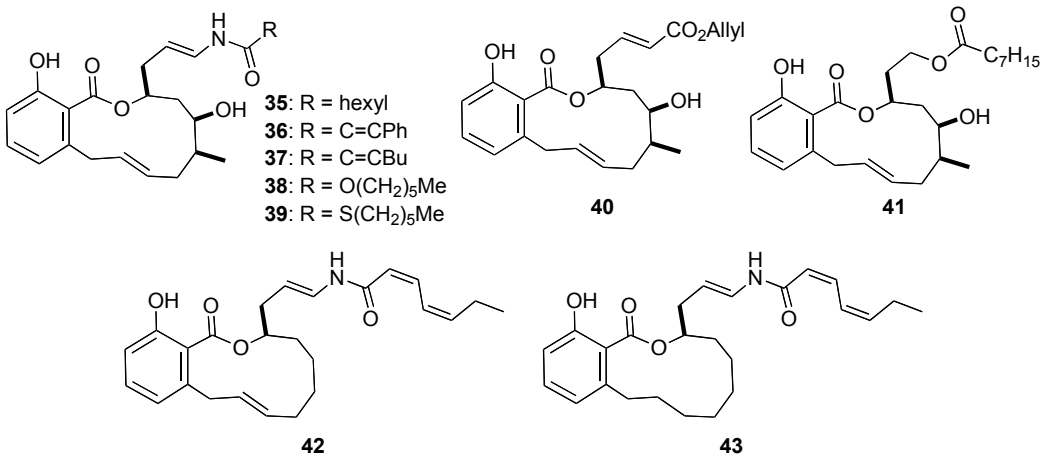


Figure 1.12: Structural analogues **35**–**43** of (-)-salicylihalamide A

Unlike other V-ATPase inhibitors (-)-salicylihalamide A (**33**) is able to discriminate between mammalian and non-mammalian V-ATPase, suggesting that it has a different binding site from classical V-ATPase inhibitors, such as bafilomycin A_1 (**44**, Figure 1.13).[34]

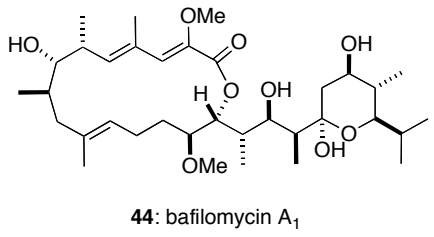


Figure 1.13: Structure of bafilomycin A_1 (**44**).

With both (-)-salicylihalamide A (**33**) and palmerolide A (**14**) having a macrolide core bearing an enamide side chain it is not inconceivable that they may share a similar mode of action. This is due to the similar *N*-acyl enamide

side chain, which in the case for the former is necessary for the irreversible binding to the protein target. It is hypothesised that salicylihalamide inhibits V-ATPase *via* the enamide side chain forming a covalent bond with a lysine residue on the enzyme (Figure 1.14).[34a,35] This is proposed to occur *via* the formation of an electrophilic *N*-acyliminium ion generated form the *N*-acyl enamide under acidic conditions, followed by attack of the active lysine residue. The adduct then fragments into a protein-imine complex with release of the amide side chain. Subsequent hydrolysis of this protein-imine complex could generate the aldehyde as found in palmerolide E (**18**).

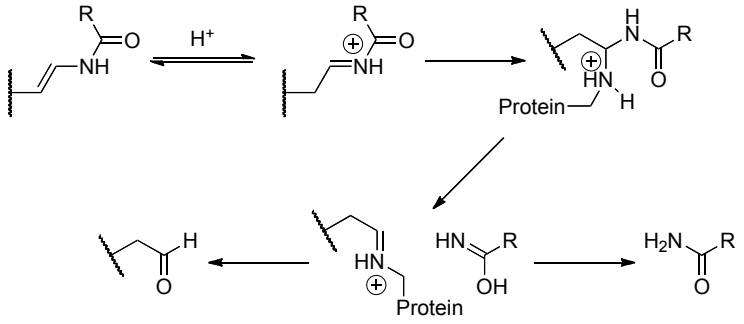


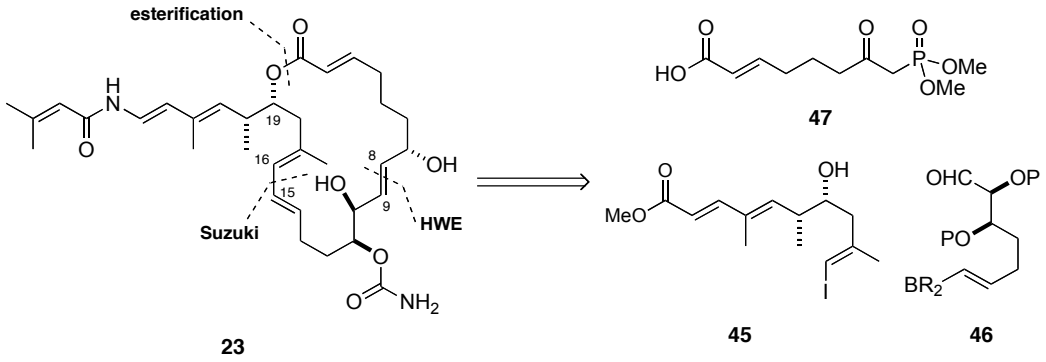
Figure 1.14: Interaction of enamide side chain with protein

1.5: Previous synthesis of palmerolide A

To date there have been three total synthesis of palmerolide A, the first being completed in 2007 by De Brabander, followed by Nicolaou and Chen shortly after, then by Hall in 2009.[21,36] There have also been several formal and partial syntheses completed.[37]

1.5.1: De Brabander's synthesis of palmerolide A

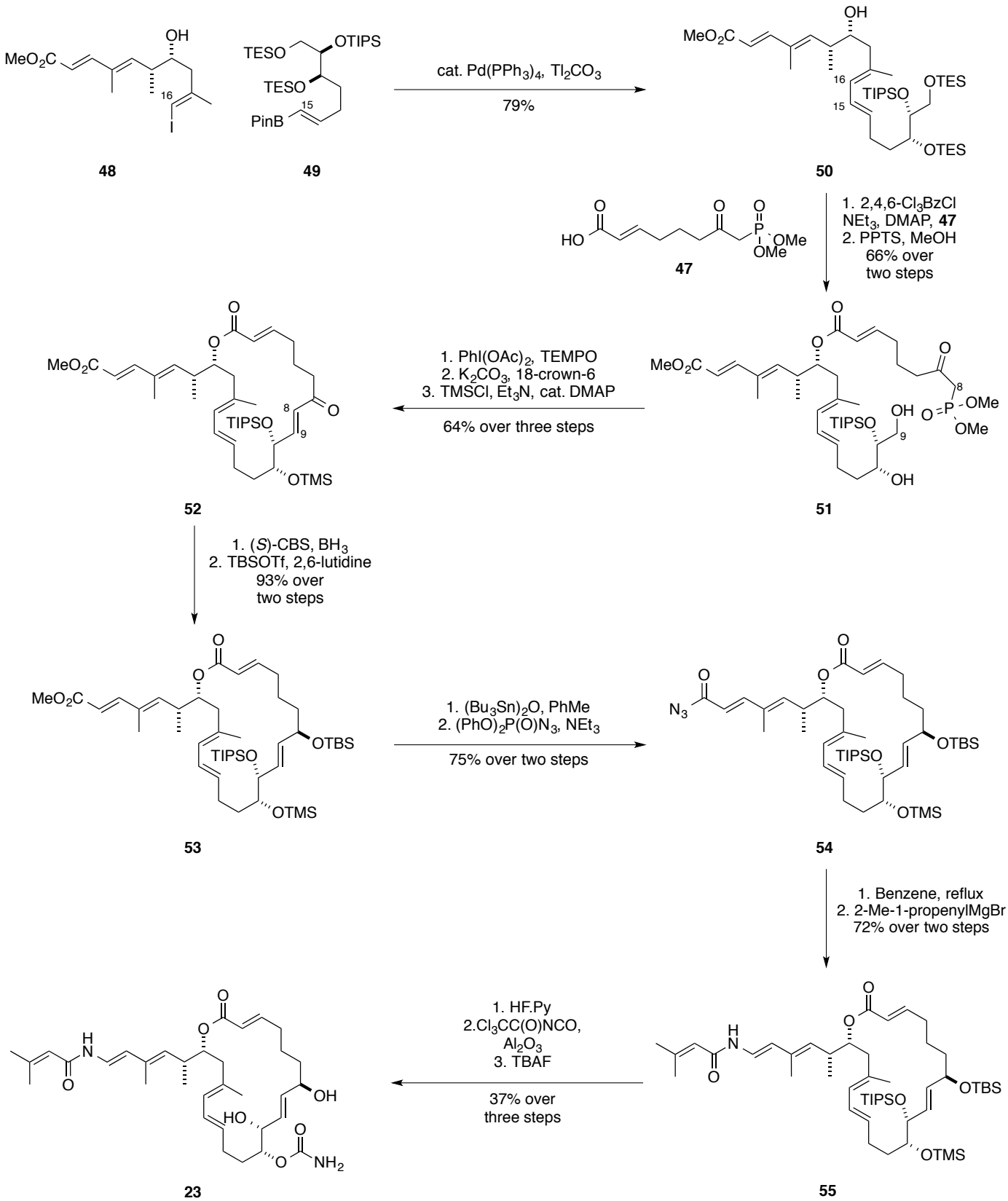
In 2007 De Brabander and co-workers synthesized the initially reported structure of palmerolide A (**23**) and the antipode (**24**) establishing the absolute and relative configuration. Their approach to assemble palmerolide A relied on a Suzuki cross-coupling reaction of vinyl iodide **45** and borane **46** to form the C15-16 bond, followed by esterification with enoic acid **47** (Scheme 1.1).[21] Macrocyclization was to be achieved *via* a Horner-Wadsworth Emmons olefination, and installation of the enamide side chain *via* a Curtius rearrangement with trapping of the isocyanate with 2-methyl propenylmagnesium bromide to give palmerolide A (**23**).



Scheme 1.1: De Brabander's retrosynthesis of palmerolide A (**23**)

In the assembly of **23**, Suzuki coupling of vinyl iodide **48** and vinyl boronate **49** using catalytic palladium (0) provided diene **50** (Scheme 1.2).[38] The diene was esterified with carboxylic acid **47** under Yamaguchi conditions,[39] which after removal of the TES protecting groups gave diol **51**. Selective oxidation of the primary alcohol **51** followed by an intramolecular Horner-Wadsworth Emmons macrocyclization and subsequent silyl protection gave macrolactone

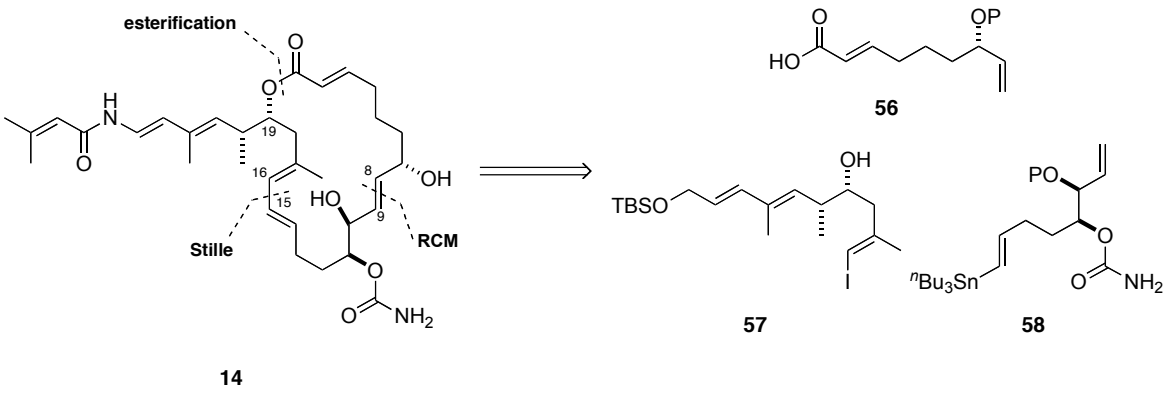
52. CBS reduction of the ketone introduced the C7 stereocentre,[40] which after TBS protection gave **53**. Ester hydrolysis of the C25-ester allowed the formation of acyl azide **54**. Heating of acyl azide **54** promoted the Curtius rearrangement and treatment of the intermediate with 2-methyl propenylmagnesium bromide introduced the enamide side chain with high levels of efficiency to give **55**. This allowed the introduction of the carbamate, which was followed by deprotection using TBAF to afford palmerolide A (**23**). The synthesis of the proposed structure of palmerolide A (**23**) was completed in a total of thirty-three steps, with a longest linear sequence of twenty-three steps with a 2.9% yield.



Scheme 1.2: Assembly of palmerolide A (**23**)

1.5.2: Nicolaou and Chen's synthesis of palmerolide A

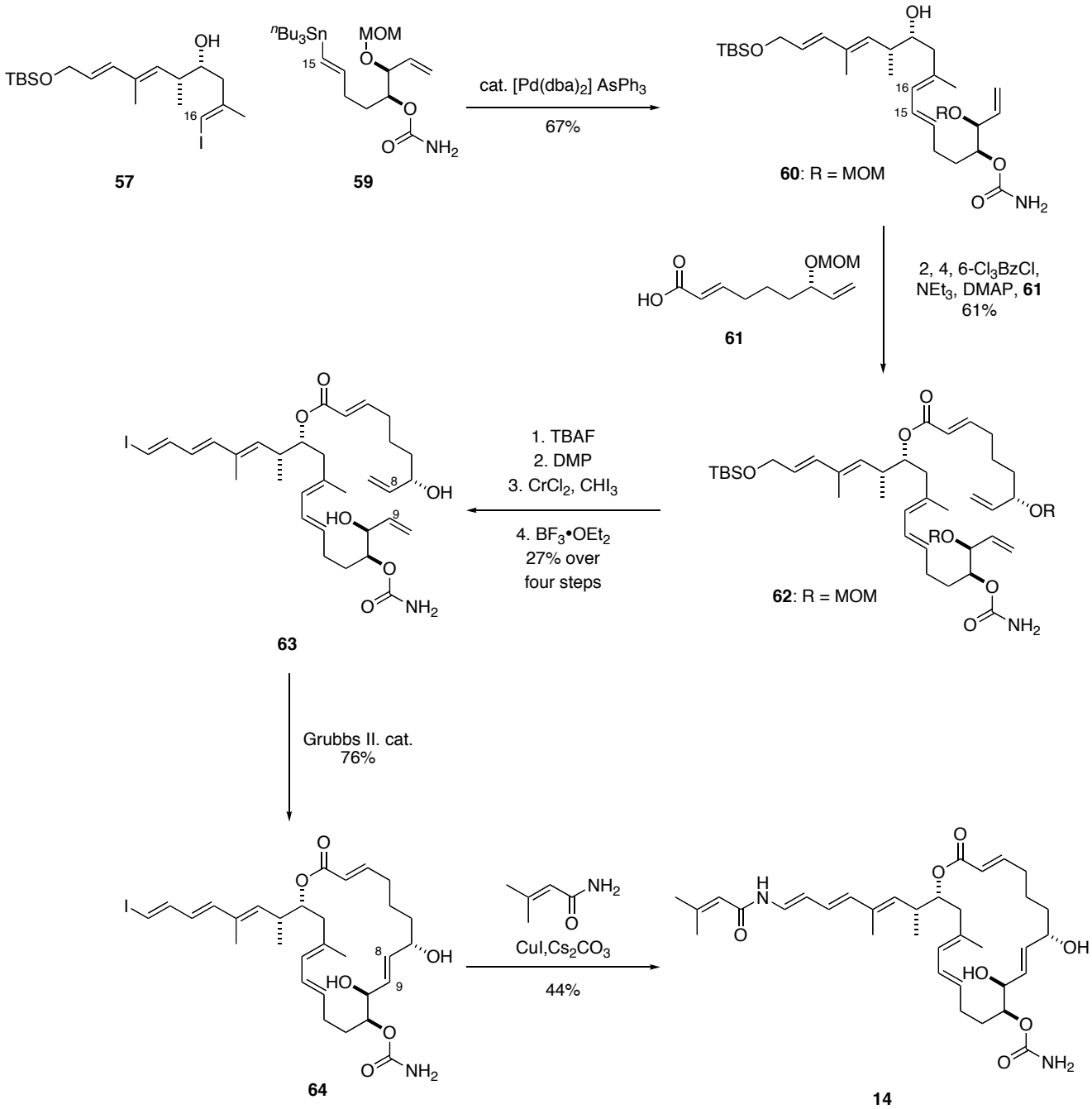
Shortly after De Brabander completed his synthesis, Nicolaou and Chen completed their synthesis of the proposed structure of palmerolide A (**23**), and subsequently reported in 2008 the synthesis of the natural palmerolide A (**14**). They envisioned that they could assemble palmerolide A (**14**) from three fragments **56**, **57** and **58** *via* a Stille coupling reaction to form the C15-16, esterification and a ring closing metathesis (Scheme 1.3).[36a,b]



Scheme 1.3: Nicolaou and Chen's retrosynthesis of palmerolide A (**14**)

The coupling of the C15-16 bond was achieved *via* Stille coupling between vinyl iodide **57** and vinyl stannane **59**,[41] which provided the tetraene **60** (Scheme 1.4). The carboxylic acid **61** was esterified with the newly formed tetraene **60** under Yamaguchi conditions to give ester **62**.[39] Introduction of the vinyl iodide was achieved by desilylation and oxidation of the primary hydroxyl, followed by a Takai olefination,[42] which after removal of the two MOM protecting groups using boron trifluoride diethyl etherate gave **63**. Exposure of adduct **63** to Grubbs II catalyst led to formation of the desired macrocycle **64** and finally installation of the enamide moiety was achieved *via*

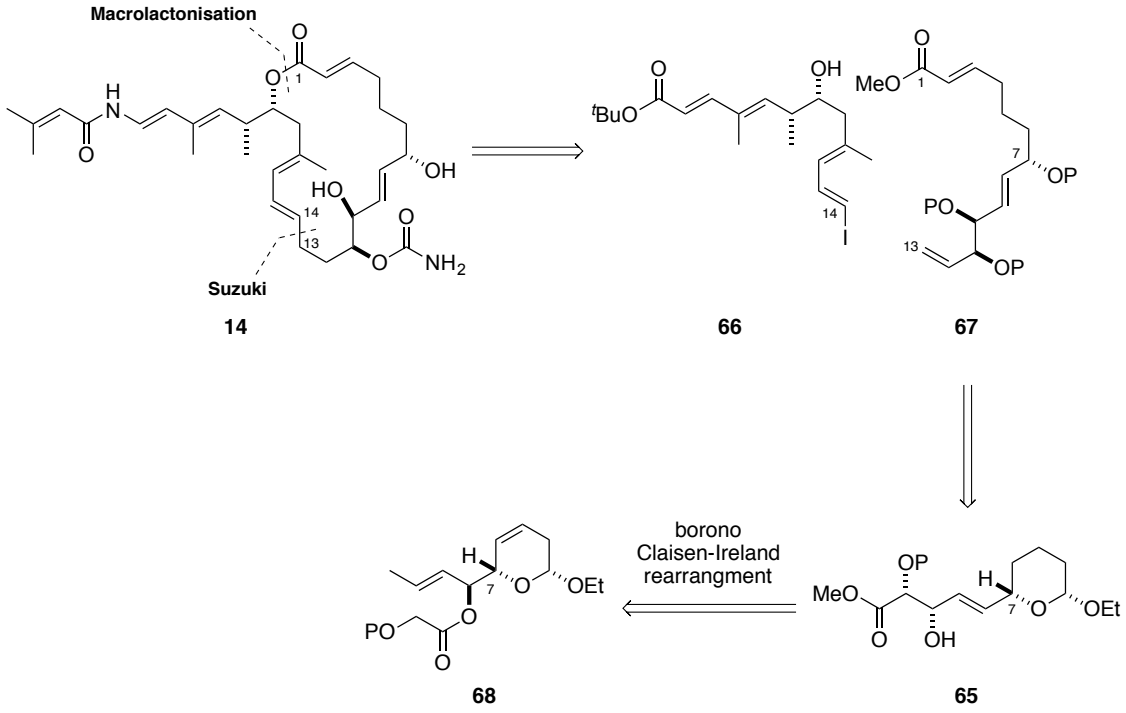
a Buchwald Cu (I)-mediated reaction to give palmerolide A (**14**). In the synthesis of palmerolide A (**14**) there were a total of 28 steps, with a longest linear sequence of fifteen steps with a 1.7 % yield.



Scheme 1.4: Assembly of palmerolide A (**14**)

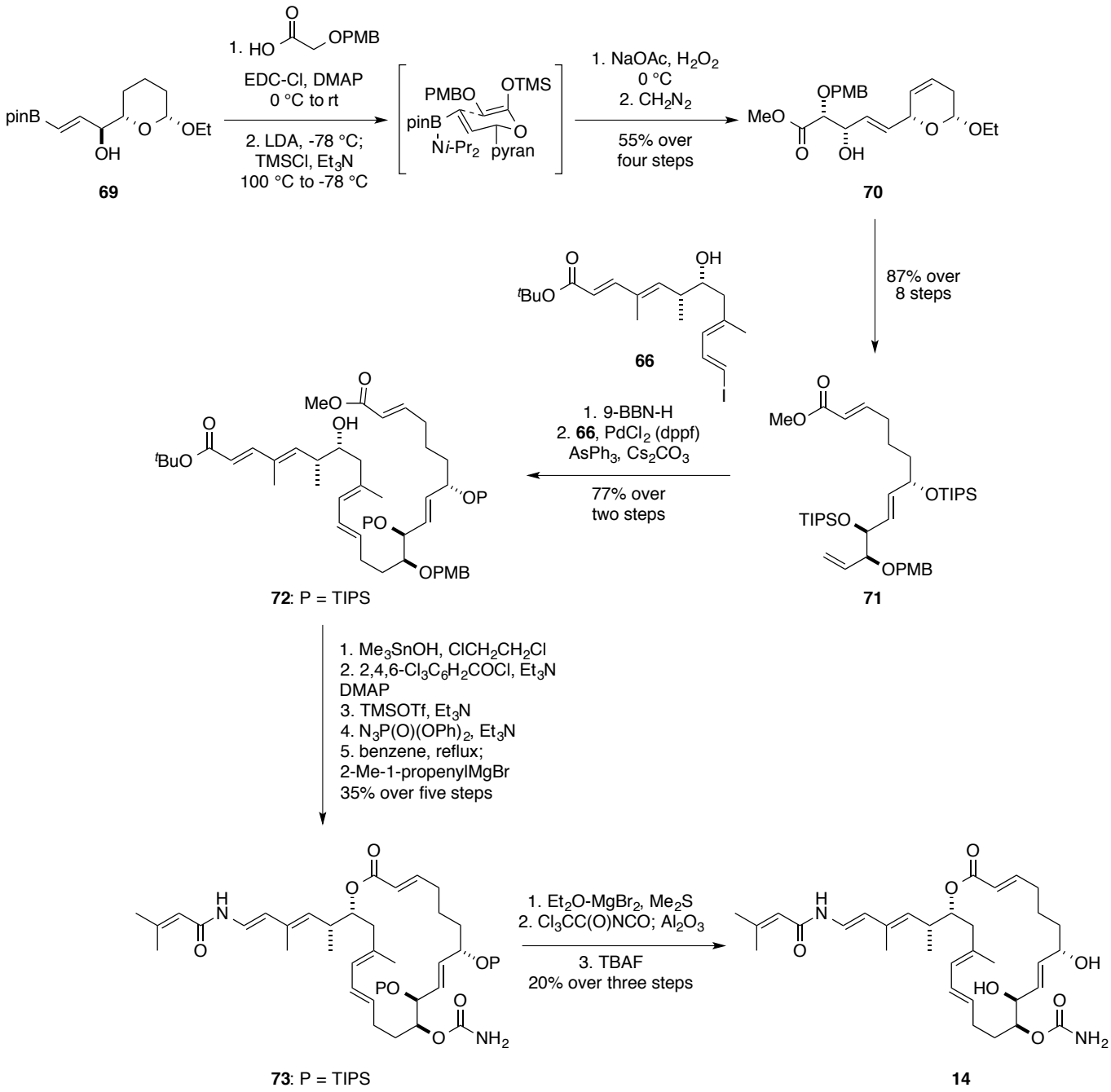
1.5.3: Hall's synthesis of palmerolide A

In 2009, Hall and co-workers synthesised palmerolide A (**14**) utilising their organoboron chemistry to prepare fragment **65**.[43] They envisaged the synthesis of palmerolide A (**14**) would be achieved by coupling vinyl iodide **66** with olefin **67**, *via* hydroboration followed by a Suzuki coupling, then macrolactonisation under Yamaguchi conditions (Scheme 1.5).[36c] Fragment **67** was to be accessed from pyran **65**, which would originate from an Ireland-Claisen [3,3] rearrangement on alkenyl boronate substrate **68**. This strategy was to exploit a boronate substituent as a masked alcohol and provide the differentiation of the C11 hydroxyl over the C10 and C7 hydroxyls.



Scheme 1.5: Hall's retrosynthesis of palmerolide A (**14**)

The synthesis of fragment **67** began with acylation of alcohol **69**, followed by formation of the enolsilane to trigger the Ireland-Claisen rearrangement (Scheme 1.6),[44] which was oxidised with retention of stereochemistry. The carboxylic acid was esterified with diazomethane to produce **70** as a single stereoisomer. From pyran **70** there was a further eight steps in order to obtain fragment **71**,[36c] which was coupled with **66** *via* a Suzuki coupling to form the C13-14 bond giving **72**. The Yamaguchi macrolactonization of **72** was achieved firstly by selective hydrolysis of the methyl ester, followed by treatment of the adduct with 2,4,6-trichlorobenzoyl chloride, DMAP and triethylamine to provide the macrolide **73**.[39] The enoate side chain was transformed into the enamide *via* a Curtius rearrangement, following the conditions used by De Brabander in their synthesis of palmerolide A to give **14**.[21] The synthesis was completed *via* nucleophilic cleavage of the PMB ether, carbamate formation and deprotection to provide palmerolide A (**14**), in a longest linear sequence of twenty-one steps and 0.8% overall yield.



Scheme 1.6: Assembly of palmerolide A (**14**)

1.6: Structural analogues of palmerolide A

In 2008 Nicolaou synthesised a catalogue of palmerolide A analogues, which were subjected to biological evaluation against an array of tumour cells.[45] Initially, diastereoisomers **23**, **24**, **74** and **75** of palmerolide A were

synthesised by inverting the stereocentres at C19 and C20, following the route proposed in their efforts to synthesise natural palmerolide A (**14**, Figure 1.15).[36a,b]

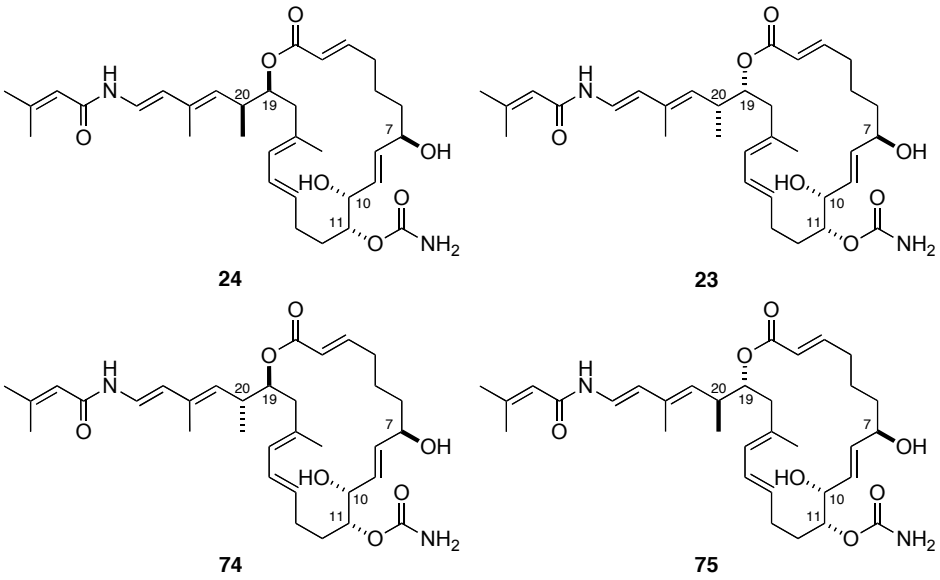


Figure 1.15: Diastereoisomers **23**, **24**, **74** and **75** of palmerolide A synthesised by Nicolaou and Chen

These compounds were tested against a panel of cancer cells using Taxol **3** and natural palmerolide A **14** as standards. Both natural and synthetic palmerolide exhibited the same potent activity against all cell lines tested, whereas the antipodal palmerolide **24** was at least 100 fold less active. Inverting the stereochemistry at the C7, C10 and C11 to give **23**; C7, C10, C11 and C19 to give **74**; and C7, C10, C11 and C20 to give **75**, all resulted in significant loss of activity (Table 1.1).[45]

Cytotoxicity of selected palmerolides against various cancer cell lines (GI_{50} in μM)

	UACC-62	MCF-7	SF268	NCI-H460	IA9	PTX22	A8
3: Taxol	0.022 ± 0.016	0.006 ± 0.001	0.026 ± 0.011	0.007 ± 0.001	0.006 ± 0.001	0.079 ± 0.001	0.021 ± 0.015
14: natural	0.057 ± 0.007	0.040 ± 0.007	0.030 ± 0.012	0.010 ± 0.001	0.038 ± 0.003	0.066 ± 0.007	0.018 ± 0.003
14: synthetic	0.062 ± 0.001	0.065 ± 0.011	0.048 ± 0.006	0.017 ± 0.004	0.059 ± 0.001	0.073 ± 0.005	0.049 ± 0.004
24: *ent*	8.077 ± 0.194	6.260 ± 0.174	9.475 ± 0.593	6.589 ± 0.054	>10	>10	8.844 ± 1.301
23	>10	>10	>10	>10	>10	>10	>10
74	5.398 ± 0.362	5.415 ± 0.247	6.830 ± 0.077	6.108 ± 0.134	>10	7.052 ± 0.474	8.634 ± 1.860
75	8.129 ± 1.187	5.567 ± 0.255	7.961 ± 0.584	7.028 ± 0.192	7.131 ± 1.143	5.865 ± 0.590	6.145 ± 0.922

Table 1.1: Activity of palmerolide A diastereoisomers **23**, **24**, **74** and **75**

Analogues **76**–**79**, shown in figure 1.16, were synthesised *via* a similar method to the palmerolide diastereoisomers **23**, **24**, **74** and **75** but without the formation of the C11 carbamate.[36a,b] Protection of the C10 and C11 hydroxyls gave **80**.

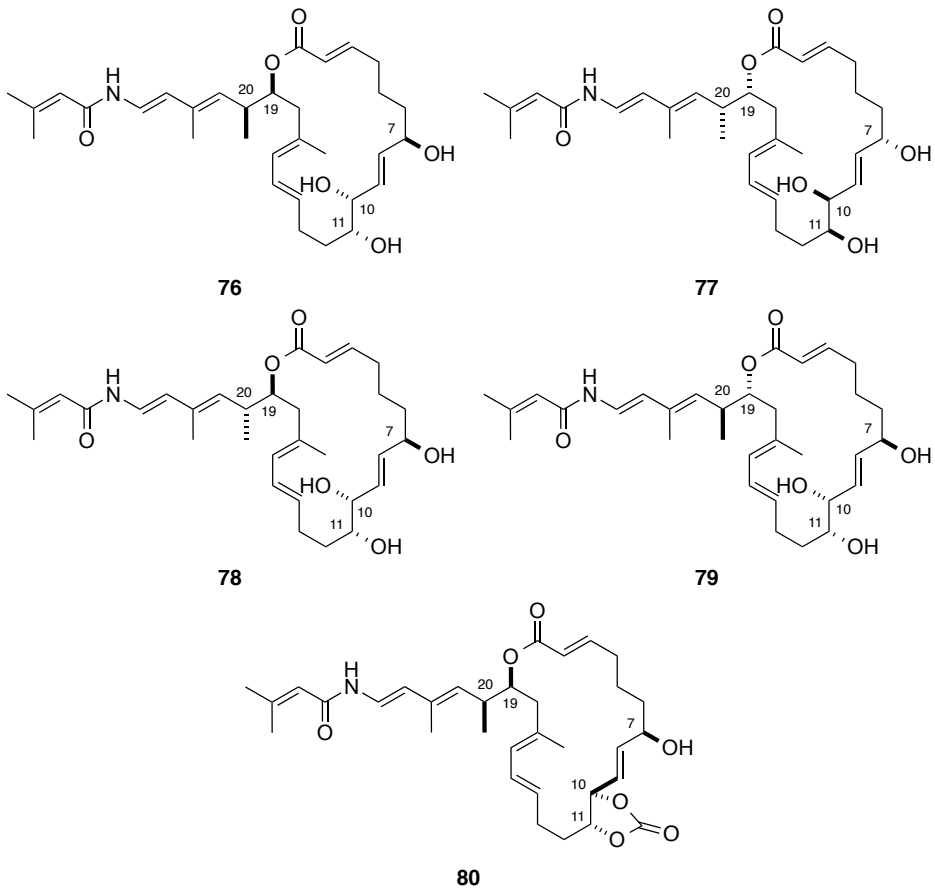


Figure 1.16: Analogues of palmerolide A **76**–**80** synthesised by Nicolaou and Chen

Removing the carbamate from the C11 oxygen of palmerolide A resulted in an approximately 5-fold decrease of activity across most of the cell lines. The carbonate derivative **80** of decarbonated palmerolide **24** was also devoid of significant activity (Table 1.2).[45]

Cytotoxicity of selected palmerolides against various cancer cell lines (GI_{50} in μM)

	UACC-62	MCF-7	SF268	NCI-H460	IA9	PTX22	A8
14: natural	0.057 ± 0.007	0.040 ± 0.007	0.030 ± 0.012	0.010 ± 0.001	0.038 ± 0.003	0.066 ± 0.007	0.018 ± 0.003
76	8.768 ± 0.698	7.299 ± 0.430	9.638 ± 0.362	8.664 ± 0.494	>10	>10	8.477
77	0.322 ± 0.088	0.200 ± 0.026	0.281 ± 0.118	0.075 ± 0.003	0.288 ± 0.017	0.627 ± 0.016	0.083 ± 0.006
78	>10	>10	>10	>10	>10	>10	>10
79	>10	8.257 ± 0.047	>10	>10	>10	>10	>10
80	>10	>10	>10	>10	>10	>10	>10

Table 1.2: Activity of palmerolide A analogues **76**–**80**

The relationship between the polarity of the enamide functionality and the potency against the cell lines was then investigated. This was achieved by utilising the Buchwald copper catalysed coupling of the vinyl iodide with varying primary amides to give a selection of enamide analogues (**81**–**86**, Figure 1.17).[36a,b,45]

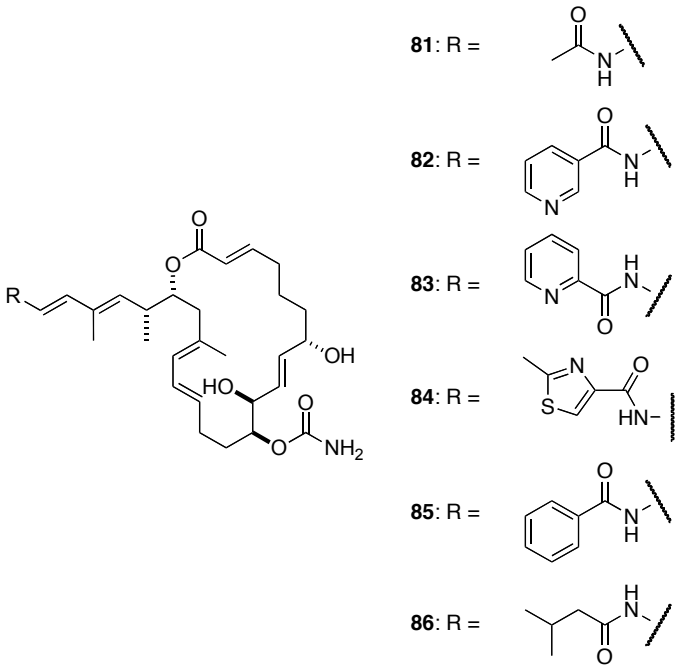


Figure 1.17: Enamide analogues **81**–**86** synthesised by Nicolaou and Chen

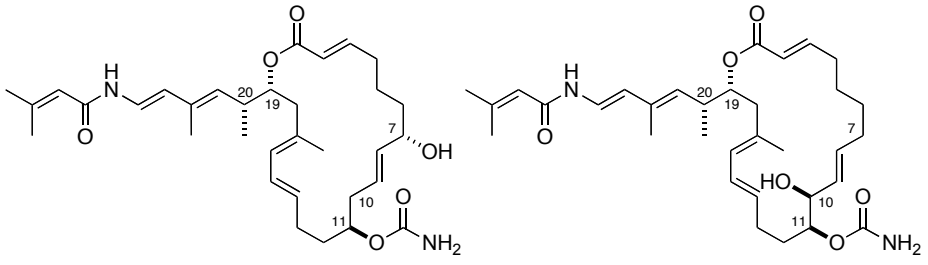
Upon changing the enamide side chain, some interesting trends were shown. Exchanging the isoprene moiety in palmerolide A (**14**), with a methyl group **81** resulted in more than a 100-fold loss of activity, but when more polar groups were substituted such as in **82**, **83** and **84** most of the activity was retained. However when the enamide side chain was converted to a nonpolar aromatic system as in **85** the compound exhibited almost a 10-fold increase in potency against several of the cells tested. When the isoprene substituent on the enamide of palmerolide A was altered to its saturated counterpart **86**, its potency remained at similar levels (Table 1.3).[45]

Cytotoxicity of selected palmerolides against various cancer cell lines (GI_{50} in μM)

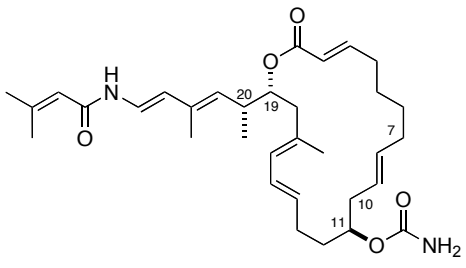
	UACC-62	MCF-7	SF268	NCI-H460	IA9	PTX22	A8
14: natural	0.057 ± 0.007	0.040 ± 0.007	0.030 ± 0.012	0.010 ± 0.001	0.038 ± 0.003	0.066 ± 0.007	0.018 ± 0.003
81	>10	>10	>10	7.291 ± 0.137	7.774 ± 1.094	>10	6.700 ± 0.411
82	0.641 ± 0.000	0.755 ± 0.004	0.592± 0.007	0.430 ± 0.047	0.618 ± 0.051	0.741 ± 0.003	0.460 ± 0.042
83	0.735 ± 0.084	0.796 ± 0.166	0.491 ± 0.132	0.078 ± 0.001	0.378 ± 0.141	0.889 ± 0.029	0.072 ± 0.004
84	8.822 ± 0.083	7.397 ± 0.262	>10	3.796 ± 0.306	7.944 ± 0.430	>10	3.514 ± 1.379
85	0.009 ± 0.001	0.007 ± 0.000	0.007 ± 0.001	0.007 ± 0.000	0.009 ± 0.001	0.039 ± 0.002	0.006 ± 0.000
86	0.067 ± 0.000	0.071 ± 0.008	0.054 ± 0.000	0.061 ± 0.000	0.067 ± 0.002	0.081 ± 0.006	0.057 ± 0.001

Table 1.3: Activity of palmerolide A enamide analogues **81**–**86**

In addition to the enamide analogues prepared, a number of macrolide analogues were prepared by varying the subunits used in the synthesis of palmerolide A. They synthesised the 20-membered macrolide without either the C7 hydroxyl **87**, or C10 hydroxyl **88**, but were unsuccessful in synthesising the macrolide missing both the C7 and C10 hydroxyls **89** (Figure 1.18). [36a,b,45]



87 **88**



89

Figure 1.18: De-oxygenated analogues **87**–**89** synthesised by Nicolaou and Chen

It was shown that the analogue lacking the C10 hydroxyl **87** lost significant activity across the all cell lines tested but for **88** where the C7 hydroxyl was removed the potency was shown to be of comparable levels to palmerolide A (**14**, Table 1.4).[45]

Cytotoxicity of selected palmerolides against various cancer cell lines (GI_{50} in μM)

	UACC-62	MCF-7	SF268	NCI-H460	IA9	PTX22	A8
14: natural	0.057 ± 0.007	0.040 ± 0.007	0.030 ± 0.012	0.010 ± 0.001	0.038 ± 0.003	0.066 ± 0.007	0.018 ± 0.003
87	6.979 ± 0.531	7.585 ± 0.252	8.764 ± 0.315	6.396 ± 0.106	7.135 ± 0.667	8.062 ± 0.037	6.691 ± 0.439
88	0.063 ± 0.001	0.074 ± 0.000	0.060 ± 0.004	0.055 ± 0.002	0.072 ± 0.001	0.076 ± 0.000	0.061 ± 0.013

Table 1.4: Activity of de-oxygenated palmerolide A analogues **87** and **88**

From this data it can be concluded that the C7 hydroxyl is not essential for activity, as the potency of **88** was comparable to palmerolide A (**14**) in all the cell lines tested. It is shown that the C11 carbamate is needed for activity and when a non-polar aromatic substituent is appended on the enamide side chain such as **85**, the potency increases.

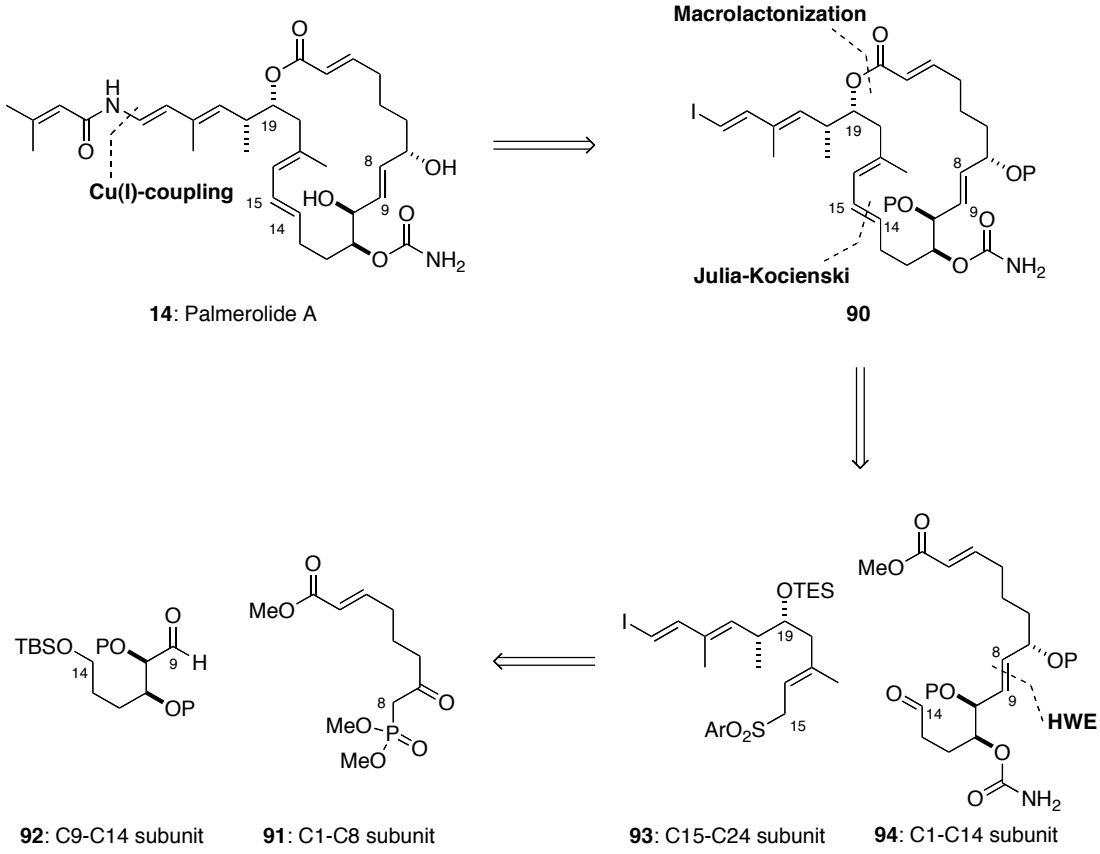
1.7: Florence strategy for synthesis of the palmerolides

1.7.1: Strategy for synthesis of palmerolide A

The primary objective of this project was to develop a flexible strategy for the synthesis of palmerolide A (**14**), in which the key subunits can be modified, allowing access to a wide range of novel analogues. The structure of palmerolide A (**14**) posed some interesting challenges for a synthetic

endeavour as the 20-membered macrocycle contains four stereocentres, four (*E*)-olefins with a C11 carbamate group and a C19 unsaturated enamide side chain.

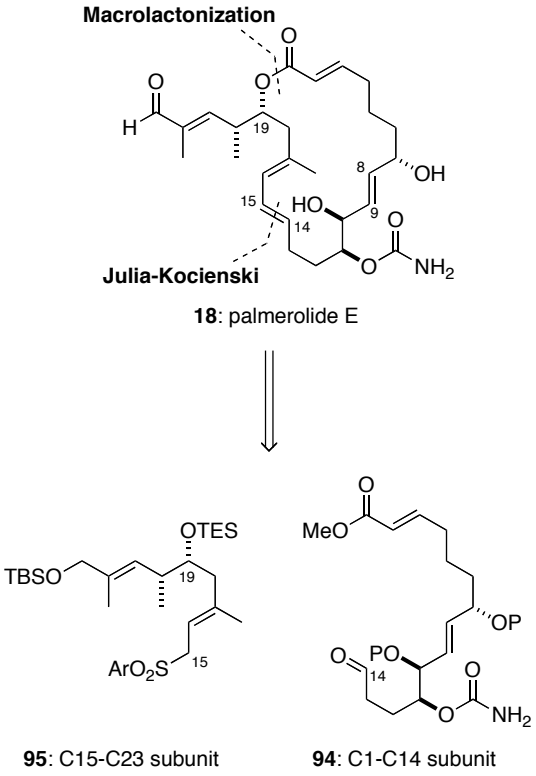
It was envisaged the most efficient way to achieve the synthesis was to devise a convergent approach, as it would allow the synthesis of palmerolide A (**14**), while also allowing access to other members of the palmerolide family and their analogues, through the alteration of the key subunits. Our strategy differs from previous synthesis as it has the functionality present at an early stage (Scheme 1.7), which has been shown to be difficult and costly to insert later on in the sequence.[21,36] This route proposes a late stage enamide coupling *via* a Buchwald coupling of the C24 vinyl iodide.[46] The macrolide core **90** is dissected into three key subunits, the C1-C8 subunit **91**, the C9-C14 subunit **92** and the C15-C24 subunit **93**. The assembly of these subunits was to be achieved by coupling the C1-C8 β-ketophosphonate **91** with the C9-C14 aldehyde **92** *via* a Horner-Wadsworth Emmons coupling to give the C1-C14 subunit **94**. The C14-C15 bond would be introduced *via* a Julia-Kocienski olefination of the elaborated C1-C14 subunit **94** and the C15-C24 sulfone **93** followed by formation of the macrocycle **90** *via* macrolactonisation.[39] This approach offers both flexibility and high levels of convergence, as the order of the key bond couplings could be reversed if necessary, while all the key functionalities are present for the core coupling to minimise post-coupling operations. Through the application of this strategy it is envisaged that it will be possible to access palmerolide A (**14**) and other members of its family, through subtle changes in key subunits.



Scheme 1.7: Retrosynthesis of palmerolide A (**14**)

1.7.2: Strategy for synthesis of palmerolide E

This attractive aspect of our present approach will allow the synthesis of novel analogues through the variation of the key subunits or the enamide side chain, while also being applicable to other fragments of the palmerolide family. Palmerolide E (**18**) can be obtained *via* the route developed for palmerolide A (**14**), but by synthesising the alternative C15-C23 subunit **95** with a protected hydroxyl, instead of the C15-C24 vinyl iodide **94** (Scheme 1.8).



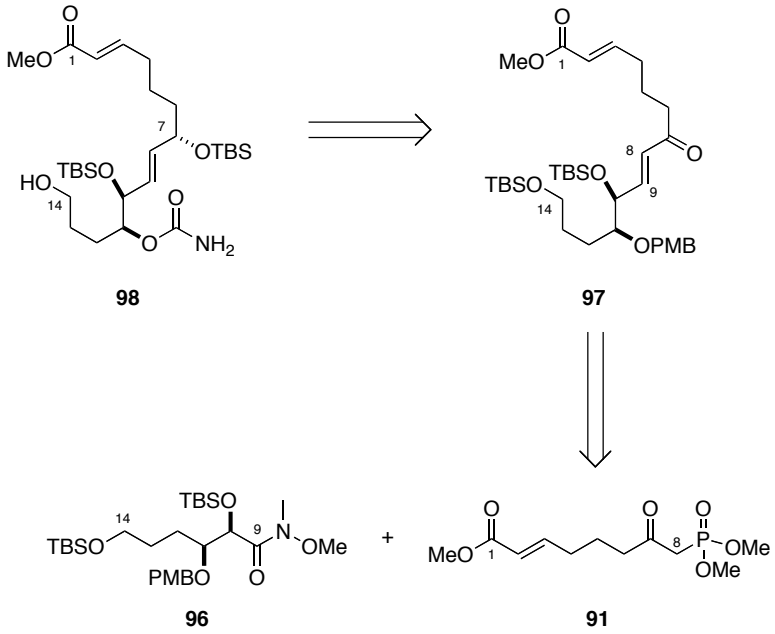
Scheme 1.8: Retrosynthesis of palmerolide E (**18**)

Results and Discussion

2.0: Synthesis of C1-C14 subunit

2.0.1: Retrosynthesis

Following the proposed retrosynthetic plan, the aim was to reduce the Weinreb amide **96** to its aldehyde then perform a Horner-Wadsworth Emmons reaction to couple the C1-C8 subunit (**91**) with the C9-C14 subunit (**96**), forming the desired C8-C9 (*E*)-olefin of C1-C14 fragment **97** (Scheme 2.1). The C7 ketone **97** was to be reduced to give the (7*S*)-hydroxyl, this would then be TBS-protected followed by removal of the C11 PMB-protecting group. Synthesis of the carbamate, then removal of the primary TBS-protecting group would give the C1-C14 subunit (**98**).

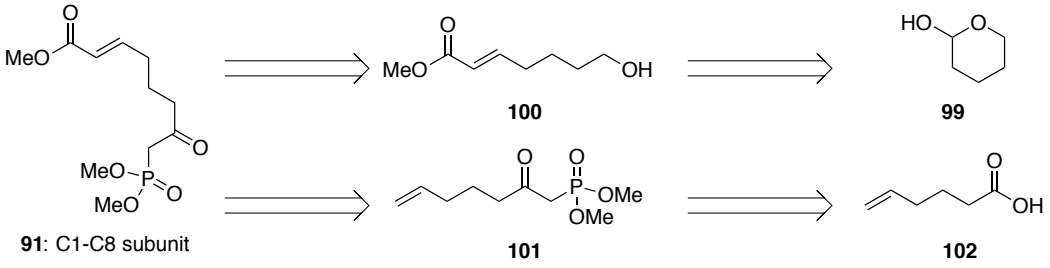


Scheme 2.1: Retrosynthesis of C1-C14 subunit **98**

2.1: Synthesis of C1-C8 subunit

2.1.1: Retrosynthesis

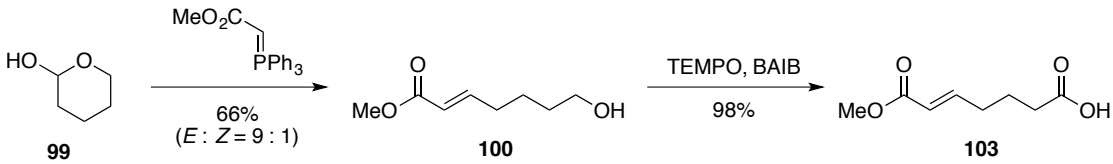
It was envisaged that the preparation of the C1-C8 subunit **91** could be achieved using either of the retrosynthetic analysis outlined in Scheme 2.2. Starting from lactol **99**, Wittig olefination would introduce the C1-C3 enoate. Oxidation of the primary alcohol **100** followed by formation of the acid chloride and addition of the lithium-anion of dimethyl methylphosphonate should furnish the requisite C1-C8 subunit **91**. The alternative approach could utilize a cross metathesis reaction to introduce the C1-C3 (*E*)-enoate from **101**. Conversion of 5-hexenoic acid **102** to the β-ketophosphonate *via* the acid chloride, followed by Grubbs cross metathesis with methyl acrylate would complete the synthesis of the C1-C8 subunit (**91**).



Scheme 2.2: Retrosynthesis of C1-C8 subunit **91**

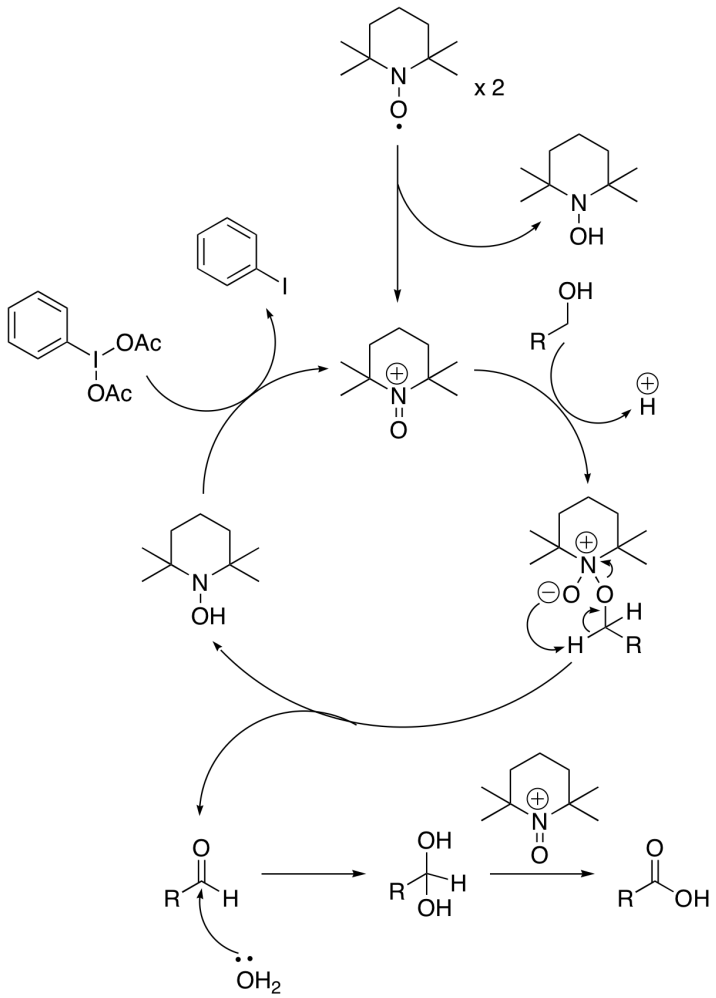
2.1.2: Synthesis of carboxylic acid 103

The initial route for the synthesis of the C1-C8 subunit **91** started with a Wittig olefination of tetrahydro-2*H*-pyran-2-ol **99** to introduce the C1-C3 enoate and provide ester **100**. Treatment of **99** with methyl (triphenylphosphoranylidene) acetate in dichloromethane provided the ester **100** in good yield with 9 : 1, *E* : *Z* selectivity (Scheme 2.3). The resulting primary alcohol **100** was oxidised with TEMPO and BAIB in acetonitrile and water to give the carboxylic acid **103** in excellent yield.[47]



Scheme 2.3: Synthesis of carboxylic acid **103**

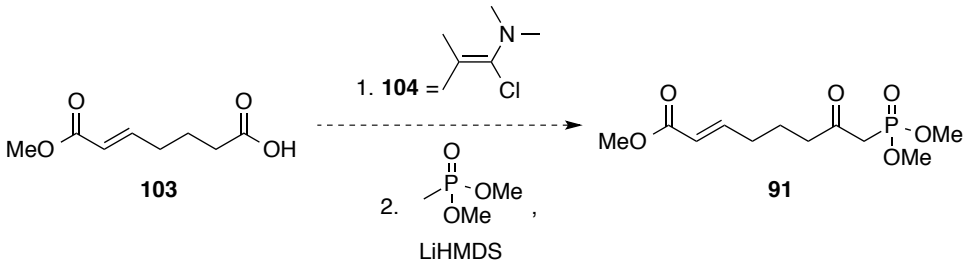
A common problem with traditional methods for oxidising alcohols to carboxylic acids is that the reagents and conditions tend to be harsh. A milder method is the TEMPO oxidation, which can oxidise the alcohol to the aldehyde or the carboxylic acid depending on the solvent system used.[48] In the reaction, TEMPO mediates the oxidation of the alcohol to the aldehyde, followed by regeneration using stoichiometric quantities of BAIB, so further oxidation can occur to give the carboxylic acid (Scheme 2.4).[49]



Scheme 2.4: TEMPO oxidation mechanism

2.1.3: Attempted synthesis of C1-C8 subunit (91)

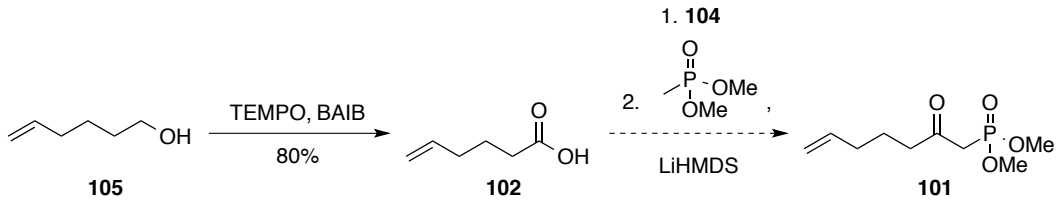
With the carboxylic acid **103** in hand, the acid chloride was synthesised *via* the reaction of **103** in dichloromethane with Ghosez reagent (**104**), a mild reagent for converting carboxylic acids into their corresponding acid chlorides.[50] The crude acid chloride was reacted directly, without any purification, with the lithium anion of dimethyl methylphosphonate in tetrahydrofuran but unfortunately this did not form the desired β-ketophosphonate **91** and no starting acid **103** was recovered (Scheme 2.5).



Scheme 2.5: Attempted synthesis of C1-C8 subunit **91**

2.1.4: Attempted synthesis of β-ketophosphonate 101

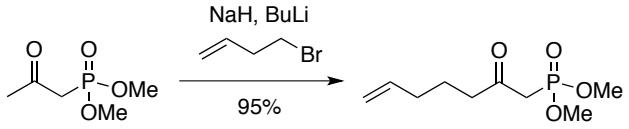
A similar route was also attempted with the introduction of the phosphonate to an acid chloride. TEMPO oxidation of 5-hexen-1-ol **105**, in acetonitrile and water (1 : 1) gave carboxylic acid **102** in 80% yield.[47] Carboxylic acid **102** was reacted with Ghosez reagent (**104**),[50] to give the acid chloride, which was used directly in the reaction with dimethyl methylphosphonate and LiHMDS in tetrahydrofuran but again the β-ketophosphonate (**101**) was not formed and the starting acid **102** could not be recovered (Scheme 2.6).



Scheme 2.6: Attempted synthesis of β-ketophosphonate **101**

2.1.5: Synthesis of β-ketophosphonate 101

Following the unsuccessful attempts to introduce the phosphonate by displacement, the C1-C8 subunit (**91**) synthesis was modified to have the phosphonate in place from the start of the sequence. Treatment of β-ketophosphonate **106** with sodium hydride and *n*-butyl lithium formed the dianion, which underwent alkylation with 4-bromobutene to afford the desired phosphonate **101** in excellent yield (Scheme 2.7).[51]



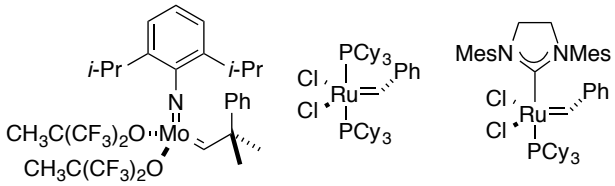
106 **101**

Scheme 2.7: Synthesis of β-ketophosphonate **101**

2.1.6: Cross metathesis reaction

Cross metathesis reactions are a powerful method for forming carbon-carbon double bonds, they can tolerate many functional groups and are reactive towards a large range of olefins.[52] Many metal catalysts have been developed for this purpose such as Schrock's alkoxy imidomolybdenum complex (**108**),[53] Grubbs I generation (**109**) and Grubbs II generation catalysts (**107**, Figure 2.1).[54,55] Molybdenum catalysts are very active but they are unstable to air and are required to be prepared and used under an inert atmosphere. To combat this Grubbs and co-workers developed ruthenium alkylidenes, these catalysts are more stable and have proved to be compatible

with numerous functional groups, becoming benchmark catalysts for these transformations.



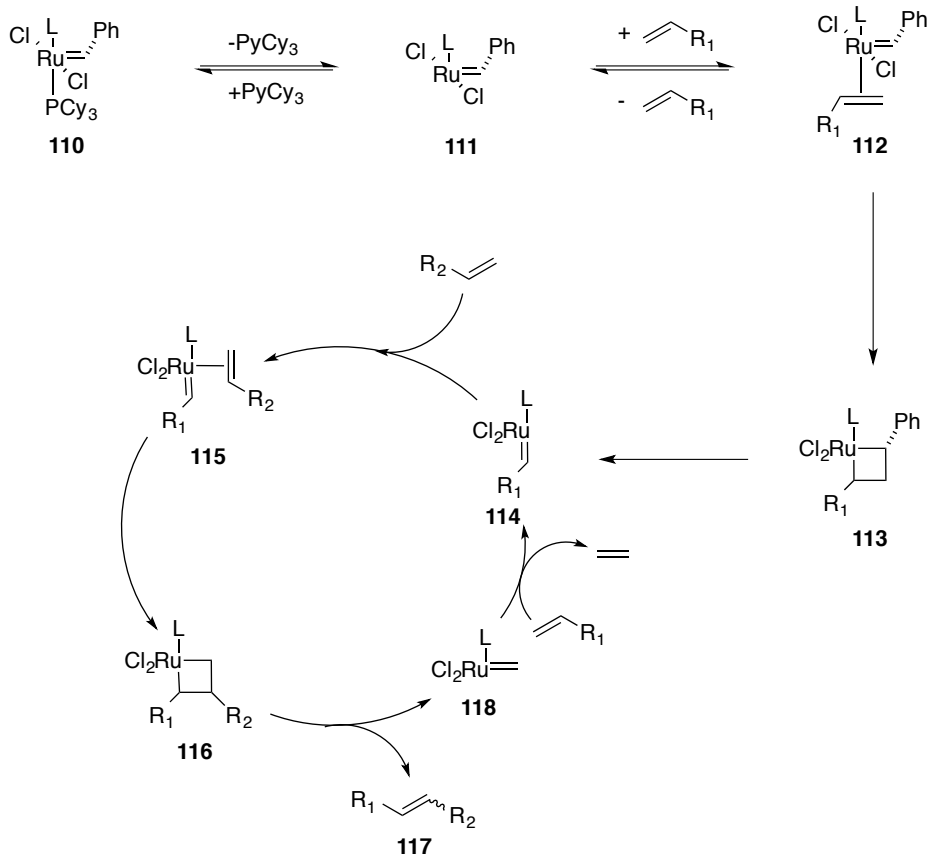
108 **109** **107**

Figure 2.1: Commonly used cross metathesis catalysts

Grubbs ruthenium-based catalysts exhibit good reactivity in a variety of cross metathesis reactions. The electron rich phosphine ligands of the ruthenium metal centre in **107** and **109** increases metathesis reactivity, and the *N*-heterocyclic carbene ligand in **107** is believed to help to stabilise the ruthenium intermediate in the catalytic cycle.[54,55]

With the appearance of well-defined catalysts, the mechanism of the olefin metathesis reaction was investigated thoroughly. After numerous kinetics experiments, Grubbs and co-workers were able to determine that the olefin metathesis reaction proceeds through a dissociative mechanism. The first step consists in the release of a phosphine from the catalyst (**110**) to provide the 14 electron species **111** (Scheme 2.8).[56,57] Ruthenium then coordinates with the olefin to give intermediate **112** which then forms metallocyclobutane **113**. Retro [2+2] cycloaddition provides metal carbenoid **114** and following coordination with the second olefin gives intermediate **115**, which then forms the second metallocyclobutane **116**. A retro [2+2] cycloaddition provides the

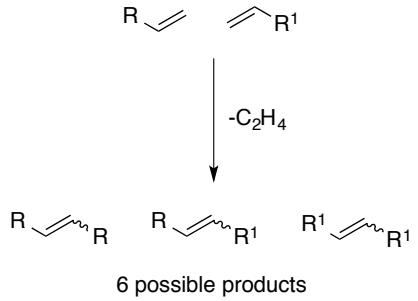
cross-metathesis product **117** as well as the propagating species **118** that can re-coordinate with the olefin and re-enter the catalytic cycle.



Scheme 2.8: Dissociative mechanism for olefin cross metathesis

In its first applications, cross metathesis suffered from the fact that mixtures of products were obtained with low levels of selectivity. Indeed, a cross metathesis reaction can give six possible products not including the unreacted starting material (Scheme 2.9). This lack of selectivity had limited the utility of cross metathesis reactions in synthesis however, significant progress has been made in the recent years. Grubbs and co-workers have investigated cross-metathesis using different classes of olefins and described a general empirical model useful to predict product selectivity.[58] By reacting an olefin

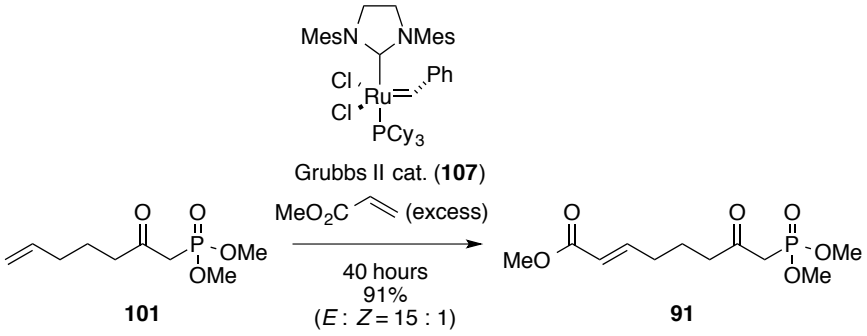
of high reactivity (electron rich) with an olefin of lower reactivity (electron poor), it is possible to achieve a selective cross-metathesis and to obtain products with excellent *E* : *Z* ratios.



Scheme 2.9: Mixture of products in cross metathesis

2.1.7: Synthesis of C1-C8 subunit (91) utilising cross metathesis

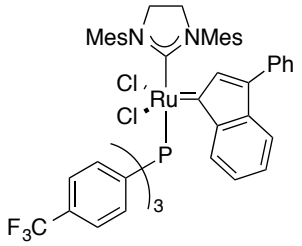
Introduction of the C2-C3 (*E*)-enoate was then achieved *via* a cross metathesis reaction of phosphonate **101** with methyl acrylate and 1 mol% of Grubbs II catalyst (**107**), which gave the C1-C8 subunit **91** in excellent yield with high levels of *E* : *Z* selectivity (15 : 1, Scheme 2.10), as determined *via* ^{1}H NMR spectroscopy.



Scheme 2.10: Cross metathesis to synthesize C1-C8 subunit (**91**)

2.1.8: Synthesis of C1-C8 subunit using catalyst 119

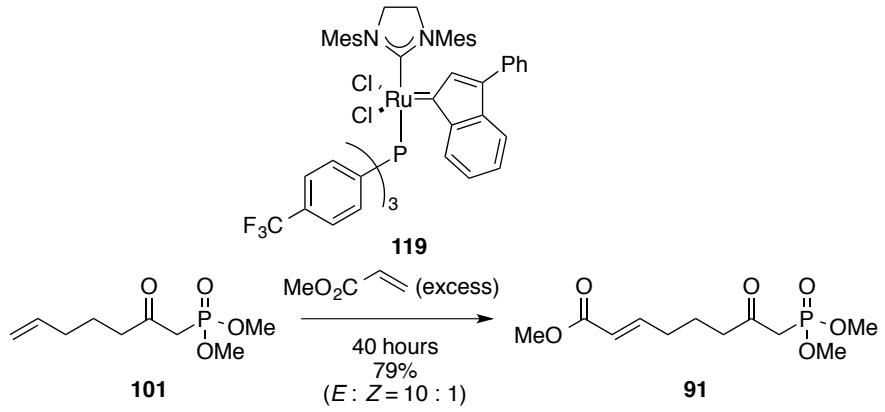
The cross metathesis reaction shown in scheme 2.10 was also attempted using a similar ruthenium based catalyst developed by Prof. Steve Nolan (**119**, Figure 2.2) with the intention of either improving the yield or the *E* : *Z* selectivity by the use of milder reaction conditions.[59]



119

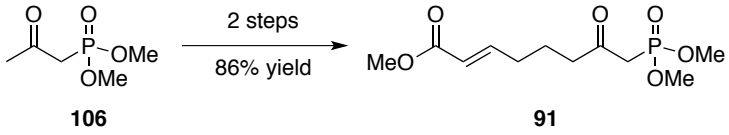
Figure 2.2: Nolan-modified ruthenium catalyst **119**

This reaction using catalyst **119** was completed using the same equivalents of reagents and 1 mol% of the catalyst. Initially when the reaction was left overnight at room temperature, there was 55% conversion with recovery of starting material, but when **119** was used in the same conditions as those used earlier in the Grubbs II cross metathesis, with heating under reflux for forty hours, the C1-C8 subunit **91** was produced with a yield of 79% and 10 : 1 *E* : *Z* selectivity (Scheme 2.11).



Scheme 2.11: Modified cross metathesis reaction

In summary the synthesis of the C1-C8 subunit **91**, was completed *via* an alkylation of the β-ketophosphonate **106** with 4-bromobutene, then a cross metathesis reaction of **101** using Grubbs II catalyst and methyl acrylate to give the C1-C8 subunit **91** in excellent yield and selectivity over the two steps (Scheme 2.12).



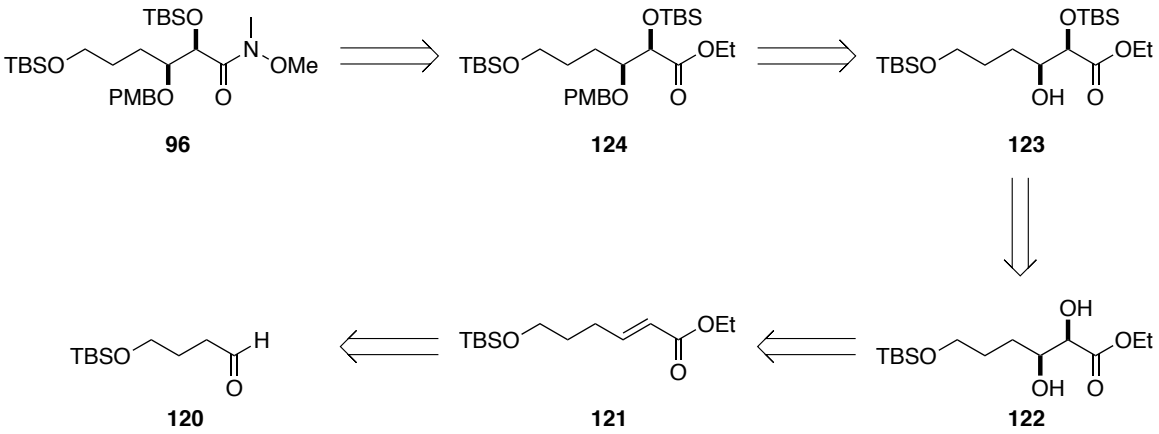
Scheme 2.12: Synthesis of C1-C8 subunit **91**

With the C1-C8 subunit **91** in hand, the attention turned towards the synthesis of the C9-C14 subunit **96**, so the Horner-Wadsworth Emmons reaction to form the C8-C9 olefin could be performed.

2.2: Synthesis of C9-C14 subunit

2.2.1: Retrosynthesis

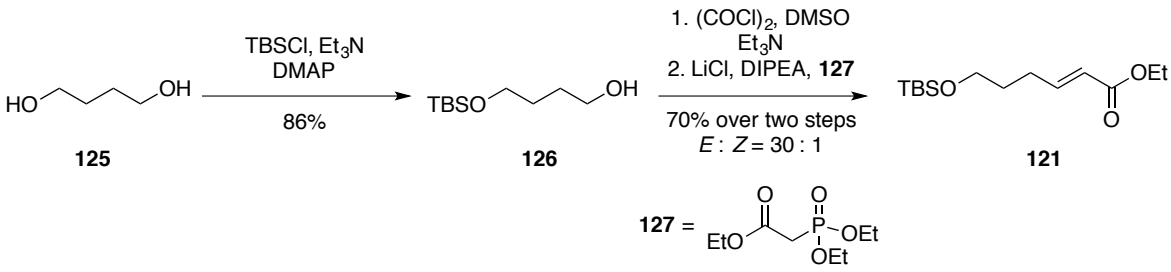
It was proposed that the fully protected C9-C14 subunit **96** could be synthesised by the reaction sequence outlined in Scheme 2.13, where a Horner-Wadsworth Emmons reaction involving triethyl phosphonoacetate and the oxidized protected diol **120**, would give enoate **121**. Sharpless asymmetric dihydroxylation of enoate **121** would provide diol **122**, which was expected to be monoprotected as its TBS-ether **123**. It was anticipated that hydrogen bonding between the β-hydroxyl and ester group of diol **122** would ensure that protection would occur primarily on the α-hydroxyl group. Subsequent protection of the β-hydroxyl as its PMB-ether should provide the fully protected C9-C14 fragment **96**. Formation of the Weinreb amide **96** then reduction would give the corresponding aldehyde to be used in the Horner-Wadsworth Emmons reaction with the C1-C8 subunit (**91**).



Scheme 2.13: Retrosynthesis of C9-C14 subunit **96**

2.2.2: Synthesis of enoate 121

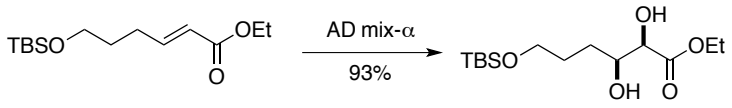
The synthesis of the C9-C14 subunit began from 1,4-butanediol **125**, which was mono-protected as its TBS-ether **126**, *via* careful control of the reaction equivalents, in excellent yield (Scheme 2.14). Swern oxidation gave the aldehyde, which was immediately followed by a Horner-Wadsworth Emmons reaction using the Masamune-Roush conditions,[60] with triethyl phosphonoacetate **127**, to provide enoate **121** in excellent yield over the two-step sequence with excellent *E* : *Z* selectivity (30 : 1). The isomers could be separated with ease *via* column chromatography.



Scheme 2.14: Synthesis of enoate **121**

2.2.3: Sharpless asymmetric dihydroxylation

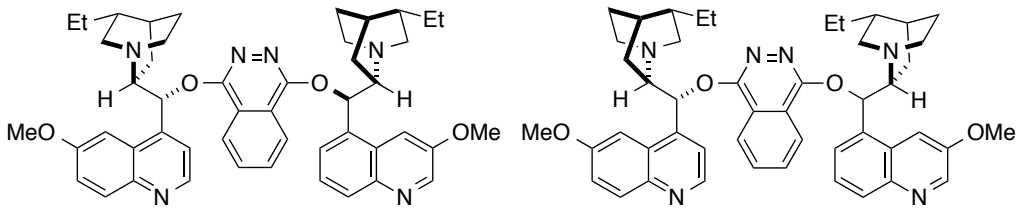
The next stage involved a Sharpless asymmetric dihydroxylation to introduce the required *syn*-hydroxylation at C10-C11.[61] Reacting AD-mix-α with enoate **121** and methanesulfonamide, gave the 1,2-diol **122** in excellent yield (Scheme 2.15).



121 **122**

Scheme 2.15: Sharpless asymmetric dihydroxylation of **122**

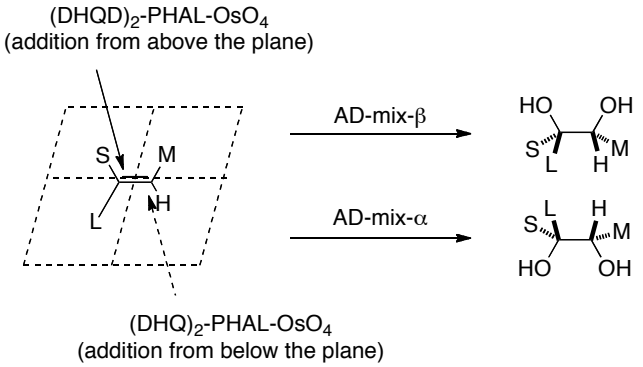
The diastereoselectivity of this reaction is controlled by the choice of cinchona alkaloid ligand, either $(DHQ)_2$-PHAL (**128**) in AD-mix-α or $(DHQD)_2$-PHAL (**129**) in AD-mix-β (Figure 2.3).[61a,b]



128: α = $(DHQ)_2$-PHAL **129**: β = $(DHQD)_2$-PHAL

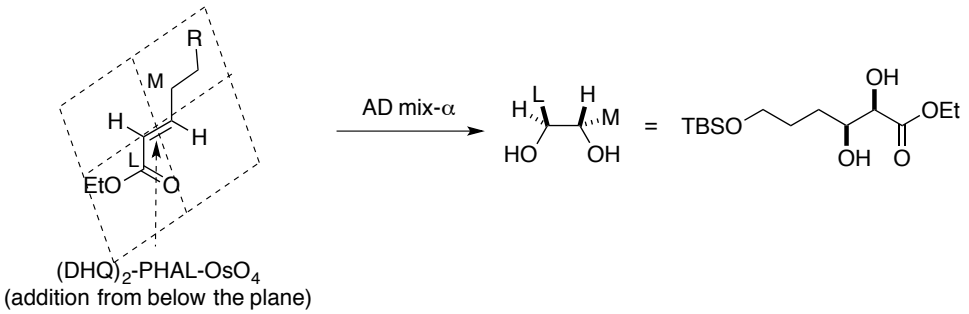
Figure 2.3: Cinchona alkaloid ligands **128** and **129**

To determine which of the cinchona alkaloid ligands will give the desired stereochemical outcome the Sharpless mnemonic must be used (Scheme 2.16).[62,63] Employing AD-mix-α leads to high levels of α-facial selectivity and gives addition from below the plane, using the mnemonic, while AD-mix-β will give the opposite.



Scheme 2.16: Sharpless mnemonic for prediction of stereochemistry

When the Sharpless mnemonic is applied to the enoate **121** (Scheme 2.17), it can be seen that the ester functionality is acting as the large substituent and the side chain as the medium substituent. With the use of AD-mix-α the stereochemistry predicted is C10-(*R*) and C11-(*S*).

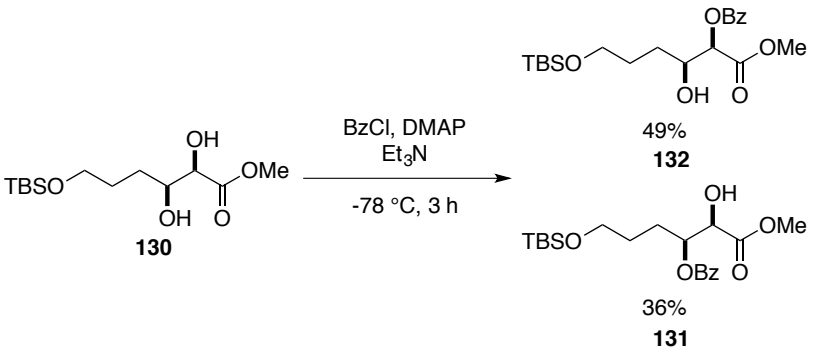


Scheme 2.17: Sharpless mnemonic applied for enoate **121**

2.2.4: Selective protection of diol 122

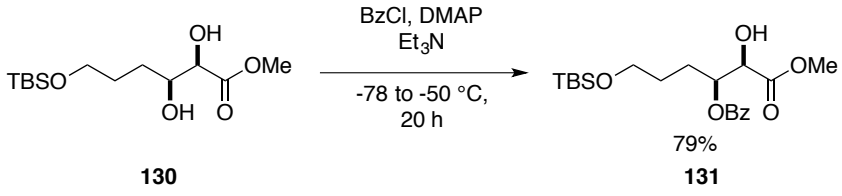
With diol **122** in hand, the focus was turned to the selective protection of the α-hydroxyl. After considerable effort Murray found that reacting methyl-diol **130** with benzoyl chloride under basic conditions, using DMAP as a nucleophilic catalyst, for three hours at -78 °C, consumed all the starting

material and upon purification, 36% of the β-protected hydroxyl **131** and 49% of the α-protected hydroxyl **132** were found (Scheme 2.18).[64]



Scheme 2.18: Attempted selective protection of diol **130**

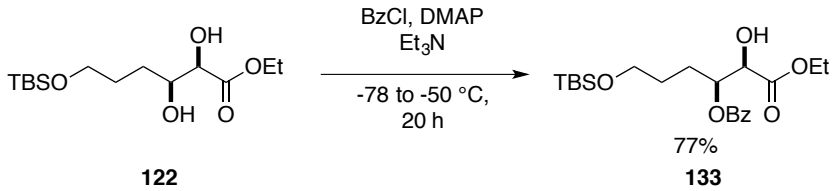
Further investigation of the reaction conditions found that the isolated yield could be improved to 79% by starting the reaction at -78 °C and allowing the reaction to progress at -50 °C for sixteen hours (Scheme 2.19). It is believed that the α-protected benzoate (**132**) forms first, as indicated by the higher yield of this product at shorter reaction times (3 h, 36%), and elevating the temperature and extending the reaction time, allows equilibration to the more thermodynamically stable β-protected benzoate (**131**).



Scheme 2.19: Selective benzoyl protection of diol **130**

Application of this protocol to diol **122**, was shown to give comparable yields under the same condition as the reaction with **130**. This reaction was also

shown to work in a multigram scale where using 4.8 g of diol **122** gave the β-protected benzoate **133** in 77% yield (Scheme 2.20).

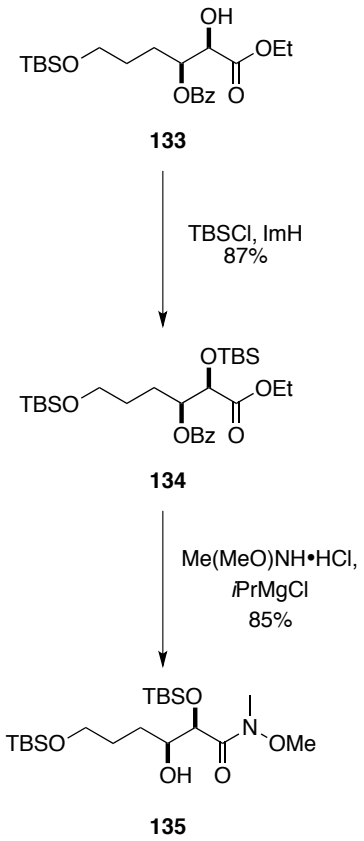


122 **133**

Scheme 2.20: Selective benzoyl protection of diol **122**

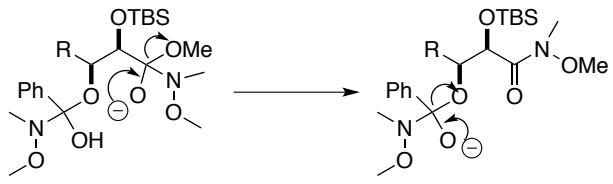
2.2.5: Synthesis of the C9-C14 subunit (96)

The β-protected benzoate **133** was then protected as its TBS-ether *via* treatment of the unprotected α-hydroxyl with TBSCl and imidazole to give the orthogonally protected diol ester **134** in excellent yield. Conversion of **134** to deprotected Weinreb amide **135** occurred in excellent yield (Scheme 2.21).



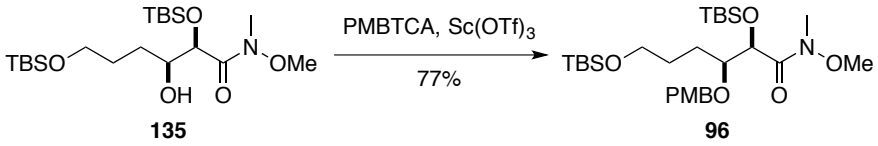
Scheme 2.21: Synthesis of Weinreb amide **135**

In the formation of Weinreb amide **135**, the conditions are shown to also remove the benzoyl protecting group. These two transformations occur stepwise as the alkoxy group is the preferred leaving group from both tetrahedral intermediates (Scheme 2.22).



Scheme 2.22: Formation of the Weinreb amide

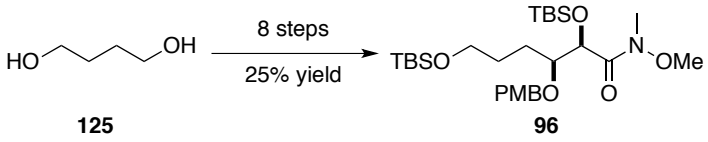
This left only the secondary C11-hydroxyl to be protected as its PMB-ether. Thus, treatment of alcohol **135** with PMBTCA and scandium triflate, provided the fully protected C9-C14 subunit (**96**) in good yield (Scheme 2.23).[65]



135 **96**

Scheme 2.23: PMB-protection to give the C9-C14 subunit (**96**)

In summary the C9-C14 subunit (**96**) was synthesised *via* a Horner-Wadsworth Emmons reaction to give the enoate **121**, then dihydroxylation to give diol **122**. This was selectively β-protected as benzoyl ether **133** and after three further steps, gave the C9-C14 subunit (**96**) in 25% yield over 8 steps (Scheme 2.24).



125 **96**

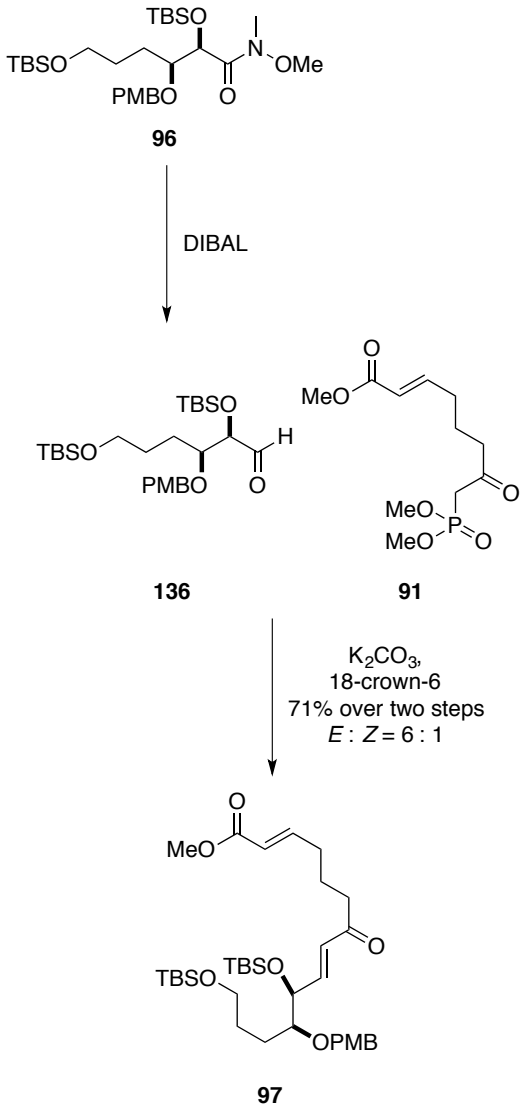
Scheme 2.24: Synthesis of C9-C14 subunit **96**

2.3: Synthesis of C1-C14 subunit

2.3.1: Horner-Wadsworth Emmons coupling

With both the C1-C8 subunit (**91**) and the C9-C14 subunit (**96**) in hand, the next step was to form the C8-C9 (*E*)-olefin of **97**. The reaction was carried out

by treating the C9-C14 Weinreb amide (**96**) with DIBAL to give aldehyde **136** that was used directly in the Horner-Wadsworth Emmons reaction with the C1-C8 subunit (**91**) using K_2CO_3 and 18-crown-6 to give the C1-C14 subunit (**97**) in a 71% yield over the two steps with good *E* : *Z* selectivity (Scheme 2.25).

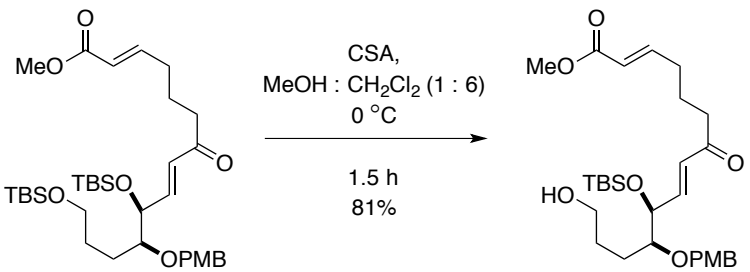


Scheme 2.25: Formation of C8-C9 (*E*)-olefin in C1-C14 subunit (**97**)

2.3.2: CSA deprotection of 97

The proposed strategy for the coupling of the C1-C14 subunit (**98**) with either the C15-C24 (**93**, palmerolide A) or the C15-C23 subunit (**95**, palmerolide E) requires that the primary TBS-ether group of **98** be cleaved in the presence of a secondary TBS. The resultant primary alcohol can then be oxidised to an aldehyde prior to performing the proposed Julia-Kocienski olefination with either **93** or **95**, which would give the pre-cyclised skeleton of either palmerolide A or E, respectively.

The selective cleavage of the primary TBS-ether in the presence of the secondary TBS-ether of **97** proceeded using CSA in a 1 : 6 mixture of methanol : dichloromethane for one and a half hours giving **137** in excellent yield (Scheme 2.26).[66] The time and ratios of methanol to dichloromethane had to be carefully monitored as if the reaction was left for too long, deprotection of the allylic C10-TBS ether was observed.

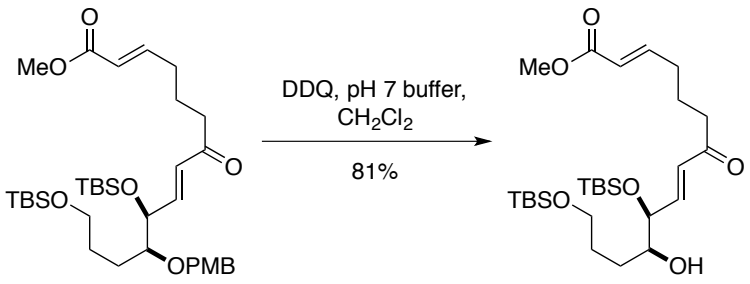


97 **137**

Scheme 2.26: Deprotection of C14-hydroxyl

2.3.3: Removal of PMB ether

With the removal of the primary TBS-protecting group shown to be successful, the deprotection of the C11 PMB-protecting group was investigated. This procedure has been shown to be problematic at later stages in previous palmerolide A syntheses, such as Hall's synthesis of palmerolide A, where the deprotection of the C11-PMB and C7- and C10-TIPS had a combined yield of 16% for the two steps.[36c] This was attributed to the benzyl ring of the PMB folding across the macrolide ring, which can interact with the diene contained within the macrolide core. Anticipating this, the deprotection was attempted before the Julia-Kocienski olefination with the C15-C24 subunit (**93**), as the C14-C15 and C16-C17 olefins were not yet in place. **97** was smoothly reacted with recrystallized DDQ to give the C11 deprotected subunit **138** in excellent yield (Scheme 2.27).

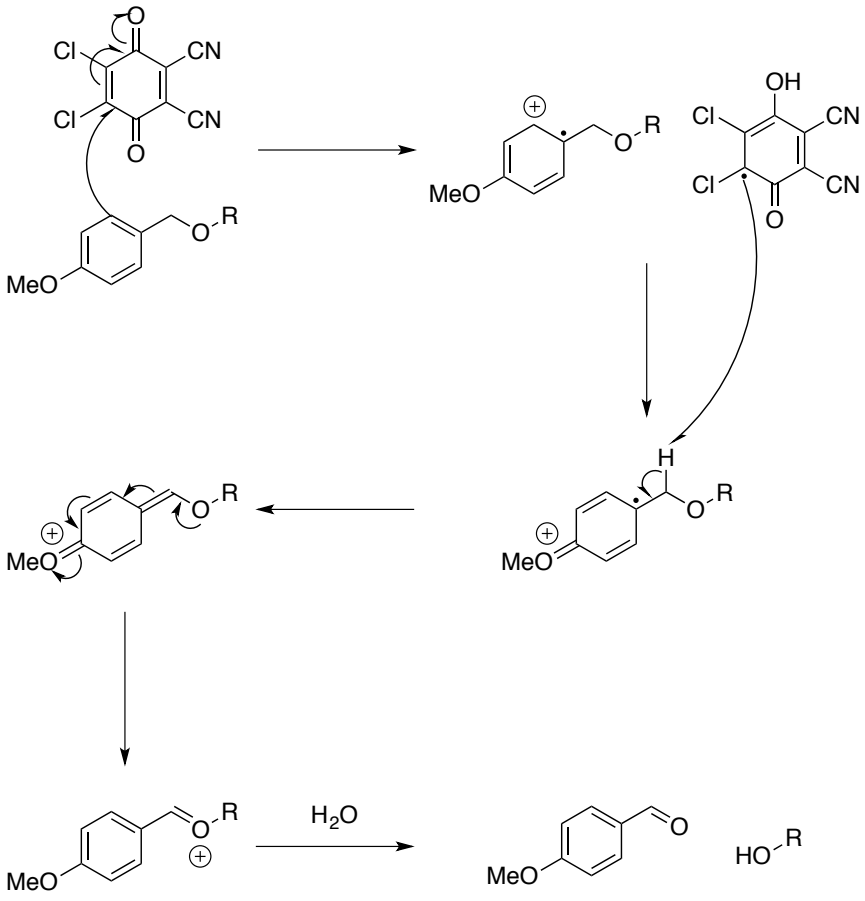


97 **138**

Scheme 2.27: DDQ deprotection of **97**

DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is a powerful and selective reagent for deprotections,[67] though it can also be used as a reagent for oxidative couplings[68] and the dehydrogenation of hydroaromatic

compounds.[69] Deprotection of the *p*-methoxybenzyl ether proceeds *via* two single electron transfers with the methoxy group stablising the intermediates, which is followed by a formal hydride transfer to give alcohol and *p*-methoxybenzaldehyde (Scheme 2.28).

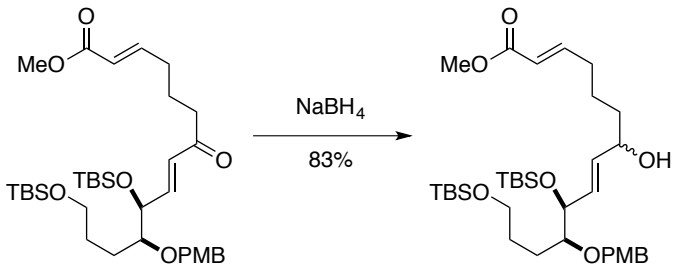


Scheme 2.28: Mechanism of DDQ deprotection

2.3.4: Reduction of C7 ketone

The next challenge to overcome was the selective reduction of the C7 ketone. Our strategy required it to be reduced giving the (7*S*)-hydroxyl, which was expected to result from using (*R*)-CBS as De Brabander has utilised this method on macrolide **52** in his synthesis of palmerolide A (**23**, Scheme 1.2).[21]

Initially the reduction was attempted with $NaBH_4$, to test that the ketone could be reduced to the alcohol (Scheme 2.29). This was completed by treating ketone **97**, with $NaBH_4$ to give alcohol **139** in 83% yield as a 1 : 1 ratio of diastereoisomers.

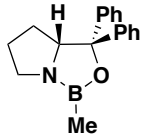


97 **139**

Scheme 2.29: $NaBH_4$ reduction of C7 ketone **97**

2.3.5: CBS reduction of C7 ketone

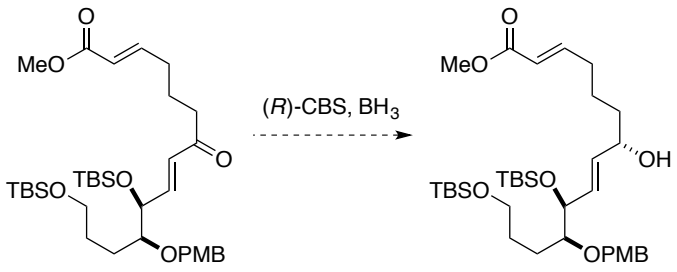
In 1987, E. J. Corey and co-workers developed the enantioselective reduction of an achiral ketone in the presence of a chiral borane.[70] One of these borane reagents is (*R*)-methyl oxazaborolidine (**140**, (*R*)-CBS, Figure 2.4), which can be used to reduce prochiral ketones to give the corresponding alcohols in high enantiomeric excess. Catalytic amounts of the CBS reagent are needed, and when treated with $BH_3 \cdot THF$ *in situ* the diborane complex is formed, where it acts as both a Lewis acid and a chiral auxiliary.



140: (*R*)-MeCBS

Figure 2.4: Structure of (*R*)-CBS (**140**)

After showing the reduction could be completed using $NaBH_4$, it was then attempted using (*R*)-CBS (**140**) to introduce the desired C7-hydroxyl selectivity (Scheme 2.30). Initially the reaction was attempted using the same conditions used by De Brabander in his synthesis of palmerolide A (**23**), but this did not provide any alcohol (**141**) and the starting ketone (**97**) was not recovered. The reaction was also attempted under various conditions with different temperatures, time and equivalents of the reagents used (Table 2.1) but all the attempts were unsuccessful.



97 **141**

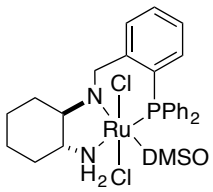
Scheme 2.30: Attempted (*R*)-CBS reduction of C7 ketone **97**

Solvent	Time	(*R*)-CBS (eq)	BH_3· THF (eq)	Temperature (°C)
THF	40 min	3	2	-40
THF	1 hr	3	3	-78
THF	4 hr	3	3	-78
THF	4 hr	3	3	-78 - -40

Table 2.1: Conditions used in (*R*)-CBS reduction of C7 ketone **97**

2.3.6: Noyori hydrogenation

With the unsuccessful reduction using the (*R*)-CBS reagent (**140**), the attention was turned to a different method, which was to use a Noyori hydrogenation,[71] with catalyst **142** (Figure 2.5) developed by Clark *et al.*[72] The Noyori asymmetric hydrogenation is used for enantioselective hydrogenation of ketones, aldehydes and imines, using a chiral ruthenium catalyst.

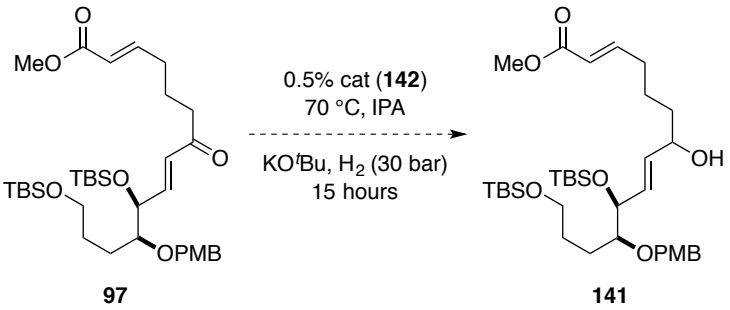


142

Figure 2.5: Catalyst **142** used in Noyori hydrogenation

The hydrogenation of ketone **97** was attempted using 0.5% of catalyst **142**, at 70 °C with KO^{t}Bu under 30 bars of hydrogen in isopropyl alcohol, but

unfortunately this did not provide any of alcohol **141** (Scheme 2.31), and the hydrogenation was found to saturate both the C2-C3 and C8-C9 double bonds.



97 **141**

Scheme 2.31: Conditions used in attempted Noyori hydrogenation of ketone **97**

2.3.7: DIP-Cl reduction of C7 ketone

The next attempt to reduce the C7 ketone was to use *B*-chlorodiisopinocampheylborane (Ipc_2BCl, known commercially as DIP-Cl) pioneered by Brown *et al*.[73] DIP-Cl has been shown to be very effective for the asymmetric reduction of simple ketones, such as alkyl ketones, α-hindered ketones and perfluoroalkyl ketones.[74] Initially the reaction was attempted using (+)-DIP-Cl, as using the mnemonic shown it was quite difficult to distinguish which group would be the large substituent and which would be the small in subunit **97** (Figure 2.6).

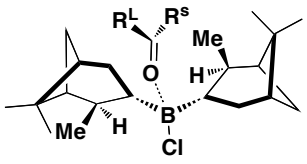
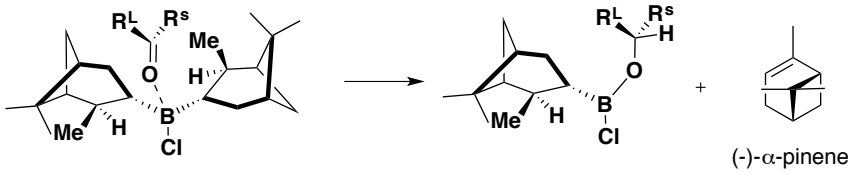


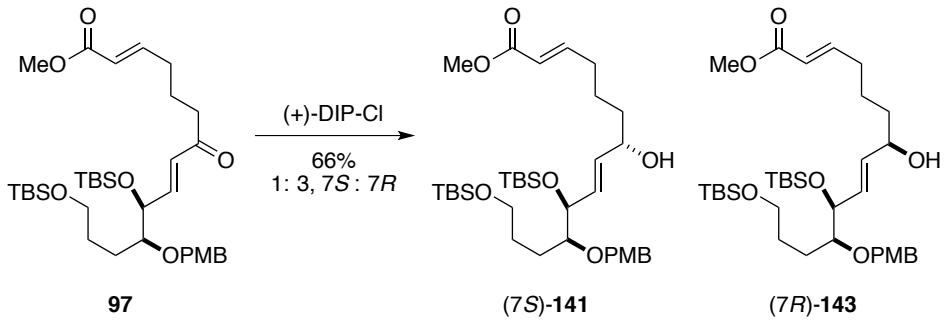
Figure 2.6: Mnemonic used to determine selectivity using DIP-Cl

DIP-Cl efficiently reduces aromatic ketones to chiral secondary alcohols by de-hydroboration and loss of pinene (Scheme 2.32).[75] The reduction proceeds *via* a six-membered cyclic, transition state where the β-hydrogen of the *iso*-pinocampheyl group is transferred to the carbonyl carbon and α-pinene is released.



Scheme 2.32: Mechanism for DIP-Cl reduction.

Treating the ketone **97** with (+)-DIP-Cl in THF at -78 °C, then warming up the reaction mixture to room temperature and stirring for sixteen hours afforded a separable mixture of (7*S* : 7*R*) alcohols **141** and **143** in good yield (Scheme 2.33).

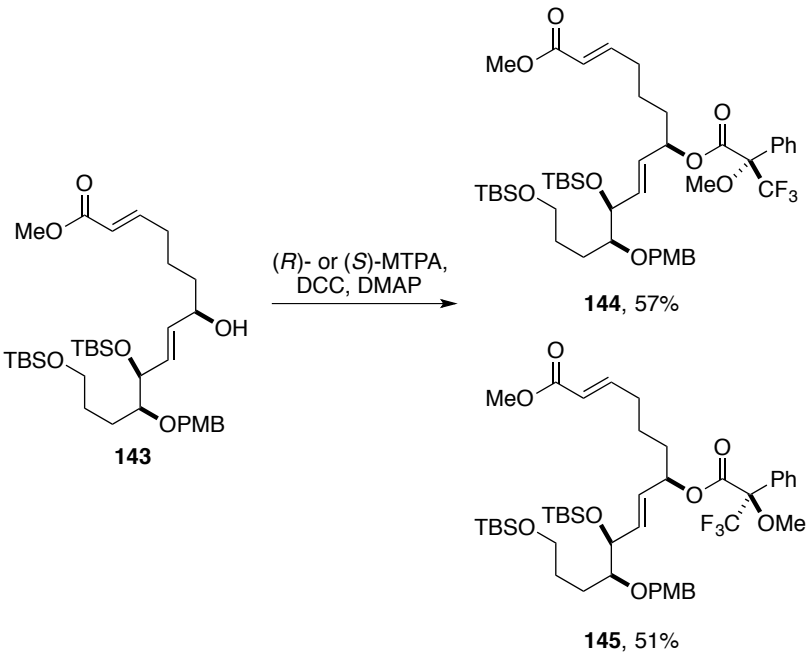


97 (7*S*)-**141** (7*R*)-**143**

Scheme 2.33: (+)-DIP-Cl reduction of C7 ketone **97**

2.3.8: Mosher ester analysis

To determine the selectivity of the (+)-DIP-Cl reduction, alcohol **143** was separately reacted with both (*R*)- and (*S*)- MTPA acids. This treatment of alcohol **143** in dichloromethane with the MTPA acid, *N,N′*-dicyclohexylcarbodiimide and DMAP at room temperature gave the MTPA esters **144** and **145** (Scheme 2.34).



Scheme 2.34: Synthesis of Mosher esters **144** and **145**

The Mosher method uses α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) esters for assigning the absolute configuration. It is based upon the assumption that the MTPA derivatives will adopt a preferred conformation in solution where the carbinol proton, ester carbonyl and trifluoromethyl group all sit in the same plane (Figure 2.7).[76] Due to the diamagnetic effect of the

phenyl group when the MTPA group adopts this confirmation, the ^{1}H NMR signals of Ha, Hb, and Hc in the (*R*)-MTPA ester appear upfield relative to the corresponding signals of the (*S*)-MTPA ester, while the Hx, Hy and Hz in the (*R*)-MTPA ester appear downfield. Therefore the absolute configuration can be assigned by calculating $\Delta\delta$ = -0.02 for as many ^{1}H NMR signals as possible for each of the (*R*)- and (*S*)-MTPA esters. Using this data it is possible to construct a molecular model showing that protons with $\delta>0$ and protons with $\delta<0$ lie on opposite sides of the MTPA plane, confirming the absolute configuration.

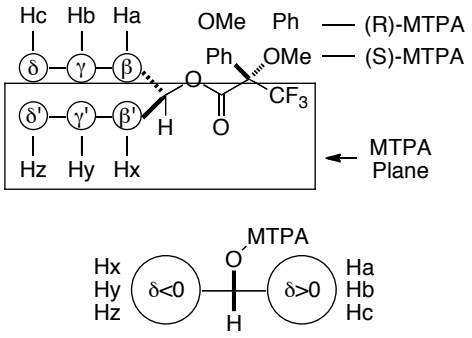


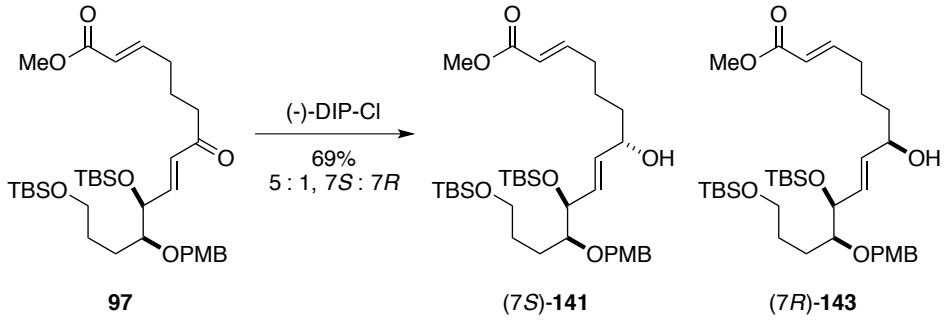
Figure 2.7: Configurational models for Mosher ester analysis

Comparison of the ^{1}H NMR of **144** and **145** showed an *upfield* shift of the C_8-C_{12} protons of **144** as the phenyl group shields them; conversely, the (*R*)-MTPA derivative **145** experienced an *upfield* shift on C_2-C_6 region (Table 2.2). Therefore, subtraction of the ^{1}H NMR δ values for the (*R*)-MTPA ester from the (*S*)-MTPA ester gives a positive value for the C_2-C_6 region and a negative value in the C_8-C_{12} region, allowing the assignment of the C7 stereocentre in the (+)-DIP-Cl reduction giving the 7*R* configuration as the major diastereoisomer.

Proton	δ*S* (ppm)	δ*R* (ppm)	δ*S* - δ*R* (ppm)
2	5.80	5.75	+0.05
3	6.87	6.88	+0.01
4	2.20	2.13	+0.07
5	1.47	1.35	+0.12
6	1.75	1.73	+0.02
7	4.31	4.29	+0.02
8	5.60	5.68	-0.08
9	5.86	5.96	-0.10
10	4.27	4.29	-0.02
11	3.28	3.30	-0.02
12	1.63	1.68	-0.05

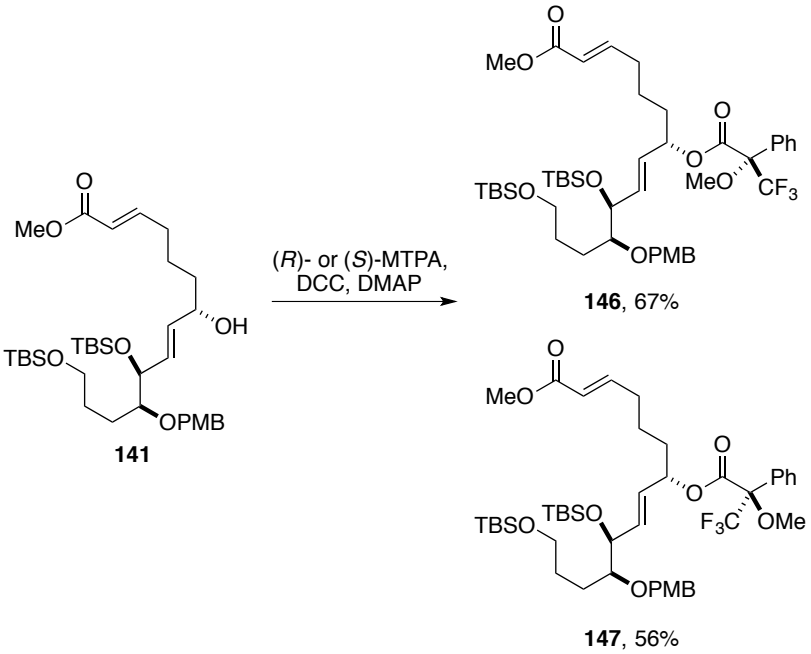
Table 2.2: Mosher ester analysis of (+)-DIP-Cl reduction of **97**

With the reaction using (+)-DIP-Cl proving successful but giving the opposite selectivity needed, the reaction was attempted with (-)-DIP-Cl (Scheme 2.35).[75] Under the same conditions treatment of **97** gave a 5 : 1 ratio in favour of what was assumed to be the desired 7*S* diastereoisomer **141**.



Scheme 2.35: (-)-DIP-Cl reduction of C7 ketone **97**

Mosher ester analysis was performed to confirm the selectivity of the (-)-DIP-Cl reduction, by treating alcohol **141** with both (*R*)- and (*S*)-MTPA acids, giving **146** and **147** (Scheme 2.36).



Scheme 2.36: Mosher ester analysis of **141**

The two (*R*)- and (*S*)-Mosher ester derivatives **146** and **147** were subjected to the same ^{1}H NMR analysis as **144** and **145** confirming the selectivity of the (-)-DIP-Cl reduction as 5 : 1 for 7*S* : 7*R* (Table 2.3, Figure 2.8), as subtraction of the ^{1}H NMR δ values for the (*R*)-MTPA ester from the (*S*)-MTPA ester gives a negative value for the C_2-C_6 region and a positive value in the C_8-C_{12} region.

Proton	δ*S* (ppm)	δ*R* (ppm)	δ*S* - δ*R* (ppm)
2	5.75	5.80	-0.05
3	6.87	6.87	0.00
4	2.12	2.20	-0.08
5	1.60	1.64	-0.04
6	1.75	1.81	-0.06
7	4.29	4.30	-0.01
8	5.68	5.62	+0.06
9	6.00	5.93	+0.07
10	4.35	4.31	+0.04
11	3.35	3.29	+0.06
12	1.65	1.61	+0.04

Table 2.3: Mosher ester analysis of (-)-DIP-Cl reduction of **97**

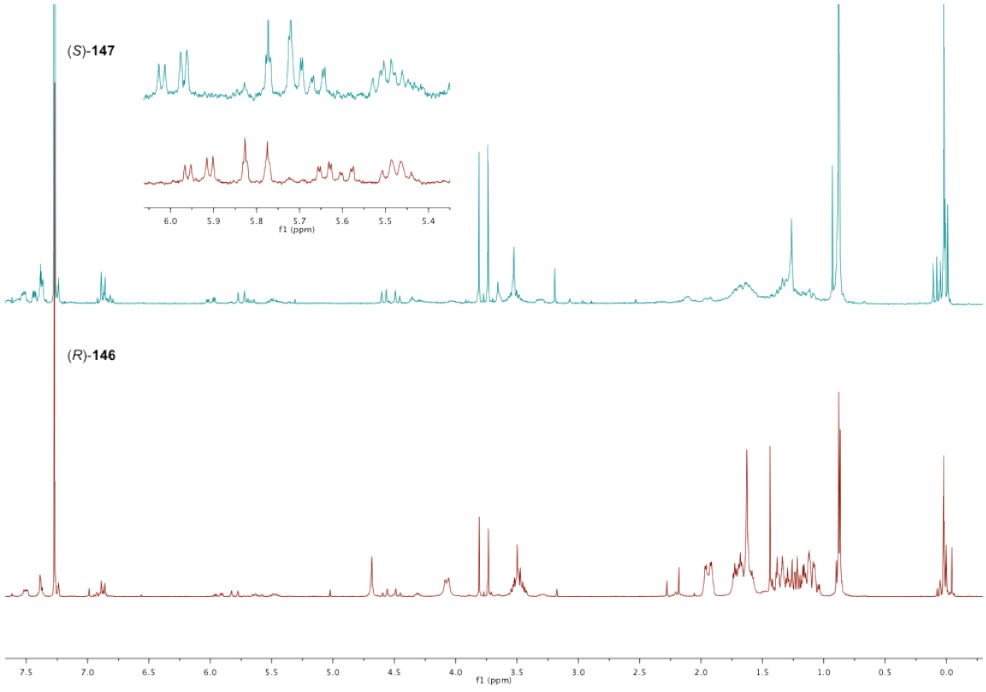
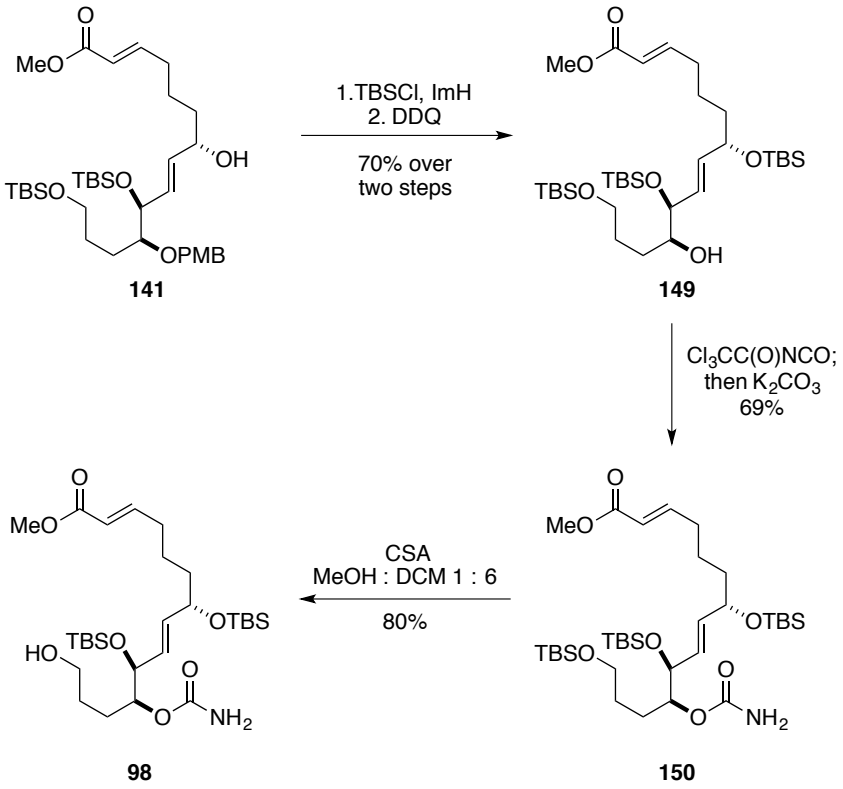


Figure 2.8: ^{1}H NMR comparison of (*R*)- and (*S*)-Mosher ester derivatives **146** and **147**.

2.3.9: Synthesis of C1-C14 subunit 98

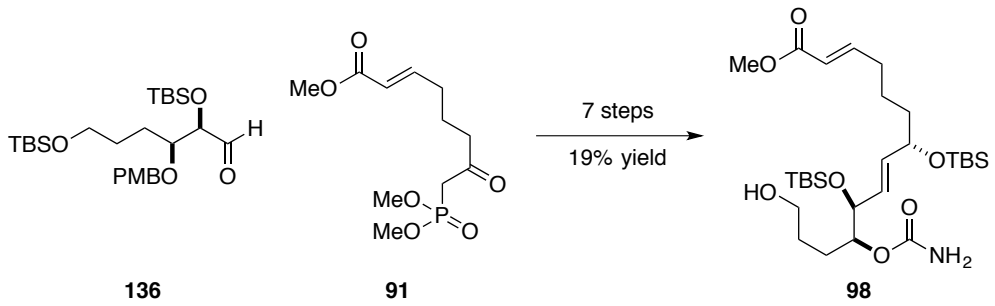
Using the conditions developed above it was attempted to synthesize the fully elaborated C1-C14 subunit (**98**). This was achieved by TBS protection of **141**, giving **148** followed by deprotecting with recrystallised DDQ to remove the PMB-protecting group to give alcohol **149** in good yield. The free hydroxyl was then reacted with trichloroacetyl isocyanate, followed by treatment with potassium carbonate in methanol to give carbamate **150**.[77] This was followed by the selective deprotection of the primary TBS-protecting group using CSA in methanol and dichloromethane, in a 1 : 6 ratio, to give the fully elaborated C1-C14 subunit (**98**) in good yield (Scheme 2.38).



Scheme 2.38: Synthesis of the fully elaborated C1-C14 subunit **98**

2.4: Conclusion

The C1-C14 subunit **98** was synthesised by reacting the C1-C8 subunit **91** with the reduced C9-C14 subunit **136** *via* a Horner-Wadsworth-Emmons to give the C8-C9 olefin **97**. The selective reduction of the C7 ketone was shown to be successful using (-)-DIP-Cl, which was then protected as its TBS-ether **148**. The PMB-ether was pre-emptively deprotected followed by formation of the carbamate **150** and deprotection of the primary TBS-ether to give the fully elaborated C1-C14 subunit **98** (Scheme 2.39) in seven steps and 19% overall yield.



136 **91** **98**

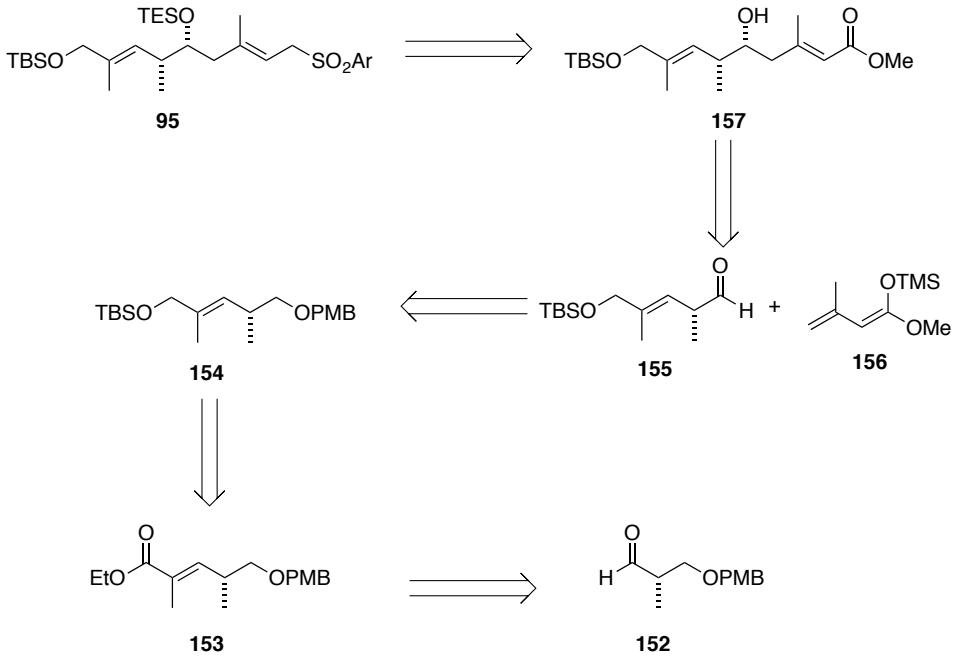
Scheme 2.39: Synthesis of C1-C14 subunit **98**

Results and Discussion

3.0: Synthesis of C15-C23 subunit for palmerolide E (18)

3.1: Retrosynthesis

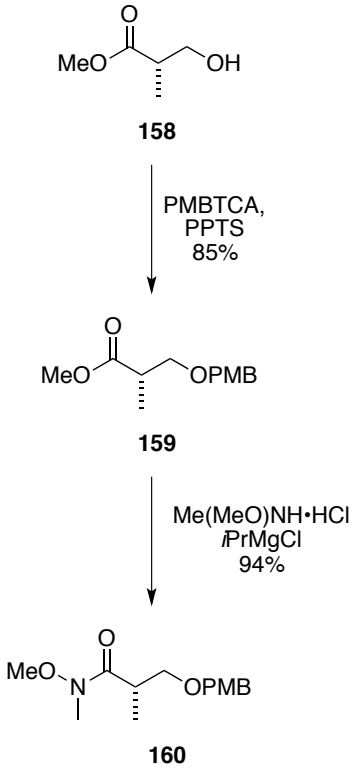
The synthesis of the unsaturated C15-C23 subunit **95** (Scheme 3.1) was envisioned to begin with a Horner-Wadsworth Emmons olefination of the (*S*)-Roche ester derived aldehyde **152**, to provide the trisubstituted enoate **153**, which could be reduced to give the alcohol then protected as its TBS-ether **154**. Elaboration of **154** to aldehyde **155** would then set the stage for the vinylogous Mukaiyama aldol reaction with silyl ketene acetal **156** under suitable Lewis acidic conditions, to generate the desired 1,2-*syn* adduct **157**. Finally, TES-protection of the C19 alcohol followed by reduction and sulfone formation at the C15 terminus to give the C15-C23 subunit **95**.



Scheme 3.1: Retrosynthesis of C15-C23 subunit **95**

3.1.1: Horner-Wadsworth Emmons olefination

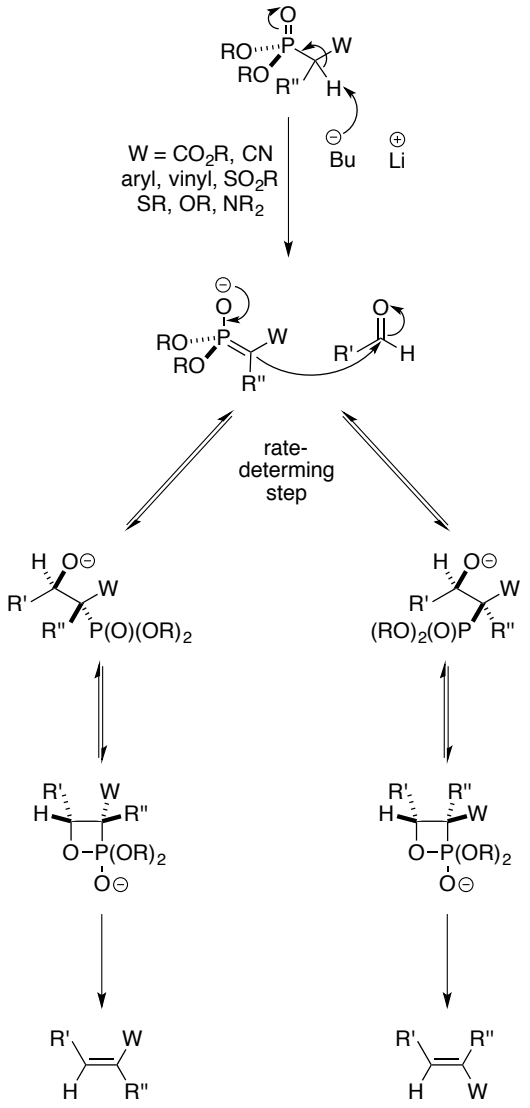
The synthesis of the C15-C23 subunit (**95**) began with PMB-protection of the free hydroxyl of (*S*)-Roche ester **158**, using PMBTCA and PPTS to give **159** in good yield (Scheme 3.2).[78] The Weinreb amide **160** was then formed by treating the protected Roche ester (**159**) with *N*,*O*-dimethyl hydroxylamine hydrochloride and *iso*-propylmagnesium chloride, ensuring the temperature of the reaction did not rise above -15 °C, giving **160** in excellent yield. Synthesizing Weinreb amide **160** to gain access to aldehyde **152** was chosen over reducing the ester **159** to the corresponding alcohol followed by oxidation to the aldehyde in order to prevent epimerization of the C20 stereocentre.



Scheme 3.2: Synthesis of PMB-protected Weinreb amide **160**

Olefin synthesis, employing phosphonium ylides was introduced by Wittig and Geissle in 1953.[79] Shortly after in 1958, Horner disclosed a modified Wittig reaction employing phosphonate-stabilized carbanions.[80] Wadsworth and Emmons investigated this further, showing that phosphonate-stabilized carbanions are more nucleophilic than their corresponding phosphonium ylides.[81] The Horner-Wadsworth-Emmons reaction is the chemical reaction of stabilized phosphonate carbanions with aldehydes or ketones to produce predominantly *E*-olefins (Scheme 3.3).[82] The reaction mechanism proceeds *via* the nucleophillic addition of the enolate to the aldehyde, which gives the two intermediates; the stereochemistry is set by steric control, where the antiperiplanar approach of the carbanion to the carbonyl group is favored when the smaller aldehydic hydrogen eclipses the bulky phosphoranyl moiety.

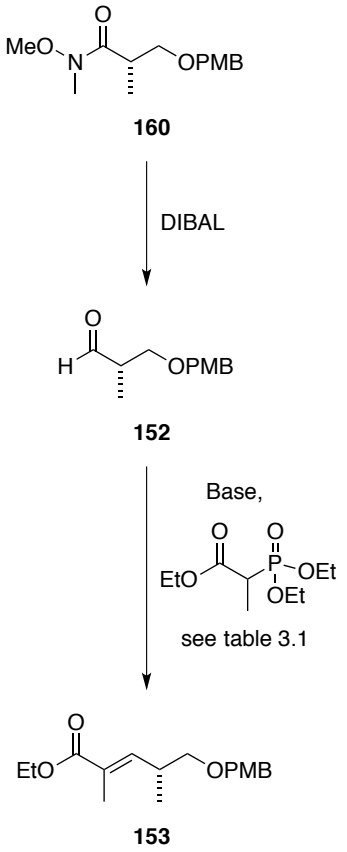
This places the ester group *syn* to the aldehyde R' group. The resultant olefin can assume the more stable *E*-orientation, as interconversion between the intermediates is possible.



Scheme 3.3: Mechanism for Horner-Wadsworth Emmons reaction

The PMB-protected Weinreb amide **160** was treated with DIBAL to give aldehyde **152**, which was used immediately and without purification, due to facile epimerization of the α-chiral aldehyde. The crude aldehyde

152 was reacted in a Horner-Wadsworth Emmons reaction using triethyl 2-phosphonopropionate to give the α, β−unsaturated ester **153** (Scheme 3.4).



Scheme 3.4: Horner-Wadsworth Emmons reaction to synthesise α, β-unsaturated ester **153**

The Horner-Wadsworth Emmons reaction of **152** was attempted using various bases and conditions. Initially it was attempted by treating of the aldehyde **152** with LiHMDS and triethyl 2-phosphonopropionate which gave the α, β-unsaturated ester **153** (E : Z = 1 : 4) in a moderate yield for the two steps (Table 3.1).[83] The selectivity of the reaction was determined by ^{1}H NMR spectroscopy,[82] which in this instance appears to be favoured as the reaction is under kinetic control.

Base	Yield (%) from **160**	*E* : *Z*
LiHMDS	58	1 : 4
LiCl, Hünig's base	65	4 : 1
$Ba(OH)_2 \cdot H_2O$ wet THF	70	9 : 1

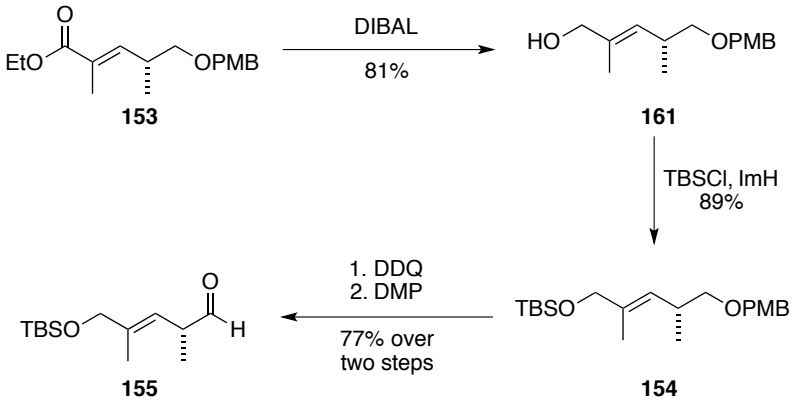
Table 3.1: Conditions used in Horner-Wadsworth Emmons reaction of **152**

Due to the excess formation of the undesired (*Z*)-isomer this reaction was attempted using the Masamune-Roush conditions.[60] Treatment of aldehyde **152** with lithium chloride, Hünig's base and triethyl 2-phosphonopropionate, gave a mixture of isomers of ester **153** (*E* : *Z* = 4 : 1) in a 65% yield for the two steps (Table 3.1). There is an increase in the *E* : *Z* ratio as the thermodynamic product is now favoured.

Although a change in the selectivity of the reaction was observed, it was believed that the 4 : 1 ratio could be increased. Activated barium hydroxide has been shown to increase the (*E*)-selectivity in the Horner-Wadsworth-Emmons reaction.[84] It has been hypothesised that the microcrystalline structure of the barium hydroxide is crucial to its catalytic activity with the reaction proceeding *via* an interfacial solid-liquid mechanism.[85] The reaction was carried out by treating a mixture of activated barium hydroxide and triethyl 2-phosphonopropionate in tetrahydrofuran, with with aldehyde **152** in wet tetrahydrofuran, giving the desired (*E*)-regioisomer **153** in a good yield for the two steps and good selectivity (*E* : *Z* = 9 : 1, Table 3.1).

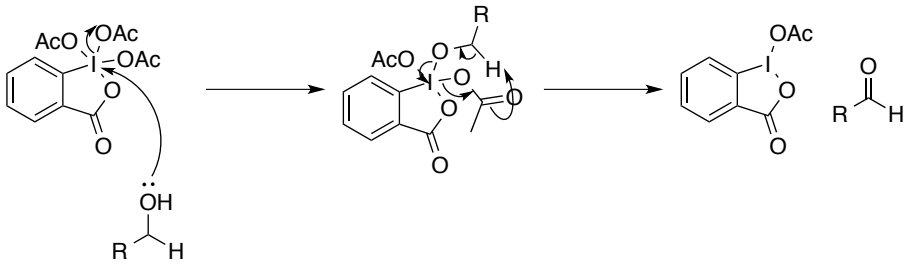
3.1.2: Synthesis of C19-C23 aldehyde 155

The synthesis of aldehyde **155** started with the reduction of ester **153**, using DIBAL, to give alcohol **161** in excellent yield. This was followed by TBS protection of alcohol **161** to afford the di-protected fragment **154** (Scheme 3.5). Deprotection of the PMB ether, using DDQ in dichloromethane followed by oxidation using Dess-Martin periodinane gave aldehyde **155**. The stage was now set to explore the introduction of silyl ketene acetal **156** in a vinylogous aldol reaction.



Scheme 3.5: Synthesis of aldehyde **155**

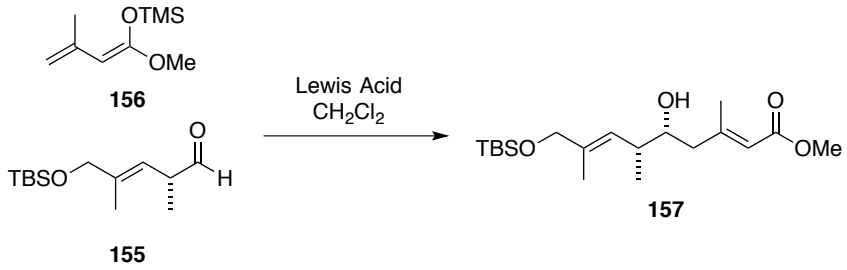
Dess-Martin periodinane is a hypervalent iodine compound, which offers selective and mild oxidation of alcohols to their corresponding aldehydes and the product is easily separated from the iodo by-product. Dess-Martin periodinane works by displacement of an acetyl group by the alcohol (Scheme 3.6). A second acetate group then acts as a base, deprotonating the alcohol to form the aldehyde.



Scheme 3.6: Mechanism for Dess-Martin periodinane oxidation

3.2: Aldol reaction

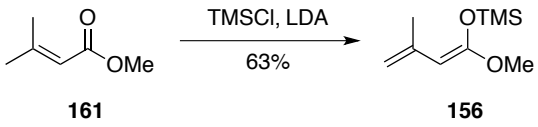
The next step of the sequence was to react the aldehyde (**155**) with silyl ketene acetal **156** to give the aldol adduct (**157**, Scheme 3.7). This was to be initially attempted using a vinylogous Mukaiyama aldol reaction.[86]



Scheme 3.7: Vinylogous Mukaiyama aldol reaction to synthesis aldol adduct **157**

3.2.1: Vinylogous Mukaiyama aldol

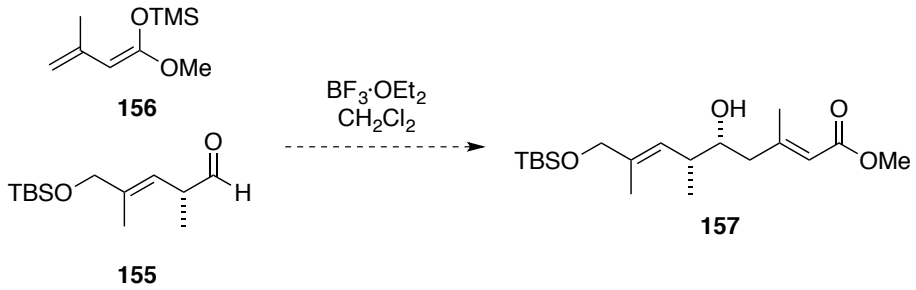
Formation of the desired 1,2-*syn* adduct **157** was to be attempted utilising the substrate controlled vinylogous Mukaiyama aldol reaction with aldehyde **155** and silyl ketene acetal **156**, prepared from methyl-3,3-dimethyl acrylate **161** (Scheme 3.8).



161 **156**

Scheme 3.8: Synthesis of silyl ketene acetal **156**

Unfortunately treatment of aldehyde **155** with silyl ketene acetal **156** and $BF_3 \cdot OEt_2$ in dichloromethane at low temperature did not form any of the desired isomer (Scheme 3.9) giving only degradation of the starting material.[85b] The reaction was attempted under various conditions with varying equivalents of reagents and Lewis acid, but each attempt provided none of the aldol adduct (**157**) and no starting material was recovered, as the use of $BF_3 \cdot OEt_2$ led to degradation of the starting material in all cases (Table 3.2).



Scheme 3.9: Attempted vinylogous Mukaiyama aldol using $BF_3 \cdot OEt_2$

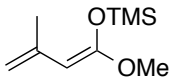
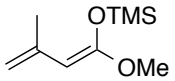
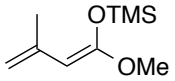
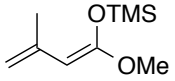
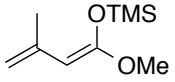
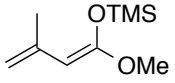
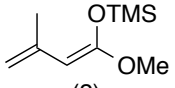
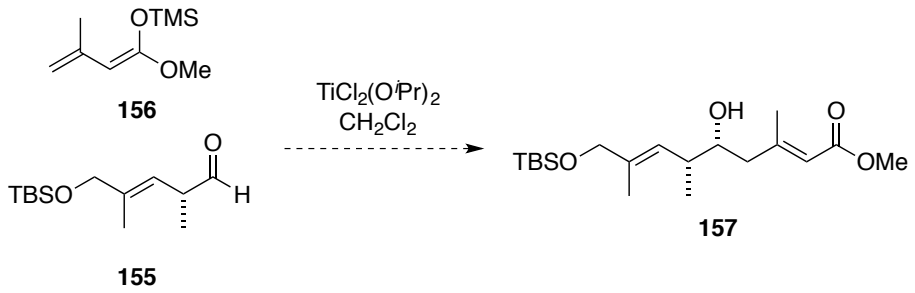
Reagent (eq)	Lewis aicd (eq)	Time (Min)	Temperature (°C)	Yield (%)
 (2)	BF_3·OEt (4)	10	-95	—
 (2)	BF_3·OEt (4)	15	-95 to -78	—
 (2)	BF_3·OEt (1)	30	-78	—
 (2)	BF_3·OEt (2)	10	-78	—
 (2)	BF_3·OEt (2)	30	-95	—
 (4)	BF_3·OEt (2)	30	-78	—
 (2)	BF_3·OEt (6)	30	-78	—

Table 3.2: Conditions attempted in vinylogous Mukaiyama aldol using BF_3·OEt_2

With the unsuccessful attempts of the vinylogous Mukaiyama aldol using BF_3·OEt_2, due to the degradation of the aldehyde **155**, the reaction was attempted using $TiCl_2(O^iPr)_2$ (Scheme 3.10).[87] This reaction was investigated using various conditions but again the starting material **155** was unrecoverable and the product **157** was not formed (Table 3.3).



Scheme 3.10: Attempted vinylogous Mukaiyama aldol of **156** and **155** using $TiCl_2(O^iPr)_2$

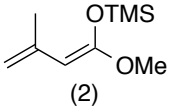
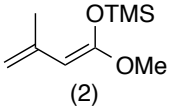
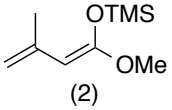
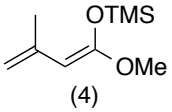
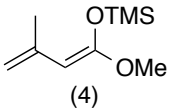
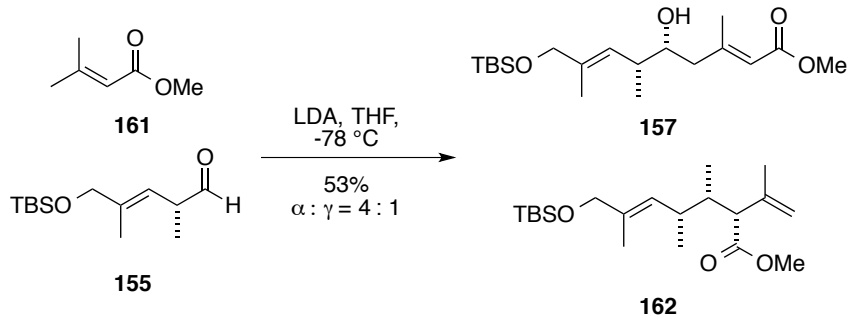
Reagent (eq)	Lewis aicd (eq)	Time (Min)	Temperature (°C)	Yield (%)
 (2)	$TiCl_2(O^iPr)_2$ (6)	180	-78	—
 (2)	$TiCl_2(O^iPr)_2$ (6)	90	-78	—
 (2)	$TiCl_2(O^iPr)_2$ (2)	180	-78	—
 (4)	$TiCl_2(O^iPr)_2$ (6)	180	-78	—
 (4)	$TiCl_2(O^iPr)_2$ (2)	180	-78	—

Table 3.3: Conditions attempted in vinylogous Mukaiyama aldol using $TiCl_2(O^iPr)_2$

3.2.2: Lithium aldol

After the unsuccessful vinylogous Mukaiyama aldol with both $BF_3{\cdot}OEt_2$ and $TiCl_2(O^iPr)_2$, a lithium aldol reaction with aldehyde **155** and acrylate **161** was

attempted to confirm that the aldol bond could be formed. Treatment of acrylate **161** with LDA and aldehyde **155** in tetrahydofuran at -78 °C gave a separable mixture of isomers (α : γ = 4 : 1) in moderate yield (Scheme 3.11).



Scheme 3.11: Lithium aldol reaction of **155** and **161**

The α-regioisomer was favoured in this reaction as it proceeds *via* a Zimmerman-Traxler transition-state (Figure 3.1).[88]

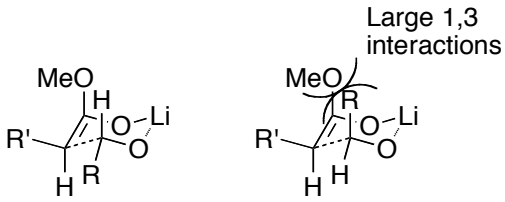
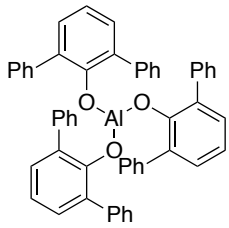


Figure 3.1: Zimmerman-Traxler transition-state

3.2.3: Yamamoto's aluminium tris-(2,6-diphenylphenoxide) aldol

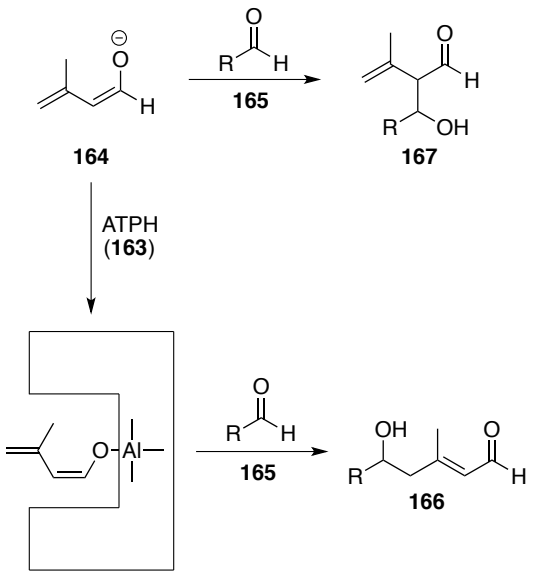
An alternative method to synthesise γ-aldol adducts is Yamamoto's aldol reaction, which utilises aluminium tris-(2,6-diphenylphenoxide) (ATPH, **163**, Figure 3.2) as a bulky Lewis acid.[89]



163

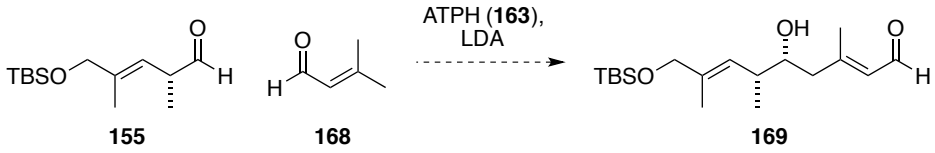
Figure 3.2: Aluminium tris-(2,6-diphenylphenoxide) (**163)**

This proceeds by complexing the ATPH **163** Lewis acid to enolate **164**, which reacts with aldehyde **165** to give the γ-aldol adduct **166** (or when no complexation with **163** occurs the α-aldol adduct **167** is formed, **Scheme** 3.12). Direct aldol reactions of conjugated esters with aldehydes, initiated with LDA using ATPH (**163**) as the key reagent, have been shown to proceed with high γ-regioselectivities.[88a,d] This can be explained by the large steric effects of the ATPH (**163**), which block attack *via* the α-carbon by encapsulating the aldehyde substrate (**164**), therefore the γ-carbon is the preferred position of attack.



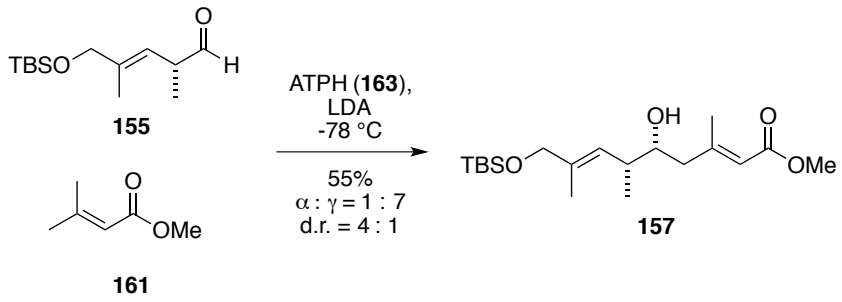
Scheme 3.12: Representation of Yamamoto's aldol reaction

Using ATPH (**163**), a mixed aldol reaction between 3-methylbut-2-enal (**168**) and aldehyde **155** in toluene with LDA as a base, was attempted (Scheme 3.13).[88] However this reaction did not produce the desired product (**169**) with the starting aldehyde **155** recovered.



Scheme 3.13: Attempted Yamamoto's aldol reaction using ATPH (**163**), aldehyde **155** and 3-methylbut-2-enal (**168**)

Due to the unsuccessful reaction using **168**, a similar reaction was tested again using ATPH reagent (**163**) but with methyl-3,3-dimethyl acrylate **161** (Scheme 3.14).[88a] This was carried out by treating acrylate **161** with a solution of ATPH **163** in toluene followed by the addition of aldehyde **155**, this was left stirring for twenty minutes to allow complexation of the substrates to the ATPH after which LDA was added and the reaction was left at -78 °C for thirty minutes. This gave the product **157** in 55% yield with good γ-regioselectivity (α : γ = 1 : 7; γ-isomer d.r. = 4 : 1). The diastereomeric ratio was obtained *via* Mosher ester analysis explained below, while the α : γ regioselectivity of the reaction was established by ^{1}H NMR spectroscopy.



Scheme 3.14: Yamamoto's aldol reaction using ATPH **163**, aldehyde **155** and methyl-3, 3-dimethyl acrylate **161**

3.2.4: Felkin-Anh control

The selective introduction of the C19-hydroxyl stereocentre in **157** is proposed to arise from a stereoselective Felkin-Anh addition of the acrylate **161** to aldehyde **155**.[90] Using a Newman projection, the largest substituent is placed furthest from both the oxygen and hydrogen, with no eclipsing interactions; this gives the lowest energy conformation possible (Figure 3.3). The nucleophile attacks at 107° from the C=O bond with two possible trajectories of attack. The nucleophile selectively attacks past the small (S) substituent of the aldehyde (**A**) which is the least hindered path, giving the less stable product as the nucleophile reacts with the most reactive conformer. This is an example of the Curtin-Hammett principle, which states that it is the relative energies of the competing transition states that control selectivity, not the relative energies of the starting materials.

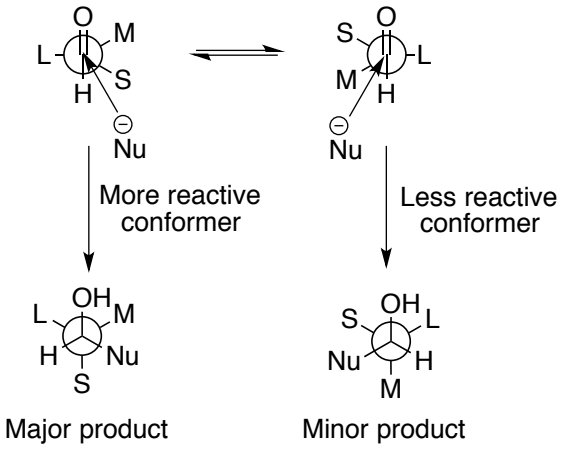
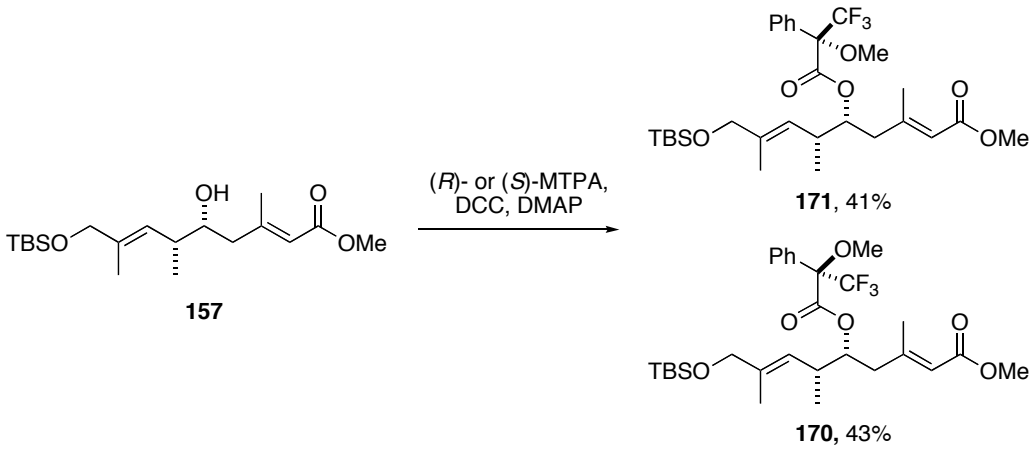
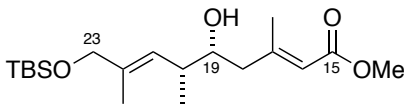


Figure 3.3: Principles of Felkin-Anh control.

The absolute stereochemistry and selectivity of the aldol reaction was confirmed *via* Mosher ester analysis. The alcohol **157** was reacted with, *N,N'*-dicyclohexylcarbodiimide, DMAP and both the (*R*)- and (*S*)-MTPA acids separately at room temperature to give the MTPA esters **170** and **171** respectively (Scheme 3.15).[75] After analysis by ^{1}H NMR spectroscopy, the aldol reaction was shown to have a diastereomeric ratio of 4 : 1 in favour of the (*R*)-diastereomer (Table 3.4).



Scheme 3.15: Mosher ester analysis of aldol adduct **157**

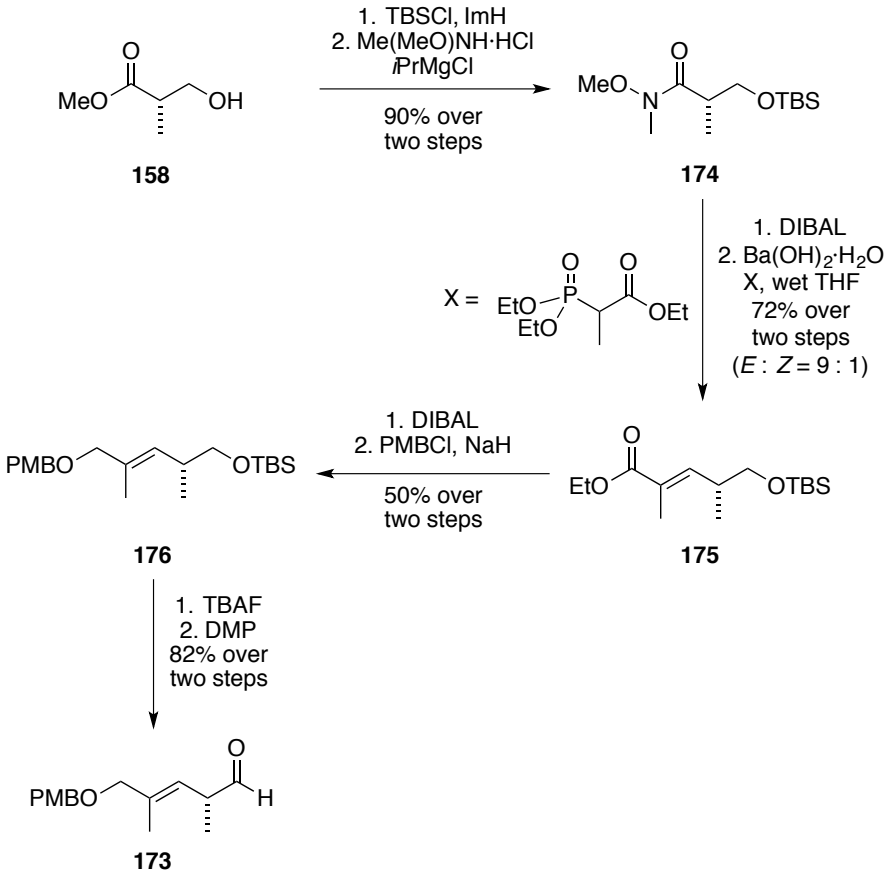


Proton	δ*S* (ppm)	δ*R* (ppm)	δ*S* - δ*R* (ppm)
16	5.80	5.75	+0.05
18a	2.29	2.21	+0.08
18b	2.13	2.07	+0.06
19	5.08	5.06	+0.02
20	2.72	2.78	-0.06
21	5.25	5.34	-0.09
23	4.01	4.03	-0.02

Table 3.4: Mosher ester analysis of aldol adduct **157**

3.3: Alternate C15-C23 synthesis (172)

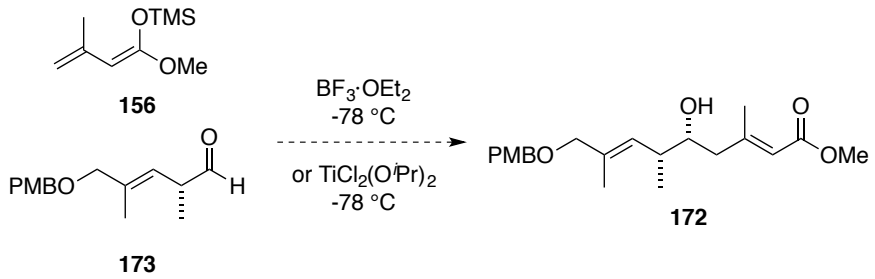
Due to the observed breakdown of aldehyde **155** during, in particular, the Mukaiyama aldol reaction, an alternative substrate (**173**) was synthesised with the TBS-protecting group replaced with a PMB-protecting group, which we believed would be less susceptible to deconstruct under the acidic Mukaiyama conditions. This was achieved *via* a similar route starting with TBS-protection of the (*S*)-Roche ester **158**, and formation of the Weinreb amide **174** (Scheme 3.16). This was then reduced to the aldehyde using DIBAL and reacted under the same conditions used previously for the Horner-Wadsworth Emmons reaction giving **175**, which after reduction of the ester and PMB-protection gave **176**. Removal of the TBS-protecting group was facilitated with TBAF under standard conditions and oxidation using Dess-Martin periodinane gave **173**, to be tested in both the Mukaiyama and Yamamoto aldol reaction.



Scheme 3.16: Synthesis of alternative C19-C23 aldehyde **173**

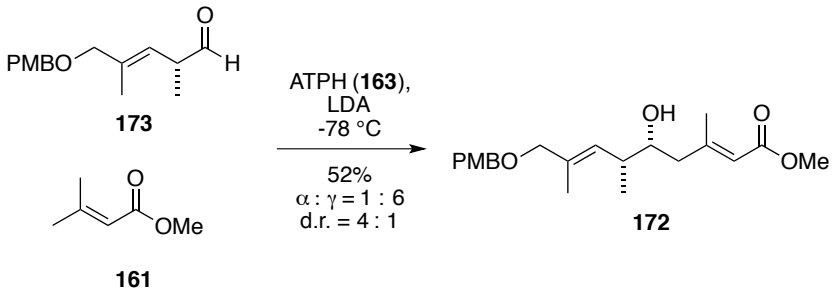
3.3.1: Aldol reaction on PMB-protected aldehyde 173

Aldehyde **173** was subjected to both the vinylogous Mukaiyama aldol conditions previously tried on aldehyde **155**. Treating aldehyde **173** with ketene acetal **156** and $BF_3 \cdot OEt_2$ at -78 °C again gave only degradation of the starting material (Scheme 3.17).[85] The aldehyde (**173**) was also reacted using $TiCl_2(O^iPr)_2$ as the Lewis acid, but again this only broke down the starting material.[86]



Scheme 3.17: Mukaiyama aldol reaction of aldehyde **173**

Again due to the failure of the Mukaiyama aldol reaction, aldehyde **176** was reacted under Yamamoto's protocol to see if the yield of the key aldol reaction could be improved. Aldehyde **176** was reacted with **161** under the conditions developed for TBS-protected aldehyde **155**, to give the PMB-protected aldol adduct **172**, albeit in a lower yield though with similar regioselectivity (α : γ = 1 : 6, γ-isomer d.r. = 4 : 1, Scheme 3.18).[88]

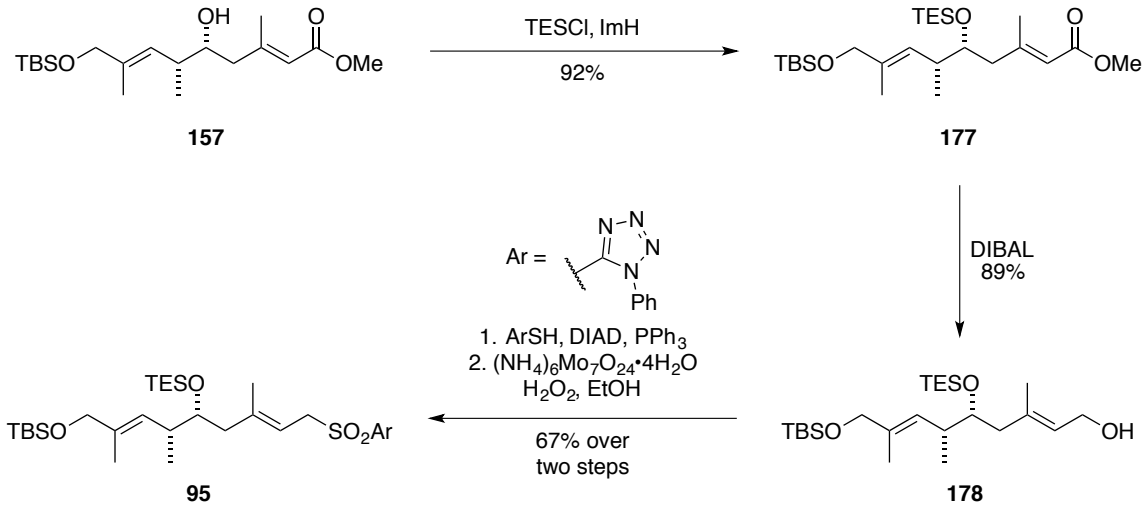


Scheme 3.18: Yamamoto's aldol reaction using ATPH **163**, aldehyde **173** and acrylate **161**

Due to the lower yield observed with PMB-protected aldehyde **173** it was decided to continue with TBS-protected aldol adduct **157** to complete the synthesis of the C15-C23 subunit **95**.

3.4: Completion of C15-C23 subunit 95

Taking forward **157**, the final steps to provide the C15-C23 subunit **95** started with the protection of secondary alcohol **157** under standard conditions using TES-chloride and imidazole in dichloromethane to give **177** (Scheme 3.19). The resulting ester was reduced using DIBAL to give alcohol **178**, and subsequent formation of the sulfone **95** *via* a Mitsunobu reaction to give the sulfide followed by oxidation completed the synthesis of the C15-C23 subunit (**95**).[91,92]

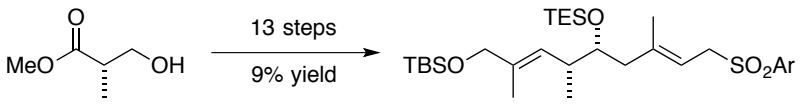


Scheme 3.19: Final steps to synthesise the C15-C23 subunit (**95**)

3.5: Conclusion

The C15-C23 subunit **95** was synthesised starting from the (*S*)-Roche ester **158**, which after PMB-protection and formation of the Weinreb amide gave **160**. This was reduced using DIBAL and used in a Horner-Wadsworth Emmons reaction with activated barium hydroxide to give

ester **153**. A further four steps generated aldehyde **155**, which was used in a Yamamoto's aldol reaction to give the γ-aldol adduct (**157**) with moderate diastereoselectivity. **157** was protected and reduced to give the free primary alcohol **178** and after formation of the sulfone finished the synthesis of the C15-C23 subunit (**95**) in a 9% overall yield over 13 steps (Scheme 3.20).



158 **95**

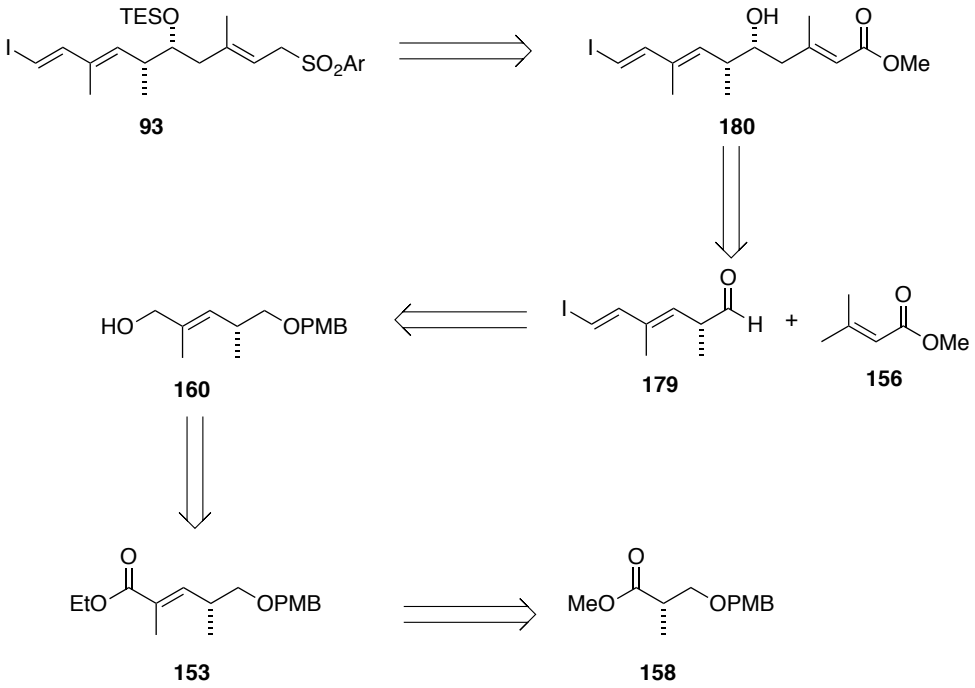
Scheme 3.20: Synthesis of C15-C23 subunit (**95**)

Results and Discussion

4.0: Synthesis of C15-C24 subunit for palmerolide A (14)

4.1: Retrosynthesis

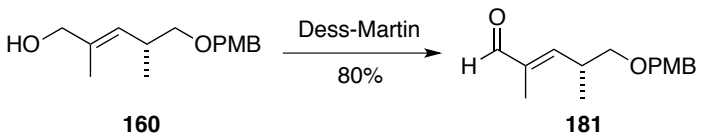
The synthesis of the unsaturated C15-C24 subunit **93** was envisioned to arise *via* a similar method to the synthesis of the C15-C23 subunit **95**, starting from the same (*S*)-Roche ester **158** through to previously synthesised alcohol **160**, obtained from reduction of ester **153**; alcohol **160** was to then be reacted in a Corey-Fuchs reaction followed by hydrostannation to form vinyl iodide **179** (Scheme 4.1). The vinyl iodide **179** was then to be reacted under the Yamamoto's aldol conditions, developed for the synthesis of the C15-C23 subunit (**95**), to give **180** followed by TES-protection and sulfone formation to give the C15-C24 subunit **93**.



Scheme 4.1: Retrosynthesis of C15-C24 subunit **93**

4.2: Synthesis of vinyl iodide 192

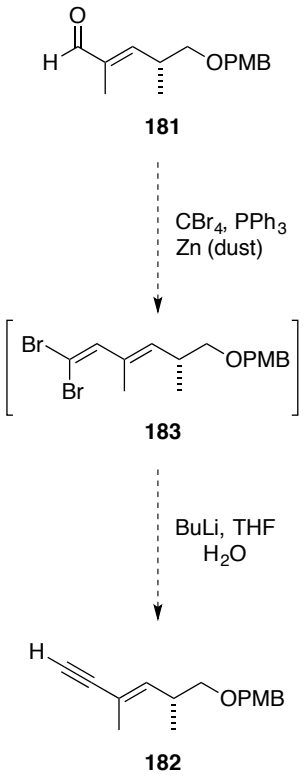
With access to alcohol **160** established in the synthesis of the C15-C23 subunit (**95**) for palmerolide E, introduction of the terminal C23 vinyl iodide was required to give the C15-C24 subunit (**93**). This sequence started with oxidation of alcohol **160** with Dess-Martin periodinane to afford aldehyde **181** in 80% yield (Scheme 4.2).



Scheme 4.2: Synthesis of aldehyde **181**

4.2.1: Synthesis of alkyne 182

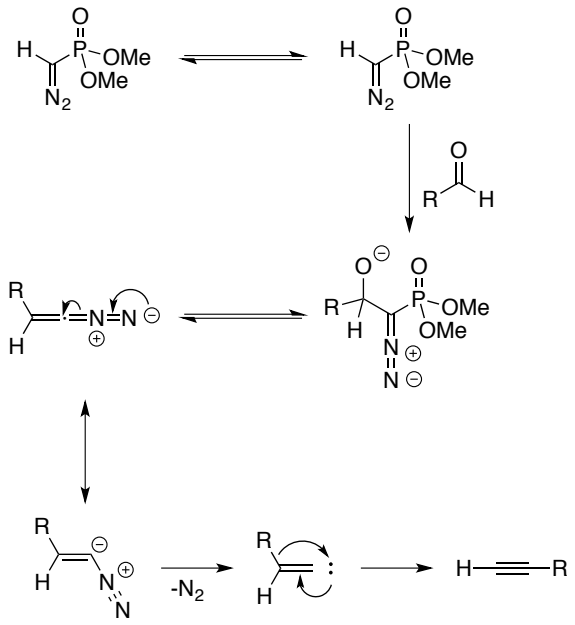
The initial attempt to synthesise alkyne **182** used a Corey-Fuchs reaction (Scheme 4.3).[93] Treatment of aldehyde **181** with carbon tetrabromide, triphenylphosphine and zinc, was expected to give *in situ* the dibromo intermediate **183**, followed by formation of the alkyne with *n*-BuLi, but unfortunately this protocol did not provide the any of the desired product **182**, the dibromo intermediate **183** or return the starting aldehyde **181**.



Scheme 4.3: Attempted Corey-Fuchs reaction

4.2.2: Seyferth-Gilbert reaction

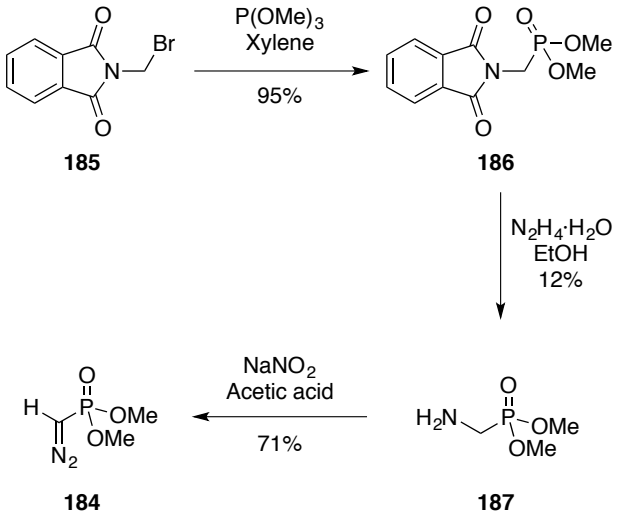
With the failure of the Corey-Fuchs reaction our attention turned to an alternative alkynylation method: the Seyferth-Gilbert alkynylation.[94] This homologation is a base promoted alkynylation, reacting the reagent (**184**) with an aldehyde to give the corresponding alkyne. It proceeds by deprotonation of the Seyferth-Gilbert reagent, which then adds to the carbonyl compound forming an alkoxide, this closes to give an oxaphosphetane. A cyclo-elimination yields a diazoalkene, which upon warming decomposes with loss of nitrogen to give the vinylidene carbene. This then undergoes a 1,2-migration to form the requisite alkyne (Scheme 4.4).



Scheme 4.4: Seyferth-Gilbert mechanism

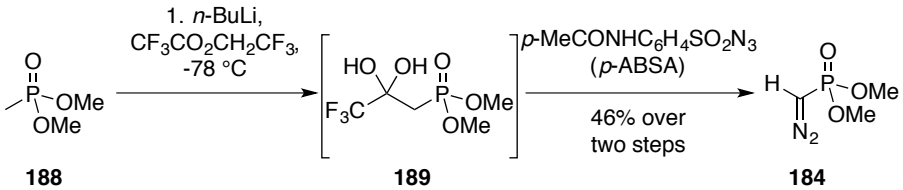
The Seyferth-Gilbert reagent can be prepared by two different methods, the first from reacting **185** with trimethyl phosphite to give **186**, this is then

treated with hydrazine to give phosphonate **187**; followed by formation of the Seyferth-Gilbert reagent **184** by reacting the amine **187** with sodium nitrite to generate the diazo phosphonate **184** (Scheme 4.5).[95]



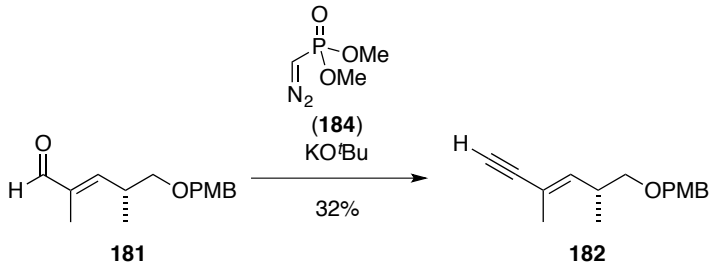
Scheme 4.5: First method to synthesise the Seyferth-Gilbert reagent (**184**)

Due to the poor yields and tricky synthesis associated with this route, an alternative route was investigated. This involved treating dimethyl methylphosphonate (**188**) with *n*-BuLi and 2,2,2-trifluoroethyl trifluoroacetate to give the intermediate **189**, which after treatment with *p*-ABSA gave Seyferth-Gilbert reagent (**184**) in two steps and an improved overall yield of 46% (Scheme 4.6).[96]



Scheme 4.6: Second method to synthesise the Seyferth-Gilbert reagent (**184**)

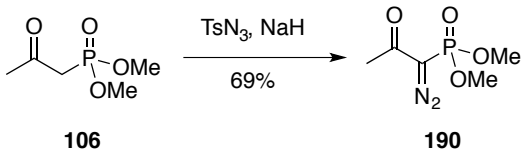
The Seyferth-Gilbert alkynylation was carried out by adding aldehyde **181** to a solution of dried potassium *tert*-butoxide and Seyferth-Gilbert reagent (**184**) in tetrahydrofuran, then stirred for 16 hours to successfully give the alkyne **182** in a 32% yield (Scheme 4.7).



Scheme 4.7: Formation of alkyne **182** using Seyferth-Gilbert reagent

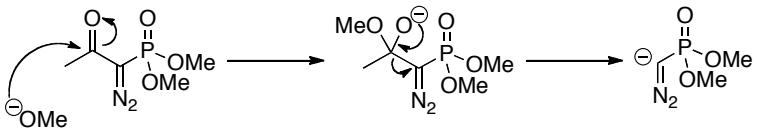
4.2.3: Bestmann-Ohira reaction

Due to both the difficult synthesis of the Seyferth-Gilbert reagent (**184**) and the poor yielding alkynylation reaction, the Bestmann-Ohira reagent (**190**) was utilized which can be synthesised readily in one step by treating dimethyl (2-oxopropyl)phosphonate (**106**) with tosyl azide and sodium hydride giving the Bestmann-Ohira reagent (**190**) in a 69% yield (Scheme 4.8).[97]



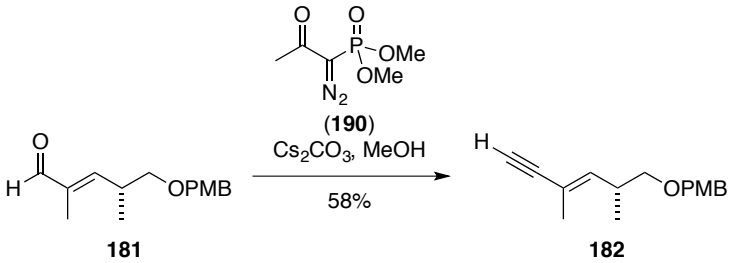
Scheme 4.8: Synthesis of Bestmann-Ohira reagent

The mechanism of the Bestmann-Ohira reaction proceeds *via* a similar method to the Seyferth-Gilbert reaction, initially there is attack of the methanol into the β-ketophosphonate, followed by loss of methyl acetate to generate the deprotonated Seyferth-Gilbert reagent (Scheme 4.9), from there the reaction follows the same route as the Seyferth-Gilbert mechanism described above.



Scheme 4.9: Bestmann-Ohira mechanism

The reaction of aldehyde **181** with the Bestmann-Ohira reagent (**190**) was carried out by treating the reagent **190** with caesium carbonate in methanol, followed by addition of aldehyde **181** at 0 °C. The solution was warmed to room temperature upon which it was left stirring overnight giving alkyne **182** in a 58% yield. This route was preferred due to the ease of reagent synthesis (Scheme 4.10).

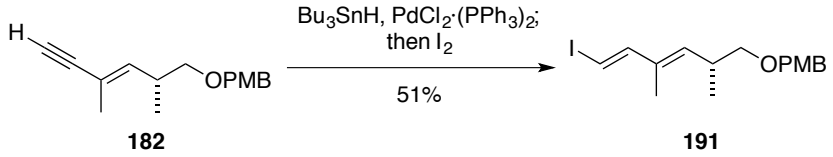


Scheme 4.10: Bestmann-Ohira synthesis of PMB-protected alkyne **182**

4.2.4: Synthesis of vinyl iodide 192

With alkyne **182** in hand the next challenge in the C15-C24 subunit synthesis was the formation of the vinyl iodide; this was expected to be achieved *via* a hydrostannylation reaction of **182**. Hydrostannylation reactions are palladium (II) catalysed *syn*-addition of the alkyl tin to an alkyne, which leads to a vinyl-stannane.[98] They are carried out under mild conditions and can tolerate the presence of a wide variety of functional groups and have been shown to give good regio- and stereo-control.

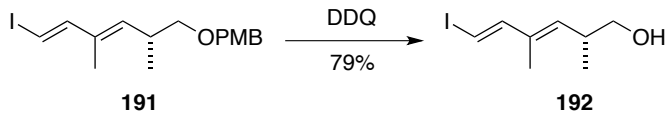
The hydrostannation was realised by treating alkyne **182** with tributyltin hydride and catalytic palladium(II) to give the vinyl stannane intermediate, after the solvent was removed the intermediate was reacted with iodine in dichloromethane to give the vinyl iodide **191** in moderate yield (Scheme 4.11).



182 **191**

Scheme 4.11: Synthesis of PMB-protected vinyl iodide **191**

The PMB-protecting group of vinyl iodide **191** then had to be removed to facilitate the subsequent aldol reaction; the deprotection was achieved by treating vinyl iodide **191** with DDQ to give alcohol **192** in good yield (Scheme 4.12).

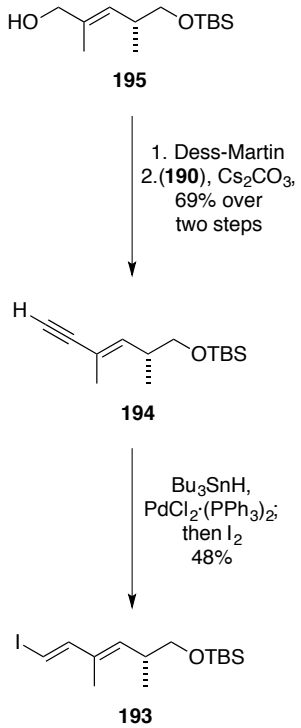


191 **192**

Scheme 4.12: DDQ deprotection of PMB-protected vinyl iodide **191**

4.3: Alternate C19-C24 subunit (192) synthesis

In an attempt to increase the yield of vinyl iodide **192**, the alternative TBS-protected vinyl iodide (**193**) was synthesised alongside the PMB-protected vinyl iodide (**191**). This was accomplished starting from the analogous alcohol **195**, which could be readily oxidised using Dess-Martin periodinane to give the corresponding aldehyde, which was treated with the Bestmann-Ohira reagent (**190**),[96] giving alkyne (**195**, Scheme 4.13). Hydrostannylation of alkyne **195** followed by iodination gave the TBS-protected vinyl iodide (**193**) in a disappointing 33% yield over the 3 steps.[97]

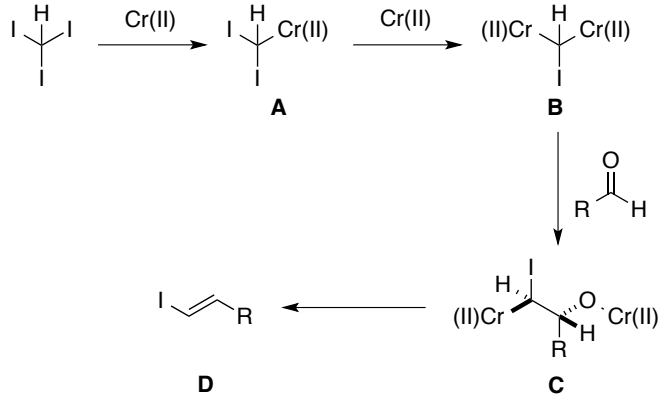


Scheme 4.13: Synthesis of TBS-protected vinyl iodide **193**

4.3.1: Takai olefination

Due to the poor yields observed for the formation of both PMB- and TBS-protected alkynes **182** and **194** and the subsequent vinyl iodides **192** and **193**, the Takai olefination was investigated as an alternative. This involves the treatment of an aldehyde with chromium (II) chloride and iodoform to synthesise the vinyl iodide.[99]

In the reaction mechanism proposed by Takai, chromium(II) is oxidized to chromium(III) upon replacing iodine from iodoform to give **A**, this is repeated to give di-chromium intermediate **B**. This geminal carbodianion complex reacts with the aldehyde in a 1,2-addition across one of the carbon-chromium bonds to give **C** and in the next step both chromium bearing groups engage in an elimination reaction to generate the desired vinyl iodide **D** (Scheme 4.14).[98]

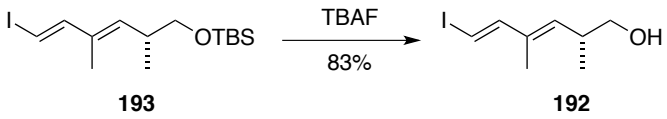


Scheme 4.14: Takai olefination mechanism

The Takai olefination was carried out on the TBS-protected aldehyde, by addition of a solution of the aldehyde and iodoform in dioxane to a solution of chromium(II) chloride in THF (Scheme 4.15). This solution was left to stir overnight giving vinyl iodide **193** in a pleasing 70% yield over the two steps with good *E* : *Z* selectivity, which was established *via* ^{1}H NMR spectroscopy.

Scheme 4.15: Synthesis of TBS-protected vinyl iodide **193** *via* a Takai olefination

With the improved formation of the vinyl iodide *via* a Takai olefination, the TBS-protected vinyl iodide **193** was deprotected using TBAF to give the previously synthesised alcohol **192**, in good yield (Scheme 4.16).

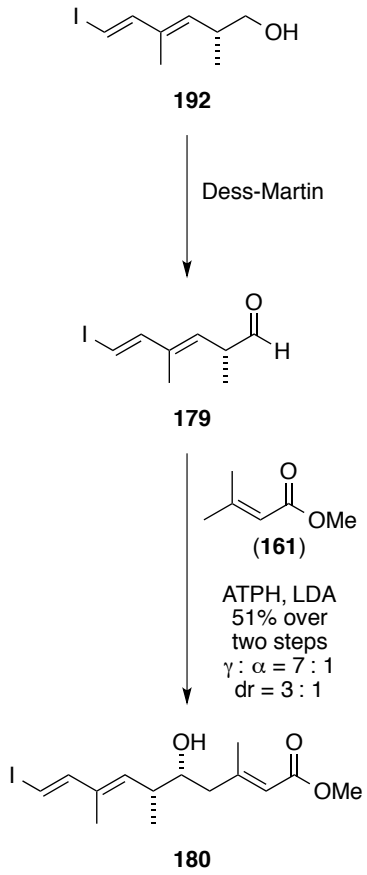


Scheme 4.16: TBAF deprotection of TBS-protected vinyl iodide **193**

4.4: Completion of C15-C24 subunit (93)

4.4.1: Yamamoto's aldol reaction

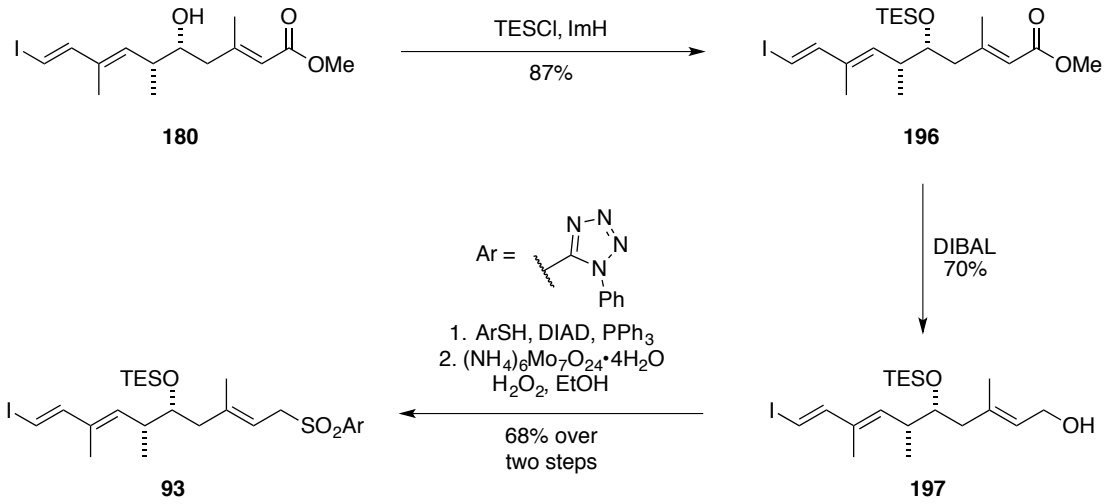
With the deprotected vinyl iodide **192** in hand, the attention was turned to the aldol reaction between the oxidised alcohol **192** and 3,3-dimethyl acrylate (**161**), to introduce the diene and the C19 stereocentre. This was achieved using the same conditions developed in the synthesis of the C15-C23 subunit (**95**), with Dess-Martin periodinane oxidation to give the aldehyde **179** in good yield, followed by Yamamoto's aldol reaction using 3,3-dimethyl acrylate (**161**), ATPH (**163**), and LDA giving vinyl iodide γ-aldol adduct (**180**), in moderate yield with 7 : 1 γ : α selectivity and a 3 : 1 *syn* : *anti* ratio (Scheme 4.17).[88]



Scheme 4.17: Synthesis of vinyl iodide aldol adduct **180**

4.4.2: Final steps towards the C15-C24 subunit (93)

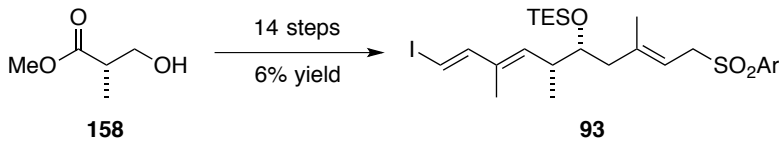
After the aldol reaction, the free hydroxyl of aldol adduct **180** was protected as its TES-ether, by reacting the alcohol **180** with TES-chloride and imidazole, to give **196** (Scheme 4.18). Ester **196** was reduced to alcohol **197** using DIBAL at -78 °C. This was then transformed to the sulfone **93**, *via* a Mitsunobu reaction to give the sulfide intermediate followed by oxidation to give the sulfone in good yield over the two steps, completing the synthesis of the C15-C24 subunit (**93**).[90,91]



Scheme 4.18: Final steps completing the synthesis of the C15-C24 subunit (**93**)

4.5: Conclusion

The C15-C24 subunit (**93**) was synthesised *via* a similar method to the synthesis of the C15-C23 subunit (**95**), but included formation of vinyl iodide **195**. This was achieved *via* a Takai olefination, which after Yamamoto's aldol reaction and formation of the sulfone gave the C15-C24 subunit (**93**) in a 6% overall yield over the 14 steps (Scheme 4.19).



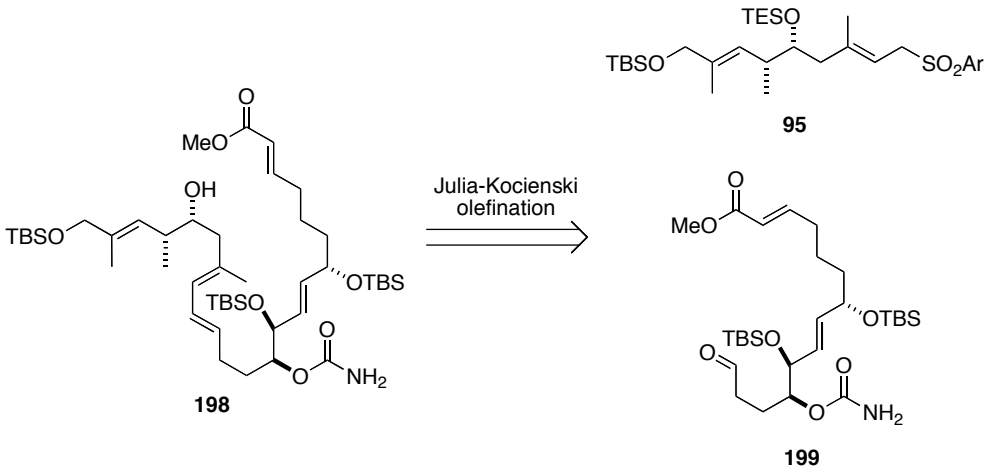
Scheme 4.19: Synthesis of the C15-C24 subunit (**93**)

Results and Discussion

5.0: Attempted synthesis of C1-C23 subunit for palmerolide E (198)

5.1: Retrosynthesis

To form the macrolide core of palmerolide E (**198**) the C1-C14 subunit (**98**) had to be coupled with the C15-C23 subunit (**95**). This was envisaged to be achieved *via* a Julia-Kocienski olefination between the oxidised C1-C14 subunit (**199**) with the C15-C23 subunit (**95**) to form the C14-C15 olefin of **198** (Scheme 5.1).

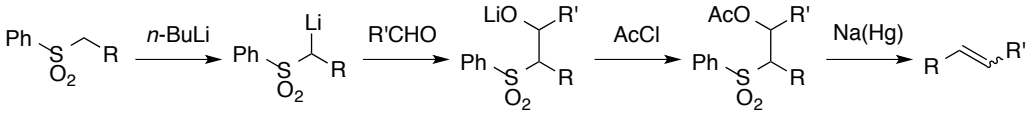


Scheme 5.1: Retrosynthesis of C1-C23 subunit (**198**)

5.2: C1-C14 subunit (98) coupling with C15-C23 subunit (95)

5.2.1: Classical Julia olefination

In 1973, Julia and Paris reported an alkene bond construction protocol *via* a reductive elimination of β-acyloxysulfones (Scheme 5.2).[100] This olefination relied on the formation of a sulfonyl anion by deprotonation of the phenyl sulfone, followed by the addition of an aldehyde to give the β-acyloxysulfone, which after acylation then reductive elimination gives the olefin. This method gave access to the alkene functionality in a stereoselective manner with (*E*)-selective products.



Scheme 5.2: Classical Julia olefination mechanism

5.2.2: Modified Julia olefination

In the 1990's, Julia and co-workers reported a modified Julia olefination reaction substituting the phenylsulfone for a heteroaryl sulfone derivative (Figure 5.1).[101] Benzothiazol-2-ylsulfones (BT sulfone) and a further three major modifications of the sulfone heterocycle have been reported, which all display various degrees of reactivity and stereoselectivity.[102,103,104]

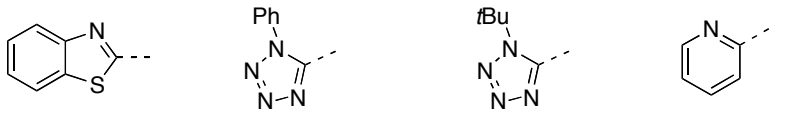
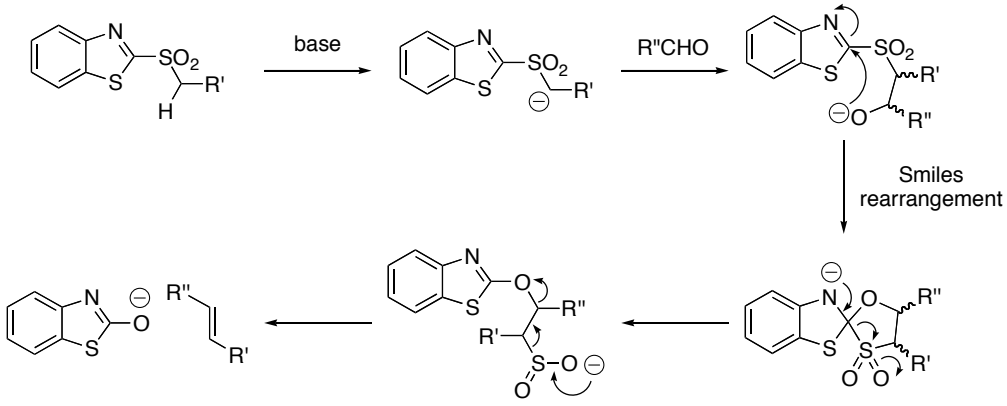


Figure 5.1: Heterocyclic variants of the modified Julia olefination

In comparison with the phenyl sulfone, the BT-sulfone protocol gives rise to the alkene product *via* an alternative pathway (Scheme 5.3).[105,106] The reaction commences with the deprotonation of BT-sulfone, and the resulting anion acts as the nucleophilic partner in the reaction manifold. This species subsequently adds to the electrophilic carbonyl component, forming a transient β-alkoxysulfone intermediate. The alkoxide, attacks the electrophilic C=N bond of the benzothiazole portion of the molecule in an intramolecular fashion. This series of consecutive reactions results in a putative spirocyclic intermediate that selectively breaks down *via* an overall Smiles rearrangement to afford the alkene together with loss of sulfur dioxide and elimination of metallated benzothiazolone.



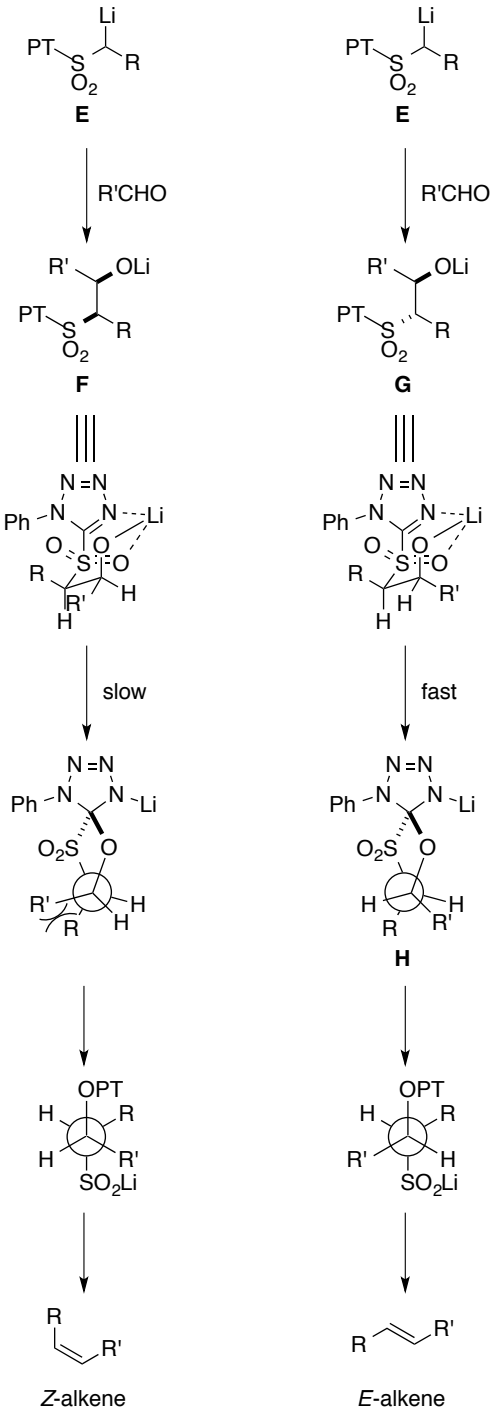
Scheme 5.3: Mechanistic rationale for modified Julia olefination

The stereoselectivity of the modified Julia olefination is dependent upon the R' and R" substituents of both the sulfone and carbonyl components. When the R' and R" groups are non-conjugated alkyl substituents, the resultant alkene product displays little or no stereocontrol. This is attributable to the poor diastereoselective addition of the aldehyde to the sulfone component. Alternatively, when the R' group is a vinyl or aryl substituent and the R" substituent is an alkyl group, the (*Z*)-alkene product dominates. This outcome can be explained by the stabilization of the metallated sulfone by the conjugated R' group, which allows the β-alkoxysulfone to undergo reversible retroaddition/addition reactions, which leads to the equilibration of the diastereomeric alkoxides (Scheme 5.3).

5.2.3: Modified Julia-Kocienski olefination

In 1998, Kocienski and co-workers reported a 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone as an alternative to the BT-sulfone for the modified Juila olefination.[101] Using the PT-sulfone there is reduced tendency to self-condense providing a greater selectivity for the *E*-alkene. Kocienski tested the effect of both solvent polarity and base counterion on the outcome of the olefination reaction. An analogous trend to the BT-sulfone was observed; increased solvent polarity enhanced the tendency towards the formation of *E*-alkenes (DME > THF > Et_2O > PhMe), as did increasing the size of the counterion ($Li^+ < Na^+ < K^+$).

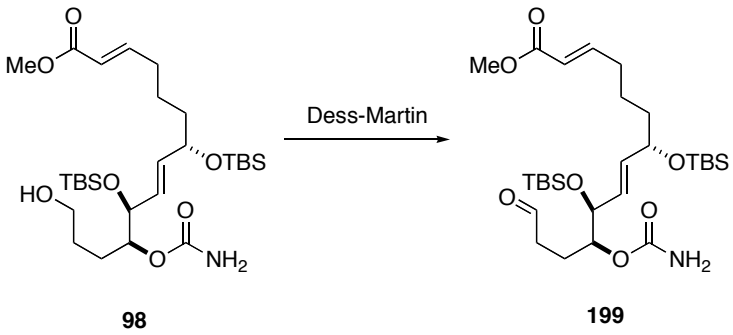
The mechanism of the modified Julia-Kocienski follows that of the BT-sulfone (Scheme 5.4),[104] initial deprotonation with base forms the lithium anion **E** and subsequent addition of a carbonyl gives the two β-alkoxysulfones **F** and **G**. However, unlike the BT-sulfone, the addition of the aldehyde to the PT-sulfone predominantly forms the *anti*-adduct **G**, due to the bulky nature of the phenyl substituent. The Smiles rearrangement orients the R groups in a *syn*-arrangement **H** to reduce the steric clash with the phenyl group and subsequent elimination of the sulfur dioxide and the PT group gives an *E*-alkene.



Scheme 5.4: Mechanism of modified Julia-Kocienski olefination

5.2.4: Attempted synthesis of C14-C15 olefin

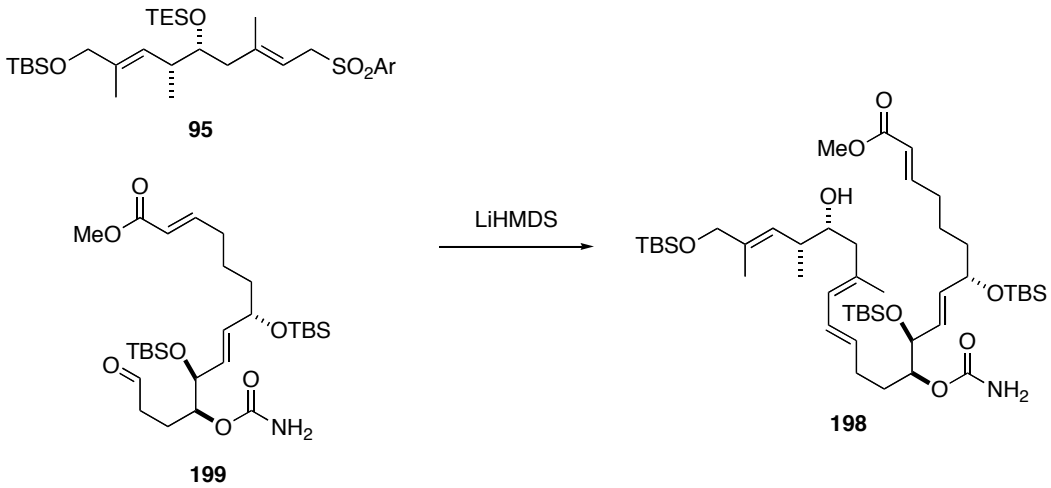
To set the stage for the Julia-Kocienski olefination alcohol **98** had to be oxidised to the aldehyde **199**. This was achieved by treating alcohol **98** with Dess-Martin periodinane to give the aldehyde **199** (Scheme 5.5).



98 **199**

Scheme 5.5: Dess-Martin periodinane oxidation of alcohol **98**

The Julia-Kocienski olefination was attempted by treating the C15-C23 sulfone (**95**) with LiHMDS at -78 °C for ten minutes then addition of the freshly prepared aldehyde **199**, the reaction mixture was left stirring at -78 °C for four hours, but unfortunately this did not give any of the C1-C23 product (**198**) and no starting aldehyde was recovered (Scheme 5.6). This reaction was attempted using various conditions and different bases but none tested provided the C1-C23 subunit **198** (Table 5.1).



Scheme 5.6: Attempted Julia-Kocienski olefination between the C1-C14 aldehyde (**199**) and the C15-C23 sulfone (**95**)

Sulfone (eq)	Aldehyde (eq)	Base (eq)	Time	Temperature (°C)	Yield (%)
1	1	LiHMDS 1.5	4 hours	-78	—
1	1.2	LiHMDS 1.5	6 hours	-78	—
1	1.2	NaHMDS 1.7	4 hours	-78	—

Table 5.1: Conditions attempted in the Julia-Kocienski olefination between the C1-C14 aldehyde (**199**) and the C15-C23 sulfone (**95**)

5.3: Conclusion

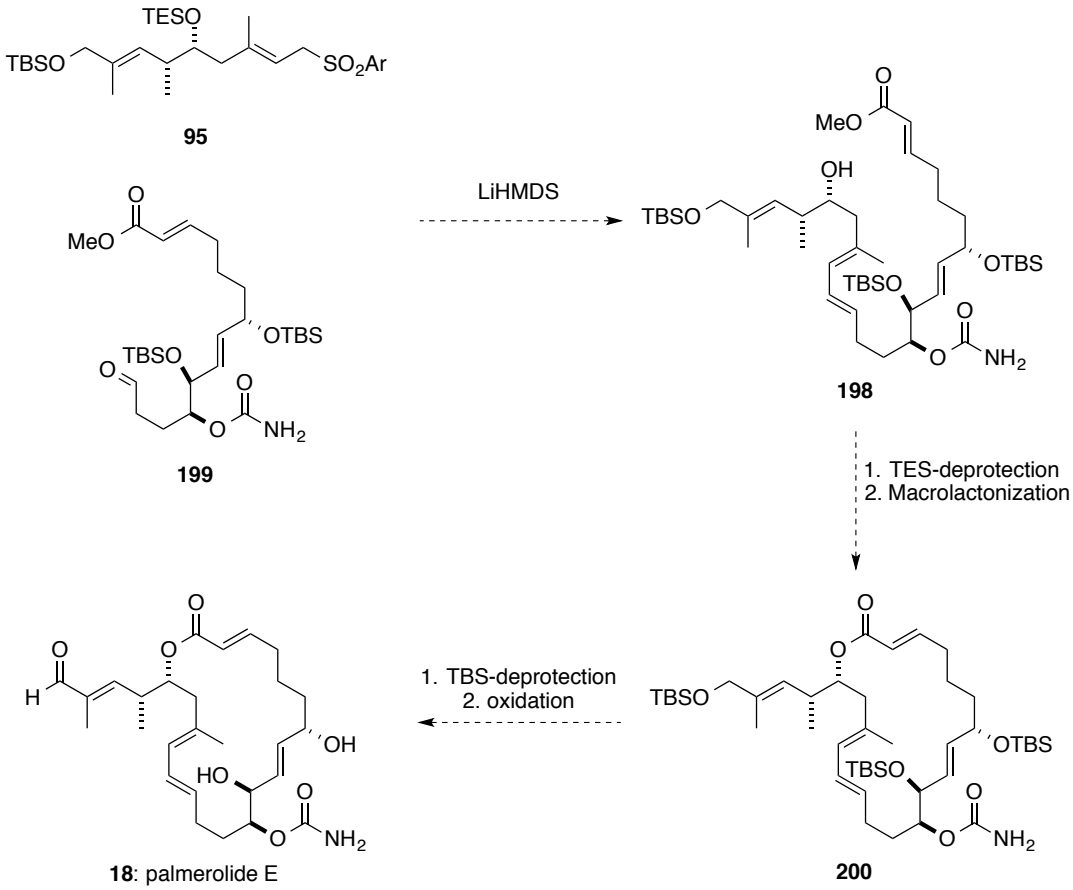
We believe the unsuccessful attempts at the Julia-Kocienski olefination, were due to the small scale of the reaction and moisture being present in the reaction mixture. Hence it is hoped that this can be rectified by increasing the scale of the reaction, or if needed by swapping the substituents and placing the sulfone on the C1-C14 subunit and the aldehyde on the C15-C23 subunit.

Unfortunately due the lack of material this reaction between the C1-C14 aldehyde (**199**) and the C15-C23 sulfone (**95**) could not be repeated and tested on a larger scale.

Summary and Future Work

6.1 Final steps towards palmerolide E (18)

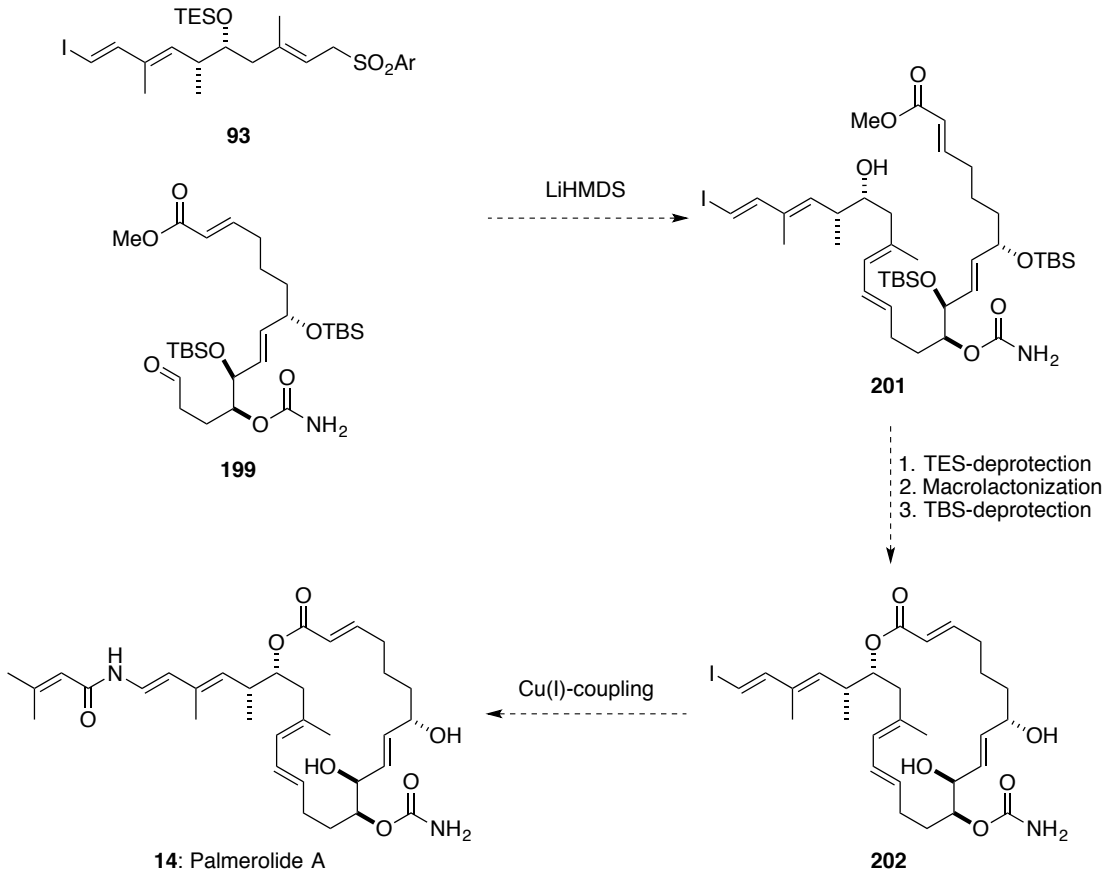
Once the problems with the Julia-Kocienski olefination, between aldehyde **199** and the C15-C23 subunit (**95**) have been overcome, there would be a further four steps to complete the synthesis of palmerolide E (**18**); involving TES-deprotection, macrolactonization, deprotection of the three TBS-protected alcohols and oxidation of the primary alcohol to the aldehyde, which would give palmerolide E (**18**) in a longest linear sequence of twenty steps (Scheme 6.1)



Scheme 6.1: Final steps towards the synthesis of palmerolide E (**18**)

6.2 Final steps towards palmerolide A (14)

The synthesis of palmerolide A (14) is expected to be completed following a similar route devised for the synthesis of palmerolide E (**18**, Scheme 6.2). A Julia-Kocienski olefination between aldehyde **199** and the C15-C24 subunit (**93**), followed by TES-deprotection and macrolactonization should furnish macrolide **201**, which after a global deprotection and introduction of the enamide would give palmerolide A (14), in a longest linear sequence of twenty steps.



Scheme 6.2: Final steps towards the synthesis of palmerolide A (14)

6.3 Summary

In the synthesis of palmerolide A (**14**), the coupling between the C1-C8 fragment (**91**) and the C9-C14 fragment (**96**) was achieved. Further elaboration gave the C1-C14 subunit (**98**), which can also be used in the synthesis of palmerolide E (**18**). The synthesis of both the C15-24 subunit (**93**) for palmerolide A and the C15-C23 subunit (**95**) for palmerolide E, have been completed with the investigation into the Julia-Kocienski coupling of these fragments with the oxidised C1-C14 subunit (**199**) under investigation. Although neither synthesis of palmerolide A or E were completed, significant

progress was made and useful information into the key fragments was obtained during these studies.

Experimental

7.1: General experimental details

All reactions were performed in flame dried glassware under a positive pressure of argon, with magnetic stirring unless otherwise stated.

7.2: General procedures

^{1}H NMR spectra were recorded on the following instruments: Bruker Avance 300 (300.1 MHz) instrument, Bruker Avance II 400 (400.1 MHz) instrument or Bruker Avance 500 (499.9 MHz) instrument. An internal reference of δ_H 7.27 and 7.16 was used for the residual protons in $CDCl_3$ and C_6D_6 respectively. The chemical shift data for each signal are given as δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where $\delta_{TMS} = 0.00$ ppm. The multiplicity of each signal is indicated by: s (singlet); br s (broad singlet); d (doublet); t (triplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); ddt (doublet of doublet of triplets); q (quartet); qd (quartet of doublets); or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants (*J*) are quoted in Hz, they are recorded to the nearest 0.1 Hz and are uncorrected. Assignments were determined either on the basis of unambiguous chemical shift, coupling pattern or by analogy to fully interpreted spectra.

^{13}C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz) instrument, Bruker Avance II 400 (100.6 MHz) instrument or Bruker Avance 500 (125.7 MHz) at probe temperature using an internal deuterium lock. The chemical shift data for each signal are reported in ppm on the δ scale (δ_{TMS} = 0). The solvent peak was used as a reference value for ^{13}C NMR: $CDCl_3$ = 77.00 or C_6D_6 = 128.06.

IR spectra were recorded on a Perkin-Elmer Paragon Series 1000 FTIR spectrometer as thin films. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Optical rotations were recorded on a Perkin-Elmer Model 341 automatic polarimeter instrument at the sodium D line (589 nm), in cells with a path length of 1 cm and are reported as: $[\alpha]_D^T$, concentration (c in g/100 mL) and solvent, where T is temperature in °C.

HRMS and LRMS (High and Low resolution mass spectrometry) were recorded using a Thermofisher LTQ Orbitrap XL mass spectrometer, Finnigan MAT 900 XLT mass spectrometer, Micromass Quattro II mass spectrometer, Water ZQ4000 mass spectrometer or a Thermofisher DSQ-II mass spectrometer by EPSRC national mass spectrometry service (Swansea, UK) using Electron Impact (EI), Electron Ionisation (ES), Chemical Ionisation (CI), Fast Atom Bombardment (FAB) or Atmospheric Pressure Chemical Ionisation (APCI) techniques. Other spectra were recorded on a Thermo Fisher Q Exactive mass spectrometeror a Waters micromass LCT

mass spectrometer by the University of St Andrews mass spectrometry service (School of Chemistry and Biomolecular Sciences).

Analytical thin layer chromatography (TLC) was carried out on E. Merck precoated (25 μm) silica gel 60 F254 plates. Reagent grade ethyl acetate, hexanes (commercial mixture), dichloromethane and methanol were purchased and used as is for chromatography. Visualisation was by absorption of UV light, or thermal development after dipping in either an aqueous solution of potassium permanganate, an ethanolic solution of phosphomolybdic acid (PMA) or an anisaldehyde dip.

Flash column chromatography was carried out on silica gel 60 (E. Merck, 40-63 μm) under a positive pressure of compressed air.

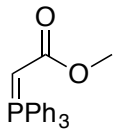
Kugelrohr bulb-to-bulb distillations were carried out using a Büchi B-585 machine. Boiling points are the actual oven temperatures.

Reagents and Solvents were purified by standard means. Dimethyl sulfoxide (DMSO) was dried over CaH_2, distilled under high vacuum and stored over 4Å molecular sieves. Methanol was distilled from magnesium methoxide in a recycling still under nitrogen. Ethyl acetate was purified by washing with 5% Na_2CO_3, and saturated aqueous $CaCl_2$ and dried with $MgSO_4$. Dichloromethane, tetrahydrofuran (THF), diethyl ether and toluene were dried by passage through two columns of alumina using an M-BRAUN SPS-800 solvent purification system. Anhydrous *N,N*-dimethylformamide was

purchased from Aldrich UK and dried by distillation from 4 Å molecular sieves onto 4 Å molecular sieves under an atmosphere of argon. Triethylamine (Et_3N) and $BF3{\cdot}Et_2O$ were distilled from CaH_2 under Ar. Oxalyl chloride was distilled from CaH_2 into potassium carbonate under argon. All other reagents were purchased from Acros UK, Aldrich UK, Fisher UK or Molekula. All other chemical were used as received, except otherwise stated in the experimental procedure. Aqueous solutions of sodium bicoarbonate ($NaHCO_3$), sodium chloride (brine), potassium sodium tartrate and ammonium chloride (NH_4Cl) were saturated. All experiments were performed under anhydrous conditions and an inert atmosphere of argon, using a vacuum manifold with argon passed through calcium chloride and self-indicating silica gel. Hexane refers to *n*-hexane and petroleum ether to the fraction boiling between 40 and 60 °C. Room temperature refers to the temperature of approximately 22 °C.

7.3: Preparation of reagents

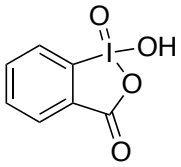
Methyl 2-(triphenylphosphoranylidene) acetate (200)[107]



To a stirred solution of triphenylphosphine (18.0 g, 68.6 mmol) in ethyl acetate (120 mL), was added a solution of methyl bromoacetate (6.50 mL, 68.6 mmol) in ethyl acetate (30 mL). The solution was left to stir for 14 h at room temperature upon which a white precipitate formed. The precipitate was filtered off, washed with diethyl ether (30 mL) and the filtrate was dried over $MgSO_4$. The mixture was dissolved in dichloromethane (150 mL), separated with 1 M NaOH (100 mL) and vigorously shaken. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ then concentrated in *vacuo* to give the product **200** (21.7 g, 95%) as a white powder.

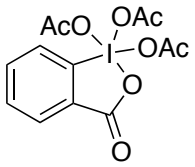
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.43 (15H, m, Ar-H), 3.53 (3H, s, O-CH_3) and 2.91 (1H, s, C-CH).

1-Hydroxy-1,2-benziodoxol-3 (1*H*)-one 1-oxide (201)[108]



2-Iodobenzoic acid (50.0 g, 200 mmol) was added to a solution of Oxone (181.0 g, 290 mmol) in water (650 mL). The reaction mixture was warmed to 75 °C then stirred at this temperature for 3 h, after which the suspension was cooled to 5 °C and left stirring at this temperature for 2 h. The mixture was filtered, then rinsed with water (6 x 100 mL) and acetone (2 x 100 mL), the precipitate was dried at room temperature for 16 h to give the product **201** (48.5 g, 87%) as a white crystalline solid.

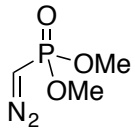
1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3 (1*H*)-one (202)[109]



1-Hydroxy-1,2-benziodoxol-3 (1*H*)-one 1-oxide **201** (48.5 g, 170 mmol) was added to a solution of Ac_2O (200 mL) and $TsOH \cdot H_2O$ (500 mg). The mixture was heated to 80 °C and stirred at this temperature for 3 h, then cooled to 0 °C. The cold mixture was filtered, and then rinsed with diethyl ether (5 x 50 mL). The resulting white crystalline solid **202** (59.5 g, 81%) was transferred to an argon flushed dark flask, and stored in a freezer.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, d, *J* = 8.1 Hz, Ar-H), 8.09 (1H, t, *J* = 8.1 Hz, Ar-H), 7.93-7.90 (2H, m, Ar-H), 2.32 (3H, s, CH_3) and 1.99 (6H, s, 2 x CH_3).

Diazomethyl dimethylphosphonate (184)[94,95]



Method A:

A solution of *N*-(bromomethyl)phthalimide **185** (10.0 g, 41.7 mmol), trimethyl phosphite (5.40 mL, 45.8 mmol) in xylene (20 mL) was heated under reflux for 5 h. The solvent was partially reduced in *vacuo* and the resulting solid was filtered and dried under vacuum to give **186** (10.9 g, 93%) as a white powder.

To a solution of **186** (8.40 g, 31.0 mmol) in ethanol (130 mL), was added hydrazine (2.65 mL, 54.6 mmol). The reaction mixture was refluxed for 1.5 h. The un-reacted phosphonate **186** was filtered off; the mixture was concentrated under reduced pressure and distilled (120 °C, 0.5 mbar) to give **187** (530 mg, 12%) as a colourless oil.

To a solution of **187** (500 g, 3.60 mmol) in dichloromethane (10 mL) at -5 °C, was added a solution of aqueous $NaNO_2$ (300 mg, 4.30 mmol) in water (3 mL), followed by acetic acid (430 mg, 7.20 mmol). The reaction mixture was stirred for 4 h at 0 °C. The reaction was quenched with aqueous potassium

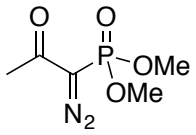
carbonate (4 mL), extracted with dichloromethane (3 x 10 mL), dried over potassium carbonate, filtered and reduced under pressure. The product was purified by distillation (87 °C, 0.5 mbar) to give the diazomethyl dimethylphosphonate **184** (380 mg, 70%) as a colourless oil.

Method B:

A mixture of dimethyl methylphosphonate **188** (2.00 g, 16.1 mmol) in THF (40 mL) was cooled to -78 °C, and *n*-butyl lithium (1.6 M in hexane, 10.1 mL, 16.1 mmol) was slowly added to the mixture and stirred for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (3.20 mL, 24.2 mmol) was added and the mixture was warmed to room temperature over 15 min. The mixture was partitioned between diethyl ether (250 mL) and 3M HCl (10 mL), and the organic layer was washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue **189** was dissolved in acetonitrile (40 mL), followed by the addition of 4-acetamidobenzenesulfonyl azide (4.10 g, 16.1 mmol). The solution was cooled to 0 °C and triethylamine (2.20 mL, 16.1 mmol) was slowly added. The solution was stirred for 16 h at room temperature and the solvent was then removed under reduced pressure. The crude residue was suspended in chloroform (20 mL) filtered and washed with chloroform (10 mL). Column chromatography (1 : 9, hexane : ethyl acetate) of the concentrated filtrate gave the product **184** (1.12 g, 46%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (1H, d, J = 10.6 Hz, C<u>H</u>) and 3.82 (6H, d, J = 10.5 Hz, O-C<u>H</u>$_3$).

Dimethyl 1-diazo-2-oxopropyl phosphonate (190)[96]

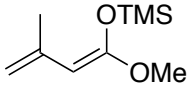


A solution of TsCl (8.00 g, 42.0 mmol) and sodium azide (2.73 g, 42.0 mmol) in acetone (120 mL) and water (120 mL) was stirred at 0 ºC for 2 h. The acetone was evaporated, and the reaction mixture was extracted from diethyl ether (3 x 80 mL), and the organic phase was dried in Na_2SO_4. Evaporation of the solvent gave tosyl azide (8.10 g, 98%) as a colourless oil.

A solution of NaH (990 mg, 41.5 mmol) in THF (150 mL) was cooled to 0 ºC. Dimethyl (2-oxopropyl)phosphonate **106** (6.26 ml, 37.7 mmol) in THF (50 mL) was added and the resulting mixture was stirred at 0 ºC for 1 h after which tosyl azide (8.10 g, 37.7 mmol) was added and left to stir for 30 min. The reaction mixture was purified by column chromatography (1 : 9, hexane : ethyl acetate) to afford Bestmann-Ohiro reagent **190** (5.10 g, 69%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (6H, d, *J* = 11.9 Hz, 2 x O-C$\underline{H}_3$) and 2.28 (3H, s, C$\underline{H}_3$).

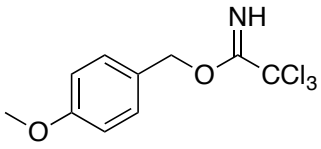
(*Z*)-Trimethyl (1-methoxy-3-methyl-1, 3-butadienyloxy)silane (156)[110]



A solution of *n*-butyl lithium (1.6 M in hexane, 32.9 mL, 52.5 mmol) was added to a solution of diisopropylamine (6.90 mL, 52.6 mmol) in THF (60 mL) at -78 °C. The mixture was stirred for 30 min and methyl-3,3-dimethyl acrylate **161** (5.00 g, 43.8 mmol) and TMSCl (7.60 mL, 56.94 mmol) were added sequentially over 15 min intervals. After 30 min the mixture was warmed to room temperature, stirred for a further 2 h, and quenched with $NaHCO_3$ (40 mL). The organic portions were extracted with dichloromethane (3 x 40 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by Kugelrohr distillation (40 °C, 0.5 mbar) to afford the silyl enol ether **156** (5.11 g, 63%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (1H, dt, *J* = 2.7, 0.8 Hz, $\underline{H}_{4a}$), 4.53 (1H, dq, *J* = 2.7, 1.4 Hz, $\underline{H}_{4b}$), 4.26 (1H, s, $C\underline{H}_2$), 3.54 (3H, s, $OC\underline{H}_3$), 1.93 (3H, dd, *J* = 1.4, 0.7 Hz, $C\underline{H}_3$) and 0.22 (9H, s, $SiC\underline{H}_3$).

4-Methoxybenzyl-2,2,2-trichloroacetimidate (203)[111]



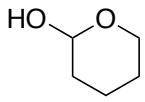
To a solution of 4-methoxybenzyl alcohol (34.0 g, 250 mmol) in a KOH (300 mL, 100g in 100 mL of H_2O) and dichloromethane (300 mL) solution was added TBA·H_2SO_4 (870 mg, 2.56 mmol). This was cooled to -10 °C upon which TCCN (29.6 mL, 294.4 mol) was added, the resulting mixture was

warmed to room temperature then left to stir for 1 h. The product was extracted with dichloromethane (3 x 100 mL), dried over Na_2SO_4, the solvent removed under reduced pressure and the residue was purified by Kugelrohr distillation (150 °C, 0.5 mbar) to give the product **203** (53.2 g, 77%) as a pale orange oil.

^{1}H NMR δ (300 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.8 Hz, Ar<u>H</u>), 6.92 (2H, d, *J* = 8.8 Hz, Ar<u>H</u>), 5.30 (2H, s, C<u>H</u>$_2$) and 3.83 (3H, s, OC<u>H</u>$_3$).

7.4: Experimental for Chapter 2

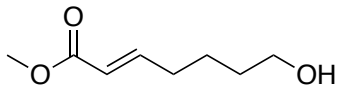
Tetrahydro-2*H*-pyran-2-ol (99)[112]



Concentrated HCl (15.0 mL, 95.1 mmol) was added to a stirring solution of 3,4-dihydro-2*H*-pyran (40.0 g, 476 mmol) in water (440 mL) at 0 °C over 10 min. The solution was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with aqueous $NaHCO_3$, the product extracted with dichloromethane (3 x 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was subsequently purified using Kugelrohr distillation (80 °C, 2 mbar) to give the product **99** (27.1 g, 56%) as a colourless oil.

***R*$_f$** 0.71 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.84-4.80 (1H, m, $\underline{H}_1$), 4.46 (1H, d, J = 4.6 Hz, O-$\underline{H}$), 3.98–3.89 (1H, m, $\underline{H}_{5a}$), 3.51–3.43 (1H, m, $\underline{H}_{5b}$), 1.83–1.69 (2H, m, $\underline{H}_2$) and 1.51–1.42 (4H, m, $\underline{H}_3$ and $\underline{H}_4$).

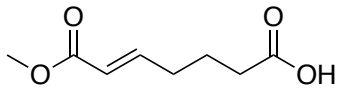
(*E*)-Methyl-7-hydroxyhept-2-enoate (100)[113]



To a stirred solution of carbomethoxymethyl triphenylphosphonium **200** (9.20 g, 27.4 mmol) in THF (100 mL) was added, 2-tetrahydro-2*H*-pyran-2-ol **99** (2.00 g, 19.6 mmol) and the mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure, and the concentrate was stirred for 45 min in a 7 : 3 mixture of diethyl ether and petroleum ether (40 mL). The resulting suspension was filtered and washed with the same mixture (10 mL). The crude mixture was concentrated under reduced pressure and the residue was purified by column chromatographed (4 : 1, hexane : ethyl acetate) to give the product **100** (2.03 g, 66%, E : Z = 9 : 1) as a colourless oil.

***R*$_f$** 0.55 (50% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.96 (1H, dt, J = 15.8, 6.8 Hz, $\underline{H}_3$), 5.82 (1H, dt, J = 15.7, 1.6 Hz, $\underline{H}_2$), 3.71 (3H, s, O-C$\underline{H}_3$), 3.68-3.61 (2H, m, $\underline{H}_7$), 2.27–2.20 (2H, m, $\underline{H}_4$) and 1.68–1.48 (4H, m, $\underline{H}_5$ and $\underline{H}_6$).

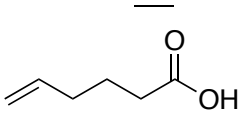
(*E*)-7-Methoxy-7-oxo-hept-5-enoic acid (103)[114]



To a solution of TEMPO (100 mg, 640 μmol) and BIAB (2.06 g, 6.41 mmol) in a mixture of acetonitrile and water (14 mL, 1 : 1), (*E*)-methyl-7-hydroxyhept-2-enoate **100** (500 mg, 3.20 mmol) was added at 0 °C. The solution was allowed to warm to room temperature where it was stirred for 12 h. The reaction was quenched with aqueous NH_4Cl (10 mL), extracted with dichloromethane (3 x 15 mL) and dried over sodium sulfate. The residue was purified by column chromatography (1 : 9, hexane : ethyl acetate) to provide the carboxylic acid **103** (0.54 g, 98%) as a colourless oil.

R_f 0.51 (50% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.07 (1H, br s, C(O)-O<u>H</u>), 6.94 (1H, dt, *J* = 15.6, 6.9 Hz, <u>H</u>$_5$), 5.84 (1H, dt, *J* = 15.7, 1.5 Hz, <u>H</u>$_6$), 3.70 (3H, s, O-C<u>H</u>$_3$), 2.36 (2H, t, *J* = 7.3 Hz, <u>H</u>$_2$) 2.26 (2H, ddt, *J* = 7.4, 7.0, 1.6 Hz, C<u>H</u>$_4$) and 1.79 (2H, tt, *J* = 7.4, 7.3 Hz, <u>H</u>$_3$)

5-Hexenoic acid (103)[115]

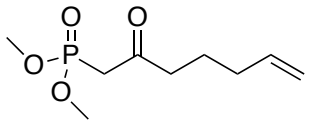


To a solution of TEMPO (625 mg, 4.0 mmol) and BIAB (12.9 g, 40.0 mmol) in a mixture of acetonitrile and water (100 mL, 1 : 1), 5-hexen-1-ol **105** (2.00

g, 20.0 mmol) was added at 0 °C. The solution was allowed to warm to room temperature where it was stirred for 14 h. The reaction was quenched with aqueous NH_4Cl (100 mL), extracted with dichloromethane (3 x 100 mL) and dried over sodium sulfate. The residue was purified by column chromatography (1 : 9, hexane : ethyl acetate) to provide the carboxylic acid **103** (1.21 g, 80%) as a colourless oil.

R_f 0.39 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.82 (1H, br s, O$\underline{H}$), 5.83-5.73 (1H, m, $\underline{H}_5$), 5.07-4.99 (2H, m, $\underline{H}_6$), 2.37 (2H, t, 7.6 Hz, $\underline{H}_2$), 2.15-2.09, (2H, m, $\underline{H}_4$) and 1.74 (2H, tt, 7.6, 7.6 Hz, $\underline{H}_3$).

Dimethyl-2-oxohept-6-enylphosphonate (101)

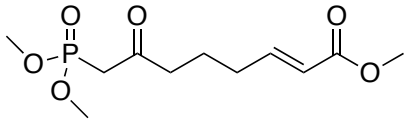


To a suspension of NaH (520 mg, 21.6 mmol, 60% dispersion in mineral oil) in THF (30 mL), dimethyl-2-oxypropylphosphonate **106** (1.70 mL, 12.0 mmol) was added drop wise, at room temperature. The resulting mixture was stirred for 1.5 h prior to the addition of a solution of *n*-butyl lithium in hexane (8.25 mL of a 1.6 M in hexane, 13.2 mmol) at 0 °C. The solution was stirred for 20 min and 4-bromobutene (1.40 mL, 14.4 mmol) was added. The resulting mixture was warmed to room temperature and stirred for a further 3 h. The reaction was quenched with 2M HCl (8 mL), extracted with dichloromethane (3 x 15 mL), the combined organic extracts were washed

with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (1 : 9, hexane : ethyl acetate) afforded the product **101** (2.45 g, 95%) as a colourless oil.

***R*$_f$** 0.47 (5% MeOH : CH_2Cl_2); **IR** (thin film) 2957, 1713, 1360, 1252, 1184, 1018, 825 and 808 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.70 (1H, ddt, *J* = 10.3, 8.6, 6.9 Hz, $\underline{H}_6$), 4.99–4.89 (2H, m, $\underline{H}_7$), 3.72 (6H, d, *J* = 11.2 Hz, PO-C$\underline{H}_3$ x 2), 3.03 (2H, d, *J* = 22.8 Hz, $\underline{H}_1$), 2.57 (2H, t, *J* = 7.3 Hz, $\underline{H}_3$), 2.00 (2H, dt, *J* = 7.2, 7.2 Hz, $\underline{H}_5$) and 1.63 (2H, tt, *J* = 7.3, 7.3 Hz, $\underline{H}_4$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.6, 137.8, 115.1, 52.9, 52.9, 43.2, 41.9, 32.7 and 22.3; **HRMS** (ES^+) calc. For $C_9H_{18}O_4P$ $[M + H]^+$ 221.0937, found 221.0937.

Methyl-8-(dimethoxyphosphoryl)-7-oxooct-(2*E*)-enoate (91)



Method A:

To a solution of dimethyl-2-oxohept-6-enylphosphonate **101** (2.20 g, 9.99 mmol) in dichloromethane (30 mL) was added methyl acrylate (30 mL) and Grubbs II catalyst **107** (100 mg, 118 μmol). The solution was heated under reflux for 16 h upon which a further portion of Grubb's second-generation catalyst **107** (100 mg, 118 μmol) was added and this was left stirring at this temperature for a further 24 h. The solution was concentrated under reduced

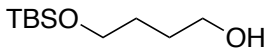
pressure and purified by column chromatography (1 : 9, hexane : ethyl acetate) to yield the olefin **91** (2.78 g, 94 %, *E* : *Z* = 15 : 1) as a brown oil.

Method B:

To a solution of dimethyl-2-oxohept-6-enylphosphonate **101** (180 mg, 820 μmol) in dichloromethane (3 mL) was added a solution of methyl acrylate (3 mL) and a solution of the Nolan-modified ruthenium catalyst **119** (10.0 mg, 8.81 μmol) in dichloromethane (5 mL). The solution was heated under reflux for 16 h upon which a further portion of the Nolan-modified ruthenium catalyst **119** (10.0 mg, 8.81 μmol) was added and this was left stirring at this temperature for a further 24 h. The solution was concentrated under reduced pressure and purified by column chromatography (1 : 9, hexane : ethyl acetate) to yield the olefin **91** (170 mg, 79 %, *E* : *Z* = 10 : 1) as a brown oil.

R_f 0.59 (5% MeOH : CH_2Cl_2); **IR** (thin film) 2957, 1713, 1653, 1437, 1254, 1182, 1018, 829 and 814 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.90 (1H, dt, *J* = 15.6, 7.0 Hz, $\underline{H}_3$), 5.81 (1H, dt, *J* = 15.7, 1.5 Hz, $\underline{H}_2$), 3.76 (6H, d, *J* = 11.3 Hz, PO-C$\underline{H}_3$ x 2), 3.76 (3H, s, C(O)O-C$\underline{H}_3$), 3.06 (2H, d, *J* = 22.9 Hz, $\underline{H}_8$), 2.63 (2H, t, *J* = 7.2 Hz, $\underline{H}_6$), 2.20 (2H, ddt, *J* = 1.6, 7.1, 7.1 Hz, $\underline{H}_4$) and 1.74 (2H, tt, *J* = 7.3, 7.2 Hz, $\underline{H}_5$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.2, 147.2, 134.2, 124.0, 52.1, 50.5, 42.0, 39.6, 25.4 and 20.5; **HRMS** (ES^+) calc. For $C_{11}H_{20}O_6P$ $[M + H]^+$ 279.0992, found 279.0996.

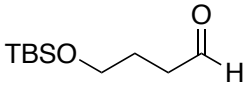
4-(*tert*-Butyldimethylsilyl)oxy-butan-1-ol (126)[116]



To a solution of 1,4-butanediol **125** (19.7 mL, 222 mmol), triethylamine (13.4 mL, 96.2 mmol) and DMAP (900 mg, 7.36 mmol) in dichloromethane (80 mL) at room temperature was slowly added a solution of TBSCl (11.2 g, 74.3 mmol) in dichloromethane (20 mL). After 16 h, the reaction solution was quenched with brine (100 mL) and the organics were extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with water (200 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (7 : 3, hexane : ethyl acetate) provided alcohol **126** (25.8 g, 86%) as a colourless oil.

***R*$_f$** 0.43 (50% EtOA : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.70-3.62 (4H, m, $\underline{H}_1$ + $\underline{H}_4$), 2.54 (1H, t, *J* = 5.4 Hz, O$\underline{H}$), 1.71-1.60 (4H, m, $\underline{H}_2$ + $\underline{H}_3$), 0.91 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.08 (6H, m, Si-C$\underline{H}_3$).

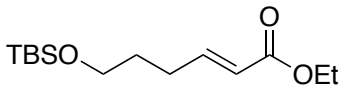
4-(*tert*-Butyldimethylsilyl)oxy-butanal (204)[115]



To a solution of oxalyl chloride (6.78 mL, 78.4 mmol) in dichloromethane (100 mL) at -78 ºC was slowly added DMSO (6.66 mL, 94.2 mmol). After 30 min, a solution of alcohol **126** (8.00 g, 39.2 mmol) in dichloromethane (50 mL) was added dropwise. After 2 h, triethylamine (19.1 mL, 274 mmol) was added and the slurry was allowed to attain room temperature. After 1 h, an aqueous solution of NH_4Cl (100 mL) was added and the organics were extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude aldehyde **204**, which was used without further purification.

***R*$_f$** 0.71 (25% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.7 Hz, C<u>H</u>O), 3.66 (2H, t, *J* = 5.9 Hz, <u>H</u>$_4$), 2.51 (2H, dt, *J* = 1.7, 7.2 Hz, <u>H</u>$_2$), 1.87 (2H, m, <u>H</u>$_3$), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.05 (6H, m, Si-C<u>H</u>$_3$).

(*E*)-Ethyl 6-(*tert*-butyldimethylsilyl)oxy-hex-2-enoate (121)[115]

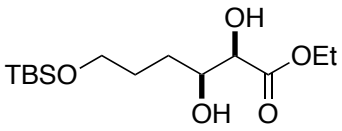


To a solution of triethyl phosphonoacetate **127** (9.36 mL, 51.0 mmol), lithium chloride (11.1 g, 262 mmol) and Hünig's base (4.30 mL, 35.2 mmol) in acetonitrile (100 mL) at room temperature was added a solution of freshly prepared aldehyde **204** (39.2 mmol) in acetonitrile (50 mL). After 18 h, water (100 mL) was added and the organics were extracted with ethyl acetate (3 ×

100 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided (*E*)-enoate **121** (7.10 g, 70% over two steps, *E* : *Z* = 30 : 1) as a colourless oil.

***R**f* 0.52 (25% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 (1H, dt, *J* = 15.7, 7.0 Hz, $\underline{H}_3$), 5.84 (1H, dt, *J* = 15.7, 1.6 Hz, $\underline{H}_2$), 4.19 (2H, q, *J* = 7.9 Hz, $OC\underline{H}_2$), 3.47 (2H, t, *J* = 6.1 Hz, $\underline{H}_6$), 2.28 (2H, ddt, *J* = 1.6, 8.4, 7.0 Hz, $\underline{H}_4$), 1.72-1.63 (2H, m, $\underline{H}_5$), 1.29 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 0.90 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.05 (6H, m, Si-$C\underline{H}_3$).

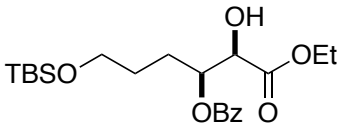
(2*R*, 3*S*)-Ethyl-6-(*tert*-butyldimethylsilyl)oxy-2, 3-dihydrohexanoate (122)



To a solution of enoate **121** (6.81 g, 26.4 mmol) in *t*-BuOH : H_2O (1 : 1, 120 mL) at 0 ºC was added methanesulfonamide (5.01 g, 52.7 mmol) and AD-mix-α (39.6 g, 1.5 g/mmol of **128**). The solution was allowed to attain room temperature, and after 16 h, sodium thiosulfate (78.6 g, 316 mmol) was added. After 1 h, water (100 mL) and dichloromethane (100 mL) were added and the organics were extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography (3 : 2, hexane : ethyl acetate) provided diol **122** (7.52 g, 93%) as a colourless oil.

***R*$_f$** 0.43 (50% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -15.1 (*c* 1.1, $CHCl_3$); **IR** (thin film) 3412, 2955, 2854, 1747, 1472, 1256, 1100, 837 and 777 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.29 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2$) 4.07 (1H, d, *J* = 2.2 Hz, $\underline{H}_2$), 3.97-3.92 (1H, m, $\underline{H}_3$), 3.74-3.65 (2H, m, $\underline{H}_6$), 1.75-1.69 (4H, m, $\underline{H}_4$ + $\underline{H}_5$), 1.32 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 0.90 (9H, s, Si-C($C\underline{H}_3$)$_3$) and 0.08 (6H, m, Si-$C\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 73.6, 72.3, 63.3, 61.2, 31.0, 29.0, 25.9, 18.3, 14.2 and -5.4; **HRMS** (ES^+) calc. for $C_{14}H_{31}O_5Si$ ($[M+H]^+$) 307.1935, found 307.1938.

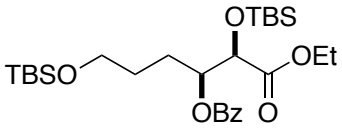
(2*R*, 3*S*)-6-(*tert*-Butyldimethylsilyl)oxy-2-hydroxy-1-ethoxy-1-oxohexan-3-yl benzoate (133)



To a solution of diol **122** (4.81 g, 16.5 mmol), triethylamine (5.76 mL, 41.4 mmol) and DMAP (60.0 mg, 570 μmol) in dichloromethane (70 mL) at -78 ºC was added benzoyl chloride (1.95 mL, 16.9 mmol) dropwise. After 1 h, the reaction solution was allowed to attain -50 ºC. After a further 16 h, an aqueous solution of $NaHCO_3$ (100 mL) was added, and the organics were extracted with dichloromethane (3 × 80 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography (19 : 1, hexane : ethyl acetate) provided benzoate **133** (5.06 g, 77%) as a colourless oil.

***R**f* 0.51 (25% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -209 (*c* 1.0, $CHCl_3$); **IR** (thin film) 3493, 2954, 2858, 1748, 1723, 1452, 1271, 1110, 835, 777 and 712 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02-7.99 (2H, m, Ar-H), 7.60-7.54 (1H, m, Ar-H), 7.47-7.41 (2H, m, Ar-H), 5.46 (1H, dt, *J* = 7.0, 2.2 Hz, H_3), 4.35 (1H, dd, *J* = 7.5, 2.2 Hz, H_2), 4.18 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.70-3.65 (2H, m, H_6), 3.11 (1H, d, *J* = 7.4, OH), 2.00-1.92 (2H, m, H_4), 1.70-1.62 (2H, m, H_5), 1.21 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.05 (3H, m, Si-CH_3) and 0.04 (3H, m, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 165.8, 133.3, 129.9, 129.8, 128.5, 74.8, 71.9, 62.8, 62.3, 28.7, 27.3, 26.1, 18.4, 14.2 and -5.2; **HRMS** (ES^+) calc. for $C_{21}H_{35}O_6Si$ ($[M+H]^+$) 411.2197, found 411.2184.

(2*R*, 3*S*)-2, 6-Bis(*tert*-butyldimethylsilyl)oxy-1-ethoxy-1-oxohexan-3-yl benzoate (134)

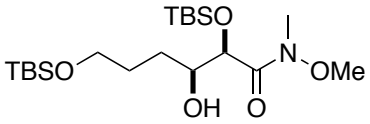


To a solution of TBSCl (2.44 g, 16.2 mmol) and imidazole (2.20 g, 32.3 mmol) in DMF (5 mL) at 0 ºC was added a solution of alcohol **133** (4.27 g, 10.8 mmol) in DMF (4 mL). After 14 h, a saturated solution of NH_4Cl (10 mL) was added and the organics were extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (40 mL) and brine (20 mL), then dried (Na_2SO_4), filtered and concentrated under

reduced pressure. Purification by column chromatography (99 : 1 to 19 : 1, hexane : ethyl acetate) provided bis-TBS-ether **134** (4.80 g, 87%) as a colourless oil.

***R*$_f$** 0.47 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -3.0 (*c* 1.0, $CHCl_3$); **IR** (thin film) 2955, 2858, 1762, 1724, 1473, 1271, 1109, 837, 778 and 711 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06-8.03 (2H, m, Ar-H), 7.58-7.52 (1H, m, Ar-H), 7.46-7.40 (2H, m, Ar-H), 5.40-5.34 (1H, dt, *J* = 7.1, 3.9 Hz, H_3), 4.41 (1H, d, *J* = 4.0 Hz, H_2), 4.13 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.68-3.60 (2H, m, H_6), 1.94-1.83 (2H, m, H_4), 1.66-1.59 (2H, m, H_5), 1.18 (3H, t, *J* = 7.3 Hz, OCH_2CH_3), 0.93 (9H, s, Si-C(CH_3)$_3$), 0.89 (9H, s, Si-C(CH_3)$_3$), 0.11 (3H, m, Si-CH_3), 0.06 (3H, m, Si-CH_3) and 0.04 (6H, m, 2 x Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 166.1, 133.0, 130.3, 129.8, 128.4, 75.2, 73.4, 62.8, 61.1, 29.0, 26.7, 26.0, 25.8, 22.8, 18.3, 14.2, -4.8 and -5.2; **HRMS** (ES^+) calc. for $C_{27}H_{49}O_6Si_2$ ($[M+H]^+$) 525.3068, found 525.3049.

(2*R*,3*S*)-2,6-Bis(*tert*-butyldimethylsilyl)oxy-3-hydroxy-*N*-methoxy-*N*-methyl hexanamide (135)

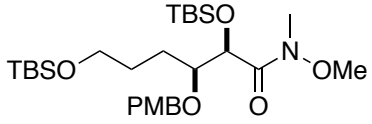


To a solution of ethyl-ester **134** (3.18 g, 6.21 mmol) and *N*,*O*-dimethyl hydroxylamine hydrochloride (900 mg, 9.11 mmol) in THF (75 mL) at -30 ºC was slowly added *iso*-propylmagnesium chloride (13.9 mL, 27.9 mmol, 2M in

THF). The reaction solution was allowed to attain room temperature and after 6 h a saturated solution of NH_4Cl (70 mL) was added. The organics were extracted with dichloromethane (3 × 80 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography (4 : 1, hexane : ethyl acetate) provided Weinreb amide **135** (2.31 g, 85%) as a colourless oil.

***R**_f* 0.40 (40% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -12.5 (*c* 1.1, $CHCl_3$); **IR** (thin film) 2930, 2857, 1726, 1646, 1473, 1387, 1255, 1098, 837, 778 and 706 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.48 (1H, d, *J* = 3.6 Hz, $\underline{H}_2$), 3.83-3.77 (1H, m, $\underline{H}_3$), 3.71 (3H, s, NOC$\underline{H}_3$), 3.68-3.63 (2H, m, $\underline{H}_6$), 3.57 (3H, s, NC$\underline{H}_3$), 1.78-1.53 (4H, m, $\underline{H}_4$ + $\underline{H}_5$), 0.94 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.90 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.13 (3H, s, Si-C$\underline{H}_3$), 0.09 (3H, s, Si-C$\underline{H}_3$) and 0.05 (6H, s, 2 × Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 72.5, 63.0, 61.2, 61.0, 33.8, 30.4, 29.1, 26.0, 25.8, 18.4, 18.3, -4.6, -5.3 and -5.3; **HRMS** (ES^+) calc. for $C_{20}H_{46}NO_5Si_2$ ($[M+H]^+$) 436.2905, found 436.2909.

(2*R*,3*S*)-2,6-Bis(*tert*-butyldimethylsilyl)oxy-3-(*p*-methoxybenzyl)oxy-*N*-methoxy-*N*-methyl hexanamide (96)

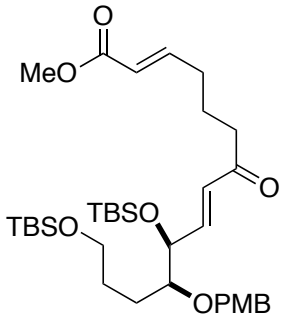


To a solution of alcohol **135** (2.00 g, 4.60 mmol) and PMBTCA (1.62 g, 5.74 mmol) in toluene (40 mL) at 0 ºC was added scandium (III) triflate

(134 mg, 240 μmol). After 6 h, the reaction mixture was filtered, and the filtrand was washed with hexane (3 x 30 mL). The filtrate was concentrated under reduced pressure. Purification by column chromatography (19 : 1, hexane : ethyl acetate) provided PMB ether **96** (1.96 g, 77%) as a colourless oil.

***R*$_f$** 0.57 (25% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -0.9 (*c* 1.0, $CHCl_3$); **IR** (thin film) 2930, 2857, 1726, 1646, 1473, 1387, 1255, 1098, 837, 778 and 706 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2H, d *J* = 8.6 Hz, Ar-H), 6.86 (2H, d *J* = 8.6 Hz, Ar-H), 4.74-4.55 (2H, m, OCH_aH_bPhOMe + H_2), 4.52 (1H, d, *J* = 11.0 Hz, OCH_aH_bPhOMe), 3.80 (3H, s, $NOCH_3$), 3.75-3.65 (4H, m, NCH_3), 3.60-3.53 (2H, m, H_6), 3.20 (3H, br s, $ArOCH_3$), 1.78-1.41 (4H, m, H_5 + H_4), 0.93 (9H, s, Si-C(CH_3)$_3$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.10 (3H, s, Si-CH_3), 0.1 (3H, s, Si-CH_3) and 0.03 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 131.0, 129.7, 113.7, 80.5, 72.9, 63.1, 55.3, 29.2, 27.3, 26.0, 25.9, 18.3, -4.7, -5.0 and -5.3; **HRMS** (ES^+) calc. for $C_{28}H_{54}NO_6Si_2$ ($[M+H]^+$) 556.3479, found 556.3484.

(2*E*, 8*E*, 10*S*, 11*S*)-Methyl-10, 14-bis((*tert*-butyldimethylsilyl)oxy)-11-(4-methoxy benzyl)oxy-7-oxotetradeca-2, 8-dienoate (97)



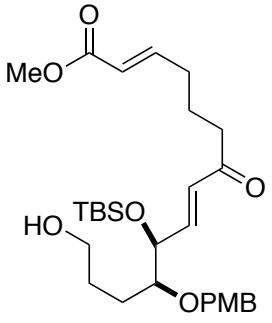
To a solution of Weinreb amide **96** (1.02 g, 1.88 mmol) in THF (20 mL) at -78 ºC was added DIBAL (3.6 mL, 3.60 mmol, 1 M in dichloromethane). After 1 h, the reaction solution was transferred to a stirring aqueous solution of Rochelle salt (30 mL) *via cannula*. After 3 h, the organics were extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure, to give aldehyde **136** which was used without further purification.

A mixture of 18-crown-6 (700 mg, 2.66 mmol), ground K_2CO_3 (3.66 g, 26.6 mmol) in toluene (50 mL) was stirred for 1 h at room temperature prior to the introduction of a solution of the freshly prepared aldehyde **136** in toluene (10 mL), followed by a solution of C1-C8 phosphonate **91** (2.10 g, 15.2 mmol) in toluene (10 mL). After 20 h, an aqueous solution of NH_4Cl (50 mL) was added and the organics were extracted with dichloromethane (3 × 50 mL) and the combined organic extracts were washed with water (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl

acetate) provided dienoate **97** (861 mg, 71% over two steps, *E* : *Z* = 6 : 1) as a colourless oil.

***R**_f* 0.33 (25% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -11.8 (*c* 1.0, $CHCl_3$); **IR** (thin film) 2929, 2856, 1722, 1674, 1612, 1514, 1247, 1093, 1035, 837 and 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m, Ar-H), 7.01-6.81 (4H, m, Ar-H, H_3 + H_9), 6.29 (1H, dd, *J* = 15.7, 1.7 Hz, H_8), 5.85 (1H, dt, *J* = 15.5, 1.4 Hz, H_2), 4.58-4.41 (3H, m, OCH_2Ph + H_{10}), 3.82 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.62-3.52 (2H, m, H_{11} + H_{14a}), 3.45-3.36 (1H, m, H_{14b}), 2.59 (2H, t, *J* = 7.5 Hz, H_6), 2.29-2.18 (2H, m, H_4), 1.85-1.59 (6H, m, H_{12} + H_{13} + H_5), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.88 (9H, s, Si-C(CH_3)$_3$) and 0.04-0.01 (12H, m, 4 × Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 166.9, 158.9, 148.6, 146.0, 130.4, 129.6, 129.5, 129.4, 121.5, 113.8, 81.8, 80.4, 72.4, 63.1, 55.3, 51.4, 39.0, 31.4, 29.5, 29.1, 27.2, 26.0, 25.8, 22.3, 18.1, -4.8, -5.0 and -5.3; **HRMS** (ES^+) calc. for $C_{35}H_{64}NO_7Si_2$ ($[M+NH_4]^+$) 666.4221, found 666.4216.

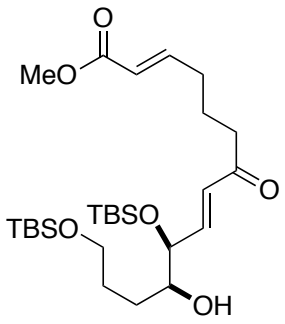
(2*E*, 8*E*, 10*S*, 11*S*)-Methyl-10-((*tert*-butyldimethylsilyl)oxy)-14-hydorxy-11-(4-methoxy benzyl)oxy-7-oxotetradeca-2, 8-dienoate (137)



To a solution of silyl ether **97** (20.0 mg, 31.0 μmol) in dichloromethane : methanol (1.4 mL, 6 : 1) at room temperature was added CSA (1.00 mg, 3.10 μmol). The reaction mixture was left to stir for 1.5 h, then quenched with a saturated solution of $NaHCO_3$ (1 mL), extracted with diethyl ether and dried over Na_2SO_4. The mixture was filtered and the resulting solution was concentrated under reduced pressure, and then purified by column chromatography (7 : 3, hexane : ethyl acetate) to give the primary alcohol **137** (13.6 mg, 81%) as a colourless oil.

R_f 0.31 (50% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -10.3 (*c* 1.0, $CHCl_3$); **IR** (thin film) 2953, 2928, 2856, 1717, 1653, 1514, 1456, 1254, 1035, 839 and 779 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.27 (2H, m, Ar-H), 6.93-6.86 (4H, m, Ar-H, H_3 + H_9), 6.30 (1H, dd, *J* = 1.8, 16.0 Hz, H_8), 5.85 (1H, dt, *J* = 1.5, 15.7 Hz, H_2), 4.61-4.49 (3H, m, OCH_2Ph + H_{10}), 3.81 (3H, s, OMe), 3.70 (3H, s, OMe), 3.60-3.57 (2H, m, H_{11} + H_{14a}), 3.44-3.40 (1H, m, H_{14b}), 3.20 (1H, br s, OH), 2.60 (2H, t, *J* = 7.5 Hz, H_6), 2.29-2.18 (2H, m, H_4), 1.82-1.56 (6H, m, H_{12} + H_{13} + H_5), 0.92 (9H, s, Si-C(CH_3)$_3$), 0.05 (3H, s, Si-CH_3) and 0.03 (3H, s, Si-CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.4, 167.0, 159.4, 148.6, 145.6, 132.1, 129.8, 121.5, 113.9, 113.7, 81.8, 80.3, 72.5, 62.8, 55.3, 51.5, 39.1, 31.4, 29.7, 29.4, 25.9, 22.2, 18.2, -4.8 and -5.0; **HRMS** (ES^+) calc. for $C_{29}H_{50}NO_7Si$ ($[M+NH_4]^+$) 552.3351, found 552.3343.

(2*E*, 8*E*, 10S, 11S)-Methyl-10, 14-bis((*tert*-butyldimethylsilyl)oxy)-11-hydorxy-7-oxotetradeca-2, 8-dienoate (138)

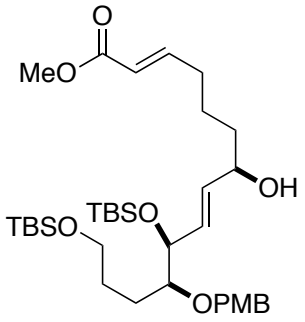


To a solution of PMB ether **97** (19 mg, 28 μmol) in dichloromethane (1.0 mL) and pH 7 buffer (100 μL) at 0 °C, was added recrystallised DDQ (13 mg, 82 μmol). The solution was stirred at room temperature for 2 h and quenched with $NaHCO_3$ (2 mL), extracted with dichloromethane (3 x 2 mL). The solution was concentrated under reduced pressure and purified by column chromatography (4 : 1 to 7 : 3, hexane : ethyl acetate) to yield the alcohol **138** (12 mg, 81%) as a colourless oil.

***R*$_f$** 0.22 (50% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +0.90 (*c* 1.0, $CHCl_3$); **IR** (thin film) 3393, 2953, 2928, 2856, 1720, 1661, 1472, 1462, 1254, 1096, 834 and 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94 (1H, dt, *J* = 15.7, 7,0 Hz, $\underline{H}_3$), 6.85 (1H, dd, *J* = 5.2, 15.9 Hz, $\underline{H}_9$), 6.25 (1H, dd, *J* = 1.6, 16.0 Hz, $\underline{H}_8$), 5.83 (1H, dt, *J* = 15.7, 1.6 Hz, $\underline{H}_2$), 4.25 (1H, ddd, *J* = 4.3, 5.0, 1.5 Hz, $\underline{H}_{10}$), 3.72 (3H, s, OMe), 3.69-3.60 (2H, m, $\underline{H}_{11}$ + $\underline{H}_{14a}$), 3.55-3.51 (1H, m, $\underline{H}_{14b}$), 3.20 (1H, br s, O$\underline{H}$), 2.59 (2H, t, *J* = 7.2 Hz, $\underline{H}_6$), 2.26-2.20 (2H, m, $\underline{H}_4$), 1.83-1.55 (6H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_5$), 0.91 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.88 (9H, s, Si-

C(C$\underline{H}_3$)$_3$) and 0.07-0.04 (12H, m, 4 × Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 166.9, 145.8, 129.7, 121.6, 75.1, 74.5, 63.2, 51.4, 39.2, 31.6, 29.7, 29.6, 29.3, 25.9, 25.9, 22.2, 18.3, 18.2, -5.0 and -5.4; **HRMS** (ES^+) calc. for $C_{27}H_{53}O_6Si_2$ ($[M+H]^+$) 529.3375, found 529.3369.

(2*E*, 7*R*, 8*E*, 10*S*, 11*S*)-Methyl-10, 14-bis((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-11-((4-methoxy benzyl)oxy)tetradeca-2, 8-dienoate (143)

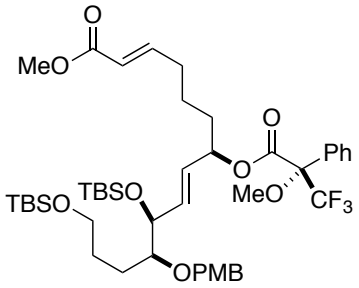


To a solution of (+)-DIP-Cl (161 mg, 500 μmol) in THF (5.0 mL) at -78 °C, was added a solution of ketone **97** (32.0 mg, 50.0 μmol) in THF (5.0 mL). The reaction was warmed to room temperature and left to stir for 16 h, when it was quenched with NH_4Cl (6 mL), extracted with diethyl ether (3 x 5 mL) and dried over $MgSO_4$ to give a mixture of diastereoisomers (7*S* : 7*R* = 1 : 3). The product was purified by column chromatography (17 : 3, hexane : ethyl acetate) to give (7*R*)-alcohol **143** (20.6 mg, 66%) as a colourless oil.

***R**$_f$* 0.32 (30% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -1.5 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.25 (2H, m, Ar-$\underline{H}$), 6.96 (1H, dt, *J* = 15.6, 7.0 Hz, $\underline{H}_3$), 6.88 (2H, d, *J* = 8.8 Hz, Ar-$\underline{H}$), 5.83 (1H, dt, *J* = 1.6, 15.6 Hz,

$\underline{H}_2$), 5.75-5.71 (2H, m, $\underline{H}_8$ + $\underline{H}_9$), 4.61-4.48 (2H, m, OC$\underline{H}_2$Ph), 4.30-4.28 (1H, m, $\underline{H}_{10}$), 4.17-4.10 (1H, m, $\underline{H}_7$), 3.81 (3H, s, OMe), 3.73 (3H, s, OMe), 3.67-3.55 (2H, m, $\underline{H}_{11}$ + $\underline{H}_{14a}$), 3.34-3.30 (1H, m, $\underline{H}_{14b}$), 2.25-2.20 (2H, m, $\underline{H}_4$), 1.90-1.47 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 × Si-C(C$\underline{H}_3$)$_3$) and 0.05-0.03 (12H, m, 4 × Si-C$\underline{H}_3$).

(*R*)-MTPA ester of 143 (144)

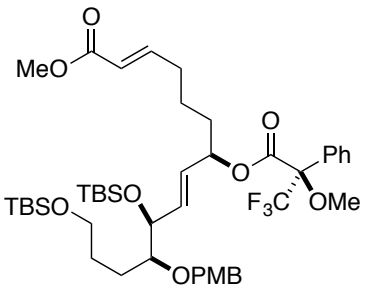


To a solution of alcohol **143** (3 mg, 4.70 μmol), DCC (2.0 mg, 9.4 μmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 μmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (*R*)-MTPA ester **144** (2.3 mg, 57%).

R$_f$ 0.42 (20%, ethyl acetate : hexane); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.50-7.47 (2H, m, Ar-$\underline{H}$), 7.42-7.38 (3H, m, Ar-$\underline{H}$), 7.28-7.25 (2H, m, Ar-$\underline{H}$), 6.90-6.87 (3H, m, Ar-$\underline{H}$ + $\underline{H}_3$), 5.97-5.95 (1H, m, $\underline{H}_9$), 5.75 (1H, dt, *J* = 1.6, 15.5 Hz, $\underline{H}_2$), 5.69-5.68 (1H, m, $\underline{H}_8$), 4.61-4.48 (2H, m, OC$\underline{H}_2$Ph), 4.30-4.27 (2H, m, $\underline{H}_7$ + $\underline{H}_{10}$), 3.81 (3H, s, OMe), 3.73 (3H, s, OMe), 3.58-3.55 (1H, m, $\underline{H}_{14a}$),

3.47 (3H, d, J = 1.1 Hz, MTPA-OC$\underline{H}_3$), 3.34-3.28 (1H, m, $\underline{H}_{11}$ + $\underline{H}_{14b}$), 2.15-2.10 (2H, m, $\underline{H}_4$), 1.85-1.34 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 × Si-C(C$\underline{H}_3$)$_3$) and 0.05-0.03 (12H, m, 4 × Si-C$\underline{H}_3$).

(*S*)-MTPA ester of 143 (145)

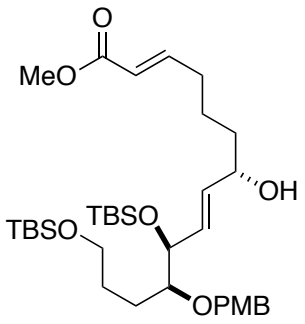


To a solution of alcohol **143** (3 mg, 4.70 μmol), DCC (2.0 mg, 9.4 μmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 μmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (*S*)-MTPA ester **145** (2.1 mg, 51%).

R$_f$ 0.43 (20%, ethyl acetate : hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.47 (2H, m, Ar-$\underline{H}$), 7.41-7.37 (3H, m, Ar-$\underline{H}$), 7.28-7.25 (2H, m, Ar-$\underline{H}$), 6.90-6.86 (3H, m, Ar-$\underline{H}$ + $\underline{H}_3$), 5.87-5.86 (1H, m, $\underline{H}_9$), 5.80 (1H, dt, J = 1.4, 15.0 Hz, $\underline{H}_2$), 5.69-.5.67 (1H, m, $\underline{H}_8$), 4.56-4.45 (2H, m, OC$\underline{H}_2$Ph), 4.32-4.30 (1H, m, $\underline{H}_7$), 4.28-4.27 (1H, m, $\underline{H}_{10}$), 3.80 (3H, s, OMe), 3.75 (3H, s, OMe), 3.56-3.54 (1H, m, $\underline{H}_{14a}$), 3.50 (3H, d, J = 1.3 Hz, MTPA-OC$\underline{H}_3$), 3.30-3.26 (1H, m,

$\underline{H}_{11}$ + $\underline{H}_{14b}$), 2.21-2.19 (2H, m, $\underline{H}_4$), 1.90-1.40 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 × Si-C($C\underline{H}_3$)$_3$) and 0.05-0.03 (12H, m, 4 × Si-$C\underline{H}_3$).

(2*E*, 7*S*, 8*E*, 10*S*, 11*S*)-Methyl-10, 14-bis((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-11-((4-methoxy benzyl)oxy)tetradeca-2, 8-dienoate (141)

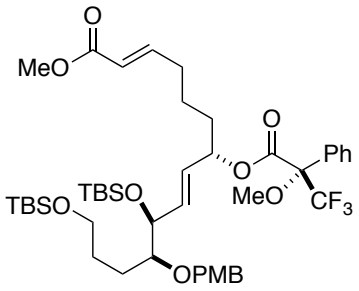


To a solution of (-)-DIP-Cl (2.50 g, 7.71 mmol) in THF (40 mL) at -78 °C, was added a solution of ketone **97** (500 mg, 771 μmol) in THF (20 mL). The reaction was warmed to room temperature and left to stir for 16 h, when it was quenched with NH_4Cl (30 mL), extracted with diethyl ether (3 x 30 mL) and dried over $MgSO_4$ to give a mixture of diastereoisomers (7*S* : 7*R* = 5 : 1). The product was purified by column chromatography (17 : 3, hexane : ethyl acetate) to give (7*S*)-alcohol **141** (350 mg, 69%) as a colourless oil.

***R*$_f$** 0.35 (30% ethyl acetate : hexanes); $[\alpha]_D^{20}$ -8.2 (*c* 1.0, $CHCl_3$); **IR** (thin film) 3402, 2951, 2928, 2857, 1742, 1514, 1247, 1093, 833 and 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.25 (2H, m, Ar-$\underline{H}$), 6.96 (1H, dt, *J* = 15.6, 6.8 Hz, $\underline{H}_3$), 6.88 (2H, d, *J* = 8.3 Hz, Ar-$\underline{H}$), 5.83 (1H, dt, *J* = 1.5, 1.55 Hz, $\underline{H}_2$), 5.74-5.69 (2H, m, $\underline{H}_8$ + $\underline{H}_9$), 4.63-4.49 (2H, m, O$C\underline{H}_2$Ph), 4.32-4.29 (1H, m, $\underline{H}_{10}$),

4.15-4.10 (1H, m, $\underline{H}_7$), 3.82 (3H, s, OMe), 3.74 (3H, s, OMe), 3.66-3.56 (2H, m, $\underline{H}_{11}$ + $\underline{H}_{14a}$), 3.37-3.31 (1H, m, $\underline{H}_{14b}$), 2.27-2.20 (2H, m, $\underline{H}_4$), 1.92-1.50 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.91 (18H, s, 2 × Si-C($C\underline{H}_3$)$_3$) and 0.06-0.04 (12H, m, 4 × Si-$C\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4, 159.6, 149.7, 134.5, 131.1, 130.8, 130.0, 121.5, 114.1, 82.7, 73.2, 72.7, 72.5, 63.7, 55.6, 51.7, 45.3, 36.8, 32.4, 30.0, 29.9, 26.2, 26.2, 24.3, 18.4, -4.4 and -4.9; **HRMS** (ES^+) calc. for $C_{35}H_{66}NO_7Si_2$ ($[M+NH_4]^+$) 668.4367, found 669.4391.

(*R*)-MTPA ester of 141 (146)

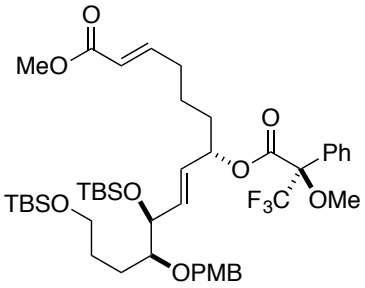


To a solution of alcohol **141** (3 mg, 4.70 μmol), DCC (2.0 mg, 9.4 μmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 μmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (*R*)-MTPA ester **146** (2.7 mg, 67%).

R_f 0.40 (20%, ethyl acetate : hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51-7.48 (2H, m, Ar-$\underline{H}$), 7.37-7.32 (3H, m, Ar-$\underline{H}$), 7.28-7.25 (2H, m, Ar-$\underline{H}$), 6.88-6.87 (3H, m, Ar-$\underline{H}$ + $\underline{H}_3$), 5.93-5.92 (1H, m, $\underline{H}_9$), 5.80 (1H, dt, *J* = 1.5, 15.4

Hz, $\underline{H}_2$), 5.63-5.61 (1H, m, $\underline{H}_8$), 4.54-4.41 (2H, m, OC$\underline{H}_2$Ph), 4.31-4.29 (2H, m, $\underline{H}_7$ + $\underline{H}_{10}$), 3.82 (3H, s, OMe), 3.73 (3H, s, OMe), 3.58-3.55 (1H, m, $\underline{H}_{14a}$), 3.49 (3H, d, J = 1.2 Hz, MTPA-OC$\underline{H}_3$), 3.30-3.26 (1H, m, $\underline{H}_{11}$ + $\underline{H}_{14b}$), 2.21-2.19 (2H, m, $\underline{H}_4$), 1.98-1.52 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 × Si-C(C$\underline{H}_3$)$_3$) and 0.05-0.03 (12H, m, 4 × Si-C$\underline{H}_3$).

(*S*)-MTPA ester of 141 (147)

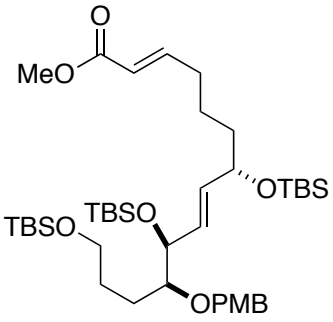


To a solution of alcohol **141** (3 mg, 4.70 μmol), DCC (2.0 mg, 9.4 μmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (2.2 mg, 9.4 μmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (*S*)-MTPA ester **147** (2.3 mg, 56%).

R$_f$ 0.42 (20%, ethyl acetate : hexane); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.52-7.48 (2H, m, Ar-$\underline{H}$), 7.39-7.35 (3H, m, Ar-$\underline{H}$), 7.28-7.25 (2H, m, Ar-$\underline{H}$), 6.88-6.86 (3H, m, Ar-$\underline{H}$ + $\underline{H}_3$), 6.01-5.99 (1H, m, $\underline{H}_9$), 5.75 (1H, dt, J = 1.6, 15.5 Hz, $\underline{H}_2$), 5.69-5.67 (1H, m, $\underline{H}_8$), 4.65-4.54 (2H, m, OC$\underline{H}_2$Ph), 4.36-4.33 (1H, m, $\underline{H}_{10}$), 4.30-4.28 (1H, m, $\underline{H}_7$), 3.79 (3H, s, OMe), 3.74 (3H, s, OMe), 3.55-

3.52 (1H, m, $\underline{H}_{14a}$), 3.45 (3H, d, J = 1.1 Hz, MTPA-OC$\underline{H}_3$), 3.36-3.30 (1H, m, $\underline{H}_{11}$ + $\underline{H}_{14b}$), 2.14-2.10 (2H, m, $\underline{H}_4$), 1.90-1.52 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 × Si-C(C$\underline{H}_3$)$_3$) and 0.05-0.03 (12H, m, 4 × Si-C$\underline{H}_3$).

(2*E*, 7*S*, 8*E*, 10*S*, 11*S*)-Methyl-7, 10, 14-tris((*tert*-butyldimethylsilyl)oxy-11-((4-methoxy benzyl)oxy)tetradeca-2, 8-dienoate (148)

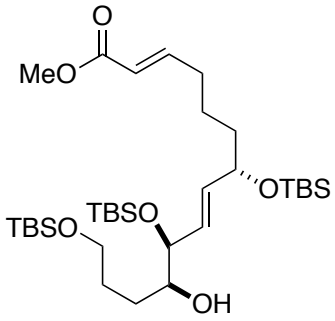


To a solution of alcohol **141** (285 mg, 440 μmol) in dichloromethane (5 mL) at room temperature, was added imidazole (57 mg, 670 μmol), TBSCl (100 mg, 585 μmol) and DMAP (5.0 mg) The mixture was stirred at room temperature for 16 h, and quenched with ammonium chloride (5 mL), the product extracted with dichloromethane (3 x 5 mL) and the combined organic extracts were dried over $MgSO_4$. The crude residue was purified using column chromatography (19 : 1, hexane : ethyl acetate) to afford the silyl enol ether **148** (301 mg, 89%) as a colourless oil.

***R*$_f$** 0.57 (20% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -13.0 (*c* 2.1, $CHCl_3$); **IR** (thin film) 3309, 2950, 2929, 2850, 1732, 1517, 1247, 1093, 1030, 835 and 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27-7.25 (2H, m, Ar-$\underline{H}$), 6.99-6.92

(1H, m, $\underline{H}_3$), 6.87 (2H, d, J = 8.3 Hz, Ar-$\underline{H}$), 5.81 (1H, dt, J = 1.5, 15.5 Hz, $\underline{H}_2$), 5.69-5.59 (2H, m, $\underline{H}_8$ + $\underline{H}_9$), 4.62-4.47 (2H, m, OC$\underline{H}_2$Ph), 4.29-4.27 (1H, m, $\underline{H}_{10}$), 4.15-4.11 (1H, m, $\underline{H}_7$), 3.81 (3H, s, Ar-OMe), 3.73 (3H, s, OMe), 3.61-3.49 (2H, m, $\underline{H}_{11}$ + $\underline{H}_{14a}$), 3.31-3.27 (1H, m, $\underline{H}_{14b}$), 2.23-2.16 (2H, m, $\underline{H}_4$), 1.75-1.44 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.92 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.89 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$) and 0.04-0.01 (18H, m, 6 × Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 159.0, 149.4, 134.1, 131.1, 129.3, 128.8, 120.9, 113.6, 82.4, 72.9, 72.8, 72.2, 63.4, 55.3, 51.3, 37.8, 32.2, 29.7, 29.5, 29.5, 26.1, 26.0, 25.9, 23.7, 18.4, 18.2, -4.6, -4.8 and -5.3; **HRMS** (ES^+) calc. for $C_{41}H_{80}NO_7Si_3$ ($[M+NH_4]^+$) 782.5232, found 782.5224.

(2*E*, 7*S*, 8*E*, 10*S*, 11*S*)-Methyl-7, 10, 14-tris((*tert*-butyldimethylsilyl)oxy-11-hydroxytetradeca-2, 8-dienoate (149)

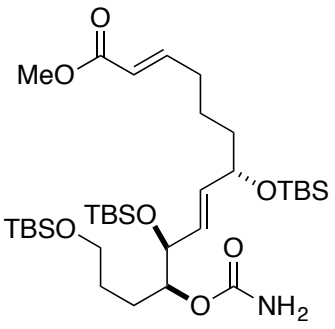


To a solution of PMB ether **148** (150 mg, 196 μmol) in dichloromethane (2 mL) and pH 7 buffer (200 μL) at 0 °C, was added recrystallised DDQ (133 mg, 588 μmol). The solution was stirred at room temperature for 3 h and quenched with $NaHCO_3$ (40 mL), extracted with dichloromethane (3 x 30 mL), and dried over Na_2SO_4. The solution was concentrated under

reduced pressure and purified by column chromatography (4 : 1 to 7 : 3, hexane : ethyl acetate) to yield the alcohol **149** (96 mg, 76%) as a colourless oil.

***R**f* 0.18 (50% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +4.0 (*c* 1.0, $CHCl_3$); **IR** (thin film) 3418, 2921, 2847, 1719, 1277, 1126, 835 and 766 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (1H, dt, *J* = 6.9, 15.7 Hz, $\underline{H}_3$), 5.82 (1H, dt, *J* = 1.5, 15.7 Hz, $\underline{H}_2$), 5.69-5.50 (2H, m, $\underline{H}_8$ + $\underline{H}_9$), 4.16-4.11 (1H, m, $\underline{H}_{10}$), 3.91-3.86 (1H, m, $\underline{H}_7$), 3.73-3.63 (5H, m, OMe, $\underline{H}_{11}$ + $\underline{H}_{14a}$), 3.43-3.37 (1H, m, $\underline{H}_{14b}$), 2.23-2.18 (2H, m, $\underline{H}_4$), 1.74-1.48 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (9H, s, Si-C($C\underline{H}_3$)$_3$), 0.89 (18H, s, 2 x Si-C($C\underline{H}_3$)$_3$), 0.09 (6H, s, 2 × Si-$C\underline{H}_3$) and 0.05-0.02 (12H, m, 4 × Si-$C\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 149.4, 136.6, 129.4, 121.2, 75.1, 72.4, 63.0, 53.6, 51.6, 37.6, 32.3, 29.9, 29.7, 29.7, 26.0, 26.0, 25.9, 23.6, 18.3, 18.2, -4.3, -4.6 and -4.7; **HRMS** (ES^+) calc. for $C_{33}H_{72}NO_6Si_3$ ($[M+NH_4]^+$) 662.4667, found 662.4651.

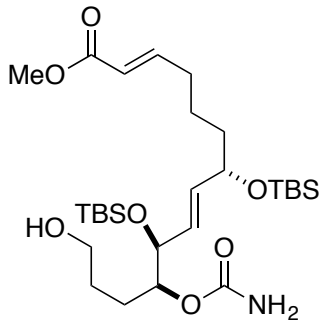
(2*E*, 7*S*, 8*E*, 10*S*, 11*S*)-Methyl-7, 10, 14-tris((*tert*-butyldimethylsilyl)oxy-11-(carbamoyloxy)tetradeca-2, 8-dienoate (150)



To a solution of alcohol **149** (80 mg, 154 μmol) in dichloromethane (2 mL), trichloroacetyl isocyanate (185 μL, 1.55 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, upon which the solvent was removed under *vacuo*, then redissolved in methanol (5.0 mL). To this dried potassium carbonate (145 mg, 1.05 mmol) was added, and this was left to stir for 16 h at room temperature, upon which it was quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over Na_2SO_4. The mixture was purified using column chromatography (7 : 3, hexane : ethyl acetate) to give carbamate **150** (74 mg, 69%) as a colourless oil.

R_f 0.29 (40% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -14.0 (*c* 0.2, $CHCl_3$); **IR** (thin film) 2953, 2928, 2855, 1717, 1707, 1506, 1065, 1051, 835 and 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (1H, dt, *J* = 6.9, 15.8 Hz, $\underline{H}_3$), 5.83 (1H, dt, *J* = 1.5, 15.7 Hz, $\underline{H}_2$), 5.71-5.53 (2H, m, $\underline{H}_8$ + $\underline{H}_9$), 4.75-4.58 (3H, m, $N\underline{H}_2$ + $\underline{H}_{11}$), 4.24 (1H, t, *J* = 5.2 Hz, $\underline{H}_{10}$), 4.14-4.04 (3H, m, $\underline{H}_7$ + $\underline{H}_{14}$), 3.73 (3H, s, OMe), 2.24-2.19 (2H, m, $\underline{H}_4$), 1.71-1.48 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 x Si-C($C\underline{H}_3$)$_3$), 0.89 (9H, s, Si-C($C\underline{H}_3$)$_3$), 0.08 (6H, s, 2 × Si-$C\underline{H}_3$) and 0.05-0.03 (12H, m, 4 × Si-$C\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.4, 156.6, 150.0, 135.6, 128.0, 121.1, 76.9, 73.1, 72.6, 65.2, 51.6, 37.7, 32.3, 30.0, 29.9, 29.9, 26.0, 26.0, 25.9, 23.7, 18.4, 18.3, -4.4, -4.7 and -4.8; **HRMS** (ES^+) calc. for $C_{34}H_{70}NO_7Si_3$ ($[M+H]^+$) 688.4460, found 688.4463.

(2*E*, 7*S*, 8*E*, 10*S*, 11*S*)-Methyl 7, 10-bis((*tert*-butyldimethylsilyl)oxy-11-(carbamoyloxy)-14-hydroxytetradeca-2, 8-dienoate (98)



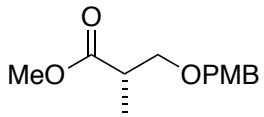
To a solution of silyl ether **150** (50 mg, 72 μmol) in dichloromethane : methanol (2.5 mL, 6 : 1) at room temperature was added CSA (2.0 mg, 11.1 μmol). The reaction mixture was left to stir for 2 h, then quenched with sodium bicarbonate (3 mL), extracted with dichloromethane (3 x 5 mL) and dried over Na_2SO_4. The mixture was filtered and the resulting solution was concentrated under reduced pressure, then purified by column chromatography (3 : 2, hexane : ethyl acetate) to give the primary alcohol **98** (41.4 mg, 80%) as a colourless oil.

***R**f* 0.28 (50% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ -8.4 (*c* 0.1, $CHCl_3$); **IR** (thin film) 3466, 3364, 2979, 2929, 2854, 1714, 1366, 1312, 1278, 1188, 1128, 835 and 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.96 (1H, dt, *J* = 6.9, 15.7 Hz, $\underline{H}_3$), 5.83 (1H, dt, *J* = 1.5, 15.7 Hz, $\underline{H}_2$), 5.70-5.53 (2H, m, $\underline{H}_8$ + $\underline{H}_9$), 4.75-4.58 (3H, m, $N\underline{H}_2$ + $\underline{H}_{11}$), 4.26-4.22 (1H, m, $\underline{H}_{10}$), 4.17-4.11 (1H, m, $\underline{H}_7$), 4.06-4.04 (2H, m, $\underline{H}_{14}$), 3.73 (3H, s, OMe), 2.23-2.20 (2H, m, $\underline{H}_4$), 1.73-1.45 (8H, m, $\underline{H}_{12}$ + $\underline{H}_{13}$ + $\underline{H}_6$ + $\underline{H}_5$), 0.90 (18H, s, 2 x Si-C($C\underline{H}_3$)$_3$), and 0.05-0.03

(12H, m, 4 × Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.8, 156.5, 148.5, 130.9, 129.4, 121.9, 77.4, 75.8, 74.8, 63.0, 52.8, 32.8, 32.0, 30.8, 29.5, 26.1, 26.0, 21.9, 18.4, 18.3, -4.4 and -4.5; **HRMS** (ES^+) calc. for $C_{28}H_{56}NO_7Si_2$ ($[M+H]^+$) 574.3595, found 574.3591.

7.5: Experimental for Chapter 3

(2*S*)-Methyl-3-(*para*-methoxybenzyl)-2-methylpropanoate (159)[117]

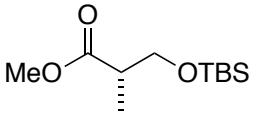


To a solution of (*S*)-Roche ester **158** (10.0 g, 84.6 mmol) in dichloromethane (200 mL) at 0 ºC, PMBTCA (28.7 g, 101.6 mmol) was added followed by careful addition of PPTS (1.00 g, 4.23 mmol). After 3 h at 0 ºC the reaction was warmed to room temperature, then left stirring for 16 h, upon which it was quenched with NH_4Cl (200 mL), washed with dichloromethane (3 x 150 mL) and dried over $MgSO_4$. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided PMB ether **159** (17.1 g, 85%) as a colourless oil.

***R**$_f$* 0.60 (30% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.7 Hz, Ar-$\underline{H}$), 6.91 (2H, d, *J* = 8.6 Hz, Ar-$\underline{H}$), 4.49 (2H, s, OC$\underline{H}_2$PhOMe), 3.82 (3H, s, PhOC$\underline{H}_3$), 3.79 (1H, dd, *J* = 9.1, 7.3 Hz, $\underline{H}_{3a}$),

3.71-3.66 (4H, m, $\underline{H}_{3b}$ + OC$\underline{H}_3$), 2.80 (1H, ddq, J = 14.4, 7.1, 5.9 Hz $\underline{H}_2$) and 1.20 (3H, d, J = 7.1 Hz, CHC$\underline{H}_3$).

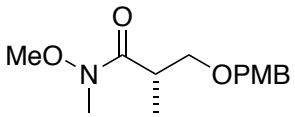
(2*S*)-Methyl-3-(*tert*-butyldimethysilyloxy)-2-methylpropanoate (205)[118]



To a solution of (*S*)-Roche ester **158** (10.0 g, 84.6 mmol) in dichloromethane (200 mL) at room temperature, was added imidazole (8.64 g, 127 mmol) and TBSCl (15.3 g, 101.6 mmol). The mixture was stirred at room temperature for 16 h, and quenched with NH_4Cl (300 mL) and the product was extracted with dichloromethane (3 x 150 mL), washed with brine (150 mL) and water (150 mL). The combined organic extracts were dried over $MgSO_4$. The crude residue was purified using column chromatography (9 : 1, hexane : ethyl acetate) to afford the silyl ether **205** (15.9 g, 98%) as a colourless oil.

***R*$_f$** 0.50 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.78 (1H, dd, J = 9.7, 6.9 Hz, $\underline{H}_{3a}$) 3.69-3.63 (4H, m, $\underline{H}_{3b}$ + OC$\underline{H}_3$), 2.66 (2H, ddq, J = 13.1, 7.0, 6.1 Hz, $\underline{H}_2$), 1.15 (3H, d, J = 7.0 Hz, CHC$\underline{H}_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$), and 0.05 (6H, m, 2 × Si-C$\underline{H}_3$).

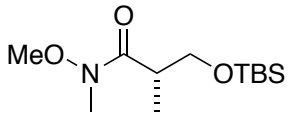
(2*S*)-3-(*para*-Methoxybenzyl)-*N*-methoxy-2, *N*-dimethyl propanamide (160)[116]



To a solution of PMB-protected Roche ester **159** (16.0 g, 67.1 mmol) and *N*,*O*-dimethyl hydroxylamine hydrochloride (10.5 g, 107 mmol) in THF (300 mL) at -30 ºC was slowly added *iso*-propylmagnesium chloride (89.2 mL, 178.4 mmol, 2M in THF). The reaction solution was stirred at this temperature for 3 h upon which a saturated solution of NH_4Cl (300 mL) was added. The organics were extracted with dichloromethane (3 x 200 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (4 : 1, hexane : ethyl acetate) provided Weinreb amide **160** (16.9 g, 94%) as a colourless oil.

***R*$_f$** 0.53 (30% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.6 Hz, Ar-H), 6.87 (2H, d, *J* = 8.6 Hz, Ar-H), 4.45 (2H, s, OCH_2PhOMe), 3.81 (3H, s, $PhOCH_3$), 3.71-3.67 (4H, m, H_{3a} + $NOCH_3$), 3.40 (1H, dd, *J* = 8.9, 5.8 Hz, H_{3b}), 3.31-3.19 (4H, m, H_2 + NCH_3) and 1.11 (3H, d, *J* = 6.9 Hz, CCH_3).

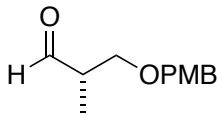
(2*S*)-3-(*tert*-Butyldimethysilyloxy)-*N*-methoxy-2, *N*-dimethyl propanamide (174)[117]



To a solution of TBS-protected Roche ester **205** (15.0 g, 64.6 mmol) and *N*,*O*-dimethyl hydroxylamine hydrochloride (9.50 g, 96.9 mmol) in THF (300 mL) at -30 ºC was slowly added *iso*-propylmagnesium chloride (146 mL, 291 mmol, 2M in THF). The reaction solution was stirred at this temperature for 3 h upon which a saturated solution of NH_4Cl (300 mL) was added. The organics were extracted with dichloromethane (3 x 200 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided Weinreb amide **174** (15.5 g, 92% yield) as a colourless oil.

***R*$_f$** 0.48 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.84 (1H, dd, *J* = 9.5, 8.1 Hz, $\underline{H}_{3a}$), 3.72 (3H, s, NOC$\underline{H}_3$), 3.54 (1H, dd, *J* = 9.5, 6.1 Hz, $\underline{H}_{3b}$), 3.25-3.10 (4H, m, $\underline{H}_2$ + NC$\underline{H}_3$), 1.08 (3H, d, *J* = 7.0 Hz, CC$\underline{H}_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$), and 0.05 (6H, m, 2 × Si-C$\underline{H}_3$).

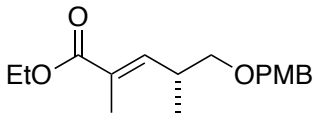
(2*S*)-3-(*para*-methoxybenzyl)-2-methylpropanal (152)[116]



To a solution of Weinreb amide **160** (10.0 g, 37.4 mmol) in dichloromethane (100 mL) at -78 °C, was added DIBAL (75.0 mL, 75.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h and quenched with aqueous potassium sodium tartrate (200 mL), and the mixture was stirred for a further 2 h. The crude product was extracted with diethyl ether (3 x 100 mL), which was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude aldehyde **152**, which was used without further purification in the next step.

R_f 0.48 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.64 (1H, d, *J* = 1.6 Hz, $\underline{H}_1$), 7.16 (2H, d, *J* = 8.7 Hz, Ar$\underline{H}$), 6.81 (2H, d, *J* = 8.7 Hz, Ar$\underline{H}$), 3.73 (3H, s, PhOC$\underline{H}_3$) 3.58 (1H, dd, *J* = 9.4, 6.7 Hz, $\underline{H}_{3a}$), 3.53 (1H, dd, *J* = 9.4, 5.3 Hz, $\underline{H}_{3a}$), 2.61-2.53 (1H, m, $\underline{H}_2$) and 1.05 (3H, d, *J* = 7.1 Hz, CC$\underline{H}_3$).

(2*E*, 4*S*)-Ethyl-5-(*para*-methoxybenzyl)-2,4-dimethylpent-2-enoate (153)[116]



Method A:

Triethyl-2-phosphonopropionate (2.44 mL, 11.4 mmol) was added to a stirring solution of LiHMDS (1.0 M in hexane, 12.4 mL, 12.4 mmol) in THF (50 mL) at -78 °C. The solution was left to stir for 20 min before the crude aldehyde **152** (9.20 mmol) was slowly added. The solution was warmed to -40 °C and stirred for 17 h. The reaction was quenched with NH_4Cl (25 mL), extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (4 : 1, hexane : ethyl acetate) to give ester **153** (1.56 g, 58% over two steps, *E* : *Z* = 4 : 1) as a colourless oil.

Method B:

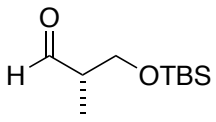
LiCl (900 mg, 19.2 mmol) was flame dried prior to use. A mixture of acetonitrile (70 mL) and LiCl, was cooled at 0 °C, and triethyl-2-phosphonopropionate (2.3 mL, 10.6 mmol) and Hünig's base (3.4 mL, 19.2 mmol) were added. The mixture was maintained at 0 °C for 20 min, and the crude aldehyde **152** (9.50 mmol) was added. The mixture was warmed to room temperature and stirred for 13 h, prior to the addition of water (40 mL). The organic portions were extracted with ethyl acetate (3 x 20 mL). The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (4 : 1, hexane : ethyl acetate) to give ester **153** (1.81 g, 65% over two steps, *E* : Z = 4 : 1) as a colourless oil.

Method C:

To a stirring solution of activated barium hydroxide (11.6 g, 35.7 mmol) in THF (150 mL), triethyl-2-phosphonopropionate (11.7 mL, 67.2 mmol) was added. The mixture was stirred for 30 min at room temperature, and the crude aldehyde **152** (37.4 mmol), in wet THF (40 : 1, THF : water, 100 mL) was added. The mixture was stirred at room temperature for 16 h, the mixture was filtered, and the crude product extracted with dichloromethane (3 x 100 mL), washed with $NaHCO_3$ (150 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (4 : 1, hexane : ethyl acetate) to give ester **153** (7.60 g, 70% over two steps, E : *Z* = 9 : 1) as a colourless oil.

***R*$_f$** 0.69 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.8 Hz, Ar<u>H</u>), 6.88 (2H, d, *J* = 8.7 Hz, Ar<u>H</u>), 6.59 (1H, dq, *J* = 9.7, 1.4 Hz, <u>H</u>$_3$), 4.45 (2H, s, OC<u>H</u>$_2$Ar), 4.19 (2H, q, *J* = 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.36 – 3.31 (2H, m, <u>H</u>$_5$), 2.89–2.78 (1H, m, <u>H</u>$_4$), 1.87 (3H, d, *J* = 1.5 Hz, =CC<u>H</u>$_3$), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2$C<u>H</u>$_3$) and 1.04 (3H, d, *J* = 6.8 Hz, CC<u>H</u>$_3$).

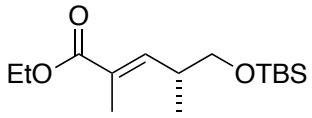
(2*S*)-3-(*tert*-butyldimethysilyloxy)-2-methylpropanal (206)[117]



To a solution of Weinreb amide **174** (10.3 g, 40.3 mmol) in dichloromethane (100 mL) at -78 °C, was added DIBAL (82.0 mL, 82.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h, quenched with aqueous potassium sodium tartrate (60 mL), then the mixture was stirred for a further 2 h. The crude product was extracted with diethyl ether (3 x 100 mL), which was washed with brine (100 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give crude aldehyde **206**, which was used without further purification in the next step.

***R**f* 0.60 (20% ethyl acetate : Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.74 (1H, d, *J* = 1.6 Hz, $\underline{H}_1$), 3.86 (1H, dd, *J* = 10.2, 5.2 Hz, $\underline{H}_{3a}$), 3.80 (1H, dd, *J* = 10.2, 6.3 Hz, $\underline{H}_{3b}$), 2.60-2.47 (1H, m, $\underline{H}_2$), 1.09 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3$), 0.87 (9H, s, $SiC(C\underline{H}_3)_3$) and 0.05 (6H, s, $Si(C\underline{H}_3)_2$).

(2*E*, 4*S*)-Ethyl-5-(*tert*-butyldimethysilyloxy)-2,4-dimethylpent-2-enoate (175)[119]

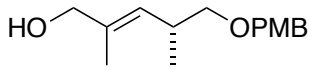


To a stirring solution of activated barium hydroxide (12.1 g, 38.3 mmol) in THF (200 mL), triethyl-2-phosphonopropionate (12.5 mL, 72.3 mmol) was added. The mixture was stirred for 30 min at room temperature, and the TBS-protected crude aldehyde **206** (40.3 mmol), in wet THF (40 : 1, THF : water, 100 mL) was added. The mixture was stirred at room temperature for 16 h, after which it was filtered and washed with hexane (3 x 80 mL), followed by

the addition of NH_4Cl (150 mL). The crude product was extracted with dichloromethane (3 x 100 mL), washed with $NaHCO_3$ (150 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (9 : 1, hexane : ethyl acetate) to give a mixture of *E* and *Z* regioisomers of **175** (8.31 g, 72% over two steps, *E* : *Z* = 9 : 1).

***R*$_f$** 0.45 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.56 (1H, dq, *J* = 9.8, 1.4 Hz, $\underline{H}_3$), 4.20 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2$), 3.87 (1H, dd, *J* = 5.2, 10.1 Hz, $\underline{H}_{5a}$), 3.81 (1H, dd, *J* = 10.1, 6.3 Hz, $\underline{H}_{5b}$), 2.75-2.64 (1H, m, $\underline{H}_4$), 1.87 (3H, d, *J* = 1.3 Hz, $=CC\underline{H}_3$), 1.30 (3H, d, *J* = 7.3 Hz, $OCH_2C\underline{H}_3$), 1.02 (3H, d, *J* = 6.8 Hz, $CC\underline{H}_3$), 0.88 (9H, s, $Si\text{-}C(C\underline{H}_3)_3$), and 0.05 (6H, m, 2 × $Si\text{-}C\underline{H}_3$).

(2*E*, 4*S*)-5-(*para*-Methoxybenzyl)-2,4-dimethylpent-2-en-1-ol (160)[120]

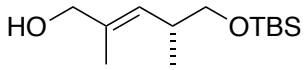


To a solution of PMB-protected ester **153** (6.70 g, 22.9 mmol) in dichloromethane (60 mL) at -78 °C, was added DIBAL (46.0 mL, 46.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h upon which aqueous potassium sodium tartrate (100 mL) was added, and the mixture was stirred for a further 4 h. The crude product was extracted with diethyl ether (3 x 60 mL), which was washed with brine (60 mL), dried over Na_2SO_4 and the

solvent was removed under reduced pressure. The crude residue was purified using column chromatography (1 : 1, hexane : ethyl acetate) to yield alcohol **160** (4.64 g, 81%) as a colourless oil.

***R*$_f$** 0.63 (50% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.8 Hz, Ar-H), 6.91 (2H, d, *J* = 8.7 Hz, Ar-H), 5.26 (1H, dq, *J* = 9.2, 1.4 Hz, H_3), 4.47 (2H, s, OCH_2Ar), 4.00 (2H, s, H_1), 3.83 (3H, s, $ArOCH_3$), 3.33 (1H, dd, *J* = 9.2, 6.7 Hz, CH_{5a}), 3.28 (1H, dd, *J* = 9.3 6.9 Hz, CH_{5b}), 2.86–2.68 (1H, m, H_4), 1.71 (3H, d, *J* = 1.3 Hz, $=CCH_3$) and 1.01 (3H, d, *J* = 6.7 Hz, $CH\text{-}CH_3$).

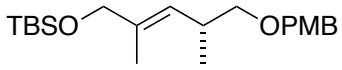
(2*E*, 4*S*)-5-(*tert*-Butyldimethysilyloxy)-2,4-dimethylpent-2-en-1-ol (195)[118]



To a solution of TBS-protected ester **175** (6.90 g, 23.9 mmol) in dichloromethane (50 mL) at -78 °C, was added DIBAL (48.0 mL, 48.0 mmol, 1 M in dichloromethane). The mixture was stirred for 3 h upon which aqueous potassium sodium tartrate (100 mL) was added, and the mixture was stirred for a further 4 h. The crude product was extracted with dichloromethane (3 x 50 mL), which was washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified using column chromatography (4 : 1, hexane : ethyl acetate) to yield alcohol **195** (5.26 g, 90%) as a colourless oil.

***R**f* 0.30 (30% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.14 (1H, dq, *J* = 9.4, 1.3 Hz, $\underline{H}_3$), 3.93 (2H, d, *J* = 4.4 Hz, $\underline{H}_1$), 3.43 (1H, dd, *J* = 9.7, 6.1 Hz, $\underline{H}_{5a}$), 3.34 (1H, dd, *J* = 9.8, 7.1 Hz, $\underline{H}_{5b}$), 2.62-2.47 (1H, m, $\underline{H}_4$), 2.34 (1H, br s, O$\underline{H}$), 1.65 (3H, d, *J* = 1.4 Hz, =CC$\underline{H}_3$), 0.92 (3H, d, *J* = 6.7 Hz, CC$\underline{H}_3$), 0.86 (9H, s, Si-C(C$\underline{H}_3$)$_3$), and 0.01 (6H, m, 2 × Si-C$\underline{H}_3$).

(2*E*, 4*R*)-1-(*tert*-Butyldimethysilyloxy)-5-(*para*-methoxybenzyl)-(2, 4)-dimethyl-pent-3-ene (154)[119]

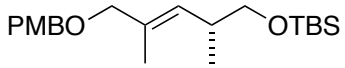


To a solution of alcohol **160** (4.25 g, 16.9 mmol) in dichloromethane (60 mL) at room temperature, was added imidazole (1.83 g, 25.5 mmol) and TBSCl (3.20 g, 20.4 mmol). The mixture was stirred at room temperature for 16 h, and quenched with ammonium chloride (60 mL) and the product was extracted with dichloromethane (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$. The crude residue was purified using column chromatography (9 : 1, hexane : ethyl acetate) to afford silyl ether **154** (5.73 g, 93%) as a colourless oil.

***R**f* 0.48 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.6 Hz, Ar-$\underline{H}$), 6.89 (2H, d, *J* = 8.7 Hz, Ar-$\underline{H}$), 5.22 (1H, dq, *J* = 9.2, 1.3 Hz, $\underline{H}_3$), 4.44 (2H, s, OC$\underline{H}_2$Ar), 4.02 (2H, s, $\underline{H}_1$), 3.81 (3H, s, OC$\underline{H}_3$), 3.33 (1H, dd, *J* = 9.1, 6.0 Hz, C$\underline{H}_{5a}$), 3.24 (1H, dd, *J* = 9.1, 7.5 Hz, C$\underline{H}_{5b}$), 2.80–2.69 (1H, m, $\underline{H}_4$), 1.64 (3H, d, *J* = 1.3 Hz, =CC$\underline{H}_3$), 1.01 (3H, d, *J*

= 6.7 Hz, CH-C$\underline{H}_3$), 0.93 (9H, s, Si-C(C$\underline{H}_3$)$_3$), and 0.08 (6H, m, 2 × Si-C$\underline{H}_3$).

(2*E*, 4*R*)-5-(*tert*-Butyldimethysilyloxy)-1-(*para*-methoxybenzyl)-(2, 4)-dimethyl-pent-3-ene (176)

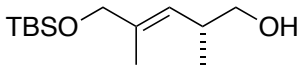


To a solution of alcohol **195** (2.00 g, 8.2 mmol) in THF (50 mL), NaH (450 mg, 11.1 mmol, 60% dispersion in mineral oil) was added at 0 ºC. After 30 min a solution of PMBCl (1.9 mL, 13.8 mmol) in THF (20 mL) was added and the resulting mixture was stirred for 3 h at 0 ºC. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the product extracted with diethyl ether (3 x 50 mL). The resulting solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (9 : 1 to 4 : 1, hexane : ethyl acetate) gave PMB-protected ether **176** (1.67 g, 56%) as a pale yellow oil.

***R*$_f$** 0.42 (30% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, Ar-$\underline{H}$), 6.86 (2H, d, *J* = 8.6 Hz, Ar-$\underline{H}$), 5.19 (1H, dq, *J* = 9.3, 1.2 Hz, $\underline{H}_3$), 4.36 (2H, s, OC$\underline{H}_2$Ar), 3.85 (2H, s, $\underline{H}_1$), 3.76 (3H, s, OC$\underline{H}_3$), 3.49-3.33 (2H, m, C$\underline{H}_5$), 2.64–2.52 (1H, m, $\underline{H}_4$), 1.68 (3H, d, *J* = 1.3 Hz, =CC$\underline{H}_3$), 0.96 (3H, d, *J* = 6.7 Hz, CH-C$\underline{H}_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$), and 0.03 (6H, m, 2 × Si-C$\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.1, 134.9, 130.9, 129.1, 127.2, 113.7, 75.0, 72.5, 68.6, 55.3, 36.4, 32.6, 25.9, 17.7, 13.7 and -5.2; **HRMS** (ES^+) Calcd. For $C_{21}H_{40}NO_3Si$ 382.2772, found $[M + NH_4]^+$

382.2770.

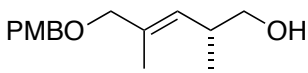
(2*S*, 3*E*)-5-(*tert*-Butyldimethysilyloxy)-2,4-dimethylpent-3-en-1-ol (207)[119]



To a solution of PMB ether **154** (4.90 g, 13.4 mmol) in dichloromethane (100 mL) and pH 7 buffer (10 mL) at 0 °C, was added DDQ (4.20 g, 18.0 mmol). The solution was stirred for 2 h and quenched with $NaHCO_3$ (1000 mL), extracted with dichloromethane (3 x 300 mL), washed with brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to yield alcohol **207** (2.85 g, 87 % yield) as a colourless oil.

***R*$_f$** 0.25 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.17 (1H, dq, *J* = 9.6, 1.4 Hz, $\underline{H}_3$), 3.96 (2H, s, $\underline{H}_1$), 3.47 (1H, dd, *J* = 10.4, 6.1 Hz, C$\underline{H}_{5a}$), 3.36 (1H, dd, *J* = 10.5, 7.9 Hz, C$\underline{H}_{5b}$), 2.71 – 2.60 (1H, m, $\underline{H}_4$), 1.65 (3H, d, *J* = 1.4 Hz, =CC$\underline{H}_3$), 0.95 (3H, d, *J* = 6.8 Hz, CC$\underline{H}_3$), 0.91 (9H, s, SiCC$\underline{H}_3$) and 0.07 (6H, s, SiC$\underline{H}_3$).

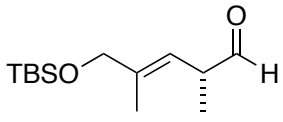
(2*S*, 3*E*)-5-(*para*-Methoxybenzyl)-2,4-dimethylpent-3-en-1-ol (208)



TBAF (8.3 mL, 8.3 mmol, 1 M in THF) was added to a solution of TBS ether **176** (1.50 g, 4.1 mmol) in THF (15 mL) at 0 ºC. After 6 h the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with diethyl ether (3 x 20 mL) and dried over $MgSO_4$. The resulting solution was concentrated under reduced pressure and purified by column chromatography (4 : 1, hexane : ethyl acetate) to yield alcohol **208** (923 mg, 89%) as a colourless oil.

***R*$_f$** 0.28 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.6 Hz, Ar-H), 6.88 (2H, d, *J* = 8.7 Hz, Ar-H), 5.21 (1H, dq, *J* = 9.5, 1.2 Hz, H_3), 4.41 (2H, s, OCH_2Ar), 3.89 (2H, s, H_1), 3.81 (3H, s, OCH_3), 3.48 (1H, dd, *J* = 10.4, 6.1 Hz, CH_{5a}), 3.38 (1H, dd, *J* = 10.5, 7.7 Hz, CH_{5b}), 2.74–2.59 (1H, m, H_4), 1.72 (3H, d, *J* = 1.3 Hz, $=CCH_3$) and 0.97 (3H, d, *J* = 6.7 Hz, $CH\text{-}CH_3$).

(2*S*, 3*E*)-5-(*tert*-Butyldimethysilyloxy)-2,4-dimethylpent-3-enal (155)



Method A:

To a solution of oxalyl chloride (156 mg, 1.23 mmol) in dichloromethane (5.0 mL) was cooled to -78 °C and a solution of DMSO (114 mg, 1.47 mmol) in dichloromethane (2.0 mL) was added dropwise over 5 min. The solution was left stirring for a further 10 min, upon which the alcohol **207** (150 mg,

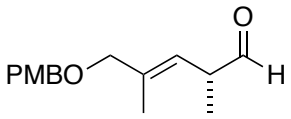
614 μmol) in dichloromethane (2.0 mL) was added dropwise. The solution was left stirring at -78 °C for 1.5 h, prior to the addition of triethylamine (435 mg, 4.30 mmol) in dichloromethane (2.0 mL). The solution was warmed to room temperature and quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a column (9 : 1, hexane : ethyl acetate) to yield aldehyde **155**, which was used immediately without further purification.

Method B:

Dess-Martin periodinane (2.25 g, 6.84 mmol) was added to a solution of alcohol **207** (1.00 g, 4.10 mmol) in dichloromethane (30 mL). The solution stirred for 2 h then quenched with sodium thiosulfate (25 mL). The product was extracted with dichloromethane (3 x 30 mL) and dried over $MgSO_4$. The product was purified by filtration through Celite®, and washing with excess petroleum ether, to give aldehyde **155**, which was used immediately without further purification.

R_f 0.55 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.51 (1H, d, *J* = 1.9 Hz, $\underline{H}_1$), 5.29 (1H, dq, *J* = 9.1, 1.4 Hz, $\underline{H}_3$), 4.07 (2H, s, $\underline{H}_5$), 3.36 – 3.25 (1H, m, $\underline{H}_2$), 1.68 (3H, d, *J* = 1.2 Hz, =CC$\underline{H}_3$), 1.18 (3H, d, *J* = 7.0 Hz, CHC$\underline{H}_3$), 0.92 (9H, s, SiCC$\underline{H}_3$) and 0.08 (6H, s, SiC$\underline{H}_3$).

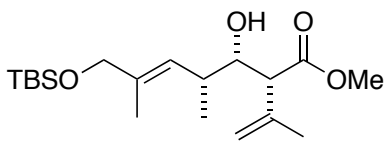
(2*S*, 3*E*)-5-(*para*-Methoxybenzyl)-2,4-dimethylpent-3-enal (173)



Dess-Martin periodinane (830 mg, 2.00 mmol) was added to a solution of alcohol **208** (250 mg, 1.00 mmol) in dichloromethane (4 mL). The solution stirred for 2 h then quenched with sodium thiosulfate (5 mL). The product was extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. The product was purified by filtration through Celite®, and washing with excess petroleum ether, to give aldehyde **173**, which was used immediately without further purification.

R_f 0.38 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.52 (1H, d, *J* = 1.8 Hz, $\underline{H}_1$), 7.27 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 6.87 (2H, d, *J* = 8.7 Hz, Ar$\underline{H}$), 5.30 (1H, dq, *J* = 9.5, 1.2 Hz, $\underline{H}_3$), 4.41 (2H, s, OC$\underline{H}_2$Ar), 3.91 (2H, s, $\underline{H}_5$), 3.79 (3H, s, OC$\underline{H}_3$), 3.36-3.18 (1H, m, $\underline{H}_2$), 1.73 (3H, d, *J* = 1.4 Hz, =CC$\underline{H}_3$) and 1.18 (3H, d, *J* = 6.9 Hz, CH-C$\underline{H}_3$).

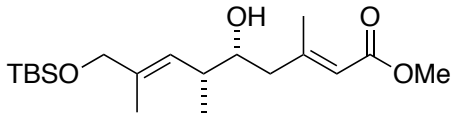
(2*R*, 3*S*, 4*R*, 5*E*)-Methyl 7-(*tert*-butyldimethylsilyl)oxy-3-hydroxy-(4, 6)-dimethyl-2-(prop-1-en-2-yl)hept-5-enoate (162)



A solution of *n*-butyl lithium (52 ml, 0.83 mmol, 1.6 M in hexane) was added to a solution of diisopropylamine (110 mL, 830 μmol) in THF (5 mL) at -78 °C. The mixture was stirred for 30 min where methyl-3,3-dimethyl acrylate **161** (70 mg, 620 μmol) in THF (2 mL) was added. After 30 min a solution of aldehyde **155** (409 μmol) in THF (1 mL) was added. The mixture was left to stir for 1 h and quenched with NH_4Cl (5 mL), the organic portions were extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct **162** (78 mg, 53%, α : γ = 4 : 1) as a colourless oil.

R_f 0.32 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +21.4 (*c* 1.0 $CHCl_3$); **IR** (thin film) 3450, 3442, 2970, 2926, 1714, 1651, 1447, 1280, 1180, 1015, 949, and 867 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.26 (1H, dq, *J* = 9.7, 1.4 Hz, $\underline{H}_5$), 5.07-5.05 (1H, m, C=C$\underline{H}_a$), 4.96–4.95 (1H, m, C=C$\underline{H}_b$), 4.00 (2H, s, $\underline{H}_7$), 3.91 (1H, ddd, *J* = 7.1, 6.8, 3.3 Hz, $\underline{H}_3$), 3.70 (3H, s, OC$\underline{H}_3$), 3.21 (1H, d, *J* = 6.6 Hz, $\underline{H}_2$), 2.56-2.50 (1H, m, $\underline{H}_4$), 2.43 (1H, d, *J* = 3.3 Hz, O$\underline{H}$), 1.84-1.83 (3H, m, =C-C$\underline{H}_3$), 1.60 (3H, d, *J* = 1.2 Hz, =C_6-C$\underline{H}_3$), 1.04 (3H, d, *J* = 6.7 Hz, C_4-C$\underline{H}_3$), 0.91 (9H, s, SiCC$\underline{H}_3$) and 0.07 (6H, m, SiC$\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2, 140.7, 134.8, 127.3, 115.1, 75.0, 68.5, 55.7, 52.1, 35.7, 30.1, 26.0, 21.6, 15.2, 13.7 and -5.1; **HRMS** (ES^+) calc. for $C_{19}H_{40}O_4SiN$ ($[M+NH_4]^+$) 374.2721, found 374.2719.

(2*E*, 5*R*, 6*R*, 7*E*)-Methyl 9-(*tert*-butyldimethylsilyl)oxy-5-hydroxy-(3, 6, 8)-trimethyl-nona-2, 7-dienoate (157)

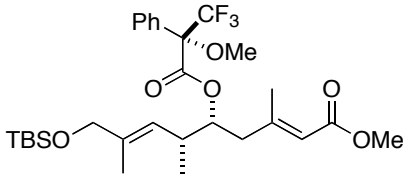


To a solution of freshly prepared ATPH **163** (6.80 mmol) in toluene (15 mL) at -78 °C was added a solution of methyl-3,3-dimethyl acrylate **161** (480 mg, 4.10 mmol) in toluene (5 mL); after 15 min a solution of aldehyde **155** (2.05 mmol) in toluene (5mL) was added. The mixture was stirred for 20 min upon which a solution of *n*-butyl lithium (2.8 mL, 4.50 mmol, 1.6 M in hexane) and diisopropylamine (643 μL, 4.50 mmol) in THF (15 mL) was added. After 30 min at -78 °C, a saturated solution of NH_4Cl (30 mL) was added, and the mixture was filtered through Celite®. The organic portions were extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct **157** (402 mg, 55% over two steps, α : γ = 1 : 7, d.r = 4 : 1) as a colourless oil.

R_f 0.30 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +7.5 (*c* 1.1 $CHCl_3$); **IR** (thin film) 3402, 2951, 1742, 1614, 1447, 1223, 1050 and 933 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (1H, q, *J* = 1.3 Hz, $\underline{H}_2$), 5.30 (1H, dq, *J* = 9.9, 1.4 Hz, $\underline{H}_7$), 4.04 (2H, s, $\underline{H}_9$), 3.70 (3H, s, $OC\underline{H}_3$), 3.53-3.47 (1H, m, $\underline{H}_5$), 2.55-

2.49 (1H, m, $\underline{H}_6$), 2.30 (1H, dd, J = 12.8, 2.4 Hz, $\underline{H}_{4a}$), 1.97 (1H, dd, J = 12.0, 5.6 Hz, $\underline{H}_{4b}$), 1.93 (3H, d, J = 1.3 Hz, =C_3-C$\underline{H}_3$), 1.64 (3H, d, J = 1.4 Hz, C_8-C$\underline{H}_3$), 1.08 (3H, d, J = 6.8 Hz, C_6-C$\underline{H}_3$), 0.91 (9H, s, SiCC$\underline{H}_3$) and 0.07 (6H, s, $SiCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 135.6, 132.8, 126.2, 113.9, 74.6, 70.3, 52.0, 39.1, 34.2, 31.1, 26.3, 20.9, 16.3, 12.7 and -5.2; **HRMS** (ES^+) calc. for $C_{19}H_{40}O_4SiN$ ($[M+NH_4]^+$) 374.2721, found 374.2721.

(*R*)-MTPA ester of 157 (171)

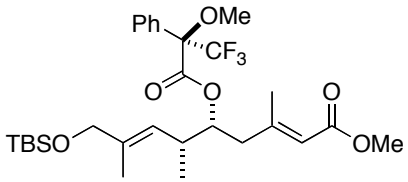


To a solution of alcohol **157** (5 mg, 14.0 μmol), DCC (5.9 mg, 38.0 μmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (6.5 mg, 38.0 μmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (*R*)-MTPA ester **171** (3.6 mg, 41%).

R_f 0.27 (10%, ethyl acetate : hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.48 (2H, m, Ar-$\underline{H}$), 7.43-7.37 (3H, m, Ar-$\underline{H}$), 5.75 (1H, q, J = 1.3 Hz, $\underline{H}_2$), 5.34 (1H, dq, J = 9.8, 0.6 Hz, $\underline{H}_7$), 5.06 (1H, dt, J = 7.7, 5.8 Hz, $\underline{H}_5$), 4.03 (2H, s, $\underline{H}_9$), 3.66 (3H, s, OC$\underline{H}_3$), 3.48 (3H, d, J = 1.1 Hz, MTPA-OC$\underline{H}_3$), 2.79-2.77

(1H, m, $\underline{H}_6$), 2.21 (1H, m, $\underline{H}_{4a}$), 2.07 (1H, m, $\underline{H}_{4b}$), 2.17 (3H, d, J = 1.3 Hz, C_3-$C\underline{H}_3$), 1.74 (3H, d, J = 1.3 Hz, C_8-$C\underline{H}_3$) and 1.03 (3H, d, J = 6.8 Hz, C_6-$C\underline{H}_3$).

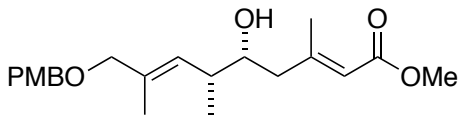
(*S*)-MTPA ester of 157 (170)



To a solution of alcohol **157** (5 mg, 14.0 μmol), DCC (5.9 mg, 38.0 μmol) and DMAP (2 mg) in dichloromethane (2.0 mL) at room temperature was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (6.5 mg, 38.0 μmol). After 6 h, the crude reaction mixture was purified directly by column chromatography (19 : 1, hexane : ethyl acetate) to give (*S*)-MTPA ester **170** (3.7 mg, 43%).

R_f 0.30 (10%, ethyl acetate : hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.47 (2H, m, Ar-$\underline{H}$), 7.41-7.37 (3H, m, Ar-$\underline{H}$), 5.80 (1H, q, J = 1.1 Hz, $\underline{H}_2$), 5.25 (1H, dq, J = 10.1, 0.8 Hz, $\underline{H}_7$), 5.10-5.07 (1H, m, $\underline{H}_5$), 3.68 (3H, s, $OC\underline{H}_3$), 3.51 (3H, d, J = 1.2 Hz, MTPA-$OC\underline{H}_3$), 2.73-2.71 (1H, m, $\underline{H}_6$), 2.29 (1H, m, $\underline{H}_{4a}$), 2.13 (1H, m, $\underline{H}_{4b}$), 2.19 (3H, d, J = 1.3 Hz, C_3-$C\underline{H}_3$), 1.67 (3H, d, J = 0.9 Hz, C_8-$C\underline{H}_3$) and 0.94 (3H, d, J = 6.8 Hz, C_6-$C\underline{H}_3$).

(2*E*, 5*R*, 6*R*, 7*E*)-Methyl 9-(*para*-methoxybenzyl)-5-hydroxy-(3, 6, 8)-trimethyl-nona-2, 7-dienoate (172)

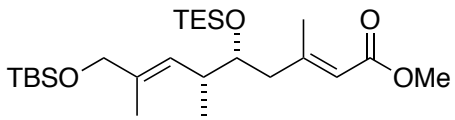


To a solution of freshly prepared ATPH **163** (3.30 mmol) in toluene (5 mL) at -78 °C was added a solution of methyl-3,3-dimethyl acrylate **161** (230 mg, 2.00 mmol) in toluene (1 mL) and a solution of aldehyde **173** (1.00 mmol) in toluene (1 mL) was added. The mixture was stirred for 20 min upon which a solution of *n*-butyl lithium (1.4 mL, 2.2 mmol, 1.6 M in hexane) and diisopropylamine (308 μL, 2.2 mmol) in THF (5 mL) was added. After 30 min at -78 °C, a saturated solution of NH_4Cl (8 mL) was added, and the mixture was filtered through Celite®. The organic portions were extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct **172** (184 mg, 52% over two steps, α : γ = 1 : 6, d.r = 4 : 1) as a colourless oil.

***R*$_f$** 0.35 (20% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +8.2 (*c* 1.0 $CHCl_3$); **IR** (thin film) 3475, 2948, 1715, 1644, 1435, 1223, 1059, 950 and 755 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.7 Hz, Ar-H), 6.91 (2H, d, *J* = 8.6 Hz, Ar-H), 5.82 (1H, q, *J* = 1.2 Hz, H_2), 5.09 (1H, dq, *J* = 10.0, 1.4 Hz, H_7), 4.49 (2H, s, OCH_2PhOMe), 4.03 (2H, s, H_9), 3.82 (3H, s, $PhOCH_3$), 3.58

(3H, s, OC$\underline{H}_3$), 3.38-3.32 (1H, m, $\underline{H}_5$), 2.35-2.29 (1H, m, $\underline{H}_6$), 2.10 (1H, dd, *J* = 13.4, 2.3 Hz, $\underline{H}_{4a}$), 2.04 (3H, d, *J* = 1.3 Hz, =C_3-C$\underline{H}_3$), 1.86 (1H, dd, *J* = 13.7, 8.8 Hz, $\underline{H}_{4b}$), 1.61 (3H, d, *J* = 1.4 Hz, C_8-C$\underline{H}_3$) and 1.01 (3H, d, *J* = 6.7 Hz, C_6-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 159.0, 135.0, 133.9, 131.1, 128.8, 126.2, 114.3, 113.6, 79.2, 75.1, 74.6, 53.6, 52.0, 39.1, 31.1, 20.9, 16.3 and 12.7; **HRMS** (ES^+) calc. for $C_{21}H_{34}O_5N$ ($[M+NH_4]^+$) 380.2431, found 380.2428.

(2*E*, 5*R*, 6*R*, 7*E*)-Methyl 9-(*tert*-butyldimethylsilyl)oxy-5-((triethylsilyl)oxy)-(3, 6, 8)-trimethyl-nona-2, 7-dienoate (177)

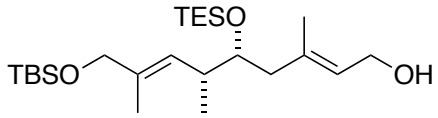


To solution of alcohol **157** (300 mg, 841 μmol) in dichloromethane (5 mL) at 0 °C was added TESCl (228 μL, 1.25 mmol), imidazole (170 mg, 2.45 mmol) and DMAP (5.0 mg, 40.0 μmol). The reaction mixture was allowed to warm to room temperature then stirred for 16 h and quenched with saturated aqueous NH_4Cl (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. The resulting solution was concentrated under reduced pressure and purified using column chromatography (9 : 1, hexane : ethyl acetate) to give silyl enol ether **177** (364 mg, 92%) as a colourless oil.

***R**$_f$* 0.28 (15% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +19.2 (*c* 1.0 $CHCl_3$); **IR** (thin film) 2950, 2929, 2850, 1732, 1617, 1435, 1225, 1082, 755 and 725 cm^{1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, q, *J* = 1.3 Hz, $\underline{H}_2$), 5.22 (1H, dq, *J* = 9.9, 1.3 Hz, $\underline{H}_7$), 4.14-4.08 (1H, m, $\underline{H}_5$), 4.03 (2H, s, $\underline{H}_9$), 3.63 (3H, s, $OC\underline{H}_3$), 2.79-2.73 (1H, m, $\underline{H}_6$), 2.27-2.22 (2H, m, $\underline{H}_4$), 1.96 (3H, d, *J* = 1.3 Hz, $=C_3$-$C\underline{H}_3$), 1.64 (3H, d, *J* = 1.3 Hz, C_8-$C\underline{H}_3$), 1.13 (3H, d, *J* = 6.6 Hz, C_6-$C\underline{H}_3$), 0.96-0.95 (6H, m, Si-$(C\underline{H}_2CH_3)_3$), 0.91 (9H, s, Si-$C(C\underline{H}_3)_3$), 0.54-0.48 (9H, m, Si-$(CH_2C\underline{H}_3)_3$) and 0.07 (6H, s, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 140.7, 132.8, 126.2, 115.6, 74.8, 70.8, 51.3, 46.9, 42.8, 32.0, 25.6, 18.5, 16.1, 12.8, 7.8, 5.9 and -5.0; **HRMS** (ES^+) calc. for $C_{25}H_{54}O_4Si_2N$ ($[M+NH_4]^+$) 488.3586, found 488.3581.

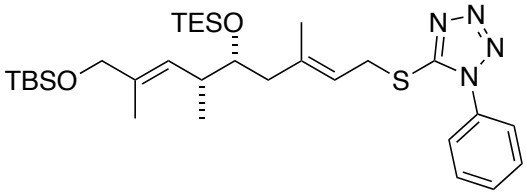
(2*E*, 5*R*, 6*R*, 7*E*)-9-(*tert*-Butyldimethylsilyl)oxy-5-((triethylsilyl)oxy)-(3, 6, 8)-trimethyl-nona-2, 7-dien-1-ol (178)



To a solution of ester **177** (280 mg, 5.94 μmol) in dichloromethane (2 mL) at -78 °C, was added DIBAL (1.18 mL, 1.18 mmol, 1 M dichloromethane). The mixture was stirred for 2 h and quenched with aqueous potassium sodium tartrate (5 mL), and the mixture was stirred for a further 4 h. The crude product was extracted with diethyl ether (3 x 5 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified using coloumn chromatography (3 : 2, hexane : ethyl acetate) to yield alcohol **178** (234 mg, 89%) as a colourless oil.

***R*$_f$** 0.46 (40% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +10.8 (*c* 0.5 $CHCl_3$); **IR** (thin film) 3418, 2951, 2921, 1457, 1008, 946 and 755 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33-5.30 (1H, m, $\underline{H}_2$), 5.24 (1H, dq, *J* = 9.9, 1.3 Hz, $\underline{H}_7$), 4.14-4.09 (1H, m, $\underline{H}_5$), 4.00 (2H, s, $\underline{H}_9$), 3.91 (2H, d, *J* = 6.8 Hz, $\underline{H}_1$), 2.81-2.78 (1H, m, $\underline{H}_6$), 2.29-2.25 (2H, m, $\underline{H}_4$), 1.69 (3H, d, *J* = 1.3 Hz, $=C_3$-$C\underline{H}_3$), 1.60 (3H, d, *J* = 1.2 Hz, C_8-$C\underline{H}_3$), 1.16 (3H, d, *J* = 6.8 Hz, C_6-$C\underline{H}_3$), 0.95-0.94 (6H, m, Si-($C\underline{H}_2CH_3$)$_3$), 0.90 (9H, s, Si-C($C\underline{H}_3$)$_3$), 0.58-0.52 (9H, m, Si-($CH_2C\underline{H}_3$)$_3$) and 0.05 (6H, s, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.9, 133.8, 125.6, 124.2, 74.1, 71.5, 58.9, 45.9, 37.9, 29.6, 26.1, 18.5, 15.4, 12.1, 7.3, 5.7 and -5.2; **HRMS** (ES^+) calc. for $C_{24}H_{51}O_3Si_2$ ($[M+H]^+$) 443.3371, found 443.3368.

(2*E*, 5*R*, 6*R*, 7*E*)-9-(*tert*-Butyldimethylsilyl)oxy-5-((triethylsilyl)oxy)-1-(sulfanyl-1-phenyl-1*H*-1, 2, 3, 4-tetrazol-5-yl)-(3, 6, 8)-trimethyl-nona-2, 7-diene (210)

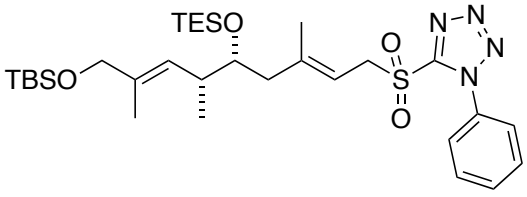


To a solution of alcohol **178** (100 mg, 225 μmol) at 0 ºC in THF (2 mL) was added 1-*H*-mercaptophenyltertrazole (60 mg, 264 μmol), triphenylphosphine (82 mg, 302 μmol) followed by DIAD (45 μL, 302 μmol) drop-wise. The reaction mixture was warmed up to room temperature and left to stir for 2 h before aqueous NH_4Cl (2 mL) was added, upon which the

resulting mixture was extracted with ethyl acetate (3 x 5 mL), and dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by column chromatography (9 : 1, hexane : ethyl acetate) to give sulfide **210** (108 mg, 80%) as a colourless oil.

R_f 0.37 (20% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +26.1 (*c* 0.5 $CHCl_3$); **IR** (thin film) 3042, 2966, 2927, 2875, 1595, 1500, 1385, 1240, 1018, 950, 759, 755 and 742 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19-7.17 (2H, m, Ar-H), 6.90-6.88 (3H, m, Ar-H), 5.29-5.26 (1H, m, H_2), 5.19 (1H, dq, *J* = 9.8, 1.3 Hz, H_7), 4.10-4.04 (1H, m, H_5), 3.99 (2H, s, H_9), 3.87 (2H, d, *J* = 7.2 Hz, H_1), 2.75-2.70 (1H, m, H_6), 2.26-2.21 (2H, m, H_4), 1.72 (3H, d, *J* = 1.2 Hz, $=C_3$-CH_3), 1.60 (3H, d, *J* = 1.2 Hz, C_8-CH_3), 1.02 (3H, d, *J* = 7.0 Hz, C_6-CH_3), 0.94-0.93 (6H, m, Si-(CH_2CH_3)$_3$), 0.89 (9H, s, Si-C(CH_3)$_3$), 0.56-0.51 (9H, m, Si-(CH_2CH_3)$_3$) and 0.05 (6H, s, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5, 139.8, 134.1, 133.8, 129.7, 129.6, 125.2, 123.6, 119.8, 74.8, 71.8, 45.8, 38.2, 31.9, 30.2, 25.5, 16.9, 15.4, 12.2, 7.0, 5.5 and -4.9; **HRMS** (ES^+) calc. for $C_{31}H_{55}N_4O_2SSi_2$ ($[M+H]^+$) 603.3579, found 603.3577.

(2*E*, 5*R*, 6*R*, 7*E*)-9-(*tert*-Butyldimethylsilyl)oxy-5-((triethylsilyl)oxy)-1-(sulfonyl-1-phenyl-1*H*-1, 2, 3, 4-tetrazole)-(3, 6, 8)-trimethyl-nona-2, 7-diene (95)

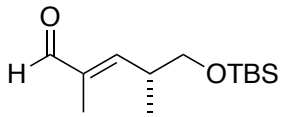


A mixture of ammonium molybdate (33 mg, 26 μmol) and hydrogen peroxide (47 μL, 1.2 mmol, 30% v/v) was allowed to stir at 0 ºC for 15 min. Half of the resulting yellow solution was added dropwise at 0 ºC to a solution of sulfide **210** (70 mg, 116 μmol) in ethanol (1 mL). The reaction mixture was stirred for 1 h at room temperature before the remaining resultant oxidant was added, and stirred for 16 h. The reaction mixture was the diluted with ethanol (1 mL) then filtered. The filtrate was portioned between water (1 mL) and dichloromethane (2 mL) followed by extraction with dichloromethane (3 x 2 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated by reduced pressure. Purification by column chromatography (9 : 1, hexane : ethyl acetate) provided sulfone **95** (60 mg, 82%) as a colourless oil.

R_f 0.25 (20% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +21.5 (*c* 0.1 $CHCl_3$); **IR** (thin film) 3049, 2955, 2927, 2870, 1498, 1449, 1354, 1015, 950, 755 and 739 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74-7.68 (2H, m, Ar-H), 7.63-7.61 (3H, m, Ar-H), 5.04-4.98 (1H, m, H_2), 4.94-4.88 (1H, m, H_7), 4.11-4.06 (2H, m, H_1), 3.89-3.85 (1H, m, H_5), 3.40 (2H, s, H_9), 2.84-2.74 (1H, m, H_6), 2.58-2.51 (2H, m, H_4), 1.56 (3H, d, *J* = 1.3 Hz, $=C_3$-CH_3), 1.27(3H, d, *J* = 1.2 Hz, C_8-CH_3), 1.01-0.93 (9H, m, C_6-CH_3 + Si-$(CH_2CH_3)_3$), 0.90 (9H, s, Si-$C(CH_3)_3$), 0.63-0.56 (9H, m, Si-$(CH_2CH_3)_3$) and 0.05-0.03 (6H, m, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.0, 136.8, 134.7, 133.5, 129.7, 129.7, 125.2, 123.9, 110.0, 74.1, 71.8, 58.7, 45.9, 39.2, 30.7, 25.9, 16.8, 16.0, 12.6, 6.8, 5.2 and -5.2; **HRMS** (ES^+) calc. for $C_{31}H_{58}N_5O_4SSi_2$ ($[M+NH_4]^+$) 652.3743, found 652.3741.

7.6: Experimental for Chapter 4

(2*E*, 4*S*)-5-(*tert*-Butyldimethysilyloxy)-2, 4-dimethylpent-2-enal (209)[121]



Method A:

Dess-Martin periodinane (7.30 g, 17.2 mmol) was added to a solution of alcohol **195** (2.10 g, 8.60 mmol) in dichloromethane (50 mL). The solution was stirred for 2.5 h, and quenched with sodium thiosulfate (50 mL). The product was extracted with ethyl acetate (3 x 30 mL), and dried over $MgSO_4$. The product was purified by filtration through Celite®, to give aldehyde **209** which was used without further purification.

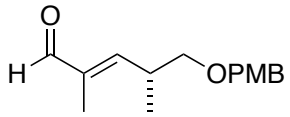
Method B:

To a solution of alcohol **195** (2.00 g, 8.18 mmol) in dichloromethane (100 mL) was added MnO_2 (7.10 g, 82.0 mmol) at room temperature. The resulting mixture was stirred for 3 h where a further MnO_2 (7.10 g, 184.0 mmol) was added. After 3 h the mixture was filtered through Celite®, and crude aldehyde **209** was used without further purification.

R_f 0.39 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.40 (1H, s, $\underline{H}_1$), 6.32 (1H, dq, *J* = 9.7, 1.3 Hz, $\underline{H}_3$), 3.59 (1H, dd, *J* = 9.9, 6.0 Hz, $\underline{H}_{5a}$), 3.54 (1H, dd, *J* = 9.9, 6.5 Hz, $\underline{H}_{5b}$), 2.89 (1H, ddd, *J* = 12.6, 9.7, 6.6

Hz, $\underline{H}_4$), 1.77 (3H, d, J = 1.4 Hz, =C-C$\underline{H}_3$), 1.06 (3H, d, J = 6.8 Hz, -CH-C$\underline{H}_3$), 0.87 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.04 (3H, s, Si-C$\underline{H}_3$) and 0.03 (3H, s, Si-C$\underline{H}_3$).

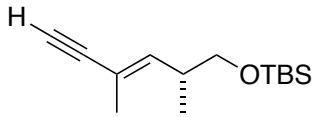
(2*E*, 4*S*)-5-(*para*-Methoxybenzyl)-2, 4-dimethylpent-2-enal (181)[122]



Dess-Martin periodinane (1.96 g, 4.63 mmol) was added to a solution of alcohol **160** (580 mg, 2.32 mmol) in dichloromethane (30 mL). The solution was stirred for 2 h, and quenched with sodium thiosulfate (20 mL). The product was extracted with ethyl acetate (3 x 20 mL), and dried over $MgSO_4$. The product was purified by filtration through Celite®, and washed with excess petroleum ether, to give aldehyde **181** which was used without further purification.

***R*$_f$** 0.70 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.33 (1H, s, $\underline{H}_1$), 7.16 (2H, d, J = 8.7 Hz, CH_2-Ar-$\underline{H}$), 6.81 (2H, d, J = 8.6 Hz, O-Ar-$\underline{H}$), 6.27 (1H, dq, J = 13.4, 9.4 Hz, $\underline{H}_3$), 4.38 (2H, s, O-C$\underline{H}_2$-Ar), 3.74 (3H, s, Ar-O-C$\underline{H}_3$), 3.30–3.37 (2H, m, $\underline{H}_5$), 2.89–3.00 (1H, m, $\underline{H}_4$), 1.70 (3H, d, J = 1.3 Hz, =C-C$\underline{H}_3$) and 1.01 (3H, d, J = 6.8 Hz, CH-C$\underline{H}_3$)

(3*E*, 5*S*)-6-(*tert*-Butyldimethysilyloxy)-3,5-dimethyl-3-hexen-1-ynylidene (194)[123]



Method A:

To a solution of dry potassium *tert*-butoxide (530 mg, 4.75 mmol) in THF (20 mL) at -78 °C, was added Gilbert reagent **184** (715 mg, 4.75 mmol) in THF (8 mL). After 5 min a solution of crude aldehyde **209** (3.96 mmol) in THF (8 mL) was added and the solution was stirred at -78 °C for 16 h, followed by 3 h at room temperature. The reaction was quenched with water (80 mL), and the product was extracted with dichloromethane (3 x 50 mL), washed with brine (50 mL) and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the crude residue was purified by column chromatography (9 : 1, hexane : ethyl acetate) to afford alkyne **194** (482 mg, 51% over two steps) as a colourless oil which was used immediately in the following reaction.

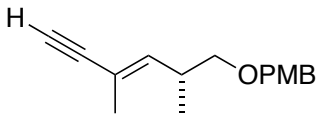
Method B:

A solution of dimethyl (1-diazo-2-oxopropyl)-phosphonate **190** (2.10 g, 10.8 mmol), crude aldehyde **209** (3.60 mmol) and Cs_2CO_3 (4.80 g, 14.4 mmol) in methanol (30 mL) was stirred at 0 ºC for 1 h, then at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (40 mL) and extracted with diethyl ether (3 x 40 mL). The

organic phase was dried with Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography (9 : 1, hexane : ethyl acetate) yielded alkyne **194** (590 mg, 69% over two steps) as a colourless oil which was used immediately in the following reaction.

***R**f* 0.61 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.20 (1H, dq, *J* = 9.1, 1.4 Hz, $\underline{H}_4$), 4.00 (1H, s, $\underline{H}_1$), 3.49-3.35 (2H, m, $\underline{H}_6$), 2.64–2.54 (1H, m, $\underline{H}_5$), 1.70 (3H, d, *J* = 1.4 Hz, =C-C$\underline{H}_3$), 0.97 (3H, d, *J* = 6.7 Hz, -C-C$\underline{H}_3$), 0.90 (9H, s, Si-C(C$\underline{H}_3$)$_3$) and 0.05 (6H, s, 2 x Si-C$\underline{H}_3$).

(3*E*, 5*S*)-6-(*para*-Methoxybenzyl)-3, 5-dimethyl-3-hexen-1-ynylidene (182)



Method A:

To a solution of dry potassium *tert*-butoxide (300 mg, 2.41 mmol) in THF (10 mL) at -78 °C, was added Gilbert reagent **184** (520 mg, 2.41 mmol) in THF (4 mL). After 5 min a solution of crude aldehyde **181** (2.0 mmol) in THF (4 mL) was added and the solution was stirred at -78 °C for 16 h, followed by 3 h at room temperature. The reaction was quenched with water (50 mL), and the product was extracted with dichloromethane (3 x 20 mL), washed with brine (50 mL) and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the crude residue was purified by column chromatography (9 : 1, hexane : ethyl acetate) to afford alkyne **182** (150 mg,

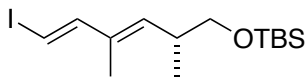
32% over two steps) as a colourless oil which was used immediately in the following reaction.

Method B:

A solution of dimethyl (1-diazo-2-oxopropyl)-phosphonate **190** (1.10 g, 5.70 mmol), aldehyde **181** (1.90 mmol) and Cs_2CO_3 (2.50 g, 7.60 mmol) in methanol (15 mL) was stirred at 0 ºC for 1 h, then at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with diethyl ether (3 x 20 mL). The organic phase was dried with Na_2SO_4. Evaporation of the solvent followed by column chromatography (9 : 1, hexane : ethyl acetate) yielded the alkyne **182** (270 mg, 58% over two steps) as a colourless oil which was used immediately in the following reaction.

***R*$_f$** 0.16 (20% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.6 Hz, CH_2-Ar-H), 6.83 (2H, d, *J* = 8.6 Hz, O-Ar-CH), 5.16 (1H, dq, *J* = 9.2, 1.3 Hz, H_3), 4.36 (2H, s, O-CH_2-Ar), 3.86 (1H, s, H_6), 3.70 (3H, s, O-CH_3), 3.25-3.14 (2H, m, H_1), 2.69–2.62 (1H, m, H_2), 1.61 (3H, d, *J* = 1.4 Hz, Me_4) and 0.91 (3H, d, *J* = 6.7 Hz, Me_2).

(1*E*, 3*E*, 5*S*)-6-(*tert*-Butyldimethysilyloxy)-1-iodo-3, 5-dimethyl-1, 3-hexadiene (193)



Method A:

In a dark environment at room temperature, a solution of alkyne **194** (200 mg, 850 μmol) in THF (7 mL) and $PdCl_2(PPh_3)_2$ (33.0 mg, 43.0 μmol) was prepared. The mixture was stirred for 2 h and Bu_3SnH (520 μL, 1.10 mmol) was added drop wise. The mixture was stirred for 10 min then concentrated under reduced pressure. Dichloromethane (8 mL) was added and the mixture was cooled to -78 °C, prior to the addition of a solution of iodine (400 mg) in dichloromethane (2 mL). After 10 min, the solution was warmed to room temperature and stirred for a further 2 h. The solution was concentrated under reduced pressure, and the crude material **193** was directly subjected to TBAF deprotection.

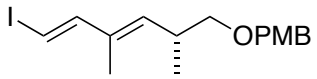
Method B:

In a dark environment a solution of crude aldehyde **209** (4.10 mmol) and iodoform (4.80 g, 12.3 mmol) in dioxane (100 mL) was added to a solution of $CrCl_2$ (5.10 g, 41.0 mmol) in THF (100 mL) at room temperature. The reaction was left stirring for 16 h, upon which aqueous $NaHCO_3$ (300 mL) was added and this mixture was filtered through Celite®. The product was then extracted with ethyl acetate (3 x 200 mL), dried over Na_2SO_4 and the crude material **193** was directly subjected to TBAF deprotection.

R_f 0.76 (10% ethyl acetate/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (1H, d, *J* = 14.6 Hz, $\underline{H}_2$), 6.15 (1H, d, *J* = 14.6 Hz, $\underline{H}_1$), 5.27 (1H, d, *J* = 9.5 Hz, $\underline{H}_4$), 3.45-3.41 (2H, m Hz, $\underline{H}_6$), 2.64 (1H, m, $\underline{H}_5$), 1.74 (3H, d, *J* = 1.3 Hz, =C-C$\underline{H}_3$), 0.97 (3H, d, *J* = 6.7 Hz, -CH-C$\underline{H}_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.03

(3H, s, Si-C$\underline{H}_3$) and 0.02 (3H, s, Si-C$\underline{H}_3$).

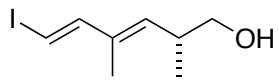
(1*E*, 3*E*, 5*S*)-6-(*para*-Methoxybenzyl)-1-iodo-3, 5-dimethyl-1, 3-hexadiene (191)



In a dark environment at room temperature, a solution of alkyne **182** (400 mg, 1.60 mmol) in THF (10 mL) and $PdCl_2(PPh_3)_2$ (68.0 mg, 97.0 μmol) was prepared. The mixture was stirred for 5 min and Bu_3SnH (1.0 mL, 3.8 mmol) was added dropwise. The mixture was stirred for 10 min then concentrated under reduced pressure. Dichloromethane (10 mL) was added and the mixture was cooled to -78 °C, prior to the addition of a solution of iodine (820 mg) in dichloromethane (5 mL). After 10 min, the solution was warmed to room temperature and stirred for a further 10 min. The solution was concentrated under reduced pressure, and the crude material **191** was directly subjected to DDQ deprotection.

***R*$_f$** 0.54 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 7.15 (1H, d, *J* = 14.7 Hz, $\underline{H}_2$), 6.83 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 6.76 (1H, d, *J* = 14.7 Hz, $\underline{H}_1$), 5.13 (1H, dq, *J* = 9.2, 1.3 Hz, $\underline{H}_4$), 4.36 (2H, s, OC$\underline{H}_2$Ar), 3.70 (3H, s, OC$\underline{H}_3$), 3.25-3.14 (2H, m, $\underline{H}_6$), 2.69–2.62 (1H, m, $\underline{H}_5$), 1.61 (3H, d, *J* = 1.3 Hz, =CC$\underline{H}_3$) and 0.91 (3H, d, *J* = 6.7 Hz, CHC$\underline{H}_3$).

(1*E*, 3*E*, 5*S*)-1-Iodo-3, 5-dimethyl-1, 3-hexadiene-6-ol (192)



Method A:

TBAF (8.20 mL, 8.20 mmol, 1 M in THF) was added slowly to a solution of TBS-protected vinyl iodide **193** (4.10 mmol) in THF (30 mL) at 0 ºC. After 2 h the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with ethyl acetate (3 x 30 mL) and dried over $MgSO_4$. The resulting solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to yield alcohol **192** (860 mg, 83%) as a pale yellow oil.

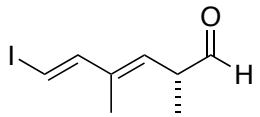
Method B:

To a solution of PMB ether **191** (530 μmol) in dichloromethane (5 mL) and pH 7 buffer (0.5 mL) at 0 °C, was added DDQ (240 mg, 1.06 mmol). The solution was stirred for 2 h and quenched with $NaHCO_3$ (100 mL), extracted with dichloromethane (3 x 30 mL and dried over $MgSO_4$. The solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to yield alcohol **192** (64.0 mg, 79%) as a as a pale yellow oil.

***R*$_f$** 0.30 (10% ethyl acetate/Hexane); $[\alpha]_D^{20}$ +40.8 (*c* 0.7, $CHCl_3$); **IR** (thin film) 3374, 2959, 2926, 2870, 1726, 1707, 1451, 1178, 1035, 1018, 960 and 752 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (2H, dd, *J* = 14.7, 0.8 Hz, $\underline{H}_2$),

6.22 (1H, dd, J = 14.7, 0.6 Hz, $\underline{H}_1$), 5.27 (1H, dt, J = 9.6, 0.6 Hz, $\underline{H}_4$), 3.55-3.49 (1H, m, $\underline{H}_{6a}$), 3.44-3.39 (1H, m, $\underline{H}_{6b}$), 2.78-2.67 (1H, m, $\underline{H}_5$), 1.78 (3H, d, J = 1.3 Hz, =C-C$\underline{H}_3$) and 0.98 (3 H, d, J = 6.7 Hz, -CH-C$\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 136.5, 136.0, 74.5, 67.6, 35.7, 16.8 and 12.5; **HRMS** (ES^+) calc. for $C_8H_{14}IO$ $[M+H]^+$ 253.0084, found 253.0079.

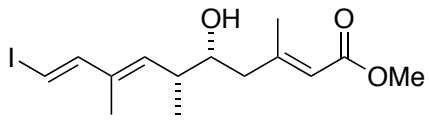
(1*E*, 3*E*, 5*S*)-1-Iodo-3, 5-dimethyl-1, 3-hexadiene-6-al (179)



Dess-Martin periodinane (1.00 g, 2.38 mmol) was added to a solution of alcohol **192** (300 mg, 1.20 mmol) in dichloromethane (5 mL). The solution was stirred for 2.5 h, and quenched with sodium thiosulfate (5 mL). The product was extracted with dichloromethane (3 x 5 mL), and dried over $MgSO_4$. The product was purified by filtration through Celite®, and washed with excess dichloromethane, which was removed under *vacuo*, to give crude aldehyde **179** that was used without further purification.

***R**$_f$* 0.47 (10% ethyl acetate : petroleum ether); **^{1}H NMR** (400 MHz, C_6D_6) δ 9.05 (1H, d, J = 1.6, $\underline{H}_6$), 6.81 (1H, dd, J = 14.7, 0.8 Hz, $\underline{H}_2$), 5.91 (1H, dd, J = 14.7, 0.6 Hz, $\underline{H}_1$), 4.73 (1H, ddt, J = 9.2, 1.3, 0.7 Hz, $\underline{H}_4$), 2.69 (1H, ddd, J = 9.0, 7.1, 1.8 Hz, $\underline{H}_5$), 1.19 (3H, d, J = 1.3 Hz, =C-C$\underline{H}_3$) and 0.79 (3H, d, J = 6.9 Hz, =CH-C$\underline{H}_3$).

(1*E*, 3*E*, 5*R*, 6*R*, 8*E*)-Methyl 6-hydroxy-1-iodo-3, 5, 8-trimethyldeca-2, 3, 8-trienoate (180)[22a,124]

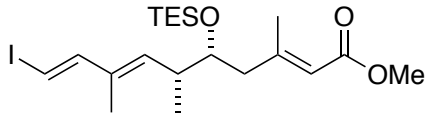


To a solution of ATPH **163** (3.95 mmol) in toluene (3 mL) at -78 °C was added a solution of methyl-3,3-dimethyl acrylate **161** (270 mg, 2.38 mmol) in toluene (1 mL); after 15 min a solution of crude aldehyde **180** (1.20 mmol) in toluene (1 mL) was added. The mixture was stirred for 20 min upon which a solution of *n*-butyl lithium (1.65 mL, 2.62 mmol, 1.6 M in hexane) and diisopropylamine (365 μL, 2.62 mmol) in THF (3 mL) was added. After 30 h at -78 °C, a saturated solution of NH_4Cl (5 mL) was added, and the mixture was filtered through Celite® and washed with diethyl ether. The organic portions were extracted with diethyl ether (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by column chromatography (14 : 1, hexane : ethyl acetate) to give aldol adduct **180** (220 mg, 51% over two steps, α : γ = 1 : 7, *d.r.* = 3 : 1) as a pale yellow oil.

R_f 0.26 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +17.7 (*c* 1.0, $CHCl_3$); **IR** (thin film) 3475, 2948, 1715, 1644, 1435, 1223, 1151, 1059 and 950 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ 6.92 (1H, dd, *J* = 14.7, 0.8 Hz, $\underline{H}_2$), 5.91 (1H, dd, *J* = 14.7, 0.7 Hz, $\underline{H}_1$), 5.80 (1H, dd, *J* = 2.1, 1.2 Hz, $\underline{H}_9$), 4.89 (1H, d, *J* = 10.0 Hz, $\underline{H}_4$), 3.44 (3H, s, $OC\underline{H}_3$), 3.16-3.23 (1H, m, $\underline{H}_6$), 2.21-2.11 (1H, m, $\underline{H}_5$),

2.18 (H, d, J = 1.2 Hz, C_8-C$\underline{H}_3$), 1.95 (1H, dd, J = 13.6, 2.3 Hz, $\underline{H}_{7a}$), 1.75 (1H, dd, J = 13.6, 9.8 Hz, $\underline{H}_{7b}$), 1.31 (3H, d, J = 1.2 Hz, C_3-C$\underline{H}_3$) and 0.87 (3H, d, J = 6.7 Hz, C_5-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 166.6, 157.2, 149.8, 136.5, 134.8, 118.1, 74.7, 73.1, 50.6, 46.7, 39.4, 19.0, 16.2 and 12.1; **HRMS** (ES^+) calc. for $C_{14}H_{25}IO_3N$ $[M+NH_4]^+$ 382.0874, found 382.0869.

(1*E*, 3*E*, 5*R*, 6*R*, 8*E*)-Methyl 6-((triethylsilyl)oxy)-1-iodo-3, 5, 8-trimethyldeca-2, 3, 8-trienoate (196)[22a,124]

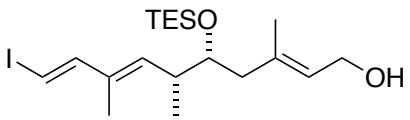


To solution of alcohol **180** (175 mg, 480 μmol) in dichloromethane (3 mL) at room temperature was added TESCl (105 mg, 705 μmol), imidazole (100 mg, 1.48 mmol) and DMAP (6.0 mg). The reaction mixture was stirred for 16 h and quenched with saturated aqueous NH_4Cl (3 mL), extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. The resulting solution was concentrated under reduced pressure and purified using column chromatography (9 : 1, hexane : ethyl acetate) to give silyl enol ether **196** (198 mg, 87%) as a pale yellow oil.

***R*$_f$** 0.69 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +33.6 (*c* 0.5, $CHCl_3$); **IR** (thin film) 2953, 2911, 2876, 1720, 1647, 1435, 1223, 1150, 1087, 1008, 739 and 725 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.02 (1H, dd, J = 14.6, 0.7 Hz, $\underline{H}_2$), 5.93 (1H, d, J = 14.6 Hz, $\underline{H}_1$), 5.87 (1H, q, J = 1.1 Hz, $\underline{H}_9$), 5.12 (1H, dd,

J = 9.7, 0.4 Hz, $\underline{H}_4$), 3.64 (1H, dt, *J* = 6.6, 5.4 Hz, $\underline{H}_6$), 3.44 (3H, s, $OC\underline{H}_3$), 2.46-2.39 (1H, m, $\underline{H}_5$), 2.25 (3H, d, *J* = 1.3 Hz, C_8-$C\underline{H}_3$), 2.10-2.08 (1H, td, *J* = 6.10, 0.95 Hz, $\underline{H}_{7a}$), 2.07 (1 H, d, *J* = 0.8 Hz, $\underline{H}_{7b}$), 1.36 (3H, d, *J* = 1.2 Hz, C_3-$C\underline{H}_3$), 0.96 (6H, m, Si-$(C\underline{H}_2CH_3)_3$), 0.89 (3H, d, *J* = 6.8 Hz, C_5-$C\underline{H}_3$), 0.56 (9H, m, Si-$(CH_2C\underline{H}_3)_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 166.6, 156.5, 149.9, 137.2, 134.4, 118.7, 74.7, 74.5, 50.6, 46.9, 38.5, 19.5, 15.6, 12.1, 7.2 and 5.6; **HRMS** (ES^+) calc. for $C_{20}H_{39}IO_3SiN$ $[M+NH_4]^+$ 496.1738, found 496.1734.

(1*E*, 3*E*, 5*R*, 6*R*, 8*E*)-6-((Triethylsilyl)oxy)-1-iodo-3, 5, 8-trimethyldeca-2, 3, 8-trien-1-ol (197)[22a,124]

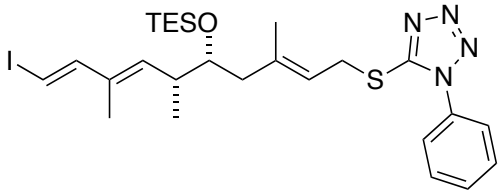


To a solution of ester **196** (160 mg, 345 μmol) in dichloromethane (2 mL) at -78 °C, was added DIBAL (690 μL, 690 μmol, 1 M in dichloromethane). The mixture was stirred for 2 h and quenched with aqueous potassium sodium tartrate (5 mL) was added, and the mixture was stirred for a further 4 h. The crude product was extracted with diethyl ether (3 x 5 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified using column chromatography (4 : 1, hexane : ethyl acetate) to yield alcohol **197** (127 mg, 81%) as a as a pale yellow oil.

***R**$_f$* 0.29 (20% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +18.5 (*c* 0.7, $CHCl_3$); **IR** (thin film) 3342, 2955, 2911, 1457, 1003, 948, 744 and 725 cm^{-1}; **^{1}H NMR**

(400 MHz, C_6D_6) δ 7.07 (1H, dd, *J* = 14.6, 0.8 Hz, $\underline{H}_2$), 5.93 (1H, dd, *J* = 14.6, 0.6 Hz, $\underline{H}_1$), 5.38 (1H, ddd, *J* = 7.8, 5.4, 1.2 Hz, $\underline{H}_9$), 5.27 (1H, d, *J* = 9.8 Hz, $\underline{H}_4$), 3.94 (2H, d, *J* = 6.8 Hz, $\underline{H}_{10}$), 3.70-3.64 (1H, m, $\underline{H}_6$), 2.52-2.48 (1H, m, $\underline{H}_5$), 2.14 (2H, qd, *J* = 13.6, 6.2 Hz, $\underline{H}_7$), 1.51 (3H, d, *J* = 0.7 Hz, C_8-C$\underline{H}_3$), 1.41 (3H, d, *J* = 1.3 Hz, C_3-C$\underline{H}_3$), 1.01-0.97 (6H, m, Si-(C$\underline{H}_2$CH$_3$)$_3$ + C_5-C$\underline{H}_3$) and 0.58 (9H, m, Si-(CH$_2$C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 150.0, 138.3, 135.0, 133.9, 129.0, 74.7, 74.2, 59.3, 45.9, 37.8, 16.9, 15.1, 12.1, 7.3 and 5.6; **HRMS** (ES^+) calc. for $C_{19}H_{39}IO_2SiN$ $[M+NH_4]^+$ 468.1789, found 468.1787.

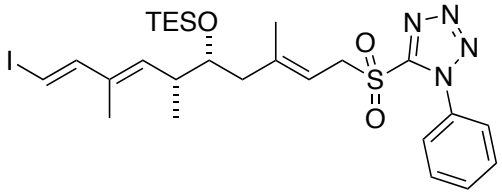
(1*E*, 3*E*, 5*R*, 6*R*, 8*E*)-6-((Triethylsilyl)oxy)-1-iodo-10-(sulfanyl-1-phenyl 1*H*-1, 2, 3, 4-tetrazol-5-yl) 3, 5, 8-trimethyldeca-2, 3, 8-triene (210)[22a,124]



To a solution of alcohol **197** (80 mg, 176 μmol) at 0 ºC in THF (2 mL) was added 1-*H*-mercaptophenyltertrazole (42 mg, 232 μmol), triphenylphosphine (61 mg, 232 μmol) followed by DIAD (32 μL, 232 μmol) dropwise. The reaction mixture was warmed up to room temperature and left to stir 2 h before aqueous NH_4Cl (5 mL) was added, upon which the resulting mixture was extracted with ethyl acetate (3 x 5 mL), and dried over Na_2SO_4. The solution was concentrated under reduced pressure and purified by column chromatography (19 : 1, hexane : ethyl acetate) to give sulfide **210** (84 mg, 79%) as a pale yellow oil.

***R*$_f$** 0.54 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +58.5 (*c* 1.0, $CHCl_3$); **IR** (thin film) 3068, 2955, 2911, 2875, 1597, 1500, 1384, 1234, 1092, 1015, 950, 759, 742 and 725 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.19-7.17 (2H, m, Ar-H), 7.05 (1H, dd, *J* = 14.6, 0.7 Hz, H_2), 6.93-6.87 (3H, m, Ar-H), 5.95 (1H, dd, *J* = 14.6, 0.5 Hz, H_1), 5.37 (1H, td, *J* = 7.9, 1.1 Hz, H_9), 5.22 (1H, dt, *J* = 9.8, 0.5 Hz, H_4), 3.90 (2H, dq, *J* = 14.6, 7.9 Hz, H_{10}), 3.62 (1H, dt, *J* = 6.2, 4.7 Hz, H_6), 2.46-2.240 (1H, m, H_5), 2.07 (2H, ddt, *J* = 20.2, 13.9, 6.6 Hz, H_7), 1.58 (3H, d, *J* = 1.3 Hz, C_8-CH_3), 1.40 (3H, d, *J* = 1.2 Hz, C_3-CH_3), 0.96 (6H, m, Si-(CH_2CH_3)$_3$), 0.92 (3H, d, *J* = 6.8 Hz, C_5-CH_3) and 0.58-0.53 (9H, m, Si-(CH_2CH_3)$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 154.1, 150.0, 139.8, 138.0, 134.3, 134.0, 129.6, 123.9, 120.8, 74.5, 74.3, 45.8, 37.7, 31.6, 16.9, 15.0, 12.1, 7.3 and 5.6; **HRMS** (ASAP) calc. for $C_{26}H_{40}ION_4SSi$ $[M+H]^+$ 611.1731, found 611.1729.

(1*E*, 3*E*, 5*R*, 6*R*, 8*E*)-6-((Triethylsilyl)oxy)-1-iodo-10-(sulfonyl-1-phenyl -1*H*-1, 2, 3, 4-tetrazol-5-yl) 3, 5, 8-trimethyldeca-2, 3, 8-triene (93)[22a,124]



A mixture of ammonium molybdate (20 mg, 15.0 μmol) and hydrogen peroxide (25 μL, 650 μmol, 30% v/v) was allowed to stir at 0 ºC for 15 min. Half of the resulting yellow solution was added dropwise, at 0 ºC, to a solution of sulfide **210** (40 mg, 65 μmol) in ethanol (1 mL). The reaction

mixture was stirred for 1 h at room temperature before the remaining resultant oxidant was added, and stirred for 16 h. The reaction mixture was the diluted with ethanol (1 mL) then filtered. The filtrate was portioned with water (1 mL) then extracted with dichloromethane (3 x 1 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (19 : 1, hexane : ethyl acetate) provided sulfone **93** (33 mg, 78%) as a as a pale yellow oil.

R_f 0.41 (10% ethyl acetate : petroleum ether); $[\alpha]_D^{20}$ +33.6 (*c* 0.5, $CHCl_3$); **IR** (thin film/) 3069, 2955, 2925, 2875, 1498, 1461, 1343, 1156, 1107, 1015, 950, 761 and 739 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.33-7.26 (2H, m, Ar-H), 7.05 (1H, dd, *J* = 14.6, 0.8 Hz, H_2), 6.87-6.85 (3H, m, Ar-H), 5.94 (2H, dd, *J* = 14.6, 0.5 Hz, H_1), 5.29 (1H, td, *J* = 7.9, 0.9 Hz, H_9), 5.22 (1H, d, *J* = 9.3 Hz, H_4), 4.08 (2H, dd, *J* = 7.9, 3.0 Hz, H_{10}), 3.63 (1H, td, *J* = 6.5, 4.1 Hz, H_6), 2.38-2.35 (1H, m, H_5), 2.10 (1H, dd, *J* = 13.6, 6.9 Hz, H_{7a}), 2.01 (1H, dd, *J* = 13.6, 6.1 Hz, H_{7b}), 1.50 (3H, d, *J* = 1.2 Hz, C_8-CH_3), 1.39 (3H, d, *J* = 1.2 Hz, C_3-CH_3), 1.01-0.89 (6H, m, Si-(CH_2CH_3)$_3$), 0.86 (3H, d, *J* = 6.7 Hz, C_5-CH_3) and 0.60-0.48 (9H, m, Si-(CH_2CH_3)$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 154.0, 149.8, 146.8, 136.6, 134.8, 133.5, 131.0, 129.4, 125.4, 111.0, 74.6, 72.6, 56.2, 45.9, 39.2, 17.0, 16.3, 12.1, 7.2 and 6.9; **HRMS** (ES^+) calc. for $C_{26}H_{43}IO_3N_5SSi$ $[M+NH_4]^+$ 660.1895, found 660.1893.

References

[1] Koehn, F.K.; Carter, G. T. *Nature*, **2005**, *4*, 206.
[2] Kerr, R. G.; Kerr, S. S. *Exp. Opin. Ther. Patents,* **1999**, *9*, 1207.
[3] Newman, D. J.; Cragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215.
[4] Gates, M.; Tschudi, G. *J. Am. Chem. Soc*. **1956**, *78*, 1380.
[5] (a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet. P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature*, **1994**, *367*, 630. (b) Chauviere, G.; Guenard, D.; Picot, F.; Senilh, V.; Potier, P. C. R. *Seances Acad. Sci. Ser.*, **1981**, *293*, 501.
[6] Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.*, **2005**, *22*, 15.
[7] (a) Bergmann, W.; Feeney, R. J. *J. Am. Chem. Soc*. **1950**, *72*, 2809. (b) Bergmann, W. Feeney, R. J. *J. Org. Chem.* **1951**, *16*, 981. (c) Bergmann, W.; Burke, D. C. *J. Org. Chem.* **1955**, *20*, 1501.
[8] Wöhler, F. *Ann. Phys.*, **1828**, *88*, 253.
[9] Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem.* **2004**, *116*, 4729.
[10] Corey, E. J.; Trybulski, E. J.; Melvin, L. S. Jr.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J. *J. Am. Chem. Soc.*, **1978**, *100*, 4618.
[11] Robinson, J. A.; *Phil. Trans. R. Soc. Lond. B,* **1991**, *332*, 107.
[12] Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
[13] a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc. Chem. Commun.* **1993**, 1166. (c) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun*. **1994**, 1605. (d) Pettit, R. K.; McAllister, S. C.; Pettit, G. R.; Herald, C. L.; Johnson, J. M.; Cichacz, Z. A. *Int. J. Antimicrob. Agents* **1998**, *9*, 147.
[14] Yeung, K.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.
[15] Dayton, P. K.; Mordida, B. J.; Bacon, F. *Am. Zool.* **1994**, *34*, 90.
[16] Amsler, C. D.; Iken, K. B.; McClintock, J. B.; Baker, B. J. In *Marine Chemical Ecology*; McClintock, J. B., Baker, B. J., Eds.; CRC Press: Boca Raton, FL, **2001**; 267.
[17] a) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J *J. Am. Chem. Soc.* **2006**, *128*, 5630; b) Lebar, M. D.; Baker, B. J. *Tetrahedron Lett.* **2007**, *48*, 8009; c) Riesenfeld, C. S.; Murray, A. E.; Baker, B. J. *J. Nat. Prod.* **2008**, *71*, 1812.
[18] a) Baker, B. J.; Diyabalanage, T.; McClintock, J. B.; Amsler, C. D *International Patent No.* WO2005/079471 A2, 1 September 2005. b) Noguez, J. H.; Diyabalanage, T.; Miyata, Y.; Xie, X. S.; Valeriote, F. A.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *Biol. Med. Chem.* **2011**, *19*, 6608.
[19] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
[20] Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870.
[21] De Brabander, J. K.; Jiang, X.; Liu, B.; Lebreton, S. *J. Am. Chem. Soc.* **2007**, *129*, 6386.

[22] a) Florence, G. J.; Wlochal, J. *Chem. Eur. J.* **2012**, *18*, 14250. b) J. H. Noguez, PhD Thesis, University of South Florida (USA), 2010 can be found under http://search.proquest.com/docview/755706684/abstract?accountid=8312.
[23] http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/incidence/ (Accessed 1st December 2012)
[24] a) Ferlay, J.; Shin, H.; Bray, F.; Forman, D.; Mathers, C.; Parkin, D. M. *Int. J. Cancer* **2010**, *127*, 2893. b) http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/mortality/ (Accessed 1st December 2012)
[25] http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/survival/ (Accessed 1st December 2012)
[26] a) Duffy, D. L.; Box, N. F.; Chen, W.; Palmer, J. S.; Montgomery, G. W.; James, M. R.; Hayward, N. K.; Martin, N. G.; Sturm, R. A.; *Hum. Mol. Genet.* **2004**, *13*, 447. b) Garcia-Borron, J. C.; Sanchez-Laorden, B. L.; Jimenez-Cervantes, C. *Pigment Cell Res.* **2005**, *18*, 393. c) Healy, E. *Photodermatol Photoimmunol Photmed*. **2004**, *20*, 283.
[27] a) Duffy, D. L.; Montgomery, G. W.; Chen, W.; Zhao, Z. Z.; James, M. R.; Hayward, N. K.; Martin, N. G.; Sturm, R. A. *Am. J. Hum. Genet.* **2007**, *80*, 241. b) Brilliant, M. H. *Pigment Cell Res.* **2001**, *14*, 86.
[28] a) Beyenbach, K. W.; Wieczorek, H. *J. Exp. Biol.* **2006**, *209*, 577. b) Huss, M.; Ingenhorst, G.; Konig, S.; Gassel, M.; Drose, S.; Zeeck, A.; Altendorf, K.; Wieczorek, H. *J. Biol. Chem.* **2002**, *277*, 40544.
[29] a) Nelson, N.; Perzov, N.; Cohen, A.; Hagai, K.; Padler, V.; Nelson, H. *J. Exp. Biol.* **2000**, *203*, 89. b) Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114.
[30] a) http://dtp.nci.nih.gov/docs/compare/compare_methodology.html. (Accessed 12th Decemeber 2012) b) Boyd, M. R.; Paull, K. *Drug. Dev. Res.* **1995**, *34*, 91. c) Weinstein, J. N.; Myers, T. G.; O'Connor, P. M.; Friend, S. H.; Fornace, A. J., Jr.; Kohn, K.; Fojo, T.; Bates, S. E.; Rubinstein, L. V.; Anderson, N. L.; Buolamwini, J. K.; van Osdol, W.; Monks, A. P.; Scudiero, D. A.; Sausville, E. A.; Zaharevitz, D. W.; Bunow, B.; Viswanadan, V. N.; Johnson, G. W.; Wittes, R. E.; Paull, K. D. *Science* **1997**, *275*, 343.
[31] Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188.
[32] a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **2001**, *66*, 1532. b) Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308.
[33] a) Wu, Y.; Seguil, O. R.; De Brabander, J. K *Org. Lett.* **2000**, *2*, 4241. b) Smith, A. B., III; Zheng, J. *Tetrahedron* **2002**, *58*, 6455. c) Smith, A. B., III; Zheng, J. *Synlett* **2001**, 1019.
[34] a) Xie, X.; Padron, D.; Liao, X.; Wang.; Roth.; De Brabander, J. K. *J. Biol. Chem.* **2004**, *279*, 19755. b) Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zahner, H. *J. Antibiot.* **1984**, *37*, 110.
[35] Loudon, G. M.; Almond, M. R.; Jacob, J. N. *J. Am. Chem. Soc.* **1981**, *103*, 4508.
[36] a) Nicolaou, K. C.; Guduru, R.; Sun, Y.; Banerji, B.; Chen, D. Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5896. b) Nicolaou, K. C.; Guduru, R.; Sun, Y.; Banerji, B.; Chen, D. Y. *J. Am. Chem. Soc.* **2008**, *130*, 3633. c) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.

[37] a) Jaegel, J.; Maier, M. E. *Synthesis* **2009**, *17*, 2881. b) Gowrisankar, P.; Pujari, S. A.; Kaliappan, K. P. *Chem. Eur. J.* **2010**, *16*, 5858. c) Pujari, S. A.; Gowrisankar, P.; Kaliappan,K. P. *Chem. Asian J.* **2011**, *6*, 3137. d) Prasad, K. R.; Pawar, A. B. *Org. Lett.* **2011**, *13*, 4252–4255. e) Prasad, K. R.; Pawar, A. B. *Chem.Eur. J.* **2012**, *18*, 15202. f) Lisboa, M. P.; Jones, D. M.; Dudley, G. B *Org. Lett.* **2013**, *15*, 886.
[38] Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531.
[39] Inanaga, J.; Hirata, K.; Saeki, H.; Kastuki, T.; Yamaguchi, M. Bull. *Chem. Soc. Jpn.* **1979**, *52*, 1989.
[40] Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
[41] Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.
[42] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc*. **1986**, *108*, 7408.
[43] a) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed*. **2006**, *45*, 2426. b) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. c) Rauniyar, V.; Hall, D. G. *J. Org. Chem*. **2009**, *74*, 4236.
[44] a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem*. **1983**, *48*, 5221. b) Pietruszka, J.; Schone, N. Eur. *J. Org. Chem*. **2004**, 5011.
[45] Nicolaou, K. C.; Leung, G. Y. C.; Dethe, D. H.; Guduru, R.; Sun, Y.; Lim, C. S.; Chen, D. Y. *J. Am. Chem. Soc.* **2008**, *130*, 10019.
[46] Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 3667.
[47] Angelin, M.; Hermansson, M; Dong, H; Ramström, O. *Eur. J. Org. Chem.* **2006**, *19*, 4323. b) Sheldon, R. A.; Arend, I. W. C. E.; Brink, G.; Dijksman, A. *Acc. Chem. Res*. **2002**, *35*, 774. c) Tashino, Y.; Togo, H. *Synlett* **2004**, *11*, 2010. d) Wang, N.; Liu, R.; Chen, J.; Liang, X. *Chem. Commun*. **2005**, *42*, 5322**.**
[48] a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974 b) Dijksman, A.; Arends, I. W. C. E.; Sheldon, A. *Chem. Commun.* **1999**, 1591. c) Rychnovsky, S. D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, *64*, 310. d) Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett*. **2000**, *41*, 4343.
[49] Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, *10*, 1153.
[50] a) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *Chem. Comm.* **1979**, 1180. b) Paterson, I.; Lyothier, I. *J. Org. Chem.* **2005**, *70*, 5494.
[51] a) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071. b) Bargiggia, F. C.; Murray. W. V. *J. Org. Chem.* **2005**, *70*, 9636. c) Gil, J. M.; Hah, J. H.; Park, K. Y.; Oh, D. Y. *Tetrahedron Lett.* **1998**, *39*, 3205.
[52] Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
[53] a) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158. b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
[54] Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974.
[55] Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858.
[56] a) Hérisson, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161.
[57] a) Sanford, M.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543. b) Sanford, M.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.
[58] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
[59] Broggi, J.; Urbina-Blanco, C. A.; Clavier, H.; Leitgeb, A.; Slugovc, C.; Slawin A. M. Z.; Nolan, S. P. *Chem.–Eur. J*. **2010**, *16*, 9215.
[60] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamume, S.; Roush, W. R.; Sakai, T., *Terahedron Lett*. **1984**, *25*, 2183.

[61] a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, K.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M., *J. Org. Chem*., **1992**, *57*, 2768. b) Kolb, H. C.; Van Nieuwenhze, A.; Sharpless, K. B., *Chem. Rev*., **1994**, *94*, 2483. c) Junttila, M. H.; Hormi, O. O. E., *J. Org. Chem*., **2009**, *74*, 3038.
[62] a) Johnson, R. A.; Sharpless, K. B.; *Catalytic Asymmetric Dihydroxylation. In Catalytic Asymmetric Synthesis:* Ojima, I. Ed. VCH publishers: New York, **1993**, pp. 227. b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317. c) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yeun, P. W.; Connel, R. D. *J. Am. Chem. Soc*. **1989**, *111*, 9243.
[63] a) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem*. **1996**, *61*, 7978. b) Hale, K. J.; Manaviazar, S.; Peak, S. A. *Tetrahedron Lett*. **1994**, *35*, 425. (c) Kyrsan, D. *Tetrahedron Lett*. **1996**, *37*, 1375.
[64] Murray, R. *Unpublished results.*
[65] Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267.
[66] Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833.
[67] a) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021. b)Hassfeld, J.; Eggert, U.; Kalesse, M. *Synthesis* **2005**, *7*, 1183.
[68] Zhang, Y.; Li, C. *J. Am. Chem. Soc.* **2006**, *128*, 4242.
[69] a) Braude, E. A.; Linstead. R. P.; Wooldridge, K. R. *J. Chem. Soc.* **1956**, 3070. b) Becker, H. *J. Org. Chem.* **1965**, *30*, 982. c) Kende, A. S.; Blacklock, T. J*Tetrahedron Lett.* **1980**, *21*, 3119.
[70] a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
[71] Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5586
[72] Clarke, M. L.; Diaz-Valenzuela, M. B.; Slawin, A. M. Z. *Organometallics* **2007**, *26*, 16. b) Diaz-Valenzuela, M. B.; Phillips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem. Eur. J*. **2009**, *15*, 1227.
[73] Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc*, **1988**, *110*, 1539.
[74] Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
[75] Brown, H. C.; Ramachandran, P. V. In *Reductions in Organic Synthesis: Recent Advances and Practical Applications,* Abdel-Magid, A. F. Ed.; American Chemical Society: Washington DC, **1996**, p. 1-30.
[76] a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1968**, *90*, 3732. b) Sullivan, J. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem*. **1973**, *38*, 2143. c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. d) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev*. ***2004***, *104*, 17.
[77] Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.
[78] Iversen, T.; Bundle, D. R.; *J. Chem. Soc., Chem. Commun.* **1981**, *23*, 1240.
[79] a) Wittig, G.; Geissler G. *Liebigs Ann*. **1953**, *580*, 44. b)Trippett, S. Q. *Rev., Chem. Soc*. **1963**, *17*, 406. c) Maercker, A. *Org. React.* **1965**, *14*, 270.
[80] a) Horner; L.; Hoffmann, H. M. R.; Wippel, H. G. *Ber.* **1958**, *91*, 61. b) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G.; Klahre, G. *Ber.* **1959**, *92*, 2499.
[81] a) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. b) Wadsworth, W. S., Jr.; Emmons, W. D. *Organic Syntheses*, Coll. **1973**, *5*, 547

[82] a) Larsen, R. O.; Aksnes, G. *Phosphorus Sulfur* **1983**, *15*, 219. b) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc*. **1966**, *88*, 5654. c) Lefèbvre, G.; Seyden-Penne, J. *J. Chem Soc., Chem. Commun*. **1970**, 1308

[83] Fürstner, A.; Nevado, C,; Waser, M,; Tremblay, M,; Chevrier, C,; Teplý, F,; Aïssa, C,; Moulin, E,; Müller, O. *J. Am. Chem. Soc*. **2006**, *129*, 9150.

[84] a) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774. b) Paterson, I.; Burton, P. M.; Cordier, C. J.; Housden, M. P.; Muahlthau, F. A.; Loiseleur, O. *Org. Lett.* **2009**, *11*, 693.

[85] Sinisterra, J. V.; Marinas, J. M.; Riquelme, F.; Arias, M. S. *Tetrahedron* **1988**, *44*, 1431.

[86] a) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319. b) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682. c) Casirahi, G.; zanardi, R.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

[87] Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816.

[88] Zimmerman, H. E.; Traxler, M. D *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[89] a) Maruoka, K; Imoto, H,; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131. b) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813. c) Saito, S.; Shiozawa, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1769. d) Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200

[90] a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145.

[91] a) Mitsunobu, O.; Yamada, N. *Bull. Chem. Soc. Jpn*. **1967**, *40*, 2380. b) Mitsunobu, O.; Yamada, N. *Tetrahedron Lett*. **1981**, *22*, 2397. c) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547.

[92] Schultz, H. S.; Freyermuth, H, B.; Buc, S. R. *J. Org. Chem*. **1963**, *28*, 1140.

[93] Corey, E. J.; Fuchs, P. L *Tetrahedron Lett.* **1972**, *36*, 3769.

[94] Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

[95] a) Bako, P.; Novak, T.; Ludanyi, K.; Pete, B.; Toke, L.; Keglevich, G. *Tetrahedron Asym.* **1999**, *10*, 2373. b) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *10*, 1379.

[96] a) Lewis, R. T.; Motherwell, W. B. *Tetrahedron*, **1992**, *8*, 1465. b) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.

[97] a) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett*, **1996**, 521. b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

[98] Zhang, H. X.; Guibé, F.; Balavoine, G.; *J. Org. Chem.* **1990**, *55*, 1857.

[99] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

[100] Julia, M.; Paris, J. –M. *Tetrahedron Lett.* **1973**, *49*, 4833.

[101] Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett*. **1991**, *32*, 1175.

[102] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett*, **1998**, 26.

[103] a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336; b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.

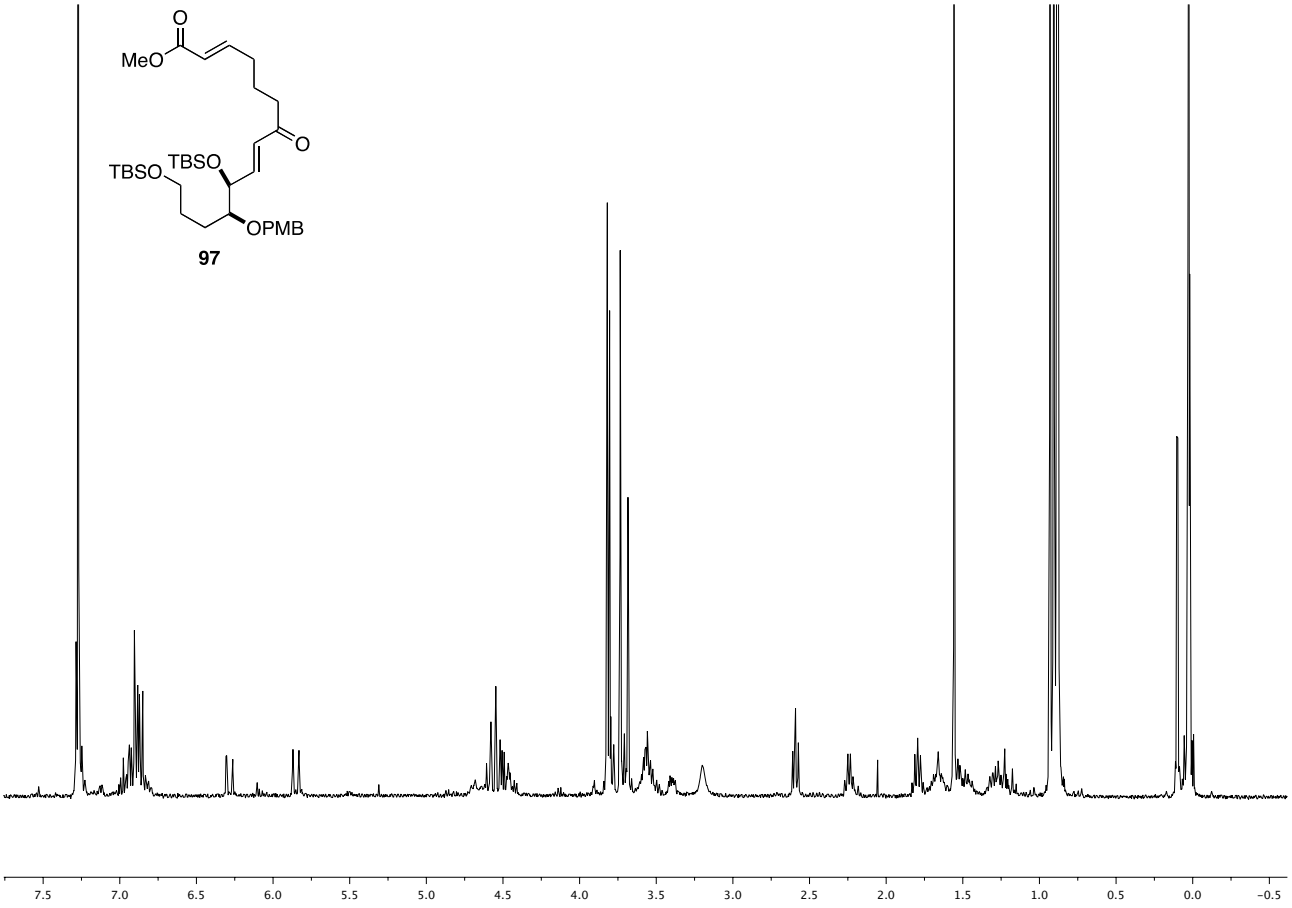
[104] Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett*, **2000**, *3*, 365.

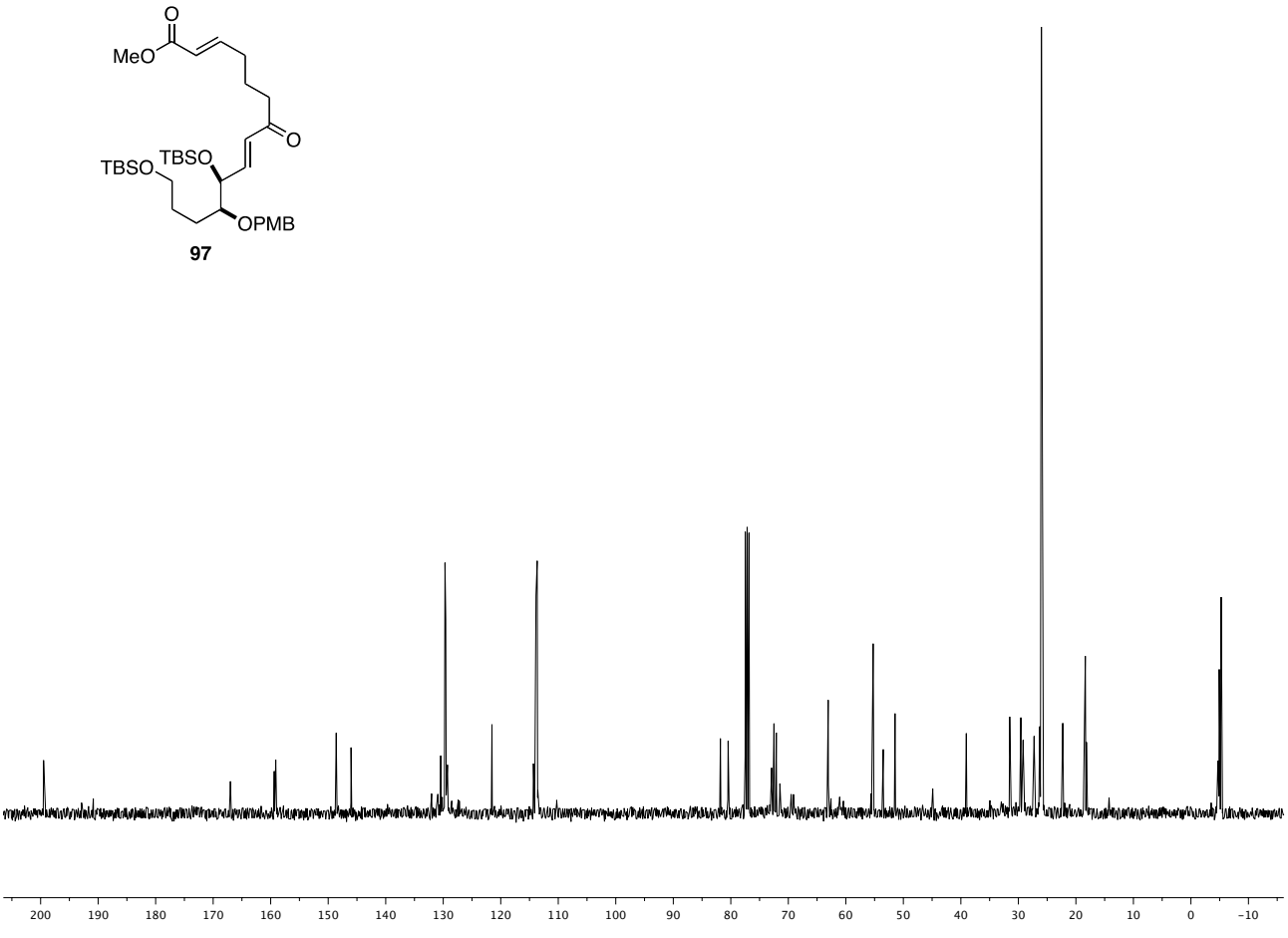
[105] Blakemore, P. R, J. *Chem. Soc. Perkin Trans. 1,* **2002**, 2563.

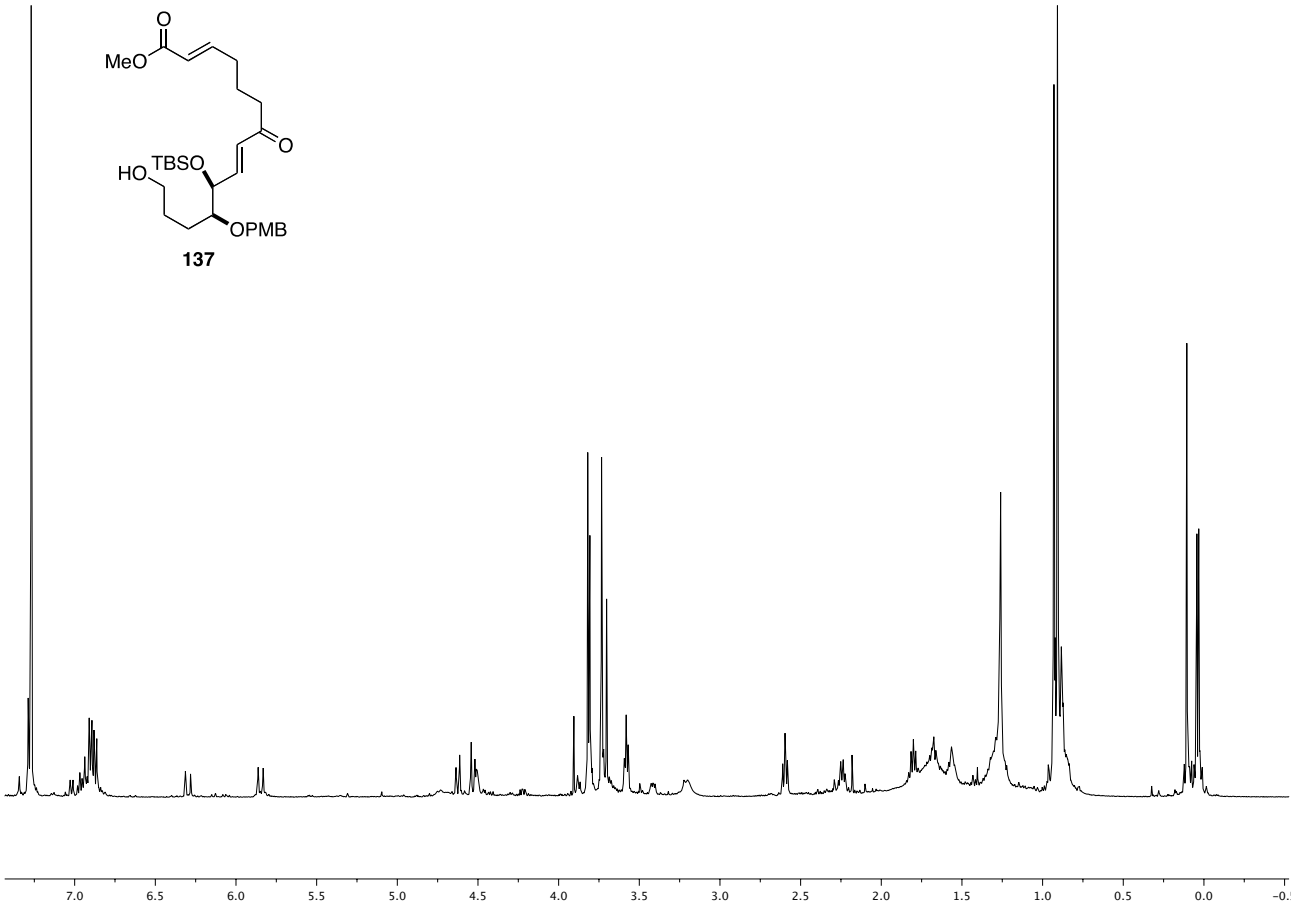
[106] Dumeunier, R. I.; Markó, E. *Modern Carbonyl Olefination* (ed Takeda. T), Wiley-VCH, Weinheim, **2004**, 104.

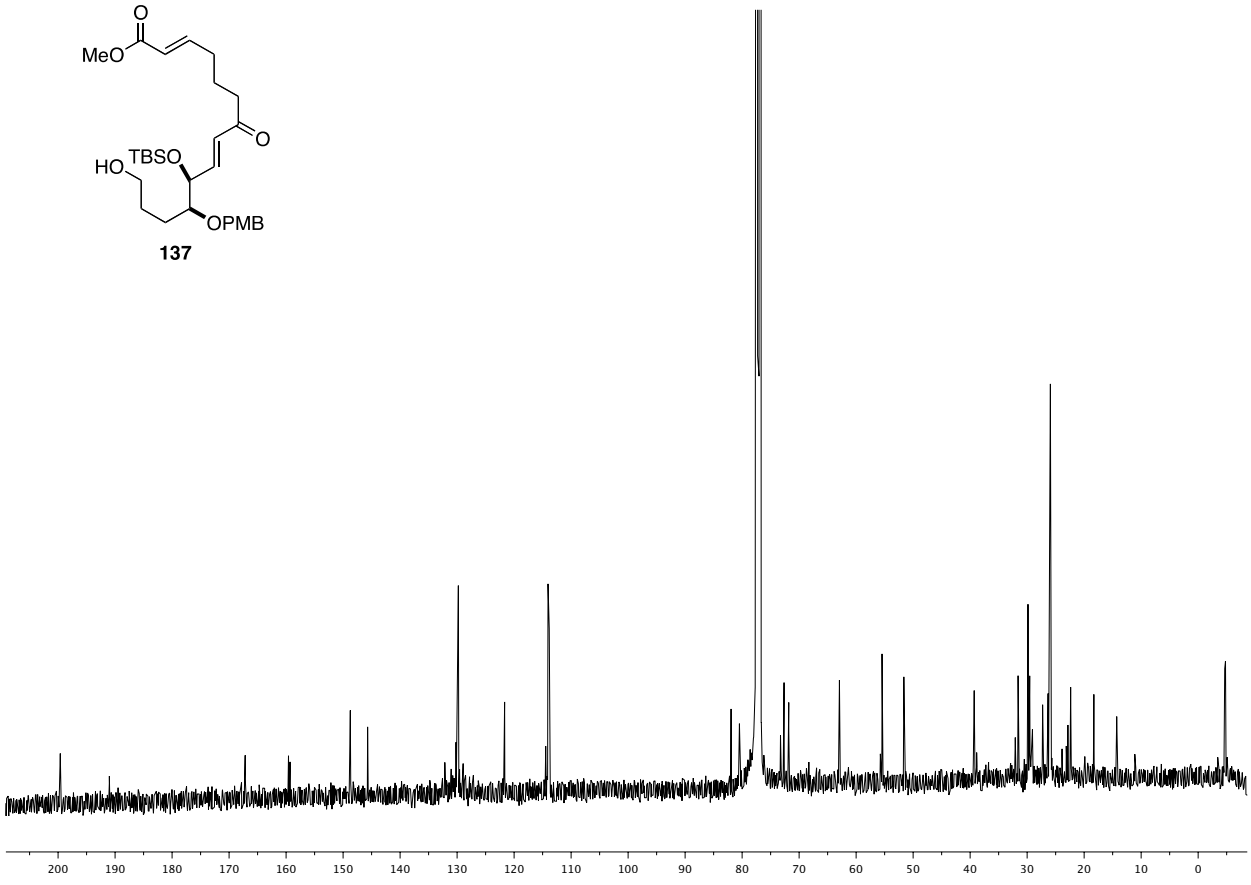
[107] Gray, G. A. *J. Am. Chem. Soc*. **1973**, *95*, 7736.
[108] Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
[109] Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*. 2899.
[110] a) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455. b) Paterson, I.; Findlay, A. D.; Florence, G. J. *Org. Lett*. **2006**, *8*, 2131.
[111] Rai, A. N.; Basu, A. *Tetrahedron Lett*. **2003**, *44*, 2267.
[112] S. Kodato, S.; Nakagawa, M.; Nakayama, K.; Hino, T. *Tetrahedron* **1989**, *45*, 7247.
[113] Little, R. D.; Muller, G. W.; Venegas, M. G.; Carrol, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371.
[114] Nicolaou, K. C.; Petasis, N. A.; Seitz, S. P. *J. Chem. Soc., Chem. Commun*. **1981**, 1195.
[115] Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933.
[116] Shimada, T.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 471.
[117] Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350.
[118] Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc*. **2001**, *123*, 9535
[119] Mendlik, M. T.; Cottard, M.; Rien, R.; Helquist, P. *Tetrahedron Lett.* **1997**, *36*, 6375.
[120] Das, S.; Abraham, S.; Sinha, S. C. *Org. lett.* **2007**, *9*, 2273.
[121] Matsui, K.; Zheng, B.; Kusaka, S.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. Eur. *J. Org. Chem*. **2001**, *19*, 3615.
[122] Diba, A. K.; Noll, C.; Richter, M.; Gieseler, M. T.; Kalesse, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8367.
[123] Shi, J.; Zeng, X.; Negishi, E. *Org. Lett.* **2003**, *5*, 1825.
[124] Procedure carried out in unison with Dr. Wlochal.

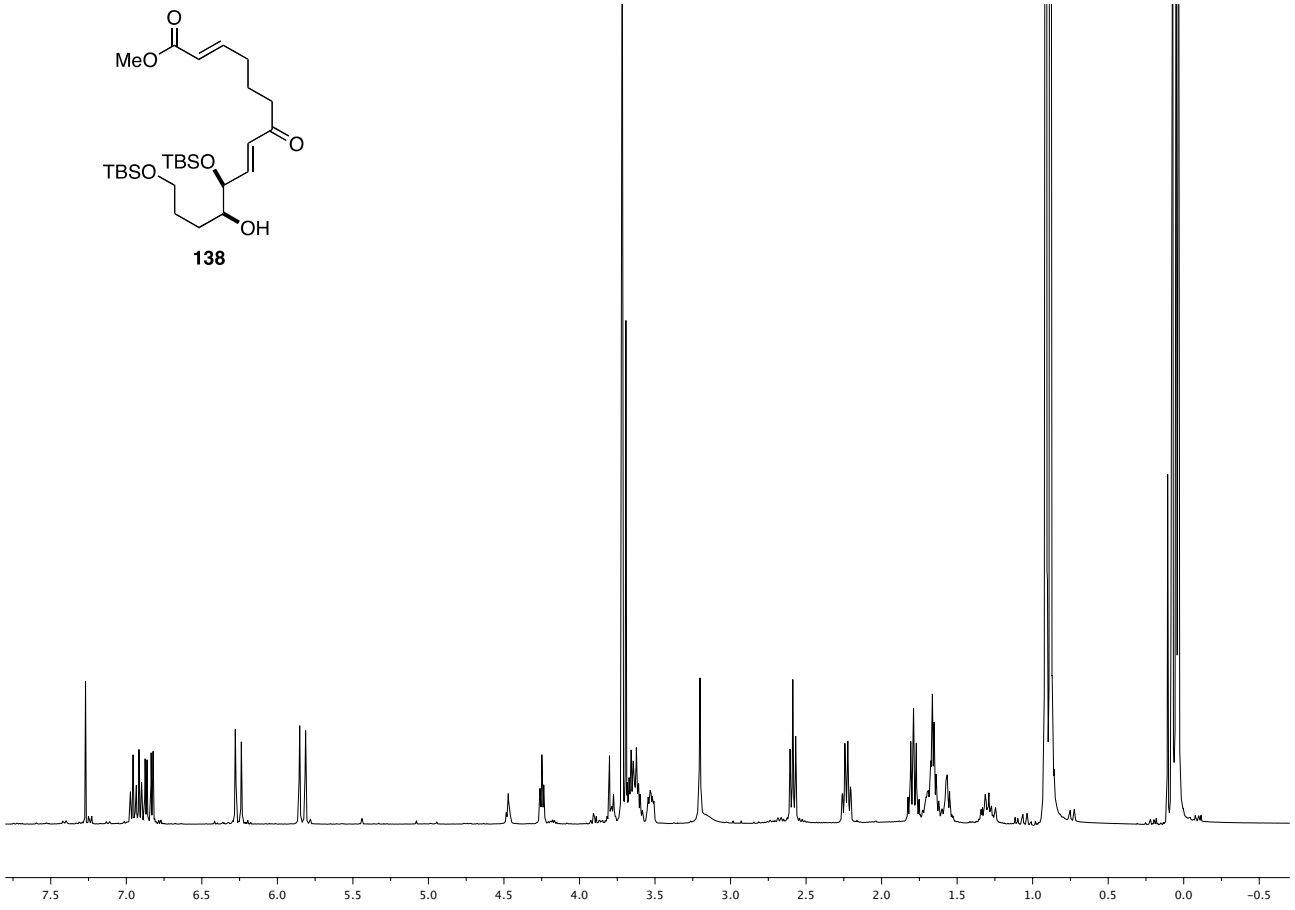
Appendix: Selected ^{1}H and ^{13}C NMR spectra


MeO
O
O
TBSO
TBSO
OPMB
97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

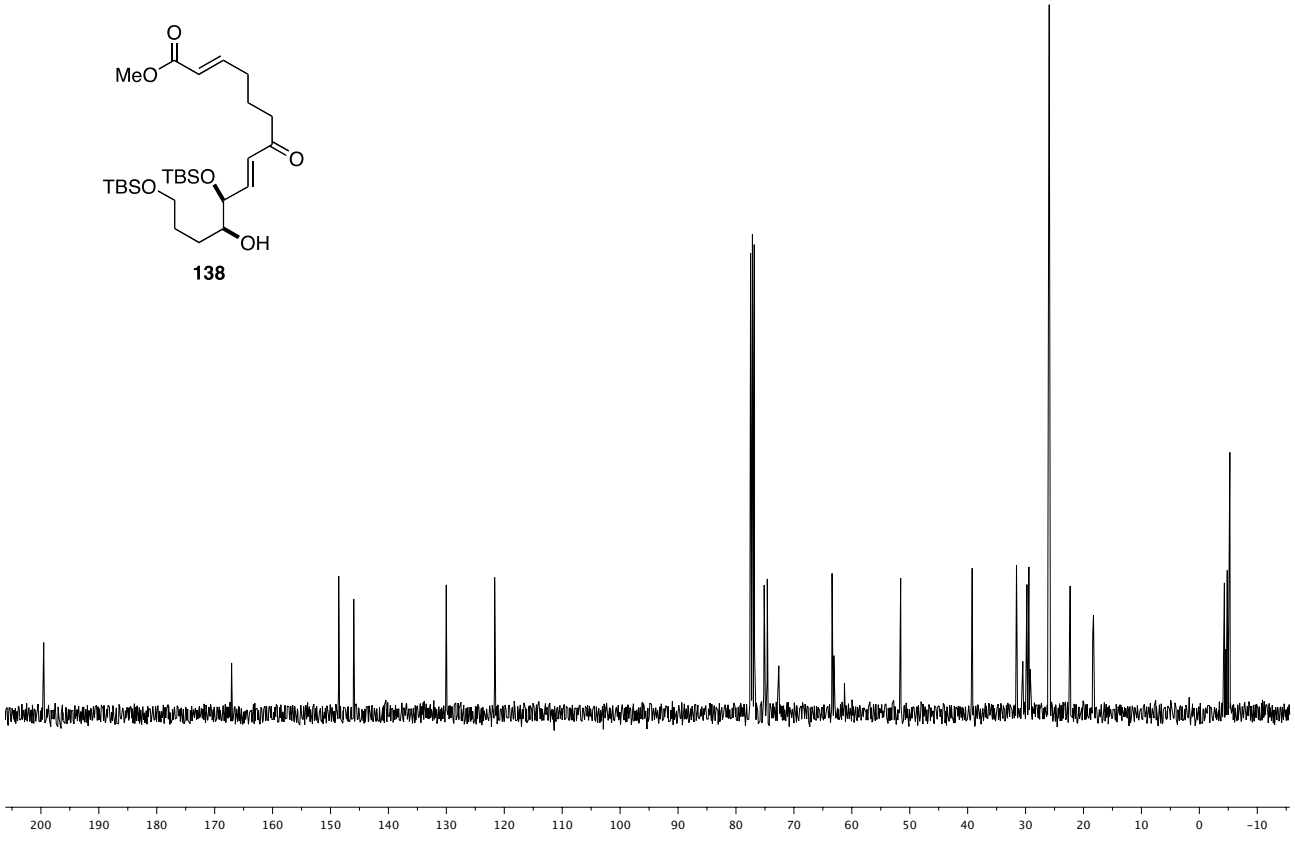

MeO
O
O
TBSO
TBSO
OPMB
97
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


MeO
O
O
HO
TBSO
OPMB
137
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

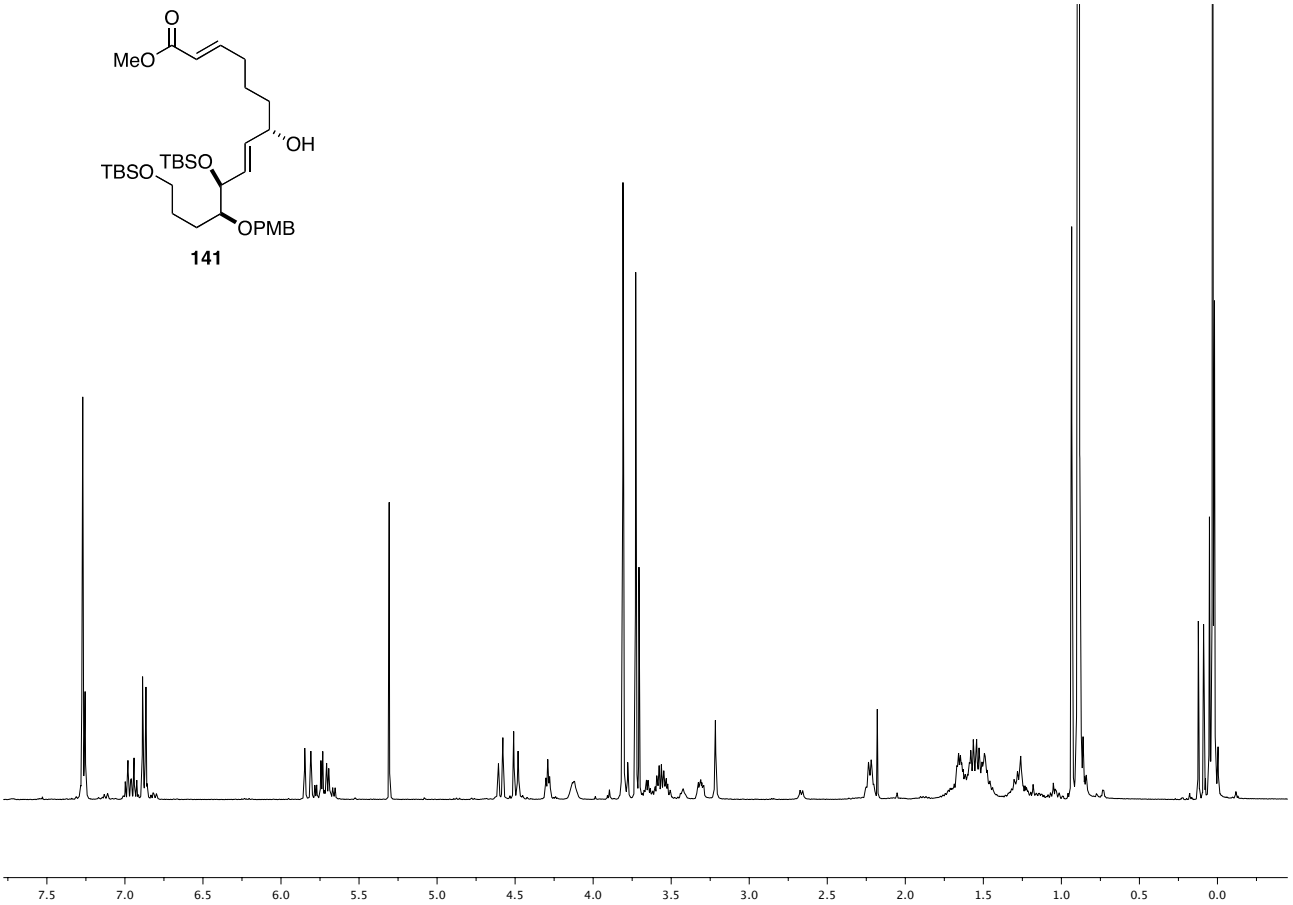

MeO
O
O
HO
TBSO
OPMB
137
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

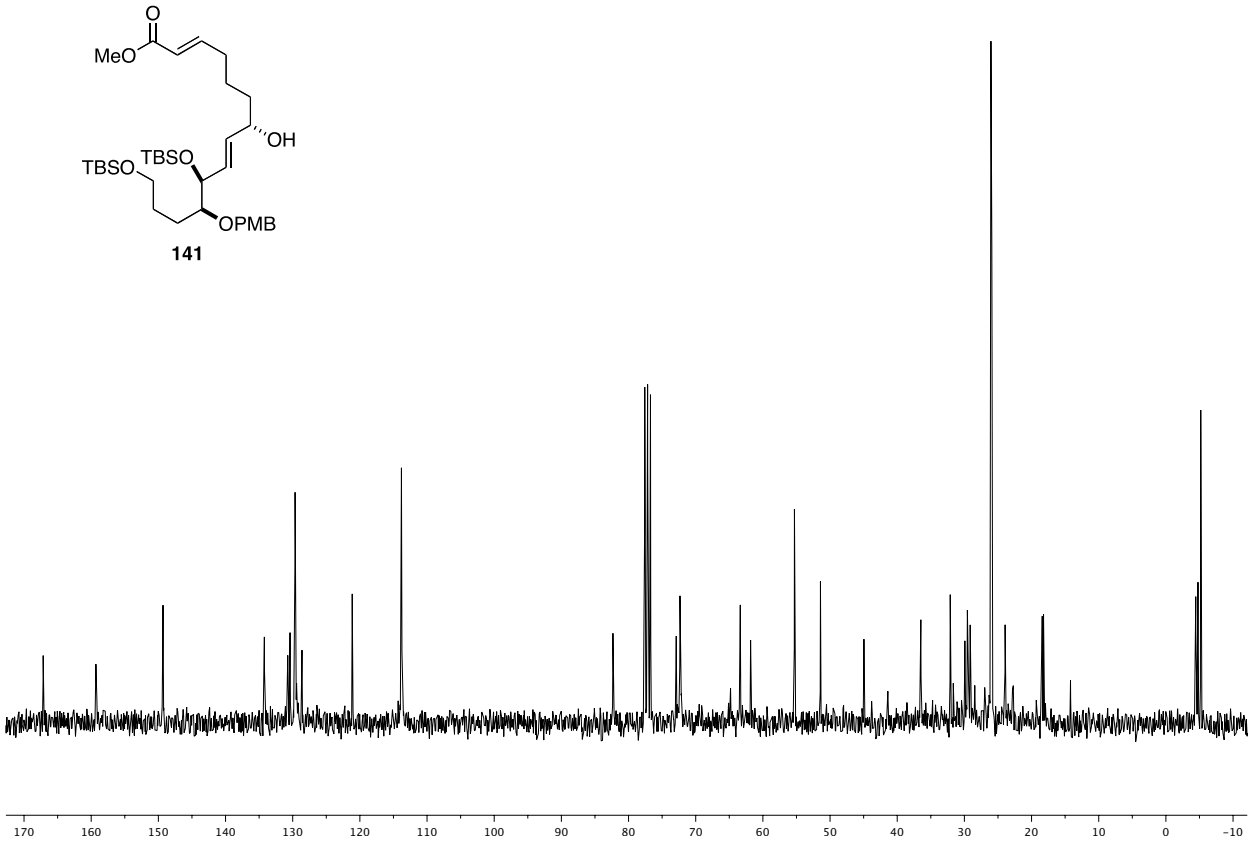

MeO
O
O
TBSO
TBSO
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

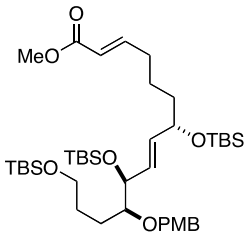
138


MeO
O
O
TBSO
TBSO
OH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

138

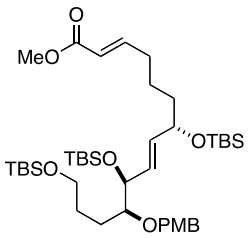

O
MeO
OH
TBSO
TBSO
OPMB
141
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


O
MeO
OH
TBSO
TBSO
OPMB
141
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
MeO
OTBS
TBSO
TBSO
OPMB

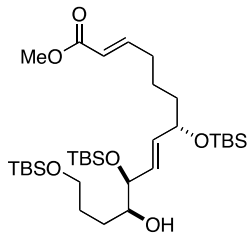
148

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


O
MeO
OTBS
TBSO
TBSO
OPMB

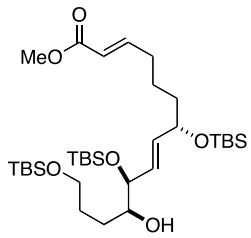
148

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
MeO
OTBS
TBSO
TBSO
OH

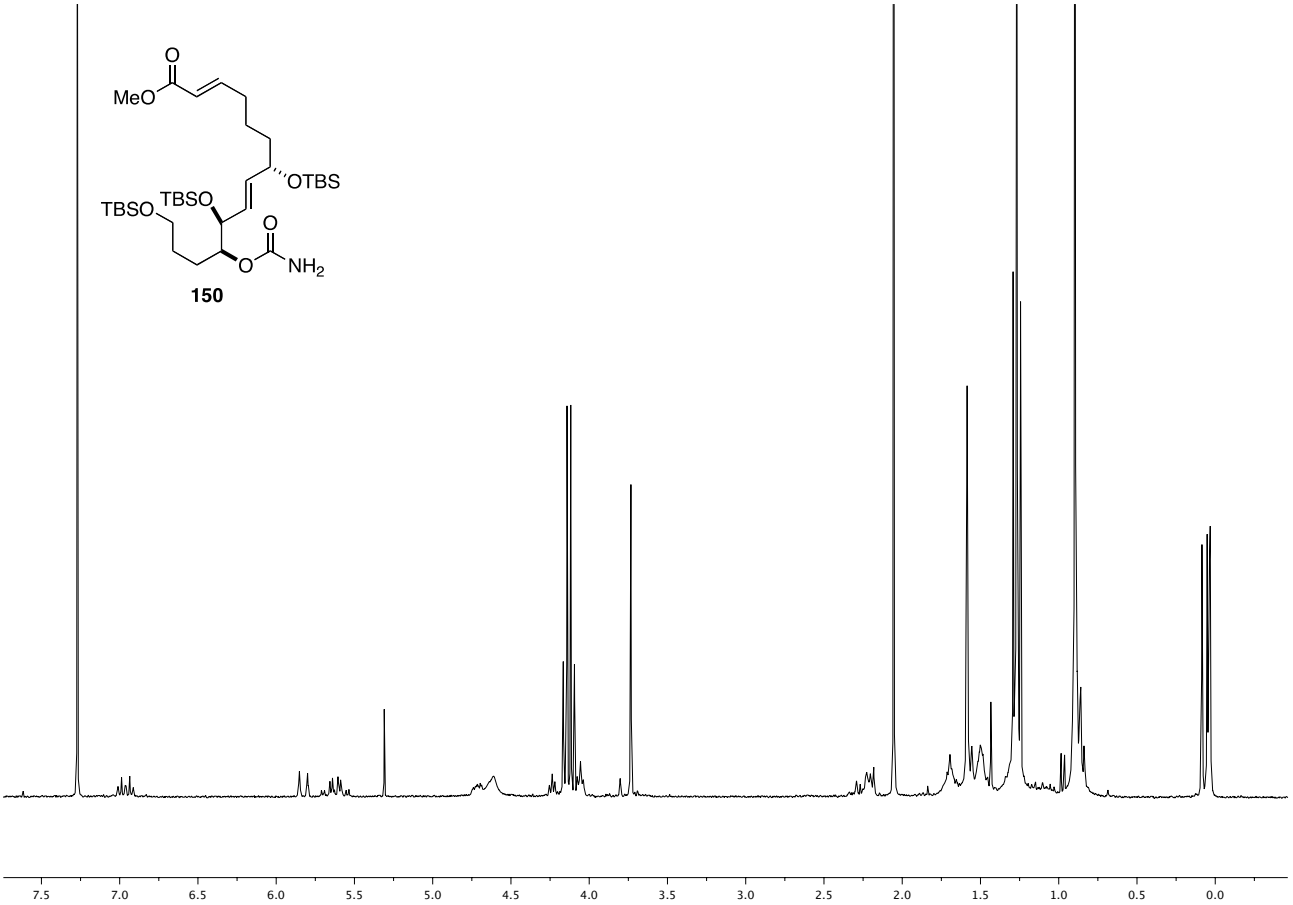
149

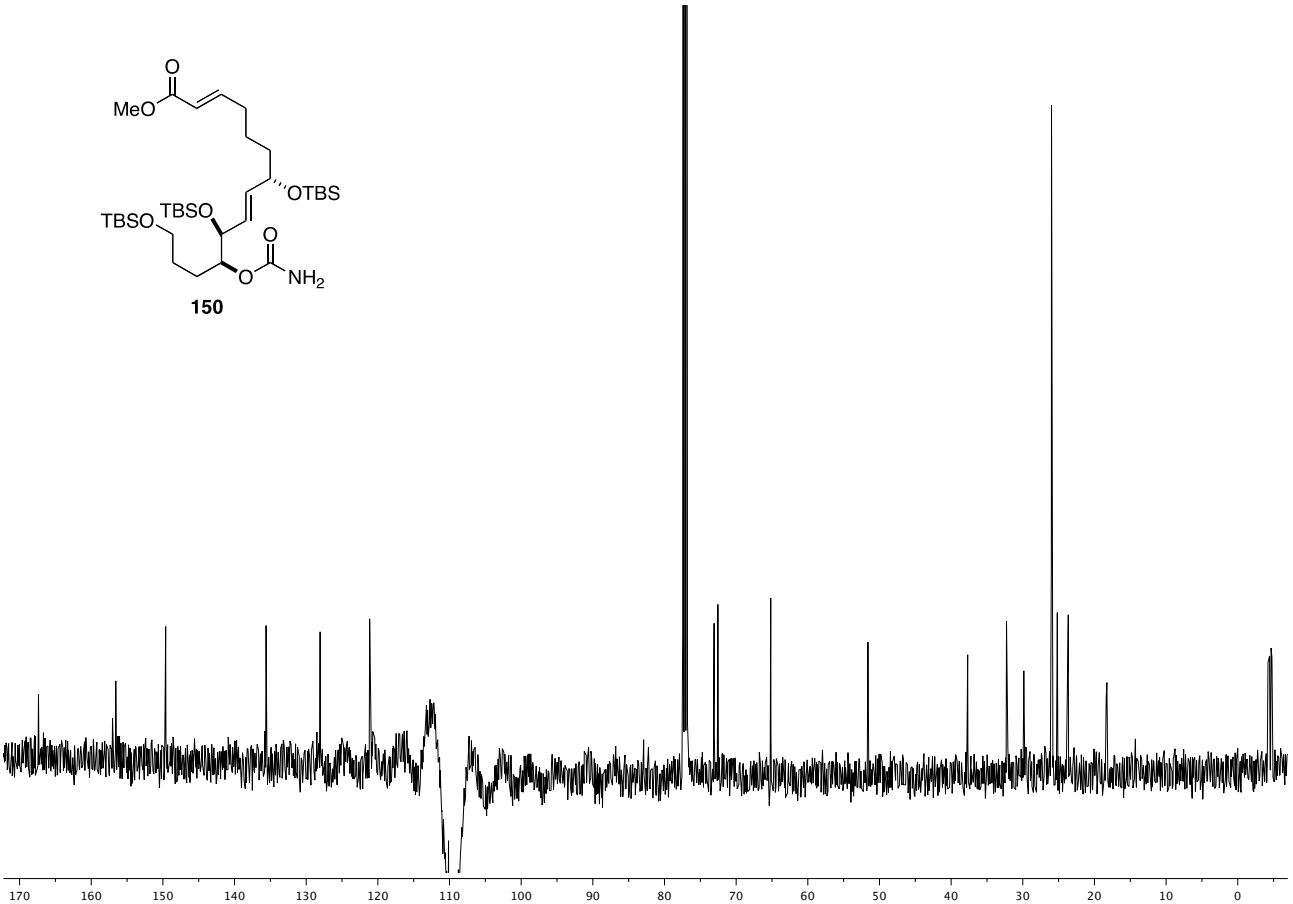
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

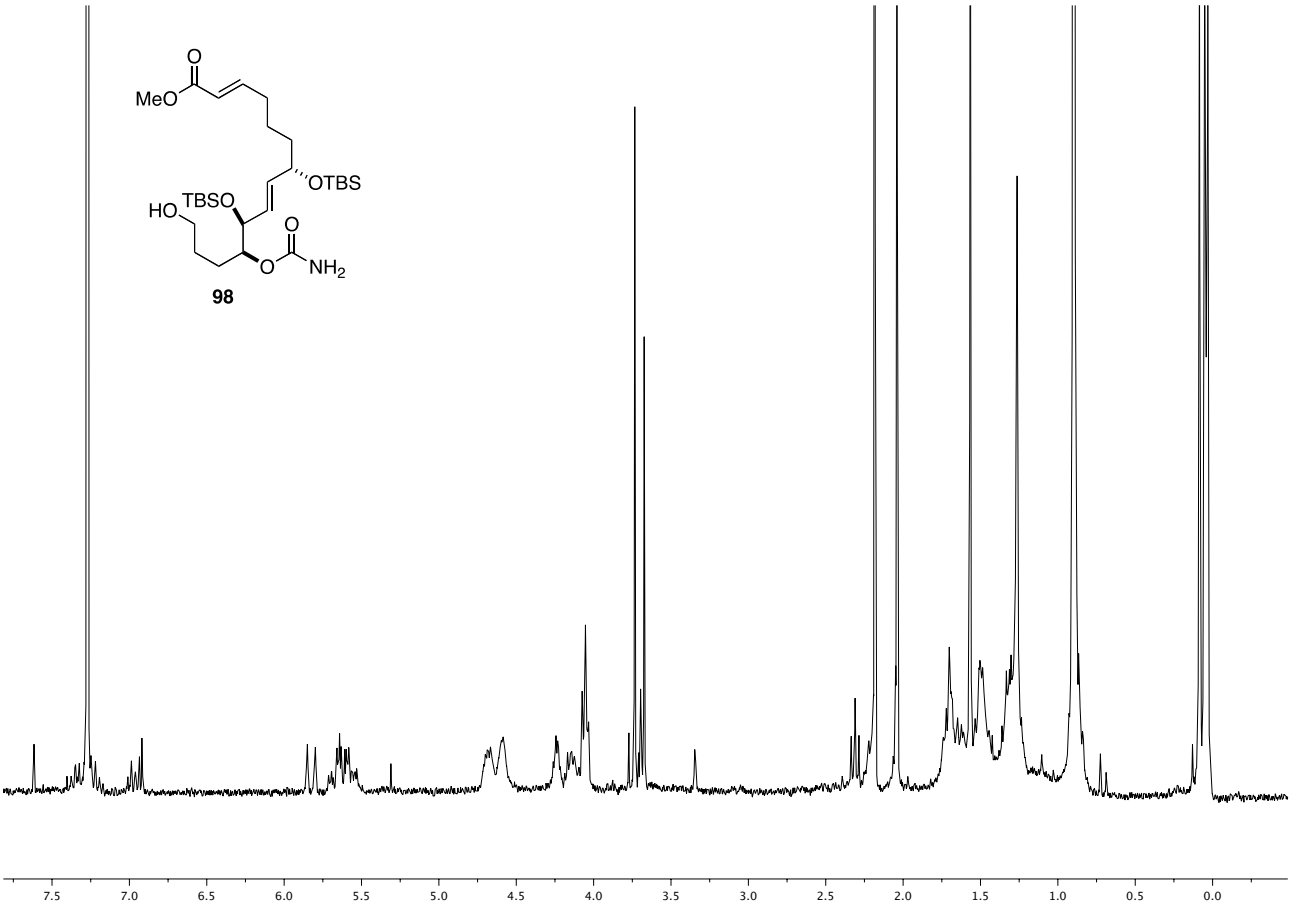

O
MeO
OTBS
TBSO
TBSO
OH

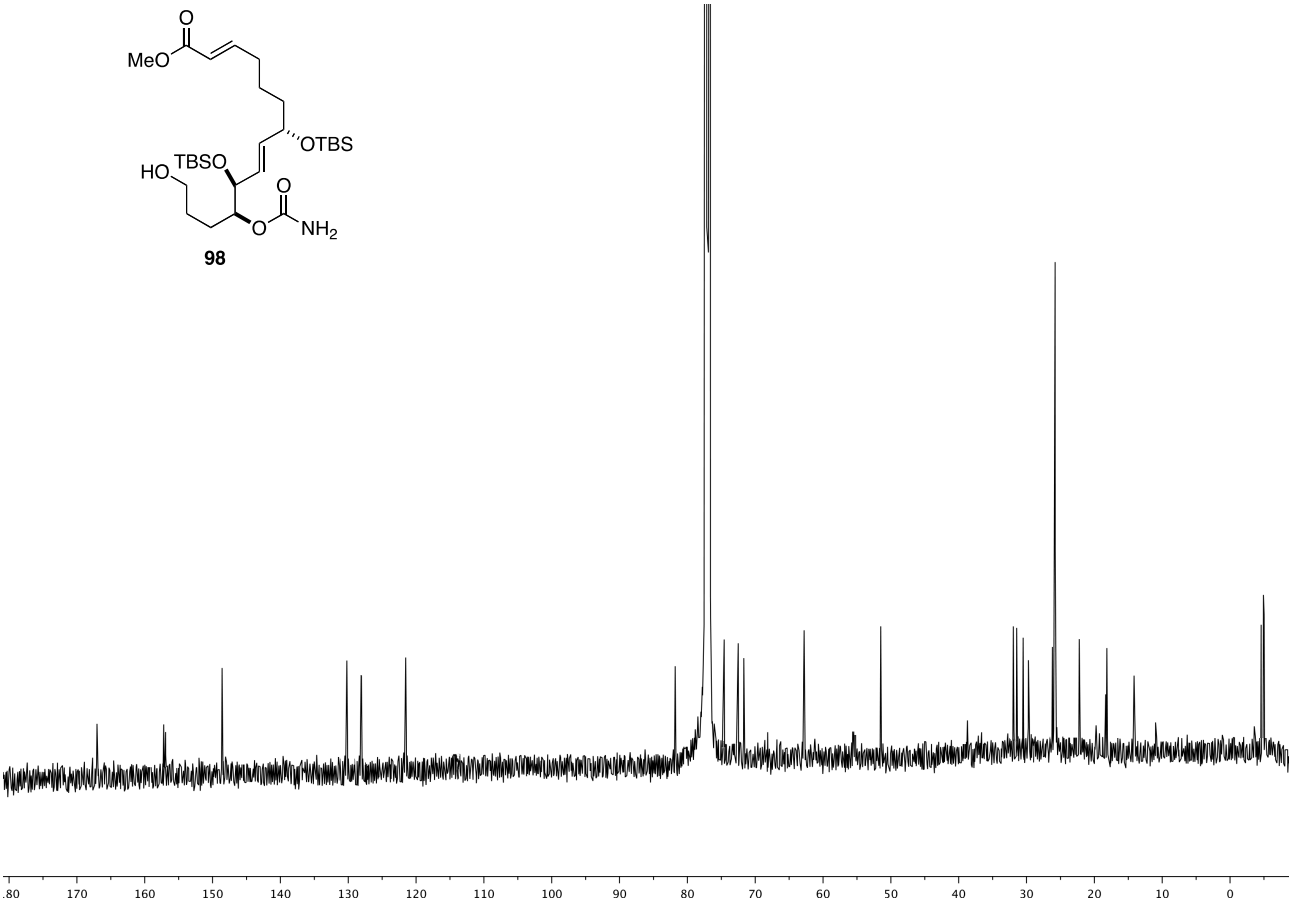
149

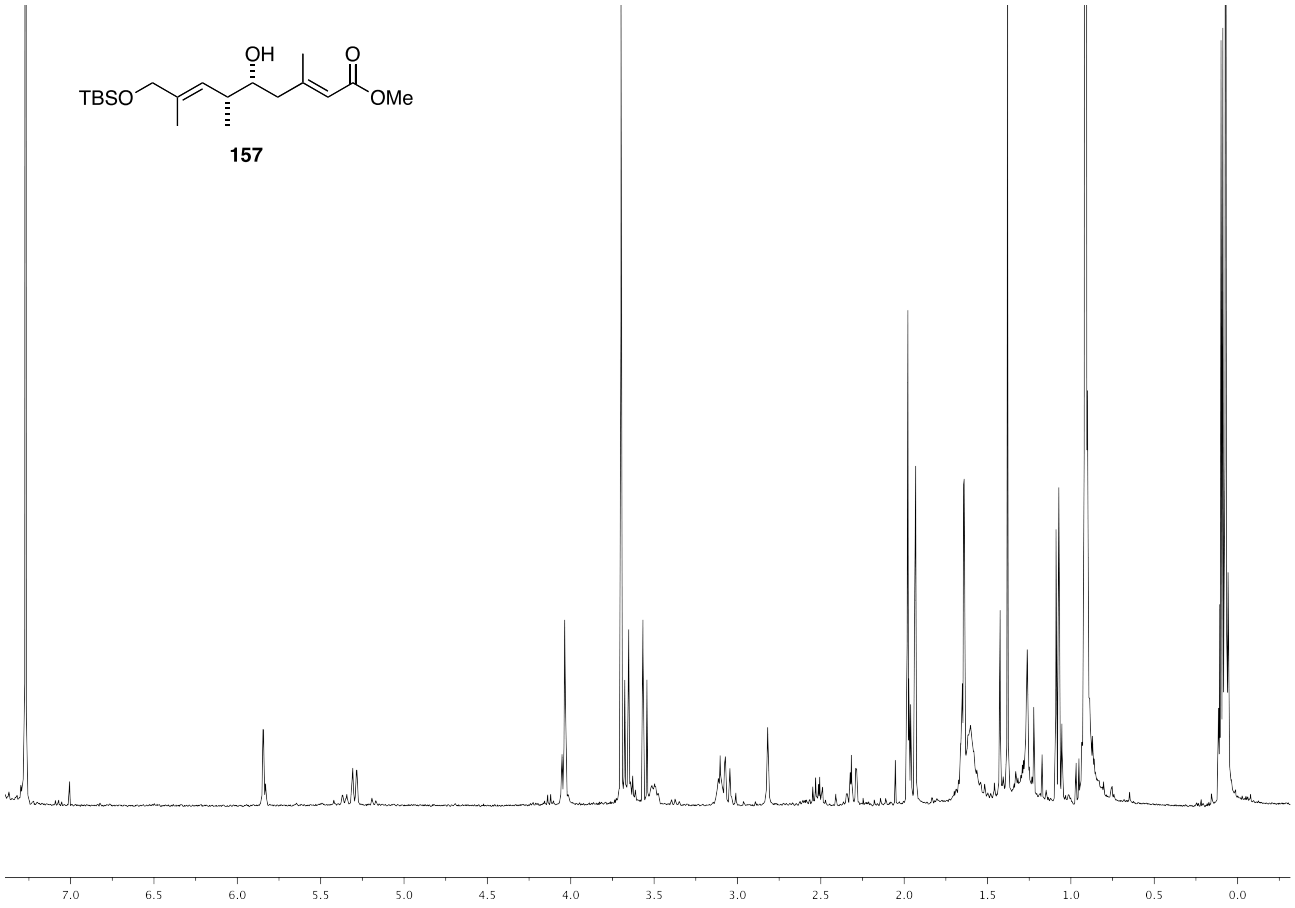
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

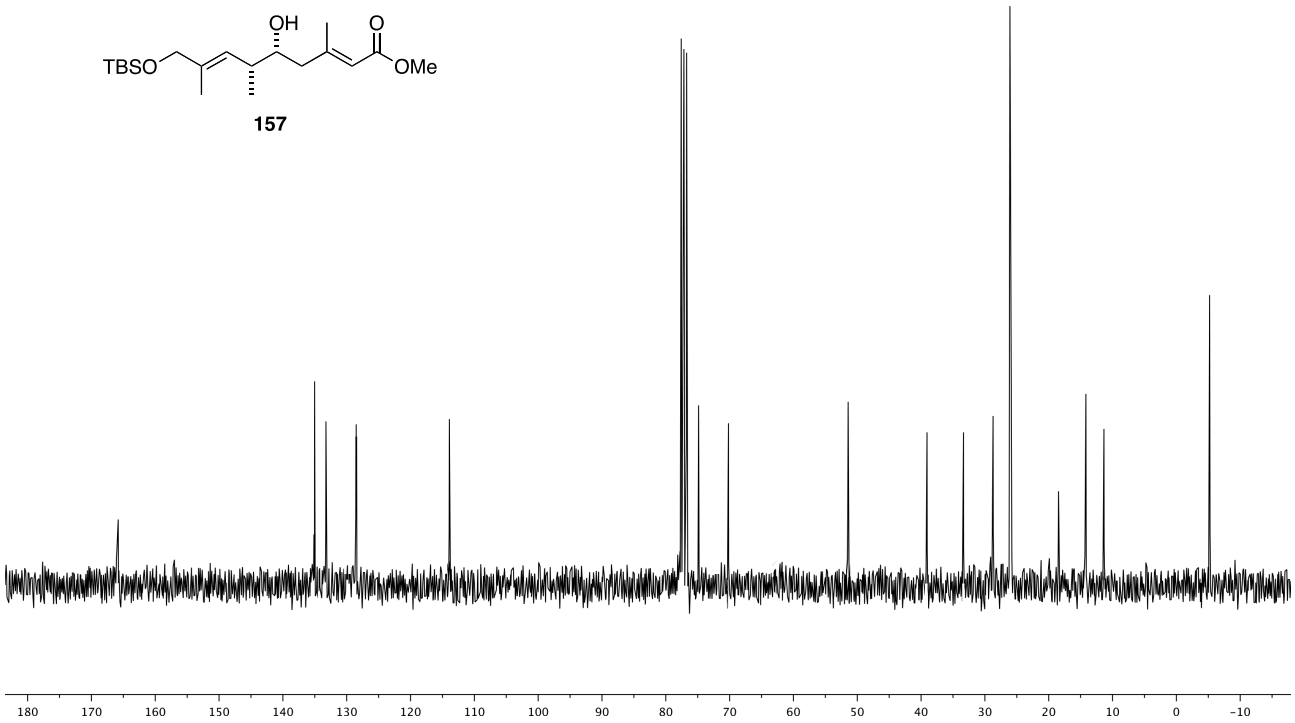

MeO
O
OTBS
TBSO
TBSO
O
O
NH2
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

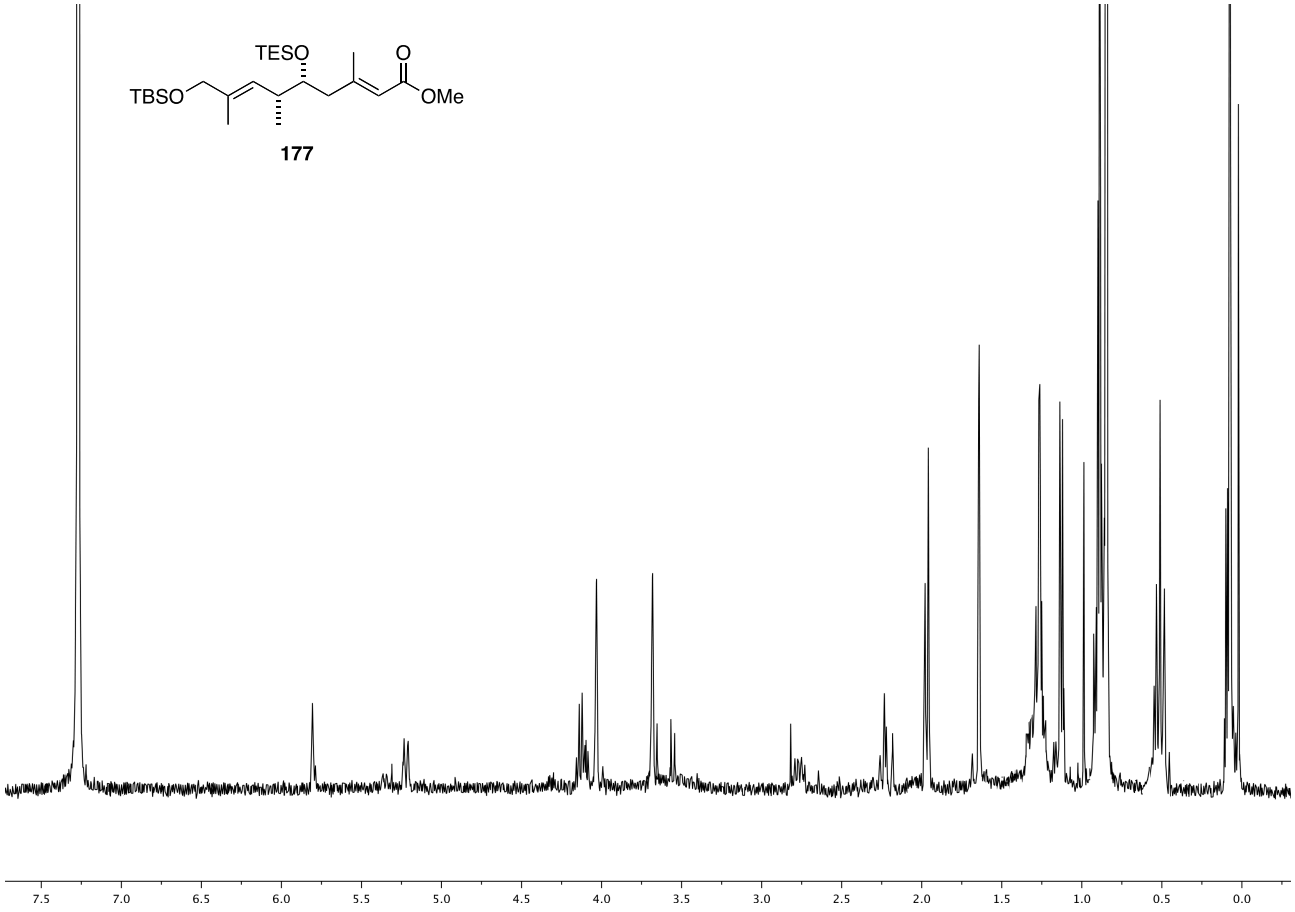

MeO
O
OTBS
TBSO
TBSO
O
O
NH2
150
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

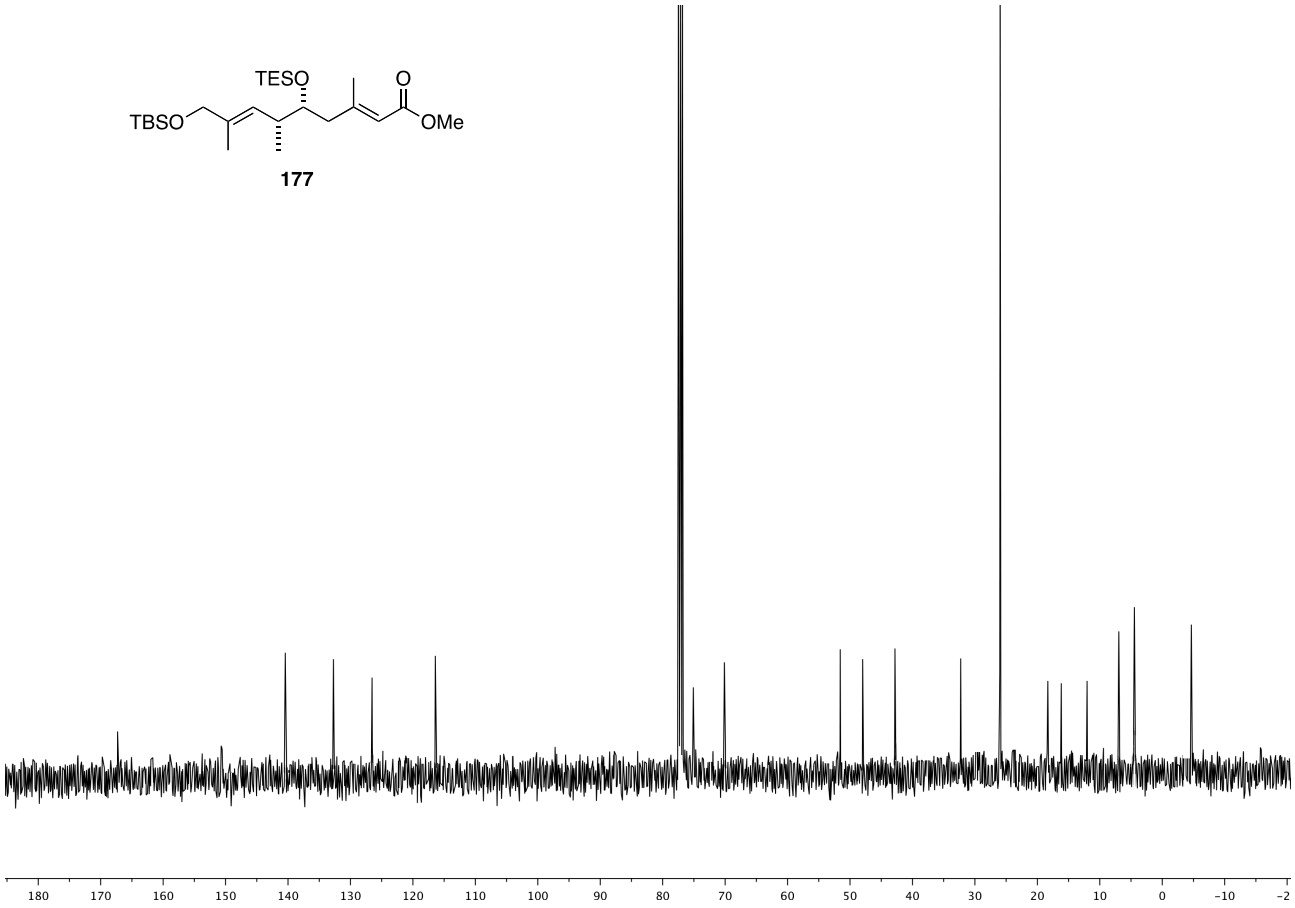

MeO
O
OTBS
HO
TBSO
O
O
NH2
98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

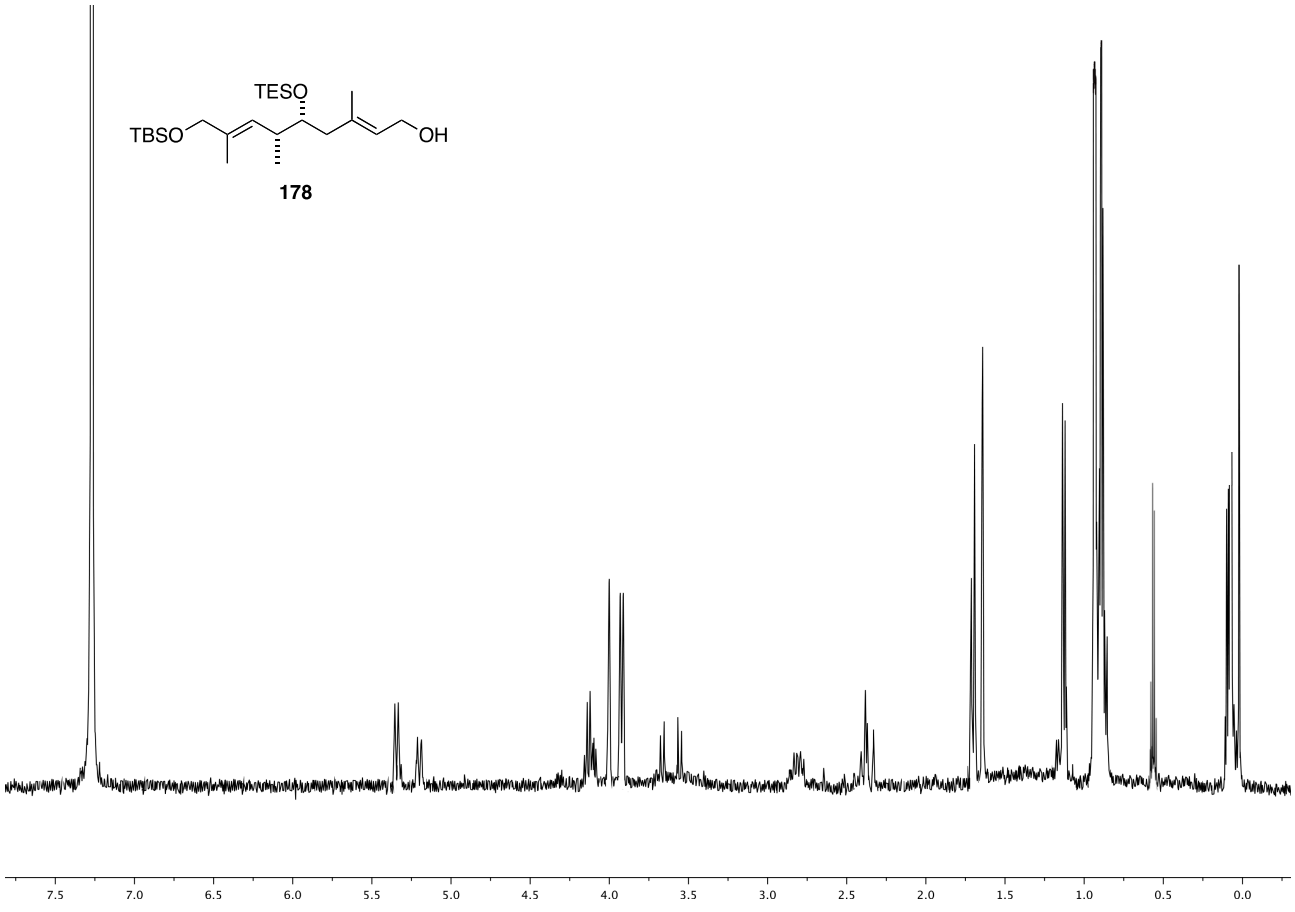

MeO
O
OTBS
HO
TBSO
O
O
NH2
98
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

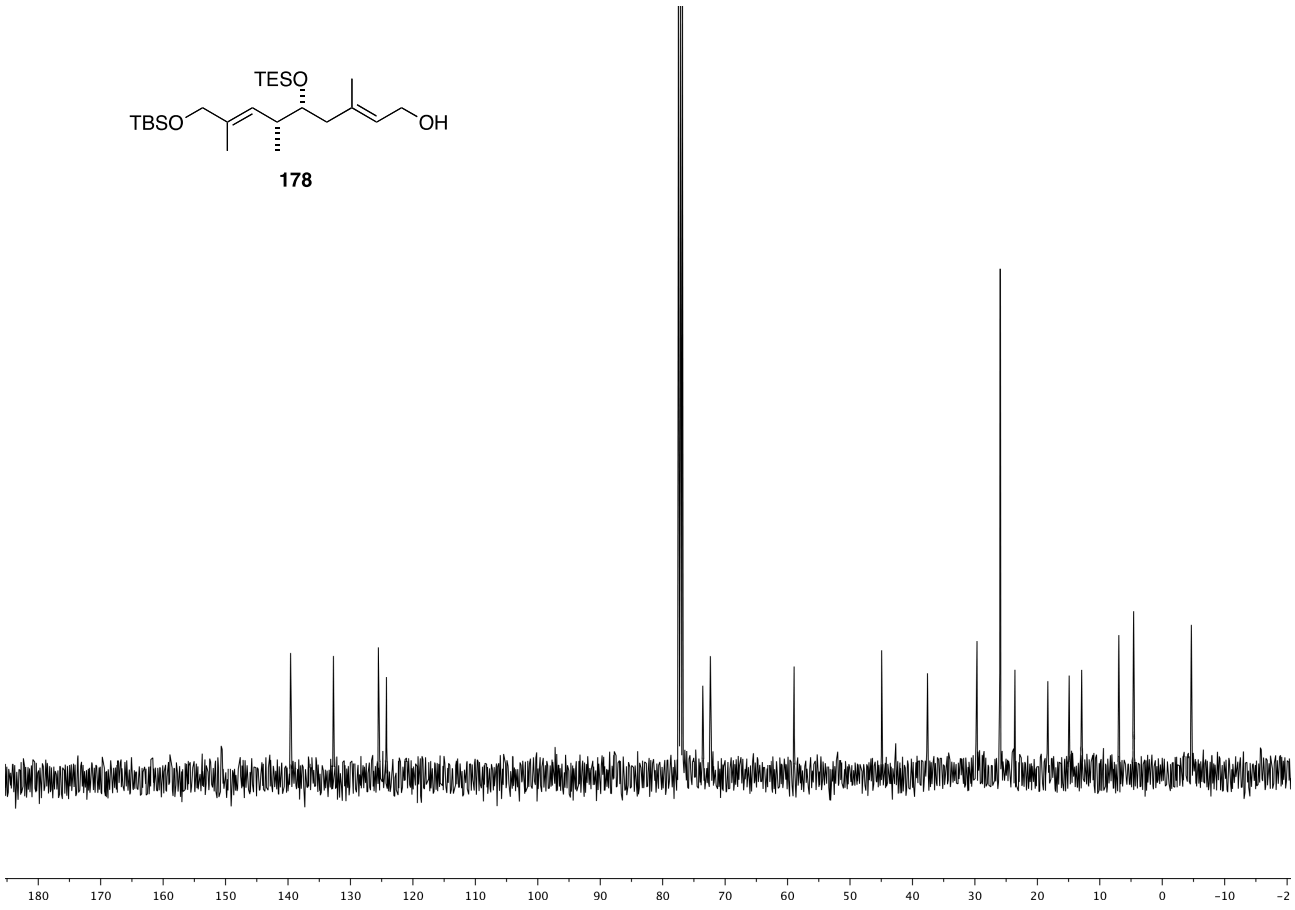

OH
O
TBSO
OMe
157
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

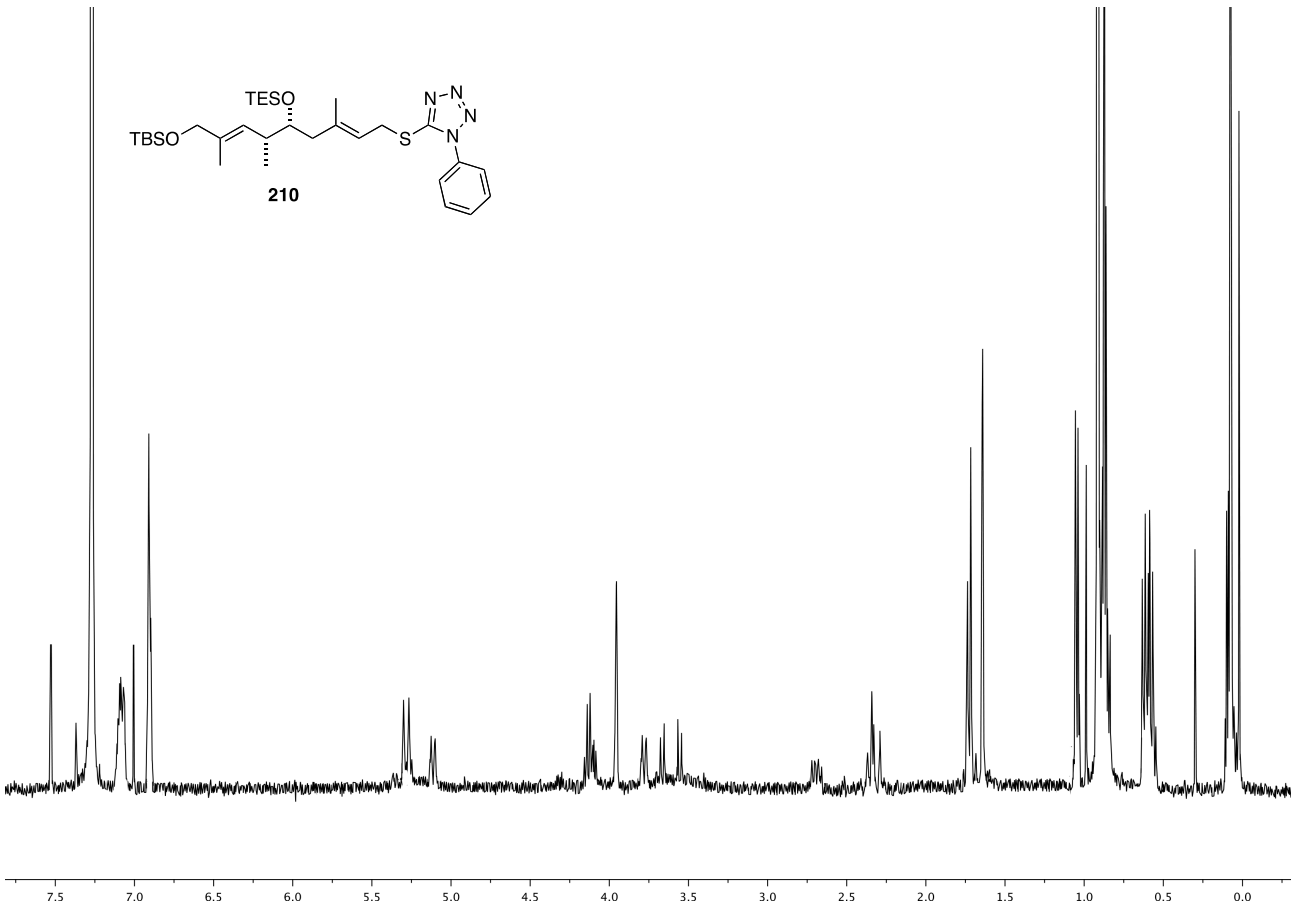

OH
O
TBSO
OMe
157
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

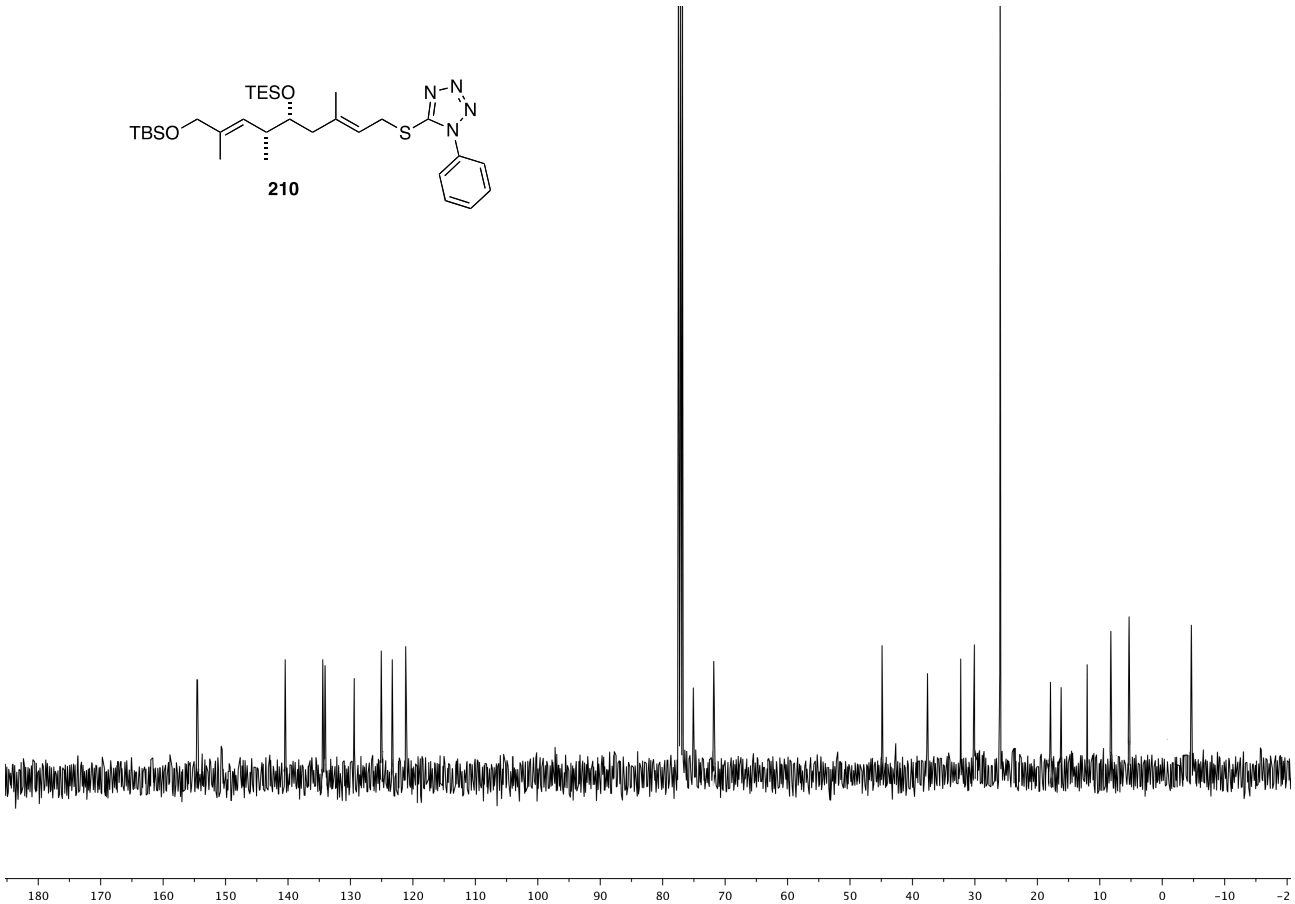

TESO
O
TBSO
OMe
177
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

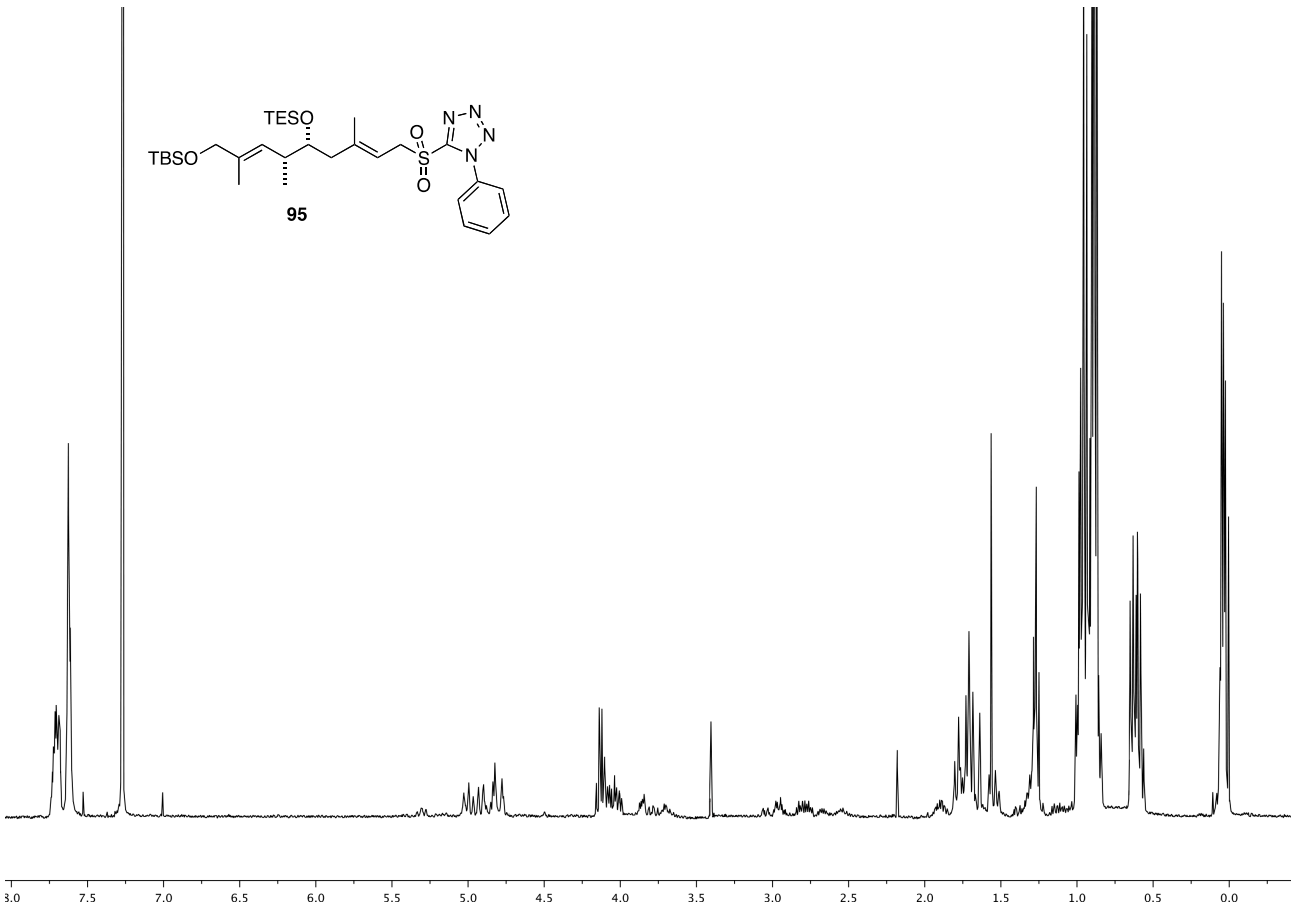

TESO
O
TBSO
OMe
177
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2

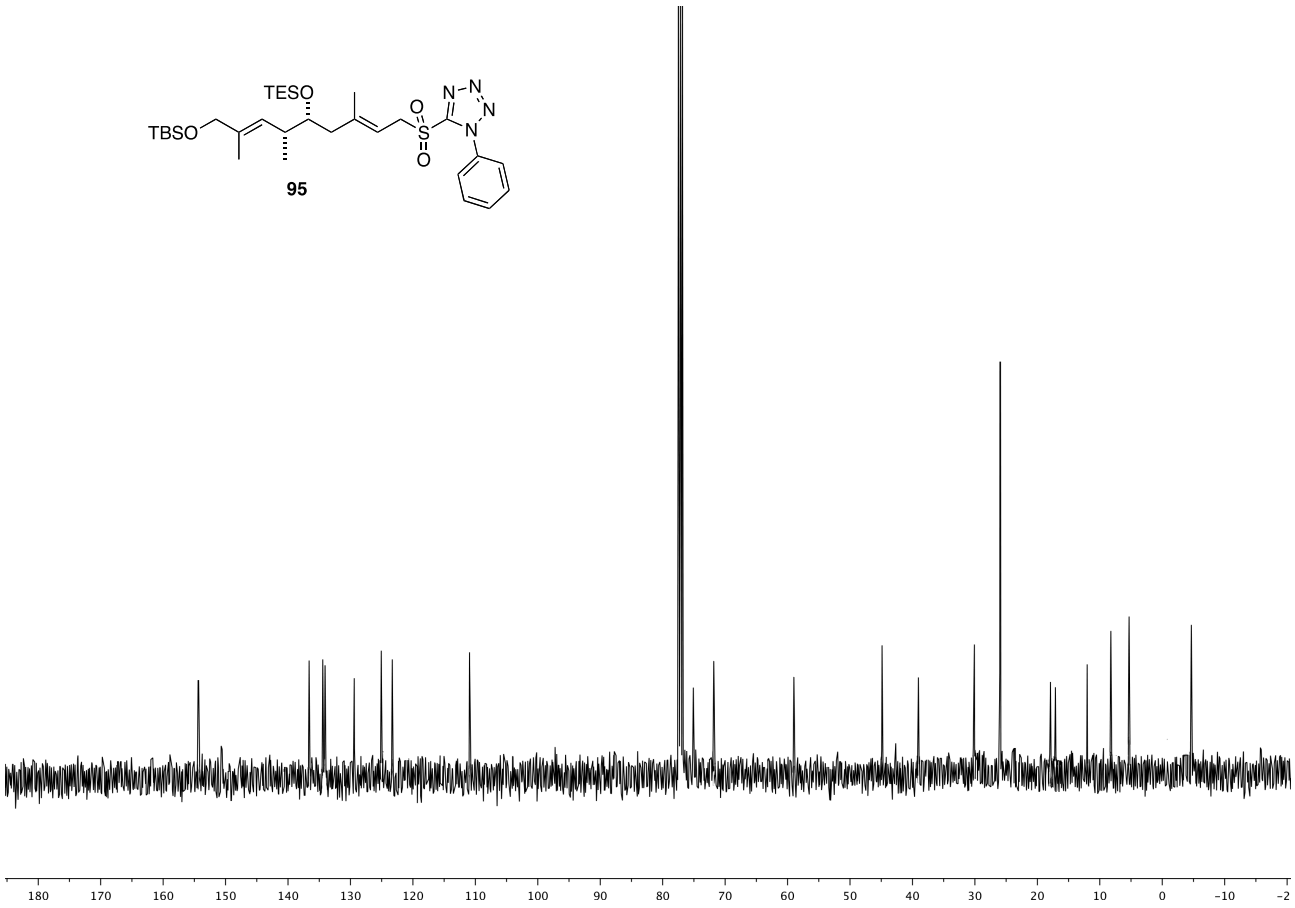

TESO
TBSO
OH
178
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

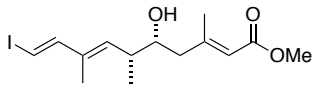

TESO
TBSO
OH
178
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2


TESO
TBSO
S
N
N
N
N
210
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


TESO
TBSO
S
N
N
N
N
210
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2

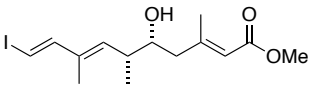

TESO
TBSO
O
S
O
N
N
N
N
95


TESO
TBSO
O
S
O
N
N
N
N
95


OH
O
I
OMe

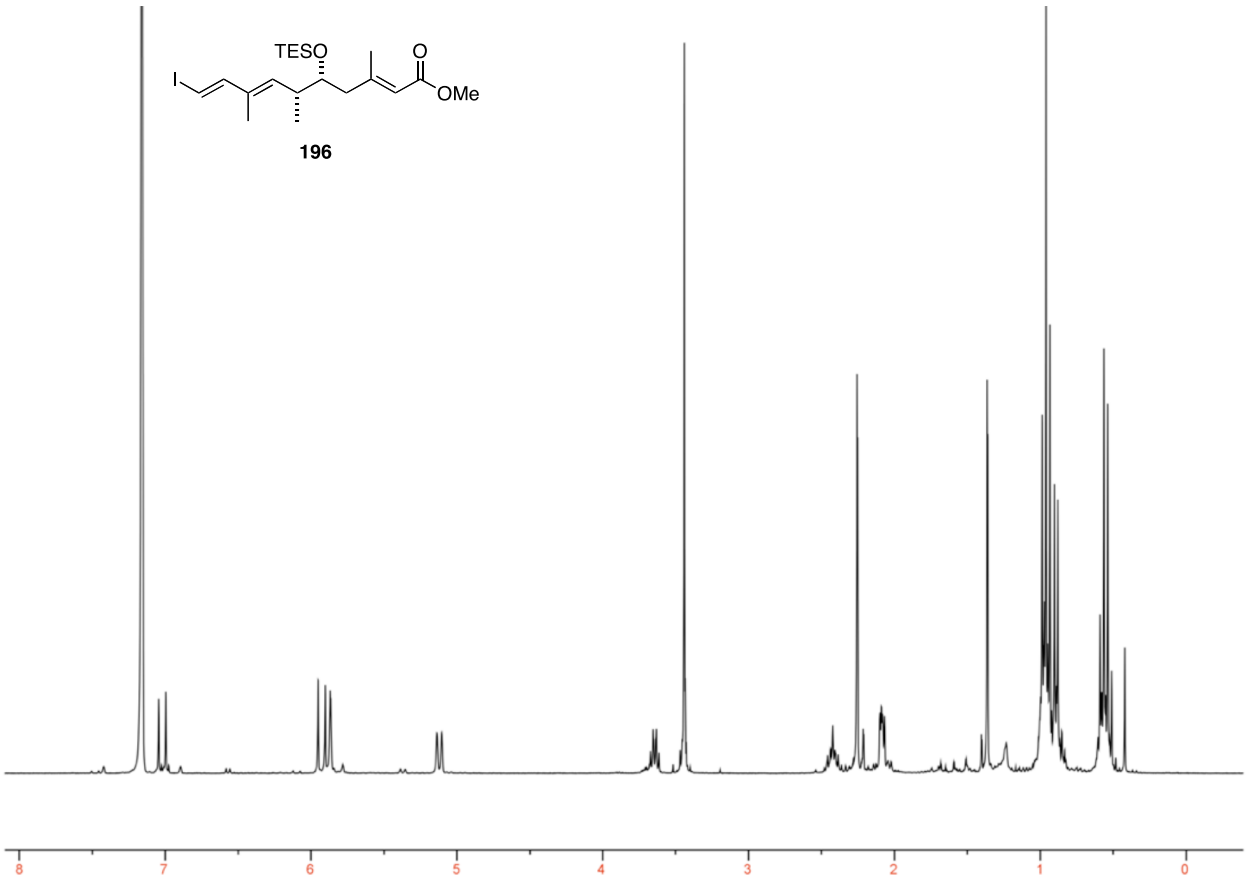
180

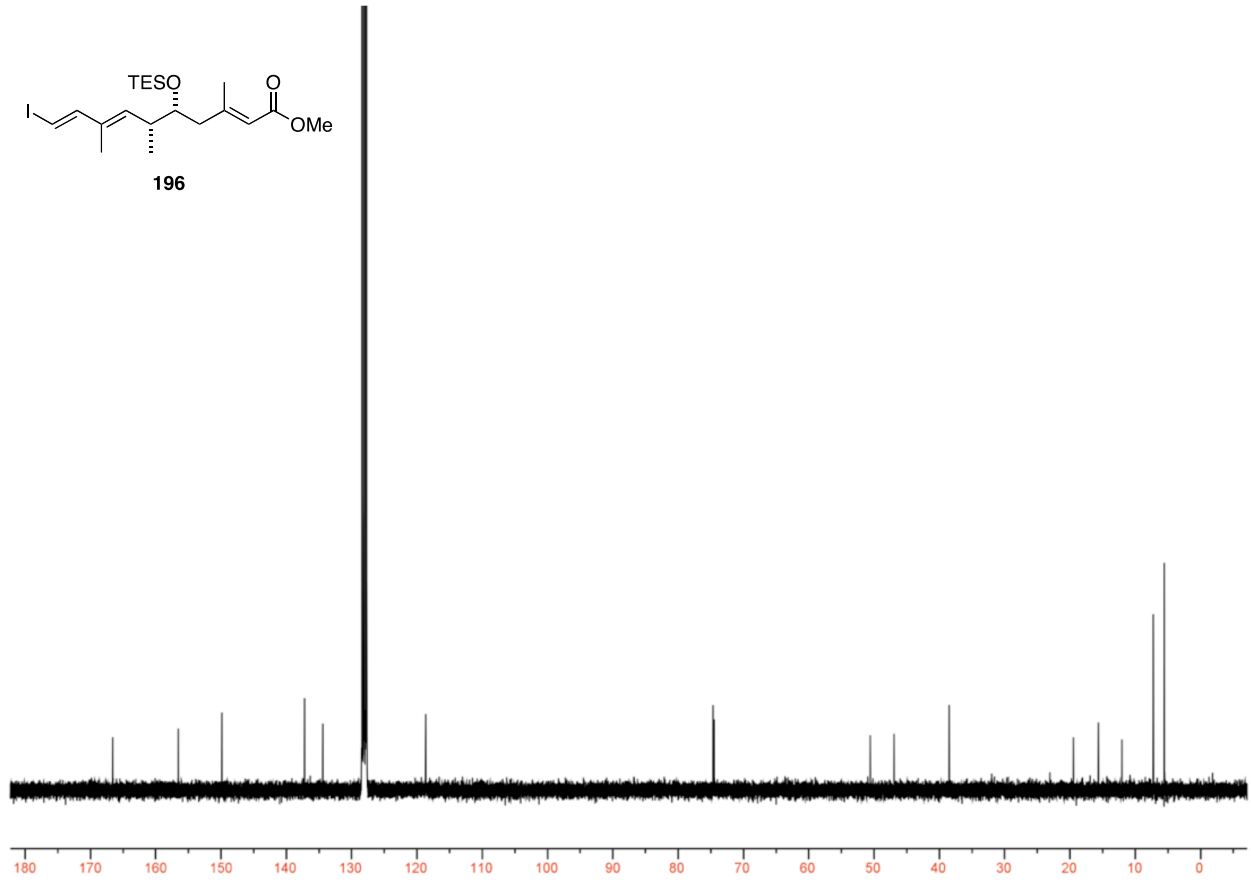
ppm 8
7
6
5
4
3
2
1
0

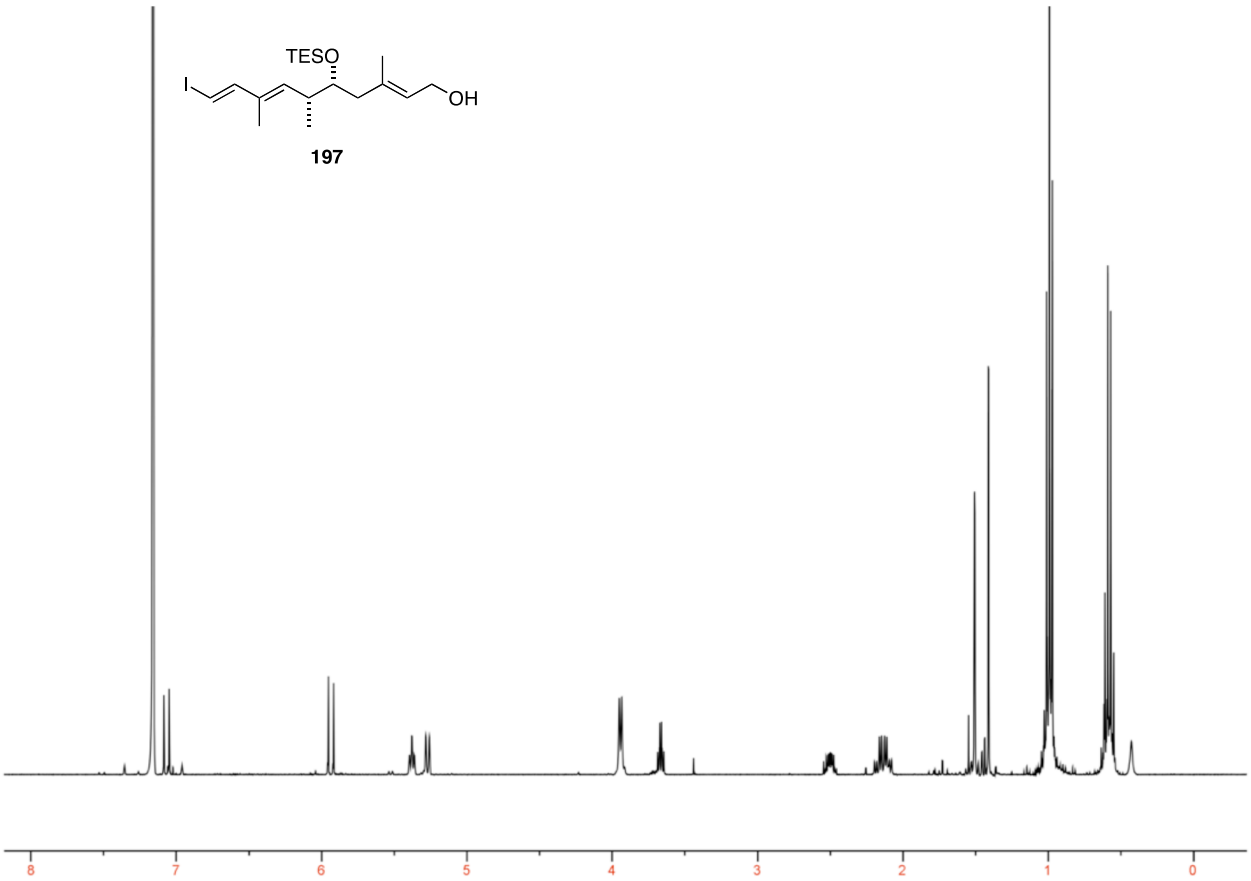

OH
O
I
OMe

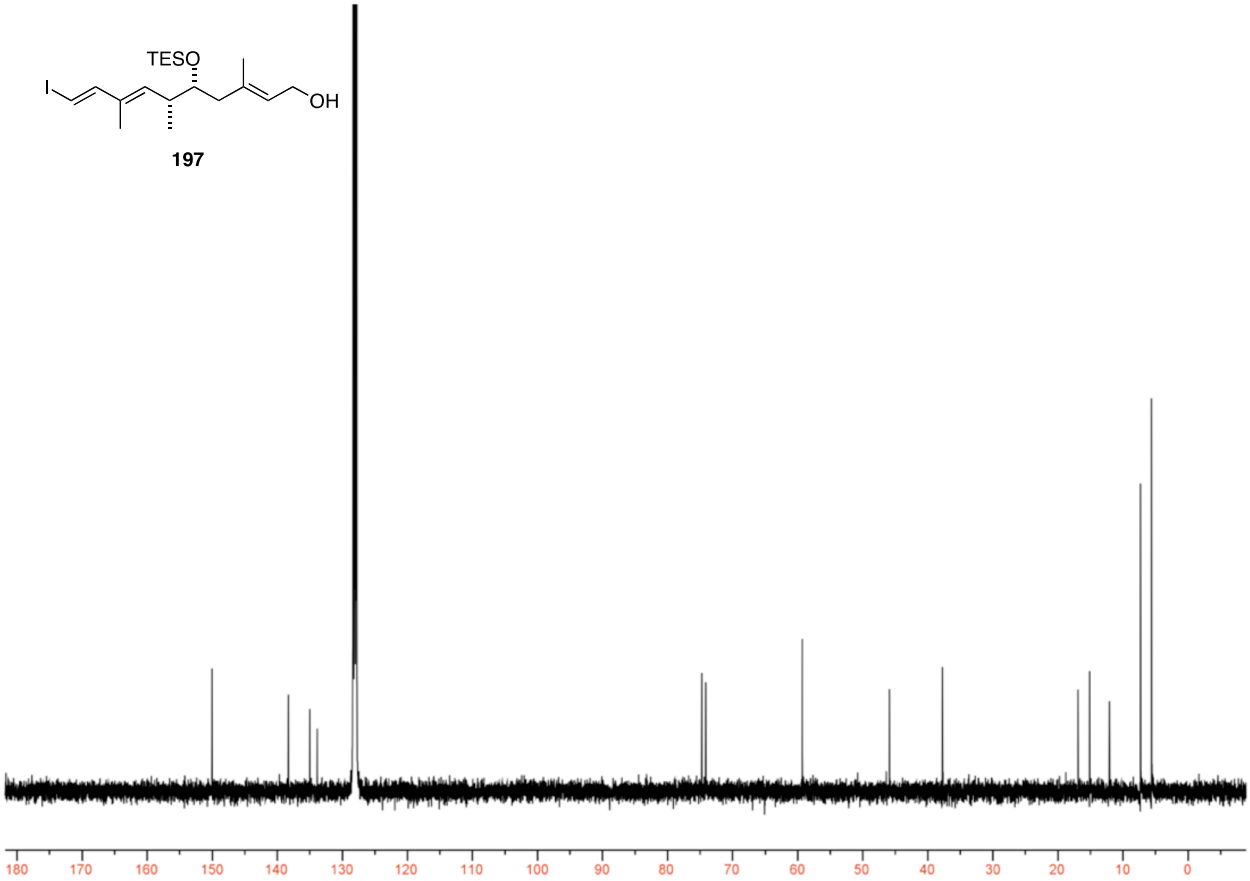
180

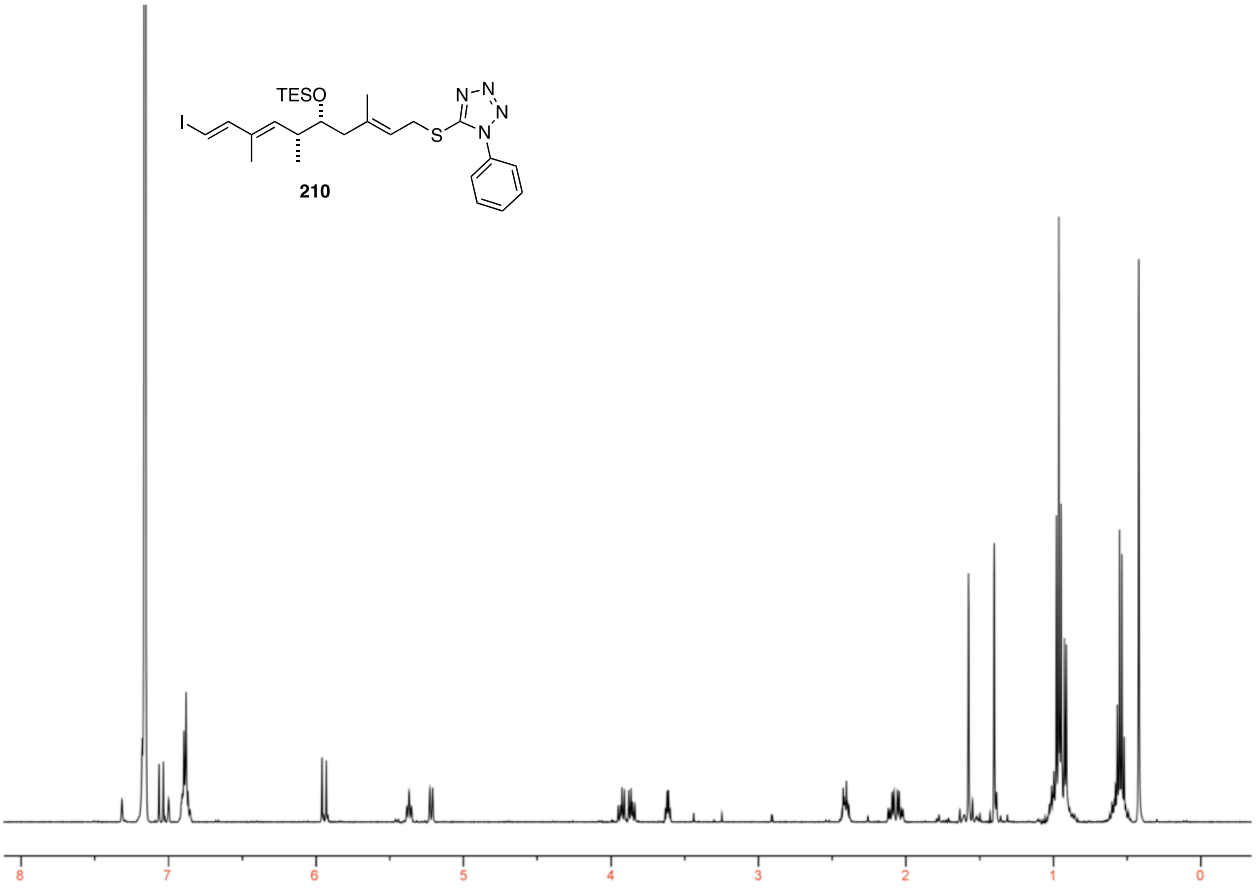
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

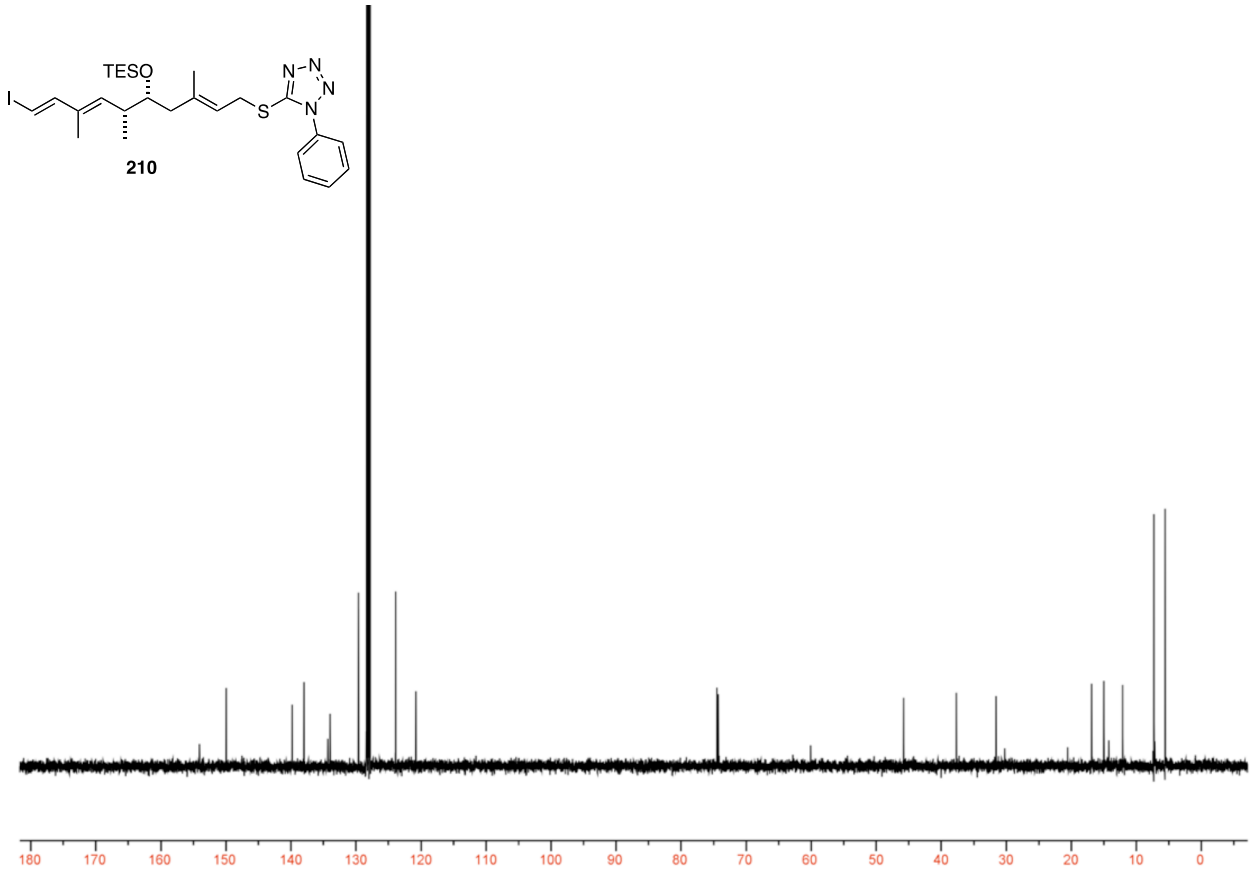

TESO
O
I
OMe
196
8
7
6
5
4
3
2
1
0

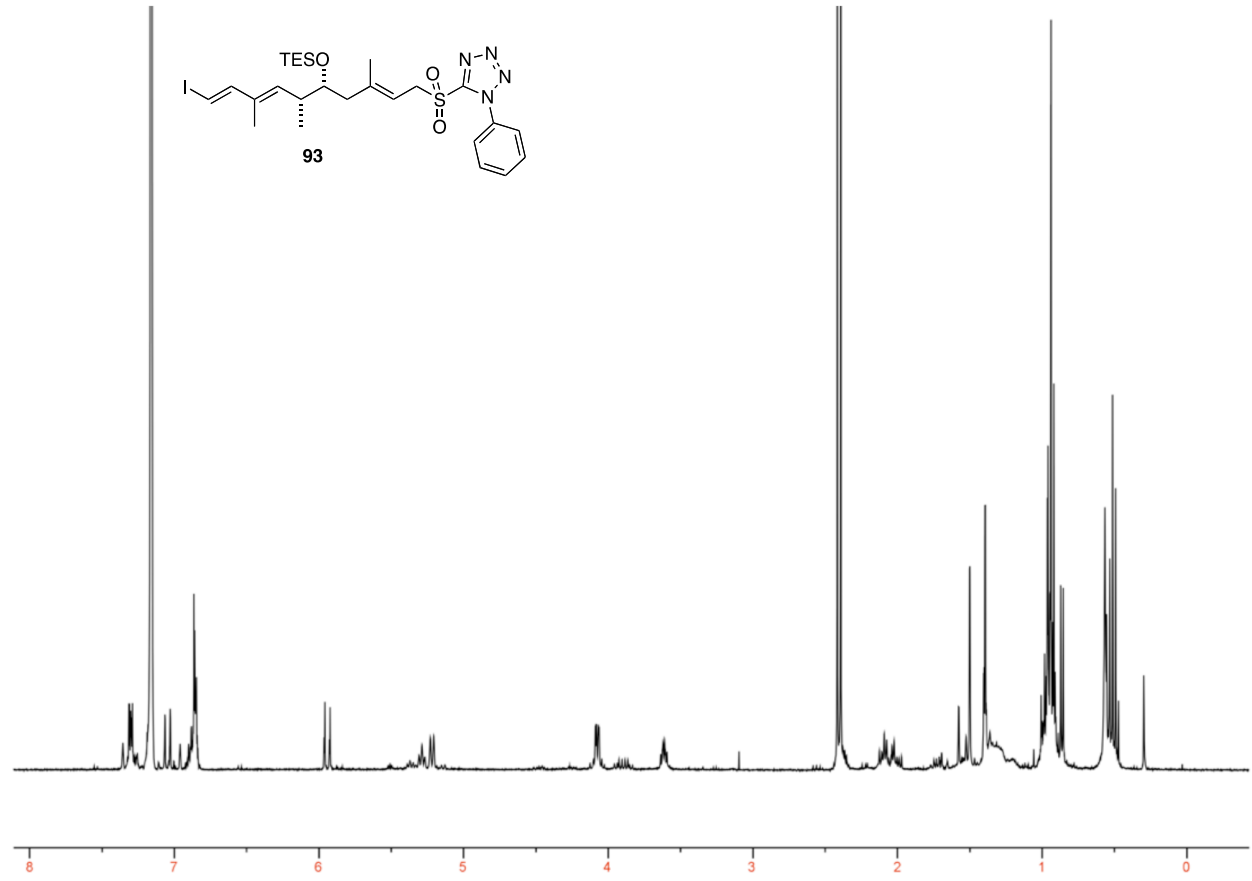

TESO
O
I
OMe
196
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

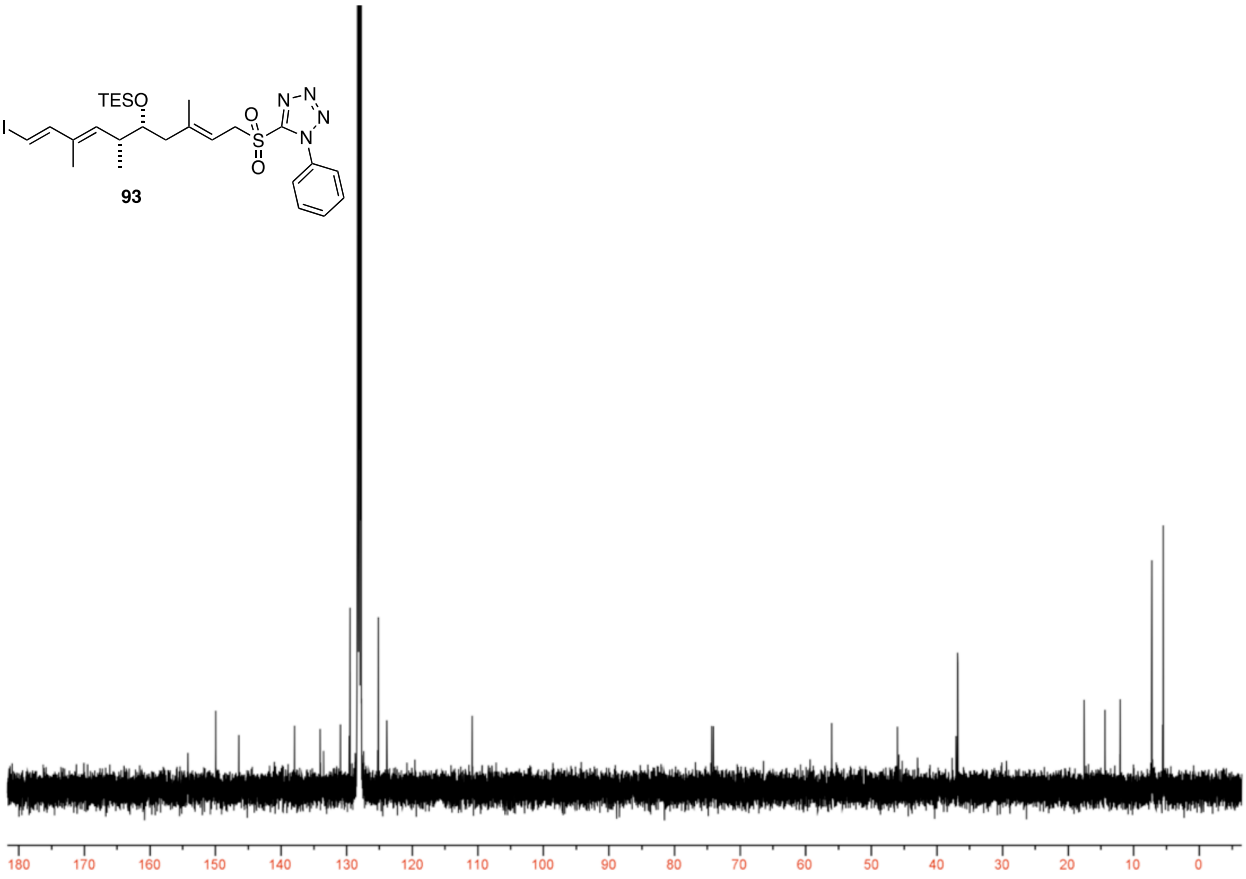

TESO
I
OH
197
8
7
6
5
4
3
2
1
0


TESO
I
OH
197
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TESO
I
S
N
N
N
N
210
8
7
6
5
4
3
2
1
0


TESO
I
S
N
N
N
N
210
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TESO
I
O
S
O
N
N
N
N
93
8
7
6
5
4
3
2
1
0


TESO
I
O
S
O
N
N
N
N
93
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0